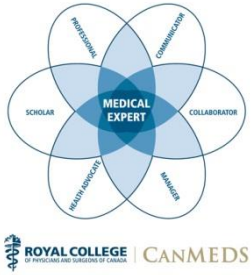
Diet-Microbial Interactions in IBD
From basics to clinics

Karen Madsen, PhD
University of Alberta

UNIVERSITY OF ALBERTA

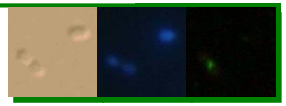


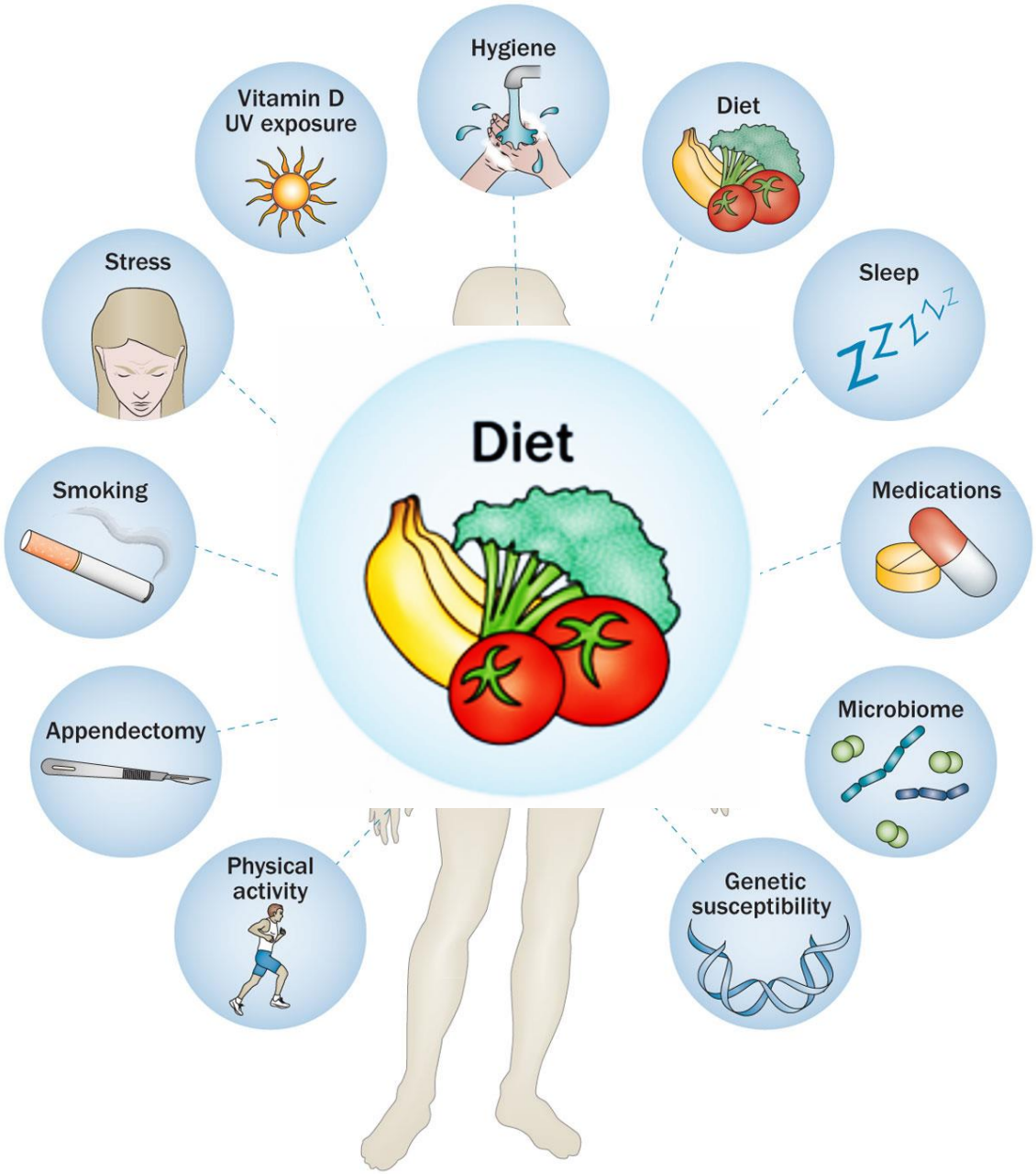
CanMEDS Roles Covered in this Session:

✓	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS framework.)
	Communicator (as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)
	Collaborator (as *Collaborators*, physicians effectively work within a healthcare team to achieve optimal patient care.)
	Manager (as *Managers*, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)
	Health Advocate (as *Health Advocates*, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)
	Scholar (as *Scholars*, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)

Disclosures

- Member of Scientific Advisor Board for Relypsa Pharmaceuticals





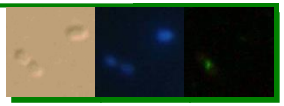
IBD – An interaction between genetics, immunology, environment and microbiome

Ananthakrishnan, A. N. (2015)
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2015.34

Diet and Risk of IBD

- **INCREASED RISK**
  - Total Fat
  - PUFA
  - Omega-6
  - Meat
- **DECREASED RISK**
  - Fiber (CD)
  - Fruits (CD)
  - Vegetables (UC)

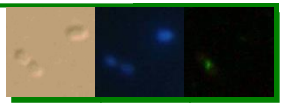
Hou et al. AJG 2011:106



Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study

- Followed a cohort of 67,581 women living in France between the ages of 40-65 from 1990-2005
- 77 incident IBD cases
  - 43 UC, 30 CD, 3 IC
- High intake of animal protein (1.72-4.46 g/kg) positively associated with increased risk of developing IBD showing a 3.3 fold increased risk of IBD
- Both fish and meat associated with risk, but not egg or dairy products

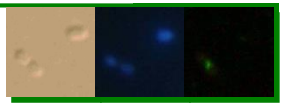
Jantchou et al. Am J Gastro 2010



A Prospective Study of Long-term Intake of Dietary Fiber and Risk of Crohn's Disease and Ulcerative Colitis

Ashwin N. Ananthakrishnan, M.D., M.P.H.[1], Hamed Khalili, M.D.[1], Gauree G. Konijeti, M.D., M.P.H.[1], Leslie M. Higuchi, M.D., M.P.H.[2], Punyanganie de Silva, M.B.B.S, M.R.C.P[1], Joshua R. Korzenik, M.D.[3], Charles S. Fuchs, M.D., M.P.H.[2,5], Walter C. Willett, M.D., Dr.P.H.[4,6], James M. Richter, M.D.[1], and Andrew T. Chan, M.D., M.P.H.[1,5]

- Nurses Health Study – 170,776 women followed over 26 yrs
- 269 incident cases of Crohn's disease and 338 cases of UC
- Intake of the highest quintile (median of 24.3 g/day) was associated with a 40% reduction in risk of CD, ***but not UC***
- Reduction greatest for ***fiber derived from fruits***
- Fiber from cereals, whole grains, or legumes did not modify risk.



REVIEW ARTICLE

Fiber in the Treatment and Maintenance of Inflammatory Bowel Disease: A Systematic Review of Randomized Controlled Trials

Linda Wedlake, MSc, RD,[*,†] *Natalie Slack, MSc, RD,*[†] *H. Jervoise N. Andreyev, PhD,*[‡] *and Kevin Whelan, PhD, RD*[†]

epublic of China

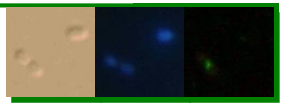
Dietary Fiber and Risk of Inflammatory Bowel Disease: Fact or Hype?

Editorials

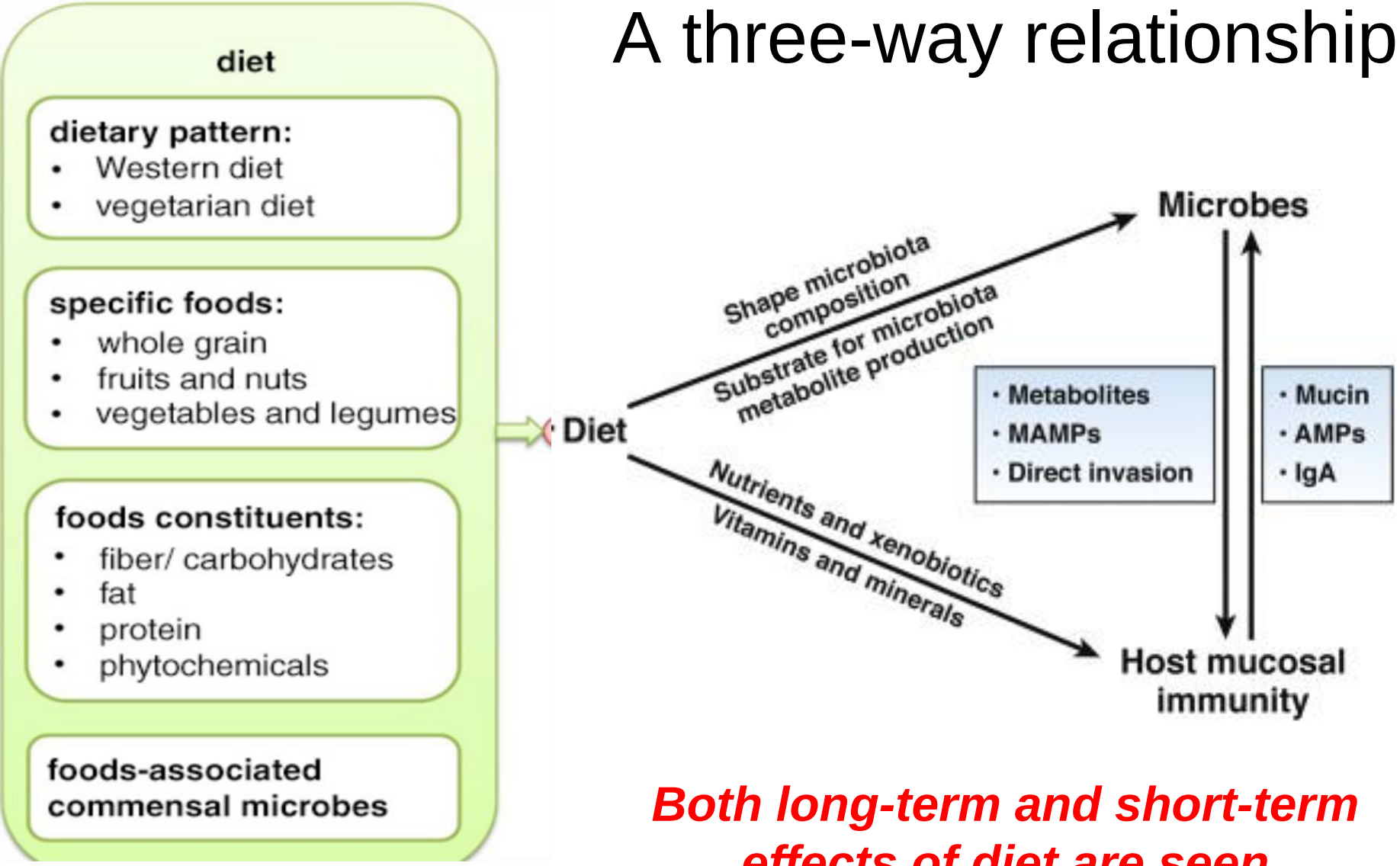
Does Consuming the Recommend Daily Level of Fiber Prevent Crohn's Disease?

How could diet trigger or modulate IBD?

