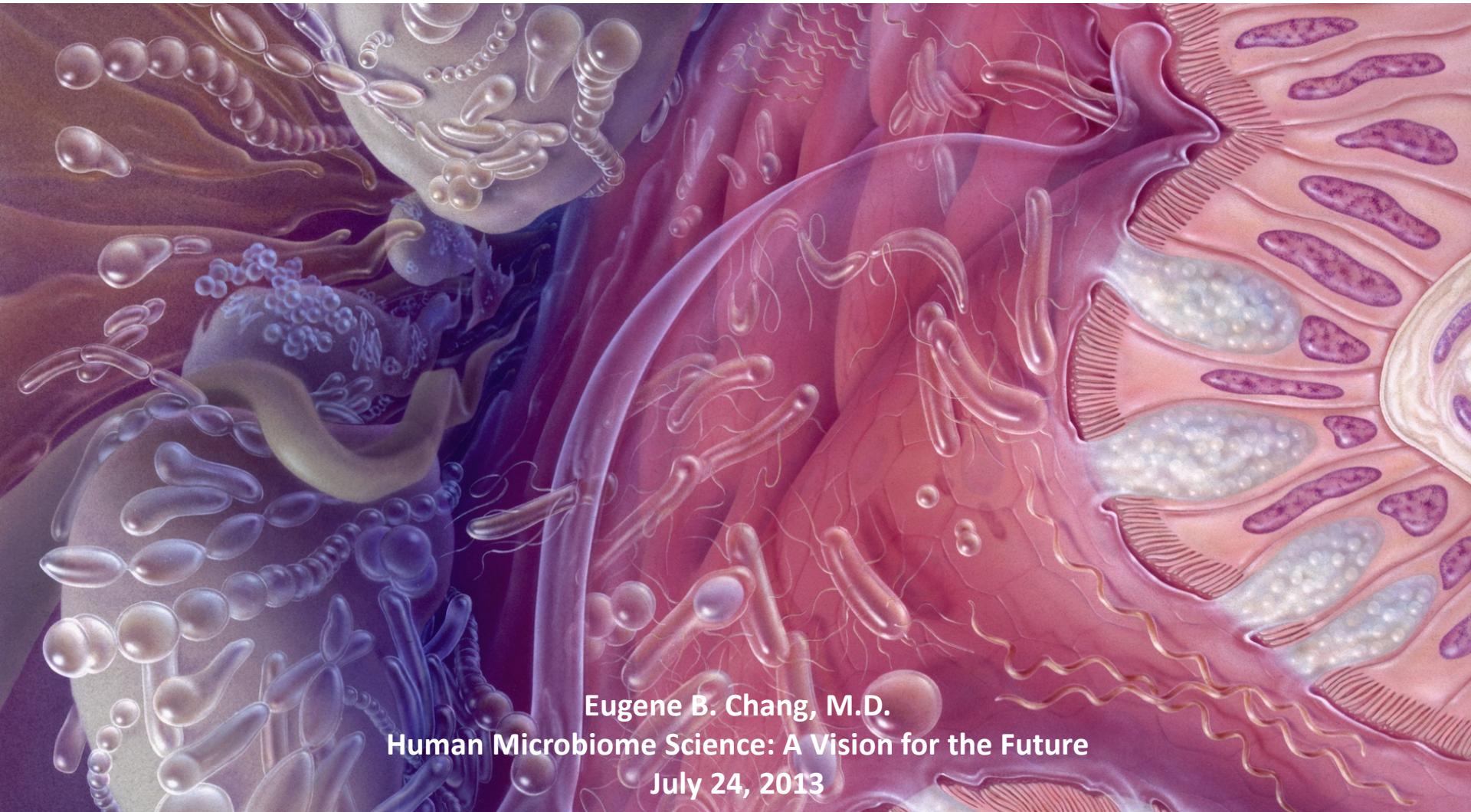


Ground Zero – the impact of the gut microbiome on host epithelial functions and responses.



Eugene B. Chang, M.D.

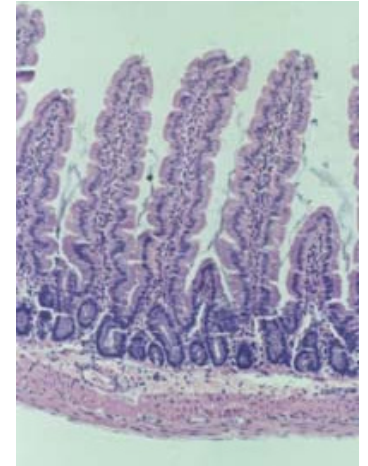
Human Microbiome Science: A Vision for the Future

July 24, 2013

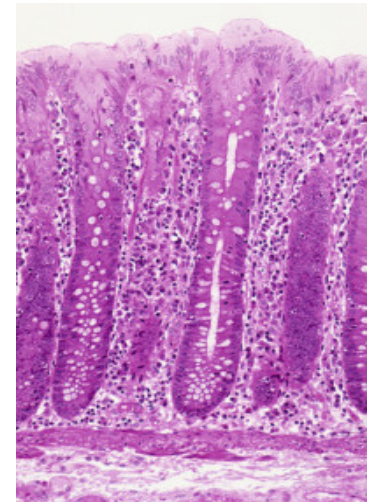
Examples of critical gut epithelial functions that are impacted by microbes

- Barrier function
 - Intestinal permeability (TJ mediated)
 - Mucus, AMPs
- Development and Adaptation
- Wound healing
- Innate immune functions
- Cytoprotection
- Nutrient/electrolyte/water transport
- Autophagy
- Proliferation/apoptosis

Small intestine

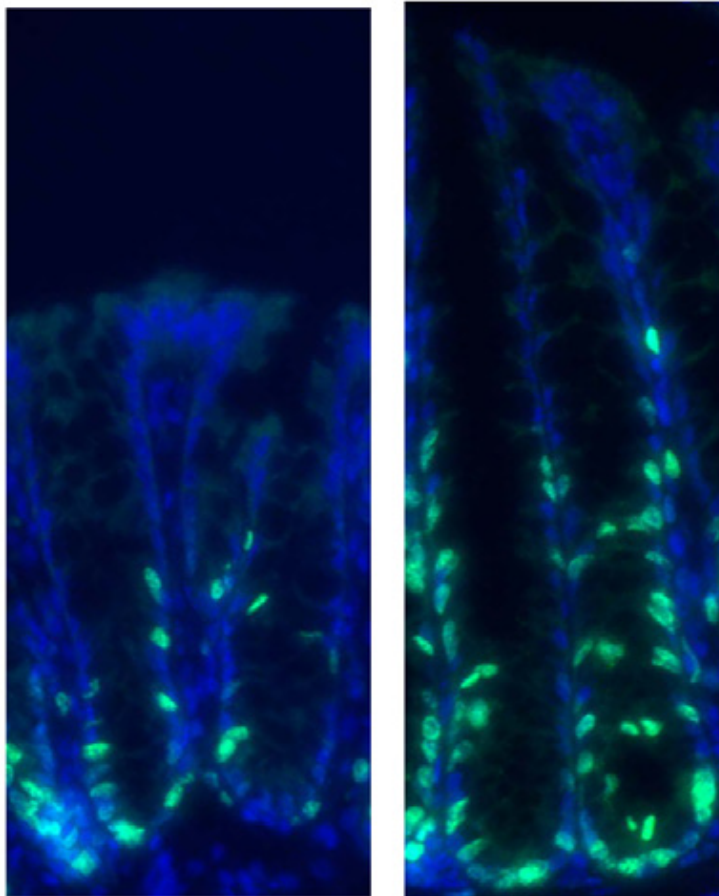


Colon



Gut microbes regulate mucosal development, proliferation, and apoptosis

Ki67 immunostaining (green)

