Executive Summary

This report results from a two-day workshop sponsored by MRC, EPSRC, BBSRC, ESRC and the TSB to assist them in their Forward Look in Regenerative Medicine, which aims to produce a coherent set of priorities for regenerative medicine research and development, taking into account current activities, opportunities, tractability, scientific, clinical and commercial relevance.

The workshop took place in London on the 5th and 6th of September 2011, with input from over 30 UK experts drawn from across industry, academia and other stakeholders. While the workshop was hosted by the sponsor group, the views expressed in this report represent those of the workshop participants, as collated over the course of the two-day meeting.

The workshop took a baseline roadmap, developed from pre-work completed by the participants and input from the sponsor group. This was then developed further during the course of the meeting to identify priority trends & drivers and then to characterise the specific challenges in taking forward therapies across a range of RM approaches.

The initial discussion on a vision for regenerative medicine in the UK, based on statements provided by participants in pre-work, demonstrated a clear consensus over the need for more discovery science / mechanistic understanding in the field. Discussions also highlighted the diversity of opinion that exists. Statements that included specific targets (for example around the level of patient population impacted by RM by 2025) were thought to be either too conservative or unrealistic by attendees. The fact that an agreed definition of RM does not exist also complicated the development of a shared vision for the space.

In prioritising relevant Trends & Drivers (see section 3.3), there was a strong emphasis on the high costs of chronic disease, aligned to an aging population and escalating costs of drug development. At the same time issues of whether pharmaceutical and biotech companies will engage in RM and see a financial reward, and that there has been little therapeutic delivery or commercial return to date from significant public investments in the area, were raised. This all pointed to a recurring theme of how RM would ‘monetize’, business models that were sustainable in the long run.

When linking Drivers to the key Application Challenges, common themes included the “demand side” issues of ageing, chronic disease, health funding & patient acceptance and “supply side” issues of reimbursement and investment in discovery and scale-up.
Executive Summary (continued)

The discussion on what application areas (i.e. therapies, support products, or other outputs from research in RM) to focus on led to some overarching themes (see section 2.3) including again the need for business models, clear management of choices in approaches to RM, strategies for immuno-suppression and stem cell expansion and handling. In deciding on which areas to focus on for further development, the voting of participants indicated that a high level scan across the possible RM approaches, as well as more specific topics such as trial design, was the best way forward. It was also observed that building public and political credibility in this emerging technology area would benefit from some 'quick-win' (or 'quick-to-market') technology types, which might include acellular approaches and the autologous (near-patient) approaches.

Ten of the higher priority Application Challenges were selected for detailed exploration (see section 4) with participants developing initial ideas for strategy and policy priorities: indicating aspiration, what we have, and how we can get from here to there.

When translating these Application Challenges into specific R&D needs there is a marked and consistent need for manufacturing processes, automation and scale-up to delivery; as well as business models and reimbursement; alongside the essential developments in disease understanding.

Looking at other Enablers, there is a clear appreciation by the group of the importance of interdisciplinary working and engagement between clinicians and researchers, including networks and infrastructure, together with the development of appropriately skilled professionals throughout the value chain. Balanced funding across basic understanding, transition and trials is also a recurring theme, as is the importance of regulation.

An initial draft of this report has been circulated to all workshop participants and all feedback and comments incorporated in this issue 2.

This report will form one input into a public report to be published early next year. It will be brought together with a portfolio analysis and input from international representatives in order to provide a clear framework for the sponsor group for the coming 5 year period.
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Executive Summary
1. Context & Background
2. Vision
3. Forward Look Landscape
4. Application Challenges
5. Areas noted for further exploration / clarification
6. Conclusions

Appendices
1. Context & Background (workshop opening remarks)

The Research Councils (MRC, BBSRC, EPSRC, ESRC) and Technology Strategy Board have agreed to undertake a Forward Look in Regenerative Medicine, in order to produce a coherent set of priorities for UK regenerative medicine research and development.

This will build on the fruits of considerable cross-Council support in the stem cell area, first started in 2003, which has seen us move from helping establish a policy framework for human embryonic stem cell research, supporting discovery science, capacity building and underpinning infrastructure, through to promoting a more translational agenda as stem cell biology itself has become more mainstream.

It must also take account of progress in other disciplines relevant to regenerative medicine, for example advances in gene therapy, biomaterials research and biomanufacturing, as well as social science.

It is therefore timely to consider the strategic needs as we seek to pull this science through to clinical impact. This exercise will of course focus on UK priorities, though we recognize that the challenges being addressed by UK groups may be global in nature, and that we will also need to identify those areas where international partnerships or collaborations may be beneficial.

As the term Regenerative Medicine has multiple meanings, it might be helpful to run through the definition we are using for the Forward Look. Regenerative medicine is an interdisciplinary approach spanning tissue engineering, developmental and stem cell biology, gene therapy, cellular therapeutics, biomaterials (scaffolds and matrices), nanoscience, bioengineering and chemical biology, It may involve:

- transplantation of stem cells, progenitors or tissue
- stimulation of dormant repair processes
- using cells as delivery vehicles: genes, cytokines, small molecules
- engineered cells / synthetic biology

This Workshop forms a critical part of a Forward Look as it provides an opportunity for the sponsors to hear the community’s views on Regen Med research and development priorities. We are also keen that these take account of priorities that might be identifiable in the broader areas of physical and social science which also have importance for regenerative medicine. Of course, we are focussing on the research and development agenda where the sponsor group has greatest influence, though we do anticipate that barriers and enabling mechanisms will also be identified in areas beyond the research domain.
1. Context & Background

The Workshop will be facilitated by Finbarr Livesey and Bill Colquhoun from Cambridge University who will work with you to develop a roadmap for UK Regenerative Medicine that we hope will define and prioritize a shared vision for the field, its drivers, applications and needs. The sponsor group are attending solely as interested observers. We are looking to you for a shared view of the future of the field.

We hope that the process of developing this shared vision will involve creative discussion between the participants and provide you with an opportunity to both explore ideas at the edge of your current activity and meet new contacts in complementary disciplines.

The primary output of the Workshop will be a short paper highlighting identified priorities, for public circulation in October 2011. Amongst or in addition to these priority areas, we recognise that the workshop might identify topics that require a level of investigation or scoping that is beyond the format of this meeting, and if so we may suggest that these are taken off line and further developed at a later date in consultation with the with appropriate experts.

As mentioned, the Workshop outputs will form the core of the sponsor’s Forward Look. Alongside this, the Forward Look sponsors are undertaking a review of their regenerative medicine investments, and will draw on the Regenerative Medicine Stock-Take, published by BIS and DH in July.

Taken together, these efforts will help identify areas that might merit increased support, taking into account available resources, potentially though collaborative efforts between the sponsors, and possibly with other players, for example in the commercial and international communities. This will result in the formulation of a coherent and realisable national plan of action, agreed amongst the sponsor group, encompassing priorities for investment and appropriate delivery mechanisms.

