

Lay Abstract.

Cancers arise from the normal tissues of the host, and are typically not seen as foreign by the immune system. T cells evolved to fight virus infections by killing our own cells in which the virus is multiplying. It is the aim of this program to "fool" the patient's T cells into "thinking" that the tumor has a virus infection. This is done by taking some T cells from the patient's body, doing gene therapy techniques on them outside the body which "educate" the T cells to recognize a protein on the surface of the tumor cells as if it were a virus protein, and then reinfuse these "designer T cells" back into the patient. Then the patient is monitored for any side effects and for tumor shrinkage. The protein that is attacked is the carcinoembryonic antigen (CEA) that is present on many types of cancer. The 1st generation version of this therapy was adequately tolerated for side effects, and showed some promising responses in the cancers, but the responses were not sustained. This was ascribed to the inability of the modified T cells to proliferate in the tumors after they were introduced into the patient, in the manner that normal T cells do when there is a virus infection. We have now modified the gene therapy method so that a more complete immune stimulation is obtained when the T cells contact the tumor. Preclinical studies suggest that the 2nd generation designer T cells will proliferate in the tumor and lead to sustained antitumor responses. This protocol is a clinical trial to test the tolerability of the method and any anti-cancer benefit.