Final Ethics of Therapeutic Use of Induced Human Pluripotent Stem Cells 1
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Towards the end of 2006 Dr. Shinya Yamanaka and Dr Kazutoshi Takahashi found a method to convert differentiated adult mouse cells into pluripotent stem cells. 3 In the following year they reported more findings: “Human iPS cells were similar to human embryonic stem (ES) cells in morphology, proliferation, surface antigens, gene expression, epigenetic status of pluripotent cell-specific genes, and telomerase activity.” 4

This scientific breakthrough showed that it was possible to reprogram somatic cells back to the pluripotency stage by modifying a few key transcription factors. 5 These reprogrammed cells are known as induced pluripotent stem cells (iPSCs) and they “exhibit the morphology of embryonic stem cells and resemble them in many ways, including maintaining their developmental potential to differentiate into derivatives of all three primary germ layers. Up to then, the only available sources for stem cell therapy were bone marrow and umbilical cord derived stem cells.” 6

Scientists want to find and study the genes which act as master regulators of chromosomes’ genes by turning them on and off in skin cells or other tissues to modify cells’ behaviour. They worked in their laboratory to discover which genes could reprogram adult cells into stem cells and how human genes could produce pluripotent stem cells without using human embryos. 7

IPSCs potential for therapies and research

What is scientifically and ethically significant is that this new procedure by-passes the use of eggs and the creation of embryos. If trials with human cells verify that this method gives rise to pluripotent stem cells, an ethical way could be available for medical research and therapies without the need of human eggs, the creation and destruction of embryos and of cloning by somatic cell nuclear transfer. This was exciting news for scientists and ethicists alike and others morally opposed to the use of human embryos as a source for ES cells for research. However, more research is needed to be make the use of induced pluripotent stem cells safe for clinical use.

The renowned scholars Dr. Holm Zaehres and Dr. Hans R. Schöler recognised the importance of Yamanaka’s work: “This is a significant turning point in nuclear reprogramming research with

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1 A shorter version of this paper was read at the 1st. Biotechnology World Congress, 14 February 2012.
2 Lecturer, Bioethics and Healthcare Ethics, Catholic Theological College within the MCD University of Divinity.
5 The scientific code for these factors are as follows; Oct3/4, Sox2, c-Mye, and Klf4.
broad implications for generating patient-specific pluripotent stem cells for research and therapeutic applications. Reprogramming of mouse and human somatic cells into induced pluripotent stem cells has been possible with retroviral expression of the pluripotency-associated transcription factors Oct4, Sox2, Nanog, and Lin28 as well as Klf4 and c-Myc. It holds great potential as a model for diseases from the perspective of the individual patient and as an alternative source of pluripotent stem cells for therapeutic applications. They discuss how the use of retroviruses as well as other expression vectors, protein transduction, and small molecules can effectively and efficiently induce pluripotent stem cells from a variety of mouse and human starting somatic cell populations.

Gojo and his colleagues compared induced pluripotent stem cells, directly reprogrammed cardiomyocytes, (heart muscles) and somatic stem cells as a cell source for future cell-based therapy. They also supported the application of iPSCs in artificial organs. They believe that tissue engineering in regenerative medicine would give rise to a new era of medical treatment for organ failure.

Dyson and Barker maintained that cell transplantation has improved to the point of becoming a potential therapy for Parkinson’s disease. They think iPSCs are a likely suitable long-term source of transplantable dopaminergic neurons.

Wallia and his associates pointed out that supporters of iPS therapy need to show to their critics that iPSCs can be proven to be safe for clinical practice. They cover in detail the pluripotency factors responsible for iPSC generation as well as the signalling pathways and epigenetic modifications ...involved in the reprogramming process. Mention is also made of problems that hinder iPSC research whose purpose is to bring iPSC therapy and other potential applications closer to success in practice.

