EVELO

Harnessing the Small Intestinal Axis (SINTAX) to resolve systemic inflammation

November 2022

Legal Disclaimer

This presentation contains forward-looking statements, including within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements concerning the development of EDP1815 and EDP2939, the promise and potential impact of our product candidates, the timing of and plans for clinical studies, and the timing and results of clinical trial readouts.

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Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and we make no representation as to the adequacy, fairness, accuracy or completeness of any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

SINTAX medicines allow for the potential treatment of all stages of inflammatory disease

EVELO

Harnessing the small intestinal axis to resolve systemic inflammation.

Bodmer M, Itano A and McInnes I (2022)
Front. Immunol. 13:1060607
doi: 10.3389/fimmu.2022.1060607

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Introduction to SINTAX medicines	Mark Bodmer
Mechanism of Action of EDP1815	Andrea Itano
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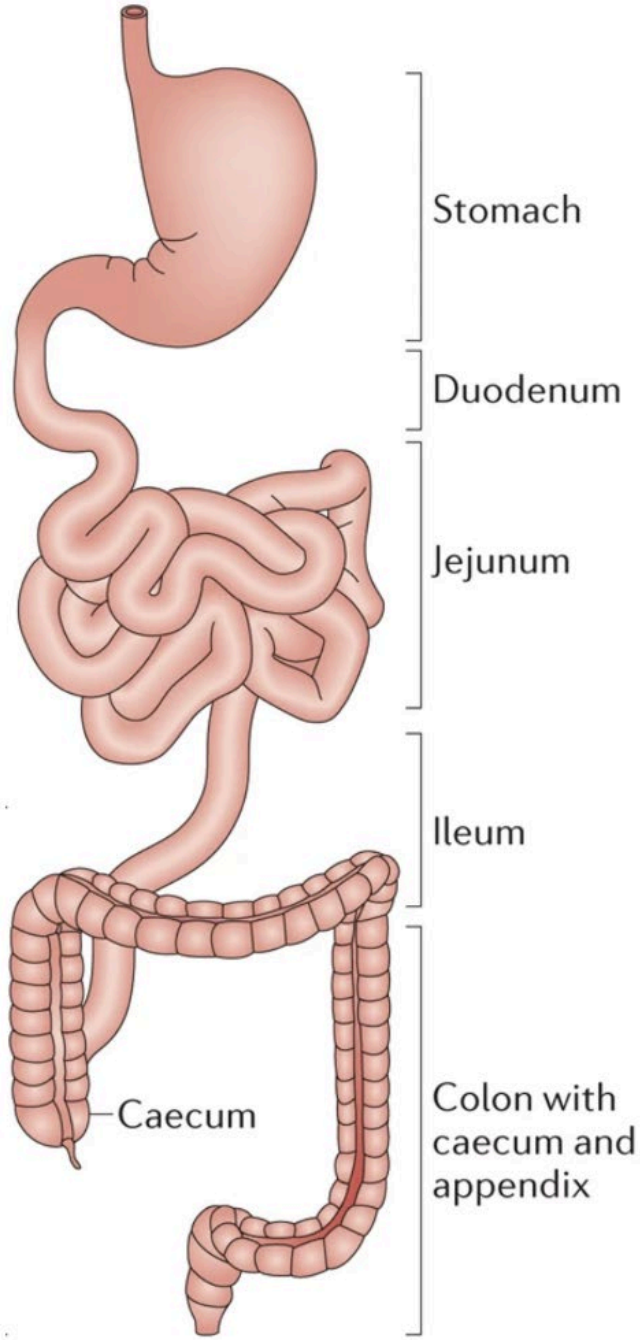
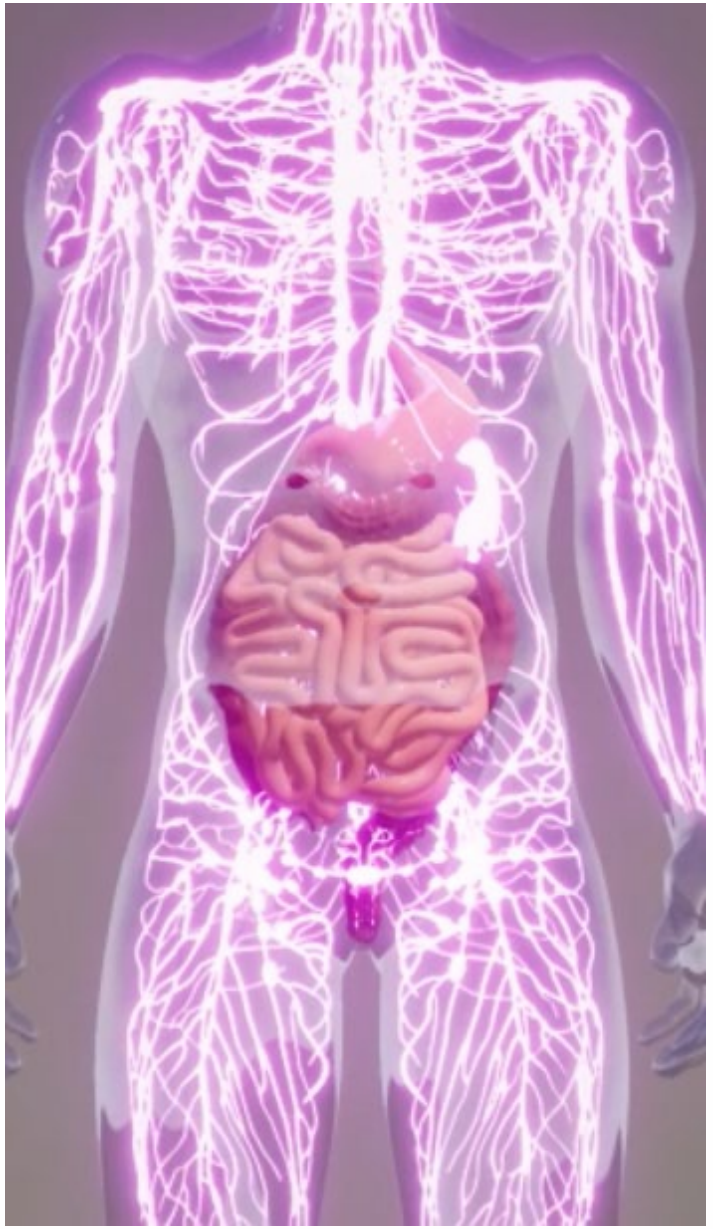
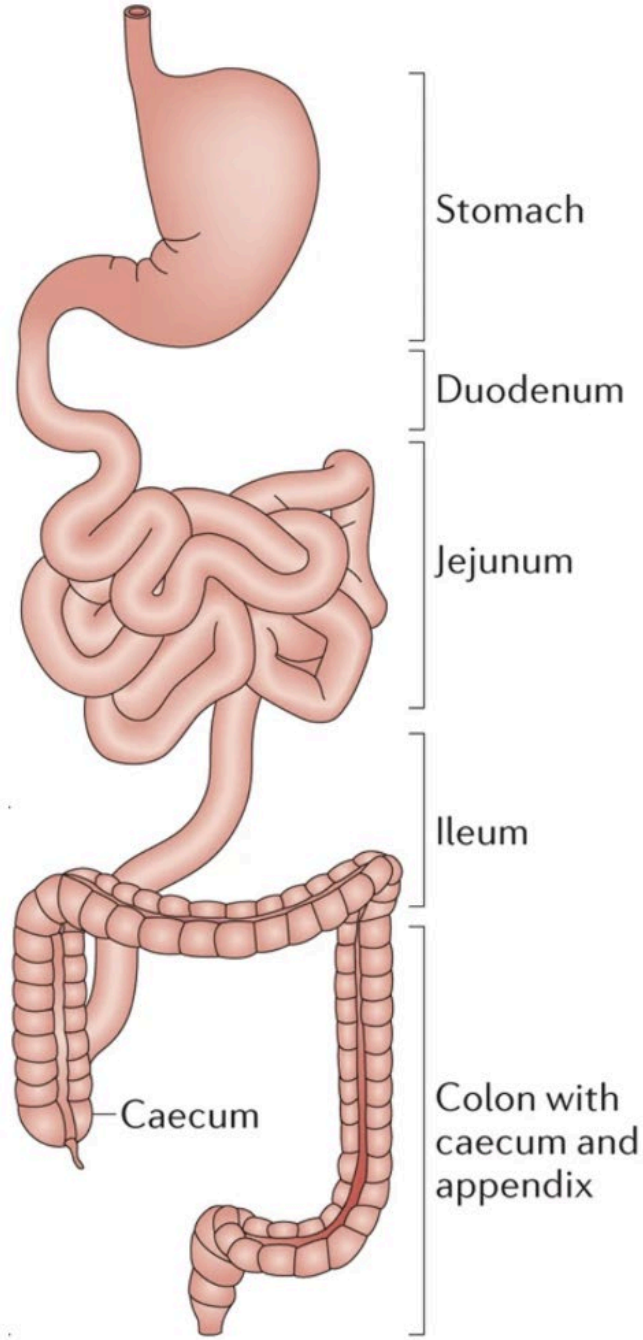
The small intestinal mucosal immune system governs inflammation throughout the body.





SINTAX
The Small Intestinal Axis

A primary role of the small intestine is to prevent *systemic* inflammatory reactions to food and to bacteria.

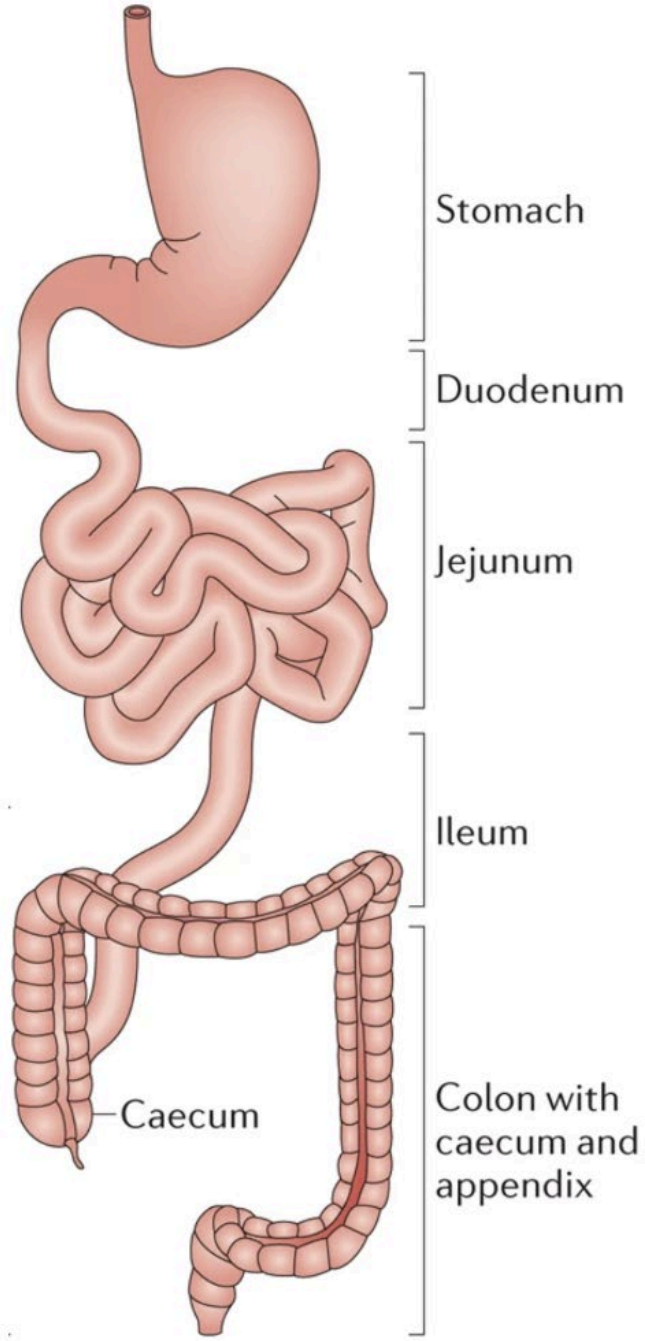


Gut mucosal and peripheral immune functions are different.

Tolerance induced in the small intestine can override peripheral inflammation.

This prevents inflammation to food and harmless microbes.

The small intestine is both the source and the target of oral medicines that resolve systemic inflammation.



Oral delivery of

Cells and extracellular vesicles (EVs)

manufactured from

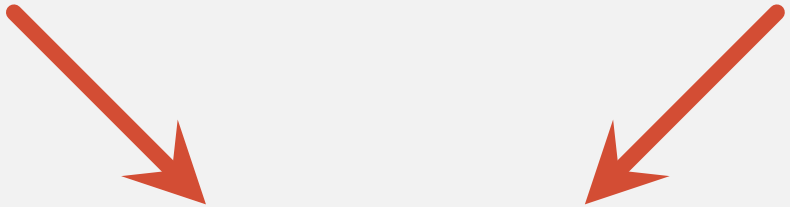
single strains of bacteria

isolated from human gut mucosa

Untapped small intestinal biology is harnessed by a novel drug modality

Oral tolerance mechanisms in the small intestine

EDP1815 and EDP2939 isolated from the small intestinal mucosa



Resolution of systemic inflammation

EDP1815 is a new modality of medicine

Origins and Biology

Non-live preparation of a strain of *Prevotella histicola* from a human duodenal biopsy

A mixture of bacterial cells and EVs

Systemic effects without systemic exposure after oral administration

No gut colonization or microbiome modification

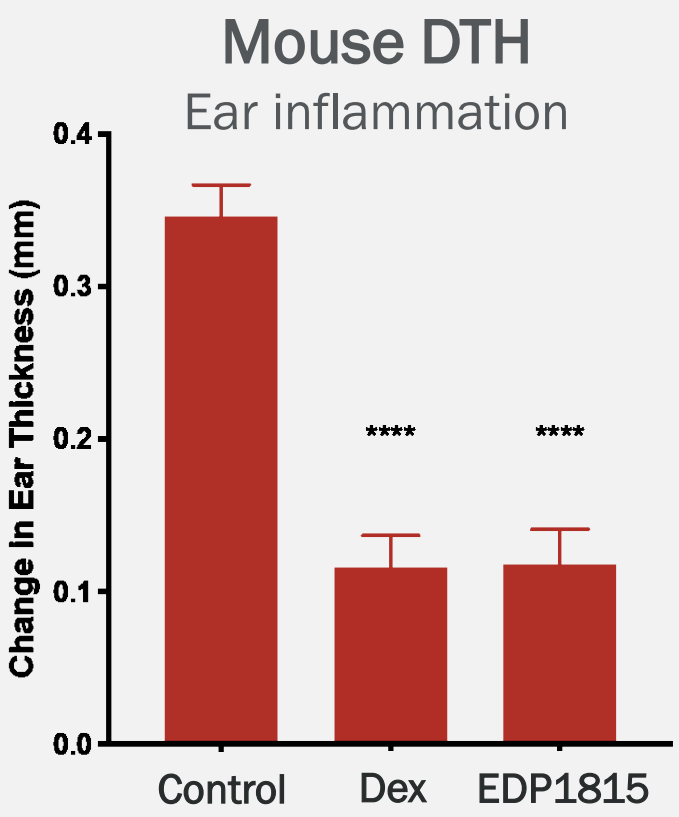
Manufacturing and Pharmaceutics

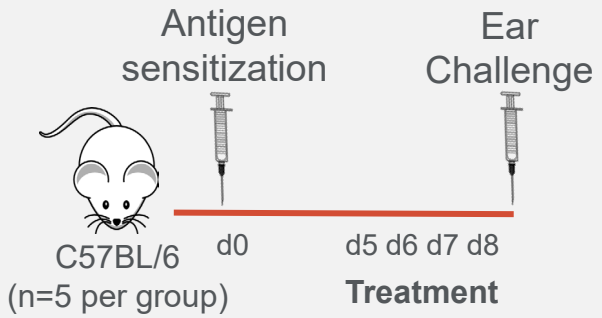
Manufacture at scale by anaerobic fermentation and lyophilization

Dry powder-in-capsule formulation

Capsule coating modulates site of delivery

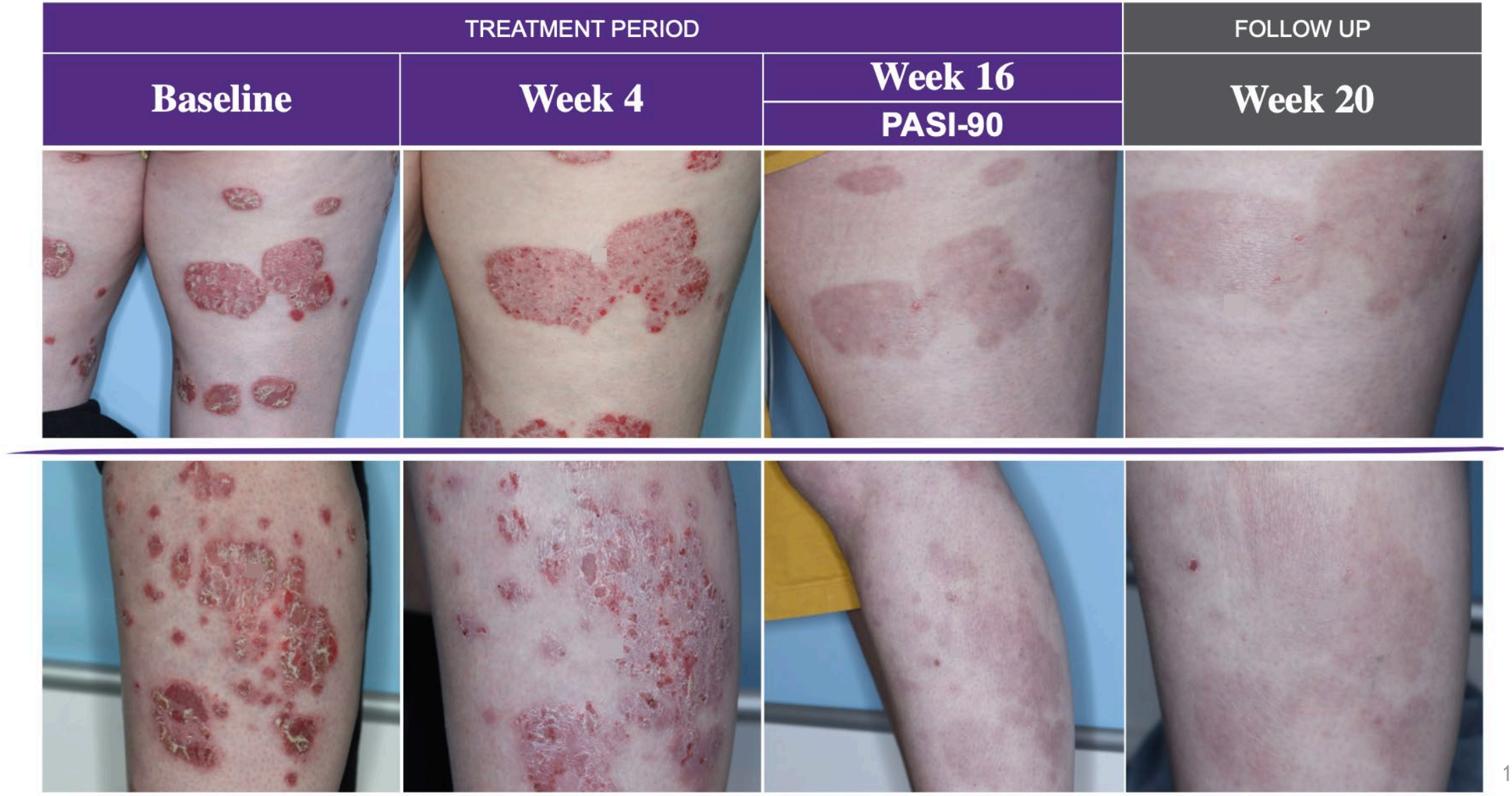
Targeting SINTAX potently resolves peripheral inflammation





