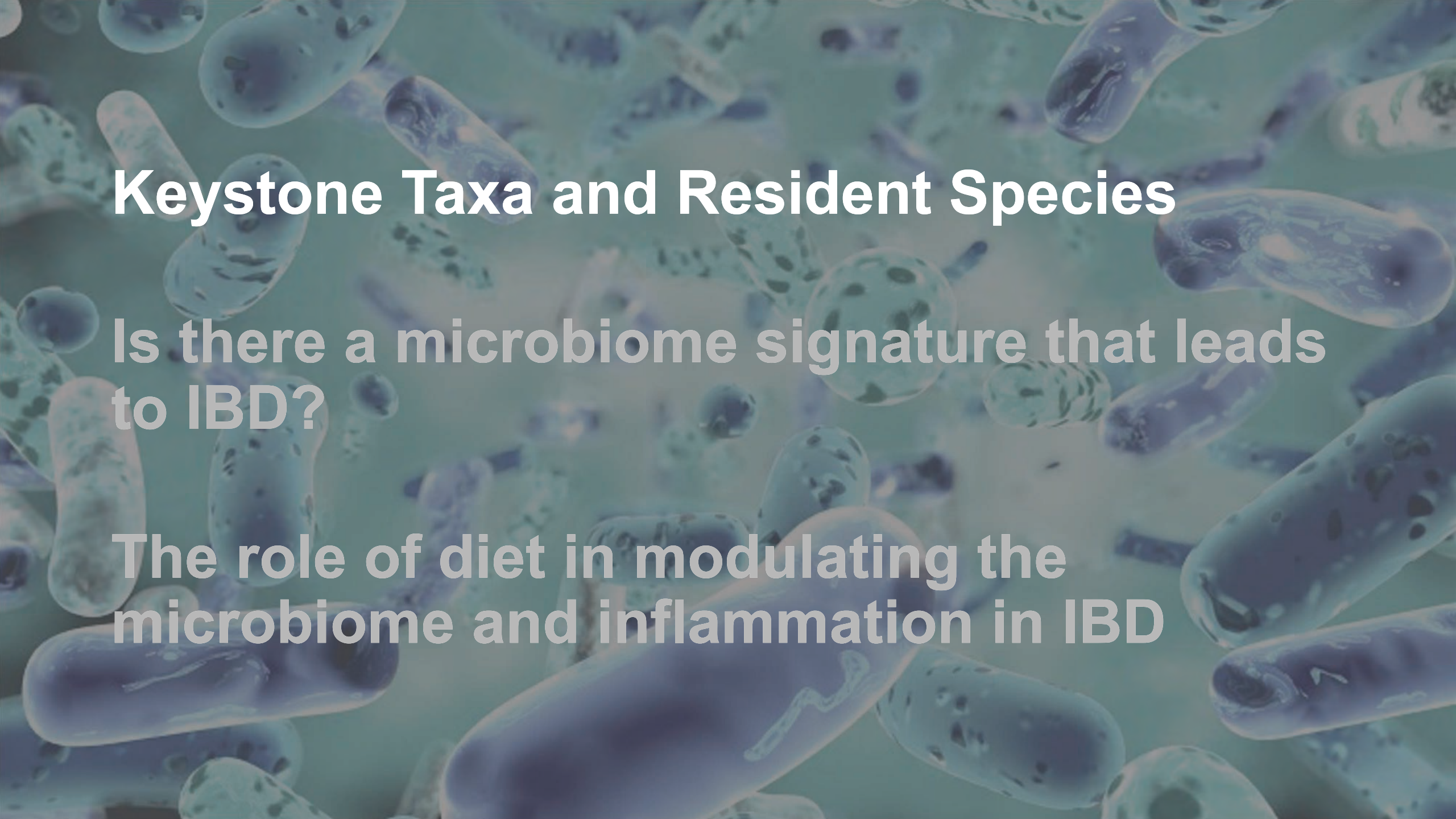
Workshop
Microbiome: Diet and Resident Bacteria

Dr. Deanna L. Gibson, Ph.D.
Professor, Biology, Faculty of Science
The University of British Columbia, Okanagan

Dr. Elena Verdu, MD, Ph.D.
Professor, Medicine, Farncombe Family Digestive Health Research Institute
McMaster University



Keystone Taxa and Resident Species

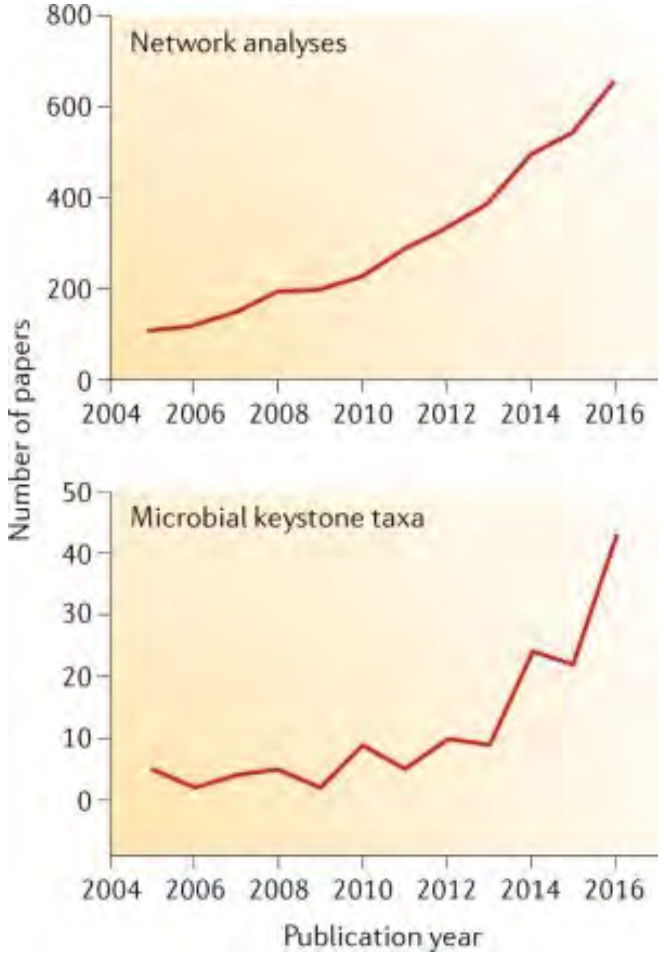
Is there a microbiome signature that leads to IBD?

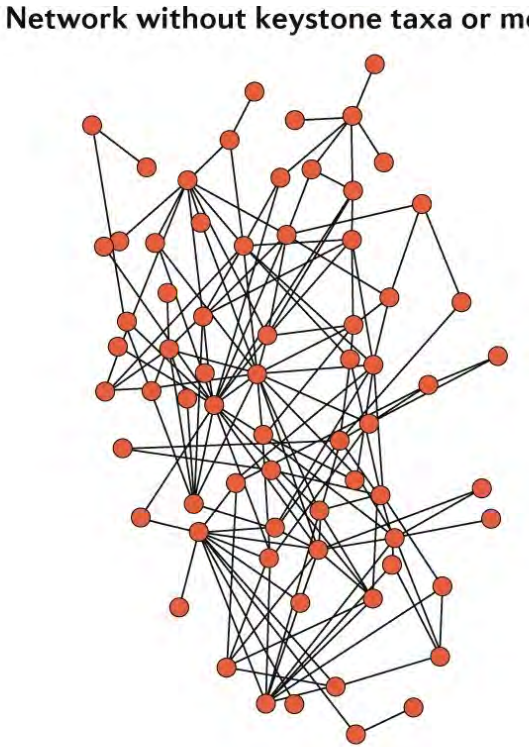
The role of diet in modulating the microbiome and inflammation in IBD

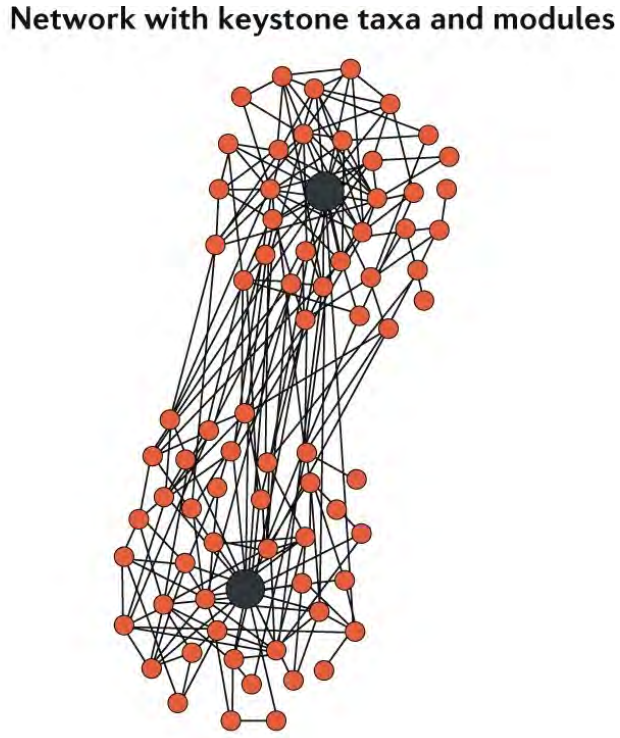
Who is Resident? Keystone Taxa

Highly connected taxa influence microbiome structure and functioning irrespective of their abundance across space and time.

- crucial role in microbial communities
- removal can cause a dramatic shift in microbiome structure and functioning



