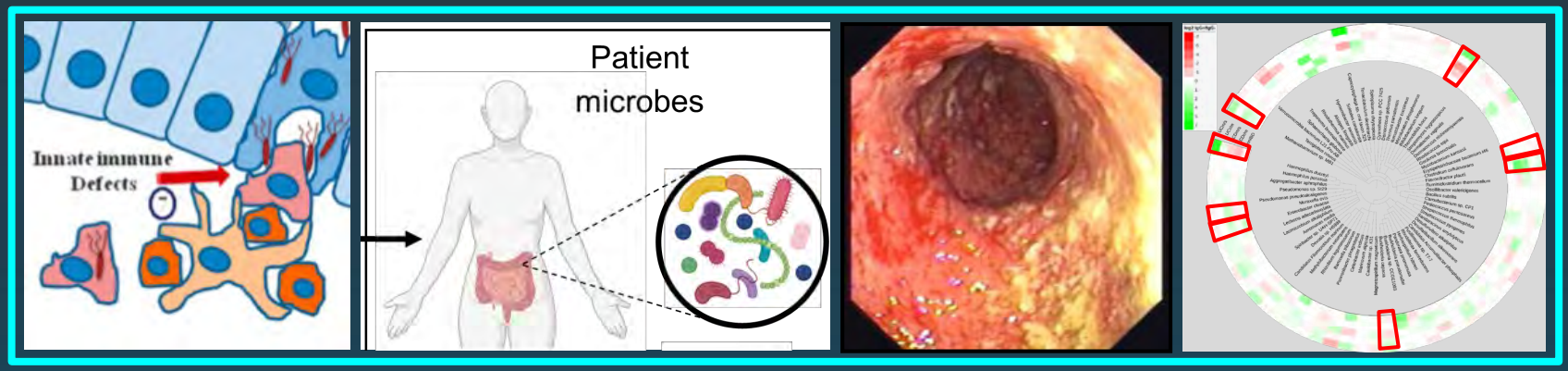
Altering the Microbiota in Clinical Practice: What's worth trying?



Eytan Wine, MD, PhD, FRCPC

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University of Alberta
Edmonton, Alberta, Canada

EPIC
Edmonton Pediatric IBD Clinic

SATURDAY, November 5, 2022
Canada Future Directions in IBD

STOLLERY CHILDRENS HOSPITAL
UNIVERSITY OF ALBERTA
QUAECUMQUE VERA

Disclosures

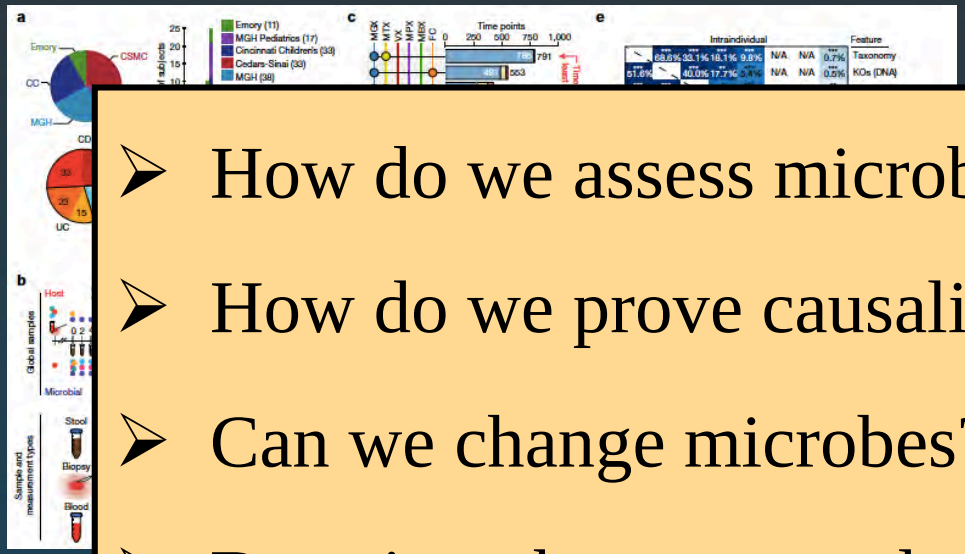
- My laboratory is funded by:
  - Canadian Institutes of Health Research (CIHR)
  - Weston Foundation
  - IMAGINE SPOR Network
- I have received honoraria from:
  - Consultant: AbbVie, Nestle Health Sciences, BioJamp, Pfizer
  - Speaker Fees: AbbVie, Janssen, Nestle Health Sciences, Mead Johnson Nutrition
- No conflicts relevant to this talk

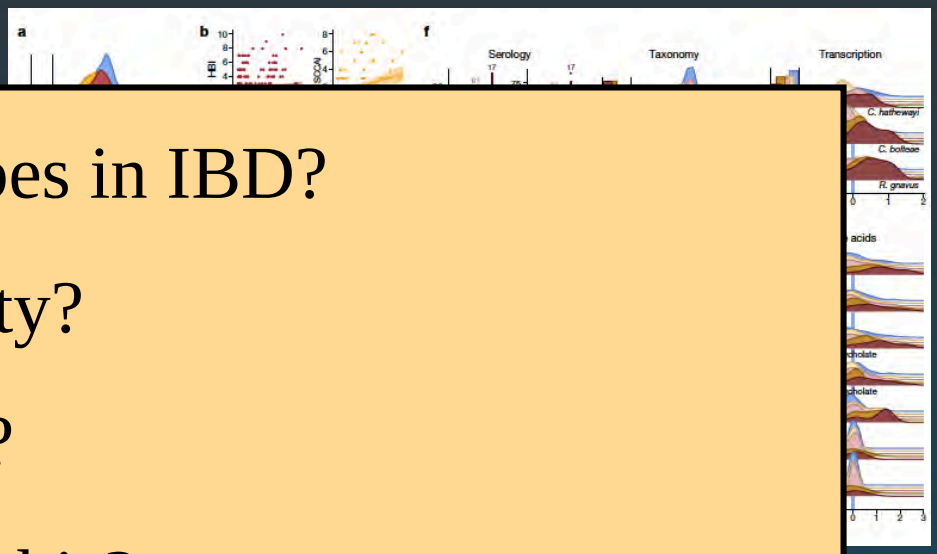
Talk Objectives

- Discuss the **rationale** for altering microbes in IBD
- Explore the **applications** of manipulating the microbiome in IBD for clinical benefit
- Consider what the **future** of microbe-altering therapy might look like

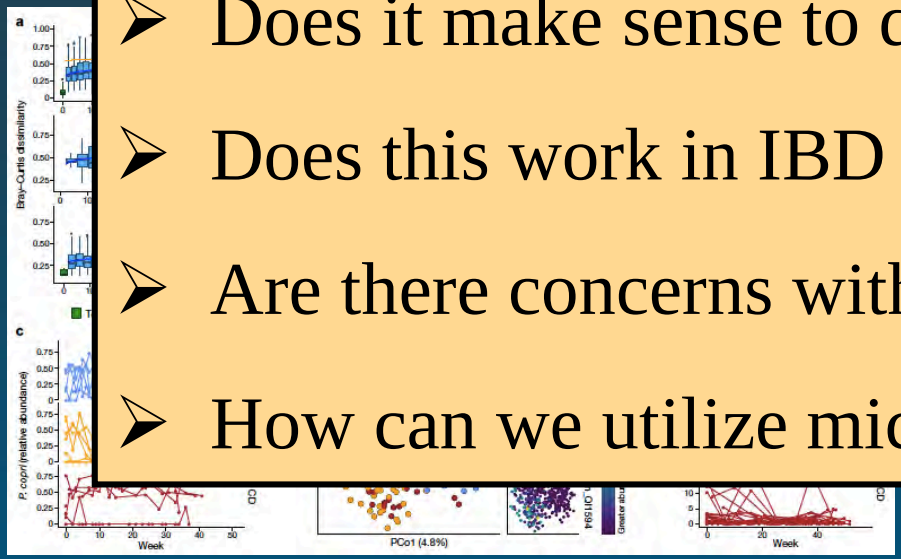
Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases

nature
International weekly journal of science





- How do we assess microbes in IBD?
- How do we prove causality?
- Can we change microbes?
- Does it make sense to do this?
- Does this work in IBD as a treatment?
- Are there concerns with microbial alteration?
- How can we utilize microbes to benefit our patients?



Lloyd-Price *et al.*, Nature 2019;569:655-9.

Biomarkers: Microbial and Host-response

Alterations in the Gut Microbiome of Children with Severe Ulcerative Colitis

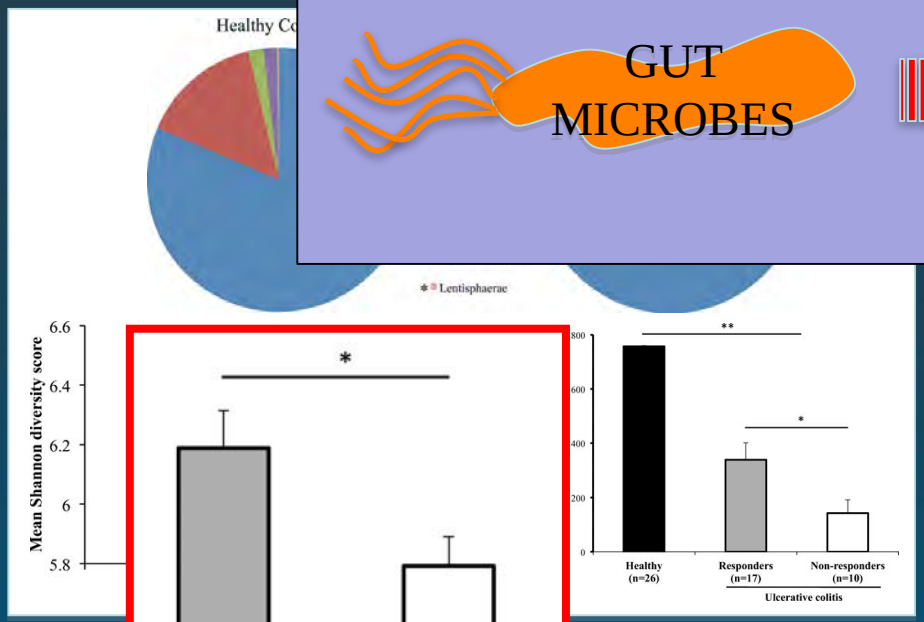
Sonia Michail, MD, Matthew Durbin, MD,* Dan Turner, MD, PhD,† Anne M. Griffiths, MD,‡ David R. Mack, MD,§ Jeffrey Hyams, MD,‖ Neal Leleiko, MD, PhD,¶ Harshavardhan Kenche, MS,* Adrienne Stolfi, MSPH,* and Eytan Wine, MD, PhD***

Inflamm Bowel Dis • Volun

Cause or effect?

Microbial diversi

response



Interleukin-6 is associated with steroid resistance and reflects disease activity in severe pediatric ulcerative colitis

Eytan Wine [a,*], David R. Mack [b], Jeffrey Hyams [c], Anthony R. Otley [d], V. Crandall [f], Neal Leleiko [g], Aleixo M. Muise [h], urner [i,1]

hn's and Colitis (2013) 7, 916–922

tion between serum cytokine levels and response to IVCS (univariate analysis).

		VCS failure n=23)	P value [a]
		9.6 (5.5–11.4)	0.50
		.76 (0.36–1.46)	0.16
		.28 (0.20–0.75)	0.96
		.44 (0.22–0.76)	0.64
		.22 (0.12–0.32)	0.76
		1.36 (0.61–2.69)	0.01
		45.6 (24.7–100.9)	0.14
IL-10	7.4 (3.4–19.6)	5.3 (3.9–11.9)	0.55
IL-12	0.95 (0.48–1.80)	1.04 (0.60–2.24)	0.91
IL-13	1.19 (0.72–2.32)	1.72 (1.29–2.46)	0.13
IL-17	5.0 (2.5–7.2)	3.4 (2.8–7.2)	0.93

Numbers represent medians in pg/mL (interquartile range).
IVCS, intravenous corticosteroids.

[a] Wilcoxon rank sum test.
[b] Indicates significant difference between groups.

Table 4 Cytokine levels correlating with ulcerative colitis severity markers.

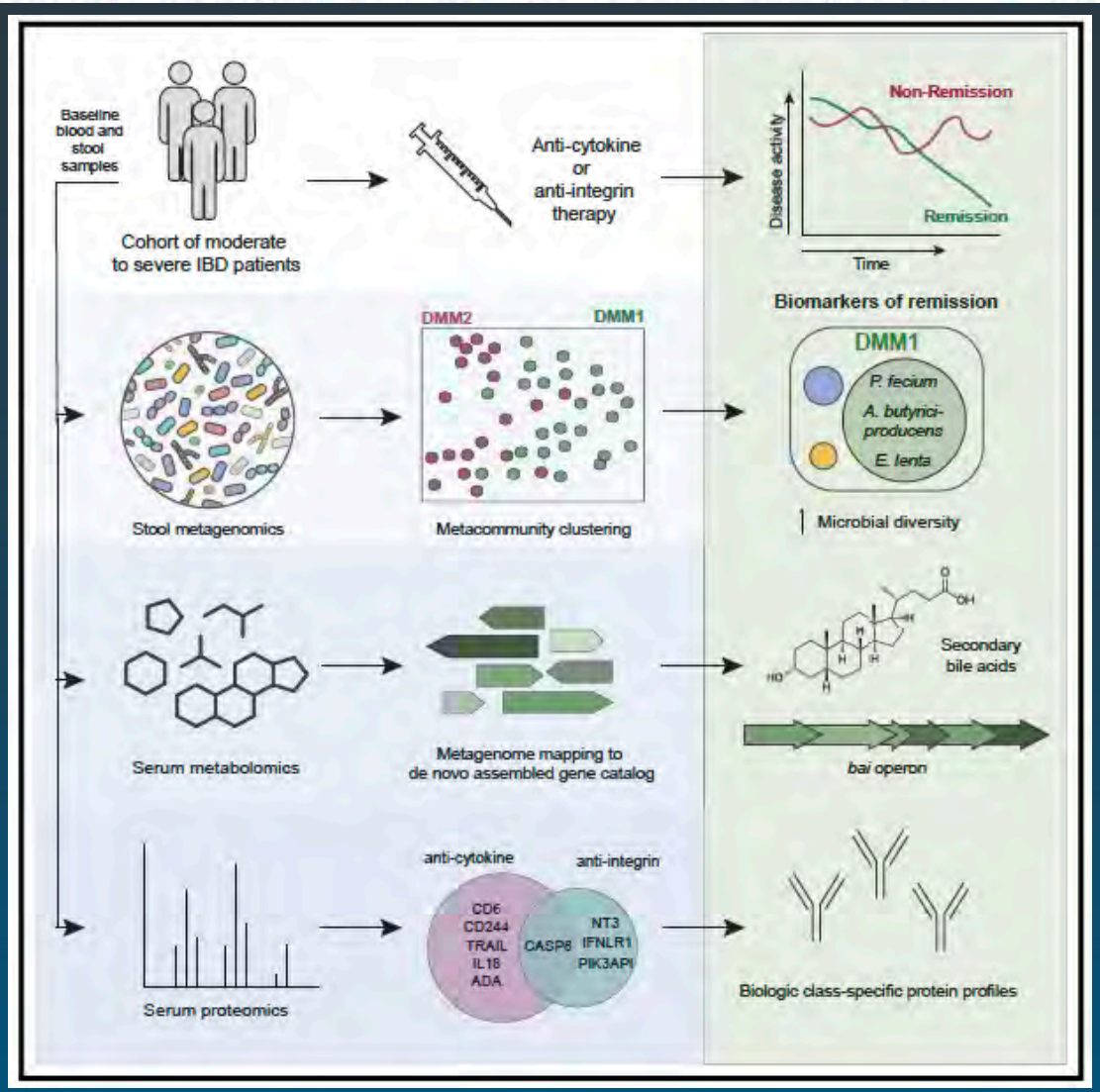
	Severity marker/index						
Cytokine	PUCAI	PGA	Albumin	CRP	ESR	Seo	Lindgren
IL-6	r=0.36 **	r=0.31 *	r=(−0.64) **	r=0.41 **		r=0.31 **	r=0.39 **
IL-17			r=(−0.43) **			r=0.35 *	
IL-1β				r=0.4 **			

Spearman's correlation analysis; only correlations with 'r' value over 0.3 are presented.

* P≤0.005.
** P≤0.001.

