

Phase II Study of Metastatic Cancer that Overexpresses p53 using Lymphodepleting Conditioning Followed by Infusion of Anti-p53 TCR-Gene Engineered Lymphocytes

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M-I-A.2. Scientific Abstract:

We and others have demonstrated the ability to engineer human PBLs to express a T-cell receptor that recognizes an HLA-A2.1 restricted epitope derived from the p53 protein. We constructed a single retroviral vector that contains both α and β chains and can mediate genetic transfer of this TCR with high efficacy (>30%) without the need to perform any selection. In co-cultures with HLA-A2 and p53 double positive tumors including melanoma, hepatoma, sarcoma, small-cell lung cancer, esophageal and breast tumors, p53-TCR transduced T cells secreted significant amount of IFN- γ but no significant secretion was observed in control co-cultures with either HLA-A2+/p53- or HLA-A2-/p53+ cell lines. Additional secretion of cytokines (IL-2, IL-4, IL-10, GM-CSF, TNF α) and chemokines (RANTES, MIP-1 α) was also observed in co-cultures with HLA-A2+/p53+ tumor lines. p53-TCR transduced PBL could efficiently kill HLA-A2.1/p53 expressing tumors (H2087, MDA-MB 231, Saos2/*143, BE-3). In addition, we also tested for specific lysis of normal tissues by p53-TCR transduced cells and there was little or no lysis of the normal fibroblasts, renal epithelia cells, resting or activated normal PBLs compared to control HLA-A2⁺/p53⁺ H2087 tumor. Based on these observations the following clinical protocol is proposed.

Patients with metastatic cancer whose tumors overexpress p53 will be entered into two cohorts based on histology: 1) patients with metastatic renal cell cancer and metastatic melanoma; and 2) patients with other types of metastatic cancer. Up to 41 patients will be enrolled in each cohort. All patients will receive a nonmyeloablative but lymphocyte depleting preparative regimen consisting of cyclophosphamide and fludarabine, and then will be treated by the adoptive transfer of autologous peripheral blood lymphocytes that have been transduced with the anti-p53 TCR retroviral vector. Following adoptive cell transfer, all patients receive high-dose IL-2 and then will receive p53 peptide vaccination. This study will evaluate the potential therapeutic role of this treatment, the survival of the transferred cells, and any potential toxicities associated with the protocol.