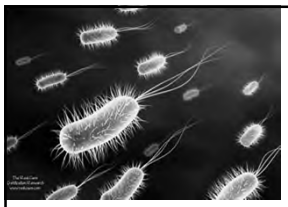


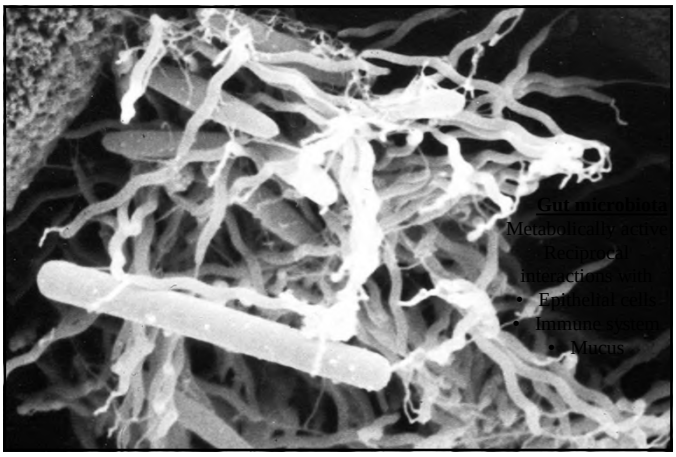
The intestinal microbiome in IBD: *Therapeutic implications*

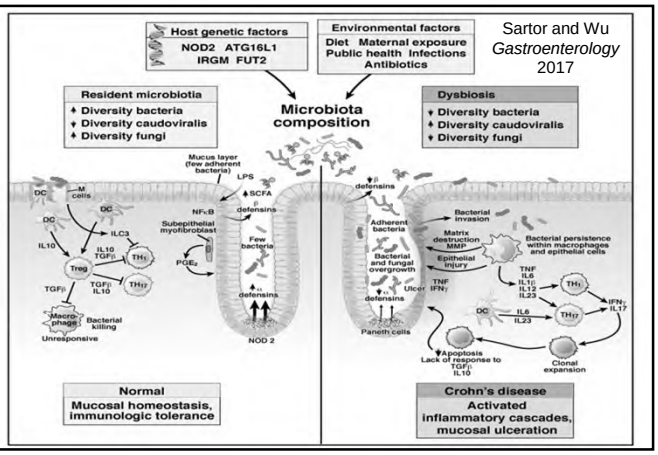
R. Balfour Sartor, M. D.

Midget Distinguished Professor of Medicine, Microbiology & Immunology

Director, Multidisciplinary IBD Center and National Gnotobiotic Rodent Resource Center

University of North Carolina- Chapel Hill

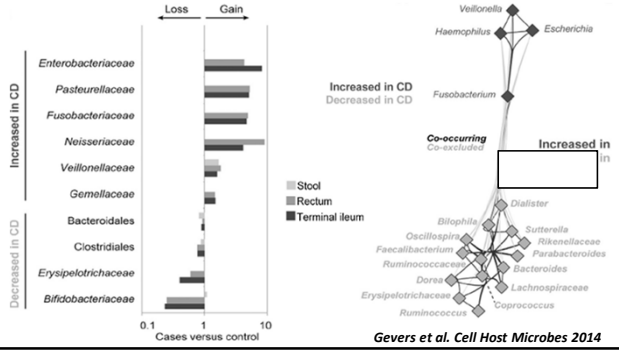




Sartor and Wu *Gastroenterology* 2017

Crohn's disease

447 patients with paediatric ***new onset*** CD (treatment naive, 3-17 years) *vs* 221 control subjects