This strategic plan – the Forward Look - will be published at the beginning of 2012 and provide a roadmap for future activity to ensure that the UK is positioned as an international leader in this area.
## 1.2 Workshop Participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Email</th>
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</table>
## 2.1. Vision

<table>
<thead>
<tr>
<th>Vision Issue</th>
<th>Votes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>High quality fundamental research delivers greater understanding of RM therapies &amp; diseases</td>
<td>27%</td>
<td>Necessary but not sufficient. Only in partnership with reverse translation. Blood cells as model - differentiation. RM and small molecules need not be in competition. Both basic and translational research are vital if we are not going to be beaten to clinical applications by other countries.</td>
</tr>
<tr>
<td>RM using Stem cells / Tissue engineering medications as drugs of choice &amp; established tool of modern medicine</td>
<td>12%</td>
<td>Translational mantra and funding priority recognises this crucial objective. Delete 'As drug of choice'. Need early therapeutic winners to pave the way for acceptance. Doesn't need to be drug of choice.</td>
</tr>
<tr>
<td>Regulatory Bodies actively playing a collaborative part in bringing innovative and potential RM therapeutics/technologies to clinical fruition</td>
<td>8%</td>
<td>Regulation needs to be consistent. EMA and MRD are actively collaborating on RM. Dialogue and fast response with regulatory bodies...engage in research industry specific. International collaboration. Social science work on China, India, South Korea and Japan provides an important context for such collaboration</td>
</tr>
<tr>
<td>RM is widely accepted in society as a whole and by policy makers as an important</td>
<td>4%</td>
<td>Definition important so not a 'catch-all'. Could lose the good will with one bad trial.</td>
</tr>
<tr>
<td>RM competes effectively with small molecule and biologics for approval and re-imbursement</td>
<td>11%</td>
<td>Must focus on where RM therapies are applicable. Importance of focus on demonstrating clinical outcomes. Need a viable business model for RM. Deliverables for patients are uncertain. Viable health economics essential. Likely to be complementary not competitive.</td>
</tr>
<tr>
<td>Provision of RM therapies for a variety of chronic and degenerative diseases that result in improved patient outcome for 25% of patients over 65 and 5% of general population</td>
<td>11%</td>
<td>At present impossible to predict scale of economic and therapeutic benefit. Too ambitious targets for 2025. Not realistic, sets false expectations. Need to prioritise common diseases in organs with regenerative potential.</td>
</tr>
<tr>
<td>RM will represent 10% of the pharma industry and save 33% of healthcare bill for chronic disease</td>
<td>8%</td>
<td>Health economics and cost effectiveness more important than savings. Political understanding this is a long/ team game. Meaningful or aspirational? Not realistic expectations. Potentially disruptive technology. RM will lead to a new industry. To early to define performance matrices</td>
</tr>
<tr>
<td>UK is seen as leading location for RM development, exploitation and application with 5 or more commercially successful companies</td>
<td>19%</td>
<td>Misses out investors. UK to be leader for RM development. How do we ensure RM industry sticks in UK? Leading location for strategically targeted RM development. Is this new? UK a key player internationally.</td>
</tr>
</tbody>
</table>
2.2. Vision commentary

A baseline “Vision” was developed from the pre-work of the participants, with eight statements being developed to reflect the different stakeholder perspectives (most, if not all, of which are mutually compatible. These were then discussed in the workshop plenary, with comments added and a final prioritizing vote. The chart at 2.1 documents these baseline vision statements, the associated comments and prioritising votes. It can be seen that the need for research was identified as the highest priority element of the vision, followed by the aspiration for UK to achieve a leadership position in RM. The societal and policy aspect was not rated highly.

In the comments on the vision statements that were presented back to the participants there were a number of issues that were raised a number of times. These included –

• The tension between translational and basic funding, in that the former could take away from the latter and that some of the push towards translation and ‘early wins’ may not be the most productive long term strategy. At the same time, these distinctions are less well-defined, inasmuch as many downstream challenges for translation to occur depend on close contact with and answers from basic science (eg about prospective carcinogenicity of cells)
• Given the size of the UK choices would always have to be made, be that in which areas of fundamental research (for example via peer review), the clinical targets or the approaches to therapies
• The definition of RM is still problematic, as it is not a hard definition and it is not helping the community find its voice or its vision. However the term RM does act as a convenient 'boundary object' allowing various actors to participate. The challenge is to segment the broad definition into more meaningful and approachable areas with which to target. In any event harder definitions are likely to be delivered in the form of regulation - eg the Advanced Therapy Medicinal Products (ATMP) classification in Europe which defines ATMPs very precisely.
• Targets for the development of RM were simultaneously thought to be both too conservative and unrealistic, possibly reflecting again the early stage of development of the area and the breadth of evidence and opinion that exists regarding the potential for RM

Importantly it was also noted that these are not mutually exclusive 'visions', but cover different perspectives from the range of stakeholders (researchers, clinicians, industry, funders, regulators, patients etc), and also that they differ in the timescale and ambition of their achievement.
3. Forward Look Landscape

3.1 Landscape
3.2 Trends & Drivers
3.3 Application Challenges
3.4 Key themes and enablers
3.5 Research & Development
3.6 Enablers
3.7 Linkages

Note: Landscape layers developed from participant pre-work and updated to reflect additions and prioritisation in workshop. Priorities indicated via colour coding – see key on each chart.
3. Forward Look Landscape – the workshop process

The graphic on page 12 (3.1 Landscape) represents the top-level roadmap view of the workshop outputs. A simplified version of the template is shown below. Time runs from left to right: moving from the past through short, medium and long terms to the future vision. The roadmap endeavours to help understand “Where do we want to go?”; “Where are we now?” and “How do we bridge the gap?”

The layers of the landscape represent different (linked) perspectives, broadly covering “Why”, “What” and “How”:

- The top layer represents the external Trends & Drivers (Social, Technological, Environmental, Economic and Political & Legal) that will influence the future of Regenerative Medicine and the perspectives of the different stakeholders who are involved (healthcare providers and funders; industrial; academic and policy makers).
- The second layer represents the Application Challenges in developing and deploying RM – embracing the core understanding and the translational aspects into use.
- The third layer captures the Research and Development needs associated with meeting the challenges identified.
- The fourth layer covers the other Enablers (eg Skills, Resources, Infrastructure and Policy instruments) that are needed for success.

The workshop started with a baseline roadmap developed from the pre-work submitted by the participants. The Trends & Drivers layer was then prioritised (see section 3.2) and the most important drivers used to focus discussion to extend the baseline Application Challenges already identified by the group. Priority Application Challenges were then selected (see section 3.3) by the group and explored in more detail in breakout groups using a structured template (see section 4). Finally the R&D (see section 3.5) and other Enablers (see section 3.6) required to deliver each of the priority Application Challenges were reviewed and these “linkages” captured in section 3.7.
3.2.1 Trends & Drivers

**Social (& Patient)**
- Past: Patient Charities/advocates
- Short term: High cost/chronic disease and diseases of repair failure
- Medium term: Public expectation/frustration at lack of CT activity
- Long term: SC Tourism

**Technological**
- Past: Need for better drugs screens and toxicology platforms
- Short term: Need for better disease models
- Medium term: CTIC starts to produce better targets and roadmaps for RM
- Long term: Incumbent/Competing technologies i.e. in cardiac failure – implantable LVADs

**Environmental**
- Past: Difficult economic environment – declining revenue & growth in pharma sector
- Short term: Significant public investment in UK stem cell science - little ROI
- Medium term: Market & Collaborative opportunities in emerging markets (China/India)
- Long term: International competition in Europe

