HUMAN GENE THERAPY 16:169–177 (February 2005)

Review

Emergence of a Scientific and Commercial Research and Development Infrastructure for Human Gene Therapy

CHRISTINE CROFTS[1] and SHELDON KRIMSKY[2]

ABSTRACT

A research and clinical subfield known as "human gene therapy" has grown rapidly since 1990, when the first human trials were approved in the United States. Using quantitative data, this paper describes and analyzes the research and commercial infrastructure, including academic centers, publications, intellectual property, and biotechnology firms, that has developed around the goal of discovering clinical applications for the modification and transport of DNA to somatic cells. Despite setbacks and few documented successes, the subfield of human gene therapy continues to serve as an influential clinical paradigm for the treatment of inherited and noninherited diseases.

INTRODUCTION

SEVERAL YEARS after scientists discovered how to use enzymes to excise and anneal segments of DNA and how to transfer the recombined segments (rDNA) into mammalian cells, clinical geneticists began exploring the applications of those techniques for somatic cell gene repair, also known as human gene therapy (HGT). In this paper, gene therapy is understood as encompassing any procedures that alter, transfer, activate, or suppress genes for diagnosis, prognosis, prevention, or treatment of diseases.

In 1980, a scientist at the University of California, Los Angeles used an HGT technique involving rDNA molecules to treat two individuals in their respective countries (one from Israel and another from Italy) in an attempt to cure their rare blood disease, β-thalassemia. Although the experimental treatments neither helped nor harmed the patients, the principal clinical investigator was found to be in violation of the National Institutes of Health guidelines for rDNA research. It took another decade before HGT was officially sanctioned for human subjects in the United States.

The first successful HGT treatments reported in the scientific literature involved a group of children afflicted with a rare genetic condition called X-linked severe combined immunodeficiency disease (X-SCID). As of January 2005, 17 out of 18 SCID patients treated by an *ex-vivo* retroviral mediated gene transfer (including 10 from France and 4 from the United Kingdom) "had their immunodeficiencies corrected with clear and sustained clinical benefits" (*The Lancet,* 2004). According to reports in the scientific literature and in meeting disclosures, 13 of 14 children with X-SCID rapidly improved. Their immune functions reached a level that permitted them to be released from the hospital. However, 3 of the 10 children treated for X-SCID in France are believed to have contracted leukemia from the treatment, which temporarily slowed down additional trials (Check, 2004, 2005). Despite the intermittent setbacks and slow starts, over the last 20 years an academic and commercial infrastructure developed around the clinical applications of HGT, years before the first successes were reported. The prospects of HGT, widely acclaimed by start-up companies and in the popular press and affirmed in the scientific literature (McCormack and Rabbitts, 2004), precipitated the growth of many centers, companies, and associations focused solely on this particular application of biotechnology. The institutional formation around HGT is especially noteworthy considering that it started well before conclusive proof of the success of gene therapy as

[1]Department of Sociology, Boston College, Chestnut Hill, MA 02467.
[2]Department of Urban and Environmental Policy and Planning, Tufts University, Medford, MA 02155.

a medical treatment had been established. One reason why the scientific networks and institutional structure around HGT experienced such a strong level of growth, seemingly incommensurate with the demonstrated potential of the technique, likely lies in the abundance of discussion and debate about human gene therapy that took place years before it was officially sanctioned in human trials. As a result of public attention and congressional support for human genomics, a research space was created for a new and bolder approach to combat genetic and nongenetic diseases. This paper examines the emergence of new networks and institutions beginning in 1990 that responded to the clinical possibilities of HGT. We focus on the growth of HGT as a scientific and medical research field by tracking the emergence of new journals, patents, government grants, venture capital companies, and specialized publications that occupied this new research space.

SCIENTIFIC, SOCIAL, AND POLITICAL CONTEXT OF GENE THERAPY INSTITUTIONS

As reports about the promises of gene therapy proliferated (Begley and Hager, 1989; Brady, 1990; Carey, 1990; Friend, 1990; Brownlee and Silberner, 1991), HGT became a highly anticipated and, therefore, in-demand technology. This demand provided an opportunity for a number of institutions to position themselves around the goal of making gene therapy a reality. Not only did the public image of gene therapy affect the pace and scope of institutional emergence, but it also influenced the formation of the goals and foci of a new research paradigm built around DNA modification and transport into somatic cells. For some disease communities, it became the promise of last resort. With investments from public and private funding sources anticipating therapeutic results, scientists created a well-integrated social network of institutions dedicated to HGT.

The first federally approved human gene transfer experiment began in 1989 at the National Institutes of Health (NIH). It involved transferring a foreign gene into the cells of a human patient to investigate a new method of cancer therapy (Anderson, 1990). After that, on September 14, 1990, a young girl with the immune disorder adenosine deaminase (ADA) deficiency was the first person in the United States treated by HGT for a genetic disease. This event proved to be a catalyst for new developments and investments in the field.

Yet the possibilities of gene therapy had been contemplated decades earlier. As molecular biology advanced and its pioneers began in the 1960s to uncover and clarify the ways in which genetic factors contribute to the etiology of disease, the idea that disease might be prevented or treated by replacing "abnormal" genes with "normal" ones entered the minds of scientists and laypersons alike (Lyon and Gorner, 1995).

The first recorded attempt at HGT was made in Germany in 1970. Three German sisters had a rare enzyme deficiency that caused them to build up a high level of arginine in their bloodstream (a condition called argininemia, which untreated results in severe neurological damage). Researchers treated the sisters with a rabbit virus believed to contain the gene for the enzyme that the body needs to metabolize arginine. The attempt to transfer a functioning gene failed (President's Commission, 1982).

