Functional Characterization of Regulatory T cell (Treg) Therapy for the Treatment of Type 1 Diabetes (T1D)

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Abstract

Purpose: Abata Therapeutics is dedicated to developing novel targeted Treg cell therapies for the treatment of intractable autoimmune conditions such as Type 1 diabetes (T1D). In recent years, Regulatory T cell (Treg) therapy has emerged as a potential intervention to restore immune tolerance and halt progression of T1D. Abata Therapeutics is currently developing an autologous TCR-engineered Treg cell therapy product targeting proinsulin for the treatment of T1D. Here, we present the *in vitro* functional characterization of representative drug product, highlighting key biological and polypharmacological features that support Treg mediated immune modulation in the treatment of T1D.

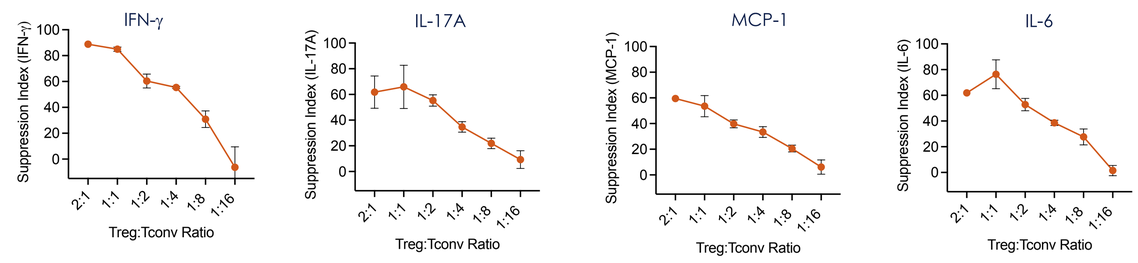
Methods: Islet-antigen targeting TCR engineered Tregs (TCR-Tregs) were functionally characterized in *in vitro* antigen-stimulated Treg pharmacology studies. Specifically, the direct and bystander suppressive capacity of TCR-Tregs against conventional CD4+ T cells, CD8+ T cells, and dendritic cells (DC), was evaluated in antigen-stimulated Treg cell-based studies *in vitro*.

Summary of Results: TCR-Tregs engineered from both healthy and T1D donors demonstrated robust direct and bystander suppression against autologous islet antigen reactive conventional CD4+ T (Tconv) and CD8+ T cells. Moreover, when interrogating DC-Treg crosstalk, a key interaction critical to limiting antigen priming of autoreactive T cells, antigen activated Tregs demonstrated greater deactivation of mature DCs as compared to polyclonal Tregs derived from a T1D donor. Collectively, these multiple mechanisms of Treg induced tolerance underscore the potential high therapeutic impact of our Treg cell therapy in treating T1D.

Conclusions: Abata has developed a proinsulin targeted TCR engineered Treg cell therapy that exhibits a vast polypharmacy. Restriction to MHC-II expressing antigen presenting cells (APCs) and target peptide in the inflamed tissue and draining lymph node affords TCR engineered Tregs the opportunity to fine-tune the autoimmune responses, resulting in both direct and broad infectious tolerance. Taken together, TCR engineered Tregs hold the potential of establishing tissue residence, halting islet β cell destruction, recalibrating the immune response, and offering hope for an improved quality of life for those affected by T1D.

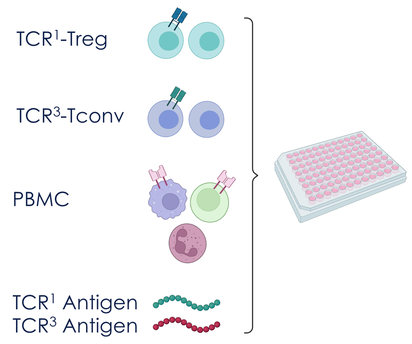
Antigen Stimulated TCR-Tregs Suppress the Production of Multiple Inflammatory Cytokines Associated with Islet Inflammation

Antigen-stimulated TCR-Tregs Inhibited the Production of Inflammatory Cytokines in Treg-Tconv-APC Co-culture Studies



