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Implications of Policy Decisions on Human Embryonic Stem Cell Research in the United States

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Ethical issues linked to the production of human embryonic stem cells solely for research purposes pose a challenge to policy makers. A significant fraction of the general public is strongly opposed to any research involving human embryonic stem cells despite its numerous potential applications. Policy makers therefore must weigh the potential life-saving benefit of this research for the patient versus public concerns and reservations. This research paper analyzes the scientific background to provide a solid basis for policy recommendations on stem cell research. After describing the current status of funding and regulation of human embryonic stem cell research, recommendations are proposed to establish a persuasive regulatory framework.

Introduction

Although research with human embryonic stem cells was recognized by the journal "Science" in 1999 as one of the most promising fields in science (Bloom, 1999), the issue of public funding remains very controversial in science policy.

Because federal law prohibits the use of public funding for any research that harms a human embryo, research projects in this area are so far exclusively conducted by the private sector. Recently, promising scientific results have been achieved in this field, and applications in tissue engineering and transplantation are now clearly envisioned. These techniques could have a major impact on the treatment of a variety of diseases (see below) which are still incurable.

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Although a number of very insightful experiments can be conducted with mammalian embryonic stem cells, clinical research will ultimately require the use of human embryonic stem cells. However, ethical issues linked to the production of human embryonic stem cells solely for research purposes pose a challenge to policy makers. A significant fraction of the general public is strongly opposed to any research involving human embryonic stem cells despite its numerous potential applications. Policy makers therefore must weigh the potential life-saving benefit of this research for the patient versus public concerns and reservations.

In order to balance the advancement of science in this field with ethical concerns, the National Institutes of Health (NIH) recently revised their funding guidelines. According to the new guidelines issued on August 23, 2000, federal funding is now available for fetal stem cell research and derivation of these cells. Derivation of embryonic stem cells is still not federally funded, and research with embryonic stem cells is only funded if these cells were derived in compliance with the NIH guidelines (Vogel, Science *289* (2000), 1442-1443).

This research paper analyzes the scientific background to provide a solid basis for policy recommendations on stem cell research. After describing the current status of funding and regulation of human embryonic stem cell research, recommendations are proposed to establish a persuasive regulatory framework.

Scientific Background

Recent scientific advances regarding the isolation and successful culturing of human pluripotent stem cell lines have generated great excitement and promise major benefits for public health. Scientific studies have demonstrated that embryonic stem cells can be made to differentiate into any specific cell type, ultimately allowing the generation of tissue that can be used for transplantation therapy without causing any adverse immunological reaction. Such research could also contribute to the understanding of complex events that occur during human development, facilitating gene discovery and drug development.

Although recent experimental success has raised expectations for the clinical potential of human stem cells, most experts believe that health care benefits will not be realized before several years of research. They are concerned that during this time the credibility of the field could be damaged by over-optimism and suggest restraint in the claims made about the potential of stem cell research.

In order to provide a solid background for political decision-makers,

scientific terms must first be explained and clarified. There are essentially three different types of stem cells that are currently employed in scientific research: embryonic stem cells, embryonic germ cells, and adult stem cells.

Embryonic stem cells can develop into any kind of tissue and are therefore termed totipotent. ***Embryonic germ cells*** are more specialized stem cells, which eventually give rise to the gonads of the embryo. Adult stem cells and embryonic germ cells occur in later stages of development. ***Adult stem cells***, such as blood stem cells, are found in human adults and can develop into more specialized cell types, such as red blood cells.

Both adult stem cells and embryonic germ cells are pluripotent, meaning that they can give rise to many but not all of the cell types necessary for fetal development. Thus, pluripotent cell types cannot develop into a fetus when placed into a woman's uterus (NIH: Stem Cells - a Primer, 2000).

To distinguish between a fetus and an embryo, an embryo in this context is defined as "the period from after the long axis appears until all major structures are represented. In humans, this is from about two weeks after fertilization to the end of the seventh or eighth week" (Harcourt Dictionary of Science). A fetus, on the other hand, is "a developing human offspring in the postembryonic period, from seven or eight weeks after fertilization to the time of birth" (Harcourt Dictionary of Science).