**Economic**
- Past: Increasing economic burden & strong pricing pressures from public healthcare payers
- Short term: Lack of organisational/system readiness for RM (Industry & clinical)
- Medium term: RM Care pathways and relative costs of treatment
- Long term: Role of FDA & Regulatory bodies to deliver clear RM

**Political & Legal**
- Short term: Need for better disease models
- Medium term: Market & Collaborative opportunities in emerging markets (China/India)
- Long term: International competition in Europe

**Health Provider & Clinician**
- Past: Increasing economic burden & strong pricing pressures from public healthcare payers
- Short term: Lack of organisational/system readiness for RM (Industry & clinical)
- Medium term: RM Care pathways and relative costs of treatment
- Long term: Role of FDA & Regulatory bodies to deliver clear RM

**Health Funder**
- Past: Increasing economic burden & strong pricing pressures from public healthcare payers
- Short term: Lack of organisational/system readiness for RM (Industry & clinical)
- Medium term: RM Care pathways and relative costs of treatment
- Long term: Role of FDA & Regulatory bodies to deliver clear RM

**Pharma, Bio & Diagnostics Industry**
- Past: Industry generally weaker at cell-based assays than at recombinant targets
- Short term: Escalating costs of drug development
- Medium term: Investment in manufacturing and commercialization
- Long term: Increasing costs of research & need for scale

**Other stakeholders (incl. research, academia & VC)**
- Past: Risk averse funding environment
- Short term: Mixed research & funding priorities - short-termism for “translation” v basic research
- Medium term: Weak VC community in this arena
- Long term: Engagement by pharma & biotech in RM => Financial reward

**Vision to 2025+**
- Stratiﬁed socio-economic demand for development of autologous and allogeneic
### 3.2.2 Trends & Drivers (1 to 20)

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<tr>
<th>Rank</th>
<th>Issue</th>
<th>Votes</th>
<th>% Score</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>High cost/chronic disease and diseases of repair failure</td>
<td>18</td>
<td>10%</td>
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<td>2</td>
<td>Mixed research &amp; funding priorities - short-termism for &quot;translation&quot; vs basic research</td>
<td>15</td>
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<tr>
<td>3</td>
<td>Aging Population</td>
<td>14</td>
<td>8%</td>
</tr>
<tr>
<td>4</td>
<td>Engagement by pharma &amp; biotech in RM ==&gt; Financial reward</td>
<td>12</td>
<td>7%</td>
</tr>
<tr>
<td>5</td>
<td>RM Care pathways and relative costs of treatment</td>
<td>11</td>
<td>6%</td>
</tr>
<tr>
<td>6</td>
<td>Role of FDA &amp; Regulatory bodies to deliver clear RM regulatory framework</td>
<td>10</td>
<td>6%</td>
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<td>7</td>
<td>Significant public investment in UK stem cell science - little ROI</td>
<td>10</td>
<td>6%</td>
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<tr>
<td>8</td>
<td>Escalating costs of drug development</td>
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<td>5%</td>
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<tr>
<td>9</td>
<td>Need for better disease models</td>
<td>9</td>
<td>5%</td>
</tr>
<tr>
<td>10</td>
<td>NHS adoption &amp; behaviour (=&gt; optimal delivery route for SC therapies?)</td>
<td>8</td>
<td>5%</td>
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<td>11</td>
<td>Stratified medicine (iPS based patient phenotyping)</td>
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<td>Increasing economic burden &amp; strong pricing pressures from public healthca</td>
<td>7</td>
<td>4%</td>
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<td>Lack of organisational / system readiness for RM (Industry &amp; clinical)</td>
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<td>Need for better drugs screens and toxicology platforms</td>
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<td>3%</td>
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<tr>
<td>15</td>
<td>Weak VC community in this arena</td>
<td>5</td>
<td>3%</td>
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<td>Market &amp; Collaborative opportunities in emerging markets (China/India)</td>
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<td>Investment in manufacturing and commercialization</td>
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<td>Patient acceptance of regenerative medicine products</td>
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## 3.2.2 Trends & Drivers (cont)

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<td>Industry generally weaker at cell-based assays than at recombinant targets</td>
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### 3.2.3 Trends & Drivers Linkages

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Matrix showing which Trends & Drivers are most influential to priority applications.
### 3.3.1 Application Challenges

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<th>APPLICATION CHALLENGES</th>
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<th>Medium term</th>
<th>Long term</th>
<th>Vision to 2025+</th>
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<td>Characterisation of endogenous stem cells</td>
<td>Increased understanding of cellular differentiation</td>
<td>Mechanisms of cellular metabolism and aging</td>
<td>Increased understanding of the tractable landscape for stem-cells</td>
<td>Definition of role of key cellular regulators</td>
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<td>Disease understanding</td>
<td>Understanding of disease mechanisms</td>
<td>Cellular heterogeneity - Cancer</td>
<td>IPSC derived cells as disease models</td>
<td>Drugs that target cancer stem cells</td>
<td>Disease vs. Molecular phenotype</td>
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<td>Disease stratification</td>
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<td>Stratification and trial design for RM</td>
<td>IPSC therapies &amp; diagnostics in stratified medicine</td>
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<td>Acellular therapies</td>
<td>Acellular products – Application &amp; proof of reimbursement</td>
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<td>Autologous therapies</td>
<td>Adult non-stem cell (somatic) therapies</td>
<td>PS based cell and tissue replacement</td>
<td>Autologous intra-operative technology</td>
<td>Autologous products (cardiac repair, neuro-regenerative treatments, autoimmune diseases, eye disease)</td>
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<td>Allogeneic therapies</td>
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<td>Non-ESC allogeneic products (eg ischemic stroke)</td>
<td>allogeneic large scale market products - market authorization</td>
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<td>Artificial stem cell niches</td>
<td>Temporary organ replacement</td>
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<td>In vivo reprogramming</td>
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<td>Endogenous repair strategies</td>
<td>Treatment of degenerative disease with small molecules</td>
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<td>Cell based screening platform</td>
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<td>Cells for drug testing and toxicology platforms</td>
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<td>Other</td>
<td>Primary, pluripotent &amp; SC-based cell therapies in diverse neurodegenerative diseases</td>
<td>Neur</td>
<td>Replicating Function (eg corneal defects, skin, cartilage)</td>
<td>Establishment of CT and TE approaches in RM for patient care</td>
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<td>Blood</td>
<td>SC banking (viability &amp; regulations) for different tissues</td>
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<td>Other Organs</td>
<td>Combination of cell therapy with acellular components</td>
<td>ES-cell based replacement or drug delivery strategies</td>
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Key: Darker colour = Higher Priority
### 3.3.2 Application Challenges

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<td>Acellular products – Application &amp; proof of reimbursement</td>
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<td>Autologous products (cardiac repair, neuro-regenerative treatments, autoimmune disease)</td>
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<td>Cells for drug testing and toxicology platforms</td>
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<td>Characterisation of endogenous stem cells</td>
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<td>Allogenic large scale market products – market authorization and entry (product)</td>
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<td>IPSC therapies &amp; diagnostics in stratified medicine</td>
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<td>Replicating Function (eg corneal defects, skin, cartilage)</td>
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<td>Increased understanding of the tractable landscape for stem-cells</td>
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<td>Drugs that target cancer stem cells</td>
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### 3.3.2 Application Challenges (cont)

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### 3.4. Key themes and enablers

