SESSION 1: TREATING THE CIRRHOTIC PATIENT

The Modulation of Intestinal Barrier and Bacterial Translocation

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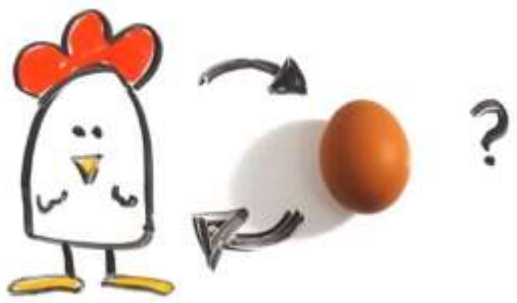
Disclosures

No financial or commercial disclosures

Increased Intestinal Permeability and Bacterial Translocation in Cirrhosis

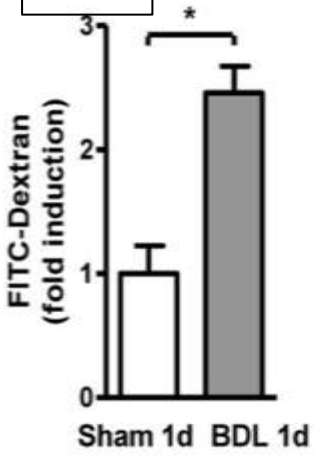
- Observed both clinically and experimentally
- Clinical implications:
  - Sepsis
  - Portosystemic encephalopathy
  - Spontaneous bacterial peritonitis
  - Hepatorenal syndrome
  - Cardiovascular complications
- Changes in gut microbiota
- Causality dilemma?

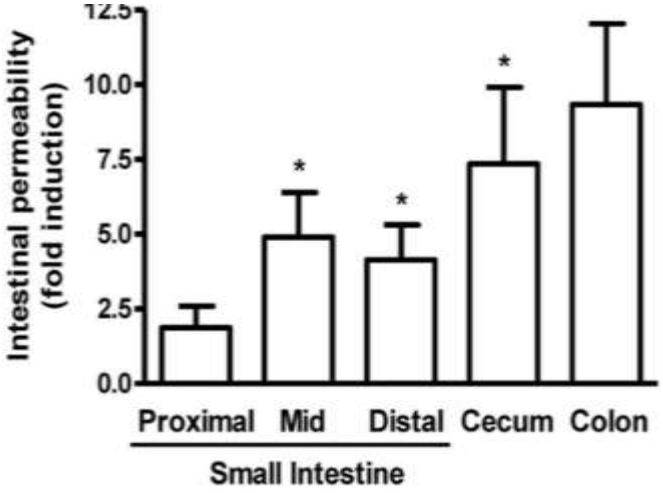


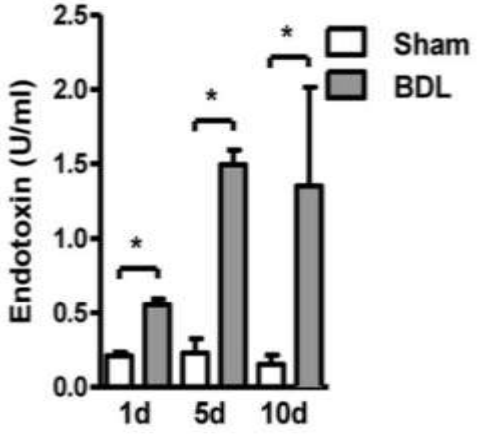
Increased Intestinal Permeability and Bacterial Translocation in Acute Liver Injury (Bile Duct Ligation)