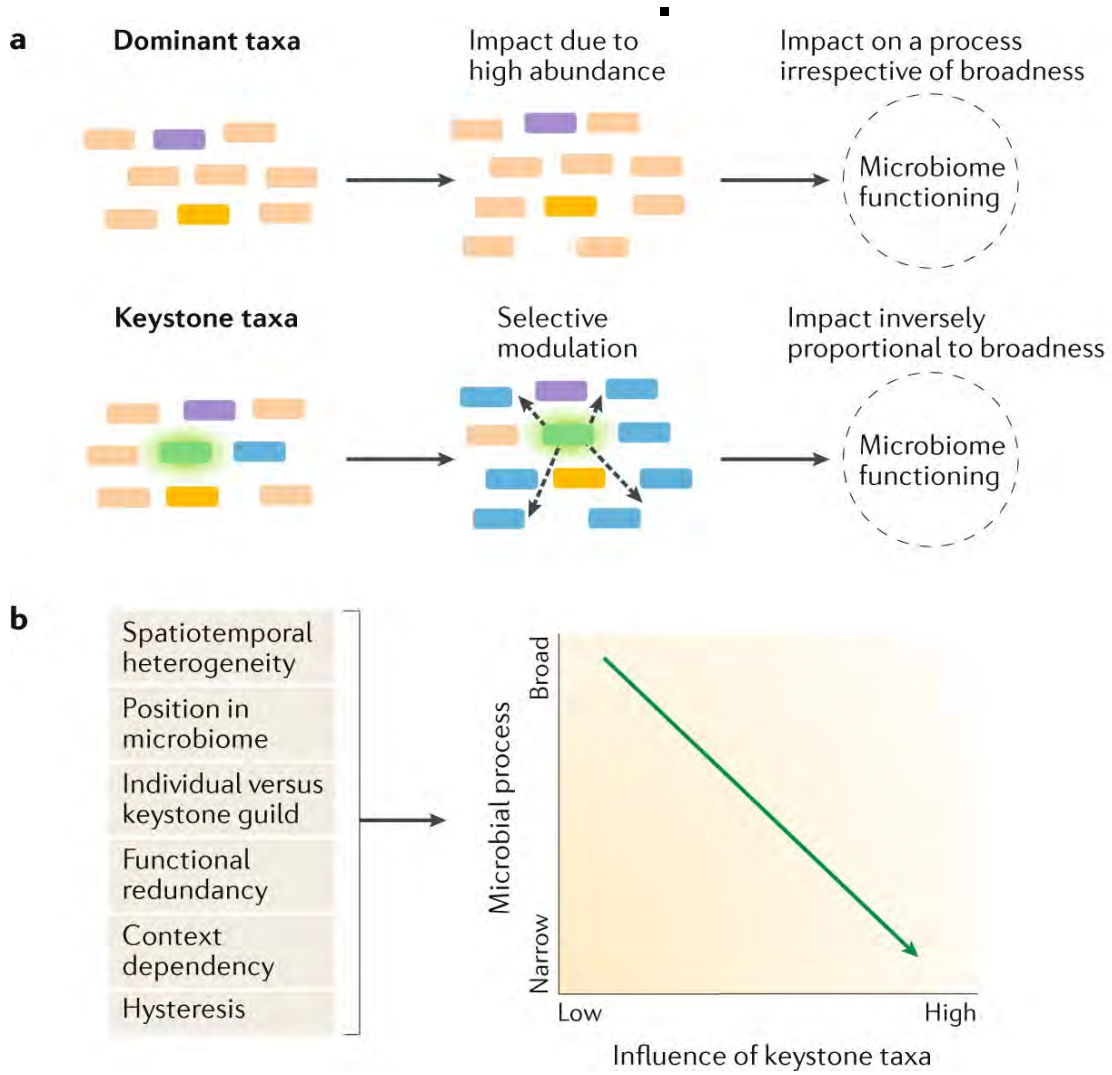


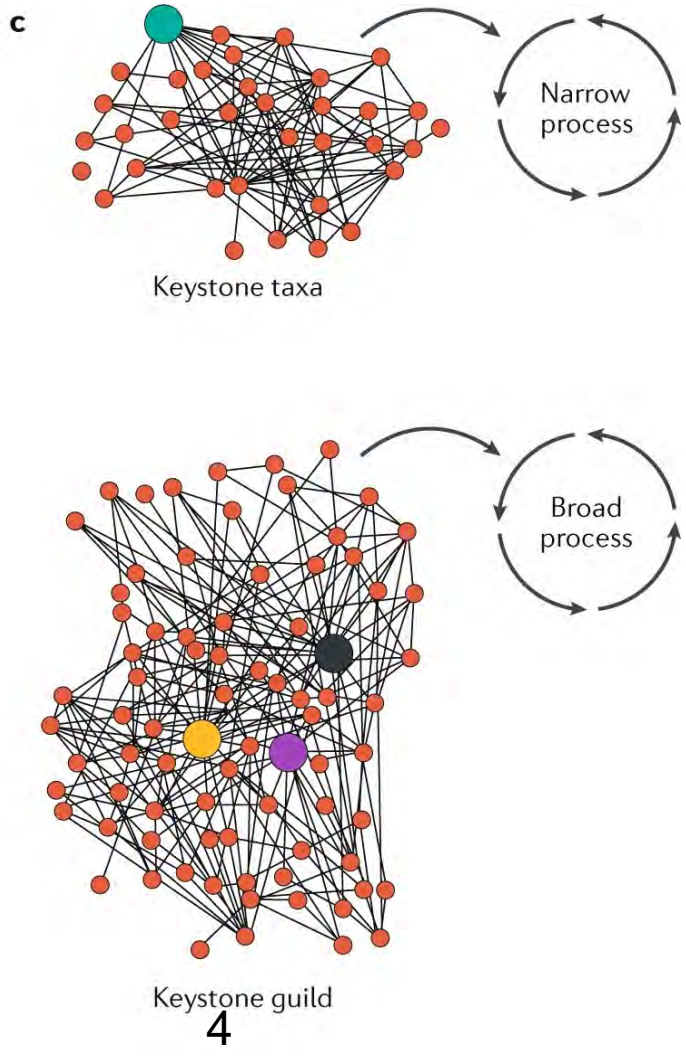


Banerjee, S., Schlaeppi, K. & van der Heijden, M.G.A. Keystone taxa as drivers of microbiome structure and functioning. *Nat Rev Microbiol* **16**, 567–576 (2018).

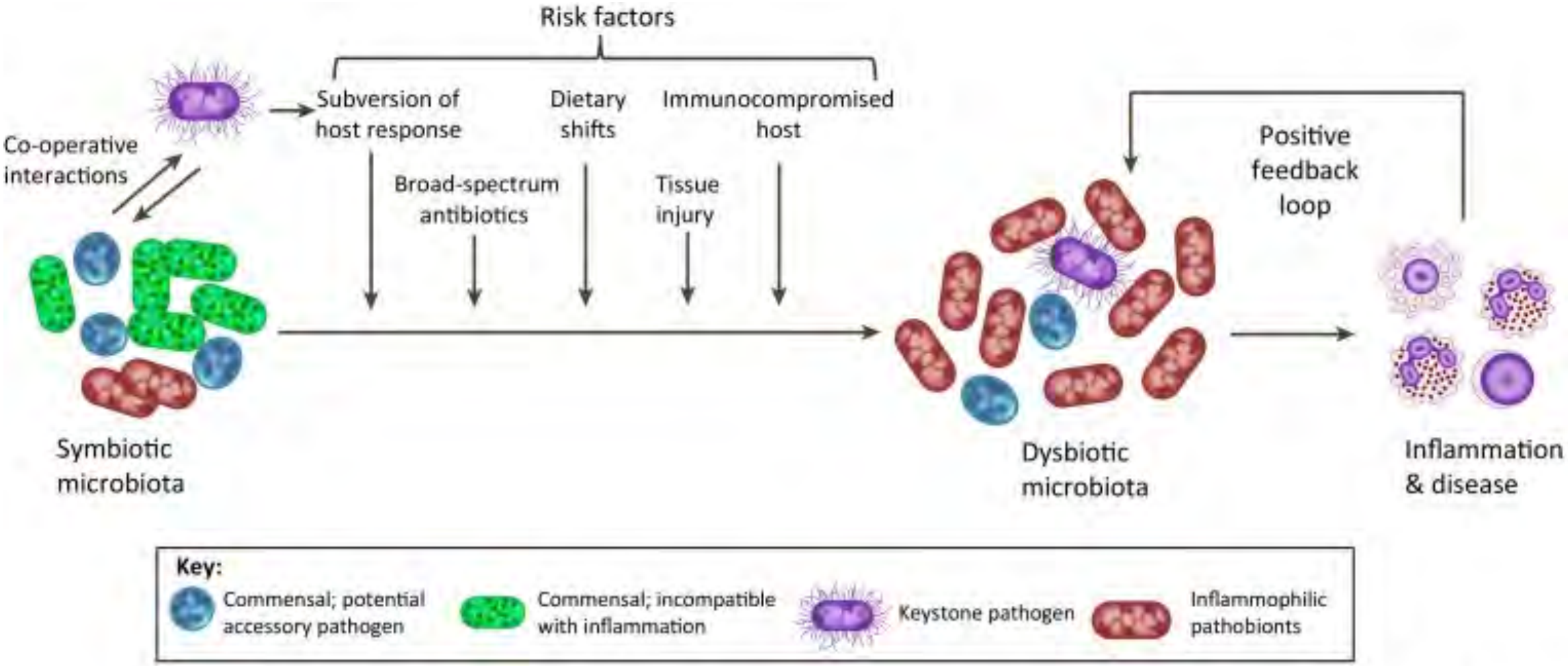
Keystone taxa in microbial communities and the factors influencing their functioning in an environment

Rare taxa can have an over-proportional influence and can also be keystone taxa.





Keystone pathogen hypothesis: Specific low-abundance microbial pathogens can orchestrate inflammatory disease by remodeling a normally benign microbiota into a "dysbiotic" one.



George Hajishengallis & Richard J. Lamont. *Nature Reviews Microbiology* 2012,10(10):717-25

Pathobiont-Symbiont continuum: Context dependent!

Pathobionts: Opportunistic microbes that emerge due to perturbations in the healthy microbiome due to complex interactions that lead to their selection and expansion.

Akermansia mucinophila: Degrades mucus and can be associated with experimental colitis and exacerbation of food allergy, but there are claims for metabolic health in obesity.

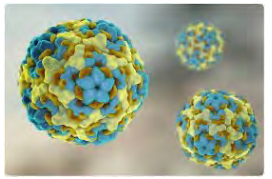
Bacteroides fragilis: Non and toxigenic chronically colonize mice, only ETBF triggers colitis and strongly induces colonic tumors in mice, while non-toxigenic secreted polysaccharide A (PSA) is a model symbiosis factor that benefits the host.

Prevotella copri: Associated with Non-westernized populations eating plant-based diets; associated with experimental colitis

Escherichia coli: Early colonizers in infants and high in Non-westernized populations but tends to be associated with inflammation in the gut; Nissle is probiotic while AIEC is associated with CD.

Jochum & Stecher. *Trends in Microbiology*, 2020; Chandra H, *et al*. *Gut Microbes*. 2021; Parrish, A. *et a*l. *Nature Microbiology* 2023

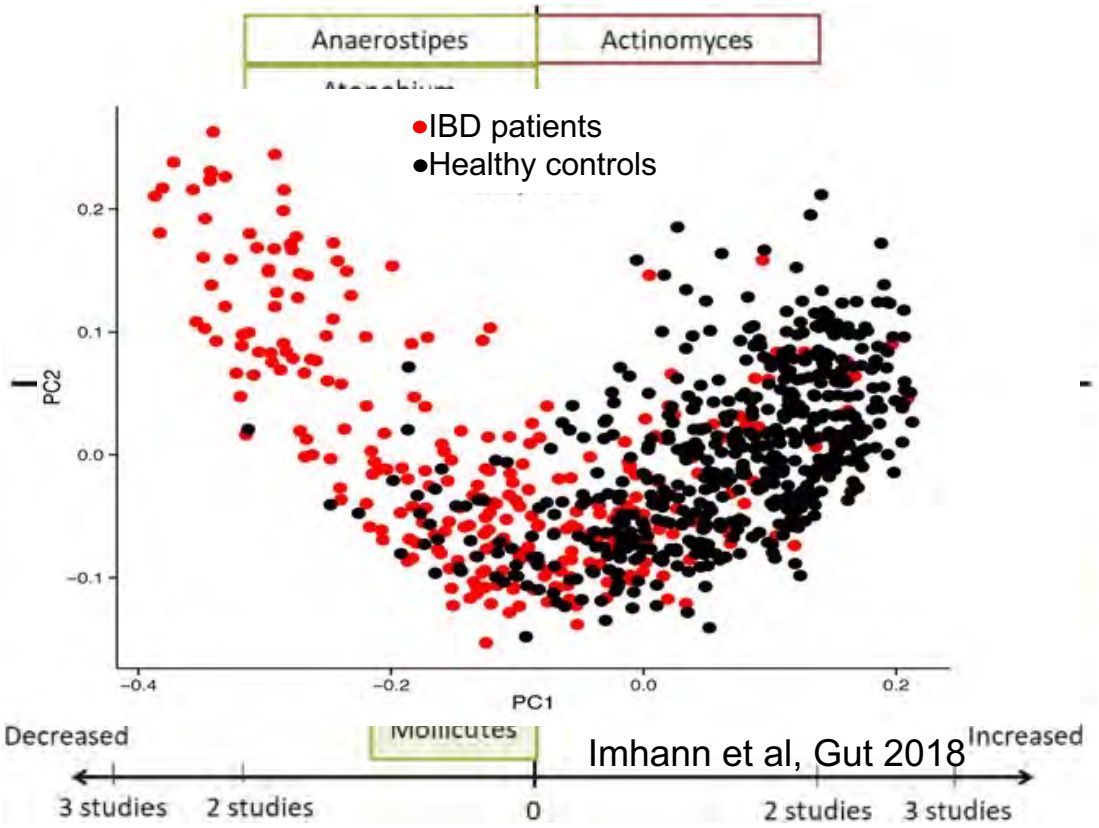
Host and microbiome exist in a delicate mutualistic relationship




Keystone Taxa and Resident Species
Is there a microbiome signature that leads to IBD?
The role of diet in modulating the microbiome and inflammation in IBD

Is there a “universal” IBD microbiome signature?

