The Gut Microbiome and Inflammatory Bowel Disease: Interplay and Potential Treatment

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Objectives

- Understand the importance and function of the human microbiota
- Understand how the immune system is designed to coexist with the microflora and react to pathogens
- The intestinal Microflora in patients with Inflammatory Bowel Disease
- Potential manipulations in the microbiota that may play a therapeutic role in the management of IBD

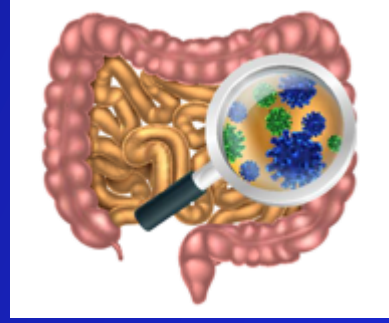
Gut Microbiome

- Absorptive surface area of the human intestine: **250 m2**

- Colonized by **trillions** of individual microorganisms

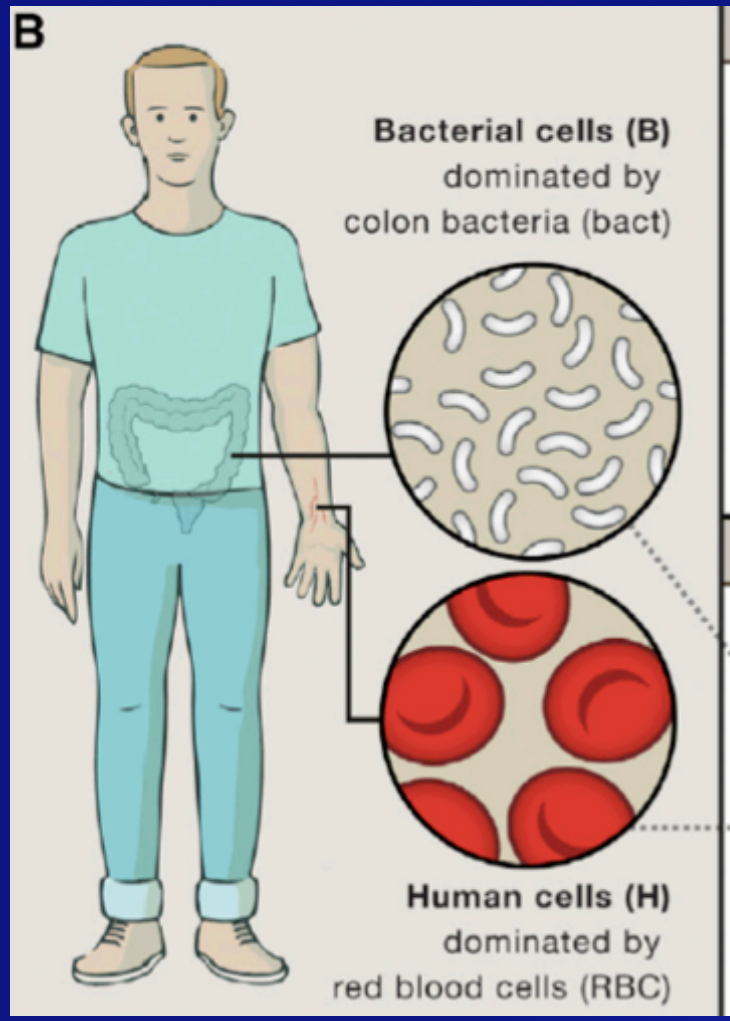
  Bacteria, archaea, fungi, phages, eukaryotic viruses

Functions of the Gut Microbiome



- Extracting indigestible ingredients from food and synthesizing nutritional factors, i.e Vitamins
- Development of systemic and intestinal immune system
- Provides signals for epithelial renewal and maintaining gut integrity
- Detoxifying harmful Xenobiotics (substances that are foreign to the body)
- Secretion of antimicrobial products, negatively selecting against pathogenic bacteria

Are we Really Outnumbered?



1972 estimate (Luckey, Am. J. Clin. Nutr.)

Used all gastrointestinal (GI) tract volume

$$\frac{B}{H} = \frac{(V_{GI} \sim 1L) \times (n_{bact} \sim 10^{14}\ cells/L)}{\sim 10^{13}} \sim 10^{14}$$

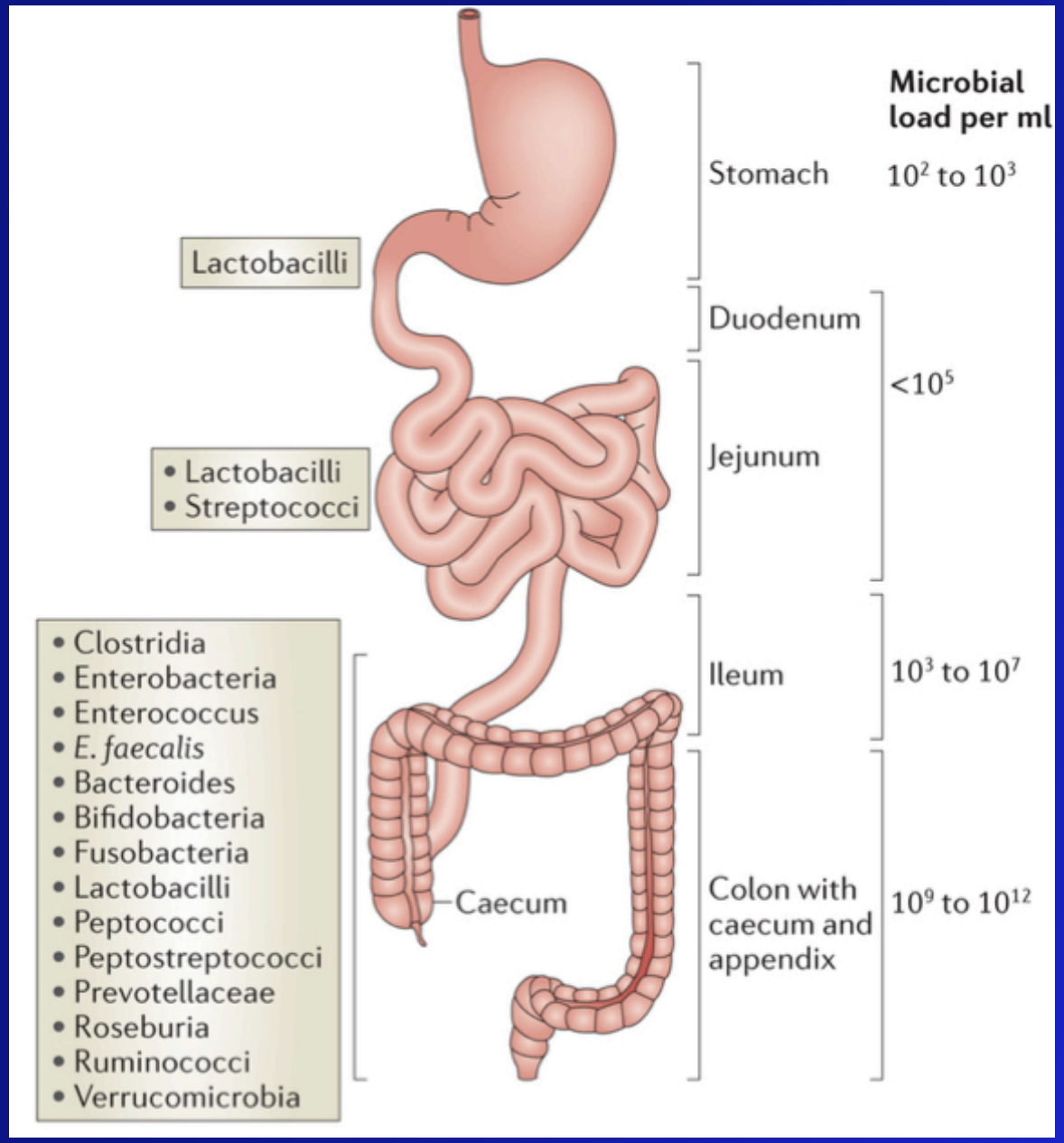
No primary reference

2016 estimate (Current study)

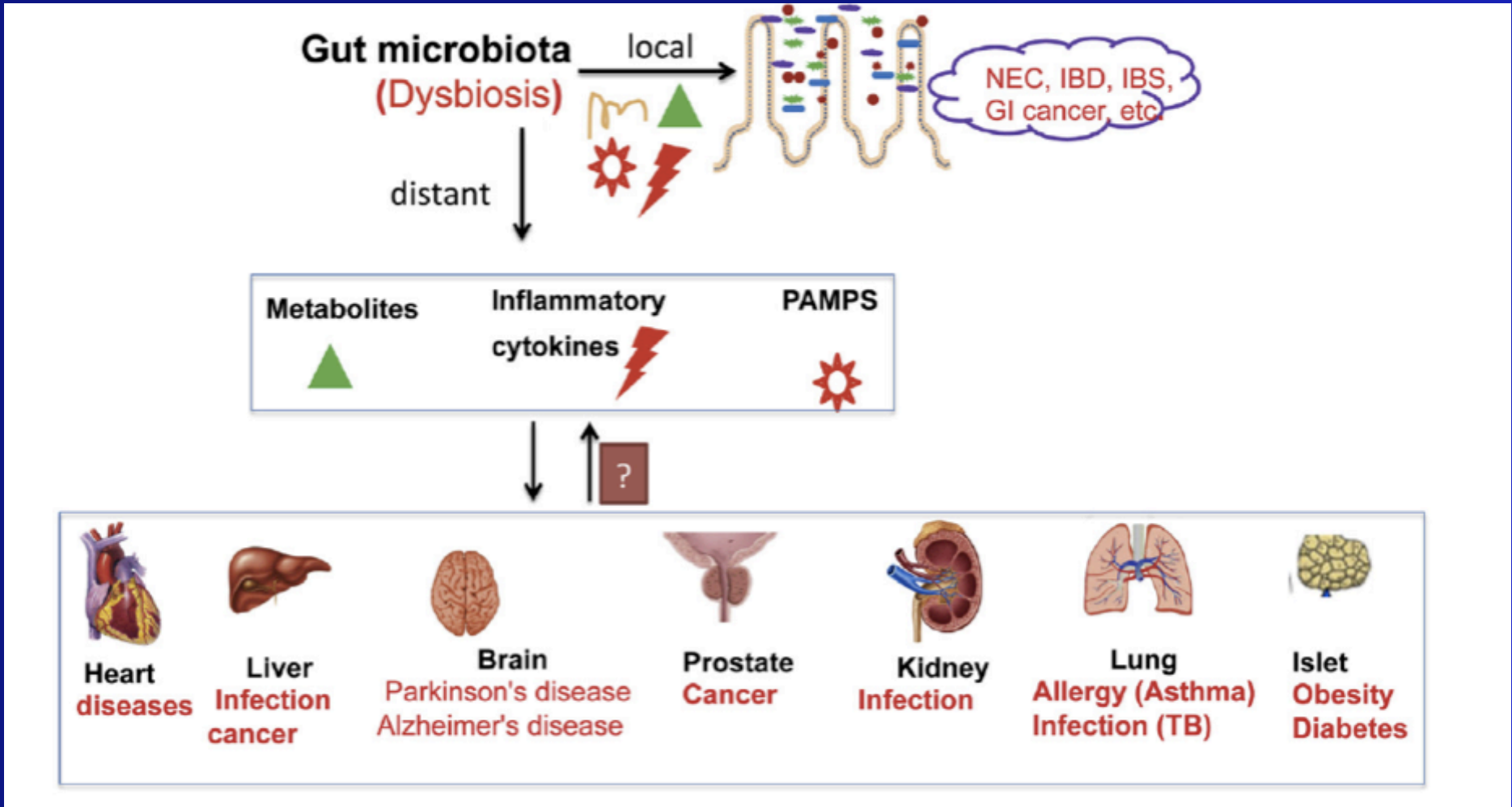
$$\frac{B}{H} = \frac{(V_{colon} \approx 0.4L) \times (n_{bact} \approx 10^{14}\ cells/L)}{(V_{blood} \approx 5L) \times (n_{RBC} \approx 5 \times 10^{12}\ cells/L)} \approx 4 \times 10^{13} \approx 3 \times 10^{13} \approx 1$$