Fujiwara reported that the appearance of beating colonies of cardiac cells from human iPSCs was increased approximately 4.3 times by the addition of cyclosporine-A [CSA] at the mesoderm stage about 13 days after fertilisation. The results of his work and that of others provided a technological basis to obtain functional cardiomyocytes from iPSCs.

Scholars’ views on future prospects of induced pluripotent stem cells

Vladislav Volarevic notes that “Disease specific … iPSCs are now available and are used to study pathogenesis of inherited and other disorders…. In addition patient-specific iPSCs generated from humans with specific diseases maintain some of the programming

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9 S Gojo, M Toyoda and A-Zumczaw, “Tissue engineering and cell-based therapy toward integrated strategy with artificial organs”. Journal of Artificial Organs, 10 June 2011 [Epub ahead of print]
characteristic of that disease. This implies that patient-specific iPSCs or iPSCs obtained from a wide variety of people encompass the broad spectrum of metabolic abilities, drug susceptibilities, resistance or susceptibility to disease and are very useful for the testing of new biological agents or drugs in order to find the most effective therapeutic agent for the treatment of iPSC-derived-patient’s disease\textsuperscript{13} it is better than testing patients to get the facts.

He makes the point that some laboratories have obtained iPSCs from patients suffering from Huntington’s and Parkinson’s diseases and managed to collect their cell abnormalities in a plastic dish and thereby provide them as they are found in patients. When these cultured cells are obtained from patients with familial dysautonomia and LEOPARD syndrome\textsuperscript{14} and “were exposed to experimental drugs for these diseases, the ‘symptoms’ were partially alleviated in culture.. This principle may result in the development of new drugs and should be applied to many other diseases for which currently there are not any efficient therapies”\textsuperscript{15}

Innovative technologies of reprogramming and derivation of iPSCs derived from patient’s own somatic cells address the above mentioned concerns. Patient derived iPSCs eliminate the potential for immune rejection and represent an ethically acceptable alternative to the use of human embryos for ESCs derivation. “An important advantage of iPSCs compared to that of adult stem cells (ASCs) is the possibility of repairing disease-causing mutations by homologous\textsuperscript{16} recombination. … Promising experiments in mice suggest that the treatment of genetic disorders sickle cell anaemia and haemophilia A with iPSCs is feasible. … In principle, this approach could be applied to any disease in humans for which the underlying mutation is known and that can be treated by cell transplantation”\textsuperscript{17}.

Notwithstanding these successes with animals, induced pluripotent stem cells are not yet ready to use for human transplants. Most iPSCs have been generated by using vectors which may not get silenced efficiently or could damage an organ’s own genes and thereby render unsafe the use of human iPSCs in cell therapies. Furthermore, iPSCs-derived haematopoietic progenitor cells have been shown to age prematurely thereby leading to the formation of tumours. As Volarevic put it: “An increased propensity of iPSC-derived neural cells to form tumours after transplantation into the brains of immune-compromised mice has been noted.”\textsuperscript{18} Hence it is imperative to improve “transgene-free approaches for derivation of new patient-specific iPSC lines.”\textsuperscript{19}

\textsuperscript{13}Human stem cell research and regenerative medicine – present and future, British Medical Bulletin, Vladislav Volarevic, 2011,1-14; advance Access, June 13.p. 9-10. Practically all of the remainder of this article is either slightly modified or directly taken from this article.

\textsuperscript{14} Dysautonomia: a hereditary condition marked by defective lacrimation skin blotching, emotional instability and motor incoordination; LEOPARD syndrome: a complex disease including skin, cardiac abnormalities, etc.

\textsuperscript{15} Vladislav Volarevic, British Medical Bulletin, 10.

\textsuperscript{16} Homologous means corresponding in structure, position, origin etc.

\textsuperscript{17} Vladislav Volarevic, British Medical Bulletin, 10-11.

\textsuperscript{18} Vladislav Volarevic, British Medical Bulletin, 11.

