INDUSTRY TREND

New Startups Move in As Gene Therapy Goes Commercial

Only 3 years ago, most biotechnology analysts considered gene therapy an experimental and unproven field—a technology for the next millennium rather than for the 1990s. But that's not how the field looks today. In 1990 researchers at the National Institutes of Health (NIH) performed the first experimental gene therapy on a human patient, a 4-year-old girl with adenosine deaminase (ADA) deficiency. This hereditary enzymatic disease had virtually wiped out her immune system, crippling her ability to fight infectious diseases. But after gene therapy, this first patient, and another girl who received the same treatment a year later, now lead essentially normal lives and go to public schools.

That pathbreaking treatment, plus a widening stream of other clinical trials, has changed the playing field for gene therapy, bringing new companies into existence and heating up the competition beyond what anyone would have predicted 5 years ago. Then, only four companies focused exclusively on gene therapy. Today nearly a dozen have gotten into the business; these jostle for position with major programs at well-established biotech companies. Even a few of the big pharmaceutical companies have gotten into the game by funding research. And many of these companies, whether in cooperation with academic researchers or on their own, are spewing forth proposals for testing gene therapy. To date, NIH and/or the Food and Drug Administration (FDA) review boards have approved a total of 43 proposals to put a variety of genes into human beings. "Three years ago people would say gene therapy was in the realm of the theoretical," says Alison Taunton-Rigby, vice president for biotherapeutics at Genzyme Corp. in Cambridge, Massachusetts. "People today believe it's real and doable."

Amid all the excitement, however, some researchers sound a cautionary note. They point out that despite extensive publicity, fewer than a hundred people have actually received gene therapy, and none of the treatments are anywhere near approval for widespread medical use. Leonard Post, vice president for experimental therapies at Parke-Davis, a division of Warner-Lambert Co., puts it this way: "There may be higher expectations for gene therapy than it can really justify right now. It's so visible, so highly reported in both the scientific and popular press," that the fervor may outpace the research. Indeed, as Richard Mulligan of the Whitehead Institute writes in an article in this issue, much more work is needed to develop safe and effective vectors for introducing genes into patients.

Still, there are plenty of companies eager to do that work, and so propel gene therapy into the marketplace. By many accounts, one corporate leader is Genetic Therapy Inc., or GTI, of Gaithersburg, Maryland. The company began in 1987 as a sort of silent partner with researchers, including NIH gene therapy pioneers W. French Anderson and Steven Rosenberg. Anderson credits GTI with pushing the entire field forward by providing—for free—the retroviruses used to introduce genes into cells. In exchange, GTI got experience and early access to new technology.

Now the company has entered a new phase. In the past year, NIH has approved two clinical trials sponsored by GTI itself—trials aimed at diseases with large potential markets: brain cancer and cystic fibrosis. And the company continues its long-standing association with Anderson, who recently moved to the University of Southern California, and funds his research on the next generation of viral vectors.

GTI has a head start in the field by virtue of being one of the "oldest" companies around. But as the field opens up, the competition is proliferating. Take one of the most common lethal genetic diseases, cystic fibrosis, or CF. The genetic defect that causes CF was identified 3½ years ago; successful gene therapy in mice was reported last summer. By December, NIH's gene therapy review board (the Recombinant DNA Advisory Committee, or RAC) had approved three proposals aimed at fixing the defect in humans; by March, two more had won approval. The biotech firms GTI and Genzyme are supporting two of the trials. And a third trial was initiated by Ronald Crystal, now at Cornell Medical Center, who 2 months ago helped found a new firm called GenVec, in Montgomery County, Maryland, to commercialize CF gene therapy. To round out the competition, a French company, Transgene, in Strasbourg, proposes to start CF clinical trials this year.

All these trials will put genes directly into the lungs or nasal cavities of patients. That strategy is called "in vivo" gene therapy—to distinguish it from earlier "ex vivo" methods, which involved inserting genes into cells in the culture dish, then putting them into people. From the point of view of many corporations, the in vivo approach is a welcome step toward commercialization. The more complicated ex vivo strategy might restrict gene therapy to advanced medical centers, whereas in vivo methods—once they prove themselves—may lead to "genes in a bottle" which can be used in ordinary clinical settings.

