Novel Variant Ig Domain (vIgD) Proteins Generated Via Directed Evolution of IgSF Domains Have Therapeutic Efficacy in Animal Models of Graft Versus Host Disease

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Abstract

We generated variant IgSF proteins with improved/high affinity binding to the T cell co-stimulatory molecule ICOS and improved capacity to inhibit both the CD28 and ICOS T cell costimulation pathways. These vIgDs are derived from a novel variant Ig domain™ platform and have unique variant hits (m and n) that stain for TNF. (f) ICOSL vIgD-Fc reduced (a) the Disease Activity Index (DAI) and (b) the survival of NSG mice treated with belatacept

**Figure 4:** CD28 and ICOSL Costimulation in Graft Versus Host Disease

- **Figure 5:** Schematic showing expressed mechanism of action for ICOSL vIgD-Fc with its capacity to inhibit both the CD28 and ICOS T cell costimulation pathways.

- **Figure 6:** ICOSL vIgD-Fc Proteins Supress T Cell Responses in vitro

- **Figure 7:** ICOSL vIgD-Fc Protects from GvHD in vivo

- **Figure 8:** ICOSL vIgD-Fc Prevents T Cell Activation in vivo and Preserves Naïve T Cell Phenotype

**Summary and Conclusions**

- A variant Ig domain (vIgD) platform has been developed to generate novel immunomodulatory Ig-based protein therapeutics with increased affinity and diversity of ligand binding, translating into superior preclinical efficacy in vivo and in vitro.
- ICOSL vIgD-Fcs demonstrate novel, high affinity binding to CD28 and ICOS and can inhibit these costimulatory pathways.
- ICOSL vIgD-Fcs demonstrate superior efficacy to belatacept (CTLA4-Ig) in vivo in human MURP baseline and inhibition of T cell proliferation and cytokine production, including many of the cytokines induced in a GvHD response.
- ICOSL vIgD-Fcs protected better than belatacept in a humanized GvHD in vivo model.
- The vIgD Therapeutic platform has broad potential to enhance the activity of biologics in treatment of human disorders driven or subject to modulatory by IgSF proteins, including autoimmunity, cancer and infectious diseases.

- Preclinical development of ICOSL vIgD-Fc (A1N-101) is underway to support clinical studies.