

Microbiome and immune system interaction in IBD

Harry SOKOL



**Gastroenterology Department
Saint-Antoine Hospital**

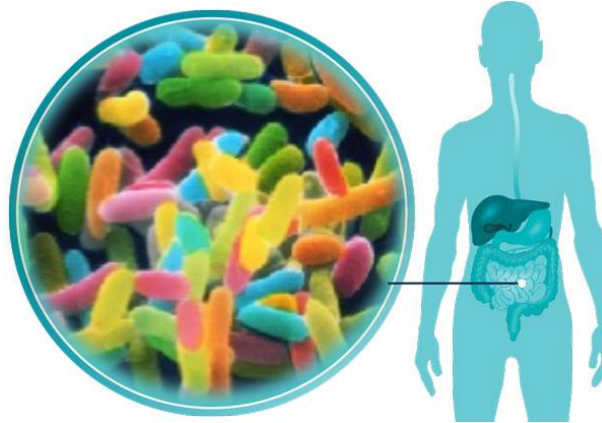


Micalis

Human intestinal Microbiota

Microbiota

Human cells



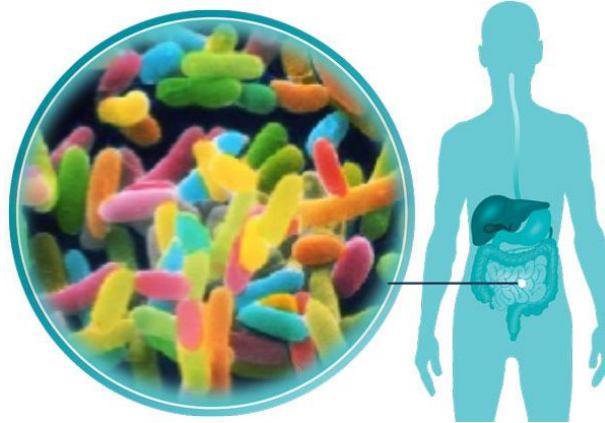
Human intestinal Microbiota

Microbiota

~2 kg

Human cells

~70 kg



Human intestinal Microbiota

Microbiota

~2 kg

10^{13} microorganisms



1 g >100 000 000 000
microorganisms



Human cells

~70 kg

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Human cells

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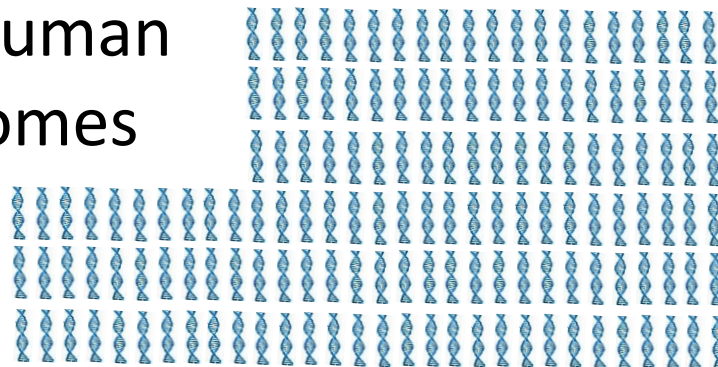


