

The microbiome, chronic abdominal pain and IBD

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Conflict of Interest Disclosure

(over the past 24 months)

Commercial or Non-Profit Interest	Relationship
Allergan	Speaker Fees, Advisory Board, Research Support

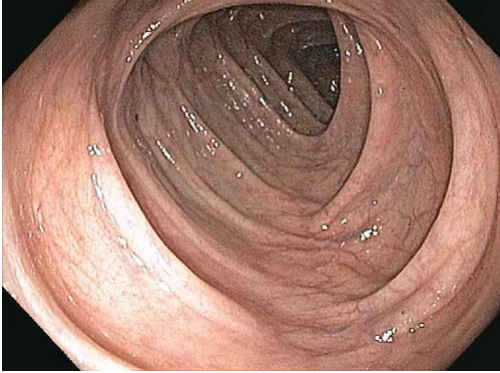
Objectives

Recognize the burden of chronic pain in the absence of inflammation in IBD

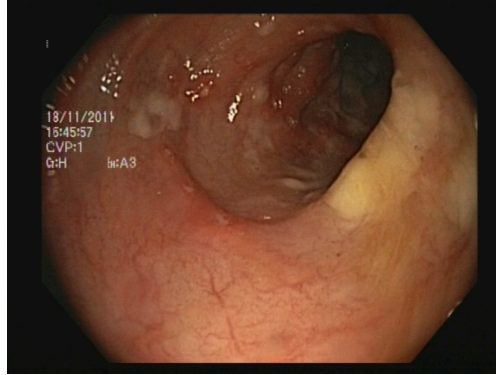
Explore how microbial manipulation modulates the development of visceral pain in a mouse model of IBD

Demonstrate that microbial-derived soluble products can sensitize pain-sensing neurons

