Orally-administered EDP1815, a monoclonal strain of *Prevotella histicola*, has potent systemic anti-inflammatory effects without systemic exposure in mice and psoriasis patients

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INTRODUCTION

The small intestine plays a central role in governing the body's immune, metabolic and neurological systems. Evelo Biosciences is developing orally delivered medicines that act on cells in the small intestine to drive therapeutic effects throughout the body. Cells in the small intestine, including epithelial and dendritic cells, continuously sample the contents of the lumen. Depending on what they detect, these cells can change their activation states in the small intestinal mucosa which in turn can modulate inflammation throughout the body by cells trafficking around the body's immune networks. We are investigating whether systemic T-cell mediated inflammatory diseases such as psoriasis may be treated with orally-administered agents which harness this effect, acting luminally in the small intestine without systemic exposure.

EDP1815 is a monoclonal strain of *Prevotella histicola* which was selected for its potent anti-inflammatory pharmacology on human immune cells *in vitro* and mouse models *in vivo*. It is an immunomodulatory strain which does not require colonization, growth or viability for its effects *in vivo*. We report the in vivo efficacy of EDP1815 in TH1- and TH17-driven models of inflammation, including keyhole limpet haemocyanin (KLH) delayed-type hypersensitivity (DTH), imiquimod-induced skin inflammation (IMQ), and experimental autoimmune encephalomyelitis in PLP-immunized SJL mice (EAE).

RESULTS

EDP1815 enhances IL-10 and IL-27 cytokine production by human inflammatory M1-type APCs

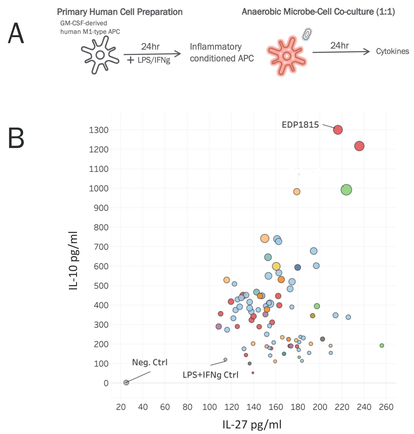

Figure 1. **(A)** Primary human cell assay. Human, CD14+ PBMCs are grown in GM-CSF to induce an M1-type pro-inflammatory phenotype. Cells are then activated for 24 hrs with LPS + IFNg. Cells are incubated with individual strains of microbes for 24 hrs, after which cytokines in the supernatant are measured by Luminex.
(B) Eighty-eight obligate anaerobes were tested in the primary human cell assay. Each point represents the average value from 3 individual healthy donors. Each color represents an individual family of microbes. The size of the circle represents the IL-10/TNFa ratio. EDP1815 induced high amounts of anti-inflammatory cytokine IL-10 and IL-27 from M1-type skewed macrophages. These data also demonstrate that each strain has a unique cytokine profile and that taxonomy is not a guide to function.

EDP1815 is efficacious in a model of peripheral T cell-mediated inflammation (KLH DTH)

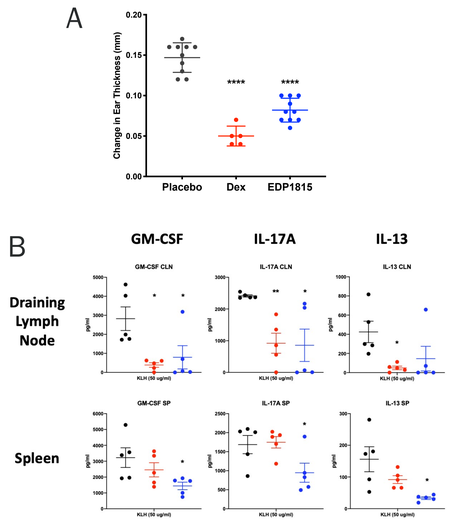

Figure 2. Delayed-type hypersensitivity (DTH) response to Keyhole Limpet Hemocyanin (KLH). C57Bl/6 mice were immunized with KLH and CFA and challenged intradermally in the ear 9 days later with KLH. Mice were treated from the day after immunization through ear challenge with placebo, dexamethasone (1 mg/kg IP QD), or EDP1815 (1.8 mg PO QD). **(A)** Ear inflammation was measured on day 9. **(B)** Ex vivo stimulation of draining lymph node or spleen cells with KLH. At the end of the DTH study, mice were sacrificed and total cells from ear draining lymph nodes and spleens were incubated with KLH for 2 days. Cytokines from supernatants were measured by MSD.

