Gene Therapy

A Brief Overview of the Past, Present, and Future

ROLAND SCOLLAY

Genteric, Alameda, California 94501, USA

ABSTRACT: Gene therapy has only recently begun to make serious progress, beginning with two approved gene therapy trials in the United States in late 1990. The death of an 18-year-old man participating in a gene therapy trial delivered a major setback in terms of public concerns, but the resulting improvements in scrutiny of trial design and ethical standards will benefit the field in the long run. The three main issues for the coming decade will be public perceptions, scale-up and manufacturing, and commercial considerations. Focusing on single-gene applications, which tend to be rarer diseases, will produce successful results sooner than the current focus on the commoner, yet more complex, cancer and heart disease.

KEYWORDS: gene therapy; clinical trials; trial design; cancer; cardiovascular disease; hemophilia

Gene therapy has had rather a bad decade. In fact, it got off to a shaky start long before the 1990s began with two unapproved trials in the early 70s and early 80s. In the first, an attempt was made to treat two young girls with arginase deficiency syndrome using *in vivo* gene therapy with wild-type Shope papilloma virus, in the hope that the viral arginase would replace the missing enzyme in the patients. The second was *ex vivo* gene therapy for β-thalassemia, a bone marrow transplant using marrow cells treated with a β-globin-containing plasmid, again in two patients. In neither case was any real follow-up reported, since both trials were stopped, but apparently neither good nor harm resulted for the patients, although the investigators did not fare so well (for discussion of the early history of gene therapy, see Wolff and Lederberg[1]).

The first serious, approved gene therapy trials happened in the United States in late 1990, when two *ex vivo* trials began. One trial employed enzyme-transduced T cells for an enzyme deficiency that causes severe combined immunodeficiency (SCID)[2]; the other used cytokine (TNF)-transduced lymphocytes that had been extracted from tumors as immunotherapy for melanoma.[3] Both trials relied on retroviruses to transfect the cells. Neither was successful, for reasons we now understand. During the rest of the 90s, the pace accelerated, and in 1999 alone 84 new trials were approved by NIH/RAC.[4] In all, as of mid-2000, almost 4000 patients have been

Address for correspondence: Roland Scollay, Ph.D., Chief Scientific Officer, Genteric, 2061 Challenger Drive, Alameda, CA 94501. Voice: 510 749 6063.
rscollay@genteric.com

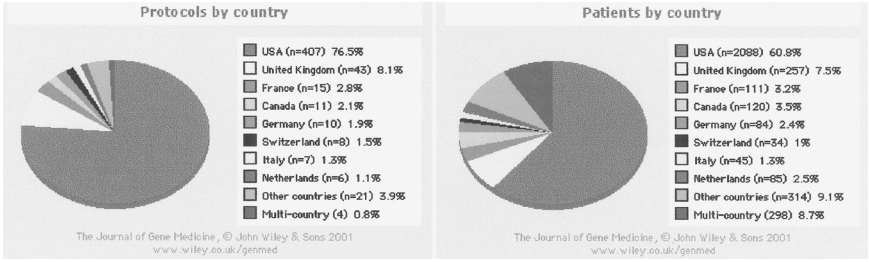

FIGURE 1. Geographic distribution of gene therapy clinical trials. Reproduced from the John Wiley and Sons, Ltd. website[5] with permission.

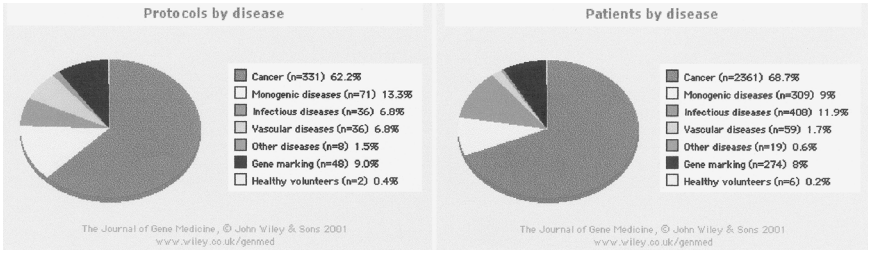

FIGURE 2. Diseases being treated in gene therapy clinical trials. Reproduced from the John Wiley and Sons, Ltd. website[5] with permission.

treated with gene therapy in more than 500 trials. A Medline search for "gene therapy" publications will find a handful in 1985, a few hundred in 1990, and more than 2000 by 1999. According to the Wiley website (Ref. 5, a good source of information on clinical trials) 77% of these protocols were in the United States, and in 69% of patients, the target disease was cancer (FIGS. 1 and 2). Only 1% of protocols reached phase three, and none have gone beyond.