Sander et al. Cell. 2016;164: 337-340

Gastrointestinal Flora

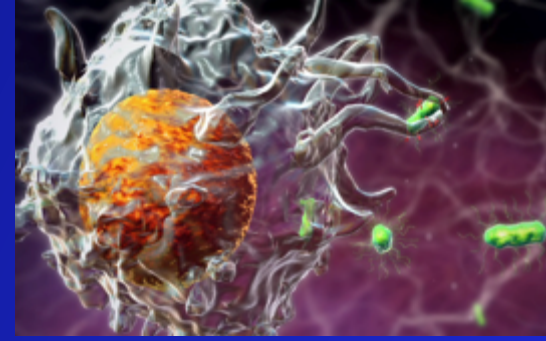


Gut Microbiota and Link to Disease



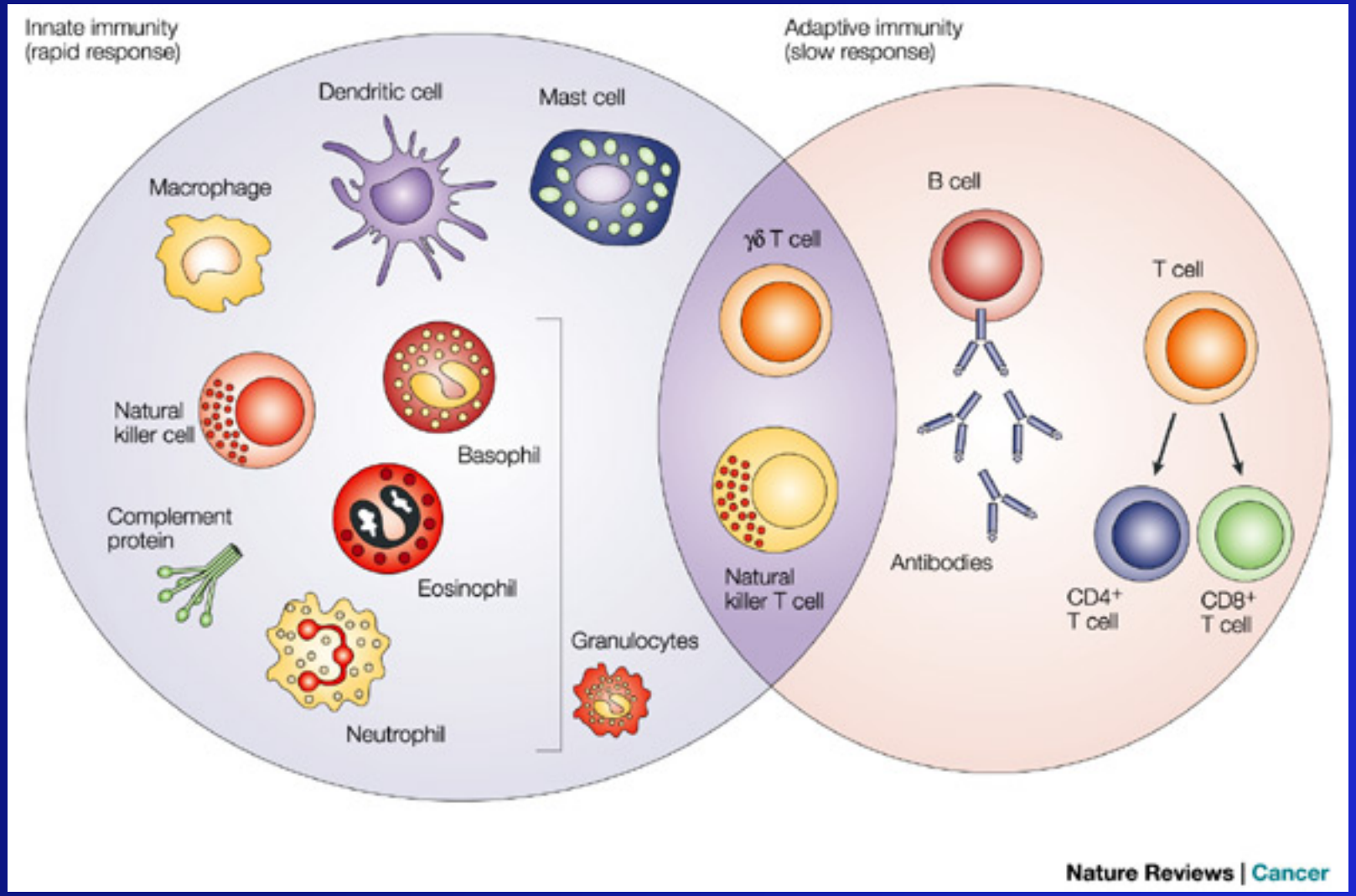
Sun et al. Genes and Disease. 2016; 1:132-139

Immune System

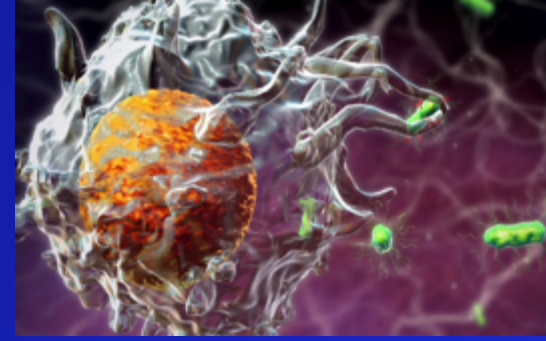


- A diffuse, complex network of interacting cells, cell products, and cell-forming tissues that protects the body from pathogens and other foreign substances, destroys infected and malignant cells, and removes cellular debris

Immune System



Defense System



Innate immunity

Barrier function

- Epithelial Layer
- Mucous layer
- Antimicrobial peptides

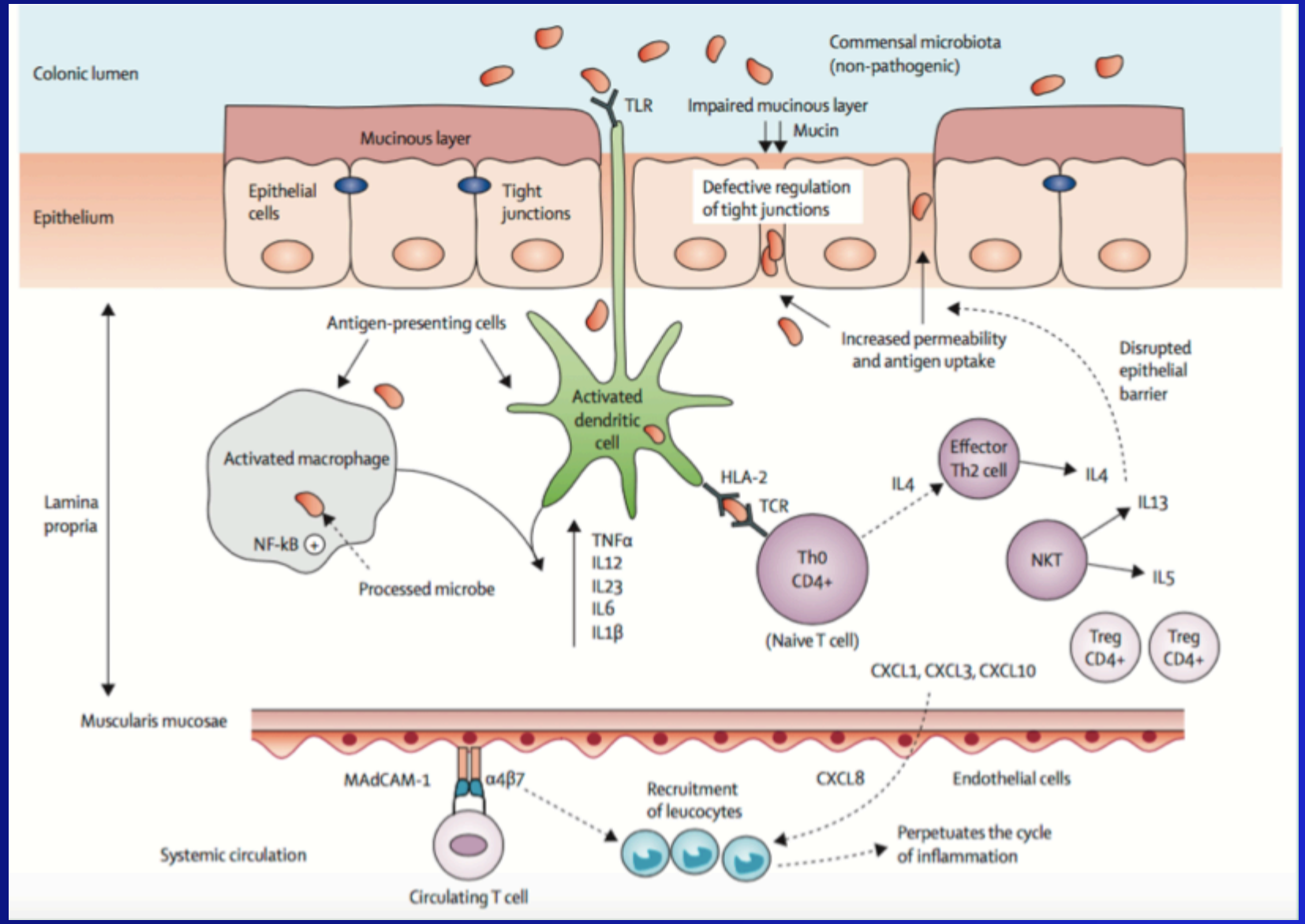
Microbial sensing and antimicrobial responses

