

This is an Accepted Manuscript of an article published in [Bioethics], available online at <http://onlinelibrary.wiley.com/doi/10.1111/j.1467-8519.2011.01896.x/abstract> (paywalled).

Self-archived in the [Sydney eScholarship Repository](#) by the Centre for Values, Ethics and the Law in Medicine (VELiM), University of Sydney, Australia

Please cite as:

Fung R, Kerridge I. Uncertain Translation, Uncertain Benefit and Uncertain Risk: Ethical Challenges Facing First-in-Human Trials of Induced Pluripotent Stem (iPS) Cells. *Bioethics*. 2013, 27(2): 89–96.

Uncertain Translation, Uncertain Benefit and Uncertain Risk: Ethical Challenges Facing First-In-Human Trials Of Induced Pluripotent Stem (Ips) Cells

Fung R, Kerridge I. (2013)

ABSTRACT

The discovery of induced pluripotent stem (iPS) cells in 2006 was heralded as a major breakthrough in stem cell research. Since then, progress in iPS cell technology has paved the way towards clinical application, particularly cell replacement therapy, which has refueled debate on the ethics of stem cell research. However, much of the discourse has focused on questions of moral status and potentiality, overlooking the ethical issues which are introduced by the clinical testing of iPS cell replacement therapy. First-in-human trials, in particular, raise a number of ethical concerns including informed consent, subject recruitment and harm minimisation as well as the inherent uncertainty and risks which are involved in testing medical procedures on humans for the first time. These issues, while a feature of any human research, become more complex in the case of iPS cell therapy, given the seriousness of the potential risks, the unreliability of available animal models, the vulnerability of the target patient group, and the high stakes of such an intensely public area of science. Our paper will present a detailed case study of iPS cell replacement therapy for Parkinson's disease to highlight these broader ethical and epistemological concerns. If we accept that iPS cell technology is fraught with challenges which go far beyond merely refuting the potentiality of the stem cell line, we conclude that iPS cell research should not replace, but proceed alongside embryonic and adult somatic stem cell research to promote cross-fertilisation of knowledge and better clinical outcomes.

1. INTRODUCTION

The past few decades have witnessed major advances in stem cell research. Adult somatic stem cells were first discovered in the 1950s with the identification of haematopoietic stem cells in the bone marrow that are capable of differentiating into all the types of blood cells in the body.¹ Subsequently, scientists reported that adult somatic stem cells exist in many other tissues, including the brain, the heart, blood vessels and skeletal muscle.² While adult somatic stem cells have successively been used in transplantation procedures to treat diseases like leukemia, they have a limited capacity for self-renewal and for the most part are lineage-restricted, only being able to differentiate into cell types associated with the organ of origin.³

These drawbacks led many scientists to shift their attention towards embryonic stem cells when it was discovered in 1999 that stem cells could be derived from human embryos left over from IVF technology, or from somatic cell nuclear transfer.⁴ This appeared to be a major breakthrough, as embryonic stem cells were pluripotent and, unlike adult somatic stem cells, could differentiate into all the types of cells in the human body. The finding that human embryonic stem cells were 'plastic' and had the capacity to differentiate into cells of specific lineages that could repair diseased or damaged tissue opened up the possibility of 'regenerative medicine'. For example, embryonic stem cells could be differentiated into midbrain dopaminergic neurons to treat Parkinson's disease or insulin-producing beta-cells to treat diabetes. However, while embryonic stem cell research has promised much, it has faced a series of scientific, practical, legal and moral barriers. For example, the creation of an embryonic stem cell line requires the destruction of the embryo, which has provoked strong moral objections based on firmly held positions regarding moral status and human dignity.⁵ Further barriers have included the legal restrictions placed on access to embryos left over from IVF technology in many countries, the technical difficulties of achieving adequate efficiency in somatic cell nuclear transfer⁶ and the scarcity of donor oocytes.⁷

In light of this, the discovery of iPS cells in 2006 – an alternative source of pluripotent stem cells possessing apparently the same differentiation capacity as human embryonic stem cells without the moral problems associated with the latter – created great excitement within the scientific community. The production of iPS cells involves transfecting adult somatic cells such as fibroblasts with certain stem-cell-associated genes by viral vectors.⁸ The resultant iPS cells have been shown to resemble embryonic stem cells with respect to a range of biological markers such as cell morphology, doubling time and mitotic activity, telomerase activity and the expression of certain stem cell genes and proteins.⁹ Some differences in iPS and embryonic stem cells, however, have been noted. Recently, Chin and colleagues showed that iPS cells and embryonic stem cells have a slightly different gene expression profile,¹⁰ while another study found that iPS cells may have limited differentiation capacity in the haemangioblast lineage and undergo premature aging.¹¹