Multi-omics reveal microbial determinants impacting responses to biologic therapies in inflammatory bowel disease

Jonathan Wei Jie Lee,[1,2,3,4] Damian Plichta,[1] Larson Hogstrom,[1,8] Nynke Z. Borren,[5,9] Helena Lau,[1,5] Sara M. Gregory,[5] William Tan,[5] Hamed Khalili,[5] Clary Clish,[1] Hera Vlamakis,[1] Ramnik J. Xavier,[1,6,7,10,*] and Ashwin N. Ananthakrishnan[5,*]

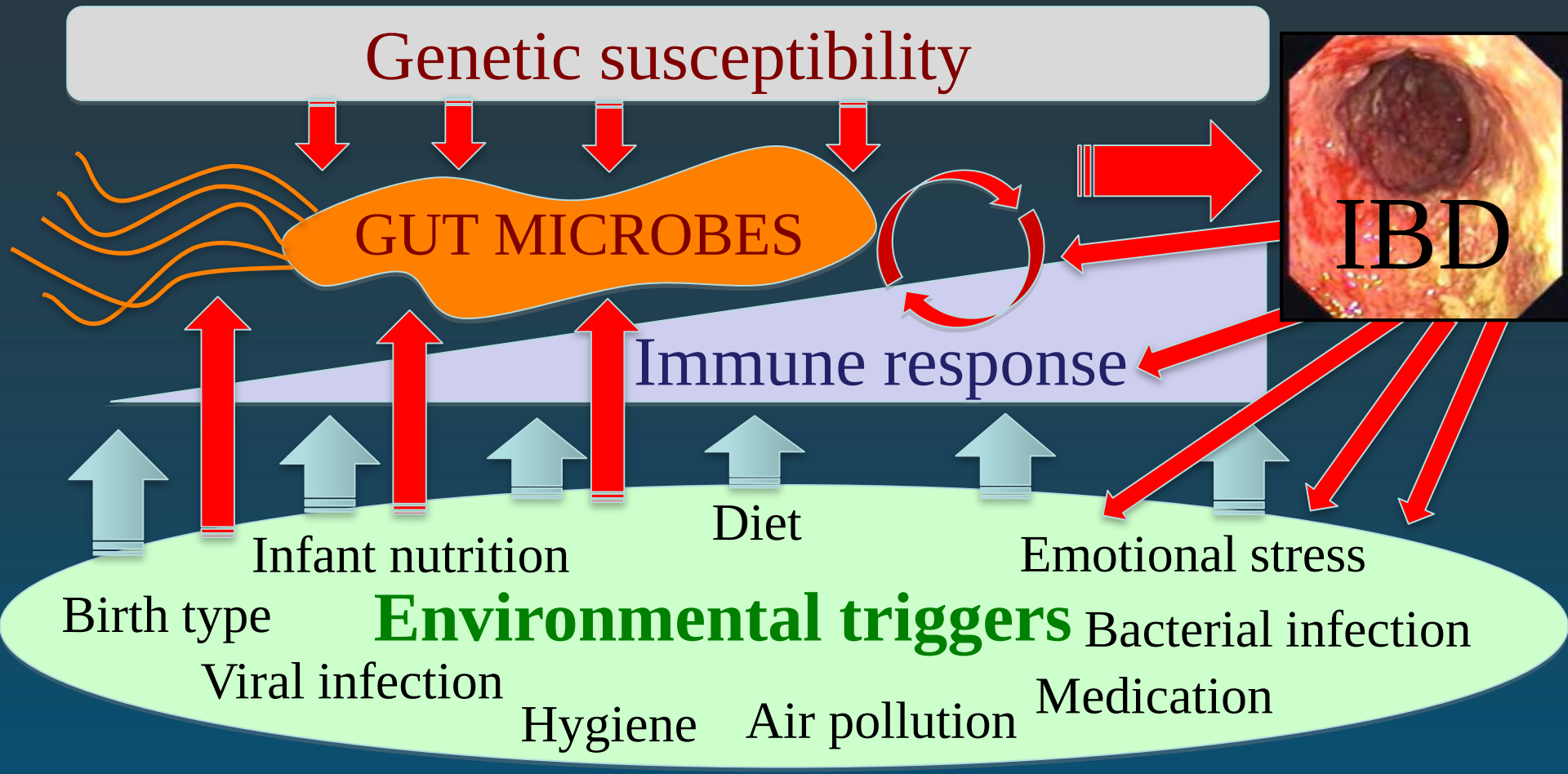


- 185 pts: Anti-TNF (79); IL-12/23 (23); integrins (85)
- Baseline predictors for early clinical (14W) and endoscopic (52W) remission
- Signature profiles
- Unique to predict therapy response

Cause or effect?

Lee *et al*,. Cell Host Microbe 2021;29:1294-304

Gut Microbes as Markers and Mediators of Disease in IBD



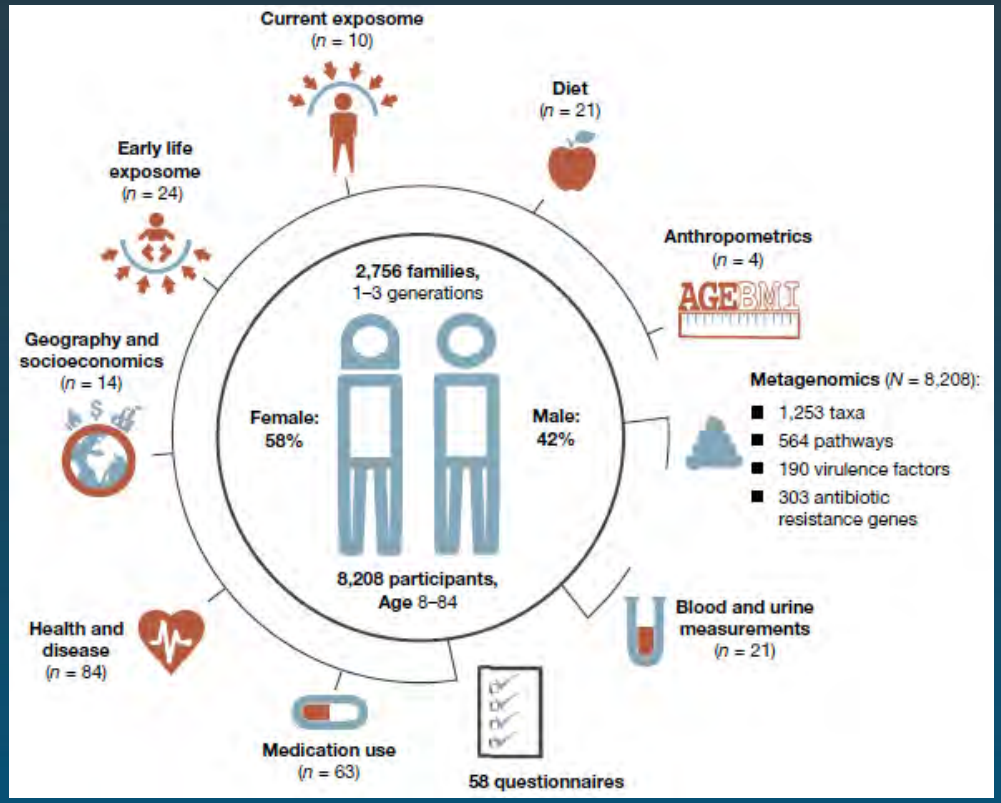
Wine E. Dig Dis 2014;32:403-8.

What shapes microbes?

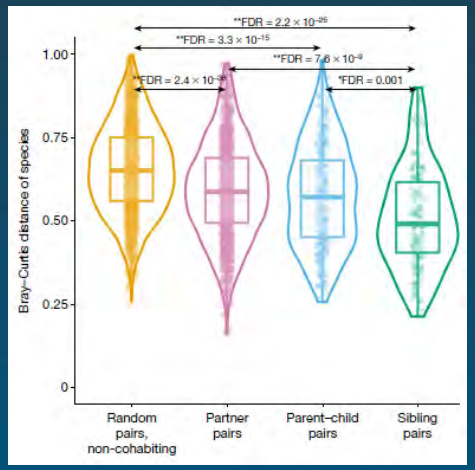
Environmental factors shaping the gut microbiome in a Dutch population

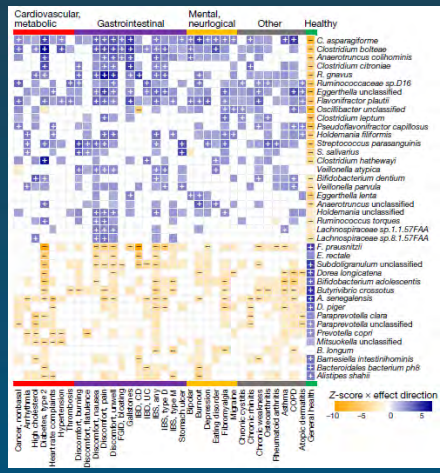
nature
International weekly journal of science

R. Gacesa[1,2,10], A. Kurilshikov[2,10], A. Vich Vila[1,2], T. Sinha[2], M. A. Y. Klaassen[1,2], L. A. Bolte[1,2], S. Andreu-Sánchez[2,3], L. Chen[2,3], V. Collij[1,2], S. Hu[1,2], J. A. M. Dekens[2,4], V. C. Lenters[5], J. R. Björk[1,2], J. C. Swarte[1,2], M. A. Swertz[2,6], B. H. Jansen[1,2], J. Gelderloos-Arends[2], S. Jankipersadsing[2], M. Hofker[3,12], R. C. H. Vermeulen[5,7], S. Sanna[2,8], H. J. M. Harmsen[9,11], C. Wijmenga[2,11], J. Fu[2,3,11]✉, A. Zhernakova[2,11]✉ & R. K. Weersma[1,11]✉



- Only 6.6% heritable
- 48.6% explained by cohabitation
- Common microbiome signatures in unrelated diseases
- Importance of early life in shaping microbiome





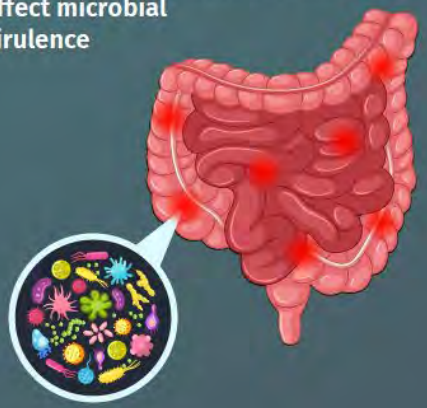
Gacesa *et al.*, Nature 2022;604:732-9.

Gut Microenvironment and Bacterial Invasion in Paediatric Inflammatory Bowel Diseases

*†Deenaz Zaidi, *Hien Q. Huynh, *Matthew W. Carroll, ‡Rupasri Mandal, ‡David S. Wishart, and *†§Eytan Wine

How the Gut Microenvironment Influences Bacterial Invasion in Inflammatory Bowel Diseases

In inflammatory bowel diseases (IBD), alterations in gut microbial composition and intestinal homeostasis may affect microbial virulence



However, the relationship between gut microenvironment and microbial virulence is unclear

Intestinal aspirates obtained via endoscopy

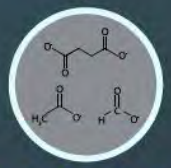
19 Patients with IBD
10 Patients without IBD

IBD microbe invasion

Invasion potential of patient microbes by gentamicin protection assay → IBD microbes alone are not more virulent than non-IBD microbes

Gut microenvironment (aspirates with *E. coli*)

Effect of gut micro-environment on *E. coli* invasion into intestinal epithelial cells → IBD aspirates induce *E. coli* invasion *in vitro*



Effect of metabolites identified in aspirates on *E. coli* invasion

Metabolites in aspirates are associated with *E. coli* invasion

- ↑ Succinate ⛓ ↑ *E. coli* invasion
- ↑ Acetate and formate ⛓ ↓ *E. coli* invasion

IBD-associated alteration of intestinal microenvironment enhances gut microbial virulence

Gut Microenvironment and Bacterial Invasion in Pediatric Inflammatory Bowel Diseases
Zaidi et al. (2020) | DOI:

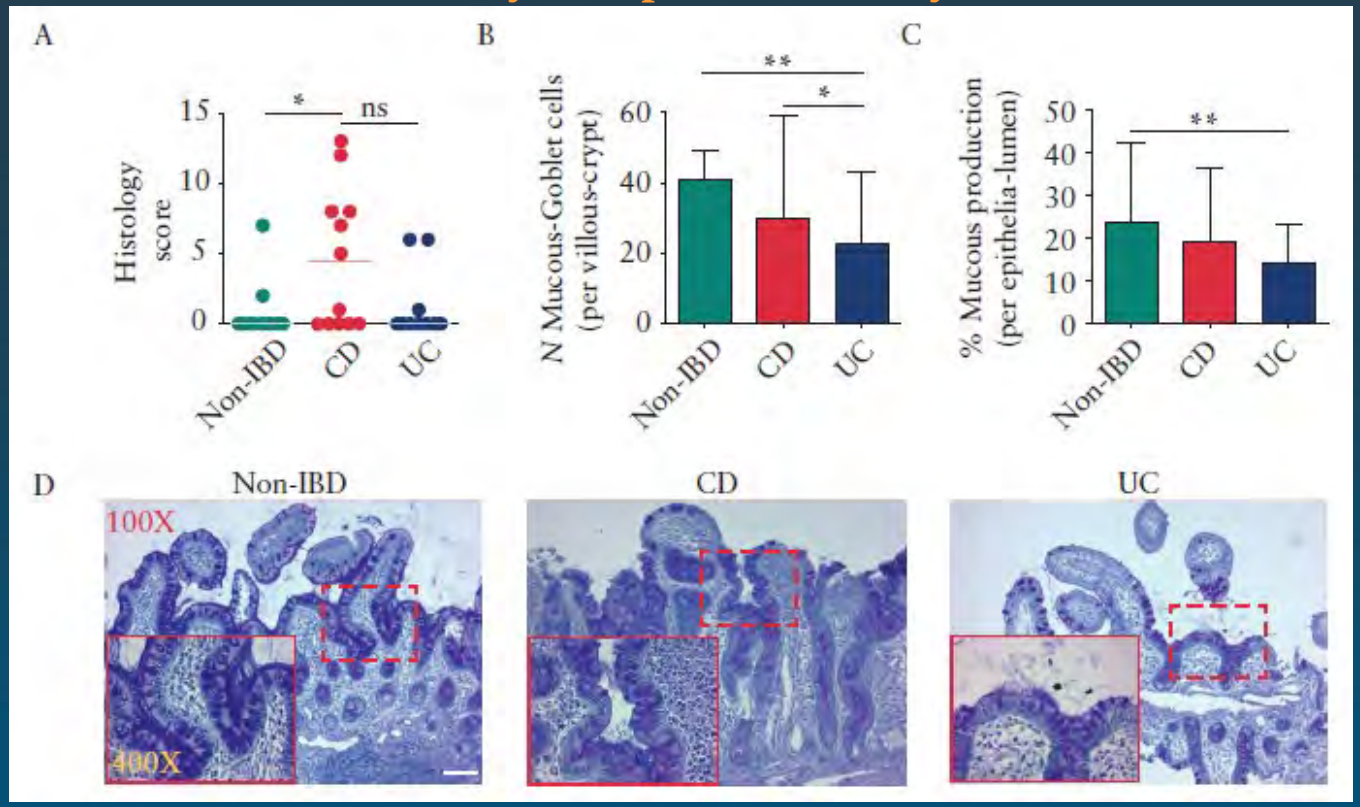
JPGN Journal of Pediatric Gastroenterology and Nutrition

Microbial Alterations in the TI of Peds UC

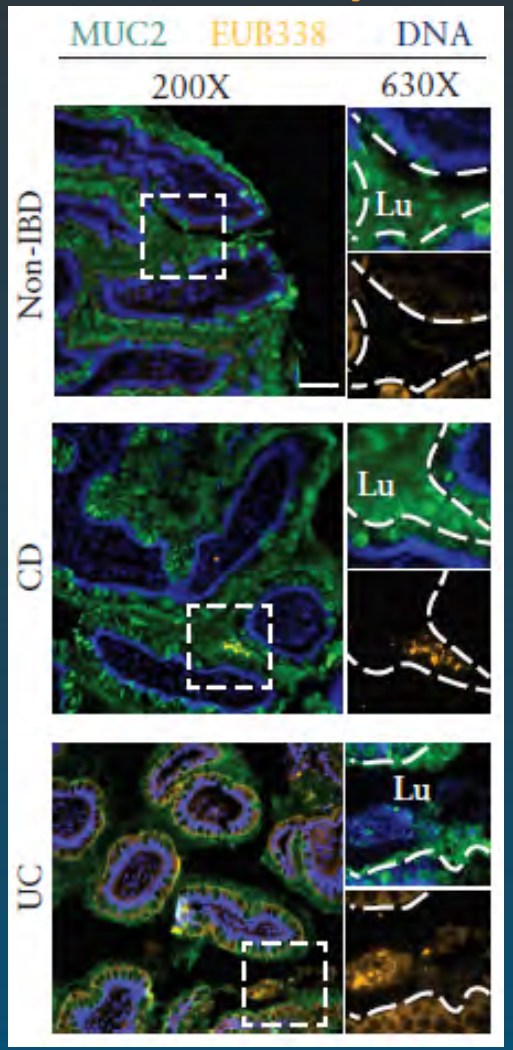
Mucosal Barrier Depletion and Loss of Bacterial Diversity are Primary Abnormalities in Paediatric Ulcerative Colitis

Misagh Alipour,[a,b] Deenaz Zaidi,[a,b] Rosica Valcheva,[a,c] Juan Jovel,[a,c] Inés Martínez,[d] Consolato Sergi,[b,e] Jens Walter,[a,d,f] Andrew L. Mason,[a,c] Gane Ka-Shu Wong,[a,c,f,g] Levinus A. Dieleman,[a,c] Matthew W. Carroll,[b] Hien Q. Huynh,[b] Eytan Wine[a,b]

TI Mucus Layer Depletion, Mainly in UC



Increased Bacterial Penetration, Mainly in UC

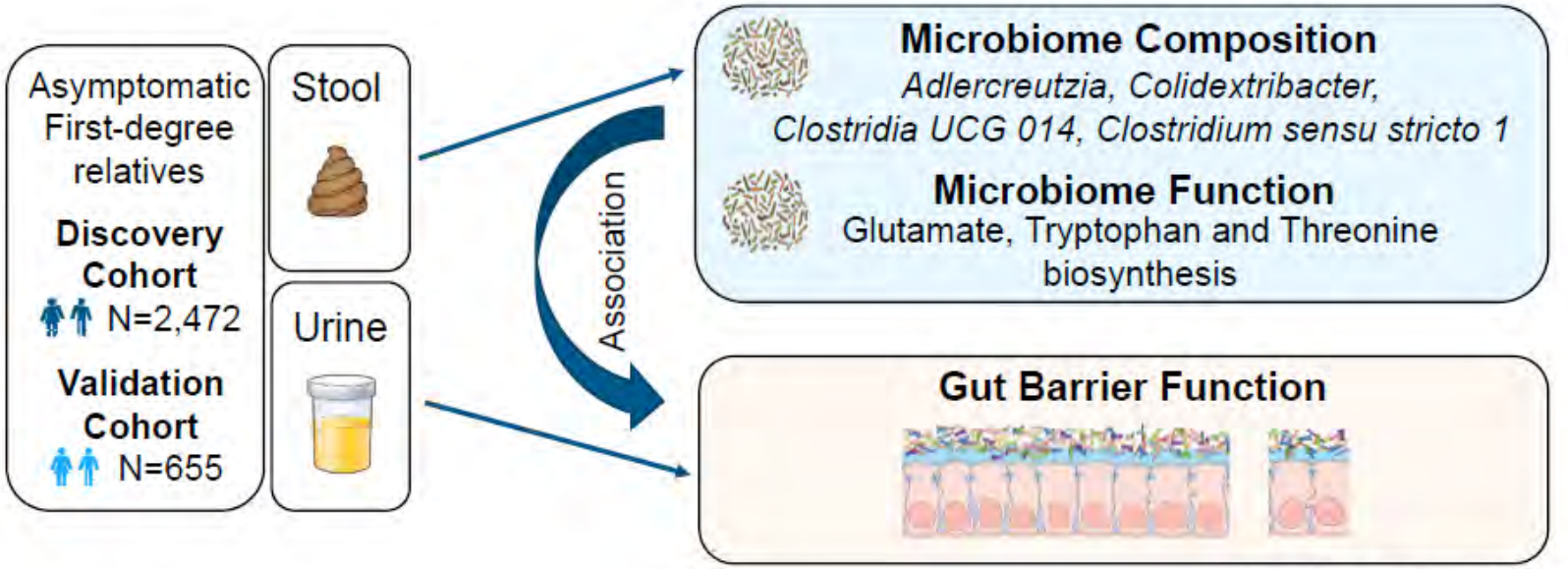


Alipour *et al.*, J Crohn Colitis 2016;10:462-71.

