

# LESSONS FOR THE STEM CELL DISCOURSE FROM THE GENE THERAPY EXPERIENCE

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**ABSTRACT** The discovery of human embryonic stem cells has pointed to the potential use of these cells in developing new approaches to therapy for many major human diseases. While there is general agreement that such applications are possible and will require a great deal of additional basic and preclinical research, some discussions of the therapeutic applications of human embryonic stem cells have been characterized by the kinds of exaggerations and elevated expectations that characterized the field of human gene therapy a decade ago. In the case of gene therapy, public perception of and confidence in the field were damaged by the hype. Most unfortunate of all, the hopes of patients and their advocates were disappointed. The eventual success of a gene therapy approach, albeit one still plagued by serious adverse events, has come through scientific advance and careful clinical application. The probable eventual use of human embryonic stem cells for therapy of human disease will also require thorough basic and clinical research, but that goal is endangered by the current level of inaccurate representations and undeliverable promises.

THE DISCOVERY AND CHARACTERIZATION of human and other mammalian embryonic stem cells has ushered in a new era of biomedicine. As with many other revolutionary developments in biomedicine, there are conflicting views of how such technology should be used. Although the current scientific,

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medical, ethical, religious, and policy discourse swirling about the derivation and potential clinical use of human embryonic stem cells reflects the great scientific opportunities provided by these cells for an understanding of human development and for the discovery of new methods of treating human disease, other aspects of the discussion are disturbingly reminiscent of the early discussions and gene therapy debates during of the 1980s and 1990s regarding another revolutionary genetic technology, gene therapy (Friedmann 1999).

### THE EVOLUTION OF HUMAN GENE THERAPY

Despite some early scientific, policy, and theological objections, the weight of the medical urgencies and the obvious correctness of the gene therapy concept quickly catalyzed a great deal of research on gene transfer that in turn led to a strong feeling of optimism that successful clinical application would be straightforward (Friedmann 1999). At the outset, it seemed that successful correction of a genetic defect would require only the identification of the responsible mutation, isolation of a “wild type” form of the gene, and a means to deliver it to appropriate cells and tissues. Indeed, as a result of the revolution in recombinant DNA technology and human molecular genetics beginning in the early 1970s, all of these needs were being realized. Genes responsible for human disease were rapidly becoming being identified and cloned, and their roles in pathogenesis were beginning to be understood. During the 1980s, efficient viral and other gene transfer vectors began to emerge that would make it possible to transfer such normal genes into defective cells and organisms (Hitt, Parks, and Graham 1999; Samulski, Mitch, and Muzyczka 1999; Shimotohno and Temin 1981; Tabin et al. 1982; Wei et al. 1981). In short order, proof of principle studies demonstrated that the introduction of wild type genes into genetically defective cells could not only restore a missing genetic function but could also reverse the resulting metabolic aberrations in model systems, thereby correcting the sometimes complex biochemical and metabolic consequences of the primary defect responsible for a disease phenotype (Willis et al. 1984).

Spurred by the resulting rosy confidence on the part of investigators, research institutions, patient advocacy groups, and the lay and scientific press, human clinical studies began in 1989 and blossomed during the early 1990s (Rosenberg et al. 1990). Many scientific symposia and other presentations during that time featured teasing initial reports of apparently impressive phenotypic corrections. Some of the scientific and lay media uncritically trumpeted the coming of gene therapy for life-threatening disorders and stoked the hopes and expectations of patients and their families, even as a few Cassandras were suggesting that clinical success was likely to be more difficult and elusive (Friedmann 1994; Verma 1994). In retrospect, this unfortunate hype could be attributed to influences from many sources, including overzealous science and research institutions, some uncritical media reports, well-intentioned disease foundations eager to bring cures

to their constituencies, and financial pressures in the emerging commercial world of biotechnology.

