

Rising Star Award



Congratulations

Dr. Heather Armstrong
University of Manitoba

CCC Rising Star: Raising awareness of the complex balance of diet and microbiome in IBD

Dr. Heather Armstrong (MSc, PhD)

Tier 2 CRC and Assistant Professor,
Department of Internal Medicine,
University of Manitoba, Canada

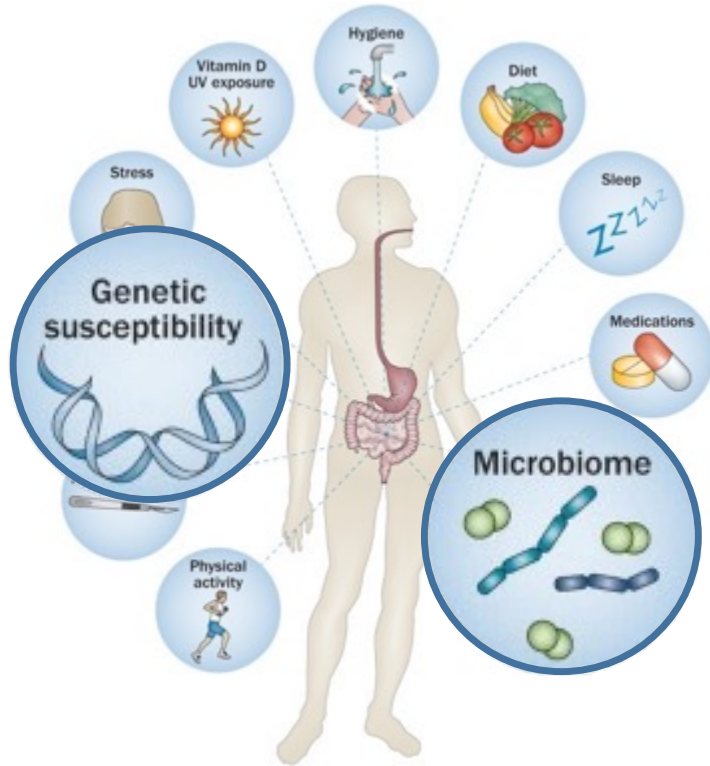


Conflicts to Disclose

Commercial or Non-Profit Interest	Relationship
ARC	Scientific Advisor
Dayhoff Technologies	Scientific Advisor
CIDCaNN	Committee Member

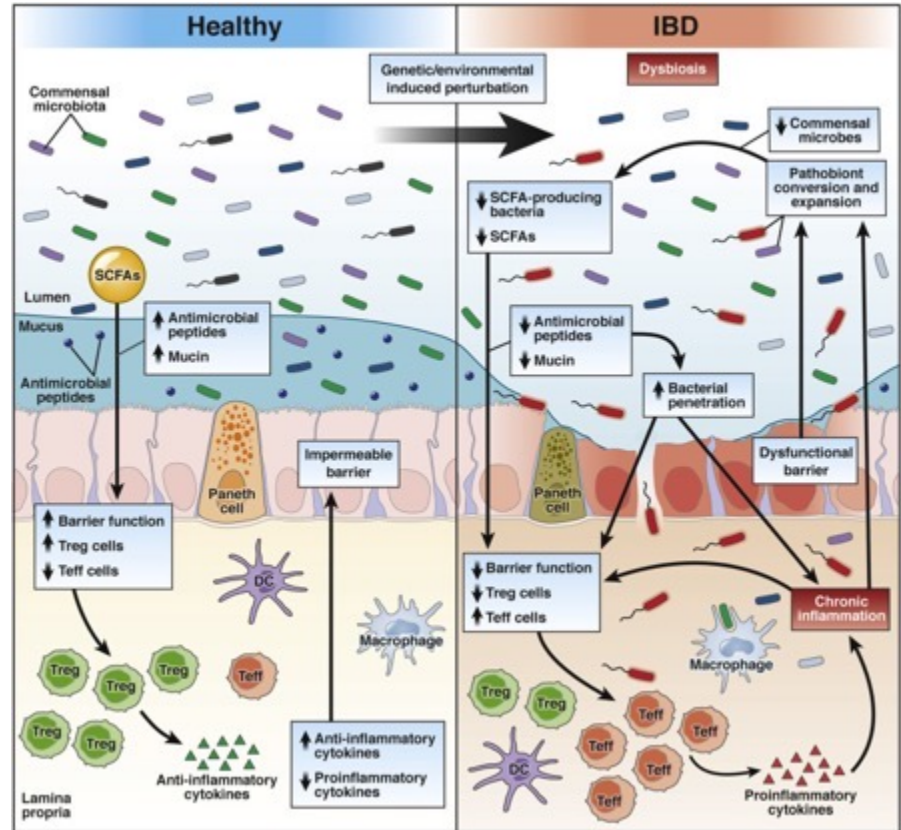
Factors that influence IBD: microbes (dysbiosis)

Complex, multifactorial



Nature Reviews | Gastroenterology & Hepatology

Ananthakrishnan Nature Rev. Gastro Hep. 2015.



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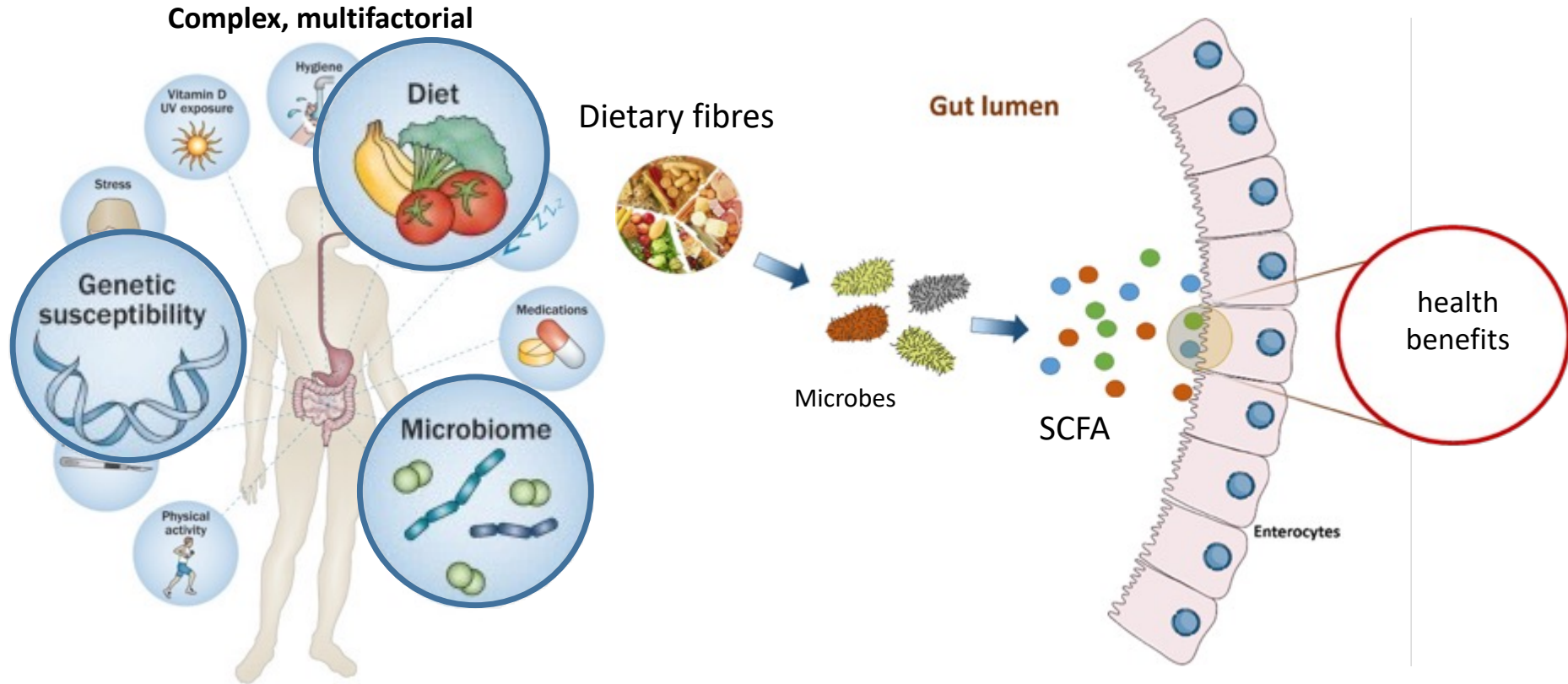
Lee Gastroenterology. 2021.

Does diet cause IBD?

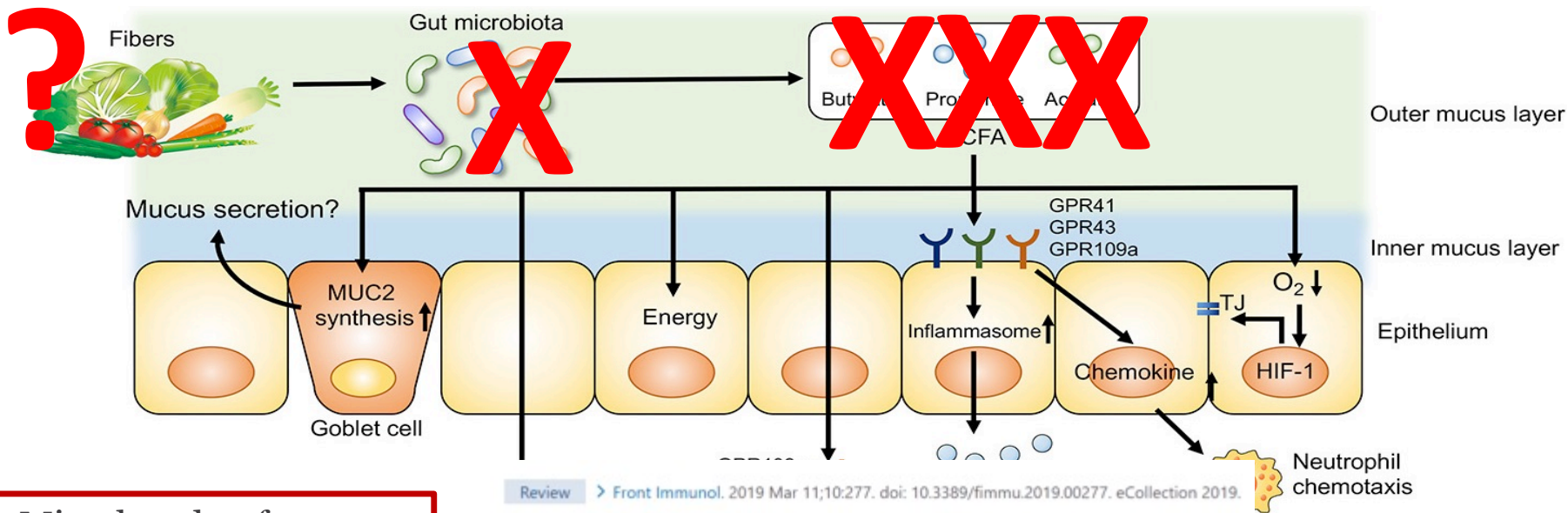
- **Epidemiologic evidence:**
 - Cohort and case control studies do show an association
- **Animal/*in vitro* studies:**
 - Multiple mechanistic links
- **Dietary therapies:**
 - EEN, CDED, and others can induce remission
- **BUT** IBD is heterogeneous!



Microbes link diet to host health



Fibers are not digested: they are fermented by microbes



Microbes that ferment fibers & produce SCFAs are typically reduced in mucosa and feces of patients with IBD

Review > Front Immunol. 2019 Mar 11;10:277. doi: 10.3389/fimmu.2019.00277. eCollection 2019.

Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases

Daniela Parada Venegas ^{1, 2}, Marjorie K De la Fuente ¹, Glauben Landskron ¹, María Julieta González ³, Rodrigo Quera ⁴, Gerard Dijkstra ², Hermie J M Harmsen ⁵, Klaas Nico Faber ^{2, 6}, Marcela A Hermoso ¹

Naïve T

Treg

Dietary Beliefs and Behavior Among Inflammatory Bowel Disease Patients

Camille Zallot, MD,* Didier Quilliot, MD, PhD,[†] Jean-Baptiste Chevaux, MD,* Carina Peyrin-Biroulet, MD,* Rosa Maria Guéant-Rodriguez, MD, PhD,* Estelle Freling, MD,* Benjamin Collet-Fenetrier, MD,* Nicolas Williet, MD,* Olivier Ziegler, MD, PhD,[†] Marc-André Bigard, MD,* Jean-Louis Guéant, MD, PhD,* and Laurent Peyrin-Biroulet, MD, PhD*

Inflamm Bowel Dis • Volume 19, Number 1, January 2013

TABLE 3. Food Exclusions (Question 3)

Food Groups	n (%)
Vegetables	39 (16.0%)
Fruits	27 (11.1%)
Cruciferous	27 (11.1%)
Tomato	25 (10.2%)
Green leafy vegetables	19 (7.8%)
Leguminous	14 (5.7%)
Spicy food	14 (5.7%)
Dairy products	10 (4.1%)
Fat products	10 (4.1%)
Citrus	8 (3.3%)
Oilseeds	7 (2.9%)
Sauce	7 (2.9%)
Alcohol	6 (2.5%)
Cereals	4 (1.6%)
Coffee	4 (1.6%)
Vinegar	2 (0.8%)
Bread	2 (0.8%)
Chocolate	1 (0.4%)
Sugar products	1 (0.4%)

- Survey in Nancy, France
- N=244 adult IBD
- 58%: diet plays a role in IBD
- 40% reported that diet leads to their flares
- 2/3 have given up on foods they enjoy

11) What food do you eat in case of relapse:

-Low residue diet	126 (51.6 %)
-Normal diet	62 (25.4 %)
-Dairy-free	34 (13.9 %)
-Other diet	28 (11.5 %)
-Gluten-free	4 (1.6%)
-NR	24 (9.8%)

Dietary Practices and Beliefs in Patients with Inflammatory Bowel Disease

Jimmy K. Limdi, MBBS,^{*,†} Divya Aggarwal, MBBS,^{*} and John T. McLaughlin, MBChB, PhD[†]

Inflamm Bowel Dis • Volume 22, Number 1, January 2016

- Survey in Manchester, UK
- N=400 adult IBD
- 57%: diet is a trigger in IBD
- 60%: symptoms are worse with certain foods
- ~50%: never received professional dietary advice

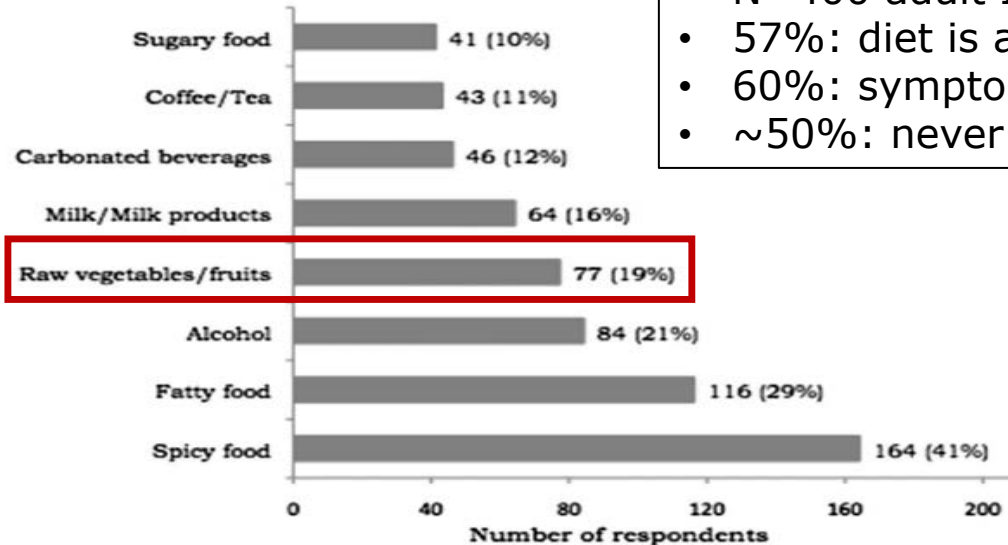


FIGURE 1. Foods that were reported to worsen IBD symptoms.

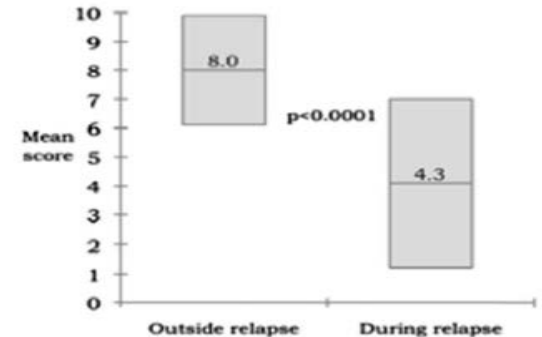
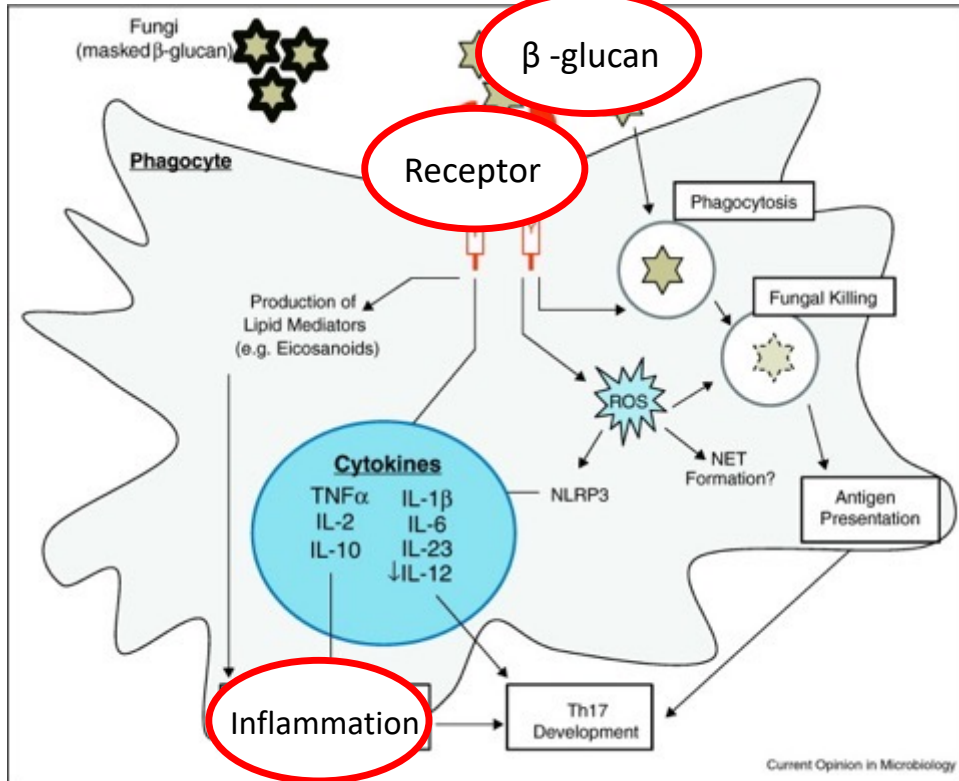
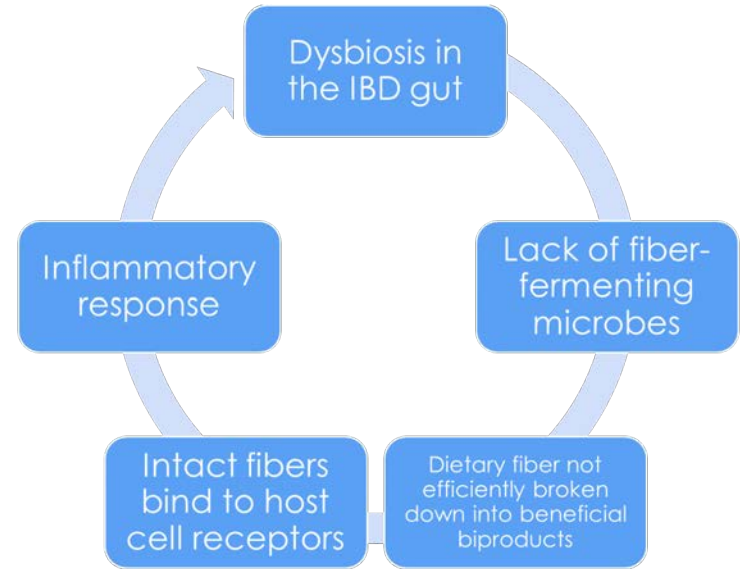


FIGURE 2. Mean scores of appetite outside and during disease relapse (Mean \pm SD).

Could unfermented fibres impact inflammation?

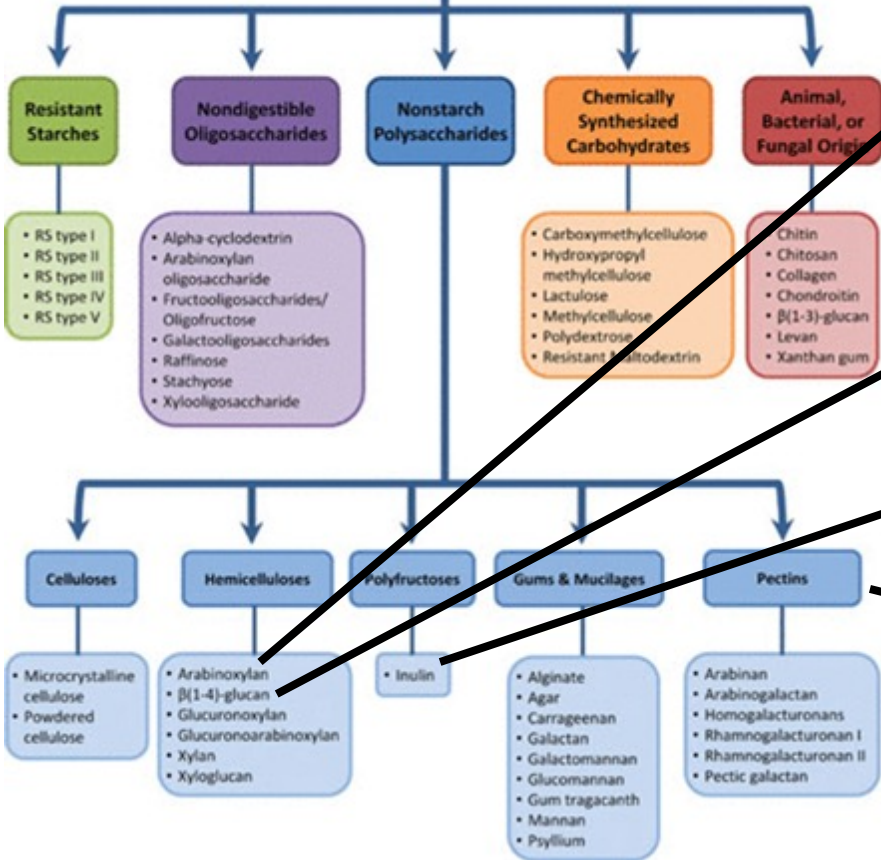


Drummond et al. 2011



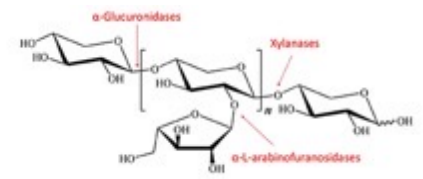
Armstrong et al. 2022; Gastroenterology

Nondigestible Carbohydrates



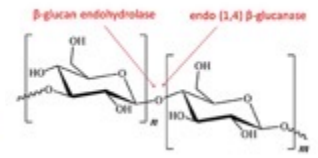
Arabinoxylan:

Cereal grains, rye, wheat, oats, barley, rice, sorghum, legumes.



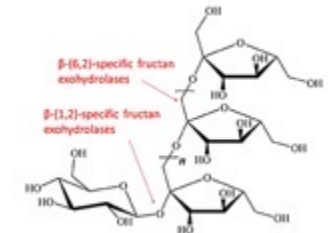
β-glucan:

Oat, barley, rice, mushrooms.



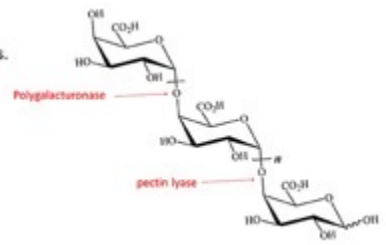
β-fructans:

Chicory root, agave, artichokes, banana, wheat, onion, garlic.