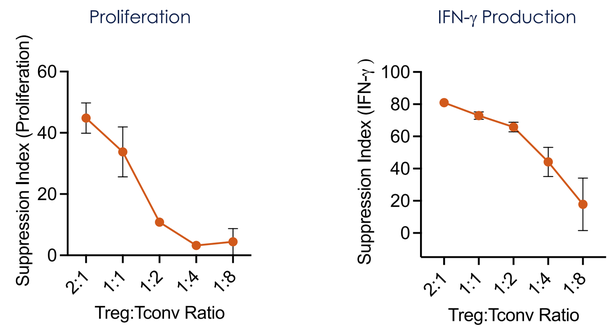
Antigen Stimulated TCR-Tregs Exhibit Bystander Suppression of Islet-Antigen Reactive Tconv Cells

Study Design



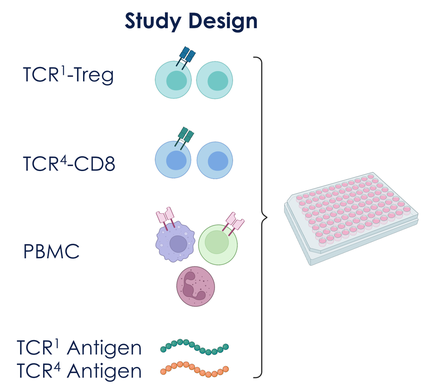
TCR1 and TCR3 are different TCRs recognizing different islet antigen epitopes presented by the same HLA-DRB1.

TCR-Treg Suppressed the Proliferation and Inflammatory Cytokine Production of Tconv Cells Recognizing A Different Islet Antigen



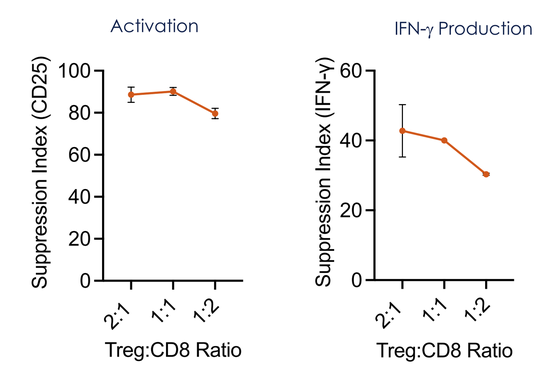
Antigen Stimulated TCR-Tregs Suppress the Activation of CD8+ T Cells

Study Design

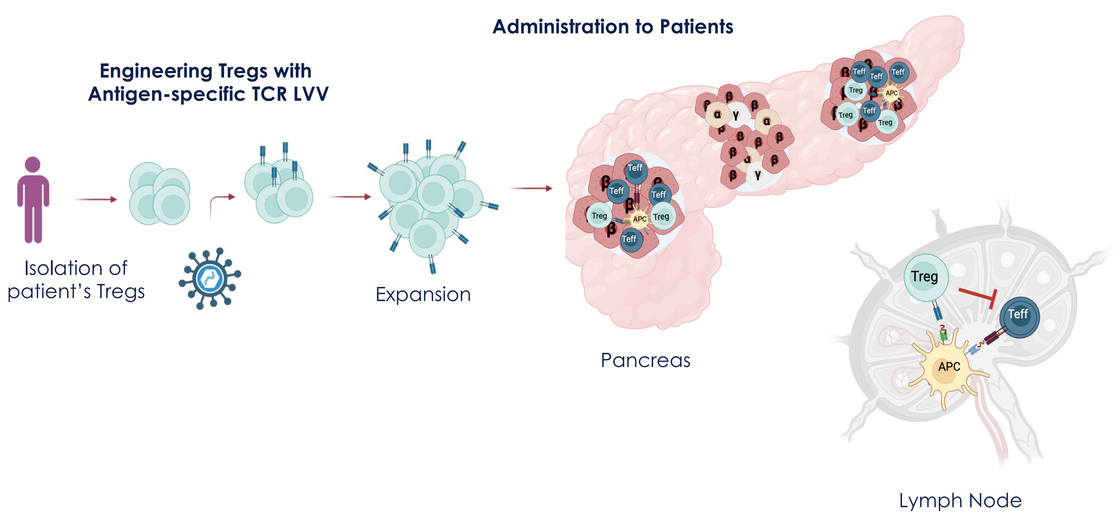


TCR1 and TCR4 are different TCRs recognizing different antigen epitopes presented by HLA-DRB1 and HLA-A, respectively.