Recent success in the field of stem cell research has triggered the hope of eventually treating a number of diseases which so far are either incurable or are curable only in conjunction with organ transplantation and its attendant and significant disadvantages. Apart from the scarcity of organ donations, a transplant patient must endure a life-long suppression of the immune system to avoid graft-host reactions. Advances in stem cell research could pose a solution to a number of cell types can be developed from undifferentiated stem cells. With tissue derived from these cells a number of diseases might eventually be cured without fear of graft-host reaction because the transplanted tissues would be immunologically identical to the patient's own cells.

Table 1

Possible Uses of Tissue Derived from Stem Cells to Treat Diseases

Cell type	*Target disease*
Neural (nerve) cells	Stroke, Parkinson's disease, Alzheimer's disease, spinal cord injury, multiple sclerosis
Heart muscle cells	Heart attacks, congestive heart failure
Insulin-producing cells	Diabetes
Cartilage cells	Osteoarthritis
Blood cells	Cancer, immunodeficiencies, inherited blood diseases, leukemia
Liver cells	Hepatitis, cirrhosis
Skin cells	Burns, wound healing
Bone cells	Osteoporosis
Retinal (eye) cells	Macular degeneration
Skeletal muscle cells	Muscular dystrophy

(source: Science 289 (2000))

While stem cells are necessary during early human development, pluripotent stem cells are found in children and adults. However, in the process of development and maturation, the potential of pluripotent stem cells to differentiate into other cell types decreases substantially.

A number of critics of embryonic stem cell research favor the use of cells in later stages of human development, such as embryonic germ cells or adult stem cells, mostly for ethical reasons. However, stem cells from adults may not have the same capacity to proliferate as younger cells. Additionally, adult stem cells do not exist in all tissues of the body, are often present in small quantities, are difficult to isolate and purify, and their numbers may decrease further with age. In addition, adult stem cells may contain more DNA abnormalities than embryonic stem cells, caused by long term exposure to sunlight and toxins as well as by errors made during DNA replication over the lifetime of the cell. Adult stem cells could also be disadvantaged compared to embryonic stem cells with respect to their shortened telomeres (the ends of chromosomes). These phenomena might trigger undesirable responses such as apoptosis (programmed cell death), which would undermine the potential utility of adult stem cells in research and medical treatment.

Research on the early stages of cell specialization may also not be possible with adult stem cells since they appear to be farther along the

developmental pathway than pluripotent stem cells. In order to determine the best source of specialized cells and body tissues for new treatments and even cures, it will be important to study the developmental potential of adult stem cells and compare it to that of pluripotent stem cells (Aldhous, 2000).

Embryonic germ cells, on the other hand, are obtained from fetal tissue after miscarriage or abortion, and thus their use carries a less heavy ethical burden than the use of embryonic stem cells. But although embryonic germ cells have some potential to develop into different types of tissue, these cells have caused abnormalities when introduced into embryos (McLaren, 2000). In addition, scientists have not been able to culture these stem cells for more than 21 days, a fact that clearly limits their use in scientific research.

It is crucial that relevant distinctions between the different cell types are made clear to both the public and to political decision makers in order to increase awareness of possible consequences for stem cell research and its future applications.

The NIH Guidelines

In compliance with federal law, the newly revised NIH guidelines state that NIH-funded scientists can work with pluripotent stem cells but with certain restrictions. The cell lines used in this research must be derived by private companies from frozen embryos discarded after fertility treatment. The donors of the embryos must have expressed informed consent and cannot accept any compensation. The NIH guidelines also seek to ensure that embryos are not created specifically for this purpose and that embryonic stem cells are not combined with animal cells. In addition, any attempts to use stem cells for reproductive cloning and the creation of human embryos are prohibited. The NIH guidelines therefore do not allow public funding to be utilized for any of the aforementioned purposes (Vogel, Science *289* (2000), 1442).

The following table summarizes the most important characteristics of the NIH guidelines for funding research with embryonic stem cells:

Table 2

NIH Guidelines for Research on Embryonic Stem Cells

Deriving new cell lines from embryo	Prohibited
Research on privately derived cell lines from embryos	Allowed
Deriving new cell lines from fetal tissue	Allowed
Research on cell lines from fetal tissue	Allowed
Research that would use stem cells to create a human embryo	Prohibited
Combining human stem cells with animal embryos	Prohibited
Use of stem cells for reproductive cloning	Prohibited
Research on stem cells derived from embryos created for research purposes	Prohibited

(source: Science *286* (1999), p. 2050)

In assessing these guidelines, a number of points are worth considering. First, it is possible that the creation of research embryos will be the only means by which to conduct certain kinds of research, for example, on the process of human fertilization.

