THE MOST REMARKABLE PROPOSAL YET

NIHRAC OKAYS MORE GENE THERAPY

WASHINGTON, D.C.—Seven new gene-transfer-based clinical protocols—including one effort to manipulate oncogenes as a means for treating human lung cancer—were recently recommended for approval by the National Institutes of Health Recombinant DNA Advisory Committee (NIHRAC, Bethesda, MD).

The protocol for treating lung cancer described by Jack Roth of M.D. Anderson Cancer Center at the University of Texas in Houston is perhaps the most remarkable proposal involving human gene transfer technology to win NIHRAC's approval to date. The Texas group is proposing to interfere with the cellular activity of the *K-ras* oncogene and to replace a mutated *p-53* suppressor gene in tumor cells. Both genes are believed to play important roles in the development of certain lethal, non-small-cell lung cancers.

Manipulating oncogenes

Roth and his colleagues are proposing to treat only those cases where a metastatic tumor blocks a patient's airways and is unresponsive to radiotherapy or chemical treatment. In the proposed gene therapy approach, no surgery would be required, because the tumors would be directly treated by injection of fluid containing two kinds of retroviral-produced agents. The first, an antisense gene, is intended to block the *K-ras* oncogene in the tumor cells blocking the patient's airway. The second consists of the *p-53* tumor-suppressor gene, which is intended to replace an inactive version of the gene in the tumor cells.

When mice with comparable lung cancers are treated with the equivalent of these two genes, there are "marked reductions in tumor growth," Roth says. However, not all tumor cells take up the new genes. Thus, the tumor blocking effects of the two oncogenes appear to be due partly to a pronounced "by-stander effect," says Roth. He and his colleagues speculate that inhibitory factors are produced by some of the cells that take up the new genes and are then somehow transmitted to other malignant cells nearby.

Even though understanding of the oncogene effects is scanty, the proposed clinical procedures are intended mainly to determine whether there is any risk of acute toxicity for those lung cancer patients whose life expectancy is little better than six months.

Gene marking protocols

With similar safety considerations in mind, committee members also reviewed several other proposals to use gene marking techniques as a way to monitor bone marrow transplant (BMT) procedures used in conjunction with chemotherapy to treat patients with a variety of cancers. Gene marking techniques use recombinant vectors to put foreign genes in human cells. Researchers then follow the fate of the foreign genes as a way to follow the fate of those human cells.

Committee members quickly endorsed a gene marking protocol described by Malcolm Brenner of St. Jude Children's Research Hospital (Memphis, TN) in collaboration with Bonnie Mills of Baxter Healthcare (Santa Ana, CA). The protocol seeks to determine whether purging of BMT cells helps during the treatment of neuroblastoma, a form of cancer affecting the central nervous system.

Similarly, the committee recommended three closely related protocols outlined by Friedrich Schuening of Fred Hutchinson Cancer Research Center (Seattle, WA). The procedures involve the use of BMT and interleukin-3 or granulocyte colony-stimulating factor to treat several types of malignancy, along with gene marking procedures to monitor the efficacy of these treatments.

In addition, NIHRAC recommended approving a gene marking protocol from Michael Lotze of the University of Pittsburgh (Pittsburgh, PA), who plans to test the effect of genetically engineered interleukin-4 as part of an effort to stimulate vigorous immune responses against tumors. It also approved a protocol from Albert Deisseroth of M.D. Anderson Cancer Center, who will use gene marking techniques to monitor cancer-cell purging during BMT procedures. Finally, the committee recommended approving a proposal from Robert Walker and Michael Blaese of NIH involving gene marking to follow the transfer of lymphocytes between identical twins in cases where the recipient is infected with HIV.

—**Jeffrey L. Fox**

THE COST TO FUTURE GENERATIONS

GENE THERAPY POLICY

WASHINGTON, D.C.—Several gene therapy policy issues were considered during the recent meeting of the National Institutes of Health's Recombinant DNA Advisory Committee (NIHRAC, Bethesda, MD). One issue deals with human gene therapy manipulations at the germ line level. Another touches on the committee's solidifying insistence that data from previously approved gene therapy clinical trials need to be submitted for review. Yet another deals with the committee's need for internal consistency in applying gene transfer safety standards and for closer coordination with officials at the Food and Drug Administration (FDA, Bethesda, MD), who also are reviewing gene transfer protocols and setting safety standards.

Germ line gene therapy is still being treated very much as a hypothetical matter. And, indeed, James Neel, a population geneticist from the University of Michigan in Ann Arbor, who came before NIHRAC as a guest speaker, urged committee members to postpone indefinitely any protocols calling for germ line genetic changes, either of the therapeutic or eugenic variety.

Germ line therapy

Neel's opinions emanate from his analysis of human genetic effects resulting from the atomic bombings in Japan at the end of World War II. Few mutations effect children of individuals exposed to the X-rays from the two bombs that exploded in Japan, thereby throwing off by at least an order of magnitude previous estimates of the effects of X-rays on mammalian species based on laboratory experiments in mice.

With this degree of uncertainty about supposedly well-understood mutational effects, it "will require another 30 years to understand the lessons of current somatic cell therapy," Neel says. Thus he calls it "inconceivable for the foreseeable future" that members of NIHRAC contemplate any proposals for human germ line gene therapy. "We have no idea of the cost to future generations of retroviral footprints or of randomly inserting genetic materials," he says. "Any defects from such procedures may be around for a long time, with a short-term gain becoming a long-term time bomb."

Although several NIHRAC members disagreed with Neel's conclusions, the majority of the committee agrees that its main business is somatic cell gene therapy, not germ cell gene therapy. Since 1988 when the committee approved the first proposal—from Steven Rosenberg and his collaborators at NIH's National Cancer Institute to use gene transfer techniques on cancer patients—it has recommended 32 clinical protocols involving gene transfers. Of that