Stem Cell Research and iPS – Ethics and Regulatory Issues Illustrated by the Case of Japan

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Japan is the only country that has decided to concentrate its efforts in developing regenerative medicine on iPS. For this reason, it has been organising its science policies in such a way so as to speed up research in this area. The discovery of iPS by a Japanese researcher, Shinya Yamanaka, and his subsequent winning of the Nobel Prize, set off enormous effort to become the world's Number One in this field. The 2012 Nobel Prize in Physiology or Medicine was awarded to Sir John B. Gurdon, professor at the University of Cambridge, and Professor Shinya Yamanaka, Director of the Center for iPS Cell Research and Application (CiRA) at Kyoto University, for their discovery that 'mature cells can be reprogrammed to a pluripotent stem cell state'.

Stem cell research and experimentation have a history of over half a century. Stem cells have the unique ability to divide and replicate repeatedly and their undifferentiated state allows them to differentiate into a wide variety of specialized cell types. Embryonic stem cells are pluripotent, and can replicate unlimitedly and differentiate into any cell of the human body. For a long time, human embryos were the only sources of such potent stem cells. But the discovery of Induced pluripotent stem cells (iPS cells) in 2006 by Shinya Yamanaka and Kazuhiko Takahashi (2006)[1] shook up the world, as iPS introduced unlimited alternative resources.

IPS cells are made from adult cells, for instance, skin cells. They are isolated and then transformed (reprogrammed) into embryonic-like stem cells through the artificial introduction of certain genes and other methods. Similar to human embryonic stem cells, iPS cells are characterized by the theoretic ability to differentiate into any kind of organ or tissue of the human body. Researchers at Kyoto University in Japan experimented using mouse cells and were the first to successfully generate iPS cells in 2006. In 2007, further experiments at Kyoto University showed that the similar methods could be used to transform human adult cells into iPS cells.

iPS cells offer immense potential for regenerative medicine and studies of disease and development. It has aroused great commercial interest, with potential applications ranging from the use of stem cells in, for instance, the treatment of disease, tissue regeneration, tissues screening and cell therapy. Diseases such as Huntington's Disease, Parkinson's Disease, and spinal cord injuries are examples of clinical applications in which stem cells could be applied to halt or even reverse serious disease conditions.

[1] Takahashi, K., and Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126, 663–676; Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., and Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131, 861–872.

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Developments in Japan

Large research projects are now carried out and the government in Japan has invested heavily in providing grants for hESC and iPS cell technologies as support for small venture companies that have been created out of technologies of major research institutions. Thus, in December 2007, the government announced 'The General Strategy to Promote iPS Cell Research'. [2] There has also been an exceptionally quick move to revise and establish governmental guidelines for stem cell research. To maximize the outcomes of the research, funding and regulatory systems for clinical translation need to undergo further reform and the participation of private companies should be encouraged.[3]

Further efforts were made towards translational research. In 2012, Yamanaka announces that he wants to build a bank of iPS stem cells for therapeutic use. The iPS Cell Stock project received permission from Ministry of Health Welfare and Labour to allow the creation of cell lines from the thousands of samples of umbilical cord blood, an important source of stem cells, held around the country. In 2013, Takahashi Masayo from RIKEN, a large natural sciences institute funded by the government, announced the application to the Ministry of Education, Culture, Sports, Science and Technology for the clinical application of retinal pigment epithelian (RPE) stem cells for macular degeneration.

International competition made the government realize the importance of intellectual property strategy. Japan's strategy aims to patent early on the basis of research to prevent company monopolies on the iPS methods developed. In total Japan has obtained seven Japanese patents relating to basic iPS cell technology, and six in the U.S. Kyoto University has obtained patents relating to basic iPS cell technology not only in the U.S. but also in Europe, Singapore, South Africa, and the Eurasian region.

International developments

Internationally, there has been great enthusiasm for developing iPS technology, not only in the US and Europe, but also in other Asian countries such as China, South Korea, Singapore and India.

By 2010, there were a number of private companies that were ready to capitalize on the iPS breakthrough technology. Thus, Advanced Cell Technology (ACT, Massachusetts) faced challenges while conducting experiments for the purpose of applying for U.S. Food and Drug Administration (FDA) approval to use iPS cells in therapeutic applications. Concerns such as premature cell death, mutation into cancer cells, and low proliferation rates were some of the problems that surfaced.

