SER-287, an investigational microbiome therapeutic, induces widespread transcriptional changes related to clinical remission in a placebo-controlled, double-blind randomized trial (SERES-101) in patients with active mild-to-moderate ulcerative colitis

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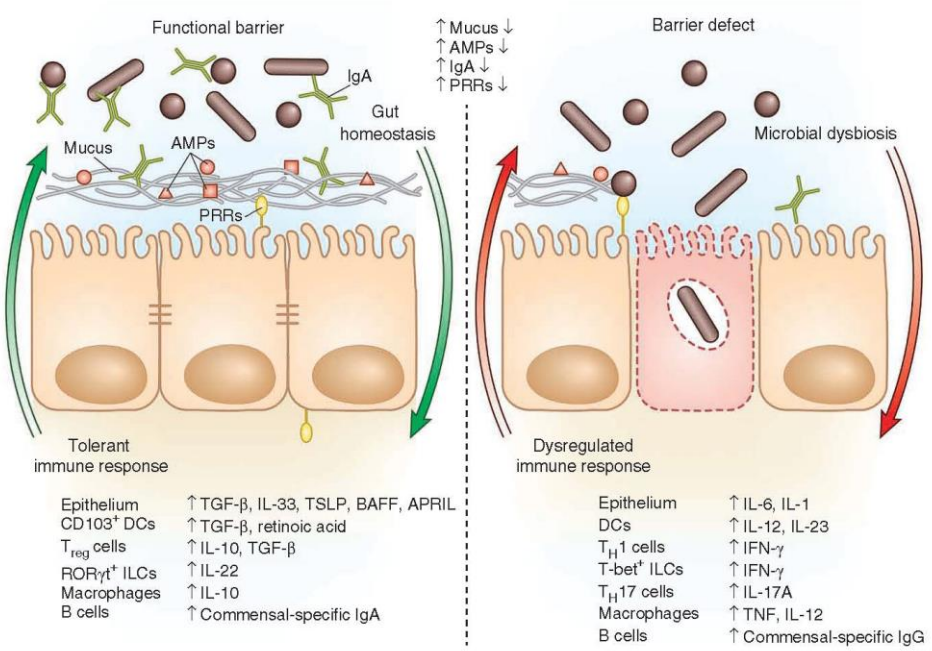
Gastrointestinal microbiota produces metabolites that prevent inflammation and maintain epithelial integrity

Microbiota can impact innate, adaptive, and regulatory immune systems.

- Microbial metabolites such as **short chain fatty acids** (SCFAs) impact gut epithelial integrity through coordinated regulation of tight junction proteins and modulation of immune mediators
- **Tryptophan metabolites** activate the immune system through binding to the aryl hydrocarbon receptor (AHR) and improve barrier function by promoting mucus production
- Microbe-mediated conversion of primary bile acids (BAs) to **secondary bile acids** enables modulation of anti-inflammatory pathways

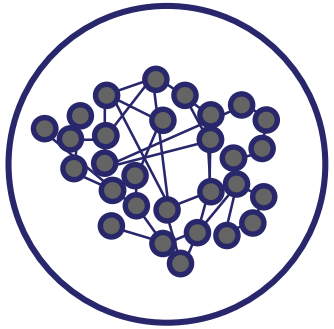


Brown et al. 2013. Nat. Immunology

Dysbiosis and loss of associated microbial functions are frequently seen in inflammatory GI diseases including ulcerative colitis.

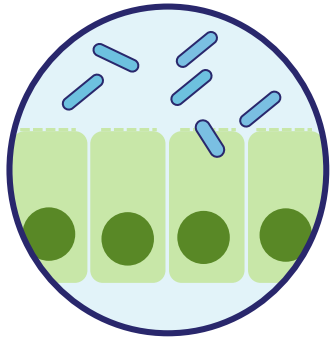
SER-287 is an investigational microbiome drug for ulcerative colitis

SER-287
Composition & Rationale for Drug Development



- Live biotherapeutic formulated for **oral dosing** composed of **firmicute spores associated with gut health**