Microbial Involvement in IBD FDRs

Altered Gut Microbiome Composition and Function Are Associated With Gut Barrier Dysfunction in Healthy Relatives of Patients With Crohn's Disease

Haim Leibovitzh,[1,2] Sun-Ho Lee,[1,2] Mingyue Xue,[1] Juan Antonio Raygoza Garay,[1,2] Cristian Hernandez-Rocha,[1,2] Karen L. Madsen,[3] Jonathan B. Meddings,[4] David S. Guttman,[5,6] Osvaldo Espin-Garcia,[7] Michelle I. Smith,[1] Ashleigh Goethel,[1] Anne M. Griffiths,[8] Paul Moayyedi,[9] A. Hillary Steinhart,[1,2] Remo Panaccione,[10] Hien Q. Huynh,[11] Kevan Jacobson,[12,13] Guy Aumais,[14] David R. Mack,[15] Maria T. Abreu,[16] Charles N. Bernstein,[17] John K. Marshall,[18] Dan Turner,[19] Wei Xu,[7] The CCC GEM Project Research Consortium, Williams Turpin,[1,2] and Kenneth Croitoru[1,2]

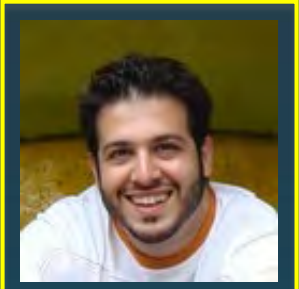


Leibovitzh *et al.*, Gastroenterology 2022;163:1364-76.

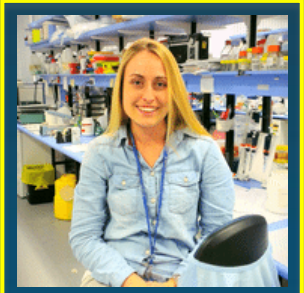
Host immunoglobulin G selectively identifies pathobionts in pediatric inflammatory bowel diseases

Microbiome

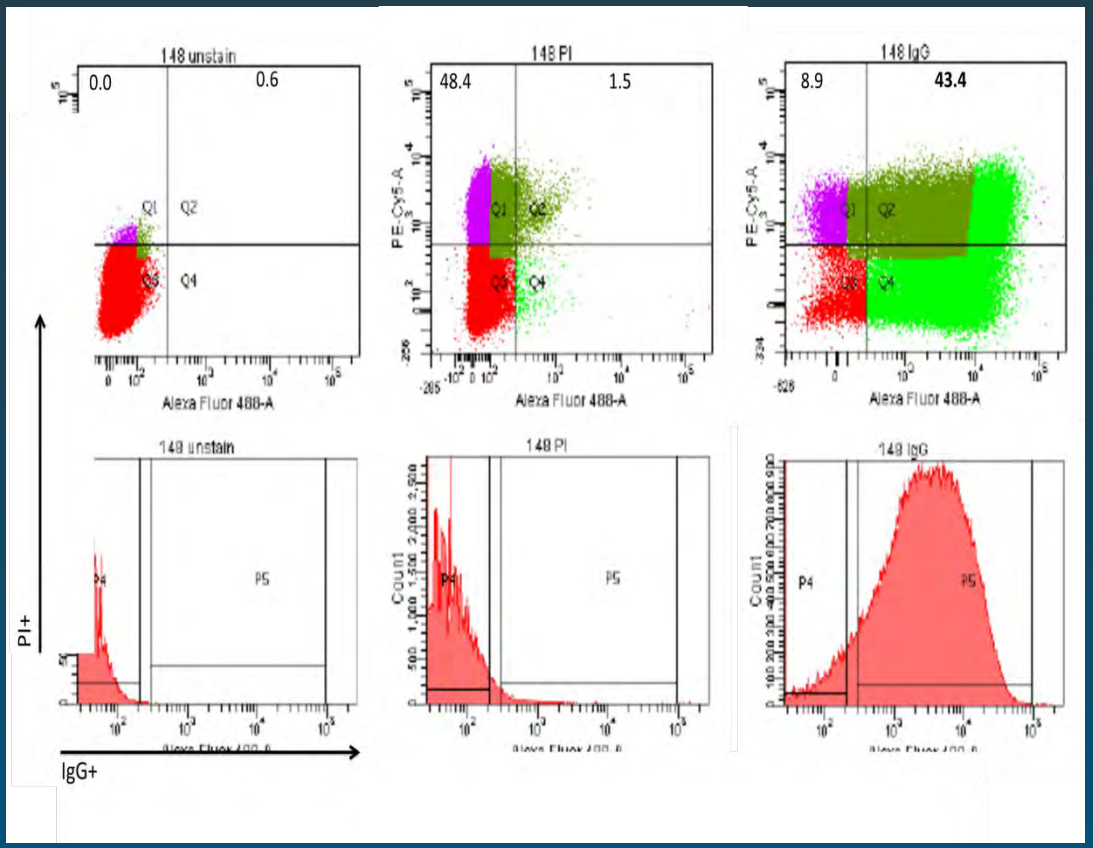
Heather Armstrong[1,2], Misagh Alipour[1,2], Rosica Valcheva[1,4], Michael Bording-Jorgensen[1,3], Juan Jovel[1,4], Deenaz Zaidi[1,2], Prachi Shah[1,2], Yuefei Lou[1,4], Cory Ebeling[5], Andrew L. Mason[1,4], Dawson Lafleur[1,2], Jeremy Jerasi[1,2], Gane K-S. Wong[1,6], Karen Madsen[1,4], Matthew W. Carroll[2], Hien Q. Huynh[2], Levinus A. Dieleman[1,4] and Eytan Wine[1,2,3*]



Misagh Alipour, Postdoc (alumnus..)

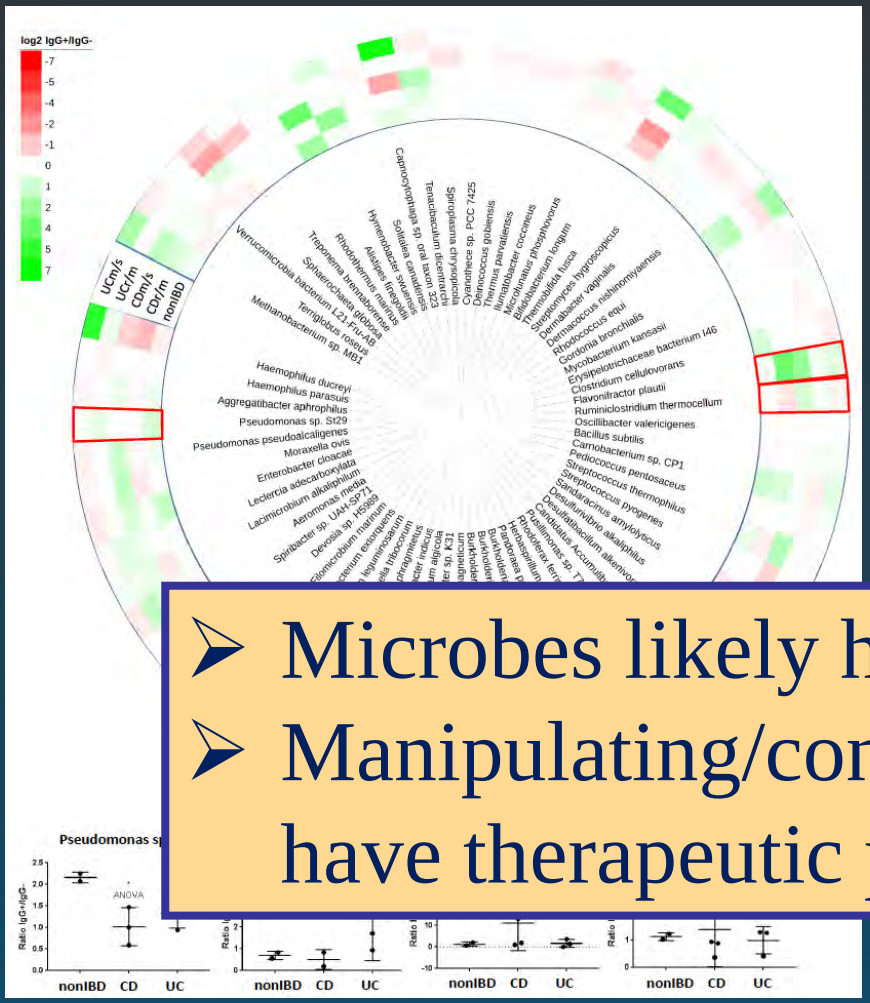


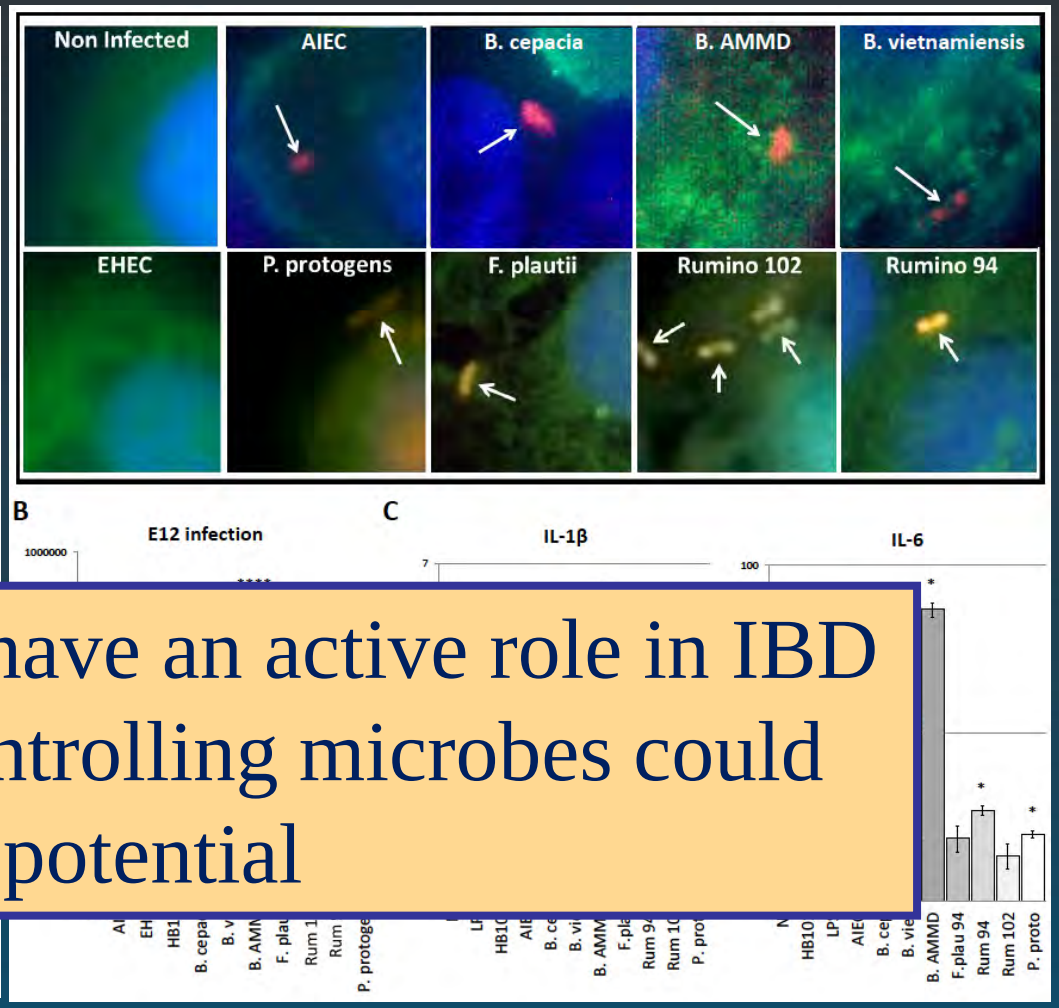
Heather Armstrong; Postdoc



FACS Identifies and Sorts IgG Coated Bacteria: [Representative of FACS sorting with shift in population of IgG^+ bacteria (43.4%)].

IgG^{+}/IgG^{-} Alterations in IBD vs Non-IBD





- Microbes likely have an active role in IBD
- Manipulating/controlling microbes could have therapeutic potential

IgG-bound bacteria are potential pathobionts (are invasive and induce an immune response)

Armstrong *et al.*, Microbiome 2019;7:1.

