SERES™ THERAPEUTICS

Ulcerative Colitis Investor Event

June 21, 2021

Forward Looking Statements

Some of the statements in this presentation constitute “forward looking statements” under the Private Securities Litigation Reform Act of 1995, including, but not limited to, our development plans, the promise and potential impact of any of our microbiome therapeutics, the ability of our clinical trials to support approval, the timing and results of clinical studies, the timing and ultimate results of the SER-109 safety data, the size of the market for SER-109, the sufficiency of cash to fund operations, and the potential benefits of Seres’ collaborations. Such statements are subject to important factors, risks and uncertainties, such as those discussed under the caption "Risk Factors" in the Company’s Quarterly Report on Form 10-Q filed on May 4, 2021, and its other filings with the SEC, that may cause actual results to differ materially from those expressed or implied by such forward looking statements. Any forward-looking statements included herein represent our views as of today only. We may update these statements, but we disclaim any obligation to do so.

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Agenda and Speakers

Introductory Remarks

Eric Shaff
President and Chief Executive Officer, Seres Therapeutics

Clinical burden of Ulcerative colitis

Stephen Hanauer, M.D.
Clifford Joseph Barborka Professor, Professor of Medicine, Northwestern University Feinberg School of Medicine

SER-287 / SER-301 Clinical development

Lisa von Moltke, M.D.
Chief Medical Officer, Seres Therapeutics

Microbiome in IBD and SER-287 / SER-301 MoA & pharmacology

Matthew Henn, Ph.D.
Chief Scientific Officer, Seres Therapeutics

Q&A

Speakers

David Arkowitz
Chief Financial Officer and Head of Business Development, Seres Therapeutics

David Ege, Ph.D.
Chief Technology Officer, Seres Therapeutics

Terri Young, Ph.D.
Chief Commercial and Strategy Officer, Seres Therapeutics

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Key Takeaways for Today's Event

- Seres is a leader in the development of microbiome therapeutics, leveraging prior clinical success and unique core drug discovery and CMC capabilities
- UC is an attractive target for microbiome therapeutics; area of strategic focus
- Company advancing both SER-287 and SER-301 as differentiated programs for UC
- Data rich SER-287 Phase 2b read-out pending in mild-to-moderate patient population – anticipate clinical data in mid-2021, microbiome pharmacological data in H2 2021

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Established Proof of Concept – SER-109 Phase 3 Results in Recurrent *C. difficile* Infection

PRIMARY EFFICACY ENDPOINT RESULTS

Time point	SER-109 (N =89) n (%) of recurrences	Placebo (N =93) n (%) of recurrences	RR (95%CI)	p-Value (p1/p2)
Week 8	**11** (12.4)	**37** (39.8)	**0.32** (0.18-0.58)	**<0.001 / <0.001**

- Highly statistically significant treatment effect compared to placebo at 8 weeks
- Absolute reduction in risk of 27%
- Results were statistically significant in both age-stratified subgroups: 18-64 years old, or 65+
- Sustained patient benefit maintained at 24 weeks

Approximately 88% sustained clinical response rate

(percentage of patients who remain free of CDI at 8 weeks)

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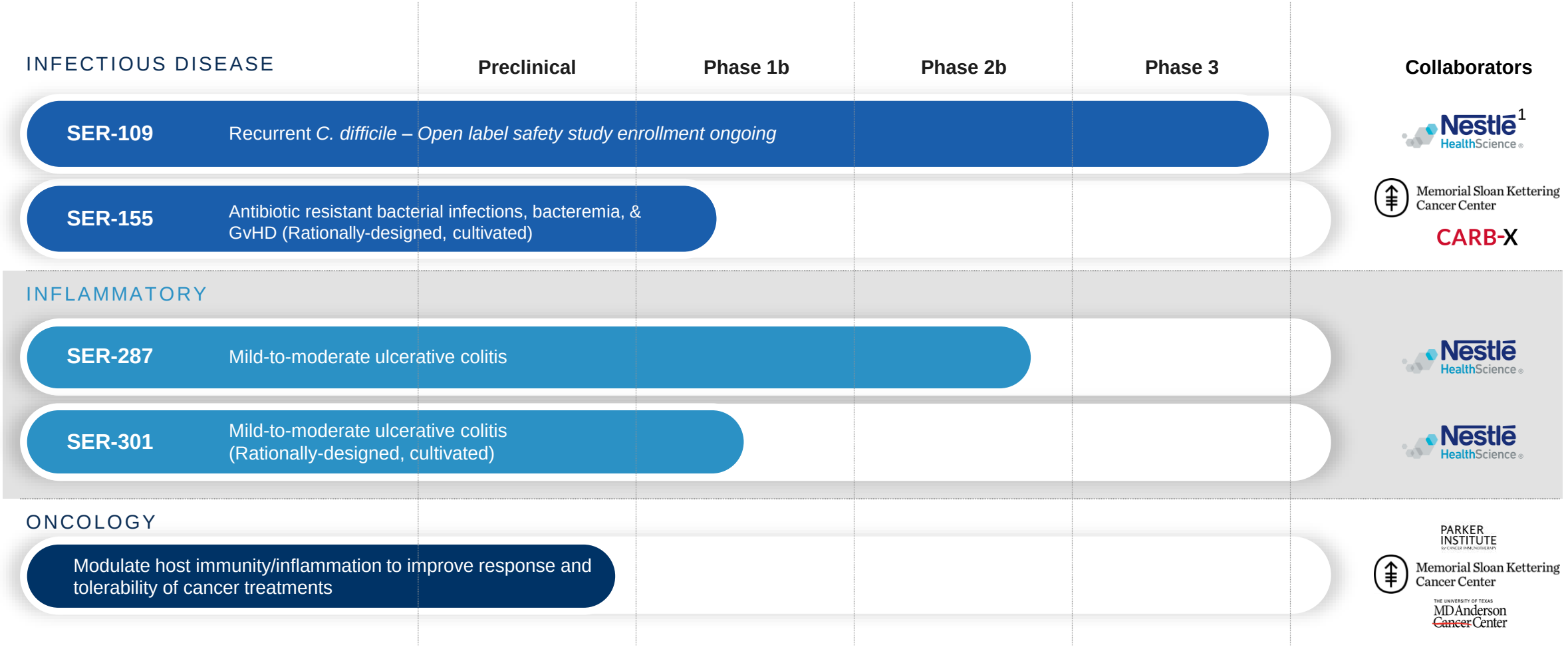
Ulcerative Colitis Is an Area of Strategic Focus



[1] Collaboration with Nestlé Health Science, announced Jan. 11, 2016, regarding *C. difficile* and IBD programs for markets outside of North America

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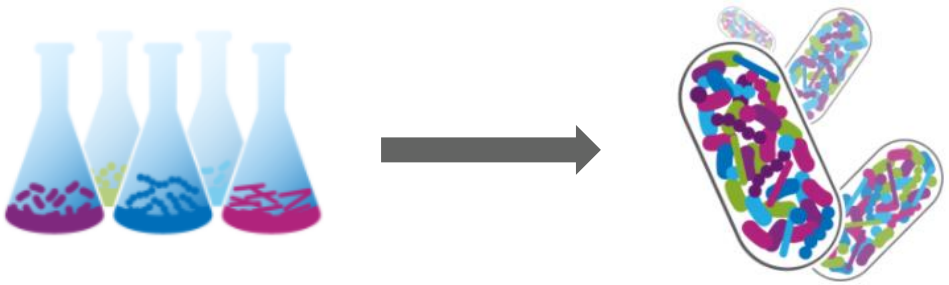
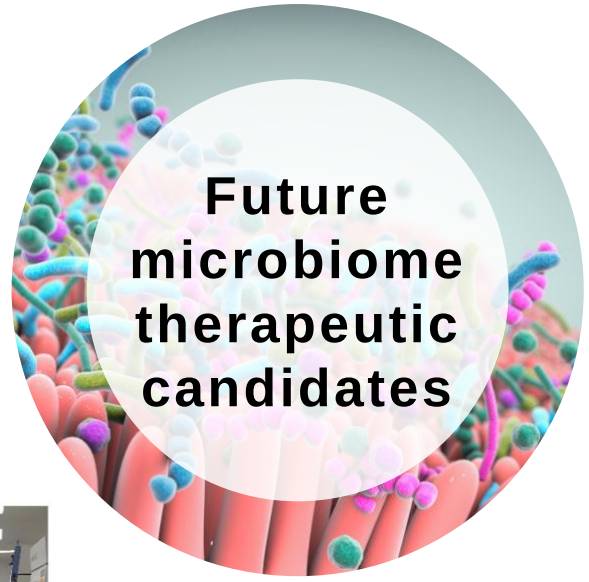
Differentiated Microbiome Therapeutic Core Capabilities



Proprietary drug discovery platform



In-house GMP manufacturing and quality control

Cell banking & inoculum

Drug substance

Drug product

Quality control

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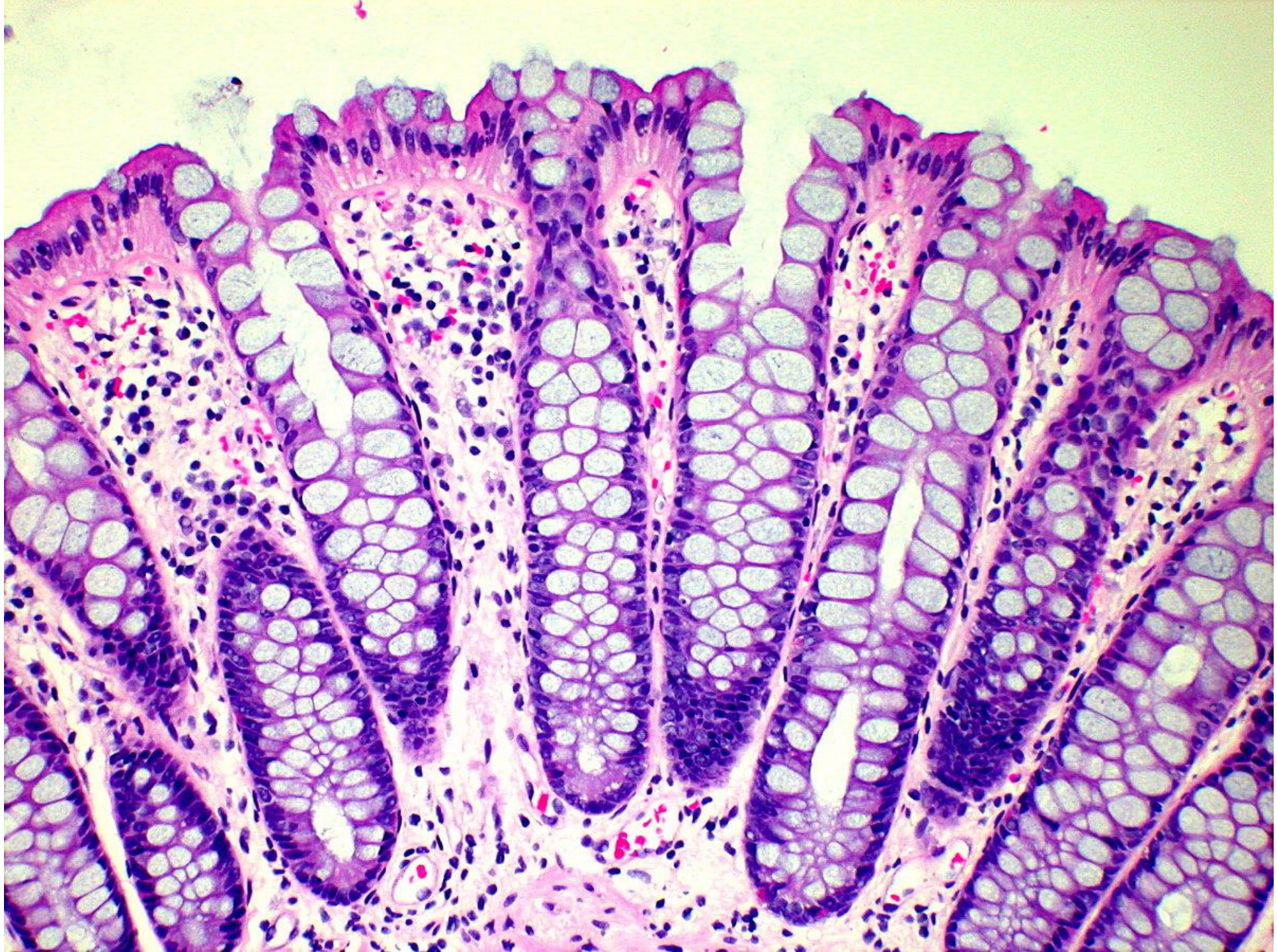
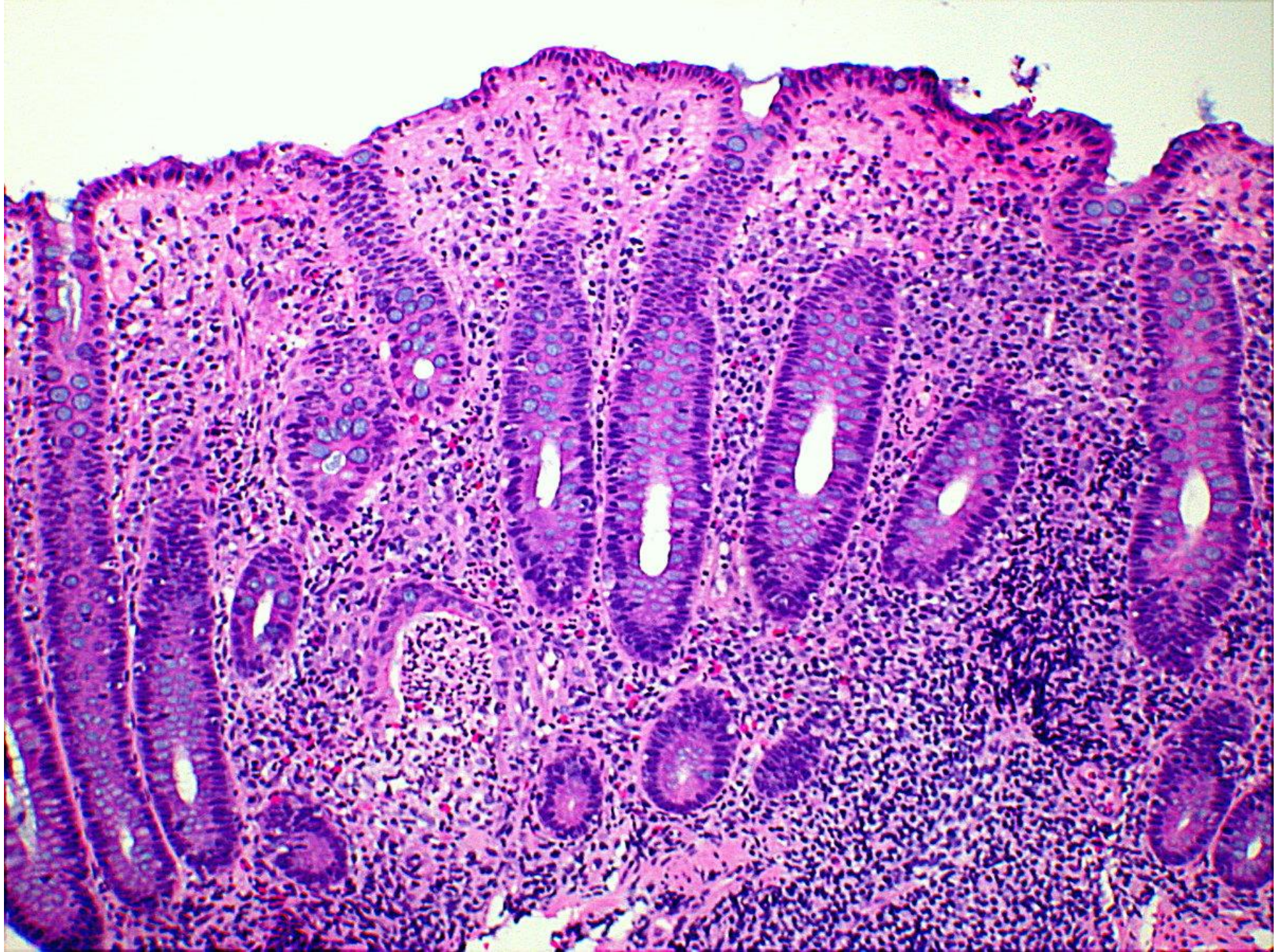
Ulcerative Colitis: Clinical Overview

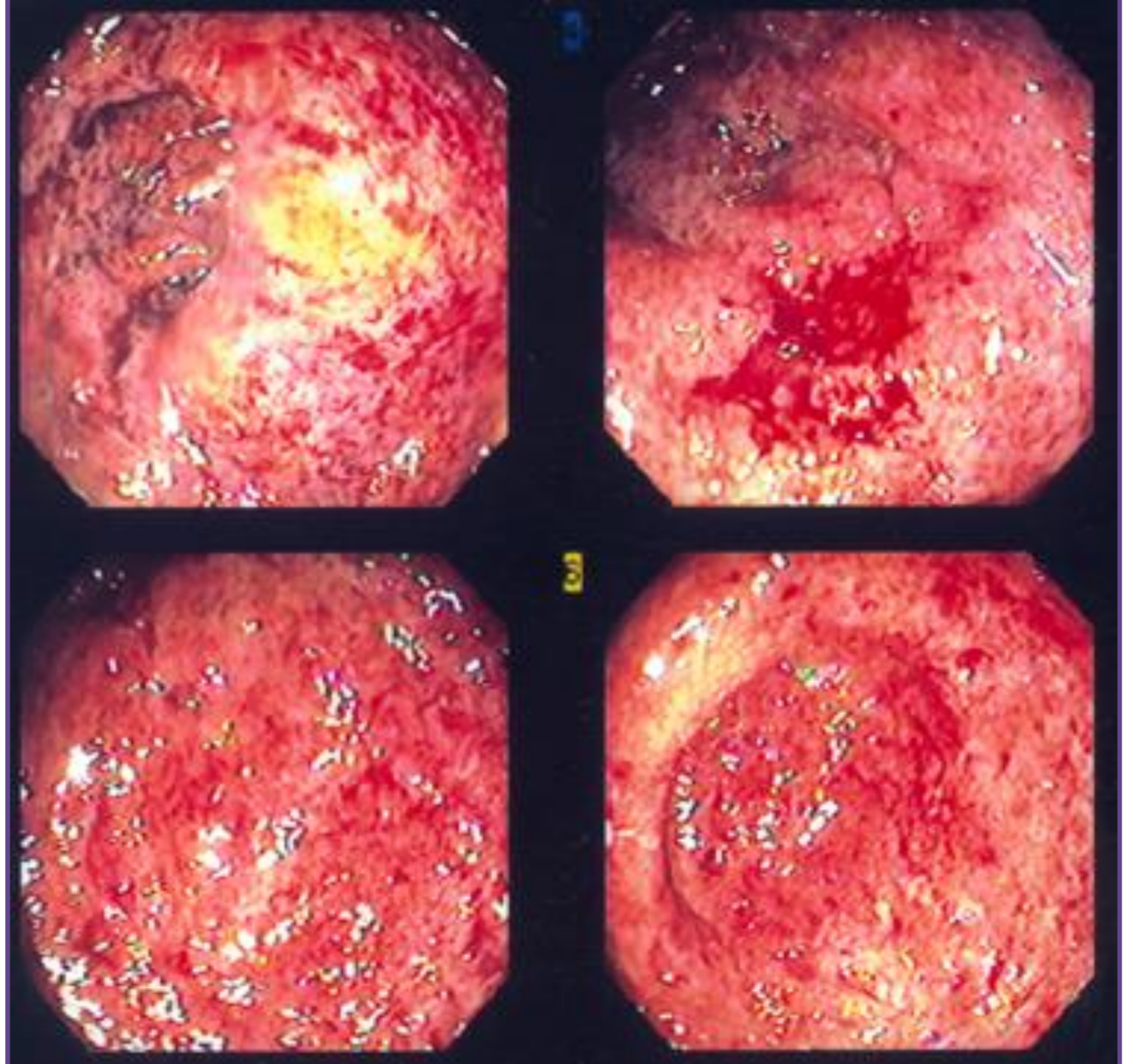
Stephen B. Hanauer, MD
Clifford Joseph Barborka Professor of Medicine
Northwestern University Feinberg School of Medicine

Ulcerative Colitis Discussion Topics

- UC disease pathology
- Clinical presentation
- Epidemiology
- Current treatment options
- Review of late state development candidates
- New therapeutic needs
- Potential for combination therapy
- Potential clinical use of SER-287

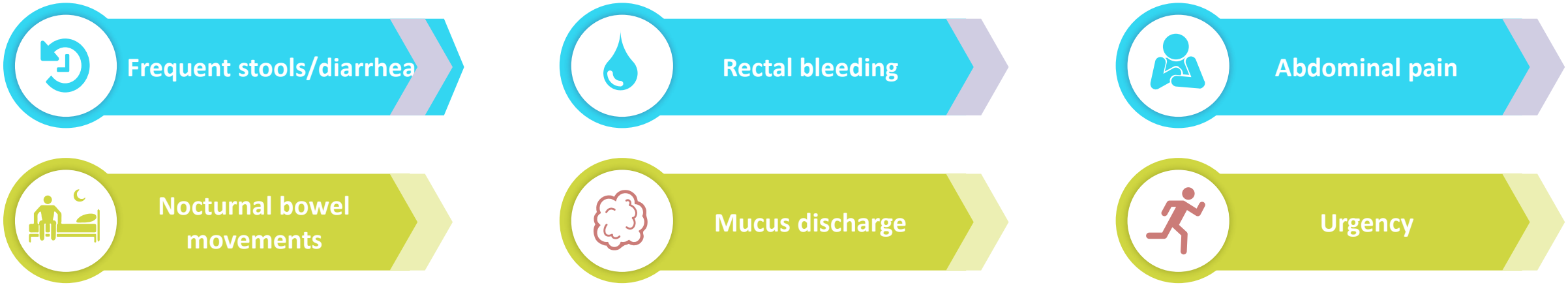






UC is a chronic condition of the colon and rectum with periods of remission and flares

Typical presentation of UC symptoms:



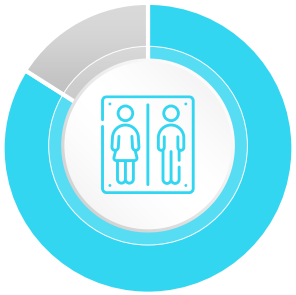
5 and 10-year cumulative risk of colectomy

10%–15%

1. Feuerstein JD et al. *Gastroenterology*. 2020;158:1450-1461. **2.** Feuerstein JD et al. *Mayo Clin Proc*. 2019;94:1357-1373. **3.** Rubin DT et al. *Am J Gastroenterol*. 2019;114:384-413

Symptoms directly impact the daily lives of patients with UC

In a 2007 online cross-sectional survey designed to collect information on the attitudes and perceptions of patients (N=451) with UC about living with their disease:



84%

said that frequent trips to the bathroom have become an expected part of life.