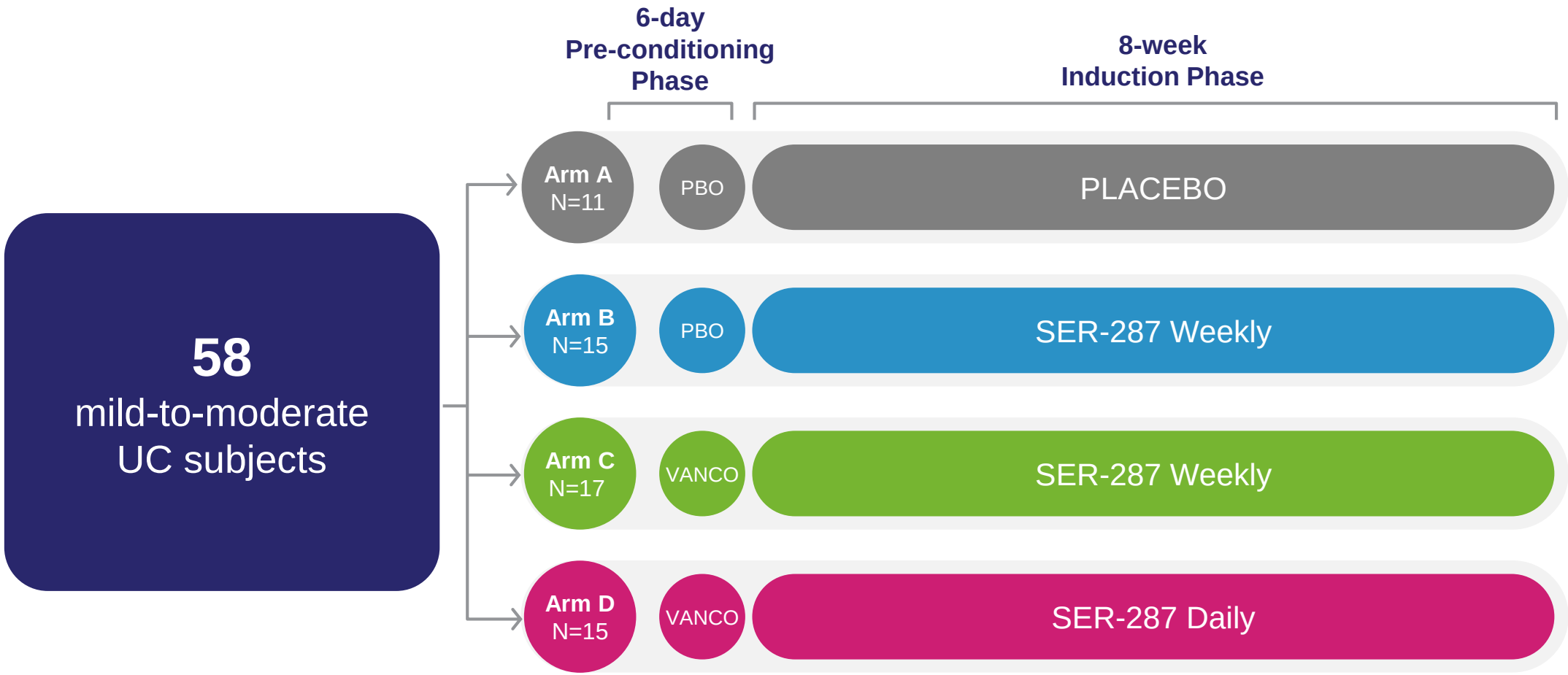
- Bacterial spores are resistant to gastric acid allowing easy formulation into capsules for **effective colonic delivery**



- Designed to to impact **multiple molecular networks key to gut barrier and immunomodulatory functions**

