34 Stem Cell Research and Applications: Monitoring the Frontiers of Biomedical Research

Audrey R. Chapman, Mark S. Frankel and Michele S. Garfinkel

In the face of extraordinary advances in the prevention, diagnosis, and treatment of human diseases, devastating illnesses such as heart disease, diabetes, cancer, and diseases of the nervous system, such as Parkinson's Disease and Alzheimer's Disease, continue to deprive people of health, independence, and well-being. Research in human developmental biology has led to the discovery of human stem cells (precursor cells that can give rise to multiple tissue types), including embryonic stem (ES) cells, embryonic germ (EG) cells, and adult stem cells. Recently, techniques have been developed for the in vitro culture of stem cells, providing unprecedented opportunities for studying and understanding human embryology. As a result, scientists can now carry out experiments aimed at determining the mechanisms underlying the conversion of a single, undifferentiated cell, the fertilized egg, into the different cells comprising the organs and tissues of the human body. Although it is impossible to predict the outcomes, scientists and the public will gain immense new knowledge in the biology of human development that will likely hold remarkable potential for therapies and cures.

Audrey R. Chapman is the program director for the Science and Human Rights Program at the American Association for the Advancement of Science. Mark S. Frankel is the program director and Michele S. Garfinkel is a program assistant with the Scientific Freedom, Responsibility, and Law Program at the American Association for the Advancement of Science. *Excerpted from* Stem Cell Research and Applications: Monitoring the Frontiers of Biomedical Research, *Preface and pp. v–xvi. American Association for the Advancement of Science and Institute for Civil Society: Washington, DC, November 1999.*

Derivation of ES cells from early human embryos, and EG and fetal stem cells from aborted, fetal tissues raise ethical, legal, religious, and policy questions. Further, the potential uses of stem cells for generating human tissues and, perhaps, organs, is a subject of ongoing public debate.

Taking all the above matters into account, the American Association for the Advancement of Science (AAAS) and the Institute for Civil Society (ICS) decided to undertake a study in order to propose recommendations for conducting stem cell research. To do so, we assembled a working group with broad expertise and diverse views to advise us and to assist with preparing a report. This study and the recommendations flowing from it were informed by the values of the members of this advisory group, the discussions that took place during a public meeting hosted by AAAS and ICS on August 25, 1999, as well as reports and recommendations of other groups in the United States and elsewhere that have reflected on the issues involved. These values include belief in the promotion of patient welfare and the social good, scientific freedom and responsibility, self-determination, encouragement of civic discourse, public accountability of scientists and research institutions, and respect for diverse religious, philosophical, and secular belief systems.

Scientists do not presume to know all the answers and ramifications of basic research in human stem cells. Many groups have recognized that there are varied social, political, ethical, and religious viewpoints to be considered in discussions about the scientific use of tissue from human embryos and fetuses. In September of 1999, after many months of public meetings, the National Bioethics Advisory Commission released a report entitled "Ethical Issues in Stem Cell Research." On 1 December 1999, the National Institutes of Health issued draft guidelines for research using human pluripotent stem cells and will receive public comment until 31 January 2000. The continuation of this dialogue among all segments of society concerning the implications of stem cell research is of utmost importance, and AAAS and ICS remain committed to fostering an ongoing educational process that informs such public dialogue.

Findings and Recommendations

- Human stem cell research holds enormous potential for contributing to our understanding of fundamental human biology. Although it is not possible to predict the outcomes from basic research, such studies will offer the real possibility for treatments and

ultimately for cures for many diseases for which adequate therapies do not exist.

The benefits to individuals and to society gained by the introduction of new drugs or medical technologies are difficult to estimate. The introductions of antibiotics and vaccines, for example, have dramatically increased life spans and improved the health of people all over the world. Despite these and other advances in the prevention and treatment of human diseases, devastating illnesses such as heart disease, diabetes, cancer, and diseases of the nervous system such as Alzheimer's disease present continuing challenges to the health and well-being of people everywhere. The science leading to the development of techniques for culturing human stem cells could lead to unprecedented treatments and even cures for these and other diseases.

