Oral delivery of a microbial extracellular vesicle induces potent anti-tumor immunity in mice

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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 distal effects throughout the body. The microbial content of the gut interacts with host cells in the intestine to control systemic immune responses and inflammation. Our approach bypasses the need to modify the microbiota by selecting orally delivered agents which interact directly with host immune cells in the small intestine.

The small intestinal axis (SINTAX™) is a network of anatomic and functional connections with the rest of the body. It acts as an immunosurveillance system, integrating signals from the environment that affect physiological processes throughout the body. It can be harnessed for pharmacological effects of orally delivered agents that are systemically effective without systemic distribution. This is a newly appreciated and potent control system for immunity and inflammation.

This suggests a control mechanism for systemic immunity centered in the small intestine. This mechanism has novel features which are of considerable interest for the development of a new class of immunomodulatory therapies.

The impact of events in the gut on the control of tumor immunity is beginning to be appreciated. We have previously shown that an orally delivered single strain of commensal bacteria induces antitumor immunity predilectively via pattern recognition receptor-mediated activation of innate and adaptive immunity. The magnitude of these effects in preclinical models appears to match the reported activity of injected bacterial extracellular vesicles which does not itself distribute to the tumor is evidence for the level of control that can be exerted via the small intestinal axis, acting locally on host cells in the gut to activate distal immune responses within the tumor microenvironment. EDP1908 is in preclinical development for the treatment of solid tumors in a variety of tumor-bearing hosts.

Some bacteria produce extracellular vesicles (EVs) that share molecular content with the parent bacterium in a particle that is roughly 1/1000 the volume in a non-replicating form.

We report here an orally-delivered and gut-restricted bacterial EV which potently attenuates tumor growth to a greater extent than whole bacteria or checkpoint inhibition. This is the first report of striking anti-tumor effects of an orally delivered microbial extracellular vesicle. The magnitude of these effects in preclinical models appears to match the reported activity of injected intra-tumoral immunostimulators. The observation that this efficacy can be achieved with an oral agent which does not itself distribute to the tumor is evidence for the level of control that can be exerted via the small intestinal axis, with no apparent safety or tolerability issues in the animal models. These data point to oral EVs as a new class of immunotherapeutic drugs. They are particularly effective at engaging the small intestinal axis, acting locally on host cells in the gut to activate distal immune responses within the tumor microenvironment, EDP1908 is in preclinical development for the treatment of cancer.

EDP1908 is an extracellular vesicle derived from a strain of Oscillospiraceae

Fig. 1. EDP1908 is an extracellular vesicle (EV) produced by a single bacterial species.

(A) Phase contrast image of Oscillospiraceae species from which EDP1908 is derived.
(B) TEM image of EDP1908 isolated from the supernatant of a liquid culture of the parent microbe.
(C) EDP1908 consists of a population of EVs with an average diameter of 68nm determined by nanoparticle tracking analysis.

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Fig. 2. Therapeutic treatment of CT26 tumor-bearing mice with either oral EDP1908 EVs, anti-PD-1 i.p., or whole microbe.

(A) EDP1908 was administered orally at 2e11 particles beginning at day 10 for 12 days vs anti-PD-1 i.p. on day 0, 6, 10, and 14.
(B) Dose-dependent control of tumor growth by EDP1908 doses from 2e6 to 2e11 particles shown at day 21. Data are median and range.
(C) The parental Oscillospiraceae strain of EDP1908 was administered at the highest tolerated concentration of 2e9 cells. The 2e7 and 2e8 doses of EVs are shown for reference. Data are median and range.

Orally administered EDP1908 has superior anti-tumor efficacy to anti-PD-1 or its parent microbe

Fig. 3. EDP1908 activates and sustains Th1-type cytokine and helper lymphocyte, DCs and IP-10 in the TME.

(A) Oral delivery of EDP1908 to tumor-bearing mice results in Th1 cytokine production.
(B) Infiltrating DC subsets.
(C) IFNγ and IL-12 production from CD8, NK, NKT g+ cytolytic and helper lymphocyte populations in the TME.

EDP1908 is not detected outside the GI tract by fluorescent biodistribution

Fig. 4. EDP1908 is retained in the gastrointestinal tract and not detected in systemic organs.

Shades of green represent fluorescence from EDP1908 EVs in the gut as measured using a small animal imaging system (Licox Pearl®).

CONCLUSIONS

EDP1908 is an extracellular vesicle derived from a strain of Oscillospiraceae. This suggests a control mechanism for systemic immunity centered in the small intestine. This mechanism has novel features which are of considerable interest for the development of a new class of immunomodulatory therapies. The impact of events in the gut on the control of tumor immunity is beginning to be appreciated. We have previously shown that an orally delivered single strain of commensal bacteria induces antitumor immunity predilectively via pattern recognition receptor-mediated activation of innate and adaptive immunity. The magnitude of these effects in preclinical models appears to match the reported activity of injected bacterial extracellular vesicles which does not itself distribute to the tumor is evidence for the level of control that can be exerted via the small intestinal axis, acting locally on host cells in the gut to activate distal immune responses within the tumor microenvironment. EDP1908 is in preclinical development for the treatment of cancer.

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