HOUSE OF LORDS

Science and Technology Committee

1st Report of Session 2013–14

Regenerative medicine

Report

Ordered to be printed 11 June 2013 and published 1 July 2013

Published by the Authority of the House of Lords

London : The Stationery Office Limited
£15.50

HL Paper 23

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Committee Staff

Staff who worked on this inquiry include Chris Atkinson (Clerk), Cerise Burnett-Stuart (Committee Assistant), James Lawrence (Policy Analyst), Rachel Maze (Policy Analyst) and James Tobin (Policy Analyst).

Contacts Details

All correspondence should be addressed to the Clerk of the Science and Technology Committee, Committee Office, House of Lords, London SW1A 0PW.
The telephone number for general enquiries is 020 7219 5750.
The Committee's email address is hlscience@parliament.uk.

CONTENTS

NOTE: Evidence is published online at www.parliament.uk/hlscience and available for inspection at the Parliamentary Archives (020 7219 5314)

References in footnotes to the Report are as follows:
Q refers to a question in oral evidence;
Witness names without a question reference refer to written evidence.

SUMMARY

Regenerative medicine involves replacing or regenerating cells, tissues or organs in the human body, in order to restore or establish normal function. It includes cell therapy, gene therapy, tissue engineering and other methods, and it has enormous potential to treat and cure diseases. It could also improve the quality of peoples' lives and generate significant economic benefits for the UK.

In this inquiry we have sought to identify what the UK is doing well in regenerative medicine and any barriers to its future development. We make recommendations to the Government that, if acted upon, would facilitate the translation of scientific knowledge into clinical practice and encourage its commercial exploitation.

The UK has many strengths in regenerative medicine, including: an excellent basic science base, potential access to hundreds of thousands of patients in a unified healthcare system, and experienced blood and transfusion services, clinicians and scientists. The UK has the chance to be a leader in this field and this opportunity must not be missed.

Private investors are reluctant to invest in regenerative medicine because of the high risks of failure to translate scientific discoveries into widely used treatments. The Government could help by simplifying and clarifying the regulatory system, enhancing support for clinical trials and backing innovative funding models. They must take action now to ensure that the UK does not fall behind other countries, such as Japan and the USA, who are already taking steps to streamline their processes. Our headline recommendations are that:

- The Health Research Authority, with the support of an independent advisory group, should take further steps over the next 18 months to streamline the overall system of regulation of regenerative medicine. In the short term, it should provide an additional advice service to help researchers navigate the "labyrinthine" regulatory system;
- The National Institute for Health Research should set up a regenerative medicine stream of its clinical research network to assist with design of clinical trials, identifying patients and finding interested clinicians;
- The Department for Business, Innovation and Skills should invest in manufacturing facilities to support the scale-up of treatments in mid to late stage clinical development;
- The Department of Health should develop a strategy to ensure the NHS is ready to provide regenerative treatments;
- The Technology Strategy Board and Economic and Social Research Council should evaluate innovative funding models, including those used in other countries and recommend one to Her Majesty's Treasury, to supplement the promising work of the Cell Therapy Catapult;
- The National Institute for Health and Care Excellence should improve its evaluation process to allow for the fact that although regenerative medicine treatments may have a high initial cost, they are likely to make big savings to the NHS in the long run; and
- The Government should appoint an independent Chair of a group tasked with co-ordinating and maintaining momentum in the delivery of regenerative medicine treatments.

Regenerative medicine

CHAPTER 1: INTRODUCTION

Purpose of the inquiry

1. Regenerative medicine is an umbrella term for the medical specialty of the regeneration of human tissue, organs and cells.[1] It has potential to treat or cure disease. Possible treatments range from a cure for diabetes to new approaches for drug screening, from curing neurological disorders to, eventually, repairing hearts. This inquiry sought to pinpoint the UK's strengths in regenerative medicine, identify barriers to translation (applying findings from basic research in a clinical setting) and commercialisation (in this case, primarily delivering treatments in the healthcare market), and recommend solutions. The UK has an enviable potential resource in the National Health Service (NHS)—access to hundreds of thousands of patients in one system—and a strong science base in this field. The Government have also been paying significant attention to developing the field. Together, these factors could combine to benefit patient wellbeing and the health of the UK economy.

2. Basic science, translation and commercialisation in this field are being well supported in some other countries. However, there is growing concern that despite positive progress so far the UK could fall behind in this area and miss out on opportunities to translate basic science to commercially viable treatments as the science develops. This opportunity must not be missed—the UK could and should be a world leader in this field.

Scope

3. Much has been written about regenerative medicine and its composite elements in recent years. We have focussed our inquiry on the translation and commercialisation of research. Given the work of previous committees of this House considering the ethics of the use of stem cells[2] and the work of other organisations on this area (such as the Nuffield Council on Bioethics),[3] we excluded ethical considerations from our terms of reference.

Methodology

4. We issued a call for evidence (set out in Appendix 3) in August 2012 and received 76 submissions. In October 2012, we held a seminar on regenerative medicine at King's College London, a note of which is set out in Appendix 4. In December 2012, we visited the California Institute for Regenerative Medicine (CIRM). A note of this visit is set out in Appendix 5. We held 17

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1 Mason, C., Dunnill, P. 'A brief definition of regenerative medicine', *Regenerative Medicine*, January 2008.

2 Stem Cell Research Committee, *Stem Cell Research* (Report, Session 2001–02, HL Paper 83), and Joint Committee on the Human Tissue and Embryos (Draft) Bill, *Human Tissue and Embryos (Draft) Bill* (Report, Session 2006–07, HL Paper 169).

3 Nuffield Council on Bioethics: *Emerging biotechnologies: technology, choice and the public good*, 2012.

evidence sessions in the House of Lords from October 2012 to February 2013.

Structure of the report

5. In the next chapter, we set out some definitions and examples of regenerative medicine. In Chapter 3, we consider the landscape of regenerative medicine in the UK. Chapter 4 discusses barriers to the translation of regenerative research and recommends strategies to address them. Chapter 5 looks at commercial issues. Chapter 6 summarises our key conclusions and recommendations.

Acknowledgements

6. The membership and interests of the Committee are set out in Appendix 1, and those who submitted evidence are listed in Appendix 2. We are grateful to all those who assisted us in our work.

7. We are also grateful to our specialist adviser, Professor Fiona Watt FRS, Director of the Centre for Stem Cells and Regenerative Medicine, King's College London, for her expertise and guidance during this inquiry. We stress, however, that the conclusions which we draw and the recommendations that we make are ours alone.

CHAPTER 2: DEFINITIONS AND EXAMPLES

What is regenerative medicine?

8. The term "regenerative medicine" is used to refer to methods to replace or regenerate human cells, tissues or organs in order to restore or establish normal function.[4] This includes cell therapies, tissue engineering, gene therapy and biomedical engineering techniques, as well as more traditional treatments involving pharmaceuticals, biologics and devices. In Boxes 1 and 2 we set out some key definitions.

BOX 1

Definitions

ATMP (Advanced Therapy Medicinal Products): innovative, regenerative therapies which combine aspects of medicine, cell biology, science and engineering for the purpose of regenerating, repairing or replacing damaged tissues or cells.[5]

Biologics: medicinal products that contain one or more active substances made by or derived from a biological source.[6]

Cells: the basic building blocks of all living things. The human body is composed of trillions of cells. They provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialised functions such as secretion of hormones, information processing, defence against disease, and transport of nutrients. Cells also contain the body's hereditary material and can make copies of themselves.[7]

Cell therapy: administration of cells to the body to the benefit of the recipient.[8]

Gene: single unit of genetic material located in the cell nucleus in chromosomes (long, threadlike structures in each of the body's cells that contain DNA). Genes contain the genetic information that influences almost all the characteristics of the individual from hair colour to risk of dying of heart disease.[9] Some genes code for proteins, the body's building blocks; others act as control switches, and others do not have any known function.

Gene therapy: deliberate introduction of genetic material into cells to the benefit of the recipient.[10]

Scaffold: support, delivery vehicle or matrix for facilitating the migration, binding or transport of cells or bioactive agents.[11]

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4 *Op. cit.* A brief definition of regenerative medicine.

5 Human Tissue Authority (HTA): *Advanced Therapy Medicinal Products Regulation and Quality and Safety Regulations*, 2008.

6 EMA: *Questions and answers on biosimilar medicines*, 2012, FDA: *What is a biological product*, 2010.

7 National Institutes of Health: *Help me understand genetics handbook*, 2013.

8 British Standards Institution (BSI): *Publicly Available Specification (PAS) 84: Regenerative Medicine—Glossary*, 2008.

9 NHS: *Introduction to genetics*, 2012: http://www.nhs.uk/conditions/Genetics/Pages/Introduction.aspx.

10 *Op. cit.* PAS 84.

11 *Op. cit.* PAS 84.

Tissue engineering: use of a combination of cells, engineering, materials and methods to manufacture *ex vivo* (outside the living body) living tissues and organs that can be implanted to improve or replace biological functions.[12]

BOX 2

Cell definitions: types, potency and therapy types

Allogeneic: where donor and recipient cells are from different individuals.[13]

Autologous: where cells are from the same individual.[14]

Differentiation: the process whereby an unspecialised embryonic or other cell acquires the features of a specialised cell such as a heart, liver, or muscle cell. Differentiation is controlled by the interaction of a cell's genes with the physical and chemical conditions outside the cell, usually through signalling pathways involving proteins embedded in the cell surface.[15]

Multipotent: cells that have the ability to develop into a limited number of specialised cell types.[16]

Pluripotent: cells that are capable of differentiating into all tissues of an organism, but are not alone capable of sustaining full organismal development.[17]

Stem cells: cells with the ability to divide for indefinite periods in culture and to give rise to specialised cells.[18]

Embryonic stem cells: undifferentiated cells derived from a pre-implantation embryo (an embryo of about 150 cells produced by cell division) or blastocyst that is pluripotent.[19]

Induced pluripotent stem (iPS) cells: human embryonic stem cell-like cell that is produced by reprogramming a cell to a state of pluripotency.[20]

Currently available treatments

9. Regenerative medicine is explained well by illustration. The following examples are a selection of treatments that are currently available. There are only two regenerative medicine treatments with European Union Marketing Authorisation (central approval which is binding in all Member States): glybera, a gene therapy to treat lipoprotein lipase deficiency (a rare disease in which patients have a defect in the gene encoding an enzyme responsible for breaking down fats); and ChondroCelect, an autologous cell therapy where a patient's cartilage cells are biopsied, grown and expanded in the laboratory

12 *Ibid.*

13 *Ibid.*

14 *Ibid.*

15 National Institutes of Health (NIH): *Stem cell glossary*, 2013.

16 *Op. cit.* PAS 84.

17 *Op. cit.* Stem cell glossary.

18 *Ibid.*

19 *Ibid.*

20 *Op. cit.* PAS 84.

and used to treat cartilage defects in knees.[21] ChondroCelect has been used in the UK in private healthcare settings but is not available through the NHS as NICE has not completed its evaluation, meaning no centrally agreed level of reimbursement can be offered.[22] Glybera has only recently been approved for use.

10. Bone marrow transplantation is widely recognised as the original stem cell therapy.[23] A bone marrow transplant involves taking healthy stem cells from the bone marrow of one person and transferring them to the bone marrow of another (or, in some cases, a patient's own healthy bone marrow).[24] Transplants are often used to treat conditions, such as leukaemia, which damage bone marrow so that it is no longer able to produce normal blood cells. In the period 2004–09, 14, 366 haematopoietic (giving rise to blood cells) transplants were performed in the UK,[25] demonstrating that this treatment is both available now in the UK and is undertaken extensively.

11. The Scottish National Blood Transfusion Service (SNBTS) developed and operates a UK-wide pancreatic islet transplantation service for patients with type one diabetes who have poor glycaemic awareness (problems recognising when their blood sugar levels become dangerously low). Islet cells, which make and release insulin, are extracted from the pancreas of a deceased donor, isolated and then transfused into the liver of a recipient patient to restart the body's insulin production in an experimental treatment. This procedure was carried out 61 times in the period 1 December 2010–30 November 2012.[26] Severe hypoglycaemia was reduced by >95% among patients who have received the treatment, and overall insulin requirement was halved, with a significant numbers of patients becoming insulin-independent.[27] There is great need for such a treatment, with up to 2, 000 of the 28, 000 people with type one diabetes in Scotland alone struggling to recognise low blood sugar levels,[28] but the number of transplants is limited by supply.[29]

12. Regenerative treatments are also used to help patients with burn injuries. Replacement skin cells can be grown from a postage stamp-sized sample of a patient's healthy skin to replace the top layer of skin (epidermis) for patients with severe burns. Cells from the skin sample are separated and grown by a process called tissue culture, which involves feeding the cells with specific nutrients and maintaining strict environmental controls so that the cells

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21 See:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000878/human_med_000698.jsp&mid=WC0b01ac058001d124
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002145/human_med_001480.jsp&mid=WC0b01ac058001d124, Q 358.

22 Cell Therapy Catapult.

23 Alliance for Regenerative Medicine.

24 NHS Choices: *bone marrow transplant*, 2012: http://www.nhs.uk/conditions/Bone-marrow-transplant/Pages/Introduction.aspx.

25 The British Society for Blood and Marrow Transplantation (BSBMT), the British Society for Haematology (BSH) and the Royal College of Pathologists (RCPath).

26 NHS Blood and Transplant Organ Donation and Transplantation Directorate Pancreatic Islet Taskforce: *2 year review of the national pancreas allocation scheme*, 2013.

27 UK Islet Transplant Consortium: *Referral guidelines: islet cell transplantation*, February 2013.

28 Scottish Government press notice: *Diabetes treatment success*, 2012.

29 Association of the British Pharmaceutical Industry (ABPI).

multiply to form sheets of skin. They can be grown on a layer of irradiated mouse cells. A surgeon then undertakes a procedure which covers (grafts) the lost or damaged skin. This grafted skin replaces the patient's top layer of skin in order to help burn wounds heal.[30]

Treatments likely to be available in the next five years

13. Having considered the limited number of treatments currently available in the UK we asked which treatments were likely to be widely available in the next five years. Regener8 (an organisation seeking to build collaboration between industry and universities) observed that treatments which supported the body's own regeneration and repair mechanisms, such as treatments that use scaffolds and matrices, were more likely to be available in the next few years than ATMPs, as were treatments that required minimal manipulation of a patient's own cells.[31] The BioIndustry Association (BIA) (a trade association for innovative enterprises involved in UK bioscience) observed that treatments likely to be available in five years would need to have regulatory approval already, or to be in late stages of clinical trials.[32] We considered some examples of treatments in the later stages of clinical development which showed some promise.

14. Clinicians at Moorefield's Eye Hospital and the company Advanced Cell Technology (ACT) are trialling a treatment for presently incurable eye diseases. They have developed embryonic stem cells (cells from early stage embryos which have the potential to develop into any type of body cell) into a specialised eye tissue type: retinal pigment epithelial (RPE) cells. Many eye diseases are caused by the degeneration or malfunction of this tissue and so replacement of destroyed RPE cells with healthy ones may be an effective treatment option for conditions[33] such as retinitis pigmentosa (a diverse group of inherited eye disorders),[34] age-related macular degeneration (an eye condition where the part of the eye responsible for central vision is unable to function as effectively as it used to, leading to gradual loss of central vision which affects nearly 50, 000 people in the UK)[35] and Stargardt's disease (juvenile macular degeneration).

15. ReNeuron (a Guildford based stem cell company) is trialling the injection of neural stem cells ("CTX cells") into the damaged brains of elderly patients who are left moderately to severely disabled by an ischaemic stroke (when blood flow leading to, or in, the brain is blocked). There are currently no therapies available for stroke patients who have a stable and fixed

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30 See, for example, Epicel: *Patient information,* 2007: http://www.epicel.com/~/media/Epicel/Files/epicel-patient-information.pdf, FDA: *Epicel cultured epidermal autograft,* 2007: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm074878.htm.

31 Regener8.

32 BioIndustry Association (BIA).

33 Advanced Cell Technology: *Retinal Pigment Epithelial Cell Program*: http://www.advancedcell.com/our-technology/act-stem-cell-related-research-pipeline/retinal-pigment-epithelial-cell-program/.

34 Royal National Institute of Blind People: *Retinitis pigmentosa*, 2012: http://www.rnib.org.uk/eyehealth/eyeconditions/eyeconditionsoz/Pages/retinitis_pigmentosa.aspx.

35 NHS Choices: *Macular degeneration*, 2012: http://www.nhs.uk/Conditions/Macular-degeneration/Pages/Introduction.aspx, GE Healthcare.

neurological deficit. This treatment seeks to reverse the damage caused to the brain.[36]

16. Imperial College London and the University of Edinburgh are taking part in a European clinical trial using stem cells to treat multiple sclerosis (MS) (a disease affecting nerves in the brain and spinal cord which causes problems with muscle movement, balance and vision).[37] Current treatments for MS are not curative.[38] Mesenchymal stem cells (stem cells derived from a patient's bone marrow) are grown and given back to the patient. It is anticipated that they might help repair the central nervous system.[39]

17. We consider clinical trials in the UK further, including additional examples, in the next Chapter.

Long-term possibilities

18. The examples above demonstrate that there are exciting potential treatments in the near-delivery end of the pipeline, but regenerative medicine also offers significant hope for treatments for a plethora of diseases in the long-term. Ongoing pre-clinical work suggests that it might eventually be possible to treat Parkinson's disease, cardiovascular disease and diabetes.[40]

The value and importance of regenerative medicine

Unmet medical need

19. Despite significant progress in medical innovation, there are still many diseases for which there are either no cures or only partially effective treatments. **The weight of evidence to our inquiry was that regenerative medicine has the potential to deliver new, innovative therapies, or even cures, where conventional approaches do not provide adequate solutions.**[41] Many submissions to the inquiry offered a "health warning", however, that public expectations must be managed as many of these treatments are relatively far from delivery to the wider public.[42] Around 30% of the UK population suffer from a chronic disease,[43] and the World Health Organisation (WHO) estimates that the UK loses $3.4 billion annually in income as a result of deaths from such conditions.[44] Chronic diseases can seriously diminish the quality of life of individuals as well as place great demands on family members and other carers.

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36 ReNeuron: *ReN001 for Stroke*: http://www.reneuron.com/ren001-for-stroke.

37 NHS Choices: *Multiple sclerosis*, 2012: http://www.nhs.uk/conditions/Multiple-sclerosis/Pages/Introduction.aspx.

38 NIH: *Clinical trials database—Stem Cells in Rapidly Evolving Active Multiple Sclerosis*, 2013: http://clinicaltrials.gov/ct2/show/NCT01606215.

39 *Ibid*.

40 BIA.

41 Alliance for Advanced Therapies, Alliance for Regenerative Medicine, Association of British Neurologists, ABPI, CIRM, Dr Paul Kemp, Korea Health Industry Development Industry.

42 Miltenyi Biotec, Oxford Stem Cell Institute (OSCI), Research Councils UK (RCUK).

43 Department of Health (DH): *Long Term Conditions Compendium of Information*, 2012.

44 World Health Organisation: *An estimation of the economic impact of chronic noncommunicable diseases in selected countries*, 2006.

Economics

20. It is widely acknowledged that the UK's National Health Service (NHS) is facing a funding crisis. According to research from the Nuffield Trust, the increasing cost of chronic disease management, coupled with increased life expectancy, means that "if NHS funding is held flat in real terms beyond this spending review period, the NHS in England could experience a funding gap worth between £44 and £54 billion in 2021–22".[45] Chronic disease management is estimated to account for 70–75% of all UK healthcare costs,[46] and chronic diseases are increasing in prevalence (as illustrated in Table 1 below). An Ernst and Young report observed that the percentage of US GDP spent on healthcare rose from 16% to 18% from 2007–09 and estimated that it would grow to 37% by 2050 without more innovative treatments.[47] The King's Fund estimate that, if healthcare spending and national income increase at similar rates, by the 2070s NHS spending will consume one fifth of total national income, rising to just over half by 2135.[48] Table 1 shows the number of people in the UK affected by specific long-term conditions.

TABLE 1
Number of people in the UK affected by specific long-term conditions[49]

Long-term condition	Number affected by each condition (patients could appear under multiple categories)		% change
	2006–07	2010–11	
Diabetes	1, 962, 000	2, 456, 000	25%
Coronary heart disease	1, 899, 000	1, 878, 000	–1%
Chronic kidney disease	1, 279, 000	1, 855, 000	45%
Stroke or Transient Ischaemic Attacks (TIA)	863, 000	944, 000	9%
Chronic obstructive pulmonary disease	766, 000	899, 000	17%
Heart failure	420, 000	393, 000	–6%
Epilepsy	321, 000	337, 000	5%
Dementia	213, 000	267, 000	25%

A rough indication of the direct costs of chronic disease can be seen in NHS programme budgeting data, which show the amount spent by primary care

45 Nuffield Trust: *A decade of austerity?*, 2012.

46 *Op. cit.* Long Term Conditions Compendium of Information, and Gemmill, M.: *Research Note: Chronic Disease Management in Europe*, 2008.

47 Ernst and Young: *Beyond border global biotechnology report*, 2011.

48 The King's Fund: *Spending on health and social care over the next 50 years*, 2013.

49 *Op. cit.* Long Term Conditions Compendium of Information.

trusts on different conditions under the old healthcare system but also include some costs for conditions which aren't chronic and do not include the cost of GP contract expenditure which the Department of Health says cannot be estimated at a disease specific level. Table 2 shows the healthcare costs associated with selected conditions.

TABLE 2

NHS programme budget expenditure[50]

Programme Budgeting Category	Gross Expenditure (£billion)					Expenditure as % of total spend
	2006–07	2007–08	2008–09	2009–10	2010–11	2010–11
Cancers and tumours	4.35	4.96	5.13	5.86	5.81	5.43
Disorders of blood	1.03	1.24	1.26	1.4	1.36	1.27
Endocrine, nutritional and metabolic problems	2.13	2.43	2.53	2.89	3	2.80
Mental health disorders	9.13	10.28	10.48	11.26	11.91	11.13
Problems of learning disability	2.49	2.86	2.93	3.15	2.9	2.71
Neurological	2.99	3.44	3.69	4.14	4.3	4.02
Problems of vision	1.38	1.60	1.67	1.93	2.14	2.00
Problems of hearing	0.33	0.42	0.42	0.5	0.45	0.42
Problems of circulation	6.9	7.23	7.41	8	7.72	7.21
Problems of the respiratory system	3.54	3.8	4.25	4.59	4.43	4.14
Problems of the gastro intestinal system	3.85	4.1	4.1	4.58	4.43	4.14
Problems of the skin	1.55	1.7	1.81	2.08	2.13	1.99
Problems of the musculoskeletal system	3.53	4.09	4.21	4.76	5.06	4.73

21. The costs of chronic disease are more than those simply of providing healthcare; chronic disease carries significant indirect and intangible costs such as the psychological dimensions of illness. Indirect costs include work absence, reduced productivity, early retirement, premature mortality, and the

[50] See www.gov.uk/government/uploads/system/uploads/attachment_data/file/156133/dh_131856.xls.xls.

implications of family members needing to act as carers.[51] It is estimated that productivity losses for employers could be over four times higher than the equivalent medical and pharmacy costs.[52] **Regenerative medicine has the potential to cure or provide more effective treatments for a number of chronic diseases, which would be of major benefit to the UK public purse given the rising expenditure on healthcare associated with chronic disease management and related indirect costs.**

22. A further consideration is that regenerative medicine could generate income for the UK economy. In a speech to the Royal Society, the Chancellor of the Exchequer, Rt Hon George Osborne MP, recognised that regenerative medicine could not only "transform current clinical approaches to replacing or regenerating damaged human organs or tissue" but could also be one of "eight future technologies where we [the Government] believe we [the UK] can be the best—where we already have an edge, but we could be world-leading".[53] The UK could see financial returns from foreign patients paying to be treated here, from the development of the domestic regenerative medicine industry and international companies setting up operation in the UK, and from companies paying to conduct clinical trials in the NHS.

Government initiatives

23. The Government have undertaken and sponsored a number of initiatives to support the field's development.

Taking stock of regenerative medicine

24. The Government published *Taking stock of regenerative medicine in the UK* in July 2011. The report sought to assess the UK's position in the field internationally, to identify barriers to development and to "lay the ground-work" for a regenerative medicine strategy. The report identified "steep technological, regulatory and strategic barriers to realising regenerative medicine's significant potential" and outlined 10 actions the Government would take to support regenerative medicine in the UK. These included taking steps to "better co-ordinate public investment and leverage funding from private sources; ensure the regulatory framework is facilitating and supported by a strong intellectual property regime, and appropriate standards; provide more clarity and help to get these highly innovative products to patients; and support the sector in the long-term, staying ahead of developments".

Life science strategy

25. In December 2011, the Government published their *Strategy for UK Life Sciences*, which set out actions to protect the UK's status as a world-leader in life science innovation, strengthen the country's life sciences industries and to help to "build a sustainable economic recovery". The three pillars of the strategy were:

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51 The Oxford Health Alliance: *Chronic disease: an economic perspective*, 2006.

52 *Op. cit.* Research note: Chronic Disease Management in Europe.

53 Her Majesty's Treasury: *Speech by the Chancellor of the Exchequer, Rt Hon George Osborne MP, to the Royal Society*, November 2012.

(1) "Building a UK life sciences ecosystem (making it easier for researchers to commercialise academic research, placing clinical research at the heart of the NHS, and empowering patients to participate in research);

(2) Attracting, developing and rewarding talent; and

(3) Overcoming barriers and creating incentives for the promotion of healthcare innovation".

26. Notable actions to which they committed included: an Early Access Scheme "to increase the speed and efficiency of routes to market approval for innovative, breakthrough therapies"; the creation of a more enabling regulatory environment for the adoption of innovative manufacturing technology; establishing a Biomedical Catalyst Fund and a Cell Therapy Technology and Innovation Centre (later to become the Cell Therapy Catapult) (more details in paragraph 50 below); and re-launching an enhanced web-based UK Clinical Trials Gateway to provide patients and the public with authoritative and accessible information about clinical trials in the UK.

Strategy for Regenerative Medicine

27. The research councils and Technology Strategy Board (TSB) *Strategy for Regenerative Medicine*, published in March 2012, identified eight key UK strategic objectives which needed to be addressed if the UK is to make the most of its current position:

(1) investment in underpinning research;

(2) studying efficacy and safety of the various therapeutic options, including cell transplantation, the stimulation of the body's own repair systems, and the use of acellular products;

(3) product development: linking early stage regenerative medicine product development with the establishment of manufacturing, transportation and delivery solutions;

(4) clinical delivery and evaluation: workshops to explore clinical trial challenges in order to establish the most effective trial designs and improve the transparency of the regulatory framework;

(5) innovation and value systems: investigations addressing issues such as the evolution of new business models, product development mechanisms (including reimbursement and adoption), and open innovation;

(6) remaining alert to international developments;

(7) focus: identify key disease areas/therapy types meriting concerted investment; and

(8) promoting interdisciplinary collaboration: bringing together of strong complementary skills, expertise and infrastructure across disciplines.

CHAPTER 3: THE CURRENT LANDSCAPE

Impact and excellence of the science base

28. The UK has a strong science base in regenerative medicine. The Department for Business, Innovation and Skills (BIS) commissioned Thomson Reuters to analyse the quality and impact of UK regenerative medicine research as part of its taking stock exercise. It found that, compared with continental averages, the UK had more highly cited research on average than the rest of Europe and Asia. North America outperformed the UK in the number of "very highly" cited articles but the UK has a strong, world-class, science base in this field.[54]

29. The UK has multiple academic centres of excellence in the field including the Wellcome Trust—Medical Research Council (MRC) Cambridge Stem Cell Biology Institute and the University of Edinburgh MRC Centre for Regenerative Medicine, as well as centres in London, Oxford and Newcastle.[55] UK researchers are "significant and regular" contributors to international scientific conferences on regenerative medicine and stem cell research.[56] Professor Michael Linden, King's College London, summed up the UK's current strength as follows: "the per capita impact that UK scientists have compared with the rest of the world—I mean UK science and biomedical science in particular—is very high".[57]

30. The Oxford Stem Cell Institute (OSCI) said that "the UK scores well in all metrics of academic output in the stem cell field, having particular strengths in disciplines such as induced pluripotency, bioengineering and scaffold design, transplantation immunology and medicinal chemistry. Many groups are of international standing and produce publications that are both influential and highly-cited".[58] Other areas of strength highlighted to us included haematopoietic stem cell research, developmental biology, gene therapy, tissue engineering and human embryonic stem cell biology.[59] Leukaemia and Lymphoma Research (LLR) offered a number of disease-specific examples: "academically the UK is leading the world in the development of cell and gene therapies for a wide range of inherited and acquired disorders including blindness, deafness, degenerative neurological conditions and cancer".[60]

Historical strengths

31. Prominent UK academics include three Nobel Prize winners: Professor Sir Martin Evans FRS, who discovered the principles for

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54 Department for Business, Innovation and Skills (BIS) and Department of Health (DH): *Taking stock of regenerative medicine in the United Kingdom*, July 2011.

55 ABPI, London Regenerative Medicine Network (LRMN), William James, NHSBTS.

56 Health Protection Agency (HPA), Q 4.

57 Q 2.

58 OSCI.

59 BSBMT, BSH, RCPath, BIA, HPA, University of Manchester, OSCI, Parkinson's UK, Professor Stephen Rimmer, Professor Sheila MacNeil and Professor John Haycock, University of Sheffield, Q 67, University College London (UCL) applied regenerative science group.

