GUT MICROBIOTA AND INFLAMMATORY BOWEL DISEASE (IBD):

CAUSATION OR CORRELATION?

The Chinese University of Hong Kong
Faculty of Medicine
Department of Microbiology

Joint Graduate Student Seminar 2017

Supervisor: Prof. Margaret Ip

Student: Dulmini Nanayakkara Sapugahawatte (Ph.D. Candidate)

Date: 2017 Dec 07

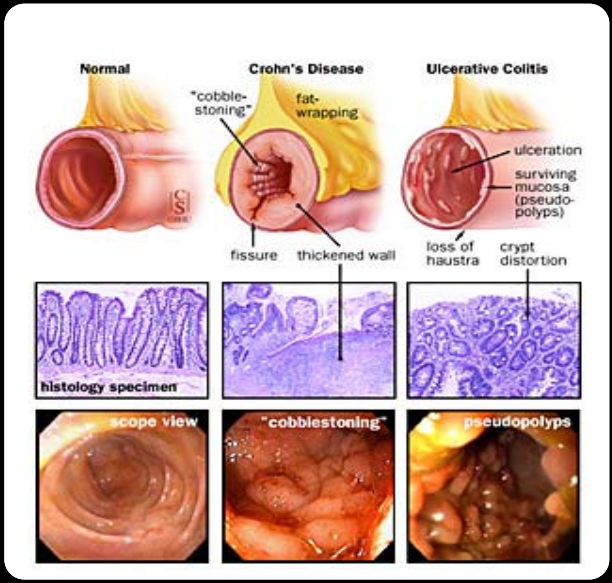
CONTENT

1. Microbial composition in IBD
2. Microbial function and metabolites in IBD
3. How to overcome human IBD
4. Future insight
5. Summary

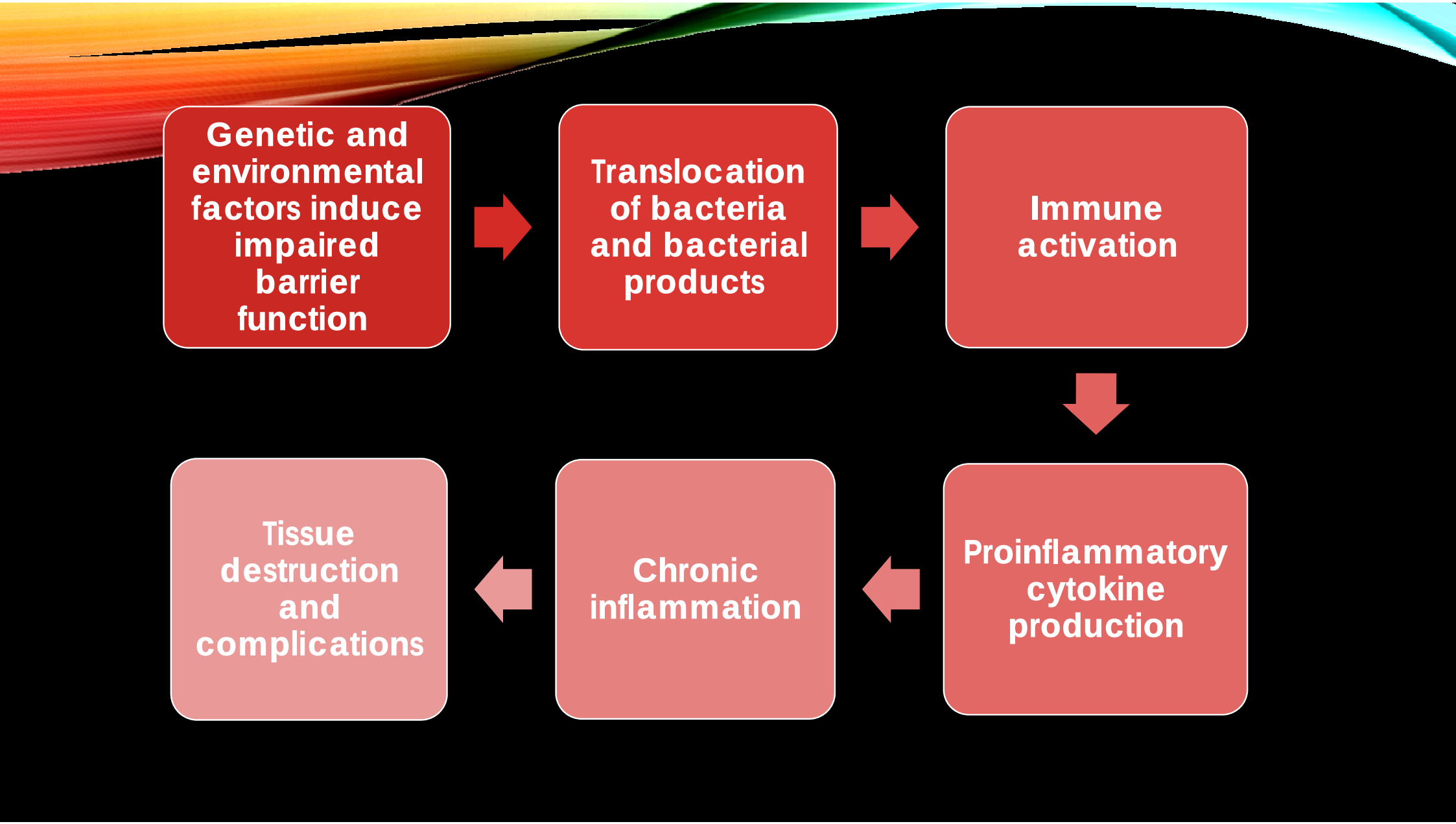
DOES THE INTESTINAL MICROBIOTA DIFFER IN PATIENTS WITH SPECIFIC DISORDERS FROM HEALTHY SUBJECTS?

