

Enabling the emergence of the regenerative medicine industry in the UK

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Enabling the emergence of the regenerative medicine industry in the UK
CEP Working Paper 2008/3

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Foreword

Regenerative medicine (RM) is widely seen as the next major source of innovation in healthcare. The ability to repair and replace damaged cells and tissue, using emerging technologies including stem cells, offers the potential of lifetime cures for many currently unmet medical needs. These include chronic and debilitating conditions such as Alzheimer's, heart failure, blindness and joint degeneration. The UK has a unique opportunity to build on its science lead in this area to both create and retain an industrial base in RM that can deliver long term health, wealth and employment. Estimates suggest that the RM industry might materially improve the health of around 1 million people per annum in the UK, generate upwards of £5 billion of commercial activity (including a very substantial export element), and employ around 15,000 people in knowledge-based research and manufacturing jobs. Specifically, RM developments could address many of the conditions associated with an aging population and the increased demands this will place on the healthcare system in coming decades.

However, there are a number of significant barriers to the emergence of regenerative medicine in the UK. The industry does not yet have a clear identity and visibility, as there are no exemplars of the conversion of emerging RM businesses into major public companies. The complex nature of the science and engineering involved, combined with a weak venture finance climate, means it is difficult for new companies to attract investment and to develop the manufacturing capability required to bring RM products to the market. The technical demands placed on developing RM companies are very high as they need to be 'polymaths' spanning biology, engineering and materials science. Finally, the regulatory environment is still evolving and reimbursement and investment models have yet to emerge.

A key point for the UK is that in regenerative medicine the product is the process and in this respect differs markedly from pharmaceutical and biotechnology products. The need for sophisticated manufacturing technology and novel skills is both a barrier and an opportunity to develop and secure a long term industrial presence in the UK. If the UK can support the emergence of new companies with embedded production capability, there is a high likelihood of maintaining a lead over other countries. There is consequently scope for more coordinated and directed action and investment by government over the next three years, much of it from within existing programmes, which will stimulate and secure an RM industrial base in the UK.

Clinical work to date is showing considerable promise, with rapid progress on cures for otherwise untreatable conditions being demonstrated in a high proportion of recipients in clinical trials. Without parallel progress on infrastructure and supporting aspects of the value chain, these new therapies will

either fail or be delayed in being brought to market. This could delay, by up to five years, access to valuable therapies and allow the UK's current scientific and commercial advantage in this space to be eroded.

Government support to the regenerative medicine industry will be crucial to the long term success of the industry. The principal policy recommendations of this report for government are:

- To provide a more coordinated response across government, academia and industry to convert the UK's science advantage in regenerative medicine into a strong and growing industry through a cross departmental forum for regenerative medicine.
- To assist developments across industry, government and the public sector to ensure that the capabilities and resources, outlined below, are in place in a timely manner and can work effectively together.
- Increase funding for UK regulatory bodies for capacity to provide more proactive support and guidance to RM SMEs, both in developing and advising on relevant regulatory criteria and, more critically, in ensuring convergence and compliance with regulations in the United States.
- Enhance research and training funding in RM to develop 'polymaths' who can embrace all aspects of RM and become the entrepreneurial focus for emerging companies.
- Create translational institutes where pilot process work can be undertaken to produce early clinical material at scale and to cost.
- Provide incentives to encourage early capital investment in process technology for RM companies.
- Support a group of innovation fellowships to enable NHS clinicians to work directly with SMEs in defining and testing novel RM products.
- Support the establishment of a specific RM trade body to assist the emergence and embedding of the industry within the UK.

Total funding requirements to deliver all the above in the next ten years is estimated to be approximately £125m, much of which could be drawn from existing grant programmes.

We commend this policy paper to you as an important and exciting opportunity for the UK.

Richard Archer
Chairman - *remedi* Project

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1. Introduction

Continuing rises in healthcare costs, growing demands on the healthcare system and expectations of increasing quality of life make the future of healthcare uncertain in countries such as the United Kingdom. Will continued investment in research and development (R&D) lead to new therapies at effective cost levels to treat higher numbers of patients across a wider set of diseases? Can the government provide increasing levels of care and improved healthcare outcomes while curtailing the growth of healthcare spending?

Regenerative medicine (RM) is widely seen as the next major source of innovation in healthcare. The ability to repair and replace damaged cells and tissue in the body could offer lifetime cures for many currently unmet medical needs, including chronic and debilitating conditions such as Alzheimer's, heart failure, blindness and joint degeneration. These are conditions linked to an ageing population and so are of particular interest for the developed economies such as the United Kingdom. The UK has strong research activity in this space, including world class capability in stem cells, arising from an informed and open approach to regenerative medicine work that combines a strong ethical basis with informed regulatory policies and well directed and substantial research funding. The UK has a leading position relative to most Western economies, including the United States where government policy and public opinion has been less supportive. A UK lead of one to two years over the competition is frequently suggested - a very significant advantage in this rapidly moving field.

This policy paper discusses the potential for the regenerative medicine industry both in and for the United Kingdom to take advantage of the public and private investments to date and the lead that appears to exist for UK research and development in this area. The paper provides policy recommendations for the support of this emerging industry based on 20 in-depth interviews with industry and clinical leaders in the UK¹, a multi-stakeholder workshop², and continuing research of the remedi Grand Challenge team over a two year period³. The aim of the paper is to strengthen the dialogue between researchers, industrialists and policy-makers, so that a shared vision of the

¹ Zimmermann, A., Rowley, E., Martin, P. and Livesey, F. (2008) Barriers to the commercialisation of the regenerative medicine industry, unpublished manuscript.

² Workshop on the future of regenerative medicine, November 20th 2007, held at One Birdcage Walk, London, organised by Dr. Anke Zimmermann, Ms. Laure Dodin and Mr. Finbarr Livesey.

³ The Regenerative Medicine Grand Challenge (Remedi) is a major five year initiative sponsored by the EPSRC, led by Loughborough University, collaborating with the universities of Birmingham, Cambridge, Liverpool, Manchester, Nottingham, Ulster. For full details please see the project website at <http://www.remedigc.org>.

opportunities and challenges facing the RM industry can emerge. With such a common vision, it is hoped that the barriers to the development of the industry can be rapidly dismantled to the benefit of patients, companies and the country.