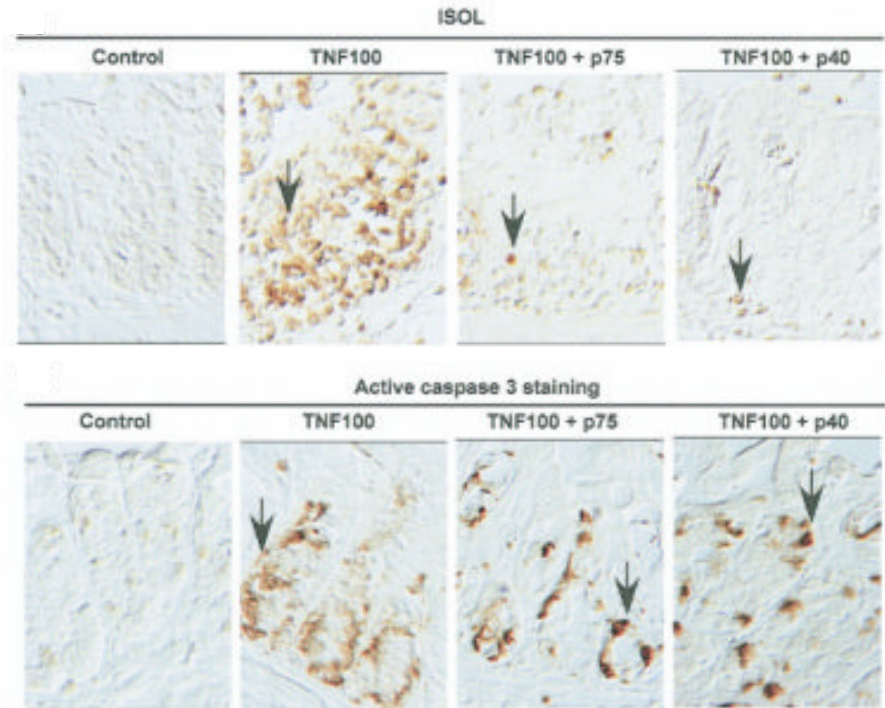


VNMAmf-B+A

Sham

(Reikvam, et al PlosOne 2011)

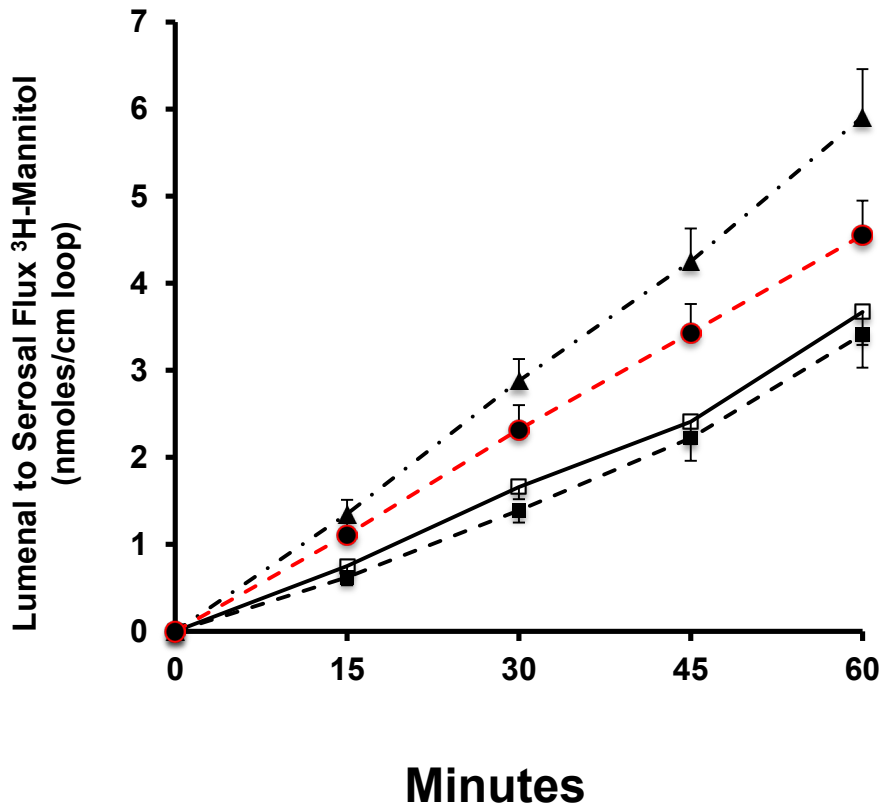
LGG-derived peptides (p40, p75)
Prevent TNF-induced apoptosis



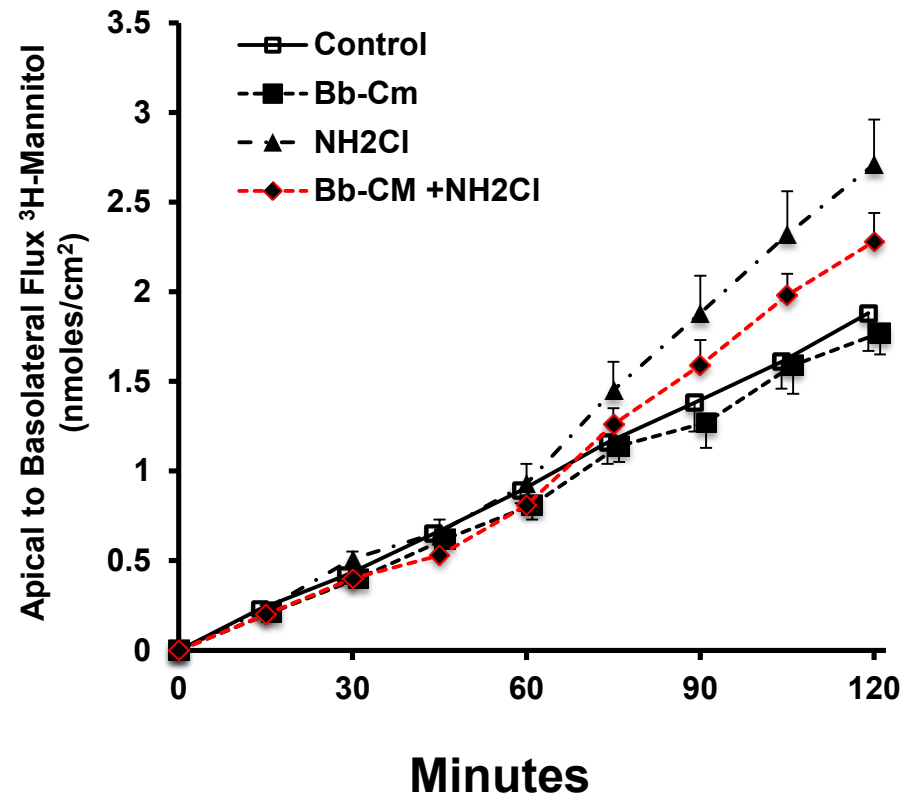
(Yan, et al Gastroenterology 2007)

Conditioned media from *Bifidobacterium breve* protects against ROS-induced barrier dysfunction

