Orally Delivered Microbial Extracellular Vesicles Modulate Systemic Inflammation Through the Small Intestinal Axis (SINTAX™)

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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.

EDP2939 is an orally-delivered and gut-restricted bacterial EV which potently attenuates inflammation in murine models of Th1 and Th17 inflammation. 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 environmental signals that link gut mucosal immunity with immunological processes throughout the body.

This suggests that SINTAX is a control mechanism for systemic immunity centred in the small intestine. This mechanism has novel features of considerable interest for the development of immunomodulatory therapies. It may be harnessed for orally delivered medicines that are systematically effective without systemic distribution.

We have previously shown clinical proof of the SINTAX mechanism with EDP1815, an orally delivered single strain of commensal bacteria. It has considerable interest for the development of immunomodulatory therapies. Some bacteria produce extracellular vesicles (EVs) that share molecular content with the parent bacterium in a particle that is roughly 1/1000th the volume in a non-replicating form.

EDP2939 is an orally effective anti-inflammatory drug requiring multiple pathways for efficacy

Conclusions

- Orally-delivered microbial extracellular vesicles enact broad-based resolution of inflammation establishing homeostatic inflammatory status
- Efficacy of EDP2939 requires the stimulation of both the TLR2 receptor and the IL-10 receptor in addition to lymphocyte homing to the intestinal lymphoid tissue
- EDP2939 induces TLR2-dependent release of IL-10
- EVs are orally-dosed, gut-restricted therapeutic with no apparent safety or tolerability issues in animal models, making for a desirable therapeutic profile

EDP2939 induces the release of IL-10 through TLR2 stimulation

EDP2939 induces anti-inflammatory cytokine secretion from human PBMCs

EDP2939 stimulates anti-inflammatory cytokine secretion from human PBMCs