



## The Microbiome in Infectious & Non-infectious Colitis

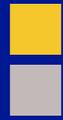
**Vincent B. Young, MD/PhD**

Department of Internal Medicine/Infectious Diseases

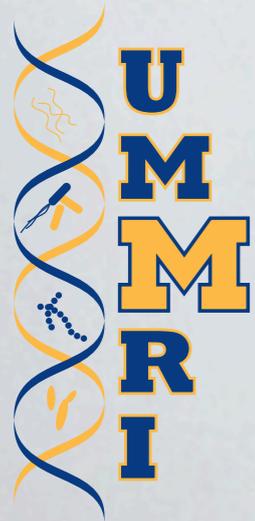
Department of Microbiology and Immunology

University of Michigan Medical School, Ann Arbor

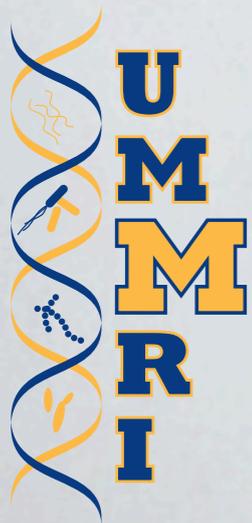
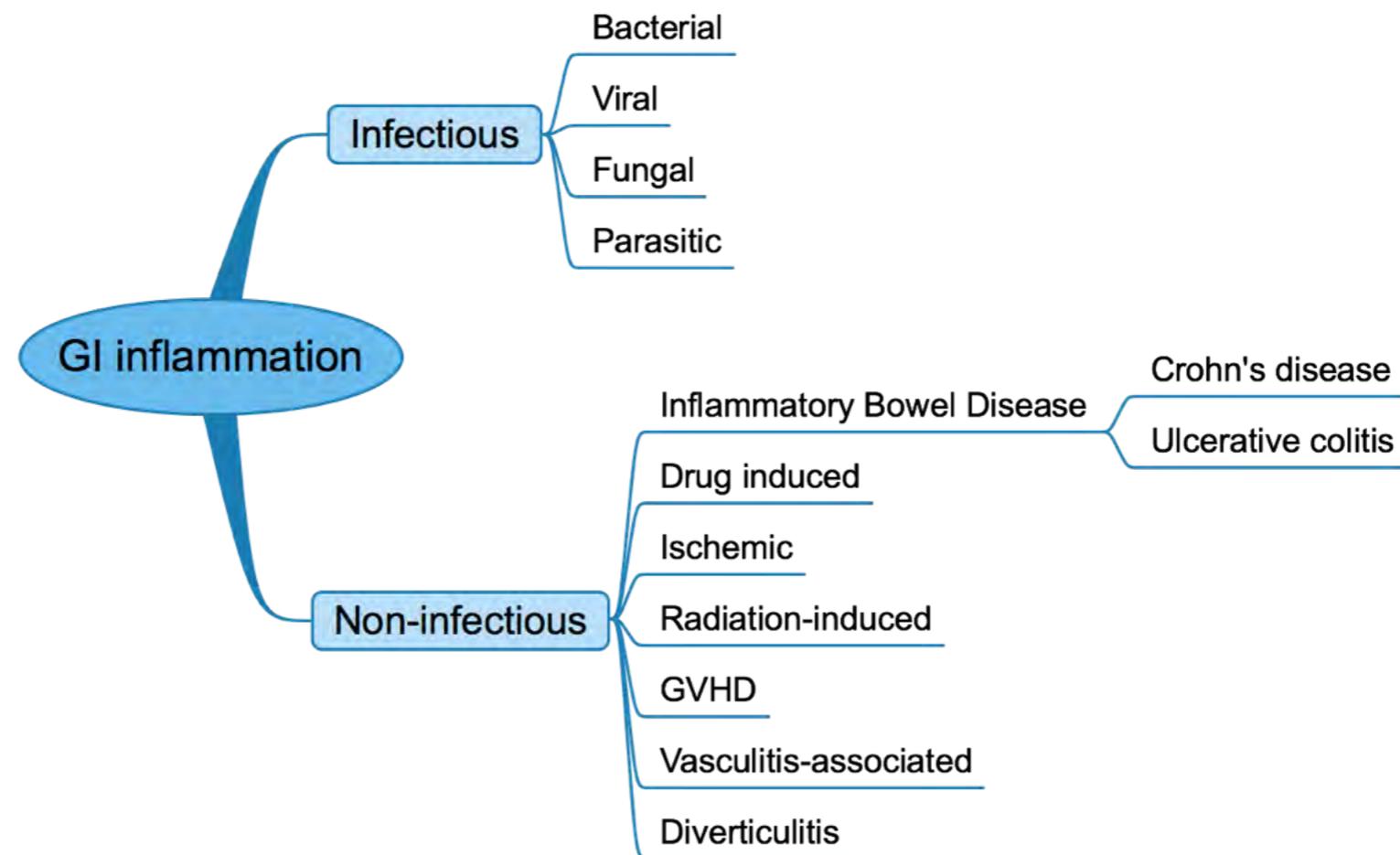


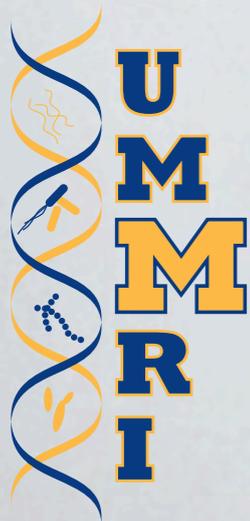


When balance is lost...



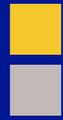
# Diseases characterized by gastrointestinal inflammation





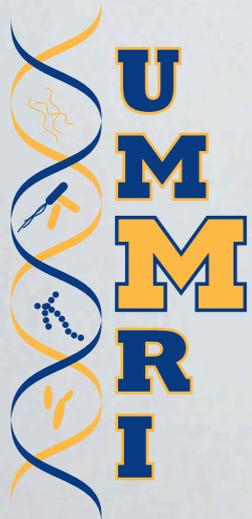
# Gaps/Needs & Challenges

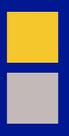
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- Results from experimentation with **model microbial communities** need to be validated and correlated with human subjects.
- There is a need for the development and validation of analytic methods to process data derived from **“multi-omic” datasets**.
- Results from microbiome studies need to be developed into **novel therapeutics**, which will require the ability to cultivate specific members of the microbiota and a deeper understanding of how to administer cultivars as potential therapies.



# Inflammatory Bowel Disease (IBD)

- Idiopathic condition affecting 1-2% of people in developed nations
- Characterized by sustained, abnormal inflammatory response involving the gastrointestinal mucosa
- Evidence point to a crucial role of the intestinal microbiota in the pathogenesis of IBD





# “Dysbiosis” in IBD

## Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases

Daniel N. Frank\*, Allison L. St. Amand\*, Robert A. Feldman†, Edgar C. Boedeker‡, Noam Harpaz§, and Norman R. Pace\*¶

\*Department of Molecular, Cellular, and Developmental Biology, University of Colorado, Boulder, CO 80309-0347; †Symbio Corporation, Menlo Park, CA 94025; ‡Department of Medicine, University of New Mexico, Albuquerque, NM 87131; and §Department of Pathology, Mount Sinai School of Medicine, New York, NY 10029

Contributed by Norman R. Pace, July 16, 2007 (sent for review June 7, 2007) PNAS (2007) 104:13780

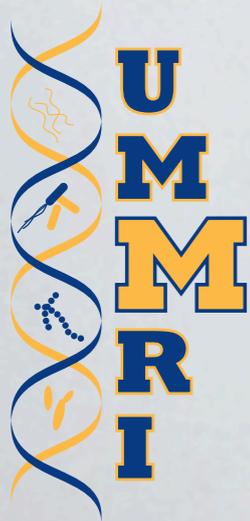
JOURNAL OF CLINICAL MICROBIOLOGY, July 2005, p. 3380–3389  
0095-1137/05/\$08.00+0 doi:10.1128/JCM.43.7.3380-3389.2005  
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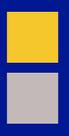
Vol. 43, No. 7

## Spatial Organization and Composition of the Mucosal Flora in Patients with Inflammatory Bowel Disease

Alexander Swidsinski,<sup>1\*</sup> Jutta Weber,<sup>1</sup> Vera Loening-Baucke,<sup>1</sup> Laura P. Hale,<sup>2</sup> and Herbert Lochs<sup>1</sup>

*Innere Klinik, Gastroenterologie, Charité Humboldt Universität, 10098 Berlin, Germany,<sup>1</sup> and Department of Pathology, Duke University Medical Center, Durham, North Carolina 27710<sup>2</sup>*



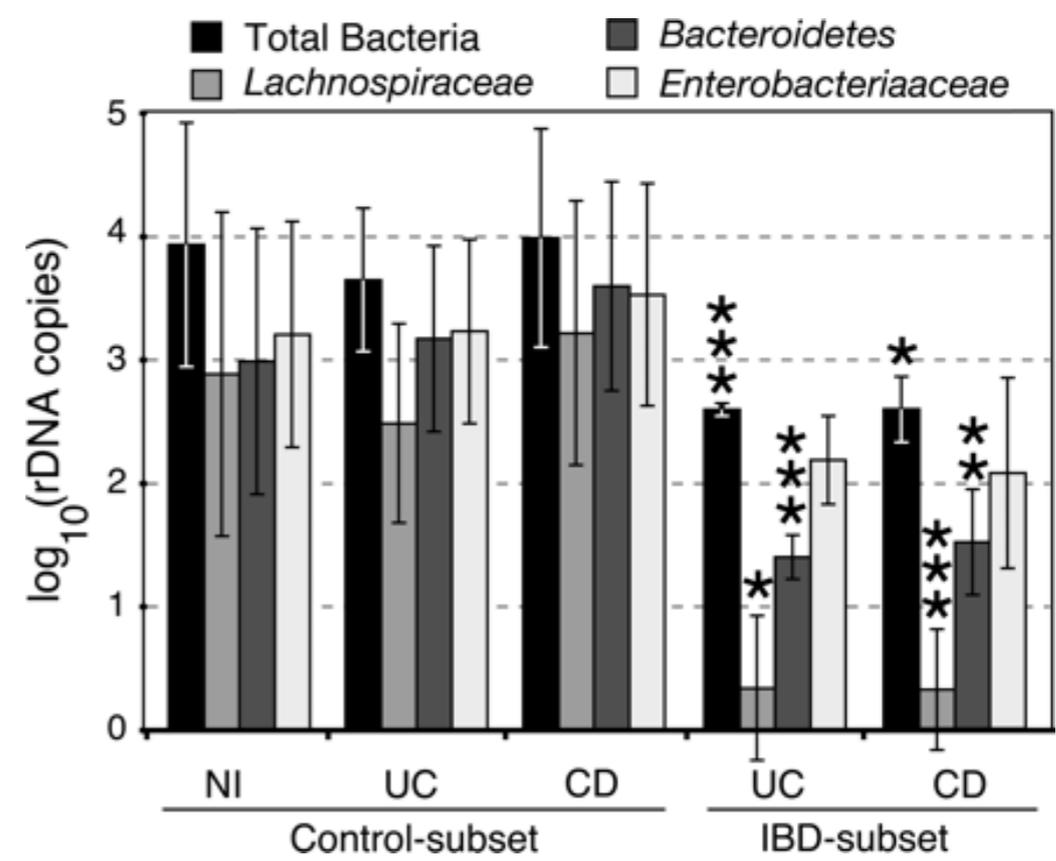
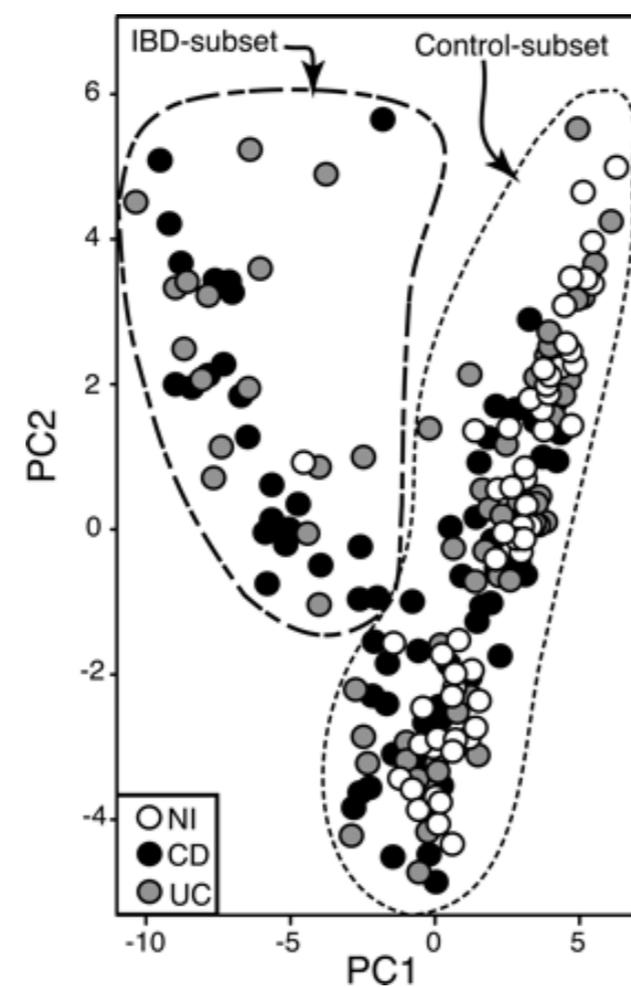


# Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases

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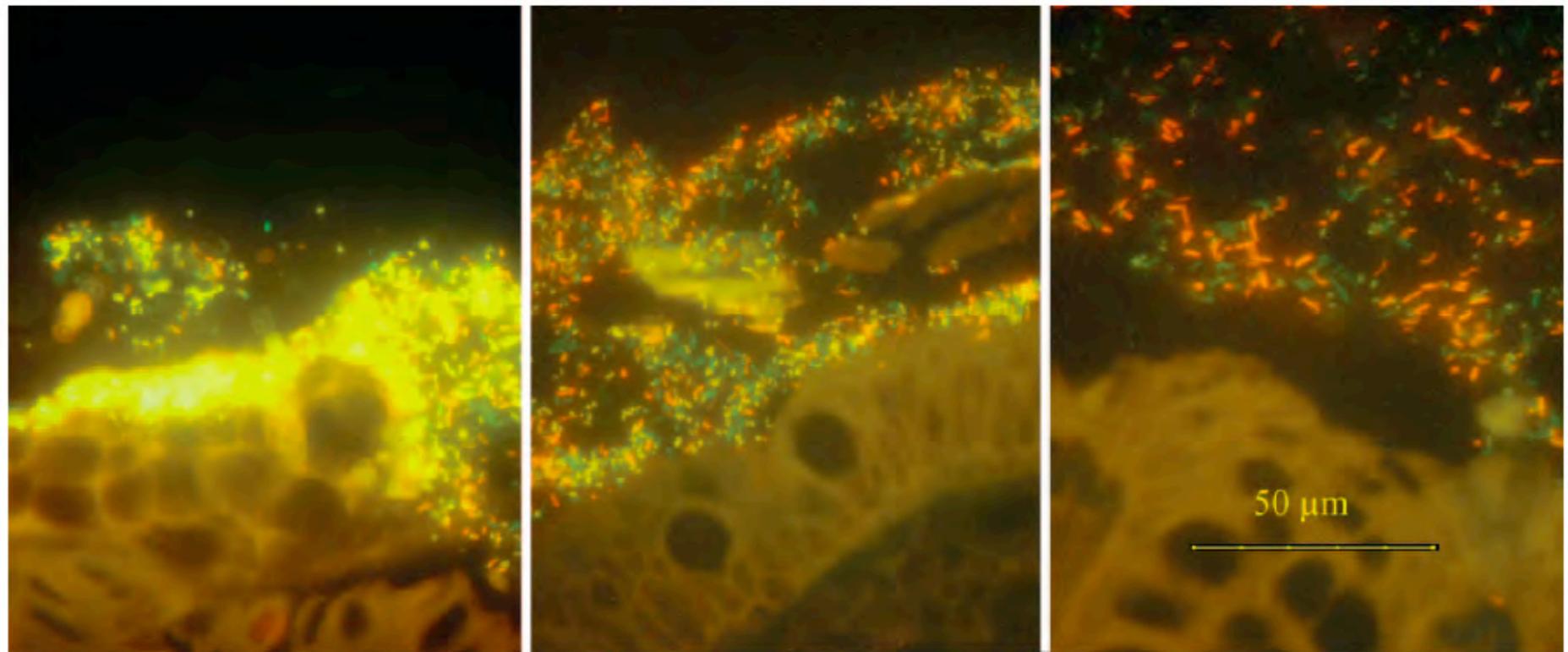


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y=Bfra r=Erec g=Eub

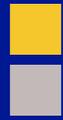


Crohn's disease

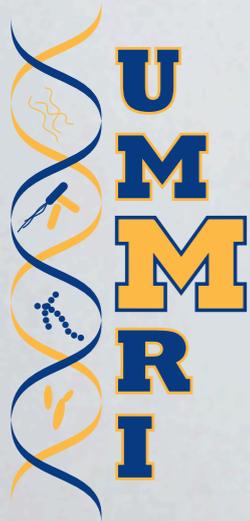
self-limited colitis

no colitis





# Gaps/Needs & Challenges



- We must move from associations between disease states and specific microbiota community structures towards an understanding of the **functional consequences** of these community alterations.
- Results from experimentation with **model microbial communities** need to be validated and correlated with human subjects.
- There is a need for the development and validation of analytic methods to process data derived from “**multi-omic**” **datasets**.
- Results from microbiome studies need to be developed into **novel therapeutics**, which will require the ability to cultivate specific members of the microbiota and a deeper understanding of how to administer cultivars as potential therapies.

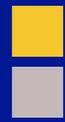
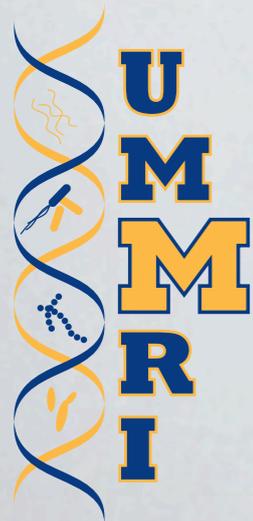
# Linking microbiome structure to microbiome function

ORIGINAL ARTICLE

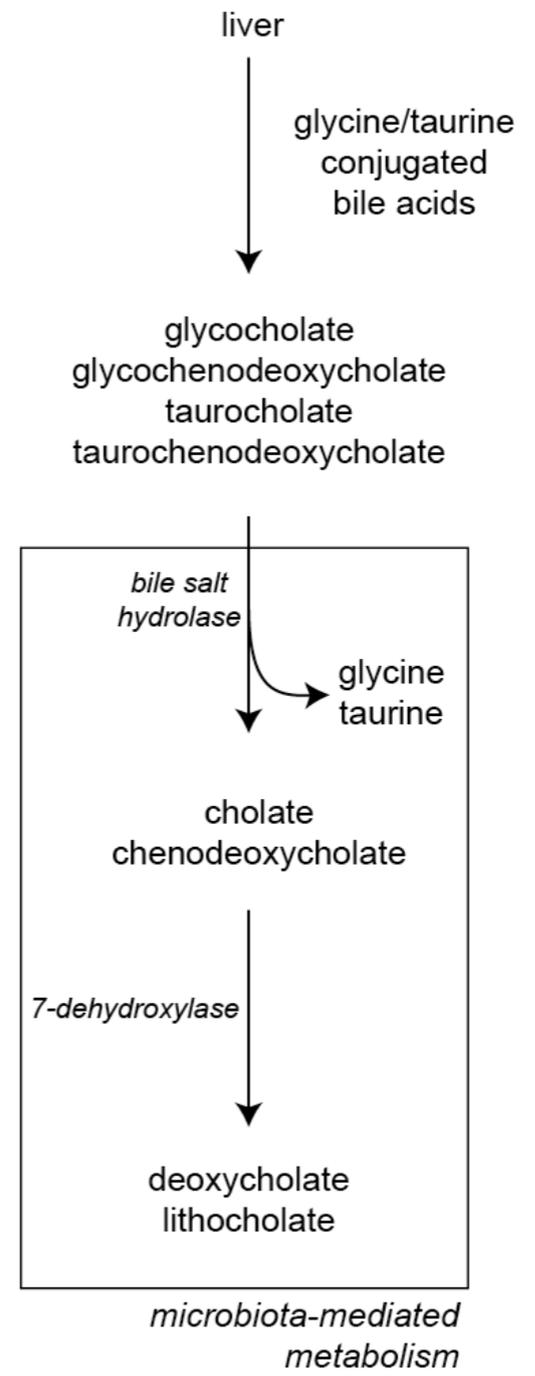
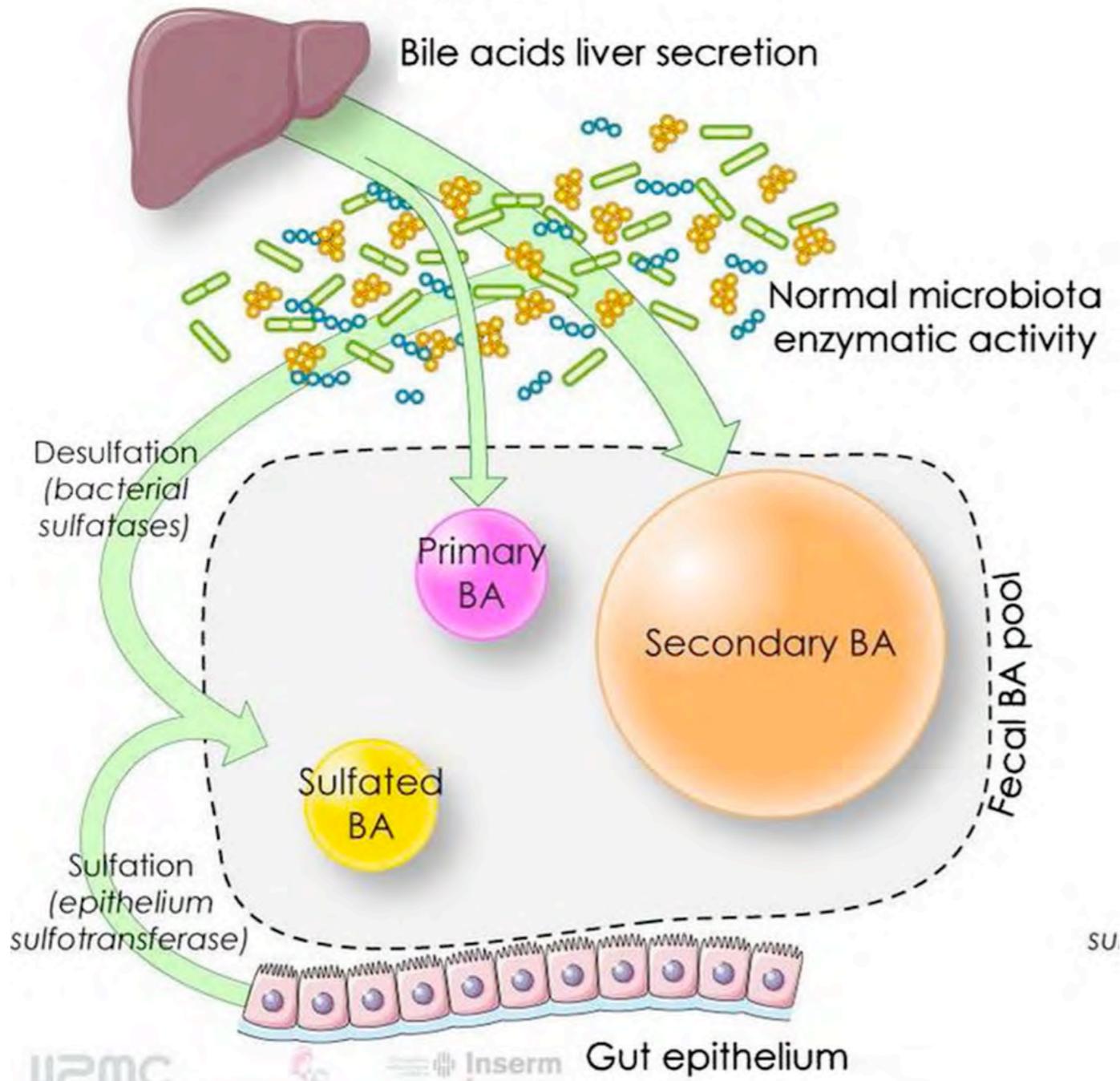
## Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases

Henri Duboc,<sup>1,2,3</sup> Sylvie Rajca,<sup>1,2,3</sup> Dominique Rainteau,<sup>1,2,4</sup> David Benarous,<sup>5</sup> Marie-Anne Maubert,<sup>1,2,4</sup> Elodie Quervain,<sup>1,2</sup> Ginette Thomas,<sup>1,2,4</sup> Véronique Barbu,<sup>4</sup> Lydie Humbert,<sup>1,2,4</sup> Guillaume Despras,<sup>2</sup> Chantal Bridonneau,<sup>6</sup> Fabien Dumetz,<sup>6</sup> Jean-Pierre Grill,<sup>1,2</sup> Joëlle Masliah,<sup>1,2,4</sup> Laurent Beaugerie,<sup>1,2,3</sup> Jacques Cosnes,<sup>1,2,3</sup> Olivier Chazouillères,<sup>7</sup> Raoul Poupon,<sup>7</sup> Claude Wolf,<sup>1</sup> Jean-Maurice Mallet,<sup>2</sup> Philippe Langella,<sup>6</sup> Germain Trugnan,<sup>1,2,4</sup> Harry Sokol,<sup>1,2,3</sup> Philippe Seksik<sup>1,2,3</sup>

Gut 2013;62:531–539. doi:10.1136/gutjnl-2012-302578

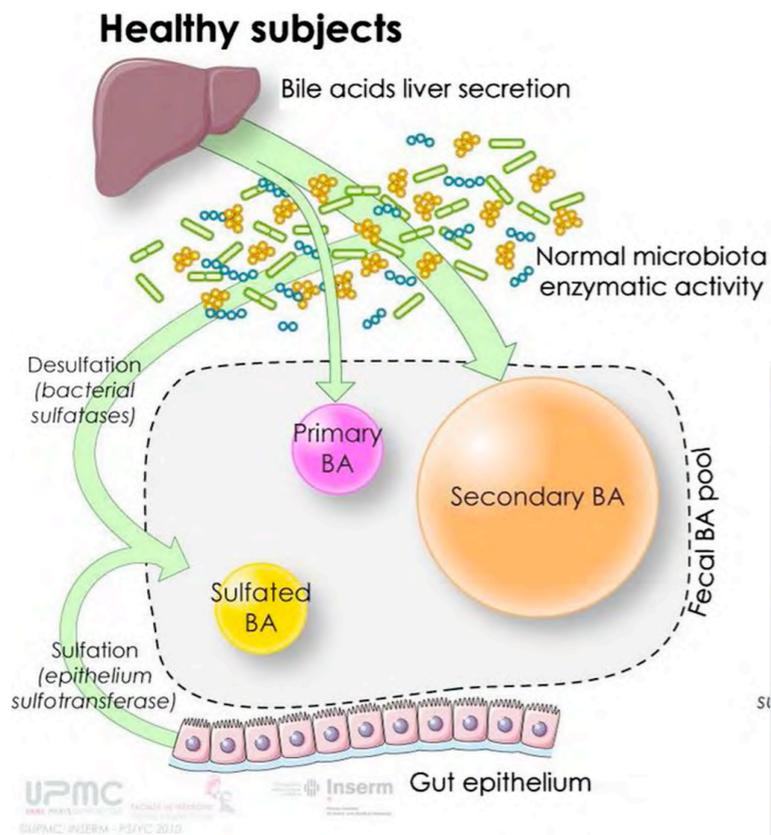


# Healthy subjects



UPMC FACULTÉ DE MÉDECINE  
INSERM  
Gut 2013;62:531-539. doi:10.1136/gutjnl-2012-302578

adapted: Britton & Young  
TIMI (2012) 20:313



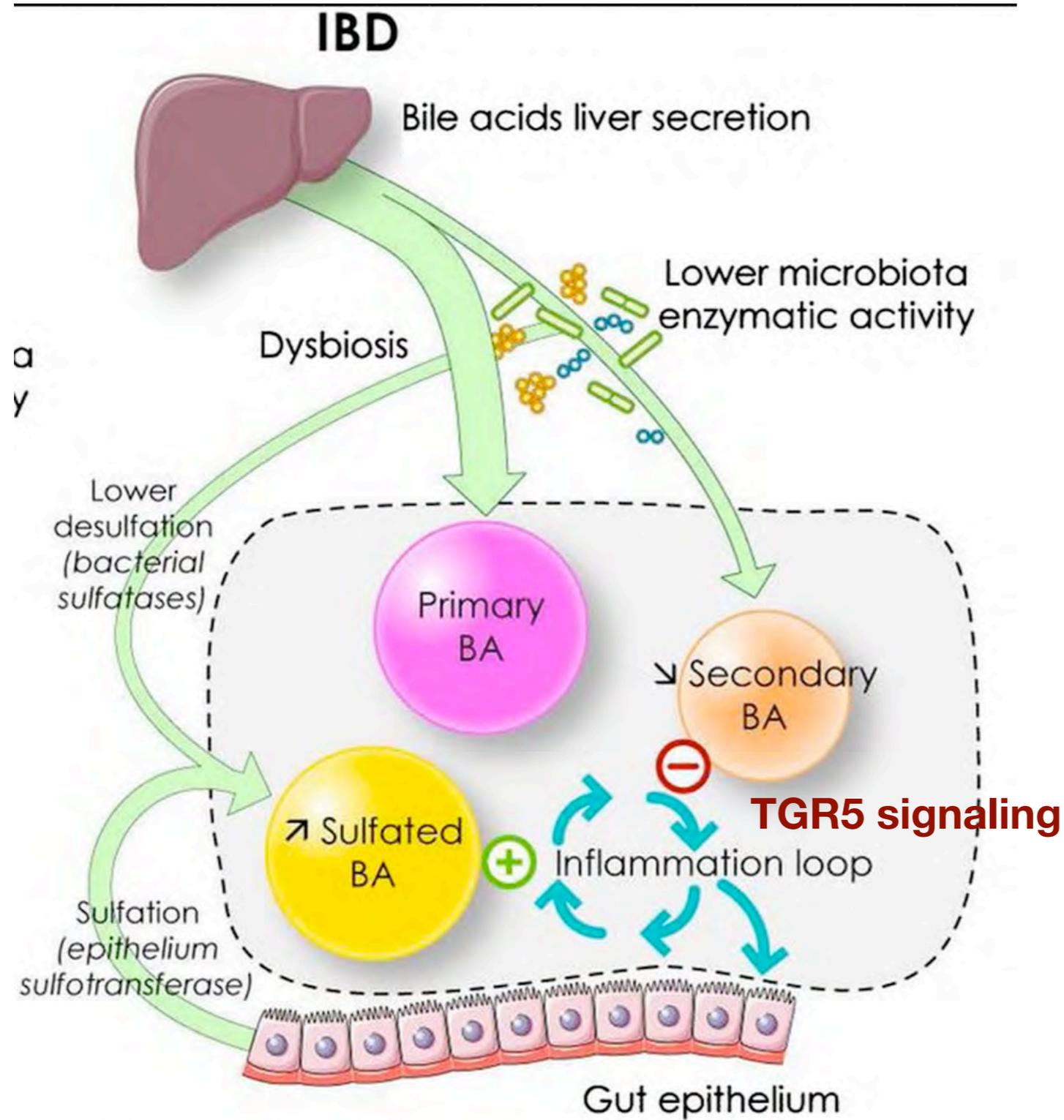
## What are the new findings

- ▶ Fecal dysmetabolism of BAs is observed in IBD.
- ▶ This dysmetabolism is linked to IBD-associated dysbiosis.
- ▶ High rates of sulphated BAs is found in faeces of IBD patients.
- ▶ Dysmetabolism of BAs could impact on inflammatory loop in IBD.

## How might it impact on clinical practice in the foreseeable future?

- ▶ BAs dysmetabolism could be used as a surrogate marker of IBD.
- ▶ Modulation of gut microbiota and/or BAs content could impact on IBD clinical course.