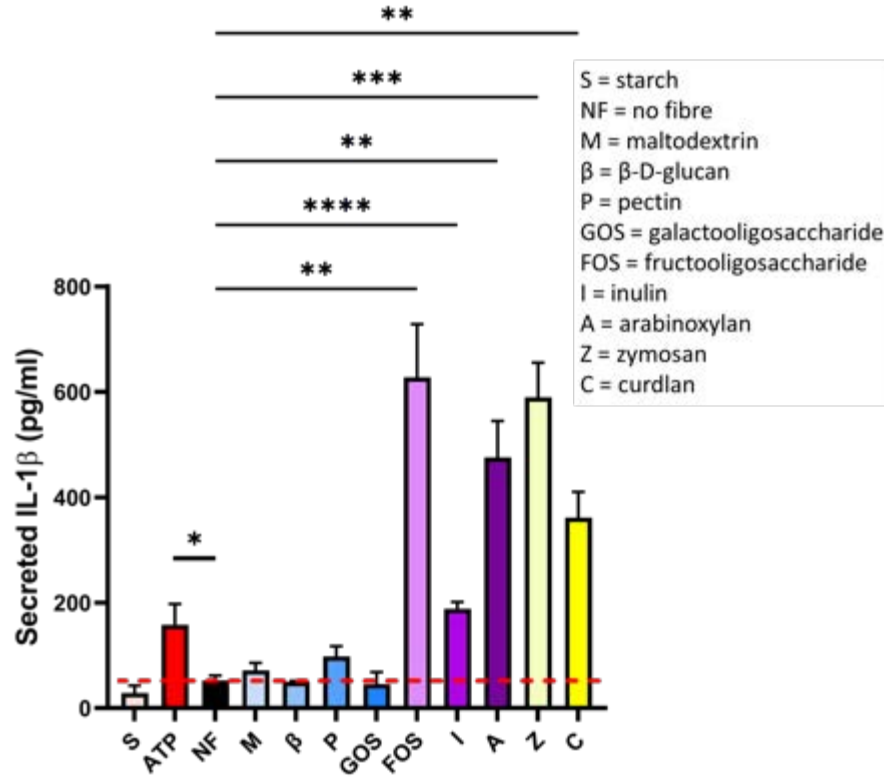


Pectin:

Fruits, vegetables, nuts.



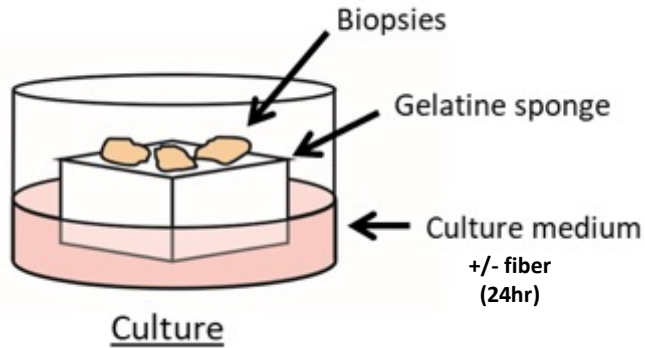
B-fructans and arabinoxylans promote inflammation



Specific unfermented fibers (B-fructans and arabinoxylans) can promote inflammation

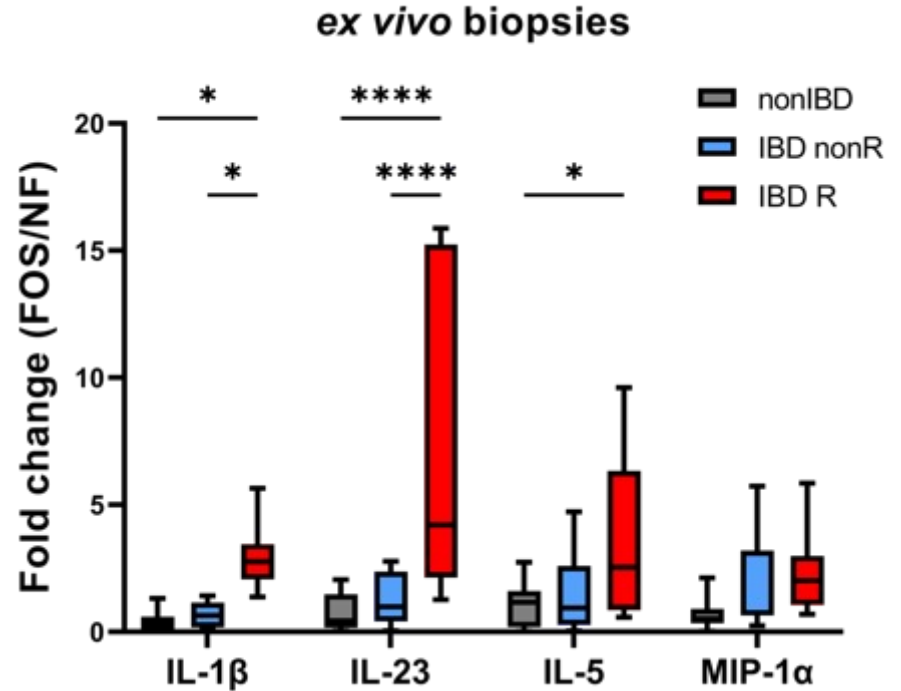
This was comparable to pro-inflammatory response to fungal carbohydrates (zymosan and curdlan)

B-fructan induces pro-inflammatory cytokines in specific IBD patients

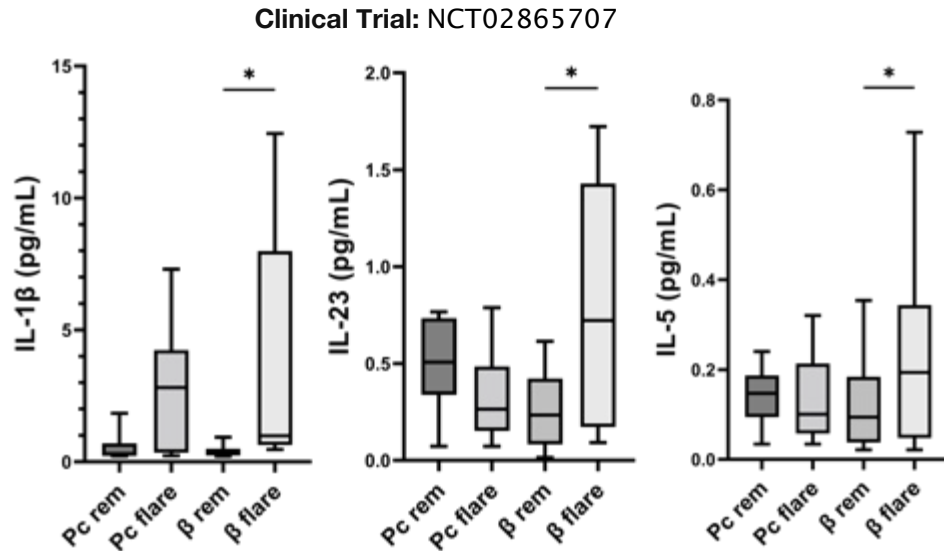


Unfermented B-fructan (chicory root; SYNERGY-1) can promote inflammation in pediatric IBD biopsies *ex vivo*

- Confirmed in clinical trial cohort



B-fructan induces pro-inflammatory cytokines in specific IBD patients

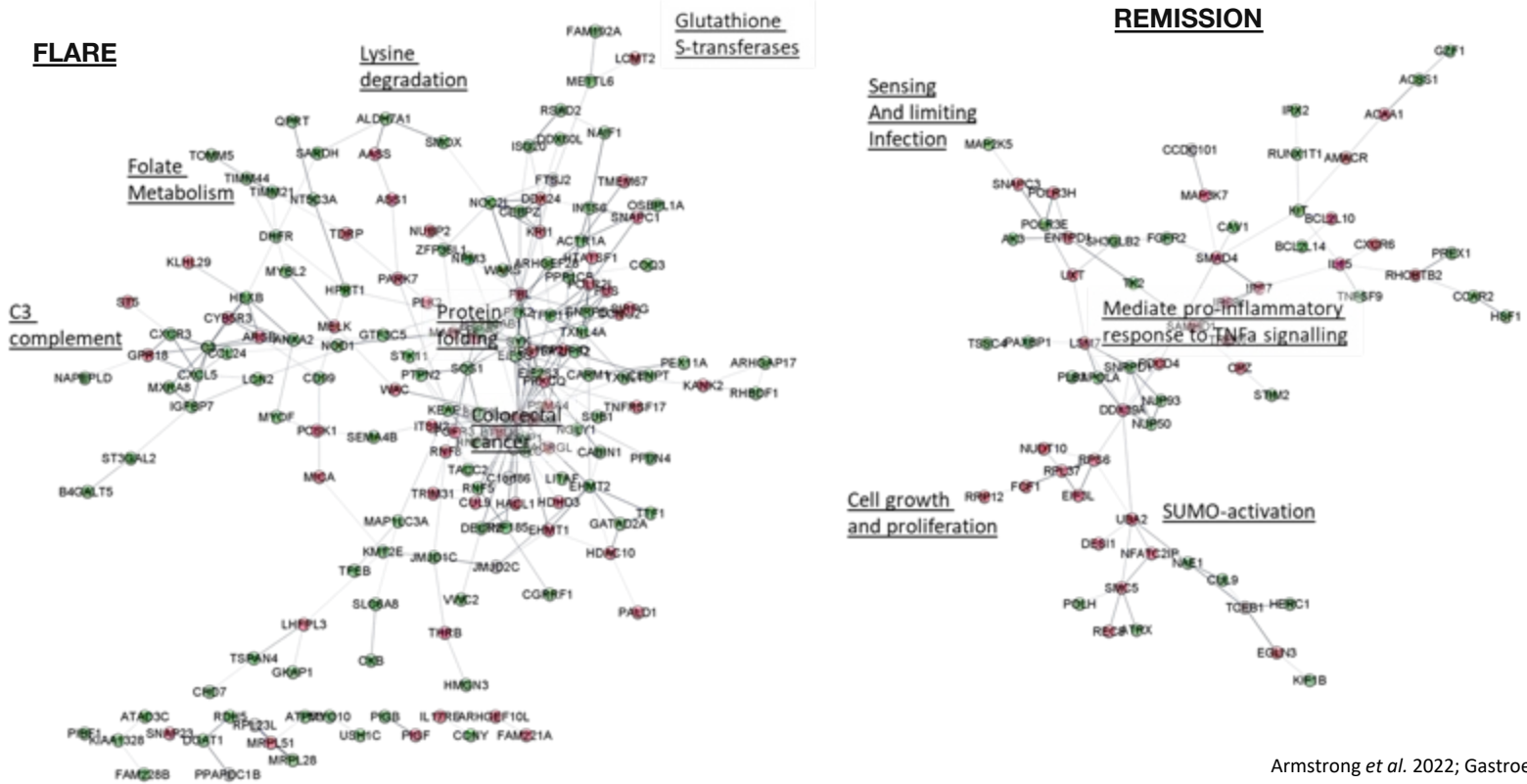


Unfermented B-fructan (chicory root; SYNERGY-1) can promote inflammation in adult IBD RCT – 15g SYNERGY 6 months