Human cells

~70 kg

10^{13} cells

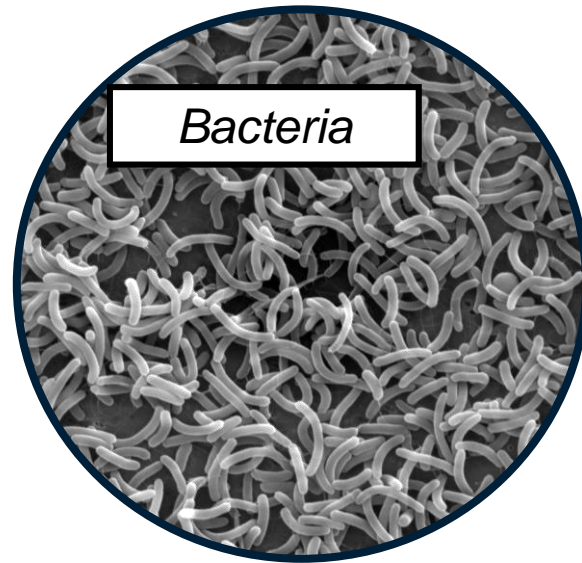
150 human genomes



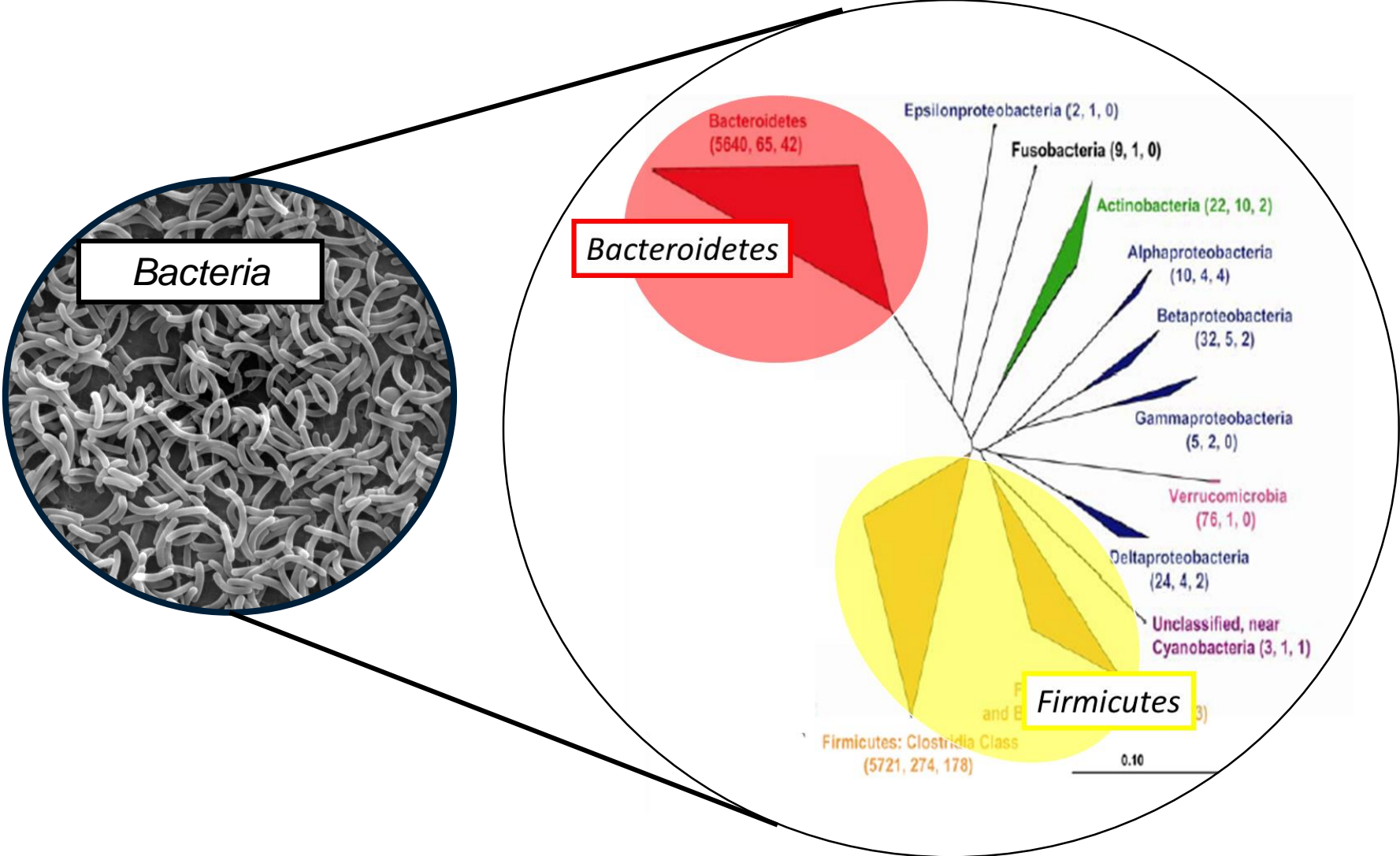
1 human genome



Gut microbiota



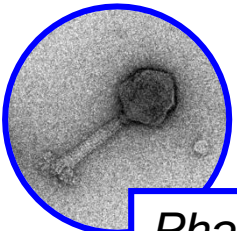
Gut microbiota



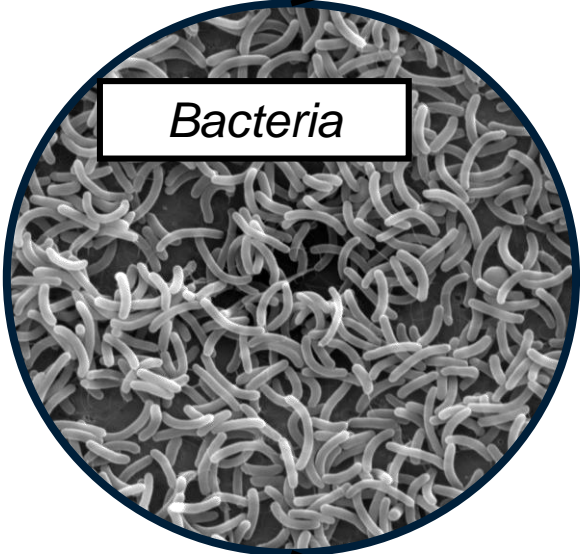
Gut microbiota



Fungi

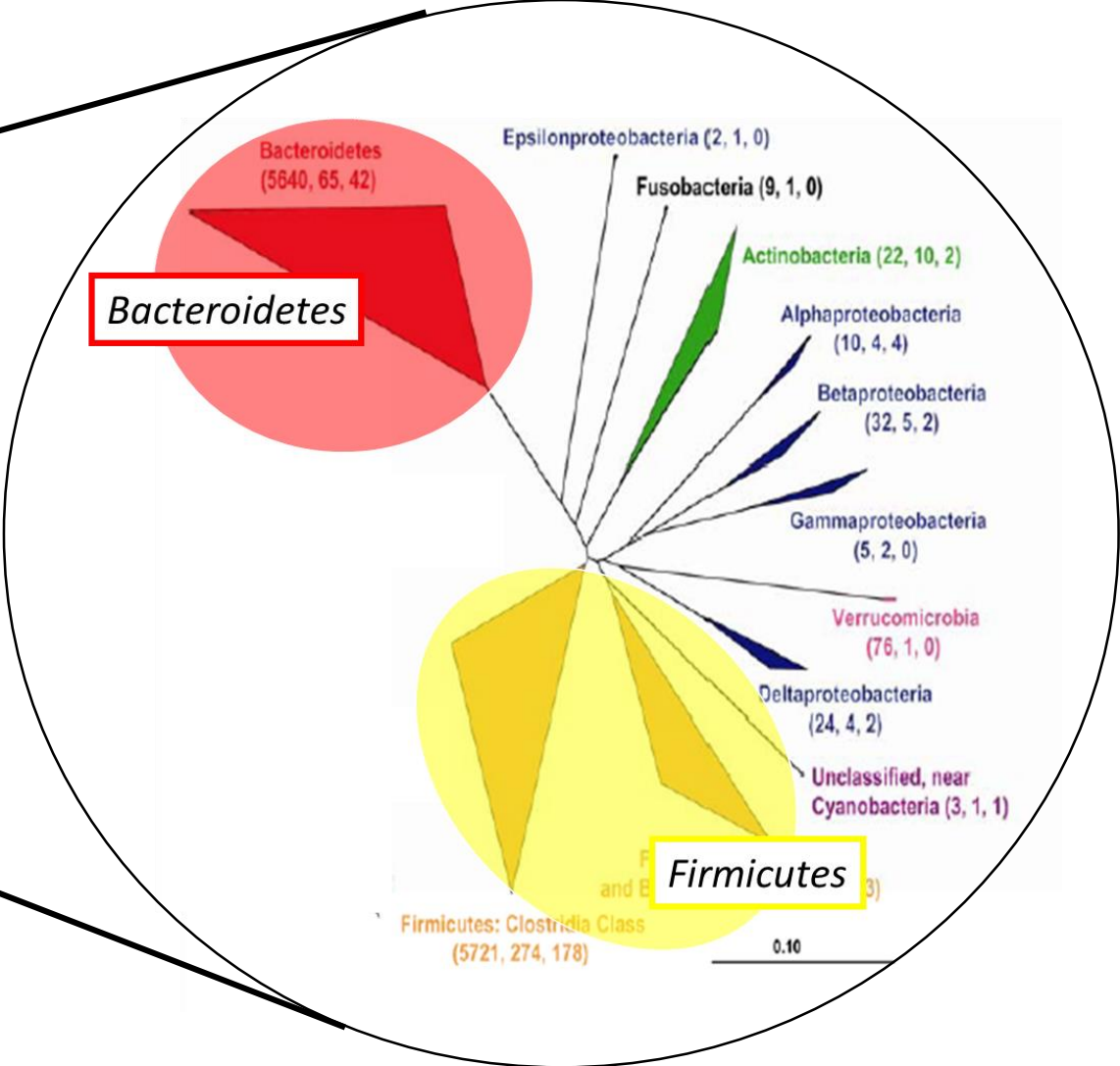


Phages

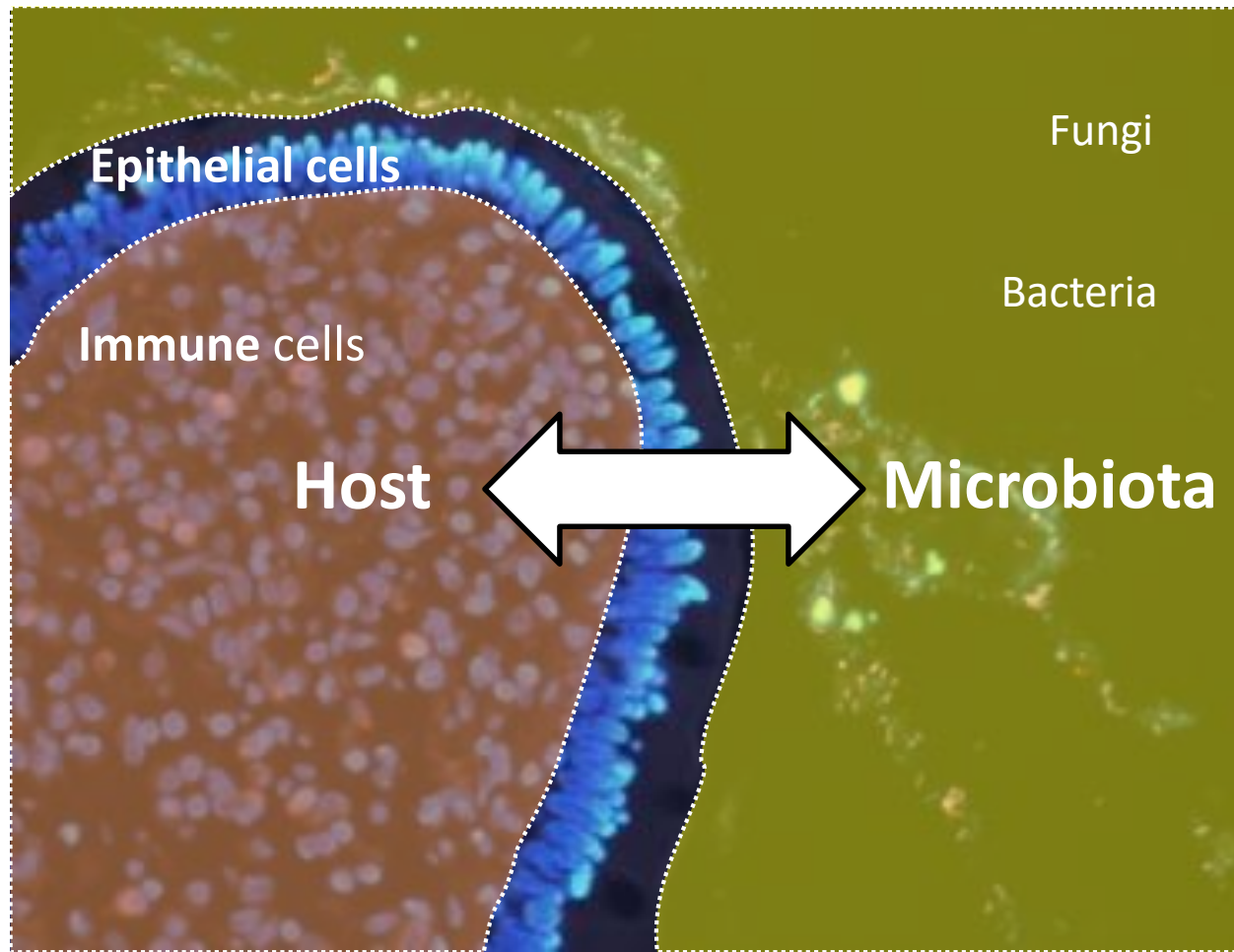


Bacteria

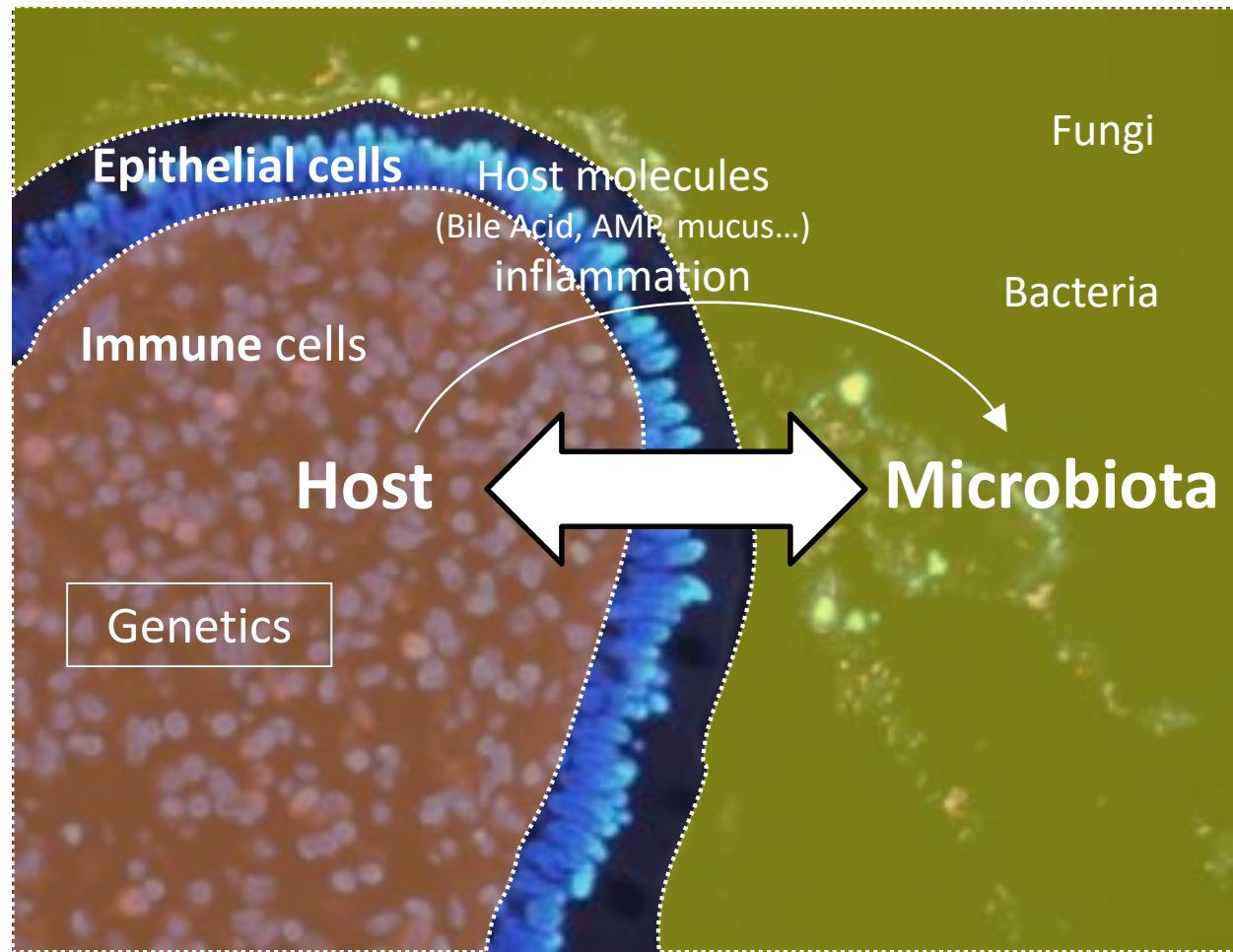
Others
- Archaea
- Protists



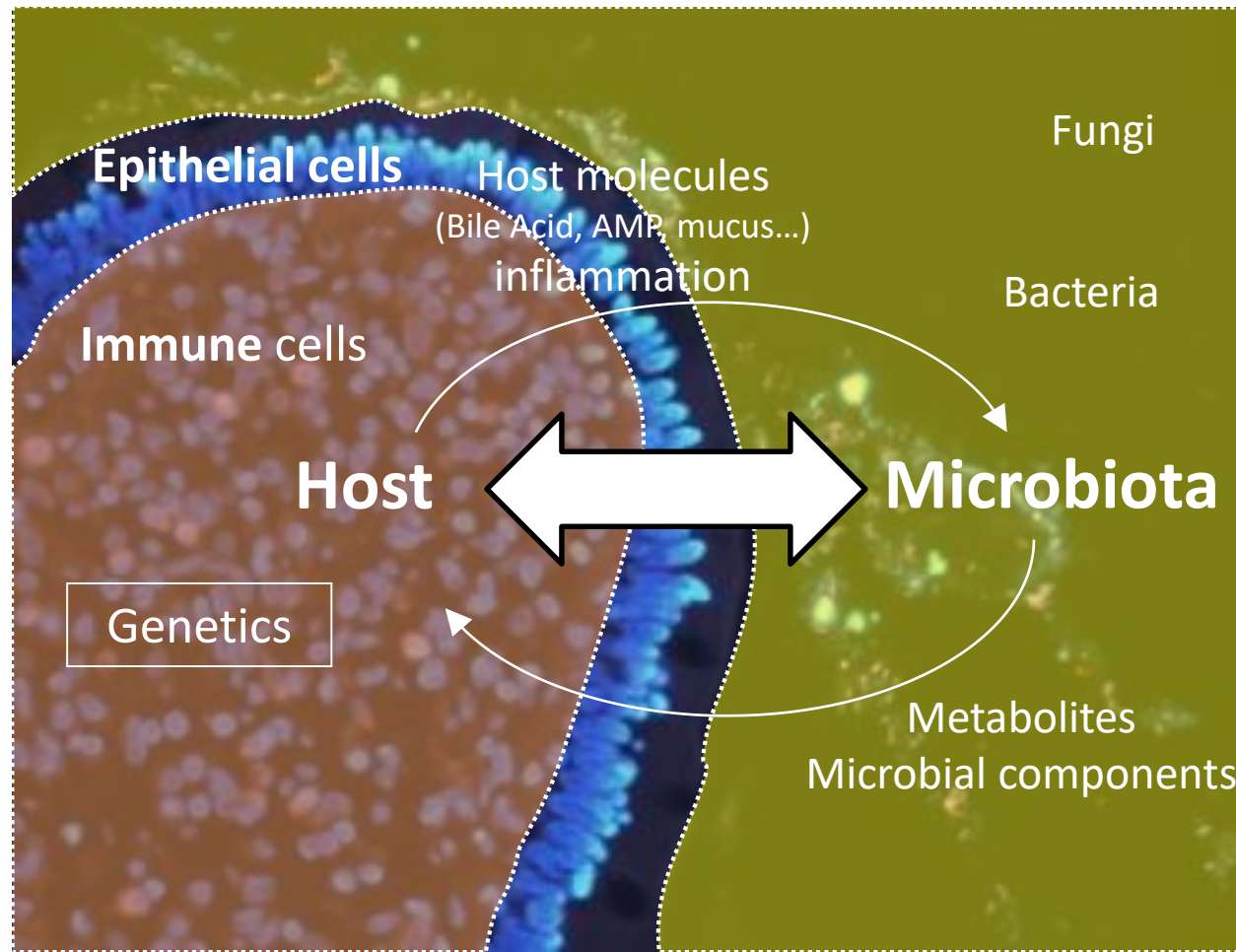
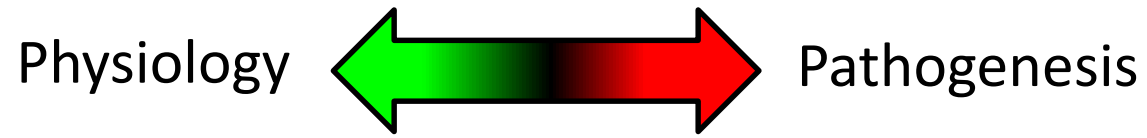
Host-Microbiome interactions



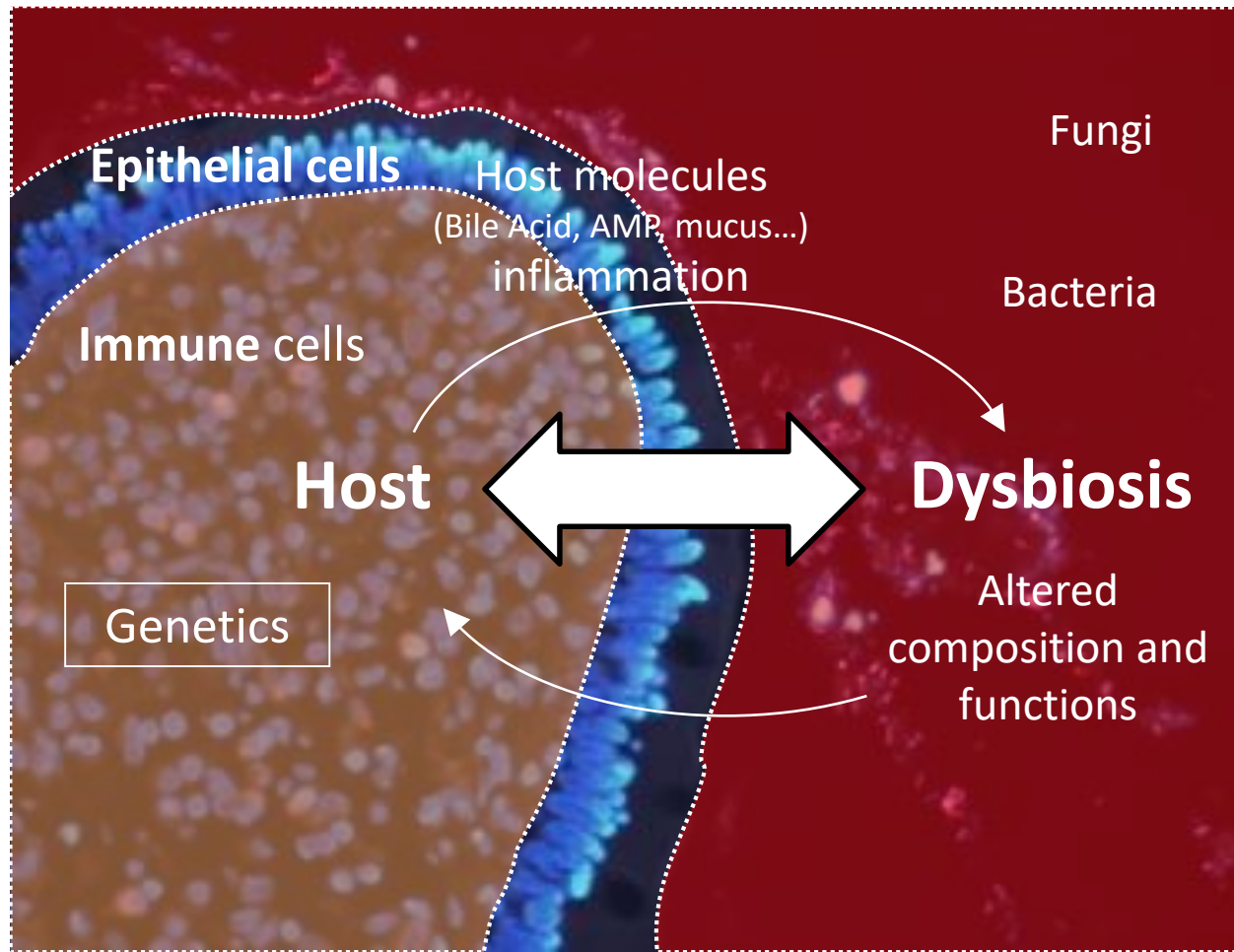
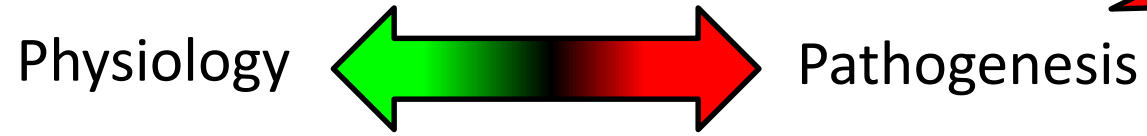
Host-Microbiome interactions