- Direct effect of specific dietary components on host immune and physiological functions
  - *Glutamine, vitamin D, histadine, tryptophan, threonine, n-3 PUFA, curcumin, polyphenols, arginine, iron, n-6 PUFA*
- Indirect effects through altering composition or metabolic activities of gut microbes
  - *Alter SCFA production, increase levels of sulfite-reducing or invasive virulent strains*
- Defined diets may remove or reduce specific antigens/toxins/metabolites or alternatively provide specific immunomodulating compounds



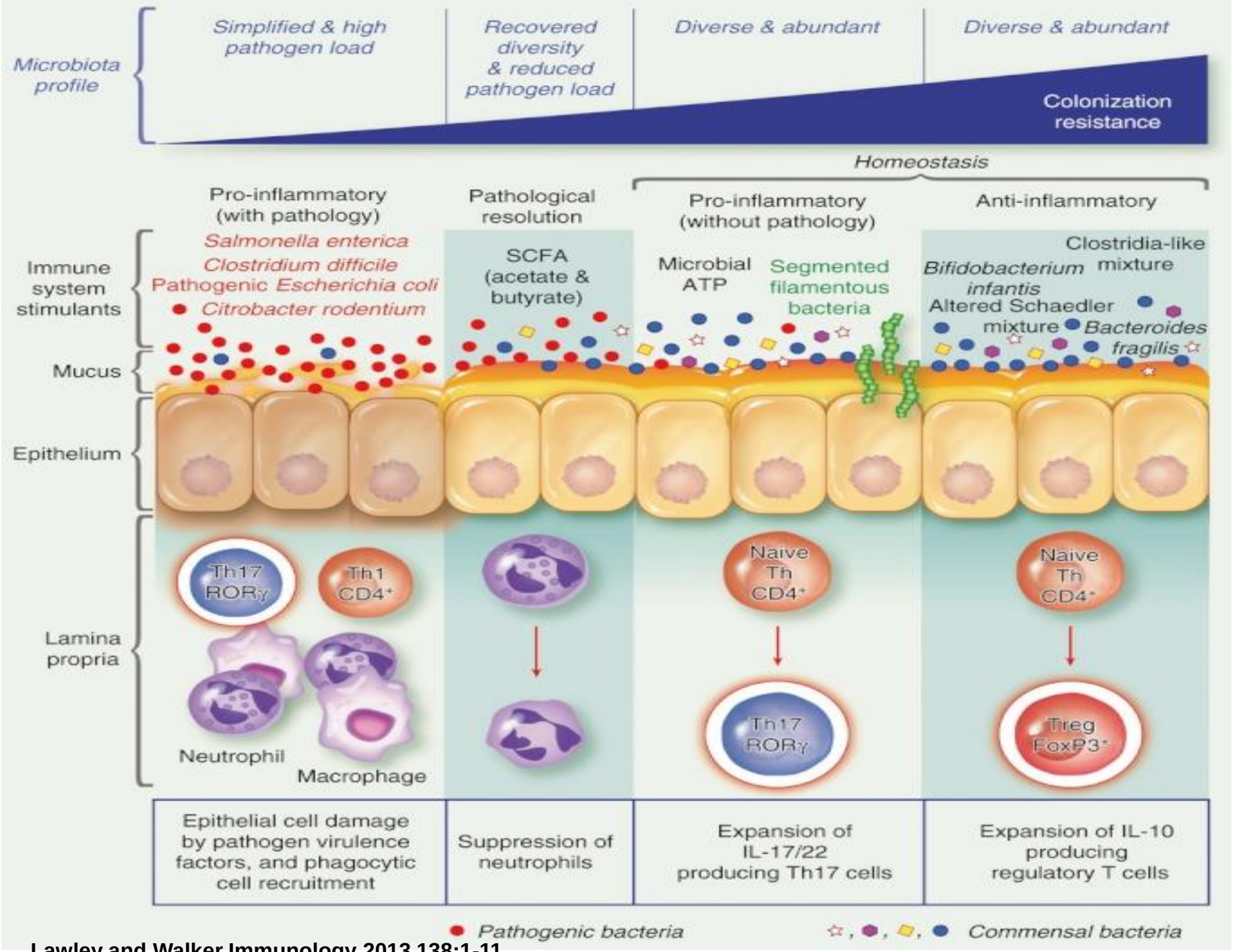
Diet – Microbes - Immunity
A three-way relationship



Both long-term and short-term effects of diet are seen

Gastroenterology, Volume 148, Issue 6, 2015, 1087–1106

MICROBES DRIVE MUCOSAL IMMUNE FUNCTION AND PROFILES THROUGH PRODUCTION OF METABOLITES AND MAMPS (TLR, NOD)

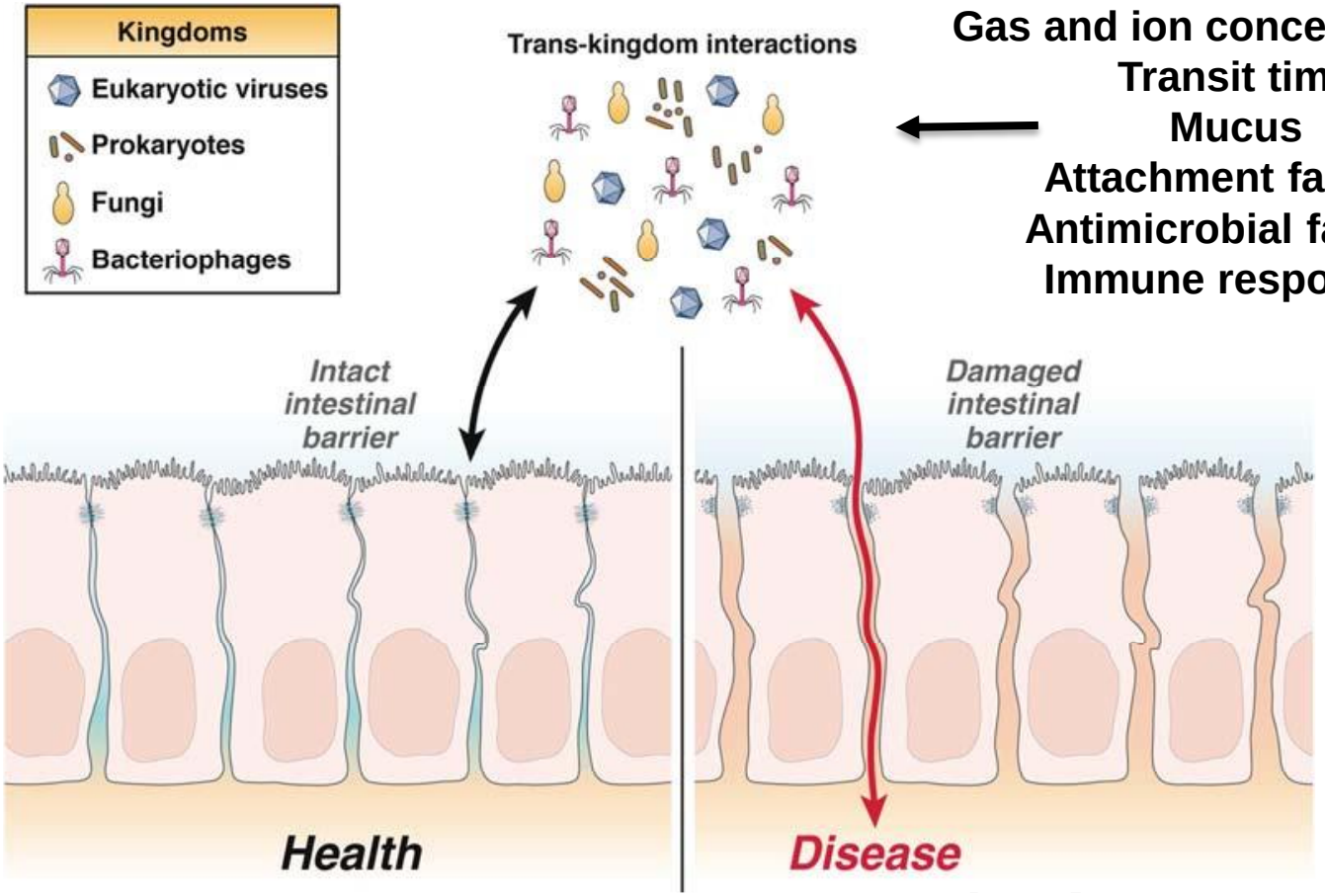


Lawley and Walker Immunology 2013 138:1-11

Predation
Competition
Parasitism
Mutualism

External (Diet)
Internal (Genetics)

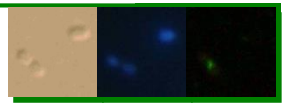
Nutrient availability
pH
Gas and ion concentrations
Transit time
Mucus
Attachment factors
Antimicrobial factors
Immune responses



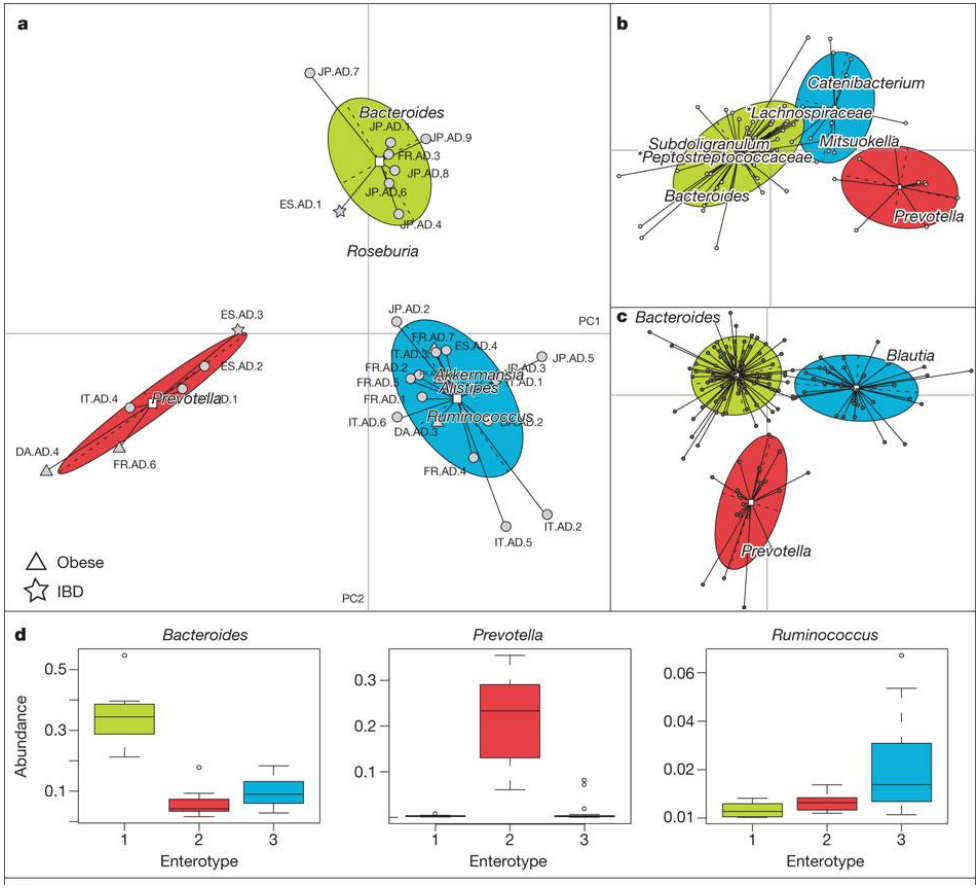
In 2011, we were divided into 3 enterotypes!

(Based on sequencing about 300 people…..)

Arumugam et al. Nature 473, 173-180. 2011



The Three “Enterotypes”



