ADVANCING GI PATIENT CARE 2022

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Beyond Probiotics in GI Diseases: How Can We More Effectively Manipulate the Gut Microbiota?

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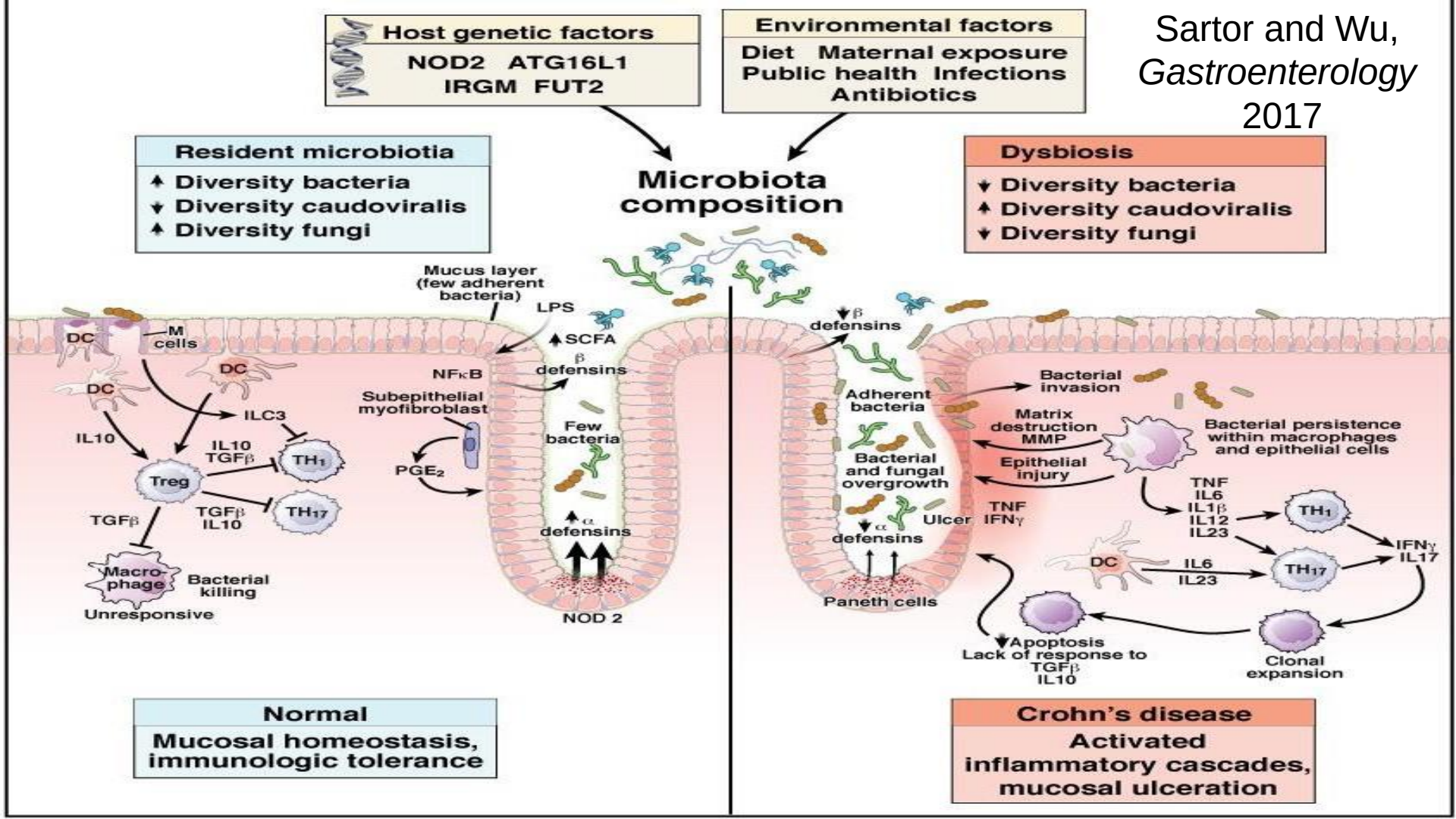
Rationale of Manipulating Gut Bacteria

- Abnormal microbial balance in many GI diseases
- Microbiota contribute to multiple GI diseases: IBD, pouchitis, *C. diff*, fatty liver, ETOH hepatitis
- Restoring microbial balance is an attractive therapeutic alternative or adjuvant approach to prolonged immunosuppression, repeated antibiotics and available therapies



Sartor and Wu, *Gastroenterology* 2017

Protective Effects of the Normal Microbiome

Property — **Example**

- Colonization resistance (prevent infection – *Clostridialis difficile*)
- Activate innate epithelial defenses (TLR/NFkB, NLR in epithelial cells, stimulation of anti-microbial peptides, mucus production)
- Educate immune responses (mucosal homeostasis – IL-10, TGFβ, inducible Treg, enhanced killing of intracellular bacteria)
- Host nutrition (SCFA provide nutrition for colonic epithelial cells, vitamin K synthesis)
- Modulate neuronal function (modulate pain threshold, enteric nervous system, CNS responses)

