Advances in regenerative medicine

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Achieving the long-term goal of routine clinical application of regenerative medicine will require close collaboration between academia, clinicians, regulators, tissue engineers and industry. Currently, some cell- and gene-based therapies are showing positive signs in the limited number of patients receiving treatment, but such applications are still far from routine and the regulatory landscape remains complex. The potential opportunities for new cell therapies must be explored alongside the ongoing developments of existing techniques to integrate the new opportunities in a truly translational approach. Researchers from academia and industry across the EU gathered at a recent conference to share results and ideas, and to consider the current status and future opportunities for regenerative medicine. Novel biomaterials, cell therapy to repair damaged tissue, and cell and tissue transplantation were discussed alongside industry challenges relating to building a stem-cell company within the current financial and regulatory landscapes.

Third-generation biomaterials provide exciting new opportunities for biomimetic, multifunctional scaffolds upon which to regenerate new cells *in vivo*, according to Nureddin Ashammakhi (Keele University, UK). The aim is to promote healing with cells similar to those which were lost, rather than scar tissue. Ashammakhi's group is working with nanobiopolymers that can be 'spun' into nanofibers of various thicknesses and mimic the function of the extracellular matrix. Active agents such as growth factors and anti-inflammatory drugs can also be incorporated in and

on the fibers, providing local, time-delayed release of bioactive compounds at the site of regeneration. Prof. Ashammakhi's group has demonstrated the orientation of such fibers can also be influenced, which is important for the regeneration of tissues such as tendon, ligament and neural tissue.

Regenerative medicine can hopefully help address the current issues surrounding transplantation to replace failing organs or tissues. The number of transplant donors is declining, the regulations for organ donation are becoming ever more stringent and recipients of donor material must undergo long-term immunosuppression to prevent rejection. By harnessing stem cells that are maintained through adult life to restore tissue function, transplantation could ultimately be replaced by cell or tissue therapy. An example of this was discussed by Julie Daniels, Director of the Moorfields Eye Hospital Cells for Sight Tissue Bank in London. Her group has developed a method of culturing limbal epithelial stem cells, which reside at the periphery of the cornea in adult humans. By growing the cultured cells either as explants or as a feeder layer on human amniotic membrane, a confluent sheet can be grown in 3 weeks. This can then be transplanted onto the eye of patients. With 60% of treated patients so far maintaining intact grafts and reporting visual improvement and pain relief, the future challenges for this technology include increasing reproducibility, efficacy and scale-up.

A further example of stem cells being used to repair injured tissue was described by Roberto Revoltella from the

University of Pisa in Italy. Permanent damage to the olfactory neuroepithelium can be caused by a number of environmental products, including certain herbicides. Revoltella's group transplanted human stem cells into mice with damaged olfactory epithelia and observed regeneration of the neuroepithelium within 30 days as compared with the untreated control animals. The stem cells were also found to have migrated and self-replicated in the damaged region, providing encouraging indications of the potential value of transplanted stem cells in tissue regeneration after damage.

Neural transplantation therapy was discussed by Rike Zietlow (Cardiff University, UK), who summarized the clinical successes achieved to date by grafting primary human embryonic mesencephalic cells into the brains of patients with Parkinson's disease, and those who have suffered stroke. However, around five embryos are needed for a successful graft, making stem cells an attractive alternative by providing a more reproducible, readily available source of cells to transplant. In addition, there are other problems to be solved in that no standardized cell preparation protocols currently exist, the number and location of deposits into the brain seem to be important, as indeed is the trajectory of the needle used to deliver the cells. Zietlow concluded that more work is needed around neural transplantation and the opportunities offered by stem cells should become integrated into ongoing research programs.

Satyan Chintawar (Laboratory of Experimental Neurology, Université Libre de Bruxelles, Brussels, Belgium) continued the theme of neural grafting, reporting his team's work on spinocerebellar ataxia type 1 (SCA1). This condition affects the Purkinje cells in the brain, resulting in a neurodegenerative disorder for which there is no cure.

Chintawar's team have grafted isolated adult neural precursor cells (NPCs) into the brains of SCA1 mouse models and seen an improvement in motor skills when compared with control mice. In SCA1 mice, the stem cells had migrated to the cerebellar cortex, reaching the Purkinje cells and wrapping around the cells via processes. Such results suggest that grafted NPCs may bestow a neuroprotective effect on SCA mice.

The potential for embryonic stem cells to become differentiated into germ cells is being investigated by Lyle Armstrong's group at the Centre for Stem Cell Biology and Developmental Genetics at the International Centre for Life in Newcastle, UK. The team are interested in the signaling pathways and position-specific messages within the early-stage embryo that determine cell fate. If properly understood, this could ultimately lead to reprogramming of cells in order to generate patient-specific pluripotent stem cells.

A critical issue facing the future of stem cell therapy is the ability to source and store cells. The UK Stem Cell Bank is based at the National Institute for Biological Standards and Control in Hertfordshire, UK, and as its Director, Glyn Stacey explained, is a key resource for stem cell researchers. Maintaining reliably, reproducible banks that store ethically sourced, quality-controlled stocks of embryonic and somatic stem cells is not without its challenges; in addition, the Bank provides independent advice and input into the regulation of cells, as well as sending cells to research groups round the world. This latter is particularly challenging owing to the different

regulatory frameworks around the world. There remain a number of technical challenges to be addressed, including culturing, preserving and characterizing cells.

At the time of the conference, a decision was pending by the Enlarged Board of Appeal of the European Patent Office with respect to three baseline patents relating to human embryonic stem cells (hESCs) owned by the Wisconsin Alumni Research Foundation. In the USA, these patents have proved unassailable; however, the European Patent Convention is less clear-cut. Intellectual property lawyer Julian Hitchcock from the Life Science Group at Mills and Reeve LLP in Cambridge, UK, outlined the implications of the upcoming decision for the industry and suggested that patentability of processes and products may be permitted, which indirectly use hESCs for commercial or industrial uses. The decision from the EPO is expected mid-July 2008.

Any discussion about regenerative medicine inevitably leads to discourse on the financial models necessary to enable ideas to be translated into the routine treatment of patients. Paul Kemp, founder and CSO of Intercytex, outlined the issues facing a company attempting to be commercially viable in the stem cell arena. Media perception, investor sentiment and regulatory changes can all influence the journey of a small company. With fewer big pharma companies to take up licenses and a traditional lack of interest in regenerative medicine, it has been difficult to construct a commercially viable business model. Products are sold directly to surgeons and are usually

very expensive, leading to questions about reimbursement. Intercytex have concluded that the only profitable business model is to be fully integrated, enabling the company to be flexible enough to respond to changes in public and private funding, as well as the regulatory scene. In addition, big pharma is becoming increasingly interested in regenerative medicine, with more public sector funding than ever going into the sector. Kemp concluded it has never been so positive for stem cell therapy companies.

Regenerative medicine currently holds great promise, despite the numerous technical, procedural and regulatory challenges that remain. With significant public funding available globally for stem cell research, as well as an increasing interest from big pharma, it is likely the speed of development will increase, hopefully to the benefit of more patients.

EuroSciCon's next stem cell meeting is being held on 29th May 2009, entitled 'Progress in Stem Cell Biology: *In vitro* Applications for Research and Development'. You can book a place by visiting the event homepage, www.regonline.co.uk/stem09.

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