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Stem Cells and Ethics: Current Issues

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Abstract

Much attention has recently turned to the promise and potential of human stem cells in therapeutic applications for the repair of cardiac tissue. The advances being made in the laboratory are exciting, and the pace at which research using human stem cells is moving from bench to bedside is extraordinary. The social, ethical, and policy considerations embedded within this area of research also require a large amount of attention and deliberation so that the scientific progress is able to successfully continue without social backlash.

Keywords

Ethics; Stem Cells; Translational Research; Policy

Background

There is much attention being given to the promise and potential of human stem cells. Advances in the use of these cells in research are happening at an accelerating rate, and the findings in both fundamental biological research and translational and preclinical animal work is exciting. Embedded in the flurry of research activity, though, are several social, ethical, and policy considerations that also require as the attention being given to the science itself and the therapeutic applications in which it may result.

The Cells

In situ, human stem cells have the ability to differentiate into a variety of cells types. Multipotent or adult stem cells are found in bone marrow, adipose, and neuronal tissue, among other places. Pluripotent, or embryonic, stem cells are found transiently in vivo in the developing embryo and were first isolated in vitro in 1998 [1]. The former can differentiate into a limited set of cell types while pluripotent stem cells can differentiate into all cell types derived from the three basic germ layers. Because of the multi/pluripotency of stem cells, researchers have spent much of the last decade or so intent on identifying ways to influence the differentiation of human stem cells into specific cell types. Through this work, scientists as well as the public hope to gain knowledge about basic biological processes, in particular, in development and differentiation and to development of potential therapies for use in the clinical setting as treatments for a number of devastating diseases and physiological traumas.

This area of research has not been without contentious political debate and social controversy in large part because of the source of human embryonic stem cells (hESC). Exciting work has been done to develop other means of creating pluripotent stem cells (e.g., parthenogenesis; [2]), blastomere biopsy [3], and induced pluripotency [4, 5] to avoid the perceived moral issues associated with hESC. That said, there is general consensus within the scientific community [6] that research on all types of human stem cells—adult, embryonic, and those derived through induced pluripotency and parthenogenesis is critical to our understanding of development and other basic biological processes and of what therapeutic value human stem cells may provide.

The Heart

Humans who have experienced a myocardial infarction or other cardiac injury are often left with a damaged area of their heart which cannot contract efficiently. Cardiac contractility depends on the function of involved cardiomyocytes. However, cardiomyocytes are incapable of cell division, which renders them quite useless once they have been damaged [7]. A deficit in healthy cardiomyocytes leads to the development or progression of heart failure. Thus, the regeneration and revascularization of cardiac muscle, a desirable therapeutic outcome, must occur at the myocardial level. This reality has shoved stem cells into the limelight of cardiovascular related research [8]. With the capability of differentiating into myocardial cells, stem cells can regenerate and revascularize damaged cardiac muscle.

Recently, there has been a focus on potential use of stem cells for treatment of a variety of diseased or damaged tissues, including cardiac tissue [9–11]. This work has occurred both in preclinical animal studies and early phase clinical trials with mesenchymal stem cells and hematopoietic stem cells, the latter of which have been used clinically for decades in the treatment of blood disorders. hESC and induced pluripotent stem (iPS) cells are also demonstrating promise with several research teams reporting successful in vitro differentiation of the stem cells into cells with cardiac phenotype in vitro and successful transplantation of these cells into animal models [12]. Others, in a proof-of-concept study, demonstrated using a murine model system that iPS cells created with human “stemness” factors successfully repaired myocardial infarction [13].

The Ethics

There are a number of ethical issues in stem cell research that merit discussion, each of significant importance, as we consider how the use of human stem cells will contribute to not only increasing our knowledge of basic and fundamental biological principles, but also how and if their use will reach clinical application. Here, we briefly discuss several pertinent ethical considerations related to stem cell research and therapy (see Table 1.)

Ethical and Social Considerations

Access to Materials

Intellectual property rights (IPR) are sometimes overlooked in the debate over social and ethical considerations of deriving and using stem cells in research. However, given that these legal rights can dictate who can (or cannot) access certain materials and what constraints may govern the use of those materials, IPR are essential elements to consider in these discussions. The Wisconsin Alumni Research Foundation (WARF), the technology transfer and licensing arm of the University of Wisconsin, holds the patents for primate stem cell technology. These patents provide a broad reach that has led many to suggest that even with the loosening of restrictions granted to academic researchers, the patents will remain contentious because of the control they provide to WARF over commercial applications of

hESC-based therapies [14]. In addition, both groups pioneering iPS cell technology, Shinya Yamanaka at Kyoto University and James Thomson at the University of Wisconsin, are applying for patents in Japan and the US, respectively. A third scientist, Kazuhiro Sakurada, Chief Scientific Officer at iZumi Bio, a biotechnology company in San Francisco, is also pushing forward with a patent application in Japan [15], which if granted would place IPR squarely in the hands of a for-profit entity. Regardless of the outcome, easy access and readily available materials are essential in any domain of research. How IPR will impact stem cell research will be determined in part by the scope of the patents granted as well as how scientists, biotech companies, and investors handle the barriers presented by IPR.

