Therapeutic Candidate ALPN-101, a Dual ICOS/CD28 Antagonist, Potently Suppresses Human/NSG Mouse Xenograft Graft vs. Host Disease (GvHD) in a Dose Ranging Study and Reduces Disease Activity in a Mouse Model of Hemophagocytic Lymphohistioctisysis (HLH)

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Abstract
Background: ALPN-101 is a potent dual inhibitor of the ICOS and CD28 T cell costimulatory pathways designed for therapeutic application in inflammatory diseases. CD28 and ICOS costimulatory pathways, respectively, and their critical role in T cell activation and autoimmune inflammation. ALPN-101 has previously been demonstrated to have potent efficacy—superior to wild type ICOS-Fc— in models of graft versus host disease (GvHD), a disease reflecting immune-mediated attack of allogeneic bone marrow by donor T cells. Here, we examined the efficacy of a single dose of ALPN-101 or repeat dosing with ALPN-101 in a DNL-SCID mouse model of the mouse model of hemophagocytic lymphohistioctisysis (HLH), a spectrum of disorders of the immune system characterized by the excessive production of cytokines by macrophages accumulating in organs such as the liver, spleen, bone marrow, and brain, which mediate significant tissue damage. Results: ALPN-101 significantly diminished T cell activation in the human PBMC-NSG GvHD model in a single dose of 100 µg or at all multiple doses tested, protecting mice from the effects of xenogeneic T cell activation in vivo. Treated animals exhibited enhanced survival and reduced disease scores compared to control mice treated with saline or placebo. Flow cytometric analysis of blood collected at 1-2 weeks post cell transfer demonstrated ALPN-101 reduced both the number and activation state of the transferred human CD4+- and CD8+ T cells. In the 40 µg study, ALPN-101 lessened several of the clinical and laboratory manifestations of HLH, including organomegaly, anemia, CD8+ T cell expansion, and liver inflammation. Conclusion: ALPN-101 is a potent T and B cell alloimmunity therapy and appears to play important roles in GvHD and other inflammatory diseases. Preclinical development is underway to clinical study of this potentially first-in-class dual ICOS and CD28 inhibitor.

Figure 1: Biological Rationale for Coinhumbination of CD28 and ICOS

Figure 2: ALPN-101 (ICOSL IgG-Fc), a Dual ICOS/CD28 Antagonist

Figure 3: ALPN-101 Blocks both CD28 and ICOS Pathways in Vitro

Figure 4: ALPN-101 Potently Protects Mice from Disease in the Human PBMC-NSG™ GvHD Model, Even After a Single Dose

Figure 5: ALPN-101 Suppresses Activated T cell Expansion & Inflammatory Cytokine Production in the Human PBMC-NSG™ GvHD Model

Figure 6: ALPN-101 Reduces CD4+ T Cell Activation and Liver Inflammation in the Periforin (Prf) Knockout (KO)/LCMV Mouse Model of Hemophagocytic Lymphohistioctisysis (HLH)

Summary and Conclusions
- ALPN-101 (ICOSL IgG-Fc) potently inhibits both the CD28 and ICOS T cell costimulatory pathways, thereby demonstrating superior inhibition of T cell proliferation and cytokine production in MLRs.
- Repeat dosing with ALPN-101 completely protects mice from disease in a humanized GvHD model, and a single dose provides similar protection to repeat doses of belatacept, at least in part by preventing the emergence of activated (ICOSL-1gG-Fc+) T cells that escape CD28 single pathway inhibition.
- ALPN-101 inhibits the expansion of both effector and regulatory T cells, while not significantly perturbing the Th1/Th2 balance, and potently inhibits inflammatory cytokine production.
- ALPN-101 reduces CD4+ T cell activation and liver inflammation in a mouse model of HLH primarily driven by CD8+ T cells. In this model, treatment with ALPN-101 inhibits the generation of CD44* activated T cells without significantly affecting the LCMV-specific CD8+ T cell response.
- Dual antagonism of ICOS and CD28 may be an effective therapeutic approach in T cell-mediated inflammatory diseases. Clinical trials with ALPN-101 are expected to begin in early 2019.

References

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