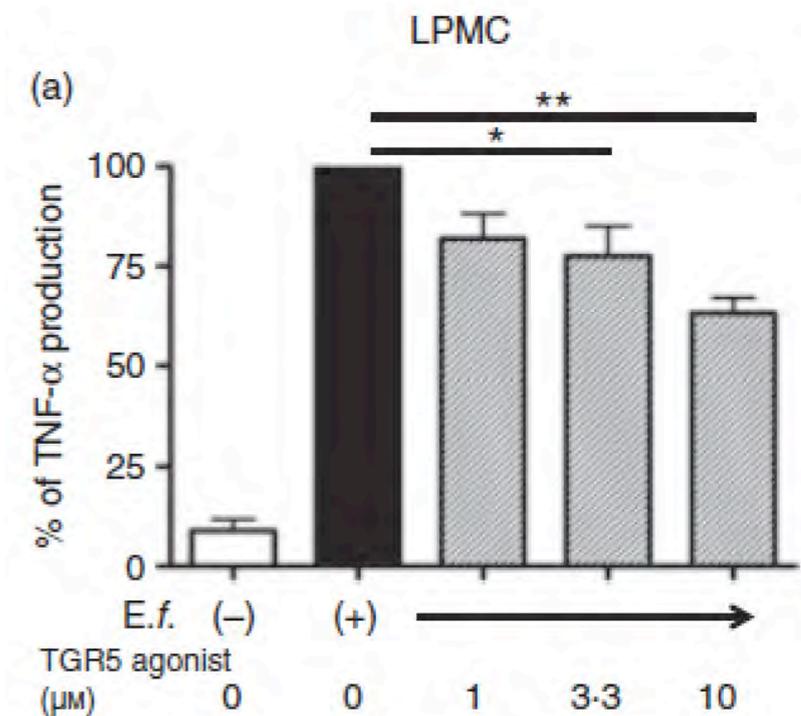
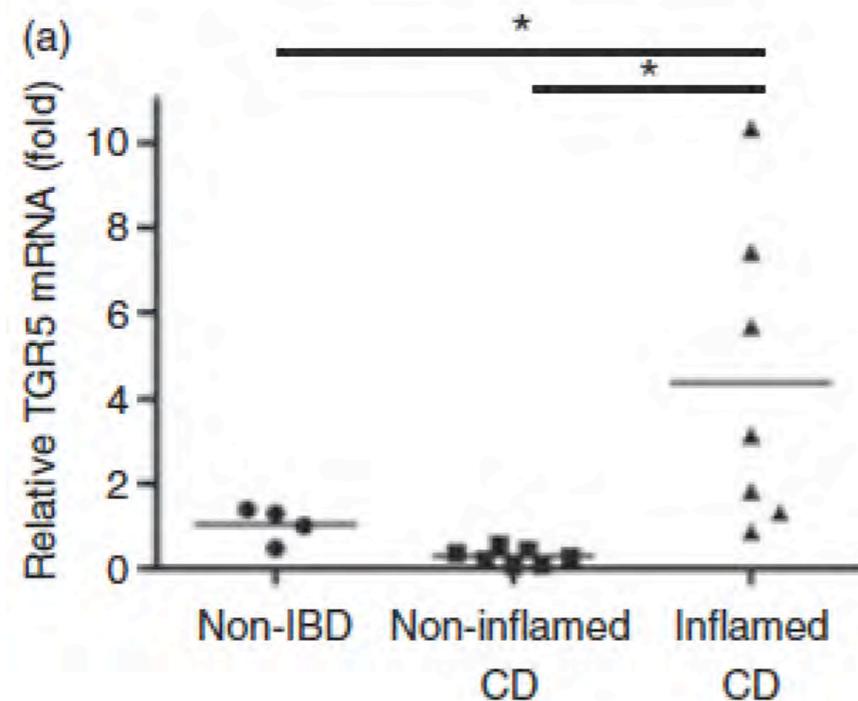
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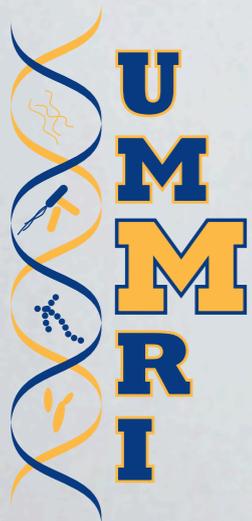
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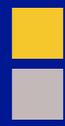
# TGR5 signalling inhibits the production of pro-inflammatory cytokines by *in vitro* differentiated inflammatory and intestinal macrophages in Crohn's disease

lamina propria mononuclear cells from CD patients



TGR5 G-protein coupled BA receptor





# More functions: Loss of microbiota fermentation in Inflammatory Bowel Disease



Mitch Sogin



Gene Chang



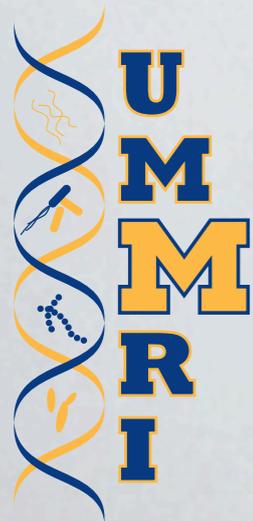
Jim Tiedje



U i i School  
Vince Young  
Tom Schmidt



Folker Meyer



Poster P41: **Marius Vital** et al.

“Investigating the role of butyrate-producing bacterial communities in the development of ulcerative colitis”

Additional challenge: how do you keep/form such interdisciplinary teams?

Journal of Infectious Diseases (1955) **91**:57-65

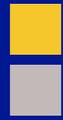
THE FATAL ENTERIC CHOLERA INFECTION IN THE GUINEA PIG,  
ACHIEVED BY INHIBITION OF NORMAL ENTERIC FLORA

ROLF FRETER\*

From the Department of Microbiology, The University of Chicago, Chicago 37, Illinois

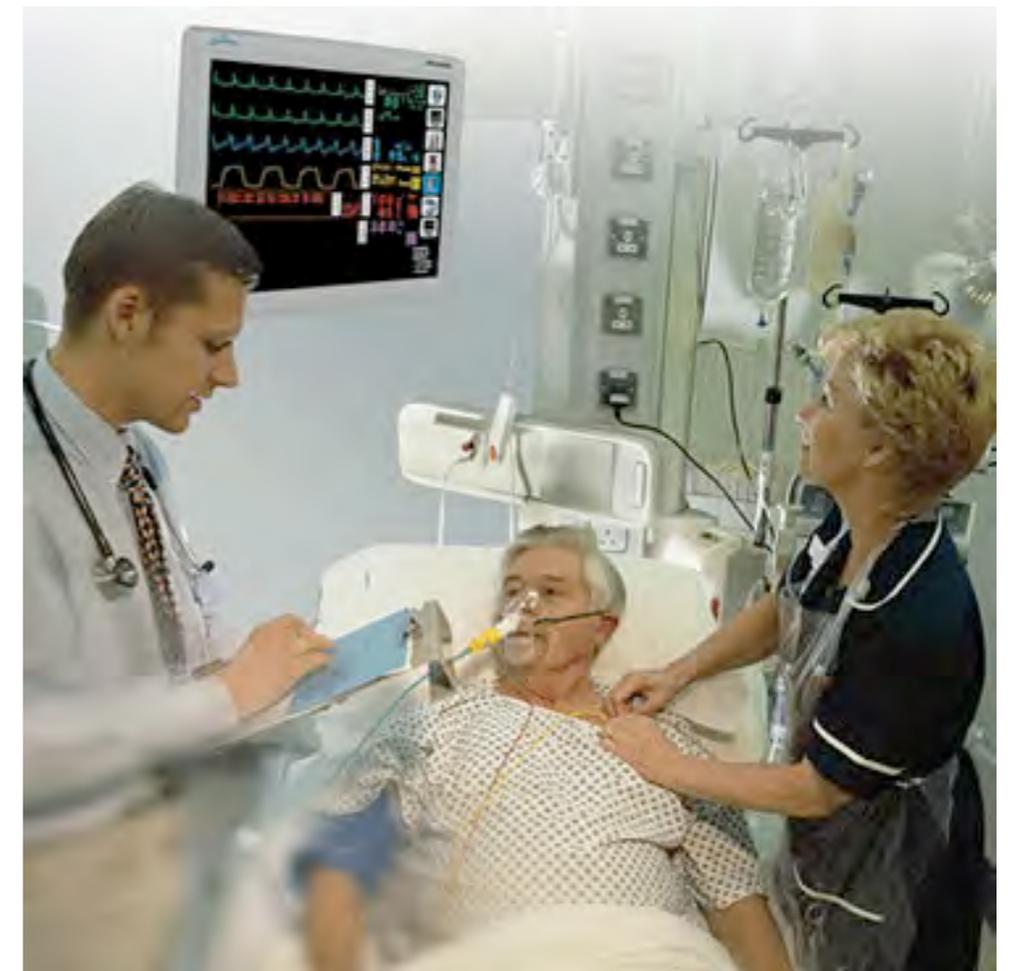
pigs. In this respect it might be worthwhile to consider the possibility of inhibitory action on the part of the normal human enteric flora as a factor in the resistance of humans to enteric diseases. This theory has—to the knowledge of the author—first been discussed by Nissle (1916). Following this line of

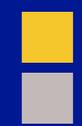
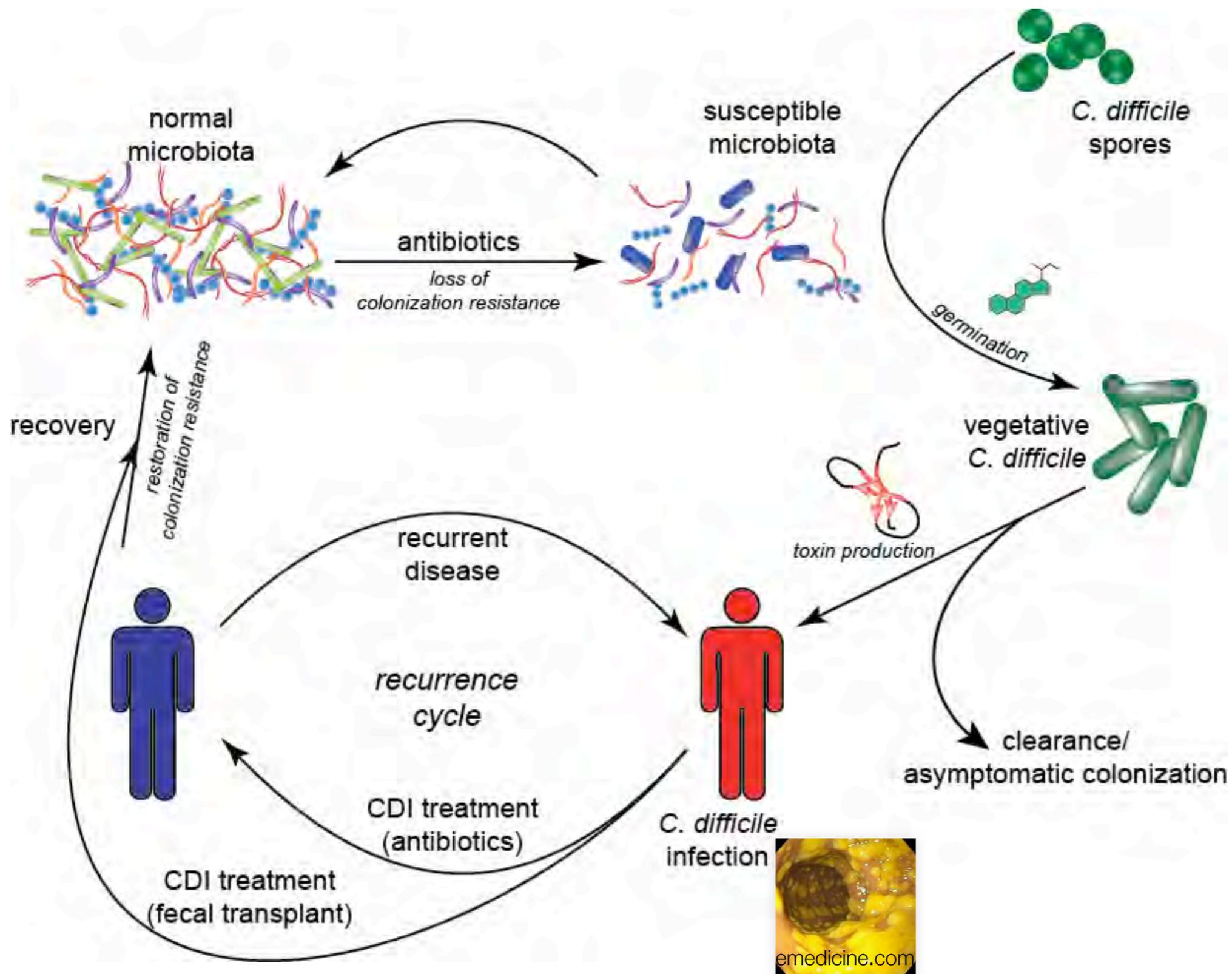




# Case

- 56 year old man with chronic obstructive pulmonary disease
- Admitted with acute exacerbation of chronic brochitis
- Treatment with cephalosporin and respiratory fluoroquinolone
- Hospital day three, develops abdominal pain, diarrhea, hypotension



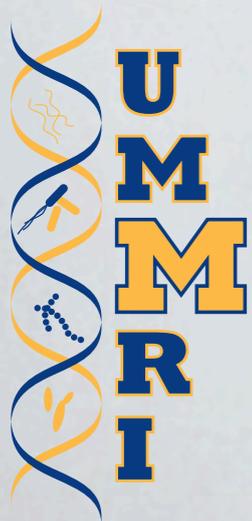


“H” stands for Human...