- ✓ Lower diversity, temporal instability
- ✓ High inter-study and inter-personal variability, methodology
- ✓ Results not always congruent between studies
- ✓ Functional changes need to be considered in addition to taxonomy



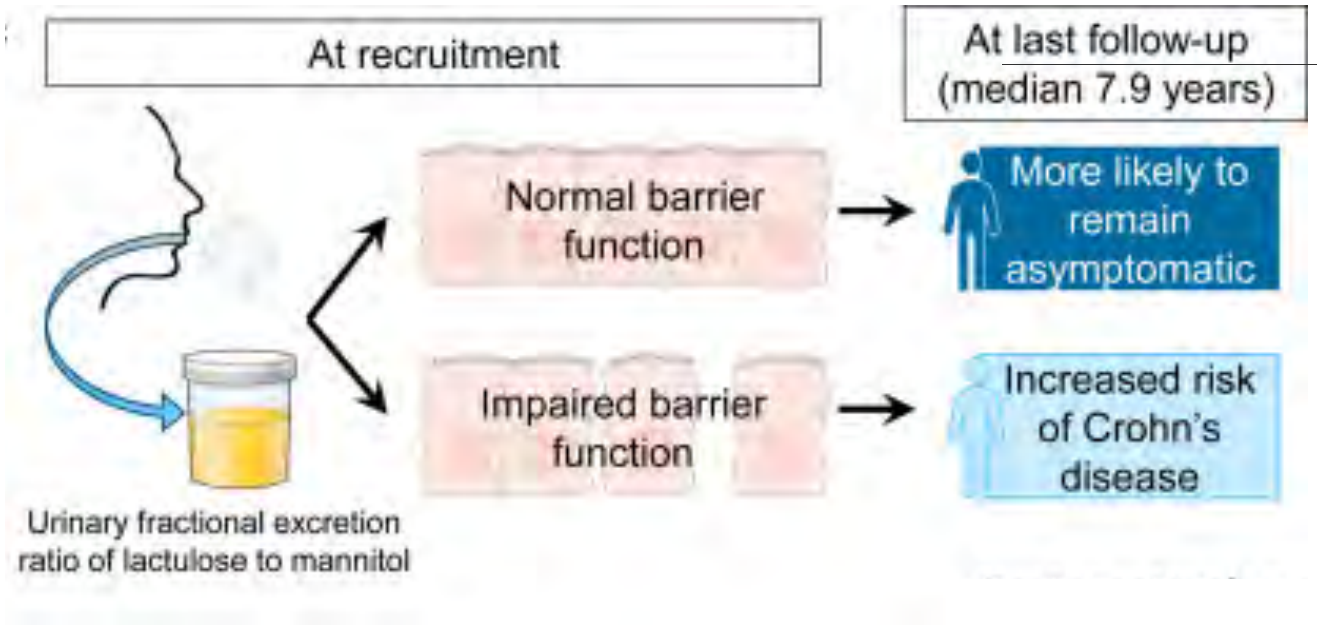
Imhann et al, Gut 2018

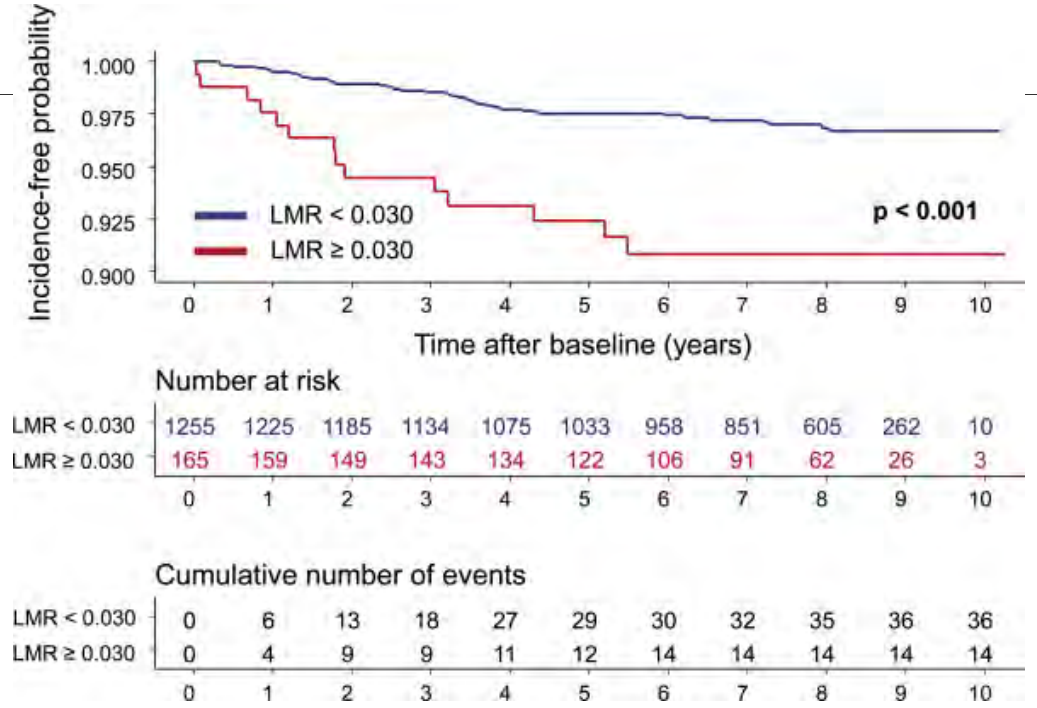
Pittayanon et al, Gastroenterol 2020

GEM PROJECT
CROHN'S AND COLITIS CANADA

What about before IBD?

Abnormal permeability precedes diagnosis of CD

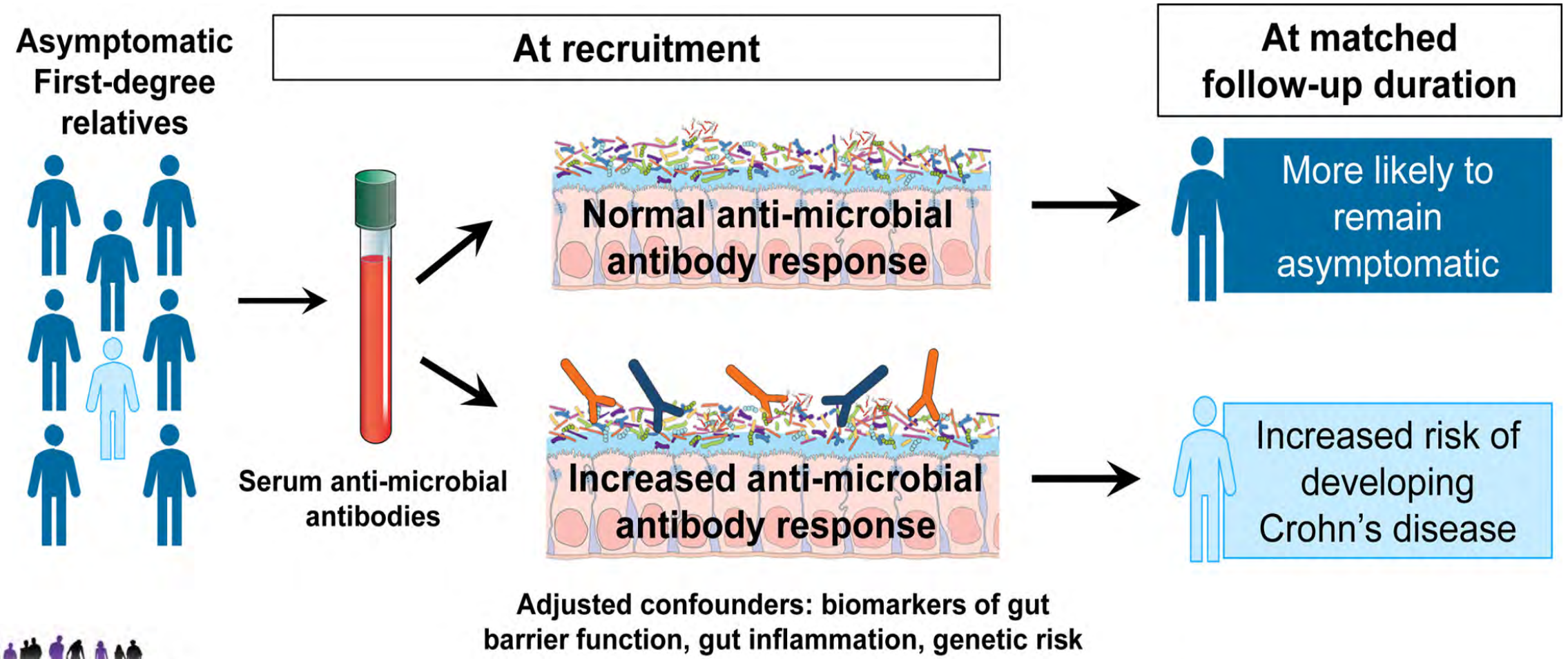




✓ **Abnormal gut barrier function may be a biomarker for risk of CD onset**

Turpin et al. *Gastroenterology*. 2020 Dec;159(6):2092-2100.e5.