\textsuperscript{19} Vladislav Volarevic, British Medical Bulletin, 11.
Research is required into the different kinds of original cells and methods of induction to find out the best way of safely generating iPSCs. For a start, as Volarevic says: "Researchers need to focus on [the] safety of iPSCs therapy in the light of the potential for cancer formation. Therefore, ... the use of use of synthetic mRNA to reprogramme human fibroblasts to pluripotency [is a new approach] for generating safe iPSCs."\textsuperscript{20} By using synthetic mRNA "the innate antiviral immune response" is eliminated.\textsuperscript{21} Hence," iPSCs have dramatically emerged as potential novel approaches to understand and treat devastating and otherwise incurable diseases."\textsuperscript{22}

Volarevic concludes: "Relatively little is known about induced pluripotent stem cells' molecular and functional equivalence to the achieved scientific and safe standing of human embryonic stem cells, which would affect their potential therapeutic utility. Addressing this question will require a careful analysis of the genomic and epigenomic integrity of human iPSCs. Further studies are necessary to develop optimized growth and differentiation protocols and reliable safety assays to evaluate the potential of stem cells and their derived specialized cells for the broader application in regenerative medicine and drug development."\textsuperscript{23} In other words, years of research are still required before it is safe to use induced pluripotent stem cells in clinical practice.

Sydney scholars Ronald K Fung, Ian H Kerridge have raised some timely ethical issues that arise from the use of human induced pluripotent stem cells. The first human trials of this novel therapy for diseases raise ethical concerns related to informed consent, patient recruitment, harm minimization and the unavoidable uncertainty and risks involved in human treatments for the first time. These concerns are genuine and merit discussion. For example, it has been learnt that induced pluripotent stem cells produced from adult fibroblast cells resemble embryonic stem cells in various ways with respect to a range of biological markers as well as the expression of certain stem cell genes and proteins. However differences between embryonic stem cells and induced pluripotent stem cells have been found.\textsuperscript{24} In particular induced pluripotent stem cells do not have the moral status of embryonic stem cells because induced pluripotent stem cells alone are incapable of giving rise to full-grown organisms.\textsuperscript{25}

Fung and Kerridge are quite explicit in their paper that they are principally concerned with issues that specifically pertain to "the point where iPS cell replacement therapy is tested on humans for the first time. While there has been extensive discourse on the ethics of human research, we will explore how these principles apply in the context of human trials of iPSC cell

\textsuperscript{20} Vladislav Volarevic, British Medical Bulletin, 11.
\textsuperscript{21} Vladislav Volarevic, British Medical Bulletin, 11.
\textsuperscript{22} Vladislav Volarevic, British Medical Bulletin, 11.
\textsuperscript{23} Vladislav Volarevic, British Medical Bulletin, 11-12. hereditary factors as well as the stable and reprogrammable nuclear changes that control gene expression for good health and maintain the integrity of human iPSCs.
\textsuperscript{24} Fung RK, Kerridge IH, "Uncertain translation, uncertain benefit and uncertain risk: ethical challenges facing first-in-human trials of induced pluripotent stem (ips) cells." Bioethics, 2011 Jul 4, p.2. 1467-85. [epub ahead of print]
\textsuperscript{25} Fung RK, Kerridge IH, "Uncertain translation, uncertain benefit..." p.2.
replacement therapy. We focus on one particular case study — Parkinson’s disease — as an exemplar for the broader ethical, epistemological and ontological challenges that arise when iPS cell therapy is translated from bench to bedside.”

Fung and Kerridge continue with further important reflections on risk assessment: “First-in-human trials of iPS cell replacement therapy will inevitably raise a number of ethical and epistemological concerns. How should potential risks and benefits be assessed and weighed up against each other? When is it appropriate to move from animal testing to human testing? What are the appropriate procedures for obtaining informed consent? (And so forth.) Although these challenges arise whenever genuinely new medical advances are translated from bench to bedside, they become particularly cogent in the case of iPS cell replacement therapy due to the unique risks which are involved, the relative unreliability of available animal models, the vulnerability of the target patient group, and the intense public scrutiny that surrounds stem cell research.”