Host-Microbiome interactions



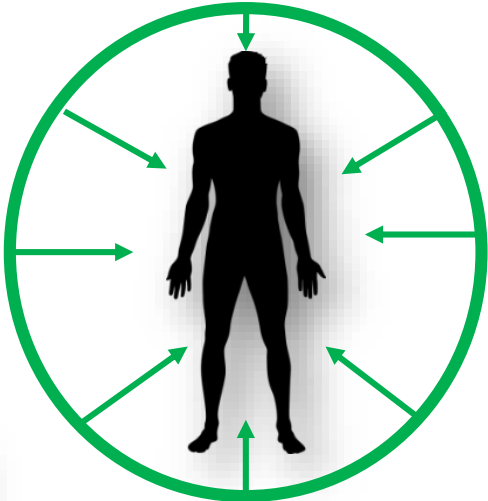
Host-Microbiome interactions



Factors impacting the gut microbiota



Genetics



Environment



Microbiota



Early life



Antibiotics



Urban life



Early life

First host-microbes interactions altered

→ Impact on immune system imprinting

→ Miseducation of immune system



Antibiotics



Urban life

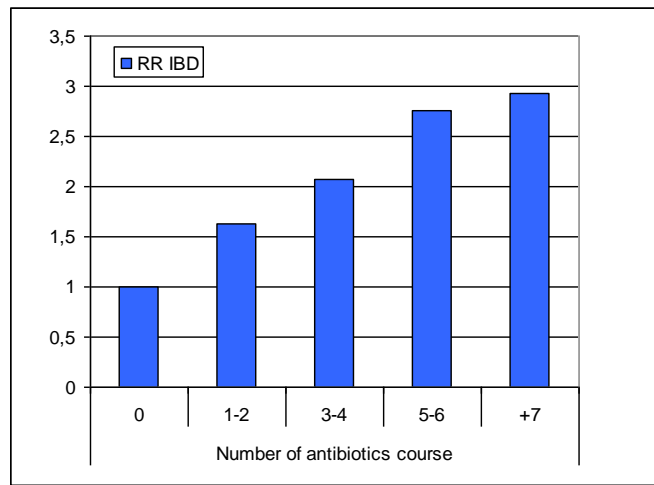


Early life

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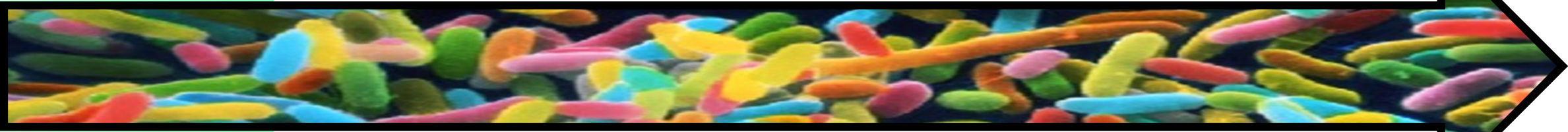
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Number of antibiotics courses in childhood correlates with IBD risk
Nationwide Danish cohort

Hviid et al. Gut 2011



Antibiotics



Urban life

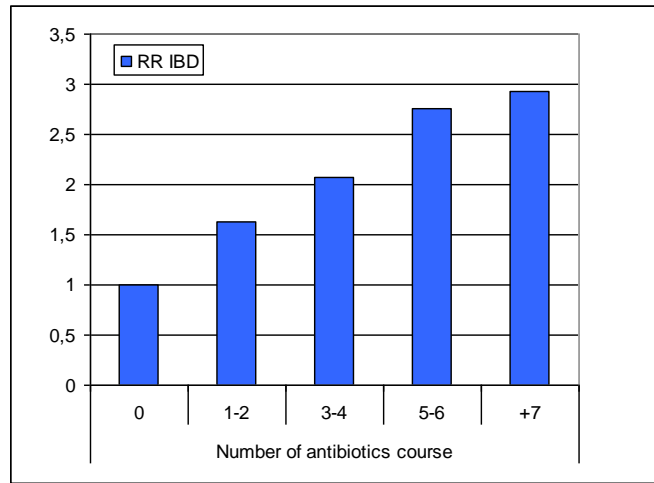


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Data on :

- C-section
- Breast feeding

Beaugerie et al. Med Hypotheses 2018



Antibiotics



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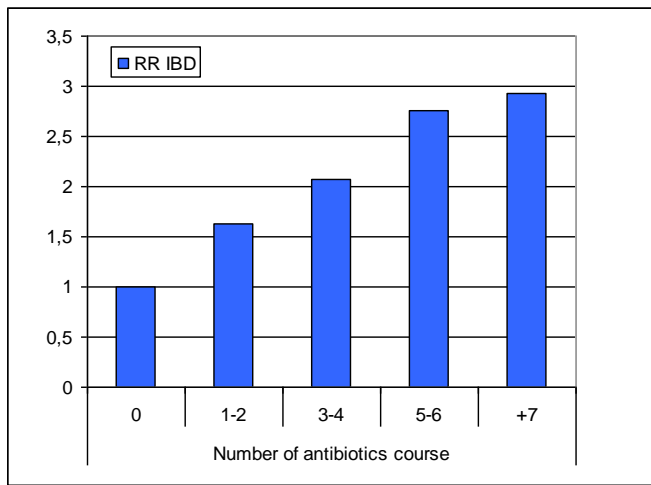


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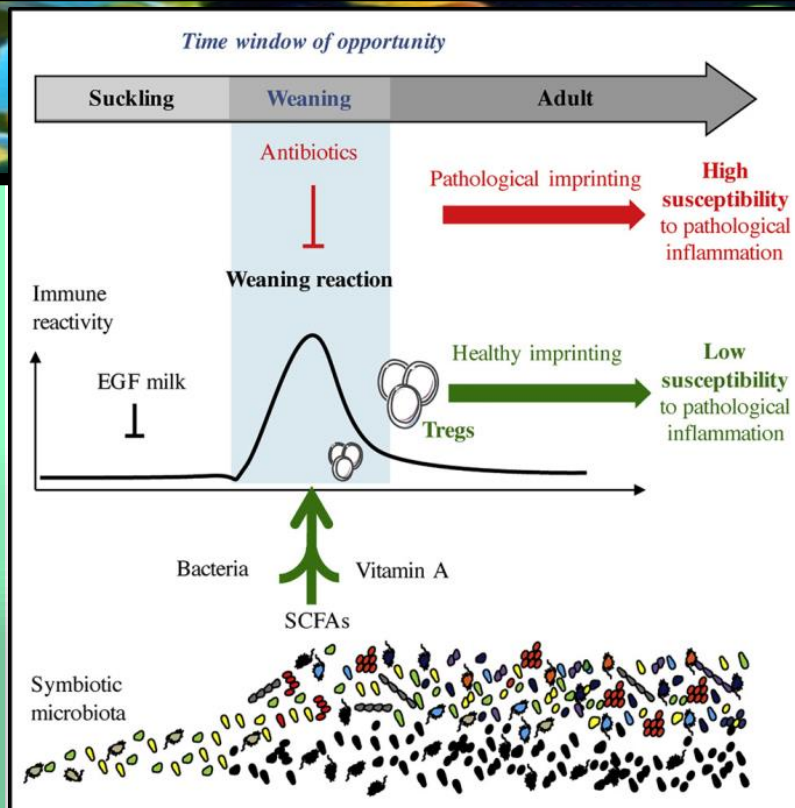
Beaugerie et al. Med Hypotheses 2018



Antibiotics



Urban life



Perturbation of gut microbiota at weaning perturbs the immune system education leading to increased susceptibility to intestinal inflammation later in life.

Al Nabhani et al. Immunity 2019

Early life

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Antibiotics



Urban life



Early life

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Adulthood



Antibiotics



Urban life



Diet



Drugs



Dietary additives
emulsifiers



Antibiotics



Smoking

Imhannet et al. Gut 2016
De Filippo et al. PNAS 2010
Dethlefsen et al. PNAS 2010
Chassaing et al. Nature 2015
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Early life

First host-microbes interactions altered

→ Impact on immune system imprinting

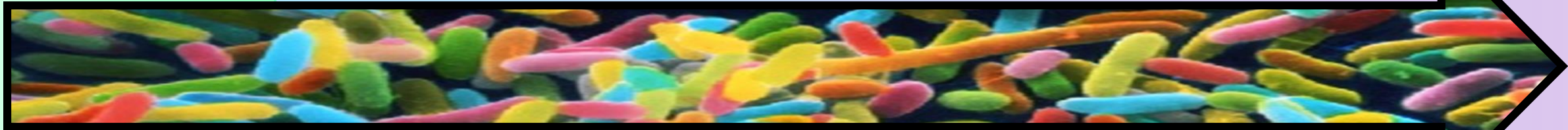
→ Miseducation of immune system

Adulthood

Perturbation of gut microbiota

→ Altered composition & functions

→ Consequences on host



Antibiotics



Urban life



Diet



Drugs



Dietary additives
emulsifiers



Antibiotics



Smoking

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GENETICS

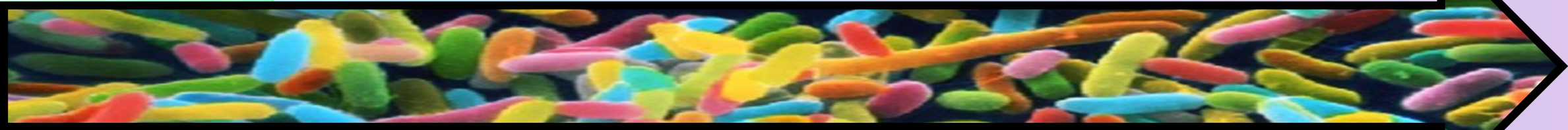
Early life

First host-microbes interactions altered

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Adulthood

- Perturbation of gut microbiota
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Antibiotics



Urban life



Diet



Drugs



Dietary additives
emulsifiers



Antibiotics



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GENETICS

Early life

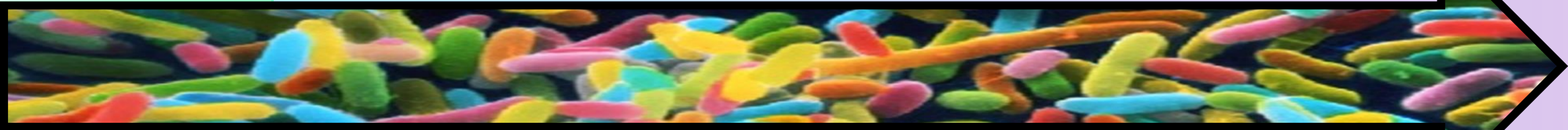
First host-microbes interactions altered

- Impact on immune system imprinting
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Adulthood

- Perturbation of gut microbiota
- Altered composition & functions
- Consequences on host

Potential effects on offspring



Antibiotics



Urban life



Diet



Dietary additives emulsifiers

Drugs



Antibiotics

Smoking



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Early life

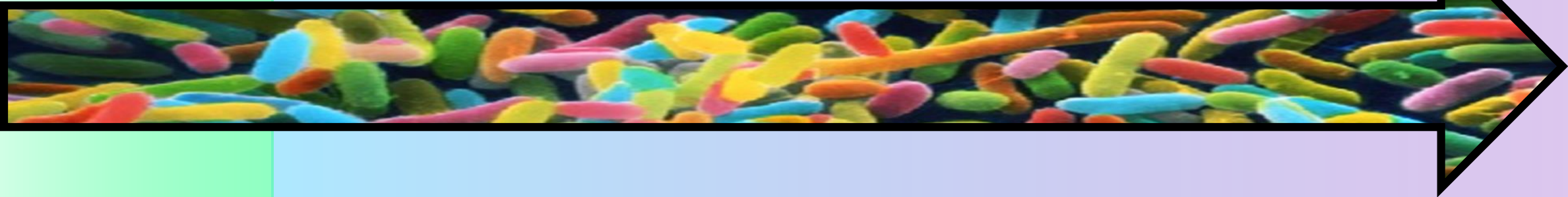
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Adulthood

Perturbation of gut microbiota

- **Altered composition & functions**
- **Consequences on host**



Is the gut microbiota an actor in IBD pathogenesis?

Is the gut microbiota an actor in IBD pathogenesis?

→ Pragmatic answer is YES!