The decade of the 90s was discouraging: all those trials and almost no success. And it finished badly in September 1999 with the widely publicized death of an eighteen-year-old man undergoing gene therapy for a liver disease at the University of Pennsylvania, an event that brought the scrutiny of the press onto the world of gene therapy. This was the first death directly attributable to gene therapy, and the ensuing publicity and investigations not only bought to light a number of clinical trials in which trial design or ethical standards were not satisfactory, but also unfairly cast a shadow over the whole field of gene therapy. The improved control and scrutiny resulting from these events can only be good for the future of the field, but the lingering concerns will take time to dispel.

Then, at the turn of the millennium, through the year 2000, anecdotal reports of the first apparent successes began to be heard, hopeful hints that real success may be just around the corner: factor IX for hemophilia,[6] transduced stem cells for X-linked SCID,[7] and oncolytic vectors.[8] In some cases, the progress came from improvements in our understanding of the vectors (e.g., hemophilia and improved adeno-associated virus vectors); in others, the vectors have changed little, but our understanding of the

genes and of the biology of the transduced cells made all the difference (e.g., treatment of SCID patients by transduction of stem cells with the common gamma chain of the interleukin receptor). Indeed, the field is learning from its mistakes, and many of the problems are now better understood. Scale-up and manufacturing issues, as well as those of quality control and safety, are being intensely studied. Well-founded skepticism has forced the field to be more rigorous, leading to a higher likelihood of success. Ten years of hard times has weeded out many approaches and put the focus on realistic and achievable technologies.

In fact this ten-year cycle is rather similar to the one that monoclonal antibodies followed: a lot of noise and high expectations based on preclinical science; ten years of failed clinical trials as the problems became apparent; then, a much more realistic approach and solutions to many of the problems; and now major clinical and commercial successes. I believe that gene therapy will follow a similar pattern and that the recent successes herald the beginnings of a decade of real progress, leading to gene therapies that will have a major impact on the practice of medicine.

What, then, are the main issues (apart from just getting it to work in the clinic) going forward over the next 10 years? They can be broadly divided into three categories:

- public perceptions
- scale-up and manufacturing
- commercial considerations

Public perceptions have indeed been influenced by the gene therapy–related death mentioned above. Furthermore, there is a general public concern about genetic engineering and genetically modified organisms, concern that has lead to demonstrations and legal challenges in Europe. The public often has a limited ability to discriminate between different forms of "genetic manipulation" and will lump even the simplest clinical gene therapy together with gene-modified crops, transgenic farm animals, and Dolly the cloned sheep, generating public resistance to all. Many people can discriminate among these issues, however, and do realize that some setbacks are inevitable with cutting-edge therapies. It will be crucial in the future that gene therapy trials are well planned and in accordance with all relevant guidelines. Then a few real successes in the clinic will soon regain popular support. The addition of a growing number of safety features into vectors should also allay fears as we move forward.

Scale-up and manufacture have long been significant obstacles for many of the best vector systems; and, even now, producing enough vector for large clinical trials is still problematic. It remains a challenge to produce vectors at commercial scale and to control production runs for mutated or recombined viruses. Nevertheless, tangible progress is being made, and it is likely that adequate systems will be available for the manufacture of many vectors by the time clinical efficacy is established in Phase III clinical trials.