60 LLR.

introducing specific gene modifications in mice using embryonic stem cells;[61] the late Professor Sir Robert Edwards FRS, who developed human in vitro fertilization (IVF) therapy[62]; and Professor Sir John Gurdon FRS, who pioneered methods to "reprogram" cells to an embryonic state.[63] The UK is also responsible for some of the developmental biology which underpins the iPS (induced pluripotent stem cells) work in Japan and the US, for which Professor Shinya Yamanaka shared the 2012 Nobel Prize with Professor Sir John Gurdon.[64] Examples of ongoing work exploring the underpinning science of regenerative medicine in the UK include: understanding mechanisms of pluripotency, the interaction between stem cells and bioengineered surfaces, and advanced imaging techniques to monitor stem cell behaviour in living tissues.[65]

32. We consider the translation of basic science to clinical research in greater depth in the next Chapter. There are a great many areas of basic science related to regenerative medicine which need further investigation, and clinical research will bring to light areas where further research is required, for example to explain underpinning mechanisms.

Clinical trials

33. Clinical trials are medical research studies to test whether different treatments are safe and how well they work.[66] Figure 1 (overleaf) sets out the different stages of clinical trials:

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61 British Heart Foundation, Nobel Foundation: *The Nobel Prize in Physiology or Medicine*, 2007: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2007/.

62 Nobel Foundation: *The Nobel Prize in Physiology or Medicine*, 2010: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2010/.

63 California Institute for Regenerative Medicine (CIRM). *The Nobel Prize in Physiology or Medicine*, 2012: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/.

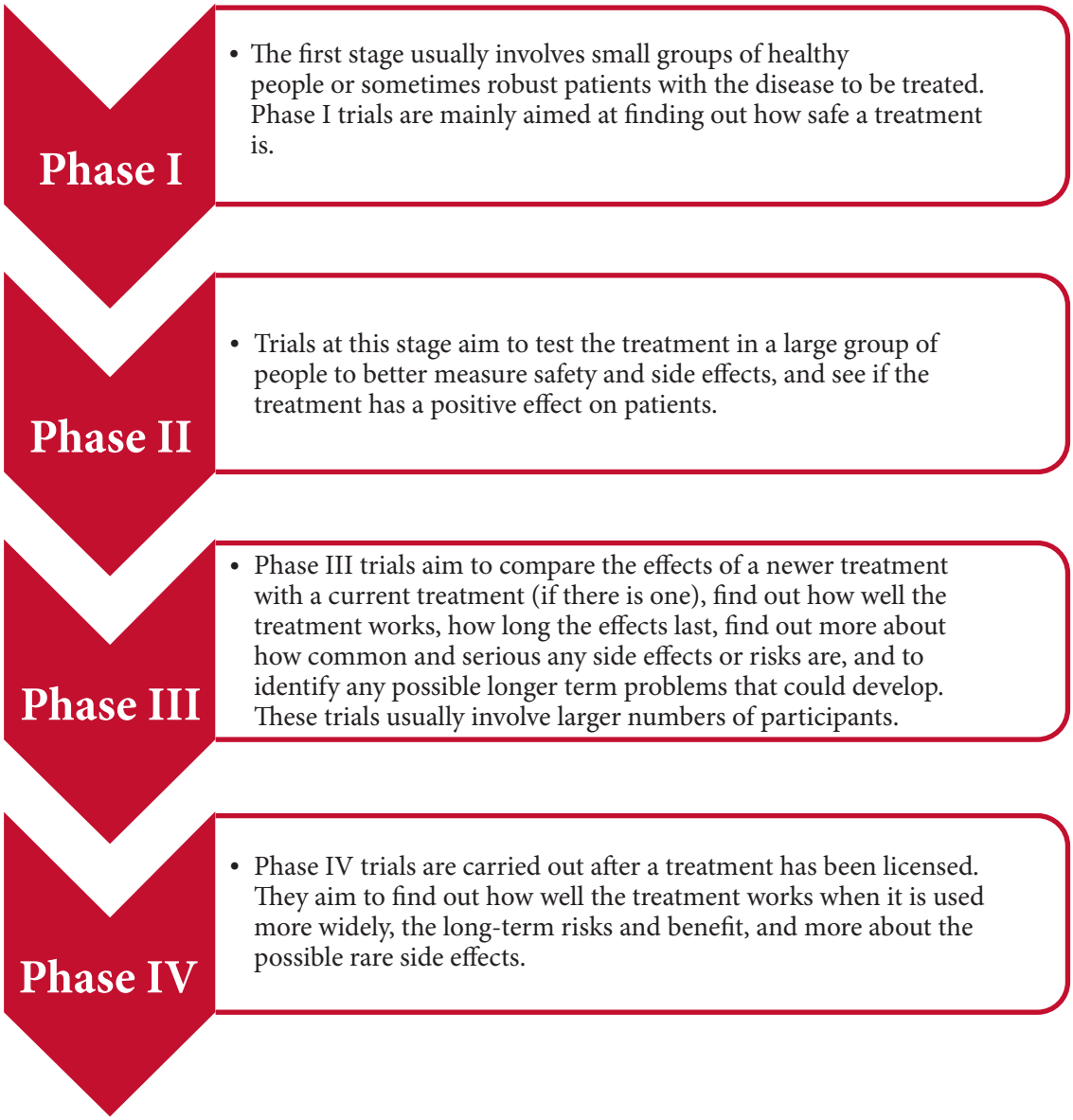
64 Professor William S. James, University of Oxford.

65 RCUK, Q 16, further supplementary written evidence from the Government.

66 National Institute for Health Research (NIHR): *Understanding clinical trials*, October 2010.

FIGURE 1

Clinical trial stages[67]



34. The UK had the second highest number of clinical trials involving ATMPs in Europe during the period 2004–10.[68] Table 3 gives details of the number of ATMP clinical trials broken down by EU Member State.

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67 Adapted from NIHR: *understanding clinical trials*, October 2010.

68 Consulting on Advanced Biologicals Ltd.

TABLE 3

ATMP clinical trials in Europe in the period 2004–10[69]

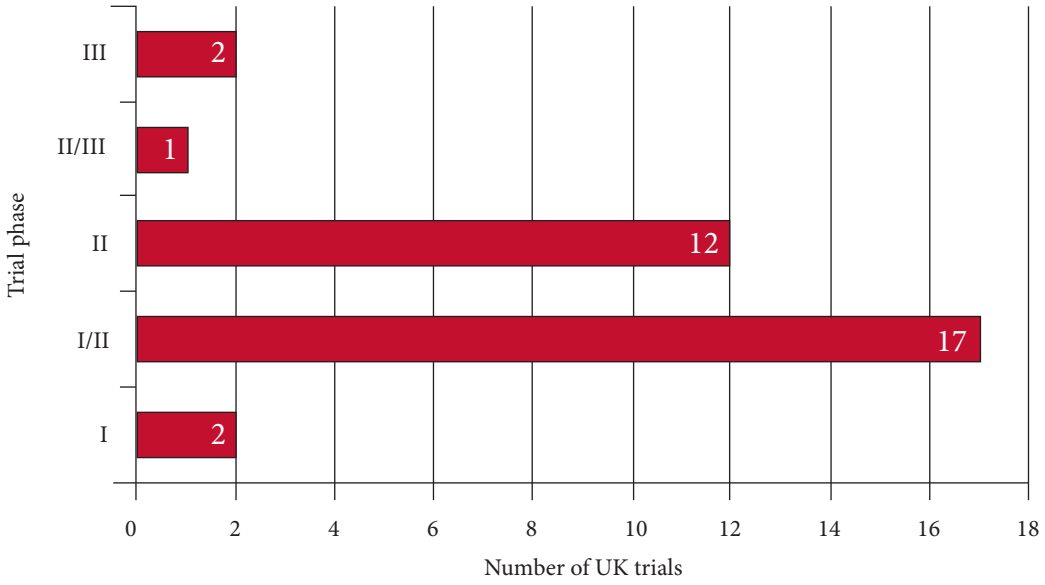
Country	Phase of Clinical Trial								Distribution of Clinical Trials		
	I	I/II	II	II/III	III	III/IV	IV	TOTAL	National	Multinational	Comments
EU/EFTA Sponsors											
Austria	1	2	5		1			**9**	4	5	
Belgium	4		7	1	1		2	**15**	12	3	
Czech Rep	1	2	3					**6**	6	0	
Denmark	6		7					**13**	14	0	(1 NC)
Finland	1							**1**	1	0	
France	4	4	9	1	3			**21**	12	9	
Germany	1	6	16	1	7	1	3	**35**	29	7	(1 NC)
Greece	1							**1**	1		
Italy	11	1	3		3			**18**	16	2	
Netherlands	6	1	10	1	1		1	**20**	5	17	(2 NC)
Norway		2	2					**4**	4		
Poland			1					**1**	1		
Spain	17	4	43	1	6			**71**	67	5	(1 NC)
Sweden	3	4	5		1			**13**	11	3	(1 NC)
UK	12	11	16		7			**46**	34	14	(2 NC)

[69] Trials registered as such on EudraCT, based on the following article: Maciulaitis, R., D'Apote, L., Buchanan, A., Pioppo, L., Schneider, CK.: 'Clinical development of advanced therapy medicinal products in Europe: evidence the regulators must be proactive', *Molecular therapy: the journal of the American Society of Gene Therapy*, 2012. NC = non commercial.

35. As of April 2013, the UK had 34 active clinical trials involving stem cells. The majority of these were early phase trials.[70] Figure 2 shows the number of ongoing stem cell therapy clinical trials in the UK.

FIGURE 2

Ongoing stem cell therapy clinical trials in the UK[71]



To illustrate this work, we set out further examples of ongoing UK clinical trials in Box 3 (these supplement the examples in paragraphs 13–17).

BOX 3

Further examples of UK regenerative medicine clinical trials

University College London (UCL) and King's College London are collaborating on a gene therapy phase I clinical trial for graft versus host disease (a disease where transplanted cells try to attack a patient's cells having identified them as "foreign").[72] T lymphocytes (T cells) carried in a graft have powerful beneficial effects and play a vital role in the eradication of leukaemia and in fighting infection, but can also damage healthy tissues and cause graft versus host disease. In this trial, T cells are modified to encode a "switch" so that they can be eliminated or "turned off" if problems arise.[73]

Cell Medica (a UK cell therapy company) is conducting a phase III trial to investigate the potential clinical benefit of a cell therapy in combination with a drug therapy to treat cytomegalovirus (a common viral infection in the herpes family) recurrence in patients following a bone marrow transplant (specifically, in this case, allogeneic haematopoietic stem cell transplant from a seropositive sibling donor).[74]

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70 Cell Therapy Catapult: *UK Clinical Trials Database*, April 2013.

71 *Ibid.*

72 NHS Choices: *Bone marrow transplant*, 2012: http://www.nhs.uk/Conditions/Bone-marrow-transplant/Pages/Introduction.aspx.

73 NIH: *Clinical trials database suicide gene therapy trial*, 2012: http://clinicaltrials.gov/ct2/show/NCT01204502?term=Dr+Waseem+Qasim&rank=3.

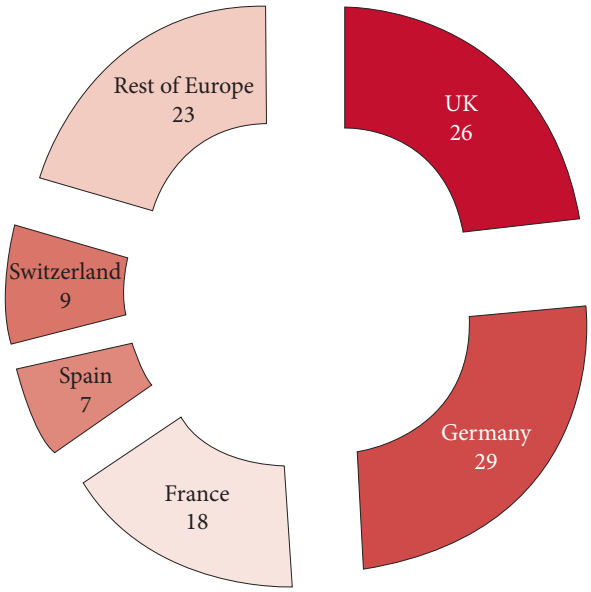
74 LRMN, *op. cit.* UK Clinical Trials Database, NHS Choices: *Cytomegalovirus (CMV)*, 2012: http://www.nhs.uk/Conditions/Cytomegalovirus/Pages/Introduction.aspx, NIH: *Regenerative Medicine*, 2007: http://stemcells.nih.gov/info/scireport/pages/chapter5.aspx.

Industry

36. Data from the Regenerative Medicines in Europe Project (REMEDiE) (Figure 3) demonstrated that the majority of regenerative medicine companies active in Europe were in the UK, France and Germany.

FIGURE 3

Regenerative medicine companies broken down by European Union Member State[75]

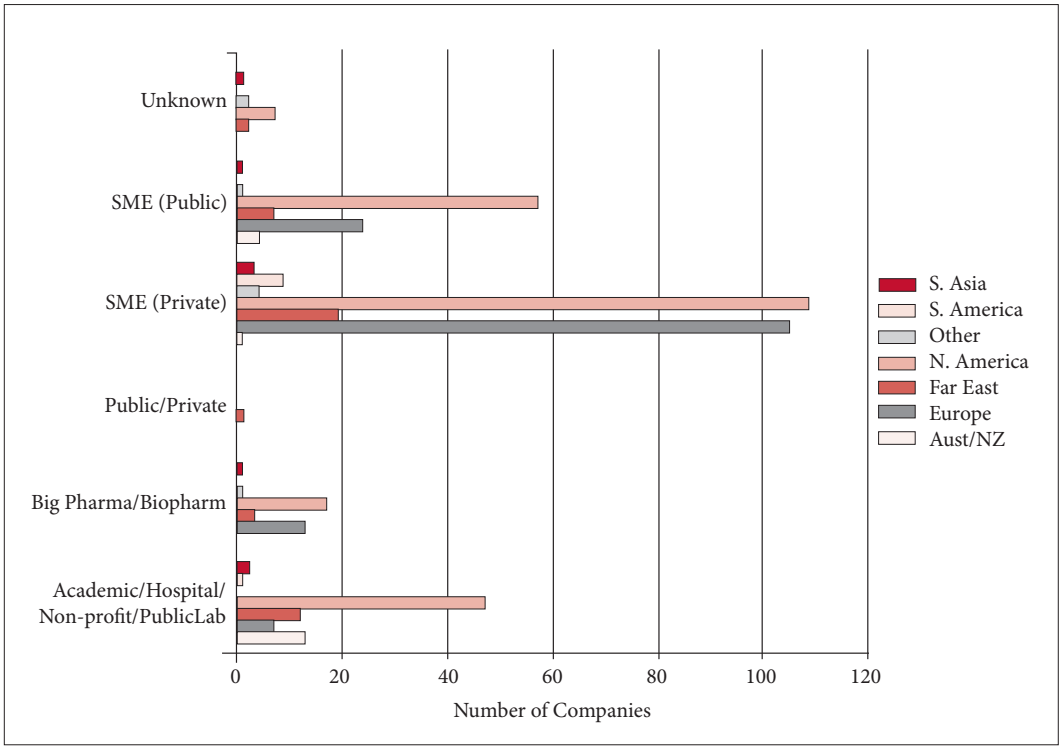


37. The chart below (Figure 4) allows us to compare the European regenerative medicine industry with the rest of the world and these data shows that, in 2010, Europe and North America had the most companies working in this field.

[75] Adapted from REMEDiE: *Regenerative medicine in Europe: emerging needs and challenges in a global context*, 2011.

FIGURE 4

Type of regenerative medicine company broken down by company size and region[76]



38. On the basis of Office for National Statistics' figures about the pharmaceutical industry, and "assuming an average of 20 employees per company", the UK Regenerative Medicine Community estimated that "regenerative medicine, and regenerative medicine-related, companies contribute around £150 million of production and £80 million gross value added to the UK economy, that is around one percent of current production figures for UK pharmaceutical manufacturing and around 10% of the global cell therapy market".[77] The Scottish Government described a rapid expansion from three companies in Scotland operating in the sector in 2004 to more than 20 companies in 2012.[78] The BIA was of the view that the UK had a complementary mix of cell therapy companies alongside service, tools and technology companies.[79]

39. Pfizer, a major pharmaceutical company, operates its regenerative medicine activities from its Neusentis Unit in Cambridge, along with a division in the United States of America. These activities focus on age related and degenerative disorders, including collaborative work with UCL and Moorfields Eye Hospital to develop a cell replacement therapy for age related macular degeneration.[80] Amgen, an international small or medium sized enterprise (SME) which discovers, develops, manufactures and delivers innovative human therapeutics, has a base in the UK hosting both commercial and research and development activities. In partnership with

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76 Derived from the REMEDiE project database: http://www.cs.york.ac.uk/satsu/remedie.

77 UK Regenerative Medicine Community.

78 Scottish Government.

79 BIA.

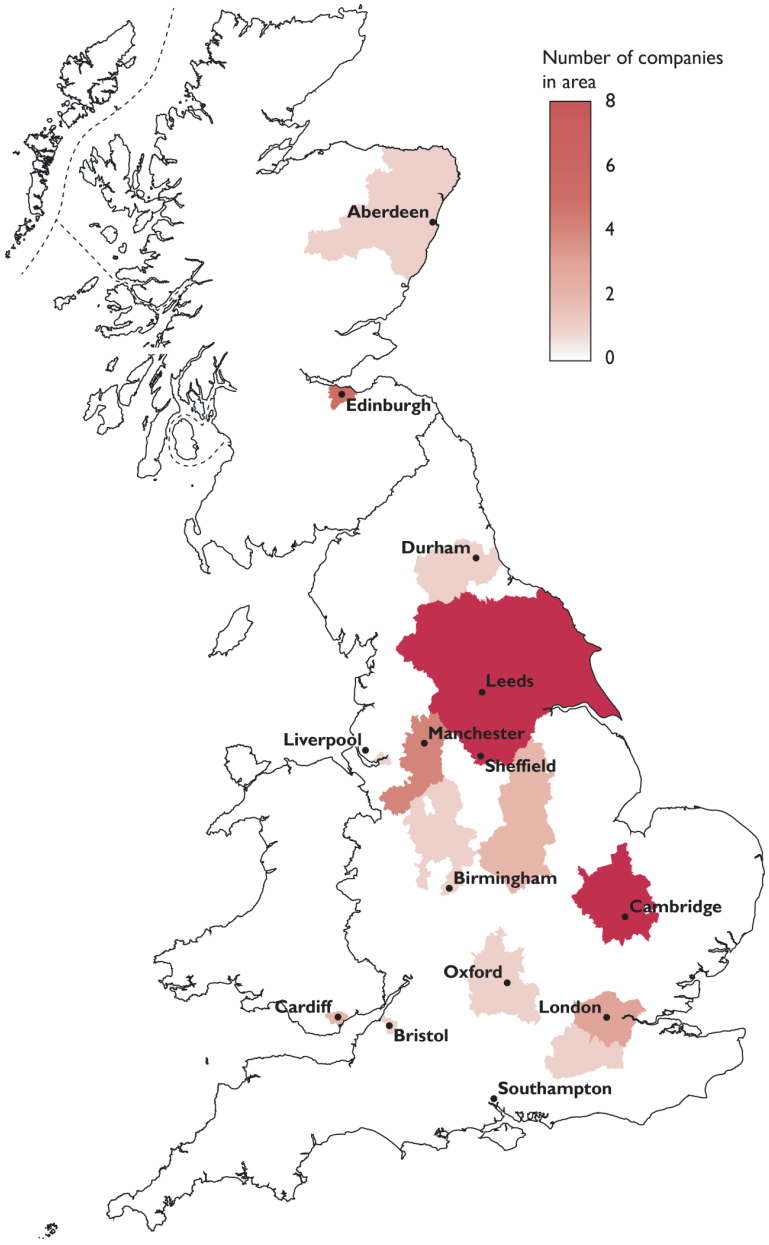
80 Pfizer.

UCB Pharma, it is developing a treatment for osteoporosis.[81] Azellon Cell Therapeutics is a spin-out company from the University of Bristol. It is developing a patented platform technology to repair damaged tissue using mesenchymal stem cells.[82] Neotherix, a spin-out from Smith and Nephew based in York, is a regenerative medicine seeking to develop and commercialise scaffolds for tissue regeneration and repair.[83] These examples show the variety of types of company working in this field in the UK.

40. The following "heat-map" (Figure 5) gives an indication of the spread of regenerative medicine companies within Great Britain by region.

FIGURE 5

Heat map of GB regenerative medicine companies[84]



81 UCB Pharma.

82 Azellon.

83 Q 283, www.neotherix.com.

84 Based on supplementary written evidence from the Government. They identified 40 businesses in Great Britain whose primary purpose was to develop regenerative medicine products.

Funding

41. The *Strategy for Regenerative Medicine in the UK* broke down available public funding for regenerative medicine research by technology readiness level (TRL). Each TRL is explained in Figure 6 (overleaf).

FIGURE 6

TRL Stages[85]

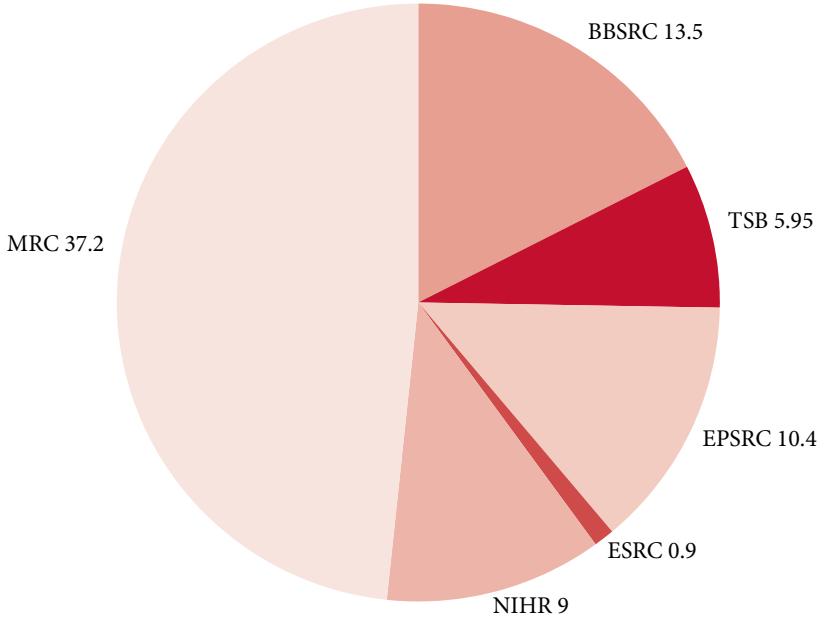
TRL 1	TRL 2	TRL 3	TRL 4	TRL 5	TRL 6	TRL 7	TRL 8	TRL 9
Basic Idea	Concept developed	Experimental proof of concept	Process validated in a laboratory	Process validated on production equipment	Process capability validated on production equipment	Capability validated on economic runs	Capability validated over range of parts	Capability validated on full range of parts over long periods
Basic research		Preclinical research		Late preclinical research	Phase I trials	Phase II trials	Phase III trials	Phase IV trials
Research		Translation/Development				Commercialisation		

[85] Adopted from written evidence from Professor Chris Mason, TSB: *Presentation outlining the vision for a Cell Therapy TIC*, May 2011, US Department of Defence: *Technology Readiness Assessment (TRA) Deskbook*, July 2009, and *op. cit.* Strategy for Regenerative Medicine.

42. In 2012, UK public sector investment in regenerative medicine was over £77 million. This is broken down by agency in Figure 7 below.

FIGURE 7

UK public sector spend on regenerative medicine (£ million)[86]



In addition, significant amounts of money have been set aside for the Regenerative Medicine Platform and Cell Therapy Catapult. We explore these, and other investments in regenerative medicine, in greater detail below.

43. Figure 8 breaks down the amount of public funding available for regenerative medicine by TRL in 2010 (although it should be borne in mind that TRLs are a guide and not entirely fixed stages).

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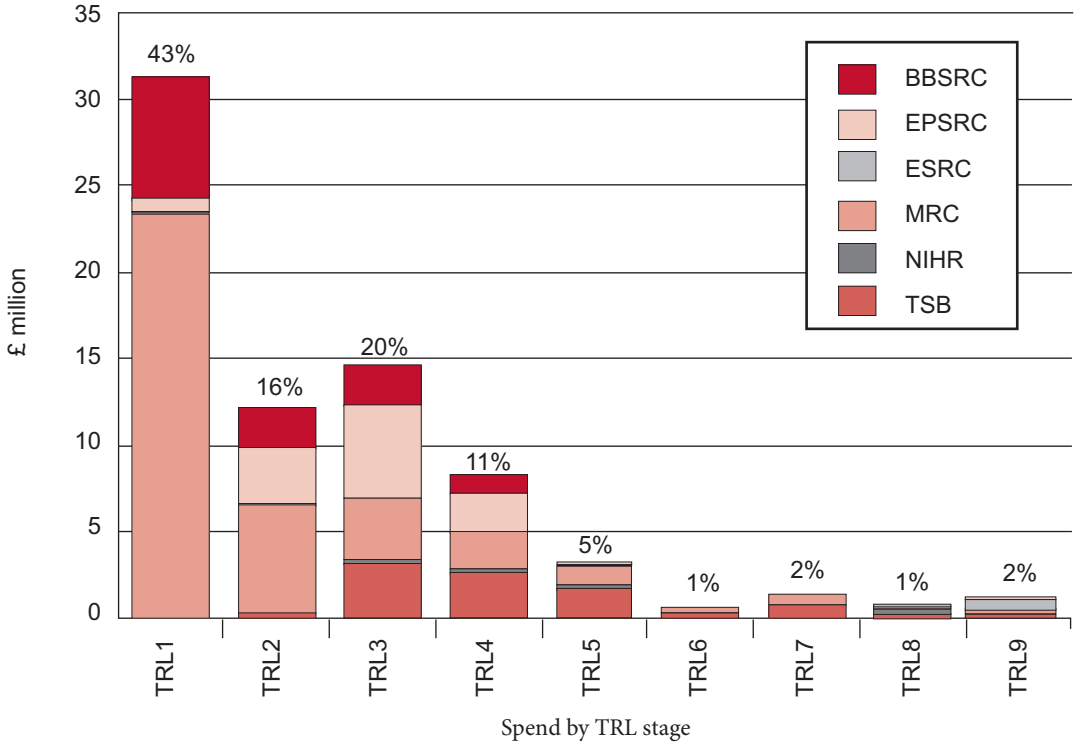
[86] Supplementary evidence from the research councils. These numbers do not included investment in the Regenerative Medicine Programme (which was only launched during 2012–13) and the level of TSB investment in the Cell Therapy Catapult is significantly lower than it will be in the future given that it was only set up in 2012. ESRC data to be updated when received.
Key: MRC: Medical Research Council; BBSRC: Biotechnology and Biological Sciences Research Council; TSB: Technology Strategy Board; ESPRC: Engineering and Physical Sciences Research Council; ESRC: Economic and Social Research Council; NIHR: National Institute for Health Research.

FIGURE 8

Regenerative medicine spend by TRL stage[87]



Basic science

44. Seventy-nine percent of public sector funding for regenerative medicine was for basic or early preclinical research in 2010. The research councils primarily fund regenerative medicine basic science through response-mode funding (that is, competitions to identify projects which are excellent).[88]

UK Regenerative Medicine Platform

45. As a result of the taking stock exercise, the Biotechnology and Biological Sciences Research Council (BBSRC), the Engineering and Physical Sciences Research Council (EPSRC) and the MRC jointly established the UK Regenerative Medicine Platform (UKRMP). It is a national programme to promote translational research in the field, and to address knowledge gaps and obstacles where more development is needed to underpin the delivery of new therapeutic approaches.[89]

46. The UKRMP initially funded the establishment of up to five interdisciplinary research hubs which brought together teams of researchers to address a number of strategically important, tractable translational challenges. These challenge areas were refined from the regenerative medicine community's responses to a scoping call for expressions of interest in the UKRMP. This investment will be up to £25 million over five years. Following this initial round, a call to establish complementary disease-focused research programmes will be launched with an anticipated £5 million or more of funding.[90]

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87 MRC, BBSRC, EPSRC, ESRC and TSB: *A Strategy for UK Regenerative Medicine*, March 2012.

