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1. Executive Summary

1.1. The REMEDiE project has examined in considerable detail the development of the field of regenerative medicine (RM), defined as the application of novel biomaterials – specifically cells (including stem cells), genes (via gene therapy) and biodegradable scaffolding materials, to achieve a regenerative effect. Three main aspects of the field are explored - the economic (innovation-related), the political (especially governance related) and the bioethical (including its legal aspects) – to compare Europe with other parts of the globe.

1.2. There is a significant European-based commercial sector, with c120 companies – the vast majority (112) small biotech firms less than 10 years old - working in the domain of regenerative medicine, including 51 cell therapy companies, of which the majority strongly favour therapies using cells from a patient's own body (autologous cell therapy) over products using cells derived from an unrelated donor or donors (allogeneic cell therapy) with very little interest in hESC approaches. The industry is concentrated in major hubs in France, Germany, and the UK, dependent on strong regional (publicly-funded) platforms.

1.3 There are major scientific and regulatory hurdles ahead as clinical trials increase, especially the ability to standardise cell batches for phase III trials, when the biological variation in cell behaviour must be shown to be within tolerable limits across multiple clinical sites to gain regulatory approval. While the US is extremely strong its lead on some fronts is declining as more and more clinical trials in autologous therapies gather pace elsewhere. Most trials are still in Phase 1, and focused on three areas, the cardiovascular, the gastrointestinal and the central nervous system. It is very likely that the next decade will be dominated by products and processes deploying autologous customised batch therapies rather than extensively available techniques.

1.4. Regulatory and political practices vary across Europe and globally. The report discusses the ways in which the sourcing of tissue – notably oöcytes for research – is subject to regulatory oversight and the degree to which this is effective. It also identifies some key differences in the political cultures shaping the field as one move, from the USA, Europe to China.

1.5. Findings in relation to key ethical and legal issues (which overlap) are summarised. Consensus on controversial topics such as those relating to regenerative medicine is fragile and often challenged on moral and political grounds. Moreover, consensuses tend to collapse rapidly as innovation disturbs agreed moral boundaries.

1.6. The full report concludes with a range of detailed policy recommendations relating to the governance, enabling and strengthening of the field and its regulatory, corporate and clinical promise.

1.7 The Report is accompanied by a separate series of detailed **Annexes** relating to the discrete results the substantive Workpackages (1-7). These reports inform the range of papers both published and in preparation during the period of dissemination activity following the end of the formal contract period of the project. They are provided as a set of (Non-public) Deliverables for the Commission.

2. Summary of Project: Context and Objectives

The prospects for a 'material science' of regenerative medicine are said to have been first mooted in the late 1970s as part of a debate about the efficacy of 'substitutive medicine' and the toll that future demands for organ replacement and prosthetic technologies might exert upon the specialism (Lagasse *et al*. 2001, Lanza and Rosenthal 2004; Koh and Atala 2004; McConnell and Turner 2005; Vacanti 2006; Gardner 2007; Lysaght, Jaklenec and Deweerd 2008; Nerem 2010; Pangarkar *et al*. 2010; Polak 2010; Badylak and Nerem 2010: 3285). Regenerative medicine therefore began as a bid, primarily among American transplant surgeons, cellular biologists, geneticists and medical device engineers, to develop salient alternatives for conventional tissue substitution methods (Lysaght and Hazlehurst, 2003; 2004; Kemp 2006; Johnson *et al.* 2010; Messenger and Tomlins 2011). Three decades have passed since the search began for the means of replenishing and regenerating the body's natural processes of repair. The commercial life science and biotechnology industries helped to seed this venture in the early 1980s, via tissue engineering start-up businesses, placing this important initiative firmly on an entrepreneurial footing from the outset (Mason and Dunhill 2008a;2008b). Start-up firms have been pivotal to the regenerative sciences worldwide but the growth of the manufacturing focused side of this science-industry complex has been dependent on a few key businesses, equipped with the expertise and technology required to turn favourable laboratory results into testable products.

Experiments with regenerative cellular engineering took place in the American entrepreneurial science and university research sectors for much for the 1980s and 1990s. Most notable among these were those at the University of Wisconsin with the announcement by Jamie Thompson's lab of development of the first human embryonic stem cell line (hESC). This and similar developments elsewhere triggered a new wave of regenerative medicine that went beyond the substitution strategy of tissue engineering toward the possibility of cell therapy itself, a regenerative medicine that would not merely replace but also restore the function of body tissue and organs.

Determining the field of inquiry

There is at present no single, universally agreed definition of RM, although recent years have seen a number of attempts to delineate the field published in the scientific literature (for example; Atala, 2007; Kemp 2006; Daar & Greenwood, 2007; Mason 2007a; Mason & Dunnill, 2008a). In order to evaluate the development of regenerative medicine in Europe, it was therefore necessary to produce a project-specific definition of RM that could be operationally applied to determine the boundaries of our inquiry – for example, in respect to which firms should (or should not) be included in the 'company universe'. Consideration of which technologies and practices should be incorporated under this definition was guided by the following core tenets:

- A focus on novel, disruptive biotechnologies that pose specific challenges for governance regimes, industrial manufacturing, and business strategies.
- In order to be considered 'regenerative', technologies and products must aim to restore, maintain, or enhance tissue, cell or organ function by stimulating, or augmenting the human body's inherent capacity for self-repair.

Approaches utilising human cells, including stem cells, gene therapy, and bioscaffolds (made from collagen or synthetic polymers) are all considered to come under the remit of this definition. Our definition therefore is as follows:

> *Regenerative Medicine is the use of cells including stem cells, genes (via gene therapy), and bio-scaffolds to stimulate or augment the body's capacity for self-repair.*

Objectives of the project
The main objectives of the project were to provide:

- A detailed analysis of the competitive position of Europe within the globalisation of regenerative medicine, the requirements of successful innovation in this field and the EU policies that need to be developed to support Europe's global advantage in the field.
- An integrated series of workpackages organised around three inter-related streams of research that constitute the platform for this analysis (the socio-economic, political and bioethical)
- An integrated quantitative relational database on the geo-economic pattern of activity within the field of regenerative medicine derived from a) ongoing review of secondary data sources and b) primary data derived from partner projects
- The use of novel methodological techniques to interrogate results using geometric mapping of data items secured by different projects in the three streams of work
- A continuing engagement with national and international policy makers and others to test and refine the implications of emergent findings for future European policy and regulation in particular.

3. Major findings

In order to integrate our results, we have organised the principal findings of the REMEDiE project according to a number of core themes which draw from various workpackages. Full reports for each WP are carried in the accompanying **Annexes.**

3.1 Innovation and firm activity at European and Global levels

3.1.1 Regenerative Medicine in Europe

One of the primary objectives of the project was to investigate the contemporary position of the European regenerative medicine (RM) industry within a global context and to track and evaluate patterns of investment in RM technologies. Four discrete approaches were developed to address these objectives: a comprehensive study of the extant 'universe' of commercial companies developing regenerative medicine products; case studies of commercialisation strategies in six Member States (the Czech Republic, France, Germany, Spain, Sweden and the UK); an extensive financial analysis of the economic robustness of the global RM industry and discussion of the position of European firms in this regard; and the construction of an international SQL database of corporate, clinical trial and patenting activity in the major global regions.

Companies developing small molecule or macromolecule (e.g. recombinant protein) therapies intended to have 'regenerative' effects *in vivo* by stimulating cell division, activation *etc* are outwith the field as they largely share the established regulatory pathways, reimbursement strategies and manufacturing processes of bio-*pharmaceutical* drug development. They do not involve any significant investment in the specialised biomaterials of regenerative medicine, nor are they likely to encounter any of the same regulatory, financial or technological barriers to development. Examples of companies self-identifying as 'regenerative medicine firms' but excluded under this approach are Renovo (Manchester, UK), developing recombinant growth factors as a therapy to regenerate tissue damaged by scarring; NKT Therapeutics (Waltham, MA, US) which uses antibodies to activate subsets of white blood cells in vivo to proliferate and fight disease (i.e. induced cell therapy), and NeuroNova AB (Stockholm, Sweden), which is developing small molecule and protein therapeutic drugs aimed at inducing regeneration in adult neural stem cells. Xenotransplantation, cell-based vaccines, traditional prosthetics or implantable medical devices (such as pacemakers), antisense or interference RNA technologies, and organ transplants are also considered to lie outside the purview of the project definition of RM as they are either insufficiently novel or are not considered to act in an appropriately regenerative fashion.

Alongside companies developing RM products for therapeutic purposes, the European company universe also includes 'secondary' firms that supply specialist services (e.g. stem cell specific media and reagents, bio-reactors optimised for growing human cells in three-dimensional configurations for tissue engineering) or technology platforms (tissue and biobanking, pluripotent cell culture for NCE screening) that engage with and support the scientific and commercial development of regenerative medicine. Firms that supply basic laboratory equipment or universal reagents and materials for cell culture (e.g. standard media, Petri dishes) are excluded as these are not specific to regenerative medicine.

Data collection on European RM firms was ongoing throughout the duration of the project. The European company universe was revised approximately every six months following its initial formulation, and 'work in progress' iterations of the dataset were presented at the project meetings (beginning in Vienna in 2009) for feedback and evaluation at international meetings in Wisconsin (2010) and Bilbao (2011). Project members, including our International Advisory Group members, based in European countries were asked to carry out online searches for 'regenerative medicine companies' in their native languages to offset any English-language bias in WP-1 data collection, and they also contributed knowledge of national resources such as the recent report by the LEEM (the French pharmaceutical industry association) on RM in France and the network of Bioregions in Germany[1], many of which provide searchable databases of local biotechnology firms. The monitoring and revision of the company data allowed the incorporation of information from online news services (including monitoring closures, mergers and acquisitions) to keep the European company universe up to date. Company websites were also checked for evidence of updating over time as an additional way of gauging whether certain firms were truly active or not.

[1] http://www.biodeutschland.org/ak-bioregio.html

3.1.2 *The European Company Universe: Principal Characteristics*

A total of 112[2] *currently active* European firms meeting the project definition of regenerative medicine were catalogued. The following section will present an initial characterisation of the European RM industry in terms of its geographical distribution, composition firm, age, size and other features.

Geographical distribution of European RM firms

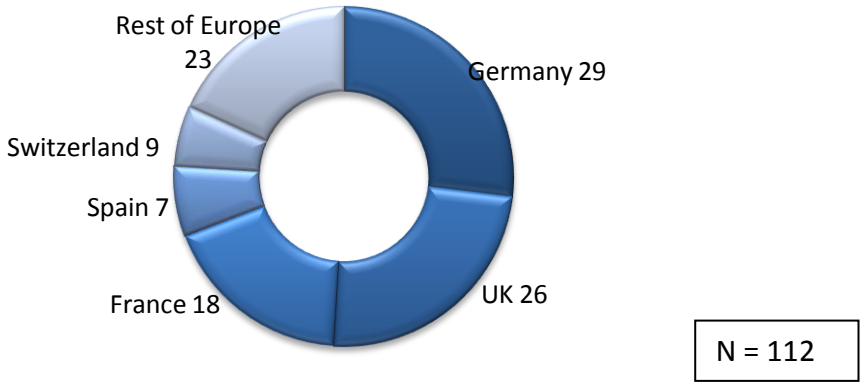


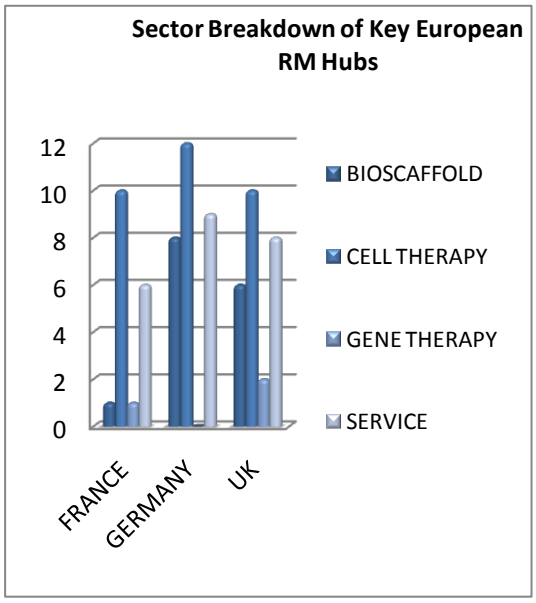
Fig 1.0 European RM firms by country

The European RM industry is heavily concentrated in countries in the north and west of Europe, with very little commercial activity in southern and eastern areas. As Fig 1.0 shows there are three main hubs of European RM activity; Germany, the UK and France. The next most active states for commercial development of RM are Spain and Switzerland, while the remainder of European companies are spread across a range of territories including Belgium, The Netherlands, Sweden, Denmark, Italy and Greece where each of these countries has at most two or three genuine RM firms within its borders. Many European countries have no commercial regenerative medicine presence at all, including the majority of states that joined the European Union in 2004.

Perhaps unsurprisingly, the major national players in commercial RM are generally those countries that have strong existing life-sciences and biotechnology industries and the attendant infrastructures. Spain, as an exception, is an important example of a country which has developed a strategic approach to the support of RM as part of a broader programme to *build* a national biotechnology sector. It is not co-incidental that the three major European hubs all have national strategies for the development of RM. The UK stem cell initiative and the subsequent Patterson Report in 2005 was perhaps the first attempt in Europe to construct a coordinated national strategy for regenerative medicine (albeit one which was highly focused on stem cell research). Other countries have since followed suit to varying degrees. In Germany, strategic support has taken a range of forms, notably the development of five major RM research centres backed by the Federal Ministry for Education and Research (BMBF) and the German Research Association (DFG), as well as a number of scientific networks and commercialisation schemes administered by different regional authorities (such as the pioneering North Rhine Westphalia Stem Cell Network

[2] This figure relates to WP1 data: later in our discussion of WP7 below, the number of European firms is higher at 132, but this includes some older no longer functioning firms

established in 2002, and Saxony's funding of RM as one of its main strategic priorities in biotechnology). France, unlike the UK and Germany, did not have a significant pre-existing tissue engineering industry as illustrated by the lack of bio-scaffold firms in **Fig 1.1**. below.



A 2007 French report by the biotechnology committee of the LEEM on 'cell therapies' made a range of policy recommendations intended to spur the development of a national regenerative medicine industry, including regulatory reform and support for the development of regional RM clusters. The outcome of this highly targeted approach is visible in that the French RM industry now has cell therapy and service sectors comparable to Germany and the UK. Moreover, like Germany, its legal constraints on hESC research are somewhat mitigated by its strong pharma/biotech sector and historic strengths in key areas such as developmental biology. As the country with the third greatest number of RM companies, it clearly has potential to be a major player, though it is unclear whether the current restructuring of the life sciences research system facilitates such a development, or proves an unwelcome distraction.

It is important to note that a country's density in terms of firm numbers does not necessarily reflect the strength of the firms based there. A number of significant European RM firms are located in countries outside the three hubs as illustrated by the cases of TiGenix (Belgium), Cellartis AB (Sweden) and Cellerix (Spain) – see Table 1.0 below for details.

Table 1.0 Selected European RM firms of interest

FIRM	COUNTRY	FOUNDED	DETAILS
Cellartis AB	Sweden	2001	Provider of human embryonic stem cell lines for development of therapeutics and drug discovery programs. Have a range of strong, high profile collaborations with multinational pharmaceutical companies including AstraZeneca, Pfizer and Novo Nordisk.
Cellerix	Spain	2004	Cellerix have an allogeneic stem cell therapy, based on multipotent cells extracted from adipose tissue in phase II trials for autoimmune disease. The company has secured previous investment from VC arms of Roche and Novartis; currently in talks to merge with TiGenix NV (see below) to create a major European RM firm.
Ectycell	France	2009	Ecytcell, a wholly owned subsidiary of French firm Cellectis, are the only European biotech developing induced pluripotent stem cells for

			human therapeutic and research tool applications. In 2010 the firm licensed significant intellectual property on IPS technology from IPS Academia Japan Inc. (Kyoto, Japan).
ReNeuron	UK	1997	To date ReNeuron are the only European firm with a stem cell therapy for neural regeneration in clinical trials (phase 1). ReNeuron's cell line is an allogeneic therapy derived from foetal neural tissue.
T2Cure	Germany	2006	T2Cure have an autologous stem cell therapy for regenerating heart muscle about to enter phase III trials. The company was the first to receive MAA certification for a stem cell product under the ATMP guidelines.
TiGenix NV	Belgium	2000	TiGenix manufacture *ChondroCelect* –the first cellular product to receive regulatory approval for the European market through the centralised ATMP system. The company also have a CE Marked bioscaffold product as a result of acquiring the UK's Orthomimetics in 2009. Merging with Cellerix.

Firm age, size and sector

The majority of European RM firms across all sectors are small (<50 employees) with only a few (N= 10) medium (<250 employees) or large (>250 employees) companies involved in the field. This is unsurprising given that there are no high-earning 'blockbuster ' RM products and the sector is regarded as highly risky by investors, even in comparison to other biotechnology fields such as genomics. Europe has historically suffered from significantly lower availability of venture capital (VC) investment compared to the US and until very recently large pharmaceutical companies have been reluctant to invest in stem cell technologies meaning there has been limited capital available to European RM firms to grow and develop. The long timescale of RM product development, the financial crisis of 2008-9 and the subsequent risk-averse investment environment have all served to exacerbate this situation. Those few large firms recorded tend to be older companies, which have added RM products, especially products with lower technical requirements and less complex regulatory pathways such as cellular bio-scaffolds or reagents, to existing product pipelines and are often not dependent on RM products alone to make a profit.

The largest single sector of the European RM 'company universe' is cell therapy firms, but there are also significant bio-scaffold and service sectors:

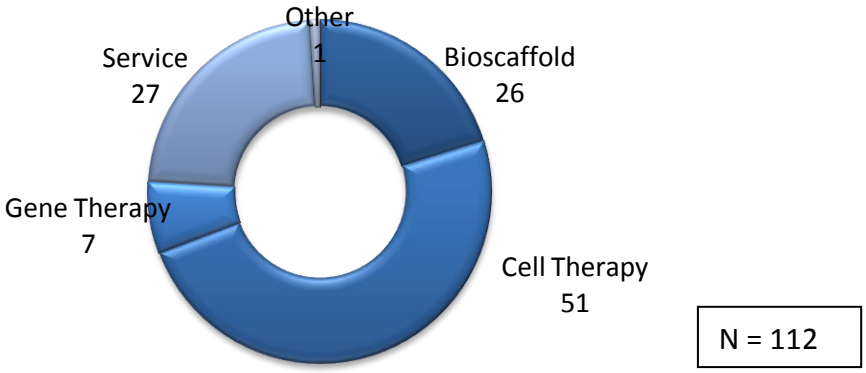


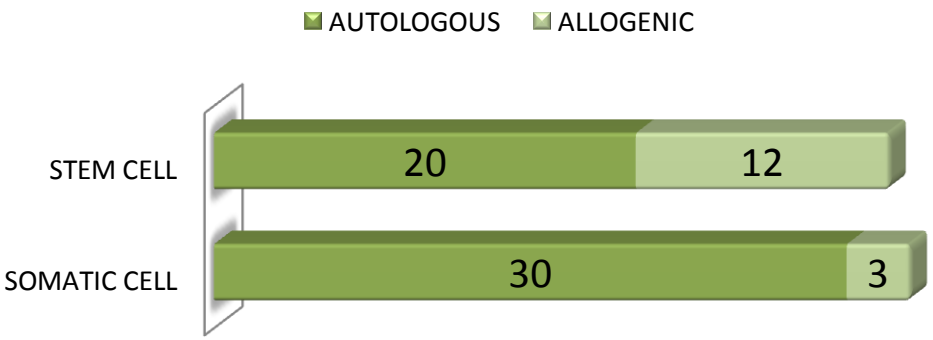
Fig 1.2 European RM Companies by Sector

There is a considerable spread in the age of RM firms. While a majority of the currently active firms have been founded since 2000, a notable proportion (c. 23%) of firms have survived from the 1990s and a few firms are considerably older. This reflects the heterogeneous composition of the RM field, with recently-founded biotechs developing stem cell therapies co-existing alongside tissue engineering era companies offering cartilage transplant services and acellular biomaterial products.

The cell therapy sector

A key aspect in assessing human cell based therapies is the source and application route of the cells. Somatic 'adult' differentiated cells and stem cells from a range of sources – embryonic, foetal, cord blood, and mature tissues can all be used to develop cell therapies. Mature somatic cells can also be reprogrammed using certain biological factors to induce pluripotency – so called induced pluripotent stem (IPS) cell technology. Cell therapies can be applied autologously – reimplanted into the patient the cells were extracted from, or allogeneically – where cells from a donor are implanted in unrelated patients. Each of the possible permutations of sources and application routes has implications for the type of business model for firms developing the cell therapy products.

A total of 65 cell therapies available or in development were recorded from the 51 identified cell therapy biotechs as several firms have more than one cell-based product or product candidate.



As Fig 1.3 above shows, European cell therapy firms are split almost equally between therapies based on stem cells and therapies based on somatic cells. However, there is a strong emphasis on autologous rather than allogeneic therapies. Interestingly, this is less the case with stem cell-based approaches than with somatic cell-based products. A further important dimension to this pattern is revealed by comparing those cell therapy products which are available (including through hospital exemption, named–patient licences, and the limited number of nationally or EMA approved products).

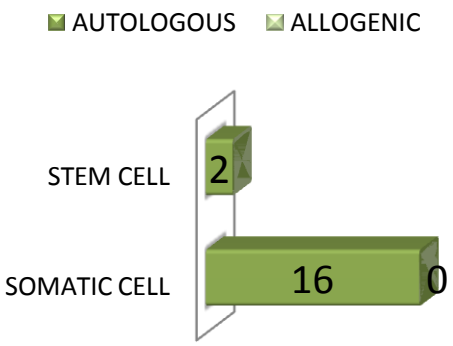


Fig 1.4 Available cell therapies by type

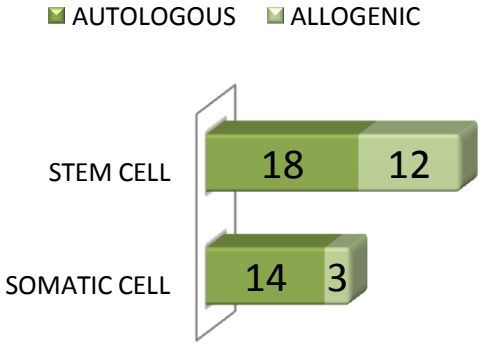


Fig 1.5 Cell therapies in development by type (N = 47)

The available cell therapies (Fig 1.4) are overwhelmingly based on autologous somatic cell therapies while the cell therapy pipeline (Fig 1.5) shows much greater investment in stem cell technologies and in the development of allogeneic approaches to cell delivery. As with the age range of firms involved, this stratification reflects the history of the RM industry. The available cell therapies are mainly tissue engineering era procedures using autologous epithelial or cartilage cells to repair skin lesions and restore cartilage damage in joints.

Autologous cell therapies, however, offer less scope for intellectual property protection (since a patient's own cells cannot be patented) and limited potential to scale up the treatment process since each patient will need their cells expanded *ex vivo* in isolation to avoid cross-contamination risks. However, they are still regarded as incurring significantly lower risk of immune rejection or the need for immunosuppressive drugs than allogeneic cells and it may be that developers intuit that smaller scale clinical delivery under hospital exemption rules and strong buy-in from clinicians will be the most readily available mode of delivery for cell therapies for the near future.

In contrast, allogeneic therapies take a 'cells as drugs' approach more likely to be viewed favourably by big pharma and other investors, potentially yielding an off-the-shelf product deliverable to much larger patient populations. Development, accreditation and standardisation of large scale automated cell culture for clinical grade applications remains a work in progress though, and may continue to present significant technical and regulatory challenges for allogeneic products in medium term (See REMEDiE Paper on clinical trials: Webster *et al*., 2011).

Cell therapy pipeline and therapeutic focus

It is largely stem cell therapies that are being developed for the more ambitious clinical indications; those that reflect the promise of RM such as cardiac repair, neuro-regenerative treatments, and autoimmune diseases. Much of this activity is currently in the early stages of clinical development (see Fig 1.6) and so is not likely to yield a flood of new therapies in the short term. Additionally, no stem cell therapy for this type of chronic disease application has yet made it through the ATMP regulatory system and despite efforts to harmonise European regulation and create a viable governance pathway for regenerative medicines there remain areas of uncertainty –and thus potential challenges – with regards to permissible amounts of variability in cell populations in multi site (i.e. late stage) clinical trials.

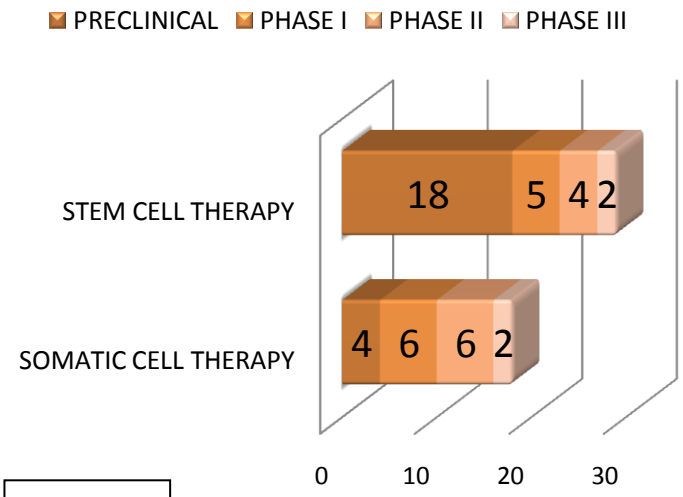


Fig 1.6

The wider picture: financial robustness of corporate actors at a global level

Beyond corporate activity at a European level, we decided it would be useful to undertake a detailed analysis of firms operating within and beyond Europe that *present themselves as falling within the regenerative medicine field* and that are stock market listed: the latter means it is possible to make a statistically detailed examination of corporate reports and accounts (Marston and Shrives 1991; Cooke 1998). In assembling this dataset, comparisons were made with other lists, including those published by Lysaght, Jaklenec and Deweerd (2008) and Martin, Hawksley and Turner (2009). Some of these firms do *not* meet our formal definition of regenerative medicine (such as Novavax [developing novel vaccines] and Proteome [primarily a service company providing assays to test protein expression in disease]). But we have decided to retain these in the overall profiling as they are indicative of the ways in which the term 'regenerative medicine' is used to signal to stock markets companies claiming to contribute to the field, and so deriving some social and economic capital by doing so.

This element of the research was divided into three stages. The sample frame for *Stage 1* was synthesized from a possible 10,000 publicly registered life sciences concerns, tissue engineering companies and biotech holdings, for which accounting entries are held on *Thompson Datastream*^{TM}. Following a detailed process of elimination, 112 companies were identified operating within and beyond Europe as publicly-listed firms (Kewell et al. 2009) presenting themselves as contributing to the field and firms where we could examine their financial capabilities and risk position; and see whether a longitudinal five year regression based panel investigation might be viable (Farrar and Glauber 1967; Marston and Shrives 1991; Cooke 1998).

Taken together, the results of the descriptive interrogation of data and a subsequent phase of regression analysis, statistically verified wider impressions that the sector was not sufficiently underwritten by venture capital to withstand the impact of the recession triggered in 2007-2008 (Pangarkar *et al*. 2010). Fiscal indebtedness amongst the firms appeared to be particularly problematic (see: Kewell et al 2009). Indeed, it seems to be the case that a culture of over-investment had not only caused the market to overheat but may have also, simultaneously, established adverse conditions in terms of risk position, profitability and research intensity among the initial sample population. Companies with a greater asset base, and with higher market value were, paradoxically, shown to be more risky, because of past stock market over-valuation and a lack of successful product efficacy.

The third stage of the research distilled the research sample down to 50 firms for more detailed analysis, which were separated from more peripheral firms through a painstaking process of cross-checking between *Thompson Datastream*^{TM} and accounting information published on company websites.

Some notable firms are apparent within this subset (see Table 2). Among the highest cash accumulators (i.e. those with increasing sales revenues and a healthy net cash flow position), most were located in the US, followed by Europe, Australia and Korea. The top three for this particular league table consists of Viromed (a South Korean firm with American participation), Geron Corp. and Oxford Biomedica (American and British companies, respectively). The international spread of the industry, from its antecedents in the United States (US), is confirmed by the presence, within this group, of some significant European firms, including Tigenix NV (now merging with Celerix), and Molmed, alongside Australasian and Asian businesses such as Mesoblast and Viromed.

Table 2: Location of leading RM firms by Net Cash Flow (In Original Currency)

VIROMED COMPANY LTD (32625U)(korea won)	27580900	South Korea /USA
GERON CORP (883003)($)	86787	USA
OXFORD BIOMEDICA (870449) (pounds)	15378	UK
MESOBLAST LTD (29961Q) (Australian dollar)	15094	Australia/USA
TIGENIX NV (50325E)(euro)	12103	Belgium
MOLMED S.P.A. (51731N)(euro)	9126	Italy
CYTORI THERAPEUTICS (15286F)($)	5167	USA
BIOHEART, INC (50143E) ($)	4976	USA

Firms in a position to generate sales income had reversed poor profitability ratios to an extent, although even the best among them were still in a negative pre-tax profit position (e.g. -4949% to -206% between 2005-2009). By contrast, the profitability of the least performing firms in the sector plummeted between 2005-2009, in one case from a negative

pre-tax margin of -637% to one of -118054%, over a four year period. Employment increased in the sector among more buoyant firms with good sales revenues (for example by a change in percentage rates of 595% for one firm and 257% for the top revenue performer). By contrast, those companies with decreasing sales revenues were clearly restructuring to diminish costs between 2005 and 2009. These firms seem only to have hired staff at the margins. That said, even some firms experiencing vast losses were recruiting by as much as 117% in terms of employment percentage alterations.

In a sector characterised by vast performance disparities, the growth percentages were extraordinary for some firms with increased sales revenues: from 325.81 at the bottom of the top ten, to 32942.86% at its apex (c.2005-2009). The overall picture is of strong income escalation for a small number of well placed competitors in the regenerative products markets and of small group moving ahead of the field. All firms within the sector are nevertheless 'cash poor' by stock market standards, remaining ostensibly dependent upon external sources of leverage, particularly with respect to the financing of programmes of expansion and Research and Development (R&D) initiatives. Some interesting trends were identified in this regard, including evidence to suggest that the state has been an arbiter of business development in Korea, while, as was seen above, regional *publicly-supported* platforms in France, Germany and the UK have similarly been key to the field's success. Geron and Transgene lead the sector in terms of market confidence, securing lucrative venture capital tie-ins and expert input from the pharmaceutical sector.

Yet despite these positive signals, there is strong evidence to suggest that even the most successful or sustainable of regenerative companies are not sufficiently ready to offer a broad spectrum of marketable product lines (e.g. Geron—which attracted significant venture capital but has only been able to conduct phase 1 and 2 clinical trials thus far).

All of these companies therefore rely strongly on various forms of esteem attractors (Kewell *et al.* 2009), including the employment of experienced directors/managers who have held prior roles in the biotech affiliates of large pharmaceutical companies (this is especially prevalent among US players); the employment of senior research scientists and venture capitalists among senior management; the creation of product related research publications in prestigious journals (e.g. Orthovita); and affiliations or collaborative agreements with large pharmaceutical companies (e.g. as licensees). This can be found among both US and European companies (e.g. Geron and Transgene). Affiliations with prestigious universities (Geron lists Duke in North Carolina), or academics (Japanese Tissues Engineering emphasises its affiliation to Harvard Med school) and government support or awards (Japanese and Korean firms) also rank as significant attractors for stock-market investors.

In summary, it can be said that even among the more prosperous and successful firms within the industry most are in a holding pattern where the development and testing of potential promising product lines allows them to continue to attract funding and expand the size of their operations. A smaller group of companies which has developed marketable product lines operates in niche markets (Orthovita, Tigenix, Biomimetic are all working on bone grafts for example).

In regard to another of our tasks – the construction of a global SQL database – our results enable us to identify some much wider, international trends, especially in regard to emergent activity over time, 'hot spots' of activity, and links between firms, trials, and intellectual property (patenting). REMEDiE has produced a quantitative database tracking geo-economic trends over time, starting in 2003, the year when the field of regenerative medicine/stem cells began to develop more rapidly worldwide. The original 'cut-off' date for collection was 2008 (as described in the initial proposal) but this was extended to the end of 2010 in the case of corporate and clinical trial data. Figure 1.7 below shows the structure of the database using the example of the US-based firm ACT.

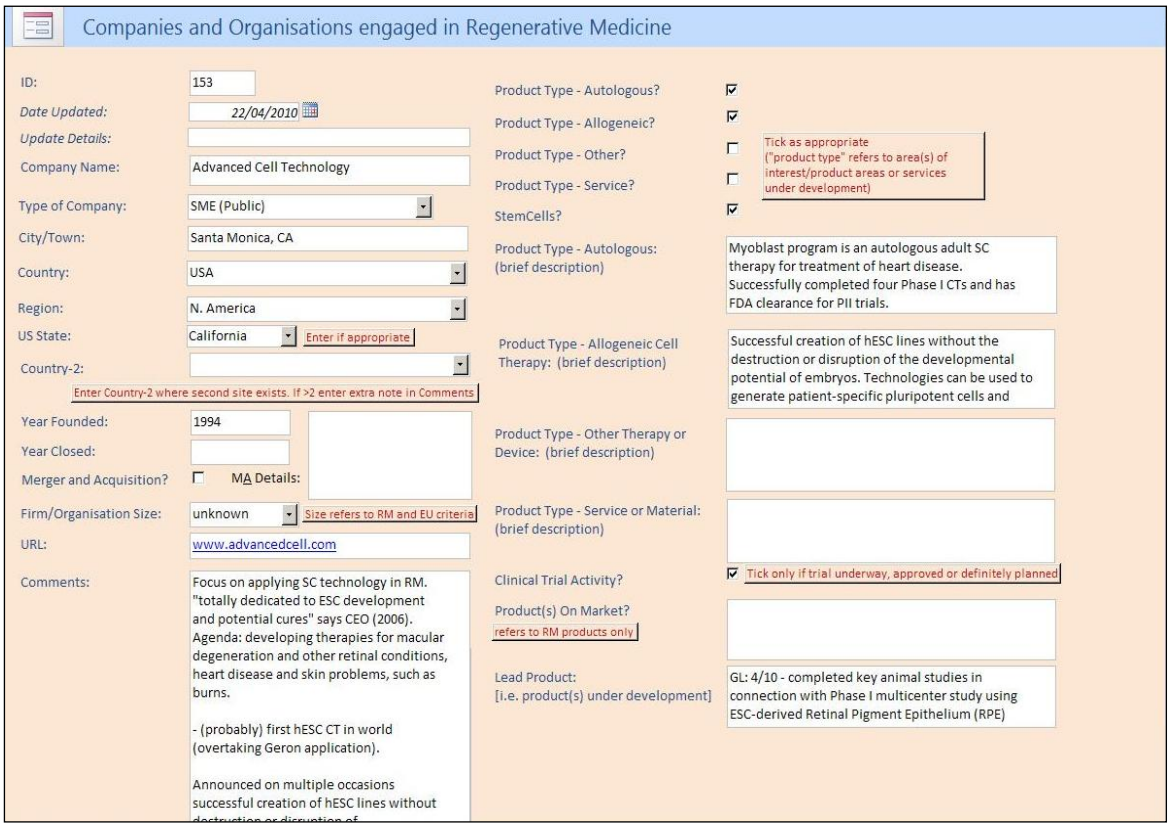


Figure.1.7 Screenshot of company entry on SQL Global Database

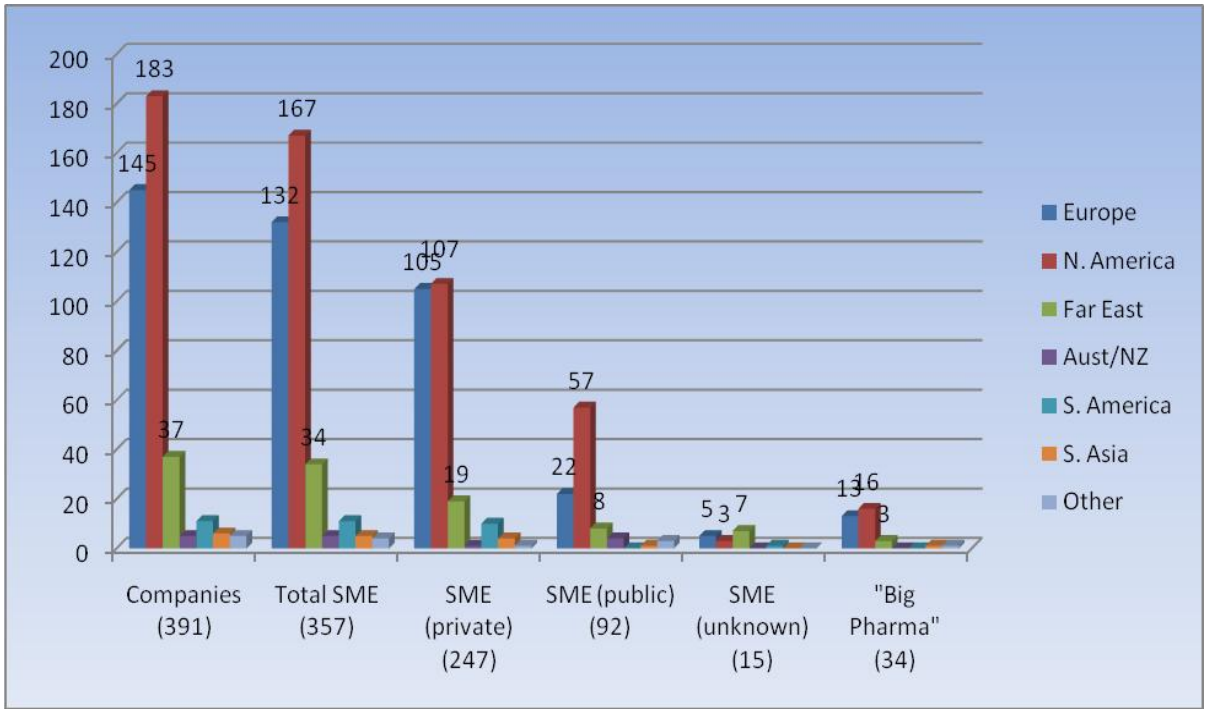
It is important to distinguish between different types of activity in the RM field. Data on the type of activity conducted by companies and other organisations is arranged in the database according to four categories: autologous; allogeneic; 'other' (e.g. therapies involving delivery via degradable bio-scaffolds and tissue engineering, gene therapy, or drug screening/toxicity - i.e. activity with a drug development focus); and services (cell-based and other service provision such as bio-scaffold production for other SMEs). In addition, the 'Organisations' table contains information on clinical trials relating to individual companies as well as RM products on the market and/or companies' lead product(s), as appropriate.

In terms of composition, n=473 entries are recorded in the 'Organisations' table, of which n=392 are companies. This data is searchable using SQL by region (Europe, N. America, Far East, S. Asia, Australia/New Zealand, S. America, and 'Other'); country (including all EU

Member States – see Figs 1.8/1.9 below); type of company (publicly-traded SME, private SME, 'big pharma' or 'academic/hospital/non-profit/public laboratory'); year founded (and closed where applicable) plus any merger details where relevant (in order to provide a dynamic picture of developments over time); and firm size. The US data can also be searched by US state providing up-to-date information on the location of 'hot-spots' of RM activity in the US. As expected, California has by far the most firms with other major concentrations in Maryland, Massachusetts, Florida, New Jersey, New York and Texas. Wisconsin has fewer firms than one might expect given the state's importance with regard to stem cell science. Such data illustrates the regional infrastructure (and so networks) that have been built in each State. The significance of the corporate data on RM is closely related to clinical trials activity because a prospective product must proceed through clinical development and obtain regulatory approval – in the case of the EU via the Advanced Therapy Medicinal Products (ATMP) Regulation.[3]

With regard to 'big pharma' involvement in the RM field this has primarily been through equity investment or direct collaboration with RM companies. These developments, whilst relatively minor at present, are nonetheless interesting because of the well-known difficulties SMEs experience in translating advanced therapies to the clinic and bringing products to market. The greater involvement of major pharmaceutical companies, such as Roche and Pfizer, may be highly significant, though this is likely to focus on induced pluripotent (rather than embryonic) cells, and toxicity testing.

Figure 1.8: The RM corporate universe by region (end of 2010).



[3] ATMPs are 'innovative, regenerative therapies which combine aspects of medicine, cell biology, science and engineering for the purpose of regenerating, repairing or replacing damaged tissues or cells', and can be a gene therapy, a somatic cell therapy or tissue engineered product 'that contains or consists of cells or tissues that have either been subject to 'substantial manipulation' or that are not intended to be used for the same essential function(s) in the recipient as in the donor and is presented as having properties for treating or preventing disease in human beings.' (Regulation (EC) No 1394/2007).

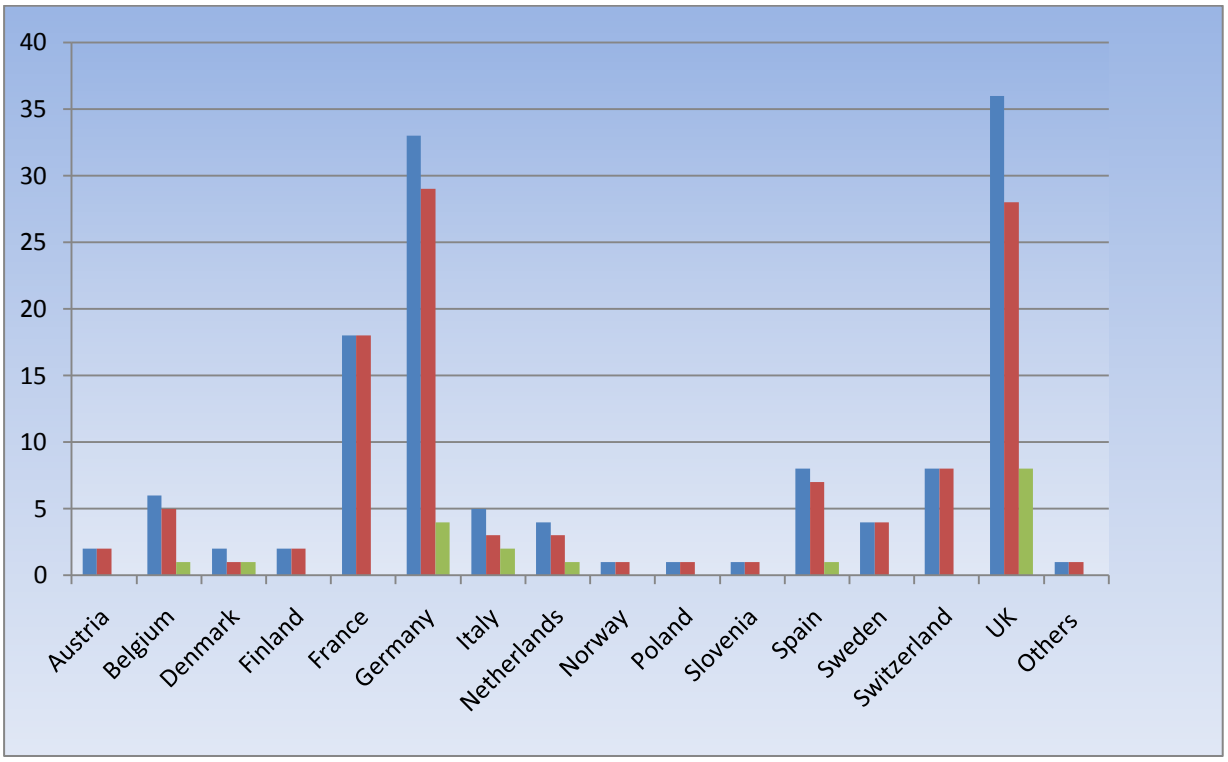


Figure 1.9: European SMEs by Member State (plus Switzerland and Norway).

Year	Number Set-up	Private Companies	Public Companies	Unknown	No. Closed
<1995	16	12	4	0	0
1995	0	0	0	0	0
1996	4	3	1	0	0
1997	10	6	3	1	0
1998	5	3	2	0	0
1999	4	3	1	0	0
2000	18	13	5	0	0
2001	9	6	1	2	0
2002	11	10	1	0	0
2003	4	2	2	0	1
2004	2	1	0	1	0
2005	4	4	0	0	1
2006	7	7	0	0	2
2007	7	6	0	1	2
2008	4	4	0	0	3
2009	3	3	0	0	6
2010	5	5	0	0	2

Figure 1.10: Year of establishment of European SMEs engaged in RM (2003 – 2010)

As can be seen, Figure 1.10 above shows a "spike" around 2000, which continued into 2001 and 2002, which is perhaps counter-intuitive. This data call into question ideas around 'lack of investment' in subsequent years because as noted above considerable investment had *already* been undertaken at the start of the decade (though again, that might have had a negative effect for some firms).

Mapping *clinical trials activity* provides a measure of the extent to which translation to the clinic is occurring in an emerging field like regenerative medicine – who is sponsoring trials, where they are located (which is not necessarily in the same country as the sponsor), what type of cell therapy (autologous or allogeneic), and at what stage (phases I, II, III) in the clinical development process. Tracing developments in clinical trials activity can also inform analysis of emerging regulatory frameworks.

WP7 has collected trials data by region and key countries for illustrative purposes (USA, UK, China, Japan and S Korea, and India, see Fig 1.11)). These countries were selected because they are amongst the most active in terms of RM clinical trials and provide a global 'spread' across regions. In the context of REMEDiE, comparisons between countries and regions can provide useful information about the positioning of European companies relative to global competitors (e.g. type of product, translational processes etc.) as well as trends and overall prospects in what is a fast moving field.

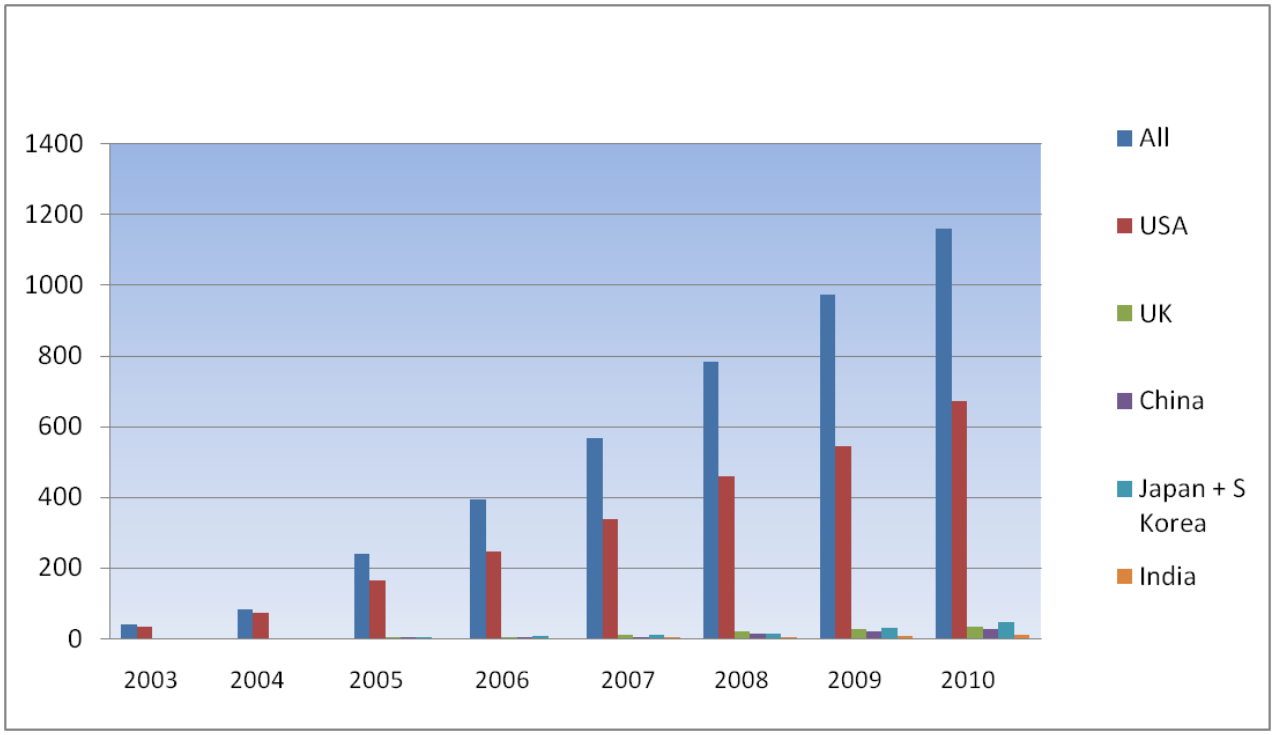


Figure 1.11: Clinical trials involving 'autologous cell therapy'
(Source: *www.clinicaltrials.gov*)

The US conducts more clinical trials than any other country in autologous cell therapy. However, US dominance has decreased in recent years as a proportion of all trials conducted with this cell-type. Interestingly, clinical trials data collected via industry-

orientated sources shows no automatic correlation between the number of companies in EU Member States and current clinical trials (CTs) activity. For example, the figures for UK, Germany and France, identified as the main EU players, are: Germany SMEs n=37, CTs n=6; UK SMEs n=36, CTs n=9; France SMEs n=19, CTs n=2. On inspection this is not surprising since of the total German SMEs, 14 have products on the market already and many of these are in the (more-established) tissue engineering sector. In the case of French SMEs, inspection suggests several firms are at an early stage in the product development process. Details of the main global corporate players in the stem cell field are presented below as Figure 1.12 along with brief commentary on notable developments.

Company	Cell Type	Cell Source	Type	Phase	Indication
Aastrom Biosciences	Non-ESC	Bone marrow	Autologous	Phase IIb (PIII announced)	CLI
Aldagen	Non-ESC	Bone marrow	Autologous	Phase I/II	CLI
Advanced Cell Technology	ESC	In vitro fertilized blastocysts	Allogeneic	Phase I/II	Stargardt's macular dystrophy
Athersys	Non-ESC	Bone marrow	Allogeneic	Phase I	ACI
BioHeart	Non-ESC	Thigh muscle	Autologous	Phase II/III	Congestive heart failure
BrainStorm	Non-ESC	Bone marrow	Autologous	Pending approval	ALS
Celgene	Non-ESC	Placenta	Allogeneic	Phase I	Crohn's disease
Cytori Therapeutics	Non-ESC	Liposuction	Autologous	Phase I	ACI
Geron	ESC	In vitro fertilized blastocysts	Allogeneic	Phase I	Spinal cord injury
International Stem Cell	Non-ESC	Unfertilized parthenogeneticaly activated oocytes	Allogeneic	Preclinical	Age-related macular degeneration
NeuralStem	Non-ESC	Spinal cord of 8-week fetus	Allogeneic	Phase I	ALS
Opexa Therapeutics	Non-ESC	Peripheral blood	Autologous	Preclinical	Diabetes
Osiris Therapeutics	Non-ESC	Bone marrow	Allogeneic	Phase III/II	Crohn's/ACI
Pluristem Therapeutics	Non-ESC	Placenta	Allogeneic	Phase I	CLI
ReNeuron	Non-ESC	Neural SCs with expansion	Allogeneic	Phase I in UK	Ischaemic stroke
Stem Cells	Non-ESC	Fetus	Allogeneic	Preclinical /Phase I	Spinal cord injury/Batten Disease

Figure 1.12: Principal companies in the stem cell field with clinical trials programmes

Developments of note with regard to clinical trials during the course of the project, because they utilise embryonic stem cells and mark the first of such trials, are the Geron trial for

treatment of spinal cord injury, which received FDA approval in 2010; and the ACT trial for Stargardt's macular dystrophy, also with FDA approval. Both platforms use *in vitro* fertilized blastocysts (derived from embryos) as cell source.

Also noteworthy is the UK's ReNeuron PISCES (Pilot Investigation of Stem Cells in Stroke) study which is the world's first approved trial of a neural stem cell therapy for disabled stroke patients and the first for any stem cell-based therapy in the UK. This does not use embryonic derived tissue however, deriving its tissue from aborted foetus instead, a point which it has made much of in respect to the recent European Court of Justice's decision to disallow patenting on embryonic-derived therapies (which may yet be reversed).

As the Table above shows, of the 15 main stem cell companies (worldwide) currently developing therapies, more than half have competing programmes in three major disease areas: cardiovascular, gastrointestinal and the central nervous system (CNS). Two areas of cardiovascular disease are focused on: critical limb ischemia (CLI)[4] and acute myocardial infarction (AMI)[5]. The major firms with clinical trials to treat CLI (n=3) are: Aastrom Biosciences [autologous procedure – the most advanced SC trial programme], Aldagen [ALD301], and Pluristem Therapeutics [PLX-PAD]. The main companies for AMI (n=3) are Osiris Therapeutics [Prochymal], Atherysys [Multstem], and Cytori Therapeutics [Celution System].

It should be noted that regulatory approvals may vary affecting product markets. For example, Belgium's TiGenix ATMP approval for ChondroCelect, has not been secured in the US: the FDA has demanded another trial before it can submit for US approval, with a 5 year delay before market approval if likely. Within a regulatory universe, difficulties can also arise over the trial period for technical or financial reasons: Spain's Cellerix has recently conducted Phase III trials on an autologous treatment, Cx401/Ontaril, and on a second product, Cx501, currently in Phase II. These programmes have however received technical set-backs and their future is unclear at this time. The UK-based Intercytex, once a leading European SME in the RM field, developed a series of non-stem cell autologous and allogeneic cell therapies for wound care, facial rejuvenation, and hairloss, which had been under clinical development for a number of years. Typical of the company's product portfolio were ICX-SKN and Cyzact (formerly ICX-PRO), topical wound care products designed to stimulate active repair and closure in persistent chronic wounds, with Cyzact completing a Phase III trial. However this and much of the company's other IP has recently been sold to other parties to meet needs for financial restructuring, the company retaining rights to one product, Valveta which is continuing in clinical development.

Beyond the analysis of clinical trials, we were keen to determine levels of patenting activity as a third dimension to our mapping and analysis of innovative activity in the field. The figures relate to patents that have been *granted* (and which we see as more significant as a result). The data comes from the latter period of our investigation – 2008/10. Of the total granted patent records (n=314), 50% (n=159) are assigned to the

[4] CLI is the obstruction of the arteries that seriously decreases blood flow to the extremities, resulting in pain, non-healing wounds, and tissue necrosis.
[5] AFI, or heart attack, results from the interruption of blood supply to the heart, causing cardiac cells, which cannot regenerate, to die.

'academic/hospital/institute/public laboratory' category, either entirely (n=138) or jointly with a company (n=5) or with individual(s) (n= 6). These figures demonstrate the significant role played by academic and other non-corporate actors in the RM field. This does not of course mean these actors commercialise these patents themselves, or indeed at all. Data is also available on the type of cell or cell source claimed in the patent (total records n=314): adult (n=213); embryonic (n=67); embryonic/pluripotent stem cells (n=35); induced embryonic/dedifferentiation of cells (n=6); induced pluripotent cells/dedifferentiation of cells (n=1); and induced pluripotent stem cells/re-programming of cells (n=3). The USA is the leading patenting region with over half of all patents granted held there, with Japan, Korea, Germany and Canada a long way behind.

One factor which may be exacerbating the investor caution in Europe we noted above is lack of certainty concerning intellectual property rights, such as patents. The issue of whether cell therapies will be patentable in the EU appears an obstacle to investment and again this is an area where stakeholders believe that US competitors enjoy a comparative advantage. However, divergent views about IP were expressed during our fieldwork: for instance, patenting in the RM field is regarded as difficult not because of EU blocks on stem cell-based patents, but because of the amount of prior art. One pharma executive described IP as "a minefield" because of the lack of certainty about who owns what and about which IP is going to be most important, and suggested that the twenty-year life of a patent was too short for cell therapies because the much lengthier R&D process left companies insufficient time on the market to recoup their investment before the entry of competitors. The relative importance of alternative forms of IP such as trade secrets and know-how were emphasised by a number of interviewees, again suggesting a marked difference between the RM sector and the wider biopharmaceutical industry.

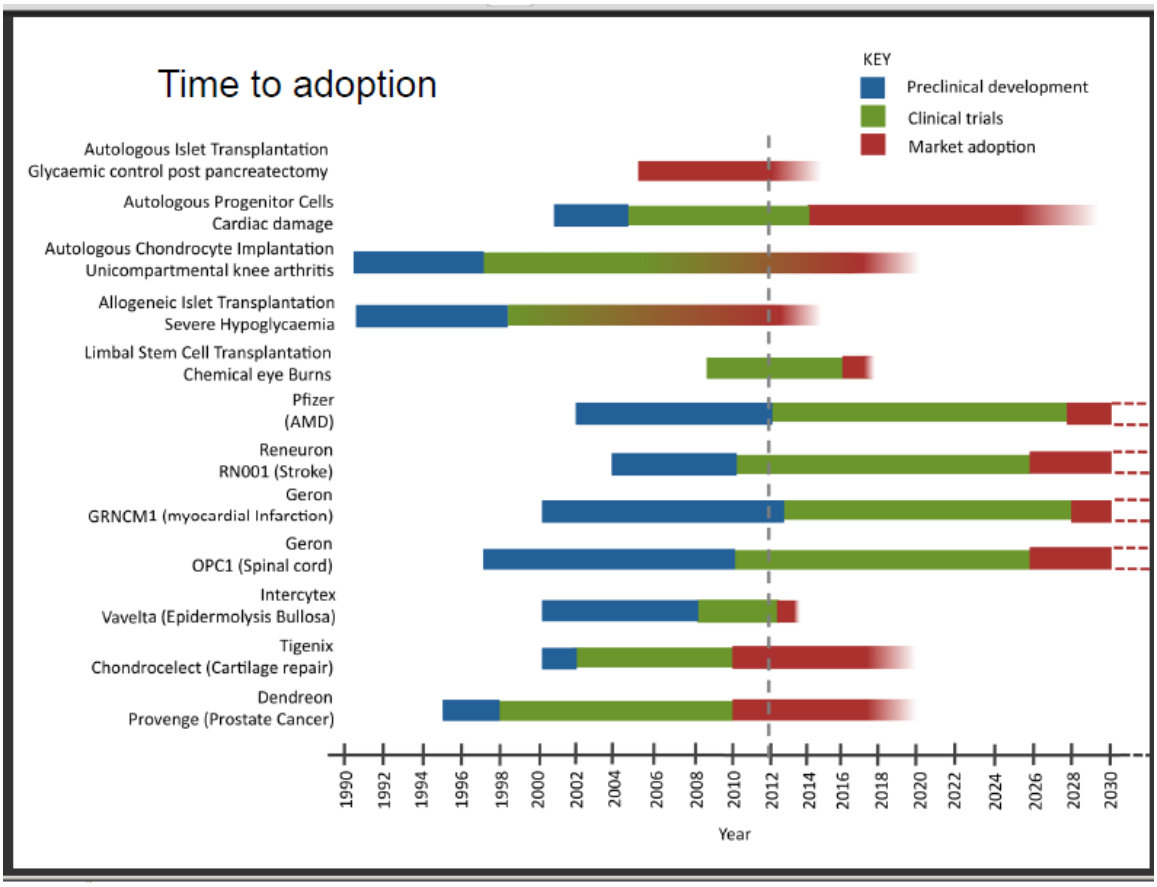
Interim conclusion: the current state of play

Regenerative medicine firms were, and remain, commercial undertakings burdened by profound anticipation, as enterprises in which substitutive medicine has long since staked its future (Johnson *et al.* 2010; Pangarkar et al. 2010). Thus, regenerative sciences are increasingly considered as valuable for the treatment of cancer, heart disease, and diabetes, as well as a plethora of orphan diseases for which there are few alternative conventional treatments. The possibility that the regenerative sciences might one day achieve this type of broad spectrum appeal, that is to say, diversify 'beyond substitution' is perhaps the key driver behind continued investment in the sector, despite its history of financial underperformance and negligible profitability (Lysaght, Jaklenec and Deweerd 2008; Mason and Dunhill 20008b; Pangarkar *et al*. 2010). However, whilst the licensing system has been centralised, the EU remains a fragmented healthcare market with diverse reimbursement systems and varied uptake of new medical technologies.

Demonstrating cost-effectiveness and gaining positive decisions from Health Technology Assessment (HTA) bodies is a significant challenge for industry and there is concern that HTA bodies have not begun to address the question of how to evaluate RM products and services. In relation to cost-effectiveness industrialists expressed concern that many of the cost-savings that RM products might offer would be *outside* the healthcare budget and that current methods of assessment would not take these into account. This is a key issues that needs to be addressed. Linked to the question of cost-effectiveness was the issue of business models. Many interviewees expressed the view that the RM sector had yet to

demonstrate the sustainability of business models for producing cell therapies. The cost of developing products, the cost of production and the size of the markets are all factors which will mean that time to clinical use/market will take many years for most products in the pipeline, as shown in Figure 1.13 below (from Whitaker, 2011). Successful products and/or procedures are likely to be those that have early links with clinicians and understand precisely what they need and how the delivery system will be able to make new offerings accessible and practicable, in terms of quicker application, greater longevity and/or enhanced efficacy measurable by clinical endpoints.

Figure 1.13



(Source: Michael Whitaker: presentation at REMEDiE international Conference, Bilbao, April 2011).

3.2 Regulation and the Governance of Regenerative Medicine

The REMEDiE project explored the regulatory aspects of the field in a number of ways. We examined (in WP2) the ways in which the sourcing of tissue – notably oöcytes for research – was subject to regulatory oversight and the degree to which this was effective. We also gathered international data on the diverse and divergent political cultures shaping the field (WP4), and the specific forms and levels of governance that characterise it, as one moves, for example, from the USA, Europe to China (WP3).

In regard to the first of these, despite being such a contentious issue, comparatively little is known on an empirical level about oöcyte procurement for research. Most literature focuses on normative and/or theoretical questions related to the question of commercializing the (female) body, questions of ethical permissibility of oöcyte

procurement for research, or questions of optimizing regulation. Existing empirical knowledge about oöcyte procurement largely refers to oöcyte procurement for IVF purposes (Waldby 2008; Ikemoto 2009). Some studies have critically analysed particular models of oöcyte procurement and individual policy debates (Throsby and Roberts 2008; O'Riordan and Haran 2009), but no empirical overview of oöcyte procurement practices for research purposes in Europe has been available so far. The objective of WP 2 was to close this gap and to map out and analyse the practices and institutions of human oöcyte procurement for research purposes in Europe.

Oöcyte donation for research purposes is among the most contested issues related to stem cell research. Although it has not become as politicized as embryo protection, oöcyte donation has caused considerable concern among academics, NGOs, feminists and researchers. In the past few years, it has attracted increased attention and became subject of a series of policy recommendations, guidelines, reports and debates. The main concerns are that the practice is onerous and bears a number of health risks to donors and that it may bring about a new form of exploitation of women.

Human oöcytes are required for somatic cell nuclear transfer and for the generation of parthenogenic stem cells. When somatic cell nuclear transfer (SCNT), also known as research cloning or therapeutic cloning, began in the late 1990s, it reinforced concerns among feminists about the emergence of a new biotech industry that would rely on access to women's bodies and bodily materials and might bring about new forms of exploitation of women. In SCNT, the nucleus of a somatic cell is transferred into a denucleated egg, which then is induced to develop into a embryonic stage of a blastocyst. Ideally, researchers would then derive stem cells and genetically-customized cells, tissue or even organs from that blastocyst that would not be rejected by the recipient's body. In 2008, the Californian biotech firm Stemagen announced it had managed to create the first cloned human blastocyst[6]. However, at the time of writing, no stem cell lines resulting from SCNT have been reported, and no patient-specific tissue has been created. Another research strategy to generate customized stem cell lines that also requires human oöcytes are so-called parthenogenic stem cells. Here, an unfertilised oöcyte is induced to develop into a blastocyst, from which embryonic-like stem cells are then derived. In January 2009, the International Stem Cell Corporation (ISCO), another Californian biotech firm, announced they had created tissue, namely layers of retinal progenitor cells, from human parthenogenic stem cells and had transplanted it into animals for testing[7].

We found that in Europe research in SCNT requiring human oöcytes is rare. Yet this situation might change again if the factors that influence demand and supply for oöcytes in the field of stem cell research change. For instance, many stem cell researchers have switched from SCNT research to induced pluripotent stem cells (iPS), viewing them as an alternative source of patient-specific stem cells without the logistical and ethical problems of using human oöcytes or embryos. However, if iPS[8] turns out to be too difficult and/or unsafe to deal with in the long run, this situation may change.

[6] http://www.stemagen.com/17jan08.htm, accessed 18.8.2010.
[7] http://www.internationalstemcell.com/news2009.htm##, accessed 18.8.2010.
[8] IPS cells form another strategy to create"patient specific" cell types, from which therapies could be developed. The procedure introduced by Shinya Yamanaka in 2006 consists of "reprogramming" somatic cells, for instance

One of the most significant reasons why this type of research is relatively rare in Europe, is the enormous logistical difficulty of acquiring sufficient numbers of human eggs, in particular of "good quality" eggs. Good quality eggs, from the point of view of research are mature, “fresh”, recently extracted eggs – in contrast to immature eggs or so-called failed-to-fertilize eggs left over from IVF. Further, oöcytes derived from younger women are of better quality. Logistical difficulties, however, do not exist in isolation from institutional and cultural contexts. The institutional and cultural embeddedness of procurement logistics becomes most obvious with regard to non-payment provisions and mechanisms of health care coverage. In Belgium, for instance, egg sharing has become rare since Belgian IVF couples were granted up to six free cycles of IVF in 2003 (Pennings 2006). Many interviewees told us that IVF patients and clinics are rather reluctant to give away oöcytes which the woman could use for her own IVF treatment. So-called non-patient donors, on the other hand, are reluctant to undergo the onerous procedure of oöcyte donation without financial gain. On the whole, several researchers we talked to emphasized that *very* few women were willing to go through the process of egg retrieval without being offered a material incentive.

Thus, one of the findings is that the feasibility and comparative attractiveness of stem cell research strategies which rely on human oöcytes should not be overrated. In Europe, they are on the contrary, rather limited.[9] Limiting factors are ethical concerns, both researchers' own concerns and perceived or anticipated public concerns, legal restrictions, availability of alternative research strategies such as iPS cells, logistical difficulties related to the delicate nature of human oöcytes (e.g. spatial distance between clinic and lab) and a great reluctance of women to donate without being paid.

On this last point the Council of Europe's Convention on Human Rights and Biomedicine of 1997 (Oviedo Convention) applies, but its provisions are rather vague. It prescribes in Art.21 that

> "The human body and its parts shall not, *as such,* give rise to financial gain."

Similarly, the Charter of Fundamental Rights of the European Union declares "the prohibition on making the human body and its parts as such a source of financial gain" (Art.3 Abs.2). Human oöcytes certainly form a part of the body; hence these provisions apply to both procurement for reproductive and research purposes. However, while both instruments seem to rule out payment *to the woman* from whom the oöcyte is retrieved, the concept of "financial gain" is not clearly defined. The Oviedo Convention does not rule out "compensation" but does not clarify either, where exactly the line is between "compensation" and "financial gain".[10] At the domestic level, all European countries where

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skin cells, by inducing viruses. The resulting cells are regarded as pluripotent and thus similar to human embryonic stem cells. Induced pluripotent stem cells are promoted by many as being more “ethical” than human embryonic stem cells or SCNT, because no eggs or embryos are needed for their generation. At the moment, however, it is not yet quite clear how strongly iPS cells actually resemble natural stem cells and how great the risk is that they cause tumors.

[9] The situation is different in California, where we also conducted interviews for reasons of comparison. Here, a number of research institutions are still experimenting with SCNT and/or the generation of parthenogenic stem cells

[10] As Judit Sandor pointed out at the REMEDiE Closing Conference 18.4.2011, Bilbao.

research cloning is legal have non-commercialization provisions in place that apply to oöcyte donation.

In Belgium, legal regulation of oöcyte donation applies both to IVF and research. Paying women in return for their eggs is prohibited; women may receive only reimbursement. The 2007 Law on Reproductive Medicine had made provisions for an eventual regulation of reimbursement through Royal decree, however this decree has not followed suit yet. Clinics, therefore, can proceed according to their own standards.[11] Belgian IVF medicine also knows the practice of egg sharing. It has become quite rare however since in 2003 Belgian IVF couples were granted up to six free cycles of IVF treatment. Ever since, egg sharing is more interesting to foreign women who come to Belgium for IVF and have to cover the costs by themselves (Pennings 2006).

In Sweden, the Genetic Integrity Act of 2006 prohibits trade in human body materials, including eggs, but does not specify the conditions of reimbursement. According to Swedish medical lawyer Rynning[12], the usual amount of reimbursement in reproductive medicine for egg cell donation is about 400€.

In Spain, a royal decree[13] has regulated egg donation since 1996.[14] Article 5 excludes payment for gamete donation. In 1998, the National Commission for Assisted Reproduction fixed the maximum amount of compensation for egg donation at. €600. Today, as several interviewees told us, so-called *compensaciones* of up to €1000 per cycle are the rule in the thriving private IVF sector in Spain. The Spanish law postulates coherent standards for biomedical research and reproductive medicine[15], allowing reimbursement or compensation without requirement of presenting receipts. Article 5 of law 14/2006 on human assisted reproduction postulates that donation must not be of commercial or profitable nature. Yet, it allows for compensations for expenses *and inconveniences*: so far, inconveniences do not need to be documented or quantified. In the U.K., in contrast, sperm, eggs or embryo providers up to now may receive reimbursement only for *documented* costs, including compensation for loss of earnings up to 250 GBP.[16] Again, this rule applies both to the IVF sector and to research. However, the Human Fertilization and Embryology Authority (HFEA) in the U.K. has just concluded a public consultation on "The changing landscape of donation", discussing whether the HFEA should revise its current compensation scheme for egg and sperm donors and switch to a model along the lines of the Spanish "compensations".[17] Its recommendations will be made public in July 2011.

A factor which is hugely important for this type of research is the infrastructural connection between stem cell research and IVF facilities, the IVF-stem cell interface (Franklin 2006), especially in the form of personal overlaps and close spatial proximity. Good quality oöcytes are an object of fierce competition between research on the one hand and IVF patients and

[11] Personal email communication with Belgian bioethicist Guido Pennings, 3.5.2010.
[12] Personal email communication 28.4.2010.
[13] *The Royal Decree* (Decreto real) 412/1996.
[14] See (Braun, Sandor et al. 2011)
[15] Concerning egg "donation", the Spanish Law on Biomedical Research of 2007 explicitly refers to the Law on Reproductive Medicine of 2006.
[16] http://www.hfea.gov.uk/500.html?fldSearchFor=payment, accessed 16.3.2010.
[17] See http://www.hfea.gov.uk/6190.html

clinics on the other. Offering financial incentives is a way for research to become more independent of these connections.

In regard to the broad, second theme relating to *political cultures* WP3 compared three major geo-political regulatory spaces of biomedicine and regenerative medicine: the US, Europe, and China. All three political systems have explicitly dealt with these pressing issues at a political and policy level, facing similar challenges. Most visibly, all three systems have undergone more or less significant institutional innovation. Pointing to convergence, all three systems have created and (partially) implemented some kind of risk-based approach to regulating regenerative therapies. However, debate over what a "regenerative" therapy is, how to define it, and whether to subsume it under existing legislation or to create some sort of *lex specialis*, has been a contentious issue.

We found important structural differences between the three countries regarding the regulation of the bio-economy and so regenerative medicine more specifically.

For the bioindustries, the US is a huge single market with one central competent authority, the US Food and Drug Administration (FDA). Preclinical and clinical R&D, as well as marketing authorization is regulated under the authority of the FDA, and FDA "project managers" usually follow a manufacturer and its products from the very beginning through the entire process of development. By contrast, in Europe industry is confronted with a highly diversified regulatory landscape. Despite increased efforts to harmonize European drug laws and regulations since the mid-1960s, regulatory idiosyncrasies persist and regulatory authority is divided between member states and the Community. Most prominently, clinical trials remain under the authority of national agencies, whereas marketing authorization (at least for "biologics" and advanced therapies) need to go through the Community's centralized procedure.

At the supranational level in Europe, regulatory competences are divided between the European Medicines Agency (EMA) and the European Commission. The "division of powers" between the two institutions provides for the EMA to deal with the technical and scientific details of the regulatory process and to develop advice or recommendations for the Commission, who finally makes the decision. Separating risk assessment ("impartial science") from risk management ("politics") has become an observable tendency in liberal "regulatory states" (Rothstein et al 2006).

The EMA operates in a different way to the FDA. The FDA combines, as many US independent regulatory agencies (cf. Gilardi 2008) do, legislative, executive, and juridical powers, whereas these powers are distributed in Europe between EMA and the Commission. The EMA is also a very young agency that has only incrementally expanded its competences, while the FDA has a long tradition and was often publicly very visible (and has been able to increase its reputation in the US public by preventing or averting public health crises, e.g. the Thalidomide disaster (Carpenter 2010, Daemmrich 2004).

Although outcomes are similar in the US and Europe, the ways in which cell products are managed are strikingly different. What was true for the GMO regulatory process, seems to hold true also for regenerative medicines regulatory policy making. As Vogel observes: "The

United States initially chose to regulate both GM food and seeds under existing laws, while EU legislation established a distinctive and complex set of new regulatory requirements that apply only to this new agricultural technology." (Vogel 2003, p 564).

Just as the FDA's regulation on stem cell-based therapies in the United States, and in Europe the European Commission's Regulation (EC) No 1394/2007 on advanced therapy medicinal products were preceded by a protracted process of negotiation, so in China the passing of the Regulations on Clinical Application of Medical Technology issued on 2 March 2009 by the Chinese Ministry of Health (MOH) involved a lengthy decision-making process. Before 2007, stem cell-based products and therapies were categorized as biological products, and applications for clinical trials had to go through the State Food and Drug Administration (SFDA) review according to Provisions for Drug Registration (SFDA Order No.17). However, during the first review processes in 2005 and 2006, the SFDA found it difficult to regulate stem cell-based products and therapies as drugs. On the verge of medical reform in China, SFDA no longer wanted to be responsible for the review. On 11 March 2008 the Chinese government announced a sweeping cabinet restructuring plan that SFDA would be put under the Ministry of Health (MOH) and the "Super Ministry of Health" would become the manager of areas such as medical services, food, drugs, and public health (Xinhua 2008).

After a long negotiation, it seems that an agreement has been reached between SFDA and MOH that in the future, regulation of stem cell clinical application would be promulgated and implemented by the MOH. A stem cell application would be applied and regulated not as a drug, but as a new medical technology for clinical application. It is interesting to note that in July 2007, MOH put "the Regulations on Clinical Application of Medical Technology (exposure draft)" and "the List of Category 3 Medical Technology (exposure draft)" on its website for more consultation and opinions from the public. This is a new and more frequently used device to generate participatory elements in the development of law in China. Meanwhile, the MOH entrusted the Committee of Association for Medical Technology Application (MTA) of the Chinese Hospital Association to constitute an expert committee and to draft "the Regulations on Human Stem Cell Clinical Application". On 24 October 2008, the MTA organized a workshop to discuss "the National Regulations on Clinical Application of Human Stem Cell Transplantation Technology (draft)". The participants recommended that the clinical application of embryonic stem cell technology should be performed more cautiously and strictly and follow ethical and moral norms. According to the Regulations of Clinical Application of Medical Technology, which came into effect on 1 May 2009, stem cell medical technology is defined as a "category 3 medical technology" and so deemed "ethically problematic", "high risk", and "still in need of clinical verification", and under the direct regulation of the MOH. The MOH has designated five institutions to review the field. However, because the detailed criteria have not been agreed, this review process has been delayed. In the meantime, the existing regulatory loopholes have been used by actors such as Beike, a medical company operating in the field of stem cell therapies and a global key actor in the world of stem cell tourism, to pursue a radical programme of clinical treatment, notably for overseas 'stem cell tourists'.

3.3 Ethical and Legal Developments and Tensions in the Field

National regulations and practices on RM differ, therefore, in the major regions of the global bioeconomy. This variation is extremely important and much more intense than in other fields of health technology. For instance, each legal system establishes specific regulatory frameworks regarding the derivation and use of stem cells. This fragmented regulatory landscape leads to forum shopping, stem cell tourism and exploitation of vulnerable population rights. This variation has also proved to be extremely inefficient from the point of view of resource allocation. An optimal level of international ethical and legal harmonization has proved to be very difficult.

REMEDiE aimed at understanding the origin, nature and consequences of the regulatory variation in which stem cell research is conducted throughout Europe. Laws in each jurisdiction are supposed to reflect a social consensus on the boundaries of what is considered acceptable for each society; however, legal frameworks for RM in each country cannot be fully explained by or attributed to the prevalence of a particular moral or political standpoint. The process of debate which leads to policy making is subject to degrees of contingency.

Consensus on controversial topics such as those relating to regenerative medicine is fragile and often challenged on moral and political grounds, with national states' sovereignty playing a key role in this matter, deflecting moves towards harmonisation. Moreover, consensuses tend to collapse rapidly as innovation disturbs agreed moral boundaries in this fast-moving field of science and technology. Finally, ethical consensus on RM is also dependent on other contingencies, including historical constraints, the existence of pressure groups, the prevalent political ideology, individual leadership of policy makers and their ability to create pragmatic regulations which "do the job" while avoiding controversy.

In this context, to what extent do bioethicists see themselves as promoting negotiation between conflicting values? How do the global structures and networks that support these functions interact and to what extent can bioethics be seen as a coherent epistemic community?

Does ideological similarity play a relevant role in mapping the communities of bioethics? Throughout the development of this research and the interviews with experts in the field, we have concluded that this hypothesis was only true in the case of major religions, especially Catholicism. Researchers who support the Church's official position on matters related to regenerative medicine create very cohesive and well-organised communities of bioethics, with their own media, impenetrable to those who are not members of these communities. Aside from this specific context, we have identified discrete communities of bioethics differentiated by cultures – especially shared language - and different academic traditions. The Anglophone area is the more internationalized or globalized one, in terms of participation of multinational bioethicists and international networks. It is also the strongest area in terms of number of participants, publications, active organisms, and funding.

One of the key domains within which bioethics affects the RM field is in regard to its role in the legal provisions surrounding patenting. Intellectual property rights, patents in particular,

can be especially important for bringing hESC inventions in regenerative medicine to the market.

Stakeholders in regenerative medicine need to exploit the benefits generated by the utilitarian trade-off between private and public interest in patent systems. Patents generate returns for publicly or privately funded research and attract investment from the market for expensive downstream activity when productivity is low or non-existent. Patents signal success in research and business, and when placed in the public they attract the attention of investors, competitors, patients and health care providers. Patents bring inventions into the public domain and enable access for others to the invention and further benefit generating activity based on the invention.

Human biological material, genes, tissues and cells serve as key research or analytical tools or products in regenerative medicine. Their treatment as things which may be subject to commercial exploitation by means of obtaining patents on them raises ethical objections on grounds of principles, inherent in the requirement of respect for human dignity, such as non-objectification, non-instrumentalisation and non-commodification applicable to the human body and its parts or elements. These bioethical requirements can be expressed in the regulation and application of the conditions of patentability as exceptions to patentability in the different patent regimes of the world. However, there are two challenges related to the possibility of establishing bioethical limitations on patenting human biological material:

- The diversity of local approaches to the applicable bioethical limitations in law; and
- The boundaries of the applicable bioethical limitations remain unclear and contested in law.

Human biological material is in fact regarded as patentable subject matter in the patent jurisdictions of the world. In Europe patent legislation, the European Patent Convention (EPC) and the EU Biotech Directive[18] (Article 5(2)), provides for the patenting as inventions of isolated elements of the human body or elements produced by means of a technical process subject to meeting the other requirements of patentability (novelty, inventive step, industrial applicability and not being excluded on public order or morality grounds). In contrast, in Europe, the simple discovery of one of the elements of the human body is not a patentable invention (Article 5(1)). In the US the human contribution of isolation, purification or modification renders human biological material as 'products of human ingenuity' as opposed to 'products of nature'[19] and thus patentable subject matter.

Patent regimes in Asia also accept the patentability of human biological material. Indian patent law denies patentability from a "discovery of any living thing occurring in nature"[20], but when the discovery leads to establishing practical use patentability is no longer refused.[21] The South Korean patent examination guidelines hold that "the method for artificially isolating substances from things in nature, not a mere discovery, is considered to

[18] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:213:0013:0021:EN:PDF.
[19] See, *Diamond* v *Chakrabarty*, 447 US 303 (1980).
[20] See *Kirin-Amgen* v *Hoechst Marion Roussel* [2005] RPC 9.
[21] Point 4.4.3, Draft Manual of Patent Practice and Procedure, 2008, ipindia.nic.in/ipr/patent/DraftPatent_Manual_2008.pdf.

be a statutory invention. So are the isolated chemical substances and microorganisms."[22] The Japanese patent examination guidelines include similar provisions.[23]

Diversity and contested boundaries: human DNA patents

Patent laws, within the above framework, have acknowledged isolated human DNA as patentable subject matter. The US and the European patent regimes both granted patents for the BRCA 1 and 2 genes and the associated diagnostic method. In Europe their patenting relied on the clear legal provisions of 'isolation' and 'technical process'; the ethical oppositions against the patents, a characteristic of European patent law, were rejected.[24] The US process focused on the fuzzy distinction between products of human nature and human ingenuity in US patent law which is now under reconsideration in an ongoing lawsuit by the American Civil Liberties Union against the BRCA 1 and 2 patents. The 2010 district court judgement, opposing previous practice, declared that isolated DNA must be regarded as products of nature, and thus unpatentable, as the process of isolation does not produce markedly different characteristics than those possessed by genes in the human body.[25] The case is now under appeal, and its outcome may change US patenting policy regarding isolated human DNA.[26] The potential global impact of US policy change is difficult to predict; in Europe only the amendment of the current liberal legislation would lead to alignment with the US practice.

Diversity and contested boundaries: human stem cell patents

In the current state of the law isolated human stem cells in general constitute patentable subject matter. Adult stem cells, pluripotent human embryonic stem cells (hES) and induced pluripotent stem cells (iPS cells) isolated from the human body are patentable products of human activity. Isolated human totipotent stem cells may, however, attract opposing legal characterizations. Patent regimes focusing on the act of isolation may treat totipotent stem cell lines as elements isolated from the human body by way of human activity and regard them as patentable subject matter. On the other hand, patent jurisdictions may also take into account the biological characteristics of totipotent stem cells and treat them not as products but as (potential) living (human) beings.

The clearest indication that totipotent cells may not be considered as patentable subject matter can be found in the European patent law. The EPC and the EU Biotech Directive (Article 5(1)) exclude from patentability the human body at the various stages of its formation and development. In the European Commission's interpretation human totipotent cells constitute a stage of development of the human body and are

[22] Point 4.1.2, Requirements for Patentability, 2010, www.kipo.go.kr/kpo/user.tdf?a=user.english.html.HtmlApp&c=60203&catmenu=ek60203.
[23] Point 1.1, Examination Guidelines for Patent and Utility Model in Japan, 2010, www.jpo.go.jp/cgi/linke.cgi?url=/tetuzuki_e/t_tokkyo_e/1312-002_e.htm.
[24] As applied in the BRCA 1 and 2 cases before the EPO, T 1213/0527 of September 2007 at www.epo.org/law-practice/case-law-appeals/pdf/t051213eu1.pdf; T 0666/05 of 13 November 2008 at www.epo.org/law-practice/case-law-appeals/pdf/t050666eu1.pdf; T 0080/05 of 19 November 2008 at www.epo.org/law-practice/case-law-appeals/pdf/t050080eu1.pdf. The ethical issues raised were informed consent, benefit sharing, and the impact of patent on public health.
[25] 09 Civ. 4515, patentdocs.typepad.com/files/opinion.pdf.
[26] This possibility was acknowledged in the US Government's amicus brief which followed the direction set in the district court judgement, www.genomicslawreport.com/wp-content/uploads/2010/11/Myriad-Amicus-Brief-US-DOJ.pdf.

unpatentable.[27] This position is supported by the ethically charged distinction in European patent law between isolated stem cells on the basis of their toti- or pluripotency, confirmed most recently by Advocate General Bot before the EU Court of Justice.[28]

There is no evidence that other patent jurisdictions would follow the same approach and exclude from patentability isolated human totipotent stem cells under the bioethical principle of non-instrumentalisation of the human body expressed in the above provision of European patent law. The invention/discovery or the products of nature/human ingenuity distinctions may not be able express the same restriction to patentable subject matter, though the general public morality clause, if a patent regime contains one, may prevent patentability. The diversity of local solutions may increase if the developing approach to human DNA patents finds ground in US patent law, which may be applied so as to exclude isolated human totipotent cells from patentable subject-matter on the ground that their characteristics are not sufficiently distinct from the characteristics they demonstrate in nature.

The European approach remains contestable. First, it effectively equates without further justification isolated totipotent cells, which are isolated biological material, with the human embryo and confers them the same moral status. Second, it avoids addressing the issue that totipotency is relative to the environment and isolated and modified totipotent cells are different from totitpotent cells in their natural environment. Third, it ignores an ethically relevant distinction alternative to the toti-/pluripotent concept pair; that between modified and unmodified stem cells. This was raised in EGE Opinion No. 16 (2002)[29] on the ethics of hESC patenting, which found that 'unmodified' hES cells and cell lines are not patentable as their patenting may violate the non-commercialization principle,[30] whereas in the light of the economic and social purpose of patent systems 'modified' hESC patenting could be allowed.

Patent regimes, with the exception of the US, are equipped with clauses which exclude inventions from patentability on grounds that the exploitation of the patent violates public order or morality, as enabled in international law by Article 27(2) of the TRIPS Agreement. The WTO (and TRIPS) member China's patent law contains an exception similar to that in other states stating that "no patent right shall be granted for any invention-creation that is contrary to the laws of the State or social morality or that is detrimental to public interest" (Article 5 of Patent Act).[31] The 1970 Indian Patent Act's morality clause provides that "inventions the primary or intended use or commercial exploitation of which would be contrary to morality" are "not inventions" (Article 3b).[32] The morality exception in South

[27] Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52005DC0312:EN:HTML.
[28] Opinion of Advocate General Bot delivered on 10 March 2011 in Case C-34/10 Oliver Bruestle, nyr.
[29] EGE Opinion No. 16 of 7 May 2002 on the Ethical Aspects of Patenting Inventions Involving Human Stem Cells, available at ec.europa.eu/european_group_ethics/docs/avis16_en.pdf.
[30] It was criticized that the principle used in this regard, 'closeness to the human body', was not established as a relevant moral consideration and as part of European culture, see Aurora Plomer (project coordinator): *Stem Cell Patents: European Patent Law and Ethics* – Report EU FP6 'Life sciences, genomics and biotechnology for health' SSALSSB-CT-2004-005251 (2008), www.nottingham.ac.uk/~llzwww/StemCellProject/project.report.pdf, at 33.
[31] See www.sipo.gov.cn/sipo_English/laws/lawsregulations/200804/t20080416_380327.html.
[32] See www.patentoffice.nic.in/ipr/patent/patents.htm.

Korean patent law reads that "inventions liable to contravene public order or morality or to injure public health shall not be patentable" (Article 32 of Patent Act).[33] The 1959 Japanese Patent Act's morality clause is formulated in the same way (Article 32).[34]

These morality clauses lack the detail and the distinctions applied in the European regime. Nonetheless, they offer potential bioethical limitations to the commercial exploitation of biomedical inventions. In the Indian patent office's interpretation being contrary to morality means that the use of the invention would "violate the well accepted and settled social, cultural, legal norms of morality". It produced an example, a "method of cloning", for an invention in breach of the requirements of morality.[35] The South Korean examination guidelines interpret the morality clause in the patent act as morality meaning a "moral sense generally accepted by a society or particular group of people".[36] There is no evidence that pluripotent hESC patents have been subject to opposition on public morality grounds in these states.

Patent law in the US, based on the patent clause of the Constitution (Section 8), does not incorporate a specific morality clause. It describes patentable inventions as "whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."[37] The 'moral utility' doctrine (Lowell v. Lewis, (1817) 15 F Cas 1018) has not been used in the case of biotechnology patents[38] and Congress has not considered the introduction of a morality requirement similar to other jurisdictions. The ethical debate relating to human stem cell research on the federal level focuses on providing federal funding to research[39] with state level legislation determining the ethical boundaries of biomedical research activity.[40]

European patent law offers the most developed system of public morality exceptions, a result of the EU Biotech Directive. It includes a general exception from patentability when the exploitation of the invention would be contrary to public order and morality (Article 6(1)) and a list of specific, ethically objectionable inventions, such as processes for cloning human beings, processes for modifying the germ-line genetic identity of human beings and uses of human embryos for industrial or commercial purposes (Article 6(2)).

The explicit public morality exceptions indicate that European patent law gives more weight to the ethical limitations of biomedical inventions than other patent regimes. More

[33] park.org/Korea/Pavilions/PublicPavilions/Government/kipo/law/patent/epat.html.
[34] www.japaneselawtranslation.go.jp/law/detail/?ft=1&re=02&dn=1&x=0&y=0&co=01&ky=patent&page=17.
[35] Point 4.3, Draft Manual of Patent Practice and Procedure, 2008, available at ipindia.nic.in/ipr/patent/DraftPatent_Manual_2008.pdf.
[36] Point 3.1, Requirements for Patentability, 2010, www.kipo.go.kr/kpo/user.tdf?a=user.english.html.HtmlApp&c=60203&catmenu=ek60203. As an example under the public order and morality rule it refers to a 'Bingo' apparatus.
[37] (Title 35 USC) (Section 101), available at http://www.law.cornell.edu/uscode/35/101.html.
[38] Libby Beadle, Selling the Stem Cell Short? An assessment of the patentability of the results of human stem cell research in New Zealand, *Canterbury Law Review*, vol. 10 (2004): 1–35.
[39] Gregory E. Pence, *Classic Cases on Medical Ethics: Accounts of the Cases that Shaped Medical Ethics* (New York: McGraw Hill Higher Education, 2008), at 185–189.
[40] See, for example, Article XXV of the State of California Constitution, www.leginfo.ca.gov/cgi-bin/waisgate?waisdocid=76297528920+0+0+0&waisaction=retrieve.

importantly, the European patent regime has not refrained from applying the exceptions to morally contestable patents. The 'industrial or commercial use of human embryos' clause proved especially controversial in the European history of human stem cell patenting separating Europe from the global market of stem cell patents and causing considerable tensions between European states with different moral approaches to human stem cell research.

According the current state of the law, pluripotent hES cells are not patentable under the EPC and presumably under the EU Biotech Directive as their process of derivation, which necessitates at the current state of the art the destruction of the human embryo from which the cell lines are obtained, constitutes an industrial or commercial use of the human embryo in the meaning of the applicable clause. There are considerable doubts whether the 'industrial or commercial use' clause may incorporate such 'embryo destruction' principle and whether any prohibition on the destruction of human embryos for research purposes should be considered instead under the general public morality clause of European patent law. This latter point is especially crucial as the 'industrial or commercial use' clause represents a Europe-wide, uniformly applicable bioethical limitation to patenting, which has the effect of transforming the 'embryo destruction' principle into a bioethical principle common to European states despite the differences between European states as to the ethical limits of human embryonic research. In contrast, the general public morality clause acknowledges a margin of appreciation of individual states making the question of patentability subject to the local ethical assessment of using human embryos for research purposes.

The first indication that (the prohibition on) 'embryo destruction' would become a common bioethical and legal principle in European patent law by way of the interpretation of the 'industrial or commercial use' clause was the European Patent Organisation (EPO) Enlarged Board of Appeal decision concerning the Wisconsin Alumni Research Foundation (WARF) hES cell line patents.[41] The decision in 2008 established that the 'industrial or commercial use' clause, which was introduced to prohibit the commodification of the human embryo, excludes the patentability of hES cells or cell lines on grounds that the production of hES cells requires the destruction of the human embryos used as sources. The Board held that the creation of the claimed product is part of its industrial or commercial exploitation, and when it involves the destruction of human embryos it will violate the said prohibition. In this case the performing of the invention (the embryo destruction) was contrary to the specific morality provision of the EPC.

The question is now before the EU Court of Justice equipped with jurisdiction to interpret the EU Biotech Directive which originally introduced the 'industrial or commercial use' clause to European patent law. The stakes are high as the judgement could open or permanently close the European patent market to hESC patents delivering or withholding the considerable benefits and the arguable disadvantages of patents to/from the European bioeconomy. The judgement will affect the patenting policy of the Member States and the patenting practice of the EPO, and the judgement will have to take into account the

[41] G-2/06, documents.epo.org/projects/babylon/eponet.nsf/0/428862B3DA9649A9C125750E002E8E94/$FILE/G0002_06_en.pdf.

differences among European states relating to the use of human embryos in stem cell research. The judgement will consolidate the interpretation of the EU Biotech Directive the provisions of which were introduced to establish a clear and coherent framework for patenting in biotechnology.

The case before the EU Court of Justice originated from Germany, where the Federal Patent Court held following EPO practice that the hESC patent in question, the 'Brüstle patent', was in breach of the 'industrial or commercial use' clause as the destruction of human embryos was a "real and integral part of the invention."[42] The German court's interpretation was strongly influenced the German Embryo Protection Act which prohibits the use of human embryos for purposes other than those from which the embryo may receive direct benefits (e.g. diagnosis or treatment of that embryo).

An indication how the EU Court of Justice would approach this question and consolidate the interpretation of the EU Biotech Directive can be found in the Opinion delivered by Advocate General Bot in the case before the court. It set a direction similar to that indicated by the EPO Enlarge Board of Appeal and the German patent court. The Advocate General suggested that the clause on the industrial or commercial use of human embryos excludes from patentability inventions which necessitated the destruction of human embryos.[43]

The Opinion is not binding on the EU Court of Justice, and it is not excluded that it will take into consideration the criticisms formulated against the current interpretation of the 'industrial or commercial use' clause. The Court of Justice, as opposed to the Advocate General, may consider the wider social and economic impact of applying the 'industrial or commercial use' clause to hESC patents and may take into account the interests of Member States where human embryonic research is regulated permissively and have an interest in global hESC research, and respect the preferences of States where human embryos are given more stringent protection. More importantly, the judgement will have to establish an interpretation of the morality clauses in European patent law which follows from the EU Biotech Directive and from the relevant bioethical principles, from human dignity in particular.

One option is to follow EPO case law and the opinion of the Advocate General. The alternative route would be dropping the 'embryo destruction' principle from under the 'industrial or commercial use' clause,[44] and examine hESC patents under the general public morality clause. This would enable the accommodation of local discretion in assessing whether the destruction of human embryos for research is acceptable in that particular community (state). This option would safeguard the diversity among European states in regulating human embryonic research.

[42] Judgement by the German Federal Patent Court, AZ: 3 Ni 42/04 (5 December 2006), juris.bundespatentgericht.de/cgi-bin/rechtsprechung/document.py?Gericht=bpatg&Art=en&sid=061f0f9e4b6bfd679ba46c7b1fd93fcb&nr=1909&pos=0&anz=1&Blank=1.pdf.

[43] Opinion of Advocate General Bot delivered on 10 March 2011 in *Case C-34/10 Oliver Bruestle*.

[44] The combination of the clause with the 'embryo destruction' principle was declared to have no legal basis under the EU Biotech Directive. See Plomer, *op. cit.*, 83.

On the level of decision-making in the European patent system the solution accepting the plurality of local bioethical approaches would cause considerable difficulties. Without being able to rely on an explicit morality clause imposing uniform requirements on the Contracting States the EPO will need to apply the general morality clause of the EPC (and the EU Biotech Directive) having regard to the diversity of national approaches on the use of human embryos for research purposes. Adopting the highest standard under the general clause and denying patentability from hES cells would satisfy the States with a prohibitive attitude to human embryonic research but it would be incompatible with the leeway granted under the general morality clause to all States in the European patent system. In contrast, allowing the patentability of hES cells under the general morality clause, having been unable to establish the 'embryo destruction' principle as a common European moral requirement, would satisfy the States with liberal regulation on stem cell research and it would enable States with a prohibitive regime to refuse enforcing the patent within their jurisdiction. This is a compromise solution and the only workable solution in a pluralist, multi-layered regime. However, the fragmentation of the system, which would follow from this approach is contrary to the rationale of the EPC and the EU Biotech Directive (Article 6(1)).

4. The potential impact of the project and its wider societal implications

4.1 The REMEDiE project has, for the first time, provided a detailed and critical analysis of the current and likely future prospects of regenerative medicine within Europe and more widely. We summarise below its key lessons concluding with a series of policy recommendations for European MS, the Commission and Parliament.

Within Europe the RM industry is highly heterogeneous, not only in terms of the different sectors, but also in terms of the multiple technological approaches – different cell sources, in- and ex-vivo gene therapies etc – being developed within each sector.

At the same time, it is important to note that the different sectors and technologies do not operate in isolation but can also act in combination with each other to develop novel regenerative strategies, for example genetically modified cells and combined cell and bioscaffold treatment options. In terms of the challenge of regulating this variety of novel technologies the centralised ATMP has been generally welcomed by industry stakeholders, primarily because of its focus regulating the *means* and not *outcomes* of innovation. However, it is also worth noting that the only cell therapy approved so far via the ATMP pathway has been an autologous, somatic cell TE product for cartilage repair. It is likely that a few well-placed 'trailblazer' firms, somewhat analogous to Geron in the US, will be the first to bring one or more of the stem cell therapies currently in clinical trials through the ATMP approval process. These 'first in' firms may well need additional support in order to establish an accepted approach that other firms will be able to follow, but will depend on access to public resources (e.g. facilitation through healthcare systems) and not just venture capital support, important though this is. As we saw earlier, such support can ultimately be damaging to firms: overinvestment and overvaluation remain the most significant structural variables clouding a picture of nascent growth within a regenerative medicine industry typified by stark performance contrasts. The existence of some leading firms is a sign of recovery, demonstrating that regenerative entrepreneurialism has a future, if in relation to a very small group of pioneering firms. This optimism could prove misplaced nonetheless, as

most of these enterprises have yet to gain a solid grounding in clinical product markets. Our data augers a further danger, in so far as investors seem to have overestimated the true value of better companies, between 2005-2009, as evidenced by the helter-skelter nature of percentage growth rates for some firms that we identified, thus far. If investors concentrate their attention solely on these firms in years to come, this might once again create the conditions for a 'bubble', similar to the periods of financial retrenchment seen in 2001 and 2007-2009, respectively.