Nevertheless, iPS cells have widely been viewed as a preferred alternative to embryonic stem cells for both scientific and moral reasons. From a scientific standpoint, the virtually unlimited supply of adult somatic cells from which iPS cells are produced provides a significant advantage over relying upon discarded embryos and limited donor oocytes to create embryonic stem cell lines. iPS cells also enable the creation of patient-specific cell lines for autologous transplantation in cell replacement therapy, thereby avoiding the risk of immunorejection.¹² And from a sociomoral perspective, iPS cell technology circumvents the moral objections against embryo destruction which is involved in the production of embryonic stem cell lines.

Since the discovery of iPS cells, much of the ethical debate has revolved around the moral status and potentiality of iPS cells and notions of moral complicity and 'contaminated' knowledge. On the one hand, some have argued that, unlike gamete-fusion or cloned embryos, iPS cells cannot be ascribed moral status because iPS cells alone are unable to give rise to a full-grown organism, and require the provision of a surrogate trophoblast by tetraploid helper cells to do so.¹³ On the other hand, others have argued that if iPS cells are shown to demonstrate totipotency, which is required for the generation of a new human life, they would essentially be human embryos, thus negating any advantage iPS cells may have over embryonic stem cells in terms of the destruction of early human life.¹⁴

While these questions are worthy of consideration, there are other important ethical issues which are raised by the clinical testing of iPS cell therapy and which have received much less attention. Some of these issues have been identified by Zareczny and colleagues, including: preventing the 'misuse' of iPS cells to derive gametes for reproductive purposes; safeguarding the privacy and

informed consent of cell donors; and minimising, in the clinical setting, the safety risks to patients which arise not only from the intrinsic properties of immortal cell lines but also from epigenetic changes acquired during the derivation process.¹⁵ In this paper, however, we are concerned primarily with those issues that pertain specifically 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 iPS cell 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.

2. APPLICATION FOR PARKINSON'S DISEASE

Parkinson's disease is a degenerative disorder caused by a loss of dopaminergic neurons in the brain that impairs motor function, with symptoms including muscle rigidity, tremor, bradykinesia and postural instability. However, non-motor symptoms are also common and include autonomic dysfunction, cognitive and neurobehavioural problems and speech difficulties. Around 30% of Parkinson's disease patients have co-existing dementia.¹⁶

While not life-threatening, Parkinson's disease is a debilitating chronic and progressive condition that is estimated to affect more than 18 million people worldwide.¹⁷ Currently available treatment options include pharmacological agents, such as L-dopa, which restores dopamine levels in the brain, and surgical procedures, such as deep-brain stimulation. All of these, however, are limited in their efficacy and may induce long-term side effects, such as dyskinesias (sudden switches between mobility and immobility) following prolonged administration of L-dopa,¹⁸ as well as brain haemorrhage and transient acute depression following high-frequency deep-brain stimulation.¹⁹

The limitations of existing treatment options for Parkinson's disease have sparked interest in iPS cell replacement therapy, in which dopaminergic neurons derived from iPS cells are transplanted in patients to restore motor function. A series of proof-of-concept studies have been performed on animal models. In 2008, Wernig and colleagues showed that iPS cells could be differentiated into midbrain dopaminergic neurons and that, following implantation into the brains of 6-OHDA-lesioned rats, these cells became integrated and caused recovery of motor function.²⁰ Importantly, however, teratomas (primitive tumours) were also identified in some of the rats' brains as a result of contamination by undifferentiated pluripotent stem cells in the cell graft. In the 2009 study by Muramatsu and colleagues, dopaminergic neurons differentiated from primate embryonic stem cells were transplanted into MPTP-lesioned cynomolous monkeys.²¹ Following transplantation, PET scans showed restored dopamine function in the brain, although there was only modest functional recovery at 12 weeks after implantation.

While these animal studies demonstrate the potential therapeutic application of iPS and embryonic stem cells to reverse the symptoms of Parkinson's disease, they also highlight the potential risks. As yet, there have been no trials of iPS cell transplantation involving human subjects; however, it is likely that first-in-human trials will be conducted within the next few years.

A first-in-human trial refers to a clinical trial in which a medical procedure, previously tested on *in vitro* or animal models, is tested on human subjects for the first time. The design of first-in-human trials may vary, from single, small Phase I studies designed to assess the safety and tolerability of an agent, to placebo-controlled double-arm phase I/II studies designed to assess both safety and efficacy simultaneously.