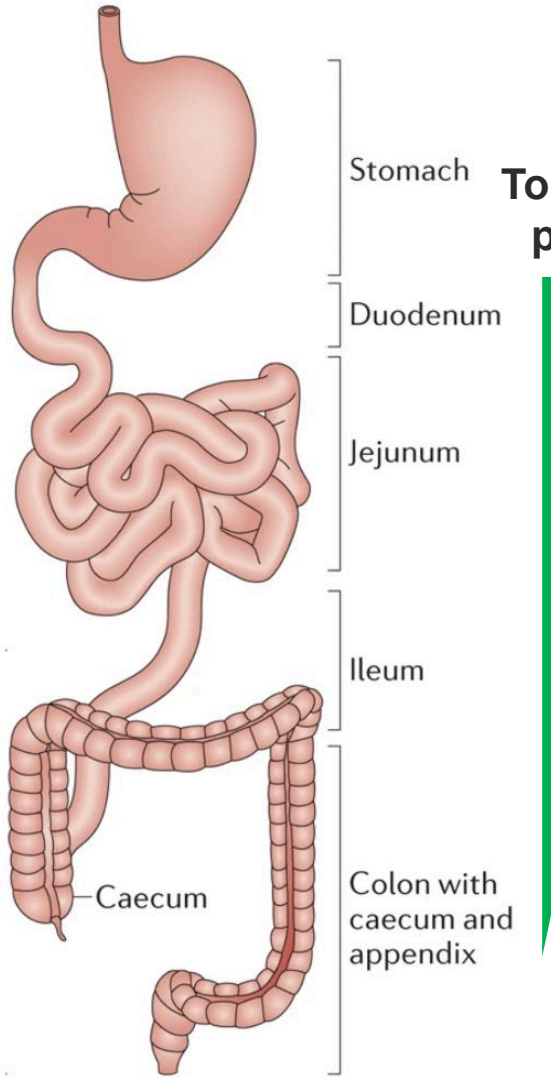
- Systemic effect without systemic exposure
- New MoA and modality for potential best-in-class efficacy in inflammatory diseases

Translation to humans - an example patient from EDP1815-201 phase 2 trial



The proximal small intestine is the target

EDP1815 efficacy in mouse ear DTH correlates with exposure in the proximal rather than distal small intestine

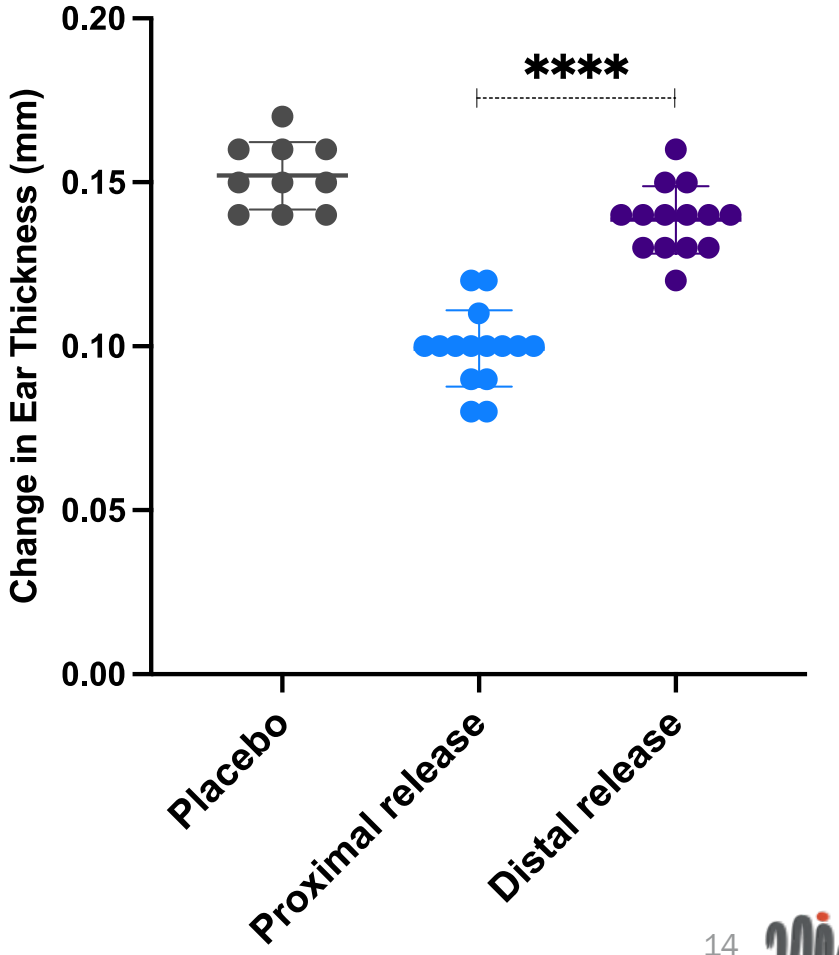


Tolerogenic potential

Mini-tablets; sub-maximal dose

- Proximal SI release
- Distal SI release

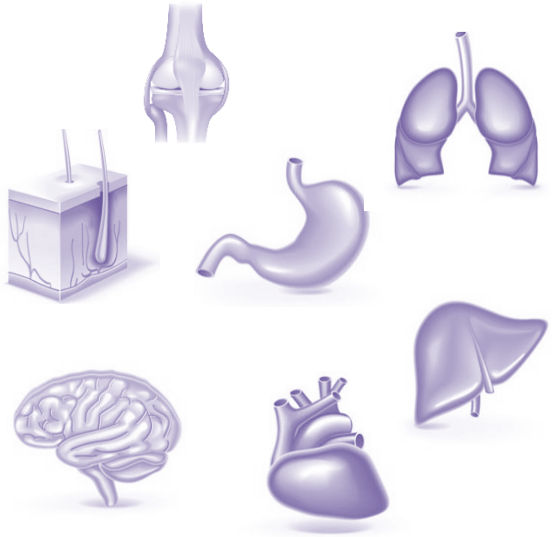
Proximal release was significantly more efficacious than distal



Broad Applicability of EDP1815: Potential Across Range of Diseases

Inflammatory Pathway	Potential blockbuster drug in dermatology	Rapid expansion to other inflammatory disease areas
Th17	PSORIASIS	• Psoriatic arthritis • Axial spondylarthritis* • Rheumatoid arthritis* • Ulcerative colitis* • Crohn's disease*
Th2	ATOPIC DERMATITIS	• Asthma* • Allergy*
Th1	HUMAN KLH	• Axial spondylarthritis • Rheumatoid arthritis • Psoriasis* • Psoriatic arthritis*

Dozens of additional diseases impacting tissues and organs throughout the body



**Simplified and non-exhaustive view of inflammation. Many inflammatory diseases are complex and involve multiple pathways of the immune system.*

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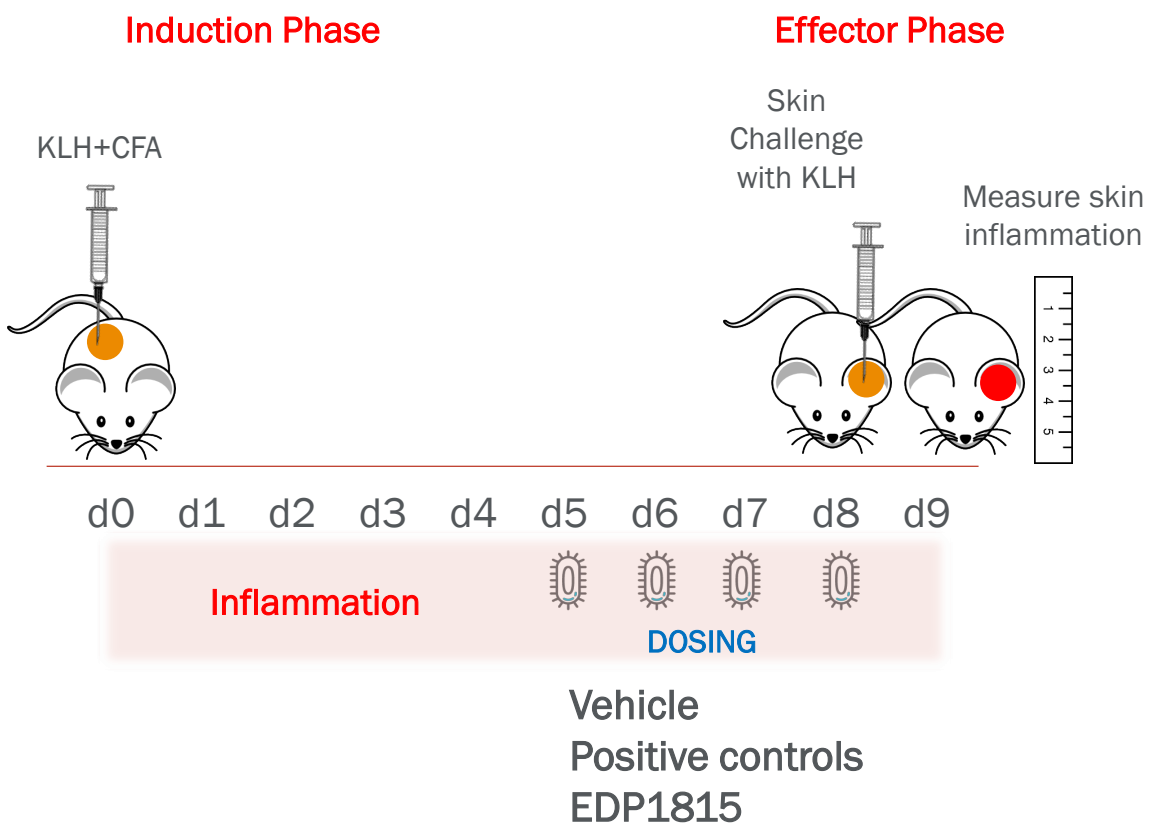
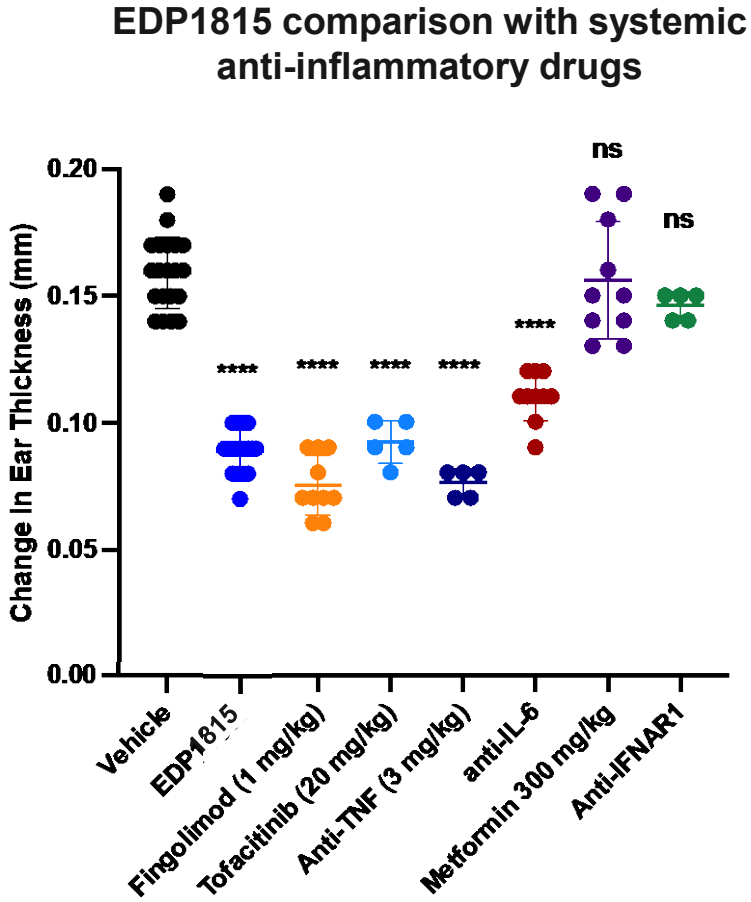
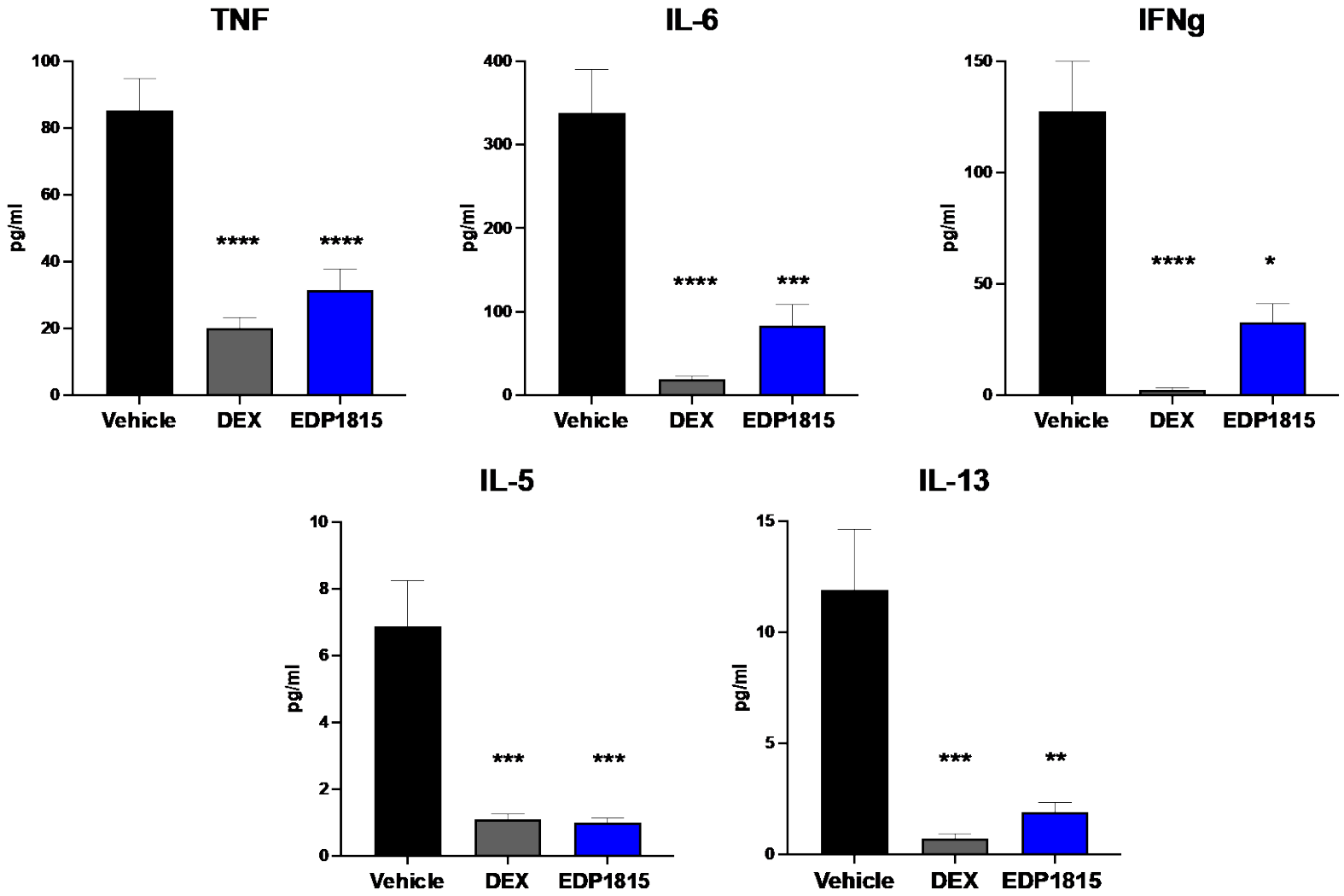
EDP1815 matches gold standard comparators preclinically

These comparators have limitations of either toxicity, cost, or route of administration





EDP1815 reduces multiple clinically validated inflammatory cytokines in the inflamed skin-draining lymph nodes of mice



Skin-draining lymph nodes were removed after skin challenge and cultured for 72 hours in vitro.

Cytokines secreted into the supernatant were measured.