SERES-101 study design in patients with mild-moderate UC

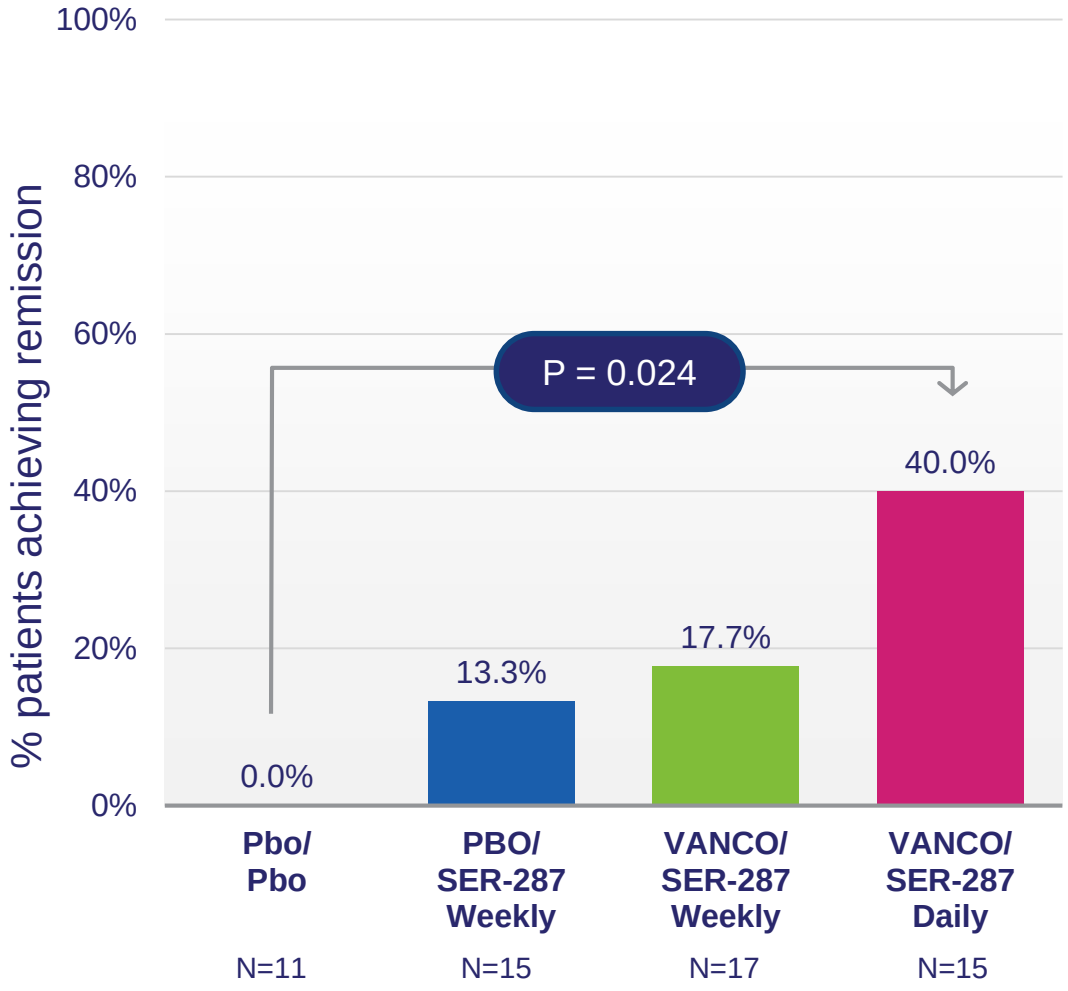
Phase 1b clinical trial



Total Modified Mayo Score (TMMS)
4 thru 10, Endscopic subscore ≥1

PBO=placebo; VANCO=vancomycin

Dose-dependent effect of SER-287 on clinical remission



Remission defined as...

- Total modified Mayo Score (TMMS) ≤2 *plus…*
- Endoscopic subscore (ESS) of 0/1

Safety profile:

- SER-287 arms had similar safety profile to placebo
- No serious drug-related adverse events were observed

ITT analysis: Subjects with missing data, or new additional UC medication during treatment period or who discontinued trial prior to day 48 = failure

Defining pharmacokinetics (PK) and pharmacodynamics (PD) of a microbiome therapeutic

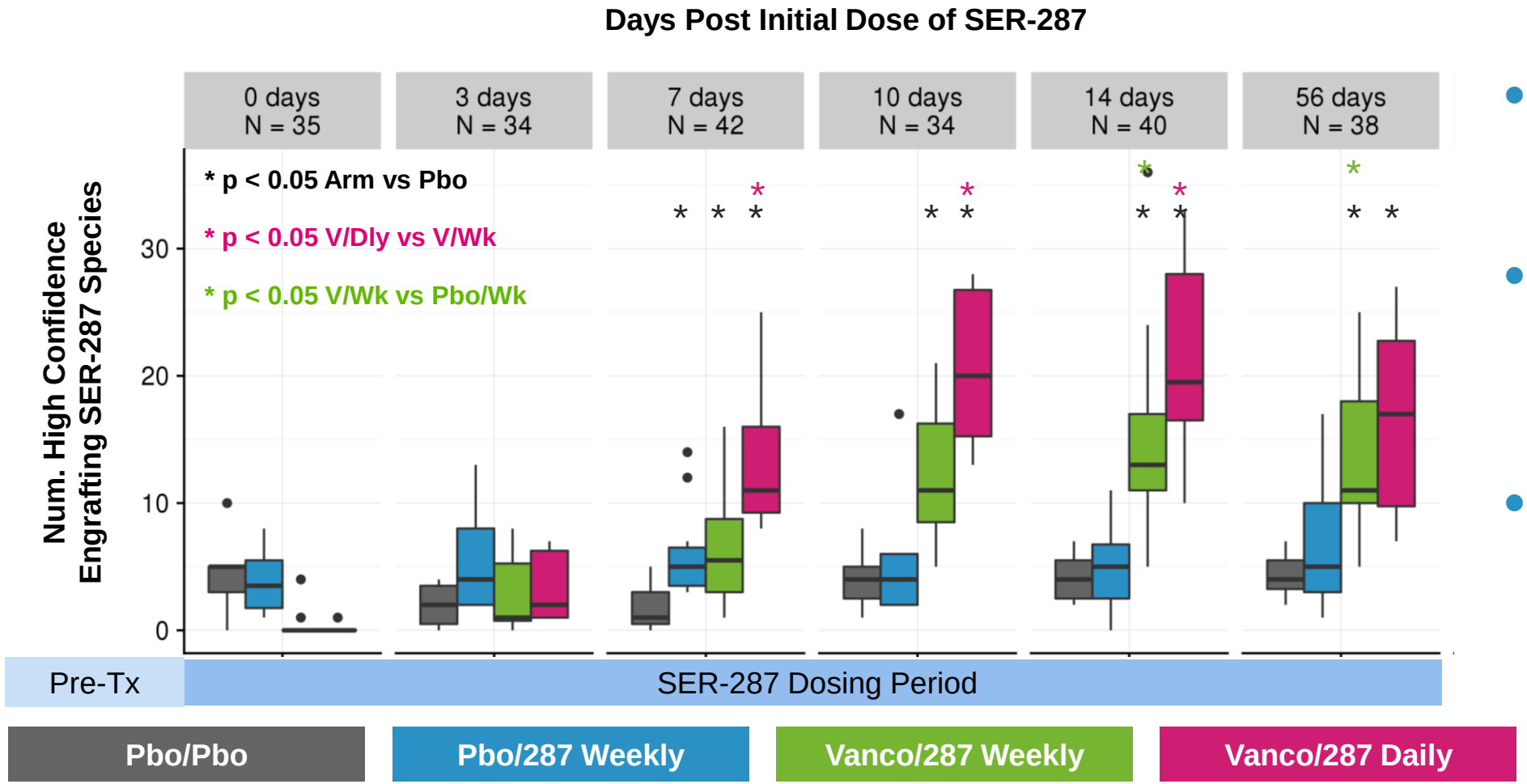
Pharmacokinetics (PK)