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.

3. RISK ASSESSMENT

One of the main principles outlined by the World Medical Association's *Declaration of Helsinki* is that clinical trials should not expose research subjects to risks that outweigh the foreseeable benefits.²² However, comparing the risks of first-in-human trials of iPS cell therapy to the potential benefits is particularly challenging as much of the benefit from such studies is to future patients and to the expansion of medical knowledge, and it is extremely unlikely that research participants would obtain any direct personal benefit.²³ Indeed, research participants in first-in-human trials are typically administered sub-threshold doses that are too small to produce a therapeutic effect, since the primary goal is to assess the toxicity of the intervention. The task of making the best interests of the research participant commensurate with the epistemic and clinical benefits to the broader medical field is therefore extraordinarily difficult.

However, it should be noted that, despite the low prospect of direct therapeutic benefit, it is possible that research subjects may obtain other kinds of personal benefit (psychological or otherwise) from participating in first-in-human trials, for example from the knowledge that they are contributing to the expansion of medical knowledge and from the close contact with researchers and clinicians throughout the research study.²⁴ Furthermore, the argument has been put forth according to which, given the severity of Parkinson's disease and the lack of efficacious therapies that are currently available, the threshold of tolerable risk should be raised when assessing whether the risks are balanced against the benefits.²⁵ From this, it is apparent that the risk-benefit analysis may be more complex, and may call for a judgement – from an ethical *and* a medical point of view – of the adequacy of currently available treatment options as well as the extent to which the status quo is unacceptably disabling both for the prospective research participant and for the broader patient community.

On the other hand, it is arguable that the risk-benefit ratio of cell replacement trials is unlikely to be particularly favourable, and that it would be difficult to justify the serious and potentially irreversible risks associated with iPS cell transplantation. In a 2001 study by Freed et al. in which patients with Parkinson's disease received foetal stem cell transplants, 15% of subjects developed dyskinesias more than one year after the surgery.²⁶ Although that particular study involved foetal stem cells, it is unclear whether iPS cell replacement therapy would produce similar long-term complications. In addition, various animal studies have demonstrated that the use of retroviral vectors in the reprogramming of iPS cells carries with it a risk of insertional mutagenesis which can lead to cancerous transformation after implantation in the patient.²⁷ And as in the case of embryonic stem cell-based therapies, contamination of iPS cell grafts with even a small proportion of undifferentiated cells may lead to teratoma formation in the host brain.²⁸ Finally, there is a significant degree of uncertainty associated with cell-based interventions as cell grafts may potentially 'de-differentiate' or migrate to unintended sites after transplantation.²⁹ All of these risks are outlined in the International Society for Stem Cell Research (ISSCR)'s *Guidelines for the Clinical Translation of Stem Cells* and are posited as justification for requiring all the more stringent pre-clinical evidence before first-in-human trials should be allowed to proceed.³⁰

The fact that iPS cell therapy targets the central nervous system when administered to patients with neurological disease adds a further layer of complexity both in epistemic and ontological terms. Because the brain is central to the construction, maintenance and manifestation of identity and of the 'self', there is the possibility that any intervention may affect not only one's physical capacities, but also one's cognition, emotion and personality.

Given the risks associated with iPS cell therapy, considerable effort has gone into identifying means by which these risks may be reduced. One potential strategy for dealing with the development of cancer cells after transplantation is the use of 'suicide' genes to render cell lines susceptible to specific drugs, such as ganciclovir, which could then be administered to the patient to ablate the transplanted cells should malignancy develop.³¹ In previous studies, this strategy has yielded varying results, with mouse embryonic stem cells transduced with the HSV-tk gene being successfully ablated by ganciclovir concentrations that were well tolerated by non-transduced cells, but mesenchymal stem cells and hematopoietic precursors being somewhat less sensitive to ablation.³² While the suicide gene approach appears promising, it remains an experimental technique and its clinical use remains a long way off.

Apart from the suicide gene approach, the *ISSCR Guidelines for the Clinical Translation of Stem Cells* also recommends minimising, insofar as possible, the use of animal components in the culture of stem cell lines for transplantation into humans, to reduce the risk of inter-species transfer of exogenous antigens, unknown viruses or zoonotic pathogens.³³ This is particularly relevant as iPS cell lines are generally maintained on mouse feeder cells.³⁴ 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.³⁵ In addition, the aforementioned *Guidelines* highlights the importance of determining 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.³⁶ 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.

