

Fact Sheet 7

Induced Pluripotent Stem Cells (iPS cells)

Stem cell science is an extremely fast moving field of research with new breakthroughs being reported almost daily. This swiftly changing landscape has seen many different stem cell types and technologies capture popular imagination including embryonic stem cells (ES cells), adult stem cells, cord blood stem cells and embryonic germ stem cells. Currently attracting a lot of public attention are some recent breakthroughs in the areas of reprogramming and in particular the discovery of a way to make a new cell type which has been named induced pluripotent stem cells (iPS cells).

Reprogramming

The term reprogramming is often used to refer to techniques developed by scientists to change the developmental potential or fate of a cell. The objective of reprogramming is to take a defined cell from the body (somatic cell), such as a skin cell, and convert it to more primitive stem cell which would be capable of developing into another cell type such as a heart or blood cell.

Currently there are two different approaches to reprogramming being investigated by scientists around the world: somatic cell nuclear transfer (SCNT) which is covered in the ASCC's Fact Sheet No.4; and the creation of iPS cells.

Both types of reprogramming are of great interest to scientists as they represent ways to potentially create patient-specific cells to study particular diseases in the laboratory or even provide replacement cells to treat a patient which would not be rejected by the immune system. However, both types of reprogramming research are in the very early stages and are many years away from a therapeutic use.

Induced Pluripotent Stem Cells

iPS cells are a type of pluripotent cell¹ artificially derived from a non-pluripotent cell, such as an adult human skin cell. This is achieved by using retroviruses to insert four genes into the human skin cells to reprogram them. Following insertion of the four genes, 4-5 weeks of culture in the laboratory is required before rare iPS cells begin to appear. To date, only between one in 5000 to one in 10000 somatic cells converts to iPS cells. Little is currently understood what actually occurs during this time however the process should become more efficient and better understood as research progresses.

iPS cells were first produced in 2006 from adult mouse cells by Shinya Yamanaka and his team at Kyoto University in Japan². More recently, human iPS cells have been reported by several groups from Japan and the United States^{3,4,5}.

¹ Pluripotent—Ability of a single stem cell to give rise to all of the various cell types that make up the body.

² Takahashi, K. and Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006, Vol 126, pp663–676

³ Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, Slukvin II, Thomson JA. Induced pluripotent stem cell lines derived from human somatic cells. *Science*, 2007, vol 318, pp1917-20.

iPS cells are believed to be similar to embryonic stem cells⁶ (ES cells are considered the 'gold standard' of pluripotent cells) in many respects but the full extent of their relationship to embryonic stem cells is still being assessed. The iPS cells generated in the recent experiments shared many characteristics of human ES cells but were not identical as the expression level of approximately 1,200 genes was greater than five fold different when the two pluripotent cell types were compared⁵.

Whilst an undeniable breakthrough in the field of reprogramming, the use of iPS cells in the clinic is many years away - if it occurs at all - as several significant hurdles need to be overcome. A downside of all the current ways to generate human iPS cells is the use of retroviruses to genetically engineer the cells to achieve reprogramming. It is still unclear how genetically stable or safe iPS cells will be for potential clinical use. Consideration of safety must also consider the implication of the over-expression of specific reprogramming genes especially when several approaches to date have relied on the over-expression of cancer causing genes.

Much of the current public interest and support surrounding iPS cells is due to the fact that generation of iPS cells bypasses the need to use human oocytes or embryos, in contrast to other methods of generating pluripotent stem cells.

Position of the Australian Stem Cell Centre

The successful generation of human iPS cells has led some to call for a ban on human ES cell research and SCNT⁷. Although the generation of iPS cells avoid some of the ethics issues associated with the use of human oocytes and embryos, issues associated with obtaining informed consent and safety for therapeutic applications remain.

The Australian Stem Cell Centre believes it is too early to draw conclusions about which types of cells – ES, SCNT, iPS or adult stem cells – will prove most useful for researchers and in the clinic (refer to ASCC Fact Sheet No 2 for an overview of all the different types of stem cells). It is also too early to know which approaches will work in which conditions⁸ and would be extremely premature and a serious mistake for any government or regulatory authority to conclude that recent developments in iPS cell research averts the need for ongoing human ES cell research. There remains overwhelming scientific justifications for proceeding with all forms of stem cell research into the future⁹. Cell types made from human embryonic stem cells have been shown to be genetically stable in many laboratories around the world and are about to be used in human clinical trials to treat spinal cord injury in California¹⁰. Stability of human iPS cells and full ES cell equivalence is yet to be demonstrated.

