UK Regenerative Medicine Platform

Outcome from UKRMP Challenge Ideas Consultation

1. Background

The UKRMP initiative was established by BBSRC, EPSRC and MRC to promote translational research in regenerative medicine and address the knowledge gaps and obstacles where more development was needed to underpin the delivery of therapeutic approaches. Currently running from 2013 to 2017, the Platform has successfully established a broad-based yet coherent interdisciplinary programme that is making inroads on the key translational challenges.

The UKRMP Hubs currently address five thematic areas:

- Cell behaviour and differentiation linked to scale-up and manufacturing;
- Engineering and exploiting the stem cell niche in order to deliver functional cells of therapeutic value;
- Safety – focusing on quantitative imaging technologies;
- Acellular approaches through the development of next generation scaffolds and biomatrices to support and delivery regenerative therapies;
- Approaches to immune modulation in support of the development and clinical testing of regenerative strategies;

These thematic areas remain key bottlenecks for the field, and overcoming these barriers is critical to move forward and deliver the great promise of regenerative medicine. The sponsor Research Councils are keen to ensure that next stage funding allows for evolution of the current Platform investment, taking account of existing strengths and scientific developments since 2013, and to understand how 'UKRMP2' might be best refreshed to make it an attractive investment option at a time of budgetary pressure.

As such an open invitation for 'Challenge Ideas' was run, between 24 August and 6 October 2016, to provide an opportunity for all interested parties to highlight scientific areas and generic technologies and platform approaches that would significantly advance the overall mission of the Platform in its next phase. This consultation would allow for exploration of opportunities for natural churn in the existing Hubs and provide ideas that would illuminate discussion as to the potential for the current Hub structure to be reconfigured and/or for new Hubs to be created.

The submissions received are to be used to inform further discussions and to help define the key requirements and final remit of a formal call for UKRMP2 Hubs, which will potentially be launched in spring 2017. This should continue to support a high-risk/ innovative and interdisciplinary approach that is distinctive from 'business as usual' funding.

2. Challenge Ideas Received

Forty five challenge ideas were received, 39 from the academic sector (17 from Hubs/Hub members) and 6 from industry, and for evaluation purposes were categorised into one of 9 broad groups which are:

1. Cell Behaviour/Characterisation/Shipping
2. Acellular approaches to 3D architecture
3. Niche, cytokines, ECM
4. Cell growth and delivery at site of interest
5. Synthetic biology, gene therapy, reprogramming
6. Manufacturing (GMP) includes viral vectors and gene therapy
7. Safety
8. Combines multiple elements of above and/or more
9. Other miscellaneous

Note that the line of demarcation between groups was taken on a pragmatic basis, and many of the proposals could easily fit into one or more of the broad groupings.

3. Review of Challenge Ideas

An International Expert Panel meeting was held on 4 November 2016 to consider the submissions.

The Panel was asked to use the submitted proposals to illuminate the key translational challenges that remain in the field as it seeks to move regenerative medicine forward, and identify where there is a strong evidence base as to ways in which these can be addressed and where the UK can have significant impact. The ideas may be in line with or different to the broad thematic areas of the current five Hubs. In particular the Panel was asked to highlight where benefit would be provided through inclusion of new ideas within a future UKRMP structure. These might be incorporated in addition to, in place of, or through a merger between one or more of the current five Hub themes.

In doing, so consideration was given to whether the challenge is both critical and broad enough such that the outputs will be of use to the wider community, and whether the conceptual ideas provided in approaching the challenge are realistic in terms of the strength of the evidence base.

Summary of findings by group:

- **Group 1 - Cell Behaviour and Characterisation (7 proposals)**

  The major focus and central point of overlap considered a strength of this group was pluripotent stem cells (PSCs) and the methodologies required to produce the cells with appropraite functionality and in a format applicable for transplantation. Analytical aspects of cell biology/differentiation and quality analysis (for safety and function) were areas deemed as pressing needs to overcome, while quality control (for product reproducibility and manufacturing) was also an area that needed further development. Post-production issues, such as cryopreservation, product shelf-life/viability and shipping, were important considerations for application but were issues that should be dealt with further downstream.

Aspects around biosensors and the ability to handle and utilise large datasets were elements that the Panel considered would be valuable for incorporation in a future Platform structure. Moreover, new thinking for manufacturing approaches such as Quality by Design should be considered as there are many tools currently available but a lack of effective utilisation/linkage to manufacturing.