88 RCUK.

89 TSB.

90 RCUK.

Regenerative Medicine Programme

47. In 2008–09, the TSB undertook to develop programmes that could support the emergence of new industries. One of those areas was regenerative medicine. The Regenerative Medicine Programme was developed in partnership with the MRC, BBSRC and EPSRC, with the aim of ensuring that UK businesses could achieve a commercially competitive edge with global impact by underpinning and enabling the best regenerative medicine businesses in the UK to flourish; and building a connected regenerative medicine community by forming well-linked programmes of work and activities to develop medicines and technology platforms.[91]

48. The programme focused on addressing challenges in three areas:

(1) "Therapeutic Development: to support companies to progress products towards or into the clinic;

(2) Tools and Technologies: to address manufacturing and safety/efficacy challenges and to build linkages in the supply chain, both business to business and business to academia); and

(3) Value systems and business models: to allow companies and stakeholders to develop a better understanding of where and how value will be created in the emerging regenerative medicine value chain and develop business models to enable businesses to best capture that value".[92]

49. The programme funded a total of 76 projects and committed £16.25 million of TSB funding, with additional funding committed by the MRC, the BBSRC, the EPSRC, the Economic and Social Research Council (ESRC) and the Scottish Government. These projects were matched with £7.5 million of funding from industry. Some examples of its efforts included direct financial support to five commercially led projects to start clinical studies, and support to enable Tissue Regenix, a University of Leeds spin-out company, to achieve AIM (the London Stock Exchange's international market for smaller growing companies) listing, which raised £4.5 million.[93] Table 4 summarises how the programme's funding was divided.

TABLE 4

Regenerative Medicine Programme grant funding 2009–11[94]

Theme	Number of projects funded	Amount of funding (£ million)
Therapeutic feasibility studies	31	2.8
Therapeutic development stage 1	16	3.6
Therapeutic development stage 2	4	1.9
Tools and technologies feasibility studies	12	1.6
Tools and technologies stage 2	10	6.6

91 TSB.

92 *Ibid.*

93 *Ibid.*

94 *Ibid.*

Value systems and business models	3	2
Stem Cells For Safer medicine programme (SC4SM)	n/a	0.5
TOTAL	**76**	**19**

Cell Therapy Catapult

50. The Cell Therapy Catapult was established in May 2012. It aims to provide additional resources and expertise to support the emerging industry, and progress therapies to the point where there is sufficient evidence of efficacy, safety, manufacturability, cost effectiveness and market potential.[95] The TSB intends the Cell Therapy Catapult to accelerate the creation of a large (>£10 billion) industry, generating both health and wealth for the UK. It operates as an independent, not-for-profit research organisation and will receive £70 million of core funding over the next five years from the TSB.[96] The Cell Therapy Catapult hopes to leverage at least £10 million a year from grant funders (other than the TSB) and £10 million a year from industry contracts.[97] The work of the Cell Therapy Catapult will be considered further in Chapter 5.

Biomedical Catalyst

51. The MRC and the TSB have collaborated to offer funding through the Biomedical Catalyst to SMEs and academics looking to work, either individually or in collaboration, to develop solutions to healthcare challenges. It provides awards for feasibility, early-stage and late-stage research and awards made so far have included regenerative medicine research.[98] For example, ReNeuron (a British stem cell business) has received a £0.4 million grant towards the funding of a UK phase I clinical trial treating patients with limb ischemia (a condition that occurs when blood flow to the limbs is severely restricted from a build up of fat in the arteries) and a £0.8 million grant to fund pre-clinical development of the company's ReN003 stem cell treatment for retinitis pigmentosa.[99]

NIHR

52. Through Biomedical Research Centres (BRCs) and Units (BRUs), the National Institute for Health Research (NIHR) is funding regenerative medicine to the sum of £9 million a year.[100] Tables 5 and 6 break down NIHR investment in the field of regenerative medicine.

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95 Cell Therapy Catapult.

96 Q 285.

97 TSB, Cell Therapy Catapult and presentation by its Chief Executive: https://catapult.innovateuk.org/documents/10726/0/CEO+AMC+FINAL.pdf/45ee556a-dd9d-4c01–88fe-6c889e633331.

98 RCUK, TSB.

99 ReNeuron press release: *ReNeuron wins two major Biomedical Catalyst grants to pursue core stem cell therapy programmes—aggregate award of £1.2 million for UK phase I clinical trial in critical limb ischaemia and UK late pre-clinical development of therapy for retinitis pigment*, 2013.

100 Q 43.

TABLE 5

Biomedical Research Centre funded regenerative medicine research[101]

NHS Organisation	Academic Partner	Research Themes	Funding 2012–17 (£ million)
Cambridge University Hospitals NHS Foundation Trust	University of Cambridge	Transplantation and Regenerative Medicine	5.4
Great Ormond Street Hospital for Children NHS Trust	University College London, Institute of Child Health	Stem and Cellular Therapies	11.5
Guy's and St Thomas' NHS Foundation Trust (2 programmes)	King's College London	Transplantation; Translational Genetics	6.7
Imperial College Healthcare NHS Trust (2 programmes)	Imperial College London	Surgery and Technology (which includes a component on Cell Therapies)	10.1
Moorfields Eye Hospital NHS Foundation Trust (2 programmes)	University College London	Gene Therapy; Regenerative Medicine and Pharmaceutics	3.5
University College London Hospitals NHS Foundation Trust	University College London	Cellular and Gene Therapy	1.5

TABLE 6

Biomedical Research Unit funded regenerative medicine research

NHS Organisation	Academic Partner	Research Themes	Funding 2012–17 (£ million)
Barts & The London NHS Trust	Queen Mary University of London	Cardiovascular Regenerative Medicine	1.5
University Hospitals Bristol NHS Foundation Trust	University of Bristol	Cardiovascular Regenerative medicine	1.4
University Hospitals Birmingham NHS Foundation Trust	University of Birmingham	Liver Regeneration, Repair and Stem Cells	0.6

[101] Further supplementary written evidence from the Government.

Leeds Teaching Hospitals NHS Trust	University of Leeds	Biomaterials and Regenerative Interventions	0.4
Oxford University Hospitals NHS Trust	University of Oxford	Orthopaedics	3.1

Third sector

53. Investment by the third sector in regenerative medicine has been growing over the last five years: over £51 million was invested in regenerative medicine between 2005 and 2010,[102] and average annual investment increased from £6 million in the period 2005–08 to £13 million in 2009.[103] Some examples of third sector funding include the British Heart Foundation's "Mending broken hearts" appeal, which aims to fundraise an additional £50 million for investment in cardiovascular science,[104] Arthritis Research UK's £5.9 million tissue engineering (multi-site) centre, which aims to regenerate bone and cartilage by using patients' own stem cells to repair the joint damage caused by osteoarthritis,[105] and £15 million of funding from the UK Stem Cell Foundation since 2005 for stem cell research projects.[106] The Wellcome Trust awarded £55.4 million related to regenerative medicine in 2011–12. In partnership with the MRC, it has invested £12.75 million to generate and characterise a large number of high quality human induced pluripotent stem cells (iPS cells).[107]

EU funding

54. The European Commission (EC)'s Seventh Framework Programme (FP) provided a budget of €6.1 billion for health research over the period 2007–13. One facet of this programme has been the Innovative Medicines Initiative (IMI) Joint Undertaking, in partnership with the pharmaceutical industry, which provided €2 billion of funding for research activities to accelerate the discovery and development of better medicines by removing bottlenecks in the development process.[108] The EC contributed €249.6 million to 37 stem cell research projects from 2007–12, through the health and SME streams of FP7.[109] Table 7 shows the breakdown of this funding by project type and year.

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[102] UK Stem Cell Foundation.

[103] Association of Medical Research Charities.

[104] Q 46.

[105] Arthritis Research UK. This figure includes contributions from the participating universities.

[106] UK Stem Cell Foundation.

[107] RCUK.

[108] European Commission: *Health research in FP7*, 2011.

[109] Presentation by Charles Kessler of the European Commission Research and Innovation DG: *EU Support to Stem Cell Research*, 2011, and correspondence.

TABLE 7

European Commission project funding for regenerative medicine 2007–10[110]

Year	Type of project	Number funded	Amount (€ million)
2007	Stem cell-based therapies	2	23.6
2007	Culture conditions	7	20.7
2008	Cells and tissues	2	23.7
2008	Biomaterials	3	33.8
2008	Endogenous cells	3	32.7
2010	RM clinical trials	7	41
2010	Tools and technologies	7	38.1
2012	Controlling differentiation and proliferation in human stem cells intended for therapeutic use	6	36
TOTAL	**n/a**	**37**	**249.6**

55. In 2012, the Stem Cells for Drug Discovery project (stemBANCC) was launched under the IMI. Its aim is to generate and characterise 1, 500 high quality patient derived iPS cell lines and provide access to them in an accessible and sustainable bio-bank. StemBANCC also aims to demonstrate proof of concept for the utility of induced pluripotent stem cells in drug discovery for hard-to-treat disorders and chronic diseases including diabetes and dementia. The UK is providing the "responsible entity" (leader of the academic and SME participants in the consortium, responsible for the scientific management and the supervision of the overall progress in collaboration with the co-ordinator) for this project, and almost one third of all partners are based in the UK.[111]

[110] *Ibid.*

[111] Further supplementary written evidence from the Government, http://stembancc.org/index.php/partners/.

CHAPTER 4: TRANSLATION

Uncertainty

56. A theme which permeated much of our inquiry was that of uncertainty. Without greater certainty of a return on their investment, namely that the science would be translated into a clinical treatment, which could be commercially viable, investors would remain reluctant to invest in regenerative medicine.[112] The route to market for drugs is well established and, although costly, an investor can be reasonably certain of a return on investment.[113] **For a regenerative medicine industry to flourish in the UK, steps must be taken to clear the path "from bench to bedside" as part of building investor confidence.**

Regulatory environment

57. **A reputation for proportionate regulation is important for the UK both in terms of inspiring confidence in potential patients and encouraging investment,**[114] and there was general agreement that the current system was sufficiently robust to protect patients. GE Healthcare, for example, described the regulatory environment as "positive yet controlled", OSCI called the system "rigorous, yet broadly permissive", Lawford Davies Denoon (a life science law firm) viewed the system as "mature", and the University of Manchester and Cytori held the UK up as a model for other countries to follow.[115] Many companies told us about positive interactions with regulators, including Azellon, Cytori and Shire.[116]

58. The current complexity of the regulatory system governing regenerative medicine was, however, a source of great frustration to various witnesses. Many argued that the system was overly difficult to navigate. Julian Hitchcock, a life science lawyer, described how international investors were deterred from investing in regenerative medicine because of this complexity, and Lawford Davies Denoon said that numerous researchers and companies choose not to base themselves in the UK because of this complex framework and associated uncertainty.[117] A researcher or company could encounter up to 11 UK or European regulators when developing a regenerative medicine product. Table 8 (overleaf) outlines their roles and remits.

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[112] Alliance for Regenerative Medicine, Azellon, Health Knowledge Transfer Network, Scottish Enterprise, UKRMC.

[113] Appendix 5.

[114] Human Tissue Authority, OSCI.

[115] GE Healthcare, OSCI, Lawford Davies Denoon, University of Manchester, Cytori.

[116] Azellon, Cytori, Shire.

[117] Julian Hitchcock, Lawford Davies Denoon.

TABLE 8

Regulators with jurisdiction over regenerative medicine in the UK[118]

Regulator	Role(s)
European Medicines Agency (EMA)	Responsible for the scientific evaluation of applications for European marketing authorisation for medicinal products (a centralised procedure).
EMA Committee for Advanced Therapies (CAT)	A multidisciplinary expert committee of the EMA to assess the quality, safety and efficacy of ATMPs and follow scientific developments in the field.
Gene Therapy Advisory Committee (GTAC)	Reviews applications to conduct clinical trials of investigational medicinal products (IMP)[119] for gene therapy (although GTAC may transfer an application to another research ethics committee where the trial is of low risk). GTAC also has responsibility for ethical review of clinical trials involving other ATMPs or cell therapies derived from stem cell lines. Now part of the HRA.
Health and Safety Executive	Operates and enforces legislation in Great Britain that aims to control the risks to human health and the environment arising from activities involving GMOs in containment under the Genetically Modified Organisms (Contained Use) Regulations 2000.
Home Office Animal Procedures Licensing Inspectorate	Considers applications for new animal procedures licences and certificates; authorises amendments to existing authorities; and revokes or varies licences and certificates as necessary.
Human Fertilisation and Embryology Authority (HFEA)	Oversees the use of gametes and embryos in fertility treatment and research.
Human Tissue Authority (HTA)	Licenses establishments which procure (obtain through donation), store, test, process, distribute and import or export human tissues and cells that will be used to treat patients (including the use of cell lines grown outside the human body for patient treatment).

[118] Based upon information about purpose and role from each organisation's website.

[119] Directive 2001/20/EC, Article 2 (d), provides the following definition for an IMP: "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form."

Regulator	Role(s)
Medicines and Healthcare Products Regulatory Agency (MHRA)	Statutory agency charged with ensuring that medicines and medical devices work and are acceptably safe.
NHS Research and Development Offices	Offices in NHS organisations which carry out checks and grant written permissions related to the Department of Health's Research Governance Framework for Health and Social Care.
Research Ethics Committee(s)	These local Committees, overseen by the National Research Ethics Service, review ethics of clinical trial applications with the purpose of safeguarding the rights, dignity and welfare of people participating in research in the NHS. Now part of the HRA.
UK Stem Cell Bank	All UK derived embryonic stem cell lines must be offered for deposit in the Bank and for the use of stem cells as a condition of the HFEA license.

59. The UCL applied regenerative science group described regulatory pathways in the UK as "labyrinthine and off-putting for overseas investigators, whilst demoralising for home investigators", and the BIA called the regulatory environment "overly complex and repetitive". The Association of British Neurologists (ABN) called for a more streamlined framework, and the British Society for Blood and Marrow Transplantation (BSBMT), the British Society for Haematology and the Royal College of Pathologists argued that the sheer number of regulatory bodies stifled innovation.[120]

60. As well as considerable evidence of a complex system, we heard that there was significant overlap between the functions of regulators. The Cell Therapy Catapult explained that this overlap existed because for many of the bodies "their role in this regulatory process … is an adaption from their primary purpose, introduced to fill gaps as the field started to emerge". The consequences of this overlap were delays and increased costs for users.[121] ReNeuron agreed that there was significant overlap in functions, and Julian Hitchcock and Lawford Davies Denoon pointed to lack of co-ordination between regulators and, in some cases, inconsistency in advice.[122] Arthritis Research UK suggested that the system was particularly confusing for products containing multiple materials, such as scaffolds and cells.[123]

61. As shown by Figure 9, the UK has the joint second highest number of competent authorities (an authority having jurisdiction) covering medicines, medical devices, organ transplantation, tissues and cells, reproduction and blood in the EU.

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120 UCL applied regenerative science group, BIA, ABN, BSBMT, BSH, RCPath.

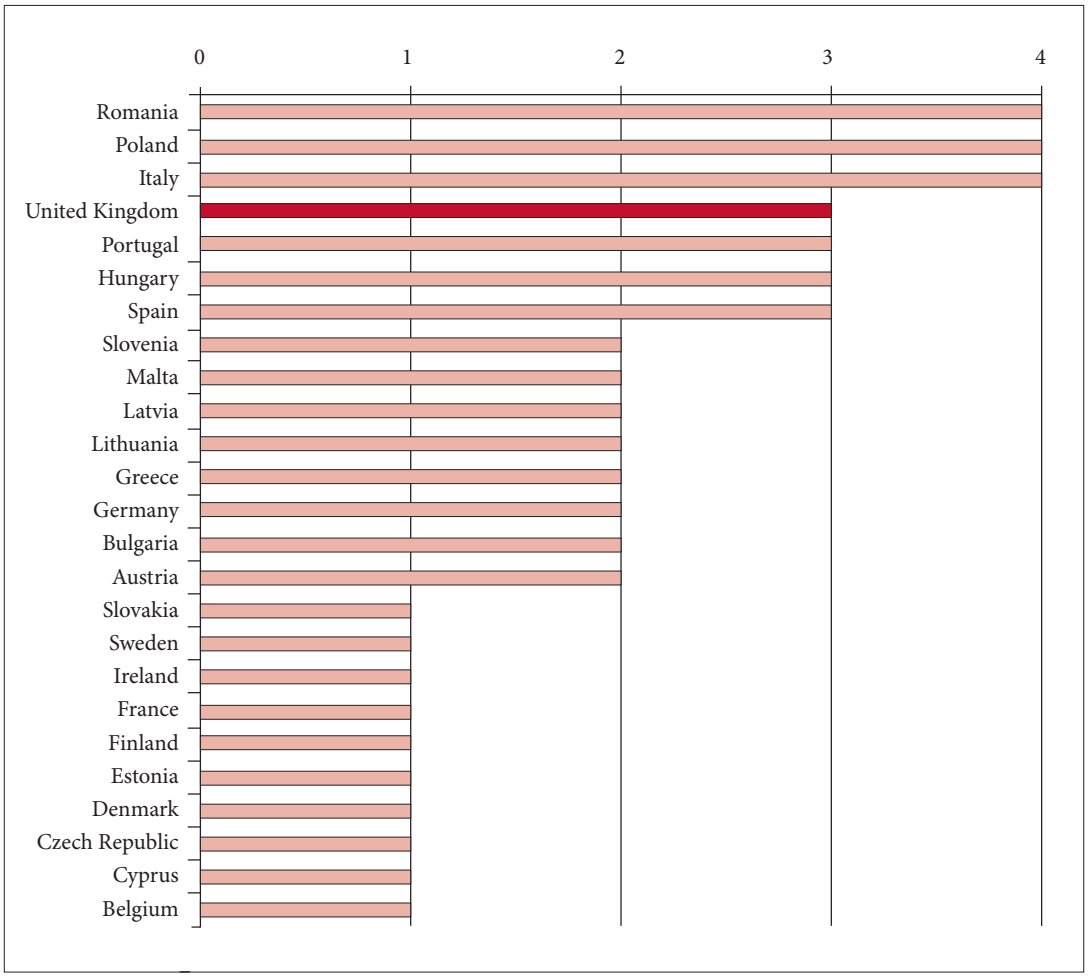
121 Cell Therapy Catapult.

122 ReNeuron, Julian Hitchcock, Lawford Davies Denoon.

123 Arthritis Research UK.

FIGURE 9

Number of competent authorities[124]



62. The NHS Blood and Transplant Service (NHSBTS) noted that some other EU countries have a single regulator, which reduces the licensing and inspection cost burden,[125] as does the USA.[126] In contrast, Aiden Courtney, Chief Executive Officer of Roslin Cells, said that the number of regulators was not the issue. Instead, he argued:

> "the challenge we have in cell therapy is that ... most of the people coming into developing cell therapy are likely to be either academics trying to start a company or new companies who are probably going through that regulatory process for the first time, and it is very difficult for them to find someone to give them the guidance to take them through the regime".[127]

63. There have been some efforts to support the industry and to improve the navigability of the regulatory route. The regulators and the Department of Health produced a UK Stem Cell Tool Kit which, most recently, took the form of an interactive website to assist researchers developing a programme of human stem cell research and manufacture.[128] Regulators have also been

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[124] Consulting on Advanced Biologicals Ltd. Data on Luxembourg and The Netherlands were not available.

[125] NHSBTS.

[126] CIRM.

[127] Q 249.

[128] Government.

trying to join-up some of their activities. For example, the Medicines and Healthcare products Regulatory Agency (MHRA) and the Human Tissue Authority (HTA) have conducted combined facility inspections.[129] The MHRA also runs a series of workshops and seminars to assist those doing research in the field, and offers advice to researchers and companies.[130]

64. In addition, the MHRA has launched an Innovation Office to allow SMEs, academics and individuals to submit queries about the regulation of medicines, medical devices and processes through their website.[131] This initiative was part of the UK Life Science Strategy, as was the establishment of an Expert Group on Innovation in the Regulation of Healthcare products, which is considering adaptive licensing, early access to medicines, the regulation of advanced manufacturing and how regulators can improve their response to regulatory innovations in future. Disappointingly, the strategy update of December 2012 indicated that this group was primarily focused on pharmaceuticals, rather than regenerative treatments.[132]

65. The European Medicines Agency (EMA) also offers advice to companies. The first type of advice is informal briefing meetings to discuss the process and relevant documentation and is free. The second is fee-based and leads to the agency producing a formal assessment of a development programme. Dr Hans-Georg Eichler, Senior Medical Officer, EMA, suggested that this resource was underused and highlighted that SMEs pay a significantly reduced fee or attract a fee waiver.[133]

66. The purpose of the newly formed Health Research Authority (HRA) is to protect and promote the interests of patients and the public in health research.[134] The HRA will work closely with other bodies, including the MHRA and NIHR, to create a unified approval process, and to promote proportionate standards for compliance and inspection within a consistent national system of research governance. The HRA is intended to:

- "provide a single route through IRAS (Integrated Research Approval System) for seeking all approvals and permissions;
- provide clear signposting through the process, with easy access to advice and support;
- embed principles and standards of review bodies to ensure tasks are worthwhile, relevant and proportionate;
- co-ordinate the activities of review bodies to remove unnecessary duplication;
- assign tasks to the relevant organization at the appropriate time and support the exchange of assurances across the system; and
- maintain a UK-wide overall approach that recognises and incorporates individual requirements of the IRAS partners".[135]

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[129] Supplementary evidence from UK regulators, Human Tissue Authority (HTA), Government.

[130] Q 300.

[131] Supplementary evidence from UK regulators.

[132] HM Government: *Strategy for UK Life Sciences One Year On*, December 2012.

[133] Q 301, Q 305.

[134] HRA: *Protecting and promoting the interests of patients and the public in health research*, March 2012.

[135] HRA: *IRAS four years on—celebrating and building on success*, 2012.

67. It is too early to assess the effectiveness of the HRA, but it has already had some success in beginning to streamline research application documentation. We are also pleased to see its feasibility study for a streamlined HRA assessment for all research in the NHS, which would combine and replace aspects of the current review by NHS Research and Development offices and Research Ethics Committees.[136]

68. We asked whether there was sufficient support for companies and researchers seeking to navigate the system. Dr Hans-Georg Eichler acknowledged that work in this field is often done by "very small companies or academic groups that have no experience in the field and are overwhelmed by the entire complex regulatory system".[137] Dr Christopher Bravery (a regulatory consultant) accepted that "the regulators themselves provide a lot of guidance" but questioned its accessibility: "all of us find it difficult to find it, even myself, when I do it for a living".[138] He also highlighted a shortage in regulatory expertise in the UK.[139] Peter Thompson, Chief Executive of the Human Fertilisation and Embryology Authority (HFEA), recognised the daunting nature of tackling the regulatory system: "it clearly is a complex pattern of regulation which has built up over time, and I can well see why anybody embarking on this would not find it as straightforward as it ought to be".[140] CIRM supports its researchers by providing advice on navigating regulatory approval from ex-Food and Drug Administration (FDA) regulatory consultants.[141]

69. Alistair Kent, Director of Genetic Alliance UK, argued for greater support for "organisations that have good ideas, potentially good products, bringing them through the system in a way that makes it clear what the hurdles are that they will have to overcome and what the standard of proof is that will be required of them, in order to satisfactorily negotiate those hurdles".[142] The Health Knowledge Transfer Network recommended a dual approach of streamlining the regulatory system and providing support to enable navigation of the current system.[143] The Health Protection Agency agreed with the need for support: "there is a clear and urgent need for companies to have access to early stage high quality advice on the application of regulation and regulatory science".[144] Those calling for increased support included Iva Hauptmannova, Head of Research and Development, Royal National Orthopaedic Hospital NHS Trust (who submitted evidence in a personal capacity), and researchers from King's College London and King's Health Partners.[145]

70. We were disappointed by the disparity in regulators' attitudes: the EMA, HFEA, HRA and HTA all acknowledged that there was room for improvement, whilst the MHRA was more focussed on what it was already

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136 Q 300, Government, supplementary evidence from UK regulators.

137 Q 296.

138 Q 335.

139 Q 332.

140 Q 318.

141 Appendix 5.

142 Q 331.

143 Health Knowledge Transfer Network (KTN).

144 HPA.

145 Iva Hauptmannova, King's College London (KCL) and King's Health Partners (KHP).

doing.[146] Professor Sir Kent Woods, Chief Executive, MHRA, told us that "the regulation is complex, but the science and the technology are complex".[147] We consider this view to be overly simplistic. Regulation must be robust and fit for purpose, but that does not justify the complex regulatory environment in the UK. Although there has been some progress, it is clear that there is still considerable room for improvement. The end users (in this case academics and companies) have expressed concern that the system is still overly complex and that there is insufficient support. This, at best perceived, lack of support must be addressed and the underlying issue of a complex regulatory system also considered. **The twin challenges of improving perceptions of the regulatory system and streamlining it are so great that both immediate and long-term action are needed.**

71. **We recommend that, as a matter of urgency, the HRA establish a regulatory advice service. This would build on the expertise of the Office for Life Science toolkit, the newly established MHRA Innovation Office and the experience of regulators. Researchers and companies require more than a web-based service. They should be assigned a single point of contact to support them in navigating the regulatory system, directing their queries to others where appropriate, but retaining ownership and oversight of the advice process. Such a service would be of short-term value to this (and the broad healthcare) sector until such a time as the regulatory environment is rationalised.**

72. During the course of our inquiry, the Department of Health published the result of its consultation on the transfer of functions from the HFEA and HTA. Both organisations have retained their functions for now, but will undergo an independent review of how they carry them out. They were also referred to the Shared Services programme, with a view to streamlining their non-specialist functions.[148] Although we welcome this review we consider it too narrow in scope.

73. **The Health Research Authority (HRA) has made some positive first steps and it must now demonstrate its effectiveness by streamlining the macro regulatory environment. We recommend that the HRA commission an independent advisory group, made up of national and international experts in regulation, to develop a designed-for-purpose regulatory system. The UK rightly has a good reputation for its robust regulatory system; it is vital that this reputation be maintained. Similarly, we acknowledge there is significant value in the expertise of some regulators. But patients, business and the taxpayer deserve a modern, designed-for-purpose, efficient regulatory system rather than one that has evolved in a haphazard, piecemeal way. An independent advisory group supporting the HRA will give it the necessary support to focus and clarify the functions of regulators. This group should give special consideration to reducing the overall number of regulators. We recommend that the group make proposals 18 months from its establishment. We will revisit this aspect of the**

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146 Q 314, Q 296, Q 318.

147 Q 300.

148 DH: *Government response to the consultation on proposals to transfer functions from the Human Fertilisation and Embryology Authority and the Human Tissue Authority*, January 2013.

inquiry to ensure that progress has been made. The HRA must simplify the regulatory route so that the development of regenerative medicine, and other innovative therapies, is not hindered.

UK Stem Cell Bank

74. The UK Stem Cell Bank was established in 2002 to provide a repository of human embryonic, foetal and adult stem cell lines.[149] CIRM recognised the bank as "an important international resource to support basic research in regenerative medicine" and praised it as "one of the top sources of stem cell lines for basic and clinical research". The HPA and CIRM both recognised the bank's international reputation for expertise in quality assurance and governance. However, we heard one case of administrative difficulties with the bank from a CIRM project leader, Professor Larry Goldstein. He described the bank as "incompetent and intransigent", and detailed his difficulties accessing two specific cell lines.[150] On its own, this is not proof that the bank is ineffective; nevertheless, its steering committee must ensure that its full potential is realised.

Clinical trials

75. Much has been written previously about the difficulties associated with setting up clinical trials in the UK. For example, the Academy of Medical Sciences published what was heralded as a seminal report on this topic in January 2011. It criticised the "complex and bureaucratic regulatory environment" which was "stifling health research in the UK".[151] The Life Science Strategy also recognised the need to improve clinical trial governance in the UK.[152] Clinical trials are a sizeable, long-term investment—the development process for a new therapy, of which they are a key facet, is estimated to cost up to $1 billion and can take between 12 and 15 years.[153]

76. The UK is a cheaper place to conduct clinical trials than, for example, the USA.[154] Many witnesses pointed out the potential advantages of conducting clinical trials in the NHS, and benefits to the NHS of these trials.[155] The primary advantage was access to patients. The NHS, as a single healthcare system, should, in theory, make it easier to identify potential patient groups for trials and to access their associated data (with appropriate permissions).[156] A Japanese researcher, Professor Sato, drew a favourable contrast between accessibility of patients in the UK compared to Japan.[157] The Association of Medical Research Charities (AMRC) reported that between 2000 and 2006 the proportion of all the world's clinical trials conducted in the UK fell from six percent to two percent, in part because of more attractive regulation and

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149 Government.

150 CIRM, HPA, Appendix 5.

151 Academy of Medical Sciences: *A new pathway for the regulation and governance of health research*, January 2011.

152 *Op. cit.* Life Sciences Strategy.

