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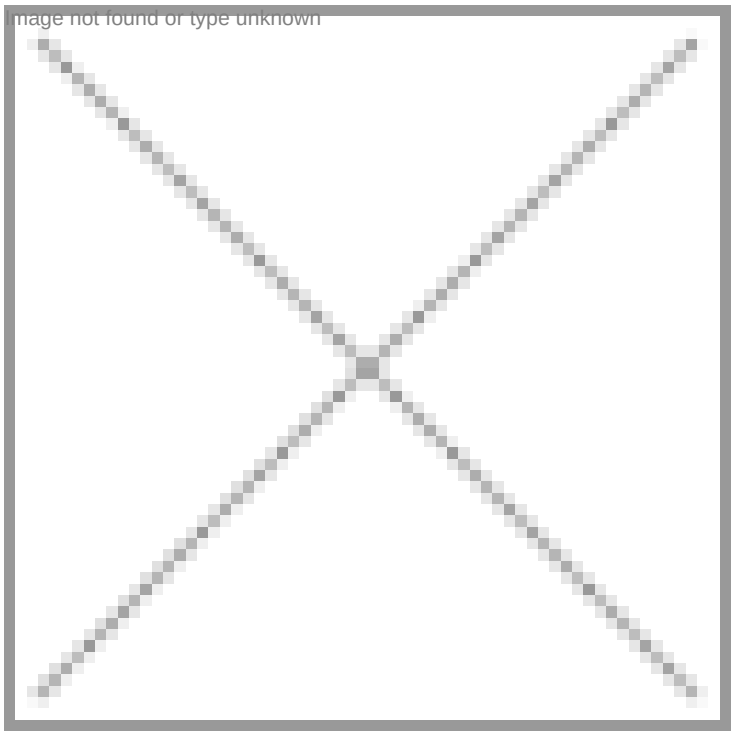

Induced Pluripotent Stem Cells

Roadmap to replace current stem cell models is still a long way before commercialization.

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Over the past 20 months, reports claiming the generation of Induced Pluripotent Stem (iPS) cells from somatic cells and having embryonic stem (ES) cell-like characteristics, has captured great attention of scientific community and general public. A lot of enthusiasm was generated particularly in the Western countries since iPS cell line was proving to be a viable alternative to the controversial Embryonic Stem Cells. This led to the rapid and premature acceptance of using iPS cells for regenerative therapy. How convincing are the evidences supporting the various claims made for the iPS cells? Are there other more plausible explanations for the same observation? What are these iPS cells? Are they really safe for therapeutic use? Should the iPS technique be considered, in the absence of any direct evidence for induction and reprogramming, as a realistic alternative for somatic cell nuclear transfer (SCNT) to generating ES-like cells?

Evolution of iPS

An astonishing breakthrough in Stem Cells occurred in 2006 when Yamanaka et al demonstrated that iPS cells could be generated from mouse embryonic or adult fibroblasts by retrovirus-mediated introduction of four factors Oct3/4, Sox2, c-Myc and Klf4. These iPS cells were similar to ES cells in morphology and teratoma formation4. The race then began in establishing a similar result in humans and incidentally the race ended in a tie when Yamanaka's group from the Kyoto's University along with Thomson's group from the University of Wisconsin-Madison both reported that they were able to reprogram a Human Somatic cell into an embryonic stem-like cell. Shi et al explored alternative strategy combining genetic and chemical approach wherein small molecules were capable of replacing viral integration of certain transcription factors and promote reprogramming process. Use of specific small molecule inhibitors suggests that loss of function of certain genes may be an effective mechanism for generating iPS cells.

This study has generated hope that the use of additional small molecules or other non genetic methods could improve reprogramming that could ultimately allow the generation of iPS cells or multipotent tissue-specific stem cells in completely chemically defined conditions without any genetic modification. iPS technology hogged the limelight in the 6th Annual Meeting of International Society for Stem Cell Research which was held at Philadelphia from June 11-14, 2008. Shinya Yamanaka announced in Closing Plenary session about development in terms of characterization, directed differentiation of iPS cells into neurons and beating cardiomyocytes. iPS cells have high clonogenic potential. They express ES cell-specific antigen profile. These cells have growth potential, gene expression pattern, telomerase activities and epigenetic status similar to ES cells.

