Common Ethical Considerations of Human-Induced Pluripotent Stem Cell Research

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Abstract

In 2006, Shinya Yamanaka generated induced pluripotent stem cells (iPSCs), which has been the major scientific event of the decade that caught the eye of many scientists, politicians, and bioethicists. The use of human embryonic stem cells (hESCs) has previously been limited by ethical issues related to the

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destruction of embryos. However, with iPSCs, scientists can now reprogram virtually any human somatic cells through the expression of a combination of embryonic transcription factors to a pluripotent embryonic stem-cell-like state, thereby avoiding the contentious destruction of human embryos. Although the clinical realities of human-induced pluripotent stem cells (hiPSCs) appear very promising, they are still laden with some ethical concerns that scientists and legal authorities in the field of iPSC research must recognize. This chapter briefly reviews some ethical issues associated with the use of hiPSCs and suggests ways to address these challenges.

Keywords

Ethics · Human-induced pluripotent stem cells · Human embryonic stem cells · Moral issue · Patenting · Reproduction · Informed consent

Abbreviations

CNV	Copy number variations
ESCs	Embryonic stem cells
FACS	Fluorescence-activated cell sorting
hESCs	Human embryonic stem cells
HFEA	Human Fertilization and Embryology Authorities
hiPSCs	Human-induced pluripotent stem cells
iPSCs	Induced pluripotent stem cells
IVF	In vitro fertilization
MACS	Magnetic-activated cell sorting
SCNT	Somatic cell nuclear transfer
SNV	Single nucleotide variation

Introduction

For decades, ethical debates regarding stem cell technology have focused mainly on human embryonic stem cells (hESCs). These cells are harvested from the inner cell mass of blastocysts (preimplantation embryos) and obtained with consent from couples receiving in vitro fertilization (IVF) treatment, from aborted fetuses, or from donated oocytes (Thomson et al. 1998; Smith 2001; Zhang et al. 2006). The embryonic origin of hESCs raises a mix of serious moral and ethical controversies about the onset of human personhood, treatment, and harm to embryos; concerns about the safety and health risks of women donating eggs, the potential exploitation of their ova, and their informed consent; and concerns about respect for human life, human dignity, and justice toward humankind. These ethical debates reveal deeply rooted individually diverging opinions about the nature and origin of human personhood, leading to differing policies and regulations of hESC research worldwide (De Trizio and Brennan 2004; Solo and Pressberg 2007; Dhar and Hsi-En Ho 2009). Furthermore, due to this diversity of opinions and cultural differences, an

international consensus regarding the regulation of hESC research does not exist (Dhar and Hsi-En Ho 2009). The resulting restrictions and prohibitions on hESC research have contributed largely to the slowness in the progress on the translation of hESC technology into clinical therapy. Hence, there was an urgent need for another substitute for hESCs with the same pluripotency potential that can bypass these ethical issues.

Shinya Yamanaka's 2006 discovery of induced pluripotent stem cells (iPSCs) was a notable breakthrough in stem cell research, which has given it a new impetus (Takahashi and Yamanaka 2006; Takahashi et al. 2007; Omole and Fakoya 2018). Scientists and bioethicists were excited at the ability to fabricate a surrogate cell with a pluripotent embryonic stem cell (ESC)-like state by the genetic reprogramming of somatic cells through the ectopic expression of a specific combination of transcription factors (Ibrahim et al. 2016). Enchanted by the extraordinary initial work of Takahashi and Yamanaka, many research groups followed their transcription factor-based reprogramming approach and reproduced the results in mice using cells from diverse tissue sources (Yu et al. 2007; Wernig et al. 2007; Maherali et al. 2007; Ahmed et al. 2011a; Buccini et al. 2012) and humans (Lowry et al. 2008; Park et al. 2008). The reprogramming technique provided an unparalleled and distinctive opportunity to researchers in the field of stem cells and regenerative medicine for possible applications, including pediatric applications, to manufacture patient-specific stem cells for human-disease modeling, drug screening and development, and customized cell therapy (Cagavi et al. 2018; Omole and Fakoya 2018; Çetinkaya and Haider 2020).