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# *C. difficile* in model systems



INFECTION AND IMMUNITY, Nov. 1986, p. 354-358  
0019-9567/86/110354-05\$02.00/0  
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Vol. 54, No. 2

## Interaction of *Clostridium difficile* and *Escherichia coli* with Microfloras in Continuous-Flow Cultures and Gnotobiotic Mice

KENNETH H. WILSON<sup>1\*</sup> AND ROLF FRETER<sup>2</sup>

*Infectious Diseases Section and Medical Service, Veterans Administration Medical Center,<sup>1\*</sup> and Department of Medicine and Department of Microbiology and Immunology, University of Michigan,<sup>2</sup> Ann Arbor, Michigan 48105*

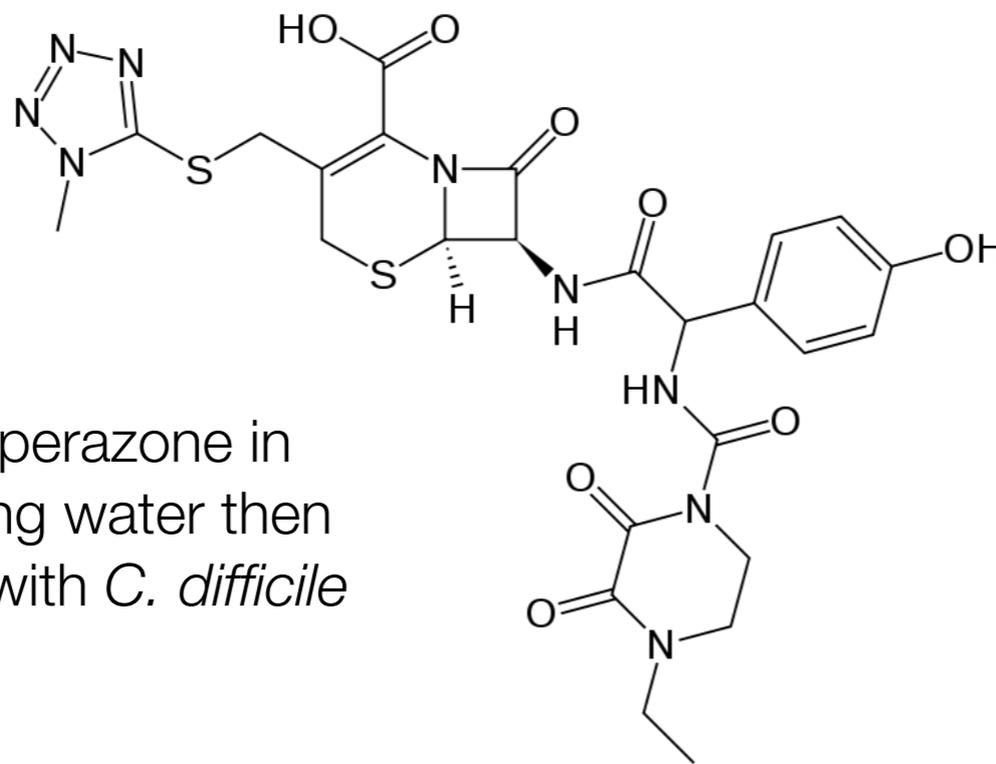
Received 16 December 1985/Accepted 15 August 1986

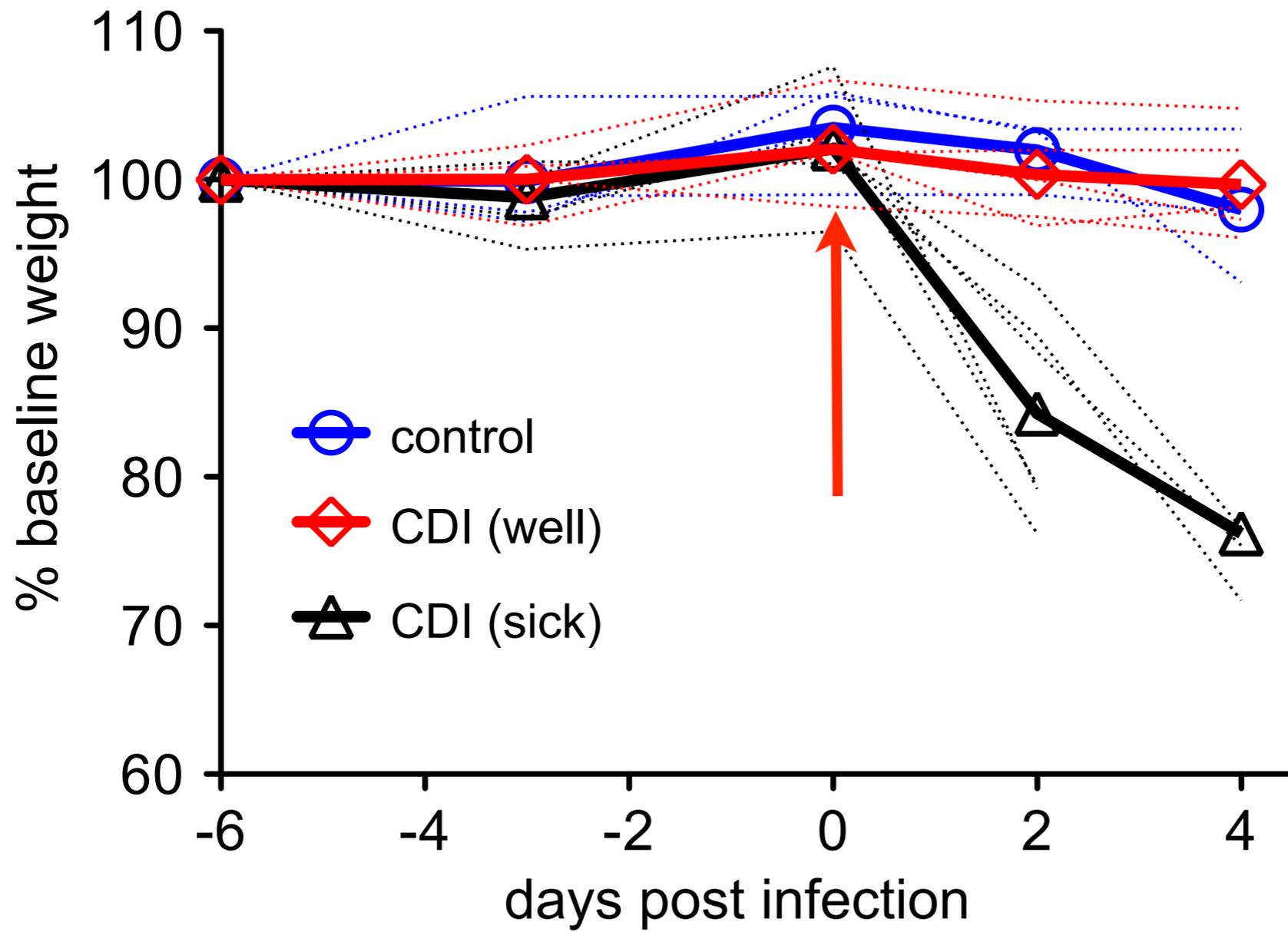
# Cefoperazone-treated mice as an experimental platform to assess differential virulence of *Clostridium difficile* strains

Casey M. Theriot,<sup>1</sup> Charles C. Koumpouras,<sup>1</sup> Paul E. Carlson Jr.,<sup>2</sup> Ingrid I. Bergin,<sup>3</sup> David M. Aronoff<sup>1</sup> and Vincent B. Young<sup>1,2,\*</sup>

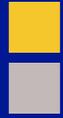
<sup>1</sup>Department of Internal Medicine/Division of Infectious Diseases; University of Michigan; Ann Arbor, MI USA; <sup>2</sup>Department of Microbiology and Immunology; University of Michigan; Ann Arbor, MI USA; <sup>3</sup>Unit for Laboratory Animal Medicine; University of Michigan; Ann Arbor, MI USA

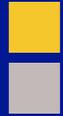
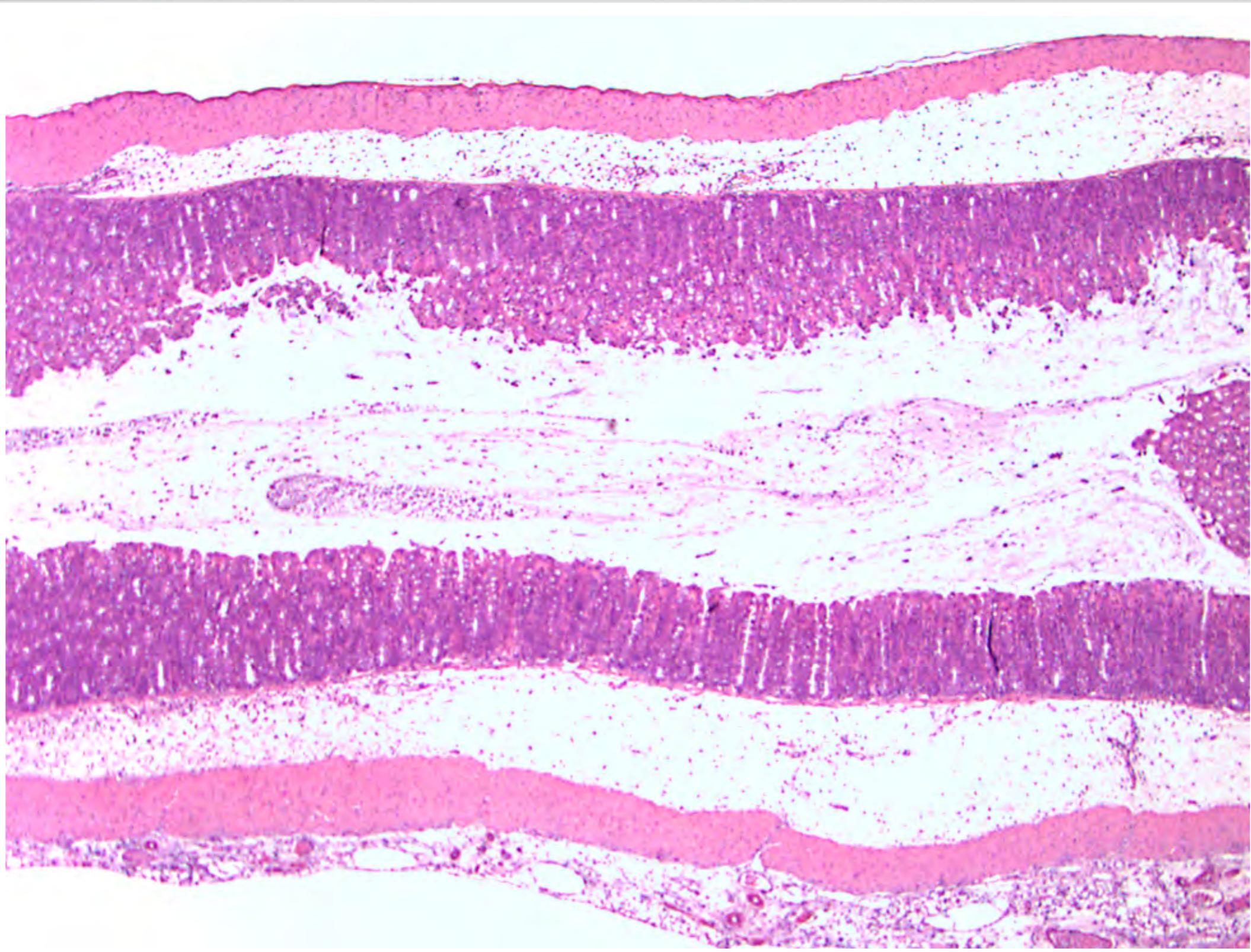
cefoperazone in  
drinking water then  
infect with *C. difficile*

