Scientific Abstract

The subject of this proposal is the use of autologous tyrosinase-specific CD8+ CTL clones for the treatment of patients with metastatic melanoma. The safety, duration of in vivo persistence and anti-tumor efficacy of this approach will be evaluated. Since tyrosinase is a normal self protein also expressed in some normal tissues, such as the eye, skin and brain, the tyrosinase-specific CD8+ CTL clones used for the initial infusions will be transduced with the HyTK retrovirus which expresses an inducible suicide gene so that the infused CTL clones can be ablated should therapy-related toxicity occur. (The use of this retrovirus for human gene therapy has previously been approved by the RAC and FDA, BB-IND# 4337). In addition, the HyTK selectable suicide gene contained in the vector will facilitate rapid analysis of the duration of in vivo persistence of the transduced clones. However, results from an earlier study employing the HyTK gene, (FHCRC protocol 827.0) , demonstrated the development of an anti-HyTK response in individuals receiving three or more infusions of HyTK-transduced CTL. This response correlated with a rapid disappearance in vivo of the transferred CTL. In order to circumvent the anti-HyTK response yet retain the margin of safety associated with infusing tyrosinase-specific CTL clones transduced with a suicide gene, this trial will consist of an initial two infusions of HyTK-transduced tyrosinase-specific CTL followed by a three week observation period for monitoring toxicity. If no toxicity is observed during this period, two further infusions of unmodified tyrosinase-specific CTL clones will be transferred. In this way, a total of four infusions of tyrosinase-specific CTL clones can be administered.

The results of this study will provide insights for the design of future trials involving antigen-specific adoptive immunotherapy for the treatment of malignancy as the identification of tumor target antigens as normal self proteins becomes an increasingly important paradigm in tumor immunology.