If the microbiota does differ, is it an important factor in the pathogenesis of the disorder?

WHAT IS IBD?



Inappropriate activation of GI tract immune system toward the gut microbiota in genetically susceptible hosts & under the influence of environmental factors

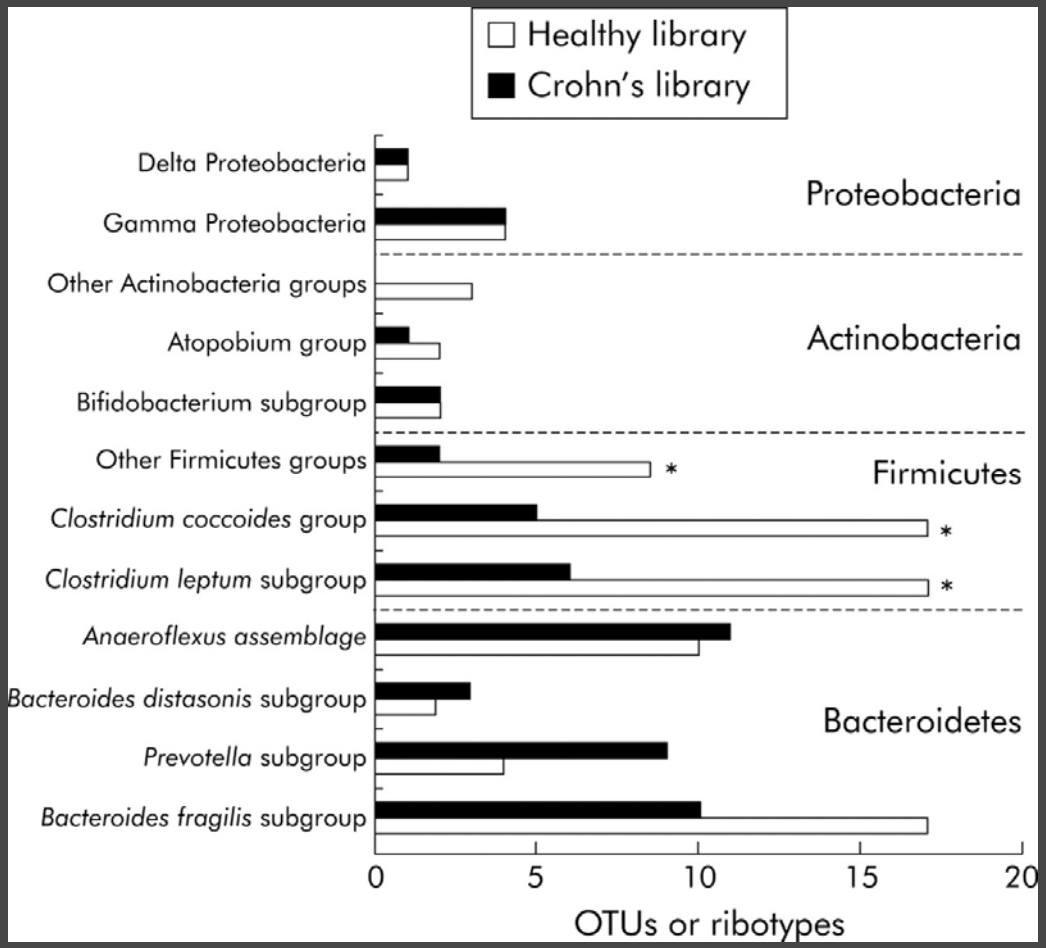

Genetic and environmental factors induce impaired barrier function
Translocation of bacteria and bacterial products
Immune activation
Proinflammatory cytokine production
Chronic inflammation
Tissue destruction and complications

MICROBIAL COMPOSITION IN IBD

IS THE GUT MICROBIOTA A CAUSE FOR IBD?