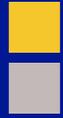
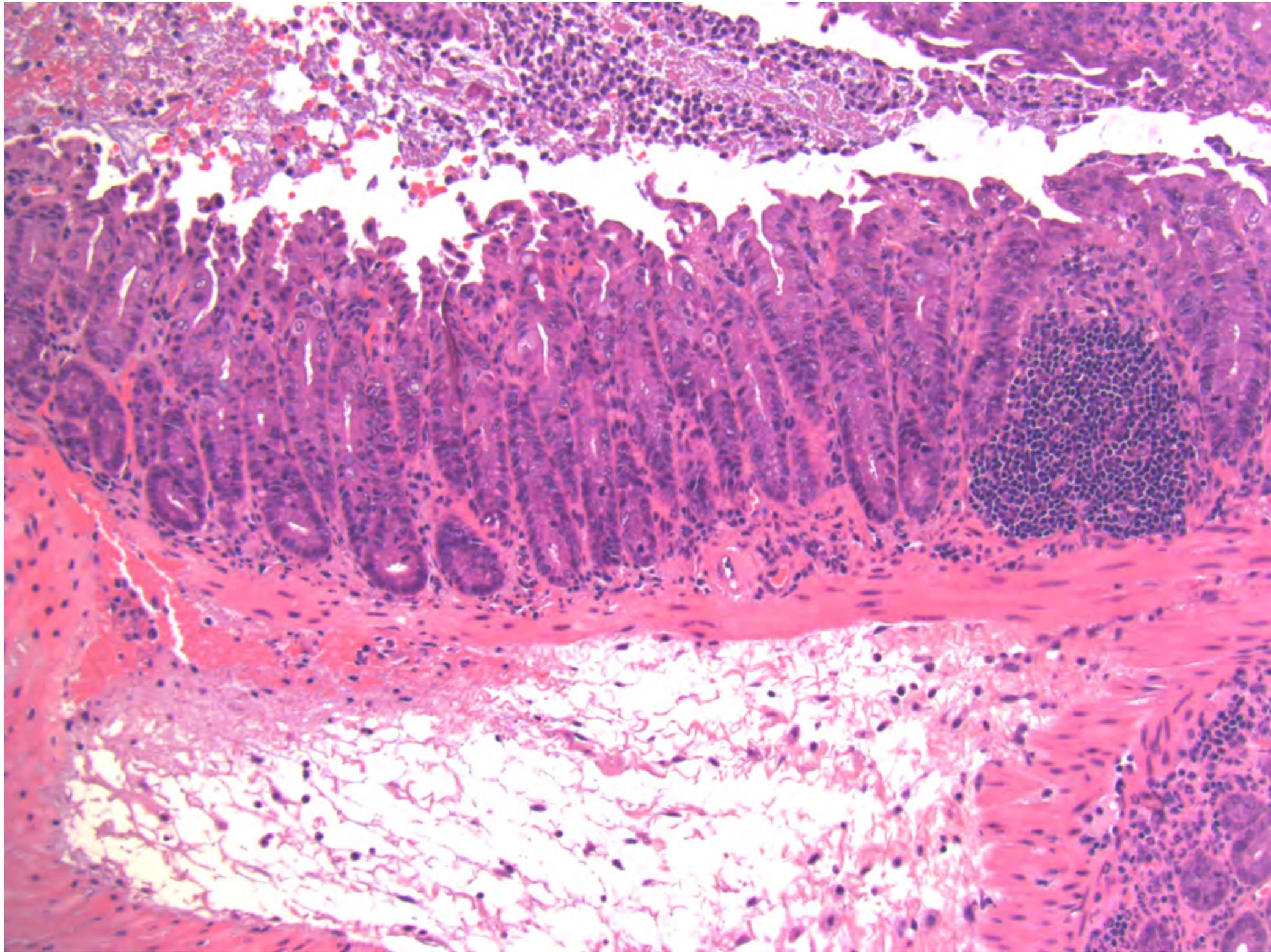




Reeves et al. Gut Microbes. (2011) **2**:145-58

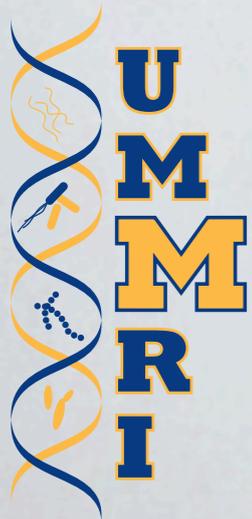


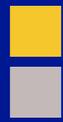




# Gaps/Needs & Challenges

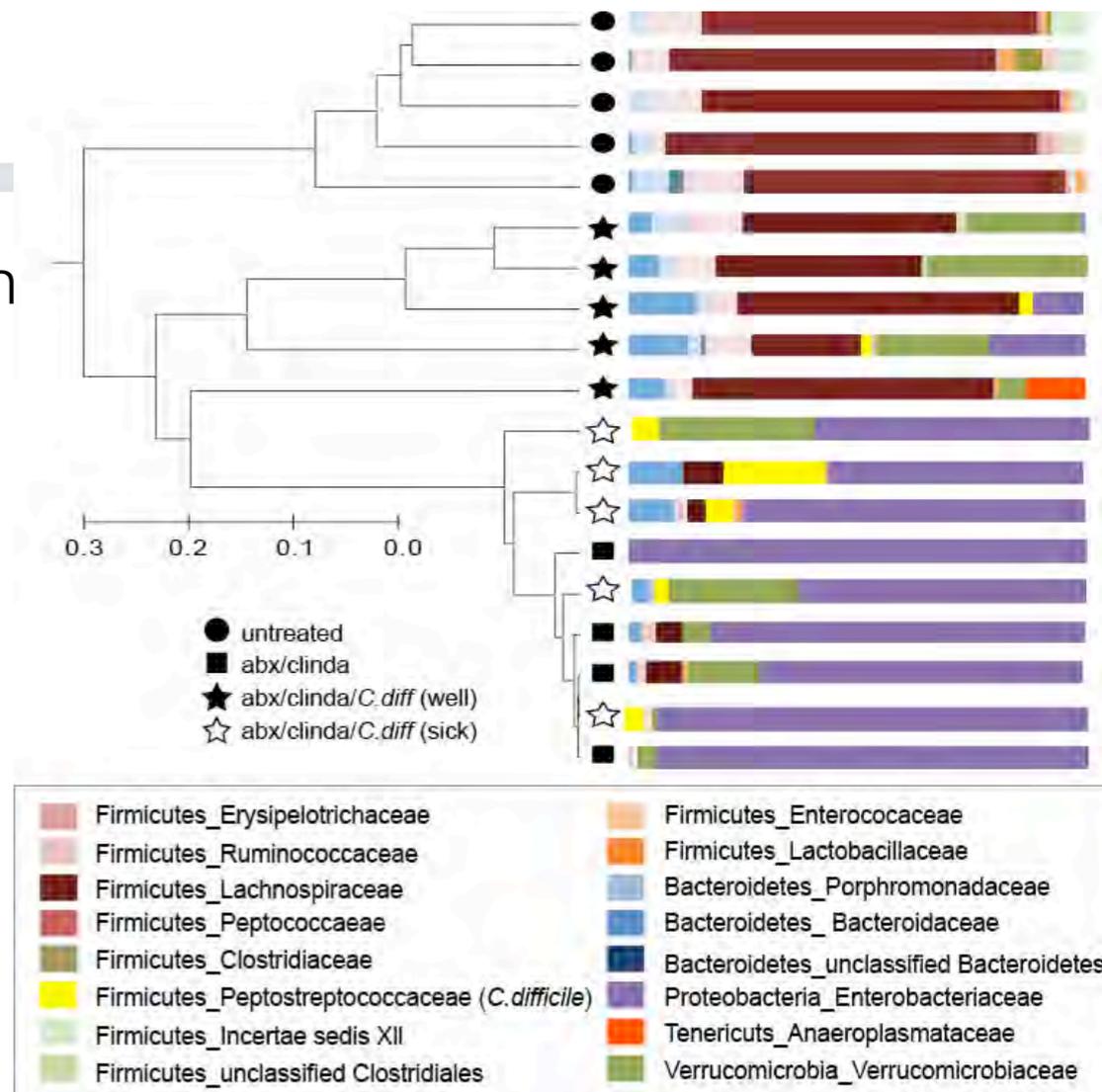
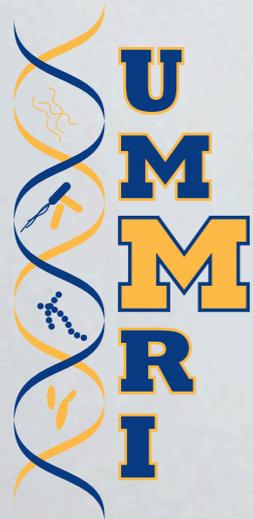
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# From molecular surveys to novel therapies

- Lachnospiraceae associated with protection/minimal disease
- *E. coli* associated with susceptibility/severe disease
- **How to move from a 16S survey association to a cultivated organism?**

