



The Royal Academy
of Engineering

Regenerative Medicine Call for Evidence

A response to the Department for Business, Innovation and Skills

March 2011

Introduction

The Royal Academy of Engineering welcomes the Department for Business, Innovation and Skills investigation into the field of regenerative medicine.

This consultation sought views on opportunities and needs in the area of regenerative medicine, as well as barriers to progress, from which Government can identify policy gaps. While unable to comment on all parts of the inquiry, the Academy has made general points on collaboration between clinicians, biologists and engineers as well as steps to bring the technology into the global health industry.

The Academy has recently published a briefing on regenerative medicine which addresses many of the issues covered in this consultation. This has been attached.

Regenerative medicine and engineering

Regenerative medicine, which aims to restore the function of diseased/damaged tissues or organs through a variety of approaches involving the use of living cells, in particular, stem cells and modulators of regenerative processes, offers the potential to meet many currently unmet medical needs. It is one technology that could replace long-term management of chronic diseases with cures for many major conditions and provide possible cures for currently untreatable conditions like spinal injury. By addressing degenerative diseases associated with ageing, regenerative medicine can not only bring social benefits but also reduce the health demands of an ageing population. The field is considered to be the next major sources of innovation in global healthcare.

The Academy sees regenerative medicine is an opportunity to demonstrate that engineering is an essential discipline to contribute the society once again. Indeed the successful translation from stem cell science to clinical therapy relies on the problem solving of key bottlenecks and innovation of new technologies and equipment.

Examples include:

- Fast detection and characterisation of stem cells – new instrument and methods to detect the ‘stemness’ of cells
- Efficient and non-tag based separation of stem cells - instruments being capable of separating large number of cells, far more efficient than a flow cytometer
- Efficient expansion (large-scale culture) of stem cells – equipment for increasing stem cell numbers by many orders in a controlled manner
- Controlled and directed differentiation - methods and technology to provide precisely defined local environment to the stem cells to generate the desired cell types
- In vivo tracing and monitoring of stem cells and tissue regeneration – non-invasive methods and equipment to trace the implanted stem cells in the human body
- Logistics of stem cell supply and implant delivery methods - equipment and devices for stem cell transport, banking and tools for stem cell homing in the human body
- Bio-safety and risk assessment of stem cell therapy - methods and mathematical models to quantify the risk of stem cell therapy

Another example of stem cell application is the use of stem cells as tools in predictive toxicology in conventional drug development is an attractive proposition; stem cell

lines (adult and embryonic) are grown to large quantity in culture and are then differentiated into the appropriate cell type, such as hepatocytes (the cells that form the main tissue of the liver). Such an approach would be more promising when combined with a functional scaffold hence to form an in vitro tissue/organ model through tissue engineering.

Although the engineering solutions are mostly based on the advances of stem cell biology, engineers can develop tools (instruments, devices, equipment, test kits) to speed-up stem cell research. The intellectual property generated, in the form of patents, know-how, software etc will be abundant. Many spin-off companies will stem out from these activities.

Consultation questions

Science and Research

1. What are likely to be the major scientific advances in the stem cell / regenerative medicine area over the next five years? Please list up to three topic areas, alongside any supporting evidence.
 - (i) Induced pluripotent stem cell (iPSC): The ability of reprogramming differentiated or primary cells to have embryonic stem cell features has been demonstrated. This represents a major advance in stem cell science. In the next five years, the efficiency of generating iPSC and the understanding of the mechanisms of cell programming and reprogramming will be improved. This will path the way for personalised stem cell therapy and tissue/organ regeneration in the future.
 - (ii) Understanding the therapeutic effect and mechanism of autologous stem cell implantation: Implanting patient own stem cells, for example, from blood or bone marrow, for the treatment of various conditions including heart infarct or liver cirrhosis, showed clinical improvements although the results is not always consistent. Understanding the effect and functions of the implanted cells will help to select and most beneficial therapy and protocol.
2. What are the major gaps in the science that need to be overcome to enable the translation and therapeutic development of the research?