Second, as in vitro fertilization techniques improve, it is likely that the supply of embryos for research from this source will decline. Nevertheless, the NIH has concluded that, from a scientific and an ethical perspective, there is no compelling reason at this time to provide federal funding for the creation of embryos for research. According to the NIH, there is an adequate supply of cadaveric fetal tissue and embryos remaining after infertility treatment for federal research projects. Currently, the derivation of human embryonic stem cells is only permitted in privately funded laboratories. Once a cell line is obtained, the stem cells could be passed on to federally funded scientists. Researchers on federal grants are, however, concerned that privately funded scientists will gain important insights and advantages through derivation and experimental manipulation of stem cells. NIH-funded researchers will be limited to the cell lines provided by private firms and will not be able to create and tailor cell lines to meet their specific needs.

Most scientists and their supporters do not view the derivation and use of embryonic stem cells as ethically distinct activities. They emphasize the close connection in practical and ethical terms between both derivation and use of embryonic stem cells and believe that it is important that federal funding be made available for protocols to derive such cells. Researchers using human embryonic stem cell lines hope to obtain substantial scientific benefits from a detailed understanding of the process of embryonic

stem cell derivation and argue that the methods of derivation may affect the properties of the embryonic stem cells.

Reliance on the distinction made between the use and derivation of embryonic stem cell lines leaves the future of the research uncertain, subject to the influence of politics and the courts. Senator Arlen Specter (R-Penn.) proposed a bill to allow funding for the use and derivation of embryonic stem cells which would end this ambiguity (Nature *406* (2000); Kennedy 2000), but the Senate rejected it (Science *290* (2000)). Specter said that he would reintroduce the bill in the new Congress, but his influence in promoting federal funding for stem cell research might be diminished since he is resigning from his position as chairman of the appropriations panel overseeing the NIH budget (Davis 2000).

Oversight and Review of Human Stem Cell Research

To ensure that the research involving stem cells is delivering the anticipated benefits and to identify any concerns which may arise, federal oversight at the local, national and institutional level is crucial to assure the public that this research is being conducted in a controlled and legal manner.

When applying for NIH funding, scientists must therefore submit their research proposals to four separate review bodies. In addition, the newly founded Human Pluripotent Stem Cell Review Group (HPSCRG) will ensure compliance with the NIH guidelines. Despite the promise of the NIH to review proposals quickly, this cumbersome process might however impose bureaucratic hurdles and delay research (Davis, 2000).

Another problem could arise if the embryonic stem cell lines currently used in federally funded research are not approved for further research according to the new guidelines because the process of their derivation did not occur in compliance with the new guidelines. In such cases some research projects could be substantially impeded, and might therefore be deferred or abandoned altogether (Kennedy, 2000).

Anonymous donation of embryonic stem cells to ensure privacy and informed consent of the donor might also conflict with the requirement of the NIH guidelines to trace back and document the precise origins of the cells (Marshall, 1999).

Conflicting Opinions

The new NIH guidelines received support from scientific groups (e.g. the American Society for Cell Biology), patient advocacy groups (e.g. the

American Heart Association and the Juvenile Diabetes Foundation International), a number of Nobel laureates, and the Clinton administration.

On the other hand, a number of right-to-life activists and religious groups, the American Cancer Society (ACS), the Coalition of Americans for Research Ethics (CARE), and some legislators oppose the use of embryos in research despite its potential medical benefits. In addition, the Vatican issued a highly critical statement on the moral implications of stem cell research, and Pope John Paul II condemned human cloning and embryo experiments (Dickson and Smaglik, 2000). President George W. Bush has stated that his pro-life views would compel him to reinstate the ban on public funding for stem cell research, but, in reality, he might not be able to overlook corporate interests in this field.

The main concern of stem cell research opponents is that abortion might be encouraged by pressuring fertility patients to donate their embryos —violating the premise of informed consent—and that ultimately the human rights of the most vulnerable members of society, the disabled and aged, might be put at risk through new views regarding eugenics or euthanasia. Some even relate this research to the horrible experiments conducted in Nazi Germany and to cloning humans.