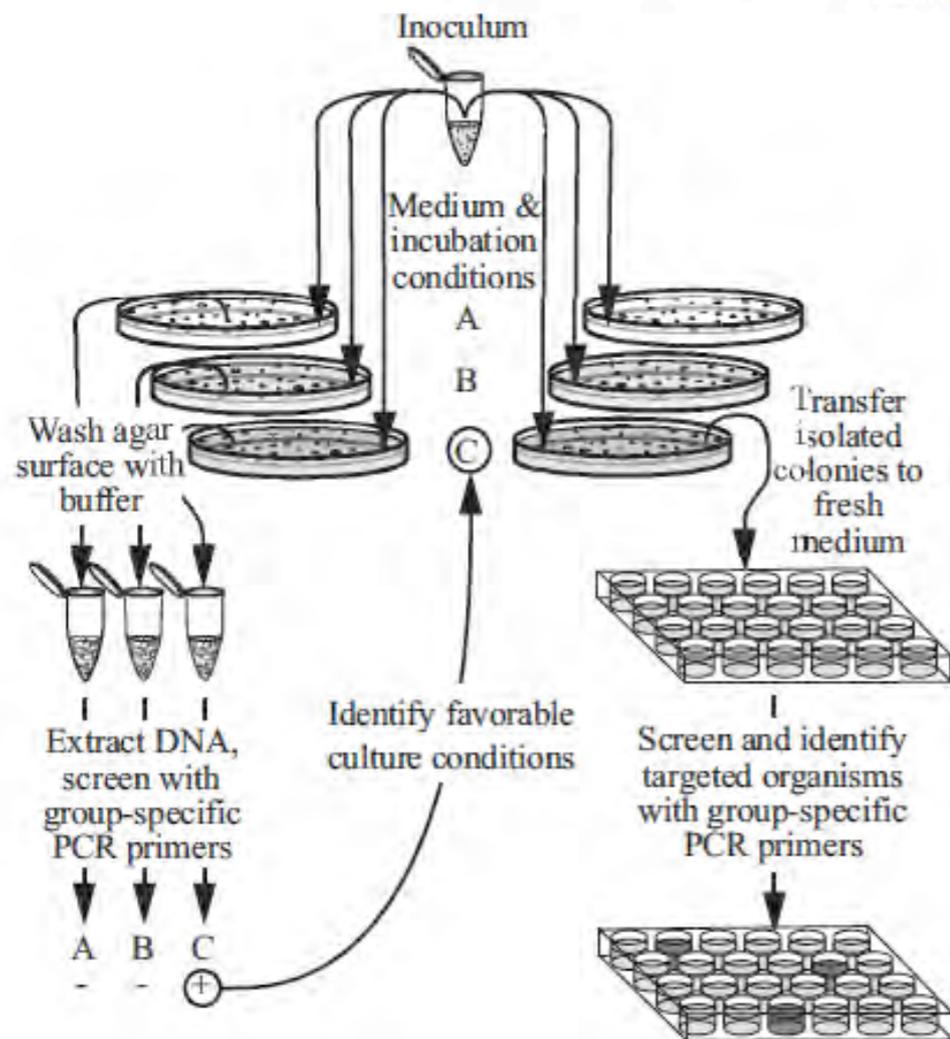


Reeves et al. Gut Microbes. (2011) 2:145-58

## New Strategies for Cultivation and Detection of Previously Uncultured Microbes

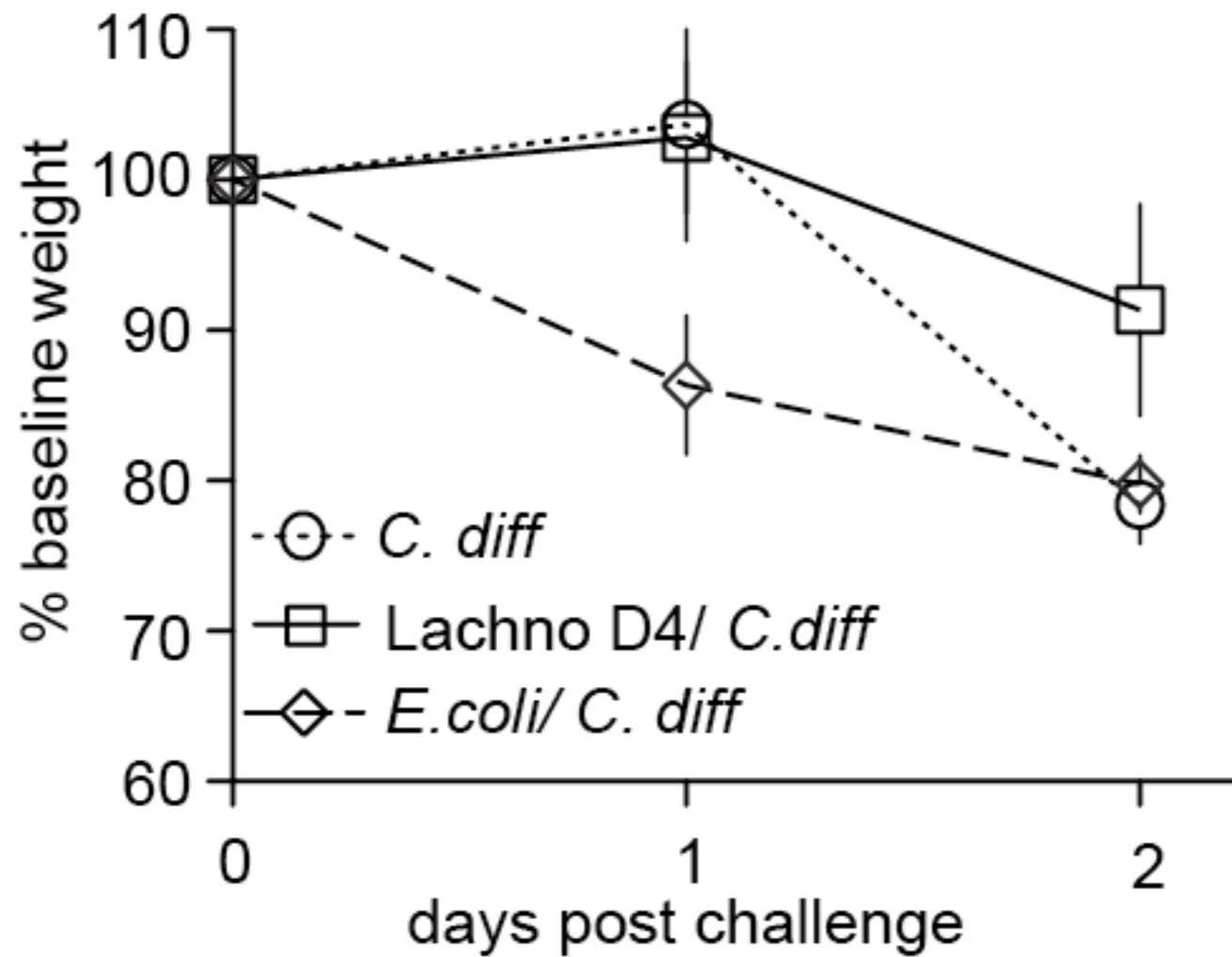
Bradley S. Stevenson,\* Stephanie A. Eichorst, John T. Wertz,  
Thomas M. Schmidt, and John A. Breznak

*Department of Microbiology and Molecular Genetics, Michigan State University,  
East Lansing, Michigan*

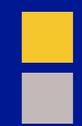
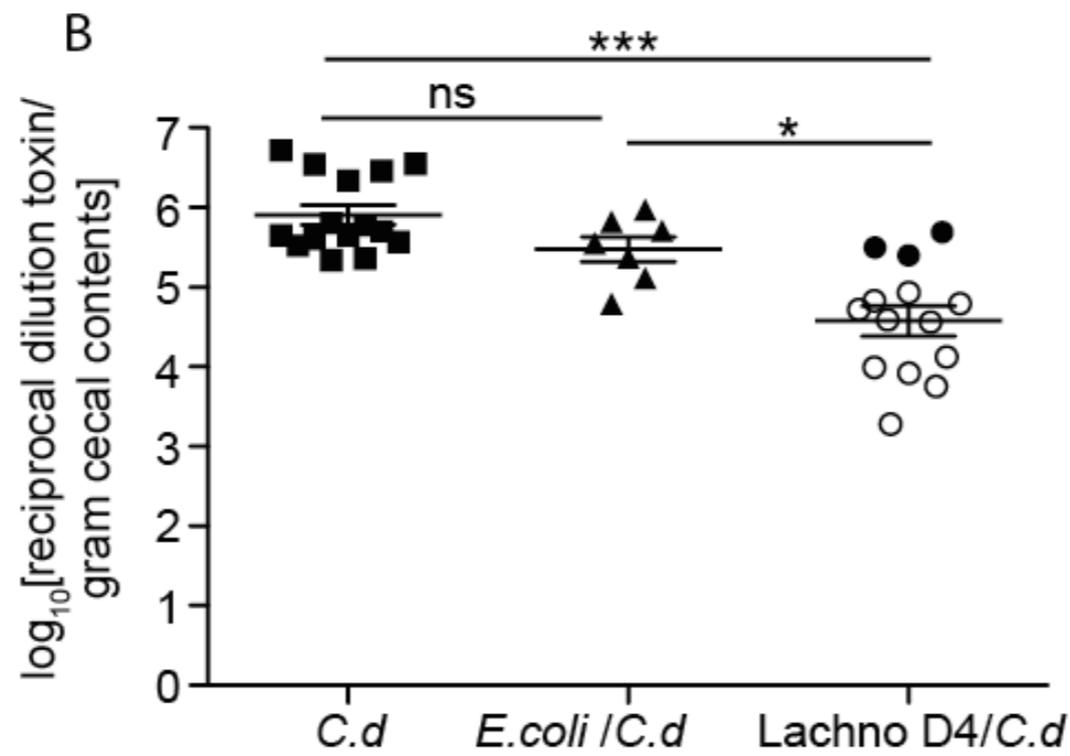
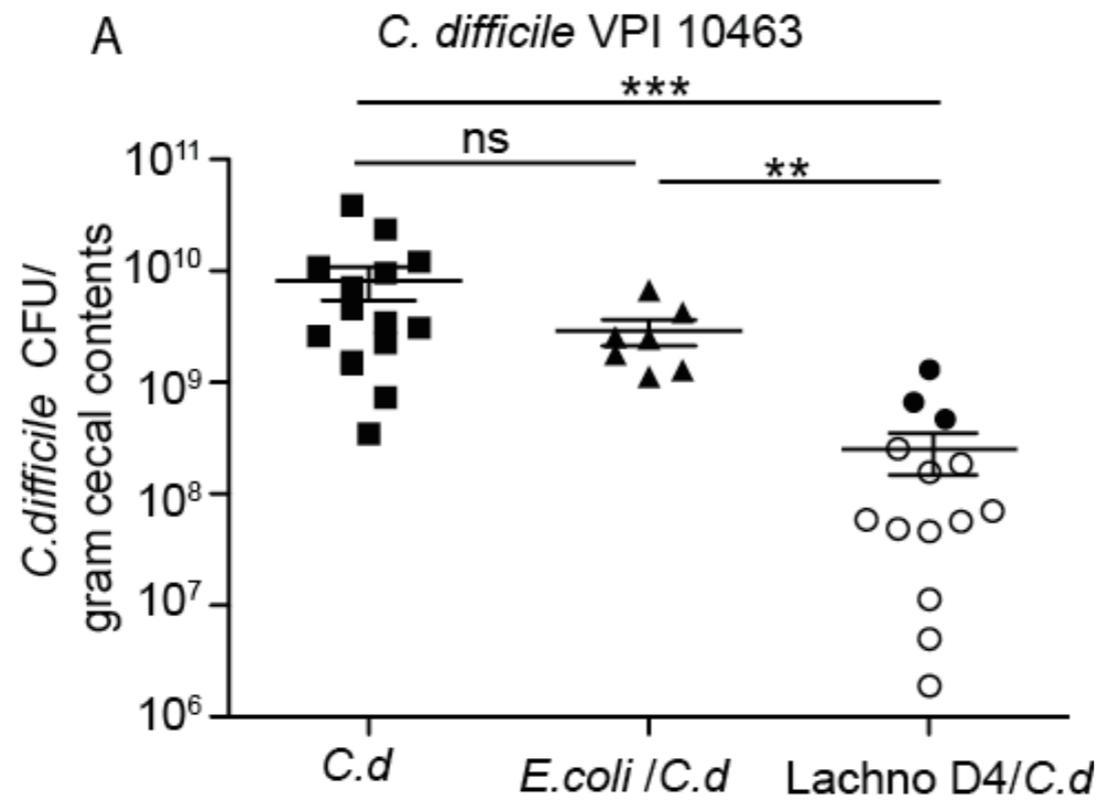