Applications of iPS cell technology

iPS cells promise several practical applications. Procedures already validated for ES cells will investigate iPS cells' potential to differentiate into functioning, specialized tissues. Working in sickle-cell anaemia, Rudolf Jaenisch and co-workers have already shown, in an elegant proof-of-concept study in the mouse, how reprogramming, tissue-specific differentiation and gene therapy can be used to cure inherited disorders.

The potential advantage of using this technology will be for generation of patient-specific cells and evaluation of diagnostic or pharmacological tests in an individualized medicine approach. In contrast to the term "therapeutic cloning" coined for SCNT-derived applications, this would be "therapeutic reprogramming". As with other biomedical research discoveries, the fields that will benefit most from these recent discoveries are that of Tissue engineering and regenerative medicine where customized tissue grafts could be made from a persons' own adult fibroblastic cell. In addition, the technology may help avoid immune rejection of replacement tissues, because an adult patient's cell could be the source of stem cells that are a genetic match to that individual.

Indeed, the potential applications for iPS technology are endless. An overlooked application of iPS cells would be using them to bypass the difficulty of working with species for which establishing ES cells is difficult or impossible. The ability to perform genetic manipulations would help to engineer traits such as disease resistance or greater muscle mass in domestic or threatened animals. Freezing batches of iPS cells from endangered species may also help to preserve them.

Ethical concern

The technology sidesteps the ethical objections raised against research in human embryonic stem cells, which are derived from early stage human embryos that are often destroyed in the process. The new technique is not without its own set of limitations, although some of those have already been resolved. One of the original genes used for reprogramming (c-MYC)

has been shown to produce tumors and cancers. With current level of knowledge, it would not be a preferred choice for patient therapy.

Commercialization

This is a consequence of any research that will have a major impact on future therapeutic interventions. As a step towards development and commercialization, Japan Education, Science & Technology Ministry has established CiRA, Centre for iPS research & Application and allocated approximately 1 billion yen ($10 million). CiRA will promote basic research and clinical application of iPS cells in understanding disease mechanisms, drug screening, toxicology and regenerative medicine.

Collaborative work between iZumi Foundation and San Francisco based J David of Gladstone Institutes are undertaking research in iPS cells that can be coaxed to regenerate injured spinal cords or damaged hearts.

PrimeGen Biotech from Irvine, CA, USA (www.primegenbiotech.com) has claimed to have successfully used non-viral technologies to reprogram adult human cells into stem cells that the Company refers to as intermediate iPS cells. They employed high efficiency particle delivery system to transport proteins and DNA molecules directly into cells from human skin, retina & kidney. They are the first to use methods that do not involve potentially tumor-causing viruses or genetic manipulations. They report that this method is faster and efficient than other known methods. However, they have not yet disclosed the details which need to be validated by various laboratories.

At the 6th Annual meeting of ISSCR at Philadelphia, Timothy Caulfield from Health Law Institute, University of Alberta, Canada presented coverage on market opportunities associated with translation of stem cell research. He expressed concern over marketing therapies with current state of information, exploitation of desperate patients, the erosion of public trust and issues of safety. Stem cell therapy market has been emerging fast on the basis of legitimate hope, substantial media coverage, lack of appropriate regulatory board and tall therapeutic claims. As per review by Select Biosciences Industry Tracking 2007 (www.selectbiosciences.com), the pharmaceutical and biotechnology community is in wait-and-watch mode with stem cell based therapy and majority of research is conducted in academic/university research communities.

Induction of pluripotency to produce embryonic-like stem cells is the hot field in stem cell research. The fact is that iPS cells have been produced in at least six different laboratories within a few months after the initial animal studies shows that the technique is robust and easily reproducible. At this point, it seems pretty certain that the iPS technique will soon replace ES cells as the preferred means of generating human stem cell lines. However, this study is still in infancy of basic science, the practical aspect of a therapy using autologous iPS is not yet clear. The safety and efficacy of these cells need to be worked out before testing in human Clinical trials.

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