Enterotype 1

= High Bacteroides

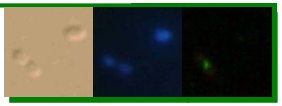
Enterotype 2

= High Prevotella

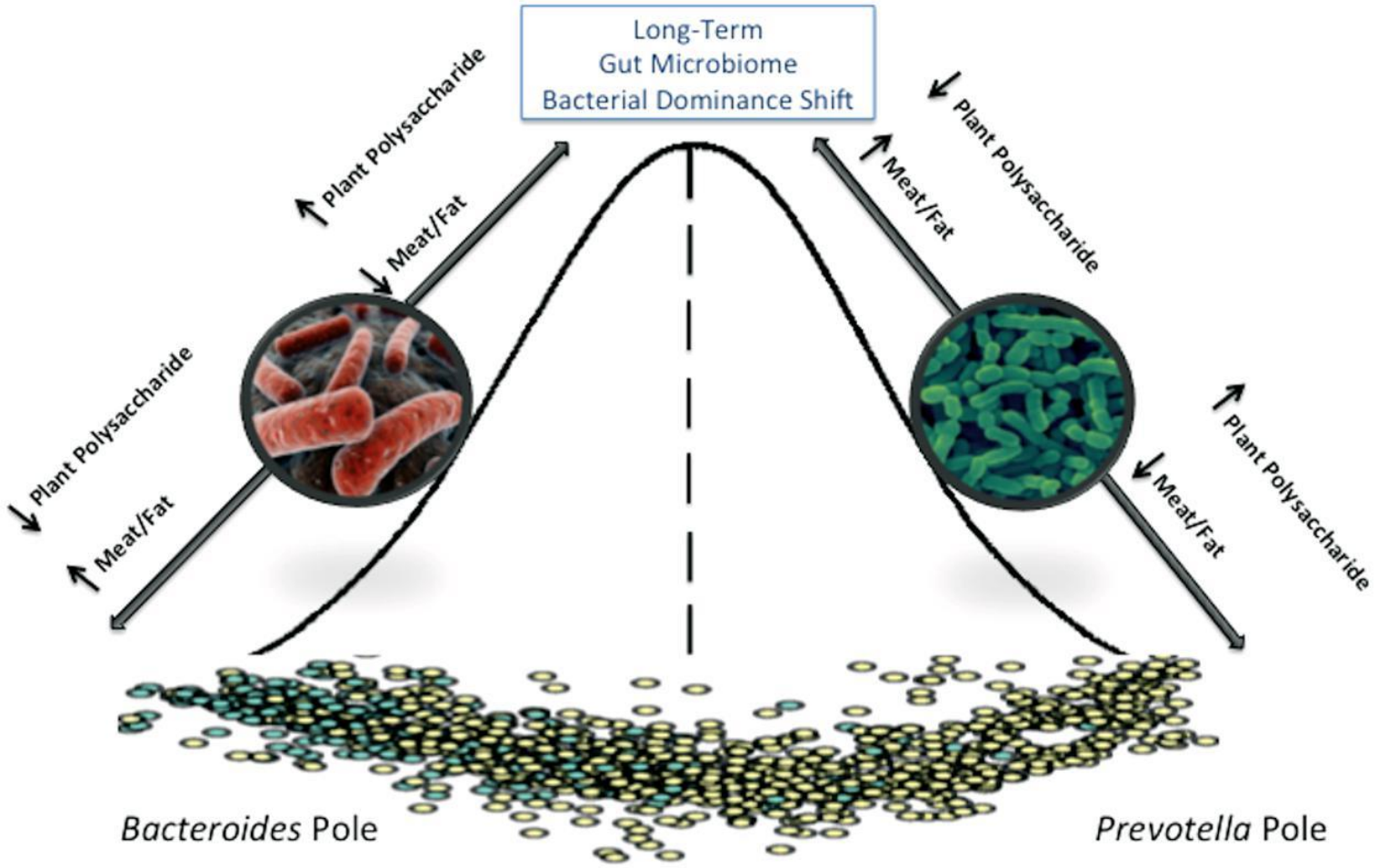
Enterotype 3

= High Ruminococcus

Arumugam et al. Nature 473, 173-180. 2011

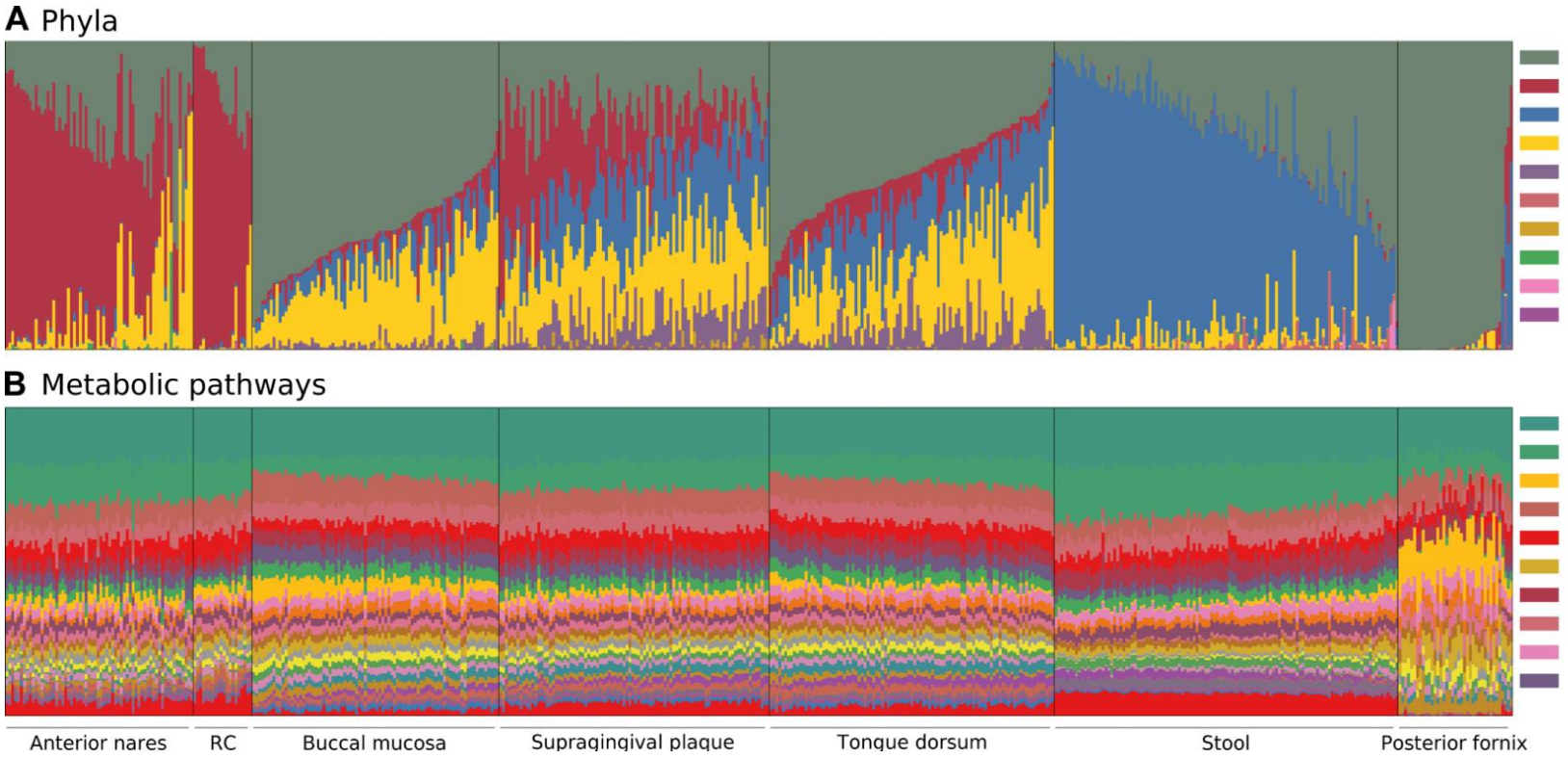


2016: Revision: More of a continuum
Diet is the main determinant of microbial composition

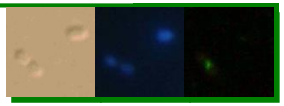


Voreades et al. Front. Microbiol. Sept 22, 2014

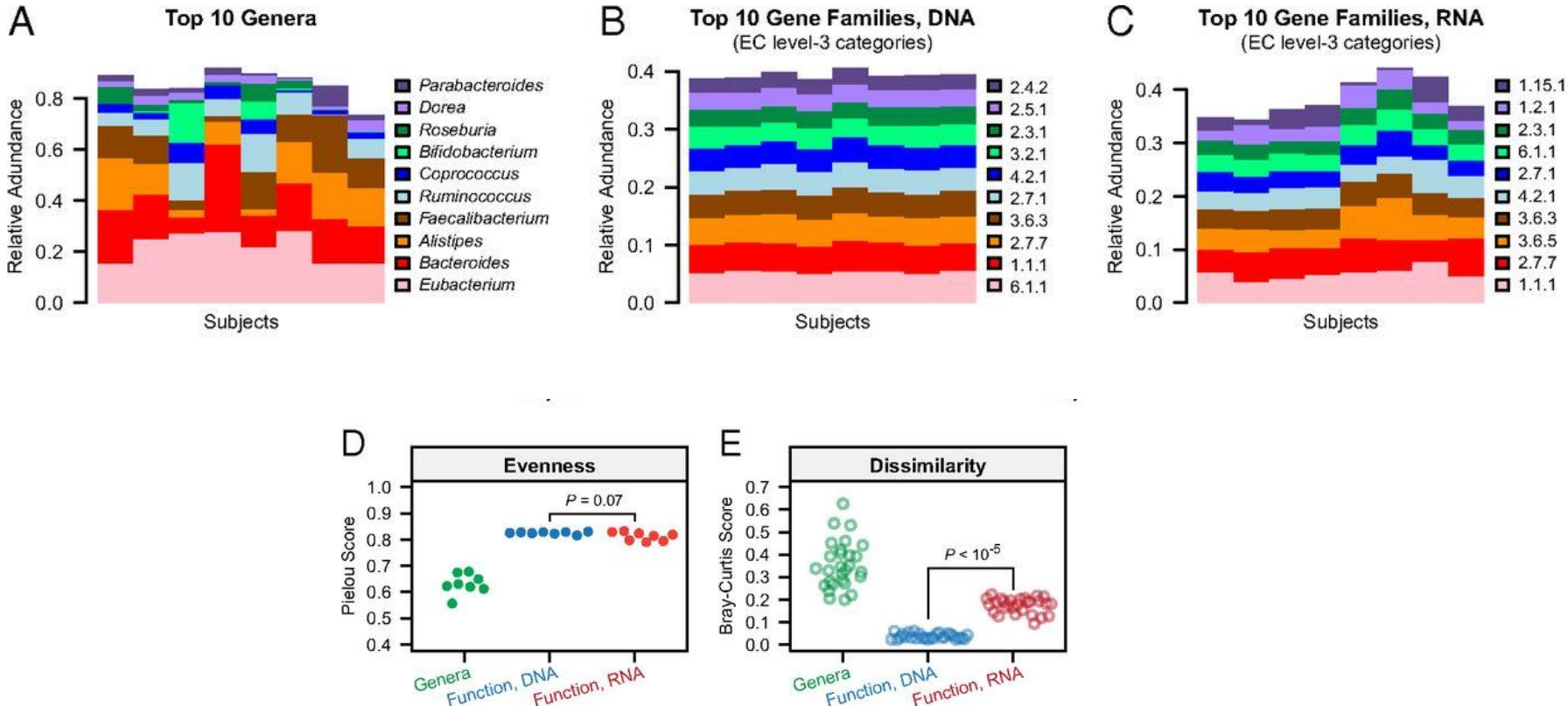
Extensive variability in microbial composition while metabolic pathways are more consistent