153 AAT.

154 Appendix 5.

155 Alliance for Regenerative Medicine, UCL applied regenerative science group, BIA, LLR.

156 UCL applied regenerative science group, Professor Stephen Craddock, Health KTN, KCL, Miltenyi Biotec, ReNeuron.

157 Professor Chiaki Sato.

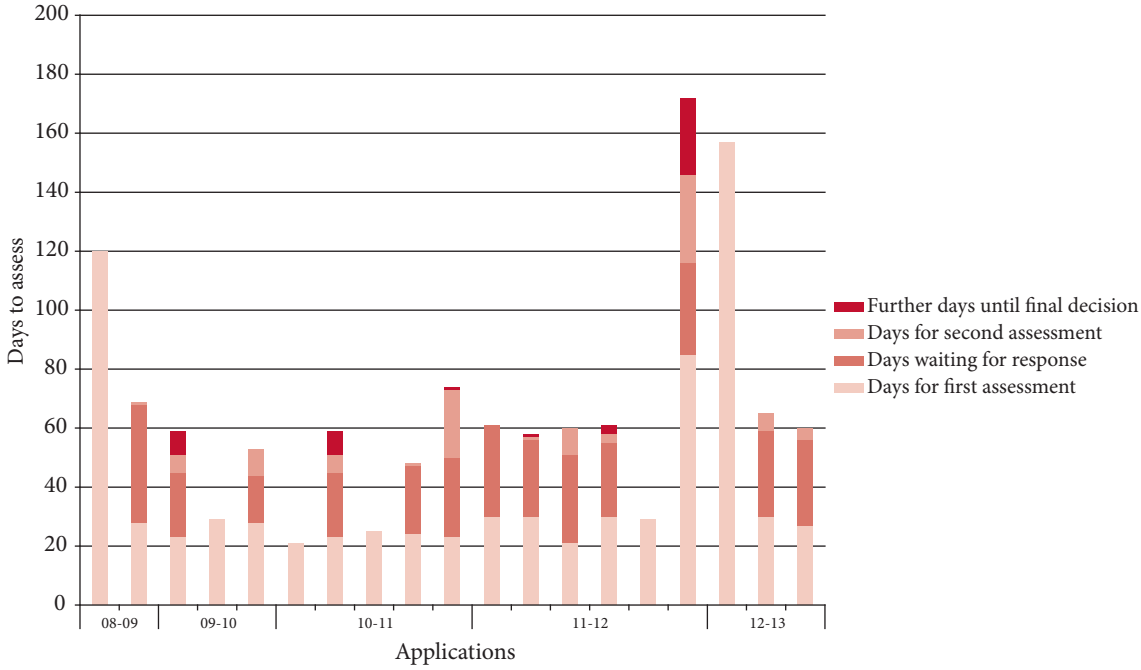
incentives elsewhere.[158] **The Government must therefore identify how the UK can become a more attractive venue for clinical trials as, currently, the number of trials does not reflect its significant benefits.**

77. We heard three primary causes for concern: the slowness of trial set-up; the lack of adequate support to set-up trials; and the design and scale of trials for regenerative medicine.

78. Several witnesses identified delays setting up clinical trials as a serious issue. The Cell Therapy Catapult said that delays to the start of clinical trials were a major obstacle to conducting clinical research in the UK.[159] The UK Stem Cell Foundation also viewed stoppages as a major issue, citing both delays in approval and difficulties in identifying patient cohorts as problems.[160] Figure 10 shows the length of time taken by the MHRA to consider regenerative medicine clinical trial applications. It shows that there is great variation in how long this process can take and it is this kind of uncertainty that can put off potential investors.

FIGURE 10

Time Taken for the MHRA to assess regenerative medicine clinical trial applications 2008–12[161]



Note: each bar refers to an individual application progressing through a sequence of stages

79. The identification of suitable patients for trials was also a cause of delay.[162] NHS research and development approval processes were perceived to be slow and,[163] despite efforts to improve its working, some witnesses were still critical of the time taken by GTAC to consider applications (even after its

158 AMRC.

159 Cell Therapy Catapult.

160 UK Stem Cell Foundation.

161 Supplementary written evidence from the MHRA.

162 UKSCF.

163 BSBMT, BSH, RCPath, Cell Therapy Catapult, LLR.

merger into the HRA).[164] The Alliance for Regenerative Medicine spelled out the consequences of these delays: "real and/or perceived bottlenecks that delay or adversely impact the speed and efficiency of clinical development … increase overall costs and erodes value".[165]

80. We heard ample evidence that more could be done to support clinical trial set-up. Professor Robin Ali, UCL, made the case for additional support for clinicians setting up clinical trials because of the "huge numbers of forms and the documentation" required.[166] He argued that "clinicians and senior academics just do not have the time to spend filling in huge numbers of forms and the documentation that is required".[167] We heard of one trial which had involved over 37, 000 pages of documentation.[168] Regener8 argued that the skills to conduct administrative preparations required for clinical trials were "not normally found within academic or small company settings".[169] LLR also identified bureaucracy associated with setting up trials as a block to translation.[170]

81. There have already been some efforts to address this need for support. The NIHR was set up with the expressed purpose "to create the best possible research environment in the NHS and build an international reputation for excellence in translational and applied research".[171] It has invested in a network of Biomedical Research Units (BRUs) and Biomedical Research Centres (BRCs). The map below (Figure 11) shows where they are located.

164 UKSCF.

165 Alliance for Regenerative Medicine.

166 Q 64.

167 Q 65.

168 Q 40.

169 Regener8.

170 LLR.

171 Tissue Regenix Group plc.

FIGURE 11

NIHR Biomedical Research Units and Biomedical Research Centres[172]

These BRUs and BRCs seek to support the translation of research to patient benefits and to drive innovation in the prevention, diagnosis and treatment of ill-health. Another NIHR initiative is the NIHR Clinical Research Network (CRN), which seeks to:

- "ensure patients and healthcare professionals from all parts of the country are able to participate in and benefit from clinical research;
- integrate health research and patient care;

[172] Based on information from the NIHR website: www.nihr.ac.uk.

- improve the quality, speed and co-ordination of clinical research, and
- increase collaboration with industry partners and ensure that the NHS can meet the health research needs of industry".[173]

82. The CRN comprises a co-ordinating centre, six topic specific research networks, a primary care research network and a comprehensive research network enabling research to be conducted across the full spectrum of disease and clinical need. It allocates and manages funding to meet NHS service support (for example, additional nursing time, pathology sessions, lab costs, imaging, additional out-patients costs) for eligible studies. One aspect of this support is the research design service, which includes expert advice on clinical trials.[174]

83. We heard mixed evidence about the efficacy of NIHR efforts. Tissue Regenix told us that: "the multifarious levels of bureaucracy we, as a partner, have to be involved with is confusing and ultimately unproductive, wasteful of time and money and this is meant to be a streamlined process".[175] The BSBMT said these efforts compared unfavourably with other national models, including that of the USA, because the USA has central funding available and its clinical trial governance structures are "less complex and time consuming".[176]

84. In contrast, the UCL applied regenerative science group regarded NIHR support as a UK strength and its provision to be "comprehensive".[177] Miltenyi Biotec spoke favourably of the support the NIHR had provided to the cell therapy landscape.[178] The UK Regenerative Medicine Community (UKRMC) considered changes by the NIHR to be "very positive"[179] and the Wellcome Trust welcomed the NIHR Research Support Services Framework.[180]

85. It is clear that the NIHR's actions to support clinical trials are welcome, but there are some questions about their adequacy. Professor Stephen Craddock, Queen Elizabeth Hospital, argued that there was insufficient funding for clinical trial support: "the major challenge to the United Kingdom realising its full translational potential primarily relates to the absence of appropriately funded clinical trials networks in areas such as regenerative medicine where the United Kingdom already possesses exceptional strong basic science and clinical teams".[181] Regener8 called for growth in this support: "specialist knowledge and the ability to navigate around the approval process are required and can be a steep learning curve for the novice. Greater provision, and expansion, of the current support from the NIHR at the local level would be a benefit in overcoming this difficulty".[182]

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173 NIHR: *Clinical Research Network*, 2013.

174 *Ibid.*

175 Tissue Regenix.

176 BSBMT, BSH, RCPath.

177 UCL applied regenerative science group.

178 Miltenyi Biotec.

179 UKRMC.

180 The Wellcome Trust.

181 Professor Stephen Craddock.

182 Regener8.

86. Many regenerative medicines treat orphan indications—those conditions occurring in relatively few patients. This causes difficulties amassing data in sufficient patients to prove safety, efficacy and patient benefit.[183] Clearly it is not appropriate to consider lowering evidence standards as patient safety must be a priority. But one way of addressing this issue would be to improve ease of identifying suitable patients. The NIHR has already made some progress in this, but other initiatives show there is further potential to speed up and ease the identification of potential participants. The Scottish Government have set up NHS Research Scotland, which helps to address this challenge by co-ordinating the rapid approval of multi-centre clinical trials across Scotland.[184] Similarly, the LLR Trial Acceleration Programme (TAP) established in 2011 has had exceptional results. It funds a central trials hub in Birmingham and supports research nurses or trial co-ordinators in 13 leukaemia centres across the United Kingdom to allow rapid recruitment to early phase studies from a 20 million population. In its first 12 months, the TAP launched two early phase clinical trials and planned to open four further studies in the following six months.[185]

87. Another difficulty associated with clinical trials was the identification of doctors who would be interested in supporting a trial.[186] A further challenge was how to ensure that treatments were developed in such a way that they were scalable when it came to increased patient numbers, an issue which we will explore in greater depth in the next Chapter.

88. **The evidence received conveys considerable demand for greater support in the design and set-up of clinical trials. There is expertise in clinical trial design and set-up in the NIHR CRN, its BRUs and BRCs, and amongst academics exploring innovative trial design. There is also considerable expertise in NICE, which could help inform trial design to ensure outcomes meet its evaluation requirements, in the MHRA, which already offers an advisory service, and amongst manufacturing experts from both industry and academia, who could provide advice to ensure that therapies are developed in a scalable fashion. Each of these groups would benefit from greater two-way interaction: to inform regulation and guidance making, and product development and trial design.**

89. **Consequently, we recommend that the NIHR establish a regenerative medicine stream of its clinical research network. Such a move would support researchers in addressing the specific needs of regenerative medicine clinical trial design, help overcome difficulties in identifying patients and ensure that doctors interested in such trials could be easily identified. The network could also facilitate dialogue with regulators on future regulatory needs and issues encountered with regulation. The regenerative medicine stream of the network should employ a hub and spoke model for allogeneic treatments, whereby it has one or two co-ordinating centres and regional operations. Given the need for clinical trials of a certain size, this network should span**

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183 Scottish Enterprise.

184 Scottish Government.

185 LLR, Professor Stephen Craddock.

186 Pfizer.

across the UK and build on existing developed infrastructures like NHS Research Scotland.

90. **The NHS would be a very attractive location for trials with these improvements, and there are reciprocal benefits to the UK in the form of inward investment, gaining further experience, potential for early market adoption and thus availability to NHS patients. The Government must ensure that this opportunity is not missed.**

91. Clinical trials in regenerative medicine have some issues specific to the field. For traditional pharmacological clinical trials, the endpoints and clinical indications are reasonably well established—safety, efficacy and patient benefit. Designing clinical trials for regenerative medicines presents some distinct challenges as there may not, for example, be a comparable therapy with which to compare efficacy. Some witnesses called for regulator-defined endpoints, indications and measures.[187] The FDA has produced similar guidance for cancer drug and biologic endpoints for treating terminal disease.[188] For investigators, and their financial backers, to know what they should be aiming to demonstrate through their trials, they need to know what evidence requirements regulators will have of them.[189] We recognise that this is a two-way process and a learning curve—regulators have as much to learn about developments in the science as researchers do about evolving regulation. CIRM run productive seminars where the FDA and scientists engage in dialogue to help achieve this end.[190] **Therefore, we recommend increased dialogue between regulators and researchers in the form of regular regenerative medicine workshops, and that the MHRA produce a series of guidance notes (to be updated bi-annually) setting out clinical trial endpoint requirements for regenerative medicine, in consultation with the industry and academic researchers. UK regulators should learn from the example of FDA-CIRM workshops and similar efforts in other countries.**

92. Ultimately, all of these efforts will be fruitless unless more is done to allow clinicians time to participate in research activities, including clinical trials. Providing time, resources and space for people to innovate was a key recommendation of Sir David Nicholson's report *Innovation, Health and Wealth*, 2011. The inclusion of research in the NHS Constitution is a positive step and the efforts of the NIHR are laudable. But the Department of Health must remain vigilant to ensure that research and development is a priority in the newly structured NHS.

Scale-up and manufacturing

93. Scaling a treatment up from a product for a handful of people, to service a large sample of people in a trial and ultimately, potentially, to patients across the nation provides specific manufacturing challenges for this industry.[191] Unlike a pharmaceutical treatment where a pharmacy can issue uniform, mass-produced tablets, regenerative medicines often require the safe

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187 ABPI, AMRC, BIA, RCUK, Welsh Government.

188 FDA: *Guidance for Industry; clinical trial endpoints for the approval of cancer drugs and biologics*, 2007.

189 Appendix 5.

190 *Ibid.*

191 ABPI, British Society for Oral and Dental Research, EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, Health KTN.

treatment and delivery of living cells. Table 9 gives an idea of scale of batches of cells required when one considers the numbers of doses potentially involved in cell therapies if delivered to sizeable groups. The number of doses of a particular cell-based treatment required in a given year can be achieved by increasing the number of doses prepared per batch.

TABLE 9

Doses per year drives cell batch size[192]

Doses per year	Doses per lot					
	50	**200**	**500**	**1, 000**	**5, 000**	**10, 000**
10, 000	200	50	20	10	2	1
25, 000	500	125	50	25	5	2.5
50, 000	1, 000	250	100	50	10	5
100, 000	2, 000	500	200	100	20	10
250, 000	5, 000	1, 250	500	250	50	25
500, 000	10, 000	2, 500	1, 000	500	100	50

94. To deliver at significant scale it will be necessary to develop closed and automated systems, and for therapies to be designed in such a way that they can be manufactured in bulk.[193] One example of the difficulties faced is the challenge of producing a large batch of cells to a standard potency and quality.[194] Manufacturing in large quantities will not only be necessary, it will also bring economies of scale.[195] Zahid Latif, Head of Healthcare, TSB, summed up the issue well: "Typically, what happens with a promising therapy that comes out of the research sector, or some of the SMEs that are often undercapitalised, is that the processes are essentially laboratory, hand-cranked processes. When they come out to be manufactured, frankly, the processes are not up to it".[196]

95. There have been initiatives to address some of these issues. The TSB Regenerative Medicine Programme had, as one tranche of its funding, a tools and technologies programme. This gave funds to projects including a high throughput platform for the discovery of GMP (Good Manufacturing Practice: quality assurance to ensure that medicinal products are consistently produced and controlled to the standards appropriate to their intended use)[197] compatible stem cell manufacturing protocols by Plasticell Limited, Cell Guidance Systems Limited, LGC Limited and NHS Blood and Transplant (NHSBT); a closed point-of-care preparation device by Lonza Biologics PLC, eXmoor Pharma Concepts Limited and Amercare Limited;

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[192] Presentation made at CIRM by Lonza. Used with permission.

[193] Q 251.

[194] RCUK, Appendix 5.

[195] LGC.

[196] Q 284.

[197] European Commission: *EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use*, 2008.

and a project to enhance cell stability during manufacture and administration by Stabilitech Limited and UCL.[198]

96. Furthermore, £5.8 million over 5 years has been invested by the EPSRC to establish a Centre for Innovative Manufacturing in Regenerative Medicine which has leveraged £13.4 million of geared funding since October 2011.[199] The Centre is a partnership between Loughborough, Nottingham and Keele Universities and industry (they currently have around 20 industry partners) together with other end users. Its vision is "to form a differentiated translational "go to" resource for regenerative medicine product developers with a focus on manufacturing science, and manufacturing system and process development".[200] Its core research themes are manufacturing and automation; characterisation; and delivery and 3D constructs (such as scaffolds). An example of one of their projects is the testing and validation of a prototype hydrostatic pressure growth chamber capable of scale-up for manufacturing for cell therapy applications. The Centre explained: "hydrostatic force applied to cells in culture leads to an increase in bone cell growth and mineralisation, two processes highly important for the regeneration of skeletal tissue. The novel Tissue Growth Technologies (TGT) bioreactor allows standard format cell culture plasticware to be used, with additional control over frequency and amplitude of hydrostatic forces applied. Such a design will allow large scale-up".[201]

97. The Association of the British Pharmaceutical Industry (ABPI) recommended that early dialogue with industry on manufacturing, scalability, transportation and delivery solutions and consideration of "commercial viability" should be funding criteria for translational and applied research.[202] LGC Limited argued that regenerative medicine innovators embarking on commercial development should outsource the manufacture of their products to contract pharmaceutical manufacturers that have established processes, skills and infrastructure to conduct this work and comply with regulatory requirements.[203] Despite these differences in approach, these views add weight to the argument that scalability must be researched, invested in and must inform the development process for a product at an early stage. CIRM have a disease team model which brings together multidisciplinary teams to work on specific disease areas, and these teams include manufacturing and scale-up experts.[204] This ensures that researchers are thinking about these issues together and CIRM bring in expertise to support them in thinking about commercial issues during development.[205]

98. **We recommend that the phase II disease teams of the TSB regenerative medicine platform, and other regenerative medicine funding programmes, specifically require researchers to involve manufacturing and scale-up experts in their development process to**

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198 Supplementary written evidence from the Government.

199 EPSRC Centre for Innovative Manufacturing in Regenerative Medicine: *Annual report*, 2011.

200 *Ibid.*

201 *Ibid.*

202 ABPI.

203 LGC.

204 Appendix 5.

205 CIRM.

ensure that translational work is scalable and therefore deliverable to a large number of patients (where the disease area requires this).

99. Very few witnesses called for a significant expansion of UK GMP capacity at present, but rather for more research to be translated to the point where it was required. Professor Williams, Professor Marc Turner, Medical Director, SNBTS and Keith Thompson, Chief Executive, Cell Therapy Catapult, all cautioned against building "steel palaces" as, they argue, to invest heavily in clean room capacity now could be short-sighted should significant breakthroughs in closed and automated systems be made in the next few years.[206] France has recently invested $143 million in a major manufacturing cluster.[207] UK investment in manufacturing must not fall behind that of its major competitors in Europe and further afield. In the first instance, greater co-ordination of UK GMP facilities through a central registry would ensure that these facilities are used to their maximum capacity.

100. **Recognising the importance of capacity to deliver therapies at scale, both for trials and wider patients populations, and the fast-moving pace of the manufacturing and scale-up field, we recommend that the TSB and EPSRC undertake an annual stock-take of regenerative medicine manufacturing capacity and make recommendations to BIS about future needs, with the first survey informing the Government's review of infrastructure investment. The Cell Therapy Catapult has begun work on such a survey so we recommend that this work is taken as a starting point. BIS must then act to ensure that appropriate infrastructure investment is made to support the field. At the very least, investment should be made in facilities to support the scale-up of treatments in mid to late stage clinical development. Money for this, and other recommendations, should be found by the re-prioritisation of budgets and innovative funding methods (discussed below).**

101. **UK capacity to manufacture at scale could be attractive to companies considering investing in or expanding operations to this country. We recommend that the UKTI Life Science Investment Organisation use the results of this survey to advise foreign companies on UK capacity to manufacture regenerative products.**

102. We heard calls for more trained technical staff in this area. Specifically, there was a need for more technical staff trained in manufacturing processes and with experience of the quality requirements.[208] Without these staff, investment in infrastructure will be wasted.

103. **We recommend that the NHS develop a training programme for technical staff to support the development of cell therapies and other regenerative therapies at scale.**

GMP requirements

104. GMP (Good Manufacturing Practice) is quality assurance to ensure that medicinal products are consistently produced and controlled to the standards

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206 Q 273, Q 251.

207 Q 175.

208 Q 245, Q 253, Q 275, Cell Therapy Catapult.

appropriate to their intended use, and as required by a product's marketing authorisation or product specification. There are particular technical and regulatory challenges in developing cell lines and expanding autologous cells for clinical use. To satisfy these standards, quality standards must be built into the development process from the start, and clinical grade GMP maintained throughout the development process (although research grade facilities may be used for non-clinical applications). This includes both a GMP compliant quality control regime (the panel of tests for the cells) and GMP compliant cell processing facilities (real estate).[209] As the report of the TSB REALISE project observed, the cost of meeting regulatory requirements for the development of cells to clinical grade GMP standard is significant.[210] Arthritis Research UK argued that the requirements for the expensive GMP compliant processes imposed by regulation are inflexible, and based on the traditional needs of drug therapies, and thus hinder development of novel cellular therapies.[211] This criticism was echoed by the Cell Therapy Catapult.[212] It advocated an approach better tailored to the therapy and stage of development which reflected requirements in areas such as batch potency, release and comparability testing. This would recognise the fact that when the product is a living cell, 'batch' sizes for cell based therapies can be very small and the testing requirements can become unfeasible both in terms of time and material requirements as well as prohibitively expensive.[213] Professor David Williams, Director of the EPSRC Centre, argued that building stronger links between the regulators and those who are regulated would be a vital step in overcoming the difficulties of GMP requirements.[214] GMP requirements are agreed at an EU level.

105. **We recommend that the MHRA canvas views from industry on the suitability of current GMP requirements and, if there is significant discontent, take these problems to the European Commission to seek agreement on overcoming them through amendments to the GMP Directive and associated guidance.**

Delivery

106. By delivery we mean the process of preparing, storing, transporting and administering a treatment to a patient. Different types of treatment require different delivery models. For example, some autologous cell treatments could be manufactured using "off the shelf" technologies. Others might require significant manipulation in specific facilities, which would require transportation both to and from a specialist centre. Similarly, allogeneic cell treatments may require preservation, storage and transportation from donor to recipient. The UCL applied regenerative science group, gave an example which illustrates the need for both infrastructure investment and clear delivery routes: the Moorefield's Eye Hospital / ACT retinal pigment epithelium cell replacement derived from human embryonic stem cell to treat Stargardt's disease (described in paragraph 14 above) is an "off-the-shelf"

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209 *Op. cit.* EU GMP Guidelines.

210 Mastroeni, M., Mittra, J., and Tait, J.: *TSB Regenerative Medicine Programme: Value Systems and Business Models, the REALISE project*, May 2012.

211 Arthritis Research UK.

212 Cell Therapy Catapult.

213 *Ibid.*

214 Q 276.

allogeneic product yet requires thawing from cryopreservation (maintenance of the viability of cells, tissues and organs by a process of cooling and storing at very low temperatures)[215] and dosing within a four hour travelling distance of the patient. It argued that "if the current clinical trials in the UK and the US continue to be successful this is an ideal candidate for commercialisation but only if an infrastructure of hospital-based "cellular pharmacies" is in place across the UK such as the three highly specialised, MHRA licensed facilities we have across UCL to deliver these products close to the patients".[216]

107. *Taking Stock* argued that the UK possessed a key advantage in the delivery of cell based products in the form of the NHSBTS and devolved equivalents. Each of these organisations is familiar with the challenges in distributing blood products, stem cells (for bone marrow and cord blood) and organs, as well as necessary tissue typing services. NHSBTS already delivers a diverse range of specialist services in human tissue and cells such as the collection, GMP production, storage and delivery of viable cell therapies.[217] In Scotland, SNBTS is already a key part of the regenerative medicine environment, undertaking clinical development of a pipeline of new therapies and taking a lead role in several multi-partner public and private projects (for example, a Wellcome Trust funded project to create red blood cells).[218] There is similar potential for the NHSBTS to partner with SMEs and researchers, either as a purchaser of specialised services of infrastructure, or as an incubator for a small number of SMEs in need of GMP production facilities.[219] Azellon is already partnering with NHSBTS in cell production for the clinical trial of its platform technology using mesenchymal stem cells (MSCs) to repair damaged knee tissue.[220] NHSBTS acknowledges that its infrastructure is pivotal to the effective manufacture and delivery of regenerative medicines.[221] Azellon note that as the number of cell products expands, NHSBTS will need to further develop its capacity to provide a cell production service at different locations, and argue that "there is a significant opportunity for NHSBTS to fill this gap using a semi-commercial approach, but with flexibility and a cost model that is more attractive for early-stage cell therapy companies".[222]

108. **It is clear that the national blood and transfusion services have the logistical capability to collect, produce, store and transport components of regenerative treatments. However, we were concerned to see that the NHS is less ready for the provision of regenerative therapies.** We were surprised that Sir Bruce Keogh, NHS Medical Director, and James Palmer, Clinical Director for specialised services, NHS England, could not point to future infrastructure needs to provide regenerative treatments on mass to patients.[223]

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215 *Op. cit.* PAS 84.

216 UCL applied regenerative science group.

217 *Op. cit.* Taking stock, Government.

218 SNBTS.

219 *Op. cit.* Taking stock.

220 Azellon.

221 NHSBTS.

222 Azellon.

223 Q 335.

109. **Investors need to see a clear pathway from development to delivery in the NHS if they are to have the confidence to invest in regenerative medicine. It is not sufficient to rely on trail blazing therapies to forge pathways to clinical delivery. The NHS must shift from reacting to regenerative medicine to a state of preparedness to deliver new and innovative treatments.**

110. **We recommend that the Department of Health establish a regenerative medicine expert working group to develop an NHS regenerative medicine delivery readiness strategy and action plan by December 2014. This group should report to the Secretary of State for Health directly and have the support of a high-profile, independent chair. The group must also contain NHS England officials, NHSBTS and devolved blood and transfusion services, regulators, researchers and industry representatives. We consider the role of the chair further in Chapter 5.**

CHAPTER 5: COMMERCIALISATION

Business models, venture capital and the funding gap

111. Finance for regenerative medicine was one of the key themes in the evidence we received. Any start-up business requires initial funding, whether that be through a government scheme, bank finance or private equity. Regenerative medicine companies in the UK have been funded in various ways.

112. The classic business model for the development of regenerative medicines has been for a company to develop, manufacture, market and sell their own products. Professor Chris Mason, UCL, noted that many such companies are small and only have one product, therefore one "hiccup" with a clinical trial or a delay for regulatory reasons can leave the company at risk of collapse. Successful business models for cell therapies are not yet established.[224] A number of regenerative medicine companies have tried to reduce their need for investment capital by providing commercial tools and services. For example, Intercytex Ltd has a service business, Cell2therapy, which provides contract translation services to other regenerative medicine businesses in order to offset Intercytex's capital requirements. The BIA suggested that this approach is not a truly viable business model in the long term.[225] Other companies had licensed products to large healthcare organisations such as Novartis, and Smith and Nephew, but the partnership did not work and some companies declared bankruptcy.[226] Still others, such as Azellon, operate as virtual businesses and so outsource the manufacture, management and conduct of clinical trials—an approach favoured by the Scottish Government and Scottish Enterprise.[227]

113. Cell therapy companies have to compete with other sectors offering shorter timescales to return on investment and, often, less financial commitment and risk when seeking finance. The prevailing view was that venture capitalists were increasingly risk adverse because of the current economic climate and so reluctant to risk investing in regenerative medicine.[228] The UK's cell therapy sector has had generally poor results from listings on AIM principally due to poor liquidity and paucity of analysts with knowledge of the cell therapy sector, according to Professor Mason. However, some venture capital companies are now investing, as the science matures and therapies are reaching late stage trials.[229] For example, venture capital investment in regenerative medicine is increasing in North America.[230] There is significant potential return on investment in this field too. For example, investors in BioTime saw cash returns of between 13 and 15 times what they had put in.[231]

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224 Professor Chris Mason, Scottish Enterprise.

225 BIA.

226 Dr Paul Kemp.

227 Azellon, Scottish Enterprise, Scottish Government.

228 ABPI, GE Healthcare, Professor Rimmer, UKRMC.

229 Professor Chris Mason.

230 Edinburgh BioQuarter.

231 Wall Street Journal: *A rare win for venture investors in regenerative medicine*, 2011.

114. Dr Kemp observed that the era of relying on large investments from venture capitalists had passed.[232] We heard similar statements when we visited CIRM, where witnesses argued that Government had to step in and meet the funding need.[233] At present, only five percent of the £70 million of the UK public sector investment is spent on mid to late stage clinical development and adoption.[234]

115. Dr Kemp argued that Government can make a difference, not only by providing more funding, but also by reducing the need for funding in imaginative ways that do not compromise the commercialisation of safe and efficacious products. He suggested that a total rethink of private equity financing was required and the only way this could happen was through some form of progressive licensing and reimbursement.[235] Professor Mason added that any solutions that reduced the uncertainty for investors would put the UK at an advantage.[236] Pfizer similarly advocated a more active role for Government, arguing they should invest more significantly at TRLs 6–8 because of the relatively small UK company developer sector. It suggested that funding should be made available for smaller companies to develop phase II trial programmes, through matched funding similar to the scheme available from CIRM.[237] Professor Mason warned of the dangers of assuming that "big pharma" or biotech would pick up regenerative medicine.[238] **Investment could be stimulated by reducing associated risk**, either by de-risking products or spreading risk by investment in a wide portfolio of candidates.[239]

The Cell Therapy Catapult Centre

116. The Cell Therapy Catapult Centre is tasked with offering a "new approach to bridging the investment 'valley of death',[240] by providing funding and support mechanisms to progress promising science through to a point where 'investable propositions' exist, which are then capable of attracting conventional commercial finance".[241] However, its current ability to fund the sector is limited by its budget. It was established in May 2012 as part of the TSB's programme of technology and innovation centres where the very best of the UK's businesses, scientists and engineers can work side by side on research and development—transforming ideas into new products and services to generate economic growth. The centres aim to help businesses to adopt, develop and exploit innovative products and technologies—the next stepping-stone on the journey to commercialisation. The seven centres, of which the Cell Therapy Catapult is one, concentrate on: high value

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232 Dr Paul Kemp.

233 Appendix 5.

234 Pfizer.

235 Dr Kemp.

236 Professor Chris Mason.

237 Pfizer.

238 Professor Chris Mason.

239 ABPI, LGC, Appendix 5.

240 The point where a business has a working prototype for a product or service that has not yet been developed enough to earn money through commercial sales. The company needs to find sufficient money to develop the prototype until it can generate sufficient cash, through sales to customers, that would allow it to be self sufficient and grow.