Mouse Jejunum

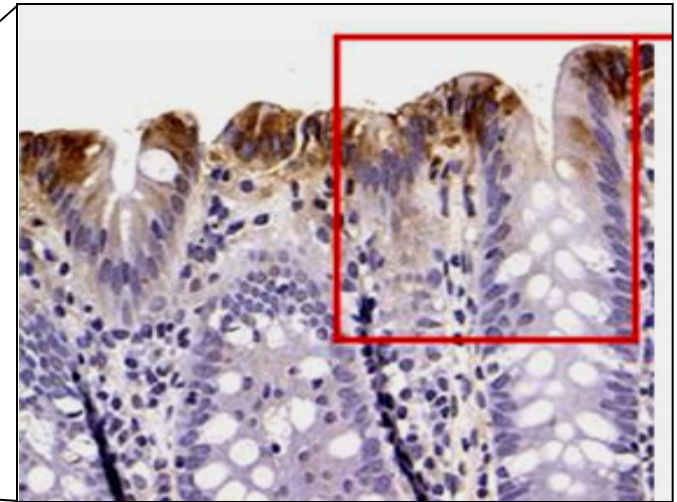
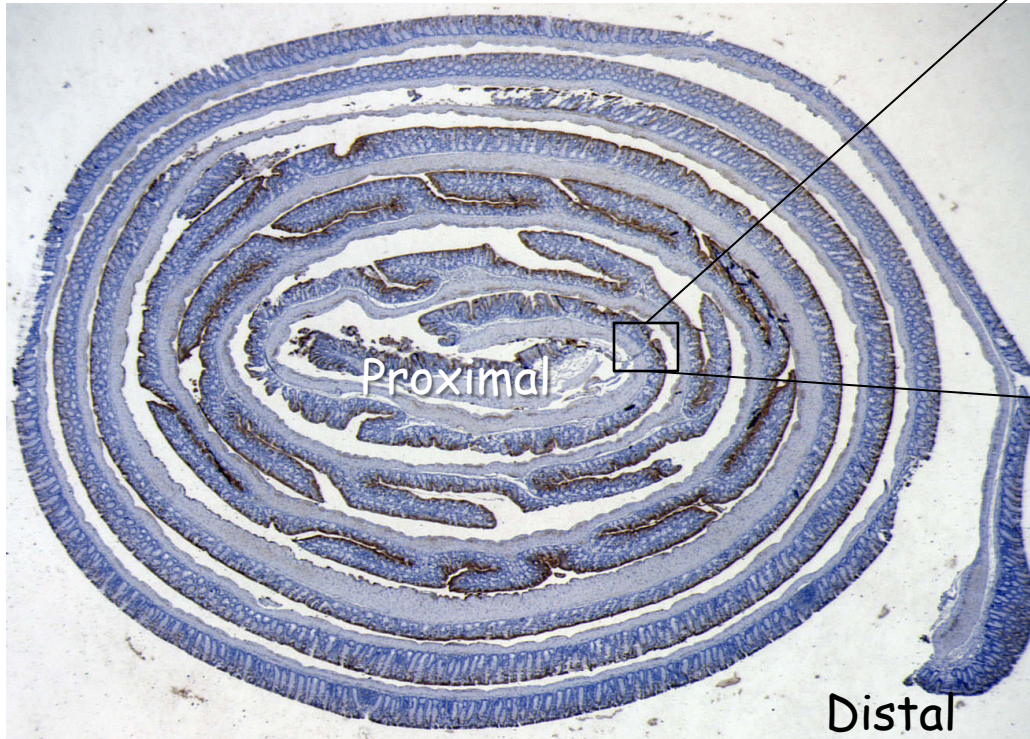


Caco2BBE

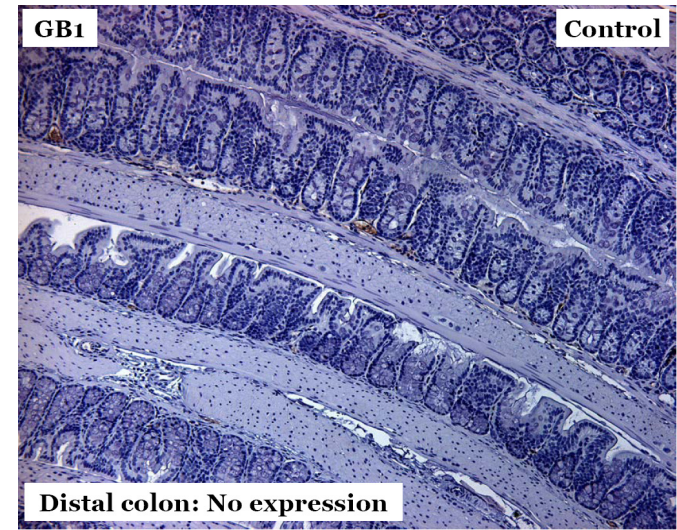


Physiological expression of inducible Hsps by surface colonocytes is maintained by gut microbes

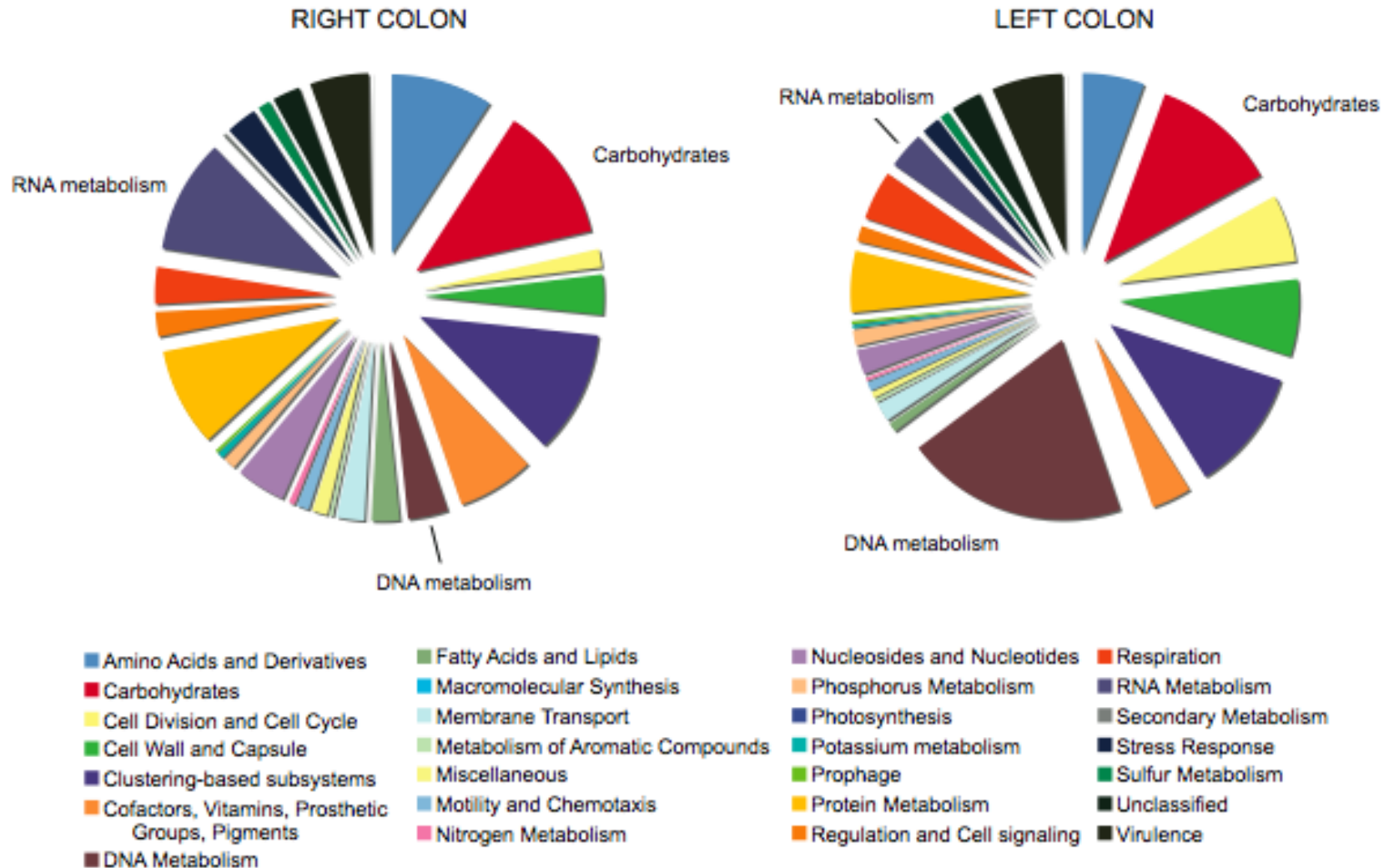
Hsp25 immunostaining (brown)