Microbiome Association With Immune-Mediated Inflammatory Diseases

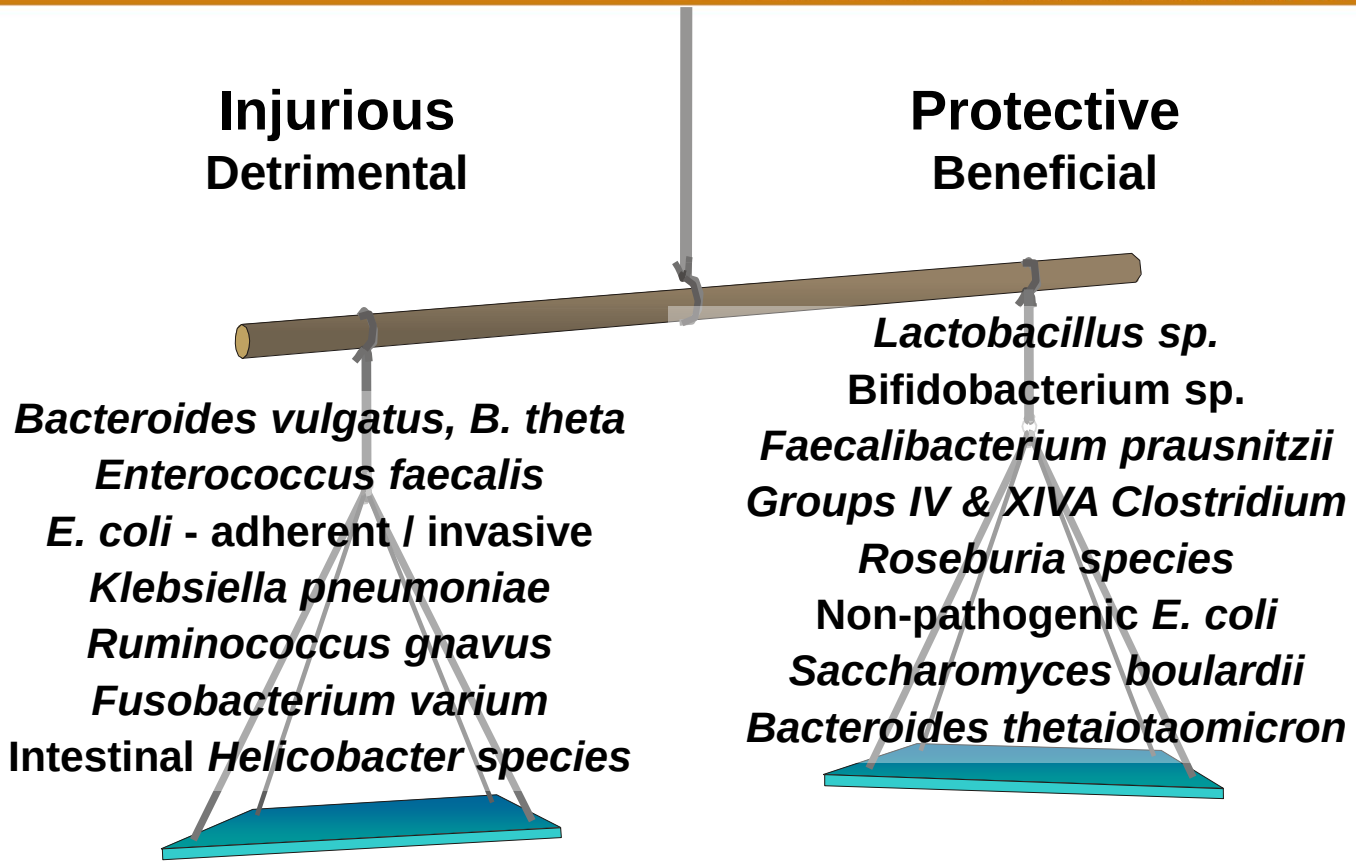
Strong
(? Causal)

- ***Crohn's disease***
- ***Ulcerative colitis, pouchitis***
- Metabolic syndrome, T2D
- ***Fatty liver, ETOH hepatitis***
- ***Spondyloarthropathy***
- Atherosclerosis, bronchitis
- ***Colon cancer***, cystic fibrosis

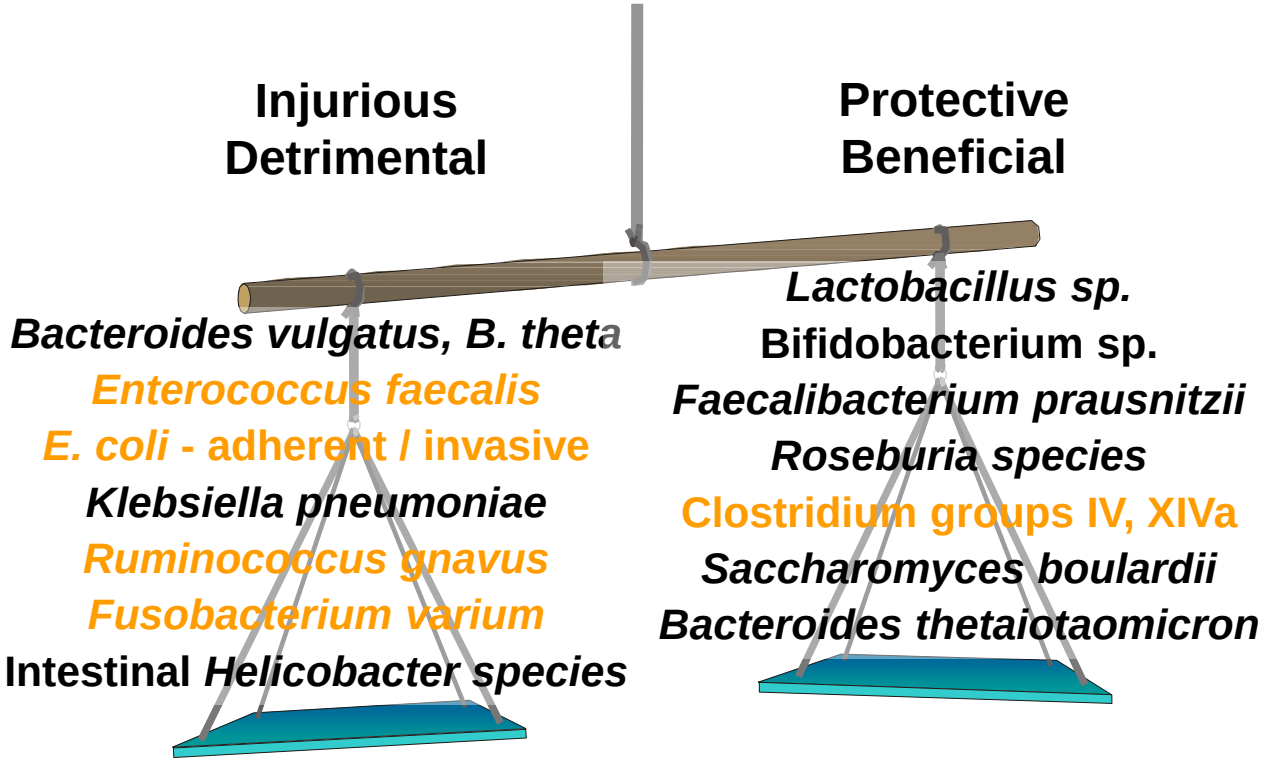
Weaker
(? Secondary but contributory)

- ***PSC***
- Psoriasis, psoriatic arthritis
- Type 1 diabetes
- Rheumatoid arthritis
- Asthma
- Osteoarthritis
- ***Celiac disease***
- Uveitis

Intestinal Inflammation vs. Homeostasis Depends on the Relative Balance of Beneficial vs. Detrimental Bacteria: *This Balance Is Unique in Each Individual - Each Individual Responds Differently to Various Bacterial Species*



Intestinal Inflammation vs. Homeostasis Depends on the Balance of Beneficial vs. Detrimental Bacteria: *Selectively Altering this Balance in an Individual Should Treat Ongoing Inflammation and Potentially Prevent Onset/Recurrence of Disease in High-Risk Hosts*



Strategies to Correct Dysbiosis in IBD

- ***Standard antibiotics and probiotics***
- Replace entire microbiome (fecal microbial transplant – *FMT*)
- Remove aggressive components (*antibiotics*, *phages, block attachment*)
- Restore missing protective microbes
- Restore missing protective *functions*
- Create a less hostile environment (*diet, remove toxic metabolites and metabolites that promote dysbiosis*)