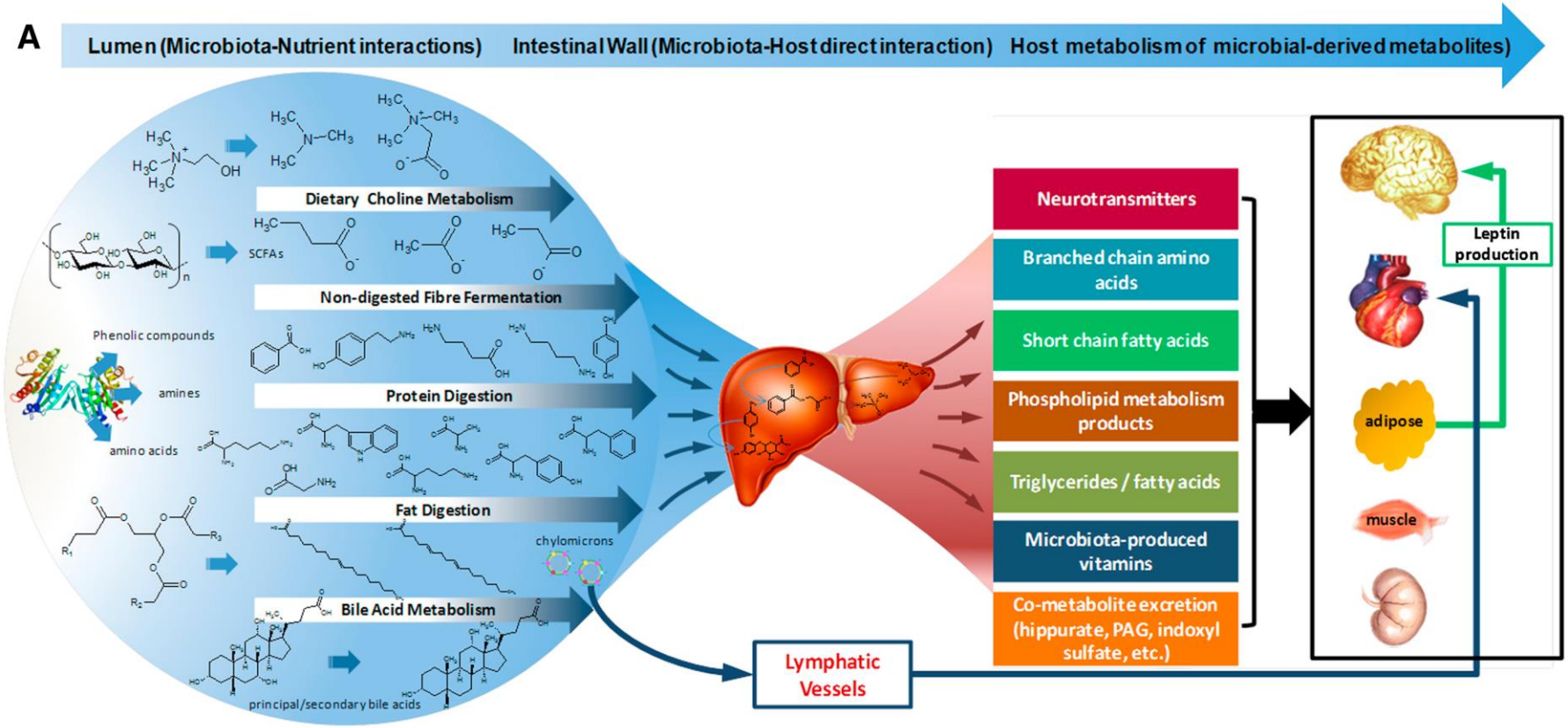
Nature 486(7402):207-214



More variability is seen at the transcriptional level



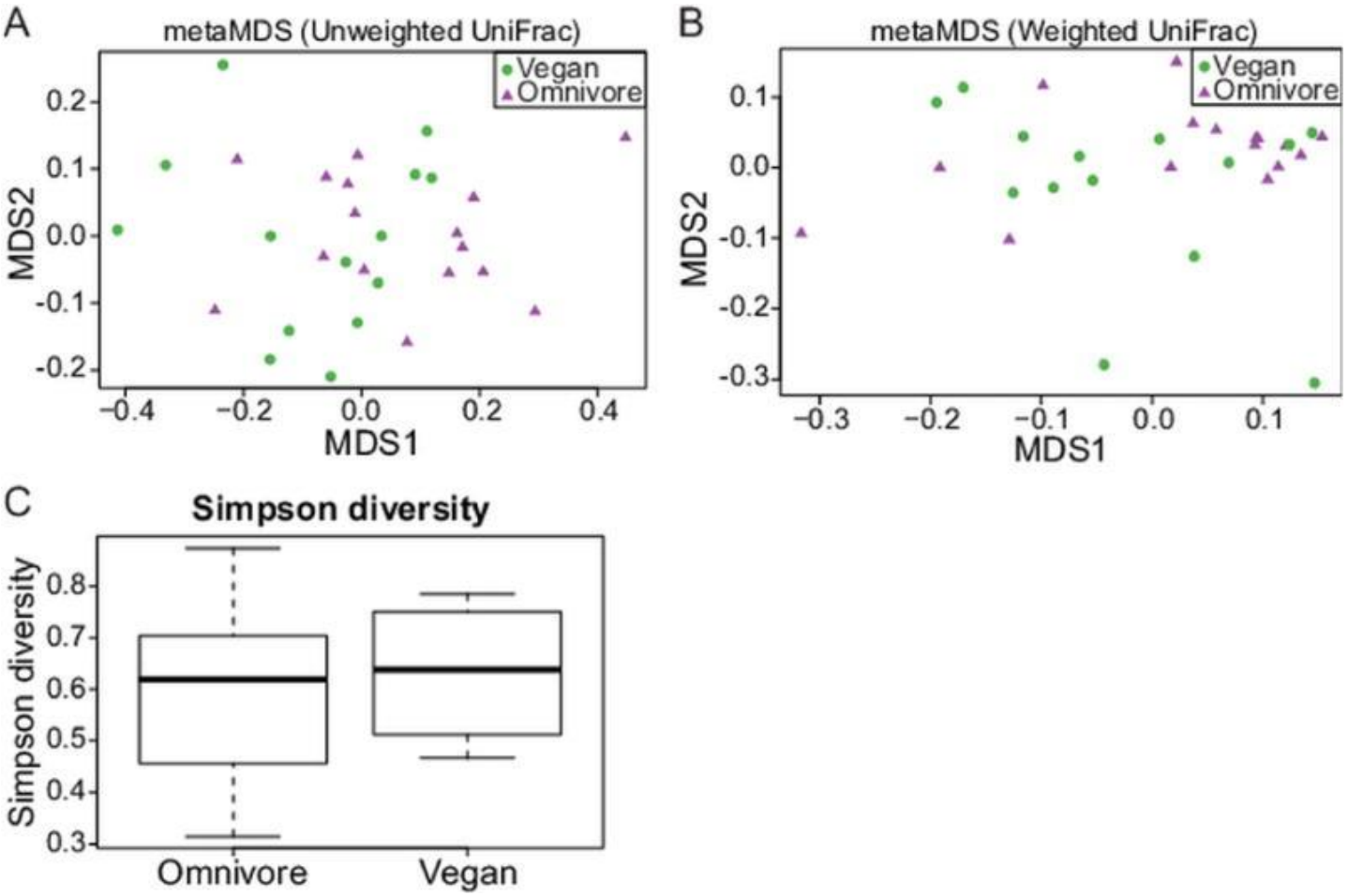
Eric A. Franzosa et al. PNAS 2014;111:E2329-E2338



Dietary compounds serve as substrates for use by gut microbiota for production of numerous small molecules

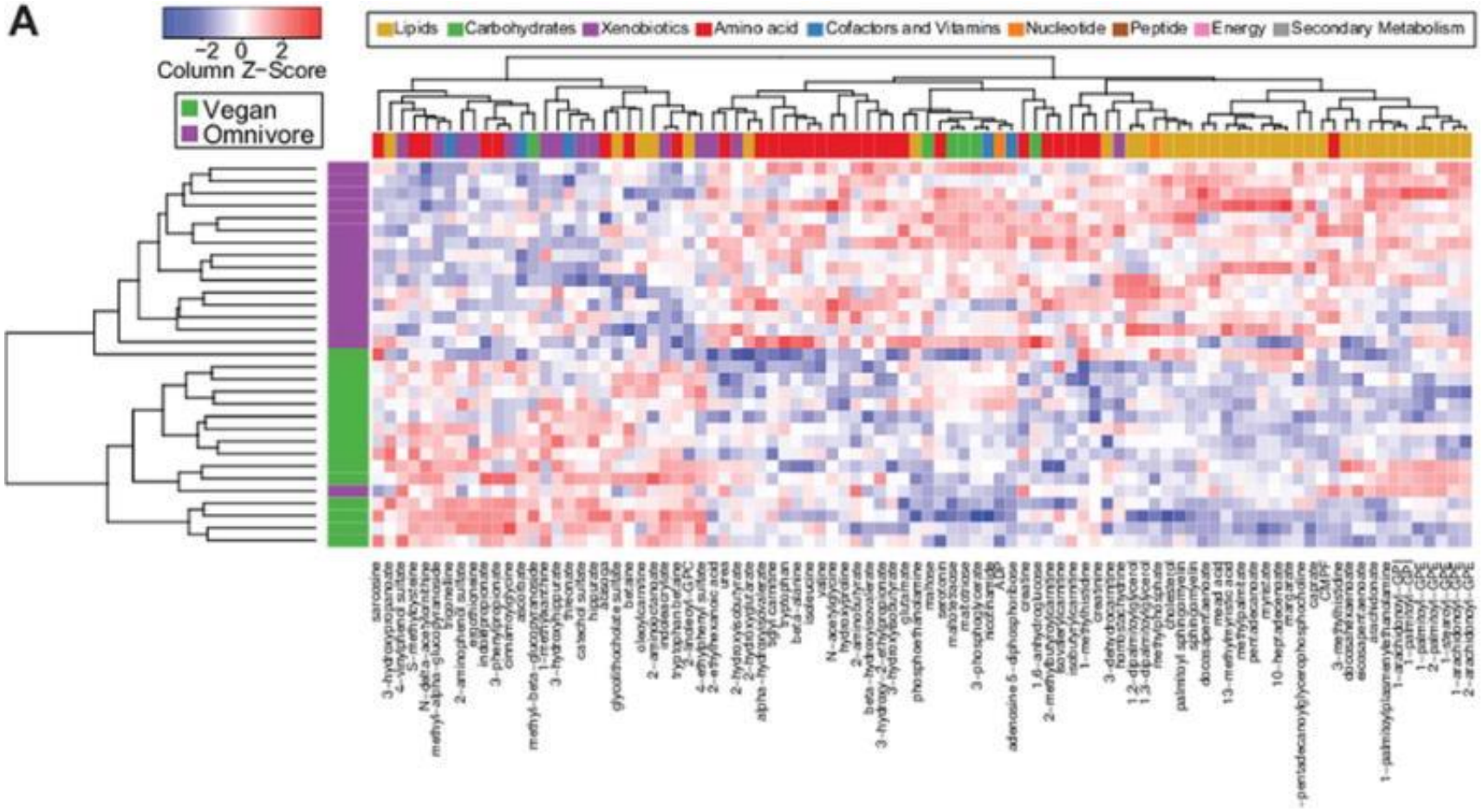
Holmes et al. Cell Metabolism 2012;16:559

Gut microbiota in omnivores vs vegans showed very modest differences

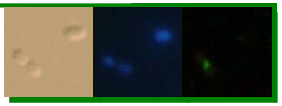


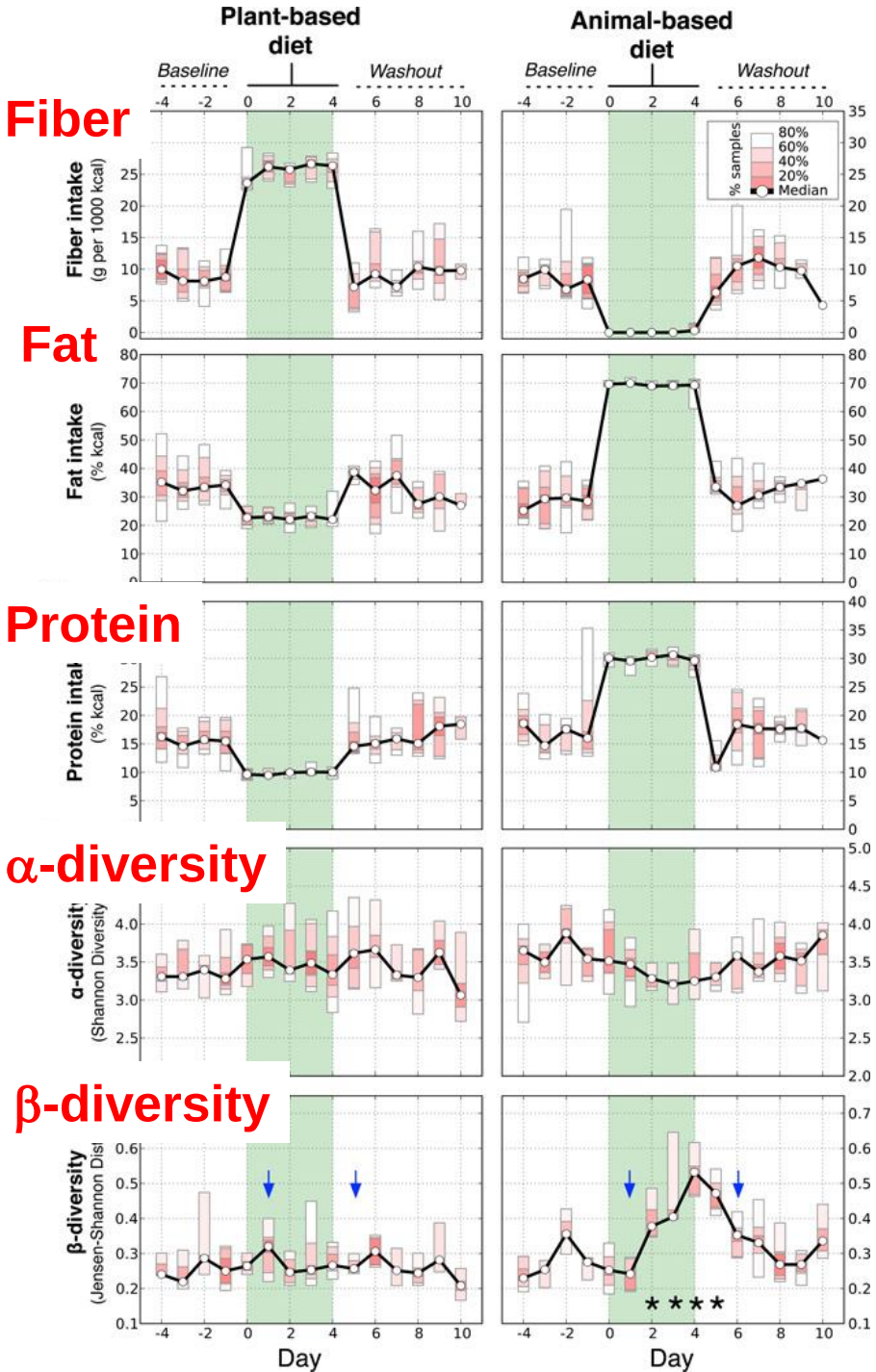
Wu et al. Gut 2014;65:63

Plasma metabolites differed significantly between omnivore and vegans



Wu et al. Gut 2014;65:63





Changing dietary intake can rapidly change microbial metabolism

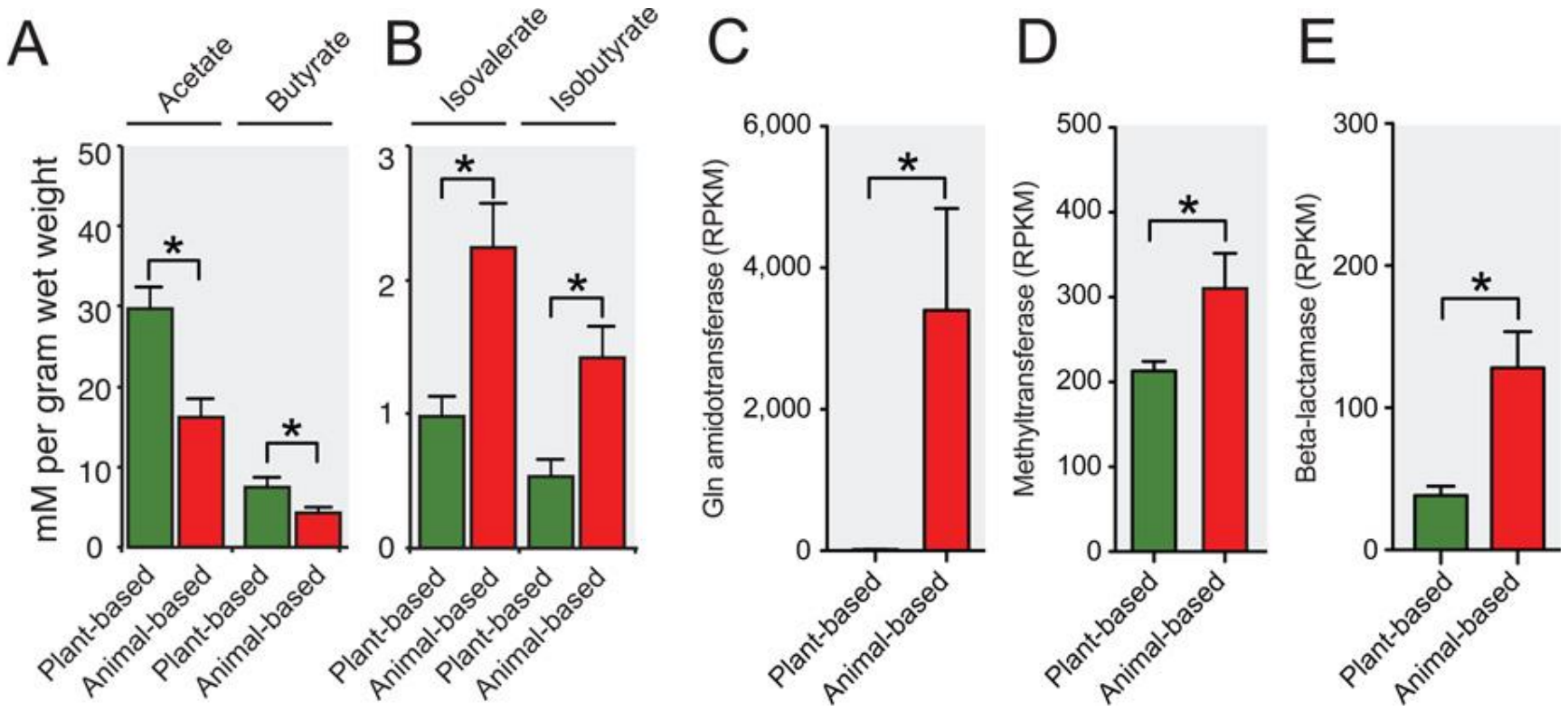
10 Healthy Volunteers

- **Consumed "Plant Diet" or "Animal Diet"**
- **Baseline (4 days)**
- **Diet (5 days)**
- **After (6 days)**