Since iPSCs appear to end the disputes over the destruction of embryos in hESC research, human-induced pluripotent stem cells (hiPSCs) have been touted by scientists and ethicists alike as ethically and morally uncomplicated alternatives to hESCs and are tipped as surrogate ESCs, and the ethics surrounding hiPSCs have been primarily evaluated in comparison with hESCs. However, even if future investigations demonstrate that hiPSCs fulfill the expectation that they could be possibly viable and superior substitutes for hESCs in disease research, regenerative medicine, and drug discovery, further scrutiny of the reprogramming technology and the resulting ethical concerns might potentially reduce some of the hiPSC-associated ethical advantages over hESCs (Zacharias et al. 2011). In the earliest report on iPSC generation, tumor formation was noticed in more than 20% of the iPSCs due to the reactivation and overexpression of c-Myc oncogene (Okita et al. 2007; Ahmed et al. 2011; Buccini et al. 2012).

There is also the safety risk of insertional mutagenesis from virus-dependent delivery methods, which can lead to tumor formation (Takahashi and Yamanaka 2006; Takahashi et al. 2007; Yu et al. 2007). Ethical and legal challenges are also associated with the potentiality of using hiPSCs for the development of human-animal chimeras, human reproductive cloning, and the derivation of human gametes (Lo et al. 2010; Ishii et al. 2013; Wu et al. 2016; Zheng 2016; Volarevic et al. 2018; Moradi et al. 2019). Additionally, such concerns as the application of intellectual property rights or hiPSC patents, donor information, and consent pose considerable challenges to the advancement of iPSCs and iPSC-based research

(Lo and Parham 2009; Zarzeczny et al. 2009; King and Perrin 2014; Orzechowski et al. 2020). While many of these ethical challenges are not unique to iPSCs but are also shared by hESCs, the ease of accessibility and the simplicity of procuring starting cell sources for iPSC development, the rapid progress in iPSC research witnessed in the last decade, and the remarkable expectations placed on iPSC technology make it very timely and crucial to consider the ethical and legal issues associated with it. Notably, hiPSCs may provide a renewable source of cells for theranostic applications with moral and ethical advantages over their counterpart pluripotent stem cells. Indeed, hiPSCs have some serious ethical concerns that scientists and bioethicists must recognize. This chapter summarizes some of the primary ethical issues associated with the use of hiPSCs, such as safety, reproduction, patenting, and informed consent/donor's right, which generally remain unfamiliar to a common reader in the field.

Safety

There remains significant uncertainty regarding the properties of hiPSCs, how they are reprogrammed, and their ability to form teratomas. The early iPSC lines were generated by transducing somatic cells using retroviral-vector-carrying gene encoding for various transcription factors (Takahashi and Yamanaka 2006; Takahashi et al. 2007). However, insertional mutagenesis using an integrative gene delivery system is a substantial safety risk of this approach, which may even result in tumorigenicity (Takahashi and Yamanaka 2006; Takahashi et al. 2007; Yu et al. 2007; Omole and Fakoya 2018). About 20% of the offspring generated in the original report on germline-competent iPSCs subsequently developed tumors, which were attributed to the reactivation of c-Myc transgene (Okita et al. 2007). Such data prompted many research groups to eliminate c-Myc from the classical quartet of transcription factors to enhance their safety profile (Nakagawa et al. 2008; Martinez-Fernandez et al. 2009). These safety risks are unique to iPSCs due to the combined effect of the overexpression of reprogramming factors and the integrative viral-vector-based delivery method used in the protocol for iPSC generation. Furthermore, incorrect or incomplete patterning and genetic instability can increase the risk of tumorigenicity (Yamanaka 2020).