2. Understanding the RM industry

Regenerative medicine has emerged as a field of research and a new industry over the past twenty to thirty years. The industry began with an initial wave of companies in the 1990s and much hype regarding stem cells and their potential. Following a decline in activity some industry experts believe the industry is now moving into a more established phase, referred to as Regenerative Medicine 2.0.⁴ This is characterised as the transition moment where basic research and development is translated into products in use with more consistent and stable growth for RM based companies.

However, as the field of regenerative medicine has emerged from a number of disciplines there is continuing confusion on the boundaries of the industry. This section provides a brief background on the definition of regenerative medicine, as well as a current snapshot of the industry and its possible potential for the UK.

2.1 What is regenerative medicine?

The regenerative medicine field has developed over the past twenty to thirty years bringing together a number of disparate fields including biomaterials engineering, production engineering, cell biology and surgery.⁵ Having roots in many disciplines has caused confusion as each group defines the industry from its perspective. The simplest definition of regenerative medicine is that it “... replaces or regenerates human cells, tissues or organs, to restore or establish normal function.”⁶

Figure 1 highlights the complexity of the field, as products can have many components, using one or more of cells, matrices (or scaffolds) and growth factors. This also shows why there are overlaps of terminology as ‘tissue engineering’ and ‘cell therapy’ are part of the regenerative medicine space. Early discussions of cell therapy led some to equate stem cell approaches to regenerative medicine.

⁴ Mason, C. (2007) “Regenerative Medicine 2.0” *Regenerative Medicine*, vol.2, no. 1, pp. 11 – 18.

⁵ For further detail on the history of regenerative medicine see amongst others Kemp, P. (2006) “History of regenerative medicine: looking backwards to move forwards” *Regenerative Medicine*, vol. 1, no.5, pp. 653 – 669 and Vacanti, C. (2006) “The history of tissue engineering” *Journal of Cellular and Molecular Medicine*, vol. 10, no. 3, pp. 569 – 576.

⁶ Mason, C. and Dunnill, P. (2008) “A brief definition of regenerative medicine” *Regenerative Medicine*, vol. 3, no.1, pp. 1 – 5. This article collects a number of definitions and provides an overview position in an attempt to reduce confusion created by the multiple perspectives included in the regenerative medicine field.

While this is an important aspect of the industry it is one part of a complex landscape of potential stretching from cell biology to process engineering and materials development.⁷

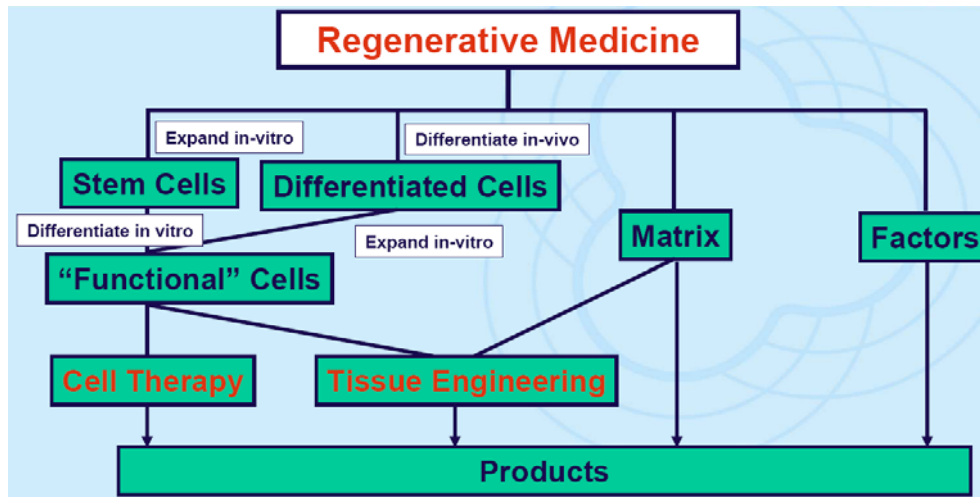


Figure 1 – definition of regenerative medicine⁸

As RM brings together cell therapy and tissue engineering it has potential applicability in a very broad range of diseases and conditions. This is both a strength and a weakness. With a broad applicability advances in regenerative medicine should have a larger impact across the healthcare system. However, given the disparate nature of the base fields for RM there is no unifying voice for the industry. Similarly patient groups do not identify with the term regenerative medicine as they are generally focused and organised by their specific disease categories.

2.2 The emergence of the RM industry

New industries emerge in many ways and follow many paths to success or failure. The regenerative medicine industry has gone through an initial period of growth and hype from the beginning of the 1990s followed by a significant contraction between 2000 and 2002 and stable growth to the present.⁹ Estimates of R&D investment between 1900 and 2000 are as high as \$2.5 billion

⁷ The issues for stem cell developments in the UK were the subject of the report of the UK Stem Cell Initiative (2005) available online at <http://www.advisorybodies.doh.gov.uk/uksci/>.

⁸ This diagram is taken from Dr. Paul Kemp's presentation to the London Regenerative Medicine Network in June 2007.

⁹ This section based on an ongoing series of reviews of tissue engineering and regenerative medicine culminating in Lysaght, M., Jaklenec, A. and Deweerd, E. (2008) "Great expectations: Private sector activity in tissue engineering, regenerative medicine and stem cell therapeutics" *Tissue Engineering*, vol. 14, no. 2, pp 305 – 315.

worldwide. However in the following three years commercial activity fell by half and the value of publicly traded companies in tissue engineering and regenerative medicine went from \$2.5 billion to \$300 million. Skin products, such as those produced by Intercytex and Organogenesis, have been amongst the first to be developed and to be successfully approved for use.¹⁰

Since that period the industry has regrouped and now appears to be building on more sustainable foundations. The original assumption that RM would develop akin to pharmaceuticals, with blockbuster products, has changed and a more realistic approach to product development is emerging. In 2007 there are approximately 170 firms worldwide operating in this space, with commercial sales of \$1500 million and a combined capital value of listed firms of \$4700 million. This indicates that the industry is transitioning from a dominant focus on research to a broader focus on translation of that research into products.