- Isolate Lachnospiraceae strain and *E. coli* strain from murine sources **using 16S data to guide cultivation efforts**
- Monoassociate germ free mice with each of these isolates
- Challenge with *C. difficile*

# VPI 10463 infection



Reeves et al., (2012) Infect Immun **80**:3786-3794



# Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

Ethan Gough,<sup>1</sup> Henna Shaikh,<sup>2</sup> and Ameer R. Manges<sup>1,3</sup>

Departments of <sup>1</sup>Epidemiology Biostatistics and Occupational Health, and <sup>2</sup>Biology, McGill University, and <sup>3</sup>Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

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PLOS PATHOGENS

## Targeted Restoration of the Intestinal Microbiota with a Simple, Defined Bacteriotherapy Resolves Relapsing *Clostridium difficile* Disease in Mice

Trevor D. Lawley<sup>1\*</sup>, Simon Clare<sup>1,2</sup>, Alan W. Walker<sup>1,2</sup>, Mark D. Stares<sup>1</sup>, Thomas R. Connor<sup>1</sup>, Claire Raisen<sup>1</sup>, David Goulding<sup>1</sup>, Roland Rad<sup>1</sup>, Fernanda Schreiber<sup>1</sup>, Cordelia Brandt<sup>1</sup>, Laura J. Deakin<sup>1</sup>, Derek J. Pickard<sup>1</sup>, Sylvia H. Duncan<sup>2</sup>, Harry J. Flint<sup>2</sup>, Taane G. Clark<sup>3</sup>, Julian Parkhill<sup>1</sup>, Gordon Dougan<sup>1</sup>

<sup>1</sup> Wellcome Trust Sanger Institute, Hinxton, United Kingdom, <sup>2</sup> Rowett Institute of Nutrition and Health, Aberdeen, United Kingdom, <sup>3</sup> London School of Hygiene and Tropical Medicine, London, United Kingdom

Petrof et al. *Microbiome* 2013, 1:3  
<http://www.microbiomejournal.com/content/1/1/3>



METHODOLOGY

Open Access

## Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut

Elaine O Petrof<sup>1\*</sup>, Gregory B Gloor<sup>2†</sup>, Stephen J Vanner<sup>1</sup>, Scott J Weese<sup>3</sup>, David Carter<sup>4</sup>, Michelle C Daigneault<sup>5</sup>, Eric M Brown<sup>5</sup>, Kathleen Schroeter<sup>5</sup> and Emma Allen-Vercoe<sup>5</sup>

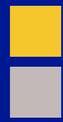
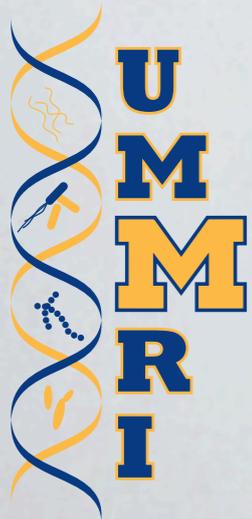
# Models without a host

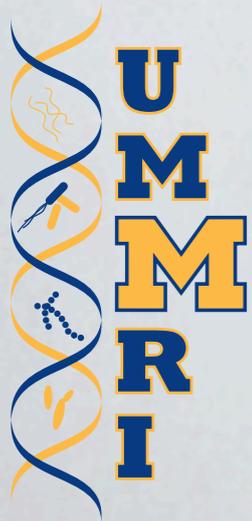
Poster P2 **Jennifer Auchtung**

“Studying interactions between *C. difficile* and complex microbial communities in human fecal bioreactors”



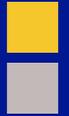
courtesy of Rob Britton/MSU



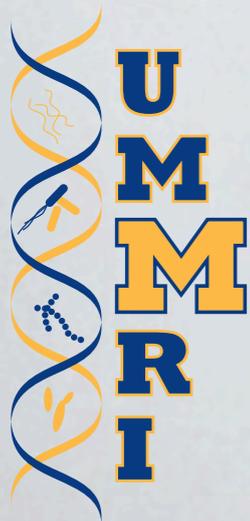


# Gaps/Needs & Challenges

- We must move from associations between disease states and specific microbiota community structures towards an understanding of the **functional consequences** of these community alterations.
- Results from experimentation with **model microbial communities** need to be validated and correlated with human subjects.
- ■ There is a need for the development and validation of analytic methods to process data derived from **“multi-omic” datasets**.
- Results from microbiome studies need to be developed into **novel therapeutics**, which will require the ability to cultivate specific members of the microbiome and a deeper understanding of how to administer cultivars as potential therapies.



“multi-‘omics” going from structure  
to function



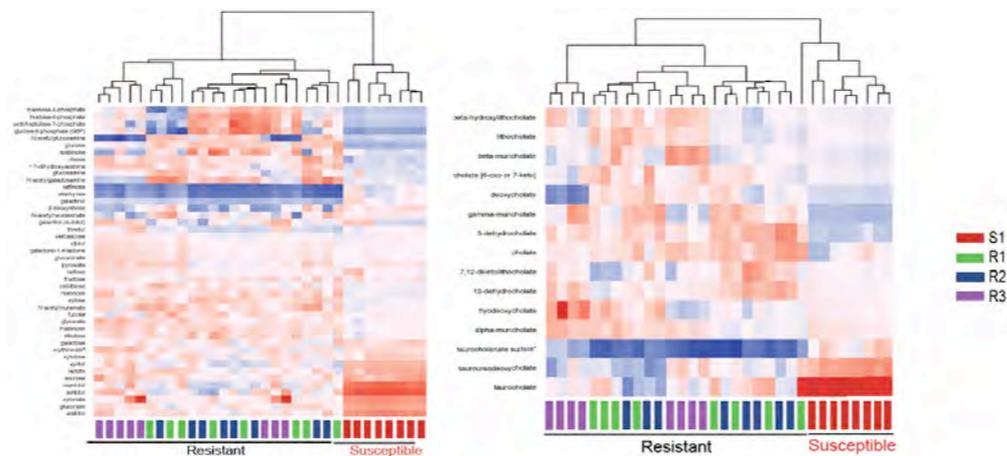
## **Integrated Metagenomics/Metaproteomics Reveals Human Host-Microbiota Signatures of Crohn's Disease**

**Alison R. Erickson<sup>1,2</sup>, Brandi L. Cantarel<sup>3</sup>, Regina Lamendella<sup>4</sup>, Youssef Darzi<sup>5,6</sup>,  
Emmanuel F. Mongodin<sup>3</sup>, Chongle Pan<sup>1</sup>, Manesh Shah<sup>1</sup>, Jonas Halfvarson<sup>7</sup>, Curt Tysk<sup>7</sup>,  
Bernard Henrissat<sup>8</sup>, Jeroen Raes<sup>5,6</sup>, Nathan C. Verberkmoes<sup>1</sup>, Claire M. Fraser<sup>3</sup>, Robert L. Hettich<sup>1</sup>,  
Janet K. Jansson<sup>4\*</sup>**

# Microbiome and metabolome state transitions of the gut microbiota after antibiotic treatment

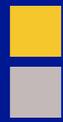
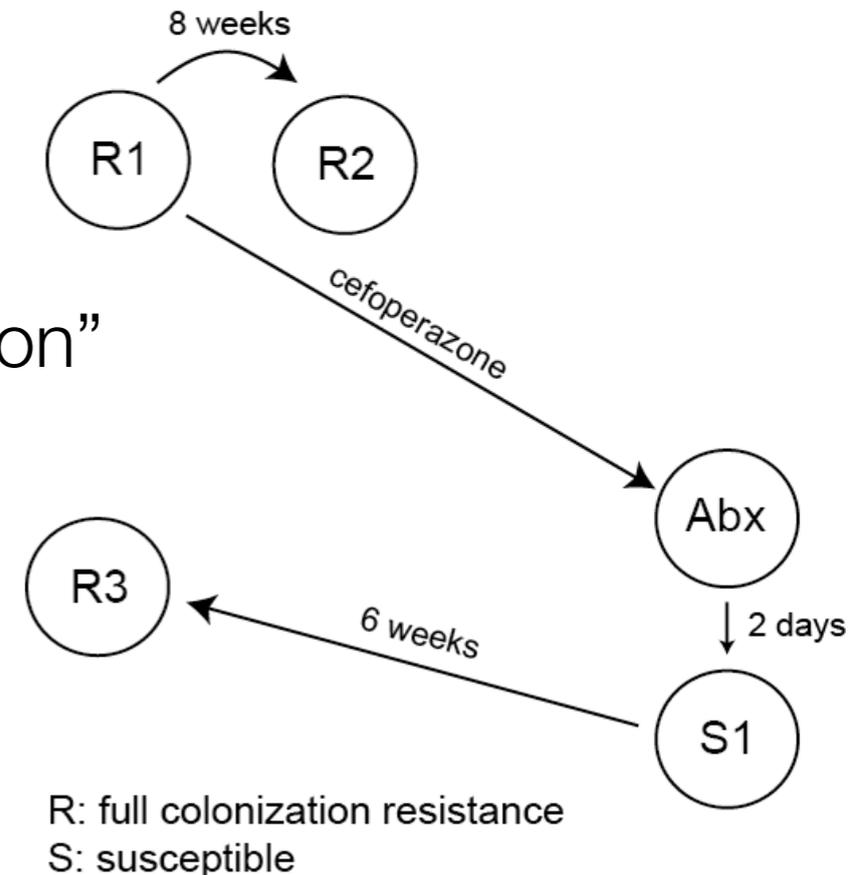
## Poster P37 **Casey Theriot**

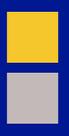
“Antibiotic-mediated shifts in the gut microbiome and metabolome leads to susceptibility to *Clostridium difficile* infection”



Carbohydrates

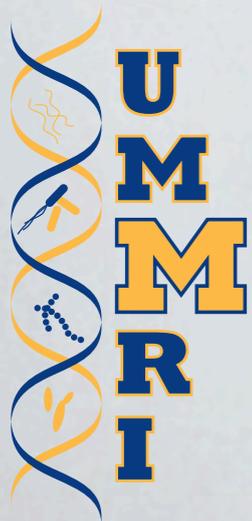
Bile acids

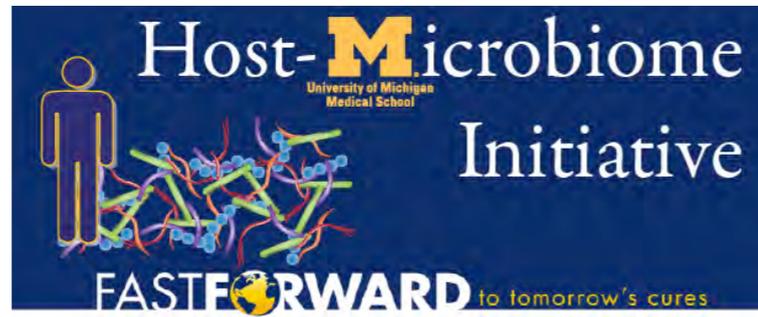




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Judith Opp



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Lung and Blood Institute

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