

iPS Cells: Mapping the Policy Issues

Amy Zarzeczny¹, Christopher Scott², Insoo Hyun³, Jami Bennett⁴, Jennifer Chandler⁵,
Sophie Chargé⁶, Heather Heine⁷, Rosario Isasi⁸, Kazuto Kato⁹, Robin Lovell-Badge¹⁰,
Kelly McNagny¹¹, Duanqing Pei¹², Janet Rossant¹³, Azim Surani¹⁴, Patrick L.
Taylor¹⁵, Ubaka Ogbogu¹⁶, Timothy Caulfield¹⁷

Corresponding Author: Timothy Caulfield, tcaulfld@law.ualberta.ca

Given the explosion of research on induced pluripotent stem (iPS) cells, it is timely to consider the various ethical, legal, and social issues engaged by this fast-moving field. Here, we review issues associated with the procurement, basic research, and clinical translation of iPS cells.

Since the 2007 announcement that adult human skin cells can be reprogrammed to act like human embryonic stem cells (hESCs) (Takahashi et al., 2007), stem cell research has experienced renewed attention and enthusiasm from scientists, the public, patient groups, and policy makers. These new cells, called induced pluripotent stem (iPS) cells have been hailed as an ethical victory (Aalto-Setälä et al., 2009 K. Aalto-Setälä, B. Conklin and B. Lo, PLoS Biol. 7 (2009), p. e1000042.Aalto-Setälä et al., 2009) because they represent a way of producing valuable hESC-like pluripotent stem cells without involving the destruction of human embryos. The development of iPS cells has also opened up stem cell research, in part due to the fact that the technology is more accessible, less expensive, and less resource constrained (i.e., does not require the use of embryos or scarce human oocytes) than that required for hESC research.

¹ Health Law Institute, University of Alberta, Edmonton, Alberta T6G 2H5, Canada

² Center for Biomedical Ethics, Stanford University, Stanford, California, 94305-5208; United States

³ Department of Bioethics, School of Medicine, Case Western Reserve University, Cleveland, Ohio, 44106-4976; United States

⁴ The Biomedical Research Centre, University of British Columbia, Vancouver, British Columbia V6T 1Z3; Canada

⁵ Faculty of Law, University of Ottawa, Ottawa, Ontario, K1N 6N5; Canada

⁶ Stem Cell Network, Ottawa, Ontario, K1H 8L6; Canada

⁷ University of British Columbia, Vancouver, British Columbia, V6T 1Z3; Canada

⁸ Centre of Genomics and Policy, McGill University, Montréal, Québec, H3A 1A4; Canada

⁹ Institute for Research in Humanities, Graduate School of Biostudies, Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8501, Japan

¹⁰ National Institute for Medical Research, London, NW7 1AA; United Kingdom

¹¹ The Biomedical Research Centre, University of British Columbia, Vancouver, British Columbia, V6T 1Z3; Canada

¹² Guang-zhou Institute of Biomedicine and Health, Guangzhou, Guangdong, 510663; China

¹³ Hospital for Sick Children, Toronto, Ontario, M5G 2L3; Canada

¹⁴ Gurdon Institute, University of Cambridge, Cambridge, CB2 1QN; United Kingdom

¹⁵ Harvard Medical School, Harvard Stem Cell Institute, Children's Hospital Boston, Cambridge, Massachusetts; 02138

¹⁶ Faculty of Law, University of Toronto, Toronto, Ontario, M5S 2C5; Canada

¹⁷ Faculty of Law and School of Public Health, Health Law Institute, University of Alberta, Edmonton, Alberta, T6G 2H5; Canada

The rapid advances in iPS cell research and the significant expectations placed upon this field make it both timely and imperative to consider the ethical, legal, and social issues (ELSI) associated with it and their impact on the iPS cell policy landscape. This was the goal of an international workshop held in association with the 2009 annual meeting of the International Society for Stem Cell Research (<http://www.isscr.org>), which brought together an international team of stem cell scientists, bioethicists, and ELSI scholars. In this article, which emerged from the workshop, we consider various ethical, legal, social, and policy issues associated with aspects of iPS cell procurement and basic research including privacy, consent, intellectual property, and potential uses. Next, we address features of clinical translation including safety, regulation, and oversight. Finally, we conclude by reflecting on the theme of exceptionalism and the overarching context of commercial pressure. Our intent is not to provide a comprehensive analysis of these complex issues or a list of recommendations but rather to highlight key areas that require both further reflection and research.