- Recognition of pathogen-associated molecular patterns (PAMPs)
- Autophagy

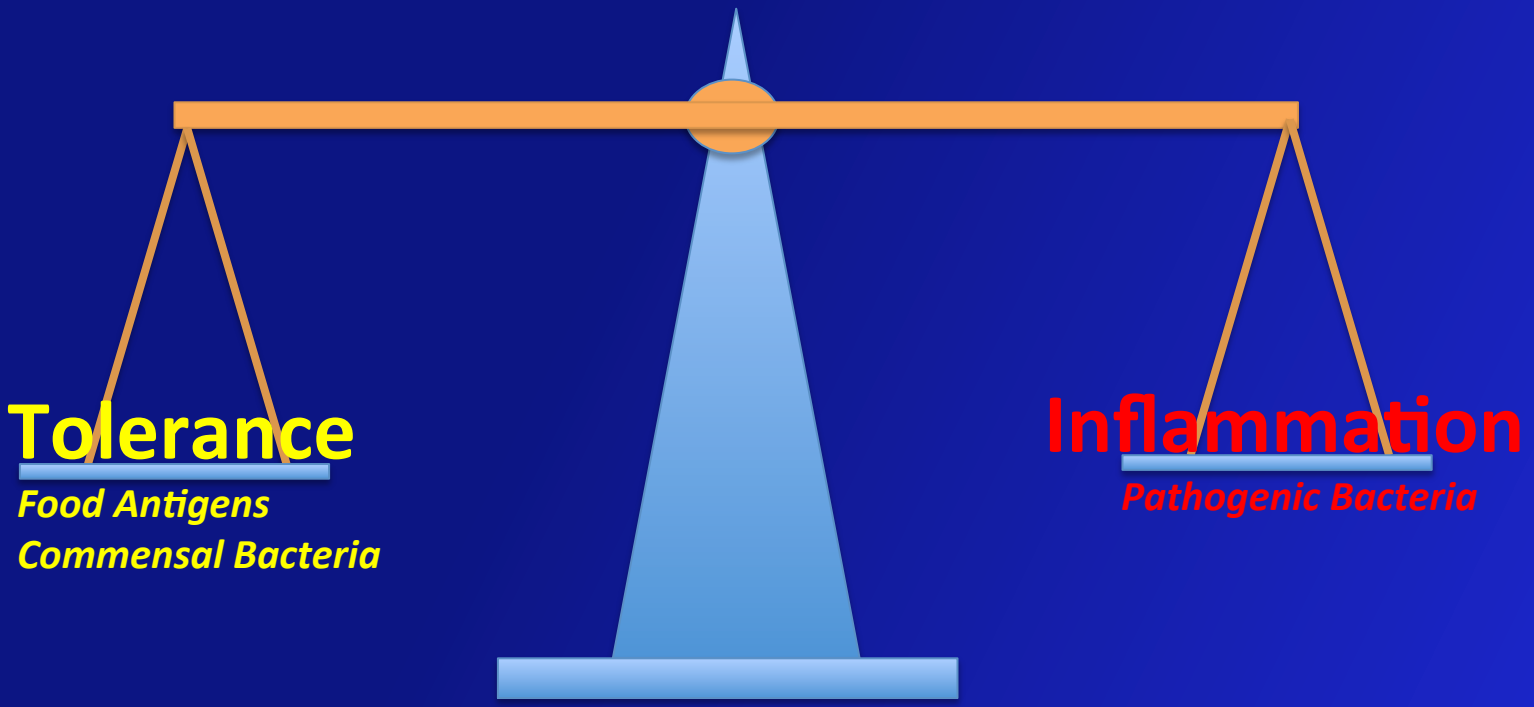
Adaptive Immunity

- Th1, Th2, Th17,
- T-regulatory Cells
- B-cells Secreting IgA

Immune system Checks and Balances



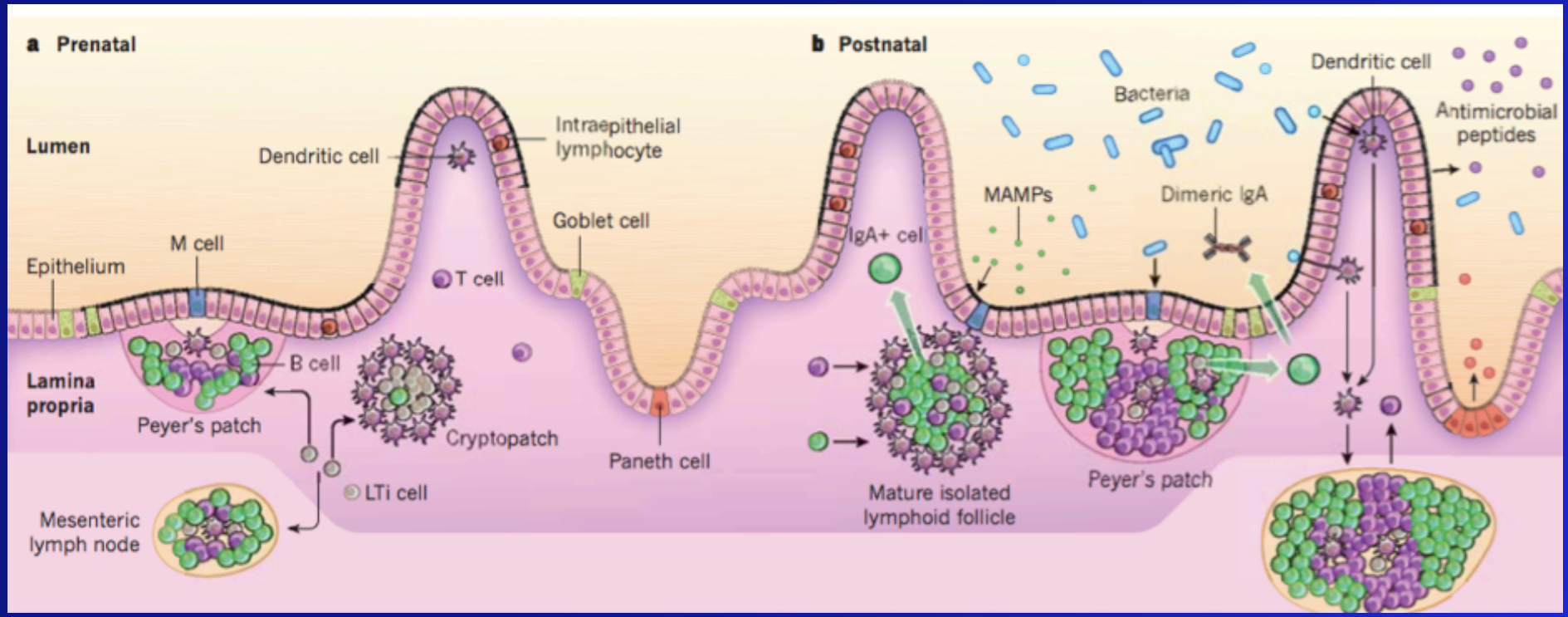
Delicate Balance in the colon



Symbiotic Relationship

- At homeostasis, the microbiota benefits from the warm, nutrient-rich environment of the gut so it can establish a relatively stable ecosystem.
- Humans in turn benefit from a highly adaptive metabolic engine that in addition to providing essential non-nutrient factors, such as vitamins and SCFA, also substantially increases our ability to harvest nutrients from food
- By establishing robust, interlinked metabolic or nutrient networks, and biofilms among its constituents, the microbiota limits the resources available to potential pathogens that must outcompete well-adapted and entrenched resident microbes

Pre- and Postnatal Intestinal Flora/Immune System

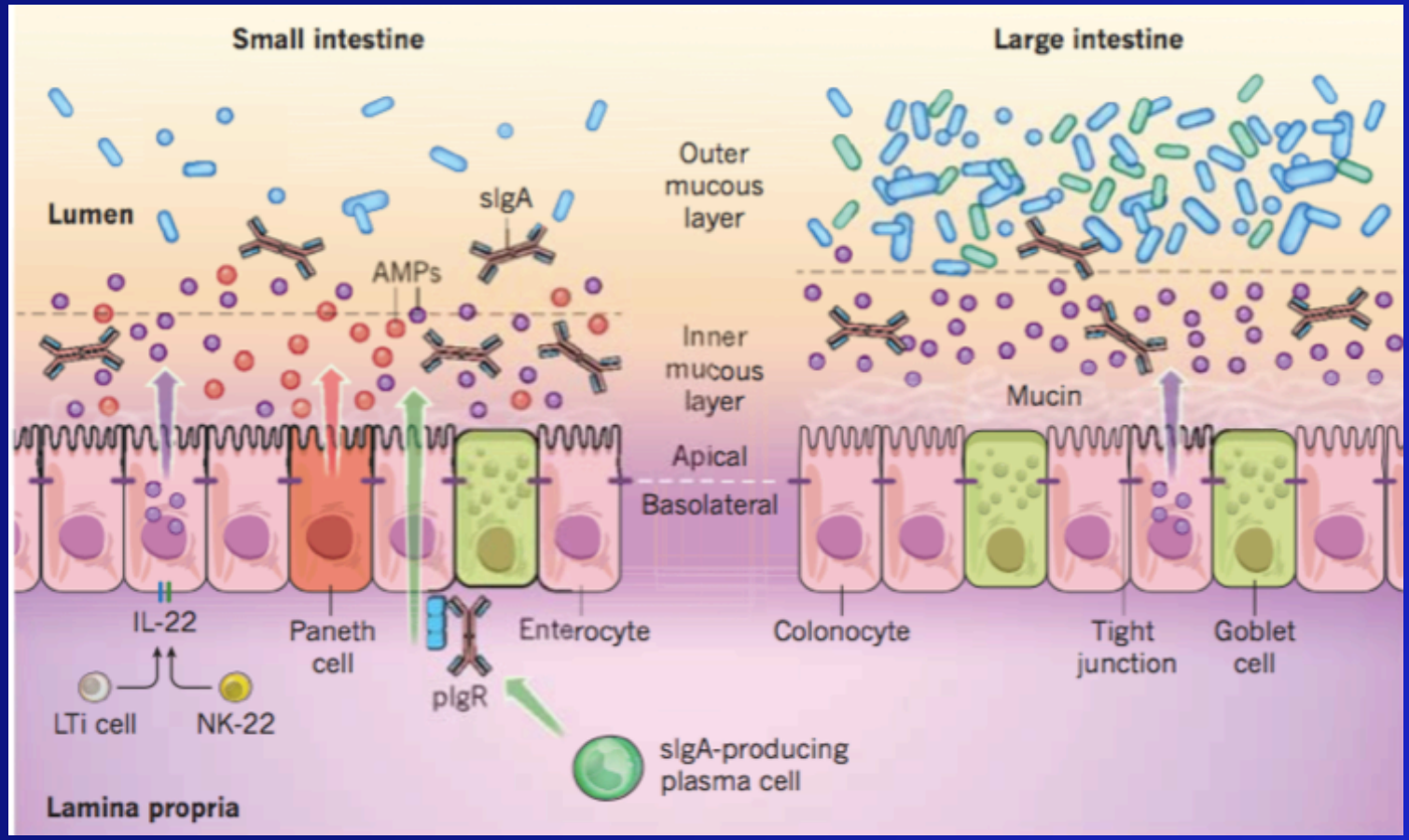


Maynard et al. Nature 2012; 489:231-241

Development of Microflora

- Every one of us enters the world devoid of microbial colonization because of the sterile environment of the womb. This germ-free existence is short-lived
- birth exposes the newborn to the microbiota of the mother, setting in motion the colonization of mucosal tissues in the digestive, respiratory and urogenital tracts, and the skin by a diverse microbiota,
- approximately 100 trillion organisms, most of which are bacteria

