Phase I/II Study of Metastatic Cancer that Expresses Carcinoembryonic Antigen (CEA) Using Lymphodepleting Conditioning Followed by Infusion of Anti-CEA TCR-Gene Engineered Lymphocytes

Principal Investigator: Steven A. Rosenberg, M.D., Ph. D., Chief, Surgery Branch, NCI

Scientific Abstract:

In contrast to antibodies that recognize epitopes on intact proteins, T cells recognize short peptide fragments (8-18 amino acids) that are presented on surface class I or II major histocompatibility (MHC) molecules and it has been shown that tumor antigens are presented and recognized by T cells in this fashion. The molecule that recognizes these peptide fragments is the T-cell receptor (TCR). The TCR is analogous to the antibody immunoglobulin molecule in that, two separate proteins (the TCR alpha and beta chains) are brought together to form the functional TCR molecule. The goal of this protocol is to transfer tumor-associated antigen (TAA)-reactive TCR genes into normal peripheral blood lymphocytes (PBL) derived from cancer patients, to return these engineered cells to patients, and to mediate regression of their tumors. This trial is similar to previous Surgery Branch TCR gene transfer adoptive immunotherapy protocols except that we will use a TCR that recognizes tumor cells based on the recognition of the carcinoembryonic antigen (CEA) on the tumor cell surface.

CEA has been found in cancers of the colorectum, breast, lung, cervix, gallbladder, stomach, pancreas, liver, prostate, urinary bladder, ovaries, and uterus, and head and neck, and in neuroendocrine tumors from the larynx, lung, and thyroid. CEA expression in normal adult tissues is limited to columnar epithelial cells and goblet cells in the colon, mucous cells in the neck and stomach, squamous epithelial cells of the tongue, esophagus, and cervix, secretory epithelial and duct cells of sweat glands, and epithelial cells of the prostate. We have designed a modified TCR (S112T) reactive to the CEA:691-699 peptide, which binds with high affinity to HLA-A2.1. T cells transduced with S112T receptor showed enhanced specific peptide and tumor cell recognition in comparison to the wild type receptor. This trial has the potential to treat HLA-A2 patients with colorectal carcinoma as well as patients with other malignancies that express CEA.

The study will be conducted using a Phase I/II optimal design. The protocol will proceed in a phase 1 dose escalation design, with three cohorts. Once the MTD has been determined, the study then will proceed to the phase II portion. Patients will be entered into two cohorts based on histology: cohort 1 will include patients with metastatic colorectal cancer, and cohort 2 will include patients with other types of metastatic cancer that express CEA. In both phases of this study, patients with metastatic cancers that express CEA will receive a nonmyeloablative but lymphocyte depleting preparative regimen consisting of cyclophosphamide and fludarabine, and then will be treated by the adoptive transfer of autologous PBL that have been genetically engineered to be reactive with CEA. Following adoptive cell transfer, all patients receive high-dose aldesleukin (IL-2). The primary objectives will be to determine if the administration of anti-CEA TCR engineered PBL and aldesleukin to metastatic cancer patients following a nonmyeloablative but lymphoid depleting preparative regimen is safe and will result in clinical tumor regression. Additional objectives include determining the *in vivo* survival of TCR gene-engineered cells.