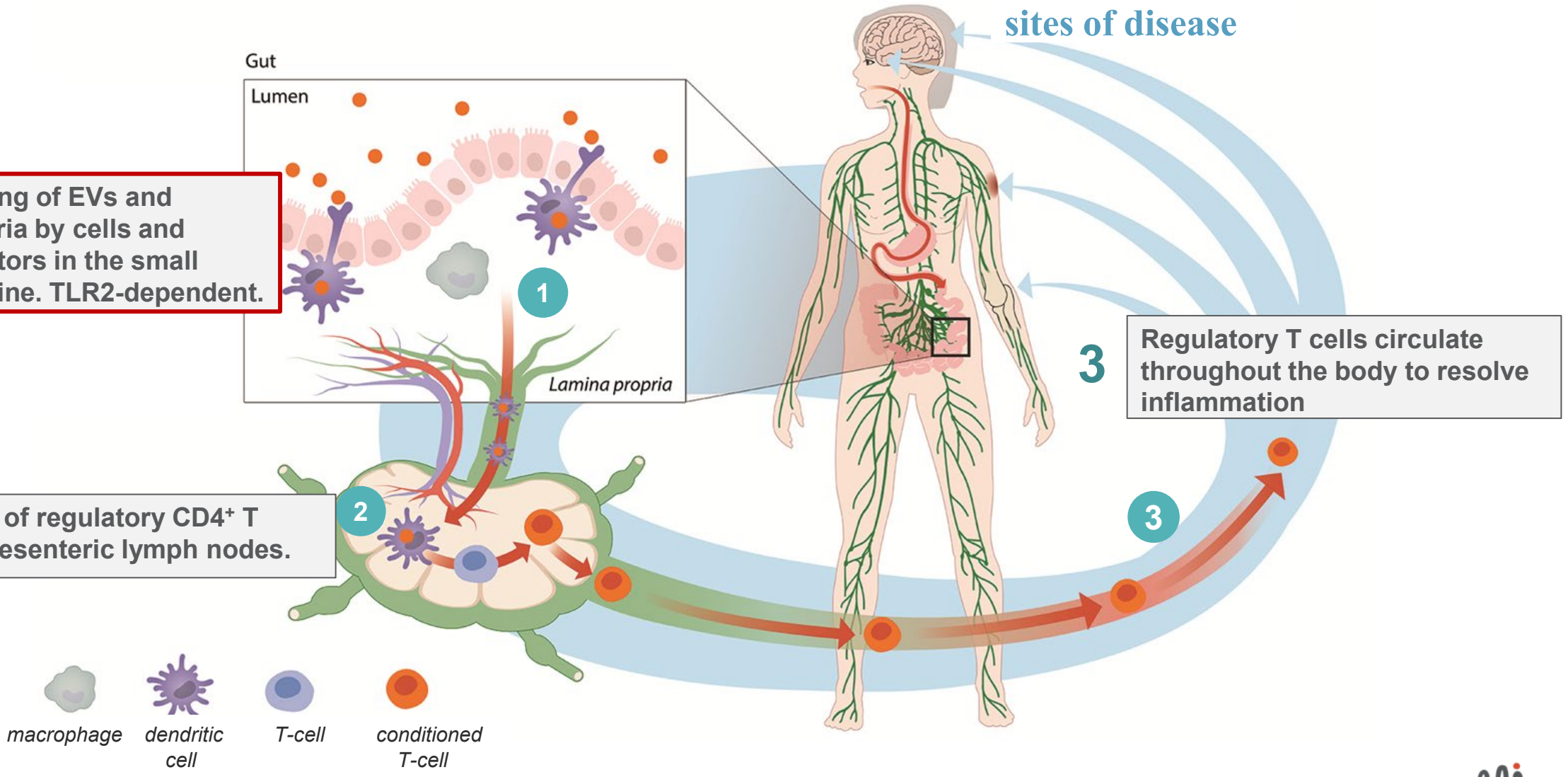
Treatment with EDP1815 reduced inflammatory cytokine production by immune cells in the lymph nodes

Three step model of inflammation resolution in the small intestinal axis

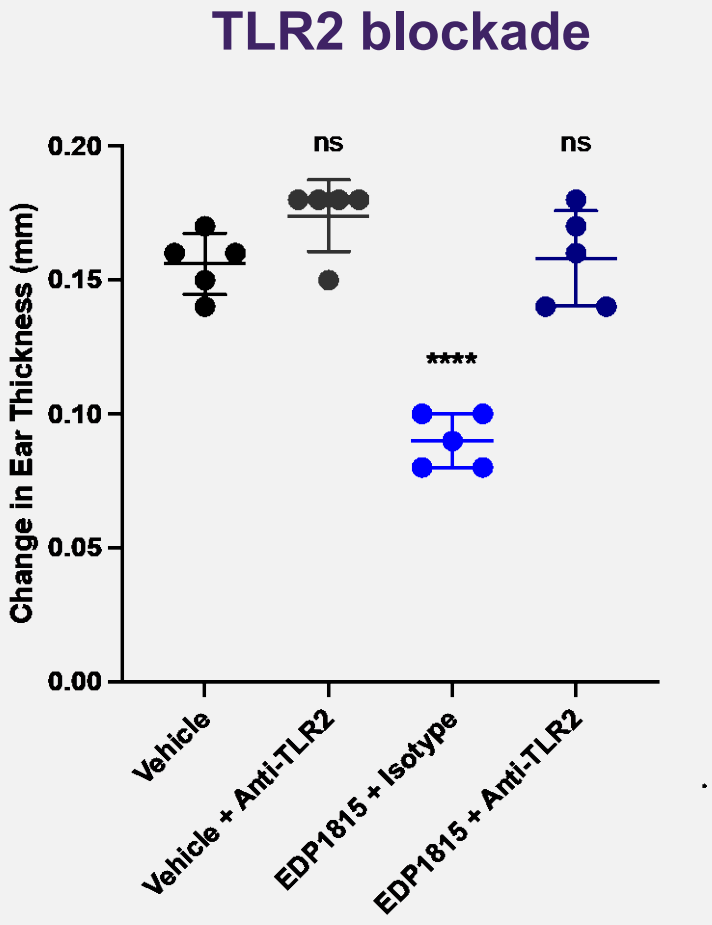
1 Sensing of EVs and bacteria by cells and receptors in the small intestine. TLR2-dependent.

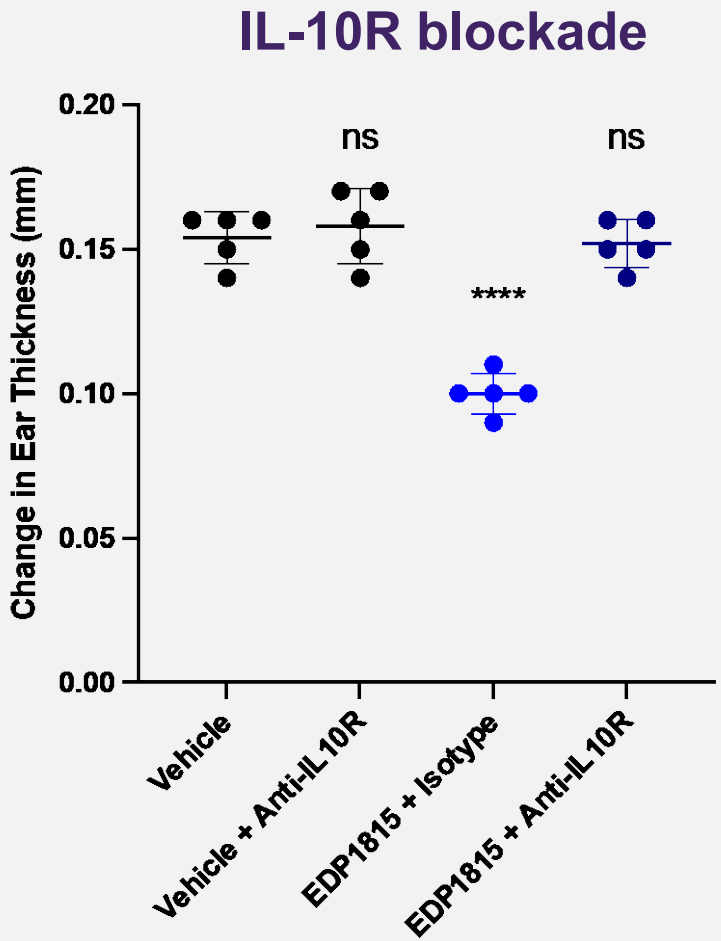
2 Induction of regulatory CD4⁺ T cells in mesenteric lymph nodes.

3 Regulatory T cells circulate throughout the body to resolve inflammation

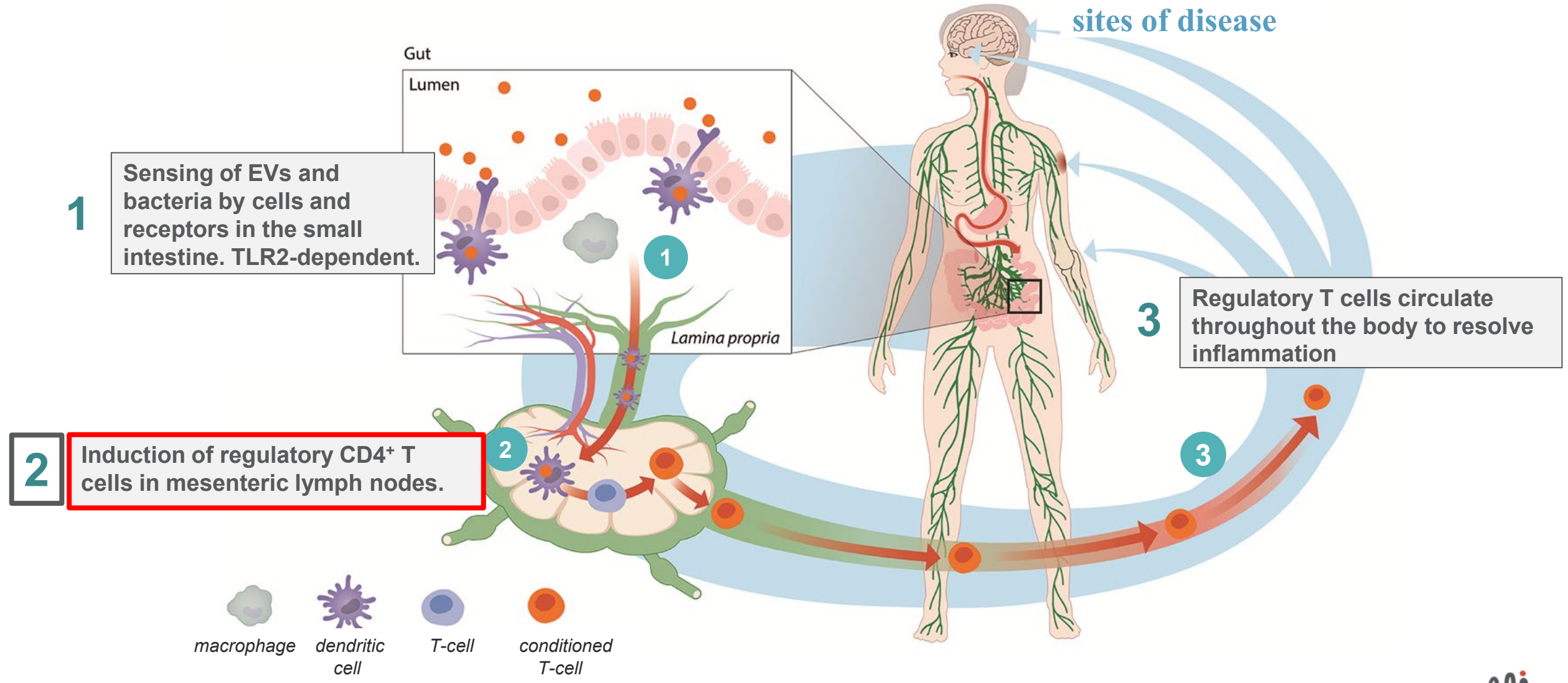


TLR2 and IL-10R are required for efficacy of EDP1815 in mouse DTH





Three step model of inflammation resolution in the small intestinal axis



1 Sensing of EVs and bacteria by cells and receptors in the small intestine. TLR2-dependent.

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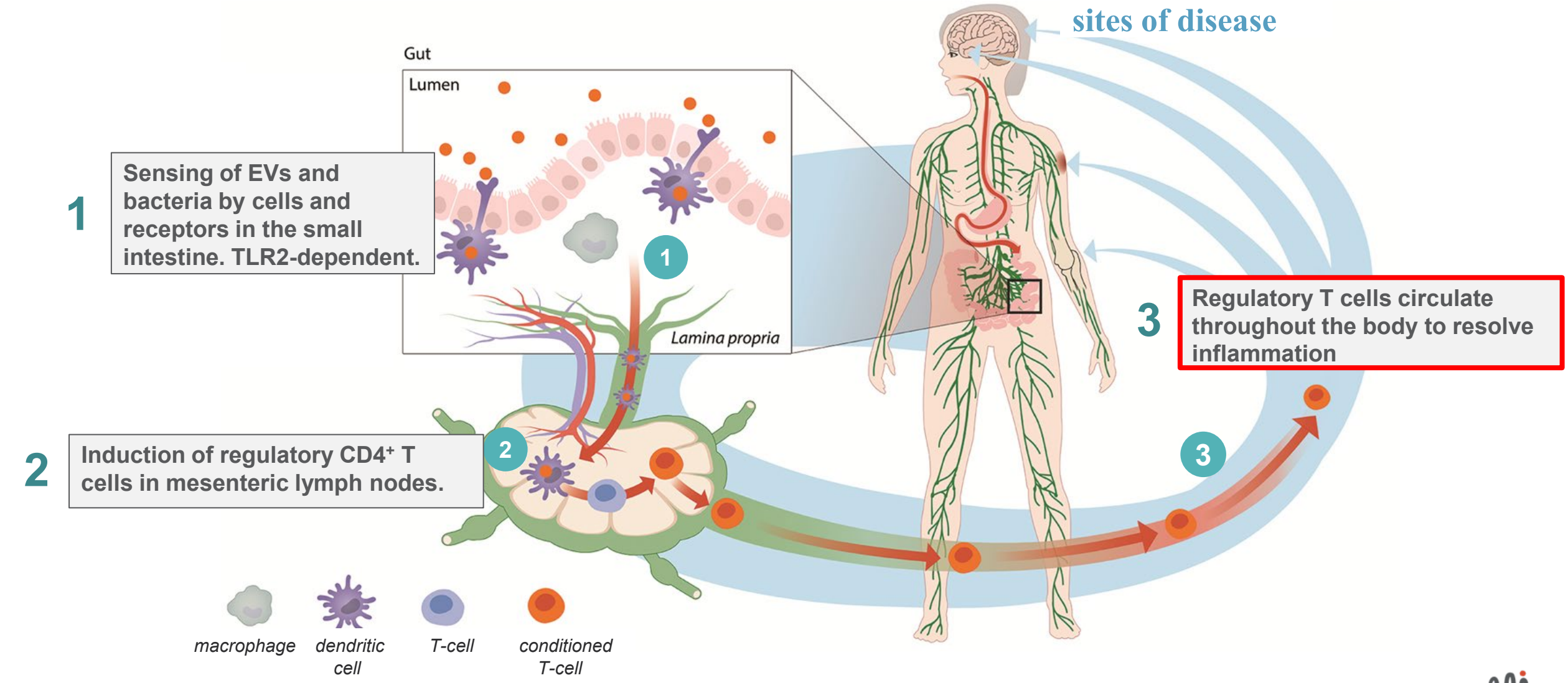
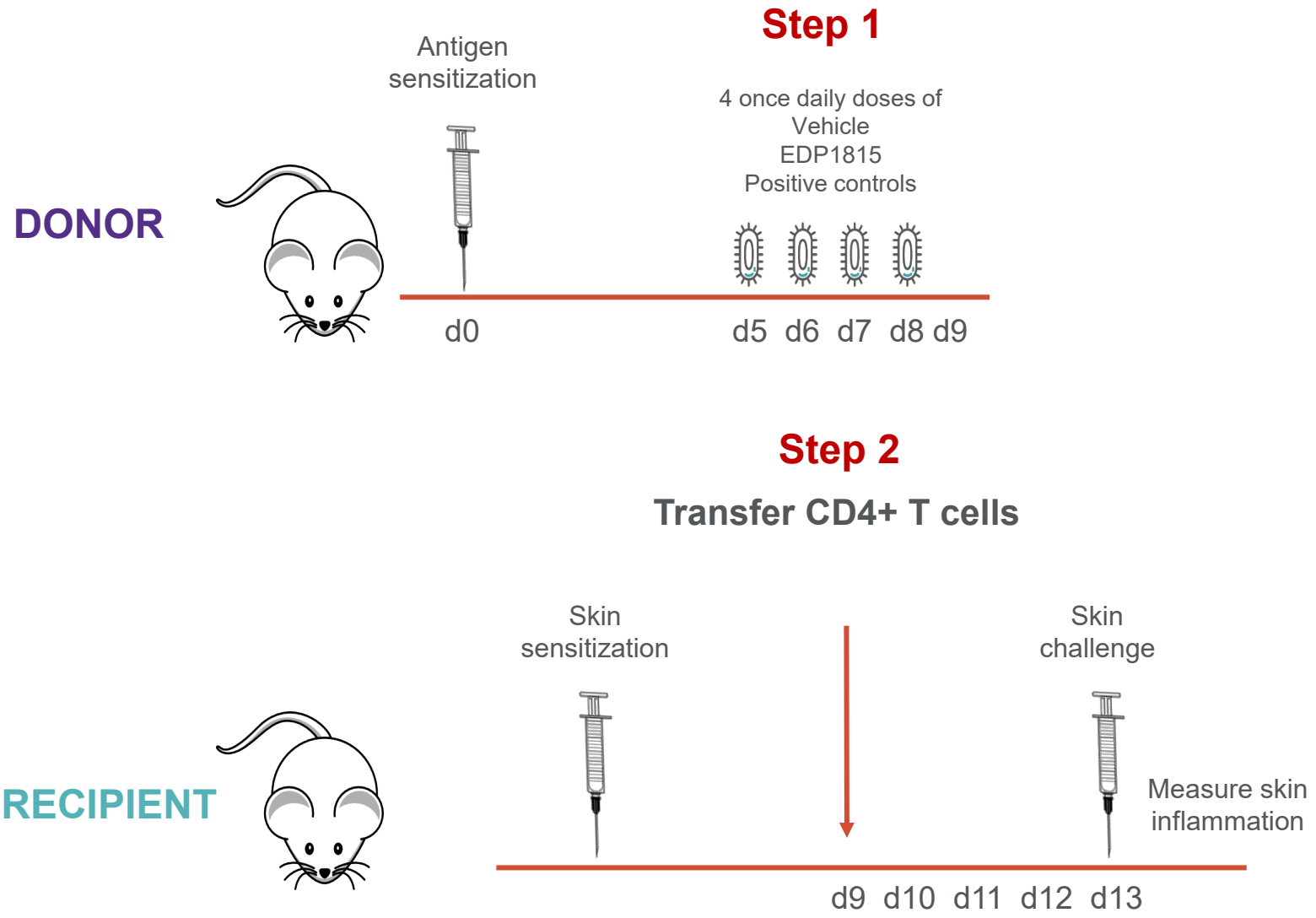
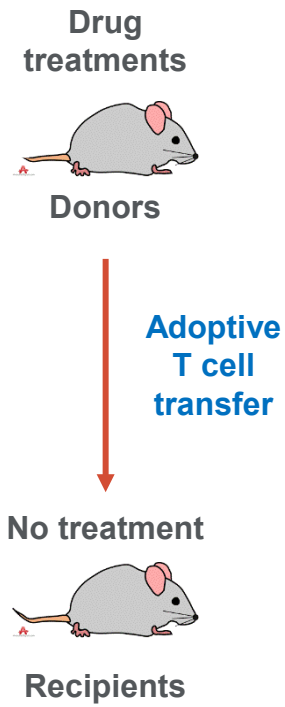
Three step model of inflammation resolution in the small intestinal axis

