DATELINE/

TALE OF TWO COMMITTEES

OPPOSITE OUTCOMES FOR AIDS TRIALS

WASHINGTON, D.C.—Two gene-therapy proposals for combating HIV infections recently ran into virtually opposite receptions from different federal review committees. These cases—one involving the National Institutes of Health (NIH, Bethesda, MD) and the other the Food and Drug Administration (FDA, Bethesda, MD)—represent a long recognized, but still unresolved, problem of overlapping federal jurisdiction for gene-therapy research.

The first protocol—submitted to NIH's Recombinant DNA Advisory Committee (NIHRAC) by David Golde and his colleagues at Memorial Sloan-Kettering Cancer Center (New York)—outlines a strategy for interfering with HIV replication. After briefly considering the protocol, NIHRAC members deferred making any recommendation, arguing that many more *in vitro* and animal studies were needed before clinical studies could begin.

The second protocol—which was submitted by Viagene (San Diego, CA) to FDA—fared much better. Agency officials convened the Vaccines and Related Products Advisory Committee, which enthusiastically endorsed Viagene's therapeutic gene-transfer approach. FDA officials quickly followed suit by approving the company's investigational new drug (IND) application.

Immunotherapy

Both the Viagene and Sloan-Kettering approaches fall under the general heading of immunotherapy, and both depend on genetic engineering to overexpress particular HIV gene products as an early step to improve patient response to the virus. Despite these similarities, however, substantial differences in the two approaches account for at least part of the dramatic difference in outcomes following federal review.

Golde and his colleagues at Sloan-Kettering plan to introduce the gene for a particular HIV element, called *tar*, into the lymphocytes of HIV-infected individuals. *tar* is a RNA segment that forms an essential complex with other HIV components during the replication cycle of the virus. The idea is to make too much of *tar* so that it can serve as a decoy, luring other viral components away from productive participa-

tion in the replication cycle. When tested in cultured human cells that were challenged with HIV, this approach led to "99 percent inhibition" of HIV replication for "greater than 21 days," the researchers report.

The Viagene approach also entails genetic manipulation of the cells of HIV-infected individuals. Except, in this case, the procedure calls for the use of fibroblasts. The aim of the Viagene team is to stimulate a better response of the host immune system against the virus. Thus, the Viagene group plans to introduce genes that overproduce HIV envelope proteins in fibroblasts, return the modified cells into the bloodstream, and then count on the artificially abundant HIV proteins to trigger cytotoxic T-lymphocytes to control or, ideally, overcome HIV infection.

"Immunologically elegant"

Other research groups are developing conventional vaccine approaches to administer HIV proteins and thereby stimulate immune-system responses against the virus, noted several members of the FDA advisory committee. The Viagene approach adheres to similar principles but is designed to stimulate T-cell immune responses, says committee member Donald Summers of the University of California's Irvine College of Medicine (Irvine, CA). It is "immunologically elegant," adds Fred Valentine of New York University Medical Center (New York). "This is very appealing. I love the experiment."

Panelists also agreed that, although animal studies can provide some assurances that the Viagene approach is safe, there are no good animal models for testing whether it will work. As a phase I clinical study, the Viagene proposal is designed to show safety and biological activity, not efficacy, according to Bruce Merchant, Viagene's vice president for clinical development and regulatory affairs. With FDA approval now in hand, the company expects to begin testing its approach in asymptomatic, HIV-infected individuals sometime before the end of the year. If the clinical phase of Viagene's undertaking were to involve collaborators at institutions receiving federal support, the company may need to come before NIHRAC before going

ahead. Viagene is "keeping open" the possibility, Merchant says.

"Untested assumptions"

During the NIHRAC review of the Sloan-Kettering proposal the atmosphere was very different. Committee members criticized the scientific merits of the proposal. For instance, NIHRAC reviewer Robert Haselkorn of the University of Chicago in Illinois called the clinical proposal "ambitious," noting that the animal experiments were "almost too good" and that "there are many untested assumptions underlying this protocol." He pointedly recommended that additional preclinical experiments be conducted before the clinical proposal is reconsidered. A second NIHRAC reviewer, Moselio Schaechter of Tufts University School of Medicine (Boston, MA), agreed with Haselkorn's assessment, concluding that "the proposal is not based on sufficient experimental data or theoretical considerations. Many of the points can be tested in animals."

Members of the Sloan-Kettering team tried to explain to NIHRAC members their reasons for coming before the committee to seek permission for an early clinical trial. The initial phase of the proposed trial is intended to test general safety questions, such as whether the immune system is adversely affected, Clay Smith of Sloan-Kettering told the committee. "We don't anticipate a therapeutic effect with an initial small number of cells," he says. The underlying impetus to move quickly into clinical trials is the fact that animal experiments can take a long time and may not be deemed relevant, whereas the "life span of AIDS patients is short," he says.

When pressed, Smith and his collaborators said that another reason not to delay coming before NIHRAC was to "initiate a dialogue" with the committee. The suggestion, though, did not convince the members of NIHRAC to enter into a lengthy discussion of the proposal. However, it prompted Henry Miller of the FDA Office of Biotechnology to invite the Sloan-Kettering representatives to visit FDA, where officials are "available to discuss the proposal all the time."

—Jeffrey L. Fox