Antigen-stimulated TCR-Tregs Inhibited Activation of and Inflammatory Cytokine Production from TCR-CD8+ T Cells

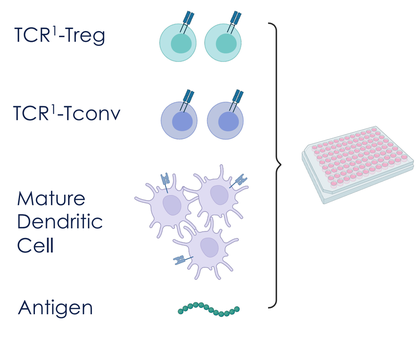


Autologous TCR-engineered Tregs Preserve Islet β Cell Mass

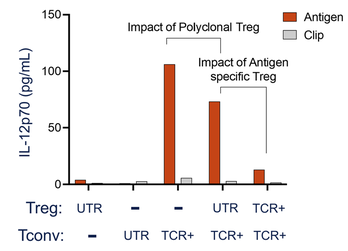


Antigen Stimulated TCR-Tregs Negatively Regulate Dendritic Cell Function

Study Design



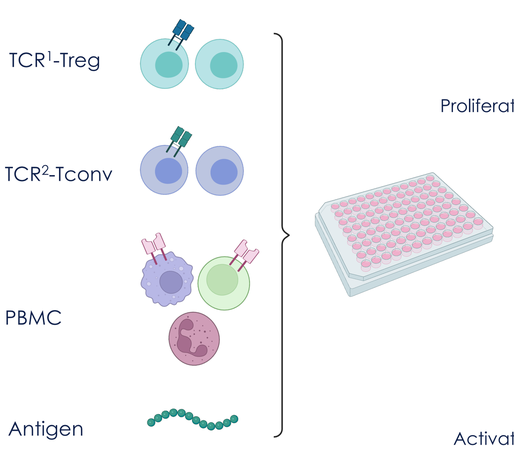
Suppression of DC Cytokine Production



Tregs/Tconv transduced with either a TCR recognizing target islet antigen (TCR+) or untransduced (UTR)

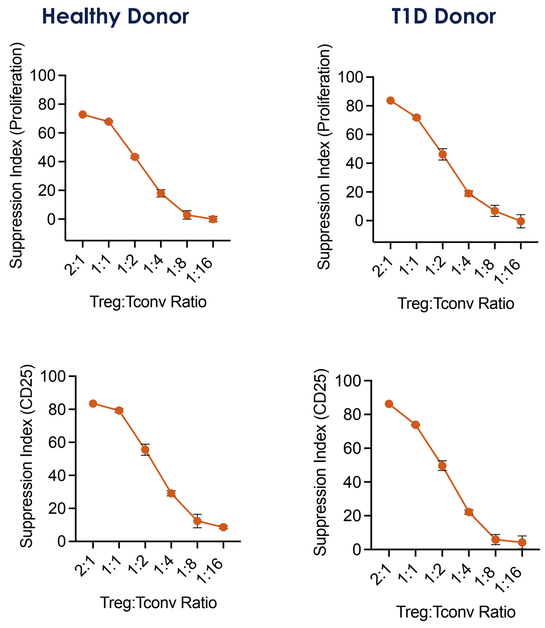
Antigen Stimulated TCR-Tregs Suppress the Proliferation and Activation of Tconv Cells

Study Design



TCR1 and TCR2 are different TCRs recognizing the same islet antigen epitope presented by the same HLA-DRB1.

Antigen-stimulated TCR-Tregs Inhibited the Proliferation and Activation of TCR-Tconv T Cells



Summary

- Abata Therapeutics has developed a proinsulin antigen targeted TCR-engineered Treg cell therapy for the treatment of T1D. *In vitro* functional studies demonstrated multiple suppressive mechanisms employed by TCR-Tregs.
- Antigen-stimulated TCR-Tregs engineered from both healthy and T1D donors showed direct and bystander immunosuppression of the proliferation and activation of Tconv cells and the secretion of inflammatory cytokines.
- Antigen-stimulated TCR-Tregs suppressed the activation and function of CD8+ T cells.
- TCR-Tregs exhibited an antigen specific reduction in dendritic cell activation *via* down regulation of inflammatory cytokine production.