As with all research, our ability even to contemplate the possibilities offered by stem cell-derived therapies is a result of many years of research. The science of stem cells dates to the mid-1960s, and many papers have been published on the isolation and laboratory manipulation of stem cells from animal models. While these models are imperfect, they are accepted in the scientific community as good initial predictors of what occurs in human beings.

There already exists evidence from animal studies that stem cells can be made to differentiate into cells of choice, and that these cells will act properly in their transplanted environment. In human beings, transplants of hematopoietic stem cells (the cells which eventually produce blood) following treatments for cancer, for example, have been done for years now. Further, somewhat cruder experiments (e.g., the transplantation of fetal tissue into the brains of Parkinson's patients) indicate that the expectation that stem cell therapies could provide robust treatments for many human diseases is a reasonable one. It is only through controlled scientific research that the true promise will be understood.

- This research raises ethical and policy concerns, but these are not unique to stem cell research.

Innovative research and new technologies derived from such research almost always raise ethical and policy concerns. In biomedical research, these issues include the ethical conduct of basic and clinical research as well as the equitable distribution of new therapies. These issues are relevant to discussions about stem cell research and its eventual applications; however, they are part of a constellation of ethical and policy concerns associated with all advances in biomedical research. Guide-

lines or policies for the use of human biological materials have been issued at many levels, from internal review boards to the National Bioethics Advisory Commission, which recently released a detailed report on the use of such materials. Existing policies cover all aspects of research, from the use of cell lines in laboratories, to human subjects protections, that will surface in the consideration of stem cell research.

- It is essential that there be a public that is educated and informed about the ethical and policy issues raised by stem cell research and its applications. Informed public discussion of these issues should be based on an understanding of the science associated with stem cell research, and it should involve a broad cross-section of society.

It is essential for citizens to participate in a full and informed manner in public policy deliberations about the development and application of new technologies that are likely to have significant social impact. The understanding of the science is particularly important for discussing ethical and policy issues. Ideally, scientists should communicate the results of their research in ways that will be readily understandable to a diverse audience, and participate in public discussions related to stem cell research.

The ethical and policy issues raised by stem cell research are not unique, but this research has received a significant amount of public attention and there is much to gain by open reflection on the implications of this sensitive area of research. Congressional hearings, public meetings by government agencies, and media coverage have pushed stem cell research issues into a spotlight. There should be continued support for the open manner that has allowed all those interested to observe or participate in these processes and for a sustained dialogue among scientists, policy makers, ethicists, theologians, and the public to consider issues that emerge with the advancement of stem cell research.

- Existing federal regulatory and professional control mechanisms, combined with informed public dialogue, provide a sufficient framework for oversight of human stem cell research.

The appearance of new technology can evoke apprehension and engender uncertainty among segments of the population about its uses. Where these concerns are related to issues having important ethical and social implications, certain levels of oversight are appropriate. But it is important to create new oversight mechanisms or regulatory burdens only when there are compelling reasons for doing so.

Federal funding would automatically trigger a set of oversight mechanisms now in place to ensure that the conduct of biomedical research is consistent with broad social values and legal requirements. While basic laboratory research with personally non-identifiable stem cells does not pose special ethical or oversight challenges, an elaborate system of review is in place for research involving human subjects, ranging from procurement issues to the conduct of clinical trials. The Federal Common Rule governing human subjects research provides for local and federal agency review of research proposals in such circumstances, weighing risks against benefits and requiring involved and voluntary consent. The Food and Drug Administration (FDA) has the authority to regulate the development and use of human stem cells that will be used as biological products, drugs, or medical devices to diagnose, treat or cure a disease or underlying condition. Further, states should adopt the Federal Government's Model Program for the Certification of Embryo Laboratories.