60%

feel like UC has ruined important moments.

73%

said not feeling well from UC has become an expected part of life.

84%

said they worry about the long-term health effects of having UC.

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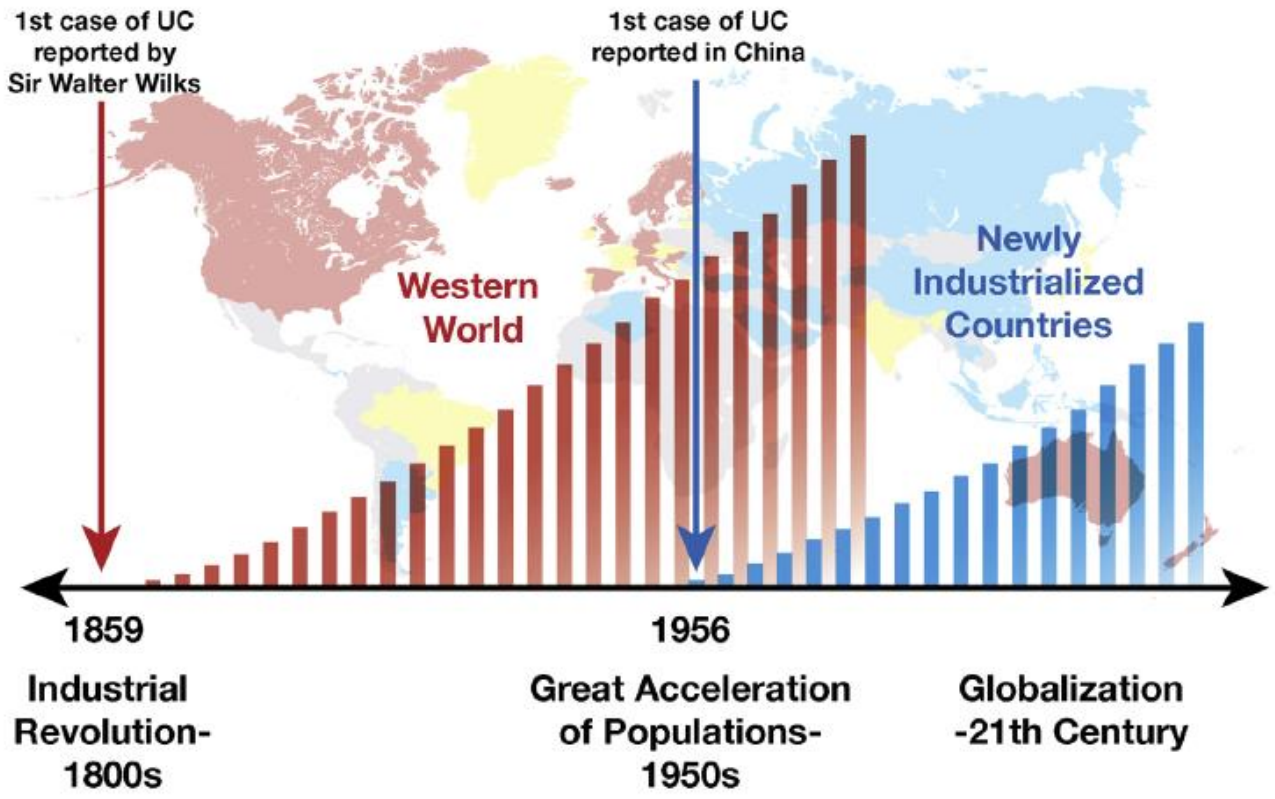
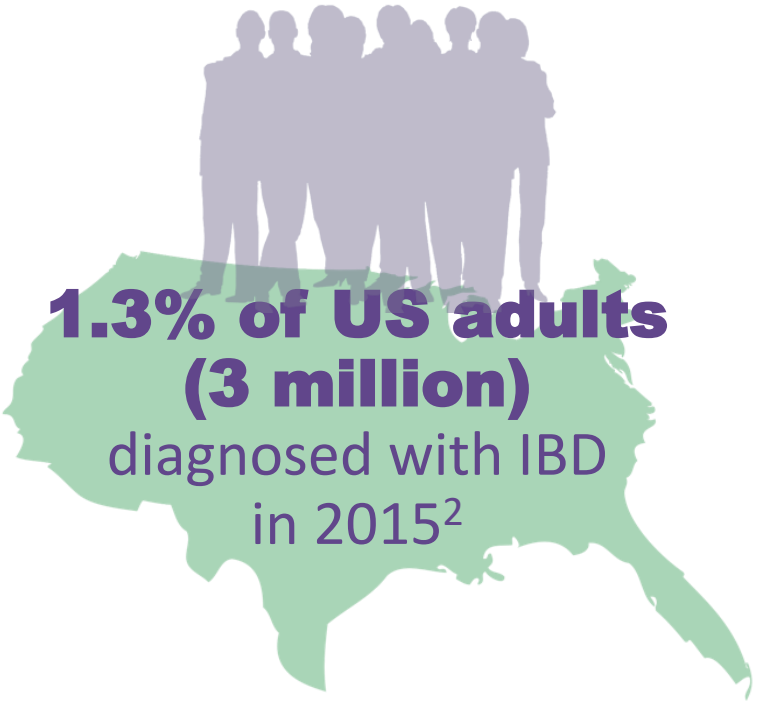
Rubin DT et al. *Inflamm Bowel Dis*. 2009;15:581-588.

IBD prevalence has been increasing in industrialized countries since the 19th century

Increasing trend of IBD in industrialized countries[1]



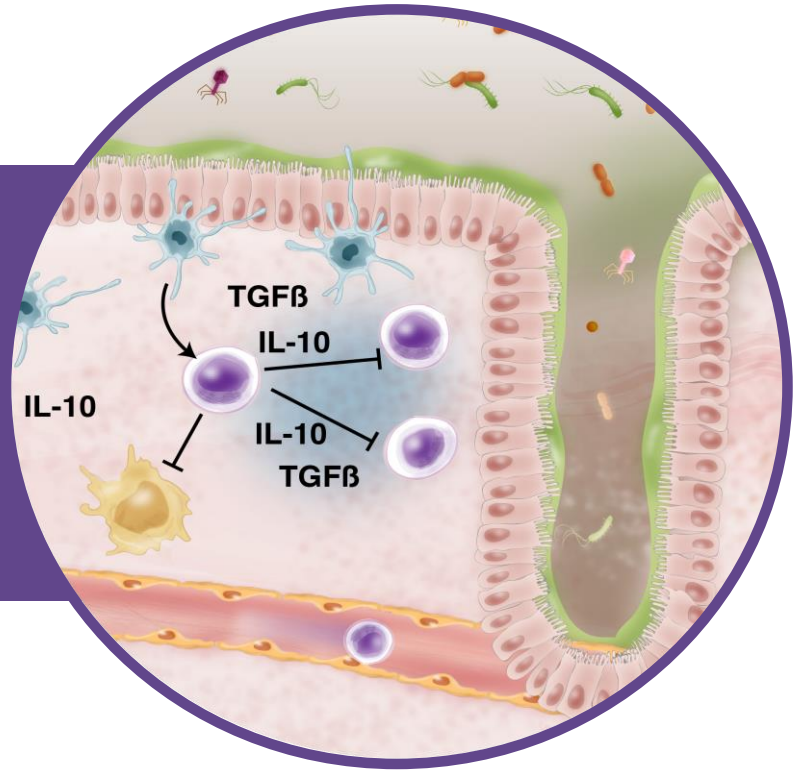


1. Kaplan GG, Ng SC. *Gastroenterology*. 2017;152:313-321. **2.** CDC. Accessed at https://www.cdc.gov/ibd/data-statistics.htm August 3, 2018.

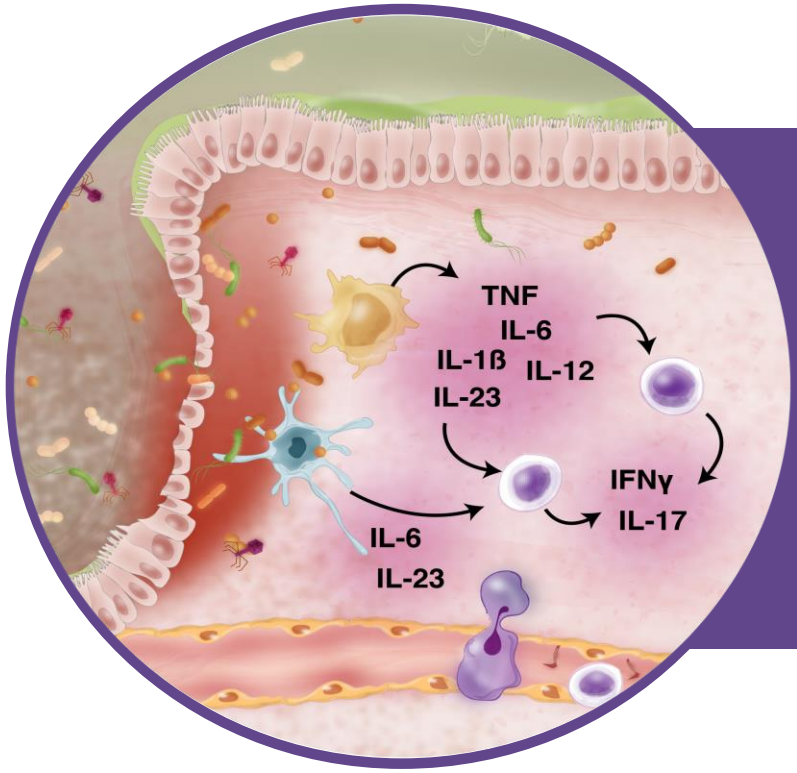
What causes IBD?

Normal

- Normal resident microbiota
- Immune tolerance
- Mucosal homeostasis



IBD



- Dysbiosis/ bacterial invasion
- Activated inflammatory cascades
- Mucosal ulceration

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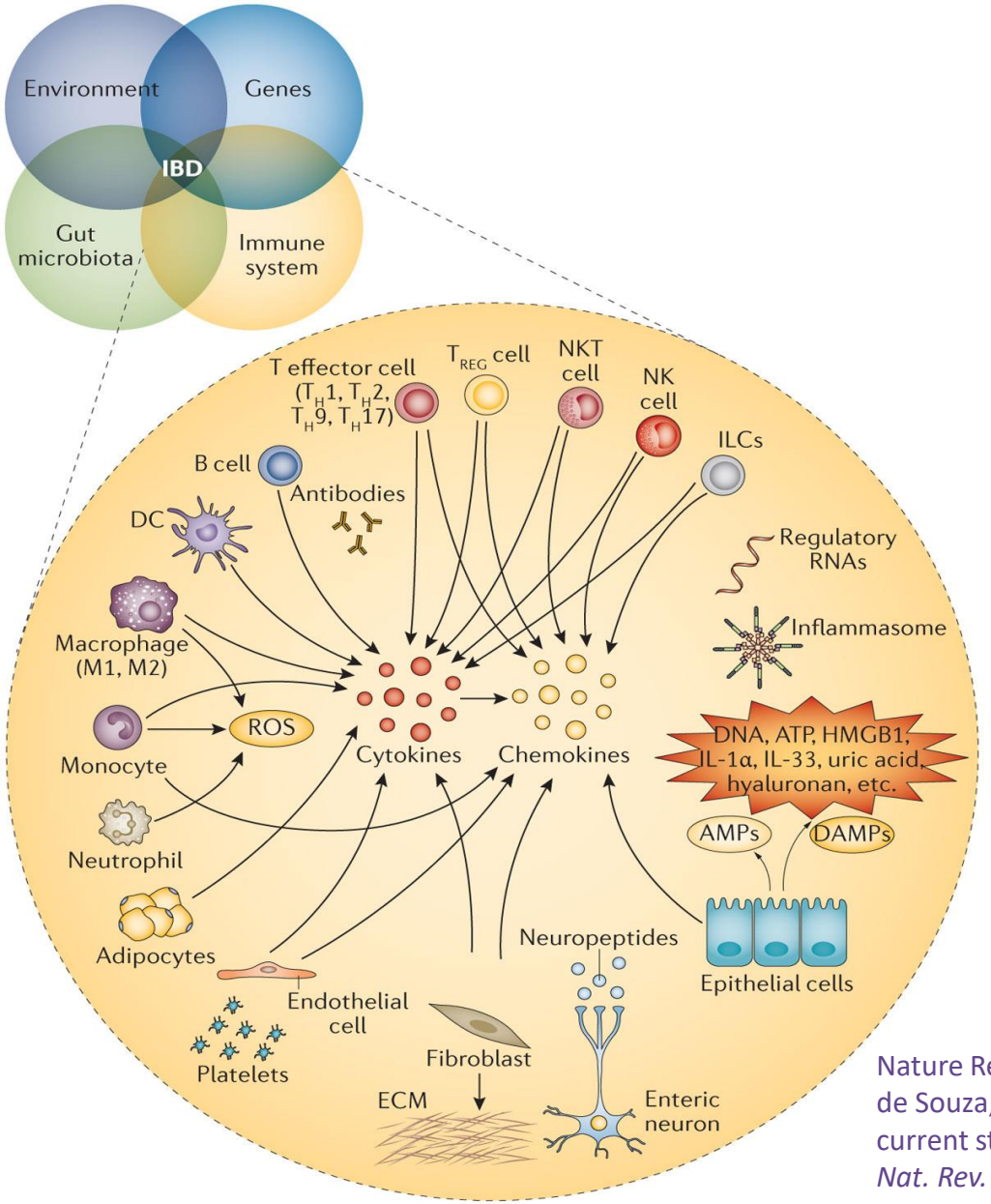
1. Coskun M et al. *Trends Pharmacol Sci*. 2017;38(2):127-142. **2.** Kaplan GG, Ng SC. *Gastroenterology*. 2017;152:313-321. **3**. Danese S et al. *Nat Rev Gastroenterol Hepatol*. 2015;12:537- 545.

Intricate universe of immune and nonimmune components involved in IBD Immunopathogenesis



IBD is complex

Nature Reviews | Gastroenterology & Hepatology
de Souza, H. S. P. & Fiocchi, C. (2015) Immunopathogenesis of IBD: current state of the art
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2016.186

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IBD is a summation of events culminating in intestinal inflammation

Genetic polymorphisms

Genetic modifications

Intestinal inflammation

Diet

Antibiotics

Mucosal disruption (NSAIDs)

Pathogens

Stressors (stress, smoking)

Environmental factors

Colonization with intestinal flora (mother / diet)

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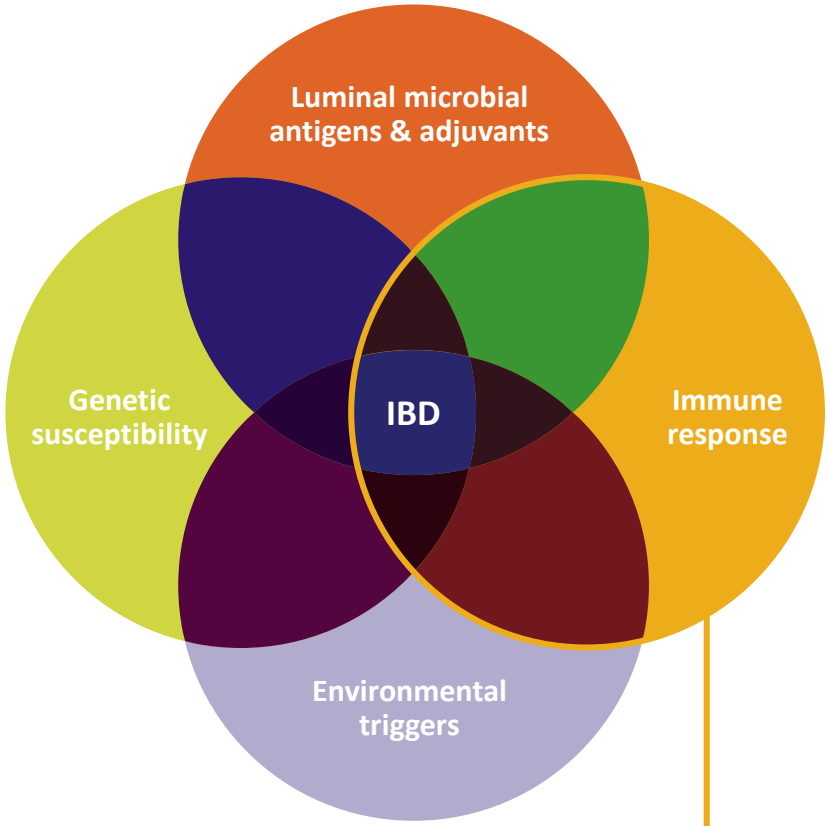
Current management of UC is directed towards host immunosuppression



Rationale for targeting immune response

- UC pathogenesis is thought to arise from disruption of immune tolerance to the gut microbiota in a genetically susceptible host

Although several new drug discoveries have been made…

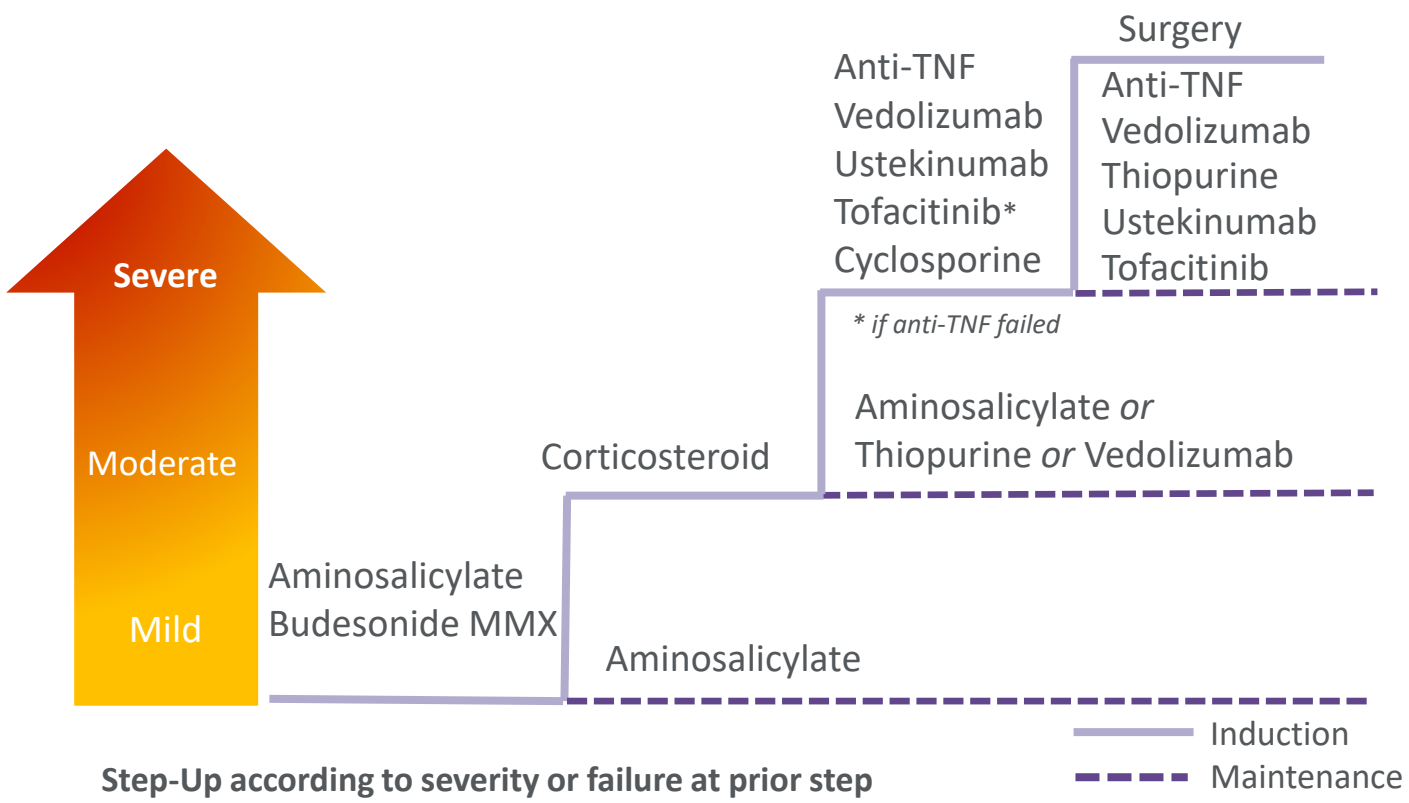
- Off-target effects observed (e.g., infections, malignancies, lymphoma)
- Modest rates of disease remission achieved
- Often require parenteral administration