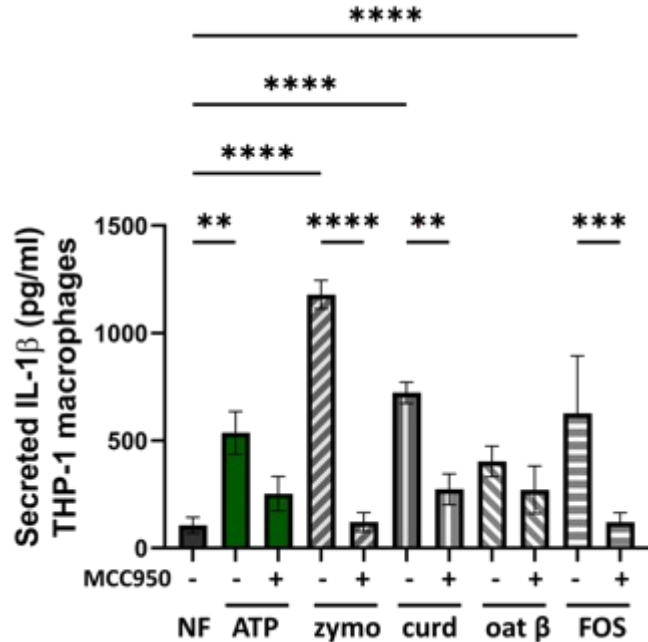
A subset of patients (~30%) flare

B-fructan induces various pathways in specific IBD patients

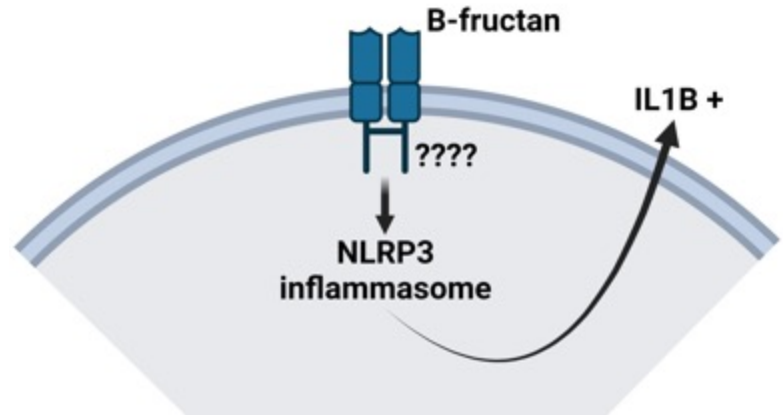
Clinical Trial: NCT02865707



B-fructan induces pro-inflammatory cytokines via NLRP3

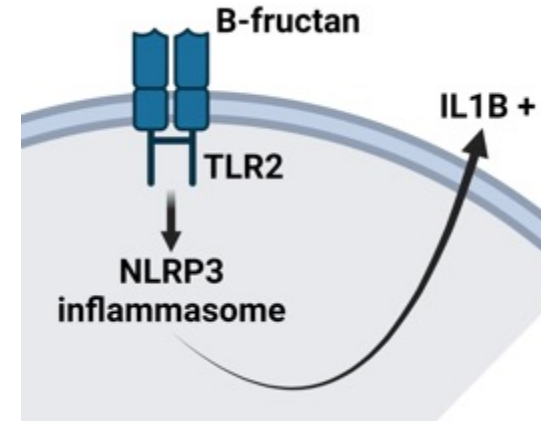
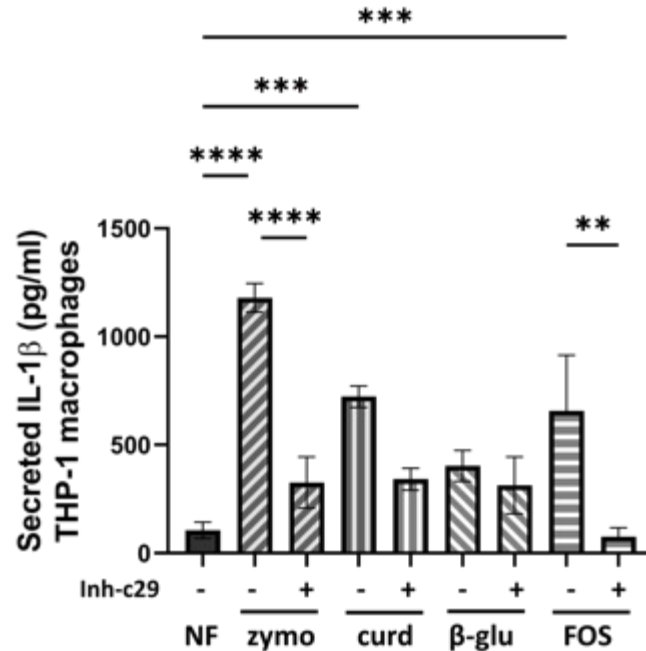
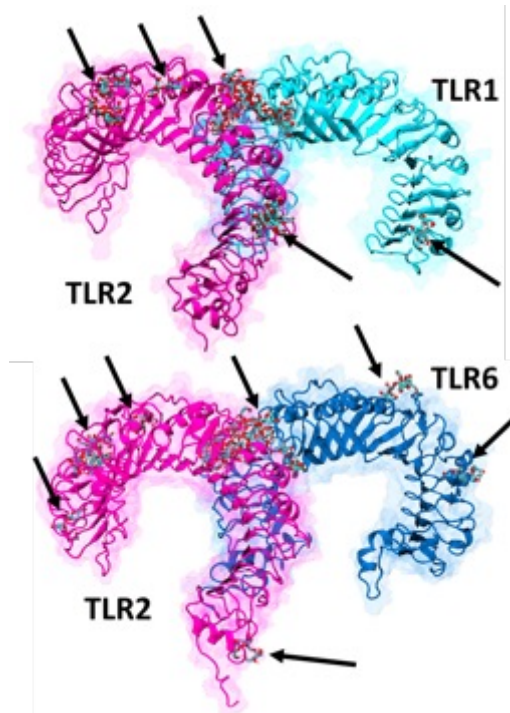


NLRP3 inflammasome inhibitors reduced IL-1B pro-inflammatory response to B-fructans (FOS)

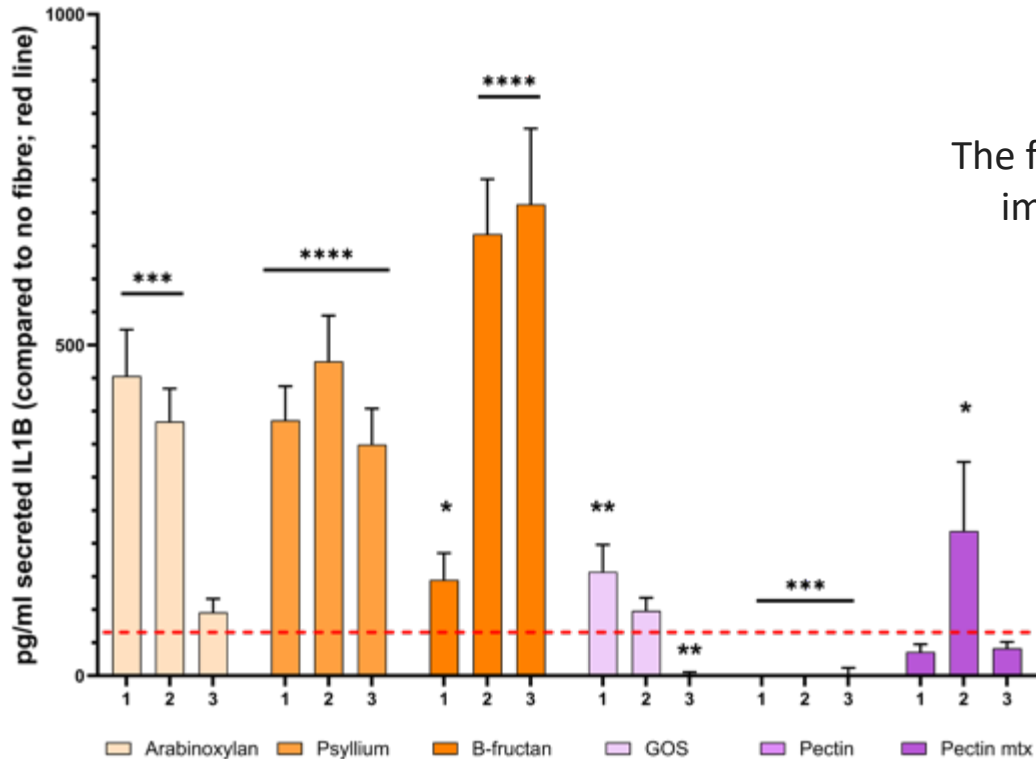


B-fructan interacts with immune cells via TLR2

Molecular dynamics identified TLR2 as the host receptor for B-fructan
TLR2 inhibitor (Inh-c29) validated the receptors role in cytokine response to B-fructan

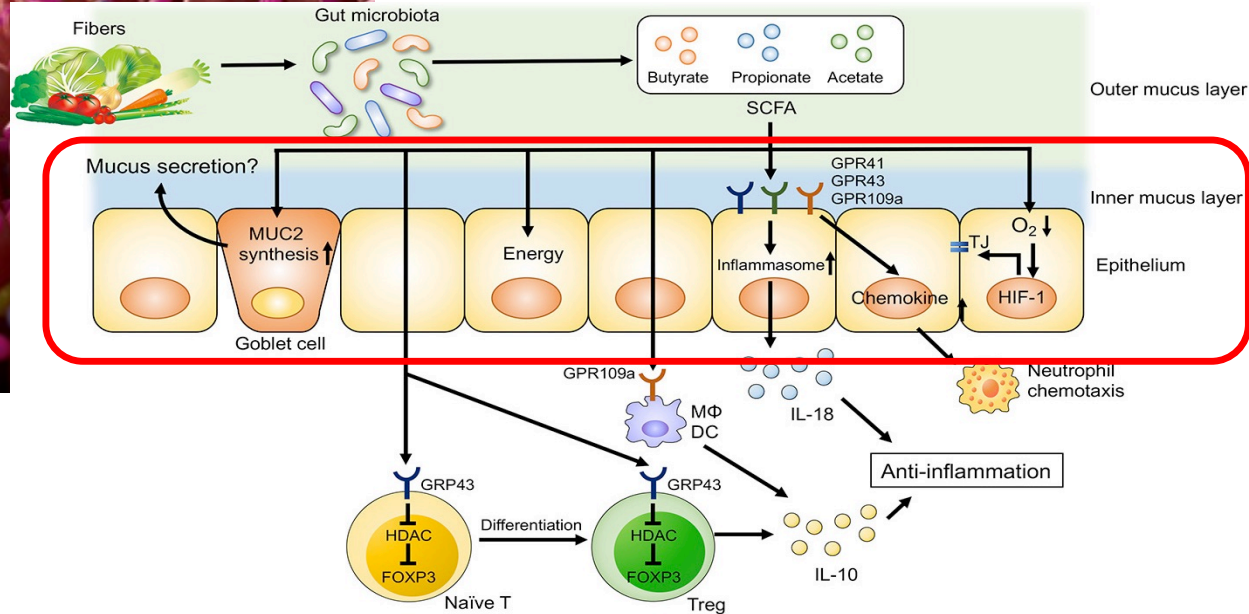
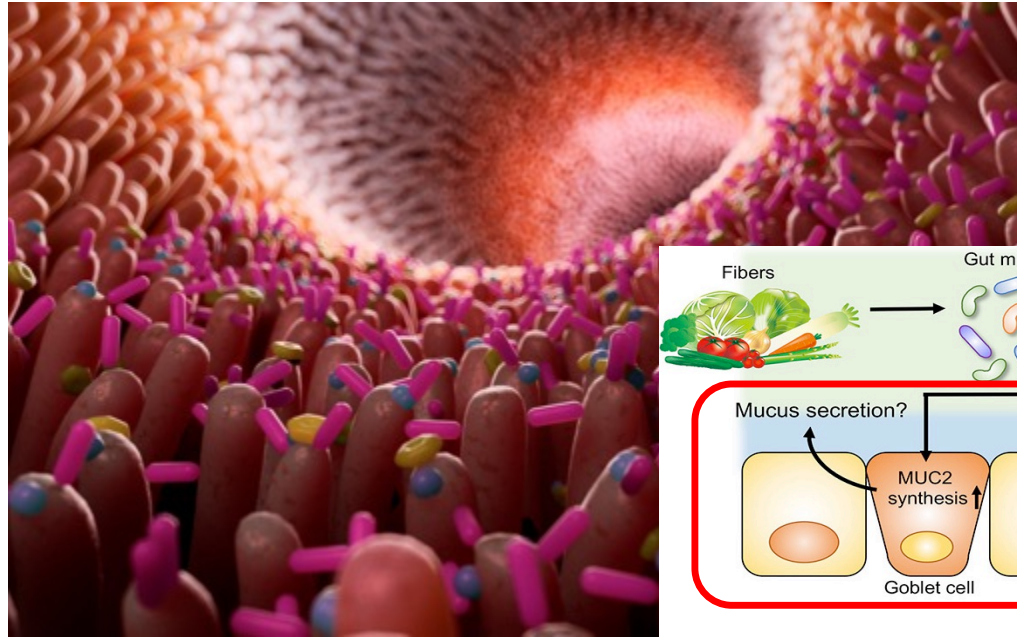


Profiling fibres from different food sources



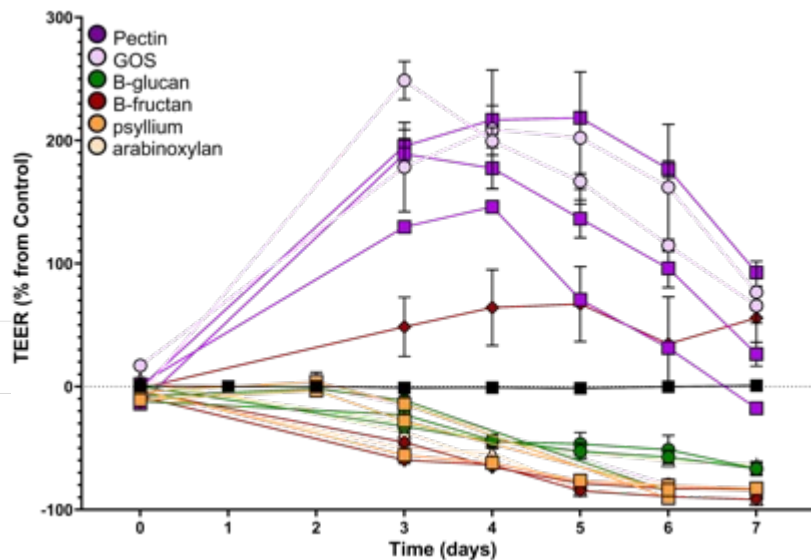
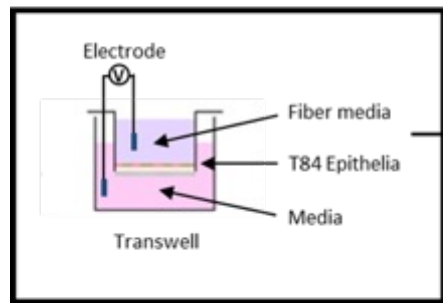
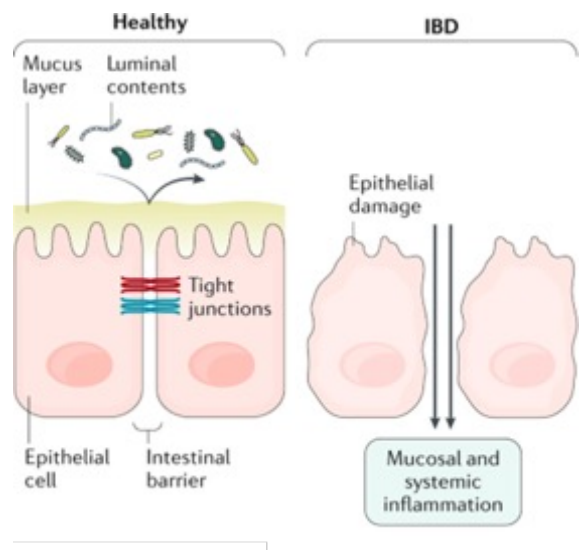
The food source and composition of the fibres impacts their interactions with host cells