At present, all our data indicate the current significance of autologous-derived therapies, trials and patenting activity. In all cases, compared with Europe, the US is the leading region globally and by a significant order. This is despite having had a restrictive legal regime at the Federal level over recent years, demonstrating the importance of the local, State-based sponsorship of the field, especially in California and Massachusetts. Although there are strong indicators pointing towards a potentially competitive position for the EU within the global RM bioeconomy - a solid research base, a high level of scientific output and a diverse group of RM firms - the global picture in the wider biotech sector suggests that the US will rapidly establish an unchallengeable dominance, based on three key advantages, namely, higher levels of R&D funding, greater access to VC finance, and the single largest market for health technologies. One leading EU firm suggested that their main US competitor was "playing in a different league" with five to ten times the amount of VC funding. One venture capital executive emphasised the disparity in growth funding, suggesting that European VC firms can build a firm to a € 50M valuation but are then forced to sell because they lack the resources to continue to the next stage. This lack of capital could have a number of consequences for commercial strategy with companies being forced into premature decisions to seek a public listing or to enter clinical trials.

Germany, one of the stronger players in RM, resembles the United States - a pharma/biotech powerhouse making a major public investment in RM despite being constrained by national restrictions on hES research. The Germans seem to have a clear European lead when measured in a number of key metrics (participation in research with other key nations like US and UK, number of RM companies, and stem cell patents, leadership of EU FP stem cell projects), suggesting that its more restrictive approach to hES research may not be an insurmountable hurdle if there is strong public investment and a robust pharma/biotech sector. This point needs to be borne in mind during the heated debate whether hES can be patented or not. With its strong emphasis on translational research in RM and its track record in the commercialisation of biotechnology, it may be that Germany will become a test-bed for resolving some of the key challenges associated with the clinical application and commercialisation of RM therapies. Paradoxically, of course, Germany is one of the more restrictive of regulatory regimes in Europe.

REMEDiE has identified diverse regimes regulating the ethical boundaries of biomedical research activity and the ethics of commercializing biomedical innovation in the world. These differences have an impact on the research environment, the model for financing research and translational activity and the use of intellectual property rights in the course of

biomedical research. The taxonomies label the different national regimes on biomedical research as permissive (liberal), intermediate and restrictive.[45]

Permissive regimes (UK, Japan, India and China) allow research on human embryos and stem cell derivation from them.[46] The permitted sources are supernumerary IVF and SCNT embryos. They apply a temporal limitation to human embryonic research, such as the '14 day rule' associated with the appearance of the primitive streak in the human embryo. Intermediate regimes (France and South Korea) allow research with limitations on embryos obtained from limited sources.[47] Restrictive regimes (Germany) prohibit human embryonic research for general therapeutic purposes and ban hESC derivation, and they may prohibit using hESC lines and products.[48] In the US stem cell research is regulated on state level, if regulated, without the federal level being constitutionally able to impose a uniform moral position. The federal disapproval of stem cell research is expressed in fiscal legislation prohibiting the federal funding of stem cell research[49] which is now under challenge before the courts.[50] While these differences are highly significant, it does not mean that a so-called restrictive regime means limited activity, for as we have seen Germany is a leading RM hub in Europe precisely through either non-hESC routes or via importing hES-based material.

The introduction of a human rights perspective on human embryonic/stem cell research has not affected the diversity of ethical and moral approaches. The Oviedo Convention on Human Rights and Biomedicine[51], created to establish a European framework concerning the human rights limitations of biomedical research and therapy, builds on the protection of human dignity and integrity. The Convention accepts the margin of appreciation of Contracting States on bioethical issues and leaves the question of hES research partially open by the provision that "where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo" (Article 18(1)). Arguably, this could encompass the destruction of human embryos in an adequately safeguarded process for the purpose of hES derivation. The more contentious provision in Article 18(2), which has prevented the ratification of the Convention by all Council of Europe States considering it as either liberal or conservative, prohibits the creation of embryos for research purposes.

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[45] www.stemgen.org/mapworld.cfm and Rosario M. Isasi & Bartha M. Knoppers (2006) Mind the Gap: Policy Approaches to Embryonic Stem Cell and Cloning Research in 50 Countries, *European Journal of Health Law* 9: 13.

[46] *United Kingdom:* Human Fertilisation and Embryology Act (HFEA) 1990 (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsLegislation/DH_080205); *Japan:* Act on Regulation of Human Cloning Techniques 2000 (www.japaneselawtranslation.go.jp/law/detail/?re=02&dn=1&x=0&y=0&co=1&yo=&gn=&sy=&ht=&no=&bu=&ta=&ky=cloning&page=1); *India:* Ethical Guidelines for Stem Cell Research 2007 (www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf); *China:* Ethical Guiding Principles on Human Embryonic Stem Cell Research 2003 (www.qmlc.com.cn/edit/UploadFile/info/2009430113029216.doc).

[47] *France:* Public Health Code, Article L2151-2 and L2151-4 (www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006072665&dateTexte=20101017), *South Korea:* Bioethics and Safety Act 2004 (eng.bprc.re.kr/gz06.htm?number=8).

[48] *Germany:* The Embryo Protection Act (www.bmj.bund.de/files/-/1147/ESchG%20englisch.pdf) and the Stem Cell Act (www.bmj.bund.de/files/-/1146/Stammzellgesetz englisch.pdf).

[49] The Dickey-Wickers amendment, a rider attached to the Balanced Budget Downpayment Act 1996,

[50] United States District Court for the District of Columbia, Civ. No. 1:09-cv-1575 (RCL) and United States Court of Appeals for the District of Columbia Court, No. 10-5287, 9 September 2010.

[51] Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, conventions.coe.int/Treaty/en/Treaties/Html/164.htm.

Key lessons relating to corporate policy and practice

- European RM firms are not distributed evenly among member states but are concentrated in established (France, Germany, UK) and emerging (Spain, Switzerland) hubs.
- The majority of firms in all states are small and financially vulnerable, and the concentration of companies in certain locations does not necessarily reflect the individual strength of those firms.
- Having a national strategic plan for the support and development of regenerative medicine is a key pre-requisite for the development of an RM sector. Most national strategies to date have focused on supporting basic or translational research but there is also support for commercialisation via state pump-priming – for example the UK Technology Strategy Board has recently committed £21.5M to fund commercially-oriented RM projects. This may help to relieve the pressure on firms often associated with dependency on venture capital.
- The following core components of national strategies for RM have been identified: a enabling legislative framework for hES research (though this need not be seen as determinant of a country's capacity to promote the field, as in Germany and, in part, the US); dedicated funding including the development of major research centres and shared infrastructure such as stem cell banks; the creation of a national network to promote scientific collaboration; the promotion of public-private partnerships and international research collaborations.
- There may also be examples of best (and worst) practice to be gleaned from national strategies and practices – Sweden and Belgium, for example do not have many RM firms but they do have a few highly performing RM biotechs.
- As part of the broader reform of EU innovation strategy, it is likely that greater coordination of the multi level governance framework will be necessary to ensure more effective support for the RM sector and to avoid unnecessary duplication of regulatory activity.

Key lessons relating to ethical and legal policy and practice

Overall, there are two issues here which deserve attention: the sourcing of RM tissues, and the patentability of tissues derived specifically from embryonic material. In regard to the first, oöcyte procurement has been important for research, and we have identified a move in research from "poor quality" oöcytes to "good quality" oöcytes. This implies a shift from less to more controversial practices of oöcyte procurement, insofar as good quality eggs from IVF patients are also of interest for the IVF patient herself, or they come from non-patients who had been offered material incentives to undertake a risky and difficult procedure. There is also a trend towards material incentives. This cannot be adequately grasped in terms of commercialization vs non-commercialization but rather as a variety of crypto-commercial strategies that enable more or less open monetary transactions, while at the same time avoiding open clashes with existing non-commercialisation provisions. We found that two different models have evolved over the past few years that allow researchers to offer economic incentives while

circumventing non-payment provisions: “egg sharing” and the reallocation of compensated oöcytes.

- One conclusion that could be drawn from these data is that the trend towards material incentives is a strategy to *release* researchers from the infrastructural requirements that tie them to the IVF sector. Being able to offer money or material incentives makes researchers less dependent on the good will of IVF patients and clinics and thus offers a way to *loosen* the IVF-stem cell interface. In light of these trends and shifts, we would predict that research strategies that require the use of eggs, such as SCNT or parthenogenetic stem cell research, will either cease (sooner rather than later) or we will see a shift from crypto- to outright commercialization of human oöcytes. The latter seems the more likely in light of the current debate in the U.K. on revising the existing reimbursement scheme where many actors advocate a switch to the more generous Spanish compensation model. The 2009 decision by the New York Empire State Stem Cell Board may generate a pull in the direction of payment too.[52].
- What the empirical data show is that there is a strong tendency to undermine and circumvent existing non-payment provisions through introducing material incentives in a legal grey zone between outright payment and strict non-payment, inter alia through "compensations" without the requirement to document expenses. If the European Union and the Oviedo Convention signatory states take that principle seriously, they should set up appropriate measures to foreclose lump-sum compensations in exchange for human oöcytes.
- With respect to the question of patentability, inventions in human embryonic/hES research represent a particularly difficult ethical issue for European patent law as many issues within this area remain ethically controversial. Patenting hES cells or cell lines must, for example, take notice of the source of these cells, more precisely, the consequences of their derivation: the destruction of the human embryo.

- The destruction of the embryo in order to harvest stem cell lines regardless of the origin of the embryo (viable donated supernumerary IVF from a parental project, non viable IVF embryo from a parental project, IVF and SNCT research embryo) is the main source of the ethical controversy surrounding this technology. The implementation of an ‘embryo destruction’ principle in patent law within the examination of patentability remains a pressing question in different patent jurisdictions.

4.2 Overall lessons for policy: recommendations from the REMEDiE project

The findings of this report clearly illustrate that RM innovation within the European Union is taking place within a complex multi-level governance framework which comprises sub-national, national and transnational networks and institutions. International alliances,

[52] The Board had decided that it was appropriate for women to be compensated for giving their oöcytes to stem cell research and that payments of up to $10,000 should be reimbursable as allowable expense under New York State Stem Cell Science (NYSTEM) contracts. See http://stemcell.ny.gov/news.html [Accessed 22 November 2010].

whether within the EU or beyond its borders, are seen by most stakeholders as a vital part of this. Our key policy recommendations below seek to address this and to do so informed by an understanding of the scientific, corporate, clinical and ethico/legal and political challenges that have been discussed above:

1. **Governance**.
   Coordination for effective policymaking requires cooperation across departments and between member states.
   a. A forum should be established which brings together all relevant EU departments and bodies, e.g. DG Research and Innovation, DG Sanco, DG Enterprise and the EMA. There are many substantive issues we have noted that need cross-department collaboration; for example, the tendency to undermine and circumvent existing non-payment provisions in regard to sourcing tissue; the need to review existing clinical trials requirements and further moves towards harmonisation; the need to clarify patenting law in relation to the destruction of embryonic material, and so on.

2. **Creating a strategy**
   a. Leading actors within RM in the EU should be brought together to explore potential for coordination and cooperation.
   b. JRC IPTS (Seville) has a strong track-record in policy reports on health biotechnology (including ATMPs) but has recently discontinued this activity. Additional funding should be provided to IPTS so that it can resume this activity.

3. **Research Infrastructure**
   a. Long-term funding should be given to infrastructure which facilitates research: creation of a European RM network including funding of annual meetings, renewed funding for a hES registry and enhanced cooperation between stem cell banks within the EU. The network should play a leading role in public engagement on RM issues as well as sharing practice on national strategies (especially drawing on practice within the three European hubs we have identified).

4. **Public sector innovation and link to the wider health care system**
   a. Increasing policy attention is focused on the role of innovation within the public sector. This may be of particular importance if, as many believe, hospital-based service delivery may be the best way to get (autologous) cell therapies in the clinic in the near-term.
   b. Many of the cost-savings that RM products might offer will be *outside* the healthcare budget and current methods of assessment (HTA) do not take these into account: this failure needs to be factored into clinical procurement and reimbursement programmes.

5. **Exporting RM products outside the EU.**
   The European Union should facilitate RM companies establishing themselves in markets outside the European Union.

a. An office should be established which gathers intelligence on the regulatory and reimbursement regimes in key international markets and which can provide advice and support to RM companies.
b. Support should be given to facilitate companies creating commercial alliances which may be necessary to enter non-EU markets.

6. Regulatory harmonization

The EU has been characterized as a regulatory state, an institution whose primary mode of policy making is regulation. The creation of a single EU process for the licensing of RM products through the ATMP has been a major achievement. The EU has unique strengths in the formation of regulatory networks and the processes of regulatory harmonization which may be of significant utility in supporting RM innovation within the EU.

a. A first step may be a negative one i.e. to identify those areas where the EU does not have capacity to act. Divergence of views between member states means that creating a common EU position regarding hES research is impossible and any effort to do so would be a diversion from more fruitful activities, related to non-hES work
b. There are aspects of the current regulatory regime which require further harmonisation e.g. regulation of clinical trials and human tissue.
c. The ATMP's hospital exemption requires clarification. Governance of those services/institutions which are exempt could be harmonized by processes outside the ATMP regulations.
d. Consideration should be given to potential role for the Institute for Health and Consumer Protection (JRC ISPRA) in technical standard-setting (there is already clear overlap of interest in some areas e.g. use of stem cells for toxicology testing is relevant to ISPRA work on major programme of work on alternatives to animal testing).

7. Intergovernmental alliances and international harmonisation

RM forms part of a global value chain of innovation. The EU should plan to access this value chain more efficiently.

a. The EU should seek intergovernmental alliances with states where RM is a priority and which have particular strengths from which the EU would benefit through an exchange relationship.

b. EMA should be given additional funding to enhance its work on international harmonization that promotes the EU model of innovation. Building on existing activity (e.g. the bilateral relationship with the FDA on pharmacogenetics, work within the ICH, and bilateral relationships with regulatory agencies in NIEs like China and India), the EMA could deepen and bolster its regulatory advisory and enabling capacity.

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Photographs from some key meetings of the Consortium

Kick-off meeting, York, May 2008

Wisconsin-Madison, 2nd Internaitonal Conference, June 2010

Bilbao, final international conference, April 2011

SEVENTH FRAMEWORK PROGRAMME
THEME SSH-2007- 8.1

PROJECT FINAL REPORT

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Project acronym: REMEDiE

Project title:
Regenerative medicine in Europe: emerging needs and challenges in a global context

Funding Scheme: Coordinated Action

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Annexes

The following annexes, which do *not* appear with the preceding report for publication, provide more detailed reports on each of the Workpackages. These reports inform the range of papers both published and in preparation during the period of dissemination activity following the end of the formal contract period of the project. They are provided as a set of (Non-public) Deliverables for the Commission.

Annex 1 REMEDiE Work Package 1: Final Report

The EU in the global market: Investing in regenerative medicine

Michael Morrison (Lead), Beth Kewell, Nik Brown

Introduction

The primary objectives of Workpackage 1 (WP1) were to investigate the contemporary position of the European regenerative medicine (RM) industry and to track and evaluate patterns of investment in RM technologies. Two discrete approaches were developed to address these objectives: an extensive financial analysis of the economic standing of the global RM industry and discussion of the position of European firms within this sphere, and a comprehensive study of the extant 'universe' of commercial companies developing regenerative medicine products. This part of the WP1 report presents the findings of the latter strand of investigation and discusses some of the key policy challenges for the European regenerative medicine industry identified by this work.

Defining Regenerative Medicine

There is at present no single, universally agreed definition of RM, although recent years have seen a number of attempts to delineate the field published in the scientific literature (for example; Atala, 2007; Kemp 2006; Daar & Greenwood, 2007; Mason 2007a; Mason & Dunnill, 2008a). In order to evaluate the commercial development of regenerative medicine in Europe, it was therefore necessary to produce a project-specific definition of RM that could be operationally applied to determine which firms should (or should not) be included in the 'company universe'. Consideration of which technologies and practices should be incorporated under this definition was guided by the following core tenets of work-package 1:

- A focus on novel, disruptive technologies that pose specific challenges for governance regimes, industrial manufacturing, and business strategies.
- In order to be considered 'regenerative', technologies and products must aim to restore, maintain, or enhance tissue, cell or organ function by stimulating, or augmenting the human body's inherent capacity for self-repair.

Approaches utilising human cells, including stem cells, gene therapy, and bioscaffolds (made from collagen or synthetic polymers) are all considered to come under the remit of this definition. The 'short-form' project definition is usually stated as follows:

> *Regenerative Medicine is the use of cells including stem cells, genes (via gene therapy), and bio-scaffolds to stimulate or augment the body's capacity for self-repair.*

Companies developing small molecule or macromolecule (e.g. recombinant protein) therapies intended to have 'regenerative' effects *in vivo* by stimulating cell division, activation etc are not considered under this definition. These types of products largely share the established regulatory pathways, reimbursement strategies and manufacturing processes of bio-pharmaceutical drug development. They do not involve any significant investment in the specialised biomaterials of regenerative medicine, nor are they likely to encounter any of the same regulatory, financial or technological barriers to development. Examples of companies self-identifying as 'regenerative medicine firms' but excluded under this approach are Renovo (Manchester, UK), developing recombinant growth factors as a therapy to regenerate tissue damaged by scarring; NKT Therapeutics (Waltham, MA, US) which uses antibodies to activate subsets of white blood cells in vivo to proliferate and fight disease (i.e. induced cell therapy), and NeuroNova AB (Stockholm, Sweden), which is developing small molecule and protein therapeutic drugs aimed at inducing regeneration in adult neural stem cells. Xenotransplantation, cell-based vaccines, traditional prosthetics or implantable medical devices (such as pacemakers), antisense or interference RNA technologies, and organ transplants are also considered to lie outside the purview of the project definition of RM as they are either insufficiently novel or are not considered to act in an appropriately regenerative fashion.

Alongside companies developing RM products for therapeutic purposes, the European company universe also includes 'secondary' firms that supply specialist services (e.g. stem cell specific media and reagents, bio-reactors optimised for growing human cells in three-dimensional configurations for tissue engineering) or technology platforms (tissue and biobanking, pluripotent cell culture for NCE screening) that engage with and support the scientific and commercial development of regenerative medicine. Firms that supply basic laboratory equipment or universal reagents and materials for cell culture (e.g. standard media, Petri dishes) are excluded as these are not specific to regenerative medicine. A decision was made not to include umbilical cord blood banks as the cord blood banking economy was already the subject of a separate study[1].

Generating the European Company Universe

Initially a basic list of more than 240 companies described as being involved with RM was compiled from a range of publically available secondary sources. These include data from published reports on regenerative medicine, notably Martin, Hawksley and Turner (2009), companies listed in commercial reports on RM, stem cells, gene therapy etc produced by *Data Monitor*, *Market Research.com* and similar organisations, membership lists produced by the UK Bio-Industry Association and corresponding organisations in other countries, and news articles from online biotech-industry news providers including *Fierce Biotech*, *Xconomy* and *European Biotechnology News*. This list was then reviewed to remove companies that were not headquartered in a European country, companies that were no longer extant as a result of closures, mergers or acquisitions, and those companies that did not fit the project definition of RM. Large pharmaceutical companies were also excluded from the European list on the grounds that, while they may have a demonstrated interest in RM, their activities are difficult to assign to a given region for comparative or profiling processes, and their

[1] See http://www.york.ac.uk/satsu/stem-cell-banking/

interest in regenerative medicine (often in cell screening for drug discovery) is only a small part of their main activity and not a significant part of their overall R&D expenditures. 'Big Pharma' involvement is covered instead by the WP 7 global database.

Much of the company evaluation was done through online searching for company websites. This approach has some obvious limitations - very small start-up firms are less likely to have an online presence compared to established firms, online information is hard to verify and may be outdated, and use of firm websites is subject to companies mediating the publicly available information about their technology, investment levels and progress in commercial development of RM therapies. However, the internet remains the most readily accessible source of information about most of these companies and every effort was made to ameliorate some of these limitations by triangulating data from multiple sources wherever possible to improve veracity of included data etc. The remaining firms were classified in terms of certain basic characteristics – firm age (by date of founding), firm size (by number of employees), geographical location (by nation state) and technological approach – cell therapy, gene therapy, bioscaffolds, and service provision (secondary companies as described above) prior to more detailed analysis.

A second layer of analysis was then applied, involving further categorisation by whether products were marketed or still in development - and if the latter, the stage of the regulatory approval process (preclinical, phase I-III) - the disease categories that products and product candidates were intended to treat (e.g. cardiac disease, diabetes, wound healing) and, for cell therapies, division by autologous or allogeneic approach, and cell type employed – adult, embryonic, foetal or cord blood-derived stem cells, somatic (non-stem cells) and reprogrammed (induced pluripotent) cells.

Data collection on European RM firms was ongoing throughout the duration of the project. The European company universe was revised approximately every six months following its initial formulation, and 'work in progress' iterations of the dataset were presented at the project meetings (beginning in Vienna in 2009) for feedback and evaluation by the other project members and, at the Wisconsin meeting in 2010, by a wider academic audience. Project members, including IAG members, based in European countries were asked to carry out online searches for 'regenerative medicine companies' in their native languages to offset any English-language bias in WP-1 data collection, and they also contributed knowledge of national resources such as the recent report by the LEEM (the French pharmaceutical industry association) on RM in France and the network of Bioregions in Germany[2], many of which provide searchable databases of local biotechnology firms. The monitoring and revision of the company data allowed the incorporation of information from online news services (including monitoring closures, mergers and acquisitions) to keep the European company universe up to date. Company websites were also checked for evidence of updating over time as an additional way of gauging whether certain firms were truly active or not.

The European Company Universe: Descriptive Characteristics

[2] http://www.biodeutschland.org/ak-bioregio.html

A total of 112 currently active European firms meeting the project definition of regenerative medicine were catalogued. The following section will present an initial characterisation of the European RM industry in terms of its geographical distribution, composition firm, age, size and other descriptives.

Geographic distribution of European RM firms

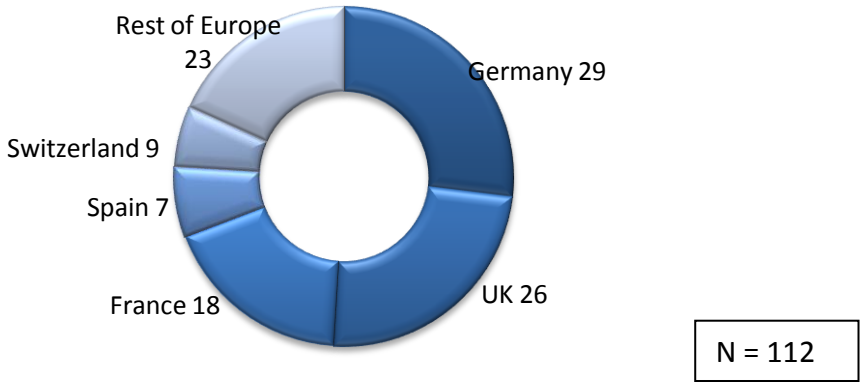
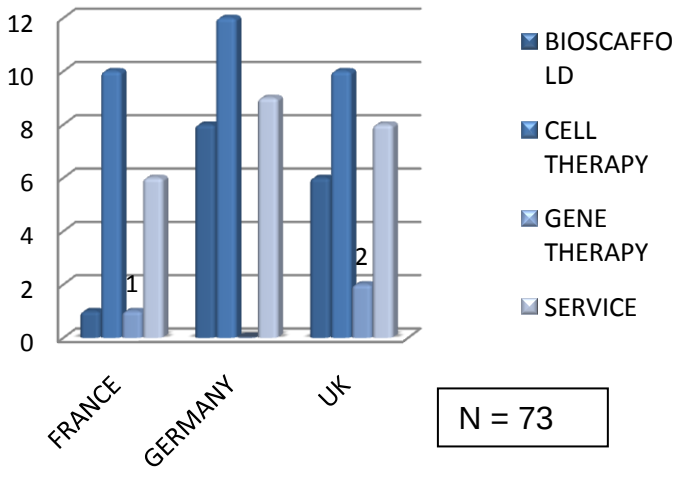


Fig 1.0 European RM firms by country

The European RM industry is heavily concentrated in countries to the North and West of Europe, with very little commercial activity in Southern and Eastern areas. As fig 1.0 shows there are three major hubs of European RM activity; Germany, the UK and France. The next most active states for commercial development of RM are Spain and Switzerland, while the remainder of European companies are spread across a range of territories including Belgium, The Netherlands, Sweden, Denmark, Italy and Greece where each of these countries has at most two or three genuine RM firms within its borders. Many European countries have no commercial regenerative medicine presence at all, including the majority of states that joined the European Union in 2004.

Perhaps unsurprisingly, the major national players in commercial RM are generally those countries that have strong existing life-sciences and biotechnology industries and the attendant infrastructures. Spain, as an exception, is an important example of a country which has developed a strategic approach to the support of RM as part of a broader programme to *build* a national biotechnology sector. It is not co-incidental that the three major European hubs all have national strategies for the development of RM in place. The UK stem cell initiative and the subsequent Patterson Report in 2005 was perhaps the first attempt in Europe to construct a coordinated national strategy for regenerative medicine (albeit one which was highly focused on stem cell research). Other countries have since followed suit to varying degrees.

Fig 1.1 Breakdown of European Hubs by sector



In Germany, strategic support has taken a range of forms, notably the development of five major RM research centres backed by the Federal Ministry for Education and Research (BMBF) and the German Research Association (DFG), as well as a number of scientific networks and commercialisation schemes administered by different regional authorities. France, unlike the UK and Germany, did not have a significant pre-existing tissue engineering industry as illustrated by the lack of bioscaffold firms in fig 1.1. A 2007 report by the biotechnology committee of the LEEM (the French pharmaceutical industry association) on 'cell therapies' made a range of policy recommendations intended to spur the development of a national regenerative medicine industry, including regulatory reform and support for the development of regional RM clusters . The outcome of this highly targeted approach is visible in that the French RM industry now has cell therapy and service sectors comparable to the UK and Germany, whilst other areas remain less developed.

It is important to note that a country's density in terms of firm numbers does not necessarily reflect the strength of the firms based there. A number of significant European RM firms are located in countries outside the three hubs as illustrated by the cases of TiGenix (Belgium), Cellartis AB (Sweden) and Cellerix (Spain) – see Table 1.0 below for details.

FIRM	COUNTRY	FOUNDED	DETAILS
Cellartis AB	Sweden	2001	Provider of human embryonic stem cell lines for development of therapeutics and drug discovery programs. Have a range of strong, high profile collaborations with multinational pharmaceutical companies including AstraZeneca, Pfizer and Novo

			Nordisk.
Cellerix	Spain	2004	Cellerix have an allogeneic stem cell therapy, based on multipotent cells extracted from adipose tissue in phase II trials for autoimmune disease. The company has secured previous investment from VC arms of Roche and Novartis and is currently in talks to merge with TiGenix NV (see below) to create a major European RM firm.
Ectycell	France	2009	Ecytcell, a wholly owned subsidiary of French firm Cellectis, are the only European biotech developing induced pluripotent stem cells for human therapeutic and research tool applications. In 2010 the firm licensed significant intellectual property on IPS technology from IPS Academia Japan Inc. (Kyoto, Japan).
ReNeuron	UK	1997	To date ReNeuron are the only European firm with a stem cell therapy for neural regeneration in clinical trials (phase 1). ReNeuron's cell line is an allogeneic therapy derived from foetal neural tissue.
T2Cure	Germany	2006	T2Cure have an autologous stem cell therapy for regenerating heart muscle about to enter phase III trials. The company was the first to receive MAA certification for a stem cell product under the ATMP guidelines.
TiGenix NV	Belgium	2000	TiGenix manufacture *ChondroCelect* –the first cellular product to receive regulatory approval for the European market through the centralised ATMP system. The company also have a CE Marked bioscaffold product as a result of acquiring the UK's Orthomimetics in 2009. In talks to merge with Cellerix.

Table 1.0 Selected European RM firms of interest

Firm age, size and sector

The majority of European RM firms across all sectors are small (<50 employees) with only a few (N= 10) medium (<250 employees) or large (>250 employees) companies involved in the field. This is unsurprising given that there are no high-earning 'blockbuster ' RM products and the sector is regarded as highly risky by investors, even in comparison to other biotechnology fields such as genomics. Europe has historically suffered from significantly lower availability of venture capital (VC) investment compared to the US and until very

recently large pharmaceutical companies have been reluctant to invest in stem cell technologies meaning there has been limited capital available to European RM firms to grow and develop. The long timescale of RM product development, the financial crisis of 2008-9 and the subsequent risk-averse investment environment have all served to exacerbate this situation. Those few large firms recorded tend to be older companies, which have added RM products, especially products with lower technical requirements and less complex regulatory pathways such as cellular bioscaffolds or reagents, to existing product pipelines and are often not dependent on RM products alone to make a profit.

The largest single sector of the European RM 'company universe' is cell therapy firms, but there are also significant bioscaffold and service sectors:

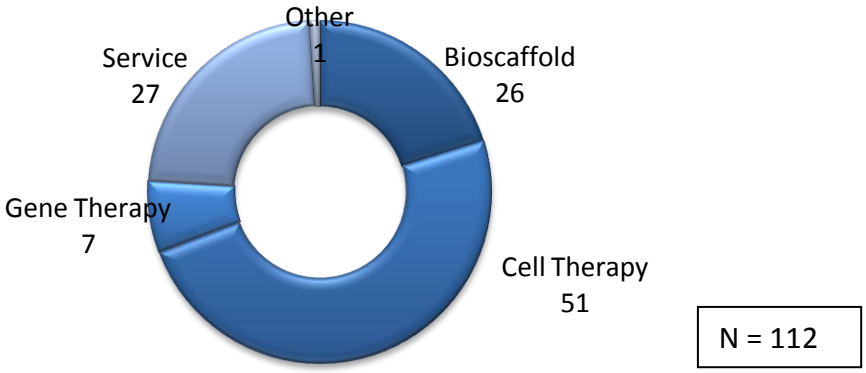


Fig 1.2 European RM Companies by Sector

There is a considerable spread in the age of RM firms. While a majority of the currently active firms have been founded since 2000, a notable proportion (apx 23%) of firms have survived from the 1990s and a few firms are considerably older. This reflects the heterogeneous composition of the RM field, with recently-founded biotechs developing stem cell therapies co-existing alongside tissue engineering era companies offering cartilage transplant services and acellular biomaterial products. The different sub-sectors of commercial RM will be discussed in greater in the subsequent section.

Key points

- European RM firms are not distributed evenly among member states but are concentrated in established (France, Germany, UK) and emerging (Spain, Switzerland) hubs.
- The majority of firms in all states are small and financially vulnerable, and the concentration of companies in certain locations does not necessarily reflect the individual strength of those firms.
- Having a national strategic plan for the support and development of regenerative medicine is a key pre-requisite for the development of an RM sector. Most national strategies to date have focused on supporting basic or translational research but there is also support for commercialisation – for example the UK Technology

Strategy Board has recently committed £21.5M to fund commercially-oriented RM projects.

- The following core components of national strategies for RM have been identified: a legislative framework for hESC research; dedicated funding including the development of major research centres and shared infrastructure such as stem cell banks; the creation of a national network to promote scientific collaboration; the promotion of public-private partnerships and international research collaborations.
- There may also be examples of best (and worst) practice to be gleaned from national strategies and practices – Sweden and Belgium, for example do not have many RM firms but they do have a few highly performing RM biotechs.

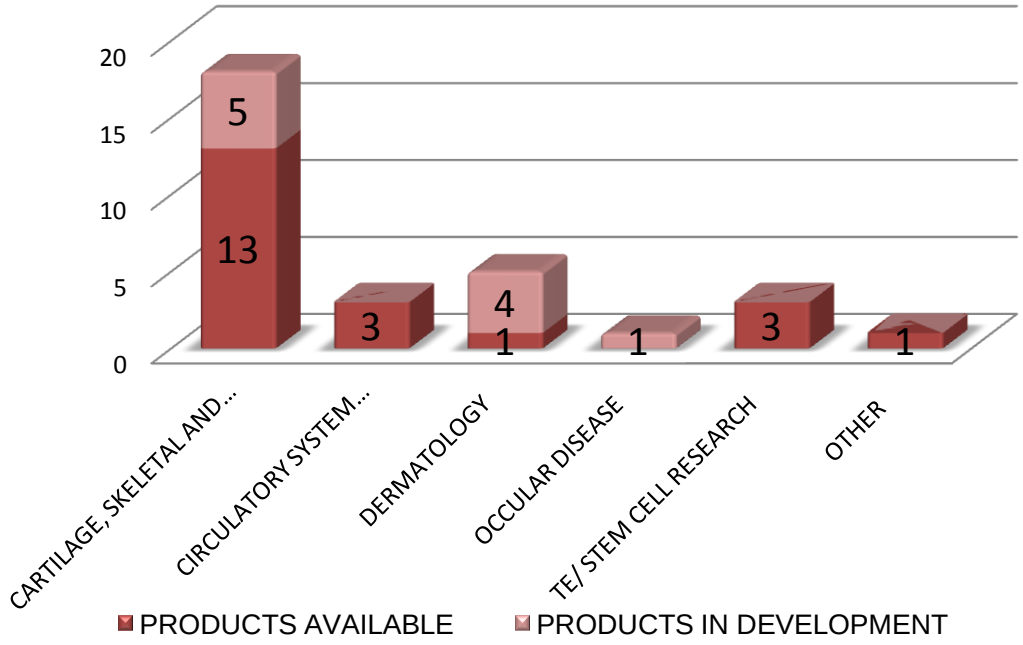
The European Company Universe: Analysis by technological sub-sector

The bioscaffold sector

Firms classified as bioscaffold producers create and market inert biomaterials, often made from decellularised collagen (of animal or human origin) or from synthetic, non-toxic polymers. Many types of cell require a surface to adhere to in order to grow and divide, and bioscaffolds in regenerative medicine encourage the proliferation of endogenous cells by providing such a surface, often in combination with the application of cell division-promoting proteins. It is important to note that while many cell therapies include a biomaterial to assist the implantation of the newly-cultured cells, this type of product is classified as 'cell therapy' (see the following section) under the project definition of RM. The firms described as bioscaffold manufacturers provide biomaterials that are applied *on their own* and repair damaged tissues by stimulating the growth of the body's own cells without any external cell culture or transplant.

Bioscaffolds have the least demanding regulatory pathway of the therapeutic regenerative medicine applications covered in this report, as they are classed as medical devices. Bioscaffolds are also easier to produce and are among the oldest commercially available RM products. As might be expected, most bioscaffolds are aimed at 'classical' tissue engineering applications such as repair of cartilage and skeletal tissue.

Fig 1.3: European bioscaffold market and pipeline



While bioscaffolds could be considered the less novel and more therapeutically limited 'poor relation' of cell therapies, such products and the companies that produce them are important when considering the regenerative medicine industry. In many cases it is these older, less risky products against which cell therapies must demonstrate greater efficiency and cost-benefit measures if the latter are to become embedded in routine medical practice in the long term. In other words, it is this component of itself that the regenerative medicine industry must surpass if the much lauded stem cell based RM industry (see e.g. Mason, 2007). Additionally, as fig 1.2 illustrates, many bioscaffold products are available (if not necessarily as a result of gaining EMA marketing approval) and new bioscaffold materials are still be developed indicating that the sector is far from moribund. Ongoing academic and medical interest in bioscaffolds is also evident (see for example, Atala, 2007) and the argument that 'tissue engineering [has] largely been replaced by cell therapy' (Mason, 2007 p25) is far from universally accepted. Indeed a small but significant number of bioscaffolds intended for TE/ stem cell research highlights an area of potential future expansion for bioscaffold technology. More advanced tissue replacement programs will require the generation of functional three dimensional cellular structures. While stem cells, especially pluripotent stem cells may be able to generate all of the tissue types required, they will still need to be grown on three dimensional bioscaffolds to replicate the complex hierarchical arrangement of naturally occurring human tissues, including for example, sufficient vascularisation to allow the growing 3D cell culture to survive (Williams & Sebastine, 2005). Thus three dimensional cell culture is a potential area of future technological development in bioscaffolds.

The cell therapy sector

A key aspect in assessing human cell based therapies is the source and application route of the cells. Somatic 'adult' differentiated cells and stem cells from a range of sources –

embryonic, foetal, cord blood, and mature tissues can all be used to develop cell therapies. Mature somatic cells can also be reprogrammed using certain biological factors to induce pluripotency – so called induced pluripotent stem (IPS) cell technology. Cell therapies can be applied autologously – reimplanted into the patient the cells were extracted from, or allogeneicly – where cells from a donor are implanted in unrelated patients. Each of the possible permutations of sources and application routes has implications for the type of business model for firms developing the cell therapy products.

A total of 65 cell therapies available or in development were recorded from the 51 identified cell therapy biotechs as several firms have more than one cell-based product or product candidate. Technological approaches that include genetically modified cells, as pursued by Mologan AG (Germany) and Molmed (Italy), or otherwise treated cells, for example Kiadis Pharma's (Netherlands) *Theralux* platform, are all included in this dataset as they still primarily involve the application of human cells for therapeutic benefit.

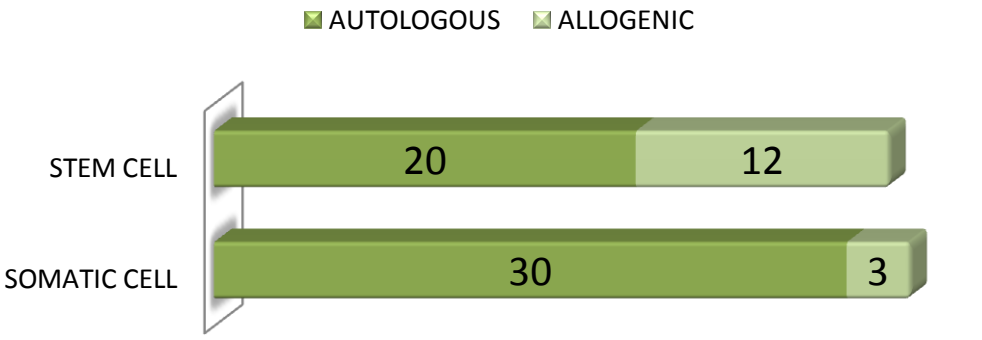


Fig 1.4 Total cell therapies by type

N = 65

As the above figure shows European cell therapy firms are split almost equally between therapies based on stem cells and therapies based on somatic cells. However, there is a strong emphasis on autologous rather than allogeneic therapies. Interestingly, this is less the case with stem cell-based approaches than with somatic cell-based products. A further important dimension to this pattern is revealed by comparing those cell therapy products which are available (including through hospital exemption, named –patient licenses, and the limited number of nationally or EMA approved products).

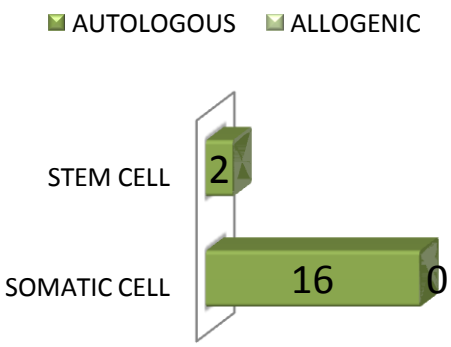


Fig 1.5 Available cell therapies by type

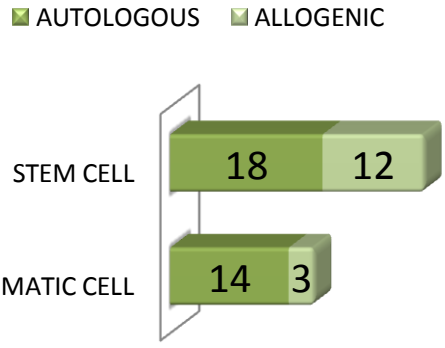


Fig 1.6 Cell therapies in development by type (N = 47)

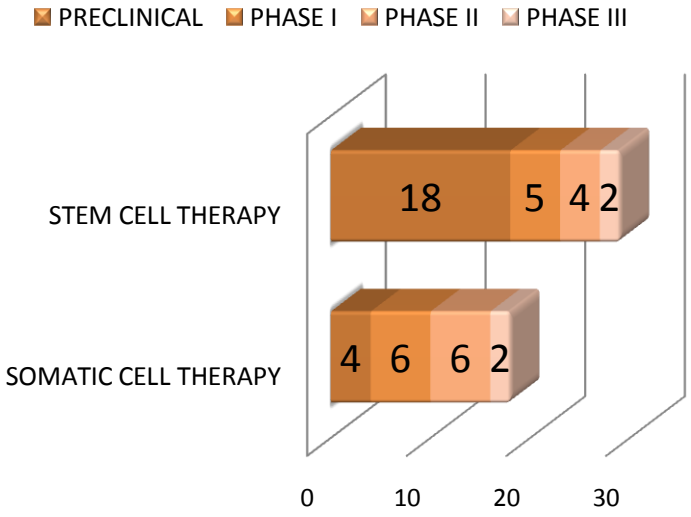
The available cell therapies are overwhelmingly based on autologous somatic cell therapies while the cell therapy pipeline show much greater investment in stem cell technologies and in the development of allogeneic approaches to cell delivery. As with the age range of firms involved, this stratification reflects the history of the RM industry. The available cell therapies are mainly tissue engineering era procedures using autologous epithelial or cartilage cells to repair skin lesions and restore cartilage damage in joints. Investment in stem cell therapies is often more recent and has opened up possibilities for allogeneic as well autologous approaches, although the former is still heavily favoured.

Autologous cell therapies offer less scope for intellectual property coverage (since a patient's own cells can't be patented) and limited potential to scale up the treatment process since each patient will need their cells expanded ex vivo in isolation (i.e. at a discrete workstation) to avoid cross-contamination risks. However, they are still regarded as incurring significantly lower risk of immune rejection or the need for immunosuppressive drugs than allogeneic cells and it may be that developers intuit that smaller scale clinical delivery under hospital exemption rules (which suits autologous application) will be the most readily available mode of delivery for cell therapies for the near future.

In contrast, allogeneic therapies take a 'cells as drugs' approach more likely to be viewed favourably by big pharma and other investors and potentially yielding an off-the-shelf product deliverable to much larger patient populations. Development, accreditation and standardisation of large scale automated cell culture for clinical grade applications remains a work in progress though, and may continue to present significant technical and regulatory challenges for allogeneic products in the short-to-medium term.

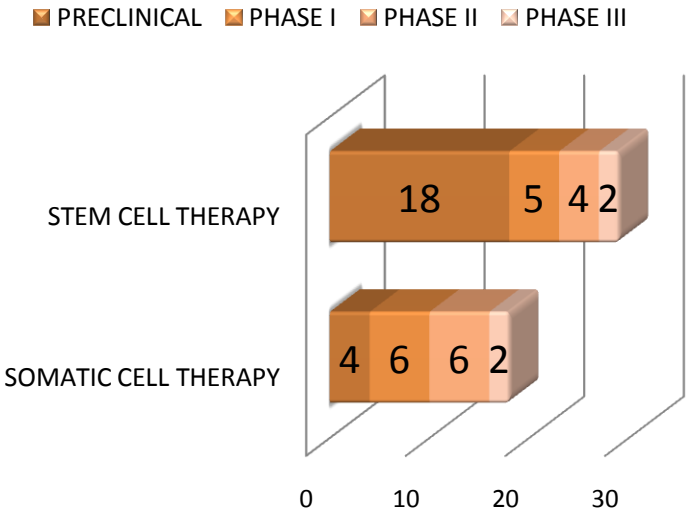
Cell therapy pipeline and therapeutic focus

It is largely stem cell therapies that are being developed for the more ambitious clinical indications; those that reflect the promise of RM such as cardiac repair, neuro-regenerative treatments, and autoimmune diseases. Much of this activity is currently in the early stages of clinical development (see fig 1.7) and so is not likely to yield a flood of new therapies in the short term. Additionally, no stem cell therapy for this type of chronic disease application has yet made it through the ATMP regulatory system and despite efforts to harmonise European regulation and create a viable governance pathway for regenerative medicines there remain areas of uncertainty –and thus potential challenges – with regards to permissible amounts of variability in cell populations in multi site (i.e. late stage) clinical trials.



Cell sources

With regards to source tissues, almost all the stem cell therapies being developed by European RM firms involve haematopoietic or mesenchymal lineages – that is 'adult' stem cell types. No European firms are developing hESC based cell therapies (as opposed to supplying hESC lines for research), most probably because of the combination of the variable state positions on the acceptability of hESC lines and the refusal to grant patent protection to inventions which involve the destruction of human embryos by the European Patent Office. Only a small number of firms, of which ReNeuron is the most notable, use foetally-derived stem cell lines and to date only two firms have invested in iPS cell technology. Of these Ectycell (Cellectis) is the most serious contender having licensed proven iPS Cell technology from Japan in 2010. In this, the



European RM industry can be said to lag behind the US where Geron (Menlo park, CA) have famously commenced recruitment for a first-in-man trial of an hESC derived therapy and a number of firms, including Fate Therapeutics (San Diego, CA), iPerian (San Francisco, CA) and Cellular Dynamics Inc (Madison, Wisconsin) are all developing iPS technology (although primarily as a drug screening and toxicity testing platform).

The gene therapy sector

The European commercial gene therapy sector is sufficiently small that it can be investigated by a characterisation of the 7 firms of which it is composed. This representation is displayed in table 1.1[3]. The concept of transferring 'healthy' or active genes into living human tissue to treat diseases has been around for over 30 years. After early controversy in the 1980s, the first officially sanctioned clinical trial of gene therapy was carried out in the US in 1990. Despite a great deal of initial promise, the field of gene therapy has been damaged by a number of high-profile safety concerns, most notably the death of a teenage patient in a 1999 gene therapy trial, and the report in 2002 that children treated with gene therapy in a French study subsequently developed leukaemia as a result of damage sustained to their DNA during the procedure (Martin & Morrison, 2006). In recent years some commentators have reported a resurgence of interest in gene therapy, and expectations that it might yet demonstrate potential as a therapeutic technology (Naldini, 2009). The age of companies recorded in the European commercial gene therapy sector reflect this turbulent history - a few firms exist from the early era of gene therapy, others from the 1990s when expectations for gene therapy were highest, and a small number of companies were founded after the safety scares of 1999-2002. The small size of the industry reflects prior periods of commercial disinvestment and industry consolidation as investors became disenchanted with the field and therapeutic and commercial success was not forthcoming.

None of these companies has a gene therapy product on the market, but in this they are no different from gene therapy companies in most other parts of the world. *Gendicine* produced by Chinese biotech firm Shenzen SiBiono Gentech remains the world's only approved gene therapy and is approved only in China where it is employed as a cancer treatment (Pearson, Jia and Kandachi, 2004). The therapeutic targets of gene therapy have changed over its history as well – while early therapeutic trials focused on rare monogenetic trials, the focus later shifted to cancer treatments, partly because it was easier to get regulatory approval for this indication than other diseases. The current European gene therapy firms appear to be focused more on complex, often metabolic or immunological diseases, perhaps as a result of the continued lack of success (*Gendicine* aside) in previously popular areas, and the need to target diseases with significant patient populations in order to achieve sufficient returns on the long-term investment of developing such a therapy.

[3] Note that genetically modified cell therapies are recorded in the cell therapy sector data.

FIRM	COUNTRY	FOUNDED	THERAPEUTIC FOCUS	LEAD PRODUCT DEVELOPMENT STAGE
Amsterdam Molecular Therapeutics	Netherlands	1998	Metabolic / blood protein deficiency diseases	Submitted for Marketing Authorisation Application to the EMA in Dec 2009
Ark Therapeutics	UK	1997	Prevention of vascular occlusion / increase of blood supply in a range of conditions	Phase IIb (but see discussion below)
Arthrogen B.V.	Netherlands	2005	Rheumatoid arthritis	Phase I commencing in 2011
Diamyd Medical A.B.	Sweden	1976	Chronic pain	Phase I completed
Digna Biotech S.L.	Spain	2003	Metabolic / blood protein deficiency diseases	Preclinical
Oxford Biomedica	UK	1996	Neurodegenerative diseases, ocular diseases	Phase I/II
Transgene	France	1979	Cancer (solid tumours)	Phase I

Table 1.1 The European commercial gene therapy sector

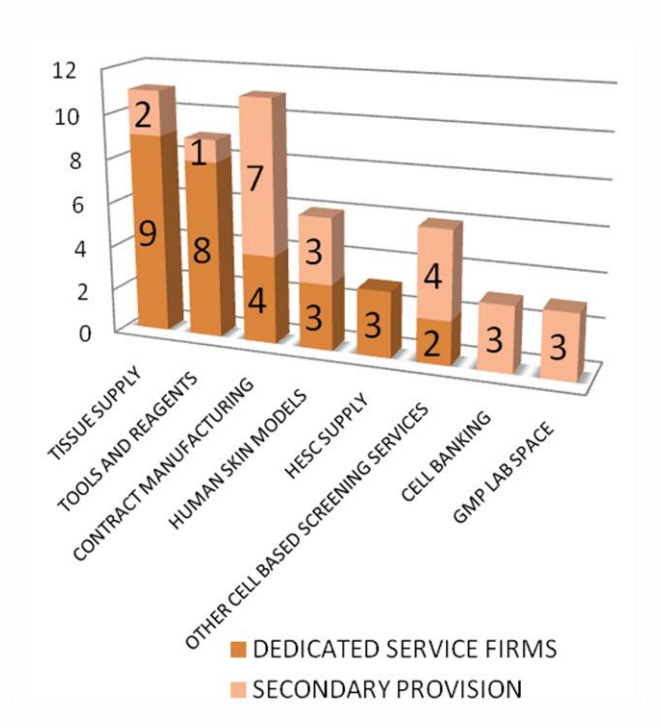
While most of the current gene therapy products in development remain in the early stages of regulatory appraisal, two firms have had recent experience with the ATMP. Amsterdam Molecular Therapeutics' lead product candidate *Glybera* for lipoprotein lipase deficiency is currently undergoing a post-phase III trial European Marketing Authorisation Application (MAA). If successful this would be only the second product second European product to be approved by the Committee for Advanced Therapies and the second gene therapy product in the world to receive marketing approval. However, the recent experience of Ark Therapeutics (UK) illustrates the uncertainty and potential hazards of a negative outcome at this stage. Ark submitted their former lead product candidate, *CerePro*, a gene therapy for malignant glioma (a form of brain cancer) to the EMA for approval in 2008. During the course of 2009 *Cerepro* received approvals for named patient supply of the drug from the French Medicines Control Agency (AFSSAPS) the Finnish Medicines Authorities (NAM). However, in December 2009 the EMA's Committee on Human Medicinal Products (CHMP) rejected Arks MAA for *Cerepro* on the grounds of insufficient evidence of efficacy. Since then Ark has undergone significant restructuring to try and reach a sustainable financial position and is currently trying to out-license both Cerepro and its next most advanced gene therapy candidate Trinam, as well as divesting much of the company's secondary business in non-RM support bandages.

The ongoing risk associated with commercial development of gene therapy is reflected in the fact that many of the other gene therapy developers such as Transgene (France), Diamyd Medical AB (Sweden) and Oxford Biomedica (UK) are developing other biotechnologies such as therapeutic vaccines and monoclonal antibodies alongside their gene therapy programmes and gene therapy may not necessarily be regarded as these firm's primary focus.

The Service sector

This category represents those companies that do not produce a primary product –that is they are not involved in producing a cell, gene or bioscaffold based therapy which is intended to be applied to the human body as a medicine - but rather engage with the novel biomaterials of regenerative medicine in ways which nonetheless can support the scientific and commercial development of regenerative medicine. This grouping also includes a number of companies that work with regenerative biomaterials – mainly human cells in novel ways which do not fit unde Fig 1.8 Dedicated and secondary service providers but are nonetheless significant.

Unlike companies producing cell and gene therapies or bioscaffolds, dedicated service firms are located almost entirely within the three hubs of Germany, France and the UK. Elsewhere RM services tend to be provided by cell therapy companies, many of which have product candidates in the early stages of development and offer cell culture-based services as a source of short to medium term revenue generation. Fig 1.8 illustrates the types of service provided and the division between dedicated service firms and secondary services offered by cell therapy developers.



The activity of dedicated RM service firms tends to be concentrated on the provision of human tissue (stem cell lines and some somatic cell types used in tissue engineering or drug toxicity screening) and on RM-specific tools and reagents (human stem cell specific culture media, specialised bioreactors for 3D tissue engineering culture etc). The services offered by cell therapy firms (no gene therapy companies and only two bioscaffold manufacturers were found to offer any kind of additional RM service provision) cover a broader range of types of service, mainly based on leveraging existing resources that a cell therapy firm is likely to have, such as GMP accredited laboratories, cell banking facilities and local expertise in

human (stem) cell culture techniques. The market for these services includes other biotechnology companies, but also academic or other publicly-funded research and, in cases where a particularly specialised service is offered, large pharmaceutical firms.

Notably, the provision of human embryonic stem cell lines is limited to three specialist providers – Cellartis AB in Sweden and Roslin Cells and Stemride International in the UK (although the latter sources much of its biological material from the US it is headquartered in London). It is pertinent that Sweden and the UK have some of the more permissive (if strict) regulatory positions on hESC research within Europe and suggests that the well documented variance in national ethical stances and /or uncertain legal positions on human embryo research in other European countries has inhibited the formation of similar enterprises elsewhere.

Key Points

- The European RM industry is highly heterogeneous – not only in terms of the different sectors, which were build into the scope of the study from the beginning – but also in terms of the multiple technological approaches – different cell sources, in- and ex-vivo gene therapies etc – being developed within each sector.
- There is also a temporal aspect to this heterogeneity with firms of significantly different ages and developing more and less novel technologies operating alongside one another.
- It is important to consider that the different sectors and technologies do not operate in isolation but can also act in combination with each other to develop novel regenerative strategies, for example genetically modified cells and combined cell and bioscaffold treatment options.
- In terms of the challenge of regulating this variety of novel technologies the centralised ATMP has been generally welcomed by industry stakeholders. However, it is also worth noting that the only cell therapy approved so far via the ATMP pathway has been an autologous, somatic cell TE product for cartilage repair.
- It is likely that a few well-placed 'trailblazer' firms, somewhat analogous to Geron in the US, will be the first to bring one or more of the stem cell therapies currently in clinical trials through the ATMP approval process. These 'first in' firms may well need additional support in order to establish an accepted approach that other firms will be able to follow

Policy challenges

European RM innovation takes place within a complex multi-level governance framework involving member states, the European Union and sub-national authorities. A key challenge facing policymakers is how best to coordinate activity within this complex network of actors. The heterogeneity of the sector and its uneven geographical distribution make this complex task more difficult as it is unlikely that a 'one size fits all' policy approach will be viable or even possible.

As this report has noted, the majority of European RM firms, including most of those developing therapeutics based around the 'high risk' biomaterials of human cells and genes,

are small and financially vulnerable. European Commission officials have already been in discussion with representatives of the biotech, pharmaceutical and VC industries to discuss solutions to the current funding crisis. Emerging policy initiatives need to give appropriate consideration to of the specific problems of the RM sector.

Several strategic options are readily discernable:

- Financial support could be distributed across the whole European industry or targeted to specific areas such as securing companies in the three existing hubs, supporting infrastructure formation in emerging RM nations such as Spain, or potentially cultivating links between firms in core and peripheral RM nations, including through future FP 7 and FP8 funding initiatives. These options are not intended to be exhaustive nor necessarily mutually exclusive.
- Different technological approaches involve different strategies for revenue generation and interact with existing regimes of regulation and healthcare provision in differing ways: allogeneic cell therapies or gene therapies may be regarded as higher risk options compared to allogeneic cell treatments, but may also be more amenable, both technically and in cost-per-unit terms, to the automated manufacturing processes needed to produce standardised therapeutic products on a large scale. Thus it is appropriate to consider how future policies could support these different requirements.
- Further to this point, while the single regulatory framework for RM therapies has been a notable achievement for the EU, further harmonisation may be possible (and desirable) in areas such as the clinical trials directive and the hospital exemption regulations. This is especially pertinent as hospital-based service delivery may be the best way to get (autologous) cell therapies into the clinic in the near-term.
- With regards to clinical trials of cell therapies, another manufacturing issue, the standardisation of cell batches, is especially pertinent to phase III trials, when variation in cell behaviour must be shown to be within tolerable limits across multiple clinical sites to gain regulatory approval. This has raised questions as to the suitability of the conventional, three-phase clinical trial design, as developed for evaluating small molecule drugs, for evaluating innovative biomaterial based therapies and also has implications for the appraisal of the current commercial pipeline of gene and cell therapy products.

Workpackage 1 (second element) Financial investment and sustainability in the RM field

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Introduction

The prospects for a 'material science' of regenerative medicine (as opposed to the antique "Promethean" myth *see:* Gardner 2007; Badylak and Nerem 2010; Polak 2010: S777 and S779) is said to have been first mooted in the late 1970s as part of a debate about the efficacy of 'substitutive medicine' and the toll future demands for organ replacement and prosthetic technologies might exert upon the specialism (Lagasse *et al*. 2001, Lanza and Rosenthal 2004; Koh and Atala 2004; McConnell and Turner 2005; Vacanti 2006; Gardner 2007; Lysaght, Jaklenec and Deweerd 2008; Nerem 2010; Pangarkar *et al*. 2010; Polak 2010; Badylak and Nerem 2010: 3285). Regenerative medicine therefore began as a bid, among American transplant surgeons, cellular biologists, geneticists and medical device engineers, to develop salient alternatives for conventional tissue substitution methods (McConnell and Turner 2005; Lysaght and Hazlehurst 2003; Lysaght and Hazlehurst 2004; Kemp 2006; Lysaght, Jaklenec and Deweerd 2008; Nerem 2010 Polak 2010; Johnson *et al.* 2010; Messenger and Tomlins 2011). Three decades have passed since the search began for the means of replenishing and regenerating the body's natural processes of repair (Badylak and Nerem 2010). The commercial life science and biotechnology industries helped to seed this venture in the early 1980s, via tissue engineering start-up businesses, placing this important initiative firmly on an entrepreneurial footing from the outset (Lysaght 1995; Lysaght and Reyes 2001; Lysaght and Hazlehurst 2003; Lysaght and Hazlehurst 2004; Vacanti 2006; Kemp 2006; Lysaght, Jaklenec and Deweerd 2008, Mason and Dunhill 2008a and b; Messenger and Tomlins 2011). Start-up firms have been pivotal to the regenerative sciences worldwide but the growth of the manufacturing focused side of this science-industry complex has been down to a few key businesses, equipped with the expertise and technology required to turn favourable laboratory results into testable products (Lysaght 1995; Lysaght and Reyes 2001; Lysaght and Hazlehurst 2003; Lysaght and Hazlehurst 2004; Kemp 2006; Lysaght, Jaklenec and Deweerd 2008; Mason and Manzotti 2010; Prescott 2010; Johnson *et al.* 2010).

Experiments with replicatory and regenerative cellular engineering took place in the American entrepreneurial science and university research sectors for much for the 1980s and 1990s, yielding vary degrees of commercial success, alongside some notable product failures (Lysaght 1995; Lysaght and Reyes 2001; Lysaght and Hazlehurst 2003; Lysaght and Hazlehurst 2004; Kemp 2006; Lysaght, Jaklenec and Deweerd 2008; Mason and Manzotti 2010; Prescott 2010; Johnson *et al.* 2010; Pangarkar *et al*. 2010). Examinations of this history depict a sector at the mercy of capricious tendencies for 'feast and famine, boom and bust' (Ibidem). The private sector segment of the replicatory and regenerative science base, has proven, over the course of time, to be especially susceptible to venture capital fads and fashions affecting substitutive medicine and tissue engineering, wherein, cyclical patterns of nourishing growth have been followed by debilitating retrenchment (Lysaght 1995; Lysaght and Reyes 2001; Lysaght and Hazlehurst 2003; Lysaght and Hazlehurst 2004;

Kemp 2006; Lysaght, Jaklenec and Deweerd 2008; Mason and Manzotti 2010; Prescott 2010; Johnson *et al.* 2010; Pangarkar *et al.* 2010).

The turn of the millennium can be seen, in retrospect, as a particularly inauspicious moment for the owners of start-up firms, and more established 'biotechs', whose efforts to launch new forms of 'regenerative entrepreneurialism' were thwarted by the evaporation of the "dot.com bubble" (*see:* Lysaght, Jaklenec and Deweerd 2008: 306-310; Pangarkar *et al.* 2010).

Lysaght's first-hand account of the 'dot.com' occlusion of commercial ambitions for the regenerative sciences, also describes the resuscitation of regenerative business ventures after 2004 (*see:* Lysaght, Jaklenec and Deweerd 2008: 306-310). The years 2005-2007 were ostensibly characterised by a renewed, fervent, entrepreneurial optimism (Lysaght, Jaklenec and Deweerd 2008: 306-310; Pangarkar *et al.* 2010), following positive publicity and stronger sales of regenerative products in the medical marketplace (*also:* Mason 2005a: 25; 2005b: 22 and 2007). Business models were adapted accordingly, although the goal of finding a 'single best way' to finance and manage these ventures proved elusive, due in no small part, to the sector's technical heterogeneity; the unknowns involved in manufacturing a new generation of pluripotent stem cell products; and the 'high stakes' gambles inherent to regenerative entrepreneurialism (*see:* Kemp 2006; Mason 2007 Pangaskar *et al.* 2010).

Research Focus, Methods and Key findings

Lysaght, Jaklenec and Deweerd (2008) established cause for thinking this upturn was based on a solid recovery, yet this period of optimism was to be prematurely truncated by the arrival of the 'credit crunch' (Kewell and Webster 2009). Lysaght's body of work poses important questions about the financial sustainability of regenerative entrepreneurialism, as a worldwide industry with American provenance, that remain as pertinent in the 2010s as they did in the 2000s (Lysaght 1995; Lysaght and Reyes 2001; Lysaght and Hazlehurst 2003; Lysaght and Hazlehurst 2004; Kemp 2006; Lysaght, Jaklenec and Deweerd 2008; Mason and Manzotti 2010; Prescott 2010; Johnson *et al.* 2010). The research we have undertaken expurgates Lysaght *et al.*'s 2008 study by examining the performance of a core group of firms (n=112 and n=49) from this pan-national contingency, based upon the reports and accounts that they each published to shareholders between 2005 and 2009 (the years for which robust data are available).

Our review of quantitative microeconomic financial data (Eastman 1984) suggested, initially, when undertaken in 2009-10, that the improvements noted by Lysaght, Jaklenec and Deweerd (2008) were overoptimistic, and would have been so irrespective of the collapse of global financial services (see: Kewell *et al.* 2009; Gruber 2009). We have latterly refined these observations through further analysis of statistical indicators. The York Management School contribution to Workpackage 1 has thus primarily 'taken the temperature' of firm performance within these sectors; firstly by establishing a view of industry structure and fiscal integrity and then examining the performance of a 'core segment' of firms, between 2005-2009.

This effort was complicated by an incomplete picture of international sectoral activity and blurred distinctions between tissue engineering companies producing non-pluripotent clinical treatments, diluted 'mixed platform' firms undertaking conventional (non-pluripotent) and viable pluripotent stem-cell manufacturing; and finally, 'pure' or undiluted regenerative medicine enterprises, focused solely on the exploitation of emerging clinical markets for replicatory treatment options (Lysaght and Hazlehurst 2003; Lysaght and Hazlehurst 2004; Hunziker et al. 2006; Kemp 2006; Mason 2007; Martin, Hawksley and Turner 2009; Rowley and Martin 2009). As a consequence, it was necessary to establish a stable list of stock market listed firms and enterprises (our main foci, given the data disclosure restrictions associated with non-listed companies) before proceeding to statistically examine corporate reports and accounts (Marston and Shrives 1991; Cooke 1998). In assembling this dataset, comparisons were made with other lists, including those published by Lysaght, Jaklenec and Deweerd (2008) and Martin, Hawksley and Turner (2009).

The research was divided into three stages. Our previous report to the European Commission (Kewell *et al.* 2009) expedites a full account of the data mining we undertook in *Stages 1* and *2* of the analysis, which was devoted to (1) the task of identifying a stable sample-population for the research; and (2) evaluating the financial performance of these companies in 2008; as a test bed for statistical validity (Hickey 1986; Marston and Shrives 1991; Cooke 1998). The sample frame for *Stage 1* was synthesized from a possible 10,000 publicly registered life sciences concerns, tissue engineering companies and biotech holdings, for which accounting entries are held on *Thompson Datastream*^{TM}. Following a detailed process of elimination, 112 companies were identified as bona fide tissue science and regenerative medicine firms, advertising prima face involvement in the development of pluripotent technologies and allied products (Kewell et al. 2009). The year 2008 was used as a benchmark, partly because of its historical relevance, and partly because 2008 was a 'good year' in reporting terms, for which a relatively large data pool existed, given the scale of the industry. Our aim was to (1) specifically pinpoint firms for which regenerative medicine was likely to be a major area of current and future investment (i.e. the serious companies in the sector); (2) examine their financial capabilities and risk position; and (3) see whether a longitudinal five year regression based panel investigation might be viable (Farrar and Glauber 1967; Marston and Shrives 1991; Cooke 1998).

After some initial calculations were performed, the decision was taken to focus on the 'industry standard' accounting categories of 'Employment', 'Research and Development expenditure (R&D)'; 'Investment'; 'Assets'; 'Liabilities'; 'Intangibles' and 'Gearing' (Ibidem). Taken together, the results of the descriptive interrogation of data aligned to the standard accounting categories listed above, and a subsequent phase of regression analysis, statistically verified wider impressions that the sector was not sufficiently underwritten by venture capital to stand the impact of the recession triggered in 2007-2008 (Pangarkar *et al*. 2010). Fiscal indebtedness amongst core RM firms appeared to be particularly problematic (see: Kewell et al 2009). Indeed, it seems to be the case that a culture of overinvestment had not only caused the market to boil over but may have also, simultaneously, established adverse conditions in terms of risk position, profitability and research intensity among the initial sample population (Ibidem). Companies with a greater asset base, and paradoxically,

with higher market value were shown to be more risky, presumably on account of past stock market over-valuation ad a lack of successful product efficacy.

The third stage of the research distilled the research sample down to 50 core regenerative businesses, which were separated from more peripheral firms through a painstaking process of cross-checking between *Thompson Datastream*^{TM} and accounting information published on company websites. This sample was subsequently refined to 49 companies, with the removal of AMGEN to avoid distorting the data by size of revenue. It is worth noting that this revised sample frame included three cord blood banks. *Stage 3* thereby mainly consisted of a detailed review of the 49 sample firms' accounting positions, as they were reported to shareholders (and financial regulators) circa 2005-2009 (the last year for which data is currently available). This 'final 49' comprised of 41 'undiluted' regenerative firms; three cord blood banks; and five 'diluted' businesses supporting mixed platforms.

Thus far, the financial health of the 'top ten' and 'bottom ten' companies have been synthesized into panel data, by way of two descriptive measures: 'Employment' and 'Sales Revenue'. We also found that most firms included in our refined sample were registered on United States (US) stock exchanges (primarily the NASDAQ, New York and Amex, n=27); with the remainder located Europe, and in one or two cases, the Pacific region (*please see*: **Table 1**, in the annexe to this Executive Summary). This suggests that the American venture capital market is still seen as the most viable by regenerative medicine firms.

Some notable 'top tens' are apparent within the data, although we have yet to complete our investigation of their scope, scale and reliability. Thus far, we have analysed their significance in terms of net-cash flow; sales and employment. Further work is to be undertaken in this respect. Among the top ten cash accumulators (i.e. those with increasing sales revenues and a healthy net cash flow position), most were located in the US, followed by Europe, Australia and Korea (*please see:* **Table 2**). The top three for this particular league table consists of Viromed (a South Korean firm with American participation), Geron Corp. and Oxford Biomedica (which are American and British companies, respectively). The international spread of the industry, from its antecedents in the United States (US), is confirmed by the presence, within this top ten, of some significant European firms, including Tigenix NV., Molmed, and Mologen AG; alongside Australasian and Asian businesses such as Mesoblast and Viromed.

Table 3 demonstrates that firms in a position to generate sales income, had reversed poor profitability ratios to an extent, although even the best among them were still in a negative pre-tax profit position (e.g. -4949% to -206% between 2005-2009). By contrast, **Table 4** suggests that the profitability of the least performing firms in the sector plummeted between 2005-2009, in one case from a negative pre-tax margin of -637% to one of -118054%, over a four year period. Employment increased in the sector among more buoyant firms with good sales revenues (for example by a change in percentage rates of 595% for one firm and 257% for the top revenue performer). By contrast, the ten companies with decreasing sales revenues were clearly restructuring to diminish costs between 2005 and 2009. These firms seem only to have hired staff at the margins. This said, even some firms experiencing vast losses were recruiting by as much as 117% in terms of employment percentage alterations (*see:* **Tables 5-6**).

In a sector hallmarked by vast performance disparities, **Table 7** shows that the growth percentages were extraordinary for some firms with increased sales revenues: from 325.81 at the bottom of the top ten, to 32942.86% at its apex (c.2005-2009). The overall picture is of strong income escalation for a small number of well placed competitors in the regenerative products markets and of a top ten moving ahead of the field. All firms within the sector are nevertheless 'cash poor' by stock market standards, remaining ostensibly dependent upon external sources of leverage, particularly with respect to the financing of programmes of expansion and Research and Development (R&D) initiatives (*please see*: **Table 8**).

Governance and ownership has latterly emerged as an important theme of the research conducted during *Stage 3*. Governance inquiry focuses on the composition of Boards of Directors. It is a form of analysis that seeks to examine firm performance and financial risk in relation to the skills, competencies and expertise afforded by company executives. As part of this undertaking, we sought to identify successful board characteristics among companies demonstrating sustainability within the sector. This goal was achieve via the interrogation of triangulated sources of information (e.g. Google Finance, Reuters, Security and Exchange Commission (SEC) reports and European 'Article 14' and Rule '26' disclosure requirements). Our preliminary findings among the top ten companies by employment growth (a significant benchmark of viability) suggest that a board combining executives and non-executives with experience in banking, finance and investment or pharmaceuticals and biotech potentially avers greater confidence among stock market investors. Some interesting trends were identified from this research, including evidence to suggest that the state has been an arbiter of business development in Korea and that Cryosave, a cord blood banking group, has benefited from investor collaboration with mine worker's pension schemes. Our research indicates, furthermore, that Geron and Transgene lead the sector in terms of market confidence, securing lucrative venture capital tie-ins and expert input from the pharmaceutical sector (*please see:* **Tables 9-10)**.

Yet despite these positive signals, there is strong evidence to suggest that even the 10 most successful or sustainable of regenerative companies are not sufficiently ready to offer a broad spectrum of marketable product lines (see e.g. Geron—which attracted significant venture capital but has only been able to conduct phase 1 and 2 clinical trials thus far). Where product lines exist, they are either in the relatively 'low tech' stem cell storage market (e.g. Cryosave) or seeking to develop surgical niche products (i.e. Orthovita).

All of these companies therefore rely strongly on various forms of esteem attractors (Kewell *et al.* 2009), including the employment of experienced directors/managers who have held prior roles in the biotech affiliates of large pharmaceutical companies (this is especially prevalent among US players); the employment of senior research scientists and venture capitalists among senior management; the creation of product related research publications in prestigious journals (e.g. Orthovita); and affiliations or collaborative agreements with large pharmaceutical companies (e.g. as licensees). This can be found among both US and European companies (e.g. Geron and Transgene). Affiliations with prestigious Universities (Geron lists Duke in North Carolina), or academics (Japanese Tissues Engineering emphasises its affiliation Howard Green of Harvard Med school) and government support or

awards (Japanese and Korean firms) also rank as significant attractors for stock-market investors.

In summary, it can be said that even among the more prosperous and successful firms within the industry most are in a holding pattern where the development and testing of potential promising product lines allows them to continue to attract funding and expand the size of their operations. A smaller group of companies which has developed marketable product lines operates in niche markets (Orthovita, Tigenix, Biomimetic are all working on bone grafts; Novavax makes vaccines; and Proteome biomarkers). Cryosave differs from all of the above in that it does not develop products but instead provides storage.

Conclusion

Regenerative medicine firms were, and remain, commercial undertakings burdened by profound anticipation, as enterprises in which substitutive medicine has long since staked its future (Lysaght 1995; Lysaght and Reyes 2001; Lysaght and Hazlehurst 2003; Lysaght and Hazlehurst 2004; Kemp 2006; Lysaght, Jaklenec and Deweerd 2008; Mason and Manzotti 2010; Prescott 2010; Johnson *et al.* 2010; Pangarkar et al. 2010). Thus, replicatory and regenerative sciences are increasingly considered as salient apertures for the treatment of cancer, heart disease, and diabetes, as well as a plethora of orphan diseases for which there are few alternative conventional treatments (Lagasse *et al*. 2001, Lanza and Rosenthal 2004; Koh and Atala 2004; McConnell and Turner 2005; Vacanti 2006; Gardner 2007; Nerem 2010; Pangarkar et al. 2010). The possibility that the regenerative sciences might one day achieve this type of broad spectrum appeal, that is to say, diversify 'beyond substitution'; is perhaps the most earnest of reasons for continued investment in the sector, despite its history of financial underperformance and negligible profitability (Lysaght, Jaklenec and Deweerd 2008; Mason and Dunhill 20008b; Pangarkar *et al*. 2010).

Share ownership models of financing appear to suffice for a disproportionately small number of regenerative medicine firms, when the size of the industry is considered. Our combined data, suggests, moreover, that economic sustainability is questionable outside the better performing 'top tens'. Whilst there is an increasingly international complexion to the industry, American remains its key base, with one or two notable success stories evident in Asia, Australia and Europe, circa 2005-2009. The scope for profitability seems far more limited in geographic terms outside of the US entrepreneurial sector.

Overinvestment and overvaluation remain the most significant structural variables clouding a picture of nascent growth within a regenerative medicine industry typified by stark performance contrasts. The existence of 'top tens' is a hopeful sign of recovery, demonstrating that regenerative entrepreneurialism has a future, if in relation to a very small group of pioneering firms. This optimism could prove Janus faced, nonetheless, as most of these enterprises have yet to gain a solid grounding in clinical product markets. Our data augers a further danger, in so far as investors seem to have overestimated the true value of better companies, between 2005-2009, as evidenced by the helter-skelter nature of percentage growth rates for some firms in the 'top tens' that have identified, thus far. If investors concentrate their attention solely on these top tens in years to come, this might

once again create the conditions for a 'bubble', similar to the periods of financial retrenchment seen in 2001 (Lysaght, Jaklenec and Deweerd 2008) and 2007-2009, respectively.

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Table 1 : Stock Exchange Registrations

Nasdaq (inc. OTC Bull, Other OTC; Nadaq Europe; Jasdaq)	23
New York and NYC Amex	4
London	7
Berlin and Frankfurt	8
Other Exchanges (Japan, Tokyo, Milan, Toronto, Australia, XETRA)	7
Total	49

Table 2: Location of the 'Top Ten' by Net Cash Flow (In Original Currency)

VIROMED COMPANY LTD (32625U)(korea won)	27580900	South Korea /USA
GERON CORP (883003)($)	86787	USA
OXFORD BIOMEDICA (870449) (pounds)	15378	UK
MESOBLAST LTD (29961Q) (austrilian dollar)	15094	Australia/USA
NOVAVAX INC (867529)(dollar)	14017	USA
TIGENIX NV (50325E)(euro)	12103	Belgium
MOLMED S.P.A. (51731N)(euro)	9126	Italy
MOLOGEN AG (681945)(EURO)	5571	Germany
CYTORI THERAPEUTICS (15286F)($)	5167	USA
BIOHEART, INC (50143E) ($)	4976	USA

Table 3: PROFITABILITY

Firms Displaying Largest Increases in Revenue 2005-2009

	Pre-tax margin 2005	Pre-tax margin 2009
1	-4949%	-206%
2	-40851%	-321%
3	-2089%	-59%
4	-134243%	-3295%
5	-117767%	-5018%
6	-1249%	-56%
7	-5701%	-2722%
8	-631%	-95%
9	+29%	+4%
10	-85%	+2%

Note:

•Firms 1-8 had negative pre-tax margin % for all 5 years

•Firm 9 had positive pre-tax margin % for all 5 years but declining

•Firm 10 had negative pre-tax margin % from 2005-2008 and this became marginally positive in 2009

•Hence, although margins are improving (except for firm 9) for top 10 firms they are still negative

Table 4: PROFITABILITY

Firms Displaying Largest Decreases in Revenue 2005-2009

	Pre-tax margin 2005	Pre-tax margin 2009
1	-2740%	*
2	-534%	*
3	-637%	-118054%
4	-151%	-11807%
5	-3566%	-11857%
6	-3847%	-8762%
7	-80%	-497%
8	-218%	-3989%
9	-2364%	-4442%
10	-258%	-1346%

*Zero sales in 2009 hence pre-tax margin % calculation not performed

Note:

• All firms had negative pre-tax margin % for all 5 years with only one exception (firm 5 had a positive pre-tax margin % in 2006 only)

•Margins are both negative and deteriorating for bottom 5 firms

Table 5: EMPLOYEES

Firms Displaying Largest Increases in Revenue 2005-2009

	Increase/decrease in employee numbers 2005-2009	Average number of employees 2005-2009
1	257%	15
2	3%	40
3	-39%	112
4	11%	40
5	21%	25
6	0%	75
7	67%	57
8	88%	22
9	595%	118
10	*	*

*Data unavailable

Note:
•Trend of increasing employee numbers

Table 6: EMPLOYEES

Firms Displaying Largest Decreases in Revenue 2005-2009T

	Increase/decrease in employee numbers 2005-2009	Average number of employees 2005-2009
1	100%	2
2	100%	7
3	-50%	188
4	81%	71
5	0%	45
6	-2%	54
7	-10%	89
8	91%	129
9	-50%	1
10	117%	73

Note:
•Mixed picture for employee numbers – some retrenchment and some expansion

Table 7: FINANCIAL STRUCTURE

Firms displaying largest increases in revenue over period 2005-2009

	Equity position positive or negative as at 2009	Debt-equity ratio as at 2009*
1	+ve	48.00%
2	-ve	*
3	+ve	0.02%
4	+ve	0.66%
5	+ve	61.12%
6	+ve	0%
7	+ve	3.32%
8	+ve	0%
9	+ve	9.07%
10	+ve	

*Excluding where equity position is negative

Note:
•Excluding firm 2 positive equity position
•Debt-equity ratios generally very low but some evidence that debt finance is available to this group of firms

Table 8: CASH ZERO DATE*

	10 firms with largest sales increases	10 firms with largest sales decreases
1	11 months	4 months
2	2 months	3 months
3	17 months	5 months
4	6 months	14 months
5	5 months	13 months
6	27 months	13 months
7	17 months	20 months
8	7 months	20 months
9	6 months	1 month
10	25 months	37 months
Average	12 months	13 months

*Calculation based on current assets (all firms have zero cash in hand)

Note:
•Most firms continue to depend on external financing

Table 9: Governance (Top 5 Employers)

Company	Year Founded/Listed	Product Lines	Area of Operation	Partnerships/ Collaborators
CRYO-SAVE NV (E)	•Founded 2000 •Listed: NYSE Euronext; Amsterdam (2009); AIM London (2007)	Specializes in the separation and storage of stem cells from umbilical cord blood	Main subsidiary in 40 countries (acquisition)	None: company acquires subsidiaries
ORTHOVITA INC ($)	•Listed: NASDAQ Global (2006); NASDAQ National (2003) (moved with new market being opened)	Is a specialty spine and orthopaedic company with a portfolio of orthobiologic and biosurgery products	US Malvern PA	No partners listed : extensive list of product related publications / academic collaborators
JAP TISSUE ENG (¥)	•Founded in 1999 •Listed: JASDAQ Neo market (2007)	Engages in the development, manufacture and sale of tissue-engineered medical products including i) cultured epidermis, cartilage and corneal epithelium and ii) laboratory cultured human tissue for cosmetic and pharmaceutical product manufacturers	Japan with representative office in the US	Advisory agreement with Howard Green of Harvard Med School

Table 10: Governance (Top 5 Employers)

Company	Year Founded/Listed	Product Lines	Area of Operation	Partnerships/ Collaborators
GERON CORP ($)	•Incorp ated in 1990 •Listed 1996	Develops biopharmaceuticals for the treatment of cancer and chronic degenerative diseases. Multiple phase 2 clinical trial for anti-cancer therapies and one phase 1 trial for spinal cord injury have been obtained Website lists 4 oncology and 6 regen. med products.	US plus wholly owned subsidiary in Edinburgh	Investment by Merck, ViaGen, Roche Sienna, collaboration with Duke University
TRANSGENE (E)		Develops immunotherapeutic products to treat cancers and chronic infectious disease; 4 products in phase 2 trial and 1 in phase 1	Illkirch and Lyon	Novartis (G) and Jennerex Biotherapeutics (US)

Annex 2 REMEDiE Work Package 2: Final Report

The European Oöcyte Economy

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Background

In the field of regenerative medicine, human oöcytes are required for somatic cell nuclear transfer and for the generation of parthenogenic stem cells. When somatic cell nuclear transfer (SCNT), also known as research cloning or therapeutic cloning, began in the late 1990s, it reinforced concerns among feminists about the emergence of a new biotech industry that would rely on access to women's bodies and bodily materials and might bring about new forms of exploitation of women. In SCNT, the nucleus of a somatic cell is transferred into a denucleated egg, which then is induced to develop into a embryonic stage of a blastocyst. Ideally, researchers would then derive stem cells and genetically-customized cells, tissue or even organs from that blastocyst that would not be rejected by the recipient's body. In 2008, the Californian biotech firm Stemagen announced it had managed to create the first cloned human blastocyst[4]. However, at the time of writing, no stem cell lines resulting from SCNT have been reported, and no patient-specific tissue has been created. Another research strategy to generate customized stem cell lines that also requires human oöcytes are so-called parthenogenic stem cells. Here, an unfertilised oöcyte is induced to develop into a blastocyst, from which embryonic-like stem cells are then derived. In January 2009, the International Stem Cell Corporation (ISCO), another Californian biotech firm, announced they had created tissue, namely layers of retinal progenitor cells, from human parthenogenic stem cells and had transplanted it into animals for testing[5].
Oöcyte donation for research purposes is among the most contested issues related to stem cell research. Although it has not become as politicized as embryo protection, oöcyte donation has caused considerable concern among academics, NGOs, feminists and researchers. In the past few years, it has attracted increased attention and became subject of a series of policy recommendations, guidelines, reports and debates. The main concerns are that the practice is onerous and bears a number of health risks to donors and that it may bring about a new form of exploitation of women.

Objectives

The purpose of work package 2 was to fill the gap of empirical data on currently existing practice of egg procurement for regenerative research in Europe.

[4] http://www.stemagen.com/17jan08.htm, accessed 18.8.2010.
[5] http://www.internationalstemcell.com/news2009.htm##, accessed 18.8.2010.

Despite the volume of argument, comparatively little has been known on an empirical level about oöcyte procurement for research. A good portion of the literature focuses on normative and/or theoretical questions related to the question of commercializing the (female) body, questions of ethical permissibility of oöcyte procurement for research, or questions of optimizing regulation. Existing empirical knowledge about oöcyte procurement largely refers to oöcyte procurement for IVF purposes (Waldby 2008; Ikemoto 2009). Some studies have critically analysed particular models of oöcyte procurement and individual policy debates (Throsby and Roberts 2008; O'Riordan and Haran 2009), but no empirical overview of oöcyte procurement practices for research purposes in Europe has been available so far. The objective of WP 2 was to close this gap and to map out and analyse the practices and institutions of human oöcyte procurement for research purposes in Europe. Specifically, it aimed to

- Gain an overview over prevalence and development of human oöcyte procurement for research purposes in Europe,
- illuminate the dynamics that drives the demand for and the supply of human oöcytes for stem cell research,
- illuminate the institutional, regulatory, and logistic infrastructure that allows for the transformation of human oöcytes into a resource for stem cell research,
- identify the main ethical, political, economic and techno-scientific forces which influence this dynamics,
- establish whether there is a trend towards a commercialization of oöcytes for research in Europe,
- assess whether this process threatens to bring about or has already brought about an exploitation of women.

Methods and Materials

The study drew from a range of primary and secondary sources:

- social science literature on the subject,
- pertinent science journals,
- various types of documents: laws, regulations, policy proposals, recommendation, position statements and the like by stem cell research networks, other biomedicine or RM-related networks, feminist groups, governments, policy-makers and other major actors,
- participation in pertinent meetings and conferences (see attached list),
- site attendance at research institutes and clinics (see attached list),
- expert interviews (over 40) with scientists, clinicians, regulators, NGO representatives, members of governmental advisory bodies, bioethicists and others (see attached list).

Main Findings

I. Extent of oöcyte procurement for research in Europe

We found that in Europe research in SCNT requiring human oöcytes is rare. Yet this situation might change again if the factors that influence demand and supply for oöcytes in the field of stem cell research change. For instance, many stem cell researchers, according to several

of our interviewees, have switched from SCNT research to induced pluripotent stem cells (iPS), viewing them as an alternative source of patient-specific stem cells without the logistical and ethical problems of using human oöcytes or embryos. However, if iPS[6] turn out to be too difficult and/or unsafe to deal with in the long run, this situation may change.

At the time we concluded fieldwork in February 2010, three research facilities were still doing research on SCNT in Europe*:* the Centro de Investigación Príncipe Felipe (CIPF) in Valencia, the Centro de Medicina Regenerativa de Barcelona (CMRB) in Barcelona, and the North East England Stem Cell Institute (NESCI) in Newcastle upon Tyne. Two further research facilities, Ghent University and the Karolinska-Institute near Stockholm, had been working on SCNT until recently but then abandoned the strategy. Upon writing this report, the research projects at CMRB and CIPF also had concluded.[7]

One of the most significant reasons why this type of research is relatively rare in Europe, is the enormous logistical difficulty of acquiring sufficient numbers of human eggs, in particular of "good quality" eggs. Good quality eggs, from the point of view of research are mature, “fresh”, recently extracted eggs – in contrast to immature eggs or so-called failed-to-fertilize eggs left over from IVF. Further, oöcytes derived from younger women are of better quality. Logistical difficulties, however, do not exist in isolation from institutional and cultural contexts. The institutional and cultural embeddedness of procurement logistics becomes most obvious with regard to non-payment provisions and mechanisms of health care coverage. In Belgium, for instance, egg sharing has become rare since Belgian IVF couples were granted up to six free cycles of IVF in 2003 (Pennings 2006). Many interviewees told us that IVF patients and clinics are rather reluctant to give away oöcytes which the woman could use for her own IVF treatment. So-called non-patient donors, on the other hand, are reluctant to undergo the onerous procedure of oöcyte donation without financial gain. On the whole, several researchers we talked to emphasized that *very* few women were willing to go through the process of egg retrieval without being offered a material incentive.

Thus, one of the findings is that the feasibility and comparative attractiveness, from researchers' point of view, of stem cell research strategies which rely on human oöcytes should not be overrated. In Europe, they are on the contrary, rather limited.[8] Limiting factors are ethical concerns, both researchers' own concerns and perceived or anticipated public concerns, legal restrictions, availability of alternative research strategies such as iPS cells, a great reluctance of women to donate (without being paid), and logistical difficulties related to the delicate nature of human oöcytes (e.g. spatial distance between clinic and lab).

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[6] IPS cells form another strategy to create”patient specific“ cell types, from which therapies could be developed. The procedure introduced by Shinya Yamanaka in 2006 consists of “reprogramming“ somatic cells, for instance skin cells, by inducing viruses. The resulting cells are regarded as pluripotent and thus similar to human embryonic stem cells. Induced pluripotent stem cells are promoted by many as being more “ethical” than human embryonic stem cells or SCNT, because no eggs or embryos are needed for their generation. At the moment, however, it is not yet quite clear how strongly iPS cells actually resemble natural stem cells and how great the risk is that they cause tumors.

[7] Information by senior researcher at CMRB, Ana Veiga, REMEDiE Closing Conference 18.5.2011, Bilbao.

[8] The situation is different in California, where we also conducted interviews for reasons of comparison. Here, a number of research institutions are still experimenting with SCNT and/or the generation of parthenogenic stem cells.****richtig? Welche?***

II. Regulatory Situation

Oöcyte procurement *for research purposes* is largely unregulated on the European level. Most recommendations and conventions on the European level refer to oöcyte procurement for *therapeutic* or *reproductive* purposes only (EGE 2000; CE 2002; EC 2004#777), and/or to *embryo* donation (EGE 2000; EGE 2007#790, 41f.).
The Council of Europe's Convention on Human Rights and Biomedicine of 1997 (Oviedo Convention) does apply, but its provisions are rather vague. It prescribes in Art.21 that

> "The human body and its parts shall not, *as such,* give rise to financial gain."

Similarly, the Charter of Fundamental Rights of the European Union postulates that "the prohibition on making the human body and its parts as such a source of financial gain" (Art.3 Abs.2). Human oöcytes certainly form a part of the body; hence these provisions apply to both procurement for reproductive and research purposes. However, while both instruments seem to rule out downright payment *to the woman* from whom the oöcyte is retrieved, the concept of "financial gain" is not clearly defined. The Oviedo Convention does not rule out "compensation" but does not clarify either, where exactly the line is between "compensation" and "financial gain".[9] We will come back to this point.

Hence, one of the findings is that the practice of procuring human oöcytes for research purposes is under-regulated on the European level, particularly the question of payment, compensation and financial incentives.

On the domestic level, all European countries where research cloning is legal have non-commercialization provisions in place that apply to oöcyte donation:
In Belgium, legal regulation of oöcyte donation applies both to IVF and research. Paying women in return for their eggs is prohibited; women may receive only reimbursement. The 2007 Law on Reproductive Medicine had made provisions for an eventual regulation of reimbursement through Royal decree, however this decree has not followed suit yet. Clinics, therefore, can proceed according to their own standards.[10] Belgian IVF medicine also knows the practice of egg sharing. It has become quite rare however since in 2003 Belgian IVF couples were granted up to six free cycles of IVF treatment. Ever since, egg sharing is more interesting to foreign women who come to Belgium for IVF and have to cover the costs by themselves (Pennings 2006).
In Sweden, the Genetic Integrity Act of 2006 prohibits trade in human body materials, including eggs, but does not specify the conditions of reimbursement. According to Swedish medical lawyer Elisabeth Rynning[11], the usual amount of reimbursement in reproductive medicine for egg cell donation is about 400€. Research using human eggs has to be approved by the respective regional ethical review board and comply with general standards for reimbursement of human subjects.[12]
In Spain, a royal decree[13] has regulated egg donation since 1996.[14] Article 5 excludes payment for gamete donation. In 1998, the National Commission for Assisted Reproduction

[9] As Judit Sandor pointed out at the REMEDiE Closing Conference 18.5.2011, Bilbao.
[10] Personal email communication with Belgian bioethicist Guido Pennings, 3.5.2010.
[11] Personal email communication 28.4.2010.
[12] See http://www.epn.se/start/startpage.aspx, accessed 19.8.2010.
[13] *The Royal Decree* (Decreto real) 412/1996.
[14] See (Braun, Sandor et al. 2011)

fixed the maximum amount of compensation for egg donation at. €600. Today, as several interviewees told us, so-called *compensaciones* of up to €1.000 per cycle are the rule in the thriving private IVF sector in Spain. The Spanish law postulates coherent standards for biomedical research and reproductive medicine[15], allowing reimbursement or compensation without requirement of presenting receipts. Article 5 of law 14/2006 on human assisted reproduction postulates that donation must not be of commercial or profitable nature. Yet, it allows for compensations in order to compensate women for expenses *and inconveniences*. Unlike reimbursement for documented expenses, as in the U.K. so far, inconveniences do not need to be documented or quantified. In practice, an exchange of money in return for eggs does take place and financial incentives form an important motivation for women to undergo egg extraction (Orobitg and Salazar 2005); personal communication Clua Obrado).

In the U.K., in contrast, sperm, eggs or embryo providers up to now may receive reimbursement only for *documented* costs, including compensation for loss of earnings up to 250 GBP.[16] Again, this rule applies both to the IVF sector and to research. However, the Human Fertilization and Embryology Authority (HFEA) in the U.K. has just concluded a public consultation on "The changing landscape of donation", discussing whether the HFEA should revise its current compensation scheme for egg and sperm donors and switch to a model along the lines of the Spanish "compensations".[17]

In practice, though, existing non-payment provisions do not necessarily rule out different models of transactions on the basis of material incentives, as we will see below.

III. Infrastructure and Logistics

A factor which is hugely important for this type of research is the infrastructural connection between stem cell research and IVF facilities, the IVF-stem cell interface (Franklin 2006). In the sector under study in our WP, the interface takes the form of personal overlaps and close spatial proximity. More often than not, the leading clinician at the facility where the oöcytes were obtained was also the researcher who led the respective SCNT project: Anna Veiga was leading researcher at the Centro de Medicina Regenerativa de Barcelona and leading clinician at Dexeus, a private hospital, also in Barcelona, from where the eggs were obtained. Alison Murdoch was leading researcher at the North East England Stem Cell Institute and clinician at Newcastle Fertility Centre at *Life*, from where the eggs were obtained, with both facilities located in the same building. Outi Hovatta, leading researcher at the Karolinska Institute, was also clinician at the Department of Obstetrics and Gynaecology at Karolinska University Hospital from where the oöcytes were obtained, both located in the same building complex. Björn Heindrycks was both a leading researcher and clinician at Ghent University Hospital, from where the oöcytes were obtained, and again research and fertility treatment took place in the same building complex.[18] Thus, it is

[15] Concerning egg "donation", the Spanish Law on Biomedical Research of 2007 explicitly refers to the Law on Reproductive Medicine of 2006.
[16] http://www.hfea.gov.uk/500.html?fldSearchFor=payment, accessed 16.3.2010.
[17] See http://www.hfea.gov.uk/6190.html
[18] Similarly, Samuel Wood was founder of Stemagen, a biotech firm in California engaged in SCNT research, and medical director at the Reproductive Sciences Center that provided the oöcytes for Stemagen's research, and founder of Select Surrogate, an egg and surrogate brokering agency, with all three facilities being located in the same building complex in La Jolla/San Diego.

extremely important for researchers to have the research site located as close as possible to the egg retrieving facility.

At the same time, however, we found that the relation between research and reproductive medicine is not only one of cooperation but also one of competition and conflicting interests. Good quality oöcytes are an object of fierce competition between research on the one hand and IVF patients and clinics on the other. Researchers rely on good relations to IVF clinics and the willingness of IVF patients to donate "spare" oöcytes – which is far from simply given.

Our finding concerning infrastructure and logistics is that stem cell research using human oöcytes has developed on the basis of an expanded IVF sector and close links between research and IVF clinics. However, we also found that existing competition between IVF and research about good quality oöcytes is a restricting factor from a research point of view. Offering financial incentives is a way for research to become more independent on these connections, as we will show below.

IV. Trends and Dynamics

Overall, we found that the expectation that SCNT would develop into an extensive research sector, accompanied by the emergence of a global market for human oöcytes has not materialized - so far. However, the situation might change again, for instance if iPS cells turn out to be too problematic for the mid term future and/or if legalization of payment schemes would induce large numbers of – young - women to sell their eggs.

As regards the dynamics of oöcyte procurement for research, we found certain trends and moves in the field:

First, we see a move in research from "poor quality" oöcytes to "good quality" oöcytes (see *Table 1*). This implies a shift from less to more controversial practices of oöcyte procurement, insofar as good quality eggs from IVF patients are also of interest for the IVF patient herself, or they come from non-patients who had been offered material incentives to undertake a risky and difficult procedure. There are two main categories of oöcytes that are comparatively easy to obtain but not quite efficient as a resource: immature oöcytes harvested in the course of IVF treatment along with mature ones, and oöcytes left over from IVF because they have failed to fertilize. Nearly all research projects we talked to had initially used oöcytes of non-optimal quality, but subsequently either switched to alternative categories of oöcytes or alternative strategies of stem cell research altogether. The team led by Björn Heindryckx from Ghent University first worked with left-over oöcytes from IVF treatment but abandoned SCNT research altogether since they did not acquire good quality oöcytes. Likewise, the team at the Karolinska Institute had worked with immature eggs and phased out SCNT. The teams at NESCI and CMRB initially used failed-to-fertilize eggs but switched to other procurement strategies. Of the research sites we looked at, the only one where – defined as – surplus oöcytes were still used *and* research cloning continued at the time we concluded our research was the Centro de Investigación Príncipe Felipe (CIPF) in Valencia. The leading researcher there, Mirodrag Stojkovic, told us that his team received eggs from the division of reproductive medicine at the Hospital La Fé. Notably, the Hospital

de la Fé is a public hospital. The fact that CIPF researchers cooperated with a big hospital where huge numbers of IVF treatments were performed and, second, that the definition of "surplus eggs" used there was a relatively comfortable - from a research perspective - might explain why the CIPF team was the only one to continue research into SCNT in Europe. Private clinics, serving customers who are usually well-off and rather self-confident, have a different view on the question of "surplus"; many of our interviewees from private clinics said that they would never ask their IVF-clientele for donating fresh good quality eggs, as one senior clinician. Montserrat Boada Palá, at Dexeus, a private fertility clinic in Barcelona, categorically explained to us.[19]

Good quality oöcytes, however, are more problematic for ethico-logistical reasons: when they come from a woman undergoing IVF, she gives up eggs she might have used for herself and it is controversial whether this practice diminishes her chances to get pregnant. When the eggs are obtained from non-patients, the woman undergoes a risky, invasive procedure without any personal medical indication or benefit.