Still, believers insist that ex vivo treatments have a role to play, at least for the next few years. For example, the next hot disease target may be Gaucher disease, a debilitating enzymatic deficiency that affects white blood cells in about 15,000 Americans. Two firms—GTI and Theragen, of Ann Arbor, Michigan—have submitted gene therapy protocols for Gaucher disease for the June meeting of the RAC. Since this disease affects blood cells, which are relatively easy to collect and put back in the body, these protocols call for ex vivo therapy.

GENE THERAPY TRIALS: SOME CORPORATE LEADERS

Company	Year Founded	Disease Targets	Status
Genetic Therapy Inc.	1987	cystic fibrosis, cancer, Gaucher disease	two clinical trials approved; one more submitted
Genzyme	1981	cystic fibrosis, Gaucher disease	one clinical trial approved
Somatix	1988	cancer, neural and blood diseases	clinical trial ongoing
Targeted Genetics	1989	AIDS, blood diseases	AIDS clinical trial ongoing
Theragen	1991	Gaucher disease, arthritis, brain diseases	clinical proposal submitted
Transgene	1980	cystic fibrosis, AIDS, and cancer	clinical proposal submitted in France
Viagene	1987	AIDS, cancer, other infectious diseases	one clinical trial approved; two submitted
Vical	1987	cancer and infectious diseases	cancer clinical trial completed

Treating inherited genetic conditions is perhaps the most obvious application of gene therapy, but it isn't the only one—or the one that has the broadest potential market. Biotech companies are also focusing on infectious diseases, including AIDS, and on many forms of cancer. In treating cancer, the goal is to insert genes that will beef up the immune system's ability to recognize and destroy tumors, and researchers have already designed some clever techniques for doing just that. Companies such as Somatix Therapy Corp. of Alameda, California; Viagene Inc. of San Diego; and Vical Inc., also of San Diego, are working to modify cancer cells to make them more recognizable to the immune system. GTI has collaborated with Rosenberg to alter lymphocytes genetically to mount a stronger attack on cancers. And GTI is also beginning clinical trials that will attempt to put a "killer gene"—a herpes virus gene—into patients' brain tumor cells; a common antiviral drug will then be given to kill all cells expressing the gene.

The basic principle of using genes to alert the immune system also can be used against infectious diseases. Vical is working on such genetic vaccines, and Viagene is among the companies specifically targeting AIDS. In yet another approach, SyStemix Inc. of Palo Alto is working on adding HIV-resistant genes to bone marrow stem cells, the precursors of lymphocytes, to help fight HIV infection.

Behind the work on these diverse disease targets—both the inherited and acquired disorders—lies a growing body of research on gene vectors, which are the vehicles for getting genes into human cells. The "traditional" vector (if a 3-year-old field can be said to have traditions) is a modified retrovirus, which infects cells and delivers its payload of genes into the genome of the host cell. Retroviruses were used in most of the early clinical trials, including those on the two young ADA deficiency patients.

But other vectors are now attracting intense interest. The CF trials, for example, will use a modified adenovirus—one of the culprits that cause common colds—that was chosen for its known penchant for the human upper respiratory tract. Adeno-associated viruses are also attacting interest. A new company, Avigen Inc. of Alameda, California, formed last fall to explore applications of this vector. And some new gene transfer options don't require viruses at all. For example, "naked DNA" technology for making genetic vaccines is under development at Vical (*Science*, 19 March, p. 1691). Vical scientists simply inject DNA into muscle, the muscle produces the desired protein, and the immune system responds. Agracetus Corp. of Madison, Wisconsin, has developed a "gene gun" that shoots tiny, DNA-coated gold beads onto cells. In their recently completed in vivo melanoma trial, Vical and University of Michigan researcher Gary Nabel attempted to transfer genes into patients by using liposomes, positively charged fat molecules that bind to DNA and can carry it directly into tumor cells. And Targetech of Meriden, Connecticut, has hooked pieces of DNA to a protein, which is then recognized by receptors on liver cells; the modified genes then enter only the liver.

For now, however, no one knows which of these delivery systems will prove safe and efficient enough to be used by thousands of people. And until that happens, says Nelson Wivel, executive secretary of the RAC committee, "gene therapy won't be a major player in the therapeutic armamentarium. There's lots to be done first." Still, Wivel and others are confident that corporate interest—and funding—for gene therapy will continue to grow rapidly. At age 3, gene therapy is already mature enough to pair up with corporate partners—and there are plenty of willing suitors eager for a match.

–Elizabeth Culotta

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