Oral treatment of EDP1815 is efficacious in a Type 17-driven model of skin inflammation (Imiquimod)

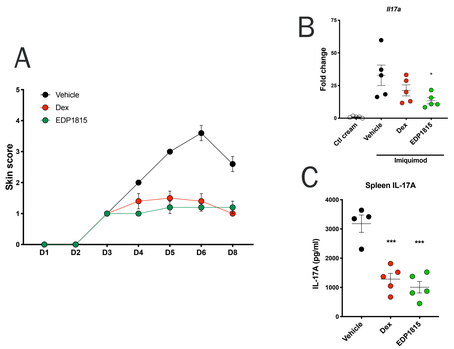

Figure 3. Imiquimod driven psoriasis mouse model. BALB/c mice were topically treated with 5% imiquimod, a TLR7 and TLR8 agonist for 7 days on the back skin and ear. Mice were treated daily from day 1 through 7 with placebo, dexamethasone (1mg/kg IP) or EDP1815 (10mg PO). **(A)** Back scores were recorded daily to measure erythema and scaling associated with psoriasis. **(B)** *Il17a* mRNA transcripts from the psoriatic skin of the mice were measured by RT-qPCR **(C)** Ex vivo stimulation of splenocytes. At termination of the study, mice were sacrificed and splenocytes were stimulated with PMA/Ionomycin for 48hrs. IL-17A was measured from supernatants by MSD.

Oral treatment of EDP1815 inhibits central nervous system inflammation in the EAE model

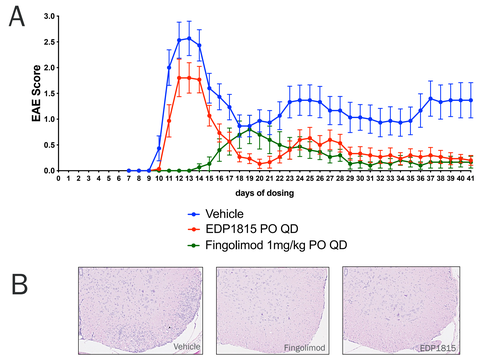

Figure 4. PLP/SJL model of relapsing-remitting experimental autoimmune encephalomyelitis (EAE). SJL mice were immunized with PLP peptide and CFA on Day 0. Mice were dosed daily from day of immunization. **(A)** Clinical score was read daily from day 7 -41, on a scale from 0 to 4, with 0 being no obvious changes in motor function, and 4 being limp tail, complete hind leg and partial front leg paralysis. **(B)** Histopathology of spinal cord taken on day 41.

EDP1815 reduces Lesion Severity Score in psoriasis patients

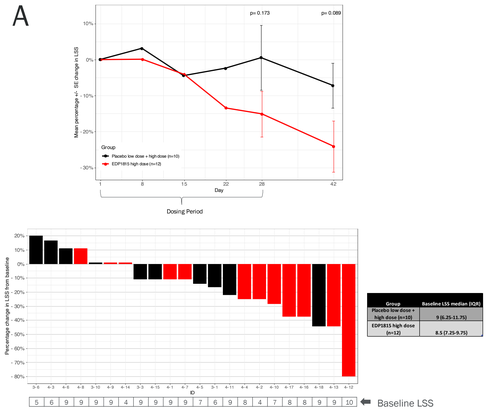

Figure 5. Twenty-two individuals with mild to moderate psoriasis were randomized to receive a daily oral administration of 2.76g of EDP1815 (n=12) or placebo (n=10) for 28 days. Safety and tolerability and Lesion Severity Score (LSS) were measured at day 42, 2 weeks after completion of dosing. **(A)** Two weeks following the completion of the 28-day dosing period, at day 42, the EDP1815-treated cohort showed continued reductions from baseline in mean LSS.
(B) Individual patient scores percentage change in LSS from baseline at day 42.

CONCLUSIONS

- EDP1815 is a proprietary strain of Prevotella histicola, that induces high levels of IL-10 and IL-27 from human primary cells, including PMBCs, dendritic cells, and macrophages.
- Oral delivery of EDP1815 is effective in multiple models of inflammation.
- EDP1815 acts through the small intestine, without colonization or systemic exposure.
- Treatment of patients with mild to moderate psoriasis results in reduction in Lesion Severity Score and improvement of biomarkers of skin inflammation, even 2 weeks following the completion of dosing, which may be indicative of a sustained clinical effect and dose response.
- Results from first clinical study in psoriasis patients warrants further investigation in a Phase 2 study.

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