

## Human immune system implanted in mice

Working separately, two California research groups have accomplished the first successful transplants of the human immune system into mice, providing a potential model for studying AIDS and other diseases without harming humans. "The findings are potentially a very important advance to dissecting the human immune system," says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

Howard Streicher, an AIDS researcher at the National Cancer Institute in Bethesda, calls the findings "creative, tremendously exciting and potentially useful as a model for AIDS." Scientists had previously infected chimpanzees with the AIDS-causing virus, HIV (SN: 5/23/87, p.331), and researchers in Italy report in the Sept. 22 NATURE that they have infected rabbits with HIV, but so far no animal has been shown to develop AIDS. The California groups are hoping, but have not yet shown, that their newly created mice can develop AIDS.

While both research teams say it was largely the search for an animal model for AIDS that drove them to attempt the recent experiments, they approached the task using different methods. In the Sept. 23 SCIENCE, Irving Weissman, Joseph McCune and their co-workers at Stanford University report transplanting thymus, liver and lymph-node tissue from human fetuses into mice. (Their findings were released last week, in part to coincide with federal hearings on the use of fetal tissue for research; see page 197, this issue.) The other group, led by Donald Mosier of the Medical Biology Institute in La Jolla, Calif., transferred white blood cells from human adults into mice, as reported in the Sept. 15 NATURE.

But both groups had to overcome the same hurdles: the possibility that the recipient's immune cells would attack the transplant, a reaction called host-versus-graft disease, or the reverse scenario, graft-versus-host disease. They cleared the first hurdle by using a strain of mice, discovered in 1983, with severe combined immunodeficiency (SCID), a genetic disease resulting in a nonfunctional immune system. SCID mice die in the first few months of life, often of infection with *Pneumocystis carinii* bacteria, also a common cause of death in AIDS patients. But SCID mice receiving the experimental transplants do not develop the infection — the first indication that the transplants work. Weissman reports transplanted mice living for 16 months; Mosier says his transplanted mice have lived for eight months.

To overcome the second hurdle, Weissman's team used fetal tissue, which is too immature to mount an immune response against the host. Although

Mosier's group performed transplants with adult human cells — already immunologically "knowledgeable" — the cells caused only mild symptoms of graft-versus-host disease in the mice, a result Mosier says he cannot explain entirely but plans to investigate.

Further proof of the transplant's success for both groups came with detailed biochemical and immunological experiments. Weissman's group demonstrated that the transplant tissues function in mice as they would in human fetuses, where immature immune cells from the liver normally pass through the thymus and lymph nodes, exiting as mature immune cells ready to attack invading microorganisms and toxins. In mice, the group found cells from the transplanted human liver in the transplanted thymus and lymph-node tissue, and, later, as mature immune cells in the circulating blood. After four to six weeks, the numbers of these immune cells begin to decrease, the team reports.

Mosier says his results indicate that a single injection of the human immune cells reconstitutes the ability to respond to antigens for the life of the SCID mouse

receiving the transplant. To test transplanted cells' ability to function immunologically, his group injected tetanus toxin into mice transplanted with blood cells from human adults previously immunized for tetanus. Eight of the 10 immunized mice produced antibodies to the toxin, they report. Mosier's group also has observed that transplanting mice with human cells containing Epstein-Barr virus leads to tumors in the mice, a finding that provides a potential model for studies of this virus.

Weissman says his technique, too, paves the way for studying other diseases. For example, transplanting pancreatic tissue into SCID mice may provide a system for investigating the malfunctions leading to diabetes, he says. A project already underway in Weissman's lab involves isolating human stem cells, the precursor cells to the entire immune system. Weissman recently reported isolating mouse stem cells (SN: 7/9/88, p.20).

Mosier's and Weissman's findings are equally important and will both lead to advances in medicine, say researchers familiar with their work. "The systems are not competitive," says Weissman. "They are two pieces of a great big pie just beginning to be understood."

— M. Hendricks

### Tailored toxin targets HIV-laden cells

A genetically engineered "guided missile" shows promise as a chemical weapon against cells invaded by the AIDS-causing HIV virus. Preliminary tests on cultured, HIV-infected cells show they are "very sensitive" to the engineered toxin, which has been designed to bind selectively only to cells actively producing HIV components. The strategy builds upon several recent advances in scientists' understanding of the molecular biology of AIDS, and in principle resembles some experimental cancer therapies.

Researchers report in the Sept. 22 NATURE the successful engineering of a bacterium to produce a hybrid protein that includes an HIV-binding molecule linked to a cell-killing toxin. The toxin is not aimed at the AIDS virus itself, since the virus typically hides — and reproduces — within the body's immune system cells. Instead, the researchers' approach takes advantage of the fact that HIV-infected cells produce on their cell surface a particular protein characteristic of the HIV outer shell, or envelope. That protein, called gp120, serves as a molecular marker of an otherwise clandestine HIV factory.

Vijay K. Chaudhary of the National Cancer Institute, Edward A. Berger of the National Institute of Allergy and Infectious Diseases (NIAID) and their colleagues designed the toxic protein to

include a portion of the so-called CD4 molecule that binds to gp120. To do so, they rewrote parts of the genetic code in an *E. coli* bacterium to make it manufacture a hybrid protein containing both the truncated CD4 molecule and the potent portion of a toxin normally produced by another bacterium, *Pseudomonas*. The "fusion protein" binds to cells expressing the gp120 protein, then sabotages their protein-making machinery. Similar, experimental approaches have been used to target and kill malignant tumors.

"What we've done is to remove the cell-binding site from the *Pseudomonas* toxin and substitute a portion of CD4," says NIAID researcher Bernard Moss. "As long as the cell is infected with HIV and is making envelope, then the toxin should kill it."

Experiments show the engineered toxin is deadly to cultured monkey kidney cells infected with a recombinant virus that mimics HIV, and to cultured, HIV-infected human white blood cells. In preliminary experiments, noninfected immune cells appear unharmed. Moss says the group is conducting further tests to determine the toxin's effectiveness against a variety of HIV-infected cells.

Toxicity studies on animals must precede any clinical trials in humans.

— R. Weiss