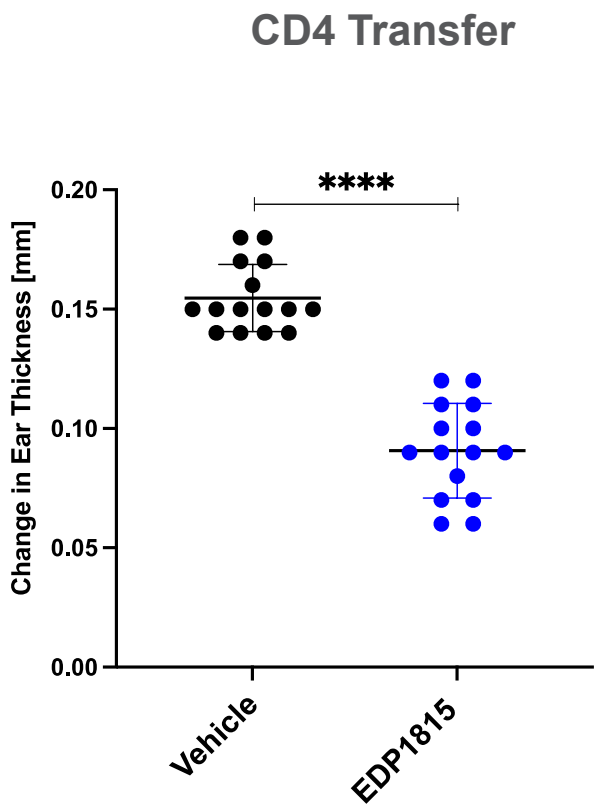


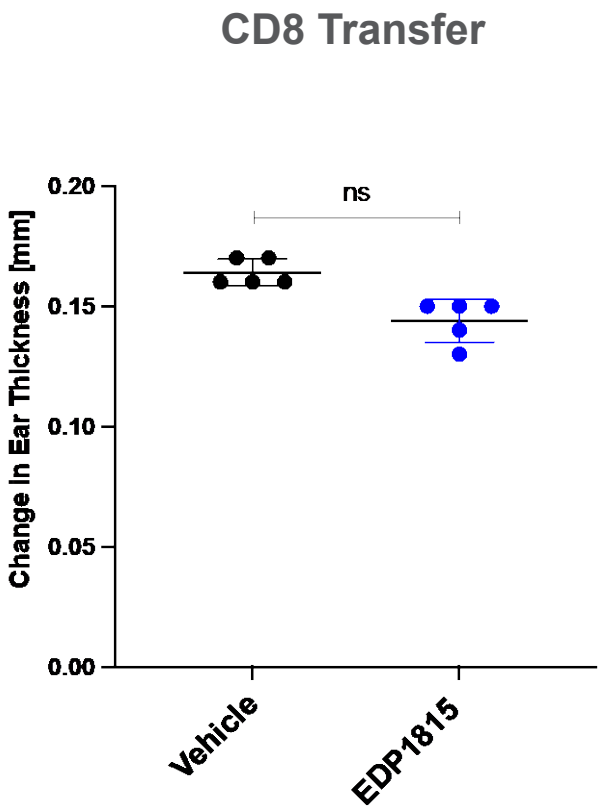
Adoptive T cell transfer confers inflammation resolution throughout the body



EDP1815 generates CD4$^+$ T cells that mediate efficacy in adoptive transfer model

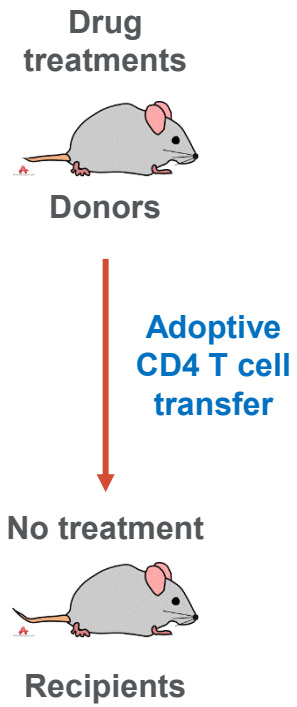


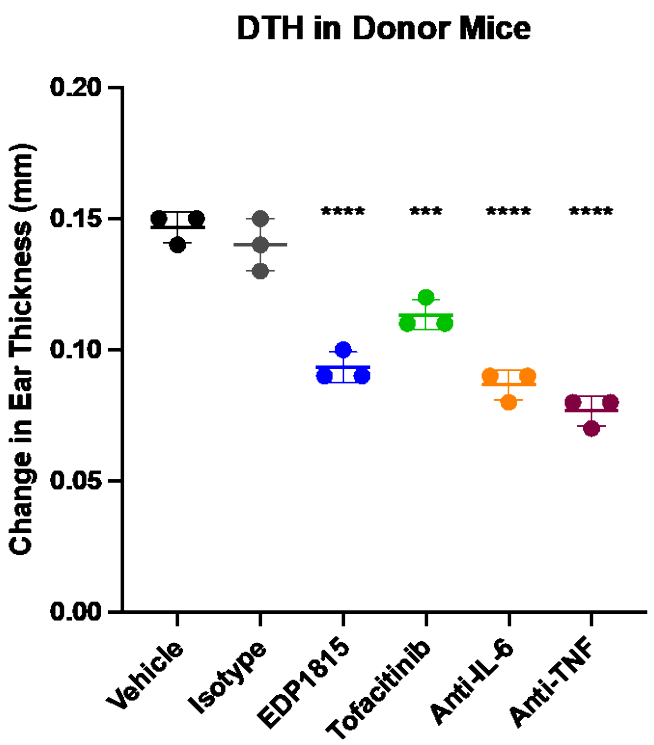


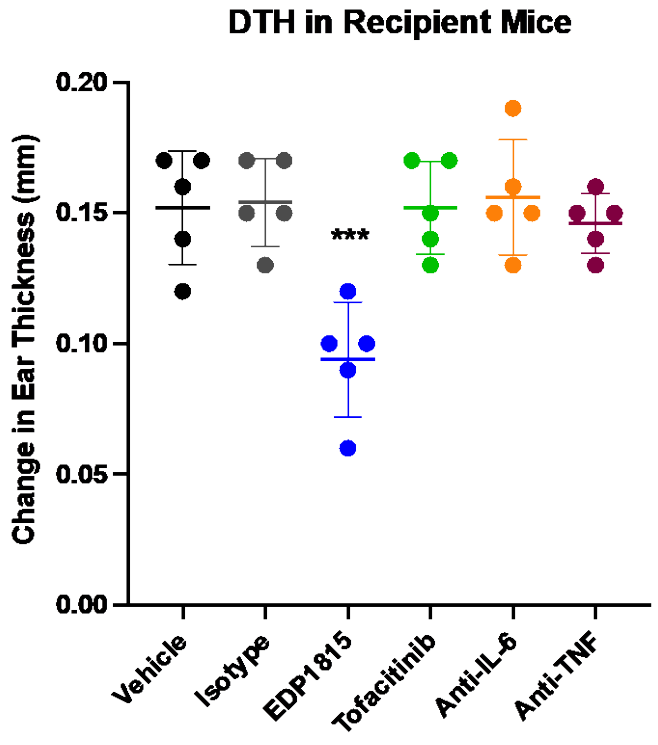


- EDP1815 treatment generates immune regulatory CD4$^+$ T cells that resolve inflammation
- Transfer of CD4$^+$ T cells (but not CD8$^+$ T cells) from donor mice to untreated recipient mice is sufficient to induce efficacy

EDP1815 induction of regulatory CD4$^+$ T cells differentiates from gold standard drugs



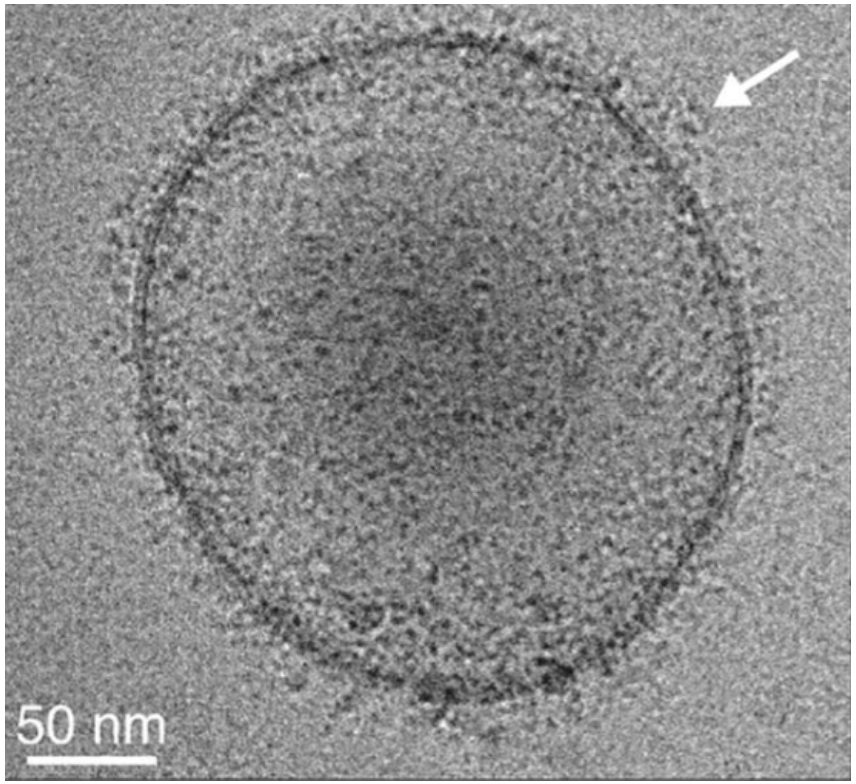


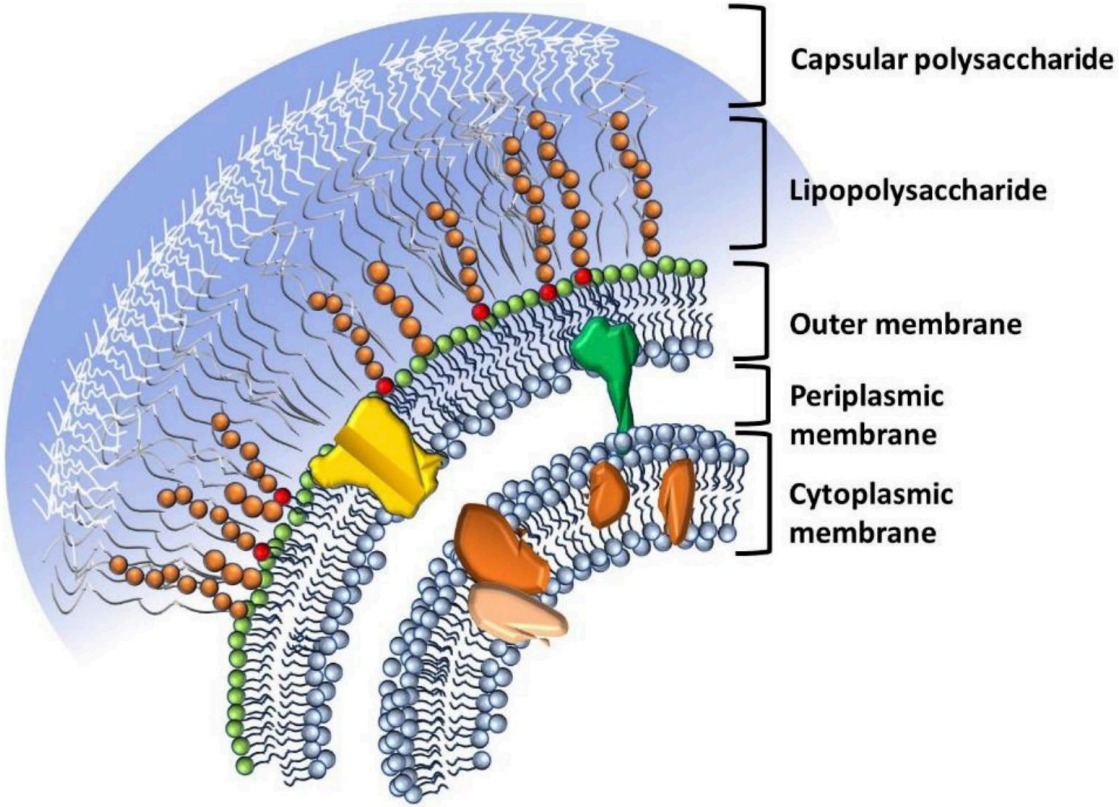


Donor mice were treated with EDP1815 or other standard of care anti-inflammatory drugs

Only EDP1815 treatment resulted in the generation of CD4 T cells that could inhibit inflammation in recipient mice

Molecular characterization of the bacterial and EV surface

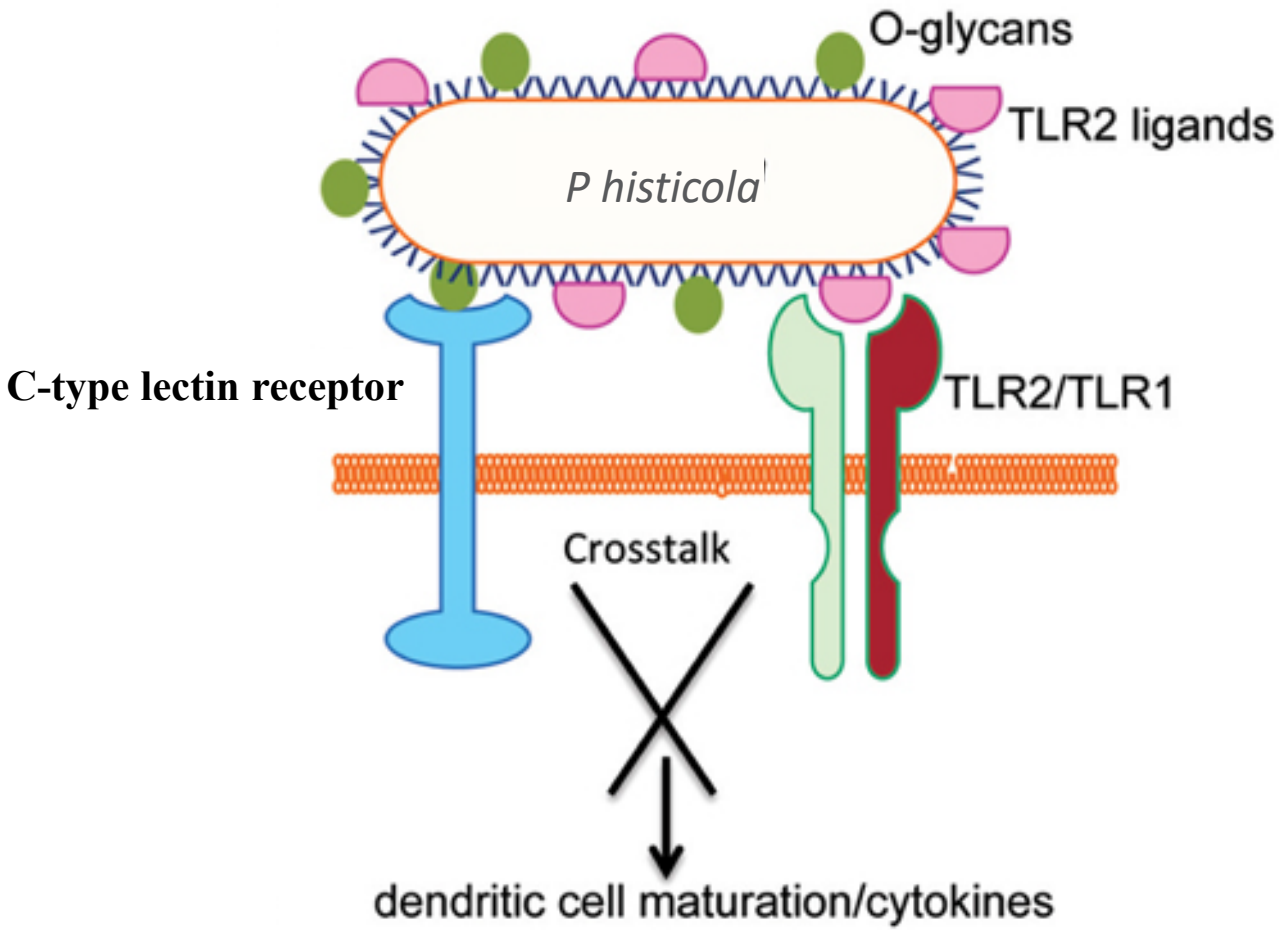




The bacterial surface layer is dense with molecules that interact with receptors on epithelial and immune cells

