LANDMARK ATTEMPT

RAC OKAYS *IN-VIVO* GENE THERAPY

NEW YORK—The Recombinant DNA Advisory Committee of the National Institutes of Health (Bethesda, MD) recently approved a novel *in-vivo* gene-therapy clinical trial for melanoma. The trial, however, still awaits approval from the U.S. Food and Drug Administration (Bethesda, MD). Principal investigator Gary Nabel of the University of Michigan (Ann Arbor) will inject melanoma tumor nodules with a recombinant DNA coding for HLA-B7, an allogeneic class I MHC, in a liposome carrier. This trial, conducted with funds from the university, represents a landmark attempt to genetically manipulate human cells without first removing them from the body.

A hallmark of cancer is its wresting away of control from the cell, resulting in wildly accelerated protein synthesis. Cancer cells are also expert at evasion, slipping through formidable biological warning systems without detection. The uniqueness of Nabel's approach (developed jointly with his wife, Elizabeth) lies in effectively "tagging" the tumor. The insertion of a gene coding for a surface antigen draws the immune system's attention like a red Ferrari does the highway patrol.

Marking cells for destruction

In the Nabels' system, the MHC molecule is an antigen, causing the kind of graft-versus-host immune response found with organ transplants. The class I MHC molecule's normal function is to present antigen to killer T cells, marking the MHC-bearing cell for destruction. It appears that the foreign MHC molecule continues to present tumor antigens to cytotoxic T cells even as the tumor is lysed. Preliminary studies in mice—with a similar system—suggest lymphocytes from one MHC-treated mouse recognize and can prevent metastases in an induced primary tumor in another mouse.

If the melanoma trials prove the gene therapy effective, the Nabels have already worked out a more sophisticated system for delivering the MHC gene to internal tumors. After insertion of a catheter in the blood vessel that feeds a tumor, inert-gas pressure drives DNA-bearing liposomes down the arterioles and into the blood-engorged tumor. Expression of MHC molecules on healthy tissue should be minimal, says Nabel, since the gene is delivered locally. Long-term autoimmune reactions shouldn't be a problem, as organ-transplant recipients haven't been significantly affected.

Successful catheterization of cancer may pave the road for future catheterized treatment of atherosclerotic plaques, anti-coagulant activity, and even induction of angiogenesis. The Nabels have already demonstrated the effectiveness of the method in delivering marker genes to surrounding endothelium of the vasculature. By linking the genes to tissue-specific promoters, they can direct expression to specific cell types.

Limitless applications?

Indeed, applications seem limitless. For both basic and applied science, the ability to deliver tissue-specific genes to the microvasculature enables selective manipulations *in vivo*. Approaches need not be limited to protein production. Negative inhibition through antisense, ribozymes, or other competing molecules are often-discussed alternatives. "The problem with intracellular approaches," says Nabel, "is that either you have to get the gene into all the cells or have an amplifier effect become dominant to cells around them." As little as three months ago he didn't think these approaches would work. "But now, with some small molecules and synthetic DNA," he says, "catheter delivery may be possible." Papers from the Nabel lab are in press or submitted, and the next few months should reveal a growing body of data about these techniques in animal models.

With patents applied for jointly with the university, Nabel takes a circumspect attitude toward commercialization of the idea. "We've talked to various companies but have not made any firm decisions about what we are going to do," he says. "Certainly we're not closed to the idea—we just don't advertise." Pausing a moment to reflect, he continues, "To be quite honest, I've been too busy to think about it."

—Stephen M. Edgington

PRODUCT OR SERVICE?

Product oriented or service oriented? Gene-therapy companies have different answers when asked what kind of businesses they hope to build.

For companies working on *in-vivo* gene-therapy methods, the answer is simple. Vical (San Diego, CA), TargeTech (Meriden, CT), and Cell GeneSys (Foster City, CA) say they expect to sell a product in a vial, along the lines of a traditional drug.

"For somebody it's a service business. The question is who."

But companies whose vectors require *ex-vivo* workup of autologous cells do face a choice. "For somebody, it's a service business," says M. James Barrett, president and chief executive officer of Genetic Therapy Inc. (TGI). "The question is, who's going to do it."

Not GTI, says Barrett. For his company, "the key focus is developing vectors as products to be used in specialized centers." *Ex-vivo* gene-therapy procedures "are not as simple as taking a pill, but it's not rocket science either," says Barrett, noting that major medical institutions are already trying to establish an early position in performing gene-therapy procedures.

John Archer, executive vice president of Somatix Therapy, agrees that "logistical headaches are better left to clinics and hospitals." For Somatix, he says, "the end product will be the retroviral product with the DNA of interest."

But Targeted Genetics Corp. (TGC) and Transkaryotic Therapies (TKT) plan to take the service route. "We question any other approach to making gene therapy a business, since there's no proprietary position in retroviral vectors," says TGC president and chief executive officer H. Stewart Parker. TGC, she says, wants to profit from its techniques for growing cells, so the company envisions a network of service centers within medical institutions. The prototypes for such a business already exist, Parker says, pointing to *in-vitro* fertilization companies operating within medical centers as one example.

For TKT, there isn't much choice about offering a service. "Our unit of sale is a patient's genetically engineered cells," says chief scientific officer Richard Selden. The company's gene-therapy system calls for altering and characterizing a single cell that can be cloned for reintroduction into the patient. "To characterize the cells requires experience working with genetically engineered cells," Selden says. "Hospitals have neither the desire nor the knowledge to do that."

—Mimi Bluestone