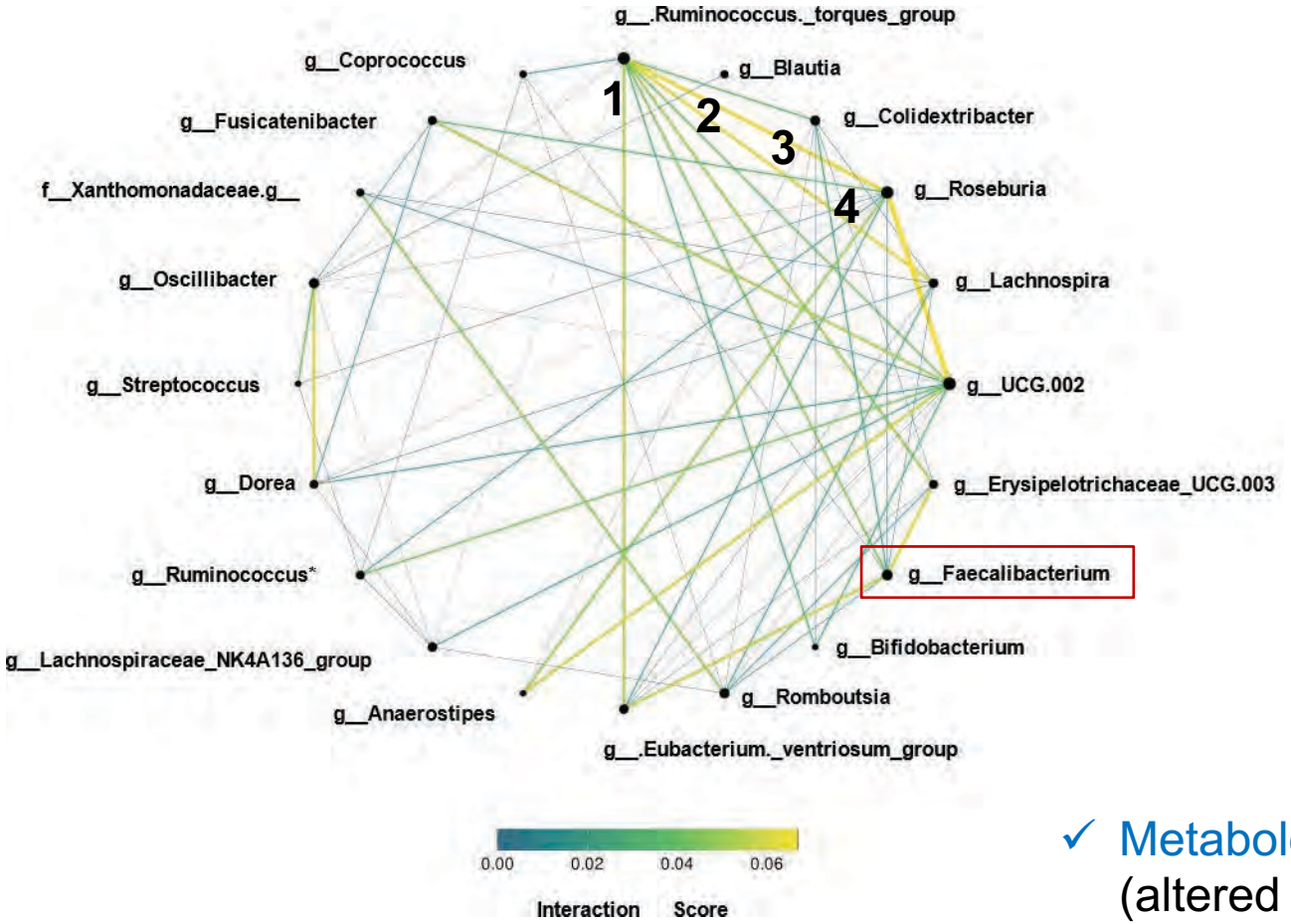
Anti-microbial antibodies associated with future onset of CD



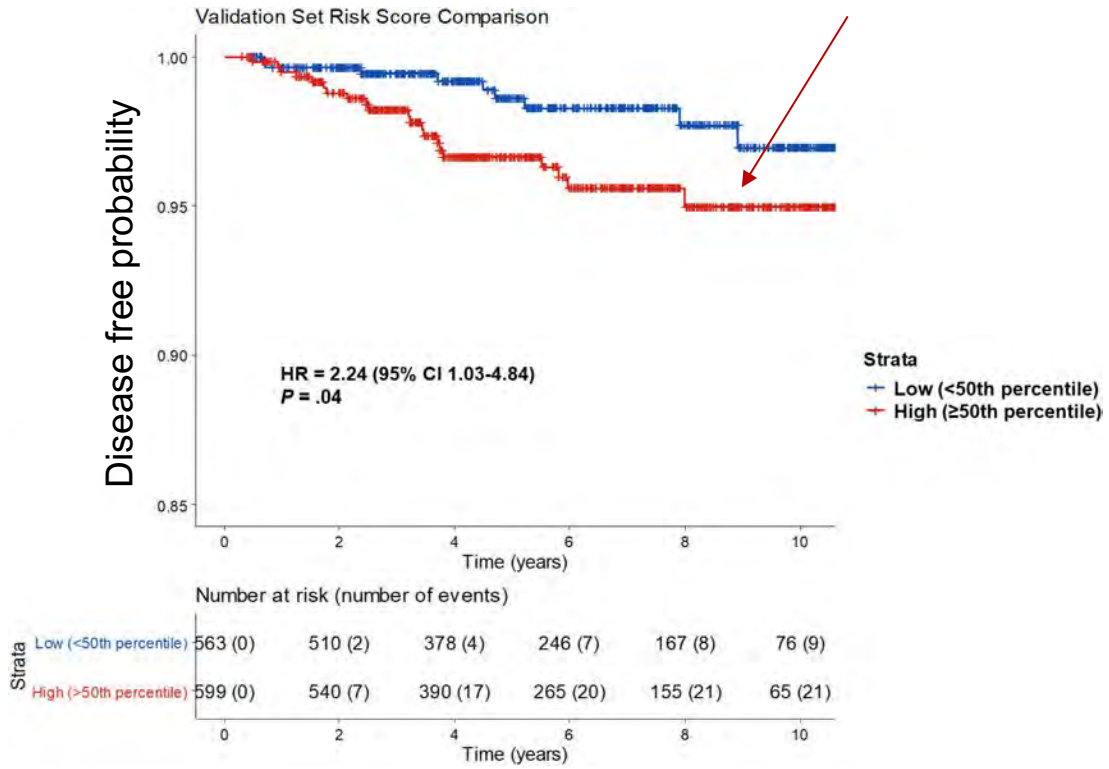
THE GEM PROJECT
genetic environmental microbial

Lee *et al*. *Gastroenterology* 2021

IBD microbiome *as a community (microbiome score)* may contribute to future Crohn's disease



Elevated Microbiome Score



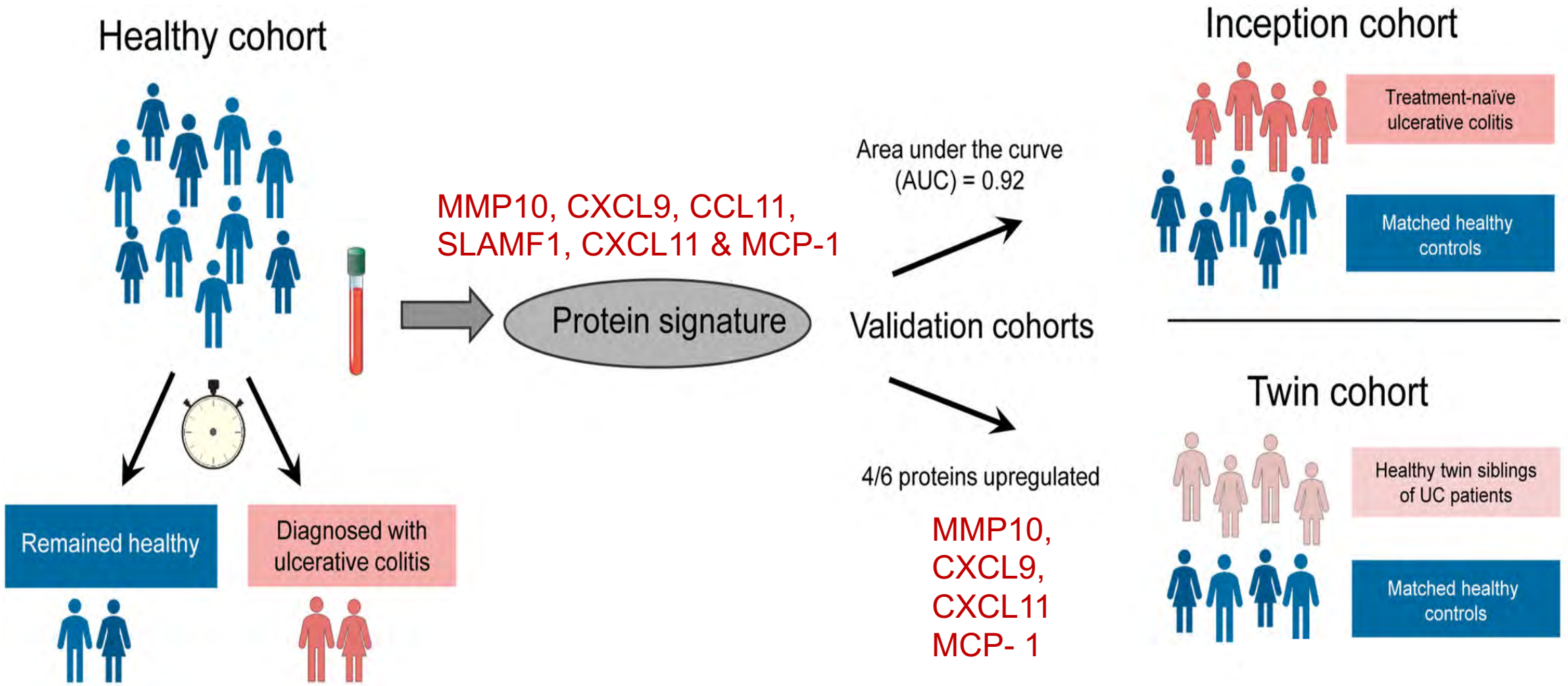
✓ Metabolome: p-cresol associated with CD and the microbiome (altered protein metabolism?) (Turpin, Unpublished)

Mount Sinai Hospital
Sinai Health System
Joseph & Wolf Lebovic Health Complex
CENTRE FOR INFLAMMATORY BOWEL DISEASE (IBD)

Raygoza Garay, Turpin, Lee *et al. Gastroenterology* 2023

THE GEM PROJECT
genetic environmental microbial

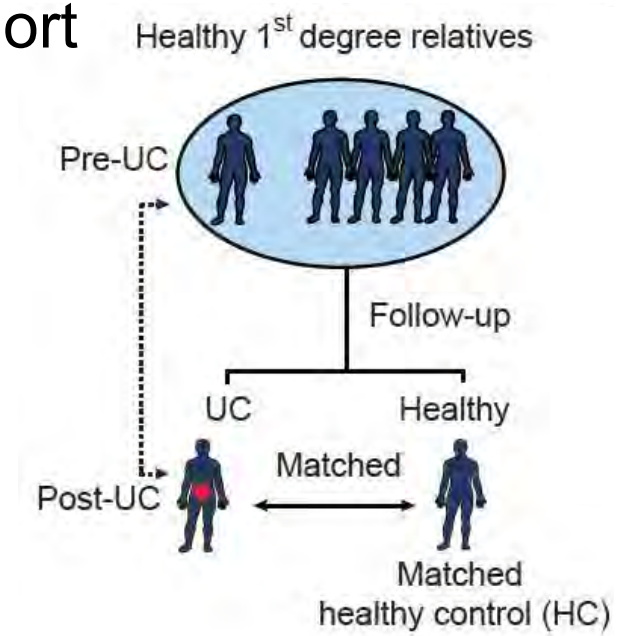
Inflammatory proteins are up-regulated before diagnosis of UC



Bergemalm *et al*. *Gastroenterology* 2021

Increased elastolytic precedes UC diagnosis

Cohort



48 matched HC

13 pre UC

9 post UC

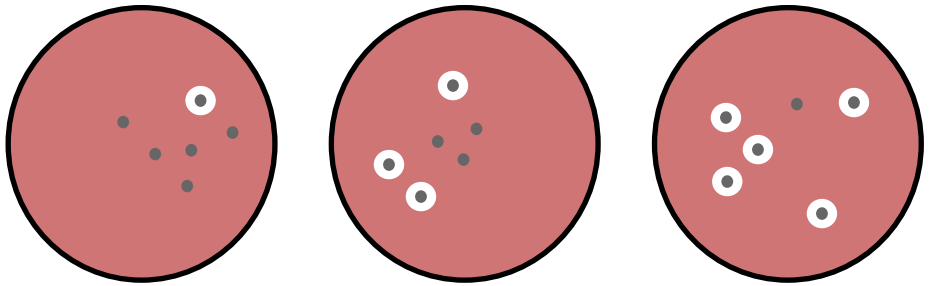
Galipeau et al. Gastroenterology. 2021; 160(5):1532-1545.