Probiotics: Clinical Trials in IBD

UC:

- *E. coli 1917 Nissle* equal to low dose 5-ASA (1.6 gm/day)[1]
- VSL #3 – uncontrolled, 75% remission 12 mo.[2], 87% response for 6 wks[3]

Crohn's:

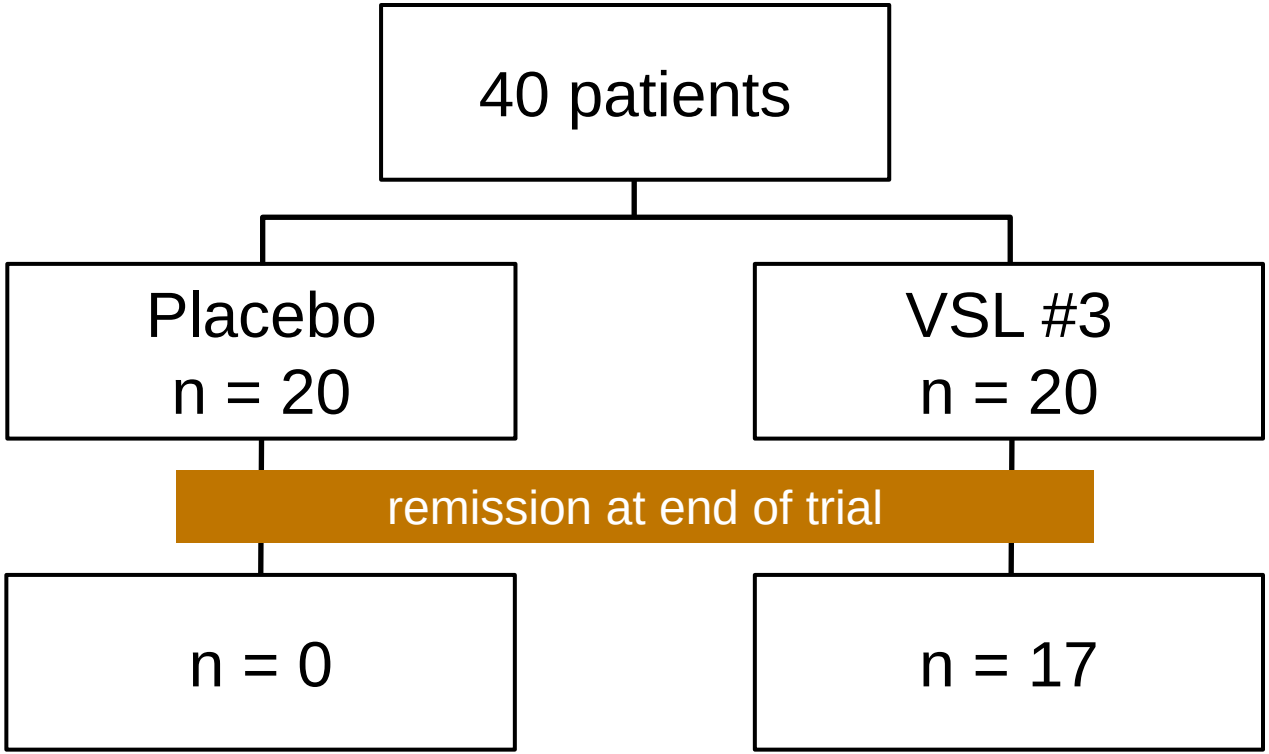
- *E. coli Nissle* superior to placebo[4]
- *Lactobacillus GG* – no effect postoperative relapse[5]

Pouchitis:

- VSL #3 – superior to placebo – treat refractory, recurrent[6]
- VSL #3 – superior to placebo – postop prevention[7]
- *Lactobacillus rhamnosus GG* – no benefit active disease[8]

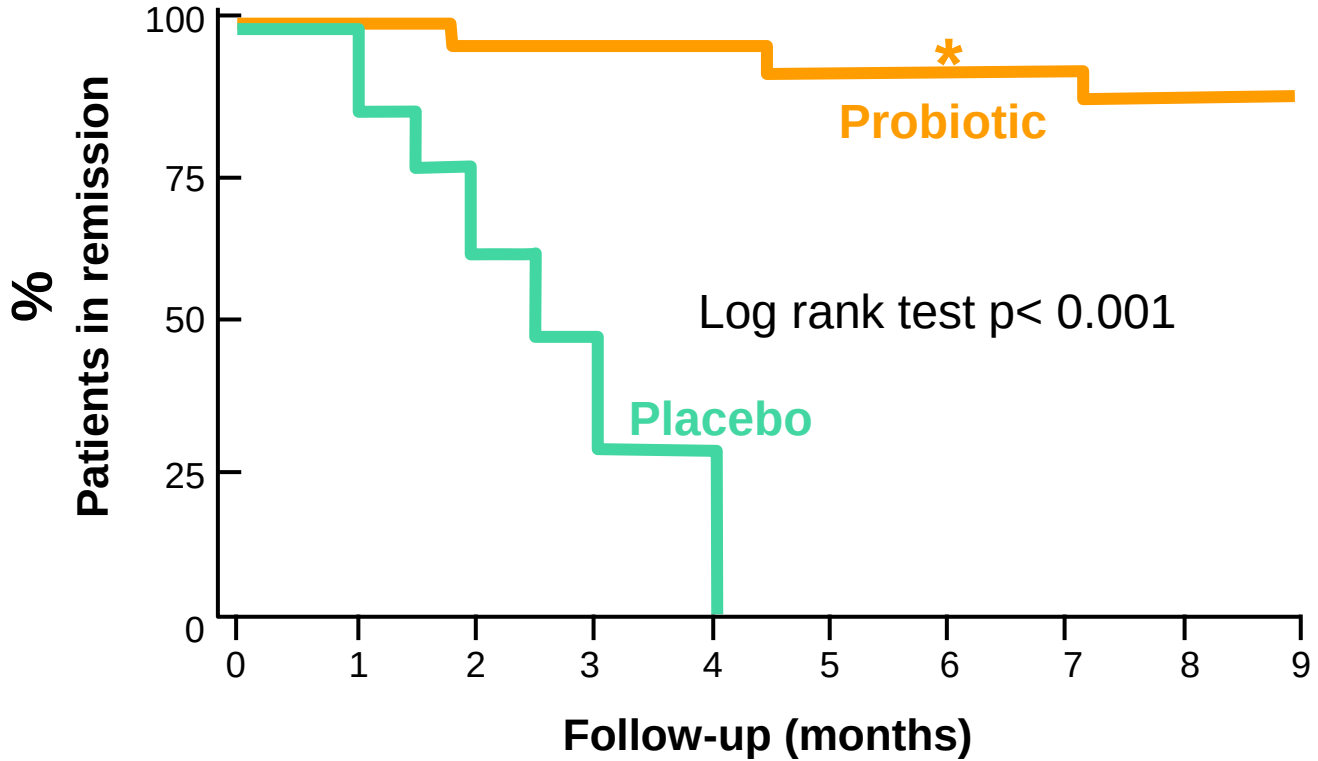
1. Kruis. 1997; Rembacken. 1999; Kruis. 2001; 2. Venturi. 1999; 3. Fedorak. 2005; 4. H. Malchow. 1997; 5. C. Prantera. 2002; 6. P. Gionchetti. 2000, 2001; 7. P. Gionchetti. 2003; 8. J. Kuisma. 2003.

