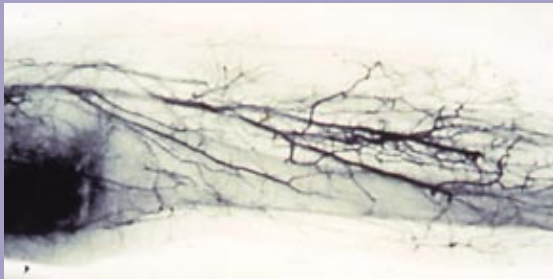


NAKED DNA THERAPY FOR BLOOD VESSELS

Photos by Rhône-Poulenc Rorer Gencell



These photographs show the growth of blood vessels following gene therapy with the VEGF gene.

Gene therapy may bring relief to millions who suffer from blood vessel disorders, which are a leading cause of early death in the U.S. In one such disorder, called *arteriosclerosis*, plaque forms on the inside of the artery wall, causing the artery to harden, thicken, and block circulation. When this plaque blocks the coronary arteries that supply blood to the heart muscle, it causes heart attacks, heart disease, and pain. When a blockage occurs in the legs, it leads to constant leg pains, sores that can't heal, and eventually amputation.

People once lost their limbs – and lives – to arteriosclerosis. Then scientists developed an artery bypass procedure, using a healthy blood vessel from elsewhere in the body to go around the blocked section of the artery. More recently, surgeons use balloon angioplasty to clear a passage in a vessel by threading a small balloon through the artery and inflating it. Both surgical techniques have negative side effects, and they usually are not permanent solutions.

Balloon Angioplasty

VEGF: MAKING A NEW PASSAGE

New gene therapy research combines the “bypass” concept with balloon angioplasty. In one experiment on a group of people with extremely advanced leg arteriosclerosis, researchers covered the outside of the balloon with *naked DNA*. In naked DNA, the therapeutic gene is not packaged in a vector but is simply spliced into a round section of DNA known as a plasmid. (See sidebar on page 11.) At first, no one expected naked DNA to deliver genes into cells in the living body. But when the plasmids come into contact with a cell, they do! Naked DNA thus bypasses the problems involved in developing a guided missile that targets blood vessel cells.

Surgeons snaked the balloon covered with naked DNA to the blockage and inflated it. The inflated balloon pressed the plasmids onto the vessel wall. The DNA entered the cells of the vessel wall and deposited a gene for a growth factor protein called *VEGF* (pronounced “veg F”) that makes new blood vessels

grow. Once inside the cells, the gene expressed small amounts of the growth factor, and that was enough to make new blood vessels grow around the blockage.

In later experiments, researchers used an even easier technique, injecting the naked DNA into leg muscles, which then produced the growth factor and led to new blood vessels. Researchers hope the new vessels will restore circulation to the legs on a long-term basis so the patients don't need to face amputation and can resume more normal lives. Researchers also hope to inject VEGF into the heart muscle to create a bypass for coronary arteries, saving future patients from the risk of open-heart surgery!