GF mice



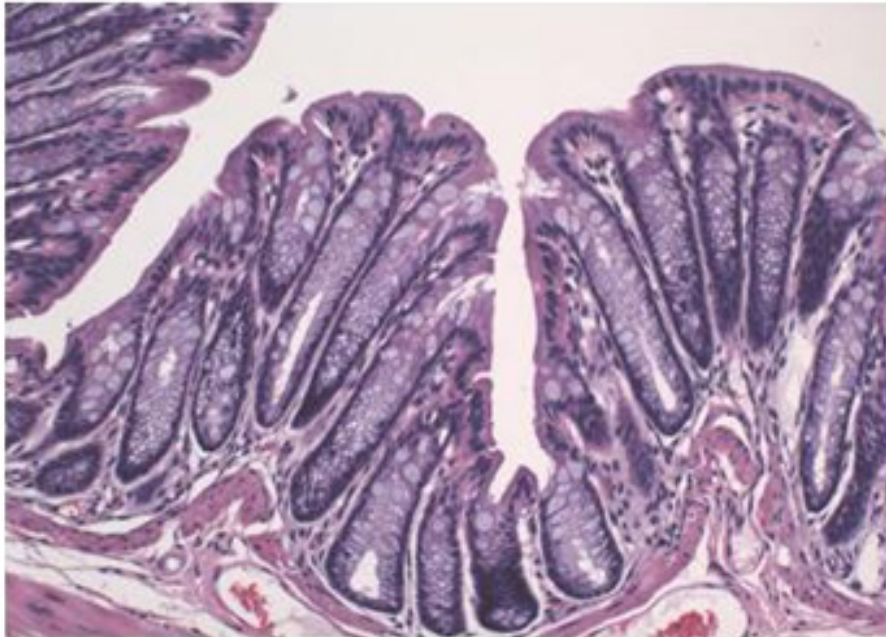
Metagenomic profiles of mucosa-associated microbiota from the healthy human colon



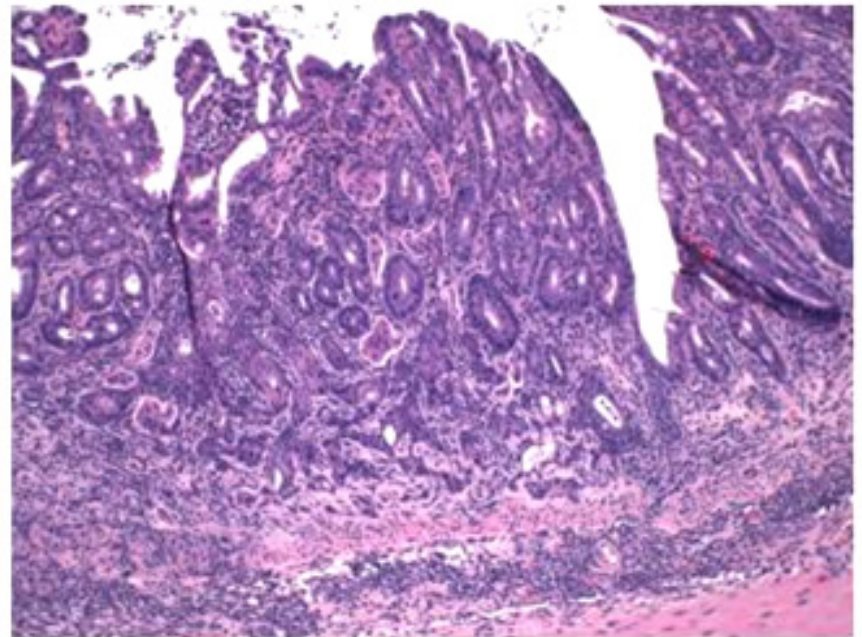
In Hsp70 KO mice, otherwise acute DSS colitis becomes chronic

Wild Type - normal

R

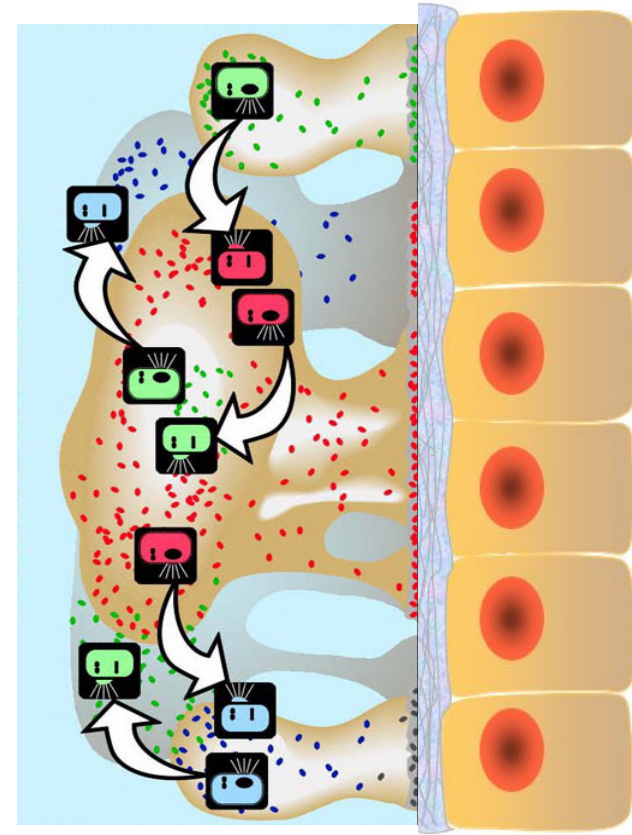


Hsp70 KO – chronic-like colitis



Identified molecular mediators that affect gut epithelial function

- QSM (e.g. CSF of *B. subtilis*)
- Innate ligands (PAMPs, MAMPs)
 - PG, MDP
 - LPS, dsRNA
- SCFAs, Lactic acid
- H₂S
- Chemotactic peptides (nFMLP)
- Metabolites



Gaps in our knowledge of gut microbial-epithelial interactions

- Rudimentary knowledge and inventories of bioactive microbe-derived factors
- Incomplete understanding of the complexity and heterogeneity of gut epithelial functions, particularly as they relate to microbial selection, assemblage and region-specific interactions.
- Incomplete vetting and understanding of the above in the context of human biology and pathobiology

Challenges and Needs

Human Studies:

- Observational and associative
- People are different and difficult to study
- Disease classifiers are inadequate
- Technology-driven
- Bottom-up approach