Other experiments in somatic gene modification and therapeutic applications in animals were prevalent throughout the 1970s and 1980s and, despite numerous setbacks, researchers seemed optimistic that their efforts to apply gene therapy to human disease would eventually succeed (Nichols, 1988).

Prompted in part by concerned public reactions to the first attempt at applying HGT to humans without ethical approval in 1980, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research undertook a 2-year study of the potential social and ethical impacts of genetic engineering (President's Commission, 1982; Martin, 1999). HGT was one of the technologies addressed by the commission. In its report, *Splicing Life*, the commission both reflected and shaped public opinion. It highlighted the range of popular views, from those who thought gene therapy was a miracle cure to those who feared it would turn patients into something less than human. The principal contribution of the commission to the future of gene therapy was its distinction between *somatic cell* and *germ line* gene therapies, also adopted by the National Academy of Sciences (Nichols, 1988). Somatic cell gene therapy (the type being applied clinically today), in which new genes replace missing or faulty ones in nonreproductive cells, is likened to tissue or organ transplantation. Conversely, germ line gene therapy (for which federal funding is prohibited in the United States) modifies the DNA of reproductive cells. If successful, germ line gene modifications are passed on to future generations. By distinguishing somatic from germ line modification, the commission was able to lend support to safe uses of HGT, while setting it apart from the more controversial eugenic interventions of germ line modification (Capron, 1990).

Debates over the social and ethical aspects of HGT persisted, with some segments of the public remaining apprehensive about gene therapy (and recombinant DNA technologies in general) (Turney, 1998). However, for the scientific community and the majority of the general public, the benefits of HGT (properly regulated) seemed to overshadow other concerns. Opinion surveys show little opposition to the use of somatic gene therapy in the treatment of disease (Macer *et al*., 1995). In 1996, Nelkin, citing *Nature-Medicine*, noted that the history of gene therapy has been an "upside down" one, "in which conceptual advances [have] become widely accepted and firmly established as medical principle before even a simple clinical instance of clinical efficacy has been demonstrated" (Nelkin, 1996, p. 36).

A LexisNexis search for the term "gene therapy" in newspapers, magazines, and periodicals published between 1990 and 2003 shows how widely it was discussed in the popular press, peaking in 2000 at 516 citations. A similar MEDLINE search of articles on human gene therapy brought up 175 citations in 1990, steadily rising to 1580 citations in 2003 (see Fig. 1A and B). By profiling patients with life-threatening hereditary diseases and emphasizing the potential medical breakthroughs of HGT, the media encouraged continued public and investor support for its clinical applications. Lyon and Gorner, authors of a history of gene therapy titled *Altered Fates*, note that "[t]he public, often characterized as intrinsically conservative and fearful of the unknown, has, in our experience, reacted positively to the prospect of gene therapy. Rather than shrink from it, most people tend to become excited about the potentialities" (Lyon and Gorner, 1995, p. 13).

Although it could be argued that the prominence of gene therapy resulted from a natural progression from scientific to