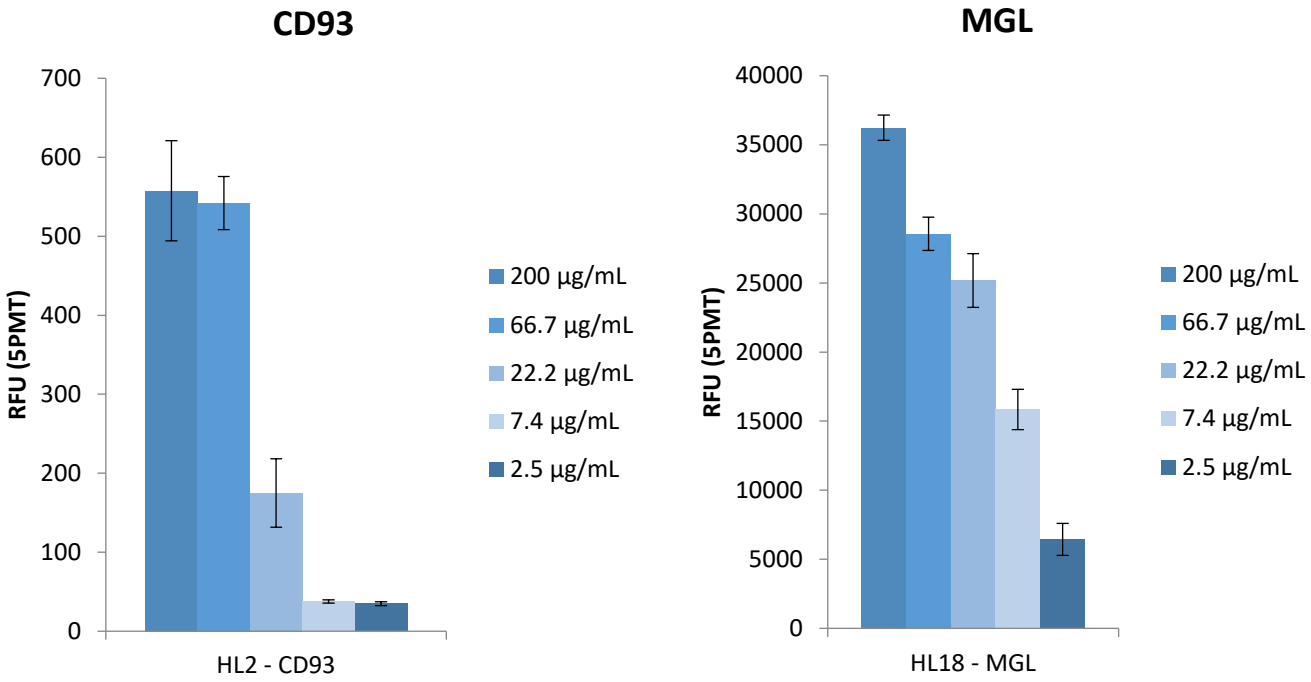
from Veeramachineni *et al.*, 2021

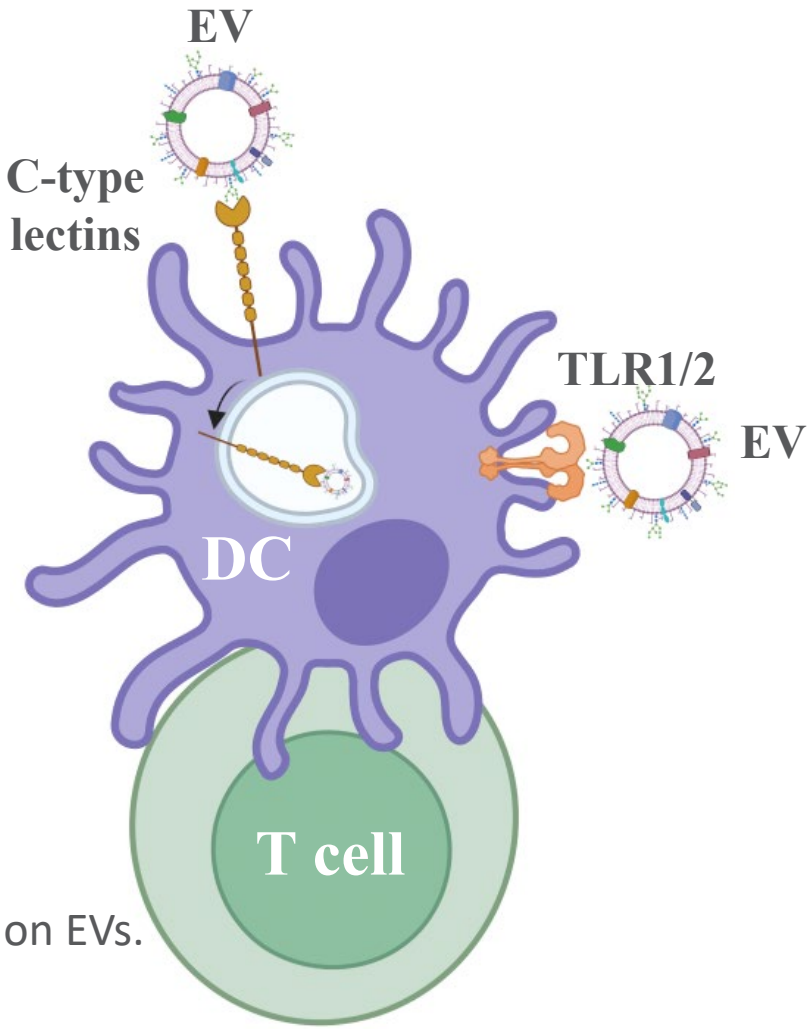
Bacterial surface structures facilitate immune cell binding and can modulate TLR2 signaling



Adapted from https://www.frontiersin.org/articles/10.3389/fmicb.2013.00310/full

Mechanism of action mediated by bacterial surface structures





Lectins expressed by human dendritic cells *in vitro* recognize structural motifs on EVs.

These interactions influence cell signaling and cytokine secretion.

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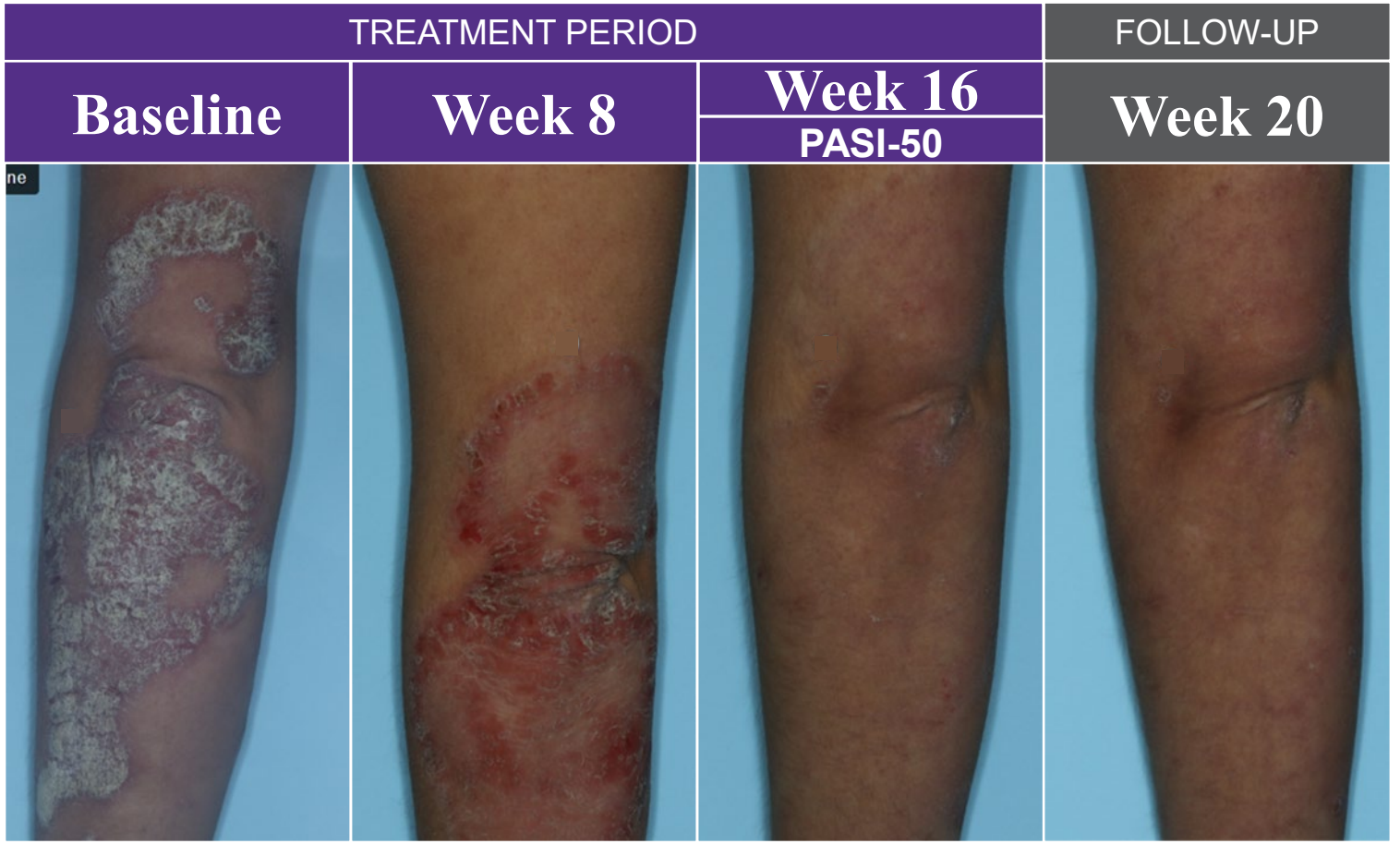
SINTAX proof-of-concept: EDP1815 in psoriasis

- Positive Phase 2 data validates SINTAX systemic inflammation resolving potential
- EDP1815 displays placebo-like safety and tolerability with durable efficacy
- Potential use across broad spectrum of inflammatory disease and severity level
- EDP1815 drug substance contains inactivated microbe and high EV content



Patient with moderate psoriasis enrolled in Phase 2 trial who achieved PASI-50 response at week 16 on EDP1815 – skin lesions improved further at week 20

EDP1815 Phase 2 trial in mild and moderate psoriasis

16-WEEK TREATMENT PERIOD

SCREENING PERIOD (up to 4 weeks)	TREATMENT PERIOD (16 weeks)

Randomized 2:1 in each arm (active:placebo)

- **Cohort 1: 1 capsule**
- **Cohort 2: 4 capsules**
- **Cohort 3: 10 capsules**

Key Inclusion Criteria:

- BSA of ≥3% and ≤10%
- PASI score of ≥6 and ≤15
- PGA score of 2 or 3

24-WEEK POST-TREATMENT PERIOD

POST-TREATMENT FOLLOW-UP (up to 4 weeks)	OPTIONAL FOLLOW-UP PERIOD (up to 20 weeks)

Week 20 | **Week 24** | **Week 28** | **Week 40**

Evaluation of Treatment Responses

- Following the 16-week treatment period all patients were followed for 4 weeks to week 20 (Part A)
- Patients on drug who achieved PASI-50 or greater at week 16 had the option to enter an additional follow-up period of up to 24 weeks following cessation of treatment (Part B)
- Eighty-three patients previously dosed with EDP1815 were followed for up to 24 weeks post-treatment
- Objective of the post-treatment follow-up period was to assess durability of response, incidence of flare or rebound and overall safety and tolerability

Summary of Endpoints

Primary Endpoint

Mean reduction in PASI score at week 16 vs. placebo using Bayesian probability

Result

80-90% probability that EDP1815 is superior to placebo at week 16 based on mean change in PASI

Responder Endpoint

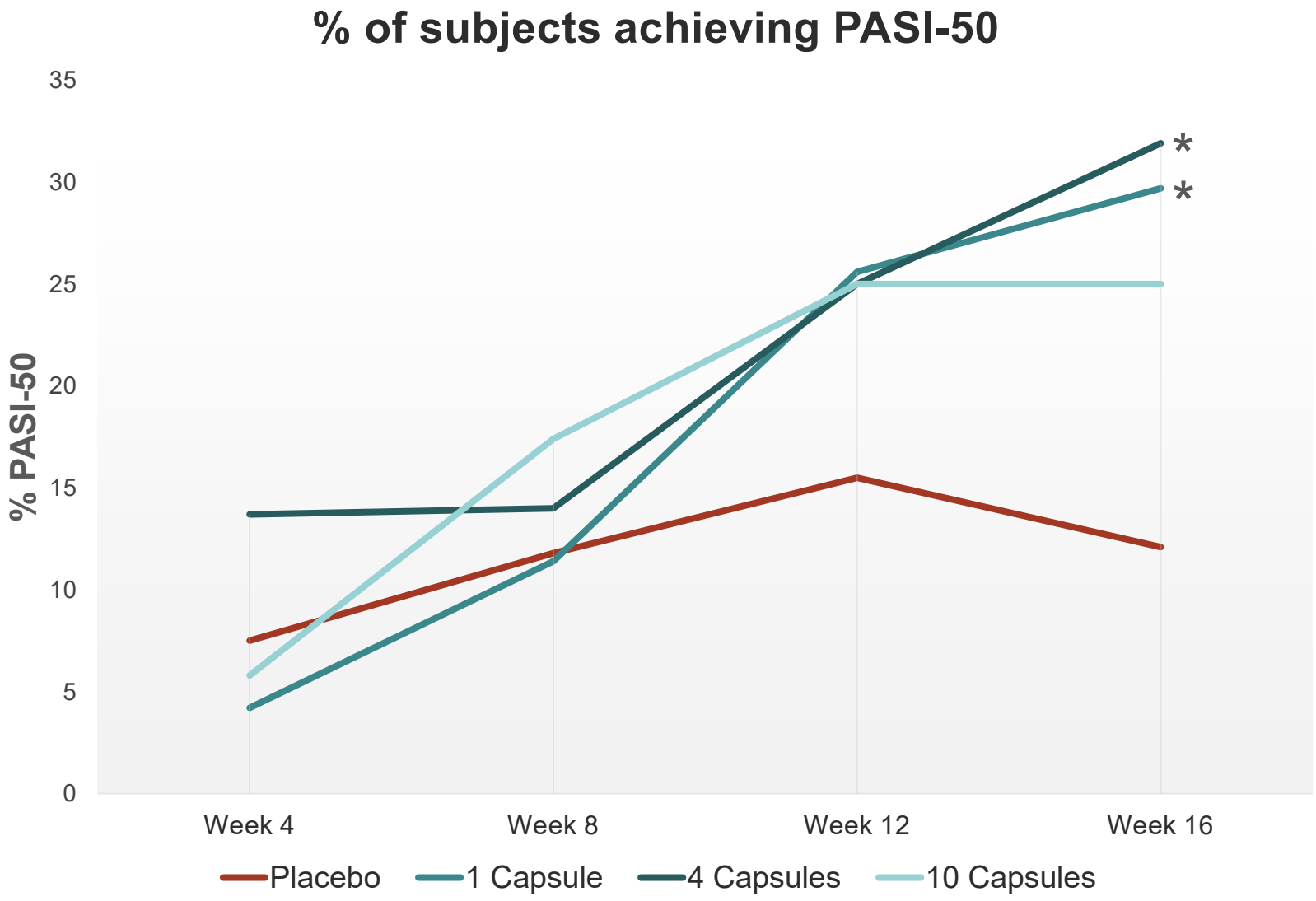
Percentage of patients achieving at least a PASI-50 by week 16

Result

Statistically significant p-value for 2 of the 3 individual dose cohorts, and directionally similar for the third

Robust PASI-50 responses with EDP1815 at week 16

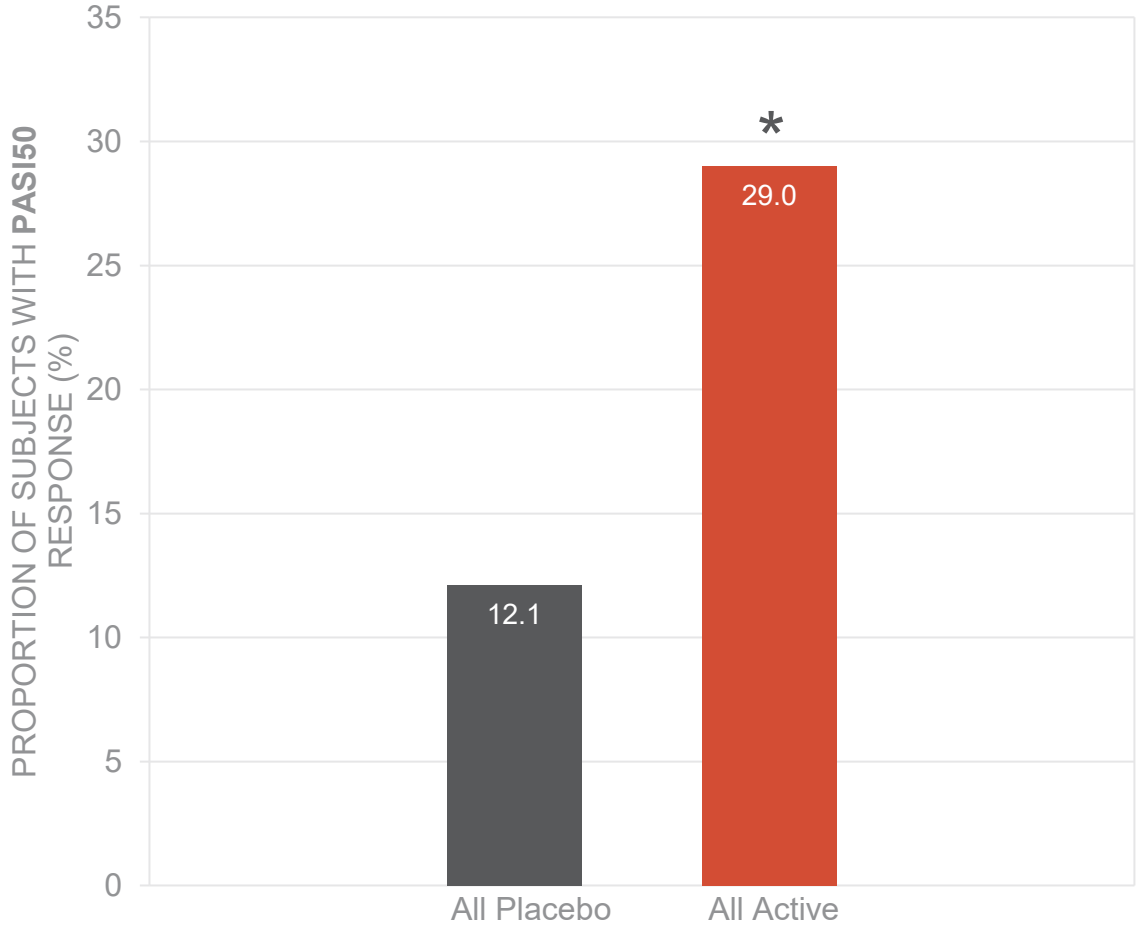
Statistically significant p-value (<0.05) for 2 of the 3 individual dose cohorts, and for all 3 cohorts when pooled