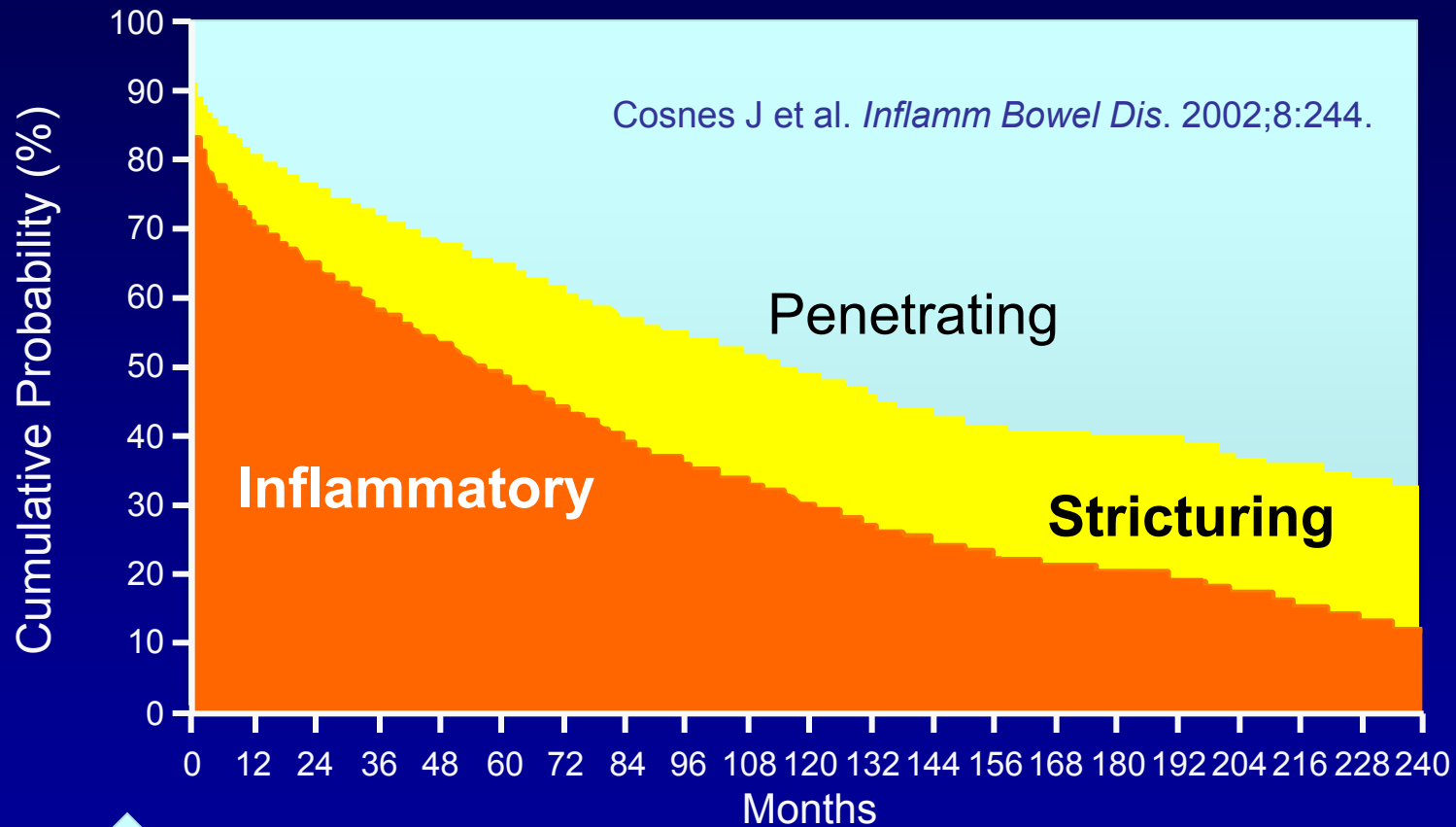
Technical:

- Sampling, QC, SOPs
- Insufficient vetting (metatranscriptomes, metagenomes, etc)
 - Better toolbox

Experimental/data analysis

- Animal and experimental models of the human condition
- Integration of data sets (host and microbe, location).
- Incomplete inventories of microbial transcriptomes, proteomes, metabolomes, etc.

IBD are progressive diseases and natural histories differ among patients



↑
T-0

↑
T-1

↑
T2

Location, location, location



Half empty, half full?



IS099093T [RF] © www.visualphotos.com

There is a solution to every problem

Surgical treatment of severe ulcerative colitis

– total colectomy with ileal-anal pouch anastomosis

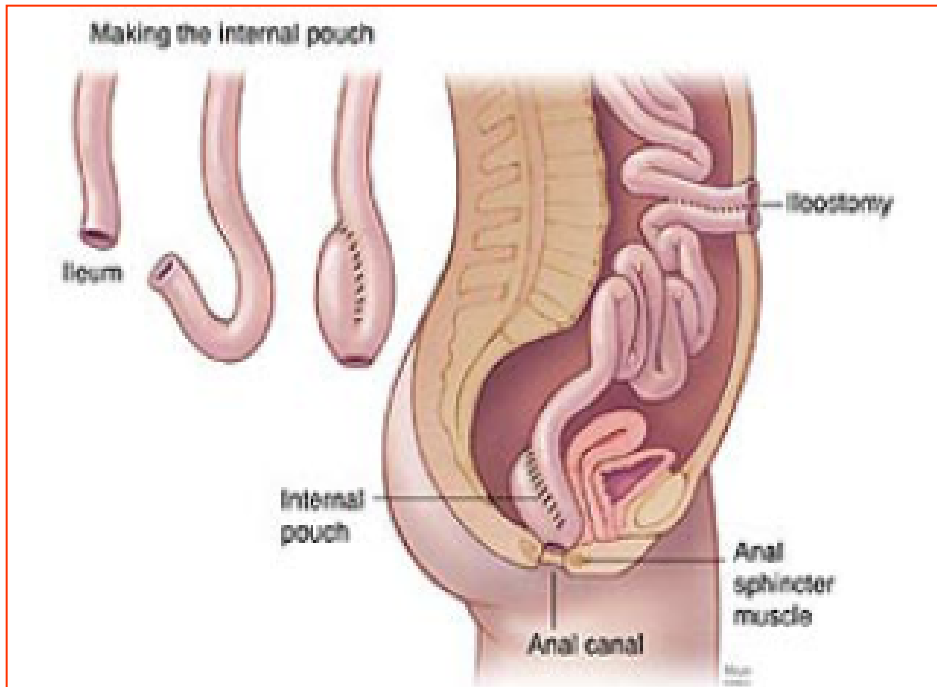


Fig. 1: Anatomy of an ileal pouch anal anastomosis. Following colectomy, the terminal ileum is fashioned into a “J-pouch” connected to the anal canal (from www.mayoclinic.com).



<http://www.gastrolab.net/ku01.htm>

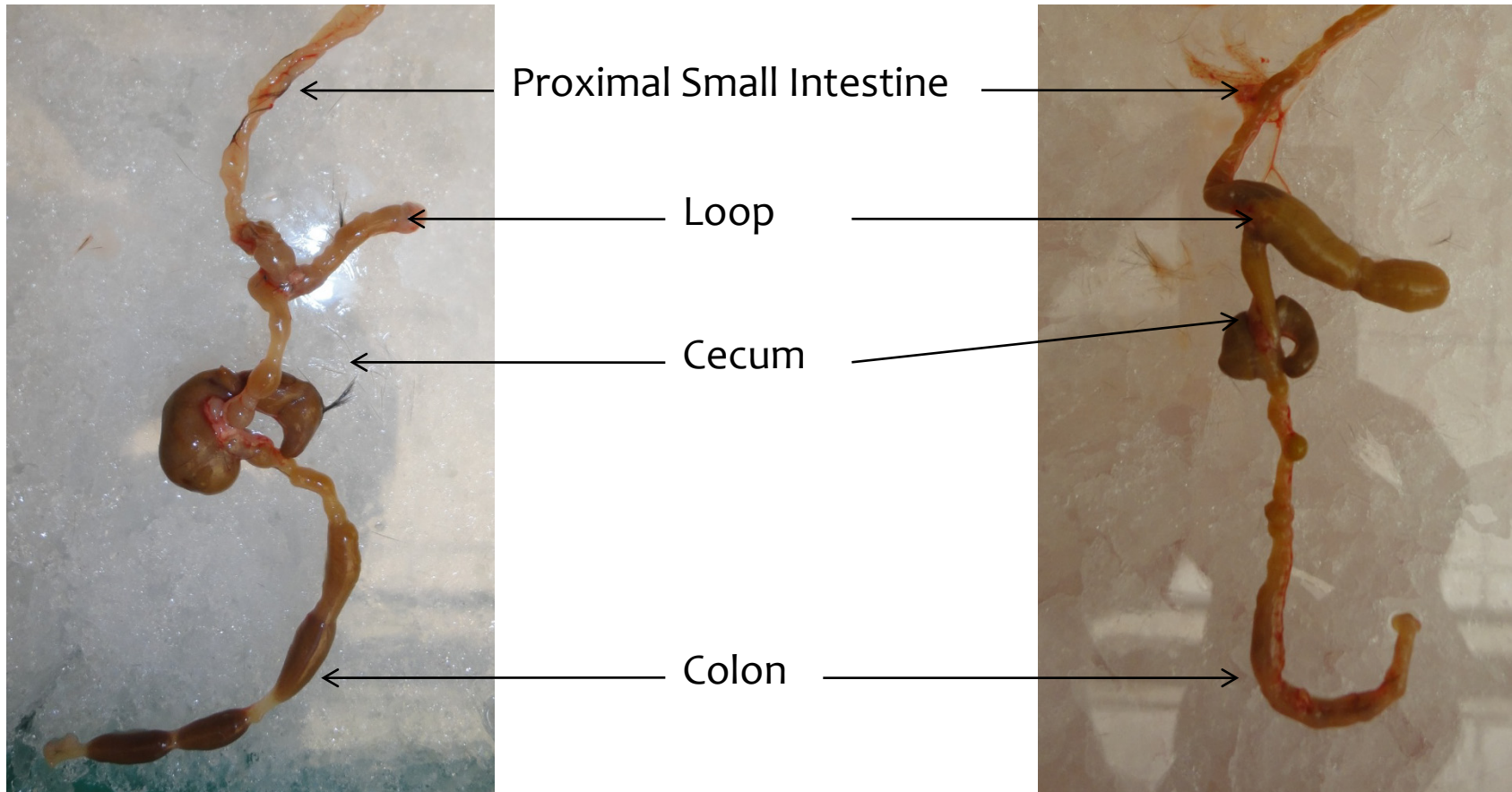
Why study pouchitis?