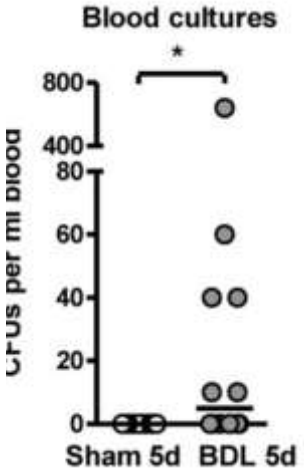
Fouts D, et al.J Hepatol. 2012

Host

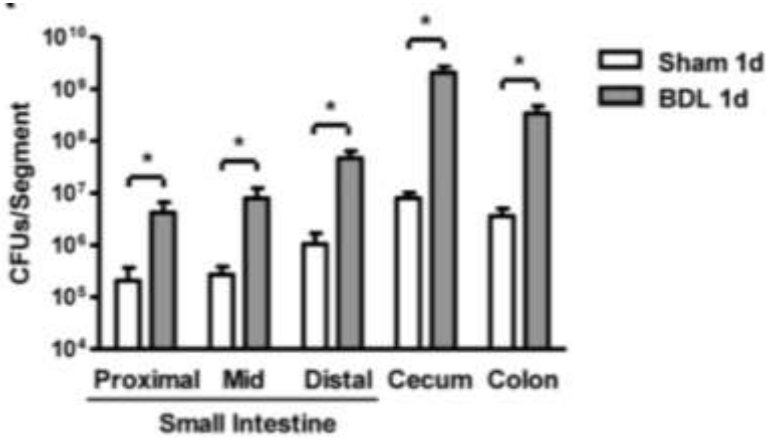


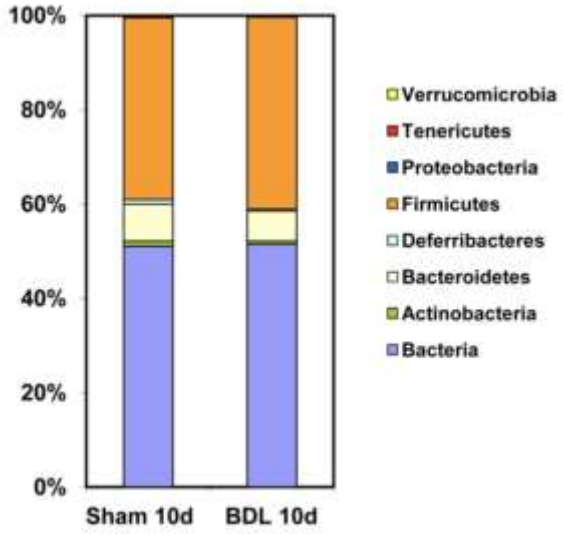






Gut Microbiome

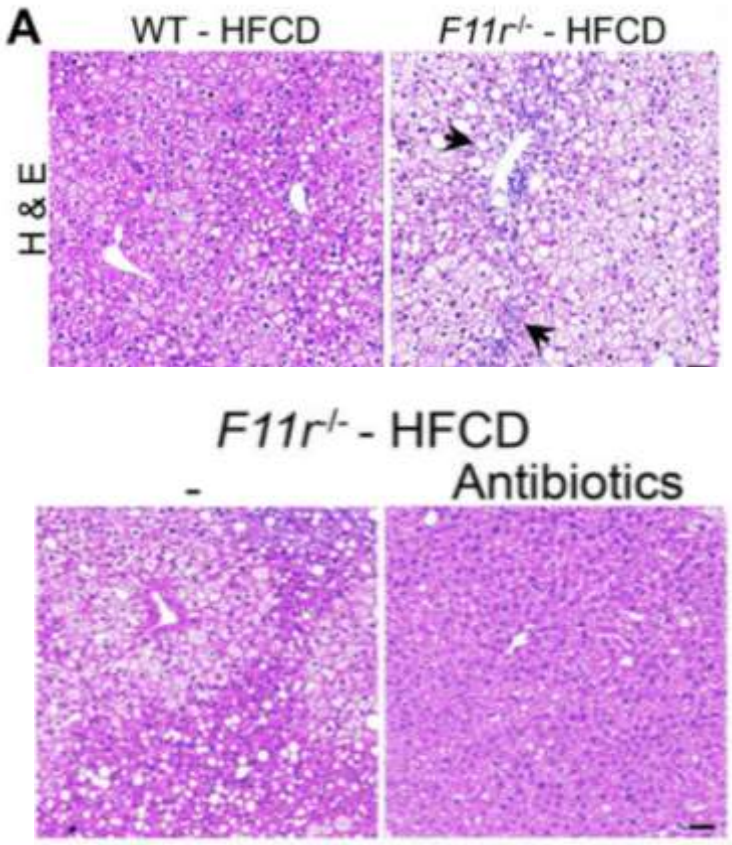




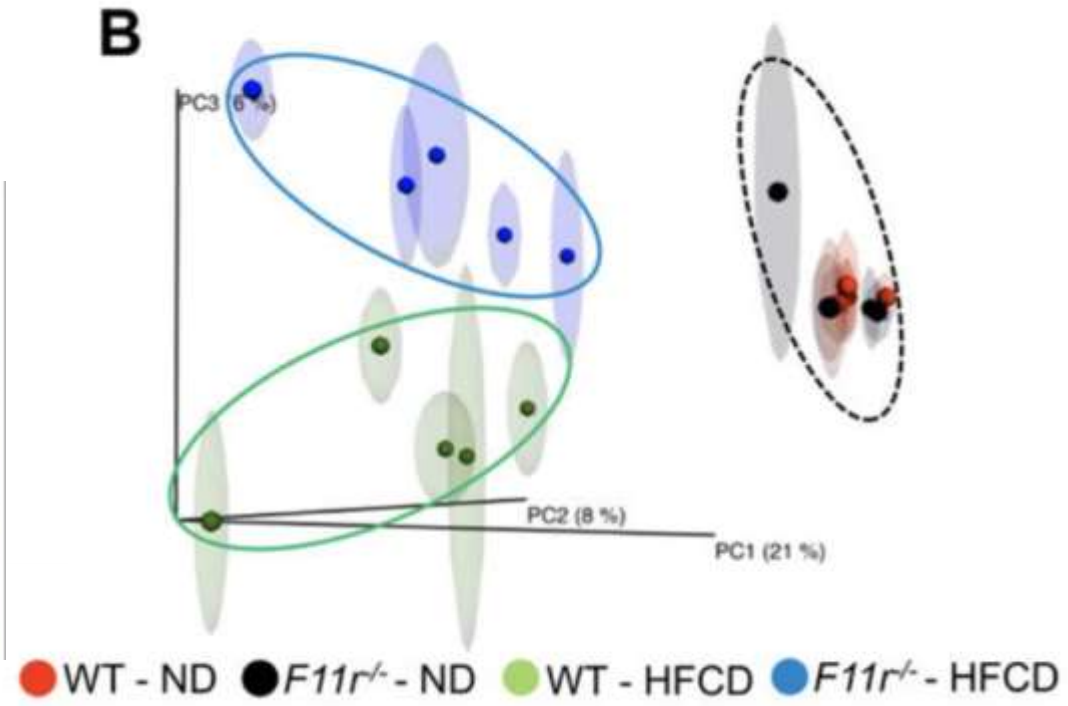
Increased Intestinal Permeability in *FR11*$^{-/-}$ mice fed HFCD Associated with the Development of Steatohepatitis

Host

Rahman K, et al. Gastroenterology 2016
FR11 encodes **Junctional Adhesion Molecule A**



Gut Microbiome



