

**REGENERATIVE MEDICINE:
BUSINESS MODELS, VENTURE CAPITAL AND THE FUNDING GAP**

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CONTENTS	Page
Executive Summary	3
1. Background	5
2. Regenerative medicine products and their development	6
3. Current Funding for RM products.....	7
3.1 The concept of a funding gap	7
3.2 Current public funding in regenerative medicine	10
3.3 Private investment in biotechnology and regenerative medicine.....	12
4. Managing the environment for business investment.....	13
4.1 Market-related factors – Value Based Pricing (VBP).....	13
4.2 Regulatory influences	14
5. Stakeholder perspectives on issues relevant to the funding gaps.	15
5.1 Business models and the nature and causes of the funding gap(s)	15
5.2 The roles of public and private investors	16
5.3 Regulation and new regulatory initiatives	17
5.4 Markets and reimbursement	18
6. Innovative funding models and stakeholder perceptions	18
6.1 Regenerative Medicine Translation Centres.....	19
6.2 Biomedical mega funds	20
6.3 Venture philanthropy.....	22
6.4 Red Investment Bank	24
6.5 Transitional portfolio model	25
6.6 Pharma-driven collaborative model	25
7. New funding models under development.....	26
7.1 Innovation Supported Capital Fund	27
7.2 A Re-Insurance Funding Model	27
8. Conclusions.....	28
8.1 Therapy development	29
8.2 Supporting infrastructure	33
8.3 Stimulating the interest of future investors.....	33
8.4 The business environment and future funding needs.....	33
9. Overview and future research needs	34
9.1 Further research needs	34
References.....	36
Annex 1. Research framework and methods.....	39

Executive Summary

This project has explored potential funding models to support the development of regenerative medicine therapies, focusing particularly on the funding gap or gaps in the later stages of clinical development. We considered which current and potential funding models could support RM innovation in the UK, based on: (1) a literature survey of reports relevant to innovative funding models for RM therapies; (2) Innogen Institute and Innogen Centre previous research and current policy engagement; (3) engagement with the ongoing work of the Cell Therapy Catapult; and (4) interviews and a workshop based discussion with other key actors in the RM innovation process (companies, policy makers, investors and healthcare professionals). We explored the range of funding models currently available across all countries with interests in RM development and considered their feasibility and viability in contributing to company strategies and product portfolios and, ultimately, to UK national competitive advantage.

We gave attention mainly to:

- **Autologous cellular products** – patients are treated with a modified version of their own cells.
- **Allogeneic cellular products** – patients are treated with cells from a single donor multiplied on a large scale and distributed widely.

Our headline conclusions are:

1. There is some evidence that the reluctance of investors to move into support for cell therapies and RM more generally is justified, and inducements to undertake investment should take account of the reasons for this caution, including lack of proven effective business models, regulatory uncertainty, lack of manufacturing capacity, poorly designed clinical trials, uncertainty about remuneration and future pricing models.
2. There is no single funding gap that, once bridged, the technology can move smoothly to future development. Depending on the chosen innovation pathway, funding gaps can emerge at different points in the route to a final market, primarily depending on whether the cellular product is autologous or allogeneic.
3. The funding models most likely to work in the short term are those with a significant public or philanthropic component.
4. Policies in support of RM developments should take account of the fluid nature of expected business models in this sector, including the extent to which future innovation pathways (autologous or allogeneic) will be disruptive or path-dependent, and which industry sectors are most likely to be able to deliver on future benefits from this technology.
5. Where an innovation pathway is likely to be disruptive for the companies concerned, contrary to conventional wisdom, there may be a case for direct government involvement, for example in market creation and support or, as has been the case in Japan, in tailoring the regulatory system to provide incentives to develop RM therapies based on iPS cells.
6. Policies should be open to considering the potentially important roles of a range of companies in developing RM and cell therapies, including particularly small and medium sized companies and, for example, blood transfusion services.
7. Taking the above points into consideration, **Regenerative Medicine Translation Centres** and **Venture Philanthropy** were seen as the most promising funding

- approaches to meet the needs for the development of cell-based therapies in the short run.
8. Other funding models considered (**Biomedical Mega fund, Red Investment Bank, and Pharma Driven Collaborative Model**) were seen as having the potential to support RM applications other than cellular therapies, or in the development of the supporting infrastructure for cell therapy development. The Transitional Portfolio Model was not seen as having any particular value in the RM context.
 9. Two funding models identified, currently in development, the **Re-Insurance Funding Model** and the **Innovation Supported Capital Fund**, both seemed promising in the longer term but had yet to be tested in the context of RM.

The following requirements for further research, analysis and investigation emerge from this research project:

1. More in-depth research with potential developers and potential funders of RM therapies and related products, undertaking financial modelling in the context of a variety of potential future innovation pathways to understand better how policies to support the innovation environment could encourage such investment in future.
2. A more intensive exploration of the policy options open to the UK government to support innovation trajectories in order to encourage future investment from a broad range of sources.

The above suggestions should become part of an integrated policy approach that identifies what components of the overall innovation ecosystem can usefully be co-located with the central cell production facilities for both autologous and allogeneic therapies, and how they can be induced to locate in the UK in a way that is less vulnerable to future international mobility.

1. Background

The Regenerative Medicine Report of the UK House of Lords Science and Technology Committee (HoL S&TC, 2013) identified a number of barriers to the translation of the UK's scientific strength in regenerative medicine (RM) from 'bench to bedside': regulation and intellectual property (IP) protection; clinical trials design; manufacturing capacity; NHS procurement strategies; NICE evaluation processes; and, the focus of this project, the lack of innovative business models leading to commercialisation. The HoL Report also identified factors that could contribute to the translation of RM science into treatments that are societally and economically beneficial (Department for Business Innovation & Skills (BIS), 2011), and explored the conditions under which RM could be enabled to flourish as a commercially viable technology as envisaged by the Technology Strategy Board (TSB) in its Strategy for UK Regenerative Medicine (TSB, 2012).

This project arose from the recommendation in Chapter 5 of the HoL Report, *Commercialisation: Business models, venture capital and the funding gap*, 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" (pp. 60-61). The HoL S&TC Report (2013) focused particularly on the funding gap at Technology Readiness Levels (TRLs) 6-8 (US Department of Energy (DoE), 2011). Although TRLs were developed mainly for IT and engineering projects and do not translate well to life sciences, these TRLs can be seen as equivalent to Phase 1, 2 and 3 respectively of clinical trial development. We explored the range of funding models that could potentially contribute to meeting this recommendation and considered their potential viability, given the current state of development of RM technologies and other factors that will influence the attractiveness of this area as a commercial investment.

Our primary focus has been on innovative funding models, but the attractiveness of any investment will depend on the industry structure, and the business model adopted by the company concerned and this will in turn be dependent on the other influencing factors identified in the HoL Report. Based on our background research, this analysis has paid particular attention to manufacturing challenges, markets, remuneration prospects and regulatory influences on development costs and timescales. These factors are currently being addressed by government departments and others to improve the attractiveness of a therapy as a commercial investment and they are also covered by other initiatives arising from the HoL Report, for example the Regenerative Medicine Expert Group (RMEG) chaired by Sir Mark Rawlins (<https://www.gov.uk/government/groups/regenerative-medicine-expert-group>).

This project considered which current and potential funding models could support RM innovation in the UK, based on: (1) a literature survey of reports relevant to innovative funding models for RM therapies; (2) Innogen Institute and Innogen Centre previous research and current policy engagement; (3) engagement with the ongoing work of the Cell Therapy Catapult; and (4) interviews and a workshop based discussion with other key actors in the RM innovation process (companies, policy makers, investors and healthcare professionals). We explored the range of funding models currently available across all countries with interests in RM development and considered their feasibility and viability in contributing to company strategies and product portfolios and, ultimately, to UK national competitive advantage. (See Annex 1. Research Framework and Methods.)

2. Regenerative medicine products and their development

The HoL Report defined RM as “methods to replace or regenerate human cells, tissue or organs in order to restore or establish normal function” (Mason and Dunnill, 2008) and included cell therapies, tissue engineering, gene therapy and biomedical engineering techniques, along with more traditional treatments involving pharmaceuticals, biologics and devices. For this project, we focused mainly on types of RM that are novel, challenging and likely to experience one or more significant funding gaps, that involve the use of living cells, and are sufficiently well developed to be at least anticipating, and preferably engaged in, clinical trials. The involvement of living cells in the final product imposes some common features on company business models in these areas but there are still significant differences in the potential business models that will apply to them, particularly related to the distinction between autologous and allogeneic cells.

- **Autologous cellular products** – patients are treated with a modified version of their own cells.
- **Allogeneic cellular products** – patients are treated with cells from a single donor multiplied on a large scale and distributed widely.

Allogeneic therapies are regarded by investors as the most commercially attractive, being more scalable, with the opportunity to serve much larger markets, but both autologous and allogeneic therapies are the subject of intense speculation and interest. *Figure 1* describes two types of autologous therapy: service-based model where cells are processed off-site probably in a centralised facility; and on-site processing requiring facilities in a clinic for processing cells and injecting them back into patients. Differences between the two types of therapy include the fact that on-site processing cannot benefit from the economies of scale of the service-based model. In allogeneic therapies (*Figure 2*), cells from a single donor are multiplied on a large scale to deliver treatments to very large numbers of patients in distributed markets.

We did not include stem cell banking or the use of differentiated stem cells for pharmaceutical toxicity or efficacy testing in this project, as both are less likely to experience a funding gap during their development. We did include the development of supporting technologies (such as cell manufacture, tools and reagents, and distribution channels) where these were seen as essential contributors to development of a viable, fundable value chain, e.g. the availability and capacity of cell manufacturing facilities. Interest in regenerative medicine has been growing and media coverage has resulted in optimism about stem cells and their potential for curing various diseases. Li et al (2014) found an increase in the number of clinical trials in novel areas, especially since 2006 with increasing industry involvement either as collaborators or as principal sponsors of the research. Approximately 25% of clinical trials had involved industry partners, mainly in the USA, not including the involvement of private Clinical Research Organizations (CROs).

A report from the Alliance for Regenerative Medicine (ARM, 2014) shows that oncology, cardiovascular, and central nervous system are the main areas where commercial companies are conducting clinical trials (*Figure 3*), signalling a change of focus for future markets compared to current areas of provision (inset in *Figure 3*).