- Unique to UC
- Microbe-dependent
- >50% pts will develop it
- Prospective design
- Easy to sample
- Pts as their own controls

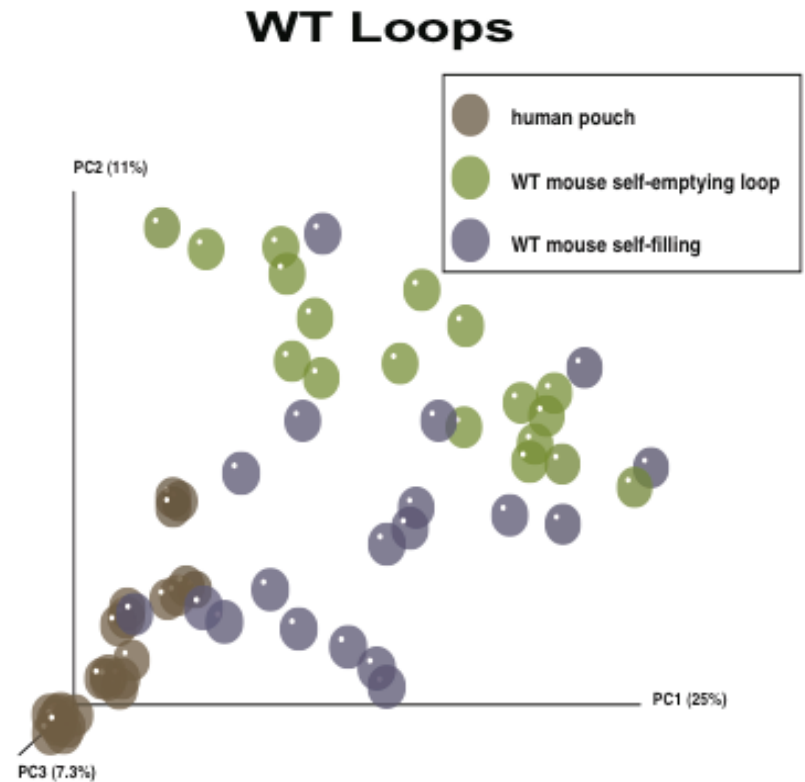
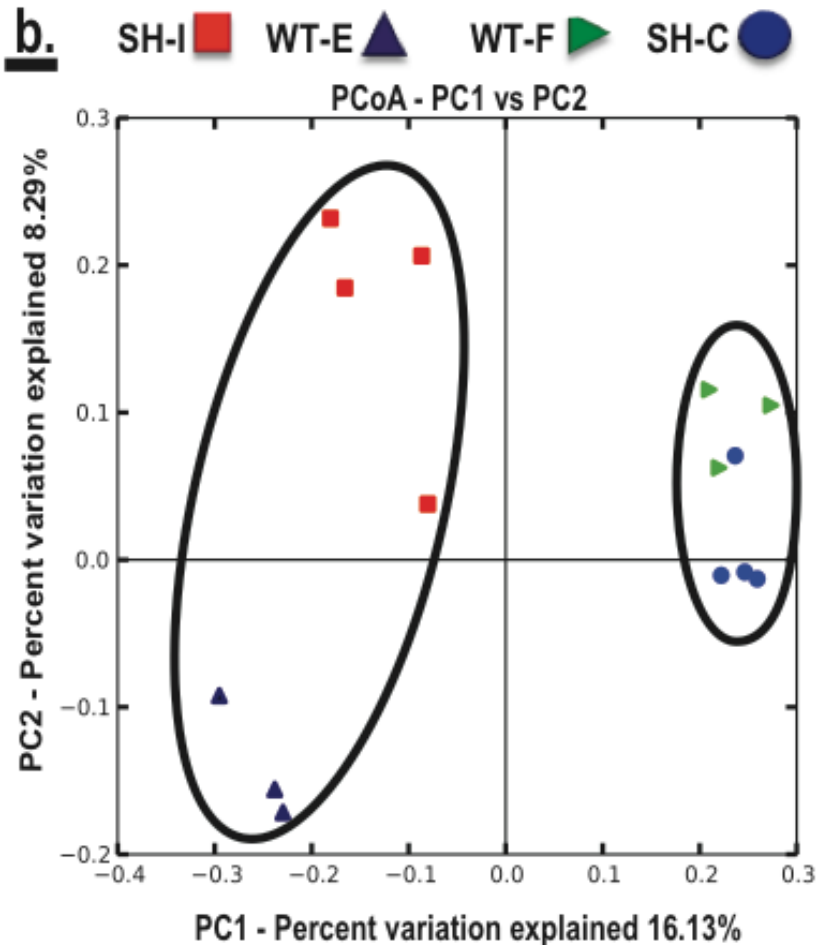
Developing a model that recapitulates conditions of the human ileal pouch

Self-Emptying (SE)

Self-Filling (SF)