Bacterial proteolytic activity correlates with proteolytic taxa from UC

✓ **Sequencing & metagenomics:**

↑ bacterial proteolytic groups in pre- & post UC
functions related to proteases

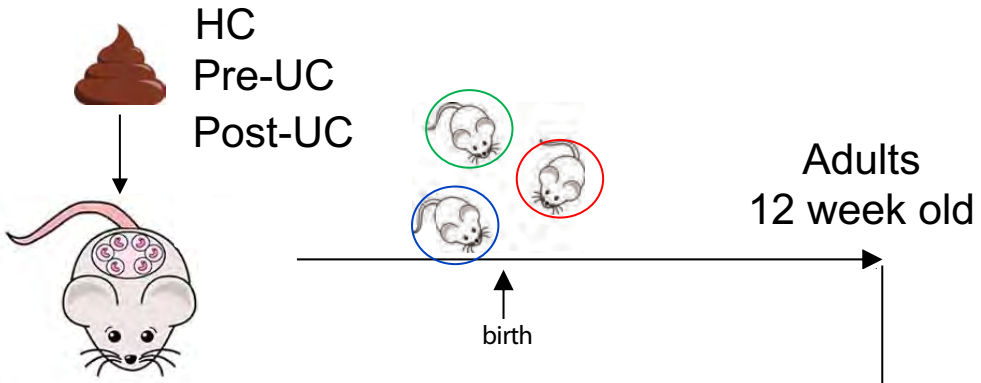
✓ **Isolates that cleave Elastin**
(Bacteroides)

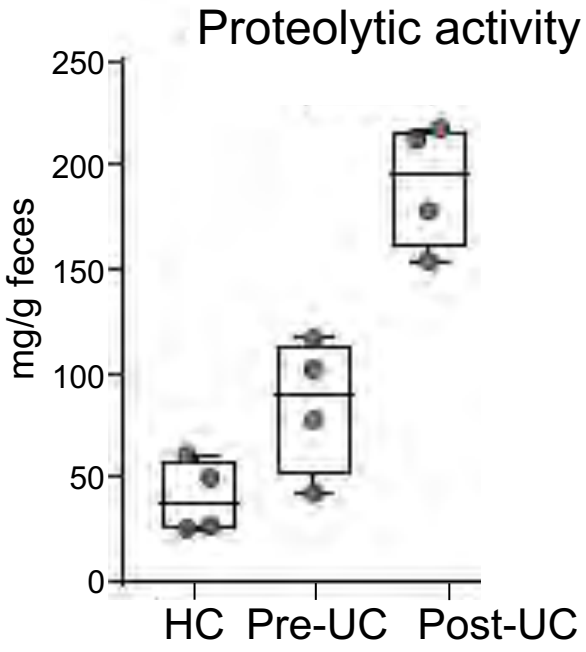


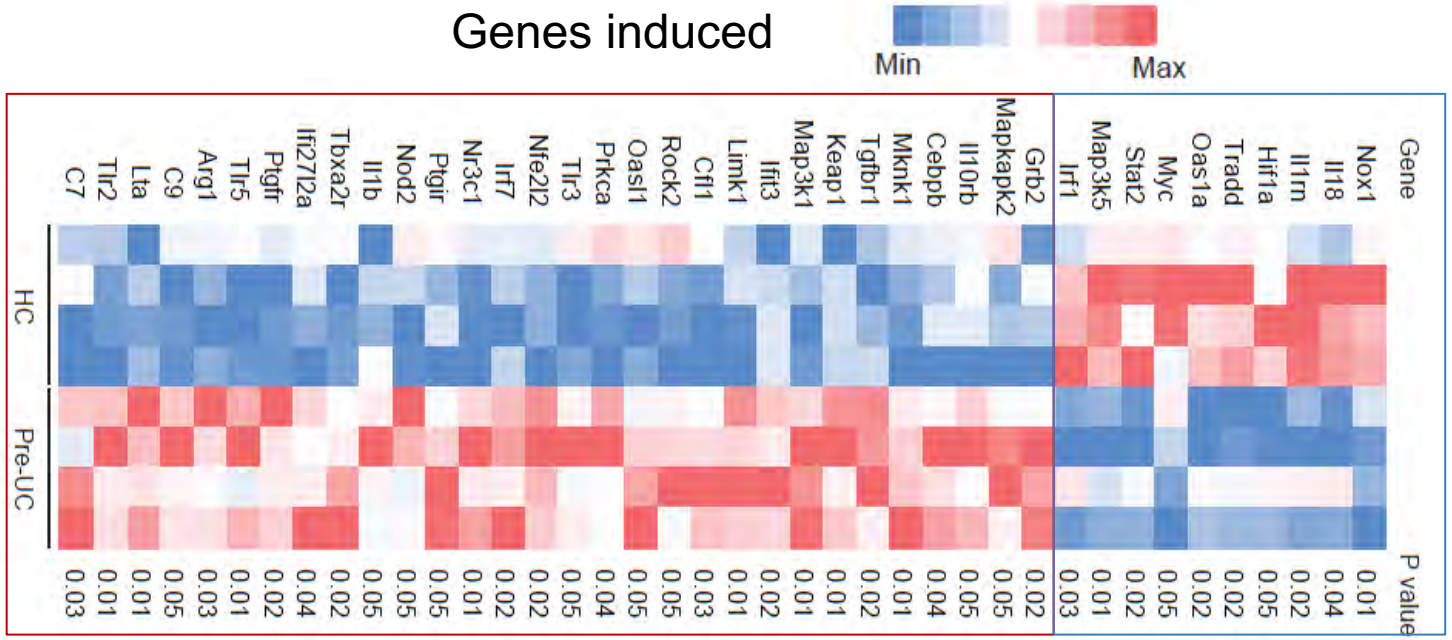
HC	pre-UC	post-UC
+	++	+++

Galipeau et al, *Gastroenterology*. 2021; 160(5):1532-1545.

Proteolytic function is transferred to GF mice





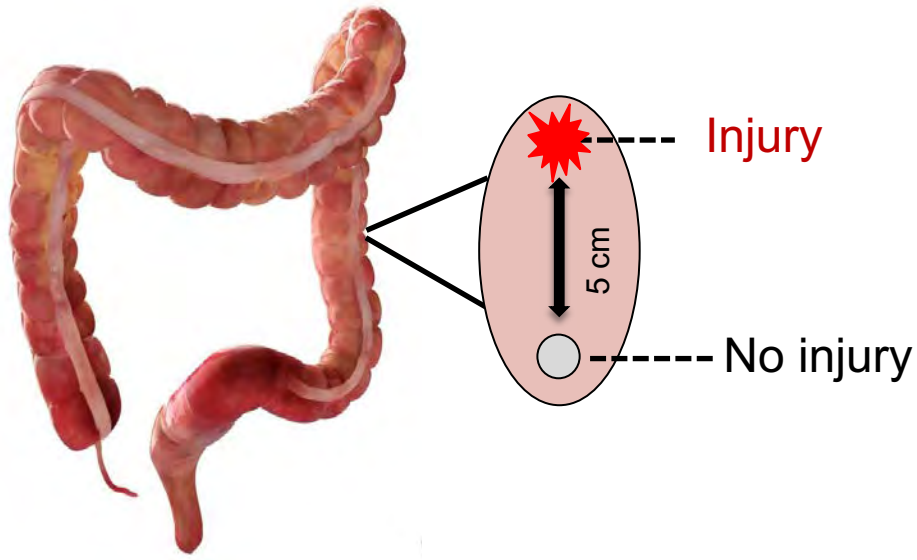


Innate immune function
Bacterial signaling

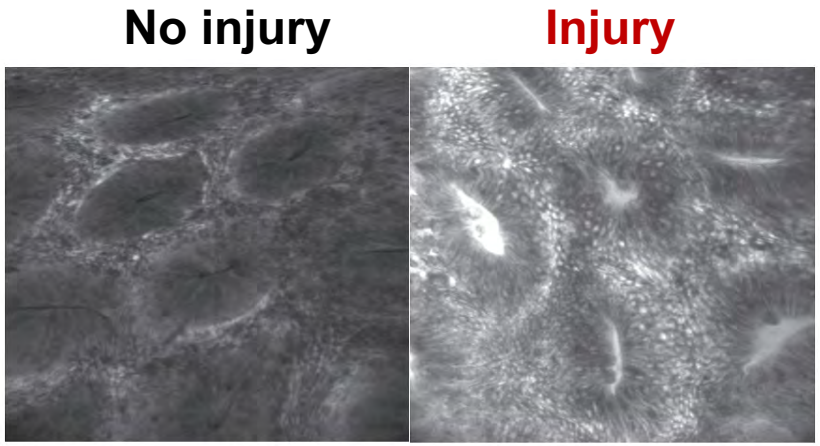
Apoptosis
Cell death
Cell regeneration

Gastroenterology. 2021; 160(5):1532-1545.

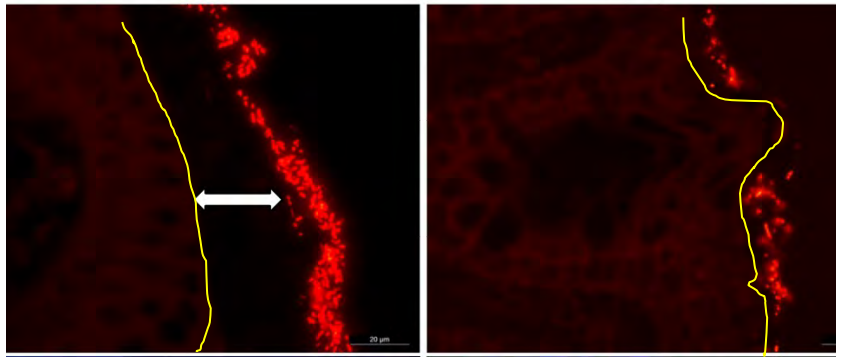
Is proteolytic imbalance associated with mucosal lesions?