Continued research and experimentation, however, has resulted in numerous advances over

[2] Ministry of Education, Culture, Sports, Science and Technology (MEXT) (2007) iPS Saibou (Jinkou-Tanousei Kansaibou) Kenkyu nado no kasokuni muketa Sougou Senryaku [the General Strategy to Promote iPS Cell Research], accessible from: http://www.lifescience.mext.go.jp/download/news/ips_senryaku.pdf

[3] Opportunities for research and development in japan - focus on advanced cellular technologies, Available at: http://www.jetro.org/opportunities_for_research_and_development_in_japan_advanced_cellular_technologies

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the last few years. In one example, the University of Michigan announced in 'Circulation Research' (2012) that they had developed innovative methods for the use of iPS cells derived from skin biopsies to create cardiac muscle cells. This accomplishment quickly fueled other research into the use of iPS cells for the reversal and repair of diseased heart tissue.[4]

A large and thriving research products market has grown into existence for iPS. According to an iPS cell market report, the sales of iPS cell research products worldwide have been growing at a rate of 14.7% per year for the past five years. In addition, 22% of all stem cell researchers now self-report as having used induced pluripotent stem cells within a research project. It is clear that iPS cells are a vital research trend within the scientific community. A distinctive feature of this report is an end-user survey of 293 researchers (181 U.S. / 112 International) that identify as having induced pluripotent stem cells as their core research focus.[5]

Scientific, Ethical and Social Issues

Traditionally, scientists have worked with both embryonic and adult stem cells as research tools. While the appeal of embryonic cells has been their ability to develop into (differentiate) into any type of cell, there has been significant ethical, moral and spiritual controversy surrounding their use for research purposes. Although some adult stem cells have differentiation capacity, it is often limited, which creates narrow options for usage. Thus, iPS cells seem a promising combination of adult and embryonic stem cell characteristics.[6] However, the use of iPS can have some drawbacks.

The factors originally selected to make iPS used viral vectors, which are associated with a high risk of tumorisation (i.e., the cells would develop into tumours as opposed to differentiating into the desired cells needed to regenerate organs or tissues). Although safer methods and technologies were soon developed,[7] such as the Sendai virus[8] and plasmids,[9] the risk of tumorisation is still an important consideration in the decision to take iPS to the clinic. Like embryonic stem cells, iPS can lead to the formation of teratomas, tumors containing tissue from various parts of the body. It is important, therefore, to control the differentiation of iPS into target cell types and to eliminate residual undifferentiated cells.[10] It is common practice to co-culture pluripotent cells with mouse-derived feeder cells, and to deliver nutritional supplementation with bovine serum. Although approved by regulatory

[4] BioInformant Worldwide, L.L.C. (2013) Complete 2012-13 Induced Pluripotent Stem Cell Industry Report. Available at: http://www.marketresearch.com/BioInformant-Worldwide-L-C-v3663/Complete-Induced-Pluripotent-Stem-Cell-7628917/

[5] Induced Pluripotent Stem Cell Industry (iPSC Market) Report Updated for 2013. Available at: http://www.prweb.com/releases/induced-pluripotent-stem/cell-ipsc-market-report/prweb10830044.htm

[6] Ryan Lister, Mattia Pelizzola, Yasuyuki S. Kida, R. David Hawkins, Joseph R. Nery, Gary Hon, Jessica Antosiewicz-Bourget, Ronan O'Malley, Rosa Castanon, Sarit Klugman, Michael Downes, Ruth Yu, Ron Stewart, Bing Ren, James A. Thomson, Ronald M. Evans, and Joseph R. Ecker, Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells, *Nature*. 2011 March 3; 471(7336): 68–73.

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authorities, their use is considered undesirable, as their properties may vary and generate side effects in cell cultures. Therefore, attempts were made to produce serum-free iPS cells.[11]

It is also argued that iPS have a form of memory, which means that they may retain unknown characteristics, and may be unsuitable for clinical application. This 'somatic memory' has become an issue because it can mark 'otherness' of the cells even after differentiation into target cell types (Dolgin 2011).[12] It is uncertain therefore whether the cells are suitable for treatment.

As there is no consensus on best practices, few companies venture into iPS cell research. This means that governments carry the main brunt of its funding. This situation castes doubts on the sustainability of the research, and how the therapies reach target patient groups. It is hoped that HLA (human leukocyte antigens)-matched iPS cell banks can provide a standardized source of research and future clinical application, and that its high quality and relatively low cost can attract industry and facilitate the move from iPS cells to clinical application.

Finally, due to the virulent competition between research centres in the world, there has been a trend in facilitating the process of translational research by adjusting regulation. As a result, political and national interests may influence the regulatory measures aimed at ensuring the safety and efficacy of clinical trials and therapeutic products. Large investments into scientific projects can cloud the judgement of researchers and governments regarding safety, especially when under pressure to develop new therapies. In addition, the large investment and hype around iPS cells has made patient groups hopeful. Unless this hope is tempered and turned into realistic expectation, the inevitable disappointment to patients may be both damaging the patients and their families and the research.

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[12] Dolgin E (2011) Flaw in induced-stem-cell model. *Nature* 470: 13; Laurent LC, Ulitsky U, Slavin I, Tran H, Schork A, Morey R, Lynch C, Harness JV, Lee S, Barrero, MJ, Ku S, Matynova M, Semechkin R, Galat V, Gottesfeld J, Izpisua Belmonte JC, Murry C, Keirstead HS, Park HS, Schmidt U, Laslett AL, Muller FJ, Nievergelt CM, Shamir R, and Loring JF (2011) Dynamic changes in the copy number of pluripotency and cell proliferation genes in human ESCs and iPSCs during reprogramming and time in culture. *Cell Stem Cell* 8(1): 106-118.

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