They go on to say that employment of animal components for the culture of stem cell lines for transplantation to humans should be avoided in order to prevent animals’ infectious diseases being passed on to humans, e.g. antigens, viruses or animal pathogens transmissible to humans:

“This is particularly relevant as iPS cell lines are generally maintained on mouse feeder cells. However, it has recently been demonstrated that it may be possible to use autologous human fibroblasts as feeder cells to support the self-renewal of iPS cell lines, and this would avoid the risks associated with the use of animal feeders.”

I agree with them that it is important to determine

“the genetic stability of iPS cell lines before they are transferred to patients, given that cells grown in culture, particularly for long periods of time, may acquire deleterious genetic and epigenetic abnormalities that could predispose them to cause serious pathologies such as tumours. Again, scientific understanding in this area is still primitive and the development of reliable assays of genomic stability will prove to be crucial in moving forward with first-in-human trials of iPS cell therapy.”

For the time being the need to lessen risks to humans of “first-in-human studies of iPS cell therapy, appears to demand extensive use of animals in research.” Fung and Kerridge rightly highlight that one of the main principles outlined by the World Medical Association’s

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26 Fung RK, Kerridge IH, “Uncertain translation, uncertain benefit…” p.3.
28 Fung RK, Kerridge IH, See p.5.
29 Fung RK, Kerridge IH, “Uncertain translation…”, Bioethics, 2011 Jul. 4, p. 5. 1467-85. [epub ahead of print]
Declaration of Helsinki is that clinical trials should not expose research subjects to risks that outweigh the foreseeable benefits.\textsuperscript{31}

Informed consent and subject recruitment

Fung and Kerridge wrote: “The heightened degree of uncertainty and risk associated with first-in-human trials underscores the importance of obtaining genuinely informed consent.” \textsuperscript{32} They point out that “it may be necessary to seek consent by proxy from surrogate decision makers in cases where the patient lacks the capacity to make an informed decision. However, this task is much more complex in the research setting than it is in the clinical setting.”\textsuperscript{33}

“Given that early-phase clinical research generally offers no or little direct benefit to the patient, and cell-based interventions including iPSC cell therapy likely pose more than a minimal level of risk, such measures would effectively preclude the recruitment of patients with Parkinson’s disease who lack competence in first-in-human trials, even where such patients may have explicitly expressed a desire to participate while they still possessed full capacity.”\textsuperscript{34}

They go on to add: “Difficult ethical issues pertaining to study inclusion and subject recruitment also arise when vulnerable patients who lack decision-making capacity are included in first-in-human trials. In the case of iPSC cell therapy research, it may be scientifically preferable to enroll comparatively ‘healthy’ patients suffering from a mild form of Parkinson’s disease, as they would be the ones most likely to experience a therapeutic benefit from the cell transplant. The challenge, therefore, lies in designing clinical trials which are not only ethically sound, but also scientifically rigorous. This is particularly important in iPSC cell research if it is to avoid the negative tide of publicity that gene therapy and human embryonic stem cell research have been met with in recent years. Indeed it is arguable that iPSC cell research will need to proceed in a way that is demonstrably above reproach, such that there are as few opportunities as possible for even misguided criticism.”\textsuperscript{35}

Despite their constructive criticisms and suggestions, Fung and Kerridge are quite supportive of the proper use of induced pluripotent stem cell therapies in their concluding statement: “We do not believe that these challenges should necessarily prevent progress in iPSC research. Indeed, given that iPSC cell replacement has the potential to restore a sense of independence and dignity to Parkinson’s disease patients by equipping them with an effective, long-term treatment, there is a strong moral imperative to support the continuation of this research. We also suggest that the ethical and scientific challenges confronting iPSC cell technology should serve as an argument in favour of continuing research on all types of stem cells, and reject the argument that iPSC cells eliminate the need for embryonic stem cell

