Health and Environmental Sciences Institute Microbiome Workshop

Human Susceptibility Session

June 26, 2018

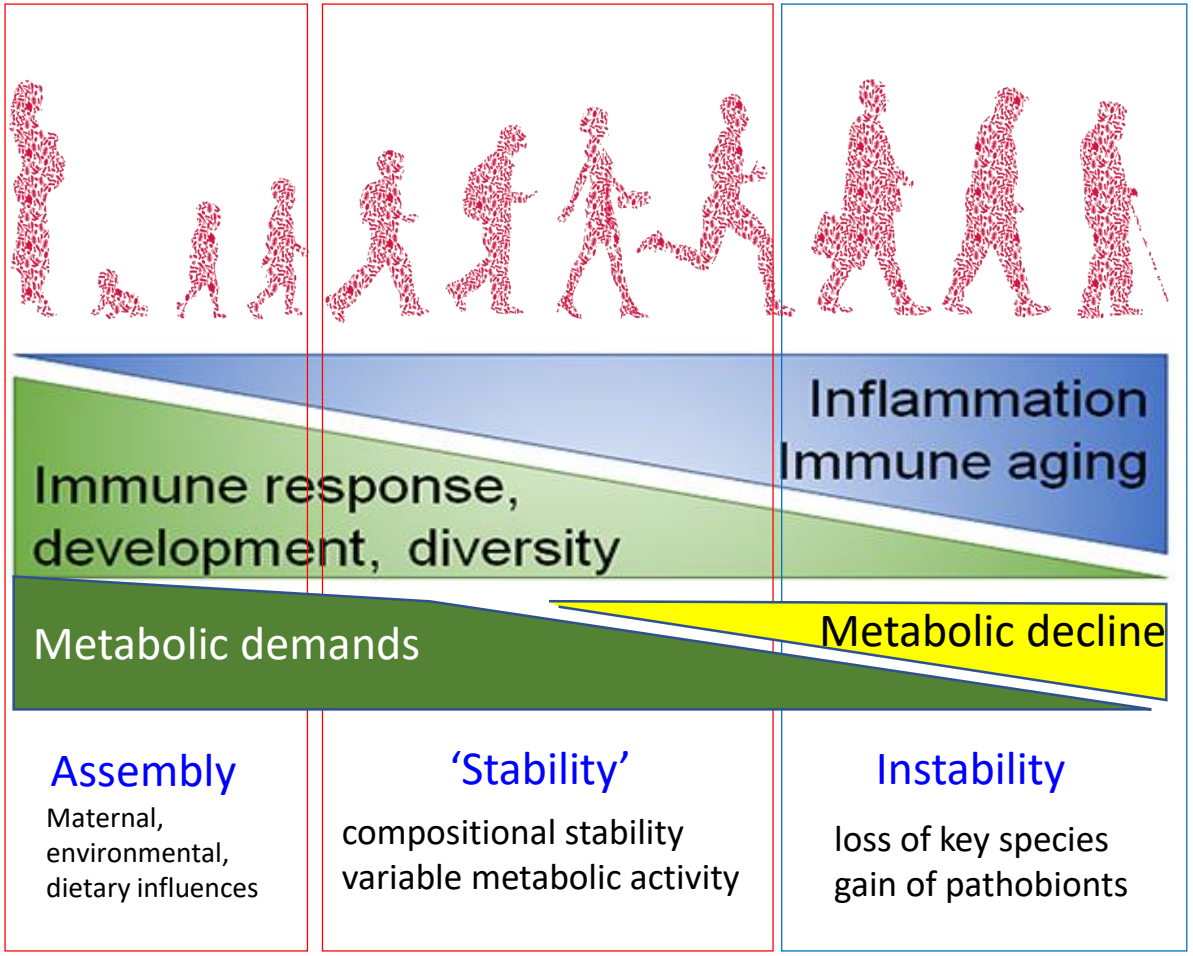
Age: the microbiome through life and its impact on host

Eugene B. Chang, MD

Knapp Center for Biomedical Discovery

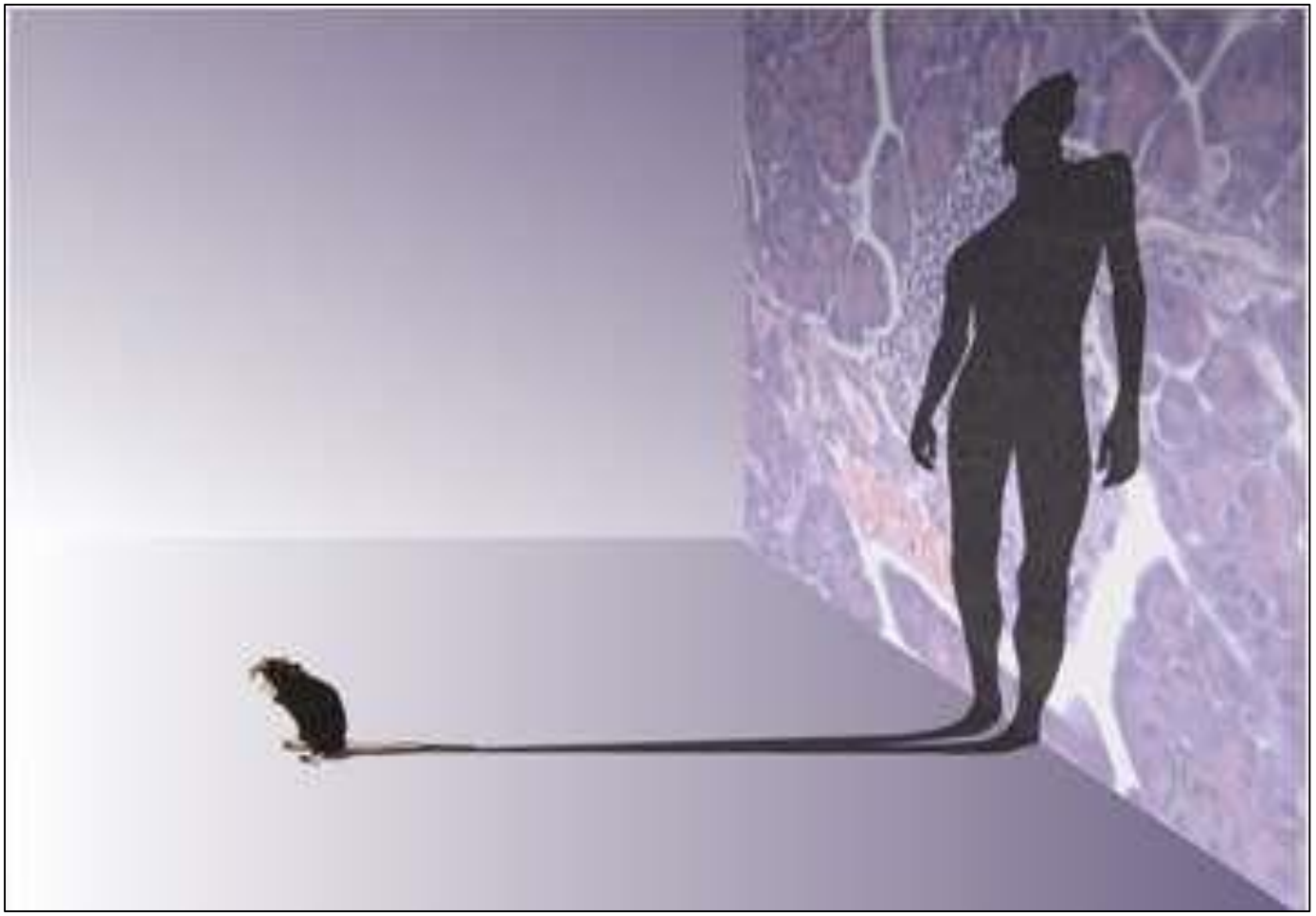
University of Chicago

Host-microbiome states change with age: Impact on human health and disease



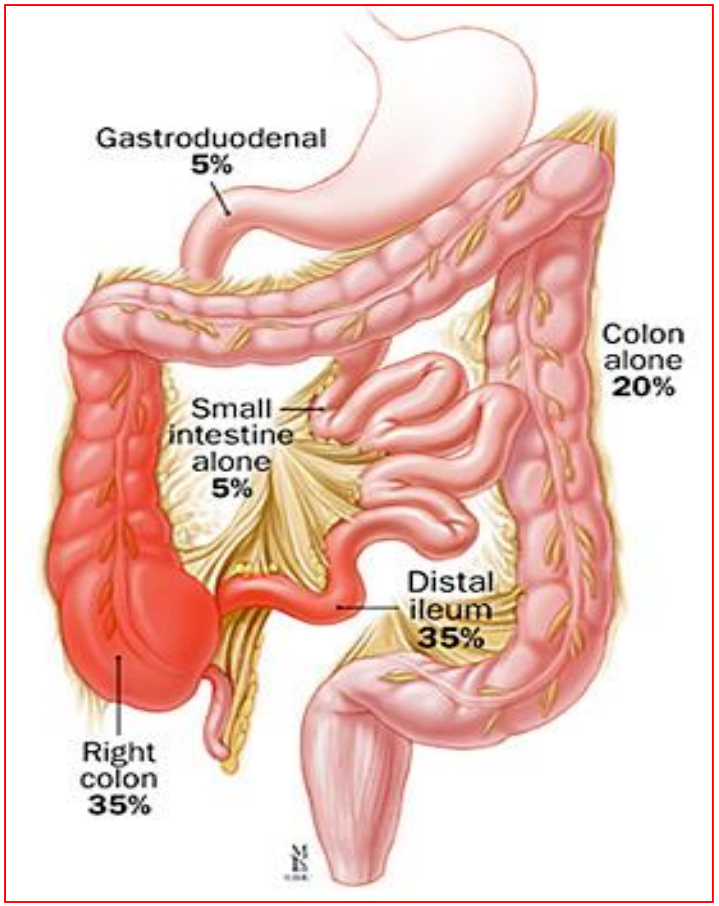
Slide adapted from one provided by Fergus Shanahan

Potential insights gained through a combination of human and experimental models

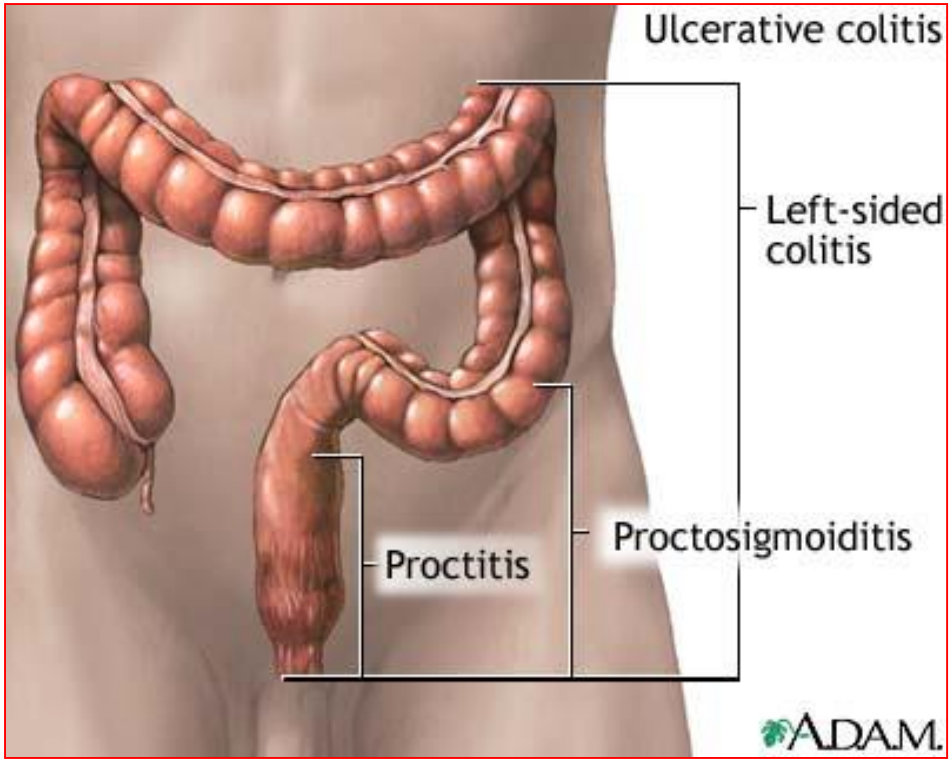


Crohn's disease and ulcerative colitis are clinical phenotypes of inflammatory bowel diseases