VSL#3 Maintains Remission in Chronic, Relapsing Pouchitis



Gionchetti et al. *Gastroenterology.* 2000;119:305-309.

Pouchitis – Maintenance of Remission by VSL3



Gionchetti P et al. *Gastroenterology*. 2000; 119:305.

AGA Guidelines for Probiotics in GI Disorders

1. In patients with ***C difficile* infection**, we recommend the use of probiotics only in the context of a clinical trial. (***no evidence, knowledge gap***)

2. In adults and children on **antibiotic treatment**, we suggest the use of *S. boulardii*; or the 2-strain combination of *L. acidophilus* CL1285 and *L. casei* LBC80R; or the 3-strain combination of *L. acidophilus*, *L. delbrueckii* subsp *bulgaricus*, and *B. bifidum*; or the 4-strain combination of *L. acidophilus*, *L. delbrueckii* subsp *bulgaricus*, *B. bifidum*, S. *salivarius* subsp *thermophilus* over none or other probiotics to **prevent *C difficile*** infection. (***conditional, low evidence)***

Su et al. *Gastroenterology.* 2020.

AGA Guidelines for Probiotics in GI Disorders

3. In adults and children with **Crohn's disease**, we recommend the use of probiotics only in the context of a clinical trial ***(knowledge gap)***

4. In adults and children with **ulcerative colitis**, we recommend the use of probiotics only in the context of a clinical trial ***(knowledge gap)***

5. In adults and children with **pouchitis**, we suggest the 8-strain combination of *L paracasei* subsp *paracasei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp *bulgaricus*, *B. longum* subsp *longum*, *B. breve*, *B. longum* subsp *infantis*, and *S. salivarius* subsp *thermophilus* over no or other probiotics ***(conditional, very low evidence)***

Su et al. *Gastroenterology.* 2020.

AGA Guidelines for Probiotics in GI Disorders

6. In symptomatic children and adults with **IBS**, we recommend the use of probiotics only in the context of a clinical trial ***(knowledge gap)***

7. In children with **acute infectious gastroenteritis**, we suggest ***against*** the use of probiotics (***Conditional, moderate evidence***)

Su et al. *Gastroenterology.* 2020.

AGA Guidelines for Probiotics in GI Disorders

8. In preterm (less than 37 weeks gestational age), **low-birth-weight infants**, we suggest using a combination of *Lactobacillus* spp and *Bifidobacterium* spp (*L rhamnosus* ATCC 53103 and *B longum* subsp *infantis*; or *L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp *infantis*, *B bifidum*, and *B longum* subsp *longum*; or *L acidophilus* and *B longum* subsp *infantis*; or *L acidophilus* and *B bifidum*; or *L rhamnosus* ATCC 53103 and *B longum* Reuter ATCC BAA-999; or *L acidophilus*, *B bifidum*, *B animalis* subsp *lactis*, and *B longum* subsp *longum*), or *B animalis* subsp *lactis* (including DSM 15954), or *L reuteri* (DSM 17938 or ATCC 55730), or *L rhamnosus* (ATCC 53103 or ATC A07FA or LCR 35) for **prevention of NEC** over no and other probiotics. (***Conditional, moderate/ high evidence***)

Su et al. *Gastroenterology.* 2020.

Strategies to Correct Dysbiosis in IBD

- Standard antibiotics and probiotics
- ***Replace entire microbiome (fecal microbial transplant- FMT)***
- Remove aggressive components (*antibiotics*, *phages, block attachment*)
- Restore missing protective microbes
- Restore missing protective *functions*
- Create a less hostile environment (*diet, remove toxic metabolites and metabolites that promote dysbiosis*)

Don’t Like Your Microbiota? Trade It in for a New Model!

Dysbiosis

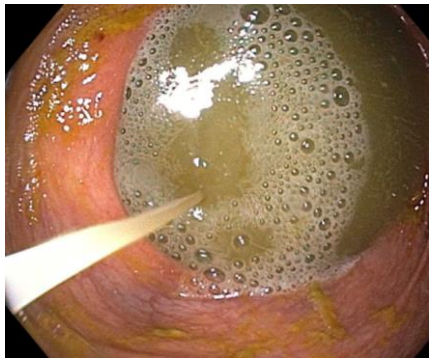
Normal microbiota

FMT Is Highly Effective for Recurrent *Clostridialis difficile*

~40 patients

Abx +/-bowel prep

Vanc + FMT



Cure at 2 months for recurrent *C. diff*

30%

90%

van Nood. *NEJM* 2013; Cammarota. *Alimentary Pharmacology Therapeutics.* 2015.

Randomised Controlled Trials

Fecal Micobial Transplant (FMT) in Ulcerative Colitis (UC)

Gastroenterology 2015

Moayyedi et al (McMaster)	Rossen et al (Amsterdam)
6 x weekly enemas **FMT** 9/38 (**24%**) v 2/37 (**5%**) P=0.03 One donor for 7 / 9 responders	2 naso-duodenal infusions wks 0 & 3 **FMT** 7/23 (**30%**) v 5/25 (**20%**) P=0.51

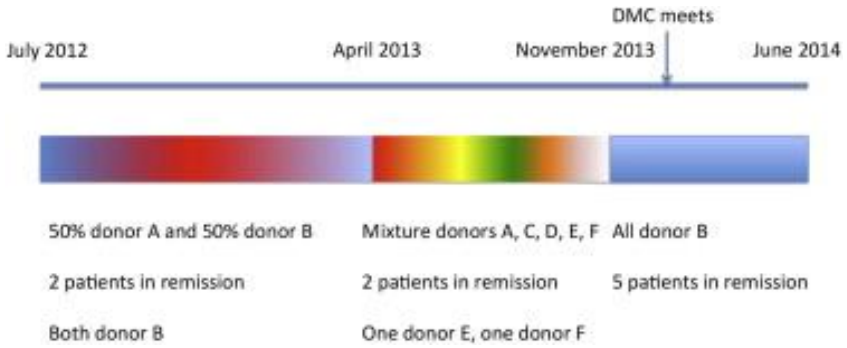
Conflicting results regarding the efficacy and optimal delivery of FMT in UC

Fecal Microbial Transplantation Induces Remission in Patients With Active UC: ***Strong Donor Effect***

Results from a Randomized Controlled Trial

	Placebo (n=37)	FMT (n=38)	*P* Value
Remission	2 (5%)	9 (24%)	.03
Response	9 (24%)	15 (39%)	.16

	Donor B	All Other Donors
Clinical Remission	7/18 (39%)	2/20 (10%)



Moayyedi P et al. *Gastroenterology*. 2015;149:102-109.

