BY DENISE MYSHKO

Gene Therapy Research *Makes Progress*

Despite some setbacks, researchers believe gene therapy is still a viable option for therapeutic research and potential innovative treatments.

With all the progress that has been made in genomics, targeting therapies to correct the defective genes responsible for disease seems quite realistic. But developing commercial gene therapies to treat diseases through modifying the expressions of an individual's genes or correcting abnormal genes has proven to be more difficult.

While hundreds of treatments that involve the administration of DNA to treat many different diseases are currently being investigated as gene therapy candidates, the Food and Drug Administration has yet to approve any human gene therapy products. In fact, only one gene therapy product has been approved by any regulatory agency, and that product is Gendicine. The approval was granted in October 2003 in China, for the treatment of head and neck squamous cell carcinoma. (See box on page 22.)

The Promise of Gene Therapy

The National Institutes of Health (NIH) of the United States is playing an important part in helping to advance research and development into applications for gene therapy. All gene therapy trials in the United States must be


H. Stewart Parker
Targeted Genetics

The database for gene therapy adverse events, or safety issues, is minimal compared with some of the other technology sectors.

approved by the FDA before they may proceed and are subject to all the regulations and standards governing any drug development trial. In addition, proposed protocols are reviewed by the Recombinant DNA Advisory Committee (RAC) of the NIH.

There are 572 gene therapy clinical trials, excluding the gene marker studies and nontherapeutic trials, of which 200 are actively being pursued, according to a report from research and consulting group Jain PharmaBiotech. The largest number (405) are for cancer.

Researchers are testing several approaches to gene therapy, including: replacing a mutated gene that causes disease with a healthy copy of the gene; inactivating, or "knocking out," a mutated gene that is functioning improperly; or introducing a new gene into the body to help fight a disease.

A carrier molecule called a vector is used to deliver the therapeutic gene to the patient's target cells. Currently, the most common vector is a virus that has been genetically altered to carry normal human DNA. Those in the field say work continues to improve the vectors, and it is certainly possible to develop a safe gene therapy.

In the United States a number of gene therapy trials are moving toward Phase III. Such research could lead to gene-based treatments for cancer, cystic fibrosis, heart disease, hemophilia, wounds, infectious diseases such as AIDS, and graft-versus-host disease.

According to Joyce Frey-Vasconcells, Ph.D., executive director of PharmaNet Consulting, two of the greatest opportunities for gene therapy lie in genetic diseases and cancer.


Christopher Reinhard
Cardium Therapeutics

"There is still a lot to be learned in cancer," she says. "There are a number of trials that are trying to transduce cytokines to gear up the native immune response. Cancer research in this area is the furthest along, and there are a couple of studies in California on genetic diseases, which are in Phase II right now. With genetic diseases, generally the trials are much smaller and are based on an endpoint of replacement therapy vs. survival so they can move along much faster."

Gene therapy also has promise in regenerative medicine, says Christopher Reinhard, chairman, CEO, and president of Cardium Therapeutics Inc.

"When gene therapy first emerged, people thought its role would be for treating genetic disorders," he says. "We've found through the use of adenovector technologies that gene therapy is also a regenerative medicine technique. Gene therapies produce a localized and sustained production of protein at the injury site. This is very different from supplying proteins produced outside of the body as with most current biologics. Proteins supplied by intravenous or other injection generally diffuse throughout the body, and they also tend to have a very short half-life because they are both dispersed and degraded quickly."

Works in Progress

The highly complex, and sometimes misunderstood, scientific research of gene therapy is often played out in the public arena, and as a result failures and setbacks are highly visible.

Gene therapy has gone through the initial excitement phase, and now researchers are working to understand the practical realities and narrow the science's focus and utility.

The most recent setback happened in July 2007. Targeted Genetics Corp. was conducting Phase I/II trials of tgAAC94, an investigational therapy for the treatment of inflammatory arthritis. On July 24, the company stopped the trial after the occurrence of a serious adverse event in one subject. The patient later died.

Although it was thought that the death could possibly be related to Targeted Genetics' product because of the timing of administration of the second dose and symptoms, later findings point to another factor. According to H. Stewart Parker, president and CEO of Targeted Genetics, a fungal infection called histoplasmosis played a significant role in the patient's death.

"The general conclusion is that it is very unlikely that our drug had anything to do with the patient's death, which was most likely caused by an undiagnosed and untreated histoplasmosis," Ms. Parker says. "After some additional molecular tests, we feel good about the product and its effectiveness.

The gene therapy market is expected to reach $5.74 billion by 2011
with an annual growth rate of 68.3%.

— Frost & Sullivan

"I don't think this tragic event should impact gene therapy," she adds. "When there is an event like this, the news is on the front page. We have some work to do to make sure that people understand gene therapy and that it has great promise."

