Gene Therapy: What Has Been Achieved After 25 Years? Successes and Failures in a New Field of Medicine

by Sheldon Krimsky

In the 1980s, somatic cell human gene therapy (HGT) was considered so promising to some that several clinical investigators were willing to risk their reputations and leave the country to experiment on desperate human subjects in ways that would have violated U.S. guidelines.[1] The media coverage of HGT focused on the most dramatic cases, typically, the potential to reverse the course of an inherited, life threatening or life limiting genetic disorder. The idea that we were not complete prisoners of our diseased genes was a powerful metaphor for human transcendence over the lottery of our genome. It took another decade before the National Institutes of Health established guidelines and set up an advisory committee process to carry out case-by-case reviews of human gene therapy experimental protocols. The first U.S. approved clinical trial for somatic cell gene transfer in humans took place in 1990.

The prospects of HGT were viewed through two lenses. Some scientists claimed that HGT would revolutionize medical therapies and that it introduces an entirely new dimension for tackling the recalcitrant disorders brought on by gene mutations. Others saw HGT as part of a continuum of drug therapies "a form of molecular medicine. In this case, the drugs were delivered in the form of DNA directly into cells, rather than indirectly through the bloodstream. The DNA codes for the production of the therapeutically proteins to be made by the machinery of the cell. In 1995, a special advisory panel to the NIH described somatic cell human gene therapy as follows:

Somatic gene therapy is a logical and natural progression in the application of fundamental biomedical science to medicine and offers extraordinary potential, in the long-term for the management and correction of human disease, including inherited and acquired disorders, cancer, and AIDS.[2]

However, the same panel warned that the putative revolutionary benefits of HGT were being oversold:

Overselling of the results of laboratory and clinical studies by investigators and their sponsors-be they academic, federal, or industrial-has led to the mistaken and widespread perception that gene therapy is further developed and more successful than it really is.[3]

In 2004, I supervised a study by Christine Crofts, a sociology doctoral student at Boston College who was interested in investigating the research infrastructure developing around human gene therapy. When she completed her inquiry, we co-authored a paper that was published in the February 2005 issue of Human Gene Therapy, from which some of the data cited in this article are derived.[4] We were interested in discovering whether there were any successful human applications of somatic cell gene therapy, the level of government funding it receives, the number of clinical trials that have been undertaken, the amount of support coming from the private sector, and the production of intellectual property resulting from the research in this topic.

We learned that a sizable cottage industry of research and development activities had grown around the prospects of somatic cell gene therapy and that, despite very limited clinical success,
infrastructure of activities has only expanded since 1990. The late New York University sociologist of science Dorothy Nelkin wrote in 1996 that the history of gene therapy has been an "upside down" affair where "conceptual advances [have] become widely accepted and firmly established as medical principle before even a simple clinical instance of clinical efficacy has been demonstrated".[5] The disciplinary and commercial activity that has grown around HGT is a strong indicator that scientists were highly confident that a major breakthrough would occur in this area of research.

While most of the science media has focused on the role of somatic cell gene transfer for inherited diseases, we found that only ten percent of all the clinical trials funded in 2004 were directed at individuals with diseases resulting from monogenic traits. Ironically, the majority of trials were directed at cancer, a disease (or complex of diseases) that is not, in most cases, associated with germ line gene mutations. Sixty-six percent of the gene therapy clinical trials in 2004 were for cancer-related diseases, where the theory of oncogenes was intriguing, but unrelated in any direct way to HGT. Rather, it relies on an interesting set of experiments described below. In any case, the cumulative pattern of clinical trials gives similar results. From 1990 through 2004, the National Institutes of Health Recombinant DNA Advisory Committee reviewed 590 human gene therapy protocols. Seventy-one percent of the trials were for cancer, ten percent were directed at monogenic diseases, seven percent for infectious diseases, and twelve percent for other diseases and disorders.

