Stem Cell Research

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Summary

Critically evaluate the decision to conduct research with stem cells.
Both the spirit of the regulations and good science require that individuals give thoughtful consideration to what defines an acceptable use of stem cells.

Comply with regulations.
Having made a considered decision to use human stem cells, no use of those cells for the purposes of research, teaching, or testing should commence that is not explicitly part of an approved protocol or specifically waived under relevant regulations.

Promote responsible use of stem cells.
If you are responsible for training others or if you observe indifference to considerations for responsible stem cell research, you should make attempts to initiate discussion, to identify relevant regulations, and to promote responsibility. If significant violations of regulations are observed, then those observations should be reported to the appropriate people in the institution.

Background

In recent years, biomedical research has been significantly altered by technologies for the derivation of human cell lines capable of differentiation into any of the cells of the human body. Such cells are sometimes called "pluripotent" because they have the power ("potency") to become many ("pluri-") different cells. It has long been known that such cells exist, but it wasn't until 1981 that stem cells were isolated from mouse embryos (Evans and Kaufman, 1981; Martin, 1981), and only in 1998 that the derivation of human embryonic stem cells was first reported (Thomson et al., 1998). This tool was quickly recognized as an opportunity to better understand normal and pathological human development, to identify and test new pharmacological therapies, and perhaps to even replace diseased tissues or organs. Many scientists viewed this as a potentially revolutionary approach to studying human biology. However, because a necessary first step was to use and destroy human embryos such research raised serious questions for some members of the public, as well as some scientists.

Opposition to Stem Cell Research

While most hESC scientists view the human embryo as human cells with great biological and scientific potential, there are many members of our society who hold religious beliefs that define the human embryo as equivalent to a human life. By this view, any harm or destruction of the human embryo is tantamount to harm or destruction of a human life. This perspective has become more than a matter of personal opinion. For many years now, under the Dickey amendment (1995), the U.S. Congress has agreed to federal restrictions on any research that would require harm or destruction of the human embryo. This restriction was partially lifted in 2001 by President Bush's announcement that research with stem cell lines existing as of August 9, 2001 could be eligible for federal funding.

Subsequently, President Obama announced a new approach to approving stem cell lines for federal funding (Obama, 2009). The question now is not whether stem cell lines were created before a particular date, but whether or not those lines meet criteria that have been defined for ethically derived stem cell lines (NIH, 2009). While the result has been an increase in the number of stem cell lines approved for federal funding, it is noteworthy that the number of lines meeting these criteria is limited (NIH Human Embryonic Stem Cell Registry). In fact, many of the lines approved under the Bush policy are not acceptable under the Obama guidelines.

It would be a mistake to assume that religion is the only basis for arguments against hESC research. It is clear that some individuals and groups are motivated more by philosophical, political, or even economic arguments. However, whether based on religion or otherwise, most polls show that opponents to hESC research may represent a minority, but that minority is substantial in size and in impact (e.g., pollingreport.com).

Sources of Stem Cells

Stem cells can be obtained from embryos, but embryos are only one of many potential sources. In the fetus, and even in an adult, stem cells can be found in many body tissues. The best known of these sources is bone marrow, in which stem cells that are capable of differentiating into different types of blood cells are produced. However, these stem cells are not pluripotent as defined above. Such cells are often called adult or tissue-specific stem cells. These cells have important, but restricted, clinical applications distinct from the wider range of possibilities with human embryonic stem cells (Wood, 2005).

Several sources of pluripotent stem cells have now been identified. One of these sources is based on the technology used to clone "Dolly" the sheep (Campbell et al., 1996), "Snuppy" the dog (Lee et al., 2005), and many other mammalian species. The first step to cloning these animals is a technique called Somatic Cell Nuclear Transfer (SCNT). SCNT in any species begins with an egg of that species from which the genetic material is removed. This egg can then be fused with an adult cell of the individual to be cloned. The result is an egg that now contains a full complement of DNA. Under appropriate laboratory conditions, that egg can be induced to divide as if it were a fertilized egg. If allowed to progress far enough, the resulting embryo can be implanted in the uterus of

an individual of the same species, potentially resulting in the birth of a clone. However, it is also possible to allow the "embryo" to develop only for the purpose of harvesting stem cells rather than implantation. This source of stem cells is particularly important for stem cell research as well as potential therapies because of the opportunity to produce stem cells and differentiated cells that are genetically and immunologically matched to the adult donor.