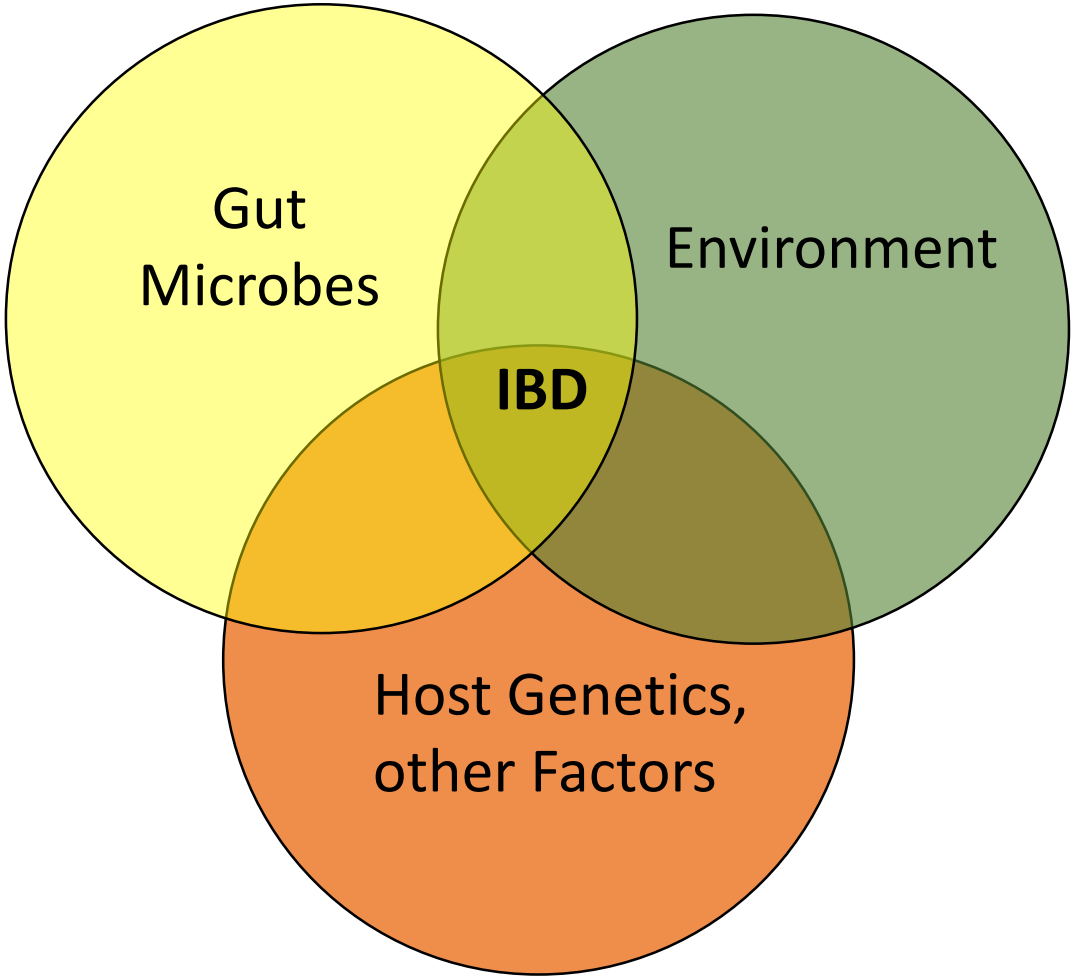
Crohn's disease



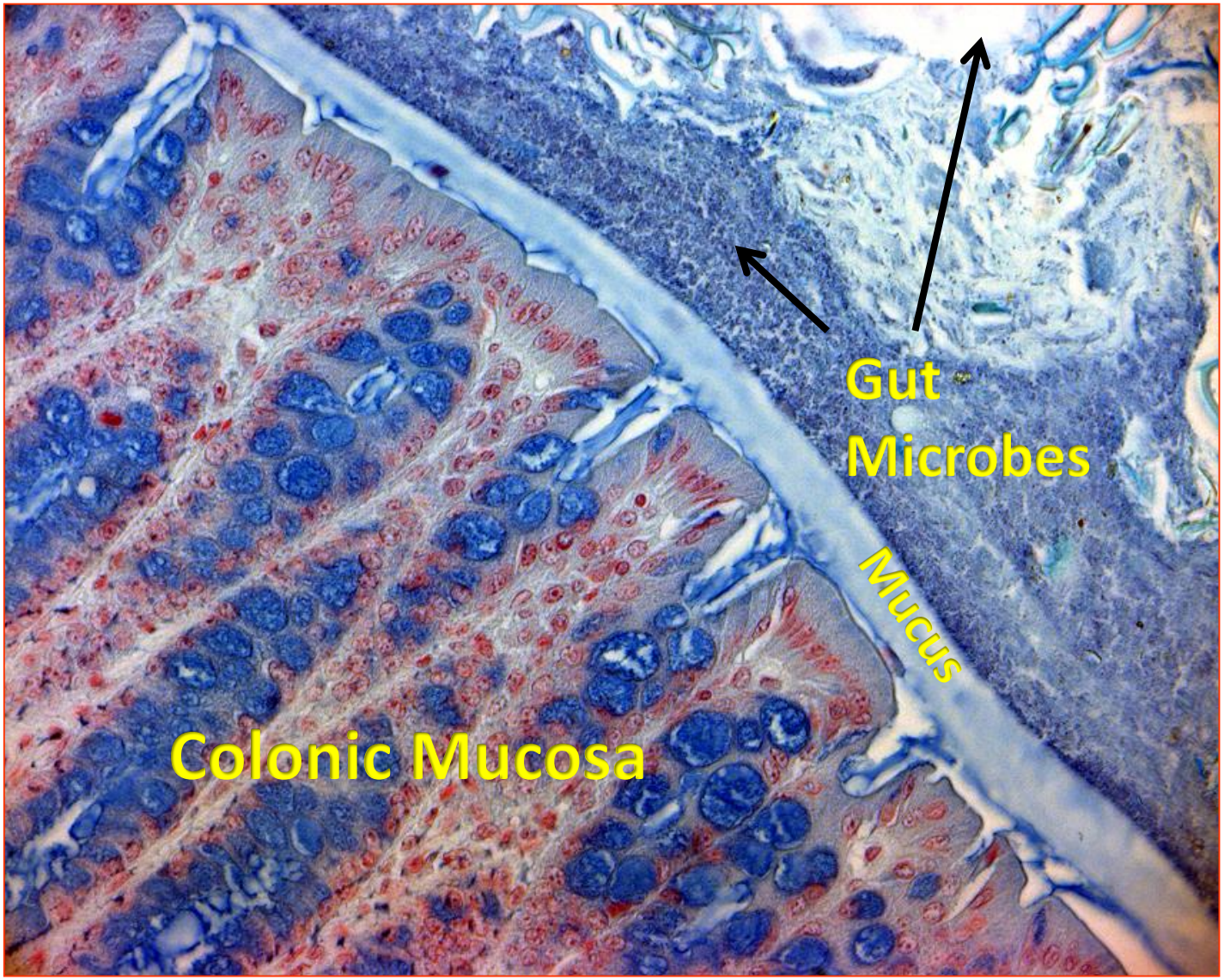
Ulcerative Colitis



Inflammatory Bowel Diseases (IBD): prototypes of complex immune disorders



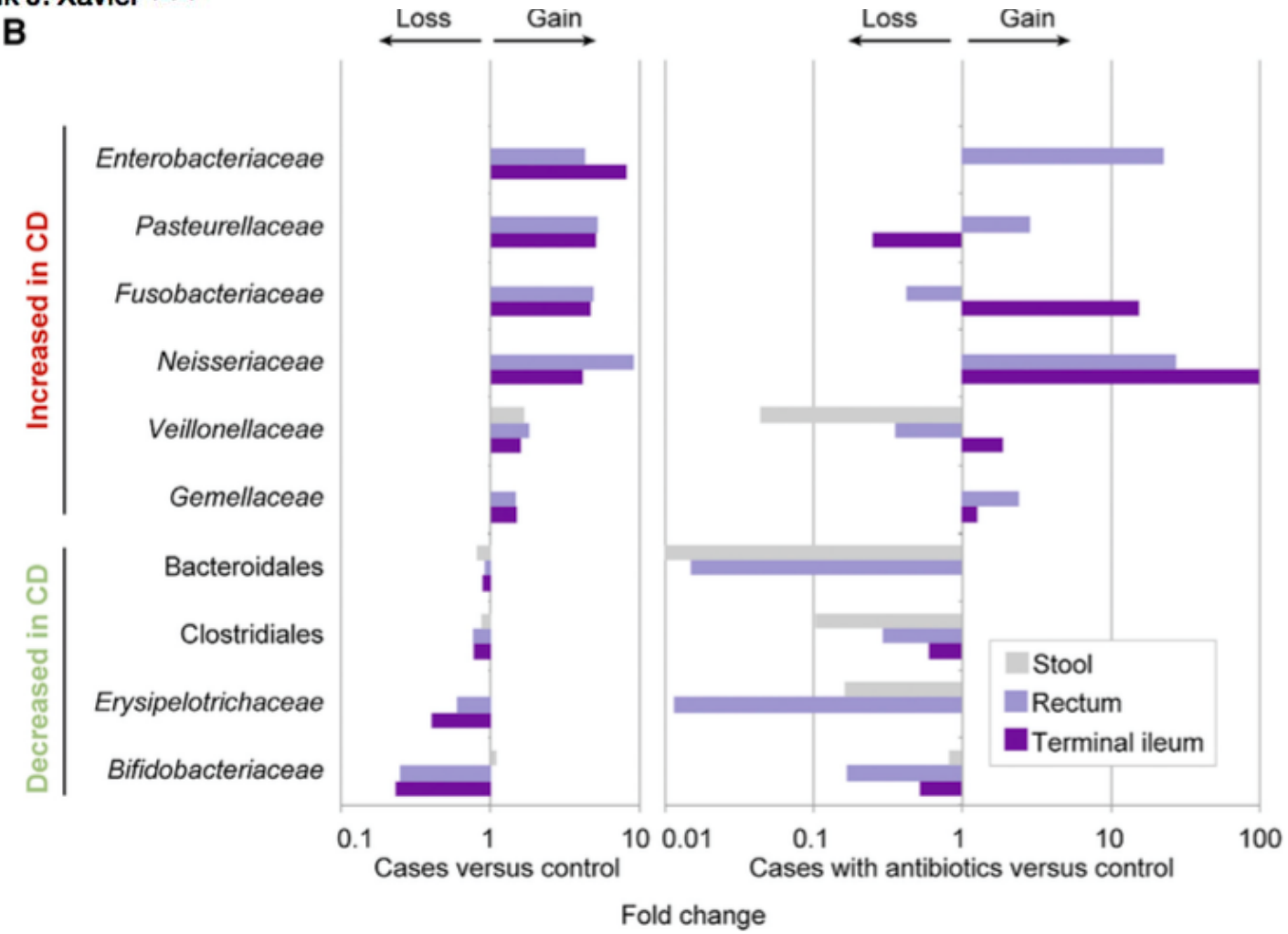
Our gut microbial organ up close



The Treatment-Naive Microbiome in New-Onset Crohn's Disease

Cell Host & Microbe
Resource

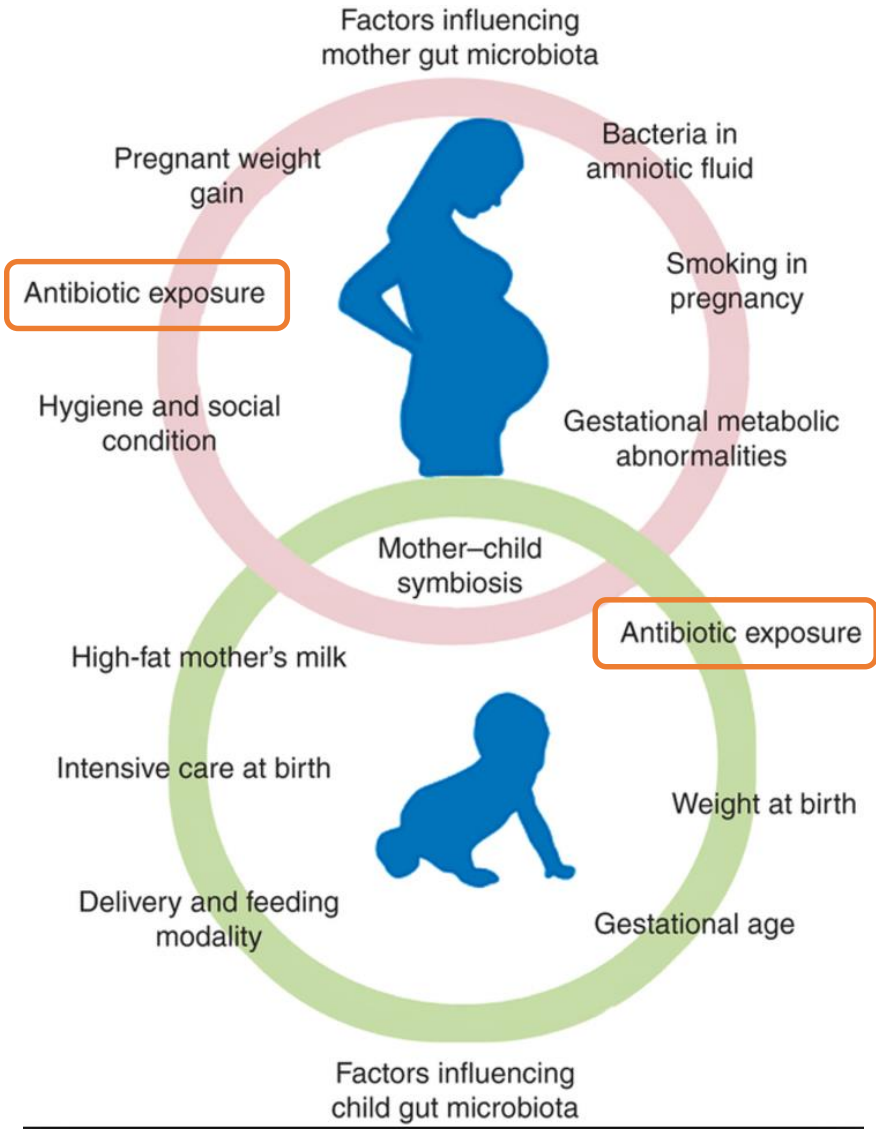
Dirk Gevers,[1] Subra Kugathasan,[4,24] Lee A. Denson,[5,24] Yoshiki Vázquez-Baeza,[6] Will Van Treuren,[7] Boyu Ren,[8] Emma Schwager,[8] Dan Knights,[9,10] Se Jin Song,[7] Moran Yassour,[1] Xochitl C. Morgan,[8] Aleksandar D. Kostic,[1] Chengwei Luo,[1] Antonio González,[7] Daniel McDonald,[7] Yael Haberman,[5] Thomas Walters,[11] Susan Baker,[12] Joel Rosh,[13] Michael Stephens,[14] Melvin Heyman,[15] James Markowitz,[16] Robert Baldassano,[17] Anne Griffiths,[18] Francisco Sylvester,[19] David Mack,[20] Sandra Kim,[21] Wallace Crandall,[21] Jeffrey Hyams,[19] Curtis Huttenhower,[1,8] Rob Knight,[7,22,23] and Ramnik J. Xavier[1,2,3,*]



Peripartum antibiotics are commonly used in mothers and infants

Facts:

- ~ 40% of pregnant women at term
- In developed countries, broad-spectrum antibiotics are prescribed more frequently during pregnancy. (Petersen et al., 2010)
- >30% of neonates are exposed to antibiotics. (Broe et al., 2014; Stokholm et al., 2013)
- In most cases, indications for antibiotic use during the peripartum period are unclear



Putignani et al., 2014. Pediatric Research

Early-in-life antibiotics, altered immune states, disease risk

Cell Reports
Article

OPEN ACCESS
CellPress

Peripartum Antibiotics Promote Gut Dysbiosis, Loss of Immune Tolerance, and Inflammatory Bowel Disease in Genetically Prone Offspring

Jun Miyoshi,[1,2] Alexandria M. Bobe,[1,2] Sawako Miyoshi,[1] Yong Huang,[1] Nathaniel Hubert,[1] Tom O. Delmont,[1] A. Murat Eren,[1] Vanessa Leone,[1] and Eugene B. Chang[1,3,*]

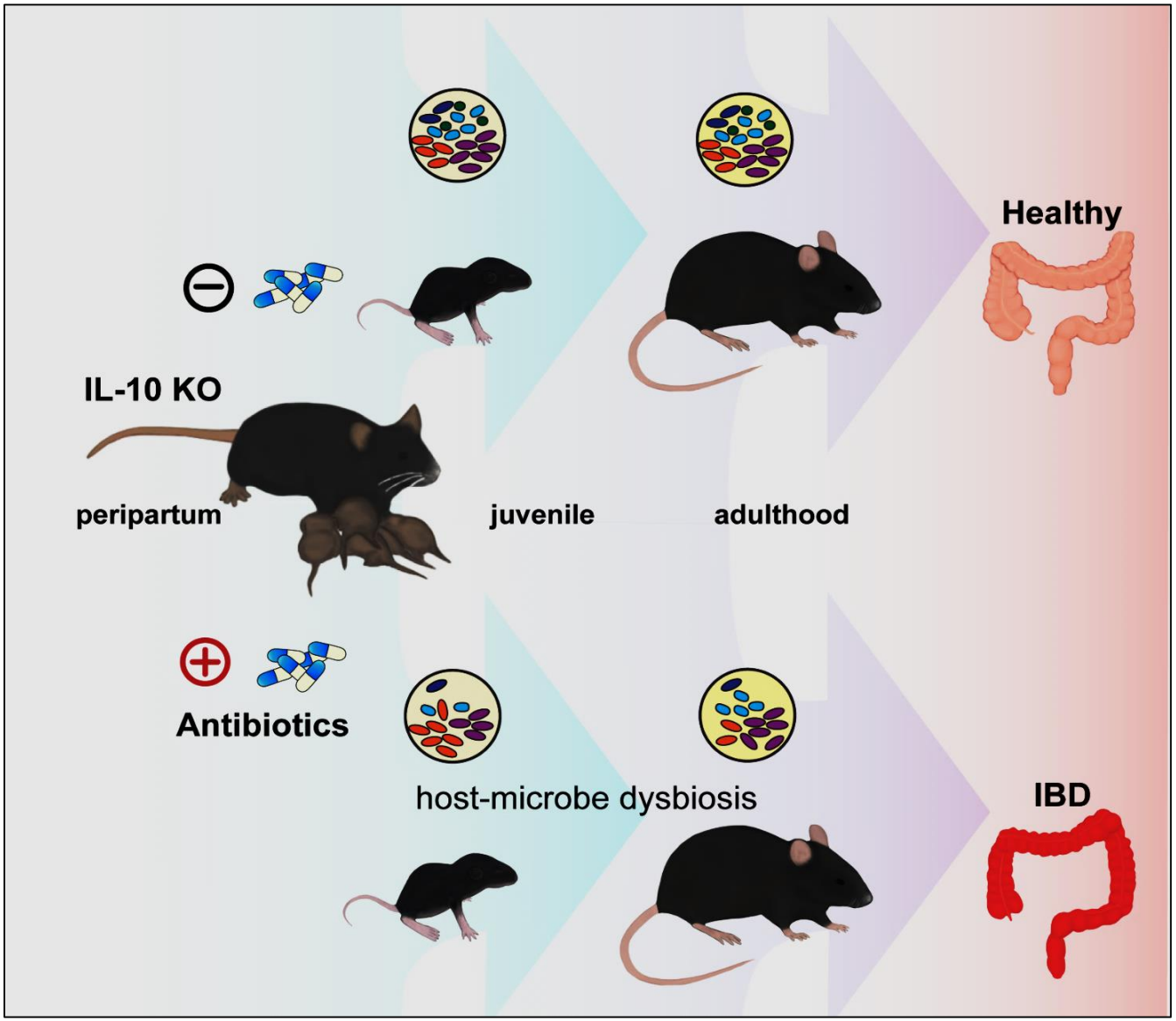
ARTICLES
https://doi.org/10.1038/s41564-017-0075-5