Second, there is a trend towards material incentives (see *Table 2*). It cannot be adequately grasped in terms of commercialization vs non-commercialization but rather as variety of crypto-commercial strategies that enable more or less open monetary transactions, while at the same time avoiding open clashes with existing non-commercialisation provisions. We found that two different models have evolved over the past few years that allow researchers to offer economic incentives while circumventing non-payment provisions: “egg sharing” and the reallocation of compensated oöcytes.

Egg sharing initially meant that women who in the course of an IVF had relatively many eggs, due to superovulation, were asked whether they would give some of them to other women who wanted IVF but could not use their own eggs for some reason[20]. The Newcastle team applied for a licence to introduce an egg sharing for research program when it turned out that they had obtained only a small number, namely 66, of fresh, mature eggs from IVF patients in the course of 2005 for their research on SCNT. In July 2006, the HFEA approved the application and the scheme was launched in September 2007. Private IVF customers can receive a 1,500 GBP reduction in treatment costs if they give about half of their eggs to NESCI for purposes of stem cell research[21]. Those 1,500 GBP will be covered by the Medical Research Council that funds the research project. Egg sharing has been approved by the HFEA although it forms an exception to the general HFEA non-payment policy concerning gametes and embryos[22]. Logically, this is somewhat incoherent, since, as expert member of HFEA Emily Jackson put it, it is payment, payment in kind, but as such is offered only to “women who happen to also be infertile” [23].

Reallocation of paid eggs is another model for negotiating non-payment provisions. Here, researchers use oöcytes obtained from so-called "non-patient donors", meaning women

[19] Personal communication Boada Palá, 9.7.2009, our translation.
[20] According to M. Boada Palá (personal communication, 9 July 2009).
[21] According to A. Murdoch, (personal communication 26 Nov 2008). See also http://www.nesci.ac.uk/news/item/egg-sharing-women-to-get-help-with-ivf-treatment-costs-for-donating-eggs-to-research [Accessed 16 March 2009], and Baylis and Mcleod (2007).
[22] http://www.hfea.gov.uk/500.html#guidanceSection4582 [Accessed 24 August 2010].
[23] According to E. Jackson, (personal communication 26 Jan 2010).

who had their egg retrieved for purposes of receiving some money and not for purposes of getting pregnant. However, they had originally yielded these eggs to IVF consumers or clinics, not to research projects. A number of these oöcytes would then be used for stem cell research instead, with the consent of the egg giver and the recipient IVF patient or couple.
In Spain, as mentioned before, so-called *compensaciones* of €1000 or even more per cycle are the rule and form an important motivation for women to undergo egg extraction (Orobitg and Salazar 2005; personal communication Clua Obrado). Most of them are students, workers and, increasingly, migrants from Latin America and Eastern Europe. According to one of our interviewees, Elisabeth Clua Obrado, who is responsible for the egg donation programme at Dexeus hospital, financial incentives play an ever increasing role for these women.

When it comes to oöcytes for research, the compensation model is rarely used in a straight-forward way. Indirectly, however, compensations were also applied by the CMRB in Barcelona. Anna Veiga, leading SCNT researcher at CMRB in Barcelona, had initially applied for permission from the relevant research review board to recruit non-patient "donors" and offer them €900 compensation for their service. The commission declined on the grounds that it considered €900 an undue incentive and suggested offering a maximum of €600 instead. With permission to offer only €600 compensation per cycle while the private fertility clinic at the same time offered €900-1000 to “donors” for reproductive purposes, Veiga decided against this model and chose to work with failed-to-fertilise eggs from IVF treatments instead. This resource, however, turned out to be inefficient. In 2009 Veiga approached the commission again, who recommended that she re-apply for permission to offer more than €600, on the grounds that failed-to-fertilise eggs had turned out unfit. Following this advice she was granted permission to use oöcytes that had originally been obtained by Dexeus, a private fertility clinic, for IVF purposes, in return for the usual amount of compensation of some €900-1000. Some of these oöcytes would then be reallocated to Veiga's research project at CMRB. Within this model, she argues, women are not paid for selling their eggs to research, since the process of egg retrieval and the monetary transaction had already been completed when the reallocation took place.[24] The advantage of this model from a research point of view is that, in comparison to egg sharing, it allows access to the eggs of women who are younger than the average IVF patient. Also in Spain, the CIPF in Valencia had already obtained a small number of oöcytes from women who received between €300 and 700 compensation in a private fertility clinic, Instituto Bernabeu, in Alicante.[25]

One conclusion that could be drawn from these data is that the trend towards material incentives is a strategy to *release* the infrastructural requirements that tie researchers to the IVF sector. Being able to offer money or material incentives makes researchers less dependent on the good will of IVF patients and clinics and thus offers a way to *loosen* the IVF-stem cell interface.

[24] The biotech firm Stemagen in California, we found, had applied a similar model of reallocating paid oocytes for reproductive purposes to research when they created the cloned blastocyst they presented in 2008 (S. Wood, personal communication 13 August 2009).
[25] According to M. Stojkovic, (personal communication 3 July 2009, and J. Ten (personal communication 29 September 2009).

Summary Findings

- The feasibility and comparative attractiveness of stem cell research relying on human oöcytes is limited. Limiting factors are ethical concerns, both researchers own concerns and perceived public concerns, legal restrictions, availability of alternative research strategies such as iPS cells, a great reluctance of women to donate (without being paid), and logistical difficulties related to the delicate nature of human oöcytes (e.g. spatial distance between clinic and lab).
- The practice of procuring human oöcytes for research purposes is underregulated on the European level, particularly the question of payment, compensation and financial incentives
- A shift has taken place from using "poor quality" to "good quality" oöcytes. It involves a shift toward ethically more problematic procurement practices insofar as good quality oöcytes obtained within IVF treatment are not "spare" in the sense that they are unsuitable for IVF. Reserving them for research means there are fewer eggs available for IVF. Fresh mature eggs from young non-patient "donors" are ethically more problematic because health risks related to hormone stimulation seem to be higher – and less explored - in younger women.
- Close personal connections and spatial proximity between stem cell research and the IVF sector have been and largely still are the prerequisite for research strategies requiring human oöcytes. Hence, the "IVF-stem cell interface" is critical for the resource human oöcytes (Franklin 2006).
- Yet, at the same time we found that a trend towards material incentives used to access women's oöcytes, mainly egg sharing and the reallocation of compensated oöcytes originally obtained for IVF purposes. These procurement strategies amount to crypto-commercialization insofar as they operate on the basis of material incentives but at the same time avoid open payment due to existing non-commercialization policies. They can be interpreted as a strategy to *release* the IVF-stem cell interface and the infrastructural requirements that tie researchers to the IVF sector.

In light of these trends and shifts, we would predict that research strategies that require the use of eggs, such as SCNT or parthenogenetic stem cell research, will either cease (sooner rather than later) or we will see a shift from crypto- to outright commercialization of human oöcytes. The latter seems the more likely in light of the current debate in the U.K. on revising the existing reimbursement scheme where many actors advocate a switch to the more generous Spanish compensation model. The 2009 decision by the New York Empire State Stem Cell Board may generate a pull in the direction of payment too.[26]

Policy conclusions

[26] The Board had decided that it was appropriate for women to be compensated for giving their oöcytes to stem cell research and that payments of up to $10,000 should be reimbursable as allowable expense under New York State Stem Cell Science (NYSTEM) contracts. See http://stemcell.ny.gov/news.html [Accessed 22 November 2010].

According to the Oviedo Convention and the Charter of Fundamental Rights of the European Union "[t]he human body and its parts shall not, *as such,* give rise to financial gain." This principle has been seriously undermined through lump-sum compensation of up to €1000,- without the requirement to document expenses. These compensations, in our view, de facto amount to a "financial gain" which contradicts the intention of the Oviedo Convention and the EU Charter of Fundamental Rights. It was not the purpose of this WP2 to develop a normative discussion for and against the commercialization of body parts in general or human oöcytes in particular. Yet, the signatory states of the Convention and the Charter had good reasons to agree on this principle which are still valid today. What the empirical data show is that there is a strong tendency to undermine and circumvent existing non-payment provisions through introducing material incentives in a legal grey zone between outright payment and strict non-payment, inter alia through "compensations" without the requirement to document expenses. If the European Union and the Oviedo Convention signatory states take that principle seriously, they should set up appropriate measures to foreclose lump-sum compensations in exchange for human oöcytes.

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Annex 3 REMEDiE Work Package 3: Final Report

EU and Global Politics: Transnational Science

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1. **Overview**

WP3 "*EU and global politics: transnational science*" is concerned with the governance of *clinical* research in the field of regenerative medicine, and especially the role of Europe in this global constellation. It explores how regenerative therapies and especially stem cell therapies move from laboratory/preclinical settings into clinical testing and use. WP3 studied the proposition that the governance of clinical research in this area is characterized by the tensions between transnational science and research communities as well as the dynamics of a globally operating bio-economy on the one hand, and the idiosyncrasies of national regulatory environments, institutional arrangements and risk cultures on the other.

1.1. Problematisation

Stem cells and clinical research are highly complex, controversial and challenging fields of governance. The entire field is still in the making (which means that only few years ago there were hardly any settled or dominant ideas, best practice concepts, clinical routines or regulatory standards. And today, there still is a lack of experience how these novel legal and institutional frameworks effect research and development practices). A range of different authorities, such as parts of the medical profession, the biopharmaceutical industry, regulatory agencies, medical research and bio-ethicists, policy makers, business analysts, as well as various publics struggle to shape the field according to their ideas and interests. These struggles take shape at various levels, such as in national parliaments, regulatory policy committees, transnational epistemic communities, as well at the level of the laboratory or the clinical research hospital.

1.2. Research objectives: propositions and research questions

A) A central regulatory issue in this field is the clinical testing of novel regenerative and cell therapies. A major dispute concerns the authoritative struggle over what constitutes a "legitimate" stem cell clinical trial, that is, what are the scientifically, medically and ethically best practices for studying and developing stem cell therapies in humans. Our research asks: *Which actors and authorities participate in the struggle over defining what a stem cell clinical trial is and how it should look like*? Our research suggests that main lines of conflict lie in the discrepancies and differences that stem from the bio-objectification of the stem cell as a therapeutic agent: as a industrially manufactured highly standardized medicinal product; as a treatment delivered by physicians in hospitals, kept "cheap and simple" (Interview UK/ 1); as a regulatory object that fits, with slight modifications, into the regime

governing pharmaceutical clinical trials, or as a practice that rather needs to be regulated within the broader framework of biomedical research and practice.

B) Clinical research regulations, in general, are highly structured by discourses of risk and uncertainty, as well as risk governance rationalities. This is especially true for stem cell clinical trials, for stem cells are considered as especially risky therapeutic agents because of vast indeterminacies due to lack of established knowledge. *How are risks defined and articulated by various authorities? Which authorities obtain the legitimacy to distribute and allocate risks among different actors/authorities, as well as among individuals and populations? How does "risk" as a discursive practice help to construct, shape, organize and "govern" the emerging field of stem cell therapy?*

C) We are interested in the ways actors in the stem cell field make sense of events, material practices, or course of action. *What are the collective ideas, discourses and imaginations that drive the rapid "move to the clinic" of (potential) stem cell applications? How do various stakeholders construct and assign meaning to their practices? In what ways does this influence their strategic decisions?* Our research suggests that different agents and stakeholders in the field conceive of stem cell therapies in different way, and differently imagine the "future(s)" of stem cell regenerative medicine.

1.3. Methodology

In our research we are interested, broadly speaking, how stem cells find their way into clinical research and experimental treatment settings.
In the last years many publications and reports identify and point to the policy challenges as well as the ethical, legal and social aspects and implications for the clinical and health care sector, public and private biomedical innovation strategies, for patients and "society" writ large.

The merit of WP3 research lies in the empirically detailed reconstruction of the structures and processes at work in translational stem cell research. WP 3 combines structural and procedural analyses on the "macro" level of state activities and governance, and a selection of detailed, empirically rich case studies ("micro" level, to study regulations in practice). On the basis of this combined evidence we envisage to develop an analytical understanding of the factors and forces that influence and shape the clinical and translational research into stem cell therapy.

Phases of research

A first phase of research primarily served the goal of exploring and mapping the field of RM according to clinical research and its regulation and governance along various lines: public/private; clinical/corporate; global/local. Geographic focus was on Europe, China, and the United States. The research included literature research (both in science and social science publications) and "desk top" research including media reports, policy documents, internet sources. Moreover, it included a series of exploratory field work in the form of "helicopter interviews" (as defined by Maarten Hajer, http://www.maartenhajer.nl/index.php?option=com_content&task=view&id=17&Itemid=19) and background talks with scientists, clinicians, policy makers, regulators, journalists, and biotechnology consultants, primarily in the UK, Germany, Austria, Brussels, and China.

A second phase of research within WP3 was conducted on the basis of exploratory research and early evidence that helped to slightly reframe and specify our research agenda. Hence, a series of qualitative, in-depth interviews were conducted with stakeholders in the afore mentioned countries plus the United States (University of Wisconsin, Madison, as one of the major RM hubs in the US). Moreover, a comparative case study approach was designed to study the (re-)negotiation and interpretation, as well as the impact of regulations on translational research practices on the "empirical ground".

Following the basic theoretical and methodological assumptions of interpretative social science methodologies, we acknowledge the constitutive role of language and symbolization for human (individual and collective) organization and agency (Yanow 2000; Gottweis 2006; Bourdieu; 1998). Drawing from methodologies of grounded theory and situational analysis, we have provided thick descriptions (Geertz 1973, Clarke 2005) of our selected case studies, based on qualitative interviews, further background talks, media analyses, literature review, content analysis of official reports and documents, web resources, as well as participant observation (site visits, workshop, conferences, etc.), where feasible. We have selected 4 cases, two in Europe, two in China to study how small biotech companies venture into stem cell therapies, establish networks with clinics, contract research organizations, manufacturing facilities and, in some cases, the pharmaceutical industry in an effort to develop stem cell therapeutics and/or to establish a clinical-grade cell therapy. Our analytical focus was on organizational and governance aspects, as well as emerging and evolving regulatory regimes that (pre-)structure and guide clinical and business agency and innovation strategies. Furthermore, we have explored the role of patients in the context of highly experimental clinical research settings.

Case studies

WP3 has conducted 4 case studies in 3 countries: Germany, the United Kingdom, and the Peoples' Republic of China. Cases were selected, loosely deploying criteria from the conventional most-similar or most-different case study design (Yin 1994), in order to enable us to analyze the stem cell clinical research field in as much heterogeneity as possible. Selection criteria included: clinical-academic v. commercial sponsor; type of investigational product: autologous / allogeneic; host/operating country; the stage of development, etc.

Case 1: ReNeuron (Guildford, UK)

ReNeuron is a commercial stem cell company that was founded out of King's College London Institute of Psychiatry in 1998. In March 2009, ReNeuron received approval from UK regulators to conduct a first-in-human study, announced as a "world's first" stem cell trial for a major neurological indication: stroke.

Case 2: Institute for Cardiovascular Regeneration/ t2cure (Goethe Universität/ Frankfurt am Main, Germany)

In cooperation with the Department of Cardiology (Goethe University Frankfurt), the ICR works on stem and progenitor cell based therapies for cardiovascular diseases. In 2008 a company, t2cure, was founded in order to take over the development of these therapies with respect to market authorization. *T2cure*, is dedicated to the development of novel progenitor cell-based regenerative therapeutics to provide new treatment options to

patients suffering from cardiovascular diseases like myocardial infarction or peripheral vascular diseases.

Case 3: Shenzhen Beike Biotech (Shenzhen, China)
Shenzhen Beike Biotech is a stem cell company that mobilizes a special business model to accelerate stem cell applications in hospitals. Although the local government of Shenzhen is in support of Beike, there are other voices who argue it is unethical to apply experimental therapies to patients and that Beike's proof of treatment effects mostly rely on patient testimonials through blogs on the company's website, but the treatments have not yet been proved by published scientific literature (Lau et al. 2008). The company's strategy for translational stem cell research seems to consist mainly of constructing a platform to link scientists, clinicians, research institutes, and healthcare institutions in an effort to create cooperation

Case 4: The Zhao team at Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China,
The case of Zhao's team from the Center of Excellence in Tissue Engineering, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, is the only case in China whose allogeneic stem cell clinical trials have obtained State Food and Drug Administration (SFDA)'s approval and moved near to the end of Phase II trials. This case study will show how stem cell research in a university setting starts with ideas in the hope of bringing treatment to patients, and describes the road from in-vitro development to animal studies and the development of control standards for clinical studies.

2. Global configurations

2.1. Regulatory politics and biomedicine

Today, political steering and national government has been gradually replaced by new forms of a "regulatory state" (Majone 1994), that is characterized by steering at arm's length – through (semi-)independent regulatory agencies that operate on a regional, national, as well as inter- and transnational scale (Gilardi 2008; Mayntz and Scharpf 2005). Moreover, state politics must be understand as crucially "globalized" in the sense, that national decision making is always crucially shaped by transnational politics, business and the global economy (Carnoy and Castells 2001; Hirsch and Jessop 2001). Andrew Barry has highlighted the crucial role of "technological zones" in the contemporary techno-political formation, where "*government operates … in relation to zones formed through the circulation of technical practices and devices*." (Barry 2001: 3). Regenerative medicine can be analyzed as such a techno-political zone – "tissue zones", in Alex Faulkner analysis (Faulkner 2009) that is regulated by attempts to classify, tame and standardize unruly tissues. As Barry notes: "*The process of standardization is intended as a process of deterritorialisation in which the mobility of capital and labour is unimpeded and across which uniform forms of social and environmental regulation are possible. But it is also a process which simultaneously forms new zones of control and regulation and creates new sites, objects and forms of political conflict."* (Barry 2001: 84)

Regulators all over the world have been confronted with the multiple challenges of governing these developments in the Life Sciences and the biotech industries, and it is often argued that – like many other policy fields alike – the governance of biomedicine has taken

on a global/transnational dimension. Scientists, clinicians and biomaterials are increasingly linked together in transnational research and development networks, and patients and their organized advocates also start to operate globally. A recent example of this is 'stem cell tourism'.

Interestingly, we can observe both global convergence and harmonization of biomedical regulations and the persistence of national/cultural idiosyncrasies. WP3 compared three major geo-political regulatory spaces of biomedicine and regenerative medicine: The US, Europe, and China. All three political systems have explicitly dealt with these pressing issues at a political and policy level, facing similar challenges. Most visibly, all three systems have undergone more or less significant institutional innovation. Pointing to convergence, all three systems have created and (partially) implemented some kind of risk-based approach to regulating regenerative therapies. However, discursive struggles over what a "regenerative" therapy is, how to define it, and whether to subsume it under existing legislation or to create some sort of *lex specialis*, was a contentious issue.

2.2. Clinical trials: practices, governance, political economy

The emerging field of stem cell therapies and its governance cannot be disentangled from the field of clinical trials more generally. However, the crucial issue here is that stem cells do not enter the pre-established field of (bio-)pharmaceutical trials and testing, but, in contrast, challenge and transform the clinical trials process itself. The emergence of stem cell therapies is the story of a problematization of clinical testing procedures, i.e. the reassessment and reframing of core categories of clinical trials, their purpose, best practices, and scientific as well as ethical legitimations. An analysis of stem cell products and the clinical trials process have been conducted within the REMEDiE Project by Webster, Haddad and Waldby (forthcoming 2012). We hence need to consider clinical research before we come back to regenerative medicine in detail.

Clinical trials refer to the testing of medical interventions (drugs, therapeutic regimes, surgical procedures) in human subjects (volunteers or patients). Their main purpose is to test the quality, safety, and efficacy of such (novel) interventions before they are authorized to be used and marketed. Both Europe and the US constitute highly risk averse regulatory environments, and industry representatives as well as some parts of organized patient groups have been lobbying for more streamlined and decreased regulatory efforts. Moreover, although clinical trials protocols (at least in the realm of more conventional pharmaceutical products and randomized controlled trials/RCTs) have been subject to increased efforts of global harmonization since the 1990s (the important role of the International Conference of Harmonization also for third parties need to be recognized, see Abraham 2002), still the regulatory regimes in the US and Europe vary significantly. For industry, the US constitutes a more or less single "technological zone" (cf. Barry 2001) with a single regulatory authority, the FDA. In Europe clinical trials authorization and oversight still is in the hands of the Member States' competent authorities. Despite efforts to harmonize European clinical trials (EU Clinical trials Directive 2001/20/EC), regulatory requirements persist to be highly divergent (O'Donnell 2007). In April 2010, the European Commission even describes the Clinical Trials Directive as "arguably the most criticized piece of legislation" passed by the Community on medicines ever since (EurActiv 2010)). In contrast to the US, in Europe – especially in Germany – the role of medical professions and their

institutionalized practices of self-regulation also contribute to European efforts to regulate the sector by means of independent regulatory agencies at arm's length.

Europe

In the European Union, cellular and gene therapy products have been legally defined in Annex I of the Human Medicines Directive (Directive 2001/83/EC) as medicinal products with additional requirements. Interestingly, the 2007 Advanced Therapies Regulation (EC 1394/2007) has established a novel regulatory framework that, for the first time, regulates products based on genes, human cells, and tissues under the same umbrella. Before the Regulation, a regulatory/legal gap analysis has shown that the European Community harmonization of medical laws provides no Community regulation for tissue engineered products. The Regulation lays down "specific rules concerning the authorization, supervision and pharmacovigilance of advanced therapy medicinal products" (ATMP). Interestingly, the regulation draws on existing regulation of gene therapy and somatic cell therapy products, and merely introduces a new definition of tissue engineered products. For different requirements still persist for these three categories, there remains a hierarchy between these products: products that fall under the category of both somatic cell as well as tissue engineered product will be regulated as the latter. In any case, if any product can be classified as gene therapy product it will be regulated as such. The risk-based hierarchy then is: somatic cells – tissue engineered products – gene therapy products. Another exception exists for combined products which consist of a ATMP and a medical device. Most importantly, the European Union Regulation concentrates on marketing authorization of ATMPs. The Community does not have any competence of regulating clinical trials which remain in the hands of national authorities (the Clinical Trials Directive 2001 sought to harmonize clinical trials standards and practices of the Member States, and to introduce obligatory GCP guidelines). Second, there exists the so-called "hospital exemption" in the Advanced Therapies Regulation, limiting its scope to ATMPs that are "either prepared industrially or manufactured by a method involving an industrial process". Excluded are

> "advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient" (Office Journal of the European Union: L 324/121, (6))

(Both the institutional organization of clinical trials as well as the "hospital exemption" are crucial differences to understand the regulation in practice as well as the political processes that have created it. We will need to analyze these two points later in this paper in a more detail)

United States

In the US, Regulation of Biologics dates back to the federal Biologics Control Act ("Virus, Serum and Toxin Act") from 1902. Since then it progressively refined, but its principles still serve today for governing cell and gene therapy products. Three central principles necessitate the manufacturer to secure control of the biological source; control of the production process, control of the bulk and final product. (cf. Kessler, Siegl, et al 1993). Pointing to the GMO controversy we see that each of these three dimensions (the bio-object, the process, and the final product) were subjects of fierce discursive struggles and political negotiations, and these struggles have taken different forms in different political

contexts (Gottweis 1998, Jasanoff 2005). Regarding regenerative medicine and stem cell therapy, it was not clear – and a matter of political negotiation – how to regulate these products. In the US, all stem cell-based products fall under category "human cells, tissues, and cellular and tissue-based products", defined in the Public Health Safety Act (PHSA) Section 361 as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient" (quoted from Halme and Kessler 2006: 1730).

The Center for Biologics Evaluation and Research (CBER) of FDA has jurisdiction over biological products, including cellular and tissue transplants, such as stem cell therapy. The CBEA Office for Cellular, Tissue and Gene Therapies (OCTGT) is the most relevant branch within CBER focused on stem cells. Since the early 1990s, the FDA has devoted considerable resources to the regulatory considerations of what have been termed human cellular- and tissue-based products (HCT/Ps). In February 1997, the FDA's sixth "Reinventing Government" report *Reinventing the Regulation of Human Tissue* and *Proposed Approach to the Regulation of Cellular and Tissue-based Products* (the Proposed Approach) focused on the increasing use of HCT/Ps, and proposed a tiered risk-based approach. The FDA's current architecture for the governance of stem cells was based on these documents. The Tissue Action Plan (TAP)' (cf. http://www.fda.gov/CbER/tissue/tissue.htm accessed 24 March 2009) was implemented in March 1998 with the purpose to develop timely the policies, regulations and guidance documents needed to implement the Proposed Approach, and the steps that FDA agreed to take in response to the recommendations made by the Government Accounting Office in their 1997 report, "Human Tissue Banks: FDA Taking Steps to Improve Safety, but Some Concerns Remain." On January 19, 2001, FDA published the first final rule "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing", which became fully effective on January 21, 2004. On 25 May 2005, the final piece of this regulatory framework was put in place when the Current Good Tissue Practice for Human Cell, Tissues, and Cellular- and Tissue-Based Product Establishments: Final Rule (the CGTP rule) became effective. Publication of the CGTP rule completed the set of regulations proposed in 1997 and issued in proposed or interim form since 2001 to implement the FDA's framework for regulation of HCT/Ps. The CGTP Rule represents the culmination of FDAs' efforts over several years to establish a comprehensive system for regulating human cell, tissue, and cellular and tissue-based products, and require HCT/P establishments to recover, process, store, label, package, and distribute HCT/Ps in a way that prevents the introduction, transmission, or spread of communicable diseases.

The Risk-based-approach in the US system provides that products that contain cells or tissues that "are highly processed, are used other than their normal function, are combined with non-tissue components, or are used for metabolic purposes" also need to be subjected to regulations governing the manufacturing and licensing of biologic products. These additional requirements appliy, interestingly, to the vast majority of stem-cell based products. Categorized as biologic, as defined in PHSA Section 351, manufacturers need to file an IND (new investigational drug) application, containing preclinical data that suggest evidence of likely safety and efficacy of the product, before they can be tested (or used) in clinical context. (cf. Halme & Kessler 2006). GMP requirements are key to this process: the manufacturer of a biologic product must demonstrate that it is "safe, pure, and potent".

Comparing US and Europe: institutions, structures, regulations

The substantial regulations, requirements and standards for bringing a stem-cell based product on the market are rather similar in the US and in Europe. Both regulatory frames emphasize quality control (GMP) and offer a risk-based assessment and classification of these products. From this technical standpoint this is not surprising, because the European Medicines Agency and its regulatory scientists have looked to their colleagues at the FDA, and there are many telephone conferences and joint meetings where regulators and regulatory scientists discuss "technical" questions and exchange their experiences. We now want to shift our focus to the institutional and policy level, stressing the differences between these two settings.

Structural differences between the US and Europe regarding (bio-)pharmaceutical research economy and its regulation:

A) For the bioindustries, the US is a huge single market with on central competent authority, the US Food and Drug Administration (FDA). Preclinical and clinical R&D, as well as marketing authorization is regulated under the authority of the FDA, and FDA "project managers" usually follow a manufacturer and its products from the very beginning through the entire process of development. By contrast, in Europe industry is confronted with a highly diversified regulatory landscape. Despite increased efforts to harmonize European drug laws and regulations within the last decade, regulatory idiosyncrasies persist and regulatory authority is divided between member states and the Community. Most prominently, clinical trials remain under the authority of national agencies, whereas marketing authorization (at least for "biologics" and advanced therapies) need to go through the Community's centralized procedure.

At the supranational level in Europe, regulatory competences are divided between the European Medicines Agency (EMA) and the European Commission. The "division of powers" between the two institutions provides for the EMA to deal with the technical and scientific details of the regulatory process and to develop advice or recommendations for the Commission, who finally makes the decision. Separating risk assessment ("impartial science") from risk management ("politics") has become an observable tendency in liberal "regulatory states" (Rothstein et al 2006).

B) Institutional level: The EMA operates in a different way to the FDA. The FDA combines, as many US independent regulatory agencies (cf. Gilardi 2008) do, legislative, executive, and juridical powers, whereas these powers are distributed in Europe between EMA and the Commission. The EMA is also a very young agency that has only incrementally expanded its competences, while the FDA has a long tradition and was often publicly very visible (and has been able to increase its reputation in the US public by preventing or averting public health crises, e.g. the Thalidomide disaster (Carpenter 2010, Daemmrich 2004).

The FDA gathers, as many US independent regulatory agencies (cf. Gilardi 2008), legislative, executive, and juridical powers, whereas these powers are distributed in Europe between EMA and the Commission. Another characteristic is historical: whereas the EMA is a very young agency that has only incrementally expanded its competences, the FDA has a long tradition and was often publicly very visible (and were able to increase their reputation in

the US public by preventing or averting public health crises, e.g. the Thalidomide disaster (Carpenter 2010, Daemmrich 2004).

C) Policy making and policy cultures: Although, as stated, outcomes are similar in the US and Europe, the ways how to approach cell products were strikingly different. What was true for the GMO regulatory process, seems to hold true also for regenerative medicines regulatory policy making. As Vogel observes: "The United States initially chose to regulate both GM food and seeds under existing laws, while EU legislation established a distinctive and complex set of new regulatory requirements that apply only to this new agricultural technology." (Vogel 2003, p 564)

D) For Europe, integration and harmonisation of both the clinical trials process and the field of "advanced therapies" must be understood as strategies to advance Europe's competitive position on a global scale, and particularly to challenge the US hegemony in the field of bioscience and the biotech industries. As one industry journal comments: "*For decades FDA was known as the "Gold Standard" for regulatory oversight of clinical trials. In 2005, updates to the 2001 Clinical Trials Directive became effective in the European Union and researchers faced a new way of regulating clinical trials. The same became true of post-market safety reporting as FDA and EMEA took divergent paths. Sponsors and clinical sites started grappling with how to be compliant with both FDA and EMEA*." (BioWorld Today 2010, URL: http://www.bioworld.com/servlet/com.accumedia.web.Dispatcher?next=T10606_10755)

China

Just like the FDA's regulation on stem cell-based therapies in the United States, and in Europe the European Commission's Regulation (EC) No 1394/2007 on advanced therapy medicinal products were proceeded by a protracted process of negotiation, also in China the passing of the Regulations on Clinical Application of Medical Technology issued on 2 March 2009 by the Chinese Ministry of Health (MOH) took a long time and involved a lengthy decision-making process. Before 2007, stem cell-based products and therapies were categorized as biological products, and applications for clinical trials had to go through the State Food and Drug Administration (SFDA) review according to Provisions for Drug Registration (SFDA Order No.17). However, during the first review processes in 2005 and 2006, SFDA found it difficult to regulate stem cell-based products and therapies as drugs. On the verge of medical reform in China, SFDA no longer wanted to be responsible for the review (interview 6). On 11 March 2008 the Chinese government announced a sweeping cabinet restructuring plan that SFDA would be put under the Ministry of Health (MOH) and the "Super Ministry of Health" would become the manager of areas such as medical services, food, drugs, and public health (Xinhua 2008).

After a long negotiation, it seems that an agreement has been reached between SFDA and MOH that in the future, regulation of stem cell clinical application would be promulgated and implemented by the MOH. A stem cell application would be applied and regulated not as a drug, but as a new medical technology for clinical application. On 24 July 2007, MOH put "the Regulations on Clinical Application of Medical Technology (exposure draft)" and "the List of Category 3 Medical Technology (exposure draft)" on its website for more

consultation and opinions from the public. This is a new and regular way to generate participatory elements in the development of law in China. In these exposure drafts, the stem cell transplantation technology was listed in the category 3 medical technology. Meanwhile, the MOH entrusted the Committee of Association forMedical Technology Application (MTA) of the Chinese Hospital Association to constitute an expert committee and to draft "the Regulations on Human Stem Cell Clinical Application". On 24 October 2008, the MTA organized a workshop to discuss "the National Regulations on Clinical Application of Human Stem Cell Transplantation Technology (draft)". The participants recommended that the clinical application of embryonic stem cell technology should be performed more cautiously and strictly and follow ethical and moral norms, which is still under discussion. According to the Reguations of Clinical Application of Medical Technology, which came into effect on 1 May 2009, the stem cell medical technology, as all "category 3 medical technology" that are deemed "ethically problematic", "high risk", and "still in need of clinical verification", is under the direct regulation of the MOH. The MOH has designated five institutions to review them from 1 May 2009 to 1 May 2011. However, because the detailed criterion had not been worked out yet, the review process has been delayed. In the meantime, the existing regulatory loopholes have been used by actors such as Beike, a medical company operating in the field of stem cell therapies and a global key actor in the world of stem cell tourism (see Chen/Gottweis forthcoming 2012).

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Annex 3.1 – Contribution to REMEDiE Project: Adjunct Report by Yuri Egorov prepared for Herbert Gottweis relating to Eurobarometer 2010

1. Introduction

Biomedical research typically enjoys substantial public support in EU countries. However, there is one field within medical biotechnology that repeatedly attracted criticism. Regenerative medicine, "the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects" (according to a definition by the NIH) promises significant improvements for an ageing population. However, it is beset with intriguing moral dilemmas surrounding the origin of living cells and tissue.

Fig. 22 in Eurobarometer 2010[27] shows the dynamics of approval for human embryonic stem cell research between 2005 and 2010. In general, average support for EU27 remained almost unchanged: slight drop of support from 69% to 67%. However, we observe substantial polarity in opinions across EU countries. While UK and Spain are among most supportive countries, Austria and Germany are at the opposite pole.

Another non-trivial phenomenon is related with the dynamics of support that goes in opposite direction across different countries. For example, we observe very high rise of support in Estonia (from 50% to 75%) and at the same time very high drop in support in Czech Republic (from 75% to 52%).

It was very difficult for scientists to explain such pattern of behavior. The goal of this study is to shed some light on those phenomena. We used both economic and social indicators from EuroStat and tried to find pronounced correlations between support of this research and corresponding socio-economic indicators. Another goal was to explain the dynamics by dynamics of socio-economic indicators. Finally, it was possible to find some regularities that partly explain the observed patterns of responses and their dynamics.

2. Economic factors

The following economic indicators have been considered[28]:

- GDP growth in 2004 and 2009, year prior to surveys (denoted as GDPgr04 and GDPgr09),

[27] Europeans and Biotechnology in 2010. Winds of change? – EC.
[28] Data source: http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/

- GDP per capita in pps in 2009, i.e. measured in purchasing power around the mean of EU (GDPcap-pps09),
- The level of pensions in 2008 measured in Euro (Pens2008),
- Unemployment rate in April 2010 (Unem2010).

GDR growth had a dramatic change between normal year 2004 (with positive rates) and 2009, the year of crisis, when it was negative for almost all EU countries. The crisis could have an effect, and the goal was to see to what extent. Fig. 1 shows that severity of crisis in 2009 (measured by change in GDP growth between 2004 and 2009) has pronounced negative effect on changes in approval of stem cell research. In other words, higher crisis perturbed support more.

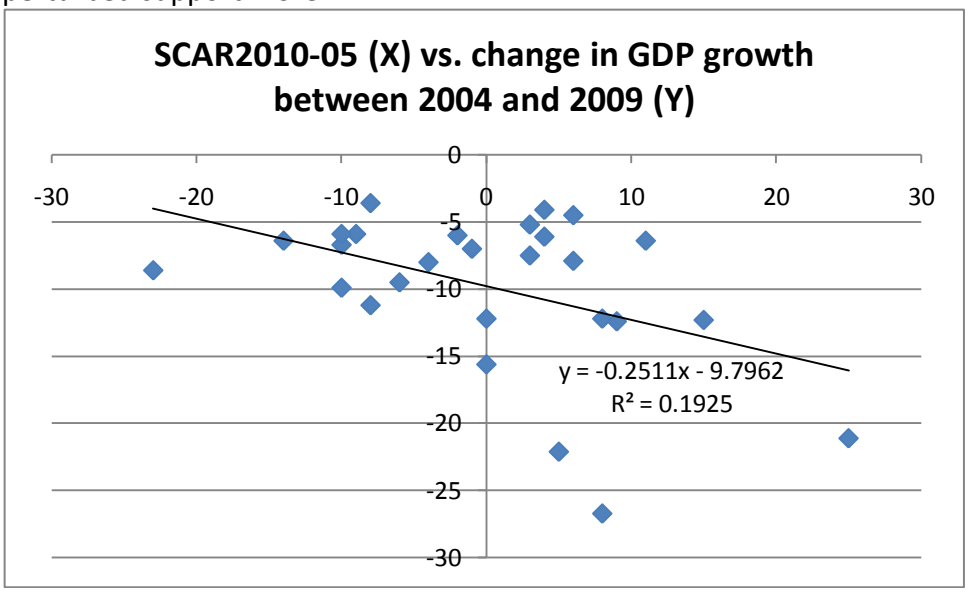


Fig. 1. *The relation between change in growth rate in 2004-2009 and change in support of stem cell approval of research (SCAR). The relation inb negative and substantial.*

Other factors (GDP per capita, pension level and unemployment rate) have much less pronounced effects, shown in Fig. 2-4. From Fig.2 we see that unemplyment rate has positive effect on public support. It might be linked with additional jobs that R&D in this industry can create.

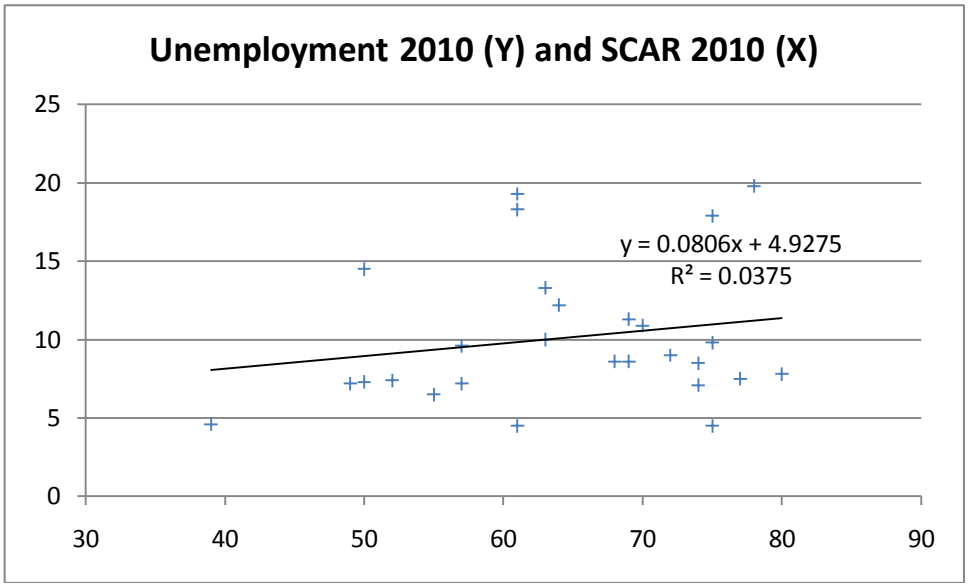


Fig. 2. *Unemployment rate has positive effect on % of approval in stem cell research (SCAR).*

Fig. 3 and 4 show that effects of DGP per capita and pension levels are small.

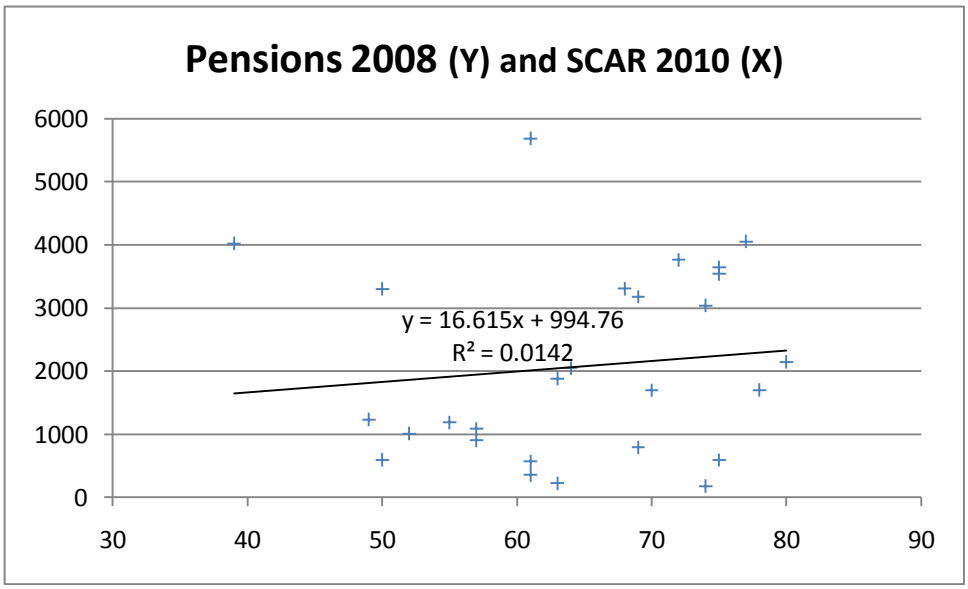


Fig.3. *There is small positive correlation between approval and pensions.*

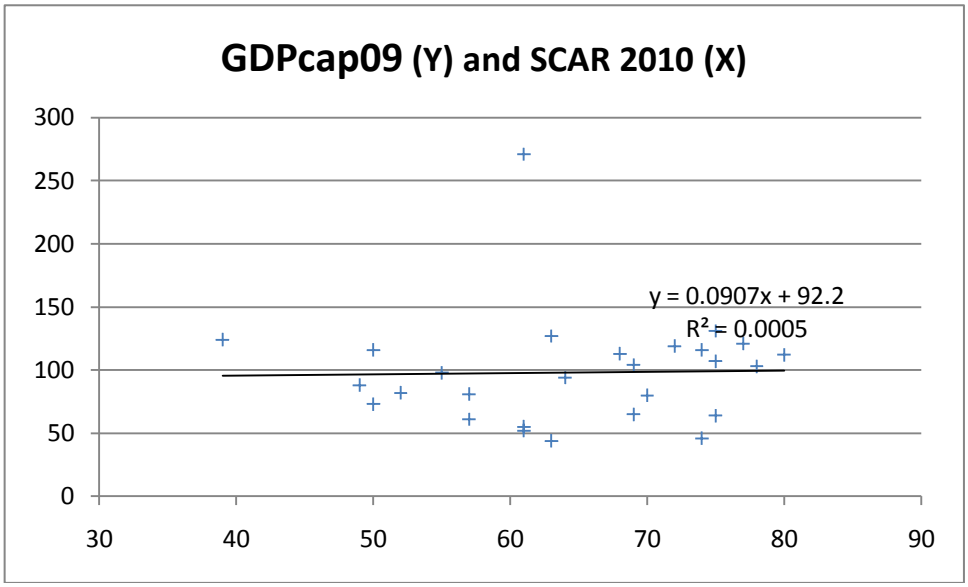


Fig.4. *The effect of GDP per capitl on SCAR is negligible.*

3. Health dynamics and cell research approval

There exists many indicators of health, but we selected one related to expected healthy years of life at birth for females[29]. The advantage of this indicator is that it does not simply measure life expectancy (that may be linked with different life quality) but also gives quantitative indicator of health. The working hypothesis was as follows. If such indicator grows over time, people see the positive results of medical research on their quality of health, and this can give public support for it. In the opposite case the negative support may grow, since results are negative. In order to do such study, 2 new variables have been introduced:

HLEf09-04 = HLEf2009 – HLEf2004; Stce10-5 = Stem cell 10 – Stem cell 05 (1)

Our hypothesis was as follows. If there is a real decline in Life expectancy of healthy years for females (HLEf), who have more pronounced difference between this index and life expectancy, the public perception (that spreads via word-of-mouth) is likely to link it with the decline in real quality of medical service.[30] Then the society might form low trust to medical system in general and would not support any research based on experiments with patients and their tissues. But if quality of health is rising, society will support such research. Fig. 5 shows the plot of both differences against each other, as well as the linear regression, showing positive trend line.

[29] Data source: http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_hlye&lang=en . Explanation is here: http://epp.eurostat.ec.europa.eu/cache/ITY_SDDS/en/hlth_hlye_esms.htm

[30] There exists asymmetric information between doctor and patient, who might be unable to judge how optimal have been the actions of doctor to keep her health and high level. Doctors also might view differently from patients the trade-off between saved life and quality of life. Besides, there is also an incentive of their income maximization, producing for example unnecessary operations.

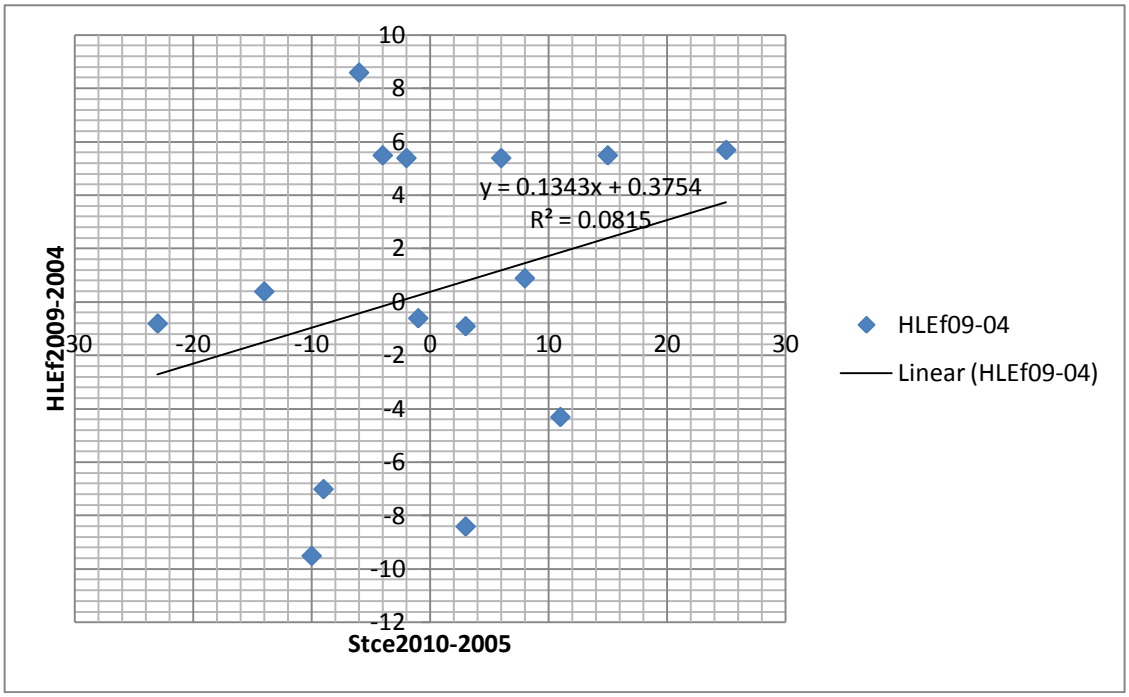


Fig. 5. *The plot between changes of health female life expectancy between 2009 and 2004 and differences in % of approval of stem cell research. The positive link is discovered with 8% of variance explained. This means that dynamics of approval is positive mostly in countries, where there is positive dynamics in health life expectancy across females.*

It is also interesting to see the raw data. They are given in Table 1.

Country	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Belgium	66,4	68,5	68,3	65,4	68,4	69,1	68,8	69	69,2	58,1	61,9	62,8	63,7	63,8	63,5
Bulgaria	:	:	:	:	:	:	:	:	:	:	:	:	73,8	65,5	65,6
Czech Republic	:	:	:	:	:	:	:	63,3	:	:	59,9	59,8	63,2	63,3	62,5
Denmark	60,7	61,1	60,7	61,3	60,8	61,9	60,4	61	60,9	68,8	68,2	67,1	67,4	60,7	60,4
Germany	64,3	64,5	64,3	64,3	64,3	64,6	64,5	64,5	64,7	60	55,1	58,04	58,3	57,4	57,7
Estonia	:	:	:	:	:	:	:	:	:	53,3	52,2	53,68	54,6	57,2	59
Ireland	:	:	:	:	67,6	66,9	66,5	65,9	65,4	64,3	64,1	65,02	65,3	65	65,2
Greece	69,2	69,6	68,7	68,3	69,4	68,2	68,8	68,5	68,4	65,2	67,2	67,86	67,1	65,8	60,9
Spain	67,7	68,4	68,2	68,2	69,5	69,3	69,2	69,9	70,2	62,5	63,1	63,27	62,9	63,3	61,9
France	62,4	62,5	63,1	62,8	63,3	63,2	63,3	63,7	63,9	64,1	64,3	64,07	64,2	64,2	63,2
Italy	70	70,5	71,3	71,3	72,1	72,9	73	73,9	74,4	70,7	66,5	64,1	61,9	61,2	61,2
Cyprus	:	:	:	:	:	:	:	:	69,6	:	57,9	63,21	62,7	65,1	65,8
Latvia	:	:	:	:	:	:	:	:	:	:	53,1	52,15	53,7	54,1	55,8
Lithuania	:	:	:	:	:	:	:	:	:	:	54,3	56,13	57,7	59,3	60,9
Luxembourg	:	:	:	:	:	:	:	:	:	60,2	62,1	61,79	64,6	64,2	65,7
Hungary	:	:	:	:	:	:	:	:	57,8	:	53,9	56,97	57,6	58	58
Malta	:	:	:	:	:	:	:	65,7	:	:	70,1	69,21	70,6	71,9	70,6
Netherlands	62,1	61,5	61,4	61,1	61,4	60,2	59,4	59,3	58,8	61	63,1	63,22	63,7	59,8	59,8
Austria	68	68	68	68	68	68	68,5	69	69,6	60,2	59,6	60,81	61,1	59,5	60,6
Poland	:	66,8	:	:	:	:	:	68,9	:	:	66,6	62,53	61,3	62,6	62,1
Portugal	63,1	60,5	60,4	61,1	60,7	62,2	62,7	61,8	61,8	52	56,7	57,62	57,3	57,2	55,9
Romania	:	:	:	:	:	:	:	:	:	:	:	:	62,3	62,6	61,4
Slovenia	:	:	:	:	:	:	:	:	:	:	59,9	61,01	62,3	60,9	61,5
Slovakia	:	:	:	:	:	:	:	:	:	:	56,4	54,43	55,9	52,3	52,3
Finland	:	57,7	57,6	58,3	57,4	56,8	56,9	56,8	56,5	52,9	52,4	52,71	58	59,4	58,4
Sweden	60	60	60	61,3	61,8	61,9	61	61,9	62,2	60,9	63,1	67,05	66,6	68,7	69,5
United Kingdom	61,2	61,8	61,2	62,2	61,3	61,2	60,8	60,9	60,9	63	65	65,1	66,1	66,3	66,3

Table 1 shows healthy life expectancy of females in different EU countries. In order to see the regularities, a graph for subset of countries is also provided.

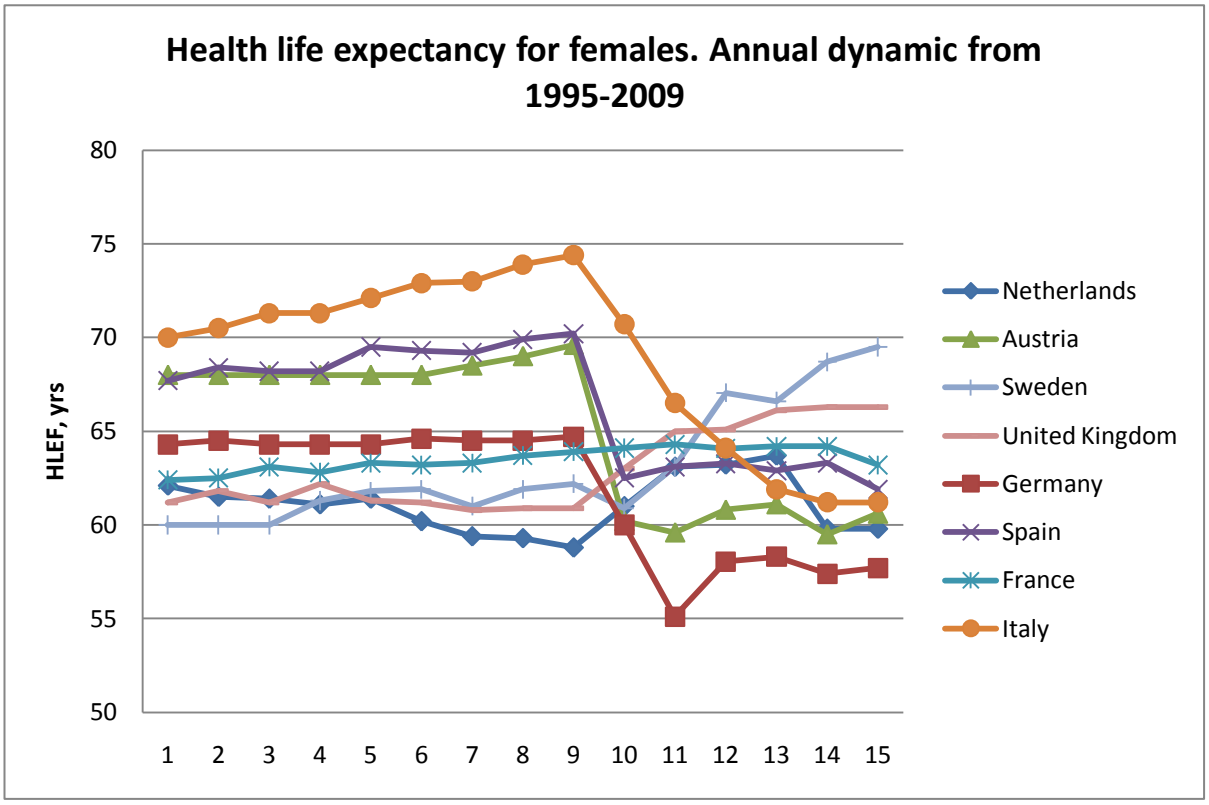


Fig.6. *Dynamics of HLEf for different countries shows quite different trends. They cannot be exaplained by methodology, since even sign of trends differs across countries. Around 2004 there is structural change, with decline for Austria, Germany and Italy, but growth for Sweden and UK. French data do not show any sructural change.*

4. Conclusions

This analysis has shown that both economic and social factors influence public opinion on SCAR. Especially interesting are the results on dynamics. The effect of economic factors is typically small (for each of them). Interestingly, unemployment rate positively correlates with support of stem cell research. But health factor dynamics has shown much more pronounced effect, explaining 8% of variance.

Appendix:
Per cent of people approving Stem cell research in 2005 and 2010.

Country	Stem cell 10	Stem cell 05
Belgium	74	76
Bulgaria	63	n/a
Czech Republic	52	75
Denmark	77	74
Germany	50	59
Estonia	75	50

Ireland	63	55
Greece	64	53
Spain	78	79
France	75	72
Italy	69	79
Cyprus	55	65
Latvia	61	53
Lithuania	61	56
Luxembourg	61	65
Hungary	69	77
Malta	57	51
Netherlands	75	71
Austria	39	53
Poland	57	65
Portugal	70	66
Romania	74	n/a
Slovenia	49	40
Slovakia	50	60
Finland	68	53
Sweden	72	78
United Kingdom	80	74
Iceland	77	n/a
Liechtenstein	n/a	n/a
Norway	74	n/a
Switzerland	57	n/a
Montenegro	n/a	n/a
Croatia	54	n/a
Form. Macedonia	n/a	n/a
Turkey	58	n/a
United States	n/a	n/a
Japan	n/a	n/a

Annex 4 REMEDiE Work Package 4: Final Report

Regenerative medicine in Europe: global competition, international links and innovation governance

Professor Brian Salter (Lead), Stuart Hogarth, Kings College London

Table of contents

Glossary

EC	European Commission
EU	European Union
EMA	European Medicines Agency
FDA	Food and Drug Administration
FP	Framework Programme
hESC	human embryonic stem cells
iPSC	induced pluripotent stem cells
RM	regenerative medicine
VC	venture capital

Acknowledgements

In the course of our research we have interviewed 52 scientists, policymakers, and industry executives from six EU member states; we are extremely grateful to all those who gave generously of their time for this process. We would like to thank our REMEDiE colleagues for their assistance, in particular Andrew Webster for his able coordination of the project, and Michael Morrison for sharing his data on the EU RM sector.

Introduction

Many EU member states are seeking competitive advantage in the emerging regenerative medicine sector. Regenerative medicine has become a priority in national life sciences research strategies, as states provide funding for major research centres, shared infrastructure such as cell banks, support for commercialisation whilst developing regulatory frameworks which facilitate research with human embryonic stem cells. At the EU level, support for RM research in FP6 and FP7 has enabled the development of scientific collaborations between scientists in member states, facilitated standardisation (for instance through the human embryonic stem cell registry) and has also benefited industry. The development of a harmonised regulatory framework for RM products is seen as a major advance on the previous patchwork of divergent national frameworks.

In this work package we sought to inform policymaking within Europe by developing a detailed picture of the current dynamics of RM innovation within Europe, and assessing the policies and alliances which Member States and the EU are adopting to strengthen Europe's position in the RM sector. To do this we have undertaken detailed case studies of six European member states: the Czech Republic, France, Germany, Spain, Sweden and the UK. For each country we have:

- mapped the strategies employed by member states in terms of national research programmes, commercialisation initiatives and international alliances;

- analysed the factors which enable (or hinder) the development of effective innovation strategies and international alliances.

Central to our analysis has been an interest in understanding how the development of national policies for supporting regenerative medicine is shaped by interactions within a complex multi-level governance framework involving EU institutions, member states and sub-national authorities.

The UK stem cell initiative and the subsequent Pattison Report in 2005 was perhaps the first attempt in Europe to construct a coordinated national strategy for regenerative medicine (albeit one which was focused on stem cell research). However, a number of countries have to some degree followed suit and the elements of national strategies for RM might include:

- a legislative framework for hESC research;
- dedicated funding including the development of major research centres and shared infrastructure such as stem cell banks;
- the creation of a national network to promote scientific collaboration;
- the promotion of public-private partnerships and
- the promotion of international research collaborations.

The development of a number of these initiatives by a given country does not on its own indicate the presence of a coordinated national strategy. One of the aims of our research was to identify not simply the initiatives being undertaken but whether these initiatives were seen as part of a strategic plan. National strategies are primarily focused on supporting basic or translational research but there is also support for commercialisation. For instance, in the UK the Technology Strategy Board has recently committed £21.5M to fund commercially-oriented projects and

In some cases data is available on levels of funding, but such data is not consistently available in all the countries studied, making direct comparison impossible.

Methodology

Our national case studies were selected using three criteria. Firstly, the country had to be one in which there was a significant level of RM research activity (even if that level was only relative to the country's size and science base, thus the inclusion of the Czech Republic which has probably a lower level of activity than any other case here). The other criteria were two variables – the strength of the domestic biotech sector and the permissiveness of the regulatory environment for research on human embryonic stem cells. We sought to have a mix of these two variables, thus Sweden and the UK both have a permissive approach to hESC research and a strong biotech sector. Spain and the Czech Republic have similarly permissive regimes but relatively under-developed biotech sectors. Conversely Germany and France have strong biotech sectors but relatively restrictive regimes for hESC research. These selections were not made to test any prior hypothesis regarding the optimal conditions for supporting RM innovation, rather we simply sought to ensure that a range of environments were explored.

For each case study we carried out a combination of desk research and stakeholder interviews. Our target was to carry out about ten interviews per case, interviewing scientists, policymakers, and industry executives (RM, pharmaceutical and VC). Interviews were conducted to provide supplementary data concerning each country's RM activity to that gathered through desk research and also to garner stakeholder views. All interviews were semi-structured using a common template but interviews were adapted to the individual's expertise and experience. Interviews lasted from 30 minutes to 70 minutes. Most were conducted face-to-face but a small proportion was conducted by phone. In total 52 interviews were conducted between September 2009 and November 2010. Interviews covered a wide range of topics from support for basic science, the market conditions for commercialization, to the regulatory environment. Interviewees were asked to identify the major barriers to progress and reflect on the key governance challenges for policymakers.

Data generated from these interviews has been used to develop a set of policy recommendations regarding innovation strategy for regenerative medicine in the European Union, which will be submitted to the European Commission and shared with research participants (including national and sub-national policymakers). All individual responses remain confidential and are presented in an anonymised form.

National strategies and national contexts

Czech Republic

In 2003 the Czech Republic became only the second European country to derive human embryonic stem cell lines. It is one of only two new EU member states where hESC research is performed (Kure, 2009). A legal framework has been established which has broad political support (with the exception of the Christian Democrat party). EU structural funds are being used to develop new scientific infrastructure and an organisational framework to support commercialization is emerging (technology transfer offices, science parks and incubators).

Context: Life sciences and biotech innovation performance

The Czech economy enjoys a strong tradition in technical and mechanical engineering. According to the European Innovation Scoreboard 2008 the Czech Republic belongs to the group of moderate innovators with innovation performance below the EU-27 average. Nevertheless, the speed of improvement of innovation performance is higher that of the EU-27. Relative strengths are in firm investments, innovators and economic effects: relative weaknesses are in human resources, finance and support and throughputs. Government spending on R&D has been growing and is higher than in most other new member states but still lags behind the EU average. The intensity of innovation has improved greatly in recent years and has reached the EU average. Business expenditures on R&D has also increased but is still below the EU average and is concentrated mainly in enterprises with foreign capital. Cooperation between research and industry is still limited in the Czech Republic, innovation carried out in the business sector is based on adopting existing technologies from abroad and not on utilising knowledge from the research sector.

There are about 23 pharmaceutical companies in the Czech Republic, eight large and around 15 medium-sized, all producing generics. The FP6 14allbio project conducted a 2007/8 survey of biotechnology in the 14 new member and accession states identified 39 biotech companies in the Czech Republic and ranked the country third, (just behind Hungary but some way behind Poland) in terms of numbers of employees. Most of these are located in or around the cities of Prague and Brno. As with other new member states, there is very little venture capital available to Czech biotech firms. (EuropaBio/Venture Valuation, 2009)

Context: Funding and innovation governance

The *Reform of the Research, Development and Innovation System in the Czech Republic* was approved by the government in March 2008. It outlines a reform strategy to address the weaknesses of the current system which is described as overly complex and highly fragmented. Twenty-two separate departments had some R&D budget, making coordination difficult and preventing a focus on large-scale support in areas of scientific

excellence. The number of grant awarding bodies has been halved and resources have been redirected to the new Technology Agency of the Czech Republic (TACR) which supports applied research and encourages public-private collaborations. Public R&D in the Czech Republic is conducted in universities, institutes of the Academy of Sciences and institutes run directly by government departments (such as the department of health). There is a gradual shift towards more of a focus on supporting research at universities. The reform focuses especially on simplification and increasing efficiency of the R&D support system, encouraging excellence in R&D, facilitating knowledge translation, improving public-private collaboration, establishing a more flexible organisational structure of public research organisations, increasing the number of trained researchers, and facilitating more international collaboration. This reform strategy will be delivered through the *National Policy of Research, Development and Innovation in the Czech Republic for 2009–2015*.

Although the current financial crisis has precluded any increase in expenditure, successive governments have viewed R&D and innovation as a priority and public investment in RDI has been relatively protected. Significant support for the Czech R&D infrastructure is coming from EU Structural Funds, for instance the new Central European Institute of Technology (CEITEC) in Brno which will provide state-of-the-art facilities for 51 biomedical research teams when it is completed. Scientists and clinical researchers in Brno have built on a longstanding collaboration with researchers at the Mayo Clinic through a new initiative the International Clinical Research Centre (ICRC), a major new facility. The government has also announced the Return programme, a funding initative to encourage Czech scientists working abroad to return home and to foreign researchers (the South Moravia region already has its own scheme: SoMoPro).

RM: the SCIENCE BASE

The main locations of regenerative medicine research in the Czech Republic are the capital Prague and the second largest city: Brno. The main hub of Prague's RM activity is the **Institute of Experimental Medicine** (IEM) the leading centre for biomedical research in cell biology, neurobiology, developmental toxicology and teratology, molecular embryology, and molecular pharmacology. The IEM Director, Professor Eva Sykova, is also head of the **Centre for Cell Therapy and Tissue Repair** (CCTTR). The IEM is the only organisation in the Czech Republic with license to work on human embryonic stem cells. The Institute now includes the **Innovation Biomedical Centre**, a business incubator built with EU structural funds in 2008, which has GLP/GMP facilities for applied research and scale-up technologies focused on regenerative medicine (the Centre is licensed to manufacture mesenchymal stem cells). These Prague groupings have close linkages with the main RM researchers in Brno: both Petr Dvorak, Head of the Department of Biology at Masaryk University in Brno, and Ales Hampl, head of Histology and Embryology at Masaryk, are also members of the IEM / CCTR. Activity in Brno will be enhanced through work at CEITEC where there will be stem cell

research in haematology and neurodegenerative disease and at ICRC where there will be more translational research on cell therapies for cardiac failure and neurodegenerative disease.

Interviewees were agreed that existing RM research groups were growing and but divided on whether the number of groups and institutions engaged in RM research was also increasing. Czech scientists expressed frustration that there is no national strategy which provides targeted support for regenerative medicine. There was some concern that this might reflect a lack of support for the field amongst policymakers, but there was also a suggestion that this was a broader issue: there has been prolonged discussion about the benefits of ring-fencing some research funding for strategic priorities but one interviewee stated there was a lack of political will and two interviewees said that there was a lack of consistency in support across administrations. There was some hope that the new Technology Agency might provide some targeted funds but also concern that the Agency's funding might be wholly absorbed by industry.

RM: Commercial sector

REMEDiE WP 1's survey of the European RM sector found no RM firms in the Czech Republic.

RM: Legal context

The Czech Republic was the first new EU member state to establish a permissive legal framework for hESC research. The national Bioethics Committee approved hESC research in 2003 and the government presented a Bill to parliament in 2005, which became law in 2006. One interviewee involved in drafting the law stated that it was largely modeled on the UK's legislation. Research can only be conducted using supernumerary embryos from licensed IVF clinics. Proposals for hESC research must go to the Ministry of Research and Education where they are passed to Research and Development Council and the National Research Ethics Committee for approval. Stem cell lines must be registered. (Kure, 2009) Scientists we interviewed expressed some concern that implementation of the ATMP regulations in the Czech Republic were creating barriers to clinical translation of cell therapies.

RM: International links

The Czech Republic has bilateral agreements with the United States, China, Singapore and Israel. Leading Czech scientists are active in international networks, for instance the Czech Science Foundation was part of the International Stem Cell Forum and International Stem Cell Initiative. The IEM has collaborations with Japan, Canada and the US.

Data on stem cell research projects funded under FP6 show that the Czech Republic was only involved in a small number of projects, and did not play the role of coordinating partner in any. The former statistic reflects the relatively small number of research teams working on RM in the Czech Republic, whilst the latter may also be a function of a lack of infrastructure to support Czech scientists applying for funding (a concern raised in two interviews). However, Czech interviewees stated that FP6/7 funding had been very important for RM research in their country and emphasized the importance of interacting with experts from other member states. Other EU funding has supported international links, for instance Marie Curie fellowships which bring a number of researchers from the Ukraine, Russia and elsewhere to the IEM. IEM has some success with attracting foreign researchers

from countries such as France, Italy and Spain. Stem cell researchers at Masaryk University have also been able to attract researchers from Finland, Bulgaria, Latin America and the UK, in part thanks to the SoMoPro initiative.

DISCUSSION

The Czech Republic has significant ambitions in life sciences research with major new facilities like CEITEC, BIOCEV and ICRC being developed. It has strengths in stem cell research and is able to attract junior researchers from other countries but may require more foreign expertise if the new facilities are to be fully exploited. However, thus far it has lacked a national strategy for regenerative medicine. To the extent that the Czech Republic's future RM activity will depend on increased resources then much may depend on how quickly the national economy recovers from the recent recession.

France

With a relatively restrictive regime for hESC research, many believe that France has entered the RM race somewhat behind the field, a sentiment expressed in a 2004 report from the French Academy of Sciences. However, France has a strong track record in developmental biology (including stem cells) and in the field of gene therapy and significant progress has been made in last few years, including the establishment of some major research centres. Nevertheless, most of our French interviewees stated that France still lacks a national strategy for regenerative medicine. The degree to which progress is also hampered by more structural weaknesses in the organisation of biomedical research is uncertain, but a 2006 report described the system as in a "state of upheaval" and a more recent independent report recommended fundamental reform to the research system. A shift towards funding translational research was seen in the development of clusters and networks such as Canceropoles and Genopoles around 2004 and to some extent this has provided a platform for recent RM funding, most notably the I-Stem initiative which is linked to the Paris Genopole cluster.

Context: Life sciences and biotech innovation performance

France ranks 11th in the Innovation Union scoreboard for EU member states and is in the middle of the countries classed as 'innovation followers'. France's main strength is public support for R&D and it has particular weaknesses in private R&D activity, especially SMEs , and limited academic-industry collaboration. The percentage of French GDP spent on R&D has been declining for some years, although it is still in sixth place on this metric when compared with other EU member states (INNO-policy: 5)

France is one of the leading EU nations in terms of pharmaceutical R&D 4,167M Eur was spent on R&D in France in 2005, just below the sum spent in Germany and well ahead of all but Switzerland (EFFPIA). In 2005 the leading French pharma firm Sanofi-Aventis was ranked third in the world in terms of its sales ($32,340M) (Daemrich, 2009: 5) and France significantly outstripped other EU states in terms of pharmaceutical production figures (34,276M Eur compared with 26,219M for Germany and 22,857 for the UK). However, in certain key respects the French pharmaceutical sector is in (relative) decline. In the 1961-70 period French firms produced 25% of all New Chemical Entities, by 1991-2000 this had dropped to 6%, a performance much worse than the other leading European pharma countries (Daemrich, 2009: 6).

France is a leading biotech country within the EU and ranks highest on a number of metrics, including number of biotech employees (50, 098), number of biotechnology firms (although it is outranked by Germany in terms of firms solely dedicated to biotech activities), and commercial biotech R&D expenditure (OECD, 2009).[31] However, for the years 2007 and 2008 it ranked behind Germany, the UK and Switzerland in terms of venture capital finance and was fourth placed in terms of its 2008 clinical pipeline (Ernst and Young, 2010: 87/96). Like other EU states it has experienced a significant downturn in VC financing, during the economic crisis (including a 69% drop in 2009), but the trade association France Biotech reported a 56% increase in 2010 (Grogan, 2011).

Context: Funding and innovation governance

The bulk of French research funding supports public research organisations (PROs) rather than universities. In the life sciences the most important are: Centre Nationale de la

[31] The UK did not provide data for this exercise.

Research Scientifique (CNRS), Institut Nationale de la Sante et de law Recherche Natonale (INSERM) and the Institut Pasteur. Inserm is the primary agency funding life sciences and health research but a number of other agencies also play a role. These bodies receive a block grant which they allocate to their own priorities. With the establishment of the Agence National de la Recherche (ANR), there has been a shift towards a more open competitive system. Enhanced funding for ANR will create greater latitude for the government to direct research strategy. Support for the industrial sector has been enhanced since the creation of the Agence de l'Innovation Industrielle which has a one billion Euro budget. Support for SMEs comes from a dedicated agency (OSEO). Charitable funding also plays a role, in particular the French Muscular Disease Association (AFM) which is funding a variety of projects, most notably co-funding the ISTEM centre with Inserm.

In 2009 France developed the National Strategy for Research and Innovation with three main goals increased private R&D investment (through targeted tax breaks and the Strategic Investment Fund); improved public-private collaboration (through the competitiveness clusters), and enhanced support for SMEs (through OSEO and France Investment). The strategy set out three priority research areas, one of which is health, well being, food and biotechnology. The government's 2009 innovation strategy was interlinked with its recovery plan for the recent economic downturn, which included an additional 325M Eur for research (INNO-Policy, 3).

STI policy is coordinated through the High council for Science and Technology but at ministerial level it is primarily the responsibility of two departments: the Ministry for Economy, Industry and Employment and the Ministry of Higher Education and Research. However, there is concern that the French innovation system is too fragmented, with a proliferation of initiatives and much power resting with individual PROs. An independent review of the organisation of life sciences and health research in France carried out in 2008 was highly critical, describing the system as "highly fragmented, characterized by a large number of government institutions with overlapping missions, research portfolios, and redundant bureaucracies." It recommended a separation of the organisations funding research and those which perform the research, and the unification of funding within a single institution (AERES, 2008). Thus far this agenda has resulted in one major intiative, the creation of AVIESAN in 2009, an umbrella organisation which brings together all the major PROs active in life sciences and health research.

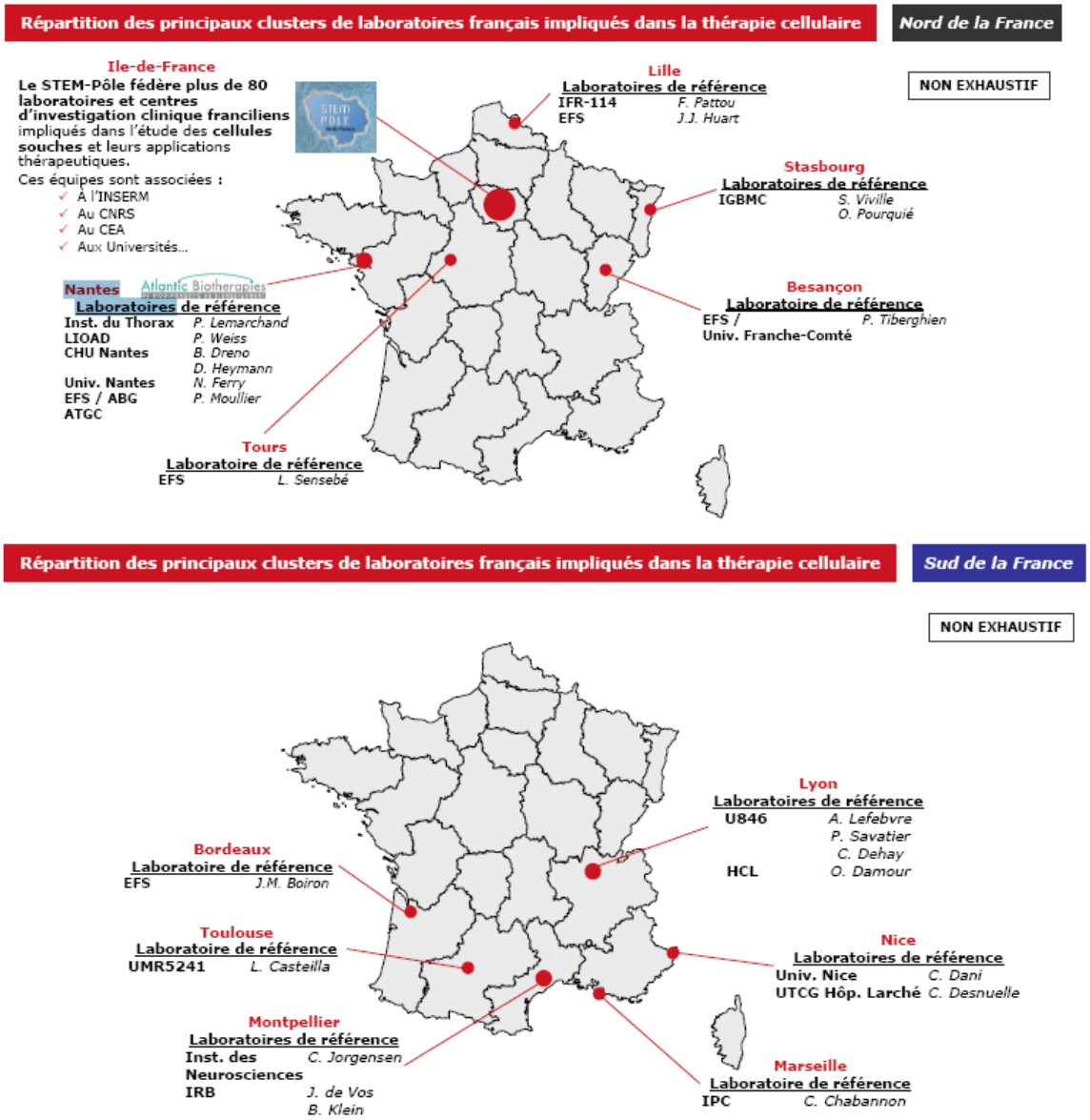
The government initiated a competitive programme for support of centres of excellence (or thematic research clusters) in 2004 – the Pôles de Compétitivité. Although this initiative was designed to prioritise funding in a relatively small number of clusters, in fact 67 clusters were successful in their bids for funding and these can now access additional funding from ANR and other ministries, each of which has ring-fenced budgets for projects within the clusters. The clusters also receive local funds from their regional authorities. The cluster policy was renewed in 2009 with a budget of 1.5Bn Eur for the period 2009-2011 (INNO-Policy, 20). There are now 71 clusters with 10 classed as global competitiveness clusters and it is these leaders which receive the bulk of funding. Like ANR, the cluster initiative is a vehicle for a greater centralization of control of R&D funding.

RM: the SCIENCE BASE

France has a number of research strengths including developmental biology. Although lacking a national strategy and somewhat behind other countries, there have been attempts to focus funding on RM. Between 2001-3 stem cell research was a major theme in a 14M

Eur programme on developmental biology run by CNRS and the ministry of research. This was followed in 2003 by a targeted call for stem cell research supported by INSERM and research charities. During this period INSERM were funding networks which brought together French stem cell scientists working on a variety of topics. Although this funding has now ceased, one interviewee told us that ANR has recently issued its first targeted call for RM projects. The development of RM research in France has built on existing strengths and the emerging clusters developed through the Pôles de Compétitivité programme. Ile-de-France area around Paris has the largest cluster of RM research groups, followed by Nantes (see below).

Geographical distribution of cell therapy research clusters (from BIONEST/LEEM, 2010)



Major initiatives

ISTEM engages in basic research but also aims to provide a technological platform for development of therapies, with a clinical focus on monogenic diseases such as Huntington's Disease. ISTEM's core funding comes from INSERM and AFM, but it also receives project funding from ANR and the EU, as well as some industrial funding (it is undertaking a 7.5M Eur project for Roche developing neural stem cells to screen Roche's compound libraries for

molecules which have the potential to treat neurodegenerative diseases) as well as local funding from regional councils. ISTEM is part of the Genopole cluster and plays a leading role in the STEM-Pole programme which brings together academic researchers in stem cell research and cell therapy in the Ile-de-France region. The Director ISTEM also has a coordinating role in the InegCELL project which brings together academic researchers and companies (VigiCell, Genosafe and Celogos).

The Institute for Research in Biotherapy (IRB) is a partnership between INSERM, the University Hospital of Montpellier and the University of Montpellier comprising basic and translational research laboratories as well as five laboratories for biotech companies. Its goal is the development of novel therapeutics (cellular and biological drugs) . Like ISTEM, the IRB receives funding from AFM and is linked into the existing regional biotech cluster initiatives: the Orpheme pole which focuses on rare diseases (led by Safnofi Aventis), and Canceropole Grans Sud Ouest, and receives regional funding. Monpellier is also home to one of France's eight cord blood banks, and the IRB has a partnership with the Establissemnt Francais du Sang (EFS) the French national body responsible for blood transfusion services, which is itself a major player in regenerative medicine in France.

EFS and Atlantic Biotherapies Cluster There are forty units authorized to conduct cell therapy in France and half of them are EFS establishments. The bulk of this activity is focused on haematopoietic stem cell transplantation. However EFS also has research laboratories working on mesenenchymal stem cells, in particular the team led by Luc Sensebe at EFS Centre-Atlantique which works on clinical grade production of MSC and is co-coordinating the FP7-funded REBORNE project which aims to run clinical trials for the use of MSC in bone grafts in orthopaedic and facial surgery. EFS has established Atlantic Bio GMP, a platform for the production of advanced therapy medicial products in Nantes. Again this is located within a major cluster, the Atlantic Biotherapies cluster which includes a number of RM companies such as Clean Cells and Atlantic Bone Screen and where there are a number of clinical trials for cell therapies. The Cluster is home to the Cell and GeneTherapy Unit at the University Hospital of Nantes which has worked with a range of companies including Clean Cells and Sanofi-Aventis.

RM: Commercial sector

REMEDiE WP 1's survey of the European RM sector revealed that France has 19 RM firms, a greater number than all but the UK and Germany. However, they are mostly young and small. The majority of them (11) are cell therapy companies. Nine of the cell therapy companies are developing/producing autologous therapies (four of whom have products on the market) and remaining two are developing allogeneic products (but none on the market). In 2009 the industry association France Biotech called for stem cell research to be a major priority for funding under the Grand Emprunt, with a dedicated funding stream of 500M Eur. It is not clear how much has been made available, but this year ANR have issued a call for public-private partnerships in a number of areas of biomedical innovation including stem cells. OSEO are also funding public-private collaborations such as the StemRed project, which brings together EFS and the French RM firm Cellectis to produce red blood cells from iPS cells. Ecytcell, a wholly owned subsidiary of French firm Cellectis, are the only European biotech developing induced pluripotent stem cells for both human therapeutic and research tool applications. In 2010 the firm licensed significant intellectual property on IPS technology from IPS Academia Japan Inc. (Kyoto, Japan).

RM: Legal context

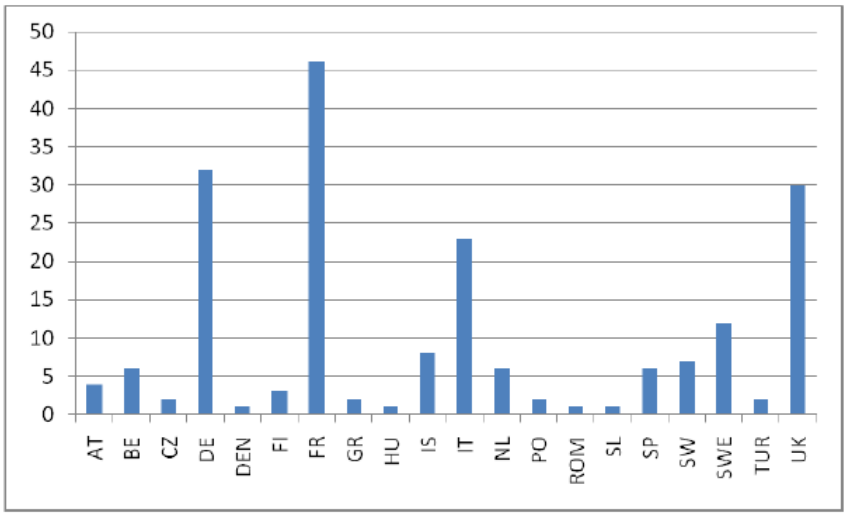
Of our six case studies, only Germany has a more restrictive framework for the regulation of hESC research. The 2003 Bioethics Law prohibits both therapeutic and reproductive cloning but allows exceptions for research which may lead to therapies for serious or incurable diseases and where there is no alternative research methods of comparable effectiveness. hESC research is under the control of the French Biomedicine Agency. Although the law was passed in 2004, the enabling Decree was not in place until 2006 and scientists expressed some frustration about the legal ambiguity of their position (The Scientist, 2006). However, since 2004 about 30 research groups and 40 projects have been authorized. The Bioethics Law is now undergoing revision and on 8 April the French Senate voted in favour of a more permissive regime but then on 28 May the French National Assembly voted against liberalisation. The outcome of this legislative process remains uncertain.

RM: International links

Leading French scientists are active in international networks, for instance Professor Margaret Buckingham is a Director of the International Society for Stem Cell Research and INSERM participated in the International Stem Cell Forum. Sanofi Aventis, France's main domestic pharmaceutical company, has launched an RM programme with two international collaborations: with the Institute of Hematology in the Chinese Academy of Medical Sciences in Tianjin, and with the Salk Institute for Biological Studies in La Jolla, California. International alliances are also being forged with foreign companies, such as the Japanese cell therapy company Cellseed which opened an R&D centre in Lyon in 2008 following a collaboration with the Lyon Tissue and Cell Bank and the Lyon Hospital Authorities.

France is the most recent EU member state to sign a collaborative agreement with the California Institute for Regenerative Medicine (in January 2011). Luo et al's data on international stem cell collaborations involving the US and UK shows that France was ranked seventh in terms of countries with the greatest number of collaborative papers with the USA and had the fifth greatest number of collaborative papers with the UK (2011).
Data on stem cell research projects funded under FP6 show that France was the country with third greatest number of partners involved in projects and (alongside Germany) was the country most frequently taking the role of coordinating partner. In projects coordinated by France partners were most commonly from the same country. Germany, Italy and the UK were the next most popular countries to partner with. The French Embassy in Berlin hosted a meeting between French and German scientists in 2007 with the aim of strengthening links with France's scientific partner of choice.

Partners in FP6 stem cell projects coordinated by France (19 projects, 20 countries, 195 partners)



Discussion

If France has had a late entry to the RM race, then it would appear to be making some efforts to catch up. Moreover, like Germany (see below) its legal constraints on hESC research are somewhat mitigated by its strong pharma/biotech sector and historic strengths in key areas such as developmental biology. As the country with the third greatest number of RM companies, it clearly has potential to be a major player, however, stakeholders such as the French pharmaceutical trade body (LEEM) continue to call for further elaboration of a national RM strategy (BIONEST/LEEM, 2010). It remains to be seen whether the ongoing restructuring of the life sciences research system facilitates such a development, or proves an unwelcome distraction.

Germany

Germany has a range of initiatives to support regenerative medicine and scientific strengths in a number of areas including stem cell research and tissue engineering. National initiatives to support regenerative medicine include the funding of a number of research centres, the establishment of a national network and the partial easing of the law governing research on hESC. National initiatives have been complemented by regional activity in some of the Federal Länder such as the pioneering North Rhine Westphalia Stem Cell Network established in 2002, and Saxony's funding of RM as one of its main strategic priorities in biotechnology. Amongst EU member states Germany has a leading role in generating stem cell inventions, a global survey of stem cell patents revealed that Germany has 4% of global total of PCT applications, the same figure as the United Kingdom and higher than any other EU member states (Bergman and Graff, 2007).

Context: Life sciences and biotech innovation performance

Germany ranks fourth in the Innovation Union Scoreboard for EU member states and is the strongest performer amongst the larger member states. Classed as an 'innovation leader', it has high R&D investment and outputs, well-established mechanisms for technology transfer and it has continued to improve its performance in recent years. Its ambition to remain competitive has led to the national High-Tech Strategy. Much of the impetus for the High-Tech Strategy arises from two concerns: Germany's strong innovation performance does not match that of leading countries outside the EU such as Canada, USA, Korea and Japan; and the country's outstanding performance in sectors such as automotive and electrical engineering is not matched in areas such as biotechnology and the life sciences.

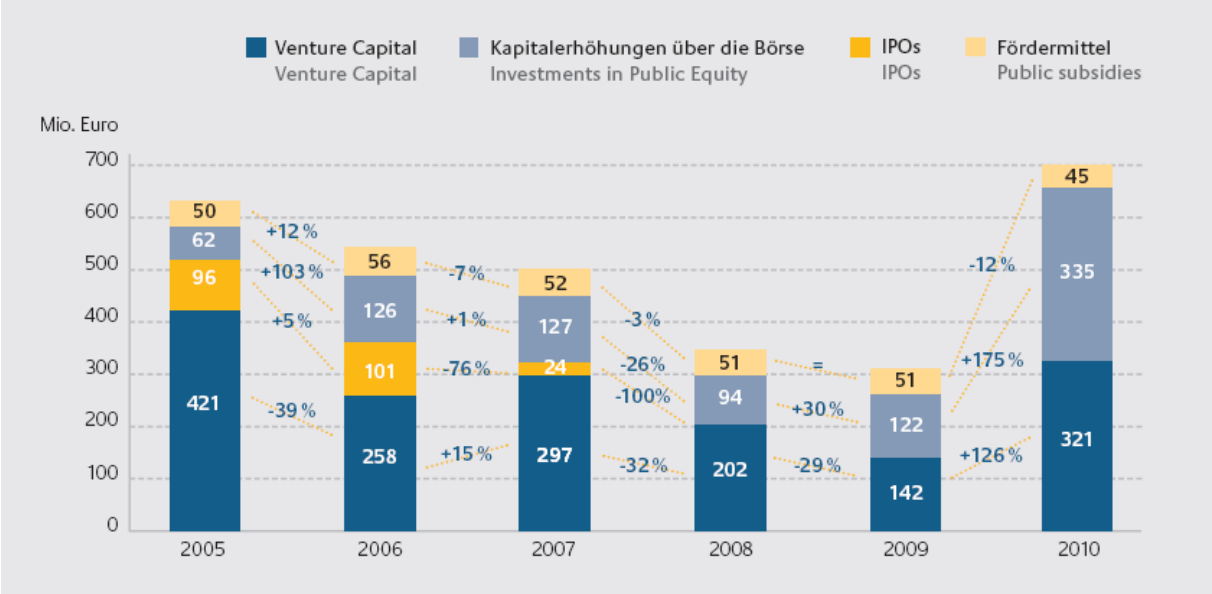
The latter is perhaps surprising given that Germany played a leading role in the development of the modern pharmaceutical industry over the last 150 years and remains a leader. For instance, in 2007 German pharmaceutical R&D investment was 4,662MEur, second only to UK and Germany had the greatest number of employees in the industry (112,500 compared with France's 103,633) (EFFPIA, 2009). However, in certain key respects the German pharmaceutical sector is in (relative) decline. In 1974 Germany had three companies in the top fifteen pharmaceutical firms (measured by sales); by 2005 it had only one (Hoechst had been acquired by Sanofi Aventis and Bayer had simply dropped off the list) (Daemrich: 5). In the 1961-70 period German firms produced 17% of all New Chemical Entities, by 1991-2000 this had dropped to 13%; not as dramatic a decline as France, but effectively a reversal of its position relative to the UK (whose share had risen from 7% to 16%) (Daemrich: 6).

Germany is one of the EU's leaders in biotechnology and nearly 45% of Germany's dedicated biotech firms are in the health sector (OECD, 2009: 57). In 2006 it had 496 dedicated biotech firms, more than any other EU country (OECD, 2009: 16/17); its biotech R&D expenditure was second only to France's amongst EU member states. (OECD, 2009: 25) and it had a far greater share of biotech PCT patent applications than any other European state (OECD, 2009: 71).[32] In 2007 and 2008 German biotech firms received far more venture capital than any other European country, although its lead dropped significantly in 2008 (Ernst and Young: 87). Figures from the German government suggest this decline in VC finance continued at a diminished rate in 2009 but that in 2010 there was a dramatic increase of 126% to 321M Eur and that this was linked to increases in IPO financing which meant a record amount of private finance going to German biotech in 2010 (biotechnologie.de 2011:

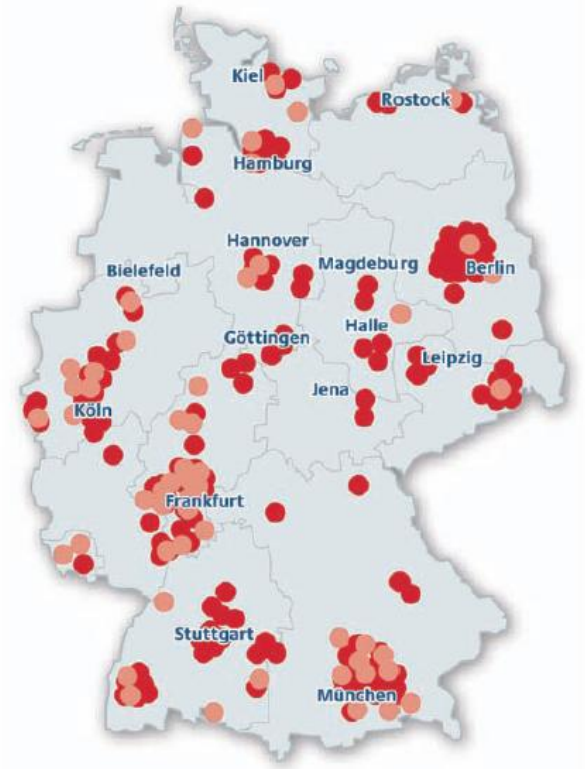
[32] Figures were not available for the UK

18). Whether this is sustainable remains to be seen, but it does suggest that EU member states who did not suffer such a severe recession may see a stronger and quicker recovery in biotech finance than others.

Sources of financing for dedicated biotechnology companies (biotechnologie.de)



Geographical distribution of dedicated biotechnology firms (firms with main activities in medicine in light red) (biotechnologie.de)



Context: Funding and innovation governance

In Germany funding for research is shared by the federal government (primarily distributed by BMBF, the research ministry and DFG, the equivalent of the UK Research Councils) and the 16 federal states (Länder) who have primary responsibility for the universities. The Federal Ministry of Health also plays an important role in health-related research and

innovation. In 2001 the division of the total public research funding was 67% federal and 33% Länder. Research is conducted across a range of institutional networks: higher education institutions (including but not only universities) which conduct both basic and applied research and are funded by both the Länder and the DGF; the Helmholtz Association of Centres which focus on long-term, high-risk or resource-intensive research and which is funded by the federal government; as is the Fraunhofer Society (FhG) which focuses on applied research, much of it financed by industry; the Max Planck Society whose institutes focus on basic research in natural sciences and humanities and which is funded by both the federal government and the Länder; as is the Leibniz Science Association. Non-academic research institution are an important and defining feature of the German R&D landscape and this diversity of actors means that innovation governance is dispersed across a range of actors and levels. Kuhlman and Shapira suggest that this decentring of authority is increasing as regional innovation policies take on greater significance, often supported by transnational networks (not least those of the European Union) (237).

National initiatives have strengthened this regionalization through the promotion of biotech clusters. The 1995/6 BioRegio programme supported the development of three major clusters around Cologne, Heidelberg and Munich. These clusters continue to be at the heart of German biotech, with their three Länder (North-Rhine Westphalia, Baden-Württemberg and Bavaria, respectively) being the location for highest number of biotech companies (biotech.de: 7) and the source of the greatest number of biotech patents in Germany (OECD, 2009: 74). Subsequent rounds of BioRegio funding supported the emergence of other clusters, perhaps most notably around Berlin. Another element to German cluster policy in recent year has been fostering innovation in East Germany. The OECD 2006 report on innovation in pharma biotechnology identified a lack of co-ordination between the federal government and the Länder as a significant problem.

The High Tech Strategy was the first comprehensive attempt to bring together all the ministries and policy areas which touch on innovation linking research funding to sectoral policy initiatives and regulatory activity. Recent policy initiatives related to the High-Tech Strategy include the Innovation Alliance to support public –private partnerships in key technology areas, the competitive Top Cluster Programme , and a number of programmes for SMEs/start-ups – SME Innovative, the ZIM Programme and the High-tech Start-Up Fund. The Strategy identified 17 priority areas in cutting-edge technologies including biotechnology.

In order to regain its status as “the World’s Pharmacy” the BMG convened Task Force Pharma in 2003 to develop a strategy for improving biopharmaceutical innovation and the BMBF launched the Pharmaceuticals Initiative for Germany for the period 2007-2011. This programme committed 800M Eur to innovative pharmaceutical development through a range of initiatives including funding for new clinical trial centres, SME biotechs, basic research on disease mechanisms and promotion of innovative treatments. The latter covered a range of approaches including cellular therapies. In 2010 the government launched the National Research Strategy Bioeconomy 2030 and the Health Research Framework Programme with a funding commitment of approximately 8 billion euros (biotechnologie.de: 25).

RM: Science base

RM has been identified as a strategic priority by the key actors in German biotech innovation: the federal government, the Länder with strong biotech clusters, the universities

and the independent research associations (Max Plank etc.). The Federal government has sought to develop a strategic approach to RM innovation. The BMG's Task Force Pharma group issued a report in 2005 which outlined an action plan for personalised medicine and tissue engineering including a national workshop and participation in international policymaking on regulation, coordination between BMG and BMBF continues. In 2007 the BMBF commissioned an independent report from CapGemini which described Germany's place in the global RM landscape and outlined a strategic approach to the funding of RM. Key issues identified were the need for greater coordination between clinics, industry, policymakers and regulatory bodies and the need for centres focused on translational research. In 2008 a dialogue was launched between the different regulatory bodies responsible for licensing, reimbursement and HTA. Since 2009 BMBF have been funding industry-academic collaborations to address barriers to translation by improving "the validation, standardization and quality assurance of RM products" (RMIG, 2010: 39). Since 2006 the Federal government has sought to build critical mass in RM research capacity by funding a number of centres with a focus on translational research. Additional measures include holding workshops with industry to discuss the regulatory pathway for products approval and reimbursement; a relaxation of the law governing hESC research and the establishment of a national network: Regenerative Medicine in Germany (RMIG).
There has been a major public investment in RM research by BMBF, DFG and the Fraunhofer Society:

- BMBF (2000-2007) 61.9M Eur
- DFG (1999-2007) 63.9M Eur
- Fraunhofer Society (2005-2010) 54.3M Eur
- Helmholtz Association (2003-2004) 32M Eur

As well as competitive grant funding, the BMBF and DFG have funded a series of centres focused on translational work:

- Berlin-Brandenburg Centre for Regenerative Therapies (BRCT) which focuses on targeted cell differentiation for promoting endogenous tissue regeneration (> 5M Eur pa)
- Translational Centre for Regenerative Medicine in Leipzig (TRM) specializes in interdisciplinary approaches in tissue engineering, cell therapy, delivery systems and imaging (>5M Eur pa)
- Centre for Regenerative Therapies in Dresden (CRTD) which is a collaborative network comprising medicine, developmental cell biology, materials and engineering in haematology, oncology, immunology, diabetes and neuroregeneration (6.5M Eur pa)
- ReBirth cluster of excellence in Hannover focuses on stem cell biology and related regenerative sciences (6.5M Eur pa)
- Reference- and Translation Centre for Cardiac Stem Cell Therapy (RTC) in Rostock (>3.4M Eur in total) (UK/RGIM workshop report: 20)

In some cases this has been matched by private funding, for instance the Hans Borst Centre for Heart and Stem Cell Research, which is part of the ReBirth cluster, is being financed with 13.5M Eur from the Braukmann-Wittenberg Foundation. In some cases initiatives have been jointly-funded by the national government and regional Länder, for instance the Translational Centre for Regenerative Medicine in Leipzig has been funded by the BMBF, the state of Saxony and the University of Leipzig; the Reference and Translation Center for Cardiac Stem Cell Therapy in Rostock has received industry support as well as funding from BMBF and the state of Mecklenburg-Western Pomerania; and the BRCT has had 40M Eur funding from the state of Berlin-Brandenburg. The research associations in Germany have also invested in RM, for instance the Fraunhofer Association has established the Fraunhofer Institute for Cell Therapy and Immunology (IZI) in Leipzig, as well as related institutes in Stuttgart, Hannover, St. Ingbert and Lübeck. The Max Plank Institute for Molecular Genetics in Berlin where James Adjaye's team work on hESC and iPS cells and Hans Schöler and his working group at the Max Planck Institute for Molecular Biomedicine in Münster.

