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Ethical Challenges for Stem Cell Research - From the Embryo to the Bedside

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Abstract

In this paper I discuss some key ethical challenges raised by stem cell-based research. After explaining the potential of stem cell research for developing effective new treatments for a variety of diseases, I explore whether the moral status of the human embryo should limit or prohibit research using embryonic stem cells. I turn next to further ethical challenges that will arise with the first human trials of stem cell-based treatments, even if the source of the stem cells poses no problem. Finally, I discuss the question of whether the use of induced pluripotent stem cells can successfully side-step questions about when a human life begins.

Keywords

bioethics, stem cells, research ethics, embryo

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The rapidly expanding field of stem cell research, and its possible applications to human health, presents a number of important and complex ethical questions. Those have been dominated by concerns about one source of pluripotent stem cells, the embryo, and whether, or when, it is ethically permissible to destroy embryos for this purpose. So I can hardly avoid discussing the embryo in this paper. But I want to go beyond it, because even with the embryo out of the picture, there are important issues that remain.

My main objective is to highlight the important features of some key ethical questions regarding stem cell research. This means I may be raising more questions than I answer.

Why Stem Cell Research Is Important

Since not every reader will be familiar with stem cells or their importance, I should start with some basics. The US National Institutes of Health maintains a web page with further information (NIH)

First, what's a stem cell? There are two important characteristics. The first is that stem cells are immortal — they can divide indefinitely. This means that a single stem cell, in the right environment, can eventually lead to millions of genetically identical stem cells.

The second characteristic is suggested by the name, "stem" cell. A stem cell can produce any of a variety of other specialized cells. And stem cells can be distinguished by how much of this potency they have. An embryo — an organism and not a single cell — is *totipotent*, meaning that it can transform itself into a complete human organism consisting of many different specialized cells and systems of tissues and organs. A stem cell taken from an embryo is *pluripotent*. Under the right conditions, it can be transformed into any of the specialized cells found in the human body. And then there are more specialized stem cells that are *multipotent*, and can transform themselves into a variety of different kinds of cells of a similar type.

We've known about multipotent stem cells for about 40 years, when they were discovered in the bone marrow. One kind of those stem cells can produce any of the variety of cells found in the blood, and we've used that knowledge to treat patients with blood disorders, like leukemia, for a long time. For quite a while, those were the only stem cells we knew about. But in recent years stem cells have been found in many other organs and

tissues. This includes the brain, and this discovery dispelled the previous belief that the nervous system could not replace dead nerve cells. Research is exploring how these more recently discovered stem cells can be used in treating disease. For example, neural stem cells can be found in the mucosal tissue in the nasal cavity, and there are studies using implants of these stem cells taken from patients with spinal cord injury. (Lima et al.)

So why is it important to do research on stem cells?

First, it's important for advancing basic biological knowledge. Stem cells are fundamental building blocks in the creation and maintenance of all kinds of organisms, and the ability to isolate and then culture them indefinitely gives us the ability to study them in the laboratory. And not just to study stem cells themselves, but to study as well the specialized cells that they can become.

But second, there is now a growing body of basic and clinical research that is directed to using stem cells, of one type or another, to replace, repair, restore, or regenerate damaged tissue. This research is aimed at treating all sorts of diseases, including diabetes, heart disease, Parkinson's disease, and spinal cord injury. The first human experiment transplanting Embryonic Stem Cell (ESC)-derived neural cells into patients paralyzed by spinal cord injury is now being conducted by Geron. More recently, Advanced Cell Technology has begun trials of implanted ESC-derived retinal cells to treat certain kinds of blindness.

No doubt others will soon follow. One especially important method of producing embryonic stem cell lines removes the nucleus from a fully differentiated somatic cell. That nucleus can then be inserted into a human

egg which has had its own nucleus removed. The egg will then reprogram the nucleus, and with stimulation will produce an embryo with stem cells that have nuclear DNA identical to the original somatic cell.

These custom-made stem cell lines can be used to study the genetic factors related to a disease — pancreatic cancer, for example, by using pancreatic cancer cells to produce a stem cell line with the same DNA as the cancer cells.

Or, they could be used as a way to develop specialized cells or tissue that could be implanted in the patient who had provided the original cell. Since these new cells would be genetically identical to the patient's other cells, the transplant would not trigger the immune reaction that accompanies other sorts of tissue implan.

This all looks like good news. We may now have a promising and radically new way to use implanted cells to treat serious diseases, while minimizing serious side-effects. What is the ethical problem?