A clear example of the fortunes of the RM industry is that of Apligraf, a skin product produced by Organogenesis first approved for use in the United States in 1997. The company could not make the product profitable and filed for bankruptcy in 2002. The company came out of bankruptcy in 2003 and now has sales of \$60 million per year with the same product. According to Lysaght¹¹ this emphasises the need for understanding the non technical side of the business – reimbursement, production and understanding the customer. All of these challenges are current for the emerging RM industry in the UK.

2.3 The potential of RM

However, a key problem for researchers, developers and advocates of regenerative medicine has been an inability to develop well bounded estimates of its market potential or the scale of benefit in terms of healthcare outcomes. The combination of the breadth of conditions that may be addressable by a regenerative medicine solution and the significant uncertainty for the technologies under development means that any single estimate is likely to be significantly in error.

Existing estimates for the world market for regenerative medicine products in 2010 range from less than \$1 billion to greater than \$500 billion.¹² The US Department of Health and Human Services (HHS) estimates “The current world market for replacement organ therapies is in excess of \$350

¹⁰ See <http://www.intercytexas.com/> and <http://www.organogenesis.com/> for further details.

¹¹ Lysaght, M., Jaklenec, A. and Deweerd, E. (2008) “Great expectations: Private sector activity in tissue engineering, regenerative medicine, and stem cell therapeutics” *Tissue Engineering*, vol. 14, no. 2, pp. 305 – 315.

¹² Salter, B. (2007) State strategies and speculative innovation in regenerative medicine: the global politics of uncertain futures, Global Biopolitics Research Group, working paper no. 20, July 2007.

billion, and the projected U.S. market for regenerative medicine is estimated at \$100 billion.”¹³ Included within these estimates is the market for stem cell based therapies, as one set of products from the regenerative medicine industry. The UK represents approximately 3% to 5% of the world healthcare market, and if the middle estimate is taken this would translate into \$3 to \$5 billion of UK based sales in terms of potential for the UK based RM companies.¹⁴

Another way to approach estimates of national impact is to assess which elements of the current healthcare budget could be affected by RM therapies. A key impact for successful RM therapies is that they will reduce the ongoing care burden for patients and the healthcare system as they are by definition directed at replacing or regenerating cells, tissues or organs to restore function and hence remove the ongoing need for care. For example, an RM-based cure for diabetes would have significant impacts on healthcare budgets around the world. The economic costs of diabetes in the United States for 2007 have been estimated at \$174 billion, including “... \$58 billion to treat the portion of diabetes-related chronic complications that are attributed to diabetes ...” and another “... \$58 billion in reduced national productivity.”¹⁵ Similarly in the UK “The total annual cost of diabetes to the NHS has been estimated ... as between £1.28 and £1.36 billion in 2007 ...”¹⁶ With an increasing number of people suffering from diabetes, the estimates for cost and lost productivity are likely to increase and so there is the potential for over £1 billion in economic impact for the UK with a RM-based cure for diabetes (if similarly priced to current immediate care).

A similar estimate for other conditions quickly highlights how significant RM could be both as a generator of positive healthcare outcomes and as an industry. For example, a recent study on dementia commented that “The total cost of care for people with late onset dementia in 2005/6

¹³ DHHS (2005) *A Future for Regenerative Medicine*, US Department of Health and Human Services, Washington D.C.

¹⁴ The World Mapper project (<http://www.sasi.group.shef.ac.uk/worldmapper/index.html>) has developed public and private healthcare spending estimates based on the United Nations Human Development Report data for 2004. Combining the data tables for public and private spending in 2001 indicates the UK is approximately 3% of total spend.

¹⁵ American Diabetes Association (2008) “Economic costs of diabetes in the US in 2007” *Diabetes Care*, vol. 31, no. 3, March 2008.

¹⁶ Gough S. (2007) “Investing in excellent diabetes care now could avert a future NHS cash crisis” *Practical Diabetes International*, vol. 24, no. 24, May 2007. See also Bagust, A. et al (2002) “The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060” *Diabetic Medicine*, vol. 19, suppl. 4, pp. 1 – 5.

prices estimated to be £17.03 billion.”¹⁷ We cannot claim that successful RM-based products will solve the myriad problems of dementia, but even if a quarter of sufferers benefited from an RM approach potentially over £4 billion in healthcare costs could be saved.

The aging of populations around the world and their associated chronic conditions will significantly increase the demands placed on healthcare systems. The ageing index (the ratio of those over 60 to those under 15 in the population) for Europe is projected to rise from 1.16 in 2000 to 2.63 in 2050.¹⁸ According to the Alliance for Aging Research, 80% of Americans over the age of 65 have a chronic illness and the majority of these have more than one chronic illness.¹⁹

The potential for impact on the nature of chronic illness and the resulting impacts on the healthcare system are obvious. However, as was the case in the first period of the industry, care should be taken not to over promise. These technologies and therapies will take time to develop and so there should be no expectation of a short run return. This is why we would estimate the potential for the RM industry in the UK to be of the order of £5 billion per year if development is successful, with further positive impacts on the national economy through lower healthcare spending and improved quality of life.

The important message is that comparatively modest investments are required now to open up the possibility of these products being developed and made available in the UK in the longer term. Other countries are investing significantly in supporting the transition to production and once the lead is lost for the UK it will be very difficult to regain.

¹⁷ Dementia UK (2007) A report into the prevalence and cost of dementia prepared by the Personal Social Services Research Unit (PSSRU) at the London School of Economics and the Institute of Psychiatry at King’s College London, for the Alzheimer’s Society.

¹⁸ UN (2001) World Population Ageing 1950 – 2050, Department of Economic and Social Affairs, United Nations.

¹⁹ Data taken from (2006) The Silver Book: Chronic disease and medical innovation in an aging nation, Alliance for Aging Research, Washington D.C. Available online at <http://www.silverbook.org/>.

3. Barriers to emergence of the RM industry in the UK

Any new industry faces a number of challenges as it emerges and attempts to grow. Some will succeed and some will fail. However, areas such as regenerative medicine have specific technical and contextual challenges that means assistance from government could raise the probability that the industry develops efficiently and embeds successfully in the UK.