Treatment strategy for ulcerative colitis

The AGA suggests early use of biologic agents with or without immunomodulator therapy, [or tofacitinib], rather than gradual step up after failure of 5-aminosalicylates. (*Conditional recommendation, very low quality evidence*)[1]

High risk for colectomy[2]
Extensive colitis
Deep ulcer
EIM
Recurrent steroids

Low risk for colectomy[2]
Limited extent
Mild colitis



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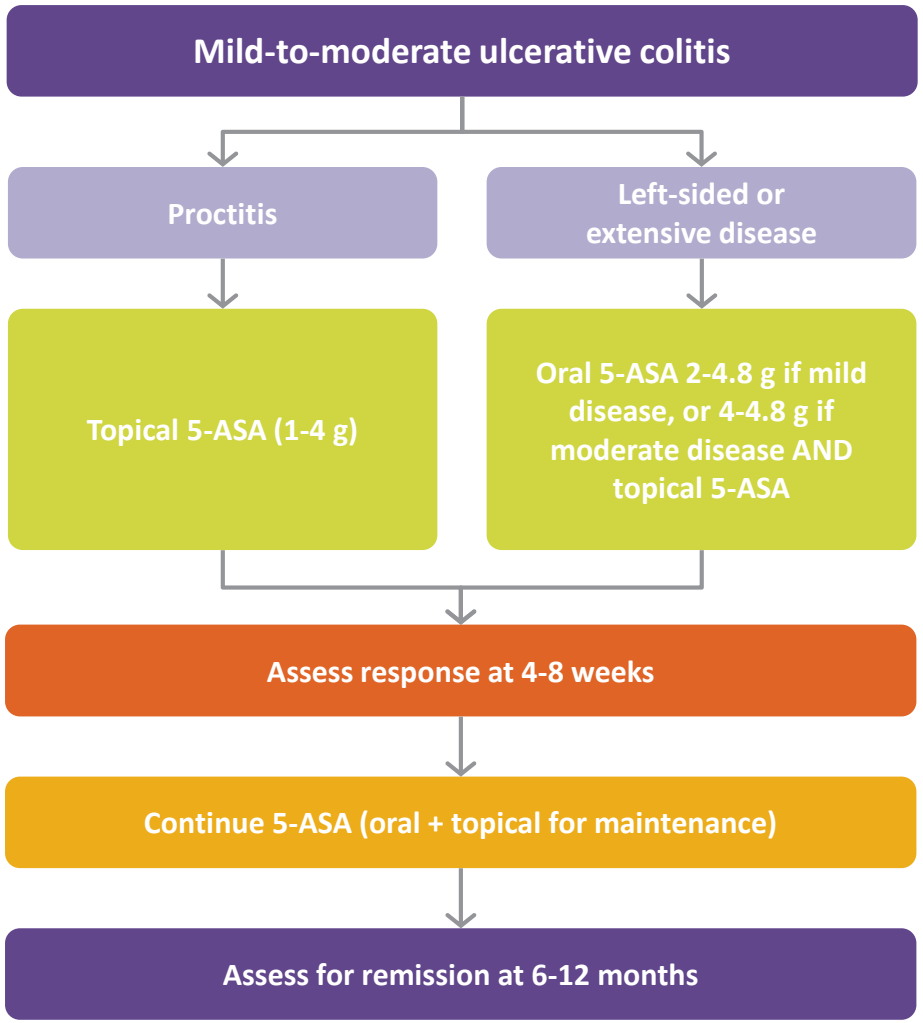
1. Feuerestein JD et al. *Gastroenterology*. 2020;158:1450-1461. 2. Dassopoulos T et al. *Gastroenterology*. 2015;149:238-245. (Adapted from Hanauer SB)

Consensus guide algorithm for the management of mild-to-moderate UC



"Step Up" Approach

- One drug class is introduced at a time to minimize drug toxicities
- This type of approach is a **reactive therapeutic strategy** responding to failure of treatment
- 5-ASAs, which are generally well-tolerated, are used for initial induction

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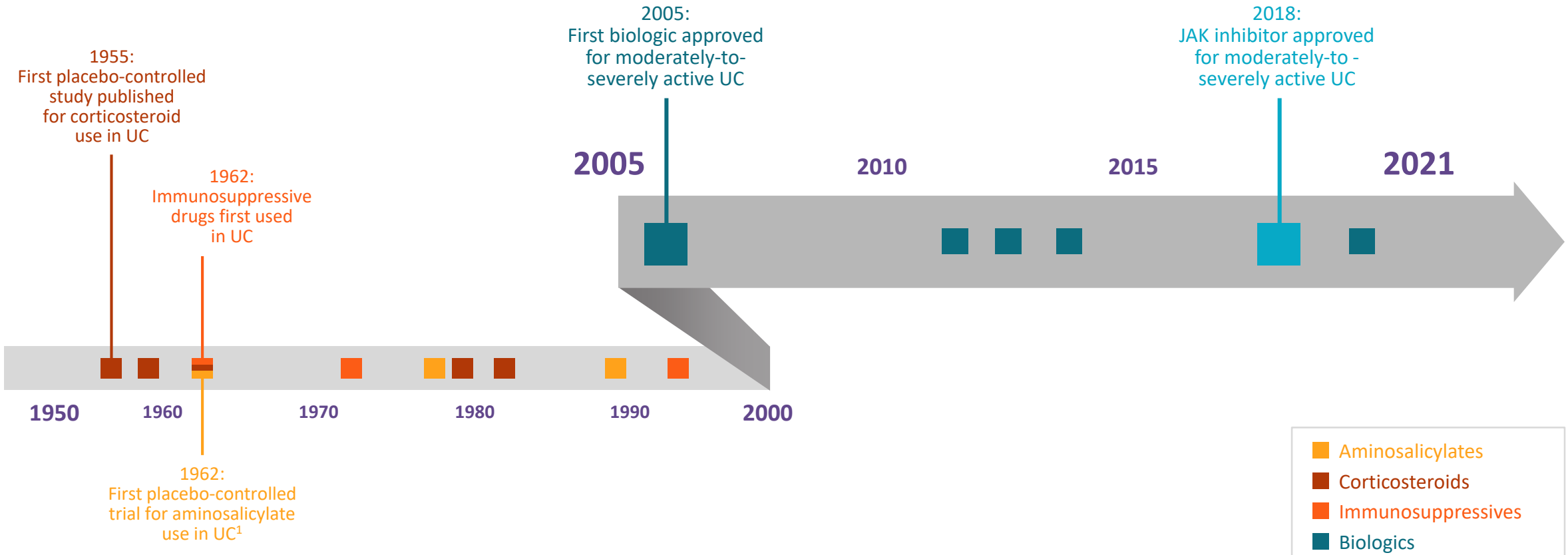
UC treatment options have been studied for more than 60 years, with more advancements since 2005



5-ASAs and immunomodulators are options for many patients with UC

	5-ASAs	Immunomodulators
Effective in select patients	Induction and maintenance of remission in mildly active UC, including proctitis, left-sided colitis, and extensive colitis[1]	Adjunctive therapy to biologics*[1,2] Maintenance in moderately to severely active UC now in remission†‡[1,2]
Formulation	Oral[3] Topical/rectal[3]	Oral[4]

*AGA specifies as conditional recommendation, low quality of evidence.[2] †Conditional recommendation, low quality of evidence per ACG and AGA.[1,2]
‡ACG specifies remission due to corticosteroid induction.[1]
5-ASA=5-aminosalicylic acid; ACG=American College of Gastroenterology; AGA=American Gastroenterological Association; UC=ulcerative colitis.

1. Rubin DT et al. *Am J Gastroenterol.* 2019;114:384-413. **2.** Feuerstein JD et al. *Gastroenterology*. 2020;158:1450-1461. **3.** Crohn's & Colitis Foundation. Fact sheet: news from the IBD help center, aminosalicylates. Published October 2018. Accessed January 13, 2021. **4.** Crohn's & Colitis Foundation. Fact sheet: news from the IBD help center, immunomodulators. Published October 2018. Accessed January 13, 2021.

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5-ASAs and immunomodulators may not be an appropriate therapy for some patients with UC

In a systematic review of randomized, controlled trials (N=8928) through 2012[1]:

41%–48%

relapse when using **5-ASAs** to maintain remission*

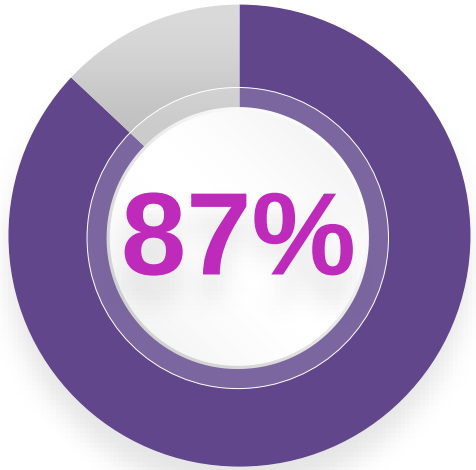
vs 58% of placebo (7 studies, n=1298), 41% of a different 5-ASA comparator formulation (6 studies, n=707), or 43% of sulfasalazine (12 studies, n=1655).

In a 2005–2010 retrospective database analysis (N=2136)[2]:

73%

relapse† while taking **immunomodulators**.‡

In an observational, European multinational, multicenter retrospective chart review (N=256, n=150§) published in 2016[3]:



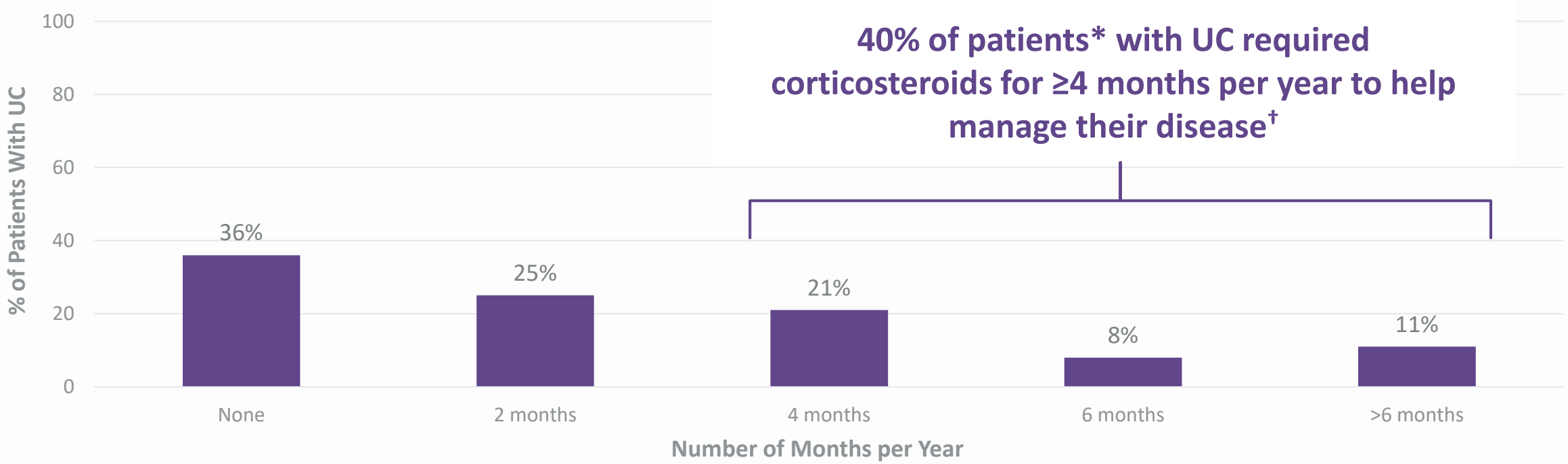
of patients with moderately-to-severely active‖ UC on conventional therapies had uncontrolled disease.¶

1. Wang Y et al. *Cochrane Database Syst Rev*. 2016;(5). doi:10.1002/14651858.CD000544.pub4. **2.** Loftus EV et al. *Inflamm Bowel Dis*. 2014;20:1361-1367. 3**.** Peyrin-Biroulet L et al. *Dig Liver Dis*. 2016;48:601-607. 6.96

40% of patients with UC reported corticosteroid use for ≥4 months in a year

A multinational 2019 survey of patients with UC (n=765) showed:

CORTICOSTEROIDS REPORTED USED TO HELP MANAGE THEIR DISEASE



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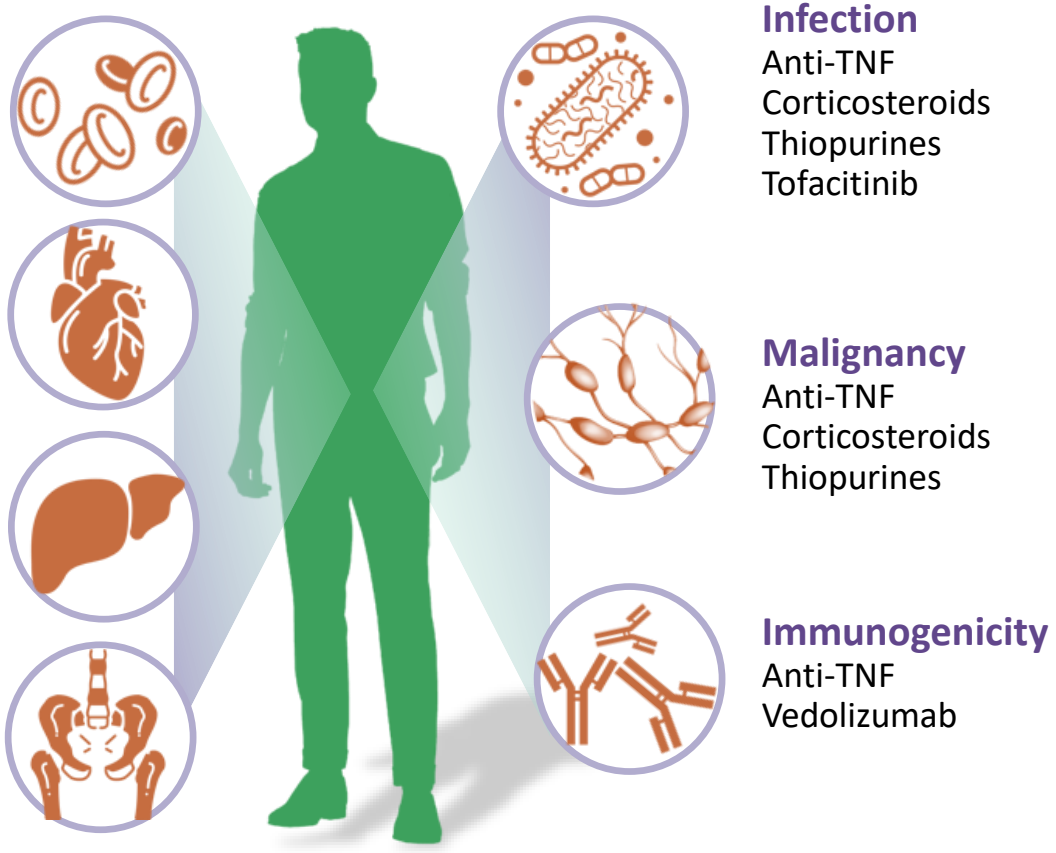
In the initially surveyed UC population (N=1030), 76% self-reported as having moderate/severe disease. †As self-reported by patients.
GAPPS=Global Assessment of Patient and Physician Unmet Need Surveys; UC=ulcerative colitis.
Afzali A et al. Poster presented at: ECCO 2020. P393.

Key safety considerations with IBD therapies



Cytopenias
Anti-TNF
Thiopurines
Methotrexate

Heart failure
Anti-TNF

Hepatotoxicity
Anti-TNF
Thiopurines
Methotrexate

Osteoporosis
Corticosteroids

Infection
Anti-TNF
Corticosteroids
Thiopurines
Tofacitinib

Malignancy
Anti-TNF
Corticosteroids
Thiopurines

Immunogenicity
Anti-TNF
Vedolizumab

Note: Prescribing information from the following products contain a boxed warning: Anti-TNF agents (serious infections and malignancy), tofacitinib (serious infections and malignancy), methotrexate (bone marrow, lung, and kidney toxicities); and thiopurines (malignancy).

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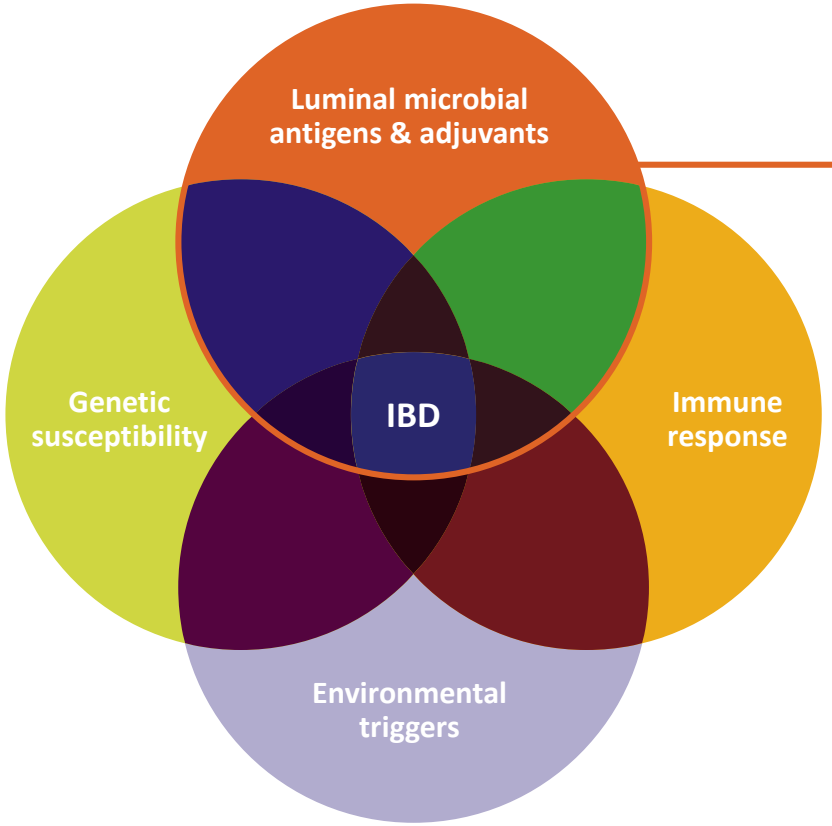
1. Lichtenstein GR et al. *Am J Gastroenterol.* 2009;104:465-483; **2.** Lichtenstein GR, et al. *Am J Gastroenterol.* 2012;107:409-1422; **3.** Yadav S et al. *Mayo Clin Proc*. 2015;90(6):738-746.

Current management of UC is directed towards host immunosuppression



To date, there are no approved drugs targeting the triggers of inflammation rather than inflammation itself

Unmet need for an oral non-immunosuppressive therapeutic agent

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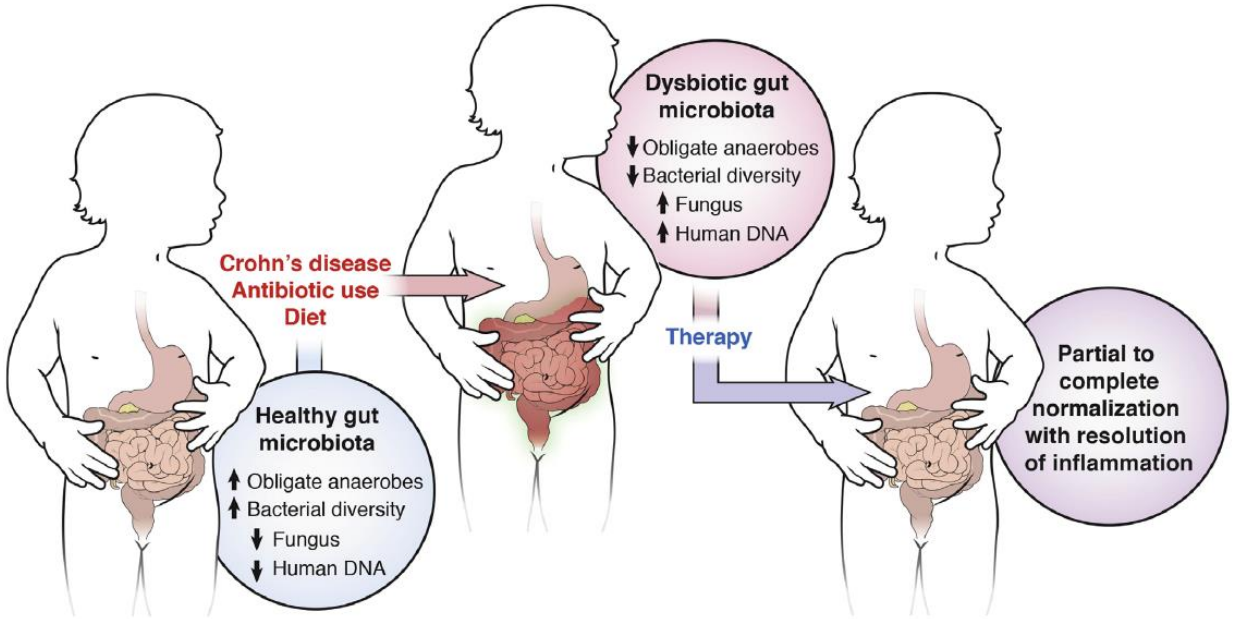
Key classes of emerging therapies

Anti-leukocyte trafficking antibodies	• Etrolizumab (anti-β7) • Anti-MAdCAM Ab • Subcutaneous formulation of vedolizumab
Anti-interleukin 23 antibodies	• Brazikumab • Risankizumab • Mirikizumab • Guselkumab
Sphingosine-1 phosphate receptor modulators (S1P1R)	• Ozanimod (FDA approval May 28, 2021) • Etrasimod
Janus kinase inhibitors	• Filgotinib • Upadacitinib

Can the arsenal of the microbiome be harnessed for disease remission?