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Modifying the gut microbiota impacts the disease severity:

- In mice models
- In human (see FMT talk)

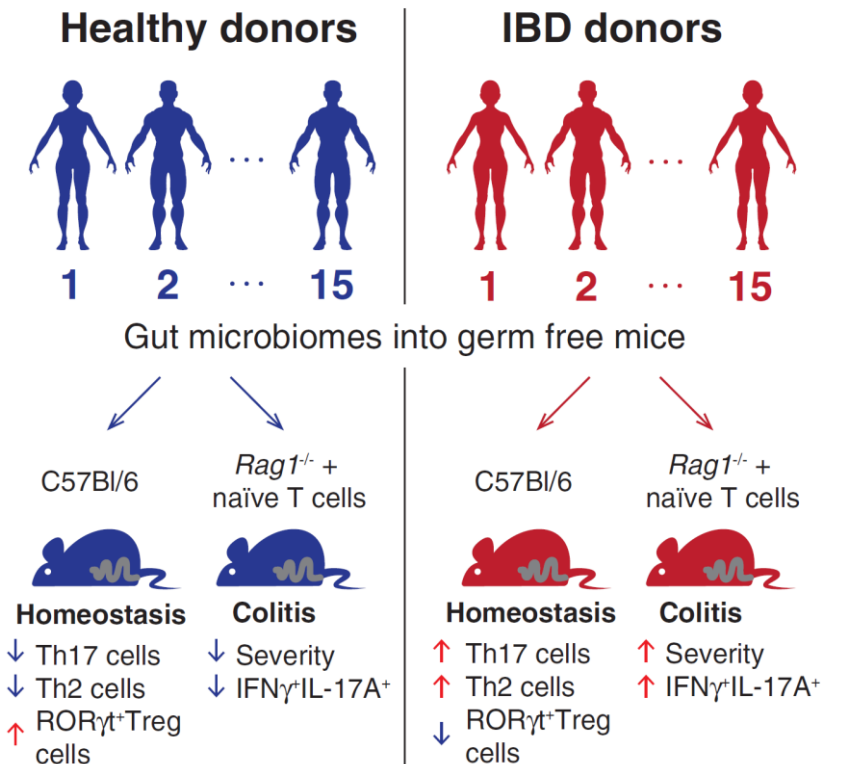
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- In human (see FMT talk)

Fecal microbiota from patients with IBD exacerbate colitis in mice

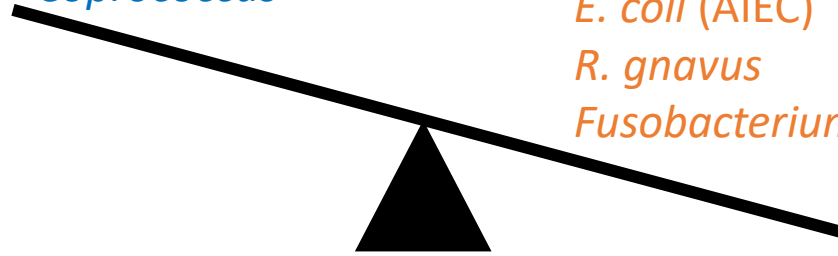


Role of microbiota alterations in IBD pathogenesis

**Altered composition of
the gut microbiota**

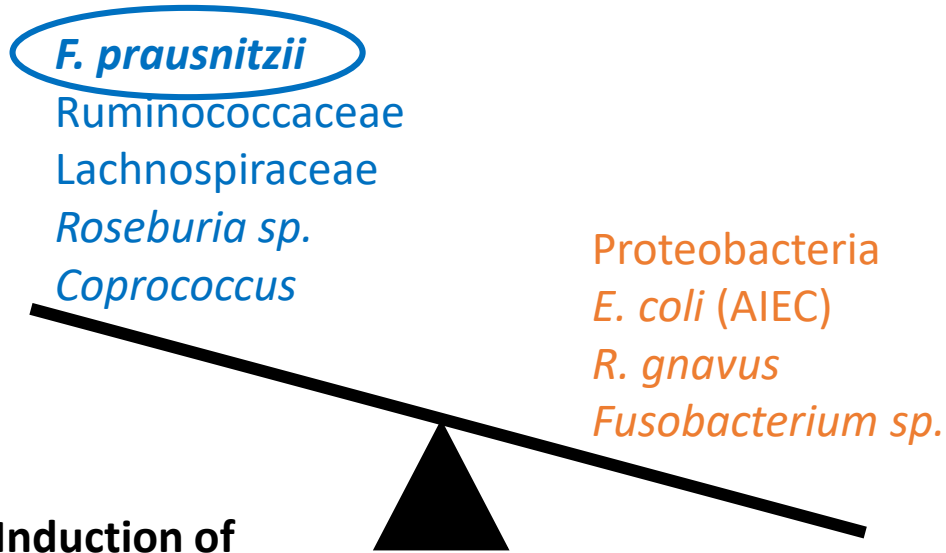
F. prausnitzii
Ruminococcaceae
Lachnospiraceae
Roseburia sp.
Coprococcus

Proteobacteria
E. coli (AIEC)
R. gnavus
Fusobacterium sp.

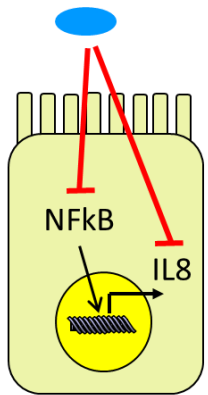


Role of microbiota alterations in IBD pathogenesis

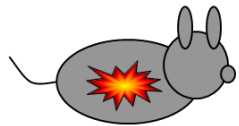
Altered composition of the gut microbiota



Anti-inflammatory effects

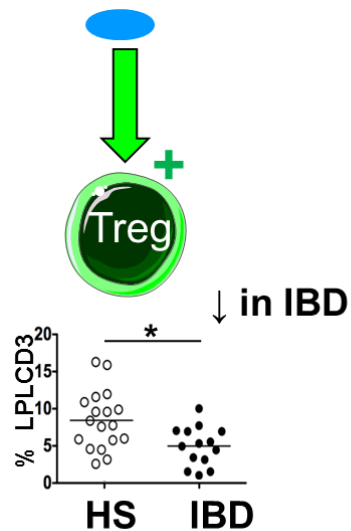


Epithelial cells



Colitis model

Induction of Human Tregs



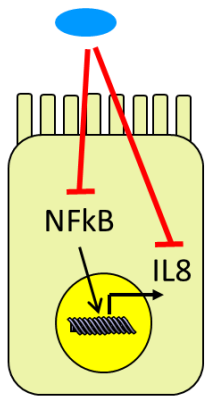
Sokol et al. PNAS 2008
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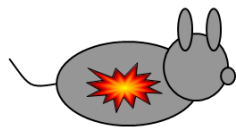
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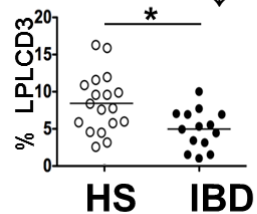
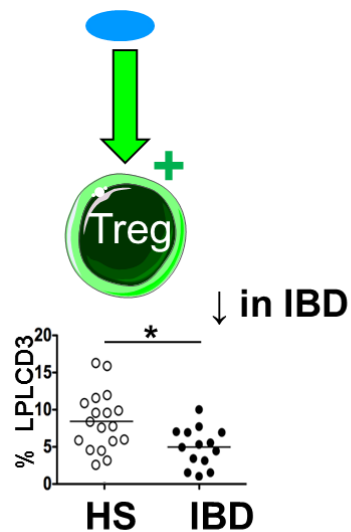


Epithelial cells

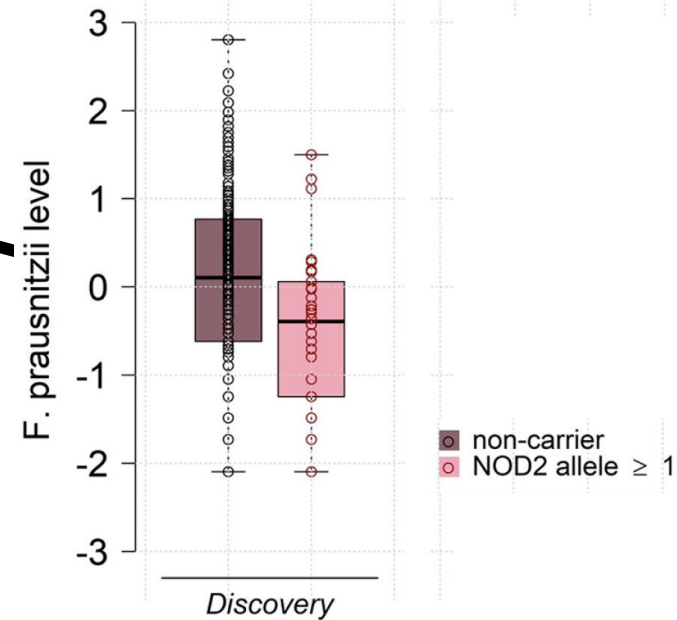


Colitis model

Induction of Human Tregs



Association signals between NOD2 variants and decreased *F. prausnitzii*



Aschard et al. Plos Genetics 2019

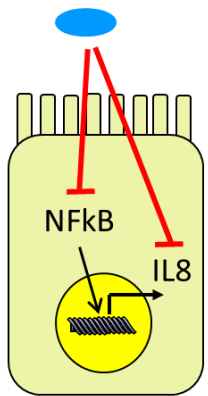
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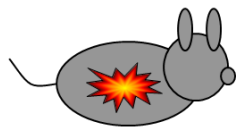
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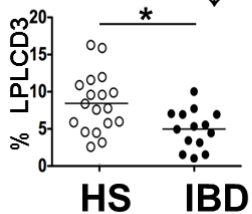
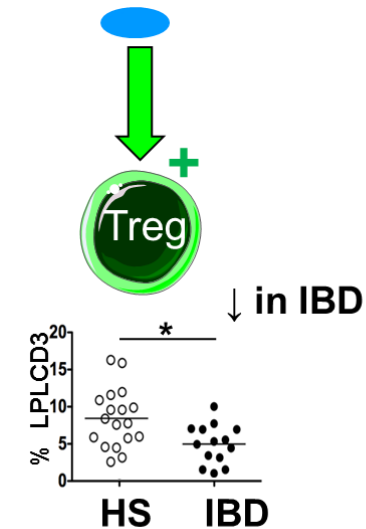


Epithelial cells

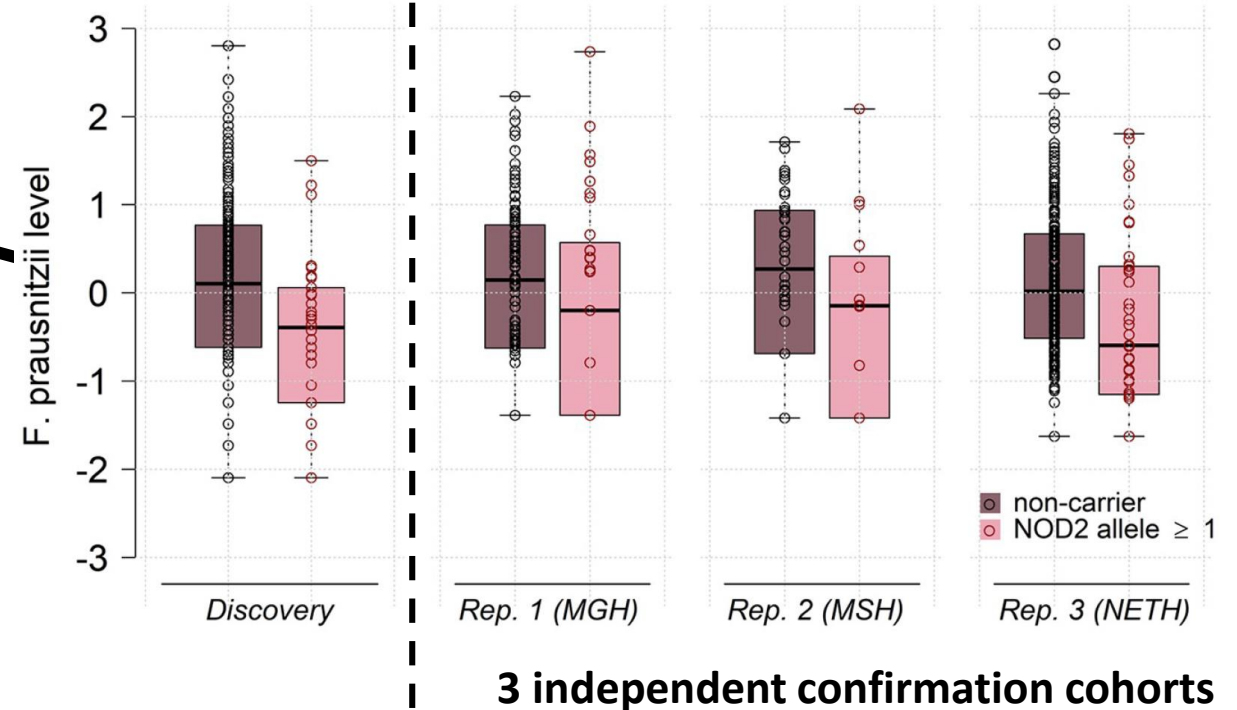


Colitis model

Induction of Human Tregs



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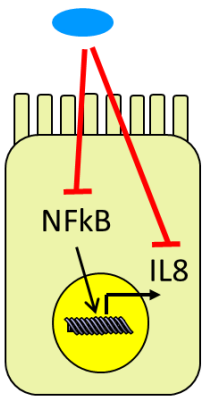
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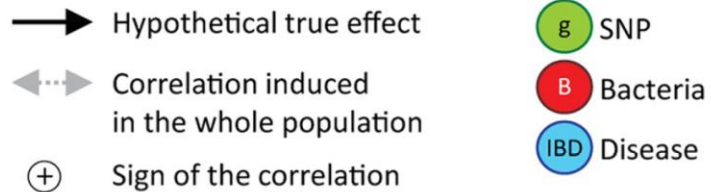
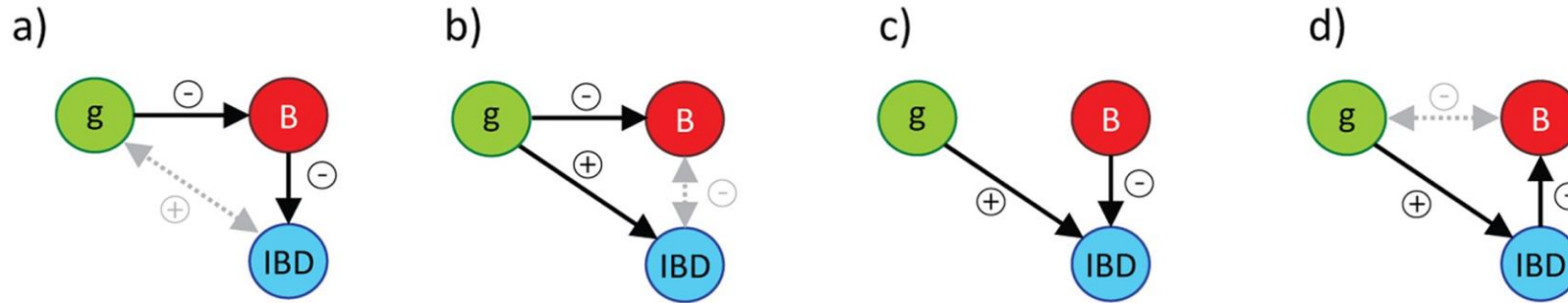
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Altered
the g