⁴ Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S.. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*. 2007, vol 131(5), pp861-72.

⁵ Park IH, Zhao R, West JA, Yabuuchi A, Huo H, Ince TA, Lerou PH, Lensch MW, Daley GQ. Reprogramming of human somatic cells to pluripotency with defined factors. *Nature*, 2008, Vol451, No 7175, pp107-222.

⁶ Embryonic stem cells—Primitive (undifferentiated) cells derived from a 5-7 days preimplantation embryo that have the potential to become a wide variety of specialised cell types.

⁷ <http://www.abc.net.au/news/stories/2008/01/16/2139559.htm>

⁸ Editorial. Proceed With Caution. *Nature Biotechnology*. Vol 23, pp 763.

⁹ Hyun, I et al. New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells, *Cell Stem Cell*, 2007, Vol 1, pp 367.

¹⁰ <http://www.geron.com>

What is required is the continuation of well regulated research in Australia consistent with current legislation governing the responsible use of human embryos and gametes in research ¹¹ and guidelines such as the *National Statement on Ethical Conduct in Human Research (2007)*. In addition, research involving iPS cells would also have to be performed in accordance with the *Gene Technology Act 2000* and overseen by the Office of the Gene Technology Regulator due to the genetic modification that is required.

Current Known iPS Cell Research Funding Initiatives

USA

The US National Institutes of Health on 13 December 2007 put out a new funding announcement¹² for *Human Pluripotent Stem Cell Research Using Non-Embryonic Sources* specifically aimed at research into reprogramming and iPS cells. The total funding available has not been specified.

The new California Institute of Regenerative Medicine (CIRM) president has indicated that CIRM has a strong interest in funding iPS and reprogramming research¹³, however at time of writing no program has been announced.

Germany

Germany currently has extremely restrictive legislation with regard to research on human ES cells. Under the German *Stem Cell Act*, derivation of human ES cells is prohibited and only stem cell lines created before 1st of May 2007 may be imported for use in research. This is a recent amendment from April this year, the cut off was previously January 1st, 2002. By adopting the proposal with 346 out of 580 votes, the members of the Bundestag have also specified the scope of application of the Stem Cell Act: as it explicitly refers to the utilisation of human embryonic stem cells in Germany, the work of German scientists abroad (e.g. in the context of international projects) will no longer constitute a criminal offence.

However, Germany has pledged to invest more money in adult stem-cell research after the iPS breakthroughs in Japan and the US. The country's research minister Annette Schavan has announced that it will "double research funds for the technology for reprogramming adult cells from €5 to €10 million a year, so that work can proceed quickly".¹⁴ Germany has no special legislation on the preparation and use of iPS cells.

This invention is recent and it is their opinion that special legislation is not really needed as adult SC will be used for those experiments only. On the contrary Germany has now expanded its fund for reprogramming research activities. Therefore the *embryo protection act* still defines and protects the embryo and the *Stem Cell Act* still prohibits the work and establishment of human ES cells with the exception of importing cells which had been established before Jan 1 2002¹⁵.

¹¹ Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006 as found at <http://www.comlaw.gov.au>

¹² <http://grants.nih.gov/grants/guide/pa-files/PA-08-043.html>

¹³ <http://www.nature.com/stemcells/2008/0801/080124/full/stemcells.2008.25.html>

¹⁴ Education and Research Minister Annette Schavan told the newsmagazine Focus <http://www.dw-world.de/dw/article/0,2144,2972580,00.html>

¹⁵ Additional information on iPS research has been provided to the ASCC by the Stem Cell Network North Rhine Westphalia, Germany's leading stem cell group.

