5th Annual
CURRENT PERSPECTIVES IN HEPATOLOGY
Emerging Topics in Liver Disease

Gut Microbiome Intersection with Chronic Liver Disease: Potential mediator in Primary Sclerosing Cholangitis (PSC)

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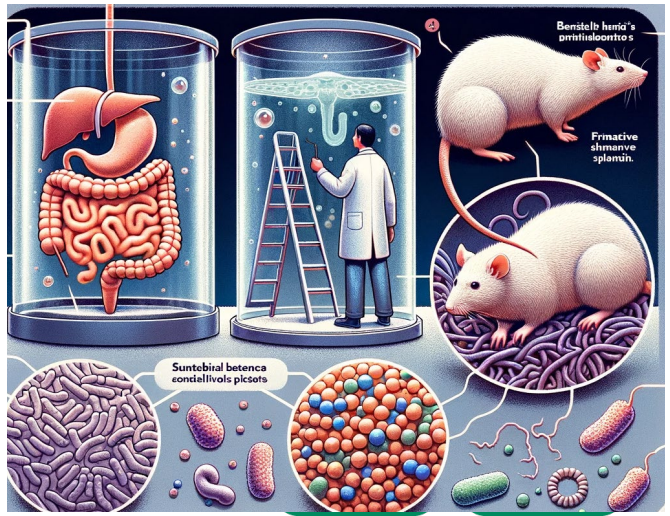


Cleveland Clinic

Disclosures

- No relevant disclosures

Learning Objectives

- Explain the role of the gut microbiome in the relationship in Chronic Liver Diseases (CLD) and Primary Sclerosing Cholangitis (PSC),
- Critically evaluate and incorporate emerging microbiome research when developing management strategies for these patients
- Apply knowledge of the gut-liver axis to improve the diagnostic process and personalize treatment approaches, potentially utilizing microbial therapies as part of a comprehensive treatment plan.
- Achieve better clinical outcomes for patients with PSC by integrating microbiome-based diagnostics and treatments into practice, thereby aiming to reduce disease progression and associated complications..

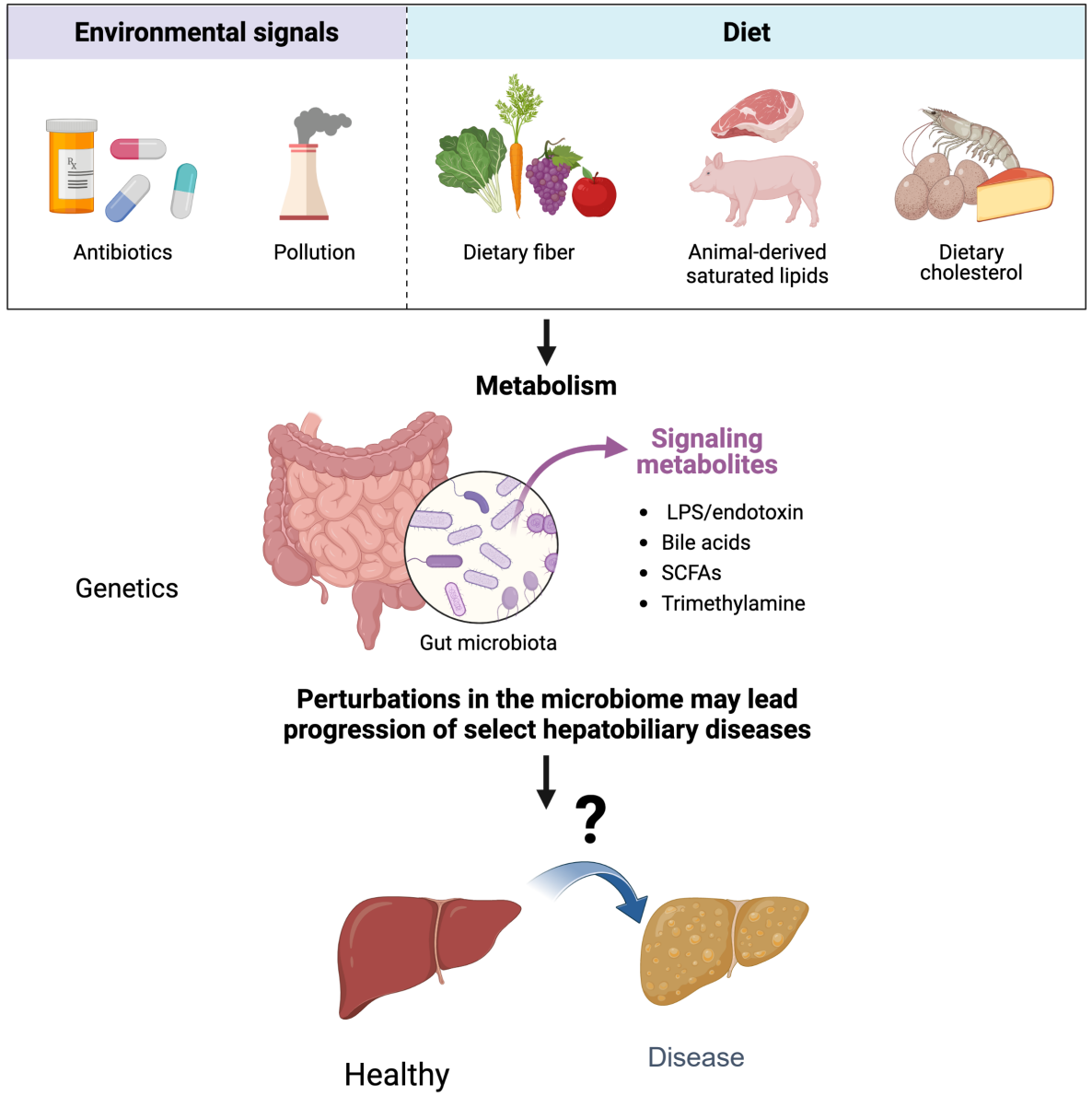
Definitions and Concepts

- **Microbiota** = collection of microbial species that form a microbial community.
- **Microbiome** = the collection of genetic material present in the genomes of the microorganisms present in a community.
- **Dysbiosis** = Derangement in the Microbiome of a community.
- **Commensal** = a microorganism that lives in intimate contact with another, deriving benefit without harming or benefiting the other.

Gu, X et al., Semin Liv Dis., 2021

Gastrointestinal Microbiome in Health

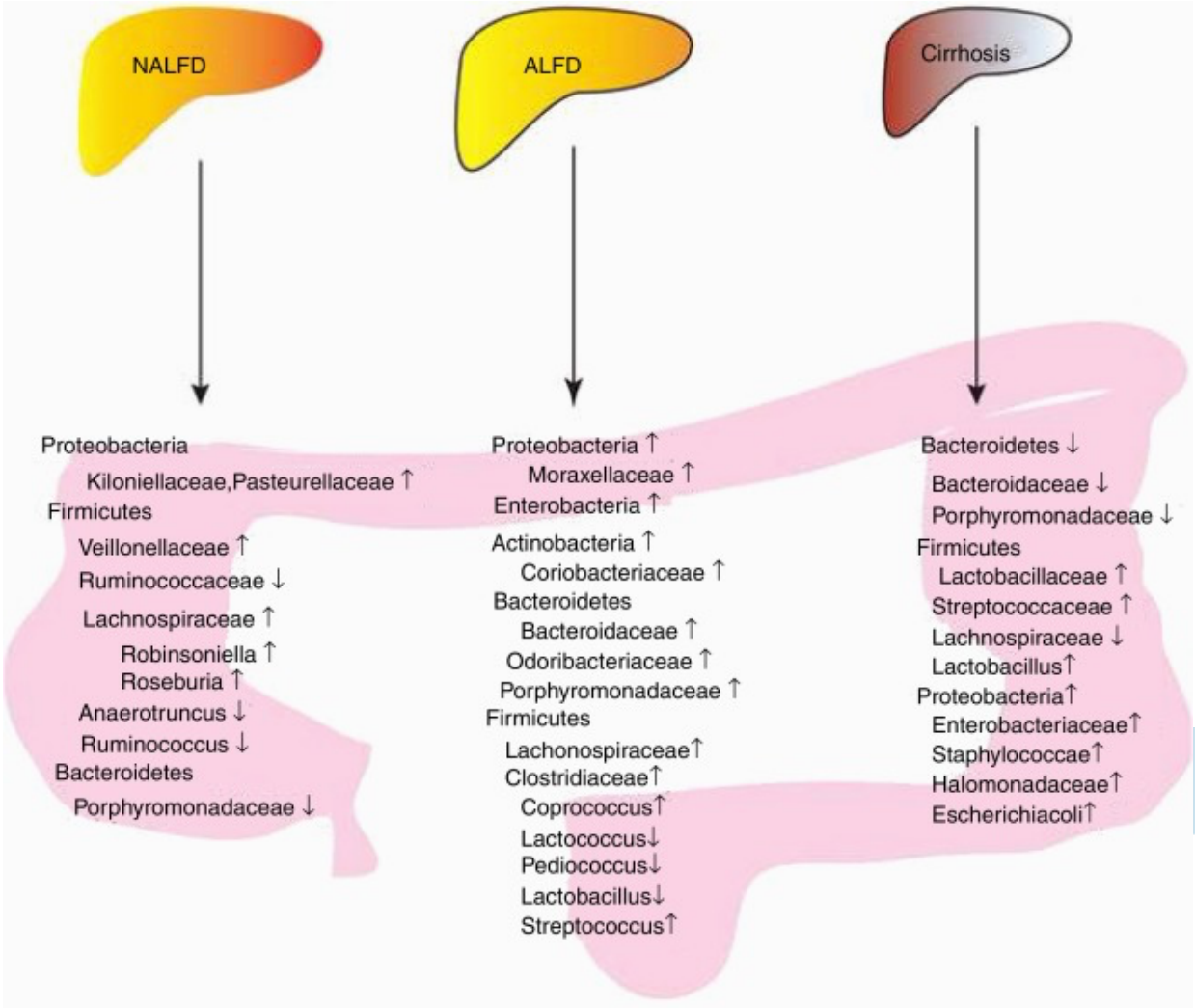
- Types of microorganisms present
  - Bacteria: >1000 species
  - Archaea (prokaryotes)
  - Virus/bacteriophages
  - Fungi (mycobiome)
  - Even protozoa in some places
- Bacterial Main Phyla
  - Firmicutes (Gram +)
  - Bacteroidetes (Gram (-)
  - Proteobacteria
  - Actinobacteria
- Influencers
  - Diet
  - Medications
  - Inflammation
  - Intestinal Region



Problem: Dysbiosis in Chronic Liver Disease

Dysbiosis + genetics + inflammation→ impairment of the intestinal epithelial barrier and immune and metabolic dysregulation in varying models of chronic liver disease.

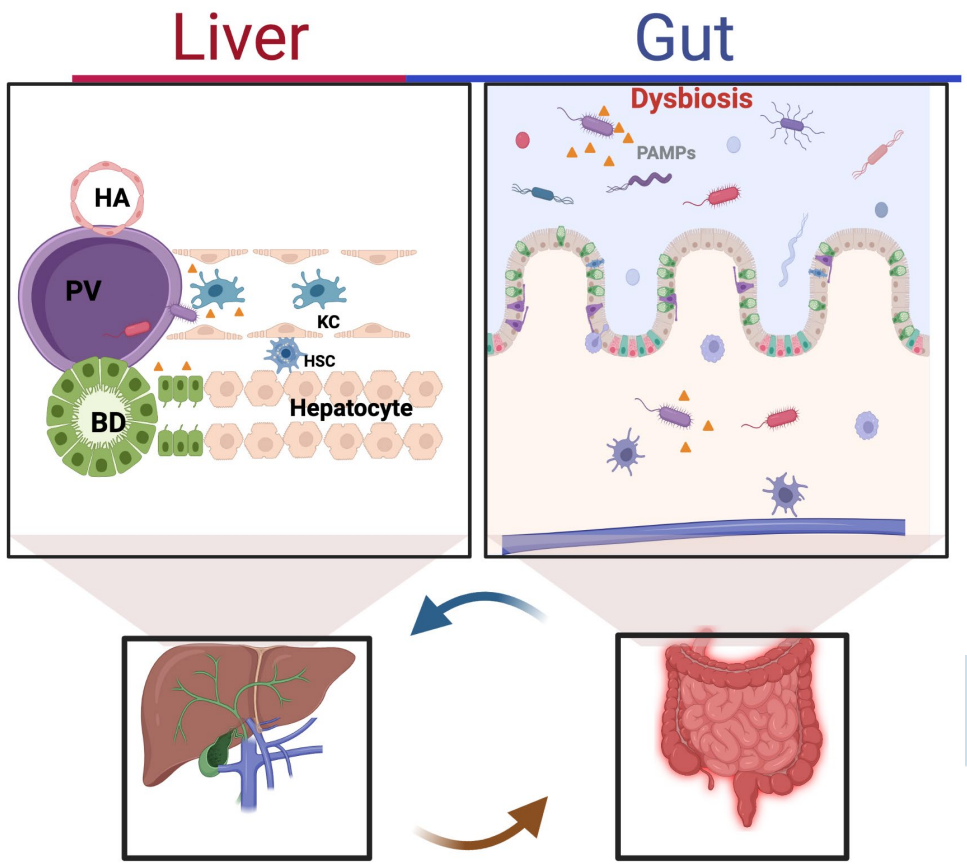
Human studies have consistently demonstrated an altered gut microbial composition in multiple chronic liver disease characterized by reduced fecal alpha and beta diversity as well as shifts in multiple bacterial taxa.