In certain respects key states have played a leading role, for instance a significant pioneering state initiative is the **Stem Cell Network North Rhine-Westphalia**. Launched in 2002, this was Germany's first stem cell network and with an annual budget of 1M Eur it now links around 30 research groups. As a founding member of the International Consortium of Stem Cell Networks it has been active in building international alliances. The network has two working groups, one on biomedical aspects of RM and the other on its social, legal and ethical aspects. NRW is one of Germany's main biotech hubs and it is home to some of its most prominent stem cell scientists, most notably Hans Schöler, Director of the Director of the Department of Cell and Developmental Biology at the Max Planck Institute for Molecular Biomedicine, in Münster. In 2008 Schöler received the Robert Koch Prize (with Irving Weissman and Shinya Yamanaka) for pioneering work on stem cell biology. Schöler was the first scientist to derive germline cells from murine embryonic stem cells (ESCs) and he has also made a major contribution to the field of iPSCs. His return to Germany in 2004 after five years in the United States was a signal of the growing momentum for stem cell research in Germany. Other leading stem cell scientists based in NRW are Oliver Brüstle, Director of the Institute for Reconstructive Neurobiology at the University of Bonn (the first German scientist to be authorised to work on hESC lines), Jürgen Hescheler at the Institute for Neurophysiology in Cologne, and Peter Wernet, Director of the Institute for Transplantation Diagnostics and Cell Therapeutics and the Netcord Stem Cell Bank for umbilical cord blood, at the University of Dusseldorf.

RM: Commercial sector

REMEDiE WP 1's survey of the European RM sector revealed that Germany has 28 RM firms, more than any other European country (the UK has 25 and France 19). Thirteen of these are more than ten years old but data on size is very limited (suggesting that they are mostly small) and only two are known to have more than 50 employees. Twelve of them are cell therapy companies, and of these nine are developing/producing autologous therapies (six of whom have products on the market), two are developing allogeneic products (but has the market) and one is developing both (but with no products yet on the market). T2Cure have an autologous stem cell therapy for regenerating heart muscle about to enter phase III trials. The company was the first to receive MAA certification for a stem cell product under the ATMP guidelines.

Policymakers we interviewed expressed some concern that German RM companies were unable to grasp the challenges associated with gaining regulatory approval and reimbursement.
The BMBF has provided significant funding to RM companies since 2000, under two programmes:

- Tissue engineering funding initiative s (43M Eur in 2000-2007)
- Regenerative technologies initiative (launched in 2008) to minimise the strategic innovation barriers to clinical studies and approval (15m Eur)

RM: Legal context

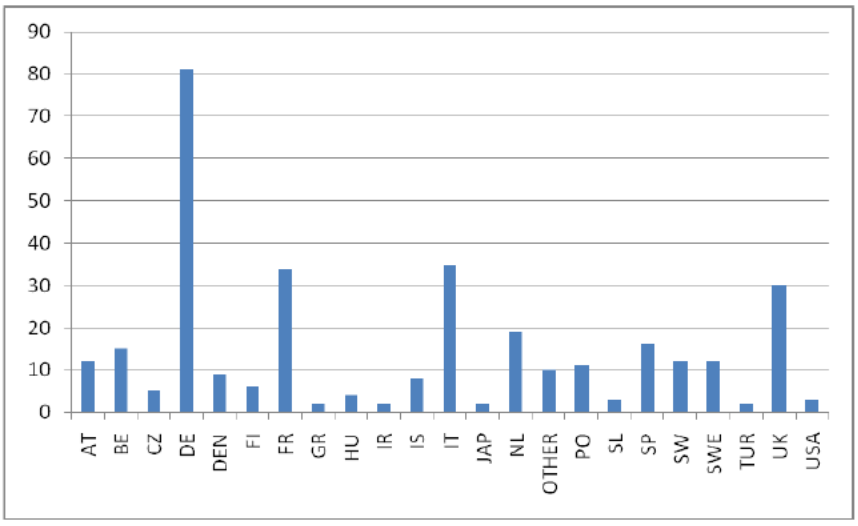
Of our six national case studies, Germany has the most restrictive legislation on hESC research. Under the 1991 German Embryo Protection Act the production of hESC lines is illegal. The 2002 Stem Cell Act restricted the import and use of hESC lines except under certain conditions: that there were no alternative research options; that the parents had given consent for the use of the embryo and it was supplied without any payment; and that the stem cell lines were already in existence on 1 January 2002. A regulatory system was put in place with the Robert Koch Institute responsible for ethical approval of hESC research and for the licensing of imports. Pressure for a relaxation of this strict regime grew, and the Act was amended in 2008 to allow the use of hESC lines produced before May 2007 and to clarify that the Act does not cover German scientists working on hESC lines abroad, thus facilitating international research collaborations. Under this system over 50 projects involving imported hESC lines had been approved by March 2010 (RMIG: 19)
This legal context has shaped the direction of RM research in Germany, with less of a focus on embryonic stem cell research and a greater focus on adult stem cell research. Views on the impact on research was mixed. One scientist, who had obtained permission to work on hESC lines, felt that the regulatory system was not overly burdensome for those who had negotiated it but that it might deter those who were new to the field.

RM: International links

As noted above, the restrictions on hESC research have limited the ability of German scientists to participate in international collaborations. Nevertheless, German scientists are active in international collaboration. For instance, Luo et al's data on international stem cell collaborations involving the US and UK shows that Germany was the country with the greatest number of collaborative papers with the USA and the second greatest number of collaborative papers with the UK (after the USA) (2011). Data on stem cell research projects funded under FP6 show that Germany was the country with greatest number of partners involved in projects by a considerable margin and (alongside France) was the country most frequently taking the role of coordinating partner. In projects coordinated by Germany partners were most commonly from the same country. France, Italy and the UK were the next most popular countries to partner with (see figure x). One interviewee indicated that the German government considered it a priority to ensure that it received a share of EC research funding commensurate with its substantial contribution to that budget.
Germany is also present in international networks, for instance the NRW Stem Cell Network has played a leading role in the International Consortium of Stem Cell Networks. Since the 2008 amendment the German government has initiated some strategic international alliances. The German Ministry of Education and Research signed a collaborative agreement with the California Institute for Regenerative Medicine in September 2009 and has set aside

12M Eur for collaborations within this framework. The first three projects to be funded under this scheme have recently been announced (http://www.bmbf.de/press/2995.php).The RMIG has initiated a process of collaboration with scientists in India and stem cell researchers in Essen have received funding from for collaboration with Chinese scientists as part of a programme of joint funding by China's National Science Foundation and the DFG. Some of our interviewees also indicated that there had been a government initiative to foster links with Chinese stem cell scientists and links to Australia. These initiatives in part reflect the importance of international collaboration within Germany's high-tech strategy which calls for recruitment of more foreign scientists, increased funding for international cooperation and a higher profile in key countries (Russia, India, Japan, Brazil and the USA). These new links build on existing alliances, for instance researchers in Berlin have collaborated with colleagues in Pittsburgh and Japan on tissue engineering projects and have educational links to a range of institutions in the US including Stanford as well as with Singapore and Australia.

Partners in FP6 stem cell projects coordinated by Germany (19 projects, 31 countries, 333 partners)



Discussion

In many ways Germany resembles the United States - a pharma/biotech powerhouse making a major public investment in RM but which is constrained by national restrictions on hESC research. However, like the US, the Germans seem to have a clear European lead when measured in a number of key metrics (participation in research with other key nations like US and UK, number of RM companies, and stem cell patents, leadership of EU FP stem cell projects), suggesting that a more restrictive approach to hESC research may not be an insurmountable hurdle if there is strong public investment and a robust pharma/biotech sector. However, there remain concerns about whether Germany will be able to maximize its strengths in the area of hESC research and that it is, in effect, punching below its weight in this field. With its strong emphasis on translational research in RM and its track record in the commercialization of biotechnology, it may be that Germany will become a test-bed for resolving some of the key challenges associated with the clinical application and commercialization of RM therapies.

Spain

Spain shares some characteristics with our eastern European case study: like the Czech Republic it has no large domestic pharmaceutical companies, nor is it one of Europe's leading biotech nations. It is thus perhaps understandable that the UK Pattison Report did not feature Spain in its analysis of international competitors. However Spain has a number of relevant scientific strengths including transplant medicine and iPS. Moreover in the last five years the Spanish government has made a strong commitment to regenerative medicine, liberalizing the legal framework for hESC research, establishing a cell therapy network, a stem cell bank and providing regional governments with funding for research initiatives. Spain also boasts what was one of Europe's most promising stem cell companies: Cellerix.

Context: Life sciences and biotech innovation performance

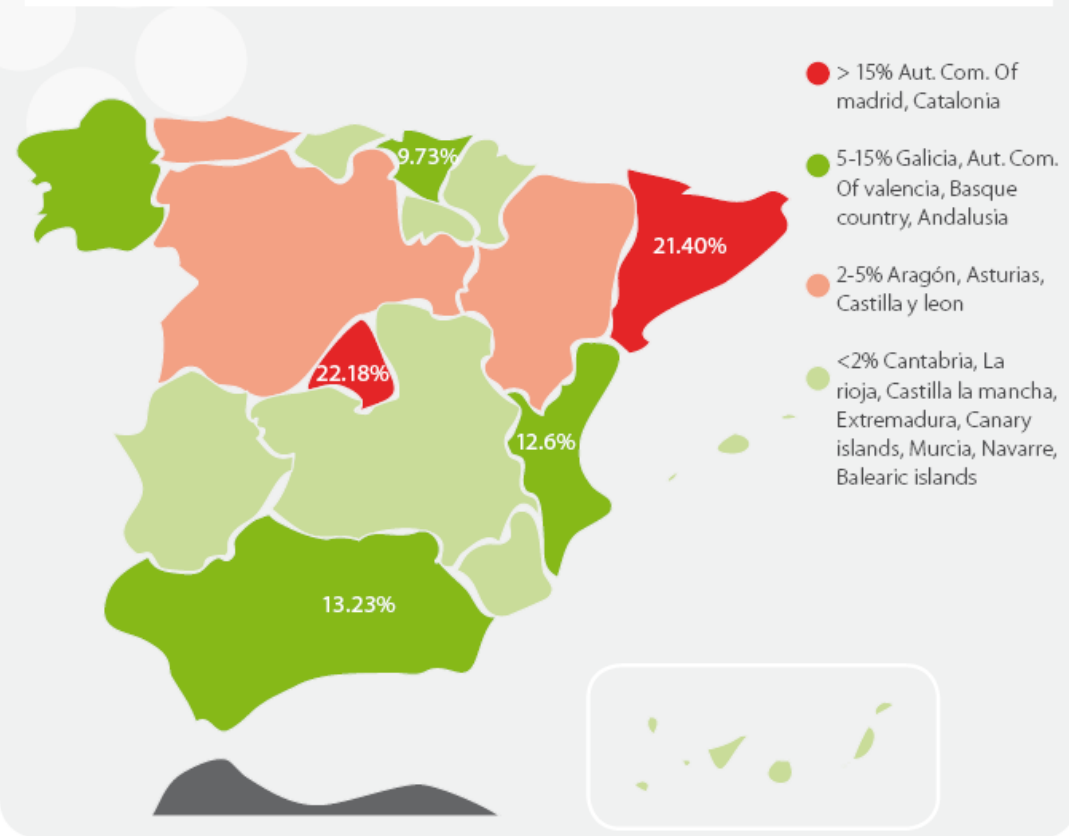
Spain ranks 15th in the Innovation Union Scoreboard for EU member states and is classed as a 'moderate innovator' . Its performance on a number of metrics is improving in particular 'finance and support' and 'firm investments' but it continues to perform poorly in science and technology when compared with the most advanced EU countries. The National Reform Programme aims to reverse this situation and a clear indication of Spain's ambitions as a knowledge economy is the creation of the Ministry of Science and Innovation in 2008 which pursues strategic objectives established under Spain's national innovation plan, including the promotion of biotechnology (see below).

Spain has no major (i.e. in the global top ten) domestic pharmaceutical firms. Its 2007 pharma R&D investment was 885M Eur, ranking it eighth amongst European states on this metric, just above Sweden. It ranked seventh in terms of pharmaceutical production for 2007 with an estimated 14,004M Eur and fifth in terms of number of employees (40,117) (EFFPIA, 2009). It ranked ninth in terms of pharmaceutical exports (7,194M Eur) but had a negative trade balance of -1,170M Eur, a characteristic shared by only one other of our case studies (the Czech Republic). However, the OECD review of biopharmaceutical innovation in ten countries ranked Spain bottom in terms of drugs under development per million capita (OECD, 2009: 117).

Spain could be characterized as a 'fast-follower' in the bioeconomy; between 2004 and 2006 it experienced the most rapid growth in the number of firms with a compound annual growth rate of 48% for dedicated biotechnology firms and it has more dedicated biotech firms than Sweden and Switzerland. (OECD 2009: 16-17). Moreover, between 1994-2001 Spain's biopharmaceutical publications grew at annual growth rate of 11.5%; higher than all other countries in the survey, including Germany, the UK and France (OECD: 106) and although the actual number of publications is still far less than these countries Spain has a better productivity rate, with more biopharma publications per 100 researchers than France, Germany and the US for the years 1994/5 and 1999/2000 (OECD: 107). However, in terms of health biotech, this rapid growth is taking time to demonstrate an impact. Spain does not feature in the list of firm having developed approved bio-therapies in the two decades between 1989-2009 (OECD: 85) and in 2008 it ranked tenth in terms of clinical pipeline (Ernst and Young: 96). Its share of VC financing is also far lower than leading biotech countries such as UK, Switzerland and France (Ernst and Young 2009: 87). Biotech is highly clustered in Spain (see figure x), particularly in Madrid and Catalonia, although Valencia, the Basque country and Andalucía are also significant. The OECD 2006 report on innovation in pharma biotechnology identified a lack of VC finance as a generic problem

across Spain's national innovation system but also highlighted a lack of entrepreneurial risk-taking (OECD: 177)

Geographical spread of biotech firms in Spain (ASEBIO, 2008)



Context: Funding and innovation governance

The Ministry of Science and Innovation is responsible for the 2008-11 RDI National Plan which sets out objectives and priorities within parameters established by the first National Plan (1988-91) and the Science Law of 1986. The plan aims to improve Spain's performance as a knowledge economy by improving the infrastructure for the private sector (technology parks etc); encouraging industry-academic linkages; increasing international collaborations; and integrating the activities of the national and regional governments.

The governance of innovation in Spain involves strategic national direction and funding but much of the delivery is the responsibility of the Autonomous Communities (AC). The RDI plan recognizes the need for better coordination between these two governance levels. National funding for biomedical research comes through the Carlos III Health Institute. Bilateral programmes have been established with the USA, Canada, Brazil, Argentina, Japan and India. Multilateral programmes have been developed in a number of fields including regenerative medicine.

Health is one of the areas prioritized for what are termed "Strategic Actions" and molecular and cellular technologies (including innovative therapies) are identified as a priority within this action. There is overlap with biotechnology which is also identified as a Strategic Action. Cell therapy and regenerative medicine are amongst the priorities highlighted within the health biotechnology strand of this action and it also features in the nanotechnology strand. The current Minister of Science and Innovation is Cristina Garmendia, a former life sciences researcher who created the spin-off company Genetrix when at the National Centre for

Biotechnology in 2001. Genetrix is the parent company of two cell therapy companies: Cellerix and Coretherapix.
Until recently the Spanish research system was based around the universities and public research centre funded by the Spanish National Research Council (CSIC). However, in the last decade the government has promoted a new model: research institutions which are independent, non-profit private foundations. This initiative has been designed to create greater flexibility and ability to recruit foreign scientists with a more flexible recruitment policy.

RM: SCIENCE base

The development of regenerative medicine in Spain has gathered pace rapidly in the last six years. Perhaps unsurprising given that at one time both the Health Minister was a stem cell scientist and the Science and Innovation Minister had been the founder of a company lined to Spain's leading RM firm. It is directed by Carlos III Health Institute through its Subdirectorate General for Research in Cell Therapy and Regenerative Medicine which oversees both research strategy and the work of the body which regulates hESC research (the Commission on Guarantees Concerning the Donation and Use of Human Tissues and Cells). The Ministry for Science and Innovation directly invested 30M Eur in international programmes (see below) but most national funding has come through the Carlos III Health Institute. Between 2005 and 2008 over 55M Eur was spent by this body (figures for 2009-11 are not available).

Carlos III Health Institute RM funding 2005-2008

2005: 18.367M Eur

2006: 10.358M Eur

2007: 15.049M Eur

2008: 12.506M Eur

Most of the money has been channeled through the Autonomous Communities (AC). All the AC were invited to bid for funding but a number of them have not done so. Perhaps surprisingly, Madrid, Spain's major biotechnology hub, has not applied for funding. Some of our interviewees suggested that this may be because the ruling party in Madrid is the Popular Party, which has is hostile to hESC research. Most of the AC funding has gone to three of Spain's Autonomous Communities: Catalonia, Andalucia and Valencia, although more recently Aragon and Castille have become involved.

RM funding to AC 2005-2008

Catalonia 10.2M Eur

Andalucia 10.8M Eur

Valencia 9M Eur

Aragon 2.8M Eur

Castille 2.25M Eur

This funding has led to the development of a number of new research centres, based on the new non-profit private foundation model outlined above.

Centre for Regenerative Medicine in Barcelona (CMRB) – amongst its scientific strengths this centre was the first to generate human IPSC lines in Europe

Andalusian Molecular Biology and Regenerative Medicine Centre in Seville (CABIMER) – this centre was established under the leadership of Bernart Soria, a leading Spanish stem cell scientist who became Spain's Health Minister in 2007.
Prince Felipe Research Centre (CIPF) in Valencia – this centre has about 250 researchers in three streams of work, one of which is regenerative medicine. This group covers a number of areas including neuronal regeneration, cardiovascular disease and cancer stem cells.

These are not the only centres of RM research in Spain. Other centres include CENATMER (the National Centre for Transplantation and Regenerative Medicine in Madrid) and INBIOMED Centre for Research on Regenerative Medicine in San Sebastian). Major biomedical research centres such as the National Biotechnology Centre in Madrid also contain RM research groups.Whilst the role of the AC is critical, the central government retains the ability to steer strategy through its control of the budget. The two other major initiatives funded by Carols III Health Institute are the National Stem Cell Bank (BNLC) and a national cell therapy network. In fact the BNLC itself is a network, consisting as it does of three nodes in Andalucia, Catalonia and Valencia, an organisational form which is perhaps indicative of the dynamics of multi-level governance in Spain's RM innovation strategy.
Interviewees suggested that the number of institutions engaged in RM research in Spain is still growing although the rate of growth has perhaps tailed off since the economic crisis.
Spain prides itself on a strong infrastructure for clinical research and the exploitation and enhancement of that infrastructure is a characteristic of RM innovation in Spain. For instance the Andalusian Initiative for Advanced Therapies has a strong translational component including development of 12 GMP facilities for cell therapy production and there are now nine RM clinical trials going on in the region.

RM: Commercial sector

REMEDiE WP 1's survey of the European RM sector revealed that Spain has seven RM firms, placing it fourth behind Germany, the UK, and France. All seven companies are small and less than ten years old. Four of them are cell therapy companies, none of whom yet have products on the market. Of these four, one is developing autologous therapies,one is developing allogeneic products, one is developing both (data on the remaining company is unclear). Spain's leading cell therapy company is Cellartis, founded in 2004, this company had an autologous adult stem cell product in phase III clinical trials but there are reports that the phase III trials encountered problems (a failure to demonstrate efficacy) and that the company has had to cut its workforce. Cellerix is now about to merge with the Belgian company TiGenix. Cellartis was spun out from the company Genetrix, which has now spun out two further RM companies: Axontherapix and Coretherapix.

RM: Legal context

Spain is unusual in being a Catholic European country which has developed relatively permissive legislation on hESC research. In 2006 the law governing IVF was updated, it now requires that couples undergoing treatment have four choices regarding any surplus frozen embryos: retention for their own subsequent use, donation to other couples, donation for a specific research project, or disposal. The Spanish Law on Biomedical Research passed in 2007 prohibits the creation of human embryos for research purposes but allows the derivation of hESCs for research or therapy as long as it does not involve fertilization and generation of viable embryos (Raya and Belmonte). It is again indicative of the important

role of the AC, that Andalucia had developed its own regulatory framework for hESC research ahead of the national law.

RM: International links

The International Research Programme in Regenerative Medicine has a budget of 30M Eur, and the 2009 funding round invested 16.3M Eur in 21 projects with 88% of the funding going to collaborations with the UK, Canada and the USA (other collaborating countries were Italy, Sweden, Netherlands, France and Germany). Additional funding under the international programme has gone to the development of manufacturing facilities for clinical scale cell therapy as the absence of such infrastructure is seen as an obstacle to international collaboration. In 2009 the scheme spent 13.7M Eur on 17 projects for such infrastructure improvement.

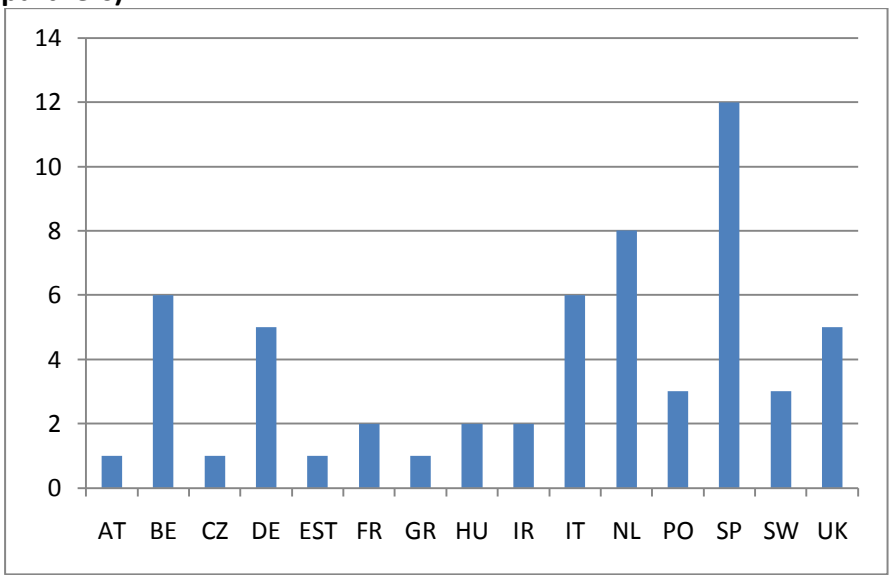
Spain participates in a number of international bodies such as the ISCF. Pablo Menendez and Ana Veiga of the Spanish stem cell bank are active internationally. Ana Veiga who heads the Catalonia node of the stem cell bank in the CMBR in Bacrelona was the joint-coordinator of the EU FP6 Human Embryonic Stem Cell registry. In 200x a two-day workshop was help in London to facilitate links between Spanish and UK scientists.

Spain was the second EU member state to sign a collaborative agreement with the California Institute for Regenerative Medicine (in December 2008). More recently the provincial government of Andalucía has signed a separate collaborative agreement (in October 2010).

Luo et al's data on international stem cell collaborations involving the US and UK shows that Spain was ranked tenth in terms of countries with the greatest number of collaborative papers with the USA and eight in terms of the greatest number of collaborative papers with the UK (2011).

Data on stem cell research projects funded under FP6 show that Spain ranked sixth in terms of number of partners involved in projects (roughly the same number as Netherlands, Switzerland and Sweden) and ranked seventh in terms of taking the role of coordinating partner. In projects coordinated by Spain partners were most commonly from the same country. The Netherlands, Italy, Belgium, Germany and the UK were the next most popular countries to partner with.

Partners in FP6 stem cell projects coordinated by Spain (6 projects, 15 countries, 58 partners)



Discussion

Although not set out in an equivalent of the Pattison Report, Spain would appear to be closest to the UK in having a coordinated national strategy for RM. Perhaps more than any of our other case studies, Spain exemplifies the dynamics of multi-level governance of RM innovation, with a central role for the provincial governments. Given its lack of a major pharma industry and limited biotech sector, the fact that Spain has more RM companies than Switzerland seems a remarkable achievement. However, it remains to be seen whether this success can be sustained through Spain's current economic crisis.

Sweden

Sweden is a leading RM nation. It has both significant scientific strengths and one of the EU's major RM companies. Although lacking a national strategy for RM, the field has been a priority for some years and a number of initiatives have been taken including development of a permissive legal framework for hESC research, funding of a stem cell bank and for research centres focused on the country's leading stem cell scientists. A report from the Swedish government's innovation agency Vinnova, sought to benchmark Sweden against some of its closest rivals (the UK, Japan and Germany)and explored the potential value for an explicit national strategy for RM.

Life sciences and biotech innovation performance

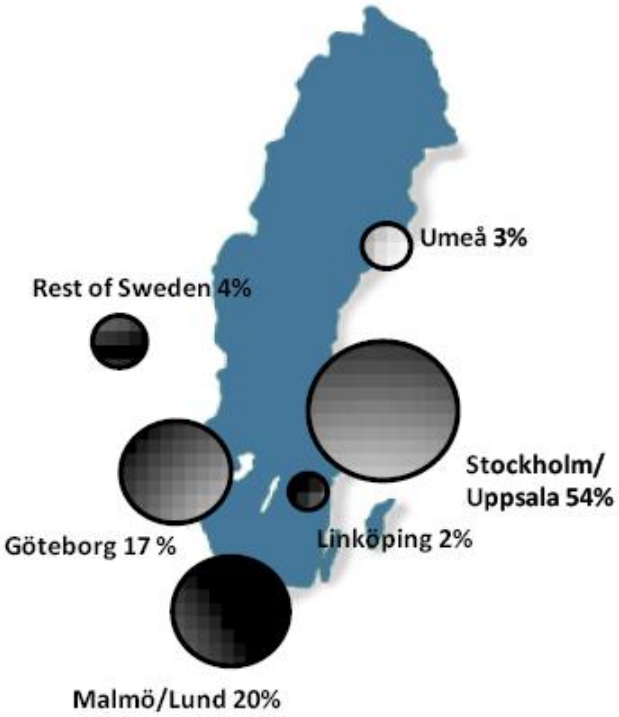
Sweden ranks first in the Innovation Union Scoreboard innovation scoreboard for EU member states for 2010 (UNU-MERIT, 2010: 4). On a number of key metrics Sweden is a global innovation leader - OECD's science and technology indicators published in 2007 rate Sweden second below the US in the ration of investment in knowledge to GDP (combined metric for spending on R&D, higher education and software); Sweden was only one of two EU countries (Finland being the other) where R&D/GDP ratio exceeded 3% and it was the global leader in R&D intensity and business R&D intensity (OECD, STI scoreboard 2007) : 24-27). Sweden is particularly reliant on its automobile industry, which has suffered in the recent economic downturn. The Swedish government invests approximately 2.3Bn EUR in R&D, but it allocated an additional 1.3Bn EUR for the period 2009-12.

The Swedish pharmaceutical industry is a major part of the high-tech sector in Sweden. It is the most research intensive industry in Sweden and 23% of all Swedish R&D personnel are employed in the industry, a higher proportion than any other sector (LIF: 53) In 2007 Swedish pharmaceutical R&D investment was estimated to be 875M Eur, ranking it ninth amongst European countries, just below Spain (although with a population five times smaller then Sweden's per capita R&D intensity is far higher) (EFFPIA). In certain key respects the Swedish pharmaceutical sector is in decline. LIF, the Swedish industry association reports that the number of clinical trials (Phase 1-4) decreased from 262 in 2004, to 187 in 2009 (LIF: 19). Astra and Pharmacia were Sweden's main pharmaceutical companies. Astra is now part of the UK company AstraZeneca following a merger in 1999, but Sweden is the location of the company R&D headquarters. About 40% of the company's R&D staff are located in the country (LIF: 56) and 28% of all life sciences employees in Sweden work for AZ (Vinnova 2007: 6). Pharmacia was acquired by the UK company Amersham in 1997 and was subsequently broken up into a number of smaller companies and collectively these continue to employ more staff in Sweden than before the company was sold.

Sweden has established a significant biotechnology sector and 89% of its biotech firms are in the health sector (OECD, 2009: 56). In 2006 it had 113 biotechnology firms, placing it below many EU member states but it had 148 dedicated biotech firms, placing it fifth amongst EU member states (OECD, 2009: 17); it ranked fourth amongst European states in terms of its biotech R&D expenditure and intensity; and it ranked highest in terms of average R&D spent per firm (OECD, 2009: 25). It ranked seventh in Europe for biotech PCT patent applications (OECD, 2009: 71).[33] Sweden had the lowest proportion of firms with less

[33] Figures were not available for the UK

than 50 employees (40%), indeed it is unusual in having nearly as many firms with 250+ employees (32), as it does companies with 50-248 employees (36) and less than 50 (45) (OECD: 14/22). There are concerns that Sweden lacks framework conditions for encouraging start-ups. In 2007 and 2008 Swedish biotech firms received just under 100M Eur in VC funding in 2007, outranking all but Denmark and the leading EU biotech countries (Germany, Switzerland, UK, France) (Ernst and Young: 87). OECD statistics on *life sciences* VC investments for the same year show a slightly different picture: only France, UK and Germany are ahead of Sweden which leads on a number of metrics such as VC investments as a percentage of GDP and live sciences VC funding as a share of all national VC investment (OECD: 97-99).



Geographical clustering of Swedish life sciences companies (Vinnovas, 2007: 36)

Funding and innovation governance

Research strategy is set out in policy bills which are prepared every four years. Primary responsibility for research policy lies with the Ministry of Education and Research but co-ordination across ministries is achieved through advisory bodies: the Research Policy Council and the Innovation Policy Council. The Ministry of Enterprise, Energy and Communications supports applied research through a body established in 2001 – the Swedish Governmental Agency for Innovation Systems (VINNOVA). Government funding for basic research in Sweden comes from the Swedish Research Council which was set up in 2001. The Council takes a strategic role in policy formation and its strategy for 2009-2012 identified a number of priorities including increased investment, more long-term investments and speeding up knowledge translation. Biomedical research is a priority area for the Council. The Council provides grants for projects, staff and equipment and fellowships but does not provide long-term funding for major research centres which comes instead from the Foundation for Strategic Research (SSF), an independent body established by the government in 1994 with its own funding capital to support world-class research in life sciences, biotechnology and

engineering which will enhance Sweden's competitiveness. Its annual budget for life sciences is 12.7M Eur and for biotech-related science and technology it is 6.8M Eur. Its primary focus is now on supporting strategic research centres (ERAWATCH national profile).
Sweden's STI policy is relatively centralized but since 2001 the 21 counties have had responsibility for regional growth programmes, which encompass innovation and knowledge creation and national policy is supposed to take into account regional development issues. Regions can compete for funds from VINNOVA through the VINVAXT programme which supports cluster initiatives such as Uppsala Bio in Uppsala.
Additional funding for stem cell research has come from domestic and international research charities, most notably the Juvenile Diabetes Research Foundation (JDRF) (in concert with the Swedish Diabetic Foundation (SDF)) and the Michael J Fox Foundation and, most recently, the Knut and Alice Wallenberg Foundation and the insurance company AFA Insurance.

RM: Science base

Sweden has a leading position in stem cell science based on a strong foundation in developmental biology. Leading Karolinska Institute researchers Urban Lendahl, Jonas Frisen and Christer Betsholtz are ranked fifth, 16th and 23rd respectively, as the most-cited researchers in developmental biology (Vinnova: 122). Sweden has strengths in a number of therapeutic areas: neurodegenerative diseases, stroke and diabetes. In 2001 when the US government identified the stem cell lines which could be used in research funded by the federal government of the 64 lines identified, 24 had been derived in Sweden (19 at Goteborg University and five at the Karolinska Institute). This was more than any other country (the US had 20).
A more strategic approach to RM research in Sweden was initiated in part as a result of external influence when the JDRF/SDF funded a programme of stem cell research in collaboration with the Swedish Research Council. The programme ran from 2002-2008 with funding of 8.4M Eur. Additional funding was available in normal competitive funding calls, and in total the Swedish Research Council allocated 12.4M Eur to stem cell research between 2002-2007 (Vinnova: 119). As this period came to an end, the 2008 research and innovation bill identified RM as a strategic priority with 6.5M Eur earmarked for the period 2010-12 and the Swedish Research Council was identified as the body to lead RM initiatives. However, at the current time there is no national strategy for RM and a lack of co-ordination between different agencies (Vinnova: 180).
The main centres for stem cell research are the Karolinska Institute, Lund University, and Göteborg University.
Lund Centre for Stem Cell Biology and Cell Therapy – established in 2003 as a strategic centre of excellence in life sciences with funding from the Swedish Foundation for Strategic Research. Research focuses on stem cell and developmental biology of the central nervous and blood systems, and development of cell therapies in these organ systems.
Karolinska Institute:
Developmental Biology for Regenerative Medicine – established as a centre of excellence in 2006 with a ten-year grant from the Swedish Research Council, the DBRM brings together many of the Institute's leading researchers

Human Regenerative Map: led by Jonas Frisen, this centre was established in 2008 by the Swedish Research Council with the aim of exploiting a variety of new techniques to measure cell turnover and tissue regeneration.
Translational Research Centre: with the aim of developing stronger interactions between basic and clinical research.
Wallenberg Institute for Regenerative Medicine Established in 2010 with a 100M SEK (just over 10M Eur) grant from the Knut and Alice Wallenberg Foundation. The Centre is led by Professor Urban Lendahl and its focus will be on the blood system and bone marrow transplantation.
Göteborg University: The Sahlgrenska Academy contains a number of research teams working on stem cell research in areas including neurology and diabetes. One major grouping is the **Molecular Cell Biology and Regenerative Medicine Group** led by Anders Lindahl focuses primarily on the cartilage and heart cell regeneration. Its work began in the 1980s with use of autologous chondrocyte transplantation for cartilage injuries but has been working on cardiac stem cells since 2005 (in a collaboration with AstraZeneca, who have their cardiovascular and metabolic disease research groups in Göteborg). The group are also collaborating with Cellartis, who are a spin-out from the University (Anders Lindahl is a Director of Cellartis).
Other institutions with RM activity include **Linköping University, which has recently received 10M SEK for research on RM applications in orthopaedics and in cardiovascular disease.**
Sweden lacks a national stem cell network but interviewees stated that there has been close collaboration between major research hubs.

RM: Commercial sector

REMEDiE WP 1's survey of the European RM sector revealed that Sweden has only five RM firms, only one of whom is developing cell therapies. The small number is perhaps unsurprising given the country's size and its (relatively) poor performance in generating biotech start-ups (see above). Nevertheless it has a high profile because it is home to Cellartis, one of Europe's major RM firms. Founded in 2001 Cellartis is a provider of human embryonic stem cell lines for development of therapeutics and drug discovery programs. The company is highly international in its activities with a range of collaborations with multinational pharmaceutical companies including AstraZeneca, Pfizer and Novo Nordisk. Cellartis has opened an R&D/production facility in Scotland.
Swedish RM firms are generally university spin-outs – Cellartis is linked to Anders Lindahl's research group in Goteborg and NeuroNova was founded by Jonas Frisen at the Karolinska Institute.

RM: Legal context

Scientists working on IVF-related research have been authorized to use spare embryos since 1991. 2005 saw the introduction of new legislation addressing research on human embryos for purposes other than IVF treatment, which is now permitted subject to ethical approval (under the 2004 law on the Ethics of Research involving Humans). SCNT is also permitted for research purposes. Whereas previous research had used surplus embryos from completed IVF treatments, the new law permits donors to provide human embryos for research purposes.

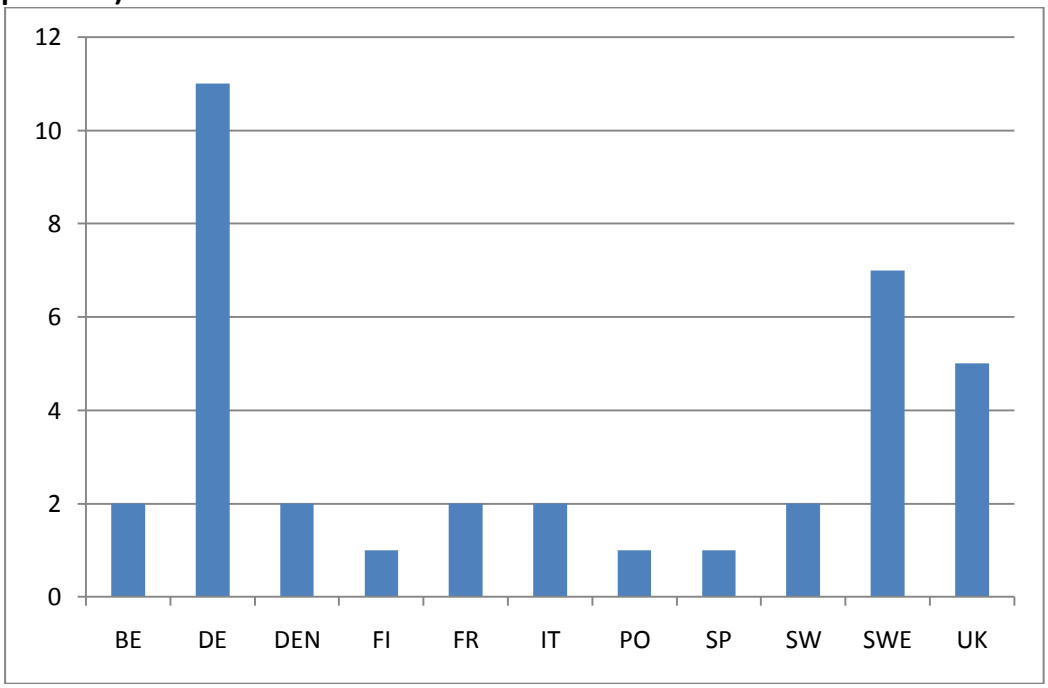
International links

International collaboration has been identified as a priority by the Swedish government. A 2008 report identified the need for a more long-term strategic approach to internationalization of research activity. Asia has become a target for collaborations and the Karolinska Institute has a strategic partnership with Singapore, including a joint PhD programme.

In terms of RM collaboration, KI have recently announced collaboration with the Institute of Advanced Biomedical Engineering and Science in Tokyo on cell therapies exploiting cell sheet engineering technology developed in Japan, and a collaboration with the University of Minnesota and the Mayo Clinic covering regenerative medicine, bio-omics, and immunity. However, (unlike France,Germany, Spain and the UK) Sweden has not entered a collaborative agreement with CIRM. Luo et al's data on international stem cell collaborations involving the US and UK shows that Sweden was not amongst the top ten countries in terms of greatest number of collaborative papers with the USA but ranked seventh in terms of collaborative papers with the UK (after the USA) (2011). According to figures from the US National Science Foundation, the relatively limited US collaboration reflects the broader situation in scientific co-publication with the US where Sweden ranks thirteenth (NSF 2010: Ch.5). However, in per capita terms Sweden would probably rank far higher.

Sweden was active in the International Stem Cell Forum and other bodies, for instance Lar Ahrlund-Richter is on the stem cell standards committee of the ISSCR, Henrik Semb is on the steering committee of the International Stem Cell Initiative, and Swedish academic and RM firms have been involved in a number of major EU-funded projects including the EuroStemCell project. Data on stem cell research projects funded by the EU under FP6 show that Sweden ranked eighth both in terms of number of partners involved in projects (roughly the same number as Netherlands, Switzerland and Spain) and in terms of taking the role of coordinating partner. In projects coordinated by Sweden partners were most commonly from Germany. Domestic partners were next most popular, followed by the UK.

Partners in FP6 stem cell projects coordinated by Sweden (5 projects, 11 countries, 36 partners)



Discussion

The establishment of a permissive regulatory framework for hESC research has allowed Sweden to build on its existing strengths in stem cell science through targeted funding (as well as much funding in open competition with other areas of biomedicine). The leading research groups have been able to consolidate their work in research centres. However, questions remain, not least amongst Swedish policymakers, about whether a more strategic approach is required to support the RM sector.

Sweden's scientific strengths are not matched by a major proliferation of RM firms, although Sweden's relatively small size must be borne in mind, and it may be argued that to have a single company the size of Cellartis is worth far more than ten start-ups with doubtful sustainability in the long-term. However, the fact that Cellartis has moved some of its operations to Scotland demonstrates the mobility of firms operating in the RM bioeconomy and signals the danger in assuming that creating value is the same as capturing value. If, as some of our industry interviewees suggested, government policy remains focused on supporting existing leading industrial sectors such as automobiles, rather than improving the framework conditions for high-tech SMEs, then it may be that regional authorities will have to play a compensatory role in trying to encourage the growth of Sweden's RM sector. The beginnings of such a strategy may be evident in Goteborg.

Sweden's unique system of registries represents a potentially valuable resource for collecting data in the post-market environment, should it be necessary to conduct long-term follow-up on patients receiving cell therapies, either to allay fears of long-term side-effects, or to demonstrate cost-effectiveness.

United Kingdom

The UK is recognized as a leading force in stem cell research as a result of historic strengths in developmental and reproductive biology and has prioritized stem cell research for nearly a decade. The UK Stem Cell Initiative set out a national strategy in 2005 and this is now being reviewed.

Context: Life sciences and biotech innovation performance

The UK ranks fifth in the Innovation Union scoreboard for EU member states and in first place amongst the countries classed as 'innovation followers' (amongst our case studies only Germany and Sweden have higher rankings) (EIS: 4). UK government figures place the UK in second place behind the United States for research excellence in a number of fields including bioscience and clinical research (Vinnova: 71).

The UK has a leading position in the European pharmaceutical sector on some key measures. In terms of pharmaceutical R&D the UK is in prime position: 5,426M Eur was spent on R&D in the UK in 2007 a sum greater than France (see above) (EFFPIA: 7). In 2005 the leading UK pharma firms GlaxoSmithKline and AstraZeneca were ranked second and fifth respectively in the world in terms of sales (GSK: $33,960M and AZ: $23,950M) (Daemrich: 6). The UK's global share of New Chemical Entities has increased in recent decades from 7% in 1961-70 to 16% in 1991-2000, in contrast to France and Germany, whose shares have declined (Daemrich: 7).

The UK is also a leading biotech country within the EU. In 2010 the UK medical biotech sector comprised 942 firms employing 36,700 people and had a turnover of £5.5bn (BIS: 4). Although it did not supply data to the most recent OECD biotech statistics report, other data shows that it has had a strong position. In 2008 the clinical pipeline of UK biotech firms was far greater than any other country; over 50% bigger than Germany, which ranked second. This lead was across all phases but significantly greater than its closest rivals in Phase III (Ernst and Young: 96). In terms of VC finance it ranked third, just behind Switzerland, but way below Germany in 2007; in 2008 it overtook Switzerland and came closer to Germany (whose financing dropped by over one-third) (Ernst and Young: 87). The UK biotech sector is spread across the country but with a heavy concentration in the East (with Cambridge as the main hub) and the South East which combined have 53% of the total turnover, 45% of total employees and 38% of the total companies (BIS: 35).

Context: Funding and innovation governance

The UK has a relatively centralized system for innovation governance which is developed and implemented by the Department for Business, Innovation and Skills (BIS) which contains the Government Office for Science and has responsibility for the Higher Education Funding Council for England, the Research Councils, and the Technology Strategy Board (TSB). However, some aspects of innovation policy have been devolved to the English regions, and to the devolved administrations of Scotland, Northern Ireland and Wales. The latter three have devolved responsibility for higher education funding and Scotland has further independence in some aspects of R&D policy. Nevertheless, all universities in the UK are eligible for funding from the main UK research councils. Research charities play a major role in funding medical research in the UK. The Association of Medical Research Charities has 126 member organisations who contributed over £1Bn in 2010 to medical research and provide about one-third of all public expenditure on medical and health research in the UK (AMRC website).

Over the last seven years UK innovation policy has been driven by a ten-year framework set out in the government's Science and Innovation Investment Framework 2004-14. The importance of this agenda was reinforced by the Sainsbury Review of Science and Innovation (2007) and a 2008 White Paper *Innovation Nation.* In 2009 the new government announced a 2.4% cut in overall spending for innovation, universities and skills and the abolition of the Regional Development Agencies, there is thus both a contraction in R&D investment and a greater centralization of some dimensions of innovation policy.

Research is conducted primarily in universities; however, the research councils also fund some major independent centres and institutes, for instance, the Medical Research Council supports 53 research units and centres as well as the National Institute for Medical Research, the MRC Clinical Sciences Centre and the MRC Laboratory for Molecular Biology. Medical charities also fund independent research organisations, such as the Wellcome Trust Sanger Institute and Cancer Research UK's London Research Institute.

Government support for industry R&D is provided through tax credits, and the Technology Strategy Board (TSB), which also has responsibility for the formulation and delivery of a national technology strategy focused on knowledge translation for innovative products and services.

In 2009 the Office of Life Sciences was established within BIS with the goal of supporting UK life sciences companies. It works across a range of policy areas, including infrastructure, finance and tax, skills and NHS market access and brings together a range of government departments including the Treasury, the Department of Health, as well as the Intellectual Property Office, the research councils and the MHRA. Scotland has established its own life sciences strategy which is the responsibility of Scottish Enterprise.

RM: Science base

The UK is recognized as a leading force in stem cell research as a result of historic strengths in developmental and reproductive biology. Notable achievements include the first isolation of mammalian embryonic stem cells at Cambridge in 1981 and the first cloning of a mammal at the Roslin Institute in Edinburgh in 1997. The UK has sought to build on this through strategic investments in stem cell science. In the 2002 spending review £40M was allocated to stem cell research. In 2004 the UK Stem Cell Bank was launched as a repository for adult, foetal and embryonic stem cell lines which are ethically derived and well-characterised. During this period significant resources were devoted to stem cell research: in 2003/4 just over £21M and in 2004/5 just over £31M (Pattison: 46). In 2005, the UK Government announced the launch of the UK Stem Cell Initiative (UKSCI), commissioning Sir John Pattison to prepare a ten-year vision for UK stem cell research by the end of 2005. The report was published in December 2005 and contained 11 recommendations [list?].

The UK National Stem Cell Network was established in July 2006. Its objectives are:

- To coordinate existing activities through the sharing of knowledge
- To facilitate interactions to promote the uptake and use of stem cells by the scientific, business and medical communities
- To act as the national focal point for interaction with overseas researchers seeking collaboration with UK researchers

- To work together with other stakeholders to ensure the effective coordination of national activities in stem cell research and its promotion in the media

In 2007/8 the UK spent £56.08 million stem cell research. £36.7M came from the research councils: the MRC invested £25.6 million, the BBSRC £10.07M, the EPSRC £5.13m and the ESRC £2.95M. The balance was invested by medical research charities including £10.11M from Cancer Research UK , and £5.07M from the Wellcome Trust (Berlin UK workshop report: 22). An audit of stem cell research spending for 2007 conducted by the MRC revealed that the bulk (56.9%) was spent on research grants, 28.6% on centres of excellence and 10.9% on fellowships (MRC: 6). A geographical breakdown of this funding revealed a heavy clustering with London receiving 31.2%, 16.7% in the East of England, 12.6% in Scotland and 12.1% in the South East of England. In terms of institutions the biggest beneficiary was Cambridge University which received 15.6%. By this metric other leading institutions were Edinburgh University (6.1%), University College London (5.4%), Oxford University (5.1%), King's College London (4.7%), Manchester University (4.5%), Sheffield University (4.4%), Nottingham University (3.4%) and Imperial College London (3.2%) (MRC: 10). 28.6

In 2009 the Technology Strategy Board launched a £21.5M programme of funding for regenerative medicine with grants made available for industry R&D. This year they have announced a competition for the development of a technology innovation centre for cell therapies. The centre will provide businesses with access to equipment and expertise, research and development capabilities and the ability to explore the potential of emerging technologies.

The government is now undertaking a review of developments over the last five years in regenerative medicine and is expected to publish a report on its findings in the summer, followed by a new strategy later in the year.

Whilst most RM innovation activity has been driven by the national government, there have also been regional initiatives. Regional stem cell networks were established in London and the East of England in 2005, prior to the development of the UK NSCN. The Scottish Stem Cell Network (SSCN) was established even earlier, in 2003, and is supported by Scottish Enterprise and the European Regional Development Fund (as well as some corporate funding). The network brings together academic institutions, clinical research groups and industry. It acts as a public voice for stem cell research and is a point of contact to facilitate international collaborations. The SSCN was the first initiative in what is now termed the Stem Cell Intervention Framework (SCIF), a strategy which includes support for Roslin Cells, a fund for translational research, and a collaboration between three universities and the Swedish company Cellartis to develop new technologies for the production of stem cells as tools for pharmaceutical research. However, the flagship project for the initiative is the Scottish Centre for Regenerative Medicine, a new £59M research and commercialization facility based in the new Edinburgh Bioquarter which will have industry, academic research and a major teaching hospital in a single site.

RM: Legal context

The UK has a relatively permissive framework for hESC research, which is regulated by the Human Fertilisation and Embryology Authority (HFEA). This body was established in 1991 under the HFEA Act which created a regulatory framework which permitted research on embryos no more than 14 days old and only for the study of infertility, miscarriage and

congenital disease. The Act was amended in 2001 to allow the use of embryos for stem cell research. The HFEA can license the derivation of stem cells from embryos that are: (i) surplus to IVF requirements, or (ii) created by IVF specifically for research purposes, or (iii) created by therapeutic cloning. Researchers who generate cell lines must deposit them with the UK Stem Cell Bank so that it can be shared with other researchers. In the same year reproductive cloning was banned under a new piece of legislation, the Human Reproductive Cloning Act.

Commercial sector

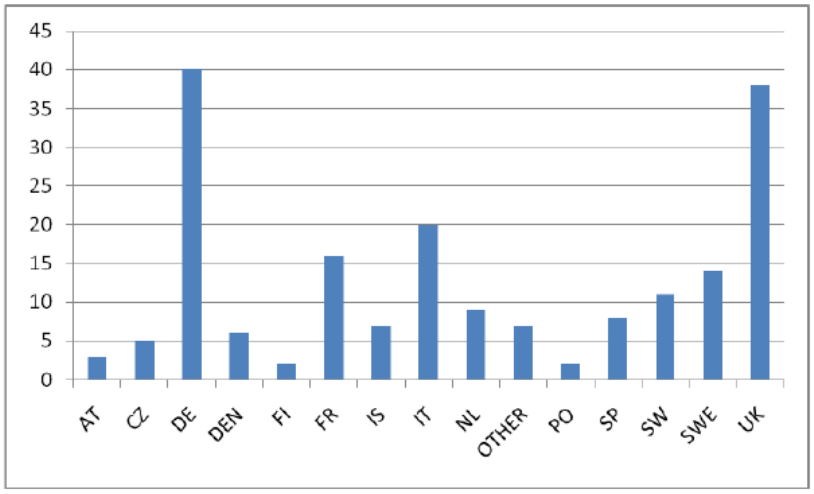
REMEDiE WP 1's survey of the European RM sector revealed that the UK has the second largest commercial RM sector in terms of number of firms. The UK has 26 firms, which is nearly 25% of all European firms and is just behind Germany which has 29. Of those companies for which data was available on size, only two of the companies are medium-sized, the remainder being small. Four of them are cell therapy companies, none of whom yet have products on the market. Eight of the firms are developing therapies (six focused on cell therapies, two gene therapies). All the cell therapy firms are developing autologous products except ReNeuron which is developing an allogeneic product and Altrika is producing both. Of these four, one is developing autologous therapies,one is developing allogeneic products, one is developing both (data on the remaining company is unclear). ReNeuron was founded in 1997 and to date they are the only European firm with a stem cell therapy for neural regeneration in clinical trials (phase 1). ReNeuron's cell line is an allogenic therapy derived from foetal neural tissue.

International links

The UK was the first country to sign a collaborative agreement with the California Institute for Regenerative Medicine (in September 2008). In May 2011 the Scottish Centre for Regenerative Medicine signed a memorandum of understanding with the Institute for Integrated Cell-Material Sciences at Kyoto University. The UK played a leading role in the International Stem Cell Forum and the International Stem Cell Initiative (the steering committee of the latter was chaired by Professor Peter Andrews of Sheffield University, and Glyn Stacey, head of the UK Stem Cell Bank, was also a member).

Luo et al's data on international collaboration in stem cell research showed that the UK's preferred partner was the USA (39%), followed by Germany (21.3%) (2011: 5). Data on stem cell research projects funded by the EU under FP6 show that the UK was the country with the second greatest number of partners involved in projects, and in terms of taking the role of coordinating partner it was third behind Germany and France. However, unlike France and Germany, UK-coordinated projects did not favour collaboration withdomestic partners; instead German partners were most frequent, then UK, followed by Italy and then France. UK scientists play a leading role in a number of FP7 projects, for instance, Austin Smith, Director of the Wellcome Trust Centre for Stem Cell Research in Cambridge, is coordinator the European Federation for Systematic Stem Cell Biology which involves 20 partners in eight countries.

Partners in FP6 stem cell projects coordinated by the UK (17 projects, 15 countries, 188 partners)



Discussion

Given its national strengths in life sciences and biotechnology and its historic achievements in developmental biology, it is perhaps little surprise that the UK is in a strong position relative to other EU member states. The national strategy set out in the Pattison Report sought to consolidate its position and ensure that the UK would be a global leader in cell therapies and technology. A wide variety of activities have been funded since then and there are major clusters of activity in London, Cambridge and Edinburgh. Smaller centres of excellence have grown in other areas such as Nottingham, Oxford and Sheffield. Although largely driven by the national government, certain aspects of RM innovation in the UK have been driven by regional initiatives, most notably the Scottish Stem Cell Intervention Framework.

At the present time the future of certain activities, such as the UK National Stem Cell Network, remains uncertain. The current review of regenerative medicine strategy by the Office of Life Sciences will provide an indication of whether RM remains a strategic priority for the UK government, although it has continued to provide targeted support through initiatives such as the TSB's regenerative medicine programme.

Stakeholder perspectives on prospects and policy challenges for commercialisation

Work package 1 has described the main characteristics of Europe's dynamic and heterogeneous commercial RM sector. However, the stakeholder interviews conducted in work package four revealed a range of shared problems facing RM firms in the EU.

Interviews were conducted with a range of stakeholders in each of the six member states, Czech Republic, France, Germany, Spain, Sweden and the United Kingdom. Interviewees from the private sector included executives at a number of European regenerative medicine firms, pharmaceutical firms with an interest in RM, venture capital funds with RM investments and a law firm specialising in the biotech sector. Other interviewees, such as policy makers and health economists, also shared their views on the challenges of commercialising RM.

The chief concern for many was a lack of private finance. It was felt that this problem has worsened in recent years, with one pharma executive suggesting that venture capital finance for RM companies began to dry up in 2004 and several interviewees suggesting that there was now no start-up capital available for new RM companies in the EU. The lack of finance was attributed to investor caution, with RM being viewed as: "too difficult and too far off ... full of regulation [and] ethically difficult" (pharma exec). Furthermore, more well-established firms which had received funding feel that they are at a significant competitive disadvantage to their US rivals. One leading EU firm suggested that their main US competitor was "playing in a different league" with five to ten times the amount of VC funding. One venture capital executive emphasised the disparity in growth funding, suggesting that European VC firms can build a firm to a € 50M valuation but are then forced to sell because they lack the resources to continue to the next stage. This lack of capital could have a number of consequences for commercial strategy; one interviewee described companies being forced into premature decisions to seek a public listing or to enter clinical trials.

One factor which may be exacerbating investor caution in Europe is lack of certainty concerning intellectual property rights. The issue of whether cell therapies will be patentable in the EU was cited by one RM industry executive as an obstacle to investment and again this is an area where stakeholders felt that US competitors enjoy a comparative advantage. However, there were divergent views about IP, for instance, another RM executive suggested that patenting in the RM field is difficult not because of EU blocks on stem cell-based patents, but because of the amount of prior art. One pharma executive described IP as "a minefield" because of the lack of certainty about who owns what and about which IP is going to be most important, and suggested that the twenty-year life of a patent was too short for cell therapies because of the much lengthier R&D process left companies insufficient time on the market to recoup their investment before the entry of competitors. The relative importance of alternative forms of IP such as trade secrets and know-how were emphasised by a number of interviewees, again suggesting a marked difference between the RM sector and the wider biopharmaceutical industry.

Another area of contrast with the established biopharmaceutical industry is the regulatory framework for RM, which is still emerging. The recent development of a centralised EU approval procedure under the Advanced Therapies and Medicinal Products regulation was welcomed by most interviewees, and the industry executives interviewed generally had a

positive view of the European Medicine's Agency's efforts. Indeed one RM executive suggested that the approval of the first ATMP produced demonstrated that EMA was being "very lenient". However, there were also concerns that the regulatory framework is still evolving and that not all aspects of regulation have been harmonised, for instance, the scope and impact of the hospital exemption remains unclear and interpretation of this aspect of the regulations seems likely to vary across member states.

Furthermore, whilst the licensing system has been centralised, the EU remains a fragmented healthcare market with diverse reimbursement systems and varied uptake of new medical technologies. Demonstrating cost-effectiveness and gaining positive decisions from Health Technology Assessment (HTA) bodies was seen as a significant challenge for industry and there was concern that HTA bodies had not begun to address the question of how to evaluate RM products and services. One UK policymaker stated that they had been in discussion with the National Institute for Clinical Excellence (NICE) about this issue and that it was clear that NICE were only just beginning to consider the methodological challenges. In relation to cost-effectiveness some industry interviewees expressed the concern that many of the cost-savings that RM products might offer would be outside the healthcare budget and that current methods of assessment would not take these into account.

Linked to the question of cost-effectiveness was the issue of business models. Many interviewees expressed the view that the RM sector had yet to demonstrate the sustainability of business models for producing cell therapies. The cost of developing products, the cost of production and the size of the markets are all factors which, it was suggested, throw doubt on the viability of business models for the sector. Perhaps unsurprisingly, one industry executive stressed the importance which their company's senior management placed on the sector having some successes which would demonstrate the value of RM, a view echoed by an industry veteran who suggested that what was needed was a genuinely novel application:

> The bottleneck which no one mentions is these things don't work in many cases. They do work in some cases, and they work spectacularly in some cases, but no-one's nailed diabetes; no-one's got a heart repaired ... no one has functionally done something yet with a cell that has not been done with something else. (RM industry executive)

Conclusions

There are strong indicators pointing towards a potentially competitive position for the EU within the global RM bioeconomy: a solid research base, a high level of scientific output and a diverse group of RM firms. However, the global picture in the wider biotech sector suggests that the US will rapidly establish an unchallengeable dominance, based on three key advantages - higher levels of R&D funding, greater access to VC finance, and the single largest market for health technologies. The current global downturn has exacerbated the difficulties faced by the EU's RM companies, in particular access to VC finance. Certain European member states are now reporting a more positive picture (France, Germany) but recovery of the sector is likely to be uneven, given that the financial crisis has been far more serious in some countries. The current financial crisis has also affected public funding for basic research (of our case studies Spain and the Czech Republic are probably the most dramatically affected).

As part of the broader reform of EU innovation strategy, it is likely that greater coordination of the multi level governance framework will be necessary to ensure more effective support for the RM sector and to avoid unnecessary duplication of activity. The findings of this report clearly illustrate that RM innovation within the European Union is taking place within a complex multi-level governance framework which comprises sub-national, national and transnational networks and institutions.

The dynamics of multi-level governance of innovation varies across the European Union, with some member states devolving significant policy capacity to regional authorities, whilst others retain more central control. An ERWATCH report on the role of the regions in the Lisbon strategy demarcated three broad categories within which our case studies are evenly divided. The example of the UK is somewhat ambiguous – with recent moves to greater centralization but a high level of devolution in certain cases, most notably Scotland.

Level of centralization of innovation governance	Case study states
countries where regional authorities have significant responsibility for a broad array of innovation policies	Germany, Spain
member states with a more centralized system of governance but where the regions have some policy role	France, Sweden
highly centralized countries with very limited regional devolution of innovation governance	Czech Republic

Since innovation policy has as one of its central plank the development of strong regional clusters, there is an implicit devolution of at least some policy capacity to regional authorities. To the extent that the primacy of cluster formation in innovation policy is an emulation of the leading US clusters, then it anticipates a move towards the US innovation system within which states play a major role. The degree to which the balance of power shifts will vary, as processes of policy transfer are mediated through the existing institutional framework of each country. Kuhlman and Shapira describe Germany's BioRegio policy as a top-down process of "'guided' regionalization" which has not diminished the power of the federal government (239).

However, despite continued focus on cluster policy as a central strand in innovation governance, some theorists have questioned the importance of physical proximity as a key factor in innovation activity, suggesting instead that organisational proximity may have greater significance and that the global dimensions of innovation activity require policies which support international alliances and networking (Okamoto, 2011). The EU's funding of RM research in FP6 and FP7 illustrate the potential value of the promotion of transnational collaboration in this emerging field and raises the question whether this should be promoted more strongly as a unique strength of the EU innovation model. International alliances, whether within the EU or beyond its borders, are seen by most stakeholders as a vital part of this, however, it is notable that whilst individual member states are now forging links with countries in North America and Asia Pacific, such global alliances are not a major focus of EU funding. Consideration should be given to enhanced support for scientific and commercial collaborations with actors outside the European Union. An imaginative approach to governance would recognize the utility of harnessing the rise of the Asia-Pacific region and the emergence of an increasingly globalised system of open innovation. For example, in developing their R&D strategies policymakers could now assess the advantage to be gained from contracting out certain components of the innovation process to the NIEs of the Asia Pacific region. Support should be given for European scientists to benefit from collaborations with colleagues in the AP region, providing an alternative (or complement) to the US, the traditional overseas partner of choice. In addition, countries such as China and India may also offer to European policy makers alternative models of both innovation governance and biotech business.

Recommendations

In 2005 the Pattison Report was cautious in its estimate of how long it might take stem-cell based therapies to reach the clinic, and sought to manage the risk of over-optimistic research investments by encouraging a broad focus which encompassed areas likely to bring more immediate benefits, such as the use of stem cells in predictive toxicology for conventional pharmaceuticals. Looking at the broader field of regenerative medicine, it seems sensible to take a similar risk-management approach to create a broad portfolio of activities ranging from fundamental research on stem cell biology through to clinical trials for more established RM technologies.

1 **Governance.** Coordination for effective policymaking requires cooperation across departments and between member states.

a. A forum should be established which brings together all relevant EU departments and bodies, e.g. DG Research and Innovation, DG Sanco, DG Enterprise and EMA.

2. **Creating a strategy**

a. Leading actors within RM in the EU should be brought together to explore potential for coordination and cooperation.

b. JRC IPTS has strong track-record in policy reports on health biotechnology (including ATMPs) but has recently discontinued this activity. Additional funding should be provided to IPTS so that it can resume this activity.

3. Research Infrastructure

a. Long-term funding should be given to infrastructure which facilitates research: creation of European RM network including funding of annual meeting, renewed funding for hESC registry and enhanced cooperation between stem cell banks within the EU. The network should play a leading role in public engagement on RM issues.

4. **Public sector innovation** Increasing policy attention is focused on the role of innovation within the public sector. This may be of particular importance if, as many believe, hospital-based service delivery may be the best way to get (autologous) cell therapies in the clinic in the near-term.

5. **Exporting RM products outside the EU.** The European Union should facilitate RM companies establishing themselves in markets outside the European Union.

a. An office should be established which gathers intelligence on the regulatory and reimbursement regimes in key international markets and which can provide advice and support to RM companies.

b. Support should be given to facilitate companies creating commercial alliances which may be necessary to enter non-EU markets.

6. **Regulatory harmonization.** The EU has been characterized as a regulatory state, an institution whose primary mode of policy making is regulation. The creation of a single EU process for the licensing of RM products through the ATMP has been a major achievement. The EU has unique strengths in the formation of regulatory networks and the processes of regulatory harmonization which may be of significant utility in supporting RM innovation within the EU.

a. A first step may be a negative one i.e. to identify those areas where the EU does not have capacity to act. Divergence of views between member states means that creating a common EU position regarding hESC research is impossible and any effort to do so would be a diversion from more fruitful activities.

b. There may be aspects of regulatory regime which require further harmonisation e.g. regulation of clinical trials and human tissue.

c. The ATMP's hospital exemption requires clarification. Governance of those services/institutions which are exempt could be harmonized by processes outside the ATMP regulations.

d. Consideration should be given to potential role for the Institute for Health and Consumer Protection (JRC ISPRA) in technical standard-setting (there is already clear overlap of interest in some areas e.g. use of stem cells for toxicology testing is relevant to ISPRA work on major programme of work on alternatives to animal testing).

e. EMA should be given additional funding to enhance its work on international harmonization. Building on existing activity e.g. bilateral relationship with FDA on pharmacogenetics, work within the ICH, and bilateral relationship with regulatory agencies in NIEs like India.

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Annex 5 REMEDiE Work Package 5: Final Report

Global Bioethics: Culture, bioethics and the negotiation of value conflict

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INTRODUCTION

Regenerative medicine (RM)[34] and, more specifically, Stem Cell Research (SCR) constitutes a promising but controversial field where social consensus is a challenge. In order to achieve normative agreements, critics and proponents of these innovative methods and interventions have to negotiate different value positions.

The controversies related to RM involve, among others, the following aspects[35]:

- The sources, derivation and use of human embryonic stem cells
- The moral acceptability of human therapeutic and reproductive cloning
- The status of the embryo and the acceptability of embryo destruction
- The commodification of human biological material (including, eggs, tissues, etc)
- The limits of using strategies to avoid aging and our hubristic quest for regenerative immortality
- The nature of the human being
- Exploitation and social justice issues
- The relevance, applications and limits of the concept of dignity, and the moral acceptability of instrumentalizing human organisms
- Risks and fears associated with mixing human and animal species
- The moral relevance of potentiality arguments and some gradualistic alternatives

[34] For the purposes of this report, we will adopt the standard definition of *regenerative medicine* (RM) that has been used in REMEDiE project, which captures the principal bioscience research, current and prospective clinical application, and commercial activity in the field. Regenerative Medicine is defined as *the application of novel biomaterials – specifically cells (including stem cells), genes (via gene therapy) and biodegradable scaffolding materials, to achieve a regenerative effect, i.e technologies aimed at stimulating or augmenting the human body's inherent capacity for self-repair*. (Ref. REMEDiE Policy Brief) Although this definition of regenerative medicine is restrictive (e.g. it does not apply to tissue implants, such as face transplants), it is appropriate to carry out the task of this Work Package and to address its core problem: whether bioethical debates in regenerative medicine have an impact in policy makers' value-laden decisions.

[35] Juengst, E. and M. Fossel (2000). "The ethics of embryonic stem cells--now and forever, cells without end." JAMA **284**(24): 3180-3184, Hyun, I. (2010). "The bioethics of stem cell research and therapy." J Clin Invest **120**(1): 71-75.

- The ethical issues surrounding the use of new technologies such as Altered Nuclear Transfer (ANT) embryos and Induced Pluripotent Stem (IPs) cells
- Tissue and eggs' donors' respect and protection: informed consent, rights to the downstream research uses of stem cell therapies
- Commercial applications of stem cell therapies
- The uses experimental techniques, including the safety of clinical trials with stem cell therapies, and the need for oversight

International regulations on SCR and RM differ from country to country. For instance, each legal system establishes specific regulatory frameworks regarding the derivation and uses of stem cells. Although laws in each jurisdiction are supposed to reflect a social consensus on the boundaries of what is considered acceptable for each society, the process of debate which leads to policy making is subject to different degrees of contingency. On the one hand, consensuses on controversial topics such as those relating to regenerative medicine are fragile insofar as they can be –and usually are- challenged on moral and political grounds. On the other, they tend to be obsolete as innovation and discoveries are made in this fast-moving field of science and technology.

Increasing globalized research and world scientific collaboration adds further challenges to national regulations in terms of interoperability, harmonization and convergence of international regulations about RM in a context of cultural diversity, as is the case among European nations. Within this context of controversy, this report seeks the two general objectives:

A. To explore and to understand the variations between international policies and practices regarding stem cell research
B. To explore the moral and scientific values that shape and underpin policy making processes

First, the main value positions in the debates about SCR and RM will be examined. It will be suggested that it is difficult to prove that the legal framework of RM practices in each country can be explained by or attributed to the prevalence of a particular moral or political standpoint. A series of reasons leads to that conclusion. 1. Critics and proponents of regenerative medicine techniques cannot be easily categorized with traditional distinctions such as religious/secular or conservatives/liberals, because these distinctions do not overlap; 2. There seems not to be a clear-cut distinction between positions which are characterized as "bio-liberal" and those which are entirely "bio-conservative"; 3. The influence of moral arguments in policy making is limited when other factors, including economic pressures, historical momentum and other pragmatic contingencies are considered; 4. The evolution of bioethical discourse and value discussions are shaped by advancements in biotechnology.

Then, a description on how policy makers usually deal with these conflicts and reach consensus will be offered. Two practical policy making processes will be described and analyzed: The Guidelines on SCR proposed by the International Society of Stem Cell Research and the Spanish Law on Biomedical Research.

METHODS

A review of the bioethical literature has been performed by using the words "ETHICS" (MeSH Terms) AND "REGENERATIVE MEDICINE" (Any field); "ETHICS" AND "STEM CELL" (any field) in *PubMed* electronic Database.

A total of 588 references were selected according to their relevance for this research.

A selection of the main *Journals* which appeared in our selection is provided below (numbers represent the total of references):

Bone Marrow Transplant	21
Stem Cells	17
Cell Stem Cell	14
Haematologica	13
Hastings Cent Rep	12
Stem Cell Rev	10
Clin Transl Oncol	8
Stem Cells Dev	8
Transplant Proc	7
Cuad Bioet	7
Transfusion	6
PLoS One	6
Blood	6
Methods Mol Biol	6
Exp Hematol	6

A selection of the main *Authors* of our selected references is provided below:

Juengst, E. T.	44
Hyun, I.	29
Soria, B.	23
Knoppers, B. M.	19
Prosper, F.	15
Bueren, J. A.	15
Roche, E.	14
Bueno, C.	14
Menendez, P.	13
Reig, J. A.	12
Hyun, I. Y.	12
Garcia-Olmo, D.	12
Isasi, R.	12
Garcia-Castro, J.	11
Martin, F.	11

A display of the main *Years* of publications of our selected references is offered below:

2010	119
2009	94
2008	61
2006	48
2007	43
2004	32
2005	27
2003	26
2002	16
2000	15
2001	14
1998	13
2011	12
1997	10
1993	9

Note: an increase of the total of annual publications related to bioethics and stem cell research is palpable.

A selection of the main Keywords which appeared in our selection is provided below

cytology	232
Animals	215
metabolism	180
physiology	145
Stem Cells	143
Female	134
Cell Differentiation	133
genetics	123
methods	116
Male	109
Adult	102
Mice	101
Cells, Cultured	92
therapy	82
ethics	81

A series of twenty three interviews have also been carried out with international experts in bioethics and/or regenerative medicine, from the following countries: Italy, Germany, China, Netherlands, Spain, Poland, Romania, United Kingdom and the United States. These interviews have offered relevant qualitative information about the situation on international variation on SCR and RM regulations, and have also helped us to map bioethics communities. Each interview has been assigned a code number for confidentiality purposes. Some testimonies of the interviewees have been included in our results.

INTERNATIONAL VARIATION IN POLICIES REGARDING SCR AND RM

1. Exploring the nature of variation

1. Regulatory framework in Europe and beyond:

By 2007, 34 countries representing some 3.5 billion people – more than half the earth's population – had policies that permitted public funds to be spent for stem cell research using embryos donated by fertility clinics with consent of the donors. The United States was not among them. Today it is on its way.[36]

http://www.mbbnet.umn.edu/scmap.html[37,38]

This variation is also seen within Europe, where some countries have more restrictive laws than others. (See map below[39])

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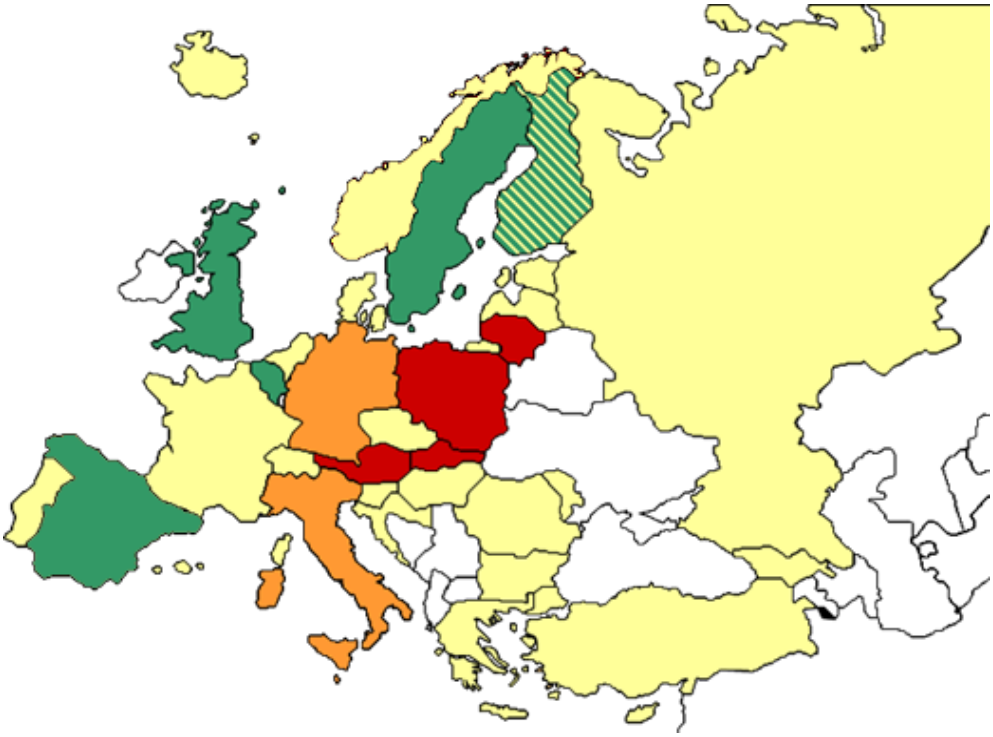
[36] http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=3336

[37] Map Explanation. Countries in light brown in the map below have flexible policies. Countries in dark brown also permit research on stem cell lines derived by using other techniques, such as nuclear transfer or research cloning. Countries in gray have restrictive policies. Countries in yellow have yet to establish a stem cell research policy. **"permissive"** = various embryonic stem cell derivation techniques including somatic cell nuclear transfer (SCNT), also called research or therapeutic cloning. SCNT is the transfer of a cell nucleus from a somatic or body cell into an egg from which the nucleus has been removed. Countries in this category include Australia, Belgium, China, India, Israel, Japan, Singapore, South Korea, Sweden, the United Kingdom and others. These countries represent a global population of more than 2.7 billion people. **"flexible"** = derivations from fertility clinic donations only, excluding SCNT, and often under certain restrictions. Countries in this category include Brazil, Canada, France, Iran, South Africa, Spain, The Netherlands, Taiwan, and others. These countries represent a global population of more than 700 million people. "**Restrictive policy" or no established policy**. Restrictive policies range from outright prohibition of human embryo research to permitting research on imported embryonic stem cell lines only to permitting research on a limited number of previously established stem cell lines. Countries with a restrictive policy include (among the most restrictive) Austria, Ireland, Norway, Poland, (among the less restrictive) Germany, Italy, and the United States. This map is designed to reflect national policy and whether or not public funds may be used to pursue stem cell research using IVF embryos donated from fertility clinics. The **black dots** show the locations of some of the leading genome sequencing research centers. Most U.S. centers are those that have been involved in the Human Genome Project. The genome sequencing centers are meant to indicate the level of scientific infrastructure and not whether stem cell genomic studies are being conducted at a given center. (http://www.mbbnet.umn.edu/scmap.html)

[38] http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=3336

[39] http://www.hinxtongroup.org/wp_eu_map.html



Color	Policy Type	Countries
	Permissive *(e.g., SCNT is specifically permitted under certain conditions)*	Belgium, Finland*, Spain, Sweden, United Kingdom
	Permissive Compromise *(e.g., SCNT is prohibited; hESC research using supernumerary IVF embryos is specifically permitted or not prohibited)*	Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland[40], France, Georgia, Greece, Hungary, Iceland, Latvia, Moldova, Netherlands, Norway, Portugal, Romania, Russian Federation, San Marino, Slovenia, Switzerland, Turkey
	Restrictive Compromise *(e.g., hESC research only permitted using cell lines created before a certain date)*	Germany, Italy
	Prohibitive *(e.g., research using embryos or cell products derived from embryos is prohibited)*	Austria, Lithuania, Poland, Slovakia

2. Lyers of variation.

Variation among countries or jurisdictions involves a number of levels, including:

[40] Finland is categorized with green and yellow stripes because the relevant law (The Act on Medical Research – No. 488/1999) does not consider the product of SCNT to be an embryo. This law explicitly allows for the use of supernumerary embryos for hESC research and it is understood that SCNT – as it is not prohibited – is permitted in the country

- Different legal systems (Civil Law vs Common Law countries)
- Different regulative models (professional guidelines vs positive laws)
- Different levels of government involvement : public (Europe) vs private (self-regulated model in Israel, China or India)
- Differing health care systems
- Public perceptions and public involvement (Pardo & Calvo,2008)

All of these factors play a role in the content of regulations (across and within jurisdictions) which also vary with regard to:

- The definition of key concepts (e.g "embryo")
- The legal treatment of the procurement of gametes, embryos and other cells from humans
- The circumstances under which the derivation and uses of hES cells is accepted
- The funding sources
- Research practice standards, privacy rules, informed consent requirements, risk assessment, etc.
- Technical standards relating to cell line derivation, banking, distribution, maintenance and use of stem cell lines
- The patent policies

3. Challenges related to international variation in a context of international stem cell research

In a context of increasing international collaboration in stem cell research, discordant regimes give rise to a number of global challenges. This variation may encourage stem cell tourism and exploitation, all of which threatens individual protection and social justice. Inconsistent and conflicting laws also prevent scientists from engaging in this research and hinder global collaboration[41]. This can negatively influence the sharing of materials and data by inhibiting collaboration at both national and international levels and by restricting the flow of knowledge and researchers.

4. Factors associated with variation

According to Caulfield, "[the] interplay between promise and controversy is partially responsible of the enormous variation that exists among the environments in which stem cell research is conducted in different jurisdictions around the world"[42].

Bioethics as a discipline has the purpose of addressing the ethical problems that arise as a result of new advancements in knowledge and technology applied to life and life sciences. Scientific breakthroughs related to life often create tensions between promises of good and the perspective of new uncertainties and risks. Scientific

[41] *http://hinxtongroup.org/docs/Hinxton%202006%20consensus%20document.pdf*
[42] Caulfield, T., A. Zarzeczny, et al. (2009). "The stem cell research environment: a patchwork of patchworks." Stem Cell Rev 5(2): 82-88.

progress in SCR and RM is an excellent example of the complexity of navigating in these waters. On the one hand, stem cell and related research has the potential to dramatically increase our understanding of human biology, and to make a true revolution in the way serious diseases and injuries can be treated. Stem cell research encompasses new approaches for the elucidation of disease mechanisms, offers promise for discovery of novel drugs, and may yield therapies for a multitude of devastating genetic, malignant, and degenerative diseases that are currently untreatable. Stem cell research is certain to advance fundamental knowledge and to have a profound impact on medicine. (The ISSCR Guidelines for Human Embryonic Stem Cell Research) Relieving suffering and promoting human welfare are, thus, compelling moral reasons to conduct stem cell research. (The Hinxton Group, Consensus Statement February 24, 2006)

On the other hand, SCR and therapies based in cell regeneration create a whole set of new situations where the interests of individuals and societies could be harmed. How to balance the therapeutic prospects of stem cell research and regenerative medicine with the complex socio-ethical issues involved is the key problem that policy makers have to deal with.

For the purposes of this report, it will be crucial to identify factors which may explain the international variation seen among countries with regard to regenerative medicine policies and, more specifically, to investigate whether value positions can explain this variance.

COMMUNITIES OF BIOETHICS

As stated in a former report of this Work Package (Report on the Data-Base Relating to Communities of Bioethics), the world should not be spoken of as a whole, at least in terms of Bioethics related to regenerative medicine. However, it is perfectly possible to distinguish, firstly, those areas in which Bioethics has not developed at all as a discipline, such as Sub-Saharan Africa (with the exception of South Africa) or some Asian regions. Secondly, there are areas where bioethics is not understood as an independent discipline, but rather subordinated to religion. This is particularly obvious in Muslim countries.

For the other countries, our initial hypothesis was that the ideological similarity should have great relevance when mapping the communities of bioethics. Throughout the development of this research and the interviews with experts in the field, we have concluded that this hypothesis was only true within shared linguistic environments. In other words, researchers form communities with other researchers with whom they share the ability to express themselves in one common language. The major religions are the only exception to this rule, especially Catholicism. Researchers who support the Church's official position on matters related to regenerative medicine create very homogeneous and well structured communities of Bioethics, with their own media, impenetrable to those who are not members of these communities. One can also speak of international communities of bioethics which are very cohesive when their members are members of any religious order.

Aside from this specific circumstance, there are barely any communities of bioethics worldwide. There is an abundance of international networks; however, they are generally limited to a cultural field defined by linguistic similarities. Within that boundary, is it possible to speak of moral identities?

VALUES WHICH SHAPE AND UNDERPIN THE POLICY MAKING PROCESS: ARE MORALITY AND POLITICS SUFFICIENTLY EXPLANATORY?

Public debates and mass media usually present ethical controversies on regenerative medicine as "wars" where two opposite and irreconcilable views face each other: one would be represented by so called "bio-liberals"; the other one is constituted by the so-called "bio-conservatives".[43] However, is there a radical difference among these sides of the debate?

First of all, it is worth noting that the political categories of "liberal" and "conservative" have not the same meaning in every country. In most European Countries, "liberal" (or more commonly "neoliberal") refers to the political vies which only requires governments to ensure individuals' negative rights, (as opposed to social and political positive rights). This conception of liberal would preclude the State intervention in domains such as health, lodging and work, which would only be governed by the laws of the market. This sort of political standpoint is usually equated –in particular by "leftists" Europeans- as conservatism. This understanding of the word "liberal" is in conflict with what "liberal" means in countries such as the US or Canada, where "laissez-faire" politics are usually conceived as "progressive". This caveat should be considered in what follows. We will use the words "liberal" and "conservative" by trying to avoid any moral connotation: "bio-liberal" will refer to the moral or political position of individuals who emphasize the importance –for the sake of common good- that the States do not intervene in, or restrict, scientific development in life sciences; "bio-conservatives" will refer to the viewpoint according to which the State should limit the freedom of bio-scientist in order to protect common good.

Critics and proponents of regenerative medicine and other potentially therapeutic or enhancement bio-technologies are often characterized as having two different ideals of what constitutes an "authentic human life". Bio-conservatives are deemed to feel comfortable in the belief that "as the power to transform our native powers increases (…) so does the possibility of *self-alienation* –for loosing, confounding, or abandoning our identity". In turn, bio-liberals are thought to support the view according to which biotechnologies increase our power of self-fulfillment. In their view, regenerative medicine would not threaten the possibility of achieving an *authentic* human life, but rather would facilitate it by empowering individuals to realize their own potential. Whereas bio-conservatives emphasize our obligation to remember that life is a gift and that we need to learn to *let things be* and to be *humbly grateful* of this gift, bio-liberals emphasize our obligation to transform that gift and to exhibit our creativity.

[43] Moreno, J. D. (2005). "The end of the Great Bioethics Compromise." Hastings Cent Rep **35**(1): 14-15.

Are these ethical frameworks so radically different? Does anybody totally embody one of them without partially embracing at the same time the other one?[44]

According to Erik Parens, critics and proponents often share more than they usually remember in the heat of the debates.[45] On the one hand, the difference between critics and proponents of biotechnologies does not equate to the difference between political "conservatives" and "liberals": many bio-critics are politically liberals and vice-versa. On the other, individuals who participate in the debates about "enhancement technologies" usually adopt, alternatively, both the "creativity" and the "gratitude" frameworks. According to Parens, "it is crucial to recognize that none of us, if we are reflective, feels comfortable only in one of these frameworks". Moving between frameworks, being ambivalent should actually not necessarily be considered a sign of confusion, but rather one of openness and thoughtfulness. To some extent, these concepts are abstractions or paradigms with analytic or heuristic value, but with a quite limited descriptive use. Is this a useful theoretical background to understand why policy makers in different countries find different solutions to treat the moral tension, referred above, between the promise and the fears of risk RM and SCR give rise?

Interestingly, even countries with seemingly similar socio-religious beliefs, legal frameworks, political systems, and levels of technical development –such as UK, Australia and Canada- have adopted diametrically opposite public policies on stem cell research. As noted by Caulfield et al. In Australia, interspecies somatic cell nuclear transfer is prohibited but somatic Cell Nuclear transfer is permitted; in Canada, the converse is likely true, while in the UK both are allowed.[46]

ALTERNATIVE EXPLANATIONS

I. Biotechnological breakthroughs are a crucial factor for the evolution of bioethical debates

Values cannot be negotiated, but they do change. And the more contentious issues come to the fore, the more values change. Regenerative medicine, being such a contentious issue and so difficult to understand using traditional parameters, can lead to certain ethical currents that have to rethink their paradigm. In this sense it may be useful to advance social consensus, for it corners more radical positions. In a sense, regenerative medicine exacerbates the conflicts we already had. If we do not use stem cells, we may not be able to heal many diseases. Society then favours their use.

Values are not immutable. Applied science and technology make them change. In the end, what has come to be known as "the technological imperative" ends up prevailing: a

[44] Erik Parens defines ethical framework as a "constellation of commitments that support and shape our responses to questions about, among many other things, new enhancement technologies" Parens, E. (2005). "Authenticity and ambivalence: toward understanding the enhancement debate." Hastings Cent Rep **35**(3): 34-41.p. 37

[45] Ibid.

[46] Adair, A., R. Hyde-Lay, et al. (2009). "Technology assessment and resource allocation for predictive genetic testing: a study of the perspectives of Canadian genetic health care providers." BMC Med Ethics **10**: 6.

significant part of what is technically possible ends up being considered morally acceptable and legal to a greater or lesser extent.

If this is so, science and technology make morality evolve, at least to the extent to which the latter guides the direction and speed of the evolution of science and technology. Nevertheless, European bioethical discourse has often considered that morality should, if not control, at least limit scientific advancements.

The German case

Without a doubt, this has been the case of some countries such as Germany, where the notion of dignity, endorsed by the memory of the abuses committed by Nazi medicine, has clearly constituted an obstacle to technological development. These kinds of concerns explain Germany's rejection of the Oviedo Convention, which authorized research with spare embryos. Germany has restricted embryo research to experiments that uses spare embryos imported from other countries. German scientists cannot create their own stem cell lines. This has created a number of objections, which characterize German politics on embryo research as authorizing a double standard. One of the interviewees commented:

> *In Germany, the debate is very much determined by what occurred in German history. I think that what happened in the time of National Socialism in terms of excluding Jews, but also treating disabled people and gypsies as inferior… These incidents, and, I think, the history of Medicine in Germany shows that, on the one hand, you have a long history of informed consent. The Parlament in Prusia, in 1906 had a law on informed consent. And one decade later... In Germany, the whole discussion on human dignity cannot be separated from this history of regarding several types types of people as inferior and not even belonging to human race,… the history of eugenics and racism… It is very important to understand the frames of the debates of embryo research, cloning, and so on. So, in these terms, you have to know the historic incidents. […] This history is very much recalled, and this should never happen again. This leads to a very cautious attitude toward everything which has to do with human embryos, and human dignity – however you define it- plays a major role in bioethical debates in Germany and other German speaking countries as well, including Switzerland and Austria and, to a certain extent, France, which has an extended history of Human Rights.*
>
> *Another factor explaining why Germany is more restrictive is civil society movement. […]Civil society movement regarding bioethics is very particular in Germany, because you don't have a strong divide between pro-life and pro-choice, which is so pronounced, for instance, in the US. In Germany, you could even say that there is a coalition between disability mouvements, feminists activist and so-called value conservatives. […] So in Germany, we do have this social-democrat tradition of being in favour of progress and technology, but this trust in technology is not so pronounced than in other countries, such as France, for instance. You can easily see, with regard to nuclear energy debate, that in Germany there is always more caution, a warning against the risks… Romanticism of the 19th century has rominticised nature… The feminist movement joined forces with disability groups, which organized themselves in terms of demanding more autonomy, to be able to live their own lives, not to be in shelter homes, so the question whether an embryo is an embryo or is to be considered a human being and to*

be protected, of course we also have these questions in Germany but… I think concerning the debate on abortion, it may also be important to know that Germany has abortion laws, it allows abortion, at least until the 12th week of pregnancy, but it's not outright accepted, but a very tricky compromise: Abortion in Germany is prohibited but is not to be prosecuted. […] It took many years until this decision was taken. It never was a matter of pro-choice vs pro-choice proponents. In Germany, unlike the US, this conflict was resolved by a sort of a compromise. No part won over the other. Something like a consensus was found, which may sound like a double standard, but, in the other hand… there was the acknowledgment of the other side. In terms of principles you could say: no compromise would ever be possible, because these are mutually exclusive positions… but I think in Germany, what was important was to say: ok, there was a position protecting the embryo and regarding the embryo as a human being, and the other position was "you could not oblige a woman who got pregnant and was in a state of pregnancy which she never wanted, you could not oblige her to carry the pregnancy to term". It was important in 1996 that this compromise was finally found and the law passed.

And I think that the conflict about human embryo research and the import of human embryonic stem cells, which was a very hot conflict around the year 2000 and which was very broadly discusses in newspapers, with a broad public participation. There, a sort of compromise was found in saying "ok, we won't allow embryo research to take place, so we want to keep our strict embryo protection law, but we also have to see the other side: researchers who want to keep up with their colleagues in other countries, then there may be something like therapeutic potential of embryonic stem cell research, and we could not cut them from scientific progress… so it was allowed to import stem cell lines from abroad, but not to produce them in Germany itself. And there was a certain date which was set, so we would only allow German researchers to use stem cell lines which were produced prior to the decision of the Parliament. So the reason behind was that Germany should not induce other researchers in other countries to use human embryos in a destructive way. So the principle of embryo protection was upheld, but at the same time the door was open, so this was the compromise that was reached.

Changes in values are introduced by science, but only by useful science

Science makes social values change by introducing a permissive and pragmatic attitude in public opinion. But this is not true for all types of scientific breakthrough, only for those scientific discoveries that truly constitute or may constitute a benefit for society. Procedures which are morally controversial end up being accepted *only if* they can provide tangible benefits for society, or for some large or influential sectors of citizenship. Procedures which only generate moral concern, without simultaneously offering social benefit, usually remain illegal. This trend may explain why "research cloning" is increasingly accepted while there is a large international consensus that reproductive cloning should be banned.[47]

[47] http://www.un.org/News/Press/docs/2005/ga10333.doc.htm

In that sense, John Harris stated this:

There is a very interesting parallel here with the cloning argument. We have just been talking about a success for rationality in my country where people have accepted the wisdom in the arguments about embryo research, but just a few years ago before that, there was a debate about cloning, a very brief debate, which ended in the shameful episode of passing on a virtually one-line law making human reproductive cloning illegal. It was enough to say "this is cloning" to get people to agree that it should be banned. But of course there is nothing wrong with cloning. As a matter of fact, assuming for a moment that God exists we should recognize that God is very fond of cloning. Identical twins are clones. One in every 270 births – 3 per 1000- is a clone.
So nature and God are in favor of cloning and this was completely overlooked in this debate and it was sufficient, as I say, just to call it cloning to convince people to be against it. That was a triumph of stupidity and prejudice over the facts and that seems to have stuck for the moment, but one of the reasons it stuck is because there is no useful purpose at the moment in cloning. We do not need it for anything. Being so, nobody has seen a reason to challenge that piece of stupidity. Despite the continual births of clones naturally all over the world without any worries about their identical genomes.
Let me add another comment to this. I would say that there was another good reason which was that a lot of those who are working on bioethics wanted to show people that they could arrive into an almost unanimous agreement on something and this was the perfect issue to demonstrate that they have arrived into something like an agreement. Yes, and I think it was shameful in a way that bioethicists, lawyers, supported the ban and the stigmatization of cloning I think it was a shameful and irrational and a very bad moment for independent impartial intellectual enquiry.

The realization that scientific and technological advances contribute to restructure our thinking and concepts, does not necessarily lead to unrestricted pragmatism and relativism. In Europe, broad regulatory frameworks, such as the Oviedo Convention, are intended to avoid this extreme. However, like other international treaties, this text is ambiguous and interpretable in some aspects. According to one of our interviewees, the ambivalence of regulations and international agreements is a common strategy to obtain agreements between countries. (Interviewee # 21) A concept or rule is created, but it is left ambiguous enough so that several countries can implement different policies without . Standard are restrictive enough for controversial practices to be under control, but exceptions are created so that potentially beneficial practices can still be carried out.

The role public opinion plays in the policy making process varies considerably

A distinction needs to be drawn between two models of policy making. In countries where RM policies are regulated by positive law, public opinion patterns may inform policy directions, and at times is directly implicated in policy making discourse. (E.g. UK : *Human Fertilisation and Embryology Authority* (2009); France: *Révision des Lois de Bioéthique*

(2010). According to Caulfield *et al. "*there is little evidence to date that policy preferences are directly linked to public views and the role public opinion plays in the policy making process varies considerably… [In some cases], there is apparent discrepancy between public opinion and policy. According to one expert, referring to the French experience of "La Révision des Lois de Bioéthique") the available democratic mechanisms to ensure the efficacy of the translation of societal inputs into law can be improved, but there was evidence in France that some aspects of the law were modified because of societal requests, including the revision of gender issues in egg donation. (Interviewee # 15)

A second model is represented by countries where professional organizations, and expert commissions –instead of politicians- take the responsibility of policy making (i.e. through Guidelines). This is the case of the USA (E.g. IOM and National Research Council: *Guidelines for Human Embryonic Stem Cell Research, (2005);* UNC at Chapel Hill: *Policy on the Use of Human Embryonic Stem Cells in Resarch* (2006). While in this model public involvement is rare, it has the advantage of being more flexible and thus enabling normative changes as innovation is developed. (Interviewee # 18)

According to the same interviewee, several factors explain international differences on what is allowed and what is not. The answer to this question is a complex mixture of where the funding comes from for this kind of research (private or public funding distinction), and laws. In the US, there is a distinction between public and private funding and, although there is not a Federal law which prohibits nuclear transfer, there are some States where human nuclear transfer is banned (Pennsylvania). In terms of country to county variance, variation has to do with who is in charge of the decision making for funding, and whether or not regional and national legislators have the authority to ban these activities. A multifactorial mixture of political reasons, law making system and the funding system (whether decision makers who are opposed to these activities can actually write conditional rules for funding these activities) could explain, according to this interviewee, international differences. (Interviewee # 18)

IMPLICATIONS OF VARIATION

Both India and China have sought to adopt regulatory and ethical government frameworks akin to those found in the US and Europe to demonstrate conformity to an emerging global regime, though these frameworks are not legally enforceable or binding on the ground. Moreover, because of the limited practical oversight of the field and the focus on patient treatment first, both China and India have as a result become centres for 'stem cell tourism'. (Policy brief)

CASES OF IRREDUCIBLE DISSENTION: CHALLENGES AND SOLUTIONS

What degree of consistency is required for effective cooperation?, How to achieve some interoperability, harmonization or convergence in stem cell research without disrespecting

pluralism on cultural, religious and social norms and values? Is public policy on morally contentious issues only feasible when there is a high level of consensus?[48]

"*The consequences of discord are too high to allow the inconsistency to continue… perhaps, the spectre of a dialogue of the deaf, with market forces driving progress on this ethically sensitive issue will bring stakeholders to the discussion table*"[49]

[48] Isasi, R. M. and B. M. Knoppers (2006). "Mind the gap: policy approaches to embryonic stem cell and cloning research in 50 countries." Eur J Health Law **13**(1): 9-25, Caulfield, T., A. Zarzeczny, et al. (2009). "The stem cell research environment: a patchwork of patchworks." Stem Cell Rev **5**(2): 82-88.
[49] Isasi, R. M. and B. M. Knoppers (2006). "Mind the gap: policy approaches to embryonic stem cell and cloning research in 50 countries." Eur J Health Law **13**(1): 9-25.

