Gene therapy seems to be moving past the “proof of principle” phase with two new treatments described at the 70th Scientific Sessions of the American Heart Association meeting held in Orlando, Fla November 9 through November 12, 1997. “It is an opening door,” said Valentin Fuster, MD, incoming American Heart Association President and director of the Cardiovascular Institute at Mount Sinai Medical Center in New York City. “It’s not definitive, but it’s certainly very exciting.”

In each case, researchers used genes to tinker with or get around disease-causing problems rather than striking directly at the cause of the disorder itself. These kinds of “incremental” gene therapies will probably become more common in the next few years as the field itself matures.

The two groups took very separate attacks on the problem of occlusion in limbs, or limb ischemia, which affects between 100 000 and 200 000 people in the United States each year. One was an in vivo experiment injecting genes directly into muscles to encourage the growth of collateral blood vessels. The second was ex vivo and involved bathing a vein graft in a solution containing an oligodeoxynucleotide (ODN) that is a transcription factor decoy to block gene activity.

Clinical researchers at St. Elizabeth’s Medical Center in Boston, Mass, attempted to stimulate the growth of collateral blood vessels in the patients’ legs that had been occluded by atherosclerotic lesions. In a technique that Jeffrey Isner, MD, of St. Elizabeth’s and Tufts Medical School called “therapeutic angiogenesis,” the researchers inserted the gene for vascular endothelial growth factor (VEGF) directly into the muscles of the patients’ legs. His hope was that VEGF would encourage the growth of blood vessels that would provide flow to the ischemic areas of the leg.

Patients could not be candidates for bypass therapy or other types of treatment, said Dr Isner. Seven patients had ulcers that would not heal, and three had chronic pain at rest. In six cases, amputation below the knee had been recommended.

Isner and his colleagues, led by Iris Baumgartner, MD, injected the naked plasmid DNA with the gene into 10 limbs of 9 patients. Two injections were given, 4 weeks apart. When they were evaluated 2 to 8 months later, 8 of the treated limbs had improved, 1 was unchanged, and 1 had gotten worse. In the limbs that had improved, Isner and colleagues measured an increase in the ankle–brachial pressure index from 0.33 to 0.47. That increase was similar to that seen when surgery or angioplasty is effective, said Isner.

The researchers evaluated the effectiveness of their therapies by diagnostic angiogram, magnetic resonance angiography, measurements of the ankle–brachial pressure, and, when possible, exercise testing. Magnetic resonance imaging demonstrated improved blood flow in 8 of the 10 legs, said Dr Isner. Angiograms indicated evidence of newly visible blood vessels in 7 of the limbs. In addition, blood pressures measured at the ankle increased after the treatment, said Dr Isner. Leg ulcers in some of the patients improved or were cured. Other patients reported less pain in their limbs. In 5 individuals tested, the speed of walking improved. Only 1 patient underwent an amputation. That patient already had significant gangrene of one foot, said Dr Isner. One patient reported no improvement.

In most patients, blood vessel growth appeared within 2 to 3 weeks of treatment, said Dr Isner. “The duration of the gene expression is only 2 to 3 weeks. That is only what we need to grow the blood vessels.”

Dr Elizabeth Nabel, Departments of Internal Medicine, Biological Chemistry, and Pathology, Howard Hughes Medical Institute, University of Michigan, Ann Arbor, said the patient’s body might only need the expression of the gene for a few weeks to a month to achieve the desired results.

“It remains to determine which population of patients will best be treated with this,” said Dr Isner. He hopes to apply the therapy to patients with coronary artery disease once these trials are finished.

Dr Isner said his studies indicated that there is no evidence of abnormal blood growth elsewhere in the body, despite the use of angiogenesis. “All clinical evidence is that there is no systemic distribution of the gene,” he said.