- **Firmicutes play a key role in modulating gut homeostasis**
- **A technologic revolution in sequencing and computational biology promises greater understanding of UC pathogenesis**
- **Improving our mechanistic understanding of the disease will lead to better biomarkers and treatments**
- **There is a great need to identify important functional microbial ecologies that elicit therapeutic responses in these complex disease pathways**
- **Fundamental question of whether we can reseed or reset gut microbial function**

The critical question is:
Can we shift an ecologic community towards a healthier functional state in a chronic inflammatory disease like UC?



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Chu H Science 2017; Cleynan I Lancet 2016; McGovern Nat Genetics 2010; Morgan Genome Biol 2012; Jostins L Nature 2012; Neurath MF Nat Rev Immunol 2014; Saleh Immunity 2011; Guo H Nat Med 2015; Kostic AD Gastroenterology 2014; Frank DN Inflam Bowel Dis 2011; Drew L Nature 2016; Lewis J Abreu Gastroenterology 2017

Clinical outcomes highlight urgent therapeutic gaps

Isn’t it time to think outside the box?

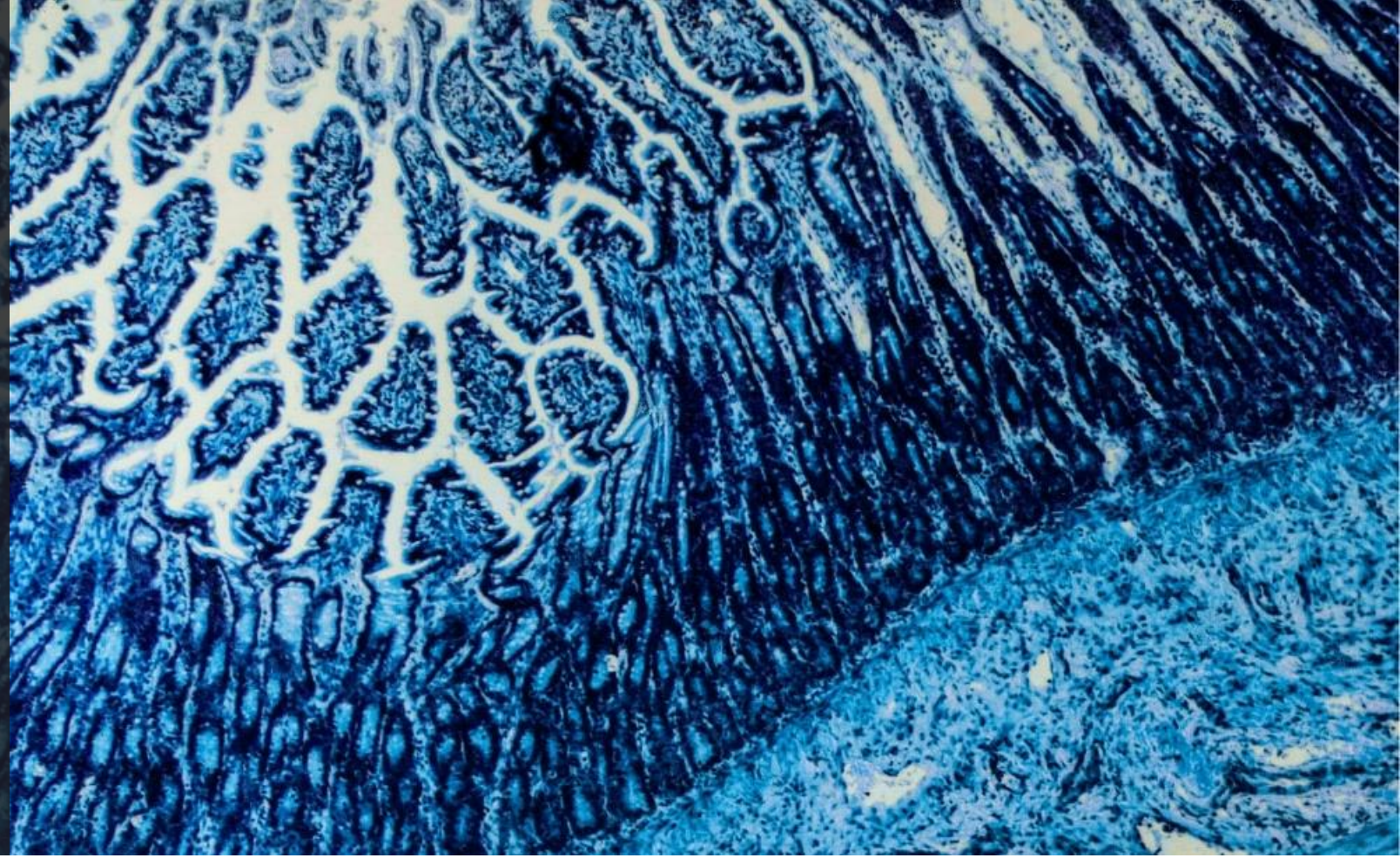
1. All approaches to date target specific components of the inflammatory cascade
2. Should we expand our therapeutic armamentarium to target other mediators of disease?

Initial positioning for microbiome therapeutics (my viewpoint)

- Mild-to-moderate UC for patients with inadequate response to aminosalicylates
  - Advantages
    - Large therapeutic gap (~50%)
    - Simple, straightforward trials with validated endpoints
    - Allows mechanistic studies
    - Second trial, straightforward trial would be head-to-head vs aminosalicylates
    - Avoids steroids which portend refractory disease, lower response rates, need to assess steroid-sparing, more complex trials
    - Avoids immunosuppressives, biologics which portend refractory disease and lower response rates
    - If foundational trials are positive, will open door to extended studies in other combinations (moderate or refractory disease, maintenance of remission, pouchitis
  - Disadvantages
    - Recruitment in earlier disease although patients "favor" microbiome approach (e.g. extensive use of probiotics and complementary therapies)

SER-287
&
SER-301
Clinical Overview

Lisa von Moltke, M.D.
Chief Medical Officer,
Seres Therapeutics



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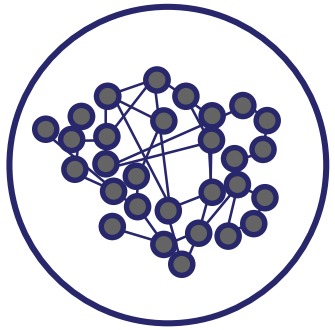
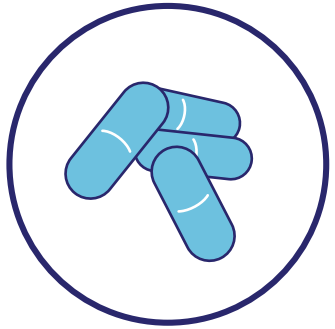
SER-287 is an Investigational Microbiome Drug for the Treatment of UC

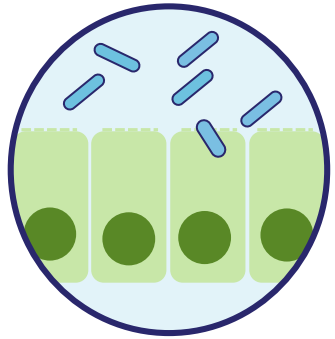
SER-287
Composition & Rationale for Drug Development



- Consortium of purified Firmicutes bacterial spores associated with gastrointestinal health
- Biologically sourced from healthy screened donors
- Spore purification process mitigates risk of transmission of infectious agents



- Spores are resistant to gastric acid allowing formulation into capsules for oral delivery
- Dormant bacterial spores germinate, replicate and engraft in the gastrointestinal tract



- Leverages compositional and functional changes in the gut microbiome to modulate colonic inflammation, the hallmark of UC
- Potential to impact network of multiple inflammatory pathways key to gut health

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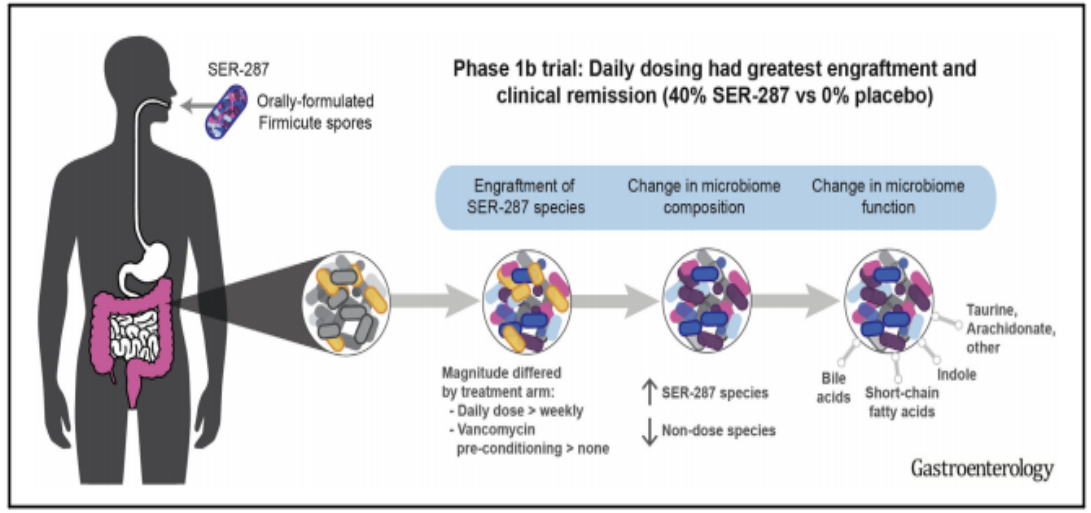
SER-287 Phase 1b Study Results Published January 2021

A Phase 1b Safety Study of SER-287, a Spore-Based Microbiome Therapeutic, for Active Mild to Moderate Ulcerative Colitis

Matthew R. Henn,[1] Edward J. O'Brien,[1] Liyang Diao,[1] Brian G. Feagan,[2] William J. Sandborn,[3] Curtis Huttenhower,[4] Jennifer R. Wortman,[1] Barbara H. McGovern,[1] Sherry Wang-Weigand,[1] David I. Lichter,[1] Meghan Chafee,[1] Christopher B. Ford,[1] Patricia Bernardo,[1] Peng Zhao,[1] Sheri Simmons,[1] Amelia D. Tomlinson,[1] David N. Cook,[1] Roger J. Pomerantz,[1] Bharat K. Misra,[5] John G. Auniņš,[1] and Michele Trucksis[1]

[1]Seres Therapeutics, Cambridge, Massachusetts; [2] Robarts Research Institute, London, Ontario, Canada; [3]University of California San Diego, La Jolla, California; [4]Harvard T.H. Chan School of Public Health, Boston, Massachusetts; and [5]Borland Groover Clinic, Jacksonville, Florida



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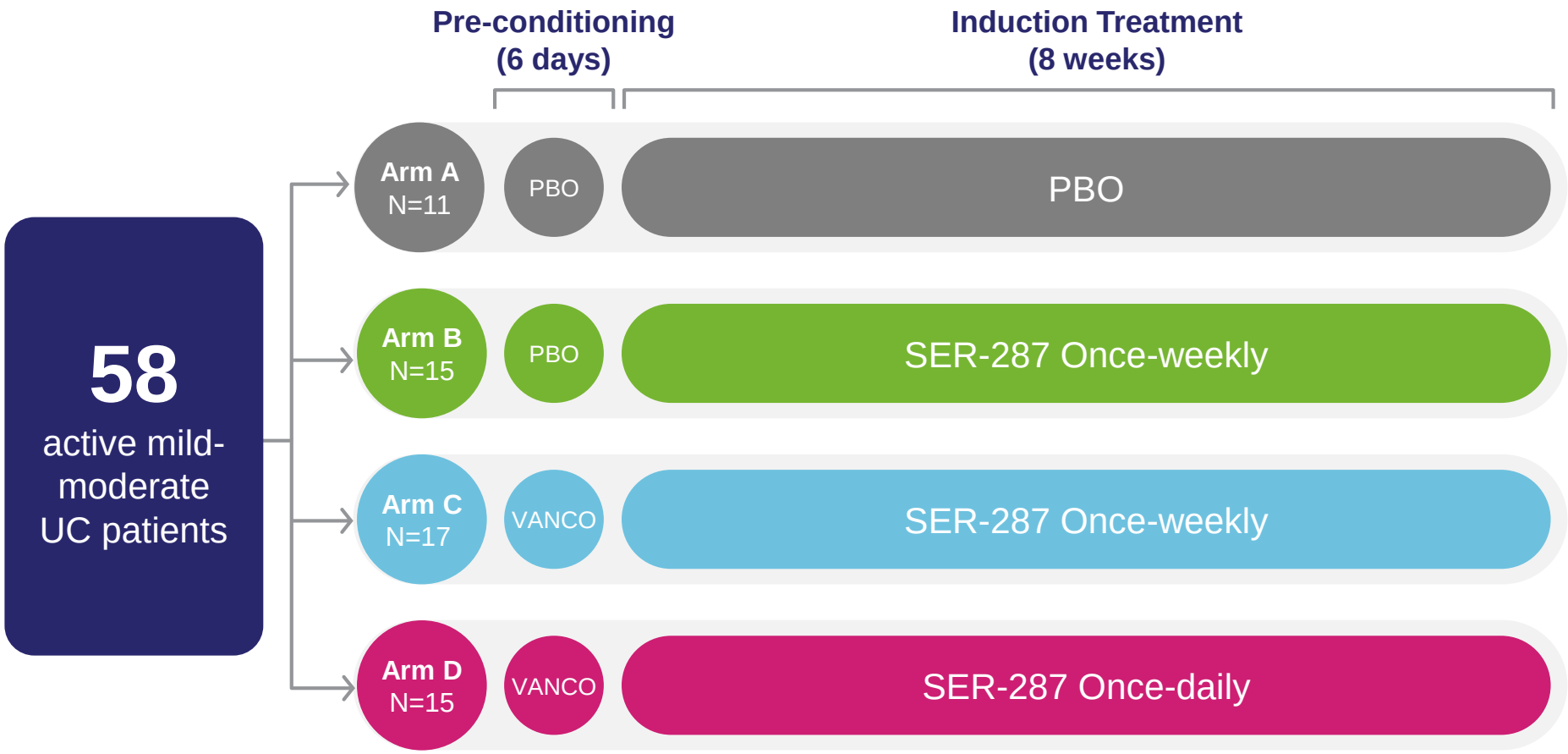
Seres Phase 1b Study Design in Mild-to-Moderate UC



Primary Objectives

- Safety and tolerability
- Change in composition of intestinal microbiome

Patient Population

- Treatment-naïve, or inadequate response or intolerance to 5-ASA, steroids, immunomodulators, biologics or small molecules

PBO = placebo; VANCO = vancomycin

Henn et al. 2021. Gastroenterology

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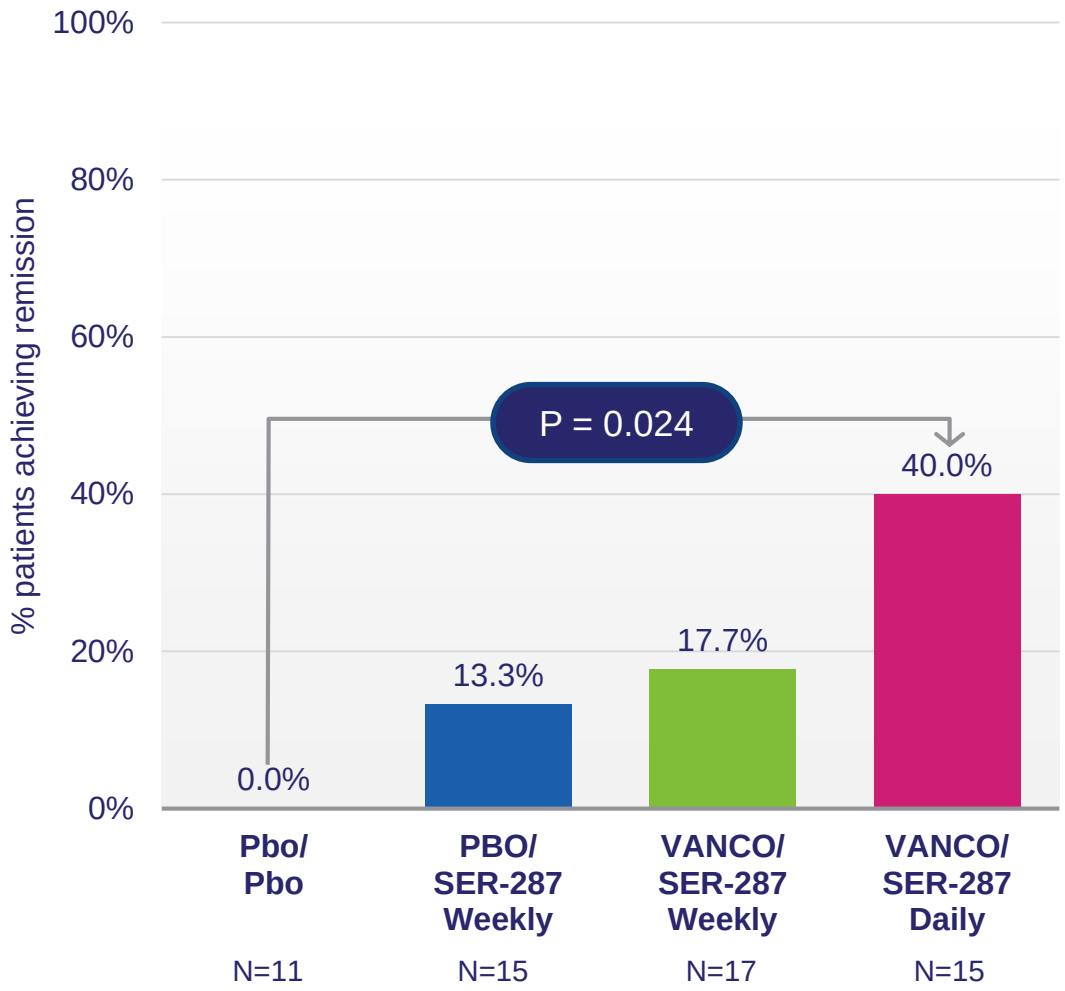
Daily Dosing of SER-287 was Associated with an Increased Rate of Clinical Remission



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

Henn et al. 2021. Gastroenterology

Clinical remission defined as:

- Total modified Mayo Score (TMMS) ≤ 2 plus
- Endoscopic subscore (ES) of 0 or 1 with blinded central read

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SER-287 was Well-tolerated

- **SER-287 similar to placebo**
- **No drug-related SAEs**
- **SER-287 daily treatment arm:**
  - No subject discontinuations due to AE
  - Fewer GI AEs: 1/15 (6.7%) vs. placebo arm: 5/11 (45.5%)

	PBO/ PBO (N = 11) n (%)	PBO/ SER-287 weekly (N = 15) n (%)	Vanco/ SER-287 weekly (N = 17) n (%)	Vanco/ SER-287 daily (N = 15) n (%)
All adverse events (AEs)	7 (63.6)	9 (60.0)	14 (82.4)	8 (53.3)
Serious AEs	0	0	0	1 (6.7)*
Adverse events of special interest (AESIs)	0	1 (6.7)	0	0
Severity of AEs				
Mild	3 (27.3)	7 (46.7)	6 (35.3)	3 (20.0)
Moderate	4 (36.4)	2 (13.3)	8 (47.1)	5 (33.3)
Treatment-related AEs	1 (9.1)	4 (26.7)	7 (41.2)	2 (13.3)
AEs leading to discontinuation of study drug	0	1 (6.7)	2 (11.8)	0

* 1 SAE was worsening depression in subject with history of depression, deemed unrelated to treatment, which did not lead to treatment discontinuation

Henn et al. 2021. Gastroenterology

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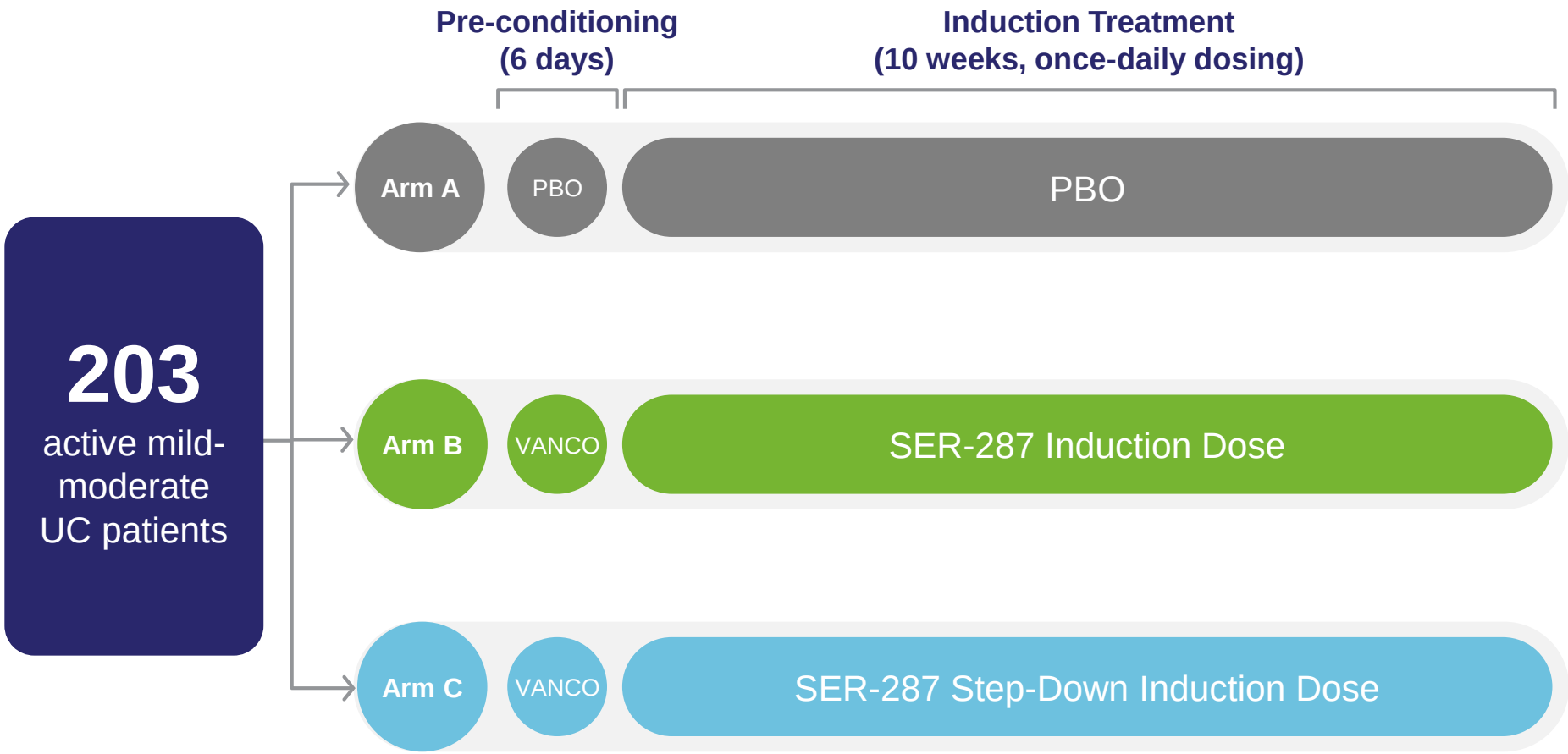
Seres Phase 2b ECO-RESET Study Design in Mild-to-Moderate UC