Privacy

One of the most significant issues associated with iPS cell procurement and research relates to the privacy interests of cell donors. As is true in other areas of human tissue research, iPS cell lines result from a living individual and, as such, carry that individual's DNA "fingerprint," which contains an immeasurable amount of information about the donor including genetic predisposition to disease. Inappropriate disclosure of this information could violate that individual's privacy and result in social, economic, or other risks (Sugarman, 2008). Related concerns regarding genetic privacy have been addressed in considerable depth in the context of genetics research (Lowrance and Collins, 2007 W. Lowrance and F. Collins, *Science* 317 (2007), pp. 600–602. Full Text via CrossRef | View Record in Scopus | Cited By in Scopus (24)Lowrance and Collins, 2007). The Genetic Information Nondiscrimination Act of 2008 in the US is an example of a legislative response to some of these concerns (<http://www.gpo.gov/fdsys/pkg/PLAW-110publ233/html/PLAW-110publ233.htm>). Even if the original cells used to derive iPS cells were isolated from a donor who is no longer alive (and stored as a clinical sample or in a cord blood stem cell bank, for example), the iPS cell DNA still contains information about close relatives of the donor and thereby engages their privacy interests.

One way for researchers to address these concerns is to de-identify or anonymize the data at the time of donation. However, there are various problems with this approach. First, there are clinical, research, and policy reasons why anonymization (that is, de-linkage from identifiable information) may not be an ideal approach. For instance, future clinical applications (e.g., transplantation) may necessitate obtaining follow-up information about the donor's health status. Second, with the advent of large-scale genome-wide association studies, technology now exists to detect a specific individual's single nucleotide polymorphism, even when de-identified and in a pooled data set (http://grants.nih.gov/grants/gwas/background_fact_sheet_20080828.pdf). Accordingly, it is important for iPS cell researchers to remain vigilant in their efforts to protect the privacy interests of their subjects by taking concrete steps such as structuring their

research so as to limit traceable cross-references to public databases and by using state of the art security measures.

In addition, iPS cell research carries the possibility of incidental findings. The concern is that, perhaps in the course of deriving a cell line, or developing a disease model, researchers will unintentionally discover that the donor suffers from some kind of condition or predisposition to disease, raising the question of what they should do with that information. The question of how to deal with incidental findings is a significant research ethics issue that impacts many areas of biomedical research and is beyond the scope of this article. Nonetheless, researchers need to be aware of this possibility and to prepare for it, especially when obtaining informed consent.

Consent, and Withdrawal of Consent

Consent is crucial whenever humans are asked to participate in research, whether as research subjects or as donors of research materials, including cells and tissue. There are numerous consent challenges that, while not unique to iPS cell research, should be considered. One of the most pressing is the nature of the consent that is required of a cell donor. According to most research ethics frameworks, research participants must provide voluntary and informed consent to participate in research protocols. This approach ensures that any assumption of risk by research participants is completely voluntary and respectful of their autonomy. This standard requires that participants be informed about the specific details of the proposed research.

The potential for iPS cell lines to be used indefinitely for future research that is not yet contemplated may make it challenging to obtain truly informed consent by traditional standards. Similar claims have been made in the comparable context of biobanking, where this issue has emerged as a contentious topic. Some commentators have argued in favor of a shift toward a broad or blanket consent model where participants consent to a wide range of generally defined research activities including, possibly, unforeseen future uses (Hansson et al., 2006). However, others stress the importance of maintaining rigorous consent standards, which requires enumerating specific research uses (Mascalzoni et al., 2008).