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<td>Clarity of targets for RM / option management</td>
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<td>Strategies for immuno-suppression</td>
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<td>Establishing efficacy</td>
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<tr>
<td>SC expansion and handling</td>
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<tr>
<td>Clean slate' for reg process - new models for clinical trials</td>
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<td>Use of small molecules to drive differentiation</td>
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<tr>
<td>A single working therapy with recognised clinical benefit</td>
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<td>Understanding proteins expressed by stem cells/ turnkey service</td>
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### 3.5.1 R & D

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<td>Biology &amp; Biomaterials</td>
<td>Use of small molecules and medicinal chemistry to direct stem cell differentiation</td>
<td>Design &amp; materials for better substrates</td>
<td>Development of improved Biomarkers</td>
<td>Robust, reproducible, IPSC generation, &amp; clearer understanding of biology</td>
<td>Genetic manipulation of human ES cells</td>
<td>Stem cell systems biology</td>
<td>Molecule targets of signalling and transcription factors</td>
<td>Non-GF dependent expansion and differentiation</td>
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<td>Safety/Efficacy</td>
<td>Concern re oncogenic potential. Local delivery or need large safety studies?</td>
<td>High-throughput high-content assays</td>
<td>Understanding adult tissue homeostasis</td>
<td>Better vectors for targeting, delivery and reprogramming</td>
<td>Understanding of mechanism of action</td>
<td>Animal models</td>
<td>Use of cell tracking tools for both preclinical and clinical</td>
<td>Better immunosuppression / immune system control</td>
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<td>Manufacturing &amp; Value Chain</td>
<td>Controlled and characterised manufacturing process</td>
<td>Cell manufacturing solutions</td>
<td>Scale up technologies</td>
<td>Transportation and formulation systems</td>
<td>Advanced sorting and purification technology</td>
<td>Xeno-free propagation</td>
<td>Tissue culture robotics</td>
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<td>Delivery</td>
<td>Cell Delivery Devices</td>
<td>Improving cell retention after grafting: cells + gel, scaffold, encapsulation, sheets,</td>
<td>In vivo delivery systems</td>
<td>Scale up of in vitro differentiation</td>
<td>Biologically controlled devices (human machine interfaces)</td>
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<td>Patient characterization</td>
<td>Understanding aging mechanisms.</td>
<td>Understanding genetic instability</td>
<td>Use of cell tracking tools / technology</td>
<td>Imaging and monitoring</td>
<td>Post-treatment Monitoring and delivery</td>
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<td>Trial Design</td>
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<td>Reimbursement &amp; Business Models</td>
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<td>More products launched through PMA+ routes with indication specific claims</td>
<td>Reimbursement path for regenerative medicine products</td>
<td>Follow the science and clinical need, commercial will follow</td>
<td>Viable business models (eg Service v Product Models)</td>
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**Key:** Darker colour = Higher Priority

RM Forward Look

Dominic Oughton  do251@cam.ac.uk  IfM
### 3.5.2 R&D Linkages

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<th>Allogenic Therapies</th>
<th>Acellular Products</th>
<th>Drug discovery and tox</th>
<th>3D Architecture and niche</th>
<th>Stratification and clinical trial design</th>
<th>Autologous and regenerative therapies</th>
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<td>37</td>
<td>Better vectors for targeting, delivery and reprogramming</td>
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<td>Non-GF dependent expansion and differentiation</td>
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<td>More products launched through PMA+ routes with indication specific claims</td>
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</table>

Matrix showing which R&D needs are most relevant to priority applications.
### 3.6.1 Enablers

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</thead>
<tbody>
<tr>
<td>Skills &amp; Knowledge</td>
<td>Improved interdisciplinary working (e.g., biology &amp; bioengineering)</td>
<td>Increase available skills (e.g., SC researchers) through dedicated training &amp; UG programmes</td>
<td>Trained clinicians, support staff, engineers, GMP production staff and Qualified Persons (QPs)</td>
<td>Know-how in understanding, CT &amp; needs to get into clinical study</td>
<td>Better reward system &amp; career paths for academic translational science</td>
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<tr>
<td>Infrastructure</td>
<td>Regulator understanding and evolution of defined</td>
<td>MHRA accredited GMP facilities for ES and ATMP products</td>
<td>Infrastructure hubs at regional level (TSB/TIC)</td>
<td>Infrastructure that facilitates big science (e.g., Francis Crick Institute &amp; Sanger)</td>
<td>Continued investment in a public stem cell bank for ESC and iPSCs</td>
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<tr>
<td>Regulation &amp; Standards</td>
<td>Sustained funding for basic and translational RM</td>
<td>Additional support resources to help UK firms export RM</td>
<td>FP7 collaborations attractive scientifically but under-resourced</td>
<td>Sustained funding for the early trials and flexibility for the design of these.</td>
<td>Ethical framework for RM treatments (e.g., in sports, aging, etc.)</td>
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<tr>
<td>Funding &amp; Incentives</td>
<td>Resolution of legal challenges to use of ES cells in the US</td>
<td>Forum for RM policy makers</td>
<td>Maintain UK visibility &amp; rep for reasonable policy</td>
<td>Consolidate role of UK as well prepared low risk partner in RM</td>
<td>Need to secure IP in UK or lose to US/SE Asia/Europe</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Policy &amp; Legislation</td>
<td>Utilise national operations with Int rep (NHSBT, NIBSC, etc.)</td>
<td>Fostering early links with clinicians (NHS)</td>
<td>Academic/industrial clinical networks / consortia</td>
<td>International partnering Europe and Asia</td>
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<td>Networks</td>
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<td>Supply Chain</td>
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<tr>
<td>Other</td>
<td>Patient cohorts inc. orphan diseases</td>
<td>Outreach to ensure buy-in from general public &amp; inform of risks of SC tourism</td>
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**Key:** Darker colour = Higher Priority
### 3.6.2 Enablers Linkages

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<tr>
<th>Rank</th>
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<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>Workshop</th>
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<td>Improved interdisciplinary working (eg biology &amp; bioengineering)</td>
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<td>Increase available skills (eg SC researchers) through dedicated training &amp; UKG</td>
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<tr>
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<td>Scale up/manufacture capacity &amp; QBD control</td>
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<td>Academic/industrial/clinical networks / consortia</td>
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<td>Costs of key reagents – growth factors, media etc</td>
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<td>Trained clinicians, support staff, engineers, GMP production staff and Qualifiers</td>
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<td>9</td>
<td>Sustained funding for basic and translational RM research (ensuring appropriate)</td>
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<td>Infrastructure hubs at regional level (TSB/TIC)</td>
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<td>Continued engagement with regulators (at defined cost?)</td>
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<td>GMP/SOP platform in NHS/HEIs to assist clinical translation</td>
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<td>Patient cohorts inc orphan diseases</td>
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<td>Infrastructure that facilitates big science (eg Francis Crick Institute &amp; Sanger)</td>
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<td>FP7 collaborations attractive scientifically but under-resourced</td>
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<td>Know-how in understanding CT &amp; needs to get into clinical study</td>
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<td>23</td>
<td>Additional support / resources to help UK firms export RM products</td>
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<td>Forum for RM policy makers</td>
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<td>Continued investment in a public stem cell bank for ESC and iPSCs</td>
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<td>26</td>
<td>Ethical framework for RM treatments (eg in sports, aging, etc)</td>
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<tr>
<td>27</td>
<td>Better reward system &amp; career paths for academic translational science</td>
<td>0</td>
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<td>Need to secure IP in UK or lose to US/SE Asia/Europe</td>
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<td>31</td>
<td>Utilise national operations with Int rep (NHSBT, NIBSC, etc.)</td>
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<td>Resolution of legal challenges to use of ES cells in the US</td>
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</tr>
</tbody>
</table>

Matrix showing which Enablers are most relevant to priority applications.
3.7 Landscape Linkages summary

Linkages between the priority Application Challenges and the other layers are indicated by a coloured square: 1 1 1

The totals at the ends of rows and columns indicate how many linkages that item has.