nature microbiology

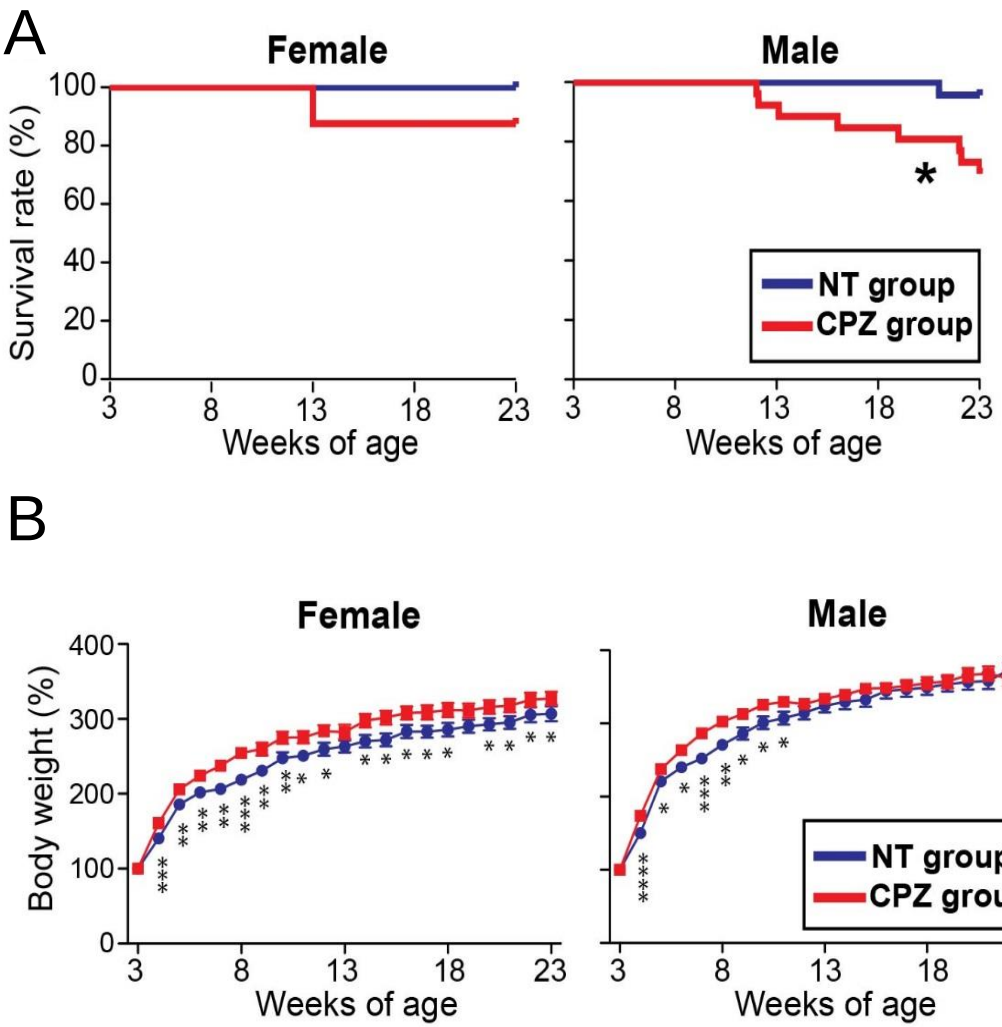
Intergenerational transfer of antibiotic-perturbed microbiota enhances colitis in susceptible mice

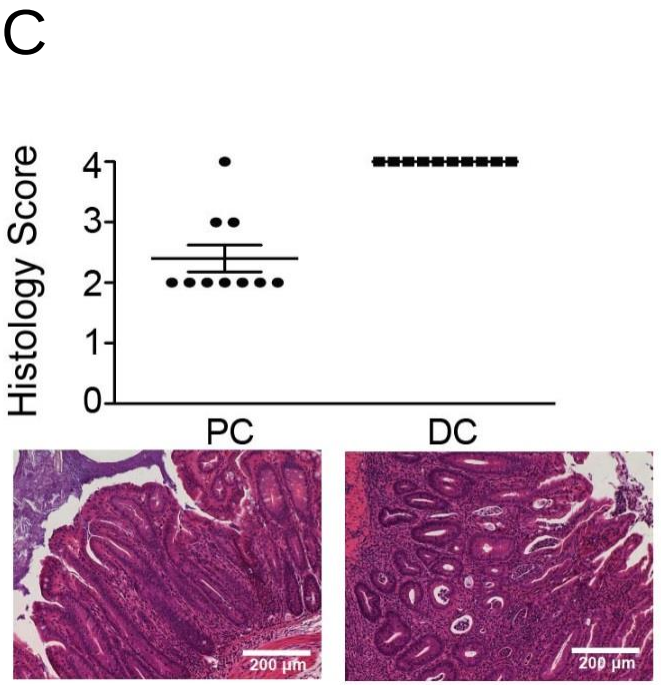
Anjelique F. Schulfer[1,2], Thomas Battaglia[3], Yelina Alvarez[3], Luc Bijnens[4], Victoria E. Ruiz[3,5], Melody Ho[3], Serina Robinson[6], Tonya Ward[7], Laura M. Cox[3,8], Arlin B. Rogers[9], Dan Knights[10], R. Balfour Sartor[11] and Martin J. Blaser[1,3,12*]

Does early life exposure to antibiotics causes gut dysbiosis, skewed immune development and increase risk for IBD in genetically prone subjects?



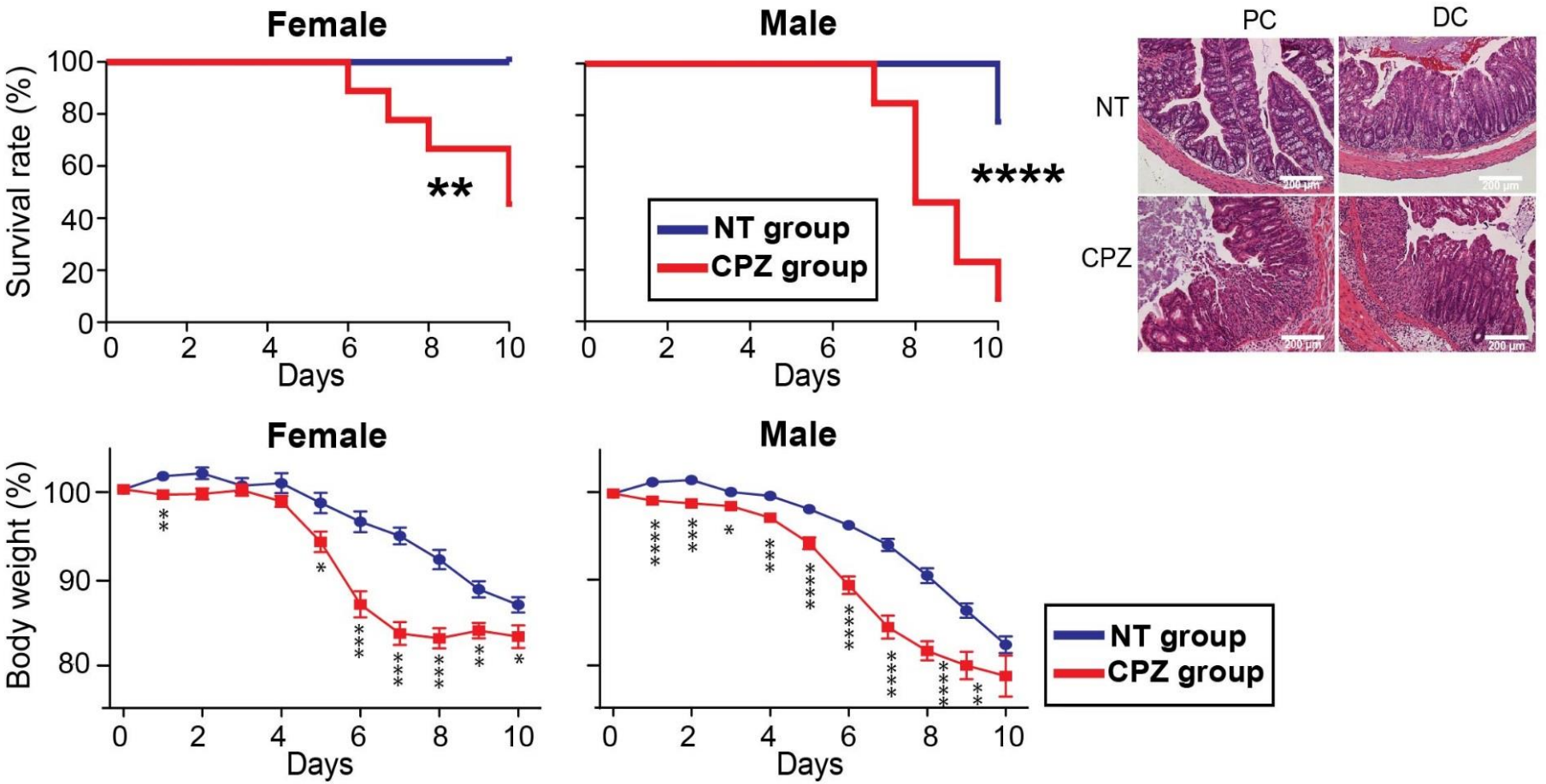
Peripartum antibiotic exposure increases the risk for spontaneous colitis in IL-10 KO offspring





Miyoshi, et al Cell Reports 2017

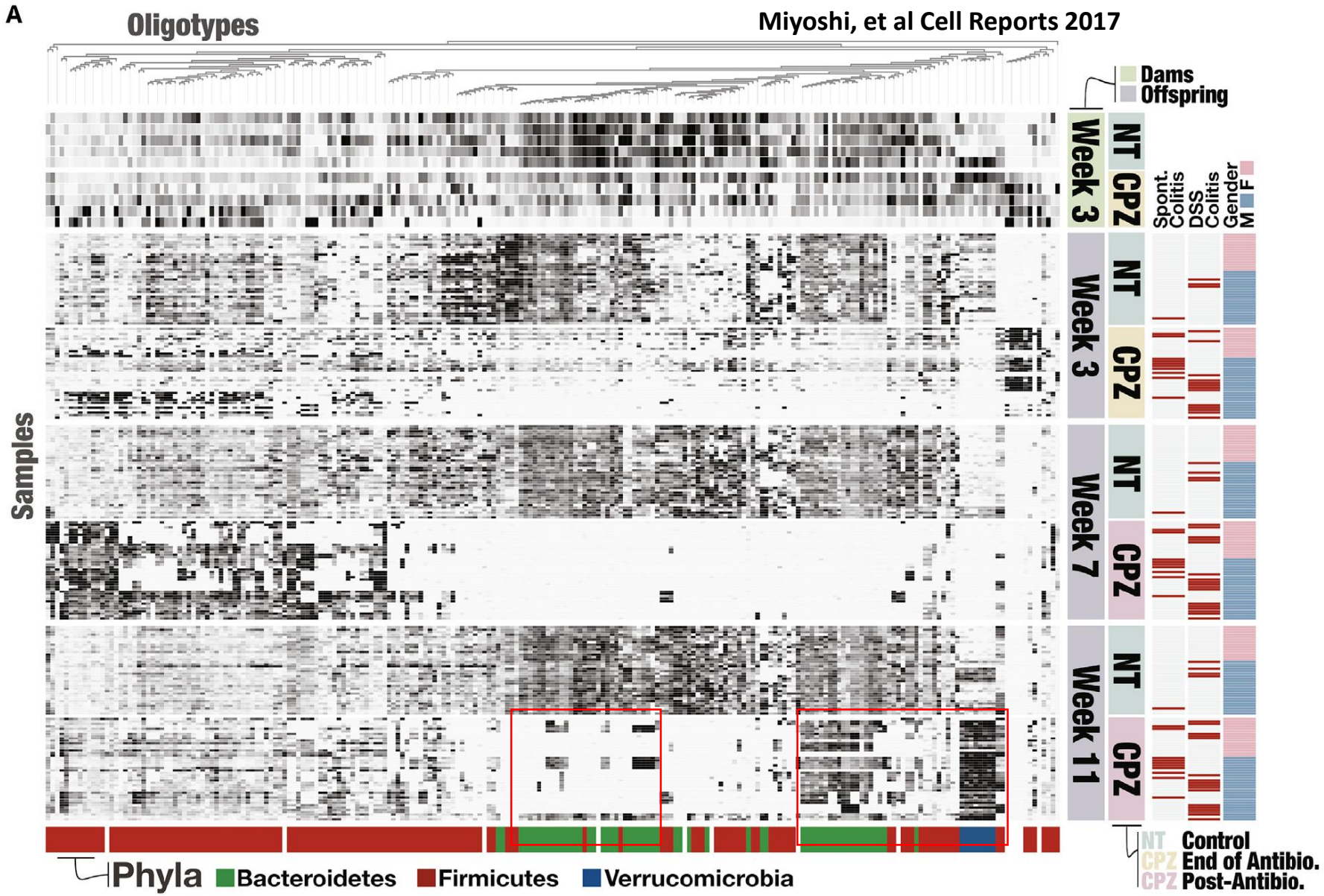
IL10KO offspring without frank colitis after exposure to peripartum CPZ are more susceptible to DSS-induced colitis



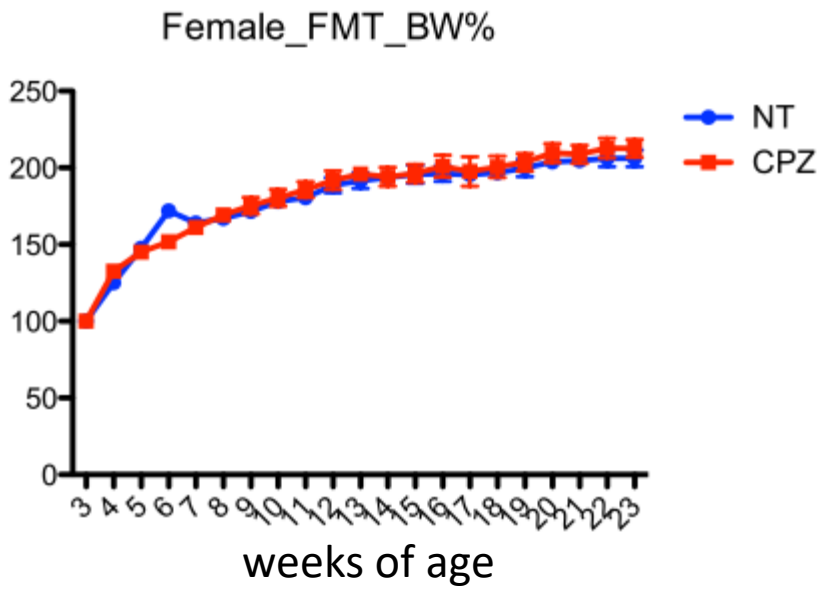
IL-10 KO mice exposed to CPZ during a critical window of development exhibit increased susceptibility to developing both spontaneous and chemically-induced colitis later in life.