Libertucci *et al*. *Am J Physiol* 2018



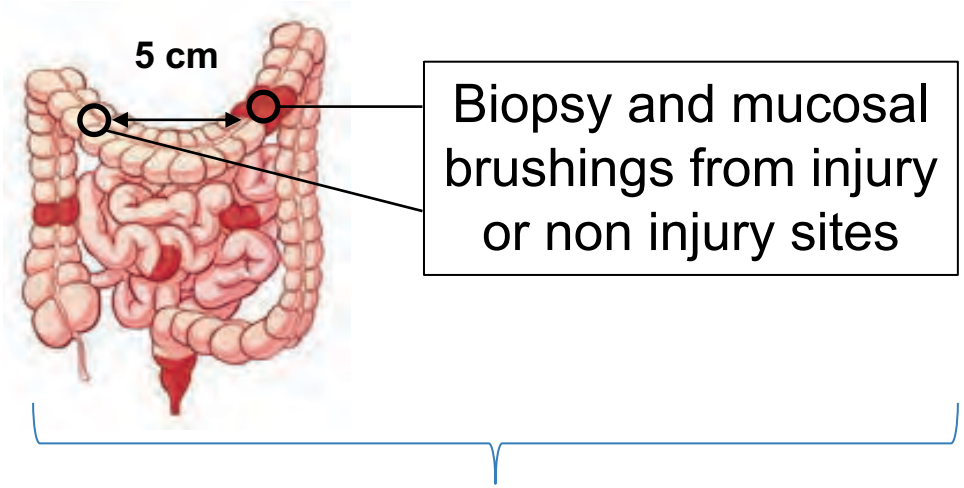
Fluorescein leak



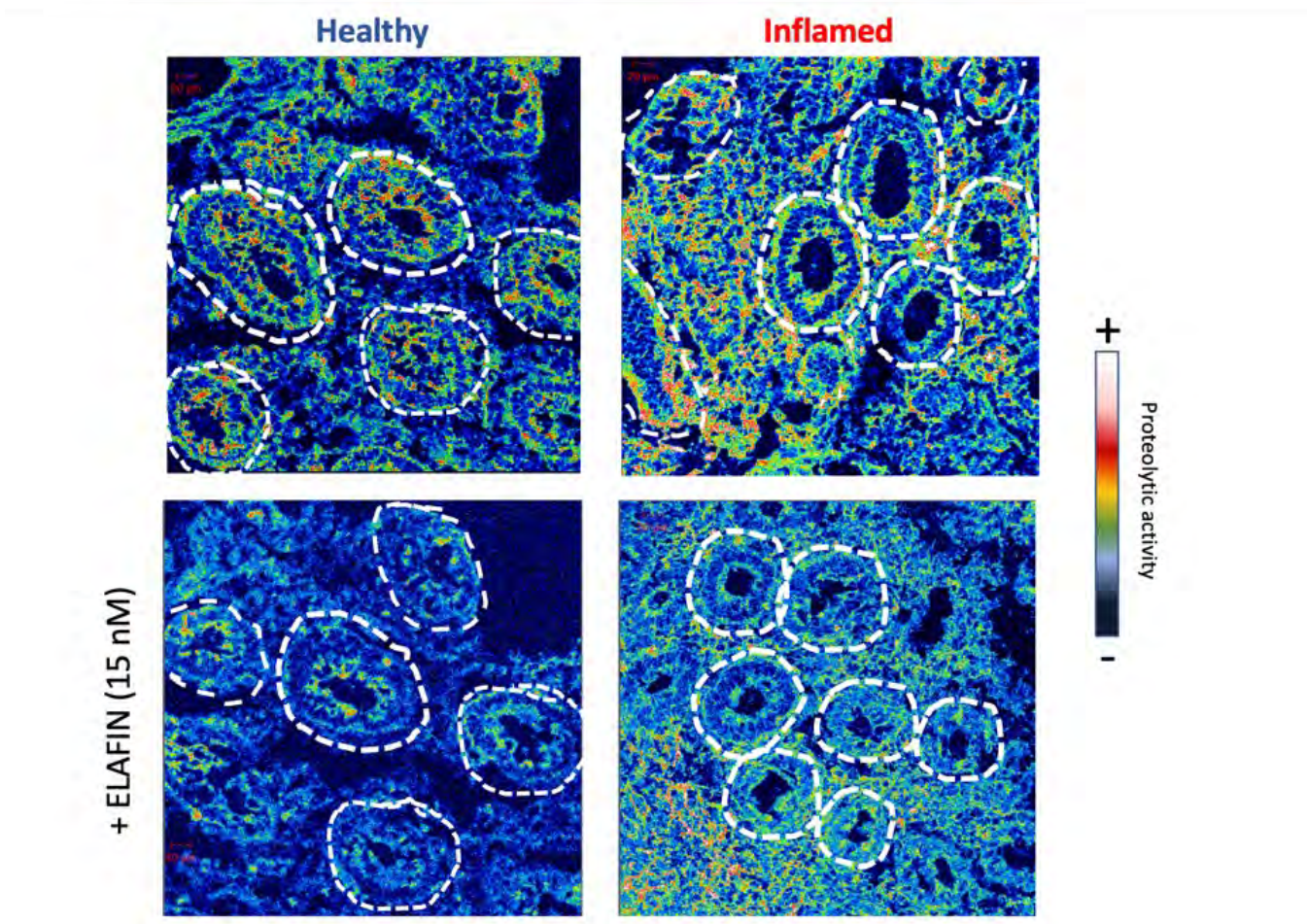
Bacteria attached to the gut lining

✓ **Active CD had fecal increase of bacterial groups with proteolytic potential**

Does bacterial proteolytic activity contribute to inflammation in affected areas in CD?



30 patients to be recruited.
Ethics approval (HiREB # 7789)

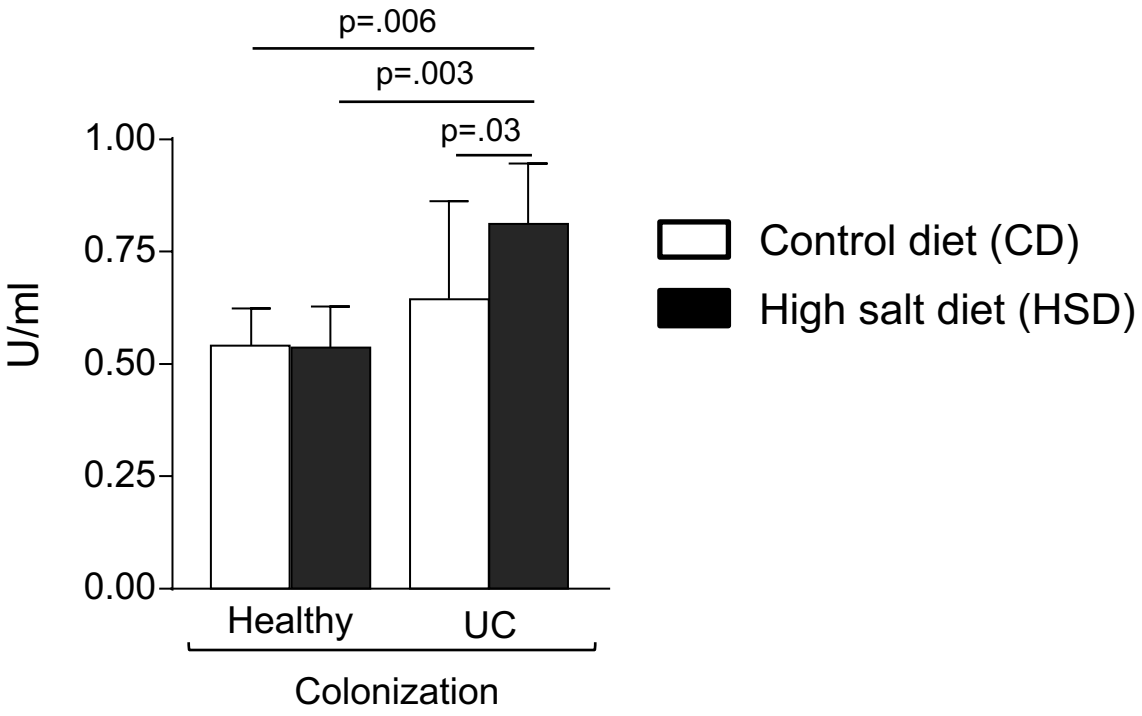


Stezo J, *et al. Unpublished*


Keystone Taxa and Resident Species
Is there a microbiome signature that leads to IBD?
The role of diet in modulating the microbiome and inflammation in IBD

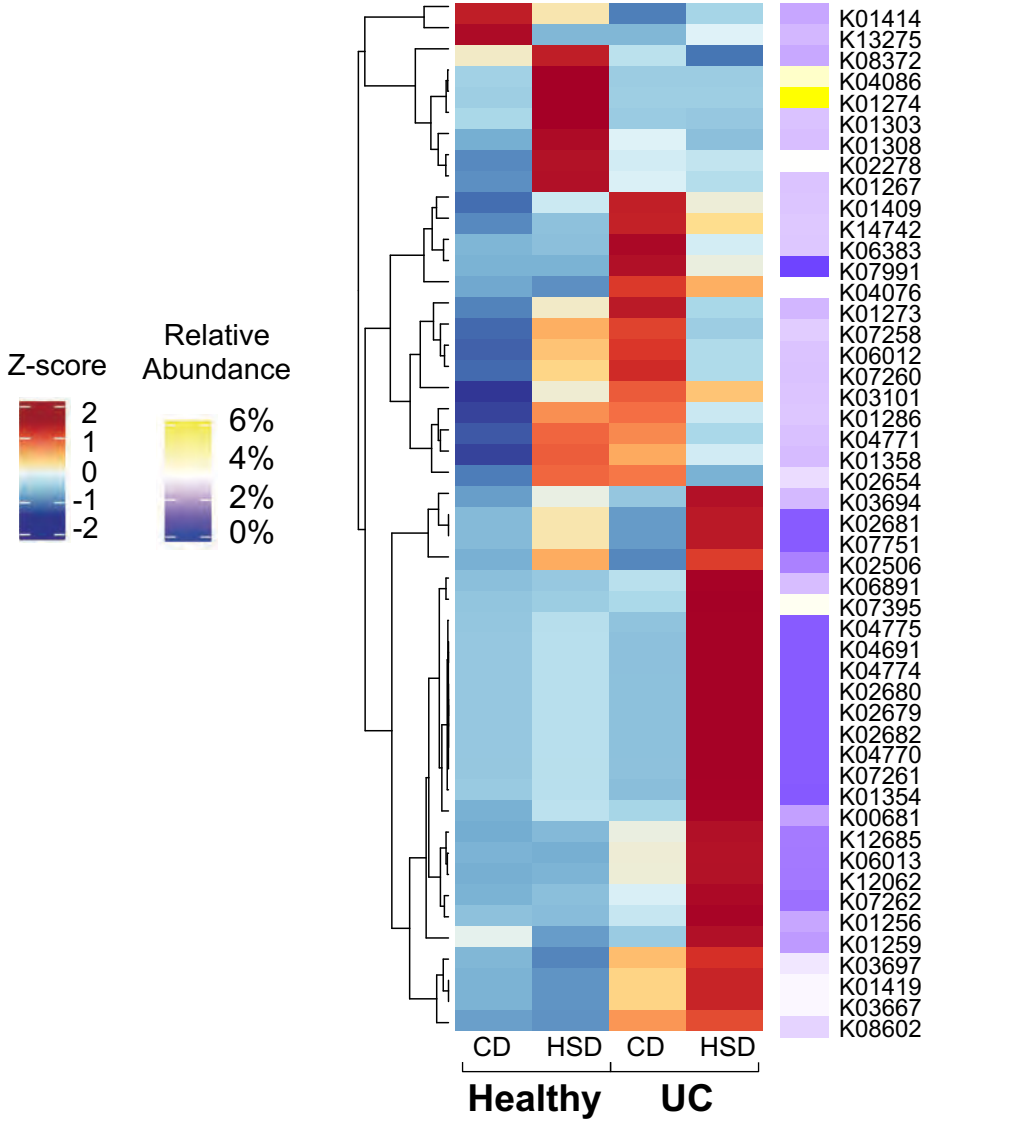
What drives increased proteolytic activity?