The gut is protected by a mucosal epithelial layer

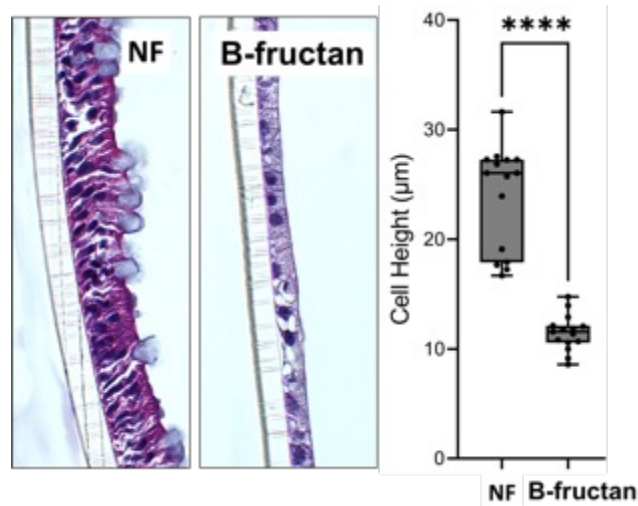
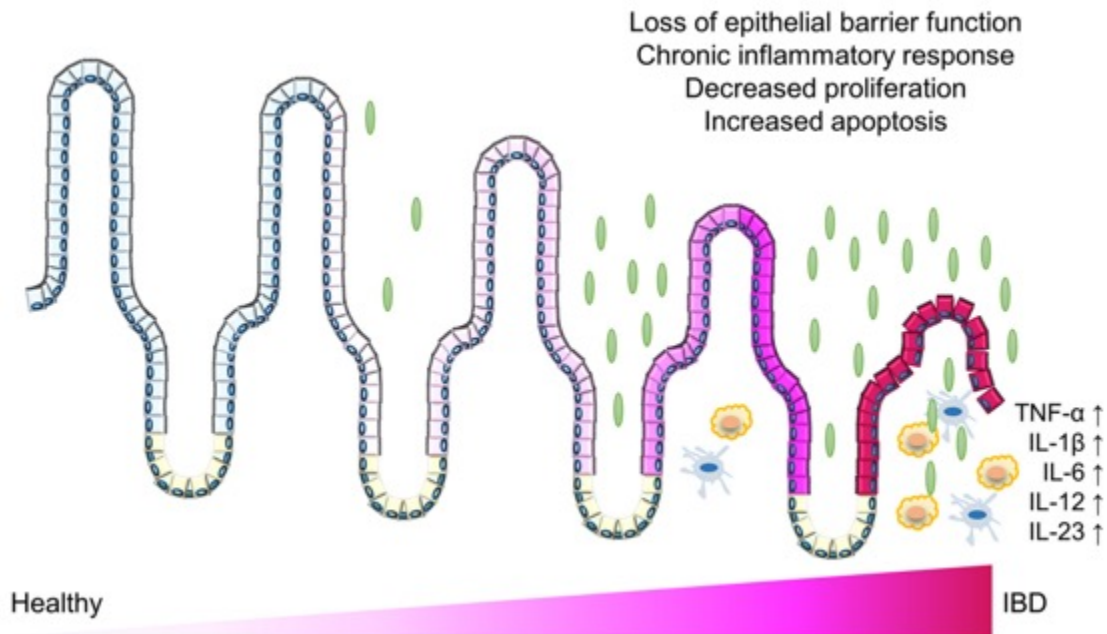


Epithelial barrier formation is differentially altered

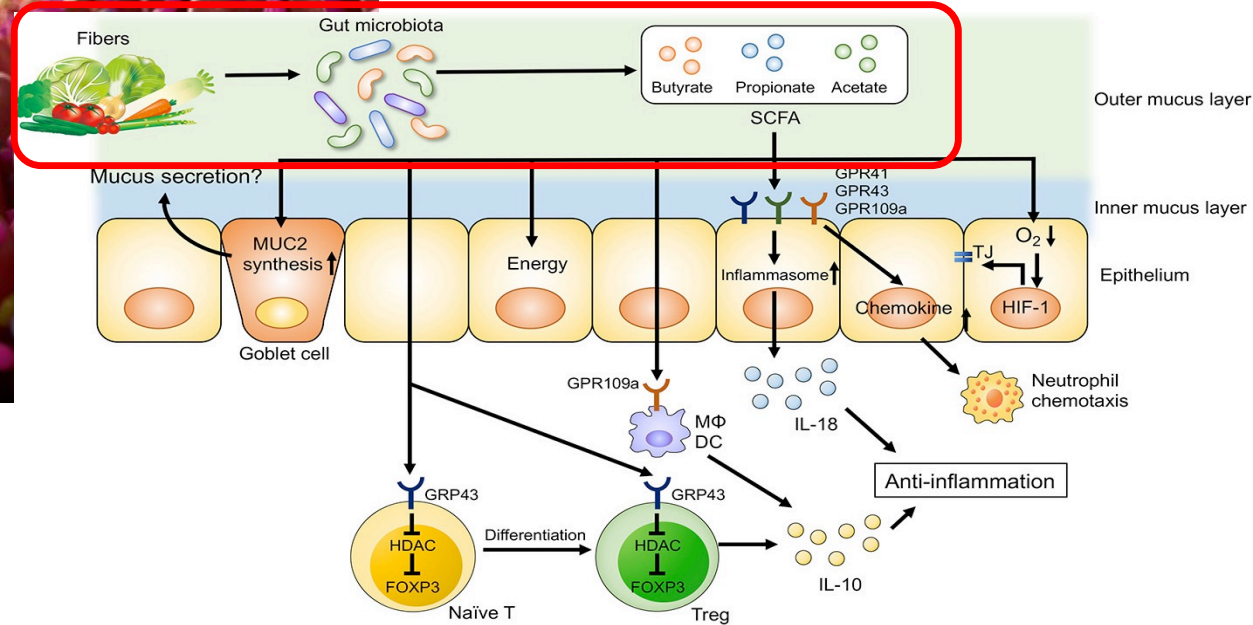
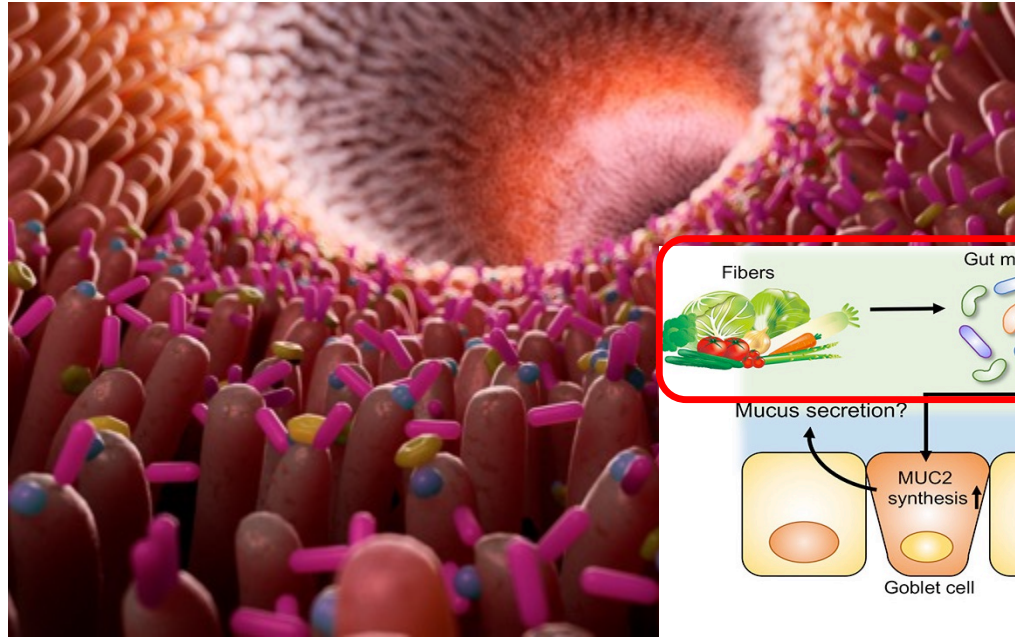
- Inulin and oligofructose improve epithelial barrier integrity
- B-D-glucan and arabinoxylan causes epithelial barrier disruption



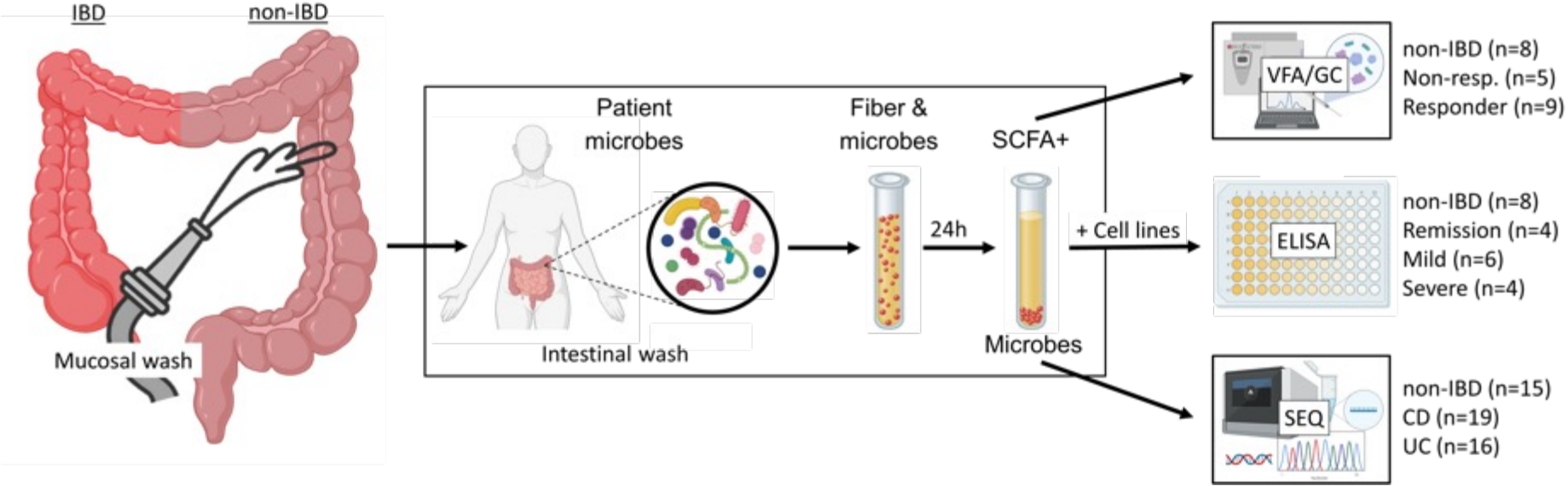
Epithelial barrier height is affected by B-fructan