Incorrect or incomplete patterning involves the persistence of undifferentiated and immature cells in the end product of the reprogramming (iPSCs) as well as the differentiated cells derived from hiPSCs. These undifferentiated contaminating cell population has been associated with teratoma formation. The risk of genetic mutations altered biology, and the attainment of tumorigenic potential from incomplete patterning and genetic abnormalities is not unique to iPSCs but relatively common to all cells, which require long-term expansion in vitro (Wang et al. 2013; Izadpanah et al. 2008; Røsland et al. 2009). Genetic alterations like chromosomal aberrations, single nucleotide mutations, and copy number variations are common during reprogramming (Turinetto et al. 2017; Yoshihara et al. 2017a; González and Haider 2021). Chromosomal alterations can either exist in the somatic cells prior to their use

for iPSC generation or originate during the reprogramming process (Yoshihara et al. 2017b; Liu et al. 2020). Indeed, the first hiPSC clinical trial in 2014 was momentarily halted after discovering mutations in the hiPSCs of the second patient, although mutations were absent in the primary somatic cells (Kimbrel and Lanza 2015; Attwood and Edel 2019). Following the transplantation of hiPSCs, the expectation is that the cells should develop normally, maintain average growth, function in the in vivo environment, and adequately replace the injured or lost cells in the diseased patient.

Nevertheless, these cells may proliferate and increase uncontrollably, creating a tumor at the implantation site. This risk of tumorigenicity might trigger extensive safety and ethical concerns about the use of hiPSCs, hence slowing the progress of its application in stem-cell-based clinical therapy. Interestingly, stem cell scientists have made some progress in addressing some of these limitations caused by tumorigenicity. The c-Myc transgene has been shown to be dispensable for reprogramming (Nakagawa et al. 2008). Thomson's group developed their iPSCs using a different set of four reprogramming factors: Oct3/4, Sox2, Nanog, and Lin28 (OSNL), substituting Nanog and Lin28 for c-Myc and Klf4 in Yamanaka's "OSKM" cocktails (Yu et al. 2007). Nonviral delivery methods (plasmid vectors, transposons), non-integrative delivery methods (Sendai virus, lentivirus, and adenovirus), and protocols based on small molecular treatment of somatic cells have been employed to eliminate the limitations caused by insertional mutagenesis (Pasha et al. 2011; Chen et al. 2013; Driscoll et al. 2015; Lee et al. 2020; Kim et al. 2020; Yoshimatsu et al. 2021).

Further intensive studies are fundamental for refining the reprogramming techniques of somatic cells and discovering how to prevent the tumorigenicity of hiPSCs. Another approach in this regard is to develop protocols for the direct reprogramming of somatic cells to the lineage of interest without passing through a pluripotency state (Ahmed et al. 2012). Reliable safety assays should be developed to evaluate the potential of hiPSCs before their application for cell therapy. The development of more effective protocols for iPSC differentiation must first be ensured to generate purified populations of hiPSCs before they are used clinically.

Regarding incorrect patterning, stem cell researchers are developing means to address tumorigenicity to meet the safety standards required for clinical therapy using iPSCs. Some purification methods have been adopted to identify and remove the residual undifferentiated pluripotent stem cells (PSCs). They include techniques such as directed differentiation and positive/negative selection markers using antibody cell sorting systems, such as fluorescence-activated cell sorting (FACS) and magnetic-activated cell sorting (MACS) (Abujarour et al. 2013; Wuputra et al. 2020). The researchers in the clinical study on spinal cord injury are contemplating the use of the suicide gene method as an additional method to prevent tumorigenicity (Kojima et al. 2019). All these methods will assist the investigators in carefully selecting iPSC lines with the highest level of purity that will be safe for the purpose of clinical application.