\textsuperscript{31} Fung and Kerridge, “Uncertain translation...” Bioethics, 2011 Jul 4, pp. 3-4.
\textsuperscript{34} Fung RK, Kerridge IH, “Uncertain translation...” Bioethics, 2011 Jul 4, p. 7
research. While iPS cells may circumvent some of the ethical issues regarding the moral status of the embryo, it is apparent that many scientific, ethical and regulatory hurdles remain and iPS cell replacement therapy is still a long way from the clinic.\textsuperscript{36}

Dr Antonio Liras has added to the therapeutic benefits that can be expected from the use of iPS therapies, viz. the treatment of haemophilia. Endothelial\textsuperscript{37} progenitor cells derived from iPSCs cells were found to "engraft within the hepatic parenchyma"\textsuperscript{38}, and functionally integrate to provide the therapeutic benefit for a phenotypic correction in haemophilia"\textsuperscript{39}. This shows that iPSC technology combined with cellular therapy is potentially capable of providing treatment for haemophilia. Granted there are no relevant results for phenotypic correction in haemophilia, it is concluded iPSC technology could represent a potential alternative based on cellular therapy.

Durnaoglu notes that many human neurological diseases are not currently curable and result in devastating neurologic sequelae. He is aware that although there remains a great deal to learn about patient-specific iPSC safety, reprogramming mechanisms, better ways to direct a specific reprogramming, the ideal cell source for cellular grafts, and the mechanisms by which transplanted stem cells lead to an enhanced functional recovery and structural reorganization, the discovery of the therapeutic potential of iPSCs offers new opportunities for the treatment of incurable neurologic diseases. However, iPSC-based therapeutic strategies need to be thoroughly evaluated in preclinical animal models of neurological diseases before they can be applied in a clinical setting.\textsuperscript{40}

In Iran, when Dr Maryam Vosough was dismayed by the great number of patients desperately awaiting for liver transplants, her eyes turned to taking advantage of cell therapy which could save patients who are in life-threatening situations, and thereby enabling them to have a chance of survival. Since she worked in the Chemistry and Chemical Engineering Research Center of Iran, she knew of the opportunities presented by the use of induced pluripotent stem cells for opening the door to possibilities of treatment and cures for diseases without running any risks of immune rejection. She and her colleagues were aware of the possibilities of patient-specific cell therapies after the production of induced pluripotent stem cells provided an opportunity that was not to be missed for Iranian patients.\textsuperscript{41} Tests with animals are fine, but they fail to satisfy the clinical needs of patients when it comes to Alzheimer's disease.

\textsuperscript{37} The endothelium is the single layer of cells that lines the heart, blood vessels and lymphatic vessels.
\textsuperscript{38} Parenchyma refers to the essential functioning of an organ as distinct from its structure.
Israel and Goldstein understood that a crucial limitation to our understanding of Alzheimer's disease is the inability to test hypotheses on live, patient-specific neurons. Patient autopsies are limited in supply and only reveal endpoints of disease. Rodent models harboring familial AD mutations lack important pathologies, and animal models have not been useful in modeling the sporadic form of AD because of complex genetics. They knew that the recent development of induced pluripotent stem cells (iPSCs) provide a method to create live, patient-specific models of disease and to investigate disease phenotypes in vitro. Israel and Goldstein discuss the genetics of AD patients and the potential for induced pluripotent stem cells to capture the genomes of these individuals and generate relevant cell types. Specifically, they examined recent insights into the genetic fidelity of induced pluripotent stem cells, advances in the area of neuronal differentiation, and the ability of induced pluripotent stem cells to model neurodegenerative diseases. They also recognized that a major problem for the understanding of AD is to run tests on live, patient-specific neurons. Tests on corpses only provide information about the diseases at the end of patients' lives. Animal models are also not suitable. Fortunately, induced pluripotent stem cells can do better: living patient-specific models of Alzheimer's disease are available in vitro, thereby enabling the genetics of AD patients to be learnt in addition to the potential for induced pluripotent stem cells to generate relevant cell types. They state: "it is possible to examine recent insights into the genetic fidelity of iPSCs, advances in the area of neuronal differentiation, and the ability of iPSCs to model neurodegenerative diseases."