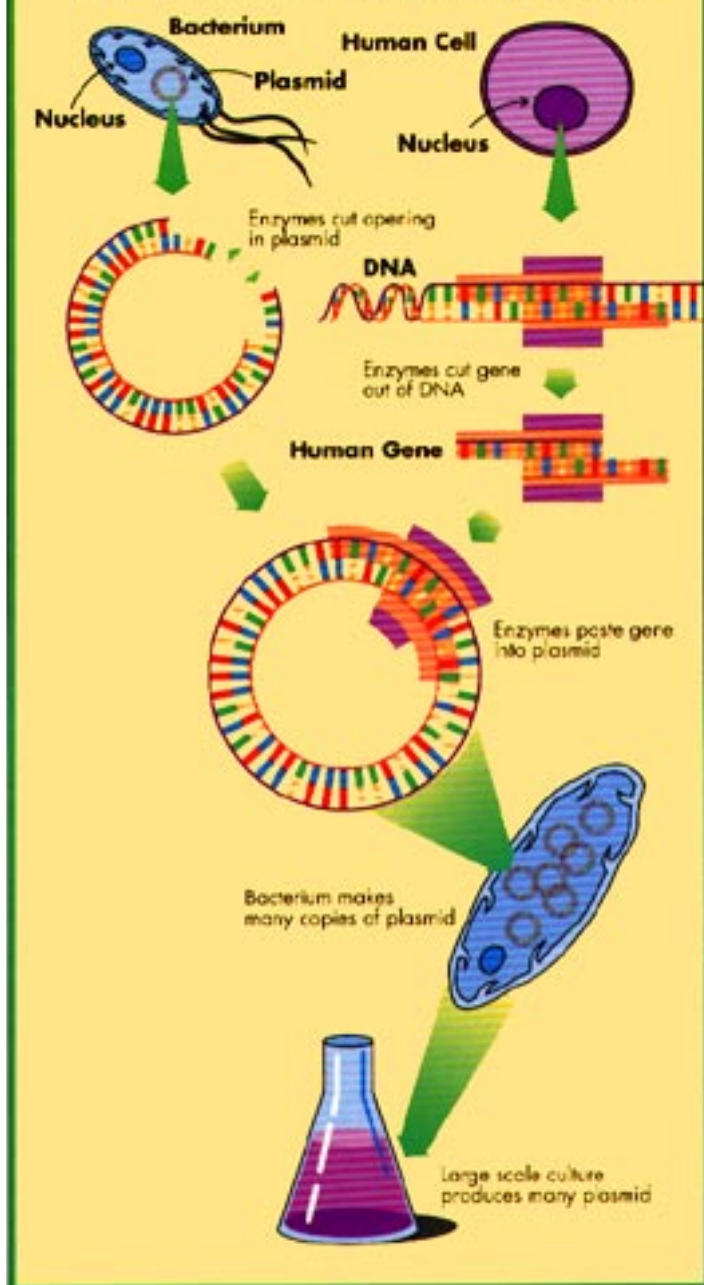
Other research uses genes that help reduce plaque buildup in arteries or that prevent the artery walls from thickening. The next article deals with another area where scientists are working within current limitations of gene therapy technology to treat very difficult diseases. □

thoughts on the future

THOUGHTS ON THE FUTURE:
RACHEL KING, MBA, CHIEF
EXECUTIVE OFFICER, GENE
THERAPY, INC. (NOVARTIS)

“In the early days, many small gene therapy companies specialized in vectors that could transfer genes to cells, but they didn't have expertise in disease biology. Today, more companies work closely with large pharmaceutical companies because they have experts in cell biology and immunology. Those experts help us determine which genes to transfer to which cells to affect the disease. This merging of different sciences is moving the field forward. It will help us develop gene delivery vehicles that combine aspects of different vectors. For example, we might take a surface protein from the hepatitis virus that targets liver cells, combine it with a virus that can place a gene in a specific site on the chromosome, and put it in a synthetic package that doesn't cause an immune reaction.”

Plasmids



Plasmids are circular DNA molecules that come from bacteria and are separate from the bacteria's chromosome. When the bacteria reproduce, they make copies of the plasmid.

To study or use a particular gene, scientists insert it in a plasmid – with the help of special “cut and paste” proteins called enzymes. “Cut” enzymes take the gene out of the chromosome and open up a section of the plasmid. A “paste” enzyme places the gene in the plasmid.

Then scientists put this plasmid into a bacterium that makes many copies of its plasmid. These plasmids can serve as naked DNA vectors – or they can produce recombinant proteins, as discussed on page 5.

RESEARCH & TRIALS

Here are some steps in the long process of developing and approving a new medical treatment for people.

Genomic Research

Identify genes and proteins involved in disease.

Cellular Research

Using laboratory cell cultures, test vectors and see whether the added gene makes the protein.

Animal Models

Develop techniques for delivering genes to animals.
Verify the production of desired proteins.
Study safety in two mammals, usually rodents and primates.

Human Clinical Trials

Phase I Trials

Focus on whether the therapy has a toxic effect on patients or causes other harm. Participants are often critically ill and/or have not responded to other forms of therapy.

if fails

if succeeds

Phase II Trials

Test whether patients express the added gene and if their health improves. To make sure these results are valid, participants must stop other treatment.

if fails

if succeeds

Phase III Trials

Test a larger number of participants in “double blind” studies* and compare the new treatment with existing treatments.

if fails

if succeeds

FDA Approval for General Clinical Use

* Double blind: To increase validity of results, neither the patient nor the investigator knows which patients receive the treatment and which receive a “blank” placebo.