Regarding genomic alterations, traditional methods like chromosomal karyotyping can detect abnormalities like deletion, duplication, and rearrangement,

and iPSC products with such abnormalities can be discarded. Minimal genetic alterations, like single nucleotide variation (SNV) and copy number variations (CNV), can be detected by next-generation sequencing technology (like whole-genome sequencing) (Yamanaka 2020). However, analyzing such minimal genetic abnormality can be difficult due to the present difficulty experienced; currently, we have to sequence a significant portion of our genome and accurately analyze and interpret the risks from the mutations detected (D'Antonio et al. 2018). The understanding and assessment of the mutational burden of iPSCs are important for their use for therapeutic applications. Indeed, it is challenging to ensure whether a mutation/mutations detected in the iPSC products will significantly increase the risk of tumorigenicity after transplantation (Yamanaka 2020). At present, extensive tests must be carried out on the iPSC products to detect significant mutations, and only stem cells that pass the test should be forwarded for clinical use. Furthermore, after successful transplantation of the iPSCs, patients should be monitored for the possibility of developing a tumor. More clinical research work is needed to accurately predict the tumorigenic possibilities of a detected mutation.

Reproduction

Indeed, one of the most distinct and ethically worrisome potential uses of iPSCs is the production of human embryos through human reproductive cloning. The use of iPSCs for human cloning is illegal and is prohibited worldwide. Generating full-term mice (considered the most stringent criterion of pluripotency) has been fulfilled using iPSCs through tetraploid complementation assays (Kang et al. 2009; Zhao et al. 2009, 2010). This assay involves the injection of iPSCs into the blastocysts of tetraploid mice, embryos that cannot develop into a fetus by themselves. The union results in reconstructed embryos that later develop into fetuses, confirming that iPSCs can form new lives. Sir John Gurdon achieved the first example of cloning using a method where somatic cells were reprogrammed to the embryonic pluripotent states with the same genetic makeup, which is termed somatic cell nuclear transfer (SCNT) (Gurdon 1962). This was followed by Sir Ian Wilmut, who used the same SCNT method to generate the first mammalian – Dolly the sheep – by somatic cloning (Wilmut et al. 1997).

SCNT involves the transfer of somatic nuclei into enucleated oocytes to reconstruct embryos (Matoba and Zhang 2018). Theoretically, this procedure is applicable to humans. Yes, human cloning from hiPSCs is technically possible despite associated safety risks (Wilmut et al. 2015). In both tetraploid complementation and SCNT, normal human oocytes or embryos will be destroyed. In tetraploid complementation, human tetraploid embryos will be generated by the fusion of human diploid embryos. Thus, the normal diploid embryo will be destroyed in the process. The low viability rate during this process will require generating many reconstructed embryos to ensure an increased birth rate of the cloned offspring. Hence, the destruction of many diploid human embryos in the process remains a limitation. Likewise, in SCNT, the enucleated oocytes are also destroyed. This is tantamount to

sacrificing many lives for one life, thus raising ethical concerns that are comparable to that of hESCs. These concerns include controversies about the onset of human personhood and the treatment and harm to embryos, concerns about the safety and health risks of women donating eggs and their potential exploitation for their ova and their informed consent, and concerns about harm to respect for human life, human dignity, and justice toward humankind. In addition, people may also choose to use genetically modified hiPSCs in human cloning to develop offspring with unique characteristics, therefore treating the cloned offspring as a tool for genetic modification or diversity. This type of gene customization of offspring will not show respect for human life. Good surveillance and regulatory processes are essential to monitoring research projects involving SCNT and tetraploid complementation. Regulations must be developed to ban human reproductive cloning explicitly.

Another ethically fraught potential use of iPSCs is the derivation of human gametes (sperm and eggs) and human-animal chimeras. The "first generation" of iPSCs did not contribute to the germline or produce adult chimeras. Yamanaka and others later modified the induction protocols, leading to the generation of iPSCs that were fully reprogrammed and proficient for adult chimera and germline transmission (Okita et al. 2007; Takahashi et al. 2007; Yu et al. 2007). Much progress has since been made in the differentiation of pluripotent stem cells into human sperms and oocytes. Protocols have now been established to successfully differentiate and develop male and female gametes from iPSCs (Panula et al. 2011; Hayashi et al. 2011, 2012; Irie et al. 2015; Sasaki et al. 2015; Yamashiro et al. 2018). It is pertinent to mention that gamete derivation from iPSCs may serve as a powerful research tool to improve our understanding of human development and assisted reproductive techniques for the management of infertility disorders (Fang et al. 2018; Zhang et al. 2020). Nevertheless, the chance that they may be considered for reproductive intents poses ethical concerns about cloning, safety, donors' consent, and the right of the unborn child to know the parents (Advena-Regnery et al. 2018). Other ethical concerns include the potential risk of changing the natural reproduction method, the generation of gametes for same-sex reproduction, and asexual reproduction (Mathews et al. 2009). Furthermore, since the induction of the hiPSCs into gamete cells is not presently a highly efficient process, an attempt to make embryos from such will result in the extensive destruction of many poor-quality embryos, thus raising the same ethical concerns as for hESCs (Mathews et al. 2009).