Figure 1: Autologous Cell Therapies (Smith, 2008)

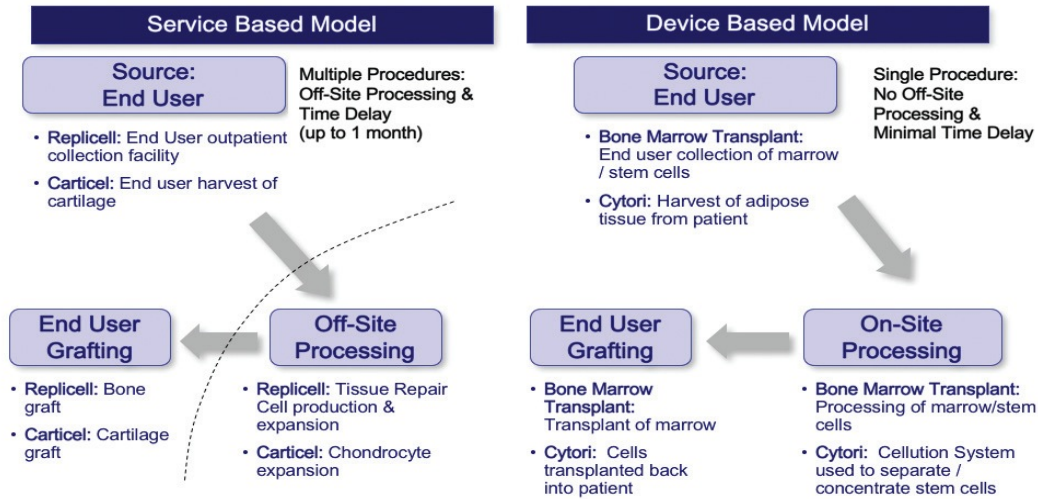
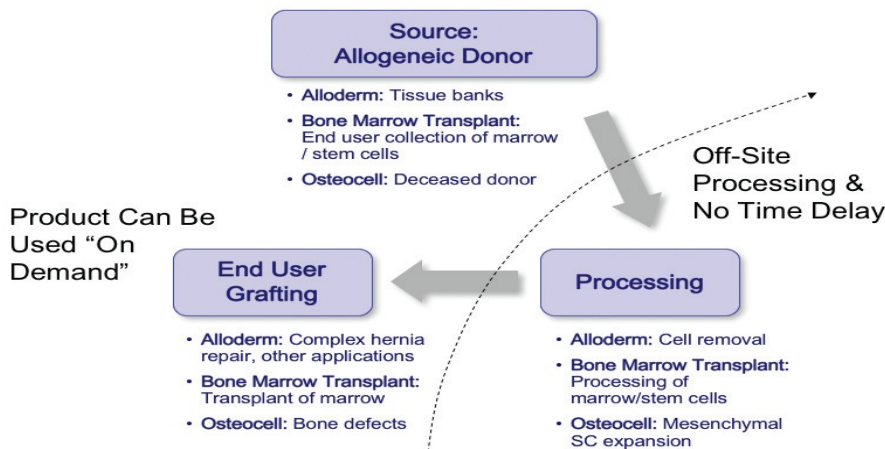


Figure 2: Allogeneic Cell Therapies (Smith, 2008)



Source: Company Information, Frankel Group Analysis

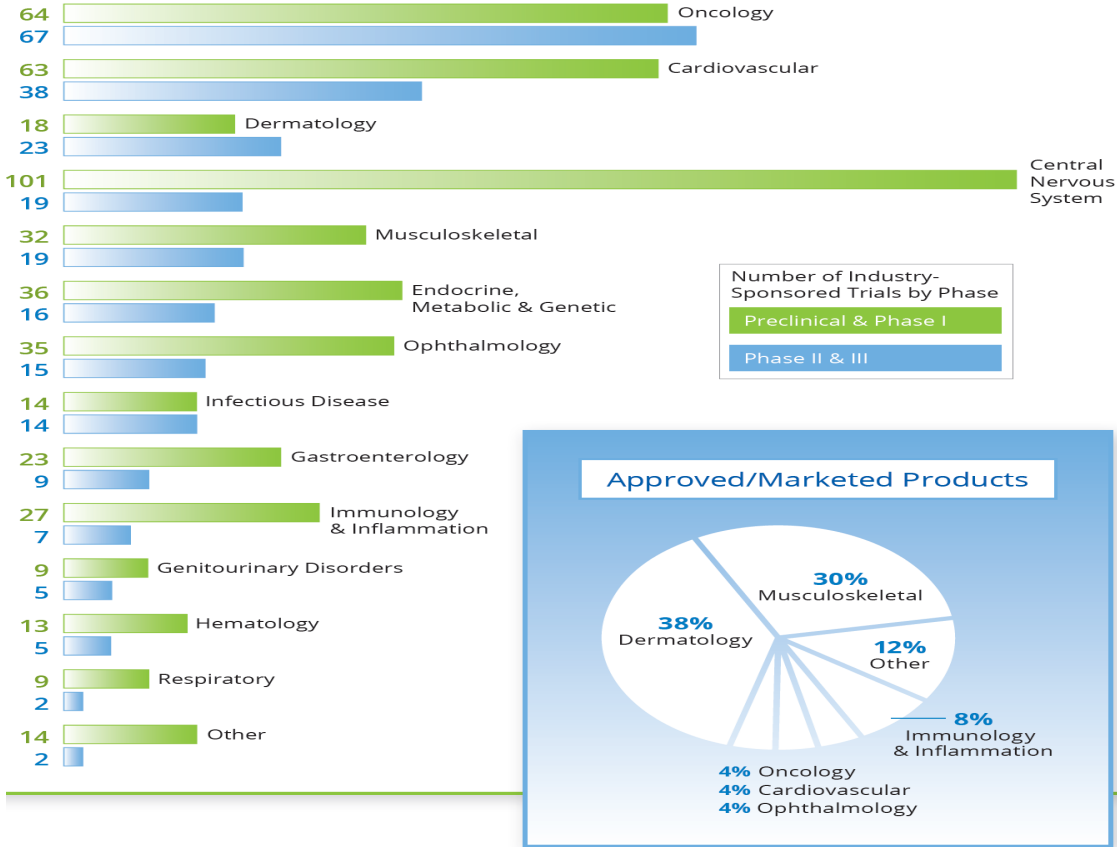
3. Current Funding for RM products

3.1 The concept of a funding gap

Ford and Nelsen (2014), in a study based on US data, note that the landscape of funding for biotechnology based companies in general has changed since the economic recession. The previous overall strategy of venture capitalists (VCs) was to have a portfolio of low risk, low return stocks and bonds that gave predictable and stable returns, accompanied by a small portion of assets in higher risk, potentially higher return vehicles, for example in the life sciences. However, generally meagre returns from life science companies led to withdrawal of capital. This shift in the funding landscape opened up space, and increased the pressure, for more innovative approaches to investment in life science companies. As shown in Figure 4, venture capital is now *proportionately* a smaller part of the overall picture and other funders have extended their interests to cover a broader range of development phases. The Ford and Nelsen paper applies to biotechnology companies in general, but these pressures are amplified

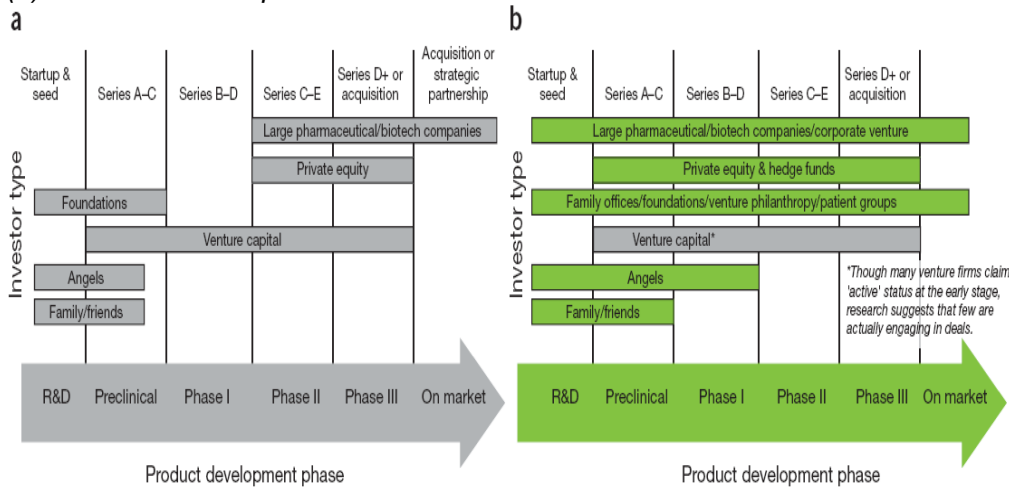
in the case of RM therapies and the options for innovative funding models are correspondingly more circumscribed.

Figure 3: Regenerative Medicine and Advanced Therapy Clinical Breakdown by Therapeutic Areas



Source: ARM-Annual Report- 2014

Figure 4: The changing funding landscape in life sciences: (a) the traditional landscape: (b) the new landscape



Source: Ford and Nelsen (2014)

We use the term 'funding gap' to refer to a sector or sub-sector wide deficit in funding for the ongoing operations or future development of innovative products and processes, particularly by small and medium sized firms. Funding gaps can be covered by investment from venture capital or angel investors, equity sales, through debt offerings and bank loans, or from public sources.

A major concern in RM therapy development has been lack of private sector funding and overall domination by the public sector (Figure 5). The HoL report suggested that the most important funding gap for RM occurs in moving from phase 2 to phase 3 clinical trials because of the requirement for expensive large scale cell manufacturing capacity at that point. However, the ARM report (2014) suggests that lack of funding for early-stage clinical trials may result in poorly designed trials generating inconclusive data that will then prove unattractive to private investors who would otherwise fund the later stages of development. Although the focus of this report is mainly on the later funding gap, it is important to bear in mind that there may also be a deficit in funding in early development phases that can have important implications for later stage funding of RM products.

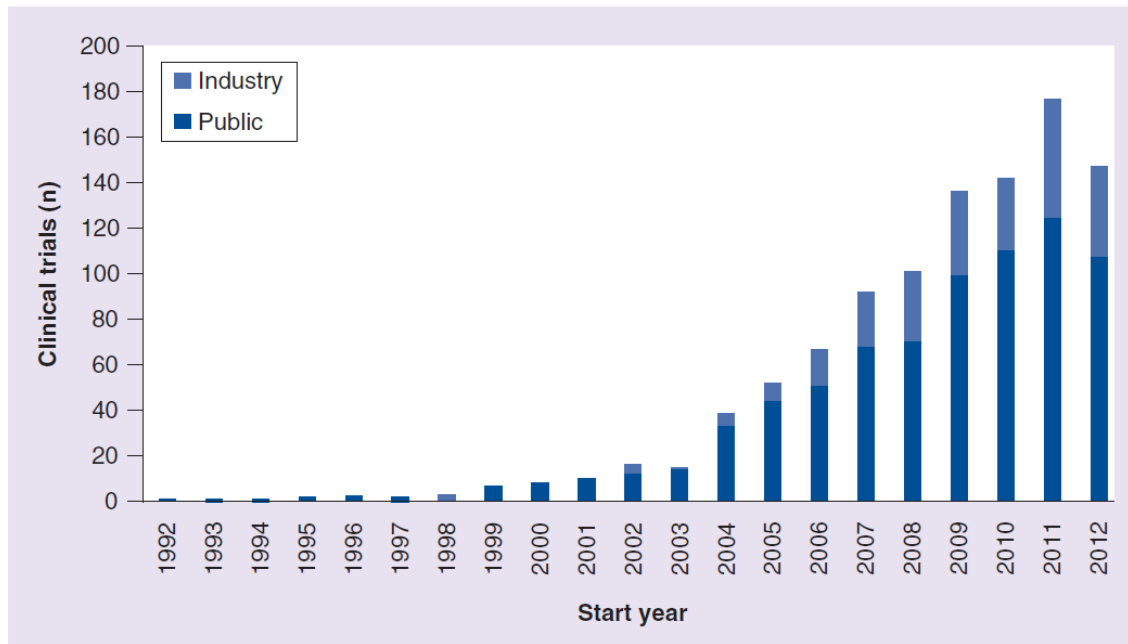
Factors contributing to the later stage funding gap, in addition to cell manufacturing capacity, include technology readiness, market opportunity and reimbursement, logistics of product delivery, inadequate business models, regulatory uncertainty, lack of ability to spread financial risk for investors, excessive focus on supply side rather than the demand-side of therapy development, lack of a holistic view on product development through different stages of clinical trials, and lack of standards in the industry (Williams *et al.*, 2010; Mastroeni *et al.*, 2012; ARM, 2014; Mittra *et al.*, 2014; VALUE Project, 2012).

The experience of the product Dermagraft, launched in 2002, illustrates how lack of market readiness to take up RM products can also create funding problems. This device for diabetic foot ulcers at an average cost of £2000/patient faced poor market uptake partly because, being classified as a device, its cost was compared against conventional wound dressings and its relative value could not be demonstrated. Withdrawn from the UK, it is now marketed by Organogenesis in the USA. Similarly, RM products that are delivered as a surgical procedure (e.g. treatment of knee meniscus tears using autologous stem cells) may not be reimbursed by healthcare systems if compared only to the lower cost of standard surgery. RM therapies often challenge existing healthcare pathways and may fail to break through into the clinic if rigid and narrow health technology assessment requirements are used. This lack of a proven track record for the industry backed by ground-breaking, high performing therapies increases the perceived industry and business risk for potential funders, who tend to base risk forecasts on historical analysis.