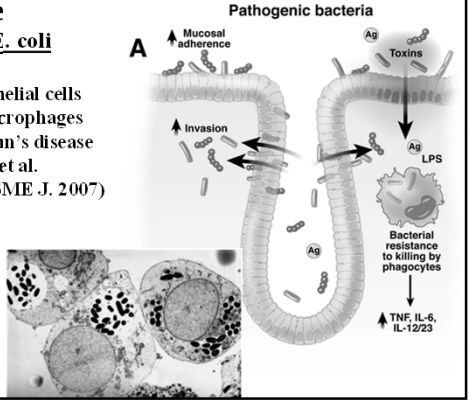


Gevers et al. Cell Host Microbes 2014

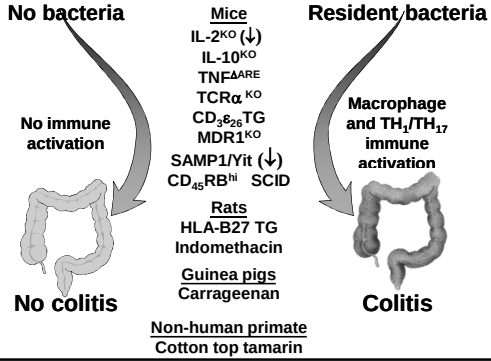
Functionally altered E. coli **are present in ileal Crohn's disease**

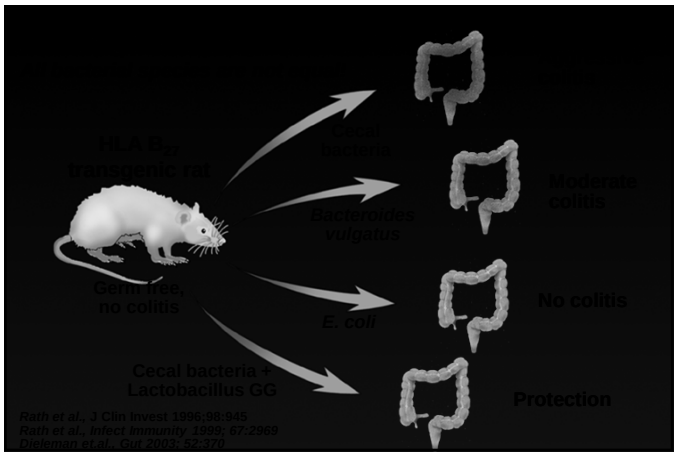
Adherent/invasive E. coli

- **Adhere to/invade epithelial cells**
- **Persist within EC, macrophages**
- **Increased in ileal Crohn's disease (Darfeuille- Michaud, et al. Baumgart, Simpson, ISME J. 2007)**
- **Bind to CEACAM 6 on ileal epithelial cells Barnich et al, JCI 2007)**



Essential Role of Resident Enteric Bacteria in the Pathogenesis of Experimental Chronic Intestinal Inflammation

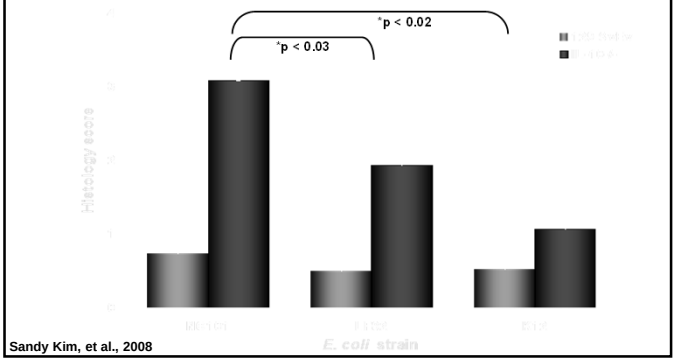




Host-specific responses to selected enteric commensal bacterial species (*Sandy Kim DDW 2005*)