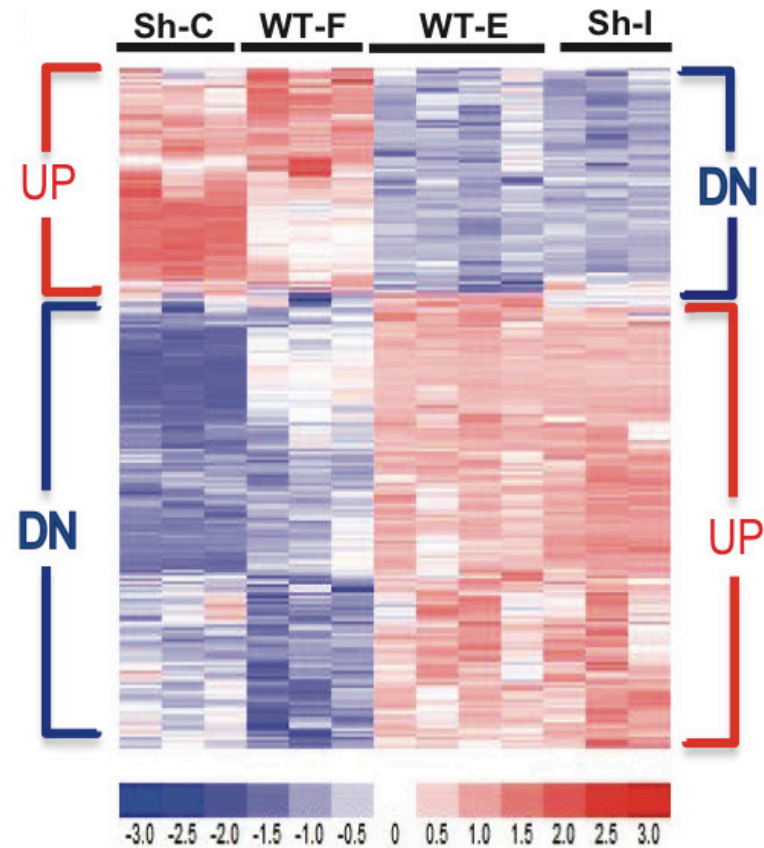
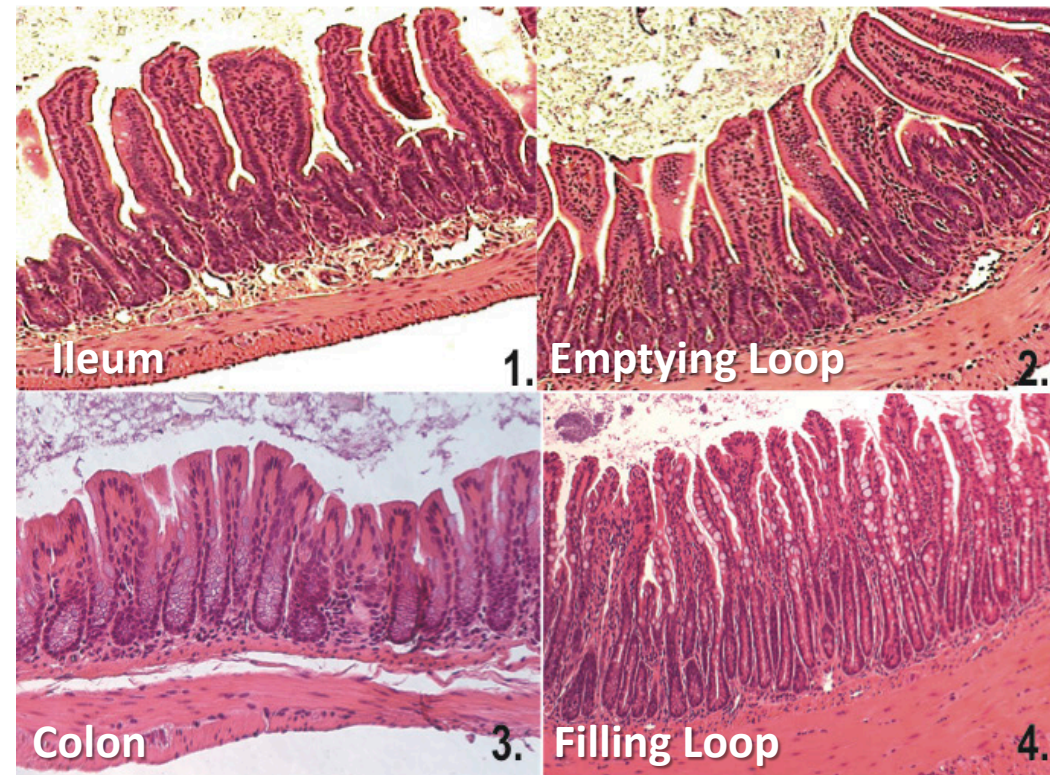
Does stasis promote a colonic-like microbiota?



If UC never involves the small intestinal mucosa, why does pouchitis occurs?

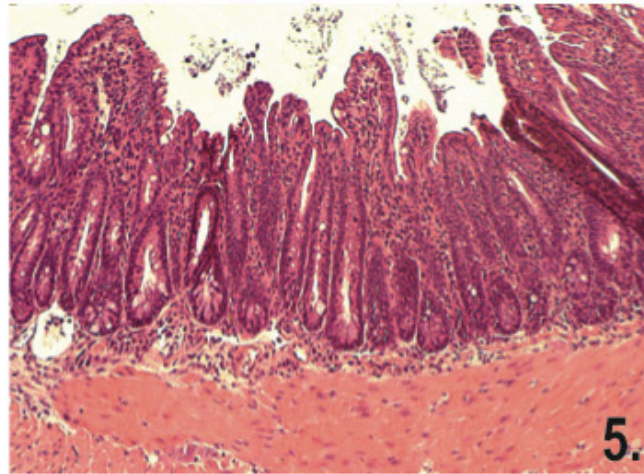
H&E mucosal histology

Microarray heat map

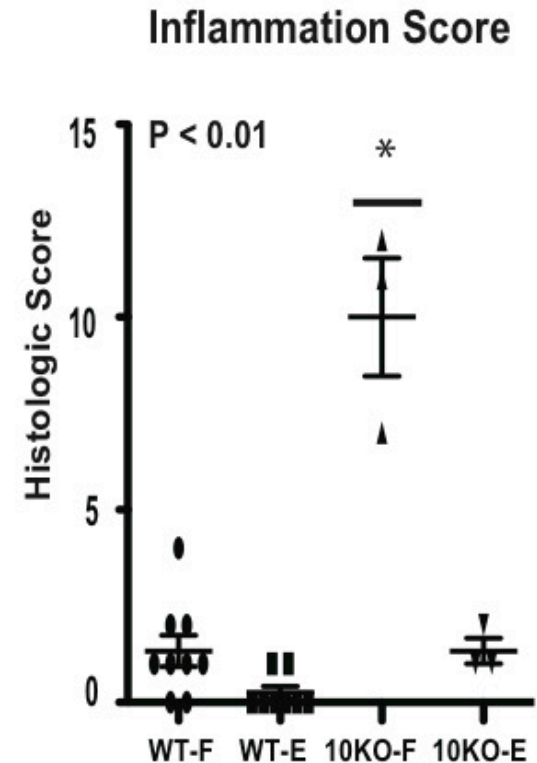
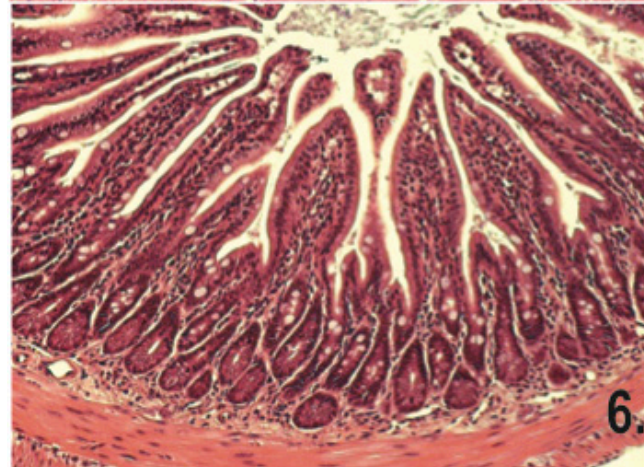


Are colonic microbiota and metaplasia sufficient to cause disease?