Complementing these regulatory mechanisms are the National Bioethics Advisory Commission (NBAC), which has demonstrated its legitimate claim to respect for its efforts as a national body to promote public input into social policy related to advances in biomedical research, and the Recombinant DNA Advisory Committee (RAC), which currently has a mandate to review the ethical and policy issues associated with gene therapy and could be authorized to change its mission to broaden its purview. These federal bodies should work with interested stakeholders in the conduct of stem cell research—professional organizations, patient disease groups, religious communities, the Congress, funding agencies and private foundations, industry, and others—so that the public can be assured that appropriate safeguards are in place as this research evolves.

Thus, at the present time, no new regulatory mechanisms are needed to ensure responsible social and professional control of stem cell research in the United States.

- Federal funding for stem cell research is necessary in order to promote investment in this promising line of research, to encourage sound public policy, and to foster public confidence in the conduct of such research.

Realizing the potential health benefits of stem cell technology will require a large and sustained investment in research. The federal government is the only realistic source for such an infusion of funds. For

those who are challenged daily by serious diseases that could in the future be relieved by therapies gained through stem cell research, public funding holds the greatest promise for sooner rather than later research results that can be transferred from the bench to the bedside. Without the stimulus of public funding, new treatments could be substantially delayed.

The commitment of federal funds also offers a basis for public review, approval, and monitoring through well established oversight mechanisms that will promote the public's interest in ensuring that stem cell research is conducted in a way that is both scientifically rigorous and ethically proper. Additionally, public funding contributes to sound social policy by increasing the probability that the results of stem cell research will reflect broad social priorities that are unlikely to be considered if the research is carried out in the private sector alone.

There are segments of American society that disagree on moral grounds with using public monies to support certain types of stem cell research. However, public policy in a pluralistic society cannot resolve all the differences that arise in national debates on sensitive social issues. In the context of stem cell research, this leads to three practical conclusions. One is a willingness to permit individuals, whether they are researchers or embryo or fetal tissue donors, to act in conformity with their own moral views on these matters. A second is the commitment to public involvement in research support when this research is related to the promotion and protection of public health, including the acquisition of new molecular and cellular insights into basic human developmental biology. A third is respect for opposing views, especially those based on religious grounds, to the extent that this is consistent with the protection and promotion of public health and safety.

- Public and private research on human stem cells derived from all sources (embryonic, fetal, and adult) should be conducted in order to contribute to the rapidly advancing and changing scientific understanding of the potential of human stem cells from these various sources.

There are three primary sources of stem cells, each with different characteristics as to how many different developmental paths they can follow and how much they can contribute to our understanding of a functioning organism. Embryonic stem cells (ES cells), derived from a very early embryo, and embryonic germ cells (EG cells), collected from fetal tissue at a somewhat later stage of development, have particular

promise for a wide range of therapeutic applications because, according to our present knowledge, they are capable of giving rise to virtually any cell type. Research on these primordial cells will also provide a unique opportunity to study human cell biology.

Adult stem cells, obtained from mature tissues, differentiate into a narrower range of cell types. As a result, many cells of medical interest cannot currently be obtained from adult-derived stem cells. It is also less feasible to develop large-scale cultures from adult stem cells. However, it is important to note that, at this time, it is only adult human stem cells that are well-enough understood that they can be reliably differentiated into specific tissue types, and that have proceeded to clinical trials.

Because the study of human stem cells is at an early stage of development, it is difficult to predict outcomes and findings at this point in time. As more research takes place, the full developmental potential of different kinds of stem cells will become better understood.

In view of the moral concerns surrounding the uses of embryonic and fetal tissue voiced by a segment of the American population, strengthening federally and privately funded research into alternative sources and/or methods for the derivation of stem cells, including further initiatives on adult stem cells, should be encouraged. Human stem cell research can be conducted in a fully ethical manner, but it is true that the extraction of embryonic stem cells from the inner mass of blastocysts raises ethical questions for those who consider the intentional loss of embryonic life by intentional means to be morally wrong. Likewise, the derivation of embryonic germ cells from the gonadal tissue of aborted fetuses is problematic for those who oppose abortion. In contrast, adult stem cell research is more broadly acceptable to the American population.

