Executive Summary:

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.

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.

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.

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.

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.

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.

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.

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 interrelated 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.

Project Results:

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.

Innovation and firm activity at European and Global levels

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 out with 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 , 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: Principal Characteristics

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 features.

Geographical distribution of European RM firms

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. 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 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.

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).

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.

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 has 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.

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).

The available cell therapies are overwhelmingly based on autologous somatic cell therapies while the cell therapy pipeline 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 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.

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 DatastreamTM. 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 DatastreamTM and accounting information published on company websites.

Some notable firms are apparent within this subset. 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.

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.

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; 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.

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.

A 'spike' around 2000 was observed, 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). 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.

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.

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).

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) and acute myocardial infarction (AMI). 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 '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 issue 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 (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.

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 . 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 .

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 turns out to be too difficult and/or unsafe to deal with in the long run, this situation may change.

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. 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 pro-hibition 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'. At 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. 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 , the usual amount of reimbursement in reproductive medicine for egg cell donation is about 400.

In Spain, a royal decree has regulated egg donation since 1996. 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 , 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. 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'. 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 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'.

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 (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' 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', but when the discovery leads to

establishing practical use patentability is no longer refused. 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.' The Japanese patent examination guidelines include similar provisions.

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. 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. The case is now under appeal, and its outcome may change US patenting policy regarding isolated human DNA. 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 unpatentable. 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.

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) 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, 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). 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). 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). The 1959 Japanese Patent Act's morality clause is formulated in the same way (Article 32).

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. 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'. 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.' The 'moral utility' doctrine (Lowell v. Lewis, (1817) 15 F Cas 1018) has not been used in the case of biotechnology patents 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 with state level legislation determining the ethical boundaries of biomedical research activity.

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. 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. 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 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.' 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.

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, 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. 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)).

Potential Impact:

The potential impact of the project and its wider societal implications

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 and 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 EUR 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.

Permissive regimes (UK, Japan, India and China) allow research on human embryos and stem cell derivation from them. 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. Restrictive regimes (Germany) prohibit human embryonic research for general therapeutic purposes and ban hESC derivation, and they may prohibit using hESC lines and products. 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 which is now under challenge before the courts. 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 , 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.

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.
- 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.

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, 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:

Governance

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

Creating a strategy

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

Research Infrastructure

- 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).

Public sector innovation and link to the wider health care system

- 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.
- 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.

Exporting RM products outside the EU.

The European Union should facilitate RM companies establishing themselves in markets outside the European Union.

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

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 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
- There are aspects of the current regulatory regime which require further harmonisation e.g. regulation of clinical trials and human tissue.
- The ATMP's hospital exemption requires clarification. Governance of those services/institutions which are exempt could be harmonized by processes outside the ATMP regulations.
- 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).

Intergovernmental alliances and international harmonisation

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

- 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.
- 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.

References

- Badylak, S. and R. Nerem (2010) 'Progress in Tissue Engineering and Regenerative Medicine'. PNAS, 197 (8): 3285-3286.
- Carpenter, D. P. (2010). Reputation and Power. Organizational image and pharmaceutical regulation at the FDA. , Princeton University Press.
- Cooke, T. (1998) 'Regression Analysis in Accounting Disclosure Studies'. Accounting and Business Research, 28 (3): 209-224.
- Daemmrich, A. (2004). Pharmacopolitics. Drug regulation in the United States and Germany. Chapel Hill / London, North Carolina Press.
- Farrar, D., and R. Glauber (1967) 'Multicollinearity in Regression Analysis: A Problem Revisited'. Review of Economics and Statistics, 49 (1): 92-107.
- Franklin, S. (2006). 'Embryonic Economies: The Double Reproductive Value of Stem Cells.' BioSocieties 1(1): 71-90.
- Gardner, L. (2007) 'Stem Cells and Regenerative Medicine: Principles, Prospects and Problems'. C.R. Biologies, 330: 465-473.
- Gilardi, F. (2008). Delegation in the Regulatory State. Independent Regulatory Agencies in Western Europe. . Cheltenham/Northhampton, Edward Elgar.
- Ikemoto, L. C. (2009). 'Eggs as Capital: Human Egg Procurement in the Fertility Industry and the Stem Cell Research Enterprise.' Signs 34(4): 763-781.
- Johnson, P., Bertram, T., Tawil, B. and K. Hellman (2010) 'Hurdles in Tissue Engineering/Regenerative Medicine Product Commercialization: A Survey of North American Academia and Industry'. Tissue Engineering: PART A 00/0: 1-11.
- Kemp, P. (2006) 'History of Regenerative Medicine: Looking Backwards to Move Forwards'. Regenerative Medicine, 1 (5): 653-669.
- Kewell, B., Mkumbuzi, W., Linsley, P., and M. Beck (2009) Accounting For The Costs Of Regenerative Medicine: A Chasm Too Far? Work Package 1: The EU in a Global Market: Investing in Regenerative Medicine.
- Kewell, B. and A. Webster (2009) 'A Tale of 'Cautious Pessimism': Biotechnology, Risk and Organisational Change in the Aftermath of the 'New Economy'. Biotechnology Journal, 4 (8): 1106-1107.
- Koh, C. and A. Atala (2004) 'Tissue Engineering, Stem Cells, and Cloning: Opportunities for Regenerative Medicine'. Journal of the American Society of Nephrology, 15: 1113-1125.
- Lagasse, E., Shizuru, J., Uchida, N., Tsukamoto, N., and I. Wiessman (2001) 'Towards Regenerative Medicine'. Immunity, 14: 425-436.
- Lanza, R. and N. Rosenthal (2004) 'The Stem Cell Challenge'. Scientific American, 290 (6): 92-99.
- Lysaght, M. (1995) 'Product Development in Tissue Engineering'. Tissue Engineering, 1 (2): 221-228.
- Lysaght, M., and J. Reyes (2001) 'Review: The Growth of Tissue Engineering'. Tissue Engineering, 7 (5): 485-493.
- Lysaght, M., and A. Hazlehurst (2003) 'Private Sector Development of Stem Cell Technology and Therapeutic Cloning'. Tissue Engineering, 9 (3): 555-561.
- Lysaght, M., and A. Hazlehurst (2004) 'Tissue Engineering: The End of the Beginning'. Tissue Engineering, 10 (1-2): 309-320.