The FDA in November 2007 removed the clinical hold on tgAAC94, and Targeted Genetics has amended the protocol to encompass suggestions made by the FDA and its independent data safety monitoring board.

The product candidate uses a recombinant AAV (adeno-associated virus) vector technology to deliver a DNA sequence that encodes a soluble form of the TNF-alpha receptor.

In November 2007, the company

announced that interim data from its Phase I/II trial of tgAAC94 suggest that the investigational therapy showed improvement in patient-reported outcome measures. The company is continuing with the Phase I/II study and plans to begin a Phase II trial of tgACC94 in the second-half of 2008. The Phase II clinical trial of tgAAC94 will be designed to evaluate efficacy and duration of response, as well as further assess safety in patients who are not candidates for systemic protein therapy, because they have at least one inflamed joint or they do not fully respond to systemic anti-TNF protein therapy.

Another company developing gene therapy products using the AAV vector is Ceregene Inc. The company is conducting Phase II trials of CERE-120 for the treatment of Parkinson's disease. Clinical and preclinical data to date suggest CERE-120 may have the ability to both improve symptoms of Parkinson's disease and slow disease progression.

FACTORS AFFECTING GENE THERAPY PROGRESS

Short-Lived Nature of Gene Therapy

Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional and the cells containing the therapeutic DNA must be long-lived and stable. Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits. Patients will have to undergo multiple rounds of gene therapy.

Problems with Viral Vectors

Viruses, while the carrier of choice in most gene therapy studies, present a variety of potential problems to the patient: toxicity, immune and inflammatory responses, and gene control and targeting issues. In addition, there is a concern that the viral vector, once inside the patient, may recover its ability to cause disease.

Multigene Disorders

Conditions or disorders that arise from mutations in a single gene are the best candidates for gene therapy. Unfortunately, some the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are caused by the combined effects of variations in many genes.

Immune Response

Any time a foreign object is introduced into human tissues, the immune system is designed to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a potential risk.

Source: U.S. Department of Energy Office of Science, Office of Biological and Environmental Research, Human Genome Program.
For more information, visit ornl.gov/hgmis.

FACTORS INFLUENCING THE GENE THERAPY MARKET

Reproducibility of Gene Therapy Methods

Gene therapy relies on the concept of site-specific recombination, thereby removing the defective gene in place. While some therapies, such as the administration of the growth hormones, have met with reasonable success, the same process needs to be replicated with genes affected in other diseases or disorders. To do so, a thorough understanding of the gene function and its interaction with other genes and transcription proteins is a necessity.

Successful Design of Clinical Trials and Regulatory Approval

With the presence of a genetically heterogeneous population in United States, Europe, and major parts of the world, clinical trials need to consider the genetic polymorphism underlying the genomes of individuals in these locations and appropriately work toward classifying the relevance of applying therapy trials using genes in their original forms.

Source: Frost & Sullivan, San Antonio.
For more information, visit frost.com.

> In the U.S., 405 out of the 572 gene therapy protocols are for cancer.
>
> — Jain PharmaBiotech

Ceregene has partnered with Genzyme Corp. for the development and commercialization of CERE-120.

CERE-120 is composed of an AAV vector carrying the gene for neurturin (NTN), a naturally occurring protein known to repair damaged and dying dopamine-secreting neurons, keeping them alive and functioning normally. NTN is a member of the same protein family as glial cell-derived neurotrophic factor (GDNF). The two molecules have similar pharmacological properties and both have been shown to benefit the midbrain dopamine neurons that degenerate in Parkinson's disease and are responsible for the major motor impairments.

"We chose AAV for a number of reasons, one of which is that when it is injected into the brain of animals, it almost exclusively expresses in neurons," says Jeffrey Ostrove, Ph.D., president and CEO of Ceregene.

CERE-120 is delivered by surgical injection to the brain. The company conducted a Phase I study in patients with midstage symptoms who are starting to fail on conventional dopamine therapy.

"The trial results revealed a 36% improvement in patient scores at 12 months," Dr. Ostrove says. "In the Phase I trial, there were almost no adverse events that were product related."

Separately, Genzyme is conducting a Phase I/II trial of a gene therapy approach designed to restore the therapeutic effectiveness of levodopa by enhancing the brain's ability to convert the chemical into dopamine. This program, which was acquired from Avigen Inc., also uses an AAV vector. Levodopa is the most common treatment for Parkinson's disease, but its efficacy diminishes as the disease progresses.