Will the consent debates associated with iPS cell research get caught up in this broader debate? The answer may be yes, as exemplified by pluripotent germline cultures derived from human testicular tissue that are unavailable for further study because of restrictions in the donors' consent forms (<http://www.nature.com/nature/journal/v460/n7258/full/460933a.html>). Such dilemmas seem likely to push the consent issues associated with iPS cell research to the foreground. The possibility of deriving gametes in vitro from iPS cells makes this issue even more acute (Kee et al., 2009). Indeed, a specialized approach to consent for iPS cell research has been suggested, where the form notifies donors about some common uses and includes a request to recontact donors if unanticipated uses emerge (Aalto-Setälä et al., 2009). The potential for uses of cell lines that some donors might find objectionable (e.g., producing human-animal chimeras, derivation of human gametes and fertilization

research, use for basic research versus transplantation, etc.) arguably also needs to be recognized and reflected in the consent process (Aalto-Setala et al., 2009).

There are, of course, many other relevant consent issues, including the question of whether and to what degree surrogate consent is sufficient for participants without capacity (e.g., can parents consent to the participation of children in iPS cell research) and under what circumstances is it acceptable to use currently stored samples for iPS cell research without consent (<http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf>; see also the UK's Human Fertilisation and Embryology Act 2008, ch. 22, Schedule 3).

In addition, traditional research ethics standards require that individuals be able to withdraw from research and terminate their participation at any time. This right to withdraw holds a central place in international research ethics frameworks (<http://www.wma.net/en/30publications/10policies/b3/index.html>; <http://conventions.coe.int/treaty/en/Treaties/Html/164.htm>). However, with hESC research, exceptions to this rule are the norm. Some guidelines suggest that donors can withdraw their consent only until the creation of an anonymized cell line (<http://www.cihr-irsc.gc.ca/e/34460.html>), and others until an embryo (or blastocyst) is used in cell line derivation (<http://www.stemcellnetwork.ca/>) or for any research project (<http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf>, para. 11.2). However, in other forms of tissue research, the right to withdraw consent endures, even allowing donors to request the destruction of their sample (<http://www.ukbiobank.ac.uk/docs/Informationleaflet130608.pdf>).

Once an iPS cell line has been created, can a donor withdraw his or her consent to participate in research and, in so doing, prohibit further research on that cell line? If the answer is yes, the implications for researchers could be immense. In some circumstances, depending on how the cell line has been used and in which jurisdictions, “it may be impossible for donors to meaningfully withdraw consent for use” (Sugarman, 2008).

Nonetheless, there are also factors that suggest a right of withdrawal should endure. It may become increasingly necessary—particularly as the research moves toward clinical use—to recontact cell donors and keep links between the cell line and the donor's ongoing health status (Aalto-Setala et al., 2009 K. Aalto-Setala, B. Conklin and B. Lo, *PLoS Biol.* 7 (2009), p. e1000042. Aalto-Setala et al., 2009). It has been argued that “if linkage and recontact is required, the right to withdraw consent, at some level, should endure” (Caulfield et al., 2007). Balancing the diverse interests associated with iPS cell research, including those of the donors and the potential social benefits of the research, will be truly challenging. Clear policy positions should be adopted and followed consistently so as to avoid unnecessary impediments to the research, while ensuring protection of individual rights.

Reach-through Rights

Related to consent withdrawal is the broader issue of the philosophical and legal underpinnings of a donor's continuing interest in controlling the scientific and commercial uses of lines generated from his or her cells, and in the nature and results of the research conducted on them. In other words, what is the extent of a donor's legal interest, if any, in resulting cell lines? Should donors have the right to receive financial benefit from commercial profits resulting from lines derived from their cells? Are they able to exert any control over the future uses of such lines? If they are able to “reach through” and exercise such rights, what is the basis of that power?