It was not until 1995, with the publication finally of the first comprehensive reports of these clinical studies, did it become generally accepted that gene therapy was going to be difficult (Blaese et al. 1995; Bordignon et al. 1995; Grossman et al. 1995; Knowles et al. 1995). These disappointing publications showed that the expression of transferred genes was generally poor and transient, and that it produced little if any ameliorative effects on the underlying pathophysiological mechanisms. Two advisory committees of the under NIH director Harold Varmus concluded in well-publicized reports that the field of gene therapy, while full of promise, was marred by a tendency to make undeliverable promises, to exaggerate the imminence of therapeutic clinical applications, and thereby to raise expectations in patients and their families to unrealistic levels (Orkin and Motulsky 1995; Varmus 1995). The panels further concluded that the gene therapy community required a higher quality of basic and clinical research, and they recommended a major restructuring of the federal mechanisms of oversight and regulation. Although this unusual rebuke of an emerging field by the director of the NIH reflected a serious broad loss of scientific and public confidence in the field, it had the beneficial effect of inspiring, in both basic and clinical investigators, a renewed commitment to rigor that, together with rapidly improving technology, produced a renewed sense of optimism for eventual clinical success.

In the ensuing several years, the gene therapy community has faced additional scientific and policy challenges, especially following the death in 1999 of Jesse Gelsinger in a gene therapy study at the University of Pennsylvania in 1999 (Raper et al. 2003). Ironically, it was at the period of greatest disappointment following that terrible event that word began to emerge of what later turned out to be the first effective therapeutic response in a human gene transfer study: the immunological reconstitution and the restoration of normal childhood lives in children suffering from X-linked severe combined immunodeficiency disease, or X-SCID (Hacien-Bey-Abina et al. 2002). Sadly, this apparent early success came with an unexpected and frightfully high cost—that of treatment-related leukemia in two of the treated children (Hacien-Bey-Abina et al. 2003). One of these two children has recently died of recurrent leukemia. Moreover, in January 2005, the French Health Products Safety Agency, the body that regulates human gene transfer studies in France, reported a clonal T-cell outgrowth in a third subject in the study, suggesting the early stage of leukemia. Fortunately, the remaining 12 or 13 patients in this study and a companion study in Great Britain seem to be well, some as long as six years after initial treatment. After decades of difficult advance and 15 years of more than 700 clinical gene transfer studies worldwide, the X-SCID results, together with similar clinical efficacy in another form of SCID caused by deficiency of the enzyme adenosine deaminase (ADA), provide definitive clinical validation of the concepts of gene therapy, even as they emphasize the serious inherent risks and the need to understand the technology far more

thoroughly than we do at present (Friedmann 2003). Even with these reservations, gene therapy has finally risen to the level required of all clinical research: a balance of honestly assessed benefits and risks. Life-threatening genetic disease has been effectively treated, perhaps even cured, by gene transfer. A new field of medicine has been born and has passed from potential to reality. Good preclinical and clinical research and experience, not wishful thinking and shortcuts, have made it so. Although the difficulties inherent in this field will probably prevent its rapid extension to other diseases, eventual advances will extend this “niche” medical technique to many more common and burdensome diseases.

### HUMAN EMBRYONIC STEM CELLS AND THERAPY

What does all this have to do with stem cells and their medical application, and are there any useful lessons from the gene therapy experience that might be learned by the parties now engaged in the stem cell controversies—the scientists, the institutions, the scientific and lay press, the political and public policy communities, and the commercial sector? If one simply replaces the phrase *stem cells* with the words *gene therapy* in much of the present-day stem cell debate and publicity, pro and con, one might recognize some of the overstated language of the early gene therapy discourse and, as before, feel discomfort with exaggeration on both sides. Particularly, one may be saddened by a tone of pandering in the name of the most vulnerable and ultimately the most important of the interested parties in this national debate: seriously ill patients and their families. In the case of gene therapy, scientists and potential constituents for gene therapy studies alike became aware that their expectations and hopes had been inflated and eventually dashed. We all learned the hard lesson that the underlying science and its clinical application could be pursued well or badly, and if it were done badly, the result would be harm to science, to public policy, and most of all to the potential recipients of the medical benefits, the patients.

In the case of the current embryonic stem cell debate, it is certainly true that most scientific discussions of possible clinical uses of stem cells diligently try to emphasize the long and difficult scientific hurdles standing in the way of effective clinical application. However, it is also true that much of the tone of the public discourse is far less circumspect and in many ways and, perhaps for some of the same reasons, seems to be recapitulating some of the miscues of the gene therapy community during early ventures into clinical application of gene transfer. As before, there is now a high level of excitement over the science, but there are also exaggerated promises of rapid clinical application, barely qualified claims of early success in model systems, and heightened expectations in desperate patients suffering from some of the most serious and inadequately treated diseases of our society—diabetes mellitus, Parkinson’s, Alzheimer’s, and other neurodegenerative diseases, cancer, etc. Even as the popular media and some advocacy groups acknowledge the need for long-term basic research and the dif-