- Public funding should be provided for embryonic stem cell and embryonic germ cell research, but not at this time for activities involved in the isolation of embryonic stem cells, about which there remains continuing debate. This approach will allow publicly-funded researchers to move more quickly toward discoveries that will lead to alleviating the suffering caused by human disease.

Although the derivation of human stem cells can be done in an ethical manner, there is enough objection to the process of deriving stem cells to consider recommending against its public funding. Further, for the foreseeable future there will be sufficient material isolated by researchers not using public funding that this exclusion will not have a negative impact on research.

There are many individuals who believe that any use of human embryos other than for achieving a pregnancy is unethical, believing that the embryo is a full human being from the earliest moments in the conception process. However, many religious traditions take a "developmental" view of personhood, believing that the early embryo or fetus only gradually becomes a full human being and thus may not be entitled to the same moral protections as it will later; others hold that while the embryo represents human life, that life may be taken for the sake of saving and preserving other lives in the future. The dialogue about these issues is ongoing in the United States, but these concerns need not exclude publicly-funded research activities on cell lines that have already been established.

- Embryonic stem cells should be obtained from embryos remaining from infertility procedures after the embryo's progenitors have made a decision that they do not wish to preserve them. This decision should be explicitly renewed prior to securing the progenitors' consent to use the embryos in ES cell research.

The most ethical source of human primordial stem cells is embryos produced for the process of in vitro fertilization whose progenitors have decided not to implant them and have given full and informed consent for the use of these embryos for research purposes. Two appropriate potential sources of donation are embryos with poor quality that makes them inappropriate for transfer and embryos remaining when couples have definitely completed their family and do not wish to donate the excess embryos to others.

Informed consent requires that the woman or couple, with substantial understanding and without controlling influences, authorize the use of their spare embryos for research purposes. Because assisted reproduction can be a stressful process, informed consent should be secured in two stages. The two-stage process would also maintain a separation between personnel working with the woman or couple who hope to get pregnant and personnel requesting embryos for stem cell research.

At the beginning of the process, personnel working with the woman or couple who hope to become pregnant should ascertain their preferences as to the future of embryos remaining after the assisted reproduction process. These options should include consent for embryo donation to another couple, consent for donation for research, and consent for destruction of the spare embryos. Once a couple has definitely decided that it has completed its family, then the couple should be approached

a second time to secure an explicit consent to use the embryos in ES cell research.

- Persons considering donating their excess embryos for research purposes should be afforded the highest standards of protection for the informed consent and voluntariness of their decision.

Securing embryos for the purpose of harvesting stem cells must proceed in a careful fashion for several reasons. These are to protect the interests of the gamete donors, to reassure the public that important boundaries are not being overstepped, to enable those who are ethically uncomfortable with elements of this research to participate to the greatest extent possible, and to ensure the highest quality of research and outcomes possible.

Consonant with good research practice, policies on the procurement of embryos should include at least the following points: (1) Women should not undergo extra cycles of ovulation and retrieval in order to produce more "spare" embryos in the hope that some of them might eventually be donated for research; (2) Analogous with our current practice for organ donation, there should be a solid "wall" between personnel working with the woman or couple who hope to get pregnant, and personnel requesting embryos for stem cell purposes; (3) Women and men, as individuals or as couples, should not be paid to produce embryos, nor should they receive reduced fees for their infertility procedures for doing so; and (4) Consent of both gamete donors should be obtained.

- Where appropriate, guidelines that can attract professional and public support for conducting stem cell research should be developed.

At present, stem cell research raises no unique ethical or policy issues. As research advances issues may emerge that challenge acceptable ethical practices and public policy. Hence, there should be opportunities for public reconsideration of the need for guidelines specifically targeted to human stem cell research. Such efforts should be informed by the most current scientific evidence and should occur through a process that encourages broad involvement by all sectors of society.

