Stem Cell Trials: Lessons from Gene Transfer Research

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Stem Cell Trials: *Lessons from Gene Transfer Research*

BY JONATHAN KIMMELMAN, FRANÇOISE BAYLIS, AND KATHLEEN CRANLEY GLASS

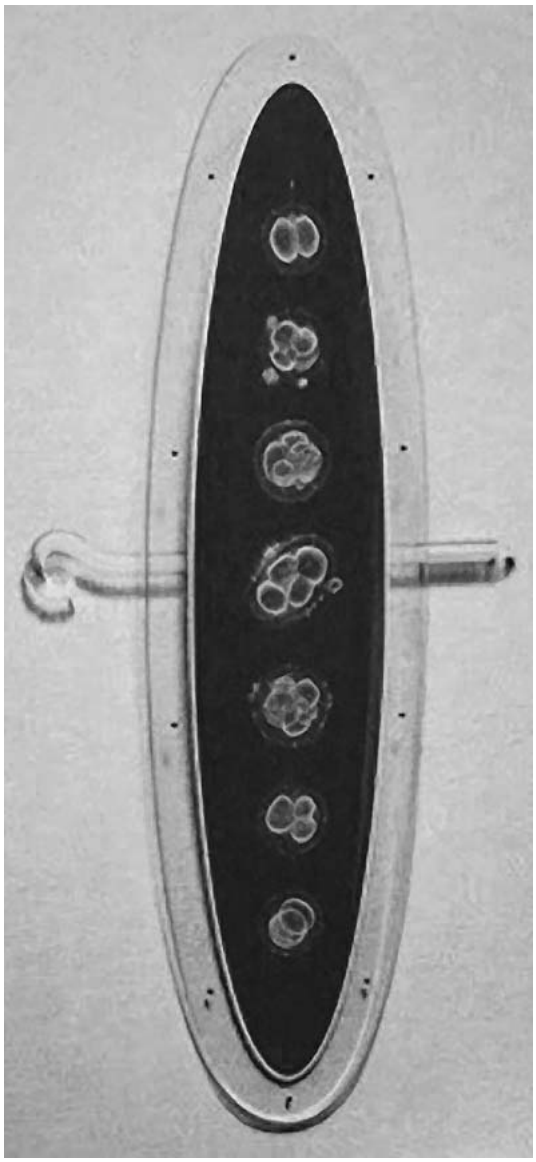
Since 1998, when James Thomson and John Gearhart reported the first successful derivation of human embryonic stem cells and human embryonic germ cells, respectively, the scientific community has championed the therapeutic potential of these cells. Indeed, despite the restrictions on embryo research in some jurisdictions and despite the recent controversy surrounding the validity of the stem cell research conducted by Woo Suk Hwang, stem cells may soon enter their first human trials—possibly within a year.

Stem cell transplantation will not be the first biotechnology to begin trials amid revolutionary expectations and moral apprehension. More than fifteen years ago, the first experiments with gene transfer in human somatic cells inspired similar hopes and fears. Gene transfer quickly evolved into a competitive research area, but its progress was checked by ethical missteps. With embryonic stem cells poised to begin human trials, now is an opportune time for scientists and ethicists to review some of gene transfer's ethical miscues.

Moving Too Quickly

From the first protocol involving humans, gene transfer was caught up in ethical controversy. In 1980, hematologist Martin Cline began gene transfer trials without prior approval from his institutional review board (IRB); neither the National Institutes of Health (which supported the study) nor committees at a collaborating institution in Israel were apprised of the fact that his protocols involved recombinant DNA. The studies were faulted for their scientific prematurity, and Cline became the first clinical investigator to be formally sanctioned by the NIH for violating human subjects regulations. In 1992, another controversy erupted when the NIH recommended canceling a contract of a prominent gene transfer researcher, Steven Rosenberg, for pursuing trials without sufficient preclinical data. Episodes like these created early impressions that gene transfer researchers were moving into human studies too aggressively.

There are various indications that some prominent stem cell researchers have not fully absorbed gene transfer's cautionary lessons. As this essay goes to press, cloning pioneer Woo Suk Hwang has admitted to ethical improprieties in obtaining human eggs and is under investigation for scientific fraud. Elsewhere, two different research groups (one backed by Geron, the other by ES Cell International) are reportedly nearing human studies despite concerns expressed by many about the safety and prematurity of such trials.



Monstrance, Part of Stilled Lives Series, by Helen Chadwick, 1996 (unfinished at artist's death). Iris print and perspex, 115 x 56 x 8 cm. © Helen Chadwick Estate, courtesy of Zelda Cheatle.

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Scientific Value

Gene transfer suffered another setback in 1995 when an NIH-commissioned review concluded that "only a minority of clinical studies . . . [had] been designed to yield useful basic information." The report emphasized that initial studies were "exploratory" and "many clinical gene therapy studies thus far have not met [high] standards [of experimental design]."

