Cardiac Gene Therapy

By Jill Max

WHEN EIGHTEEN-YEAR-OLD Jesse Gelsinger died less than three years ago while participating in a gene therapy trial for ornithine transcarbamylase (OTC) deficiency at the University of Pennsylvania, the field of gene therapy took a hit that sent it reeling. The FDA temporarily halted clinical gene therapy trials and the public shied away from what it perceived as a dangerous new treatment that could all too easily go awry. Despite these setbacks, however, gene therapy retains its promise as a new approach to treat a host of diseases, and coronary heart disease is emerging as one of the most likely targets.

Millions of people stand to benefit from any new treatment of heart disease, including gene therapy. According to the American Heart Association, more than 12 million people in the U.S. suffer from coronary heart disease. It is the leading cause of death in this country. More than 600,000 percutaneous transluminal coronary angioplasties (PTCA's), and more than 500,000 coronary bypasses were performed in 1999 in the U.S. alone. What's more, there are about 100,000 patients who can't be helped by any known treatment or medicine.

The major problem involved in coronary heart disease is blocked arteries. Atherosclerosis, the development of artery-clogging plaques, and ischemia, a condition in which the heart muscle is deprived of oxygen and nutrients, can lead to angina, which is pain or discomfort caused by reduced blood supply to the heart muscle. They can also lead to a heart attack, known as a myocardial infarction, where blood supply is severely reduced or stopped completely.

Nature has its own way of dealing with blocked arteries. In a process called angiogenesis, the body upregulates genes to stimulate the growth of new capillaries, which develop into larger blood vessels. In the heart, this is sometimes so successful that a "natural bypass" will be created, in which a new artery grows to take over blood flow from a clogged artery.

Therapeutic angiogenesis aims to do the same thing. By injecting the same proteins or genes that the body naturally produces into the heart muscle or the coronary artery, scientists are now able to prompt the heart to start its angiogenic motor to grow new blood vessels. While there is a risk that other diseases, like cancer, might be able to hijack the new blood supply, research so far has proven the therapy to be safe.

There are about 20 different known angiogenic growth factors, and scientists are working with a handful of them to try to stimulate

angiogenesis. Vascular endothilial growth factor-1 (VEGF-1) was the first of the family of growth factor genes discovered. There are now at least five different isoforms, including VEGF-2 and VEGF-121. The most important feature that VEGF-1 and VEGF-2 share is the ability to stimulate endothilial cells – the cells that become blood vessels – in ischemic tissue. VEGF-121 is the type that binds the least to heparin, a substance that inhibits blood coagulation, which in theory may allow it to diffuse easier.

Another type of growth factor, called fibroblast growth factor-4 (FGF-4), is one of the key genes in developing the human heart in embryogenesis. After birth, it shuts off, but researchers hope that administering it will kick start the process of blood vessel growth. "While VEGF stimulates capillary growth, FGF can stimulate larger blood vessels," said Michael Simons, M.D., Chief of Cardiology at Dartmouth Medical School and a pioneer in protein therapy for coronary heart disease. "But neither of these may be the long-term answer for cardiac gene therapy," he said. It may be that a combination of growth factors is required, or that some type of master-

