Stemming the tide of degenerative disease

Professor Paul Fairchild explains the issues and opportunities surrounding his work in the field of regenerative medicine, and outlines the experiences that have brought him to this area of study.

What is the history of induced pluripotent stem cells (iPSCs)? When were they first discovered and what progress has since been made towards their characterisation?

The first demonstration that fully differentiated somatic cells could be reprogrammed to a state of pluripotency was published by Professor Shinya Yamanaka in 2006 – a seminal piece of work for which he was awarded the Nobel Prize for Physiology or Medicine in 2012. Since this first proof of principle, there have been numerous advances in the field, in the application of iPSCs to strategies for drug development and toxicity, for example, and their use as valuable tools for the modelling of rare disease states in humans for which no animal models are available. Perhaps most exciting has been the prospect of differentiating iPSCs into cell types required by the individual from which they were first derived, to replace cells that are worn out or lost to chronic or degenerative disease.

This would represent a form of personalised medicine with the potential to help address the healthcare challenges presented by a rapidly ageing population.

How has your career path and research background led to your current position as co-Director of the Oxford Stem Cell Institute?

I initially trained as an immunologist and worked on the molecular and cellular basis of autoimmune disease and transplant rejection. As a way of understanding these processes in mouse models of disease, I developed protocols for the differentiation of mouse embryonic stem cells into populations of dendritic cells. It soon became clear that only an interdisciplinary approach to regenerative medicine was likely to provide solutions to the many technical and scientific challenges that would have to be addressed in order to...

Tumour defence

Researchers at the University of Oxford’s Oxford Stem Cell Institute are investigating the potential of induced pluripotent stem cells to deal with a wide range of medical problems – with some of their most promising work focusing on immunology.

DENDRITIC CELLS ARE one of the immune system’s first lines of defence. Present in areas of tissue that come into contact with the external environment, such as the skin, nasal cavity, lungs and digestive tract, their job is not to attack foreign bodies, but to generate peptide fragments from their protein components. These peptides are presented to T cells that subsequently coordinate a neutralising immune response. In this way, dendritic cells play a crucial role in governing the immune response to foreign material – whether favouring an aggressive response or instead advocating tolerance. Consequently, making use of such cells in the development of immunotherapies represents a clear opportunity for controlling the body’s immune response, with positive impacts for mitigating the pathology of diseases such as cancer and HIV infection.

The realisation of such novel therapeutic approaches, however, is not without obstacles – most significantly, the procurement of an appropriate source of dendritic cells. The most effective candidates would be derived from pluripotent stem cells since their production can be scaled up accordingly but, until recently, the only source of these has been human embryos, and ethical debate on the issue has hindered progress.

LOW-HANGING FRUIT

The answer to this problem may lie in induced pluripotent stem cells (iPSCs); produced by returning differentiated adult cells to a state where they can be coaxied to take on the function of an alternative cell type. Although this procedure is still being optimised, it presents none of the ethical restrictions of using embryonic stem cells, which are also at risk of becoming malignant if inadvertently administered to patients along with the desired differentiated cells. Conversely, immunotherapeutic dendritic cells may rapidly influence the outcome of the immune response leaving their mark, irrespective of whether they subsequently die – in fact, their death will help prevent malignancy.

For these reasons, Professor Paul Fairchild, co-Director of the Oxford Stem Cell Institute (OSCI) at the University of Oxford, refers to dendritic cells as ‘the low-hanging fruit of induced pluripotency’. By administering dendritic cells derived from a patient’s own iPSCs, Fairchild and his colleagues believe it will be possible to elicit powerful immune responses to eradicate disease, or to induce tolerance to counteract harmful immune pathology. With the support of 43 laboratories from 17 departments across the University, the OSCI is a multidisciplinary venture that could well be set to lift the lid on regenerative medicine.

STUDIES IN ONCOLOGY

The main problem with dendritic cell immunotherapy to date has been the limitations...
bring therapies based on pluripotent stem cells to the clinic. With generous financial backing from the Oxford Martin School, and the vision and help of numerous colleagues, I founded the Oxford Stem Cell Institute to unite stem cell biology and regenerative medicine across the University. This has since facilitated far greater collaboration between groups and the building of critical mass in the field.

Can you explain the mechanisms behind antigen cross-presentation and the significance it has to your work?

Dendritic cells are often referred to as ‘professional antigen presenting cells’ by virtue of their capacity to take up protein antigens from their microenvironment and cleave them into small peptide fragments for presentation to helper T cells — identified by their surface expression of the CD4 molecule. Cross-presentation refers to the capacity of some dendritic cells to present peptides from these antigens, to both CD4+ and CD8+ T cells, enabling them to seek out and destroy the appropriate target cells. This property is especially relevant to the treatment of cancer since it permits the repertoire of CD8+ cytotoxic T cells to be deployed against a developing tumour.

How will the use of iPSCs serve to overcome the extensive ethical issues that have been present in stem cell research since its inception?

Although pluripotency can be readily exploited in regenerative medicine and cell replacement therapy, significant ethical issues have greatly hindered progress. The only available source of PSCs has traditionally consisted of embryos from in vitro fertilisation clinics that are surplus to requirements. The use of embryos as a source of cells has frequently impinged on ethical sensitivities, greatly complicating stem cell research in countries such as the US. Given that induced pluripotency offers opportunities to derive PSCs from fully differentiated adult somatic cells, the requirement for human embryos no longer applies.

What obstacles still need to be overcome before the use of iPSCs can be realised in a clinical setting?

Although induced pluripotency offers prospects for the treatment of a broad range of chronic and degenerative diseases, there are significant challenges that will first need to be addressed before it can be applied routinely in the clinic. The need for cells to integrate functionally into the target tissue and survive indefinitely without becoming malignant is the minimum requirement of cell replacement therapy, but one which is still some way from being realised.

THE FRUITS OF LABOUR

The implications of this work for the field of cancer immunotherapy are far-reaching in themselves — but there is the additional impact that the induction of tolerance may have for autoimmune conditions and allograft rejection, which the OSCI team is also investigating. “Having secured our intellectual property position, the next step is to identify the best commercial partners with whom to realise the clinical benefits of this technology,” enthuses Fairchild. By sharing the fruits of their labour in this way, the Oxford researchers aim to ensure a rich harvest for all.