- **Animal Diet**
  - **Increased abundance of bile-tolerant microbes (*Alistipes, Bilophila, Bacteroides)***
  - **Decreased abundance of Firmicutes (*Roseburia, E. rectale, Ruminococcus bromii)***

David et al. Nature 2014:505

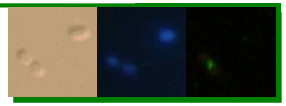
Changing diet rapidly alters microbial activity and gene expression



SCFA

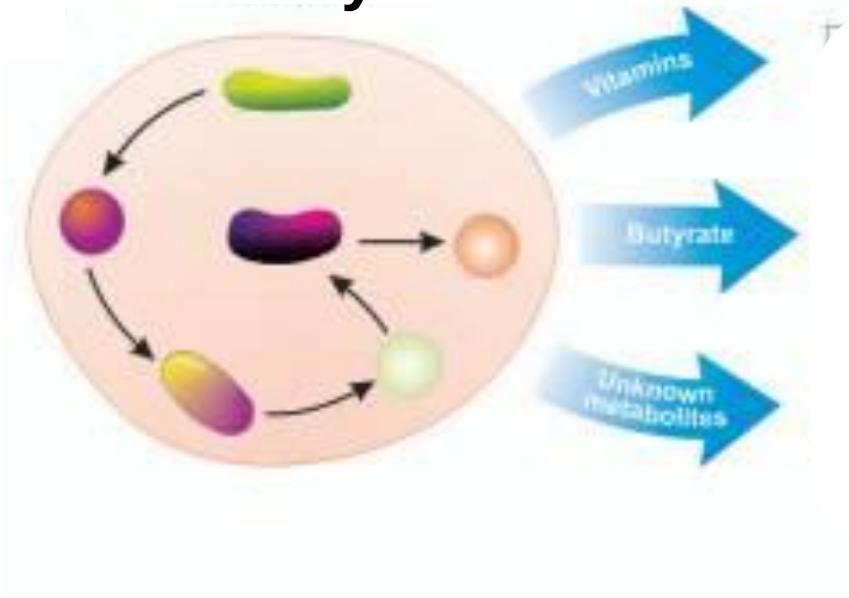
Gene Expression

David et al. Nature 2014:505



Integrated microbial metabolism necessary for health

Healthy Gut



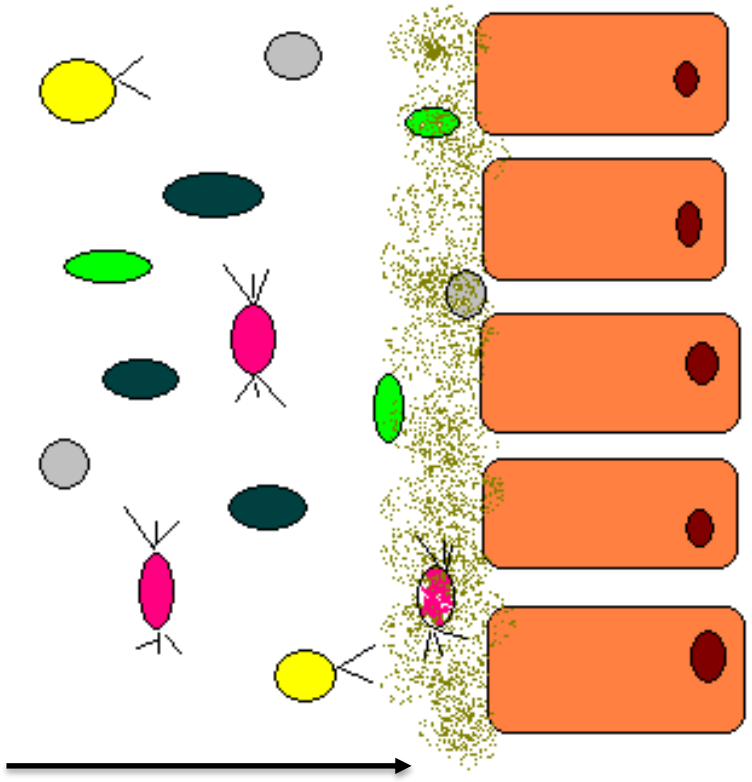
Metabolites required for human health

Lactobacillus
Enterococcus
Bifidobacteria

Erysipelotrichaceae
Inserta Sedis XIV
Lachnospiraceae
Veillonellaceae
Ruminococcaceae

Lactate
Acetate → Acetyl-CoA

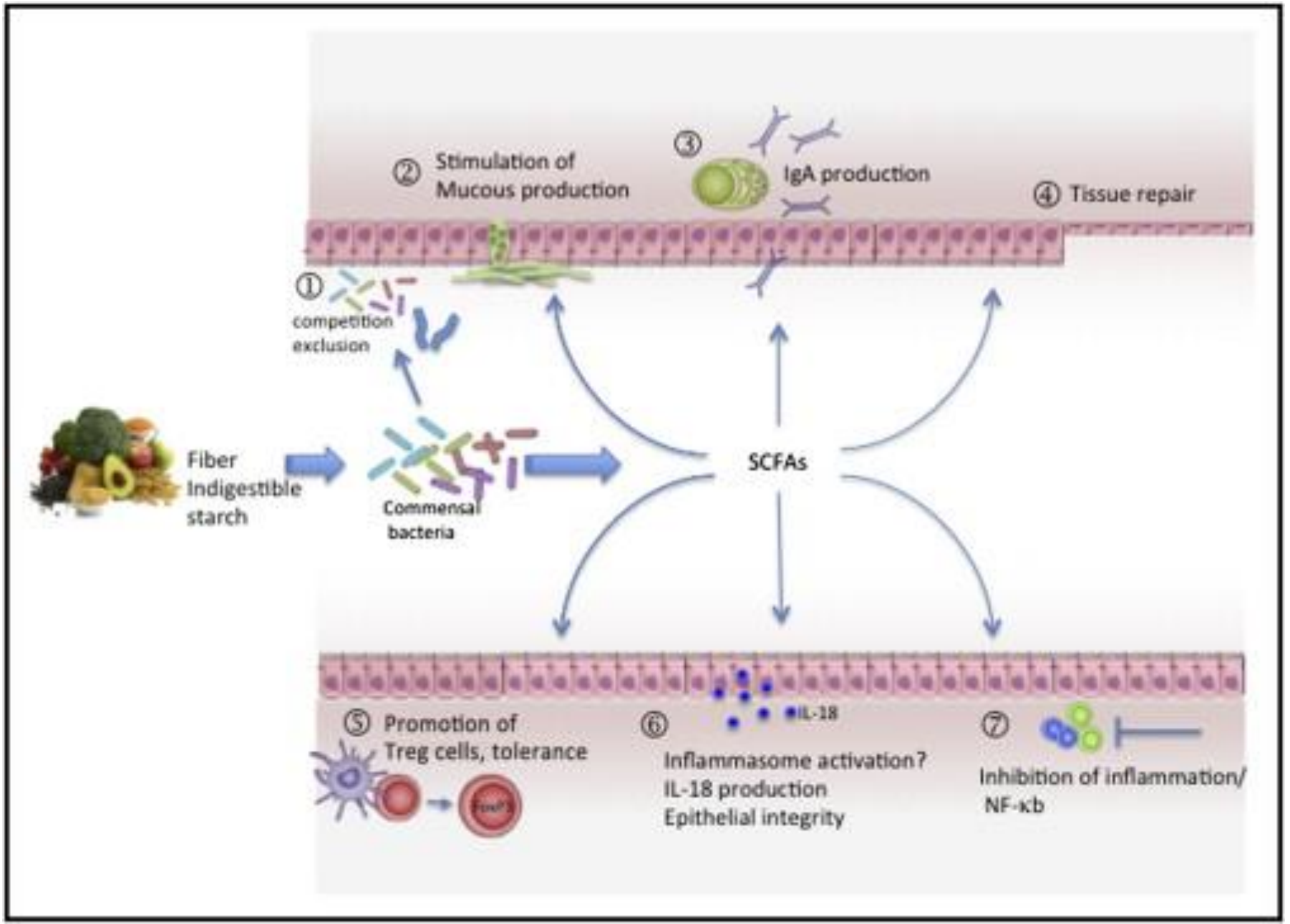
BUTYRATE



Butyrate transported into the epithelium by specific ion transporters (MCT1, MCT4, AE2)

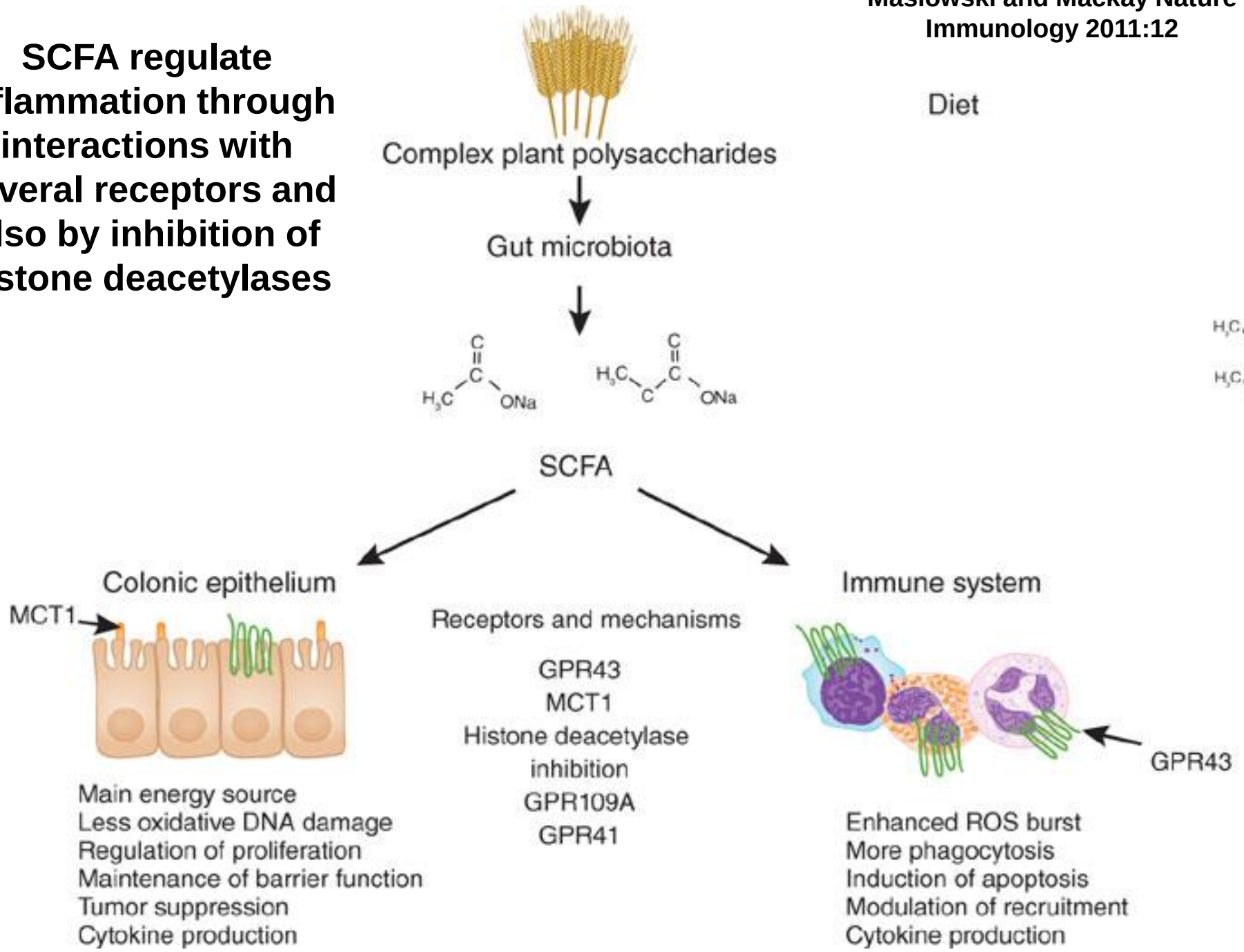
FIBER AND SCFA

SCFA exert many beneficial effects

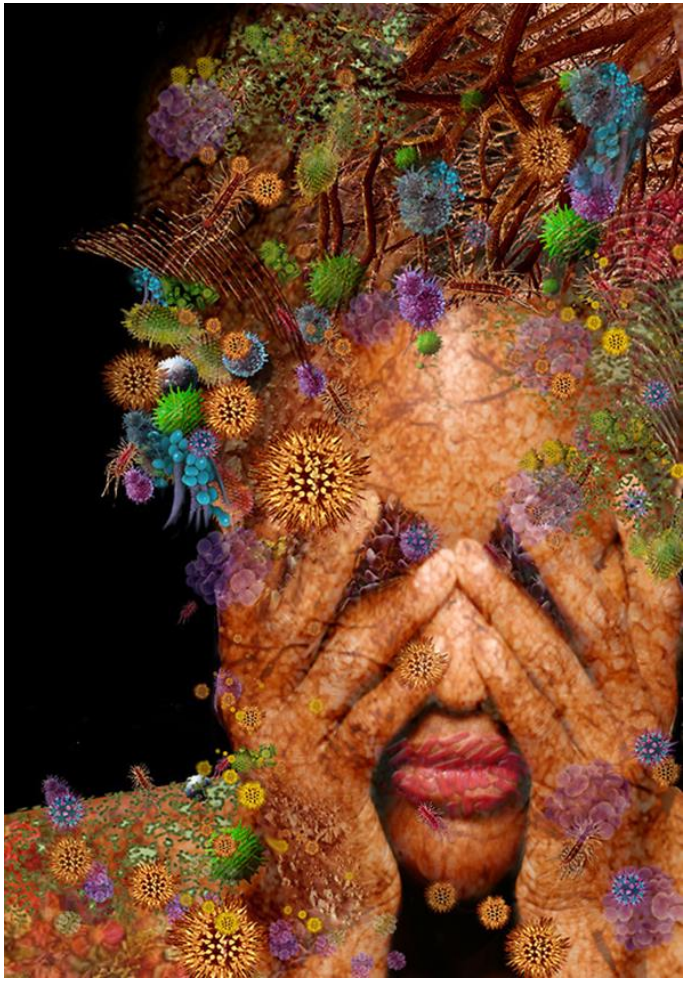


Maslowski and Mackay Nature Immunology 2011:12

SCFA regulate inflammation through interactions with several receptors and also by inhibition of histone deacetylases