Elastolytic activity



Hann A, *et al*. Unpublished

Microbial genes regulating protease function



HSD associated with inflammation and IBD

- HSD has been shown to induce an inflammatory immune tone (Th17 cells) and worsen colitis through microbiota in mice
- A high salt is a large component of ultra-processed foods or the “Westernized” diet that has become increasingly prevalent
- Ultra-processed food intake has been associated with increased risk of IBD

Does HSD increase fecal proteolytic activity and exacerbate colitis?

Tubbs *et al*, *J. Immunol* 2017; Miranda, *et a*l. *Microbiome.* 2018; Narula, *et al. BMJ*. 2021; Kleinewietfeld, *et al*. *Nature* 2013

A Mediterranean-like fat blend promotes protective immunity and a microbiome supporting gut health.

GUT MICROBES
2022, VOL. 14, NO. 1, e2055441 (23 pages)
https://doi.org/10.1080/19490976.2022.2055441

Taylor & Francis
Taylor & Francis Group

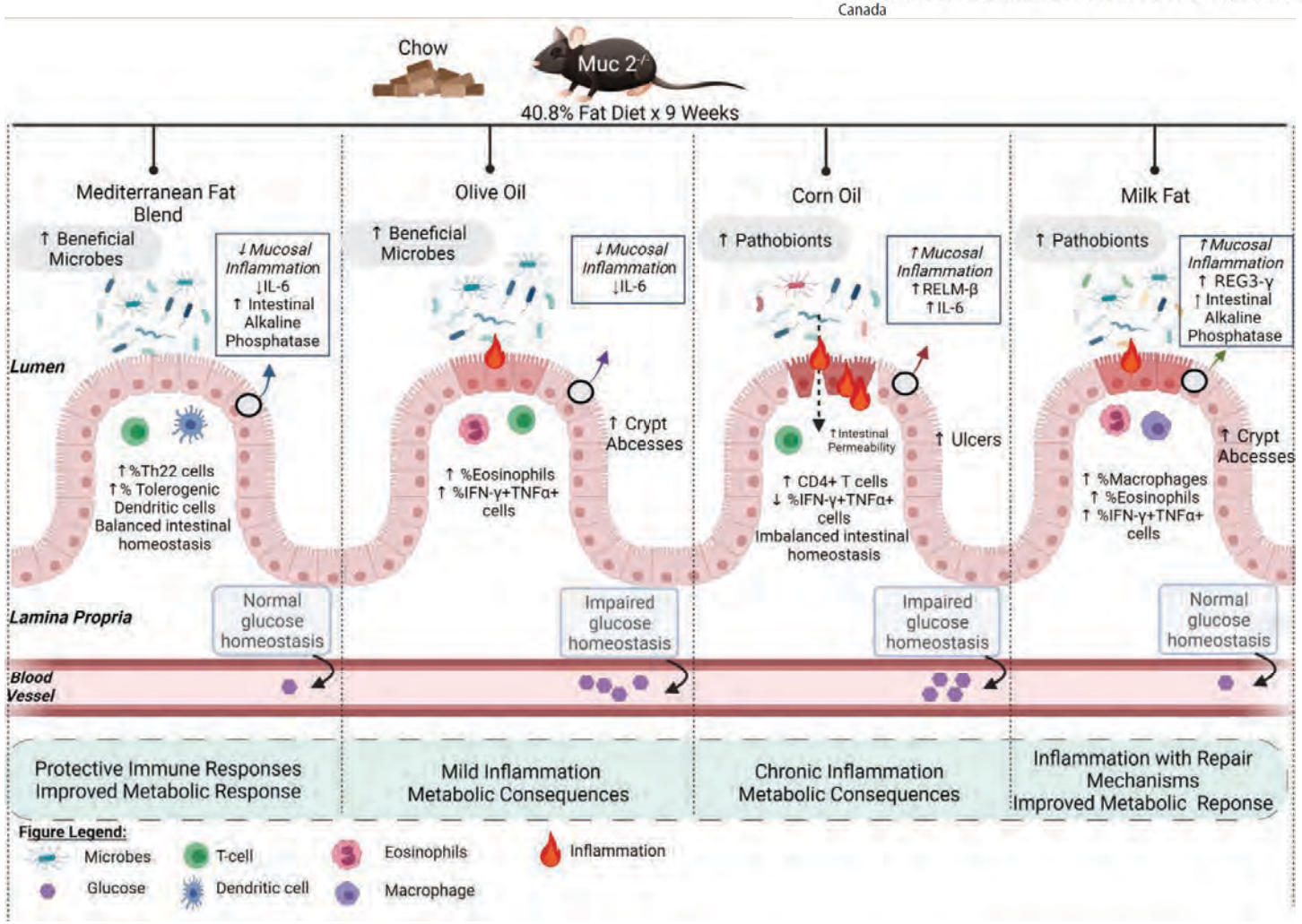
RESEARCH PAPER

OPEN ACCESS Check for updates

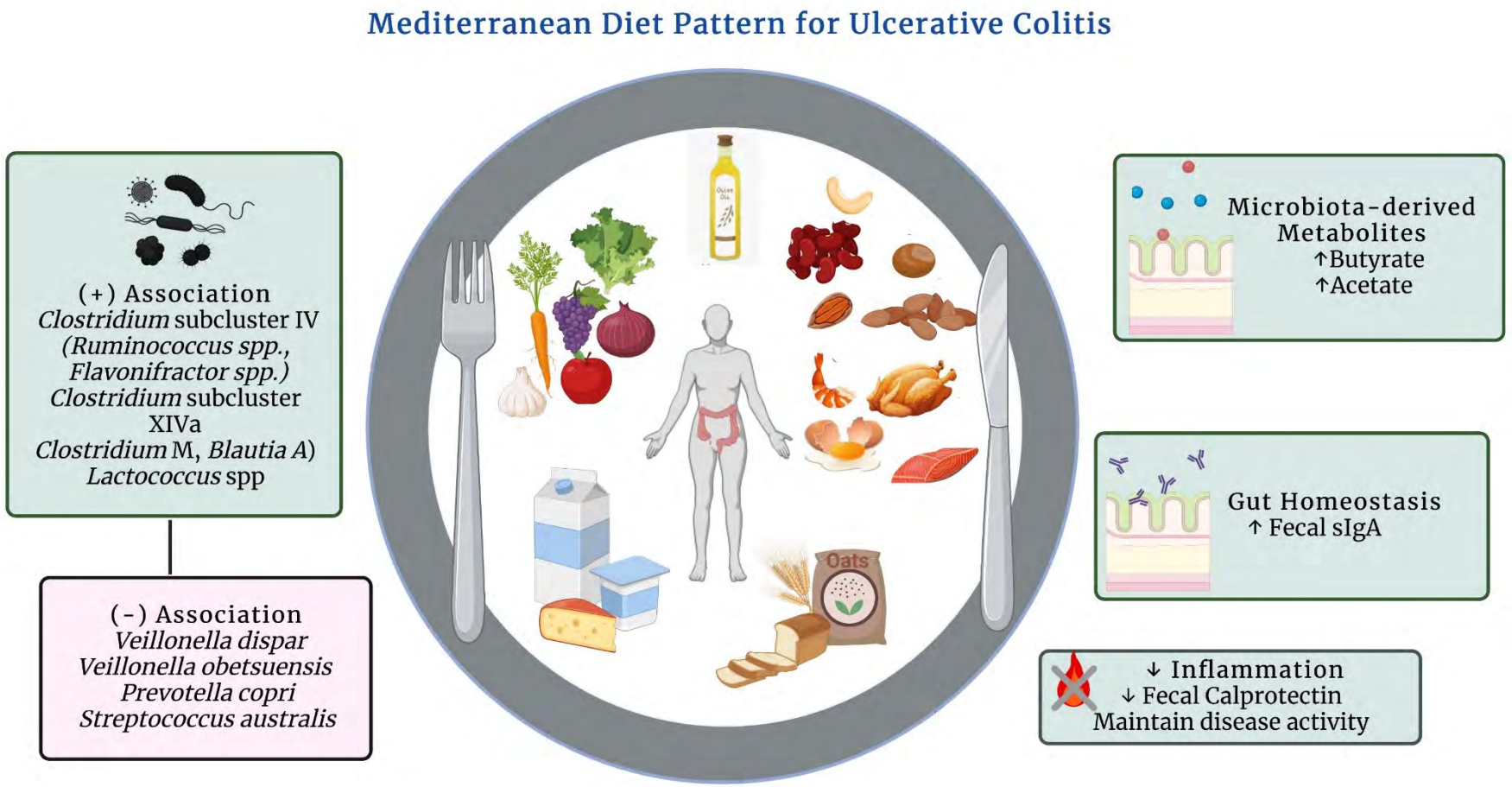
A Mediterranean-like fat blend protects against the development of severe colitis in the mucin-2 deficient murine model

Natasha Haskey[a], Jiayu Ye[a], Mehrbod Estaki[b], Andrea A. Verdugo Meza[a], Jacqueline A. Barnett[a], Mitra Yousefi[c], Blake W. Birnie[d], Samantha Gruenheid[e], Sanjoy Ghosh[a], and Deanna L. Gibson[a,d]

[a]Department of Biology, University of British Columbia - Okanagan Campus; Kelowna, British Columbia, Canada; [b]Department of Pediatrics, University of California, San Diego, La Jolla, California, USA; [c]The Center for Phenogenomics Infection & McGill University Research Centre on Complex Traits; McGill University, Montreal, Quebec, Canada; [d]Department of Medicine, University of British Columbia - Okanagan Campus, Kelowna, British Columbia, Canada; [e]Associate Professor - Department of Microbiology and Immunology, McGill University, Montreal, Quebec, Canada