What is in the Dish

hESC lines are considered the gold standard for human stem cell research and therapy [16] and expertise and comparisons of other stem cells, including iPS cells, with hESC viewed as critical to advancements on all fronts [17]. Progress toward development of clinical applications of hESC is farther ahead than with iPS cells and as such, the first clinical trials using pluripotent stem cells are applying hESC technology [18]. Since there is a general agreement within the scientific community in order to reap their full potential, it is essential to push forward all types of stem cell research—using hESC and adult stem cells and pluripotent stem cells derived by other means, public debates around the source of hESC, and their use will not soon dissipate. The issues of when personhood begins and the inherent and perceived rights of an entity with the potential to become a person and how those compare to the rights of a person will continue to be a part of political and public dialog on stem cell research. While philosophers and religious scholars have debated these issues for hundreds of years, the nature of these debates, especially in the context of stem cell research, will hopefully shift away from the more recent contentious and politically controversial rhetoric, forcing people to “choose” sides. Beneficial outcomes will result if the conversation turns toward one in which individuals of differing views begin to listen to each other optimizing shared understanding and interpretation of societal concerns, values, and desired outcomes.

Returning Results and Predicting Future Use

Similar to researchers conducting genome wide association studies and creating biobanks [19], stem cell scientists will have to deal with issues linked to collecting and keeping tissue for future, unspecified use [20]. When tissue is collected from gamete, embryo, and somatic cell donors, genetic information is being collected. Genetic and genomic profiling of the tissue is important for research purposes, and if cell lines derived from the tissue may be used in clinical application, then medical histories linked to the tissue may also be important to collect. DNA itself is a unique identifier, and with a bit of additional personal information for each sample, the potential for individual identification is feasible generating concerns about privacy and confidentiality [21–24]. Additionally, what should occur if during the genomic analysis researchers discover a medically relevant finding that can be linked to an individual donor? Should that finding be returned to the individual and if so, how? Under what conditions ought such findings *not* be returned to donors? Donors currently satisfied with how the tissue they provide might be used may have moral or social objections to future uses that cannot be predicted at time of collection [20, 25, 26]. What kind of limitations on future use can donors request? Is there a level of uncertainty that donors will need to accept?

The points we have just briefly discussed do not lack in importance; however, there is an ethical and social concern that may not be receiving as much public scrutiny and discussion as some in the biomedical ethics and policy community believe it ought to receive. The safe translation of therapies resulting from stem cell research will be dependent in part on

establishing efficient and efficacious regulatory oversight [27], as well as realistic expectations and timelines for clinical trials, and a truly authentic informed consent process.

Safe Translation

The potential for human stem cell research to lead to therapeutic applications for a number of devastating medical conditions has resulted in a situation not unique to stem cell research: high hope for cures and treatments for debilitating disease on the part of individuals and families affected by disease and much hype for quick and definitive success in finding these cures and treatments on the part of disease advocacy groups, stem cell research supporters, and scientists. The media often adds to this phenomenon by providing overenthusiastic and promising reports on scientific findings [28]. Political controversy surrounding hESC research has also added to making advancements with any type of stem cell in the context of disease of newsworthy interest.

The combination of the high hopes and hype can create a number of problematic situations: the disappointment in the inability of science to deliver quickly, pressures to move forward fast with clinical trials, and patients and families seeking—almost urgently, treatments and participating in clinical trials that may not meet safety and ethical standards [29]. The latter situation, sometimes referred to as “stem cell tourism,” is not new but is becoming more common as more applications using stem cells are pushed toward clinical trials [30]. Medical facilities often located in countries that lack the rigorous oversight found in the United States and many European countries advertise proven cures and treatments, luring patients overseas. The patients and their families sacrifice large sums of money; outcomes are unpredictable and have resulted in many times in either only temporary “fixes” or a worsening of the condition [30, 31]. There is often no follow-up by the clinicians performing these procedures and upon return to their home country, patients present themselves to physicians who find themselves providing follow-up care for procedures that they may not endorse and for which they have no detailed background information.

The International Society of Stem Cell Research convened a task force in 2008 to address the concerns noted above [29]. The outcome was a set of guidelines issued at the end of that year. These guidelines are intended to provide a framework for use in the international research community for oversight and conduct of clinical trials, especially in the context of stem cell research. This document outlines the fundamental principles essential for the conduct of ethical and professional biomedical research: independent oversight and review, voluntary and authentic informed consent, and social justice and distribution.