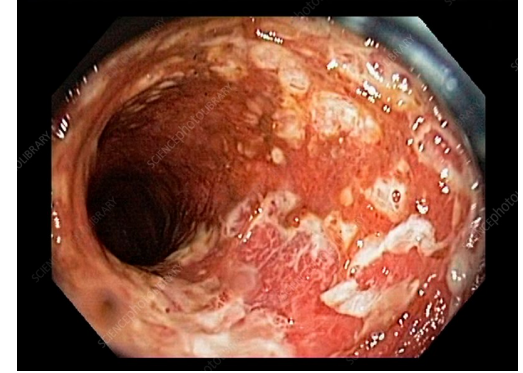
Goal of treatment is mucosal healing



Normal Colon



Mild Crohn's

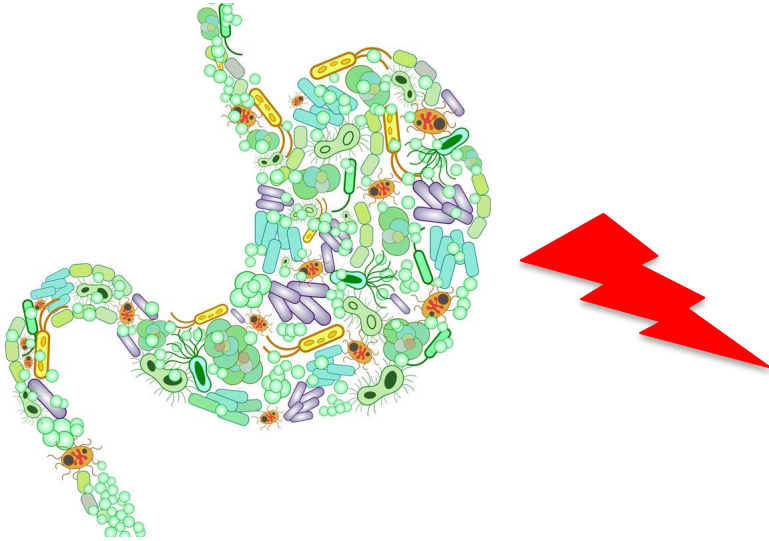


Ulcerative Colitis

MUCOSAL HEALING

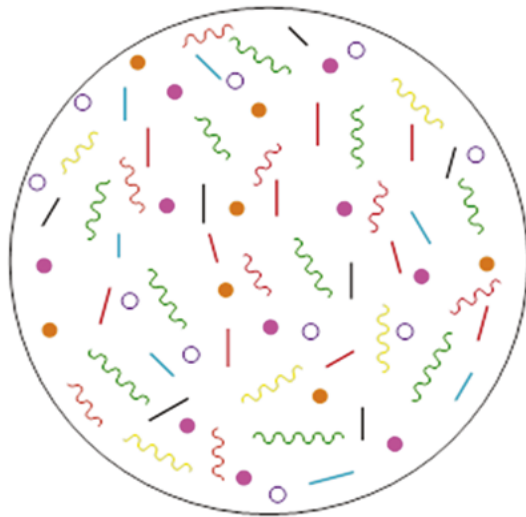
- ≥ 20% of IBD patients experience chronic pain despite endoscopic remission
 - High level of anxiety, depression, poor quality of life
 - Prevalence of widespread somatic pain in the absence of inflammation?
- **Few data surrounding the pathophysiologic mechanisms of chronic pain in the absence of inflammation**
 - Limited effective treatments

Role of the microbiome??

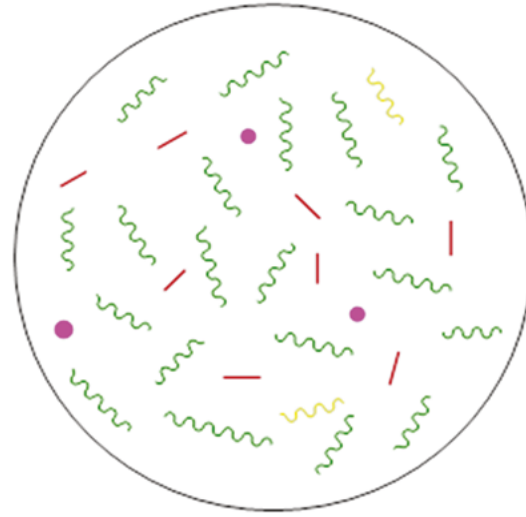


DYSBIOSIS persists despite ENDOSCOPIC remission

A Normal healthy intestine



B Intestinal Dysbiosis



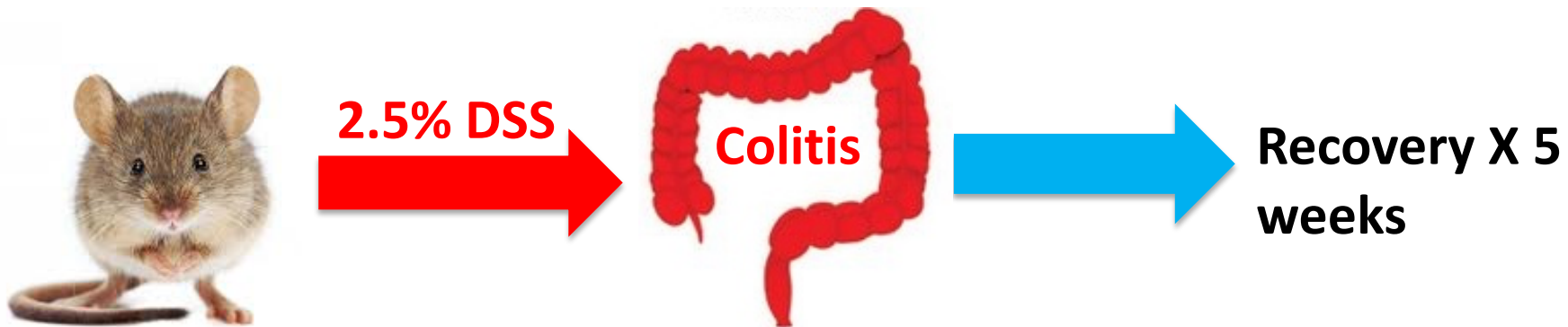
DeGruttola *et al. Inflamm bowel dis* 2016, 22:1137-1150
Halfvarson *et al. Nat Microbiol* 2017, 2: 17004
Hotte *et al. PloS one* 2012, 7: e37932
Lopez-Siles *et al. Front Cell Infect Microbiol* 2018, 8: 281

Manichanh *et al. Gut* 2006, 55: 205-211
Martinez *et al. Am j gastroenterol* 2008, 103: 643-648
Shutkever *et al. Inflamm bowel dis* 2018, 24: 1597-1605

