ALPN-303, AN ENHANCED, POTENT DUAL BAFF/APRIL ANTAGONIST ENGINEERED BY DIRECTED EVOLUTION FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND OTHER B CELL-RELATED AUTOIMMUNE DISEASES


Alpine Immune Sciences Inc, Immunology, Seattle, United States of America; Alpine Immune Sciences Inc, Translational Sciences, Seattle, United States of America; Alpine Immune Sciences Inc, Protein Therapeutics, Seattle, United States of America; Alpine Immune Sciences Inc, Protein Engineering, Seattle, United States of America; Alpine Immune Sciences Inc, Bioanalytical Sciences, Seattle, United States of America

Background: BAFF and APRIL are TNF superfamily members that form homodimers and heterodimers that bind TACI and BCMA on B cells; BAFF also binds B cell development, differentiation, and survival, particularly for plasmablasts and plasma cells, and play critical roles in the pathogenesis of B cell-related autoimmune diseases. In nonclinical models, inhibition of either BAFF or APRIL alone mediates relatively modest effects, whereas their co-neutralization dramatically reduces B cell function, including antibody production. Fc fusions of wild-type (WT) TACI (e.g. atacicept and telitacicept) target both BAFF and APRIL and have demonstrated promising clinical potential in e.g. systemic lupus erythematosus (SLE) and IgA nephropathy but have not yet clearly exhibited long-term and/or complete disease remissions.

Objectives: To generate a dual BAFF/APRIL antagonist with inhibitory activity superior to WT TACI and BCMA and with the potential to improve clinical outcomes in B cell-mediated diseases.

Methods: Our directed evolution platform was used to identify a potent variant TNFR domain (vTD) of TACI that exhibits significantly enhanced affinity for BAFF and APRIL as compared to WT TACI; this TACI vTD domain was fused to a human IgG Fc to generate the therapeutic candidate ALPN-303. ALPN-303 was evaluated for functional activity in: 1) human lymphocyte assays, 2) the NOD.Aec1Aec2 spontaneous model of Sjogren's syndrome (SjS), 3) the bm12-induced mouse model of lupus, 4) the NZB/NZW F1 spontaneous model of lupus, and 5) preclinical rodent and cynomolgus monkey pharmacokinetic/pharmacodynamic studies.

Results: ALPN-303 inhibited BAFF- and APRIL-mediated signaling in vitro in human lymphocyte assays, with significantly lower IC50 values than WT TACI-Fc and belimumab comparators. In all mouse models evaluated, administration of ALPN-303 rapidly and significantly reduced key lymphocyte subsets including plasma cells, germinal center B cells, and follicular T helper cells. ALPN-303 significantly reduced autoantibodies and sialadenitis in the spontaneous SjS model, inhibited glomerular IgG deposition in the bm12-induced model of lupus, and potently suppressed anti-dsDNA autoAbs, blood urea nitrogen levels, proteinuria, sialadenitis, kidney lesions, and renal immune complex deposition in the NZB/W lupus model. As compared to WT TACI-Fc, ALPN-303 exhibited higher serum exposure and significantly and persistently decreased titers of serum IgM, IgG, and IgA antibodies in mice and cynomolgus monkeys (Figure 1).

Conclusion: ALPN-303 is a potent BAFF/APRIL antagonist derived from our directed evolution platform that consistently demonstrates enhanced immunomodulatory activity and efficacy in vitro and in vivo, superior in preclinical studies to anti-BAFF antibody and WT TACI-Fc. This novel Fc fusion molecule demonstrates favorable preliminary developability characteristics, including higher serum exposures and more potent immunosuppressive activities, which may enable lower clinical doses and/or longer dosing intervals than WT TACI-Fc therapeutics. ALPN-303 may thus be an attractive development candidate for the treatment of multiple autoimmune and inflammatory diseases, particularly B cell-related diseases such as SLE, SjS, and other connective tissue diseases. Preclinical development is underway to enable the initiation of clinical trials later this year.


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indicating that microglia cells may carry out the antigen presentation process seen in transcriptomic data. Low levels of serotonin and noradrenaline were observed at both 3 and 6 months of age in lupus mice; these aberrancies were mainly attributed to decreased serotonin synthesis as evidenced by intact serotonin metabolism (no differences were observed at its metabolite: 5-hydroxyindoleacetic acid). Analysis of the remaining regions of the brain combined with studies of metabolic activities of various brain regions by PET-CT scanning is in progress.

Conclusion: Immune cell trafficking from the periphery combined with marked inflammatory response in the hippocampus under the neuropsychiatric phenotype in NZW/B murine lupus. Our data indicate increased expression of activated myeloid cells -including microglia- in the hippocampus of lupus mice culminating in increased antigen presentation and decreased neurotransmitter levels.