Anti-infla



Epithelial
cells



HS IBD

Sarrabayrouse et al. PLOS Biol 2014
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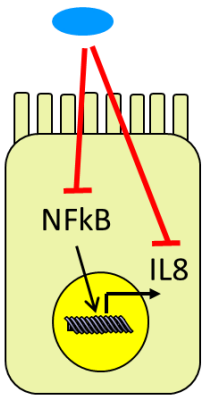
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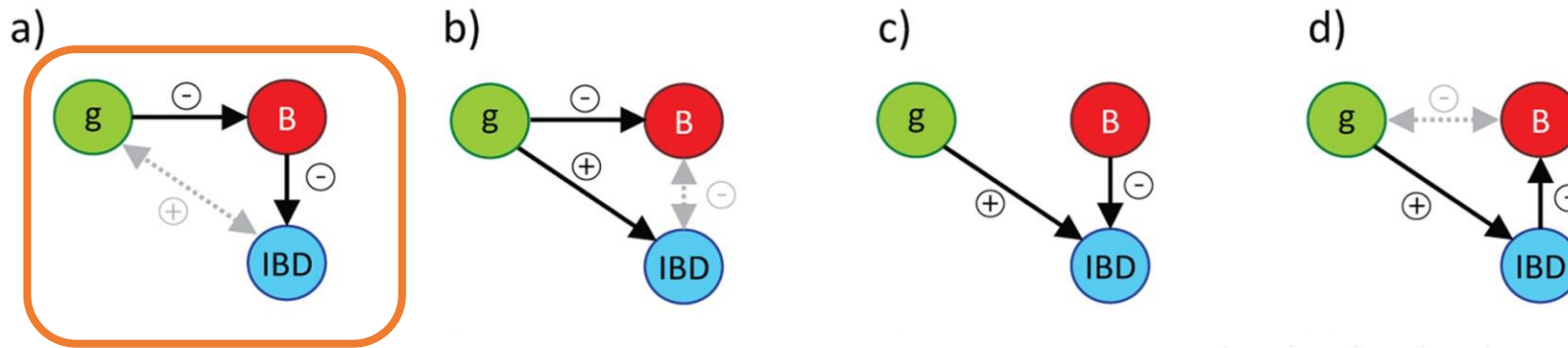
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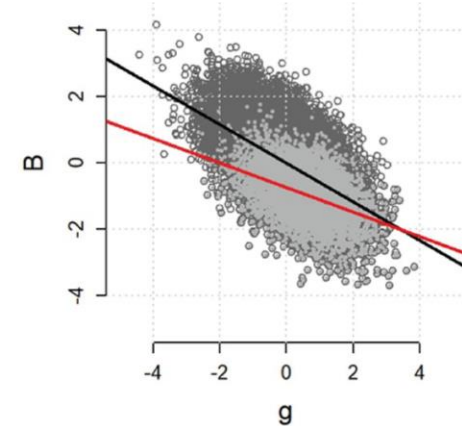
Anti-infla



Epithelial
cells



- Hypothetical true effect
- ↔ Correlation induced in the whole population
- ⊕ Sign of the correlation
- Correlation in the population
- Correlation in cases only
- g SNP
- B Bacteria
- IBD Disease
- Population
- Cases



Mathematical modeling suggesting causality

HS IBD

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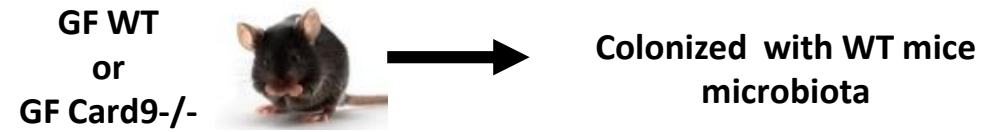
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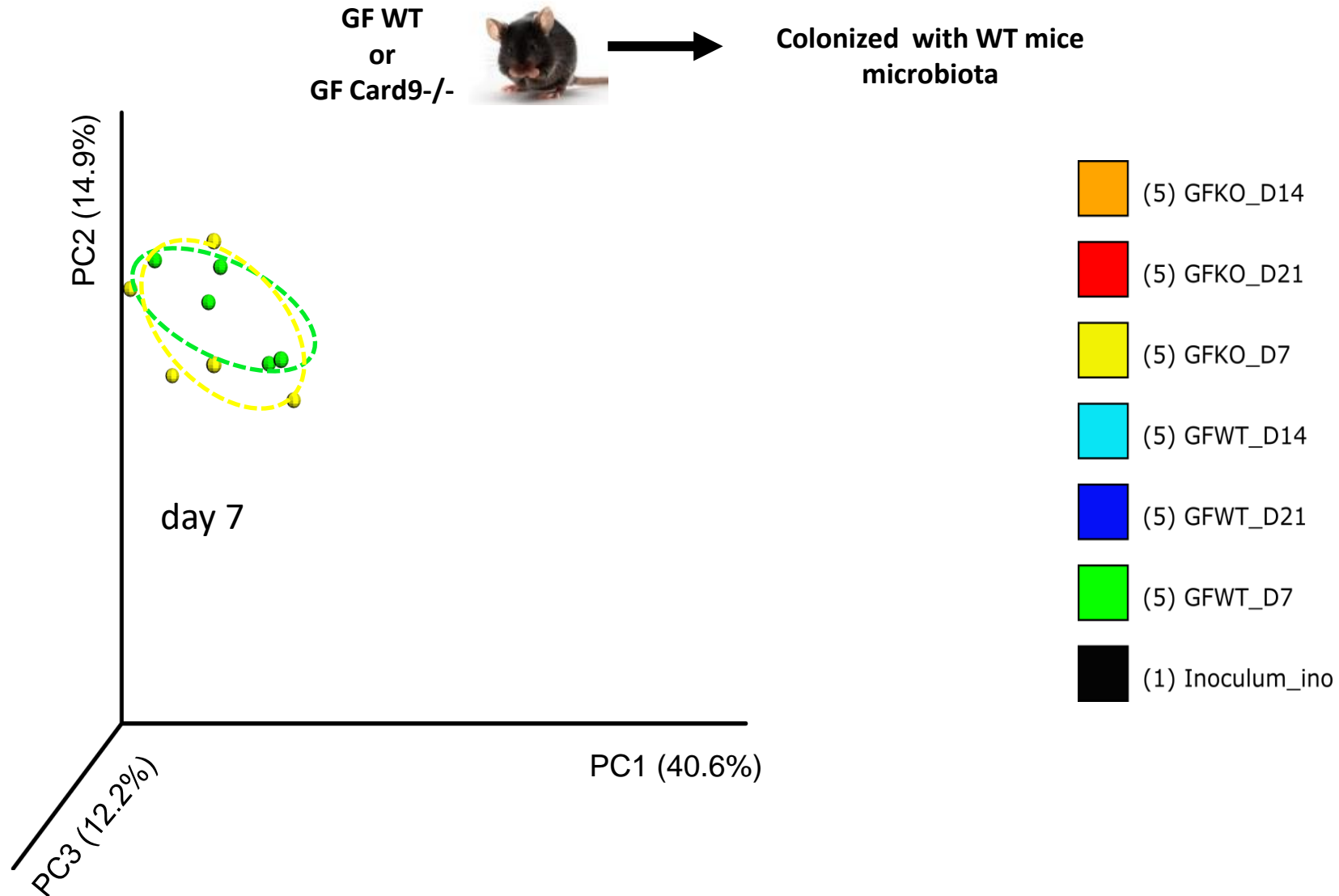
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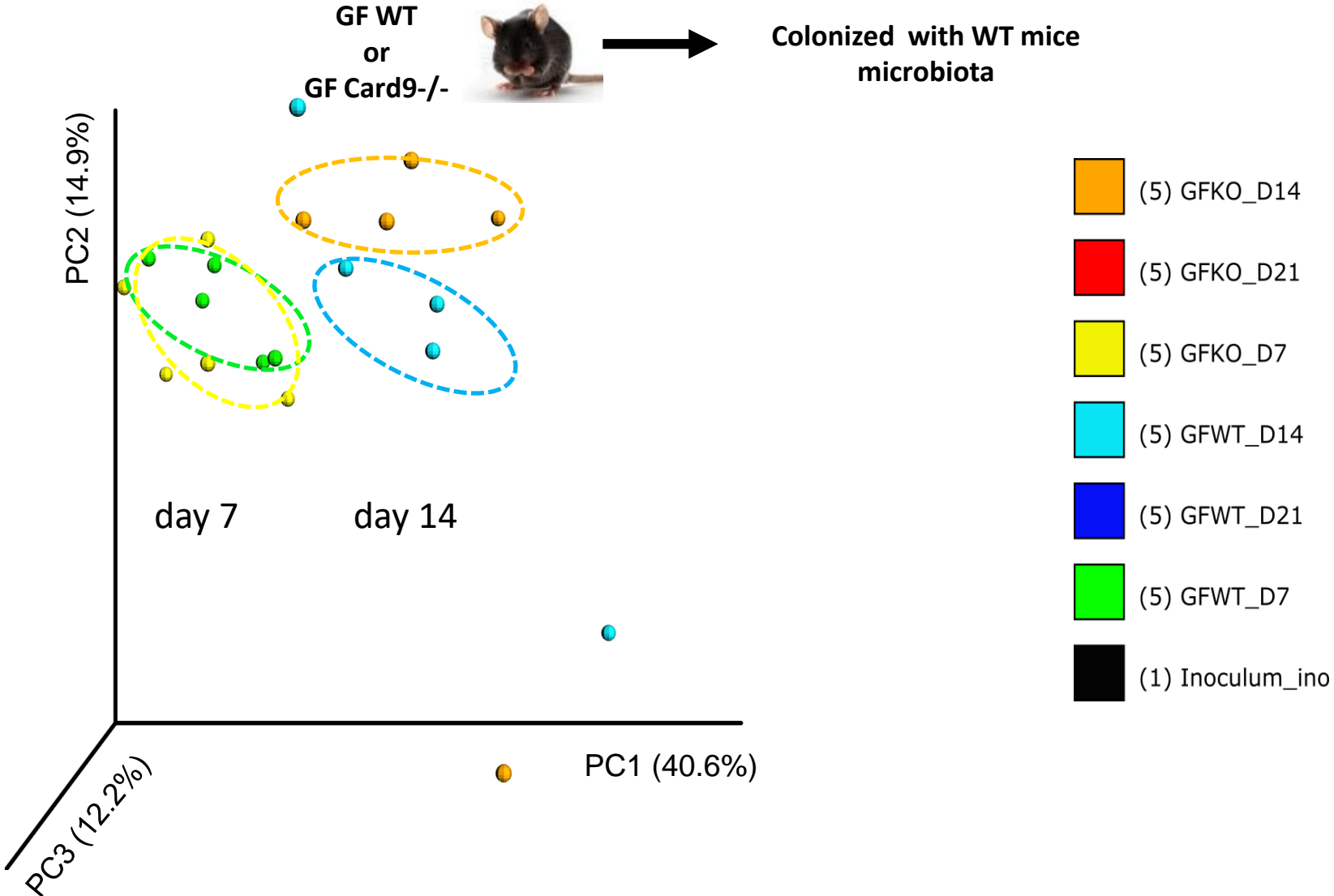
Role of Card9 in shaping the gut microbiota