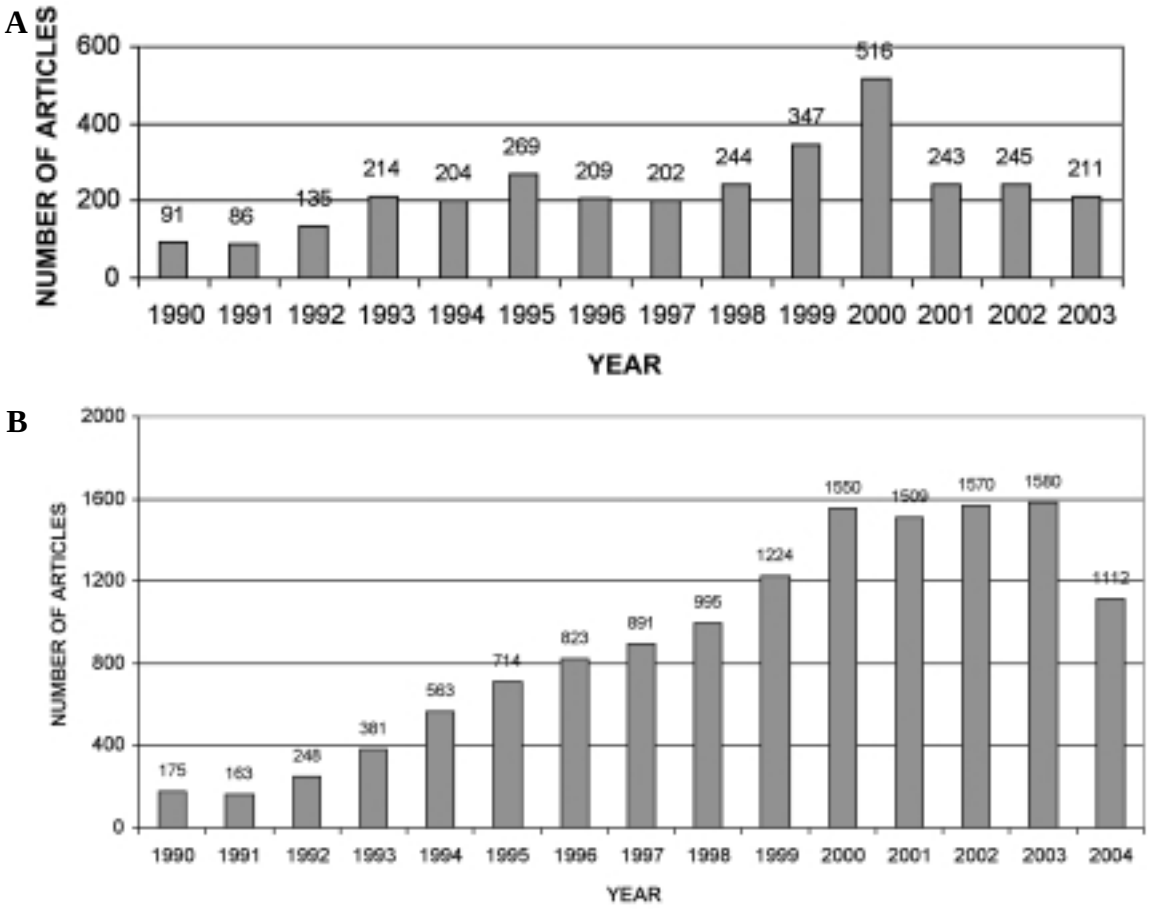

FIG. 1. (**A**) Number of newspaper, magazine, and journal articles mentioning human gene therapy published annually, 1990–2003. *Source*: LexisNexis Guided News Search, "General News" website (web.lexis-nexis.com/universe), 2004. (**B**) Number of human gene therapy articles published annually, 1990–2004 (from MEDLINE). *Source*: MEDLINE, OVID, 1966–2005. Search limited to humans, English language. Accessed February 11, 2005.

medical knowledge (in large part relating to increased understanding of genetic disease, achievements in rDNA, and progress in the Human Genome Project), or what McGinn terms *technical knowledge push* (McGinn, 1991), the public's anticipation and expectations of benefits from gene therapy contributed perhaps even more significantly to the commercial and scientific growth of the field (*technology pull*).

CLINICAL TRIALS

After the first U.S.-authorized HGT clinical trial occurred in 1990, activity in the field grew rapidly. More than 300 clinical protocols for human gene therapy were approved in less than 8 years (Anderson, 2003). As early as 1991, it became clear that rather than simply focusing on inherited (or genetic) diseases, gene therapy efforts would be applied to noninherited diseases, particularly cancer (Martin, 1999). According to the *Journal of Gene Medicine* gene therapy clinical trials database, 918 gene therapy trials had been or were being conducted worldwide by 2003 (*Journal of Gene Medicine*, 2004). Cancer research, with its high profile and large funding base, quickly dominated the gene therapy field.

Four main strategies exist for clinical trials using HGT in cancer treatment (Martin and Thomas, 1996):

- Developing new forms of immunotherapy such as the proliferation of cell populations in the immune system that have antitumorigenic properties
- Transferring drug-resistant genes into noncancer cells to protect them from chemotherapy toxins
- Targeting tumor cells with genes encoding protoxin-activating enzymes
- Enhancing or restoring the function of tumor suppressor genes

By late 1996, cancer was the target disease of more than 70% of U.S. gene therapy trials (Martin, 1999). At present, 66% of gene therapy clinical trials are designated for cancer research. Monogenic diseases, vascular diseases, and infectious diseases have garnered 9.8, 8.3, and 6.5%, respectively, of all gene therapy clinical trials (see Fig. 2). The clinical experimentation of HGT techniques for cancer has an advantage over trials for monogenic diseases, because the relative abundance of cases that cancer offers improves chances of recruitment for clinical trials (S. Rusconi, Department of Medicine, University of Fribourg, Pérolles, Switzerland; personal communication).

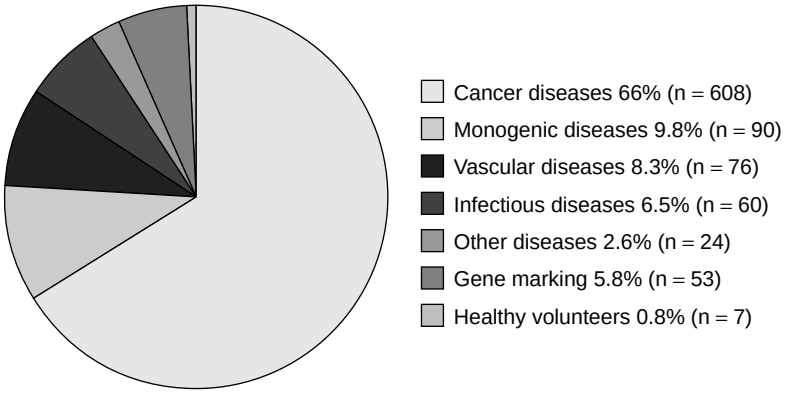

FIG. 2. Indications addressed by gene therapy clinical trials. Both completed and ongoing clinical protocols from around the world are addressed. *Source*: Reprinted by permission from the *Journal of Gene Medicine* (www.wiley.co.uk/genmed/clinical), 2004.

As of June 2003, the National Institutes of Health Recombinant DNA Advisory Committee (RAC) reported 590 reviewed gene therapy clinical trial protocols, 417 of which (70.7%) were aimed at treating cancer. Figure 3 shows the distribution of RAC-reviewed trials by disease targeted. In February 2004, Cavazzana-Calvo *et al*. reported in *Nature* that there were 888 approved gene therapy trials throughout the world. The United States, the United Kingdom, and Germany had the highest number of approved trials with 613, 96, and 55, respectively (see Table 1).