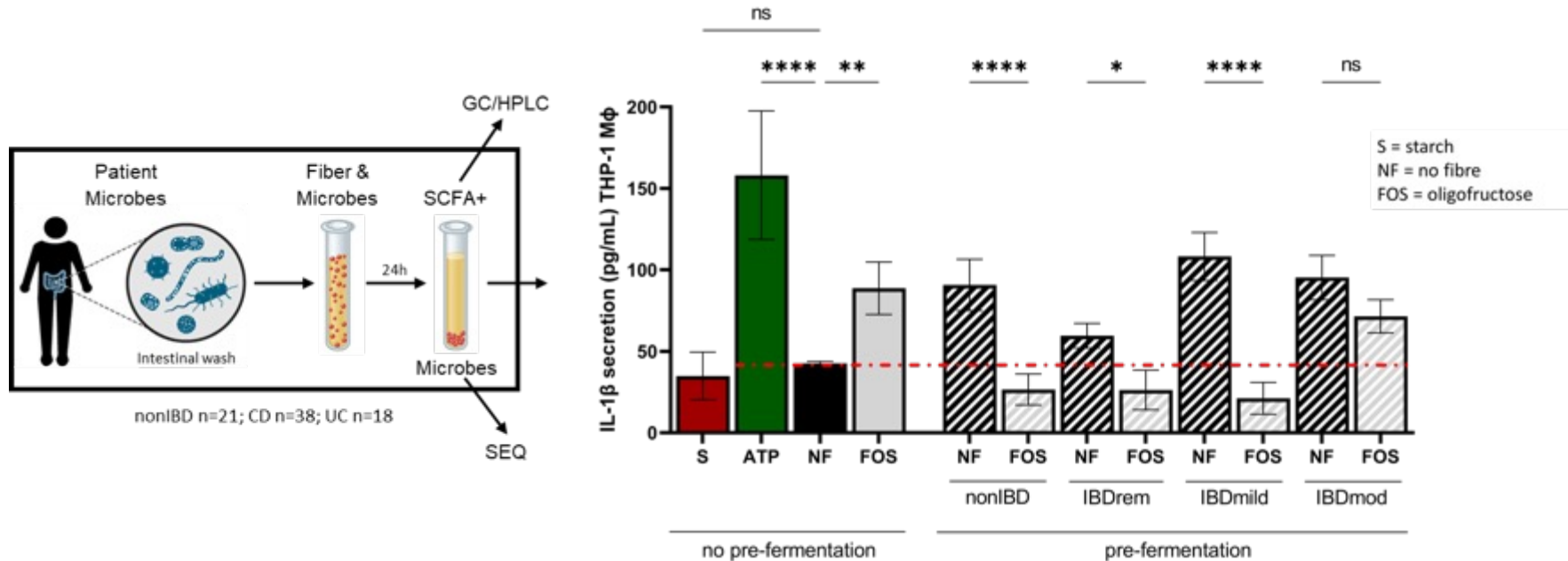
Gut microbiota community role in fermentation



Whole gut microbiota collected from gut washes

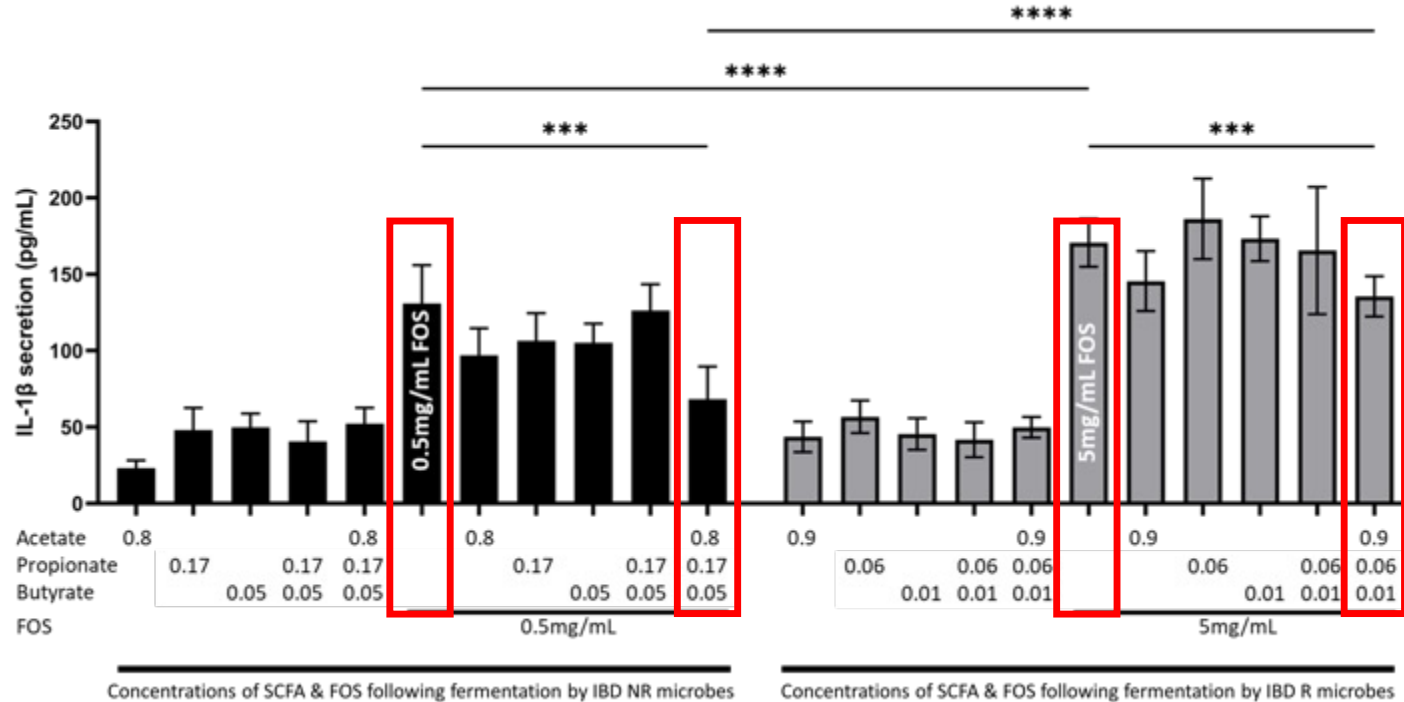


B-fructan fermentation by microbiota prevents inflammatory response



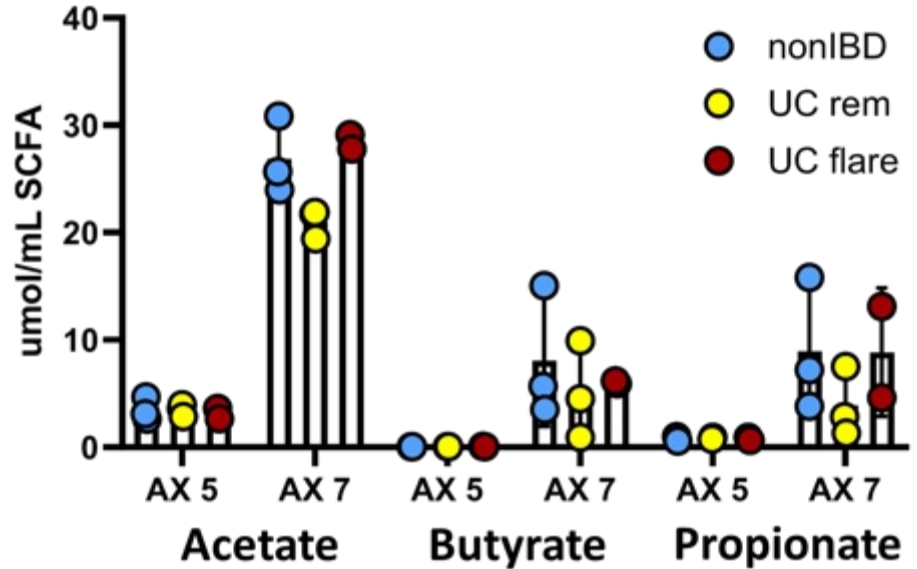
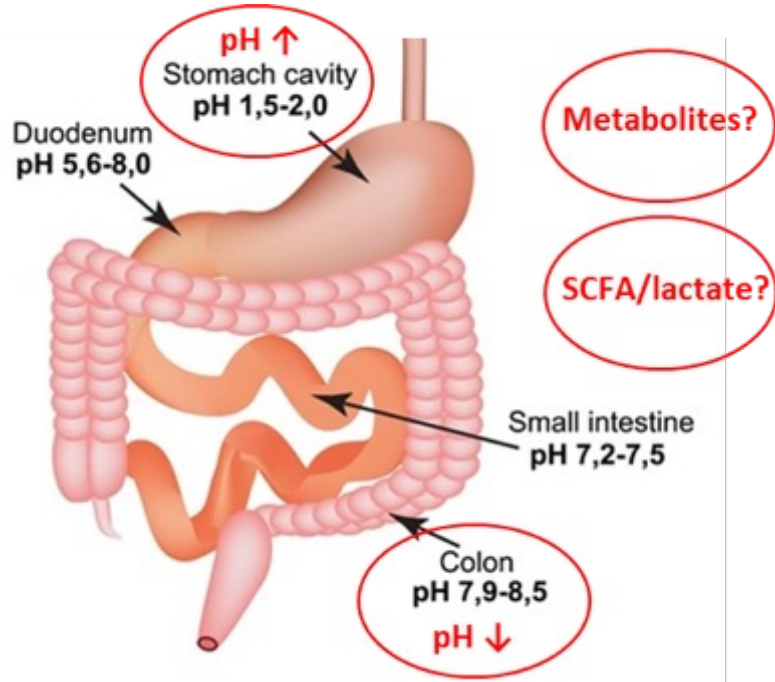
Fermentation of B-fructan (FOS) with whole gut microbes from IBD patients with active inflammation did not reduce pro-inflammatory response to fibre

Inflammatory response is a combination of \uparrow whole B-fructan and \downarrow SCFA



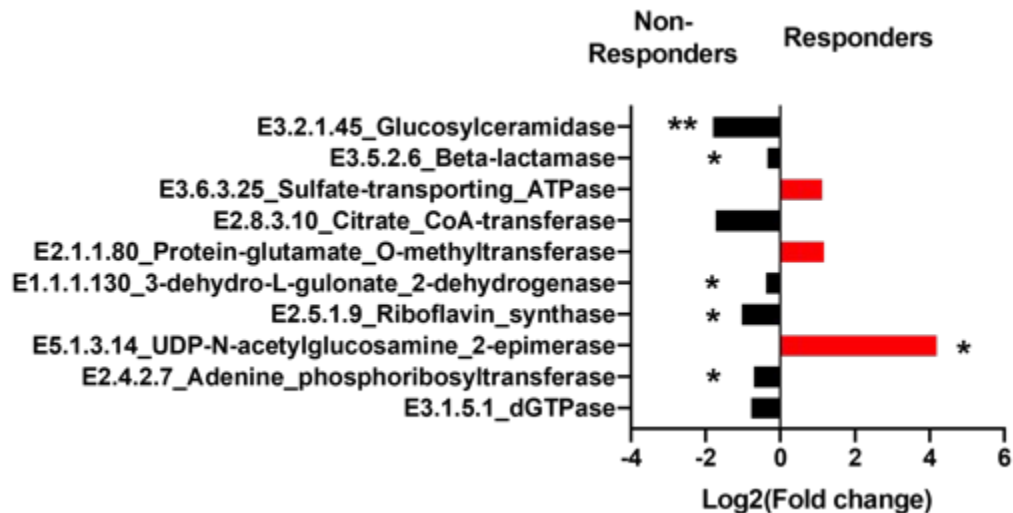
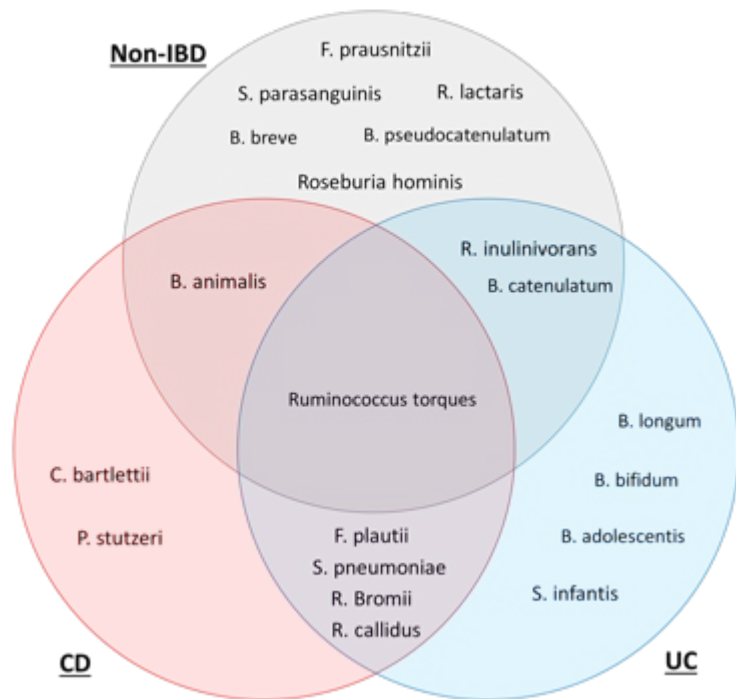
Changes in the gut microbiome alter our responses to environmental factors

Changes in pH in the IBD gut impacts microbe ability to ferment fibres – functions altered significantly vs composition



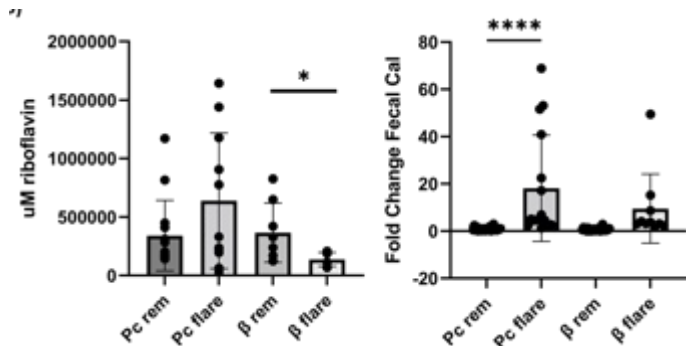
Select Microbes and Microbe Pathways are Involved in Response to B-fructans

Shotgun metagenomics – Intestinal washes



Microbial enzymes were validated in our RCT of B-fructans in adult IBD

Shotgun metagenomics – Intestinal washes



Clinical Trial: NCT02865707

RCT patient relapse = lower riboflavin
synthase produced by microbes

AND

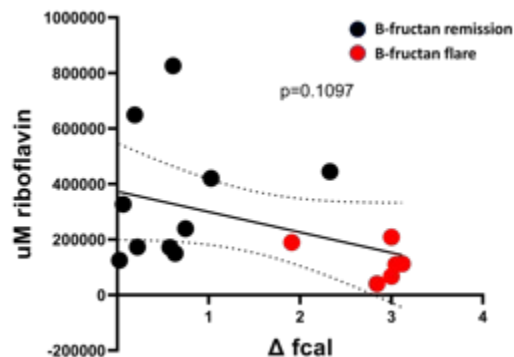
Lower riboflavin in stool at baseline

Biomarker of response to B-fructans?