Because of their novelty, stem cell transplantation trials will necessarily involve high levels of indeterminacy regarding risks, methods, and standards. Considering such uncertainty, the move from animal to human trials requires first that the questions asked not be answerable using in vitro or animal models, and second, that the protocol be designed so as to maximize its yield of knowledge. Moreover, participants in early trials are unlikely to benefit directly. Maintaining a favorable ratio of harms to benefits, as required under all major codes of ethics, will thus demand exacting scientific and safety standards for early phase I trials and care in the selection of research participants.

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The Therapeutic Misconception

Patient advocates have often misconstrued gene transfer trials as aimed at delivering therapy, and researchers have frequently contributed to this conflation of research and therapy. However, trials impose requirements (for example, in phase I studies, doses are administered that are anticipated to be subtherapeutic) that abrogate medicine's mandate to provide personalized care. Whereas the primary goal of clinical practice is patient care, the primary goal of research is knowledge production.

Novel interventions like gene transfer are unproven, and investigators who promote the perception that early phase trials are therapeutic mislead their patient-participants. The concern about therapeutic misconception is heightened for gene transfer research because the trials generally enroll research participants with incurable illnesses, and studies have repeatedly shown that severely ill subjects are prone to misinterpreting clinical research as aimed at delivering care.

Similarly, early stem cell transplantation trials will likely target severely ill participants suffering from currently incurable conditions like Alzheimer's and Parkinson's diseases, multiple sclerosis, and spinal cord injury. The scientific nature of these early studies, however, should argue against presenting such trials as therapeutic.

Overselling the Science

Over the years, some gene transfer enthusiasts have advanced extravagant claims about its promise. Yet despite almost seven hundred approved trials in the United States, no gene therapies have been approved for clinical use in the United States or Europe. Only a few trials are regarded as showing efficacy, and important questions remain regarding the safety of these interventions.

The 1995 NIH panel that criticized gene therapy studies for not yielding useful information also admonished gene transfer investigators for creating a "widely held, but mistaken, perception that clinical gene therapy is already highly successful." Unrealistic portrayals of medical potential cloud ethical deliberations by promoting the therapeutic misconception, undermining the scientific aspects of trials, and drawing attention away from the risks that such experiments pose to research participants. When elevated expectations collide with scientific setbacks or publicized mishaps, a field's credibility suffers.

Stem cell transplantation research shows some indications of following a similar course—witness slogans like "save lives with stem cells," used to promote California's Proposition 71. Like gene transfer research, which adopted the term "gene *therapy*" long before safety and efficacy had been established, stem cell research has embraced terms such as "*therapeutic* cloning" that threaten to obfuscate the ethical issues. A second important parallel has been the attempt to defuse controversy by reconstructing terminology. Just as "human genetic engineering" was replaced by "gene therapy," "cloning" may give way to the less charged "nuclear transplantation"—as a group of scientists argued in a 2002 essay, "Please Don't Call It Cloning," in *Science*.

News reports also commonly contain overreaching assertions. In many instances, cell researchers have attempted to caution the public against unrealistic expectations, but not always. After Ron Reagan, in his address to the Democratic National Convention, implied that a stem cell cure for Parkinson's disease could be widely available in ten years, leading researchers like John Gearhart went on record praising Reagan for doing "a good job."

Lastly, excitement about a new intervention's therapeutic possibilities can easily obscure unresolved safety questions. Safety concerns about ex vivo gene transfer have been reawakened following the unexpected development of leukemia in three volunteers (one of whom died) in an ap-

parently successful study on the use of gene transfer to treat a type of severe combined immunodeficiency. These concerns parallel the uncertainties surrounding the tumorigenic potential of transplanted, stem cell-derived tissues.

Conflicts of Interest

Fields like gene transfer and stem cell research are characterized by investigators who have a strong drive to succeed. Many are invested not only professionally but also financially in the success of their trials. Although financial conflicts of interest are widely regarded as posing risks to scientific quality and patient safety, these concerns were confronted belatedly within gene transfer research following the 1999 death of Jesse Gelsinger, a volunteer in a study in which a principal investigator maintained a significant financial interest in the outcome of the trial. Shortly afterward, the *Washington Post* reported that two leading researchers who had founded gene transfer companies had failed to report several deaths to the NIH as required (none were ever clearly attributed to gene transfer). In response, the American Society of Gene Therapy issued a policy that urged investigators with financial interests in study sponsors to limit their role in patient selection, the informed consent process, and clinical management of a trial.

Financial conflicts of interest for individuals and institutions are likely to loom large in stem cell transplantation trials. Partly this is because restrictions in U.S. federal funding of stem cell research have driven much of the research into the private sector. Companies such as Geron, which holds exclusive rights to therapies and diagnostics derived from some of the first stem cell lines, may exert a significant influence over the development and availability of stem cell technologies. Additionally, in the period since the earliest gene transfer trials, the relationship between academia and the private sector has been reconfigured; university researchers are encouraged even more strongly today to patent their work, to court venture capitalists, and to develop spinoff companies. These developments are likely to amplify challenges in assuring ethical rigor in stem cell transplantation studies.