Although many new gene therapy clinical trials continue to be approved and conducted each year, their progress has not been without controversy. In 1995, NIH Director Harold Varmus appointed a panel to "assess the current status and promise of gene therapy and provide recommendations regarding future NIH-sponsored research in this area" (Orkin and Motulsky, 1995, p. 1). The panel determined that gene therapy clinical trials were not demonstrating a satisfactory level of efficacy, and its members were concerned that the "overselling of 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 than it actually is" (Orkin and Motulsky, 1995, p. 2). They feared that this misconception could both cause patients to ignore other potentially effective treatment options and lead to the neglect of much-needed further research on basic gene therapy techniques (Wadman, 1995). The panel recommended that future gene therapy clinical trials be geared toward more fundamental aspects of the technology that could realistically achieve measurable success, discouraged the NIH from expanding its gene therapy programs or funding, and asked gene therapy researchers to be more cautious in discussing their study results. The number of gene therapy protocols received for review by the NIH decreased somewhat between 1995 and 1996, suggesting that the panel recommendations may have had a slight dampening effect on HGT clinical trial activity (Recombinant DNA Advisory Committee, 2003). Nonetheless, the continuing growth of HGT trials and NIH grants awarded since 1996 indicates that the demand for gene therapy treatments remains a strong influence on development in this field (see Fig. 4).

GOVERNMENT INSTITUTIONS

The longitudinal funding activity of several government agencies illustrates the growth experienced in the field of gene therapy since 1990. The number of NIH grants awarded pertaining to gene therapy rose quite steadily after 1990, peaking at 1985 awards in 2001 (Fig. 4). The NIH has been involved with gene therapy from its inception, first in its regulatory capacity and second through its funding. The Recombinant DNA Advisory Committee (along with the Food and Drug Adminis-

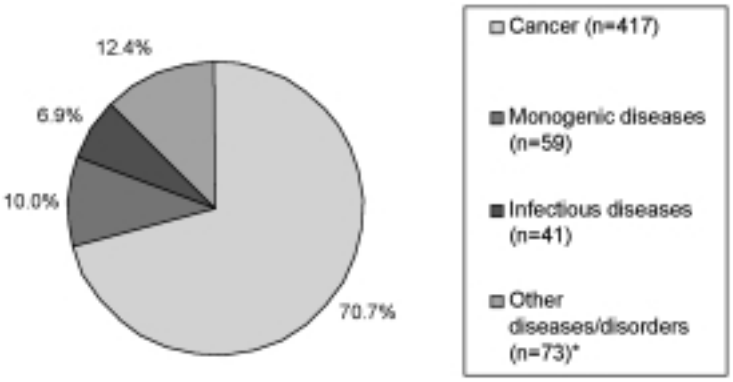

FIG. 3. Gene therapy clinical trial protocols reviewed by the Recombinant DNA Advisory Committee through June 2004. *Source*: Clinical Trials in Human Gene Transfer (RAC website, http://www4.od.nih.gov/oba/rac/clinicaltrial.htm), 2004. *This category includes vascular diseases, Alzheimer's disease, Parkinson's disease, ulcers, renal disease, and eye disorders, among others.

TABLE 1. APPROVED GENE THERAPY TRIALS IN 2004[a]

Country	*No. of trials*	*Country*	*No. of trials*
Australia	12	Japan	10
Belgium	15	Mexico	1
Canada	12	Netherlands	6
China	3	New Zealand	2
Czech Republic	1	Poland	3
Egypt	2	South Korea	1
Finland	3	Spain	3
France	18	Sweden	2
Germany	55	United Kingdom	96
Israel	21	United States	613
Italy	10		

[a]*Source*: Cavazzana-Calvo *et al.* (2004).

tration) was responsible for creating guidelines for human gene therapy experiments and for approving all U.S. clinical protocols. The NIH, which is considered by many to be the hub of the world's biomedical research community, also housed many of the earliest gene therapy researchers and their projects (including W. French Anderson, the director of the September 1990 inaugural gene therapy trial) and continues to conduct gene therapy trials relating to conditions such as cancer, diabetes, and immunodeficiency (National Institutes of Health, 2003).

The NIH has also collaborated with gene therapy start-up companies, providing resources and technologies to support their efforts (Thompson, 1994; Lyon and Gorner, 1995; Jain, 2000). It aided the development of gene therapy firms through the participation of its employees in Cooperative Research and Development Agreements (CRADAs), which, under the Federal Technology Transfer Act of 1986, both allowed and encouraged government employees to collaborate with private industry (Martin, 1999).

Anderson was the first federal employee to participate in a CRADA, fulfilling what lawmakers suggested was government scientists' "patriotic duty to collaborate with private industry to speed publicly funded research to the public" (Lyon and Gorner, 1995, p. 125). The sense of urgency underlying the creation of CRADAs seems fittingly applied to the growth of gene therapy, where basic and applied research were nipping at each oth-

