



Cellular Alchemy: Breakthroughs in Canadian Stem Cell Research

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Canadian scientists have long been in the vanguard of stem cell research. In 1963, Canadian scientists James Till and Ernest McCulloch were the first to identify the stem cell, becoming the fathers of what is now one of the fastest-growing fields in modern science. In 2005, the journal *Nature Immunology* published a list of the 35 most significant stem cell research papers published within the last half of the 20th century: Canadians had written nearly half of them (Encyclopedie Canadienne, 2005). Today, Canadian scientists continue with this legacy, publishing cutting-edge research into the therapeutic uses of stem cells. Within the past year, Canadian researchers have made significant progress in stem cell research, from being the first to create induced pluripotent stem cells from horse cells, to finding a way of directly converting human skin cells into progenitor blood cells (Science Daily, 2011). These discoveries present exciting new possibilities for modern medicine, such as treatments for arthritis in humans, or a limitless supply of blood cells for cancer patients. With the numerous innovations in the field of stem cells being pioneered by Canadian scientists, it is difficult to deny that the engineering of stem cells in Canada is Canada's top biotechnology story of the year.

The very definition of stem cells – unspecialized cells with the capability of differentiating into numerous types of cells – is an excellent metaphor for the countless potential applications of stem cells in therapeutic medicine (Stem Cell Information, 2009). The most obvious application of stem cells, which divide repeatedly over their lifespan and can differentiate into nearly any type of cell, seems to be tissue regeneration. Indeed, much of stem cell research is devoted to finding ways of regenerating lost or damaged cells in the body – such as degenerated myelin sheaths in multiple sclerosis, or bone marrow transplants in leukemia patients. However, while Canadian scientists have been leading participants in such research, they have also taken stem cell research one step further by revolutionizing the process in which stem cells are produced.

For years stem cell research was considered to be a highly controversial field because it often used embryonic stem cells. Then, in 2006, stem cell research took a huge leap forward when a team of scientists in Japan managed to create induced pluripotent stem (IPS) cells from somatic cells (Stem Cell School, 2011). These cells were seen as a major breakthrough, as they had all the properties of stem cells, yet avoided the ethical issues associated with using embryonic stem cells. Since then, scientists have focused on finding ways of applying the remarkable properties of stem cells to real-life medicine – research of which Canadian scientists have been at the forefront.

Canadian scientists made a world first in 2011 when they were able to generate induced pluripotent stem cells from horse cells (Science Daily, 2011). Though the idea of using horse stem cells in human medicine may sound rather bizarre, it actually presents exciting new possibilities for therapeutic medicine in humans. Because horses have similar muscle and tendon systems to humans, IPS cells from horses could potentially help address chronic muscle



and joint diseases, such as arthritis, in humans (Science Daily, 2011). Furthermore, horses may provide a more suitable environment in which to test potential stem cell therapies, as opposed to mice (Science Daily, 2011).

A team led by Dr. Andras Nagy of Mount Sinai Hospital and Dr. Lawrence Smith at the University of Montreal's Faculty of Veterinary Science accomplished this feat by using a transposon-based method, in combination with a tetracycline inducible system, to introduce transgenes containing the reprogramming factors Oct-4, SOX2, KLF4, and c-Myc into horse fibroblasts, or skin cells (Nagy et al., 2011). Transposons are sequences of DNA that can move or transpose themselves to new positions within a cell's genome, while a tetracycline inducible system is a method of turning gene transcription on or off based on the presence of the antibiotic tetracycline (Encyclopædia Britannica, 2011). The final cells had a full set of DNA and readily formed complex teratomas, or germ cell tumors, with all three types of embryonic germ layers. When transplanted into immunocompromised mice, these cells were able to differentiate and form different types of cells – essentially, they displayed all the characteristics of IPS cells (Nagy et al., 2011).

However, while IPS cells in themselves are an exciting discovery, their use still presents several issues. They are extremely time-consuming to produce, requiring days or even months to fully mature. IPS cells have also demonstrated a higher propensity than embryonic stem cells (ESCs) to form tumors once transplanted into the body: a 2010 study in the journal *Stem Cells* found that IPS cells are far more tumorigenic than ESCs (Gutierrez-Aranda et al., 2010). Using ESCs decreases the risk of forming tumors, but raises complex ethical issues. Furthermore, ESCs only produce cells of a fetal type, which are of little use in treating adults. Consequently, two goals in stem cell research have been to find faster, more efficient ways of producing IPS cells and to resolve the safety issues surrounding IPS cells.

The researchers from McMaster University made a stunning breakthrough in 2010 when they created progenitor blood cells from skin cells, bypassing the middle pluripotent step altogether (Science Daily, 2010). Progenitor cells are similar to stem cells in that they differentiate into different types of cells, but are more committed than stem cells (Children's Hospital Boston, 2011). The team from McMaster University infected human dermal fibroblasts with a virus that inserted the Oct4 gene. This gene activated haematopoietic, or blood-making, transcription factors in the cells. With specific cytokine treatment, researchers were able to generate cells with the pan-leukocyte marker CD45; essentially, cells that were capable of giving rise to all types of blood cells, including erythrocytes (red blood cells), thrombocytes (platelets), as well as monocytes and granulocytes, two types of white blood cells (Szabo et al., 2010). Though a virus was used to insert the Oct4 gene, the cells produced never demonstrated any pluripotent characteristics. The experiment was successful with cells from humans who ranged in age from newborn babies to sixty-five plus, demonstrating that the process appears to be independent of age. Finally, when inserted into mice, the engineered blood cells showed no adverse side effects and appeared to function normally, foreshadowing a positive future for uses of these cells in humans (Science Daily, 2010).

The groundbreaking discoveries made at McMaster University have broad implications for medicine and have garnered international attention. Not only does this conversion pathway create a much higher proportion of skin cells than previous methods, it is far faster, working in a matter of hours as opposed to days or even months. The potential for patients to receive



healthy, perfectly matched blood products created from their own skin eliminates the necessity of finding compatible blood or bone marrow donors, a potentially difficult and time-consuming process (The Guardian, 2010). In the near future, it is possible that patients suffering from cancer, anemia, and other blood conditions will be able to receive personalized and perfectly healthy blood products. Clinical trials may begin as soon as 2012 (Science Daily, 2010).

Though researchers in the past have also been able to generate functional somatic cells from fibroblasts in mice without first creating pluripotent cells, the researchers at McMaster University were the first to do so with human cells and the first to generate blood cells. By bypassing the middle pluripotent step, these scientists have laid the foundation for other research teams to create other types of cells, such as pancreatic and muscle cells, from skin cells, and avoid the complications associated with induced pluripotency. Their groundbreaking research into the programming of skin cells has cemented Canada's position as a world leader in stem cell research.

The year of 2010 has been an exciting one for Canadian stem cell research. The generation of IPS cells from horse cells and the direct conversion of skin cells into blood progenitor cells are but two of many innovations made in the field of stem cell research by Canadian scientists. Canadians have also done research into safer ways of producing IPS cells and using IPS cells derived from the liver to test the toxicity of drugs (Stem Cell Network, 2011). Through bioengineering, simple somatic cells have become the foundation for a promising future of regenerative medicine. The amazing work being done at a cellular level by Canadian scientists is truly cellular alchemy.



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