Abortion opponents state that funding stem cell research tacitly supports the derivation of stem cell lines and, as a consequence, the destruction of embryos. Pro-life activists also point out that the NIH guidelines do not clarify existing laws, but rather circumvent them. Indeed, federal law prohibits the NIH from funding work that harms a human embryo, but federal funds are still made available for the purchase of embryonic stem cell lines. Although these cell lines are derived by privately funded researchers, they are using procedures that result in the destruction of the embryo. However, considering that more than a million elective abortions are performed annually in the United States and that the embryos are normally discarded after such procedures, it seems unlikely that an abortion is encouraged solely to donate the embryo for research purposes. Accurate documentation of the source of embryonic stem cells will represent a task that cannot be completed satisfactorily because of patient confidentiality concerns; assurance of informed consent and privacy of the donor of these cells should be emphasized. At the same time, it must be made clear to the donor that acceptance of compensation of any sort or specification of the purpose of the donation is impossible. Opponents of abortion could also still favor stem cell research since there exist a number of methods to derive stem cells without harming an embryo (Robertson, 1999).

Most of the conflicting opinions in this area arise between scientists and their supporters who value ethical concerns and the protection of embryos more highly than scientific advances and potential medical treatments. Using a similar strategy as the NIH, opponents of stem cell research simply terminate their contributions or do not make any donations that might be used in the field of embryonic stem cell research. The American Cancer Society (ACS), for instance, which raises $500 million annually, has left the Patients Coalition for Urgent Research (pCURE) because it is lobbying Congress to support stem cell research. The ACS, on the other hand, came to this decision through pressure from officials of the Catholic church, given the withdrawal of some 100 lay Catholics from a breast-cancer fund-raising event (Wadman 1999).

Ethical Considerations

Recent developments in human stem cell research have raised hopes for groundbreaking new clinical therapies, but deep moral concerns are related to research involving human embryos. Opinions vary widely about whether the potential benefits outweigh the ethical costs of this research. Very few disagree with the view that the human embryo deserves respect as a form of human life, but there is considerable disagreement about the form of such respect and the level of protection of human life at different stages of development.

For those who believe that the embryo has the moral status of a person from the moment of conception, any activity that would destroy an embryo is unacceptable. At the other end of the spectrum, some argue that an embryo does not deserve any particular moral consideration. The NIH, however, argues that the respect due to the embryo increases as it develops but that this respect, in the early developmental stages in particular, may properly be weighed against the potential benefits arising from the discussed research.

Although public policy in a pluralistic society cannot resolve all differences that arise regarding controversial issues, due to the sensitivity of this issue, it is imperative to proceed cautiously and to further stimulate the important public debate about the profound ethical issues regarding this potentially beneficial research.

The International Perspective

The NIH is a major source of grants for scientific research not only in the United States but also for a number of laboratories abroad. The funding policy of the NIH therefore significantly influences the decision-making process in other countries.

Other scientifically advanced societies, however, might apply less stringent ethical guidelines, thus leaving federally supported U.S. scientists at a disadvantage compared to researchers in other countries (Nature *406* (2000); Kennedy, 2000; Dickson and Smaglik, 2000). Ethical guidelines and policy statements in other countries therefore also need to be considered carefully.

Japanese scientists are not allowed to work with human embryonic stem cells so far, but the Japanese Council for Science and Technology is currently discussing final guidelines for stem cell research.

An advisory board of the **European Union** recommended in November 2000 to fund all types of research involving stem cells, particularly adult stem cells. Work that created embryos solely for research purposes was discouraged, as "excess" embryos existed in fertility clinics and would otherwise be discarded (Vogel, Science *290* (2000), 1673).

In the **United Kingdom** - perhaps the most permissive country—the House of Commons recently passed a law that allowed cloning of embryos up to 14 days of embryonic development (Vogel, 2001; Süddeutsche Zeitung, 20 December 2000).

Despite the recommendations of the European Union, the **French** Government will soon submit a bioethics bill to the parliament that proposes to permit research with human embryonic stem cells and would not explicitly forbid therapeutic cloning of human embryos to create embryonic stem cells (Butler 2000).

Germany's embryo-protection law prohibits research that harms a human embryo and bans the production of human embryonic stem cells. Although legislation is unlikely to be revised in the near future, the law does not prohibit the import of already derived embryonic stem cells (Schiermeier, 2000).

Conclusion and Policy Recommendations

Recent advances in the area of stem cell research suggest substantial clinical benefits over existing treatments, as well as improvements of scientific knowledge in the field of embryonic development. In light of these encouraging results, achieved entirely by privately funded scientists, the NIH has revised its funding guidelines in order to permit publicly funded researchers to actively engage in this important and rapidly evolving field.

