

NIH Panel Okays Human Gene Transfer Test

A National Institutes of Health (NIH) advisory panel has given the go-ahead for a team of researchers to inject genetically engineered cells into humans. The experiment, which the panel said could be performed on no more than 10 terminally ill cancer patients, represents the first approval by a U.S. government agency for the use of gene-altered cells in humans.

Scientists say they expect the procedure will neither help nor harm the cancer patients — who will be chosen from a pool of consenting individuals with life expectancies of less than three months — but should provide valuable

information that may lead to improvements in a promising new cancer therapy. More significantly, the experiments will provide the groundwork for other tests, not yet approved, in which scientists would insert therapeutically beneficial genes into patients' cells.

The tests must gain final approval from NIH Director James B. Wyngaarden and the Food and Drug Administration (FDA). But officials of both the NIH and the FDA have hinted strongly that such approval would be forthcoming if the protocol passed muster with the Recombinant DNA Advisory Committee (RAC), the NIH panel of scientists and ethicists that gave

its approval this week. "We hope to be in patients by the first of the year," says W. French Anderson of the National Heart, Lung, and Blood Institute, who will perform the human studies with Steven A. Rosenberg and R. Michael Blaese, both of the National Cancer Institute.

The RAC's green light comes after months of discussion and controversy, in which experts wrestled with the scientific and ethical uncertainties inherent in the unprecedented application of genetic technology to human patients. In particular, the committee expressed concern about the safety of a genetically engineered retrovirus that will be used to insert a "marker" gene into a sample of the patients' white blood cells. The proposed experiments would be the first to expose humans intentionally to a retrovirus. The experiment will use only retroviruses not known to cause human disease and that have been stripped of their ability to reproduce.

The experiment builds upon ongoing research by Rosenberg and his colleagues at the National Cancer Institute. In those experiments, the researchers remove white blood cells from tumors in patients suffering from malignant melanoma, a deadly form of skin cancer. They grow the cells in culture with an immune-stimulating hormone called interleukin-2, then reinfuse billions of the beefed-up cells into the same patient from whom they were taken. Unpublished results given the NIH panel indicate about half the treated patients show significant improvement.

The new experiments are designed to provide information about why some patients respond to this treatment and others don't. Before reinfusing the cultured white cells into patients, the researchers will use a disabled retrovirus to "infect" some of the cells with a gene that will make the cells resistant to an antibiotic. These cells will be easy to find in subsequent blood and tissue samples, allowing researchers to map their "traffic patterns," survival time and biochemical characteristics in patients showing different clinical responses. If Anderson and his colleagues find that clinical improvement is, as they suspect, associated with white cells that produce specific biochemical factors, they hope to insert into future batches of cultured cells genes coding for increased production of those factors.

"Ten patients will be enough to demonstrate the safety of the procedure," says Rosenberg. "Very quickly I hope we'll be coming back to [the RAC] with a proposal to insert genes with therapeutic potential." — R. Weiss

No-fault fat: More praise for fish oil

Studies have suggested that underfed animals live longer (SN: 8/27/88, p.142) and suffer less autoimmune disease. Now researchers are eliciting similar benefits without the belt-tightening. In fact, their well-fed mice eat a high-fat diet. Their only prescription is that the fat the mice eat must be fish oils rich in omega-3 fatty acids.

Immunologist Gabriel Fernandes, at the University of Texas Health Science Center in San Antonio, conducted the studies using hybrid mice with a genetic susceptibility to lupus or rheumatoid arthritis — inflammatory diseases in which antibodies attack the body's own tissues. One group of each strain of mice received a restricted diet (60 percent the normal calories with 5 percent corn oil as its fat). Similar groups of about 25 animals were allowed to eat as much as they wanted. The only difference in their diets was the source of the high (40 percent of calories) fat levels: lard, corn oil or fish oil.

Mice on the lard and corn-oil diets died slightly earlier than normal for these strains. And before they died, the lard-fed animals developed inflamed blood or lymph vessels, thickened blood vessels and accelerated kidney disease. Mice on the fish-oil and calorie-restricted diets not only lived twice as long as normal, but produced half the normal levels of harmful autoantibodies and showed lower-than-normal inflammation. They also were free of kidney disease — which normally afflicts all of these mice. Moreover, the fish-oil diet yielded blood cholesterol levels just half of normal — and even lower than those in the low-fat, calorie-restricted animals.

The studies, reported last week at the American Chemical Society national

meeting in Los Angeles, indicate that for maximum efficacy, the fish oils must not undergo oxygen-mediated chemical reactions. Preventing oxidation can pose a challenge, Fernandes explains, because omega-3 fatty acids are extremely susceptible to it.

One way to limit oxidation is to keep the fats in the fish. At the University of Massachusetts' Marine Science Station in Gloucester, Herbert Hultin measured omega-3 oxidation in Atlantic mackerel and cod that had been refrigerated for up to 10 days, frozen up to eight months, pan fried, broiled or baked. In no case did measurable levels of their lipids oxidize, he reports. However, once the fish was minced, oxidation occurred rapidly. Hultin says this suggests that oxidation-promoting chemicals are sequestered in fish tissue until physically liberated, as in mincing.

Though it's widely assumed that fatty oceanic fish provide the best source of omega-3 fatty acids, food scientist Paul Addis has identified comparable freshwater alternatives. A cold environment is one factor causing fish to accumulate omega-3s in their tissue, notes Addis, who is at the University of Minnesota in St. Paul. Because Lake Superior "borders on being classified an arctic lake," Addis says, he investigated omega-3 levels in its inhabitants.

He studied lean lake trout, deep-water lake trout, whitefish, chub, smelt, burbot, sucker and lake herring. All but the burbot and smelt were as rich in these fatty acids as the Chinook salmon, a fish renowned for its omega-3 levels. Far and away the leader was the deep-water lake trout. Depending on size, this species contained up to three times as much omega-3 oil as the Chinook salmon. — J. Raloff