Almost two decades of experience with the Recombinant DNA Advisory Committee's (RAC) oversight of recombinant DNA research suggest that the RAC could be an effective institutional focal point within the federal government to facilitate the type of public dialogue on stem cell research proposed here, and to coordinate efforts to develop new

guidelines, where needed. The RAC has a proven track record of providing an open forum for sorting out complex ethical issues and of defusing conflict. Furthermore, it has acquired a degree of legitimacy among scientists in both the public and private sectors, with its widely accepted Points to Consider in the design and conduct of gene therapy.

- In order to allow persons who hold diverse moral positions on the status of the early embryo to participate in stem cell research to the greatest degree possible without compromising their principles, and also to foster sound science, stem cells (and stem cell lines) should be identified with respect to their original source.

Patients and researchers should be able to avoid participating in stem cell use if the cells were derived in a way that they would consider to be unethical. As a matter of good scientific practice, records are routinely maintained on the sources of biological materials. It is of utmost importance that documentation of the original source of the stem cells can be made readily available to researchers and to potential recipients of stem cell therapies.

- Special efforts should be made to promote equitable access to the benefits of stem cell research.

The therapeutic potential for treating and possibly curing many serious diseases constitutes a major rationale for large-scale investments of public and private resources in human stem cell research. To justify funding stem cell research on the basis of its potential benefits, particularly the use of public resources, however, requires some assurance that people in need will have access to the therapies as they become available.

Several factors make it unlikely that there will be equitable access to the benefits of this research. Unlike other western democracies, the United States does not have a commitment to universal health care. More than 44 million people lack health insurance and therefore do not have reliable access even to basic health care. Others are underinsured. Moreover, if stem cell research were to result in highly technological and expensive therapies, health insurers might be reluctant to fund such treatments.

Overcoming these hurdles and assuring equitable access to the benefits of stem cell research in this country will be a politically and financially challenging task. It is therefore appropriate to begin considering how to do so now in advance of the development of applications. The

federal government should consider ways to achieve equitable access to the benefits derived from stem cell research.

- Intellectual property regimes for stem cell research should set conditions that do not restrict basic research or encumber future product development.

The U.S. Patent and Trademark Office (PTO) has already stated that purified and isolated stem cell products and research tools meet the criteria for patentable subject matter. When research is funded by the private sector, as is currently the case with stem cell research, and is patented, it is a private matter whether and under what terms new intellectual property is obtainable for research purposes or development. This is of particular concern because the private sector will not invest resources in potential applications that they consider to lack commercial value, but that may have considerable therapeutic promise.

Given the promise of stem cell research, it is important to encourage the development of broadly beneficial therapeutic products with widespread access. This objective could be achieved in a variety of ways. Government investment in promising areas of research would enable federal agencies and laboratories to hold patents and to exercise them in ways that enhance development and contribute to the dissemination of this stem cell technology. Congress or the PTO should define a strong research exemption that would give third parties access to stem cell products and research tools for research purposes without having to obtain permission from the patent holder. Another possibility is to require compulsory licensing under limited and clearly defined circumstances.

- The formation of company-based, independent ethics advisory boards should be encouraged in the private sector.

Private sector research has played a crucial part in the advancement of research on stem cells. The leadership exhibited by the company that has sponsored all of the published human embryonic and germ cell research to date in establishing an external Ethics Advisory Board to develop guidelines for the ethical conduct of such research is laudable. While these private sector boards are not a substitute for public oversight and guidance, they can be a positive influence on the way that industry-funded stem cell research proceeds.

The credibility and impact of such ethics advisory boards will be enhanced if they review ethical issues at the start-up phase of the research, have multidisciplinary membership, including representatives from the

local community, give minimum, if any, financial compensation for service, and share their own findings and recommendations with other companies. The latter provision could be especially helpful in developing a "case law" in the private sphere that would inform public efforts to develop national guidelines.