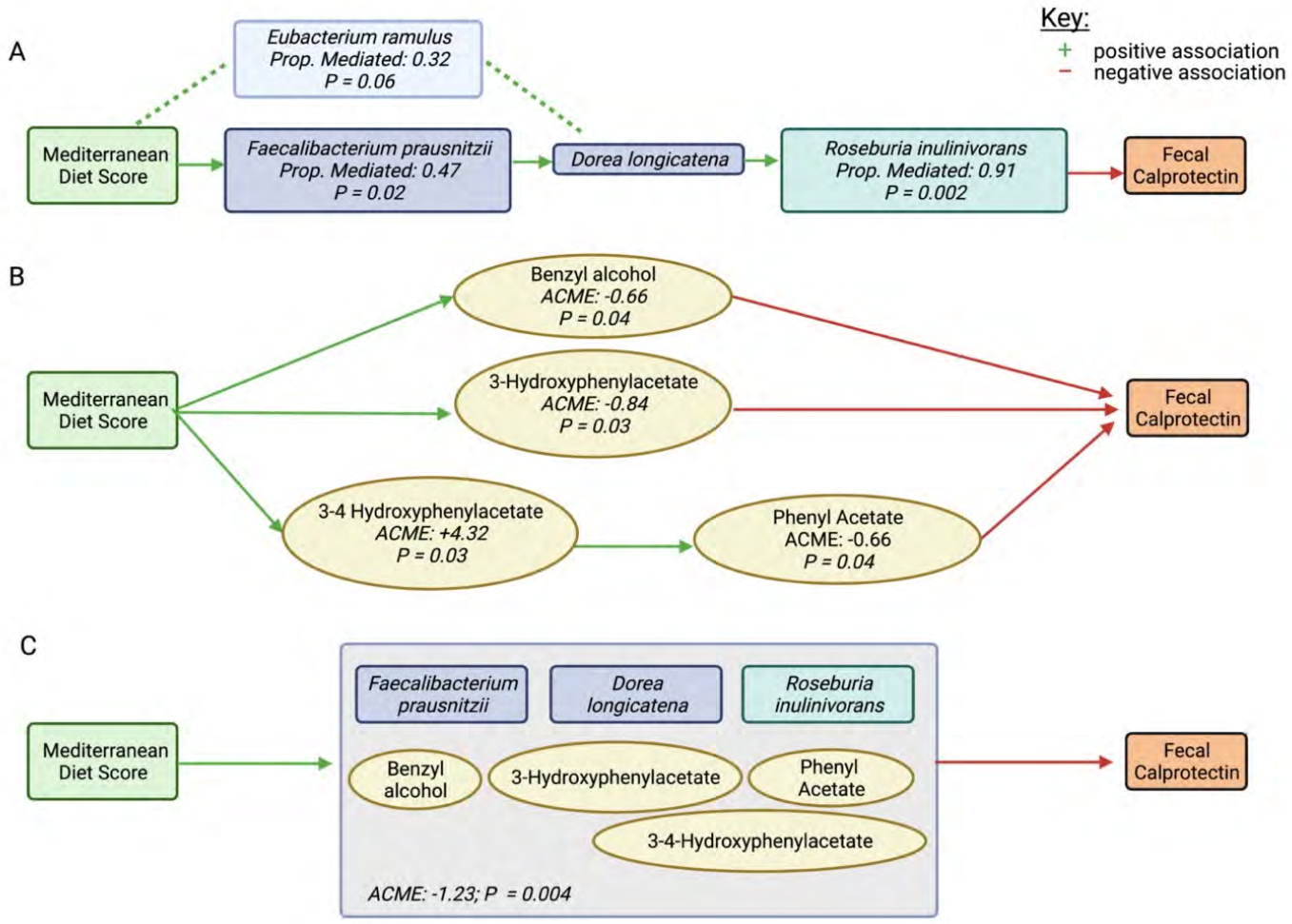


A Mediterranean diet pattern could be recommended as a remission diet to UC patients to help support disease management alongside front-line therapy drugs.



Haskey N, Estaki M, Ye J, Shim RK, Singh S, Dieleman LA, Jacobson K, Gibson DL. A Mediterranean Diet Pattern improves intestinal inflammation concomitant with reshaping of the bacteriome in ulcerative colitis: A randomized controlled trial. J Crohn's Colitis. 2023 Apr 24:jjad073. doi: 10.1093/ecco-jcc/jjad073. PMID: 37095601.

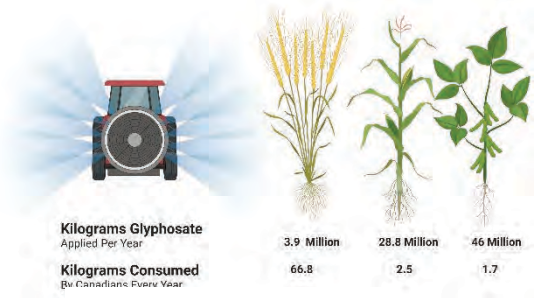
Functional guild and metabolite cluster mediating the relationship between mucosal inflammation and adherence to the Mediterranean Diet in UC



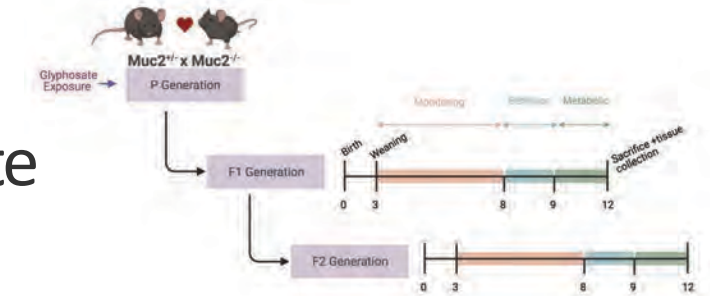
Strauss JC, *et al*. *Int J Mol Sci*. 2023 Apr 15;24(8):7323.

Another uniquely Western dietary element: food-associated glyphosate as a cause of colitis?

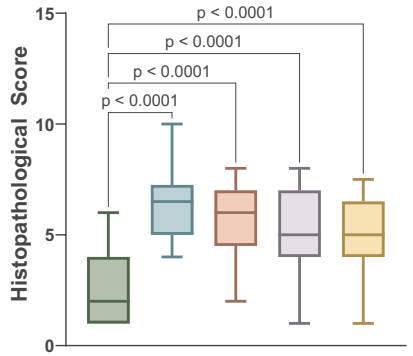
Background

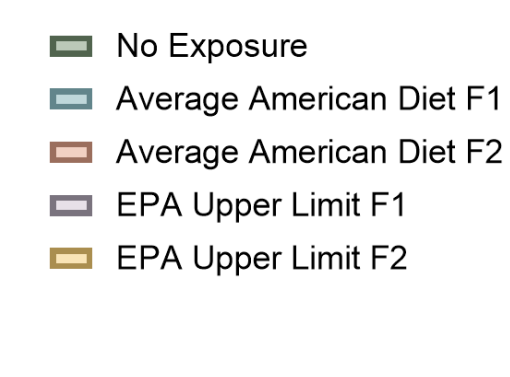


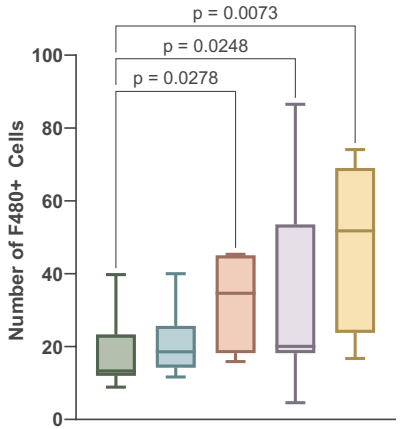
Experimental Design

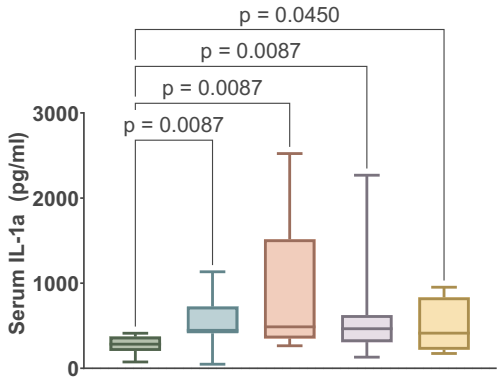


Colitis Resistant

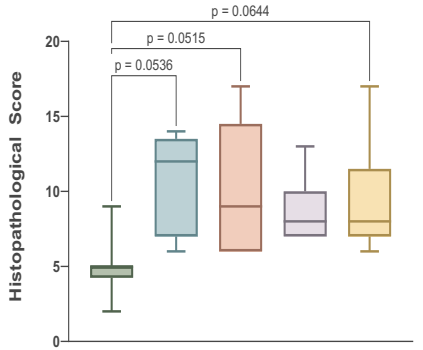


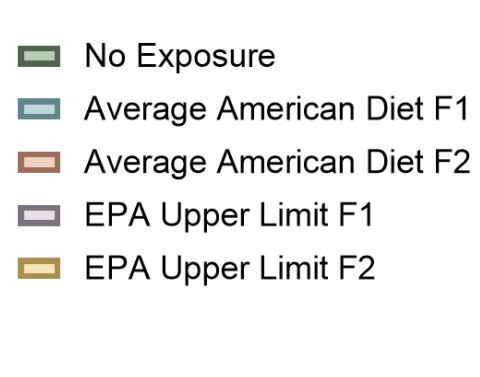


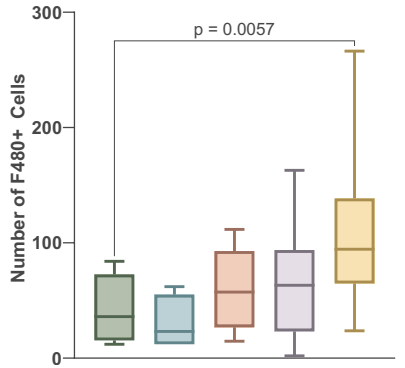


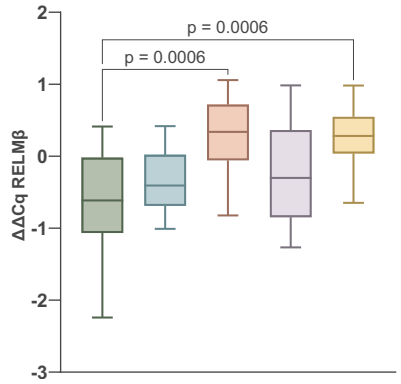


Colitis Susceptible









Outstanding Questions:

Are keystone species (real?) and important for IBD?

- Is IBD “infectious”?

Is there an IBD microbiome signature?

- Are there specific species that are causing IBD?
- Are there specific species that can protect against IBD?

Can a one-size-fits-all diet be implemented to improve the management of IBD?

How do diets affect a patient’s microbiome on a personalized basis?

Can we use live biotherapeutics (keystone?) or consortiums to induce rebiosis and treat IBD?

Workshop
Microbiome: Diet and Resident Bacteria

Dr. Deanna L. Gibson, Ph.D.
Professor, Biology, Faculty of Science
The University of British Columbia, Okanagan

Dr. Elena Verdu, MD, Ph.D.
Professor, Medicine, Farncombe Family Digestive Health Research Institute
McMaster