This begs the question: should a block be placed on all first-in-human trials of iPS cell replacement therapy until adequate safeguards, such as the suicide gene approach, have been developed and tested, even if this would significantly delay the translation from bench to bedside? And how does one weigh up the need to ensure the safety of research participants in first-in-human trials against the potential benefits of expedited access to cell replacement therapy for the broader patient community?

4. THE TRANSLATIONAL GAP: MOVING FROM BENCH AND BEAST TO BEDSIDE

What makes risk assessment in first-in-human trials in Parkinson's disease research particularly challenging is the absence of reliable animal models. The two models of Parkinson's disease which are generally used to evaluate novel therapeutic strategies are the 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP)-treated primate and the 6-hydroxydopamine (6-OHDA)-lesioned rat.³⁷ Although these toxin-based models succeed in recreating selective nigrostriatal cell death and show extensive motor dysfunction, the administration of the toxins causes acute, severe dopaminergic depletions, resulting in 'a static disease state that represents a snapshot of the later stage of the disease, but fails to capture its progressive nature or, consequently, the dynamic process of compensation.'³⁸ As such, pre-clinical evidence of safety gleaned from these animal models may not be accurate in predicting safety in humans. Furthermore, data on differentiation and targeting obtained from animal testing may differ for humans due to species-specific parameters such as cell-

cell signalling pathways, hormone and cytokine effects and response to other biochemical signals. For example, a new class of drugs (monoamine uptake inhibitors) that had produced promising results in MPTP-treated nonhuman primate models resulted in only a very limited level of functional improvement and a high incidence of side effects when tested in humans for the first time.³⁹ In this way, inconsistencies between animal models of Parkinson's disease and the human condition make it particularly difficult to accurately predict both the potential risks and the potential efficacy during first-in-human trials.

The point at which one chooses to move from animal testing to human testing is therefore both an ethical question and an epistemological one. According to the *Declaration of Helsinki*, adequate animal experimentation should be conducted prior to launching first-in-human trials in order to collect pre-clinical evidence of safety and efficacy.⁴⁰ Kimmelman has suggested three criteria to assess the strength of pre-clinical evidence in first-in-human trials: internal validity, external validity and correspondence. Internal validity is a measure of the methodological rigour of the pre-clinical animal testing. In practice, this may refer to *a priori* power calculations to ensure an appropriate number of animals per test group, randomisation and blinding of treatment allocation and outcome assessment. External validity refers to the selection of the animal model that most accurately models the human disease and fits the scientific question being asked. The third criterion is correspondence between pre-clinical and clinical studies, where the hypothesis being tested, the protocol and the parameters in the animal model and the first-in-human trial should match.⁴¹

Kimmelman's proposal raises a number of ethical questions when applied to iPS cell replacement therapy. According to his logic, as animal models which most closely recapitulate the human disease are desirable, it is arguable that pre-clinical testing should be carried out on humanised primates in which some of the key signalling molecules are replaced by the corresponding human counterparts, or which have a humanised environment for tumour growth, as a means of validating the tumourigenicity of iPS cell grafts.⁴² But while it may be ideal from a scientific standpoint to perform testing on an animal model which most closely resembles human beings, this may be ethically problematic as it becomes more difficult to draw clear differences between the animal model and the human target population, a problem that LaFollette and Shanks describe as 'causal functional asymmetry'.⁴³ And while researchers are generally supportive of the 3Rs approach to animal research, (reduce, refine and replace),⁴⁴ as the *ISSCR Guidelines on the Clinical Translation of Stem Cells* make clear, 'physiological integration and long-lived tissue reconstitution are the hallmarks of stem cell-based therapeutics', and these properties can only be adequately assessed using animal models, including small animal models, large animal models and, where necessary, non-human primates.⁴⁵ At the current time, therefore, the desire to reduce the risks to human participants of first-in-human studies of iPS cell therapy appears to demand extensive use of animals in research.

5. INFORMED CONSENT AND SUBJECT RECRUITMENT

The heightened degree of uncertainty and risk associated with first-in-human trials underscores the importance of obtaining genuinely informed consent. While consenting to participate in research is never straightforward, several aspects unique to iPS cell therapy and to Parkinson's disease make the process of obtaining informed consent in first-in-human cell therapy trials particularly challenging. Firstly, the competence of Parkinson's patients to give informed consent may be compromised due to their impaired cognitive capacity, vulnerability and dependency. As noted previously, around 30% of patients suffering from Parkinson's disease have co-existing dementia, with the prevalence reaching 80% for late-stage patients.⁴⁶ In addition, 30% of hospitalised patients with Parkinson's disease may suffer from delirium, which is a transient reduction of consciousness resulting from drug-related side effects or co-morbid medical conditions.⁴⁷ As a consequence, some patients with Parkinson's disease may lack the intellectual capacity to meaningfully appreciate the

full implications of iPS cell replacement trials, including the potential risks and benefits of participation, and thus be unable to provide informed consent.