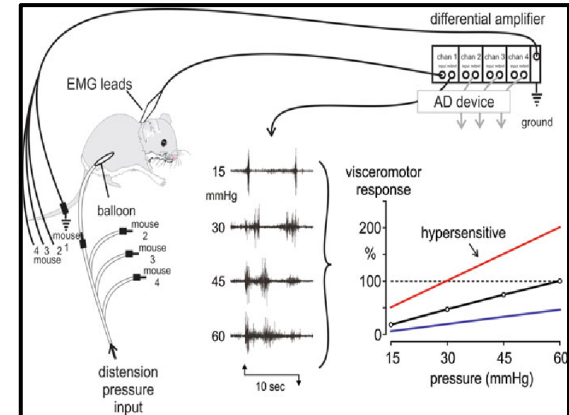
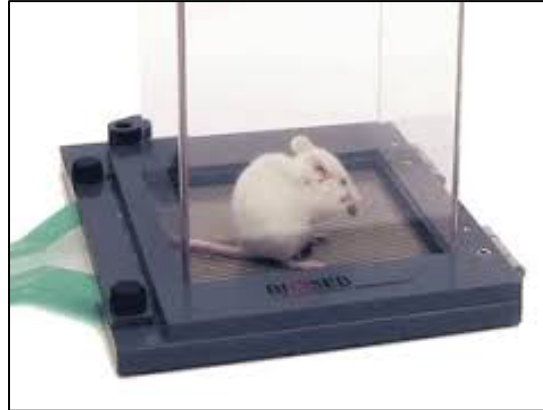
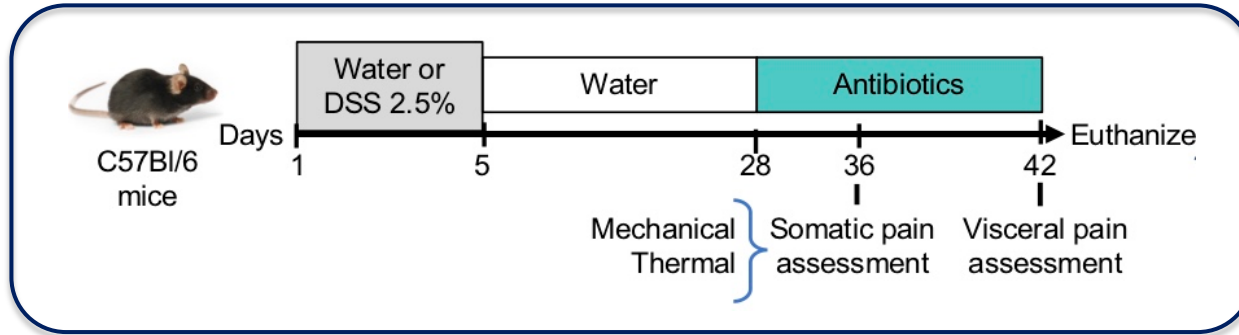
- IBD patients with chronic pain **in endoscopic remission** display **increased** TRPV1 expression
- Microbial products directly activate TRP channels
 - Microbial manipulation alters TRPV1 function
- Bacteria can directly or indirectly stimulate nociceptors
 - Metabolites (SCFA)

The dysbiotic microbiome, via TRP channel modulation, plays a **causal role in the development of chronic visceral but not somatic pain in the post-inflammatory state in IBD**