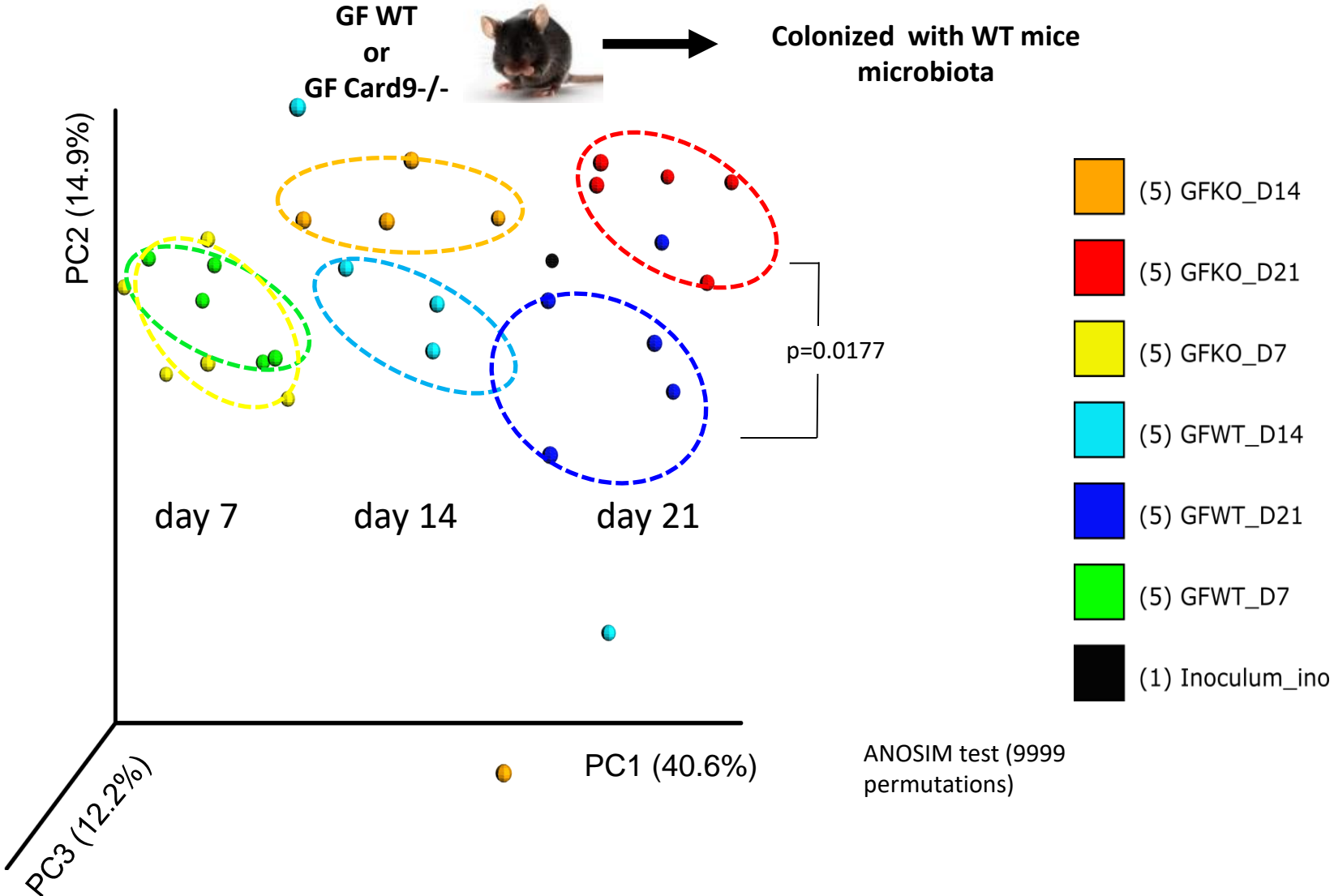
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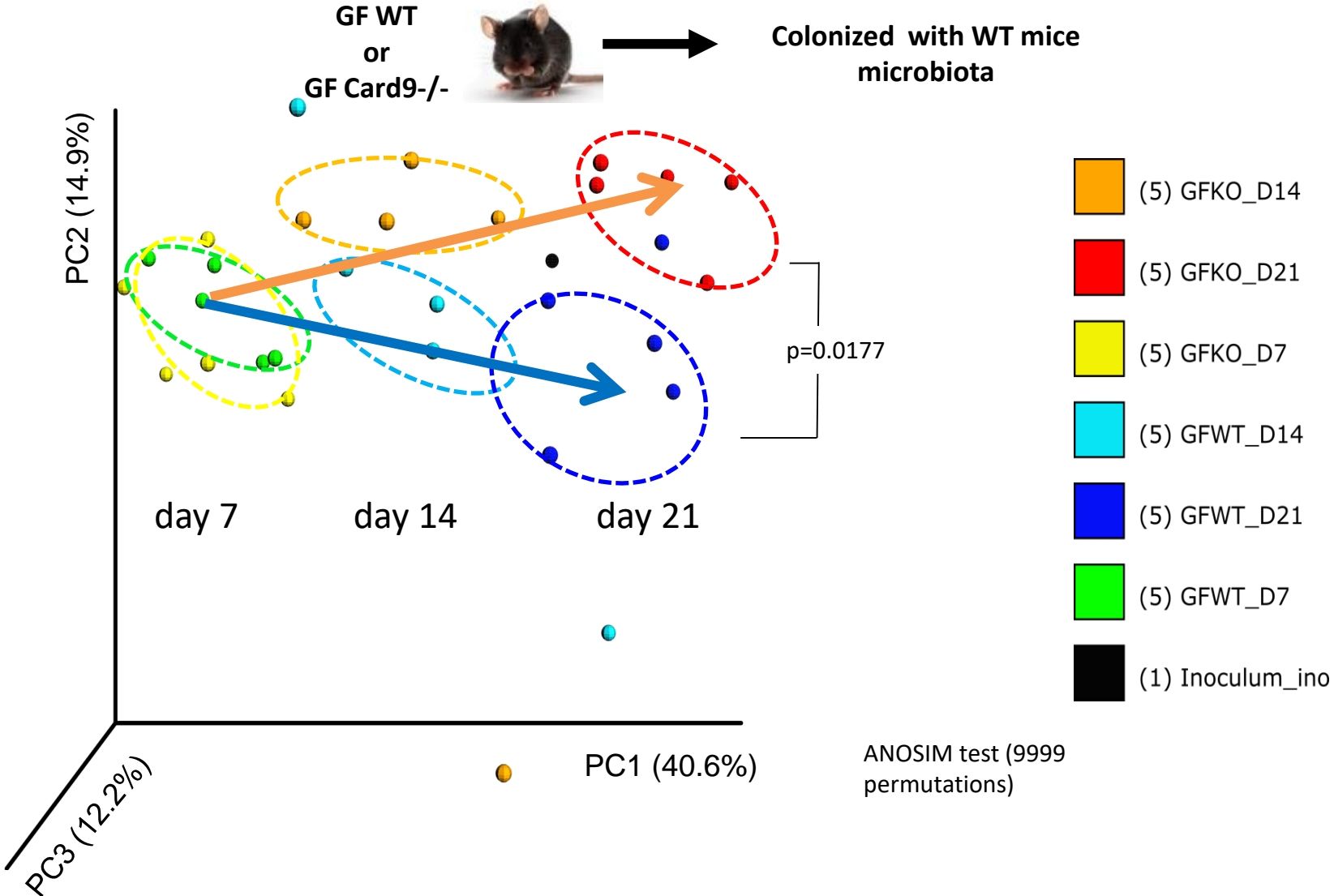
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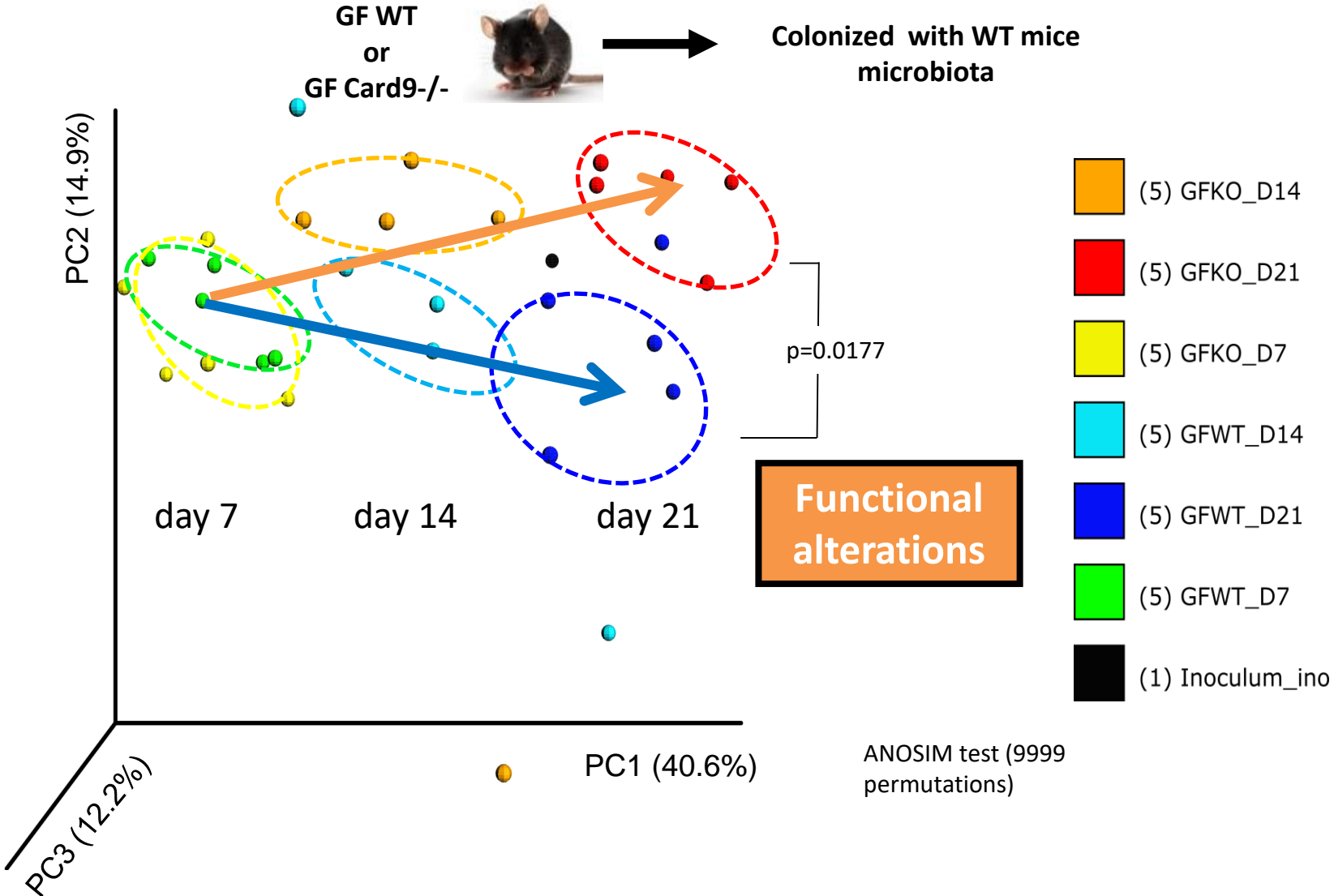
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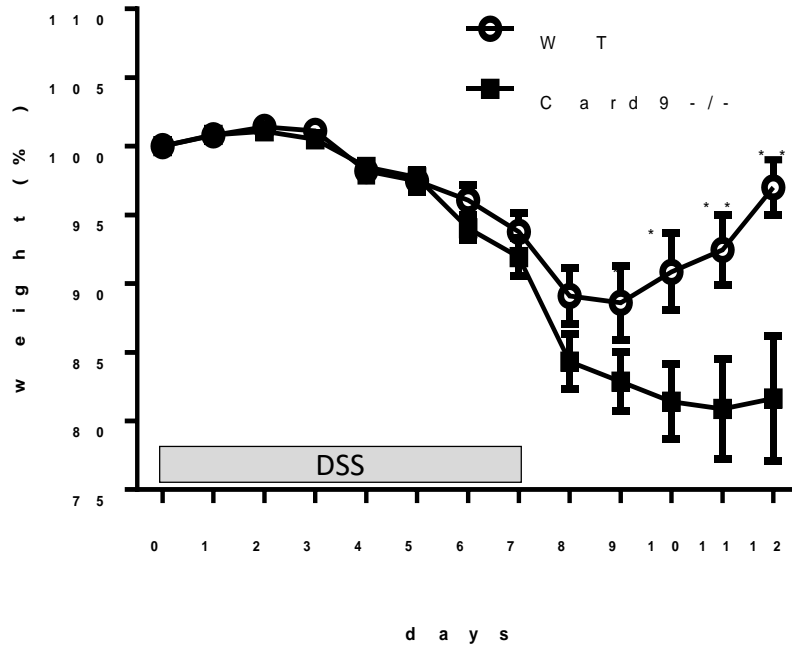
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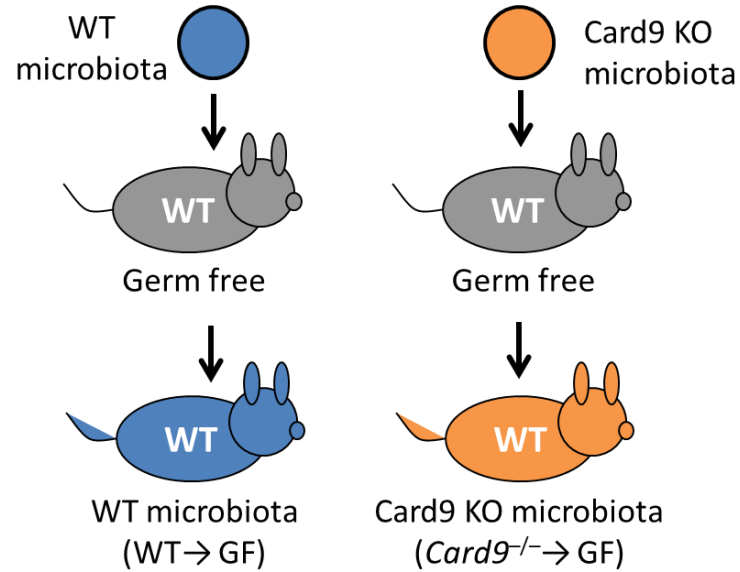
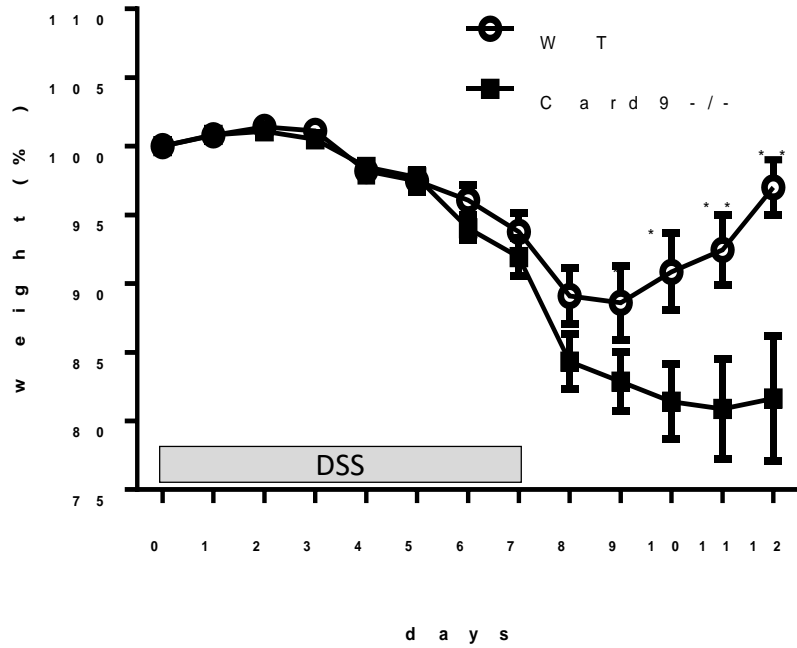
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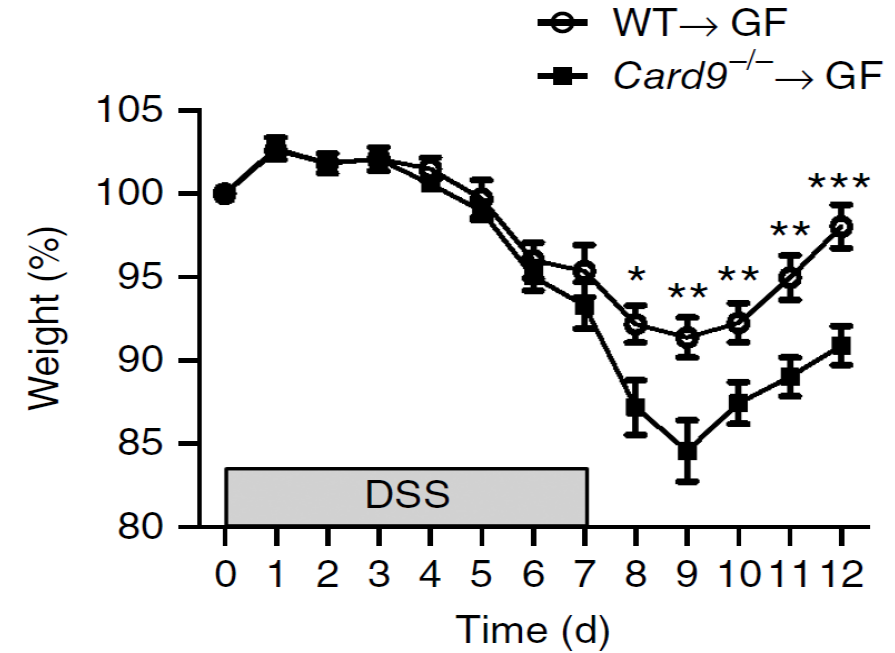
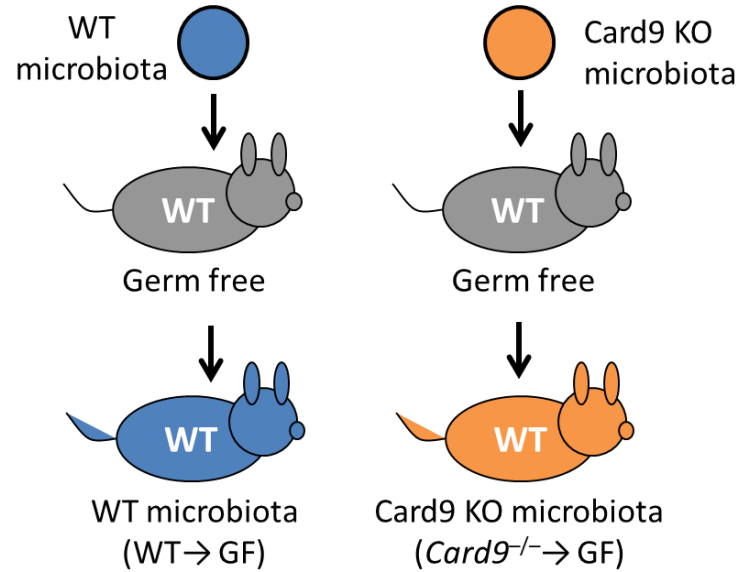
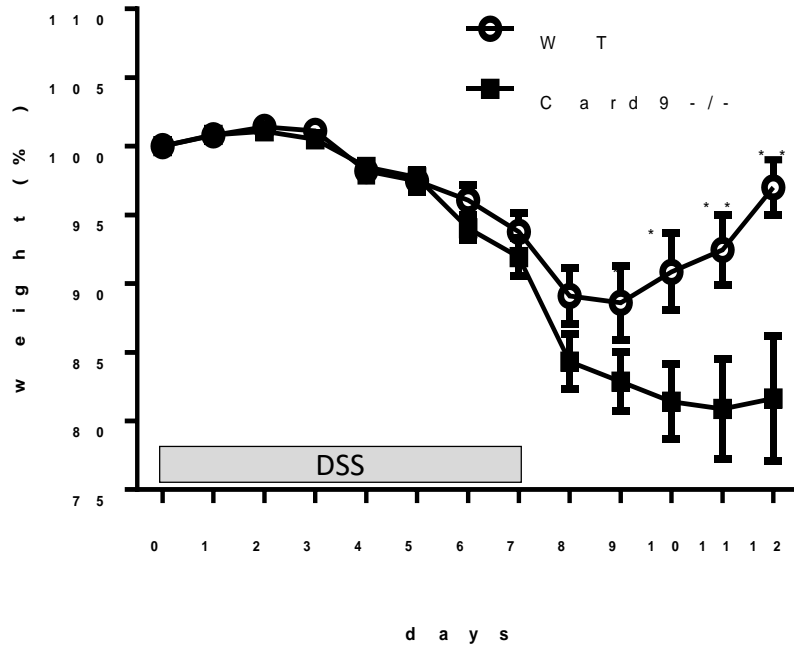
Card9 KO mice are more susceptible to DSS-induced colitis