Genzyme is working on other programs as

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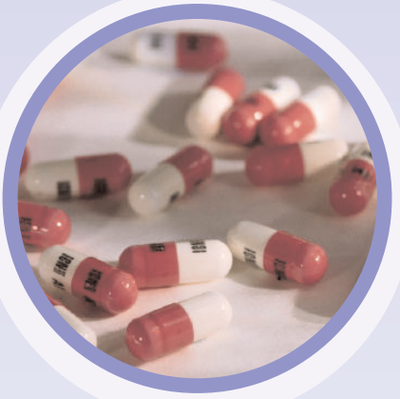

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The science of gene therapy is compelling, and we all believe that when gene therapy is able to be commercialized, this will change the treatment of many diseases.

Dr. Jeffrey Ostrove
Ceregene

well. The most advanced is in a Phase II clinical trial examining the safety and effectiveness of locally delivered Ad2/HIF-1a, an engineered form of the HIF-1a gene using an adenovirus vector for the treatment of peripheral arterial disease (PAD). PAD is a common circulatory problem in which narrowed arteries reduce the blood flow to a patient's limbs. Genzyme's therapy is designed to promote the growth of new blood vessels and improve circulation in the limbs of patients with peripheral arterial disease.

"We chose to use an adenovirus vector for that program for a couple of reasons," says Sam Wadsworth, Ph.D., group VP for translational research at Genzyme. "First, the manufacturing methods for adenovirus are more advanced than other vectors. Second, the performance characteristics of the adenovirus vector are ideal for this indication, which involves having the therapeutic protein, HIF-1 alpha, expressed for a relatively short period of time."

Dr. Wadsworth says the PAD program uses a very localized approach; the vector itself is injected into the muscle of the affected leg.

"This is a very good way to deliver this type of therapeutic," he says. "We like to think of gene therapy as a local therapy."

Genzyme also has preclinical gene therapy programs to address Niemann-Pick disease, a lipid storage disorder in which harmful quantities of a fatty substance (lipids) accumulate in the spleen, liver, lungs, bone marrow, and the brain; age-related macular degeneration; and amyotrophic lateral sclerosis.

For its lead product candidate, Generx, Cardium Therapeutics also is using an adenovirus vector. Generx is in Phase III trials for the treatment of myocardial ischemia (insufficient blood flow within the heart muscle) and associated angina due to coronary heart disease. The adenovector platform delivers the fibroblast growth factor 4 (FGF-4) gene to stimulate angiogenesis. Helping the body produce new blood vessels reduces myocardial ischemia, which is the underlying cause of angina.

"Generx is a disease modifier, and it stimulates an angiogenic process to enhance the circulation or the perfusion of the heart," Mr. Reinhard says. "The product uses a standard diagnostic catheter. We administer the drug into the large capillary veins. There is a receptor in the heart called the coxsackie-adenoviral receptor and the drug is believed to be taken up by these receptors and then produces FGF-4, a localized protein in the heart tissue where it is needed."

The Ups and Downs of an Emerging Market

Despite progress in the clinic, analysts at Frost & Sullivan say gene therapy is an emerging market and has only recently begun to spring up in the last year or so.

With only one gene therapy approved in the world, the market is expected to grow.

Frost & Sullivan estimates that the gene therapy market could reach $5.74 billion by 2011 with an annual growth rate of 68.3% largely due to investments from investors in the life-sciences sector and research grants that promote gene therapy research in universities and spin-off companies.

Gendicine Stands Alone

China-based Shenzhen SiBiono GeneTech Co. Ltd. made history by being the first company in the world to successfully commercialize a gene therapy product. In October 2003, SiBiono obtained the Drug License, Production Approval, and GMP Certificate from the China State Food & Drug Administration (SFDA) for the recombinant human Ad-p53 injection, trademarked as Gendicine.

Gendicine is made up of two components: normally functioning p53 genes and an adenovirus carrier or vector to transport this p53 into cancer cells.

In various documents, company officials have defined Gendicine in more technical terms as "a replication incompetent, recombinant, human adenovirus of serotype 5 engineered to contain the human wild-type p53 tumor suppressor gene."

In simpler terms, Gendicine is injected directly into tumors with the aim of restoring normal p53 restraints on growth, thereby rendering cancer cells less virulent.

Gendicine was approved for use in head and neck squamous cell carcinoma (HNSCC). Reports also link its experimental use in the clinical trial setting to treat cancers of the digestive tract (esophageal, gastric, colon, liver, pancreas, gallbladder, rectum), lung cancer, sarcoma, thyroid gland cancer, breast cancer, cervical cancer, and ovarian cancer. In addition, advanced cancer patients with no other feasible avenues of treatment are being allowed, on a case-by-case basis, to receive the new drug.