Example 1 – Microbial composition

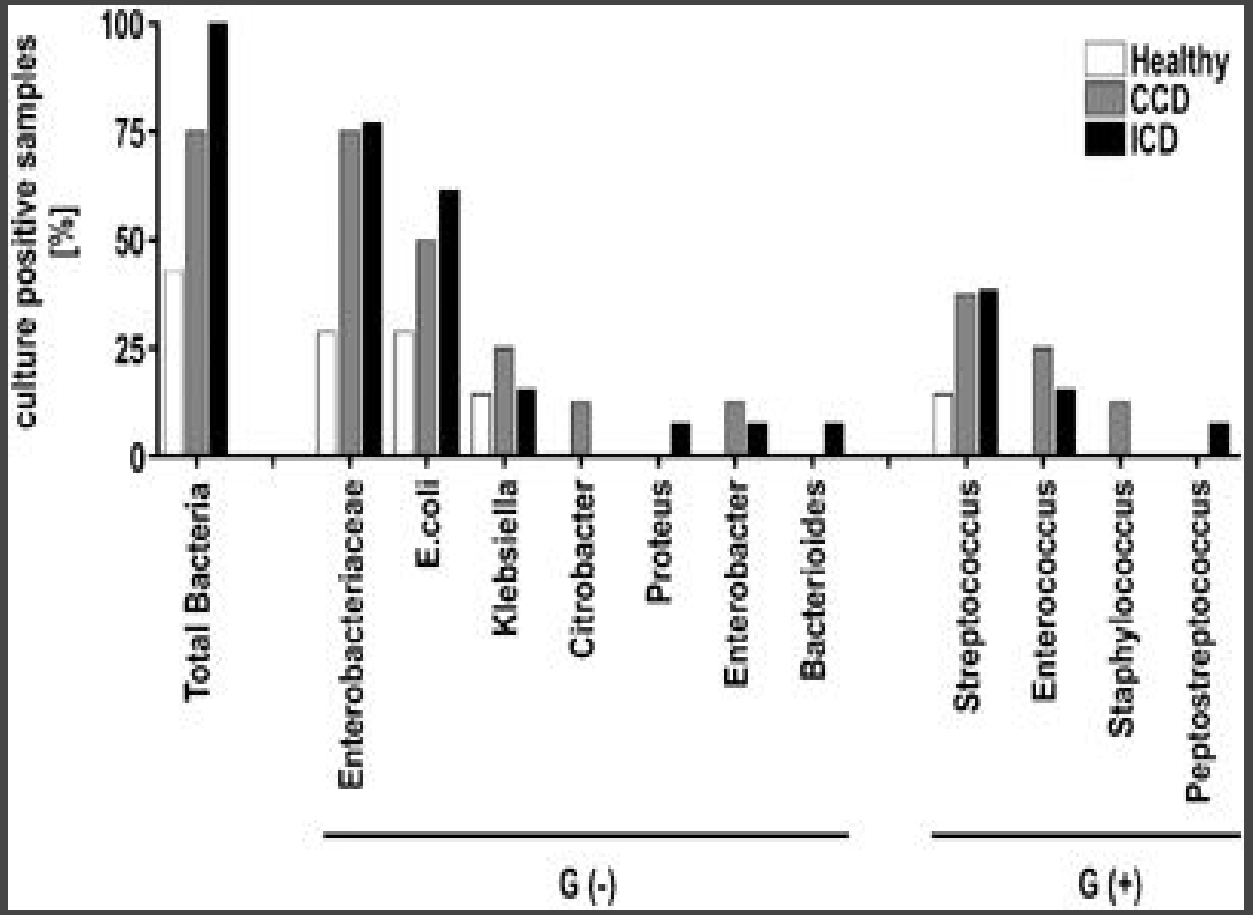
Manichanh *et al.*, 2005



Example 2

Microbial composition

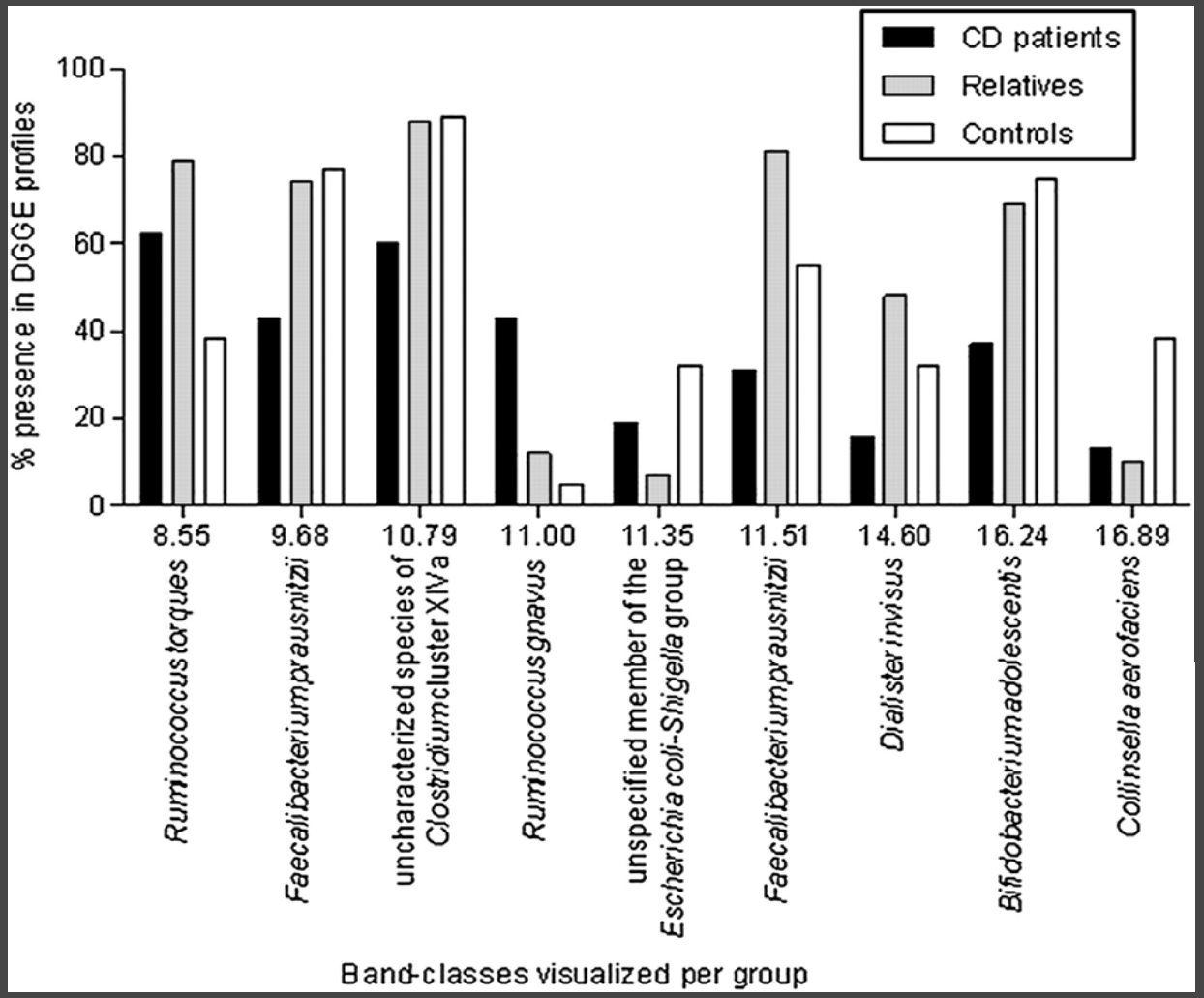