THE ISSCR GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH

Any attempt to create global guidelines, such as the International Society for Stem Cell Research *Guidelines for Human Embryonic Stem Cell Research*, have to face a difficult challenge: different understandings regarding core values and principles endure between policy makers, society representatives and researchers at the international level. The ISSCR' *Guidelines for Human Embryonic Stem Cell Research* acknowledge the moral pretention of universality as they state that "human stem cell research must ensure that human biological materials are procured in a manner according to globally accepted principles of research ethics." However, this document also states that "any and all stem cell research shall be conducted in accordance with any applicable laws and regulations of the country or region where such research takes place, recognizing and respecting that certain laws and regulations may be applicable to individual researchers, regardless of where the research will take place". (5.1) How can pluralism be respecte while not falling into moral relativism? What has been the position of this international organism with regard to disagreements?

One of our interviewees is one of the *ISSCR Guidelines for Human Embryonic Stem Cell Research* task force members. He was asked to what extent this organism had to deal with the tension between respect for pluralism and aspiration for universal guidelines. Here is his answer:

> *It was a bouncing at that we had to trait straight… between declaring guidelines that we thought to be truly international, and in that respect they were supposed to be universal, but also a sense that should be…. the researchers had to act locally, in various countries that have very different situations, very difficult cultural attitudes, and various policies and laws, so the way we tried to present the guidelines was in the following manner: We always said: these are meant to be professional guidelines or recommendations for the field provided for by the international society of researchers, but of course in your own individual locale it is your responsibility to first and foremost follow the applicable laws and policies to you as a researcher. And then where there is room for any further guidance, you are more than welcomed to use the guidelines. So we recognized that of course everybody has the responsibility to follow the laws in their own locale. So it is recognized that policies and laws are different country by country and we do not have of course the authority or the desire to tell people these countries do what we think is right. On the other hand, there are countries where there is no regulation at all, and researchers are asking for more guidance. […] When we make international guidelines for stem cell research, we don't have to reinvent the research ethics realm, we just have to make it relevant for the field of stem cell research, so we could look at international declaration for research ethics, such as the Declaration of Helsinki, the Belmont Report, and documents like that.*[50]

The authors of these guidelines and the ISSCR' Guidelines for translational research had to face some other challenges. They had to reach consensus on at least three controversial points on which there was initial disagreement among its members. These points were research cloning, payment for egg donors, and the question whether tissue donors should be allowed to participate in the clinical trials.

[50] In the Guidelines, there is reference to the Nuremburg Code of 1947, the Declaration of Helsinki of 1964 and amendments, the Belmont Report of 1979, the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects of 2002, and the UNESCO Universal Declaration on Bioethics and Human Rights of 2005.

The debate about research cloning

For long, somatic cell nuclear transfer (SCNT) or "therapeutic cloning" has been the only way scientists could imagine deriving patient specific cell lines. In 1998, a new way to obtain patient specific stem cells was discovered: Induced pluripotent stem cells, (iPS cells). For some, this important discovery in the scientific landscape is likely to abandon the need to turn to SCNT, which necessarily require the destruction of the embryo. Others consider that IPS cells cannot totally replace SCNT, because these new cells have not the same capacity to reproduce and because of some cases of cancer generated in patients treated with these cells.[51]

The controversy on payment for egg donors

This controversial aspect was solved by the ISSCR Guidelines by not recommending reimbursement in principle, and allowing exceptional case-by-case authorizations by a ESCRO:

> *Except when specifically authorized by the SCRO process, no reimbursement of direct expenses or financial considerations of any kind may be provided for donating embryos or gametes that have been generated in the course of clinical treatment and are in excess of clinical need or deemed of insufficient quality for clinical use. […] People who elect to donate stored materials for research should not be reimbursed for the costs of storage prior to the decision to donate. Reimbursement for direct expenses incurred by donors as a consequence of the consent process may be determined during the SCRO process. (11.5a)*

The question whether tissue donors should be allowed to participate in the clinical trials.

This issue was solved by ensuring equal access to participate in research and by strengthening the legal requirements of tissue donors' informed consent, as belonging to a vulnerable population. The ISSCR' *Guidelines for Stem Cell Research* ensures equal opportunity to participate in stem cell research: "Persons should be afforded a fair opportunity to participate in research, and they must be treated justly and equitably", but adds that "caution must also be taken to ensure that persons are not exploited during the procurement process, especially individuals who are vulnerable due to their dependent status or their compromised ability to offer fully voluntary consent". The quality of informed consent process is particularly crucial for patients donating somatic cells for disease-specific stem cell studies, as they might otherwise donate under a false expectation that they will benefit directly from eventual medical applications of their patient-specific stem cells:

> *Consistent with well established principles of justice in human subject research, there must be a reasonable relationship between those from whom such materials*

[51] Hyun, I. (2008). "Stem cells from skin cells: the ethical questions." Hastings Cent Rep **38**(1): 20-22, Hyun, I. (2010). "The bioethics of stem cell research and therapy." J Clin Invest **120**(1): 71-75.See also http://www.bioeticanet.info/genetica/UnMICHIGAN.pdf

are received and the populations most likely to benefit from the research. Finally, the voluntary nature of the consent process must not be undermined by undue inducements or other undue influences to participate in research. (11)

The ISSCR itself provides a recommendation for Dispute resolution in international collaborative stem cell research:

Any conflicts of interest or other conflicts or disputes that may arise in the course of any international collaboration, for example, disagreements or difference of opinions between researchers from different countries involved in common projects, may be resolved in accordance with an agreed-upon dispute resolution mechanism in a forum with international representation from countries doing research and clinical trials in human stem cells. Members of the forum will, as appropriate, seek guidance from experts in the fields of science, ethics, law and medicine from different national, social and religious backgrounds. It is recommended that all international collaboration agreements incorporate a dispute resolution provision providing that any disputes or differences shall be settled through mediation or arbitration by international forum, and this provision shall stipulate whether or not any decision made by the forum will be binding on the relevant parties.(13)

1. Introduction

Spain is, to this day, one of the pioneering countries in stem cell research, forming part of the so-called G-4, together with the United States, Canada and the United Kingdom. The groups located in Communities such as Andalusia, Valencia or Catalonia are situated at the forefront of excellence at a worldwide level, therefore causing Spanish publications about these subjects to possess a far greater impact than those of countries such as France or Germany. This situation is no doubt owed to the concurrence of a series of facts of a different nature that have combined to make it possible.

The first of said facts was the firm bid of the different governments involved, central as well as those of the autonomous communities which make up Spain, to make biotechnology a strategic sector in this country. With that aim, between the years 2000 and 2005 great efforts were made to bring scientists of enormous international prestige in this field to Spain. Therefore, in 2004 Juan Carlos Izpisúa began to combine his position as director of the Gene Expression Laboratory at the Salk Institute in San Diego (California) with the direction of the Centre of Regenerative Medicine in Barcelona (CMRB). In 2005, Bernat Soria transferred all the research that he had been carrying out in Singapore to Spain and came to direct the new Andalusian Centre of Molecular Biology and Regenerative Medicine (CABIMER) in Sevilla, the largest of its kind in Spain. Subsequently, on 7th July 2007, Soria would be named Health minister in Spain, in an undoubtable show of the enormous importance that biotechnology aroused for the Spanish government. In January 2006, finally, the Valencian Community entrusted the Serbian scientist Miodrag Stojkovic with the development of scientific stem cell research in the Prince Felipe Research Centre (CIPF).

The arrival of these scientific leaders in Spain would not have been possible, however, if an adaptation of the current legal reality to the necessities of scientific research had not previously taken place. In this sense, it should be stressed that between 1996 and 1999 Sentences 212/1996 and 116/1999 of the Constitutional Tribunal Court had already ratified the possibility that in Spain scientific research on embryos left over from assisted reproduction technology could be carried out. Shortly thereafter, in 2003 *Law 45/2003, 21 November, by which Law 35/1988, 22 November, concerning Assisted Reproduction Technologies is modified* allowed the use of embryos left over from assisted reproduction technologies existing at that time for research[52]. It is important to stress that said regulation was developed under the government of the Partido Popular, that is to say, the party which receives the bulk of the most conservative votes regarding this issue. It still proves significant, however, that in order to approve this disposition, said government resorted to the denomination of leftover embryos as "*biological structures obtained at the moment of*

[52] The reason for which only "pre-embryos cryoconserved previous to this law's coming into effect" was that the regulation itself excluded the possibility of creating in the same cycle of in vitro fertilisation a number of embryos superior to that which would be transferred to the uterus of the expectant mother, that is, in principle, three.

de-freezing", thereby avoiding the use of the most common expression regarding the aforementioned (embryo).

This regulatory context was essential for the scientific development which was experienced in Spain starting in 2003. Nevertheless, it was soon clear that the scientific situation raised legal issues that the existing regulations at that time could not solve. The principal issue of these was the response that would have to be given to the transfer of human cell nuclei to previously enucleated ovaries, a technique designated Human Somatic Cell Nuclear Transfer (hSCNT), and commonly known, though somewhat vaguely, as "therapeutic cloning". This technique, considered at that time to be an essential tool for research related to stem cells, urgently needed a legal development which would allow scientists to know what kind of scenario they would have to face in case they wished to use it. The newly elected government (March 2004) had declared itself, even before rising to power, supportive of allowing this possibility. To that effect, nevertheless, it was necessary to develop new regulations. The framework in which this development would become possible was far from being pacific.[53]

[53] Interviews 16 and 21

2. The problems which had to be faced by the development of Spanish regulations. Pressure groups and constitutional limitations.

The government that resulted from the elections of March 2004, the most tumultuous of modern Spanish democracy[54], had to face up to a market logic, in the field of regenerative medicine, due to two key factors. On the one hand, the existence of pressure groups of different types, each of which advocated a regulatory modification adjusted to its own aims. On the other hand, a regulatory field marked by that established in the Spanish Constitution of 1978 and the sentences of the Constitutional Tribunal Court that specified regarding the sense of its formulation, and in the Oviedo Convention of 1997[55]. In this section we will attempt to explain both factors.

2.1 – Pressure groups and factors

A variety of pressure groups were drawn up around the debate which preceded the Spanish law on Biomedicine.

Firstly, a group made up of the scientists themselves, who pressured the government in order to obtain a regulatory modification that would transmit legal security to the experiments that were then being carried out, as well as amplifying the field of those that could be carried out, in order to cover stem cells produced by means of nuclear transfer. In this group the pressure exerted by B. Soria himself, who expressed in public his intention to move his research, from Singapore to Spain only if he were offered legal guarantees, should be noted.[56]

This stance had been reinforced since years before by a large number of Spanish universities (34), which ended up sending letters addressed to the then Spanish Minister of Science and Technology, Josep Piqué, in order for him to authorise experiments with embryonic stem cells by means of the use of available frozen embryos or those which can be generated for their use in cell therapy [57].

- Thirdly, the group consisting of patient associations. In this case, diabetic associations were the most belligerent, spearheading the fight for regulatory acceptance of experiments with embryonic stem cells. So, for example, in February 2002, the Federation of Spanish Diabetics (Federación de Diabéticos Españoles) delivered to the Ombudsman 1.330.000 signatures in favour of research with embryonic stem cells[58].

Contrary to the previous ones, the group composed of associations for the defence of human life, closely linked to the Catholic Church, with strong support in Spain. These

[54] They took place some days after the terrorist attacks of 11 March in Madrid.

[55] Romeo Casabona, C. M., "La cuestión jurídica de la obtención de células troncales embrionarias humanas con fines de investigación biomédica. Consideraciones de política legislativa", *Law and the Human Genome Review*, nº 24, January-July 2006

[56] In an interview given to the newspaper *El Mundo* in February 2003, the scientist was asked about the offer that the autonomous government of Andalusia had made him, about taking his research with embryonic progenitor cells, to which he responded: "I have answered that if I had said yes to Singapore I wasn't going to say no to Seville. I comprehend that the autonomous governments have many rivalries regarding public health material. The thing is that I want a written offer, in which I am authorised to work with embryonic progenitor cells, accompanied by a well-reasoned legal report. The frustrating thing would be to begin the project, obtain the funding for said project, and then, later, resign because we cannot start. It's the hardest thing that can happen to a scientist." http://www.elmundo.es/salud/2003/513/1044636161.html

[57] http://www.elpais.com/articulo/sociedad/34/universidades/piden/Pique/permita/investigar/celulas/madre/elpepisoc/20021026elpepisoc_3/Tes

[58] http://hazte-escuchar.blogalia.com/historias/2964

associations were, in turn, backed by some denominational universities (the University of Navarre, Francisco of Vitoria, etc), professional or academic associations (like the Spanish Association of Bioethics and Medical Ethics – AEBI), as well as by multiple intellectuals and university professors. All these associations were strongly opposed to any type of regulatory expansion which would involve the creations of embryos for research. This implied an emphatic no to the use of the nuclear transfer technique with human cells for the generation of stem cells.

- Once the new socialist government was elected, the government which had become the principal opposing party, the Partido Popular (PP) was, as far as it was concerned, in a complicated situation. On the one hand, they were conscious that their connections with some Catholic sectors would act as a lever to present a resource of unconstitutionality in case a future regulatory development was to permit the creation of embryos for research. Although the PP had at its disposal sufficient members of Parliament and senators to present this resource, they undoubtedly preferred to avoid it, to not have to face the political wear of having to counter the demands of scientists and patient associations. Furthermore, one of the communities which had bid most strongly for the research, Valencia, was governed by the Valencian PP, which approved of a new, more progressive regulation. Therefore, the stance of the principal opposing party was rather ambiguous: on the one hand, they preferred not to counter the law; on the other, they probably would be unable to avoid it, given the expectations placed on them by the most conservative sector of their voters, if they were to cross certain red lines.

2.2.- Legal limitations.

2.2.1.- Constitutional limitations.

The 1978 Spanish Constitution indicated in its Article 15 that *"Everyone has the right to life and physical or moral integrity, without in any case being submitted neither to torture nor inhuman or degrading punishments or treatments."* The interpretation that should be given to the expression "everyone" had been the object of great controversy starting from the promulgation of the first Spanish laws regarding the decriminalisation of abortion in specific cases in 1985[59]. At that time, in its famous sentence number 53/1985, the Spanish Constitutional Court had already declared that embryos should not be considered people, but merely as legal rights worthy of protection, at least within reason[60], which meant as much as denying them all possible tenure of the fundamental right to life. Going a step further, the Constitutional Court sentences 212/1996 and 116/1999 had rejected their condition as persons in legal terms[61]. Nevertheless, those same sentences adopted a gradualist approach regarding the protection to be given to human life which excluded the consideration of anything submitted to commerce, which indicated a tendency to consider its use as a mere means to an end inacceptable.

[59] Regarding the legal statute of human embryos in Spanish regulations, see: Romeo Casabona, C. M., "El estatuto jurídico"

[60] The life of the nasciturus, as soon as it represents a fundamental value – human life – guaranteed in Article 15 of the Constitution, represents a legal right whose protection is found in said fundamental constitutional precept.

[61] "It should be remembered that neither non-implanted embryos, nor, indeed, mere gametes are, for all intents and purposes "human persons", therefore their availability for the Banks following the course of the fixed amount of time, can only with difficulty go against the right to life (article 15 of the Spanish Constitution) or human dignity (article 10.1 of the Spanish Constitution)" (STC 116/1999, f. j. nº 11).

The final result of all this jurisprudential development was the construction of a regulatory framework regarding human embryos based on two fundamental issues. Firstly, differentiating between viable and non-viable embryos. If the former had the privilege of consideration as protected legal goods, the second, characterised as such according to only biological criteria, were not susceptible to said condition, being considered in practice as an entity equivalent to any other human biological structure. Secondly, a distinction between the creation of embryos for research and the use for such a purpose of embryos left over from assisted reproduction technology was implicitly established. While the second was explicitly accepted, the first seemed to clash radically with the consideration of legal rights protected by the Spanish Constitution[62].

2.2.2.- Limitations originating from the Oviedo Convention

Spain was one of the signatory states of the *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*, commonly known as the Oviedo Convention, as well as of its Additional Protocols, among which was included one of particular importance in that which concerns regenerative medicine, that regarding the clonation of human beings. These implementations came into effect in Spain on January 1st 2000, following their ratification by Parliament. The Oviedo Convention significantly limited the possibility to create embryos for therapeutic or research purposes, stipulating in its article 18.2 that "*the creation of human embryos for research purposes is prohibited".*

It should be taken into account that among the signatory countries of the Oviedo Convention, there was only one, Sweden, that allowed the use of nuclear transfer for research purposes.[63]. The difference that exists between Sweden and Spain is that, unlike Spain, Sweden signed the agreement, but never managed to ratify it. This means that when they drew up their legal modifications to permit these practices they did not have to face the problem of their accomodation to article 18.2. Spain found itself in a different situation that brought them face to face with an added regulatory difficulty.

3.- The government before the circumstances. Possible options.

The bid for research with stem cells was, as we have already mentioned, one of the firm lines of the new government. More specifically, the executive government contemplated the possibility of protecting with regulations the constitution of cellular lines by means of nuclear transfer. That aside, this orientation presented two objections of great significance: on the one hand, the opposition of the "pro life" movements; on the other, the

[62] In fact, the LIB (the Law of Biomedical Research) declares in its preamble that "In accordance with the gradualist perspective on the protection of human life set out by our Constitutional Court in rulings such as 53/1985, 212/1996 and 116/1999, this Law expressly prohibits the creation of human preembryos and embryos exclusively for the purpose of experimentation".

[63] In that sense, the Swedish Code of Statutes no 2006:351, entitled The Genetic Integrity Act (2006:351), of 18 May 2006, states in its *Chapter 5. Measures for purposes of research or treatment using human eggs,* Section 3, that "Experiments for the purpose of research or treatment on fertilised eggs and eggs used for somatic cell nuclear transfer may be carried out no longer than up to and including the fourteenth day after fertilisation or cell nuclear transfer respectively. If a fertilised egg or an egg used for somatic cell nuclear transfer has been used for such an experiment, it shall be destroyed without delay when the measure has been accomplished".

regulatory obstacles already introduced. To face these obstacles, the government had several options:

- Not to act, that is to say: leave a regulatory void with regards to nuclear transfer
- Report the Oviedo Convention in order to permit research with human embryos created for that purpose.
- Attempt to find some legal formula which would allow them to approve nuclear transfer without explicitly admitting the creation of embryos for research purposes without having to report the Convention.

Next, we will study each one of these possibilities.

3.1.- The possibility of not acting. The Finnish example.

The first among the possibilities that the government was considering was that of not acting, that is to say, leaving nuclear transfer submerged in a legal void. This, *de facto*, meant, at first sight, permitting it, as Law is subject to the clause that "what is not forbidden is allowed". This is, in fact, the formula that was used in Finland, a country which has signed and ratified the Oviedo Convention. There, the *Medical Research Act*, of 1999, is still in force; that is to say, a considerably old regulation that considers the embryo to be exclusively the result of a fertilisation.[64]. In this way, although its Article 26[65] establishes penalties for the creation of embryos for research purposes, these are not extended to biological structures originating from nuclear transfer, which, not being derived from a fertilisation, do not enter into the definition of "embryo". Leaving the matter there, the problem which arose from article 18.2 of the Oviedo Convention was obviated: even when said problem was interpreted in an extensive manner, that included cells produced by means of SCNT, the lack of a sanctioning regulation would allow, in practice, the use of this technique for research.

In Spain, this formula presented several problems. The first was that the regulatory void was not an ideal solution for the scientific community that had to carry out its work with a high degree of uncertainty. Neither did it seem that a solution of this type would eliminate the response from pressure groups adverse to SCNT, who could make themselves easily heard if a scientist were to put into practise this type of experiment[66]. To this it must be added that the intention to develop a Law of Biomedical Research in fact excluded this possibility, given that it was clearly inadmissible to obviate this issue in a regulation of that type. The sum of all these factors led to it being impossible for the Spanish government to have recourse to these channels.

[64] Its Section 2, devoted to definitions, states that *"embryo means a living group of cells resulting from fertilisation not implanted in a woman's body".* Vid. http://www.finlex.fi/en/laki/kaannokset/1999/en19990488.pdf

[65] Section 26, in fact, imposes penalties on anyone who *"conducts research with the aim of:*

1. *cloning human beings;*
2. *creating a human being by combining embryos;*
3. *creating a human being by combining human gametes and genes from animals."*

[66] Even reporting it to the courts. Let us not forget, in this sense, that clonation is a crime in Spain.

3.2.- The presentation of amendments or the reporting of the Oviedo Convention and the development of a regulation that would allow for the creation of embryos for research.

The second option that the Spanish executive government could adopt would be just to present an amendment to the Convention, a possibility anticipated in its articles 5 and 6. Nevertheless, the procedure of modifying the document was so exceedingly slow and complex that it would only with difficulty be reconcilable given the compelling need to approve the Law of Biomedical Investigation. Furthermore, nothing guaranteed that the rest of the signatory countries would accept the introduction of said amendment. The sum of all of these determinants made it, in practice, exceedingly arduous to embark on that road.

A simpler option from a procedural point of view was the reporting of the Oviedo Convention. Now, this possibility was complex for several reasons.

Firstly, the time necessary for the presentation of reserves had already gone by when the possibility of developing the Law of Biomedical Investigation arose.[67]. Secondly, reporting an agreement signed so recently did not seem overly serious. This was particularly important if we keep in mind that said agreement had been signed precisely in Spain, which had given this country a special prominence in its proceedings. To the aforementioned it must be added that said report would not directly provide a green light for the use of cellular structures obtained by nuclear transfer, but rather would leave this issue in the hands of a decision by the Constitutional Court, if anyone were to take the question to that forum. The reporting of the agreement would bring with it, therefore, serious inconveniences in exchange for very few advantages.

3.3.- The search for an acceptable legal formula.

In light of the other options, it seemed evident that the best alternative for the government would be to attempt to find some legal formula which would allow them to approve nuclear transfer without explicitly admitting the creation of embryos for research purposes or having to report the Convention. This complex formula would probably allow them to satisfy the interests of the different pressure groups as well as the legal limits to which the executive government found itself submitted. But was this possible from a technical point of view? As we will see in the following epigraph, Spain demonstrated that it was indeed.

4.- The Spanish solution

The solution finally adopted by Spain was that of considering, simply, that a nuclear transfer under no circumstances generates a human embryo. For this purpose, Law 14/2007, of 2 July, on Biomedical Research defined an embryo (article 3.1) as *"a phase of embryonic development from the moment in which the fertilised ovocite is found in the uterus of a woman until the beginning of organogenesis and which ends 56 days from the moment of fertilization, with the exception of the computation of those days in which the development could have been stopped".* In this way, the regulation designated as embryos only the cellular structures which come into being as the result of a fertilization. Given that in a nuclear transfer there is no fertilization whatsoever, it is obvious that in that case we cannot speak of a human embryo. In this way, the "Spanish solution" imitated to a large extent the "Finnish solution" (in both cases the key piece of the puzzle consisted in

[67] See Article 36 of the Convention.

maintaining a definition of *embryo* strictly linked to fertilisation), but solving the legal void that was produced in the Nordic country (in Spain, unlike Finland, there did exist an explicit regulatory precaution that facilitated the use of cellular nucleus transfer techniques) much more satisfactorily.

In concordance with this approach, article 33 of the Law indicates the following:

Article 33. Obtaining of embryonic cells.

1. The creation of human pre-embryos and embryos exclusively for experimentation purposes is prohibited.

2. The use of any technique for obtaining human stem cells for therapeutic or research purposes is allowed, but only when it does not entail the creation of a pre-embryo or an embryo exclusively for this purpose, in accordance with the terms provided in this Law, including the activation of ovocites through nuclear transfer.

Based on this terminological construction, Spanish legislators affirmed in the Preamble to the Law that "*In accordance with the gradualist perspective on the protection of human life set out by our Constitutional Court in rulings such as 53/1985, 212/1996 and 116/1999, this Law expressly prohibits the creation of human preembryos and embryos exclusively for the purpose of experimentation. However, the use of any technique for collecting embryonic stem cells for therapeutic or research purposes that does not entail the creation of a preembryo or of an embryo exclusively for this purpose, and in the terms provided by this Law, is allowable.*"

The final result of this solution was that all the pressure groups showed themselves to be sufficiently satisfied for the law to be accepted without any major explicit controversies. The acceptance of research by means of nuclear transfer satisfied the majority of patient associations or the researchers and academics that supported them. The inclusion in the law of an article whose wording explicitly prohibited the creation of embryos for research, as far as they were concerned, allowed the pro-life movements in general and the Catholic Church to save themselves the trouble of organising manifestations against a law that had a great deal of support from the citizens. This, in turn, relieved the Partido Popular of all pressure to present an appeal of unconstitutionality before the law. This risk of appeals of unconstitutionality was minimised in the law's preamble itself, explaining with a great amount of detail just why it was coherent with previous regulations. As one of those interviewed pointed out:

- *Question: La impresión que uno tiene cuando tiene cuando entiende la ley es que esta ley es bastante avanzada, bastante permisiva con respecto a otros países…*

- *Answer: Es un poco paradójica…, pero pregúntame*

- *Question: La cuestión es cómo no han saltado las alarmas de los sectores más conservadores en este país*

- *Answer: Es lo que yo me preguntaba. Yo les informé, y dije que no creía (y acerté) que hubiera algún recurso de constitucionalidad. Era imprevisible si podría haber o no un recurso de inconstitucionalidad a la ley. Pero que si se hacía así, vinculándose la ley, literalmente incluso, citando, transcribiendo algunos preceptos, los más importantes, en la propia ley, sería más difícil que el tribunal constitucional pudiera declararla inconstitucional. Y como así se hace, a pesar de que haya esa excepción tan importante de la clonación, el resto de la ley era en*

ese sentido, yo creo que se quedaron sin argumentos. Y sobtr todo quizá tal vez porque para eso necesitas que haya un rencor social. No hubo en Madrid ninguna manifestación a favor de la vida. Esto, la gente que está muy metida en estos temas, en el campo científico, o de la ética , del derecho o de otras… pueden entender qué es eso de las células troncales, y qué tienen que ver con los embriones, y podrían tomar posición, pero el común de los mortales no entienden suficiente como para pensar "eso es un aborto", "eso es quitar vidas". El político, se queda entonces sin ese respaldo […] En resumen, el PP no ha tenido ese tipo de reacción social, que le hubiera forzado a presentar un recurso de inconstitucionalidad. Porque a veces no les interesa tocar cosas aunque muchas veces no estén de acuerdo. Porque el político pragmático al fin y al cabo tiene que hacer cuentas. Y debió ver que eso iba a generar una discusión tremenda y no le iba a dar más votos, sino acaso quitárselos. Desde el punto social el tema de la clonación se ve como algo muy técnico. Y desde el punto de vista jurídico tampoco está tan claro: no se sabe lo que hubiera podido pasar, pero no hubiera sido fácil que el Tribunal constitucional se hubiera opuesto a esta ley. A mí la verdad es que sí que me llamó la atención. Yo creí que no se iba a producir, y no se produjo ese recurso.

- *Question: Parece que esta ley ya se hizo con esa previsión, para que no fuera vulnerable a un recurso de inconstitucionalidad.*

- *Answer: Sí, claro, por lo menos en lo que yo tuve implicación, lo hice pensando así. Yo primero llegué al convencimiento (y creo que en eso fui sincero)[…] que no estaba tan claro que la transferencia nuclear constituyera un embrión…*

  […]como estaba la ley de Reproducción Asistida, teníamos que ser coherentes, porque no vamos a tener en la Ley de Investigación Biomédica solo embriones y en la otra también pre-embriones. Y como el ordenamiento jurídico es un todo, aquí se nos puede venir la definición de embrión de la otra ley y no sabemos lo que puede ocurrir. Tenemos que revisar todo para que haya coherencia con la otra ley. Y una de las condiciones fue meter esto, y otra meter también la definición de embrión, y esto al fin y al cabo, parece que podría dar un entendimiento al Convenio de Oviedo, cuando habla de embrión, distinto. Porque para otro Estado, el artículo 18.4 del Convenio, el embrión sería el embrión más el preembrión. En cambio para nosotros no está dividido… (Interview 21)

5.- The Spanish solution. Criticism

Is the Spanish solution, in any case, upright? Some authors, without making a specific mention of it, have accepted the argument that protects it [68]. Others, on the other hand, have indicated that the consensus cited comes from "label fraud"[69] consisting in

[68] In fact, this line of argument was already assumed by a judge of the British High Court, Justice Crane. See: Plomer, A., "Stem Cell Research in the UK: from Parliament to the Courts", *Law and the Human Genome Review*, nº 16, 2002, pages 188 and following. There are, furthermore, authors of recognised prestige that have supported this same hypothesis. See also: Savulescu, J. «Should we clone human beings? Cloning as a source of tissue for transplantation», *Journal of Medical Ethics*, 25/ 2, April 1999, page 90; Atlan, J. «Possibilités biologiques, impossibilités sociales», in AA. VV., *Le clonage humain*, Ed. du Seuil, París, 1999, pages. 36-37.

[69] Romeo Casabona has written on this matter that "the proposals which attempt to mark the differences between one zygote and another, looking for their own new designation for that which is obtained by means of activation

having taken away the name of embryo from a biological reality that, in reality, has the same potential as a zygote from a fertilisation. Does this type of criticism make any sense? On one hand, it may seem that, sure enough, it does. We should not forget, in this sense, that the transfer of cell nuclei has been capable of generating adult individuals of other species of mammals, Dolly being only the first example. This evidence has caused several European countries[70] and Japan[71] to change the traditional definition of an embryo as being the product of fertilisation to another in which the decisive element in the definition is the potential for a biological structure. Therefore, to state that the transfer of a nucleus can create a human embryo and to make the consequent criticism that an omission such as that contained in the Spanish legislation does not adequately fit with the current scientific situation is correct.

It is also true that concluding that the transfer of the nucleus inevitably creates a human embryo is doubtful from the scientific point of view. According to one of our respondents this argument was taken into account by the legislator:

- *Question*: *La ley de investigación biomédica, al definir embrión, lo limita al resultado de una fecundación, y distingue el proceso de la transferencia nuclear de la fecundación. Esto hace que la transferencia no pueda dar lugar a un embrión. ¿Es esto correcto?*

- *Answer: Es correcto, porque aquí habla de ovocito fecundado, sí.*

- *Question*: *Si hubiera dicho ovocito activado… ahí ya*

- *Answer: Ahí incluiría todo, porque un espermatozoide activa. Pero fecundación se refiere a un espermatozoide que penetra un embrión… Osea que lo otro lo está dejando aparte*

- *Question*: *Y es lo que va a permitir luego que la ley autorice la transferencia nuclear*

- *Answer: Claro, porque por lo menos legalmente, (aunque intentando basarse en conocimiento y en datos científicos) no es lo mismo una cosa que la otra.*

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of ovocytes by nuclear transfer, are not acceptable, as that contributes nothing significant to distinguish or distance one reality from another. In Law, this resource is known as "label fraud": through a certain *nomen iuris* one tries to mask a designated situation or legal treatment that has nothing to do with its formal designation" (Cf: Romeo Casabona, C. M., "La cuestión jurídica de la obtención de células troncales embrionarias humanas con fines de investigación biomédica. Consideraciones de política legislativa", *Law and the Human Genome Review*, nº 24, January-July 2006, pages. 90 y 91)

[70] In Germany, the Law guaranteeing the protection of embryos with regards to the importation and use of embryonic stem cells of human origin (Stem Cell Law), of 28 June 2002, offers, in its article § 3. 4 the following definition of embryo: "an embryo is any human totipotent cell that has the ability to divide itself and lead to a human individual as long as the necessary conditions required for said process are fulfilled:" In this same sense, it would be convenient to mention the Belgian regulations, which define an embryo as the "cell or united system of cells with the ability to develop and lead to the growth of a human being". In an almost identical sense, the Dutch Embryo Act of 1st September 2002 indicates, in its first section, dedicated to definitions, that an embryo is "the cell or cell group with the ability to develop and lead to the growth of a human being."

[71] In Japan, the Law regarding regulations about techniques of human clonation and other similar techniques, of 30 November 2000, characterises, in its article 2, an embryon as "A cell (excepting germ cells) or cells that could become a human being by means of *in utero* development in a human or animal, and that has/have not yet begun the forming of the placenta."

Legalemnte aquí se establece con toda claridad que no es lo mismo, basándose en lo que yo creo, además, que es una opinión unánime.

In short, the most reliable conclusion would probably be to maintain that, from a scientific point of view it would be absurd both to argue that all transfers of nuclei give rise to an embryo as they never do, at least if one accepts the notion of an embryo being based on the idea of the potential to create a person. This is the most widely accepted view today in legal doctrine and in some of the legal systems that have already accepted the changes that have occurred in biotechnology, as we have discussed previously.72

It is doubtful, therefore, that the Spanish Law on Biomedical Research is adequate for the current state of knowledge regarding embryos. It is possible, nevertheless, that this lack of precision is deliberate, accepted as the price that had to be paid to be able to satisfy the demands of all the pressure groups involved in the discussion.

The creation of a human clone in the future will probably make this form of definition unsustainable, but there are two things that have to be said in its defence. Firstly, the Law on Biomedical Research is not trying to define the embryo in general, but rather to define it only "for the purposes of that law". This can, of course, lead to legal inconsistencies (it does not make sense that in the same legal system the same reality is defined in different ways according to what suits the legislator). Secondly, it has to be borne in mind that the Law on Biomedical Research will surely manage to cover SCNT in humans in sufficient time for this technology not to be necessary. The emergence of new options such as IPS cells would seem to indicate this. Consequently, this provisional solution will have had an optimum result, if we take into account all the determining factors.

[72] See: De Miguel Beriain, I., *La Clonación, diez años después (Cloning, Ten Years On)*, Granada: Comares, 2008.

REMEDiE WP5 Main Findings Brief

Main objectives

National regulations on RM and Stem Cell Research (SCR) differ from country to country. This variation is extremely important and much more intense than in other fields of health technology. For instance, each legal system establishes specific regulatory frameworks regarding the derivation and uses of stem cells.

A fragmented regulatory landscape as is the case within European Nations leads to forum shopping; stem cell tourism and exploitation of vulnerable population rights. This variation has also proved to be extremely inefficient from the point of view of allocation of resources. at the European-level, this has not hindered the problems. A sufficient level of international legal harmonization has probed unreachable in this field.

The WP5 aimed at understanding the nature of the regulatory variation in which stem cell research is conducted throughout Europe: what factors can explain this variation? Is it due fundamentally to social-national values? How does the European policy-making community interpret and use the moral directives produced by bioethics? What is the real impact of guiding bioethical principles and values in the normative instruments? Is it possible to identify any system of balance between conflicting cultural values? In this context, to what extent do bioethicists see themselves as promoting negotiation between conflicting values? How do the global structures and networks that support these functions interact and to what extent can bioethics be seen as a coherent epistemic community?

Main results

We examined two cases where some level of harmonization had been reached in the international and national levels: ISSCR Guidelines for Human Embryonic Stem Cell Research and Spanish regulation of RM.

Our conclusion for this part of the study was that, although laws in each jurisdiction are supposed to reflect a social consensus on the boundaries of what is considered acceptable for each society, the process of debate which leads to policy making is subject to different degrees of contingency. It is difficult to prove that legal frameworks for RM in each country can be explained by or attributed to the prevalence of a particular moral or political standpoint

On the one hand, consensuses on controversial topics such as those relating to regenerative medicine are fragile insofar as they can be –and usually are- challenged on moral and political grounds. National states sovereignty plays an intense role in this matter. On the other, consensuses tend to be obsolete as innovation and discoveries are made in this fast-moving field of science and technology. Consensuses on RM are also dependent on other contingencies, including: historical constraints, the existence of groups of pressure, the prevalent political ideology, individual leadership of policy makers and their ability to create pragmatic regulations which “do the job” while avoiding controversy. In this context, to what extent do bioethicists see themselves as promoting negotiation between conflicting values? How do the global structures and networks that support these functions interact and to what extent can bioethics be seen as a coherent epistemic community?

Our initial hypothesis was that the ideological similarity should have great relevance when mapping the communities of bioethics. Throughout the development of this research and

the interviews with experts in the field, we have concluded that this hypothesis was only true in the case of major religions, especially Catholicism. Researchers who support the Church's official position on matters related to regenerative medicine create very cohesive and well structured communities of Bioethics, with their own media, impenetrable to those who are not members of these communities.
Aside from this specific circumstance, we have identified discrete communities of bioethics differentiated by cultures – especially shared language - and different academic traditions. The Anglophone area is the more internationalized or globalized one, in terms of participation of multinational bioethicists and forming of international networks. It is also the stronger area in terms of number of participants, publications, active organisms, and funding.

Broad Policy Implications

In respect to bioethics, there appears to be an emerging transactional or "irenistic" model that is gaining support within Spain and which could be used to foster dialogue among other (non-Anglo-phone) cultural communities. On the IP front, inventions in human embryonic/hESC research represent a particularly difficult ethical issue for European patent law as many issues within this area remain ethically controversial. Patenting hESC cells or cell lines must, for example, take notice of the source of these cells, more precisely the consequences of their derivation, the destruction of the human embryo. The destruction of the embryo in order to harvest stem cell lines irrespective of the origin of the embryo (viable donated supernumerary IVF from parental project, non viable IVF embryo from parental project, IVF and SNCT research embryo) is the main source of the ethical controversy surrounding this technology. The implementation of an 'embryo destruction' principle in patent law within the examination of patentability remains a pressing question in different patent jurisdictions.

It is important to keep in mind that, as stated by some of the people interviewed, the rising of new biotechnologies may be extremely useful in order to arrive into new consensus in bioethics related to medicine regenerative. In that sense, it is necessary to understand that every new scientific challenge implies the necessity of a response. In some cases, an ethical paradigm may find really hard problems to do so, as far as it is precisely that new development which defies the constellation of facts it is built on. That is why something like the use of IPS cells technology to create mammal clones may be extremely useful in order to test the real implications of those paradigms that use the concept of potentiality, for instance.
In the concrete arena of the regulation of these issues, we concentrated in the Oviedo Convention, as far as it was signed by most of the EU members and so it is quite a common regulation in the EU. In that part, we arrived to a conclusion: the Oviedo Convention created a serious problem for all those countries willing to use technologies such as somatic cell nuclear transfer (therapeutic cloning) to originate stem cells. In order to avoid it, some of those countries have not ratified the Convention (such as Sweden), while others decided to use an strategy based on the characterization of the embryo exclusively as the result of a fecundation to avoid all possible problems (Spain, Finland). This made us wonder if consensuses are as solid as they seem to be in theory.

Annex 6 REMEDiE Work Package 6: Final Report

EU AND GLOBAL BIOETHICS: INTELLECTUAL PROPERTY AND CULTURAL DIFFERENCE

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Intellectual property rights, patents in particular, remain essential for bringing inventions in regenerative medicine to the market. Patent systems by bridging the gap between human intellectual activity and the market enable the commercialization of biomedical research and secure the private and public benefits which patents offer to stakeholders and the state. The temporary legal monopoly granted by patent law enables the patent holder to recoup his investments put into the innovative process by means of exploiting his rights under patent law. In exchange, the invention is made public enabling further upstream and downstream research, translation into products or therapies and other, mainly commercial activities. In sum, patent systems ensure that inventions are disclosed for the benefit of society and inventors benefit from the commercial opportunities presented by the limited monopoly of the patent.

Patents in the bio-economy provide the asset with which (start-up) companies may attract speculative investment to finance further basic or translational research or development. Investment secured by patents as corporate assets may be crucial in ensuring the survival of companies in the period of developing the invention into a product or a therapy. Patent systems are essential elements of business strategy in the bioeconomy focusing on creating revenue (by selling the asset-laden start-up company) or sustaining economic activity. For policy makers patents are key instruments in economic policy promoting growth and innovation.

Stakeholders in regenerative medicine need to exploit the benefits generated by the utilitarian trade-off between private and public interest in patent systems. Patents generate returns for publicly or privately funded research and attract investment from the market for expensive downstream activity when productivity is low or non-existent. Patents signal success in research and business, and when placed in the public they attract the attention of investors, competitors, patients and health care providers. Patents bring inventions into the public domain and enable access for others to the invention and further benefit generating activity based on the invention.

For patent systems to deliver the said private and public benefits the law must provide a clear and coherent framework regulating the requisites of obtaining and exploiting a patent. Patent laws establish conditions for the patentability of inventions. Some of these

conditions are technical, intrinsic to the special area of patent law, such as novelty, inventive step and industrial applicability. Others concern more general issues, such as the boundaries of human innovative activity expressed in the definition of what constitutes patentable subject matter and in the clauses excluding the patentability of inventions contrary to public order or morality.

Human biological material, genes, tissues and cells serve as key research or analytical tools or products in regenerative medicine. Their treatment as things which may be subject to commercial exploitation by means of obtaining patents on them raises ethical objections on grounds of principles, inherent in the requirement of respect for human dignity, such as non-objectification, non-instrumentalization and non-commodification applicable to the human body and its parts or elements. These bioethical requirements can be expressed in the regulation and application of the conditions of patentability as exceptions to patentability in the different patent regimes of the world. There are two challenges related to the bioethical limitations of patenting human biological material:

- The diversity of local approaches to the applicable bioethical limitations in law; and
- The boundaries of the applicable bioethical limitations remain unclear and contested in law.

Human biological material is regarded as patentable subject matter in the patent jurisdictions of the world. In Europe patent legislation, the European Patent Convention (EPC) and the EU Biotech Directive[73] (Article 5(2)), provides for the patenting as inventions of isolated elements of the human body or elements produced by means of a technical process subject to meeting the other requirements of patentability (novelty, inventive step, industrial applicability and not being excluded on public order or morality grounds). In contrast, the simple discovery of one of the elements of the human body is not a patentable invention (Article 5(1)). In the US the human contribution of isolation, purification or modification renders human biological material as 'products of human ingenuity' as opposed to 'products of nature'[74] and thus patentable subject matter.

Patent regimes in Asia also accept the patentability of human biological material. Indian patent law denies patentability from of a "discovery of any living thing occurring in nature"[75], but when the discovery leads to establishing a practical use patentability is no longer refused.[76] The South Korean patent examination guidelines hold that "the method for artificially isolating substances from things in nature, not a mere discovery, is considered to be a statutory invention. So are the isolated chemical substances and microorganisms."[77] The Japanese patent examination guidelines include similar provisions.[78]

[73] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:213:0013:0021:EN:PDF.
[74] See, *Diamond* v *Chakrabarty*, 447 US 303 (1980).
[75] See *Kirin-Amgen* v *Hoechst Marion Roussel* [2005] RPC 9.
[76] Point 4.4.3, Draft Manual of Patent Practice and Procedure, 2008, ipindia.nic.in/ipr/patent/DraftPatent_Manual_2008.pdf.
[77] Point 4.1.2, Requirements for Patentability, 2010, www.kipo.go.kr/kpo/user.tdf?a=user.english.html.HtmlApp&c=60203&catmenu=ek60203.
[78] Point 1.1, Examination Guidelines for Patent and Utility Model in Japan, 2010, www.jpo.go.jp/cgi/linke.cgi?url=/tetuzuki_e/t_tokkyo_e/1312-002_e.htm.

Diversity and contested boundaries: human DNA patents

Patent laws, within the above framework, have acknowledged isolated human DNA as patentable subject matter. The US and the European patent regimes both granted patents for the BRCA 1 and 2 genes and the associated diagnostic method. In Europe their patenting relied on the clear legal provisions of 'isolation' and 'technical process'; the ethical oppositions against the patents, a characteristic of European patent law, were rejected.[79] The US process focused on the fuzzy distinction between products of human nature and human ingenuity in US patent law which is now under reconsideration in an ongoing lawsuit by the American Civil Liberties Union against the BRCA 1 and 2 patents. The 2010 district court judgment, opposing previous practice, declared that isolated DNA must be regarded as products of nature, and thus unpatentable, as the process of isolation does not produce markedly different characteristics than those possessed by genes in the human body.[80] The case is now under appeal, and its outcome may change US patenting policy regarding isolated human DNA.[81] The potential global impact of US policy change is difficult to predict; in Europe only the amendment of the current liberal legislation would lead to alignment with the US practice.

Diversity and contested boundaries: human stem cell patents

In the current state of the law isolated human stem cells in general constitute patentable subject matter. Adult stem cells, pluripotent human embryonic stem cells (hESC) and induced pluripotent stem cells (iPS cells) isolated from the human body are patentable products of human activity. Isolated human totipotent stem cells may, however, attract opposing legal characterizations. Patent regimes focusing on the act of isolation may treat totipotent stem cell lines as elements isolated from the human body by way of human activity and regard them as patentable subject matter. On the other hand, patent jurisdictions may also take into account the biological characteristics of totipotent stem cells and treat them not as products but as (potential) living (human) beings.

The clearest indication that totipotent cells may not be considered as patentable subject matter can be found in the European patent law. The EPC and the EU Biotech Directive (Article 5(1)) exclude from patentability the human body at the various stages of its formation and development. In the European Commission's interpretation human totipotent cells constitute a stage of development of the human body and are unpatentable.[82] This position is supported by the ethically charged distinction in European patent law between isolated stem cells on the basis of their toti- or pluripotency, confirmed most recently by Advocate General Bot before the EU Court of Justice.[83]

There is no evidence that other patent jurisdictions would follow the same approach and exclude from patentability isolated human totipotent stem cells under the bioethical

[79] As applied in the BRCA 1 and 2 cases before the EPO, T 1213/0527 of September 2007 at www.epo.org/law-practice/case-law-appeals/pdf/t051213eu1.pdf; T 0666/05 of 13 November 2008 at www.epo.org/law-practice/case-law-appeals/pdf/t050666eu1.pdf; T 0080/05 of 19 November 2008 at www.epo.org/law-practice/case-law-appeals/pdf/t050080eu1.pdf. The ethical issues raised were informed consent, benefit sharing, and the impact of patent on public health.

[80] 09 Civ. 4515, patentdocs.typepad.com/files/opinion.pdf.

[81] This possibility was acknowledged in the US Government's amicus brief which followed the direction set in the district court judgment, www.genomicslawreport.com/wp-content/uploads/2010/11/Myriad-Amicus-Brief-US-DOJ.pdf.

[82] Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52005DC0312:EN:HTML.

[83] Opinion of Advocate General Bot delivered on 10 March 2011 in Case C-34/10 Oliver Bruestle, nyr.

principle of non-instrumentalization of the human body expressed in the above provision of European patent law. The invention/discovery or the products of nature/human ingenuity distinctions may not be able express the same restriction to patentable subject matter. The general public morality clause, if the patent regime contains one, may prevent patentability. The diversity of local solutions may increase if the developing approach to human DNA patents finds ground in US patent law, which may be applied so as to exclude isolated human totipotent cells from patentable subject-matter on the ground that their characteristics are not sufficiently distinct from the characteristics they demonstrate in nature.

By all means, the indicated European approach remains contestable. First, it practically equates without further justification isolated totipotent cells, which are isolated biological material, with the human embryo and confers them the same moral status. Second, it avoids addressing the issue that totipotency is relative to the environment and isolated and modified totipotent cells are different from totitpotent cells in their natural environment. Third, it neglects an ethically relevant distinction alternative to the toti-/pluripotent concept pair; that between modified and unmodified stem cells. This was raised in EGE Opinion No. 16 (2002)[84] on the ethics of hESC patenting, which found that 'unmodified' hES cells and cell lines are not patentable as their patenting may violate the non-commercialization principle,[85] whereas in the light of the economic and social purpose of patent systems 'modified' hESC patenting could be allowed.

Diversity and contestable legal solutions are also apparent in the patenting of pluripotent hES cells. The issues raised in this context reach beyond acknowledging human biological material as patentable subject matter and concern raising (further) bioethical objections in the patenting process. Patent regimes, with the exception of the US, are equipped with clauses which exclude inventions from patentability on grounds that the exploitation of the patent violates public order or morality, as enabled in international law by Article 27(2) of the TRIPS Agreement.

The WTO (and TRIPS) member China's patent law contains an exception similar to that in other states stating that "no patent right shall be granted for any invention-creation that is contrary to the laws of the State or social morality or that is detrimental to public interest" (Article 5 of Patent Act).[86] The 1970 Indian Patent Act's morality clause provides that "inventions the primary or intended use or commercial exploitation of which would be contrary to morality" are "not inventions" (Article 3b).[87] The morality exception in South Korean patent law reads that "inventions liable to contravene public order or morality or to injure public health shall not be patentable" (Article 32 of Patent Act).[88] The 1959 Japanese Patent Act's morality clause is formulated in the same way (Article 32).[89]

These morality clauses lack the detail and the distinctions applied in the European regime. Nonetheless, they offer potential bioethical limitations to the commercial

[84] EGE Opinion No. 16 of 7 May 2002 on the Ethical Aspects of Patenting Inventions Involving Human Stem Cells, available at ec.europa.eu/european_group_ethics/docs/avis16_en.pdf.
[85] It was criticized that the principle used in this regard, 'closeness to the human body', was not established as a relevant moral consideration and as part of European culture, see Aurora Plomer (project coordinator): *Stem Cell Patents: European Patent Law and Ethics* – Report EU FP6 'Life sciences, genomics and biotechnology for health' SSALSSB-CT-2004-005251 (2008), www.nottingham.ac.uk/~llzwww/StemCellProject/project.report.pdf, at 33.
[86] See www.sipo.gov.cn/sipo_English/laws/lawsregulations/200804/t20080416_380327.html.
[87] See www.patentoffice.nic.in/ipr/patent/patents.htm.
[88] park.org/Korea/Pavilions/PublicPavilions/Government/kipo/law/patent/epat.html.
[89] www.japaneselawtranslation.go.jp/law/detail/?ft=1&re=02&dn=1&x=0&y=0&co=01&ky=patent&page=17.

exploitation of biomedical inventions. In the Indian patent office's interpretation being contrary to morality means that the use of the invention would "violate the well accepted and settled social, cultural, legal norms of morality". It produced an example, "method of cloning", for an invention in breach of the requirements of morality.[90] The South Korean examination guidelines interpret the morality clause in the patent act as morality meaning a "moral sense generally accepted by a society or particular group of people".[91] There is no evidence that pluripotent hESC patents have been subject to opposition on public morality grounds in these states.

Patent law in the US, based on the patent clause of the Constitution (Section 8), does not incorporate a specific morality clause. It describes patentable inventions as "whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."[92] The 'moral utility' doctrine (Lowell v. Lewis, (1817) 15 F Cas 1018) has not been used in the case of biotechnology patents[93] and Congress has not considered the introduction of a morality requirement similar to other jurisdictions. The ethical debate relating to human stem cell research on the federal level focuses on providing federal funding to research[94] with state level legislation determining the ethical boundaries of biomedical research activity.[95]

European patent law offers the most developed system of public morality exceptions, a result of the EU Biotech Directive. It includes a general exception from patentability when the exploitation of the invention would be contrary to public order and morality (Article 6(1)) and a list of specific, ethically objectionable inventions, such as processes for cloning human beings, processes for modifying the germ-line genetic identity of human beings and uses of human embryos for industrial or commercial purposes (Article 6(2)).

The explicit public morality exceptions indicate that European patent law gives more weight to the ethical limitations of biomedical inventions than other patent regimes. More importantly, the European patent regime has not refrained from applying the exceptions to morally contestable patents. The 'industrial or commercial use of human embryos' clause proved especially controversial in the European history of human stem cell patenting separating Europe from the global market of stem cell patents and causing considerable tensions between European states with different moral approaches to human stem cell research.

According the current state of the law, pluripotent hES cells are not patentable under the EPC and presumably under the EU Biotech Directive as their process of derivation, which necessitates at the current state of the art the destruction of the human embryo from which the cell lines are obtained, constitutes an industrial or commercial use of the human embryo in the meaning of the applicable clause.

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[90] Point 4.3, Draft Manual of Patent Practice and Procedure, 2008, available at ipindia.nic.in/ipr/patent/DraftPatent_Manual_2008.pdf.

[91] Point 3.1, Requirements for Patentability, 2010, www.kipo.go.kr/kpo/user.tdf?a=user.english.html.HtmlApp&c=60203&catmenu=ek60203. As an example under the public order and morality rule it refers to a 'Bingo' apparatus.

[92] (Title 35 USC) (Section 101), available at www.law.cornell.edu/uscode/35/101.html.

[93] Libby Beadle, Selling the Stem Cell Short? An assessment of the patentability of the results of human stem cell research in New Zealand, *Canterbury Law Review*, vol. 10 (2004): 1–35.

[94] Gregory E. Pence, *Classic Cases on Medical Ethics: Accounts of the Cases that Shaped Medical Ethics* (New York: McGraw Hill Higher Education, 2008), at 185–189.

[95] See, for example, Article XXV of the State of California Constitution, www.leginfo.ca.gov/cgi-bin/waisgate?waisdocid=76297528920+0+0+0&waisaction=retrieve.

There are considerable doubts whether the 'industrial or commercial use' clause may incorporate such 'embryo destruction' principle and whether any prohibition on the destruction of human embryos for research purposes should be considered instead under the general public morality clause of European patent law.

This latter point is especially crucial as the 'industrial or commercial use' clause represents a Europe-wide, uniformly applicable bioethical limitation to patenting, which has the effect of transforming the 'embryo destruction' principle into a bioethical principle common to European states despite the differences between European states as to the ethical limits of human embryonic research. In contrast, the general public morality clause acknowledges a margin of appreciation of individual states making the question of patentability subject to the local ethical assessment of using human embryos for research purposes.

The first indication that (the prohibition on) 'embryo destruction' would become a common bioethical and legal principle in European patent law by way of the interpretation of the 'industrial or commercial use' clause was the European Patent Organisation (EPO) Enlarged Board of Appeal decision concerning the Wisconsin Alumni Research Foundation (WARF) hES cell line patents.[96] The decision in 2008 established that the 'industrial or commercial use' clause, which was introduced to prohibit the commodification of the human embryo, excludes the patentability of hES cells or cell lines on grounds that the production of hES cells requires the destruction of the human embryos used as sources. The Board held that the creation of the claimed product is part of its industrial or commercial exploitation, and when it involves the destruction of human embryos it will violate the said prohibition. In this case the performing of the invention (the embryo destruction) was contrary to the specific morality provision of the EPC.

The question is now before the EU Court of Justice equipped with jurisdiction to interpret the EU Biotech Directive which originally introduced the 'industrial or commercial use' clause to European patent law. The stakes are high as the judgment could open or permanently close the European patent market to hESC patents delivering or withholding the considerable benefits and the arguable disadvantages of patents to/from the European bioeconomy. The judgment will affect the patenting policy of the Member States and the patenting practice of the EPO, and the judgment will have to take into account the differences among European states relating to the use of human embryos in stem cell research. The judgment will consolidate the interpretation of the EU Biotech Directive the provisions of which were introduced to establish a clear and coherent framework for patenting in biotechnology.

The case before the EU Court of Justice originated from Germany, where the Federal Patent Court held following EPO practice that the hESC patent in question, the 'Brüstle patent', was in breach of the 'industrial or commercial use' clause as the destruction of human embryos was a "real and integral part of the invention."[97] The German court's interpretation was strongly influenced the German Embryo Protection Act which prohibits

[96] G-2/06, documents.epo.org/projects/babylon/eponet.nsf/0/428862B3DA9649A9C125750E002E8E94/$FILE/G0002_06_en.pdf.

[97] Judgment by the German Federal Patent Court, AZ: 3 Ni 42/04 (5 December 2006), juris.bundespatentgericht.de/cgi-bin/rechtsprechung/document.py?Gericht=bpatg&Art=en&sid=061f0f9e4b6bfd679ba46c7b1fd93fcb&nr=1909&pos=0&anz=1&Blank=1.pdf.

the use of human embryos for purposes other than those from which the embryo may receive direct benefits (e.g. diagnosis or treatment of that embryo).

An indication how the EU Court of Justice would approach this question and consolidate the interpretation of the EU Biotech Directive can be found in the Opinion delivered by Advocate General Bot in the case before the court. It set a direction similar to that indicated by the EPO Enlarge Board of Appeal and the German patent court. The Advocate General suggested that the clause on the industrial or commercial use of human embryos excludes from patentability inventions which necessitated the destruction of human embryos.[98]

The Opinion is not binding on the EU Court of Justice, and it is not excluded that it will take into consideration the criticisms formulated against the current interpretation of the 'industrial or commercial use' clause. The Court of Justice, as opposed to the Advocate General, may consider the wider social and economic impact of applying the 'industrial or commercial use' clause to hESC patents and may take into account the interests of Member States where human embryonic research is regulated permissively and have an interest in global hESC research, and respect the preferences of States where human embryos are given more stringent protection. More importantly, the judgment will have to establish an interpretation of the morality clauses in European patent law which follows from the EU Biotech Directive and from the relevant bioethical principles, from human dignity in particular.

One option is to follow EPO case law and the opinion of the Advocate General. The alternative route would be dropping the 'embryo destruction' principle from under the 'industrial or commercial use' clause,[99] and examine hESC patents under the general public morality clause. This would enable the accommodation of local discretion in assessing whether the destruction of human embryos for research is acceptable in that particular community (state). This option would safeguard the diversity among European states in regulating human embryonic research.

On the level of decision-making in the European patent system the solution accepting the plurality of local bioethical approaches would cause considerable difficulties. Without being able to rely on an explicit morality clause imposing uniform requirements on the Contracting States the EPO will need to apply the general morality clause of the EPC (and the EU Biotech Directive) having regard to the diversity of national approaches on the use of human embryos for research purposes. Adopting the highest standard under the general clause and denying patentability from hES cells would satisfy the States with a prohibitive attitude to human embryonic research but it would be incompatible with the leeway granted under the general morality clause to all States in the European patent system. In contrast, allowing the patentability of hES cells under the general morality clause, having been unable to establish the 'embryo destruction' principle as a common European moral requirement, would satisfy the States with liberal regulation on stem cell research and it would enable States with a prohibitive regime to refuse enforcing the patent within their jurisdiction. This is a compromise solution and the only workable solution in a pluralist, multi-layered regime. The fragmentation of the system, which would follow from this approach and which is contrary to the rationale of the EPC and the EU Biotech Directive, is the responsibility of Article 6(1) of the EU Biotech Directive.

[98] Opinion of Advocate General Bot delivered on 10 March 2011 in *Case C-34/10 Oliver Bruestle*.

[99] The combination of the clause with the 'embryo destruction' principle was declared to have no legal basis under the EU Biotech Directive. See Plomer, *op. cit.*, 83.

Global and European Diversity in Regulation

Diversity is the single most important characteristic of regimes regulating the ethical boundaries of biomedical research activity and the ethics of commercializing biomedical innovation in the world. These differences have an impact on the research environment, the model for financing research and translational activity and the use of intellectual property rights in the course of biomedical research. The taxonomies label the different national regimes on biomedical research as permissive (liberal), intermediate and restrictive.[100]

Permissive regimes (UK, Japan, India and China) allow research on human embryos and stem cell derivation from them.[101] The permitted sources are supernumerary IVF and SCNT embryos. They apply a temporal limitation to human embryonic research, such as the '14 day rule' associated with the appearance of the primitive streak in the human embryo. Intermediate regimes (France and South Korea) allow research with limitations on embryos obtained from limited sources.[102] Restrictive regimes (Germany) prohibit human embryonic research for general therapeutic purposes and ban hESC derivation, and they may prohibit using hESC lines and products.[103] In the US stem cell research is regulated on state level, if regulated, without the federal level being constitutionally able to impose a uniform moral position. The federal disapproval of stem cell research is expressed in fiscal legislation prohibiting the federal funding of stem cell research[104] which is now under challenge before the courts.[105]

The introduction of a human rights perspective on human embryonic/stem cell research has not affected the diversity of ethical and moral approaches. The Oviedo Convention on Human Rights and Biomedicine[106], created to establish a European framework concerning the human rights limitations of biomedical research and therapy, builds on the protection of human dignity and integrity. The Convention accepts the margin of appreciation of Contracting States on bioethical issues and leaves the question of hESC research partially open by the provision of Article 18 (1) that "where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo." Arguably, this could encompass the destruction of human embryos in an adequately safeguarded process for the purpose of hESC derivation. The more contentious provision in Article 18(2), which has prevented the

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[100] www.stemgen.org/mapworld.cfm and Rosario M. Isasi & Bartha M. Knoppers (2006) Mind the Gap: Policy Approaches to Embryonic Stem Cell and Cloning Research in 50 Countries, *European Journal of Health Law* 9: 13.

[101] *United Kingdom:* Human Fertilisation and Embryology Act (HFEA) 1990 (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsLegislation/DH_080205); *Japan:* Act on Regulation of Human Cloning Techniques 2000 (www.japaneselawtranslation.go.jp/law/detail/?re=02&dn=1&x=0&y=0&co=1&yo=&gn=&sy=&ht=&no=&bu=&ta=&ky=cloning&page=1); *India:* Ethical Guidelines for Stem Cell Research 2007 (www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf); *China:* Ethical Guiding Principles on Human Embryonic Stem Cell Research 2003 (www.qmlc.com.cn/edit/UploadFile/info/2009430113029216.doc).

[102] *France:* Public Health Code, Article L2151-2 and L2151-4 (www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006072665&dateTexte=20101017), *South Korea:* Bioethics and Safety Act 2004 (eng.bprc.re.kr/gz06.htm?number=8).

[103] *Germany:* The Embryo Protection Act (www.bmj.bund.de/files/-/1147/ESchG%20englisch.pdf) and the Stem Cell Act (www.bmj.bund.de/files/-/1146/Stammzellgesetz englisch.pdf).

[104] The Dickey-Wickers amendment, a rider attached to the Balanced Budget Downpayment Act 1996,

[105] United States District Court for the District of Columbia, Civ. No. 1:09-cv-1575 (RCL) and United States Court of Appeals for the District of Columbia Court, No. 10-5287, 9 September 2010.

[106] Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, conventions.coe.int/Treaty/en/Treaties/Html/164.htm.

ratification of the Convention by all Council of Europe States considering it as either liberal or conservative, prohibits the creation of embryos for research purposes.

European diversity has not been mitigated by the application of the European Convention on Human Rights (ECHR) to bioethical issues. The Convention, constrained by its subsidiary nature expressed in the margin of appreciation doctrine, has also demonstrated sensitivity to the local bioethical appreciation of human embryonic research. Article 2 of ECHR on the right to life attracted a deferential approach from the European Court of Human Rights when it faced the question whether the rights of an 'unborn child' should be protected under the ECHR.[107]

[107] *Brueggemann and Scheuten* v *Germany*, (1981) 3 EHRR 244, *Paton* v *UK* (1981) 3 EHRR 408, *Open Door Counselling* v *Ireland*, (1993) 15 EHRR 244, *V.O.* v *France*, App. 53924/00, 08/07/2004, ECHR 2004-VIII, *Evans* v *UK*, App. 6339/05, 10/04/2007, nyr., and *S.H. and Others* v *Austria*, App. 57813/00, nyr.

Detailed Report on Major Findings

1. The bioethics of regenerative medicine: diversity and contested boundaries

Regenerative medicine, biomedical research in the field of regenerative medicine is subject to limitations established by bioethics. These boundaries in this evolving area of life sciences are by no means novel. Biomedical research using human biological material, in particular human embryos for basic research and beyond must observe the general ethical principle of respect for human dignity. Concerning human embryonic research the moral status of human embryos is debated with the intensity familiar from the earlier debates on abortion or IVF treatment.

The issues of research design and translation of research results to therapies are connected to the bioethical ground rule of informed consent of research subjects and patients. Obtaining patents on research tools (e.g. molecules or cell lines) and products/applications (e.g. bioengineering scaffolds or diagnostics) raise the broader socio-ethical concerns of freedom of research, public control, access and benefit sharing. Patenting human DNA and human embryonic stem cells (hESC) are especially controversial in light of the relevant bioethical principles which prohibit the commodification of the human body and its parts and question whether human embryos can be created for research purposes and these embryos can be destroyed in the research process.

Progress in regenerative medicine holds a great promise to humankind. Bringing that promise to fruition may not, however, transgress the ethical and legal boundaries of human scientific activity. Perhaps, the most pressing issue in this context is the conflict between preserving the values expressed in the principles of bioethics and securing the interest of the market in biomedical research bringing investment and innovation into the domain. Rose indicated clearly that biomedical progress, apart from bringing benefits to humanity, is nowadays regarded as primarily economic generating valuable intellectual property and a bioeconomy lucrative to economic operators, investors and the state which transforms patients into autonomous and responsible consumers of commercialized health care products and services.[108]

The bioethics of regenerative medicine covers a much broader area than the conflict between ethics and the market. In a 2009 paper the main bioethical issues associated with human embryonic and stem cell research and cell, tissue and organ regeneration research within the wider area of regenerative medicine were identified as the bioethics of human embryonic stem cell research, the safety concerns raised by induced pluripotent stem cell research (iPS), the ethics of research design, the ethics of testing on human research subjects, informed consent, therapeutic misconception and the divide between therapy and human enhancement.[109]

[108] Nikolas Rose, *The Politics of Life Itself* (Princeton, NJ: Princeton Univ. Press, 2006), at 2 and 4.
[109] Nancy M.P. King, Chris Nero Coughlin, Mark E. Furth, Ethical Issues in Regenerative Medicine, *Wake Forrest University Research Paper Series in Legal Studies*, Working Paper No. 1380162, 2009, ssrn.com/abstract=1380162, at 3.

The general bioethical implications of the narrower field of human embryonic stem cell research are no less complex. The following bioethical issues were associated with hESC research in a 2001 book on the hESC ethical debate.[110]

- The bioethics of the sources of hESC, such as
    - Human embryo *in utero*;
    - Supernumerary donated human embryo from an IVF parental project;
    - Supernumerary human embryo from IVF research project;
    - Somatic nuclear transfer (SCNT) embryo for reproductive purposes;
    - SCNT embryo for research purposes;
    - Cadaverous foetal tissue;
    - Umbilical cord blood; and
    - Hybrids (human-animal).
- The bioethics of hESC derivation
    - Embryo destruction and the moral status of human embryos: at the current state of art pluripotent hESC from human embryos are derived by destroying the outer shell of the blastocyst, which would become the placenta, and culturing cells from the inner cell mass; and
    - Derivation from aborted foetus: produces human germ cells the abilities of which are uncertain.
- The moral status of derived hES cells:
    - Totipotent and pluripotent stem cells
- Limits of human scientific activity:
    - Human enhancement; and
    - Human procreation.
- The donor's informed consent (oocyte, aborted foetus and embryo donation).
- The locus of authority for ethical decision-making (private/public, executive, legislative, judicial, ethical assessment boards, ethical advisory panels, international bodies (the European Patent Convention bodies, EU institutions)).
- The ethics of commodification and for-profit research.
- Social justice, benefit sharing, burden distribution and (equal) access.
- Research design, risk prevention and avoiding risks (controlling cell differentiation and immune rejection and avoiding cancer (teranoma) formation).

The most publicized and controversial issue in human embryonic stem cell research concerns the derivation of hES cells from human embryos. At current state of art this necessitates the destruction of the human embryo used as the source. Human embryonic stem cells have been applauded as having inestimable value in biomedical research and offering the potential of organ and tissue regeneration and the treatment of serious maladies, such as heart disease, diabetes and neurological diseases. hES cells have unique

[110] Introduction, in Susanne Holland, *et al*. (eds.), *The Human Embryonic Stem Cell Debate* (London: MIT Press, 2001), at xviii-xxii.

biological characteristics. They are pluripotent (able to develop into many types of tissues), immortal (able to continue dividing indefinitely without losing their genetic structure (prolonged undifferentiated proliferation)), malleable (can be manipulated without losing cell function) and they express telomerase enabling the cells to grow and divide. The benefits offered by hES cell research come at a cost, which cost may be unacceptable under the bioethical principles regulating the moral status of the human embryo.

The moral status of human embryos attracts deeply divided viewpoints in different societies and communities. Some argue that a full moral status must be granted to the embryo from fertilization. Others maintain that a full moral status should be available only after implantation to uterine wall, leaving the blastocyst with lesser protection, or later after the development of the primitive streak as suggested by the '14-day rule' referring to the approximately 14 days necessary for the appearance of the primitive streak. Gradualists propose that full moral status may be acquired by gradually obtaining the capacities of a human being. Again others believe that a moral status is gained at birth.

Viewpoints also differ whether human embryos should be given the same protection regardless their origin. Embryos *in utero*, pre-implantation supernumerary IVF embryos, IVF embryos created from donated biological material for research purposes and embryos cloned by SCNT for research purposes may attract different assessment as to their moral status. The methods of human embryo creation also attract different moral judgment affecting the moral status of the embryos created. According to Parens the IVF method is more widely accepted than SCNT and IVF embryos may enjoy a higher moral status than SCNT embryos.

Diversity, as demonstrated by the case of the moral status of human embryos, is a key feature of mapping the ethical boundaries of human activity in biomedicine. Regulatory regimes in the world draw up restrictions, conditions, procedures and safeguards for biomedical research reflecting on universally acknowledged principles, such as respect for human dignity, and locally determined benchmarks, such as permitting the creation of human embryos for research purposes. The pluralism of local solutions is visible especially when regimes regulate ethically contestable research, such as the harvesting of hES cells. In characterizing this diversity, Pellegrino contended that local culture and ethics are inextricably bound to each other with local ethical systems developing from the synthesis of local cultural assertions and universal principles subject to constant change.[112]

1.1. Diversity in the ethical viewpoints

The diversity of viewpoints on the ethical boundaries of biomedical research is made apparent in the published opinions of the abundant national and regional, secular and religious ethical advisory bodies. While the basic themes are universal, such as the beginning of human life or the moral status of the human embryo, the responses reveal

[111] Erik Parens, *On the Ethics and Politics of Embryonic Stem Cell Research*, in S. Holland et al (eds.), *The Human Embryonic Stem Cell Debate*, (London: MIT Press, 2001), 37, at 46-48 stating that whereas SCNT embryos are not genetically unique and may only be respected for their research and therapeutic value, IVF embryos are unique and considered as outcomes of human reproduction.

[112] Edmund D. Pellegrino, *Prologue: Intersections of Western Biomedical Ethics and World Culture*, in Edmund D. Pellegrino et al. (eds.) *Transcultural Dimensions in Medical Ethics*, (Frederick, MD: University Publishing Group, 1992), 13, at 13.

considerable, often incommensurable conflicts between different ethical positions. In the following, the opinions of various ethical advisory bodies on human embryonic stem cell research are presented.

In the US, where most of biomedical research is regulated on state level, the formulation of a federal ethical viewpoint may only have an impact on federal policy, such as the federal funding of biomedical research. The various bioethical advisory committees appointed by successive administrations produced a number of extensive reports. In 1994 the Human Ethics Research Panel, based on the opinion that human (pre-implantation) embryos have a lesser moral status than persons, which, however, warrants serious moral considerations as a developing form of human life, recommended that research should be allowed on human embryos in a limited time frame and for limited purposes.[113]

The federal ethical committee created under the Clinton administration, the National Bioethics Advisory Commission (NBAC), in its 1999 report[114] accepted that ethical positions regarding the moral status of the human embryo differ in society and different sources of human embryos may attract different moral positions. With this background the report suggested that "the immediate scientific uses of embryonic stem or embryonic germ cells can be satisfied by the derivation and use of cell lines derived from foetal tissues and from embryos remaining after infertility treatments have ended." The argument provided by the NBAC in support of hESC derivation from supernumerary IVF embryos is based on utility suggesting that between the ethical considerations of promoting biomedical research and protecting human embryos a balance can be found when, instead of discarding them after a successful IVF treatment, supernumerary embryos are destroyed in the process of generating "stem cell for bona fide research".

The report contended, while accepting that human embryos should "merit respect as a form of life, but not the same level of respect accorded to persons", that the benefits derived from stem cell research are higher than the harm induced. It continued that the moral status of human embryos can be respected by regulating the conditions of and restraints on research activity. In particular, the destruction of human embryos may take place "only with good reason" when "no less morally problematic alternatives are available" and the human embryos are not "the object of sale" before destruction.

The liberal ethical position on the federal level changed when in 2005 a report from the President's Council on Bioethics,[115] appointed by the Bush administration, suggested that in the US the protection of human life from the earliest stages of development, including the human embryo, is an ethical norm accepted widely in society. It held that seeking therapies by means of destroying human embryos is ethically unacceptable and in order to reconcile scientific progress with the requirements of bioethics, biomedicine must find ethically acceptable sources for hES cells. Its critics claimed that in a diverse and pluralist society, such as that of the US, advocating a full moral status and personhood of embryos as a clear

[113] Human Ethics Research Panel, *Report of the Human Embryo Research Panel*, (Washington, DC: National Institutes of Health, 1994).
[114] National Bioethics Advisory Commission, *Ethical Issues in Human Stem Cell Research* (1999), available at bioethics.georgetown.edu/pcbe/reports/past_commissions/nbac_stemcell1.pdf.
[115] The President's Council on Bioethics, *Alternative Sources of Human Pluripotent Stem Cells. A White Paper*, (Washington DC: The President's Council on Bioethics, 2005).

majority position is a misconception.[116] The implications of the change of ethical viewpoints will be demonstrated in the examination of the federal political reactions to stem cell research.

In France the intermediary bioethical framework for human embryonic research emerged in the 1980s. The French National Ethics Advisory Committee in its 1984 opinion recognized human embryos as potential human beings who are or were alive.[117] The creation of human embryos by IVF or SCNT for research purposes, which is prohibited by law, was regarded by the Committee as representing the use of embryos 'purely and simply' as tools or objects and which would breach human dignity.[118] In contrast, it suggested that supernumerary IVF embryos from a parental project should be available for research in addition to aborted dead embryos and fetuses from which cells and tissues may be collected and used for diagnostic, therapeutic and scientific purposes subject to informed consent.[119] In the Committee's opinion research on supernumerary IVF embryos remains acceptable subject to informed consent, safeguarding the anonymity of donors and without remuneration or any commercial element.[120]

The restrictive German biomedical research regime builds on opinions from the German Ethics Council. The Council supported the prohibition of both research and reproductive cloning on bioethical grounds[121] and found, with a minority opinion supporting a complete ban on hESC research, the provision in German law that only imported hESC should be available for research the only solution compatible with the ethical principle of non-instrumentalization.[122] It also suggested more effective and stricter rules regarding hESC importation.[123] An alternative view was formulated by the rival Central Ethics-Commission which held that supernumerary embryos should be used for research purposes lacking an alternative research method and the importation of hESC must not be hindered. The statement, however, rejected that human embryos should be produced for research purposes by IVF and held that reproductive cloning is unacceptable.[124]

In the permissive UK regime the Nuffield Council on Bioethics suggested that cell derivation from donated human embryos does not violate the moral status of the human embryo as it does not represent a lack of respect for the embryo. Further, it held since diagnostic and reproductive research on human embryos is permitted in the UK there are no ethical grounds for banning human embryonic research for therapeutic purposes. Regarding the source of embryos the report saw no compelling reason to pursue further methods of

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[116] Wybo Dondorp and Guido de Wert, *On waving the embryos banner. Embryonic stem cell research and moral reasoning in recent reports from the USA, the Netherlands and France*, available at www.regenerative-medicine.jp/whitepaper/638.pdf, at 7.
[117] Avis 1, CCNE, 1984, available at www.ccne-ethique.fr/avis.php.
[118] Avis 8, CCNE, 1986, available at www.ccne-ethique.fr/avis.php.
[119] Avis 1, CCNE, 1984, Avis 53, CCNE, 1997 and Avis 67, CCNE, 2001, available at www.ccne-ethique.fr/avis.php.
[120] Avis 18, CCNE, 1989 and Avis 53, CCNE, 1997, available at www.ccne-ethique.fr/avis.php.
[121] *Opinion on Cloning for Reproductive Purposes and Cloning for the Purposes of Biomedical Research* (2004), available at www.ethikrat.org/_english/publications/Opinion_Cloning.pdf.
[122] *Opinion on the Import of Human Embryonic Stem Cells* (2001), available at www.ethikrat.org/_english/publications/stem_cells/Opinion_Import-HESC.pdf. Nine members of the majority held the position that the derivation of hES cells from supernumerary embryos is ethically acceptable.
[123] *Opinion – Should the Stem Cell Law be Amended?* (2007), available at www.ethikrat.org/_english/publications/Opinion_Should_the_Stem_Cell_Law_be_amended.pdf.
[124] *Stellungnahme der Zentralen Ethikkommission zur Stamzellforschung* (2002), available at www.zentrale-ethikkommission.de/downloads/Stammzell.pdf.

creating embryos to supplement the number of embryos available for research by donation from IVF parental projects.[125]

On the European level an ethical opinion accepting the multiplicity of ethical viewpoints on the local level was essential. The European Group on Ethics (EGE), the European Union ethical advisory body, suggested that hESC derivation from human embryos must be assessed with view to variety in the Member States in regulating human embryonic research and accepted that the moral status of the human embryo must be examined with reference to the principle of non-instrumentalization.[126] The derivation of stem cells from umbilical cord blood and fetal tissue and the derivation of human adult stem cells were seen as ethically unproblematic provided that the ethical requirement of informed consent is observed. Regarding the question of acceptable sources, EGE maintained that whereas IVF spare embryos from a maternity project may be used for research purposes the creation of research embryos by IVF is ethically unacceptable. It argued that the availability of supernumerary parental IVF embryos for research renders the creation of embryos for research purposes unnecessary. Concerning SCNT embryos EGE expressed its concerns that widespread cloning would lead to the devaluation (trivialisation) of human embryos, increase pressure on women as sources for donated oocytes and increase the risk of instrumentalization. Again, EGE concluded that the availability of alternative sources makes the creation of research embryos by SCNT unnecessary.

The European Group on Ethics' Opinion No. 12 (1998)[127] formulated the view, in an attempt to balance the ethically equally important factors of scientific progress and respecting "all members of the human family", that an increased protection of the human embryo in biomedical research is necessary and the socio-ethical diversity prevailing in Europe concerning the status of human embryos and human embryonic research must be respected. Refraining to determine the moral status of the human embryo in Europe the EGE focused on collateral ethical issues, such as giving priority to respecting the right to life, informed consent, research supervision and transparency. The only clear prohibition provided concerned the implantation of research embryos into a uterus after manipulation.

In a similar tone, Opinion No. 22 (2007)[128] avoided creating a European definition of the moral status of human embryos and targeted other important bioethical principles in research, such as necessity (seeking alternative methods) and the primacy of the human being. The opinion implied that supernumerary IVF embryos from a parental project could be used for research purposes. This was apparent from the declaration on the obligations of research applicants to state that the hES cells used in the project were derived from this particular source. The opinion, however, also suggested that, if possible, embryo destruction by means of hESC derivation should be avoided as applicants should seek to use alternatives to hES cells or alternative sources of hES cells. In connection to donors' rights it was emphasized that human embryos are not neutral objects and this should be reflected in conducting the donation process.

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[125] Nuffield Council on Bioethics – *Stem Cell Therapy: Ethical issues. A Discussion Paper* (2000), available at www.nuffieldbioethics.org/sites/default/files/Stem cell therapy discussion paper.pdf.

[126] Opinion No. 15 (14/11/2000) – *Ethical Aspects of Human Stem Cell Research and Use*, available at ec.europa.eu/european_group_ethics/docs/avis15_en.pdf.

[127] Opinion No. 12 (23/11/1998) – *Ethical Aspects of Research Involving the Use of Human Embryo in the Context of the Fifth Framework Programme*, available at ec.europa.eu/european_group_ethics/docs/avis12_en.pdf.

[128] Opinion No. 22 (13/07/2007) – *The Ethics Review of hESC FP 7 Research Projects*, available at ec.europa.eu/european_group_ethics/activities/docs/opinion_22_final_follow_up_en.pdf.

The religious moral opinions on biomedical research also reveal a plurality of viewpoints. The Church of England adopted a liberal view on human embryonic research following a gradualist/developmental approach to the moral status of the human embryo as opposed to an absolutist view demanding protection from fertilization, and it agreed with the '14-day rule' laid down in UK human embryonic research regulation. It voiced the necessity of finding a balance between promoting scientific and medical development and ensuring the protection of human dignity and "vocation of human kind".[129] The Church of England expressed its support to research on supernumerary IVF embryos donated from a parental project and on SCNT embryos and, subject to conditions, the use of cytoplasmic hybrid embryos. In contrast, the creation and use of IVF research embryos were regarded as morally unacceptable.[130] The production and use of true hybrids for research was also opposed.[131]

The Catholic Church holds a diametrically opposing view. It advocated that human dignity and integrity and the right to life must be respected in a way which excludes any form of instrumentalization and commodification of human beings and avoids their destruction. On these grounds, breaching the integrity and the destruction of human embryos for the benefit of other individuals without delivering direct benefits to the embryo was declared morally unacceptable.[132] A full moral status was granted to IVF embryos as full respect of dignity of human being must be warranted from conception "independently of the practical circumstances in which his life begins."[133] Human cloning, research or reproductive, was declared as violating human dignity.[134]

The hESC declaration of the Pontifical Academy for Life[135] held that human embryos, enjoying a full moral status from fertilization, must not be created (by IVF and SNCT) or used (destroyed) for the purpose of hESC derivation. General therapeutic utility was announced as a morally unacceptable ground for intervention with the integrity of the human embryo. The declaration emphasized that from the moment of conception the embryo is more than a mass of cells, as stated in the *Evangelium Vitae* (1995). It added that the use of hESC cells

[129] Church of England – Mission and Public Affairs Council, *Embryo Research: Some Christian Perspectives*, available at www.cofe.anglican.org/info/socialpublic/science/hfea/embryoresearch.pdf.
[130] Church of England – Mission and Public Affairs Council, *Response to the HFEA Consultation on Hybrids and Chimeras*, available at www.cofe.anglican.org/info/socialpublic/science/hfea/chimeras.pdf.
[131] Church of England – Mission and Public Affairs Council, *Response to the Call for Evidence from the Joint Committee on the Draft Human Tissue and Embryos Bill*, available at www.cofe.anglican.org/info/socialpublic/science/hfea/humantissue.pdf.
[132] Catholical Church - Pontifical Academy for Life, *Ninth General Assembly Concluding Communiqué on the Ethics for Biomedical Research for a Christian Vision* (2003), available at www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pont-acd_life_doc_20030226_ix-gen-assembly-final_en.html.
[133] Catholic Church – Pontifical Academy for Life, *Tenth General Assembly Final Communique on The Dignity of Human Procreation and Reproductive Technologies Anthropological and Ethical Aspects* (2004), available at www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pont-acd_life_doc_20040316_x-gen-assembly-final_en.html.
[134] Catholic Church – *Observations on the Universal Declaration on the Human Genome and Human Rights (UNESCO Declaration) 1997*, available at www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_08111998_genoma_en.html and Catholic Church – Pontifical Academy for Life, *Reflections on Cloning*, available at www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_30091997_clon_en.html.
[135] Catholic Church – Pontifical Academy for Life, *Declaration on the Production and the Scientific and Therapeutic Use of Human Embryonic Stem Cells*, available at www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_20000824_cellule-staminali_en.html.

remains unethical, notwithstanding the fact that the cell lines were produced by other researchers or procured from the market. Only adult stem cells (and modified adult stem cells) represent an ethical source for biomedical research.

The Islamic view, provided that a single Islamic viewpoint can be distilled, is essentially permissive derived from the scholarly proposition that human life begins when the soul enters into the developing human being, placed between days 40 and 120 after conception.[136] Despite the moral requirements of embryonic sanctity and respect for human embryos the use of supernumerary IVF embryos for research purposes has been regarded in some communities as permissible under Islamic law, which promotes beneficial and necessary human activity for the public good and research and treatments for diseases.[137] Western bioethical influences are not excluded, as demonstrated by the Iranian ethical guidelines on human embryonic research drafted with the intention to secure Iran's leading position in the region in biomedical research. It includes the '14-day rule' and allows research on supernumerary IVF embryos, but prohibits the creation (IVF and cloning) of embryos for research purposes and the creation of hybrids.[138]

The opinions range from utilitarian, bioethically oriented and to conservative. Some introduce distinctions based on the degree of development of the human embryo and the different sources from which human embryos may be obtained for research. The diversity of ethical views is also reflected in the various political announcements in different states regarding permissibility of stem cell research.

1.2. Diversity in the Political Viewpoints

Mapping political viewpoints further confirms diversity in defining the ethical boundaries of biomedical research. The example of the US demonstrates how politics would oscillate between different ethical viewpoints. The European examples show how political views may be formulated disregarding the diversity of local approaches and how respect for value pluralism can be expressed on the European level.

Apart from the federal funding debate and regulating research in human subjects (fetal research) there is no comprehensive federal policy on biomedical research. The turbulent debate on the federal funding of stem cell research revolves around US presidential policies determining the availability of federal financing which mirrored the opinion of the presidential ethical advisory body in office. In Pence's words the federal politics of the human embryo focused on approving federal funding for research which saw periods where funding was not made available or was frozen and periods when federal funding was able to supplement the private funding human embryonic research had been receiving.[139]

In 1994 President Clinton gave green light to research on supernumerary IVF embryos but only endorsed the creation of human embryos for research purposes in 1998.[140] The presidency of George Bush Jr. meant a 180 degree turn in the federal politics of hESC research. In 2001 the Bush administration decided, on the basis of legislation passed in 1996,

[136] Mansooreh Saniei, Human Embryonic Stem Cell Research in Iran: The Role of the Islamic Context, *SCRIPTed*, vol. 7, no. 2. (August 2011), 325, which makes it similar to the Jewish approach which dates the beginning of human life 40 days after conception.
[137] *Ibid.*, at 329.
[138] *Ibid.*, at 330.
[139] Gregory Pence, *Classic cases on medical ethics* (McGraw Hill Higher Education, 2004) at 185–189.
[140] Parens (2001), at 37.

to exclude the derivation of further hESC lines from embryos from federal funding.[141] In a presidential address Mr. Bush held that federal funds may only be used for hESC research provided that the stem cells were derived from an embryo that was created for reproductive purposes and was no longer needed, that informed consent was obtained for the donation of the embryo, the donation did not involve financial remuneration and the process of derivation commenced prior to the date of the presidential address.

2001 saw the introduction of Mr. Weldon's Bill for the Human Cloning Prohibition Act 2001 intending to exclude the cloning of human embryos for all purposes. The repeated attempts (from 2001 to 2011) to amend the US Code and introduce a federal ban on human cloning were defeated in Congress. The idea of a ban on cloning originated from the President's Council on Bioethics 2002 report 'Human Cloning and Human Dignity: An Ethical Enquiry' which called for a complete ban on reproductive cloning and a moratorium on therapeutic cloning. On hESC research the report was divided with the majority urging its prohibition on grounds that it violates the respect owed to human embryos and the minority suggesting that within the '14-day rule' research should be permitted. The minority added that cloned early-stage embryos have no special moral status and should be treated like other biological material.[142]

A 2007 Executive Order[143] addressed the ethically responsible ways of hESC research. It emphasized that ethically acceptable sources of hESC lines exclude cell lines which necessitated the creation of embryos for research purposes or destroying, discarding or subjecting to harm a human embryo. It also held that the destruction of embryos violates the principle of non-commodification and that human embryos are "members of the human species". The Executive Order envisioned the US progressing in biomedical research while maintaining the clearly established ethical boundaries and standards of medical research and respecting human life and dignity.

The debate reached another turning point in 2009 when the Obama administration reviewed the federal funding moratorium imposed in 2001. The 2009 Executive Order[144] emphasised the necessity of hESC research for the purposes of enhancing human biomedical knowledge and creating new therapies. In the terms of the executive order research eligible for funding must be responsible and scientifically worthy and must be permitted by law.

European level politics, despite the diversity of domestic approaches, has argued for stringent controls on human embryonic research on bioethical grounds. The Council of Europe Parliamentary Assembly adopted two recommendations[145] in the 1980s concerning the use of human embryos and fetuses in research. These recommendations envisaged the creation of a much narrower framework for biomedical research than that currently available in most of the Contracting States. The recommendations of the Committee of Ministers concerning medical research on human beings and biological material of human

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[141] *Address to Nation on Stem Cell Research from Crawford Texas*, 37 Weekly Compl. Pres. Doc. 1149 (9 August 2001) and Executive Order No. 13,435, 72 Fed. Reg. 34,591 (20 June 2007).

[142] The President's Council on Bioethics, *Human Cloning and Human Dignity: an Ethical Enquiry* (2002), available at bioethics.georgetown.edu/pcbe/reports/cloningreport/.

[143] Executive Order (13435 of 20 June 2007), available at img.slate.com/media/40/13435-stemcells.pdf.

[144] Executive Order (13505 of March 2009), available at edocket.access.gpo.gov/2009/pdf/E9-5441.pdf.

[145] Recommendation 1100 (1989) – *On the Use of Human Embryos and Foetuses in Scientific Research*, available at assembly.coe.int/Mainf.asp?link=/Documents/AdoptedText/ta89/EREC1100.htm and Recommendation 1046 (1986) – O*n the Use of Human Embryos and Foetuses for Diagnostic, Therapeutic, Scientific, Industrial and Commercial Purposes*, available at assembly.coe.int/Mainf.asp?link=/Documents/AdoptedText/ta86/EREC1046.htm.

origin contain principles similar to those established in the Oviedo Convention on Human Rights and Biomedicine.[146]

More radical opinions were voiced in a 2003 Parliamentary Assembly resolution.[147] The resolution maintained that hESC derivation necessitates the destruction of human embryos which is "against the right to life of all humans and against the moral ban on any instrumentalization of humans." The resolution, however, made a retreat from this strong moral view when it formulated its recommendations to the Contracting States which mention seeking alternative sources and technologies for hESC creation and adequate regulation and supervision of research in states where hESC derivation from embryos is allowed. The Contracting States were also called to prioritize the ethical features of research over its utilitarian and financial aspects.

The European Union, involved in the regulation (harmonization) of many aspects of biomedical research, opted for political statements reflecting the findings of the EGE. The European Commission's position regarding hESC research drew upon Opinion 15 of the EGE and found that opinions in Europe about human embryonic research is divided according to the different ethical, philosophical and religious traditions of the Member States.[148] Plomer cited the conclusions of a 2003 European Commission inter-institutional seminar which stated that the fundamentally incompatible moral positions of different Member States on hESC research cannot be reconciled.[149] Respect for European ethical pluralism was not appreciated in a Resolution from the European Parliament in 2000, issued in response to the UK's permissive legislation on therapeutic cloning, which suggested banning all forms of human cloning and called for the review of IVF techniques in order to reduce the number of supernumerary embryos. The Resolution was based on respect for human dignity and life and declared that research cloning trespasses upon the boundaries of biomedical research.[150]

1.3. Diversity in the Law

The legal framework for regulating biomedical research on national, regional and global level reveals a diversity of approaches and in case of overarching regional and global regimes respect for the diversity of local solutions. Plomer contended that "there is a wide variation in norms and laws regulating biomedical research both within and outside Europe."[151] Diversity is the single most important characteristic of regimes regulating the ethical boundaries of biomedical research activity and the ethics of commercializing biomedical innovation in the world. These differences have an impact on the research

[146] *Recommendation R (90) 3 of the Committee of Ministers to Member States Concerning Medical Research on Human Beings*, available at cm.coe.int/ta/rec/1990/90r3.htm and *Recommendation Rec (2006) 4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin*, available at www.coe.int/t/e/legal_affairs/legal_co-operation/bioethics/texts_and_documents/Rec_2006_4.pdf.

[147] Council of Europe Parliamentary Assembly Resolution 1352(2003), *Human Stem Cell Research*, available at assembly.coe.int/Main.asp?link=http%3A%2F%2Fassembly.coe.int%2FDocuments%2FAdoptedText%2Fta03%2FERES1352.htm.

[148] European Commission Staff Working Paper – *Report on hESC Research* (2003), available at ec.europa.eu/research/press/2003/pdf/sec2003-441report_en.pdf

[149] Aurora Plomer, *The Law and Ethics of Medical Research* (Abingdon: Routledge-Cavendish, 2005), at 67.

[150] European Parliament – *Resolution on Human Cloning* (2000), available at www.academiavita.org/english/AltriDocumenti/org_int/parl_europeo/clonazione/Ris_clo_2000_EN.pdf.

[151] Plomer (2005), at 24.

environment, the model for financing research and translational activity and the availability of intellectual property rights in the course of biomedical research.

The available taxonomies label the different national regimes on biomedical research as permissive (liberal), intermediate and restrictive.[152] The permissibility of regulatory regimes in this taxonomical system refers to a number of factors: how they regulate embryo use and destruction in research and how they regulate and implement the ethical and procedural safeguards of biomedical research.[153]

Permissive regimes (UK, Japan, and South Korea) allow research on human embryos and stem cell derivation from them.[154] The permitted sources are supernumerary IVF and SCNT embryos. They apply a temporal limitation to human embryonic research, such as the '14-day rule' associated with the appearance of the primitive streak in the human embryo. Intermediate regimes (France, India and China) allow research with limitations on embryos obtained from limited sources.[155] Restrictive regimes (Germany) prohibit human embryonic research for general therapeutic purposes and ban hESC derivation, and they may prohibit using hESC lines and products.[156] In the US stem cell research is regulated on state level, if regulated, without the federal level being constitutionally able to impose uniform ethical regulatory boundaries. The federal disapproval of stem cell research is expressed in fiscal legislation prohibiting the federal funding of stem cell research[157] which is now under challenge before the courts.[158] A detailed illustration of national legal frameworks follows below.

1.3.1 THE GLOBAL LEGAL FRAMEWORK

Before turning to the local regulatory systems the global instruments establishing common bioethical principles should be examined. The UNESCO Universal declaration on the human genome and human rights in 1997 provides a list of universally accepted bioethical principles, such as respect for human dignity, non-commercialisation, benefit sharing, and scientific progress.[159] The World Medical Organisation Helsinki Declaration called for risk and benefit assessment in biomedical research, the examination of the necessity of

[152] www.stemgen.org/mapworld.cfm and Rosario M. Isasi & Bartha M. Knoppers, Mind the Gap: Policy Approaches to Embryonic Stem Cell and Cloning Research in 50 Countries, *European Journal of Health Law* vol. 13, no. 1 (2006), 9.
[153] Rosario M. Isasi and Bartha M. Knoppers, Beyond the permissibility of embryonic and stem cell research: substantive requirements and procedural safeguards, 21(10) *Human Reproduction* (2006), 2474–2481, at 2475.
[154] UK: Human Fertilisation and Embryology Act (HFEA) 1990, available at www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsLegislation/DH_080205, Japan: Act on Regulation of Human Cloning Techniques 2000, available at www.japaneselawtranslation.go.jp/law/detail/?re=02&dn=1&x=0&y=0&co=1&yo=&gn=&sy=&ht=&no=&bu=&ta=&ky=cloning&page=1, South Korea: Bioethics and Safety Act 2004, available at (eng.bprc.re.kr/gz06.htm?number=8).
[155] France: Public Health Code, Article L2151-2 and L2151-4, available at www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006072665&dateTexte=20101017, India: Ethical Guidelines for Stem Cell Research 2007, available at www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf, China: Ethical Guiding Principles on Human Embryonic Stem Cell Research 2003, available at www.qmlc.com.cn/edit/UploadFile/info/2009430113029216.doc.
[156] The Embryo Protection Act, available at www.bmj.bund.de/files/-/1147/ESchG%20englisch.pdf and the Stem Cell Act, available at www.bmj.bund.de/files/-/1146/Stammzellgesetz englisch.pdf.
[157] The Dickey-Wickers amendment, a rider attached to the Balanced Budget Downpayment Act 1996,
[158] United States District Court for the District of Columbia, Civ. No. 1:09-cv-1575 (RCL) and United States Court of Appeals for the District of Columbia Court, No. 10-5287, 9 September 2010.
[159] Universal Declaration on the Human Genome and Human Rights, available at portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html.

research, the protection of privacy and confidentiality and observing the requirement of informed consent.[160] The 2002 CIOMS Guidelines, among others, specify that the ethical acceptability of research depends on whether the research activity respects and protects the ethical limits of human research activity within that community.[161]

The UN Human Cloning resolution demonstrated a division among states in the matter of prohibiting of all forms of human cloning "inasmuch they are incompatible with human dignity and the protection of human life."[162] The disagreement prevented the adoption of a binding agreement in this matter. The most important concern raised by the states opposing the resolution was that it had not been clarified what the protection of human life meant and whether the ban would cover both reproductive and therapeutic cloning, the latter permitted and considered socially beneficial in a number of states.

1.3.2 A REGIONAL LEGAL FRAMEWORK: EUROPE

The European framework produced respectable results in achieving a common ground among European states. The Council of Europe Oviedo Convention on Human Rights and Biomedicine[163], with a focus on the human rights limitations of biomedical research and therapy, builds on the protection of human dignity and integrity and confirmed the primacy of the human being over the interests of science and society (Articles 1 and 2). Despite the aspiration to create uniformity on the level of general principles, the Oviedo Convention mirrors the diversity of European attitudes to biomedical research. Deference to local appreciation is found in the Explanatory Report (para. 18) stating that the term 'everyone', the subject of the right to respect of human dignity alongside with 'human beings', should be determined in national law.[164] The Convention leaves the question of hESC research partially open by the provision of Article 18(1) that "where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo." Arguably, this could encompass the destruction of human embryos in an adequately safeguarded process for the purpose of hESC derivation. The more contentious provision in Article 18(2), which has prevented the ratification of the Convention by all Council of Europe States considering it as either liberal or conservative, prohibits the creation of embryos for research purposes.

The Charter of Fundamental Rights of the European Union, now legally binding within the scope of European Union law, also offers a catalogue of common bioethical principles, such as human dignity and integrity and the right to life. Regarding human integrity the Charter refers to free and informed consent, non-commercialization and the prohibition of eugenic practices and human reproductive cloning. Human embryonic research, the boundaries of hESC research, issues central to the European debate, are not addressed

[160] World Medical Association, *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, available at www.wma.net/e/policy/b3.htm.
[161] Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), available at www.cioms.ch/guidelines_nov_2002_blurb.htm.
[162] United Nations General Assembly. *United Nations Declaration on Human Cloning* (2005), Resolution adopted by the General Assembly 59/280, available at www.un.org/News/Press/docs/2005/ga10333.doc.htm.
[163] Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, available at conventions.coe.int/Treaty/en/Treaties/Html/164.htm.
[164] There is some contradiction as the term 'human being' was given definition covering all human beings from the beginning of human life without defining what the latter concept means (fertilised egg, zygote, foetus etc.). This questions the scope of local appreciation in defining 'everyone'.

directly. In Article 51(1) the 'horizontal provisions' (ensure that the regulation of biomedical research in the Member States is not affected by the Charter.