*p<0.05

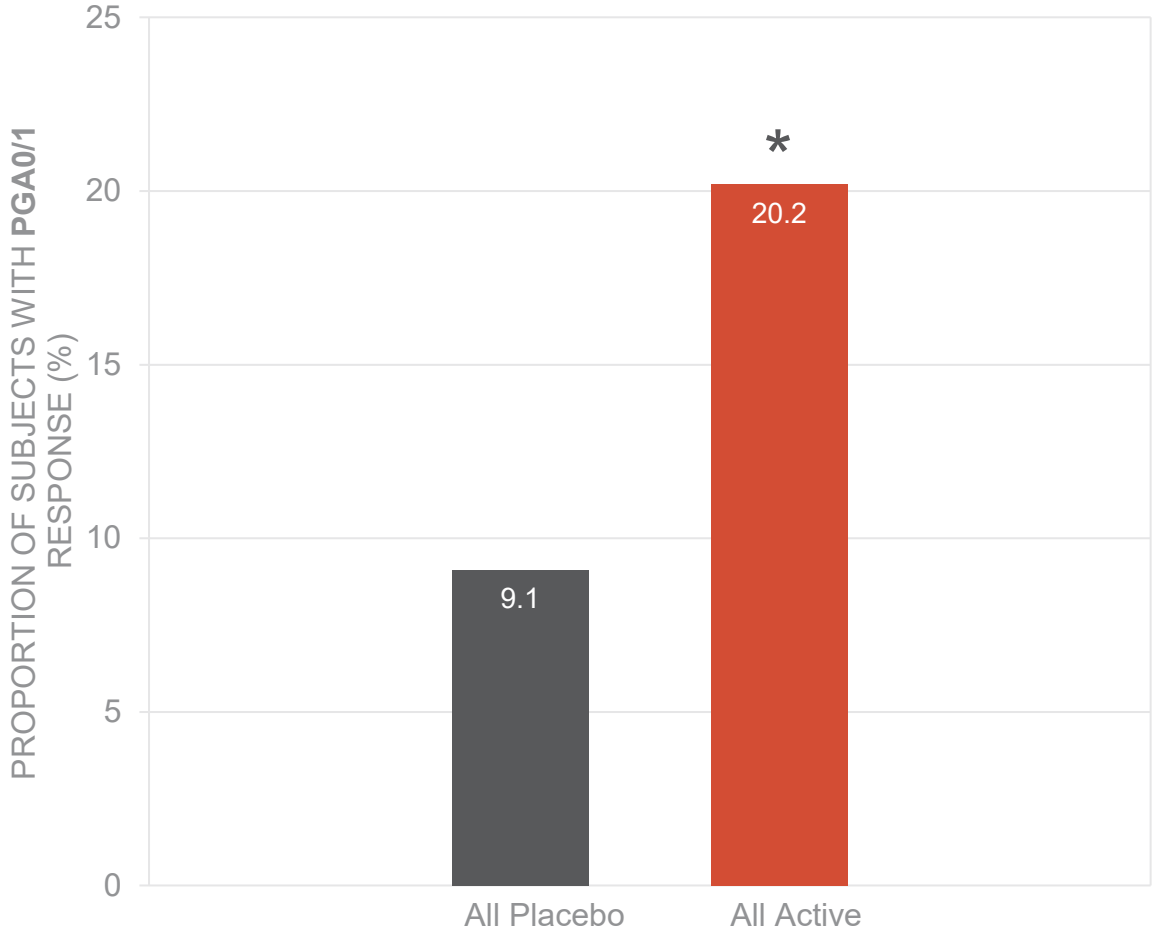
Statistically significant increase in clinically meaningful endpoints

PASI-50



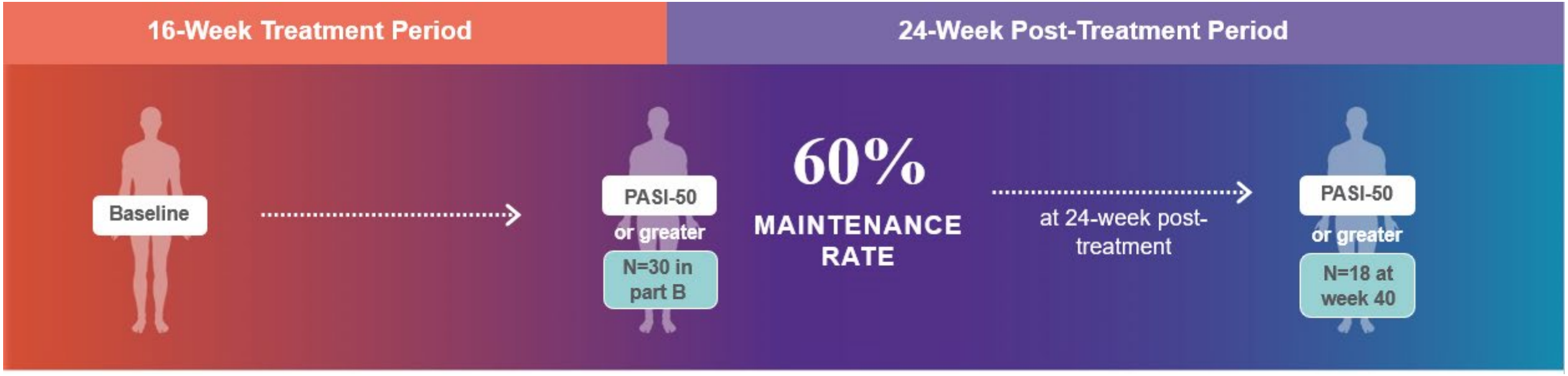
*p<0.05

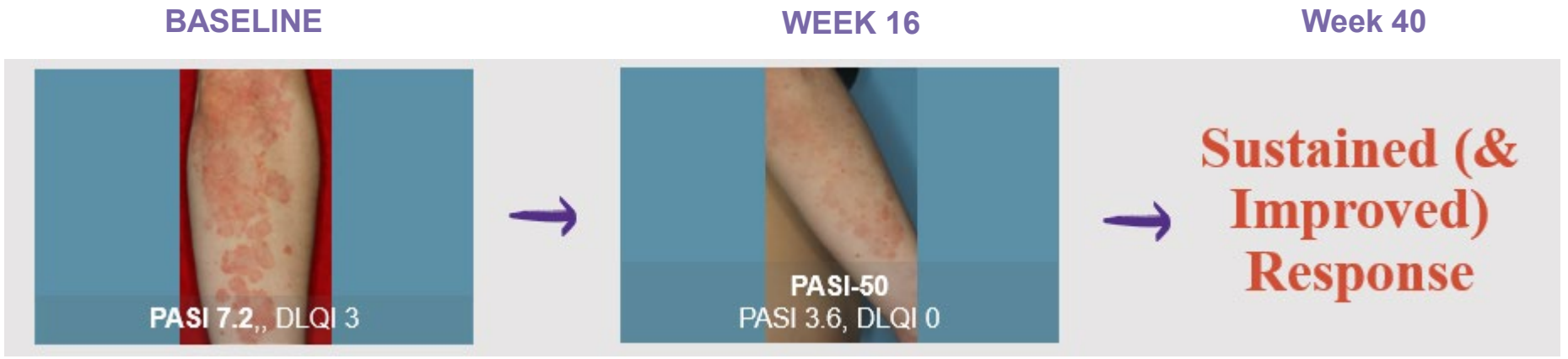
PGA-0/1



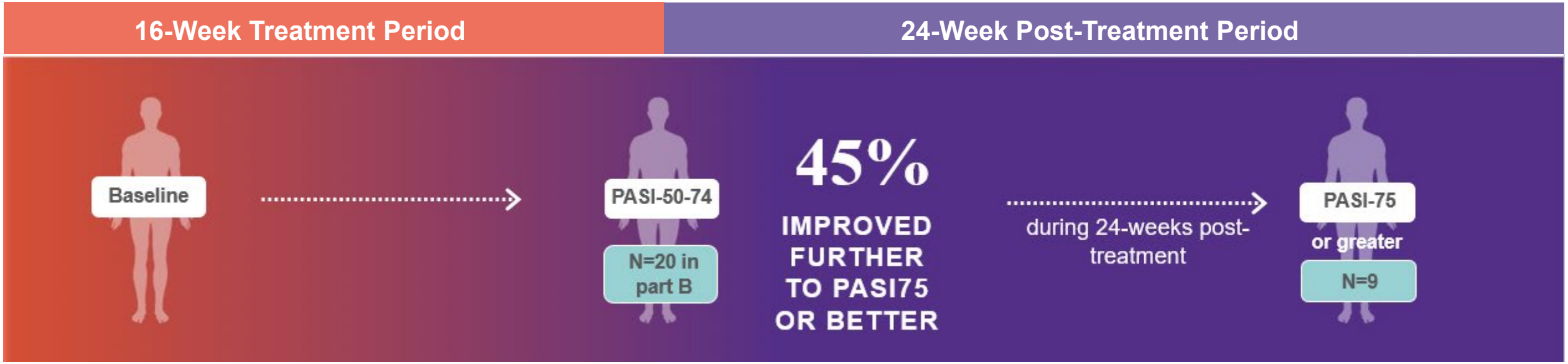
*p<0.05

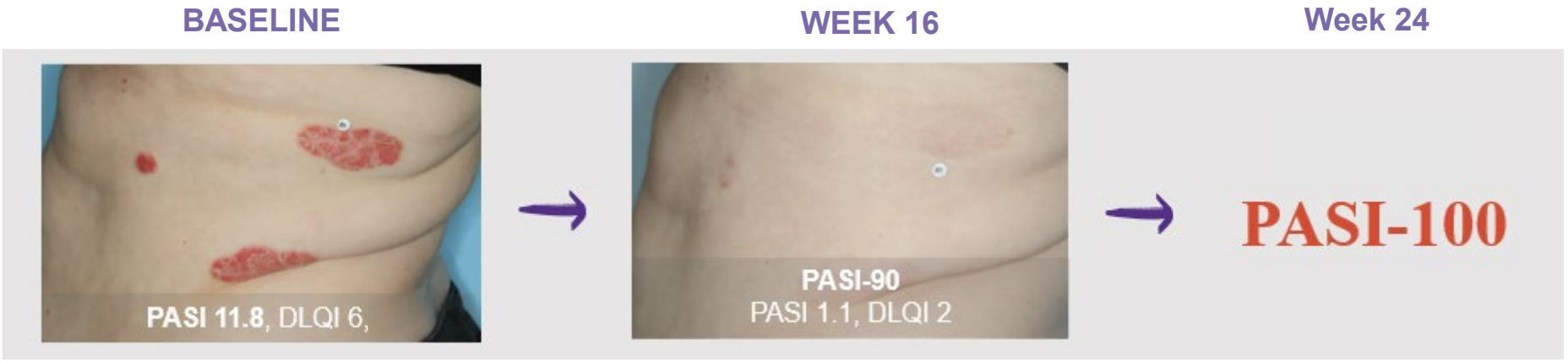
Durability of clinical responses seen 24-weeks post treatment





Deepening of clinical responses seen 24-weeks post treatment





Placebo-like safety and tolerability observed in EDP1815-201

- AE profile of EDP1815 is comparable to placebo across 16 weeks of dosing and up to 24 weeks follow-up
- No related SAEs
- Gastrointestinal or Infection AE rate comparable to placebo
- AE profile no different in the drug responders (≥PASI-50)

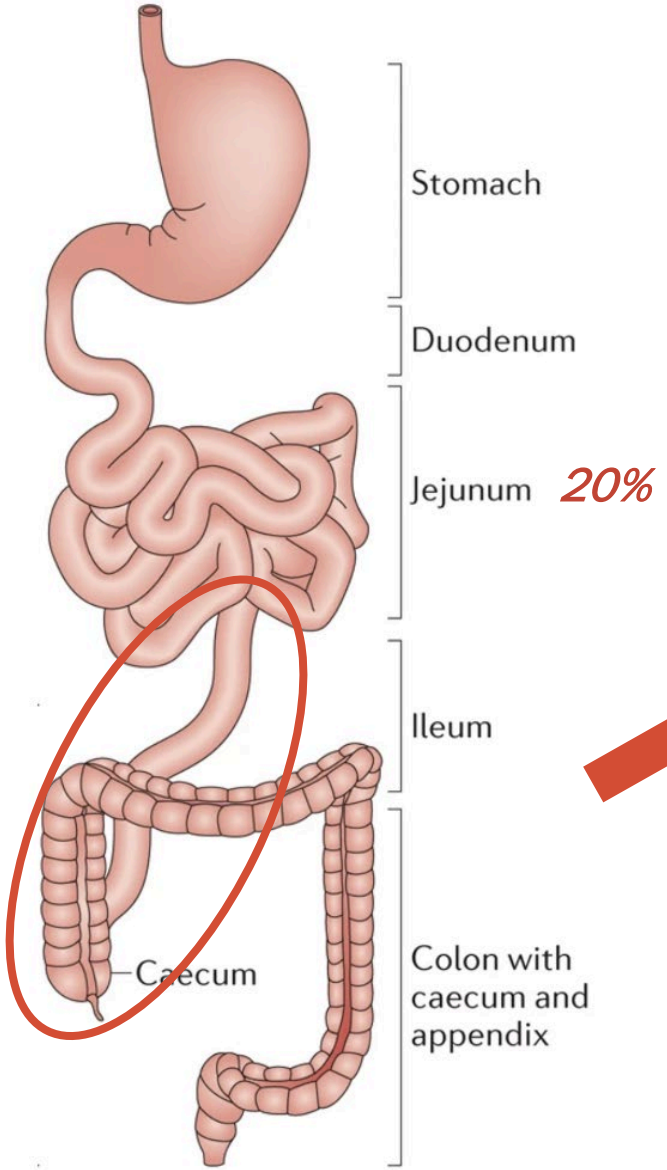
Preclinical exposure to drug higher in the small intestine enhanced efficacy.

Faster release polymer coat on EDP1815 capsules gave substantially faster release by scintigraphy in healthy human volunteer scintigraphy trials

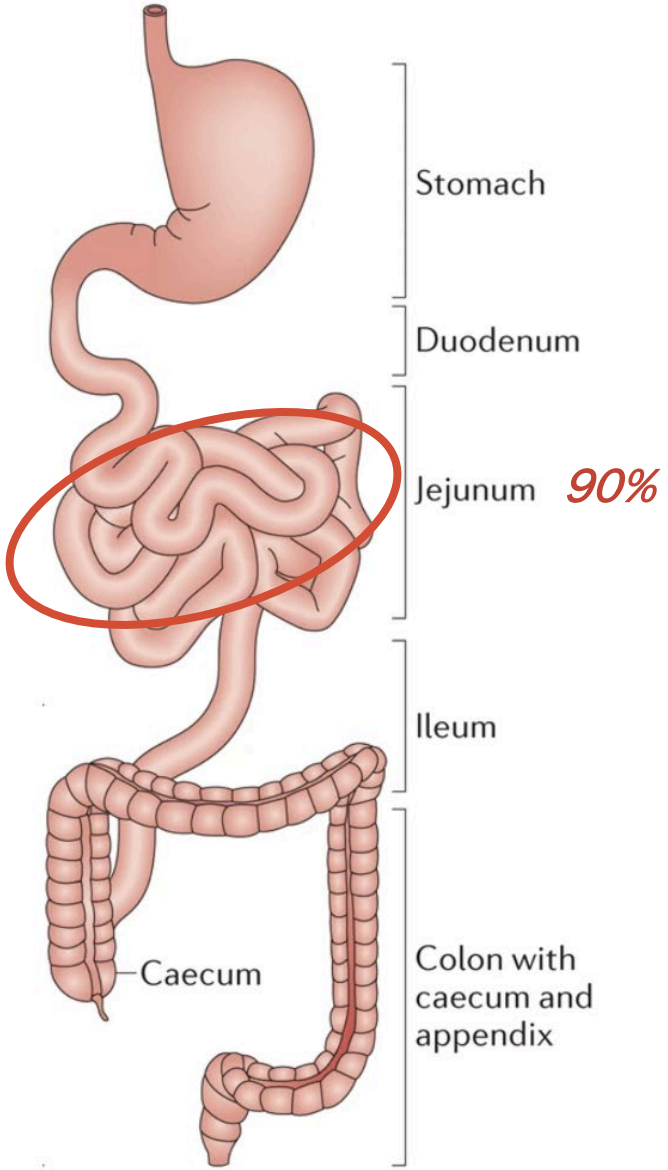
Human scintigraphy studies showed 90% of capsules release the drug in the proximal small intestine with faster release

Faster release enhanced preclinical efficacy

Original release EDP1815



Faster release EDP1815/EDP2939



Release profile used in clinical studies

Original release

- EDP1815 Phase 1b studies
- EDP1815-201 Phase 2 psoriasis
- EDP1815-207 Phase 2 atopic dermatitis cohorts 1-3. Data expected early 1Q23

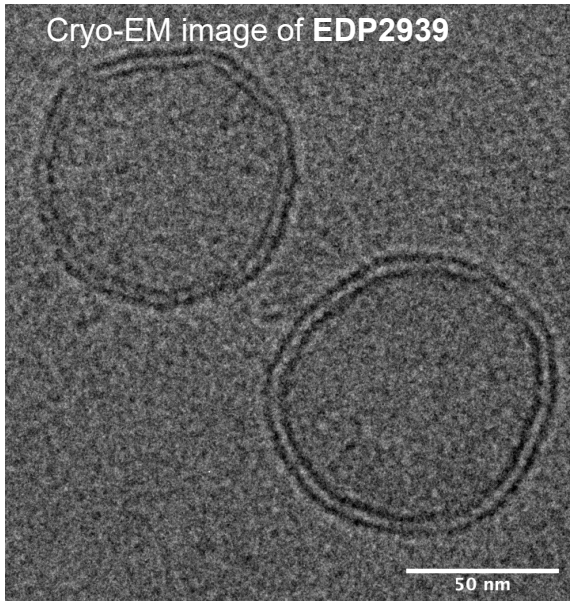
Faster release

- EDP1815-207 Phase 2 atopic dermatitis cohort 4. Data expected 2Q23
- EDP2939 Phase 2 psoriasis. Data expected 2H23