Stem Cells and Embryos

The first problem is that until very recently, the only source of pluripotent stem cells has been the embryo. At the blastocyst stage, about 5 days after fertilization, stem cells can be found in the embryo's inner cell mass. Normally, obtaining embryonic stem cells destroys the embryo. The embryo is a genetically unique, individual, human organism? a new human life, some would say. And so the question is whether it is ethically permissible to destroy this new life, even for the noble purpose of

advancing medical knowledge or curing terrible diseases. After all, no one would support the unwilling sacrifice of even one person for this purpose. Why should it be permissible to sacrifice the embryo?

The embryo and abortion

To make some progress on this question, it will first be useful to draw some contrasts between the ethics of sacrificing embryos and the ethics of abortion. Although there are points of contact, the ethics of destroying *in vitro* human embryos may be different than the ethics of abortion.

Some *supporters* of a right to abortion argue, for example, that even if the fetus (or embryo) is regarded as a person with an independent right to life, the woman carrying it is also a person who may not have an obligation to continue supporting that other person's life with her own body. The argument here uses an analogy to forced organ donation. Even if you need one of my kidneys to stay alive, you don't have a right to take it against my will. By the same token, even though the fetus needs the mother's body to stay alive, it doesn't have the right to commandeer it without regard to her own wishes.

If this is a person's view about the ethics of abortion decisions, she might support the right to abortion, and yet be ethically troubled by the destruction of embryos for stem cell research. In the latter case, the embryo's life is not dependent on another's body, and so there is no conflicting set of rights to provide the justification for its destruction.

From the other direction, some *opponents* of abortion base at least part of their opposition in what they see as the relatively trivial reasons

that some women may have for seeking an abortion. This is an anti-abortion position that will permit abortions to save the life of the mother, since this may seem a reason comparable to the imperative to sustain the life of the fetus. When forced to a choice, it's the mother's life we should choose. From this position, one might have a much more tolerant attitude toward the use of embryos for potentially life-saving research and treatment, than toward most abortion decisions. Thus, we have the example of U.S. Senator Orrin Hatch, sponsor of the perennial Human Life amendment to the US Constitution that would ban most abortions in the United States, coming out in favor of stem cell research.

Regarding the moral status of the embryo itself, there is a range of possible views.

The embryo is a new human being

One ethical position starts with the claim that once conception has taken place, a new human biological individual has come into being. The embryo is just a later stage in that new human life. If we add the assumption that all human lives have equal moral standing, then embryonic stem cell research becomes ethically objectionable. Just as it would be wrong to destroy one of us even to conduct potentially life-saving research, so too it's equally wrong to destroy an embryo, another human life morally comparable to ours, for this purpose.

Ethically, this places a lot of weight on possessing a human genome, to the exclusion of the many other properties fully developed human beings have that we think are morally significant. This perspective takes the position that there are really *no* morally relevant differences between

embryos and the rest of us with regard to the value of our lives. Many people think this is implausible.

It also has to deal with some biological and philosophical complexities regarding just when a new *individual* has begun. For example, prior to the development of the primitive streak (around 14 days after the first cell division), embryos possess their greatest ability to divide, producing two or (rarely) more genetically identical embryos. So when did those two individuals begin? After the division of the original embryo, one might say. But what existed before that? A different individual? What happened to him? Did he cease to exist? If he did, then the new individuals can't trace their beginning back to the conception of the original embryo. Should we say, then, that the two new individuals somehow already existed within the original single individual? How could two distinct individuals occupy the same space at the same time?

All these complexities make it difficult to determine clearly when a new human *individual* begins in the developmental process. But that has not stopped policy makers from using 14 days as a common legal limit for research on human embryos, even if it has no unambiguous moral justification.

Finally, this position may have some highly implausible implications. The rate of natural human embryo death, after conception, is very high. Some estimate that 50% of embryos will die before implantation, resulting in the death of millions a year. If these embryos have equal moral standing with the rest of us, this is a staggering public health problem that deserves investment of tremendous resources. But almost no one would accept that conclusion. (Ord)

The difficulties facing this position lead many people on to the next one.

The embryo can become a person

The second position claims that it's not just being a new biological individual that matters — it's the potential to become a fully developed human being like you and me, which in the future clearly possess all the qualities of persons to which we attach moral significance. It's this *potential* that gives the embryo its special moral standing.

Note that unlike the previous perspective, on this second position it doesn't matter whether or when twinning might occur. The embryo that divides into two had the potential to become a person all along — in fact, the potential to become two persons! And so, research on embryos older than 14 days would not in itself be any more objectionable than research before that time.