Post-inflammatory DSS model

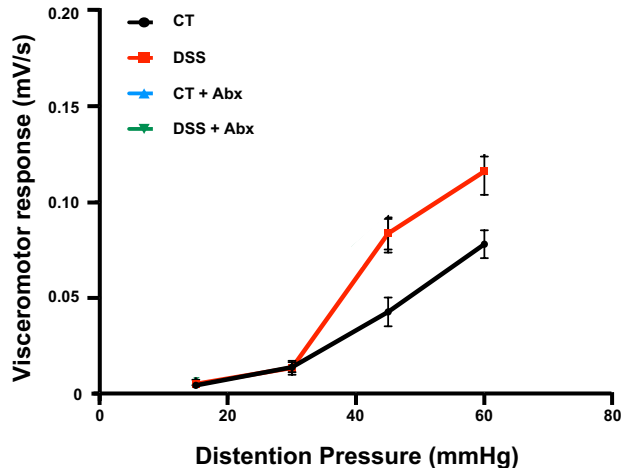


Experimental Paradigm

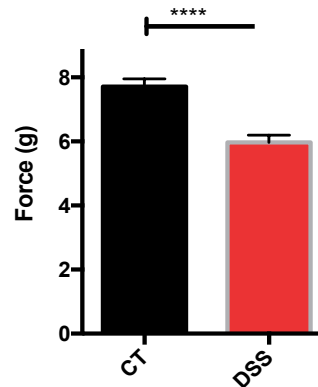


Post-inflammatory DSS mice exhibit both visceral and somatic hyperalgesia

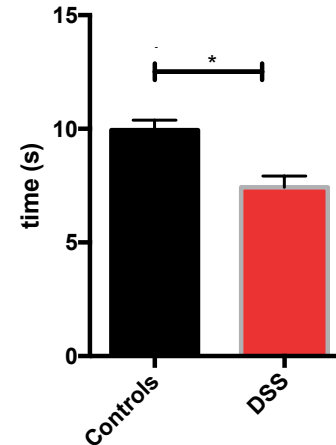
Colorectal distention



von Frey Test

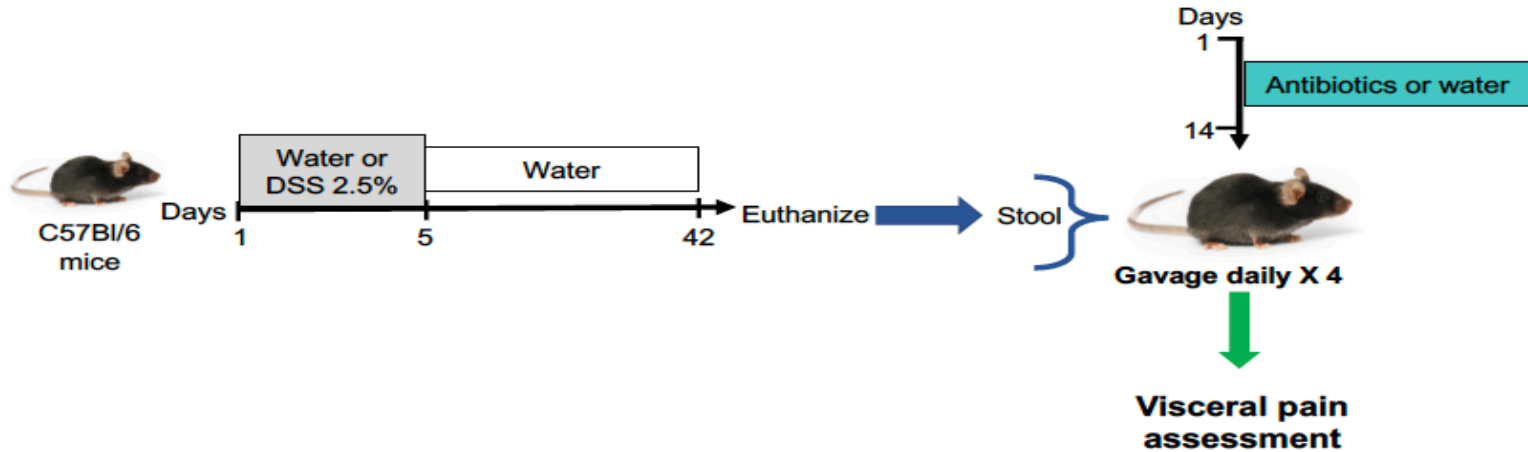


Hot plate



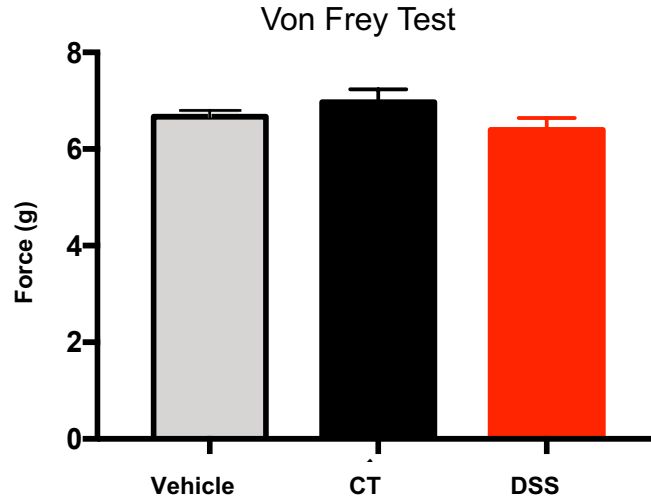
Controls (CT): n= 15, DSS: n= 15, CT + Abx: n=13 and DSS + Abx: n =15.