Immune system Checks and Balances



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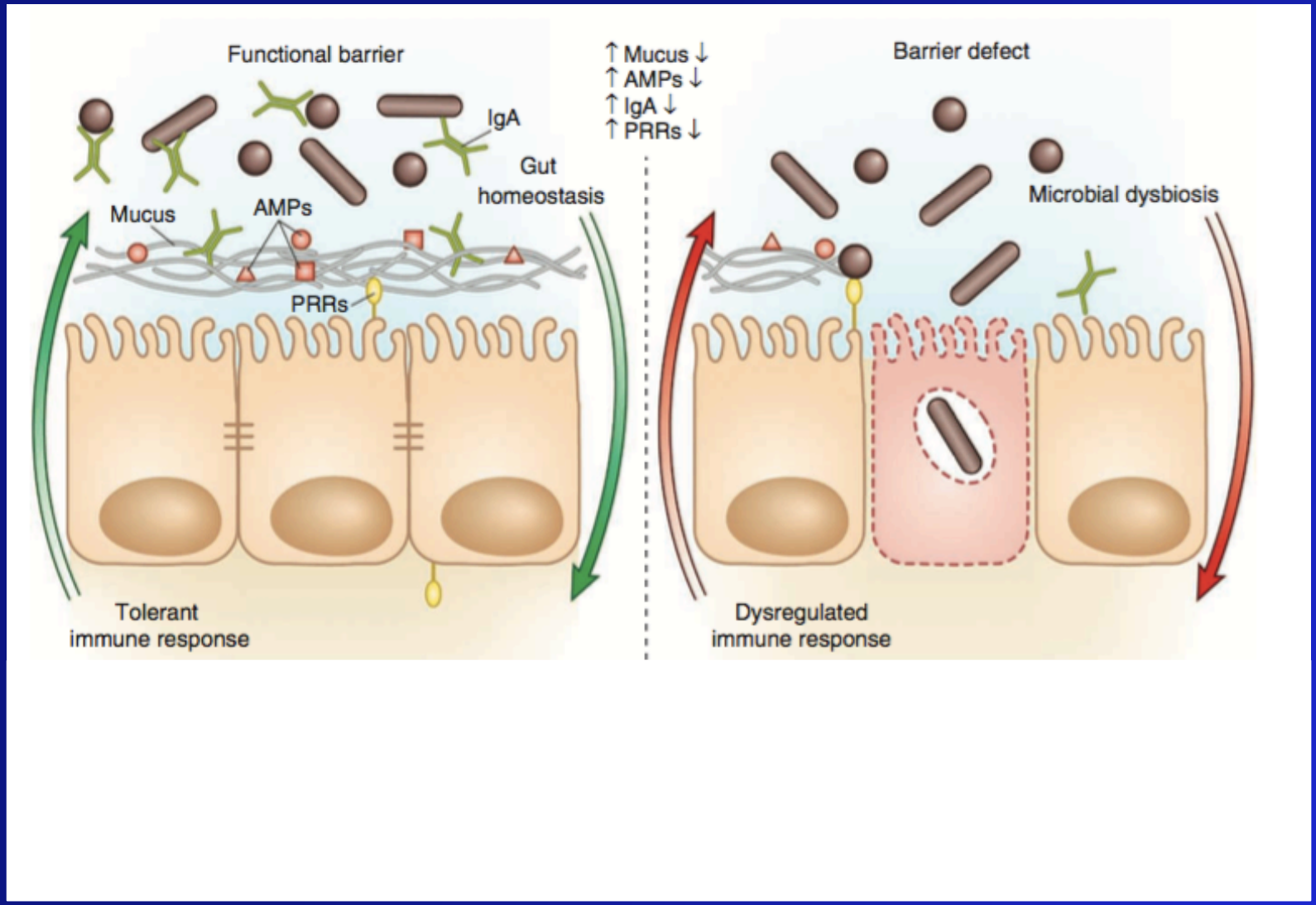
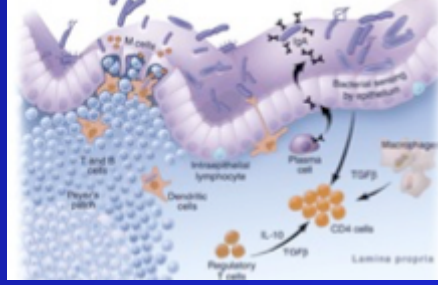
Immune system Checks and Balances



Brown E et al. Nature Immunology 2013; 7:660

GI Immune system Conclusions



- Complex network of innate and adaptive immunity that shapes and allows for dialogue between the host and microbiota.
- While the immune system allows for coexistence with the microbiota, able to provide robust protection against transient infections
- Defects in the GI immune system leads to dysbiosis or Opportunistic Infections.

Early use of Colonic Flora in Human Ailments

- 4th Century, during the Dong-jin dynasty in China
- Traditional medicine doctor Ge Hong successfully used human fecal suspensions for patients who were stricken with food poisoning or severe diarrhea.

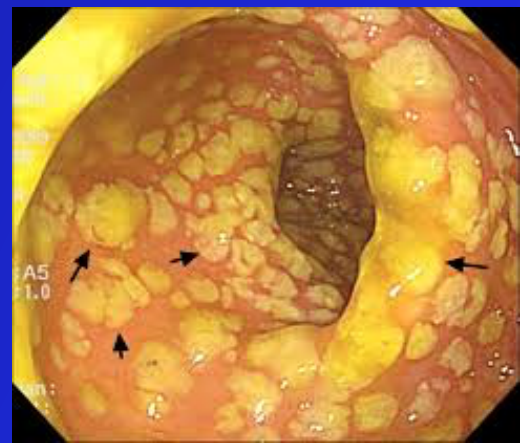
Early use of Colonic Flora in Human Ailments

- 16th Century, Li Shizen traditional Chinese medicine
- “Yellow Dragon Soup”: dried or fermented stool from healthy donors mixed into a broth

Early use of Colonic Flora in Human Ailments

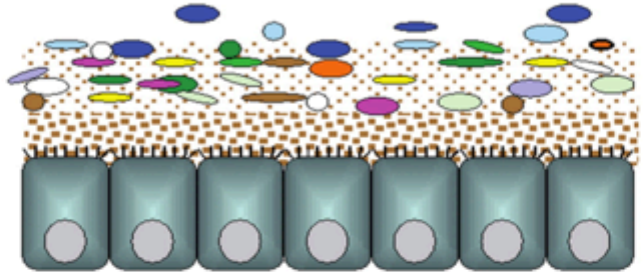
- 1950's an American surgeon, Dr. Eismann, described the use of fecal enemas in the treatment of pseudomembranous enterocolitis a consequence of antibiotics

- Resulted in dramatic improvement in patient's condition within 2 days



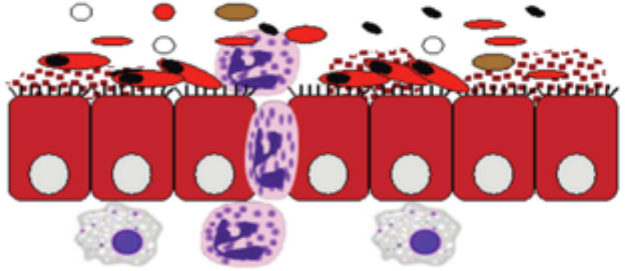
- Diverse and abundant microbiota
- Firmicutes, Bacteroidetes and Actinobacteria dominant
- Healthy levels of SCFA production
- Intact mucosal barrier
- No overt inflammation

a)



Health

b)

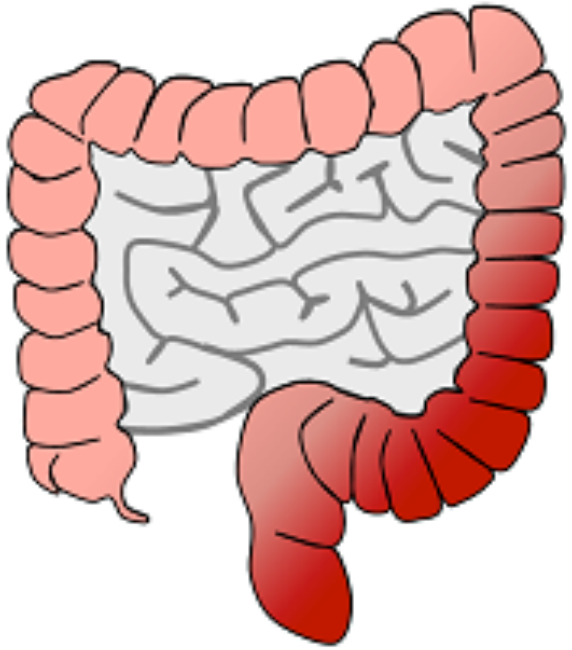


Dysbiosis

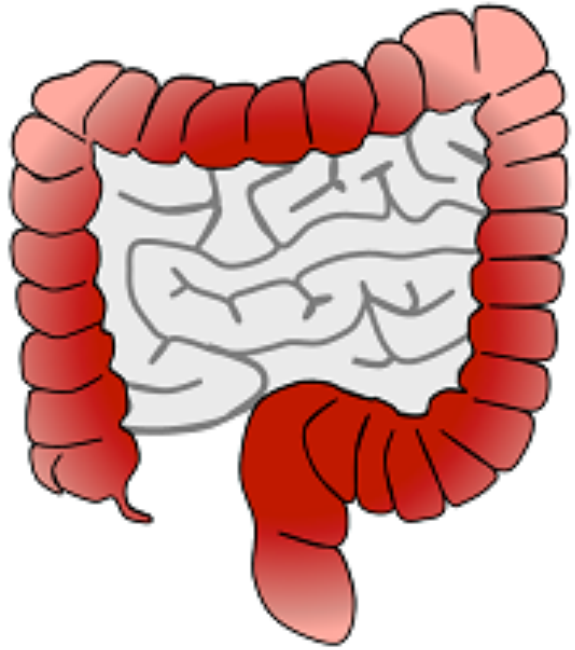
- Microbiota diversity reduced
- Elevated *Enterobacteriaceae*/opportunistic pathogens
- Skewed SCFA profile
- Disruption of mucosal barrier
- Host inflammatory response initiated

Alan W et al. Pharmacological Research. 2013; 69: 75-86

Inflammatory Bowel Disease (IBD)



Ulcerative Colitis (UC)



Crohn's Disease (CD)

Inflammatory Bowel Disease (IBD)

Crohns Disease

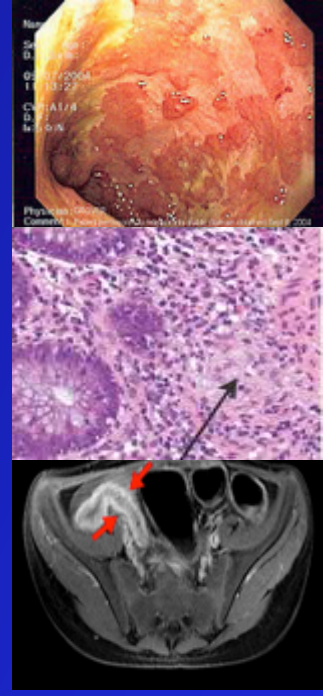
- **Patchy Transmural**
- Inflammation affecting any part of the GI tract
- Incidence 6-8/100,000
- Abdominal pain and diarrhea

Ulcerative Colitis

- **Diffuse Mucosal** Inflammation
- Limited to the colon
- Incidence 9-12/100,000
- Rectal Bleeding (tenesmus and urgency)

5% of IBD affecting the colon that can not be classified (features of both). **IBD-Unclassified**. "*Indeterminante colitis*" is reserved for when COLECTOMY has been performed and pathologist still unable to Classify

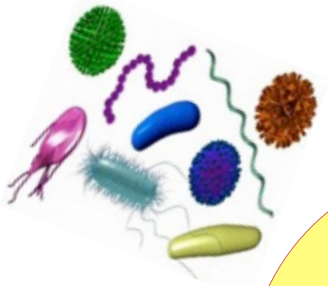
Diagnosing IBD

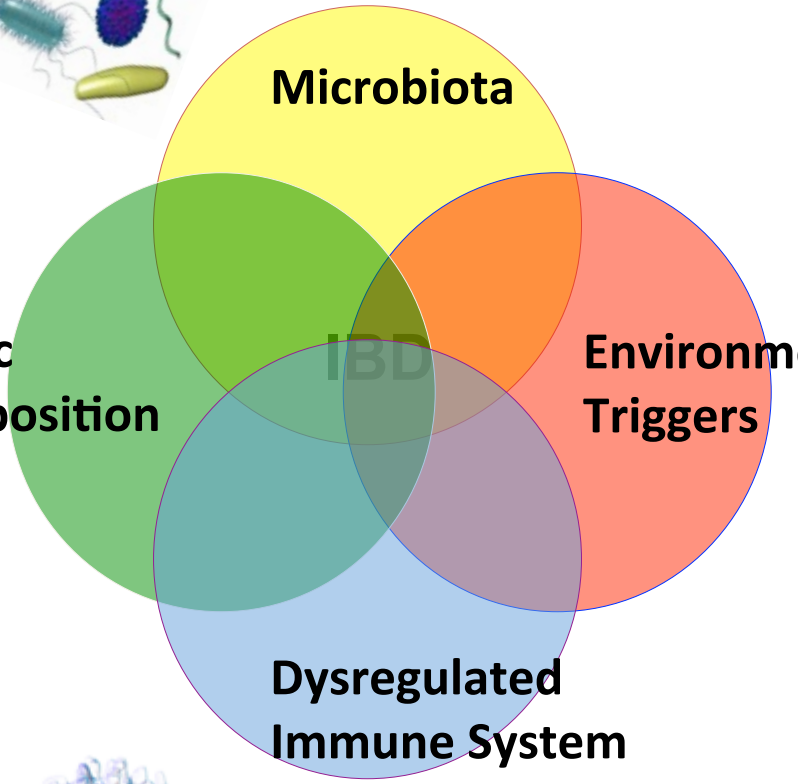


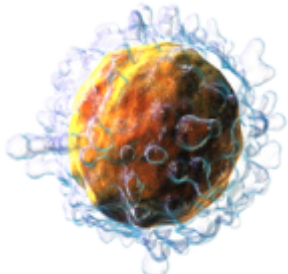
- **Clinical picture**
- **Endoscopically, Pathology**
- **Imaging**