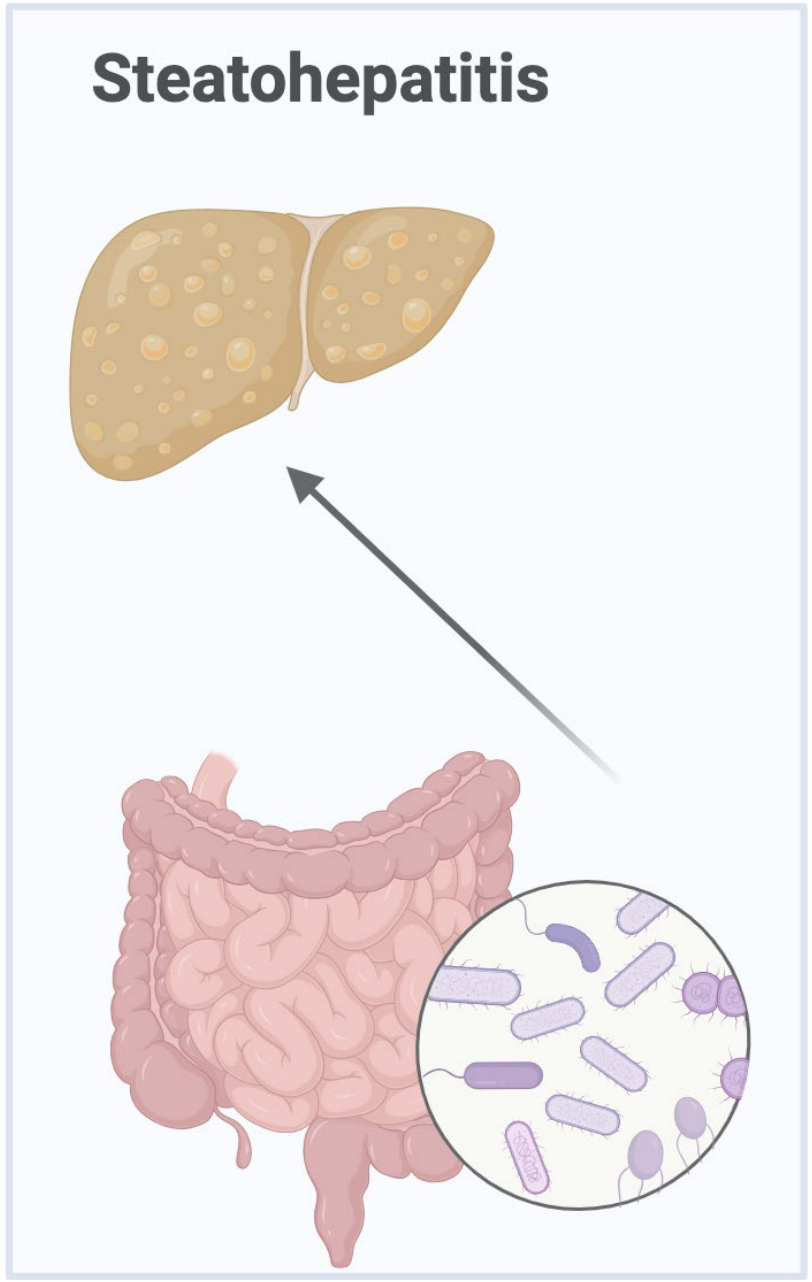


Liu, G. et al. 2019

Potential Solution

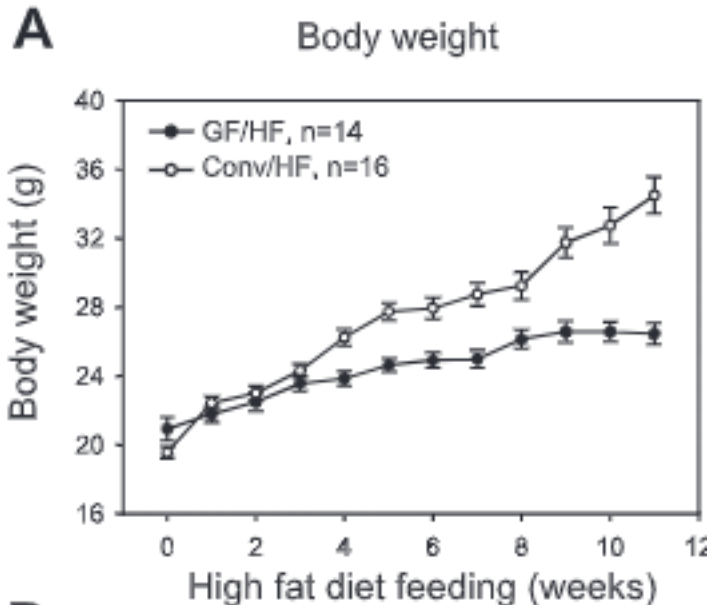
- Restoration of healthy intestinal flora through manipulation of the gut microbiome:
  - Fecal microbiota transplantation (FMT)
  - Antibiotics
  - Phage therapy
  - Fecal microbiota transplantation

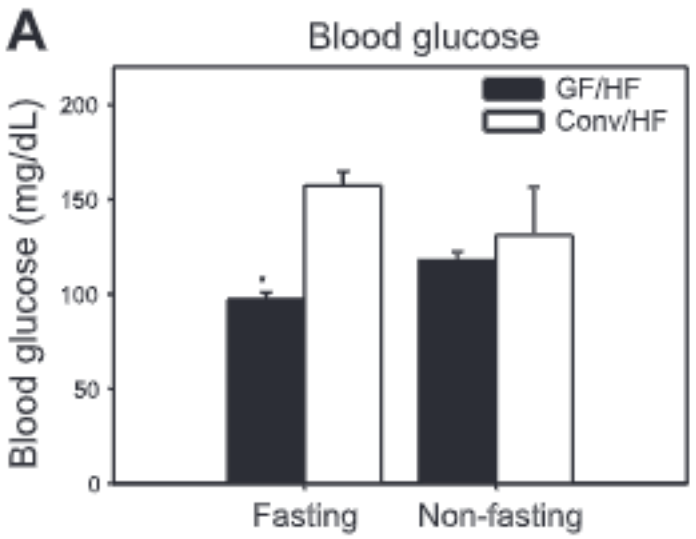


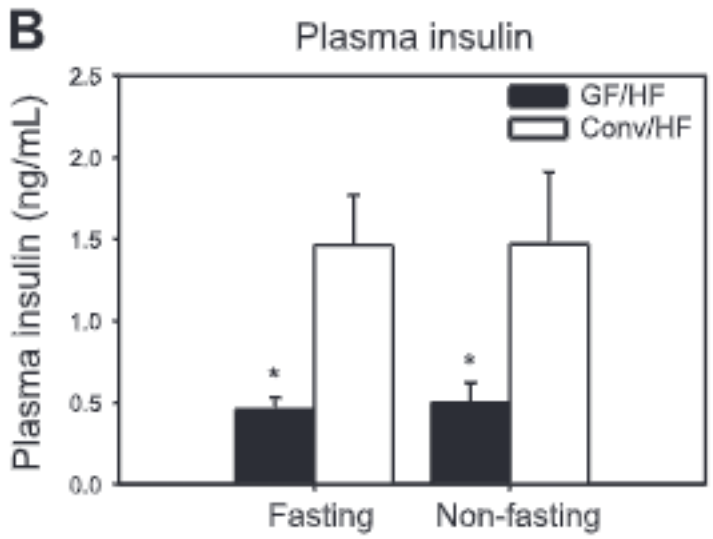


Microbial influence in MASH?