The existence of a funding gap or gaps, and the inability of regions or countries (especially in Europe) to stimulate the transformation of venture capital (VC) from being an intermediary that solves finance-specific problems, to being one that provides both financial resources and non-financial added value, are the subject of debate (Rosiello *et al.*, 2011), for example considering whether the state should intervene directly or indirectly as an investor or use other means to solve market failure problems. Nightingale *et al.* (2009) argue that, "If the affected firms genuinely have high potential, this gap would warrant public intervention to address and correct any under investment." As a result, the state has been drawn into such markets both as an alternative investor to venture capital firms, and as a co-investor with them, for example via 'hybrid' VC funds. On the other hand Bottazzi *et al.* (2004) and Da Rin *et al.* (2006) suggest that the

idea of closing a funding gap through public intervention is misleading and that policy-makers should refrain from direct investment and focus on defining appropriate taxation and fiscal institutional conditions to stimulate VC investments and entrepreneurship. Both approaches justify public intervention on the basis of supply-side failures, an implicit assumption being that the pre-conditions for the development of a market already exist.

Figure 5: Industry and publicly funded clinical trials



Source: Li et al., 2014

For other authors, however, a market requires both a buyer and a seller to execute transactions of exchange, supportive institutions that regulate the behaviour of both sides, and a critical mass of players for long term sustainability (Rosiello *et al*, 2011). On these premises the emergence of a VC market cannot be stimulated by supply side tools that focus solely on capital provision or fiscal conditions. Institutional arrangements are required to regulate market transactions and the existence of a *remediable* funding gap cannot be assumed.

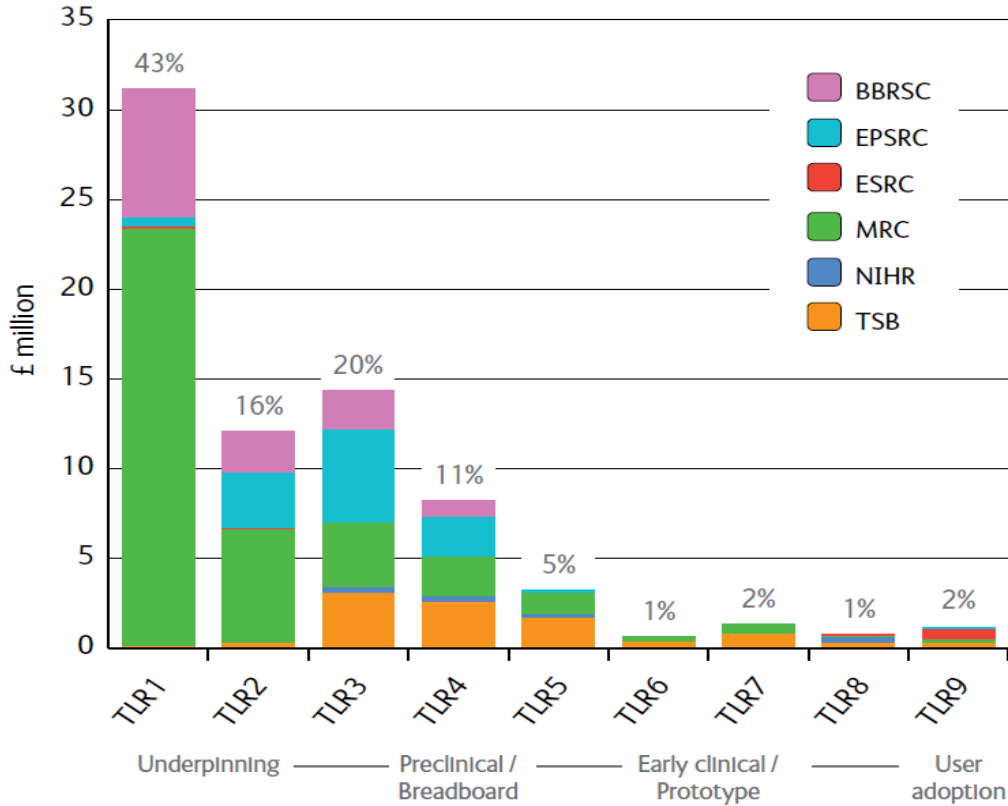
3.2 Current public funding in regenerative medicine

The UK public sector spent approximately £77 million on Regenerative Medicine in 2012 (MRC, £37.2 million; BBSRC £13.5 million; NIHR, £9 million; EPSRC, £10.4 million; TSB, £5.95 million; EPSRC, £0.9 million). Figure 6 shows how this public funding is allocated to different stages of technology development, with basic research (technology readiness levels (TRL) 1-3) taking up approximately 79% of total public funding. However, TRLs 1 - 3 constitute less than 10% of the time and cost to develop a new product so other sources of investment will be needed to enable long-term viability of the RM sector.

In 2012, the UK Cell Therapy Catapult was launched to support companies working in this area. It is a not-for-profit organisation with a budget of over £70 million until 2017. The Biomedical Catalyst, a joint program between MRC and TSB, is another source of

public funding for regenerative medicine, supporting SMEs in the general healthcare domain, to help in overcoming the early stage funding gap. Although the Biomedical Catalyst covers a broad domain of research, regenerative medicine is one of its priority areas.

Figure 6: Breakdown of public funding in various stages of regenerative medicine development



Source: TSB, 2012

The European Commission has contributed €249.6 million from 2007-2012 to stem cell research projects (HoL, 2013). Also, in 2012, the Innovative Medicine Initiative (IMI) launched the €26 million Stem Cells for Biological Assays of Novel Drugs and Predictive Toxicology (STEMBANCC) project to develop 1500 induced pluripotent stem cell (iPSC) lines to be used by researchers to test drug efficacy and safety for a range of diseases including diabetes and dementia.

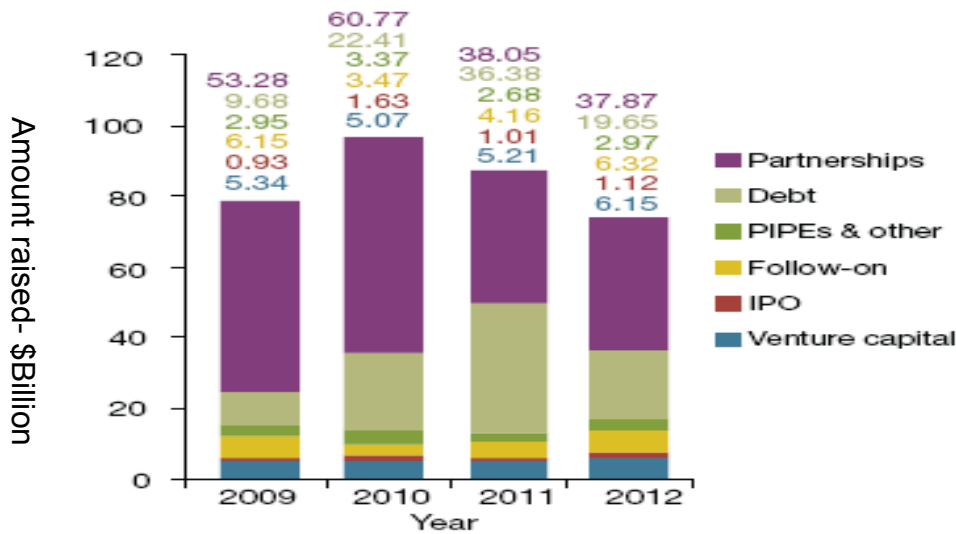
Third sector investment in regenerative medicine has also been increasing: between 2005-2010 over £51 million was invested in regenerative medicine, and in 2011-2012 the Wellcome Trust awarded £55.4 million in this area. Also, in partnership with the MRC, the Wellcome Trust has invested £12.75 million to generate and characterise iPSC lines (HoL, 2013). However, such philanthropic contributions have mainly funded basic research, an exception being Syncona Partners, a limited liability partnership (LLP) launched by the Wellcome Trust in 2012 (£200 million) to fund small, profitable businesses that have transformed a healthcare market, covering a broad range of innovative healthcare technologies, including RM.

3.3 Private investment in biotechnology and regenerative medicine

Figure 7 shows that (i) there was a drop in private investment in the global biotech industry between 2010 and 2012 and (ii) partnerships make up the highest contribution from private investment with the role of venture capital being insignificant. However, recent data suggest that this trend is reversing and in 2013 investment in early-stage biotechnology rose 26% to \$2.7 billion (up from \$2.1 billion in 2012) while late-stage funding decreased from \$2.1 billion to \$1.9 billion for the same period. There was thus a shift in 2013 from follow-on to early-stage funding (105% increase in investment in the latter and 23% decrease in investment in the former) (Vlahos and Karacsony, 2014).

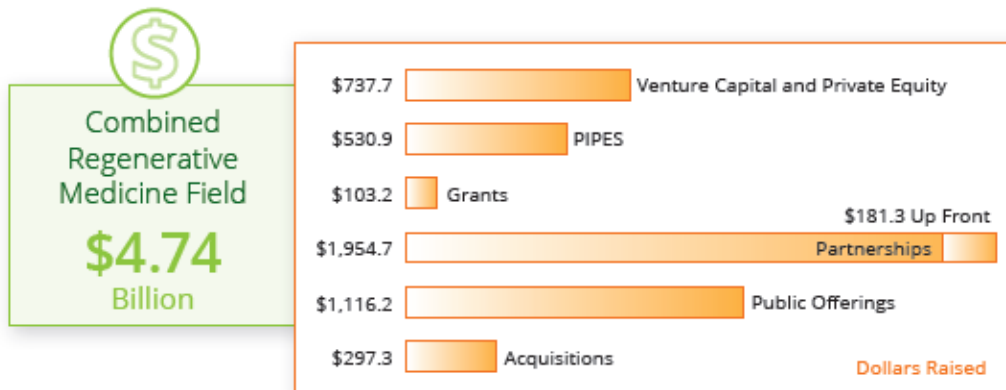
For regenerative medicine, Figure 8 shows that, from March 2013-March 2014, investments in partnerships and funding from VC funds were beginning to signal the potential attraction of the sector for private investors. Nevertheless, compared to biotechnology as a whole (Figure 7) with approx. \$60 billion investment in 2012, the \$4.7 billion investment in RM (Figure 8) is relatively small.

Figure 7: Global biotech industry financing



Source: Huggett, 2013

Figure 8: Funding raised in RM from March 2013-2014



Source: ARM, 2014

4. Managing the environment for business investment

In considering whether to invest in a particular company, an investor will pay most attention to the overall industry structure and dynamics, the company's business model, markets for products, quality and experience of the management team, as well as social, environmental and ethical risks. Factors in the business environment that could impact positively or negatively on the ability of the management team to implement the business model will also be important. Regulatory, market and pricing issues are key environmental influences that will determine the viability of future funding models for new RM products and the associated risks. Intellectual property (IP) related issues are also very important in considering the viability of RM business models (Courtney *et al.*, 2011), but were not included in this project. While Section 5 focuses on the views of the stakeholders we consulted on potential funding models, it is important to bear in mind that without a supportive business environment, as noted above in Section 1, incentives directed solely towards funding models may fail to deliver the expected benefits. This will be particularly true for the allogeneic therapies that are expected to be the most commercially attractive options.

4.1 Market-related factors – Value Based Pricing (VBP)

One of the most significant developments in the UK that could impact on commercial development of RM therapies was expected to be the move towards VBP by the National Institute for Health and Care Excellence (NICE). The HoL (2013) Report on RM (paragraph 143) noted the inadequacy of NICE's evaluation process for innovative treatments on the grounds that it did not consider long term savings that would off-set high upfront costs. The VBP model takes account of additional value gains and wider health benefits, which the conventional quality adjusted life years (QALY) approach does not capture and could demonstrate how early investment in the field could unlock other treatments with significant economic impact, both in terms of savings to the health system and increased potential work productivity. The HoL report suggests that the Department of Health should evaluate the VBP model for RM therapies one year after it is implemented in 2014 to determine payment for new drugs. Key challenges for RM are to demonstrate how therapies can fit into established healthcare pathways and so be taken up by healthcare providers, and conventional cost-benefit approaches that are too limited in scope to demonstrate the value of RM.

