Autologous T Cells as a Personalized Treatment for Patients with Cancer

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The adoptive transfer of anti-tumor T cells can mediate regression of established metastatic cancers in patients. In a series of three sequential clinical trials we treated patients with metastatic melanoma using autologous tumor infiltrating lymphocytes (TIL) selected for anti-tumor activity. These cells were adoptively transferred to patients following the administration of a lymphodepleting regimen of cyclophosphamide and fludarabine with or without whole body irradiation. In three pilot trials objective response rates of 49% - 72% (RECIST criteria) were observed. Twenty of 93 patients (22%) achieved a complete tumor regression of widespread cancer and 19 of these 20 patients have ongoing complete responses at 59 to 104 months. Significant correlations with the incidence of patient response were seen with persistence of the infused transferred cells at one month, longer telomeres of the transferred cells, and the percent and number of CD27+ infused cells. There was no evidence of T regulatory cells in the infused samples, though there was an inverse correlation between the likelihood of objective clinical response and reconstitution with Foxp3+ CD4+ T cells in the peripheral circulation at 1 week. New techniques utilizing exomic sequencing have been used to identify multiple mutated antigens recognized by TIL.

Because melanomas are the only histologic type of cancer that readily gives rise to TIL with demonstrable anti-tumor activity, we have begun a series of clinical trials using the transduction of genes encoding cytokines or anti-tumor T cell receptors (TCR) into normal peripheral lymphocytes for use in adoptive cell transfer. Anti-tumor TCRs have been identified that recognize the MART-1 and gp100 melanoma/melanocyte antigens and 30% of melanoma patients receiving autologous cells transduced with genes encoding these TCRs showed an objective response. Autologous cells transduced with genes encoding the anti-NY-ESO-1 TCR cancer-testes antigen mediated objective clinical responses in 80% of patients with synovial cell sarcoma and 50% of patients with melanoma. Patients with B

cell lymphomas exhibited an 80% objective regression rate using cells transduced with a CD19 chimeric antibody TCR. The cellular and molecular mechanisms of T cell destruction of cancers are under active investigation.

These studies demonstrate the power and potential of adoptive T cell immunotherapy to mediate the regression of established metastatic cancers in humans.