Legal rationales are one of the most often cited sources of reach-through rights, and yet their application is far from straightforward. For instance, the question of whether donors retain a property interest in their bodily tissues or genetic matter after providing it for research purposes has been touched on by a number of American courts (e.g., *Greenberg et al. v. Miami Childrens Hospital Research Institute* 264 F. Supp. 2d 1064, SD. Fla. 2003; *Washington University v. Catalona*, 437 F. Supp. 2d 985, E.D. Mo. 2006, http://www.circare.org/lex/03cv01065_opinion.pdf; *Moore v. The Regents of the University of California* 51 Cal. 3d. 120, 793 P.2d. 479, 271 Cal. Rptr. 146, CA. 1990). In each of these cases, the Court rejected the claims of research participants to property rights on the biological materials that they contributed to research. The Court in *Washington University v. Catalona* noted the existence of strong public policy arguments against allowing research participants to retain control over biological samples they provide. Nevertheless, confusion and uncertainty remain regarding the state of the law in this area as no definitive jurisprudence has emerged. And, of course, international variation in legislation, jurisprudence, and philosophical approaches add even more complexity to the use of property rights in this context.

Autonomy and dignity are also commonly used to support donor's reach-through rights. Indeed, there are numerous cases where courts have reinforced an autonomy-derived right of control over tissue and health information (for Canadian examples, see *R. v. Dyment*, 1988, 2 S.C.R. 417, 429: “such information remains in the fundamental sense one's own, for the individual to communicate or retain as he or she sees fit,” and *McInerney v. McDonald*, 1992, 2 S.C.R. 138). Similarly, in research ethics policy frameworks, autonomy is usually the dominant theme. Will this approach withstand careful scrutiny in the realm of iPS cell research where the donor's original cells are significantly manipulated, transformed, and expanded in different ways by researchers? Though the resultant iPS cell line is genetically identical to the donor, the cells are arguably transformed into a new and distinct product that bears little resemblance to the cells originally taken from the donor. Does this methodological reality limit the donor's right of control? Alternatively, the resultant cell lines contain the donor's genetic information and the potential for future linkage to personal information. In addition, giving donors more lasting control may encourage donation. To what extent do these factors mean that the donor should maintain a reach-through right of control?

Intellectual Property Challenges

Efficient application of intellectual property rights can present a major challenge to innovation and is expected to play a significant role in the progress of iPS cell research. It has been speculated that hESC patent activity has (or may) impede research and development in this area (Loring and Campbell, 2006). On the other hand, there are also strong arguments in favor of patents and their role in innovation. Undoubtedly, more research is needed to determine whether the concerns about patents are justified and to assess the actual impact of patents on research and development (Caulfield et al., 2008).

In the US, controversies about overbroad claims (which cover the cells and the methods to grow them), aggressive licensing schemes, and patent challenges have been hallmarks of James Thomson's foundational hESC patents. These patents have been confirmed and remain in force until 2015, but the challenges resulted in a clarification of the claims and a change in licensing policy. Conversely, the European Patent Office recently denied a similar claim on moral grounds following the European Union's Directive on the legal protection of biotechnological inventions, adopted in 1998 ([http://documents.epo.org/projects/babylon/eponet.nsf/0/428862B3DA9649A9C125750E002E8E94/\\$FILE/G0002_06_en.pdf](http://documents.epo.org/projects/babylon/eponet.nsf/0/428862B3DA9649A9C125750E002E8E94/$FILE/G0002_06_en.pdf)). A clause in the Directive has been interpreted to preclude patents on inventions that required the destruction of human embryos on the grounds that they are contrary to *ordre public*, or “public order.” It is instructive to observe the patent landscape in the hESC field as the path of iPS cell patenting is likely to be influenced by these precedents.