Gut microbiota required for Western diet induced metabolic syndrome

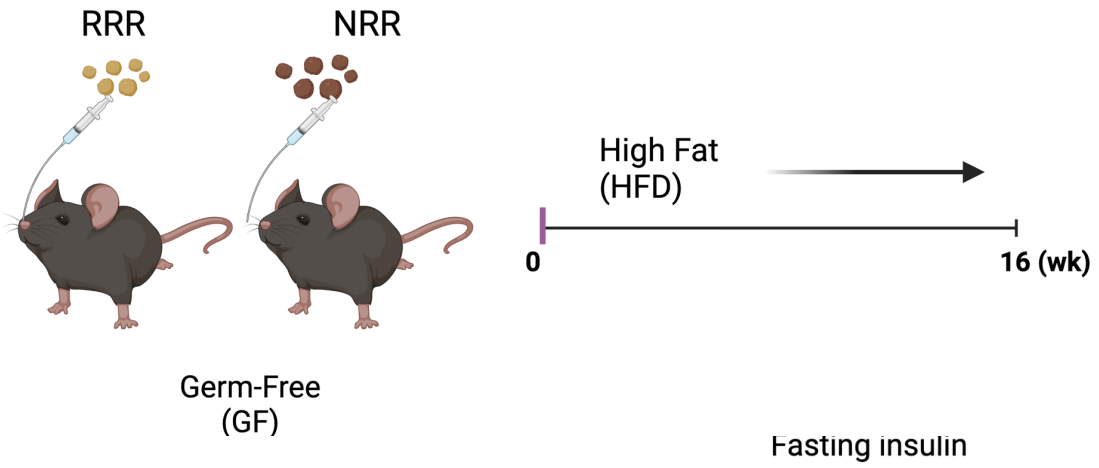


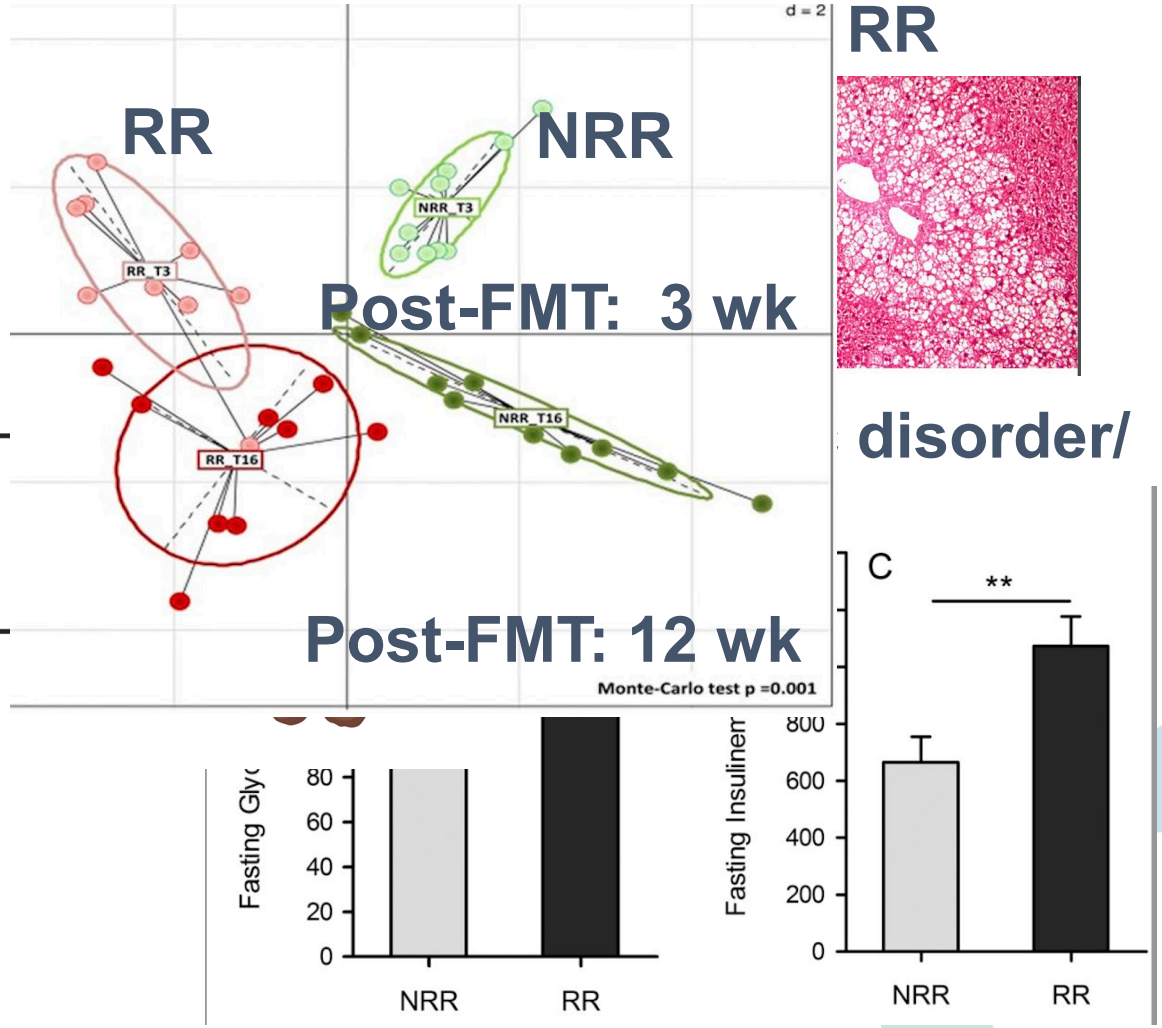




Rabot S, et al. Faseb J, 2010

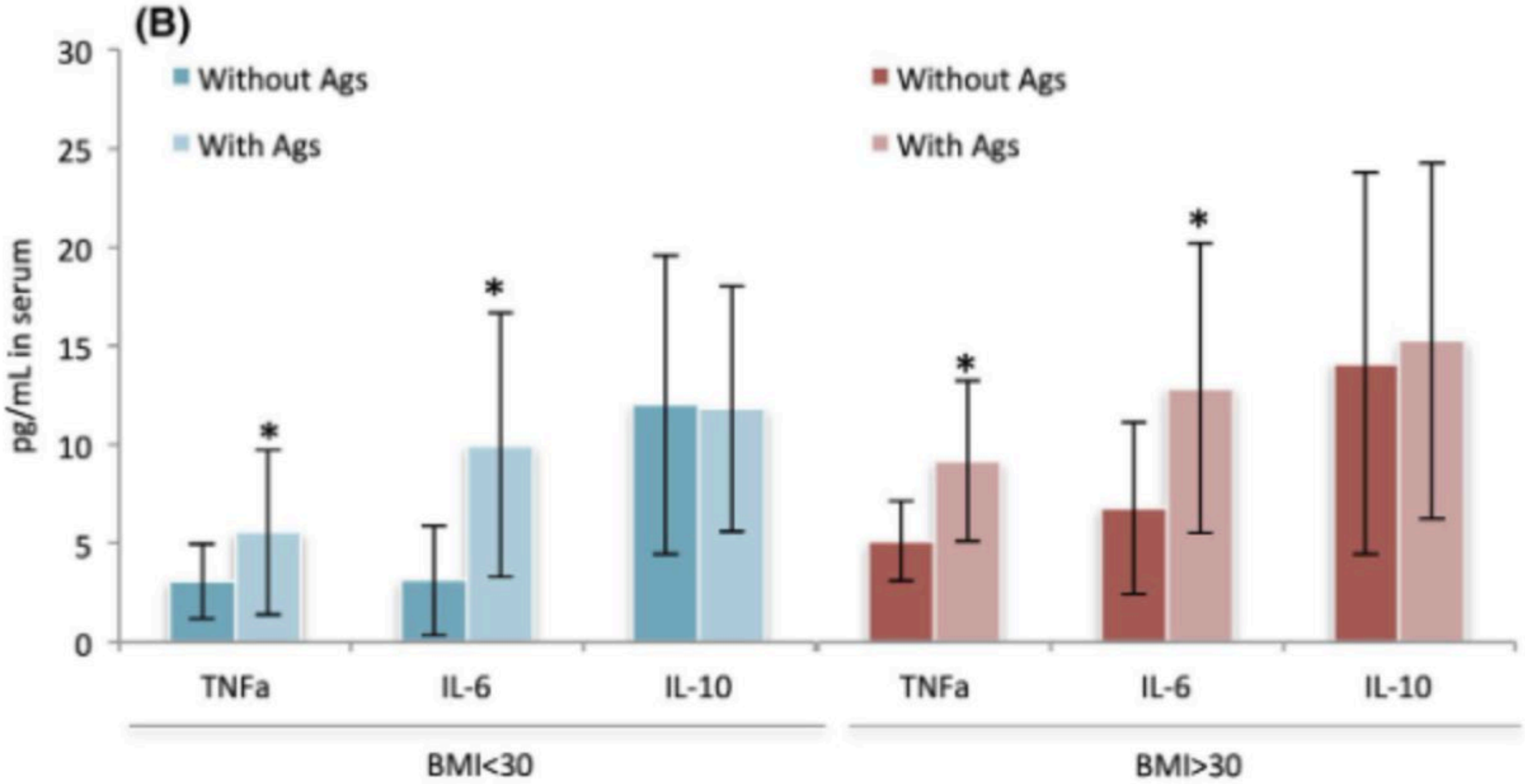
Gut microbiota contributes to the development of NAFLD independently of obesity





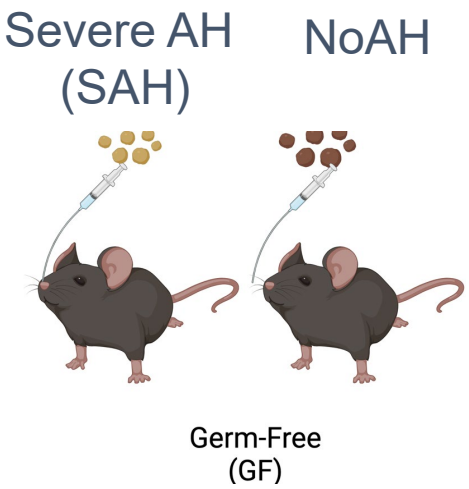
Le Roy, T et. al, Hepatology, 2012

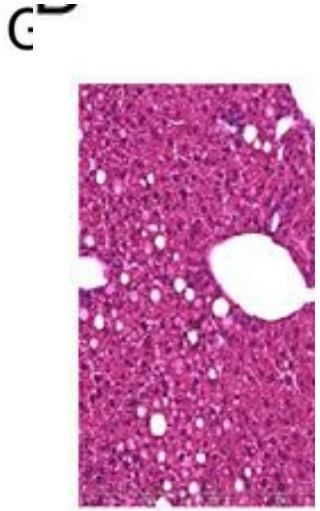
Bacterial antigens as well as age were BMI-independent factors related to increased systemic inflammation in NAFLD

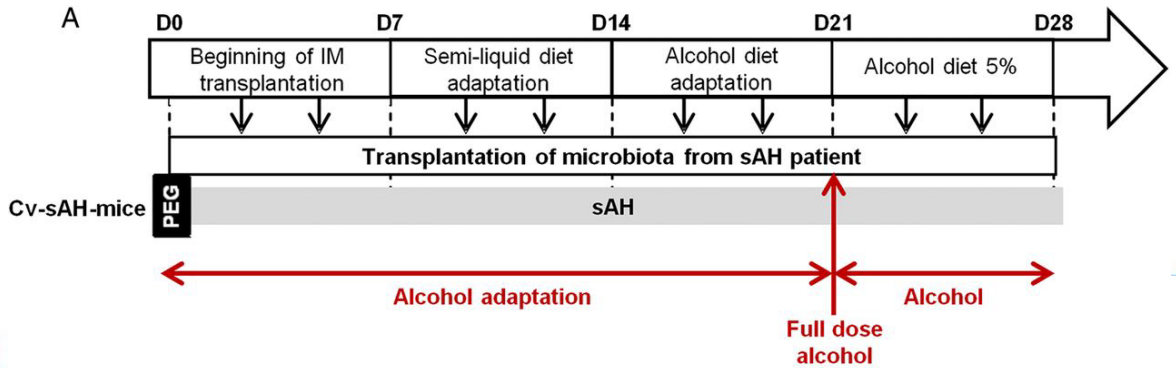


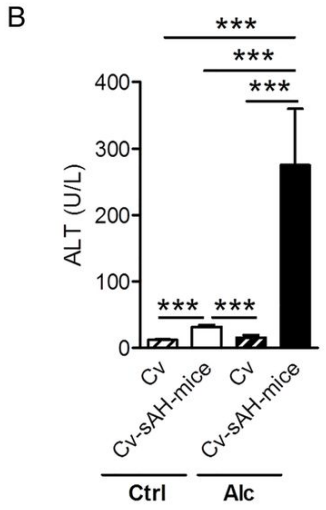
Hurtado, I et al. Liv. Int. 2020

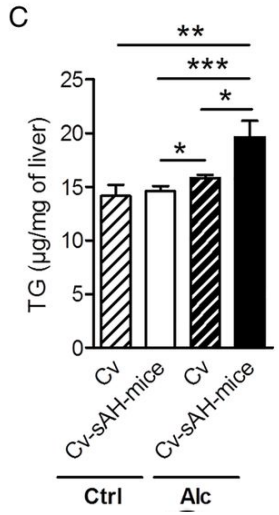
Post severe AH fecal transfer results in transmission of steatophepatitis amplified with dietary adaptation

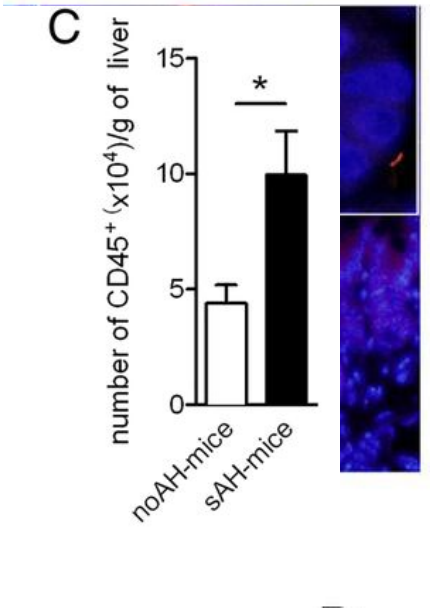






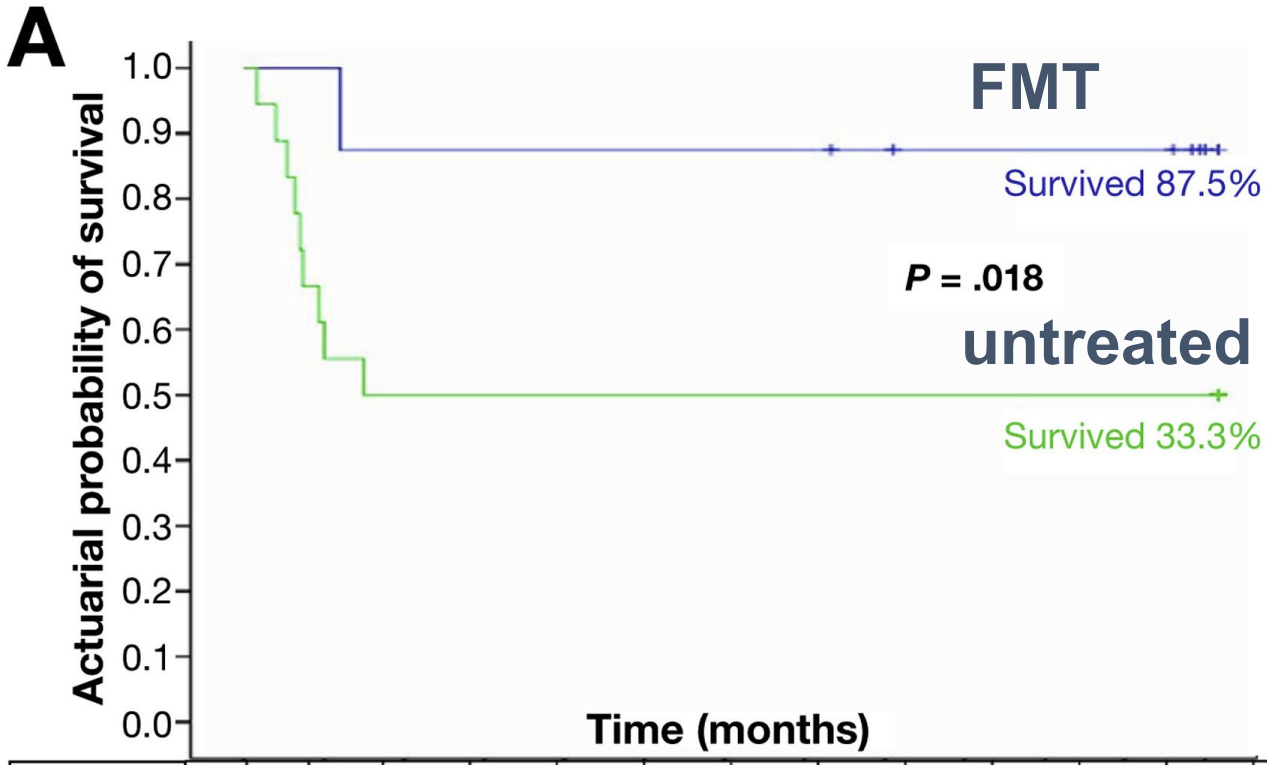






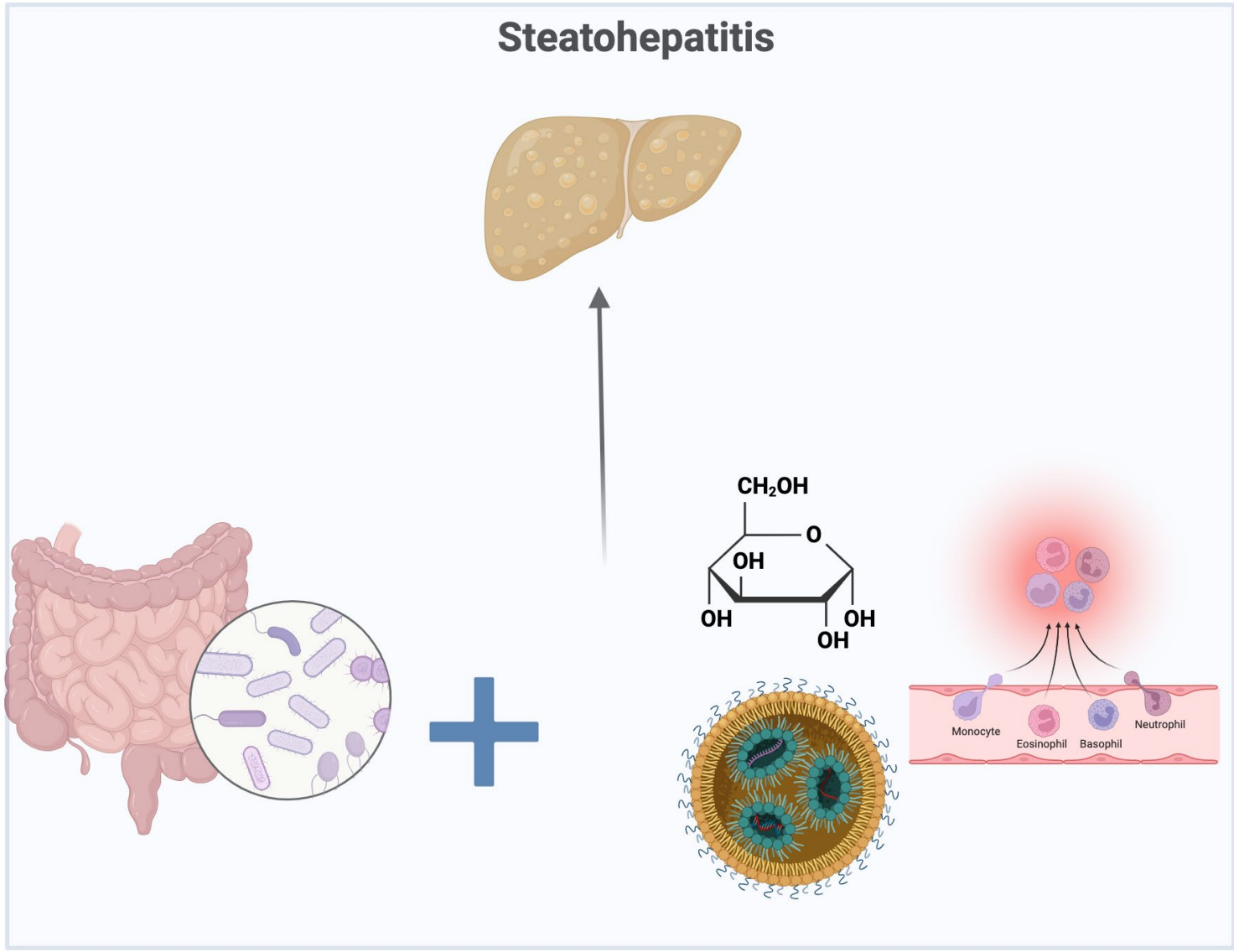
Llopis M, et al., Gut, 2016

FMT improves survival in steroid-ineligible patients with severe alcoholic hepatitis