Baumagart *et al.*, 2007



Example 3

Disease Vs environment & genetics

Joossens *et al.*, 2011

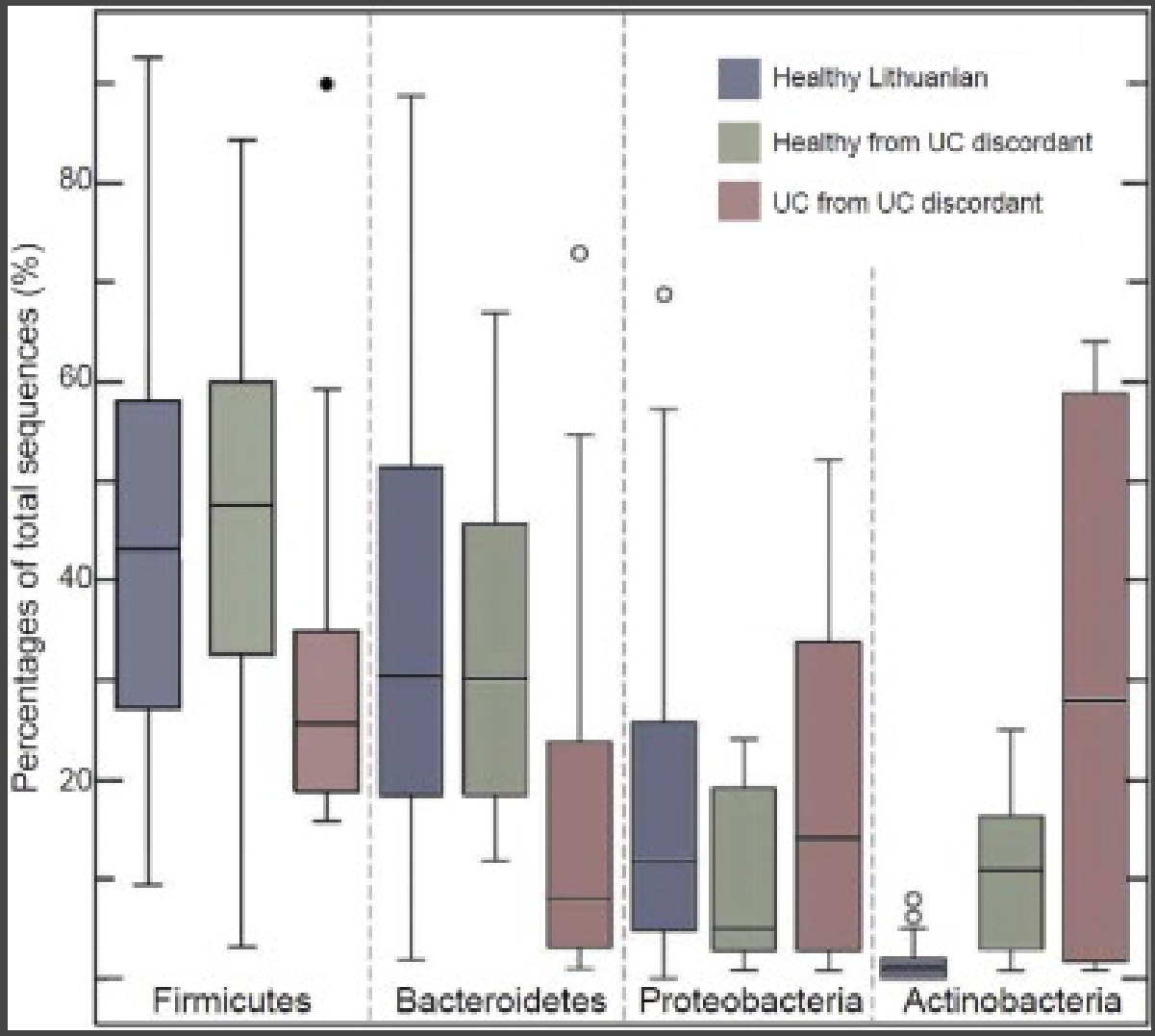


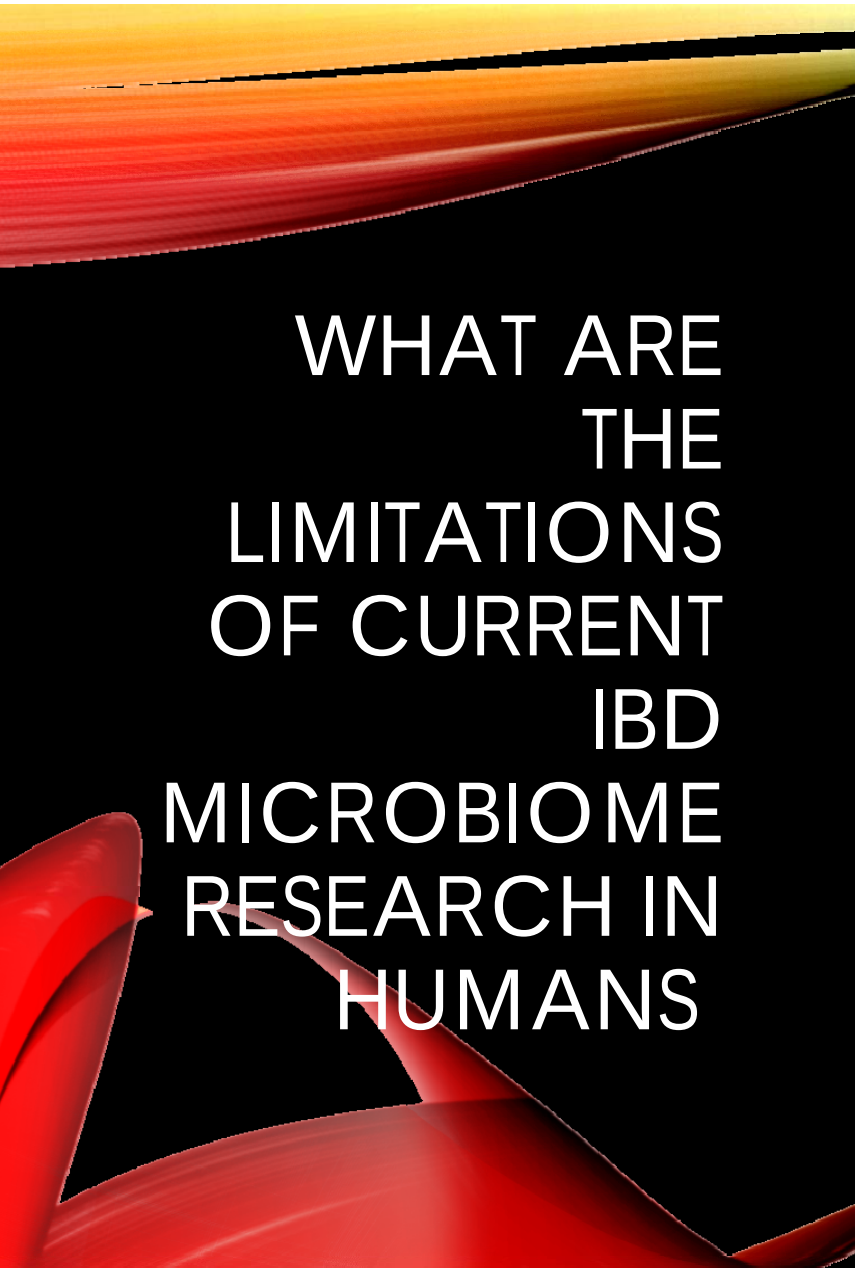
Example 4

Disease Vs genetics

Lepage *et al.*, 2011

Healthy Lithuanian individuals
Hu - healthy siblings from the UC discordant twin pairs
UC - UC siblings from the UC discordant twin pairs