This section outlines the current barriers to the emergence of the RM industry in the UK as seen by a range of stakeholders, including company managers, researchers and clinicians, collected through one on one interviews and in a group workshop.²⁰ The barriers are discussed briefly, outlining the issue and why it is of concern for the UK. The next section of the report discusses how these barriers are being addressed and what additional measures may be required to assist the development of a strong RM industry in the UK.

3.1 Clarity of identity and vision

Regenerative medicine suffers from not having a single voice as it brings together a number of disciplines and addresses a wide range of diseases and conditions. The multiple perspectives on what is included and what is not, what other areas overlap or are contained within the industry and how to think about the development of the RM space all stem from having a broad potential impact requiring multidisciplinary development. Without a common definition of the industry there will continue to be a lack of coherence to support for the research and development of new RM therapies. The emergence of standards (such as PAS83 and PAS 84 from the BSI²¹) and a number of articles on the definition of the industry²² will help, but it is an issue which needs to be resolved quickly so that there is a clear voice for the industry and a shared direction of development.

Beyond definitions, it is not clear whether the industry is coherent with a shared vision of what the industry is and what its potential (both in terms of healthcare outcomes and economic impact) is to

²⁰ The interviews were completed between August and December 2007 and the workshop was held in November 2007.

²¹ See (2006) PAS83: Guidance on codes of practice, standardised methods and regulation for cell based therapeutics, BSI Standards available online at <http://www.bsi-global.com/en/Shop/Publication-Detail/?pid=000000000030139919> and (2008) PAS84: Regenerative Medicine Glossary, available online at <http://www.bsigroup.com/en/Standards-and-Publications/Industry-Sectors/Healthcare/PAS-84/2nd-promo/>.

²² For example Mason, C. and Dunnill, P. (2008) "A brief definition of regenerative medicine" *Regenerative Medicine*, vol. 3, no.1, pp. 1 – 5.

the UK. The industry is at a very early stage of emergence and therefore does not yet have a clear structure or high levels of public awareness. There are no blockbuster products in broad use in the healthcare system and it is unlikely that any blockbusters will emerge in the short term.

At the same time, there are few recognised leaders within the industry, either in terms of individuals or companies. There are notable exceptions, such as Dr. Paul Kemp²³, Dr. Chris Mason²⁴ and Dr. Stephen Minger²⁵, but until a broad group of leaders emerge there will be a lack of coherence to the RM industry and few role models for other potential companies in their embryonic stages of development to model their development on.

This leads to a number of difficulties which are at the root of regulatory, funding and public acceptance issues. Without public pressure for the products of the RM industry there is lower demand than might otherwise be expected. Similarly, investors with little access to knowledge of the industry are unlikely to risk capital supporting young companies. Finally, support from government is likely to be lower as the inclusion of the industry in funding calls and policy support will be dependent on the profile of industries within government departments such as BERR and DIUS, the Office for Strategic Coordination of Health Research (OSCHR), and support agencies providing funds for development.

3.2 No investment model and lack of translational funding

Section 2.3 discussed the potential for regenerative medicine and the difficulties in producing reliable projections at this early stage of development. This high level of risk in development is compounded for venture capital investment by a lack of clear business models. Venture capital investors cannot see where their exit will be and therefore there is no incentive to step into the space. At the same time, the business model for a broad range of RM-based products has not yet been clarified. The pharmaceutical approach of scale may not be open to regenerative products as they could be produced in batches of one within the clinic. This leads to a lack of translational funding and compounds the view of the UK as a location that is good for development but not for commercialising products.

Funding for the translational of science into products in regenerative medicine has begun to emerge, with the EPSRC support of the Regenerative Medicine Grand Challenge and the TSB investment in

²³ Dr. Paul Kemp founded Intercytex and is Chief Scientific Officer and Executive Director, further details available from <http://www.intercytexas.com/icx/about/management/kemp>.

²⁴ Dr. Chris Mason is Senior Lecturer in Biochemical Engineering at UCL, further details available from <http://www.ucl.ac.uk/biochemeng/staff/mason.htm>.

²⁵ Dr. Stephen Minger is Senior Lecturer and Director of King's Stem Cell Biology Laboratory, King's College London.

cellular therapies in 2006 and 2008. However, these investments need to be deepened if the transition from science to product is to be negotiated successfully, especially as there are complex production issues that remain to be solved and which will continue to need research effort.

Only recently has it become clear that, in addition to world class biological science, RM requires critical process and manufacturing expertise to produce cost-effective and competitive therapies. This makes RM significantly different from the pharmaceutical and classical biotech sectors where the cost of manufacture is comparatively small, and the process technology is somewhat straightforward. In RM the process is the product. The need for sophisticated RM manufacturing technology is both a barrier to progress and an opportunity to develop and secure a long term industrial presence in the UK.

The recent Sainsbury Review specifically identified RM as an example of the new high added value manufacturing industries that could revitalise the UK's industrial base.²⁶ The report commented that "As new industries emerge from the science base, production is typically more closely linked to R&D and involves higher skills and more sophisticated processes. Production in regenerative medicine, for example, involves a very advanced knowledge of biology coupled with sophisticated process and automation knowledge." However, there is little production capability, from clinical trials phase one through to scale production for use in day to day clinical settings, in the UK (although some efforts have been made, for example by Intercytex and at University College London). This is because investment in RM companies is difficult and fragmented. The general venture finance climate is weak, the poor experience with conventional biotech investments remains a barrier and there are, as yet, no exemplars of conversion of emerging RM businesses into major public companies, with consequent investor returns. In addition, rapid evolution of RM companies will require comparatively early capital investments in process technologies for pilot and full scale manufacture - an investment area venture funds have traditionally never covered. In essence, the financial markets are not yet functioning effectively in the RM space and this is a major barrier for the rapid transition from academic research to viable supply of competitive therapies.

3.3 Regulatory uncertainty

The regulatory framework for RM products in the UK is necessarily still evolving, albeit the UK is ahead of many other countries in its regulatory thinking and flexibility. Where practical, approaches from pharmaceuticals and biotech are being carried across. However, these do not address all the specific issues in developing, testing and producing RM therapies. In addition, EU guidelines are not always aligned with UK directives with further scope for confusion.