Some commentators have pointed to history, noting that what derailed gene transfer research was a hope and hype phenomenon: scientists and other supporters were touting the technology to be a cure for many diseases and conditions [28, 32, 33]. Clinical trials were pushed forward, perhaps more quickly than they should have been, and when several tragic and well-publicized adverse events occurred, there was backlash. The FDA has granted approval for a few stem cell safety trials to begin, including one to StemCells, Inc. to test neuronal stem cells in treatment of a fatal pediatric condition—Batten's disease and another to Geron to test hESC in repair of spinal cord injury¹. These are largely uncharted waters. Experts—both in the scientific and the biomedical ethics and policy communities, note that these trial approvals may be coming too soon. The Batten's disease trial will be done in children, which raises the regulatory issue of when and under what conditions it is appropriate to conduct pediatrics safety study (The Hastings Center Report, January to

¹We note that at the time of this writing the FDA had placed a hold on the Geron Corporation trial. (New York Times, August 19 2009, page B8)

February; [34]). In the latter case, the preclinical data being used to justify the Geron trial has generated some discussion within the scientific community. The severity of the conditions of the animals used in these studies was not at the level many expect the clinical trial participants to have, and no large animal studies were done [18]. The reference to the gene transfer research is intended to be a cautionary reminder to scientists, patients, and other stem cell supporters. Let's not allow exciting advances, large levels of enthusiasm, and strong desires to help those who are ill hyperaccelerate the process. Research participants and their families need to be fully informed of all happenings from beginning to end. Transparency is a must and serves to benefit all involved.

Fully Informed

The consent process and ensuring that research participants are fully aware of risks and benefits and have sufficient information to make an autonomous decision, plagues all biomedical research. Lack of understanding on the part of trial enrollees can cause research participants to believe that they are receiving actual treatment for their conditions rather than partaking in a clinical trial. In fact, this concept of therapeutic misconception is often directly linked to faulty consent processes [35]. While not an issue unique to stem cell research, ensuring an authentic informed consent process for human stem cell trials will be key to avoiding a derailment experienced in gene transfer research.

In many cases, individuals first in line to participate in these trials—whether these trials are within the boundaries of US regulatory oversight or being held outside the US, are desperate for some treatment or cure. The participants are very ill and in some instances, the clinical trials present what many of these patients and their families perceive to be as their only option. This begs the question of whether these individuals (and their families, especially when the patient is a child) are vulnerable—whether each is able to make an independent and sufficiently informed decision about what is in his or her best interest. Many patients and their families are information seekers and tech-savvy and approach these trials armed with knowledge. That is, on one level they do fully comprehend that no therapeutic benefit may be achieved and in fact, potential harm is a very real risk; understand the likely necessity of foregoing current disease management and therapies to participate. They wish to participate to simply be doing something, if not directly for themselves, then at least others in the future. However, this does not remove the probability that there is an underlying hope that the direct benefit will be gained.

These concerns do not necessarily mean that we hold-off on human stem cell clinical trials. Rather, they suggest that scientists and ethics scholars ought to place an emphasis on truly understanding what an authentic consent process is and how to ensure that is what takes place all the time. This will require collaborative efforts to generate empirical data from studying current processes and determining patient expectations and comprehension needs. Fully understanding this dichotomy of motivation and how to balance it with fundamental ethical principles of human subjects research may facilitate how we look back on this period of biomedical research history.

Conclusion

No doubt, the excitement of research using human stem cells in repair of damaged cardiac tissue and other areas of regenerative medicine will continue. As the science moves from bench to bedside, it is just as important to give serious attention to the social, ethical, and policy considerations surrounding it. *Completely* resolving the issues we have raised may not be feasible, but moving discussion and work on them *in parallel* with the science is a necessity.

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Table 1
The scientific, clinical, ethical, social, and policy considerations of stem cell research

1. Potential scientific use	
All three stem cell types	Model systems for research on human disease Tools for drug development Tools for drug development
Human embryonic stem cells	Gold standard for iPS cell work Tool for understanding fundamentals of human developmental processes, both normal and abnormal
Human adult stem cells	System for determining signaling pathways in cell maturation
Human induced pluripotent stem cells	Resource for studying process of reprogramming
2. Potential clinical use	
All three stem cell types	Source of cells and tissues for repair or replacement
Human adult and induced pluripotent stem cells	Source of autologous cells and tissues
3. Some potential ethical and social issues	
All three stem cell types	Intellectual property constraints on use of the research materials Access to the medical and therapeutic technologies developed from stem cells Individual donors' understanding of uncertainty of future use of their donated gametes, embryos, or somatic cells Privacy and confidentiality of gamete, embryo, or somatic cell donors Returning medically relevant information to gamete, embryo, or somatic cell donors Hyperbole of safety and efficacy of therapies under development Individual recipients' understanding of the origin of materials used in their therapy or treatment
Human embryonic stem cells	Source of cells
4. Some potential policy considerations	
Carefully and thoughtfully examining of intellectual property rights provided to and governing stem cell research materials (i.e., human embryonic stem cells, human induced pluripotent stem cells) and developed medical therapies	
Emphasizing experimental nature of study trials and focusing efforts on communicating full information to participants and obtaining authentic consent from them	
Rethinking the goals of the informed consent process for individuals donating cells and tissues for stem cell research use	
Collecting and analyzing empirical data to determine expectations of cell and tissues for stem cell research	
Collecting and analyzing empirical data to determine expectations and understandings of participants in stem cell clinical trials, especially early phase studies	
Encouraging and promoting civil debates on moral views and individual values in the context of stem cell research	