- ~~***Blood Test- Anti-Flagellin, Anti-Omp C, Anti-Cbir, p-ANCA***~~

Pathogenesis of IBD

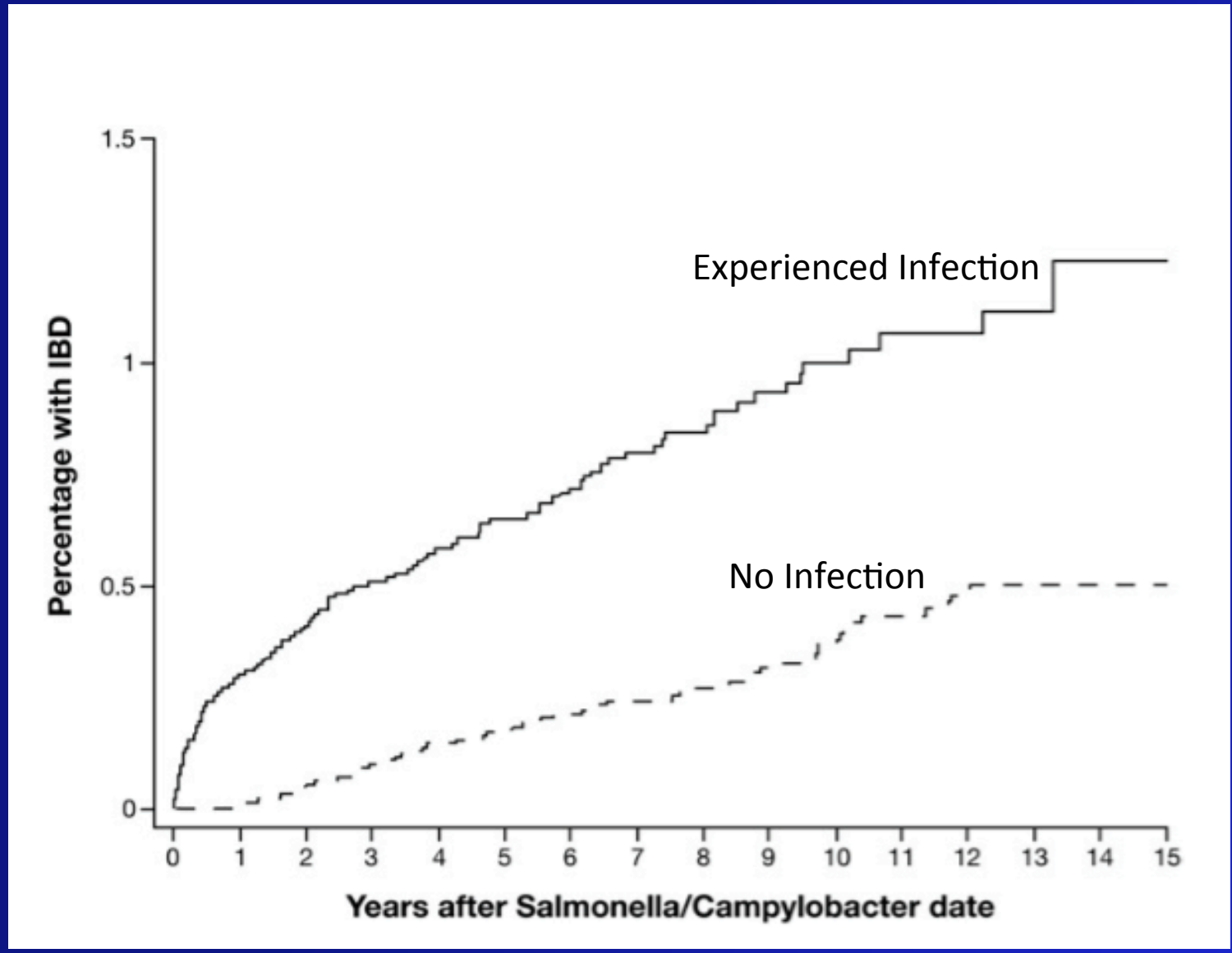






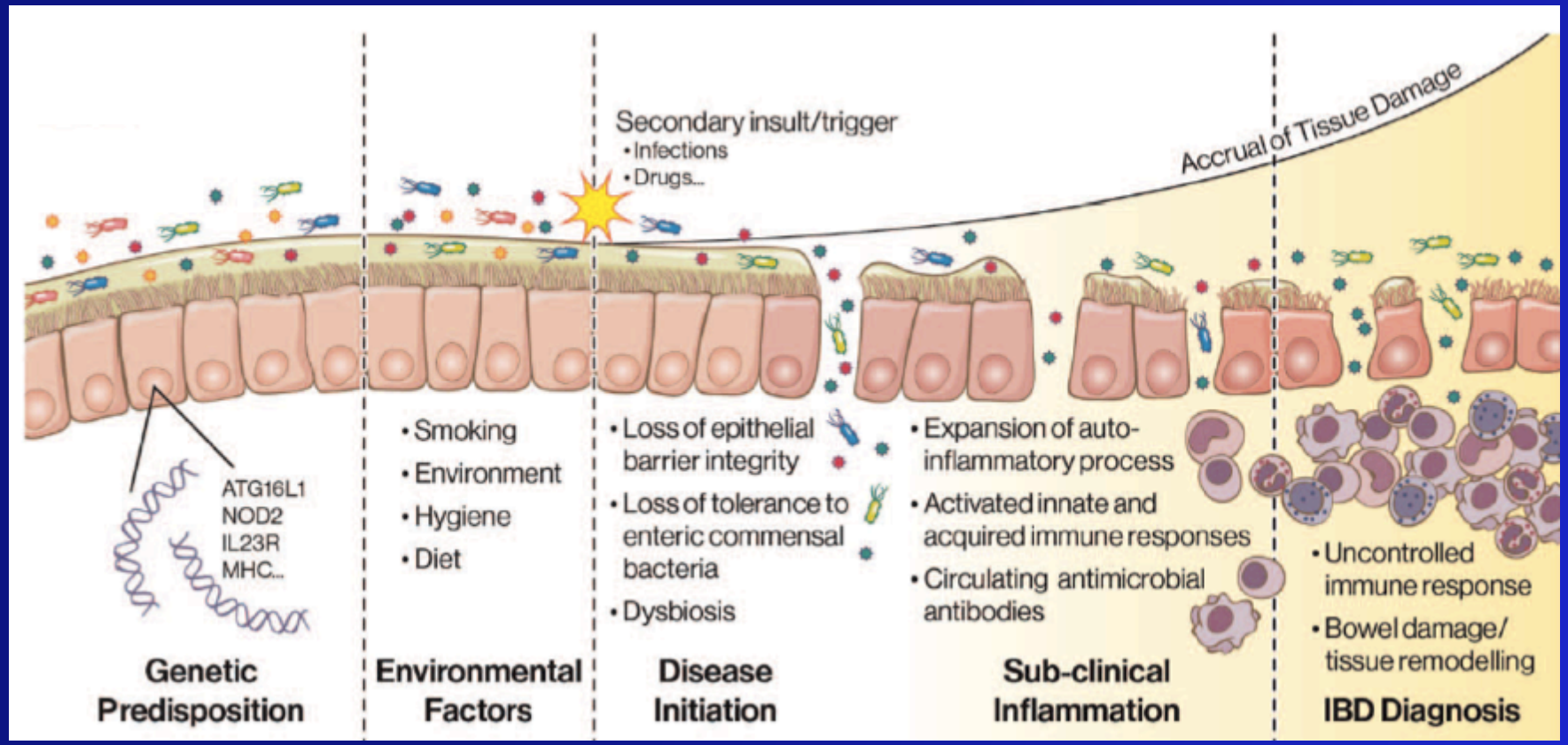
Molodecky et al. Gastroenterol and Hepatol. 2010: (6); 339-46

Pathogenesis of IBD



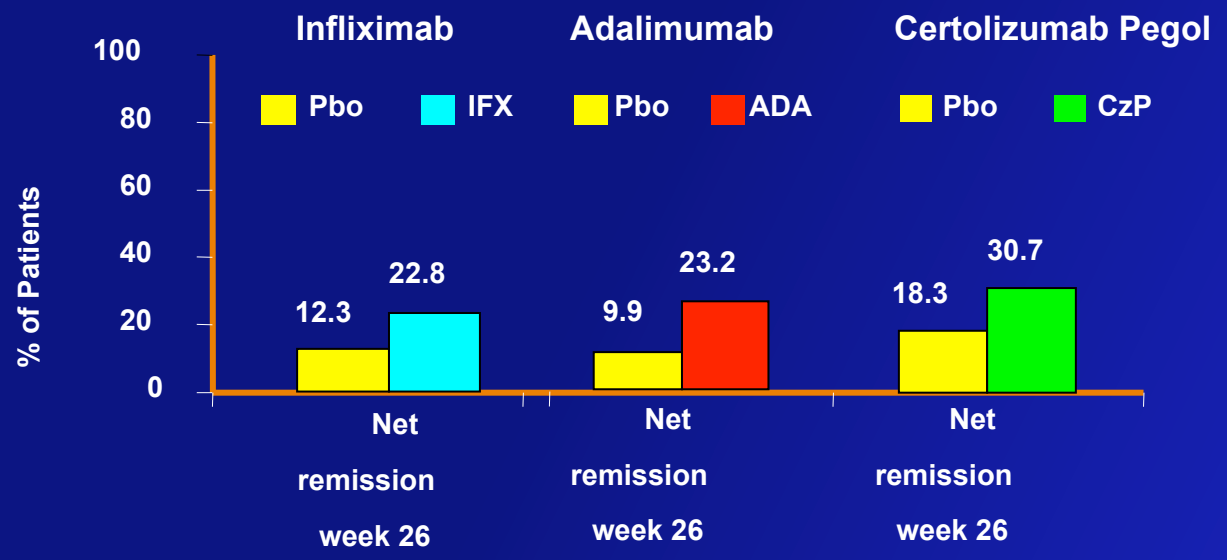
Gradel et al. Gastroenterology. 2009;137: 495-501