Potentially, iPS cell technology may face barriers from patent activity, largely because of the many approaches used to create iPS cells and the limited knowledge of whether and how these cells differ from each other and from hESCs. On first analysis, the patent applications by Shinya Yamanaka (who discovered iPS cells and was granted a patent in Japan) and other inventors (including Bayer's Kazuhiro Sakurada and the University of Wisconsin's James Thomson) appear extraordinarily broad, encompassing all human pluripotent stem cells and their derivatives. It is possible that patents for hESC derivation methods may encompass iPS cell derivation processes, although the US Patent and Trademark Office refused to consider an initial attempt to include iPS cells under Thomson's original composition claim. As is true for all patent applications, in the context of iPS cell-related claims patent examiners will need to determine whether the discoveries are new, not obvious to someone skilled in the art, and useful.

Other questions remain. Is each variation of a reprogramming technique a newly patentable process, an unpatentable obvious next step, or an activity lacking inventiveness? If the process is patentable, is the resulting iPS cell a different and patentable product or has the inventor merely developed a new way to make an already protected iPS cell? If a patented technique is applied to a new cell type, can the new cell type be patented independently from the original? Different iPS cell lines show different gene expression patterns and traits, are more or less amenable to differentiation, or are more or less efficiently reprogrammed. Determining whether any, some, or all of these traits satisfy the requirements for patenting is crucial to determining which iPS cell lines and derivation techniques are entitled to patent protection (Vrtovec and Scott, 2008).

The patent landscape is important not only for efficient research progress but also for the commercialization and clinical translation of the technology. Patenting can impede development of innovative technologies when multiple patents held by different inventors are necessary to move the technology from basic research to useful clinical products or processes. Because of the uncertainty of a patent's reach, it can be cost prohibitive to identify those patents that are relevant to the work necessary to create the medical advances being pursued. The primary concern is that if patents proliferate in a research area, they will develop into a thicket too complicated and expensive to negotiate in order to efficiently exploit the technology for human benefit (Bergman and Graff, 2007). More research is necessary to probe the degree to which these concerns are supported by relevant evidence.

The Ethical Use of iPS Cell Technology

Despite the fact that iPS cell research was initially hailed as a technology that would help resolve some of the most controversial ethical dilemmas associated with hESC work, various ethical challenges that were first raised with early stem cell research remain, including concerns about the creation of embryos for research and about cloning. Further, these are joined by other emerging issues, such as the derivation of gametes. Although many of these issues were first engaged by hESC research, the relevant ease with which iPS cell samples can be obtained (versus embryos), the fact that they can potentially be taken without knowledge or consent, and the general accessibility of this technology (compared to hESC research) mean that issues of use warrant particular consideration.

A crucial part of iPS cell research, which is necessary to move the field toward clinical uses, is the development of animal models to test the function and safety of iPS cell therapies. However, some animal models raise ethical and policy issues that must be considered. At the most extreme end, tetraploid complementation may allow human cloning. By introducing iPS cells into tetraploid blastocysts, one can create an entire animal whose genetic makeup is identical to the somatic cell donor including the mitochondria, in contrast to somatic cell nuclear transfer (SCNT) methods. However, some evidence suggests that hESCs and iPS cells may correspond more closely to mouse epiblast-derived stem cells. These cells are obtained from early post-implantation embryos rather than from blastocysts and, while still pluripotent as judged by *in vitro* differentiation and teratoma formation, are unable to contribute to chimeras after reintroduction into pre-implantation embryos. It is possible that human iPS cells will similarly be unable to make new embryos. The UK's governing legislation would permit at least a limited test of this theory, but any resulting human embryos could not be kept after the appearance of the primitive streak or beyond 14 days *in vitro* and could not be implanted. Questions remain regarding whether iPS cells are really equivalent to hESCs, and more research on both types of stem cells is required.