By 2004, the number of gene-therapy trials approved worldwide was 888. The countries with the highest number of approved HGT trials were the United States with 613, United Kingdom with 96 and Germany with 53. [6]

What is it about HGT that has attracted so much attention among cancer researchers? First, experimentation with HGT techniques for cancer has an advantage over trials for monogenic diseases because there are so many more cases of cancer. This means the chance of recruiting people into a clinical trial is much greater. Second, the funding levels for cancer research are significantly higher than those for monogenic diseases.

These reasons aside, it seemed that there still must have been some reasonable hypotheses about how HGT could be used in cancer therapy to justify the attention it had received. We found four main strategies for using HGT in cancer treatment. They all involve the delivery of genes into cells either in vitro (before the genetically altered cells are delivered into humans) or in vivo (by the use of delivery mechanisms that get the genes into the appropriate cells in the human subject).

For example, there is the transfer of drug-resistant genes into non-cancer cells to protect them from the cell-toxicity of chemotherapy agents. The strategy here is to protect all the neighboring cells except the target cells from the chemotherapy. This would permit the use of higher levels of the locally-directed chemotherapy agent.

A second strategy is the targeting of tumor cells with genes encoding enzymes that activate a toxin that kills the cell. Without the toxin, neighboring cells would not be affected by the chemotherapy agent.

Third, on the assumption that tumor suppressor genes (TSGs) can prevent the growth of tumors, scientists are looking at the use of somatic cell gene transfer to enhance or restore the function of TSGs in the relevant cells that are tumorigenic.

A fourth strategy is to increase the proliferation of cell populations in the immune system that have anti-tumorigenic properties.

These strategies are all based on the unconfirmed hypothesis that genes can be transported into target cells stably and safely, and that the transported genes will encode the correct proteins, and that the amount of protein production will be sufficient for the task.

Monogenic Prospects

Clinical gene transfer protocols for inherited monogenic disorders have been approved for: adenosine deaminase deficiency, alpha-1-antitrypsin deficiency, chronic granulomatous disease,
Canavan disease, cystic fibrosis, familial-hypercholesterolemia, Fanconi's anemia, Gaucher disease, Hunter syndrome, ornithine transcarbamylase deficiency (OTC), and severe combined immunodeficiencies syndrome (SCIDS).

Eighteen-year-old Jesse Gelsinger died in 1999 after he was recruited into an experimental gene therapy trial at the University of Pennsylvania. The purpose of the trial was for the clinical team to gain some understanding of how HGT might contribute in helping to treat infants with Jesse's genetic disorder, OTC. People with this disorder cannot break down ammonia, a natural byproduct of protein metabolism. Jesse was able to stay alive with a strict diet and large amounts of medication. Jesse's death resulted in a short period of retrenchment and soul searching about the prospects and dangers of HGT, but research activity in the field bounced back fairly rapidly. All the indicators we could find illustrated a field undergoing sustained growth " even without an unambiguously marketable product or therapy.

There were 159 NIH grants that had the term "gene therapy" in the title or abstract in 1990, and the number rose steadily until 1996, when 629 were approved. In 1997, the number of grants more than doubled to 1335. The number peaked at 1985 in 2001, and dropped to 1599 in 2003.

The commercial aspect of HGT was also developing quite robustly toward the turn of the century. From 1990 through 1996 there were thirty gene therapy-related U.S. patents issued. In 1997, 49 patents were issued. By 2002 and 2003, 131 and 125 gene therapy patents were issued respectively. The total patent count from 1990 through 2003 is 759.

Many companies dedicated to gene therapy began forming around 1990. Over a period of thirteen years 151 companies have been formed. A review of Medline between 1990 and 2003 shows a dramatic annual rise in gene therapy research articles, from 177 published in 1990 to 1666 published in 2003. In that same period, nine journals dedicated to HGT were founded.[7]

Success?