WHAT ARE THE LIMITATIONS OF CURRENT IBD MICROBIOME RESEARCH IN HUMANS

- Wide clinical spectrum of ulcerative colitis and Crohn's disease cannot be captured in single studies
- Many microbial taxa are fastidious
- Microbiome studies have focused on bacteria - What about others
- Microbiota composition is markedly different between fecal and mucosal samples
- Most studies focus on microbiota composition rather than function
- Most studies characterize the gut microbiota using 16S ribosomal RNA tagged sequencing
- Microbiome studies in IBD are confounded by treatment interventions and the effects of inflammation
- Most published results are based on cross-sectional and not prospective longitudinal cohort studies

MICROBIAL FUNCTION AND METABOLITES IN IBD

WHAT ARE THE EFFECTS OF MICROBIAL METABOLITES ON IBD?

Morgan *et al.*, 2012

- Effects of small molecule (<1,500 Da) products on IBD pathogenesis
- 12% of metabolic pathways of IBD patients were markedly different, compared with just 2% of genus-level clades in healthy individuals
- Changes in amino acid biosynthesis and carbohydrate metabolism pathways reduced
- Genes related to oxidative stress increased

- **Functional differences Vs. compositional differences**

Adoptive T cell transfer model

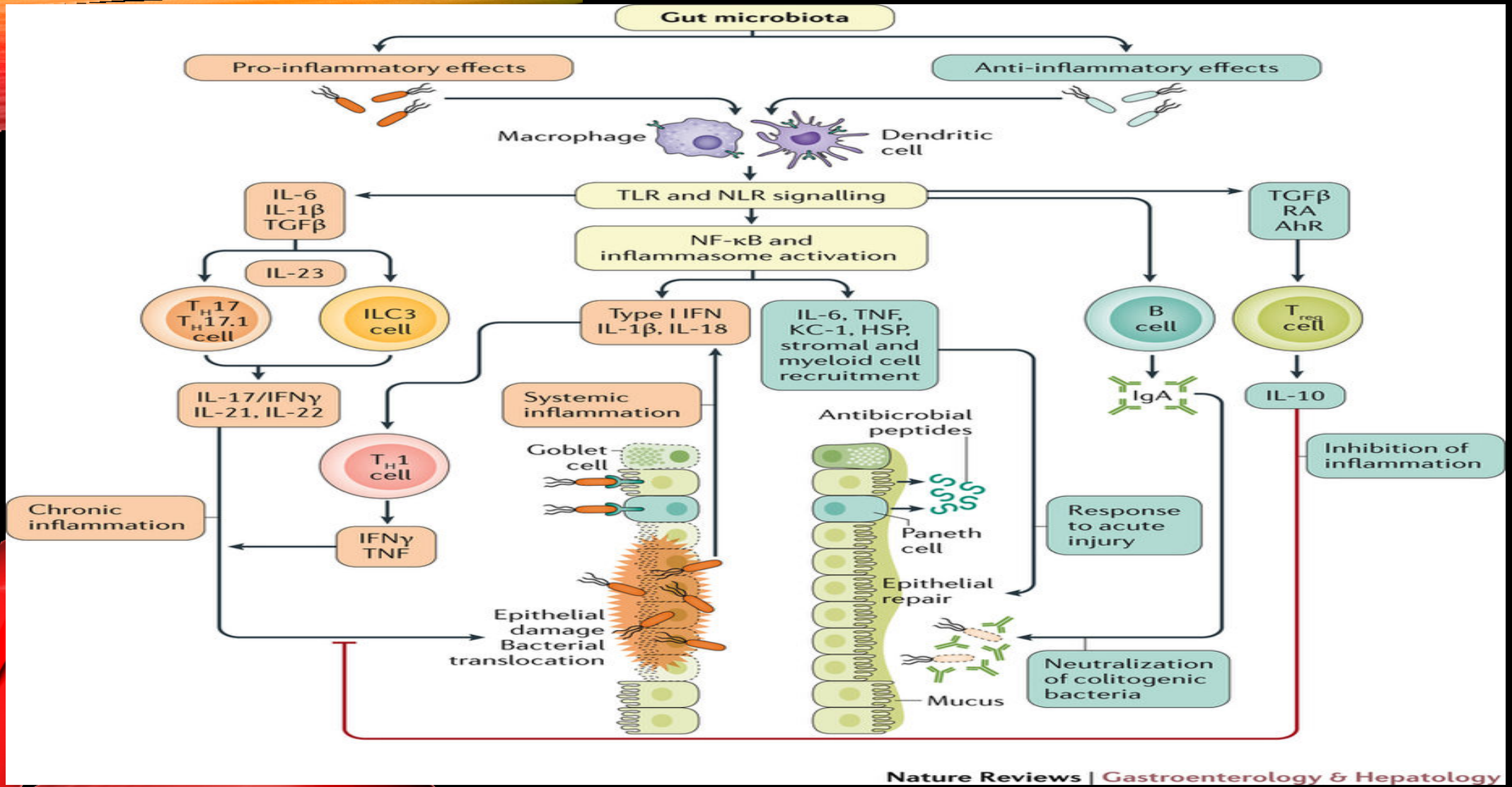
