Stem cell solutions

Associate Professor Randall D McKinnon discusses his pioneering efforts to develop safe, effective stem cell therapies suitable for patients affected by brain injuries or disease

How did you come to focus your research on stem cells and regenerative medicine?

Our current work on stem cells was a natural progression from our initial studies on brain development. Following my training in virology and cancer research, a group that was studying myelin-forming cells of the central nervous system (CNS) recruited me into neurobiology. My task was to create an immortal form of myelin precursor cells in culture, a strategy modelled after the approach used to elucidate the haematopoietic cell lineage. By accident, I found a way to isolate and expand myelin precursor cells without immortalising them, using fibroblast growth factor. This approach has subsequently been exploited by many groups and made cell culture studies on non-immortalised cells possible for many fields of research, including stem cell biology. It has also allowed the expansion of cultured cells for cell therapy and regenerative medicine.

Why has your current research project used multiple sclerosis (MS) as the disease focus?

Our research objectives are to develop cell therapy approaches to restore brain health, and the link to MS is indirect. The US National MS Society (NMSS) was supportive in my early career development and I have since remained faithful to their core objectives. One of my goals has been to repay their investment by not relying on NMSS funding to support my continuing research projects. I would prefer to see them invest public donations into the next generation of young scientists.

Recent observations from preclinical trials suggest potential for neural and progenitor cell transplants as a treatment for injured brains. Can you elaborate on the consequences of these findings?

Animal studies, mostly in immune-tolerant newborn rodents, clearly show that cell transplants in the brain can be as effective as in any organ system. There is considerable evidence to suggest it will also work in adults. This body of work has led us to our current focus in this field: finding a source of safe, ethical and effective replacement cells.

What are the advantages and disadvantages of generating patient-specific replacement cells through autologous fibroblast reprogramming?

Since these cells are derived from the patients’ own skin cells, they represent an ethically neutral cell population that will not generate an immune response and thus will not be rejected by the host immune system. At present, the main disadvantage is that the reprogramming process is slow and inefficient, requiring a prolonged cell culture environment that can promote chromatin instability and generate cells with tumour potential.

In addition, a major hurdle in this field is elucidating how reprogramming works. The process is slow and inefficient; we cannot identify the initial founder cells and only identify reprogrammed cells long after the process has occurred. Such retrospective studies can lead to ambiguity. For example, the high efficiency of reprogramming dermal fibroblasts into neurons suggests there were neural crest precursors in the starting population and questions whether this represents true lineage reprogramming. From a practical standpoint this may not matter since the process generates neurons. However, we cannot further advance the field if we do not clarify and understand the process.

Another issue underappreciated by most, and unacknowledged by many, is cross-contamination in cell cultures. Many labs use common reagents and facilities to maintain both dermal fibroblast founders and embryonic stem cells, and even a low level of cross-contamination could yield the apparent reprogramming that the investigators seek. In more than a few studies to date, the results appear to reflect investigator will rather than experimental fact. Scientists in this field, as in all fields, need to be aware of the perils of the TD Lysenko story and letting preconceived
doctrine dictate experimental results.

Where do you see the greatest potential for improving the efficiency of biological reprogramming?

It is hard to say where it will come from and what it will be, but as with all fields of science we will improve the process simply by examining every possible aspect of the mechanisms involved. One exciting emerging area is direct reprogramming in vivo.

In what ways do you foresee your methods impacting an ageing population?

Cell therapy for the brain is directed at delaying or preventing the progression of neurological impairment. Hopefully, we will be able to fix the damage in our lifetime so that the brain will not wear out before the rest of the body.

A cure for multiple sclerosis

At Rutgers University in New Jersey, USA, a team is carrying out cutting-edge research aimed at advancing stem cell therapies. The scientists hope their findings will contribute to the development of a cure for a devastating neurological condition.

**DAMAGE TO THE** brain and spine is notoriously tricky to treat. This is largely due to the fact that the central nervous system (CNS) does not have an innate capacity for self-repair; when neurons and glia are destroyed as a result of injury or disease, they are not replaced. Therefore, the development of regenerative treatments is essential for clinical progress.

Although stem cell therapy is the most likely route for such treatments, the CNS lacks sufficient numbers of endogenous stem cells, meaning that transplantation would be required. Current research in this area is therefore focused on the identification of an appropriate source of histocompatible, ethically acceptable and non-tumorigenic stem cells for this purpose.