Chimeras are single organisms containing cells from two or more organisms – that is, it contains two or more sets of DNAs, with the genetic code to make two or more separate organisms. Human-animal chimeras have been used enormously by scientists to improve our understanding of gene function and regulation and disease mechanisms and for testing experimental drugs and gene therapies (Levine and Grabel 2017). They are excellent models of human tissues than nonchimeric animals because they are improved systems for human disease modeling. They provide the opportunity to research human cells and tissues in vivo without the necessity for human experimentation. The technology of interspecies blastocyst complementation has already been used to develop rat organs in mice and vice

versa (Kobayashi et al. 2010; Isotani et al. 2011; Yamaguchi et al. 2017), though human-mouse chimera research is the routine.

Recent advances in genome-editing and stem-cell technology have led to extending this research to larger animals, such as pigs. The combination of gene-editing technology and interspecies blastocyst complementation has made it possible to use hiPSCs to generate individualized human organs, thus raising the opportunity of addressing the dire shortage of organs for transplantation (Wu et al. 2017). However, the growing amounts of human tissues in these chimeras and the potential availabilities of these tissues in morally significant sites, such as the brain, raises strong ethical concerns and questions about the moral status of these animals (Savulescu 2016). How many human cells are considered "too many" in a human-animal chimera's brain? How many human cells are considered "too many" in the human-animal chimera's body altogether? How many would human cells make a mouse brain start thinking human thoughts? What would happen if an animal with human nervous tissues become self-aware and start thinking and feeling like a person? How do we know if we have crossed the commonly accepted dividing line of human decency, dignity, and morality regarding human-animal chimera research? No one knows the answers to these questions, at least not yet.

Nevertheless, these questions reveal the main ethical dilemmas that bioethicists are worried about – that chimeric animals with humanized organs may develop human-like consciousness, which will be ethically unacceptable (Bourret et al. 2016; Kwisda et al. 2020). For further in-depth analysis and detailed arguments and public debates on these concerns, please refer to the works reported by Marino, Knoepfler, Palacios-Gonzalez, DeGrazia, and Greely (Degrazia 2007; Palacios-González 2015; Knoepfler 2016; Marino et al. 2017; Koplin and Wilkinson 2019; Greely and Farahany 2021). Going forward, further debates and research are essential to tackle this major ethical dilemma connected with human-animal chimerism. Therefore, we strongly recommend the practical recommendations for chimeric research contributed by Hyun and colleagues (2007).

Overall, the ethical objections to all the issues raised concerning reproduction include the sanctity of human life, human dignity, safety, manipulation of genetic diversity, violation of the clone's rights, etc. (Pattinson 2007). Despite these ethical objections, the Human Fertilization and Embryology Authorities (HFEA) in 2007 agreed for a cytoplasmic hybrid research program to proceed in the United Kingdom (Editorial (Lancet) 2007; Mayor 2008). Meanwhile, in the United States (September 2015), the National Institutes of Health (NIH) announced the discontinuation of the research funding of iPSC-derived chimeras due to additional controversial ethical issues, which require the attention of enforced policies (NIH, Human Pluripotent Cells into Non-human Vertebrate Animal 2015a, Web, July 1, 2021; NIH, Staying Ahead of the Curve on Chimeras 2015b, Web, July 1, 2021). The authors agree that all aspects of stem cell research should be covered by legislation and strict licensing procedures to curtail the potential for the abuse of this technology. However, we also believe that a flexible, less restrictive regulation that considers the proper justification for embryo research will eventually benefit all.

