Mechanism and Proof of Concept for a Novel, Orally Delivered, Gut-Restricted Drug Candidate for the Treatment of Psoriasis and Other Inflammatory Diseases

Douglas Maslin, Kritika Ramani, Adam N. R. Cartwright, Nancy Carpenter, Leslie Wardwell-Scott, Andrea Itano, Duncan McHale

Evelo Biosciences, Cambridge MA (Disclosure: all listed authors are employees of Evelo Biosciences)

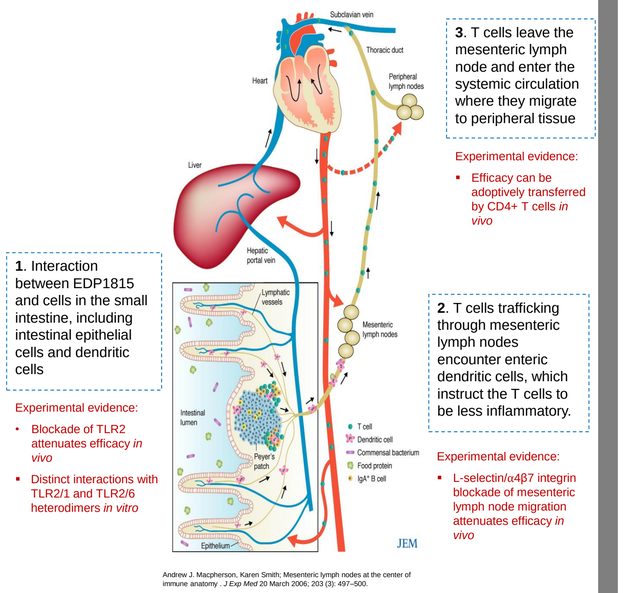
Introduction

Evelo Biosciences is developing a new class of oral medicines which engage the immune system in the small intestine with anti-inflammatory effects throughout the body.

The small intestinal axis (SINTAX™) is a network of anatomic and functional connections with the rest of the body. It acts as a sensory system, integrating mucosal immunology with systemic immunological processes. SINTAX is a control mechanism for systemic inflammation that is centered in the small intestine. Targeting SINTAX is of considerable interest for the development of a new modality of oral immunomodulatory therapies.

EDP1815 is a pharmaceutical preparation of a single strain of *Prevotella histicola*. EDP1815 potently attenuates murine models of TH1, TH2, and TH17- inflammation. Orally delivered EDP1815 exerts its effects through direct action on host cells in the gut without exposure beyond the gut. It is non-replicating and does not colonize the gut, nor alter the microbiome.

Mechanism of Action of EDP1815



1. Interaction between EDP1815 and cells in the small intestine, including intestinal epithelial cells and dendritic cells

Experimental evidence:

- Blockade of TLR2 attenuates efficacy *in vivo*
- Distinct interactions with TLR2/1 and TLR2/6 heterodimers *in vitro*

3. T cells leave the mesenteric lymph node and enter the systemic circulation where they migrate to peripheral tissue

Experimental evidence:

- Efficacy can be adoptively transferred by CD4+ T cells *in vivo*

2. T cells trafficking through mesenteric lymph nodes encounter enteric dendritic cells, which instruct the T cells to be less inflammatory.

Experimental evidence:

- L-selectin/α4β7 integrin blockade of mesenteric lymph node migration attenuates efficacy *in vivo*

Andrew J. Macpherson, Karen Smith; Mesenteric lymph nodes at the center of immune anatomy . *J Exp Med* 20 March 2006; 203 (3): 497–500.

MoA Step 1: EDP1815 engages TLR2

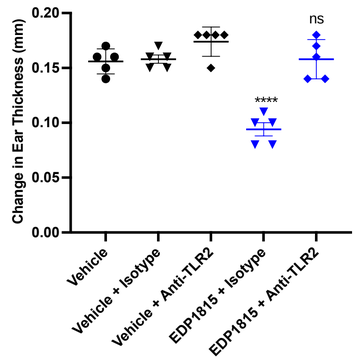


Fig 1. EDP1815 requires TLR2 for reduction of ear inflammation in a model of delayed-type hypersensitivity (DTH).
Mice were immunized with an antigen, keyhole limpet hemocyanin (KLH) emulsified in Complete Freund's Adjuvant (CFA) and challenged intradermally in the ear 8 days later with KLH. TLR2 blocking antibody or isotype control (200 ug/dose IP) were dosed every 3 days from the day of immunization through ear challenge. EDP1815 (10 mg PO) and vehicle control (sucrose) were dosed daily from day 5 through the day of the ear challenge (day 8). Ear inflammation was measured on day 9. ****p < 0.001 by 1-way ANOVA followed by Dunnett's test for multiple comparisons.

MoA Step 2: Efficacy requires migration of lymphocytes to mesenteric lymph nodes

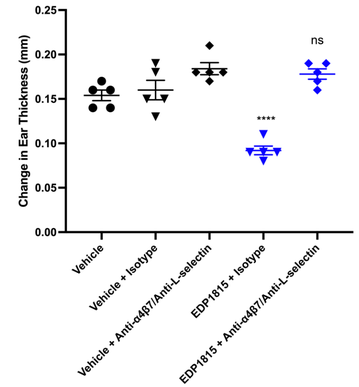


Fig 2. EDP1815 requires α4β7 and L-selectin signaling to mediate migration of lymphocytes into mesenteric lymph nodes for efficacy.
Mice immunized with KLH + CFA were challenged intradermally in the ear 14 days later with KLH. Anti-α4β7 and anti-L-selectin blocking antibodies (250 ug/dose each IP) or isotype control (500 ug/dose IP) were dosed every 2 days from the day of immunization through day 6. EDP1815 (10 mg PO) and vehicle control (sucrose) were dosed daily from day 5 to day 8. Mice were rested from day 9 through day 14 and challenged on day 14. Ear inflammation was measured on day 15. ****p < 0.001 by one-way ANOVA followed by Dunnett's test for multiple comparisons.