Endpoints

- Primary: Clinical remission
- Key secondary: Endoscopic improvement
- Exploratory: maintenance for remitters; open-label for non-remitters

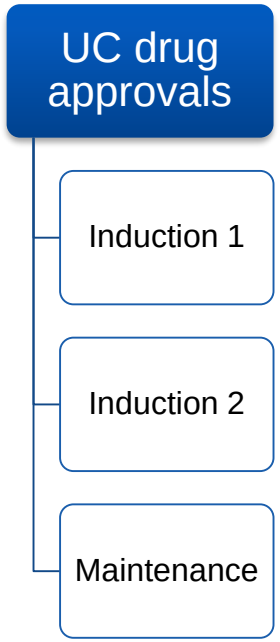
Patient Population

- Inadequate response or intolerance to 5-ASA, steroids, immunomodulators, biologics or small molecules

PBO = placebo; VANCO = vancomycin

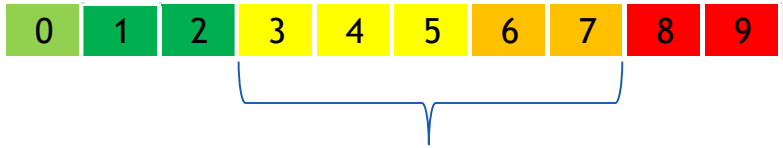
ECO-RESET: Designed in Accordance with FDA's UC Guidance Document (2016), and Could Serve as 1 of 2 Required Pivotal Induction Studies to Support BLA

Paradigm of pivotal UC studies* supporting UC drug approvals



3-Component Modified Mayo Score (3CMMS)

Score	Range
Stool Frequency (SF)	0-3
Rectal Bleeding (RB)	0-3
Endoscopic Subscore (ES)	0-3
~~**Physician's Global Assessment (PGA)**~~	~~0-3~~
3-Component Modified Mayo Score (3CMMS)	0-9



ECO-RESET mild-to-moderate 3CMMS range

ECO-RESET endpoint definitions

Endpoint	Subscore	Score details
Clinical Remission (primary)	**SF**	0 or 1 with at least 1-point decrease from baseline
	RB	0
	ES	0 or 1 on modified Mayo Score with at least 1-point decrease from baseline (central reader)
	No occurrence of UC flare during treatment period	
Endoscopic improvement (key secondary)	**ES**	Decrease from baseline of at least 1-point (central reader)

* Various combinations of induction/maintenance study design options possible

3CMMS = 3-component modified Mayo score; ES = endoscopic subscore; PGA = physician's global assessment; PRO = patient-reported outcome; RB = rectal bleeding; SF = stool frequency

US FDA, Department of Health and Human Services, CDER. Guidance for Industry: Ulcerative Colitis: Clinical Trial Endpoints; 2016

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ECO-RESET: Expected Learnings and Defining Successful Outcomes

Clinical remission (primary endpoint)

Clear signal of clinical efficacy versus placebo (mid-2021)

Endoscopic remission/improvement, symptomatic remission

Clear signal of clinical efficacy versus placebo, supporting the primary endpoint (mid-2021)

Rich data set

Enables subgroup analyses to inform future clinical development (e.g., microbiome endpoints 2021 H2, biomarker data, patient population)

Safety profile

Ideally comparable to placebo with no concerning safety signals (mid-2021)

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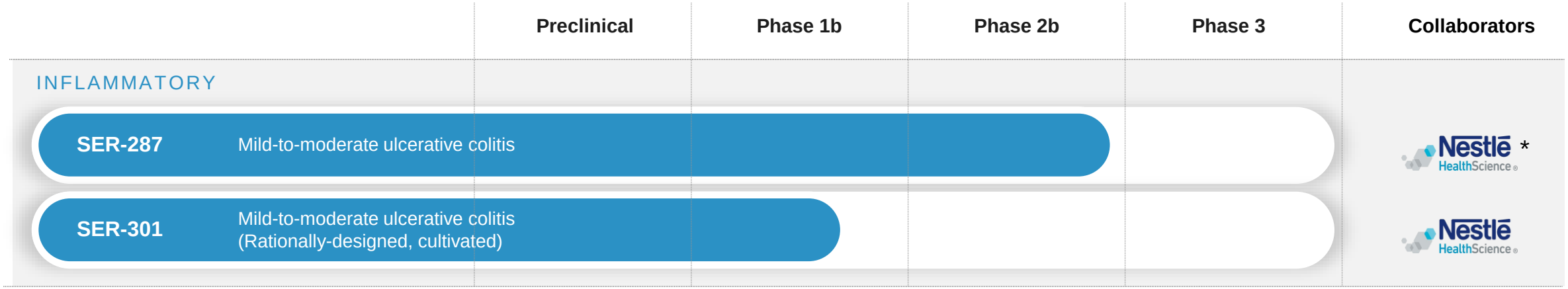
SER-301 Design Leveraged Reverse-Translational Clinical & Scientific Experience with SER-287 in Mild-to-Moderate UC



SER-287	SER-301
Consortium of Firmicutes bacteria formulated as spores	Consortium of Firmicutes bacteria formulated as spores and vegetative bacteria
Broad diversity of Firmicutes that includes active bacteria	Optimized consortium of active Firmicutes species
Biologically-sourced: fractionation and purification of Firmicutes bacterial spores from healthy screened donor stool	Cultivation and fermentation of bacteria from strain library master cell banks

* Collaboration with Nestlé Health Science, announced Jan. 11, 2016, regarding *C. difficile* and IBD programs for markets outside of North America

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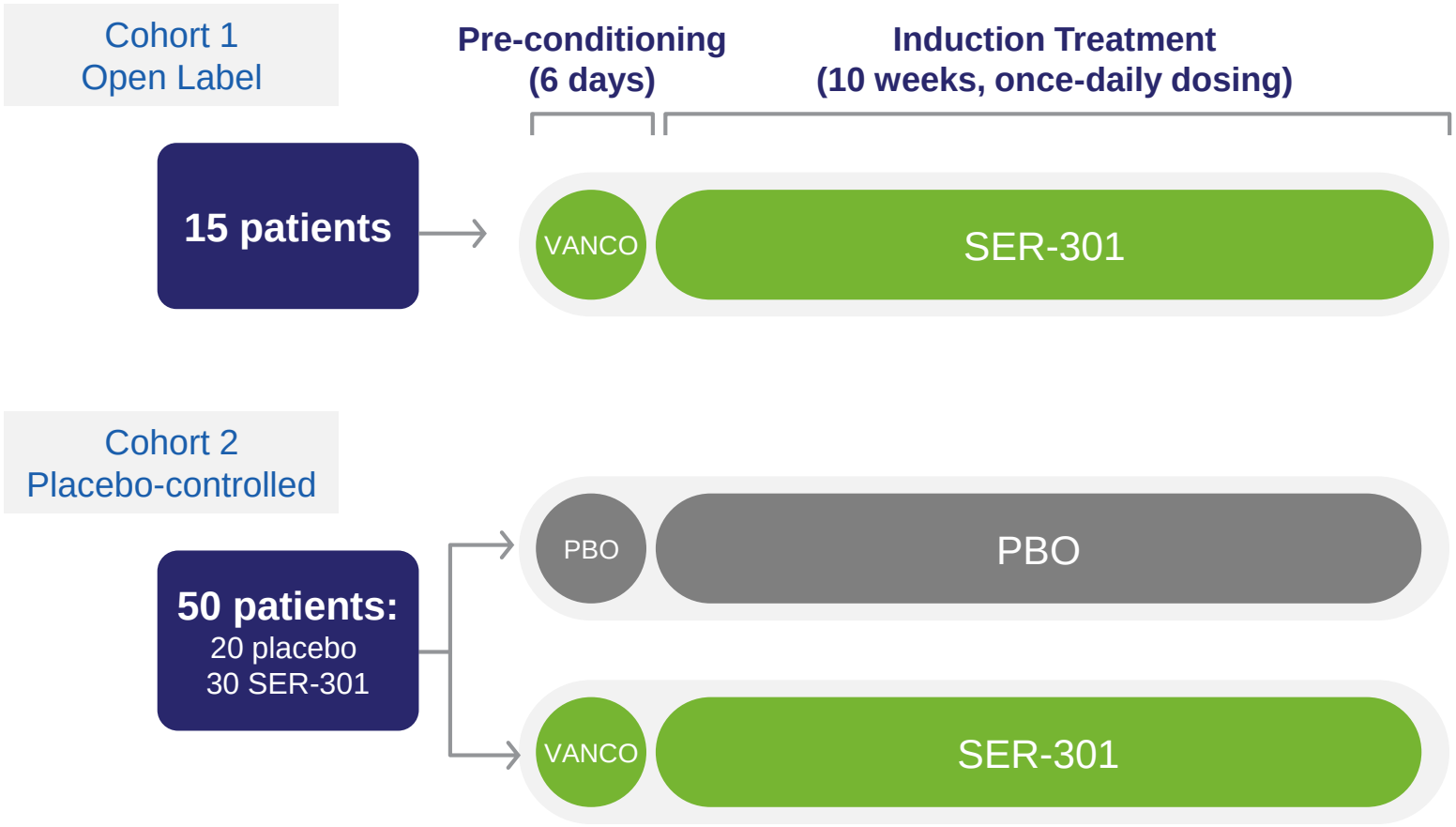
SER-301-001 Phase 1b Study in Patients with Active Mild-to-Moderate Ulcerative Colitis: Australia & New Zealand (Currently Enrolling)



Endpoints

- Primary: Safety & tolerability
- Cohort 2 secondary: clinical endpoints (e.g. endoscopic improvement)

Patient Population

- Treatment-naïve, or inadequate response or intolerance to 5-ASA, corticosteroids or immunomodulators
- No prior UC biologic or small molecule use

PBO = placebo; VANCO = vancomycin

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Potential for Further SER-287 Clinical Development in IBD

Clinical development opportunity	Details
Progress towards BLA	Initiate SER-287 2nd pivotal induction study + pivotal maintenance study (single study)

Additional opportunities for microbiome therapeutics	• Moderate-to-severe UC
	• Maintenance treatment after clinical remission with any 1st or 2nd line treatment
	• Combination treatment in either mild-to-moderate or moderate-to-severe UC:
	  ○ For difficult to treat UC;
	  ○ To increase efficacy rates during induction;
	  ○ To reduce relapse during maintenance therapy
	• Other IBD indications where microbiome therapy may be safe and effective (e.g. Crohn's Disease, pouchitis)

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Seres UC Franchise Summary

SER-287 Phase 2b ECO-RESET study aims to build upon the strong data from the Phase 1b study. Topline induction data is expected in mid-2021.

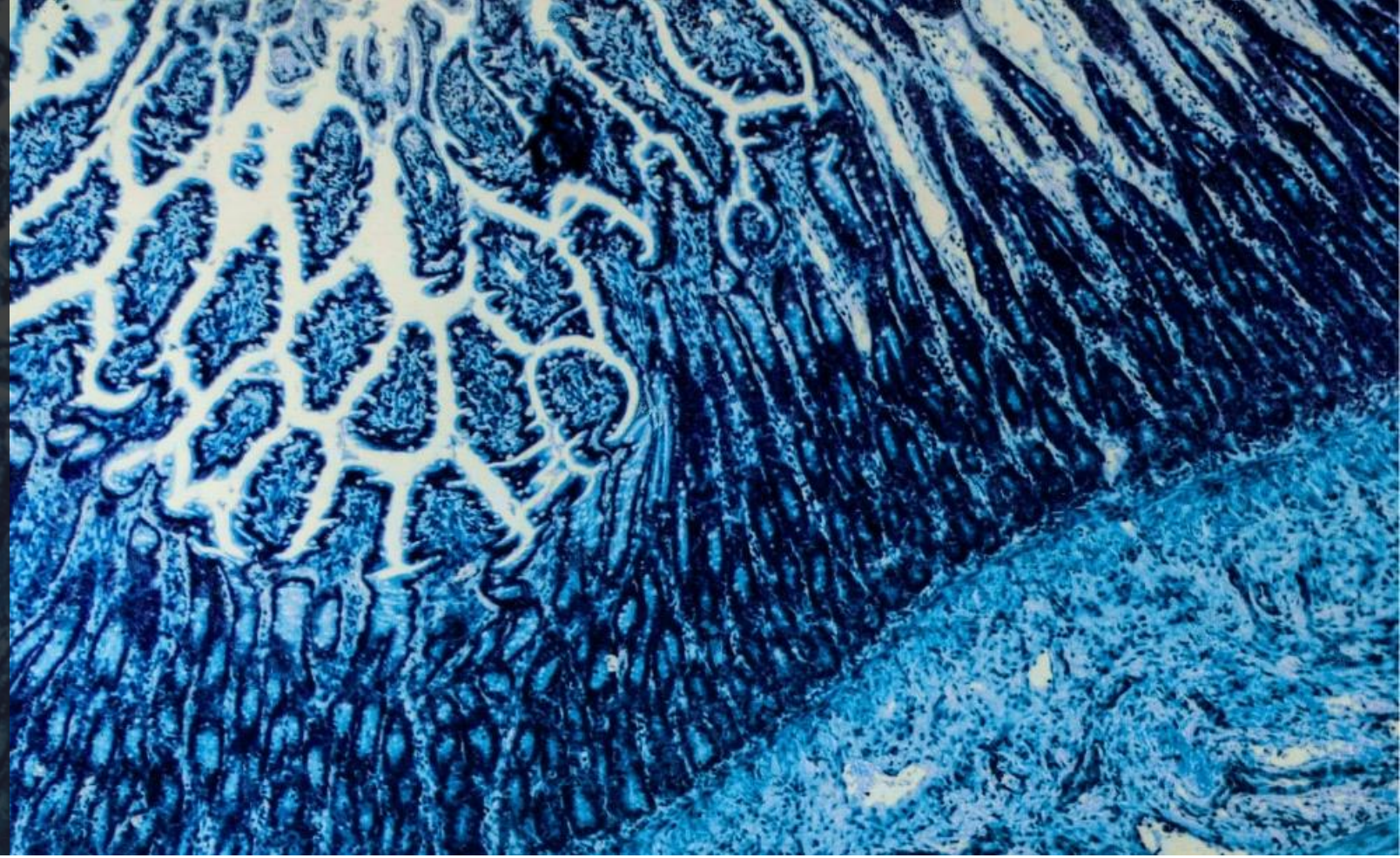
SER-301 Phase 1b study aims to investigate safety & tolerability and explore clinical efficacy signals.

Both studies will have translationally-rich data sets to best inform clinical development plans and Seres' overall UC franchise

SERES THERAPEUTICS™

Microbe-Host Interactions in IBD & UC

Matthew Henn, Ph.D.
Chief Scientific Officer,
Seres Therapeutics



SERES THERAPEUTICS™

Seres' differentiated, innovative platforms enable rapid progress from target ID through clinical development in areas of significant unmet medical need

Microbiome & IBD

- Integrity of the gastrointestinal microbiome is compromised
- Bacteria & microbe-associated metabolites modulate host immune pathways
- Addressing disease requires understanding interaction between microbes and human cells & tissues

Seres Drug Candidates

- Novel drug technology that leverages millions of years of coevolution between bacteria and hominids
- Target restructuring disrupted GI microbiome and gut metabolic landscape to modulate multiple disease-relevant pathways
- Innovative platforms that integrate human and nonclinical data sets to de-risk discovery

SERES THERAPEUTICS™

Gastrointestinal Microbiome Involved in Pathogenesis of IBD

Science Trans. Med. 2018

Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome

Arnau Vich Vila[1,2]*, Floris Imhann[1,2]*, Valerie Collij[1,2]*, Soesma A. Jankipersadsing[2†],
Thom
Xiaof
Marij
Lude
Mart
Daisy

Cell Host & Microbe 2018

Compositional and Temporal Changes in the Gut Microbiome of Pediatric Ulcerative Colitis Patients Are Linked to Disease Course

Melanie Schirmer,[1,2] Lee Denson,[3] Hera Vlamakis,[1,26,27] Eric A. Franzosa,[1,2] Sonia Thomas,[4,23] Nathan M. Gotman,[4]
Paul Rufo,[5] Susan S. Baker,[6] Cary Sauer,[7] James Markowitz,[8] Marian Pfefferkorn,[9] Maria Oliva-Hemker,[10] Joel Rosh,[11]
Anthony Otley
Anne Griffiths,
Jeffrey Hyams

Nature 2019

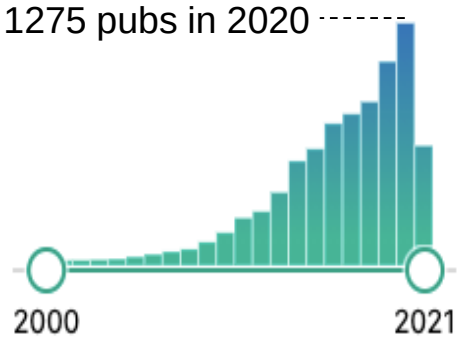
Multi–omics of the gut microbial ecosystem in inflammatory bowel diseases

Jason Lloyd–Price[1,2], Cesar Arze[2], Ashwin N. Ananthakrishnan[3], Melanie Schirmer[1,3], Julian Avila–Pacheco[4], Tiffany W. Poon[1],
Elizabeth Andrews[3], Nadim J. Ajami[5], Kevin S. Bonham[1,2], Colin J. Brislawn[6], David Casero[7], Holly Courtney[3], Antonio Gonzalez[8],
Thomas
Mahade
IBDMDB
Dermot
Eric A.