Are there Effective Interventions for Increased Intestinal Permeability and Bacterial Translocation in Cirrhosis?

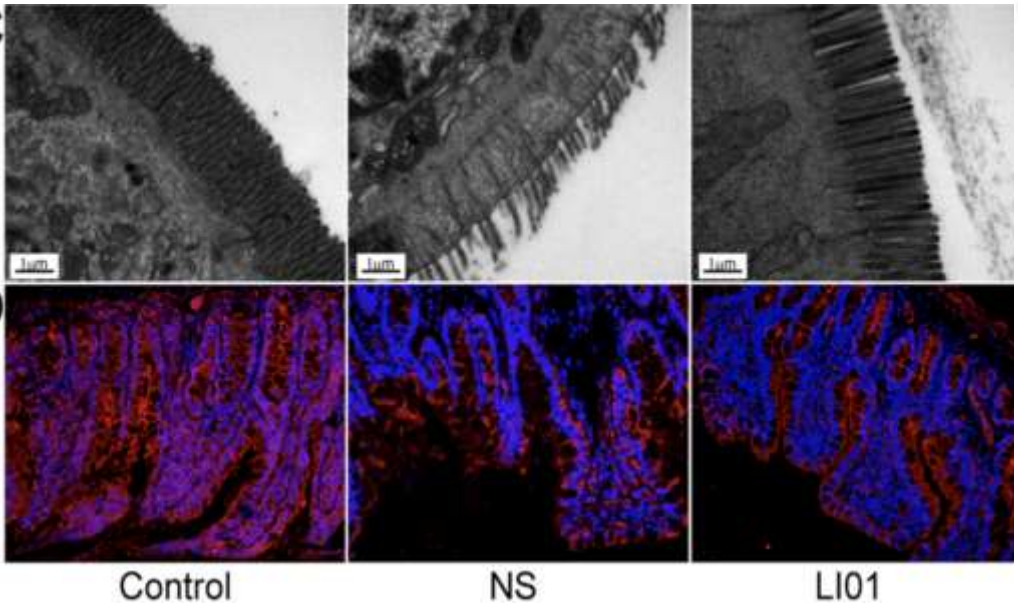
- Targeting host pathways directly
  - Pregnane X-receptor (PXR) – counter-regulates endotoxin mediated inflammation and maintains the integrity of intestinal epithelium
  - Bile acids and FXR agonists
  - Cytoprotective Stress Proteins (Hsp70, HMGB1)
- Manipulating the gut microbiome
  - Antibiotics
  - Pre-, pro-, and post-biotics
  - Fecal Microbiota Transplant (FMT)