The science gap is no doubt the poor understanding and inability to predict and control stem cell differentiations. This does not only affect the efficacy but also the safety of stem cell therapy.

3. How close are we in the UK and globally to delivering therapeutics in the regenerative medicine field? What, if anything, is holding back progress?

In the UK, we are not.

There is not enough technology research – the current focus of the field is too heavily based on the science.

Many autologous stem cell therapy procedures are tested in China and some are likely to be approved within three years.

4. In which therapeutic areas is clinical impact most likely in the near (<5 years) and longer term (<15 years)?

Five year targets: minimally manipulated autologous cells and stem cells (cells taken from an individual and genetically manipulated, or without, before being transferred back to the original donor). This procedure is suitable for the treatment of chronic diseases and conditions.

Fifteen year targets: allogenic cells (cells taken from a different individual to the recipient), once the immunological challenges are overcome. This is following the ultimate goal of true 'stem cell medicine' and the procedure will have off-the-shelf availability. Within fifteen years such an approach is likely only ready for acute and vital cases.

5. If you collaborate internationally, do you currently undertake research in partnership with groups and companies in i) Europe, ii) N America, iii) Asia, iv) more than one of these regions (specify). Do you expect this to change over the coming decade – if so, towards which region?

The University of Leeds collaborates with Europe and America. Asia is increasingly becoming an important partner.

There is a need to identify targets for technology solutions which can be made commercially viable globally.

Oxford University Institute of Biomedical Engineering has collaborative projects with Asia (China). One important factor to consider is the patent population.

Translation and Commercialisation of Research

6. What are the strengths and weaknesses of the UK when it comes to the commercialisation of regenerative medicine research? What could be done to improve the situation?

The UK's strengths are in the credibility of a strong science base and innovation within SMEs.

The UK's weaknesses are in the difficulty in conducting clinical trials, lack of collaborative teams having all three groups (stem cell biologists, engineers and clinicians) and the lack of funding for translational research.

There is an urgent need for special programs for translational research on regenerative medicine. One condition for obtaining such funding is, for example, to demonstrate the team must have expertise in stem cell biology, engineering and surgery. To establish a number of centres of excellence to develop platform technologies to enable such translation is also suggested.

More emphasis needs to be placed on cell-free products which recruit the patient's own stem cells.

In order for the UK to develop a sustainable regenerative medicine industry, there should be a requirement to ensure that components of the supply chain are present:

- Translational institutes where pilot work can be undertaken to produce early clinical material at scale and to cost
- Academics with specialist scientific knowledge in basic stem cell biology

- Funding for clinical and translational stem cell research
 - Requirement for clinical grade cell lines
 - Ability to scale-up production of stem cell lines to produce master cell banks (MCB) and working cell banks (WBC) of consistent quality
 - Understanding of the quality control and quality assurance requirements related to production of cell-based therapies
 - Clarity with respect to the regulatory environment and understanding of the clinical trial requirements
 - Devices to enable delivery of therapies
 - Understanding of the re-imburement process.
7. What are three specific barriers preventing the development and application of stem cell derived tools and technologies, and how might these be overcome?
- (i) Difficulty in conducting clinical trials
 - (ii) Difficulty in conducting animal testing
 - (iii) Re-imburement structure of the NHS and lack of involvement and enthusiasm of NHS clinicians

The first two come from regulation restrictions. The third one is due to the structure of NSH and work load of doctors. Increasing funding significantly would help.

We have noted two specific barriers:

- (i) The UK per review system which involves fundamental cell biology rather than technologists
 - (ii) There is too much early-stage research funding with insufficient innovation translation funding.
8. The development of many regenerative medicine therapies will require collaborations across disciplines and with end-users – how can these collaborations be better facilitated to accelerate translation in this area?