This argument from potentiality has a long and complex history, and a thorough exploration of it is beyond the scope of this paper. One complexity is knowing which sorts of moral claims mere potentiality can support. Clearly, just because an embryo is potentially a voter doesn't mean it now has a right to vote. Something more must be said to support the conclusion that its potential gives it a right to life equal to the person it will become, but is not yet.

The second complexity arises because there are different kinds of "potentiality." What, for example, is the relevance of "potentiality" for

embryos that are not going to be implanted in a womb, and so as a matter of fact will never develop further? Perhaps it is ethically permissible to use embryos that under the circumstances will never develop their potential, because they don't have the *actual* potentiality to become a person. An alternative is to claim that what's ethically important is the innate or *intrinsic* potentiality of the embryo, a potentiality it possesses independently of the conditions necessary for its actually developing into a person. The question here will be why this intrinsic potentiality should matter, since by itself it will not lead to development of a person. (See Lizza)

If one adopts actual potentiality as the criterion, then embryos left over from IVF procedures, which will never be used by anyone for reproductive purposes, could ethically be used for embryonic stem cell research and therapy. And indeed, in most countries these are the only embryos on which stem cell research is legally permitted.

The policy forbidding research on embryos after 14 days is almost always combined with the policy allowing research only on embryos that will not under the circumstances develop into persons. Note, however, that each policy is justified by a different view about the moral standing of the embryo, and these are incompatible. If the embryo is sacred because it is a biological individual, it doesn't matter that it won't develop into a person under the circumstances. And if the embryo is sacred because it has the potential to become a person, the possibility of twinning is irrelevant. This means that a policy that combines the two restrictions may have no coherent moral justification.

Persons have interests; embryos don't

We've now reached the last stage in a continuum of views about the embryo. It's not the embryo itself that has special moral standing — it's the creature the human embryo will normally become — a person. Beings have rights, and others have obligations toward them, only when those beings have interests that can be promoted or thwarted. This requires at least the capacity for sentience, and with it the capacity for pleasure and pain. And so, even a fetus may not have any interests to be protected until sometime early in the 3rd trimester, so people will argue, when its brain has developed enough to support at least some level of consciousness. And, pushing this view even farther, a being may not have a personal interest in remaining alive unless it has the capacity to understand itself as a creature with a future; unless, that is, it is *self*-conscious. So not even fetuses, let alone embryos, have a right to life. (See Tooley for the classic defense of this perspective.)

This view would appear to give us a free hand to do whatever we want with embryos, since they have no interests or rights to be protected, and we have no obligations to them. But even people who hold this position about the moral standing of the embryo often think there should be some limits on how they are used.

The embryo is at least owed "respect."

Even if we think that the embryo has no intrinsic moral claims of its own, we might still believe some ways of using it might be wrong. This is sometimes expressed in terms of the "respect" we owe to it, by virtue of its being a potent symbol of human life.

A possible analogy here is with our treatment of dead bodies. We may think the dead no longer have interests of their own that require our protection, but we still think their bodies are owed respectful treatment.

And so, with embryos, we may think it disrespectful to use them for trivial purposes — to develop a new stem-cell based Olay rejuvenating cream, perhaps. Or, we might think it is disrespectful to *create* embryos specifically for the utilitarian purpose of using them for research or therapy, since this symbolically threatens to undermine the prohibition against sacrificing human beings for the sake of others. And we may think it's more respectful of embryos left over from IVF treatment to use them for research than to simple destroy them. (Manninen)

The philosophical problem here is in determining just what the parameters are of "respect" for embryonic life. We have a well-developed tradition that tells us how to treat the dead (and I should note that these standards are very culturally relative). We don't have any such tradition with regard to embryos, and so we may find ourselves making it up as we go along.

Induced Pluripotent Stem Cells to the Rescue?

A method for *creating* pluripotent stem cells has for many people seemed to offer a way to escape all these ethical complexities in harvesting stem cells from embryos. Induced pluripotent stem cells (iPSC) are created from a fully differentiated somatic (body) cell by using various techniques to reprogram its DNA to a pluripotent state. This is an area of research that is making rapid progress, both in demonstrating the potency of iPSC's, and

in eliminating the risks of cancer and other mutations created by some techniques used in their production.

If iPSC's prove as safe and effective as ESC's, then many people think that stem cell research and therapy can simply set aside debates about the beginnings of human life. But that may be too quick a conclusion.