- **Group 2 – Acellular approaches to 3D architecture (8 proposals)**

  This group was reasonably homogenous in the overall acellular approach but could be broken down into either complex 3D or decellularised approaches. Competence across the UK in both avenues is very strong, however, the long term scalabiltiy of decellularised approaches was considered limited due to constraints on the availability of human tissue. Nevertheless, it was considered that work in this area could offer important insights into 3D architecture and functionality. Overall the members agreed that the acellular area provided considerable opportunity looking forward. There was less enthusiasm for the ideas offered in the areas of tissue engineeering or bioprinting where novel or unique aspects beyond use of current techniques/approaches were lacking and where the UK did not have a competitive edge. Similarly those that were further from the patient, such as self-assembling materials or those with gradient properties, represented areas where more fundamental research would be needed before it was ready for full inclusion in a platform of this type. Moving forward, it was considerd that a mixed portfolio of the 3D and decellularised approaches would provide the best option. The panel also considered that vascularisation was a key aspect of either approach and vital for inclusion in any future programme. In addition the use of heterotypic systems would be increasingly important for progress towards the goal of assembing pre-vascularised structures for transplantation.

- **Group 3 - Niche, cytokines, ECM (5 proposals)**

  The ideas submitted under this heading (niche elements and factors involved such as small molecule approaches, cytokines and extracellular matrix (ECM) production) provided a very strong set of ideas with strong underlying scientific capability. The Panel agreed that there remains a considerable need for integrating these agendas to better understand how cells, the ECM and the niche interact to promote survival and functional integration, which should be pursued through a rational rather than arbitrary approach. The inclusion of forward looking plans in this direction would provide a valuable extension to the Platform's capabilities. In terms of more novel ideas, the suggested approaches to effect cell fate changes in vivo were considered innovative and interesting, although the linkage between in vitro and in vivo approaches needed to be developed further. Nevertheless this was an area ripe for exploitation which could provide new avenues to promote cell survival after therapeutic intervention.

- **Group 4 - Cell growth and delivery at site of interest (4 proposals)**

  The proposals in this group generally linked to niche biology through acellular approaches but specific details on the stem cell component and biological insights were often lacking across the piece. The Panel members considered delivery of cells an extremely important aspect of regenerative medicine, but that progress would require concepts to be incorporated alongside detailed knowledge of how long cells survive, functional outcomes, how cells are handled, where they are delivered and the associated immune responses. However, whilst significant UK expertise in this area was recognisable, no overall or unifying approach was presented amongst this group of proposals and looking forward this should be a factor. The question of whether manufacturing should be integrated with delivery was also raised.

- **Group 5 - Synthetic biology, gene therapy and reprogramming (6 proposals)**

  The convergence of cell and gene therapy as a route to changing cell fate (ie. direct reprogramming without going through a pluripotent stage) was considered to be an exciting and vaible new dimension that should be pursued. This had particular relevance to the niche area (as noted in Group 3) and could in prinicple provide a step change to the field, although considerrable validation work remained to be done and this should not be considered as a 'quick fix' approach. Suggestions to couple gene therapy to acellualr delivery were viewed similarly as were ideas to generate bespoke or designer cells. It was noted that autologous cell therapies involving genetic modification were not likely to be a viable route forward, outside of the heaemotological domain, given the economic issues relating to scalability. Similarly an epigenetic modification approach was not considered viable as a tranasltional route forward at this juncture, given the considerable knowlege gaps underlying this area.

- **Group 6 - Manufacturing (GMP) includes viral vectors and gene therapy (3 proposals)**

  Proposals received in this group were quite disparate and/or conceptual, and did not readily sit within the UKRMP platform agenda. Overall there was a sense that an opportunity exists for true novelty in manufacturing which moves beyond current approaches, for example towards the development of closed systems and new automated approaches. The Panel considered that the field should consider adaptive manufacturing looking forward, given the complexity of the approaches needed to generate viable, functional therapeutic products.

- **Group 7 – Safety/Imaging (3 proposals)**

  The proposals in this group covered isolated elements of safety through imaging modalities, but which failed to fully link between in vitro and in vivo or preclinical translation into the clinic. Novel aspects presented included the development of non-destructive imaging, while the use of imaging for assessing revascularisation remained an untapped opportunity. Overall the Panel considered this topic to be vitally important for the field, with considerable expertise in the UK to be well positioned to take this forward.

- **Group 8 - Combines multiple elements of above and/or more (3 proposals)**

  The panel noted that modualting immunogenicity remains a major issue for the field, and that it was only peripherally considered in the received submissions. The panel members agreed it was imperative that this topic is incorporated in a future UKRMP structure, and that in doing so it was brought closer to patient studies. The other element to be extracted from this group of proposals for further consideration was the application of gene editing technology, which is becoming a major player in stem cell biology and immuno cell therapy, as discussed under Groups 3 and 5.

- **Group 9 - Other miscellaneous (6 proposals)**

  This brought together an eclectic group of proposals, a number of which centred on a single disease focus, without much consideration of the broader landscape. The Panel considered the proposals highlighted that clinical opportunities might be realised where there was considerable traction in the field. The area of traumatic wound treatment was considered particularly attractive, given that military health/rehabilitation offered a route towards early adoption in a clinical setting. Additionally, it was noted that there might be mutual benefit obtained

between coherent connectivity of the organ transplant and regen med communities.

4. Next steps

The submitted 'Challenge Ideas' and recommendations from the Expert Panel will be used to offer advice to the UKRMP sponsors to inform the development of a full funding call for 'UKRMP2'.