Dr Isner estimated that no more than 1% of cells actually took up the naked DNA. For that reason, he said, only a few good cells secreting VEGF are needed to encourage the therapeutic effect. R. Sanders Williams, MD, chief of the cardiology division at the University of Texas Southwestern Medical School in Dallas, said the findings are interesting and are 1 of 10 or 12 approaches currently being considered. “I think it will take us a long time to sort out what is really the best thing clinically,” he said.

Dr Isner agreed that the results are still preliminary, but he said, “I hope the ability to grow new blood vessels can be another therapeutic option.” He hopes that the treatment might be applicable in other problems, including coronary artery disease. Dr Isner does not promise that therapeutic angiogenesis will replace coronary artery bypass grafting or angioplasty in the near future. “Ultimately, if one can show that this does work effectively in the heart, one could imagine that one could defer the initial surgical or angioplasty treatment,” he said.

In the second therapy, Michael Mann, MD, an instructor in medicine at Harvard Medical School, and Victor J. Dzau, chairman of medicine at Brigham and Women’s Hospital at Harvard, described a genetic therapy aimed at preventing neointimal hyperplasia in grafted leg vessels.

“Bypass grafts fail routinely,” said Dr Dzau. “In a patient aged 60 who gets a triple bypass graft, the probability of one or more failing by age 65 is high. The question then is ‘Will we
do angioplasty or stent this?” He and Dr Mann hope their treatment will obviate that need by reducing the growth of new cells in the grafted vein.

Their strategy seeks to redesign the venous walls so that they respond to pressure in much the same way that arteries do. “If you take a vein and put it into the arterial side, the vein is a very thin structure acutely exposed to arterial pressure. It gets injured because of the tremendous pressure and the wall tension,” he said. “In order for this vein to function as a bypass graft, it will have to adapt quickly by thickening.”

However, he said, the typical thickening procedure results in neointimal hyperplasia that promotes accelerated atherosclerosis in the grafted vein. He and coworkers wondered what would happen “if we were able to block the cells from undergoing cell-cycle division. Would we not therefore force these smooth muscle cells to undergo hypertrophy, lay down a matrix, and make a vessel that looks closer to an artery?”

By changing the adaptive biology of the grafted vein, “we end up with a vessel that has some of the mechanical characteristics that, to some extent, are some of the biological characteristics of an artery,” he said. Although he does not yet claim success in the attempt, he said the laboratory results indicate that morphologically, the vein looks like an artery.

They did this by recognizing a transcriptional “maestro” called E2F that binds and activates genes in the cell cycle. “So what we did is synthesize a double-stranded DNA that copies the important sequences,” said Dr Dzau. These short ODN sequences are homologous to key cell-cycle–gene promoter regions and act as transcription factor decoys that inhibit activation of genes that are key to formation of the neointimal hyperplasia, said Dr Dzau.

The decoy can compete for binding and sequester the transcriptional factor so that this factor (E2F) can bind the various genes and therefore cannot activate them, said Dr Dzau. The veins were bathed in an ODN-containing solution. Subsequent study showed that the DNA was present in a majority of cells, although it did not incorporate into the nucleus. Animal studies indicated that the effect of preventing neointimal hyperplasia can last as long as 6 months, said Dr Dzau.

Dr Mann said, “One of the unique aspects of this type of gene therapy is that, unlike most gene therapies, we are actually attacking a problem that is quite common.” The first five patients treated under the protocol were “open-label,” he said, meaning that physicians knew they had received veins treated with the ODN sequences. One of the first five was a technical failure, said Dr Dzau. The other four seem to be doing well. “The first five patients, however, allowed us to assess whether we could perform the genetic manipulation in the operating room,” said Dr Mann. That proved feasible, he said.

A subsequent 41 patients were enrolled in a placebo-controlled, double-blind trial of the technique, and no results are forthcoming from that study as of yet. “I believe this is the first truly double-blinded study of gene therapy,” said Dr Dzau.

Like Dr Isner, Drs Mann and Dzau believe their technique may have application in coronary artery disease, in the treatment of bypass grafts. Dr Mann said discussions of using the technique in such patients are ongoing, and he hopes that a clinical trial can start within the next few months.

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