²⁶ Lord Sainsbury (2007) *The Race to the Top: Review of UK government's science and innovation policies*, HM Treasury.

In conjunction with physicians and developers, there is considerable scope to create and maintain a regulatory environment in the UK that allows early but safe clinical evaluation of novel RM therapies and the rapid conversion of these to generally available treatments. Most of the emerging RM technology comes from SMEs so a regulatory approach is required that allows these small companies to work effectively with regulators. This implies more expertise and resource for regulators to guide and advise the RM SMEs who would otherwise lack the necessary professional expertise in regulatory matters.

The regulation of development also needs to align with the demands of the US market, as this will be a lead market for many companies. The approach taken by the FDA is in some ways more flexible than that in the UK and companies need to be prepared to interact with a system which is different from that they face in the UK. This may again point to more proactive linkages between regulators, companies and other support agencies such as the UKTI in assisting companies to develop here but export to large markets elsewhere. To the greatest extent possible, UK regulatory practice must acknowledge and align with US market needs.

3.4 Polymaths required

The nature of RM demands the bringing together of deep biological knowledge and complex engineering skills. As well as understanding the biology of healing processes, for example, engineers are required to provide production capability for innovative RM products. This blending of skill sets is difficult to achieve but it is required for companies which spin-out of university research and in larger existing companies trying to develop in this area. Essentially there is a need for engineers who understand biology and biologists who understand engineering

Beyond the technical and scientific knowledge required to operate in the RM industry, there appears to be a lack of entrepreneurship amongst UK graduates, with lower levels of total entrepreneurial activity for those who graduated after 2000 compared to those who graduated pre-2000.²⁷ This could be limiting the emergence of the industry and may continue to be a barrier to company formation and growth in general. Extending the training and skills development of graduate students should be a priority to assist in the development of industries such as regenerative medicine.

²⁷ Harding, R. (2007) Graduate Entrepreneurship in the UK: summary report from GEM UK data, National Council for Graduate Entrepreneurship, research report 003/2007.

3.5 Difficulties in moving from idea to clinic

For start-up companies (and some larger companies) understanding the stages and complexities of taking an idea through development and on to use by clinicians remains difficult. The figure below shows a simplified version of this process, which involves at least seven separate organisations and gates where the product may be denied access to the next stage of the process. No clear roadmap exists for RM companies on the number of hurdles that they will face in taking a therapy from an idea in the science base to a commercial product in use. Some of this is due to the regulatory uncertainties discussed above. However, the environment in which innovative therapies are introduced in the NHS is also an issue. For example, the evidence level required for reimbursement is onerous for RM products which have a different scale to pharmaceutical products.

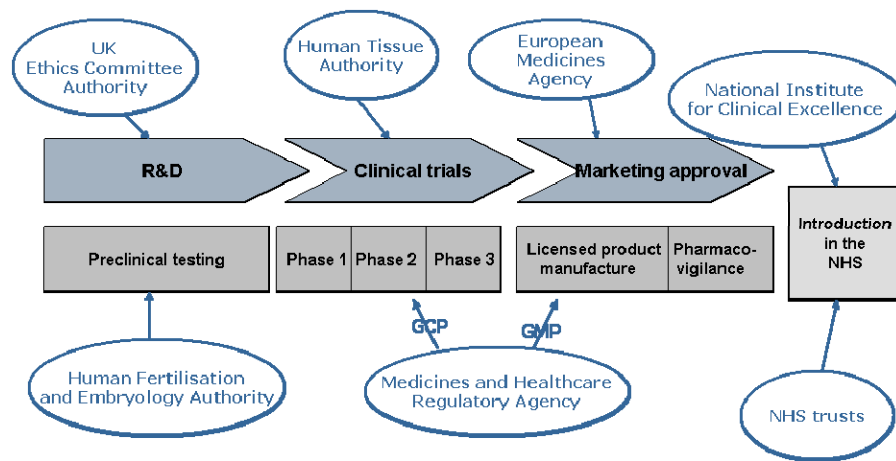


Figure 2 – Simplified path from research to product

The process above is based on the established gating for pharmaceutical products which is not directly applicable to regenerative medicine based products which may be made in batches of one specifically for a single patient. The concept of a clinical trial in these circumstances is open to question and more research is required to clarify what will be an acceptable trial for such products.

The scale of the NHS is again both a barrier and an opportunity - having effectively a single large customer in the UK could be an advantage if managed correctly, but for an emerging RM company, the NHS can also appear to be an intimidating and bureaucratic partner. The increased emphasis on innovation within the NHS is a positive trend, but there remains much to do before the translational relationships with the RM supply side work as well as they will need to.

Overall the NHS is seen as a poor adopter of new technology, with few incentives for clinicians to attempt to bring radical or innovative therapies into use. If there is low demand for new therapies at the point of use it will remain difficult for UK based RM companies to understand the clinical needs

they are trying to serve and to find a path to a customer for their products. This reduces the likelihood of RM companies basing themselves in the UK for development and therefore making production here unlikely as well. New structures to allow clinicians to be involved in innovative developments are required.

3.7 The challenge from North America

For companies in high technology areas emerging from the science base where to locate their activities is a key decision. Access to key resources, such as university research and intellectual property, a supportive environment for development and the market that can be accessed from the company location all play a part in deciding where to locate. For UK researchers and developers starting an RM company, whether to remain here or to have operations in the United States is a difficult choice.

The US represents the largest developed market for new medical products aligned to a flexible regulatory structure that is open to the products of the RM industry. There is an obvious negative in terms of research and development using new stem cell lines, but it is expected that with the presidential election in November of 2008 this stance is likely to change. According to the Associated Press both Senator Obama and Senator McCain support relaxing the rules regarding federal funding of stem cell research.²⁸ Public attitudes in the United States to embryonic stem cell research have also become more positive in the past number of years, with the percentage of adults indicating that they somewhat or strongly favour such work being at its lowest in 2002 (35%) rising to a high of 58% in 2005.²⁹

²⁸ "Where do they stand: Obama, McCain on the issues" *Associated Press*, June 3rd 2008.