Miyoshi, et al Cell Reports 2017

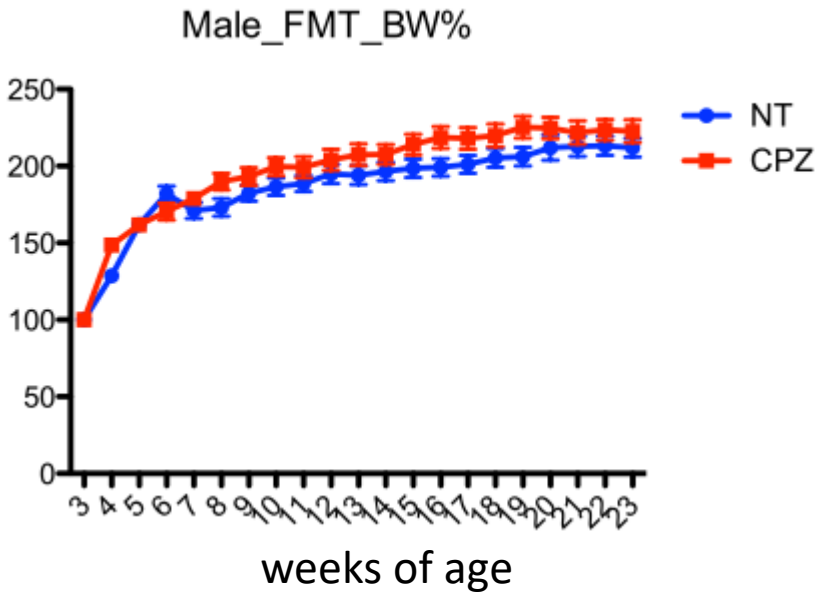
Peripartum CPZ treatment induces persistent and significant gut dysbiosis in IL-10 KO offspring



Gain or loss of microbiota function?



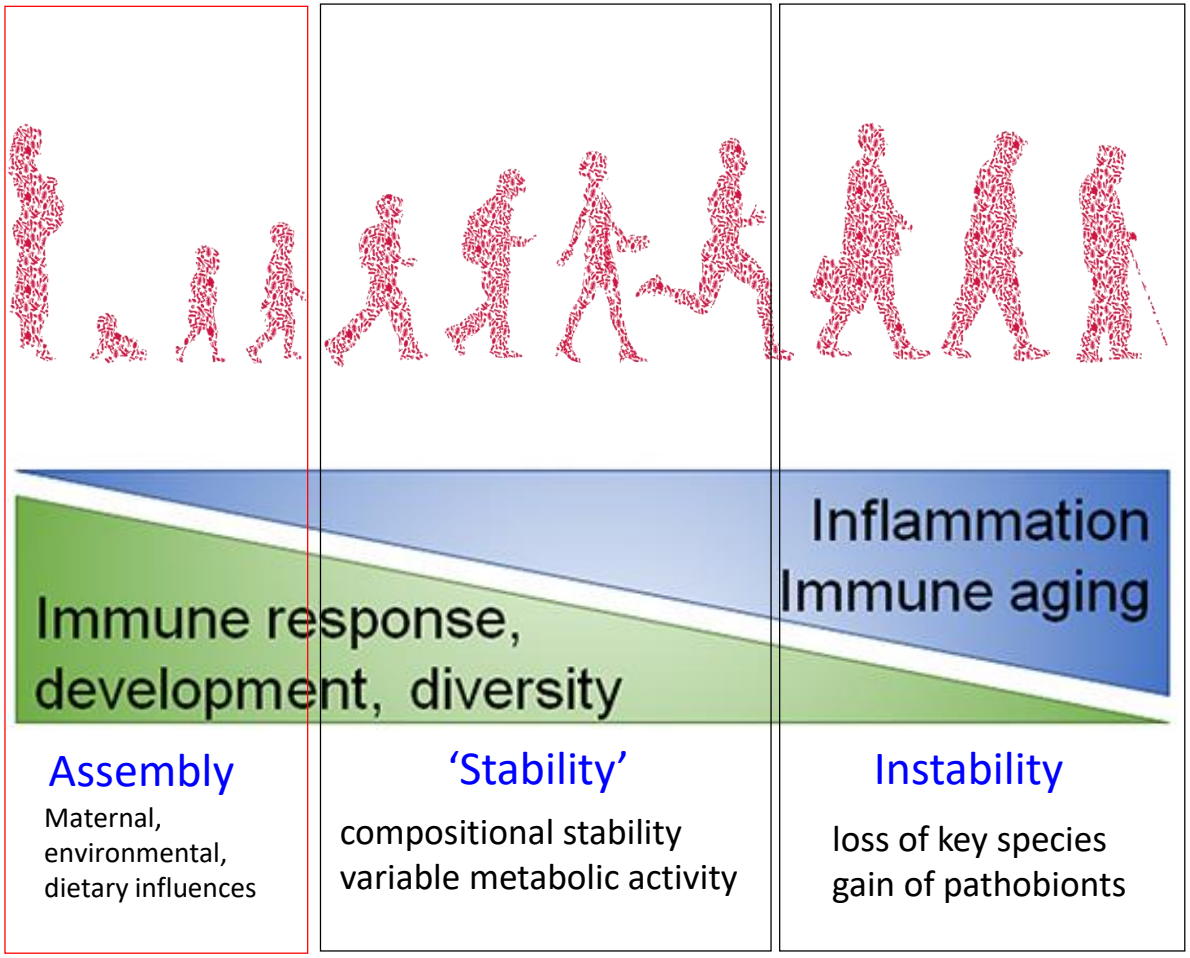
10 female pups in each group



10 male pups in each group

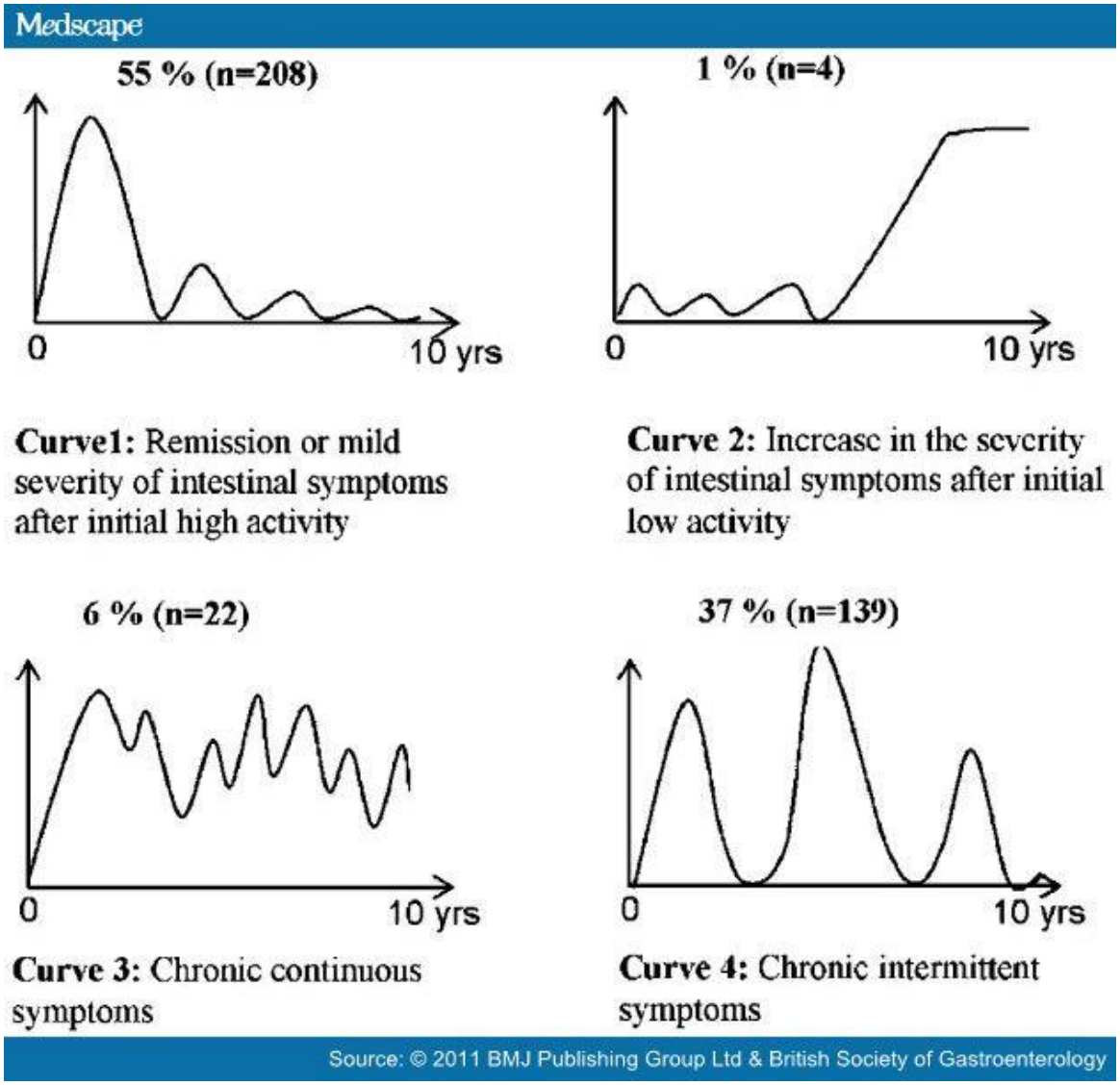
Miyoshi, et al Cell Reports 2017

Host-immune states with aging: Impact on human health and disease



Slide adapted from one provided by Fergus Shanahan

Limitations of cross-sectional studies in IBD



Why study ulcerative colitis with total colectomy and ileal pouch anal anastomosis (IPAA)?

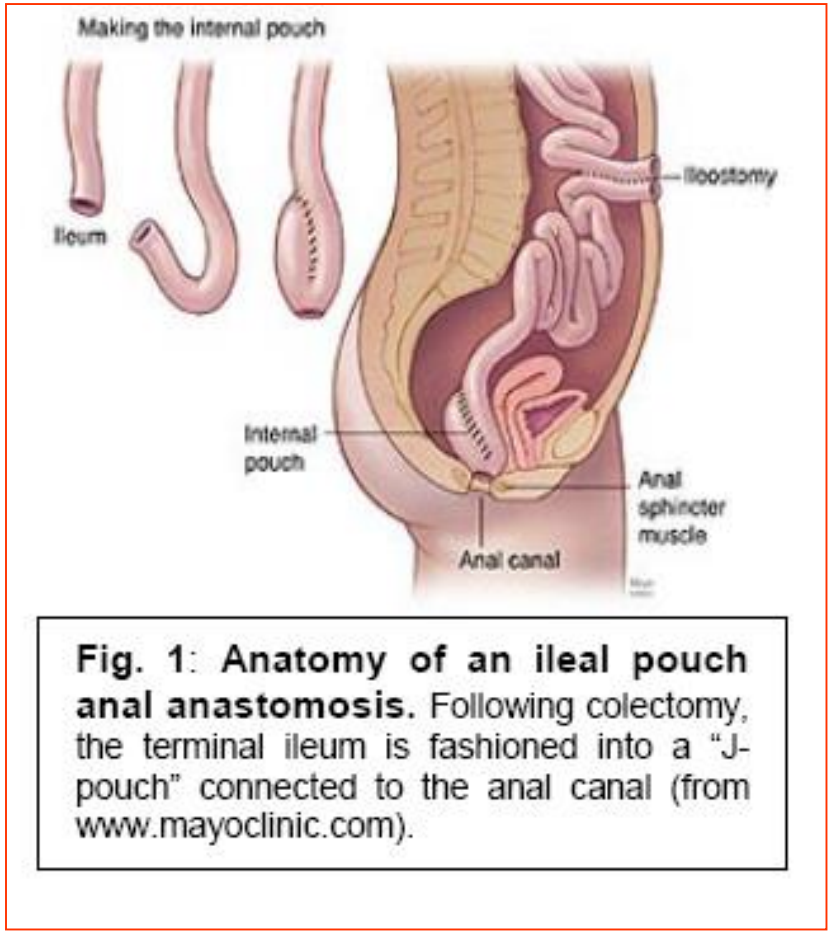


Fig. 1: Anatomy of an ileal pouch anal anastomosis. Following colectomy, the terminal ileum is fashioned into a "J-pouch" connected to the anal canal (from www.mayoclinic.com).