Current Microbe-Altering Approaches

- Antibiotics: selective removal
- Pro/prebiotics: selective addition
- FMT: community level change
- Nutrition: change microenvironment
- (Early life: pioneer effect and immune education)

Antibiotics in IBD

European Crohn's and Colitis Organisation

ESPGHAN

The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update

Patrick F. van Rheenen,[a] Marina Aloi,[b] Amit Assa,[c] Jiri Bronsky,[d] Johanna C. Escher,[e] Ulrika L. Fagerberg,[f] Marco Gasparetto,[g] Konstantinos Gerasimidis,[h] Anne Griffiths,[i] Paul Henderson,[j] Sibylle Koletzko,[k,l] Kaija-Leena Kolho,[m] Arie Levine,[n] Johan van Limbergen,[o] Francisco Javier Martin de Carpi,[p] Víctor Manuel Navas-López,[q] Salvatore Oliva,[b] Lissy de Ridder,[e] Richard K. Russell,[r] Dror Shouval,[s,t] Antonino Spinelli,[u,v] Dan Turner,[w] David Wilson,[j] Eytan Wine,[x] Frank M. Ruemmele,[y,z]

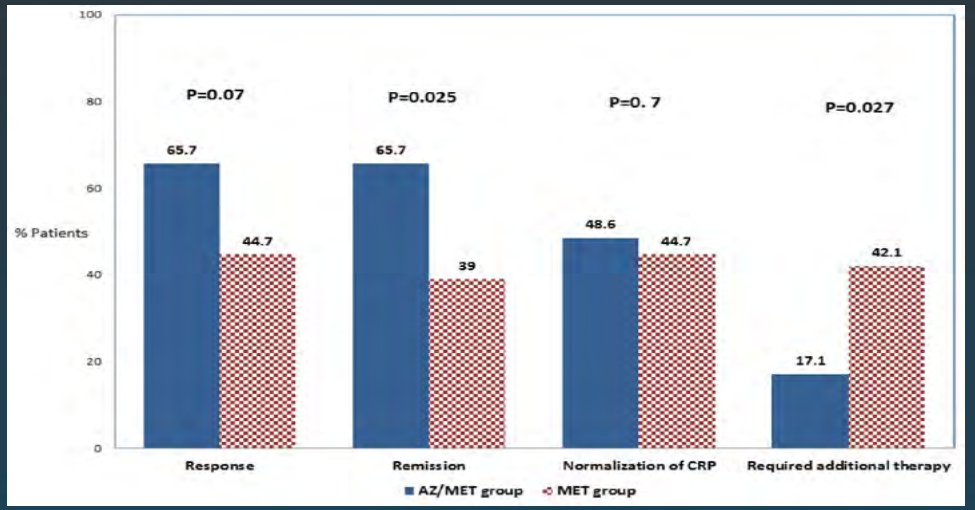
11.2. Antibiotics

Evidence

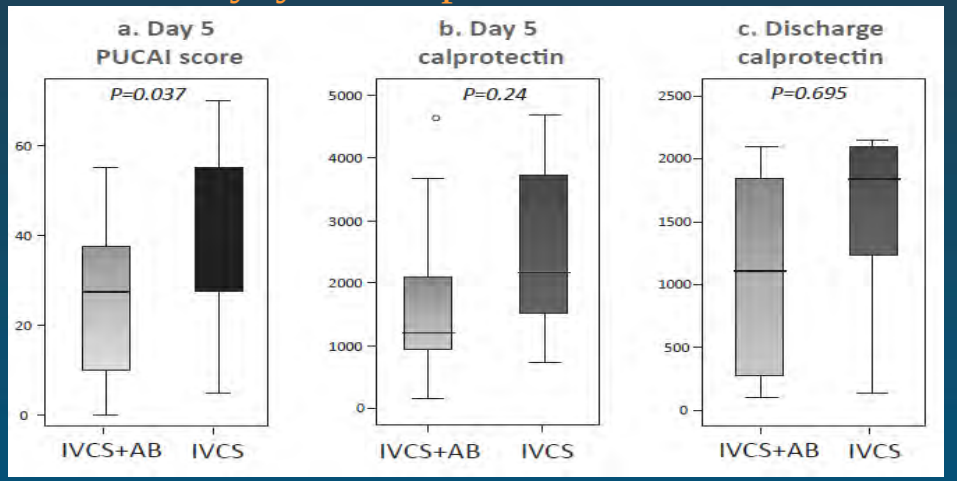
In the only paediatric RCT, a combination of azithromycin and metronidazole for 8 weeks was more effective than metronidazole alone for induction of clinical remission at 8 weeks in mild-to-moderate CD [66% vs 39%; $p = 0.025$]. However, the primary outcome measure, defined as a decrease in PCDAI >12.5 points, was not statistically different between groups [66% vs 45%; $p = 0.07$]. Faecal calprotectin declined significantly in the combination group but not in the metronidazole group. However, levels in both groups remained high at 8 weeks.[250]

According to a recent Cochrane review in adults, the effect of antibiotics on both induction and maintenance of remission in CD is uncertain and adverse events were not increased with antibiotics compared with placebo.[251] The effect of antimycobacterial therapy is not clear in CD patients, due to the very low quality of evidence.[252]

Azithromycin and metronidazole for CD



Amoxicillin, vancomycin, metronidazole, & doxycycline/ciprofloxacin for ASC



Van Rheenen et al,. JCC 2021;15:171-94. Levine *et al.*, Gut 2019;68:239-47. Turner *et al.*, IBD 2020;26:1733-42.

Pro/prebiotics in IBD

European Crohn's and Colitis Organisation

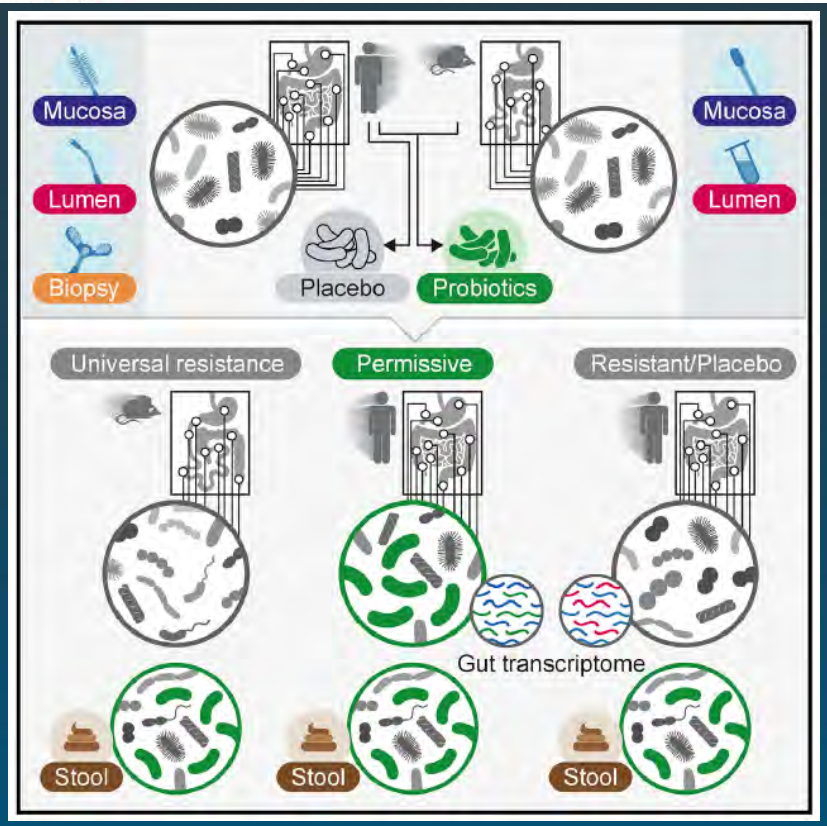
ESPGHAN

ECCO-ESPGHAN statement 21

In patients with CD, probiotics should not be used to induce or maintain remission. LoE: 2 | Agreement: 100%.

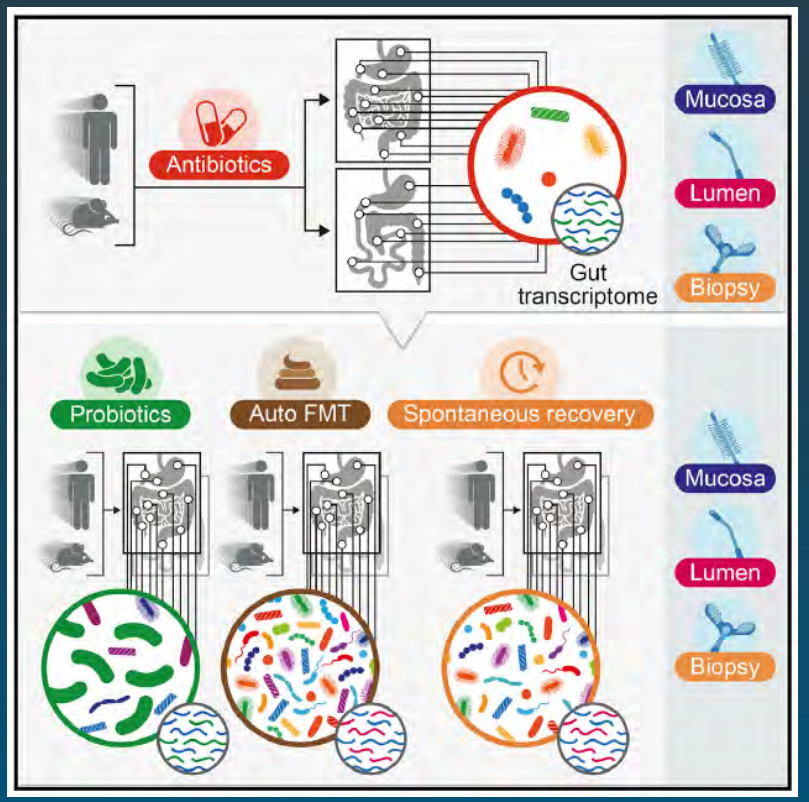
Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features

Niv Zmora,[1,2,11] Gili Zilberman-Schapira,[1,11] Jotham Suez,[1,11] Uria Mor,[1,11] Mally Dori-Bachash,[1] Stavros Bashiardes,[1] Eran Kotler,[3,4] Maya Zur,[1] Dana Regev-Lehavi,[1] Rotem Ben-Zeev Brik,[1] Sara Federici,[1] Yotam Cohen,[1] Raquel Linevsky,[1] Daphna Rothschild,[3,4] Andreas E. Moor,[3] Shani Ben-Moshe,[3] Alon Harmelin,[5] Shalev Itzkovitz,[3] Nitsan Maharshak,[6,7,8] Oren Shibolet,[6,7,8] Hagit Shapiro,[1] Meirav Pevsner-Fischer,[1] Itai Sharon,[9,10] Zamir Halpern,[6,7,8,12,*] Eran Segal,[3,4,12,*] and Eran Elinav[1,12,13,*]



Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

Jotham Suez,[1,11] Niv Zmora,[1,2,11] Gili Zilberman-Schapira,[1,11] Uria Mor,[1,11] Mally Dori-Bachash,[1] Stavros Bashiardes,[1] Maya Zur,[1] Dana Regev-Lehavi,[1] Rotem Ben-Zeev Brik,[1] Sara Federici,[1] Max Horn,[1] Yotam Cohen,[1] Andreas E. Moor,[3] David Zeevi,[3,4] Tal Korem,[3,4] Eran Kotler,[3,4] Alon Harmelin,[5] Shalev Itzkovitz,[3] Nitsan Maharshak,[6,7,8] Oren Shibolet,[6,7,8] Meirav Pevsner-Fischer,[1] Hagit Shapiro,[1] Itai Sharon,[9,10] Zamir Halpern,[6,7,8,12,*] Eran Segal,[3,4,12,*] and Eran Elinav[1,12,13,*]



Van Rheenen *et al*. JCC 2021;15:171-94. Zmora *et al*., Cell, 2018;174:1388-405. Suez *et al*., Cell, 2018;174:1406-23.

Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

Paul Moayyedi,[1] Michael G. Surette,[1] Peter T. Kim,[2,3] Josie Libertucci,[1] Melanie Wolfe,[1] Catherine Onischi,[3] David Armstrong,[1] John K. Marshall,[1] Zain Kassam,[4] Walter Reinisch,[1] and Christine H. Lee[3]

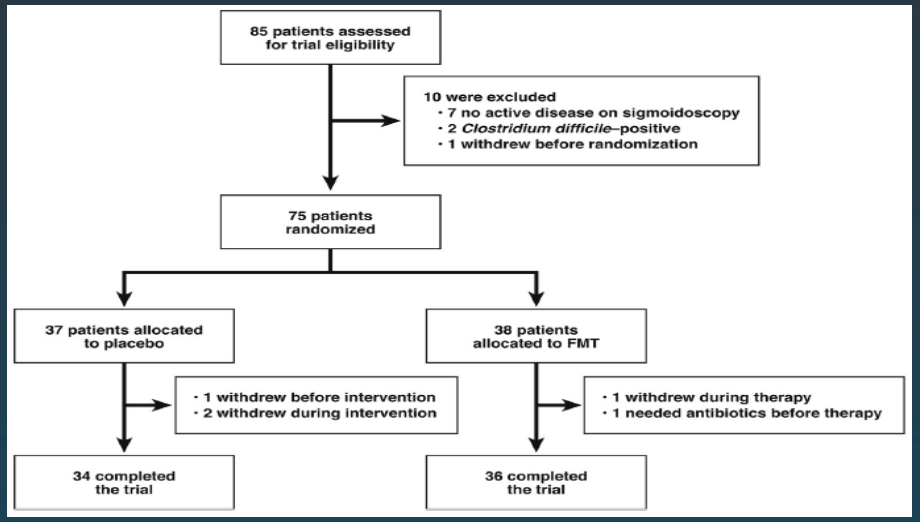
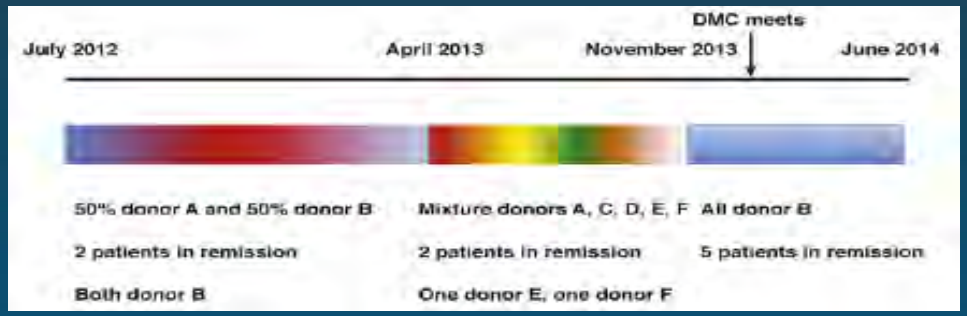


Table 2. Outcome Measures Comparing Fecal Microbial Transplantation With Placebo

Outcome	Placebo (n = 37)	FMT (n = 38)	*P* value
Clinical remission,[a] n (%)	2 (5)	9 (24)	.03
Clinical response,[b] n (%)	9 (24)	15 (39)	.16
Full Mayo score	6.34	6.09	.42
IBDQ score	149.38	152.13	.44
EQ-5D score	70.07	68.52	.99
CRP, *mg/L* (n = 17 placebo, n = 15 FMT)	3.3 ± 3.4	4.9 ± 5.9	.38
ESR, *mm/h* (n = 17 placebo, n = 15 FMT)	13.1 ± 11.2	15.9 ± 17.0	.59
Proportion with high ESR, n (%)	4 (24)	3 (20)	1.0
Proportion with high CRP, n (%)	5 (29)	2 (13)	.40
Patients with serious adverse events n (%)	2[c] (5)	3[d] (8)	1.0

- Active UC (scope); 50 mL FMT enema weekly x 6
- Primary endpoint: remission (endo Mayo 0) at week 7
- Study stopped early (futility), but…
- 7 of 9 remission were Donor B
- 3/4 <1y vs. 6/34 > 1y in remission



Gastroenterology 2015;149:102–109

Systematic Review and Meta-analysis: Fecal Microbiota Transplantation for Treatment of Active Ulcerative Colitis

Neeraj Narula, MD, FRCPC, Zain Kassam, MD, MPH,† Yuhong Yuan, PhD,* Jean-Frederic Colombel, MD,‡ Cyriel Ponsioen, MD, PhD,§ Walter Reinisch, MD,* and Paul Moayyedi, MBChB, PhD, MPH**

TABLE 1. Definition of Outcomes from Trials Included

First Author	Year	Inclusion Eligibility for Trial	Combined Clinical and Endoscopic Improvement	Definition of Clinical Remission	Definition of Clinical Response	Definition of Endoscopic Remission
Costello	2017	Mild-to-moderate UC (Mayo score 3–10, with endoscopic subscore ≥2)	Mayo score <3 and endoscopic Mayo score ≤1	SCCAI ≤2	≥3 point reduction in Mayo score	Mayo endoscopic score ≤1
Moayyedi	2015	Mild-to-moderate UC (Mayo score ≥4, with endoscopic subscore ≥1)	Mayo score <3 and endoscopic Mayo score = 0	Mayo score <3	≥3 point reduction in Mayo score	Mayo endoscopic score = 0
Paramsothy	2017	Mild-to-moderate UC (Mayo score 4–10, with endoscopic subscore ≥1)	Mayo score <3 and ≥1 reduction in endoscopic Mayo score	Mayo score <3	≥3 point reduction in Mayo score, or 50% or greater reduction from baseline in combined rectal bleeding plus stool frequency subscores, or both	Mayo endoscopic score = 0
Rossen	2015	Mild-to-moderate UC (SCCAI 4–11, with endoscopic subscore ≥1)	SCCAI ≤2 and ≥1 reduction in endoscopic Mayo subscore	SCCAI ≤2	≥1.5 point reduction in SCCAI	Mayo endoscopic score = 0

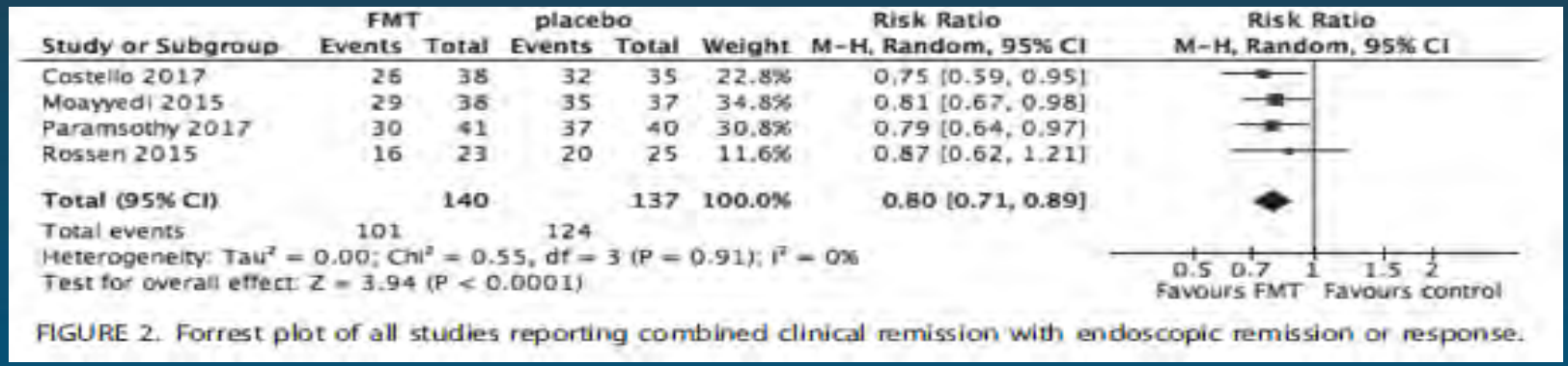


FIGURE 2. Forrest plot of all studies reporting combined clinical remission with endoscopic remission or response.

Narula *et al*,. IBD 2017;23:1702-9.