The European framework indicates that diversity among European states is the prevailing characteristic of regulating the ethical boundaries of biomedical research. The locus of ethical judgments and regulation is on the state level subject to meeting the 'thin' layer of common requirements. European diversity is apparent: states disagree regarding the acceptable sources of human embryos for research and whether the destruction of embryos in the research process is permitted. The history of the cloning prohibition in the Oviedo Convention reveals the lack of a regional consensus on this matter.

The introduction of a human rights perspective to biomedical research regulation in Europe sustained the diversity of local ethical approaches. Not even the application of the European Convention on Human Rights[165] (ECHR) would mitigate European diversity. The ECHR, constrained by its subsidiary nature expressed in the margin of appreciation doctrine, demonstrated sensitivity to the local ethical appreciation of the boundaries of biomedical research. Article 2 ECHR on the right to life attracted a deferential approach from the European Court of Human Rights when it faced the question whether the rights of an 'unborn child' should be protected under the ECHR.[166]

The lack of a European consensus on the moral status of the human embryo approached from the fundamental right to life was made apparent in the judgment in V.O.[167] in which having implied that the safeguards of the Convention would be applicable to the human embryo the court declared that the question when the right to life begins belongs to the margin of appreciation of the Contracting States. The court expressly referred to the lack of a European consensus on the nature and status of human embryos and that the Contracting States are increasingly active in regulating independently human embryonic research.

The court, nonetheless, indicated that under the human dignity requirement of the ECHR human embryos might be granted a protected moral status. It acknowledged the 'potentiality' of human embryos and their "capacity to become a person". Reading into the provisions the ECHR a full moral status of human embryos was, however, declared to be subject to the margin of appreciation doctrine. This was clarified in a subsequent judgment where the margin of appreciation of Contracting States led the court to decide that in the light of domestic regulation, which denies a legal status from human embryos, the human embryos in the particular case did not have a right to life.[168]

Accepting the diversity of domestic approaches to biomedical regulation was last confirmed in a 2010 judgment concerning infertility treatment, now referred to the Grand Chamber, in drafting which the variety of regulatory approaches to treatment and the diversity of treatment methods among European states was an important factor.[169] The court held that

> Since the use of IVF treatment gives rise to sensitive moral and ethical issues against a background of fast-moving medical and scientific developments, and since the questions raised by the case touch on areas where there is no clear common ground

[165] European Convention for the Protection of Human Rights and Fundamental Freedoms, available at www.echr.coe.int/NR/rdonlyres/D5CC24A7-DC13-4318-B457-5C9014916D7A/0/ENG_CONV.pdf.
[166] *Brueggemann and Scheuten* v *Germany*, (1981) 3 EHRR 244, *Paton* v *UK*, (1981) 3 EHRR 408, *Open Door Counselling* v *Ireland*, (1993) 15 EHRR 244, *V.O.* v *France*, App. 53924/00, 08/07/2004, ECHR 2004-VIII, *Evans* v *UK*, App. 6339/05, 10/04/2007, nyr., and *S.H. and Others* v *Austria*, App. 57813/00, nyr.
[167] Paras. 80, 83, 84 and 85, *V.O. v. France*, App. 53924/00, 08/07/2004, ECHR 2004-VIII.
[168] Paras. 54 and 56, *Evans v. UK*, App. 6339/05, 10/04/2007, nyr.
[169] Paras. 68, 69, 74 and 75-85, *S.H. and Others v. Austria*, App. 57813/00, nyr.

amongst the Member States, the Court considers that the margin of appreciation to be afforded to the respondent State must be a wide one.

With regard to the limits of domestic discretion available in regulating bioethical issues the court suggested that "concerns based on moral considerations or on social acceptability are not in themselves sufficient reasons" for excessively restrictive regulation. This, however, does not entail that the Contracting State would be prevented from making the initial decision to permit or prohibit certain biomedical activities; this limitation to domestic discretion only applies to the adoption of a regulatory framework in relation to which the State concerned must ensure that the requirements of the ECHR are observed. The court rejected a number of claims based on bioethical principles presented in defense of domestic regulation, such as reducing risk, protecting women from exploitation and preventing the commercialization of ova donation, on the grounds that the rigor of the challenged measure was excessive.

Respect for local diversity was also expressed in the abortion cases under the ECHR. The now dissolved European Commission of Human Rights regarding German abortion legislation suggested that there was no evidence that the parties to the ECHR had agreed to a particular solution regarding the right of an unborn child to life.[170] The deferential position of the Commission was later confirmed in *Paton* v *UK*[171] where it observed the difference between national legal approaches and maintained the right to life does not have a prenatal application under the Convention, which, however, does not exclude respect for the unborn under the Convention. The divergence of national interpretations and determinations of morals and local appreciation in ethical questions were also acknowledged under the ECHR in the *Open Door* case before the court.[172]

1.3.3 LOCAL REGULATION: EUROPE

Under the flexible, overarching European legal framework a diversity of local approaches bourgeons. There are highly developed regulatory regimes establishing broader or narrower boundaries for biomedical research. State level regulation reflects the various ethical viewpoints voiced by local ethical advisory bodies.

The restrictive German regulatory system for human embryonic/stem cell research is based on two acts, the Embryo Protection Act and the Stem Cell Act. The Embryo Protection Act[173] prohibits the improper use of human embryos defined as a use not serving the preservation of the embryo. It also prohibits the creation of embryos for other than reproductive purposes. Furthermore, it bans human cloning and the formation of chimeras and hybrids.[174]

The 2002 Stem Cell Act[175] introduced a general prohibition on the importation and utilization of hES cells with a derogation from that prohibition. Section 2(4) of the Act

[170] *Brueggemann and Scheuten* v *Germany*, (1981) 3 EHRR 244.
[171] *Paton* v *UK*, (1981) 3 EHRR 408.
[172] *Open Door Counselling* v *Ireland*, (1993) 15 EHRR 244.
[173] Available at www.bmj.bund.de/files/-/1147/ESchG%20englisch.pdf.
[174] The German Ethics Council recommended that cloning, both research and therapeutic should be prohibited, *Opinion on Cloning for Reproductive Purposes and Cloning for the Purposes of Biomedical Research* (2004), available at www.ethikrat.org/_english/publications/Opinion_Cloning.pdf. The Central Ethics-Commission, however, considered that on the balance of the relevant factors therapeutic cloning should be encouraged, see *Forschungsklonen mit dem Ziel Therapeutischer Anwendungen* (2006), available at www.zentrale-ethikkommission.de/downloads/TherapKlonen.pdf.
[175] Available at www.bmj.bund.de/files/-/1146/Stammzellgesetz englisch.pdf.

exempted hES cells from the prohibition provided that they had been harvested before 1 January 2002 in another state according to the regulations of that state from supernumerary IVF embryos created in a parental project. The setting of an ethically relevant date is a practice similar to that introduced in US federal law concerning the federal funding on hESC research.

The importation and use of 'exempt' imported hES cells must also comply with the Embryo Protection Act and as a general rule their derivation must not contravene the 'major legal principles of the German legal system'. Research on 'exempt' stem cells must also demonstrate that it meets the requirement of necessity, in particular, that it would contribute to expanding knowledge in basic research and developing diagnostic, preventive or therapeutic applications and that there was no alternative to research using hESC lines.

Establishing a general prohibition and providing a derogation on imported hES cells is a restrictive compromise. The German Ethics Council was deeply divided on this issue. The majority opinion supported the solution implemented in the act. The considerable minority advocated a ban of hESC import on grounds that it is ethically impermissible for breaching the principle of non-instrumentalization. Nine members of the majority held the position that the derivation of hES cells from supernumerary embryos is ethically acceptable.[176] In 2007 the Ethics Council while accepting that the Stem Cell Act may remain unchanged suggested more effective and stricter rules regarding hESC importation.[177]

In the UK the Human Fertilization and Embryology Act (HFEA) 1990[178] provides the backbone of biomedical research regulation. The HFEA was enacted after lengthy public debate (starting from the 1984 Warnock Report) concerning the rights of the human embryo, in particular, its right to life and whether a specific moral status should be accorded to human embryos in law.[179] In this public debate the consensus emerged that the embryo does not have the moral status of an adult *per se*. Nevertheless, it should be given protection due to its potentiality to become a person the first indication of which is the development of the primitive streak 14 days after fertilization. The '14-day rule' is an essential distinction in UK biomedical research regulation as it forms the basis of permitting research on a human embryo which has not reached the 14-day limit. Research, including hESC derivation, after the emergence of the primitive streak is not permitted. The sources available for hESC derivation include supernumerary IVF embryos from a parental project, IVF research embryos and embryos created for research purposes by SCNT.

The UK regime regards hESC research as beneficial and determines that it should be permitted in order to increase knowledge about embryonic development, diseases and therapeutic responses to diseases.[180] The regime prohibits reproductive cloning and the implantation of research embryos into a uterus, but enables therapeutic cloning and the creation of admixed embryos. A strict regulatory regime is in place on the supply, the storage and the use of embryos. According to a report in the UK around 50% of

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[176] *Opinion on the Import of Human Embryonic Stem Cells* (2001), available at www.ethikrat.org/_english/publications/stem_cells/Opinion_Import-HESC.pdf.
[177] *Opinion - Should the Stem Cell Law Be Amended?* (2007), available at www.ethikrat.org/_english/publications/Opinion_Should_the_Stem_Cell_Law_be_amended.pdf.
[178] Human Fertilisation and Embryology Act (HFEA) 1990, available at, www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsLegislation/DH_080205.
[179] On the background of the HFEA, see *Stem Cell Research and Regulations under the Human Fertilisation and Embryology Act 1990*, available at www.parliament.uk/documents/commons/lib/research/rp2000/rp00-093.pdf.
[180] Human Fertilisation and Embryology (Research Purposes) Regulations 2001/188, available at www.legislation.gov.uk/uksi/2001/188/contents/made.

supernumerary IVF embryos are unused leaving in the period between 1991–2005 1.2 million embryos available for research only 6.9% of which was actually used (82955).[181]

The intermediate regime of France prohibits reproductive cloning.[182] In the opinion of the National Ethics Committee (NEC) it would seriously endanger the essential original indetermination and other fundamental traits of a person and that person would become a means in the service of an alien end.[183] The creation of human embryos by IVF or SCNT for research purposes is also prohibited.[184] In the NEC's view, without this prohibition embryos would be purely and simply be used as tools or objects and human dignity will not be respected.[185] This leaves only supernumerary IVF embryos from a parental project available for research in addition to aborted dead embryos and foetuses from which cells and tissues may be collected and used for diagnostic, therapeutic and scientific purposes subject to informed consent.[186]

According to the Public Health Code supernumerary IVF embryos must be obtained for the purpose of producing major therapeutic progress without an alternative scientific route. Research must be carried out under an authorization and it must not cause damage to the embryo. The implantation of a research embryo into a uterus is prohibited.[187] It is in harmony with the logic of the French system that the destruction of surplus IVF embryos was not found unconstitutional considering the lack of an obligation in law to store IVF embryos unused in the parental project for an indeterminate length of time.[188]

The 2006 Fagniez report[189] proposed a slightly broader framework for human embryonic research. It recommended continuing embryo research to supernumerary IVF embryos and allowing the creation of research embryos by SCNT. The report insisted on distinguishing between research embryos created by IVF and SCNT and stated that SCNT embryos are compatible with the Oviedo Convention. Commentators suggested that the Fagniez report challenged the view that the 'products' of SCNT should be considered as embryos. In their interpretation embryos may only be created by fertilization making SCNT embryos ineligible for the protection embryos may receive. This suggests a definition for human embryos where the right and duty of their protection is associated with the process of creation and not with their capacity to develop into a human being.[190]

In a socially and culturally largely homogenous Europe there is evidence of internal diversity in regulating the bioethical limits of biomedical research. Diversity rests on

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[181] Carol C. George, Open Access and the Regulation of Commercialisation of Human Stem Cell Lines in the UKSCB, 7(2) August, SCRIPT*ed* (2010) 254.

[182] See also Avis 52, CCNE, 1997 (mentioning any use of ES cells with the aim of creating several human embryos), available at www.ccne-ethique.fr/avis.php.

[183] Avis 54, CCNE, 1997, available at www.ccne-ethique.fr/avis.php.

[184] Code de la Santé Publique, Article L2151-2 and L2151-4, available at www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006072665&dateTexte=20101017. See Avis 53, CCNE, 1997 (also mentioning the collection of human embryos conceived *in vivo* by uterine lavage before transplant) and Avis 67, CCNE, 2001, available at www.ccne-ethique.fr/avis.php.

[185] Avis 8, CCNE, 1986, available at www.ccne-ethique.fr/avis.php.

[186] Code de la Santé Publique, Article L1241-5. See Avis 1, CCNE, 1984, Avis 53, CCNE, 1997 and Avis 67, CCNE, 2001, available at www.ccne-ethique.fr/avis.php.

[187] Code de la Santé Publique, Article L2151-5.

[188] Conseil Constitutionnel, Decision 94/343/344 DC, available at www.conseil-constitutionnel.fr/conseil-constitutionnel/francais/les-decisions/acces-par-date/decisions-depuis-1959/1994/94-343/344-dc/decision-n-94-343-344-dc-du-27-juillet-1994.10566.html.

[189] Pierre-Louis Fagniez, *Cellules souches et choix éthiques* (Paris: Ministère de la santé et des solidarités, 2006), available at www.ladocumentationfrancaise.fr/rapportspublics/064000623/index.shtml.

[190] Dondorp and Wert, *On waving*.

conflicting ethical positions reflecting the social and cultural views of the particular community. Even with the availability of regional frameworks, voicing a strong human rights agenda, European diversity persists.

1.3.4 LOCAL REGULATION: THE UNITED STATES

The US regulatory system for biomedical research is defined by the separation of state and federal competences and the division between public and private morality. With biomedical research regulation enacted on state level the federal level is prevented from establishing federal bioethical limitations to biomedical research. The exception is regulating the federal financing of research through which the federal bioethical principles could be expressed. Federally funded research will be subject to the 'public' ethical guidelines produced by the National Institutes of Health (NIH). In contrast, privately funded research, provided that it complies, if available, with state level regulation, may be carried out with reference only to the private ethical standards of the fund provider and the research organization.

An area where federal regulation was constitutionally available is human foetal research. Foetal research came to the focus of political debate in the 1970s in the wake of *Roe* v *Wade*[191], a landmark decision from the US Supreme Court establishing the constitutional framework for the regulation of abortion. The dominant concern that liberalizing abortion would give rise to unprecedented research activity on human subjects and material led to regulating 'Fetal Research' in the US Code (S. 289G).[192] The provision enables research on fetuses subject to the requirements that the fetus benefits from the intervention, unnecessary risks are avoided and no alternative solutions are available. Further provisions are provided in the federal research guidelines[193] which are based on the 'Belmont Report' leading to the drafting of the 'Ethical Guidelines for the Protection of Human Subjects of Research' in 1979.[194]

The regulation of stem cell research is a contentious issue in the US. The focus of the debate on the federally funded 'presidential' cell lines, the quality and availability of which is subject to dispute, is misleading as on state level with the aid of public funding (California) or with the support of private funding (Wisconsin) hESC research has been flourishing making the US and US companies leaders in global biomedicine. It was suggested that refraining from interfering with privately funded research to isolate and use hES cells while maintaining a high profile ethical debate on the federal funding of a technology which involves the destruction of human embryos is hypocritical.[195] The issues of state and federal level regulation are separated.

1.3.4.1 STATE LEVEL REGULATION

The state level regulation of stem cell research in the US reveals considerable diversity. Regulatory regimes differ regarding the permissible sources of stem cells (IVF, SCNT or cadaverous tissue) and the permitted research activities. They range from permissive to

[191] *Roe* v *Wade* (410 U.S. 113 (1973).
[192] Pence (2004), at 184–185.
[193] Research involving human subjects, Common Rules, Code of Federal Regulations, Title 45, Part 46, available at www.hhs.gov/ohrp/refernces/comrulp2.pdf and NIH Guidelines for the Conduct of Research Involving Human Subjects (2004), available at ohsr.od.nih.gov/guidelines/GrayBooklet82404.pdf.
[194] Available at ohsr.od.nih.gov/guidelines/belmont.html.
[195] Søren Holm, Are countries that ban human embryonic stem cell research hypocritical?, 1(3) *Regenerative Med.* (2006) 357.

prohibitive.[196] For a permissive state level regulatory framework California provides an example. In California stem cell research has been given political priority. The California Institute for Regenerative Medicine (CIRM) was created under Proposition 71 with 3 billion $ in bonds to fund hESC research.[197] The proposition's intention was to promote scientific and therapeutic advances by creating state funding for stem cell research. The ethical limits and framework of funded research are also determined. These are circumscribed in principles, such as safe and ethical research, informed consent, respect for patients' rights and protecting privacy. Proposition 71 contended that hESC research will relieve the difficulties of financing healthcare and admitted that the state intends to benefit from the patents, licensing and royalties derived from research activity.

Proposition 71 added Article XXV to the California Constitution. Section 5 established the constitutional right to conduct stem cell research which includes "research involving adult stem cells, cord blood stem cells, pluripotent stem cells, and/or progenitor cells." It also holds that pluripotent hES cells may be derived from SCNT embryos or donated supernumerary IVF embryos ("IVF products").[198] Section 3 prohibits funding for reproductive cloning.

The CIRM regulations provide further exclusions from state funding.[199] Excluded activities include reproductive uses of SCNT, chimeras, transfer of research embryo after manipulation to uterus and the culture in vitro any intact human embryo or any 'product' of SCNT, phartenogenesis and androgenesis after the appearance of the primitive streak or after 12 days without counting the period the embryo was kept in a frozen state. The prohibition of these activities was established in the California Department of Public Health Guidelines for Human Stem Cell Research (Section 3) which also applies to research activities not financed by CIRM.[200] The CIRM regulations also provide a framework for benefit sharing from inventions financed by CRIM. They include revenue sharing obligations, limits on granting exclusive licenses, access requirements on inventions and drugs developed and licensing reporting obligations.

1.3.4.2 FEDERAL REGULATION

The federal regulatory efforts focus on the federal financing of stem cell research and the regulation of research using federal funding. Federal funding for hESC research was first envisioned in the 1994 report of the Human Ethics Research Panel.[201] This was followed in 1996 by the Dickey-Wickers amendment[202], a rider attached to the Balanced Budget Downpayment Act 1996, implementing a ban on spending federal money on stem cell research. It prohibited the use of federal funding for the creation of human embryos for research purposes and research in which human embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on

[196] Available at www.ncsl.org/default.aspx?tabid=14413.
[197] Available at www.cirm.ca.gov/files/PDFs/Administrative/prop71-3.pdf.
[198] Available at www.leginfo.ca.gov/cgi-bin/waisgate?waisdocid=76297528920+0+0+0&waisaction=retrieve.
[199] Available at www.cirm.ca.gov/cirm-operations/Regulations.
[200] Available at www.cdph.ca.gov/services/boards/HSCR/Documents/MO-HSCRGuidelines-10-2008.pdf.
[201] Human Ethics Research Panel, *Report of the Human Embryo Research Panel*, (Washington, DC: National Institutes of Health, 1994).
[202]

foetuses under federal regulation. The 1999 NBAC Report[203] suggested the exemption from the ban of research on (stem cell derivation from) supernumerary IVF embryos from a parental project.

The NIH, the agency responsible for distributing federal research funding in the life sciences, sought legal advice regarding federal funding ban. Harriet Rabb's legal advice contended that the ban only excludes the derivation of hES cells from an embryo from funding allowing further federally funded research on the hESC lines available to the NIH. The argument put forward in this regard was that the Dickey-Wickers amendment only spoke of human embryos and not stem cell lines.[204]

The 2001 presidential address by the Bush administration reaffirmed the legal position under the federal funding ban allowing federal funding for the available 'presidential' hES cells.[205] The Obama administration's 2009 Executive Order[206] indicated that research will be eligible for federal funding if it is responsible and scientifically worthy and must be permitted by law.

The detailed rules of federal funding are provided in the 2009 NIH Guidelines for Human Stem Cell Research.[207] The guidelines provide two key principles: responsible research with hES cells, as they are valuable tools of basic biomedical research, leading to therapeutic application and free donation of embryos having obtained voluntary and with informed consent. For research on available hESC cells to be eligible for federal funding it must be demonstrated that they have been derived from donated IVF supernumerary human embryos from a parental project. The guidelines provide, in line with the Dickey-Wickers amendment, that NIH federal funding cannot be used for the derivation of stem cells from human embryos and research using hES cells derived from other sources, including SCNT, parthenogenesis, and/or IVF embryos created for research purposes, is not eligible for NIH funding. The federal guidelines are not applicable to privately funded hESC research.[208]

The most recent development in the federal funding debate was the 'Lambert injunction' served by a US District Court on 23 August 2010 against the spending of federal funds under the new guidelines.[209] In examining the case for an injunction the court found that the 2009 NIH Guidelines violated the Dickey-Wickers amendment which in the court's view explicitly prohibited the use of federal funding for research in which a human embryo or embryos are destroyed. The argument that not all elements of research are affected by the restriction, making hES cells derived before the federal funding ban eligible for federal funding, was rejected as in the court's interpretation the legislation's intent covered all research in which an embryo is destroyed. If the Dickey-Wickers amendment was only to cover acts directly connected to embryo destruction, such as hESC derivation, the legislature would have enacted the act expressing that particular limitation.

Building on this, the court went on to conclude that hESC research must be considered as research in which the human embryo is destroyed and rejected that actual research on hESC

[203] National Bioethics Advisory Commission, *Ethical Issues in Human Stem Cell Research* (1999), available at bioethics.georgetown.edu/pcbe/reports/past_commissions/nbac_stemcell1.pdf.
[204] Parens (2001), at 38.
[205] *Address to Nation on Stem Cell Research from Crawford Texas*, 37 Weekly Compl. Pres. Doc. 1149 (9 August 2001) and Executive Order No. 13,435, 72 Fed. Reg. 34,591 (20 June 2007).
[206] Executive Order 13505 of March 2009, available at edocket.access.gpo.gov/2009/pdf/E9-5441.pdf.
[207] NIH Guidelines for Human Stem Cell Research, available at stemcells.nih.gov/policy/2009guidelines.htm.
[208] Non-NIH guidelines may be used instead, such as the National Academies` Guidelines: Final Report of the National Academies` hESC Research Advisory Committee and 2010 Amendments to the National Academies` Guidelines on hESC Research, available at www.nap.edu/catalog.php?record_id=12923.
[209] United States District Court for the District of Columbia, Civ. No. 1:09-cv-1575 (RCL).

lines can be separated from the act of derivation of hESC from human embryos. This outcome is rather similar to the position of the German court in the Brüstle case stating that research on hES cell lines cannot be separated from the prior destruction of human embryos.[210] The injunction used the terms "it necessarily depends upon the destruction of the human embryo" and the derivation of hESC from an embryo is "an integral step" in conducting hESC research.

In response to the injunction, the NIH suspended the financing of research on the available hESC lines. The NIH Director's response to the injunction suggested that scientific and therapeutic progress should be given priority when the hESC lines are already available.[211] A few weeks later the Lambert injunction was ordered to be stayed in appeal[212] and the NIH lifted the suspension on funding.[213] The lawsuit continued June 2011 with the exchange of briefs.

These features make the US regulatory system unique. With the separation of public and private, state and federal it is difficult to treat the US as a homogenous system. There is internal diversity between state regulations and between state and federal policy. Further, the boundaries of permitted biomedical research activities remain contested.

1.3.5 LOCAL REGULATION: ASIA

Mapping the regimes of Asia further supports the contention that diversity reigns in biomedical research regulation. The social and cultural particularities of Asian states suggest profound differences from Western regimes which, however, on the level of regulation remain unsubstantiated. The selected Asian states, China, India, Japan and South Korea have adopted biomedical research regulations, either in legal measures or legally non-binding guidelines, which incorporate similar bioethical principles and detailed regulation relating to those principles available in Western regimes. This demonstrates the influence of international instruments and Western jurisdictions, for instance the UK. Following Western patterns in bioethical regulation indicates adherence to Western bioethical standards.

In many of these countries the state is actively involved in promoting scientific research and generating social and political support. Biotechnological firms are applauded as front runners of the economy (Beike Biotech, China),[214] scientists who report a breakthrough are elevated to the status of national celebrities (Hwang in South Korea) and innovative research centres receive special status and earmarked state investment (CiRA at Kyoto University, Japan).[215] In Asian states, for instance in India, there is considerable political and social pressure on biomedical research to produce results which would be applicable in therapy.

Regenerative medicine in Asian states has not avoided public controversies. They related to offering stem cell therapies globally without conducting prior clinical trials and establishing clear therapeutic benefits (Beike Biotech, China),[216] unsupervised therapeutic practices by private providers (India) or publishing falsified research results from research conducted in breach of bioethical principles (Hwang in South Korea).

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[210] See Part 2.
[211] Available at www.nih.gov/about/director/08262010statement_stemcellinjunction.htm.
[212] United States Court of Appeals for the District of Columbia Court, No. 10-5287, 9 September 2010.
[213] Available at www.nih.gov/news/09102010_stemcell_statement.htm.
[214] www.beikebiotech.com/index.php?option=com_content&view=article&id=406:china-breaks-ground-on-largest-comprehensive-stem-cell-storage-and-processing-facility&catid=10.
[215] www.jsps.go.jp/english/e-first/selected_p.html.
[216] www.escif.org/ESCIF,,extra_navi,unproven_therapies,unproven_therapies.htm.

The Asian states under scrutiny have either intermediate or permissive regimes on biomedical research. Japan and South Korea have permissive research regimes. India and China has implemented an intermediate system. The Asian regimes are not dissimilar from regimes in other parts of the world (e.g. UK).[217] They enable similar human embryonic research practices, however, they may differ in the form and detail of regulation, the safeguards they make available and the way they monitor and supervise the functioning of the system.

Biomedical research regulation is produced in different forms in these states. China and India adopted non-legal guidelines, Japan has legislation and guidelines in place and South Korea decided to utilize a binding legal measure. The monitoring and enforcement of these regulations face considerable difficulties in some of these states.[218]

A common point in the research regulations under examination, and in research regulatory systems in other parts of the world, is that they all prohibit reproductive cloning. In China reproductive cloning was first prohibited by the 'Four No-s' policy of the Ministry of Health (no to endorsing, permitting, supporting and accepting reproductive cloning experiments)[219] and was subsequently reaffirmed in the 24 December 2003 'Ethical Guiding Principles on Human Embryonic Stem Cell Research'.[220] The Indian ethical guidelines for stem cell research (2007) prepared by the Indian Department of Biotechnology and the Indian Council of Medical Research prohibit reproductive cloning in Article 6.3.[221] Reproductive cloning is prohibited in South Korea in the Bioethics and Safety Act 2004 (Article 11)[222] as it is in Japan in the Act on Regulation of Human Cloning Techniques 2000.[223]

Stem cell research is subject to principles similar to those in other regimes in the world. Supernumerary IVF embryos from a parental project and SCNT embryos are regarded as legitimate sources of hES cell lines.[224]

South Korean law provides a legal definition of the moral status of human embryos.[225] The South Korean Constitutional Court held in 2010[226] that early-stadium human embryos

[217] The similarity of the Chinese arrangements with UK regulations was emphasised in the Medical Research Council – China UK Research Ethics (MRC-CURE) Report 2009, available at www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC006303. The Japanese regime's similarity with that in UK was indicated by the UK Stem Cell Initiative's (UKSCI) country file, available at www.advisorybodies.doh.gov.uk/uksci/global/japan.htm.

[218] On enforcement problems see, Dominique S. McMahon and Halla Thorsteinsdóttir, Lost In Translation: China's Struggle To Develop Appropriate Stem Cell Regulations, 7(2) August, SCRIPT*ed* (2010) 283, at 287-288 and Margaret Sleeboom-Faulkner, *Human Embryonic Stem cell Research (hESR) in East Asia: An Institutional Approach to Bioethical Reorientation*, Full Research Report, ESRC End of Award Report, RES-350-27-0002 (Swindon: Economic and Social Research Council, 2009).

[219] Dominique S. McMahon *et al*., Cultivating regenerative medicine innovation in China, 5(2) *Regen. Med.* (2010) 35, at 40. UKSCI reported a 1998 government declaration prohibition reproductive cloning, available at www.advisorybodies.doh.gov.uk/uksci/global/china.htm.

[220] Ethical Guiding Principles on Human Embryonic Stem Cell Research, available at www.qmlc.com.cn/edit/UploadFile/info/2009430113029216.doc.

[221] Ethical Guidelines for Stem Cell Research, available at www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf.

[222] Bioethics and Safety Act 2004, available at eng.bprc.re.kr/gz06.htm?number=8.

[223] Act on Regulation of Human Cloning Techniques 2000, available at www.japaneselawtranslation.go.jp/law/detail/?re=02&dn=1&x=0&y=0&co=1&yo=&gn=&sy=&ht=&no=&bu=&ta=&ky=cloning&page=1.

[224] China: Ethical Guiding Principles on Human Embryonic Stem Cell Research, India: Ethical Guidelines for Stem Cell Research (Article 5), South Korea: Bioethics and Safety Act 2004 (Articles 17 and 22), Japan: Article 2 Act on Regulation of Human Cloning Techniques 2000.

[225] Interview with Professor Na-Kyoung Kim, Singshin University, REMEDiE, December 2010.

(between conception and 14 days after conception) are not subjects of human rights. It argued that early embryos may not be conceived as human beings as they only represent the beginning of the process of creating human life and before the development of the primitive streak they may not be treated in law as independent human beings. It concluded that the use of supernumerary IVF embryos, which will be discarded after the parental project, for research purposes is constitutional.

The creation of embryos by SCNT for research purposes were endorsed particularly strongly in South Korea. The South Korean act extensively regulates therapeutic cloning for the purposes set out in the Bioethics and Biosafety Act, a legacy of the Hwang era (Article 22). In the case of India the creation of research embryos using IVF for the specific purpose of deriving hESC lines is also permitted subject to the approval of the relevant supervisory bodies and researchers must establish that it is critical and essential for the proposed research.[227]

Human embryonic research is subject to further ethically based limitations. First, all the states under scrutiny have introduced a form of the '14-day rule' rule, familiar from other jurisdictions (UK), as a deadline for intervention on embryos available for research. China's guidelines speak of a deadline of 14 days after fertilisation or the nuclear transfer for hESC derivation. In India the similar rule is framed as 14 days after fertilisation or after the formation of the primitive streak, whichever is the earlier (Article 6.3). South Korea opted to implement a deadline which considers the evolution of the embryonic primitive streak in the developmental process (Article 17).[228] Japan also follows the 14 day rule (Article 4).[229]

The derivation of stem cells is permitted from other sensitive sources. China lists among the potential hESC sources fetal cells from accidental spontaneous or voluntarily selected abortions and germ cells voluntarily donated. In India human embryonic germ cells derived from primordial germ cells of the fetus may be used[230] and according to the Department of Biotechnology, Ministry of Science and Technology website aborted (spontaneous or induced) fetal tissue may also serve as a stem cell source.[231]

The 'supply side'[232] of hESC research is also regulated. The rules cover informed consent, procurement/donation, approval and supervision and non-commercialization.[233] The Indian guidelines even highlight the purposes for which hESC lines may be derived from embryos.[234] The South Korean regulation is closely tied to Hwang's rise and fall. The creation in 2004 and subsequent modification in 2008 of the Bioethics and Safety Act followed Hwang's change of fortune. This is not to say that Hwang's research was not conducted in a heavily regulated environment littered with guidelines on research and clinical conduct,

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[226] Case 2005/346 (27/05/2010).
[227] Articles 5 and 6.2.
[228] It also applies to SCNT embryos (Article 12.3 Enforcement Decree of the Act).
[229] See also The Guidelines for Derivation and Utilization of Human Embryonic Stem Cells, available at www.lifescience.mext.go.jp/files/pdf/32_90.pdf.
[230] Article 5.2, Ethical Guidelines for Stem Cell Research.
[231] Available at dbtindia.nic.in/uniquepage.asp?id_pk=118.
[232] MRC-CURE (2009), at 20. See also Brian Salter, *Bioethical Governance and Basic Stem Cell Science: China and the Global Biomedicine Economy*, Interim Draft available at access.kcl.clientarea.net/content/1/c6/03/03/66/wp25.pdf, at 11.
[233] China: Guiding Principles; India: Articles 6.1 and 11; South Korea: Articles 17-21; Japan: Stem cell guidelines: Articles 4 and 5. The Chinese regulatory principles resonate strongly Western bioethical principles, Salter, *ibid*. The regulation of supply in China and Japan was described as developed in Sleeboom-Faulkner, 2009.
[234] Article 9: increasing scientific knowledge, developing diagnostic and therapeutic methods, and increasing the ethnical (genetic) diversity of hESC lines.

however, their monitoring and genuine enforcement became secondary when research results promised economic growth and global scientific leadership.[235] In its current form the South Korean provisions regulate the storage and disposal of embryos (Article 16), the permitted research purposes for their use (Article 20.4) and the registration and distribution of stem cell lines (Article 20.2 and 20.3) The permitted sources of oocytes for SCNT are regulated in the Enforcement Decree of the Act (Article 12.3).

The Japanese guidelines specify the purpose of hESC research, which is basic research, and exclude further research before the adoption of the appropriate guidelines (Article 2). The permitted purposes within basic research, which must be scientifically necessary and rational, are biomedical research and research for therapeutic application (Article 26). A further important rule is that only such hES cells may be used for research which have been derived in accordance with the guidelines. Foreign hES cell lines may also be used in research provided they are classified as compatible with the guidelines (Article 27). The guidelines have introduced prohibitions concerning the handling of hES cells, such as the creation of an individual from hES cells, the introduction of hES cells into a human embryo or fetus and the production of germ cells from hES cells (Article 27). The guidelines also contain rules on hES cell line distribution (Articles 28 and 29).

Research regulation in these states covers other ethically sensitive areas. They all prohibit the implantation of research embryos into a human or non-human uterus.[236] Concerning hybridization, it is unclear whether in China the fusion of human genetic material with non-human eggs is prohibited. In 2002 a Chinese research team revealed that they were generating stem cells by transferring nuclei from human skin into rabbit eggs in an attempt to avoid the use of human eggs.[237] One report said it is not prohibited,[238] another stated that they heard conflicting views on this matter.[239] The 'Guiding Principles' do, however, prohibit the hybridization of human germ cells with germ cells of other species. Hybridization is prohibited in South Korea.[240] In India it is considered as a restricted area of research subject to approval by the supervisory authorities.[241] Hybridization in Japan is subject to rules similar to those applicable to hESC research with the exception that exportation and importation prohibited.[242]

Other sources of bioethical regulation in China[243] reveal further bioethical principles. The 2007 (11 January) new Regulation on Ethical Review of Biomedical Research involving Human Subjects states that (the ethical review of) research must be subject to the laws of China and "the recognized bioethical principles". Article 1 suggests that the interests of biomedical research must be reconciled with "protecting human life and health,

[235] Shawn H.E. Harmon and Na-Kyoung Kim, A Tale of Two Standards: Drift and Inertia in Modern Korean Medical Law, 5(2) August SCRIPT*ed* (2008) 267, at 268. The regulatory instruments are: Guidelines for Good Clinical Practice 1987, Guidelines on Human Stem Cell Research and Supervision 2001, Guidelines of Ethics for the Medical Professional 2001, Guidelines on Research on Cloning Lives 1999.
[236] China: Guiding Principles; India: Article 6.3; South Korea: Article 11; Japan: Article 3 of Act.
[237] Available at www.advisorybodies.doh.gov.uk/uksci/global/china.htm.
[238] McMahon, Cultivating regenerative medicine innovation (2010), at 39.
[239] MRC-CURE (2009), 20.
[240] Article 12: transfer of embryos between two different species.
[241] Article 6.2.
[242] Guidelines for Handling of a Specified Embryo 2001, available at www.lifescience.mext.go.jp/files/pdf/30_82.pdf.
[243] Available at www.chinaphs.org/bioethics/regulations_&_laws.htm#_Toc161968266. See also MRC-CURE (2009), Report Appendix.

safeguarding human dignity, respecting and protecting the legal rights and interests of human subjects."

The 1998–2003 Interim Regulations on the same subject indicate striking a balance between the protection of human life and dignity and the basic bioethical principles and promoting the development of biomedical sciences (Article 1). The regulations prohibited reproductive cloning and interestingly "any research using human embryo and aborted fetus" (Chapter 8, Article 25). The selling and buying of human cells, tissues and organs were also prohibited.[244] The 2003 Ministry of Health Guidelines on Human Assisted Reproductive Technologies provides prohibitions similar to that in the stem cell Guiding Principles.

1.3.5.1 CHINA

In explaining the Chinese approach to biomedical research regulation the underlying bioethical and cultural viewpoints prevailing in society can be recalled. In China reports suggested that embryos are not regarded as human life which should be protected from destruction. Chinese culture does not see an embryo as a person and people are indifferent about the potential ethical controversies of stem cell research. One report[245] indicated that stem cell research is conceived as acceptable by the population. The same source confirmed that SCNT and other forms of contested technologies represent "no serious cultural and societal problems" as they are widely supported. New medical technologies are seen as able to improve the human condition and "the general population may also be highly supportive of technologies that are based around the idea of using the body to heal itself, which one interviewee said fit well with the concepts of popular traditional Chinese medicine."

McMahon et al. in a 2010 paper based on interviews with Chinese experts pointed out that

> There was a consensus amongst our interviewees that these permissive regulations are supported by Chinese culture and values, and that many of the oppositions to stem cell research prevalent in the Western world are absent.[246]

Further, they suggested that the Chinese population does not regard an embryo as having personhood making the creation and use of embryos for research purposes ethically uncontested in China. This is matched by the approval by the public of new technologies which are thought to increase general welfare and individual well-being by giving rise to new therapeutic applications.[247]

A similar finding was made by the UK Stem Cell Initiative (UKSCI) report concerning the public perception of hESC research in China which places the importance of potential medical benefits over the protection of the moral status of human embryos. The UKSCI also reported that in China hESC lines have been produced from supernumerary IVF embryos, therapeutic human embryonic cloning for harvesting hESC lines has taken place with success and stem cell lines have been isolated from human foetuses with a view to carry out large-scale transplantation studies in primates.[248] The widespread application of stem cell

[244] This is also prohibited in the Regulations on Human Assisted Reproductive Technologies 2001.
[245] McMahon, Lost in Translation (2010), at 290-291.
[246] McMahon, Cultivating regenerative medicine innovation (2010), at 39.
[247] *Ibid.*, at 40.
[248] Available at www.advisorybodies.doh.gov.uk/uksci/global/china.htm.

therapies in the clinical environment[249] and China as a primary destination in stem cell tourism[250] also support these conclusions.

Another report suggested that there are lesser inhibitions with regards embryo destruction for research purposes in China as compared to Western countries. An important factor in this is the abundance of frozen IVF embryos due to the Chinese one-child population control policy and the technology used in IVF. The only possible option for couples if they wish to give utility to the frozen embryos is to donate them for research purposes as donation to other couples is forbidden and would breach principles of kinship and family.[251]

Other reports emphasized moral pluralism and diversity in China and spoke about the coexistence of old moral traditions and new Western ethical principles in society.[252] Chinese attempts in bioethical regulation have been characterized as building through regulation a universal bioethical common ground with 'Chinese particularities' to represent Chinese culture and society.[253]

China has been an active player in shaping the global bioethics agenda[254] and its stem cell guidelines forms part of global bioethical consensus on stem cell research.[255] An interview with Ren-zong Qiu revealed that in drafting the stem cell guidelines there was emphasis on local and global dialogue between different stakeholders and other actors, regulators, bioethicists and scientists, with a view to ensure that the bioethical framework for research activity will be broadly accepted.[256]

Pluralism in Chinese bioethics was also supported by interviews included in a recent report where the interviewees revealed that biomedical regulations in China were designed "within the context of Chinese religion and culture while also taking into account the internationally accepted ethical norms."[257] The MRC-CURE report suggested that China has accepted the relevant international (Western) bioethical documents and guidelines, however, their effective local implementation may be lacking and they do not exclude application of 'non-Western' principles.[258]

As to 'non-Western' principles Confucianism provides the primary source. In the Confucian tradition a human being begins with birth, a baby born is considered one year old and although it acknowledges the continuity between the fetus and the baby born alive, the fetus is not regarded as a human being or a person. Value lies not in human life but in living life in an ideal way.[259] In Taoism human life and death are not particularly important ethical issues, which also applies to Buddhism.[260]

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[249] See MRC-CURE (2009), at 21.
[250] Aaron D. Levine, Stem Cell Tourism: Assessing the State of Knowledge, 7(2) August SCRIPT*ed* (2010).
[251] Boon Chin Heng, Growing Surplus of Frozen Embryos in China Offers Opportunities for the Development of hESC Banking, Editorial, 2(6) *Regen. Med.* (2007) 873-874, at 873.
[252] Ole Döring, China's Struggle for Practical Regulations in Medical Ethics, *Nature Reviews Genetics*, vol. 4 (2003): 233–239, at 236.
[253] *Ibid.*, 233. Adherence to the universal common ground: China endorsed the WMA Helsinki Declaration (2000) and the UNESCO Universal Declaration on Human Rights and Biomedicine (1998).
[254] Salter, Bioethical governance, at 8.
[255] *Ibid.*, 9.
[256] Interview with Prof Ren-Zong Qiu, REMEDiE, 2010.
[257] McMahon, Lost in Translation (2010), at 290.
[258] MRC-CURE (2009), at 9.
[259] Ren-Zong Qiu, *Medical Ethics and Chinese Culture*, in Edmund D. Pellegrino, *et al.* (eds.) *Transcultural Dimensions in Medical Ethics* (Frederick, MD: University Publishing Group, 1992), at 169.
[260] *Ibid.*, at 169–170.

The MRC-CURE report pointed out that beyond informed consent it is unclear to what extent Confucianism influences research ethics in China. The report mentions divergent opinions in this respect, one attaching a significant influence to Confucianism in Chinese bioethics so as to make it different from the bioethics of the West, the other stating that traditional values are undergoing radical changes in China and, in any case, the cultural-ethical landscape is characterized by multiplicity as in any other country. The report highlighted that there are contrasting views on the moral status of the human embryo, but public discourse in this matter has been limited.[261]

A further report[262] recalled a view (Ren-zong Qiu) which held that following the Confucian view, which holds that a person begins with birth as only after birth has it a body, a shape and psyche and rational, emotional and social-relational capacity, an embryo is not a person and killing an embryo may not be equated with killing a person. On the other hand, a human embryo is the beginning of human biological life, therefore, it deserves respect. The duty to protect the embryo, however, does not extend to excluding the manipulation or destruction of the embryo when sufficient reasons require so, for example, saving human lives.

The same report referred to another opinion (Yanguang Wang) which suggested that provided that there are alternative sources for the derivation of hES cells human embryo destruction must be avoided. Similarly, if supernumerary IVF embryos are available the creation of embryos for research purposes must not be regarded as necessary. The creation of embryos for research by IVF or SCNT may only be permitted if supported by sufficient reasons.

A third Chinese opinion, mentioned in the report (Ziying He) approached the question from the perspective of the observer. It suggested that people feel differently towards an embryo, a mass of cells, and towards a living human being. Another cluster of opinion held that the benefit for patients and the public interest justified hESC research. An alternative opinion held that the above opinions are the product of collectivism based on Confucianism which puts the benefit and welfare of the community or nation before the protection of an embryo. A legal opinion voiced that the rights of the embryo under the law on inheritance make it a legally recognizable entity, the rights and dignity of which must be fully protected.

Another report suggested that most members of the Chinese scientific community believe that a human embryo merely represents biological life and not human life, therefore, it does not have the same value as a human being. It does not follow, however, that biological life should not be protected and should not be given respect and appropriate treatment in research. Research should be subject to bioethical principles on biomedical research such as necessity, informed consent and voluntary donation, safety and efficiency and non-commercialization.[263]

1.3.5.2 SOUTH KOREA

In mapping the South Korean approach regarding the ethical boundaries of biomedicine the importance of science in the national imagination as a building block of growth and nation

[261] MRC-CURE (2009), at 8.
[262] Yanguang Wang, *Chinese Ethical Views on Embryo Stem (ES) Cell Research*, in Song Sang-yong *et al.* (eds.), *Asian Bioethics in the 21st Century*, available at www.eubios.info/ABC4.htm.
[263] Benfu LI, *The Significance of Human Embryo Stem Cell Research and its Ethical Disputes*, in Song Sang-yong *et al.* (eds.), *Asian Bioethics in the 21st Century*, available at www.eubios.info/ABC4.htm.

building must be taken into account.[264] Scientism as a cultural element has determined South Korean economic and research policy within which biotechnology was given a primary role, subject to the restraints in biomedical research regulation, such as a the Bioethics and Biosafety Act 2004.[265] Scientific progress for the common good has been said to trump the ethical principles protecting the individual.[266] Confucian values, the importance of family relations, were reported to be diminishing in the clinical setting[267] and the impact of familism on individual provisions of biomedical law is difficult to trace, although it is present for example in the area of organ transplantation as regulated by the Organ Transplantation Act 2000.[268] The exposure of Hwang's scientific misconduct and deliberate breach of basic bioethical principles, such as non-commercialisation and informed consent, which meant the exploitation of the more than 100 female donors of more than 2000 oocytes, was a sobering experience. The creation and use of human embryos without producing concrete scientific results was condemned as an unacceptable waste.[269]

A report on the moral status of embryos suggested that the manipulation of human embryos is generally regarded as acceptable in South Korean society. Public opinion regards advancements in hESC research as social and economic triumphs. The report also mentioned a Buddhist opinion according to which the destruction of embryos for research purposes could be seen as an offering in a Buddhist sense for the people with incurable diseases.[270]

In an interview[271] Na-Kyoung Kim indicated that the considerable distance between biomedical regulation and traditional South Korean social values can be explained by biomedicine and bioethical regulation being a recent development. In this process the dominant Western ideologies found their way into the South Korean debate without much resistance from traditional value sets which had been unprepared to address the biotechnological revolution. The interview highlighted that there is no clear distinction between the local and the Western debate, and the general legal and policy environment of biomedical research resembles that in other countries in the world without acknowledging particular local or Western influences in South Korea. Further, in South Korea the dominant religions, Buddhism, Catholicism and Protestantism, which coexist peacefully in the pluralist South Korean society, has not launched attacks on government economic and research policy and regulation.

It has been suggested that the South Korean regime represents a triumph of scientific interests. Avoiding substantive change after the Hwang scandal was regarded as a sign of continuing dominance of science and economic benefits in the South Korean collective imagination.[272] South Korea remains "clung to the desire to promote biotechnology and not unduly hinder biotech development."[273]

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[264] Harmon (2008), at 268.
[265] Interview with Prof. Na-Kyoung Kim, Singshin University, REMEDiE, December 2010.
[266] In particular, with respect to oocyte donation for SCNT projects, see www.advisorybodies.doh.gov.uk/uksci/global/korea.htm.
[267] Harmon (2008), at 293.
[268] Interview with Prof. Na-Kyoung Kim, Singshin University, REMEDiE, December 2010.
[269] See, National Bioethics Committee's Report on Bioethical Problems in Hwang Woo-suk Research (2008), available at eng.bprc.re.kr/gz06.htm?number=4.
[270] Young-Rhan UM, *Dispute over Scientific Research Involving Human Embryos in South Korea*, in Song Sang-yong *et al.* (eds.), *Asian Bioethics in the 21st Century*, available at www.eubios.info/ABC4.htm.
[271] Interview with Prof. Na-Kyoung Kim, Singshin University, REMEDiE, December 2010.
[272] Harmon (2008), at 293.
[273] *Ibid.*, 281.

1.3.5.3 INDIA

In India government policy is generally supportive of biomedical research and urges the development of therapeutic applications.[274] The highly detailed ethical guidelines for stem cell research (2007) prepared by the Indian Department of Biotechnology and the Indian Council of Medical Research intends to strike a balance between the therapeutic potential of stem cell research and the ethical and socio-economic implications thereof.[275] The protection of donors, research subjects and patients is considered being of primary importance. In its introduction it appears sympathetic towards hESC related technology, such as SCNT (Article 1). Nonetheless, it also aspires to ensure compliance with the relevant bioethical principles, in particular, with those established in the "Ethical Guidelines for Biomedical Research on Human Participants" issued by the Indian Council of Medical Research (Article 2 and 3).

The research guidelines actually specify what scientific and therapeutic progress is expected from stem cell research (Article 9). While the Indian regime is geared towards promoting research it appears to have regard to the ethical and social consequences of scientific activity. Article 10 of the guidelines expressly mentions the duty of researchers to take account of public concerns relating to human embryonic research and Article 11.7 mentions that any clinic/research personnel who have a conscientious objection to hES cell research should not be coerced to participate or impart information.

The broader social focus of scientific research regulation in India is more apparent in the 2006 'Ethical Guidelines for Biomedical Research on Human Participants'.[276] This document entails a part named 'General Statement' which sets as the purpose of biomedical research to gain knowledge "about the human condition in relation to its social and natural environment, mindful that the human species is one of the many species of this planet." It includes further important principles, such as non-commodification, non-exploitation, human dignity, public interest and distributive justice.

The social implications of biomedical research have also been taken into account with regards to patenting in the stem cell guidelines. In Article 15 it was expressed that the commercial exploitation of stem cell research through IP rights was beneficial, however, the benefits arising from commercialization must be returned to the community which has contributed to the commercial success of the invention, in particular, patient groups and researchers. It was reported that the Draft Guidelines wanted to leave the patenting issue open which could have resulted in a more heavily contested patenting practice such as that in European patenting before the EPO.[277] The current wording of the guidelines only mentions benefit-sharing as an essential condition in commercialization.

A similar view was taken regarding patenting in gene research in the 'ethical policies' formulated by the Ministry of Science and Technology, Department of Biotechnology.[278] The documents includes the familiar condition that the human genome, part of human body or any human material in its natural state cannot become the subject of a direct financial gain which, however, does not exclude human gene patenting subject to the applicable national

[274] Prasanna Kumar Patra and Margaret Sleeboom-Faulkner, Bionetworking: Guidelines and Practice in Stem Cell Therapy Enterprise in India, *SCRIPTed* , vol. 7, no. 2 (August 2010): 295, at 298.
[275] Available at www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf.
[276] Available at www.icmr.nic.in/ethica_guidelines.pdf.
[277] Saionton Basu, Regulating Stem Cell Research in INDIA: Wedding the Public to the Policy, *Current Science*, vol. 90, no. 11 (2006): 1478, at 1478.
[278] Available at india.gov.in/outerwin.php?id=dbtindia.nic.in/uniquepage.asp?id_pk=113.

and international rules. The document also speaks in a very detailed manner about benefit sharing, in particular, by suggesting that profit making entities should dedicate a percentage of their earnings arising out of the knowledge they derived by the use of human genetic material to the benefit of the community.

In an interview conducted with Professor Ananda Chakrabarty the Indian patent system was described as market driven with the production of wealth and social development in its focus. By means of protecting inventions in the biomedical field it intends to contribute to increasing the quality of life in India and enhancing accessible therapies to individuals. He concluded that expanding the morality clause in Indian patent law to include the 'embryo destruction' principle, as in Europe, must make allowances for the social advantages attainable through the patent system.[279]

To achieve a more complete picture of the Indian moral landscape the findings of a recent report must be mentioned. It highlighted that in India public debate concerning the religious and ethical boundaries of biomedical research is absent. Scientists are not required to enter into a debate about when life begins and they can pursue their scientific goals without facing any ethical hurdles concerning human embryonic research. It was reported that religious, political and political concerns do not conflict with research activity.[280]

The report also pointed out that while activities falling under the state regulatory umbrella receive minimal bioethical challenges, private endeavours into stem cell therapy and research are often regarded as controversial and receive negative public opinion. It speaks of "moral and ethical comfort zones" of peer reviewed and regulated science and uneasiness in India with unscrutinised science.[281]

A 2010 paper highlighted that despite strict state level regulation on stem cell research and therapy, stem cell therapy is offered by a considerable number of providers.[282] The report indicated that the impact of the guidelines is especially limited in the private sector, where institutions and individual practices claim to provide treatment by stem cell technology with success in violation of the stem cell therapy guidelines. The shaft between the public and the private sector with regards to compliance with the research guidelines and the shortcomings in regulatory oversight can be explained by the lack of enforceable regulation paired with effective sanctions in the field which is thought to be remedied by a new bill, the Biomedical Research on Human Participants: Promotion and Regulation Bill 2007.

1.3.5.4 JAPAN

The Japanese system, akin to other permissive systems, is based on a compromise between enabling hESC research and ensuring that the principles of biomedical research are observed. The Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells while accepting the scientific advantages of stem cell research appears to show great concern to its ethical implications. It accepts that the human embryo is the beginning of human life and wishes to reconcile this with the fact that human embryos are the sources of

[279] Interview with Ananda Chakrabarty, REMEDiE, 17/9/2010.
[280] Aditya Bahardwaj and Peter Glasner, *Local Cells, Global Science: The Rise of Embryonic Stem Cell Research in India* (Abingdon: Routledge, 2008), at 83–84.
[281] *Ibid.*, 86–91.
[282] Patra and Sleeboom-Faulkner (2010).

hESC lines valuable for research. In this respect, it sets out fundamental bioethical rules in order to avoid the violation of human dignity in hESC research.[283]

The details of protecting human dignity in hESC research are revealed in Article 3 which speaks about the careful and conscientious handling of human embryos and hES cells taking into consideration that a human embryo is the beginning of human life. However, this does not entail excluding the human embryo as a source of hES cells. Regarding supernumerary IVF embryos from a parental project their special treatment is specified as ensuring that they will not be used for the original purposes and they will surely be discarded by the donors (Article 6).

An ESCR report suggested that the emphasis on the careful handling of embryos is prompted by a fear of scandal and strong social control over research activities. This in turn resulted in a widespread awareness among scientists of the need to respect the human embryo, even though this does not characterize every researcher's approach.[284] The details of the Japanese regulations led the same report to conclude that the Japanese regime was strict keeping research activity under close scrutiny.[285] The same report mentioned that hESC research has a high value in Japan due to the rapid aging of society hoping that science will bring cures.

Another report[286] pointed out that human dignity has traditionally played a central role in debates on hESC research in Japan. The direction of the debate differed from that in Europe, in particular, in Germany, as the Japanese interpretation of human dignity differs from the European approach which only speaks about the dignity of humans leaving other living beings out of consideration. The report also mentioned that the debate in Japan about whether the instrumentalization of human embryos breached human dignity was much less intensive. The reason for this was that the dominant ethical approach regarding human embryonic research does not conceive embryos as persons or subjects with rights, only as entities which deserve respect in their treatment.

1.3.6. Summary

Beyond shared core bioethical principles, such as respect for human dignity, the global landscape of biomedical research regulation is characterized by diversity and contested boundaries. The ethical and political opinions expressed reveal a multiplicity of competing positions regarding the ethical limits of biomedical research activity. The arguments would follow a utilitarian line, establish a compromise between competing values or stand for an absolute protection of human life and integrity. The overarching global and regimes guarantee respect for diversity and the local appreciation of bioethical dilemmas.

Mapping the multi-layered European landscape reveals similar characteristics. The European level while establishing a common framework, which may be introduced on human rights grounds, acknowledges local diversity and leaves drawing the controversial boundaries of biomedical research to the local level. The human rights approach, a distinctively European development, sustains European diversity. On the national level there is considerable divergence, in particular, in defining the moral status of the human embryo and regulating acceptable biomedical practices.

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[283] Preface of Guidelines, available at www.lifescience.mext.go.jp/files/pdf/32_90.pdf.
[284] Sleeboom-Faulkner (2009).
[285] *Ibid.*
[286] Jun Matsuda, *The Regulations for Research on Human Embryos in Japan and Germany*, available at www.hss.shizuoka.ac.jp/shakai/ningen/staffs/matsuda/20070622.pdf.

The US represents a particular case of ethical and legal heterogeneity. On the federal level there is sign of oscillation between a liberal ethical approach respecting the pluralism of views and a conservative position advocating among others a full moral status of embryos. Positions on state level may differ from the federal approach and from viewpoints adopted in other states. The US faces the problems of its own multi-layered system where federal and state competences for the regulation of biomedical research are separated and the application of federal policy extends only to federally funded research leaving privately financed research comply with a private system of bioethical principles.

The Asian regimes contribute further to global diversity in regulating the bioethical boundaries of biomedical research. There is evidence of considerable Western influences with Western ethical principles, such as the '14-day rule' in human embryonic research, filling the 'bioethical vacuum'[287] left by traditional principles. Adherence to and the monitoring and enforcement of these principles is, however, often lacking. In some instances, there is evidence of a separation between public rules and private practices.

The Asian societies examined are characterised by a pluralism of Western and traditional value systems. Nonetheless, the prevailing attitude to biomedical research is supportive raising no moral objections against practices which may be condemned in European societies. Biomedical research practices are culturally accepted. The ethical debate on life sciences is often muted. The value of human life, especially in the earliest stages, and its worthiness for protection are reported to be approached from viewpoints different from those in Western societies. A gradualist viewpoint is legally expressed in South Korea. Priority is given over early human life to the interests and needs of society, obtaining the benefits of scientific progress and the development of new therapies to tackle public health crises. The social and equity aspects of biomedical advances are given considerable weight in India.

1.4. Human dignity and global diversity

The various ethical, political and legal documents on biomedical research, despite their considerable diversity on local, regional and global levels, identified human dignity as a common benchmark for biomedical research activity. Human dignity was relied upon in debating and regulating biomedical research practices facing the contentious issue of the moral status of human embryos. The international documents on biomedical research (the UNESCO Universal Declaration on the Human Genome and Human Rights and the Council of Europe Oviedo Convention on Human Rights and Biomedicine) declared that in biomedical research respect for human dignity must be ensured and research activity must be conducted subject to safeguards for the protection of human dignity and fundamental rights. Human dignity now forms part of European patent law relating to biomedical inventions as indicated in **PART 2**.

The question we need to examine is whether human dignity can serve as a benchmark in a pluralist ethical and regulatory environment, such as that of biomedical research.

Following the distinction between the two dominant functions associated with human dignity in bioethics, 'human dignity as empowerment' and 'human dignity as constraint',[288] human dignity in the biomedical context represents the individual's autonomy and self-

[287] Sleeboom-Faulkner (2009).
[288] Deryck Beyleveld and Roger Brownsword, *Human Dignity in Bioethics and Biolaw*, (Oxford: OUP, 2001), at 11.

determination, expressed in the principle of informed consent, and establishes the limits of scientific intervention for the protection of the individual concerned or for the purpose of upholding the values shared by the community. The fundamental bioethical principle of informed consent of human research subjects and patients, laid down among others in the 1974 Nuremberg Code and the 1964 World Medical Organization Helsinki Declaration, represents the interpretation of human dignity as the individual's right of self-determination. In contrast, 'human dignity as constraint' in contemporary bioethics means that "biomedical practice (...) should be driven, not by the vagaries of individual choice, but by a shared vision of human dignity that reaches beyond individuals."[289] Opinions differ whether this shared vision of human dignity is determined locally in a particular society or can be imposed universally as a value protected in any civilized society.

In this logic, respect for human dignity imposing a limitation to biomedical research appears as a communitarian value. This interpretation of human dignity conflicts with the traditional principles of bioethics, such as autonomy, beneficence, non-maleficence and justice, which emphasize the importance of individual autonomy and establish the limits to scientific or medical intervention from an individualistic perspective. Constraining biomedical research or therapeutic intervention on grounds of human dignity as a shared value represents a step beyond safeguarding individual autonomy and focuses on protecting human dignity in instances where individual autonomy is impaired or not available. In this sense, human dignity supplements the bioethics based on individual autonomy.

The Oviedo Convention, as suggested by Plomer, incorporate both functions of human dignity as its provisions at the same time promote the autonomous choice of individuals in biomedical research and impose limits on human research activity for the protection of humanity, of "the rights and dignity of the human species as a whole."[290]

This universalistic aspiration of the Oviedo Convention relying on the interpretation of human dignity as a communitarian value appears to be at odds with its dedication to sustain European value pluralism and respect the local appreciation of contentious bioethical questions, such as human embryonic research. Europe's pluralism requires a concept which acknowledges the social and cultural contingency of human dignity. A universal concept of human dignity is claimed to ignore social and cultural diversity and in Robert Baker's words leads to 'cultural blindness'.[291]

The socio-cultural relativist concept of human dignity is not without criticism. Challenges against this interpretation of human dignity as a useful concept in bioethics range from claims which contend that as a result of unworkable relativism human dignity in the bioethical domain has been reduced to respect for individual autonomy[292] and human dignity means no more than human equity,[293] or that a relativist concept of human dignity gives way to mere "olfactory moral philosophy" which simply relies on our "moral nose".[294]

Human dignity fits into the 'principlism' of modern bioethics producing a fundamental principle to which actors of all beliefs and positions could adhere. However, its relativist and contextualist reading enables incorporating the drive in law and policy-making to

[289] *Ibid.*, at 29.
[290] Plomer (2005), at 38–39.
[291] Robert Baker, A Theory of International Bioethics: Multiculturalism, Postmodernism and the Bankruptcy of Fundamentalism, *Kennedy Institute of Ethics Journal*, vol. 8, no. 2. (1998), 203.
[292] Ruth Macklin, Dignity is a Useless Concept, *British Medical Journal*, vol. 327 (2003), 1419–1420.
[293] John Harris and John Sulston, Genetic Equity, *Nature Reviews Genetics*, vol. 5 (2004), 796–800.
[294] John Harris, Cloning and Human Dignity, *Cambridge Quarterly of Healthcare Ethics* , vol. 7 (1998), 166–167.

accommodate divergent, non-hierarchical visions of the bioethical limits of human activity. When the ethical principle of respect for human dignity is translated into the fundamental right of respect for human dignity in the legal domain pluralism and flexibility can be introduced to legal regimes enabling them to address issues on which moral opinions are divided, as proved by the Oviedo Convention.

The availability of human dignity as a benchmark for pluralistic regimes is reinforced by Plomer's contentions that "human dignity (and the right to life) are indeterminate concepts which admit different interpretations and applications depending on one's moral theoretical perspective" and "social convergence and agreement on the universal or fundamental character of general values such as human dignity or life need not therefore connote or reflect agreement on the particular interpretation or concrete application to be given to these concepts".[295] The communitarian interpretation of human dignity makes global diversity sustainable in biomedical research regulation.

The concept of human dignity may be broken down to the principles of non-objectification, non-instrumentalization and non-commodification/commercialization. These principles are essential in the treatment of human biological material for the purposes of biomedical research. Following the Kantian approach objectification refers to the prohibition of regarding human beings as means and not as ends. Human beings as ends have dignity which admits no equivalent in exchange (as opposed to objects which have a price) which excludes the fungibility of human beings.

In Wilkinson's terminology, objectification means "to treat as a mere object" something that it is not an object e.g. a human being. Instrumentalization is a specific form of objectification which stands for the wrongful use exploitation of things that are not objects. One form of wrongful use exploitation is the commodification of human beings.[296]

He also argued that the human body and its parts are more than objects due to their intimate relationship with the person. Following this logic, it is ethically objectionable when the human body or its part is treated as it is not intimately related to the person. He stated that "body-objectification is very much parasitic on the idea of person-objectification."[297] Campbell also contended that the human body is a material object different from others.[298]

Nussbaum listed seven ways of treating persons as objects. These are instrumentalization, which is treating a person as a tool or means to reach an objective, the denial of a person's autonomy, inertness, which is treating a person as lacking agency, fungibility, which is treating a person interchangeable with others, violability, which stands for a lack of respect of one's bodily integrity, ownership, which is treating a person as property, and denial of subjectivity, which is neglecting a person's experiences.[299]

Harris disagreed that the instrumentalization of the human body or body parts would represent an automatic breach of human dignity. He contended that blood transfusion represents an example of using others as means and it is generally conceived as compatible with human dignity.[300]

Following Wilkinson's definition commodification, a type of objectification, is a social practice or a legal arrangement which allows things to be bought and sold treating them as

[295] Plomer (2005), at 70–71.
[296] Stephen Wilkinson, *Bodies for Sale* (London: Routledge, 2003), 27.
[297] *Ibid.*, at 53–54.
[298] Alistair V. Campbell, *The Body in Bioethics* (Abingdon: Routledge-Cavendish, 2009), at 26.
[299] Martha Nussbaum, Objectification, *Philosophy and Public Affairs*, vol. 24 (1995), at 256–257.
[300] John Harris, *The Value of Life* (London: Routledge, 1965), at 143.

commodities. In a narrower, moral sense it is the morally objectionable practice of treating other human beings, the human body and its parts as commodities. In a normative sense, commodification means treating things as commodities which are not commodities.[301] It is expressed in the widely used legal definition that the human body and its parts shall not give rise to financial gain (Oviedo Convention).

The key concept under the non-commercialization principle is fungibility. In this context commercialization means treating persons, bodies and body parts as fungible, as interchangeable and not unique. Monetization is a further concept indicating the exchange of persons, bodies and body parts for money.

Radin, suggesting that commodities are alienable, fungible and commensurable, held that human bodies must be defined as 'contested commodities' as human beings, while have the freedom of choice to treat their bodies as commodities, have a more complex personhood which cannot be expressed in a purely commercial relationship involving a human being and his body parts.[302]

Beyleveld and Brownsword indicated that the non-commercialization doctrine creates a considerable tension within the concept of human dignity.[303] They stated that while disposing the human body or body parts for commercial gains is contrary to human dignity as it represents treating human beings as means and not ends, denying the choice to decide over our own body and body parts is in conflict with our personal autonomy and self-determination, also protected under human dignity. They concluded that the commodification of the human body and its parts is not a violation of human dignity, defined as personal autonomy, but it may be restricted in the case that human dignity as a value external to the self, the communitarian value, conflicts with the proprietary rights of the individual.

The non-commodification principle within human dignity, therefore, represents the point where the individualistic and communitarian concepts of human dignity clash. Provided that the communitarian concept of human dignity prevails another conflict becomes relevant, that between the universalistic and relativist interpretation of human dignity. While a universalistic approach may press for prohibiting the commodification of the human body and its parts, the relativist concept of human dignity allows for the local appreciation of whether the commodification of the human body and its parts is socially and culturally acceptable. The same applies to the non-objectification and non-instrumentalization principles.

Human biological material (molecules, cells and tissues) is regarded as patentable subject matter in the patent jurisdictions of the world.[304] Patent systems are commodity systems through which inventions are introduced into the market enabling their commercialization. Patents are a form of temporary ownership whereby the patent holder may limit the commercial use of the invention by others and allow access to the invention for returns. Patents on human biological material, therefore, represent a method of commercialization of the human body and its elements.

The ownership on human biological material represented by a patent and the possibility of commercialization offered by the patent system bring patent law into the realms of bioethics and make the principle of human dignity (the principles of non-objectification,

[301] Wilkinson (2003), at 44–45.
[302] Margaret. J. Radin, *Contested Commodities* (Cambridge, MA: Harvard Univ. Press, 1996), at 56.
[303] Beyleveld and Brownsword (2001), at 29.
[304] **PART 2.**

non-instrumentalization and non-commodification/commercialization) relevant to the patenting process. Patent law in relation to biomedical inventions should respond to general bioethical claims, such as that formulated by Dickenson that no property rights should be allowed on the human body, especially a right to income and capital.[305]

The reaction of patent laws to the dilemma, as explained in **PART 2**, was the introduction of the discovery and invention distinction and the application of the public morality/public order exception from patentability to biomedical inventions. In European patent law the distinction between inventions and mere discoveries of human body parts and the treatment of certain cells (human totipotent cells) as a stage of the development of the human body represent the inclusion of human dignity into the assessment of patentability. The exclusion from patentability of inventions which would lead to the commercial or industrial use of human embryos is a manifestation of the non-commodification principle.

Human embryonic stem cells represent a difficult case for ethically advanced patent regimes. These cells derived from human embryos raise two significant ethically contested issues related to human dignity (and the right to life): that human embryos are available (and created) for research purposes and that human embryos are destroyed in the process of derivation. There is also the preliminary question whether the commercialization of hES cells by means of patents is acceptable under human dignity.

European patent law offers a number of solutions to these ethical dilemmas. The question whether hESC patenting is in contravention of the non-commodification doctrine can be examined under the general public morality clause. This was drafted so as to accommodate the divergent ethical viewpoints prevailing in the different European states participating in the European patent system. As a result, it acknowledges the non-commodification principle as a communitarian value contingent upon the judgment of a particular society and the relevant cultural context. There is no evidence that European states would all consider the patenting of hES cells as contravening the principle of non-commodification.

The destruction of human embryos in the process of harvesting hES cells may also be examined under the general public morality clause in European patent law. In this framework, the divergent viewpoints on the moral status of human embryos can be expressed and the moral status of different embryos (supernumerary IVF, IVF research and SCNT research embryos)[306] could be contrasted. As it will be highlighted in **PART 2**, European patent law excludes the patentability of hES cells on grounds that the destruction of research embryos is covered by the clause on the commercial or industrial use of human embryos, an explicit public morality clause expressing a moral common ground among European states. It is doubted that the scope of the non-commodification principle expressed in the 'commercial or industrial use' clause would cover the act of killing human embryos and that embryo destruction in biomedical research would be 'industrial' or 'commercial' in the meaning of these terms provided by patent jurisprudence.

Making human embryos available for hESC derivation could violate the non-objectification/instrumentalization and non-commodification principles. In the process of

[305] Donna Dickenson, *Property in the Body* (Cambridge: CUP, 2007), at 69.

[306] Parens argued that the supernumerary IVF embryos attract a different moral assessment from that applicable to embryos created for research purposes: the difference is that spare embryos were originally created as ends in a parental project whereas research embryos were created as means for biomedical research, Parens (2001), at 45.

derivation research embryos are considered and used as objects, as sources of valuable stem cells. In case derivation is performed on a commercial basis, the non-commodification principle applies. The latter could trigger the application of the 'industrial or commercial use' clause for patent applications involving hES cells, but the commercial orientation of practices needs to be established. The non-objectification principle may be raised under the general public morality clause in European patent law which, however, gives way to the local appreciation of the question whether the treatment of research embryos as objects would violate human dignity.

The global debate on patenting human biological material reveals a richness of ethical arguments. In relation to DNA patents, often labeled hazily as patents on life, Wilkinson collected the main strands of the debate.[307] The arguments include the propositions that patenting life (DNA) is morally equivalent or similar to slavery, that it involves the commodification of human biological material and the commodification of persons. Commodification is the most often recited argument against the patenting of human biological material. Its weakness is that human biological material can be objectified and commoditized in a normative sense. In this respect, Wilkinson distinguishes three potential arguments: first, human biological material is necessary for and/or constitutive of humanity or personhood, second, human biological material has cultural and symbolical importance, and third, human biological material has an inherent value and 'dignity'. In his view none of these arguments are conclusive and only the commodification of persons argument may be raised validly against patenting human biological material. In this regard, Wilkinson rejected that persons are identified by their human biological constitutions and that persons would have personal property on their own biological material. However, the possibility that persons would be valued solely for their biological material without accepting their other values may result in commodifying persons. On this basis, excluding from patentability human biological material, human embryonic stem cells in particular, on the basis of the general public morality clause in European and other patent laws has a rather feeble basis.

Assessing DNA patents (and patents on human biological material) on the basis of human dignity raises, as contended by Beyleveld and Brownsword, further normative problems. They argued that while DNA patents may be incompatible with the communitarian concept of human dignity, expressed in the principle of non-commodification, in case the donor's autonomy was respected DNA patents remain compatible with the individualistic aspect of human dignity. Obtaining the full informed consent of donors ensures that the relevant segment of human dignity is observed.[308]

Human dignity as a bioethical principle combines multiple limitations to biomedical research activity and in certain views, should enable multiple interpretations of these limitations by different communities. Its variable framework is a factor which should be observed in the context of patenting human biological material. On the face of it, the commercial character of patents and the ownership inherent in patents conflicts with the normative considerations of human dignity. However, the boundaries in the ethics of biomedical patenting remain contested and subject to divergent appreciation on the local level. The diversity of local viewpoints on the bioethical limitations to biomedical research activity must be acknowledged in the patent jurisdictions of the world that apply bioethical standards in the patenting process.

[307] Wilkinson (2003), at 199-219.
[308] Beyleveld and Brownsword (2001), at 205.

2. Cultural diversity, bioethics and intellectual property rights in regenerative medicine

Intellectual property rights, patents in particular, are considered as ordinary practice in biotechnological research and business. Even in relatively new areas such as human embryonic stem cell research a considerable body of patents has been developed.[309] Biotechnological and biomedical patenting looks back to a considerable history[310] marked with a number of grave controversies, the most relevant of which focused on the bioethical issues inventions in the life sciences imported into the 'sterile environment'[311] of patent law. The last decade, mainly due to the introduction of the European Union Directive on patenting in biotechnology[312] (Directive), has been especially loaded with debates concerning the bioethical boundaries of human innovative activity in the life sciences and commercialization of biomedical inventions through patenting.

Placing bioethical restraints on patenting is a commercially highly relevant issue as emerging industries in the bioeconomy without marketable products or services require a tangible asset, mainly in the form of patents, to attract interest.[313] In new, rapidly developing areas of science, such as biomedicine, patents play a significant role as they contribute to the dissemination of knowledge and enhance further upstream or downstream research and commercial activity.[314] Biomedicine is a high-risk, expensive and research-intensive activity that demands large amounts of investments which may only be secured by sufficiently wide and valuable patent portfolios.[315] The various economic rationales of patenting are also important for biomedicine – patents have the effect of increasing output from resources used for innovation, they are devices which enable inventors to capture the returns from their investments in the invention, they may represent prospective rewards in a market where patents are considered as assets to attract further investments, and patents by means of the element of disclosure contribute to the development of research and subsequent downstream applications.[316]

This utilitarian vision of patenting suggests a need for an ever stronger patent system which, by enhanced legal protection, increases the incentive to pursue research and invest.

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[309] Karl Bergman and Gregory D. Graff, The Global Stem Cell Patent Landscape: Implications for Efficient Technology Transfer and Commercial Development, *Nature Biotechnology*, vol. 25, no. 4 (April 2007), 419–424.

[310] Graham Dutfield and Uma Suthersanen, *Global Intellectual Property Law* (Cheltenham: Edward Elgar, 2008), at 299–312.

[311] Ethical neutrality is accepted as the norm in patent law, see E. Richard Gold, *The Unexamined Assumptions of Intellectual Property*, European University Institute Working Paper RSCAS No. 2004/45. The ethical neutrality of patent law contested in EPO Interview with Dr Ingrid Schneider, available at documents.epo.org/projects/babylon/eponet.nsf/0/F172DE5BB2B9B15BC12572DC0031A3CB/$File/Interview_Schneider.pdf, in which Dr Schneider stated that patents are "never value-neutral" and "patent granting never was a neutral device but an interventionist instrument of the state to foster progress."

[312] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:213:0013:0021:EN:PDF.

[313] See Brian Salter and Catherine Waldby, *Contested Governance in Human Embryonic Stem Cell Science: Uncertainty and Standardisation in Research and Patenting*, Global Biopolitics Research Group, Working Paper no. 24 (2007), (London: Kings College, University of London).

[314] Interview with Ananda Chakrabarty, REMEDiE, 17/9/2010.

[315] Graham Dutfield, *Intellectual Property Rights and the Life Science Industries – A Twentieth Century History* (Dartmouth: Ashgate, 2003), at 153.

[316] See e.g. Edmund W. Kitch, The Nature and Function of the Patent System, 20(2) October, *Journal of Law and Economics* (1977) 265–290, at 266–267; Claude Barfield and John E. Calfee, *Biotechnology and the Patent System* (Washington: The AEI Press, 2007), at 24–35.

Such a reading of the patent system, however, must be confronted with the arguments highlighting that patenting systems have created their own hurdles for scientific activity (i.e. patent holdups and patent thickets, patent trolls and expensive licensing),[317] and that the emphasis on patenting in science has upset research priorities by encouraging wrong research and discouraging genuinely useful basic research that would have impact on society, for instance, by enabling access to crucial medicines.[318] Patents have been held responsible for increasing the cost of innovation and reducing access to innovation and for the premature closure of technologies.[319] The perceived negative impact of patents on innovation in biotechnology led experts to advocate the replacement of 'old' IP with 'new' IP which would enhance sharing and collaboration and lead to greater levels of innovation and better access to new products and services.[320]

Patenting in biomedicine is a rapidly moving field, packed with contentious issues and subject to heavy litigation and numerous extra-legal oppositions and claims.[321] In the socio-ethical debate on patenting the patent system, the nature of patens, is often misrepresented as granting complete legal monopolies on 'life' and preventing access to strategic research tools, such as hES cells. Instead, the patent system should be seen as a means of introducing incentive to the innovative and commercial process by offering a reward and certain legal control over the invention by enabling the patent holder to exclude others from certain uses of the invention. Any challenge initiated against the patent system must take account of the effect it may have on the incentive factor in innovation.[322]

Granting a patent is only the first step in the commercialization of an innovation. Without an adequate licensing strategy and strategy for royalties commercialization may fail. The legal entitlements derived from a patent do not provide a monopoly over the use and marketing of the invention. A patent does not give immunity from the law; the actual use of the patented invention could be subject to limitations and prohibitions imposed by regulation. On this basis, the ethical opposition to a certain innovation may need to be addressed outside of patent law in the provisions regulating research or the use of products in the market. Any examination of patenting must take into account these characteristics and complexities of the system.

Intellectual property rights, patents in particular, remain essential for bringing inventions in regenerative medicine to the market. Patent systems by bridging the gap between human intellectual activity and the market enable the commercialization of biomedical research and secure the private and public benefits which patents offer to stakeholders and the state. The temporary legal monopoly granted by patent law enables the patent holder to recoup his investments put into the innovative process by means of exploiting his rights under patent law. In exchange, the invention is made public enabling

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[317] Nancy.T. Galllini, *The Economics of Patents: Lessons from Recent US Patent Reform* (2002), in Robert P. Merges et al. (eds.), *Economics of Intellectual Property Law*, Volume I (Cheltenham: Edward Elgar, 2007) 63, at 68–69.

[318] See, Luigi Palombi, The role of patent law in regulating and restricting access to medicines, *SCRIPTed* vol. 6, no. 2. (August 2009), at 394.

[319] William R. Cornish et al., *Intellectual Property: Patents, Copyrights, Trade Marks and Allied Rights* (London: Sweet and Maxwell, 2003), at 19.

[320] *Toward a New Era of Intellectual Property: from Confrontation to Negotiation* – A Report by the International Expert Group on Biotechnology, Innovation and Intellectual Property, 2008, available at ssrn.com/abstract=1260099.

[321] Phillip W. Grubb, *Patents for Chemicals, Pharmaceuticals and Biotechnology* (Oxford: Oxford University Press, 2004), at 226.

[322] Interview with Julian Hitchcock, REMEDiE, 16/6/2010.

further upstream and downstream research, translation into products or therapies and other, mainly commercial activities. In sum, patent systems ensure that inventions are disclosed for the benefit of society and inventors benefit from the commercial opportunities presented by the limited monopoly of the patent.

Patents in the bioeconomy provide the asset with which (start-up) companies may attract speculative investment to finance further basic or translational research or development. Investment secured by patents as corporate assets may be crucial in ensuring the survival of companies in the period of developing the invention into a product or a therapy. Patent systems are essential elements of business strategy in the bioeconomy focusing on creating revenue (by selling the asset-laden start-up company) or sustaining economic activity. For policy makers patents are key instruments in economic policy promoting growth and innovation.

Stakeholders in regenerative medicine need to exploit the benefits generated by the utilitarian trade-off between private and public interest in patent systems. Patents generate returns for publicly or privately funded research and attract investment from the market for expensive downstream activity when productivity is low or non-existent. Patents signal success in research and business, and when placed in the public they attract the attention of investors, competitors, patients and health care providers. Patents bring inventions into the public domain and enable access for others to the invention and further benefit generating activity based on the invention.

For patent systems to deliver the said private and public benefits the law must provide a clear and coherent framework regulating the requisites of obtaining and exploiting a patent. Patent laws establish conditions for the patentability of inventions. Some of these conditions are technical, intrinsic to the special area of patent law, such as novelty, inventive step and industrial applicability. Others concern more general issues, such as the boundaries of human innovative activity expressed in the definition of what constitutes patentable subject matter and in the clauses excluding the patentability of inventions contrary to public order or morality.

Human biological material, genes, tissues and cells serve as key research or analytical tools or products in regenerative medicine. They have a market value and they can be subject to ownership in the form of intellectual property rights. Their treatment as things which may be subject to commercial exploitation by means of obtaining patents on them raises ethical objections on grounds of principles inherent in the requirement of respect for human dignity, such as non-objectification, non-instrumentalization and non-commodification applicable to the human body and its parts or elements. These bioethical requirements can be expressed in the regulation and application of the conditions of patentability as exceptions to patentability in the different patent regimes of the world.

Incorporating bioethical considerations into the patenting process represents a challenge to patent systems and to the commercialization of biomedical invention through those systems. There is a diversity of local approaches regarding the bioethical limitations applicable to biomedical research and the boundaries of these limitations remain contested. The previous Part presented evidence that human stem cell research attracts diverse regulatory responses, permissive, intermediate or prohibitive, and stakeholders disagree where to draw the limits of human embryonic research. The underlying principle of respect for human dignity, the centerpiece in the principlism of modern bioethics, also acknowledges diverse interpretations and conflicting positions. The contestable moral

status of human (research) embryos played an important role in the debate surrounding the patentability of biological material derived from human embryos.

The reaction of patent systems to the challenge of diversity and contestability in bioethics brought about by patents on human biological material has been different. European patent law reacted by incorporating bioethical considerations within the patenting process which presented a ground for challenging morally contestable bio-patents. In the US, Congress has so far refrained from amending federal patent law so as to accommodate the ethical dilemmas of biomedical research. The US Patent and Trademark Office (USPTO) and US courts apply traditional patent doctrine to determine the patentability of biomedical discoveries. In other national patent regimes equipped with morality clauses to exclude ethically objectionable inventions we found no evidence of imposing bioethical limits onto patenting. In the following, after examining the relationship between the patent system and biomedical research an overview of how patent systems in the world addressed the bioethical dilemmas of patenting human biological material will be provided.

2.1. The patent system and biomedical research

Patent systems are based on the premise that economically and socially significant innovative activity will be promoted by granting in law to the patent holder a right to control competition in the market segment covered by the patent for a limited amount of time and enabling the patent holder to recoup its investments by exploiting its rights under patent law. In exchange, the invention will be made public enabling further upstream research and downstream activities, such as product development or translation into therapeutic application. Thus, patent law represents a utilitarian balance (trade-off) struck between the promotion of innovation as a public policy and the private, economic interests of the inventor.

Patents in the bioeconomy have a further function. They provide the intangible asset with which small, start-up companies may attract speculative investment to finance further basic or translational research or product development. Investment secured by patents as corporate assets may be crucial in ensuring the survival of companies in the economically difficult period of translational research when productivity is low or non-existent. Patents are essential elements of business strategy focusing on creating revenue (by selling the asset-laden start-up) or sustaining economic activity and as a result they are key to economic policy promoting growth and innovation. Patents are a signal of success in biomedical research and business; they are placed in the public to attract the attention of investors, competitors, patients and health care providers.

A positive story-line of patent systems was summed up in a simple equation by Schneider according to which "patents equal innovation, equals economic development, equals therapeutic improvement, equals beneficence for general wealth, and thus benefit for the common good."[323]

In this reading, patent systems are fair. They reward the individual for carrying out and financing a socially valuable activity; that is creating knowledge used as a resource by other members of society without exhausting it. Patents are contracts between the state and the inventor under which the invention is disclosed for the benefit of society and the inventor

[323] Ingrid Schneider, Can Patent Legislation Make a Difference?, in Sebastian Hauns et al. (eds.), *Politics of Intellectual Property* (Cheltenham: Edward Elgar, 2009), 129, at 134.

benefits from the commercial opportunities presented by the limited monopoly of the patent. Patent systems also offer benefits to investors and corporations interested in the exploitation of the patent. In Drahos' view patents beyond a simple promise of returns to the inventor represent a public guarantee for returns on private commercial investment.[324]

However, biomedical advances, promising life-saving treatments and better health for humanity, may find the utilitarian rationale of patent systems narrow. Biomedical inventions challenge patent law with non-utilitarian considerations such as human dignity, justice, social good, public interest (public health) and benefit allocation. Patient interest and general human values in therapy question patent driven innovation and business models favoring investment from venture capital and profit. Patents are burdened with an intrinsic conflict – they increase the supply of new inventions by constraining access to them[325] – which is difficult to reconcile with the access demands of patients and health care systems towards biomedical research.

Socially relevant inventions, such as isolated DNA or stem cells, often produced by using public funds in public institutions and marketed through spin-off companies,[326] raise the question whether patent systems with their obvious economic orientation and reward-system favoring individuals are able to satisfy common public policy needs. The ability of patent systems to contribute to achieving public policy aims is further questioned by operational difficulties patent systems face hindering the delivery of the promised public and private benefits. Strategic patenting, multi-patenting, the creation of patent thickets may be economically reasonable for patent holders, which are often unproductive, rent-seeking 'patent trolls', as they create revenue without creative or productive activity. These economically rational practices may, nonetheless, be in contravention with the public interest element of promoting research and innovation inherent in patent law and they may undermine further scientific and commercial activities, such as the translation of basic research to clinical application, and practices ensuring patient access to therapies.

Patent systems, burdened with these restrictive private practices, have endured serious criticisms in relation to socially valuable core biotechnological inventions, such as the WARF stem cell patent protected under US Patent No 6,200,806. It has been questioned whether in these instances the balance (the trade-off) between ensuring advances in biomedicine for the benefit of society (humanity) and the need to attract investment and express the commercial value of inventions by granting a limited monopoly to the patent owner has been struck adequately.[327] Basically, the traditional tenets of patenting systems were seen as inadequate in the market of biomedical innovation where research and innovation promises great social and economic value and where innovation generated by the pressure of competition in an open access market of inventions without patents may hold more rapid and advanced developments. The for-profit rationale of patent exclusivity was seen as inappropriate in the field of biomedical research.

Drahos argued that in biotechnological research the role of patents in driving innovation has been limited. Research is carried out in public institutions financed by public money

[324] Peter Drahos and John Braithwaite, *Information Feudalism* (London: Earthscan Publications, 2006), at 42–43.
[325] Kitch (1977), at 282.
[326] Patent law has become one of the main mechanisms by which public knowledge assets have been privatized, Drahos and Braithwaite (2006), at 160.
[327] Vincent J. Filliben, Patent Law and Regenerative Medicine: A Consideration of the Current Law and Public Policy Concerns Regarding Upstream Patents, *Wake Forrest Intellectual Property Law Journal* vol. 9, no. 3 (2009), 238, at 239.

driven by the curiosity of individuals and their hunger for professional recognition. He also argued that patents are not inevitable means of successful commercialization as 'patents do not make buyers'. In his view, the role of patents in biotechnology is reduced to offering a financial opportunity to exploit knowledge for a very high rate of returns as guaranteed by the patent system as opposed to the low return promised by public knowledge. Patent systems, stripped of their other functions, merely deliver the returns investors hoped from the biotechnological sector.[328]

A frequently voiced criticism of research tool (DNA and stem cell) patenting in biomedicine is that upstream patents represent additional costs and time, as a result of complex licensing arrangements, suffocating downstream innovation.[329] Apart from slowing down the innovative and translational process patents have been reported to promote an academic culture of secrecy.[330] Further, basic research tool patents, as research hold-ups, may stifle upstream research carried out by public institutions committed to widely disseminating their discoveries.[331]

Lee discussed the ways in which biomedical research tools can hider scientific research.[332] He mentioned that patents on a 'keystone' research tool can single-handedly hold up research, the need to bundle multiple licenses for various patents can generate transaction costs rendering research prohibitively expensive which leads to a wasteful under-exploitation of resources, and that patent thickets, multiple overlapping patents covering a single technology, often prevent successful downstream activity.

Joly listed a number of factors indicating that stem cell patents, especially patents on key stem cell technologies, compromise further research, translation and commercialization.[333] First, the fragmentation of patent ownership between many private and public actors impedes an effective negotiation process between parties. Also, broad dominant patents on fundamental research tools have the ability of disproportionately influencing research and development. The different assessment of patentability in different jurisdictions of product claims covering controversial technologies, such as hESC, creates legal uncertainty and the inconsistency of the law on the non-commercial research exemption makes its application difficult. Further, a mixture of private and public funding and varied institutional policies in the public sector create confusion as to ownership and IP policies. Also, academic collaboration is negatively affected by exclusive patent rights. Finally, national policies and legislation on stem cell research and stem cell patenting are often misaligned causing inter-operability problems.

The patent hold-ups or the 'tollbooths' maintained by crucial patents, such as a patent on a fundamental research tool, however, may not suffocate completely the basic or translational research process. Public law and private law solutions can tackle the negative impact of patents on downstream and upstream research, other activity and patenting. The most common public law instrument is the (non-commercial) research exception in patent

[328] Drahos and Braithwaite (2006), at 155.
[329] Donna M. Gitter, International Conflicts Over Patenting Human DNA Sequences In the United States and the European Union, *NYU Law Review*, vol. 76 (2001), 1623, at 1669.
[330] Yann Joly, Flora Wahnon and Bartha Knoppers, Impact of the Commercialization of Biotechnology Research on the Communication of Research Results: North American Perspective, *Harvard Health Policy Review*, vol. 8 (2007), 46, at 47.
[331] Peter Lee, *Contracting to Preserve Open Science: The Privatization of Public Policy in Patent Law* (2008), at 6, available at works.bepress.com/peter_lee/2.
[332] *Ibid.*, at 9–10.
[333] Yann Joly, Clinical Translation of Stem Cell Therapies – Intellectual Property and Anticipatory Governance, *SCRIPTed*, vol. 7, no. 2 (August 2010), 265, at 268.

law enabling access to and the use of the patented invention. In case the licensing policy and other activity of the patent holder prohibit further research or trials the state may intervene under the compulsory licensing provisions in patent law. Also, patent pools, patent clearinghouses, protected commons, information-sharing frameworks and stem cell banks have been used to deal with the access and the collaboration problem caused by patents for non-profit activities.[334]

Further examples of public law solutions are the US legislative attempts curbing patent protection on biomedical research tool patents such as the Genomic Research Accessibility Act and the Genomic Research and Diagnostic Accessibility Act, the first of which attempted to ban DNA patenting, the second providing infringement exemptions for non-commercial research and diagnostics. Regulating a shorter patent term could also address the access problem by driving inventions back to the public domain and reducing the costs of licensing.[335] Furthermore, restrictive patentability conditions and a strict patentable subject matter doctrine may represent a solution for the access problems caused by patents.[336] Davis suggested that the application of the 'essential facilities doctrine' of competition law in the patent domain could establish an obligation on patent holders to provide access to the invention for their competitors.[337]

Private law solutions could include signing memorandums of understandings between the relevant parties, such as that signed between the Public Health Service (umbrella organization incorporating the NIH) and the WiCell Research Institute holding licenses for the WARF patents concerning the patents on partially federally funded stem cell lines,[338] enabling access to the inventions for publicly funded non-commercial research. Another solution to deal with access problems under private law is when patent-holders or economic operators aiming for biotechnological patents offer R&D contract packages to research institutions, such as that embedded into the IP policy of the California Institute for Regenerative Medicine (CIRM).[339]

Lee in discussing private and public law solutions wrote about 'privatizing' patent regulation and creating a contractual construction of a biomedical research commons in place of the patent system.[340] He argued that the shift from property to contract provides a new perspective on how patents may achieve public policy goals – the property character of patents promotes invention, disclosure and commercialization, however, other policy considerations, such as further upstream and downstream activity, may only be achieved through curbing these property rights by means of a "contractually-enforced right to include."[341]

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[334] Matthew Herder, *Two Models of Commercializing Stem Cell Science: Creating Conditions for Collaboration*, (2009), available at papers.ssrn.com/sol3/papers.cfm?abstract_id=1437690.
[335] Laurie L. Hill, The Race to Patent the Genome: Free Riders, Hold Ups, and the Future of Medical Breakthroughs, *Texas Intellectual Property Law Journal*, vol. 11 (2003), 221, at 251.
[336] Lee (2008), at 11.
[337] Amy R. Davis, Patented Embryonic Stem Cells: The Quintessential "Essential Facility"?, *Georgetown Law Journal*, vol. 94 (2005), 205, at 209.
[338] Memorandum of Understanding between WiCell Research Institute Inc. and Public Health Service, US Dept. of Health and Human Services (2001), available at ott.od.nih.gov/pdfs/WiCellMOUhuman.pdf. On the NIH - WARF negotiations, see Rebecca S. Eisenberg and Arti K. Rai, *Proprietary Considerations*, in Robert P. Lanza *et al.* (ed.), *Handbook of Stem Cells*, Vol. 1, (Amsterdam: Elsevier, 2004), at 793–798.
[339] 17 Cal. Code Reg. § 100300-100310 and 100400-100410 and CIRM's IP Policies for Non-Profit and For-Profit Organizations (2006), available at www.cirm.ca.gov/faq/pdf/IPPNPO.pdf and www.cirm.ca.gov/faq/pdf/ForProfitorg.pdf.
[340] Lee (2008), at 54.
[341] *Ibid.*,

The so called 'tragedy of the anticommons' argument[342], which stands for inhibiting by granting patents the development of life-saving therapies, can be countered by emphasizing the benefit of openness (disclosure) patents bring into the processes of innovation and commercialization avoiding a culture of secrecy in biomedical research. In examining the access problems associated with patents it is crucial to realize that patents are only granted for a limited amount of time and patents, taking into account the time required for translating the result of basic research into therapeutic or diagnostic applications, are likely to expire before the patent holder is able to market a product or application. Studies have also demonstrated that patents and licensing only very rarely or do not inhibit research by other scientists.[343] WARF's recent licensing policy was declared as especially favorable to further basic research.[344]

As a possible direction for the development of patent law which is able to accommodate these diverse utilitarian and non-utilitarian demands Schneider suggested the reconsideration of patent law as 'regulatory law'. This means the opening of patent law to acknowledge the conflicts inherent in patenting, the broader socio-economic effects of patents and the issues of pre- and post-patenting practices without delegating these to other social and legal arenas. She stated that this required the reconceptualisation of patent offices as regulatory agencies in which form their activity is no longer objective and value-neutral and consists of the mere application of law, but covers policy-making and determining the development of technology and the implications of technology on society.[345]

In principle, patent systems offer considerable private and public benefits to biomedical research and the bioeconomy. They provide a tested channel for the commercialisation of inventions and the classical trade-off of patents remain attractive on utilitarian grounds. The potential social and other non-utilitarian benefits of biomedical innovation and the unusual characteristics of the 'market' for biomedical products and therapies, however, question the suitability of patent regimes to act as intermediaries between inventors and investors, the industry, patients and health care systems. The ethical contestability of certain biomedical research practices represents a further challenge for patent systems. The complications arise not only from the possibility of incorporating bioethical considerations into the examination of the patentability of human biological material, but also from the diversity and contestability of viewpoints regarding the applicable ethical principles.

2.2. Patent systems and bioethical diversity

The overview of the ethical, political and legal positions on human embryonic research in Part 1 highlighted the diversity of views in different societies and communities in the world.

[342] Michael A. Heller and Rebecca S. Eisenberg, Can Patents Deter Innovation? The Anticommons in Biomedical Research, *Science*, vol. 280, no. 5364 (May 1, 1998), 698–701, at 698.
[343] Gregory C. Ellis, Emerging Biotechnologies Demand Defeat of Proposed Legislation That Attempts to Ban Gene Patents, *Richmond Journal of Law and Technology* vol. 15, no. 1 (2008), 1–35, at 31; John P. Walsh, Ashish Arora, and Wesley M. Cohen, Research Tool Patenting and Licensing, and Biomedical Innovation, in S. Merrill, R. Levin, M. Meyers, eds., *Innovation in a Knowledge-Based Economy* (Washington DC: National Academies Press, 2003), 285–304, at 298–299.
[344] On WARF's licensing policy for ES cell lines, see *Nature Biotechnology*, vol. 25, no. 4 (April 2007), 387.
[345] Schneider (2009), at 154.

Biomedical research regulatory regimes range from permissive, intermediate and restrictive reflecting different visions of what is ethically permitted, demonstrating that the ethical boundaries of research remain contestable. It is a different question, however, whether patent regimes in relation to biomedical innovations would acknowledge the ethical limits of biomedical research activity and commercialization in biomedicine and notice the diversity and contestability of ethical positions.

Primarily, the bioethical objections to patenting in life sciences is that patents serve as gateways to the commercialization of human biological material, DNA sequences or cell lines, which are not regarded as objects and commodities. Objections to their patentability, based on the morality clause(s) in patent law, rely on the premise that the exploitation of the invention by means of a patent would be contrary to the ethical principle of respect for human dignity. Ethical considerations may manifest in the exclusion from patentable subject matter and patentability the human body and its parts, totipotent human stem cells, the human embryo and pluripotent hES cells.