Cell 2019

Therapeutic Opportunities in Inflammatory Bowel Disease: Mechanistic Dissection of Host-Microbiome Relationships

Damian R. Plichta,[1] Daniel B. Graham,[1,2,3,4] Sathish Subramanian,[5] and Ramnik J. Xavier[1,2,3,4,*]



Indexed PubMed papers with terms microbiome & IBD/UC/Crohn's

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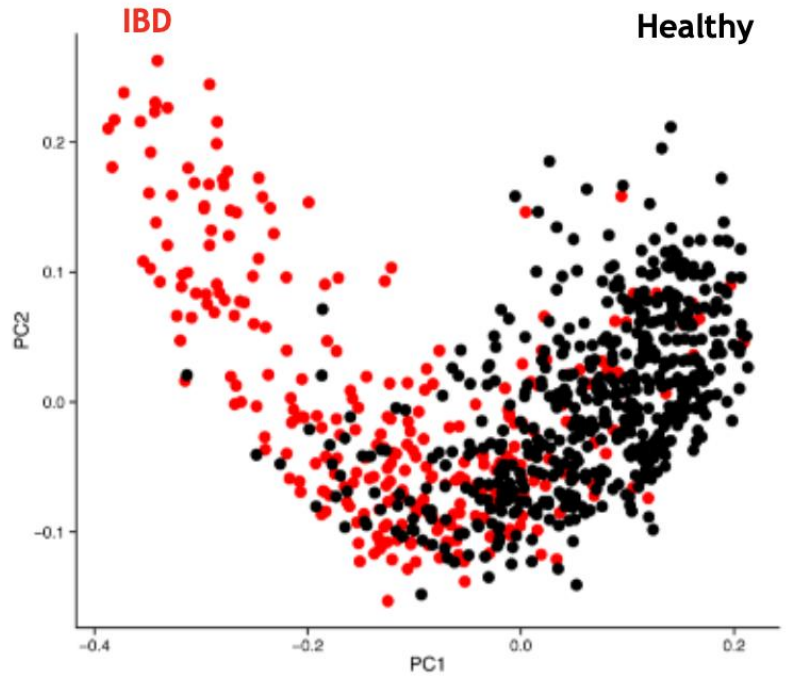
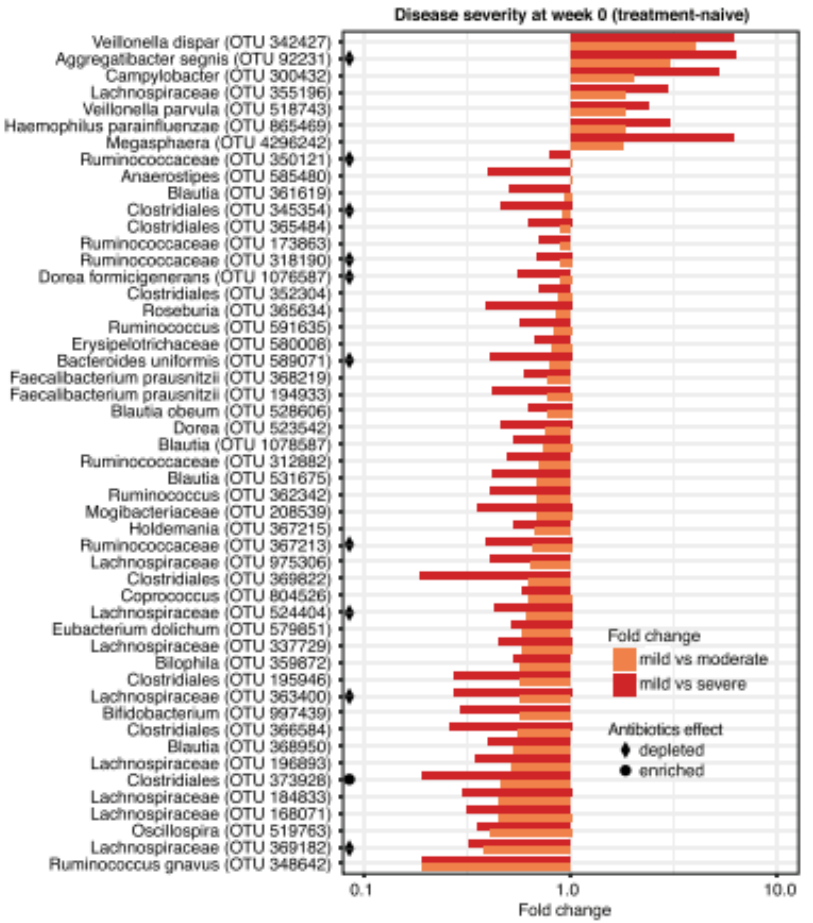
Composition of Microbiome Linked to IBD in Both Adults and Pediatrics

Adults with UC, colonic or ileal Crohn's



Imhann et al. 2018. Gut

Pediatric (4-17 yo) with UC



Schirmer et al. 2018. Cell Host & Microbe

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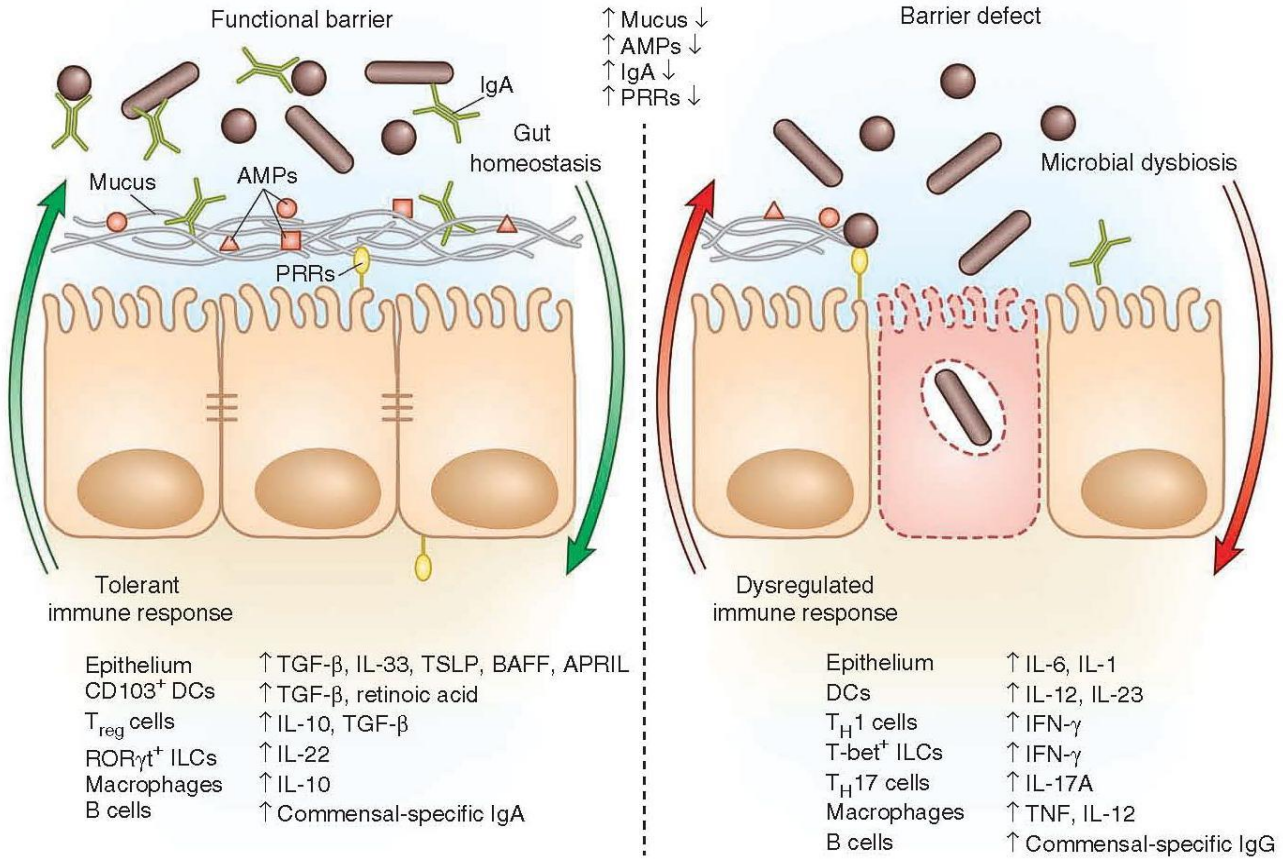
Microbe-Associated Metabolites and Antigens Can Impact Gut Epithelial Integrity and Host Inflammation & Immunity

Inflammatory Homeostasis

Microbe-associated metabolites promote **mucosal** and **epithelial integrity**, and **anti-inflammatory** responses



Brown et al. 2013. Nat. Immunology

Inflammation

Microbial products or antigens stimulate mucosal immune cells and activate toll-like receptors (TLRs) to produce **pro-inflammatory** cytokines

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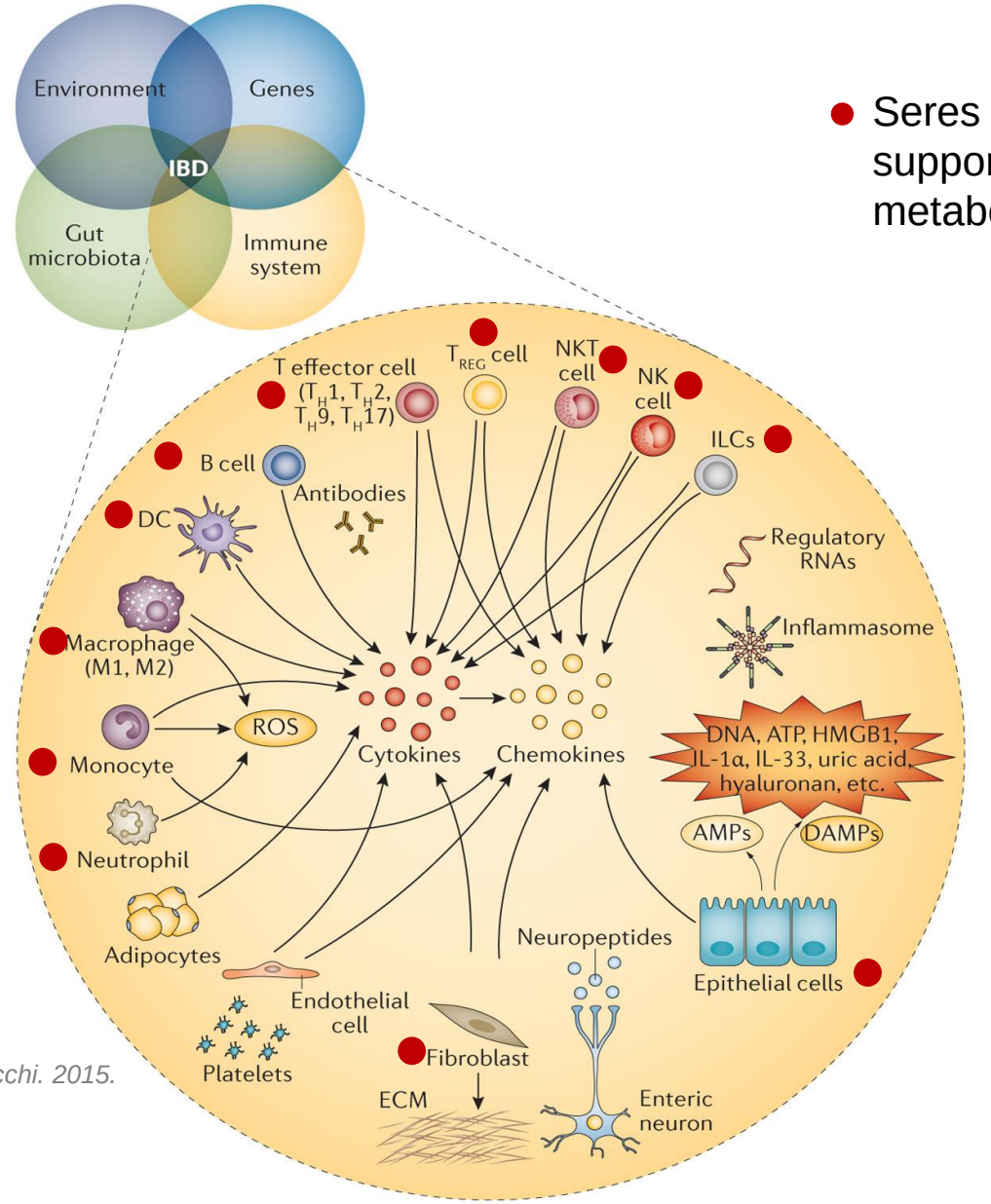
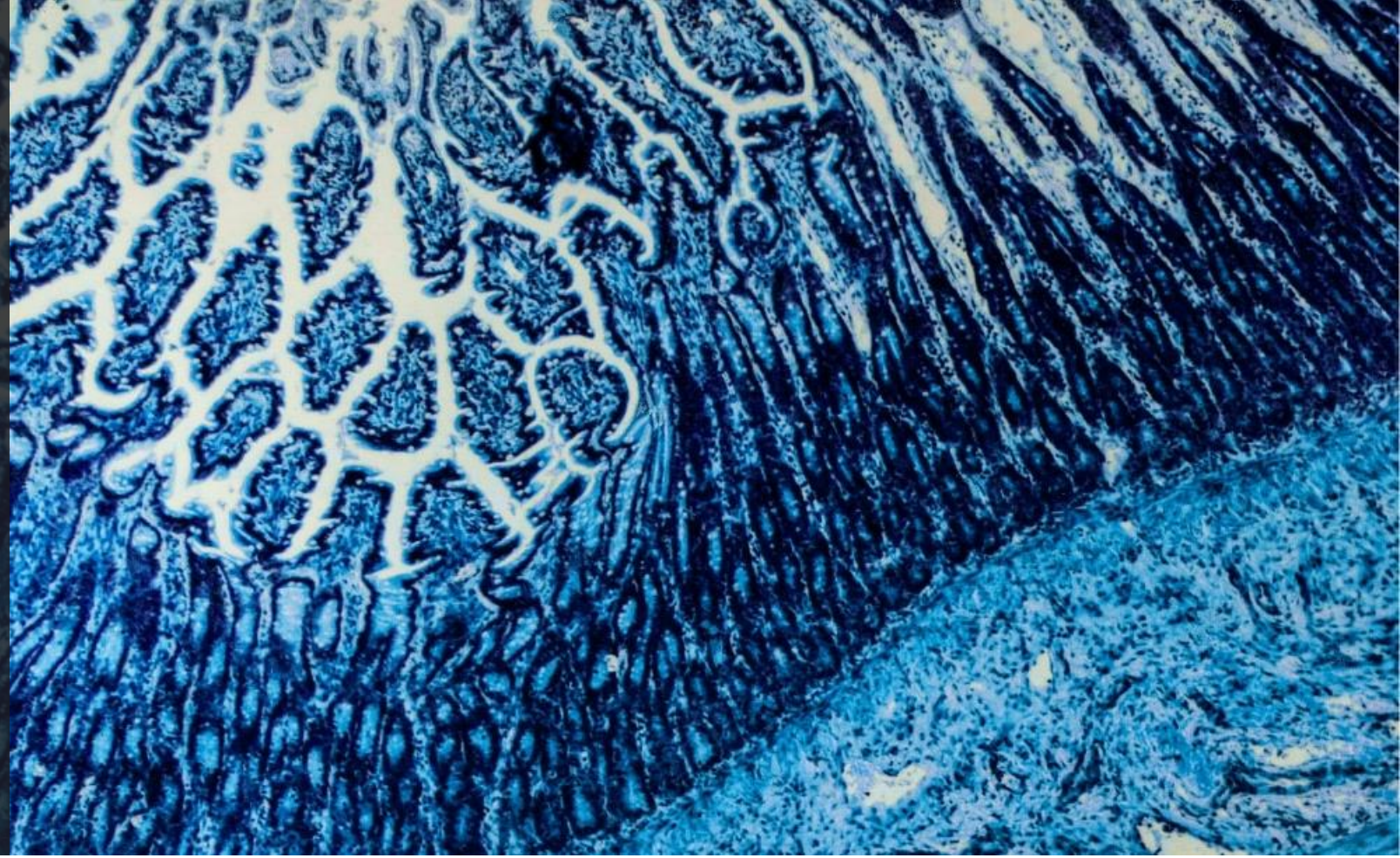
Gastrointestinal Microbiome Intimately Connected to Host Immune System Function



- Seres internal data and/or published literature support role of microbes, microbe-associated metabolites, or microbial products and antigens

Image adapted from: de Souza, & Fiocchi. 2015. Nat. Rev. Gastro. Hepatol.

Microbiome Therapeutics for UC



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Seres Microbiome Therapeutics are Bacterial Consortia Designed to Have Specific Pharmacological Properties

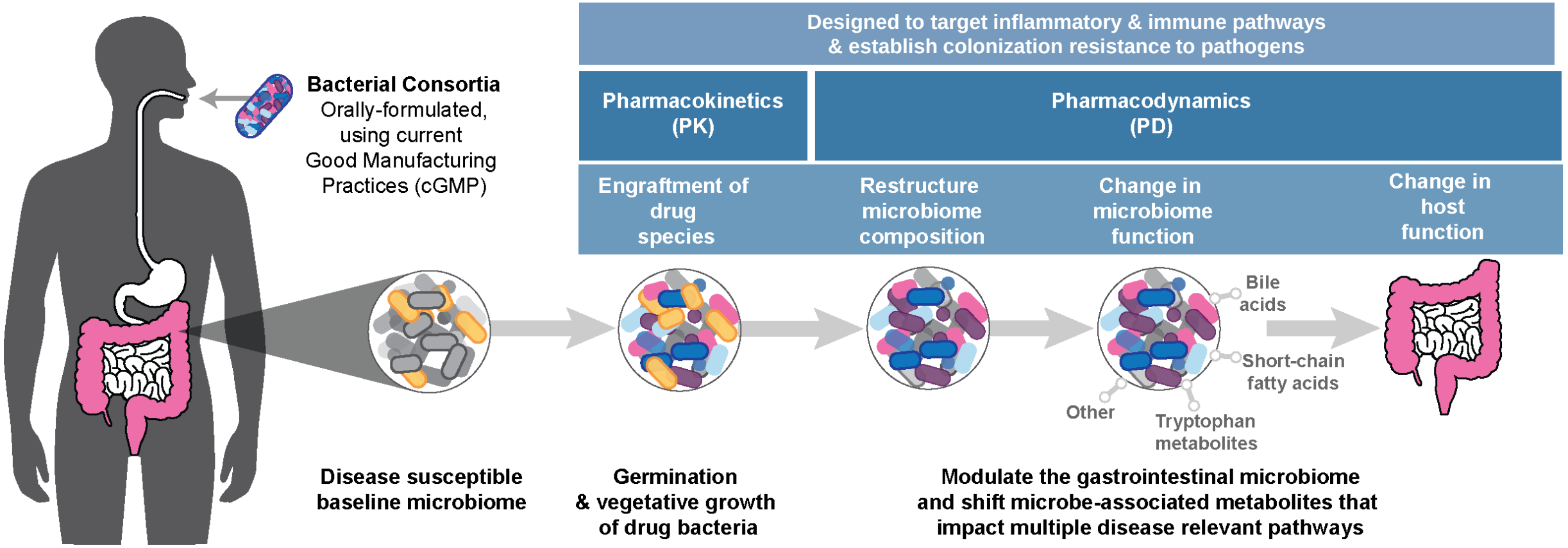
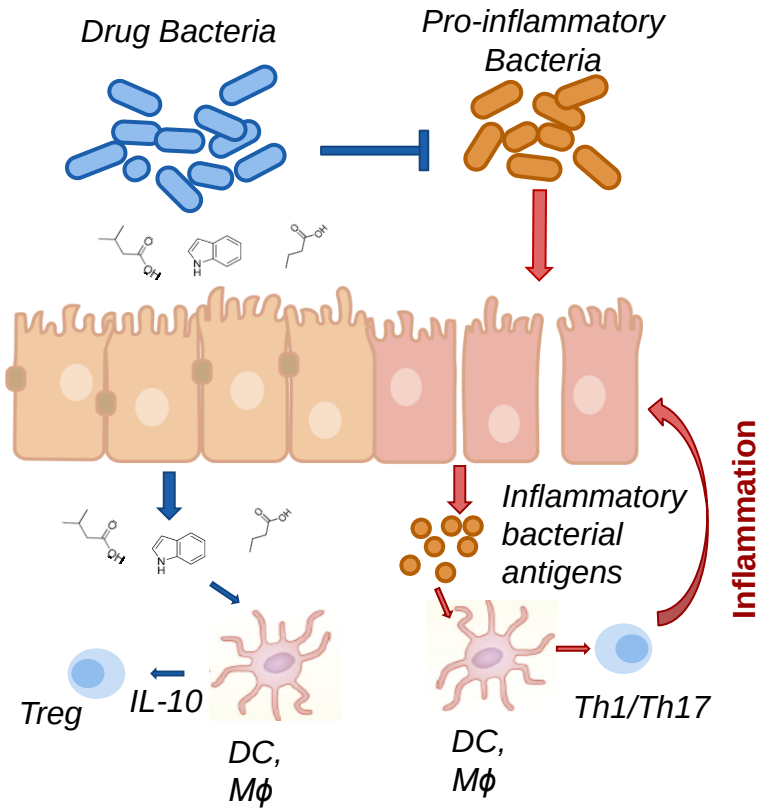


Figure adapted from Henn et al. 2021. Gastroenterology

Seres UC Therapeutic Candidates are Consortia of Bacteria that Have Potential to Target Multiple Triggers of Ulcerative Colitis Pathology

SER-287
- Consortia of Firmicutes bacteria formulated as spores
- Biologically-sourced; broad diversity of Firmicutes that includes active bacteria
- Phase 2b

SER-301
- Consortia of Firmicutes bacterial strains formulated as spores or vegetative cells
- Strains cultivated from master cell banks; rationally-optimized active species
- Phase 1b

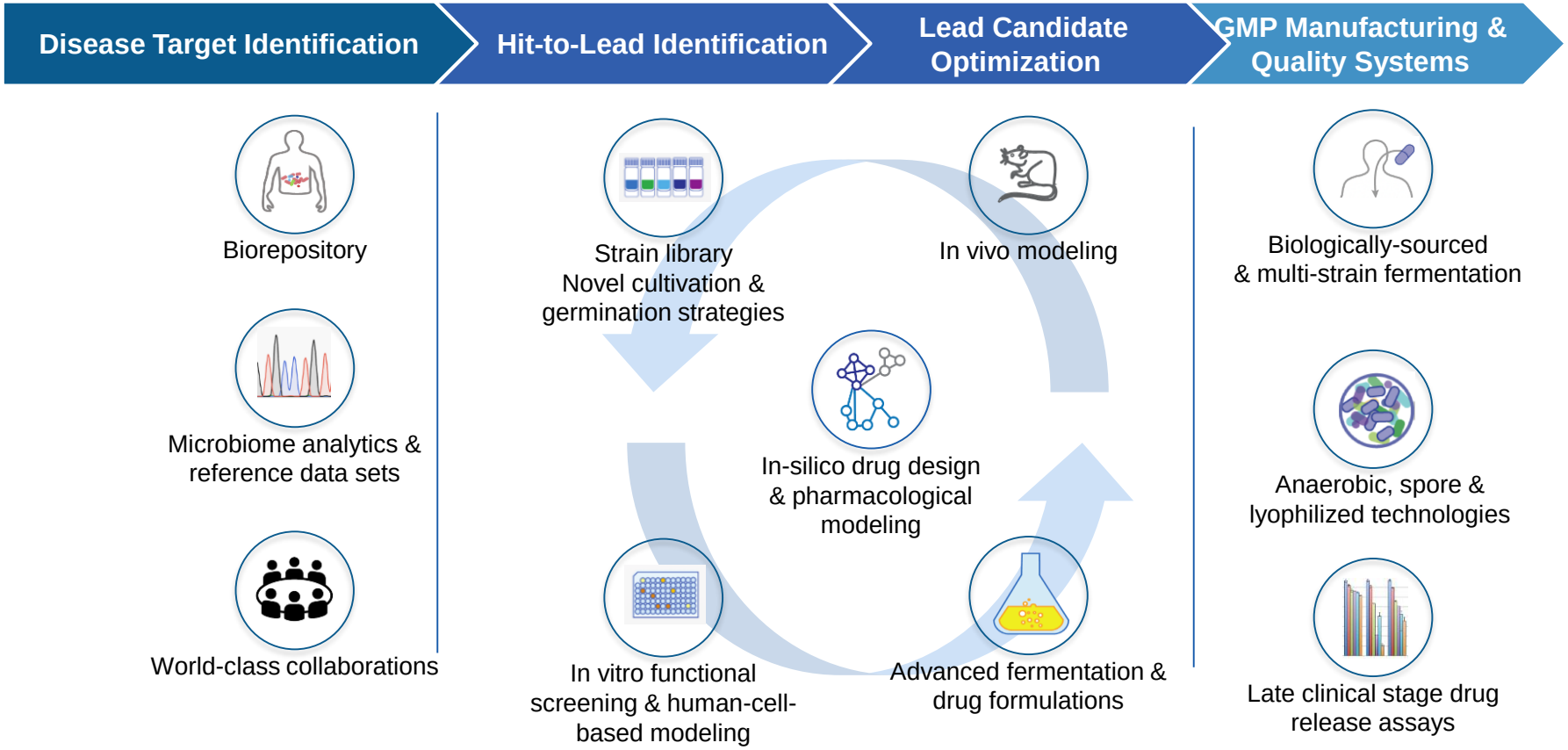


Reduce the abundance of pro-inflammatory bacteria and epithelial cell inflammation