Pathogenesis of IBD



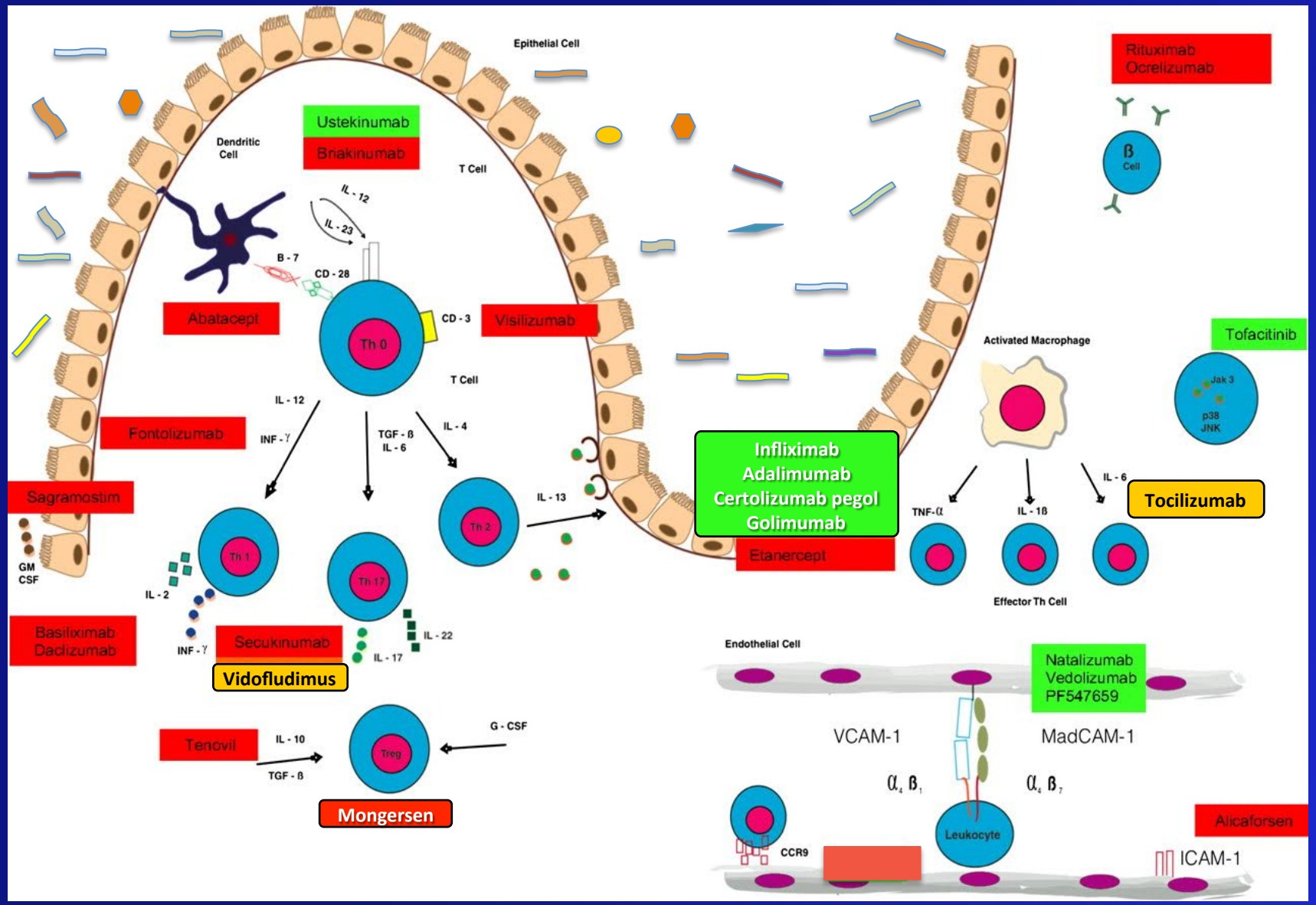
Torres J, et al. Gut July 2016 Vol 65 No 7

Overall Remission at 6 Months: Infliximab, Adalimumab, Certolizumab Pegol,



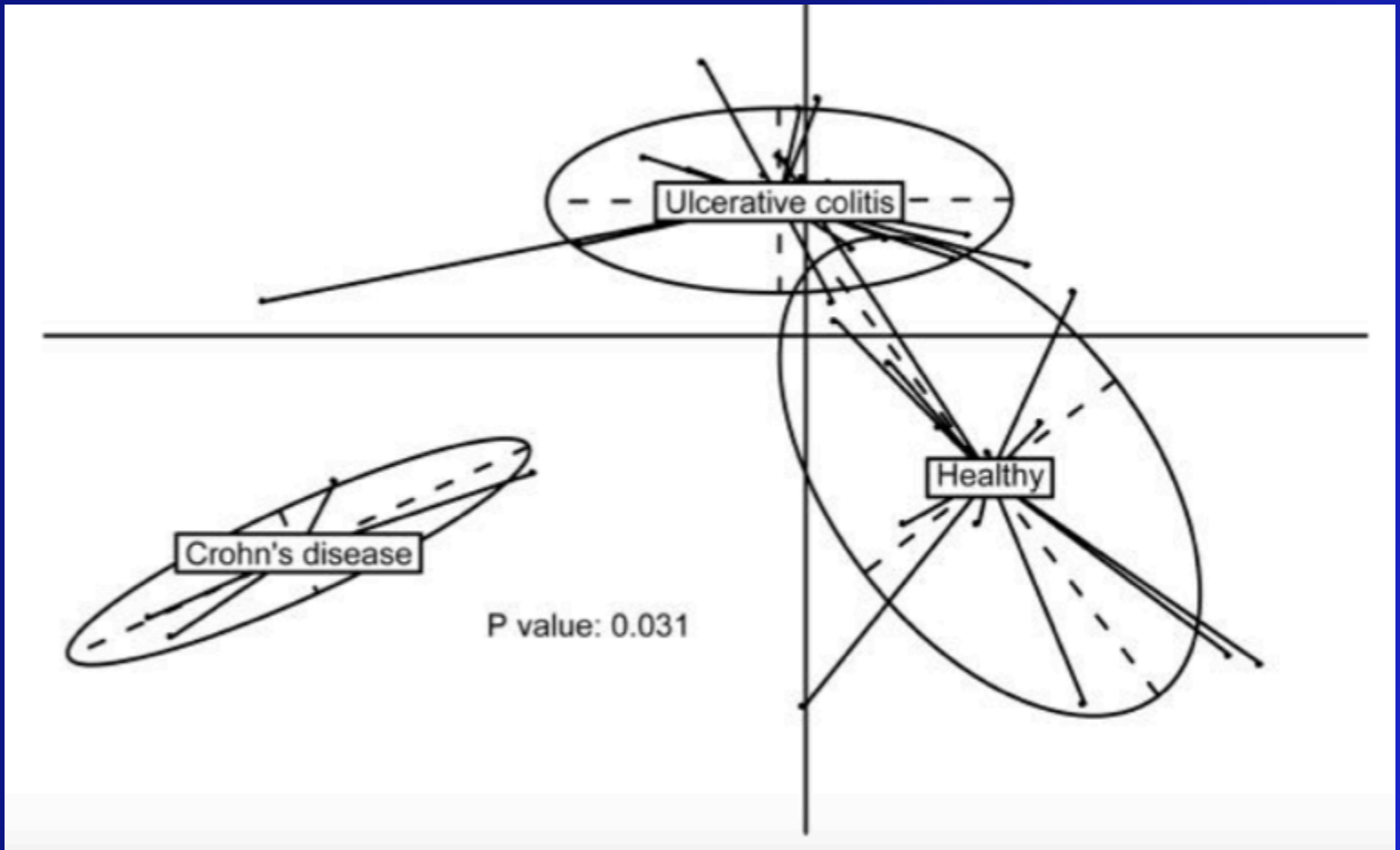
1. Schreiber et al. New Engl J Med 2007;357:239-250
2. Hanauer et al. Lancet 2002;359:1541-49
3. Colombel et al. Gastroenterology 2007;132:52-65

Effective and non-effective treatment in IBD



Danese S *et al. Gut* 2012;61:918–932

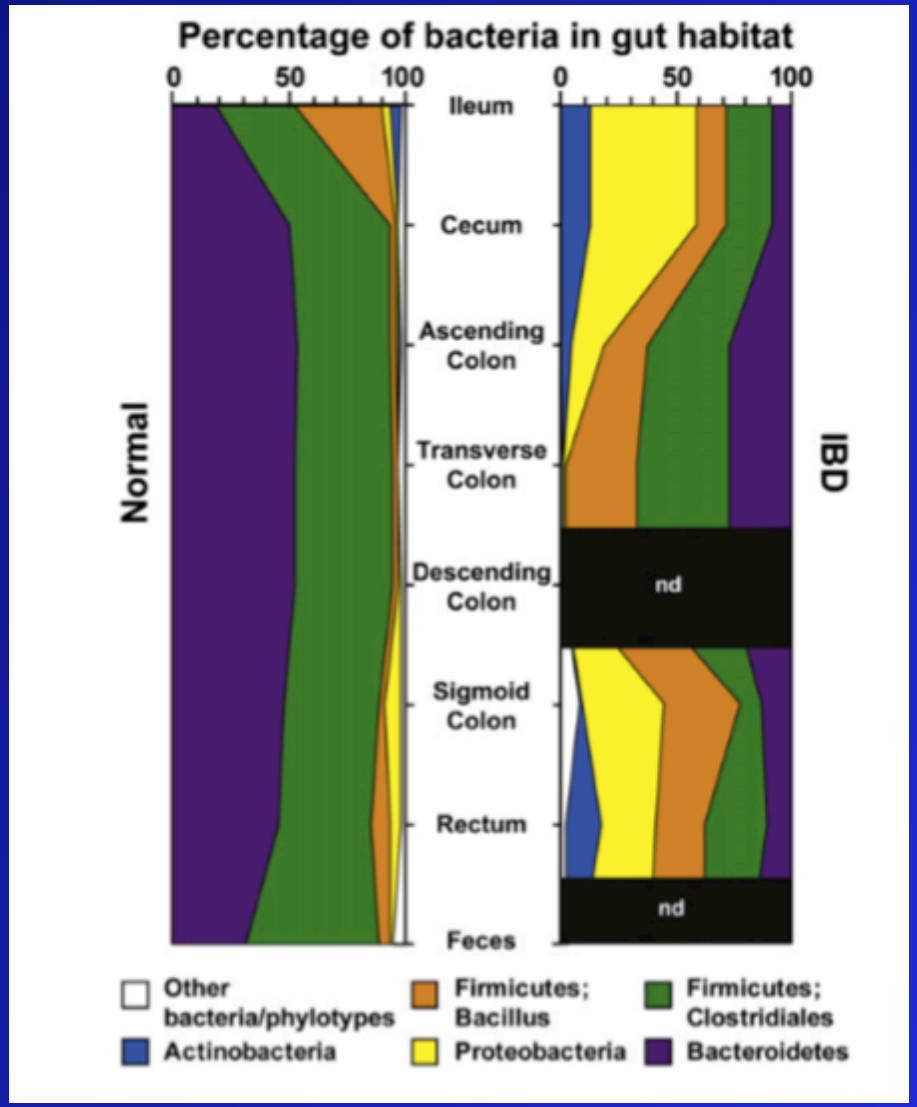
Patients with IBD have a unique microbial flora



Qin et al. Nature. 2010 Mar 4; 464(7285): 59–65.

Gut Microbiota are Disrupted in IBD

- Decrease in beneficial Firmicutes(Clostridia sp.) able to induce immune tolerance and reduce colitis in animal models
- Increases in Proteobacteria (E. coli and Enterobactericea) Generally aerotolerant Organisms able to manage oxidative stress. Injurious in animal models of intestinal inflammation



Peterson et al. Cell Host & Microbe 2008;3:417-427

Cause or Consequence?