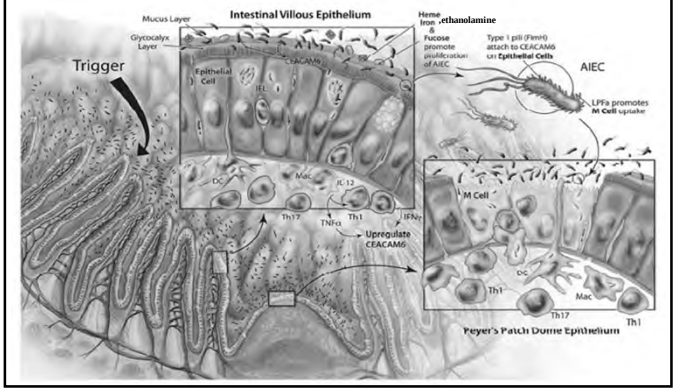
Host	Monoassociated bacteria	Outcome
HLA B27 TG rat	*Bacteroides vulgatus*	Colitis (cecal predominant)
	E. coli	No inflammation
	Enterococcus faecalis	No inflammation
IL-10 deficient mouse	*B. vulgatus*	No inflammation
	E. coli	Colitis (cecal predominant)
	E. faecalis	Colitis (distal), duodenal obstruction
BM → $CD_3\varepsilon$ TG mouse	*B. vulgatus*	No inflammation
	E. coli	No inflammation
	E. faecalis	No inflammation

Different *E. coli* strains induce variable degrees of colitis in monoassociated IL-10-/- mice

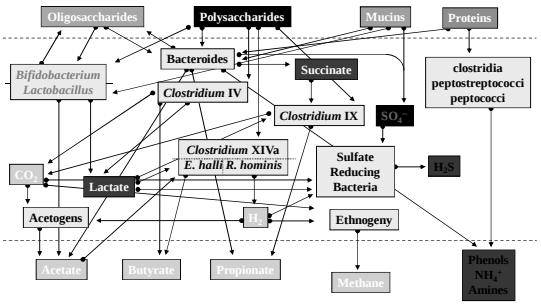


Sandy Kim, et al., 2008

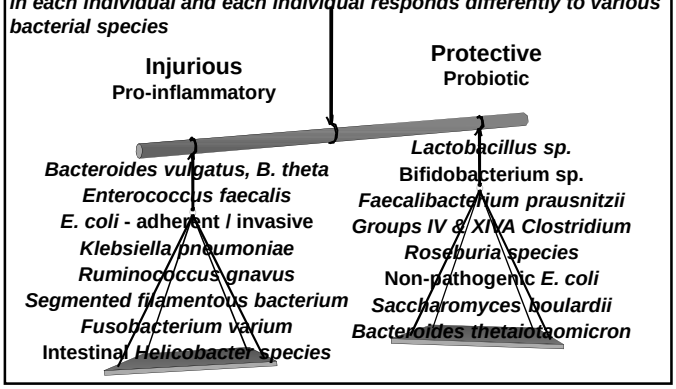
Adherent/ invasive *E. coli* are increased in ileal Crohn's disease and colon cancer, cause exp. ileocolitis and colon cancer



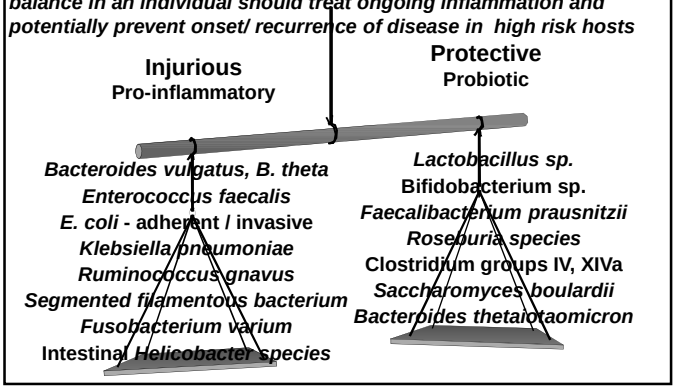
Metabolism in the colonic ecosystem



Intestinal inflammation vs. homeostasis depends on the relative balance of beneficial vs. detrimental bacteria: *This balance is unique in each individual and each individual responds differently to various bacterial species*



Intestinal inflammation vs. homeostasis depends on the relative balance of beneficial vs. detrimental bacteria: *Selectively altering this balance in an individual should treat ongoing inflammation and potentially prevent onset/ recurrence of disease in high risk hosts*



What Tools Do We Have to Restore a Healthy Microbiome?