faculties of clinical applications, in some cases they, and even a few scientists, present a far more optimistic picture of imminent clinical benefit than seems prudent. It might be argued that even if such exaggeration is inaccurate, it can serve a the useful educational purposes of raising the level of public and scientific awareness, of enhancing the understanding of this vital new area of biomedical research, and of providing needed research resources, and that in the long run, that may be a good thing for science and even for those relying most on its success, the patients. But the gene therapy community has learned that there can be a high cost for this kind of service: painful disappointment for desperate patients who have been led to expect relief from disease, as well as public disillusionment and at least a temporary loss of confidence in the entire scientific enterprise in response to the probably inevitable setbacks and adverse events.

The present climate of overstatement and exaggerated expectation in the embryonic stem cell discourse may predestine it to a similar future. In fact, the first such major disappointment may have already occurred. In January 2005 it was found that all of the federally approved embryonic stem cell lines contain mouse elements derived from the mouse feeder layers required for their growth in culture. These elements may predispose grafted cells to be destroyed by an immune response in human patients into whom such cells have been grafted, resulting in the loss of the therapeutic effect. The implication, of course, is that none of the federally approved cell lines, all grown with the help of mouse cell “feeder layers,” may be suitable for human therapeutic intervention.

As with gene therapy, embryonic stem cell-based medicine is very likely to achieve eventual clinical success. While we all hope that clinical translation of stem cell biology will be as facile, effective, and trouble-free as is sometimes portrayed, it is far more likely that clinically useful advances will come more slowly through incremental advances requiring long periods of steady basic, preclinical, and clinical research. The pursuit of this and any difficult and controversial new area of science requires careful science, effective communication with enlightened policy makers and legislators, enthusiastic advocacy, an educated and supportive educated public, and responsible commercial application.

The divisive, politicized, and sometimes fact-blind and wish-driven national discourse on the clinical use of embryonic stem cells, the inadequate federal funding, and the perceptible public sense of urgency surrounding research and clinical needs has produced important alternative, privately funded academic and private research efforts (Vastag 2004). The most ambitious is a major new governmental program, the California Stem Cell Research and Cures Initiative. This initiative, approved by the voters of California, provides \$3 billion in state-generated funds over a period of 10 years to establish a California Regenerative Medicine Institute to support stem cell research and its clinical applications in California. Similar, albeit smaller, programs are being put into place in a number of other states. Even though some of the political rationale for these programs has unfortunately been fueled by a familiar degree of exaggeration regarding immi-

nent clinical success, these new state funding efforts certainly promise to fill a part of the research gap left at the traditional federal level, by putting desperately needed research materials and funds into effective research hands. Very sadly, unless there is a change at the federal level in response to the revelation of universal contamination of existing approved cell lines, a large part of preclinical research and all of the eventual clinical applications will unfortunately be carried out without the benefit of federal funding and oversight. A maximally effective national effort in this important field will be much more difficult, if at all possible, without greater federal involvement. We are already witnessing a shift of the center of gravity of this area of research away from the United States and toward countries with less politically encumbered approaches to scientific advance.

#### OVERSIGHT IN DIFFICULT NEW AREAS OF HUMAN BIOMEDICINE

One of the factors that led to success in gene therapy was the careful and constructive role played by the U.S. regulatory and review bodies—the Recombinant DNA Advisory Committee (RAC) at the NIH and the Food and Drug Administration—in shepherding the basic and preclinical work to the bedside (Friedmann, Noguchi, and Mickelson 2001). The models provided by these oversight mechanisms set standards for clinical work in gene therapy that have been so effective that they have been emulated worldwide. Because an increasing amount of research into clinical use of human embryonic stem cells will be carried out at the state level and in the private sector, it will be vital that equally effective and publicly responsible oversight mechanisms be established in those settings. The California initiative is being designed to emphasize high-quality research and maximal public access to the processes and products of research supported through this novel funding mechanism. Included in such a mechanism should be an RAC-like function to provide detached oversight to speed appropriate clinical application, as originally proposed for gene therapy technology (Friedmann and Roblin 1972). The careful design of these new stem cell research and funding mechanisms and of the bodies charged with ensuring public access and oversight can help to avert the missteps of the early gene therapy clinical experience and eventually bring this important new technology to the bedside to relieve suffering and treat disease.

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