Patentability

A patent gives an inventor the monopoly right to commercialize an invention for a limited period. Comparable to other property types, a patent makes the inventor the owner of the invention, while the intellectual property right remains valid. This concept of ownership has sparked ethical debate in relation to the patentability of life, centered on the objectification and commercial exploitation of living creatures (Schrecker et al. 1997). Intellectual property rights, when efficiently applied, can present a stumbling block to the progress of iPSC research. There are many approaches used for the generation of iPSCs. If investors hold several patents for these many iPSC generation methods, this can impede the translation of the technology from bench to bedside. Although European patent law (Fig. 1) is set up to protect a person's dignity, the development of iPSCs has opened a worrying loophole (Meskus and de Miguel Beriain 2013). The European Union Court of Justice, on October 18, 2011, delivered a crucial judgment in the aspect of human embryo

Fig. 1 UK and European legal framework for stem cell line patenting

protection in the case C-34/10 *Oliver Brüstle* vs. *Greenpeace eV.* By referring to the meaning of Article 6(2)(c) of Directive 98/44/EC, this case law clarified that those inventions, which involved human embryo destruction at any point, could not be patented (Spranger 2012). However, iPSCs were not in the contemplation of lawmakers when the Biotechnology Directive (Council Directive 98/44/EC and Parliament, from July 6, 1998) was drafted in 1999 (https://eur-lex.europa.eu/legal-contenEN/TXT/?uri=celex%3A31998L0044). Based on the ruling, patents on stem cells generated from excess embryos from IVF or SCNT or through parthenogenesis will be banned. However, since iPSCs were not derived from embryos, the ruling leaves the door open to patents on iPSCs. Subsequently, in the United Kingdom, regulatory guidance has been offered, which opens the door for the patenting of iPSCs, potentially reviving ethical concerns (UKIPO. Inventions involving human embryonic stem cells, 2015, March 25, 2015).

The authors recommend a participatory, inclusive, and transparent process in establishing a workable iPSC patent system that considers the different moral values of all stakeholders in the stem cell field. Creating such a system may not be an easy task, considering the different moral values of all stakeholders. However, if accomplished, this will facilitate the bridging of a moral divide and ensure a consensus that benefits all. More debate and research are essential if we are to close the gap between patents and innovations.

Informed Consent and Donors' Right

Like any other research involving humans, consent is vital for hiPSC research, whether humans participate as research subjects or donors. Usual ethical standards require that participants are fully informed about the specific details of the proposed study, and they are expected to provide voluntary and well-informed consent to participate in the study. Informed consent ensures that the rights, interests, and dignity of patients are protected and respected. Individuals donating somatic cells for iPSC generation should have enough information and answers to address their concerns. The UK Stem Cell Toolkit (USCTK) summarizes iPSC applications concerning legislation (NIH, UK Stem Cell Toolkit 2018, July 1, 2021). These regulations can be used to determine what to include in a consent form. Informed consent should state if the donated cells involved research or clinical applications, genetic modification, animal testing, in vitro or in vivo trials, and whether it will be involved in a therapeutic or diagnostic product with any potential licensing and if there will be risks, complications, and uncertainties. Donors should refuse specific applications, and the right to withdraw one's cell lines should be discussed clearly in the form. If other applications were not mentioned in the initial document, consenting the donor to be recontacted for such an effect could prevent conflict (Zarzeczny et al. 2009; Aalto-Setälä et al. 2009; Orzechowski et al. 2020). Clear explanations and consent will need to be provided as well for patients treated with iPSCs.

