ANB032, a Novel BTLA/HVEM Therapeutic Antibody, Inhibited T cells Derived from Atopic Dermatitis Patients In-vitro

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Abstract

B and T lymphocyte attenuator (BTLA) is an immune checkpoint molecule that contributes to the regulation of T cell function. The role of BTLA as a regulator of inflammatory disease and cancer has been demonstrated via genetic and animal models. Recently, several studies have described soluble checkpoint molecules, including soluble BTLA (sBTLA), in the serum or in tumors of diseased patients that correlates negatively with disease outcome, suggesting that sBTLA is a biomarker and/or a direct mediator of immune suppression.

ANB032 is a novel anti-BTLA monoclonal antibody that modulates BTLA signaling in-vivo. In an acute humanized murine GVHD disease model ANB032 significantly prolonged animal survival, reduced pathogenic human T cell activation and expansion, and reduced BTLA expression in a dose-dependent manner. Furthermore, sBTLA level from human T cells in the GVHD model. ANB032 also induced sBTLA release in cynomolgus monkeys treated with ANB032, in a dose-dependent manner. Together, the data demonstrates that ANB032 inhibits T cell-mediated inflammation in-vivo and ANB032-mediated release of sBTLA is a biomarker and/or direct mediator of the immunosuppressive mechanism of ANB032 in vivo.

We investigated the levels of sBTLA and LIGHT in atopic dermatitis patient-derived serum samples. We observed that sBTLA was significantly decreased, while LIGHT, an inflammatory ligand of HVEM, was significantly increased compared to healthy donors, suggesting dysregulation of a normal immune suppressive pathway in the setting of inflammatory disease.

Using in-vitro human primary patient-derived PBMC stimulation assays, we demonstrated that ANB032 reduced T cell proliferation, reduced secretion of IFNγ, and reduced T cell BTLA expression from both atopic dermatitis-derived and healthy donor-derived PBMC. We propose that ANB032, by directly inhibiting T cell activity and inducing sBTLA release, has the potential to restore immune suppression in atopic dermatitis.

Conclusions

We investigated the ability of ANB032, a novel BTLA/HVEM modulating therapeutic antibody, to inhibit T cell function in an in-vitro humanized model of GVHD and in-vivo as a treatment for atopic dermatitis patients. ANB032 was efficacious in a humanized model of GVHD, reducing T cell activation, expansion and expression. ANB032 also reduced the release of human sBTLA into the serum in the GVHD model. Additionally, sBTLA was released into the serum of cynomolgus monkeys treated with ANB032 and decreased T cell activation in vitro and T and B cells in a dose dependent manner (data not shown). We hypothesize that BTLA is shed from the surface of T cells and that sBTLA is a pharmacodynamic marker of ANB032 activity.

Using sBTLA as a biomarker of immune suppression, we identified that atopic dermatitis patients had lower serum sBTLA and higher LIGHT levels compared to healthy normal control individuals, suggesting dysregulation of T cell activity in-vivo.

In in-vitro human primary patient-derived PBMC stimulation assays, we demonstrated that ANB032 reduced T cell proliferation, reduced secretion of IFNγ, and reduced T cell BTLA expression from both atopic dermatitis-derived and healthy donor-derived PBMC.

We propose that ANB032, by directly inhibiting T cell activity, has the potential to restore immune suppression in inflammatory diseases where dysregulated T cells mediate pathophysiology, such as in atopic dermatitis.