FMT for GI Diseases

Indications:

- Recurrent *C. diff* infection
- Investigational: UC; hepatic encephalopathy; Crohn's disease; pouchitis; metabolic syndrome/fatty liver; immune checkpoint inhibitor therapy

Problems:

- **Transient engraftment**
- Transmission of unknown pathogens, multidrug resistant *E. coli*
- Sepsis in immunocompromised host
- **Variability of donor microbiota and efficacy**

Summary: The ***Potential*** of Manipulating the Microbiota Remains Greater Than Current Results

- Antibiotics helpful in a few selected indications: pouchitis, Crohn's colitis, ? postoperative CD
  - Broad spectrum, combinations needs further exploration UC and CD
- Combination probiotics may help recurrent pouchitis, prevent NEC
- Prebiotics: No clear benefits, but poorly studied
- FMT variable results, but minority enter remission, limited duration, strong donor effect

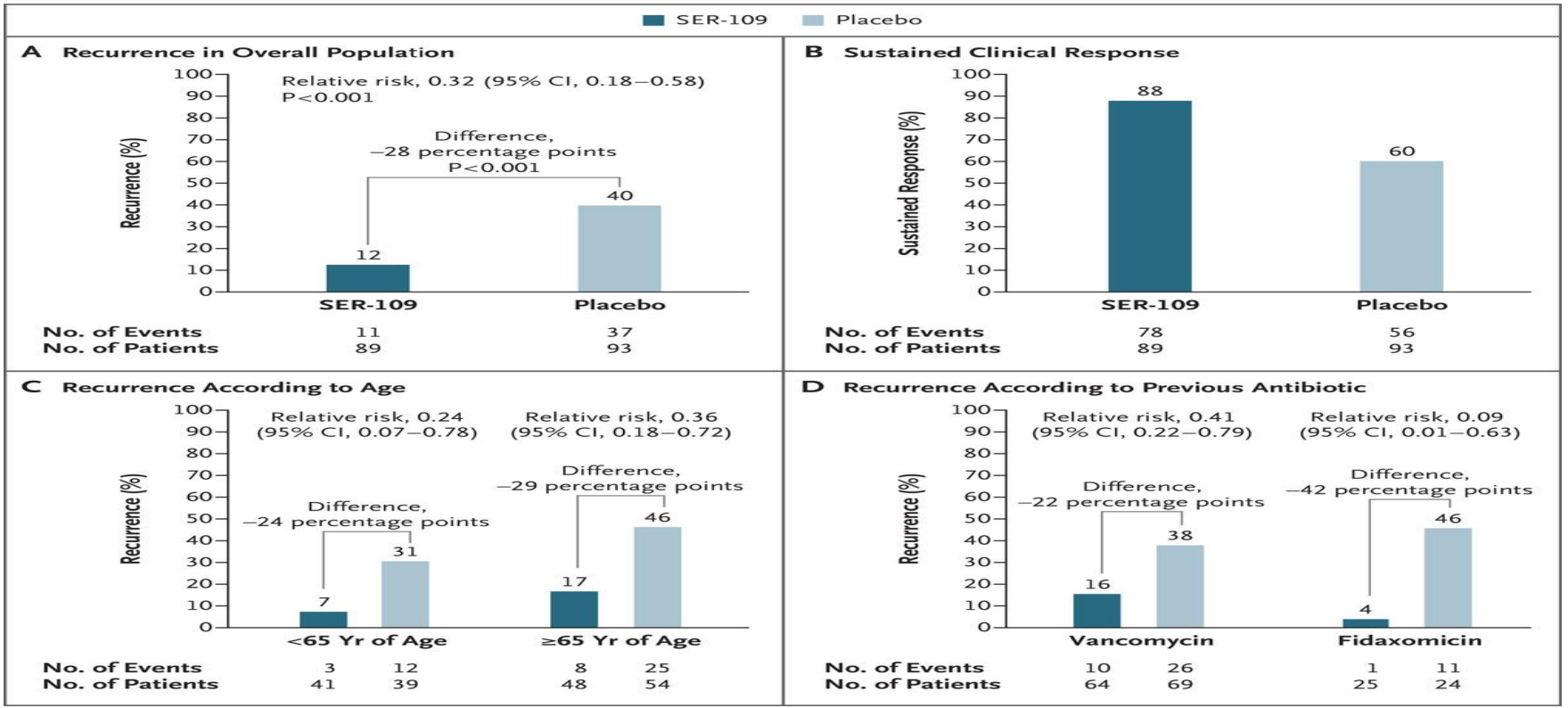
Conclusion

Either our hypothesis that resident microbiota provide the dominant drive the inflammatory response of IBD is incorrect,
or ***we are using the wrong approaches***

Synthetic Consortia of Resident Bacterial Species *vs.* Random Donor-Derived Fecal Transplants