Considering whether and how VBP can work (Rafferty, 2013), two amendments were proposed to NICE's methods of assessing cost per QALY: (i) relevant costs would be extended beyond those falling on the NHS to include costs to carers and those arising from changes in employment; (ii) QALYs, instead of being based purely on duration and quality of life, would be weighted to reflect severity and the end of life experience. Although these changes could be dealt with by amending NICE's methodology guide, concerns arose from the use of employment criteria as this could undermine the principles of equity within the NHS. Also there could be unintended consequences of extending the cost perspective beyond the NHS in that it would favour some diseases and treatments but disadvantage others. Thus, an effective treatment for a disease with high care requirements (Alzheimer's disease) or one that enabled continued employment (multiple sclerosis) would involve a higher perceived benefit/cost ratio and hence a more favourable cost per QALY. On the other hand, a drug that extends survival in a highly dependent state (many cancer drugs) could incur a higher cost and hence a worse cost per QALY. Furthermore, increasing the range and scope of 'value' could require substantial and additional research to produce the data required by NICE to

make its decision, which would be borne by the company. For a small RM company this would not be insignificant and could put pressure on the business model.

In the face of these disagreements on the methods to be used for value based assessment (VBA) of medicines under VBP, NICE instituted a consultation on VBA in 2014. However, there was little agreement among the 121 organisations that responded to the consultation and further work in this area has been shelved as of September 2014 (<http://www.binleys.com/newsItem.asp?ItemID=3186&thisYear=2014>).

4.2 Regulatory influences

The regulatory system for allogeneic products in the EU provides a centralised procedure that aims to reduce the risks and uncertainties faced by developers. However it imposes very high regulatory hurdles for safety, efficacy, quality and post-marketing surveillance and its basis on a pharmaceutical model of regulation raises challenging issues, particularly for the small companies that are at the forefront in developing these products (Mitra *et al.*, 2014). The principal regulatory questions on safety and efficacy are: the appropriateness of animal models for preclinical testing, and probable future regulatory requirements at this early stage of development; along with requirements for the design and execution of Stage 2 and 3 clinical trials. Such factors will inevitably affect the decisions of potential investors in this area regarding the future viability of such investments.

Policy makers and others are beginning to respond to increasing concerns in a range of areas about the impact of specific regulatory initiatives on innovation in RM. An expert panel convened by the US Institute of Medicine (Lenzi *et al.*, 2014) has reviewed the activities of the National Institute of Health (NIH) Recombinant DNA Advisory Committee (RAC) and suggested relaxing the vetting requirements for gene therapy clinical trials, claiming that the risks are no greater than in other areas of experimental medicine. The RAC panel has required researchers to file a description of all experiments and then publicised the proposals and held public meetings before approving any trials, significantly lengthening the regulatory process. Given that the public now has a more positive view of gene therapy as a result of some good clinical outcomes, the report recommends that the RAC should be replaced by a body with a broader mandate to examine all forms of risky clinical research and not to exceptionalise gene therapy. Although this proposal has not been formally accepted and does not suggest the total removal of a regulatory hurdle, it does highlight a growing move to normalise some areas of experimental medicine and to modify the regulatory landscape to facilitate innovation and clinical uptake.

In a similar direction, Japan has announced a fast-track approval process for stem cell therapies (Nature Medicine, 2013), the first example of a country creating a new pathway specifically for RM, stimulated by Japan's historically slow regulatory process and the desire to facilitate development of iPS cell technologies, originating from Japanese research. Under Japan's Pharmaceutical Affairs Law regenerative therapies must, like small-molecule drugs, undergo a conventional three-stage clinical trial process to get marketing approval from Japan's Pharmaceutical and Medical Devices Agency. The proposed amendments will create a new, separate approval channel for RM where, instead of phased clinical trials, companies will have to demonstrate efficacy in pilot studies: involving 10 or perhaps fewer patients if the change is dramatic; or a few hundred if improvement is more marginal. If efficacy can be "surmised," the treatment could be approved for commercial use and, crucially for such expensive treatments, for

national insurance coverage. Treatments would then be subject to post-approval surveillance for 5-7 years. The expected approval time for a new therapy under this scheme is three years.

A cost/value issue for the Japanese approach arises from requiring patients who receive the therapies to pay the 30% of costs required under Japan's national insurance plan, equivalent to asking them to pay for the privilege of serving as the subjects of medical experiments. Also, since the patients are paying, studies cannot be randomized or blinded, and paying patients may be more likely to experience placebo effects (Nature Medicine, 2013).

Finally, in the UK there is continuing debate about the role and future of the 'hospital exemption' route to clinical application. The Advanced Therapy Medicinal Products (ATMP) Regulation (EC Regulation 1394/2007) distinguishes between hospital-based and commercial research, and specifies different regulatory requirements for hospitals growing cells for autologous treatments on a non-routine basis. In the UK, the 'hospital-exemption' permits medical doctors or surgeons in hospitals to provide treatments to patients that have not been approved for trial or full licensing. This provides an opportunity to develop RM treatments within the clinic, but it is not a commercial option because of the requirement that the treatment not be provided on a 'routine basis' and be for a named patient. The issue has been raised as to what constitutes "non-routine" preparation of ATMPs. The MHRA, in its guidance notes, takes the view that it is not feasible to provide a simple numerical formula that would clearly delineate the boundary between routine and non-routine production. However, the Agency believes that it is possible to give some indication/guidance. The MHRA will monitor the use of the exemption and may amend or extend the guidance in the light of subsequent experience.

<http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/Othermedicinesconsultations/CON051874>)

The ATMP regulation also prohibits use of the hospital exemption route for the production of clinical trial data in preparation for a future market authorisation application. The hospital exemption is continually being reviewed so its future as a mechanism to facilitate RM in the clinic is uncertain.

5. Stakeholder perspectives on issues relevant to the funding gaps.

We interviewed potential investors, financiers, company managers, and researchers, and held a discussion with the representatives of public bodies, companies, investors and universities who attended our workshop (see Annex 1). These people are collectively referred to below as 'stakeholders' and the discussions and interviews led, as reported in this section, to useful commentary on business models, the nature of funding gaps, the appropriate roles of public and commercial funding for RM applications, regulation, and reimbursement issues. In the sections below, quotes from stakeholders are in italics.

5.1 Business models and the nature and causes of the funding gap(s)

There is a common view in the literature and among the experts we consulted for this project that the funding gaps being experienced today for RM products are similar to those that affected earlier generations of innovative medical products such as bio-pharmaceuticals. This leads to the conclusion that such issues are capable of being

resolved (bio-pharmaceuticals' funding problems having been resolved when a pharmaceutical business model was developed and the regulatory system was aligned with the needs of the new products), and that it will take a similar time (10-15 years) to resolve them for RM technologies. However Innogen Institute research has questioned this assumption (Tait, 2007), as did some of the experts we consulted, based on the considerably greater disruptive potential of RM therapies for conventional pharmaceutical business models.

A recurring theme in discussions was the difference between autologous and allogeneic therapies, but with no consensus on how the differences would be reflected in the future shape of RM-related innovation pathways and the associated funding opportunities. For example, although the allogeneic approaches seem more attractive commercially in the long term, the technical and regulatory challenges there are much greater than for autologous treatments. Autologous treatments are therefore further ahead in demonstrated clinical utility and current commercially feasible opportunities are mainly in autologous treatment. Although commercially feasible allogeneic treatments are likely to be developed eventually, so far very little clinical utility has been demonstrated in that area, compared to successes in autologous cell therapy.

These issues are related to the current lack of serious interest in RM therapies from large pharma companies (mentioned by all our respondents), given the disruptive nature of this technology for current pharmaceutical business models. However, there was also a view that '*... pharma business models had better evolve or they will go out of business*', and RM therapies were seen as part of a move towards more personalised approaches to health care. One view was that '*There will be some health care treatments that work across the board, and allogeneic treatments will be a part of that, but autologous may be bigger – stratified if not personalised. Pharma companies are backing off from RM just now.*' Blood transfusion services, rather than pharmaceutical companies were seen to be very well placed to deliver these new business models.

Barriers reinforcing the current funding gaps were seen to be in scaling up products, in the regulatory system, in fragmentation of decision makers, and in reimbursement (given pressures on potential primary markets to save money on health care). This led to the comment that '*time to value*' is the big challenge – current interventions to accelerate early clinical trials and in translational funding can be seen in terms of assisting developers with 'time to value'.

The biggest risks for an investor were seen to be around future uncertainty about regulatory oversight, putting RM '*somewhere between a risk and an opportunity*'.

5.2 The roles of public and private investors

The amount of early stage innovative and clinical work in RM related development that is being publicly funded and being conducted by academic researchers and bodies like the blood transfusion service was seen as an unusual state of affairs. The important question now was seen as "*to determine how much modality this investment is going to have*".

There was a general view that the role of government should be to set the conditions for private capital success, addressing tax and capital formation conditions around particular technologies to enable private capital rather than to leverage or direct it. If Government tries to *be* the market it distorts prices and the risk environment and can cause private

capital to withdraw. Likewise, a loan to a biotech company in the early stages was not seen as a good idea because the company would have to securitise its IP for a loan that it would not be able to repay for 8 – 10 years. A better option for the company would be to ask for equity secured by its IP.

Accelerating the amount of funding coming into the area in order to accelerate the rate of development of therapies was seen as potentially dangerous if it resulted in a “*clinical disaster*” that could “*really hammer your market*”. Rather than focusing on funding, a more urgent task was seen to be orchestration of the interactions across the whole value system and communicating the right messages to keep everyone on board. The example of gene therapy was mentioned several times as a case where inappropriate haste led to long term damage to an innovation trajectory.

Viewing public funding as part of a process of translation, subsidies can help younger companies convince the funding community that they have value, and much of that value will reside in commercial IP. How much of that IP will be in the UK is a key question.

5.3 Regulation and new regulatory initiatives

A major problem for RM was seen to be the lack of a defined regulatory path to market. Regulatory authorities were described as “...*having different conversations with different developers in different countries*”. This regulatory uncertainty means that “... *it takes longer, it is more expensive and mistakes will be made along the way*”. There were also seen to be practical regulatory challenges in the distribution of cells in the recipient’s body: for omni- or pluri-potent cells monitoring the nature of the final cell type; long term monitoring for carcinogenic potential and the lack of technology to answer these questions. “*Not only are we having to think of solutions to unanswered questions, we’re actually having to come up with actually what might be some of the questions*” The cost of regulation as part of the development process was expected to increase through sequential stages of clinical trials and the overall cost also to continue to increase. This then led to questions of reimbursement in the context of a niche market. A related point was the reflection that harmonisation of regulatory systems is an important requirement, along with some exemplars of cases that have moved all the way through the system.

Some stakeholders identified more fundamental issues with the appropriateness of the current regulatory approaches. RM therapies as they have evolved were seen as more akin to organ transplantation than to pills that either do or do not work, and transplantation was seen as “*not really an industry*”. From one perspective: “*The industry has ... tried to take learning from drugs, devices or biologics and put them into regenerative medical products where it’s a ... totally different therapy and business model. ... It’s got to be a gradual adoption of the therapy and the earlier we can get into that adoption the better, rather than wait 15 years for a licensing event and then find out that NICE isn’t going to reimburse it.*” Another view was: “*The surgical involvement is more akin to medical devices but they are not medical devices in that their regulatory pathway is more akin to biologics, but they’re not biologics because they have more of a surgical input, so they’re a hybrid*”. Such issues were seen to be having an important influence on the availability of funding.

There were mixed views on the usefulness of the Japanese regulatory initiative described in Section 4.2. For some, as an adaptive licensing-type of approach it was seen as potentially useful. On the other hand, although it may make it easier to get

started and so lead to more people moving into the sector, as the first step in a very lengthy process it was not expected to reduce the overall cost or timescale of development.

5.4 Markets and reimbursement

The market for supporting tools and technologies (for example for manufacture, distribution, delivery or monitoring) was seen as an important adjunct to that for RM therapeutics themselves. Such tools and technologies will be an integral part of RM value chains and will need to be available in the right form (co-innovation) and at the right time (co-evolution) to enable development of therapies. Reimbursement for the development of tools will depend on the expected viability of the market for the therapy and so the two markets are inextricably related, but potentially separately funded and regulated, e.g. through the development of standards.