Introduction to SINTAX medicines	Mark Bodmer
Mechanism of Action of EDP1815	Andrea Itano
EDP1815 Clinical Results and Plans	Duncan McHale
Next Generation: EVs and EDP2939	Mark Bodmer

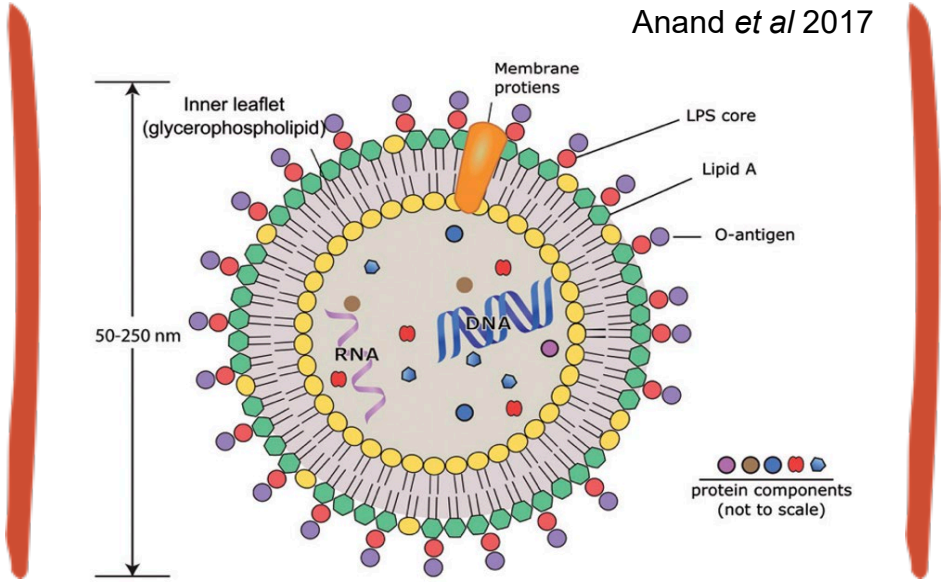
Bacterial extracellular vesicles (EVs) mediate cell-cell communication

EVs are naturally shed lipoprotein nanoparticles



Macromolecular content is a subset of the parent cell

Anand *et al* 2017



Small volume enables diffusion / target engagement

$$D = \frac{k_B T}{6\pi \eta r}$$

Stokes-Einstein Equation

EDP2939 is the first EV SINTAX medicine

Origins and Biology

A naturally non-living product shed into culture supernatant during fermentation of the parental bacterial strain

Systemic effects without systemic exposure after oral administration

No gut colonization

Manufacturing and Pharmaceutics

Manufacture at scale by anaerobic fermentation, EV purification, lyophilization

Dry powder-in-capsule formulation

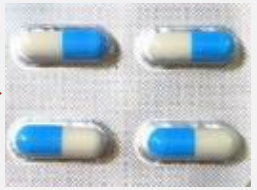
Capsule coating modulates site of delivery

EDP2939 and EDP1815 are based on a single strain of *Prevotella histicola* from the duodenum of a human donor

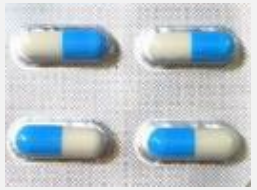
Fermenter

Centrifuge

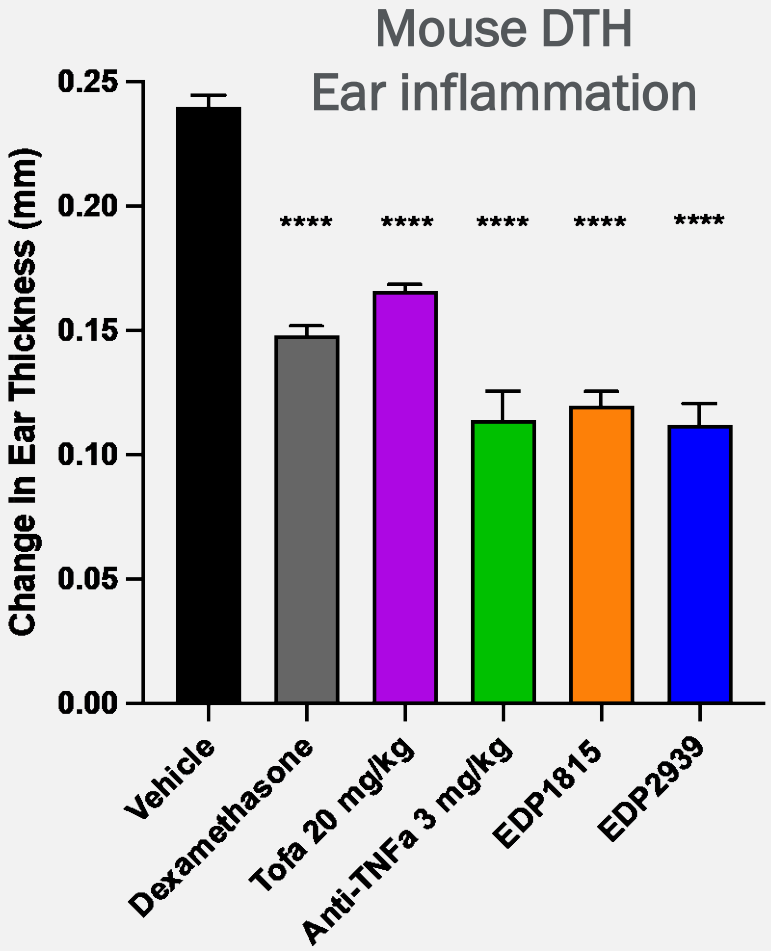
EDP2939
Supernatant contains EVs

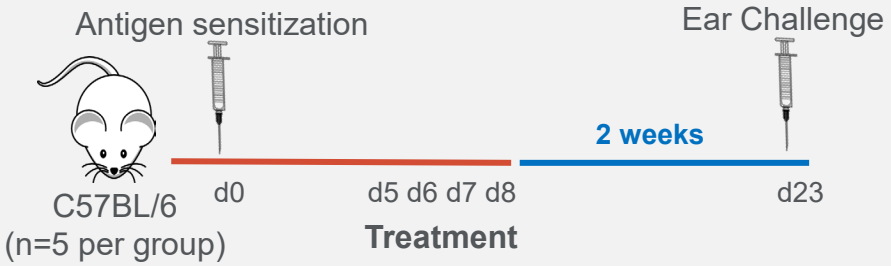


EDP1815
Pellet contains non-viable bacterial cells and EVs



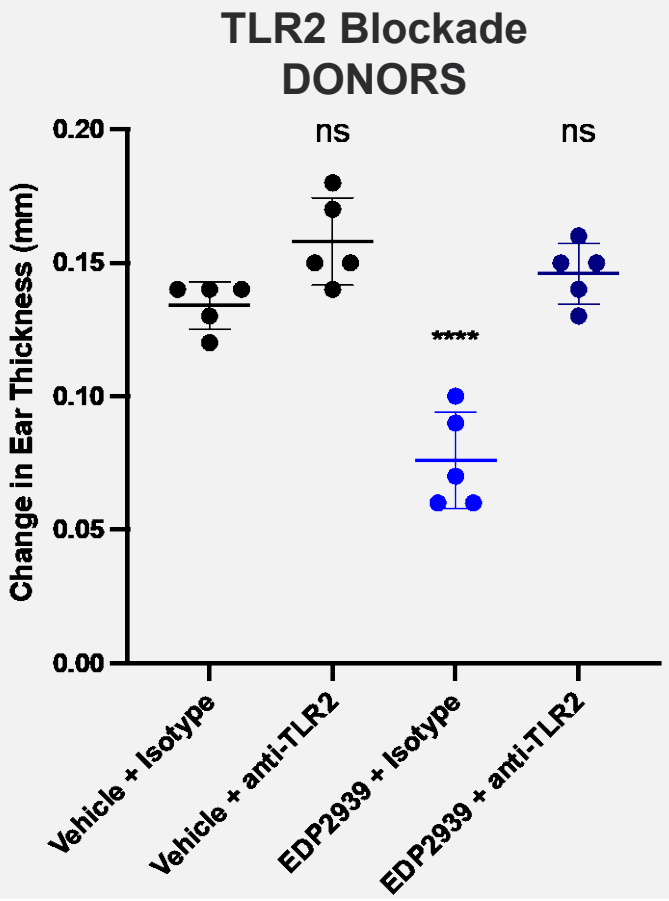
EDP2939 purified EVs match the maximal efficacy of EDP1815

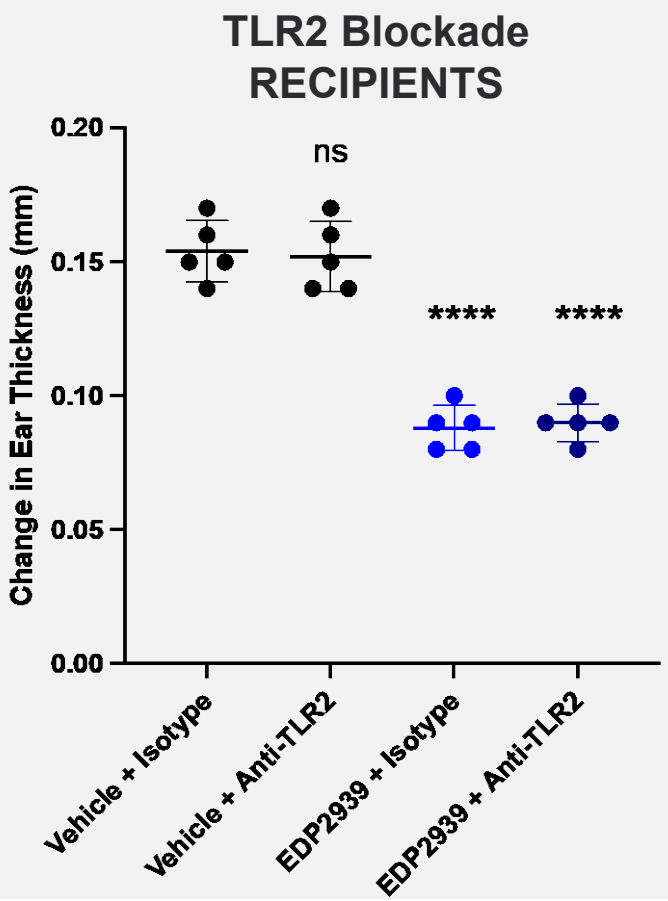




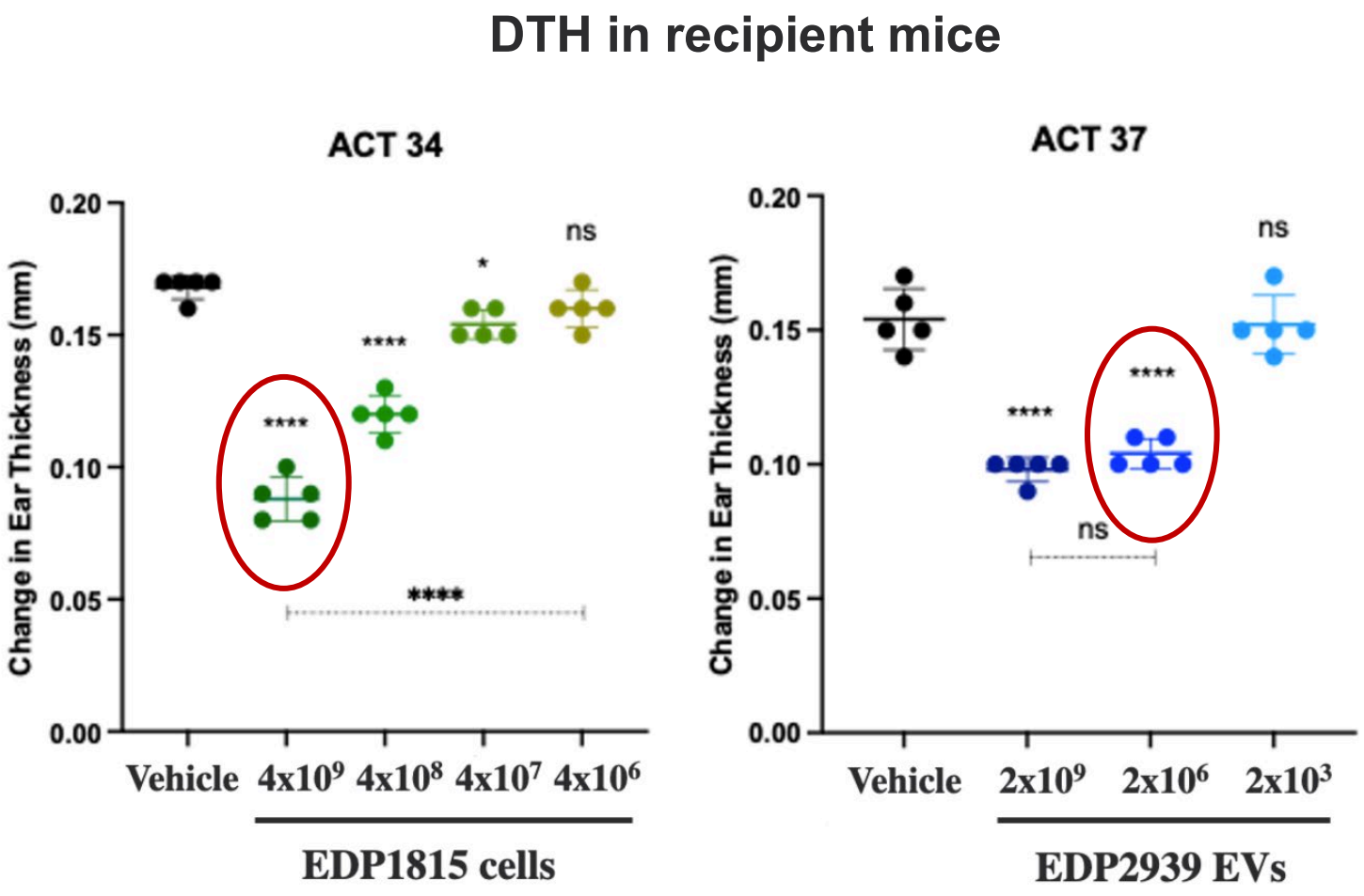
- EDP2939 is fully efficacious as a purified EV preparation in the absence of bacterial cells.
- EDP1815 and EDP2939 share a mechanism of action

Action of EDP2939 is dependent on TLR2 in donors not recipients in mouse adoptive cell transfer





EDP2939 and EDP1815 are dose-dependent inducers of CD4^{+} T cells that are anti-inflammatory in untreated recipient mice



X-axis: dose of EDP1815 or EDP2939 in donor mice.

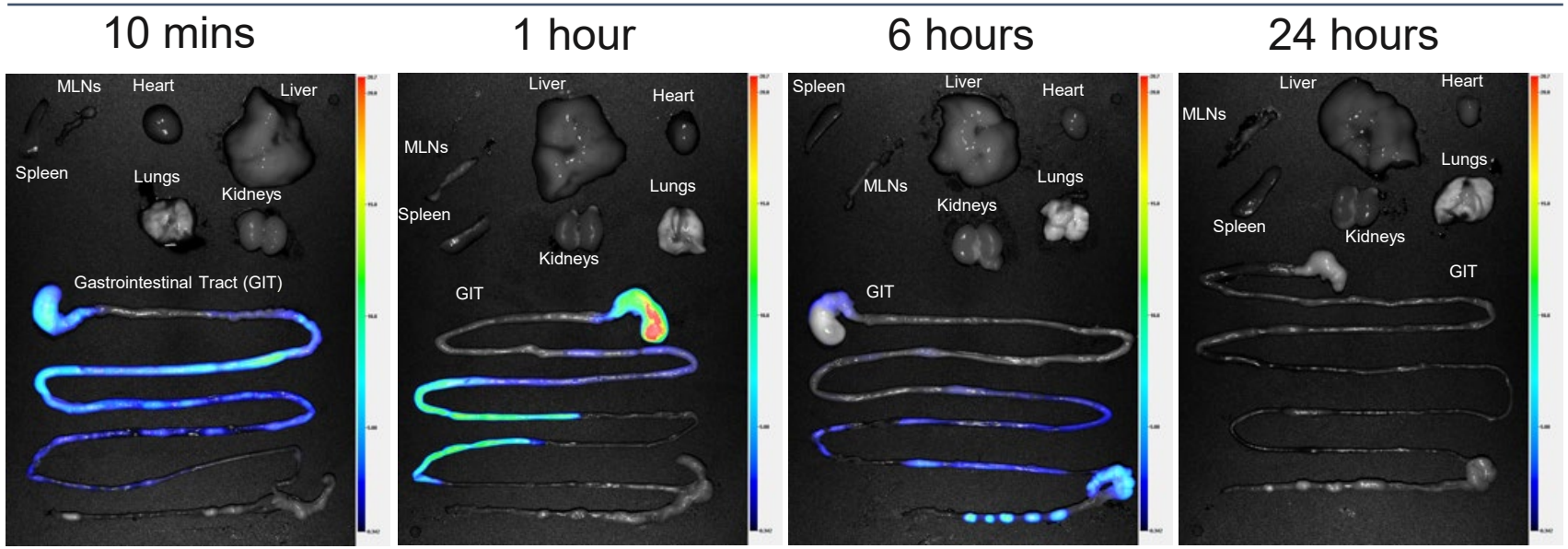
Y-axis: response in recipients after CD4 cell transfer.

EDP2939 was highly potent in the absence of bacterial cells.