The discoveries of by induced pluripotent stem cells by Yoshinori Yoshida, and Shinya Yamanaka  has opened up new avenues to generate patient- and disease-specific pluripotent stem cells. Human iPSC cells may be useful for understanding the mechanisms of diseases and for drug screening. Moreover, the iPSC cell technology may play a major role in regenerative therapy in the future. However, they stress the important point that iPSC cell technology has several issues that remain to be overcome, including the present low efficiency of iPSC cell generation without genetic alterations, the possibility of tumor formation in vivo, and unregulated growth of the remaining cells that are partially reprogrammed and refractory to differentiation. These issues must be solved before iPSC technology can be successfully used in clinical applications."

Lasala and Minguell have reported: that peripheral vascular disease is the leading cause of limb ischemia (inadequate blood flow) which is manifested by limping, ischemic rest pain, ulcers or gangrene. It is the result of peripheral arterial disease due to atherosclerosis — a disease of arteries in which fatty plaques develop on the inner walls and block blood flow. Lately some centres around the world have begun clinical trials using stem cells as a

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43 Yoshinori Yoshida, MD, PhD; Shinya Yamanaka, MD, PhD, Recent Stem Cell Advances: Induced Pluripotent Stem Cells for Disease Modeling and Stem Cell-Based Regeneration Circulation. Journal of the American Heart Association, 2010, 122:80-87.
treatment for limb ischemia’s pains, ulcers and gangrene. There is general agreement that stem cells, including iPSCs, are effective for treating the symptoms of limb ischemia.  

Peng and Zeng note that Alzheimer's disease, Parkinson's disease, Huntington's disease and Friedreich's ataxia are the most common human neurodegenerative diseases pathologically characterized by a progressive and specific loss of certain neuronal cell populations. The exact mechanisms of neuronal cell death in these diseases are unclear, although some forms of the diseases are inherited and genes causing these diseases have been identified. At present effective clinical therapies for many of these diseases are not available. However, induced pluripotent stem cells (iPSCs) in culture may very well provide a powerful tool for in vitro neurodegenerative disease modelling as well as an unlimited source for cell replacement therapy. In their review they summarise recent progress on iPSC generation and differentiation into neuronal cell types. They realize that there is scope for using iPSCs and that it is worth studying their potential application for in vitro disease mechanism study and in vivo cell replacement therapy.

German researchers also have found that induced pluripotent stem cells (iPSCs) can be generated from different somatic cell types through the expression of a set of transcription factors in an abnormal place. iPSCs are amenable for the correction of gene mutations by recombinations that correspond in structure, position and origin. Induced pluripotent stem cells acquire all the features of embryonic stem cells including pluripotency and can thus give rise to any cell type of the body. Patient-derived iPSCs may be an ideal source for studying diseases in vitro and treating different disorders in the clinic.

The discovery of methods to convert somatic cells into induced pluripotent stem cells (iPSCs) through expression of a small combination of transcription factors has raised the possibility of producing custom-tailored cells for the study and treatment of numerous diseases. Indeed, iPSCs have already been derived from patients suffering from a large variety of disorders. Among other issues, Hochedlingle and Harnessing review recent progress that has been made in establishing iPSC-based disease models and highlight possible solutions to overcome barriers. Scientists working in this area believe that a better understanding of the molecular basis of pluripotency, cellular reprogramming and lineage-specific differentiation of iPSCs is necessary for progress in regenerative medicine.