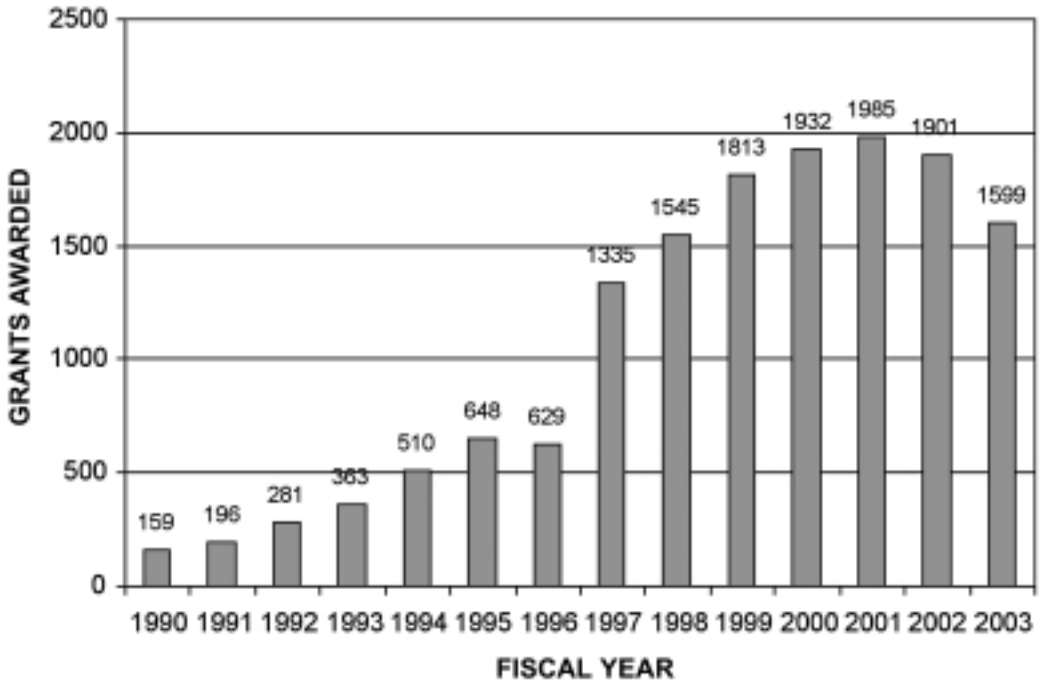

FIG. 4. NIH grants awarded for gene therapy, 1990–2003. Data were obtained by querying the NIH Computer Retrieval of Information on Science Projects (CRISP), a database of federally funded biomedical research. Records were selected by year and included if "gene therapy" appeared in their titles and/or abstracts. *Source*: CRISP database (http://crisp.cit.nih.gov), 2004.

ers' heels. As a highly in-demand technology, gene therapy could not afford to work within traditional institutional constraints. HGT is the kind of research program technology transfer was designed for, namely one requiring collaboration between government, business, and academia where the sector boundaries were sufficiently permeable to accommodate rapid clinical response to laboratory discoveries.

Increasing commercial activity in gene therapy since 1990 is also reflected in the number of U.S. patents issued. Between 1990 and 1995 there were a total of 13 patents issued with the term "gene therapy" cited in the title, abstract, or patent claims. During 1996, 17 HGT patents were awarded; that number increased to 49 and 91 over the next 2 years and rose to 131 in 2002 and 125 in 2003 (see Fig. 5). By the end of 2003, a total of 761 gene therapy patents had been issued. Because it takes an average of 22 months from the point of application for a patent to be issued (United States Patent and Trademark Office, 2003), we can infer that patent applications began accelerating around 1993. The gene therapy patents, which largely involve delivery systems, provided the key incentive for commercial investments in HGT. The venture capital pouring into HGT was a clear example of the effectiveness of federal policies such as the Bayh–Dole Act and the establishment of CRADAs between government employees and the private sector.

INDUSTRY

There has been a steady increase in new start-up companies predicated on human gene therapy since the year of the first clinical trial. Figure 6 shows the patterns of new firm formation from 1990 through 2001. In 12 years, 156 biotechnology firms cited HGT as one of their primary missions. Several of these firms have either been absorbed into larger companies or have folded as a result of the stock market downturn in 2000 or of the decline in the overall public image of HGT.

Many potential reasons for changes in industry growth rates may likely apply to gene therapy, including high levels of competition for scarce intellectual or personnel resources, the limited economic carrying capacity of the industry, and saturated potential markets. HGT firms were formed without a single successful product making it to market. If existing companies cannot report any tangible success, investors may be reluctant to fund new start-ups to achieve similar goals. Gene therapy researchers are well aware of how the challenges they face in creating marketable results limit business and funding opportunities (Stolberg, 1999). Highly publicized failures in the field, such as the tragic death of 18-year-old clinical trial participant Jesse Gelsinger in 1999, can also limit opportunities for new companies to be welcomed into the industry. At the same time, new approaches to or discoveries in gene therapy can revitalize growth, because a new company might seem more likely to be unfettered by obligations to outdated or dead-end technologies.

The high confidence placed in the potential medical impacts of gene therapy suggests that, although growth can be tempered by factors such as those listed above, a lack of success does not necessarily restrict commercial interest. Further, the conceptualization of gene therapy as a therapeutic (and even sometimes as a "drug," in the context of approaches intended to develop therapies with short-term effects that are administered repeatedly) has empowered the industry by earning many gene therapy companies the support and funding of large pharmaceuti-