Until 2005, researchers had been frustrated in their attempts to duplicate with human cells the same success achieved with SCNT in many other mammalian species. Some researchers were considering the possibility that SCNT in humans would be for all practical purposes impossible. This view was apparently proven wrong when the laboratory of Dr. Hwang Woo Suk published a report demonstrating successful derivation of stem cell lines from eleven separate cases of human SCNT (Hwang et al., 2005). Hwang, whose laboratory had cloned the first dog (Lee et al., 2005), was seen as so far ahead with SCNT that other laboratories around the world suspended attempts to achieve human SCNT, choosing instead to collaborate with Hwang's laboratory. Unfortunately, the story began to unravel in late 2005 and by the next year it was clear that the results announced in Dr. Hwang's paper were entirely falsified (Kennedy, 2006). Because researchers throughout the world had chosen to not pursue SCNT, this line of research was set back a year or more. It wasn't until 2008 that scientists at Stemagen successfully reported human SCNT (French et al., 2008).

Although SCNT has both scientific and therapeutic benefits, it still raises significant ethical questions, particularly because it depends on women who are willing and able to donate some of their eggs. Egg donation is not free of risk and, therefore, many bioethics committees and regulatory bodies have decided to err on the side of caution by prohibiting payment for eggs donated for the purposes of stem cell research. While on the one hand this position might be seen as paternalistic, the case can be made that any significant payment might lead those who are young or poor to overlook the possible risks of donation. The debate about payment is likely to continue, but it is clear that SCNT depends on a resource (human eggs) that is in limited supply and that can be obtained only through a time-consuming and invasive procedure.

An ongoing hope is that pluripotent cells might be found without the need for either human embryos or eggs. A number of reports have suggested that such cells might be found, for example, in amniotic fluid (De Coppi et al., 2007) and testes (Conrad et al., 2008). Another approach, reprogramming of adult cells, has been found to be far easier than expected and provisionally as good as or better than other sources of cells. In brief, cells (e.g., fibroblasts) are obtained from an individual, treated with a viral vector to introduce as few as 4 genes which, effectively, dedifferentiate (reprogram) the cells to become pluripotent stem cells (Takahishi et al., 2007; Yu et al., 2007). These cells are now commonly referred to as induced pluripotent stem (iPS) cells. Although these findings are intriguing, it remains to be seen whether the various alternative sources of pluripotent stem cells will prove to have the same qualities as the stem cells derived from human embryos (Hyun et al., 2007).

Regulations and Guidelines

In just ten years (1998-2008), the field of human embryonic stem cell research evolved rapidly. Almost certainly, because of intense public scrutiny, the landscape for regulations and guidelines has also evolved rapidly. Unfortunately, the regulatory environment for this research varies not only across international borders, but significant differences are found even among the states of the United States. It is neither useful nor possible to describe regulations in each of these jurisdictions both because of extensive variation and because regulatory changes continue to be driven by changing public opinion and rapid advances in the sciences. However, a few examples are useful to illustrate the complex and often conflicting approaches to stem cell research across international and interstate borders.

Internationally, the environment for stem cell research ranges from a virtual prohibition to a near absence of restriction (Isasi and Knoppers, 2006). Several countries, including Austria, Norway, and Poland, have prohibited any human embryo research. Others, such as the U.S. and Germany, prohibit the use of federal funds for hESC research, but in the face of public pressure both countries have adopted national policies that allow the use of federal funds for stem cell lines created before August 2001 and May 2007, respectively. Finally, for all practical purposes, China and Singapore are examples of countries with relatively few restrictions on hESC research.