241 Cell Therapy Catapult.

manufacturing, offshore renewable energy, satellite applications, connected digital economy, future cities and transport systems. In October 2012, the Prime Minister announced an investment of £200 million in the Centres and said that they should leverage over £1 billion of public and private investment over an initial five year period.[242] The network of seven centres is based on the German Fraunhofer-Gesellschaft model of 66 institutes and research units undertaking applied research that support industry and technology transfer as part of a national innovation eco-system. The Fraunhofer-Gesellschaft attracts an annual research budget of approximately €1.9 billion.[243]

117. Many witnesses welcomed the Cell Therapy Catapult.[244] The Alliance for Regenerative Medicine viewed the development of the Cell Therapy Catapult to promote the field of cell therapy and providing infrastructure support to companies to run clinical trials or manufacture cell therapies as a real strength of the UK.[245] Edinburgh BioQuarter agreed that the Cell Therapy Catapult "will undoubtedly add weight" to the UK's strength in regenerative medicine "as it becomes fully established".[246] Dr Paul Kemp, Chief Executive Officer of Intercytex, welcomed the Cell Therapy Catapult, although he expressed concern that it must not "just push treatments into the clinic in order to reach some governmental set milestone". He continued:

> "I know there is a lot of hope in the whole Regenerative Medicine community that the Cell Therapy Catapult will have a positive impact but also a lot of nervousness that the Cell Therapy Catapult will either soak up all the future Government funding for this sector or at worst become 'state sponsored competition' to SMEs struggling to develop their own products or services".[247]

118. Edinburgh BioQuarter pointed out that the level of funding for the Cell Therapy Catapult was "relatively modest by comparison with, for example, the $3 billion fund established by the Californian Institute for Regenerative Medicine (CIRM) or the NIH's $1.3 billion annual stem cell budget", although these models are all slightly different.[248] The Medical Technologies Innovation Knowledge Centre argued that "to fully realise the commercial and clinical potential of regenerative medicine, higher levels of funding are likely to be required to take technologies through to the market".[249] Regener8 took a similar view, in that "although recent public funding for the Biomedical Catalyst and Cell Therapy Catapult is extremely welcome, considerably greater funding will be needed to maintain and secure the UK's favourable position in the development of regenerative therapies".[250] ReNeuron agreed that "the sums available are relatively small (when the costs of taking a therapy from pre-clinical proof-of-concept to phase II are considered) and are likely to be distributed widely in the sector. It is unlikely

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242 Cell Therapy Catapult, Government, TSB.

243 TSB.

244 BIA, GE Healthcare, Paul Kemp, London Regenerative Medicine Network, Pfizer and Regener8.

245 Alliance for Regenerative Medicine.

246 Edinburgh BioQuarter.

247 Dr Paul Kemp.

248 Edinburgh BioQuarter.

249 Medical Technologies Innovation Knowledge Centre.

250 Regener8.

therefore that these initiatives alone will be sufficient to address the continuing funding concerns of the regenerative medicine sector". It also compared the funding with the scale of funds made available by CIRM and recommended "consideration of further innovative and cost-effective funding vehicles, possibly based on the French Citizens' Innovation Funds (CIFs) model" (which are explored further in paragraph 126 below).[251]

119. The NHSBTS took a different view, arguing that "the challenge is not the availability of money, especially with the recent creation of the BioMedical Catalyst, Cell Therapy Catapult and Regen Med Platform, but confusion as to which fund/scheme/organisation researchers should approach." Its proposed solution was "a road map that enables organisations to map their position in the development process against the most relevant funding resource".[252]

120. The TSB commented that the Cell Therapy Catapult should meet the need established in consultation with the community for "focussed support" to enable companies to build the clinical evidence base necessary to "de-risk their value propositions and leverage the significant funding necessary to bring products to market". It acknowledged that more needs to be done, particularly as the later stages of the development of these therapies are expensive for companies.[253]

121. The London Regenerative Medicine Network (LRMN) highlighted that "it is vital to continue to learn lessons from established centres around the world regarding project selection, focus and delivery to ensure we catch up in translating our research into products".[254] The NHSBTS similarly argued that the Cell Therapy Catapult needed to learn from German and Canadian examples.[255] The Cell Therapy Catapult Chief Executive Officer, Keith Thompson, confirmed that he was looking to international models and learning lessons from their leaders, such as Professor Alan Trounson, President of CIRM.[256]

122. The Cell Therapy Catapult has an enormous range of activities planned including:

- taking products into the clinic, derisking them for further investment;
- providing clinical expertise and access to NHS clinical partners;
- being a source of regulatory expertise;
- providing technical expertise and infrastructure to ensure products can be made to GMP and delivered cost effectively;
- generating national and global opportunities for collaboration; and

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251 ReNeuron.

252 NHSBTS.

253 TSB.

254 LRMN.

255 NHSBTS.

256 Q 288.

- providing access through its network to business expertise, grants and investment finance so that commercially viable products are progressed and investable propositions generated.[257]

123. These are all helpful goals and yet the Cell Therapy Catapult only has a budget of up to approximately £70 million over five years. Whilst it is right for the Cell Therapy Catapult to share its expertise, as it establishes itself, it must first focus on developing investable propositions and building connections (including with investors).

124. **The Cell Therapy Catapult was only set up in May 2012 and we recognise that there is significant potential in the venture. However, we are concerned that it is seeking to achieve too much, too quickly, given the level of funding. We recommend that the TSB and Cell Therapy Catapult prioritise its activities to enable the Cell Therapy Catapult to focus on taking high growth potential projects through clinical trial to be phase III trial ready and developing links with the regenerative medicine community.**

125. **Furthermore, given the large number of potential funders, the TSB, research councils and NIHR should produce an online funding guide, regularly updated, to help researchers and SMEs know where they should apply at each stage of research and development in regenerative medicine.**

Alternative financing

126. There is real merit in considering further innovative and cost-effective funding vehicles, for example, based on the French Citizens' Innovation Funds model, which is advocated by the BIA and ReNeuron.[258] This model offers a tax-advantaged investment product with an income tax break on up to £15, 000 of investment which is pooled and used to support innovative, research-intensive companies.[259] It is currently being evaluated by Her Majesty's Treasury.[260] Other popular models currently being discussed are "megafunds" of up to $30 billion, financed by securitised debt and equity, which spread investment across a diverse portfolio of medical innovations—possibly with some form of government guarantees to encourage investors.[261] The state of California issued $3 billion of general obligation bonds to fund stem cell research. Other possible forms of investment include option deals, one-product financings from venture capitalists, and pre-initial public offering royalty-based financing.[262]

127. **There is insufficient TRL 6–8 funding available to support this fast-developing field. It would be unrealistic to depend exclusively upon additional funding coming from venture capitalist or "big pharma" investment. A mechanism must be found to fill this gap. Therefore, we recommend that the ESRC and the TSB commission an evaluation of innovative funding models, which spread risk and most**

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257 Cell Therapy Catapult: *Growing a UK cell therapy industry that delivers health and wealth*, 2012.

258 ReNeuron, BIA.

259 BIA: *Citizens' Innovation Funds; engaging the public with UK innovation*, 2012.

260 HL Deb, 11 Mar 2013, column WA41.

261 The Economist: *Financing medical research*, 2013.

262 See http://bostonbiotechwatch.com/tag/venture-capital/.

likely will contain a degree of government matched funding or be underpinned by government guarantees, and recommend how additional funding could be provided for late stage clinical development in this field. The Government have said that this field has enormous potential and that they will support it. They must "put their money where their mouth is"; BIS and Her Majesty's Treasury must adopt the policy recommendation of the ESRC and TSB study.

Intellectual Property

128. Patents, which are registered as intellectual property (IP) rights granted by a country's government as a territorial right for a limited period, make it illegal for anyone except the owner or someone with the owner's permission to make, use, import or sell an invention in the country where the patent was granted. They have traditionally been a significant lever in attracting private investment in technology and development as they help to provide a return on investment by allowing the sale or licensing out of an invention.[263] Examples of regenerative medicine patents granted in the UK include: a peripheral nerve-growth scaffold; inducing human pluripotent stem cells; biocomposite skin substitutes for wound healing; collagen matrix for supporting cell growth; multipotent stem cells from human adipose tissue; and a method of decellularisation of a membranous sac or bladder, prior to transplant.[264]

129. We heard mixed views on the importance of patenting to the commercial exploitation of regenerative medicine. A number of witnesses viewed patentability as critical. The Alliance for Regenerative Medicine argued that, given the high levels of both initial and continued investment needed to develop a regenerative medicine treatment, without IP protection potential funders such as venture capitalists would be reluctant to invest the amount of capital necessary.[265] Similarly, Professor John Haycock, Professor Stephen Rimmer and Professor Sheila MacNeil, University of Sheffield, argued that the absence of patenting was a limiting factor on the development of spin-out companies or partnerships from academic research propositions because a granted patent is viewed as a key asset to a start-up firm seeking to demonstrate potential for investment.[266] Concern was also raised by Miltenyi Biotec that in the absence of a patented 'product' there was no obvious business model beyond that of essentially offering an expert service, which they considered harder to commercialise.[267]

130. Others argued that the importance of patenting in regenerative medicine may have been overstated. Professor Mason suggested that, given the multi-disciplinary nature, complex supply chains, specialist knowledge, and delivery challenges involved in developing a regenerative medicine treatment, patenting is potentially unnecessary as those innate barriers would work to protect value and investment.[268] Indeed, some witnesses, such as King's College London and King's Health Partners, argued that it was the technical

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263 UK Intellectual Property Office (IPO): *patents*, revised 2013.

264 Supplementary evidence from the IPO.

265 Alliance for Regenerative Medicine.

266 Professor John Haycock, Professor Stephen Rimmer and Professor Sheila MacNeil, University of Sheffield.

267 Miltenyi Biotec.

268 Professor Chris Mason.

knowledge, expertise and those processes used to develop regenerative medicine treatments, rather than the treatments themselves, from which key commercial benefits would be derived.[269] The Government pointed out that even if patents were an incentive to innovation, they offered no guarantee of feasibility, quality or commercial merit.[270]

131. Pfizer argued that the importance of patenting varied depending on the type of regenerative medicine involved. For example, small molecule programmes were more likely to depend on composition of matter patents, but cell-based therapies would have more complex IP positioning—where data exclusivity and expertise ("know how") could indeed be as important as patenting. There may be a large number of patents involved in regenerative medicine.[271]

132. Our expert panel of venture capitalists viewed patents as a "simpler" way of attracting investment, as the commercial potential was more easily seen, but recognised that there was commercial potential in enabling technologies and know-how. Dr Nigel Pitchford, Managing Director of Healthcare, Imperial Innovations, said: "we would consider know-how, particularly processing and manufacturing know-how, as being intellectual property within the context of a company. If it is held, is well researched and highly reproducible, we would consider that to be intellectual property, not within the classic sense of having a patent but within the sense of it being a valuable asset that the company owns and can gain leverage on".[272] To patent, for example, the technology developed to inject cells into patient's eyes is not to stifle the progress of research, but rather is a valuable mechanism to ensure return on investment in that development, and consequently to make future investment in regenerative medicine more likely.

133. **There is significant commercial potential in the enabling tools and technologies, and commercial know-how associated with regenerative medicine—the regenerative medicine community must ensure that investors are aware of this potential. UK Trade and Investment has a specific programme to attract inward investment in regenerative medicine and so we recommend that they support the field by informing investors about the economic potential of investment in the field.**

134. We heard significant concerns about the impact of a recent European Court of Justice (ECJ) ruling which affected the patenting of human embryonic stem cells. In 2011, the ECJ upheld Greenpeace's challenge of a patent held by Professor Oliver Brüstle which protected a method of transforming human embryonic stem cells into neurons. In its judgment, the Court ruled that such procedures violated existing restrictions on the industrial or commercial use of human embryos.[273] As a result of the Court's ruling, regenerative medicine procedures or treatments which derive from the destruction of human embryonic stem cells cannot be patented in Europe. This decision cannot be appealed. The UK's Intellectual Property Office has issued revised guidance on the patentability of treatments involving human embryonic stem cells in the wake of the decision. That guidance states that

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269 King's College London and King's Health Partners.

270 Government.

271 Pfizer.

272 Q 181.

273 *Greenpeace v Brüstle*.

where the implementation of an invention requires the use of cells that originate from a process which requires the destruction of a human embryo, the invention is not patentable, even if the claims of the patent do not refer to the use of human embryos.[274]

135. There was much discussion around the implications of this ruling. Julian Hitchcock said there was such a serious misunderstanding about its implications that some researchers thought they should abandon work in this field in Europe.[275] Alex Denoon, Partner, Lawford Davies Denoon, described the concerns about it signalling "the end for European or British embryonic stem cell research" as "a fallacy".[276] GE Healthcare said there was a "lack of clarity" following the judgment and "additional uncertainty" for investors, a view which Research Councils UK shared.[277] Sean Dennehey, Chief Executive of the Intellectual Property Office (IPO), reminded us that "most areas of regenerative medicine are patentable": materials isolated from the human body, such as cells or isolated genes and their use in therapy, are patentable. Methods of tissue engineering, such as culture techniques, delivery methods or cell scaffolds, are also patentable.[278] **There is significant scope for patenting within the field and much of the negative publicity around the Brüstle ruling seems to have overstated the implications.**

136. The final issue raised on IP was the cost of prosecuting patents. Azellon, NHSBTS and Professor John Haycock, Professor Stephen Rimmer and Professor Sheila MacNeil all highlighted the great expense of patenting beyond initial filings.[279] Professor Mason and Azellon also suggested that, in many cases, universities were ill-equipped to deal with the commercial aspects inherent within the patenting framework, and to support applications and patents over the timeframes required (and in multiple territories).[280] The IPO suggested that this could be overcome if universities were more selective about which countries they filed patents in.[281] This suggested a lack of shrewdness when it comes to patenting in universities. NHSBTS had an alternative suggestion: they recommended assistance in the form of grants or tax credits to remove the barrier to patenting and commercialisation. Professor Haycock, Professor Rimmer and Professor MacNeil argued that it was necessary to provide more support for academics in national and regional filing, potentially through a collective government sponsorship mechanism.[282] Julian Hitchcock raised the idea of a common national clearing house for regenerative medicine intellectual property.[283]

137. **Concern over the cost of patenting, the sufficiency of support available for innovators and questions about the ability of universities**

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274 IPO: *Inventions involving human embryonic stem cells*, 2012.

275 Julian Hitchcock.

276 Q 213.

277 GE Healthcare, RCUK.

278 Q 198.

279 Azellon, NHSBTS and Professor John Haycock, Professor Stephen Rimmer and Professor Sheila MacNeil, University of Sheffield.

280 Professor Chris Mason, Azellon.

281 Q 203.

282 Professor John Haycock, Professor Stephen Rimmer and Professor Sheila MacNeil.

283 Julian Hitchcock.

to recognise the potential in regenerative medicine patents lead us to conclude that the TSB should set-up a time-limited support fund for regenerative medicine patents. This fund should be open to university researchers who wish to pursue patents beyond the first stage, so that potential income from regenerative medicine products is not lost. Such a fund would help foster this fledgling industry and be a helpful tool until university patent offices are better placed to deal with the potential value of these products.

138. Although patents are not essential to commercialisation they can be a valuable tool. The TSB Smart scheme (formerly known as the Grant for Research and Development) provides matched funding for small and medium sized businesses, including pre-start-ups and start-ups, which can be used to establish IP position and to protect IP.[284] Furthermore, the Government introduced a preferential regime for profits arising from patents, known as a Patent Box, in April 2013. It allows companies to apply a reduced 10% corporation tax rate to profits attributed to patents and certain other similar types of IP.[285] Tissue Regenix argued that this scheme would do little to help early-stage pre-revenue companies but acknowledged that it would be beneficial to companies at a later stage such as itself. It voiced concerns that the Patent Box will complicate how licences are drafted, as a result of the need to ensure distinction between patent box eligible and ineligible income streams.[286] Alex Denoon said that the scheme was attracting interest from companies not previously active in the UK.[287] We concluded that there is already considerable support available for SMEs seeking assistance with IP.

Evaluation and the pricing of treatments

139. NICE is responsible for providing the NHS with advice on effective, good value healthcare. The two mechanisms it has for this, which can be used to assess regenerative medicines, are: the Interventional Procedures Pathway which reviews efficacy and safety; and Health Technology Appraisals which examine the cost effectiveness and cost consequences of a treatment.[288]

140. In order to be commissioned for use on the NHS, a therapy has to be assessed by NICE and approved for use through normal commissioning routes, or go through individual approval processes within Primary Care Trusts (PCTs) and Clinical Commissioning Groups (CCGs) and be reimbursed through different payment mechanisms. NICE is often accused of giving too much consideration to cost effectiveness, at the expense of clinical-effectiveness.[289] It employs a method known as the QALY (quality adjusted life year) to compare different treatments and their clinical effectiveness. Put simply, the QALY gives an idea of how many extra months

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284 Government.

285 TSB.

286 Tissue Regenix.

287 Q 208.

288 NICE.

289 Health Committee, *National Institute for Health and Clinical Excellence,* (8th Report, Session 2012–13, HC 782).

or years of life of a "reasonable quality" a person might gain as a result of treatment.[290]

141. We heard significant reservations about the suitability of the economic models NICE uses when it came to assessing the cost-benefit of regenerative medicines. Regenerative medicines which are curative in nature can have high up-front costs but will make significant savings for the healthcare system, as well as wider societal and economic impacts such as releasing people back to work and reducing the benefits bill, which were not considered to be given appropriate consideration under current arrangements.[291] For example, one study suggested that savings in direct healthcare costs in the USA could be up to $250 billion per year from chronic diseases such as heart failure, stroke, late-stage Parkinson's disease, spinal cord injury, and insulin-dependent diabetes.[292] A recent Austrian trial of a regenerative treatment for diabetic ulcers demonstrated how a cure could provide savings in sterile dressings alone of £30, 000 per annum, per patient.[293] An estimated £14 billion is spent a year on the treatment of diabetes and its complications in the UK—a cure for this disease would represent a significant saving to the healthcare system.[294] OSCI went so far as to describe current pricing structures as "largely irrelevant" as regenerative medicine will, more often than not, be curative rather than an ongoing treatment for symptoms.[295] The NHSBTS argued that regenerative treatments were more akin to transplants than drugs, in that costs are realised immediately whilst savings are accrued over time (reduced chronic care etc), and so required alternative reimbursement models.[296] The Government acknowledged that current reimbursement models were inadequate and that "a much closer link between the price the NHS pays and the value that a new medicine delivers to patients and to society is needed".[297] Under the current evaluation mechanism, a cure would only be considered affordable if it cost no more than two years of conventional therapy[298]—this situation is clearly unacceptable.

142. **We consider the NICE model for evaluating innovative treatments and cures to be inappropriate. It must devise suitable models that give appropriate consideration to the long-term savings sometimes offered by high up-front cost treatments.** Investors must see a clear path from the bench to the bedside if they are to invest, and a key component of this is reimbursement; a product must be bought at a suitable price by healthcare systems to generate an income.[299] This nascent industry will have higher costs for its first few treatments as efficiencies of scale are still being strived for, in the same way that many new technologies initially have a high

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290 Government.

291 Azellon, Cell Therapy Catapult, Health Knowledge Transfer Network, Parkinson's UK, RCUK, Tigenix, OSCI, UKRMC, UK Stem Cell Foundation.

292 Royal Society of Chemistry.

293 UCL applied regenerative science group.

294 Kanavos, P., van den Aardweg, S., Schurer, W.: *Diabetes expenditure, burden of disease and management in 5 EU countries*, 2012.

295 OSCI.

296 NHSBTS.

297 Government.

298 Cell Therapy Catapult.

299 ABPI, Alliance for Regenerative Medicine, GE Healthcare, Miltenyi Biotec.

price which quickly drops.[300] Whilst economies of scale must be sought in the long-term, there needs to be some recognition from NICE that costs will initially be higher as the field emerges, and that without appropriate reimbursement further medicines may not be developed, or certainly will not attract investment for swift development. This matters both in terms of patient care and for the potential benefit to UK plc. Other countries, such as France, Germany, Italy and Spain allow higher prices for new, innovative treatments.[301]

143. **The first few regenerative medicine products will invariably be more expensive than products further down the line. Other countries, such as France, have evaluation and reimbursement systems which provide for this. NICE must ensure that its evaluation process recognises the higher initial costs of innovative treatments, without compromising its goal of assessing value-for-money in healthcare. Part of its value-for-money consideration should be that early investment in this field could unlock other treatments with significant economic impact, both in terms of savings to the health system and increased potential work productivity.**

144. From 2014, NICE will take on the role of full value assessment in the new value-based pricing system. The new price threshold structure, according to the consultation papers, would have:

- "higher thresholds for medicines that tackle diseases where there is greater "burden of illness": the more the medicine is focused on diseases with unmet need or which are particularly severe, the higher the threshold;
- higher thresholds for medicines that can demonstrate greater therapeutic innovation and improvements compared with other products; and
- higher thresholds for medicines that can demonstrate wider societal benefits."[302]

145. This sounds promising to us and could address many of the concerns about reimbursement raised, but it is too soon to make an assessment of the proposed plans. It also remains unclear whether value-based pricing, which applies to "branded medicines", will extend to all forms of regenerative medicine.[303] The London Regenerative Medicine Network stated that, depending on its final form, value-based pricing seemed likely to work as beneficially for cell therapies and regenerative medicines as for other new medicines as it can take account of additional value gains and wider health benefits, which the traditional "QALY" approach may have missed. The Government are confident that it will "provide a broader assessment of a medicine's value, taking into account factors such as unmet need and wider societal benefits".[304] The MRC and the TSB cautioned that: "the challenging UK reimbursement environment may drive regenerative medicine product

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[300] Regener8, Professor Rimmer, Professor MacNeil, Professor Haycock.

[301] UCB Pharma.

[302] DH: *A new value-based approach to the pricing of branded medicines*, 2010.

[303] *Ibid.*

[304] Government.

development outside the UK".[305] This reinforces that there is no room for error when it comes to reimbursement.

146. **Value-based pricing may resolve the difficulties which companies with high up-front cost treatments that provide long-term savings currently experience when seeking approval, but the devil will be in the detail of the system. We recommend that the Department of Health commit to an evaluation of value-based pricing after the first year of operation. We have no doubt that other Parliamentary committees, such as the House of Commons Health Committee, will keep a watching brief on this area—this is vital as appropriate reimbursement is of great importance to the health of both this emerging industry and the established pharmaceutical industry.**

147. Dr Schopen, Vice-President for Global Commercial Operations, Tigenix and others raised the issue of comparability.[306] NICE evaluate proposed reimbursement levels against a benchmark spelled out by the submitter: either the cost of another ATMP, or a treatment with similar outcomes. Where one or neither of these exist, it is difficult for companies to show comparability and so demonstrate value for money.[307] The VALUE project discussed difficulties identifying a suitable comparator when evaluating the cost-effectiveness of Apligraf. NICE, allegedly, failed to recognise the cost savings of healing a chronic wound quickly and effectively.[308]

148. **NICE must ensure that it gives guidance to companies developing novel treatments on how to demonstrate comparability. One mechanism for this may be the seminars, developed as part of the life science strategy, which aim to show innovators how to demonstrate value. NICE's processes must allow for difficulties demonstrating comparability for innovative treatments.**

149. Private health insurers may be quicker to adopt new therapies than the NHS because they have developed their own procedures for evaluating the cost-benefit of offering a certain treatment. For example, Bupa have developed an algorithm to do this. Bupa offers ChondroCelect to private patients in the UK whereas the public healthcare system is still evaluating it.[309] Belgium adopted this therapy in a very timely manner and agreed reimbursement rates with Tigenix (the company who produce it) within six months. We consider it desirable that NICE learn lessons from other countries and the private healthcare sector about how they evaluate regenerative treatments.

150. Many witnesses were optimistic that adaptive licensing—an approach to enable earlier access to a medicine on a conditional approval basis, with further data on efficacy and safety collected following such an approval—would help the industry's specific issues.[310] Japan is already considering a revised system of fast-track approval for stem cell therapies.[311] Similarly, the

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[305] *Op. cit.* Strategy for Regenerative Medicine.

[306] Q 216.

[307] Cell Therapy Catapult.

[308] TSB: *VALUE project final report*, 2012.

[309] Bupa, Q 219.

[310] ARMC, Oxford-UCL Centre for the Advancement Sustainable Medical Innovation, Q 75, Q 79, QQ 87–88, RCUK.

[311] Cyranoski, D: 'Japan to offer fast-track approval path for stem cell therapies' *Nature Medicine*, 2013.

President of the United States commissioned his Council for Advisers on Science and Technology to produce a report on supporting innovation in drug discovery, development and evaluation.[312] Reimbursement was described by Dr Paul Kemp as the "missing key" to regenerative medicine business models[313], and some witnesses argued that staggered reimbursement[314]—which could be one outcome of adaptive licensing, some form of dual track approval system or early access schemes—would encourage investors to invest earlier as it provided a clearer and more immediate potential return on investment. **The UK Government must ensure that its pricing and reimbursement systems are fit for purpose otherwise companies will base themselves in other countries.**

Risks of regenerative medicine tourism

151. Unproven, poorly regulated treatments have the potential to cause serious harm to patients. Furthermore, they could cause serious harm to the regenerative medicine industry as high-profile cases could damage public and investor confidence in it.[315] Examples of serious accidents, which could have been prevented by more robust regulation, include one that occurred at the German XCell-Center; the Centre was closed following the death of a child who had received stem cells injected directly into the brain.[316] An Israeli boy underwent stem cell therapy in Russia to treat spinal cord injury and ended up with multiple tumours in his spine.[317] The Italian Government recently authorised the use of an unproven treatment using mesenchymal stem cells on a group of patients, a decision roundly condemned by prominent UK academics.[318] The Alliance for Regenerative Medicine points to multiple instances of businesses offering commercial stem cell therapies, for which they charge large sums of money, which have never been clinically validated and are unproven.[319] Where patients are suffering from incurable diseases, we can understand the attraction of "miracle cure" claims of treatments. But the UK has robust safety and efficacy standards for a reason: to protect patients. Edinburgh BioQuarter suggest that the UK is home to companies offering to collect and store adult stem cells, at a price, in the hope that one day they might be clinically useful to an individual, and that this service "overplays the current state of knowledge and preys upon the worried well".[320]

152. **In an era when access to information about these offerings, and ability to travel, is so great, the UK Government must take action to protect its citizens from rogue therapies at home and abroad. The primary tool to combat this is information. Patients must have access to information about the safety and efficacy of these types of treatments. The Government recommend that patients always consult their physicians about the possibility of travelling for**

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312 Appendix 5.

313 Q 87.

314 Q 82, QQ 87–88.

315 Edinburgh BioQuarter, GE Healthcare, OSCI, Pfizer.

316 Edinburgh BioQuarter.

317 Parkinson's UK.

318 EuroStemCell: *Scientists raise alarm as Italian Government rules on unproven stem cell therapy*, 2013.

319 Alliance for Regenerative Medicine.

320 Edinburgh BioQuarter.

treatment—this is, of course, correct. Furthermore, the NIHR has produced guidance for patients considering travelling abroad for treatment. We recommend that the Foreign and Commonwealth Office (FCO) partner with the Department of Health to develop a website, in the same model as FCO travel advice for countries, which, in the first instance, contains summary assessments of the strength of safety measures in place for innovative therapies abroad. In time, they might develop this further, in partnership with organisations such as the International Society for Stem Cell Research (who have begun work in this area), to identify unproven therapies and those who provide them.

Hospital exemption

153. In Europe, medicinal products that are categorized as ATMPs are regulated under the EU ATMP Regulation. This Regulation requires ATMPs to be granted centralised European marketing authorisation by the European Commission following assessment by the European Medicines Agency (EMA). Under the ATMP Regulation there is an exemption for ATMPs which are prepared either on a non-routine basis and used within the same member state in accordance with a medical prescription for an individual patient ("the hospital exemption"), or to supply ATMPs as unlicensed medicines ("specials") to meet the special clinical needs of an individual patient under the direct responsibility of the clinician where an equivalent licensed product is not available.[321]

154. The BIA, Chris Mason, NHSBTS, Tigenix and the UK Regenerative Medicine Community called for the harmonisation of the interpretation of the hospital exemption to bring innovative, effective and safe therapies to all European patients,[322] because inconsistent interpretation of the Hospital Exemption in member states and routine preparations of treatments under an exemption impedes development. There is less incentive for a company to go through the marketing approval process if their product can be used by this "back door", and this in turn limits the number of patients it is available to.[323] Considerable discontent was expressed about the hospital exemption, in its current form, in a European Commission public consultation on the relevant regulation. Concern was raised about the scope for varied interpretations of "preparations on a non-routine basis".[324]

155. **The current EU ATMP Regulation is unclear. Terminology used such as "preparation on a non-routine basis" leaves too much room for interpretation. There is also uncertainty about whether a hospital exemption is still permissible when a fully validated, centrally approved Advanced Therapy Medicinal Product (ATMP) is available. We recommend that the UK Government, during the review of the ATMP Regulations, make the case at the European Commission level for clarity on these two points in the revised Regulations.**

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321 Regulation (EC) No 1394/2007: *ATMP Regulations*.

322 BIA, Chris Mason, UK Regenerative Medicine Community, Tigenix.

323 Alliance for Advanced Therapies, NHSBTS, Tigenix.

324 European Commission: *Summary of the responses to the public consultation on Regulation (EC) No. 1394/2007 on ATMPs*, 2013.