- Kinetics of product engraftment: the presence of spore-forming bacteria from the drug in subjects over time

Pharmacodynamics (PD)

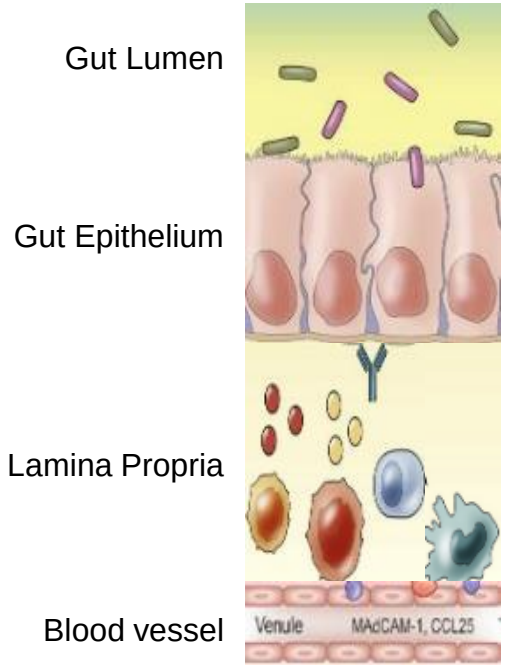
- Overall changes in the composition of the microbiome *(“Who’s There?”)*
- Functional alterations in microbial metabolites and host gene expression & biomarkers *(“What are they doing?”)*

SER-287 engraftment (PK) is dose-dependent and facilitated by vancomycin pre-conditioning



- Significant engraftment observed starting one week post-dosing
- Engraftment is significantly higher in arms with vancomycin pre-conditioning
- Engraftment in vancomycin arms is dose-dependent; significantly greater in daily dose

Metabolic pathways modulated by SER-287 can impact host inflammatory and immune state