Note: These linkages only represent a provisional view developed by each breakout team and are not necessarily comprehensive.
3.7.2 Linkages commentary

The chart shown as 3.2.1 indicates the linkages between the different layers of the roadmap. Reading from left to right, these show how the Priority Application Challenges are responding to key Drivers, and how in turn each of these Application Challenges will draw on R&D and other Enablers for delivery.

Adopting this structured approach to characterising each Application Challenge reveals some interesting cross-cutting issues:

In the Drivers, “demand side” issues of ageing, chronic disease, health funding & patient acceptance and “supply side” issues of reimbursement and investment in discovery and scale up are well represented across the range of Application Challenges.

In the R&D Layer there is a marked and consistent need underpinning the range of Application Challenges for manufacturing processes, automation and scale-up to delivery; as well as business models and reimbursement; alongside the essential developments in disease understanding.

Looking at other Enablers, there is a clear appreciation by the group of the importance of interdisciplinary working and engagement between clinicians and researchers, including networks and infrastructure, together with the development of appropriately skilled professionals throughout the value chain. Balanced funding across basic understanding, transition and trials is also a recurring theme, as is the importance of regulation.
## 4. Priority Application Challenges (explored in breakout groups)

<table>
<thead>
<tr>
<th></th>
<th>Application Challenges (for breakout groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Endogenous Repair strategies <em>(note: significant commonality with C: Acellular products)</em></td>
</tr>
<tr>
<td>B</td>
<td>Allogeneic products</td>
</tr>
<tr>
<td>C</td>
<td>Acellular products <em>(note: significant commonality with A: Endogenous Repair strategies)</em></td>
</tr>
<tr>
<td>D</td>
<td>Cells for drug testing and tox platforms</td>
</tr>
<tr>
<td>E</td>
<td>3D architecture/niche for form and function</td>
</tr>
<tr>
<td>F</td>
<td>Stratification and trial design for RM</td>
</tr>
<tr>
<td>G</td>
<td>Autologous products and therapies <em>(note: combines 5\textsuperscript{th} &amp; 7\textsuperscript{th} ranked Application Challenge from 3.4.2 as synonymous)</em></td>
</tr>
<tr>
<td>H</td>
<td>Neuro – primary pluripotent and Stem Cell based therapies</td>
</tr>
<tr>
<td>I</td>
<td>Blood - primary pluripotent and Stem Cell based therapies</td>
</tr>
<tr>
<td>J</td>
<td>Other organs - primary pluripotent and Stem Cell based therapies</td>
</tr>
</tbody>
</table>

See over for outputs from breakout group exploration of Priority Application Challenges.

**Key:**

- Comment from original breakout team
- Additional comment from wider group in carousel review
Describe desirable “Future State”:

- Harness the biologic capabilities more effectively

Current Status (including UK Capability)

- Cytokines and Chemokines growth factors. Developmental biology stronger in some areas than others
- Play to mainstream pharma

R&D Gaps, Enablers & Barriers

- Identity of the normal tissue system cells of their fate decisions. Image markers. Number and state at acquisition in disease
- Multiple cell types required in same organs
- HTS: cell read-outs, chemical and synthetic libraries, ECM libraries
- System biology (Better predictions) e.g. Dosage
- Regular monitoring in model organisms
- Learn from paracrine activators in exogenous stem cells
- Aim cell therapy at activity endogenous repair

Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps Enablers & Barriers

- Few unique regulatory challenges
- Drug repurposing
- Inter-disciplinary, synergies across organ systems. Synergies from basic to applied to clinical

What role could the RM Forward Look Sponsors play in delivering Future State

- Fund the work!
- Networks, training, shared facilities
- Safer vectors for refrigeration in situ
- Inter-disciplinary, synergies across organ systems. Synergies from basic to applied to clinical

What role could other stakeholders play in delivering Future State

- Clinicians, trial design, patient advocacy
- Safer vectors for refrigeration in situ, protech based methods
- Availability of the protech In? For the clinically relevant quantity secure to the bank
- IP bottleneck of activity requires more than 1 protech at more than 1 company

Fit with 2025 Vision for UK Regenerative Medicine

- Fix the unfixable
- Better patient outcomes
- Economically effective tool for clinicians
- Commercially successful UK RM Industry

We need to...

- erythropoietin established as up-and-coming example
- Thymosin B4 as example
- Can you ever simulate 3D structural repair?
- This is an important ‘near target’ in several organs
- Potential need for targeted delivery and drug growth to ensure safety

What role could the RM Forward Look Sponsors play in delivering Future State

- Fix the unfixable
- Better patient outcomes
- Economically effective tool for clinicians
- Commercially successful UK RM Industry

The benefits would be:

- Clinical outcomes
- Clinical savings
- Commercial success
- Relatively low investment
- Could also benefit exogenous cell therapy

Knowledge Gaps in this group:

- Adult stem cell identity, markers, clues, signals for the relevant organ systems
Describe desirable “Future State”:

A robust underpinning of basic research | Increased commitment from Pharma | 20 potential products in clinical trials | 2-5 companies in UK with products on the market

Current Status (including UK Capability)

Strong academic research base | Developing translational capability | A few products in pre-clinical development | 6-10 UK companies currently in the space

R&D Gaps, Enablers & Barriers

Government buy in and political will | Good regulation and supportive regulators | BSI and standards including NIBSC | Low clinician involvement

Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps & Enablers

Challenge of interdisciplinary research - funding, publication | Lack of interdisciplinary research between stem cell biology and immunology | Improved capability in genetic modification | Need for national multi-disciplinary network with significant clinician involvement

What role could the RM Forward Look Sponsors play in delivering Future State

Leadership role in international collaboration – including flexibility in funding | Rolling review of priorities | Focussed funding priority areas with strategic UK relevance | Closer integration with commercial organisation

What role could other stakeholders play in delivering Future State

Global perspective on regulation - MHRA/ FDA collaboration, Conditional product approval phase II | NIHR/NHS – increased facilitation and funding of clinical trials | NHS increased market ‘pull’ | NICE – transparency of regenerative med economics and route to reimbursement

Fit with 2025 Vision for UK Regenerative Medicine

Better patient outcomes | Economically effective tool for clinicians | Commercially successful UK RM Industry

Team:

CM | PF | JT

We need to.....:

Prioritisation and focus | Incentivise interdisciplinary research and translation | Creation of favourable environment for inward investment and retention of UK expertise or companies

This could be delivered by.....:

Joined up UK funding | Long-term commitment to escalating resource requirement over decades | Loose criteria to build critical mass

The benefits would be:

Increased health, wealth and job retention

Knowledge Gaps in this group:

Multiple knowledge gaps from discovery to market | Genetic instability in long term processed cells | Cell autonomous is per active basis of benefits?