The NIH guidelines represent an unsatisfying compromise in an attempt to balance the support of stem cell research and ethical concerns of the general public. In addition, NIH guidelines fail to establish a clear ethical and regulatory framework for the private sector, whose research is

neither federally supervised nor publicly disclosed, thus applying different moral standards to privately and publicly funded research. Interestingly, the focus has been on governance of the federal funding process rather than on national regulation. But the current NIH guidelines and their funding policy significantly limit the potential of stem cell research, leaving this promising field without the full benefit of the entire American scientific community, much of which operates in institutions that are dependent upon federal sources of support.

The varying and conflicting views on stem cell research must be thoroughly considered by policy makers, since it is unlikely that the NIH guidelines can be liberalized without the consent of opponents. Given these conflicting values, it might only be politically feasible to relax the guidelines successively. A thorough but efficient oversight and review process should be established in order to assure the public that stem cell research is conducted in a controlled and scientifically valid manner and that ethical concerns are seriously addressed.

The current NIH guidelines fail to adequately provide a solution to the issue of public funding for embryonic stem cell research. The guidelines allow federal funds to be used for the actual stem cell research but not for the derivation of the cell lines. Researchers receiving federal funds will inevitably use federal grant money to order stem cell lines from private companies, which derive them, though the actual derivation is not allowed to be publicly funded.

Federally funded researchers should, however, be permitted to use public funding also for the derivation of embryonic stem cell lines. This will not only enable government-supported laboratories to adjust the properties of these cell lines to their own needs, but also allow them to conduct research to address basic scientific questions in the field of embryonic development.

To promote research in the both public and private sectors, either privately funded scientists should have to comply with the NIH guidelines or the guidelines should be made more permissive, so not to disadvantage publicly funded research. Adequate ethical caution should always be emphasized over economic interests, however.

In order to eventually achieve clinical benefits and important scientific insights, experimentation with embryonic stem cells, embryonic germ cells and adult stem cells must all be permitted for scientists utilizing public funding.

Although it is difficult to exert ethical control over a science that is progressing very rapidly, it is crucial that sufficient respect be attributed toward human life, even in light of potential medical benefits of stem cell

research. When considering the ethical implications of stem cell research, it is important to note that a number of methods exists that allow the derivation of embryonic stem cells that do not harm an embryo, and that such derivation and use of stem cells cannot be separated in either practical or ethical terms.

Society must define clear boundaries in order to provide scientists with appropriate expectations and requirements when conducting stem cell research. The transfer of an embryo created by cell nuclear replacement into the uterus of a woman (so called "reproductive cloning"), mixing of live animal and human embryonic stem cells, or the creation of an embryo solely for research purposes should continue to be prohibited by the NIH as long as this research is considered unacceptable by the public. The guidelines, however, should be revisited as soon as scientific advances, possible new applications, and public opinion suggest any regulation changes.

It is also important to closely observe the policy decisions regarding stem cell research made by other countries. Ultimately, however, the United States must be aware of its leading role in this field. American decision makers must consider their influence on the science policy in other countries, but must also stake out an independent position in research policy that is tailored to meet its specific concerns.

Although the aforementioned recommendations aim to modify the NIH guidelines governing publicly funded stem cell research, such changes may not be immediately feasible given the current political situation. President George W. Bush will have a significant influence on whether public funding of stem cell research will be continued. He has issued a statement criticizing the new guidelines, although corporate interests will most likely prevent him from banning federally funded stem cell research altogether. The new Bush administration could reject the current distinction that the NIH makes between use and production of embryonic stem cells, or it might require a change in the guidelines at the administrative level. It is therefore not at all certain that the newly issued guidelines will remain unchanged in the near future (Kennedy, 2000; Davis, 2000; Aldhous, 2000).

In light of the unique scientific and medical opportunities of stem cell research, the current NIH guidelines present an inadequate framework to support progress in this field. In order to equally enable publicly and privately funded scientists to contribute to the full potential of this promising research, the NIH should revise its guidelines and make federal funding also available for the derivation of stem cell lines. The guidelines

should however ensure a public review and oversight process in order to balance the promotion of responsible scientific advancement with ethical concerns and to encourage a continuous interdisciplinary discussion.

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