Treatment of B Cell Malignancies with T Cells Expressing an Anti-CD19 Chimeric Receptor: Assessment of the Impact of Lymphocyte Depletion Prior to T Cell Transfer

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Scientific Abstract:

Adoptive transfer of tumor infiltrating lymphocytes (TIL) is an effective therapy for advanced melanoma[1], and we have found that adoptive transfer of T cells that were transduced with the genes of tumor-antigen-specific T cell receptors caused regressions of melanoma in some patients[2]. Another approach to adoptive T cell therapy is to engineer T cells to express chimeric antigen receptors (CARs). CARs combine a single chain Fv (scFv) component that is derived from a monoclonal antibody with T cell activation moieties[3;4]. We have constructed and extensively tested an anti-CD19 CAR. T cells that are transduced with gamma-retroviruses encoding the sequence of this CAR can specifically recognize and kill CD19-expressing target cells including primary chronic lymphocytic leukemia cells. These anti-CD19-CAR-transduced T cells also produce the cytokines interferon-γ (INFγ) and IL-2 specifically in response to CD19. We propose to conduct a clinical trial in which gamma-retroviruses encoding the anti-CD19 CAR will be used to transduce T cells from patients with advanced B cell malignancies.

The anti-CD19 CAR used in our work consists of three main components: the variable regions of the anti-CD19 monoclonal antibody FMC63[5], part of the CD28 costimulatory molecule, and the signaling domain of the CD3 zeta chain[6]. This receptor is referred to as FMC63-28. The DNA encoding this receptor was cloned into the MSGV1 retroviral vector backbone[7] to form the plasmid. This plasmid is referred to as MSGV1-FMC63-28. Our data have demonstrated that after being subjected to a REP, anti-CD19-CAR-transduced T cells produce IFN-γ in response to CD19-expressing target cells but not in response to CD19-negative cells. The cells can also kill primary CLL cells.

We hypothesize that lymphocyte-depletion with fludarabine and cyclophosphamide will enhance persistence of the adoptively transferred anti-CD19 T cells. Murine studies demonstrate enhanced anti-tumor efficacy of transferred T cells in lymphocyte-depleted hosts compared to lymphocyte-replete hosts[8]. Our proposed trial will be the first randomized trial to evaluate the impact of immunosuppression on the persistence of adoptively transferred T cells in humans.

Initially, the protocol will proceed in a phase 1 dose escalation design, with three cohorts of n=3 to determine the maximum tolerated dose. In phase 1, patients with a CD19-expressing lymphoma or chronic lymphocytic leukemia will receive lymphocyte-depleting chemotherapy consisting of intravenous cyclophosphamide (60 mg/kg X 2days) and fludarabine (25 mg/m^2 X 5 days), anti-CD19-CAR engineered peripheral blood lymphocytes (PBL), and high dose aldesleukin (720,000 IU/kg q8h for a maximum of 15 doses). Once the MTD has been determined, the study then will proceed to the phase 2 portion. Patients will be randomized to two treatment arms. Patients assigned to treatment arm 1 will receive fludarabine and cyclophosphamide chemotherapy as described above in order to induce lymphocyte depletion prior to infusion of the anti-CD19-CAR-transduced T cells, and high dose aldesleukin. Patients assigned to treatment arm 2 will receive anti-CD19-CAR transduced T cells and high dose aldesleukin without

chemotherapy. This trial design will allow us to rigorously assess the impact of prior lymphocyte-depletion on the persistence of adoptively transferred T cells in patients.