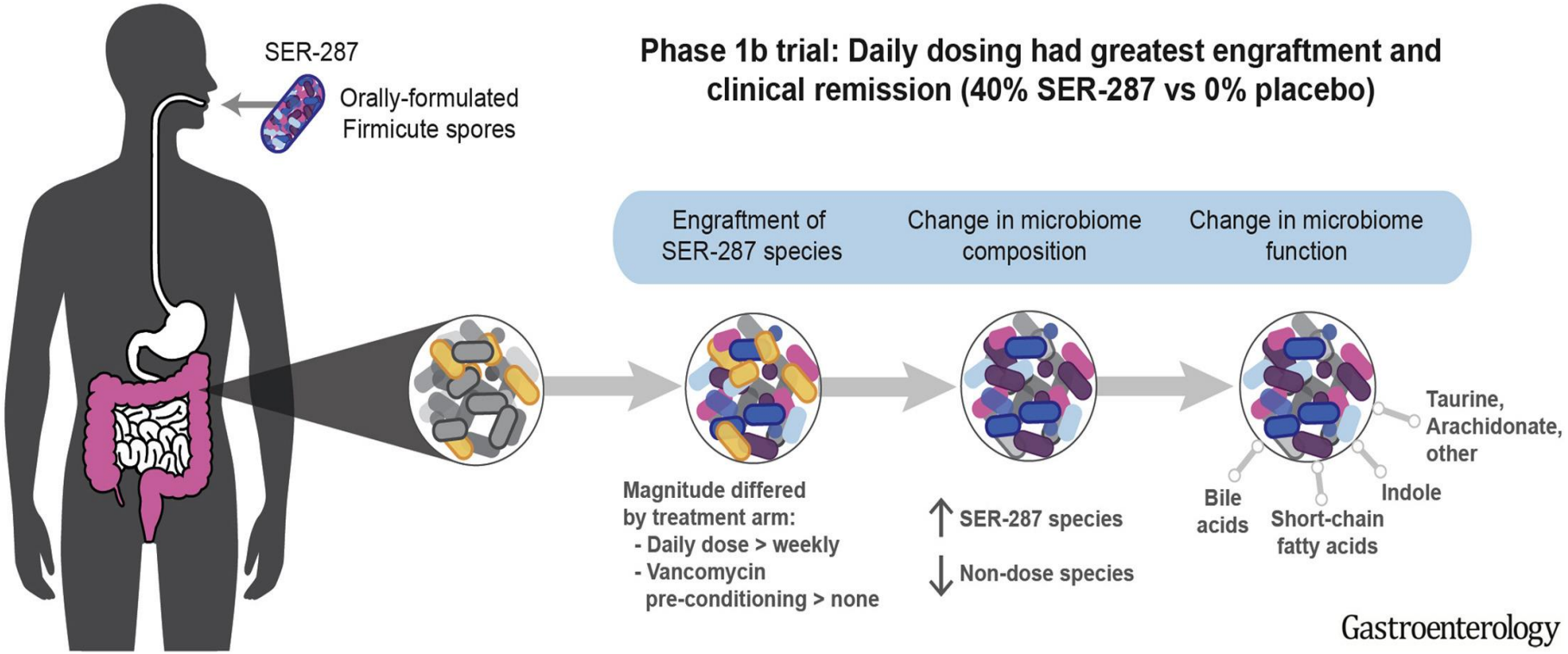
- Defined *composition* – ***eliminate risk of infections***
- Ability to **individualize *therapy*** – ***match optimal replacement for various dysbiotic profiles***
- More reproducible results – ***eliminate variability in outcomes***
- Simplify regulatory approval with defined composition
- Manufacture under standard, highly controlled culture conditions – ***eliminate variability in outcomes***
- Increase patient acceptance – ***decrease “yuk” factor***

Resident Bacterial Spores (SER-109) Decrease Recurrence of *C. difficile* Infection Up to 8 weeks (Intention-to-Treat Population)



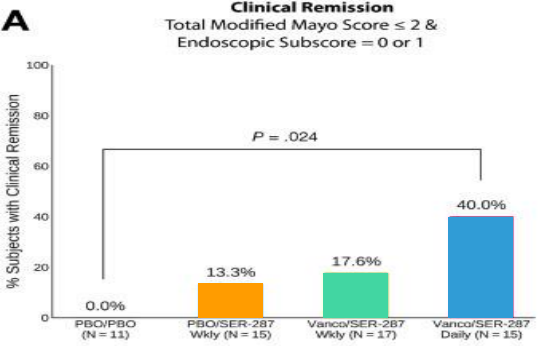
P Feuerstadt et al. *N Engl J Med.* 2022;386:220-229.

