NIHRAC and FDA ponder gene-therapy risks

WASHINGTON, D.C.—An attempt to devise safety standards for viruses used as gene-carrying vectors in human gene therapy sparked controversy at a recent meeting of the National Institutes of Health Recombinant DNA Advisory Committee (NIHRAC, Bethesda, MD). The committee is at odds with officials from the Food and Drug Administration (FDA, Bethesda, MD), who share responsibility for evaluating, setting, and revising safety standards for vectors and other materials used in gene-therapy procedures.

The first line of gene-therapy vectors has consisted of RNA-containing retroviruses that, in their native form and under some circumstances, give rise to tumors in rodents and nonhuman primates. However, before such viruses are used in human subjects, their genes are extensively modified to render the viruses no longer "competent" to replicate by themselves or, presumably, to cause tumors of any kind.

Until recently, these retrovirus-based vectors were thought to be irreversibly disarmed. But last year researchers at Genetic Therapy Inc. (GTI, Gaithersburg, MD) identified a "break-through" replication-competent retrovirus in a vector batch that they were testing, according to Gerard McGarrity, GTI's vice president for development. It was "definitely a recombinant virus, not a contaminant," says McGarrity. This spontaneously produced, genetically reverted form of retrovirus was readily detected by using the quality-control assays run routinely just for such purposes. The break-through appears to have been a one-time occurrence among the 50 large-scale production runs conducted so far.

Nonetheless, the incident has helped to stir tensions between FDA officials and investigators at GTI. FDA officials "have had us chasing our tails doing unnecessary assays," says GTI collaborator French Anderson, who is formerly of NIH and now at the University of Southern California School of Medicine (Los Angeles, CA), referring to recent efforts to evaluate the break-through vector batches and other materials being produced at GTI.

There are at least four safety barriers in place between GTI vector production—at which time a spontaneous break-through is most likely to occur—and the introduction of the carefully screened, vector-containing materials into patients. Moreover, based on the break-through incident at GTI and on tumor development in monkeys exposed to high doses of similar retroviruses, Anderson estimates that the chances of gene-therapy patients developing malignancies following exposure to retroviral vectors are extremely remote.

FDA officials view the issue more cautiously and are proposing that a series of highly sensitive assays for detecting such viruses be put in place. "There is no evidence that the present assays need to be improved,"

NIHRAC okays gene therapy for cystic fibrosis

NIHRAC approved three gene-therapy protocols for cystic fibrosis and heard results suggesting gene therapy reduces cholesterol.

WASHINGTON, D.C.—Three similar proposals to begin clinical testing of gene-therapy schemes for treating cystic fibrosis (CF) patients were approved at a recent meeting of the National Institutes of Health Recombinant DNA Advisory Committee (NIHRAC, Bethesda, MD). All three protocols make use of adenovirus vectors, the first clinical approvals of such vectors.

NIHRAC also heard preliminary but tantalizing information suggesting that a gene-therapy approach may be working to reduce blood-cholesterol levels in a patient with a severe inherited cholesterol-receptor disorder that typically leads to early death. Even as optimism about gene therapy appears to be building, however, committee members are trying to anticipate the impact of this new technology in the context of health-care reform and to ensure that gene therapy remains available for anyone who needs it.

The three protocols for treating CF patients were submitted by Ronald Crystal at NIH's National Heart, Blood, and Lung Institute; James Wilson at the University of Michigan Medical Center (Ann Arbor, MI); and Michael Welsh of the Howard Hughes Medical Institute at the University of Iowa (Iowa City, IA).

The CF trait is carried as a recessive gene, and it results in a defective or missing membrane chloride-ion transport protein. Without a normal version of that protein, cell functions are severely disrupted in several organs, particularly the lungs, which fill with debris and become subject to an escalating series of infections. The disease affects about 30,000 Americans, whose median survival age is 28.

All three gene-therapy protocols are similar, as they propose the use of similar adenovirus-vector-based means for carrying replacement genes to generate the missing membrane ion-transport proteins in cells lining the airways of CF patients. The initial clinical experiments aim mainly to test the safe use of the new adenovirus-vector systems and to determine what biological reactions, including immune-system responses, they may trigger.

Plans now call for the single administration of these potentially therapeutic agents to individual patients. However, genes carried on these replication-deficient adenovirus vectors, unlike those on retrovirus vectors, do not integrate into the DNA of cells that they infect. Hence, even if the adenovirus-vector systems successfully transfer functioning membrane transport proteins into cells lining the airways of CF patients, the corrective effects are expected to be transient at best, according to Crystal, Wilson, and Welsh.

Eventually, if the approach appears promising, repeated administration of the gene-carrying vectors will undoubtedly be required. Because adenovirus is immunogenic, some NIHRAC members suspect that repeated administration of this product could lead to its clearance by the immune system, undermining therapeutic effects. But since CF alters lung physiology in so many ways—for example, stimulating protease production that might miti-

Anderson says, arguing that converting these assays from research tools into routine assays will be expensive, robbing valuable resources from the "search for cures to help patients." Anderson adds that "holding the assay procedures as a threat over us is horrendous. It could bring the whole biotechnology industry to its knees, making it impossible for anyone but a Merck or a DuPont to do business."

