CANCER RESEARCH

SOME SUCCESS WITH AUTOLOGOUS GENE THERAPY

VIENNA, Austria—Following the successful completion of the first authorized gene transfer study in humans, the Clinical Research Committee of the National Cancer Institute (NCI, Bethesda, MD) has approved a new study. It will use genetically modified tumor-infiltrating lymphocytes overexpressing tumor necrosis factor (TNF) to treat a small group of patients with advanced malignant melanoma. Now other authorities, including the Recombinant DNA Advisory Committee and the Food and Drug Administration (FDA, Bethesda, MD), must sanction the work.

The proposed study is the continuation of the work of Steven Rosenberg and his colleagues at NCI, which started in 1985 with the use of lymphokine activated killer (LAK) cells in adoptive immunotherapy against cancer. LAK therapy itself had been successful but controversial because of the severity of the side effects. Speaking at the Institute of Molecular Pathology Conference on Genetic Transfer and Alteration in Biology and Medicine held here in May, Rosenberg described how his group had first tried to identify cells that would have a more potent anti-cancer activity than LAK cells: "Where better to look for a cell with reactivity against a cancer than within the cancer itself?"

This approach led to the identification of tumor infiltrating lymphocytes (TILs). Those isolated from a given patient's tumor (specifically, in malignant melanoma) recognise tumor antigens which are present on cells of an autologous melanoma but not on normal cells from the same patient or on other tumor cells. TILs can recirculate through the peripheral blood system and can specifically localise to cancer deposits. When used to treat advanced metastatic melanoma, fully 40 percent of patients showed objective regression.

This targeting ability potentially makes TILs good delivery vehicles for molecules that could further increase antitumor activity. At the planning stage are projects in which recombinant TILs expressing genes for TNF, interferon, or interleukin-2 (IL-2) are used in autologous transfer protocols. But before such studies could be considered, Rosenberg and colleagues needed to find out a bit more about the activity of TILs.

In January 1989 they obtained final approval for a seven-patient study in which TILs carrying the *neo*^{R} marker gene were used in patients with advanced malignant melanoma. The *neo*^{R} gene was inserted by retroviral transfer into autologous TILs and, after extensive safety testing for virus replication competence and IL-2 dependence, around 3×10^{11} cells were returned to the patient.

Biopsies showed that by three days after transfer of the cells, TILs were already present in the tumor nodules: after 19 days, the tumor was overrun with TILs. In one patient who is still disease-free 10 months later, the treatment resulted in the complete disappearance of 30 melanoma metastases.

The next step for the NCI group is to use TILs expressing TNF genes to treat other melanoma patients. In the run up to the clinical studies, they have been able to insert the TNF gene into TILs and achieve a 20–90 fold increase in TNF production. In this way, they hope to achieve high concentrations of TNF within the tumor without producing toxic levels systemically. —**John Hodgson**