Microbiome engraftment

↓

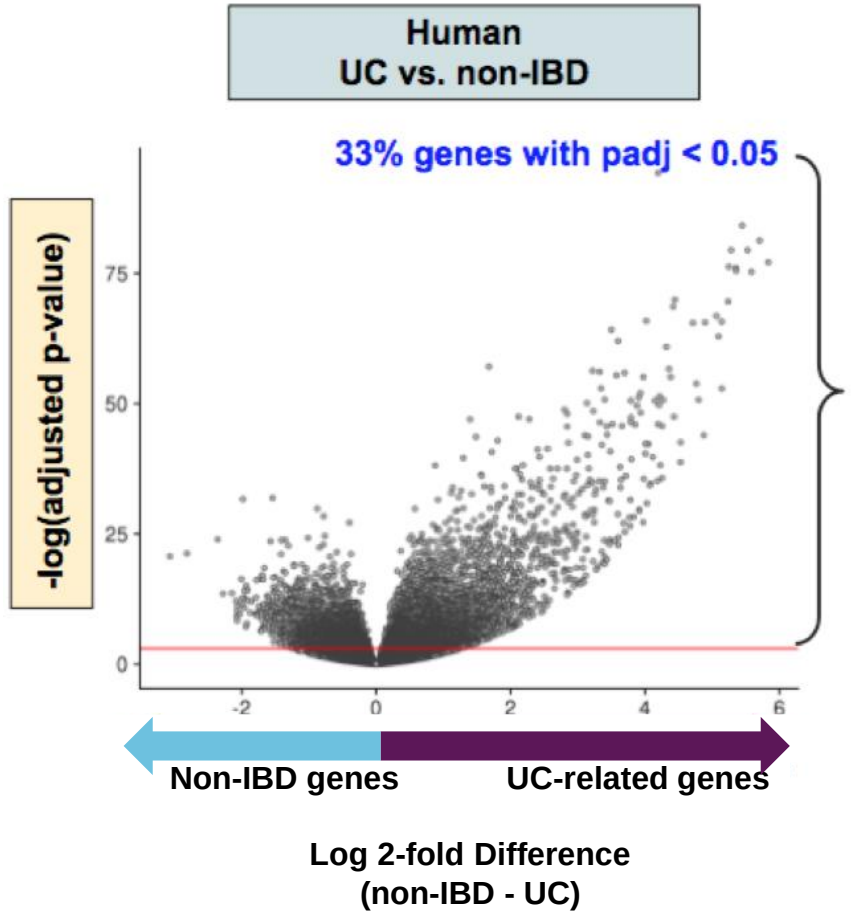
Microbe-mediated metabolic pathways

↓

Host transcription

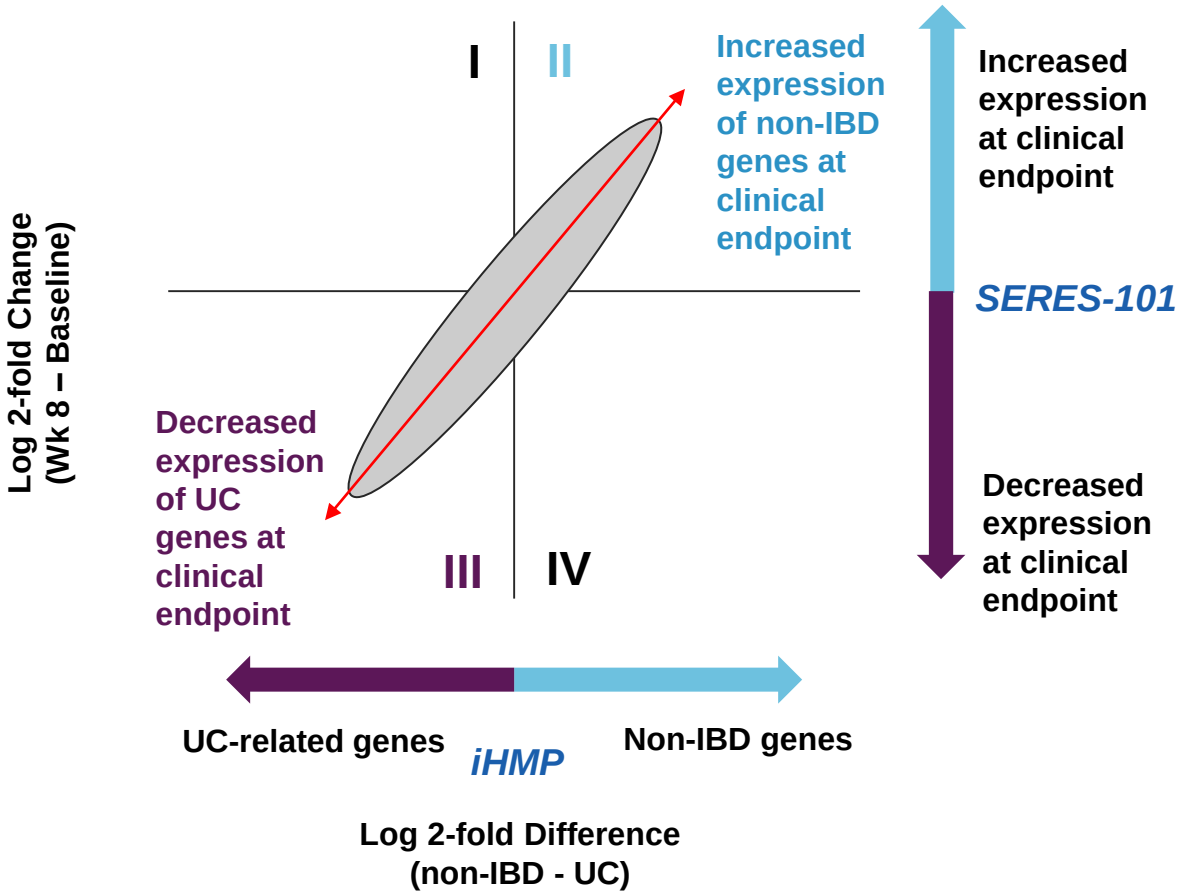
Establishing a reference dataset for host transcriptomic analysis (PD)

- Transcriptomics data from the **Integrative Human Microbiome Project (iHMP)** IBD Cohort (34 subjects with UC and 24 non-IBD control patients) were used to define human genes upregulated in ulcerative colitis vs non-IBD subjects
- Seres' analysis of iHMP transcriptomics data from rectal biopsies identified 8727 differentially expressed genes associated with UC
- These data provide an unbiased reference for comparison of changes from baseline to week 8 in all subjects in the SER-287 Phase 1b study