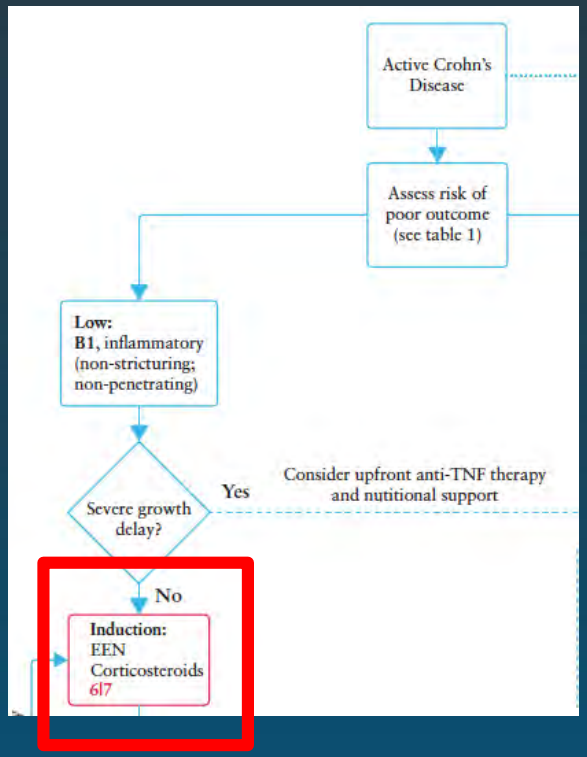
EEN: Guidelines and Mechanisms

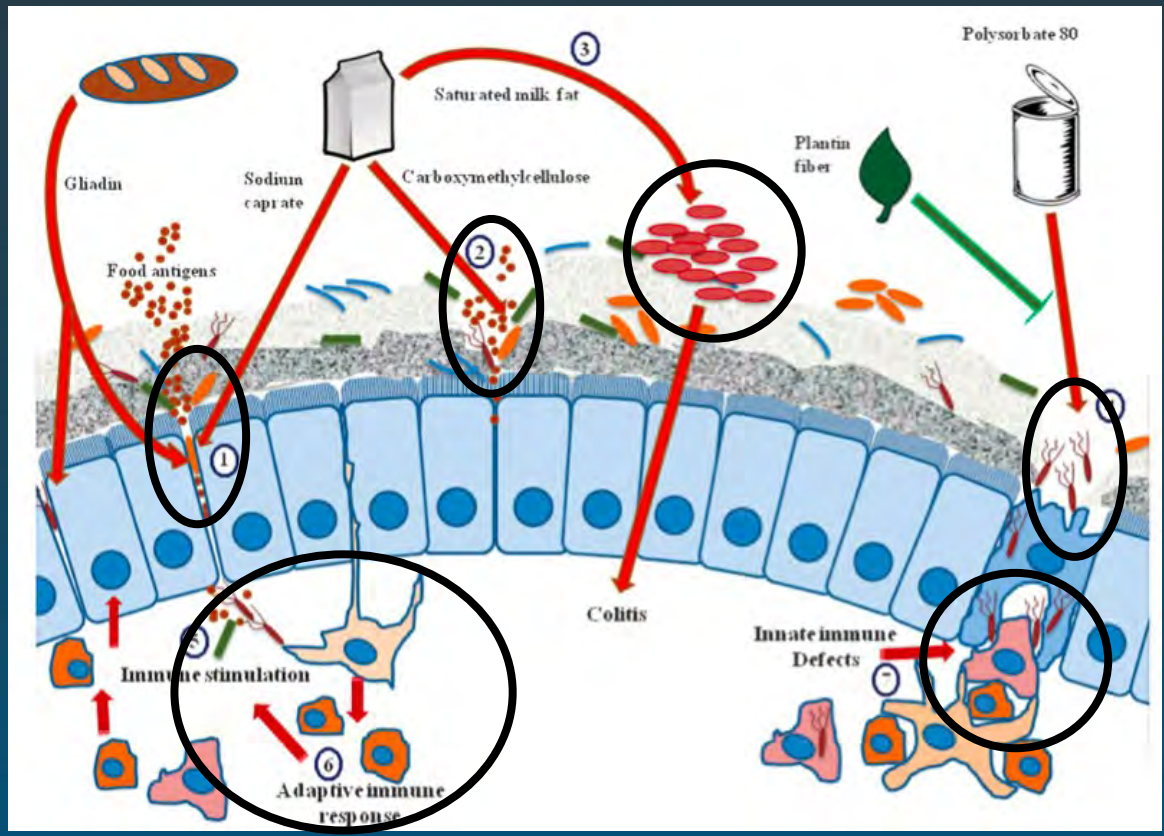
European Crohn's and Colitis Organisation

ESPGHAN

ECCO-ESPGHAN statement 6

In children with active luminal CD, dietary therapy with exclusive enteral nutrition [EEN] is recommended as first line for induction of remission. LoE: 2 | Agreement: 92%.





Van Rheenen *et al*. Journal of Crohn's and Colitis 2021;15:171-94.

Levine & Wine, Inflamm Bowel Dis 2013;19:1322-9.

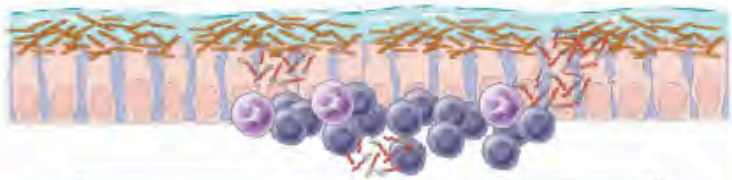
Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial

Arie Levine,[1,§] Eytan Wine,[2,§] Amit Assa,[3,4] Rotem Sigall Boneh,[1] Ron Shaoul,[5] Michal Kori,[6] Shlomi Cohen,[7] Sarit Peleg,[8] Hussein Shamaly,[9] Avi On,[10] Peri Millman,[11] Lee Abramas,[1] Tomer Ziv-Baran,[4] Shannan Grant,[12,13] Guila Abitbol,[14] Katherine A. Dunn,[15] Joseph P. Bielawski,[15] and Johan Van Limbergen[13,16,17,§]

§ Co-senior author

Dietary Therapy: Crohn's Disease Exclusion Diet + Partial Enteral Nutrition vs. Exclusive Enteral Nutrition

Western Diet



Habitual Diet Triggering Crohn's Disease
Increased Proteobacteria Dysbiosis, Intestinal permeability, Inflammation, Active Disease

EEN

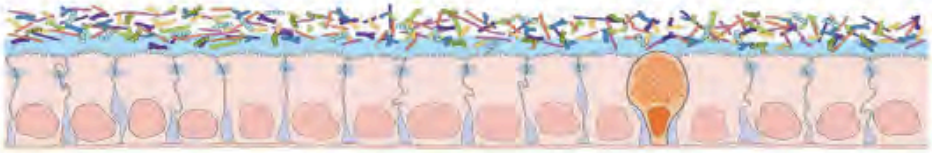
Western Diet

CDED+PEN

CDED

Remove
Animal Fat
Wheat
Dairy
Red Meat
Emulsifiers
Maltodextrin
Carrageenan

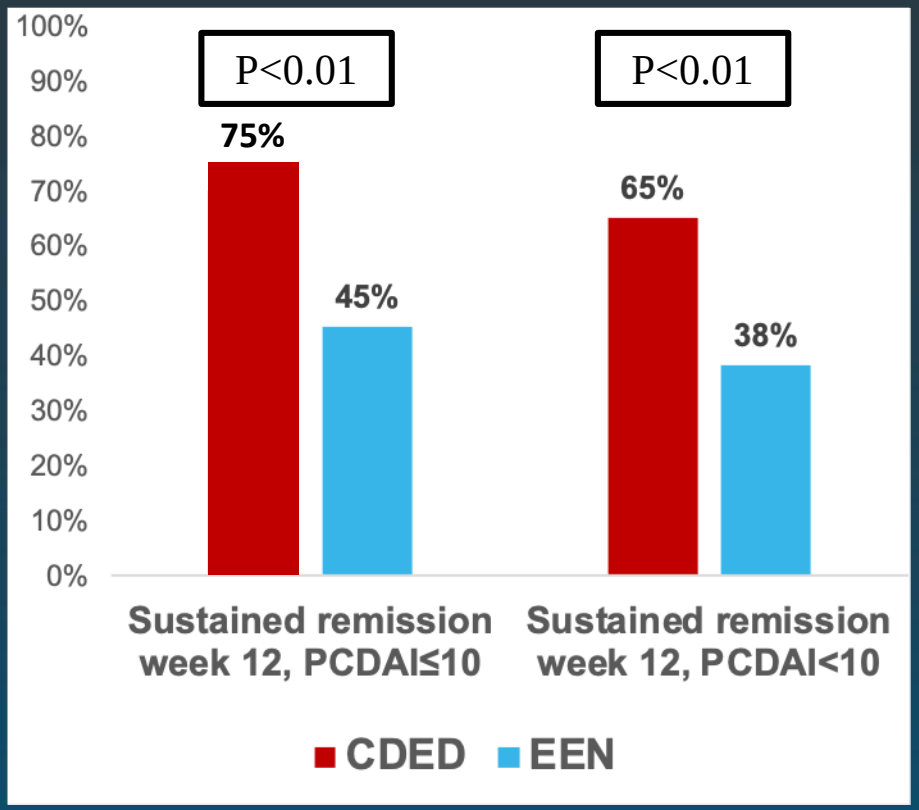
Add
Fruits
Vegetables

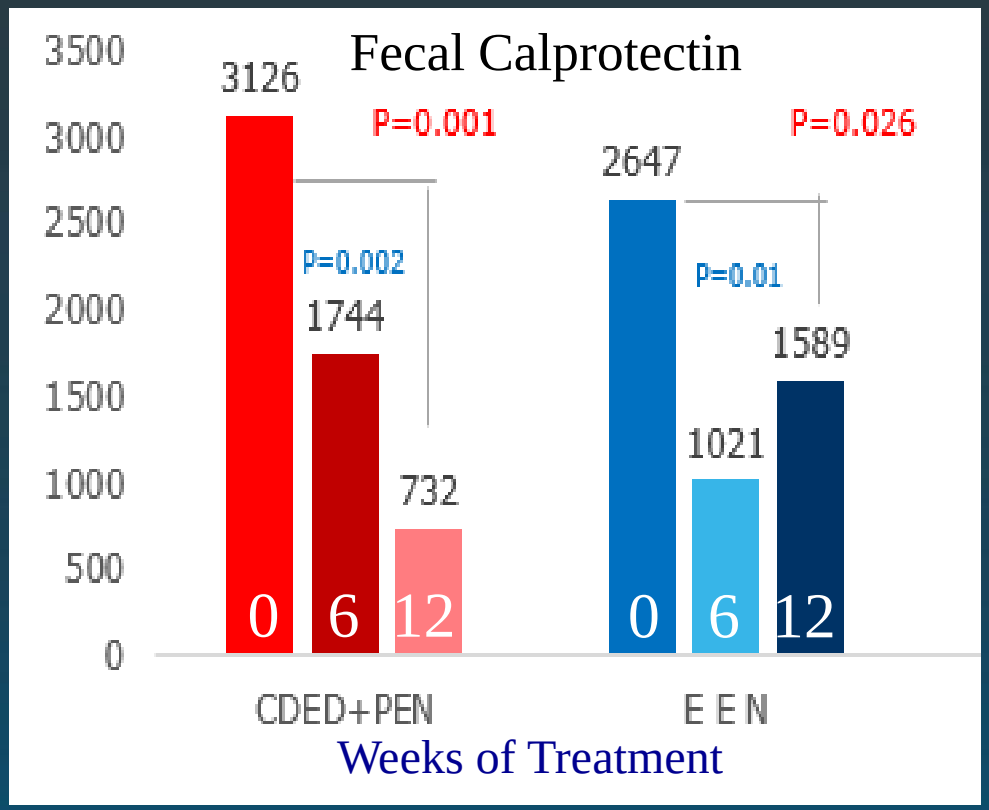


Crohn's Disease Exclusion Diet+ PEN vs. EEN
Primary endpoint: CDED+PEN is better tolerated than EEN
Secondary endpoints:
Both CDED+PEN and EEN are effective to achieve remission at week 6
CDED+PEN is superior to sustain remission and reduce inflammation at week 12
CDED+PEN: associated with reduction in Proteobacteria and Intestinal Permeability

Levine, Wine, *et al. Gastroenterology 2019;157:440-50.*

Sustained Remission & Fecal Calprotectin are Superior at week 12 with CDED





What does this do to gut microbes?

Levine, Wine, *et al. Gastroenterology Aug 2019;157:440-50.*

- CDED: similar changes from week 0 weeks 6

- EEN: seen o 6 - not maint week

Metabolome Changes With Diet-Induced Remission in Pediatric Crohn's Disease

Gastroenterology ARTICLE IN PRESS

Mohammed Ghiboub,[1,2] Susanne Penny,[3] Charlotte M. Verburgt,[1,2] Rotem Sigall Boneh,[4] Eytan Wine,[5] Alejandro Cohen,[6] Katherine A. Dunn,[7] Devanand M. Pinto,[3] Marc A. Benninga,[2] Wouter J. de Jonge,[1,8] Arie Levine,[4] and Johan E. Van Limbergen[1,2,9]

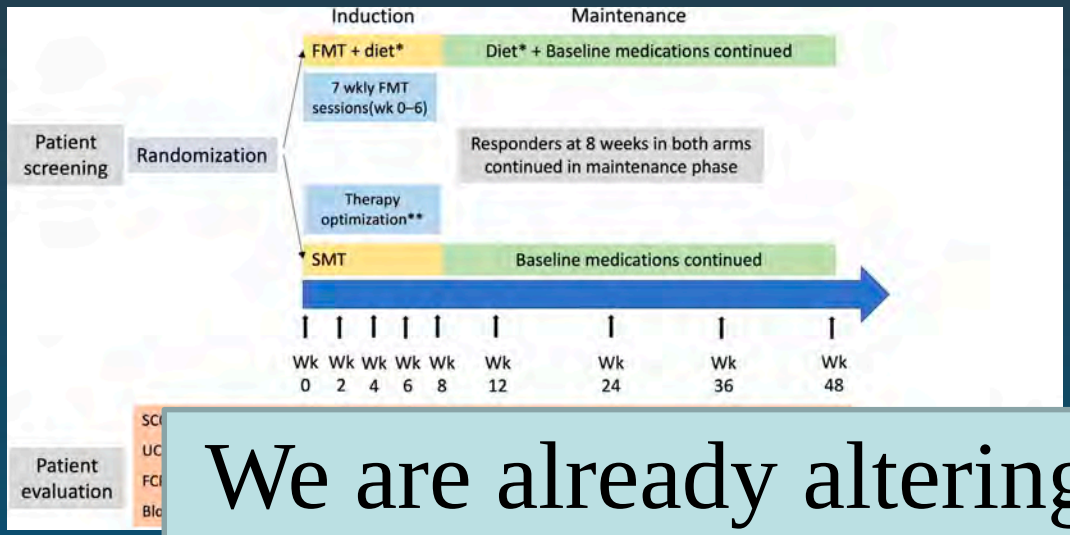
Successful Dietary Therapy in Paediatric Crohn's Disease is Associated with Shifts in Bacterial Dysbiosis and Inflammatory Metabotype Towards Healthy Controls

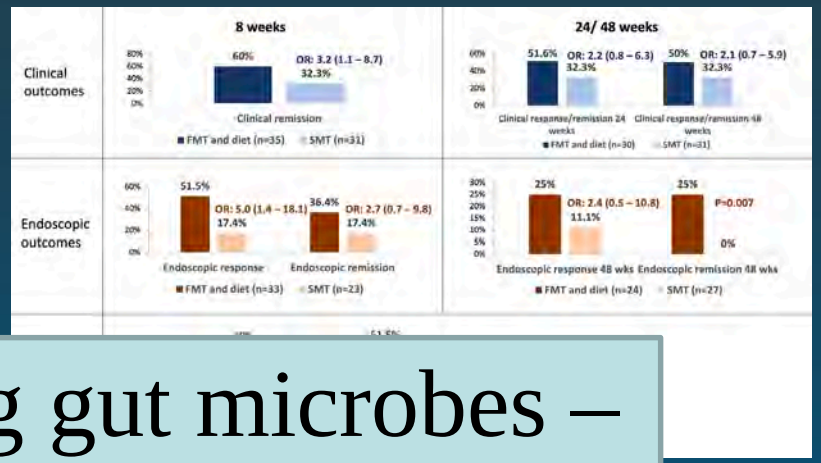
JCC

Charlotte M. Verburgt,[a,b,c*] Katherine A. Dunn,[d*] Mohammed Ghiboub,[a,b] James D. Lewis,[e,f] Eytan Wine,[g] Rotem Sigall Boneh,[h] Konstantinos Gerasimidis,[i] Raanan Shamir,[j] Susanne Penny,[k] Devanand M. Pinto,[k] Alejandro Cohen,[l] Paul Bjorndahl,[m] Vaios Svolos,[i] Joseph P. Bielawski,[e,m] Marc A. Benninga,[a] Wouter J. de Jonge,[b,m,n] Johan E. Van Limbergen[a,b,o]

Microbe-altering diets: UC

Faecal microbiota transplantation with anti-inflammatory diet (FMT-AID) followed by anti-inflammatory diet alone is effective in inducing and maintaining remission over 1 year in mild to moderate ulcerative colitis: a randomised controlled trial





We are already altering gut microbes – what's next??