- Lysaght, M., Jaklenec, A., and E. Deweerd (2008) 'Great Expectations: Private Sector Activity in Tissue Engineering, Regenerative Medicine, and Stem Cell Therapeutics'. Tissue Engineering: Part A, 14 (2): 305-319.
- Marston, C., and P. Shrives (1991) 'The Use of Disclosure Indices in Accounting Research: A Review Article'. British Accounting Review, 23 (3): 195-210.
- Martin, P., Hawksley, R, and A. Turner (2009) The Commercial Development of Cell Therapy- Lessons for the Future? Survey of the Cell Therapy Industry and the Main Products in Use and Development. Part 1: Summary of Findings. EPSRC Remedi Report, Institute for Science and Society, The University of Nottingham
- Mason, C. (2007) 'Regenerative Medicine: The Industry Comes of Age'. Medical Device Technology pp.25-28.
- Mason, C. and P. Dunhill (2008a) 'A Brief Guide to Regenerative Medicine'. Regenerative Medicine, 3 (1): 1-5.
- Mason, C. and P. Dunhill (2008b) 'The Strong Financial Case for Regenerative Medicine and the Regen Industry'. Regenerative Medicine, 3 (3): 351-363.
- McConnel, C. and L. Turner (2005) 'Medicine, Ageing and Human Longevity: The Economics and Ethics of Anti-Ageing Interventions'. EMBO Reports, 6: S59- S62.
- Messenger, M. and P. Tomlins (2011) 'Regenerative Medicine: A Snapshot of the Current Regulatory Environment and Standards'. Advanced Healthcare Materials, 23: H10-H17.
- Nerem, R. (2010) 'Regenerative Medicine: The Emergence of an Industry'. Interface, 7: S771-S775.
- 'Riordan, K. and J. Haran (2009). 'From reproduction to research. Sourcing eggs, IVF, and cloning in the UK.' Feminist Theory 10(2): 191-210.
- Pangarkar, N., Pharoah, M., Nigam, A., Hutmacher, D., and S. Champ (2010) 'Advanced Tissue Sciences Inc.: Learning From the Past, A Case Study of Regenerative Medicine'. Regenerative Medicine, 5 (5): 823-835.
- Pennings, G. (2006). 'Subsidized in-vitro fertilization treatment and the effect on the number of egg sharers.' Reproductive Medicine Online 13(1): 8-10.
- Polak, Dame Julia (2010) 'Regenerative Medicine. Opportunities and Challenges: A Brief Overview'. Interface, 7:S777-S781.
- Rothstein, H., M. Huber, et al. (2006). 'A Theory of Risk Colonisation: The spiralling regulatory logics of societal and institutional risk.' Economy and Society 35(1): 91-112.
- Rowley, E. and P. Martin (2009) Barriers to the Commercialisation and Utilisation of Regenerative Medicine in the UK. EPSRC Remedi Report, Institute for Science and Society, The University of Nottingham.
- Vacanti, C. (2006) 'The History of Tissue Engineering'. Journal of Cellular and Molecular Medicine, 10(3): 569-576.
- Vogel, D. (2003). 'The Hare and the Tortoise Revisited: The New Politics of Consumer and Environmental Regulation in Europe.' British Journal of Political Science 33(04): 557-580.
- Waldby, C. (2008). 'Oocyte markets: women's reproductive work in embryonic stem cell research.' New Genetics and Society 27(1): 19-31.
- Webster, A., C. Haddad, et al. (2012). 'Experimental heterogeneity and standardization. Stem cell products and the clinical trials process.' Biosocieties (forthcoming, 2012).

List of Websites:
http://www.york.ac.uk/satsu/remedie

Professor Andrew Webster (Coordinator)
andrew.webster@york.ac.uk