A common comment was that, when small companies target niche RM therapies, they will need to be able to service an international market; the sales force will be specialised and the market small, although potentially widely distributed in a few specialist centres. The market was seen to be more similar to that for a surgical technique than for a drug but once a small niche grows to become the norm in clinical care, pharma companies were expected to take an interest, probably by acquiring the companies active in the niche. This outcome was related to a comment on the probable loss of revenue to the country that provided the support to build up the company/industry and the question whether there is anything that a government can do to enable development within its jurisdiction of a new thriving industry sector based on the public funding that it has provided.

In the UK, NICE was seen as an important part of the picture, but the proposed value-based pricing approach (section 4.1) was not regarded as particularly helpful in the context of RM therapies. A circular argument was seen to be involved in that data would be needed on which to base the pricing calculations, and the therapy would need to be fairly well developed before such data could be collected. Also, given that NICE tends not to support small, specialised, expensive procedures, the view was that RM would probably be developed first in the USA or Japan. One stakeholder commented that UK companies should focus on international markets rather than the NHS, but this then raises subsequent questions about the ability of companies to make a strong case for future investment to be retained within the UK as they grow and develop.

6. Innovative funding models and stakeholder perceptions

Our exploratory research for this project covered a broad range of potentially innovative funding models and we selected the following as being sufficiently innovative for more detailed consideration, either because they had been applied in other contexts with potential for application to RM, or because they have only recently begun to be deployed in the context of RM therapies: translation centres; mega funds; venture philanthropy; investment bank; transitional portfolio; and pharma-driven collaboration. The following sections each describe briefly the nature of the funding model, and the subsections in each case outline comments on the model from the stakeholders we consulted.

6.1 Regenerative Medicine Translation Centres

RM Translation Centres are being set up in several countries with the aim of helping companies through the gap from 'proof of concept' to Phase 2 clinical trials where the bulk of the activity in RM therapy development is located just now, and representation of this model is building globally, including for example: in the UK the Cell Therapy Catapult and Catapult Manufacturing Centre, the California Institute for Regenerative Medicine (CIRM) and the Canadian Centre for the Commercialisation of Regenerative Medicine (CCRM). Similar initiatives have also been set up in four other US States, Germany, Korea, Australia and Japan, each with significant baseline public funding.

Following the approval of the California Stem Cell Research and Cures Act in 2004, the issuance of \$3 billion in state bonds was authorised to support stem cell research over 10 years through the establishment of the CIRM, the total budget committed up to the end of 2013 being \$1.79 billion for 604 projects (CIRM, 2011). CIRM has been criticised for devoting 69% of its budget to the research needs of the academic community and most of the rest to training and facilities, instead of focusing more on commercial opportunities. So far, observational trials, Phase 1 clinical trials or Phase 1/2 trials are under way for the following diseases: spinal cord injury, heart disease, HIV/AIDS, Huntington's disease, solid tumours, leukaemia, and sickle cell disease (<http://www.cirm.ca.gov/our-progress/cirm-funded-clinical-trials>). However, the institute is being advised to focus more on commercialisation and translational processes and is expanding its funding activities to include commercial organisations (Mason et al. 2012).

CCRM, considerably smaller than CIRM, was founded in 2011 with \$15 million in Canadian federal funding matched by \$10 million in contributions from industry and other institutions. It has had a more commercial focus from the beginning, encouraging industry partnerships that acquire specific IP privileges, recruiting people with business and product development expertise to accelerate commercialisation, and building an industry consortium involving 37 leading companies in RM. The organisation's structure involves three translational platforms: cell reprogramming and engineering; cell manufacturing; and biomaterials and devices. The CCRM translational model with its strong focus on moving RM technologies across the early stage funding gap is attracting imitators among other publicly funded initiatives of this nature (Schachter, 2014) but it is too early to evaluate its success.

In the UK, the TSB Cell Therapy Catapult, still in its formative stages, is closest to this model (Schachter, 2014). Its goal is to build a £10 billion industry within the UK, and its focus is on removing process development risk and also on reimbursement. As with the CCRM it is too early to tell how effective this translational model will be.

6.1.1 Comments from stakeholders

The CIRM was seen as having diverted most of its funding towards academic led projects with a strong research focus. A common view was that much of its fund had already been spent, mainly on buildings and research with only a very small proportion going into companies that are commercialising the technology, maybe too little and too late to have an impact. As a result VC funds are not taking an interest. The view was that CIRM should have used a portfolio distribution model for their funding approach and spread the money more evenly across core enabling technologies, buildings, research, and commercial applications. Also, the CIRM was set up so that income goes back into state coffers, unlike an evergreen fund where profits go back to the fund so that it

becomes self-maintaining. Some stakeholders cautioned against dismissing the CIRM too readily in that they are now seen to be moving in a more commercial direction, and they have raised additional funding to enable them to do so.

The CCRM was seen as having been more strongly industry led from the beginning, in that “*companies are expected to pay to join the club*”, but, according to one stakeholder, “*it’s not clear what you get back*”. The model was defended by others who pointed to the large scale of funding and the fact that they have identified approximately 90 high value projects suitable for investment.

The concept of a Regenerative Medicine Translational Centre was seen to be building on the assumption that the development of RM therapies will follow a similar pattern to bio-pharmaceuticals but with fewer systemic safety issues, leading to a success rate for clinical trials of ~30 – 33%, resulting in an *easier* future path to commercialisation. An important aspect of translation centres is building an infrastructure for commercial scale production within 5 – 10 years. Underlying the expected success of such initiatives is the view that venture funders perceive the technology to be “*not yet de-risked*”, partly because they do not see the infrastructure for commercialisation and partly (in the US) because of political risks around the use of stem cells. RM Translation Centres are designed to develop the infrastructure to take the technology from proof of concept to Phase 1/2 trials where the issues are to optimise the technology and then to produce the cells in sufficient quantities for clinical trials.

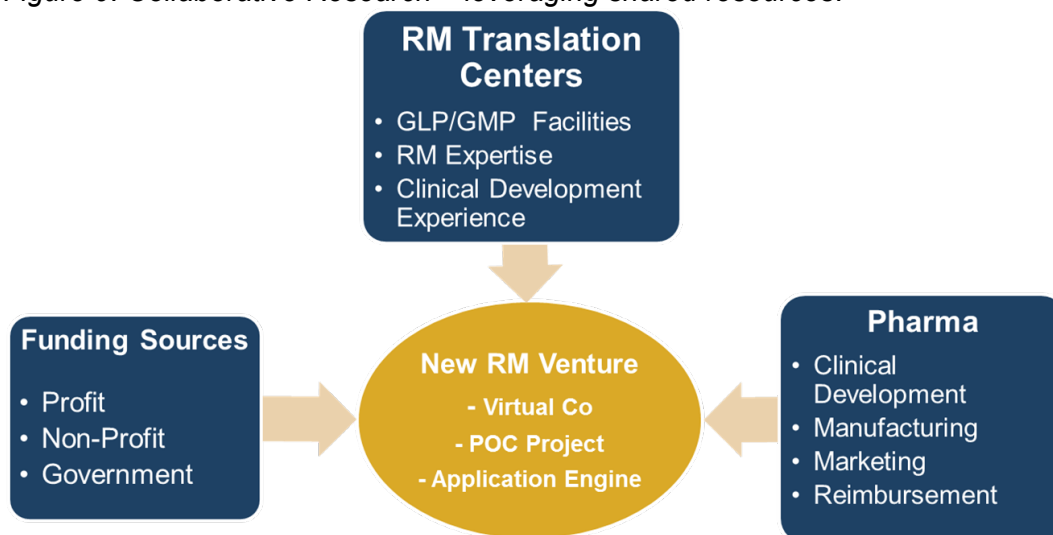
Translational centres have space, facilities and equipment to move technologies through this early stage funding gap but have not yet begun to address the later Phase 3 – market funding gap. More development is particularly seen to be needed at that point, with a focus particularly on the manufacturing challenge and the need for clinical grade good manufacturing practice (GMP) facilities, requiring substantial capital investment with no great return. Contract research organisations (CROs) are expected to be able to produce the large numbers of cells that will be needed for these later stage developments (e.g. Lonza, Progenitor Cell Therapy) but the expectation was that public funding will have to build this infrastructure, e.g. through the Medical Research Council (MRC) or through philanthropic funding (e.g. Wellcome Trust).

As shown in Figure 9, this approach is expected to bring together a variety of funding resources, including those of pharmaceutical companies (although notably not venture capital) with the facilities of a translation centre, to create a new form of RM venture organisation relevant to allogeneic therapies, for very large patient populations, requiring large scale production facilities.

6.2 Biomedical mega funds

Some authors have argued that advanced financial engineering (given a number of simplifications and assumptions) could represent a solution to the reluctance of venture capitalists and pharmaceutical and biopharmaceutical companies to continue to take risks to bring innovative but highly uncertain therapies to market (Fernandez *et al.*, 2012; Fagnan *et al.*, 2013a, b). These papers propose a new financial tool, a ‘mega fund’, to funnel up to \$30 billion into the discovery of biological, cancer and orphan drugs.

Figure 9. Collaborative Research – leveraging shared resources.



Source: Bonfiglio (2013)

The proposal in such a case is to increase the amount of capital available for biotechnology investment by bringing together investors who would not normally invest in early product development stages in exchange for a small percentage of royalties or licensing revenues from successful drugs. By creating a mega-fund of up to \$30 billion to invest in approximately 150 therapeutic programmes, the probability that at least two of them will succeed could be higher than 99%.

Several such drug royalty investment companies exist but they only invest in drugs that have already been approved. A mega fund of the type proposed would invest at an earlier, riskier stage, and spread the risk using techniques found elsewhere in finance such as securitisation of future revenues, e.g. from drug compound licenses into debts called 'research-backed obligations'. The creation of a large, diversified investment portfolio with clinical programmes at different stages of development would allow for risk-management (requiring securitisation) and uncertainty reduction based on the skewness of financial returns from investments in biopharmaceutical businesses operating on a blockbuster model. By supporting many programmes simultaneously, the probability that at least some of them will be successful is assumed to be dramatically increased with a predicted revenue of \$2 billion, assuming 10 years of IP protection after approval.

Based on such assumptions and historical data, Fernandez *et al.* (2012) and Fagnan *et al.* (2013a, b) claim that a \$5 to \$15 billion mega fund could yield 9 to 12 percent returns for equity investors, and 5 to 8 percent returns for 'research-backed obligation' holders. Such returns *at low risk* could, it is claimed, attract large investors such as Pension Funds who do not currently invest in this type of health care initiative. It is, however, questionable whether this approach could provide a solution for investment in high risk technologies such as RM by creating an opportunity for investors to become more patient in funding longer term activities. This funding model's assumptions are all based on the circumstances that pertain to bio-pharmaceutical drug development, and are unlikely to be valid for allogeneic cell based therapies. However, they may be relevant to RM developments that can contribute to conventional approaches to drug development through toxicity testing or diagnostic developments.

A funding model that has similarities to the mega fund approach, and also to crowd funding, is the BioIndustry Association (BIA) Citizens' Innovation Fund (CIF) (BIA, 2013), involving a tax deduction of 40% of the amount invested, up to £15,000 annually. The BIA proposal builds on a successful French CIF that raised over €6 billion, focusing on medical therapeutics in areas of unmet need such as cancer, diabetes or dementia. In contrast to existing tax-advantaged schemes that are targeted to high net-worth individuals, CIFs would be offered to the retail market, mid net-worth individuals, to raise large amounts of funding through relatively small individual subscriptions. From an initial flurry of activity around the CIF in 2012, linked to discussions on the 'Valley of Death' (House of Commons Science and Technology Committee (HOC S&TC, 2013)) for innovative SME funding, there has been little or no follow-up of this idea.

6.2.1 Comments from stakeholders

The idea that if you have a large fund a proportion of the fund can take riskier investments and amortise that risk over the whole portfolio was questioned, the problem being that it becomes a serious management challenge to support a lot of small investments and fund managers may give less time to the middle or later stage companies. Also generally, small specialised VC funds will out-perform large funds and specialised VC funds will out-perform generalist funds. Finding a structure that gives big investors a single interface through to multiple small specialised technology funds was seen as an important part of the future scene (see Section 7). A key point would be how the mega-fund is managed. With venture investing, unlike the stock market, there is the potential to have an enormous impact, positive or negative, on the companies that are funded and it is important when a fund engages with a company that they spend time helping to improve the asset.

