S-MER peptide specifically binds to serum amyloid A (SAA), a stress pro-inflammatory protein, which generates aggregated amyloid deposits in the IBD colon (de Villiers et al. Cytokine 12:1337-1347, 2000). Our studies further provide in vitro evidence, strengthened by in vivo experiments, that SAA is a significant target of this pentamer. To this end, the S-MER peptide (but not the corresponding scrambled peptide) inhibits the release of the pro-inflammatory cytokines IL-6 and IL-1β from SAA-activated fibroblasts. Furthermore, the S-MER peptide was found to retard the early stages of amyloid-type aggregation of SAA in solution (Fig 2). Adopting the β-sheet conformation, MTADV would display opposing hydrophobic and hydrophilic faces that could interact with the β-sheet-forming amyloidogenic sequences in SAA. This suggests that the mechanism of action for the S-MER peptide in vivo may depend on its ability to slow the aggregation of SAA, thus reduce its contribution to chronic inflammation. Finally, using bioinformatics and qRT-PCR, we have found the pentamer up-regulates sets of genes involved in resistance to chronic inflammations. Hence, our study provides both a new potential drug (MTADV) and a new therapeutic target candidate (SAA) for IBD.

ICOS is a costimulatory receptor highly related to CD28, upregulated upon T cell activation and mediating costimulatory signals in post-activation T cells - suggesting ICOS may be more relevant in active disease. In contrast, CD28 predominates in naive T cells and is less critical in activated, effector and/or memory T cells. ALPN-101 is an Fc fusion protein of a human inducible T cell costimulator ligand (ICOSL) variant immunoglobulin domain (vIgD) engineered to inhibit simultaneously the CD28 and ICOS pathways. It has been shown to have potent in vitro immunosuppressive activity and in vivo efficacy in models of disease for which implication of CD28 and ICOS has been reported (e.g. aGVHD, inflammatory arthritides, Sjogren's, lupus, MS). Its safety, tolerability, and dose-dependent pharmacokinetics/dynamics are under study in a Ph1 healthy volunteer study. Here, we evaluate ALPN-101 in vitro using PBMC from Crohn's and ulcerative colitis patients demonstrating superior suppression of T cell activation and cytokine release and show its efficacy to both prevent and treat disease in a mouse T cell transfer model of chronic colitis.

Methods: Primary cell assays were performed with PBMC stimulated with K562 cells (CD80+, CD86+, ICOSL-, anti-CD3 (OKT3)+) to evaluate suppression of cytokine release and compare to single pathway inhibition. ALPN-101 was assessed in the CD4+CD45RBhi T cell-induced colitis model either singly dosed on Day 0 or 14 or repeat dosed 2x/week starting at Day 0 or 14 through Day 41, respectively. Serum cytokine and flow analysis of blood was performed throughout the study. Clinical presence of colitis was assessed using a disease activity index based on weight loss and stool consistency. At end of study, colon were measured and assessed histologically. Results: ALPN-101 suppressed cytokine release (IFNy, IL-2) from healthy or IBD patient PBMCs superior to single pathway inhibitors. In vivo, preventively or therapeutically, a single dose of ALPN-101 was efficacious to significantly improve multiple colitis readouts. Repeat dosing completely prevented onset of colitis. ALPN-101-treated mice gained weight and had colon weight-to-length ratios similar to the no-colitis cohort and demonstrated significant suppression of T cells and pro-inflammatory cytokines (e.g. TNFα, IL-12/23, IL-6).

Conclusion: Dual pathway inhibitor ALPN-101 is superior to single pathway inhibition in human in vitro and mouse in vivo translational studies and may be a novel therapeutic candidate for the treatment of IBD. Clinical trials for ALPN-101 in multiple inflammatory diseases are planned and underway.

AZD4205, A SELECTIVE, GI TRACT-ENRICHED SELECTIVE JAK1 INHIBITOR FOR CROHN’S DISEASE: PRECLINICAL EVIDENCE AND PHASE I DATA

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Background: AZD4205 is an oral, ATP-competitive, JAK1 selective inhibitor. Nonclinical data showed its higher drug concentration within the