Immune tolerance challenge | Immunology | Regenerative Medicine Forward Look
Describe desirable “Future State”:

- Multiple successful commercial products
- Platform delivery solutions
- Lower hanging fruit
- Broader application

Current Status (including UK Capability)

- Strong fundamental research capability
- Clearer regulatory paths
- EU – a more mature and better defined regulatory environment
- Commercial route to market
- Manufacturability – scale-up

R&D Gaps, Enablers & Barriers

- Definition of commercial targets
- Pre-clinical models
- Patient Stratification
- Appropriate clinical end points
- Basic understanding of repair mechanisms
- Biology of decellularized matrices
- Clinical trials expensive, access to the right patients

Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps

- Policy clearer and more acceptable
- Convergence of industry sectors (medical and pharma)
- Greater academic multi-disciplinary efforts for combination approaches

What role could the RM Forward Look Sponsors play in delivering Future State

- Coherence of strategy
- High level inclusivity (NIMR/ Wellcome)
- Defining the role of UK value chain
- Convergence Sponsors

What role could other stakeholders play in delivering Future State

- Global stakeholder identification
- Global direction for approaches (of market regulation)
- Integrate additional sponsors

Fit with 2025 Vision for UK Regenerative Medicine

- Better patient outcomes
- Economically effective tool for clinicians
- Commercially successful UK RM Industry

We need to…..:

- Multiple, commercially successful products
- Platform delivery solutions
- Acell: Understand biologic scaffolds better – optimise synthetics (decorated)

This could be delivered by…..:

- Convergence of research council sponsors
- Investment biologics
- Appropriate clinical trial end point
- Clearer regulatory paths

The benefits would be:

- Combination of technology with potential for re-investment – smaller step changes
- Early ROI
- Increased engagement of VCs and companies
- Public and political credibility
- Better engage with Htech assessment

Knowledge Gaps in this group:

- Pre-clinical models
- Patient stratification
- Basic understanding of repair mechanisms
- Host/ technology inventions
**Regenerative Medicine Forward Look**

**Application Challenge: Drug Discovery and Toxicology**

<table>
<thead>
<tr>
<th>Describe desirable “Future State”:</th>
<th>Human cell based predictive models are validated and used for all drug testing and regulatory evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Status (including UK Capability)</td>
<td>Still exploratory, uncertain protocols for differentiation, inconsistent inhomogeneous outcomes</td>
</tr>
<tr>
<td>Disease susceptibility markers</td>
<td>Pharma uses hepatocytes &amp; cardiomyocytes from US, UK and Sweden commercial sources</td>
</tr>
<tr>
<td>Accessibility to affected populations (at risk of adverse reactions) is a barrier to ethical cell sourcing</td>
<td>Generally monolayer, single cell-type test systems</td>
</tr>
<tr>
<td>Robust and reliable HTP stem cell derived assays</td>
<td>Methodologies for inducing disease state (not genetic disease)</td>
</tr>
<tr>
<td>Validate relevant and specific biomarkers in cellular systems for whole systemic effects</td>
<td>Genetically at risk patient populations are all/mostly in tox testing models</td>
</tr>
<tr>
<td>Needed: series of cellular models + in silico + PBPr modelling that effectively predicts risk and can be validated as realistic</td>
<td>Patient specific treatment regimes</td>
</tr>
</tbody>
</table>

**R&D Gaps, Enablers & Barriers**

<table>
<thead>
<tr>
<th>R&amp;D Gaps</th>
<th>Enablers &amp; Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease susceptibility markers</td>
<td>Development of models outside of Pharma primary focus</td>
</tr>
<tr>
<td>Covering genetic diversity in tox susceptibility</td>
<td>Also Pharma will not focus on disease mechanisms as world acceptance with RC support</td>
</tr>
<tr>
<td>Efficacy models different from tox models/Cost/Test</td>
<td>Training for: good stem cell culture, scale-up and QA</td>
</tr>
<tr>
<td>Accessibility to affected populations (at risk of adverse reactions) is a barrier to ethical cell sourcing</td>
<td>Big regulatory gap exists in application/validation of cellular systems for toxicity testing</td>
</tr>
<tr>
<td>Robust and reliable HTP stem cell derived assays</td>
<td>Coordinated development of precompetitive solutions</td>
</tr>
<tr>
<td>Validate relevant and specific biomarkers in cellular systems for whole systemic effects</td>
<td>Minimum panel of genotypes for tox</td>
</tr>
<tr>
<td>Needed: series of cellular models + in silico + PBPr modelling that effectively predicts risk and can be validated as realistic</td>
<td>Knowledge of genotypes which modulate response to treatment</td>
</tr>
</tbody>
</table>

**What role could the RM Forward Look Sponsors play in delivering Future State**: 

<table>
<thead>
<tr>
<th>Sponsors</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support for development of more homogenous and/or defined populations of target cells</td>
<td>Support genetically based bio-sensory development</td>
</tr>
<tr>
<td>Immediate interface between commercial users and donors of materials to use in tox testing</td>
<td>Role of NC3Rs</td>
</tr>
</tbody>
</table>

**What role could other stakeholders play in delivering Future State**: 

<table>
<thead>
<tr>
<th>Sponsors</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel monitoring devices and analytical techniques</td>
<td>Reliable/reproducible supply at a distance</td>
</tr>
<tr>
<td>Reference materials</td>
<td>Support for development in scale up of cellular systems</td>
</tr>
<tr>
<td>Reference methods/protocols</td>
<td>Common ontologies to make sense of multiple sources of data</td>
</tr>
</tbody>
</table>

**Fit with 2025 Vision for UK Regenerative Medicine**: 

<table>
<thead>
<tr>
<th>Sponsors</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better patient outcomes</td>
<td>Economically effective tool for clinicians</td>
</tr>
<tr>
<td>Commercially successful UK RM Industry</td>
<td></td>
</tr>
</tbody>
</table>

**We need to…..:**

| Need | Develop human cell based predictive models for drug testing for tox regulation |

**This could be delivered by…:**

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Organotypic 3D models for main UK prioritised targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCs: knowledge for system model development</td>
<td>Industry: Scale-up applications</td>
</tr>
</tbody>
</table>

**Regulators: Validation | Is this within scope?**

**The benefits would be:**

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Every stakeholder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug discovery also needs tools for manipulating cells</td>
<td>Drugs: Cheaper, Safer, Fewer side effects</td>
</tr>
</tbody>
</table>

Opportunity for patient derived IPSC for diagnosis and personalised medicine

**Knowledge Gaps in this group:**

<table>
<thead>
<tr>
<th>Gap</th>
<th>Cells functional maturity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular development, genetic susceptibility variants</td>
<td>Scale-up of HTP</td>
</tr>
</tbody>
</table>

**Regulatory understanding, validation and acceptance**
Describe desirable “Future State”:

- Improved therapies – endogenous & exogenous
- Cartilage and bone recreating large tissue structures
- New insights into normal physiology
- Disease mechanisms
- Personalised medicine
- Biliary structures in liver 2D B-cells don’t make insulin

Current Status (including UK Capability)

- Engineering is good
- Cell Biology – develop biology heritage
- Transplantation – clinical expertise exists
- Silos
- Islet Tx goes into ‘filthy’ liver