The variation across international borders in stem cell regulations should not be taken as a sign that the international stem cell community has been silent about the responsible conduct of stem cell research. The International Society for Stem Cell Research (ISSCR), (one of the leading international stem cell research organizations, has established a variety of guidelines that are now widely accepted throughout the stem cell research community (ISSCR, 2006). Key principles of these guidelines are:

- "All experiments pertinent to human embryonic stem cell research that involve pre-implantation stages of human development, human embryos or embryonic cells, or that entail incorporating human totipotent or pluripotent cells into animal chimeras, shall be subject to review, approval and ongoing monitoring by a special oversight mechanism or body equipped to evaluate the unique aspects of the science. Investigators should seek approval through a process of Stem Cell Research Oversight (SCRO)."
- "Given current scientific and medical safety concerns, attempts at human reproductive cloning should be prohibited."
- "…privacy and confidentiality of personal information should be protected with the utmost care. Caution must also be taken to ensure that persons are not exploited during the procurement process, especially individuals who are vulnerable due to their dependent status or their compromised ability to offer fully voluntary consent. …there must be a reasonable relationship between those from whom such materials are received and the populations most likely to benefit from the research. Finally, the voluntary nature of the consent process

must not be undermined by undue inducements or other undue influences to participate in research."

While the U.S. has significant restrictions on the use of federal funds for stem cell research, such research is still permitted to the extent allowed under state laws. As with international stem cell regulations, tremendous variation can be found among different states (National Conference of State Legislatures, 2008). As of 2008, South Dakota prohibits hESC research, while some states (e.g., California, New York) have been not only permissive of stem cell research, but have approved significant public funding dedicated to hESC research.

The fact that some states are highly permissive of stem cell research does not mean that such research occurs in the absence of either regulations or guidelines. Nationally, guidance that is generally accepted has come from the National Academy of Sciences. Following their initial report (Committee on Guidelines for Human Embryonic Stem Cell Research, 2005), the NAS has published amendments in 2007 and 2008 (Human Embryonic Stem Cell Research Advisory Committee, 2007 and 2008). Two key points in those guidelines are:

- "To provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES cell research, each institution should have activities involving hES cells overseen by an Embryonic Stem Cell Research Oversight (ESCRO) committee."
- "An IRB …should review all new procurements of all gametes, blastocyst, or somatic cells for the purpose of generating new…cell lines."

One of the states that has been most receptive to hESC research is California. In 2004, a significant majority of California voters approved Proposition 71, creating a mechanism for allocating $3 billion for stem cell research over a 10-year period. This voter approved initiative also put in place a framework to promote scientific, legal and ethical oversight for stem cell research through the creation of the California Institute for Regenerative Medicine (CIRM). The resulting requirements for CIRM-funded research have generally been extended to all stem cell research in California. Under California law (California Institute for Regenerative Medicine, 2008), key requirements for stem cell research include requirements for review of the research by the equivalent of an ESCRO Committee, criteria for acceptable derivation of materials that are to be used for research use, and categories of research that are specifically prohibited.

Discussion

Case Study[i]

Scientists and clinicians in a private institute (in another country) have reported the birth of a child who is a genetic clone of her mother. Using the same technology as was used to create Dolly the sheep, the scientists had taken the DNA from one of the future

mother's cells, and inserted that DNA into one of her eggs. The resulting cell was stimulated to begin dividing, resulting in a blastocyst (embryo) that could be implanted in the mother's uterus. Nine months later, the first known human clone was born.

Karl is an assistant professor recently hired at Smalltown University. Karl's primary research focus is human embryonic stem cells. He is using stem cell lines produced at other research institutions for his own studies to see if he can stimulate those cells to differentiate into nerve cells. Some of his experiments include transplanting those cells into mice to assess the factors that help those cells transform into human neurons integrated into the mouse brain. He is the only faculty member at SU working in stem cell research.

Roxie is a news reporter with the primary news outlet in Smalltown. She is typical of many of the residents of Smalltown, and believes that once an egg is fertilized it is the equivalent of a human life. Roxie has just received the report of the first human clone. Because she believes this story would be of significant interest to her readers, she contacts the press office at SU and asks to speak to a scientist about this report on human cloning. She is introduced to Karl, who is described as an expert in the field of stem cell research.

