Designing Cells to Deliver Drugs

As technical roadblocks slow some approaches to gene therapy, new avenues may lead to treatments for disorders including AIDS, cancer, heart disease, and emphysema

THE AIDS PATIENT needs soluble CD4, the protein that blocks the AIDS virus from penetrating his cells. He needs a steady dose, one that does not have to be administered several times a day.

The man who had a heart attack could use some TPA or tissue plasminogen activator to keep his blood from clotting where surgeons implanted an artificial vessel.

The victim of emphysema, whose lung tissue is riddled with holes that make breathing slow and painful, might live a long and healthy life if only a natural protective hormone called alpha-1 antitrypsin could be delivered directly to his lungs.

Then there is the cancer patient whose life might be prolonged by genes carrying potent antitumor agents deep inside tumors.

And, of course, there is the child whose immune system is horribly weak because he was born without a functioning gene for adenosine deaminase (ADA), which is essential to the T and B lymphocytes that are the very backbone of the immune system.

What each of these patients needs is gene therapy.

A few years ago, only the child with ADA deficiency, a classic genetic disease, would be thought of as a candidate for gene therapy. But today, largely because of research that has come to fruition within the past couple of years, the list of diseases in the would-be gene therapists' repertoire has grown to include the more common afflictions of mankind: AIDS, heart disease, cancer, emphysema, maybe even neurological disasters like Alzheimer's.

Gene therapy is not just for genetic diseases any more. Ironically, these new avenues have been opened up because a technical barrier has appeared on the main road.

The idea of curing disease by repairing a broken gene is one of the simplest concepts in medicine. At heart, a gene is nothing more than a chemical set of instructions for the production of a specialized product. Now that genes are routinely isolated and cloned, it ought to be simple to replace a broken gene with a whole one—especially in organs such as blood and bone marrow, which can be easily taken out of the body, modified, and put back in.

Thus, it seemed obvious a decade ago that the place to start was with the pluripotent stem cells of bone marrow—the cells from which oxygen-carrying red blood cells and immunologically active white blood cells are derived. The genetic repair would be permanent. Once the stem cell has a normal gene, all its progeny will too.

The script is simple. But its execution has proved formidable.

"The stem cell has really turned out to be a bear," says Harvard hematologist David G. Nathan. "It is so hard that some people have given up for now." Stem cells are hard to get hold of in any quantity—they are very rare and difficult to infect with retroviruses. "You can get expression for a couple of weeks," he says. "Then the cells mature and it stops."

Would-be gene therapists are coaxing lymphocytes and endothelial cells to make "genetic drugs."

Geneticist Leon E. Rosenberg, dean of medicine at Yale, says the challenge is to find "a factor" or "factors" that are essential to the production of stem cells so they can be grown in large numbers for study. "Once that happens," he predicts, "it will be a whole new ball game. And I think that things are moving." But until then, bone marrow gene therapy is on hold.

In the meanwhile, the field is suddenly broadening as researchers, temporarily defeated by stem cells, have imaginatively turned their attention elsewhere. If they can't use stem cells, they decided, they'd get around the problem by finding clever ways to deliver the proteins or hormones those genes ought to be making. Efforts are being directed at selectively turning certain lymphocytes, endothelial cells, and other types of accessible cells into what amount to in vivo drug delivery systems by splicing into them genes that code for specific proteins.

Instead of correcting a genetic error at its source—the patient's own gene—researchers propose to design genetically specialized cells to make "genetic drugs." It is, one might say, a step away from gene therapy in its purest sense. But it may be a step closer to experimental therapy of human disease.

These new approaches rely heavily on the past decade's research on retroviruses at laboratories all across the country, much of which was recently reviewed by Theodore Friedmann in the 16 June issue of *Science*.

Similarly, a paper in this issue (p. 799) describes progress in ongoing stem cell research in the mouse.

The following news articles discuss some of the research at the forefront of the idea of using endothelial cells and lymphocytes to transfer genes into patients.

As promising as these projects are, they still face some difficult technical and regulatory hurdles. More than any other form of medical research, any form of gene therapy based on recombinant DNA technology is closely controlled by the National Institutes of Health where the work is under the purview of the Recombinant DNA Advisory Committee (RAC), the RAC's human gene therapy subcommittee, and, finally, the director of NIH itself. The Food and Drug Administration is also part of the regulatory loop, as are the local institutional boards at hospitals around the country.

Nationwide, only one human gene experiment has been authorized. Last spring, researchers at the NIH inserted a marker gene into potentially therapeutic lymphocytes for patients terminally ill with malignant melanoma (*Science*, 26 May, p. 913). The protocol was reviewed and re-reviewed a total of 15 times before final approval.

That first test was a successful attempt to show that genes can be safely introduced into lymphocytes and expressed in a living patient. It likely has paved the way for the next round of studies, especially if the tests involve the therapeutic delivery of agents made by genes. Acknowledging that it is risky to guess, researchers nonetheless predict protocols for the delivery of ADA to immunologically deficient children or soluble CD4 to victims of AIDS will be next on the agenda for NIH review.

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