Pouchitis

Highlights

- ~50% pts will develop it in <2y
- Incidence in UC>>FAP
- Microbe-dependent
- Prospective design
- Easy to sample (unprepped)
- Pts as their own controls
- Control group (FAP)

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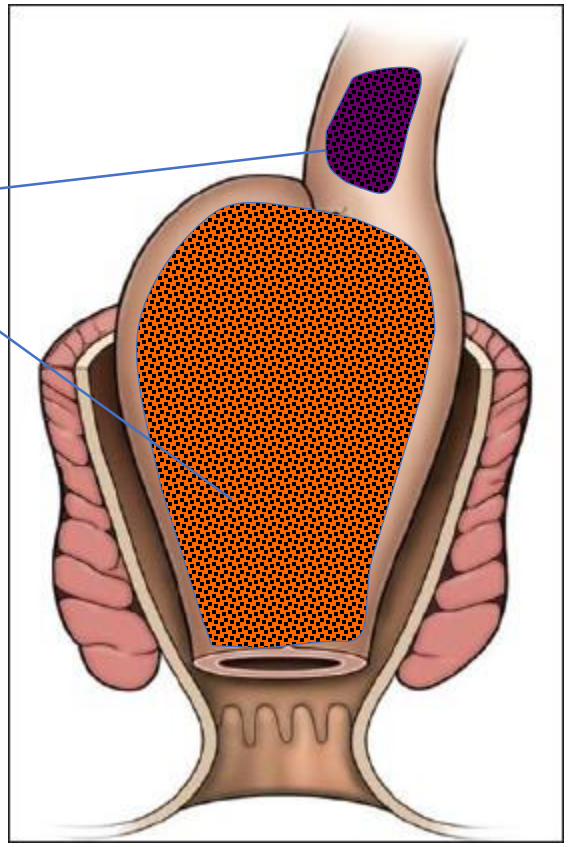
Study design and sampling points

Mucosal biopsy and luminal aspirate

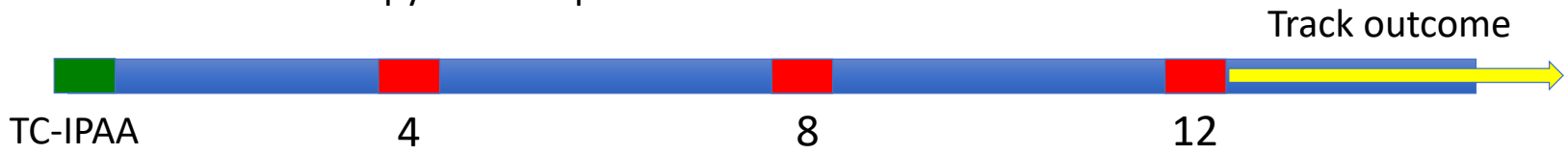


FAP patients – studied only at one time point > 2 yrs after IPAA

Sample analysis

- **Patient**
  - Histology
  - Gene Expression
  - Clinical metadata
- **Microbiome**
  - Membership (16S)
  - Function profile
  - Cultivars

Pouchoscopy and biospecimen collections



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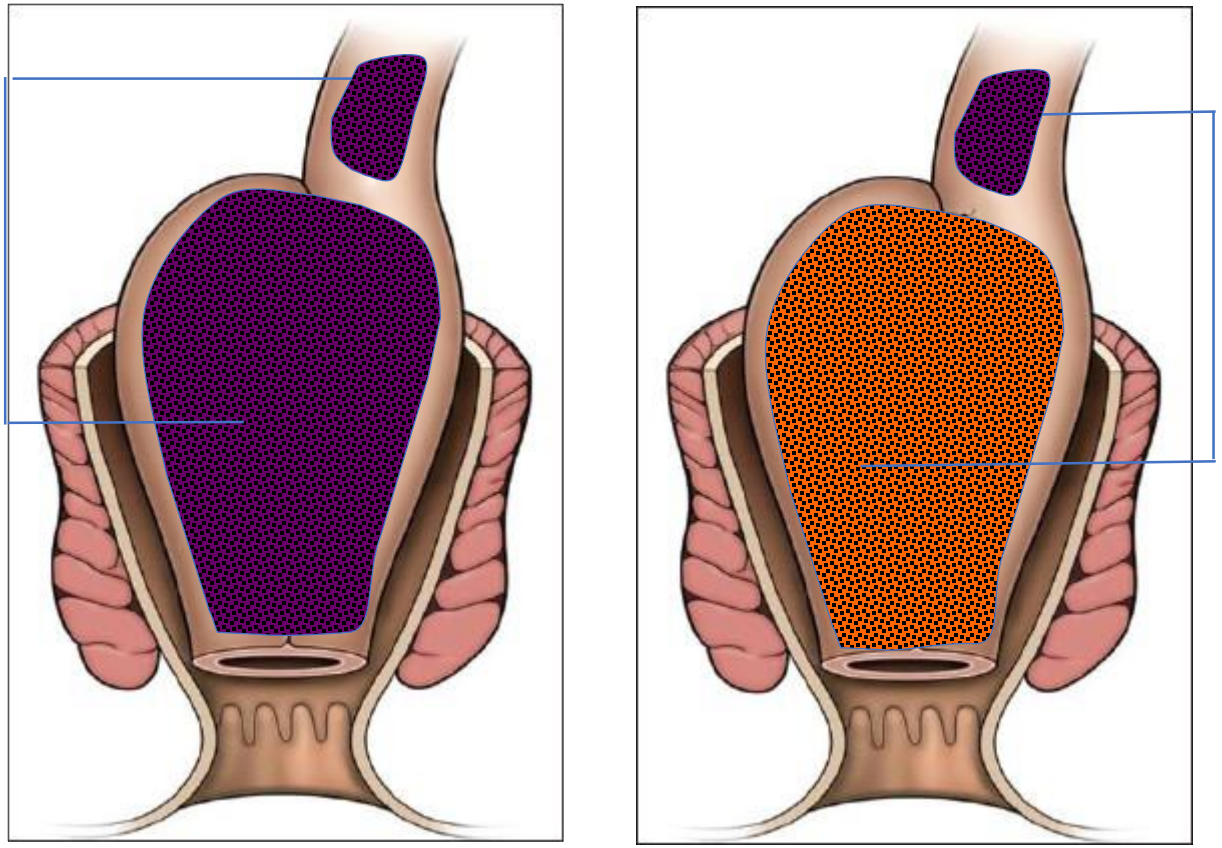
UC patients exhibit differences in tissue response to gut microbiota (coding and nc RNA)

Non-UC (FAP) patients

UC patients

No significant differences in genes in transcriptomes



>6000 genes different

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Pathways represented in the UC pouch transcriptome

- Colonic metaplasia
- Changes in the extracellular matrix and growth factors
- Enhanced immune activation
- Suppressed xenobiotic metabolism and P450 signaling

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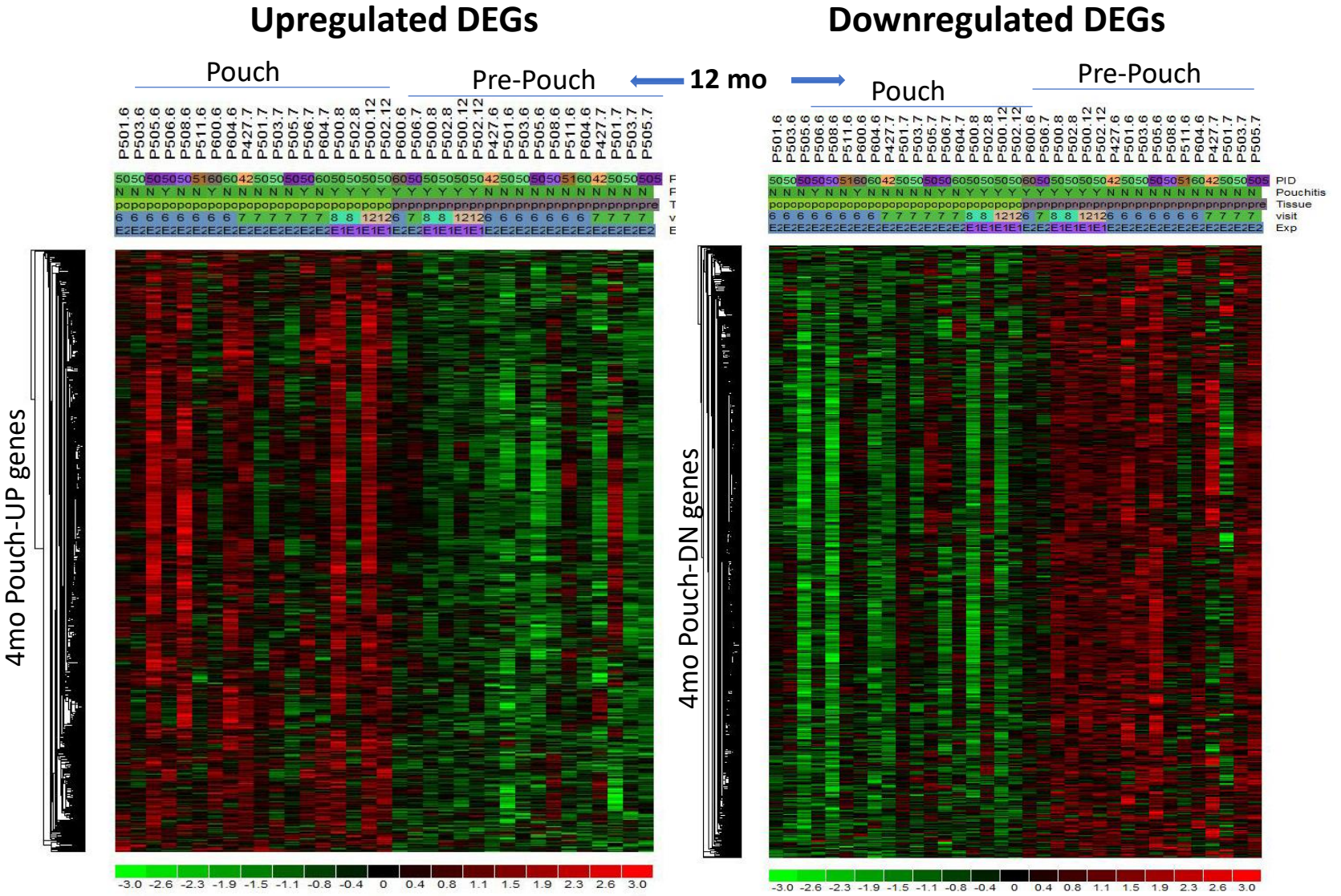
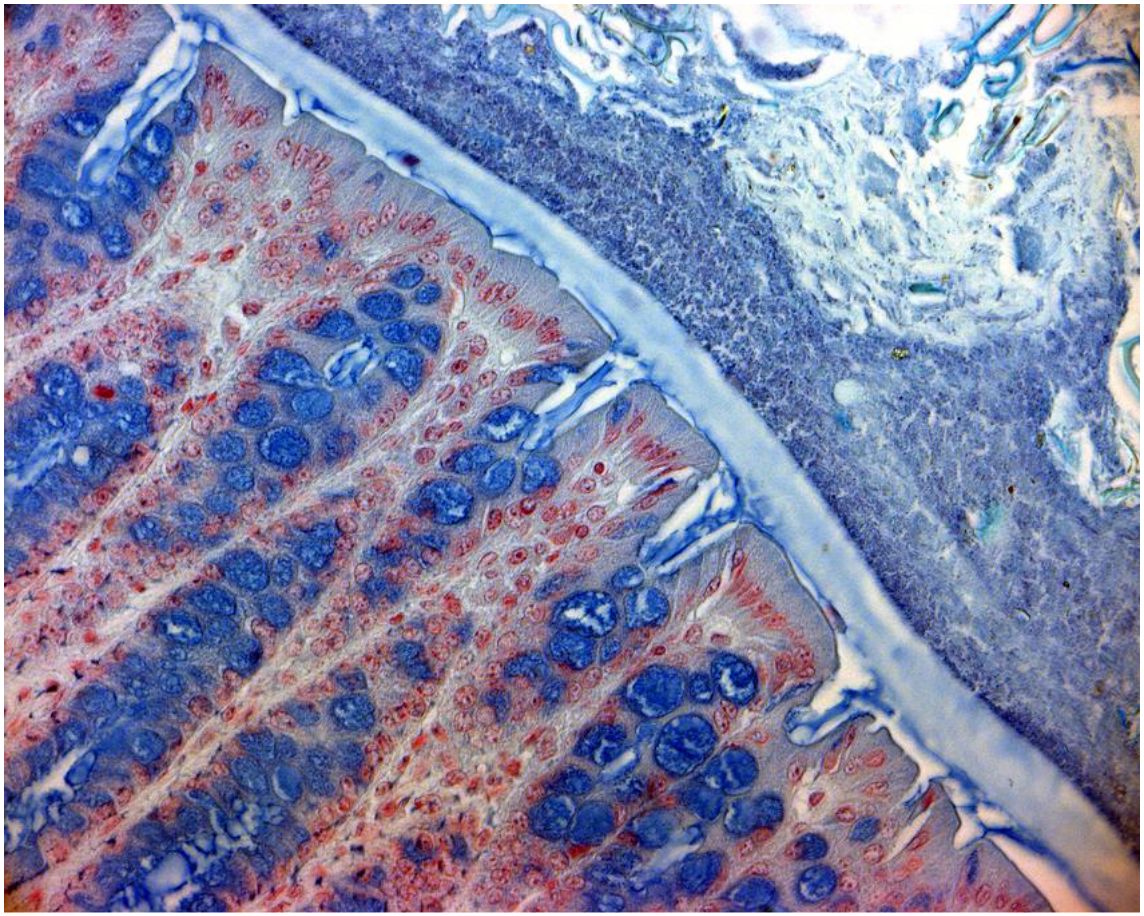
Aberrant gene expression profiles of the UC pouch are evident at 4 months after pouch functionalization

(Illumina HiSeq 75bp, PE)



What about the role of gut microbes in the development of UC pouchitis?



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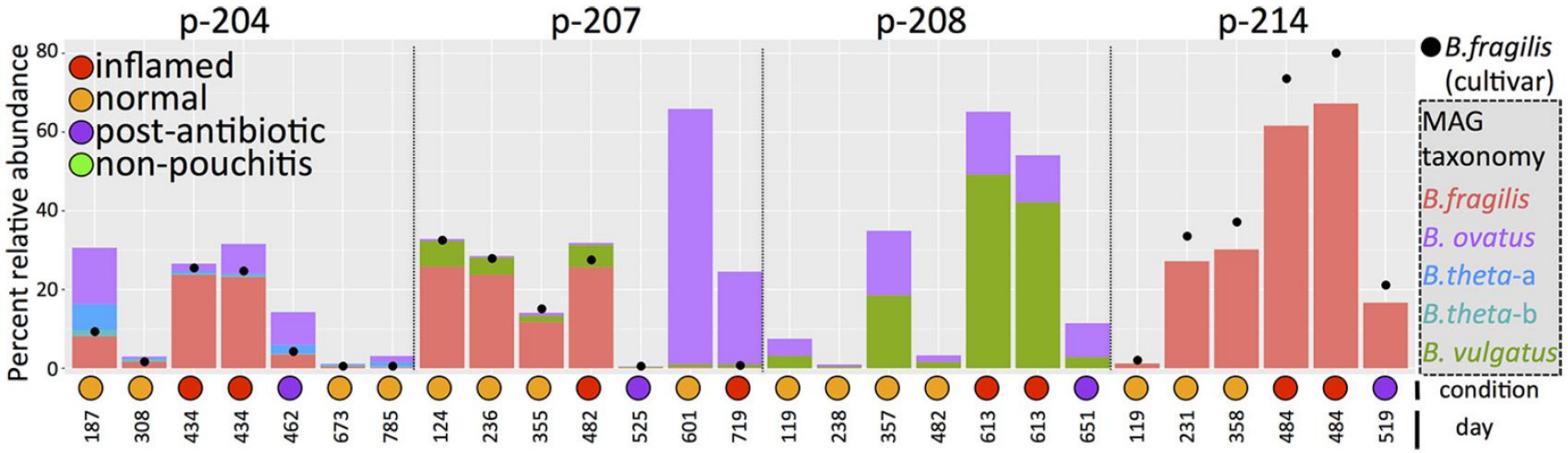
Patient-Specific *Bacteroides* Genome Variants in Pouchitis