Kedia *et al.*, Gut, in press.

Canada Future Directions: Altering the Microbiota

- Using microbes to direct therapy
- Microbial products and metabolites
- Using phages to change microbes
- Microbe-directed diets (fibre)
- Personalized diets

Central Hypothesis:

FFQ

Clinical Data

Previous Diet → **Response to Therapy**

16S rRNA

Altered Gut Microbes

Stool SCFA

Altered Gut Microenvironment

Stool Metabolomics

Overall objective: define relationship between diet, gut microbiome, and microenvironment in pediatric IBD, and how these correlate with clinical outcomes → goal of improving dietary therapy for IBD.

IMAGINE

Inflammation, Microbiome & Alimentation Gastro-Intestinal & Neuropsychiatric Effects

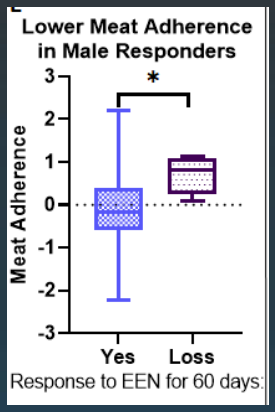
THE CANADIAN CHILDREN INFLAMMATORY BOWEL DISEASE NETWORK:

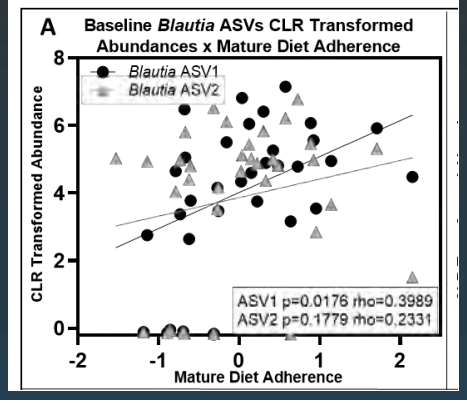
A PARTNERSHIP WITH THE child FOUNDATION

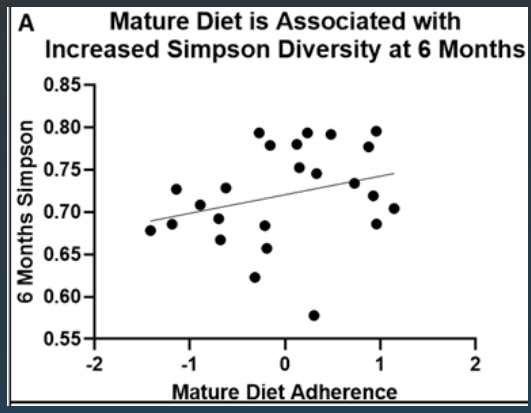
Preliminary Findings:

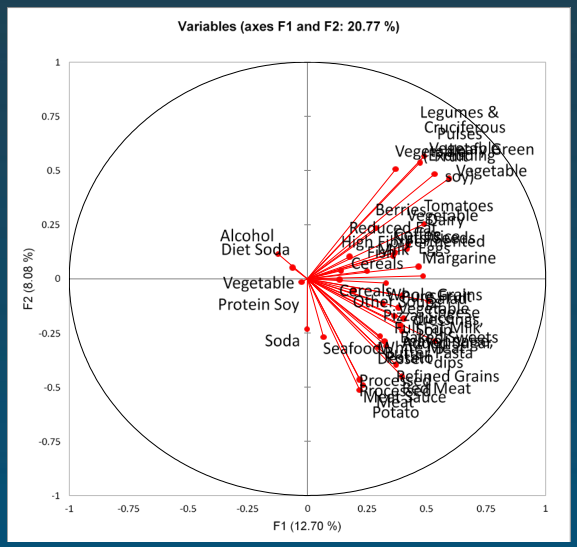
Dietary patterns and food correlations extracted from 96 Network patients (PCA-based)

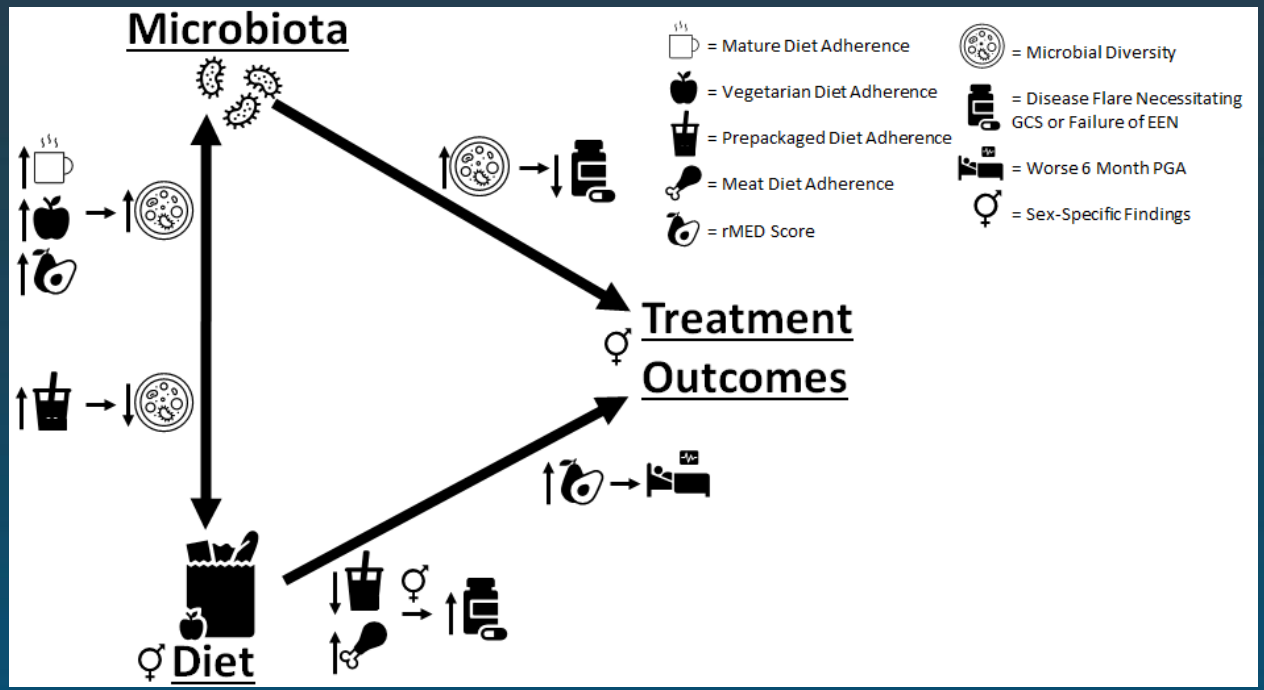
Vegetarian	Meat	Pre-Packaged	Mature
Whole Grains	Rice, Rice Noodles, Couscous	High Fiber Cereals	Chicken, Turkey without skin/fried
Vegetable Soup	Other Soups	Sugary Condiments	Fish
Soy/Tofu	RedMeat	Breaded Fish	Seafood
Salad Dressing	Pork	Diet Soda	Vegetables
Fruit	Liver Organs		Fruit
Full Fat Dairy	Chicken, Turkey with skin or fried		Coffee
Butter			Alcohol
			Milk Alternatives
Chicken, Turkey with skin/fried	Chicken, Turkey without skin	Lean Red Meat	Pizza
	Granola Bars	Processed Meat	











Dijk... & Wine. Paper under revisions.

THE CANADIAN CHILDREN INFLAMMATORY BOWEL DISEASE NETWORK:
A PARTNERSHIP WITH THE child FOUNDATION

Bacterial Components Suppress Th17

IMMUNOLOGY

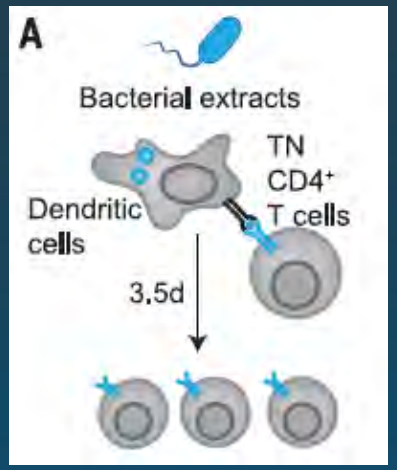
A conserved Bacteroidetes antigen induces anti-inflammatory intestinal T lymphocytes

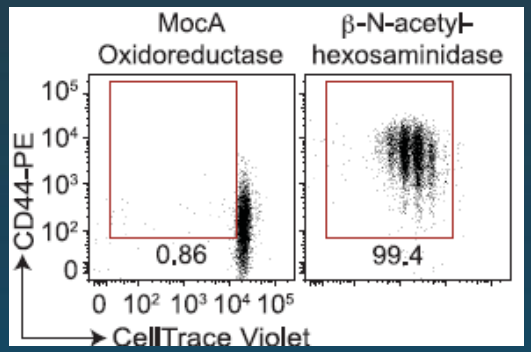
Djenet Bousbaine[1,2,3]†, Laura I. Fisch[2]‡, Mariya London[4]‡, Preksha Bhagchandani[2,3], Tiago B. Rezende de Castro[4,5], Mark Mimee[3,6,7], Scott Olesen[3,8], Bernardo S. Reis[4], David VanInsberghe[1,9], Juliana Bortolatto[5], Mathilde Poyet[3,8], Ross W. Cheloha[2], John Sidney[10], Jingjing Ling[2], Aaron Gupta[4], Timothy K. Lu[3,6,7], Alessandro Sette[10,11], Eric J. Alm[3,8], James J. Moon[12], Gabriel D. Victora[5], Daniel Mucida[4,13], Hidde L. Ploegh[2,3]*, Angelina M. Bilate[3,4]*

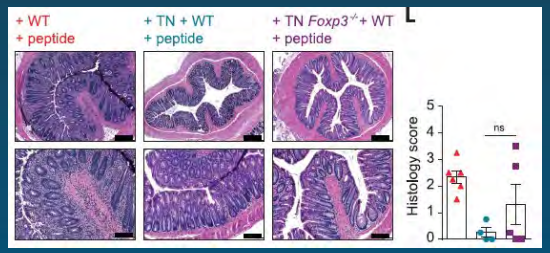
Bousbaine *et al.*, *Science* **377**, 660–666 (2022) 5 August 2022

Science

AAAS

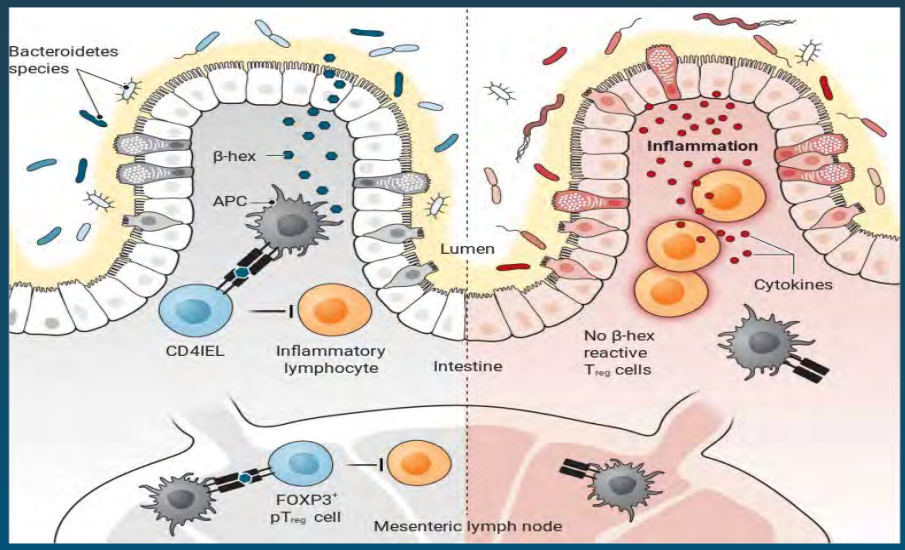






CD4IELs: protective

- Microbial metabolite drives protective CD4IELs
- Together with Tregs – suppressed inflammation
- Bacterial Ag prevents development of IBD in mice
- Could delivery of a bacterial antigen prevent IBD in humans?



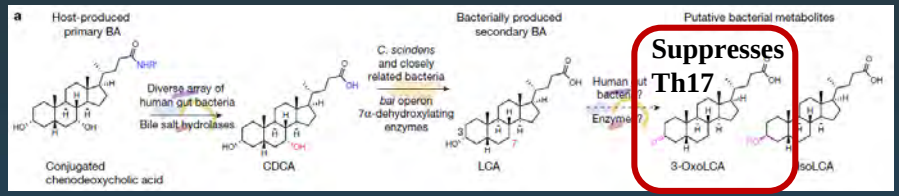
Shenoy & Koch. *Science* 2022;377:575-6.

Bacterial Metabolites Impacting Immunity

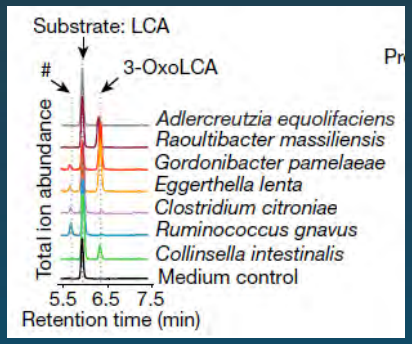
Human gut bacteria produce T_H17-modulating bile acid metabolites

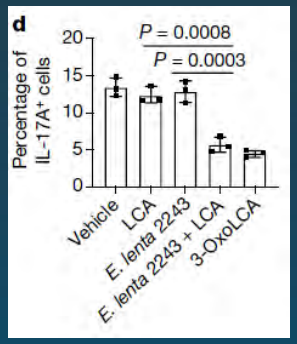
Donggi Paik[1,15], Lina Yao[2,15], Yancong Zhang[3,4], Sena Bae[4,5], Gabriel D. D'Agostino[2], Minghao Zhang[6], Eunha Kim[1], Eric A. Franzosa[4,5], Julian Avila-Pacheco[3], Jordan E. Bisanz[7], Christopher K. Rakowski[8], Hera Vlamakis[3,9], Ramnik J. Xavier[3,9,10,11], Peter J. Turnbaugh[7,12], Randy S. Longman[13], Michael R. Krout[8], Clary B. Clish[3], Fraydoon Rastinejad[6], Curtis Huttenhower[3,4,5], Jun R. Huh[1,14] & A. Sloan Devlin[2]

nature
International weekly journal of science

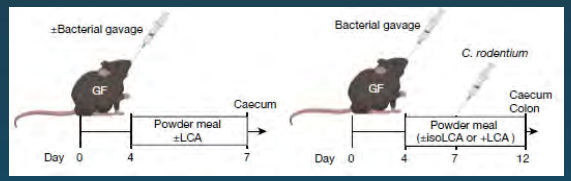


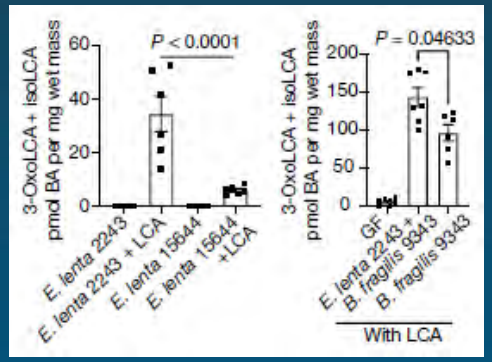
Bacterial 3-OxoLCA suppresses Th17



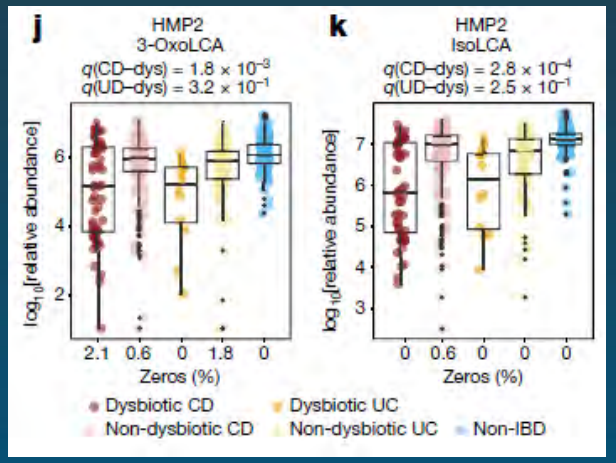


3-OxoLCA-producing bacteria prevent *C. rodentium* colitis

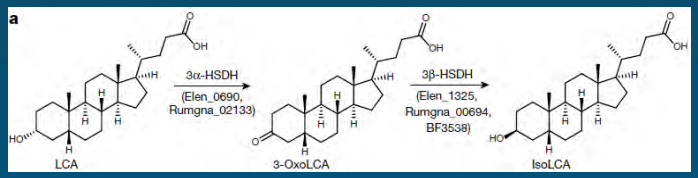




IBD patients (esp. with dysbiosis) have reduced OxoLCA and related microbes



Specific bacterial enzyme identified



Paik *et al.*, Nature 2022;603:907-12.
Wine. Gastroenterology 2022;163:333-4.