Arguably one of the most unique and ethically fraught potential uses of iPS cell technology is the derivation of gametes. Researchers have already claimed to have successfully derived sperm from mouse cells (Nayernia et al., 2006; see also Kee et al., 2009). Although the derivation of gametes using iPS cells may be an important research

tool, the possibility that they may be used for reproductive purposes raises ethical concerns including, but not limited to, consent issues, safety, concerns about cloning, the potential to surreptitiously have a child by an unwilling donor, and the potential right of a child to know his or her parents. These issues, among others, are starting to receive international attention (http://www.hinxtongroup.org/Consensus_HG08_FINAL.pdf). Despite these concerns, iPS cell technology may improve assisted reproduction practices and assist in advancing our scientific understanding of basic development and fertility.

Pluripotent stem-cell derived gametes are challenging from a regulatory perspective. In vitro-derived gametes, whether from hESCs or iPS cells, will have to be tested in the laboratory at some point for functionality. This testing will require the creation and destruction of embryos, which of course remains a highly contentious topic. Although some jurisdictions, including the UK and Singapore, permit the creation of human embryos for research purposes, other jurisdictions prohibit the practice. Many jurisdictions only permit in vitro development of a human embryo for up to 14 days (Australia, Canada, Estonia, Finland, France, Hungary, Iceland, India, Israel, Japan, Slovenia, Singapore, South Africa, Spain, Sweden, Switzerland, UK) (Isasi and Knoppers, 2006 R. Isasi and B. Knoppers, *Eur. J. Health Law* 13 (2006), pp. 9–26. Isasi and Knoppers, 2006). This regulatory patchwork may prevent the study of the development of gametes derived from iPS cells. If this research is deemed to be important and desirable, regulators will have to address the current limitations imposed in different jurisdictions and assess whether they meet the needs and expectations of their publics.

Clinical Translation

A major hope associated with iPS cell technology is that it will facilitate personalized cell therapies for treating human disease. However, the issues associated with prospective clinical use of these cells are complex. The following discussion is not intended to be comprehensive but merely to raise key issues that need to be considered. Transplantation of iPS cells, or their derivatives, into humans during clinical application of the technology raises at least two significant safety concerns. The first centers on the in vivo properties of immortal cell types, and the second on the fact that potential therapies may include genetically manipulated cell types. Given this, the regulatory hurdles are likely to be high. The relative novelty of this technology may also require new methods of quality assessment and evaluation, especially as iPS cell production is scaled up to meet the therapeutic quantities needed.

Defining cell types is likely to prove challenging and regulators will need to consider a variety of questions. These include defining the characteristics of an iPS cell and addressing differences in cell type, derivation process, and differentiation potential. How will genetic alterations be defined and characterized? Variations in iPS cell processing and manufacture may make it challenging to assess the safety and potency of iPS cell products for clinical use. For example, the genomic stability of iPS cells during culture is not yet well established, and assays of the genetic and epigenetic status of iPS cells are still in flux. It is imperative that regulators and scientists work together to develop uniform reference standards for acceptable changes in iPS cells during culture to ensure

the quality and safety of iPS cell products and to facilitate comparisons across many different cell lines.

One important question is whether iPS cells will be governed by the same regulations that apply to other cell-based products, or whether they will be treated as exceptional, thus warranting a unique regulatory pathway. Given the particular characteristics of iPS cells (and of their derivation processes), traditional cell-based product review is likely to be relatively complicated and lengthy. Conversely, if iPS cells are deemed to be exceptional and distinct, new rules and procedures could be developed to govern their use. For example, a new stem cell research oversight committee with specialist skills could facilitate smoother and faster clinical translation. However, such a view of exceptionalism could also trigger a level of increased scrutiny. Many jurisdictions have yet to address this issue, leaving iPS cells unregulated or in limbo.

Another important issue is whether every new iPS cell line will need to be considered as an individual product for evaluation or whether a process approval approach will suffice. Given that the cells are heavily manipulated in culture, that each cell type has its own in vitro and in vivo homeostatic behavior, and that the same lines behave differently in different hands, it seems unlikely that standard approval processes for stem cells will be applied. However, the cost implications associated with individual cell line approvals would likely be prohibitive for general clinical use, and almost certainly for personalized treatments. One solution might be to allow approval based on methods (as in surgical procedures) rather than on products. Regulators and developers should be able to use their experience from past cell therapy approvals to inform and speed future iPS cell Investigational New Drug Applications (in the US), and similar processes in other regions.

