

## Non-Technical Abstract

Melanoma is a malignant disorder of pigmented skin cells. Melanoma is curable in most patients through surgical resection when detected at an early, localized stage. Patients with advanced or recurrent disease are not curable with currently available therapies, and respond poorly to conventional cancer treatment with systemic chemotherapy. Melanoma is unique among human cancers in that the immune system appears to be capable of reacting to the malignant cells in a high proportion of patients. In theory, the immune system has the potential to control or even eliminate cancer cells from the body, but the response is weak in most patients. Defining and strengthening this immune response has become an important focus of research and experimental treatment for melanoma. Experimental research performed in the last decade has identified a number of protein or “antigens” expressed in melanoma cells that represent important, specific targets of the immune response to melanoma. Special immune cells called T-lymphocytes recognize these antigens using a unique cell surface molecule called a T-cell receptor. The T-cell receptor endows a T-cell with the ability to initiate an immune response to a specific antigen. Using recombinant DNA technology, it is possible to genetically isolate or clone the genetic material that codes for a T-cell receptor with defined specificity. The genetic material encoding the T-cell receptor can be introduced into other T-cells, endowing these cells with the capacity to respond to the antigen recognized by the original T-cell. In theory, this technique could be applied in a clinical context to genetically reprogram large numbers of T-cells to recognize a melanoma specific antigen, with the objective of initiating a therapeutic immune response to the tumor. We have developed an experimental treatment for melanoma based on the use of retroviral gene transfer to express a cloned T-cell receptor in T-cells isolated from the circulation. The T-cell receptor used in our protocol is specific for an antigen called MART-1. The MART-1 antigen is expressed in nearly all patients with melanoma who have inherited an immune protein called HLA-A2. (Forty percent of Caucasian individuals are positive for HLA-A2.) We have shown that it is possible to isolate T-cells from the circulation, genetically modify the cells with a retrovirus encoding a MART-1 specific TCR, and reprogram these T-cells to specifically kill target cells expressing MART-1. In this application, we propose a clinical trial designed to test the safety of this experimental treatment. Patients with advanced melanoma will be treated with genetically modified T-cells expressing the MART-1 specific T-cell receptor. The dose of T-cells will be systematically increased in sequential groups of patients to test for toxicity. One-half of patients will also be treated with interleukin-2 (IL-2), a T-cell growth factor necessary for the survival and full functional activity of T-cells. The endpoints of this clinical trial are toxicity, survival and function of the genetically modified T-cells in the circulation, and tumor response. Data from this study will provide important information necessary in designing subsequent clinical trials to define the therapeutic effectiveness of this experimental therapy.