However, while it is well-documented that many patients with Parkinson's disease may temporarily or permanently be incapable of making decisions for themselves, both in the clinical and the research setting, it is often extremely difficult to accurately identify those patients in whom this is the case. In part, this is because capacity may not directly correlate with the clinical or pathological severity of disease, and because the most widely used tests of capacity, including the Mini-Mental State Examination (MMSE),⁴⁸ the Abbreviated Mental Test Score (AMTS)⁴⁹ and the MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR),⁵⁰ all have significant limitations, particularly when used to test patients with global neurological disease. For example, the MMSE has been shown to have limited sensitivity and specificity in patients with mild to moderate Alzheimer's disease.⁵¹ According to another study, even where dementia diagnosis, MMSE scores and scores from the Instrumental Activities of Daily Living (IADL) test were correlated, the consent status of only 64% of the individuals was appropriately judged.⁵²

Given the challenges both in establishing capacity and in obtaining informed consent among such patients, additional mechanisms may be required to recruit research participants in a manner that is ethically appropriate. Possible approaches include using 'consent monitors' to conduct formalised interviews with prospective subjects,⁵³ or written tests to ensure that they have an adequate understanding of the protocol and that their consent is voluntary.⁵⁴ In particular, the *ISSCR Guidelines for the Clinical Translation of Stem Cells* identifies several key aspects that should be addressed when explaining the protocol to research participants – that 'this may be the first time the experimentally-derived cells have been administered to humans, that animal studies may not predict effects of cell therapies in humans, that the aim of the study may simply be to assess safety, that the risks are unknown, and that, historically, some human participants in early drug trials have experienced serious adverse effects, including death.'⁵⁵ In essence, the aim is to minimise any misconceptions that patients may have regarding participation in a first-in-human trial.

Furthermore, it may be necessary to seek consent by proxy from surrogate decision makers (SDMs) 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. When SDMs have to decide whether or not a particular medical treatment should be commenced or withdrawn, they are advised to consider an advance directive (where one exists), to make the decision the patient would have made were they competent, and to carefully consider the best interests of the patient.⁵⁶ In contrast, the main focus of clinical research is not the well-being of the participant – although this is always of fundamental ethical significance – but the production of generalisable knowledge which benefits the wider community. The values underpinning participation in research studies may therefore be rather different to the clinical setting. SDMs entrusted with the decision to 'allow' their loved one to participate in clinical research must weigh up not only the risks and benefits of the research and their loved one's well-being but also the values they held that may be of influence, such as their altruism or wish to contribute to advances in medical knowledge.

As a consequence of concerns regarding the validity of surrogate-decision-making, many jurisdictions permit SDMs only to consent to 'minimal risk research' where the research provides no direct benefit to the patient.⁵⁷ Given that early-phase clinical research generally offers no or little direct benefit to the patient, and cell-based interventions including iPS 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. Although these restrictions are soundly based on protecting vulnerable individuals and limiting the extent to

which a third party can expose another to the risk of harm, they may also unreasonably impinge on the autonomy of the patient.

In view of this, some have advocated the use of Advance Research Directives (ARDs) in which competent individuals may prospectively consent to future or ongoing participation in research should they lose the capacity to give consent.⁵⁸ An ARD could enable consent through documentation of one's values and attitudes to research, one's explicit preferences regarding research participation and/or through nomination of a SDM who may be empowered to make decisions about research participation in much the same way that an Advance Care Directive (ACD) enables expression of autonomy in the clinical setting. Such measures would clearly be applicable to early-stage Parkinson's disease patients in light of the fact that many may develop dementia. And as with ACDs in clinical practice, the value of including nomination of a SDM in an ARD is that they provide a safeguard process by which, if the research experience is judged to be causing distress or inconsistent with the patient's scope of consent, the SDM may validly over-ride the ARD and withdraw participation in the clinical trial.