The advantage of a mega fund is *not* that you can diversify the risk: the minimum sized fund for RM, given its cycle, would be ~\$150-200 million, allowing 10-15 investments in the portfolio and to have risk diversified. A larger fund would make more investments but would have more failures. However, a \$2 billion fund could promote collaborations between different technologies, aggregate them into a single project and change some of the landscape, e.g. through a RM Translation Centre. The advantage of a larger fund would be its ability to invest in lower return developments such as enabling technologies that might be critical for the development of a particular core therapeutic. For example, a cell manufacturing facility could support investments in 7 – 8 other businesses through that manufacturing business. The advantages of a large fund are thus not in risk diversification but in the ability to promote collaborations between different groups that would otherwise compete and, given the size of the fund to draw together technologies in a way that a smaller fund could not manage.

6.3 Venture philanthropy

Venture philanthropy works to build stronger societal organisations by providing them with both financial and non-financial support in order to increase their impact (<http://evpa.eu.com/#&panel1-1>). It adopts financial techniques used by venture capitalists and applies them to philanthropic goals and has been adopted as a strategy by some of the major disease based charitable foundations. These bodies engage in focused research to speed up development of drugs or treatments for specific diseases, requiring collaboration across industry, government and academia, and including the use of performance measurement for monitoring and making decisions about future funding.

Philanthropic investors will maximise their investment capacity without compromising the interests of their patient groups.

Venture philanthropy provides both financial and non-financial support for translational process, focusing on therapies for specific diseases, for example through orphan drug developments that fall outside the interests of pharmaceutical companies. They may be prepared to take more risks compared with pharmaceutical companies that prioritise profits and shareholder interests and they can thus become a 'virtual pipeline' for drug development from discovery to clinical trials and launching to markets. They often leverage their millions (in comparison to the billions invested by the pharmaceutical industry) to help companies to cross the important funding gaps, rather than funding the whole development process. Disease-focused foundations using venture philanthropy invested approximately \$90 million in biopharmaceutical companies for drug development in 2008, a 20% increase from 2007 and 13 times more than in 2000 (Feldman and Graddy-Reed, 2013).

One example in the UK is the Cystic Fibrosis Foundation (CFF) with \$260 million investment in drug development since the mid-1990s and currently 30 drugs in development with 22 companies. In 2012 the CFF introduced Kalydeco, a drug that doubles the life expectancy of CF patients. Another is Syncona Partners, a venture philanthropic organisation being developed by the Wellcome Trust to hold investments in a small number of businesses that can prove both their utility and value-for-money. This is a £200M 'ever-green' investment, adopting a philanthropic approach but also seeking commercialisation of products (<http://www.synconapartners.com/strategy/#sthash.lspNvbHw.dpuf>). Syncona Partners work closely with the management team of the companies they invest in and will invest at any stage where their expertise, network and approach will add value, covering devices, therapeutics, diagnostics, IT, and investing on a global basis, from £1 – £20 million per company. The investment that is closest to RM is Nightstar RX Ltd, a company developing and commercialising a retinal gene therapy for choroideremia, an inherited cause of blindness. However they do not seem to have plans to invest in areas of RM where the funding gaps are most intractable.

6.3.1 Comments from stakeholders

Given that RM technologies have less commercial appeal there was a perceived requirement for philanthropy to support them because *"they are too important to leave solely to the unavailable or unstable venture funding"*. Given a permanent philanthropic platform, the less commercial parts of the development process can continue regardless of any one donation. This was considered by some to be the most likely source of investment in RM in the immediate future. Another observation was that probably the biggest change in the last 15 years around philanthropic funding has been the emergence of models where philanthropic organisations fund at specific milestones as does venture funding.

Some medical charities were perceived as beginning to make a big difference, e.g. Epidermolysis Bullosa charity (DEBRA), British Heart Foundation, arthritis related patient groups, each being eager to fund private work because they want the clinical benefits. Local small charities and patient groups can also make important contributions. *"Given that there is a lot of passion in medicine that is not in other areas"*, high net worth individuals such as the Gates Foundation, sometimes influenced by events in the family of such people, can be an important factor. Such initiatives, if handled appropriately, can

return funds to the charity (an evergreen fund), and charities will drive better articulation of the value of the work, this being a key step in increasing the value of the IP.

There was a view that effective non-profit organisations developing therapeutics for a market will need to adopt the venture model, to fund in milestones for specific developments towards a market, not just to do research. A non-profit evergreen fund in New York focuses on technologies related to blood and any profits go back into the fund for further investment.

6.4 Red Investment Bank

This model is based on the concept of the Green Investment Bank (UKGIB), launched in the UK in 2012 with £3 billion in capital from the UK taxpayer, using specialists to investigate the feasibility of proposed projects. This bank focuses on the gap in long term investment in green projects, addressing market failure and externalities and acting as a catalyst to encourage other types of private investment through the development of infrastructure, increasing the confidence of investors. Borrowers are expected to return the loan after they reach the point of income generation. The UKGIB is thus 'for profit' because the capital available is below the desired levels and the long-term mission is to 'crowd-in' rather than 'crowd-out' the initial capital.

Following a similar approach, the initiation of a 'Red Investment Bank' could address market failures in the commercialisation of RM therapies, for example where value based pricing does not factor in the long-term benefit to society or infrastructure is still under-developed. However, unlike green projects that only deal with market uncertainty, investment in regenerative medicine also has to deal with technological and regulatory uncertainty and the resulting relatively higher levels of risk may make this model non-viable for cell therapies themselves. A Red Investment Bank could, however, support the development of infrastructure projects such as cell manufacturing facilities.

6.4.1 Comments from stakeholders

This model raised questions about governments putting money or leverage into the system in a way that can distort markets and discourage private investment, making the point that government is better off focusing on setting the conditions for private capital. *"Government should be creating an environment that makes it attractive for other money to come in and we shouldn't be asking the government directly for money to finance companies. Government money should be used to leverage private capital"*. This perspective was based on the understanding that because RM is a high risk investment any loan would need to be under-written by government. However, the point was also made that this would be very useful if managed as an evergreen fund where profits on the investment are put back into the fund.

It was also noted that, unlike energy infrastructure projects which only have financial risk on their return on investment, in RM therapeutics success is binary, project either fail or succeed and even if they succeed, they will not generate profits until long after the commencement of clinical trials. Thus loan financing is not a viable option although, if the funding model is carefully designed it could facilitate market entrance for clinically approved therapies in the later stages of clinical development, at Phase 3 clinical trials. At this stage there is less risk of technological failure and such investment could help to ensure a return on the investment. This model could also be used to fund development

of supporting activities such as cell manufacturing facilities, distribution networks, and clinical facilities.

6.5 *Transitional portfolio model*

The aim of the transitional portfolio model is to build a portfolio of exploitable, innovative products in-licensed from academic research centres, spin-off companies and SMEs and to advance these to a stage where they can be out-licensed to a pharmaceutical company or VC. The model is proposed as an answer to the lack of traditional sources of funding from VCs or big pharma companies that are interested in early stage biotechnology.

As an example of this approach, the biotechnology investment company Biomotiv is associated with the Harrington Project for Discovery & Development in Cleveland, Ohio. It **aims** to get new biomedical advances from academia into the clinic, positioning its programmes for an out-licensing deal with a biotech or pharma company that can take them the remaining distance to regulatory approval within 36 months. Biomotiv is interested in all disease areas and types of therapeutics, including small molecules, antibodies, proteins, cell therapies, and nucleotides. It seeks opportunities from pre-clinical to early-clinical stages of development and will also consider drug repurposing opportunities. Its focus is on whether a large company will buy the product, not on any particular product type. The company is not financially equipped to take a project through phase II clinical trials and, where the expected development timescale is longer than they are able to cover, the company whose project they are funding will need to seek alternative sources of funding, e.g. from VC.

With \$50 million donated by the Harrington family and additional funders such as angels and VC firms, Biomotiv aims to raise \$100 million on a for-profit basis. The Advisory board, five former heads of research from pharma companies such as J&J, Pfizer, and Aventis, select which products should be funded and which should be continued at specific decision points. The company will invest up to 10 million dollars in a project to take it to a point where it can be out-licensed. Funding of a company is on a monthly basis, as long as the project is making technical progress and the market interest for it continues. If the project fails to reach its milestones, or they find better use for Biomotiv funds compared to what the portfolio is holding, they will stop the funding and return the IP to its source.

6.5.1 *Comments from stakeholders*

This model is in the early stages of development but the general perception was that it would not be attractive to companies developing RM therapies, or indeed to any small company, given the lack of certainty beyond a month-to-month basis. Our informants also questioned the logic behind the stage-based model, which can be very stressing to receivers of the funds and prevent them from developing a long term plan for their product development.

6.6 *Pharma-driven collaborative model*

The pharma-driven collaborative funding model, while not necessarily innovative, reflects a change of direction for large pharma companies that are beginning to show some interest in at least some aspects of RM. Investments of interest would be those that relate to the core interests of the firm, including allogeneic therapies, small molecules

that can stimulate tissue regeneration and related tools and platform technologies. However, some companies have indicated an interest in autologous therapies. This model would cover:

- Conventional mergers and acquisitions, strategic alliances and licensing deals
- Corporate Venture Capital (CVC) (Ford and Nelson, 2014)

CVC is an expanding area that involves non-financial firms (such as pharma companies) making equity investments in entrepreneurial companies, often to acquire technology and build new competencies related to their own pipeline needs. CVC funds provide signals to other investors about the value of specific technologies to potential corporate customers and such investments give firms information to guide strategic technology investment. An innovative approach here for RM is that a large pharma firm could fund numerous such partnerships to support early-stage technologies as they transition from an academic environment to new start-up companies that might align with the investor's core research capabilities.

Examples of this model include: Pfizer's Worldwide Research and Development (WRD) that partners WRD assets with predefined buy-back rights, leverages non-dilutive funding and establishes disease-specific area alliances with biopharma companies and private equity and VC groups; and Johnson & Johnson's \$12.5 million investment in Capricor's phase 2 clinical trial for a stem cell therapy for heart regeneration.

6.6.1 Comments from stakeholders

Comments on this approach related mainly to the lack of attractiveness of RM as an investment for a large pharmaceutical company and their lack of willingness or ability to adopt more stratified approaches to product development. Large companies were seen as a rich source of talent, knowledge, capital and even risk but their approach is to use other companies to their benefit. They are seen by some as an important part of the innovation ecosystem but they need to be managed within it and not allowed to exploit it. When a small company is acquired by a big company, a lot of downstream innovation, jobs, tax revenues (the benefits that government support aims to get) disappear, so pharma are not always benevolent players in the system.

Many comments on this approach related to the lack of fit between RM and existing big pharma business models. A model is being developed for vaccines but cell therapies are even more difficult than that and would be highly disruptive. However if, as some people felt, the pharma model is migrating towards a more stratified approach for more niche markets, this situation could change.

The blood transfusion service was proposed as a sector for which RM technology would be incremental and path dependent. Unless cell therapies can be developed as autologous products for a mass pharmaceutical market, companies will continue to hang back until they can see where the market is going and when there is so much uncertainty in the market it is much more difficult to raise funding.

7. New funding models under development

The lack of investment in development of RM therapies is beginning to lead to creative thinking about new funding approaches. Two of our stakeholders were developing

innovative funding approaches that could be seen as specialised types of mega fund designed to stimulate the interest of very large investors in therapeutic applications of RM, bringing in specialist expertise to reassure potential funders of the plausibility and viability of the therapy. Both initiatives also include an element of philanthropy.

7.1 Innovation Supported Capital Fund

This proposed model builds on the fact that, although the world is not short of risk capital this is not finding its way to investable opportunities in life sciences. On the understanding that what is missing is expertise in both the financial and the technological aspects of innovative developments, the model builds on a process of demonstrating the opportunities and providing a comfortable way for investors to develop a risk strategy. In summary it involves making the case to large private capital investors on why they should take notice of an advanced innovative technology. Two important points are: the economic value that can be extracted from this new technology in the future; and the enormous potential human benefit (the philanthropic element). The model aims *“to make money for its investors and also to make a difference”*.