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**MENDING MYELIN**

At Rutgers University, Associate Professor Randall McKinnon is leading a research group focused on identifying novel strategies for enhancing CNS myelin repair. To this end, the team employs a number of experimental systems and molecular genetics approaches. “The use of animal models has been an essential part of bringing remarkable advances to fruition,” states McKinnon.

As the material that forms a layer around neural axons, myelin is essential for healthy CNS function. Pinpointing repair strategies would have applications both in cases where brain or spinal cord injury affect CNS myelin and as a treatment for demyelinating diseases, the most common of which is multiple sclerosis (MS). Typically diagnosed in individuals between the ages of 20 and 50, MS is a chronic condition for which there is currently no cure. Symptoms can include loss of balance, poor coordination, problems with vision and speech, memory and concentration difficulties, tremors, numbness, extreme fatigue and paralysis. The development of an effective stem cell therapy could therefore have significant clinical applications for the 2.3 million individuals living with the disease worldwide.

**REPROGRAMMING CELLS**

One strategy for creating suitable cells for transplantation has already been explored by the McKinnon group: namely, the reprogramming of the patient’s own autologous fibroblasts into pluripotent stem cells, which can then be differentiated into the required cell grafts. This is based on a technique pioneered by the stem cell engineer and Nobel Prize winner Dr Shinya Yamanaka in 2006. “As a result of this groundbreaking work, we can now transform a patient’s own skin cells into any number of organ-specific cell types,” enthuses McKinnon. Stem cells derived from a patient’s own body are ideal as they will not generate an immune response and be rejected following transplantation.

Since then, the McKinnon lab is now extending this strategy to develop a technique that enables the direct reprogramming of fibroblasts into graftable cells – thus completely eliminating the need for an induced pluripotent stem cell stage. The
MULTIPLE SCLEROSIS

- An estimated **2.3 million** people are living with MS around the world
- Women develop MS **two to three times** more often than men
- The average individual in the US has a **one in 750** chance of developing MS (0.1 per cent)

MS CAN FOLLOW THE FOLLOWING DISEASE COURSES:

- **Primary-progressive MS (PPMS)** – affects 10 per cent of patients
  Characterised by steadily worsening neurologic function without the relapse/remission pattern.

- **Progressive-relapsing MS (PRMS)** – affects 5 per cent of patients
  Characterised by steadily progressing disease from diagnosis onwards, with occasional exacerbations but no remissions.

- **Relapsing-remitting MS (RRMS)** – affects 85 per cent of patients
  Characterised by clearly defined attacks of worsening neurologic function.

- **Secondary-progressive MS (SPMS)** – 90 per cent of RRMS patients transition to SPMS
  Characterised by a more steady progression of the disease, with or without relapses.

Source: US National Multiple Sclerosis Society

FROM BENCH TO BEDSIDE

Of course, even after the scientists have successfully identified a novel source of reprogrammable cells, there remain numerous obstacles that must be traversed before such findings can be made available to patients. Any new treatment must make its way through clinical trials before moving from bench to bedside – an expensive and time-consuming process that will most likely require significant investment from the pharmaceutical industry.

However, McKinnon is confident that the long journey ahead will be more than worth it – and not just for individuals affected by MS or other conditions or injuries associated with CNS myelin. “The progressive loss of function we all experience in ageing is just a slow version of the cell loss seen in injury and disease,” he explains. “As such, any advances in therapy for the injured brain will most certainly find their way into alleviating neurodegeneration in ageing.” In light of the fact that the global population is getting older and thus is increasingly susceptible to age-related neurodegenerative diseases, any progress towards developing novel treatments and interventions in this area would be welcomed and encouraged.

studies are focused on using epigenetic chromatin remodelling factors to help improve the conversion efficiency. Furthermore, past experiences indicate that the transplantation of cultured cells can increase the risk of adverse effects for patients: “Cells in culture can – and do – go through genome rearrangements, and these cells, once placed back in a recipient, can generate neoplastic growth,” McKinnon outlines. “There have now been several examples where culture-amplified mesenchymal stromal cells have generated neoplasms after transplantation in patients.”

McKinnon’s group is now working to develop a safer cell reprogramming technique; the researchers suspect that the answer to this may lie in using gene delivery methods to directly reprogramme accessible cells in vivo in the brain, thus eliminating the need to culture graft cells. The goal is to identify suitable target cell populations for reprogramming, and to date they have identified pericytes and NG2 cells as populations of interest.

CELL REPLACEMENT THERAPY FOR THE CENTRAL NERVOUS SYSTEM

OBJECTIVES

- To develop cell therapy approaches for restoring brain health
- To research neural progenitor cell transplants as a treatment for injured brain and spinal cord

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