EDP2939 pharmacology depends on action in the small intestine

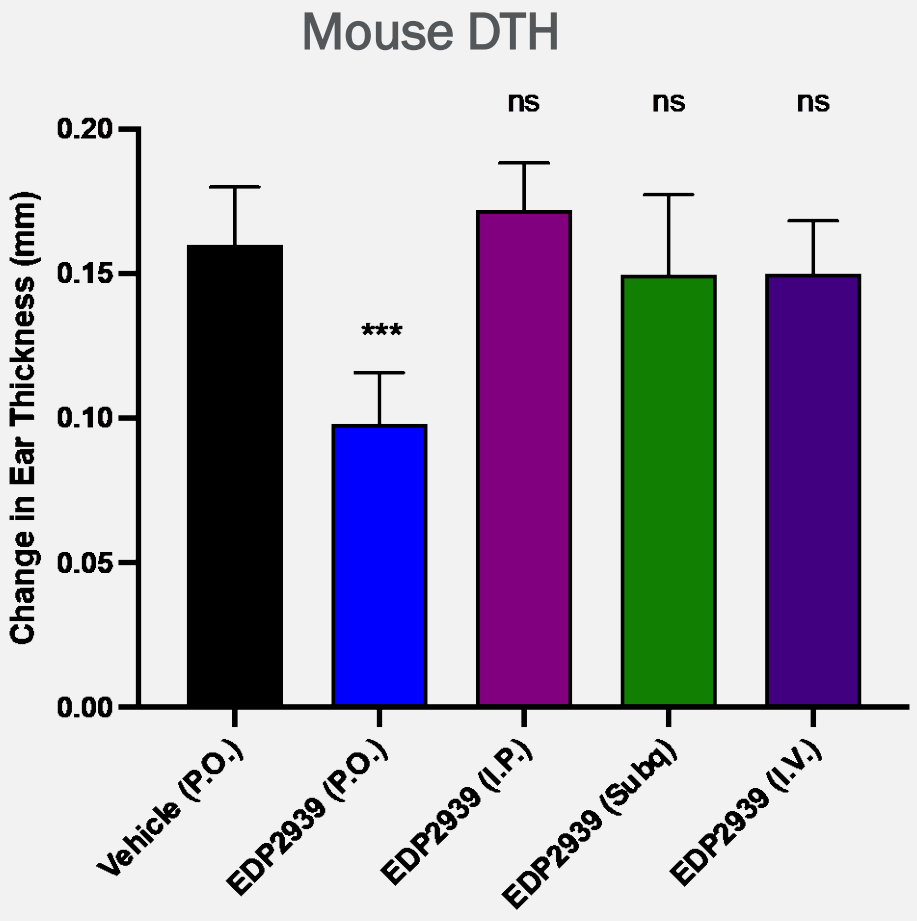
Orally delivered EVs are gut restricted in mice

Time post oral gavage of EDP2939



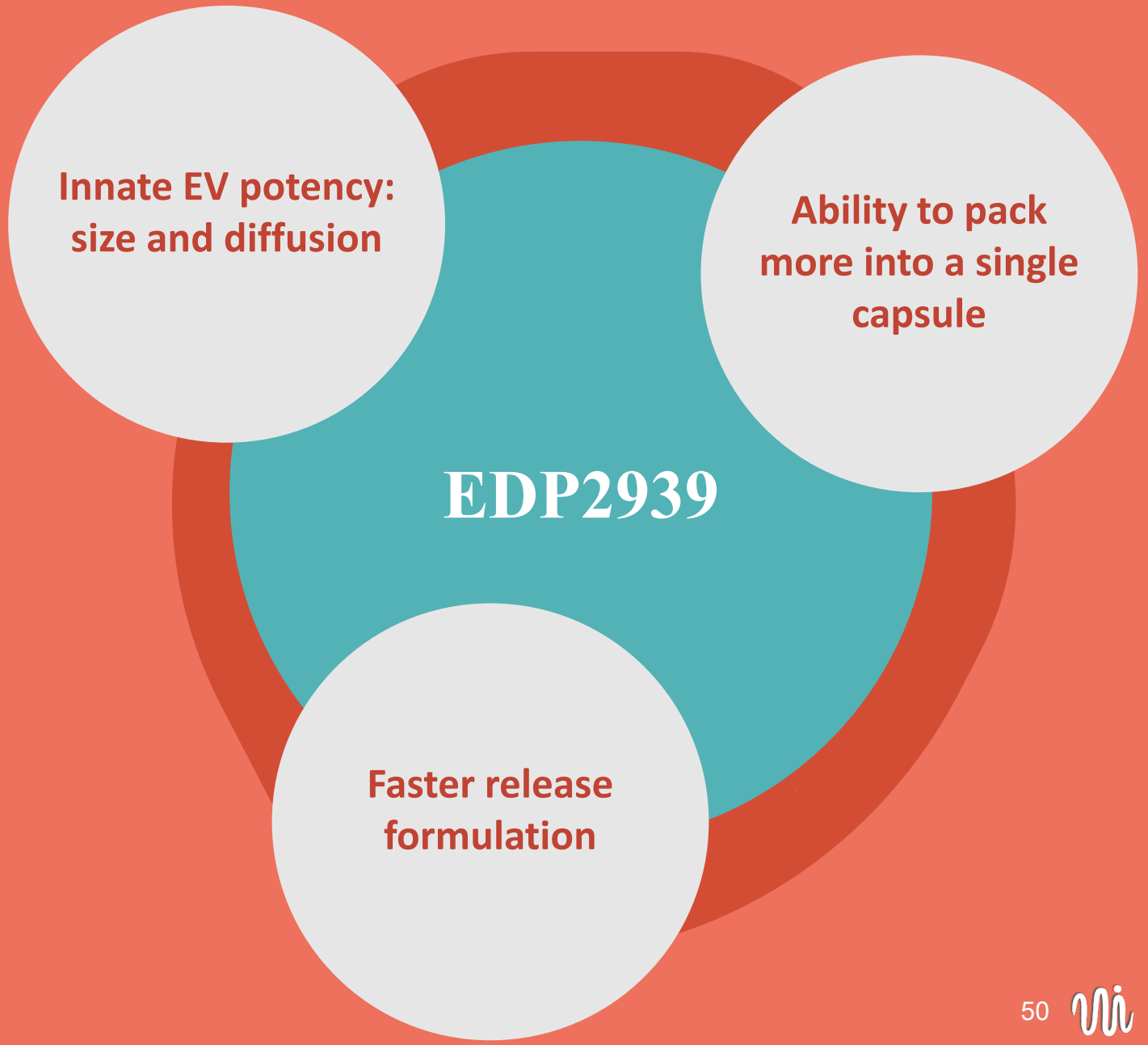
Fluorescence biodistribution studies show that orally delivered EDP2939 did not leave the GI tract

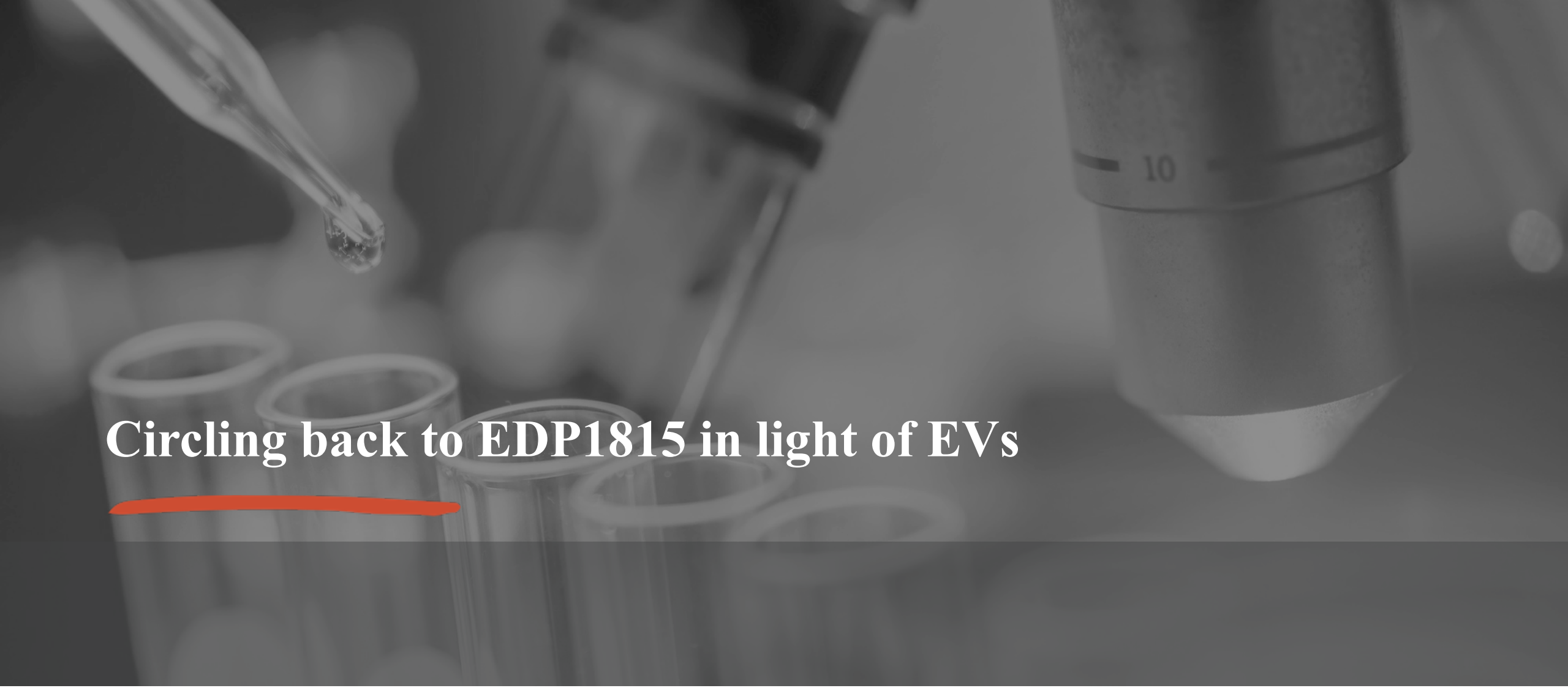
The peripheral effect of SINTAX is dependent on signaling in the gut



- Only oral administration was efficacious
- i.p., s.c., and i.v. had no effect
- This is a direct demonstration of the small intestinal axis mechanism of action

Three independent pharmacological factors predict EDP2939 improved efficacy

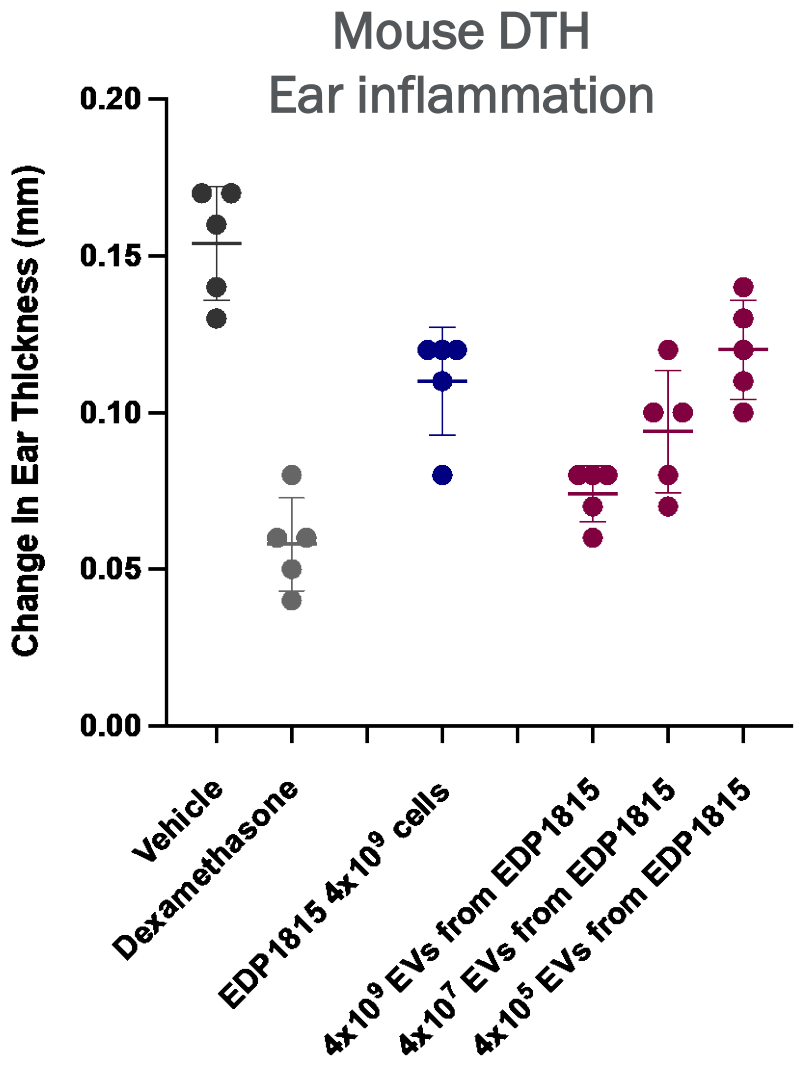




Circling back to EDP1815 in light of EVs

EVs extracted from EDP1815 were efficacious preclinically

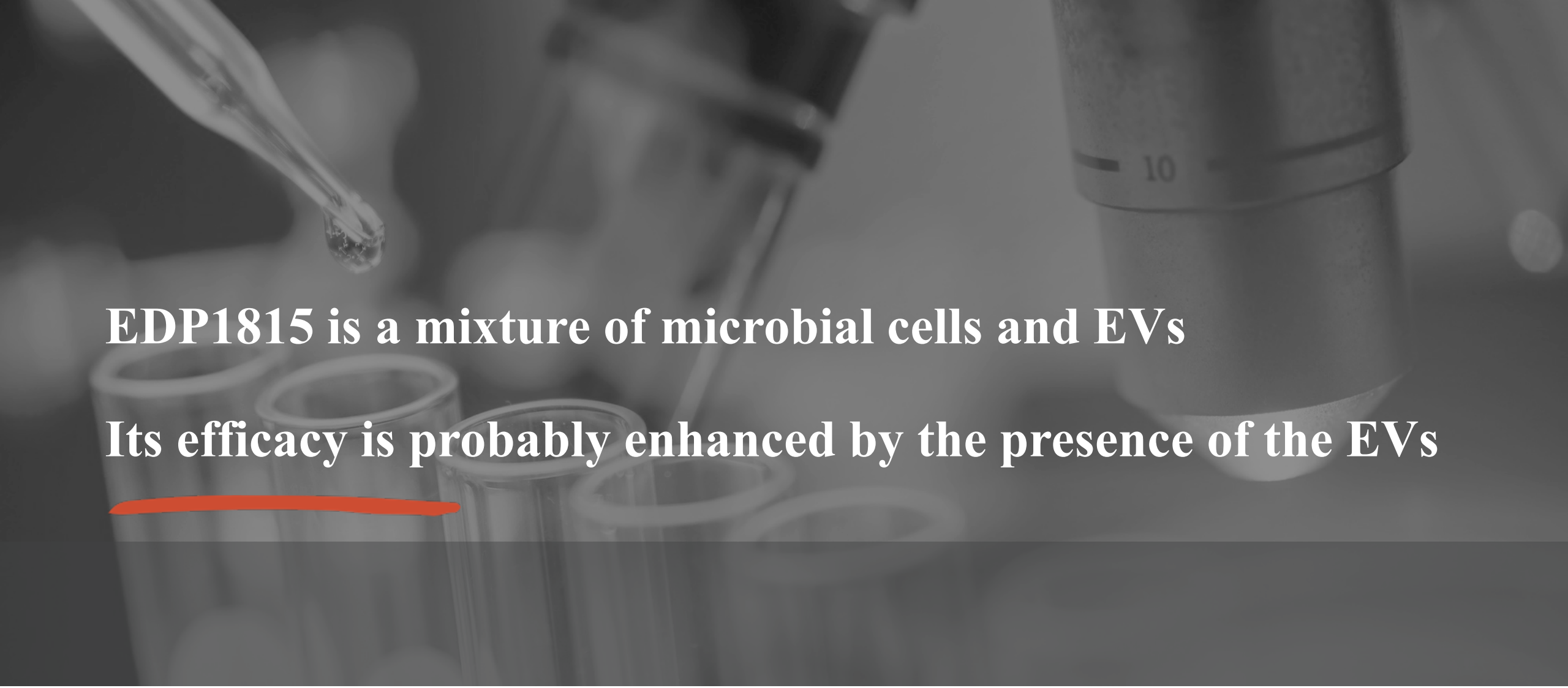
Vesicles extracted from EDP1815 were potent in mouse DTH



The microbial preparation of EDP1815 drug substance contains EVs.

Drug substance was solubilized and EVs extracted from the soluble fraction.

These extracted EVs were potently active in a mouse in vivo DTH assay

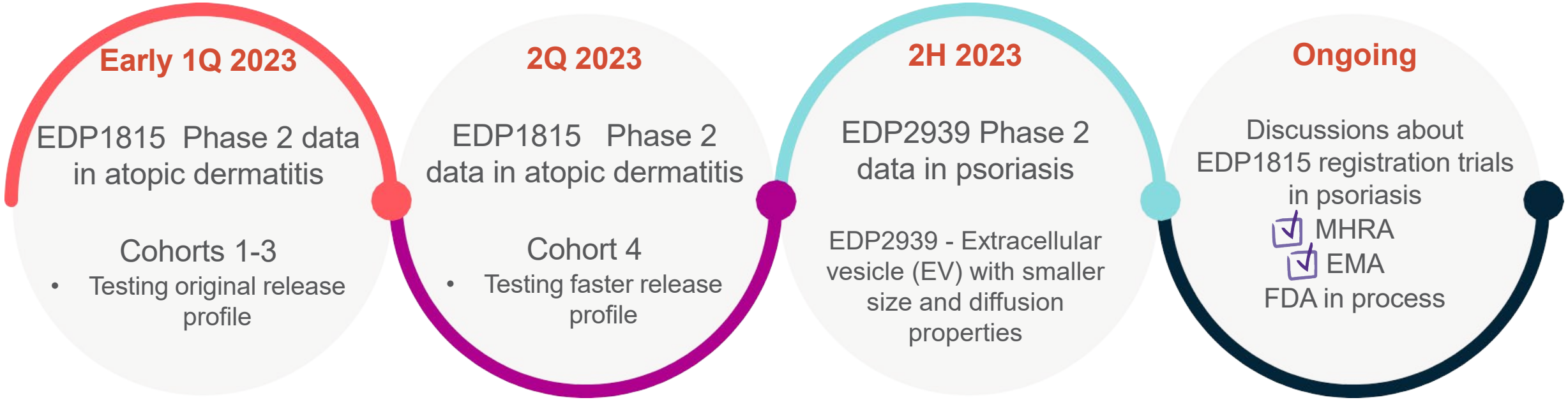


EDP1815 is a mixture of microbial cells and EVs

Its efficacy is probably enhanced by the presence of the EVs

2023: A Landmark Year for Evelo

Multiple transformative catalysts expected



3 inflection points test different parts of Evelo strategy; each has increasing potential efficacy

Translation to humans - an example patient from EDP1815-201 phase 2 trial