Japan

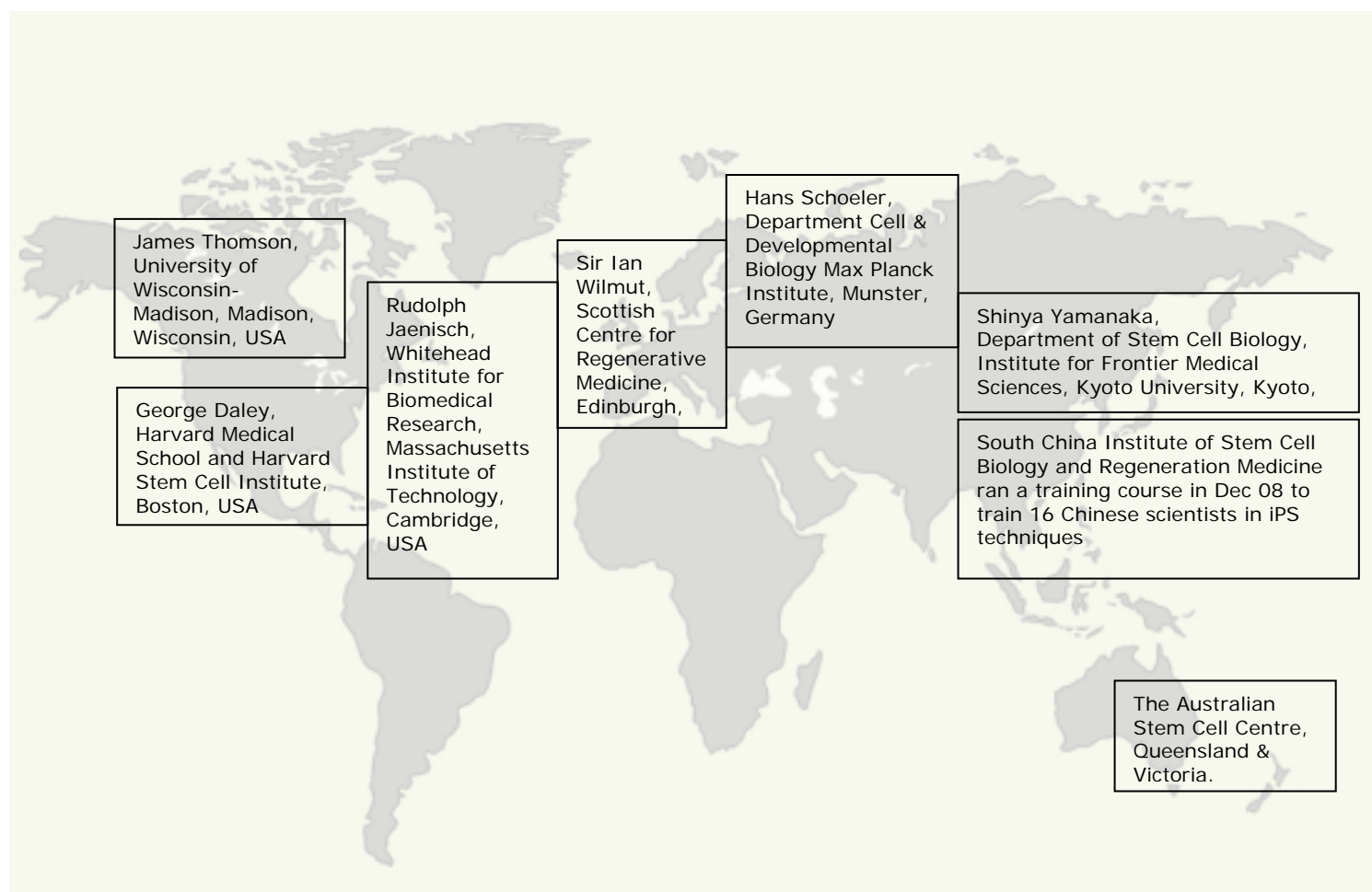
The Japanese Government has proposed to spend up to ¥10 billion over the next five years to promote research on iPS cells. The proposal also includes the setting up of major iPS research centre at Kyoto University¹⁶.

Australia

In June 2008 Sydney IVF Limited and the Australian Stem Cell Centre (Melbourne node) received \$550,000 from the NSW and Victorian Governments to progress this new frontier of stem cell research. The following month the Queensland Government announced a grant for \$308,000 to the Australian Stem Cell Centre's Queensland node to extend and expand the iPS research that state.

Where is the iPS Cell Research Occurring?

At time of writing the groups involved in or known to be interested in getting involved in research into iPS cells are:



¹⁶ <http://search.japantimes.co.jp/cgi-bin/ed20080111a1.html>