²⁹ Data taken from figure 7-18 *Science and Engineering Indicators 2008*, National Science Foundation. Survey respondents were asked "On the whole, how much do you favor or oppose medical research that uses stem cells from human embryos?"

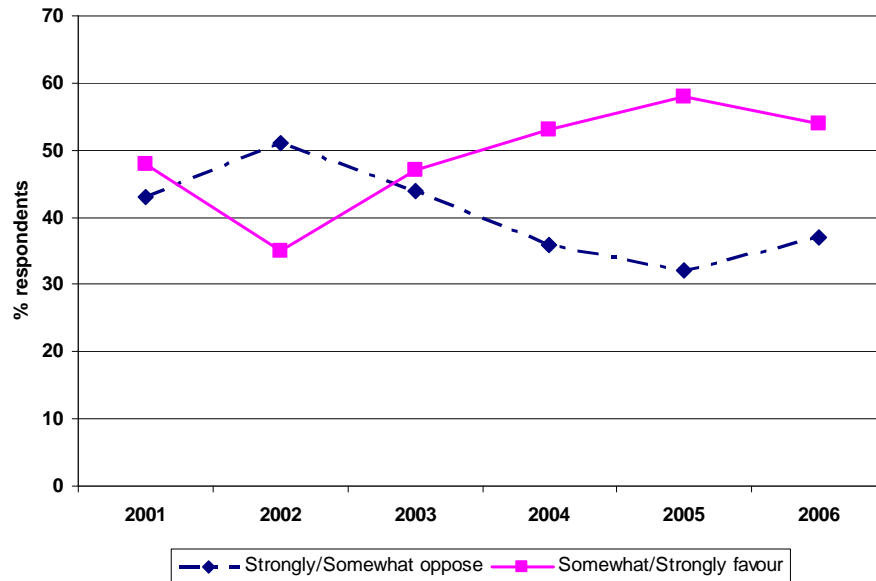


Figure 3 – Public opinion on embryonic stem cell research in the United States 2001 - 2006³⁰

As the public attitude towards such work shifts, there are increasing public and private investments in the regenerative medicine area. The California Institute for Regenerative Medicine (CIRM) is the most obvious with \$3 billion in state funding provided by the passage of Proposition 71 in 2004 (although according to the CIRM it has spent \$530 million to date).³¹ A key centre of excellence in research and development of regenerative medicine therapies is the McGowan Institute for Regenerative Medicine.³² The Institute was founded in 2001 with an explicit mission to bring together faculty across disciplines and to pursue rapid commercialisation of new technologies (although it does not have scale production facilities at present). The scale of the work being undertaken at the McGowan Institute is highlighted by the recent announcement of an \$85 million joint project with the US Armed Forces and Wake Forest University Baptist Medical Center to develop new treatments for wounded soldiers.³³ With such significant investments being made with such clear targets the lead for UK researchers is likely to erode.

³⁰ Ibid.

³¹ For further details see the CIRM website at <http://www.cirm.ca.gov/>.

³² More details on the McGowan Institute are available on their homepage at <http://www.upmc.com/services/mirm>.

³³ The announcement has attracted significant press coverage for example <http://www.newsweek.com/id/136309>.

4. Addressing the barriers to commercialisation

This is a crucial time as the industry transitions from its initial research bias, to having products and technologies that need to be translated from a research environment into clinical use.³⁴ There is a key role for government to play in supporting that transition especially to ensure that the public interest is at the heart of these developments for patient benefit and overall contribution to the national economy.³⁵ The significant investment and support from government to date should not be minimised, however there are a number of clear and targeted initiatives that will raise the potential for capturing the return on those investments within the UK.

This section outlines recommendations for public investment and support to assist in the development of the regenerative medicine industry to the benefit of the UK economy. There are five core areas which require significant funding and a number of supporting elements that would enhance the larger investment. An estimate of the investment required is in the order of £125 million with the majority of that spend occurring in the first five years.

4.1 Translational institutes

RM is an ideal target for the emerging concept of "Translational Medicine", under which the interface between the researcher, manufacturer and physician is closer and mutually supportive. RM therapies will be delivered primarily in a hospital setting requiring ease of use and new physician skills. This interface is critical, particularly for autologous therapies where the patient is the donor of the source material and which may require local processing for conversion to the final therapy form.

Translational institutes would support the type of interdisciplinary research required for the production and development of new RM products. In such institutes basic research is carried out alongside production (to clinical trials scale) so that there is close interaction between biologists, engineers and clinicians. Each institute would have laboratory space co-located with production capability as well as potentially space for incubating new RM companies. A possible model for this kind of work is the McGowan Institute discussed in section 3.7 or the MRC Regenerative Medicine centre in Edinburgh which covers the "... full spectrum of research - from basic mechanisms of stem cell regulation, via rigorous translational studies to provide the basis for new therapies, to clinical trials with stem cells and their derivatives."³⁶

³⁴ Mason, C. (2007), "Regenerative Medicine 2.0" *Regenerative Medicine*, vol. 2, no. 1, pp. 11 – 18.

³⁵ Salter, B. (2007) "State strategies and speculative innovation in regenerative medicine: the global politics of uncertain futures" Global Biopolitics Research Group Working Paper no. 20, July 2007.

³⁶ Further details available on their website at <http://www.scrm.ed.ac.uk/>.

Funding for such a venture could be developed under the aligned funding approach proposed by the Sainsbury Review.³⁷ Bringing together the support of the EPSRC, BBSRC, Technology Strategy Board and a number of RDAs would provide the scale required for one to two such institutes to be developed. Estimates of the investment required for such an institute would include £5 million in capital costs with ongoing salary and consumables costs of £2.5 million. Over a ten year cycle this would be approximately £6 million in funding per year for two translational institutes.

4.2 Investment support for production

The issues with private investment for production scale up of RM are significant. Existing vehicles for encouraging investment in smaller high risk companies (such as VCTs and EIS) do not specifically target either production or innovative healthcare products. In order to assist initial investments in this type of activity with the specific intention of introducing new therapies into the healthcare system, a new vehicle which explicitly supports this type of capital investment is recommended. These should be structured as capital allowances for venture investors to receive tax relief on investments specifically in production for areas such as regenerative medicine. An upper limit for the allowances should be set in the order of £5 million per year.