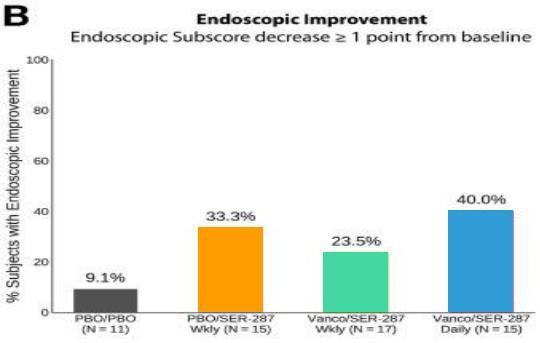
Clostridium Spores in Active UC

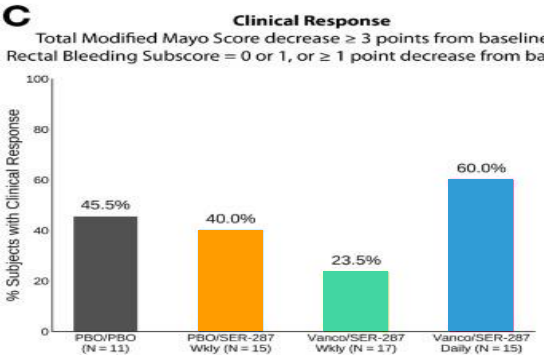


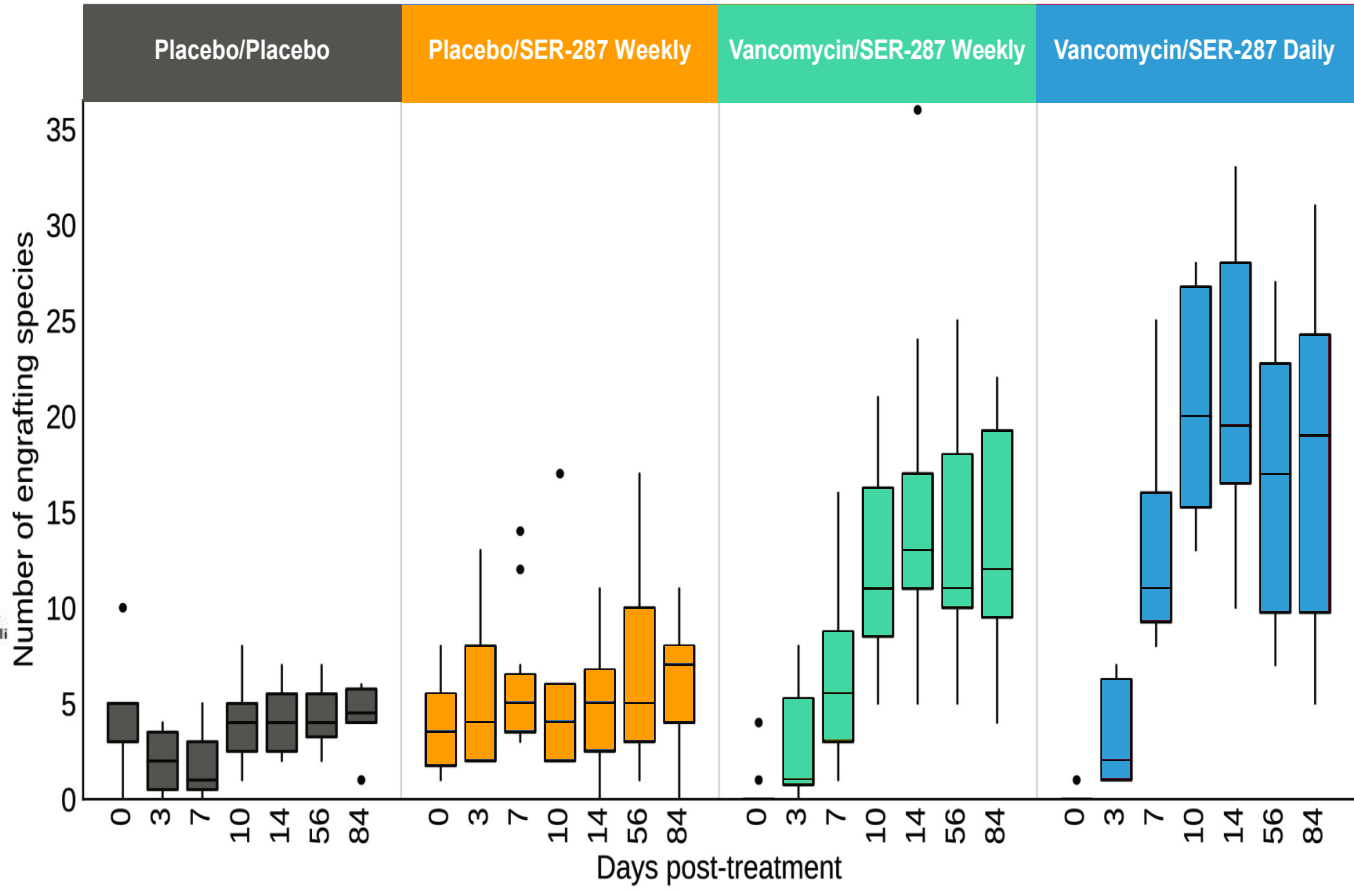
Henn et al, *Gastroenterology* 2021

Clinical efficacy is determined by spore engraftment



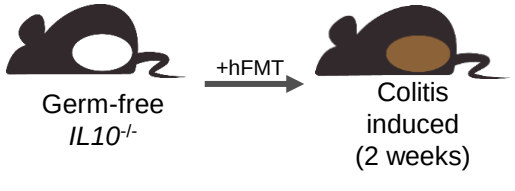




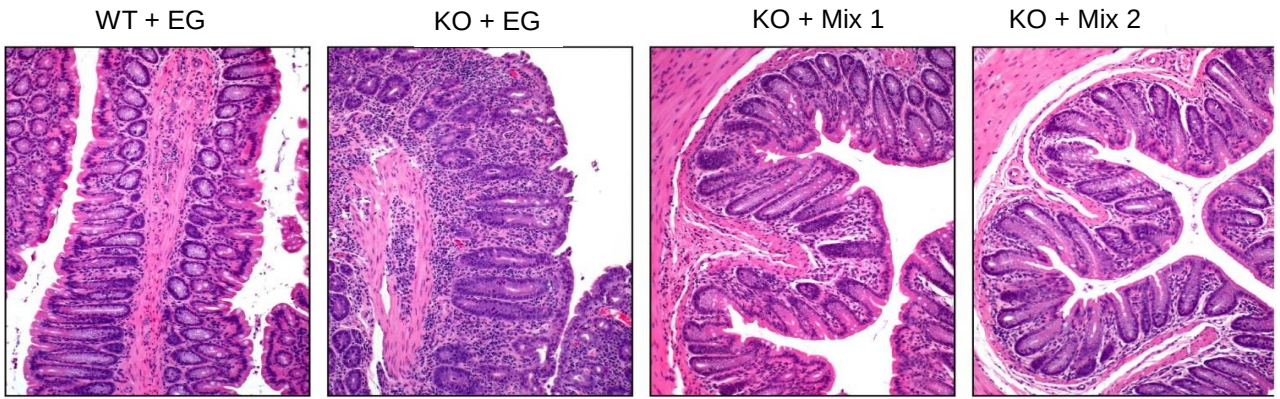


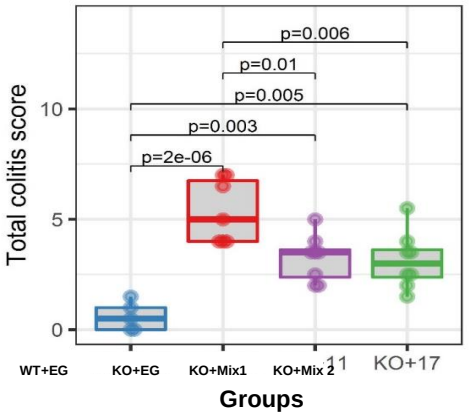
Henn et al, *Gastroenterology* 2021

17 Clostridium Stains and 11 Strain Subset Treat Colitis in a Humanized Mouse Colitis Model



- IL10 deficient mice
- Disease triggered by healthy human fecal microbiota transplant (hFMT)
- VE202 mixtures administered 2 weeks after disease initiation, when active colitis (treatment protocol)





Aki Oka, Yoshi Mishima. DDW. 2018.

Missing Microbial Functions in the IBD Dysbiotic Gut Microbiome

Function	Reference
SCFA synthesis	Arpaia et al, 2013; Smith et al, 2013; Vernia et al, 2000 & 2003
Bile acid conversion	Duboc et al, 2013
Indole synthesis	Circumstantial evidence, e.g. Berstad et al, 2015
Bacteriocin synthesis	antagonism
Siderophore synthesis/ uptake	Niche competition with opportunistic pathogens
Essential nutrient fluxes	Key for engrafting and optimal performance

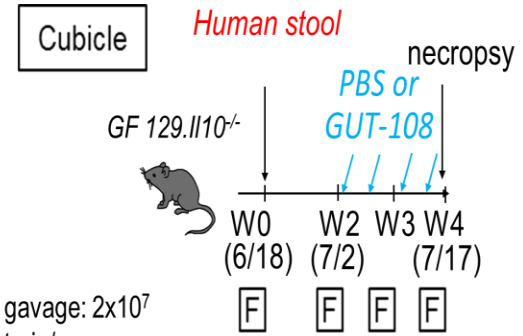
Van der Lelie et al. *Nat Comm.* 2021.

GUT-108 Experimental Design

Disease triggered by human fecal microbiome transplant in IL-10 -/- mice

Strain Nr.	Butyrate	Propionate	GABA	Indole	Bile Acid
I		+	+	+	7-α-HSD, CGH, 3-oxo-5-α
II		+	+	+	CGH, 3-oxo-5-α, SBS
III	+				7-α-HSD, CGH, Taurine uptake
IV	+		+		7-α-DH, 7-α-HSD, CGH, SBS
V		+	+		CGH, 3-oxo-5-α
VI	+				7-α-HSD, CGH, LCD, Taurine uptake
VII					3-α-HSD, 3-β-HSD
VIII					7α/β –DH, LCD
IX					7-α-DH, 3-α-DH, 7-α-HSD, CGH, LCD
X		+	+	+	SBS
XI	+	+			LCD

Van der Lelie et al.
Nat Comm. 2021.