As mentioned earlier, we know that with SCNT we can create a new individual by implanting the nucleus from a somatic cell into an enucleated egg, which will then reprogram the somatic cell nucleus so that the resulting organism will develop into an embryo, and into a mature individual. That is how Dolly, the first mammalian clone, was created. This process is much more efficient using stem cells, whether ESC's or iPSC's. We also know that as stem cells proliferate, they will clump into embryo-like ("embryoid") masses; indeed, this is one indicator of the potency of a stem-cell line. Recent research has discovered factors present in stem-cell embryoids which support the development of different tissue layers, and which are also vital to normal embryonic development. (Baker) No such embryoids have developed into fully functional embryos. But since the human genome contains the instructions for the creation of human embryos, it may be possible in the future to create embryos from stem cells derived from somatic cells.

This research, and the possibilities it suggests, raises an interesting question. When an individual develops from an embryo that was itself created using SCNT or directly from a stem cell line, when did that individual begin? As an embryo? Or earlier than that? The individual's genetic identity, after all, predates the embryo, and traces all the way back

to the original somatic or stem cell from which the embryo was created.

And once we understand how to initiate and maintain the process of embryo creation, what should we say about the potentiality of somatic or stem cells?

Would it be the same sort of potential as an embryo has? One might say that an stem cell or somatic cell has the potential to become a person only if it is manipulated in certain ways and placed into the right environment, while an embryo has an inherent potential to become a person. But as we saw earlier in the discussion of potentiality, one might respond that the embryo's actual potential also depends on being placed in the environment of a uterus, and in the case of IVF embryos, being placed in the liquid nitrogen that preserves their potential.

So is there a clear ontological distinction between the potentiality of the stem cell and the potentiality of the embryo? And even if there is, is it a significant *ethical* boundary? The iPS cell may have a different kind of potential, one might say, but it is still a potential to become a person. Why should that potential, even if different than the embryo's, have no ethical significance whatsoever?

If the potentiality of the stem cell and the potentiality of the embryo are indeed similar, then we will be faced with a choice. Either the embryo's potentiality gives it no moral standing because the stem cell has none; or even stem cells have special moral standing because the embryo does. (Sagan and Singer; George and Lee).

Stem Cells to the Bedside

If the goal of stem cell research is to develop treatments for human disease, then at some point we need to try these out in humans. These first in human trials raise a set of ethical concerns that are largely independent of the source of the stem cells.

As the last topic in my discussion, I will explore some of these, using Geron's safety trial of ESC-derived neural cells in patients who have recently become paraplegic from a spinal cord injury. (Geron) The implantation of such cells in rats subjected to a spinal cord injury produced significant (although not complete) return of the ability to walk and bear weight.

To start, I will draw attention to four features of this trial:

1. Subjects must have functionally complete spinal cord injury
2. They are enrolled only 7-14 days after their injury
3. The primary endpoint is safety: (what sort of undesirable side effects occur?), but
4. Some measures will be taken to detect any indications off improvement

As a Phase 1 trial, the Geron study raises a problem inherent in such trials.

The Geron study is primarily designed to determine how safe it is to inject stem-cell derived products into human beings. Because this has never been done before, the nature and likelihood of the possible risks is

not very well understood. This is a level of uncertainty significantly greater than other contexts where we have more experience with a class of agents, such as cancer chemotherapies. And we know that certain risks are possible. These include graft vs. host disease when the derived cells are genetically different than the patients; the risk of teratomas or other cancers, especially if undifferentiated cells are contaminating the implant; the uncertain effects if the transplanted tissue migrates to other locations; and perhaps others. When considering the range of possible risks of stem-cell derived implants, one has to recognize that implants, unlike most other therapies, remain in the body indefinitely, and so the time period in which a risk might manifest itself is indefinitely long.

But while the trial is primarily looking for harmful effects, the patients who will enroll in the trial will be primarily motivated by hope of benefit. They have just suffered a devastating injury, resulting in a radical loss of abilities they had taken for granted, and upon which their previous lives had been built. They will understandably be desperate for a cure at this stage in their injury — we know that people with paralyzing spinal injuries are much more willing to undertake risky research or treatment soon after their injury than they are later. (Illes) This is because with time, they learn to adjust to their new condition and lead lives they find satisfying. At that stage they are less inclined to take risks that might make them worse off than they are.

So these newly-injured patients are highly motivated to overlook the risks, and exaggerate the likely benefits, no matter what they are told in the consent form. Is their consent, then, truly informed? Or is it instead the product of a "therapeutic misconception" that impairs their ability to make a decision that is truly in their best interests and serves their goals?

This problem arises in many other types of Phase 1 trials, and with cancer chemotherapy trials drawing a great deal of commentary. But there is reason to be especially concerned about the power of the therapeutic misconception in stem cell research.