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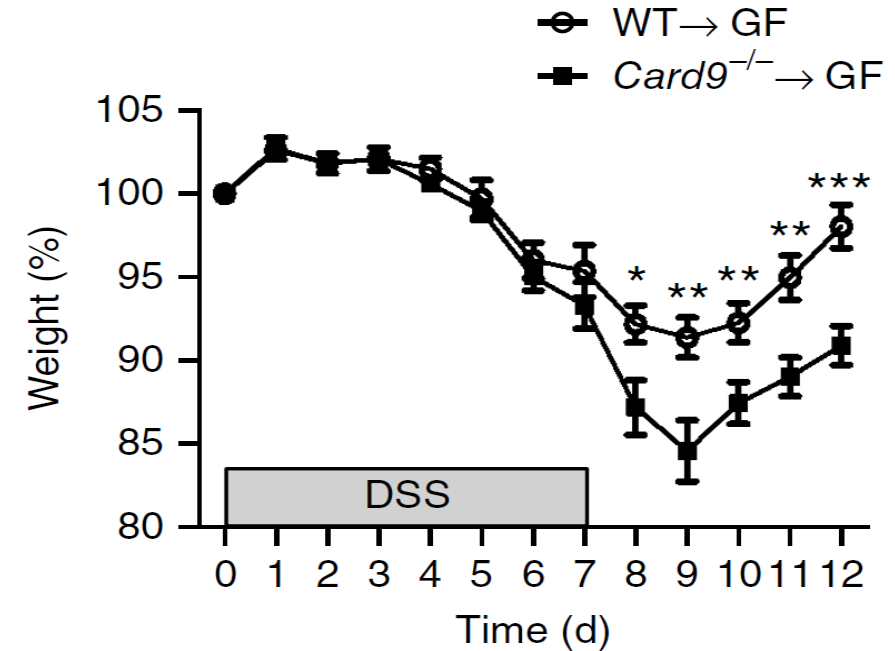
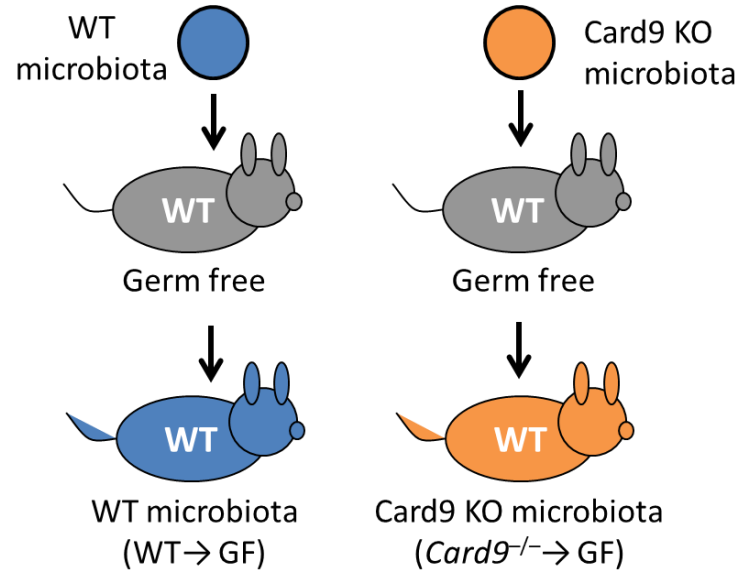
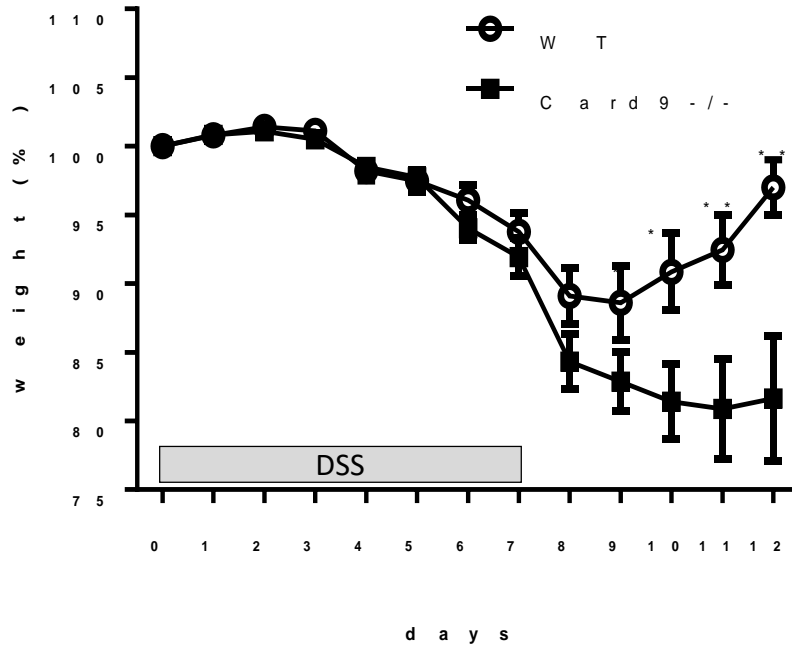


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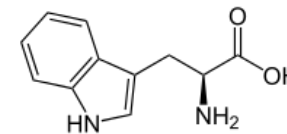
Susceptibility to colitis transferred by the gut microbiota

Card9 KO mice are more susceptible to DSS-induced colitis



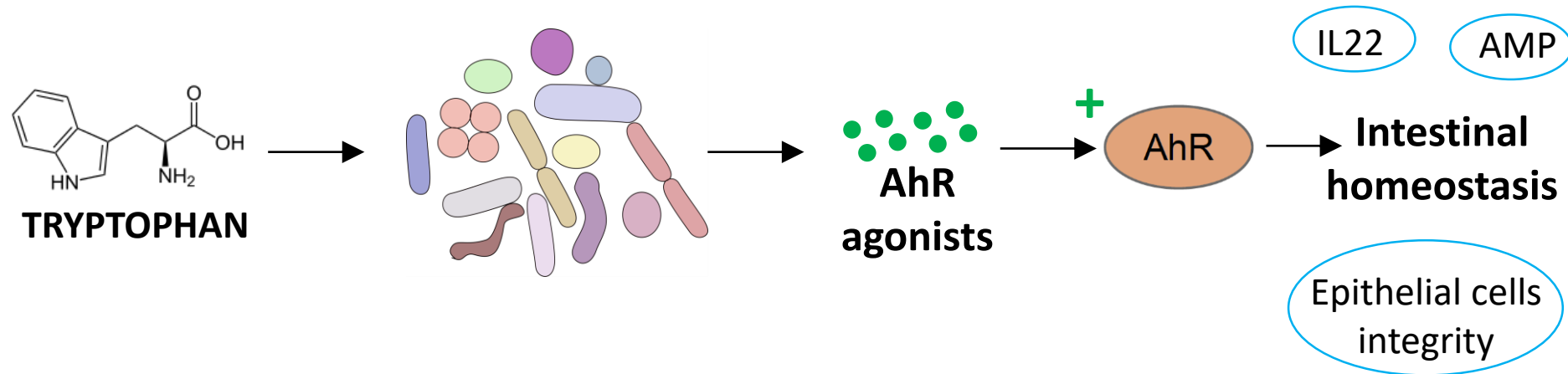
Susceptibility to colitis transferred by the gut microbiota

➔ Mechanism related to Tryptophan



Card9^{-/-} mice exhibits impaired tryptophan metabolism

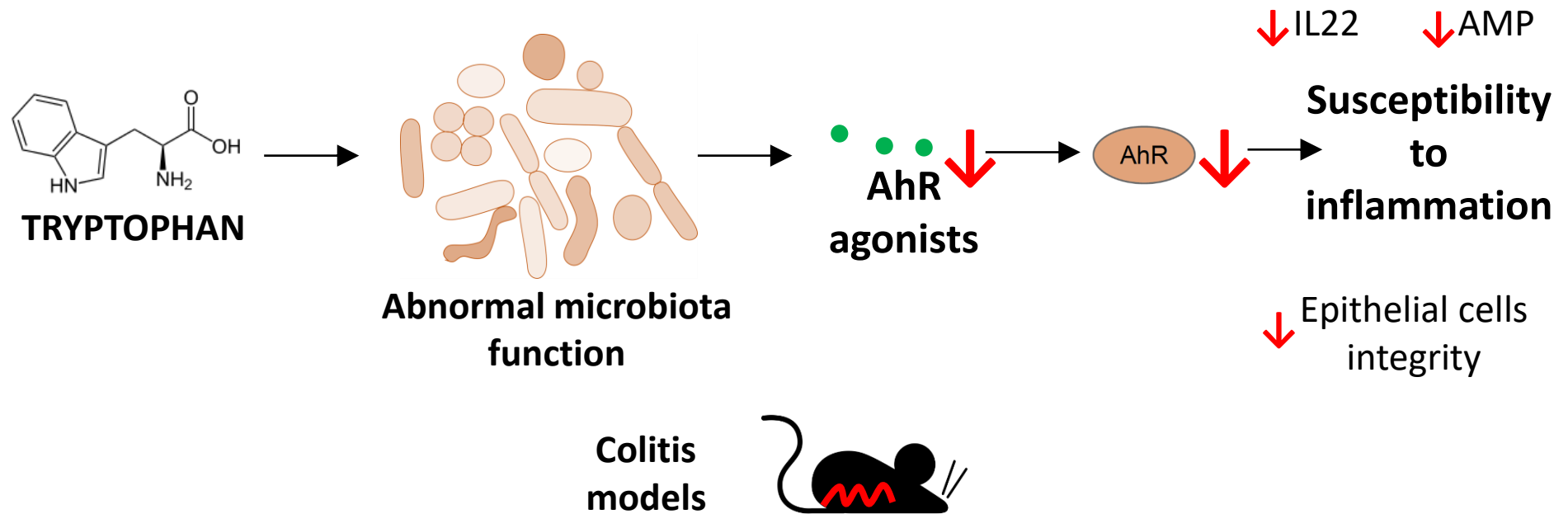
Key role of Microbiota-derived AhR agonists in intestinal homeostasis



