Section 2. Scientific Abstract

This single-center, proof-of-concept human gene therapy trial (protocol IRB#2011-1169) evaluates the safety, feasibility, and persistence of adoptively transferred CD19-specific autologus T cells in research participants with advanced B-lineage chronic lymphocytic leukemia (CLL) after receiving cyclophosphamide and fludarabine chemotherapy. The T cells, are rendered specific for CD19 by electrotransfer, using a Nucleofector device, of two *Sleeping Beauty* (SB) DNA plasmids expressing (i) SB11 hyperactive transposase and (ii) transposon coding for chimeric antigen receptor (CAR), designated CD19RCD28, that can activate T cells through chimeric CD28 and CD3-ζ endodomain upon binding cell surface CD19 via a scFv derived from a mouse monoclonal antibody. In compliance with current Good Manufacturing Practice (cGMP) for Phase I/II trials, the genetically modified T cells are recursively expanded to clinically-meaningful doses on gamma-irradiated artificial antigen presenting cells (aAPC, designated "clone 4") derived from a master cell bank (or a derived working cell bank) of K562 cells that were genetically modified by lentiviral transduction to express (i) CD19, (ii) 4-1BBL (CD137L), (iii) CD86, (iv) CD64 and (v) membrane-bound IL-15 (mIL-15). The same SB DNA plasmids and aAPC are currently used for three investigator-initiated clinical trials NIH/OBA RAC# 0804-922, 0910-1003, 1001-1022 with respective FDA approved IND#s 14193, 14577, 14739 which infuse patient-derived and donor-derived CD19-specific T cells after autologous and allogeneic hematopoietic stem-cell transplantation. Research participants will be eligible to receive one intravenous infusion of patient-derived genetically modified *ex vivo*-propagated T cells after lymphodepleting chemotherapy. The primary objective of this study is to assess the safety, feasibility, and persistence of genetically modified T cells. The secondary objectives are to assess the (i) host immune response against the CD19-specific CAR, (ii) homing ability of the adoptively transferred T cells, and (iii) disease response. The first patient will be enrolled in the first cohort at T-cell Dose level 1:$>5X10^7/m^2$ but $\leq 5X10^8/m^2$ and after patients have completed 3 T-cell infusions, the successive cohorts of patients to Dose levels 2 and 3 will be enrolled. The T-cell infusion dosing for subsequent cohorts are : Dose level 2:$>5x10^8/m^2$ but $\leq 5\ x10^9/m^2$ Dose level 3: $5x10^9/m^2$ but $\leq 5x10^{10}/m^2$. A maximum of 30 patients will be enrolled. We will employ a 3+3 design to find the maximum tolerated dose of genetically modified CLL-patient derived T cells. In summary, this gene and cell therapy protocol is a continuum of our efforts to develop immunotherapies for $CD19^+$ malignancies based on adoptive transfer of autologous T cells that express CAR after SB-mediated transposition and selected propagation on designer aAPC.