R&D Gaps, Enablers & Barriers

- Bio-engineering community insufficiently focussed on stem cells
- Core development – bio don’t see the intellectual challenge
- Insufficient recognition: Grants, publications
- Engineers don’t understand the biological questions
- Immunology interface with regenerative medicine
- Inter-disciplinary teams

Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps & Barriers

- UK self-centred, self-satisfied. Need to look internationally
- Barrier: Existing boundaries between specialties
- Teaching: CRTFs inter-calibrated BScs stem cell focussed
- Cell niche biology vs mechanical properties
- Develop approaches to standardisation

What role could the RM Forward Look Sponsors play in delivering Future State

- Keeping enthusiasm for inter-disciplinary funding
- UKNCSN
- Centres
  - Doctoral Acct
  - ‘Give’ money, don’t tread on toes with project/programme
- AMRC links. Patient advocacy

Long term funding of inter-disciplinary teams = Centres

- Monitoring of Tissue Engineered Products in vivo
- Can be challenging from IP pharm/bio tech cautious without composition of matter

What role could other stakeholders play in delivering Future State

- AMRC links. Patient advocacy
- Long term funding of inter-disciplinary teams = Centres
- Monitoring of Tissue Engineered Products in vivo
- Can be challenging from IP pharm/bio tech cautious without composition of matter

We need to…..:

- Match problems to solutions
- Define generic targets or prioritise clinical applications

This could be delivered by…..:

- Change in mindset, worthwhile levels of funding
- Link to acellular products
- Consortia to build critical mass

The benefits would be:

- Speed up delivery of patient benefit
- Well received by regulators

Knowledge Gaps in this group:

- Combining products. Cell efficacy enhanced by 3D architecture
- New applications for existing drugs
- Combination product. Cell efficacy enhanced by 3D architecture
- More sophisticated cell-based drug screens
- Diabetology, acute liver failure, eye skin cartilage bone
- Protecting cells from immune rejection
- New applications for existing drugs
- Combination product. Cell efficacy enhanced by 3D architecture
- More sophisticated cell-based drug screens

Fit with 2025 Vision for UK Regenerative Medicine

- Better patient outcomes
- Economically effective tool for clinicians
- Diabetology, acute liver failure, eye skin cartilage bone
- Protecting cells from immune rejection
- New applications for existing drugs
- Combination product. Cell efficacy enhanced by 3D architecture
- More sophisticated cell-based drug screens

Team:

Kevin
Fiona
Neil
**Application Challenge: Stratification and clinical trial design**

**Describe desirable “Future State”:**

- Get through clinical trials to market
- Stratification of efficacy
- Stratification on risk
- Stratification on cost
- Provisional approvals
- Phase 2 to determine surgical protocol for phase 3

**Current Status (including UK Capability):**

- Cell trials are different from NCEs + NBEs + Devices
- Can’t predict dose, can’t predict PKs
- Can’t predict for risk
- Company killer – one shot only!
- Constant reinventing the wheel
- Not engaging with those that know

**R&D Gaps, Enablers & Barriers:**

- Cells are not drugs, also dual response doesn’t work
- Potency in poly-pharmacy product
- Wouldn’t it be nice to know – ATMP increasingly encouraged to ask this to academics
- Pharmacoeconomic and reimbursement

**Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps Enablers & Barriers:**

- Product
- Cost benefit cure vs. treatment

**What role could the RM Forward Look Sponsors play in delivering Future State:**

- Train and educate investigators and networking industry
- Provide interface with regulators
- Product chain
- Cell tracking
- Statistical design for C.T of C.T

**What role could other stakeholders play in delivering Future State:**

- Harmonisation
- Reduce duplicate approvals

**Fit with 2025 Vision for UK Regenerative Medicine:**

- Better patient outcomes: Essential
- Economically effective tool for clinicians: Yes
- Commercially successful UK RM Industry: Yes

**This could be delivered by:**

- Reimbursement for Investigational Treatment prior to license
- What can be learnt from vaccines?
- Biomarkers and cell therapy
- Echo importance of early reimbursement
- Social science input: implications for governance changes needed?

**The benefits would be:**

- Without it there is no cell based NM

**Knowledge Gaps in this group:**

- Statistical design
- End points QOL
- Consensus of cell therapy trial system as different
**Application Challenge: Autologous Products and Therapies**

**Team:**
- AH
- IR
- DJW

**Describe desirable “Future State”:**
- Routinely available therapeutics
- Affordable local processing
- Without expansion step?
- With expansion step
- Constructs
- Demonstrated efficacy and clinical experience

**Current Status (including UK Capability):**
- Autologous mesenchymal for orthopaedics
- Musculoskeletal but limited efficacy
- Primary cell skin
- Limbal
- Clinical evaluations in progress
- Too expensive
- Regulatory and financial work rounds?
- Matching requirements
- Hema malignancies

**R&D Gaps, Enablers & Barriers:**
- Where and how are you going to manufacture?
- Intra operative
- Near patient
- Local automation
- Centralised
- Isolation and purification and steps
- Platform/ process that supports validation
- Shelf life constraints

**Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps:**
- Clarify regulatory coverage of near patient solutions and intra-operative procedures
- Medicine or device?
- Level of manipulation?
- Requirement for funding characterisation related to MOA
- Definition of population cells e.g. 80% show marker
- Health economics more traceable procedure
- Educating clinicians

**We need to…..:**
- Focus on technology solutions exploiting the best cell types
- Decide on the manufacturing strategy
- Resolve regulatory context
- Work on adoption

**This could be delivered by…..:**
- Biologists, engineers, clinicians, regulators working smartly to support innovation
- And social scientists!

**The benefits would be:**
- Early patient outcomes
- Reduced patient risk
- Commercial wins
- Change in the innovation system

**Knowledge Gaps in this group:**
- Can IPSC technology ever be harnessed for autologous cell therapy
- High quality characterisation of function
- 3D solution
- Interface biology/ engineers
- Genome instability, cell maturity
- Reduced patient risk

**Fit with 2025 Vision for UK Regenerative Medicine:**
- Better patient outcomes
- Early therapeutic wins
- Economically effective tool for clinicians
- Commercially successful UK RM industry
- Automation platform supplier/ product is the local process
- Media plastic ware
Regenerative Medicine Forward Look

Application Challenge: Neuro

Describe desirable “Future State”:
- Licensed therapeutics
- Eye, AMD, Vascular, Diabetic
- Basal ganglia, PD, HD, Stroke??, MS, Alz
- Other Targets, Alz x

Pipeline from basic science to trials to commercial prod without road blocks

Current Status (including UK Capability)
- UK strong initial trials already. Facilities regs NIHR helpful
- TIC in RM Gov is pro-RM
- Pressure to progress to trials prematurely. Political/gov/ universities/ Ref companies/ refinancing

R&D Gaps, Enablers & Barriers
- Strategy, Cell repair neuro-protection
- Cells – differentiation, specificity, stability, safety
- Implantation. Survival, stability, immunology, technical
- Pre-clinical. GLP/GMP for animal/tox production
- Gov expectation of payback this parliament

Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps Enablers & Barriers
- Funding for non blue sky res. For systematic parameter determination
- Regulatory costs for GMP validation and maintenance
- Infrastructure qualified QC & QP personnel + manage on uni establishment
- Clinical R&D priorities
- UK vs. EU vs. FDA vs. EMEA?? What standards should we work to?
- European influence & framework. How to maintain EU competitiveness in international environment
- TIC: Access to national centre of expertise in translational tissue

We need to: 1. Achieve a 1st success. 2. Establish a pipeline. 3. Determine most safe/ effective strategy

Alt1: 1 pluripotent cell line full validated and QC with expanding set of differentiation protocols for different applications
Alt2: Diverse set of lineage specific cell lines for each application

R&D Gaps: Alternative therapeutics
- In parallel. Industry/ funders/sponsors smoothing translational pathway safety, tox, reg, GMP etc
- Basic dev biology, basic stem cell biology, translational trials to establish framework

Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps Enablers & Barriers
- Strategies
Alt1 – Repair, Alt2 protection, Alt3 plasticity, Alt4 compensation

Is CNS too challenging a strategy for cell therapies?