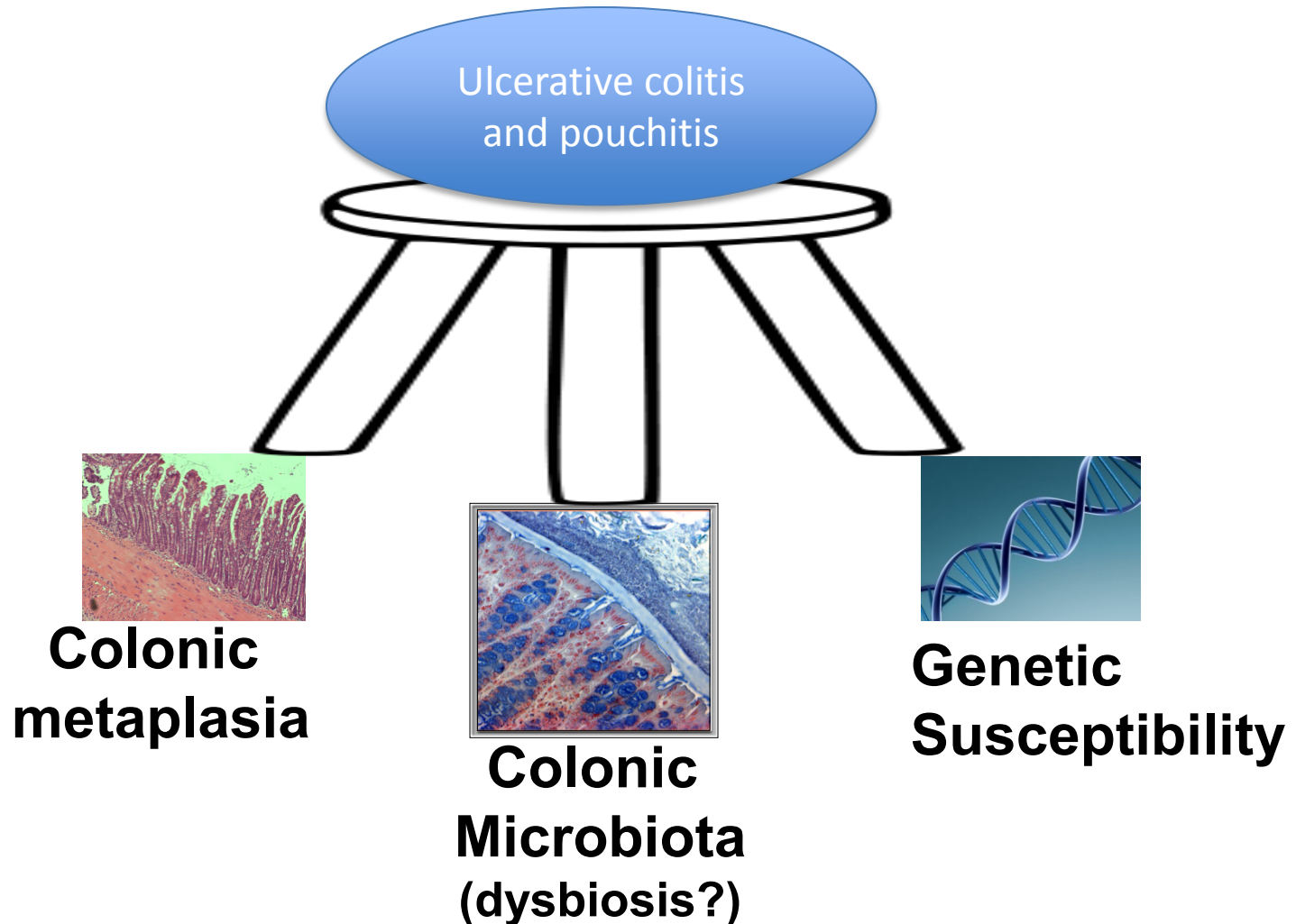
IL-10^{-/-} mouse
Self-filling loop



IL-10^{-/-} mouse
Self-emptying loop

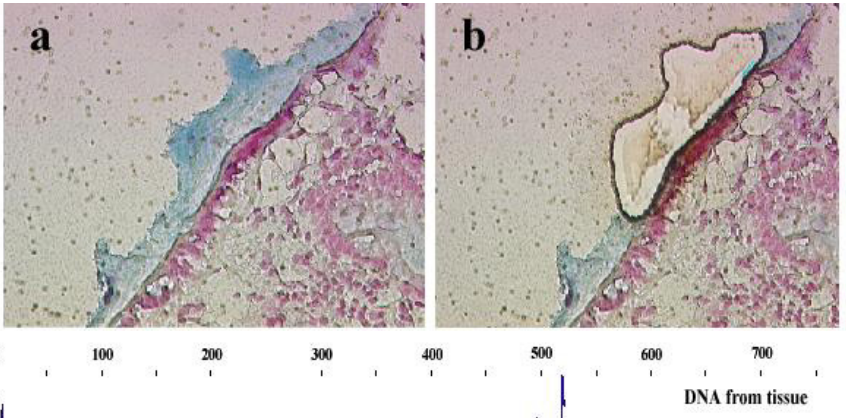
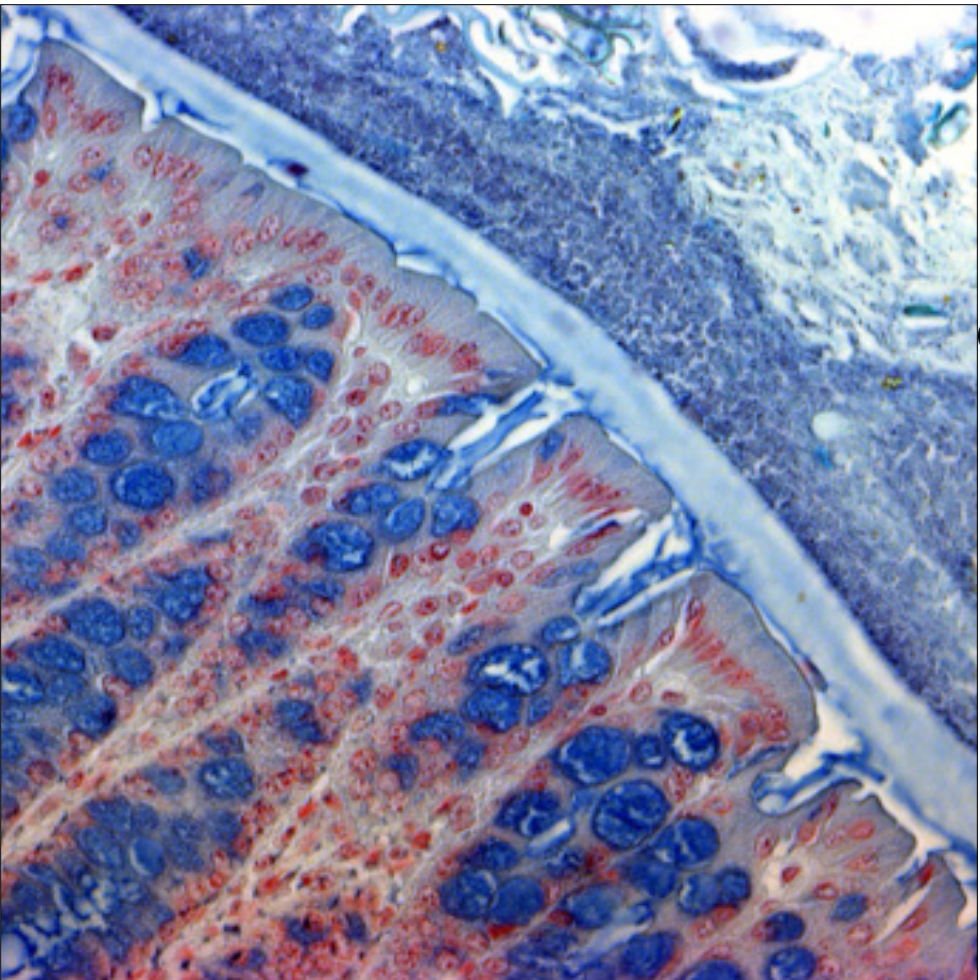


Working model for UC pathogenesis: The perfect storm

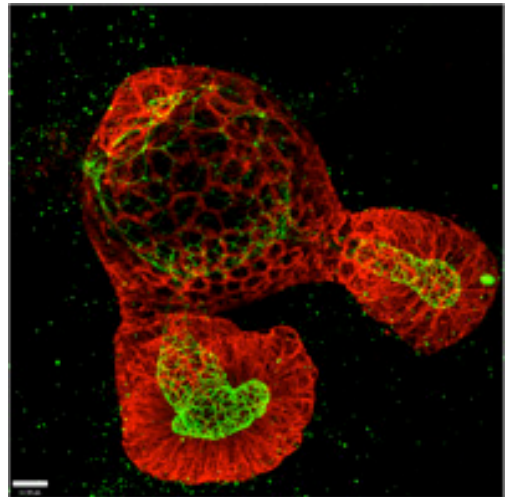


Challenge: The gut mucosa is a multicellular

Laser capture microdissection



Enteroid



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