Group		0	1	2	3	4	5	6	7	8	9	10	11	12	Total
FMT N = 8	At risk	8	7	7	7	7	7	7	7	7	7	7	7	7	7
	Events	0	1	0	0	0	0	0	0	0	0	0	0	0	1
HC N = 18	At risk	18	10	9	9	7	6	6	6	6	6	6	6	6	6
	Events	0	8	1	0	2	1	0	0	0	0	0	0	0	12

Philips CA,et. al., CGH, 2017


Steatohepatitis
CH2OH
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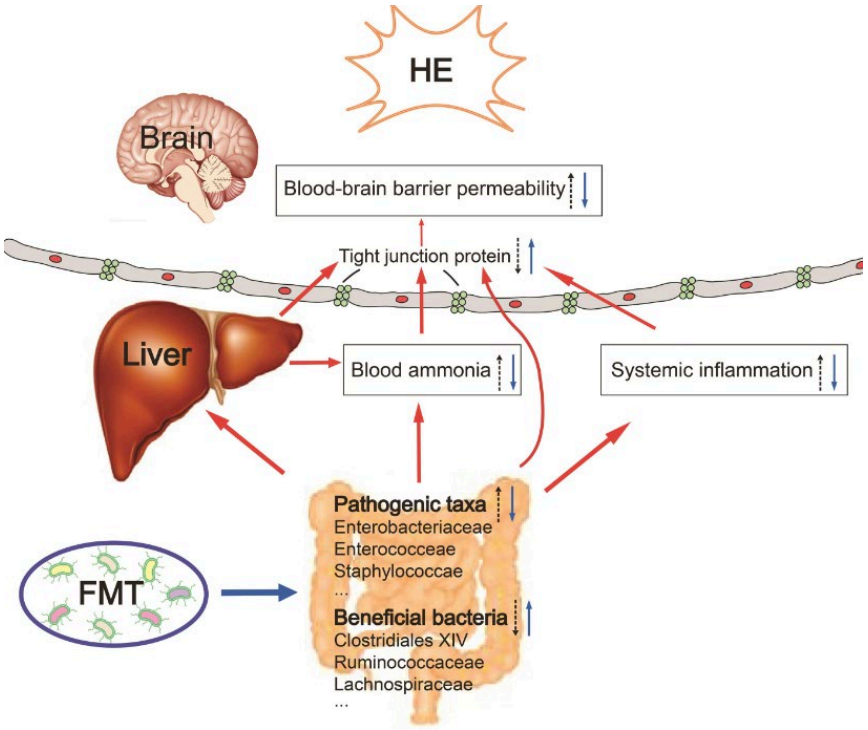
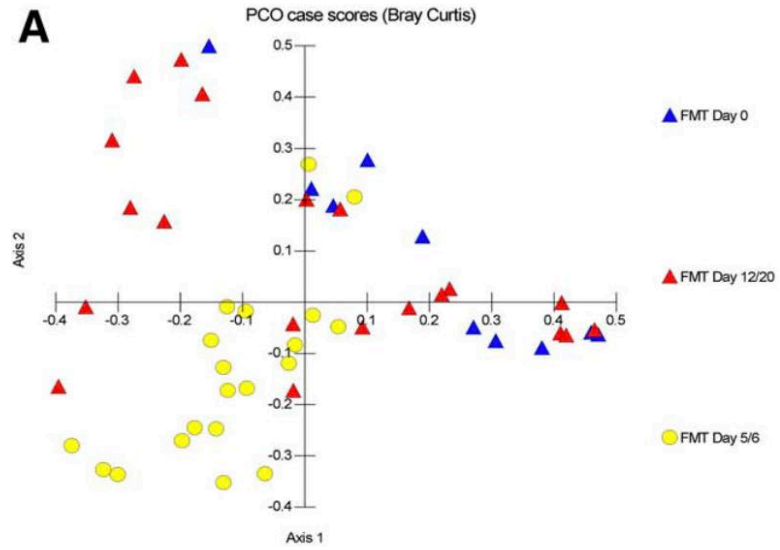
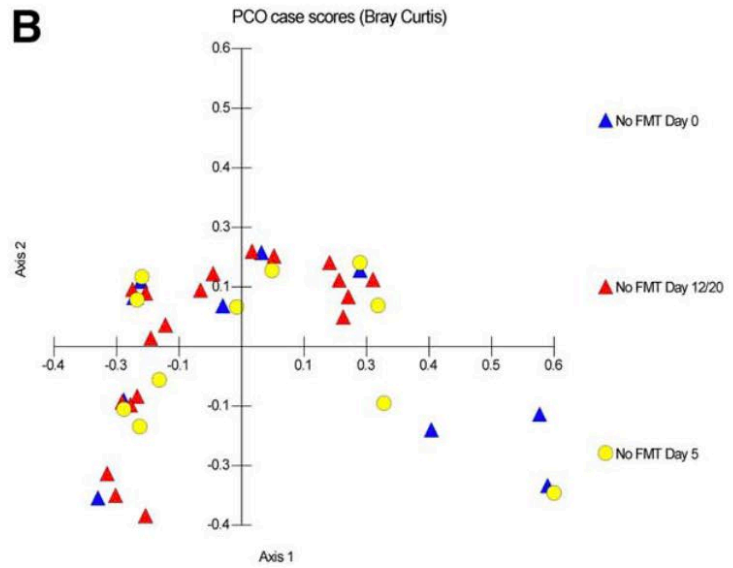
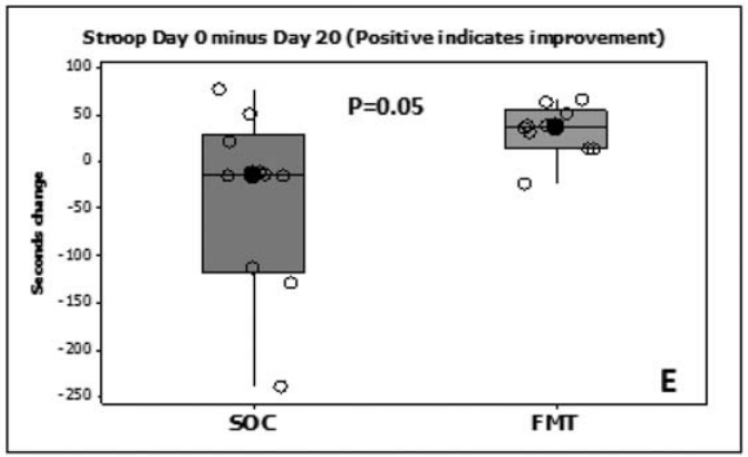
OH
OH
OH
OH
Monocyte
Eosinophil
Basophil
Neutrophil

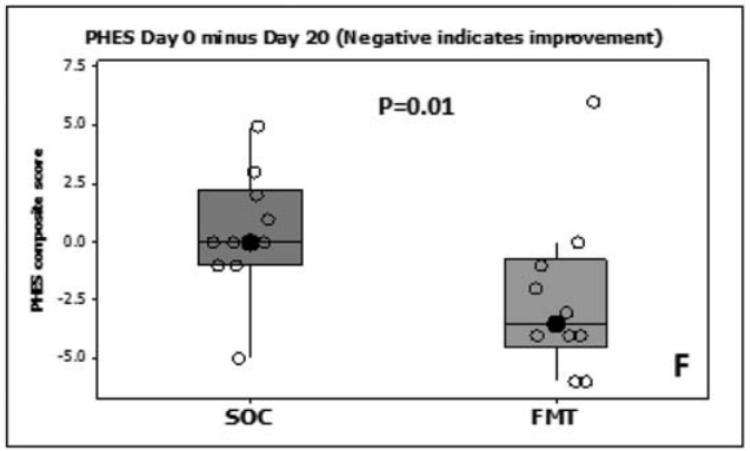
Therapeutic FMT HE efficacy







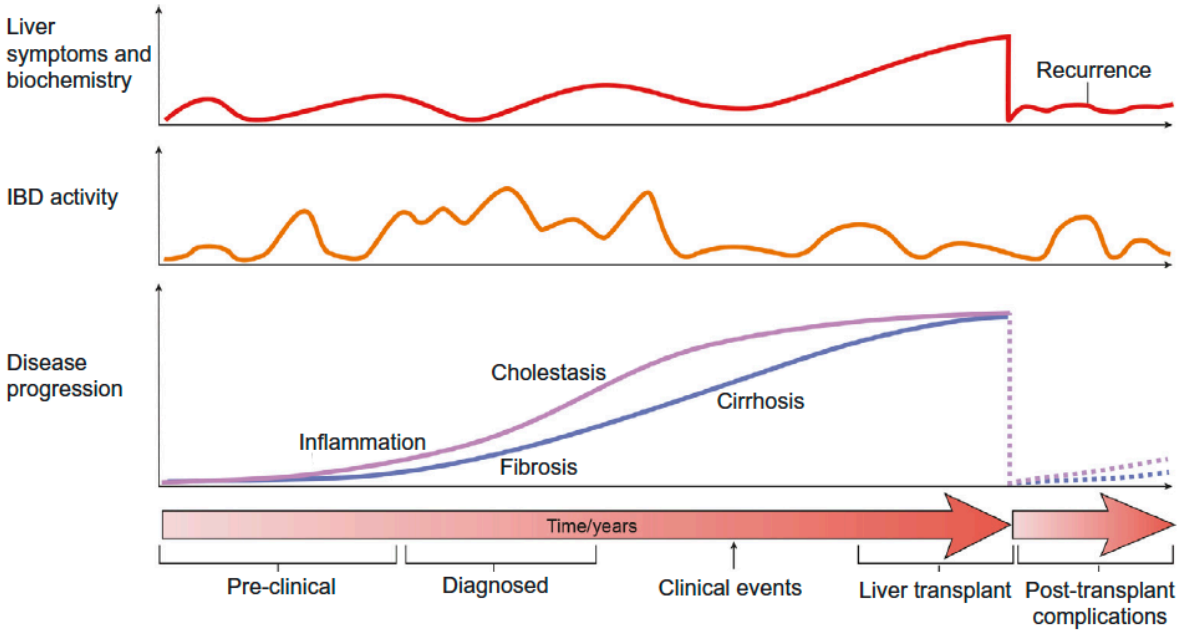




Bajaj, J. et al, Hepatology 2017

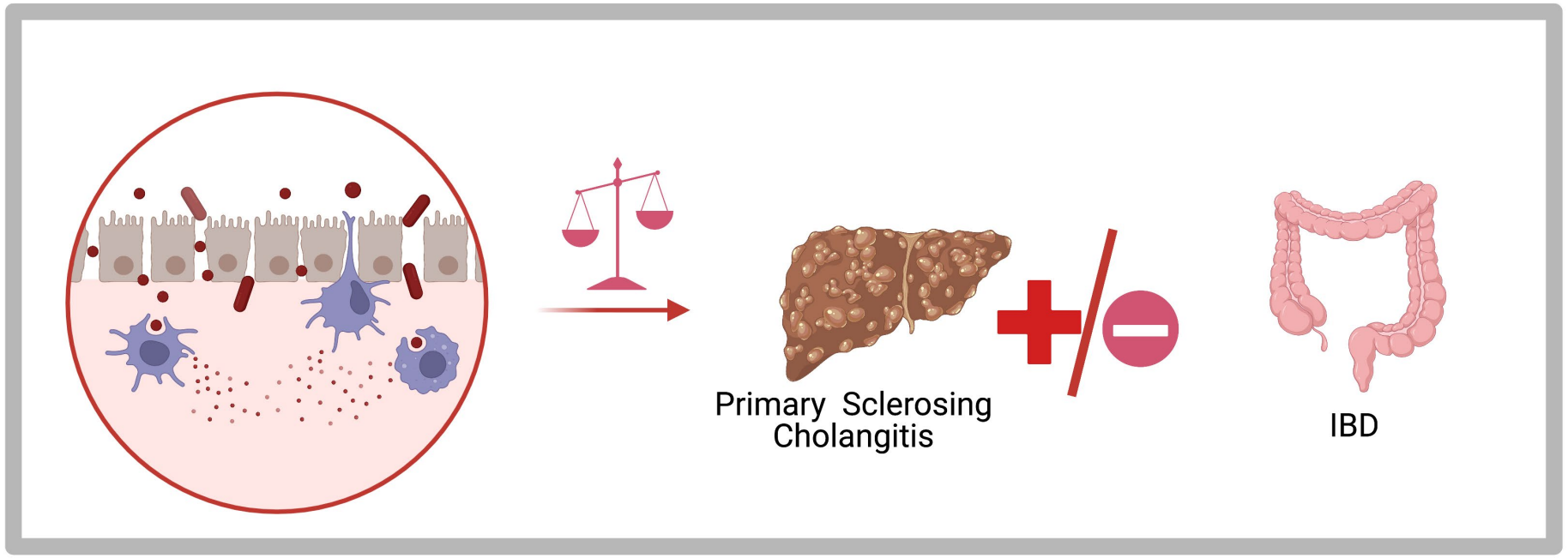
Understanding Primary Sclerosing Cholangitis (PSC)

- **Disease Progression:** multi-focal biliary strictures → fibrosis → cirrhosis.
- **Clinical Associations:** Strong links with IBD and GI/Hepatobiliary malignancies.
- **Treatment Landscape:** Currently **no cure** with notable post-transplant recurrence.