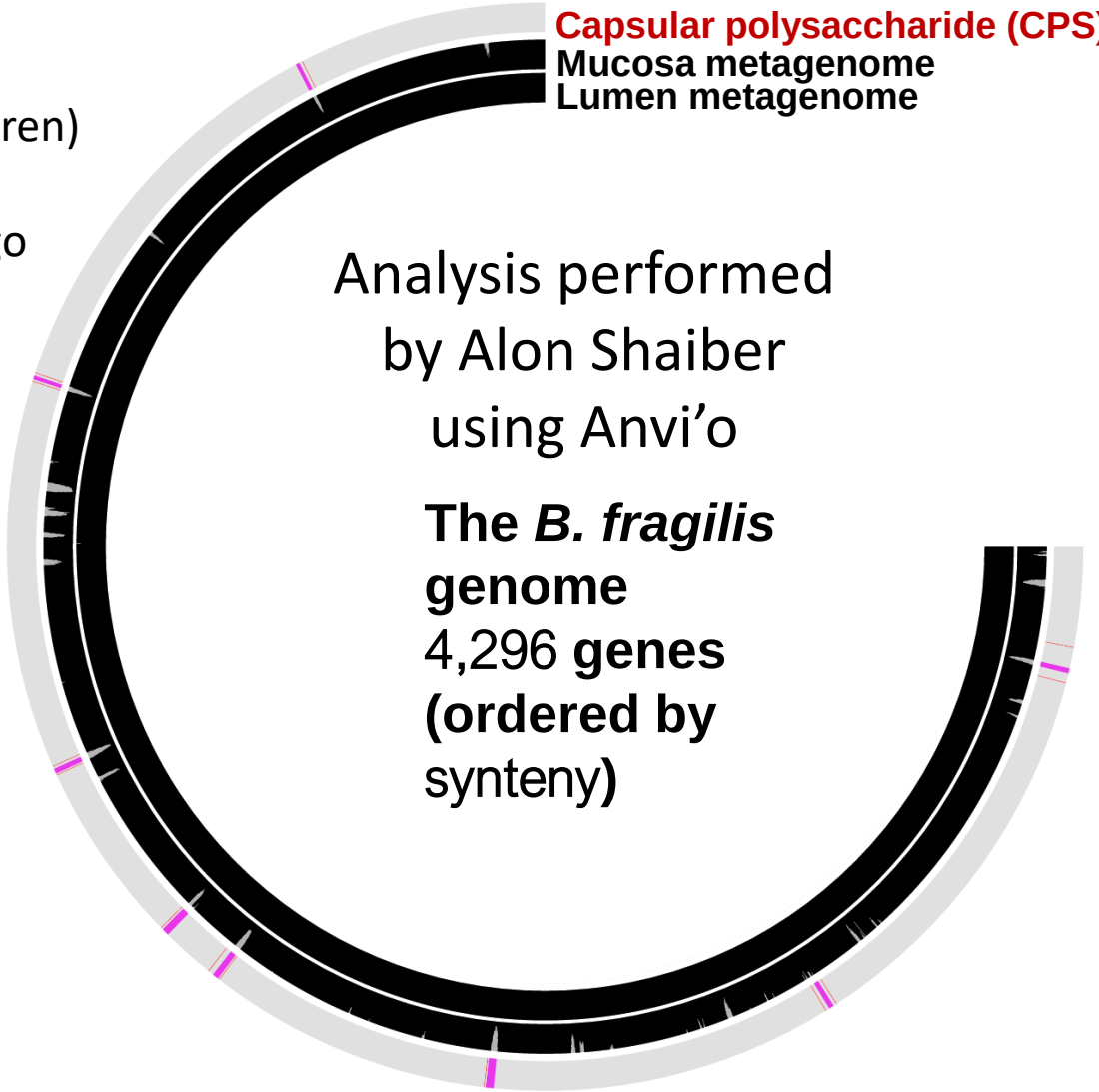
Joseph H. Vineis,[a] Daina L. Ringus,[b] Hilary G. Morrison,[a] Tom O. Delmont,[b] Sushila Dalal,[b] Laura H. Raffals,[c] Dionysios A. Antonopoulos,[b,d] David T. Rubin,[b] A. Murat Eren,[a,b] Eugene B. Chang,[b] Mitchell L. Sogin[a]

B. fragilis blooms before and during pouchitis in some, but not all patients



Anvi'o [Analysis and Visualization Platform for 'omics Data]

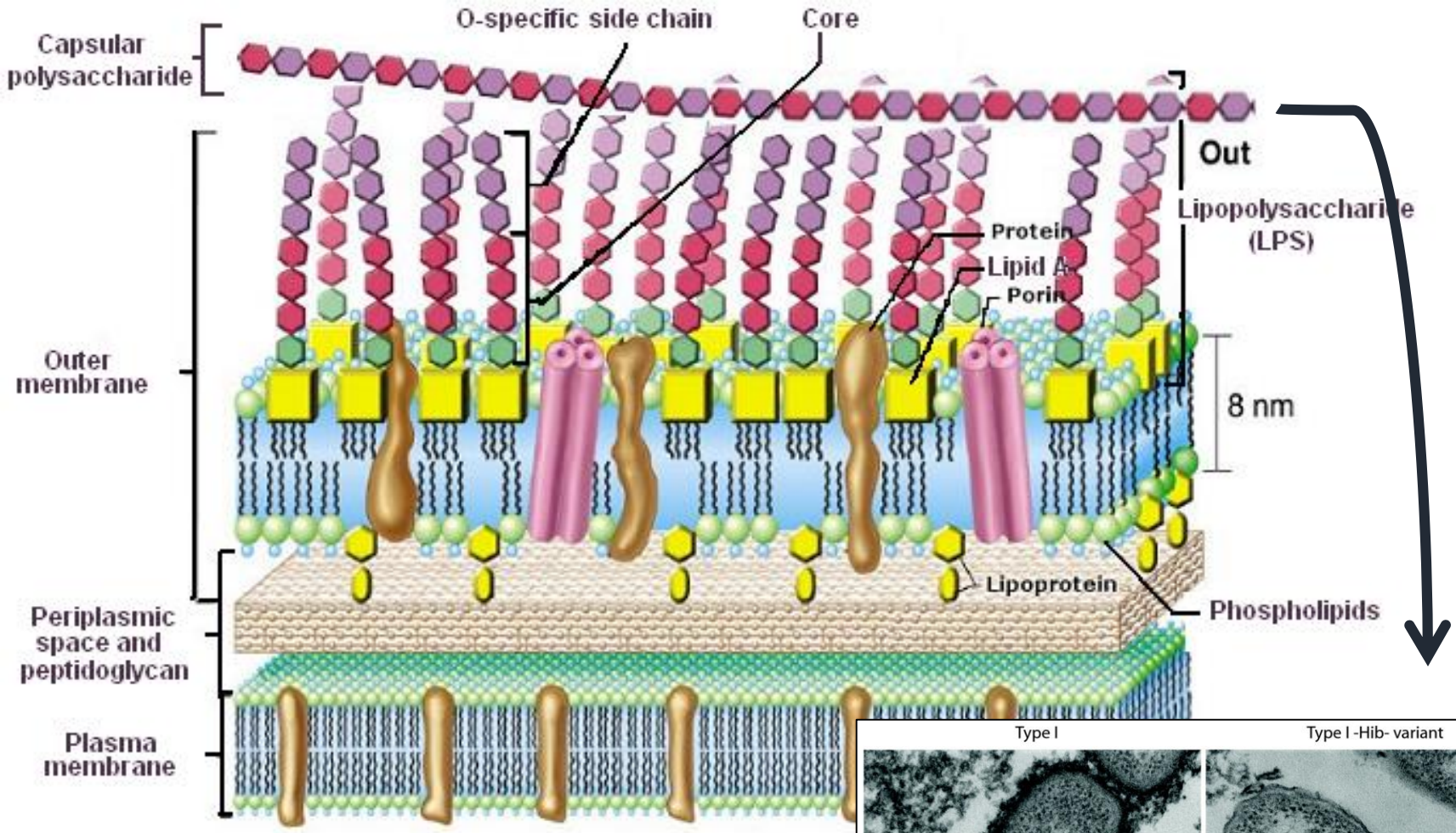
A. Murat Eren (Meren)
Assistant Professor
University of Chicago



Analysis performed by Alon Shaiber using Anvi'o

The *B. fragilis* genome
4,296 **genes (ordered by** synteny**)**

Genomic hot spots: Capsular polysaccharides



Proposed three stage model for the development of pouchitis

Stage I

3-4 months

FAP

~50%

Healthy

UC

Stage II

1. Compensated state of immune activation and inflammation
2. COLONization

~50%

Stage III

~50%

Pathobiont(s)

Pouchitis

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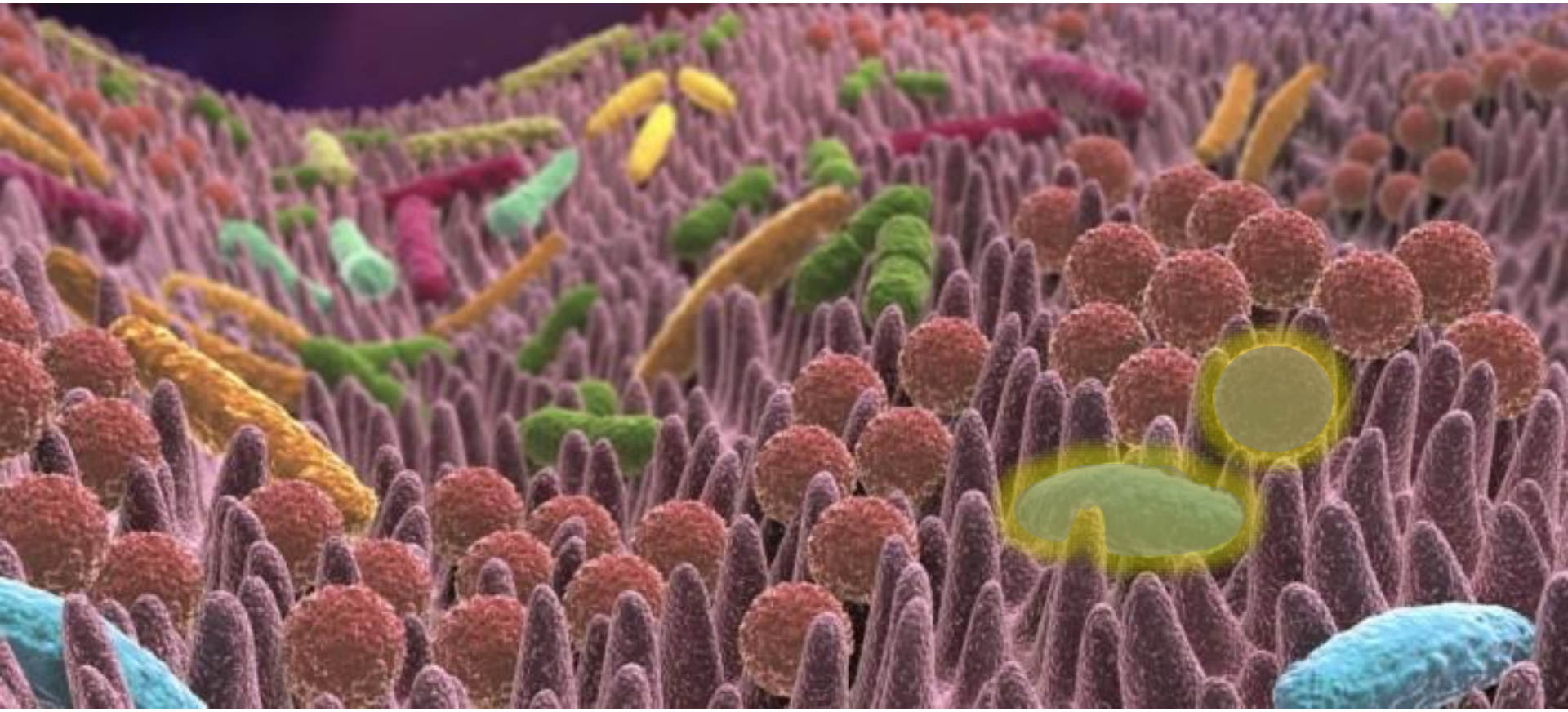
IBD pathobionts – what should we be looking for?



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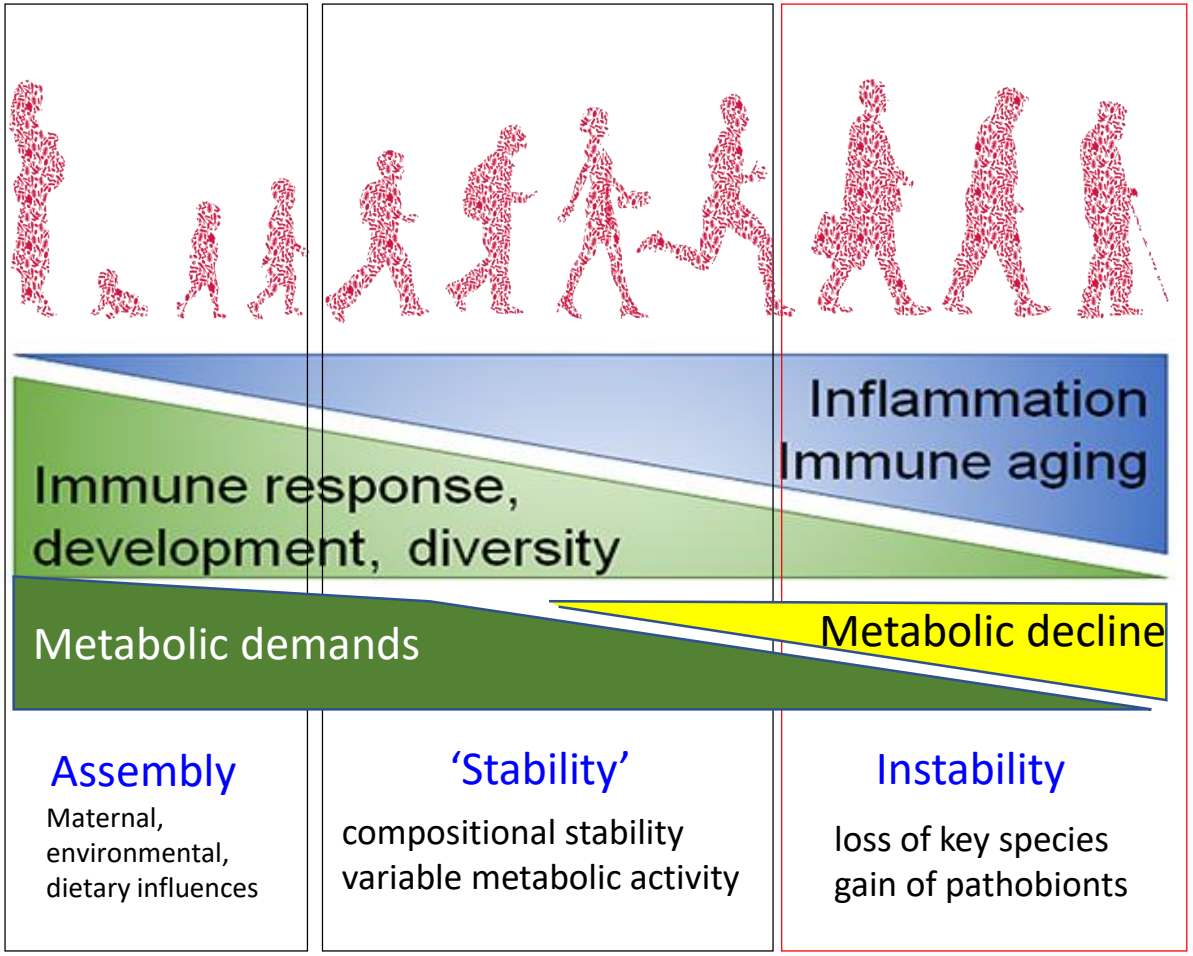
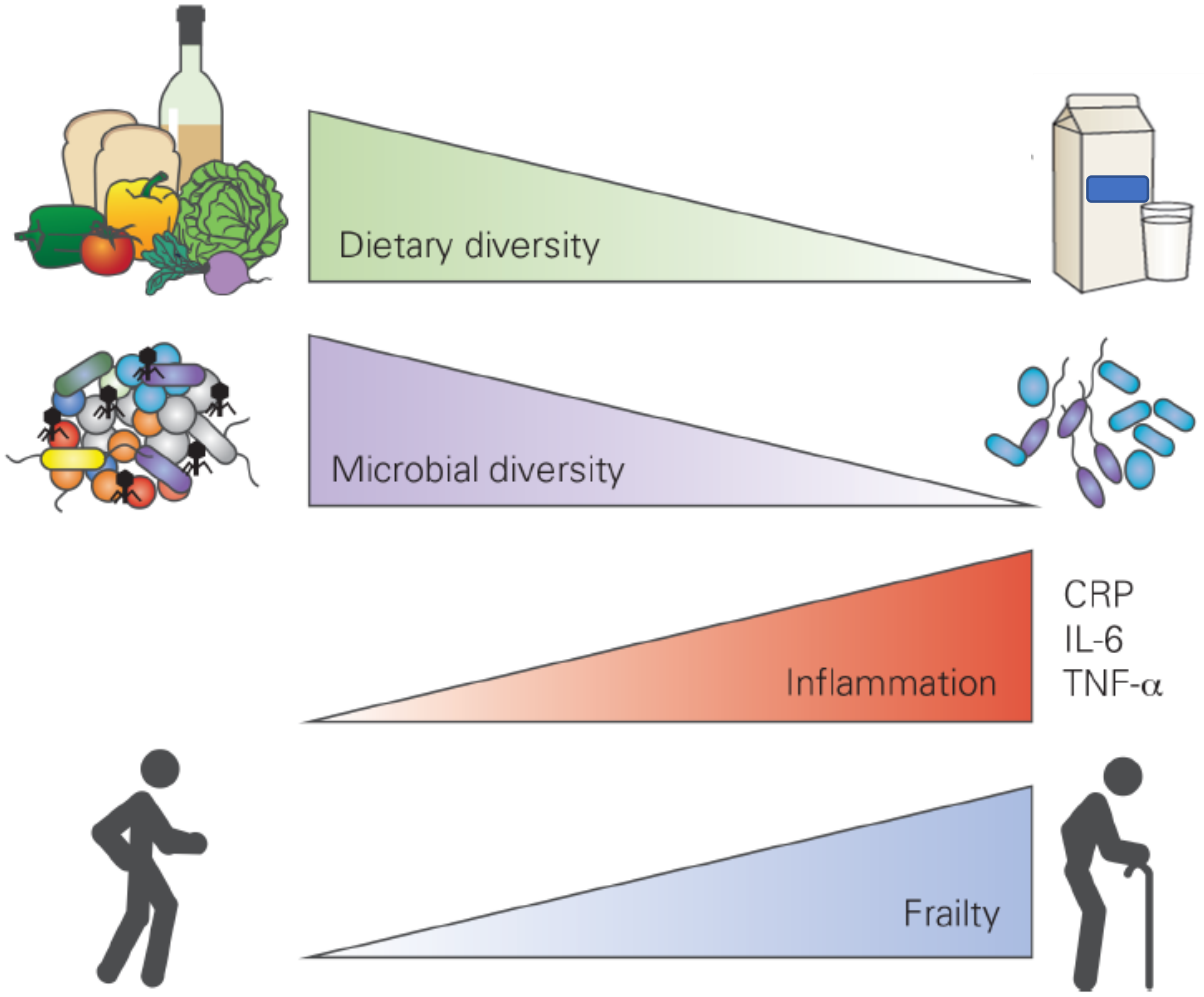
Host-microbiome states change with age: Impact on human health and disease