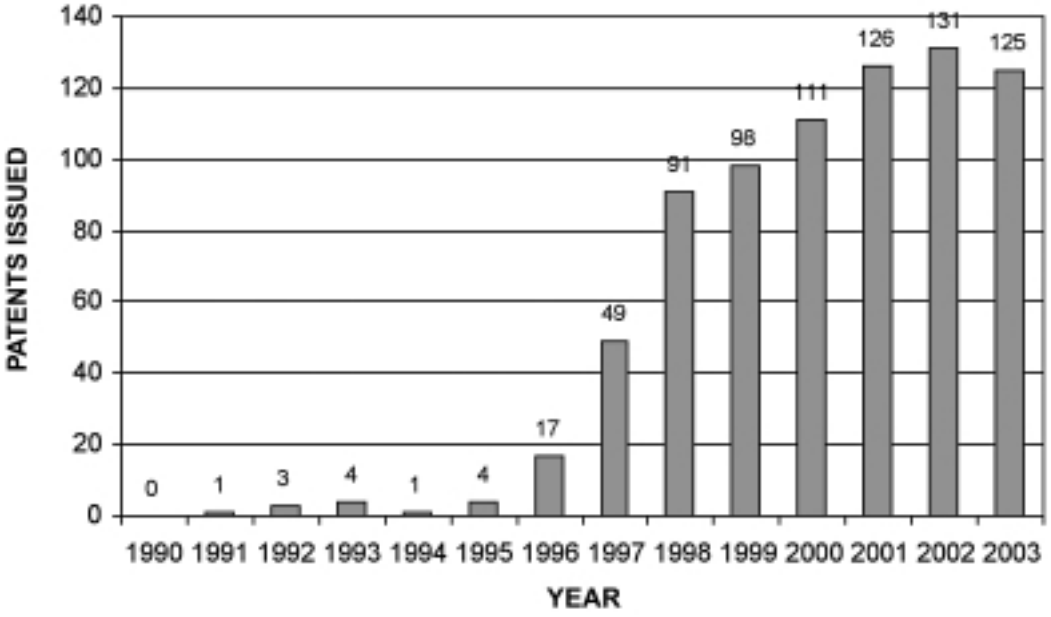

FIG. 5. Gene therapy-related patents issued, 1990–2003. Data were obtained by querying the U.S. Patent and Trademark Office Patent Full-Text and Full-Page Image Database. Records were selected by year and by whether they included "gene therapy" in their titles, abstracts, or "claim(s)" section (which "point out and distinctly claim the subject matter which the applicant regards as the invention"). *Source*: Patent Full-Text and Full-Page Image Database, U.S. Patent and Trademark Office (www.uspto.gov/patft/index.html), 2004.

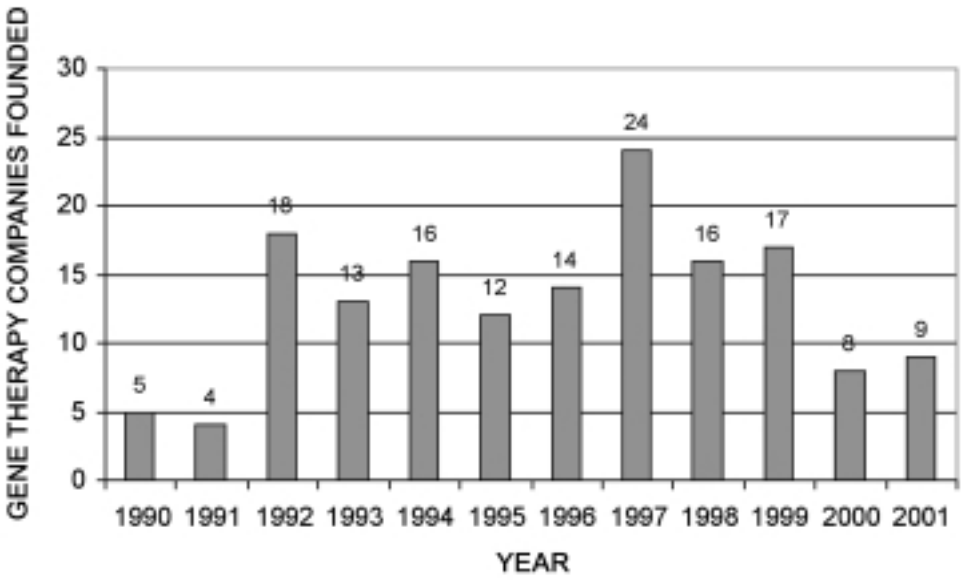

FIG. 6. Gene therapy companies founded, 1990–2003. Data were obtained from the following sources: *Genetic Engineering News*, 2003: GEN Biotechnology Database (http://www.gendatabaseonline.com); Jain (2000); and *Journal of Gene Medicine* (2003). Online Gene Therapy Companies Interactive Database. Accessed at URL http://www.wiley.co.uk/genmed/companies. Companies included were either dedicated to gene therapy or had a strong focus on gene therapy and were involved in either the identification of gene therapy application opportunities, development and/or testing of gene therapy techniques or delivery methods, and/or the development of products necessary for gene therapy. Website no longer available.

cal companies (Martin, 1999). Small and medium-sized biotech companies usually can carry a product only to phase II clinical trials. If an HGT product reaches stage III, these companies must rely on licensing or joint ventures with a major pharmaceutical company to proceed to phase III human trials.

The continuing influx of government funds to private gene therapy research and the close interconnections between government, industry and academic research organizations also create a safety net for gene therapy companies that not every scientific industry can boast. Perhaps even more significant is that many start-ups focused on using gene therapy in broader clinical contexts, beyond the treatment of heritable diseases, although the latter garnered most of the media attention in relation to HGT.

ACADEMIC CENTERS, JOURNALS, AND PROFESSIONAL ASSOCIATIONS

Since 1990, more than two dozen major universities have created centers or programs dedicated to HGT research. Given the expectations for gene therapy to reach clinical application, the majority of these research entities are located within medical schools, not science departments (emphasizing the applied nature of research activity in the field). Academic gene therapy research is not simply geared toward advancing knowledge or developing new techniques, but, instead, like its government and industry counterparts, it is actively involved in applied clinical research. In addition to academic programs, close to a dozen major gene therapy centers (sometimes referred to as "academic centers of excellence") have been founded at U.S. universities since the first gene therapy clinical trial, and much subsequent clinical trial activity has been or is being carried out at (or with the assistance of) these institutes (Jain, 2000). These centers serve as both the embodiment of and a location for the collaboration occurring between government, academia, and industry. An examination of the personnel, projects, and clinical trial activity shared between academic gene therapy centers, government institutes such as the NIH, and gene therapy companies demonstrates the strength and coherence of the social systems that have formed around gene therapy, which includes the "invisible colleges," or informal networks of researchers within which knowledge and ideas are shared, that facilitate innovation and growth within a field (Crane, 1972). These networks in gene therapy have grown despite the lack of widely applicable clinical successes.