The VC community was described as being *“not as technical as the future requires it to be”*. It needs to be demonstrated to large investors putting in \$20 – \$200 million how they can make the investment in a risk-controlled way through a highly technical, highly structured investment platform supported by a team of people ensuring good governance, fiduciary duty, reporting investment returns and outcomes. Successful venture funders in life sciences are seen to be in need of specialist knowledge of the field and to be able to stay abreast of rapidly moving developments of the science and technology.

The role of government support in this model would be to take some of the early risk out of the situation for investors. Currently, beyond that point, the traditional VC model is seen as not very effective because of lack of the technical or scientific expertise that is crucial to de-risking, supplied in this model by the investment platform.

This type of VC model would solicit private capital from large investors and, as technologists plus investors, they would invest in places that give a good return both for investors and also for a public beneficial outcome for human health. It focuses on very specialised technologies, and the best people to lead such investments are technologists who are also investors. This model is currently being developed in the context of synthetic biology but it is expected also to have potential in application to RM. There is seen to be a huge opportunity to bring private capital from around the world into places like the UK that are doing cutting edge research and *“to fund the best applications to everybody’s benefit”*.

7.2 A Re-Insurance Funding Model

This novel funding model is based on the understanding that RM has two potential routes to market in the UK. Firstly, the NHS is the largest market for RM but given its size and its limited budget it is under pressure to optimise its reimbursement strategy. It is thus unlikely to be willing to reimburse therapies that are costly unless they demonstrate significant improvement in patient health. Private health care provision can be a potential option for RM, but patients tend to switch insurers frequently so that reimbursing RM therapies can be lossmaking for health insurance companies:

“...if you look at the average length of time that any one client stayed with a private healthcare provider, and whether you’re individual health insurance or whether it’s group insurance the times will be slightly different but it’s only a matter of a couple of years. If you’re AXA why would you pay for a relatively expensive therapeutic for which, by the time that the individual is likely to switch insurers, it’s your competitor that now benefits from the accrued health benefits attributed to RM.”

The innovative approach here is to focus on the reinsurance industry that insures the insurers. For them movement of individual patients between different insurers does not constitute a loss, given that the health insurers are covered by the same reinsurance company.

This ‘back to basics’ approach thus considers first who benefits from the delivery of RM products and therefore who might fund such developments (the re-insurance sector). Following from that it focuses on how to value RM products and from which perspective (e.g. providing a potential cure, managing chronic conditions better and avoiding co-morbidity). The nature of these benefits makes clear the mismatch with currently feasible RM business models and the large pharma business model. Considering how to value such benefits (e.g. in the context of value based pricing) providing the evidence of savings would be a major potential cost to any developer and this model will provide support to funders in terms of evidence of clinical viability. In the UK, the Clinical Practice Research Datalink (CPRD) (<http://www.cprd.com/intro.asp>) could provide data as a basis for such valuations but is not currently willing to do so. However, there is interest in the re-insurance industry in providing such valuations as a prelude to setting up a new type of financing vehicle to get funding into the RM sector and to support market penetration of products and there is also interest in the US.

Although involving reinsurers is not strictly speaking a funding model, this could reinforce the reimbursement for RM therapies, which, in turn, could decrease the risk and increase the profitability of clinically approved therapies.

8. Conclusions

This project was set up to evaluate innovative funding models that could spread risk and promote innovation in regenerative medicine, particularly to address funding gaps at later stages in the development pathway involving Phase 2 and 3 clinical trials. As this remit implies, the conventional clinical trial development model that is being considered for allogeneic therapies is widely regarded as the eventual basis for successful future business models for RM therapies. However, given the more rapid development of autologous therapies to date, along with the doubts expressed by some stakeholders about the eventual viability of this allogeneic model, we have continued to discuss the prospects for autologous therapies in this project, although consideration of innovative business models to support this route to a market was beyond the capacity of this short project.

As recognised by this project’s remit, there is likely to be a continuing need for state, or other non-commercial funding to enable either autologous or allogeneic therapies to be adopted in health care markets (Schachter, 2014). Based on the literature review and contributions from stakeholders, there was a general consensus on the scale of the current difficulty in finding viable funding models for RM therapies – the problem was seen to be very difficult to resolve at least in the short term, requiring significant injection

of non-commercial funding and most of the funding models we considered included an element on non-commercial involvement.

The general view among stakeholders we consulted was that the role of government should be to set the conditions for private capital success, addressing tax and capital formation conditions around particular technologies to *enable* private capital rather than to leverage or direct it. Direct public involvement in the creation of markets or other support for innovation was seen as likely to distort prices and cause private capital to withdraw.

However, an alternative perspective on such questions has recognised that, *for truly path-breaking technologies*, the state has always played an important role in shaping technology trajectories and creating markets, generating economic activity that would not otherwise have happened and opening up new markets that private investors can subsequently move into (Mazzucato, 2013). Which of these scenarios is more relevant to RM therapies will depend partly on whether they are seen as part of the continuous evolution of the pharmaceutical industry business model as applied to allogeneic therapies or as the start of a radically new approach to health care provision based on either allogeneic or autologous treatments or both, each of these views having been put forward by some of our stakeholders.

There is no current experience on which to judge the likely viability of funding models for RM therapies themselves, so the funding models we considered for this project were mainly those being proposed to deal with funding gaps in other areas of life science innovation. From a longer list of possibilities, we selected for further consideration those that seemed most likely to offer realistic prospects to be applied in the context of RM therapies. We considered funding models from the point of view of their ability to support development of therapies themselves and also of the supporting infrastructure for therapy development. We also considered separately two innovative approaches that are currently in formative stages of development.

Table 1 summarises the expected positive and negative attributes of the funding models we considered.

8.1 Therapy development

The funding approaches described in Section 6 have mainly been developed or proposed for innovative areas of life science that are more mature than RM but they could be relevant to allogeneic therapies moving along a development pathway that is modelled on drug development in the pharmaceutical industry. However, Regenerative Medicine Translation Centres (Section 6.1) and the Reinsurance Funding Model (Section 7.2) are both being developed specifically with regenerative medicine in mind.

The difficulties facing any allogeneic RM therapy in negotiating the expected pathway are not being underestimated. The barriers noted in the HoL (2013) Report (regulation, IP protection, clinical trial design, manufacturing capacity, market procurement strategies, and evaluation processes) were all noted in documents we studied and by stakeholders involved in this project and were cited as reasons for the observed funding gap in that they created uncertainty and risk for potential funders.

The difficulties inherent in this expected sectoral path-dependency stem partly from the assumption that the industry structure and appropriate business model for development

of RM therapies will eventually be that followed by molecular pharmaceutical products, first small molecules and then bio-pharmaceuticals. The regulatory framework, market expectations, and even value based pricing have all been developed to date around the precedent of molecular products, and this is one important facet of the lack of attraction of such investments for private sector funders.

There were some commonalities among the innovative funding models we focused on in Section 6. Regenerative Medicine Translation Centres (CIRM, CCRM, UK Cell Therapy Catapult), Venture Philanthropy, Red Investment Bank and the Transitional Portfolio all involved an element of public or philanthropic funding to support small companies in developing and demonstrating to VC or pharmaceutical companies the future viability of their business models, with a view to attracting larger scale funding to enable Phase 2/3 clinical trial development.

Biomedical mega funds and the pharma-driven collaborative model, on the other hand, are both based on private commercial funds only and seek to spread the risks of failure across a broader range of projects by increasing the scale of the fund. Mega funds have only been applied so far to drug development and there was scepticism among stakeholders we consulted about the willingness of investors to invest through this model in RM, given the perceived higher risk of failure in development attached to these therapies. However, the uncertainty attached to such projections was highlighted by one stakeholder who expected a considerably lower rate of failure in clinical trials for RM than is the case, for example, for bio-pharmaceuticals. The Corporate Venture Capital model (Section 6.6) discussed under this heading is being used by some large pharma companies to invest in RM therapies, but stakeholders were uniformly sceptical about the willingness of such companies to invest *significantly* in RM and also about the overall value of such investment for the sector as a whole, if it does take place.

The concept of a Red Investment Bank was seen as being only applicable towards the very late stages of development of a therapy. An element of public or philanthropic funding does increase the attractiveness and likelihood of success for a funding model but in the case of the Transitional Portfolio or Red Investment Bank, this was not seen as counteracting other disadvantages of the approach.

As noted above, the most useful role for public funding is most often seen as being to set the conditions for private capital success rather than to act in a way that distorts markets or leads to withdrawal of private capital. However, as noted above, for path-breaking innovation it is also increasingly realised that the public sector may need to have a role in creating markets and shaping the innovation trajectory. Similar to this potential function of the state, the role of philanthropic funding is often to divert funding in specific directions, towards specific diseases. These two sources of non-commercial investment can thus act in complementary ways to support developments in RM, although both would be vulnerable to loss of public or donor support if a major investment in a RM therapy were to fail. Given the high risk profile of RM therapies it would be wise to consider how to protect the value generated from such investments in the event of failure of a therapy at some stage in development.