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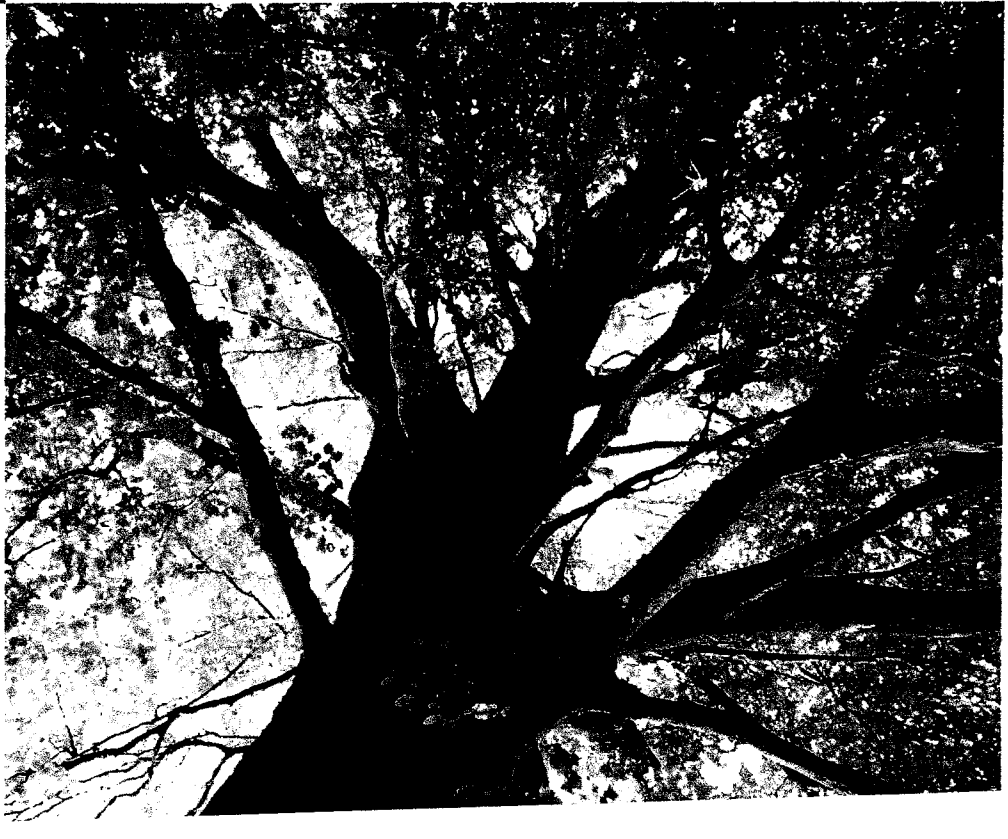

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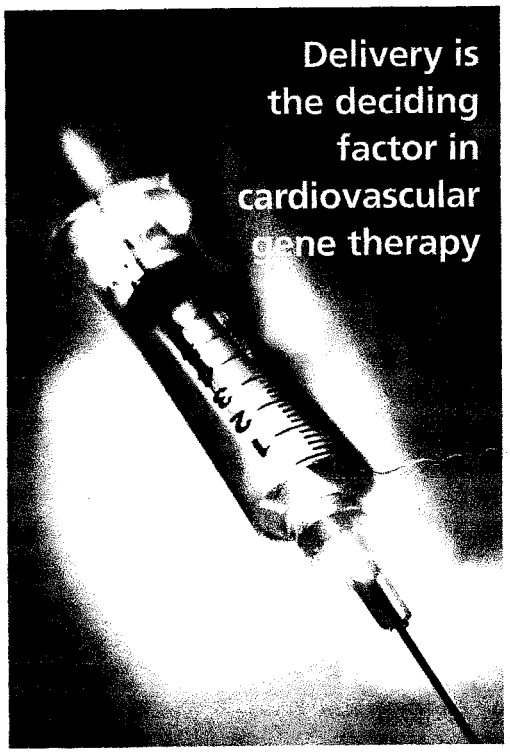
switch gene is the best bet. Genzyme Biosurgery is currently conducting Phase I trials using hypoxia-inducible factor-1 alpha (HIF-1 alpha), which resides upstream from VEGF. It acts as a switching signal to turn on VEGF, and may possibly stimulate other growth factors as well.

Deciding which gene to use is just part of the gene therapy process. "Delivery is the deciding factor in cardiovascular gene therapy," said Jack W. Reich, Ph.D., Chairman and CEO of Collateral Therapeutics, Inc., a company whose gene therapy product GENERX, which uses FGF-4, is about to enter Phase III clinical trials. GENERX is delivered via cardiac catheterization directly into the coronary artery, a process which Reich said is minimally invasive and is similar to delivering the dye for an angiography. In fact, the therapy can be done in conjunction with an angiography, making it possible to combine diagnosis and treatment.



Cardiac gene therapy can also be administered via intramuscular injection into the heart. This approach allows for localized delivery to the areas of ischemia and may mean that the therapy will be more efficient because the drug stays in the heart where it's needed, without a lot of diffusion into the rest of the body, according to Henrik Rasmussen, Ph.D., Senior V.P., Clinical Research and Regulatory Affairs for GenVec, another company whose product is being tested.

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Most current studies use an adenovirus, an inactive cold virus, to deliver the gene. But some researchers have been using a plasmid, or single strand of DNA, to deliver the gene. The theory behind using naked DNA is that since heart disease is chronic, it's likely that patients will need to be treated more than once. "If a virus is used to deliver the gene, patients may develop antibodies which will render the treatment less effective," explained Douglas Losordo, M.D., Chief of Cardiovascular Research at St. Elizabeth's Medical Center in Boston, MA and principal investigator of trials involving VEGF in collaboration with Vascular Genetics Inc. "It may also mean the treatment is safer," he said.