Patent laws objecting the patenting of certain biomedical inventions on bioethical grounds does not mean that biomedical research activity leading to and based on the invention would be prohibited. Research may continue within the framework of local research regulation. However, the commercially oriented innovative process will be deprived of the benefits patent systems offer to the inventor and society in general. On one hand, this appears as a significant competitive disadvantage to economies and commercial operators the competitors of which in other markets may be able to draw upon the benefits of the patent system. On the other, biomedical science will remain open science and the adverse impact of patents on scientific progress and society can be avoided. Nevertheless, the fissure between biomedical research regulation and patent law represents a problem for the state which at the same time appears to discourage an activity by rejecting the patentability of inventions produced and encourage the same activity by permitting it under research regulation. This is the case when the ethical boundaries of patentability in biomedicine are established on a supranational level whereas the limits of biomedical research within the broader framework of its international obligations are determined locally by the state (Europe).

From a global perspective, biomedical innovation faces a diversity of approaches in various patent regimes towards the bioethical boundaries of patenting. Outside the territorial scope of European patent law there is no evidence that patent systems would acknowledge the particular bioethical restraints of patenting biomedical inventions. US patent law lacks an explicit morality exception to patentability and other systems with morality clauses have refrained from its application to human biological material. The diffusion of bioethical principles into patent law remains a predominantly European development imposed on European states from the European level either by the EU or by the European Patent Convention.

Multiplicity in the domain of bioethics and patent regimes has a further consequence. In European patent law when imposing common bioethical limitations on patenting on the European level the diversity of local, state level positions on those limitations must be taken into account. European patent law may only draw upon uniform bioethical principles in the patenting process when the contracting states have agreed to the application of those principles in a uniform manner. In contrast, lacking an ethical common ground European patent law must refrain from dictating a uniform solution and express respect for the diverse national ethical positions. Respect for European multiplicity has come to the centre

of the debate whether the prohibition on the destruction of human research embryos should be applied as an ethical limitation common to Europe concerning the patentability of hES cells harvested from those embryos.

In the following, a global overview of the application of ethical limitations to the patenting of biomedical inventions will be provided. The focus is on diversity; diversity between different local regimes and respect for diversity in local regimes under an overarching regional system. The issues raised have long been debated but remained unresolved. Joly lists two key questions waiting for resolution: the uncertainties regarding patentability in biomedicine as a consequence of the multiplicity of ethical positions in different communities and the "current patent thicket" in hESC technology representing "vexing issues" for investors and economic operators interested in the commercialization of biomedical inventions.[346]

2.2.1 THE GLOBAL FRAMEWORK

The global framework for intellectual property laws is found in the TRIPS Agreement which in the field of moral exceptions to patenting established the rule (Article 27(2)) which holds that States "may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human life or health". It adds that a legal prohibition in domestic law in itself will not suffice in applying the public morality exception.

That only the possibility of incorporating a morality clause is mentioned under the TRIPS Agreement indicates that the place of ethical requirements in patent law and their interpretation is approached differently in world. A World Intellectual Property Organization draft document spoke openly about the notion of morality in patent law being determined on the national level and emphasized that moral pluralism and divergence in ethical judgments should be the norm in patenting.[347] This makes examining the different local solutions on incorporating bioethical restraints into patent law unavoidable.

2.2.2 LOCAL PATENT SYSTEMS

Europe has a multi-tiered patent system consisting of the national patent systems and the European Patent Organization (EPO) established by the European Patent Convention (EPC) which "provides for a cost-saving mechanism" of European scale by enabling the grant of a bundle of national patents.[348] Despite the strong economic and regulatory rationale the European Union has failed to introduce a single European patent. The morality provisions of all participating patent regimes were subject to harmonization under the EU Biotech Directive (Directive 98/44/EC).

The Directive's original intentions were predominantly economic. It was to establish the foundations in intellectual property law of a competitive European biotechnology industry by harmonizing patent laws in the Member States to provide uniform conditions of patent

[346] Joly (2010), at 266.
[347] World Intellectual Property Organization, *Intellectual Property and Bioethics. An Overview*, Consultation Draft, available at www.wipo.int/export/sites/www/freepublications/en/life_sciences/932/wipo_pub_b932ipb.pdf.
[348] Hanns Ullrich, *National, European and Community Patent Protection: Time for Reconsideration*, European University Institute Working Paper, Law No. 2006/41, at 2.

protection throughout the European Union. In the course of the legislative process, however, following the incentive of the European Parliament the economic rationale of the Directive was supplemented with a strong ethical motivation.[349] In fact, opening an ethical perspective on European patent harmonization led the European Commission to realize that the regulatory divergence sought to be remedied by the Directive rested more in the regulation of the ethical aspects of biomedical advancement.[350]

The morality clauses to be implemented in national patent law, which also found their way into the European Patent Convention, are regulated by Article 6 of the Directive. Paragraph 1 includes the exception from patentability when the exploitation of the invention would be contrary to public order and morality. Paragraph two produces a list of inventions which are excluded from patentability representing a European ethical common ground deliberated in the legislative process leading up to the adoption of the Directive. These are:

- processes for cloning human beings,
- processes for modifying the germ-line genetic identity of human beings,
- uses of human embryos for industrial or commercial purposes, and
- processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

US patent law has traditionally taken a diametrically opposite position regarding the incorporation non-utilitarian, value based considerations into the patenting process. US patent law lacks a morality clause that would give statutory grounds for an ethical test of patentability. It describes patentable inventions as "whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."[351] It is for Congress to assess whether a morality clause may be inserted into the Patent Act.

The exclusion of an ethical assessment of the patentability of biomedical inventions is associated with a number of utilitarian benefits. It was suggested that this makes the US attractive for researchers, investors and inventors in the biomedical domain as its patenting system delivers the benefit these actors demand from patent law.[352] The 'patent first, ask questions later' approach[353] favors research and the industry and reflects a purpose for the patent regime dominated by utility and considerations of general welfare[354] leaving the ethical assessment of research and industrial activity to other areas of regulation. The utility driven approach to patenting is adequately represented by Bayh-Dole Act 1980[355] which

[349] See E. Richard Gold and Alain Gallochat, The European Biotech Directive: Past as Prologue, 7(3) *European Law Journal* (2001) 331–366, at 336–343 and Aurora Plomer (project coordinator): *Stem Cell Patents: European Patent Law and Ethics* – Report EU FP6 'Life sciences, genomics and biotechnology for health' SSALSSB-CT-2004-005251 (2008), available at www.nottingham.ac.uk/~llzwww/StemCellProject/project.report.pdf, at 17–22.
[350] Gold and Gallochat, *Ibid.*, at 337.
[351] Title 35 USC, Section 101, available at www.law.cornell.edu/uscode/35/101.html.
[352] Interview with Julian Hichcock, REMEDiE, 16/6/2010.
[353] Borrowed from Margo A. Bagley "Patent First, Ask Questions Later": Morality and Biotechnology in Patent Law", 469 *William and Mary Law Review* (2003).
[354] Barfield and Calfee (2007), at 24.
[355] Pub. L. No. 96-517, 35 USC 200-211.

enabled the patenting of inventions created using federal funding for the purpose of putting government funded inventions into use and increasing the competitiveness of US industry.

The primary orientation of the US patent regime towards securing the successful commercialization of inventions has a constitutional basis. Section 8 of the US Constitution entrusts Congress with the power "to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries". Federal patent legislation also had to take notice of the Preamble of the Constitution which mentions the promotion of general welfare as a fundamental aim. Following this logic, a patenting regime will contribute to the general welfare if it enhances scientific progress and innovation by fulfilling its function without imposing unnecessary restrictions on innovators and other commercial operators.[356] The Patent Clause of the US Constitution merely requires from Congress "to promote a balance between encouraging innovation and avoiding stifling competition by awarding monopolies."[357]

In US patent law morality has been given an extremely limited compass and the use of the 'moral utility doctrine' derived from the patentability requirement of usefulness (Lowell v. Lewis, (1817) 15 F Cas 1018) has not been used in the case of biotechnology patents.[358] The federal funding debate, which is the form of expression of disagreement on the federal level with ethically contestable bioethical research practices, tried to find its way into the patenting arena by means of the 'Weldon Amendment'[359] which proposed the prohibition of funding for the USPTO for the purposes of patenting human organisms without defining whether human embryos and stem cells are considered as belonging to this conceptual category. The pressure on patent law to make the US biotechnology industry attractive to investors in Filliben's view meant that "patent protection has increased, arguably at the expense of moral and ethical considerations and possibly to the disadvantage of progress in the field."[360]

The patent regimes of Asia with respect to the recognition of the biomedical limitations to patenting take an intermediate position. The patent laws in the jurisdictions examined all include a general morality clause. The WTO (and TRIPS) member China's patent law contains a clause similar to that in other states stating that "no patent right shall be granted for any invention-creation that is contrary to the laws of the State or social morality or that is detrimental to public interest" (Article 5 Patent Act).[361] Rule 9 of the Implementing Regulations to the Patent Act includes the familiar provision that the exception under Article 5 may not be applied merely because the exploitation of the invention is prohibited by law.[362] The 1970 Indian Patent Act's morality clause provides that inventions the primary or intended use or commercial exploitation of which would be contrary to morality are "not inventions", in other words, they are not patentable (Article 3b).[363] The morality exception in South Korean patent law reads that "inventions liable to contravene public order or

[356] Interview with Professor Ananda Chakrabarty, REMEDiE, 17/9/2010.
[357] Filliben (2009), at 243.
[358] Libby Beadle Selling the Stem Cell Short?, 10 *Canterbury Law Review* (2004) 1, at 1.
[359] The Science, State, Justice, Commerce and Related Agencies Appropriations Act of 2007, available at thomas.loc.gov/cgi-bin/query/z?c109:H.R.5672:.
[360] Filliben (2009), at 241.
[361] Available at www.sipo.gov.cn/sipo_English/laws/lawsregulations/200804/t20080416_380327.html.
[362] Available at www.sipo.gov.cn/sipo_English/laws/lawsregulations/200804/t20080416_380326.html.
[363] Available at www.patentoffice.nic.in/ipr/patent/patents.htm.

morality or to injure public health shall not be patentable" (Article 32).[364] The 1959 Japanese Patent Act's morality clause is formulated in the same way (Article 32).[365]

The morality clauses lack the detail and the distinctions applied in the European regime. Nonetheless, other documents provide insight into their interpretation. In the Indian patent office's interpretation being contrary to morality means that the use of the invention would "violate the well accepted and settled social, cultural, legal norms of morality". It produced an example, "method of cloning", for an invention in breach of the requirements of morality which assumedly refers to reproductive cloning if the rules of Indian bioethical regulations are considered.[366] The South Korean examination guidelines interpret the morality clause in the patent act as morality meaning a "moral sense generally accepted by a society or particular group of people". For further interpretative guidance it called to the objective of the patent act as a point of reference. It added that the patentability of an invention will be excluded on grounds of morality if its aim is to contravene the rules of morality, or its disclosure or use would breach public morality.[367]

2.2.2.1 DIVERSITY AND CONTESTED BOUNDARIES: DNA PATENTING

Human biological material is regarded as patentable subject matter in the patent jurisdictions of the world. In Europe patent legislation, the European Patent Convention and the EU Directive (Article 5(2)), provides for the patenting as inventions of isolated elements of the human body or elements produced by means of a technical process, subject to meeting the other requirements of patentability (novelty, inventive step, industrial applicability and not being excluded on public order or morality grounds). Isolated human biological material as inventions is contrasted in European patent law to the simple discovery of one of the elements of the human body ((Article 5(1)), not regarded as patentable.[368] In the EU Court of Justice's interpretation, in harmony with the requirement of respect for human dignity, these provisions ensure that only the result of inventive, scientific or technical work are patentable, and biological data existing in their natural state in human beings are only patentable where it is necessary for the achievement and exploitation of a particular industrial application.[369]

The European distinction between discoveries and inventions, also demonstrated very clearly by the assessment of human totipotent cells as patentable subject matter, is not value neutral. It was confirmed by the European Commission that the discovery/invention distinction concerning the human body and its parts, together with other provisions of the Directive, guarantees that the principle of respect for human dignity (non-instrumentalization) is observed. It was also emphasized that by imposing a dual burden on the patentability of human gene sequences, first the invention/discovery hurdle, second the

[364] Available at park.org/Korea/Pavilions/PublicPavilions/Government/kipo/law/patent/epat.html.
[365] Available at www.japaneselawtranslation.go.jp/law/detail/?ft=1&re=02&dn=1&x=0&y=0&co=01&ky=patent&page=17.
[366] Point 4.3, Draft Manual of Patent Practice and Procedure, 2008, available at ipindia.nic.in/ipr/patent/DraftPatent_Manual_2008.pdf.
[367] Point 3.1, Requirements for Patentability, 2010, available at www.kipo.go.kr/kpo/user.tdf?a=user.english.html.HtmlApp&c=60203&catmenu=ek60203: as an example under the public order and morality rule it refers to a 'Bingo' apparatus.
[368] Isolation is a step from knowing to being able, European Commission response to Written Question P-2281/00 by Marie-Noëlle Lienemann (PSE) to the Commission. Application of Directive 98/44/EC on the legal protection of biotechnological inventions. *Official Journal* 081 E, 13/03/2001, 184–185.
[369] Para. 75, Case C-377/98, *The Netherlands* v *Council and Parliament* (9 October 2001), available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:61998J0377:EN:HTML.

general patentability requirements, the Directive ensures that the ethical principle of non-instrumentalization is respected.[370]

In the US the human contribution of isolation, purification or modification renders human biological material as 'products of human ingenuity' as opposed to 'products of nature' in the meaning of the judgment in *Diamond* v *Chakrabarty*[371] and thus patentable subject matter. This was reaffirmed in the 2001 revision of the USPTO Examiners Guidelines.[372] Patent regimes in Asia also accept the patentability of human biological material. Indian patent law denies patentability from of a "discovery of any living thing occurring in nature"[373], but when the discovery leads to establishing a practical use patentability is no longer refused.[374] The South Korean patent examination guidelines hold that "the method for artificially isolating substances from things in nature, not a mere discovery, is considered to be a statutory invention. So are the isolated chemical substances and microorganisms."[375] The Japanese patent examination guidelines include similar provisions.[376]

Patent laws, within the above framework, have acknowledged isolated human DNA as patentable subject matter. The US and the European patent regimes both granted patents for the BRCA 1 and 2 genes and the associated diagnostic method. In Europe their patenting relied on the clear legal provisions of 'isolation' and 'technical process'; the ethical oppositions against the patents, a characteristic of European patent law, were rejected.[377] The US process focused on the fuzzy distinction between products of human nature and human ingenuity in US patent law, which is now under reconsideration in an ongoing lawsuit by the American Civil Liberties Union against the BRCA 1 and 2 patents. The 2010 district court judgment, opposing previous practice, declared that isolated DNA must be regarded as products of nature, and thus unpatentable, as the process of isolation does not produce markedly different characteristics than those possessed by genes in the human body.[378] The case is now under appeal, and its outcome may change US patenting policy regarding isolated human DNA.[379] A more detailed description of the broader European and US patenting process for BRCA 1 and 2 is given in Part 3.

The product of nature or human ingenuity distinction, which opened the scope of patentability exceptionally wide, expresses the endorsement by the US patent regime the

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[370] Development and implications of patent law in the field of biotechnology and genetic engineering, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52002DC0545:EN:HTML.
[371] 447 US 303 (1980).
[372] Utility Examination Guidelines, 66 Fed. Reg. 1092, 1095.
[373] See *Kirin-Amgen* v *Hoechst Marion Roussel* [2005] RPC 9.
[374] Point 4.4.3, Draft Manual of Patent Practice and Procedure, 2008, available at ipindia.nic.in/ipr/patent/DraftPatent_Manual_2008.pdf.
[375] Point 4.1.2, Requirements for Patentability, 2010, available at www.kipo.go.kr/kpo/user.tdf?a=user.english.html.HtmlApp&c=60203&catmenu=ek60203.
[376] Point 1.1, Examination Guidelines for Patent and Utility Model in Japan, 2010, available at www.jpo.go.jp/cgi/linke.cgi?url=/tetuzuki_e/t_tokkyo_e/1312-002_e.htm.
[377] As applied in the BRCA 1 and 2 cases before the EPO, T 1213/0527 September 2007, available at www.epo.org/law-practice/case-law-appeals/pdf/t051213eu1.pdf, T 0666/05 13 November 2008, available at www.epo.org/law-practice/case-law-appeals/pdf/t050666eu1.pdf, T 0080/05 19 November 2008, available at www.epo.org/law-practice/case-law-appeals/pdf/t050080eu1.pdf. The ethical issues raised were informed consent, benefit sharing, and the impact of patent on public health.
[378] 09 Civ. 4515, available at patentdocs.typepad.com/files/opinion.pdf.
[379] This possibility was acknowledged in the US Government's amicus brief which followed the direction set in the district court judgment, available at www.genomicslawreport.com/wp-content/uploads/2010/11/Myriad-Amicus-Brief-US-DOJ.pdf.

aim of contributing to the general welfare by enhancing scientific progress and promoting economic growth.[380] Acknowledging biological material (living matter) produced or presented as a result of human contribution as patentable subject matter followed the spirit of the US Constitution the purpose of which would have been defeated if patent law had taken a different turn, for instance, by incorporating bioethical considerations.[381] The judgment in fact referred to Thomas Jefferson's claim from the time the Constitution was created that 'ingenuity should receive a liberal encouragement'. The amicus briefs submitted in the case held the opinion that patenting of living matter was a matter of national and general public interest as it would support innovation and competitiveness in a crucial newly emerging segment of high technology.[382]

DNA patents, as demonstrated by the ongoing US case, put pressure on the traditional boundaries of patent doctrine. Inventions involving human biological material are not novel, useful and non-obvious in the same way as a mechanical instrument or a chemical compound. The distinction between discoveries and inventions or products of nature and human ingenuity is blurred and the threshold of inventive step is lowered. Following this line Hawkins argued that DNA sequences are discoveries in the traditional sense as they are available in the human body and their biological function has always existed; the description of their functions falls short of the traditional utility requirement.[383] The human contribution of isolation and purification was seen as insufficient to distinguish them from a discovery and the process of isolation may only support the patenting of the process and not the product, the human DNA.[384]

2.2.2.2 DIVERSITY AND CONTESTED BOUNDARIES: HUMAN STEM CELL PATENTS

Isolated human stem cells as isolated human biological material constitute in general patentable subject matter. Adult stem cells, pluripotent human embryonic stem cells (hESC) and induced pluripotent stem cells (iPS cells) isolated from the human body are patentable products of human activity. Isolated human totipotent stem cells may, however, attract opposing legal characterizations. Patent regimes focusing on the act of isolation may treat totipotent stem cell lines as elements isolated from the human body by way of human activity and regard them as patentable subject matter. On the other hand, patent jurisdictions may also take into account the biological characteristics of totipotent stem cells and treat them not as products but as (potential) living (human) beings.

The clearest indication that totipotent cells may not be considered as patentable subject matter can be found in European patent law. The EPC and the EU Biotech Directive (Article 5(1)) exclude from patentability the human body at the various stages of its formation and development. In the European Commission's interpretation human totipotent cells constitute a stage of development of the human body and are unpatentable.[385] This position

[380] Diamond v. Chakrabarty, 447 US 303 (1980).
[381] Interview with Professor Ananda Chakrabarty, REMEDiE, 17/9/2010.
[382] Dutfield (2003), at 156.
[383] Naomi Hawkins, Human Gene Patents and Genetic Testing in Europe: A Reappraisal, 7(3) December, SCRIPT*ed* (2010), at 455.
[384] Sigrid Sterckx, Some Ethically Problematic Aspect of the Proposal for a Directive on the Legal Protection of Biotechnological Inventions, 20 *European Intellectual Property Law Review* (1998) 123, at 124–125.
[385] Development and implications of patent law in the field of biotechnology and genetic engineering, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52005DC0312:EN:HTML. Human embryos are excluded from patentable subject matter under the same provision.

is supported by the ethically charged distinction in European patent law between isolated stem cells on the basis of their toti- or pluripotency, confirmed most recently by Advocate General Bot before the EU Court of Justice.[386]

There is no evidence that other patent jurisdictions would follow the same approach and exclude from patentability isolated human totipotent stem cells under the bioethical principle of non-instrumentalization of the human body expressed in the above provision of European patent law. The invention/discovery or the products of nature/human ingenuity distinctions may not be able express the same restriction to patentable subject matter. The general public morality clause, if the patent regime contains one, may prevent patentability. The diversity of local solutions may increase if the developing approach to human DNA patents finds ground in US patent law, which may be applied so as to exclude isolated human totipotent cells from patentable subject-matter on the ground that their characteristics are not sufficiently distinct from the characteristics they demonstrate in nature.

The Canadian Intellectual Property Office`s (CIPO) approach to patenting human biological material offers an interesting, although rather similar, alternative. The CIPO`s Stem Cell Notice[387] distinguishes between higher and lower life forms and determines the question of patentability on this basis. Fertilized eggs, embryos and totipotent stem cells are higher life forms and unpatentable. Totipotent stem cells are declared to have the same potential as fertilized eggs to develop into an entire living being and considered to be equivalents of fertilized eggs from the perspective of patentability. In contrast, pluripotent and multipotent stem cells, which do not have the potential to develop into a higher life form, are patentable subject matter. Without indication regarding the rationale of the Stem Cell Notice, which he found in contravention with the case law of the Canadian Supreme Court on patentable subject matter (*obiter dicta* in *Harvard v Canada*, 2002 SCC 76, *Monsanto v Schmeiser*, 2004 SCC 34), Hagen speculated that the distinction used was influenced by EPO practice and the UKIPO's notice of stem cell patents from 2007.[388]

By all means, the indicated European approach remains contestable. First, it practically equates without further justification isolated totipotent cells, which are isolated biological material, with the human embryo and confers them the same moral status. Second, it avoids addressing the issue that totipotency is relative to the environment and isolated and modified totipotent cells are different from totitpotent cells in their natural environment. Third, it neglects an ethically relevant distinction alternative to the toti-/pluripotent concept pair; that between modified and unmodified stem cells. This was raised in the European Group on Ethics (EGE) Opinion No. 16 (2002)[389] on the ethics of hESC patenting, which found that 'unmodified' hES cells and cell lines are not patentable as their patenting may violate the non-commercialization principle,[390] whereas in the light of the economic and social purpose of patent systems 'modified' hESC patenting could be allowed.

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[386] Opinion of Advocate General Bot delivered on 10 March 2011 in Case C-34/10 *Oliver Brüstle*, nyr.
[387] CIPO Office Practice Regarding Fertilized Eggs, Stem Cells, Organs and Tissues (2006), available at www.cipo.ic.gc.ca/epic/site/cipointernet-internetopic.nsf/en/wr002953.html.
[388] Gregory R. Hagen, Potency, Patenting and Performation: The Patentibility of Totipotent Cells in Canada, 5(3) December, SCRIPT*ed* (2008), at 516-517.
[389] Opinion No. 16 (07/05/2002) – *Ethical Aspects of Patenting Inventions Involving Human Stem Cells*, available at ec.europa.eu/european_group_ethics/docs/avis16_en.pdf.
[390] It was criticized that the principle used in this regard, 'closeness to the human body', was not established as a relevant moral consideration and as part of European culture, see Plomer (2008), at 33.

Isolated pluripotent hES cells meet the definition of patentable subject matter in Article 5 of the Directive. Their biological characteristics prevent raising the argument used in the case of human totipotent cells that they would constitute the human body at a stage of its formation and the human intervention of isolation distinguishes them from simple discoveries. The patenting of these isolated cells, however, attracts further bioethical objections as the process of their derivation from the blastocyst at the current state of art destroys the human embryo and demand from industry for hES cells could lead to the instrumentalization and commodification of the human embryos used as sources.

At the current state of the law, pluripotent hES cells are excluded from patentability under the EPC and presumably under the EU Biotech Directive as their process of derivation, which necessitates the destruction of the human embryo from which the cell lines are obtained, constitutes an industrial or commercial use of the human embryo in the meaning of the applicable clause. The 'industrial or commercial use' clause (Article 6(2) of Directive) equated with the prohibition on the destruction of human embryos of all origin for the purpose of research clause proved especially controversial in the European history of human stem cell patenting separating Europe from the global market of stem cell patents and causing considerable tensions between European states with different moral approaches to human stem cell research.

There are considerable doubts whether the 'industrial or commercial use' clause may incorporate such 'embryo destruction' principle and whether any prohibition on the destruction of human embryos for research purposes should be considered instead under the general public morality clause of European patent law. In principle, the 'industrial or commercial use' clause is the manifestation in patent law of the ethical principle prohibiting the commercialisation of the human embryo, established as common to European states in the EU Directive, and there is no indication that it would incorporate a European 'embryo destruction' principle. In absence of indications to the contrary, the 'embryo destruction' principle belongs under the general public morality clause of European patent law which, as opposed to the explicit morality exceptions to patentability, acknowledges local diversity in the interpretation of the moral status of embryos, in particular, in distinguishing between different sources of human embryos available for research.

This latter point is especially crucial as the 'industrial or commercial use' clause represents a Europe-wide, uniformly applicable bioethical limitation to patenting, which has the effect of transforming the 'embryo destruction' principle into a bioethical principle common to Europe despite the differences between European states as to the ethical limits of human embryonic research. In contrast, the general public morality clause acknowledges a margin of appreciation of individual states making the question of patentability subject to the local ethical assessment of using human embryos for research purposes.

Respecting the multiplicity of local approaches relating to stem cell research in European patent law, which by applying the morality clauses to morally contestable patents has selected a path distinct from other patent regimes in the world, is a valid proposition. There are various opinions on the moral status of human embryos and about the limits scientific activity must observe. The different moral arguments are rooted in local society and culture representing the views of a particular community and expressed by the diversity of national biomedical research regulations and the bioethical limits and safeguards they prescribe.

The cause of 'European bioethical exceptionalism' in patent law and the ongoing, socially and economically extremely relevant debate on the boundaries of morality clauses in biomedical patenting is the European Union's legislative effort to introduce bioethical

principles into the area of patent law, the EU Biotech Directive. The Directive was an effective means of inducing bioethical convergence among European states by way of establishing ethical limitation clauses to patenting, implemented in the EU Member States and by the European Patent Convention, which emerged from years of political negotiations in the European institutions, most notably the European Parliament. The Directive, however, never admitted that bioethical convergence would jeopardize the deeply-rooted differences among European states regarding the ethical limits of biomedical research.

The Directive's commitment to European value-pluralism was expressed in the European Commission's 2002 implementation report.[391] It emphasized that the Directive was to ensure that the Member States enjoy a margin of maneuvering with regard to the general morality clause in order to ensure that inventions are evaluated in the ethical, social and philosophical context of each state. As to the explicit morality exclusions the report stated that they must be applied uniformly in all the Member States. Another indication that the Directive encapsulated respect for diversity was that in the European Commission's reading the Directive did not affect the autonomy of Member States to regulate the ethics of biomedical (hESC) research and its own role is exhausted in promoting a debate on ethics while maintaining the diversity of cultures and sensitivities in Europe.[392]

Multiplicity under the general morality clause is recognized in the preamble in the formula that "morality correspond in particular to ethical or moral principles recognized in a Member State."[393] It is further affirmed in the EU Court of Justice's interpretation of the general morality clause which "allows the administrative authorities and courts of the member states a wide scope for maneuver in applying this exclusion."[394] The EU Court acknowledged that by means of awarding a margin of appreciation to states the particular difficulties to which the use of certain patents may give rise in the social and cultural context of each member state can be taken into account.[395] In contrast, the explicit morality clauses of the directive were seen as limits to local discretion.[396]

In Germany the clearly expressed bioethical limits on patenting of the Directive were welcomed, at least by the German Ethics Council.[397] The Ethics Council's opinion emphasized that germ cells, human organs, human embryos, hES cells and cells lines must not be patentable. Processes for the formation of chimeras using human germ cells and parthenogenetic processes using human genetic material and organisms created by these processes must also be excluded from patentability.

With regard to the application of the 'commercial or industrial use' clause to hES cells the opinion contemplated that this provision might not be applicable when the embryos are not used for commercial or industrial but for therapeutic or research purposes, for which the derivation of hES cells or cell lines is an example. This, however, requires exploring the differences between commercial/industrial and therapeutic/research use.[398]

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[391] Development and implications of patent law in the field of biotechnology and genetic engineering, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52002DC0545:EN:HTML.
[392] Joint answer to Written Questions P-2852/00 and P-2931/00 by the European Commission, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:92000E2931:EN:HTML.
[393] Point 39 of Preamble, Directive 98/44/EC.
[394] Para. 37, Case C-377/98.
[395] Para. 38, Case C-377/98.
[396] Para 39, Case C-377/98.
[397] *Opinion – The Patenting of Biotechnological Inventions Involving the Use of Biological Material of Human Origin* (2004), available at www.ethikrat.org/stellungnahmen/pdf/Stellungnahme_Biopatentierung.pdf.
[398] *Ibid.*, at 30.

More importantly, the opinion pointed out that hESC patenting would be prohibited in Germany because patent law refers to the Embryo Protection Act as a background measure which prohibits 'embryo-consuming techniques' and the production of hES cells and cell lines. However, inventions involving 'exempt' cells could be patentable as their use in research is in compliance with the Embryo Protection Act.[399]

UK patenting practice, under Section 1(3) and Schedule A2(3) (Section 76A) of the Patents Act 1977[400] implementing the relevant provisions of the Directive, also reacted to the changes introduced by the Directive. The first UK Intellectual Property Office (UKIPO) practice notice in 2003[401] held that under the Patents Act 1977, which excluded from patentability uses of human embryos for industrial or commercial purposes, the UKIPO will not grant patents for processes of obtaining stem cells from human embryos as it represents uses of human embryos for industrial or commercial purposes prohibited in UK and European patent law. The UKIPO will also refrain from granting patents to human totipotent cells as patenting such cell would constitute a patenting of the human body at its various stages of formation and development.

The practice notice held that in case of hES cells their therapeutic potential must be considered in the patenting process. Therefore, "on balance, the commercial exploitation of inventions concerning human embryonic pluripotent stem cells would not be contrary to public policy or morality in the United Kingdom." As a result, the UKIPO will grant patents for inventions involving pluripotent hES cells.

This latter approach regarding hES cells was reaffirmed in a revised practice notice in 2009.[402] It came, however, with a qualification that the patenting of inventions involving pluripotent hES cells will continue in the UK subject to the condition that "the invention could be obtained by means other than the destruction of human embryos."[403] This was a reflection from the UKIPO to the EPO WARF ruling and represented a detachment of the bioethics of stem cell patenting from the bioethics of stem cell research in the UK.

In France the patenting regime implemented the Directive[404] which was found compatible with the French constitution by the Constitutional Council.[405]

The desire to maintain local diversity by the Member States in the face of the Directive was expressed in the considerable resistance to the national implementation of the Directive in which Member States attempted to delay implementation or applied terms in the domestic law which departed from the wording of the Directive. The Member States were also reported to connect the new morality provisions in patent law with the bioethical principles provided in their domestic biomedical research regulation regimes.[406] Belgium was planning the introduction of a general morality clause that instead of commercial exploitation intended to mention "inventions produced through means that are contrary to public order and morality", which according to commentators would have breached the

[399] *Ibid.*, at 31.
[400] Available at www.ipo.gov.uk/patentsact1977.pdf.
[401] Available at www.ipo.gov.uk/pro-types/pro-patent/p-law/p-pn/p-pn-stemcells.htm.
[402] Available at www.ipo.gov.uk/pro-types/pro-patent/p-law/p-pn/p-pn-stemcells-20090203.htm.
[403] Available at www.ipo.gov.uk/pro-types/pro-patent/p-law/p-pn/p-pn-stemcells-20090203.htm.
[404] French Patent Code (Code de la Propriété Intellectuelle) (Article L611-17-18), available at www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006069414.
[405] Conseil Constitutionnel 29 July 2004 Decision 2004-498 Dc, available at www.legifrance.gouv.fr/affichJuriConst.do?oldAction=rechJuriConst&idTexte=CONSTEXT000017664801&fastReqId=429005223&fastPos=2.
[406] Plomer (2008), at 23–27.

Directive and the TRIPS agreement.[407] The Italian attempt at implementation, which failed to transpose beyond the general clause the explicit morality exceptions of the Directive, was declared a breach of European Union law.[408]

In the years after implementation there was considerable uncertainty whether hES cells would be patentable under the Directive. The 2002 implementation report[409] failed to take a stance in this regard. Although it called attention to the possible applicability of the 'human body and its elements' clause of the Directive concerning the invention/discovery distinction and recalled the statements of EGE Opinion No. 16 (see below), reference to the process of hESC derivation and the 'embryo destruction' principle was not made.

The 2005 report[410] provided more clarity. With regard to pluripotent hES cells the Commission indicated that the general morality clause under Article 6(1) would be available to refuse their patentability.[411] As an attempt at reassuring the Member States the Commission, in light of the divergences which prevail among the member states in defining the moral status of embryos and the ethical boundaries of human embryonic research, refrained from making a final legal assessment and declared that it will continue monitoring the relevant developments in Europe and assessing their ethical and economic (regulatory) implications.[412]

The ethical limits of patentability in European patent law were subject to intensive debate in various European political forums. The politically exposed resolution of the European Parliament in 2005 produced a strict reading of the Directive when it produced views which rejected interventions in the human germ line, the cloning of the human being in all phases of its development and research on human embryos which destroys the embryo.[413] It affirmed that for patentability the functions of human gene sequences must be delineated accurately (purpose-bound or function-bound patenting of human genes) and that germs cells are excluded from patenting on the basis of the 'human body and its elements' clause under Article 5 of the Directive.

More controversially, the resolution insisted that since the derivation of hES cells implies the destruction of human embryos, the patenting of procedures involving hES cells or cells that are grown from human embryonic stem cells is a violation of the 'industrial or commercial use' clause of the Directive. The resolution indicated a reading of the Directive which implied that the 'embryo destruction' principle had been accepted by the Directive as a general and legally binding bioethical rule in Europe.

The 1999 Recommendation of the Council of Europe Parliamentary Assembly on biotechnology and intellectual property focused on benefit sharing and the social impact of patenting.[414] It also formulated a strong opinion on maintaining a strict distinction between

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[407] Gold and Gallochat (2001), at 350.
[408] Case C-456/03, *European Commission* v *Italy* (16 June 2005), available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:62003J0456:EN:HTML.
[409] Development and implications of patent law in the field of biotechnology and genetic engineering, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52002DC0545:EN:HTML.
[410] Development and implications of patent law in the field of biotechnology and genetic engineering, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52005DC0312:EN:HTML.
[411] Similar legal assessment given in Plomer (2008), at 23-27.
[412] A study was launched by the Commission in this field, available at ec.europa.eu/research/biosociety/pdf/mb_states_230804.pdf.
[413] European Parliament Resolution on Patents for Biotechnological Inventions (26 October 2005), available at www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P6-TA-2005-0407+0+DOC+XML+V0//EN.
[414] Recommendation 1425 (1999) On Biotechnology and Intellectual Property.

discoveries and inventions when the patent claim involved genes, cells, tissues or organs. The more radical biotechnologies recommendation (2000) called for the renegotiation of the Directive to provide a solution in conformity with the Council of Europe Oviedo Convention.[415]

The ethical issues of patentability in biomedicine were addressed in a 1994 recommendation.[416] It laid down the principles of non-instrumentalisation and non-commodification of the human body and advised transferring a number of bioethical prohibitions into patent law. These included germ line modification, cloning, chimera and hybrid production, and eugenic practices. The recommendation heavily criticised the utilisation of the then available morality clause under the EPC system and referred to the morality clauses of the 1994 version of the proposal of the Directive as simplistic.

The first indication that (the prohibition on) 'embryo destruction' would become a common bioethical and legal principle in European patent law by way of the interpretation of the 'industrial or commercial use' clause was the European Patent Organization Enlarged Board of Appeal decision concerning the Wisconsin Alumni Research Foundation (WARF) hES cell line patents.[417] The Directive's morality provisions were also integrated into the European Patent Convention system. The key provisions are Article 53(a) EPC establishing the exception to patentability on grounds of morality and Rules 27-30 of the Implementing Regulations to the EPC which transposed the relevant provisions of the Directive. The Directive serves as a supplementary means of interpretation to these provisions. With the implementation of the Directive in the EPC system the European Patent Organization gained jurisdiction for the determination of the bioethical boundaries of biomedical inventions in European patent law without the possibility of oversight from the European Union and limited redress available for the EPC Contracting States.[418]

With the WARF stem cell patent case the EPO found itself in the epicenter of the moral controversies surrounding the patenting of biomedical inventions. The EPO's first major attempt as an arbitrator of sensitive bioethical dilemmas in the field of biomedicine was its decision in the 'Edinburgh patent' case.[419] The Opposition Division of the EPO having found that in the absence of uniform moral standards in Europe concerning human embryonic/hESC research the 'industrial or commercial use' clause must be interpreted as excluding patents on hES cells derived from embryos in the process of which the embryos were destroyed.

The decision, at odds with the European Commission's vision of the morality provisions of the Directive, appears to dismiss the interpretation suggested in EGE Opinion No. 16 on the ethics of stem cell patenting (see below) and embrace the single restrictive dissident position to that Opinion. In any case, the EPO decision met the approval of the European Parliament which in a resolution reflecting on the granting of the patent[420] had declared that germ cells (totipotent stem cells) cannot be patented under the Directive and the "the patenting of procedures involving human embryonic stem cells or cells that are grown from

[415] Recommendation 1468 (2000) On Biotechnologies.
[416] Recommendation 1240 (1994) On the Protection and Patentability of Material of Human Origin.
[417] EPO Enlarged Board of Appeal G-2/06, documents.epo.org/projects/babylon/eponet.nsf/0/428862B3DA9649A9C125750E002E8E94/$FILE/G0002_06_en.pdf.
[418] See Plomer (2008), at 86–89.
[419] European Patent No. EP0695351.
[420] Resolution of the European Parliament with Special Regard to Patent EP 1257168 (a1) and Patent EP 695351 (the Edinburgh Patent), P6_TA(2005)0407, OJ C272 E/440 (9/11/2006).

human embryonic stem cells is a violation" of the 'industrial or commercial use' clause of the Directive.

The EPO WARF decision confirmed in 2008 that the 'industrial or commercial use' clause, which was introduced to prohibit the commodification of the human embryo, excludes the patentability of hES cells or cell lines on grounds that the production of hES cells requires the destruction of the human embryos used as their sources. The decision rejected to make a distinction between human embryos according to their origin, developmental phase and acceptable uses – distinctions key to national regulations on embryonic research. Instead, the duty of protection embedded in the Directive and the EPC was interpreted to cover all human embryos.

The Board held that the creation of the claimed product is part of its industrial or commercial exploitation, and when it involves the destruction of human embryos it will violate the said prohibition. In this case the performing of the invention (the embryo destruction) was contrary to the specific morality provision of the EPC. In the Board's view this follows directly from the Directive and the EPC not allowing different interpretation. It found unnecessary to discuss points such as whether a European standard of public morality should be applied in the case, whether it is relevant that research in certain European countries involving the destruction of human embryos is permitted, or whether the benefits of the invention for humanity should be balanced against the prejudice to the embryo.

The EPO decisions offer the reading that while European patent law may not build on a European consensus regarding the 'embryo destruction' principle within the framework of the general public morality clause, the moral consensus regarding the commercial or industrial exploitation of human embryos excludes (the patentability of inventions which include) the destruction of embryos in biomedical research. Certainly, patenting hES cells derived from human embryos *may* lead to the industrial or commercial exploitation of human embryos, but there is no indication that the killing of human embryos would equal an industrial or commercial use (the commodification) of those embryos in the sense of the applicable provision of European patent law.

Regarding the route taken with respect to pluripotent hESC patents by the EPO the report coordinated by Aurora Plomer, perhaps the most comprehensive analysis of European patent law, stem cells and bioethics, formulated a number of strong critical points. One of their main argument was that pluripotent hESC may only fall under the 'commercial or industrial use' clause when hESC derivation involves processes that could be defined as commercial and industrial use; that is as defined in the law a "direct, repetitive use of the human embryo as a raw material in a chemical, mechanical or technical process."[421] Equating commercial or industrial use with embryo destruction in creating the invention is a legally ill-conceived interpretation of the Directive.

Furthermore, the report pointed out that the uniform approach imposed by EPO practice or an alternative uniform solution produced under the general morality clause is unacceptable in the light of both the leeway granted by the Directive to European states in this regard and the definitional differences among European states which had originally prompted granting a margin of discretion to them in the Directive.[422] It held that imposing a "uniform moral bar on patents on hESC whose derivation necessarily involves embryo destruction" has no legal basis under the Directive.[423]

[421] Plomer (2008), at 75.
[422] *Ibid.*, at 83 (confirmed by an interview made with Julian Hitchcock, REMEDiE, 16/6/2010).
[423] *Ibid.*

A uniform 'embryo destruction' principle in patent law, as advocated by the EPO, finds no support in forums equipped with jurisdiction develop or indicate the emergence of common European bioethical principles. The human rights instruments in Europe, as we have seen, provide a loose-knit common framework for biomedical research and treatment.[424] Nevertheless, they do not indicate that a European wide consensus has emerged concerning the 'embryo destruction' principle which was embraced vigorously by the EPO.[425] The opinions drafted by the European Group on Ethics, an independent expert body established alongside the European Commission to issue opinions on the ethical implications of science and new technologies, do not suggest otherwise.

The most significant opinion in this respect, EGE Opinion No. 16 (2002) on the ethics of hESC patenting[426], focused on the morality provisions in European patent law as created by the Directive. The opinion introduced new conceptual distinctions to the debate. It distinguished between 'modified' and 'unmodified' hES cells and found that 'unmodified' hES cells are not patentable as their patenting may violate the non-commercialization principle.[427] The opinion, which acknowledged the economic and social purpose of patent systems, was, however, supportive of 'modified' hESC patenting and found no ethical reasons for a complete ban of the patenting of hES cells and cell lines. The 'embryo destruction' principle was left unaddressed by the majority. The single dissident opinion claimed that the patentability of hES cells must be excluded on ethical grounds as the derivation of hES cells involved the destruction of the embryo used as the source of the cells.

A 1993 opinion[428] of the EGE, issued early in the lengthy legislative process of the Directive, formulated an essentially permissive position on the ethical limits of patenting biotechnological inventions with the condition that the Directive would have to address in detail the ethical questions that may arise in patenting certain areas of biomedical research.

The EPO's determination to pursue a uniform 'embryo destruction' principle under the 'commercial or industrial use' clause remains puzzling. A possible explanation is that a shift towards the highest, in this case the most restrictive standard appears as the safest option amidst the plurality of ethical positions. Providing the highest level of protection to human embryos must be acceptable on ethical grounds to all affected parties. Furthermore, the solution devised by the Directive that the patentability of hES cells must be addressed under the general morality clause having regard to the margin of appreciation allowed to states under that clause entails extreme difficulties for an agency in a decisional situation. The accommodation of local social, ethical and cultural factors in the patenting process before the EPO is unrealistic considering the irreconcilable differences between domestic approaches to stem cell research. Patent authorities are generally regarded as ill-equipped to act as arbiters in controversial bioethical cases.[429]

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[424] See, Part 1.

[425] See Plomer (2008), at 59.

[426] Opinion No. 16 (07/05/2002) – *Ethical Aspects of Patenting Inventions Involving Human Stem Cells*, available at ec.europa.eu/european_group_ethics/docs/avis16_en.pdf.

[427] It was criticized that the principle used in this regard, 'closeness to the human body', was not established as a relevant moral consideration and as part of European culture, Plomer (2008), at 33.

[428] Opinion No. 3 (30/09/1993) – *Ethical Questions Arising from the Commission Proposal for a Council Directive for Legal Protection of Biotechnological Inventions*, available at ec.europa.eu/european_group_ethics/docs/opinion3_en.pdf.

[429] Interview with Julian Hitchcock, REMEDiE, 16/6/2010 and EPO Interview with Dr Ingrid Schneider, available at

The compromise solution is allowing the hESC patent in absence of a European ethical common ground noting the possibility that the enforcement of the patent in individual states could be prevented by relying the general morality clause in the domestic context. Deferring the moral decision making (judgment) and the balancing of countervailing values, which would attract as much criticism as the current state of the law, would fit into the current legal framework of European patenting. Nevertheless, producing a legally sound patenting solution would not mean an end to the European debate. The patent granted would be regarded as ethically unacceptable by actors opposing human embryonic research and the effect of deciding against the enforceability of the patent in individual states would undermine further integration in biotechnology, the original purpose of the Directive.

EPO practice concerning the general morality clause, which is to be interpreted narrowly, demonstrates that acknowledging the plurality of moral positions is not alien from the EPO. An EPO Board of Appeal interpretation of the general morality clause[430] provides that the clause focuses exclusively on the immoral exploitations of inventions and inventions cleared under the explicit clauses are not automatically compatible with the general requirements of morality. In the Board's view it requires careful assessment what is covered by the morality clause as there is no single definition of morality based on economic or religious principles which would be acceptable as a standard in European culture. In such a pluralist environment the application of the general morality clause by the EPO would involve the careful weighing of countervailing interests embedded in an ethical dilemma. The scenario when there are irreconcilable differences in ethical views and the interests in conflict are incommensurable was not addressed by the Board.

The Board continued its assessment with citing a 1995 decision[431] in an attempt to define the concept of morality under the EPC. That decision stated that

> The concept of morality is related to the belief that some behavior is right and acceptable whereas other behavior is wrong, this belief being founded on the totality of the accepted norms which are deeply rooted in a particular culture. For the purposes of the EPC, the culture in question is the culture inherent in European society and civilization. Accordingly, under Article 53(a) EPC (the general morality clause), inventions the exploitation of which is not in conformity with the conventionally-accepted standards of conduct pertaining to this culture are to be excluded from patentability as being contrary to morality.

As the Board accepted it, establishing these standards in the patenting procedure may require a considerable volume of evidence from different sources. Polls, for instance, have a limited value of proof.

In another decision the Board held that the rejection of the invention by a number of citizens cannot be equated with a breach of the general requirements of morality.[432] The Board suggested that in the end, the general morality clause involves a decision between the benefits obtainable (e.g. in therapy) by means of the invention and the moral limitations regarding that particular invention.

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documents.epo.org/projects/babylon/eponet.nsf/0/F172DE5BB2B9B15BC12572DC0031A3CB/$File/Interview_Schneider.pdf.

[430] EPO Boards of Appeal Decision, *President and Fellows of Harvard College*, T 0315/03 (6 July 2004), available at legal.european-patent-office.org/dg3/pdf/t030315ex1.pdf.

[431] EPO Boards of Appeal Decision, T 356/93 *Plant Genetic Systems N.V.* (21 February 1995) at paras. 5-6, available at legal.european-patent-office.org/dg3/pdf/t930356ex1.pdf.

[432] EPO Boards of Appeal Decision, T 0475/01 *Bayer CropScience GmbH* (15 June 2004), available at legal.european-patent-office.org/dg3/pdf/t010475du1.pdf.

EPO case law suggests the application of two separate tests under the general morality clause.[433] The first is the 'public abhorrence' test requiring an overwhelming public consensus in Europe that the exploitation or publication of the patent would be immoral. The 'unacceptability' test holds that the disadvantages of the patent to society outweigh the advantages or that the grant of the patent would be unacceptable in the light of the conventionally accepted standards of conduct in European culture. Both assume the necessity of finding an ethical common ground in pluralistic Europe.

It appears that the EPO is aware of the difficulties of applying the general morality clause under the EPC in the morally pluralistic environment of Europe. The task imposed by the general morality clause is nearly impossible when the ethical opinion on a new technology is deeply divided. It is likely that in absence of a settled interpretation in Europe of the moral position of an invention the EPO is prevented from presenting a *negative* decision regarding the patentability of that invention under the general morality clause. This leaves the EPO with the option, if available, of resorting to one of the explicit morality clauses representing a European consensus. When the general morality clause for want of a European consensus is inapplicable and the explicit morality clauses do not exclude the invention, patentability should be allowed with the possibility that the contracting states may prevent the enforceability of the patent on moral grounds within their jurisdiction.

Eventually, the European Union Court of Justice will have to decide what constitutes a permissible interpretation of the morality clauses under the Directive. Its judgment will determine whether 'embryo destruction' falls under the scope of the 'industrial or commercial use' clause and how the general morality clause accommodates diverse ethical viewpoints concerning a single invention. The case of Professor Brüstle[434] now before the EU Cour originated from Germany, where the Federal Patent Court held following EPO practice that the hESC patent in question was in breach of the 'industrial or commercial use' clause as the destruction of human embryos was a "real and integral part of the invention".[435] The German court's interpretation was strongly influenced the German Embryo Protection Act which prohibits the use of human embryos for purposes other than those from which the embryo may receive direct benefits (e.g. diagnosis or treatment of that embryo).[436]

An indication how the EU Court of Justice would approach this question and consolidate the interpretation of the EU Biotech Directive can be found in the Opinion delivered by Advocate General Bot in the case before the court. It set a direction similar to that indicated by the EPO Enlarge Board of Appeal and the German patent court. The Advocate General suggested that the clause on the industrial or commercial use of human embryos excludes from patentability inventions which necessitated the destruction of human embryos.[437]

The Opinion is not binding on the EU Court of Justice and it is not excluded that it will take into consideration the criticisms formulated against the current interpretation of the 'industrial or commercial use' clause. The Court of Justice, as opposed to the Advocate

[433] Beadle (2004).
[434] The questions referred in Case C-34/10 *Oliver Brüstle* are available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:100:0019:0019:EN:PDF.
[435] Judgment by the German Federal Patent Court, AZ: 3 Ni 42/04 (5 December 2006), available at juris.bundespatentgericht.de/cgi-bin/rechtsprechung/document.py?Gericht=bpatg&Art=en&sid=061f0f9e4b6bfd679ba46c7b1fd93fcb&nr=1909&pos=0&anz=1&Blank=1.pdf.
[436] See, in detail in Part 3.
[437] Opinion of Advocate General Bot delivered on 10 March 2011 in Case C-34/10 *Oliver Brüstle*, nyr.

General, may consider the wider social and economic impact of applying the 'industrial or commercial use' clause to hESC patents, and may take into account the interests of Member States where human embryonic research is regulated permissively and have an interest in global hESC research and respect the preferences of States where human embryos are given more stringent protection. More importantly, the judgment will have to establish an interpretation of the morality clauses in European patent law which follows from the EU Biotech Directive and from the relevant bioethical principles, from human dignity in particular.

One option is to follow EPO case law and the opinion of the Advocate General, provided that the EU Court finds their conclusions compatible with the Directive. The alternative route would be dropping the 'embryo destruction' principle from under the 'industrial or commercial use' clause and examine hESC patents under the general public morality clause. This would enable the accommodation of local discretion in assessing whether the destruction of human embryos for research is acceptable in that particular community (state). This option would safeguard the diversity among European states in regulating human embryonic research.

On the level of decision-making in the European patent system the solution accepting the plurality of local bioethical approaches would cause considerable difficulties. Without being able to rely on an explicit morality clause imposing uniform requirements on the Contracting States the EPO will need to apply the general morality clause of the EPC (and the EU Biotech Directive) having regard to the diversity of national approaches on the use of human embryos for research purposes. Adopting the highest standard under the general clause and denying patentability from hES cells would satisfy the States with a prohibitive attitude to human embryonic research but it would be incompatible with the leeway granted under the general morality clause to all States in the European patent system. In contrast, allowing the patentability of hES cells under the general morality clause, having been unable to establish the 'embryo destruction' principle as a common European moral requirement, would satisfy the States with liberal regulation on stem cell research and it would enable States with a prohibitive regime to refuse enforcing the patent within their jurisdiction. This is a compromise solution and the only workable solution in a pluralist, multi-layered regime. The fragmentation of the system, which would follow from this approach and which is contrary to the rationale of the EPC and the EU Biotech Directive, is the responsibility of Article 6(1) of the EU Biotech Directive.

The EU Court would also have to address the issue whether the German implementation of the Directive, which tied the morality clauses to the applicable domestic biomedical research legislation, the Embryo Protection Act, is acceptable under EU law. The strict provisions of the German act should not justify incorporating an 'embryo destruction' principle into the 'industrial or commercial use' clause provided that the interpretation of industrial or commercial use, introduced above following Plomer, is accepted. In contrast, the general public morality clause may be interpreted in the light of bioethical principles expressed in domestic legislation. This is what the margin of appreciation of states under the general morality clause of the Directive offers to states in Europe. Ultimately, this means remitting the ethical assessment under the appropriate morality clause to the domestic court as it was achieved in an earlier German case, *Omega Spielhallen*,[438] with regards to the constitutional requirement of respect for human dignity.

[438] Case C-36/02 *Omega Spielhallen* (14 October 2004), available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:62002J0036:EN:HTML.

European patent law, burdened with a bioethical framework unavailable in other states of the world, faces a difficult choice. Reaffirming existing EPO and domestic practice may keep hESC patenting simple from a legal and governance perspective, noting that it may be contrary to the provisions of the Directive. In contrast, recasting in patent law the bioethical boundaries of European hESC patenting to ensure compliance with the directive would lead to fragmentation in law and obstacles to effective patent governance, both a result of respecting European ethical and legal diversity.

Patent legislation created on the European level

Ethically relevant distinctions determined on the local level, such as distinctions between acceptable and unacceptable hESC sources (i.e. supernumerary IVF embryo from parental project, IVF embryo for research, SCNT embryo for research) and the plurality of national bioethical viewpoints distilled in the political process.

The stakes are high as the EU Court judgment could open or permanently close the European patent market to hESC patents delivering or withholding the considerable benefits and the arguable disadvantages of patents to/from the European bioeconomy. The judgment will affect the patenting policy of the Member States and the patenting practice of the EPO and it will consolidate the interpretation of the EU Biotech Directive the provisions of which were introduced to establish a clear and coherent framework for patenting in biotechnology.

Advocate General Bot's preoccupation with producing a solution under the Directive uniform to all states affected by the Directive. The Directive's efforts to take account of the ethical, social and economic implications of biotechnological patents and the diversity of local approaches to biomedical research (e.g. the definition of the human embryo or the ethical distinctions between different sources of human embryos) render the effort of the Advocate General to provide a purely legal, decontextualized analysis of the Directive dubious. The Advocate General assumed that a uniform solution is required and that only a uniform solution would resolve the difficulties caused by local diversity. This may be supported by the Directive`s intention to foster further integration in the biotechnology market, but this approach is certainly at odds with the lack of competence of the European Union to harmonize bioethical principles in Europe.

The EU Directive set out an ambitious framework for the introduction of bioethical principles into the patenting of biotechnological inventions. This framework, as regards human biological material, ensures in the EU Court of Justice's interpretation "that the human body effectively remains unavailable and inalienable and that human dignity is thus safeguarded."[439] It is based on provisions which either establish unmovable bioethical boundaries, such as the non-commodification of the human body and the human embryo, or provide for the consideration of the diversity of local viewpoints regarding contentious bioethical issues, such as in the general public morality clause. The Directive represents a European consensus, deliberated in the European Union legislative process, committed to certain common bioethical principles and sustaining diversity in the local appreciation of contested bioethical boundaries. Any objection to the patentability of hES cells must be fitted within this framework.

At the current state of the law the moral objection against destroying human embryos is linked to the non-commodification principle expressed in the `industrial or commercial use` clause. The critics of this solution pointed out that the reasoning applied by the EPO in

[439] Para. 77, Case C-377/98.

framing its European 'embryo destruction' principle is legally indefensible and clashes with positions regarding the bioethical limits of biomedical research in the European Union, under the EHCR and in the Member States.[440] The Plomer-report highlighted that there is no European consensus on the level of protection human embryos are morally and legally entitled to in Europe and in this environment the EPC as modified by the Directive does not enable the EPO to impose uniform ethical standards on Europe.[441] This should indicate the boundaries of the coming interpretation of the Directive by the EU Court of Justice.

Furthermore, it crucial for the court's assessment that the TRIPS prevents states from imposing obligations on patent applications other than that allowed under the Agreement. The TRIPS advocates the equality of technologies and demands from the Contracting States to refrain from unduly interrupting their patent laws, for instance, by way of implementing excessive restrictions on ethical grounds.[442] Similarly, a potential misinterpretation of the morality clause, as alleged in the WARF EPO case, could infringe the obligations of states under the TRIPS. The Plomer-report emphasized that the 'moral guillotine' of the EPO WARF decision is incompatible with the TRIPS.[443]

The European patent regime is an exception in the world in many respects. First, proclaims and applies in the patenting process the ethical principles delimiting innovative activity in biotechnology. Also, it maintains a patent system which is intended to accommodate the diversity of bioethical viewpoints in European states. Finally, it is based on a multi-tiered regional system of governance with multiple loci of authoritative interpretation. The great strength and weakness of the regime lies in the same place; it enables in a multi-level environment the assessment of the complex, often competing and incommensurable considerations of patenting in biomedicine.

The consolidation of the ethical-legal controversies of European patent law in the area of regenerative medicine, expected from the EU Court of Justice in Brüstle. In absence of a unitary European patent,[444] the non-hierarchical, multi-tiered European patent regime must consider moral pluralism and local moral assessment as its virtues. In legal terms and from a governance perspective this may appear as unsatisfactory,[445] nevertheless, it provides a solution with more benefits than open regulatory competition in the field of biomedical innovation.

2.3. Summary

In a globalised economy and globalised law for that economy the presumed cultural differences diminish. The approach of national patent laws on biomedical inventions is shaped by international agreements – globally, but less intensively by the TRIPS, regionally, but with high intensity by the EPC and the EU Directive. Borrowing legal solutions from other jurisdictions to be transplanted in the domestic legal system also reduces diversity.

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[440] Plomer (2008), at 83 and116.
[441] *Ibid.*, at 55.
[442] Gold and Gallochat (2001), at 359–360, 362.
[443] Plomer (2008), at 77–78.
[444] Its most recent revival: European Commission Proposal for a Regulation of the European Parliament and the Council implementing enhanced cooperation in the area of the creation of unitary patent protection, COM(2011) 215/3.
[445] It was stated that the Directive is defective and full of loopholes: in particular it fails to expel ethical considerations from patent law, see Tade Matthias Spranger, Europe's Biotech Patent Landscape: Conditions and Recent Developments, *Minnesota Intellectual Property Review*, vol. 3 no. 2 (2002) 235–249, at 249.

The implementation of an 'embryo destruction' principle in patent law within the examination of patentability remains a pressing questions in different patent jurisdictions despite the appearance of an allegedly ethically unproblematic, although admittedly risky, technology which enables the creation of pluripotent stem cells from somatic cells, therefore reducing the need for hES cell lines.[446]

Regulatory diversity based on ethical and cultural divergences among European states has remained a concern that might inhibit the realisation of the economic and social benefits associated with biomedicine.

The legislative history of the Directive indicates non-instrumentalisation and accommodating local diversity under the general morality clause. The explicit morality clauses suggest. No indication that hES cells (pluripotent) would be subject to a European , embryo destruction. The application of the Directive whether the absolute clauses on patentability would impose restrictions uniform bioethical

The European legal landscape is characterized by multiplicity based on local discretion and by an overarching framework imposing uniform requirements while respecting local diversity. An important characteristic of the European framework is that in contrast to European human rights law, European economic law in the narrower field of intellectual property rights has been driven to establish a bioethical common ground in human embryonic research. With the Opinion of the Advocate General published in March 2011[447] it appears likely that European patent law and patent laws in Europe will introduce a uniform 'embryo destruction' principle despite the national differences in determining the ethical limits of biomedical research regulation.

Since the creation of the ethically enhanced EPC framework the EPO has exercised its jurisdiction under redesigned morality clause and delivered patent decisions which defined the interpretation of the morality exceptions in the European patenting landscape. These decisions point towards a European consensus on the patentability of ethically controversial technologies, in particular, of hES cells or cell lines. The EPO embraced the 'embryo destruction' principle within the 'industrial or commercial use' morality clause and elevated it into the position of a Europe wide accepted bioethical norm.

3. Local LIMITATIONS to Global Patenting in Regenerative Medicine: Case Studies

In the era of globalised health care industry and biomedical research a clash between global expectations and local regulatory and value systems is inevitable.[448] In the absence of robust global value systems and regulation and with regional regulatory frameworks acknowledging local discretion global aspirations, i.e. securing global patents or managing a global framework for biomedical research and clinical trials, are required to adhere to rule and value systems established on the local level. This means incorporating regulatory diversity into global research and business strategies and realizing that the same activity, research and business model may not be implemented in different jurisdictions.

The challenge of diversity, the cost and burden of adhering to different sets of local cultural, bioethical and legal standards, has been addressed in attempts at global and regional harmonization. The most significant example is the European Union which has been pursuing an active program of harmonization in the broader area of biomedical research.

[446] The new technology (iPS) was considered not as an alternative, but a complementary technology, *ibid*., at 6–7.

[447] Opinion of Advocate General Bot delivered on 10 March 2011 in Case C-34/10 *Oliver Brüstle*.

[448] See David C. Thomasma, Evolving Bioethics and International Human Rights, in David N. Weisstub and Guillermo D. Pintos: *Autonomy and Human Rights in Health Care* (Dordrecht: Springer, 2008), at 11.

Harmonization was achieved by measures, such as the Directive on the legal protection of biotechnological inventions, the Regulation on advanced therapies and the Directive on medicinal products for human use.[449] While harmonization has had considerable achievements, mainly in areas where consensus on the limits of biomedical research was in reach, such as expressing in legal terms the principle of non-instrumentalization and non-commodification of the human body, in more contentious issues, such as the moral status of human embryos or from what sources may human embryos used for research, harmonization instead of imposing uniform rules gave way to local discretion. Developments encroaching upon local discretion, such as the adoption of a uniform 'embryo destruction' principle in European patent law has been received with suspicion. States favoring their sovereign assessment of the ethical limits of biomedical research are concerned that such development endangers local economic, research and development and health-care policies.

The diversity of local approaches regarding the ethical limits of biomedical research and patenting in biomedicine has affected the opportunities of corporations and research institutions in obtaining a global protection for their patents. This has an impact on their global research and business strategies which, in the case of crucial basic research tool or diagnostic method patents, affects local economies, health-care systems and, inevitably, human life. The problems the diversity of national approaches to biomedical patenting may entail can be accurately demonstrated by three case studies on global patenting. The first case study deals with the patent litigation history of the Myriad BRCA 1 and 2 patents, relating to inventions of key DNA based diagnostic method of breast and ovarian cancer. The second examines the turns of the hES cell global patenting saga. Both of these instances reveal the sharp contrast between the utility driven US patent system and the ethically charged European patent law. The third case study deals with the global patent war waged for the intellectual property rights on iPS technology and the structures created for the rapid dissemination and commercialization intellectual property relating to this fundamental tool in regenerative medicine.

3.1. Global Patents on Genes for Cancer Testing

The BRCA 1 and 2 patents, granted in 2001, were the result of research at the University of Utah and were assigned to Myriad, a spin-off company for commercialization. The patent description covers the DNA sequence for BRCA 1 and 2 and a method for its diagnosis. The patenting in the US faced no difficulties as under the distinction between products of nature and products of human ingenuity, as introduced in *Diamond* v *Chakrabarty*,[450] isolated human DNA sequences with a sufficient description of their utility are regarded as patentable inventions.

[449] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:213:0013:0021:EN:PDF, Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, available at ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf.

[450] 447 US 303 (1980).

The European reception of Myriad's patents was less straightforward. The general legal background for human DNA patents in European patent law is fairly clear. As opposed to US patent law, it applies a strict distinction between discoveries and inventions. Article 5(1) of the EU Biotech Directive contends that the discovery of parts of the human body (and the human body) is not regarded as inventions and excludes their patenting. However, paragraph 2 of the same Article holds that human biological material, such as DNA sequences, isolated from the human body or produced in a technical process are indeed inventions and, therefore, patentable subject to the requirements of patentability under the Directive. One of these requirements is avoiding the exclusion of inventions from patentability on bioethical grounds as provided in Article 6.

The European patent (No. 699754) on the Myriad diagnostic method[451] met with opposition and the patent was put before the EPO Board of Appeal (BoA). The patent claim was amended and the BoA accepted that the amended patent was compatible with the EPC.[452] Thus the diagnostic method patent of Myriad was given protection under the EPO framework, however, in a form narrower than originally claimed by Myriad.

Myriad was also required to amend its other patents under the EPC. The application for gene patent No. 705903[453,] granted originally in 2001, had to be modified to a large extent and was accepted finally as patentable by the BoA in 2008.[454] The isolated BRCA 1 gene patent[455] (No. 705902) was also substantially amended retaining only the claims relating to a specific nucleic acid probe and vectors containing gene sequences; the appeal against the modification was rejected by the BoA.[456] The two gene patents were found by the BoA to satisfy the industrial applicability requirement as they are not mere research tools but as capable of being applied commercially in diagnosis. A similar conclusion was reached regarding the diagnostic method patent.

In the BRCA 1 gene patent decision the BoA was requested to address the question whether human DNA sequences should be classified as discoveries instead of inventions as gene sequences appear in nature. The BoA rejected this possibility as European patent law accepts that elements isolated from the human body including the sequence or partial sequence of a gene are patentable, even if the structure of that element is identical to that of a natural element.[457] The focus of European patent law on isolation as the human contribution which transforms discoveries into patentable inventions fits into global trends on patenting human biological material. Its result is essentially similar to that of the product of nature/product of human ingenuity established in US patent law; that is lowering the threshold of the inventive step requirement to performing biotechnological interventions, such as isolation, modification or purification. The ongoing lawsuit against Myriad in the US, discussed below, may alter US patenting policy on human gene patents which may have global implications in patenting practice.

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[451] Method for Diagnosing a Predisposition for Breast and Ovarian Cancer.
[452] T 0080/05 19 November 2008, available at www.epo.org/law-practice/case-law-appeals/pdf/t050080eu1.pdf.
[453] Mutations in the 17q-Linked Breast and Ovarian Cancer Susceptibility Gene.
[454] T 0666/05 13 November 2008, available at www.epo.org/law-practice/case-law-appeals/pdf/t050666eu1.pdf.
[455] 17q-Linked breast and ovarian cancer susceptibility gene.
[456] T 1213/05 27 September 2007, available at www.epo.org/law-practice/case-law-appeals/pdf/t051213eu1.pdf.
[457] Same conclusion reached in T 0666/05. The diagnostic method claim was also cleared following the same argument in T 0080/05. The diagnostic method claim was found as patentable steps of technical nature are performed on a tissue sample of a human subject and not on the human or animal body which is not acceptable under Article 53(c) EPC.

The bioethical objections, the most genuinely European element in the Myriad saga, raised against the BRCA 1 patent were also rejected, just as in the earlier Relaxin gene patent case.[458] The requirements, presented in objection to the patent, that prior informed consent needs to be obtained from donors and that a system (agreement) for benefit sharing needs to be arranged were found without foundation in the European patent regime. Without express provisions in the EPC (and the Directive) supporting such requirement, the BoA was not prepared to extend the general public morality clause to incorporate these bioethical principles. It declared that prior express informed consent is for national law to regulate in the research process, and not a requirement in European patent law. Support for this conclusion was also found in the judgment of the EU Court of Justice in Case C-377/98 on the validity of the EU Directive which stated that European patent law (the Directive) does not "extend to activities before and after" granting the patent and that the Directive does not exclude national law demanding compliance with ethical rules outside the scope of the patenting procedure.[459] The Advocate General's opinion in the same case reached the same conclusion (that patent law is not the appropriate framework for the imposition and monitoring of the informed consent requirement).[460]

The requirement of benefit sharing, which concerned the adverse socio-economic impact of creating a monopoly by granting a patent on a DNA sequence, and, in particular, reduced patient access to diagnosis and increased costs for health care systems affecting patient treatment as a result of the patent, was found to fall outside the scope of the public morality clause of the EPC on grounds that the clause refers to the exploitation of the invention and not the effects of the exploitation of the patent. The argument that in this particular case the exploitation of the patent overlapped with the exploitation of the invention and had an adverse impact on public health was rejected on the grounds that the BoA may not distinguish between technical fields in interpreting the conditions of patentability. Crucially, the BoA argued that the economic effects of patents are not for the BoA to assess and such considerations may not be introduced into the examination of patentability. It continued that examining the patentability of inventions may not lead to declaring an invention unpatentable on the basis that the patent will deliver the economic benefit (the exclusionary nature) generally associated with patents. Patents create a protected position on the market by enabling the patent holder to prevent competitors from using the invention; this cannot be challenged in the patenting process.[461]

The challenge against Myriad's patent continued with the argument that the EU Directive was implemented in some of the Member States with a view that the socio-economic and ethical concerns of gene patents are taken into account in the patenting process. This was rejected on grounds that the national implementation of the Directive is a

[458] The objection raised concerned the breach of human dignity – that DNA patents would represent a patent over life and that DNA patents was a form of slavery. In the Opposition Division's interpretation the morality clause may only be invoked in the case of inventions which would universally be regarded as outrageous. It accepted, however, that if the three ethical objections were well founded, the patentability of the gene sequence would be excluded. *Official Journal* of EPO, 1995, 388. Confirmed in EPO Board of Appeal Decision, *Howard Florey Institute* T 0272/95 (23 October 2002),available at legal.european-patent-office.org/dg3/pdf/t950272eu2.pdf

[459] Paras. 79-80, Case C-377/98, *The Netherlands* v *Council and Parliament* (9 October 2001), available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:61998J0377:EN:HTML.

[460] Opinion of Advocate General Jacobs delivered on 14 June 2001 in C-377/98, *The Netherlands* v *Council and Parliament*, available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:61998C0377:EN:PDF.

[461] T 0666/05 and T 0080/05 accepted these arguments established in T 1213/05 relating to the socio-economic impact of patents as valid.

matter irrelevant from the perspective of the EPC and that there is no indication in the law that the correct implementation of the Directive under the EPC would have required the adoption of an approach similar to that in certain EU Member States (France and Germany).

Despite the hostile reception in Europe Myriad managed to secure patent protection for the BRCA 1 and 2 genes and the related diagnostic method both in the US and Europe. In Europe the gene patents encountered severe opposition on bioethical and public policy grounds reflecting the concerns which had arisen in society with regards to human DNA patents. This resulted in severe delays in obtaining the patents for the European market. The past years saw further challenges in the patenting domain threatening the global position of Myriad in the market of cancer diagnosis.

The latest challenge, now in the US market, came from a case before the US District Court for the Southern District of New York which on 29 March 2010 invalidated certain Myriad BRCA 1 and 2 patents.[462] The summary judgment was delivered in a case which originated from the lawsuit of the American Civil Liberties Union with Myriad, the University of Utah and the USPTO on the opposing side. The patents, those involving isolated DNA sequences and those involving methods for comparing gene sequences, were invalidated under Section 101 of the Patent Act on patentable subject matter. In the court's opinion the claims on isolated DNA sequences are insufficiently distinct from DNA naturally occurring in the human body; the isolated DNA sequences in question were declared to be products of nature under US patenting doctrine. The human intervention, isolation, was not found to produce markedly different characteristics than that possessed by genes in the human body. This development contradicts previous patenting practice in which isolated genes were held to possess distinct chemical characteristics.

Myriad appealed the decision. The next round is scheduled before the Court of Appeals of the Federal Circuit for April 2011. Regarding the potential outcome of the appeal a dissenting opinion from Judge Dyk at the Court of Appeals of the Federal Circuit in a case involving porcine virus DNA needs to be mentioned.[463] The judge suggested that isolated DNA may be unpatentable as in order for a product of nature to be patentable it must be qualitatively different from the product occurring in nature with markedly different characteristics from characteristics found in nature. He concluded that it is unclear whether isolated DNA would have such characteristics leading to its differentiation under patent law from DNA in the human body.

With the reassessment of the product of nature/human ingenuity distinction doctrine in relation to human DNA patents these judgments indicate how in absence of previous rulings from the Court of Appeals of the Federal Circuit and the Supreme Court on gene patents the law and patenting policy will develop in the US. The possible change of direction was also acknowledged in the US government's amicus brief to the case in appeal which stated that isolated human genes are a product of nature and not patentable under the Patent Act.[464] The potential global impact of US policy change is difficult to predict; in Europe only the amendment of the explicit clause of the EU Biotech Directive could lead to a similar change.

It was an interesting turn in the Myriad global patenting saga when in 2010 Myriad offered one of its patents "as a gift (...) to the Australian people"; in a commentator's view this was to avoid that the litigation in Australia would lead to a damaging end as it

[462] *ACLU* v *Myriad Genetics*, 09 Civ. 4515, available at patentdocs.typepad.com/files/opinion.pdf.
[463] *Intervet Inc.* v *Merial Ltd.*, Fed Cir 4/8/2010.
[464] www.genomicslawreport.com/wp-content/uploads/2010/11/Myriad-Amicus-Brief-US-DOJ.pdf.

happened in the recent US case.[465] The Australian litigation is a test case to challenge the validity of Myriad's patents which despite Myriad's offer has not been closed.[466] If the surrender of the patent is accepted the case would come to an end, but at the same time Myriad's position would weaken in the Australian market opened for Myriad's competitors to enter.

Myriad's global position has also been weakened by new research and commercial developments in diagnostic testing for cancer. With the appearance of new and cheaper testing methods in 2010[467] and the announcement of two European research hospitals to utilise diagnostic tests offered by other companies[468] Myriad's domination supported by its global patents is under challenge. The adverse court rulings limiting its patents have already induced Myriad to raise the costs of its diagnostic tests considerably. Myriad's commercial position looks vulnerable with the overwhelming majority of its profits coming from a single product and a single market (US) where it is the exclusive provider of the diagnostic methods.[469]

Myriad has already pronounced to expand its business in the European market where its patents remain unchallenged.[470] As to its European patents it is questionable whether it will be able to improve its position by relying or enforcing them contrary to public opinion and policy. With the patents to expire within a few years the commercial position of Myriad in the global market may need to be enforced by competitive means other than intellectual property rights.[471]

The European possibilities for gene patents, which are brighter than those in the current circumstances in the US, should be seen in the light of the 2010 judgment in Case C-428/08 Monsanto from the Court of Justice of the European Union.[472] The Court of Justice emphasised that patenting gene sequences under the EU Biotech Directive is subject to indication of the function the DNA sequence performs. For the gene sequence to enjoy patent right protection under the Directive it must be able to perform the function for which it was originally patented. Moreover, the Directive precludes national patent law to grant absolute protection to gene sequences regardless whether they are able to perform its function. This also applies to patents granted before Directive. The judgment reflects national practices (Germany, France, Italy and Luxembourg) in the implementation of the Directive limiting the scope of DNA patents to the function and purpose of the gene sequence.[473] It also resonates with Opinions 3 and 8 of the European Group of Ethics which held that gene sequences may only be patented when the identified function attached to a human gene allows new scientific or therapeutic possibilities and the intended use of the

[465] www.genomicslawreport.com/index.php/2010/10/07/update-continued-speculation-on-myriads-motives-down-under/.
[466] www.genomicslawreport.com/wp-content/uploads/2010/10/Cancer-Voices-Australia.pdf.
[467] Tom Walsh et al., *Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing*, available at www.pnas.org/cgi/doi/10.1073/pnas.1007983107 and Steven L. Salzberg et al., Do-it-yourself genetic testing, 11 GENOME BIOLOGY (2010), 404.
[468] www.genomeweb.com/sequencing/two-european-labs-turn-next-gen-sequencing-brca12-testing?page=show.
[469] *Ibid.*
[470] investor.myriad.com/releasedetail.cfm?ReleaseID=486336.
[471] www.genomicslawreport.com/index.php/2011/03/01/how-will-myriad-respond-to-the-next-generation-of-brca-testing/#more-5337.
[472] Case C-428/08 *Monsanto* (6 July 2010), available at eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:62008J0428:EN:HTML.
[473] Ingrid Schneider, *Civil Society Challenges Biopatents in the EU*, PROPEUR NEWSL. (Prop. Reg. Eur. Sci., Ethics & L. Project, Birmingham, U.K.), Summer 2005 at 3, available at www.propeur.bham.ac.uk/1stnewsletter.pdf.

patent is sufficiently specific and identified.[474] Opinion 3 with reference to the ongoing legislative process of the Directive urged the European Community to take a stand against the commercial exploitation of the human body.

The global patentability of human DNA remains a contested territory with diverse solutions in patent laws. The approaches range from excluding it from patentable subject matter to limiting the scope of the patent by imposing requirements on the patentability of genes. The difference in the routes taken by European and US patent law is reinforced by the treatment of the BRCA 1 and 2 diagnostic method claim. In the US it was found to fail to meet the 'machine or transformation test' in US patent law and was considered as an abstract mental process, therefore unpatentable.[475] In contrast, the EPO claimed that the diagnostic method was patentable it being performed on a tissue sample of a human subject. Diagnostic methods are excluded from patentable subject matter under the EPC in the case when "the method steps of technical nature belonging to the preceding steps which are constitutive for making a diagnosis as an intellectual exercise are performed on a living human or animal body".[476]

3.2. Global patents on HES cells

The patenting history of the Wisconsin Alumni Research Foundation (WARF) hES cells is another indication how diversity in patent laws, in how patent law links with the bioethical limitations of human innovative activity, affects the global commercial exploitation of inventions through patents in biomedicine. The difference is visible – while in the US the WARF stem cells were patented (US Patent No. 5,843.780 (1996), 6,200,806 (1998) and 7,029,913 (2001)) and licensed exclusively to Geron Corp. involved in financing Thomson's research at Wisconsin University, the EPO, despite patents having been granted to the WARF cells in European states, such as the UK or Sweden, rejected the WARF patent on bioethical grounds. The law in Europe remains unsettled with the EU Court of Justice now having the opportunity to affirm or amend the practice developed by EPO on the patentability of hESC patents.

Lacking explicit bioethical provisions in US patent law the WARF patents were not challenged in the US on ethical grounds as in Europe. Nonetheless, the WARF cells being essential research tools for up- and downstream biomedical research have been subject to contestation. The recently decided re-examination of WARF's 7,029,913 patent, which as a result was invalidated by the USPTO Board of Patent Appeals and Interferences, concerned the technical questions of anticipation and obviousness in the light of prior art of the invention.[477] While the invalidation liberated the research community from a crucial patent, WARF`s other hESC patents and the license agreements relating to them remain unaffected.

The patenting of the WARF cells attracted an entirely different consideration in Europe. The US route, where federal patent law lacking a general and the explicit public morality

[474] Opinion No. 3 (30/09/1993) – Ethical Questions Arising from the Commission Proposal for a Council Directive for Legal Protection of Biotechnological Inventions, available at ec.europa.eu/european_group_ethics/docs/opinion3_en.pdf and Opinion No. 8 (25/09/1996) –The Ethical Aspects of Patenting Inventions Involving Elements of Human Origin, available at ec.europa.eu/european_group_ethics/docs/avis8_fr.pdf.
[475] *ACLU* v *Myriad Genetics*, 09 Civ. 4515, available at patentdocs.typepad.com/files/opinion.pdf.
[476] T 0080/05 and T 0666/05 relying on Opinion G 1/04 of the EPO Enlarged Board of Appeal.
[477] *Foundation for Taxpayer and Consumer Rights and Public Patent Foundation* v *WARF*, B.P.A.I. No. 2010-001854, 4/28/10.

clauses is prevented from having to accommodate the federal and state-level bioethical positions on stem cell research, is not available in European patent law. The EPC and national patent laws following the EU Biotech Directive provide for the exclusion of patentability of inventions in breach of public morality identifying four explicit bioethical limitations uniformly applicable in Europe. One of them, the clause concerning the industrial or commercial use of human embryos, proved to be crucial for the commercialisation strategy of WARF and Geron.

After a long opposition process before the EPO against the WARF stem cell patents the Enlarged Board of Appeal confirmed in 2008[478] that the 'industrial or commercial use of human embryos' clause, which was introduced to prohibit the commodification of the human embryo, excludes the patentability of hES cells or cell lines on grounds that at current state of the art the derivation of hES cells requires the destruction of the human embryo used as the source. The decision rejected to make a distinction between embryos according to their origin, developmental phase and acceptable uses, a distinction key to national regulations on human embryonic research. Instead the duty of protection embedded in the EU Biotech Directive and the EPC was interpreted to cover all human embryos.

As a justification for the application of the 'industrial or commercial use' clause the Board held that the creation of the claimed product (hES cells) is part of the industrial or commercial exploitation of hES cells. When the process of creation involves the destruction of human embryos it will violate the prohibition laid down in the rule concerning uses of human embryos for industrial or commercial purposes. The Board continued that it is not the act of patenting but the performing of the invention (the embryo destruction) that is contrary to the morality provision of the EPC. The arguments that the Board needs to establish whether the prohibition of the destruction of (research) embryos is a common European standard of morality, that research in certain European countries involving the destruction of human embryos to obtain stem cells is permitted, and whether the benefits of the invention for humanity should be balanced against the prejudice to the embryo were not discussed by the decision.

Human embryonic stem cell patents are by no means a closed chapter in the history of European patenting. In the multi-layered European patent system there are multiple forums for the interpretation of the bioethical limitations of patentability imposed by the EU Biotech Directive. Now, it is for the EU Court of Justice, equipped with jurisdiction for the interpretation of the Directive, to provide an interpretation of the 'industrial or commercial use' clause and establish whether the 'embryo destruction' principle should be regarded as a bioethical common ground for Europe.

The case before the EU Court originated from Germany involving a challenge mounted by Greenpeace against the stem cell patent of Professor Oliver Brüstle registered in Germany in 1999[479] and granted under the EPC in 2006.[480] In 2006 the German Federal Patent Court responded to the dilemma whether the patentability of an invention should be excluded on the grounds that the invention entailed the use of hES cells the derivation of

[478] EPO Enlarged Board of Appeal, G-2/06, documents.epo.org/projects/babylon/eponet.nsf/0/428862B3DA9649A9C125750E002E8E94/$FILE/G0002_06_en.pdf.
[479] Patent number DE 197 56 864 (C1).
[480] Patent number EP 1040185. Patented in Japan under number P2001526884 and in the USA under number US2008213888.

which inevitably necessitated the destruction of the human embryos used as their resource by annulling the German patent to the extent that it involved the production and use of cells created form hES cells which had been derived from human embryos.[481]

The legal basis of the decision, not dissimilar from the EPO WARF decision, was the explicit morality exception in European and German patent law which prohibits the uses of human embryos for industrial or commercial purposes as stipulated by the EU Biotech Directive and the implementing domestic legal provision. The judgment held that in the case of a patent involving hES cells embryo destruction in the course of the derivation of those cells cannot be treated as a distant and potentially irrelevant possibility – it is a real and integral part of the invention. The fact that human embryonic stem cell lines are essential to the invention is sufficient to exclude the invention from patentability as the destruction of human embryos is a necessary preliminary activity. The question whether this ethical issue can be expressed in patent law was resolved, with heavy references to the local legal and ethical environment, in the following way.

The German court was convinced that the 'industrial or commercial use' clause, uniformly applicable in European states, should be read in the light of the German Embryo Protection Act which prohibits the improper uses of human embryos including the derivation of pluripotent stem cells from human embryos. The Act only enables the use of human embryos from which the embryo may directly benefit (e.g. diagnosis or treatment of that embryo), and obtaining stem cells from the embryo for further research and therapies does not represent such a case – the hoped benefit is distant and general. The court's final conclusion was that the 'industrial or commercial use' clause demonstrates that the legislator had given supremacy to the constitutional protection of human embryos over the inherently commercial characteristics of inventions.

As to exemption of imported hES cells under the Stem Cell Act, harvested outside of German jurisdiction, the Federal Patent Court noted that it does not follow from the ethical acceptability of hESC importation under biomedical regulation that inventions involving imported hES cells would automatically be regarded as patentable. The court expressed the view that the constitutional protection of human embryos goes beyond the distinction applied in bioethical regulation based on their country of origin and the date of their destruction. It held that in the case of imported hES cells the ethical assessment of their creation must not be left out of account in patent law.

The analysis of the reasoning in the EPO and the German decisions is provided in Part 2. The European patenting of hES cells depends on whether the EU Court of Justice would be able to depart from the legal position adopted in Germany by the EPO and the German court. The opinion of the Advocate General on 10 March 2011 indicated otherwise echoing the tenor of the EPO WARF decision concerning the patentability of hES cells under European patent law.[482] The concept of uses of human embryos for industrial or commercial purposes, which has dominated the legal assessment of hESC patents, was interpreted in the following way.

The first issue the Advocate General sought to clarify was whether there was a definition for 'human embryo' common in Europe and whether this definition, given for the purposes

[481] Judgment by the German Federal Patent Court, AZ: 3 Ni 42/04 (5 December 2006), available at juris.bundespatentgericht.de/cgi-bin/rechtsprechung/document.py?Gericht=bpatg&Art=en&sid=061f0f9e4b6bfd679ba46c7b1fd93fcb&nr=1909&pos=0&anz=1&Blank=1.pdf.

[482] Opinion of Advocate General Bot delivered on 10 March 2011 in Case C-34/10 *Oliver Brüstle*, nyr.

of the Directive, would include human pluripotent stem cells. According to the Opinion the concept of a human embryo applies from the fertilization stage to the initial totipotent cells and to the entire ensuing process of the development and formation of the human body including the blastocyst. The unfertilized ova into which a cell nucleus from a mature human cell has been transplanted or whose division and further development have been stimulated by parthenogenesis are also included in the concept of a human embryo in so far as the use of such techniques would result in totipotent cells being obtained. However, human pluripotent stem cells are not included in that concept because they do not in themselves have the capacity to develop into a human being.

The second issue the Advocate General dealt with was whether the prohibition of human embryo destruction is an ethical principle common to Europe under European patent law. According to the assessment, which follows that of the EPO and the German court, inventions are unpatentable when the application of the technical process for which the patent is filed necessitates the prior destruction of human embryos or their use as base material, even if the description of that process does not contain any reference to the use of human embryos. The Advocate General added that the exception for inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it is applicable under this rule.

The most striking feature of the opinion was that it expressly avoided the ethical, social, commercial and scientific implications of the issue declaring it as a matter for pure legal assessment based on scientific evidence. The general legal considerations on human life in national or international law were also neglected. The argument for decontextualizing hESC patenting was that with such a complex background only a legal analysis could provide a solution acceptable to all the Member States.

The analysis of the Advocate General's opinion is provided in PART 2of this Report. The opinion has affirmed that patenting hES cells in Europe is subject to considerations different from those applied in other parts of the world. It is now for the EU Court of Justice to examine on the basis of the EU Biotech Directive that the link created first by the EPO's legal reasoning between the 'industrial or commercial use' clause and the destruction of research embryos is good law and the European patenting market should stay isolated from the global scene for biomedical patenting. The other option would be the eradication of the difference in the European approach to hESC patenting which, however, as explained in **PART 2** would introduce a new element of diversity – that among European states following the local appreciation of the acceptability of human embryonic research.

3.3. Global iPS patents

The short but vivid patenting history of iPS cells offers invaluable insight into processes in global biomedical patenting. Here, not the ethical controversies of the patents provide grounds for discussion but the intensive race between iPS research hubs around the world to obtain the crucial patent in a lucrative local market. Somatic cell redifferentiation, the creation of pluripotent cells by inducing somatic cells to redifferentiate, is generally regarded as the alternative technology for the production of pluripotent cells which avoids the dominant ethical controversy of hESC research, the destruction of human embryos in

the process of stem cell derivation.[483] In principle, inventions based on iPS technology do not face the ethical restraints in patenting which are applicable to human embryo based hESC research.

Patenting activity in iPS technology has not remained immune to controversies despite the lower bioethical sensitivity of cell redifferentiation. Without the gene and hESC patent battles coming to a conclusive end a new front has been opened in the patent war in the field of biomedical inventions. The invention of the core technology is associated with Shinya Yamanaka at Kyoto University who produced the first non-human iPS cells in 2006 and the first human iPS cells in 2007. James Thomson from the University of Wisconsin published a similar technology for the production of human iPS cells on the same day Yamanaka's research was published in 2007. Other researchers were also successful in developing and using iPS technology, namely Rudolf Jaenisch from the Whitehead Institute (US) and Kazuhiro Sakurada then working for Bayer Schering Pharma in Japan.

The first human iPS cell patent in the world was issued in Japan (2008-131577) upon the application by Kyoto University where the iPS pioneer Shinya Yamanaka is a research professor at the renowned iCeMS (Institute of Integrated Cell-Material Science and directs the CiRA (Centre for iPS Cell Research and Application). The patent was based on a 2008 divisional patent application which followed Kyoto University's much broader international patent application in 2006 (PCT/JP2006/324881). The patent was granted in 2008 by the Japanese patent office in a fast-tracked rapid examination within 3 months of the original request for examination. The 2008 patent involves human iPS cell technology and was claimed to ensure protection for Yamanaka's invention while the 2006 global application, which involved a claim for iPS cell technology from all species (except a germ cell), is under examination. The divisional patent application and the expedited process was necessary in order to avoid constraints by overlapping patents from other operators, such as Bayer Schering, iZumi Bio and iPierian, and allegedly to keep the patent and the invention in the public domain.[484]

Speeding up the patenting process was crucial for Kyoto University as in 2007 in the Japanese patent race Bayer Schering submitted a human iPS cell technology patent application based on Sakurada's work (2007-159382). Bayer Schering claimed that they had priority over the Yamanaka-claim as they had managed to create human iPS cells three months before Yamanaka (and Thomson) published the results of their groundbreaking iPS research. While in Japan with the grant of the 2008 divisional patent for Kyoto University Bayer Schering's claim for priority was defeated, in the UK the UKIPO decided to grant the iPS patent to Bayer Schering on 12 January 2010 (GB0810897.9). This was the second iPS patent in the world and the rights to the patent claims was acquired by iPierian, a company based in San Francisco with which Sakurada had been affiliated. Yamanaka, Sakurada and iPierian (formerly iZumi Bio) were known to have been affiliated in the early stages of iPS research.

The geographically segregated patent landscape was further divided when the US patent for the most lucrative US market was snatched in February 2010 by Rudolf Jaenisch and Konrad Hochedlinger and biotech company Fate Therapeutics Inc. which now holds an exclusive licence. The situation was similar to that in Japan and the UK with the difference

[483] Nancy M.P. King, Chris Nero Coughlin, Mark.E. Furth, Ethical Issues in Regenerative Medicine, *Wake Forrest University Research Paper Series in Legal Studies*, Working Paper No. 1380162, 2009, ssrn.com/abstract=1380162, at 6-7.
[484] www.icems.kyoto-u.ac.jp/e/.

that in the US Jaenisch claimed (2003) priority over Yamanaka`s technology. Jaenisch is said to have created the theoretical background on the basis of which Yamanaka was able to produce human iPS cells.

In the meantime, Kyoto University acquired in 2009 two more iPS patens in Japan (2009-056747 and 2009-056750) which describe novel methods for the generation of iPS cells and the induction of differentiation. By now more than 70 research groups have filed iPS patent applications. The latest developments in iPS technology which render the technology behind the early iPS patents obsolete[485] may make the patenting turmoil surrounding the Kyoto-type technology now irrelevant.

The geographical division within the iPS patent landscape, which is an acute problem for holders of foreign patents that wish to enter the US market, was attempted to be remedied on 7 May 2010 when a new non-exclusive licensing agreement on the Kyoto iPS patents with US-based CellularDynamics International (CDI) and iPS-Academia Japan (iPS-AJ) was concluded. CDI is the world's largest producer of cellular tools derived from iPS cells, and was founded by James Thomson. Cellular Dynamics International (CDI) and its sister company, Stem Cell Products, Inc. (SCP), were originally formed based on hES cell technology and IP licensed from the Wisconsin Alumni Research Foundation. Motivated by the promise of iPS cell technology, CDI and SCP merged in 2008 into a single company, Cellular Dynamics International. iPS-AJ manages iPS cell-related intellectual property owned by Kyoto University developed by Yamanaka.

This agreement was the first international licensing agreement of the Kyoto iPS patents. It was concluded according to iPS-AJ's licensing policy which emphasizes the importance of utilizing intellectual property arising from iPS technology for the benefit of society in line with the aims of the Council for Science and Technology Policy's "Guidelines for Research Licenses for Intellectual Property Rights Stemming From Government-Funded Research and Development at Universities, etc. (May 23, 2006)" and its "Guidelines for Facilitating the Use of Research Tool Patents in the Life Sciences (March 1, 2007)."[486] Accordingly, non-profit entities are granted nonexclusive licenses that, as a general rule, are free of royalties. Licensing to profit-making entities is also fundamentally nonexclusive, and royalties will be set at a level that is both appropriate and reasonable to encourage wide-ranging utilization of the fruits of iPS cell research. It was claimed that iPS-AJ's licensing policy is largely similar to that of WARF relating to hESC technology and should represent a balance between the need to access the invention for further research and to protect the patent holders' rights.

February 2011 saw the conclusion of another global licensing agreement on the Kyoto iPS cells, now with iPierian. The agreement is in fact a "series of intellectual property agreements creating a unified, worldwide patent estate"[487] on iPS technology. In the agreements iPierian assigned to Kyoto University the iPS patents it acquired from Bayer Schering and in turn iPS-AJ granted iPierian non-exclusive worldwide rights to its own patents. The licensing agreement was declared to be concluded with the intention to disseminate the Kyoto patents non-exclusively to maximise research results and proceed to translation into pharmaceuticals and therapies as soon as possible. The agreement makes

[485] Luigi Warren et al., Efficient Reprogramming to Pluripotency and Directed Differentiation of Human Cells with Synthetic Modified mRNA Cell, *Stem Cell* (30 September 2010), available at www.cell.com/cell-stem-cell/fulltext/S1934-5909(10)00434-0.
[486] ips-cell.net/e/index.html.
[487] www.cira.kyoto-u.ac.jp/e/pressrelease/other/110201-165450.html.

iPierian, which works together with other iPS research centers in the world, the global centre for the commercialization and industrialization of iPS technology.

The patenting history of iPS technology so far has avoided the bioethical controversies of human DNA and stem cell patenting. The main ethical dilemma of the technology, whether it is possible to halt cell differentiation at the pluripotent stage avoiding the generation of totipotent cells,[488] has not been addressed in patent law. This may revive the unsettled bioethical debate on the distinction between totipotent and pluripotent cells in patent law. iPS patenting may also shed new light to ethical issues in other areas of bio-patenting. As one of our interviewee pointed out, the relevance of gene technology in iPS should revive interest in the limits of gene patenting[489] already under review in US patent law.

[488] Øyvind Baune et al, *The Moral Status of Human Embryos with Special Regard to Stem Cell Research and Therapy*, in Lars Østnor (ed.), *Stem Cells, Human Embryos and Ethics: Interdisciplinary Perspectives* (Springer, 2008), at 17.
[489] Interview with Julian Hitchcock, REMEDiE, 16/6/2010.

ANNEX 7 REMEDiE Work Package 7: Final Report

Database of European and wider activity: geo-coded mapping of RM

Dr Graham Lewis, SATSU, University of York

Introduction

WP7 was tasked with mapping global developments in regenerative medicine (RM) according to three domains: RM companies, clinical trials, and patent activity. In addition to data gathered discretely via the fieldwork conducted for other REMEDiE work packages, WP7 has derived data from secondary sources to produce a quantitative database tracking geo-economic trends over time, starting in 2003, the year when (for various scientific and commercial reasons) the field of regenerative medicine/stem cells began to develop more rapidly worldwide. The original 'cut-off' date for collection was 2008 (as described in the initial proposal) but this was extended to 2010 in the case of corporate and clinical trial data. There were some difficulties with patent data collection which served to reduce the collection period. Importantly, WP7 has also sought to utilise visualisation techniques to present this statistical data in an accessible graphical fashion.

Data on the first two of these domains was collected in an SQL Access database (see Figure 1 for illustrative purposes) and for reasons explained below the clinical trials data was deposited in an Excel spreadsheet. In addition to its main task: providing a publicly available database on RM developments, WP7 also served as an internal resource for other work packages (e.g. WP1 utilised WP7 data for a WP1 'subsidiary' database of European firms). The methods used, sources, and type of data collected, are described below for each of the three domains. In addition, we briefly discuss some methodological issues and concerns raised by the work and, in particular, the sources used for the work package. The principal findings are highlighted in the relevant section of the report.

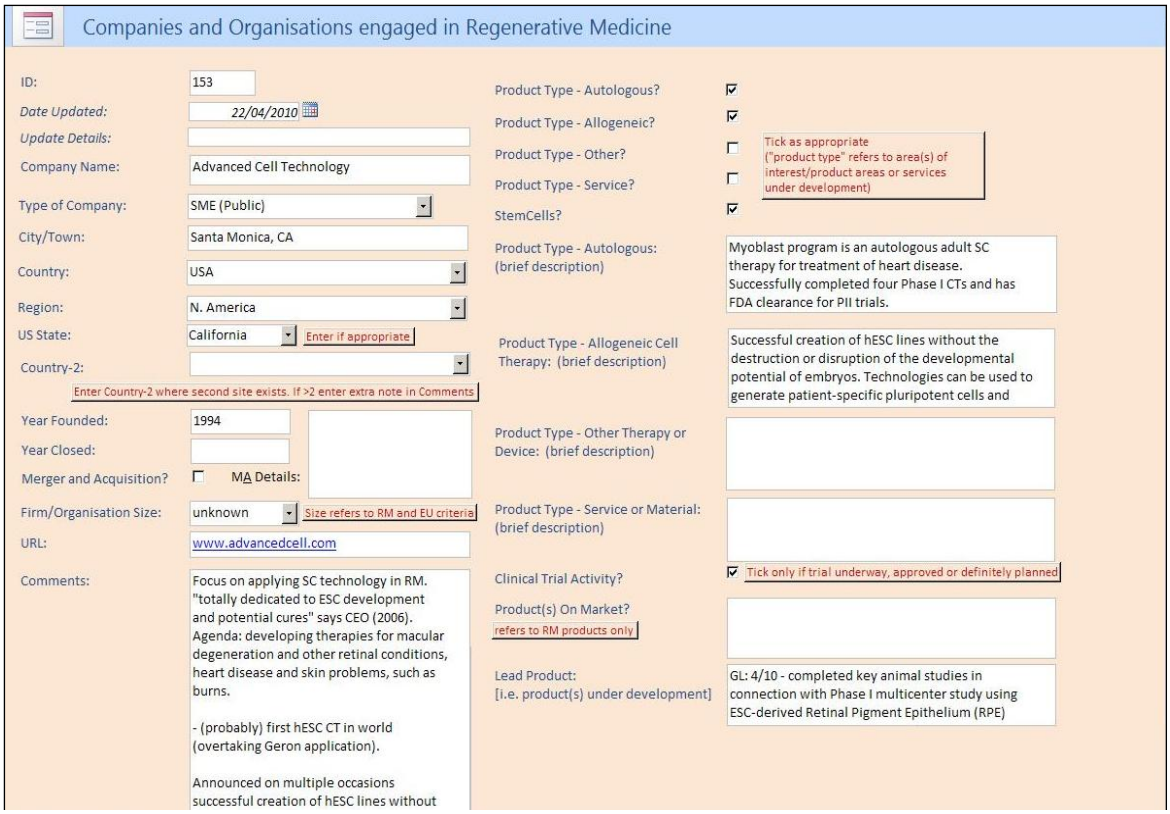


Figure 1: Form view of 'Organisations' Table (companies and other organisations) in WP7 Access database.