4.3 Expanding the role of the regulator

The continuing development of appropriate regulation for RM products make starting a company and predicting the route and time to market very difficult. While the AMTP regulation has provided some clarity (at the EU level) it is still likely that many products will be dealt with on a case by case basis as the regulator engages with the industry.

To assist smaller companies (especially start-ups coming from the science base) reduce the regulatory risk that they face, we propose increasing the capacity of the regulator to be proactive rather than reactive to innovative products. In this way, companies could get guidance directly from the regulator in advance of any submission for marketing authorisation or clinical trials providing them with clarity on potential requirements and allowing the regulator to see and adapt to the issues that such innovative products may bring to light.

This would involve having specific regulatory positions which were service based to assist SMEs in developing industries such as regenerative medicine. These new positions could also be tasked with monitoring EU regulatory developments in emerging technology areas. We would estimate the need for 5 such positions and for these to be funded at a senior level to attract experienced regulators.

³⁷ See Sainsbury Review recommendations 5.5 and 2.4 (footnote 25).

At the same time there is a need for monitoring and adaptation to the regulation of RM products in the United States. If UK companies are not supported in entering the US market, while maintaining research, development and production in the UK, there is a higher likelihood that these companies could relocate entirely to the US. A strong connection should be made between regulators and support agencies such as UK Trade and Investment (UKTI). This would provide other agencies with a better understanding of regulation and its importance in areas such as regenerative medicine.

4.4 Developing polymaths

The demands of a multidisciplinary area like regenerative medicine are very high for those wishing to start and build a company. As well as having to have an understanding of the underlying biology, company founders will have to become conversant in process engineering, complex regulation and new product development for a difficult customer.

Individuals with these skills are in short supply. The funding of doctoral training centers (DTCs) across a number of biology and healthcare related areas and in particular the recent £10 million funding for two DTCs related to regenerative medicine is a strong positive move. However, these research focused doctorates are likely to complete in 2012 and there is a need for talented personnel on a shorter time frame. Therefore we propose a Masters level qualification, possibly tied to a translational institute, specifically aimed at deepening the technical expertise of rising stars in the RM field while providing them with the business skills required to start and successfully grow a company.

Potential funding for such a Masters would possibly include –

- Six months to one year of course development
- A full-time course Director who would oversee the development and running of the course
- Access to laboratory space
- Support for industrial placements for students
- Salaries for 3 – 4 faculty and at least one administrator

As well as providing places for 20 – 30 full time students in the Masters course a number of executive education modules should be developed and offered using the faculty for the Masters course. These courses would be subsidised for the first 3 to 5 years, as the companies requiring their support develop and grow. After this the courses would be offered on a fee basis and would assist the transition of the Masters to be self sustaining.

4.5 Support for a trade association

In order to bring the industry together under one banner, and to provide it with a clear voice to funders and supporters, there is a need for a trade association to emerge for regenerative medicine. Over time it is likely that such an association would emerge, but only once the industry was well established with clear boundaries and companies of sufficient scale. Given the critical period of development, support for a trade association could speed up the emergence of the industry by providing clear direction and vision of the potential of the industry to members and to potential investors, as well as a more direct interface for government with the industry.

There are leading groups emerging, for example that developed through the Regenerative Medicine Grand Challenge, but these do not have the capacity to form and run a true trade association. Support for initial meetings, office space and a salary for the head of the trade association would be relatively cheap but could provide necessary focus early in the lifecycle of the industry in the UK. It would be expected that the association would become self sustaining after 3 to 5 years, as companies should engage and support the activities by that stage.

4.6 Assisting clinicians to introduce new therapies

As discussed above, the NHS can be a difficult environment to introduce new and radical therapies. For SMEs there can appear to be too much bureaucracy and for clinicians they may not have the time or the incentives to attempt to introduce new approaches to care. The acceptance by clinicians of RM products will be key to the continued growth of the industry.

Innovation fellowships could provide leading clinicians with the incentive to work with emerging therapies by providing them with six months to a year to investigate and work with new clinical approaches. At a minimum such fellowships should buy out 50% of the clinician's time and support should be provided to link the fellows with leading RM companies early in their development process. Assuming a clinician with a base salary of £150K per year³⁸ and 50% buy out ten fellowships would cost approximately £750K excluding employment costs.

³⁸ Based on the mid point of the clinician pay scale quoted on the NHS Careers website <http://www.nhscareers.nhs.uk/details/Default.aspx?Id=553>.

4.7 Estimated costs

Please note that all estimates are in constant 2008 pounds.

Item	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Assumptions
Translational institutes	15.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	£10M in capital costs with £5M in operating costs (salaries, consumables ...) per year
Capital allowances	5.00	5.00	5.00	5.00	5.00						Upper limit on allowed allowances for private capital investment in RM facilities
Increased R&D funding (1)	5.00	5.00	5.00	5.00	5.00						Aligned research funding across the Research Councils, TSB and RDAs
Skills support (2)	1.00	1.00	1.00	1.00	1.00						Development of Masters course for new type of polymath and continued professional development courses offered from the base of the Masters
Regulatory capacity (3)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	Increased personnel with the specific remit to work with RM companies ahead of submissions
Trade association	0.25	0.15	0.15	0.15	0.15						Support for the activities of a trade association and salary costs for the head of the association
Innovation fellowships (4)	0.75	0.75	0.75	0.75	0.75						10 fellowships, 50% buy out with 150K baseline salary
Totals	27.50	17.40	17.40	17.40	17.40	5.50	5.50	5.50	5.50	5.50	

Notes

- 1 Based on order of magnitude of Grand Challenge projects to support 2 - 3 significant projects
- 2 Estimated based on discussions with recent Masters programmes set up in technology and enterprise
- 3 Based on maximum salaries of 100K per new regulator
- 4 Taking the mid-point of current clinician salaries from NHS data on pay scales available from <http://www.nhscareers.nhs.uk/details/Default.aspx?Id=553>

