Role of CD28 Signaling in Mice on Homeostatic Reconstitution on T Cells following Lymphodepletion

Nitish Sood[1,2]; Rebecca Crepeau, Ph.D.[2,3]; and Mandy Ford, Ph.D.[2,3]

[1]Summer Undergraduate Program in Emory Renal Research, Atlanta, GA, USA; [2]Department of Surgery, Emory School of Medicine, Atlanta, GA, USA; [3]Emory Transplant Center, Emory University School of Medicine, Atlanta, GA, USA

Emory University will soon commence a Phase 2 clinical trial testing the efficacy of Lulizumab, a drug that selectively targets CD28 signaling thereby preventing T cell activation. Preclinical studies have shown this drug to be superior to calcineurin inhibitors in reducing kidney transplant rejection rates. Patients will be T cell depleted (TCD), rendering them lymphopenic at the time of transplant. It is unclear what effect CD28 dAb treatment will have on T cell phenotypes following homeostatic reconstitution (HR) in these patients. Previous studies have shown that HR causes increased differentiation of naïve T cells into memory cells and to premature senescence. We hypothesized that blocking CD28 signaling in T cells could prevent this differentiation and change in phenotype. We investigated this question using a murine model of TCD and skin transplantation. Four groups of mice (n = 16): no treatment control, TCD alone, CD28 dAb alone, and both TCD and CD28 dAb were established. Mice were sacrificed at 6 weeks post-grafting, and blood and tissues were collected for flow cytometric analysis. Using traditional flow cytometry analysis, we found that treating TCD mice with CD28 dAb controlled HR-induced differentiation and senescence of CD4+ T cells. These results were consistent in across the blood, lung, and spleen, and were also confirmed using an unsupervised machine-learning approach. As it is currently believed that memory T cells are responsible for costimulatory blockade resistant rejection, we believe further analysis could help determine the specific mechanism behind costimulatory blockade resistant rejection and therefore help reduce kidney transplant rejection rates.