The steps leading to production of a replication-competent retrovirus from a production vector at GTI represent a "stochastic event," meaning that "every lot must be viewed separately," says FDA's Philip Noguchi. "The data available to FDA suggest that it is reasonable to do other testing" and that, with additional information, questions about assays and safety can be "addressed with data, not hearsay," says Noguchi, adding that "the hazard is not incompatible with treating patients."

Meanwhile members of NIHRAC appear to favor an approach other than a wholesale move to new, more sensitive detection assays. "It is unreasonable to keep chasing assays in the absence of durable risk—especially for assays that have not been validated," says committee member Dusty Miller of the Fred Hutchinson Cancer Research Center (Seattle, WA). "We're all in the same frame of mind. We realize that, if we get a patient disaster, the field can't move ahead. We need to find a balance between the safety of patients and the practicality of doing assays. We can improve them, but they can't cost $500,000 an assay."

Committee member Robertson Parkman of Childrens Hospital of Los Angeles (Los Angeles, CA) suggests that simpler alternatives—such as extending culture periods of samples from production-line batches to verify that they are free of any replication-competent viruses—be considered as an alternative way of assuring safety. He and other members of the committee also point out that there is no evidence of gene-therapy and gene-marker clinical procedures having harmed any recipients so far.

Nonetheless, safety is not taken for granted, and NIHRAC members were not swayed by an unusual plea—even when it was cast in life-and-death terms—to set aside their usual review procedures for the sake of a young woman from Iowa whose brain tumor has failed all available treatments. In taking up this constituent's case, Senator Tom Harkin (D-IA) asked NIH Director Bernadine Healy to "give timely consideration to individual compassionate-plea requests for approval of gene-therapy procedures for terminally ill patients." Although sympathetic, Healy told Harkin that gene therapy is too new "to even begin consideration on a compassionate-plea basis."

However, arrangements were made for one of the patient's physicians, Ivor Royston of the San Diego Regional Cancer Center (San Diego, CA), to come before NIHRAC to argue for a special review procedure. He recently engineered samples of her tumor cells to produce interleukin-2 and now proposes reintroducing those cells "to simulate an anti-tumor immune response."

Although this single-case clinical proposal is pending before FDA, it also requires NIHRAC review and approval before Royston can proceed. Several NIHRAC-meeting participants noted that they are receiving many more inquiries requesting enrollment of desperate patients in gene-therapy protocols than they can accept. Moreover, gene-therapy protocols are now being designed mainly to test safety, rather than to prove efficacy. Thus, there was wide agreement among members of the committee that the Royston proposal could not receive a "reasoned review" without first adhering to steps designed to ensure a full public airing.

The potential penalty for going ahead without NIHRAC approval is loss of federal-grant support for his institution, Royston notes. In pleading with committee members to modify their procedures and to consider his and similar compassion-based gene-therapy clinical protocols, Royston hinted that he might "abide by FDA regulations" if the agency grants him the approval he is seeking, instead of abiding by "NIH guidelines, which are not law."

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gate such immune-system effects—Crystal and others contend that there is no way to determine efficacy without testing for it directly.

In a separate development involving another heritable disorder that leads to early death, the University of Michigan's Wilson reviewed the progress of one of his patients being tested in a clinical trial approved by NIHRAC in 1991. The patient, a 29-year-old woman, has severe familial hypercholesterolemia, a condition in which a missing cell receptor for lipid metabolism leads to high blood cholesterol and its accelerated deposition throughout the circulatory system.

The patient has been followed for more than a six-month period after surgery to remove liver cells and replace them with genetically engineered cells that make the missing cell receptor. During that period, her "baseline for circulating lipids has been lowered by 15 percent to 25 percent," compared to before she was treated, Wilson reports. She also appears now to be responsive to cholesterol-lowering drugs, which were ineffective before the gene-therapy treatment. Wilson plans to expand the initial trial to include five instead of the originally intended three patients.

With such tantalizingly optimistic findings coming before the committee, counteractive anxiety levels are rising among some NIHRAC members. "We are concerned that the research subjects being selected are people of privilege," says Doris Zallen of the VA Polytechnic Institute and State University Humanities Center (Blacksburg, VA). Much of this concern focuses on disparities in insurance coverage and the omission of women and minorities from early clinical trials.

A majority of NIHRAC members, moreover, agreed to send a letter to NIH Director Bernadine Healy. It raises the issue of covering long-term medical costs for those who participate in such early trials, and it recommends that this issue be carefully studied, particularly as it may affect clinical research in rapidly developing fields such as gene therapy.

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Devising safety standards for viruses used as gene-carrying vectors in human gene therapy has sparked controversy.