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Neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease and Amyotrophic Lateral Sclerosis, are characterized by a not fully understood neuron loss in different regions of the central nervous system, which contributes to the relevant dysfunctions in patients. The application of cell replacement therapy using human embryonic stem cells, though having attracted much attention, has been hampered by intrinsic ethical problems. It has been demonstrated that adult somatic cells can be reprogrammed into the embryonic state, called induced pluripotent stem cells. It was soon realized that induced pluripotent stem cells may be an alternative source for cell replacement therapy, because they raise no ethical problems and using patient-specific induced pluripotent stem cells for autologous transplantation will not lead to immunological rejection. What's more, certain types of neurons derived from patient-specific induced pluripotent stem cells may display disease-relevant phenotypes. Thus, patient-specific induced pluripotent stem cells can provide a unique opportunity to directly investigate the pathological properties of relevant neural cells in individual patients, and to study the vulnerability of neural cells to pathogenic factors in vitro, which may help reveal the pathogenesis of many neurodegenerative diseases. In this review, recent developments in cellular treatment of neurodegenerative diseases using induced pluripotent stem cells is summarised, and the potential value of induced pluripotent stem cells in the modelling of neurodegenerative disease is discussed.\footnote{Chen C, Xiao SF. Induced pluripotent stem cells and neurodegenerative diseases, Neuroscience Bulletin 2011 Apr;27(2):107-14.}

Some patients suffer from ataxia which causes shaky movements and unsteady gait that result from the brain’s failure to regulate the body’s posture and the strength and direction of limb movements. One variety of this is known as Friedrich’s ataxia which is an inherited disorder appearing first in adolescence. Jun Liu and his team have generated induced pluripotent stem (iPS) cell lines derived from skin fibroblasts of two Friedrich ataxia patients. These iPS cell lines, following correction of the mutated gene, could provide a useful source of immune-compatible cells for transplantation therapy.\footnote{Jun Liu, Paul, Verma, Mirella Dotti and Alice Pebay, Robert Williamson, Generation of induced pluripotent stem cell lines from Friedrich ataxia patients. Stem Cells Reviews, 2011 Sep;7(3):703-13.}

Induction of pluripotency by transcription factors has become a commonplace method to produce pluripotent stem cells. Great strides have been made in our understanding of the mechanism by which this occurs—particularly in terms of transcriptional and chromatin-based events—yet only a small part of the complete picture has been revealed. Understanding the mechanism of reprogramming to pluripotency will have important implications for improving the efficiency and quality of reprogramming and advancing therapeutic application of induced pluripotent stem cells. It will also help to reveal the machinery that stabilizes cell identity and to instruct the design of directed differentiation or lineage switching strategies.
To inform the next phase in understanding reprogramming, Liu, Verma, Dottorandi, Pebbey and Williamson review the latest findings, highlight debates and outline future challenges.  

Martin Pera says that iPSCs have far-reaching potential for use in research and in regenerative medicine. “But the ultimate value of these cells as disease models or as sources for transplantation therapy will depend on the fidelity of their reprogramming to the pluripotent state, and on their maintenance of a normal genetic and epigenetic (involving aspects other than DNA sequence) status.” He states that five recent surveys - including three in this issue of Nature - “show that the reprogramming process and subsequent culture of iPSCs in vitro can induce genetic and epigenetic abnormalities in these cells. The studies raise concerns over the implications of such aberrations for future applications of iPSCs.”

Power and Rasko examine how cell reprogramming is likely to transform regenerative and reproductive medicine and highlight some of the medical, moral, and political hurdles that it faces. It also argues that induced pluripotent stem cells are more ethically problematic than most people believe and that cell reprogramming will not solve the stem cell controversy but complicate it further.

A Critique; Demetrio Neri

Demetrio Neri admits that the general public as well as politicians take for granted that induced pluripotent stem cells can be safely and ethically used for research, and hopefully, for therapeutic purposes. These hopes rest on the grounds of their conviction that induced pluripotent stem cells are not embryos but they do resemble human embryonic pluripotent stem cells derived from destroyed embryos as much as iPSCs are also pluripotent.