Antibiotics for Prophylaxis and Treatment of Intestinal Barrier Dysfunction and Bacterial Translocation

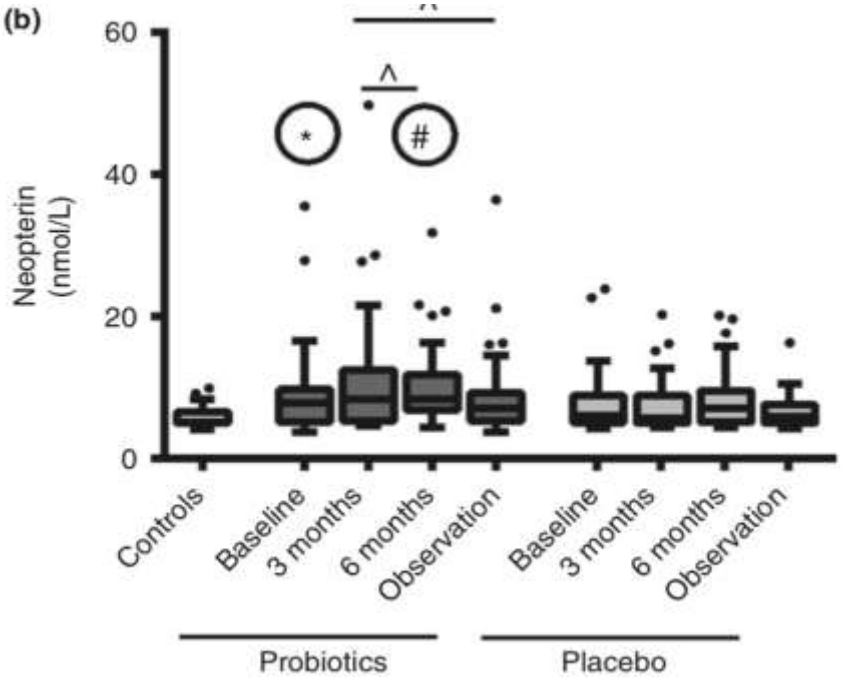
- Pros:
  - Effective (neomycin, metronidazole and ciprofloxacin)
  - Rifaximin – alters functional, but not compositional profile (Bajaj J, et al. PLoS One 2013)
- Cons:
  - Non-specific (collateral damage)
  - Limited use for prophylaxis: (Multi-drug antibiotic-resistance, *C. difficile*)
  - Systemic off-target and side effects

How Effective are Pre-, Pro-, and Post-biotics as Interventions for Increase Intestinal Permeability and Bacterial Translocation in Cirrhosis?

***Lactobacillus salivarius* LI01 or *Pediococcus pentosaceus* LI05 in CCl4- induced liver cirrhosis**
Shi D, et al. Sci. Reports 2017

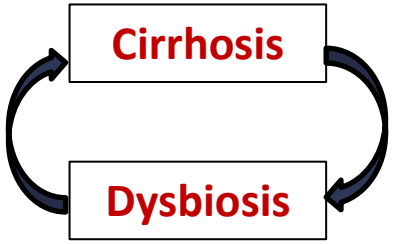


RCT of multispecies probiotic vs. placebo in human subject with cirrhosis. Horvath A, et al. Alim. Pharmacol Ther. 2016



Can we do better? What are the challenges and unmet needs?

- Chicken and egg scenario – Can the vicious cycle be broken?



- What is a healthy microbiome? How can “good” and “bad” microbes be distinguished?
- Limits and technical challenges of studying the gut microbiome.
- Incomplete annotations and low resolution of microbiome analysis
- Limitations and in-the-box approaches of clinical study design
- Interventional goals (prevention, prophylaxis, treatment, restoration?)