Trivedi et al, 2020
Takakura W, Tabibian J, Bowlus C, 2017
Rizvi and Gores,2013
Karlsen, TH, et. all, 2017

Microbial influence in PSC

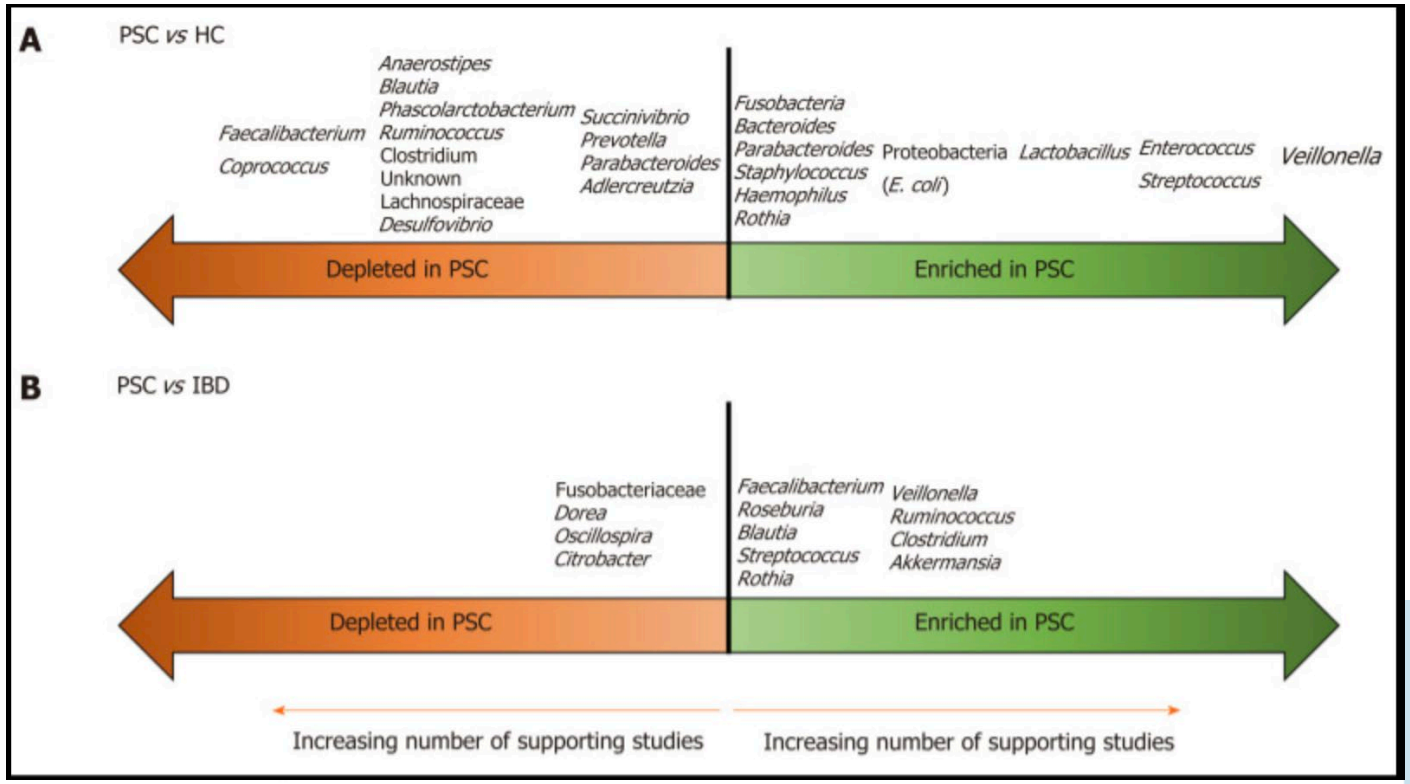


- ?PATHOGENESIS

-?THERAPEUTIC POTENTIAL

PSC and IBD strong microbiotal association

- 50% ⇩ recrudesce risk of PSC prior to or within liver transplant
- Treatment with antibiotics in PSC patients was associated with reductions in liver biochemistry.
- PSC-IBD fecal analysis show enriched levels of certain species, including *Veillonella, Klebsiella pneumoniae. Streptococcus* and *E. faecalis*, among others
- Decreased abundance of presumed protective fecal Lachnospiraceae



Nakamoto N, et al *Nat Microbiol*. 2019
Kummen M et al. *Gastroenterology*, 2020
Liwinski T et al. *Gut* 2020
Lindstrom L, et al., Scand J Gastro. 2018

Lindstrom, L et. al, Scand J. of Gastro., 2018
Ricciuto, A et. al, Curr. Gastro Reports, 2018
Shah, A et al., Semin Liver Dis, 2019

Heterogeneity in microbial species in PSC, IBD, and HC cohorts, but common bacterial taxonomy exists

Impact of intestinal microbiota in PSC

Study	Sample Origin	N, PSC +/- IBD	Microbiological Assessment	PSC enriched	PSC depleted
Kummen 2017 et al.	Stool	85	16s rRNA V3-V4	HC:**Veillonella (g)** (*V. dispar, V. parvula)*	HC/UC: *Desulfovibrio,* unknown (g) **Lachnospiraceae** & **Clostridiales** (g)
Bajer et al., 2016	Stool	43	16s rRNA V4	HC: Rothia, **Enteroccoccus, Streptococcus, Veillonella (g)**	*Adlercreutzia equolifaciens Prevotella copri* ***F. prausnitzii,*** *R. gnavus*
Sabino et al., 2016	Stool	66	16s rRNA V4	HC: Enterococcus, **Streptococcus,** Fusobacterium, **Veillonella,** Fusobacterium & Lactobacillus (g)	vs HC: Firmicutes, ***Anaerostipes***
Iwasawa et al., 2017	Stool	27	16s rRNA V1-2	HC: *E. faecium,* ***E. faecalis****, Strep. parasanguinis,* ***Veillonella parabacteroides***	vs HC: *P. distasonis,* ***Anaerostipes*** *Hadrus, Blautia obeum*
Ruhlemann et al., 2019	Stool	137	16s rRNA V1-2	HC: (g) **Veillonella,** Streptococcus, **Lactobacillus, Enterococcus,** Proteobacterium, Parabacteroides	vs HC: *C. Holdemanella, Desulfovibrio,* ***Faecalibacterium, Clostridium IV***

Microbial populations differ substantially between the gut lumen, bile and mucosal surfaces

Study	Sample Origin	N, PSC +/- IBD	Microbiological Assessment	PSC enriched	PSC depleted
Lemoinne et al., 2020	Stool	49	16s rRNA V3-V4	***Veilonella*** *and Proteobacteria* Fungal: Exophiala	Firmicuites Fungal: *Saccharomyces cerevisiae*
Kummen et al., 2021	Stool	136	**metagenomic WGS**	*Clostridum asparagiforme, E.coli (unclassified)*	*Eubacterium, Ruminoccus obeum, B. intestinalis*
Rossen et al, 2015	**ileum mucosa**	12	16s rRNA V4	uncultured Clostridiales II	-
Quraishi et al, 2020	**Sigmoid mucosa**	20	16s rRNA V4	**PSC-IBD v UC:** *B. fragilis, Roseburia, Sheanella, C. ramosum*	no changes
Torres et al, 2016	**ileum, colon mucosa**	20	16s rRNA V4	Barnesiellaceae Blautia, *R. obeum*	No difference by region
Liwinski et al, 2020	**Duodenal mucosa, bile**	46	16s rRNA V4	Duod: *E.coli* + ***Veilonella dispar*** Bile: ***E. faecalis,*** *Proteobacteria,* ***Veilonella dispar, Staph. Neisseria***	

Liver biochemical effects on Metronidazole and Vancomycin RCT in PSC

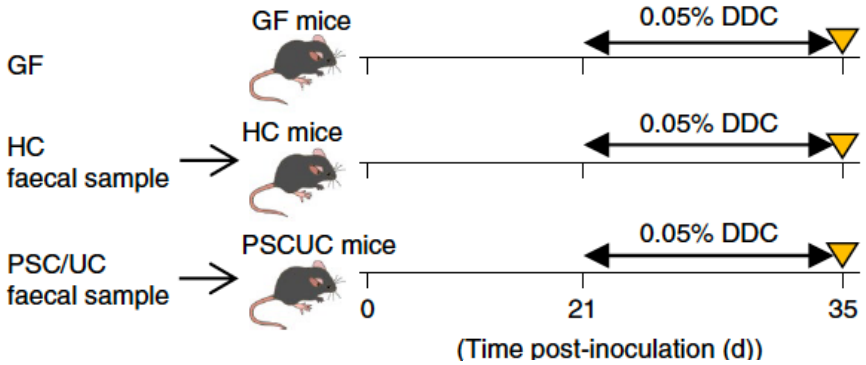
Study (year), location	Drug	Study Design, n	Duration	Primary Endpoint
Farkkila et al. (2004) Finland	*Metronidazole 800mg +UDCA vs Placebo*	*RCT, 80, median age 16-65*	*3 years*	*ALP: -52% (MTX) v -38% (placebo), p=0.05*
Tabibian et al. (2013), USA	MTZD or Vancomycin (125mg or 250mg TID/QID	RCT, 40 median age: 40	12 weeks	ALP: -40% & 46% (vanc doses) +13% & -33% (MTZD doses), **p<0.05 only vanc**
Rahimpour et al. (2016), Iran	Vanco 125mg QID or placebo	RCT, 29, median age: 34	12 weeks	MRS -0.59, ALP: -53%(vanc) MRS +/-0.5, ALP-8% (placebo) , **p=n.s.**

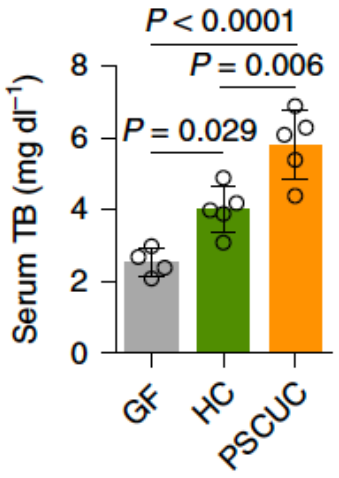
Active RCT with Vancomycin in PSC

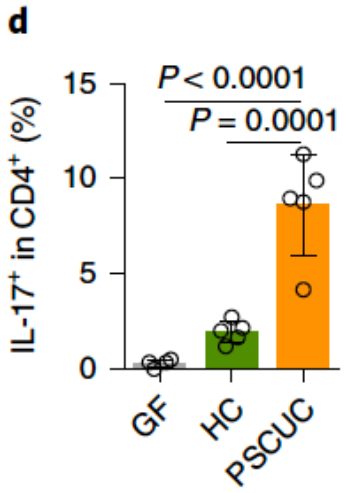
- NCT05876182: (>15-70yo, dose: 750, 1500mg Italy, up to 24 weeks)

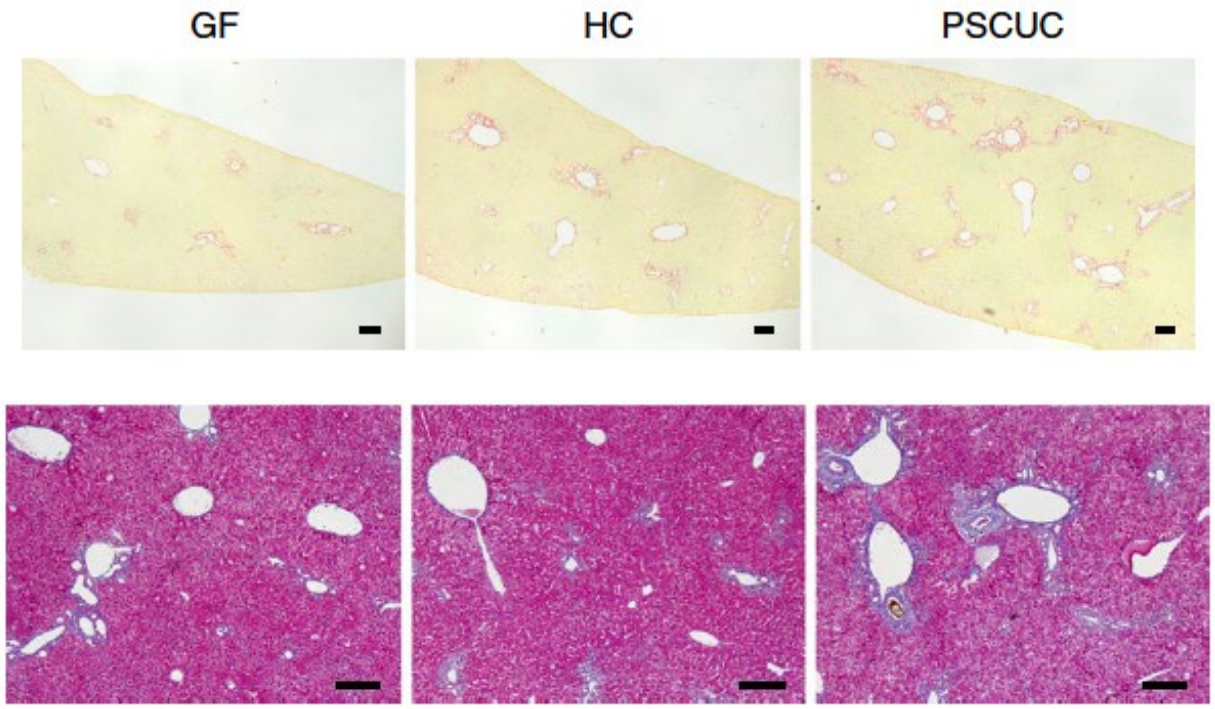
- NCT03710122: (18-76yo, OVA, AZ,USA up to 18 mo)

Gut microbiota from PSC/UC promotes the hepatobiliary injury along with the liver TH17 response