Can we transfer pain?

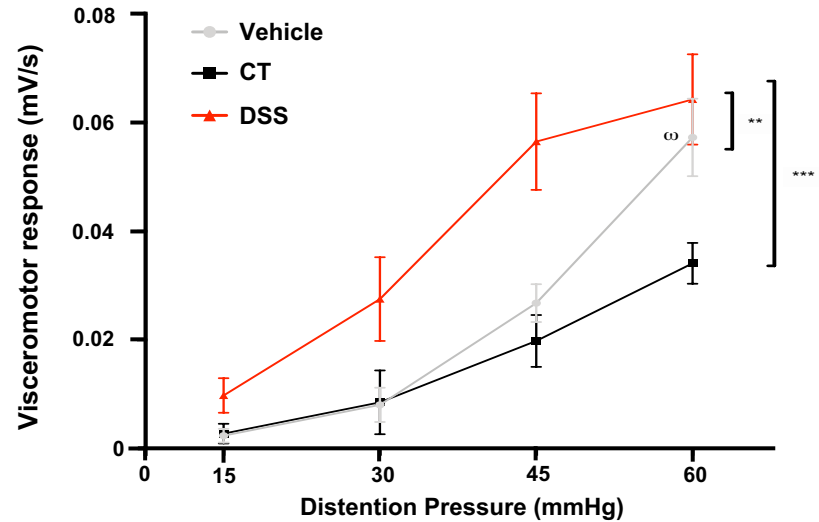


FMT transfers visceral pain

A



B

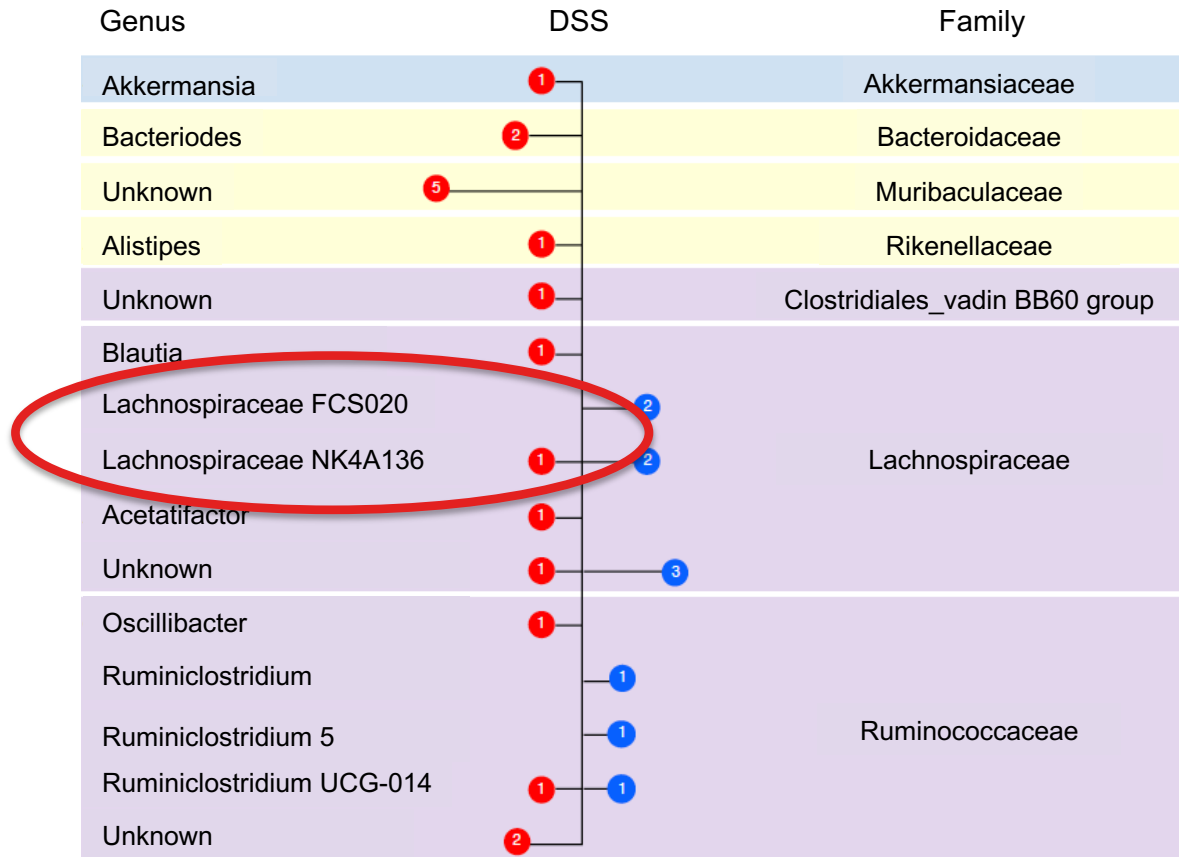


Vehicle: n=10

CT: n= 7

DSS: n= 11

Post-inflammatory DSS mice exhibit changes in the microbiome

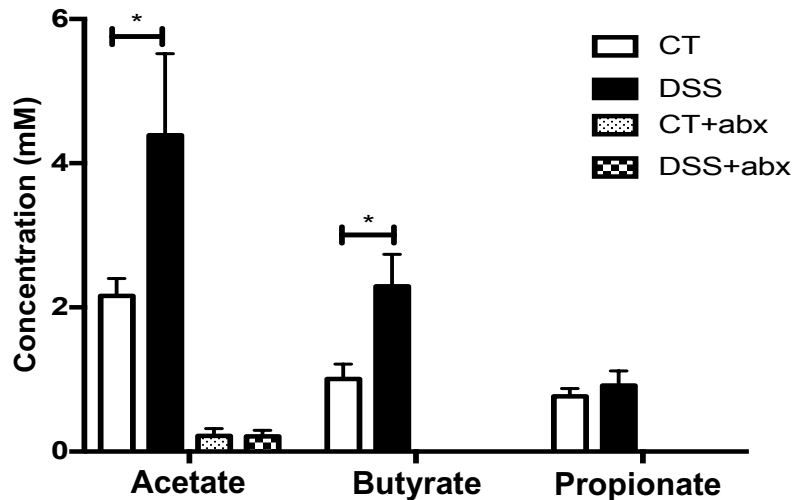


N=6/group

Post-inflammatory DSS mice exhibit changes in SCFA content

A