The stem cell superhero

Their vulnerability to the therapeutic misconception is fed by media stories that laud the hypothetical benefits of stem cell therapy while ignoring the possible risks. The understanding of risk and benefit communicated in informed consent forms, and the understanding the patient brings with her from the broader cultural and political discourse are often two different things. The broader discourse speaks in images and metaphors, not facts and theories; its "logic" is associational and allusive, not inferential or evidence-driven, and is therefore both more subtle and more powerful.

Stem cells have tremendous metaphorical value, having been portrayed as a kind of medical "superhero." (Burns). They harness primordial life forces. Stem cells are the very root of life itself. They offer the ultimate natural cure, not the artificial ingredients and poisons that ordinary medicine injects into us. Stem cells can reanimate the body — a holy power, like Jesus raising Lazarus from the dead. And they can replace worn-out parts at will. Fixing a damaged liver is as simple as replacing a dented fender — a seductively simple and easy to understand model of disease and its treatment.

Stem cells, then, have a metaphorical power possessed by few other treatment methods, and this power is almost sure to influence decisions by

patients to enroll in trials of stem cell therapy.

Are we left with the conclusion that the welfare of vulnerable, desperate patients is being sacrificed for the good of medical advances that may help future patients? At least in the case of this trial, I think not. We can avoid, or at least soften, this stark conclusion by designing a trial that minimizes risk, while maximizing the chances of benefit. If we can do that, the patient may still have a therapeutic hope, but will have less of a therapeutic *misconception*.

I think this is what Geron has done, in two ways.

First, they are enrolling early stage spinal injury patients, rather than patients with long-standing injuries. At first glance, this looks like a poor strategy for combating the therapeutic misconception. We know that late-stage patients are more skeptical about any possible benefit, and more concerned about the risks of being left worse off (Illes) — so aren't they *less* subject to the therapeutic misconception?

These late-stage patients are right to think that the chances of producing re-growth or new growth in a long-standing injury are probably much lower. But the risks to these patients will probably be *the same* as the risks for the early-stage patients who are more recently injured. This is a reason to recruit early-stage patients instead. The risks to them are probably the same, but the chances of any benefit are probably greater. And so the risk-benefit ratio is better in general for early-stage patients than it would be for late-stage patients.

Second , Geron is recruiting patients with complete spinal cord

injury. There is an important prognostic difference between complete and incomplete spinal cord injury. Patients with incomplete injury are more likely to see at least some spontaneous recovery of function in the first weeks or months after injury. This difference has both a scientific and an ethical implication.

The scientific implication is that it would be much more difficult to reliably detect any improvement of function in patients with incomplete injuries that was due to the stem cells, since it would be much more likely that such improvement was spontaneous, rather than due to the transplant.

The ethical implication is that the risk-benefit ratio for patients with incomplete injuries would be worse, because the benefit from the transplant would be lower. For both kinds of patients, the net benefit gained from the implant is the difference between the level of function they would have had without the implant, and the level of function they have with it. That difference is in general smaller for patients with an incomplete injury, because in general the level of function they would have without the implant is higher.

Since they are subject to the same risks as those with complete injuries, but stand to benefit less, patients with incomplete spinal cord injuries should not be included in this Phase 1 trial.

In its design of this trial, Geron has mitigated the ethical risks of the therapeutic hope these patients will undoubtedly bring with them, by selecting a group of patients who have the best chance of benefit from their participation.

Conclusion

Embryonic stem cells have been the major source of ethical controversy regarding stem cell research. There is no definitive resolution of debates regarding the moral standing of the embryo, and key features of current policy regarding stem cell research may be ethically incompatible. Although the development of iPSC's has been welcomed by many as an escape from debates about the embryo, it may open up equally difficult questions about the moral status of stem cells themselves, however derived.

The almost mythological image of stem cells raises special challenges for the ethical conduct of the first human trials, and the risks that desperate patients will exaggerate the chances of any therapeutic benefit. The ethical significance of that risk, however, can be reduced by designing trials that enroll patients with the best chance of a favorable risk-benefit balance from their participation.

There are other difficult questions raised by stem cell research that I don't discuss in this paper. One concerns the fact that any research or therapeutic program that relies on somatic cell nuclear transfer (SCNT) needs a supply of human eggs. How will that need be met, so that the women who are egg donors are fairly compensated, while avoiding the exploitation of poor women? (Baylis and McLeod). Another problem is raised by the desperate hopes of patients who look to clinics offering unproven "stem cell" treatments. How should such clinics be regulated, to both protect vulnerable patients from fraudulent, expensive, and potentially dangerous "treatment," while allowing for responsible clinical innovation that may uncover unexpected avenues for research that

leading to proven therapies? (Lindvall)

These and other issues will keep stem cell research at the center of moral controversy for some time to come.

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