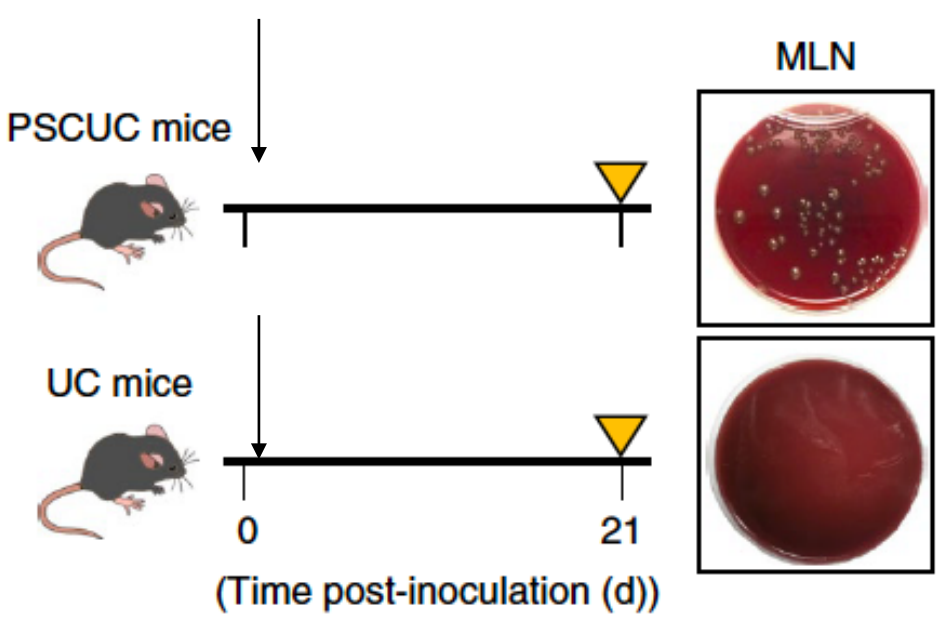


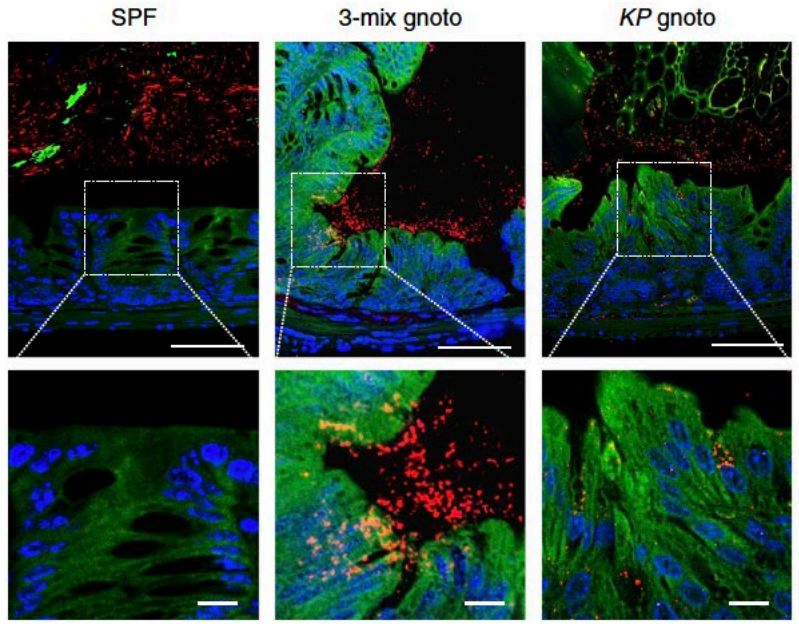




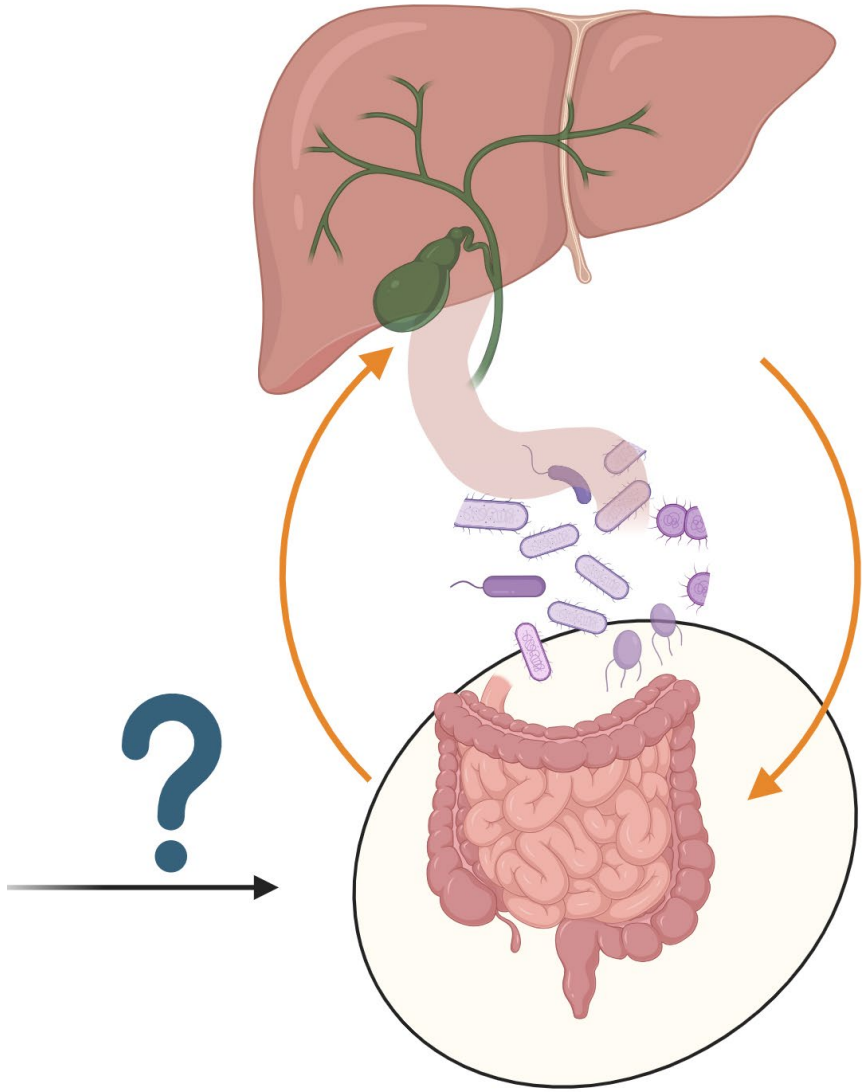
Nakamoto, N et al, Nature Micro. 2019

Transferability of PSC phenotype by human-murine FMT





Nakamoto, N et al, Nature Micro. 201



Vancomycin for IBD in PSC

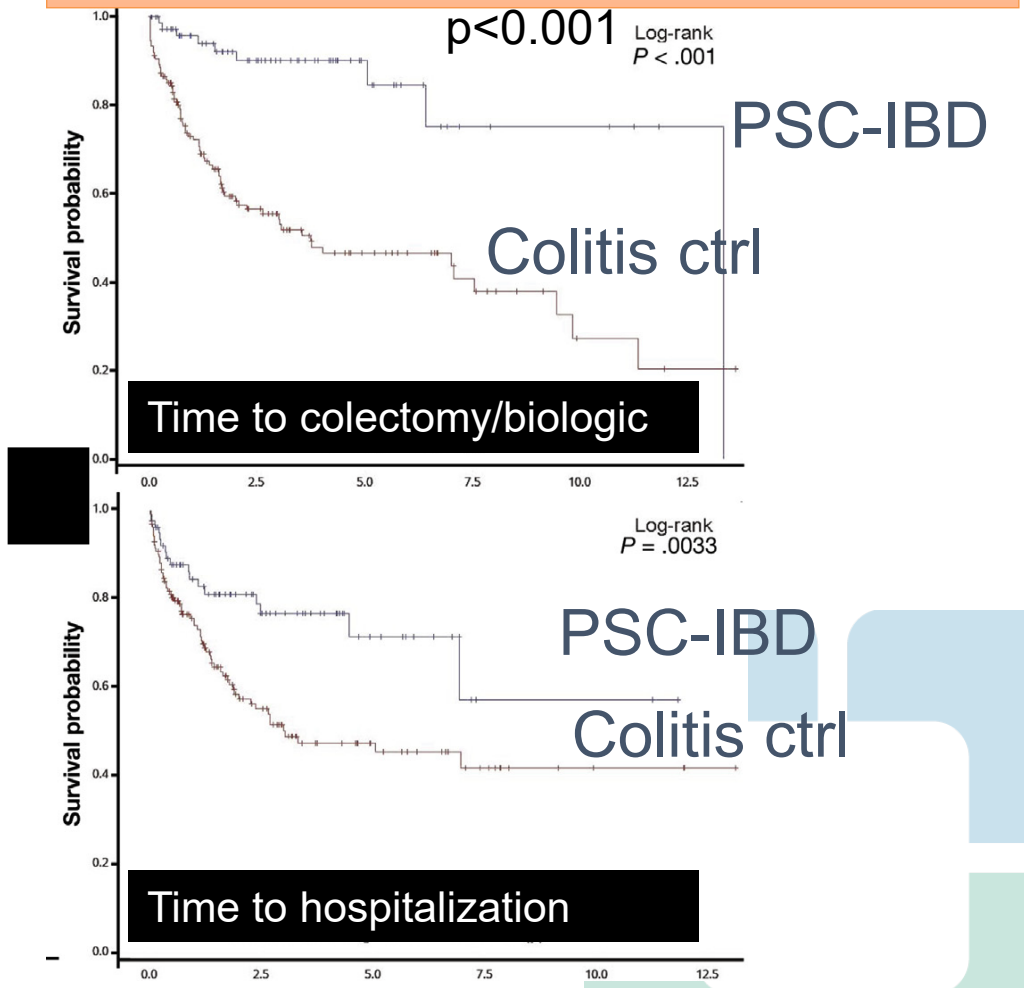
Reference	Study Type	Population	Vanco intervention	Outcome	F/U duration
Dao at al. 2019[1]	Letter, retrospective	N=8 UC-PSC, adult, 5 s/p LT	125 mg po qid x 6-8 wks, then tapered to bid or tid	Total Mayo score 0-2 (from 6-11) with endo sub-score 0-1 (from 2)	9-36 months
de Chambrun et al. 2018[2]	Case series, retrospective	N=3, UC-PSC, adult	500 mg po bid	PGA 0 (from 2-3), Mayo endo sub-score 0 (from 2-3), histologic healing	15-50 months
Tan et al. 2018[3]	Letter, retrospective	N=12, UC-PSC, children	Minimum 3 months	Mean PUCAI 1.8 (from 26), FCP <200 (from mean 1055 µg/g) and Mayo endo sub-score 0	Mean 8.1 months

Children with PSC-IBD Display Milder Clinical Activity

	Adjusted OR (95% CI) Clinical Remission	P
PSC	**2.94 (1.78-4.87)**	**<0.001**
Time (y)	1.52 (1.31-1.76)	<0.001
Age at IBD Dx (y)	1.06 (1.00-1.13)	0.039
Male	1.57 (0.95-1.59)	0.078
Endo severity (baseline)	1.12 (0.62-1.72)	0.41
Pancolitis	1.04 (0.62-1.72)	0.89
Current steroids	1.35 (1.06-1.71)	0.014
Current immunomodulator	1.56 (1.06-2.30)	0.025
Current biologic	1.89 (1.37-2.62)	<0.001

Ricciuto A, et al. Clin Gastroenterol Hepatol, 2018

Adjusted HR 0.24 (95% CI 0.12-0.52), p<0.001

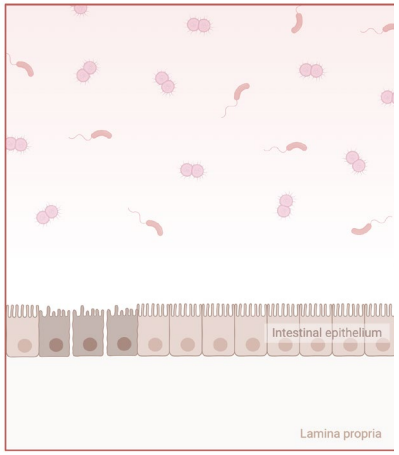


Amongst patients in clinical remission, PSC-IBD patients have more active endo disease:

Median (IQR)	PSC-IBD (N=20)	Colitis Controls (N=25)	P
UCEIS	2 (0-3)	0 (0-1.5)	**0.03**
Pancolonic UCEIS	1.2 (0.5-2.5)	0 (0-0.9)	**0.007**

Ricciuto A, Carman N, et al. Am J Gastroenterol 2021

PSC-IBD Phenotype



Microbiome

Pancolits
Often worse on the right with rectal sparing

Mild symptomatology

?

Increased colorectal cancer risk

Subclinical Inflammation

?

Clinical significance

Novel model to explore mechanisms linking PSC to IBD

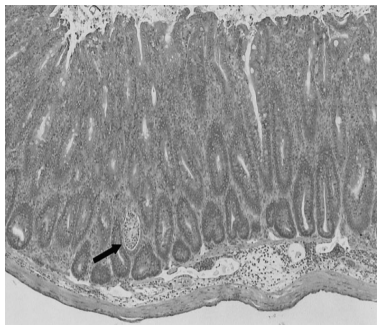
Interleukin-10-Deficient (*IL-10*$^{-/-}$) Mice

- IL-10 is a key immunoregulatory molecule
- *IL10*$^{-/-}$ mice develop spontaneous chronic colitis (Kuhn et al, 1993)
- Dependent on resident microbiota (Sellon et al, 1998)

Wild-type

Il10$^{-/-}$

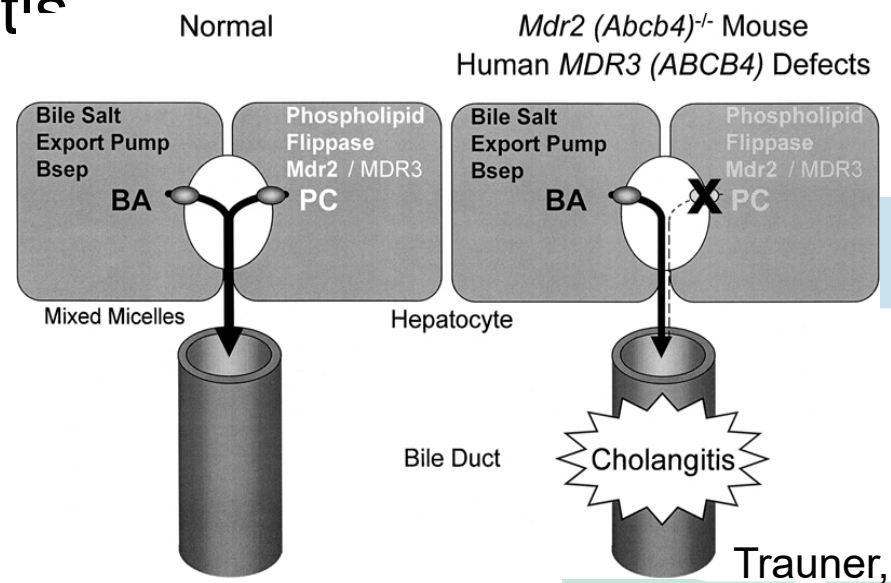
Colitis



+

Multi-Drug Resistant Gene-2 (*MDR2*$^{-/-}$) Mice

- MDR2 is a phosphatidylcholine floppase
- Deletion causes pericholangitis and periductal fibrosis.
- MDR2-/- mice do not develop colitis