To deliver regenerative medicine products it is necessary to apply multi-disciplinary science. The interaction between biology and engineering means the two disciplines must be intimately locked together. Clinicians should engage with engineers and biologists throughout the development process. Younger scientists have multiple sets of vocabulary and their multi-disciplinary contribution should be fostered. Incentives to foster and enable such multi-disciplinary partnerships to thrive are needed. One way to do so is to establish collaborative research centres with special funding.

Engineers have a key role to play in translating advances in cell biology and biomaterials into useful treatments. To do this, there is a need to engage more with biologists and clinicians to ensure engineering principals are applied. Beyond the basic research, the following are necessary:

- Ensure there is a market and define it explicitly
- Improve funding streams and define investment models
- Establish what price the market will pay and compare to cost of manufacture
- Understand the underlying science of the product in terms of critical attributes
- Acquire and equip production facilities
- Recruit and train staff
- Develop a stable process
- Make the product and develop quality control systems

- Continue regular dialogue with regulatory bodies
- Define and finance clinical trials.

The establishment of a regenerative medicine industry requires an environment where world leading scientists are co-located with leading clinicians, where innovations at the laboratory bench can quickly be translated into human clinical testing, often via *in vitro* and *in vivo* disease models and by the use of screening tools that more accurately mirror relevant human pathologies. An infrastructure is required to support this approach that combines leading edge research technologies and capabilities with state of the art clinical facilities and an ability to move seamlessly between the two.

9. How can the regulatory uncertainties inherent to many aspects of this field be most effectively mitigated? Are there examples of regulatory practice in other regions of the world that the UK can learn from?

No comment.

10. What are the key requirements necessary for future investment in UK companies? Is this investment most likely to come from traditional VC, big pharma or other sources?

Venture capital investment is currently very limited because of the lack of commercial exits and without government support the industrial base could be at risk of collapse. The situation calls for a national strategy to grow the industrial base and retain it in the UK.

A complex and challenging regulatory landscape is faced by UK companies and discourages inward investment. However, the specific focus that the Technology Strategy Board is putting on regenerative medicine has the potential to increase translational efforts.-

The commercial focus needs to be on global markets and products, not specifically the NHS or UK market.

Getting Regenerative Medicine Therapies into the Clinic

11. Do we have the right infrastructure to deliver clinical trials of new regenerative medicine therapeutics in the UK? If not, what else is required?

No comment.

12. Does the NHS have the resources (skilled workforce, infrastructure, facilities etc) to support the efficient adoption of new regenerative medicine technologies?

No comment.

13. What enablers and policy needs are required for the effective translation of regenerative medicine technologies to healthcare?

Creating a regenerative medicine industrial base able to treat many patients will require more than technology and setting up a business. It is necessary to incentivise investors and to understand their investment models.

To build a bridge into the NHS for the adoption of regenerative medicine therapies, specialists in regenerative medicine will need to consider:

- Proof of clinical efficacy
- Showing the benefit to the patient
- Showing the benefit to the NHS
- Assessing the impact on tariffs
- Setting out how the treatment can be integrated into current practice and any service re-design it will call for
- Considering if the implementation can be linked to NHS's key policies such as by demonstrating that it leads to improvements in patient safety
- Considering if the introduction of the treatment will require more, or fewer skilled staff.

14. Do the recommendations in the AMS report (<http://www.acmedsci.ac.uk/p47prid88.html>) on research regulation address barriers in this area?

No comment.

15. Do you believe regenerative medicine will be affordable through the NHS on a large scale or will it be a niche market? Can you explain your answer in terms of reimbursement pathways, and any supporting evidence?

Yes, although it will take some time. The cost can be examined from two aspects:

- (i) The cost of regenerative therapy will be reduced through technology innovation, correct business model, and pricing. There is a consistent drive to reduce the stem cell therapies to meet the NHS requirement.
- (ii) The cost of alternative will increase. The life span of patients with the degenerative conditions will increase, and cost of no treatment and to society will increase.

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