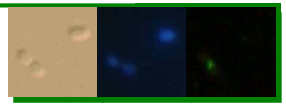


INFLAMMATION

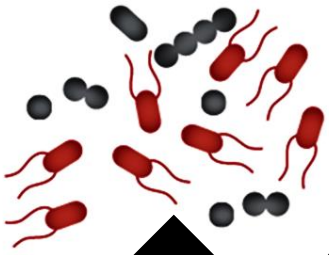


Intestinal Inflammation Induces *Dysbiosis*

Intestinal inflammation enhances the growth of certain *facultative anaerobes* while decreasing the growth of *obligate anaerobes*



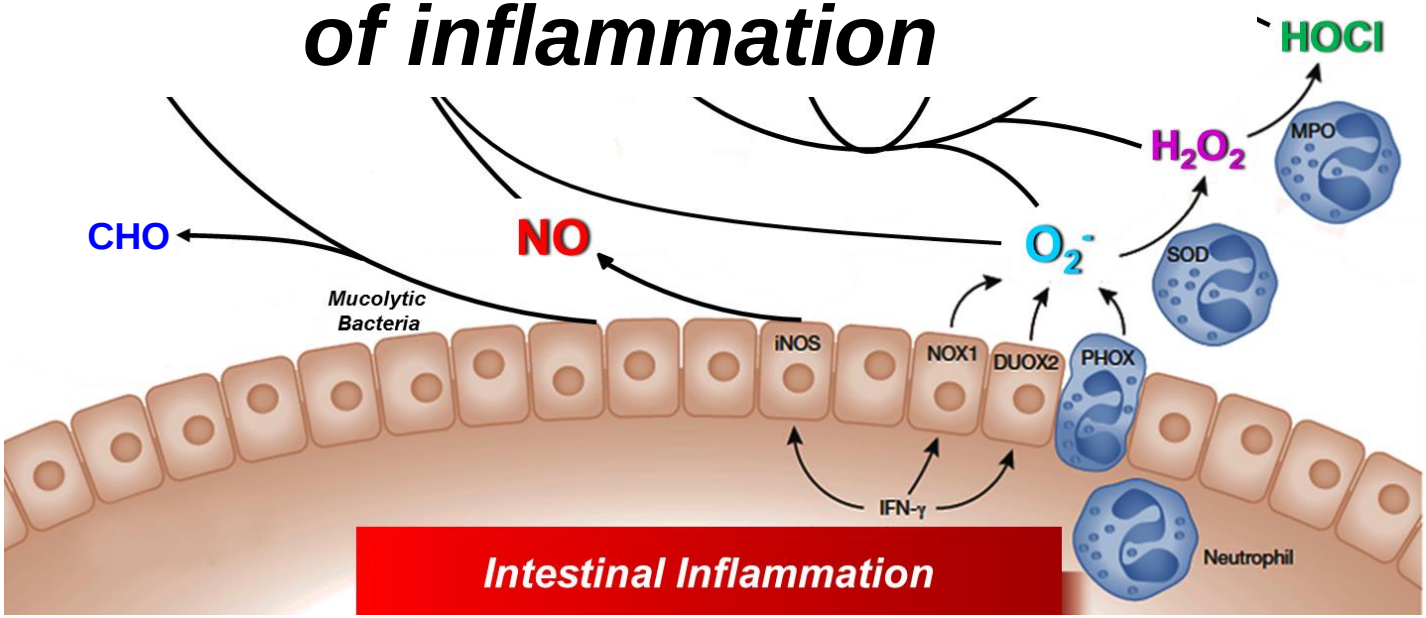
Products of Inflammation Feed the Expansion of *Colitogenic Pathobionts*



Anaerobic Respiration

Clostridia
Bacteriodia
Enterobacteriaceae

Implies that the dysbiosis in IBD patients is a consequence of inflammation

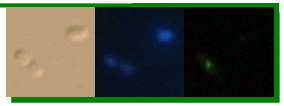


Modified from Winter et. al. EMBO, 2013

Common alterations in microbiota associated with IBD

- **Decrease in Bacteroides and Firmicutes**
- **Decreases in Clostridia, Ruminococcaceae, Lactobacillus, Faecalibacterium prausnitzii, Bifidobacterium**
- **Increase in Proteobacteria (e.g. Enterobacteriaceae)**
  - Increases in γ-proteobacteria; E. coli (AIEC)
- **Increased Presence of Fusobacterium**

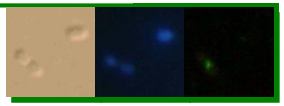
Kostic et. al. Gastroenterology, 2014



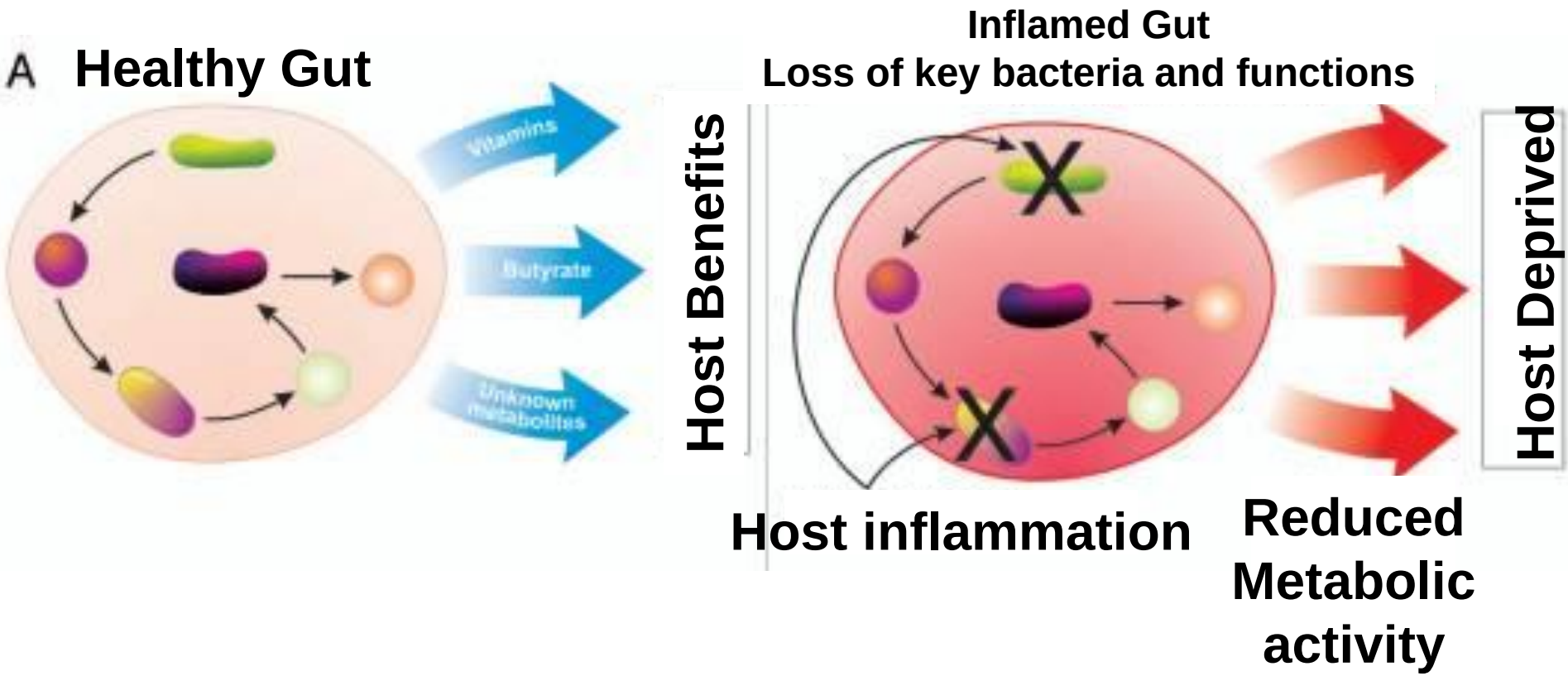
Alterations in microbial function in IBD

- Increased oxidative stress protection pathways
  - increased cysteine and GSH transport
  - increased riboflavin and sulfur metabolism
  - increased pentose phosphate shunt pathway
- Increased sulfate transport and metabolism
- Increase in amino acid transport
- Decrease in short chain fatty acids and metabolism
- Decreased in amino acid biosynthesis

from Morgan et. al., 2012; Kostic et. al. 2014

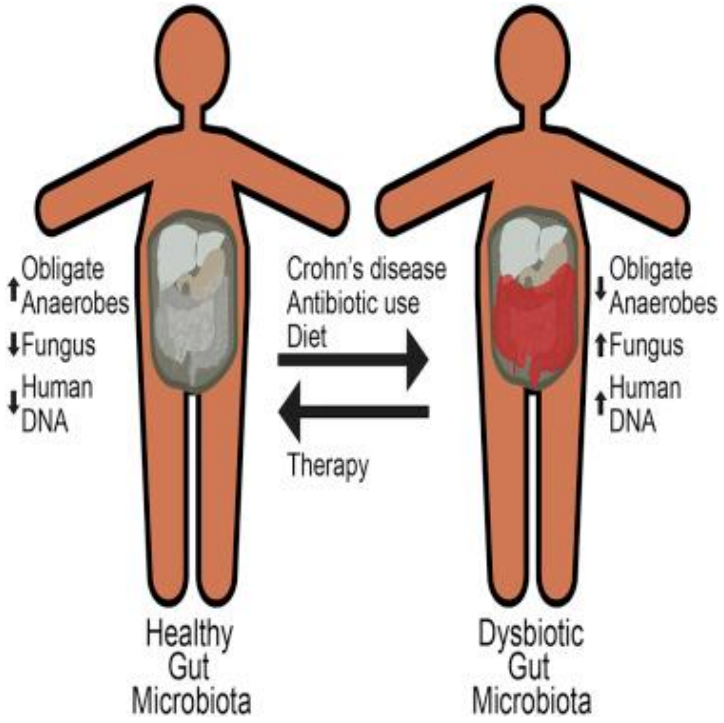


Integrated microbial metabolism necessary for health

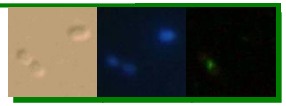


Inflammation, Antibiotics, and Diet as Environmental Stressors of the Gut Microbiome in Pediatric Crohn's Disease

James D. Lewis,[6,7,9] Eric Z. Chen,[6,9] Robert N. Baldassano,[1] Anthony R. Otley,[3] Anne M. Griffiths,[4] Dale Lee,[1,2] Kyle Bittinger,[8] Aubrey Bailey,[8] Elliot S. Friedman,[7] Christian Hoffmann,[8] Lindsey Albenberg,[1] Rohini Sinha,[8] Charlene Compher,[5] Erin Gilroy,[6] Lisa Nessel,[6] Amy Grant,[3] Christel Chehoud,[8] Hongzhe Li,[6] Gary D. Wu,[7,*] and Frederic D. Bushman[8,*]