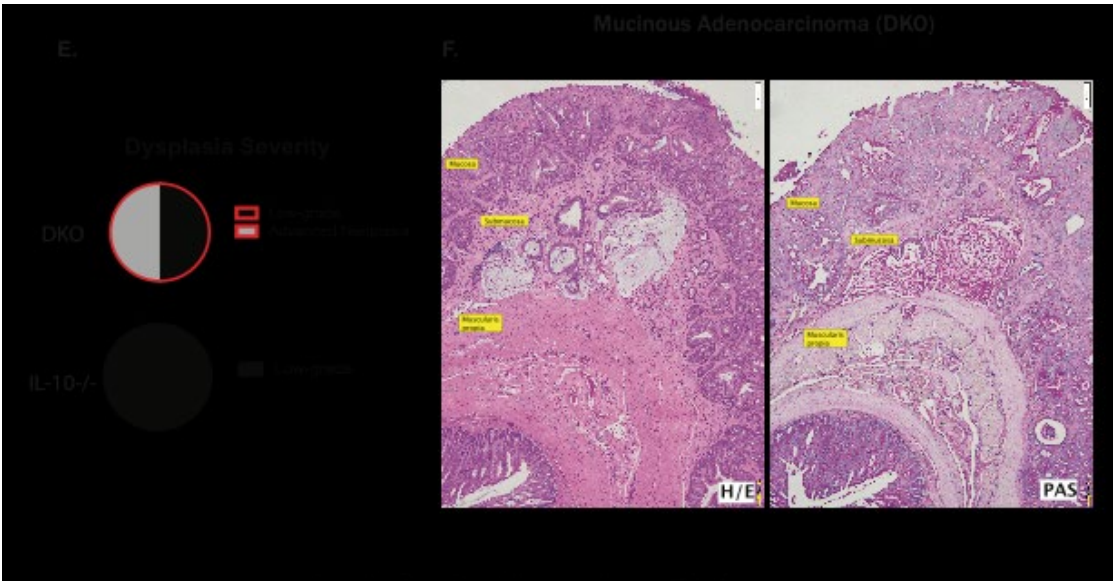
Trauner, 2007

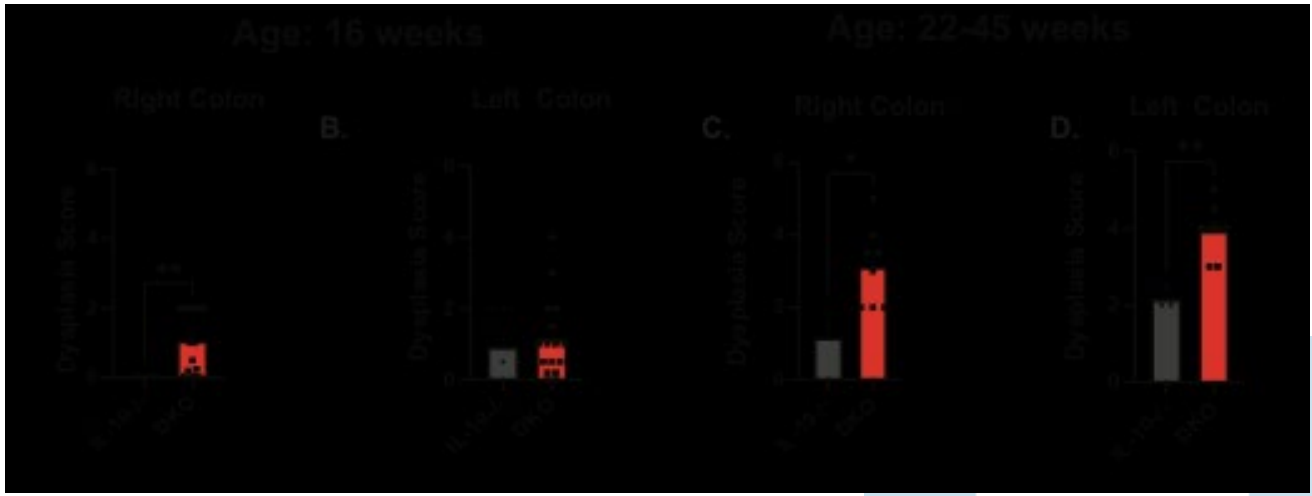
DKO develop spontaneous right-sided predominant colorectal dysplasia with colitogenic activity

IL-10 (IBD only)

DKO (PSC-IBD)

PSC-IBD model

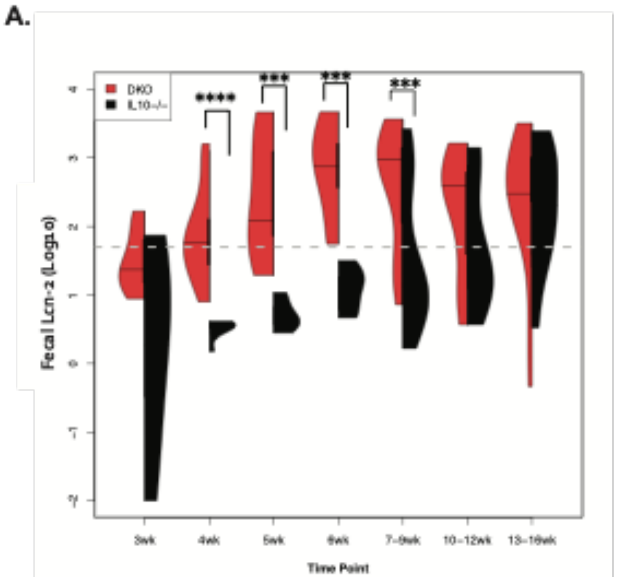


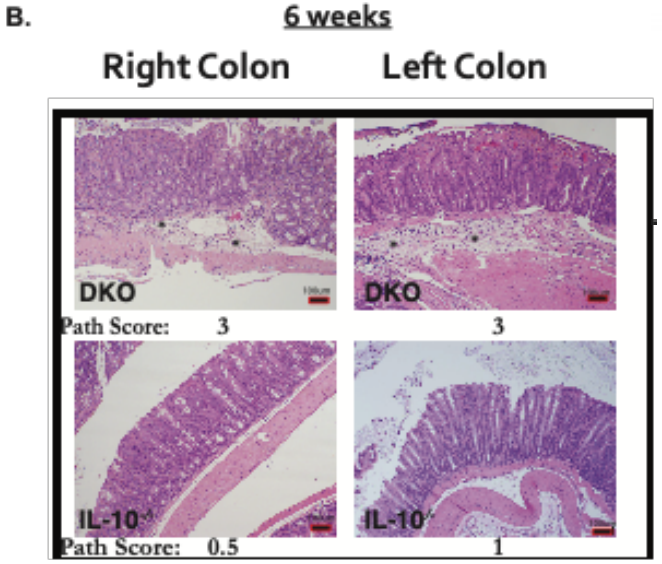


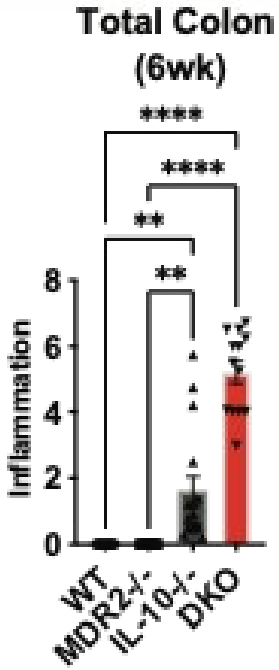
Awoniyi, M, under review

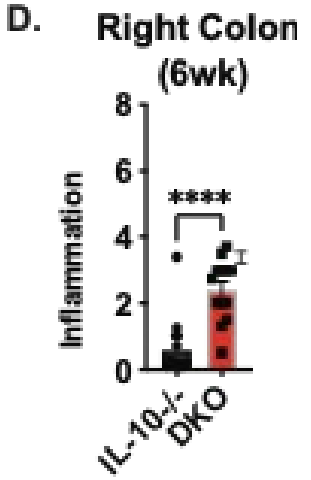
Early pancolitis with right-sided predominance precursor to colitis-associated dysplasia

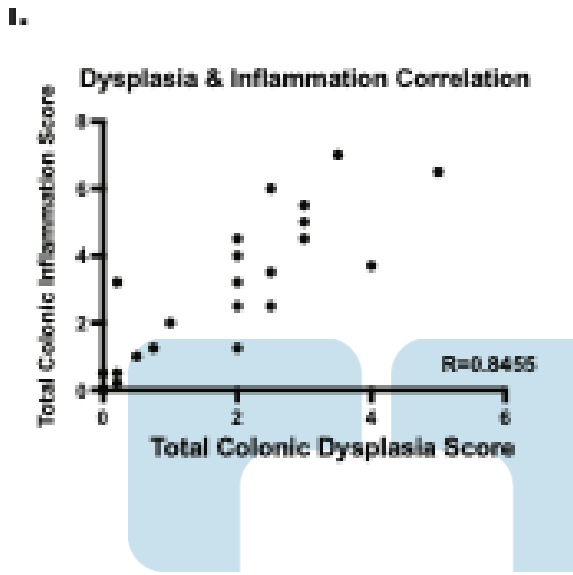
IL-10 (IBD only)
DKO (PSC-IBD)





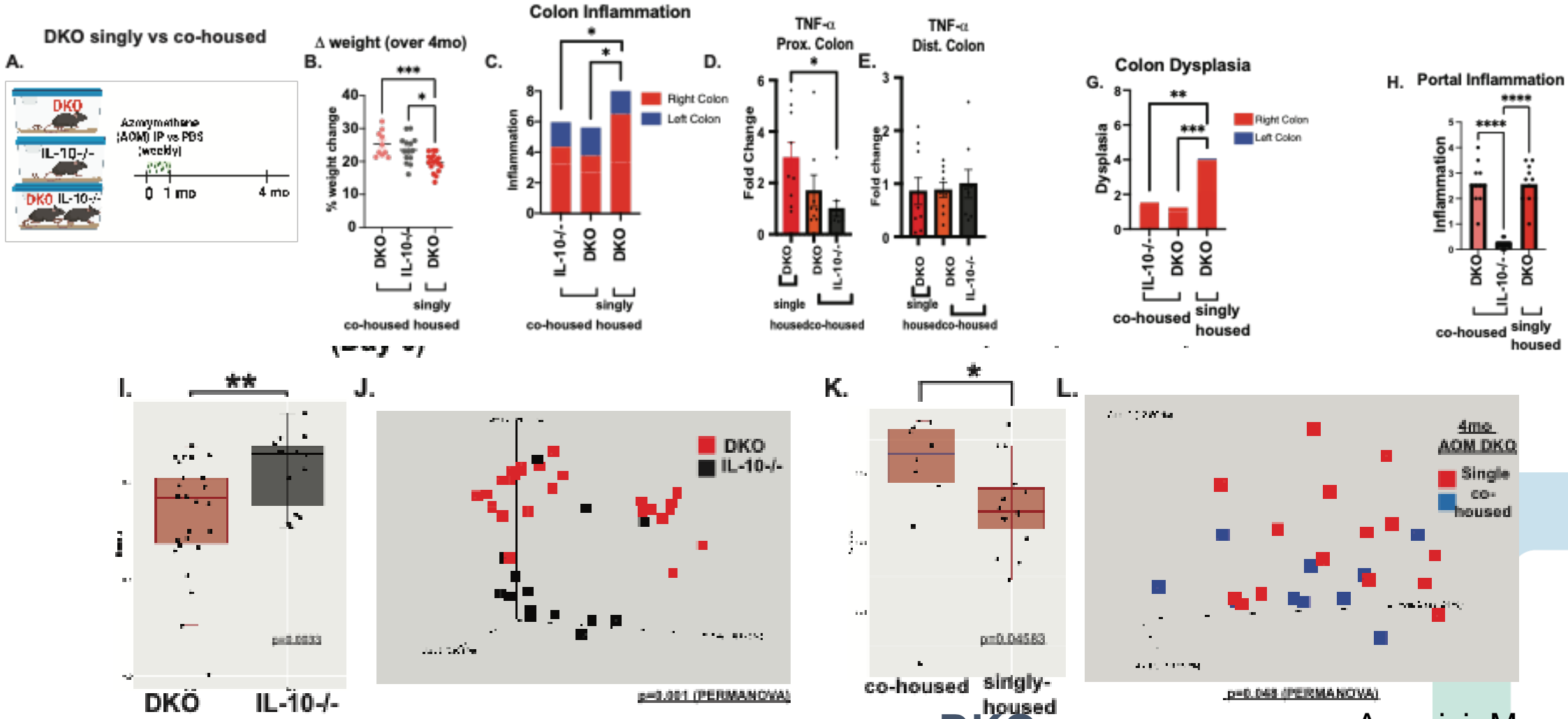






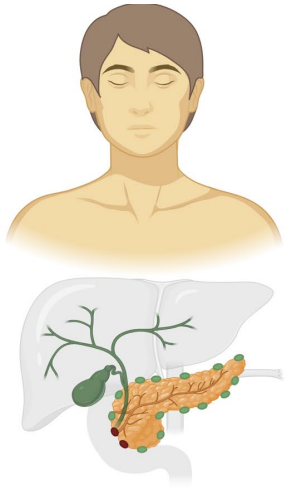
Awoniyi, M, under review

Coprophagic fecal transfer results in attenuation of colitis associated dysplasia in AOM PSC-IBD model