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Transparency

There is a particular need for researchers in new fields to be forthcoming with information that can improve the safety of trials and enable the public to remain informed about the field's progress. Gene transfer investigators, while held by the NIH to unusually high standards of public disclosure, have not always shared safety information willingly. After the death of Jesse Gelsinger, an investigation by the NIH revealed that over six hundred adverse events involving adenovirus-based vectors had not been reported to the NIH as required under its guidelines.

The environment for stem cell transplantation research may again prove to be public disclosure's antagonist. A public/private divide in the rules governing research in the United States and the overwhelmingly private sponsorship of stem cell research could shelter many investigators from obligatory public reporting. The politically sensitive nature of stem cell research may also discourage investigators from volunteering trial information to the public. Nevertheless, transparency advances several ethical ends. Trials have little scientific value unless their results are disseminated, and pooling adverse event information allows immature fields to quickly identify safety concerns. In addition, the public cannot meaningfully participate in stem cell transplantation policy discussions unless it receives current information on the progress of research.

Three Recommendations

■ **1. A National Body Should Oversee Stem Cell Transplantation Studies.** Gene transfer research has benefited from the existence in several countries of national bodies that publicly review protocols and address questions of safety, quality, and ethics. We urge national authorities to establish a similar system of national oversight for stem cell transplantation studies. This recommendation is consistent with research guidelines and relevant legislation in Canada and the United Kingdom, but contrary to a recent report from the U.S. National Academy of Sciences, which recommends a system of national oversight but does not recommend centralized review of research protocols.

Unfortunately, the federal ban on funding research involving the derivation of stem cells restricts the U.S. govern-

ment's ability to require centralized review of stem cell transplantation studies. Alternatives to federal oversight should therefore be contemplated. One possibility would be the creation of an interstate review committee by states funding stem cell research; such a body would emulate the original Recombinant DNA Advisory Committee's system for reviewing gene transfer protocols. Short of such concerted state efforts, professional societies with an interest in stem cells might devise a system for the voluntary review and public reporting of transplantation protocols.

■ **2. A Mandatory International Registry of Studies Should Be Established.** We recommend another salutary practice well established for gene transfer: the establishment of an international registry of human studies. (See http://www.wiley.co.uk/genmed/clinical/ for a registry of gene transfer studies.) We also recommend that editors of journals likely to publish stem cell transplantation reports require preregistration of protocols as a condition for publication. (Journal statements on preregistration presently would not apply to initial stem cell transplantation trials, since they exempt phase I studies.) Trial registration would provide a means for scientists, policy-makers, ethicists, and the public to remain abreast of ongoing work on stem cell transplantation.

■ **3. A National Panel Should Be Created to Set Guidelines for Studies.** Stem cell transplantation studies raise ethical and scientific questions not routinely encountered in clinical research. For example, transplantation investigators may need to devise consent language to convey "moral" risk related to stem cell derivation. Stem cell researchers might also develop a set of standards and guidelines intended to maximize the value of information sought in human studies. Given the politically sensitive nature of stem cell tissues, transplantation researchers might also wish to discourage members of their field from pursuing studies aimed at medical enhancements.

Although the NAS guidelines for the responsible practice of stem cell research offer very little comment on transplantation trial ethics, they do call for the establishment of a national body to "assess periodically the adequacy of the guidelines proposed . . . and to provide a forum for a continuing discussion of issues involved in [stem] cell research." The mandate of this body could usefully be expanded to explicitly refer to stem cell transplantation research. Consistent with the NAS recommendation, we recommend that a high-level national panel of scientists and ethicists be convened to devise national ethical guidelines for stem cell transplantation studies.

The need for such measures may be heightened by one way stem cell research is significantly different from gene transfer research. Whereas the latter is now regarded as a natural extension of practices likes bone marrow transplantation, stem cell research raises some special ethical and political issues, including the moral status of embryos, informed consent from egg/embryo donors, and the acceptability of treating embryonic tissues as mere commodities. The politicization of debates over these issues may cause some investigators to bristle at what they consider to be ethical roadblocks to transplantation research, but the penalties for failing to appreciate the complex ethical terrain are likely to be greater than has been the case for gene transfer research.

As the curtain rises on stem cell transplantation trials, the field will at least have enjoyed a luxury available only to understudies: extra time to review its script and learn from its predecessors' missteps.[1]

Acknowledgement

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1. A version of this essay containing references is available at http://www.mcgill.ca/biomedicalethicsunit/about/kimmelman/.

Stem Cell Research: *The California Experience*

BY DAVID MAGNUS

It has been nearly a year since the groundbreaking passage of Proposition 71, the law that created the California Institute for Regenerative Medicine (CIRM) and authorized bonds that would provide $3 billion in funding for stem cell research. As the first anniversary approaches, what is the state of human embryonic stem cell research?

At this point, CIRM has yet to produce any research, and in fact it has not even sold any bonds to fund the research. Opponents of Proposition 71, having failed at the ballot box, have taken to the courts. Arguments in state court claim that there is not sufficient state oversight. While the suits meander

David Magnus, "Stem Cell Research: The California Experience," *Hastings Center Report* 36, no. 1 (2006): 26-28.