&

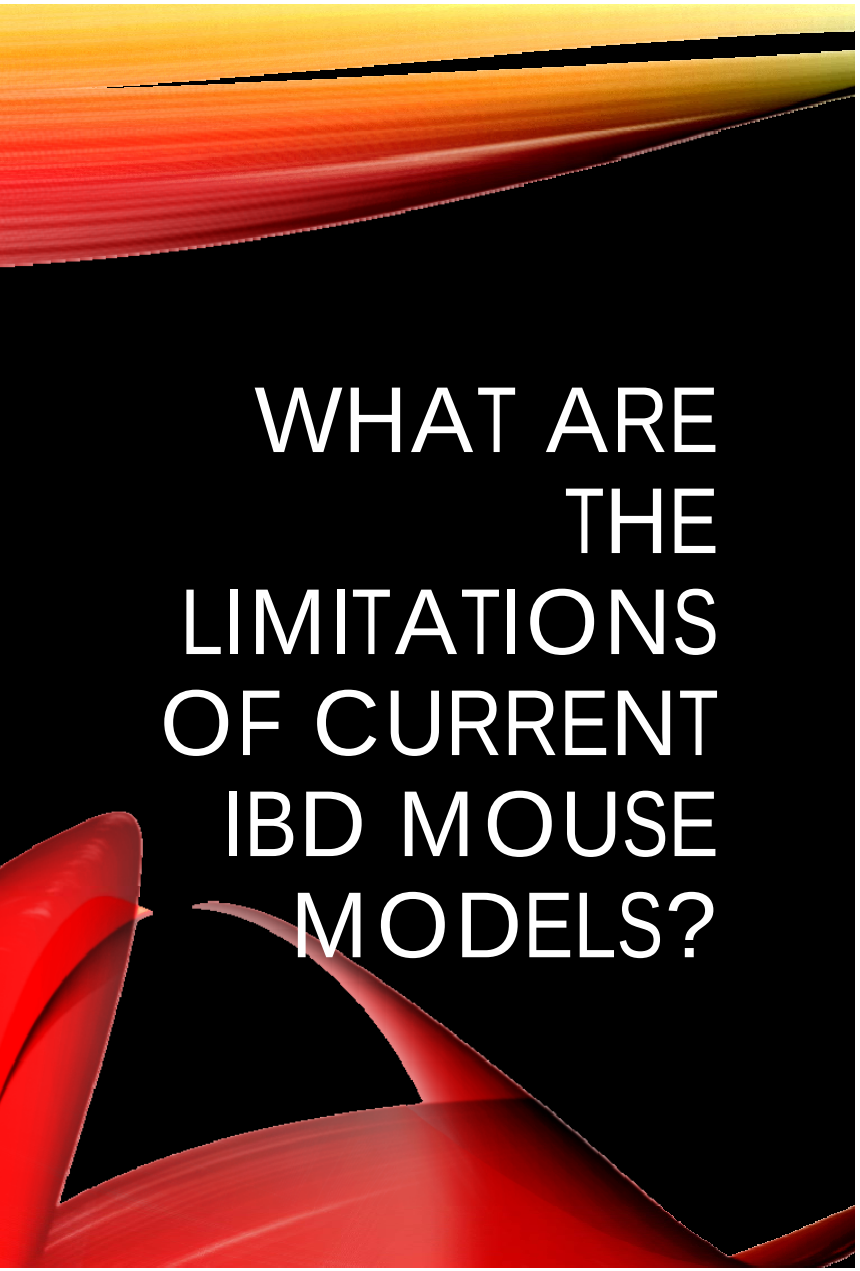
Inflammatory environment

Mohamed R. and Lord GM., 2016

- germ-free animals do not develop colitis
- colonization with a defined cocktail of specific pathogen-free (SPF) bacteria is also required for colitis to develop
- Conversely, co-colonization with the human symbiont *Bacteroides fragilis* reverses the inflammatory effects of *Helicobacter hepaticus* by promoting Treg-cell development

- **Inflammatory potential of individual pathobionts is ultimately determined by the overall composition of the gut microbiota**


Gut microbiota
Pro-inflammatory effects
Anti-inflammatory effects
Macrophage
Dendritic cell
IL-6
IL-1β
TGFβ
TLR and NLR signalling
TGFβ
RA
AhR
NF-κB and inflammasome activation
IL-23
T_H17 $T_H17.1$ cell
ILC3 cell
Type I IFN IL-1β, IL-18
IL-6, TNF, KC-1, HSP, stromal and myeloid cell recruitment
B cell
T_{reg} cell
IL-17/IFNγ IL-21, IL-22
Systemic inflammation
IgA
IL-10
Antibicrobial peptides
T_H1 cell
Goblet cell
Inhibition of inflammation
Chronic inflammation
IFNγ TNF
Paneth cell
Response to acute injury
Epithelial repair
Epithelial damage Bacterial translocation
Neutralization of colitogenic bacteria
Mucus
Nature Reviews | Gastroenterology & Hepatology



WHAT ARE THE LIMITATIONS OF CURRENT IBD MOUSE MODELS?