REFERENCES:

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OP0042

BLOCKING OF CD103+ TISSUE RESIDENT MEMORY T CELLS (TRM) AS A THERAPEUTIC STRATEGY IN SJÖGREN’S SYNDROME

1Department of Medicine and Medical Specialties, University of Palermo, Italy; 2Department of Biopathology (Institute of Pathology and Genetics), University of Palermo, Italy; 3Department of Pathology, University of Palermo, Italy; 4Shanxi Medical University, Department of Pathology, Shanxi Bethune Hospital and Shanxi Academy of Medical Sciences, Taiyuan, China; 5Azienda Ospedaliera “Ospedali Riuniti Villa Sofia-Cervello”, Pathology Unit, Palermo, Italy

Background: Tissue-resident memory T cells (TRM), are recently identified T cell populations featuring tissue localization and expression of markers of tissue homing, CD69 and CD103. Their role in the pathogenesis of psoriasis is well known. The study aimed to address the role of CD4+ and CD8+ TRMs in the pathogenesis of psS and to explore the therapeutic targeting of the tissue residency marker of TRM CD103.

Methods: An animal model of experimental psoriasis (ESS) obtained by immunization of female C57BL/6 mice (n=10) with salivary glands (SG) protein extract and Freund’s complete adjuvant used to investigate the dynamic of infiltration of SG by CD4+ and CD8+ TRMs, their survival and the impact of CD103 blockade. For the therapeutic intervention, at 10-weeks post-inmunization, the salivary gland was cannulated via Wharton’s duct, and an anti-CD103 neutralizing antibody or vehicle-injected. The mice’s saliva flow rate was assessed, and SGs were analyzed by Flow-cytometry and immunohistochemistry (IHC). The frequency and localization of TRMs was analyzed in minor SG of sicca syndrome (nSS) and psS patients (n=39) by flow cytometry and IHC. The expression of genes involved in the tissue retention of TRMs was assessed in SG by quantitative PCR.

Results: Upon the ESS progression, a significant progressive increase in CD4+CD103+ cells frequency was observed from 5wk to 20wk post-immunization (p<0.001), where the CD8+ were the most abundant, followed by CD4+. Consistently, CD103+CD8+ T cells were detected within the lymphocytic infiltration of SG from ESS mice. Sorted purified SG CD10+CD3+CD8+ T cells showed higher Granzyme B, TGF-alpha expression compared to CD103+CD3+CD8+ at both mRNA and protein levels. Notably, ESS mice treated with anti-CD103 showed improvement in salivary function (p<0.05) and reduced lymphocytic infiltrations measured as focus score (FS) (p<0.01) and area-fraction (p<0.01). Consistently, anti-CD103 treatment completely reduced CD103+ cells and IFN-gamma, Granzyme B+ and TNFa+ CD8+ cells. Next we performed phenotypic analysis of CD45+CD103+ immune cells in the SG of pSS patients observing an increase in both with CD8+CD103+CD69+ and CD4+CD103+CD69+ (p<0.05). Finally, IHC showed that the expansion of TRMs in pSS salivary glands was accompanied by a down-regulation of E-cadherin glandular expression and their migration outside the epithelium in the context of inflammatory infiltrates. SG of patients with pSS showed a significant up-regulation of BLIMP1, KLF2, and STIP1+ and down-regulation of ITGB2, CXCL9 and CXCL10, and IL-15 involved in the tissue recruitment and long-term survival of TRMs were significantly modulated in pSS salivary glands.

Conclusion: TRM are expanded and activated in the SG of pSS and ESS, participating in the organization of tissue inflammation. Although the mechanisms behind this expansion are still not fully understood, CD103 could be a valuable novel therapeutic target to prevent lymphocytic infiltrations and glandular destruction in Sjogren syndrome.

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OP0043

INCREASED RISK OF SEVERE INFECTIONS AND MORTALITY IN PATIENTS WITH NEWLY DIAGNOSED SYSTEMIC LUPUS ERYTHEMATOSUS: A POPULATION-BASED STUDY

K. Zhao1,2, H. Xie1,3, L. Li4, L. A. Avila5, J. Esdaile3,5, Simon Fraser University, Health Sciences, Burnaby, Canada; 1Athuris Research Canada, Biostatistics, Richmond, Canada; 2The University of British Columbia, Experimental Medicine, Vancouver, Canada

Background: Systemic lupus erythematosus (SLE) is a chronic disease with a broad spectrum of autoantibodies and clinical manifestations. As much as 45%...