Produce immunomodulatory metabolites that improve epithelial barrier integrity

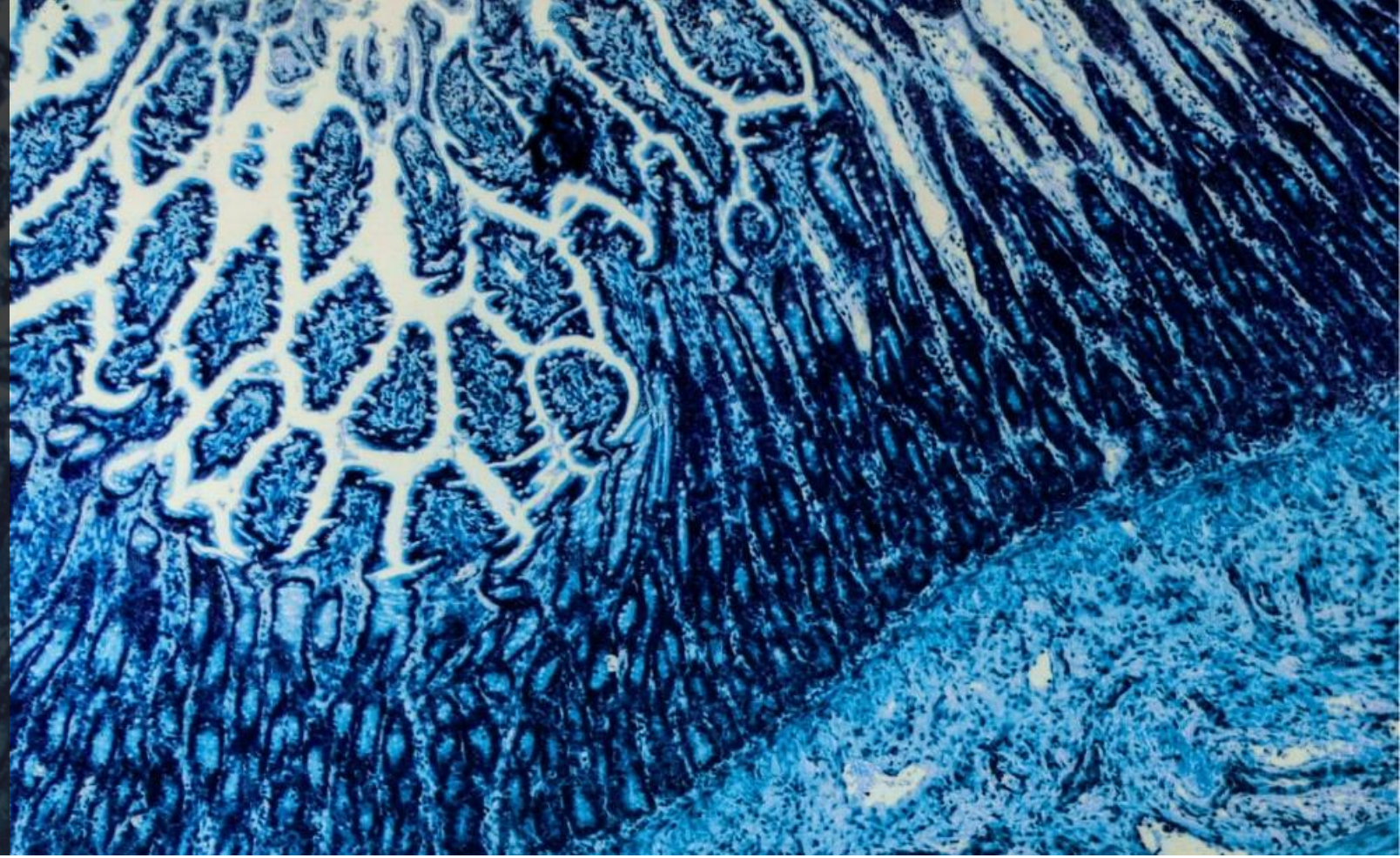
Decrease cytokine-induced inflammation and modulate T cell populations

Seres Differentiated Research Engine Delivers End-to-End Drug Development from Target Identification Through GMP Manufacturing



SER-287
SER-301

MoA & Pharmacology



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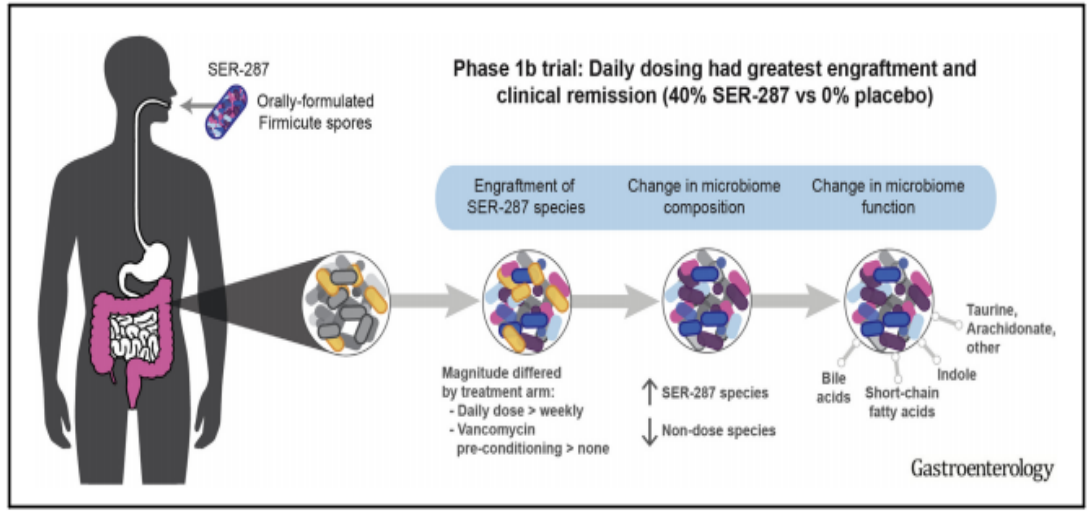
SER-287 Phase 1b Study Results Published January 2021

A Phase 1b Safety Study of SER-287, a Spore-Based Microbiome Therapeutic, for Active Mild to Moderate Ulcerative Colitis

Matthew R. Henn,[1] Edward J. O'Brien,[1] Liyang Diao,[1] Brian G. Feagan,[2] William J. Sandborn,[3] Curtis Huttenhower,[4] Jennifer R. Wortman,[1] Barbara H. McGovern,[1] Sherry Wang-Weigand,[1] David I. Lichter,[1] Meghan Chafee,[1] Christopher B. Ford,[1] Patricia Bernardo,[1] Peng Zhao,[1] Sheri Simmons,[1] Amelia D. Tomlinson,[1] David N. Cook,[1] Roger J. Pomerantz,[1] Bharat K. Misra,[5] John G. Auniņš,[1] and Michele Trucksis[1]

[1]Seres Therapeutics, Cambridge, Massachusetts; [2] Robarts Research Institute, London, Ontario, Canada; [3]University of California San Diego, La Jolla, California; [4]Harvard T.H. Chan School of Public Health, Boston, Massachusetts; and [5]Borland Groover Clinic, Jacksonville, Florida



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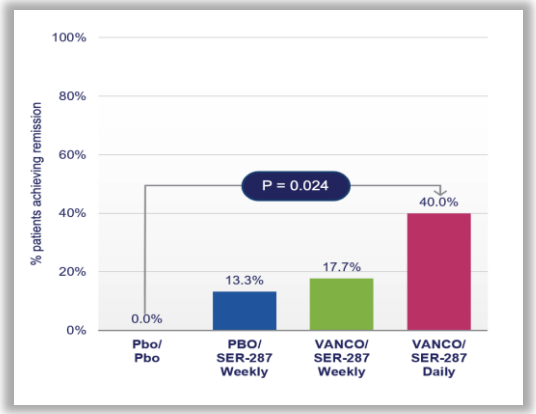
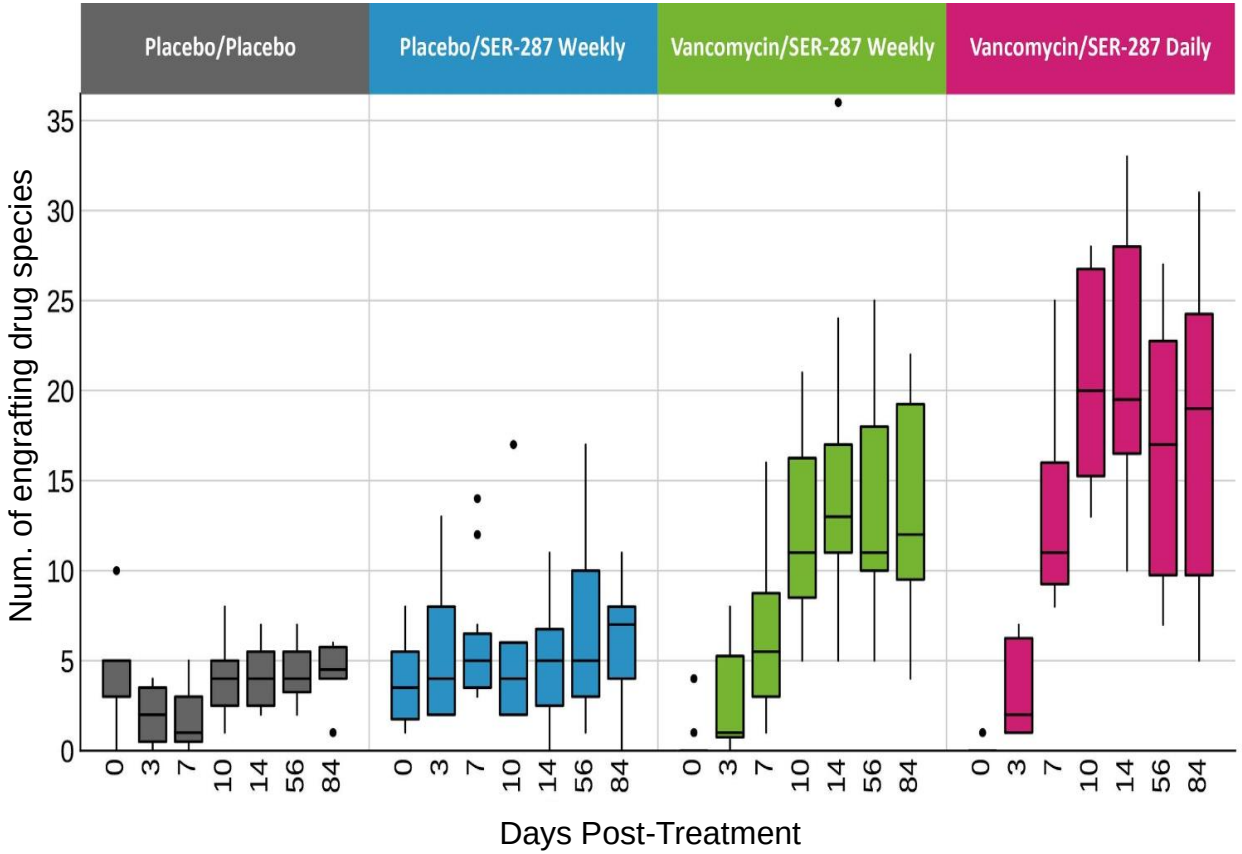
PK: SER-287 Bacteria Durably Engraft in Subjects and are Associated with Clinical Remission

Preconditioning of microbiome followed by daily dosing of SER-287 was associated with greatest engraftment & clinical remission

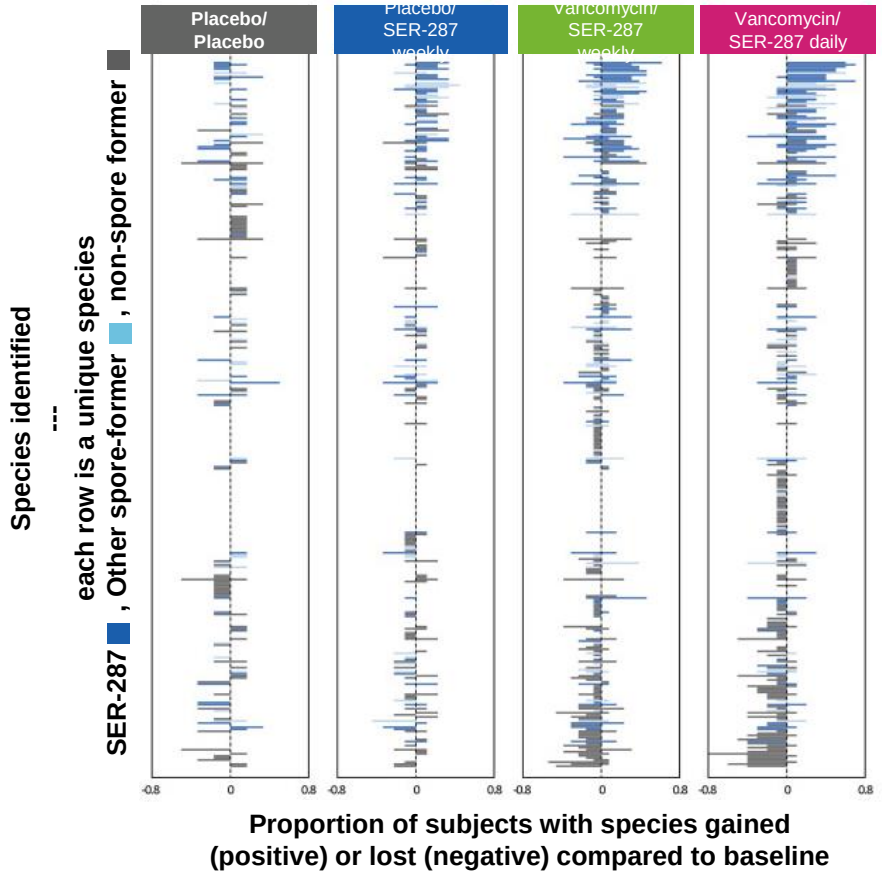




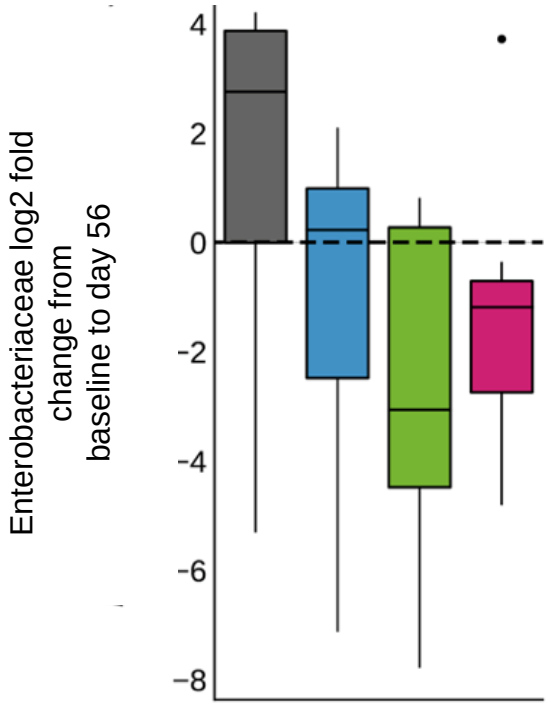
Henn et al. 2021. Gastroenterology

PD: SER-287 Restructures the Microbiome and Reduces the Abundance of Pro-Inflammatory *Enterobacteriaceae*

SER-287 treatment results in a broad shift in the overall composition of spore & non-spore gut species by 8 weeks post-treatment



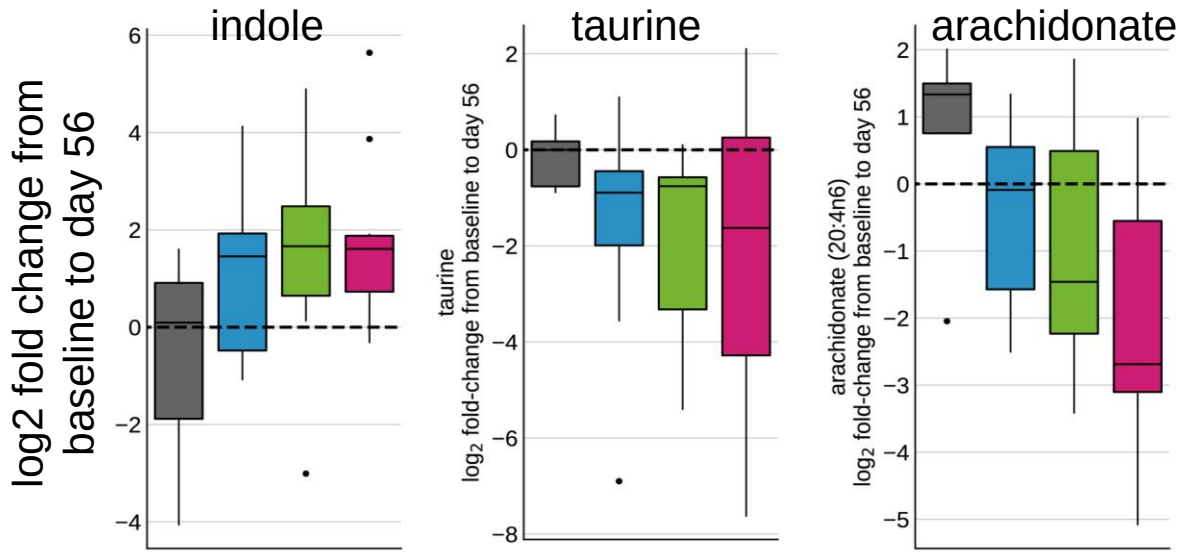
Decrease in pro-inflammatory *Enterobacteriaceae* post-treatment is associated with SER-287 treatment & clinical remission



Henn et al. 2021. Gastroenterology

PD: Clinical Remission is Significantly Associated with Changes in Microbiome and Microbe-Associated Metabolism

Microbially-mediated metabolites that modulate host inflammation & barrier integrity are significantly associated with SER-287 treatment & clinical remission

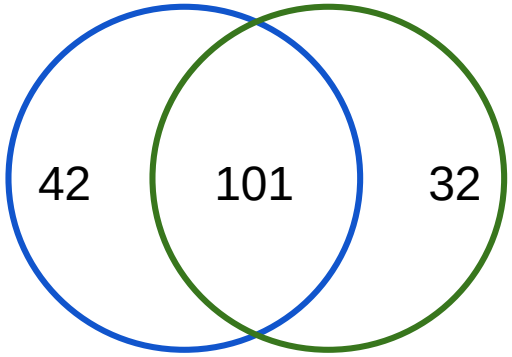


38 metabolites associated with both SER-287 & clinical efficacy

Henn et al. 2021. Gastroenterology

PD: Intestinal Biopsy Gene Expression Data Support SER-287 Treatment Association with Modulation of Multiple Host Inflammation & Immune Pathways

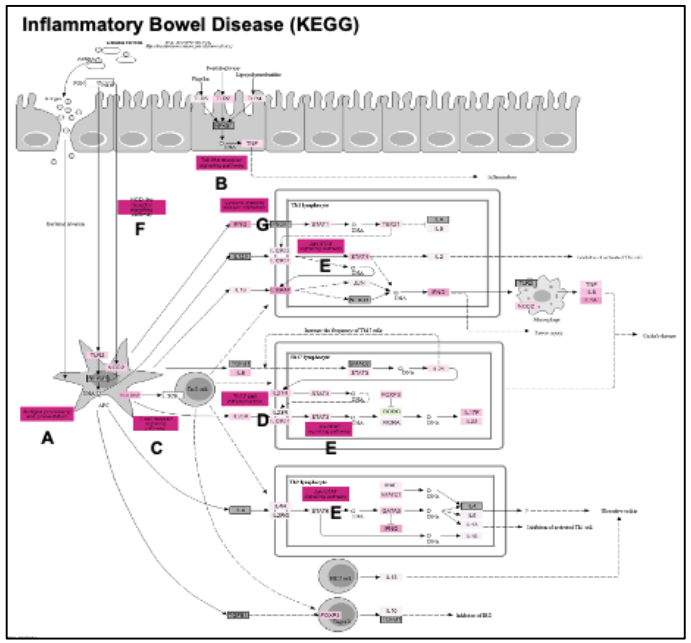
Pathways associated with treatment with SER-287



Pathways associated with clinical remission in UC patients

e.g. Shared Pathways

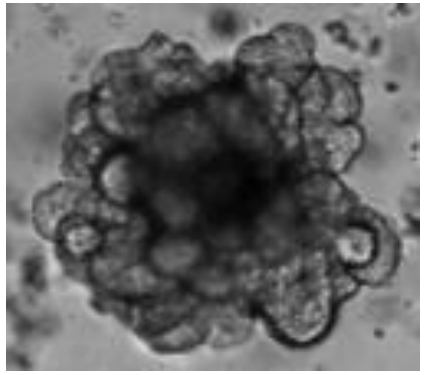
Cytokine-cytokine receptor interaction
Chemokine signaling
Jak-STAT signaling
TNF signaling
Th17 cell differentiation
Th1 and Th2 cell differentiation
T cell receptor signaling
NK cell mediated toxicity
NF-kappa B signaling
IL-17 signaling
Toll-like receptor signaling