Under what circumstances can the participants withdraw from a study? Should a time limit be considered for patient withdrawal? It can get quite complicated when it comes to withdrawal in stem cell research or cell therapy trials. All the steps involved, from obtaining somatic cells from donors to using them to generate iPSCs, are very expensive and time-consuming. So imagine a worse scenario where several donors request a withdrawal after establishing iPSC lines and, at the point, where the iPSCs are to be employed for a clinical study. Such a withdrawal will be very damaging to the research project, and it will be a complete waste of time, money, and other resources (Sugarman 2008). Although the usual standards of research ethics require that participants withdraw from the study at any time, and thus this right must be recognized, there can be "points of no return" that research participants should be informed about (Zarzeczny et al. 2009; Moradi et al. 2019). Points of no return can be when transplanted cells (in cell therapy trials) cannot be removed from the patient's body, thus receiving an irreversible treatment. Even cells donated for research (e.g., to a stem cell bank) may be challenging to withdraw if they have already been used to create a cell line. If there are any such points of no return relevant to given research projects, prospective participants should be informed about them. All this vital information, and the time limit for withdrawal, should be well specified in the consent form (Caulfield et al. 2007). It is indeed a challenge to balance the varied interest linked with iPSC research, considering the prospective benefits of the investigation as well as the interest of the donor. Nevertheless, the apparent policy positions should be adopted and followed through consistently to avoid unnecessary impediments to the research while ensuring the respect and protection of donors' rights.

Closely related to informed consent is the donor's right to control the scope of the research carried out on their cells as well as the scientific and commercial uses of stem cell lines derived from their cells. The stem cell lines will carry the deoxyribonucleic acid (DNA) of the donor, which contains a wealth of information, including the genetic susceptibility of the donor to disease. The disclosure of such information could inappropriately breach the donors' right to their privacy (Sugarman 2008). In the USA, the federal law termed "Genetic Information Non-discrimination Act of 2008" is a typical example of a legislative way of addressing such issues (Taylor 2012). Donors' rights regarding iPSC research may be exercised in various ways. Some donors may not permit their cells to be injected into humans, and they may oppose all animal research or the mixing of human and animal genetic materials. These objections may lead to friction between obtaining the benefit of iPSC research and respecting the donor's autonomy.

One excellent way to address this issue is to preferentially utilize somatic cells only from donors willing to support and allow all forms of basic research into stem cells. However, this strategy has its risks. There is a danger of introducing bias in research if one decides to select only cells from donors who allow all forms of basic research. Additionally, what if those cells do not exhibit the properties needed for the research project? What if the recruitment of this type of subjects who agree to all forms of research takes considerable time and slows down the research project?

Another approach is for researchers to ensure they give precise and thorough explanations about the nature of stem cell research when obtaining informed consent. Although an informed consent procedure that provides complete and relevant information, which enables autonomous decision-making, should be the goal of every recruitment process, this standard is probably not generally lived up to. Providing comprehensive explanations about the nature of stem cell research to the prospective participant can be a difficult task. Information about stem cell research can be quite complicated, and some details may not be understood if one does not provide some background details. In general, whatever approach is considered, the pros and cons should be thoroughly debated before recruiting patients for the study.

Conclusion

The use of stem cells remains a controversial topic despite the advent of hiPSCs. While their generation does not involve the destruction of an embryo, as with ESCs, debates on how they should be used are still relevant (Hug and Hermerén 2011). To address all the issues considered in this chapter and ensure that hiPSCs are not exploited or used unethically, pertinent regulations must be implemented. Perhaps the recent workshop held by the NIH can serve as a model for proactive policy evaluation (NIH VideoCast – Workshop on Animals Containing Human Cells 2015; NOT-OD-15-158: NIH Research Involving Introduction of Human Pluripotent Cells into Non-human Vertebrate Animal Pre-gastrulation Embryos). If stem cell scientists, bioethicists, and policy makers can maintain an open dialogue about the current state of research, then potential ethical issues on the horizon can be tackled in advance. Such an approach would allow hiPSCs for human treatment to be appropriately moderated without blocking vital research progress that will benefit all.

Cross-References

- ▶ Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes (hiPSC-CMs) as a Platform for Modeling Arrhythmias
- ▶ Induced Pluripotent Stem Cells

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