

Scientific Abstract

Neuroblastoma is the most common extracranial solid tumor of childhood. When widely disseminated most patients are expected to relapse. We plan to redirect the patient's cellular immune system to GD-2 a disialoganglioside strongly expressed by most neuroblastomas and only weakly expressed on normal tissue. We have generated a chimeric T-cell receptor (TCR) linking the variable domains of an anti-GD2 monoclonal antibody to the signaling portion of human CD3-zeta. When human T-cells are retrovirally transduced with this construct they kill GD-2 expressing targets. A major barrier to use of chimeric TCR transduced T-cells, however, is the lack of full activation and lack of subsequent persistence in vivo partly caused by the lack of co-stimulation provided by many tumors. We plan to overcome this deficit by transducing EBV-specific T-cells (EBV-CTLs). More than 50% of neuroblastoma patients are EBV sero-positive and earlier studies with EBV-specific CTLs has shown persistence and function of the cells in vivo for several years. We hypothesize that transduced EBV-CTLs will be activated and persist in response to EBV-positive cells when stimulated through their native TCR. These bi-specific cells will also kill neuroblastoma cells recognized by their GD-2 targeted chimeric TCR. We plan to fully test this hypothesis by simultaneously infusing both transduced peripheral blood T-cells and transduced EBV-CTLs to EBV sero-positive patients with advanced neuroblastoma. A small difference in the non-coding region of the retroviral construct used to transduce these different cell types will allow differential tracking by real-time quantitative PCR. If this hypothesis is correct, other tumor antigens could be targeted using a similar approach.