The questions Roxie brings to the interview are wide-ranging. Some of the initial questions are for background information: How does this technology work? How easy is it? She next asks questions about the cloned human, such as: Is it safe (what are the risks to the mother and child)? Is this legal in this country? Is it ethical to create human life in this way? Later, the interview turns to the work of Karl. Roxie is very concerned about experiments in which human nerve cells will be inserted into the brain of a mouse. She now asks about the possibility that the mouse will have a human brain: Will it be smarter? Will it be able to think like a human? Will it be a human trapped in the body of a mouse? And all of these questions then lead to some fundamental questions: Are scientists playing god when they conduct these kinds of experiments? Who decides which experiments will and won't be done?

Assuming that Karl has agreed to do this interview, and you had a good idea what type of questions would be asked by Roxie, then how would you advise Karl about the things that he should and should not say and do in the interview?

Discussion Questions

1. Describe three examples of potential benefits from human embryonic stem cell research that are less likely to be achieved by other available approaches.
2. Describe at least one instance in which misconduct or insensitivity to public concerns helped to increase opposition to human embryonic stem cell research. Identify federal or state regulations and guidelines that were apparently direct responses to such abuses.
3. What are the responsibilities of an ESCRO or SCRO Committee?
4. In your institution, what minimal changes (e.g., addition or removal of stem cell lines to be studied) to your protocol require review and approval of the ESCRO

or SCRO Committee? What changes are of a magnitude to require submission, review, and approval of a new protocol?

5. If you observed another investigator abusing the privilege of stem cell research, who should be notified?
6. Describe your criteria for the acceptable use of human embryos and stem cells. Consider the importance and likelihood of benefits to be obtained, the source of the material being used (e.g., egg donation for SCNT vs. iPS cells), the nature of the proposed experiments (e.g., in vitro vs. insertion of human cells into a non-human species), and rationale for the proposed research (e.g., basic science, prevention or treatment of disease, or technology that would allow enhancement of an otherwise normal individual)..
7. What forums are available in your institution to examine the ethical and/or legal ramifications of stem cell research? What, if anything, can you do to promote such discussion?

Additional Considerations

Clearly, from an ethical perspective, stem cell research constitutes one of the most complex of the numerous domains of research. Many considerations might be listed here, but three seem to be particularly noteworthy.

Public Scrutiny

Stem cell research is likely one of the most watched areas of academic endeavor in the history of academia. This is a direct consequence of two very different public perceptions of this research. Internationally, and certainly within the borders of the U.S., the majority of the public has recognized in this research a potential for a virtual revolution in medicine. It remains to be seen whether this will be the case, but this segment of the population is highly attentive and supportive of all that is happening in stem cell research. In addition, there is a second group, which is very much opposed to human embryonic stem cell research. While most polls and votes indicate that this group is in the minority, it is nonetheless a substantial minority. Among the members of this second group, there is a highly principled belief that harm or destruction of a human embryo is the equivalent of harm or destruction of a human child. For this group, the possible benefits of stem cell research cannot be on the table if those benefits in effect require the taking of human lives. For these reasons, this group is also watching stem cell research closely and seeking alternatives that do not require the use of human embryos. Scrutiny by both supporters and opponents of stem cell research places a higher obligation on stem cell researchers than for other areas of research. In short, mistakes by stem cell researchers are not likely to be overlooked. An ethical lapse, misuse of funds, or violation of regulations will not be merely a matter of individual concern. It is highly likely that such mistakes will reflect at least on the individual's institution, and also on all of stem cell research, if not science in general.