** Raw data available at https://ibdmdb.org/tunnel/public/summary.html*

Transcriptomic response in SER-287 subjects compared to reference iHMP data

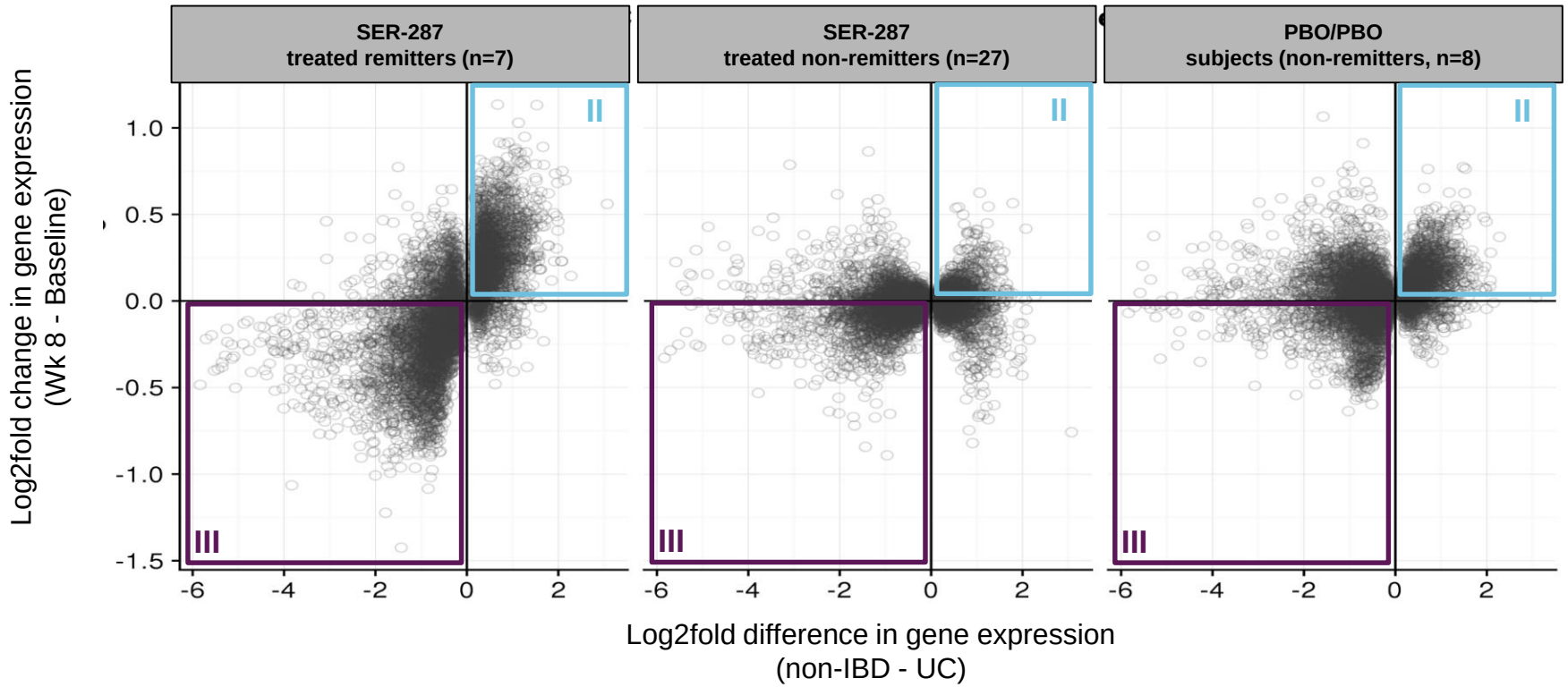


- Each gene is arrayed on the X-axis according to it's differential expression in the iHMP reference data
- The Y-axis displays log 2-fold change in the SER-287 data (Week 8 - baseline)
- 6527 of the 8727 genes from the iHMP dataset are detected in SER-287 data

Hypothesis: gene expression of remitting patients will skew toward Quadrants II and III

Clinical remission is associated with shifts in UC and non-IBD gene expression

Shift in expression of disease-related genes
among SER-287 treated remitters, not observed in non-remitters

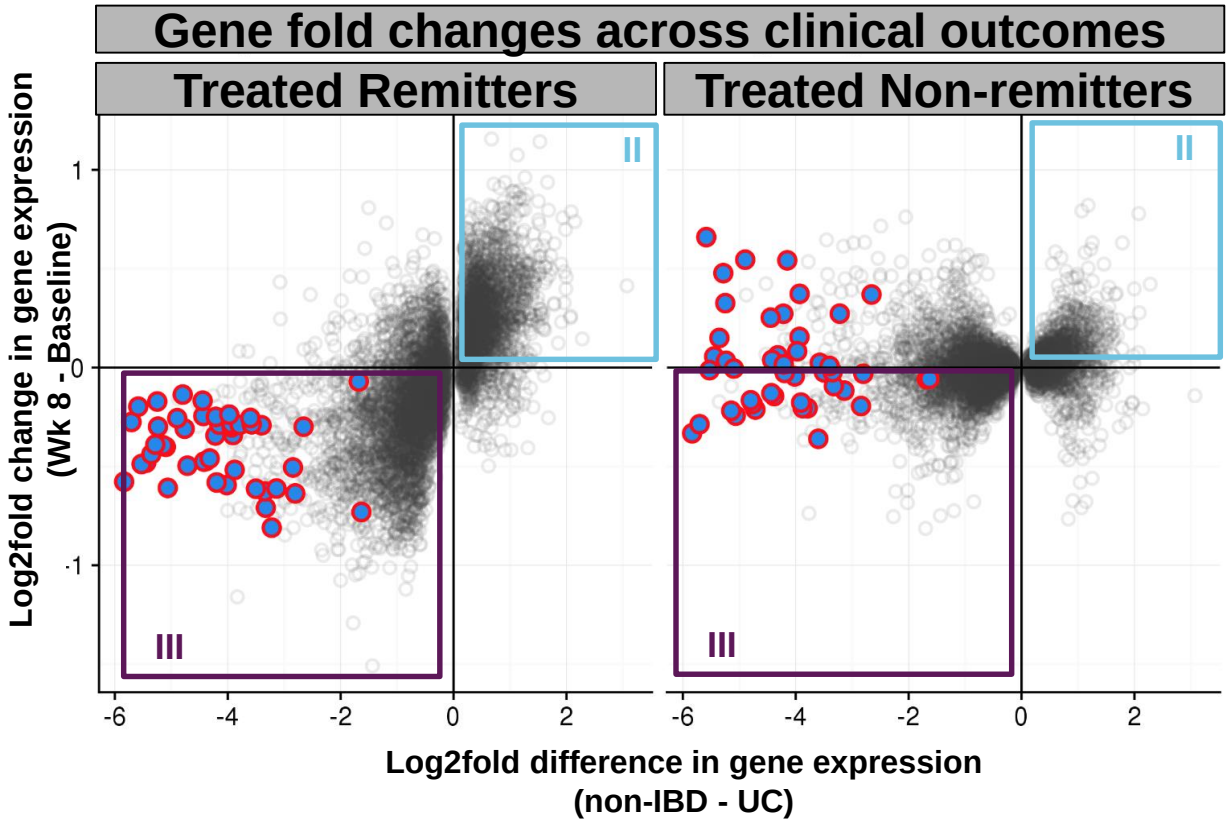


II - Increased expression of non-IBD genes at Wk 8

III - Decreased expression of IBD genes at Wk 8

SERES-101 remitters have decreased gene expression in pathways associated with inflammatory and immune responses