Select fermentable fibers should be avoided
in **specific** IBD patients

TAKE HOME: these patients matter too!



How does dietary fibre intake change over time in IBD?

Examine the avoidance patterns of specific fiber subtypes in IBD patients and how this relates to disease progression



Living with IBD Cohort
155 IBD patients



FFQ:
(fiber consumption patterns)
Baseline- Week 52



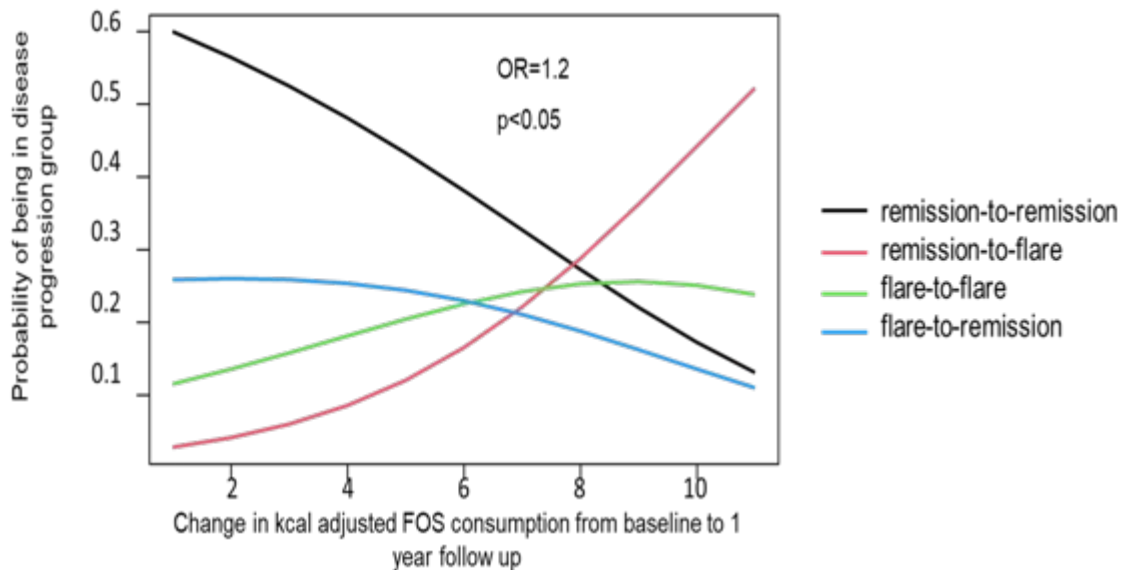
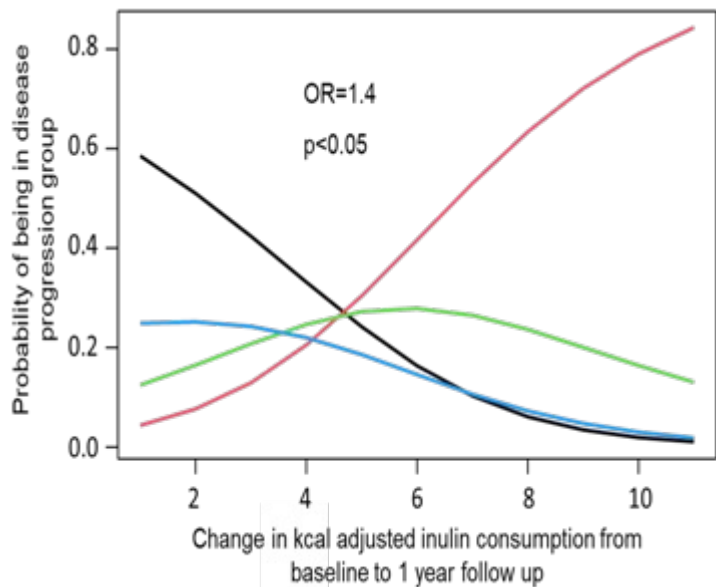
Fecal calprotectin:
(disease severity) Baseline-
Week 26-Week 52



Statistical analysis:
Correlation between the shift in
fiber consumption/ avoidance
and disease remission/flare

How does dietary fibre intake change over time in IBD?

Consumption of FOS and inulin is negatively correlated with disease flare in IBD patients



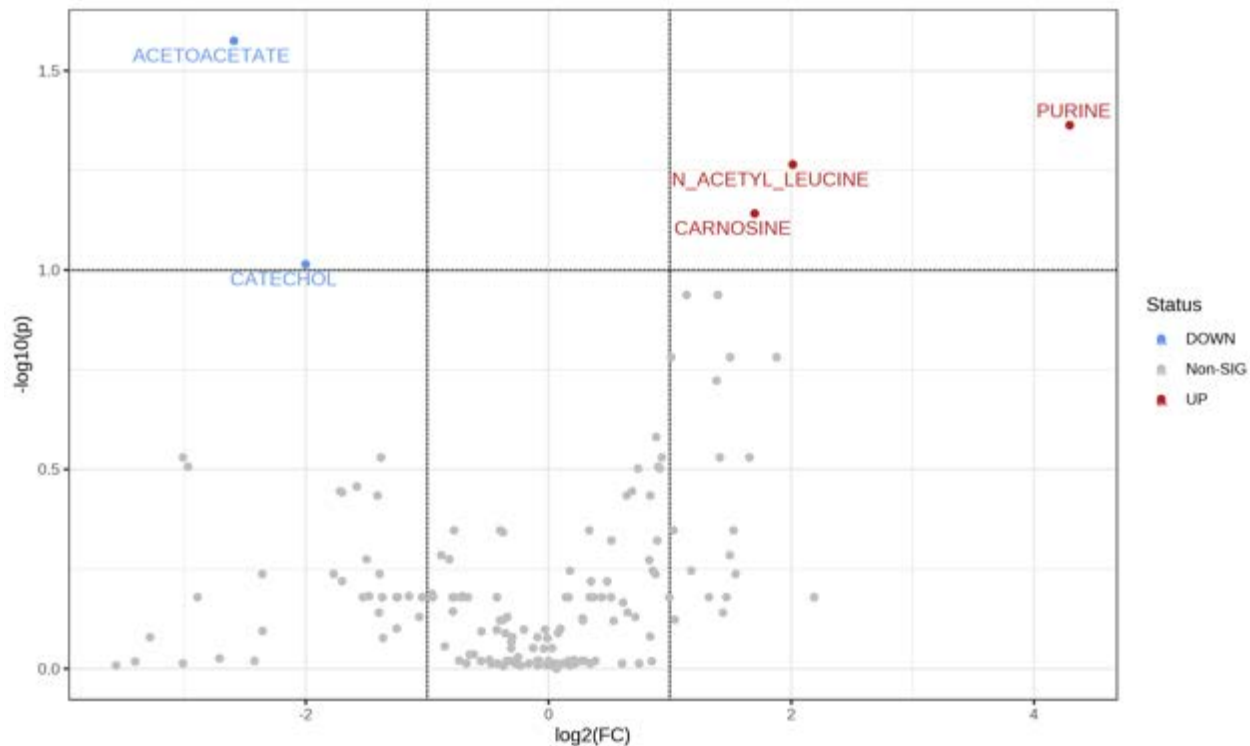
Completing analysis of microbiota and stool metabolomics

Changes in the gut microbiota appear to precede changes in B-fructan consumption followed by flare



Completing analysis of microbiota and stool metabolomics

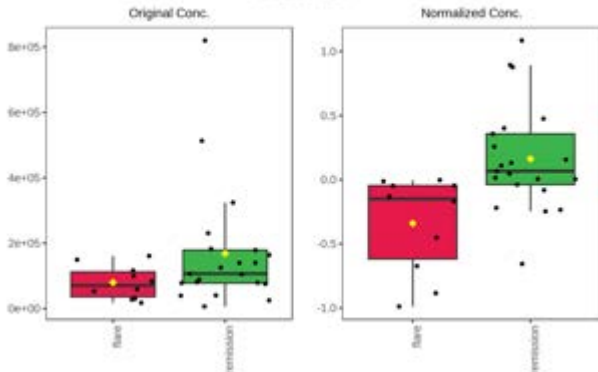
Changes in the gut microbiota appear to precede changes in B-fructan consumption followed by flare



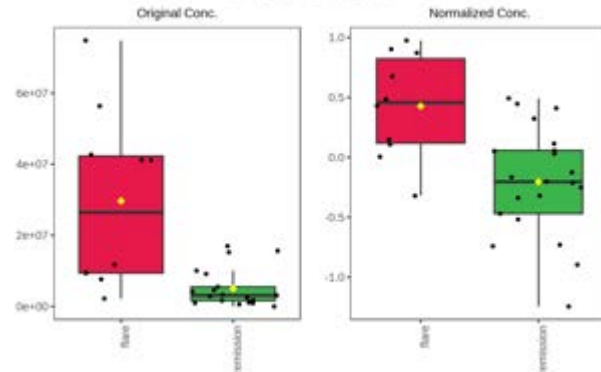
Completing analysis of microbiota and stool metabolomics

Changes in the gut microbiota appear to precede changes in B-fructan consumption followed by flare