Harmonisation

156. Regenerative medicine is a global market and, to attract investment and ensure the rapid development of the field, there is a need for greater harmonisation of regulatory standards and requirements across the world. For example, currently cell:device combinations are regulated as ATMPs in the EU but as medical devices in the US, which means each requires different data from clinical trials.[325] There are already initiatives to harmonise regulatory requirements including the International Conference on Harmonisation (ICH), and a European Medicines Agency-Food and Drug Administration (EMA-FDA) joint committee.[326] The Cell Therapy Catapult gave examples of areas where there is not yet harmony: the requirements for non-clinical models and quality requirements (control of starting materials, acceptability of cell lines derived in the UK due to historical concern over BSE/TSE risk, need for full GMP, sterility tests, environmental monitoring in GMP suites and qualified person release).[327] **To realise the full potential of this global industry, and to ensure that the UK is an attractive location for regenerative medicine companies to invest in and to undertake their clinical trials in, the UK Government must take the lead in promoting harmonisation of regulatory requirements.**

157. One area where the UK is already leading the world is the development of standards. A standard is an agreed way of doing something and British Standards Institution (BSI) standards are the distilled wisdom of people with expertise in their subject matter and who know the needs of the organizations they represent. The BSI has published three cell therapy and regenerative medicine publicly available specifications (PAS) which provide guidance to companies operating in this domain.[328] LGC chairs the BSI RGM/1 standards committee, which is a national committee that acts as a forum for stakeholders to identify overlapping and common standardisation interests, with a view to agreeing priority work items for regenerative medicine standards in the UK.[329] The National Institute for Biological Standards and Control plans to launch a new initiative to develop standards and reference materials for cell-based medicines in 2013 which will bring regulators, industry and clinical academics together to discuss the key issues in safe and reproducible delivery of cell-based medicines, with the intention of holding a series of focused meetings to make practical progress in this area.[330] These discussions about standards are promising and the more standards are established and agreed, the more barriers to translation and commercialisation are removed.

Co-ordination and final conclusion

158. Having surveyed this field extensively, and compared UK activities to work in other countries, our overriding concern is that there is currently a lack of co-ordination in the field. There are many piecemeal activities but no single person or organisation is leading and co-ordinating the development of a

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325 UKRMC.

326 HPA.

327 Cell Therapy Catapult.

328 Government.

329 LGC.

330 HPA.

joined-up approach to regenerative medicine. The closing of the Stem Cell Networks will not help.[331] There is great hope that the Cell Therapy Catapult will provide this co-ordination and yet the Cell Therapy Catapult must focus its activities to develop phase III investable propositions, by supporting promising clinical research.

159. **Regenerative medicine has the potential to save lives and to help support the UK economy. The UK has a great potential resource in the NHS which could make it an attractive place for investment. But the UK is currently underprepared to realise the full potential of regenerative medicine. The many words which have been spoken about regenerative medicine must translate to action, and quickly. We must not miss out on this opportunity to lead the world in this work.**

160. **Accordingly, we recommend that the Government also appoint the chair of the independent regenerative medicine delivery expert working group as the UK's regenerative medicine champion. This person would foster links between the many stakeholders (including, but not limited to, investors, basic scientists, clinicians, manufacturing experts, delivery networks, regulators), drive forward the regenerative medicine agenda and represent the UK's interests on the global stage. This champion should have a budget and support from a Government office.**

[331] Regener8, Scottish Government.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

The value and importance of regenerative medicine

161. The weight of evidence to our inquiry was that regenerative medicine has the potential to deliver new, innovative therapies, or even cures, where conventional approaches do not provide adequate solutions (paragraph 19).

162. Regenerative medicine has the potential to cure or provide more effective treatments for a number of chronic diseases, which would be of major benefit to the UK public purse given rising expenditure on healthcare associated with chronic disease management and related indirect costs (paragraph 21).

Uncertainty

163. For a regenerative medicine industry to flourish in the UK steps must be taken to clear the path "from bench to bedside" as part of building investor confidence (paragraph 56).

Regulatory environment

164. A reputation for proportionate regulation is important for the UK both in terms of inspiring confidence of potential patients and encouraging investment (paragraph 57).

165. The twin challenges of improving perceptions of the regulatory system and streamlining it are so great that both immediate and long-term action are needed (paragraph 70).

166. We recommend that, as a matter of urgency, the HRA establish a regulatory advice service. This would build on the expertise of the Office for Life Science toolkit, the newly established MHRA Innovation Office and the experience of regulators. Researchers and companies require more than a web-based service. They should be assigned a single point of contact to support them in navigating the regulatory system, directing their queries to others where appropriate, but retaining ownership and oversight of the advice process. Such a service would be of short-term value to this (and the broad healthcare) sector until such a time as the regulatory environment is rationalised (paragraph 71). **(Recommendation 1)**

167. The Health Research Authority (HRA) has made some positive first steps and it must now demonstrate its effectiveness by streamlining the macro regulatory environment. We recommend that the HRA commission an independent advisory group, made up of national and international experts in regulation, to develop a designed-for-purpose regulatory system. The UK rightly has a good reputation for its robust regulatory system; it is vital that this reputation be maintained. Similarly, we acknowledge there is significant value in the expertise of some regulators. But patients, business and the taxpayer deserve a modern, designed-for-purpose, efficient regulatory system rather than one that has evolved in a haphazard, piecemeal way. An independent advisory group supporting the HRA will give it the necessary support to focus and clarify the functions of regulators. This group should give special consideration to reducing the overall number of regulators. We recommend that the group make proposals 18 months from its establishment. We will revisit this aspect of the inquiry to ensure that

progress has been made. The HRA must simplify the regulatory route so that the development of regenerative medicine, and other innovative therapies, is not hindered (paragraph 73). (**Recommendation 2**)

Clinical trials

168. The Government must therefore identify how the UK can become a more attractive venue for clinical trials as, currently, the number of trials does not reflect its significant benefits (paragraph 76).

169. The evidence received conveys considerable demand for greater support in the design and set-up of clinical trials. There is expertise in clinical trial design and set-up in the NIHR CRN, its BRUs and BRCs, and amongst academics exploring innovative trial design. There is also considerable expertise in NICE which could help inform trial design to ensure outcomes meet its evaluation requirements, the MHRA which already offers an advisory service, and amongst manufacturing experts from both industry and academia, who could provide advice to ensure that therapies are developed in a scalable fashion. Each of these groups would benefit from greater two-way interaction: to inform regulation and guidance making, and product development and trial design (paragraph 88).

170. Consequently, we recommend that the NIHR establish a regenerative medicine stream of its clinical research network. Such a move would support researchers in addressing the specific needs of regenerative medicine clinical trial design, help overcome difficulties in identifying patients and ensure that doctors interested in such trials could be easily identified. The network could also facilitate dialogue with regulators on future regulatory needs and issues encountered with regulation. The regenerative medicine stream of the network should employ a hub and spoke model for allogeneic treatments, whereby it has one or two co-ordinating centres and regional operations. Given the need for clinical trials of a certain size, this network should span across the UK and build on existing developed infrastructures like NHS Research Scotland (paragraph 89). (**Recommendation 3**)

171. The NHS would be a very attractive location for trials with these improvements, and there are reciprocal benefits to the UK in the form of inward investment, gaining further experience, potential for early market adoption and thus availability to NHS patients. The Government must ensure that this opportunity is not missed (paragraph 90).

172. Therefore, we recommend increased dialogue between regulators and researchers in the form of regular regenerative medicine workshops, and that the MHRA produce a series of guidance notes (to be updated bi-annually) setting out clinical trial endpoint requirements for regenerative medicine, in consultation with the industry and academic researchers. UK regulators should learn from the example of FDA-CIRM workshops and similar efforts in other countries (paragraph 91). (**Recommendation 4**)

Scale-up and manufacturing

173. We recommend that the phase II disease teams of the TSB regenerative medicine platform, and other regenerative medicine funding programmes, specifically require researchers to involve manufacturing and scale-up experts in their development process to ensure that translational work is scalable and

therefore deliverable to a large number of patients (where the disease area requires this) (paragraph 98). (**Recommendation 5**)

174. Recognising the importance of capacity to deliver therapies at scale, both for trials and wider patients populations, and the fast-moving pace of the manufacturing and scale-up field, we recommend that the TSB and EPSRC undertake an annual stock-take of regenerative medicine manufacturing capacity and make recommendations to BIS about future needs, with the first survey informing the Government's review of infrastructure investment. The Cell Therapy Catapult has begun work on such a survey so we recommend that this work is taken as a starting point. BIS must then act to ensure that appropriate infrastructure investment is made to support the field. At the very least, investment should be made in facilities to support the scale-up of treatments in mid to late stage clinical development. Money for this, and other recommendations, should be found by the re-prioritisation of budgets and innovative funding methods (paragraph 100). (**Recommendation 6**)

175. UK capacity to manufacture at scale could be attractive to companies considering investing in or expanding operations to this country. We recommend that the UKTI Life Science Investment Organisation use the results of this survey to advise foreign companies on UK capacity to manufacture regenerative products (paragraph 101). (**Recommendation 7**)

176. We recommend that the NHS develop a training programme for technical staff to support the development of cell therapies and other regenerative therapies at scale (paragraph 103). (**Recommendation 8**)

177. We recommend that the MHRA canvas views from industry on the suitability of current GMP requirements and, if there is significant discontent, take these problems to the European Commission to seek agreement on overcoming them through amendments to the GMP Directive and associated guidance (paragraph 105). (**Recommendation 9**)

Delivery

178. It is clear that the national blood and transfusion services have the logistical capability to collect, produce, store and transport components of regenerative treatments. However, we were concerned to see that the NHS is less ready for the provision of regenerative therapies (paragraph 108).

179. Investors need to see a clear pathway from development to delivery in the NHS if they are to have the confidence to invest in regenerative medicine. It is not sufficient to rely on trail blazing therapies to forge pathways to clinical delivery. The NHS must shift from reacting to regenerative medicine to a state of preparedness to deliver new and innovative treatments (paragraph 109).

180. We recommend that the Department of Health establish a regenerative medicine expert working group to develop an NHS regenerative medicine delivery readiness strategy and action plan by December 2014. This group should report to the Secretary of State for Health directly and have the support of a high-profile, independent chair. The group must also contain NHS England officials, NHSBTS and devolved blood and transfusion services, regulators, researchers and industry representatives. We consider the role of the chair further in Chapter 5 (paragraph 110). (**Recommendation 10**)

Business models, venture capital and the funding gap

181. Investment could be stimulated by reducing associated risk (paragraph 115).

182. The Cell Therapy Catapult was only set up in May 2012 and we recognise that there is significant potential in the venture. However, we are concerned that it is seeking to achieve too much, too quickly, given the level of funding. We recommend that the TSB and Cell Therapy Catapult prioritise its activities to enable the Cell Therapy Catapult to focus on taking high growth potential projects through clinical trial to be phase III trial ready and developing links with the regenerative medicine community (paragraph 124). (**Recommendation 11**)

183. Furthermore, given the large number of potential funders, the TSB, research councils and NIHR should produce an online funding guide, regularly updated, to help researchers and SMEs know where they should apply at each stage of research and development in regenerative medicine (paragraph 125). (**Recommendation 12**)

184. There is insufficient TRL 6–8 funding available to support this fast-developing field. It would be unrealistic to depend exclusively upon additional funding coming from venture capitalist or "big pharma" investment. A mechanism must be found to fill this gap. Therefore, we recommend that the ESRC and the TSB commission an evaluation of innovative funding models, which spread risk and most likely will contain a degree of government matched funding or be underpinned by government guarantees, and recommend how additional funding could be provided for late stage clinical development in this field. The Government have said that this field has enormous potential and that they will support it. They must "put their money where their mouth is"; BIS and Her Majesty's Treasury must adopt the policy recommendation of the ESRC and TSB study (paragraph 127). (**Recommendation 13**)

Intellectual Property

185. There is significant commercial potential in the enabling tools and technologies, and commercial know-how associated with regenerative medicine—the regenerative medicine community must ensure that investors are aware of this potential. UK Trade and Investment has a specific programme to attract inward investment in regenerative medicine and so we recommend that they support the field by informing investors about the economic potential of investment in the field (paragraph 133). (**Recommendation 14**)

186. There is significant scope for patenting within the field and much of the negative publicity around the Brüstle ruling seems to have overstated the implications (paragraph 135).

187. Concern over the cost of patenting, the sufficiency of support available for innovators and questions about the ability of universities to recognise the potential in regenerative medicine patents lead us to conclude that the TSB should set-up a time-limited support fund for regenerative medicine patents. This fund should be open to university researchers who wish to pursue patents beyond the first stage, so that potential income from regenerative medicine products is not lost. Such a fund would help foster this fledgling industry and be a helpful tool until university patent offices are better placed

to deal with the potential value of these products (paragraph 137). (**Recommendation 15**)

Evaluation and the pricing of treatments

188. We consider the NICE model for evaluating innovative treatments and cures to be inappropriate. It must devise suitable models that give appropriate consideration to the long-term savings sometimes offered by high up-front cost treatments (paragraph 142). (**Recommendation 16**)

189. The first few regenerative medicine products will invariably be more expensive than products further down the line. Other countries, such as France, have evaluation and reimbursement systems which provide for this. NICE must ensure that its evaluation process recognises the higher initial costs of innovative treatments, without compromising its goal of assessing value-for-money in healthcare. Part of its value-for-money consideration should be that early investment in this field could unlock other treatments with significant economic impact, both in terms of savings to the health system and increased potential work productivity (paragraph 143). (**Recommendation 17**)

190. Value-based pricing may resolve the difficulties which companies with high up-front cost treatments that provide long-term savings currently experience when seeking approval, but the devil will be in the detail of the system. We recommend that the Department of Health commit to an evaluation of value-based pricing after the first year of operation. We have no doubt that other Parliamentary committees, such as the House of Commons Health Committee, will keep a watching brief on this area—this is vital as appropriate reimbursement is of great importance to the health of both this emerging industry and the established pharmaceutical industry (paragraph 146). (**Recommendation 18**)

191. NICE must ensure that it gives guidance to companies developing novel treatments on how to demonstrate comparability. One mechanism for this may be the seminars, developed as part of the life science strategy, which aim to show innovators how to demonstrate value. NICE's processes must allow for difficulties in demonstrating comparability for innovative treatments (paragraph 148). (**Recommendation 19**)

192. The UK Government must ensure that its pricing and reimbursement systems are fit for purpose otherwise companies will base themselves in other countries (paragraph 150). (**Recommendation 20**)

Risks of regenerative medicine tourism

193. In an era when access to information about these offerings, and ability to travel, is so great, the UK Government must take action to protect its citizens from rogue therapies at home and abroad. The primary tool to combat this is information. Patients must have access to information about the safety and efficacy of these types of treatments. The Government recommend that patients always consult their physicians about the possibility of travelling for treatment—this is, of course, correct. Furthermore, the NIHR has produced guidance for patients considering travelling abroad for treatment. We recommend that the Foreign and Commonwealth Office (FCO) partner with the Department of Health to develop a website, in the same model as FCO travel advice for countries, which, in the first instance,

contains summary assessments of the strength of safety measures in place for innovative therapies abroad. In time, they might develop this further, in partnership with organisations such as the International Society for Stem Cell Research (who have begun work in this area), to identify unproven therapies and those who provide them (paragraph 152). (**Recommendation 21**)

Hospital exemption

194. The current EU ATMP Regulation is unclear. Terminology used such as "preparation on a non-routine basis" leaves too much room for interpretation. There is also uncertainty about whether a hospital exemption is still permissible when a fully validated, centrally approved Advanced Therapy Medicinal Product (ATMP) is available. We recommend that the UK Government, during the review of the ATMP Regulations, make the case at the European Commission level for clarity on these two points in the revised Regulations (paragraph 155). (**Recommendation 22)**

Harmonisation

195. To realise the full potential of this global industry, and to ensure the UK is an attractive location for regenerative medicine companies to invest in and to undertake their clinical trials in, the UK Government must take the lead in promoting harmonisation of regulatory requirements (paragraph 156). (**Recommendation 23)**

Co-ordination and final conclusion

196. Regenerative medicine has the potential to save lives and to help support the UK economy. The UK has a great potential resource in the NHS which could make it an attractive place for investment. But the UK is currently underprepared to realise the full potential of regenerative medicine. The many words which have been spoken about regenerative medicine must translate to action, and quickly. We must not miss out on this opportunity to lead the world in this work (paragraph 159).

197. Accordingly, we recommend that the Government also appoint the chair of the independent regenerative medicine delivery expert working group as the UK's regenerative medicine champion. This person would foster links between the many stakeholders (including, but not limited to, investors, basic scientists, clinicians, manufacturing experts, delivery networks, regulators), drive forward the regenerative medicine agenda and represent the UK's interests on the global stage. This champion should have a budget and support from a Government office (paragraph 160). (**Recommendation 24**)

APPENDIX 1: LIST OF MEMBERS AND DECLARATIONS OF INTEREST

Members:

† Lord Broers
† Lord Cunningham of Felling
Lord Dixon-Smith
Baroness Hilton of Eggardon
Lord Krebs (Chairman)
Baroness Manningham-Buller
Lord O'Neill of Clackmannan
Lord Patel
Baroness Perry of Southwark
Lord Peston
Lord Rees of Ludlow
Earl of Selborne
Baroness Sharp of Guildford
† Lord Turnberg
Lord Wade of Chorlton
Lord Willis of Knaresborough
Lord Winston

† Co-opted Member

Declarations of Interest

Lord Broers
Fellow, Royal Society
Fellow, Royal Academy of Engineering
Chairman, Bio-Nano Centre Ltd
Chairman, Diamond Light Source Ltd

Lord Cunningham of Felling
None

Lord Dixon-Smith
None

Baroness Hilton of Eggardon
None

Lord Krebs
Principal, Jesus College, Oxford
Chairman, Oxford Risk Ltd
Fellow, Royal Society
Fellow, Academy of Medical Sciences
Trustee, Nuffield Foundation

Baroness Manningham-Buller
Governor, the Wellcome Trust
Chair, Council and Court of Imperial College of Science and Technology
Director, Wellcome Trust Sanger Institute

Lord O'Neill of Clackmannan
None

Lord Patel
Chancellor, Dundee University
Fellow, Academy of Medical Sciences
Fellow, Royal Society of Edinburgh
Member, Medical Research Council (October 2012)
Chairman, Cancer Research UK Centre, Dundee University
Former Chairman, UK Stem Cell Network
Former Chairman, Stem Cell Oversight Committee and Stem Cell Bank

Baroness Perry of Southwark
Former Chairman, Clinical Governance Committee for the Addenbooke's NHS Trust and the University of Cambridge School of Clinical Medicine
Patron, Alzheimer's Research Trust

Lord Peston
None

Lord Rees of Ludlow
Fellow, Royal Society
Honorary Fellow, Academy of Medical Sciences

Earl of Selborne
Fellow, Royal Society
Fellow, Society of Biology

Baroness Sharp of Guildford
None

Lord Turnberg
Trustee, Wolfson Foundation
Scientific adviser, Association of Medical Research Charities (AMRC)
Fellow, Academy of Medical Sciences
Chair, All-Party Parliamentary Group on Medical Research

Lord Wade of Chorlton
None

Lord Willis of Knaresborough
Chair, Association of Medical Research Charities (AMRC)
Chair, Stem Cell Bank Steering Committee

Lord Winston
Member, EPSRC
Fellow, Academy Medical Sciences
Fellow, Royal Academy of Engineering
Professor, Imperial College
Chairman, Genesis Research Trust (stem cell research)
Member, UK Stem Cell Foundation Trust
Fellow, Royal College of Physicians
Fellow, Royal College of Obstetricians and Gynaecologists
Fellow, Society of Biology
Home Office Animal Research Licence Holder

A full list of Members' interests can be found in the Register of Lords Interests: http://www.publications.parliament.uk/pa/ld/ldreg.htm

Professor Fiona Watt acted as Specialist Adviser for this inquiry and declared the following relevant interests:

Member, European Molecular Biology Organization, 1999
Fellow, Academy of Medical Sciences, 2000

Fellow, Royal Society, 2003
Honorary Foreign Member, American Academy of Arts and Sciences, 2008
Member, Academia Europaea, 2009
Board of Directors, International Society for Stem Cell Research (ISSCR), 2002–2013
Scientific Advisory Board, Canadian Stem Cell Network, 2006–
Scientific Advisory Board, Harvard Stem Cell Institute, 2006–
North East England Stem Cell Institute (NESCI) Scientific Advisory Board, 2008–
Scientific Advisory Board, Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University, 2008–
Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA) Scientific Advisory Board, 2008–
Wellcome Trust Investigator Awards, expert review group, Cell and Developmental Biology, 2011–
Member, Steering Committee for the UK Stem Cell Bank, 2011–
Scientific Advisory Board, Ontario-wide Stem Cell initiative and Centre for Commercialization in Regenerative Medicine, 2011–
Contributor, New Strategy for UK Regenerative Medicine, published 2012
Scientific Advisory Board, Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), 2012–
Scientific Advisory Board, Institute of Molecular Medicine, Lisbon, 2013
Judging panel member, L'Oréal-UNESCO UK and Ireland National Fellowships For Women in Science, 2013
Jury member, New York Stem Cell Foundation-Robertson Stem Cell Investigator Awards Program, 2013
Scientific Advisory Board, California Institute for Regenerative Medicine (CIRM), 2013–
Scientific Advisory Council, National Centre for Cell Science, Pune, India, 2013–
Advisory Board, Scientists in International Contexts (PI: EH Ecklund), 2013–
Editorial Board, Current Opinion in Cell Biology, 1994–
Member, 'Faculty of 1000' online review service (section head, stem cells and regeneration), 2001–
Editorial Board, Seminars in Cell and Developmental Biology, 2005–
Editorial Board, Current Stem Cell Research and Therapy, 2005–
Editorial Advisory Board, Expert Review of Dermatology, 2005–
Editorial Board, Cell Stem Cell, 2006–
Editorial Board, StemBook, 2008–
Editorial Board, Journal of Molecular Cell Biology, 2009–
Editorial Advisory Board, EMBO Molecular Medicine, 2009–
Deputy Editor, eLife, 2011–
Editorial Board, Stem Cell Reports, 2012–
Recent Grant Support
Wellcome Trust, MRC, European Union and CRUK for stem cell research;
Royal Society Wolfson Research Merit Award;
Wellcome Trust/MRC Strategic Award (PI with Richard Durbin) UK human iPS cell initiative;
Co-PI, UK Regenerative Medicine Hub for Engineering and Exploiting the Stem Cell Niche

APPENDIX 2: LIST OF WITNESSES

Evidence is published online at www.parliament.uk/hlscience and available for inspection at the Parliamentary Archives (020 7219 5314)

Evidence received by the Committee is listed below in chronological order of oral evidence session and in alphabetical order. Those witnesses marked with * gave both oral evidence and written evidence. Those marked with ** gave oral evidence and did not submit any written evidence. All other witnesses submitted written evidence only.

Oral evidence in chronological order

**	QQ 1–20	Professor Charles ffrench-Constant, Professor of Multiple Sclerosis Research; Director; Theme leader Neural Differentiation and Tissue Repair, Centre for Regenerative Medicine, University of Edinburgh
**		Dr Ludovic Vallier, Stem Cell Institute, University of Cambridge
*		Professor Steven Sacks, Professor of Nephrology; Head of the Division of Transplantation Immunology and Mucosal Biology and Director of the Medical Research Council (MRC) Centre for Transplantation, King's College London
*		Professor Michael Linden, Professor of Virology, and Director of the University College London (UCL) Gene Therapy Consortium, King's College London
**	QQ 21–41	Professor Peng Tee Khaw, Moorfield's Eye Hospital, University College London (UCL)
*		Professor Roger Barker, University of Cambridge
**		Professor Michael Schneider, Imperial College London
*	QQ 42–63	Professor Dame Sally Davies, Chief Medical Officer and Chief Scientific Adviser, Department of Health (DH)
*		Medical Research Council (MRC)
*		Wellcome Trust
*		British Heart Foundation (BHF)
*	QQ 64–80	Professor Robin Ali, Professor of Human Molecular Genetics, University College London (UCL)
*		Professor Graham Lord, Professor of Medicine and Head of Department of Experimental Immunobiology, and Director of NIHR Biomedical Research Centre, Guy's and St. Thomas' NHS, King's College London
**		Sir John Tooke, Vice-Provost (Health), Head of the Medical School and Academic Director of the Academic Health Science Centre, University College London (UCL)

*	QQ 81–127	Dr Paul Kemp, Intercytex Ltd
*		Professor Anthony Hollander, Head of the School of Cellular and Molecular Medicine at the University of Bristol, and Chief Scientific Officer, Azellon
**		Smith & Nephew
*	QQ 128–169	Dr Ruth McKernon, Pfizer
*		Professor Chris Mason, Professor of Regenerative Medicine Bioprocessing, University College London (UCL)
*		Michael Hunt, ReNeuron
**	QQ 170–195	Dr Navid Malik, Head of Life Sciences Research, Cenkos Security
**		Dr Nigel Pitchford, Managing Director of Healthcare, Imperial Innovations
**		Dr Steven Dyson, Partner, Healthcare team, Apax Partners
**	QQ 196–213	Intellectual Property Office (IPO)
*		Lawford Davies Denoon
**		Professor Peter Andrews, Arthur Jackson Professor of Biomedical Science and Co-Director of the Centre for Stem Cell Biology, University of Sheffield
*	QQ 214–243	National Institute for Health and Clinical Excellence (NICE)[332]
*		TiGenix NV
*		Bupa Health and Wellbeing UK
**	QQ 244–266	Aidan Courtney, Roslin Cells Limited
*		Scottish National Blood Transfusion Service (SNBTS)
*		UK Stem Cell Bank
*	QQ 267–282	Professor David Williams, Engineering and Physical Science Research Council (EPSRC) Centre for Innovative Manufacturing in Regenerative Medicine
*		Keith Thompson, Cell Therapy Catapult Centre
**		TAP Biosystems
*	QQ 283–294	Keith Thompson, Cell Therapy Catapult Centre
*		Technology Strategy Board (TSB)
*	QQ 295–316	Medical and Healthcare products Regulation Agency (MHRA)

[332] NICE's name was changed from the National Institute for Health and Clinical Excellence to the National Institute for Health and Care Excellence on 1 April 2013. Its evidence was submitted in its former name and so is recorded as such. Recommendations we make to it use its current name.

**		European Medicine Agency
*		Health Research Authority
*	QQ 317–329	Human Fertilisation and Embryology Authority (HFEA)
*		Human Tissue Authority (HTA)
**	QQ 330–342	Genetic Alliance UK
*		Consulting on Advanced Biologicals (CAB) Ltd
*		LGC Limited
*	QQ 343–356	Professor Sir Bruce Keogh, NHS Medical Director
**		Professor Richard Lilford, University of Birmingham
*		NHS England
*	QQ 357–366	Rt Hon Earl Howe, Parliamentary Under-Secretary of State and Government Spokesperson, Department of Health (DH)
*		Rt Hon David Willetts MP, Minister of State for Science and Universities, Department of Business, Innovation and Skills (BIS)

Alphabetical list of all witnesses

	Alliance for Advanced Therapies (AAT)
	Alliance for Regenerative Medicine (ARM)
**	Professor Peter Andrews, University of Sheffield
	Anscombe Bioethics Centre
	Anthony Nolan
	Applied regenerative science group, University College London (UCL)
	Arthritis Research UK
	Association of British Neurologists (ABN)
	Association of British Pharmaceutical Industry (ABPI)
	Association of Medical Research Charities (AMRC)
*	Azellon Cell Therapeutics Ltd
	BioIndustry Association (BIA)
*	British Heart Foundation (BHF)
	British Society for Blood and Marrow Transplantation (BSBMT)
	British Society for Haematology (BSH)
	British Society for Oral & Dental Research (BSODR)
	Professor Robert Brown, University College London (UCL)
*	Bupa
	California Institute for Regenerative Medicine (CIRM)
	Cambridge National Institute for Health Research

CASMI (Oxford-UCL Centre for the Advancement of Sustainable Medical Innovation)

* Cell Therapy Catapult Limited

* Consulting on Advanced Biologicals (CAB) Ltd

Trevor Cook, partner at Bird & Bird

Professor Charles Craddock, University Hospital Birmingham

Cytori Therapeutics

Professor Dame Kay Davies, Dr Lee's Professor of Anatomy, University of Oxford

Professor Stephen Davies, University of Oxford

* Department of Business Innovation and Skills (BIS)

* Department of Health (DH)

Professor Stephen Dunnett, Cardiff University

** Dr Steven Dyson, Apax Partners

Edinburgh BioQuarter

Engineering and Physical Sciences Research Council (EPSRC)

* Engineering and Physical Science Research Council (EPSRC) Centre for Innovative Manufacturing in Regenerative Medicine

** European Medicine Agency

** Professor Charles ffrench-Constant, University of Edinburgh

GE Healthcare

* Genethon (France) Gene Therapy GMP Facility

** Genetic Alliance UK

Iva Hauptmannova, Royal National Orthopaedic Hospital (RNOH) NHS Trust

Professor John Haycock, University of Sheffield

Health Protection Agency (HPA)

* Health Research Authority (HRA)

HealthTech and Medicines Knowledge Transfer Network (Health KTN)

* Headquarters Surgeon General, Ministry of Defence (MOD)

Julian Hitchcock (Counsel, Lawford Davies Denoon)

* Professor Anthony Hollander, University of Bristol and Azellon

* Human Fertilisation and Embryology Authority (HFEA)

* Human Tissue Authority (HTA)

** Intellectual Property Office (IPO)

JACIE (Joint Accreditation Committee-ISCT & EBMT)

Professor William James, University of Oxford

* Paul Kemp PhD

** Professor Peng Tee Khaw, University College London (UCL)
* King's College London (KCL)
King's Health Partners (KHP)
Korea Health Industry Development Industry (KHIDI)
* Lawford Davies Denoon (LDD)
Leukaemia & Lymphoma Research (LLR)
* LGC Limited
Life Science Investment Organisation of UK Trade and Investment
** Professor Richard Lilford, University of Birmingham
* Professor Michael Linden, King's College London (KCL)
London Regenerative Medicine Network (LRMN)
Professor Sheila MacNeil, University of Sheffield
** Dr Navid Malik, Cenkos Security
* Professor Chris Mason, University College London (UCL)
* Medical Research Council (MRC)
Medical Technologies Innovation Knowledge Centre, University of Leeds
* Medicines and Healthcare products Regulatory Agency (MHRA)
Miltenyi Biotec Ltd
* National Institute for Health and Clinical Excellence (NICE)[333]
National Institute for Social Care and Health Research (NISCHR)
* NHS Blood and Transplant (NHSBT)
* NHS England
* NHS Health Research Authority
Nutech Mediworld
Oxford Stem Cell Institute (OSCI)
* Parkinson's UK
* Pfizer
** Dr Nigel Pitchford, Imperial Innovations
Dr Mahendra Rao, National Institutes of Health
* Regener8
* ReNeuron
* Research Councils UK (RCUK)
Professor Stephen Rimmer, University of Sheffield
** Roslin Cells Limited

[333] NICE's name was changed from the National Institute for Health and Clinical Excellence to the National Institute for Health and Care Excellence on 1 April 2013. Its evidence was submitted in its former name and so is recorded as such. Recommendations we make to it use its current name.