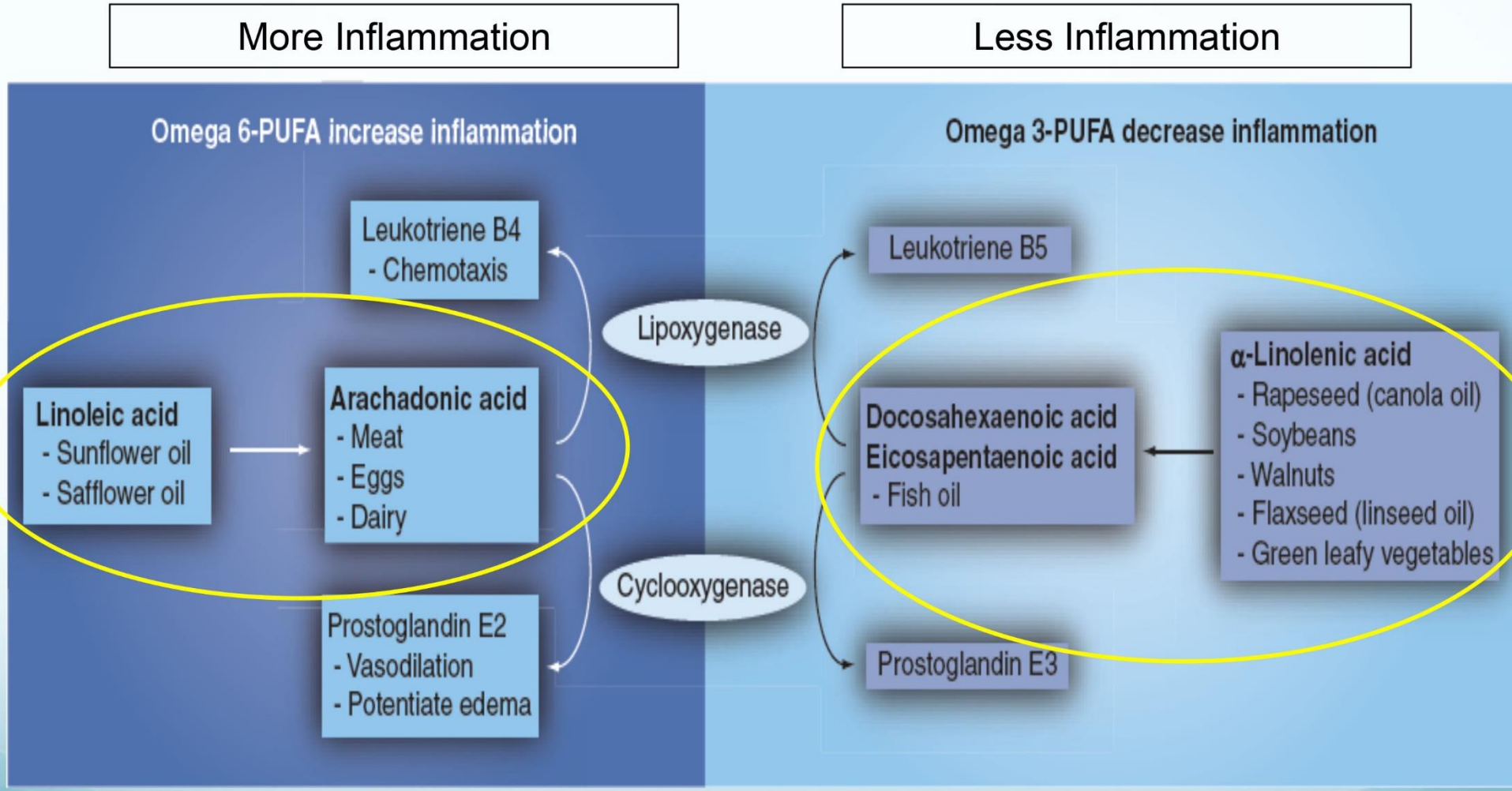


- **Pediatric patients with active CD were treated with enteral nutrition, PEN, or anti-TNF therapy**
- **Microbiota among responders became more similar to healthy controls with both anti-TNF (parenterally) and enteral nutrition (direct effect on gut microbes)**
- ***Demonstrates that reducing inflammation can restore gut microbial balance***



DIETARY FAT

Omega 6/Omega 3 Ratios



Higgins P. AIBD2015

Hou et al. Therapy. 2010, 7(2)

Gastroenterology 2014;146:929–931

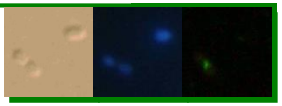
BRIEF REPORT

Interactions Between the Dietary Polyunsaturated Fatty Acid Ratio and Genetic Factors Determine Susceptibility to Pediatric Crohn's Disease

Irina Costea,[1] David R. Mack,[2] Rozenn N. Lemaitre,[3] David Israel,[4] Valerie Marcil,[5] Ali Ahmad,[6,7] and Devendra K. Amre[7,8]

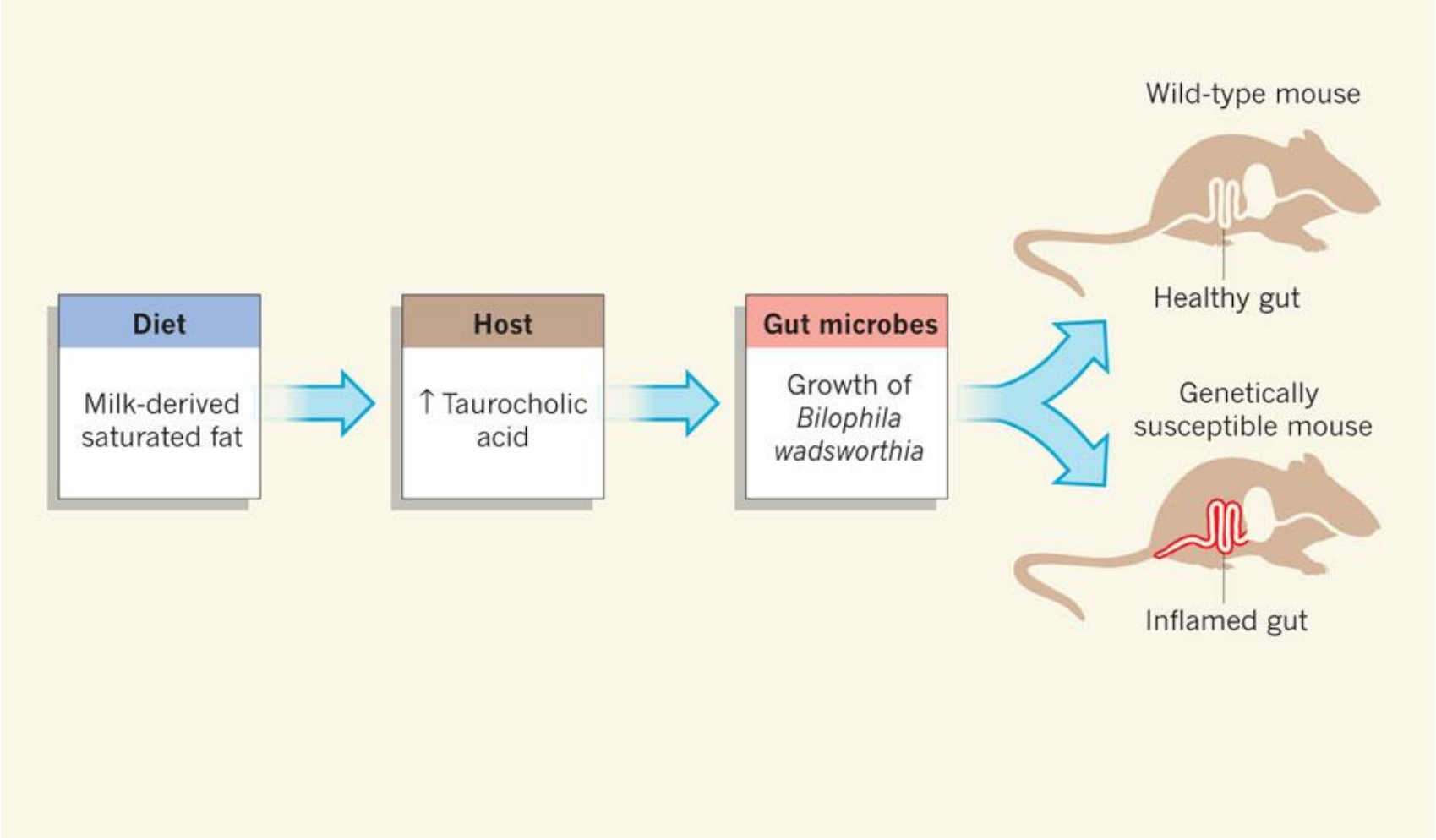
BRIEF REPORT

- Intake of increased dietary ratios of ω6/ω3 PUFA have been implicated in pathogenesis of CD
- In a study of 182 children newly diagnosed with CD, it was found that children who consumed a higher dietary ratio of ω6/ω3 PUFA were susceptible for CD if they were also carriers of specific variants in fatty acid metabolism, CYP4F3 and FADS2 genes
- Implicates diet-gene interactions



DIETARY FAT-INDUCED SHIFTS IN BILE-ACID PRODUCTION AND COMPOSITION CAN ALTER GUT MICROBES AND INDUCE INFLAMMATION

Milk-derived fat promoted taurine conjugation of bile acids which increased the availability of organic sulphur used by sulphite-reducing pathobiont, which in turn promoted colitis in IL-10-/- mice



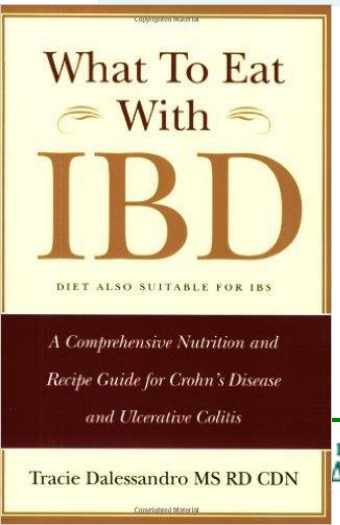
Devkota et al. Nature 487(7405): 2012

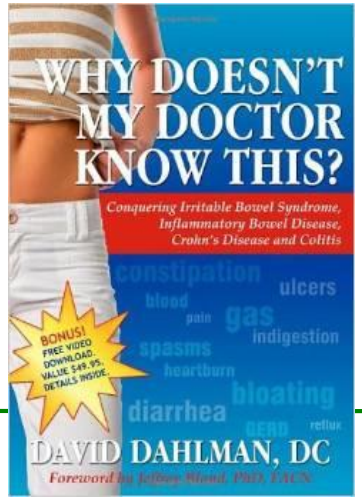
WHAT IS THE EVIDENCE FOR EFFECTIVE USE OF DIET AS THERAPY?

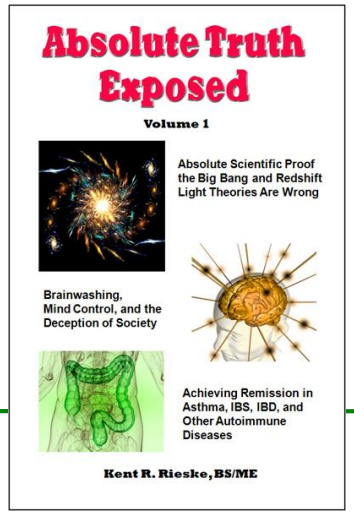
Hou et al. CGH 2014:12(10

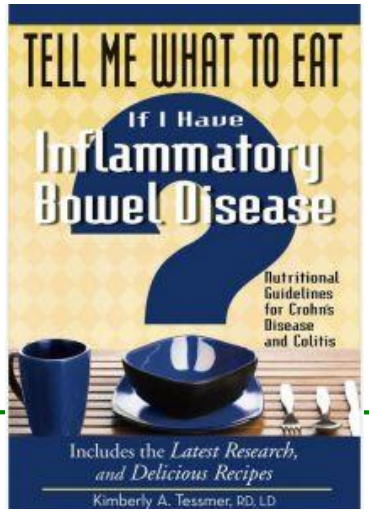
IBD Diet Information on the Internet

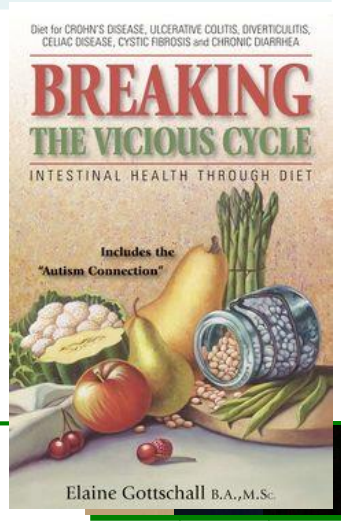
Food	Include (%)	Avoid (%)	Internally Conflicting (%)
Fruits	24	44	32
Vegetables	57	22	21
Red meat	20	80	
Whole grains	26	56	18
Refined grains	40	60	
Dairy	17	69	
Nuts	4	79	17