However, ARDs also raise difficult ethical questions, particularly whether it should be permissible to prospectively consent to the full spectrum of research, including high-risk research.⁵⁹ This is particularly salient for neuroscience research where efforts to target the central nervous system may entail a substantial degree of risk. Indeed it is debatable whether the promise of generalisable knowledge – without any prospect of personal benefit – is sufficient to offset very high risk exposure to a vulnerable participant – even if they express a willingness to participate. It is also debatable whether individuals can ever sufficiently anticipate or fully appreciate what the future experience of research participation as a cognitively impaired person will be like, and thus whether ARDs have any validity as a means for obtaining informed consent in research studies.

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 iPS cell therapy research, it may be scientifically preferable to enrol 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. However, while patients with mild Parkinson's disease are more likely to be able to decide for themselves whether they wish to participate in the clinical trial, it may be ethically difficult to justify subjecting these 'healthier' patients to the substantial and unknown risks of such an early-stage trial, especially when their condition is stable and manageable by other available treatment options, and the balance of risks against benefits is probably unfavourable. Alternatively, while it may be more 'attractive' to recruit late-stage Parkinson's patients who have no other viable treatment options and for whom participation in the trial may provide a last source of hope, these patients may also be more susceptible to therapeutic misconception,⁶⁰ be unable to provide informed consent and be least likely to benefit from the cell therapy, leading to the false negative conclusion that the trial intervention provides no therapeutic benefit.

The challenge, therefore, lies in designing clinical trials which are not only ethically sound, but also scientifically rigorous. This is particularly important in iPS 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 iPS 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.'⁶¹

6. CONCLUSION

It is undeniable that there are many ethical challenges, apart from those relating to questions of moral status and potentiality, which must be overcome before the translation of iPS cell technology from bench to bedside can be realised. These ethical challenges are brought into sharp focus during first-in-human studies of iPS cell therapy for Parkinson's disease, due to the uncertainty and risk associated with cell-based interventions, the unreliability of animal models and the difficulty of recruiting research subjects given the prevalence of cognitive impairment amongst the target patient group.

We do not believe that these challenges should necessarily prevent progress in iPS cell research. Indeed, given that iPS 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 iPS cell technology should serve as an argument in favour of continuing research on *all* types of stem cells, and reject the argument that iPS cells eliminate the need for embryonic stem cell 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 regulatory⁶² hurdles remain and iPS cell replacement therapy is still a long way from the clinic. The bioequivalence of iPS and embryonic stem cells has yet to be conclusively proven, and embryonic stem cells remain the most realistic source of hope for patients with diseases such as spinal cord injury and blindness which cannot be treated with adult stem cells and for which iPS cell therapy has not been sufficiently investigated. Equally, research on adult somatic stem cells should continue as significant progress has been made in recent years, with the identification of certain adult stem cell types that can 'transdifferentiate' or give rise to cell types seen in organs or tissues other than those expected from the cells' predicted lineage.⁶³ Parallel research on iPS, embryonic and adult somatic stem cells will inevitably provide opportunities for the cross-fertilisation of knowledge, thereby expanding our understanding of the molecular basis of human biology and facilitating the development of safer and more effective therapies in the future.

Ronald K.F. Fung is a research scholar at the Centre for Values, Ethics and the Law in Medicine (VELiM) at the University of Sydney.

Ian H. Kerridge is Director and Associate Professor of Bioethics at the Centre for Values, Ethics and the Law in Medicine (VELiM) at the University of Sydney and Staff Haematologist/BMT Physician at Westmead Hospital, Sydney.

Footnotes

1 National Institutes of Health, US Department of Health and Human Services. 2009. *The National Institutes of Health resource for stem cell research: Stem Cell Basics*. Bethesda, MD. Available at: <http://stemcells.nih.gov.ezproxy1.library.usyd.edu.au/info/basics/defaultpage> [Accessed 19 May 2010].

2 Ibid.

3 Ibid.

4 Ibid.

5 Y. Hotta. *Ethical Issues of the Research on Human Embryonic Stem Cells*. *J Int Bioethique* 2008; 19: 77–85.

6 K.H. Campbell et al. *Sheep Cloned by Nuclear Transfer from a Cultured Cell Line*. *Nature* 1996; 380: 64–66.

7 G. Pennings et al. *ESHRE Task Force on Ethics and Law 12: Oocyte Donation for Non-reproductive Purposes*. *Hum Reprod* 2007; 22: 1210–1213.

8 K. Takahashi et al. *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*. *Cell* 2007; 131: 861–872.

9 J. Yu & J.A. Thomson. *Pluripotent Stem Cell Lines*. *Genes Dev* 2008; 22: 1987–1997.

10 M.H. Chin et al. *Induced Pluripotent Stem Cells and Embryonic Stem Cells are Distinguished by Gene Expression Signatures*. *Cell Stem Cell* 2009; 5: 111–123.