Commercial considerations have heavily influenced the direction of gene therapy development. The fact that many gene therapy trials and much gene therapy research is being done within companies or sponsored by companies, with the ultimate aim of developing these therapies commercially as "drugs," has put pressure on researchers and companies to develop therapies for large-market indications. This means that

rarer diseases, such as some of the single-gene-mutation, inherited diseases, get less attention, while major diseases, such as cardiovascular disease and cancer, are greatly emphasized. This is a pity for two reasons. First, rare diseases that could potentially be treated quite soon using gene therapy are getting little attention. Second, these same "rare" diseases are, in fact, often much easier targets for gene therapy, with well-defined, well-understood target genes for delivery. Factors VIII and IX for the treatment of hemophila are good examples of well-understood drugs with very accessible clinical targets. They have received some attention from smaller biotechnology companies, but many other diseases remain untouched. The pressure to treat larger indications like cancer has lead to a predominance of trials for these diseases (approximately 70% of all gene therapy trials to date have been in cancer), and this has been one of the reasons there have been so many unsuccessful clinical trials in the last 10 years. In most cases it has not been clear which genes to use in the treatment of these complex diseases, and many trials have been tests for the efficacy of the genes being investigated, rather than tests of a gene delivery technology using genes that we know will work if delivered at adequate levels. In other words, many of these trials have involved two very serious unknowns, the ability to deliver the gene and the efficacy of the gene, once delivered. Furthermore, it has not always been clear which of the two failed.

The second major commercial issue relates to intellectual property. Most gene therapies involve complex treatments upon which multiple patents impinge. Patents or licenses for vector systems or their individual components, promoters, regulatory elements, targeting elements, the therapeutic gene, the manufacturing process, and so forth are all required for a single therapy. Few, if any, companies can gather together all they need for the optimal treatment, because other companies that control key components often have unrealistically high ideas of their value, and the additive effect of the royalties on the many components involved (royalty stacking) becomes seriously limiting. This means that therapies going to the clinic are not always the very best available; rather, they are those for which the licenses are held, another factor contributing to the high failure rate of gene therapy trials to date. This is quite distinct from the world of small molecular drugs, where each competing company fully controls a single drug entity, and the public process of clinical trials can select the best among them.

Because the field of gene therapy urgently needs some additional successes in order to continue to attract public support as well as research funds and investments, it would perhaps be wise to focus on achieving success in the short term with the easier, but less profitable diseases, rather than failing with the big-market indications. Furthermore, it may be in everyone's best interest if there were many more cooperative arrangements between diverse interests (collaborations, joint ventures, consortia, etc.) in order to bring the very best combinations of technology to bear on the clinical problems being addressed. This will require a cooperative, rather than a competitive, spirit. Commercially, this may mean waiting for success to bring recognition or profit, rather than demanding short-term gain in the form of large upfront licenses and fees. There has been some evidence of such positive interactions in recent months, but a lot more cooperation will be needed if the new field of gene therapy is to reach its potential in the near future. I am optimistic that both the cooperation and the success will happen in the coming decade.

NOTES AND REFERENCES

1. WOLFF, J.A. & J. LEDERBERG. 1994. An early history of gene transfer and therapy. Hum. Gene Ther. **5:** 469–480.
2. BLAESE, R.M., K.W. CULVER, A.D. MILLER, *et al*. 1995. T-lymphocyte-directed gene therapy for ADA-SCID: initial trial results after 4 years. Science **270(5235):** 475–480.
3. ROSENBERG, S.A., *et al*. 1992. Immunization of cancer patients using autologous cancer cells modified by insertion of the gene for tumor necrosis factor. Hum. Gene Ther. **3:** 57–73.
4. More information on U.S. clinical trials can be obtained from the NIH site (http://www4.od.nih.gov/oba/clinicaltrial.htm).
5. John Wiley website: http://www.wiley.co.uk/wileychi/genmed/clinical/.
6. KAY, M.A., C.S. MANNO, M.V. RAGNI, *et al*. 2000. Evidence for gene transfer and expression of factor IX in hemophilia patients treated with an AAV vector. Nat. Genet. **24:** 257–261.
7. CAVAZZANA-CALVO, M., S. HACEIN-BEY, G. DE SAINT BASILLE, *et al*. 2000. Gene therapy of severe combined immunodeficiency (SCID)-X1 disease. Science **288:** 669–672.
8. KHURI, F.R., J. NEMUNAITIS, I. GANLY, *et al*. 2000. A controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer. Nature Med. **8:** 879–885.