In his article Demetrio’s thesis is “that focusing the discussion only on the sources of stem cells has prevented a complete appreciation of what is at stake. To substantiate my thesis, I take into consideration two issues: the first has to do with the potential of the cells obtained through some of the new approaches (iPS included), the second (and decisive) with the argument of the ‘indirect complicity’.”

Neri goes on to raise the question whether induced pluripotent stem cells could be de-differentiated back to the totipotent state – in which case, Neri holds, they could be deemed to be embryos. As Neri says: “What matters is the potential to give rise to an individual,


whenever you find this potential or think you have a faint possibility of finding it.”

He goes on to draw support from John Harris who noted:

“If hESCs can do everything a totipotent cell or an embryo can, then those who accord full moral status to the embryo should treat hESCs, as well ICM cells (which have the same potential), as moral equals to the embryo and thus as if they share whatever moral status the embryo has.”

Demetrio’s comment is: “The same applies to iPS and any other embryonic-like stem cells.”

Neri, however, seems unaware that this could only occur if some positive action were taken to achieve this substantial change -- it is not a matter of the natural spontaneous generation of a human individual arising from a cluster of human iPSCs. Both a human sperm and a human egg are two distinct entities: the human sperm is a just a sperm that has no intrinsic ontological value. Indeed millions of sperm are lost in urine throughout the world on a daily basis without any regrets or moral problems. The same may be said of each human oocyte (egg): it is not an embryo. Neither a human sperm nor a human oocyte is an embryo. But once a sperm and human oocyte fuse to become a new cell, the fertilised human egg, a new human life is formed which is endowed with inviolable value. The sperm and oocyte lose their own separate ontological identities, if all goes well, and become a human embryo the zygote. The same biological process takes place following acts of adultery: the sex acts are unethical, but any embryo formed in this way is endowed with the intrinsic and inviolable value of a human being. Children born out of marriage are entitled to all the human rights of other children.

Neri argues that it would also be unethical for scientists to use human embryos or hips cells which he practically equates with human embryos on account of their assumed potentially to form embryos. Neri also thinks it would be unethical to make use of knowledge gained from endangering or destroying such potentially human iPS cells.: “A politician who favors or supports a law to permit destructive human embryo experiments or hips cells would be involved in material cooperation in their destruction: Neri takes the argument further: “If voting could involve a form of complicity, why not the use of ‘contaminated’ knowledge?”

This could occur by teaching how to do unethical experiments or worse promoting them.

We should not forget that many unethical experiments, some lethal, were conducted on prisoners in concentration camps in the Nazi era in Germany, Poland and France. Jews were


not regarded as human beings and d were treated accordingly. However, some experiments were conducted or authorized by distinguished scientists, in some cases with international reputations. At least two of the experiments, on hypothermia and explosive decompression, yielded useful medical information that is now part of the scientific canon. And in a number of instances the sponsoring entity was the Luftwaffe, the Nazi German airforce, which was interested in improving the battlefield performance of its surgeons.

Some drugs or medications, e.g. vaccines that were unethically obtained by means of destructive research on human beings or embryos many ago may be ethically used today, especially in life saving situations. Catholic teaching is not narrow in this regard where real needs exist and great therapeutic benefits may be obtained:

"Of course, within this general picture there exist differing degrees of responsibility. Grave reasons may be morally proportionate to justify the use of such "biological material". Thus, for example, danger to the health of children could permit parents to use a vaccine which was developed using cell lines of illicit origin, while keeping in mind that everyone has the duty to make known their disagreement and to ask that their healthcare system make other types of vaccines available. Moreover, in organizations where cell lines of illicit origin are being utilized, the responsibility of those who make the decision to use them is not the same as that of those who have no voice in such a decision."

The scientific truths about iPS cells and their inherent properties discovered by Yamanaka and Takahashi by perfectly ethical methods are plain truths deserving of universal respect. Indeed, they have been hailed as such by all, except Neri.

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60 Congregation for the doctrine of the Faith, Dignitatis Personae, N. 35.