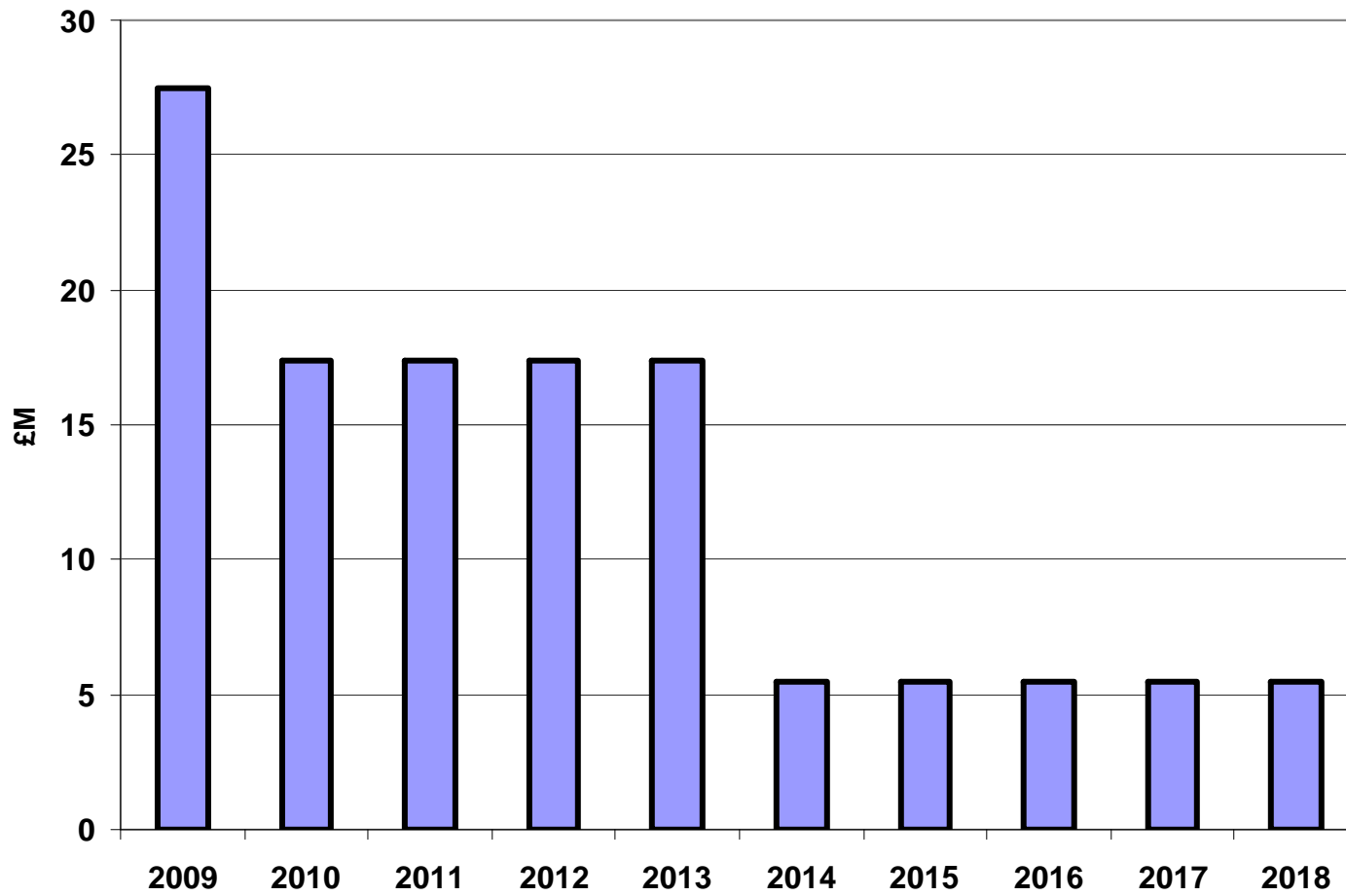


Figure 4 – estimated spend profile for public support for RM industry

5. Moving forward

Subjectively, the RM industry might materially improve the health of around 1 million people per annum in the UK, generate upwards of £5 billion of commercial activity and employ around 15,000 people in knowledge-based research and manufacturing jobs. There is a three to five year window as the industry becomes established for investments in R&D to be matched with investment in production capability (including infrastructure, regulation, skills etc.) The potential return from the RM industry will be based on the additional healthcare benefits it can provide, the commercial returns to companies based in the UK, the returns to the economy as a whole in terms of jobs and revenues to the exchequer) and the potential of foreign direct investment from companies wishing to invest in regenerative medicine.

A blend of public and private action is required now if there is to be a stable and significant RM industry based in the UK in the long term. The actions outlined above in section 4 highlight public action that could significantly affect the emergence of the industry. A wide number of agencies and departments will need to be involved including the Department of Health, the Technology Strategy Board, the Research Councils and OSCHR, as well as regulators and clinicians. Private sector investment requires the confidence of these actions prior to significant involvement.

Other countries are moving quickly in this field and investing significantly. For example, a recent report on the investments of the United States National Institutes of Health (NIH) in regenerative medicine estimates that the NIH is spending over \$600 million on tissue engineering and regenerative medicine per year.³⁹ Such examples show the depth of activity in the field and the extent of public involvement across the world.

The nature and complexity of regenerative medicine, where the product is the manufacturing process, implies that there is an opportunity for embedding significant parts of the value chain in the UK. The investments that occur in the coming years will determine the shape of the industry and the UK is well placed to take advantage. However a final word of caution. The early hype of the industry, where regenerative medicine was referred to as the 'hottest' job in 2000, led quickly to disappointment. Investments in research alone were not enough. The supporting infrastructure of regulation, demand

³⁹ Wang, F. Sipe, J. D., Kelley, C.A., (2008) Support for tissue engineering and regenerative medicine by the National Institutes of Health, chapter 29 in Mao, J.J., Vunjak-Novakovic, G. Mikos, A. G., Atala, A. (eds) Translational Approaches in Tissue Engineering and Regenerative Medicine, Artech House, Boston

for innovative therapies and the production of highly skilled polymaths are as important as the headline levels of investment in research and development. With these in place the UK can be a leader in regenerative medicine and can reap the broad benefits of this industry.

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