11 Q. Feng et al. *Hemangioblast Derivatives from Human Induced Pluripotent Stem Cells Exhibit Limited Expansion and Early Senescence*. *Stem Cells* 2010; 28: 704–712.

12 E. Kiskinis & K. Eggan. *Progress Toward the Clinical Application of Patient-specific Pluripotent Stem Cells*. *J Clin Invest* 2010; 120: 51–59.

13 M.L. Condit, P. Lee & R.P. George. *Ontological and Ethical Implications of Direct Nuclear Reprogramming: Response to Magill and Neaves*. *Kennedy Inst Ethics J* 2009; 19: 33–40.

14 F. Baylis. 2008. *ES Cells and iPS Cells: A Distinction with a Difference*. Garrison, NY: The Hastings Center. Available at: <http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=730> [Accessed 7 Sep 2010].

15 A. Zarzeczny et al. *iPS Cells: Mapping the Policy Issues*. *Cell* 2009; 139: 1032–1037.

16 N. Caballol, M.J. Martí & E. Tolosa. *Cognitive Dysfunction and Dementia in Parkinson Disease*. *Mov Disord* 2007; 22: S358–S366.

17 A. Samii, J.G. Nutt & B.R. Ransom. *Parkinson's Disease*. *Lancet* 2004; 363: 1783–1793.

18 Ibid.

19 B.P. Bejjani et al. *Transient Acute Depression Induced by High-frequency Deep-brain Stimulation*. *N Engl J Med* 1999; 340: 1476–1480.

20 M. Wernig et al. *Neurons Derived from Reprogrammed Fibroblasts Functionally Integrate into the Fetal Brain and Improve Symptoms of Rats with Parkinson's Disease*. *Proc Natl Acad Sci U S A*. 2008; 105: 5856–5861.

21 S. Muramatsu et al. *Multitracer Assessment of Dopamine Function after Transplantation of Embryonic Stem Cell-derived Neural Stem Cells in a Primate Model of Parkinson's Disease*. *Synapse* 2009; 63: 541–548.

- 22 World Medical Association (WMA). 2008. *Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects*. Ferney-Voltaire, France: WMA. Available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>[Accessed 16 May 2010].
- 23 International Society for Stem Cell Research (ISSCR). 2008. *Guidelines for the Clinical Translation of Stem Cells*. Deerfield, IL: ISSCR. Available at: http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf[Accessed 20 Oct 2010].
- 24 R. Dresser. *First-in-Human Trial Participants: Not a Vulnerable Population, but Vulnerable Nonetheless*. *J Law Med Ethics* 2009; 37: 38–50.
- 25 International Society for Stem Cell Research, *op. cit.* note 23.
- 26 C.R. Freed et al. *Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease*. *N Engl J Med* 2001; 344: 710–719.
- 27 K. Okita, T. Ichisaka & S. Yamanaka. *Generation of Germline-Competent Induced Pluripotent Stem Cells*. *Nature* 2007; 448: 313–317.
- 28 L. Dawson et al. *Safety Issues in Cell-based Intervention Trials*. *Fertil Steril* 2003; 80: 1077–1085.
- 29 *Ibid.*
- 30 International Society for Stem Cell Research, *op. cit.* note 23.
- 31 L. Barzon et al. *Transcriptionally Targeted Retroviral Vector for Combined Suicide and Immunomodulating Gene Therapy of Thyroid Cancer*. *J Clin Endocrinol Metab* 2002; 87: 5304–5311; International Society for Stem Cell Research, *op. cit.* note 23.
- 32 M.U. Fared & F.L. Moolten. *Suicide Gene Transduction Sensitizes Murine Embryonic and Human Mesenchymal Stem Cells to Ablation on Demand – a Fail-safe Protection against Cellular Misbehavior*. *Gene Ther* 2002; 9: 955–962.
- 33 International Society for Stem Cell Research, *op. cit.* note 23.
- 34 M. Chen et al. *Role of MEF Feeder Cells in Direct Reprogramming of Mousetail-tip Fibroblasts*. *Cell Biol Int* 2009; 33: 1268–1273.
- 35 K. Takahashi et al. *Human Induced Pluripotent Stem Cells on Autologous Feeders*. *PLoS One* 2009; 4: e8067.
- 36 International Society for Stem Cell Research, *op. cit.* note 23.
- 37 E. Lane & S. Dunnett. *Animal Models of Parkinson's Disease and L-dopa Induced Dyskinesia: How Close Are We to the Clinic?* *Psychopharmacology (Berl)* 2008; 199: 303–312.
- 38 *Ibid.*: 306.
- 39 E.J. Frackiewicz et al. *Brasofensine Treatment for Parkinson's Disease in Combination with Levodopa/carbidopa*. *Ann Pharmacother* 2002; 36: 225–230.