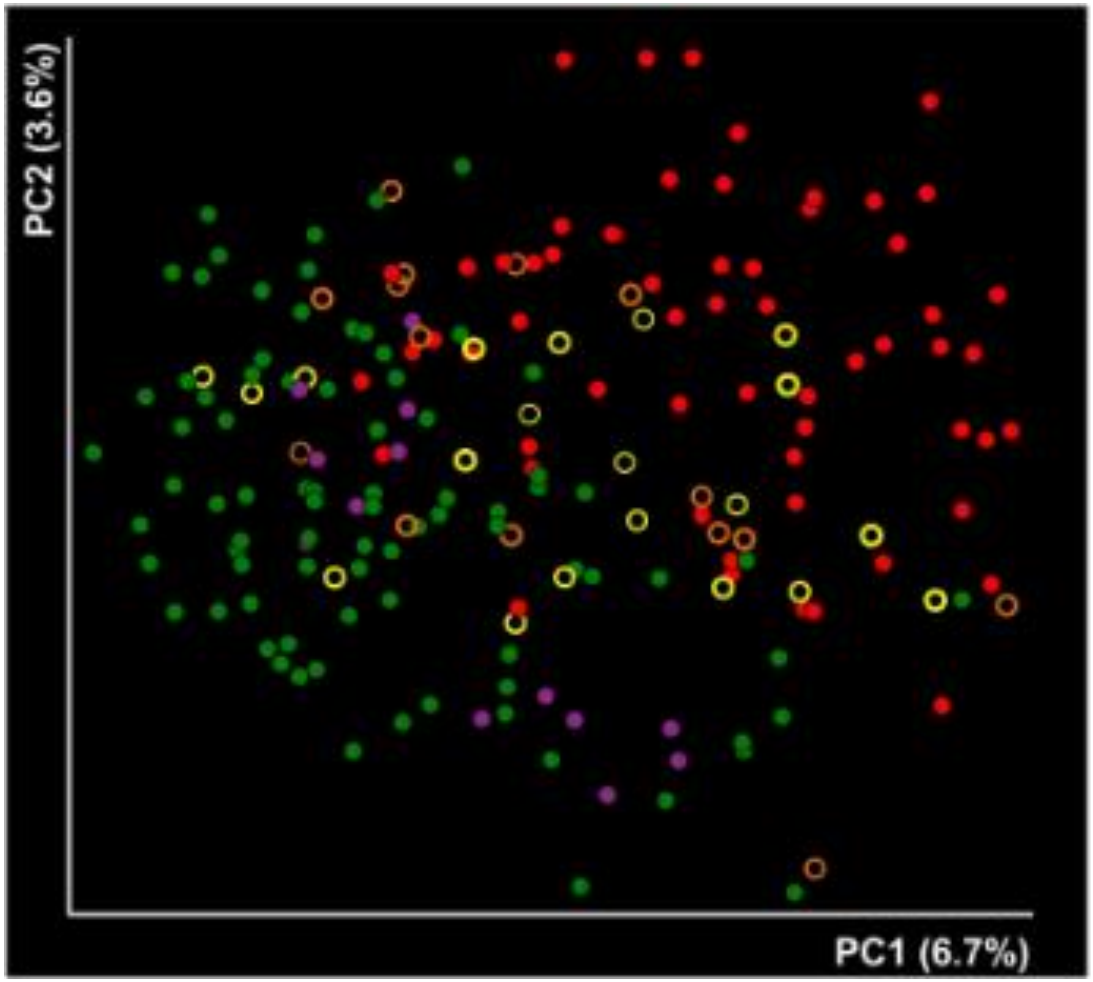
Slide adapted from one provided by Fergus Shanahan

Diversity as staple not spice of life



Shanahan *et al*. *Gut* 2017
Claesson *et al.* ***Nature* 2012**

Gut bacteria vary with where you live

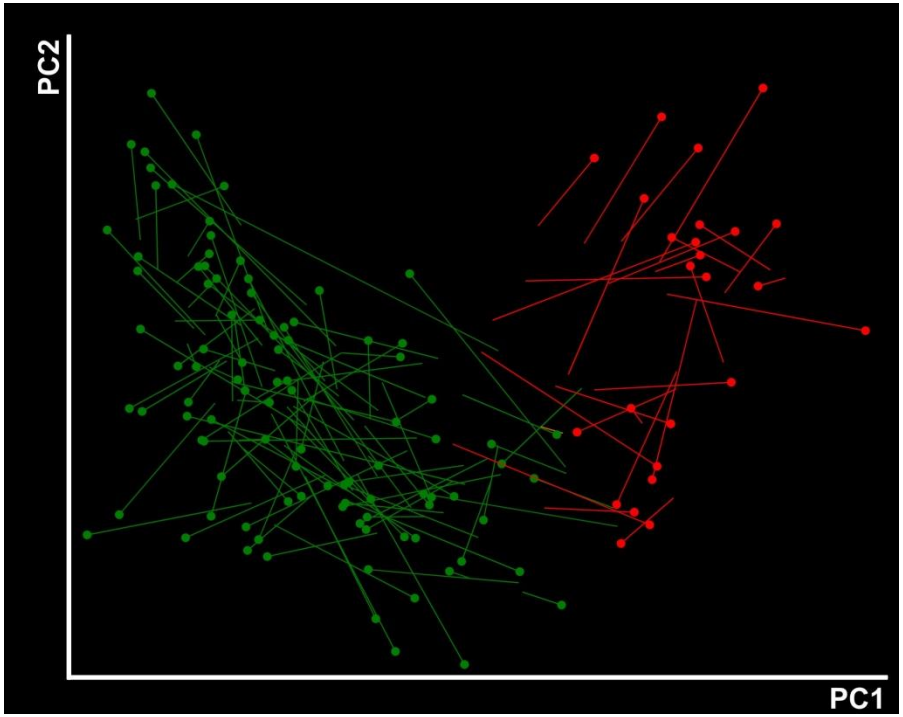


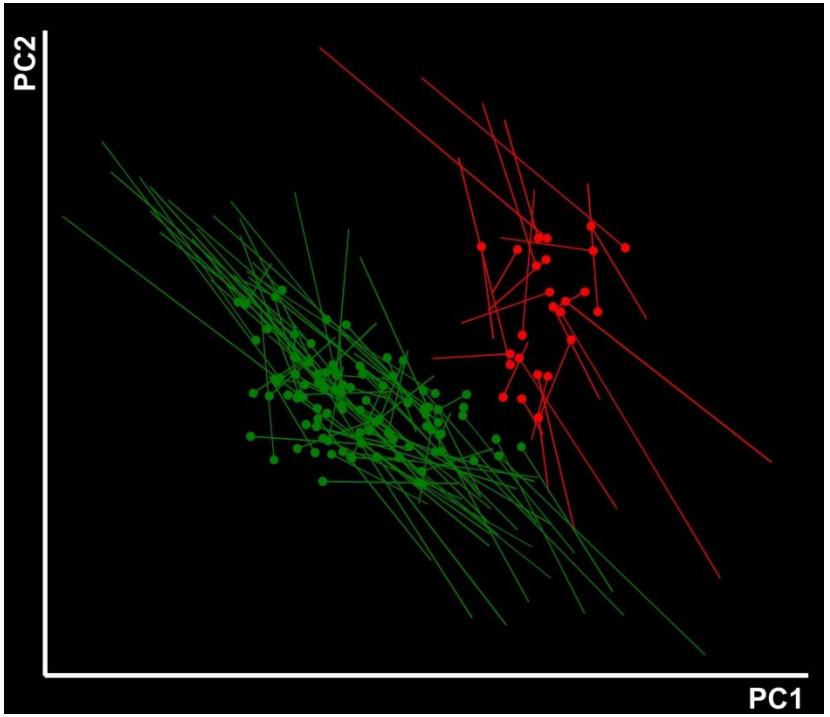
Community Day Hospital Rehab Long-stay Young control

