Gene Transfer Test: So Far, So Good

Code broken on data from one patient; cancer board gets report on preliminary results

WHEN NIH PHYSICIANS began the first human gene transfer trials this spring, they hoped to show that anticancer white blood cells destroy tumors by selectively seeking out malignant tissue. Preliminary results from the first of five patients indicate that the experiment is working the way they predicted it would.

The gene transfer experiment was reviewed and rereviewed a total of 15 times before receiving final approval by the director of the National Institutes of Health at the beginning of this year. In addition, it was subject to one lawsuit that sought to block the test on the grounds it had not received sufficient prior review. That suit failed in court and the experiment, which has been heralded as the first authorized test of human gene transfer, began on 22 May (*Science*, 26 May, p. 913).

The experiment, conducted by Steven A. Rosenberg of the National Cancer Institute, involved therapy with tumor-infiltrating lymphocytes, or TIL cells, which has produced significant remission in a few patients with advanced melanoma that is generally resistant to existing forms of treatment (*Science*, 23 June, p. 1430). In an attempt to explain why TIL therapy works when it does, as well as why it fails more often than not, TIL cells were transduced in culture with a bacterial "marker" gene that would enable researchers to see where the antitumor lymphocytes go in the body. Rosenberg is one of a three-man team that includes R. Michael Blaese of NCI and W. French Anderson of the heart institute.

The patients' own lymphocytes were extracted from bits of solid tumor, labeled with the bacterial gene for resistance to the antibiotic neomycin (NeoR), grown to massive quantities, and then reintroduced into the patients' bloodstreams.

Speaking at a meeting of the National Cancer Advisory Board on 18 September, Rosenberg reported data from one patient whose tumors shrunk significantly after TIL therapy. Rosenberg's presentation to the board was scheduled at the request of industrialist Armand Hammer, the presidentially appointed chairman of the White House cancer panel that oversees the federal war on cancer. The NCI news office then called a press conference.

The patient, a 26-year-old woman with black, ulcerous masses of melanoma at as many as 30 sites on her body, is experiencing the kind of dramatic tumor regression that encourages Rosenberg to persist in experimenting with "adoptive immunotherapy" which produces some benefit in about 50% of patients.

"The data from this patient tell us several things, even though this is all very preliminary," Rosenberg reported. "First, the gene-labeled TIL cells did go to tumor in a patient whose melanoma is regressing. Second, the cells do survive in the body. Third, adding a marker gene to the TIL cells has not changed their characteristics."

Rosenberg also reported safety data from all five patients who have received gene-labeled TIL cells so far. None has suffered any toxicity from the inert marker gene that was transferred along with the lymphocytes.

Blood samples and tumor biopsies were taken from each of the patients before the gene-labeled TIL cells were infused, and again on days 3, 5, 14, and 19 after therapy. All samples were blind. So it was only when the code for one patient was broken last week that Rosenberg and his colleagues got the news they were hoping for.

The TIL not only travel to tumors but also survive—even after 3 weeks, gene-labeled TIL could be found circulating in the bloodstream. Clearly, it is too early to say how long the TIL cells will persist but it is known that some lymphocytes live for years.

"It is possible that we would have found out that the cells did not survive or that they don't go to tumor after all," Rosenberg said. "We are encouraged to find that this is not the case, although when we break the code on the other patients it is possible we will see opposite results."

From the beginning, the plan was to study gene-labeled TIL cells in five patients and assess the results before proceeding to infuse an additional five allowed under the gene transfer protocol. "Once we have analyzed the data from the five patients we've treated so far, we may modify the protocol a little," Rosenberg said.

Then what? If data continue to suggest a connection between TIL cells homing in on tumors and tumor shrinkage, the researchers will begin searching for information about which cells in the TIL constellation are doing the job. "TIL are heterogeneous," Rosenberg told *Science*. "There may be 50 different cell types in there."

Beyond that, the hope is to use TIL cells as a vehicle for getting additional anticancer agents into tumors in an attempt at actual gene therapy. The NeoR gene is a marker, pure and simple, offering no therapeutic advantage. The next step will be to ask approval of a protocol to insert a gene for an active antitumor agent into the TIL population—perhaps a year from now. A likely candidate is the gene for human tumor necrosis factor (TNF) which has already been succesfully transferred to human lymphocytes in vitro.

■ BARBARA J. CULLITON

Rosenberg Says No CRADA

Steven A. Rosenberg's pioneering gene transfer experiments are very much a collaborative effort with R. Michael Blaese who, like Rosenberg, is with the National Cancer Institute, and W. French Anderson of the National Heart, Lung, and Blood Institute.

Two weeks ago, *Science* reported that these experiments are dependent on an additional collaborative player—a small biotechnology company called Genetic Therapy, Inc., with which Anderson and Blaese have each signed a CRADA or cooperative research and development agreement. CRADAs, new to the world of NIH, include provisions for royalty payments to collaborating scientists if projects turn out to be financially successful and require that company information be held in confidence in certain well spelled-out circumstances.

Science reported erroneously that Rosenberg also has a CRADA with Genetic Therapy, Inc. In fact, Rosenberg says that while he sees the advantages of CRADAs, he prefers to operate without any obligation to keep research data confidential and, therefore, has decided not to be a party to the formal cooperative agreement with Genetic Therapy. ■ **B.J.C.**