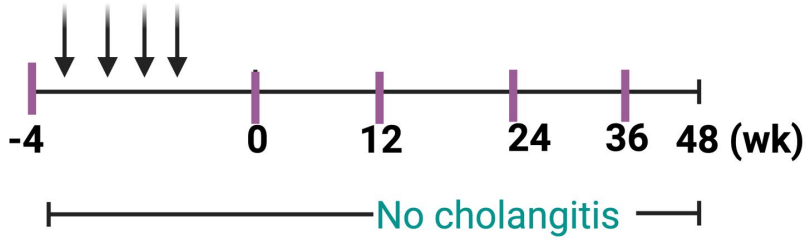
Awoniyi, M, under review

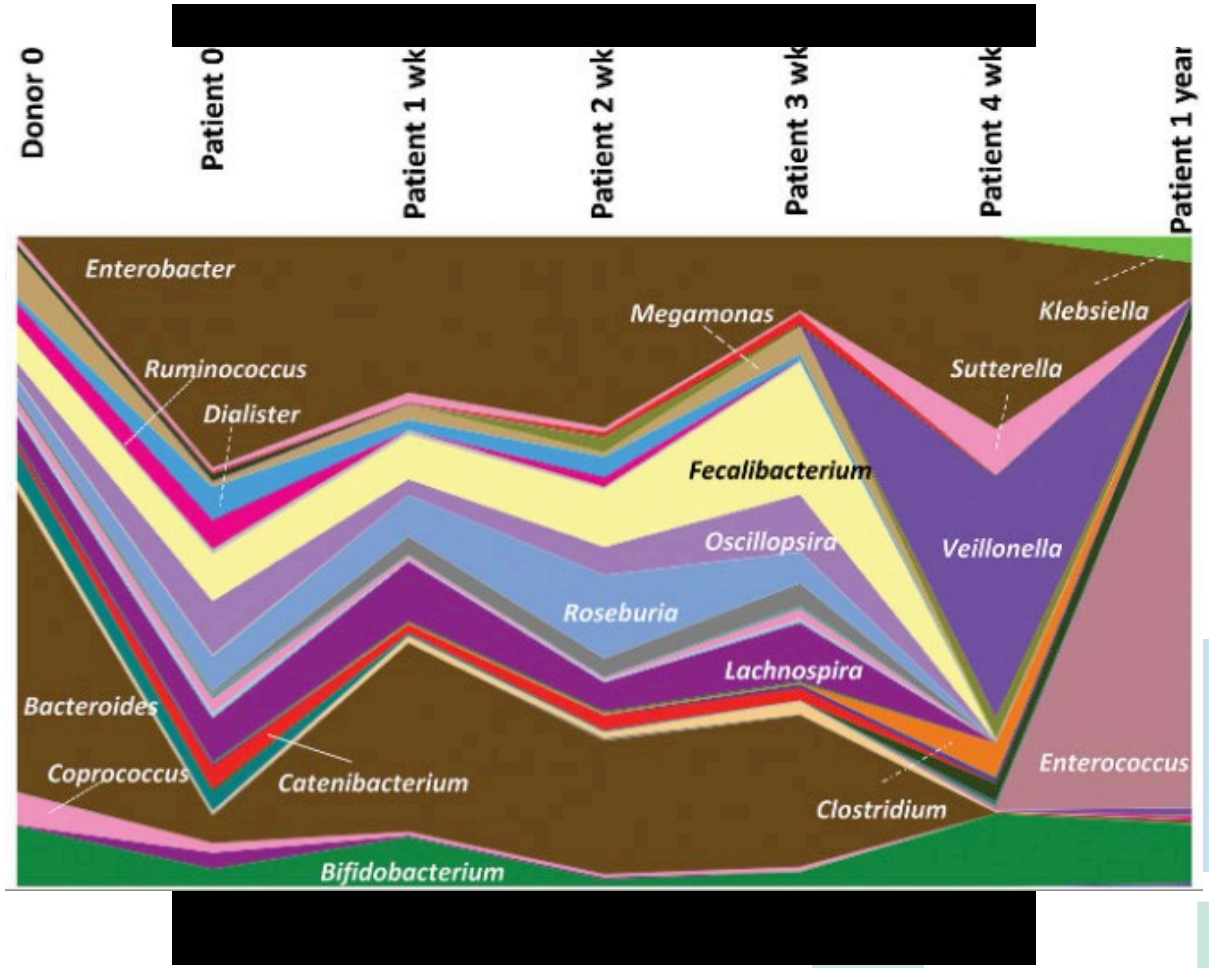
FMT Application: Case Report of Resolution of Recurrent Cholangitis in PSC patient



38yo PSC
Recurrent bacterial cholangitis x4 in 6mo

non-PSC donor duodenal FMT

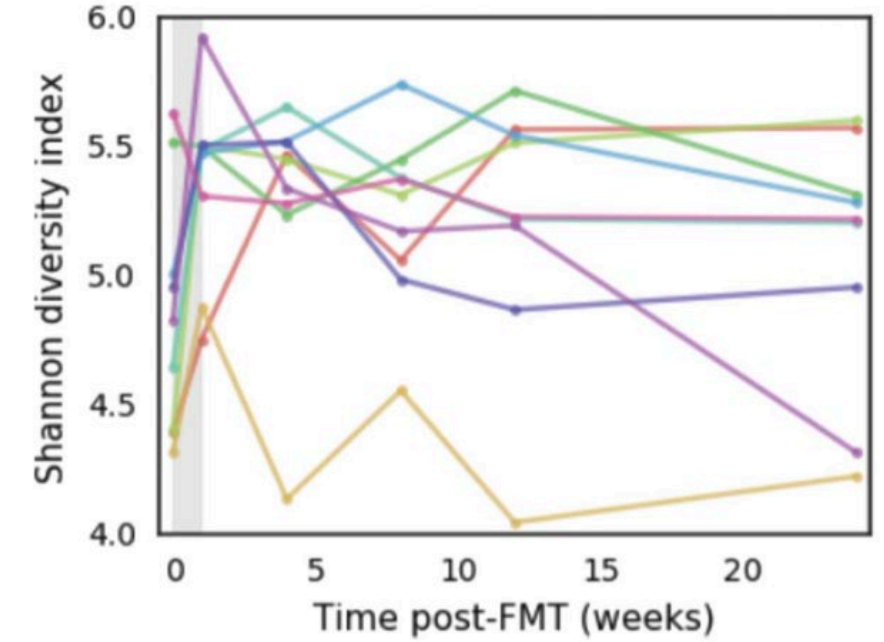


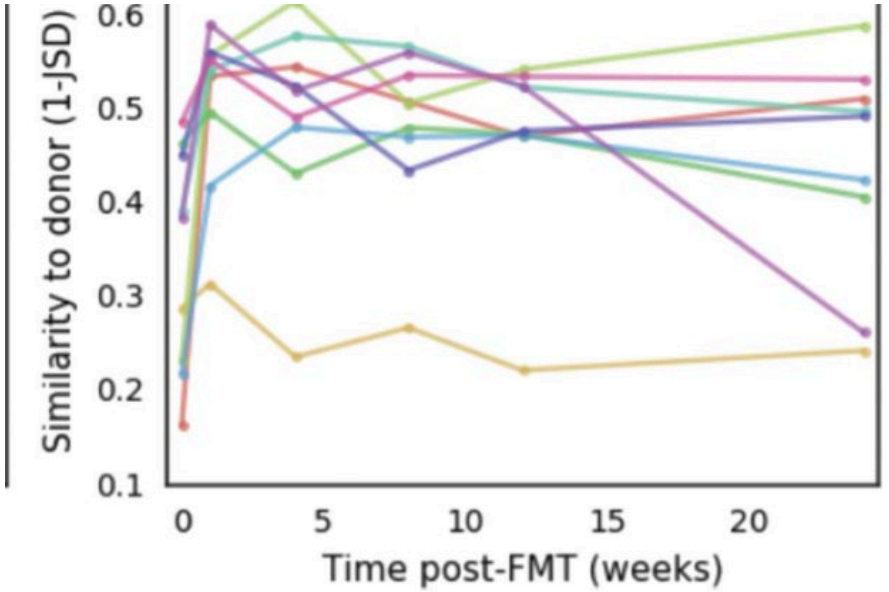


Phillips, C et al. J. Clin. Trans. Hep., 2018

Fecal Microbiota Transfer Safe in PSC

- Open label pilot
- N=10
- Single donor (colonoscopy)
- No adverse events occur
- Stable engraftment related changes (24wk)
- Endpoints underpowered

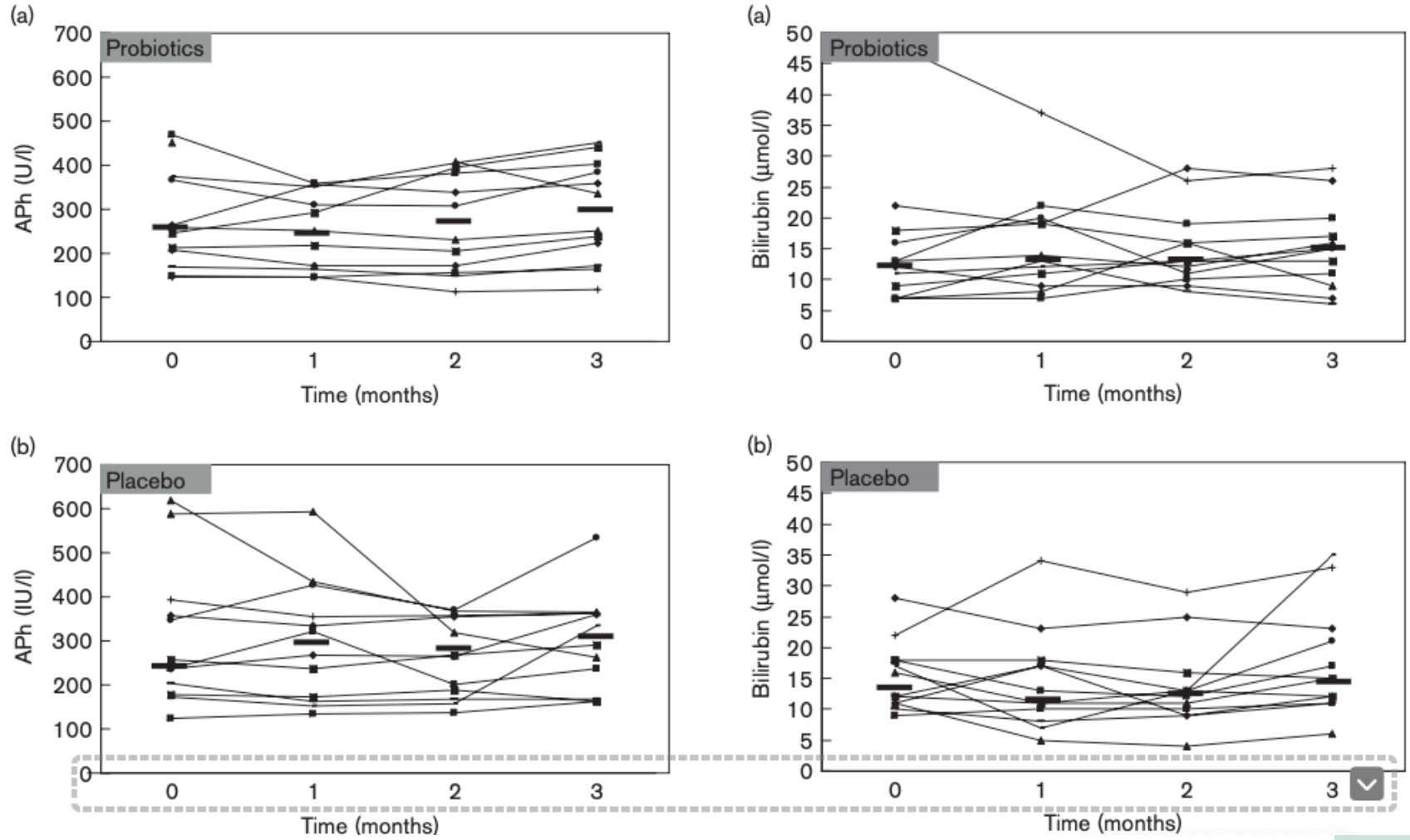




Cleveland Clinic

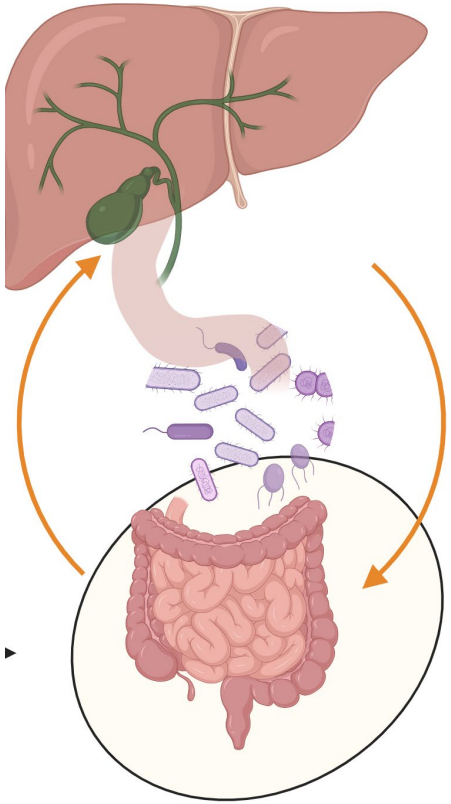
Allegretti, J et al. Am J. Gastro 2019

Lactobacillus/Bifidobacillus supplementation are ineffective in short-term PSC outcomes



Key Takeaways

- The gut microbiome is implicated in CLD; roles vary by disease.
- PSC: A window into the gut-liver axis, crucial for hepatology and IBD.
  - Antibiotics for PSC: Potential but not yet standard.
  - FMT in PSC: Safe in trials, efficacy under study.



Future Directions

- Research Imperatives:
  - Expand research into microbiome pathophysiology and treatment targets.
  - Conduct clinical trials with microbiome biomarkers.
  - Increase metagenomic and metabolomic studies for targeted insights.
  - Utilize diverse models for broader understanding.
- Closing Note:
  - Collaboration is key to translating microbiome research into PSC management advancements.

UNC HEALTH CARE

Every life deserves world class care.