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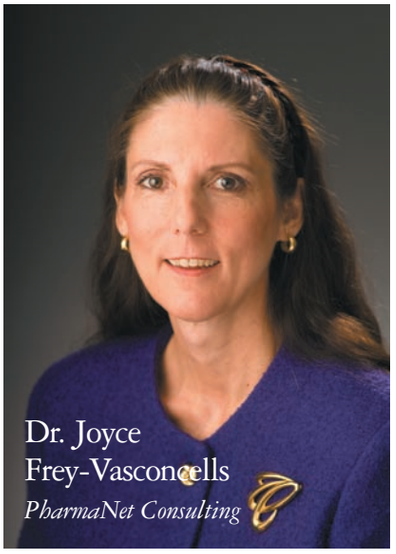

Patients are still very encouraged by gene therapy, which holds a lot of promise, especially for genetic diseases and cancer.

Frost & Sullivan analysts speculate that the market could boom after 2011, reaching $3.5 billion by 2011 in the cancer research segment alone. Similarly, in Europe the market is expected to reach $1.1 billion by 2011.

The key factors that could influence the market for gene therapy in the United States and Europe include a mix of technological and regulatory issues that need to be monitored closely.

Gene therapy has faced scrutiny almost from the start. The death of 18-year-old Jesse Gelsinger in 1999 during a study at the University of Pennsylvania appeared to be the direct result of the gene therapy treatment he was receiving for ornithine transcarboxylase deficiency (OTCD). He died from multiple organ failure four days after starting the treatment. Jesse's death is believed to have been triggered by a severe immune response to the adenovirus vector carrying the gene.

Another blow came in January 2003, when the FDA placed a temporary halt on all gene therapy trials using retroviral vectors in blood stem cells. The FDA took this action after it learned that a second child treated in a French gene therapy trial had developed a leukemia-like condition; another child had developed a similar condition the previous August. In that study, researchers used a retroviral vector carrying a therapeutic gene into blood stem cells of several young children, and returned these cells to the patients. Still, nine of the 11 children had promising results and could leave the hospital and lead relatively normal lives.

"The publicity around gene therapy means when there is a serious adverse event, there is generally negative press," Dr. Frey-Vasconcells says. "But gene therapy is no different from any other investigational product. Our responsibility is to make sure we've done everything possible to make the product as safe as possible."

In addition, Dr. Ostrove says gene therapy research has faced several developmental challenges.

"The majority of gene therapy trials are in oncology, which is a hard field," Dr. Ostrove says. "Many gene therapy trials involve late-stage cancer patients. In other cases, the patients' immune systems mounted a response against the vectors and shut down their expression. Additionally, many of the first gene therapy trials were conducted at academic institutions where the primary focus was on innovative research but often at the expense of employing commercially feasible methods and products."

The key factors that could influence the market for gene therapy in the U.S. and Europe include a mix of technological and regulatory issues that need to be monitored closely.

— Frost & Sullivan

Dr. Frey-Vasconcells says finding the right vectors also has been a challenge.

"In the early 1990s, much of the research involved ex vivo transduced cells, which didn't have longevity," she says. "Now researchers have found numerous ways to deliver the vectors directly. While there are a number of trials using direct administration, I believe integration is still an issue. The trial in France, which led to the temporary halt on trials by the FDA, shows that we have no control on where these genes will integrate on the DNA." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

JOYCE L. FREY-VASCONCELLS, PH.D. Executive Director, PharmaNet Consulting, Princeton, N.J.; PharmaNet Consulting, part of PharmaNet Development Group, provides solutions to the many potential obstacles inherent in designing, planning, and coordinating regional and global clinical trial programs. For more information, visit pharmanet.com.

JEFFREY M. OSTROVE, PH.D. President and CEO, Ceregene Inc., San Diego; Ceregene is a biotechnology company focused on the development of gene therapies for neurodegenerative disorders. For more information, visit ceregene.com.

H. STEWART PARKER. President and CEO, Targeted Genetics Corp., Seattle; Targeted Genetics is a biotechnology company committed to the development of innovative targeted molecular therapies for the prevention and treatment of acquired and inherited diseases with significant unmet medical need. For more information, visit targen.com.

CHRISTOPHER J. REINHARD. Chairman, CEO, and President, Cardium Therapeutics Inc., San Diego; Cardium Therapeutics is a medical technology company primarily focused on the development and commercialization of novel biologic therapeutics and medical devices for cardiovascular and ischemic disease. For more information, visit cardiumthx.com.

SAM WADSWORTH, PH.D. Group VP, Translational Research, Genzyme Corp., Cambridge, Mass.; Genzyme is a biotechnology company focused on rare inherited disorders, kidney disease, orthopedics, transplant, cancer, and diagnostic testing. For more information, visit genzyme.com.