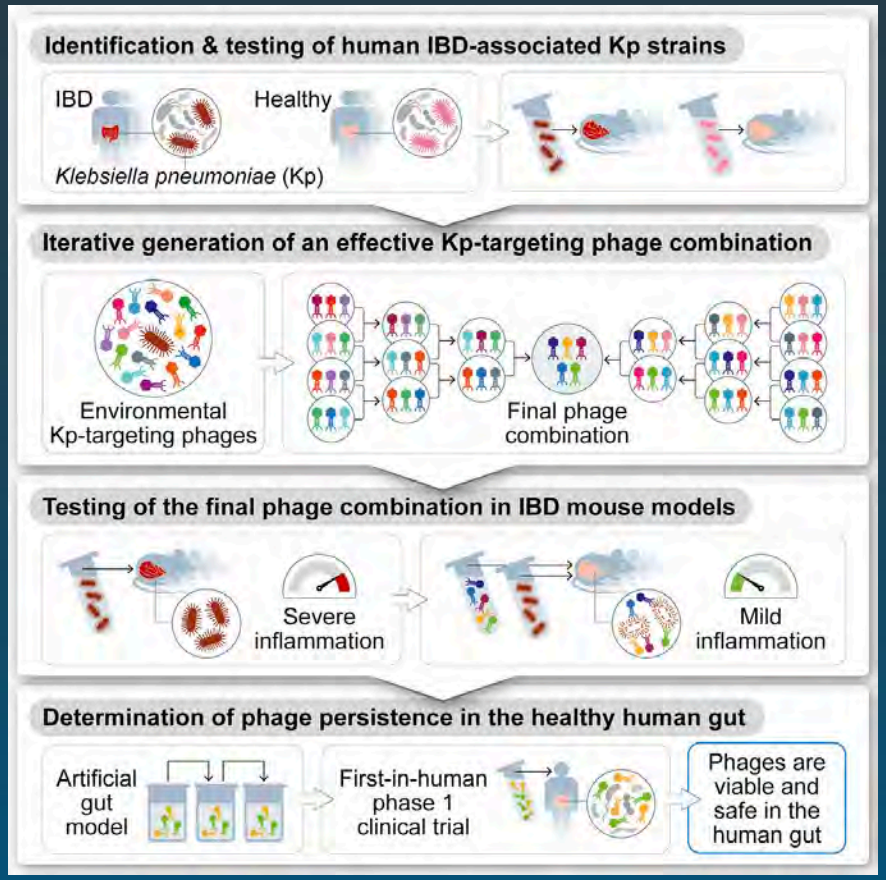
Phages Target Pathobionts in IBD

Targeted suppression of human IBD-associated gut microbiota commensals by phage consortia for treatment of intestinal inflammation

Cell

Cell *185*, 2879–2898, August 4, 2022

- Excellent rationale for suppressing pathobiont in IBD
- Feasibility of using phages for this goal
- Possible new microbe-altering therapeutic options



Wine. Gastroenterology 2022, *in press*.

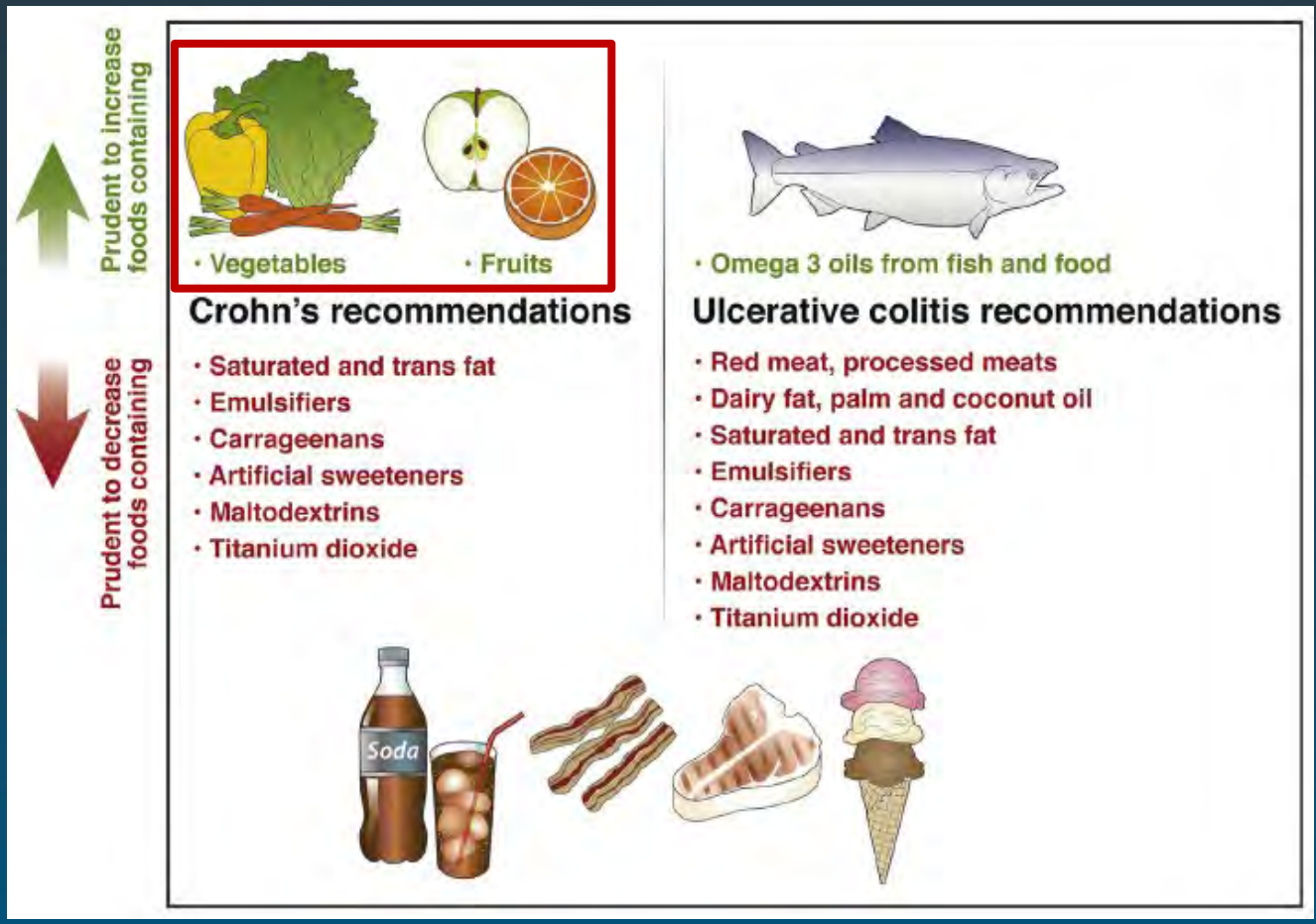
Federici *et al.*, Cell 2022;185:2879-98.

IOIBD dietary guidance: Fibre benefits in IBD

Dietary Guidance From the International Organization for the Study of Inflammatory Bowel Diseases

Arie Levine,[*,a] Jonathan M. Rhodes,[‡,a] James O. Lindsay,[§,a] Maria T. Abreu,[||,a] Michael A. Kamm,[¶,a] Peter R. Gibson,[#,a] Christoph Gasche,[**,a] Mark S. Silverberg,[‡‡,a] Uma Mahadevan,[§§,a] Rotem Sigall Boneh,[*] Eytan Wine,[||||,¶¶] Oriana M. Damas,[||] Graeme Syme,[##] Gina L. Trakman,[¶] Chu Kion Yao,[#] Stefanie Stockhamer,[‡‡] Muhammad B. Hammami,[§§] Luis C. Garces,[||] Gerhard Rogler,[***,a] Ioannis E. Koutroubakis,[‡‡‡,a] Ashwin N. Ananthakrishnan,[§§§] Liam McKeever,[|||||] and James D. Lewis[||||||,a]

Clinical Gastroenterology and Hepatology 2020;18:1381–1392



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)

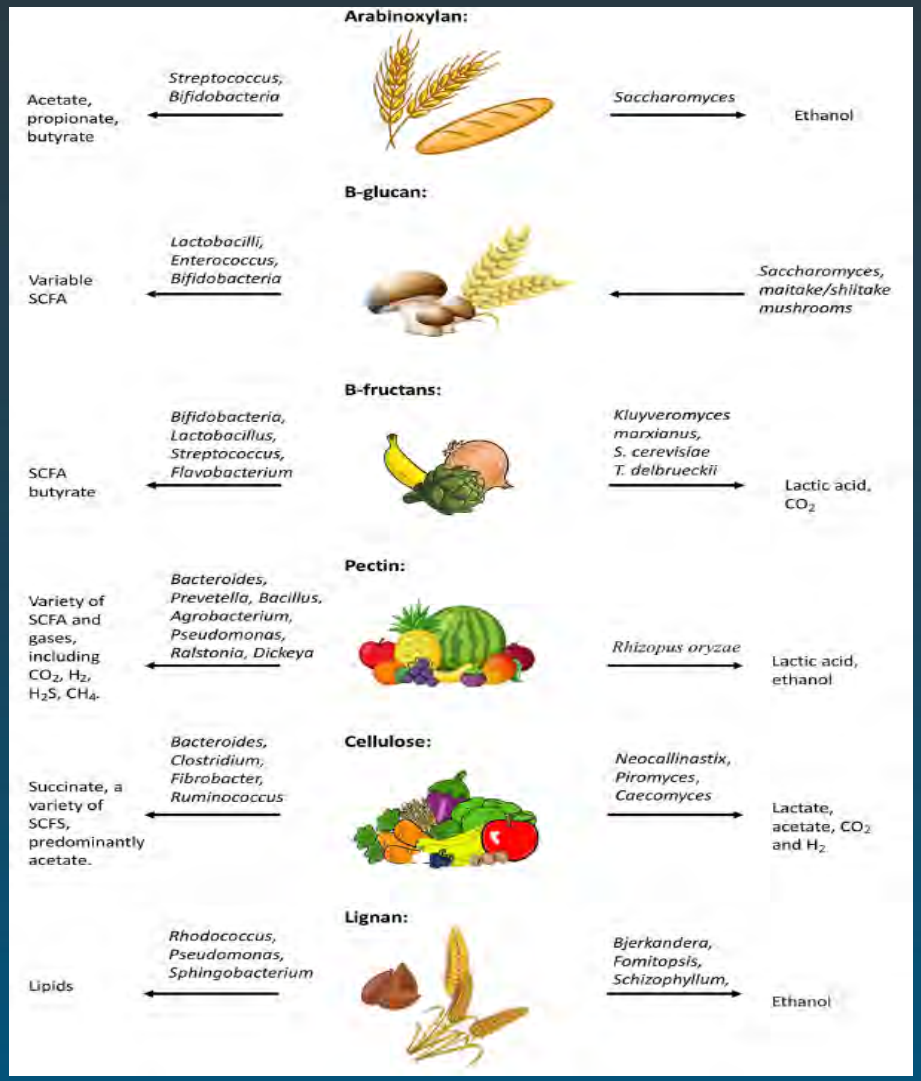
Food Groups	*n* (%)
Vegetables	39 (16.0%)
Fruits	27 (11.1%)
Cruciferous	27 (11.1%)
Tomato	25 (10.2%)
Green leafy vegetables	19 (7.8%)
Leguminous	14 (5.7%)
Spicy food	14 (5.7%)
Dairy products	10 (4.1%)
Fat products	10 (4.1%)
Citrus	8 (3.3%)
Oilseeds	7 (2.9%)
Sauce	7 (2.9%)
Alcohol	6 (2.5%)
Cereals	4 (1.6%)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

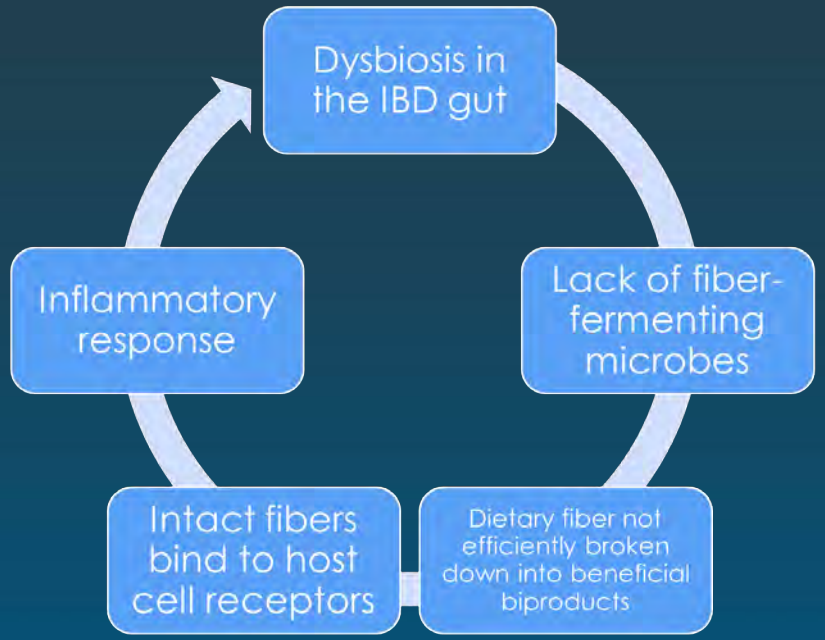
11) What food do you eat in case of relapse:	
–Low residue diet	126 (51.6 %)
–Normal diet	62 (25.4 %)
–Dairy-free	34 (13.9 %)
–Other diet	28 (11.5 %)
–Gluten-free	4 (1.6%)
–NR	24 (9.8%)

Not All Fibers Are Born Equal; Variable Response to Dietary Fiber Subtypes in IBD

Heather Armstrong [1,2], Inderdeep Mander [1], Zhengxiao Zhang [1,3], David Armstrong [4] and Eytan Wine [1,2,5]*

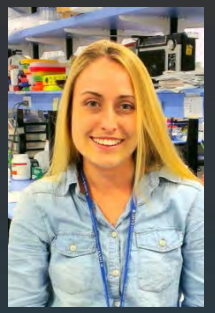


Hypothesis: unfermented fibre (dysbiosis in IBD) can stimulate a proinflammatory immune response

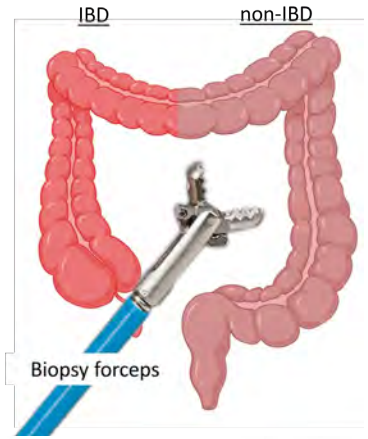


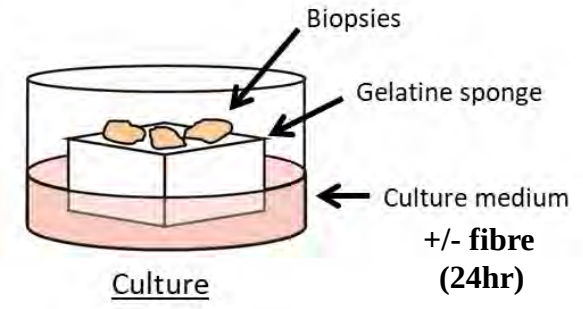
Armstrong *et al.*, Front Pediatr 2021;8:620189.