One practical impediment to the efficient development of shared standards results from commercial pressures. It is instructive to examine the initial approval earlier this year by the US Food and Drug Administration (FDA) of a clinical trial by Geron of hESC-derived oligodendrocyte progenitor cells in spinal cord injury patients, which was subsequently placed on hold pending further data. The basis upon which the company was able to satisfy the FDA regarding safety, efficacy, and manufacturing remains confidential. Accordingly, new applications cannot learn from the Geron precedent. Such regulatory structure challenges are not unique to the FDA and are faced by comparable agencies in many regions. Potential policy solutions to these challenges, such as requiring companies entering or already in Phase 0 or 1 clinical trials to make their key safety data available for researchers and oversight committees, must be considered.

These challenges are amplified by international variations in regulatory regimes. In many countries, the regulatory pathway for the clinical use of iPS cells is very complex, and in others, the scope and nature of this area of regulation is unsettled. As the iPS cell field develops, there may be consortia approaches to biobanking iPS cell lines, where a number of smaller biobanks merge their information to facilitate subsequent inter-jurisdictional sharing of materials. Although potentially beneficial, these activities will

inevitably encounter ethical, regulatory, and institutional discontinuities based on jurisdictional differences in policies and regulation.

Conclusions

The relative ease of access to iPS cell technology presents a new opportunity for researchers to become involved in the stem cell arena. In many cases, these new entrants have not played a role in the past debates surrounding hESC research and they may bring fresh perspectives to otherwise well-trodden discussions. Accordingly, it is an ideal time to engage in thoughtful debate regarding the issues raised by iPS cells, with a view to producing clear and consistent policies in this realm, and perhaps contributing to the broader stem cell research discourse. This ethical examination should also consider other key concerns not addressed here, such as social justice, therapeutic misconceptions regarding prospective treatments, potential harm to vulnerable populations, fair access to useful treatments, and the premature use and implementation of therapies for financial gain. The impact of the increasing pressure to move toward clinical translation and commercialization should also be considered. The mistakes associated with gene therapy, including the push to produce clinical applications and the associated clinical trial debacle (Wilson, 2009), and the type of initial hype and alarm that surrounded the first uses of SCNT, must be avoided. Nonetheless, approaching iPS cell developments in a measured manner does not preclude embracing the profound scientific and therapeutic potential of this exciting area.

Despite the significant commonalities with hESC research, iPS cell technology is distinct in a number of ways and shares elements with other domains of biomedical research such as genetics and gene transfer. The analysis that accompanied these areas can inform issues associated with iPS cell technology. That said, the degree to which iPS cells and the issues they raise are sufficiently unique from other forms of research, thus warranting exceptional treatment, remains an open question. A focused consideration is needed to determine, in a clear and principled manner, where iPS cell technology fits in the broader research policy framework.

The profound promise of iPS cell research cannot be responsibly separated from attendant ethical, legal, and social issues. Given the potential risks involved and the global nature of this fast-moving field, thoughtful consideration of the relevant issues and responsible action on the part of scientists, policy makers, and stakeholders alike is necessary. It will be important to encourage comprehensive education among researchers (especially new entrants to the field of stem cell research) regarding emerging guidelines and principles in order to encourage careful adherence to these policies. These steps are necessary to safeguard public trust and facilitate responsible pursuit of the exciting possibilities associated with iPS cell research.

Acknowledgements

We thank Canada's Stem Cell Network for funding the workshop “iPS Cells: Mapping the Policy Issues” and this resulting paper, the ISSCR for its support of this initiative, and Ken Taymor, Director of the Berkeley Center for Law, Business, and the Economy.

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