- Antibiotics (selective, broad spectrum, nonabsorbable)
- Probiotics (traditional, ***resident species*** and genetically engineered)
- Prebiotics and diet
- Combinations (antibiotics, probiotics, and prebiotics)
- Microbial transplantation (fecal microbial transplant or ***complex groups of defined bacterial species***)

Randomised Controlled Trials Fecal Micobial Transplant (FMT) in Ulcerative Colitis (UC)

Gastroenterology 2015

Moayyedi et al (McMaster)	Rossen et al (Amsterdam)
6 x weekly enemas	2 naso-duodenal infusions wks 0 & 3
FMT 9/38 (**24%**) v 2/37 (**5%**) P=0.03	**FMT** 7/23 (**30%**) v 5/25 (**20%**) P=0.51
One donor for 7 / 9 responders	

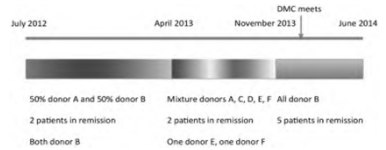
Conflicting results regarding the efficacy and optimal treatment modality of FMT in UC

Fecal Microbial Transplantation Induces Remission in Patients With Active UC: ***Strong Donor Effect***

Results from a Randomized Controlled Trial

	Placebo (n=37)	FMT (n=38)	*P* Value
Remission	2 (5%)	9 (24%)	.03
Response	9 (24%)	15 (39%)	.16

	Donor B	All Other Donors
Clinical Improvement	**7/18 (39%)**	**2/20 (10%)**

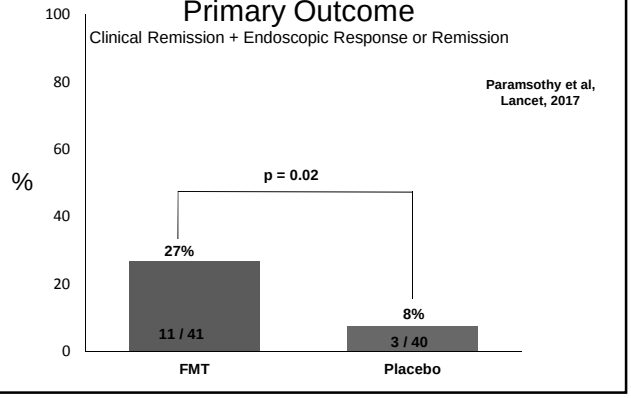


Moayyedi P, et al. *Gastroenterology*. 2015;149:102-109.

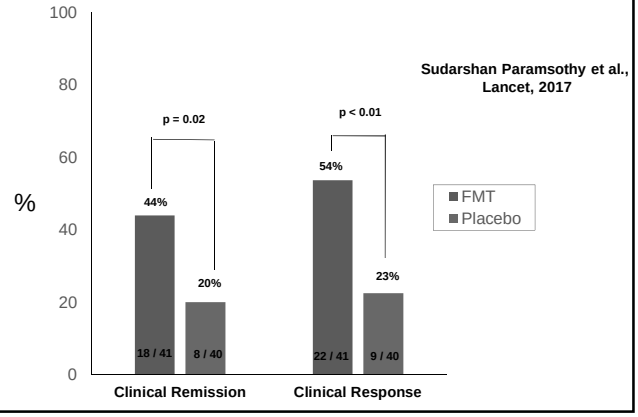
Australian FOCUS Study: FMT 5 d/wk x 8 wks

Primary Outcome

Clinical Remission + Endoscopic Response or Remission



Clinical Outcomes, Week 8

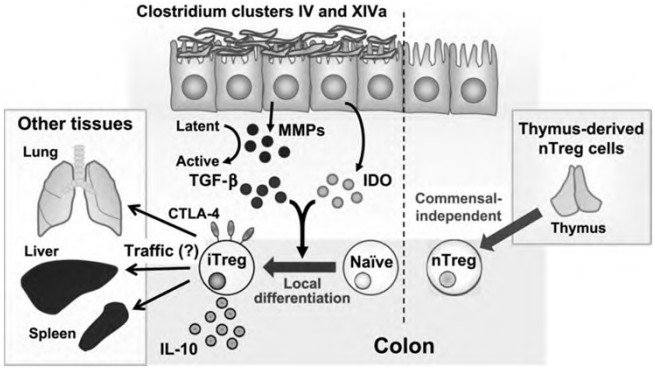


Synthetic Complex Resident Bacterial Species vs Random Donor-Derived Fecal Transplants