Professor Anne Rosser, Cardiff University

Royal College of Pathologists (RCPath)

Royal Society of Chemistry (RSC)

Dr Angela Russell, University of Oxford

* Professor Steven Sacks, King's College London (KCL)

Chiaki Sato, University of Tokyo

** Professor Michael Schneider, Imperial College London

Scottish Enterprise

Scottish Government—Alex Neil MSP Cabinet Secretary for Health and Wellbeing

* Scottish National Blood Transfusion Service (SNBTS)

Shire

** Smith & Nephew

Dr John Snowden, Sheffield Teaching Hospitals

** TAP Biosystems

* Technology Strategy Board (TSB)

* TiGenix NV

Tissue Regenix Group plc

** Sir John Tooke, University College London (UCL)

UCB Pharma Ltd

UCL Institutes of Child Health and Women's Health

UK Regenerative Medicine Community

* UK Stem Cell Bank

UK Stem Cell Foundation

University of Manchester

** Dr Ludovic Vallier, University of Cambridge

Professor Andrew Webster, Science and Technology Studies Unit (SATSU) University of York

* Wellcome Trust

Wellcome Trust Sanger Institute

Welsh Government

Dr Robert Westwood, ex Pharma & Biotech Industry

Dr Graham Wynne, University of Oxford

APPENDIX 3: CALL FOR EVIDENCE

26 July 2012

The House of Lords Science and Technology Committee, chaired by Lord Krebs, is conducting an inquiry into regenerative medicine. The Committee will be looking, in particular, at whether the UK is in a position to facilitate the translation of knowledge from world-leading research to treatments and to benefit from the commercial opportunities that they present. It also seeks to explore how realistic some of the reported claims of regenerative treatments and therapies are, both in the UK and internationally.

Scope

The term "regenerative medicine" is used to refer to any methods to replace or regenerate human cells, tissues or organs in order to restore or establish normal function. This includes cell therapies, tissue engineering, gene therapy and biomedical engineering techniques, as well as the more traditional therapies of pharmaceuticals, biologics and devices. Examples of such treatments are the transplantation of a new trachea grown using the patient's own stem cells and the use of a hormone (Erythropoietin) to promote red blood cell production. The inquiry will also extend to cell therapies that have applications in other areas of medicine, for example, the use of cell therapies to control immune responses to conditions such as paediatric steroid resistant GvHD,[334] or the use of stem cells for drug screening.

The UK is a world leader in many areas within the field of regenerative medicine, particularly the platform technology cell therapies. Foresight's Technology and Innovation Futures report states that regenerative medicine could be a driver of growth for the pharmaceutical sector if regulatory, financial and translational research challenges can be overcome.[335] Regenerative medicine has the potential not only to lead to significant improvements in the treatment of chronic diseases (such as diabetes and certain kinds of blindness) but also to generate economic benefits for the companies that develop therapies and related infrastructure (such as manufacturing equipment). The deadline for written evidence submissions is Thursday, 20 September 2012.

Questions:

The Committee invites submissions on the following points, with practical examples where possible (please only answer the questions of relevance to you):

The research base

(1) How does the UK rank internationally in the scientific field of regenerative medicine?

(2) Where does the UK have strengths and weaknesses in the field?

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[334] Graft versus Host Disease, a common disease amongst transplant or tissue graft patients where the hosts immune system attacks the transplanted cells.

[335] See: http://www.bis.gov.uk/assets/bispartners/foresight/docs/general-publications/10–1252-technology-and-innovation-futures.

(3) Who are the major funders of research in the field of regenerative medicine? What funding is available to support this research?

Application of the science

(4) Is the science being translated into applications? What are the current applications of the science of regenerative medicine for the treatment of disease in the UK and internationally? Which treatments are available on the NHS or through private healthcare?

(5) What potential does regenerative medicine hold to treat disease in the next 5–10 years? What is the reality versus the headlines about what the science will deliver?

Barriers to translation

(6) Are the actions outlined in the Government's *Strategy for UK Life Sciences*, their report: *Taking Stock of Regenerative Medicine in the UK*, and the Research Council and Technology Strategy Board's *Strategy for UK Regenerative Medicine* sufficient to encourage the safe development of regenerative medicine treatments and to overcome the significant regulatory barriers and challenges to innovation in this inter-disciplinary field? If not, what more action is required? In particular:

  (a) What difficulties are encountered when conducting clinical trials and how could these be overcome?

  (b) What other difficulties are encountered conducting translational research within the NHS and how could these be overcome?

  (c) What barriers are encountered when seeking approval for the use of such treatments on the NHS or through private healthcare?

Barriers to commercialisation

(7) What is the current, and potential future, commercial value of the sector to the UK economy? What is its value to society?

(8) Where there is market failure, are Government providing sufficient incentives in the current commercial environment to attract investment in companies working in this high risk area? If not what more should Government do?

  (a) What role does patenting play in the commercial development of regenerative treatments?

  (b) What business models are most appropriate to support the development of regenerative treatments?

  (c) What are the barriers to securing finance to develop such treatments?

  (d) Are the pricing structures for the use of such treatments on the NHS appropriate to support their development?

  (e) What infrastructure barriers exist within the NHS, or externally, that prevent the scaling-up or commercial development of such treatments?

International comparisons

(9) What could the UK learn from its competitors about supporting the development and commercialisation of regenerative medicines?

(10) How do regulations that govern the development of regenerative medicines in other countries and at an EU level impact on the development of regenerative medicines in the UK?

(11) Is there sufficient harmonisation between the standards and regulations that govern the development of regenerative medicines in different countries?

(12) What risks do UK citizens face when travelling to other countries for regenerative treatments? How do the safeguards in place to protect their interests in the UK compare to those overseas?

APPENDIX 4: SEMINAR HELD AT KING'S COLLEGE LONDON, GUY'S CAMPUS

23 October 2012

Members of the Committee present were Lord Broers, Lord Cunningham of Felling, Lord Dixon-Smith, Baroness Hilton of Eggardon, Lord Krebs (Chairman), Lord O'Neill of Clackmannan, Lord Patel, Earl of Selborne, Baroness Sharp of Guildford, Lord Wade of Chorlton, Lord Willis of Knaresborough and Lord Winston.

A seminar was held at the Guy's Campus of King's College London to provide the Committee with an opportunity to discuss the Regenerative Medicine inquiry with academic experts, industry representatives, funding organisations, and representatives of the Department of Health, the Department for Business, Innovation and Skills (BIS), and the Technology Strategy Board (TSB).

In attendance:

Professor Fiona Watt (Specialist Adviser to the Committee), Chris Atkinson (Clerk), Cerise Burnett-Stuart (Committee Assistant), Rachel Maze (Policy Analyst), and James Tobin (Policy Analyst).

Presentation speakers: Dr Rob Buckle (MRC); Dr Rupert Lewis and Dr David Griffiths-Johnson (Department for Business, Innovation and Skills); Dr Mark Bale (Department of Health); Dr Zahid Latif (Technology Strategy Board), Michael Hunt (ReNeuron).

Roundtable participants: Professor Charles ffrench-Constant (University of Edinburgh); Professor David Williams (EPSRC Centre for Innovative Manufacturing); Robin Lovell-Badge (National Institute for Medical Research, London); Professor Amanda Fisher (Imperial College London); Anthony Hollander (University of Bristol); Professor Chris Mason (UCL); Steve Bates (BIA); Becky Purvis (AMRC); Priya Umachandran (Wellcome Trust); Alex Denoon, (Lawford, Davies and Denoon); and Tim Allsop (Pfizer).

Overview of UK Research Excellence in Regenerative Medicine—Rob Buckle, Medical Research Council

Rob Buckle opened by providing a definition of Regenerative Medicine treatments, including the approaches and timescale for delivery. Concentrating on cell therapy, a number of approaches were identified. The first, autologous cell therapies, employ cell matter taken from an individual to treat that individual (so called "self to self" treatments). There are currently numerous clinical trials under way in this area, including for the treatment of bone/joint, cardiovascular, eye, liver and neurological disorders. In most cases, stem cells are removed from the patient, often minimally processed, and then reintroduced as part of treatment in the same area or bodily system. Results in heterologous systems—taking stem cells from one area such as the bone marrow, and using it to repair neurological issues for example—have so far proven unconvincing.

In contrast, allogeneic cell therapies where the donor and recipient are different (so called "one-to-many" treatments) have potentially broader potential. However, their use is dependent upon the use of immune suppression or donor matching (as in bone-marrow transplants). There are currently clinical trials underway in this

area on skin conditions, stroke, Parkinson's Disease, corneal repair, and Advanced Macular Degeneration (AMD). There is also notable future potential in induced Pluripotent Stem Cell (iPS)-based, and directly-differentiated cell-based, treatments. Finally, a range of activity was being undertaken on endogenous repair, which involves the use of growth factors and small molecules to stimulate repair processes. The MRC, for example, was funding such research in the areas of heart repair and multiple sclerosis.

An examination of the therapeutic pipeline across these areas revealed that there were currently 36 studies at the preclinical-early stage of development (33 academic-led, and three commercially-led.) Six studies were at the preclinical-late stage (five academic-led, and one commercial). Finally, 19 studies were at clinical phases I/II (14 academic-led, and five commercial). When viewed by disease area, the largest number of studies—and, indeed, in many cases the most developed—were muscloskeletal and eye-related conditions.

With regard to the strength of the science base, of the top five research nations (US, China, UK, Japan and Germany) UK researchers generated more articles per researcher, more citations per researcher, and more usage per article authored.[336] The UK's share of the top one percent of most highly cited papers was 13.8% in 2010, second only to the USA. The UK citation impact in regenerative medicine is also higher than for the UK science base more generally.[337] The UK is also a leading collaborator for others, including the USA and Germany.

The main funders of research in regenerative medicine are the research councils, the Department of Health (particularly through the NIHR), the TSB and research charities. Support is largely provided by competitive, response-mode funding. However, there are also areas where the direct stimulation of activity is needed, and therefore targeted schemes (including translational funding) are also provided. Funding is also directed at research infrastructures, international partnerships, and capacity-building, which receives approximately 10% of MRC funding in this area. Research activity overall is co-ordinated through both the UK Regenerative Medicine Forum and the International Stem Cell Forum.

In 2008, research council funding was approximately £43.5 million which represented around 66% of the total research spend on regenerative medicine. The MRC was the largest contributor of this funding at £37.7 million (52% of the research council total). The BBSRC contributed £12.8 million (18%), the EPSRC £11.3 million (16%) and the TSB £8.8 million. The NIHR and ESRC contributed approximately one percent of research funding respectively. Since 2008, the MRC's financial contribution to research in regenerative medicine has approximately doubled (£72.6 million per annum), with funding for 353 projects. When analysed by "technology readiness level"—a spectrum which begins at underpinning research through to user adoption—the majority of research council spending on regenerative medicine remains at the earlier "underpinning" or "preclinical/breadboard" stages. Relatively small numbers of funded projects are at "early clinical-prototype" or "user adoption" phases. That reflects current understanding of the field, and how difficult it is to translate projects into later stages of development.

In terms of current UK strategic investments, there are a number of Centres of Excellence in regenerative medicine research in the UK which the MRC and other

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336 According to the findings of BIS: *International Comparative Performance of the UK Research Base*, 2011.

337 *Op. cit.* Taking stock.

research councils help to fund.[338] The MRC is also engaged in strategic funding partnerships designed to accelerate therapeutic development in this area, including with the British Heart Foundation, and with the California Institute of Regenerative Medicine. In November 2012, a joint £12 million initiative between the Wellcome Trust and the MRC will be announced on Human Induced Pluripotent Stem Cells. There is also the UK Stem Cell Bank, which exists to provide human embryonic stem cell lines in an ethically sourced and quality controlled manner, and industry relationships in the form of Stem Cells for Safer Medicines (SC4SM) public private partnership involving pharmaceutical companies using this technology for drug development. Broader support for the area is also provided through a number of NIHR Biomedical Research Centres, and the Blood Transfusion Services which offer distribution and manufacturing capability.

There remain a number of challenges which need to be addressed in the field, however, as identified in the recent UK strategic review. There is a need for better interdisciplinary working between different groups such as biologists, bioengineers and material scientists, and different regenerative medicine centres. There are also issues with regard to controlling cell phenotype and function, in terms of how they are differentiated to form different tissues, while animal models used to test functionality and safety are also not particularly predictive in this area. Particular challenges also exist with regard to potency, or which cells, how many and what mode of action will be needed for a potential treatment, and immunomodulation, so that risks around transplant rejection can be prevented. New tools and technologies will be required for the development of regenerative medicine treatments. How to meet demand for manufacturing facilities and GMP production will also be an important issue. There is also regulatory uncertainty in this area, including how phase I trials should be designed to meet requirements and the appropriate level of monitoring and follow-up. New business models will also be needed for commercial development.

Looking to the broader strategic approach to these issues and challenges, *A Strategy for UK Regenerative Medicine* was published in March 2012. The Strategy aimed to detail how this area of fast-moving discovery science could be best exploited, and to drive translational approaches and build on the UK's strong science base. To this end, the Strategy documents an injection of £95 million into new strategic funding over the next five years which will be channelled into specific initiatives such as the UK Regenerative Medicine Platform, the TSB Cell Therapy Catapult Centre and new MRC and Wellcome Trust partnerships.

In response to a question on the comparative spending ratios between the UK and the US on early science through to translational/commercial stages, Dr Buckle said it was difficult to get an accurate picture across American providers. However, he believed that they would be broadly similar. When questioned on whether the relatively low levels of translational funding (in comparison with earlier stage research funding) demonstrated in both countries was the result of a lack of resource or a lack of projects to fund, Dr Buckle said that at the current time there was not a (comparatively) large demand for translational funding. In response to a further question on the funding of translational research, Dr Buckle added that the MRC have a specific budget for translational science in regenerative medicine, which has been set at a level capable of satisfying the level of high quality demand,

338 They include the Stem Cell Institute in Cambridge, with the MRC in partnership with the Welcome Trust; the MRC Centre for Regenerative Medicine in Edinburgh; the EPSRC, BBSRC, TSB Medical Technologies Centre in Leeds; and the ESPRC Centre for Innovative Manufacturing in Loughborough.

which had remained steady over the last few years. The deployment of that budget is managed through a funding committee formed four years ago, and which has the capacity for industry partnership. With the TSB, the MRC has also launched the Biomedical Catalyst Fund, which aims to provide funding to bridge the "valley of death" where proof of concept is needed before large scale investment can be attracted, and which can absorb the demands of clinical studies in this area as they emerge. Dr Buckle suggested that the result of these various initiatives was a harmonised funding landscape in this area.

In response to a question about the role of charitable organisations, Dr Buckle said that they were very much acting as partners with the research councils in translational research. He added that industry interest in this area is largely represented by small and medium sized enterprises rather than "big pharma", with companies involved in both the development of treatments, and the development of tools and technologies. The MRC is explicitly trying to encourage industry partnership with targeted funding.[339]

First Roundtable—What potential does regenerative medicine hold to treat disease in the next 5–10 years?

The discussion began with a short introduction from each external participant providing a brief overview of particular points of interest. The potential impact of small molecule therapies, not least because it is a model that pharmaceutical companies are already very comfortable with, was highlighted. The benefits provided by cell reprogramming—the technology for turning different types of somatic cells back into stem cells—were also explained.

It was argued that any supposition that human iPS or human embryonic stem cells should be used for cell replacement was argued to be potentially naive. One possible alternative focus for research attention might be "directed reprogramming", whereby rather than turning a differentiated cell right back into an embryonic stem cell it is turned into a required material that is perhaps mid-way (or at some other point) in the differentiation process.

Autologous therapies were already being deployed. Whilst such therapies were not perfect, they illustrated that it was possible to remove, manipulate, and then reinsert cells, and provide some demonstrable therapeutic effect. It was felt that there was considerable tractability in this area, which would only increase over the next few years as these therapies continue to develop and improve. Tissue engineering—using cells to create tissues outside the body and then implant them—was also identified as a key area for potential. However, considerably more development in the fundamental science would be required, and developing a suitable business model could be particularly complex.

Niche derived factors—factors made by the local environment where the stem cells exist, and which control the activity of those stem cells—and their small molecule agonists and antagonists could be very important over the next 5–10 years.

The benefits derived in the next 5–10 years were very much going to be governed by what is currently in clinical trials. According to the clinicaltrials.gov database, (excluding duplicates) there were around 1, 900 trials ongoing. The overwhelming majority were clinician-sponsored, a mode which, it was suggested, historically has not had good results, principally as a result of issues such as lack of later-stage

[339] The principle route for this funding would be from the MRC to a university, who would then subcontract to a company.

funding. Public companies, rather than clinicians, tend to be well set up for such later stage trials. There were estimated to be about 45 public companies engaged in around 60 active trials, roughly split between 40% at phase I, 40% at phase II, and 20% in phase III. It was argued that there would only be a very small number of therapies coming through in the next 5–10 years, although there was potential for treatments for very small patient groups to progress faster.

Manufacturing capability was identified as an issue. A large scale therapy which would be distributed widely to a large number of patients was unlikely in the next 10 years, as the processes necessary for the scale-up of such treatments did not currently exist. More positively, the UK does possess considerable strength in the area of gene therapy, and the increasing convergence of gene and cell therapies in particular presents a considerable area of future potential.

It was suggested that the level of translational activity in the UK was low in comparison to other countries with more permissive regulatory regimes, which was of particular concern.

The UK Stem Cell Bank was identified as a key resource, particularly given the presence there of clinical grade stem cell lines for research. It was suggested that commercial actors seldom dealt with the UK Stem Cell Bank, preferring instead to deal directly with those who had deposited lines there. Furthermore, as there is currently no mechanism for the long-term exclusive use of a cell line by a company developing a cell therapy, and no ability for a company to control how deposited cells are used, there exists a barrier to commercial investment.

Second Presentation—Mark Bale, Department of Health; Rupert Lewis and David Griffiths-Johnson, Department of Business, Innovation and Skills: the Policy Environment

Mark Bale outlined that the approach of Government since 2000 had been to take a neutral perspective with regard to the source of stem cells, but to be as supportive and enabling as possible with regard to regulation pertaining to derivation, clinical trials and therapeutic application. That work takes place within the wider constraints imposed at a European level.

Speaking directly to the issue of regulation, Dr Bale said that the Government are conscious of the perception that there is a multiplicity of regulators. However, there were very good reasons for the established system. Responding to a question on why the Government had chosen not to locate the regulation of all research functions within the Human Research Authority (HRA), as it had originally intended, Dr Bale said that the Government had undertaken consultation on this issue. He added that in his view, stem cells and other regenerative medicine treatments constituted a very small proportion of the responsibilities of the HFEA and HFA—it was not their core business. Therefore, to remove these functions from those bodies and to place them in the HRA, for example, might in fact increase the resource necessary to deal with them. There might be a need to take on new staff for example, where this expertise already exists in the existing structure.

Dr Bale continued by outlining which regenerative medicine treatments and processes, and at what stage, were currently within the remit of which regulator. Dr Bale acknowledged that the regulatory structure may appear complicated, but said that there had been considerable efforts to raise awareness and increase understanding through initiatives such as the Stem Cell Toolkit, alongside workshops and further guidance materials.

Rupert Lewis outlined the recent steps that BIS had taken to support the development of regenerative medicine, including the creation of the Cell Therapy Catapult. He also pointed to the work undertaken by the British Standards Institute, which had published a number of standards and guides on issue areas such as the use of human cells for clinical application. Measures were also available to improve access to finance, such as the use of tax credits and the TSB's Regenerative Medicine Programme. Dr Lewis added that there were particular programmes which aimed to address the problem of the "valley of death", including Enterprise Capital Funds which seek to leverage private sector investment and demonstrate potential to venture capital. The Enterprise Investment Scheme also exists to provide tax relief for investors.

Dr Lewis then highlighted the potential implications of the recent European Court of Justice ruling in *Brüstle v Greenpeace*. Dr Lewis said that the Government was concerned about the potential impact of this decision for research using human embryonic stem cells, and had made representations to the European Commission on this issue. The Intellectual Property Office had also issued a revised practice note in light of this ruling. Dr Lewis said that reaction to the decision across the research community had been mixed. He noted that, whilst there was concern if an invention could not be patented, the complexity and expertise needed to develop a regenerative medicine treatment could still provide commercial protection and exclusivity in the absence of a patent.

Dr Lewis noted the wide recognition of the potential of regenerative medicine as a growth opportunity internationally. A number of countries were currently investing in regenerative medicine, particularly in the area of translational research. While some countries such as Japan had chosen to focus on particular areas (iPS cells), the UK had retained a broad approach, preferring to be led by the science. The UK has particular areas of strength in research impact and collaboration, and on the number of companies operating in the area.

Zahid Latif then outlined the role of the Technology Strategy Board in supporting regenerative medicine. As a funder, a key challenge for the TSB was to go to business and find out what was necessary to secure investment into regenerative medicine. Clinical studies proving efficacy was identified as a key requirement, as was the need to invest in the underpinning tools and technologies necessary to develop regenerative medicine, as well as the treatments themselves. Dr Latif said the final area that the TSB needed to examine and "unpack" was value systems and impact modelling—i.e. what is regenerative medicine, is it a product or a service? How should the reimbursement challenges be addressed as a result? The TSB ran a series of competitions for funding from 2009–11 to focus on these areas.

Dr Latif continued by highlighting that the business and operating models present in the regenerative medicine sector differed significantly from traditional pharmaceutical models. As a result, funding programmes had to be designed in a particularly bespoke way in order to address key concerns, including, for example, access to finance. Dr Latif identified a number of success stories, where companies had benefitted from such an approach. Further work, including the creation of the Biomedical Research Catalyst, is currently being undertaken in order to overcome issues such as the "valley of death". Finally, Dr Latif highlighted the work of the Call Therapy Catapult, which provides access to knowledge and expertise as well as access to the finance which companies need.

Members of the Committee raised the question of whether the current regulatory environment facilitated the development of regenerative medicine, or presented a

potential barrier to that development. A discussion about access to finance, an unclear and complex regulatory system, and uncertainties about reimbursement followed. It was pointed out that the regulatory rules are the same across Europe. What may be different is the UK is the presence of multiple regulators, and the need to work with different regulators depending in the stage and type of treatment under development. The outreach work that was being done by the regulators to industry in order to overcome any uncertainties or apprehension was outlined. However, it was pointed out that whilst the regulatory environment in the UK was well-regarded, the multiplicity of regulators in the UK created an environment where inconsistent and occasionally contradictory advice was given, and there was no mechanism to resolve such inconsistency.

Third Presentation—Michael Hunt, ReNeuron

Michael Hunt, Chief Executive of ReNeuron opened his presentation by providing a brief background about the work of ReNeuron, and their work as a small company taking a regenerative medicine treatment through basic research into clinical trials. Mr Hunt then outlined some of the challenges the company faced going forward, including securing finance to develop further avenues of treatment so far unexplored due to those financial constraints, the specific concerns of ensuring purity and potency of cell lines, and broader issues of developing an effective business model and negotiating the regulatory landscape. Speaking in particular to those regulatory burdens, Mr Hunt said that in his experience the processes involved had often proved to be complex, inefficient, and subject to considerable overlap between regulatory agencies. By way of illustration, he said that ReNeuron had been subject to eight different inspections, by three regulatory bodies, in the preceding twelve months. Mr Hunt said if reviews could be implemented to make the regulatory process more timely and proportionate, the UK would be more attractive to those seeking to develop regenerative treatments such as themselves.

Turning to the issue of funding, Mr Hunt said that private investment into UK companies was currently small in comparison to other areas, notably the United States. He said that, despite the progress being made in the field both in the basic science and translationally, investors were still demonstrating reluctance to commit funding. Similarly, with regard to publically provided funding, there were some funds available in the UK for translational research, but again this was a fraction of what small companies in the US were able to access.

Looking at positives in the UK landscape, Mr Hunt said that in general the UK Government had proven to be supportive of regenerative medicine, and there were increasing levels of research council funding available. He also particularly welcomed the establishment of the Cell Therapy Catapult. Finally, Mr Hunt highlighted the benefits presented by the NIHR and the NHS, and the presence of trade bodies particularly focused on regenerative medicine.

Second Roundtable—Where could the Committee's inquiry best add value?

Moving around the table, suggestions were heard regarding the areas where the Committee might be able to add the most value and the key questions that it might seek to address in its inquiry.

It was argued that one of those areas should be the regulatory framework and the creation of an active mechanism to pull products through from basic research, through clinical trials, into commercialisation.

Another view was that it was best to focus on what was achievable in regenerative medicine, in comparison to what was considered aspirational, and how one engaged the full community effectively.

In addition to examining regulatory issues, guidance provided to companies working in the field should be considered. It was suggested that, given the timing of the inquiry, the ongoing discussions on the EU Horizon 2020 programme would be a particularly pertinent issue to consider. The development of effective business models was a key issue, requiring close interaction with regulators, and also dialogue across the regenerative medicine community.

Another area where the Committee might add significant value, where there is currently uncertainty, was the adoption of treatments and technologies in the NHS. It would be important to address the issue of stem cell tourism, not least with regard to unscrupulous providers preying on those desperate for treatment. It was considered vital that the Committee examine adoption and reimbursement, not least in balancing up-front costs with potential long-term savings, with a view to convincing Government to provide more support and assistance in these areas. It was also important to concentrate on the finance and funding gap which currently exists.

Attention should be given to the small and niche products being developed as well as the so-called "blockbuster treatments". Support for the key role of large and small charities in addressing issues such as access to finance and adoption of regenerative treatments by healthcare providers including the NHS could be considered. It was argued that advice and support services need to be significantly improved. The possibility of early-phase reimbursement should be explored.

It was suggested that translation and commercialisation were often confused when in reality they were two very different parts of the development pathway. The UK was very good at basic research, getting better at translation, but extremely poor at commercialisation. In order to develop the UK's regenerative medicine sector, this last issue in particular needed significant focus. Access to finance, and a need for Government support to encourage investment was also highlighted. Finally, the significant challenges in terms of trial design and implementation, and the need for a skilled workforce to meet these challenges, merited attention.

APPENDIX 5: VISIT TO CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE (CIRM), UNITED STATES

Members visiting: Lord Krebs (Chairman), Lord Cunningham of Felling, Lord Patel, Baroness Perry of Southwark and Lord Willis of Knaresborough. In attendance: Mr Chris Atkinson (Clerk) and Professor Fiona Watt (Specialist Adviser).

Monday 3 December—Wednesday 5 December 2012, five members of the Committee, (accompanied by the Specialist Adviser and Clerk) visited the California Institute for Regenerative Medicine (CIRM). The aims of the visit were to learn from the work of CIRM, to see some of the groundbreaking translational work being undertaken in California, and to learn from the experience of those who have successfully commercialised regenerative treatments.

Day One

Introductions and welcome

Senator Art Torres, CIRM Board member; Dr Alan Trounson, CIRM President; and Ian Sweedler, CIRM Senior Counsel for International Programs, welcomed the Committee on behalf of the agency, Governor and Mayor. The "unique experiment" of CIRM was discussed including the proposition to create it (passed in 2004), the general obligation bonds which fund it, and the focus on getting treatments to patients.