The number of scientific publications in gene therapy increased rapidly during the early years of the field's development, growing from fewer than 50 in 1989 to more than 1200 in 1996 (Martin, 1999). At least nine refereed academic journals specifically focusing on gene therapy have been created since 1990 (see Table 2), further demonstrating the substantial

TABLE 2. REFEREED GENE THERAPY JOURNALS CREATED SINCE 1990[a]

Journal name	*Year first issued*
Human Gene Therapy	1990
Cancer Gene Therapy	1994
Gene Therapy	1994
Journal of Gene Medicine	1999
Genes and Immunity	2000
Gene Therapy and Regulation	2000
Molecular Therapy	2000
Current Gene Therapy	2001
Genetic Vaccines and Therapy	2003

amount of institutional support that the field has experienced. In addition to facilitating knowledge transmission in the field and publicizing the activities of various research organizations, these journals provide an opportunity for the "invisible college" of gene therapy to be extended and strengthened. Their editorial boards are staffed by personnel affiliated with every sector of the gene therapy field. Further, the emphasis of these journals on clinical trial activities underscores the dedication of the field to applied research.

A number of U.S. and international gene therapy professional associations have also formed since 1990. The U.S. association, called the American Society of Gene Therapy (ASGT), was founded in 1996 and today has more than 3000 members. The stated mission of the ASGT is to strengthen the connections between various gene therapy institutions. The blurred boundaries between the various institutions and the interactions between the various fields have become integral to its maintenance and to the fulfillment of HGT research goals, as indicated by the overlap between human gene therapy and cancer research.

CONCLUSION

Because the research space created for gene therapy in science and medicine was premised on widely publicized expectations of new clinical strategies and the proclaimed urgency for this space to be filled, gene therapy received a level of intellectual and financial support that facilitated rapid and steady expansion. To realize these expectations, gene therapy institutions engage in collaborative research efforts that cross institutional boundaries and that merge academic and commercial endeavors.

Perhaps the main issue that faces these institutions is whether their current networks can be sustained. The lack of significant gene therapy clinical trial successes over the past 14 years (as well as more recent high-profile failures) may prove to have an impact great enough to counteract the anticipation and demand from disease groups, clinicians, and research scientists that have fueled the growth of gene therapy thus far.

One of the few documented successes of gene therapy has been reported for children with X-linked severe combined immunodeficiency disease, who have experienced healthy immune function, in some cases for as much as 3 years after gene therapy treatments. However, the success in the treatment of X-SCID patients has been shrouded in controversy since 3 of the 10 patients treated at a French clinic, despite the benefit to their immune systems, developed leukemia. The discovery of the patients' cancer forced the researchers involved to temporarily stop the clinical trials until a proper analysis of what caused the leukemia was accomplished (*Gene Therapy Weekly*, 2003). Further, the "gene therapy causes cancer" mood that followed made many scientists and those who fund them hesitant to begin new gene therapy research. Therefore, it seems that even in those rare instances when gene therapy achieved its intended purpose, the possibility that it might also cause severe side effects from the retroviruses has thus far kept it from being identified as unambiguously successful. However, some scientists now believe that they understand the mechanism that brought on the leukemia in the HGT trials and contend that they are able to minimize the risk (Berns, 2004). Meanwhile, animal studies are revealing new risks such as acute toxicity and autoimmune anemia (Brunetti-Pierri *et al*., 2004; Gau *et al*., 2004).

Although many claim that the slow progress of HGT is quite understandable in a field still in its "infancy," others contend that this "excuse" seems invalid for a field well over a decade old (McNeish and Seckl, 2002). Unlike stem cell research, there remains broad popular acceptance of HGT as an approach to treat life-threatening genetic diseases. However, if clinical success remains elusive, a feeling of "enlightened impotence," or helplessness to address the genetic aspects of disease, may eventually cause biomedical research interests to focus less on those aspects of the HGT program designed to correct faulty genes (Nelkin, 1996). Moreover, if gene therapy continues to be an industry without marketable products, private funding may prove increasingly difficult to secure.

Future study of the social networks and institutions that have developed around gene therapy will clarify how the fluidity of institutional boundaries affects the design and practice of gene therapy research. A detailed analysis of the funding that supports gene therapy research and clinical trials (and the groups or organizations that supply it) might also shed further light on the complex interconnections of government, industry, and acadème, as well as provide a deeper understanding of why the field continues to grow. In addition, a closer examination of the scope and goals of gene therapy clinical trials (and how they may have changed since the 1995 NIH panel recommendations), the impact of the Gelsinger case, and the contribution of HGT to cancer therapy could offer some insight into the direction in which the field seems to be heading and how it is attending to the challenges it has faced.

ACKNOWLEDGMENTS

We thank Dr. Stuart Newman and Dr. Sandro Rusconi for thoughtful suggestions on an earlier version of this paper, as well as Dr. James Ennis for recommending several helpful resources, and Carol Costa for her assistance with the *Genetic Engineering News* Biotechnology Database. We also wish to declare that we have no financial interests (research funding, equity, intellectual property, or honoraria) in the biotechnology industry or any of the companies mentioned in this paper.

REFERENCES

ANDERSON, W.F. (1990). Why start a new journal on human gene therapy? [editorial]. Hum. Gene Ther. **1,** 1.

ANDERSON, W.F. (2003). History of gene therapy. Available at URL http://www.frenchanderson.org/history/history.asp (accessed February 2005).

BEGLEY, S., and HAGER, M. (1989). Brave new gene therapy. *Newsweek*, February 13, p. 65.

BERNS, A. (2004). Good news for gene therapy. N. Engl. J. Med. **350,** 1679–1680.

BRADY, D. (1990). Signals of hope (Gene therapy may cure cystic fibrosis). *Maclean's Magazine*, October 1, p. 52.

BROWNLEE, S., and SILBERNER, J. (1991). The age of genes. *U.S. News & World Report*, November, p. 64.

