Tab 3: Non-Technical Abstract

Non-technical abstract :

It is now well understood that human tumors have antigens that make them recognizable to the immune system, and that naturally occurring tumor immune responses are associated with improved survival in a variety of cancers. The central problem to harnessing a patient's immune system to fight their tumor is that the tumor can induce tolerance, or resistance to, recognition by the immune system. This is a major issue with cancer vaccines, and natural T cell responses are often not strong enough to fight the tumor. One way to overcome this problem is to generate optimal higher affinity, or stronger, T cells capable of tumor recognition. Recent advances in T cell culture and genetic modification technologies have recently made this approach possible. **The hypothesis driving the proposed clinical study presented in this RAC submission is that a person's own (autologous) T cells can be genetically engineered to target their myeloma tumor cells and delay progression or reverse their disease.** To do this, we isolated T cells that are specific for a type of antigen present on some myeloma tumors, called cancer testis antigens. We then generated higher affinity T cell receptors using a laboratory method developed by our collaborators at Adaptimmune Ltd. These T cell receptors, or TCRs, can be genetically inserted into a patient's T cells to generate tumor specific T cells. One type of cancer testis TCR is being evaluated, and it works in patients with a certain gene phenotype HLA-A201. To test our hypothesis using the candidate TCR, we designed a Phase I/IIa, open label, study to evaluate the safety, bioactivity and anti-tumor effects of autologous (self) CD4 and CD8 T cells expressing the "NY-ESO-1^{c259}" TCR in patients with progressed or relapsed myeloma, following failure from a standard therapy for myeloma called autologous stem cell transplant. Patients who are HLA-A201 positive and whose myeloma tumors express a certain protein, either NY-ESO-1, or LAGE-1, or both, are eligible for this study. T cells will be isolated from patients using a process called apheresis, which allows for collection of white blood cells without removal of other blood components. T cells will then be genetically modified in the laboratory using a gene delivery system derived from a virus, called a lentiviral vector. This vector permanently modifies the T cells to express the NY-ESO-1^{c259} TCR. The cells will then be further expanded in the laboratory. The vector to deliver the TCR will be manufactured according to Good Manufacturing Practices at the Center for Biomedicine and Genetics in the City of Hope, Duarte California. The cells will be manufactured at the GMP compliant Clinical Cell and Vaccine Production Facility (CVPF) at the University of Pennsylvania, which has safely produced 474 T cell products for 336 patients up to July, 2012. Patients will be treated at the University of Pennsylvania. Cell product will be administered as a single dose of total 1 to 10 billion cells. Subjects will be followed until their disease progresses up to 5 years post infusion. At that point, patients will be periodically for up to 15 years post infusion in accordance with FDA Guidance for monitoring for delayed adverse events for lentiviral vectors. The clinical trial is designed to demonstrate safety and indications of efficacy, to support development of a larger, controlled study, where the effectiveness of this approach is rigorously tested.

Rationale

Multiple myeloma is the second most common hematologic cancer worldwide, with an estimated annual incidence of 16,000 and annual mortality of 11,000 per year. MM patients have only a 20% chance of surviving longer than 10 years. Although significant improvement in therapy has occurred over the past decade with the development of new drug regimens, the only curative therapy remains allogeneic stem cell transplant which is highly toxic and for which a majority of patients are ineligible. Therefore new approaches are desperately needed. The purpose of this proposed trial is to evaluate genetic enhancement of a patient's own T cells to target their tumor in patients with advanced myeloma.