The one application of HGT reported as successful in the primary medical literature is its use to treat a class of genetic diseases known as severe combined immunodeficiency syndrome (SCIDS), which is considered fatal without bone marrow transplants. In 1990, two girls with severe cases of SCIDS underwent the first approved gene therapy treatments in the United States. They are now college students, but still receive regular injections to bolster their immune system. [8]

The first announcement of unambiguously successful treatments came in 2002 when the results of ten French children treated by somatic cell gene therapy were reported.[9] The favorable outcome was mixed, however, with news that three of the children contracted leukemia from the retrovirus used to carry the genes into the cells " an effect known as "insertional mutagenesis".[10]

Some scientists believe they can minimize the risks of leukemia because they have discovered the particular combination of genes that gave rise to it.[11] Others speak of the HGT trial as a guarded success because, while iatrogenic leukemia is a serious complication, they believe it has a good treatment record, whereas untreated SCIDS has a much higher mortality rate. In December 2004, The Lancet reported the successful treatment of four children with X-linked SCIDS, ranging in age from four to thirty-three months. All patients were doing well after treatment and exhibited varying degrees of recovery of immunological cell numbers and immune function. Doctors were able to discontinue immunoglobulin replacement therapy for two patients eighteen and twenty-one months after HGT treatment. Also, unlike with the French children, there were no major complications reported in the British patients. The UK study concluded: "Gene Therapy is an effective treatment for SCID-X1 and for adenosine-deaminase-deficient SCID. Our findings suggest superior reconstitution and lower morbidity and mortality than with mismatched bone-marrow transplantation". [12] Scientists from Italy and Israel reported successful treatments of two SCIDS patients who now live normal lives and have been taken off enzyme replacement therapy.[13]

As of January 2005, 17 out of 18 SCIDS patients treated by an ex-vivo retroviral mediated gene transfer "had their immunodeficiencies corrected with clear and sustained clinical benefits".[14]
While the positive responses to HGT treatment for 17 SCIDS patients is a welcome and dramatic outcome, there remain a host of unknowns and concerns.

In the past, human gene therapy researchers in the United States violated federal rules when they failed to report unexpected adverse events associated with the therapy. Fewer than five percent of the serious adverse events were reported. There are uncorroborated allegations that six unreported deaths may be attributable to HGT.

Questions remain over whether the therapeutic gene will eventually stop being expressed and whether the benefit from the HGT, namely the reconstitution of the immune system in the case of SCIDS, will be temporary or permanent. There are concerns that there will be more cases of leukemia from HGT. One recent publication in which no cases of "insertional mutagenesis" were observed remained cautious: "This risk cannot be clearly defined. At latest analysis we have not observed any evidence of clinically manifest insertional mutagenesis, although our follow-up is short in comparison. Slight differences in protocols might affect the risk, but we do not believe this possibility to be likely".[15]

Some patients still required prophylactic medication after somatic cell gene therapy. Other risks of HGT are beginning to be reported in primate studies that may complicate the risk benefit assessment.[16]

Notwithstanding the remarkable successes in the activation of a non-functional immune system, at least partially for the 17 SCID patients, HGT remains in its infancy and is regularly oversold to the media and to the venture capital community. Until the leukemia problem can be eliminated, it is unlikely that HGT will be adopted as "standard of care" for SCIDS patients. Moreover, the message we get is that HGT will cure "defective genes" and make people whole again. In reality most of the HGT research has been brought under the umbrella of oncology and has less to do with repairing "defective genes" than with delivering drugs to treat individuals who have suffered damage to the genes in their somatic cells.

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References

1. In July 1980, Martin Cline, a biomedical scientist at UCLA transplanted cells genetically altered in vitro into the bone marrow of two women with an inherited blood disease called beta thalassemia major. One woman was a 16 year old from Italy and a second was a 21 year old from Israel. See, Sheldon Krimsky, Biotechnics and Society, New York: Praeger, 1991, pp. 164-165.


3. Ibid., p. 2


13. Ibid. 2410-2413


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