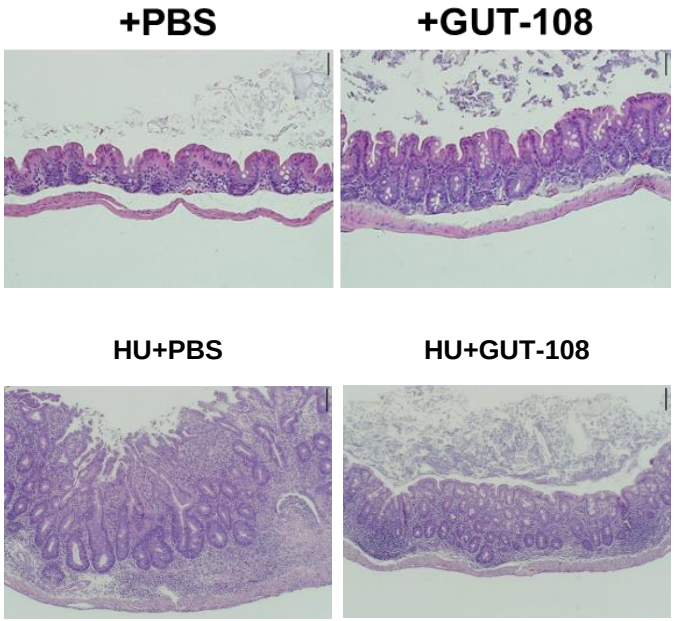
GUT-108 gavage: $2x10^7$ bacteria/strain/mouse

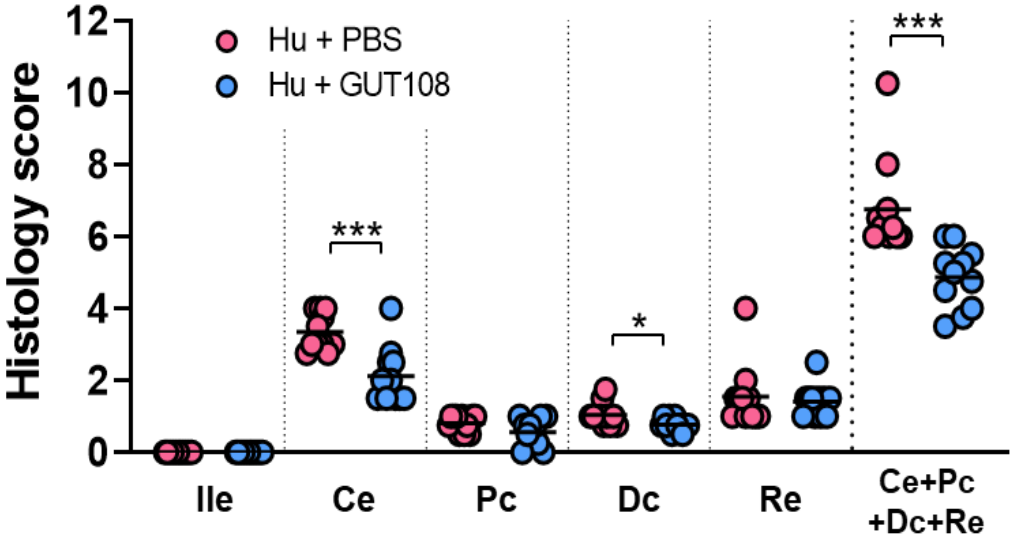
GUT-108

- Simplified 11 strain consortium based on proprietary strains.
- Same functions covered as by GUT-103, but further optimized for IPA synthesis and bile acid conversion.

GUT-108 Therapeutic Study: Reversing Colitis Caused by Human Fecal Transplant in IL10 -/- Mice

Histologic evidence of colitis





Van der Lelie et al. *Nat Comm.* 2021.

Improving Current Techniques to Restore a Healthy Microbiota

- Select approach and targets based on an individual's microbiota pattern ***(customized approach- selectively replace missing/ dysfunctional bacteria)***
- Concentrate on ***protective resident species*** with a good chance to colonize and function in the intestine
- ***Refine fecal transplants,*** identify characteristics of optimal donors and determine their effectiveness and duration in IBD
- Determine whether ***dietary approaches*** can alter composition and metabolic function of microbiota in therapeutic or preventive manners
- ***Target outcomes based on metabolic function and dominant antigens*** rather than bacterial profiles

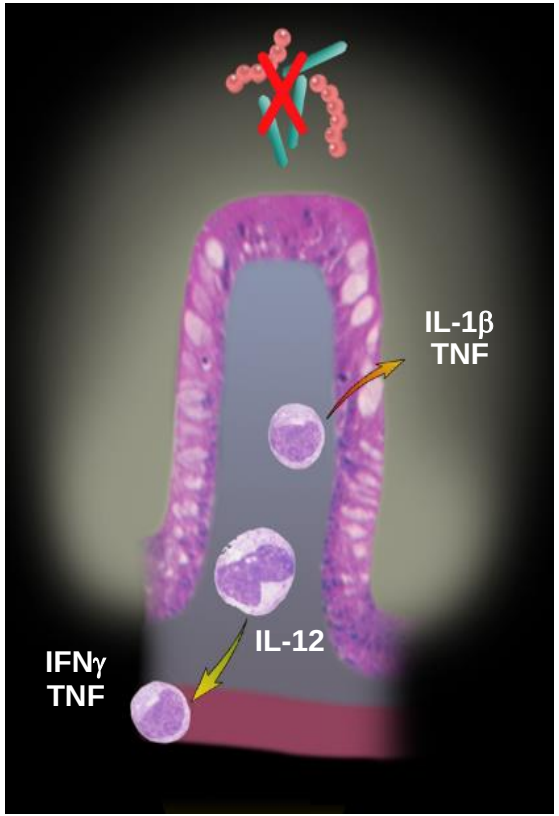
Sequential, Safer Approach to Treating IBD: Maintain Long Term Remission by Correcting Dysbiosis and Dietary Management

Eliminate antigenic drive

Antibiotics, probiotics *prebiotics, diet, fecal transplant,* block bacterial binding, enhance bacterial killing (stimulate defensins) Remove pathobiont-promoting metabolites

Paralyze TH_1, $TH_{17,}$ innate immune responses

Steroids, biologics, small molecules



Restore mucosal barrier function

SCFAs, probiotics, fiber/ prebiotics

Stimulate regulatory cell activity (TR_1, TH_3 , Treg, B cells, DC)

Omega 3 FAs, retinoic acid, vit D, *Bacteroides fragilis PSA. Clostridium subsets*, *F. prausnitzii*, Lachnospiraceae, rationally designed consortia