40 World Medical Association, *op. cit.* note 22.

41 J. Kimmelman. 2010. *Gene transfer and the ethics of first-in-human research: lost in translation*. Cambridge, UK: Cambridge University Press.

42 L.D. Shultz, F. Ishikawa & D.L. Greiner. *Humanized Mice in Translational Biomedical Research*. *Nat Rev Immunol* 2007; 7: 118–130.

43 H. LaFollette & N. Shanks. *The Origin of Speciesism*. *Philosophy* 1996; 71: 41–61; J. Rachels. 1990. *Created from Animals*. Oxford: Oxford University Press: 220. According to the theory of ‘causal functional asymmetry’, the logical dilemma arises where the assertion that humans and non-human animals share significant biological mechanisms, such that experiments on the latter can shed light on the former, seems to be at odds with the claim that they are, at the same time, substantially different as far as moral capacity is concerned. As Rachels succinctly puts it, ‘If the animal subjects are not sufficiently like us to produce a model, then the experiments may be pointless . . . but if the animals are enough like us to provide a model, it may be impossible to justify treating them in ways we would not treat humans.’

44 Editorial. Reduce, refine, replace. *Nature Immunol* 2010; 11: 971.

45 International Society for Stem Cell Research, *op. cit.* note 23, pp. 8–9.

46 Caballol et al., *op. cit.* note 16.

47 S.K. Inouye & L. Ferrucci. *Elucidating the Pathophysiology of Delirium and the Interrelationship of Delirium and Dementia*. *J Gerontol A Biol Sci Med Sci* 2006; 61: 1277–1280.

48 M.F. Folstein, S.E. Folstein & P.R. McHugh. *Mini-mental state. A Practical Method for Grading the Cognitive State of Patients for the Clinician*. *J Psychiatr Res* 1975; 12: 189–198.

49 B. Cullen et al. *A Review of Screening Tests for Cognitive Impairment*. *J Neurol Neurosurg Psychiatry* 2007; 78: 790–799.

50 P.S. Appelbaum et al. *Competence of Depressed Patients for Consent to Research*. *Am J Psychiatry* 1999; 156: 1380–1384.

51 S.Y. Kim & E.D. Caine. *Utility and Limits of the Mini Mental State Examination in Evaluating Consent Capacity in Alzheimer's disease*. *Psychiatr Serv* 2002; 53: 1322–1324.

52 B.S. Black et al. *Predictors of Providing Informed Consent or Assent for Research Participation in Assisted Living Residents*. *Am J Geriatr Psychiatry* 2008; 16: 83–91.

53 D.J. Mathews et al. *Cell-based Interventions for Neurologic Conditions: Ethical Challenges for Early Human Trials*. *Neurology* 2008; 71: 288–293.

54 International Society for Stem Cell Research, *op. cit.* note 23.

55 International Society for Stem Cell Research, *op. cit.* note 23, p. 13.

56 L.C. Kaldjian et al. *Dementia, Goals of Care, and Personhood: a Study of Surrogate Decision Makers' Beliefs and Values*. *Am J Hosp Palliat Care* 2010; 27: 387–397.

57 Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. 1998. *Tri-council policy statement: Ethical conduct for research involving humans*. Ottawa, ON. Available at: <http://pre.ethics.gc.ca/eng/policy-politique/tcps-eptc>[Accessed 10 Oct 2010].

58 R. Pierce. *A Changing Landscape for Advance Directives in Dementia Research*. *Soc Sci Med* 2010; 70: 623–630.

59 Ibid.

60 For a more detailed analysis of the phenomenon of therapeutic misconception which is widely observed in clinical research, see: N.M. King et al. *Consent Forms and the Therapeutic Misconception: the Example of Gene Transfer Research*. *IRB* 2005; 27: 1–8.

61 Mathews et al., *op. cit.* note 53, p. 291.

62 T. Caulfield et al. *Stem Cell Research Policy and iPS Cells*. *Nat Methods* 2010; 7: 28–33.

63 National Institutes of Health, US Department of Health and Human Services, *op. cit.* note 1.