Most mouse models rely on gene knockouts, whereas human risk alleles seldom lead to complete loss of function

Mouse models usually explore the effect of a single gene, whereas in humans there are often multiple alleles involved

Immune responses differ between mice and humans

Mice do not capture the genetic and environmental diversity of human populations

Mouse experiments fail to account for variables such as medication exposure, smoking and diet that are inherent in human research

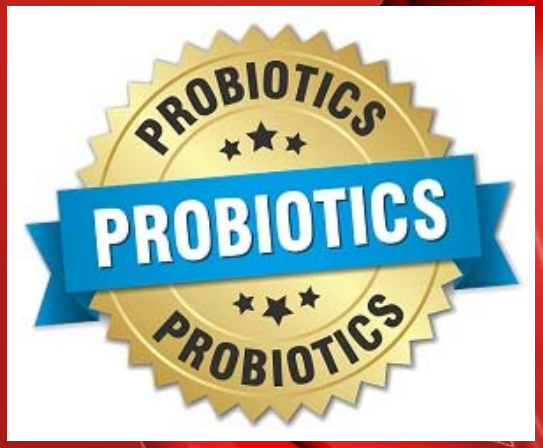
SO……

HOW TO OVERCOME HUMAN IBD

HOW TO OVERCOME HUMAN IBD – CLINICAL EVIDENCE?

Example 1

Use of probiotics



James *et al.*, 1989 and sanders e*t al.*, 2012

- Post-surgical patients with ulcerative colitis who have undergone ileal pouch-anal anastomosis
- Predisposed to inflammation of the ileal pouch
- probiotics effectively prevent the complication following successful antibiotic treatment

BUT.....

Example 2

Alterations to diet

- Enteral nutritional therapy (ENT) with elemental, semi-elemental, or polymeric formulas can be used as first-line therapy for the induction of remission in Crohn's disease and has been associated with both clinical improvement and mucosal healing

- In contrast, another study showed, initial shifts in microbial composition towards even greater dysbiosis relative to healthy individuals

BUT.....

Example 3

Fecal Microbiota Transplantation

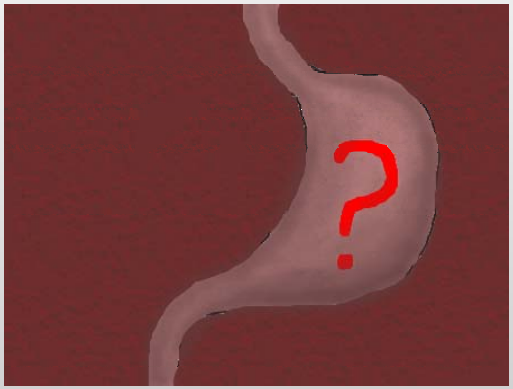
- success of FMT for the treatment of refractory *Clostridium difficile* infection
- higher complexity of IBD compared to *C. difficile* colitis

- Cui *et al.*, 2015
  - pilot study of FMT in adult refractory Crohn's disease resulted in high rates of clinical remission and clinical improvement

- Suskind *et al., 2015*
  - clinical benefit in a small cohort of patients with Crohn's disease in children

- Rossen *et al., 2015*
  - FMT was fail to show effective result than placebo in inducing clinical and endoscopic remission in ulcerative colitis in adults

BUT.....



CURRENTLY...!!

- The association studies, animal models and early therapeutic trials collectively point to an important role of the gut microbiota and their metabolites in IBD pathogenesis.

- Translating these insights into viable therapeutic approaches might be challenging and require an investment in human subject research to definitively demonstrate cause–effect relationships.

WHAT ARE NEXT?

- What are the very early events in IBD pathogenesis?
- Can microbiota testing be used as a reliable marker?
- What are the antigens in the intestinal lumen that drive T-cell activation in IBD?
- What is the best way to administer FMT?
- What will be the long-term outcomes of FMT for IBD?
- How can we refine microbial therapies beyond FMT?
- Can microbial-based therapies be used to prevent, rather than treat, IBD?
- What is the role of the virome in IBD?

IN A NUT SHELL

- Alterations in intestinal microbial composition have long been associated with chronic inflammation
- Dysbiosis alters not only the composition of the intestinal microbiota, but also its metabolome
- While the microbiota plays a key pathogenic role in IBD, chronic inflammation, in turn, promotes dysbiosis
- Animal studies have elucidated key immunological pathways in the pathogenesis of IBD
- Microbial-based treatments will likely have a role in the future management of IBD

Thank you

Q & A