Panel one

The Committee then met Dr Anne-Marie Duliege, Affymax and CIRM Board Member; Dr Edward Lanphier, Sangamo Biosciences Incorporated; Dr Thomas Okarma, BioTime; and Dr Edward Penhoet, Alta Partners and Member of the President's Council of Advisors on Science and Technology (by telephone), to discuss biotechnology venture funding and the biotechnology environment in California.

It was suggested that the Bay Area biopharmaceutical environment was extremely dynamic. This success was attributed in part to historical funding. Some were less optimistic currently because of the lower availability of capital, and because regulation was more significant and stringent. When specifically discussing stem cell research it was suggested that the path was less certain and consequently venture capitalists were not yet ready to support it widely so the Government should step in—as CIRM does. It was argued that it remains to be seen how costly it will be to bring stem cell to patients. It was noteworthy that the FDA had shown flexibility when it came to clear unmet medical need and orphan drugs, but on the whole it was perceived as becoming more conservative—wanting more certainty about efficacy and safety.

There was undoubtedly spectacular science in the field of regenerative medicine. To unlock patient benefit, research had to be encouraged, capital for translation provided, access to patients established and economic benefit demonstrated. It was argued that relying on federal government funding to adequately enable basic and early translational research was not sustainable and so private sector solutions and private sector incentives had to be sought. But as one moves away from drugs and monoclonal antibodies it was very hard to raise venture capital. Venture capitalists

needed to see how they could make money and a near term return. Creating incentives for "big pharma" to invest would also be valuable. It was suggested that CIRM was a great alternative for capital, but not a long term solution to creating an economic model that drives incentives for early investment.

It was argued that there was less venture capital for autologous cell therapies, gene therapies and other regenerative medicines because there had been fewer successful business models when one compared regenerative medicine companies to other investments possibilities such as technology. Big pharmaceutical companies now have venture funds and are investing in this space. They can receive a tax free return on it from the investment tax credit. It was suggested that "the pull" through from basic to translational work was currently low because few products had got through successfully. One strategy to jumpstart the field and attract investment was investment in an array of opportunities so see quicker returns.

The decision of Geron to stop supporting regenerative medicine and to halt its spinal cord injury clinical trial was set out as a case study of how hard it was to do truly innovative work. Possible factors influencing that decision included the economic burden of developing human embryonic stem cell therapies, the long timeline for a return on investment and the significant risks involved. Relevant assets had been acquired by BioTime who would take the work forward but finding investment to do that had not been easy.

The importance of continued good relationships between the biotech industry and academic research was underlined. President Obama was very interested in maintaining the country's leadership in biotech and had commissioned his Council of Advisers on Science and Technology to undertake a study on the drug development process.

In further exploring the ecosystem of venture capital funding it was suggested that a quick return was always valued. Timeliness of return on investment in regenerative medicine was not consistent with investor expectations or wishes.

Finally, the difficulties associated with patenting regenerative medicine were compared with those in biotech. A comparison was drawn between the 20 years of research to optimise monoclonal antibodies before industry ("big pharma" and biotech) were convinced of the science and clinical application. It was suggested that because much of the invention in regenerative medicine was occurring in industry, this was riskier for investors.

Panel two

The Committee discussed manufacture, scale-up and GMP for cellular therapies, and clinical development of non-cellular therapies with Dr Gerhard Bauer, University of California (UC) Davis; Dr Patricia Olson, CIRM Executive Director of Scientific Activities; and Dr Phil Vanek, Lonza.

The Committee heard presentations about ongoing clinical work in UC Davis, including work to develop an HIV gene therapy treatment and collaborative work with Stanford University to manufacture induced pluripotent stem cells to treat epidermolysis bullosa. UC Davis does its GMP work in-house and also contracts out those facilities—around 40% of its contracts are private ones. Its GMP facilities are run on a quasi-commercial basis. It has six fully operational suites, which are running at capacity. CIRM had invested $12.5 million in this facility.

If a CIRM funded technology reaches a certain level of commercial success then a small portion of revenue from that goes back to the state general fund to repay taxpayers for investment in this research. The CIRM model was discussed further. Teams are encouraged to think early about how they will scale-up and manufacture any potential treatment. CIRM provides lots of tools and support for researchers such as webinars and access to consultants. The work of a disease team is milestone-driven and has specified outcomes. The CIRM model would be explored in greater detail later.

CIRM co-funds work with the UK MRC, China, Australia and other partners all over the world. They are very focussed on getting work into the clinic. Proposals submitted in response to requests for applications (RFAs) are evaluated by panels of reviewers who have expertise in various areas in addition to experts in the particular disease area. CIRM has a pool of reviewers (of approximately 150). They particularly encourage applications from multidisciplinary teams.

Lonza have been working on manufacturing challenges associated with cell therapy for around 12 years. It is seeking to answer the question: how can it help this industry materialise on a cost-effective practical basis? It considers key bottlenecks or challenges, and works to develop possible solutions. These challenges include keeping cells consistent, viable and recoverable in downstream processing.

Lonza starts with the end in mind: how can this treatment be mass produced for a patient population? Delivery at scale has many practical challenges such as dose and logistical issues. It was argued that manufacturing could not continue at current scale: Lonza wants to invent technologies that start with a lot size of 500–100 and to manufacture 5, 000–10, 000 doses per lot. These issues need consideration now before we run out of raw materials, such as serum. Automation and scale-up will be achieved through the next generation of technologies such as suspension bioreactors, and these new technologies could impact the development process.

CIRM provides some funding for considering these issues through its tools and technologies stream. The Committee then discussed delivery systems with the panel, including the specific example of how a macular degeneration treatment could be delivered to thousands of patients. Difficulties with achieving patents for processes were then discussed and it was suggested that patents were easily designed around. Transportation and shipping problems were discussed: there were specific needs for cryopreservation, validation and guarantees of time from manufacture to clinic. Down the line, a hospital-based cell pharmacy might be a necessity for allogeneic treatments. The question of whether one should bring the patient to the therapy or the therapy to the patient was raised. One model for addressing some of these issues was the Alpha clinic network which CIRM was exploring the feasibility of.

Panel three

The Committee met with Dr Larry Goldstein, UC San Diego and Sanford Consortium for Regenerative Medicine; Dr Michael Longaker, Stanford University; and Dr Thomas Rando, Stanford University and Palo Alto Veterans Affairs Medical Center, to discuss interdisciplinary centres and perspectives on the state of regenerative medicine science.

The Sanford Consortium for Regenerative Medicine is a partnership with independent charitable status, comprising universities and research institutes in the San Diego area. Through its layout and ethos it seeks to promote

interdisciplinary working, in recognition of the need for collaboration between clinicians, scientists and engineers to deliver new treatments. It is striving to develop organisational systems to reward co-operation, and is bringing together groups to accelerate the movement of fundamental science into clinical applications.

The business model for regenerative medicine had not yet been proven. It was suggested that it was equally possible to develop commercially successful but medically less useful products as useful medical products which were not a commercial success.

Interdisciplinary research from collaboration between Stanford University and Veterans Affairs Medical Centres was discussed. They have a specific interest in disorders that often affect veterans and receive funding from the US Department of Defence. It was suggested that rehabilitation and regeneration go hand-in-hand—seeking to restore function and tissue. The Department of Defence also funds an Armed Forces Institute of Regenerative Medicine (AFIRM) which is a multi-institutional, interdisciplinary network working to develop advanced treatment options for our severely wounded servicemen and women.

Stanford University provides "accelerators" to progress basic science through to translation and commercialisation. It draws together legal expertise on IP and ethics, business skills to consider the business model, and the knowledge of the engineering school to drive entrepreneurship. Its medical centre has raised funding to build a therapeutics centre and it hopes to prevent the stem cell institute being an isolated "ivory towers". It will do clinical trials with bone marrow and stage four breast cancer in the first instance. One central office considers licensing and Stanford has a handful of excellent examples of patent return. Faculties often form companies and license use. If Stanford can't license it then they either drop prosecution of the patent or the investigator is free to start up a company to do so.

A question was raised about whether it was helpful to compare the model for IP and equity sharing during the technology boom with the situation now for stem cells and regenerative medicine. It was suggested that what was needed was to diversify risk by spreading it across a well-filled pipeline because regenerative medicine was perceived as high risk science and investment.

The CIRM disease team model was discussed further. It was thought that of the first round of teams at least seven of the 14 teams would get to clinical trial. The benefit of a four year deadline was a "flurry effect" of activity. Two projects are already in clinic. Academics had bought into the model relatively quickly. Where necessary, additional expertise and management could be brought in to help so that teams met their milestones. Typical investment in a disease team was around $20 million over four years. Each would consist of four or five investigators as well as six to ten people in labs.

It was suggested that biomedical science and engineering was "living off the fruits" of investment 10, 15, and 20 years ago. The private sector would not make investments in twenty year ROI propositions—so there was a role for the public sector to play. One of the major returns on investment in regenerative medicine would be a reduction in healthcare costs. In its more recent RFAs, CIRM had highly encouraged corporate partnerships which they argued was realistic as, because CIRM providing some of the capital investment, they were helping de-risk the proposal.

The Committee was encouraged to "be bold". Those who drafted proposition 71, which established CIRM, were now considered to be visionaries. The UK has an

extraordinary scientific community. It needed to take risks in supporting this field. Disease has an enormous cost (for example, Alzheimer's Disease in the US has healthcare costs of $250–500 billion a year) not just from healthcare costs but in lost wages, the social bill and other indirect costs. A "can-do" approach like that of California was desirable. The UK needed, like CIRM, to build in front of its researchers: to think forward and prepare the space for where they are going. It was further suggested that money wasn't enough—incentives were needed and providing scientists with a way to do it. It was also important that universities recognised the value of translational and commercial work; assessment of the quality of science shouldn't rest solely on numbers of papers published. The importance of collaborative working was again stressed. Training grants were one lever to encourage medics to engage with research.

The UK Stem Cell Bank was described as "incompetent and intransigent". Dr Larry Goldstein had a very negative experience trying to secure the use of two cell lines in his research to the point that he gave up and used lines from elsewhere.

Panel four

The Committee then discussed models for translation through industry-academic relationships, including collaborations, spin-offs, and licensing with Dr Karen Aboody, City of Hope; Dr Dennis Clegg, UC Santa Barbara; Dr Peter Coffey, UC Santa Barbara; Dr Henry Klassen, UC Irvine; and Dr Clive Svendsen, Cedars-Sinai.

The Committee heard about the research and businesses of these researchers. For example, therabiologics was a spin-off company whereas jCyte Inc employed a virtual company model whereby it licensed the IP. It was suggested that, in the current economic climate, investors were very risk adverse and so researchers had to take development further than previously was the case before industry would step in. Industry was reluctant to pick up trials before they had phase II data. Academic-industry and philanthropic partnerships were possible solutions to this dual valley of death (as financing phase I trials was also problematic).

The California Project to Cure Blindness had some "big pharma" and VC interest already if it were taking its work to a phase III trial.

The London Project to Cure Blindness had been severely delayed by unclear interactions with GTAC. Professor Coffey was frustrated by delays and considered the UK regulatory pathway to be extremely complex. In contrast, he spoke highly of his interactions with the MHRA.

Cedars-Sinai hospital was a medical centre with a science and clinical side in the same hospital. Their focus is personalised medicine, and potentially getting stem cell therapies for a wide range of diseases. Medical centres were one important model for translation because they can do R&D without the commercial pressures. It was argued that private health insurers should be convinced of the savings afforded by regenerative medicine and also encouraged to invest.

CIRM host quarterly webinars with the FDA. It recognised that regenerative medicine is a learning process on both sides: for the FDA and people working in research. Through these webinars, meetings and papers CIRM seeks to help people understand what is required of them by regulators and to educate the regulators on the developing science. It was suggested that the FDA was getting much better at handling regenerative medicines.

Day two

Panel one

The Committee met with Mr Louis Breton, Calimmune; Dr Paul Laikind, Viacyte; and Mr Martin McGlynn, StemCellsInc, as witnesses from regenerative medicine companies in the translational through clinical stages.

Calimmune has the ambition to be the first company to provide a one-time cost effective HIV therapy. It was developing a combination therapy which was based on a natural mutation whereby people who lack CCR5 receptor have complete protection. It was about to embark on phase I/II trials in the US and Australia, and had investigator-initiated studies in the UK and France. Calimmune secured private investment because there was a well-developed and strong science base underpinning it. The company benefited from around 14 interactions with the FDA before submitting for IND (investigational new drug) approval.

Viacyte explained its VC-01 combination product which functions as a replacement pancreas delivering cells which differentiate to insulin and other cofactors and delivered using a propriety encapsulated delivery system. It was soon to begin phase I trials. This could be a cure for type one diabetes and an effective therapy for type two diabetes. CIRM's enthusiastic support for the project had been crucial.

StemCellsInc focuses on the central nervous system (CNS) and the liver. It started by developing an encapsulation technology and now sought to address unmet medical needs through the development of stem cells as therapeutic agents to treat damage to or degeneration of major organ systems. It was founded by four prominent academics. The company had benefited from the increasingly collaborative approach of the FDA and recommended that it become as much advisory as regulatory.

It was suggested that, in general, IP was not as valuable or useful in the reagents world as it was in that of therapeutics because prosecuting patents was very expensive and time consuming, and reagent life cycle can be very short.

The companies were already thinking about scale issues. A key challenge was demonstrating to regulators that stem cells could be reproduced at scale to the same, regulatory-required standard. Scalability was considered a critical requirement for attracting finance.

The attraction of the Australian R&D tax incentive was discussed. Views were mixed on whether "cash" or tax credits were more desirable. A further facet of CIRM's provision, namely its loans scheme, was discussed.

Panel two

Regulatory obstacles, pathways and engagement were discussed with Dr Lauren Black, Charles River Laboratories; Dr Joy Cavagnaro, Access BIO; Dr Ellen Feigal, CIRM Senior Vice President of Research and Development; and Dr Thomas Okarma, BioTime.

Geron's IND application was the first received by the FDA for an embryonic stem cell-derived therapy and the largest it had ever received (21, 000 pages). Geron had to invest substantially in animal modelling to demonstrate efficacy.

A lot was asked of FDA reviewers: to assess INDs at relative pace and to take a view on whether they were ready for humans and, if so, at what dose. The FDA

was, however, viewed as a well-informed regulatory body. Regenerative medicines are much more complex than drugs and so there was a lot of uncertainty. To reduce some of the uncertainties, investment in animal modelling could greatly improve confidence. The majority of regulatory files submitted to the FDA Center for Biologics, Evaluation and Research's (CBER) Office of Cellular, Tissue and Gene Therapy were from research sponsors rather than commercial ones.

Insufficient harmonisation was identified as a problem—for example, Apligraf is regulated in different countries as a device, a biological or as a medicinal product. Unique and novel therapies can be daunting to regulators. The FDA was beginning to work internationally—such as its pilot programme of parallel scientific advice with the EMA. Dialogue was critical to its learning. Similarly, academia needed to understand more about assessing safety, efficacy and potency. CIRM has done a lot of work to educate investigators. It is uniquely placed to bring people together to increase knowledge on all sides. Webinars are one tool that CIRM use.

It was suggested that industry wants regulators to tell them what to do but they can't always because they don't have sufficient information on the various technologies to provide general guidance. One recent example of guidance the FDA had finally issued was *Draft Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products*, although it was suggested that this guidance document could become quickly dated as advancement in these fields were rapidly developing. Ways to improve the functionality of the FDA were discussed. There were mixed views about the efficacy of the FDA and the merits of the UK regulatory system.

Comparisons were drawn between the use of surrogate markers for HIV/AIDs and the need for similar initiatives to support orphan conditions, to increase the number of trial approvals. Any good regulatory framework for cell therapy needed to involve consultation with scientists, industry, the public and regulators. Patient advocate groups could be a powerful voice for change. It was suggested that the public needed better educated about risk-benefit.

CIRM bring in regulatory experts to support their disease teams. The FDA has also started approaching CIRM for assistance in gathering information or hosting events.

Panel three

Dr Alan Trounson, CIRM President; Dr Irv Weissman, Stanford University; and Mr Ian Sweedler, CIRM Senior Counsel for International Programs, discussed international collaborations with the Committee.

Professor Weissman described his scientific research and his experiences of commercialising this work. His CIRM funded leukaemia disease team was developing therapeutic antibodies directed against surface markers present in much larger amounts on LSC (leukaemia stem cells that are responsible for maintaining the disease) than on the surface of normal blood forming stem cells. This project is a collaboration with Dr Paresh Vyas at Oxford University, supported through CIRM-MRC collaborative funding.

He argued that the UK had better infrastructure for clinical trials than the USA because of its unified healthcare system and highlighted the potential for reimbursement this also provided. He observed that a permanent cure with one treatment required completely radical health economic models and pricing

strategies. He continued: big companies will not invest until they are shown that it's a business for them.

Difficulties encountered trying to equip patients to make informed decision about unproven treatments were then discussed. The example of private cord blood banks making unproven claims about treating genetic diseases was given.

Alan Trounson recommended talking to academics about what they needed and founding a UK agency that delivered on that vision: assess where scientists are going and ask "what do they need to make this effective?" The UK should encourage collaboration and support scientists. He also introduced the concept of Alpha clinics which CIRM was exploring to deliver therapies.

Initial reactions from "big pharma" about the possibility of partnering with CIRM and gradually taking greater ownership (and providing more investment) as trials progressed from phases I–IV were positive. The sometimes conflicting desires of business executives and clinicians were discussed. The potential of investment from insurance companies was also considered. Investment by the Veterans Association was further explored.

It was also considered necessary to create a "revolving door" attitude in universities whereby it was normal and indeed recognised as valuable for academics to take leaves of absence to set-up companies.

Panel four

The Committee discussed regenerative medicine health care delivery barriers with Dr Graham Creasey, Stanford University; Dr Natalie DeWitt, CIRM Special Projects Officer; Dr Benton Giap, Santa Clara Valley Medical Center; Dr Steve McKenna, Santa Clara Valley Medical Center; Dr Bruce Quinn, Foley Hoag; and Dr Alan Trounson, CIRM President.

Some results of the (initially Geron run) stem cell based thoracic spinal cord injury treatment trial were discussed. The importance of looking, initially, for evidence of effect rather than cure was underlined. Issues surrounding patient identification and recruitment and multi-site trials were discussed. Research networks and logistical models needed further development. One of the possible solutions to difficulties with trial design was earlier interaction with regulators about outcome measures. The FDA was considered to be actively encouraging early interactions. Adaptive licensing was also discussed.

CIRM's alpha clinic network model to build clinical infrastructure to deliver cell therapeutics was considered further. These clinics would help identify what would work well for stem cell therapy trials, as well as helping define practical needs such as human resources. They could also work to help improve public perceptions, through education and counselling work.

The Canadian, German, US and UK healthcare systems were compared, including their reimbursement mechanisms. The benefits of the NHS as a single healthcare system were again highlighted.

Day three

Panel one

The Committee met with Ms Elona Baum, CIRM General Counsel and Vice President of Business Development; Dr Ellen Feigal, CIRM Senior Vice President

of Research and Development; and Dr Alan Trounson, CIRM President, to discuss funding for research at various stages from translational through clinical—the "valley of death" and the CIRM model.

CIRM is seeking to build pathways to cures and accelerate relevant research. The cost of healthcare, as set out in analysis in a recent Ernst and Young report, is spiralling and regenerative medicine offers a hope for containing them. But, fundamentally, CIRM wanted to see patients made better. Their model is helping academics optimise their clinical development of research in such a way that it is investment ready.

CIRM has a strategic partnerships award to attract industry engagement and investment in CIRM funded stem cell research. The intent of the Initiative is to create incentives and processes that will: (i) enhance the likelihood that CIRM funded projects will obtain funding for phase III clinical trials (e.g. follow-on financing), (ii) provide a source of co-funding in the earlier stages of clinical development, and (iii) enable CIRM funded projects to access expertise within pharmaceutical and large biotechnology partners in the areas of discovery, preclinical, regulatory, clinical trial design and manufacturing process development.

This initiative requires applicants to show evidence of either having the financial capacity to move the project through development or of being able to attract the capital to do so. This may be evidenced by, for example, (i) significant investment by venture capital firms, large biotechnology or pharmaceutical companies and/or disease foundations; or (ii) a licensing and development agreement with a large biotechnology or pharmaceutical company or a commitment to enter into such an agreement executed prior to the disbursement of CIRM funding. CIRM strategic partnership awards are evaluated by scientists but they also have business and product development experts on the panel.

CIRM funding can be seen by other funders and industry as a validator—it lends credibility to research. This is true in terms of attracting "big pharma", small business innovation research and private interest. CIRM have spent a lot of time at the interface with angel, VC and pharma investors, showing them the potential in the field. To attract these groups in, CIRM are thinking creatively about how to interact with them—for example, offering them mentoring roles to projects and organising conferences.

Disease team management was discussed in greater detail. Success criteria and milestones are set and agreed in advance. Funding tranches are tied to these. A formal milestone review process is in place. Outcomes of these review meeting are the green light to go forward because they are on the right track, recommending a change of track or a change in milestones if that is realistic, or to terminate the project. CIRM can convert a disease team project back to translational research with reduced scope and budget if necessary. CIRM has withdrawn funding from underperforming projects. In between milestone review meetings, CIRM work with the teams to undertake: progress reports, annual reports, visits and regular phone calls. CIRM not only fund—they nurture, support and fund. CIRM is teaching external agencies about its milestone process and suggested that collaborative funders depend on them for this expertise. Finally, problems around shaping requests for applicants were discussed.

Panel two

The Committee then discussed financing models for regenerative medicine research and development with Dr Jonathan Thomas, CIRM Governing Board Chair; and Dr Alan Trounson, CIRM President.

The sale of general obligation bonds in California was discussed, including the CIRM bond as agreed by proposition 71. CIRM is funded by 30 year bonds. Ultimately, it is intended that this investment will be offset by reduced healthcare costs. The bonds are bought up quickly as they are seen as a good investment. CIRM has been exploring options for finance after the period covered by the bonds.

Bob Klein and political leaders including Governor Schwarzenegger had been instrumental in getting the proposition passed. Other countries have expressed interested in the finance model. Stem cell research in the US is being supported privately, including by philanthropists, and so other possible funding models include "venture philanthropy" as many philanthropists are interested in curing disease. Private health insurance might be a further source of investment. The establishment of public-private partnerships in the area would be helpful, perhaps even mega funds. A general principle observed was that investment attracts investment: when CIRM invested up to $20 million in Viacyte (who are developing a diabetes therapy), the juvenile diabetes foundation brought an additional $5 million to the project on the strength of CIRM's investment. The initial investment in CIRM was seen as a "pulse" that would start the ball rolling of investment in this field.

CIRM undertake a lot of outreach work. But they are careful not hype too high because that could destroy the integrity of its message. Finally, CIRM's governance structure was discussed.

Conclusions

The Committee then deliberated on key "take home" message from the visit and agreed the following:

Funding

- Phase I and II clinical trials are unlikely to be funded by the private sector—the Government cannot expect this.
- The importance of public-private partnership (private coming off the back of public). The necessity of incentives (Australian model). Is exploring a public bond a possibility?
- There is a significant difference between cell therapies and drugs: they are so different that you can't generalise.
- Different health economic models are required because potentially one could have one-time treatments with a higher up-front cost which offered long-term savings. The example was given of "curing" diabetes rather than managing it.
- Does the UK have an incentive structure for academics setting up companies? Lessons should be learnt from the Stanford model, including the importance of a culture of being able to step from academia to industry and back.

Delivery and scale

- For some treatments there will be a need for significant thought about how one delivers lots of cells to lots of patients around the world.
- GMP facilities. Is there a possibility of a smaller number of facilities in the UK bringing more in? Could they have a more commercial model? They should draw in external users.

Regulation

- There was conflicting evidence about the efficacy of the UK system but agreement on the need for greater engagement between regulators and stakeholders. There might be value in funding work on appropriate regulatory models.
- It would be helpful if regulators were proactive in advising people rather than reactive to applications.

CIRM model

- CIRM is transformative not just by providing money but through its leadership. We were impressed by the disease teams model—bringing people together to do things that mightn't do separately.
- "Be bold", take risks, don't expect 100% success.
- Four year target for getting to clinic; go-no go milestones; and support to achieve. CIRM truly did "lay down the gauntlet". It has impressive possible outcomes. Its interventionist style is markedly different from the UK's.

Other points of note

- Critique of the UK Stem Cell Bank.
- The unique advantage of the NHS for clinical trials.
- The value of MD PHDs and the importance of opportunities for clinicians to work in labs.
- A need for better public education.
- Exploit the possibility of using the NHS to bring in international work. Do not fear contract working.
- Good examples of hype and hope—such as private cord blood banks.
- Positive examples: ARMD, HIV, artificial pancreas to treat diabetes.
- The value of "can-do" collaboration. The importance of networks.

APPENDIX 6: ABREVIATIONS AND ACRONYMS

AAT	Alliance for Advanced Therapies
ABN	Association of British Neurologists
ABPI	Association of the British Pharmaceutical Industry
ACT	Advanced Cell Technology
AIM	The London Stock Exchange's international market for smaller growing companies
AMRC	Association of Medical Research Charities
ARUK	Arthritis Research UK
ATMP	Advanced Therapy Medicinal Products
BBSRC	Biotechnology and Biological Sciences Research Council
BIA	BioIndustry Association
BIS	Department for Business, Innovation and Skills
BRCs	Biomedical Research Centres
BRUs	Biomedical Research Units
BSBMT	British Society of Blood and Marrow Transplantation
BSE	Bovine Spongiform Encephalopathy
BSH	British Society for Haematology
BSI	British Standards Institution
CAT	Committee for Advanced Therapies
CCG	Clinical Commissioning Groups
CIFs	Citizens' Innovation Funds
CIRM	California Institute for Regenerative Medicine
CRN	Clinical Research Network
DH	Department of Health
DNA	Deoxyribonucleic acid
EC	European Commission
ECJ	European Court of Justice
EFTA	European Free Trade Association
EMA	European Medicines Agency
EPSRC	Engineering and Physical Sciences Research Council
ESRC	Economic and Social Research Council
EU	European Union
FCO	Foreign and Commonwealth Office
FDA	Food and Drugs Administration
FP	Framework Programme

GB	Great Britain
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
HFEA	Human Fertilisation and Embryology Authority
HPA	Health Protection Agency
HRA	Health Research Authority
HTA	Human Tissue Authority
ICH	International Conference on Harmonisation
IMI	Innovative Medicines Initiative
IP	Intellectual Property
IPO	Intellectual Property Office
iPS	Induced Pluripotent Stem Cells
IRAS	Integrated Research Approval System
IVF	In Vitro Fertilisation
KCL	King's College London
KHP	King's Health Partners
KTN	Knowledge Transfer Network
LLR	Leukaemia and Lymphoma Research
LRMN	London Regenerative Medicine Network
MHRA	Medicines and HealthCare products Regulatory Agency
MRC	Medical Research Council
MS	Multiple Sclerosis
MSCs	Mesenchymal Stem Cells
NC	Non Commercial
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NHS	National Health Service
NHSBTS	National Health Service Blood and Transplant Service
OSCI	Oxford Stem Cell Institute
PAS	Publicly Available Specifications
PCT	Primary Care Trust
QALY	Quality Adjusted Life Year
RCPath	Royal College of Pathologists
RCUK	Research Councils UK

REMEDiE	Regenerative Medicines in Europe
RM	Regenerative Medicine
RPE	Retinal Pigment Epithelial
SC4SM	Stem Cells For Safer Medicine programme
SMEs	Small and Medium sized Enterprises
SNBTS	Scottish National Blood Transfusion Service
STFC	Science and Technology Facilities Council
TAP	Trial Acceleration Programme
TGT	Tissue Growth Technologies
TIA	Transient Ischaemic Attacks
TIC	Technology Innovation Centre
TRA	Technology Readiness Assessment
TRL	Technology Readiness Level
TSB	Technology Strategy Board
TSE	Transmissible Spongiform Encephalopathie
UCL	University College London
UKRMC	UK Regenerative Medicine Community
UKRMP	UK Regenerative Medicine Platform
UKSCF	UK Stem Cell Foundation
UKTI	UK Trade and Investment
US(A)	United States (of America)
WHO	World Health Organisation

APPENDIX 7: RECENT REPORTS FROM THE HOUSE OF LORDS SCIENCE AND TECHNOLOGY COMMITTEE

Session 2007–08

1st Report Air Travel and Health: an Update
2nd Report Radioactive Waste Management Update: Government Response
3rd Report Air Travel and Health Update: Government Response
4th Report Personal Internet Security: Follow-up
5th Report Systematics and Taxonomy: Follow-up
6th Report Waste Reduction
7th Report Waste Reduction: Government Response

Session 2008–09

1st Report Systematics and Taxonomy Follow-up: Government Response
2nd Report Genomic Medicine
3rd Report Pandemic Influenza: Follow-up

Session 2009–10

1st Report Nanotechnologies and Food
2nd Report Radioactive Waste Management: a further update
3rd Report Setting priorities for publicly funded research

Session 2010–12

1st Report Public procurement as a tool to stimulate innovation
2nd Report Behaviour Change
3rd Report Nuclear Research and Development Capabilities
4th Report The role and functions of departmental Chief Scientific Advisers
5th Report Science and Heritage: a follow-up

Session 2012–13

1st Report Sports and exercise science and medicine: building on the Olympic legacy to improve the nation's health
2nd Report Higher Education in Science, Technology, Engineering and Mathematics (STEM) subjects
3rd Report The implementation of open access