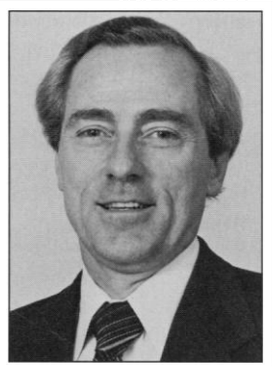
Stem-Cell Gene Therapy Moves Toward Approval

An NIH advisory committee gives the nod to a new strategy for genetic therapy based on a rare type of blood cell

IF A PROPOSED EXPERIMENT AT THE National Institutes of Health gets the expected go-ahead, gene therapy may move one step closer to the long-awaited goal of curing—not just treating—inherited diseases.

Originally, researchers feared that the toughest problem in gene therapy would be coaxing the inserted gene to perform properly, but that hasn't turned out to be the case. Instead, the main roadblock has been getting the gene into the best target cells, especially the stem cells of the bone marrow, which until now have defied all efforts to isolate and manipulate them.

But now a team of NIH researchers, led by W. French Anderson of the National Heart, Lung and Blood Institute, and R. Michael Blaese and Kenneth Culver of the National Cancer Institute, thinks it has found a way to insert genes directly into stem cells. It relies on an innovative commercial technique for identifying and concentrating the few stem cells that circulate in the bloodstream—a technique that's now undergoing improvement in a number of labs, including one whose work is described in this issue of *Science* (see page 1137). The NIH team wants to try it as part of its ongoing gene-therapy experiment, the first such venture approved, to treat two young girls with severe combined immune deficiency (SCID). Says Anderson: "We're talking about the possibility of a cure."



W. French Anderson

That strategy took a big step toward realization on 11 February, when the NIH Recombinant DNA Advisory Committee gave the team permission to add this new technique to its existing protocol. Although the experiment must still be approved by NIH director Bernadine Healy and by the Food and Drug Administration, no snags are expected.

SCID is an inherited illness that destroys the body's immunity against even normally innocuous infections. Because of a defective gene, SCID patients are missing an enzyme, adenosine deaminase (ADA), that protects certain white blood cells from a metabolic toxin. The stem cells would be an ideal target for delivering the normal ADA gene, both because they are immortal and because they give rise to all the body's blood cells. Thus, if the defect could be corrected in these cells, all the subsequent white cells that originate from them should be healthy.

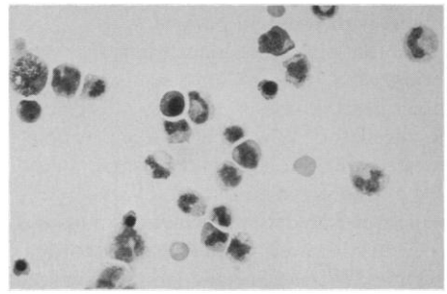
But when Anderson, Blaese, and their colleagues began their SCID gene-therapy trials in September 1990, there was no simple way to target these cells because they are so rare. Even in the bone marrow, stem cells account for only one in every 10,000 to 100,000 cells, and they are even rarer in the blood, averaging about one in a million. Instead, the NIH team has been inserting the ADA gene into mature white blood cells, which—unlike stem cells—have a short lifespan. The treatments seem to be shoring up the immune system as hoped, the researchers say. But, this approach cannot cure the disease because the corrected cells eventually die and must be replenished.

Since the NIH gene-therapy experiment began, however, several research teams and biotech companies have been working on a technique for ferreting out stem cells, using a monoclonal antibody that recognizes a cell surface marker called CD34. The cornerstone of the new Anderson-Blaese protocol is a CD34-based stem cell collection system now being marketed by CellPro Inc., a biotech firm in Bothell, Wash. CD34 does not recognize stem cells exclusively, since between 1% and 3% of all bone marrow cells carry the CD34 marker, including an unknown fraction of stem cells. But the NIH investigators think that it could be specific enough for gene therapy, based on previous experiences using this system in bone marrow transplantation.

Over the past 3 years, research teams from CellPro and the Fred Hutchinson Cancer Research Center have shown that collecting CD34-positive cells from the bone marrow, pooling them, and using them without any other cells can replace the bone marrow, says Ronald Berrenson, vice president of biological research and medical affairs at CellPro. The technique has made it possible to collect enough stem cells so that these cells migrate back to the patients' bone marrow, where they regenerate the full repertoire of blood cells.

The gene-therapy experiment proposed by the NIH group will be similar to the bone marrow transplants, but they will rely on CD34-positive cells taken from the bloodstream. And in the NIH study the CD34-positive cells will be treated with the normal ADA gene before they are given back to the children in a transfusion. The hope is that enough stem cells will carry the normal gene and accumulate in the patients' bone marrow to produce healthy blood cells that restore immune function.

The method isn't without snags, however. To collect enough white blood cells for a transplant, patients have to endure from three to 10 repetitions of a 6-hour procedure known as leukophoresis, says Curt I. Civin, director of pediatric oncology at Johns Hopkins University. The CD34 cells are then purified from the pooled white blood cells.



CYNTHIA DUNBAR

Needles in a haystack. *Stem cells.*

This process should become less arduous for patients as researchers improve techniques for increasing the quantity of stem cells in the blood. Current methods rely on treating the patient with the white blood cell growth factor called granulocyte colony stimulating factor (G-CSF). A mixture of additional growth factors should yield even greater quantities. "Once we get the right cocktails, one leukophoresis will be enough," predicts Hopkins' Civin. The scientific "bartending" needed to formulate these cocktails is progressing rapidly. Tsvee Lapidot and colleagues at the Hospital for Sick Children in Toronto, for instance, working with SCID mice receiving human bone marrow, have used a unique growth factor combination that generates all the red and white cells normally found in human blood; their work is decribed in this issue of *Science*. But Anderson, Blaese, and Culver aren't waiting for additional refinements. If the approvals come as expected, their new experiment could start this summer. ■ LARRY THOMPSON

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