In vitro Human Cell-Based Assays Can Confirm SER-287 MoA and Demonstrate Direct Modulation by Drug Bacteria

Example: Induce Remission-Associated Transcriptional Changes in Colonic Organoids *In Vitro*

Primary colonic organoids



+/- IFNγ

+/- SER-287
SER-301

Gene expression analyses

KEGG pathway	Human Colonic Organoids		SER-287 Ph1B Biopsies
	IFNg vs. media NES	SER-287 + IFNg vs. IFNg NES	Remitters vs. Non Remitters NES
Cell death pathways			
Apoptosis	1.449	-1.442	*-1.101*
Necroptosis	2.094	-1.971	*-1.130*
Inflammation-related pathways			
Inflammatory bowel disease	2.560	-1.615	-2.506
IL-17 signaling	2.166	-1.590	-1.839
Cytokine-cytokine receptor interaction	3.033	-2.238	-2.429
JAK-STAT signaling	2.201	-1.710	-2.166
NF-kappa B signaling	2.401	-1.879	-2.237
TNF signaling	3.153	-1.790	-2.046
Toll-like receptor signaling	2.371	-1.607	-2.128
NOD-like receptor signaling	3.082	-2.156	-1.845
Antigen processing and presentation	2.937	-1.205	-0.783
Other signaling pathways			
PPAR signaling pathway	*-1.348*	1.501	*1.051*

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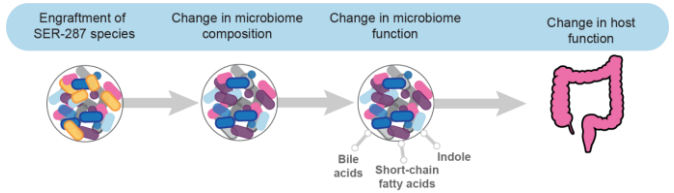
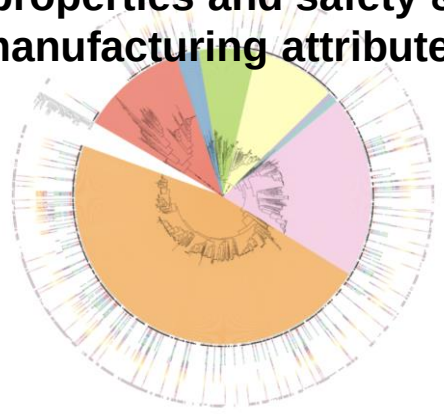
SER-301: Next Generation Investigational Microbiome Therapeutic for UC Designed to Optimize Desired Pharmacological Properties

SER-287 microbiome signatures of clinical remission



Microbiome signatures from across clinical portfolio & collaborations

Expansive strain library with characterized functional properties and safety & manufacturing attributes



In silico **Computational design of consortia**

> 30 design parameters

In vitro Screening of Compositions

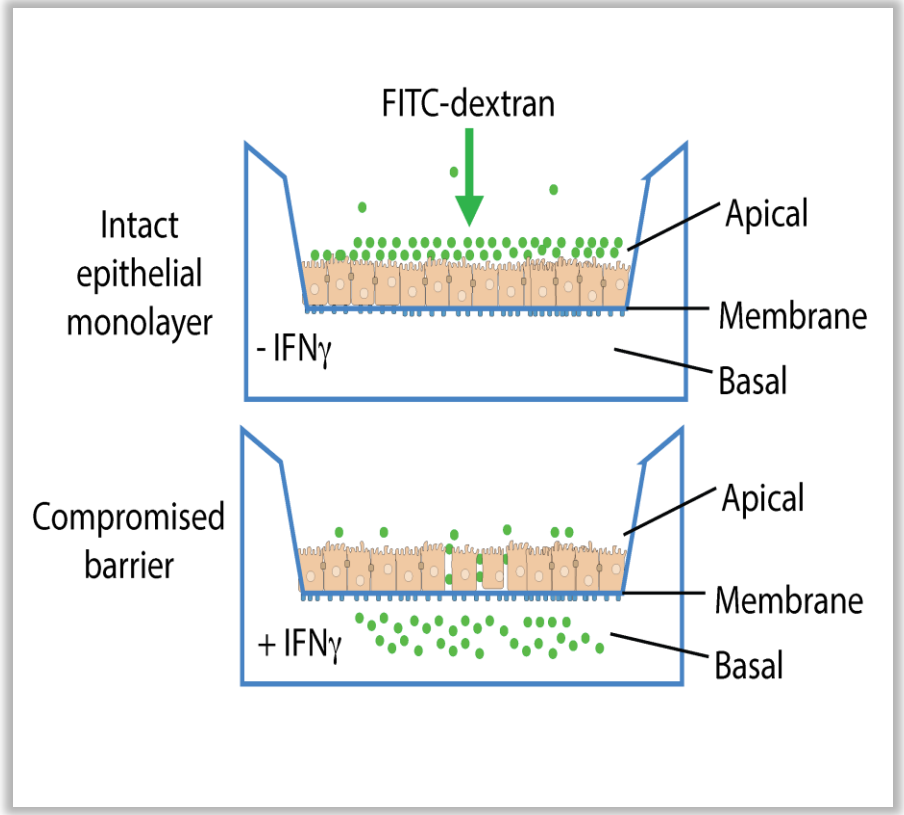
In vivo Confirmation of Activity

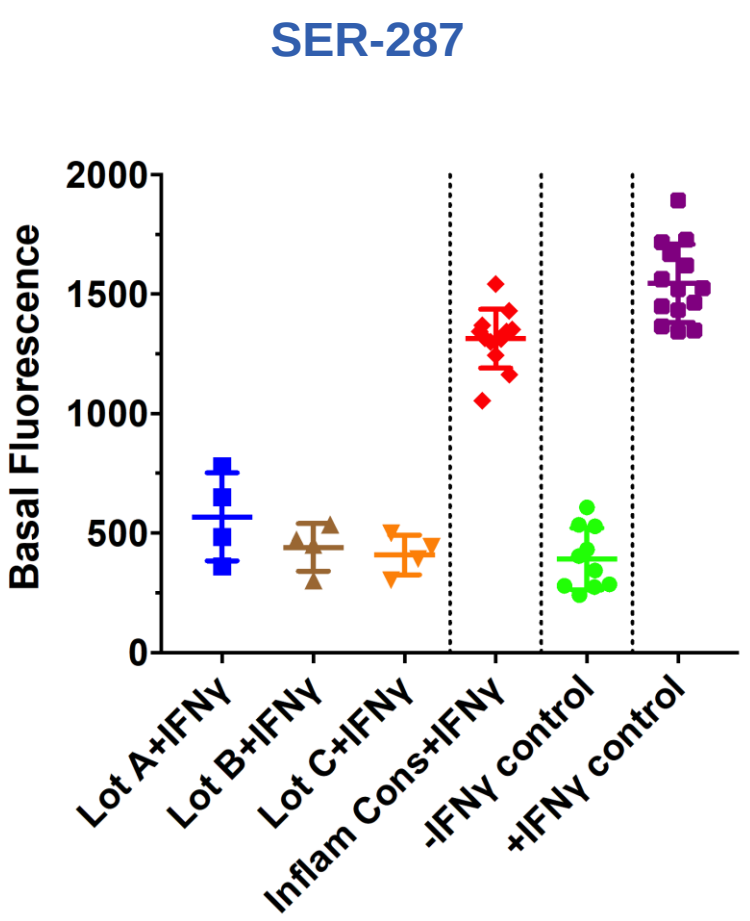
SER-301

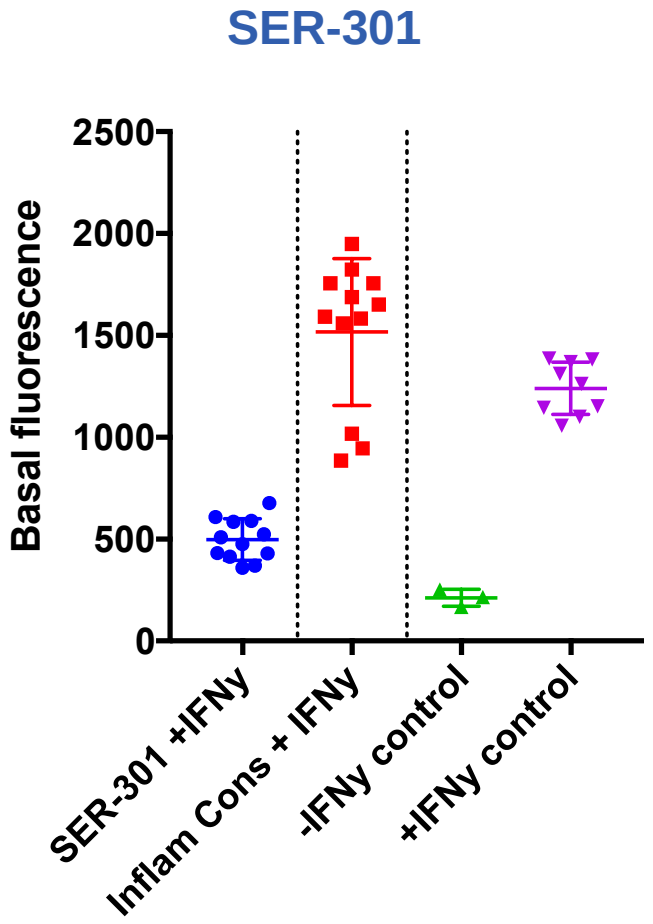
SERES THERAPEUTICS™

In vitro Human Cell-Based Assays Can Confirm SER-287 MoA & Enable Optimization of Pharmacological Properties of SER-301

Example: protect epithelial barrier from INFγ-mediated damage in vitro







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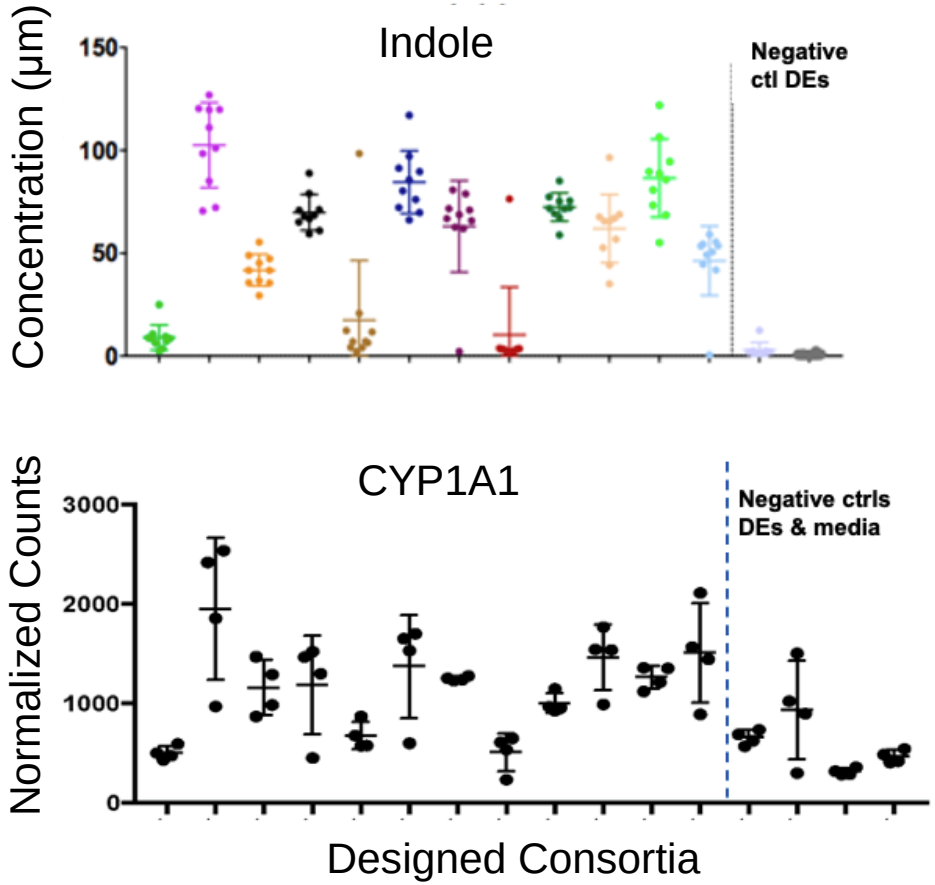
In vitro Human Cell-Based Assays Enable Optimization of Pharmacological Properties of Consortia Like SER-301

Example: Indole production and activation of UC-relevant anti-inflammatory genes in organoid model for UC



Measured function: indole production

- Bacterial tryptophan metabolite associated with clinical efficacy in SER-287 Ph1B.
- Known agonist of Ahr pathway which is involved in epithelial barrier integrity and immunomodulation.

Transcriptional correlate: *CYP1A1*

- Encodes an enzyme of the cytochrome P450 superfamily, acting in lipid and xenobiotic metabolism.
- Under the control of Ahr pathway, involved in barrier protection and immunomodulation.

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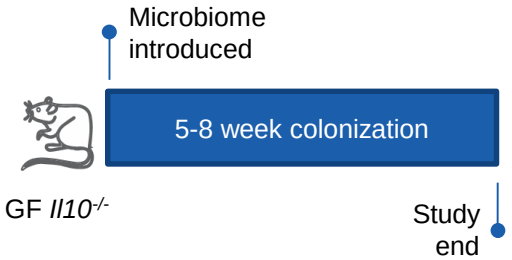
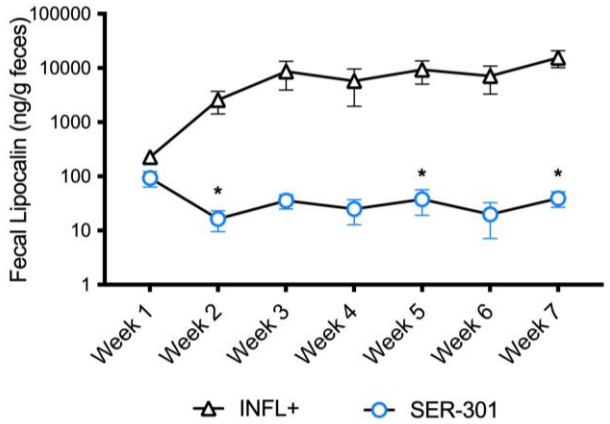
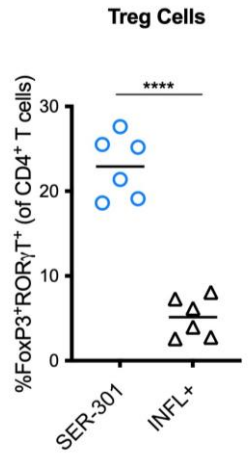
SER-301 Promotes Regulatory Immune Responses and Does Not Induce Colitis in a Spontaneous Colitis Mouse Model



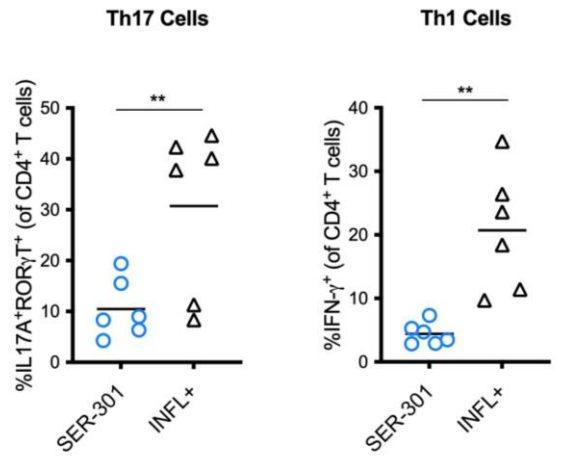
Fecal lipocalin levels remain or below baseline



Anti-inflammatory Tregs are increased



Pro-inflammatory Th1 and Th17 cells are not induced



Mice were colonized with either SER-301 or a composition containing strains isolated from UC patients with proinflammatory properties ("INFL+").

Digestive Disease Week 2021 – “Poster of Distinction”

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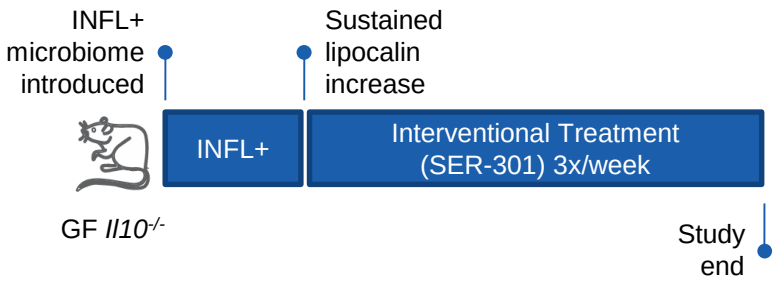
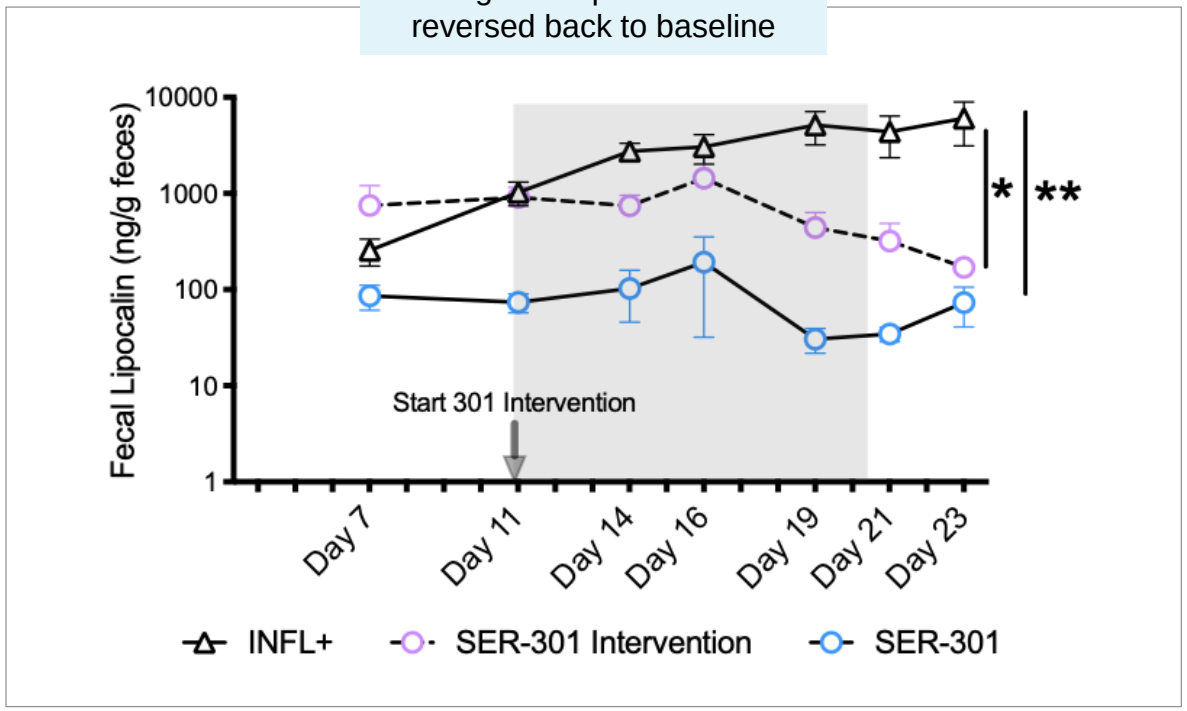
‘Avatar Mouse’ Interventional Treatment Model Using SER-301 Attenuates Intestinal Inflammation in the *IL10$^{-/-}$* Spontaneous Colitis Mouse Model



Rising fecal lipocalin levels reversed back to baseline



Mice first colonized with the proinflammatory INFL+ composition received interventional doses of SER-301 after intestinal inflammation was established.

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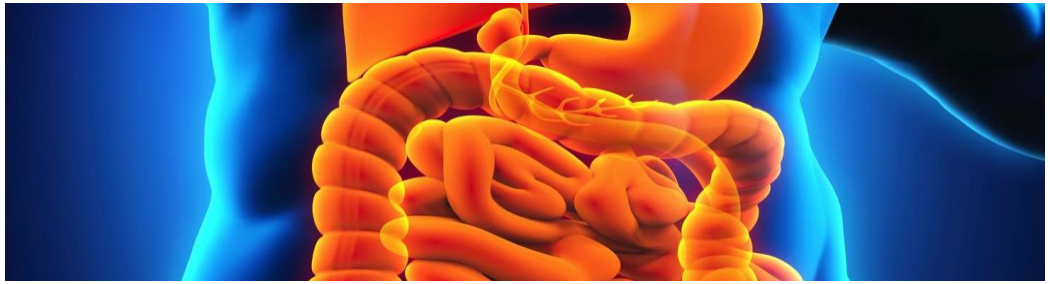
Opportunity for Microbiome Therapeutics in Additional Therapeutic Areas



- Deep understanding of the sweeping role of the microbiome in health:
  - Resistance to pathogens
  - Gut & systemic inflammation
  - Innate & adaptive immunity
  - Regulation of metabolism
- Novel drug discovery and development platform
- Option to pursue multiple diseases with high unmet need

Highly productive R&D engine pursuing multiple promising potential opportunities

- Infectious (e.g. Antibiotic-resistant infections)
- Inflammatory (e.g. Crohn's, pouchitis, RA)
- Oncology (e.g. tumor progression & bacteremia)
- Immune modulation & autoimmune diseases
- Metabolic & cardiovascular (e.g. NASH, Type 1 Diabetes)
- Neurologic & CNS diseases

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Q&A

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