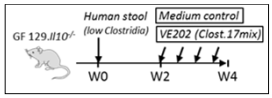
- Defined *composition*—***eliminate risk of infections***
- Ability to individualize *therapy*—***match optimal replacement for various dysbiotic profiles***
- More reproducible results—***eliminate variability in outcomes***
- Simplify regulatory approval with defined composition
- Manufacture under standard, highly controlled culture conditions—***eliminate variability in outcomes***
- Increase patient acceptance—***decrease "yuk" factor***

Clostridium subsets induce colonic Treg cells

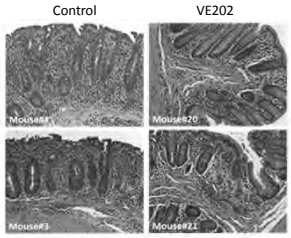
K. Atarashi et al, *Science* 331:337-341,2011; *Nature*, 2013



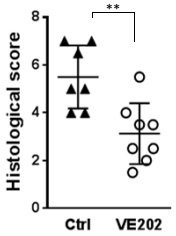
17 Clostridium sp. treat established colitis in humanized Il10$^{-/-}$ mice



Histology score ↓

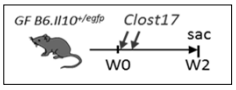


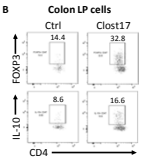
Representative histology pictures. Distal colon. H.E. staining. 200x. Week4.



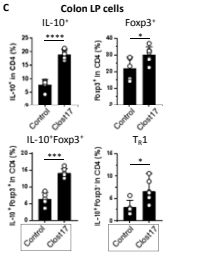
Histological score. Cecum, proximal-, mid- and distal (-rectum)- colon were assessed for histological scoring. Error bar shows SD. **p<0.01, Student's t-test. Week4. Ctrl: medium control.

Clost17 stimulate IL-10 production by LP T cells and induce Treg



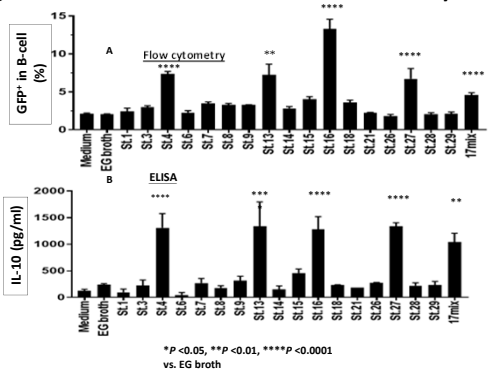


ex-GF IL-10 reporter mice colonized with Clost17. Flow dot plots of FOXP3 intracellular staining and IL-10 (GFP) from colon LP cells from ***Clost* 17** -colonized ex-GF mice or medium control mice (**Ctrl**). The percentage in CD4 in CD3$^+$CD4$^+$ gated cells is shown



ex-GF IL-10 reporter mice colonized with Clost17. FOXP3 intracellular staining and IL-10 from colon LP cells from **Clost17**-colonized mice or medium-gavaged mice (**Control**). ANOVA t test. *P<0.05, *** P<0.001, ****P<0.0001.

