Anti-CD83 CAR T cells can selectively kill alloreactive T cells to prevent or treat GVHD or organ allograft rejection. Also, HLA disparate (off the shelf) anti-CD83 CAR-T cells can kill alloreactive T cells without being rejected themselves. This suggests anti-CD83 CAR T cells could protect a second allogeneic CAR T cell from rejection, essentially allowing any allogenic CAR T cell, or cell therapy in general, to be used “off the shelf.” Like CD83, IL-6Rα is selectively expressed on alloreactive T cells. A dual IL-6Rα/CD83 CAR T cell was designed to enhance the specificity of CAR T cell targeting of alloreactive T cells, yet preserve donor immunity against cancer and infectious pathogens.

COMMERCIAL OPPORTUNITY

- The rationale for a human, dual IL-6Rα/CD83-targeted CAR T cell to mediate immune tolerance is that IL-6 receptor activation induces T cell alloreactivity and promotes GVHD. GVHD is a leading cause of non-relapse mortality after allogeneic hematopoietic cell transplantation (alloHCT). GVHD occurs when donor T cells are intolerant of the host. IL-6 facilitates STAT3 phosphorylation via JAK2 kinase. CD4+ T-cell JAK2/STAT3 activity is increased by IL-6 in alloHCT recipients who later develop GVHD. These data show that IL-6 signals contribute to GVHD but prevention is incomplete when targeting the IL-6 pathway alone. Moreover, broadly inhibiting the signal transduction elements of the IL-6 receptor ameliorates the symptoms of GVHD, but increases the risk for opportunistic infections by impairing natural killer cells and cytotoxic T lymphocytes due to shared signaling pathways with alloreactive T cells.

- CD83 is differentially expressed on allo-activated, human, conventional CD4+ T cells (Tconv), with minimal expression on regulatory T cells (Treg). In a human T cell mediated xenogeneic GVHD model, CD83 CAR T cells were shown to provide lasting protection from alloreactive T cells. Moreover, IL-6Rα expression is essentially restricted to alloreactive, CD83+ Tconv.

- A dual IL-6Rα/CD83-targeted CAR T cell may prevent and treat GVHD by providing exquisite specificity against alloreactive T cells. Thus, sparing immune effectors and components of innate immunity that lack concurrent expression of IL-6Rα and CD83. This technology is expected to improve alloHCT survival and solid organ transplant success by eliminating the need for broad immune suppression. Further, a dual IL-6Rα/CD83-targeted CAR T cell will facilitate the use of banked, off the shelf cell therapy by mitigating rejection by host immunity.

TECHNOLOGY

IL-6Rα is co-expressed on alloreactive, CD83+ Tconv. Bar graph shows CD83/IL-6Rα co-expression on DC-allostimulated human T cells after 8 hours of stimulation. ANOVA. **** = P<0.0001.

PUBLICATION/PATENT

- Provisional patent application filed January 22, 2020 for Dr. Davila and Dr. Betts.