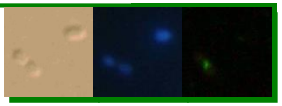




Evidence for Dietary Treatment for IBD

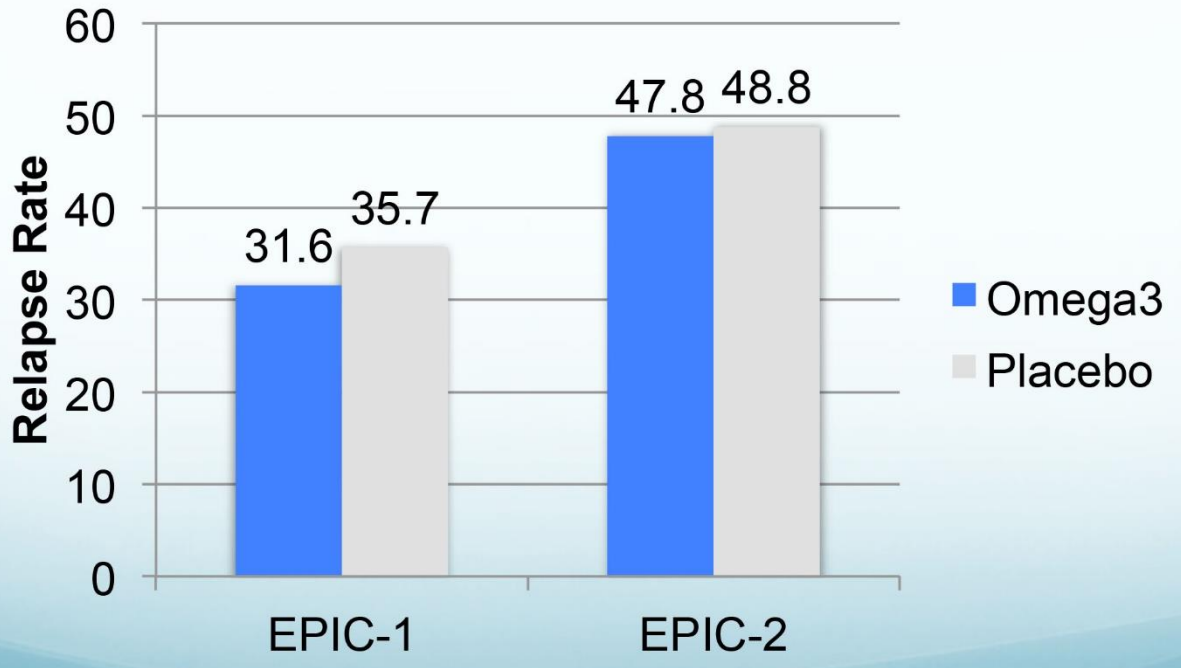
- Numerous small case series, RCT (n=11)
  - Low-fiber
  - High fiber
  - Vegetarian
  - Lactose-free
  - Specific carbohydrate
  - Low FODMAP
  - Paleolithic
  - Gluten-free
  - IBD-Anti-inflammatory diet
- Some trends towards alleviating symptoms
- ***No clear positive studies***

Shah et al. Nutrition in Clinical Practice 30:462. 2015; Knight-Sepulveda et al. Gasto Hepatol 2015;11:511



Failed Trials of Fish Oil

- Fish Oil – EPIC 1 and EPIC 2, N=738
- Two well designed RCTs of omega 3 fatty acids in Crohn's disease

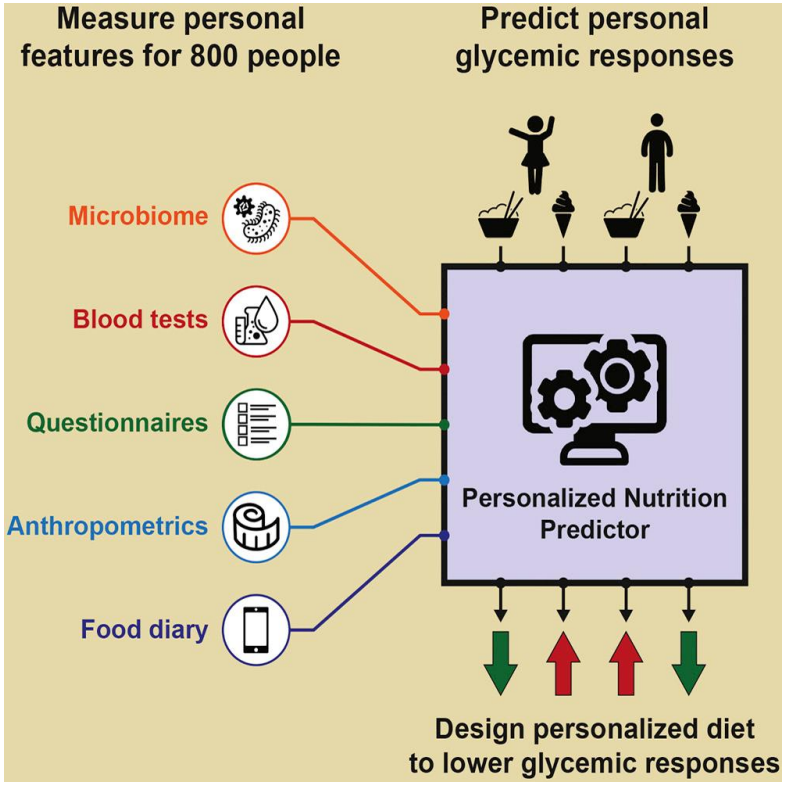


Feagan et al. JAMA. 2008;299(14)


So why are dietary interventions not showing more positive effects in human studies?

Personalized Nutrition by Prediction of Glycemic Responses

David Zeevi,[1,2,8] Tal Korem,[1,2,8] Niv Zmora,[3,4,5,8] David Israeli,[6,8] Daphna Rothschild,[1,2] Adina Weinberger,[1,2] Orly Ben-Yacov,[1,2] Dar Lador,[1,2] Tali Avnit-Sagi,[1,2] Maya Lotan-Pompan,[1,2] Jotham Suez,[3] Jemal Ali Mahdi,[3] Elad Matot,[1,2] Gal Malka,[1,2] Noa Kosower,[1,2] Michal Rein,[1,2] Gili Zilberman-Schapira,[3] Lenka Dohnalová,[3] Meirav Pevsner-Fischer,[3] Rony Bikovsky,[1,2] Zamir Halpern,[5,7] Eran Elinav,[3,9,*] and Eran Segal[1,2,9,*]

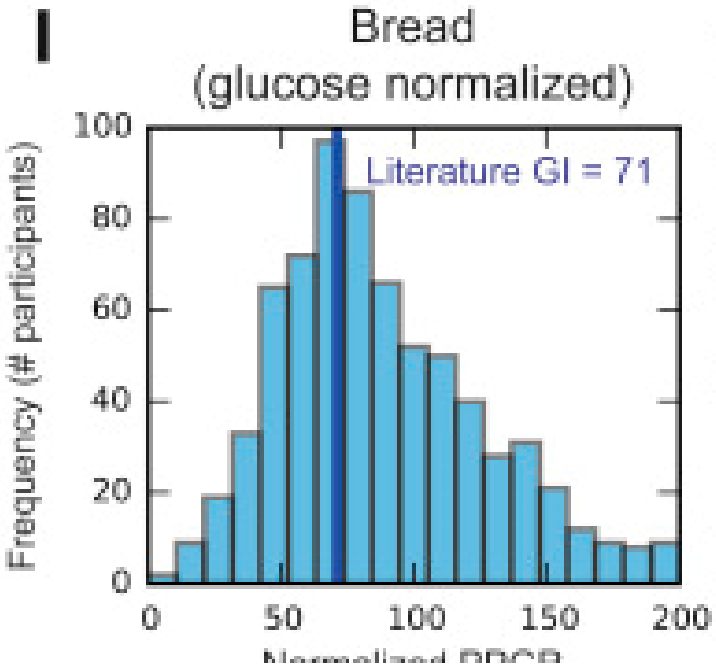


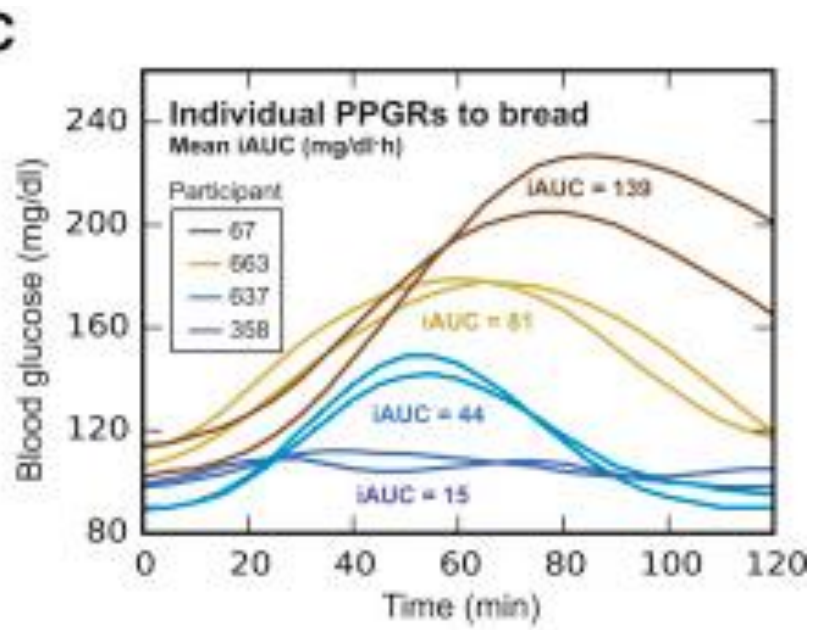
- Continually monitored glucose levels in 800-person cohort (18-70 yrs) in response to various meals
- Logged all activities and food eaten
- Analyzed gut microbiome
- Blood tests
- Anthropometrics
- Questionnaires for food frequency, lifestyle, medical

Response to food is highly personalized

Zeevi et al. Cell Volume 163, Issue 5, 2015, 1079–1094

Response to food was highly personalized



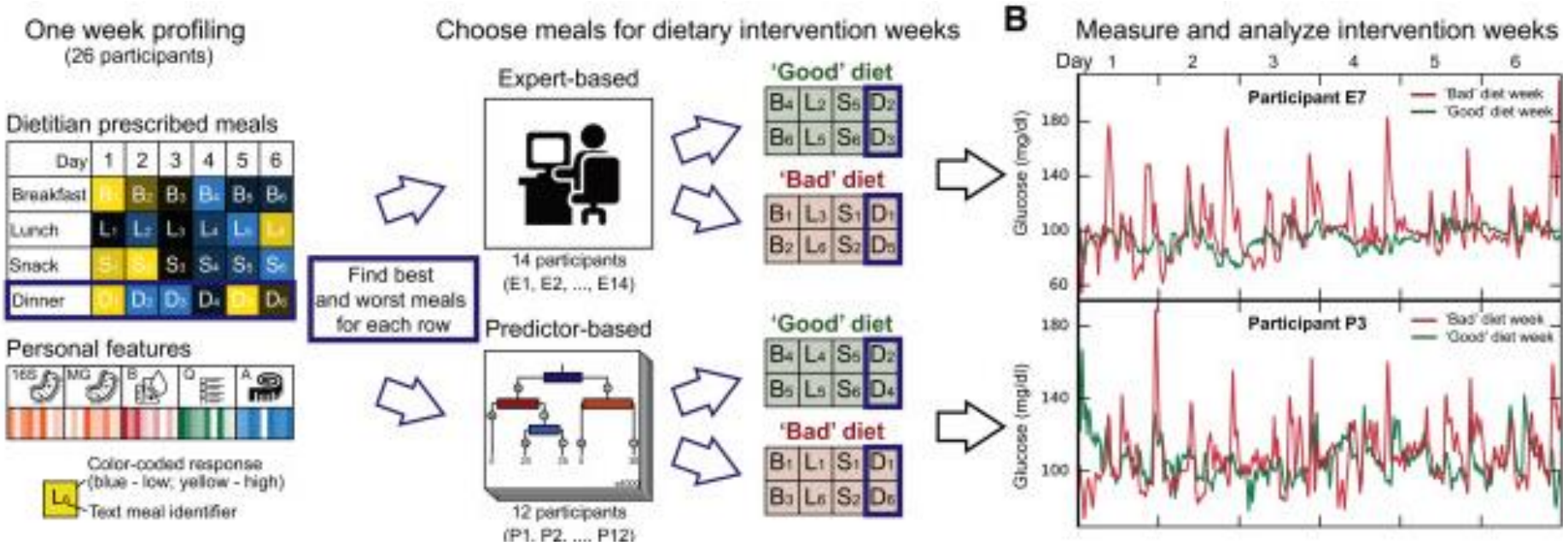


- **Postprandial glycemic response (PPGR) highly variable between individuals but reproducible per person and per meal**

- **PPGR associated with known risk factors (BMI, HbA1c, CRP) and with *gut microbiome***

Zeevi et al. Cell Volume 163, Issue 5, 2015, 1079–1094

Individual tailoring of diets was necessary to reduce daily glucose fluctuations



- **Integrating datasets allowed for the individual tailoring of diets that were effective in reducing daily glucose spikes**

Zeevi et al. Cell Volume 163, Issue 5, 2015, 1079–1094

Challenges for Diet Studies

- Problems with blinding
- Design of control (placebo) diets
- Controlling what patients eat
- Large diversity in dietary intake
- Accuracy of dietary intake measurements over long term studies is questionable
- Need RCTs with very large sample sizes
- No intellectual property
- Individualized responses to food




The eatwell plate

FOOD STANDARDS AGENCY
food.gov.uk

Use the eatwell plate to help you get the balance right. It shows how much of what you eat should come from each food group.

Summary

- There is extensive scientific evidence from animal models and epidemiologic studies that dietary factors influence both the risk of developing IBD and modulating existing disease
- While long-term dietary intake is a main determinant of gut microbial composition, rapid effects on microbial metabolism can be seen in response to dietary changes
- Gut “dysbiosis” in IBD likely reflects an adaptive response of a complex microbial community to environmental stress caused by intestinal inflammatory processes
- At the current time, data on the use of specific dietary interventions to treat or prevent IBD remains inconclusive
- In the future, it is likely that development of long-term and short-term dietary interventions based on an individual’s own physiological responses will be possible