Regenerative medicine companies and other organisations

Corporate data was collected by comprehensive on-line searching of company websites over time, with subsequent 'triangulation' using other sources such as industry-based newsletters and reports to ensure the robustness of the data. The corporate domain was extended beyond companies to include a number of important academic and other centres, particularly those located in the USA (though the primary analysis and findings remain focused on company data as specified in the WP7 brief). Although incomplete in terms of global reach, this 'non-corporate' data provides useful additional information given the role of academic and other non-profit institutions in both the development of RM science and the formation of 'spin-out' companies.

In terms of composition, n=473 entries are recorded in the 'Organisations' table, of which n=392 are companies. This data is searchable using SQL by region (Europe, N. America, Far East, S. Asia, Australia/New Zealand, S. America, and 'Other'); country (including all EU Member States); type of company (publicly-traded SME, private SME, 'big pharma' or 'academic/hospital/non-profit/public laboratory'); year founded (and closed where applicable) plus any merger details where relevant (in order to provide a dynamic picture of developments over time); and firm size. The US data can also be searched by US state providing up-to-date information on the location of 'hot-spots' of RM activity in the US (see Figure 8).

The significance of the corporate data on RM is closely related to clinical trials activity because a prospective product must proceed through clinical development and obtain

regulatory approval – in the case of the EU via the Advanced Therapy Medicinal Products (ATMP) Regulation.[490] Unless a company can achieve these steps it is not going to be successful. Data on the main players and product development to date in the stem cell field is provided later in the discussion of the WP7 clinical trials data.

With regard to corporate engagement, we are also developing the analysis of WP7 data on 'big pharma' involvement in the RM field. To date, this involvement has primarily been through equity investment or direct collaboration with RM companies. These developments, whilst relatively minor at present, particularly in the context of the overall interests of the pharmaceutical industry, are nonetheless interesting because of the well-known difficulties SMEs experience in translating advanced therapies to the clinic and bringing products to market. The greater involvement of major pharmaceutical companies, such as Roche and Pfizer, may be highly significant, though this is likely to focus on induced pluripotent (rather than embryonic) cells, and toxicity testing.

It is important to distinguish between different types of activity in the RM field. Data on the type of activity conducted by companies and other organisations is arranged in the database according to four categories: autologous; allogeneic; 'other' (e.g. therapies involving delivery via degradable bio-scaffolds and tissue engineering, gene therapy, or drug screening/toxicity - i.e. activity with a drug development focus); and services (cell-based and other service provision such as bio-scaffold production for other SMEs). In addition, the 'Organisations' table contains information on clinical trials relating to individual companies obtained from industry newsletters and related sources, that complements the discrete clinical trials data also collected as part of WP7 (see below); and finally, RM products on the market and/or companies' lead product(s), as appropriate.

Turning to methodological issues, the collection of corporate data from company websites is potentially problematic for a number of reasons. For example, firms inevitably seek to promote themselves in order to attract investment, and also to recruit key staff – what in sociological terms has been called the generation of 'promissory futures' which help shape the trajectory of new medical technologies.[491] Claims about the type of work being undertaken and/or its progress to date or the benefits of the particular platform developed or utilised by a company may therefore be suspect. Secondly, both the scientific and the more industry-orientated literature provide a variety of definitions for regenerative medicine. One of the first steps required was to define what REMEDiE and WP7 in particular

[490] ATMPs are 'innovative, regenerative therapies which combine aspects of medicine, cell biology, science and engineering for the purpose of regenerating, repairing or replacing damaged tissues or cells', and can be a gene therapy, a somatic cell therapy or tissue engineered product 'that contains or consists of cells or tissues that have either been subject to 'substantial manipulation' or that are not intended to be used for the same essential function(s) in the recipient as in the donor and is presented as having properties for treating or preventing disease in human beings.' (Regulation (EC) No 1394/2007).

[491] On a related subject, see M. Morrison and L. Cornips, 'Performing commercial futures in regenerative medicine: an evaluation of the strategies & promise of the business of regenerative medicine derived from analysis of industry news articles.' REMEDiE working paper, May 2010. www.york.ac.uk/media/satsu/res-remedie/remedie-reports/rm-futures-executive-summary-final.pdf

meant by the term.[492] Related to such concerns, the activities of some firms who identify themselves as 'RM companies' did not fit the project's definition of RM. For all these reasons we carefully scrutinised company's claims and endeavoured to corroborate them against other sources. One therapeutic category that some commentators include in the definition of RM is the so-called 'cancer vaccines' and similar products, and in therapeutic terms this type of agent appears to be increasingly important.[493] However, despite their potential importance, firms engaged in this area were excluded from WP7 because the focus is on *cancer* stem cells rather than the manipulation of autologous or allogeneic *healthy* cells.

Conducting web-based research also brings a series of well-documented problems: the variability in the quality of information available, including considerable out-of-date information, and the 'language bias' of the web is also likely to skew results. Information about previous incarnations of now defunct or merged firms can also quickly disappear. We were also surprised to discover that in several cases it was simply not possible to determine if a company was publicly quoted or privately owned from company websites or, in some cases, when a company had been founded. Whilst we are confident of the quality of the WP7 corporate data it is nonetheless important to recognise the methodological caveats inherent in collecting such data. The data is, however, probably much more robust than that informing the market-based reports that are often advertised for sale at considerable expense by business information companies. We already have had expressions of interest in our own dataset and findings for the private sector (eg from a major player Genzyme) but are making our results publicly available after the reporting period so they are available to all. The figures below provide summative data on corporate activity: the database itself carries considerably detailed information about each company.

[492] Namely, the application of novel biomaterials – specifically cells (including stem cells), genes (via gene therapy) and biodegradable scaffolding materials, to achieve a regenerative effect. In other words, technologies aimed at stimulating or augmenting the human body's inherent capacity for self-repair.
[493] Dendreon's Provenge, an autologous immunotherapy recently approved for use in the EU, is a good example.

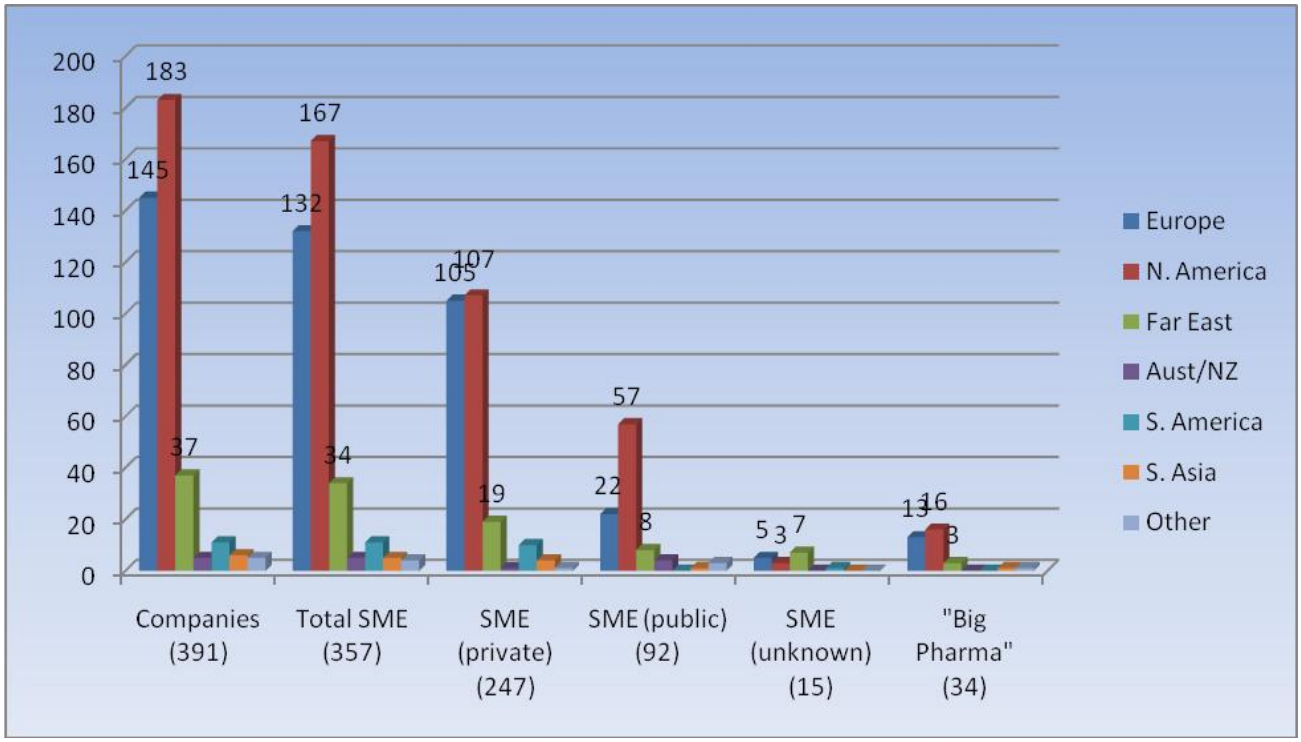


Figure 2: The RM corporate universe by region in 2010.

- Note: 'Big Pharma' includes device and service/tools companies in addition to large pharma companies engaged in some form or other with RM (usually either equity investment or collaboration with SMEs). WP7 data suggests the sector is increasingly interested in RM.

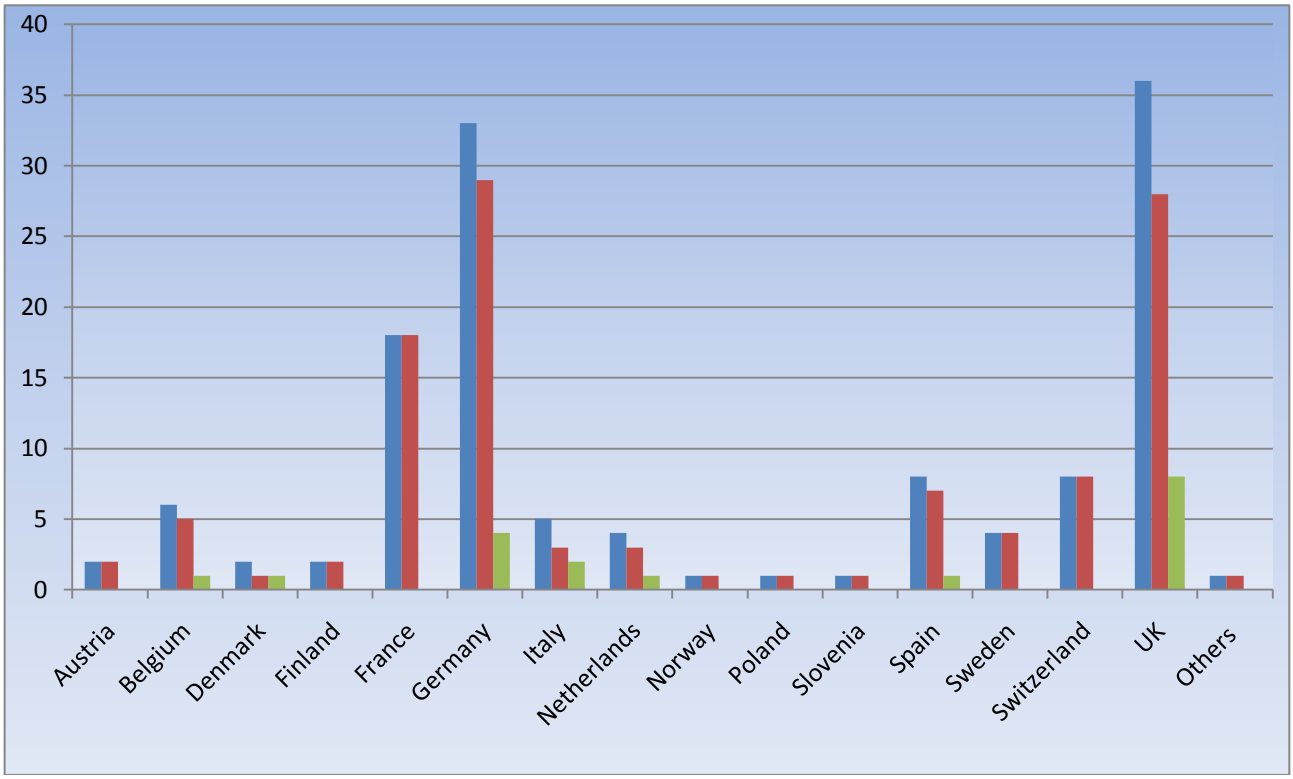


Figure 3: European SMEs by Member State (plus Switzerland and Norway).

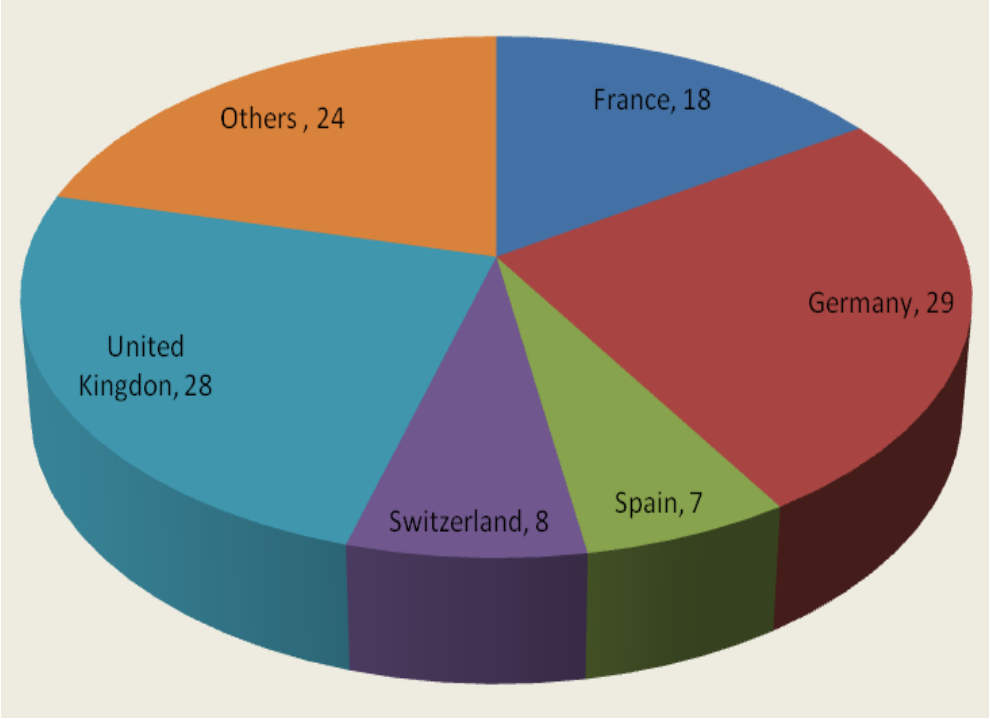


Figure 4: European SMEs by Member State (plus Switzerland and Norway) – major players.

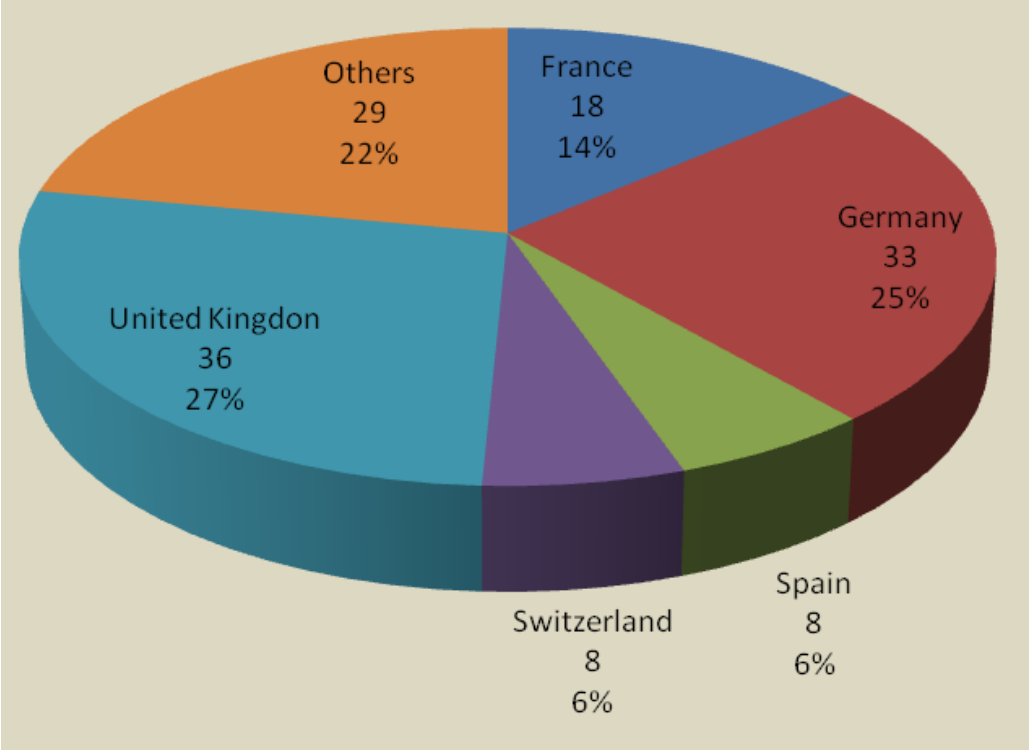


Figure 5: Major players - European SMEs 2003 to 2010 by Member State plus Switzerland.

- Figures 4 and 5 show there has been no change in the relative position of the major players in Europe as measured by number of firms.

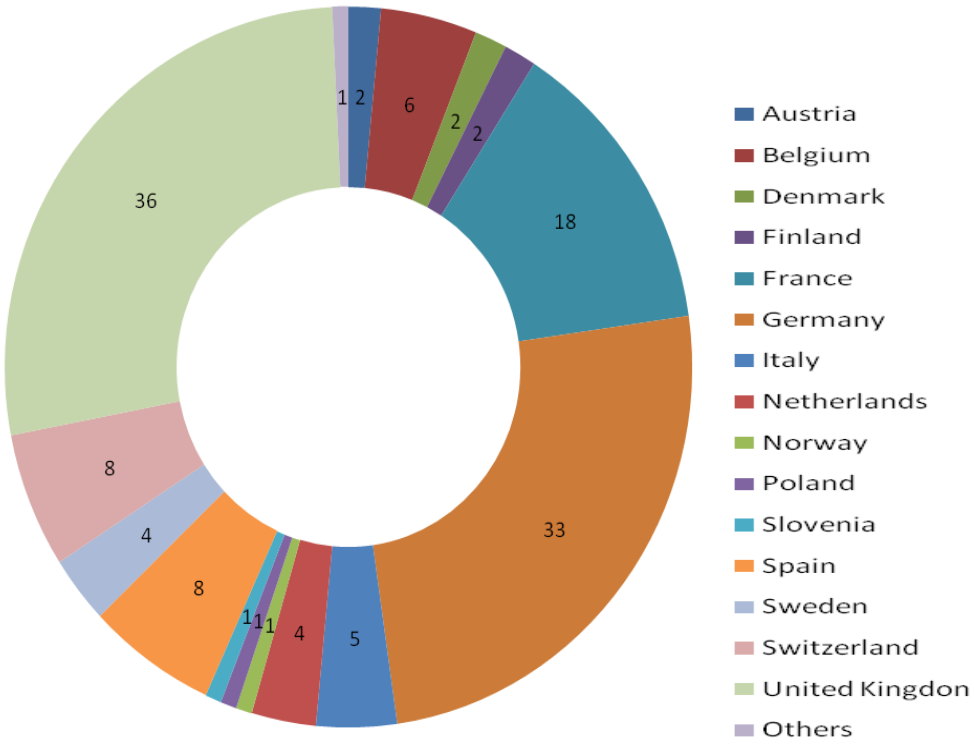


Figure 6: Total No. of European SMEs over period 2003 to 2010

Year	Number Set-up	Private Companies	Public Companies	Unknown	No. Closed
<1995	16	12	4	0	0
1995	0	0	0	0	0
1996	4	3	1	0	0
1997	10	6	3	1	0
1998	5	3	2	0	0
1999	4	3	1	0	0
2000	18	13	5	0	0
2001	9	6	1	2	0
2002	11	10	1	0	0
2003	4	2	2	0	1
2004	2	1	0	1	0
2005	4	4	0	0	1
2006	7	7	0	0	2
2007	7	6	0	1	2
2008	4	4	0	0	3
2009	3	3	0	0	6
2010	5	5	0	0	2

Figure 7: Year of establishment of European SMEs engaged in RM (2003 – 2010)

- WP7 plotted the trajectory of European SMEs over time. Data back to 'Prior to 1995' appears because these firms are still in existence. The number of companies established each year (column 2) is broken down into Private, Publicly-traded, and 'Unknown' status in columns 3, 4 and 5 respectively. Under 'Number Closed' (column 6), no data prior to 2003 was collected.

- Figure 7 shows a "spike" around 2000, which continued into 2001 and 2002, which is perhaps counter-intuitive. This data may call into question ideas around 'lack of investment' in subsequent years because it may be the case that considerable investment had *already* been undertaken at the start of the decade.

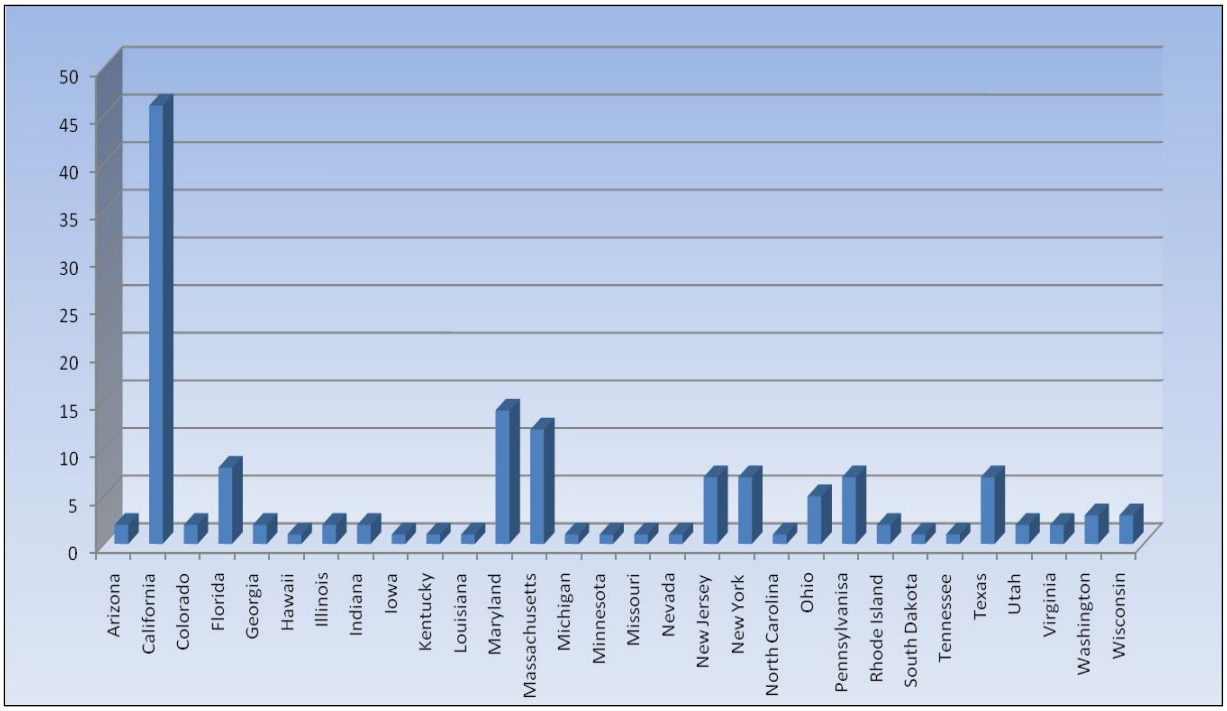


Figure 8: US corporate universe by State

- WP7 collected location data for US companies to determine 'hot-spots' of activity in the RM field. As expected, California has by far the most firms with other major concentrations in Maryland, Massachusetts, Florida, New Jersey, New York and Texas. Wisconsin has fewer firms than one might expect given the state's importance with regard to stem cell science. However, such data, whilst useful in itself, says nothing about the importance of individual companies or their location with regard to the development of advanced therapies. What it does tend to illustrate, however, is the regional infrastructure (and so networks) that have been built in each State.

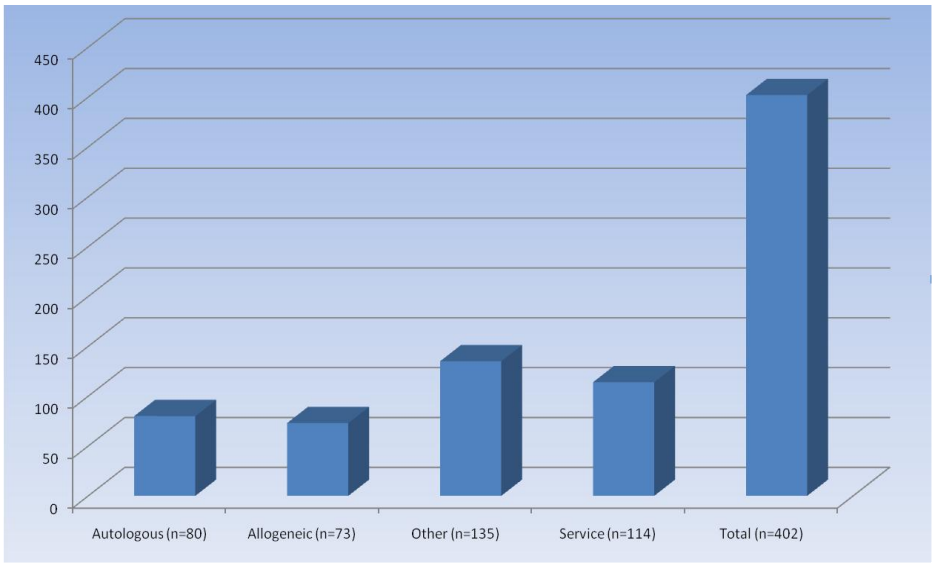
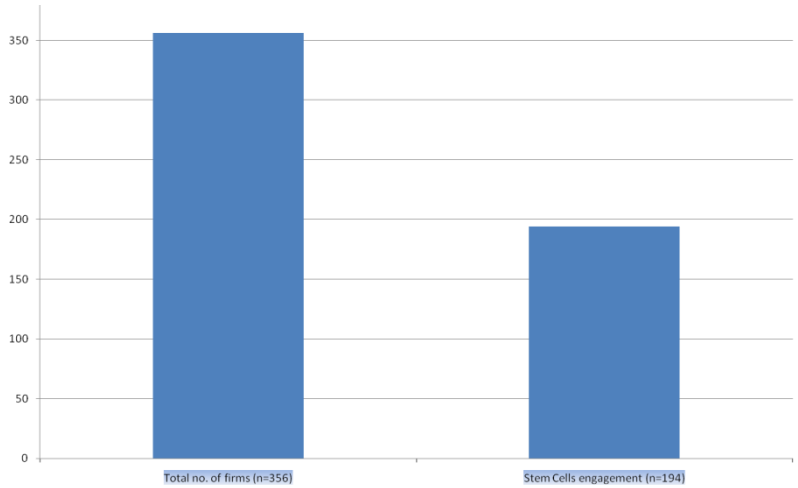


Figure 9: Corporate universe by product type

- WP7 categorised engagement in RM according to four types: autologous, allogeneic, 'other' and service (see above for description of these categories). Total number of records in 'Organisations' table in WP7: n=356, which means that n=46 companies (13%) are engaged in more than one type of activity.



- WP7 mapped the global activity in stem cells compared to all RM activity, with following results: total companies, n= 356; number engaged in Stem Cells, n=194.

Clinical trials and regenerative medicine

Mapping clinical trials activity provides a measure of the extent to which translation to the clinic is occurring in an emerging field like regenerative medicine – who is sponsoring trials, where they are located (which is not necessarily in the same country as the sponsor), what type of cell therapy (autologous or allogeneic), and at what stage (phases I, II, III) in the clinical development process. Tracing developments in clinical trials activity can also inform analysis of emerging regulatory frameworks.

WP7 has collected trials data by region and key countries (n=6) for illustrative purposes (USA, UK, China, Japan and S Korea, and India). These countries were selected because they are amongst the most active in terms of RM clinical trials and provide a global 'spread' across regions. In the context of REMEDiE, comparisons between countries and regions can provide useful information about the positioning of European companies relative to global competitors (e.g. type of product, translational processes etc.) as well as trends and overall prospects in what is a fast moving field. However, as we discuss below, the collection of RM clinical trials data is not a straightforward exercise.

Data was obtained from the US National Institutes for Health (NIH) clinicaltrials.gov database and stored as a spreadsheet (rather than in the main WP7 database). This was because the data is already publicly available but also for technical reasons to do with the structure of the clinicaltrials.gov database. Cumulative data from 2003 to 2010 was collected for the countries/regions listed above using the search terms: 'autologous cell therapy', 'allogeneic cell therapy', and 'stem cell(s)'.

However, clinical trials data collected via industry-orientated sources as part of the WP7 corporate universe work referred to above, shows no automatic correlation between the number of companies in EU Member States and current clinical trials (CTs) activity. For example, the figures for UK, Germany and France, identified as the main EU players, are: Germany SMEs n=37, CTs n=6; UK SMEs n=36, CTs n=9; France SMEs n=19, CTs n=2. On inspection this is not surprising since of the total German SMEs, 14 have products on the market already and many of these are in the (more-established) tissue engineering sector. In the case of French SMEs, inspection suggests several firms are at an early stage in the product development process. Details of the main global corporate players in the stem cell field are presented below as Figure 14 along with brief commentary on notable developments.

The use of the clinicaltrials.gov database raises a number of methodological questions: to what extent does data obtained from this source accurately reflect global activity in RM given it is operated by a US government agency? Do all countries (such as China for example) routinely submit information on RM trials? It seems unlikely that this is the case (although there are a number of Chinese trials recorded plus it is possible that data submission rates will increase over time). Also, the NIH database generates different results depending on whether or not searches using the same terms include phase information (phase I, II, III, IV) compared to when these variables are omitted from the search operation. Whilst the variation is not great it is somewhat disconcerting and raises concerns about the robustness of data in public databases in the context of RM.[494] More generally, there is also a lack of clarity regarding what constitutes a clinical trial and the boundary between trial and therapy is not as well-defined as in other therapeutic areas. For example, hospitals in some countries offer RM procedures as treatments although they have not been the subject of formal clinical trial protocols (partly because they have been progressed through the 'hospital exemption' route). On a more subtle level, development paths for autologous treatments, in particular, are characterised by clinician-led procedures, rather than 'off the shelf' products, and this non-linear process may blur the boundary between what constitutes a clinical trial and what counts as a treatment. Finally, we should note that the European Medicines Agency (E MA) has recently made its 'EudraCT' database publicly available (https://eudract.ema.europa.eu/) and this will provide another data source for this type of information in the future.

For illustrative purposes, data is provided on 6 countries (plus 'all countries') over time: USA; UK; China; Japan and S. Korea; and India. The 'X' axis displays the number of clinical trials.

[494] Unfortunately, the clinicaltrials.gov operator was unable to shed light on why this discrepancy occurs.

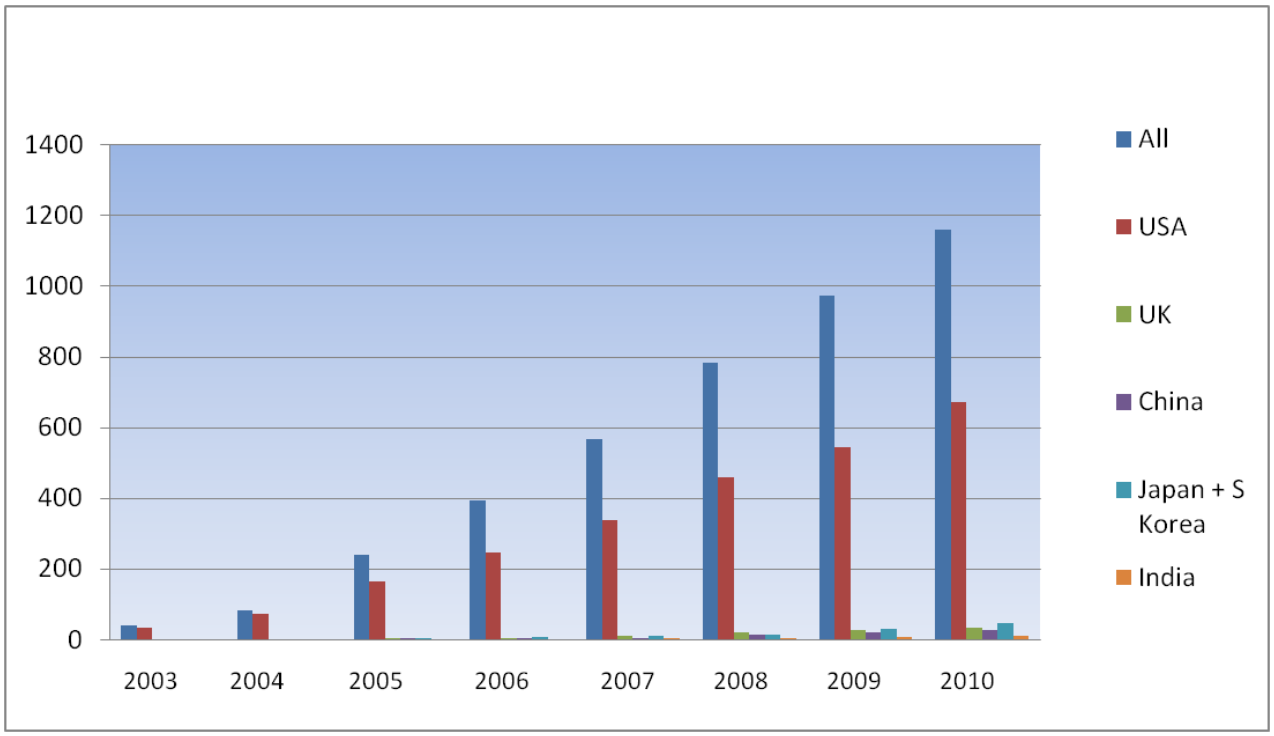


Figure 11: Clinical trials involving 'autologous cell therapy' (Source: www.clinicaltrials.gov)

- The US conducts more clinical trials than any other country in autologous cell therapy.

However, as Figure 11 shows, US dominance has decreased in recent years as a proportion of all trials conducted with this cell-type.

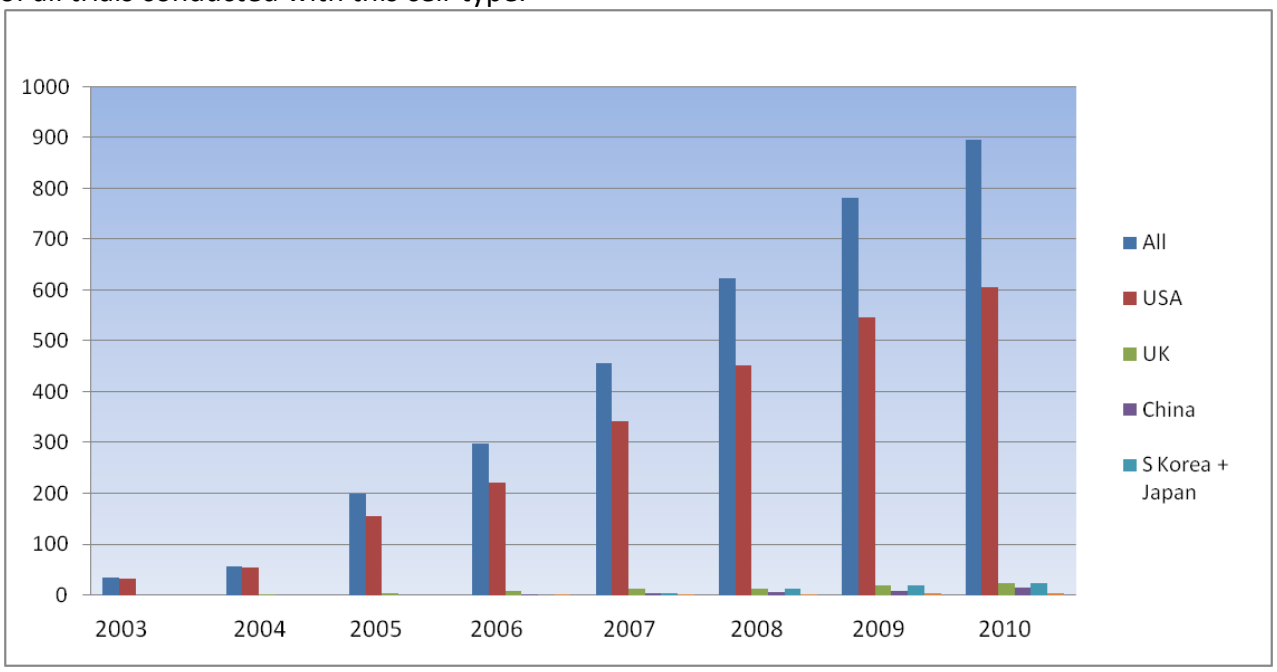


Figure 12: Clinical trials involving 'allogeneic cell therapy' (Source: www.clinicaltrials.gov)

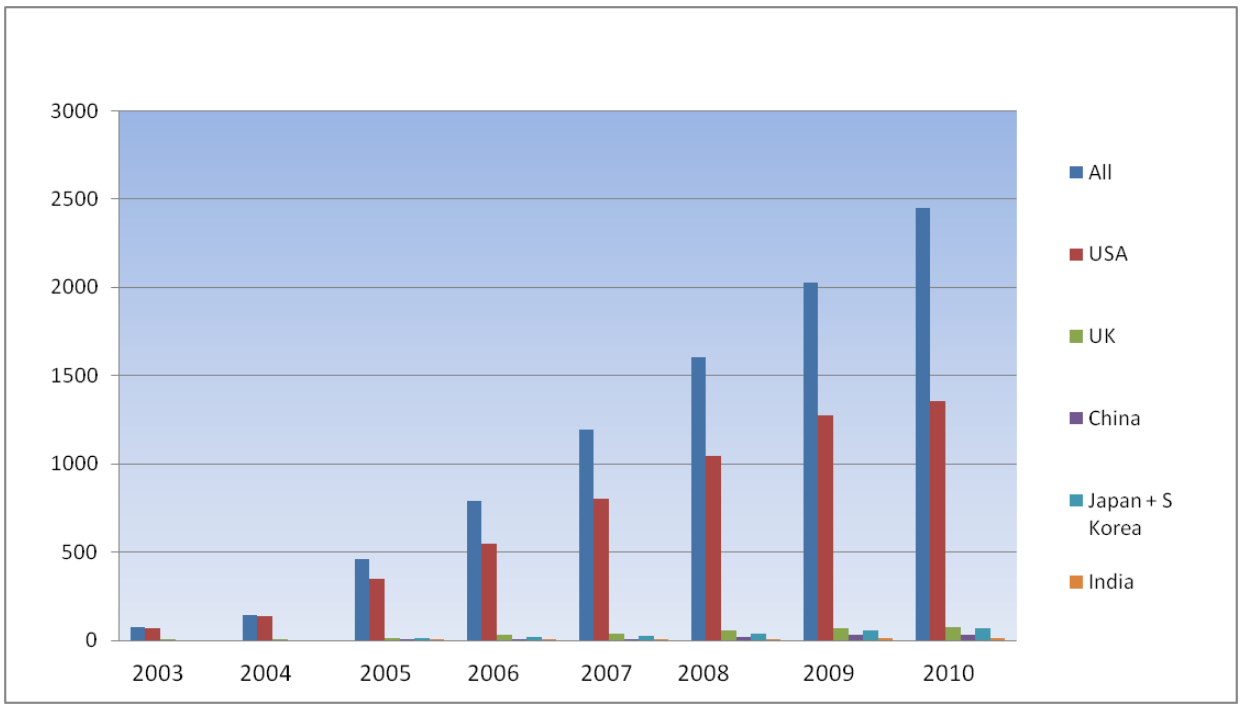


Figure 13: Clinical trials involving 'stem cells' (Source: www.clinicaltrials.gov)

Company	Cell Type	Cell Source	Type	Phase	Indication
Aastrom Biosciences	Non-ESC	Bone marrow	Autologous	Phase IIb (PIII announced)	CLI
Aldagen	Non-ESC	Bone marrow	Autologous	Phase I/II	CLI
Advanced Cell Technology	ESC	In vitro fertilized blastocysts	Allogeneic	Phase I/II	Stargardt's macular dystrophy
Athersys	Non-ESC	Bone marrow	Allogeneic	Phase I	ACI
BioHeart	Non-ESC	Thigh muscle	Autologous	Phase II/III	Congestive heart failure
BrainStorm	Non-ESC	Bone marrow	Autologous	Pending approval	ALS
Celgene	Non-ESC	Placenta	Allogeneic	Phase I	Crohn's disease
Cytori Therapeutics	Non-ESC	Liposuction	Autologous	Phase I	ACI
Geron	ESC	In vitro fertilized blastocysts	Allogeneic	Phase I	Spinal cord injury
International Stem Cell	Non-ESC	Unfertilized parthenogeneticaly activated oocytes	Allogeneic	Preclinical	Age-related macular degeneration
NeuralStem	Non-ESC	Spinal cord of 8-week fetus	Allogeneic	Phase I	ALS
Opexa Therapeutics	Non-ESC	Peripheral blood	Autologous	Preclinical	Diabetes
Osiris Therapeutics	Non-ESC	Bone marrow	Allogeneic	Phase III/II	Crohn's/ACI
Pluristem Therapeutics	Non-ESC	Placenta	Allogeneic	Phase I	CLI
ReNeuron	Non-ESC	Neural SCs with expansion	Allogeneic	Phase I in UK	Ischaemic stroke
Stem Cells	Non-ESC	Fetus	Allogeneic	Preclinical /Phase I	Spinal cord injury/Batten Disease

Figure 14: Principal companies in the stem cell field with clinical trials programmes

Developments of note with regard to clinical trials during the course of the project, because they utilise embryonic stem cells and mark the first of such trials, are the Geron trial for treatment of spinal cord injury, which received FDA approval in 2010; and the ACT trial for

Stargardt's macular dystrophy, also with FDA approval. Both platforms use *in vitro* fertilized blastocysts (derived from embryos) as cell source.

Also noteworthy is the UK's ReNeuron PISCES (Pilot Investigation of Stem Cells in Stroke) study which is the world's first approved trial of a neural stem cell therapy for disabled stroke patients and the first for any stem cell-based therapy in the UK. This does not use embryonic derived tissue however, deriving its tissue from aborted foetus instead, a point which it has made much of in respect to the recent European Court of Justice's decision to disallow patenting on embryonic-derived therapies.

As the Table above shows, of the 15 main stem cell companies (worldwide) currently developing therapies, more than half have competing programmes in three major disease areas: cardiovascular, gastrointestinal and the central nervous system (CNS). Two areas of cardiovascular disease are focused on: critical limb ischemia (CLI)[495] and acute myocardial infarction (AMI)[496]. The major firms with clinical trials to treat CLI (n=3) are: Aastrom Biosciences [autologous procedure – the most advanced SC trial programme], Aldagen [ALD301], and Pluristem Therapeutics [PLX-PAD]. The main companies for AMI (n=3) are Osiris Therapeutics [Prochymal], Atherysys [Multstem], and Cytori Therapeutics [Celution System].

Mention should also be made of European companies conducting non-stem cell development programmes. For example, Belgium's TiGenix has received EU approval under the ATMP for ChondroCelect, a non-stem cell cartilage repair product. But in the US, the FDA has demanded another trial before it can submit for US approval, with a 5 year delay before market approval if likely. TiGenix also has a CE-marked approval for a bio-scaffold, TGX002, for aiding joint repair, which is close to entering the market.

Spain's Cellerix has recently conducted Phase III trials on an autologous treatment, Cx401/Ontaril, and on a second product, Cx501, currently in Phase II. These programmes have reportedly received set-backs and their future is unclear at this time. However, the company has two allogeneic products, Cx601 (Phase II) and Cx611 (preclinical development) which is also under development. All these products are designed for treatment of fistulas and skin regeneration. What may turn out to be as important is the announced merger of TiGenix and Cellerix to form *Europe's largest and most successful regenerative medicine company to date.*

Finally, the UK-based Intercytex, once a leading European SME in the RM field, developed a series of non-stem cell autologous and allogeneic cell therapies for wound care, facial rejuvenation, and hairloss, which had been under clinical development for a number of years. Typical of the company's product portfolio were ICX-SKN and Cyzact (formerly ICX-PRO), topical wound care products designed to stimulate active repair and closure in persistent chronic wounds, with Cyzact completing a Phase III trial. However this and much

[495] CLI is the obstruction of the arteries that seriously decreases blood flow to the extremities, resulting in pain, non-healing wounds, and tissue necrosis.
[496] AFI, or heart attack, results from the interruption of blood supply to the heart, causing cardiac cells, which cannot regenerate, to die.

of the company's other IP has recently been sold to other parties, although the company has retained rights to one product, Valveta which is continuing in clinical development.

Patent activity in regenerative medicine

Patent activity is a standard measure of how a technological field is developing and the third dimension of WP7 was to map the patent landscape from 2003 to 2008 and through to 2010. It proved difficult to access reliable patent data and the collection of appropriate data was problematic throughout WP7, in part because of a significant additional cost this would have incurred to the project and in part because of the heterogeneous classifications of stem cell activity used by patent offices. However, data was eventually collected in a more robust and systematic way on Stem Cell patents granted for the 20 month period Nov. 2008 to Jun 2010.[497] We acknowledge the assistance of the UK National Stem Cell Network (UKNSCN) and the UK Intellectual Property Office (UKIPO) in providing this data. The searchable patent information available is as follows: Issuing Patent Office; Patent Number; Date Granted; Assignee Country[498]; Patent Assignee; Type of Organisation (company, academic etc., individual(s), or any of these as joint assignees); Type of Claim (adult, embryonic, embryonic/pluripotent stem cells, induced embryonic/dedifferentiation of cells, induced pluripotent cells/dedifferentiation cells, and induced pluripotent cells/reprogramming of cells); Patent Title; and Patent Abstract. A brief analysis of the data is provided below.

Who has been patenting stem cells? Of the total granted patent records (n=314) in WP7, 50% (n=159) are assigned to the 'academic/hospital/institute/public laboratory' category, either entirely (n=138) or jointly with a company (n=5) or with individual(s) (n= 6). These figures demonstrate the significant role played by academic and other non-corporate actors in the RM field. This does not of course mean these actors commercialise these patents themselves, or indeed at all. Nonetheless, the WP7 patent data confirms that the non-corporate sector is an important part of the RM universe. It is also important to note that patents do not have to be assigned to a company or organisation and may be owned by individuals, either alone or in combination with other parties.

The WP7 data shows the following figures for other assignees: assigned to individual(s) (n=23); jointly to individual(s) and a company (n=4); jointly to individual(s), a company and an 'academic etc' organisation (n=1).

[497] Note that data on patent *applications* is not currently included in the database.
[498] Note that patents can be assigned to companies and/or individuals in more than one country.

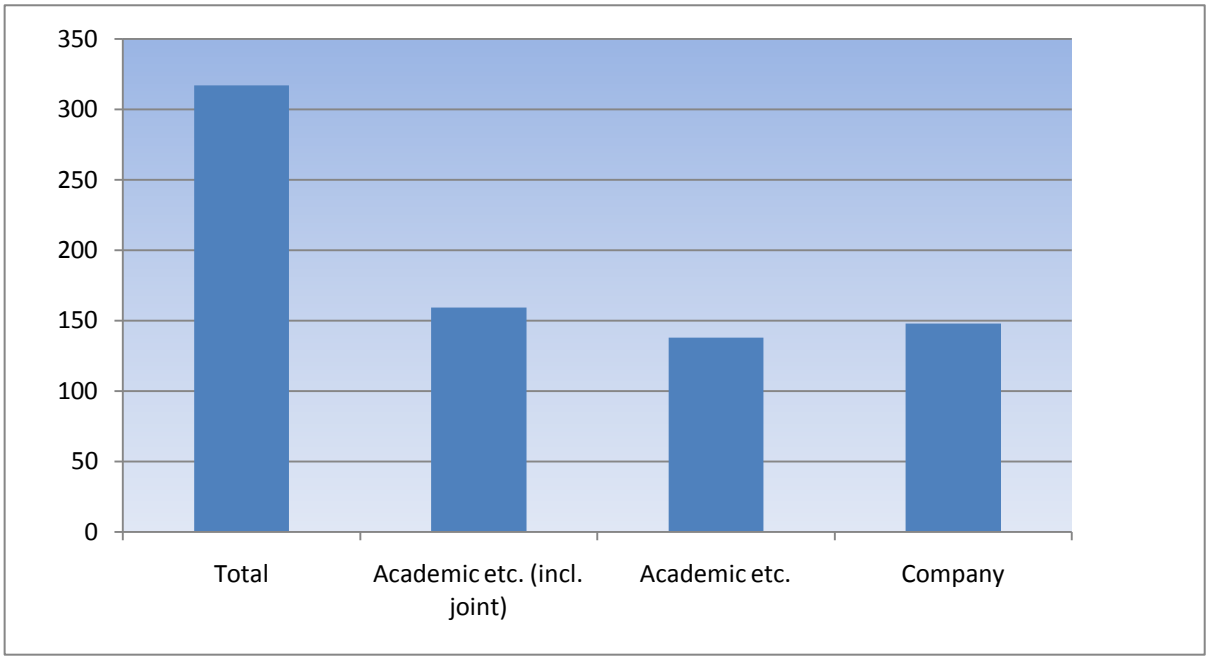


Figure 15: Comparison of distribution of assignees between 'academic/hospital/non-profit/public laboratory' category (incl. jointly granted) and companies over period November 2008 to June 2010.

Type of cell claimed: Data is also available on the type of cell or cell source claimed in the patent (total records n=314): adult (n=213); embryonic (n=67); embryonic/pluripotent stem cells (n=35); induced embryonic/dedifferentiation of cells (n=6); induced pluripotent cells/dedifferentiation of cells (n=1); and induced pluripotent stem cells/re-programming of cells (n=3) – see Figure 16 below.

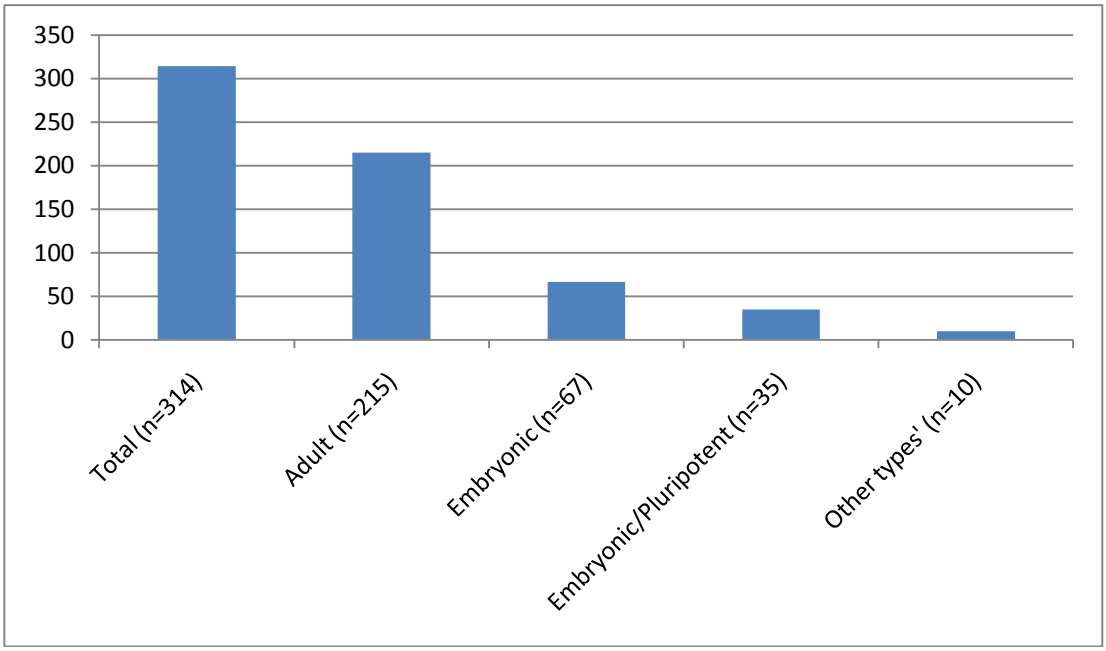


Figure 16: Granted stem cell patents by type of cell claim, Nov. 2008 – Jun 2010.

Stem cell patents and assigned countries: The assigned country for all types of stem cell patent in the WP7 database is as follows: Australia, n= 4; Canada, n=12; China, n=2 (including n=1 jointly with Taiwan); Cyprus, n=1; France, n=6; Germany, n=18 (including n=1 jointly with USA); India, n=1; Israel, n=11; Italy, n=5; Japan, n=28; Korea, n=13; Netherlands, n=1; Singapore, n=5; Spain, n=1; Sweden, n=4; Switzerland, n=7; Taiwan, n=7 (in addition to n=1 joint patent with China – see above); UK, n=12, plus n=1 joint patent with USA; USA, n=171 plus n=1 joint with Germany, and n=2 joint with Japan.

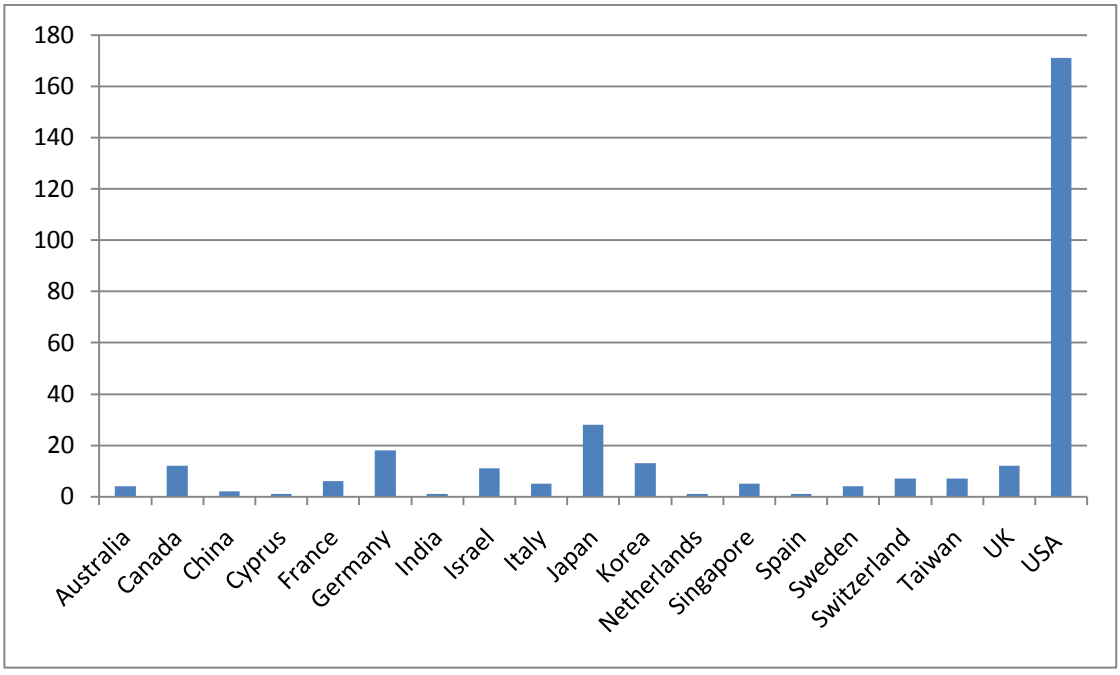


Figure 17: Stem cell patents by country, Nov. 2008 – Jun 2010.

Stem cell patents over time

The time span of the data collected on patents is too limited to draw any conclusions with regard to trends and the figures presented are for illustrative purposes only: 2008, n=29; 2009, n=159; 2010 (until June, i.e. 6 months), n=126.

Conclusion

WP7 has secured an extensive body of data which is to be made publicly accessible. The data show how the field is growing unevenly and yet how there are core centres of activity in Europe (centred on France, Germany and the UK) as well as a small number of primary firms who are moving towards later stage trials and so product approval from via the ATMP. There are overlapping patterns too in the dataset that indicate the current significance of autologous-derived therapies, trials and patenting activity. In all cases, compared with Europe, the US is the leading region globally and by a significant order. This is despite having had a restrictive legal regime at the Federal level over recent years, demonstrating the importance of the local, State-based sponsorship of the field, especially in California and Massachusetts. Similar dynamics have been at work in Australia, where Federal support for the field has been relatively recent, yet state support in Victoria and New South Wales enabling genuine growth. The data confirm the much more detailed analysis for Europe provided in WP1 that describes the importance of public/private regional networks and platforms to foster real growth. It appears that the field is now consolidating around a number of areas, regions and disease areas. As more products are submitted to the ATMP for approval (currently there are very few), we can also expect the regulatory approval process to speed up.

SEVENTH FRAMEWORK PROGRAMME
THEME SSH-2007- 8.1

PROJECT FINAL REPORT

Grant Agreement number: 217180

Project acronym: REMEDiE

Project title:
Regenerative medicine in Europe: emerging needs and challenges in a global context

Funding Scheme: Coordinated Action

Period Covered from: May 1 2008 to April 30 2011

Part B of Final Report:

Plan for the use and dissemination of results

Plan for the use and dissemination of foreground results

This section of the Final report relates to the range of activities that have already been undertaken during the period of the project in regard to the dissemination of results, as well as to prospective dissemination ahead. In addition, Tables 1 and 2 below carry information relating to peer-reviewed scientific papers and all the various dissemination events relating to formal presentations in workshops, conferences and related arenas.

Policy-related (international)

The project partners attended the Making Perfect Life conference organised by the Science and Technology Options Assessment office in the European Parliament. Partners presented to the meeting via a panel and special presentation on the interim findings from the project. The conference explored the argument that there is a convergence between a range of contemporary innovative technologies – artificial intelligence nanotech, regenerative medicine, synthetic biology, robotics etc – that are breaking down the boundaries between biology and technology, each of these two feeding into each other in novel ways that pose regulatory and governance challenges at national and international levels. This broad theme fitted well with REMEDiE's own agenda but we are cautious about accepting the 'convergence' argument given that these different domains have quite distinct regulatory and commercial paths. A subsequent meeting with STO is being arranged for the autumn of 2011.

While in Brussels, the project team also met with MEPs (hosted by MEP Linda McAvan) and members of the Commission, to discuss the emerging findings and their implications for legislation and policy. An Overview specially prepared for the meeting formed the basis of the discussion. Some of the issues that emerged from these discussions were concerns the MEPs had over:

- Clinical trials and their organisation and potential modification to respond to the specific challenges found in the regenerative medicine field
- Cord blood banking (an area that we are doing some very detailed work on in York parallel to the REMEDiE project)
- The oversight and control of egg donation/procurement across Europe
- Stem cell tourism
- Global developments – especially in Asia – and their implications for governance and innovation

In March 2011 REMEDiE members, Stuart Hogarth, Michael Morrison and Andrew Webster visited the offices of Dr Arnd Hoeveler, Director of Health Biotechnology in the European Commission, to present some of the emergent findings from WP1 and 6 relating specifically to innovation and governance in the field. The 40pp publishable report will be sent to them after it has been lodged with the Commission. The main interest will relate to our work on the problems of securing a business model for SMEs.

We shall also be dispatching the publishable report of the results of the project to the members of the European Parliament with whom we are already linked (notably the ENVI [Environment, Health and Food Safety] Committee), the European Group on Ethics in Science and New Technologies, DG Enterprise (with respect to its role in fostering innovation), the key European regulatory agencies (especially the recently established Committee for Advanced Therapies within the EMEA), and for the OECD, which is supporting the 'Bio economy to 2030 Initiative'.

In regard to *international science* links, REMEDiE partners also have established strong links with the International Stem Cell Forum and Initiative who will receive information about the results. Our work has been disseminated within Europe via the Commission's SCOOP (Socioeconomic sciences: Communicating outcomes oriented to policy) project in November 2010, and via the Stem Cells International newsletter in autumn 2011.

REMEDiE members are also part of a new FP7 COST Action (2010-2014) – 'Bio-objects and their boundaries: governing matters at the intersection of society, politics, and science', which includes examining developments in regenerative medicine. REMEDiE results will be disseminated throughout this network.

We will also discuss with EuroStemCell with whom we are registered as a member the possibility of their acting as a sponsor for the major, global database we have created through our work on WP7 in order to maintain it over the coming 2-3 years if possible. REMEDiE is also registered (via the Coordinator's membership) on the 'StemCell Direct' registry of European researchers working in the field.

In July 2011, Morrison (WP1 lead) is presenting our work to the Tissue Engineering and regenerative medicine (TERM) Consortium conference in Brussels. The European Clinical researcher International Network (ECRIN) will be sent the REMEDiE paper (Webster et al 2012) on clinical trials.

Commercial-related (international)

REMEDiE results (publishable report) will be despatched to the European Venture Capital Association, European *Medical* Technology Industry Association, EuropaBio (The European Association for BioIndustries), and the European Tissue Engineering Association via the REMEDiE website.

Policy related national

There have been various national policy organisations with which we have made contact during the project and who have been keen to learn from our results. Partner activity relating to this, beginning with the Coordinator of the project is summarised below.

UK (Webster/Coordinator):

Our work has been picked up by the UK Department for Business, Innovation & Skills and is being cited and drawn on in detail (especially WP1 and WP7) for its forthcoming report on regenerative medicine. In addition, the Coordinator has been invited to the Medical Research Council's 'lead expert' 'Forward Look' group to provide guidance on key issues within the field prior to a UK-wide workshop later in 2011 on how it might be developed. The UK partner is also involved in a proposal to establish a new translational medicine centre to be funded by the Technology Strategy Board.

Prior to this, early REMEDiE results were drawn on in 2009 to inform a submission to the UK House of Commons Science and Technology Committee Bioengineering Inquiry. The Coordinator also presented material in 2009 from the project related to stem cell banking at a UK/Spanish meeting hosted by the Foreign and Commonwealth Office, and later on the same issue at a 2010 meeting organised in London by the Society for Low Temperature Biology.

In regard to the ethical and legal findings, we will be contacting the Nuffield Council on Bioethics in the UK with which we already have strong links through the Director, Hugh Whittall. The Council has a strong interest in the ethical implications of emerging technologies.

Partner 1 (Webster/York) and Partner 6 (Salter/KCL) have been (and remain) closely involved in the UK National Stem Cell Network as members of its national Steering Committee, and been able to deploy, where appropriate, lessons and results from the project during the past three years.

The Coordinator was invited to give the opening keynote address in January 2011 at Norway's event launching its 'Year of Science'; he drew on REMEDiE to explore the social contract between society and biotechnology, and subsequently was invited to provide a summary of REMEDiE results at a closed meeting of members of the Norwegian Research Council and other stakeholders (clinical and corporate).

Germany (Braun/WP 2 lead)

Dagmar Friese, Head of Biotechnological Innovation/Genetic Engineering at German Federal Ministry of Health has provided very valuable comments on the project and will be sent the public report. In addition, our report will be sent to the Federal Ministry of Education and Research, the Central Ethics Commission for Stem Cell Research (ZES) at the Robert Koch Institute in Germany, the German Ethics Council, the Institute Mensch, Ethik, Wissenschaft (IMEW), and the Central Ethics Commission of the Federal Chamber of the German Medical Association.

Austria (Gottweis WP 3 lead)

Gottweis has links to the Bioethics Commission of the Federal Chancellor, the Bioethics Commission of the City of Vienna, the Federal Ministry of Science, Austrian Science Fund, Dialog Gentechnik, and the Max-Perutz Laboratories, Vienna. Our report will be sent to these bodies, as well as the Drug and Medical Technology Agency.

Spain (Itziar WP5 lead)

The Medicine and Health Product Agencies in Spain will receive reports based on the REMEDiE results, as will the Ministry of Health (Ministerio de Sanidad Y Consumo, and the Stem Cell Bank in Barcelona and the Fundacion Inbiomed-Inbiobank; others to be contacted include the Instituto Carlos III, the Autonomic Health Administration, and Members of the National Commission of Bioethics. In addition, all those delegates (many from Spain) who attended the final REMEDiE conference in Bilbao will receive a copy of the public report.

Hungary (Sandor WP6 lead)

The Magyar Biotechnologiai Szovetseg (the Hungarian Biotechnology Association), the Hungarian Ministry of Health, Social and Family Affairs, and the Hungarian National Health Council, which has strong representation from civil society organisations will receive reports based on the REMEDiE results.

Patient organisations and the wider public
There are various groups with which REMEDiE partners have as planned, established links with. At a European level the European Patients' Forum (EPF), an important conduit for disseminating results to over 2000 patient charities, carried in its Newsletter, news of the REMEDiE project during 2010, and has since been involved in discussions about a possible EU-wide project exploring patient charity engagement upstream in the stem cell field (and not merely, as is typically the case, downstream in regard to 'public understanding'/ or 'public engagement' activities.

In regard to civil society, the Coordinator has presented on REMEDiE to the UK's Women's Institute, and has prepared a short paper for inclusion in the summer 2011 edition of the University of York's *Research and Innovation* magazine which is distributed to 3000 readers worldwide. He also chaired a public meeting on regenerative medicine held in York in May 2011.

Partner 1 (York) has also established a blog on the REMEDiE website:
See http://blogs.collabtools.org.uk/remedie/

A contract with Palgrave for a text in the *Health, Technology and Society Series* is in preparation.

TEMPLATE A1: LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS										
NO.	Title	Main author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Permanent identifiers[1] (if available)	Is/Will open access[2] be provided to this publication?
1	Perfect Copy? Law and Ethics of Reproductive Medicine	Judit Sandor (ed)			*Center for Ethics and Law in Bioemdicine*	*Budapest*	*2009*	*pp. 1 - 175*	ISBN 978-963-9776-75-3	YES
2	Managing Access to Biobanks : How Can we Reconcile Individual Privacy and Public Interests in Genetic Research?	Graeme Laurie, Pierre Mallia, Judit Sandor et al. (2010)	*Medical Law International*,	Vol 10 (4)	A.B. Academic Publisher	U.K.	2010	Pp.315–337		NO
3	Bioethical governance and basic stem cell science: China and the global biomedicine economy.	Salter B and Qiu, R.	*Science and Public Policy*	Vol 36 (1)		*Basingstoke*	*2009*	*pp. 47-59*		YES
4	State strategies and the global knowledge economy: the geopolitics of regenerative medicine.	Salter B	*Geopolitics*	Vol 14			2009	pp. *1-31*		No

[1] A permanent identifier should be a persistent link to the published version full text if open access or abstract if article is pay per view) or to the final manuscript accepted for publication (link to article in repository).

[2] Open Access is defined as free of charge access for anyone via Internet. Please answer "YES" if the open access to the publication is already established and also if the embargo period for open access is not yet over but you intend to establish open access afterwards.

5	The global politics of stem cell science: regenerative medicine in transition	Gottweis H, Salter B, Waldby C	Book in Health, Technology and Society Series		*Palgrave*	*Basingstoke*	2009		ISBN-13: 978-0-230-00263-0	No
6	China, globalisation and health biotechnology innovation: venture capital and the adaptive state.	Salter B	*East Asian Science and Technology: an International Journal.*	Vol 3(4)			2009	*pp.401-420*		YES
7	Governing innovation in the biomedicine knowledge economy: stem cell science in the USA.	Salter B and Salter C	*Science and Public Policy*	Vol 37(2)			2010	*pp. 87-100*		No
8	Regenerative medicine in Europe: global competition and innovation governance	Hogarth S and Salter B	*Regenerative Medicine.*	Vol 5(6)			2010	*pp. 971-85.*		No
9	Biomedical innovation and the geopolitics of patenting: China and the struggle for future territory	Salter B	*East Asian Science and Technology: an International Journal.*	*Forthcoming*			2011			YES
10	Patenting human pluripotent cells: balancing commercial, academic and ethical interests	Bahadur, G. and M Morrison	*Human Reproduction*	Vol 25 (1)	*Oxford University Press*	*Oxford*	*2010*	*pp. 14-21*	http://humrep.oxfordjournals.org/content/25/1/14.full	No
11	Beyond the 'embryo question': human embryonic stem cell ethics in the context of biomaterial donation in the UK	Bahadur, G. and M Morrison	*Reproductive Biomedicine Online*	Vol 21 (7)	*Elsevier Ltd*	*Amsterdam*	*2010*	*pp. 868-874*	http://www.rbmojournal.com/article/S1472-6483%2810%2900639-5/abstract	No
12	Der bioökonomische Zugriff auf Körpermaterialien. Eine politische Positionssuche	S. Schultz and K. Braun	In, S. Lettow (ed.): *Bioökonomie. Objekte, Praxen, Strukturen*	Forthcoming	transcript	Bielefeld	2011			No

13	Spendende Verkäuferinnen. Eizellen für die Klonforschung	S. Schultz and K. Braun	Berliner Debatte Initial	Vol 4		Berlin	2010	28-40		No
14	Women's Eggs for Research: Without Payment?	S. Schultz	*Biopolitical Times*	10/14/2010			2010		www.geneticsandsociety.org/article.php?id=5413	YES
15	Ohne Bezahlung? Forschung mit Eizellen in Kalifornien	S. Schultz and K. Braun	Gen-ethischer Informationsdienst	Vol 198			2010	33-35		No
16	Regenerative Medicine and New Labour Life Science Policy: Rhetoric's of Success, Narratives of Sustainability and Survival	Kewell, B. and M. Beck	*Prometheus*.	Forthcoming			2012			YES
17	Probability But Not As We Know It' – Ignorance Construction in Biotechnology and Genomic Discourse	Kewell, B.	*Journal of Technology, Knowledge and Society*	Vol 5 (6)			*2009*	*1-18*		No
18	A Tale of 'Cautious Pessimism': Biotechnology, Risk and Organisational Change in the Aftermath of the 'New Economy'.	Kewell, B. and A. Webster	*Biotechnology Journal*	Vol 4 (8)			*2009*	*1106-1107*		YES
19	Law, Ethics, Religion, and Clinical Translation in the 21st Century	A. Webster	*Stem Cells*	Vol 28			2010	1915–1917		YES
20	Clinical trials in regenerative medicine: stem cell heterogeneity and the disciplining of ectopic life	A. Webster, C. Haddad, and C. Waldby	*Biosocieties*	Forthcoming			2011			No
21	Stem cell governance in China: from bench to bedside?	H. Chen	*New Genetics and Society*	Vol 28 (3)			2009	267-282	DOI: 10.1080/14636770903151984	No
22	Cord Blood Banking in China: Public and Private Tensions	H. Chen	*East Asian Science, Technology*	Forthcoming			2012			YES

			and Society							
23	Participation and the New Governance of Life	H. Gottweis	*Biosocieties*	Vol 3			2008	265-285		No
24	Stem cell treatments in China: rethinking the patient role in the global bio-economy	H. Gottweis and H Chen	*Bioethics*				2009			No
25	Cord Blood Banking in China: Public and Private Tensions	H. Chen	*East Asian STS Journal*	Forthcoming			2011		ISSN: 1875-2160	YES
26	The Endless hESC Controversy in the United States: History, Context, and Prospects	H Gottweis	*Cell Stem Cell*	Vol 7 (5)			2010	555-85	DOI 10.1016/j.stem.2010.10.008	No
27	Explaining Hwang-Gate: South Korean Identity Politics between Bionationalism and Globalization	H. Gottweis, and K. Byoungsoo	*Science, Technology & Human Values*	Vol 34			2010	501-524		No
28	Biobank Governance in the Post-Genomic Age	H. Gottweis, and G. Lauss	*Personalized Medicine*	Vol 7			2010	1-9		No
29	Biobanks need publicity	H. Gottweis and G. Gaskell	*Nature*	Vol 471			2011	159-60		YES
30	Stem Cell Treatment in China: Rethinking the Patient Role in the Global Bio-Economy	H. Chen and H. Gottweis	*Bioethics*	Forthcoming			2012			No
31	El embrión humano después de Dolly: nuevas pautas para nuevos tiempos	I. de Miguel **Beriain**	*Revista de Derecho y Genoma Humano*	Nº 29. Julio-Diciembre			2009	45-66		YES
32	Quimeras e híbridos: ¿Problema ético o problema para la ética?,	I. de Miguel **Beriain**	*Dilemata*	Vol 6			2011	101-122	ISSN 1989-7022	No
33	Clonación e investigación con células troncales humanas: debate ético y jurídico	I. de Miguel **Beriain**	*IN*MORENO MUÑOZ, M. (Ed.), *Perspectivas en la*		Editorial Comares	Granada	2010	229-250		No

			investigación con células troncales: aspectos científicos, éticos, sociales y legales							

TEMPLATE A2: LIST OF DISSEMINATION ACTIVITIES								
NO.	Type of activities[3]	Main leader	Title	Date	Place	Type of audience[4]	Size of audience	Countries addressed
1	Presentation	M. Morrison	Measuring Innovation: A Brief Introduction to the REMEDiE Project	26 November 2009	Innovative Health Technologies: Health Systems in Transition Workshop, Internet Interdisciplinary Institute, University of Catalonia, Spain	Scientific Community	20	Spain/UK
2	Presentation	M. Morrison	European RM Firms and their Strategic Approaches'	9 June 2010	Regenerative Medicine in the 21st Century, University of Wisconsin Madison, USA	Social scientists, regulators, bioscientists	60	Global
3	Presentation	M. Morrison	Visions of Health and Wealth: The Role of Expectations in Commercial Regenerative Medicine	2 September 2010	EASST, Trento, Italy	Scientific Community	c. 40	Global
4	Presentation	M. Morrison	Regenerative Medicine: Prospects and Challenges'	7 February 2011	Institutos de Políticas v Bienes Publícas, CSIC, Madrid, Spain	Scientific Community	15	Spain
5	Presentation	M. Morrison	Dynamics of cell science and commercial niches in regenerative medicine	18 April 2011	REMEDiE closing conference, Bringing Regenerative Medicine to the Clinic: Trials and Tribulations in Europe and Beyond University of the Basque Country, Bilbao, Spain	Scientific Community	100	Spain
6	Presentation	M. Morrison	Dynamics of cell	7 April 2011	British Sociological Association conference 2011	Scientific	c. 40	International

[3] A drop down list allows choosing the dissemination activity: publications, conferences, workshops, web, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters, Other.

[4] A drop down list allows choosing the type of public: Scientific Community (higher education, Research), Industry, Civil Society, Policy makers, Medias ('multiple choices' is possible.

			science and commercial niches in regenerative medicine		London School of Economics, London, UK	Community		
7	Interview / podcast	M. Morrison	Interview with Dr Michael Morrison	Forthcoming in 2011	Online (Globalising European Bioethics Education – GLEUBE)	Scientific Community, Civil Society	N/A	Global
8	Presentation	J Sandor	Stem Cell Conference. European Conference Center	**5 June 2008**	Budapest	International researchers	c. 150	Europe
9	Presentation	J Sandor	"Lost in Translation? − Relevance of Scientific Terms in Shaping Contemporary Medical Law".	August 8-12 2010	The 18th World Congress on Medical Law Zagreb	International, lawyers, medical doctors	c. 120	Global
10	Panelist	J Sandor	Making Perfect Life. Bio-engineering in the 21st century	10th November 2010	Brussels, Belgium	MEPs	c. 120	Europe
11	Presentation	H Chen	Stem Cell Governance in China: From Bench to Bedside?	October 28-31 2009	34th Society for Social Studies of Science (4S) Annual Meeting Washington DC, USA	International researchers	c.30	Global
12	Presentation	H Chen	Governance of Stem Cell Translational Research: the Chinese Road	November 14-15 2009	Brocher workshop: "Beyond the Embryo: Transnational, Transdisciplinary and Translational Perspectives on Stem Cell Research Geneva, Switzerland	International researchers	c.30	Europe
13	Presentation	H Chen	Towards the Biopolitics of Translational Stem Cell Research	November 22-25, 2009	Asia-Pacific Science, Technology and Society Network Conference Brisbane, Australia.	International Researchers	c.100	China

14	Presentation	H Gottweis	The Politics of Regenerative Medicine: Challenges Ahead	January, 21st 2009	Presentation at the London Regenerative Medicine Network Meeting London, UK	Bioscience and social science researchers	c.80	China/USA
15	Presentation	H Gottweis	Afternoon Address - Ethics and Politics of Stem Cell Research Issues	March 14-17, 2009	Presentation at Qatar Stem Cell Workshop on Science & Policy Qatar	Government and academic audience	c.20	Qatar/global
16	Presentation	H Gottweis	Understanding Differences in Stem Cell Governance	May 7-8, 2009	Presentation at the Conference "Beyond Pattison: Challenges to Stem Cell Translation and Policy", Wellcome Trust Centre, London	Social science, science policy, and bioscience communities	c.80	Global
17	Presentation	H Gottweis	Biobanks: Success or Failure? Tung University	September 26, 2009	Presentation at International Conference: The Foundation and Prospective of a Life Science Governance Research Framework Presented at the National Chiao centre Hsinchu, Taiwan	International researchers		China
18	Presentation	H Gottweis	Integrated Biobank of Luxembourg: Understanding its Public Perception	October 20, 2009.	Presentation at l'Amphithéâtre du Centre Hospitalier de Luxembourg, Luxembourg	Social science		Luxembourg and /Europe
19	Presentation	H Gottweis	Bio-nationalism in South Korea: Between Stem Cells and BSE	Nov 23-25, 2009	Presentation at the Asia-Pacific Science, Technology and Society Network Conference Brisbane, Australia	International social science researchers		South Korea and Global
20	Presentation	H Gottweis	Life, Death, and Democracy	July 2-7, 2010	Presentation at the ESOF European Science Open Forum Turin, Italy	International social science researchers		Global focus
21	Life, Death, and Democracy,	H Gottweis	Presentation at Conference "Challenging Democracy: Science and Public Trust"	October 13-15, 2010	Academia Engelberg, Engelberg	International social science researchers		China/Europe

22	Presentation	H Gottweis	Ethics and societal aspects in transplantation and gene-therapy approaches for neurological diseases Presentation at the 20th Annual Meeting of NECTAR	November 24-27,2010	Presentation at the 20th Annual Meeting of NECTAR Freiburg, Germany			Europe
23	Presentation,	H Gottweis	Irreconcilable Conflicts in the Politics of Life and Death	April 5, 2011	Presentation at the Centre for Medical Science and Technology Studies Copenhagen, Denmark	International social science researchers		Global focus
24	Presentation	H Gottweis & Chih-hsing Ho	Resisting Research Populations?	April 2010	The 3rd Pan Pacific Symposium on the Stem Cells Research Taiwan	International social science and bioscience researchers		East Asia
25	Presentation	H Gottweis, C Haddad, and H. Chen	Towards a Common Regulatory Framework: Comparative Developments in Europe and China	June 9-10	Paper presented at Regenerative Medicine in 21c: Managing Uncertainty at Global Level The Pyle Center, University of Wisconsin-Madison, USA.	Social scientists, regulators, bioscientists	60	Global
26	Presentation	H Gottweis and H Chen	Stem Cell Treatment in China: Rethinking the Patient Role in the Global Bio-Economy	August 25-29, 2010	Presentation at the 35th Society for Social Studies of Science (4S) Annual Meeting Tokyo, Japan	International social science community		East Asia
27	Presentation	H Gottweis and H Chen	The Current Context in China and the US: Comparative Analysis of Innovation in the Field "Conference	April 18-19, 2011	Bringing Regenerative Medicine to the Clinic: Trials and Tribulations in Europe and Beyond" Regenerative Medicine in Europe (REMEDiE) Closing Conference Bilbao, Spain	International social science, bioscience and regulatory communities		China
28	Presentation	C. Haddad	Stem Cell Clinical	13-15	Presentation at the Brocher Foundation	International		Global focus

			Trials. A Social Science perspective on scientific and regulatory uncertainty and heterogeneity	November 2009	International Workshop: „Beyond the Embryo“ Geneva	social science researchers		
29	Presentation	C. Haddad	Clinical trials and the problem of risk regulation	24 March, 2010	Presentation at the LSG international workshop Vienna, Austria	Social science community		US/Europe
30	Presentation	C. Haddad	Experimental Politics. Stem cells and the governance of clinical trials Conference	April 18-19	Regenerative Medicine in Europe (REMEDiE) Closing Bilbao, Spain	International social science, bioscience and regulatory communities		US/Europe
31	Presentation	B. Salter	EU and global politics: states, strategies and alliances	May 7-8, 2009	Presentation at the Conference “Beyond Pattison: Challenges to Stem Cell Translation and Policy”, Wellcome Trust Centre, London	Social science, science policy, and bioscience communities	c.80	European and global
32			Europe in the global regenerative bioeconomy: the challenges of multi-level governance	November 2009	Presentation at Centre for Biomedicine and Society, London	Social science, science policy, and bioscience communities	c.30	Europe
33	Presentation	B. Salter and S Hogarth	EU and global politics: states, strategies and alliances	July 2, 2009	Presentation at Centre for Biomedicine and Society, London	Social science community	c.40	Europe
34	Presentation	S Hogarth and B. Salter	The European Union and the global political competition for future position in regenerative medicine	June 9-10	Paper presented at Regenerative Medicine in 21c: Managing Uncertainty at Global Level The Pyle Center, University of Wisconsin-Madison, USA.	Social scientists, regulators, bioscientists	60	Global

35	Presentation	S Hogarth and B. Salter	The European Union and the global political competition for future position in regenerative medicine	July 2010	Presentation at annual meeting of the UKSCN in Nottingham	Science community	c.250	Europe
36	Presentation	S Hogarth	The European Union and the global political competition for future position in regenerative medicine	December 2010	Presentation to the Department of Business, Innovation and Skills, London, UK	Policy community/civic service	5	UK and Europe
37	Presentation	S Hogarth	The European Union and regenerative medicine: innovation strategy and commercial prospects	March 2011	DG Research and Innovation, Brussels	Policy community	4	Europe
38	Guest Lecture	I. de Miguel Beriain	"El embrión humano ante la bioética, el derecho, la investigación y la medicina"	2nd - 6th July, 2008	The National University of Distance Learning-UNED Denia, Spain	Bioethicists		Global focus
39	Presentation	I. de Miguel Beriain	El concepto de embrión en la Ley 14/2007, de 3 de julio, de Investigación Biomédica	1st - 3rd, July, 2008	UNIJES Congress, held in Madrid	Bioethicists		Global focus
40	Presentation	I. de Miguel Beriain	La reciente regulación de los Análisis Genéticos en Portugal. Estudio comparado con la legislación española	4-5 May 2009	XVI Conference in Law and the Human Genome, Bilbao, Spain	Bioethicists		Global focus

41	Presentation	I. de Miguel Beriain	Quimeras e Híbridos: Nuevo Desafío para la Bioética	1-3 July 2009	International Congress "Derecho y Nuevas Tecnologías" organized by the Law Schools of the University of Deusto, The Comillas Pontifical University (ICADE) and The Ramon Llull University (ESADE),			Global focus
42	Presentation	I. de Miguel Beriain	Clonación e Investigación con Células Troncales Humanas: Debate Ético y Jurídico	29th October, 2009	Mediterranean Centre (University of Granada) "Perspectivas en la investigación con células troncales: Aspectos científicos, éticos, sociales y legales"	Bioethicists		Global focus
43	Presentation	I. de Miguel Beriain	Pero ¿qué hay de malo en clonar	12 November 2009	Symposium Bioderecho y Biotecnología University of León	Social scientists		Global focus
44	Presentation	I. de Miguel Beriain	Biología Sintética	22 April 2010	XVII Conference in Law and the Human Genome, organized by the University of Deusto	Lawyers, bioethcists		Global focus
45	Workshop presentation	I. de Miguel Beriain	Los conceptos de autonomía y dignidad en ética de la investigación	31 May-1 June	Workshop of Bioética y cultura científica: Ética de la investigación. VI. Taller de Éticas Aplicadas. DILEMATA Donostia-San Sebastián, Spain	Bioethicists, lawyers		Global focus
46	Presentation	I. de Miguel Beriain	Europa: ¿Un espacio para seres clonados	7th to 9th July, 2010	XXI Summer Academy of The National University of Distance Learning-UNED Spain	Social scientists		Europe
47	Presentation	I. de Miguel Beriain	La clonación a debate	14th to 16th of July, 2010.	The National University of Distance Learning-UNED, under the title "Bioética y Derechos Humanos Pontevedra Spain	Social scientists		Europe
48	Presentation/paper	K.Braun, J. Sandor and S Schultz	Oöcytes for research: between commercialization and anti-payment provisions – the case of Spain and the European	April 18-19, 2011	REMEDiE Closing Conference: Bringing Regenerative Medicine to the Clinic: Trials and Tribulations in Europe and Beyond Bilbao, Spain	Scientists and Social Scientists	100	Global

			framework					
49	Guest lecture	K Braun	The Female Body and the Global Tissue Economy	23 Nov. 2010	Stockholm University	Social science students and colleagues	20	Sweden
50	Presentation	K Braun	Oocytes for Research: Inspecting the Mobilisation-Commercialisation Continuum	27–29 Sept., 2010	Gender and Health Conference Linköping	Researchers in medicine and social sciences	40	Europe, North America
51	Panel	S.Schultz	Mobilizing Eggs – mobilizing women	Sep 1-4, 2010	European Association for the Study of Science and Technology (EASST) Conference: Practicing Science and Technology. Performing the Social Trento	STS scientific community	30	Global
52	Panel	K. Braun/S. Schultz	Vendors, victims, workers – models of citizenship in current debates on egg procurement for research	June 30 - July 2, 2010	Beyond Citizenship: Feminism and the Transformation of Belonging", Birkbeck, University of London	Gender studies researchers and practitioners	30	Global
53	Panel	K. Braun	Configuring Biocapital and the Tissue Market	7-8 May 2009	Wellcome Trust, London	Scientists and Social Scientists	100	Global
54	Presentation	B Kewell	Beyond the Bull Market: Biocapital and Regenerative Medicine in a Changing Financial World	7-8 May 2009	'Beyond Pattison: Challenges to Stem Cell Translation and Policy Wellcome Trust, London	Social science, science policy, and bioscience communities	100	UK/Europe
55	Presentation	B Kewell	Accounting for the Costs of Regenerative Medicine: A Chasm Too Far?	7-10 October 2009	REMEDiE Workshop, Tulbingerkogel Hotel and Conference Centre, Vienna, Austria	Social scientists	25	Europe
56	Panel	B Kewell	Regenerative Medicine in The 21c: Managing Uncertainty At The	June 9-10, 2010	Paper presented at Regenerative Medicine in 21c: Managing Uncertainty at Global Level	International social science community, regulators and	100	Global

			Global Level'		The Pyle Center, University of Wisconsin-Madison, USA.	bioscientists		
57	Presentation	B Kewell	Accounting for the Costs of Regenerative Medicine: A Chasm Too Far?	7-10 October 2009	REMEDiE Workshop, Tulbingerkogel Hotel and Conference Centre, Vienna, Austria	Social scientists	25	Europe
58	Panel	B Kewell	Bringing Regenerative Medicine To The Clinic: Trials and Tribulations in Europe and Beyond'	18-19 April, 2011	REMEDiE Closing Conference, Bilbao	Scientists and Social Scientists	100	Global
59	Panel	G. Lewis	Investing in Regenerative Medicine - Financial Investment Patterns & Clinical Trials	June 9-10, 2010	Paper presented at Regenerative Medicine in 21c: Managing Uncertainty at Global Level The Pyle Center, University of Wisconsin-Madison, USA.	International social science community, regulators and bioscientists	100	Global
60	Presentation	G Lewis	Key findings of the REMEDiE database	18-19 April, 2011	REMEDiE Closing Conference, Bilbao	Scientists and Social Scientists	100	Global
61	Presentation/Podcast	A Webster	Stem Cell Research and Society	7 August 2008	University of Sydney	Social scientists	100	International
62	Presentation	A Webster	Standardising stem cells: gaining stability but creating new uncertainty?	8 August 2008	11th Stem Cell Workshop, New South Wales Network, Australia	Policy practitioners, industrialists and stem cell scientists	70	Australia, Europe, USA
63	Workshop convenor	A Webster	Automating stem cell science: from GMP to the clinic	23 September 2008	Joint ESRC/EPSRC invited workshop, London	Scientists and SMEs	20	UK
64	Presentation	A Webster	'Celling' Science	4 Feb 2009	University of Newcastle, UK	Social scientists	20	UK
65	Presentation	A Webster	The globalization of regenerative	26 February 2009	Birmingham University Stem Cell Centre	Clinical School	30	Global

			medicine: core issues concerns and implications			research staff		
66	Presentation	A Webster	Transnational stem cell banking	12 October 2009	UK Stem Cell Bank/Spanish Stem Cell Bank joint meeting, Royal Society, London	Bioscientists, Stem Cell Bank staff	40	UK/Spain
67	Presentation	A Webster	Regenerative Medicine in a Global Context	9-10 June 2010	REMEDiE Second Annual International Conference, University of Wisconsin-Madison	Social scientists, regulators, bioscientists	60	Global
68	Presentation	A Webster	Regenerative Medicine: Findings from the REMEDiE Project	10 -11 November 2010	Making Perfect Life Conference, European Parliament Brussels	MEPs and researchers	120	Europe
69	Keynote address	A Webster	Biotechnological development, science-society and the social contract	19 January 2011	National Strategy for Biotechnology, Research Council of Norway	Ministers, civil servants, social scientists, bioscientists	250	Norway and Europe
70	Presentation	A Webster	Stem cell banking in the bio-economy: production, distribution and consumption	22 March 2011	Society for Low Temperature Biology Annual Symposium, Linnaean Society, London	Bioscientists	25	Global
71	Keynote address	A Webster	Bio-objects, Bio-subjects and bio-agents: Tracking socio-material realities	19th May 2011.	European Commission Bio-Objects COST Action, University of Vienna	Social scientists, bioethicists	100	Global

A General Information *(completed automatically when **Grant Agreement number** is entered.*

Grant Agreement Number:	**217180**
Title of Project:	*Regenerative medicine in Europe*
Name and Title of Coordinator:	Professor Andrew Webster

B Ethics

1. Did your project undergo an Ethics Review (and/or Screening)? • If Yes: have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final project reports? Special Reminder: the progress of compliance with the Ethics Review/Screening Requirements should be described in the Period/Final Project Reports under the Section 3.2.2 *'Work Progress and Achievements'*	***Yes***
2. Please indicate whether your project involved any of the following issues (tick box) :	***YES***
RESEARCH ON HUMANS	
• Did the project involve children?	
• Did the project involve patients?	
• Did the project involve persons not able to give consent?	
• Did the project involve adult healthy volunteers?	
• Did the project involve Human genetic material?	
• Did the project involve Human biological samples?	
• Did the project involve Human data collection?	√
RESEARCH ON HUMAN EMBRYO/FOETUS	
• Did the project involve Human Embryos?	
• Did the project involve Human Foetal Tissue / Cells?	
• Did the project involve Human Embryonic Stem Cells (hESCs)?	
• Did the project on human Embryonic Stem Cells involve cells in culture?	
• Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?	
PRIVACY	
• Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	
• Did the project involve tracking the location or observation of people?	
RESEARCH ON ANIMALS	
• Did the project involve research on animals?	
• Were those animals transgenic small laboratory animals?	
• Were those animals transgenic farm animals?	
• Were those animals cloned farm animals?	
• Were those animals non-human primates?	
RESEARCH INVOLVING DEVELOPING COUNTRIES	
• Did the project involve the use of local resources (genetic, animal, plant etc)?	
• Was the project of benefit to local community (capacity building, access to healthcare, education etc)?	
DUAL USE	
• Research having direct military use	No
• Research having the potential for terrorist abuse	

C Workforce Statistics

3. Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator		1
Work package leaders	3	4
Experienced researchers (i.e. PhD holders)	3	5
PhD Students	1	1
Other		

4. How many additional researchers (in companies and universities) were recruited specifically for this project?	**None**
Of which, indicate the number of men:	

D Gender Aspects

5. Did you carry out specific Gender Equality Actions under the project?

○	Yes
√	No

6. Which of the following actions did you carry out and how effective were they?

		Not at all effective				Very effective
❑	Design and implement an equal opportunity policy	○	○	○	○	○
❑	Set targets to achieve a gender balance in the workforce	○	○	○	○	○
❑	Organise conferences and workshops on gender	○	○	○	○	○
❑	Actions to improve work-life balance	○	○	○	○	○
○	Other:					

7. Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed?

○ Yes- please specify

√ No

E Synergies with Science Education

8. Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?

√ Yes- please specify : The Coordinator arranged REMEDiE participation in regional UK science festival in York.

○ No

9. Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?

√ Yes- please specify : the REMEDiE website carries a full range of material about the project

○ No

F Interdisciplinarity

10. Which disciplines (see list below) are involved in your project?

○ Main discipline[5]: 5.2; 5.4; 6.3

○ Associated discipline[5]: ○ Associated discipline[5]:

G Engaging with Civil society and policy makers

11a Did your project engage with societal actors beyond the research community? *(if 'No', go to Question 14)*

√	Yes
○	No

11b If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?

○ No

○ Yes- in determining what research should be performed

√ Yes - in implementing the research

√ Yes, in communicating /disseminating / using the results of the project

[5] Insert number from list below (Frascati Manual).

11c In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?	√ ○	Yes No

12. Did you engage with government / public bodies or policy makers (including international organisations)

○	No
○	Yes- in framing the research agenda
√	Yes - in implementing the research agenda
√	Yes, in communicating /disseminating / using the results of the project

13a Will the project generate outputs (expertise or scientific advice) which could be used by policy makers?

√	Yes – as a **primary** objective (please indicate areas below- multiple answers possible)
○	Yes – as a **secondary** objective (please indicate areas below - multiple answer possible)
○	No

13b If Yes, in which fields?

Agriculture		Energy		Human rights	
Audiovisual and Media		Enlargement		Information Society	
Budget		Enterprise		Institutional affairs	
Competition	x	Environment		Internal Market	
Consumers		External Relations		Justice, freedom and security	
Culture		External Trade		Public Health	x
Customs		Fisheries and Maritime Affairs		Regional Policy	x
Development Economic and Monetary Affairs		Food Safety		Research and Innovation	
Education, Training, Youth		Foreign and Security Policy		Space	
Employment and Social Affairs		Fraud		Taxation	
		Humanitarian aid		Transport	

13c If Yes, at which level?

- ○ Local / regional levels
- √ National level
- √ European level
- √ International level

H Use and dissemination

14. How many Articles were published/accepted for publication in peer-reviewed journals?	**By the close of contract (April 30 2011) there were 33**
To how many of these is open access[6] provided?	**12**
How many of these are published in open access journals?	**11**
How many of these are published in open repositories?	**1**
To how many of these is open access not provided?	**21**
Please check all applicable reasons for not providing open access:	
❑ publisher's licensing agreement would not permit publishing in a repository ❑ no suitable repository available ❑ no suitable open access journal available ❑ no funds available to publish in an open access journal ❑ lack of time and resources ❑ lack of information on open access ❑ other[7]: ……	**x**

15. How many new patent applications ('priority filings') have been made? *("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).*		**N/A**
16. Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark	**N/A**
	Registered design	**N/A**
	Other	
17. How many spin-off companies were created / are planned as a direct result of the project?		**N/A**
Indicate the approximate number of additional jobs in these companies:		

18. Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

❑ Increase in employment, or	❑ In small & medium-sized enterprises
❑ Safeguard employment, or	❑ In large companies
❑ Decrease in employment,	❑ None of the above / not relevant to the project
√ Difficult to estimate / not possible to quantify	

19. For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (*FTE = one person working fulltime for a year*) jobs:	*Indicate figure:* *26.3 FTE*

[6] Open Access is defined as free of charge access for anyone via Internet.
[7] For instance: classification for security project.

Difficult to estimate / not possible to quantify	❑

I Media and Communication to the general public

20. As part of the project, were any of the beneficiaries professionals in communication or media relations?

○ Yes √ No

21. As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?

○ Yes √ No

22 Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

√	Press Release	√	Coverage in specialist press
❑	Media briefing	√	Coverage in general (non-specialist) press
❑	TV coverage / report	❑	Coverage in national press
√	Radio coverage / report	❑	Coverage in international press
√	Brochures /posters / flyers	√	Website for the general public / internet
√	DVD /Film /Multimedia	√	Event targeting general public (festival, conference, exhibition, science café)

23 In which languages are the information products for the general public produced?

❑	Language of the coordinator	√	English
❑	Other language(s)		