Inulin/oligofructose induce IL-1β secretion in Macrophage and in biopsies cultured *ex vivo*

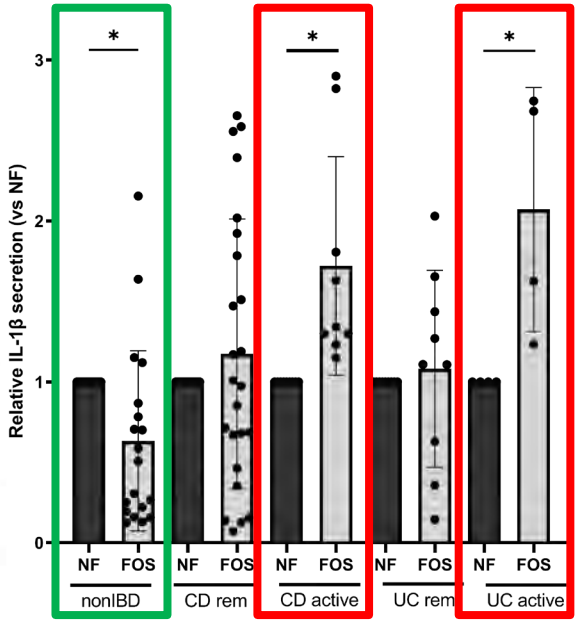


Heather Armstrong
Former Postdoc

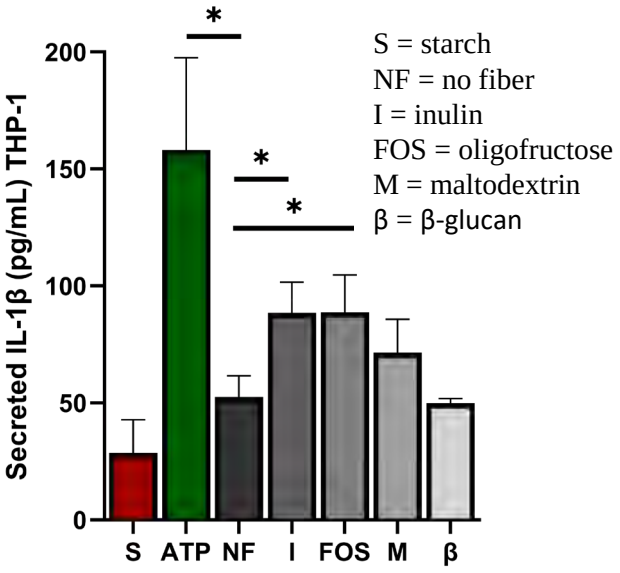




FOS promotes IL-1β secretion for biopsies *ex vivo*, only in active IBD



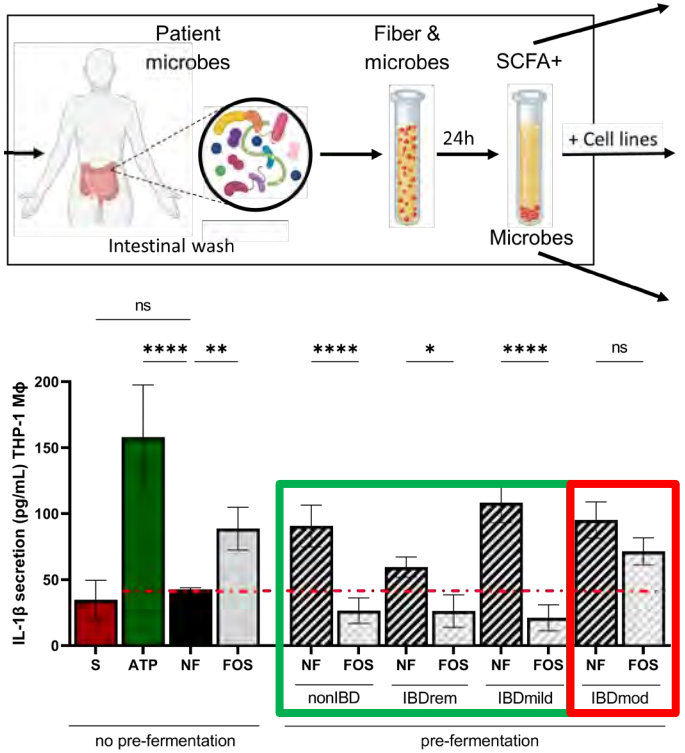
Differential IL-1β secretion from macrophages *in vitro*



Armstrong... & Wine. *Gastroenterology, in press.*

Mucosal Microbes Reduce IL-1β, but not with Active IBD

Microbial communities, incubated with FOS, suppress IL-1β secretion by macrophages, but increase IL-1β when collected from active IBD

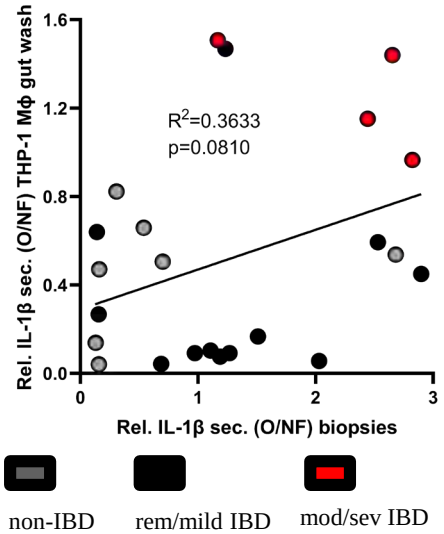


What happens to fibre fermentation?

How does this affect human cells?

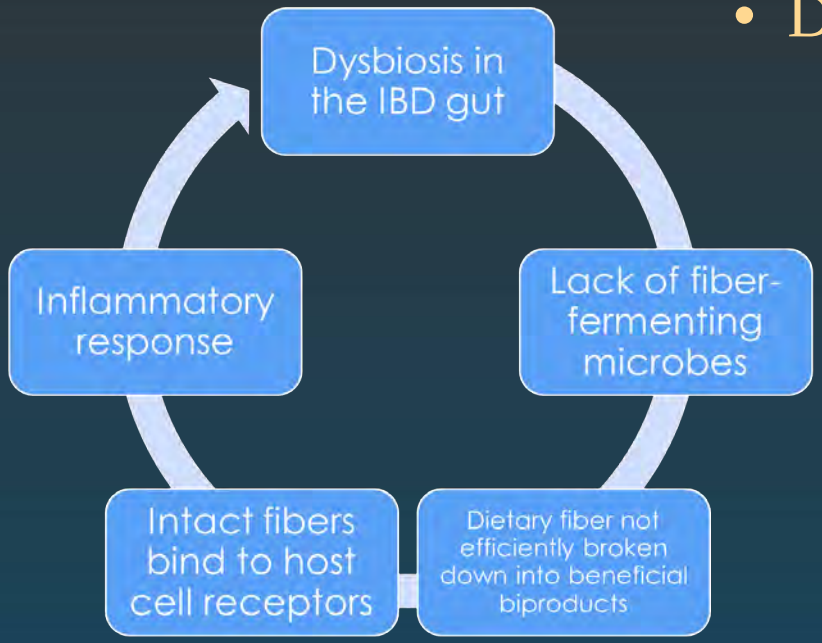
How are microbes involved?

FOS-induced microbial effects on IL-1β secretion by macrophages correlates with impacts on biopsies



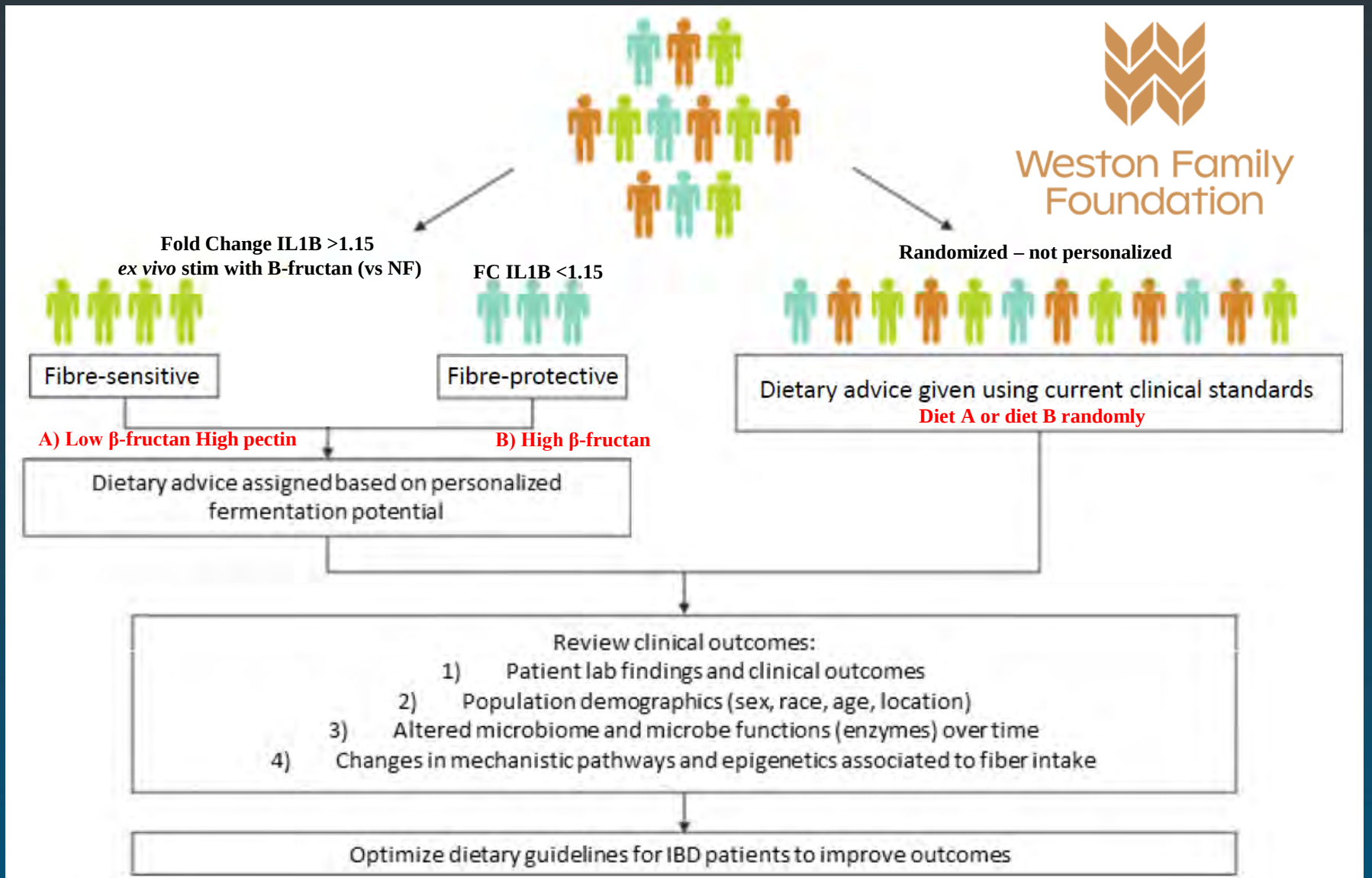
Armstrong... & Wine. *Gastroenterology, in press.*

Our Findings to Date



- Dietary fibres (inulin/oligofructose)
  - ➢ Pro-inflammatory in specific immune cell types and anti- in others
  - ➢ Promote inflammation in pediatric IBD biopsy tissues
  - ➢ Greater in patients with active inflammation
- Select microbes are able to ferment these fibers and reduce inflammation
- Dietary fiber intake in pediatric patients correlates with inflammation
- Potential for precision medicine: patient-specific dietary recommendations

Developing and testing PERSONALIZED DIETS



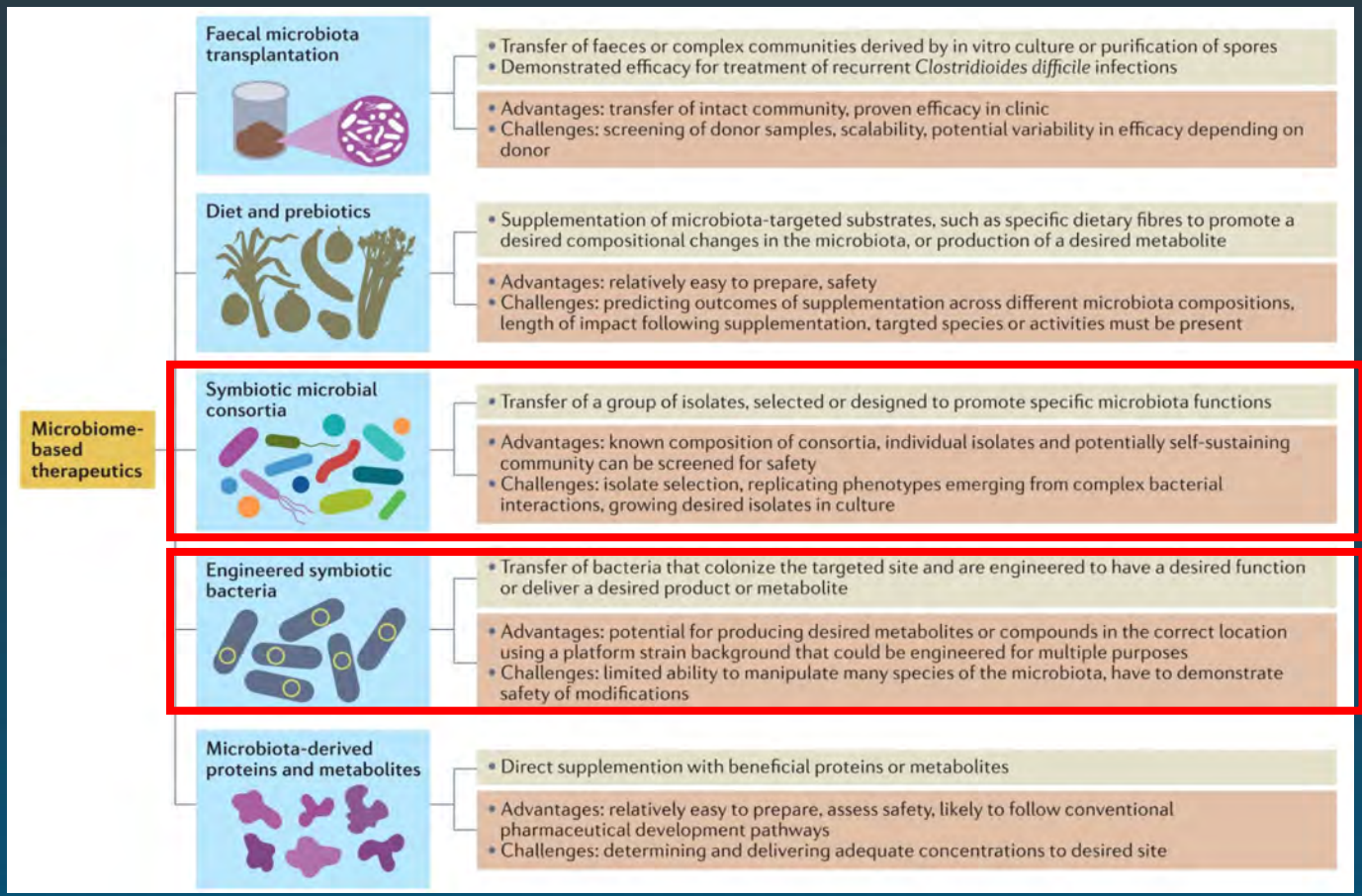
Additional Microbe-Altering Approaches

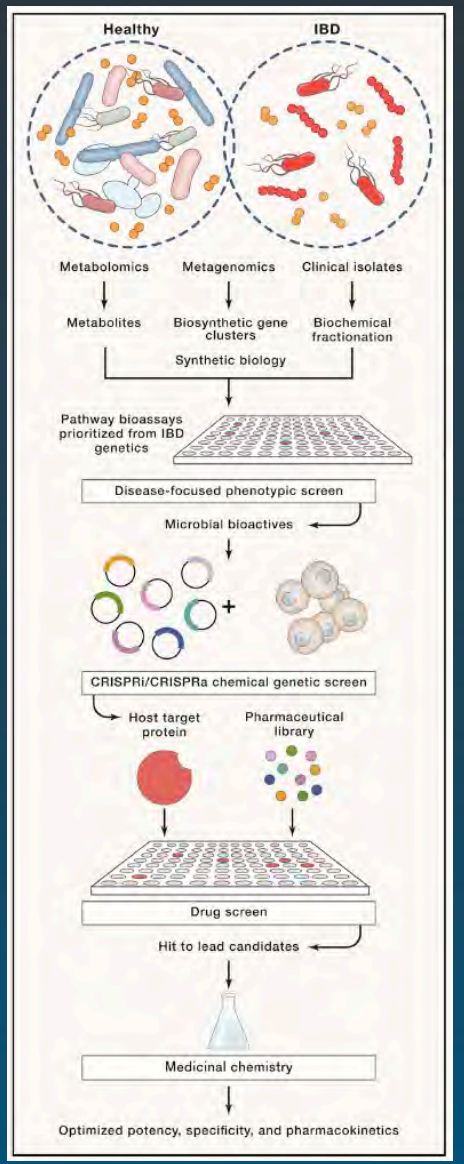
Therapeutic Opportunities in Inflammatory Bowel Disease: Mechanistic Dissection of Host-Microbiome Relationships

Damian R. Plichta,[1] Daniel B. Graham,[1,2,3,4] Sathish Subramanian,[5] and Ramnik J. Xavier[1,2,3,4,*]

Microbiome-based therapeutics

Matthew T. Sorbara and Eric G. Pamer





Sorbara & Pamer. Nat Rev Microbiol 2022;20:365-80.
Plichta *et al.*, Cell 2019;178:1041-56.

The Canadian Children Inflammatory Bowel Disease Network:

A Partnership with the child Foundation

Role of Microbes in the Pathogenesis of PIBD: From Discovery, through Causation, to Novel Treatments

1A: Patients and Samples:
Inception Cohort
Prospective Collection { UC PSC VEO-IBD Controls
CIDsCaNN IMAGINE

1B: Samples: Stool, serum, biopsies, Washes

1C: Pathobiont Discovery:
a. Culture-enriched metagenomics
b. IgG-bound bacteria
c. Physical microenvironment
d. Mucus penetration

Table 1: *Cohorts, sample collection and data analyses*

Cohort	Patient #	Samples collected / key analyses	Key data analyses (details below)
Classic UC	75 stored + 100 new (3yr)	**Stool** (total n=250): 16S, 18S*, *selective metagenomics**, *culture-enriched metagenomics**, *bile acids**, *stool microenvironment**.	• Pathobiont discovery • Mucosa vs stool microbes • Correlation with response to therapy • Host-microbe interactions on gut-liver axis • Host-microbe interactions
PSC- IBD	25 stored + 20 new/yr x 3yr		
VEO-IBD	20 new/yr x 3yr	**Biopsies**: microbiome **Luminal washes**: *microenvironment, SCFAs*, bile acids**	
		Urine & Serum: *metabolomics*	

* analyses in *italics* will be done for selected patients only, based on initial screening

CIHR Team Grant Co-NPAs:
Bruce Vallance & Eytan Wine

Conclusions

- Microbial alterations in IBD – makes sense!
- We are already doing this!
- Challenges:
  - Defining normal; causality; treatment targets
  - Complexity and accessibility to clinicians: KT
- Opportunities:
  - Personalized therapies
  - Combination therapy: start with life-style; diet
  - Integrating new technologies and idea – culture shift
- Future outlook: microbes used to guide and treat IBD

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- IMAGINE SPOR Network

Crohn et Colite Canada
Crohn's and Colitis Canada

CIHR IRSC

Weston Family Foundation

SATURDAY, November 5, 2022
Canada Future Directions in IBD

IMAGINE
Inflammation, Microbiome & Alimentation | Gastro-Intestinal & Neuropsychiatric Effects

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