We examined the top 40 differentially expressed genes in iHMP data set relevant to UC disease activity



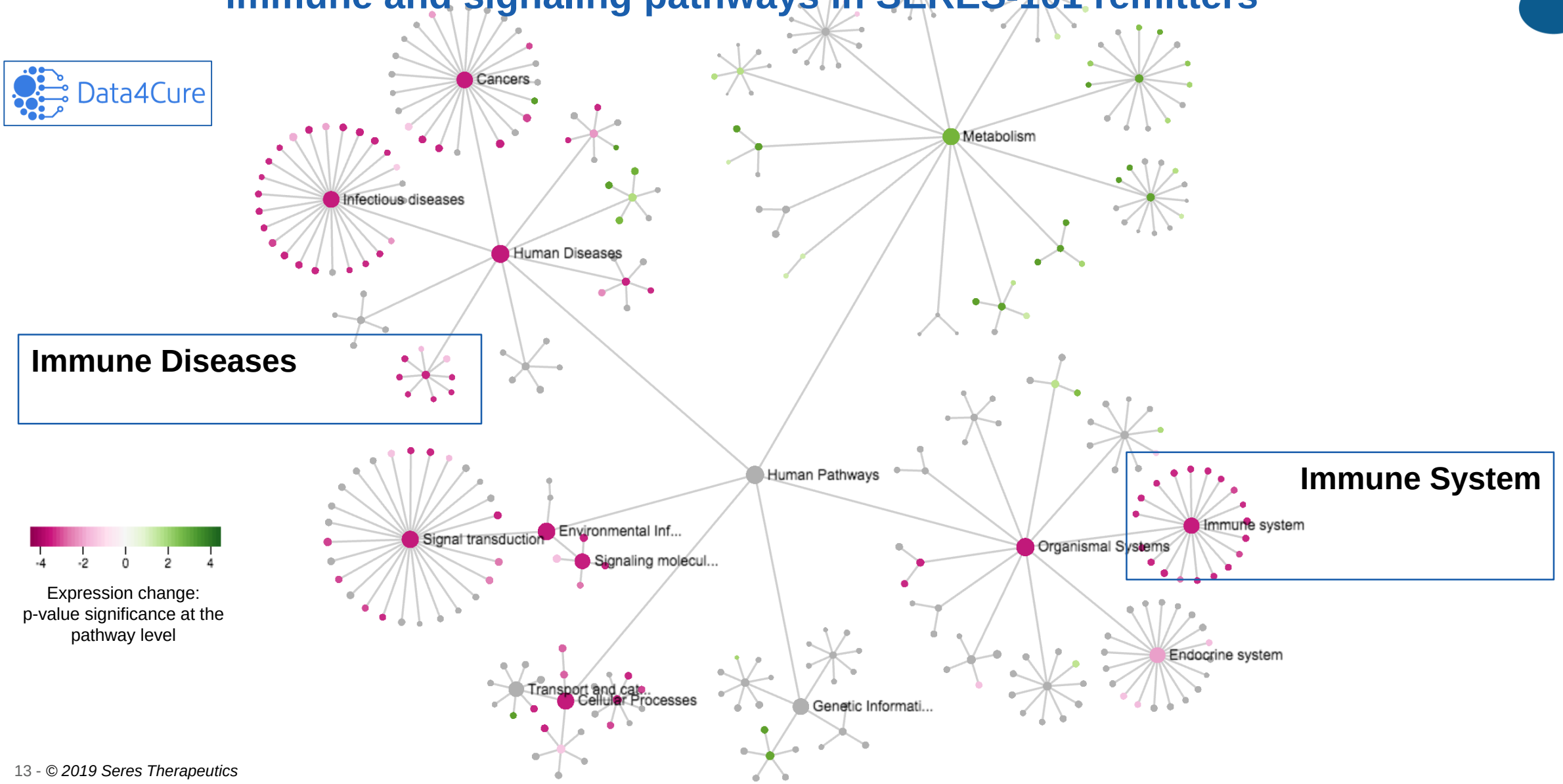
Using the iHMP top 40 gene set, we observe expression decreases in **cytokines, cytokine receptors and immune activators consistent with disease improvement**

Other genes with significant expression changes include:

- **mucin production and barrier integrity genes**
- **pattern recognition receptors (TLRs and NLRs)**
- **matrix metalloproteinases and antibacterial defense genes**

II - Increased expression of non-IBD genes at Wk 8
III - Decreased expression of IBD genes at Wk 8