Table 1. Positive and negative comments on viability of proposed funding models

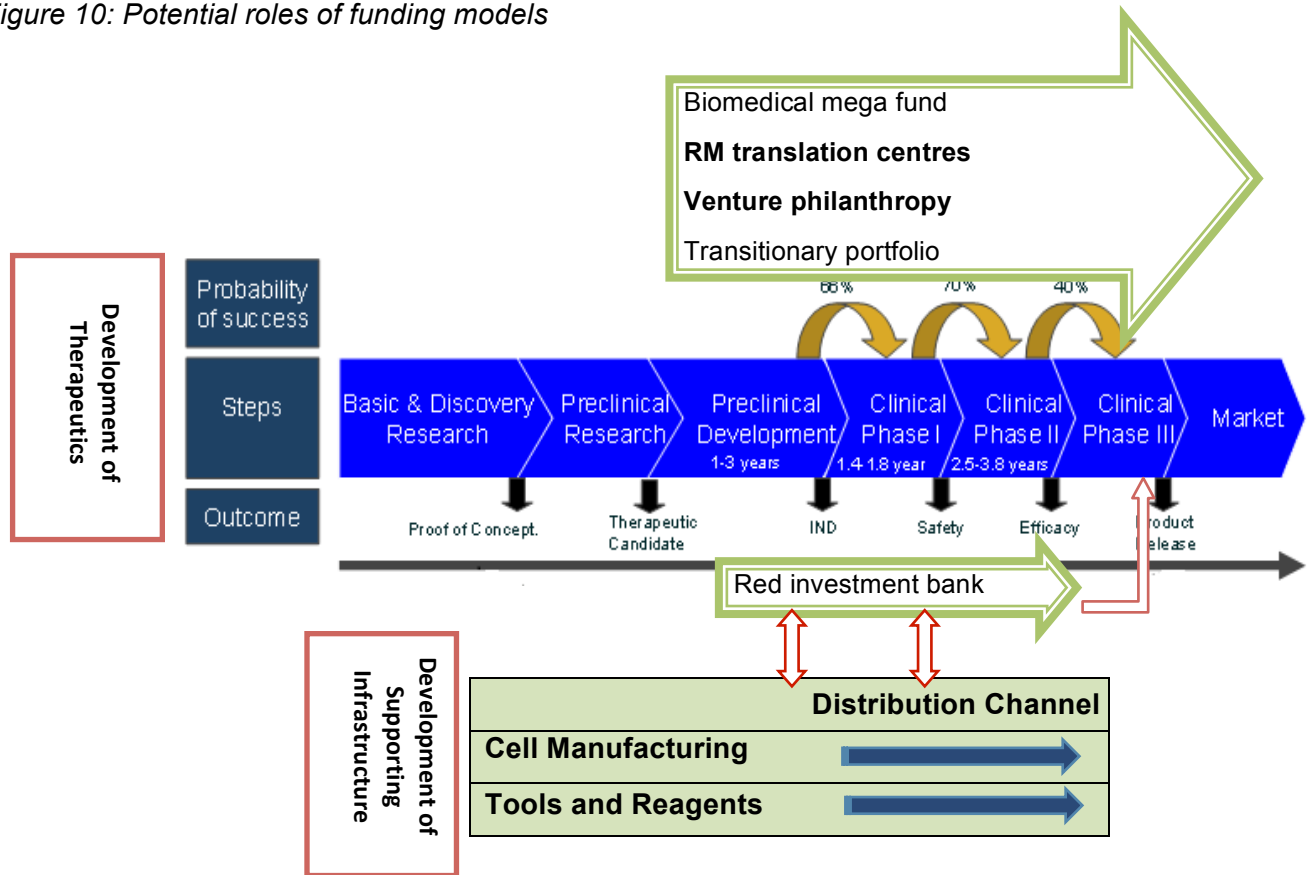
Positive aspects	Negative aspects
Regenerative Medicine Translation Centres	
<p>Overall seen as one of the most potentially useful funding models. Helpful aspects were the focus on translational programmes (CCRM) and on process development and building infrastructure for commercial scale production (UK CTC). Its ability to draw in funding from other sources (e.g. Pharma) could eventually lead to a new form of RM venture organisation.</p>	<p>The CIRM was seen to have too much focus on academic research, along with the requirement to return income to the state rather than using it to support future developments. A disadvantage of the CCRM was the expectation that companies will pay to participate despite it being unclear what the returns will be. Most such centres are not yet addressing the funding gap from Phase 3 to market.</p>
Biomedical Mega Fund/Citizens' Innovation Fund	
<p>Seen as potentially relevant to RM contributions to conventional therapies. It is a novel source of funding, from mid-net worth individuals, but that does not make it viable for this purpose. A large enough fund could potentially change the innovation landscape by investing in enabling technologies, e.g. through a RM Translation Centre.</p>	<p>Overall seen unlikely to be useful for the most challenging funding gaps in development of cell therapies. Also unlikely to be valid for cell therapies or to be robust to negative outcomes Small specialised VC funds tend to out-perform large generalist funds and it will be a management challenge to support many small investments, disadvantaging mid- and late-stage companies.</p>
Venture Philanthropy	
<p>Overall seen as one of the most potentially useful funding models. Its focused approach to research can speed up development and it gives both financial and non-financial support and staff personal experience can leverage additional support. These funds are more 'patient' and willing to take risks than VC or pharma and could become part of a 'virtual pipeline' for development of cell therapies. They have flexibility to invest where they can add value for patients and adopts an 'evergreen approach' re-investing proceeds into future developments, giving longer term stability.</p>	<p>In future Venture Philanthropy should work towards developing a venture type funding model based on milestones.</p>
Red Investment Bank	
<p>Would only be useful if managed as an 'evergreen' fund to support infrastructure development and manufacturing facilities, and perhaps also transition of clinically approved therapies from Phase 3 trials to a market.</p>	<p>Overall seen as not a very promising funding model for anything other than development of infrastructure and supporting technologies. This funding model could distort markets and discourage private investment. Also loan financing is not helpful in supporting start-up companies.</p>
Transitional Portfolio	
	<p>This was not expected to be attractive to the companies that would be in receipt of such funds, particularly the uncertainties attached to a monthly decision making cycle. The focus on whether a large company would be interested to buy into the product was also seen as unlikely to be viable for a cell therapy.</p>

Pharma Driven Collaborative Model	
This approach was seen as potentially viable if the pharmaceutical business model were to migrate towards more niched applications.	This model was not expected to be taken up by investors, given the unattractiveness of cell therapies for a large pharma company, seen as not yet willing to adopt a stratified medicine approach. The exploitative nature of most pharma-based collaborations was also seen as a negative aspect of this model.

Figure 10 demonstrates where these six funding models could potentially contribute to the development of the RM sector, the models highlighted in bold being those that were seen by stakeholders as most likely to be viable in the context of the development of therapies in the immediate future, as summarised in Table 1.

With the exception of the transitional portfolio, the funding models we considered all had some positive features that could potentially be combined across models to give more creative support to development of RM therapies. For example mega funds, if managed appropriately, could enable more effective collaboration across different groups of actors involved in the development of therapies; or venture philanthropy could inject a more patient-focused approach that could mitigate some risks.

Figure 10: Potential roles of funding models



Adapted from Bonfiglio, 2013.

8.2 Supporting infrastructure

The supporting infrastructures included in Figure 10 are essential to the development of therapeutics – cell manufacture, tools and reagents, and distribution channels. However there is a circular argument at play here in that there will only be an incentive to develop the supporting infrastructure once it is clear that the associated therapies are likely to be viable; and yet the infrastructure needs to be developed in order to demonstrate the clinical viability of the therapies through clinical trials. This reinforces the comment of one stakeholder that the development of infrastructures is also likely to require a significant element of public funding.

Thus the way risk can be spread is different for infrastructure compared to therapies. There is less technological uncertainty than for a therapy, but there is a market risk if the therapy itself should fail. Project debt financing through a mechanism like the Red Investment Bank may be a credible approach to developing cell manufacturing facilities, tools and reagents, and distribution channels and could benefit such projects if they only need to pay back the Investment Bank, or to pay interest on the investment, when they begin to generate profits, i.e. when it is clear that the associated therapy will be viable. In this case, although the resources required for developing and enhancing the industry are provided, the limited risk of failure means that the investment bank could grow its budget over time and expand their area of investments to broader sets of activities within RM, provided it was funded on an 'evergreen' basis.

8.3 Stimulating the interest of future investors

Given that the problem is not lack of money looking for investment opportunities but lack of attractive investment opportunities in RM, two of the stakeholders we interviewed were developing interesting new approaches to bringing commercial investment into the RM sector (Section 7), from venture capital and from re-insurers. These approaches would be relevant to therapies at the later stages of clinical trials (Phase 2 – 3). In both cases there is an element of philanthropic motivation in developing the approach, for the good of society, although not of philanthropic funding. Also, both approaches are in the early stages of development and it is not yet certain that funders will engage in the proposed process. However, they are innovative and promising and should be kept under review and if possible supported.

8.4 The business environment and future funding needs

There was some variation in stakeholder opinions around the possibility of eventually closing the funding gap, depending on the extent to which the funding problems facing allogeneic RM therapies were perceived as resolvable in the medium term through the development of viable, fundable, big-pharma compatible business models (see Section 5.1). For some stakeholders, viable future business models for both autologous and allogeneic therapies were regarded as fundamentally incompatible with those of large pharmaceutical companies, leading to speculation about a more radical change in the future shape of the health care innovation sector.

9. Overview and future research needs

Our headline conclusions are:

1. There is some evidence that the reluctance of investors to move into support for cell therapies and RM more generally is justified, and inducements to undertake investment should take account of the reasons for this caution, including lack of proven effective business models, regulatory uncertainty, lack of manufacturing capacity, poorly designed clinical trials, uncertainty about remuneration and future pricing models.
2. There is no single funding gap that, once bridged, the technology can move smoothly to future development. Depending on the chosen innovation pathway, funding gaps can emerge at different points in the route to a final market, primarily depending on whether the cellular product is autologous or allogeneic.
3. The funding models most likely to work in the short term are those with a significant public or philanthropic component.
4. Policies in support of RM developments should take account of the fluid nature of expected business models in this sector, including the extent to which future innovation pathways (autologous or allogeneic) will be disruptive or path-dependent, and which industry sectors are most likely to be able to deliver on future benefits from this technology.
5. Where an innovation pathway is likely to be disruptive for the companies concerned, contrary to conventional wisdom, there may be a case for direct government involvement, for example in market creation and support or, as has been the case in Japan, in tailoring the regulatory system to provide incentives to develop RM therapies based on iPS cells.
6. Policies should be open to considering the potentially important roles of a range of companies in developing RM and cell therapies, including particularly small and medium sized companies and, for example, blood transfusion services.
7. Taking the above points into consideration, Regenerative Medicine Translation Centres and Venture Philanthropy were seen as the most promising funding approaches to meet the needs for the development of cell-based therapies in the short run.
8. Other funding models considered (Biomedical Mega fund, Red Investment Bank, and Pharma Driven Collaborative Model) were seen as having the potential to support RM applications other than cellular therapies, or in the development of the supporting infrastructure for cell therapy development. The Transitional Portfolio Model was not seen as having any particular value in the RM context.
9. Two funding models identified, currently in development, the Re-Insurance Funding Model and the Innovation Supported Capital Fund, both seemed promising in the longer term but had yet to be tested in the context of RM.

9.1 Further research needs

Requirements for further research, analysis and investigation that emerge from this short research project include:

1. More in-depth research with potential developers and potential funders of RM therapies and related products, undertaking financial modelling in the context of a variety of potential future innovation pathways to understand better how policies to support the innovation environment could encourage such investment in future.

2. A more intensive exploration of the policy options open to the UK government to support innovation trajectories in order to encourage future investment from a broad range of sources.

Basic science conducted in the UK will inevitably become geographically mobile in translation to future products. It is not yet clear that we have a sufficient basis in place in the UK to anchor these innovative technologies here, so that the UK as a whole can reap the benefits to health and the economy from its investment in basic science. The above suggestions should become part of an integrated policy approach that identifies what components of the overall innovation ecosystem can usefully be co-located with the central cell production facilities for both autologous and allogeneic therapies, and how they can be induced to locate in the UK in a way that is less vulnerable to future international mobility.

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Annex 1. Research framework and methods

Phase 1 – Analysis and evaluation of the funding gap and its context (1 month)

Phase 1 research included: a meeting with TSB to confirm the parameters of the proposed project; desk research and a meeting with the UK Cell Therapy Catapult to ask their advice on important areas of focus for this research. Documentary evidence was collected on: the UK's RM capacity and industrial capabilities across the range of RM application areas; the nature, location and extent of the funding gap or gaps relevant to developments in RM; potential innovative funding models that could support RM development. Including public and commercial sources.

Phase 2 – Funding models for innovative RM products (3 months)

In Phase 2 we consolidated our database on the range of RM specific funding models under consideration, in the UK and internationally, both public and commercial, and also models operating in other technology sectors that could be applicable to RM. Funders of new technologies will base decisions on their confidence in the business models of the target investment but, as was recognised in the HOL Report (para 112, p56) successful business models for cell therapies, as for many other RM applications, have not yet been established. This compounds the uncertainty, (i) for potential investors and (ii) for this analysis in judging the likely impact of future funding models.

For each funding model identified as potentially relevant to the RM context, we developed a description of its key features as a basis for discussion of its potential benefits and likely future applicability and value. Our final list of models considered potentially useful in this context is discussed in Section 5 of this report. None of the models on this list is truly innovative, some have been developed in other countries (e.g. the USA, Canada) or in other industry sectors (pharmaceuticals, energy) but all would be innovative to some extent for RM in the UK and could contribute to UK competitive advantage.

Given the current uncertainty about future successful business models for RM related developments, we also considered initiatives designed: (i) to adapt regulatory systems to reduce development time-frames; or (ii) to adapt pricing regimes to reflect the benefits of the product. Such initiatives, operating in the innovation ecosystem, will affect the judgement of potential investors about the viability of company business models. We also conducted 7 interviews with investors, financiers, company managers, and researchers to discuss their views on the nature of the funding gaps they are experiencing and on the potential of the innovative funding models to benefit commercialisation of RM products. Recordings of these interviews were transcribed and key insights included in our analysis, in the form of comments on the funding models proposed in Section 5 and also additional innovative approaches to funding that we had not previously considered.

Phase 3 – Stakeholder commentary and evaluation (1 month)

In Phase 3 we invited participants (5 from public bodies involved in RM development; 5 from RM companies and investors; 4 from universities and one from ESRC) to a workshop in London. This workshop had the dual purpose of presenting our findings to representatives of our target audience for this report and also getting their feedback on

our approach and proposals. Discussion focused on the proposed innovative funding models and their likely implications, singly or in combination, for company strategies, product portfolios and ultimately for UK national competitive advantage. Discussions at the meeting were recorded and transcribed and key insights included in our analysis.