But some researchers believe that using a virus is more efficient. "The whole point of a vector is to get the material into the cell," said Cindy Grines, M.D., director of the cardiac catheterization laboratories and the interventional cardiology training program at William Beaumont Hospital in Royal Oak, MI, and lead author of a recent study called the Angiogenic GENe Therapy (AGENT) trial, which was done in collaboration with Collateral Therapeutics. "A naked plasmid is not very efficient."

But whether a viral vector is better than naked DNA, or which gene or combination of genes works better and how they should be delivered, is still up for speculation. No cardiac gene therapy has yet been approved by the FDA. Results from the AGENT trial, the first placebo-controlled double-blind trial, were encouraging. Sixty patients treated with Ad5-FGF4 (GENERX) were able to increase their exercise treadmill time significantly compared to a placebo group of 19 patients. "In many cases, the results were similar to patients who undergo bypass surgery, and better than those who are treated with medication or angioplasty," said Reich of Collateral Therapeutics.

The stage is now set for Collateral Therapeutics, which has emerged as the industry leader, to start Phase III trials. One trial will take place in the U.S., involving up to 100 medical centers and as many as 500 patients. "It's the largest gene therapy trial the

FDA has ever authorized, according to the FDA," said Reich. A similar trial will take place in Europe. According to William Li, M.D., President and Medical Director of the Angiogenesis Foundation, "the proof of angiogenesis will be in the Phase III trials."

But even if Collateral Therapeutics is the first to cross the finish line, other companies are in hot pursuit. Researchers working in collaboration with Vascular Genetics recently completed two trials with 30 patients each, using VEGF-1 and VEGF-2. Patients treated with the gene, particularly VEGF-2, reported a marked decrease in their angina. A randomized, double blind multi-center Phase II/III trial involving 400 patients who will be treated with VEGF-2 and followed for three months is about to begin. Researchers say the results could be pivotal and may pave the way for FDA approval.

Meanwhile, GenVec's Phase II testing of its cardiac gene therapy using VEGF-121 'BioBypass) is nearing completion and Phase III testing may begin as early as the beginning of 2003. Valentis, Inc. is also currently conducting Phase II trials using VEGF-165.

While therapeutic angiogenesis to treat ischemia and angina is by far the most widely applied form of cardiac gene therapy research so far, other applications are emerging as well. One of these is to use angiogenesis to treat congestive heart failure, a condition in which the heart is unable to pump enough blood to meet the body's needs, and which affects almost five million people in the U.S. Collateral Therapeutics recently obtained a patent for a gene transfer technology developed at the University of California for a cardiac adenylylcyclase (AC) gene which has been shown to enhance cardiac function in preclinical studies.

In another approach to treating congestive heart failure, researchers from Massachusetts General Hospital in Boston recently reported that they were able to restore normal function to damaged heart cells by injecting them with a genetic derivative of phospholamban, a cardiac protein that blocks normal calcium flow inside heart cells. By inhibiting the protein, calcium movement was improved and the cells were able to relax and contract normally. Preclinical trials are currently underway to test the therapy in live animals.

Collateral Therapeutics is also focusing on gene therapy aimed at heart muscle regeneration to improve cardiac function. The company is sponsoring research to identify genes that could prevent or reduce scar tissue in the heart. Last June, researchers at the University of Texas Southwestern Medical Center at Dallas identified a new protein called myocardin, which turns on cardiac genes and is essential for heart formation. If it turns out to be a kind of master gene, it could play a role in repairing hearts that have been damaged by heart attacks.

Cardiac gene therapy, in particular angiogenesis, may some day change the way coronary heart disease is treated, but right now it's still in its infancy. "We're in the first loop of the race," said Li, of the Angiogenesis Foundation. As research progresses, it's likely that the therapy will be used in conjunction with existing treatments, that combination therapy using several genes will be developed, or that it could be tailored to individual patients. "We're beginning to understand that there's enormous heterogeneity in patients," said Li, pointing out that just as penicillin doesn't work for everyone, gene therapy may be more successful in some patients than in others. "The ability to generate angiogenesis for cardiovascular disease has the same implications as antibiotics did for infections." There's little doubt that it will someday play a major role in cardiac medicine.

Jill Max is a freelance science writer from Trumbull, Connecticut.

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