Special Respect

A case can be made that the human embryo deserves special respect (Robertson, 1999). At first glance, such a statement may seem unnecessary to supporters of stem cell

research and hypocritical to its opponents. Stem cell researchers might argue that since the majority of the public favors such research, and presuming that the researchers are working in a jurisdiction that makes such research legal, then they should no longer have to give any more consideration to human embryos or eggs than they might give any other human cell. Conversely, opponents who view the human embryo as a human life might argue that "special respect" is meaningless if the embryo is still going to be harmed or destroyed. There is, however, a middle ground between these views. As implied by Robertson's argument (1999), respect does not have to be absolute; it can be in varying degrees. Such respect may not mean that we will abandon human embryonic stem cell research, but we still can and should recognize that it is a privilege to conduct this research. The circumstances under which human eggs or embryos are made available to research are anything but trivial. Under those circumstances, we recognize the precious nature of those human cells. That privilege is one that cannot be taken lightly. In fact, most of us already have internalized a recognition of the differential value we would place on a developing embryo, a fertilized egg, an egg, or sperm. For example, if only some, but not all, of the above could be saved in the face of imminent danger, most of us are likely to put greatest value on the embryo. In practice, this special value means that we have an obligation to ensure that those cells are put to the best possible use in a project that has been reviewed and approved for ethical, legal, and scientific merit.

Origins and Uses

Because much of the debate about human embryonic stem cell research has focused on the embryo, it is easy to overlook that this is not the only ethical challenge requiring consideration. While the origins of stem cells are important and cannot be dismissed, we must also ask about the ethical challenges in the conduct of basic and clinical stem cell research. Many such considerations are characteristic of any research (e.g., standards for recordkeeping, sharing of data, addressing conflicts of interest, or allocating credit), but some issues are specific to stem cell research. Two areas that are of particular note are chimeras and clinical trials.

Chimeras: A chimera is defined in various ways, but the principle is that one organism consists of components that are demonstrably derived from two or more distinct species. The name chimera comes from a monster in Greek mythology that was a combination of different animals (typically a lion, goat, and snake). In biology, chimeras can now be formed either by inserting cells from one species into the adult of another species, or by creating an embryo that begins with cells from two or more species. In principle, it seems that our society already accepts the possibility of saving a child's life by replacing a defective heart with one that is non-human (e.g., a baboon heart, Altman, 1984), but we are much less comfortable with creating a non-human animal that might have human features (e.g., a human face, ear, or hand). Having the appearance of a human is problematic more because of our discomfort than because it necessarily raises some direct ethical dilemma. However, we have reason to be much more concerned about a human nervous system (i.e., do we have a risk of a non-human animal achieving levels of awareness and understanding that would make it sufficiently human to be deserving of human protections?) or human gametes (i.e., do we have a risk of two non-human animals reproducing with human gametes, thereby producing a human, or largely human, organism?). These questions are very much hypothetical and, if not

impossible, highly improbable under the circumstance that the ethical, legal, scientific, and social environment is not one that favors these goals. Nonetheless, responsible science and policy require that one concern for reviewers of stem cell research is to address the potential risks with experiments that involve the mixing of stem cells from two or more species.

Clinical Trials: In the very near future, we are likely to see clinical trials based on reputable, pluripotent stem cell research. We are already seeing numerous stem cell "trials" worldwide that are arguably questionable, and sometimes criminal. By taking advantage of public awareness of and excitement about stem cell research, it is now possible to find groups that will offer to treat or cure almost anything in the context of a clinical "trial" that typically has no control group and for which participants must pay for participation. Payments for such "trials" are often on the order of $10,000 or more. Whether intentional or not, these trials are likely to be scams with little chance of success. Particularly under these circumstances, the stem cell field must meet a higher than average standard before approving the first clinical trials with this very new approach to treating disease. To do otherwise risks a backlash against all of stem cell research if initial trials unexpectedly result in a worsening of disease, serious side effects, or even death. All of these are possible outcomes no matter how much work has been done before the first trials in humans. Therefore to decrease that risk the scientific community can and should set a high bar both for the circumstances under which such a trial should be attempted and for the design of the research study to ensure the highest level of protections for informed consent and the welfare of the research participants.

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Endnote

[i] This case was contributed by Dr. Michael Kalichman (kalichman@ucsd.edu) of the University of California, San Diego. ©2008