Bacteria are necessary for inflammation

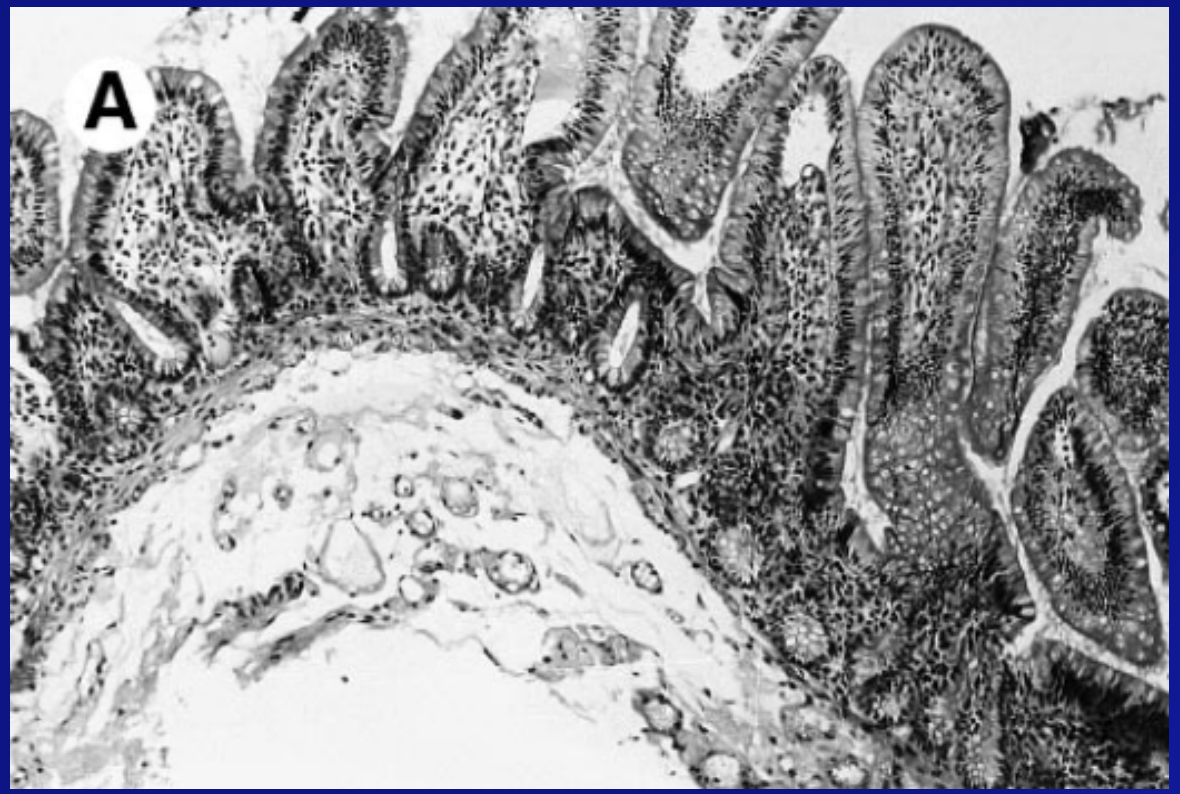
- Strains of susceptible mice (IL-10 deficient) who are Germ-free do not develop spontaneous colitis
- Mice develop colitis from transfer of feces from mice with active colitis
- RHB-104 molecule which has activity towards *Mycobaterium avium subspecies paratuberculosis* showed positive safety and efficacy results for the treatment of Crohn's disease

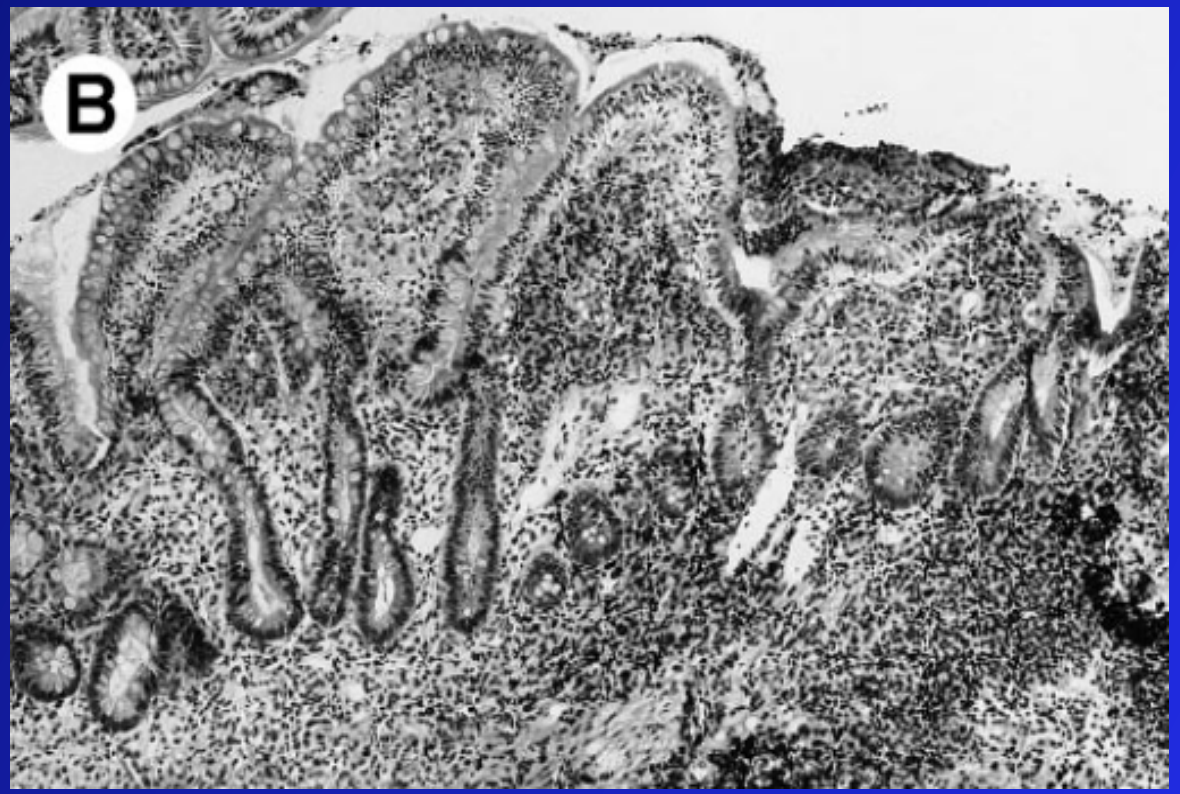
Evidence to support that the dysbiosis is the result of the intestinal inflammation

- Gene expression and bacterial composition is actual different in intestinal regions with active disease versus unaffected areas

Sartor et al. Gastroenterology 2017; 152:327-39

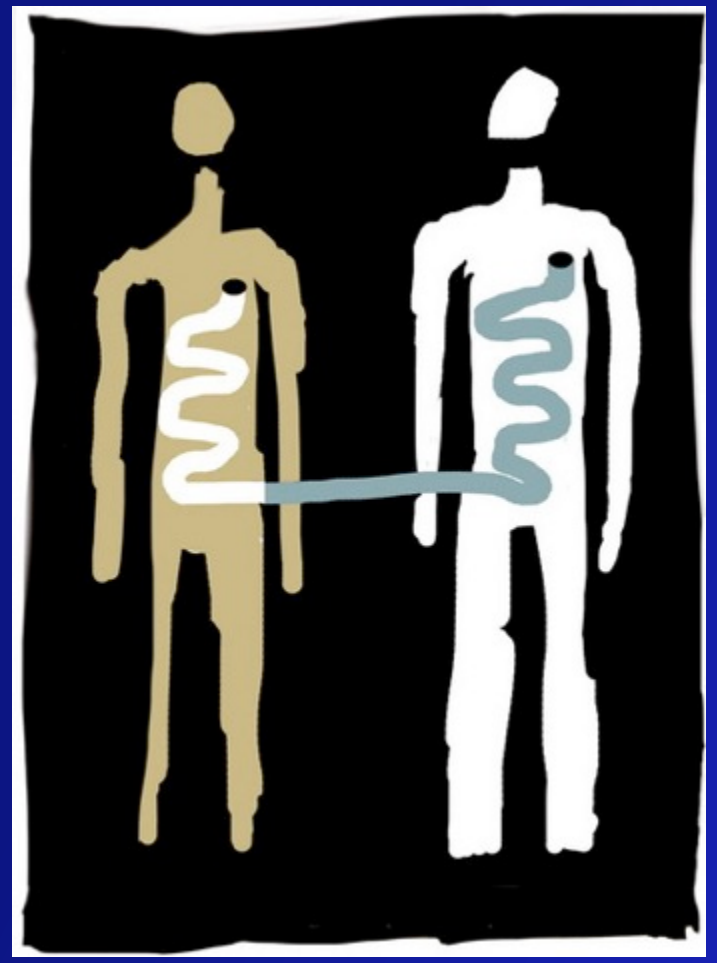
Microbial flora and recurrent Crohn's Disease after surgery



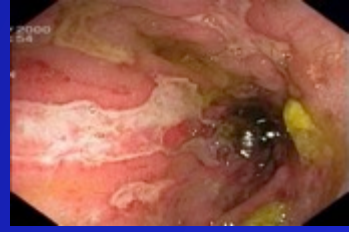


D'Haens et al. Gastroenterology. 1998;114 : 262-267

FMT for IBD?



Are we there yet?



FMT for Crohn's

- Limited to Case Series or Cohort Studies
- NO RCTs
- No high quality evidence

FMT for Ulcerative Colitis

	Rossen et al. 2015	Moayyedi et al. 2015	Paramsothy et al 2017	Costello et al 2019
Study population	Adults, mild to moderate UC	Adults, mild to moderate UC	Adult, moderate to severe UC	Adult, mild tomoderate UC
Total Patients Enrolled	50	75	81	73
Donor stool	Single donor per patient, fresh	Single donor per patient, fresh or frozen	Pooled Donors (3-7)	Pooled Donors (3-4), *anaerobically prepared*
Placebo				
Primary endpoint	Remission: activity score ≤ 2 and ≥ 1 point decrease in Mayo score at week 12.	Remission: Mayo score ≤ 2 and endoscopic score of 0 at week 7.	Steroid-free clinical remission with endoscopic remission or response	Steroid Free Remission
Dose/Route of delivery	Nasoduodenal tube 2 doses	Retention enema weekly x 6 doses	Colonoscopy enemas 5 days per week for total of 8 weeks	Colonosopy 2 enemas over 7 days.
Subjects achieving primary endpoint (remission)	No	Yes	Yes	Yes

Moayyedi et al. Gastroenterology 2015; 149:102-109
Rossen et al. Gastroenterology 2015;149:110-118
Paramsothy et al. Lancet 2017; 389:1218-1228
Costello et al. JAMA 2019; 32:156-164

