Human Gene-Splice Test Considered

Researchers at the National Institutes of Health have proposed injecting genetically altered human cells into cancer patients. If approved by federal health officials, the experiment would be the first U.S. government-sanctioned use of genetically engineered cells in humans.

The experimental procedure will provide no immediate benefits to the cancer patients, scientists say, but it may eventually help researchers improve the efficacy of a promising cancer therapy. Moreover, many view the experiment as an important — and controversial — first step toward the use of gene-altered cells to correct disease-causing genetic defects in humans. Experiments in animals suggest such "gene therapy" may prove useful against thousands of hereditary diseases, but a variety of medical and ethical concerns have stalled the start of human experiments.

The proposed trial combines recent advances in cancer therapy — spearheaded by Steven A. Rosenberg at the National Cancer Institute — with work by National Heart, Blood and Lung Institute researcher W. French Anderson, a pioneer in the art of inserting foreign genes into mammalian cells.

In recent, ongoing research, Rosenberg has been isolating from the tumors of cancer patients small numbers of tumor-infiltrating lymphocytes (TIL cells) — a class of white blood cell that attacks tumor cells (SN:10/4/86, p.222). After culturing these cells for 30 days with a growth factor, interleukin-2, he reinoculates each patient with up to 10^{11} progeny of the patient's own TIL cells, along with further infusions of interleukin-2. The procedure has helped shrink tumors in about half the approximately 25 patients treated so far.

Researchers suspect that in unimproved patients, the TIL cells either are dying too quickly or may be losing some of their tumor-killing properties. But even after injecting TIL cells with radioactive "labels," the group has had difficulty determining their ultimate fate.

"Radioactive labels allow researchers to follow cells for about three or four days," says R. Michael Blaese, chief of the National Cancer Institute's cellular immunology section and co-developer of the newly submitted protocol. "But for long-term studies . . . you'd have to give so much radioactivity that you'd alter the function of the cells you are marking, or you'd expose the patient to unacceptable levels of radioactivity."

In an attempt to get around these problems, Blaese, Rosenberg and Anderson propose to insert stable genetic "markers" into cultured TIL cells before reinoculating patients. With methods developed by Anderson, researchers can use a retrovirus to insert into TIL cells a gene that confers resistance to the antibiotic neomycin. Experiments on animals have shown that scientists can easily identify such "transfected" TIL cells in subsequent biopsy specimens and test them to see how effectively they are attacking tumor cells.

"This is the only way I'm aware of that will allow us to actually fish these cells out — cells that we put in some weeks or months before — actually get them back and then answer some questions about how they are behaving," Blaese said in an interview. Because the marker is incorporated into a cell's DNA, he adds, each cell's progeny can be identified and tested as well. Moreover, the initial 30-day culture period will give scientists a chance to test the gene-altered cells for unusual changes or viral contaminants — concerns that have been unresolved in previous gene therapy proposals — before injecting them into patients.

Although the current proposal simply calls for inserting a marker gene, later proposals may seek approval for the insertion into TIL cells of genes that code for the production of potentially therapeutic factors such as interleukin-2 or tumor necrosis factor, Blaese says. "There is reason to suspect that we could make these cells more efficient cancer killers if we were to put these additional genes in," he says.

Scientists and government officials received copies of the experimental protocol last week. Their review of biosafety and ethical considerations is expected to take several months. — *R. Weiss*

Galactic views through thick and thin

More luminous than ordinary galaxies but less intensely radiant than quasars, Seyfert galaxies fall somewhere between the two extremes. Now an astronomer reports evidence that a doughnut-shaped ring of opaque material obscures the very center of at least one Seyfert galaxy. Moreover, this arrangement allows some light to escape from the galaxy's center — like a searchlight emerging from the doughnut's hole. Reflections of that light from dust clouds near the doughnut allow astronomers to peek into the otherwise hidden galactic center.

"For the first time, we know what the center of a [Seyfert] galaxy looks like from two different directions," says Joseph S. Miller of the University of California at Santa Cruz. In the direct line of sight, we get an obscured view of the galaxy's nucleus, he says. From the dust-cloud reflections, we see clearly into the galactic center.

To identify this effect, Miller used a special instrument to study polarized light coming from the center of the Seyfert galaxy known as NGC 1068. The galaxy's hidden nucleus, less than a light-year across, is such a tiny fraction of the galaxy's full width that no telescope could pick it out. Despite its size, however, that nucleus sends out an immense quantity of radiation in the form of visible light and radio waves.

Miller's discovery may force revisions in the way Seyfert galaxies are classified. Traditionally, astronomers have divided Seyfert galaxies into two types, based on the characteristics of their emitted light. In general, typical spectra from Seyfert galaxies contain prominent lines signifying the emission of particular wavelengths of light by various elements present in their central regions. The spectra of Type 1 Seyfert galaxies feature a broader hydrogen line than those of Type 2.

Miller's results show that NGC 1068 looks like a Type 2 galaxy when observed through the doughnut of obscuring matter and like a Type 1 galaxy when viewed by reflected light. "It could well be the case that there's just one kind of Seyfert galaxy, and it depends on which way we're looking as to what we call it," Miller says. Alternatively, Type 1 galaxies may have thinner rings hiding less of their central regions than Type 2 galaxies. More recent observations show that NGC 1068 is not unique.

Although astronomers don't yet understand the nature of a Seyfert galaxy's obscuring ring or disk, light from these galaxies shows evidence that their centers often contain large quantities of intensely heated gas (SN: 4/27/85, p.262). "As we go from different Seyfert galaxies to quasars, we've determined that the structure of this [obscuring] disk changes," says Miller. "Quasars appear to have a very thin disk. It is only in Seyfert galaxies that we see a big, thick disk." Those characteristics may be related to how much energy these central sources put out. "We now have the possibility of constructing a complete picture of what's going on in the nuclei of quasars and active galaxies." — *I. Peterson*