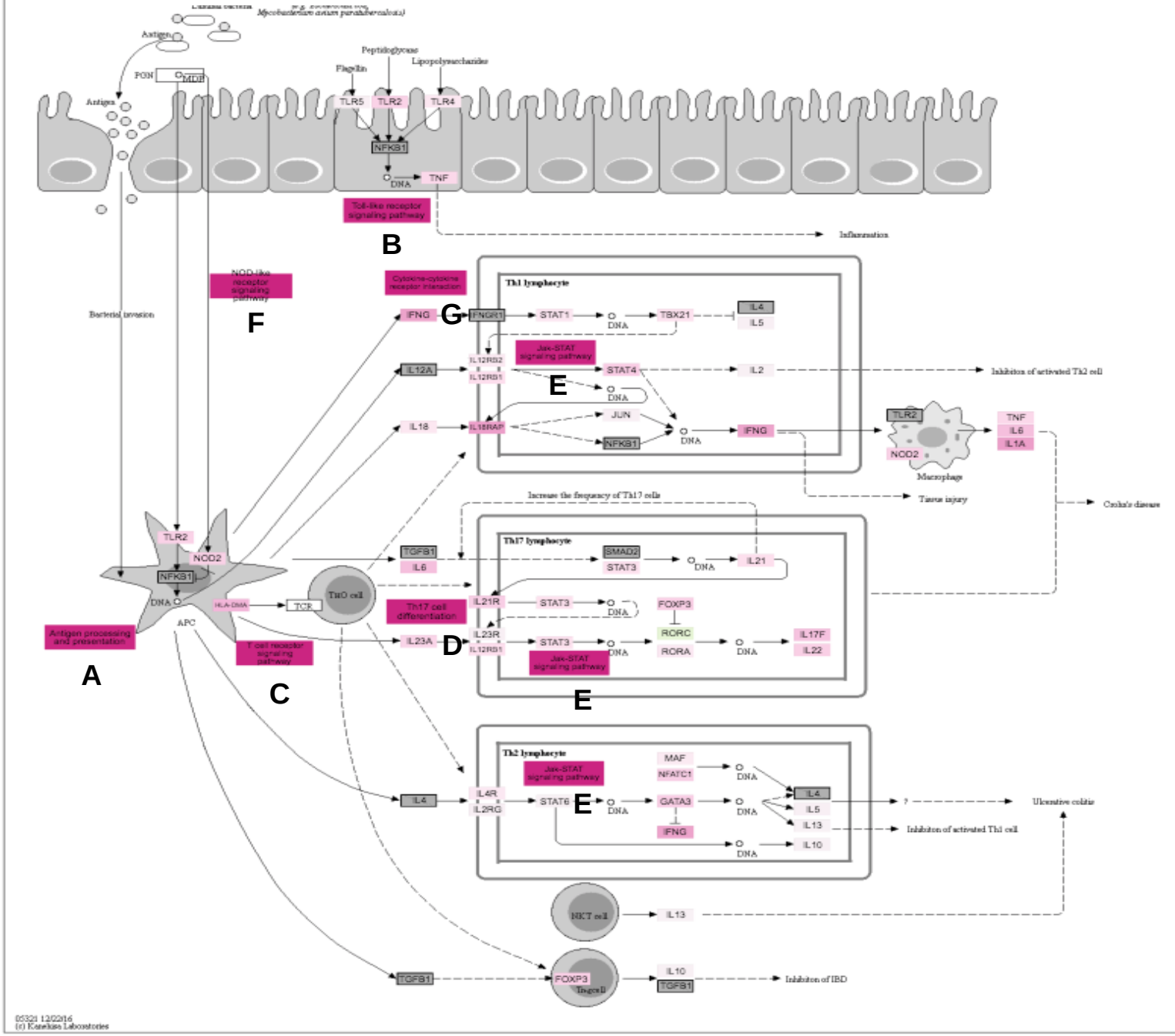
Global KEGG analysis shows significant shifts in multiple immune and signaling pathways in SERES-101 remitters



Pathways implicated in IBD are heavily down-regulated in SERES-101 remitters

	Label	Expression change
A	Antigen processing and presentation	-3.4544
B	Toll-like receptor signaling pathway	-3.466
C	T cell receptor signaling pathway	-3.4778
D	Th17 cell differentiation	-3.4803
E	Jak-STAT signaling pathway	-3.4856
F	NOD-like receptor signaling pathway	-3.4902
G	Cytokine-cytokine receptor interaction	-3.5136

Inflammatory Bowel Disease (KEGG)



Conclusion

- SER-287-treated remitters exhibited widespread gene expression changes compared to baseline
- These changes are characterized by decreased expression of UC-related genes and increased expression of non-IBD genes, using the integrative Human Microbiome Project data as a reference
- The involved genes encompass a range of pathways associated with inflammatory and immune responses as well as epithelial barrier function in UC
- The changes in gene expression are consistent with SER-287, a novel microbiome therapeutic, modulating multiple pathways relevant to disease activity in UC, and provide a basis for understanding its mechanism of action

Acknowledgements

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Patients and Physicians in SER-287 Trials

Matthew Henn & Seres R&D Team

Kevin Horgan & Seres Clinical Team

John Aunins & Seres CMC Team