Knowledge Gaps in this group:
- Immunology
- Human Dev biology
- Regen. Biology

Ongoing Pipeline
- Master hESC line vs. Multiple different business models

Real therapies: Safe effective reliable for major health issues

Human xeno?

To what extent is this immediate progress?

Human xeno?

Human xeno?

Human xeno?

Human xeno?

Human xeno?

Human xeno?

Human xeno?
Describe desirable "Future State":

- Donor free cost effective TTI free sufficiency
- Challenging blood groups e.g. Thalassemia
- Market Understood
- Solid tumours

Current Status (including UK Capability)

- Components RCC PC
- Input cell CD34 UPC LESc EPS Expandable CD34s
- HSC exogenous repair of other tissues
- Haematopoietic cancers, tumour homogeneity

R&D Gaps, Enablers & Barriers

- Understanding differentiation pathways
- Scale: 96m units
- Engineering: scale, complexity, density
- Quality standards, regulatory framework, better understood
- Reduction of nucleated cells, single cell suspension

Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps

- Enormous funding required. From where?
- Research Council help
- Pre – clinical genetic instability epigenetics etc

- MC34, AML, ALL as model systems
- Engineering micro fluidics imaging
- Definition of cancer stem cells

- Intellectual property
- Access to patients, consent, tissue banking

We need to.....:

- Focus on red cells as a paradigm
- Focus on tumour heterogeneity
- Integrated multi-disciplinary ac/ academia/ industry/ clinic (value sharing)
- 10 years horizon (haem tumours)
- Scientific coord – advice to regulators

This could be delivered by.....:

- Blood delivery model as model for RM delivery
- Money incentives
- Culture change spin-outs
- Critical mass + consortia

The benefits would be:

- Know market safer – TTI sufficiency enable or more complex therapies

Knowledge Gaps in this group:

- See above

Fit with 2025 Vision for UK Regenerative Medicine

- Better patient outcomes
- Economically effective tool for clinicians
- Commercially successful UK RM Industry

Younger cells, longer survival, old cells probably bad

Manufacturing costs @ £125m/ unit ancillary costs £3-400/unit

£150m + realistic?
Describe desirable "Future State":

Blood vessels, Liver, Cartilage, MSC therapy, Optimise, Pancreas, Muscle, Gene therapy?

Current Status (including UK Capability)

Immature UK plur-potent derived human hepatocytes, Good evidence for partial recovery in Cirrhosis with realistic regeneration and signals understood, Human tissue services UK, Pluripotent B cells glucose responsive. Immature?

R&D Gaps, Enablers & Barriers

Lack of strategic groupings, ‘Understanding maturity’ of reps from ESC/ IPSC, Large animal models, Cell tracking cell labelling at GMP, Genetic regulation of EC cells to produce tools for understanding mechanism, Scale-up, NHS + patient cohorts + good R&D platform, GMP knowledge of human SC derived therapeutic cells

Policy, Funding, Regulatory, Skills, Knowledge, Infrastructure & Networks Gaps Enablers & Barriers

Scale to compete internationally? Fewer targets, Critical mass clusters, Clinical centre for regen med/ clinical trials office to interface, exploit existing NHS R&D, NHS + patient cohorts + good R&D platform

What role could the RM Forward Look Sponsors play in delivering Future State

Need sponsorship/ influence of disease/organ strategic groupings, Basic - Clinical, Sponsor meetings for junior clinicians now

What role could other stakeholders play in delivering Future State

Charities/ patient groups, NHS, Industry, Facilitate junior clinicians having series of time in regen med

R&D Gaps, Enablers & Barriers

Complete heterogeneous tissues, Epithelium: skin, airway etc. Improve organ complexity, Gene therapy - over stepping trials = projects, Very good UK basic mouse work and human studies

Application Challenge: Other organs


The benefits would be:

Health and wealth grow, NICE criteria adoptable therapy

Knowledge Gaps in this group:

Large animal models, Control of differentiation/ stability, Stem cell labelling/ trading

Application Challenge: Other organs

1. Form strategic groupings 2. Prioritise realistic clinical targets that will read out on an NHS ‘NICE’ cost benefit analysis

This could be delivered by…..:


We need to…..:

1. Form strategic groupings 2. Prioritise realistic clinical targets that will read out on an NHS ‘NICE’ cost benefit analysis

The benefits would be:

Health and wealth grow, NICE criteria adoptable therapy

Knowledge Gaps in this group:

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Application Challenge: Other organs


The benefits would be:

Health and wealth grow, NICE criteria adoptable therapy

Knowledge Gaps in this group:

Large animal models, Control of differentiation/ stability, Stem cell labelling/ trading
5. Areas noted for further exploration / clarification

The workshop and subsequent review by participants highlighted a number of areas for further exploration as the Forward Look is progressed by the Sponsors. These include:

• Gene therapy may have been under represented in the discussions
• The social sciences may not have had sufficient input, for example on innovation dynamics, and this may be important in an area of such interdisciplinarity
• The repeated discussion on interdisciplinarity did not extend to industrialists, which may be a weakness for translation
• In developing the Forward Look, individual priority challenges will need to be examined further to include consideration of timing of both R&D priorities and enablers specific to that challenge, resulting in greater specificity to the general landscape.
• The need for better approaches to 'immune suppression' is mentioned on a number of occasions, but might be better termed ‘immune intervention’ - a much broader term that could encompass immune suppression, immunological tolerance, immune privilege etc.
6. Conclusions

The workshop highlighted the many opportunities that Regenerative Medicine might enable, as well as identifying some of the challenges for setting research and funding priorities in the area, due to its lack of clear definitional boundary, early stage of development and need for interdisciplinary approaches.

Significant detail was provided in each of the key application areas (from allogeneic therapies to trial design and patient stratification) and a number of key issues were raised repeatedly. These include –

• The RM community needs to have a clearer definition of itself so that confusion over what approaches are included and how it is reported may be overcome

• There is a great deal of basic scientific understanding still required across the RM space and this will remain a priority for the foreseeable future

• Innovative trial design and methodological development will be key for cellular approaches to prosper

• Choices will have to be made as the UK funding base may struggle to provide the necessary critical mass to support the breadth of approaches included in RM

• Providing structures to allow and incentivise teams to come together around disease areas may be a productive method for increasing the return on future funding

• Building public and political credibility in this emerging technology area would benefit from some 'quick-win' (or 'quick-to-market') successes.