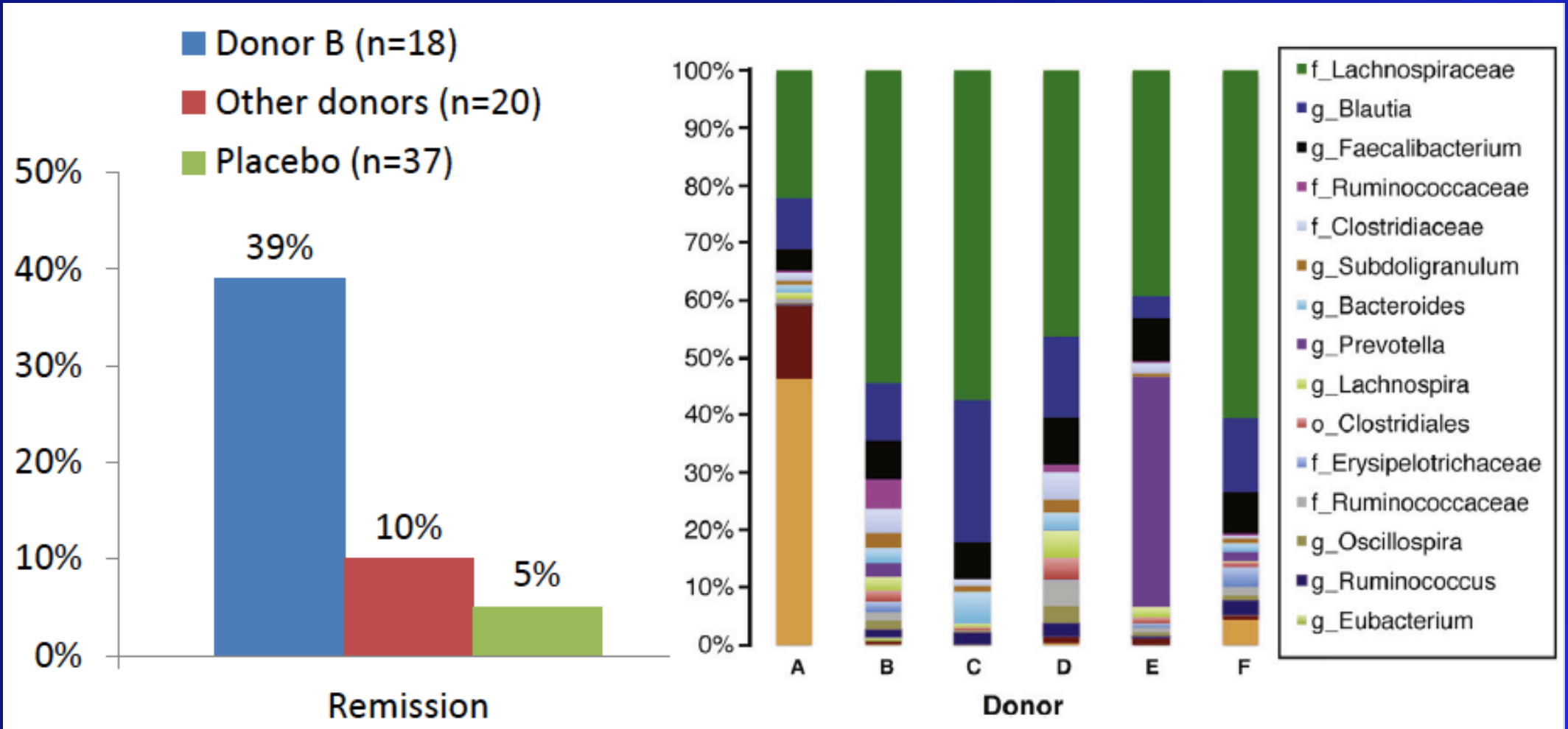
FMT for Ulcerative Colitis

- The primary outcome was achieved in 32% receiving pooled donor FMT compared with 9% receiving autologous FMT

- Five of the 12 participants (42%) who achieved the primary end point at week 8 following donor FMT maintained remission at 12 months.

Costello et al. JAMA 2019; 321(2):156-164

FMT for Ulcerative Colitis



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

Putting things in Perspective for FMT in Ulcerative Colitis

- Published trials of FMT in UC have demonstrated similar rates of remission between 24% and 32%.
- Clinical trials of the approved biologic drugs adalimumab and vedolizumab in UC showed efficacy rates of only 9% and 17%, respectively (though these studies enrolled patients with more severe disease).
- Patients with UC have been observed to require multiple FMT dosing, differing from treatment of CDI in which the efficacy of a single FMT is greater than 90%

Kelly et al. *JAMA.* 2019;321(2):151-152

Potential Concerns with FMT

- FMT maintenance therapy in IBD is likely required to maintain durability

- The long-term effects of manipulating the microbiome are unknown and there are theoretical concerns that risk of immune-mediated or microbiome-associated conditions may be transmitted with donor stool

Short Term side effects with FMT

- Nausea
- Abdominal Bloating
- Increase in the number of bowel movements
- Low Grade Temperature

Short Term side effects with FMT

- Nausea
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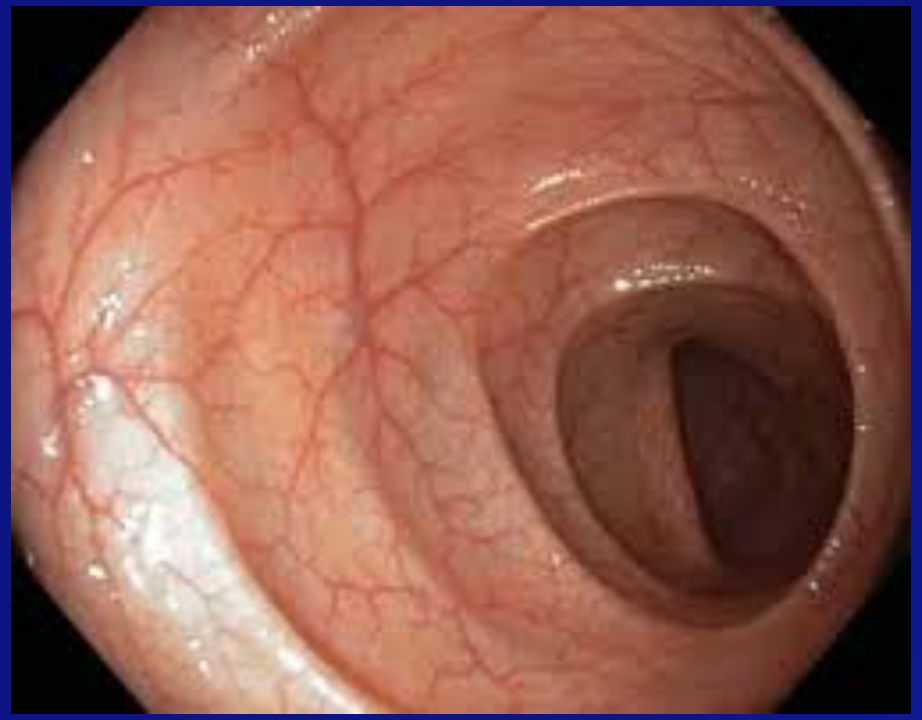
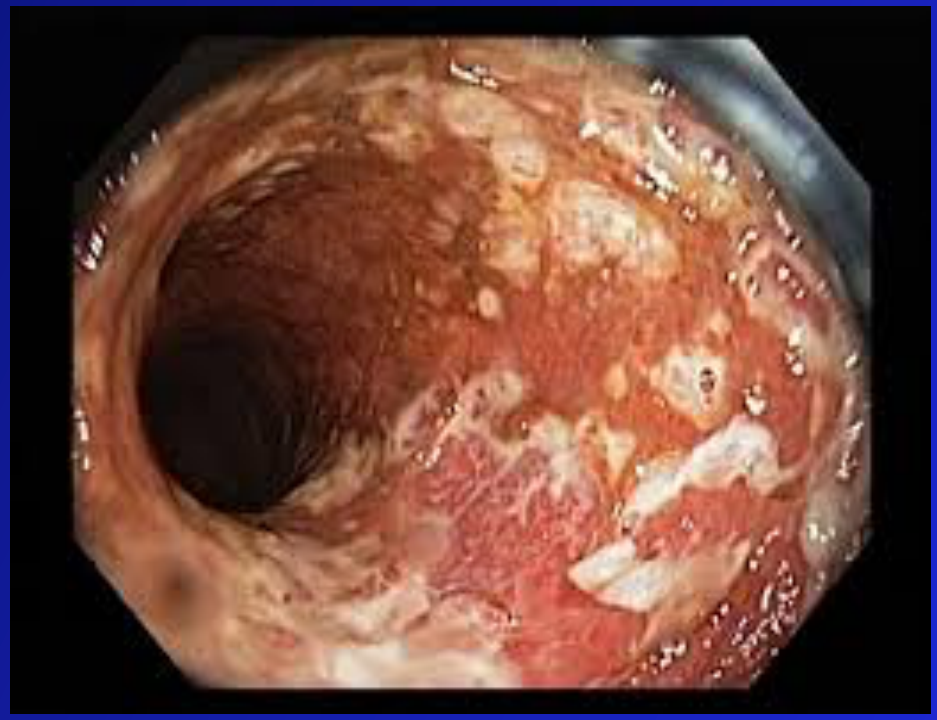
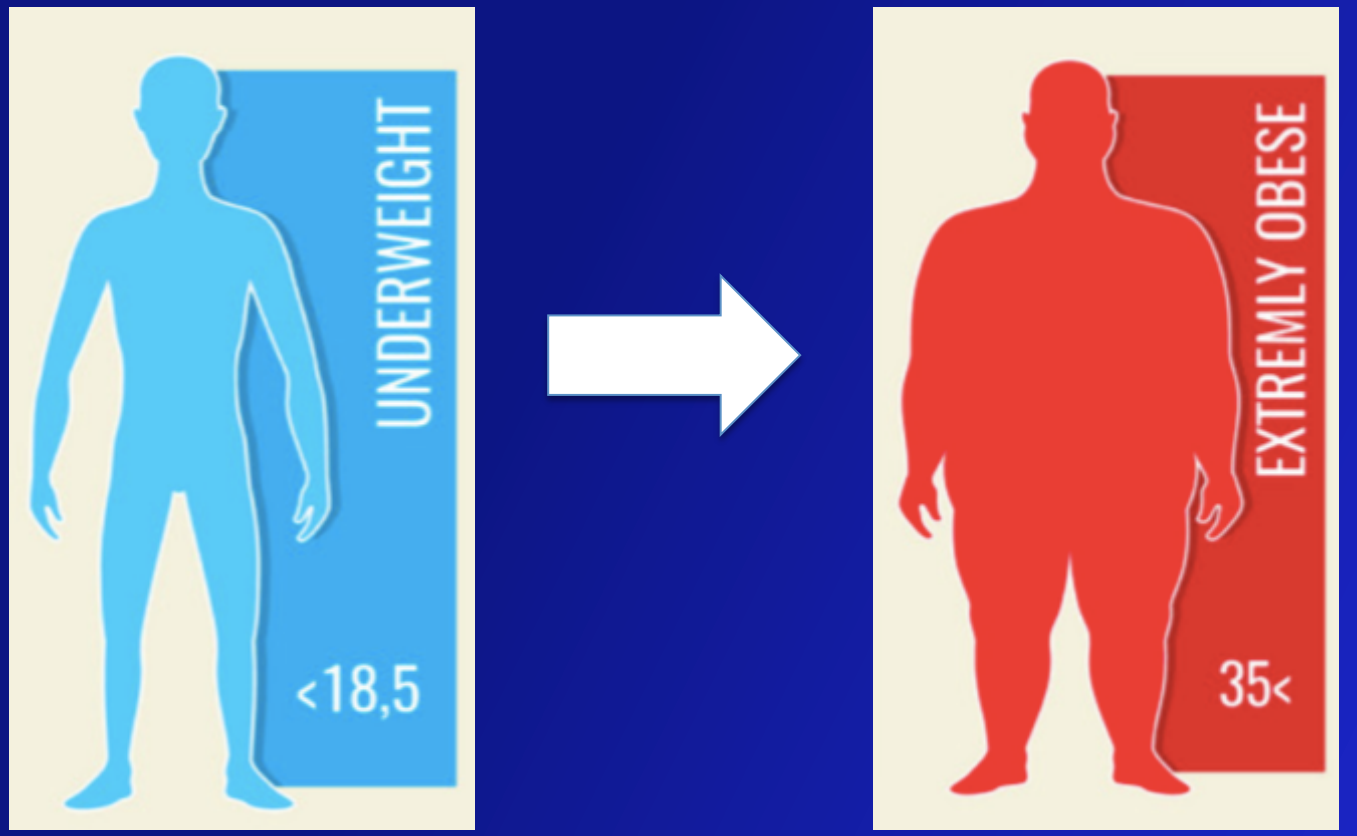
Long Term side effects with FMT?





Long Term side effects with FMT?



Long Term side effects with FMT?

Conclusions

- The intestinal immune system is specifically designed to tolerate the beneficial gut microflora while also being able to respond to enteric pathogens.
- Dysbiosis has been linked to many different types of diseases
- Patients with inflammatory bowel disease have unique and specific alterations to their intestinal microbiome
- Results from trials of FMT for patients with Ulcerative colitis seem to be promising , but more studies and standardization of treatment are needed.
- FMT for patients with Crohn's does not currently have any large trials, (***clinicaltrials.gov 10 trials listed***)