MoA Step 3: Efficacy can be adoptively transferred by CD4+ T cells

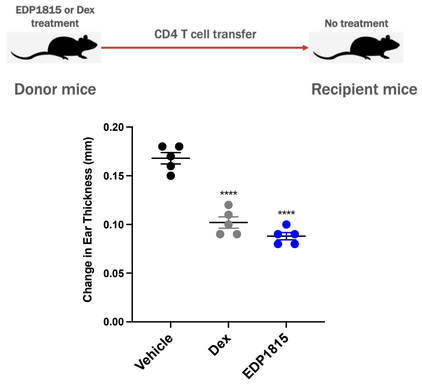


Fig 3. Adoptive transfer study – CD4+ T cells transferred from EDP1815-dosed to untreated mice mediated efficacy in a DTH model of inflammation.
Mice were immunized with KLH + CFA and dosed with vehicle, dexamethasone (1 mg/kg IP), or EDP1815 (10 mg PO) from day 5 through day 9. On day 9, CD4+ T cells isolated from donor animals treated with vehicle, dexamethasone, or EDP1815 were adoptively transferred in recipient animals which were immunized but did not receive any treatment as described in figure 4. Three days later mice were challenged intradermally in the ear with KLH. Ear thickness was measured 24h later. **p < 0.01, *p<0.05 by one-way ANOVA followed by Dunnett's test for multiple comparisons.

Oral treatment with EDP1815 is efficacious in a Th17-drive model of skin inflammation

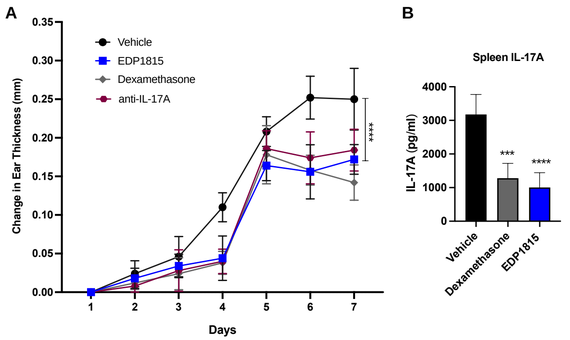


Fig 4. EDP1815 leads to reduction in ear thickness in Imiquimod-driven psoriasis mouse model
BALB/c mice were topically treated with 5% imiquimod, a TLR7 and TLR8 agonist for 7 days on the ear. Mice were treated daily from day 1 through 7 with vehicle, dexamethasone (1mg/kg IP) or EDP1815 (10mg PO). Anti-IL-17 was dosed at 200ug/dose on days 2, 4 and 6. (A) Ear scores were recorded daily to measure inflammation associated with psoriasis. (B) 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.

EDP1815 Treatment Led to Clinical Improvements in Psoriasis Patients

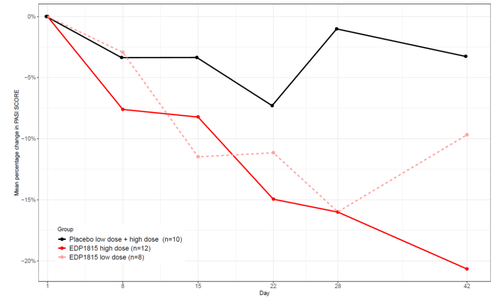


Fig 5. EDP1815 led to reductions in PASI in two cohorts of patients with psoriasis.
EDP1815 was evaluated in a phase 1b randomized double-blind clinical study, which included 2 dose cohorts of 12 and 18 patients with mild to moderate psoriasis randomized 2:1 active:placebo. Doses were $1.6x10^{11}$ bacterial cells or $8.0x10^{11}$ cells of freeze-dried powder in enteric capsules dosed once daily for 28 days, with follow-up off drug through 42 days. The percentage change in the Lesional Severity Score (LSS) and the PASI score were measured at baseline, Day 28, and Day 42. Placebo subjects were pooled across both cohorts.
EDP1815 was well tolerated at both doses, with a safety and tolerability profile comparable to placebo. At day 28, the percentage reduction in PASI for EDP1815 cohorts was 16%, compared to 1% for placebo. At day 42, the percentage improvement from baseline increased to 21% in the high dose cohort. The percentage reduction in LSS scores at 28 days were 15% and 23%, compared to a 1% increase from baseline in the placebo group.

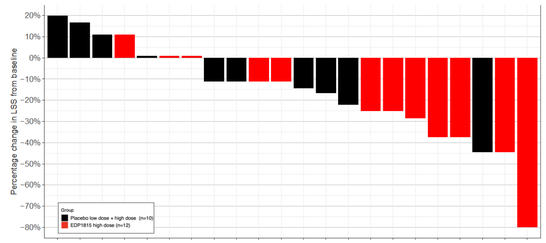


Fig 6. EDP1815 led to reductions in PASI in two cohorts of patients with psoriasis.

Conclusions

1) EDP1815 modulates systemic inflammation through its interaction with innate immune receptors including TLR2.
2) SINTAX therapeutics alter circulating immune-cell phenotypes, without systemic exposure.
3) Preclinical effects in Th17 models translate into early signs of clinical benefit in psoriasis.
4) No safety or tolerability signals have been observed either preclinically or clinically.

These data support further clinical development of EDP1815 and SINTAX therapeutics, and a phase 2 study in psoriasis is underway (NCT04603027).