BRUNETTI-PIERRI, N., PALMER, D.J., BEAUDET, A.L., CAREY, K.D., FINEGOLD, M., and NG, P. (2004). Acute toxicity after high-

dose systemic injection of helper-dependent adenoviral vectors into nonhuman primates. Hum. Gene Ther. **15,** 35–46.
CAPRON, A.M. (1990). The impact of the report, Splicing Life. Hum. Gene Ther. **1,** 69–71.
CAREY, J. (1990). Cells that carry messengers of health. *Business Week*, May 28, p. 74.
CAVAZZANA-CALVO, M., THRASHER, A., and MAVILIO, F. (2004). The future of gene therapy. Nature **427,** 779–781.
CHECK, E. (2004). Gene therapists hopeful as trials resume with childhood disease. Nature **429,** 587.
CHECK, E. (2005). Gene therapy put on hold as third child develops cancer. Nature **433,** 561.
CRANE, D. (1972). *Invisible Colleges: Diffusion of Knowledge in Scientific Communities* (University of Chicago Press, Chicago).
FRIEND, T. (1990). New frontier: Designer genes take on cancer; treatment takes battle inside body. *USA Today*, October 30, p. 1A.
GAU, G., LEBHERZ, C., WEINER, D.J., GRANT, R., CALCEDO, R., MCCULLOUGH, B., BAGG, A., ZHANG, Y., and WILSON, J.M. (2004). Erythropoietin gene therapy leads to autoimmune anemia in macaques. Blood **103,** 3300–3302.
GENE THERAPY WEEKLY. (2003). Severe combined immunodeficiency: Scientists discover cause of leukemia that halted treatment trial for X SCID. November 6, p. 29.
JAIN, K.K. (2000). *Special Report on Gene Therapy Companies* (John Wiley & Sons, Chichester, UK).
JOURNAL OF GENE MEDICINE. (2004). Gene therapy clinical trials worldwide. Provided by the *Journal of Gene Medicine* and available at URL www.wiley.co.uk/wileychi/genmed/clinical (accessed February 2005).
LYON, J., and GORNER, P. (1995). *Altered Fates: Gene Therapy and the Retooling of Human Life* (W.W. Norton, New York).
MACER, D.R.J., AKIYAMA, S., ALORA, A.T., ASADA, Y., AZARIAH, J., AZARIAH, H., BOOST, M.V., CHATWACHIRAWONG, P., KATO, Y., KAUSHIK, V., *et al*. (1995). International perceptions and approval of gene therapy. Hum. Gene Ther. **6,** 791–803.
MARTIN, P.A., and THOMAS, S.M. (1996). *The Development of Gene Therapy in Europe and the United States: A Comparative Analysis*, pp. 69–78. STEEP Special Report No. 5 (University of Sussex Science Policy Research Unit, Brighton, UK).
MARTIN, P.A. (1999). Genes as drugs: The social shaping of gene therapy and the reconstruction of genetic disease. Sociol. Health Illness **21,** 517–538.
MCCORMACK, M.P., and RABBITTS, T.R. (2004). Mechanisms of disease: Activation of the T-cell oncogene LMO2 after gene therapy for X-linked severe combined immunodeficiency. N. Engl. J. Med. **350,** 913–922.
MCGINN, R.E. (1991). *Science, Technology and Society* (Prentice Hall, Englewood Cliffs, NJ).
MCNEISH, I., and SECKL, M.J. (2002). Gene therapy approaches for cancer. In *Gene Therapy: The Use of DNA as a Drug*. Brooks, G., ed. (London: Pharmaceutical Press).
NATIONAL INSTITUTES OF HEALTH. (2003). Clinical Trials website. Available at URL www.clinicaltrials.gov (accessed February 2005).
NELKIN, D. (1996). Covering gene therapy: Beware the hype. Quill **84,** 34–36. (Available at www.FACSNET.org)
NICHOLS, E.K. (1988). *Human Gene Therapy* (Harvard University Press, Cambridge, MA).
ORKIN, S.H., and MOTULSKY, A.G. (1995). Report and recommendations of the panel to assess the NIH investment in research on gene therapy. Available at URL http://www.nih.gov/news/panelrep.html (accessed February 2005).
PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH. (1982). *Splicing Life: The Social and Ethical Issues of Genetic Engineering with Human Beings* (U.S. Government Printing Office, Washington, D.C.) p. 44.
RECOMBINANT DNA ADVISORY COMMITTEE. (2003). Clinical Trials in Human Gene Transfer (protocol list). Available at URL http://www4.od.nih.gov/oba/rac/clinicaltrial.htm (accessed February 2005).
STOLBERG, S.G. (1999). Five questions: The long horizon of gene therapy. *New York Times*, December 12, Section 3, p. 4.
THE LANCET. (2004). Efficacy of gene therapy for SCID is being confirmed. [Editorial]. **364,** 2155.
THOMPSON, L. (1994). *Correcting the Code: Inventing the Genetic Cure for the Human Body* (Simon & Schuster, New York).
TURNEY, J. (1998). *Frankenstein's Footsteps: Science, Genetics and Popular Culture* (Yale University Press, New Haven, CT).
UNITED STATES PATENT AND TRADEMARK OFFICE. (2003). Patent Full-Text and Full-Page Image Database. Available at URL www.uspto.gov/patft/index.html (accessed February 2005).
WADMAN, M. (1995). Hyping results "could damage" gene therapy. Nature **378,** 655.

Address reprint requests to:
Dr. Sheldon Krimsky
Department of Urban and Environmental Policy and Planning
Tufts University
97 Talbot Avenue
Medford, MA 02155

E-mail: sheldon.krimsky@tufts.edu

Received for publication October 7, 2004; accepted October 14, 2004.

Published online: February 21, 2005.