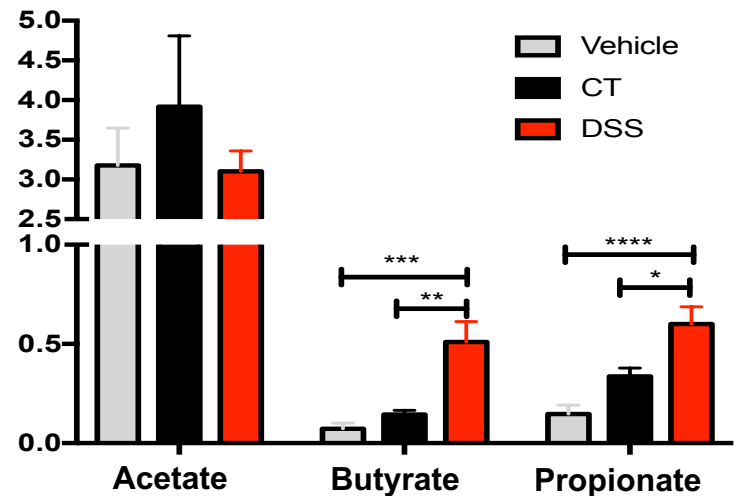
Post-inflammatory



n = 6/group

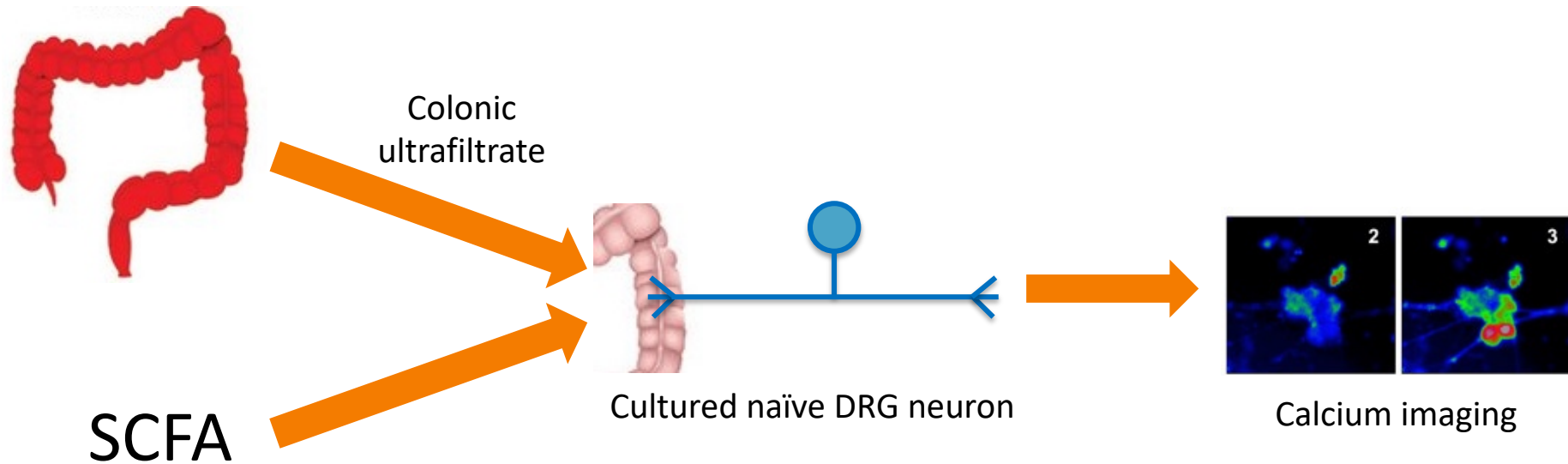
B

FMT



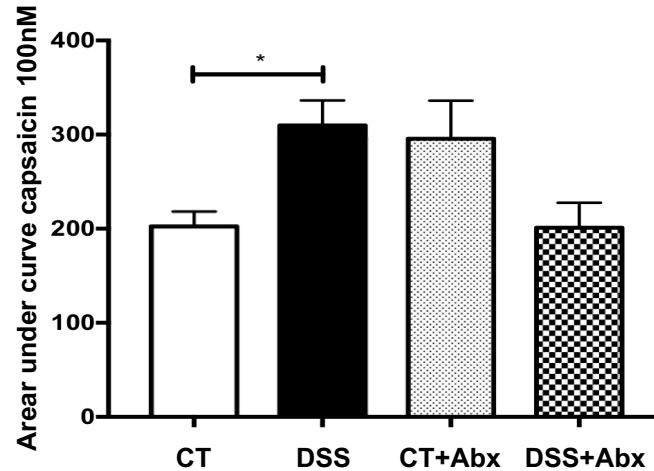
Veh: n = 12, CT: n = 7, DSS: n = 11

In vitro evaluation of visceral pain

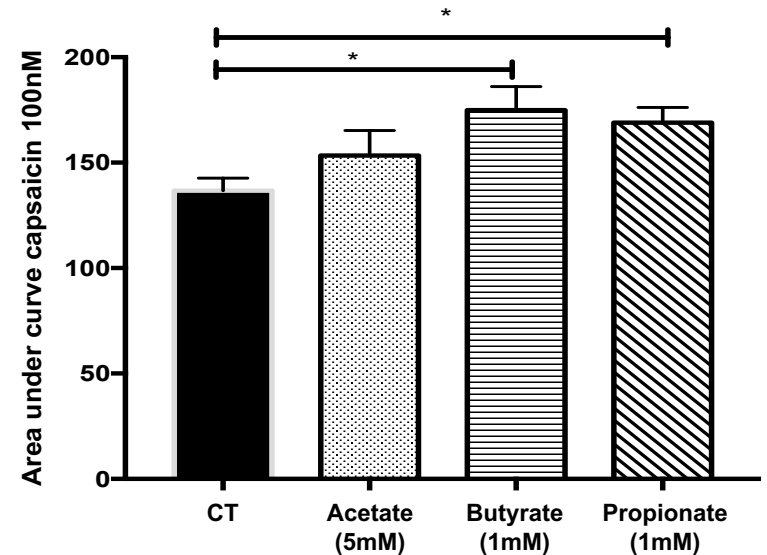


Microbial-derived soluble factors may modulate TRPV1 sensitization

A



B



n = 6/group

- The microbiome may play a role in the development of chronic visceral pain in IBD patients
- Microbial manipulation may provide novel therapies for chronic pain in IBD
 - Use of fecal transplant, and/or agonism/antagonism of particular microbial metabolic pathways

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WE ARE
THE
99%



RESPECT
THE
MICROBIOME!