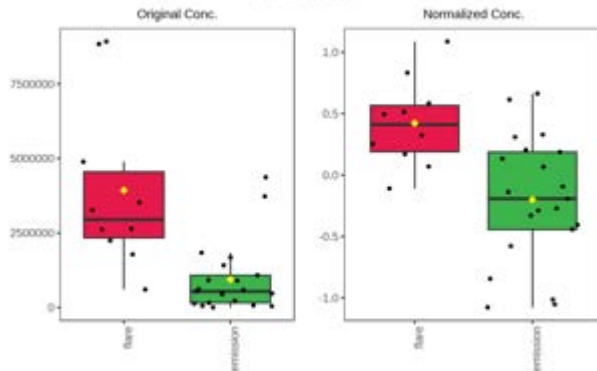
CATECHOL



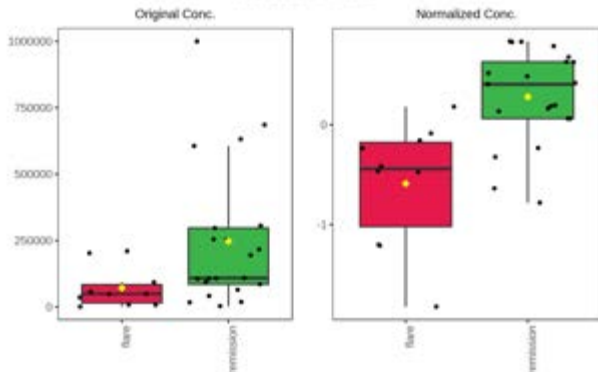
N_ACETYL_LEUCINE



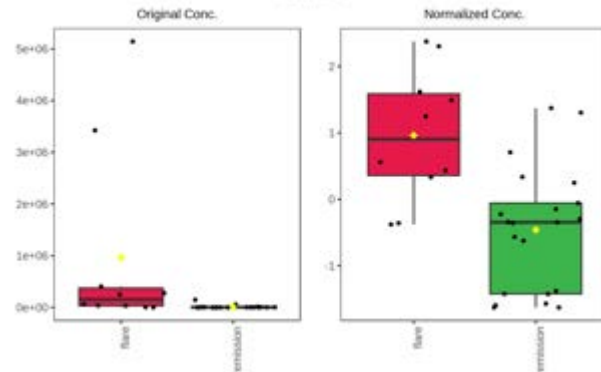
CARNOSINE



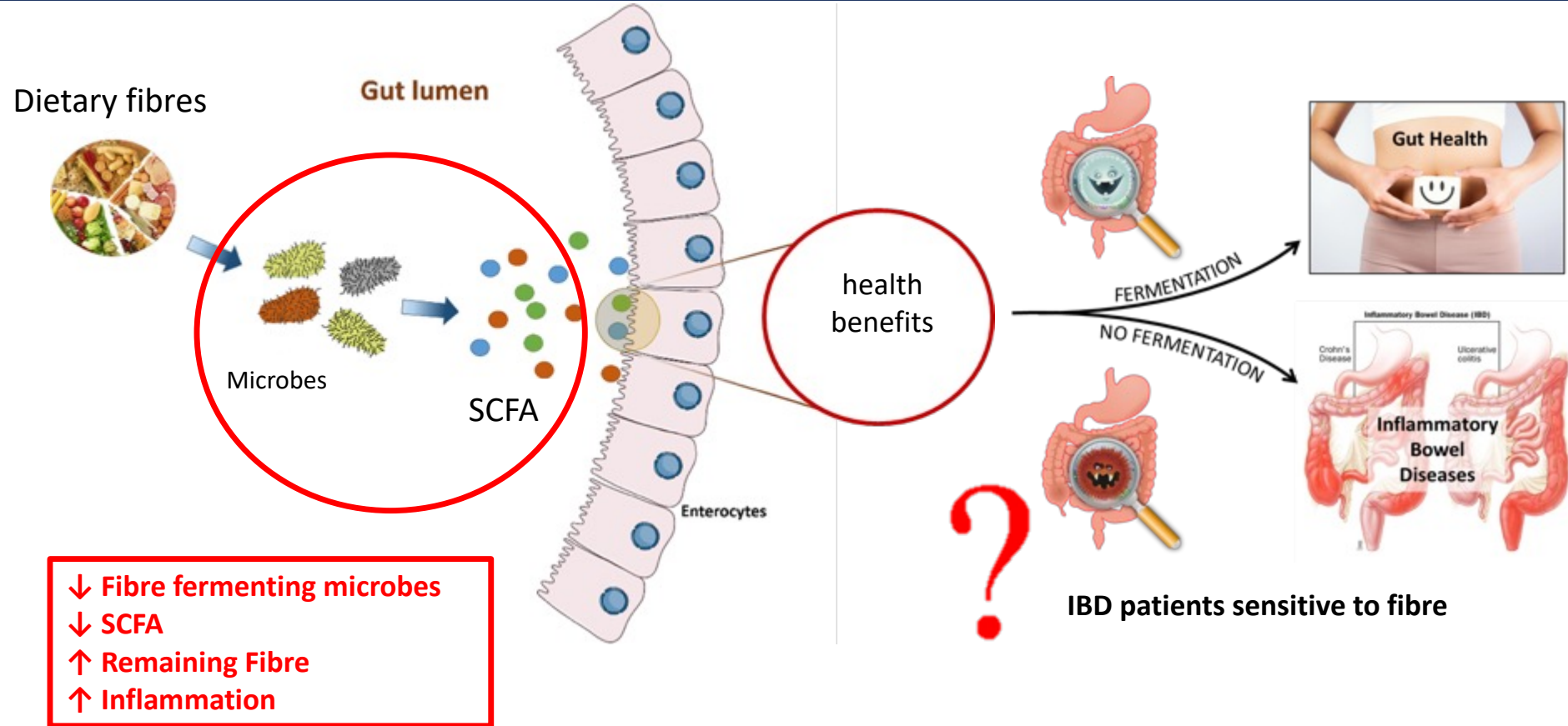
ACETOACETATE



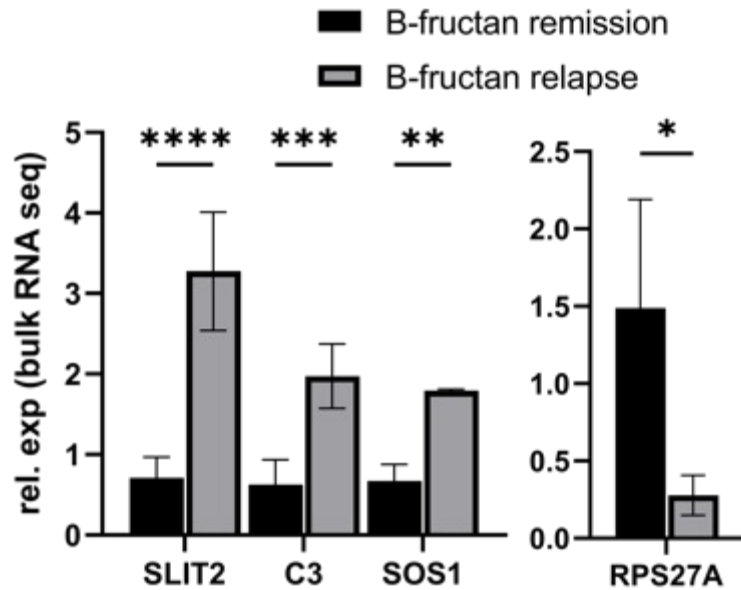
PURINE



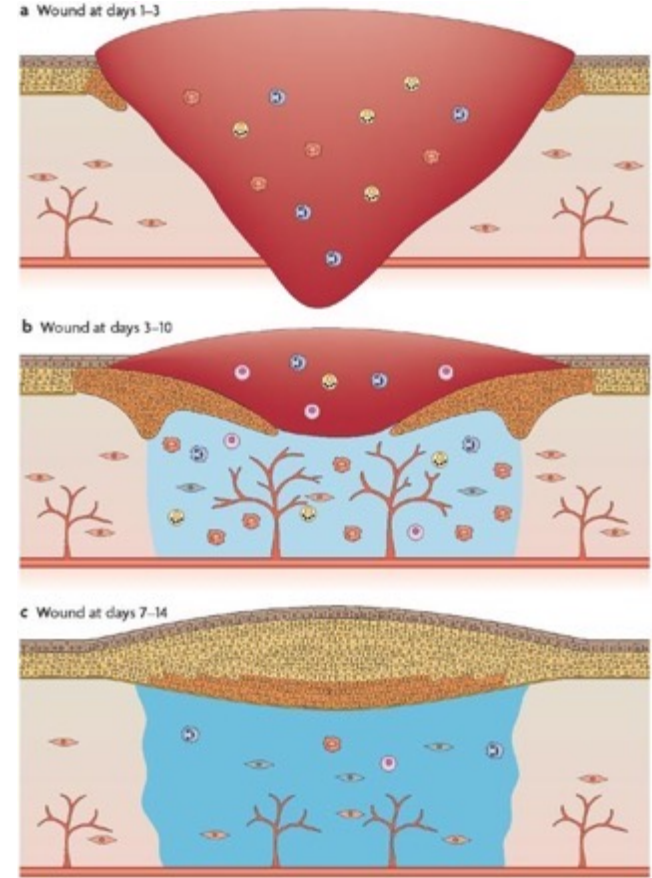
Fibre fermentation products (SCFA+FOS) dictates pro-inflammatory response



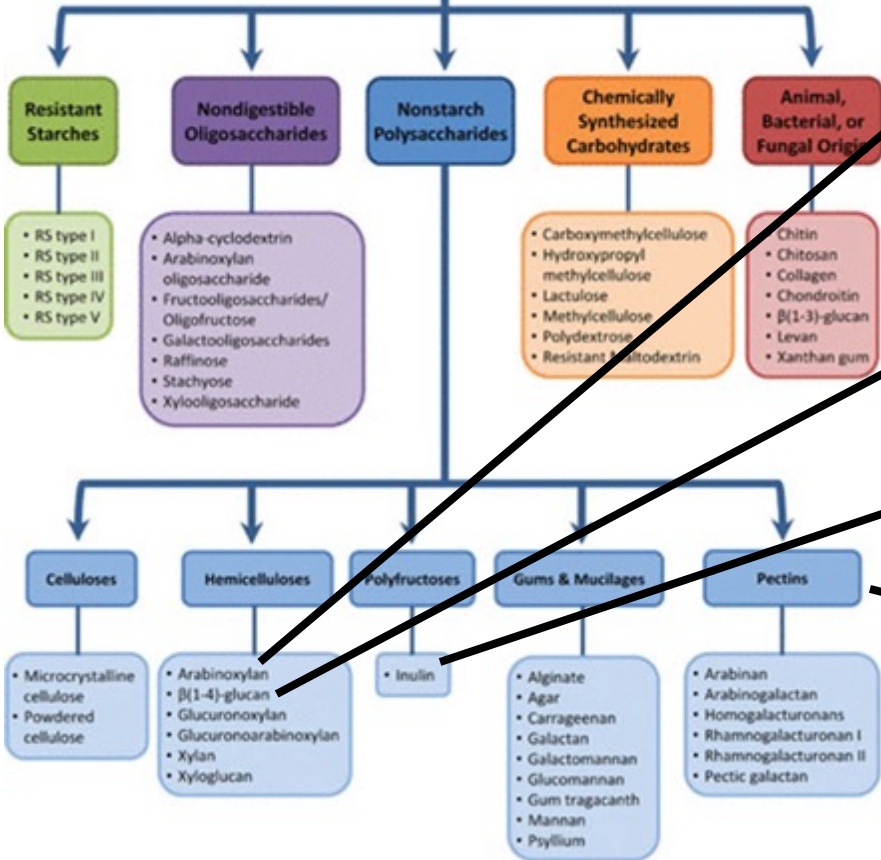
UC patient relapse following B-fructan consumption was correlated with increased markers of colon cancer



Wounding of the gut and persistent inflammation in IBD is associated with colon cancer risk

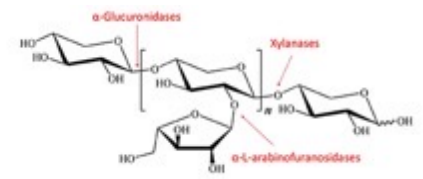


Nondigestible Carbohydrates



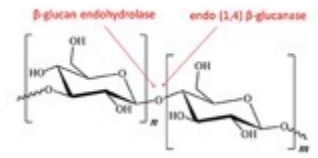
Arabinoxylan:

Cereal grains, rye, wheat, oats, barley, rice, sorghum, legumes.



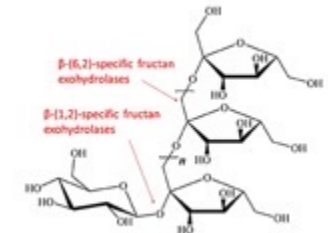
β-glucan:

Oat, barley, rice, mushrooms.



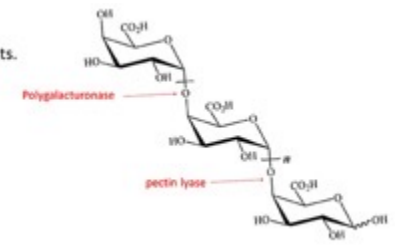
β-fructans:

Chicory root, agave, artichokes, banana, wheat, onion, garlic.



Pectin:

Fruits, vegetables, nuts.



Translating our findings to the clinic

Biomarkers
(stool)



Personalized
Diets



Prebiotics/Probiotics/Products



- Can we use our microbial enzyme stool test (**biomarkers**) to predict response to fibres?
- Developed **clinical scoring system** to predict a patients degree of sensitivity to select fibres
- Developing and testing **personalized dietary interventions**
- **Randomized control trial (recruiting)**

Conclusion

- YES – dietary fibres provide clear benefits
- *BUT* - the **type**, **source** and **quantity** of fiber is extremely important
- *AND* – without the right microbes present, does what we eat still benefit us??



Conclusion

- YES – dietary fibres provide clear benefits
- *BUT* - the **type** and **quantity** of fiber is extremely important
- AND – without the right microbes present, does what we eat still benefit us??
- FUTURE – precision medicine
 - Patient specific dietary recommendations

One cure does not fit all...



Armstrong Lab:

Dr. Eunice Ouali
Vi Vu
Richard Miller
Terri-Lyn Jeanson
Edgar Delbert
Renee Nadeau
Ramsha Mahmood
Samuel Lawal
Reihane Khorasani
Hana Olof
Athalia Voisin

Wine Lab:

Dr. Eytan Wine
Dr. Michael Bording-Jorgensen
Simona Veniamin
Christopher Cheng

CEGIIR & UAlberta:

Dr. Thava Vasanthan
Dr. Ben Willing
Dr. Levinus Dieleman
Dr. Karen Madsen
Naomi Hotte

UCalgary:

Dr. Kris Chadee
France Moreau
Hayley Gorman

UManitoba:

Dr. Deanna Santer
Dr. Charles Bernstein
Dr Wael El-Matary
Dr. Liam O'Neil
Dr. Ruth Ann Marrie
Dr. Carol Hitchon

The EPIC Team Edmonton:

Dr. Hien Huynh
Dr. Matthew Carroll
Alex Petrova

Dr. Zhengxiao Zhang (**Jimei University**)

Dr. Jens Walter (**APC Microbiome**)

Dr. Elena Verdu (**McMaster University**)



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