Elderly

Claesson *et al.*, 2012 *Nature*

Microbiota & diet correlation by duration in long-stay care





FFQ ● Microbiota

N/A (C+DH) Week 0to6 (Rehab) Week 6 to Year 1 Year 1+

Claesson *et al.*, 2012 *Nature*

Potential impact of the aging gut microbiome on human health

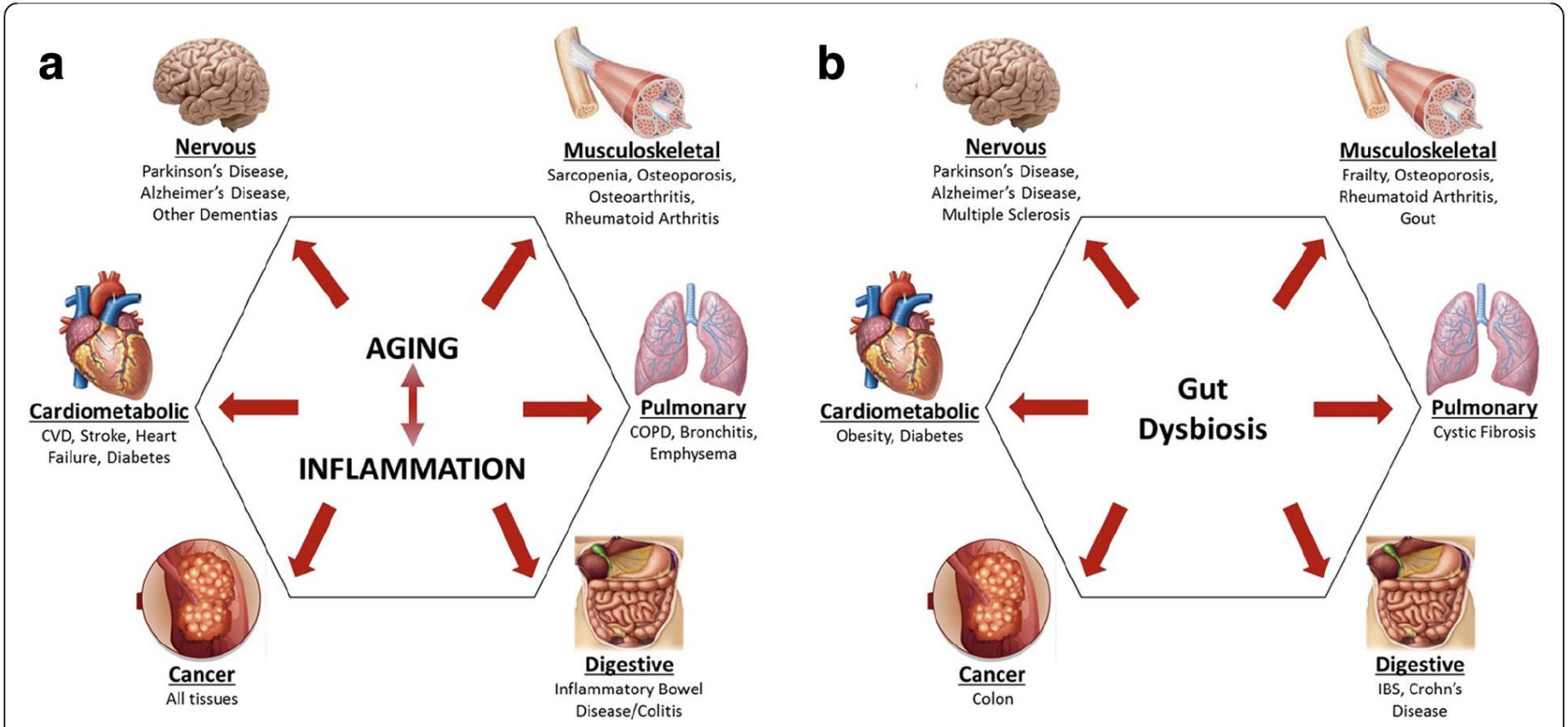


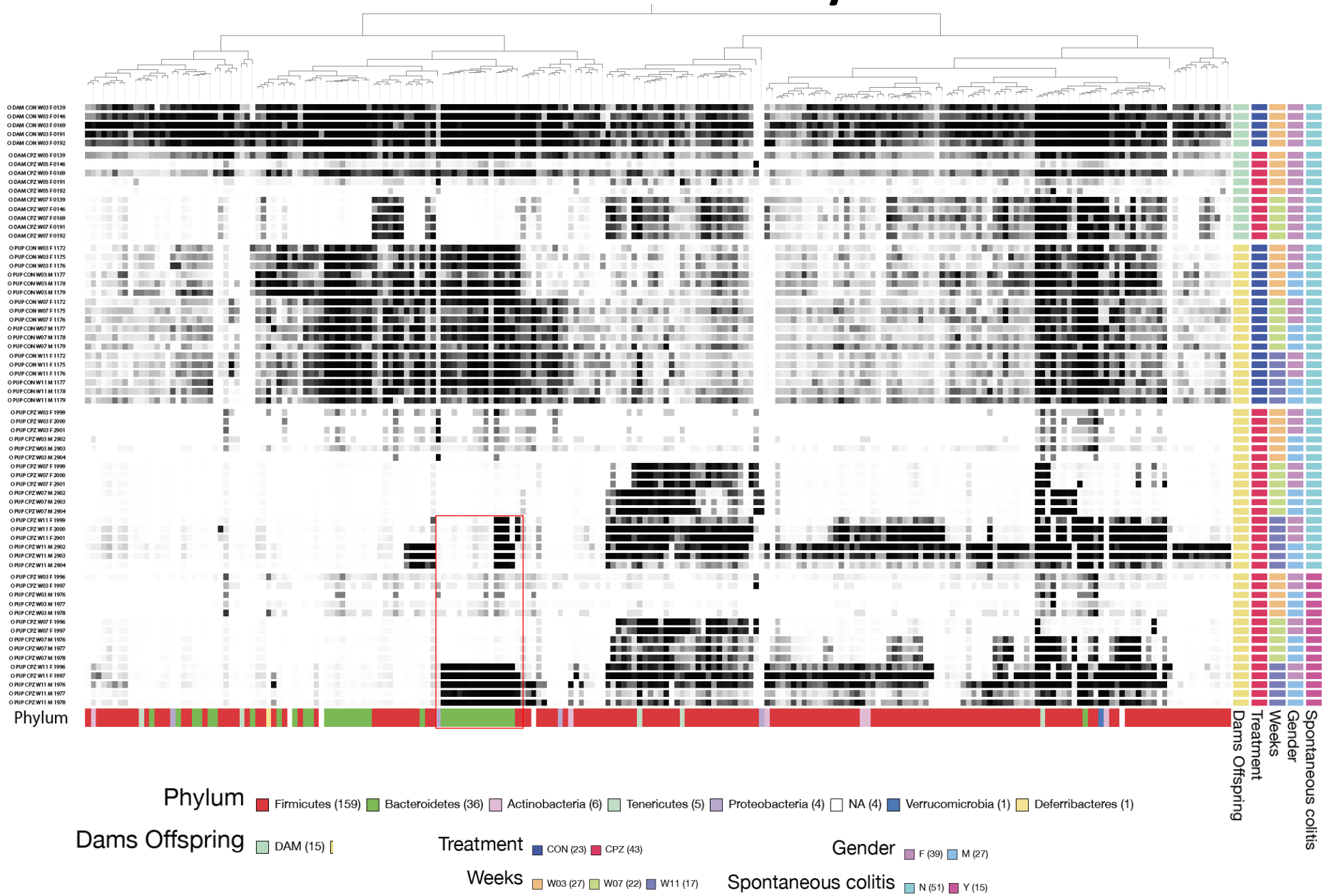
Fig. 2 a Prominent health conditions with both biologic age and chronic inflammation as central risk factors. **b** Prominent health conditions with evidence linking them to gut dysbiosis. Note the similarities between the conditions associated with aging and inflammation and those associated with gut dysbiosis

Buford. Microbiome (2017) 5:80

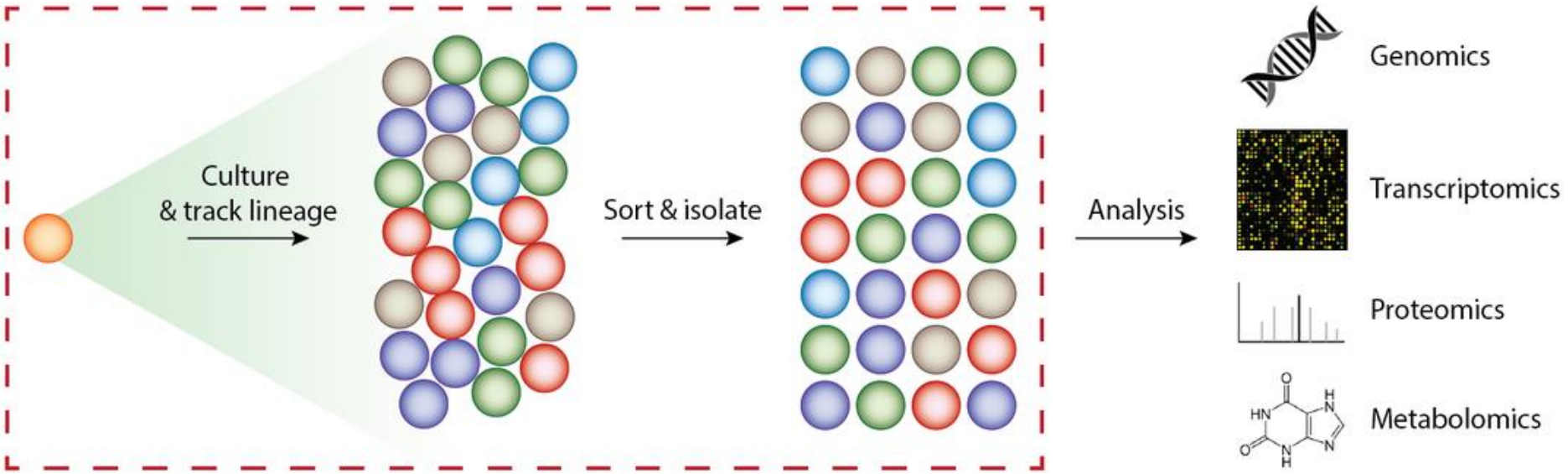
Key questions posed for this workshop

- Many factors can influence responses such as genetics of the individual/subpopulation, diet, concomitant disease and drugs, etc. Maybe. What evidence do we have on these factors playing a role in the microbiome particularly as it affects human susceptibility? Shown
- Are there groups of bacteria that signal impact on the microbiome? How would you go about ranking or prioritizing the bacterial subgroups? (1) Building next generation of functional tools to study microbial strains and consortia in context. (2) Combination of human and experimental models, (3) longitudinal and interventional study designs
- How do we account for different functioning capacities when we think of species level diversity? (combine with second question?) Species-level is insufficient resolution
- What would the most impactful work that a public-private consortium could contribute to this area? Promoting and funding innovative team science that goes beyond description and observation; Focus on bold, transformative agendas. Use both human and experimental approaches.
- How do changes in the gut microbiome produce adverse effects that can impact the health of the host and result in the presence of biomarkers? What approaches have been successful? What have failed? Too early to tell
- What would the most impactful work that a public-private consortium like HESI could contribute to this area? See above

Metagenomic-assembled genomes (MAGs) selected for further study



Tay Lab – Microfluidics for Life Sciences



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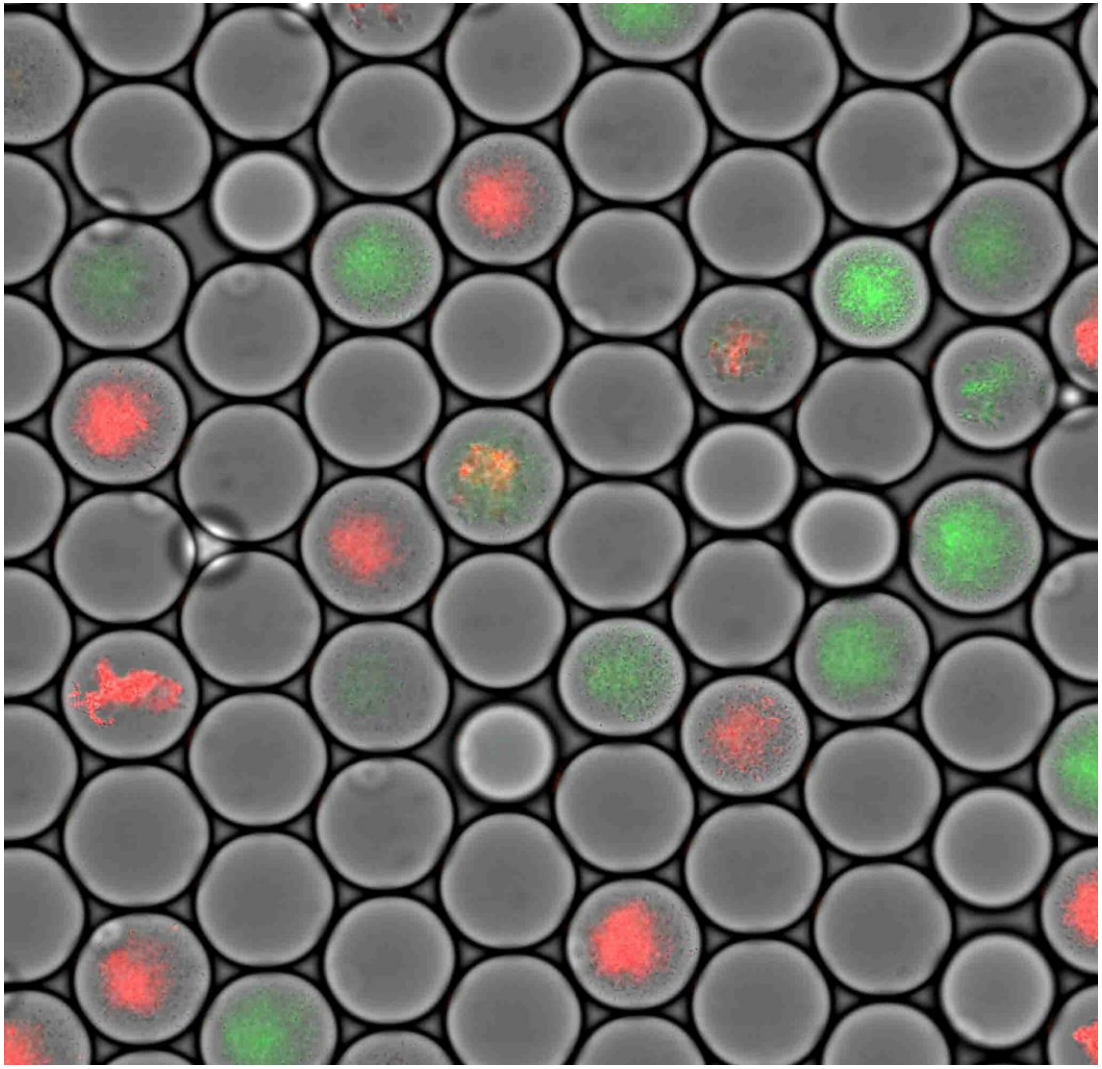
Microfluidic separation of Microbes

Poisson Distribution

$$P(X = x) = \frac{e^{-\lambda}}{x!}\lambda^{x}$$

x: number of bacteria in a single droplet

λ = (Number cells/mL)/(Number drops/mL)



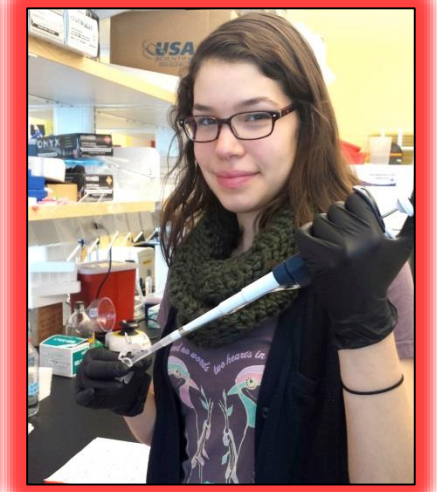
Red and Green E. Coli after Culture

Perinatal Antibiotics and Immune Tolerance Team

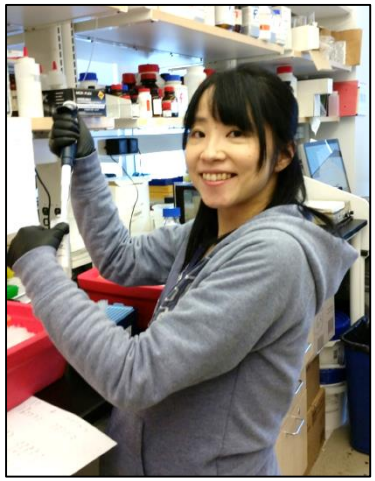
Vanessa Leone

Jun Miyoshi

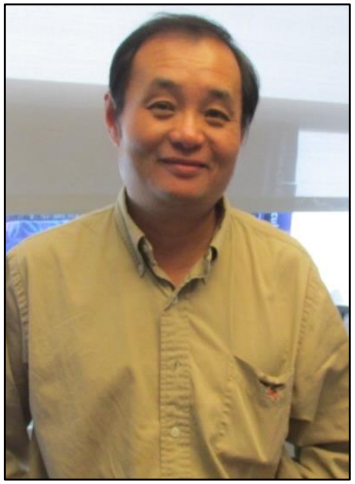
Alex Bobe



Sawako Miyoshi



Yong Huang



A. Murat Eren (Meren)

Nate Hubert

Acknowledgements (UC pouchitis)

UChicago

- Sushila Dalal
- David Rubin
- Jeannette Messer
- A. Murat Eren*
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- Tom Delmont
- Yeva Shan
- Mirae Lee
- Sean Crosson
- Aretha Feibig
- Joel Pekow
- Bana Jabri
- Yong Huang
- Daina Ringus
- Yun Tao
- Xiaorong Zhu
- Kristin Kearney
- Amy Duong
- Savas Tay
- Bill Watterson

UMich

- Eric Martens

HMS

- Laurie Comstock

UNC

- Shehzad Sheikh

Argonne Nat'l lab

- Dion Antonopoulos

MBL

- Mitch Sogin
- Joe Vineis
- Hilary Morison

Mayo Clinic

- Laura Raffals

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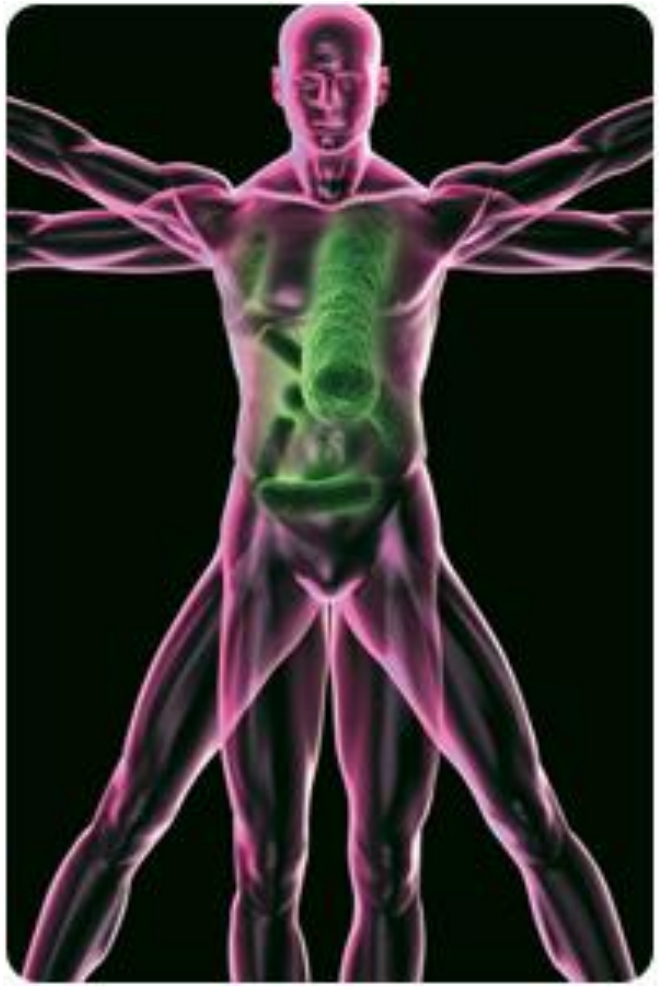
- NIDDK (P30 DDRCC; HMP)
- GI Research Foundation
- David and Ellen Horing Research Fund



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