Unit 5: A Brief History of induced Pluripotent Stem (iPS) cell research

In 1998, James Thomson at the University of Wisconsin, Madison was the first scientist to isolate and culture human Embryonic Stem Cells (hESCs), paving the way for future scientists to study their role in development, cellular properties, identification markers, and even how to coax them to differentiate into other mature cell types. But the freedom to create new human embryonic stem cell lines did not last long. In 2001, President George W. Bush limited federal funding to 64 pre-existing stem cell lines. Today, eleven of those lines are being used around the world for research, and although federal funds may be used to study them, these pluripotent stem cells are not viable for use in therapies. These hESCs are contaminated with mouse proteins from the nutrient-providing "feeder layer" of mouse fibroblast cells necessary for the propagation of each line. Since Bush's decision, a highly-charged debate and an uncertain public policy outlook have dominated the field of stem cell research in the United States.

For years, Somatic Cell Nuclear Transfer (also known as cloning) was viewed by the research community as the most promising path towards cellular sources that might avoid immune rejection by the patient. In 2005, South Korean Dr. Woo-Suk Hwang's therapeutic cloning research was exposed as fraudulent and the technology has yet to be performed successfully with human cells. One of the rate-limiting challenges for SCNT technology is the availability of human female eggs. Although some scientists hope that the research community will overcome the biological barriers inherent to therapeutic cloning, this technique still has ethical concerns because it requires the creation and destruction of human embryos.

In 2007, researchers found a brilliant solution to the problems of immune rejection and use of human embryos to create new stem cell lines. Dr. Shinya Yamanaka of Kyoto University, Dr. George Daly of Harvard University, and Dr. James Thomson reported inserting several genes to reprogram adult skin cells back to a pluripotent (embryonic) stem cell state and referred to these cells as induced Pluripotent Stem (iPS) cells. A pragmatic advantage of this technology is that most labs have the capacity to generate iPS cells using common viral delivery systems. A clinical advantage to iPS cells is that immune rejection issues are avoided, since the starting adult cells are taken directly from the patient. To date, it is believed that iPS cells can be differentiated into any cell type, just like embryonic stem cells. In case you were wondering: Dr. Yamanaka's four gene mix includes Oct 3/4, Sox2, Klf4, and c-Myc.

Problems remain with this technology, however. The use of lenti-viral delivery of the genes into the genome can lead some cells in the reprogrammed population to become cancerous. c-Myc is a powerful oncogene (cancer-causing gene) as well as a "stemness" gene (one that promotes pluripotency). Other combinations of "stemness" genes have been used that don't include c-Myc and a next step could be to use small molecules to activate and control the expression of these genes. At present, the creation of iPS cells is a powerful advance for basic and translational research. Recently, scientists at the Harvard Stem Cell Institute created 20 disease-specific stem cell lines using this technique; in another advance, Douglas Melton reprogrammed pancreatic cells into insulin-producing islet cells for the treatment of Type 1 diabetes.