Fecal Microbiota Transplant from a Single Stool Donor Improves Hepatic Encephalopathy: A Randomized Clinical Trial

(Bajaj J, et al. Hepatology 2017)

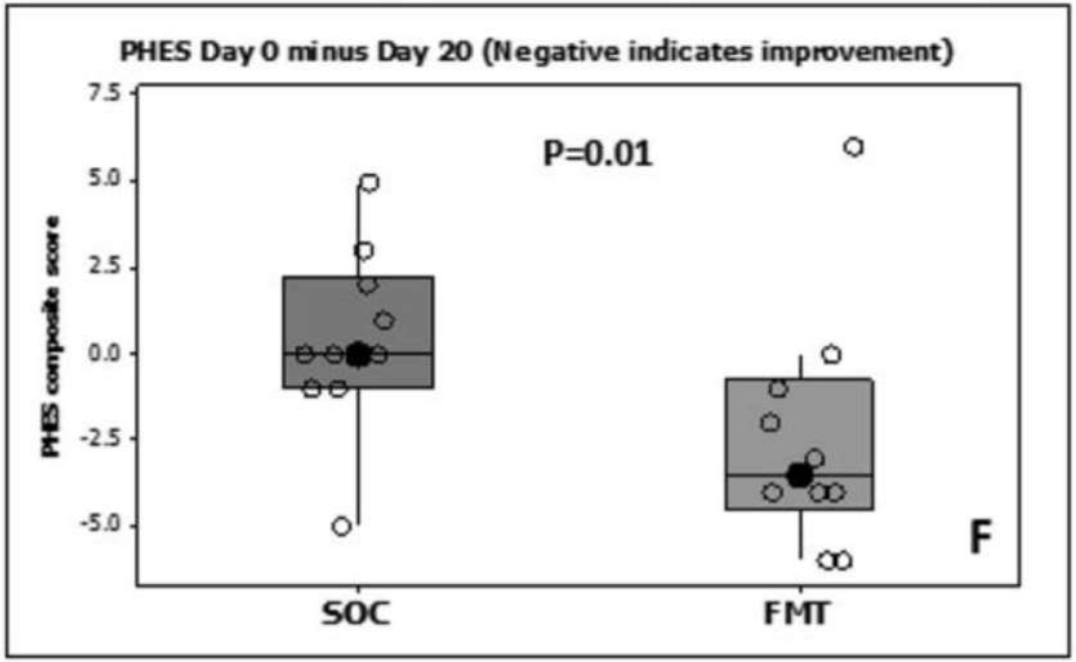
- Open-lab, randomized clinical trial with 5m follow-up in men with cirrhosis.
- 5 day pre-treatment with broad spectrum Abx, followed by a FMT x 4 within a 30 day period
- *Primary outcome* – Safety of FMT c/w SOC
- *Secondary outcome* – serious adverse events (SAE), cognition (PHES, Stroop), microbiota, and metabolomic changes.

Fecal Microbiota Transplant from a Rational Stool Donor Improves Hepatic Encephalopathy: A Randomized Clinical Trial

(Bajaj J, et al. Hepatology 2017)

Results:

- FMT was well tolerated and no significant adverse effects observed.
- Significant improvement in HE with FMT



Fecal Microbiota Transplant from a Rational Stool Donor Improves Hepatic Encephalopathy: A Randomized Clinical Trial

(Bajaj J, et al. Hepatology 2017)

Results:

- FMT reduced hospitalization
- Transient drop in MELD score and microbial diversity following pretreatment Abx – restored post-FMT
- Increased Ruminococcaceae, Bifidobacteriaceae, and Lactobacillaceae (well represented in donor FMT).
- *Standard of care group did not receive pretreatment ABx

Unmet Needs and Opportunities

- **Breaking the vicious cycle**
  - Earlier intervention (before ESLD)
  - Host targets: Development of new compounds targeting host nuclear receptors, TJ complexes, immune function, inflammatory mediators, fibrosis, etc.
  - More effective and lasting microbiome-based approaches
    - FMT
    - Defined FMT
    - Specific or Genetically-modified commensal strains
    - Prebiotics, post-biotics
- **More precision and less empiricism**
  - ID of specific microbial targets and mediators
  - Advances in technologies for both clinical and experimental studies
  - Application of high resolution bioinformatics to ID strain- and genomic-level virulence elements
  - Better definition of a “healthy” microbiome in the context of the individual and disease
- **Better pre-clinical models coupled with human-subjects related research**

The Future