4 members of Clost17 preferentially increase IL-10 in spleen cells following ex-vivo stimulation with individual bacterial lysates



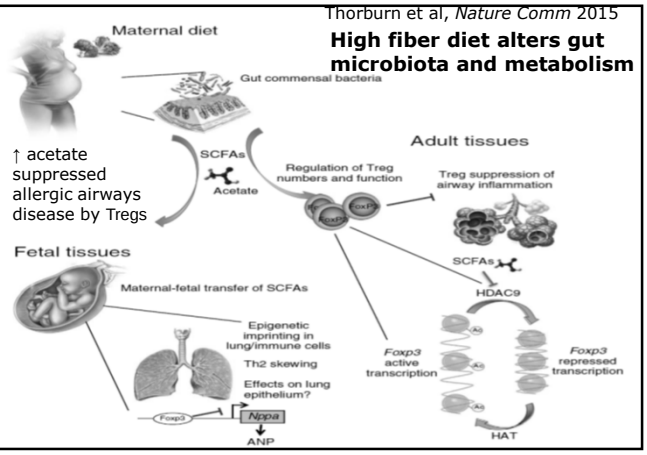
*P <0.05, **P <0.01, ****P <0.0001 vs. EG broth

Improving Current Techniques to Restore a Healthy Microbiota

- Select approach and targets based on analysis of an individual's microbiota pattern ***(customized approach-selectively replace missing/ dysfunctional components)***
- Concentrate on ***protective resident species*** that have good chance to colonize and function in the intestine
- ***Refine fecal transplants,*** identify characteristics of optimal donors and determine their effectiveness and duration in IBD
- Determine whether ***dietary approaches*** can alter composition and metabolic function of enteric microbiota in therapeutic/preventive manner
- ***Target outcomes of metabolic function and dominant antigens*** rather than 16S bacterial profiles

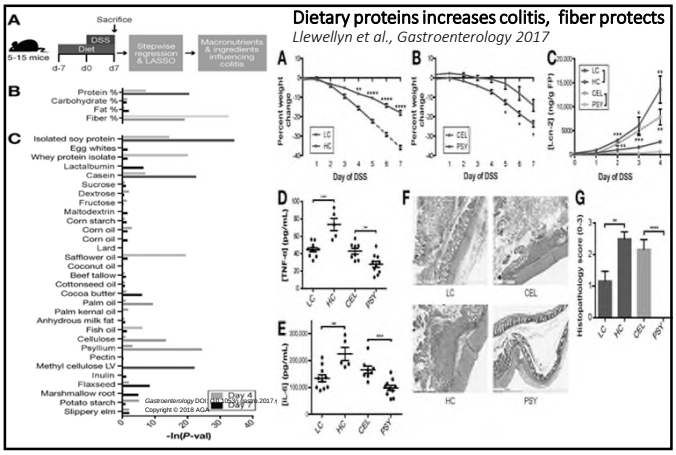
Thorburn et al, *Nature Comm* 2015

High fiber diet alters gut microbiota and metabolism



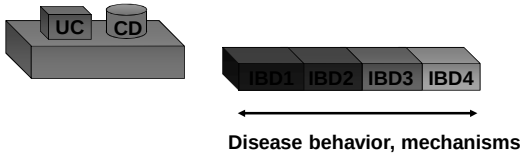
Dietary proteins increases colitis, fiber protects

Llewellyn et al., Gastroenterology 2017



Defining IBD: current vs. future

Names vs. Mechanistic subsets



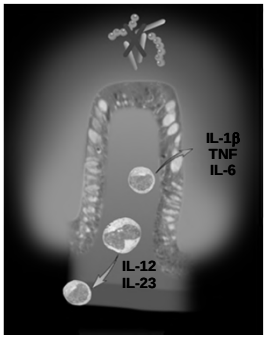
From Dermot McGovern

Sequential, safer approach to treating IBD:

Maintain long term remission by alternative approaches

Eliminate antigenic drive
Antibiotics, probiotics *prebiotics, fecal transplant, diet,* block bacterial binding, enhance bacterial killing (stimulate defensins, GM-CSF, hydroxychloroquin)

Paralyze TH_1, TH_{17} innate immune responses
Steroids, biologics



Restore mucosal barrier function
SCFAs, probiotics fiber/prebiotics Growth factors, trefoil factor, epithelial stem cells

Promote regulatory cell activity (TR_1, TH_3, Treg, B cells, DC)
Rapamycin, Omega 3 FAs, retinoic acid, vit D *Bacteroides fragilis PSA. Clostridium subsets, F. prausnitzii*, worms