Inflammatory bowel disease

Card9: IBD susceptibility gene

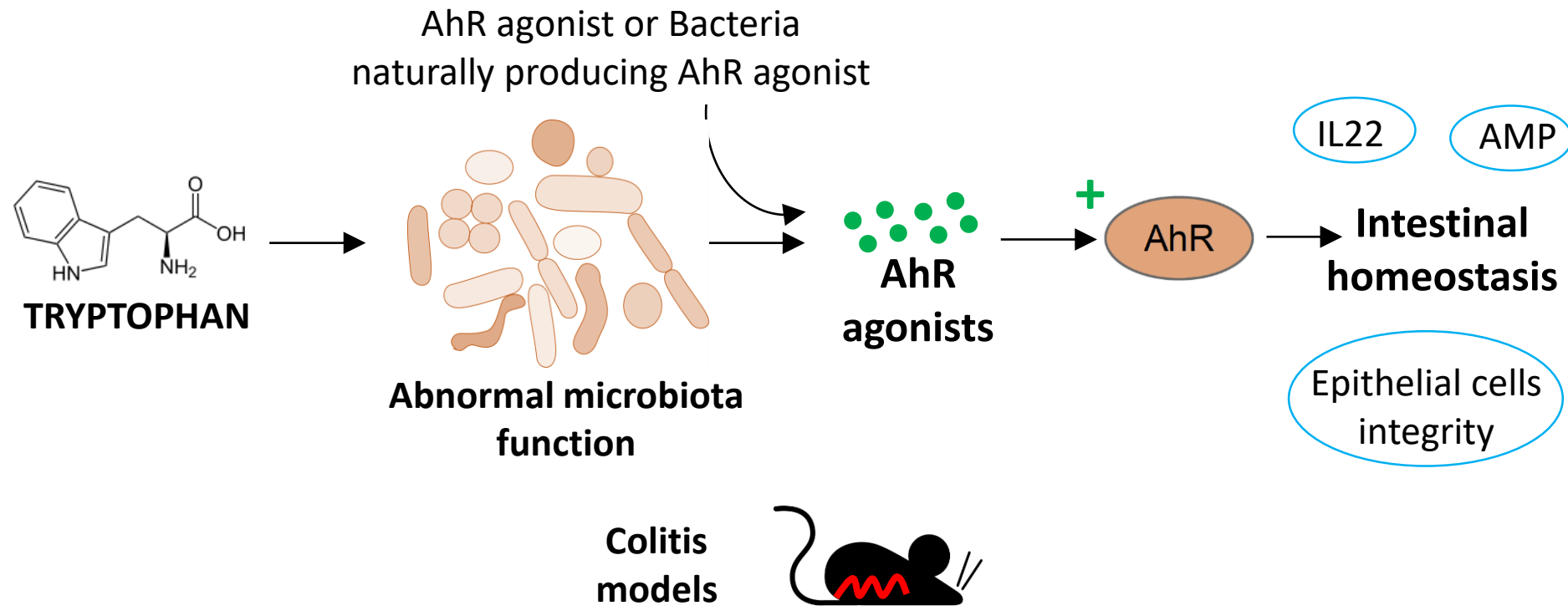
Card9^{-/-} mice



Inflammatory bowel disease

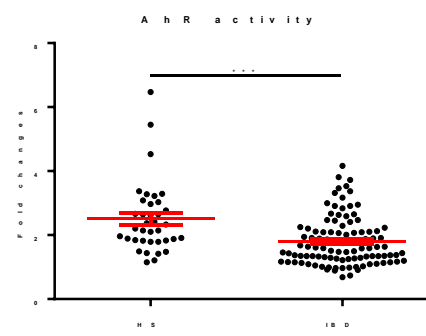
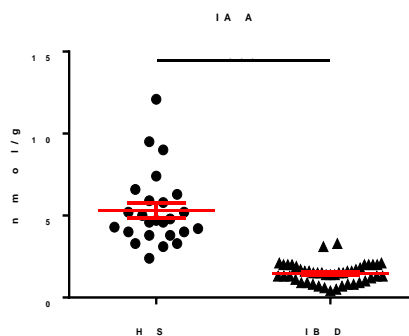
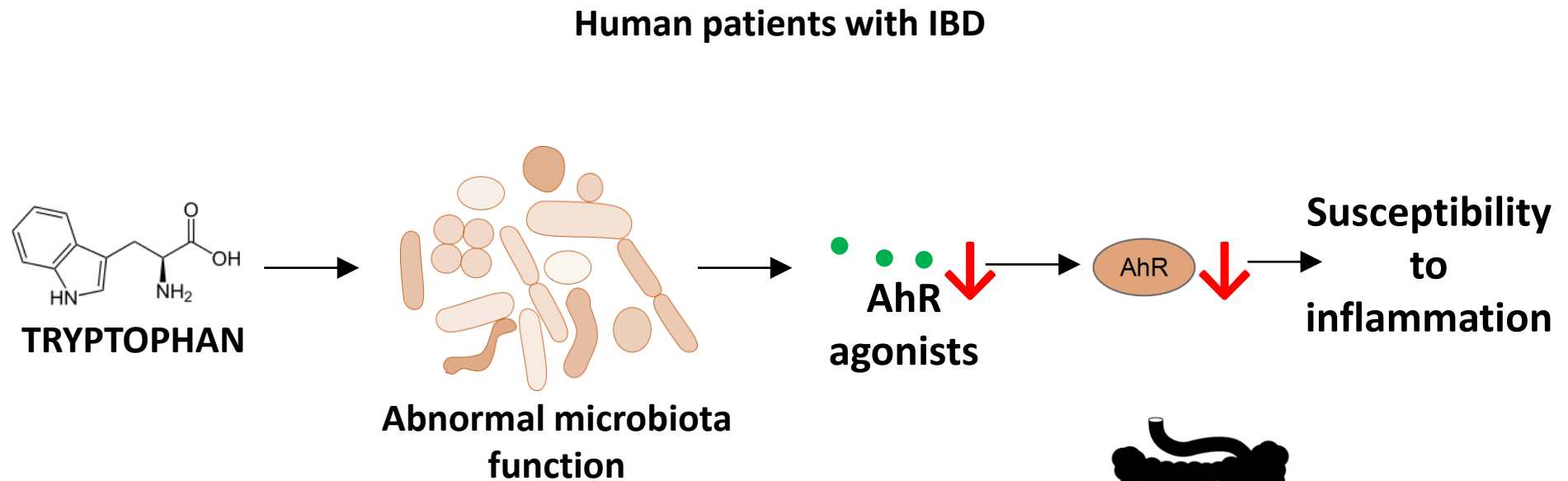
Card9: IBD susceptibility gene

Card9^{-/-} mice



Inflammatory bowel disease

Card9: IBD susceptibility gene

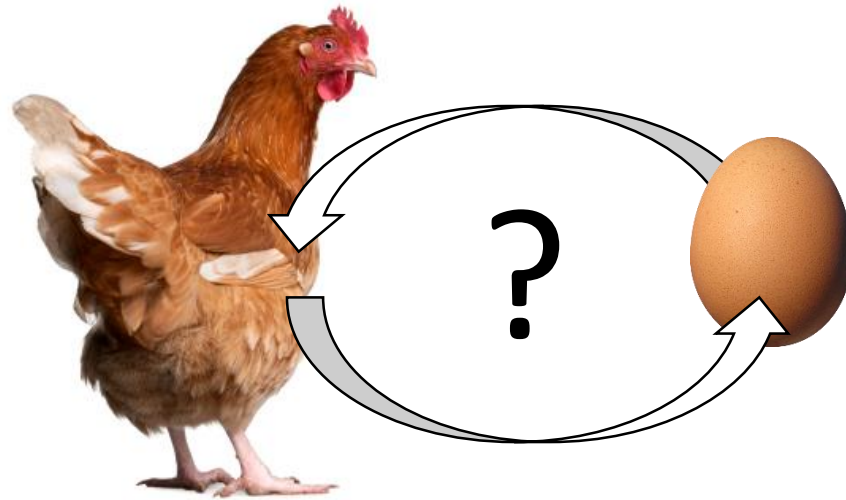


IBD



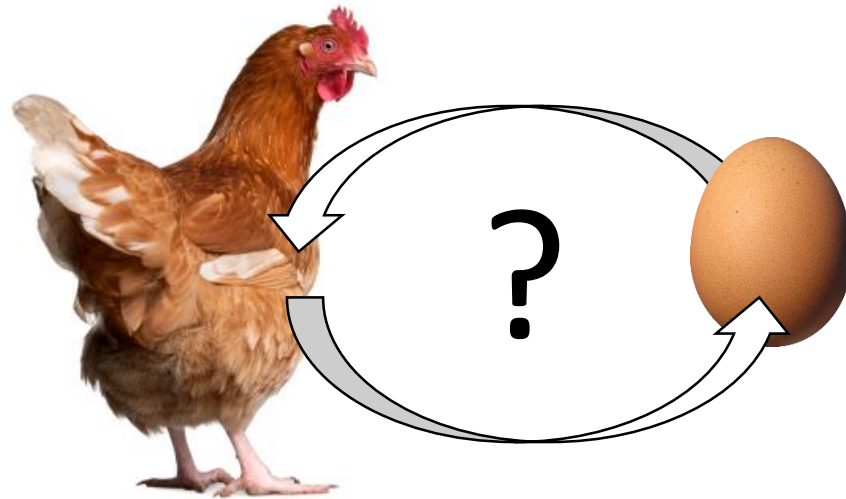
Conclusion 1

- Gut microbiota in IBD pathogenesis:
chicken or egg?



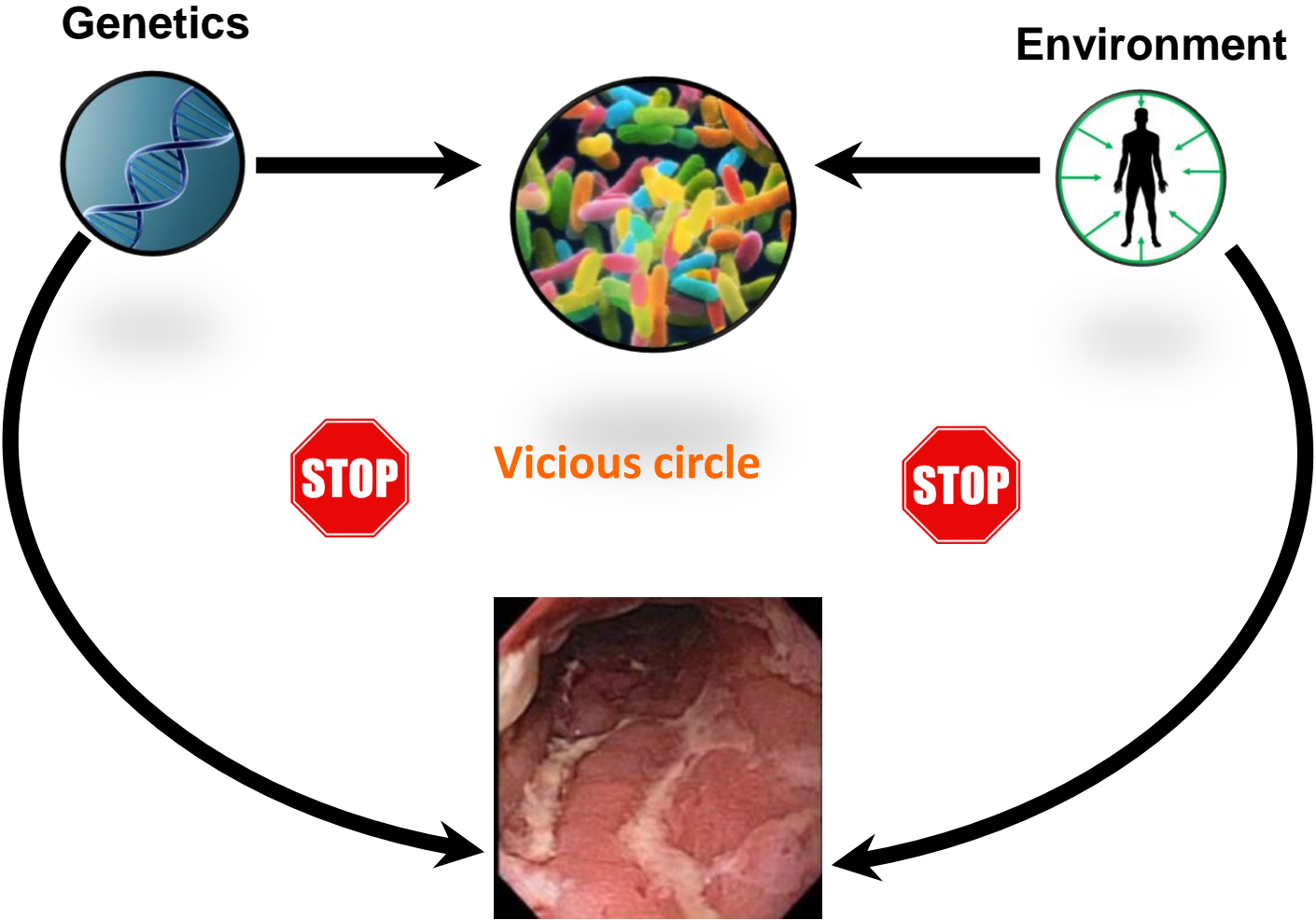
Conclusion 1

- Gut microbiota in IBD pathogenesis:
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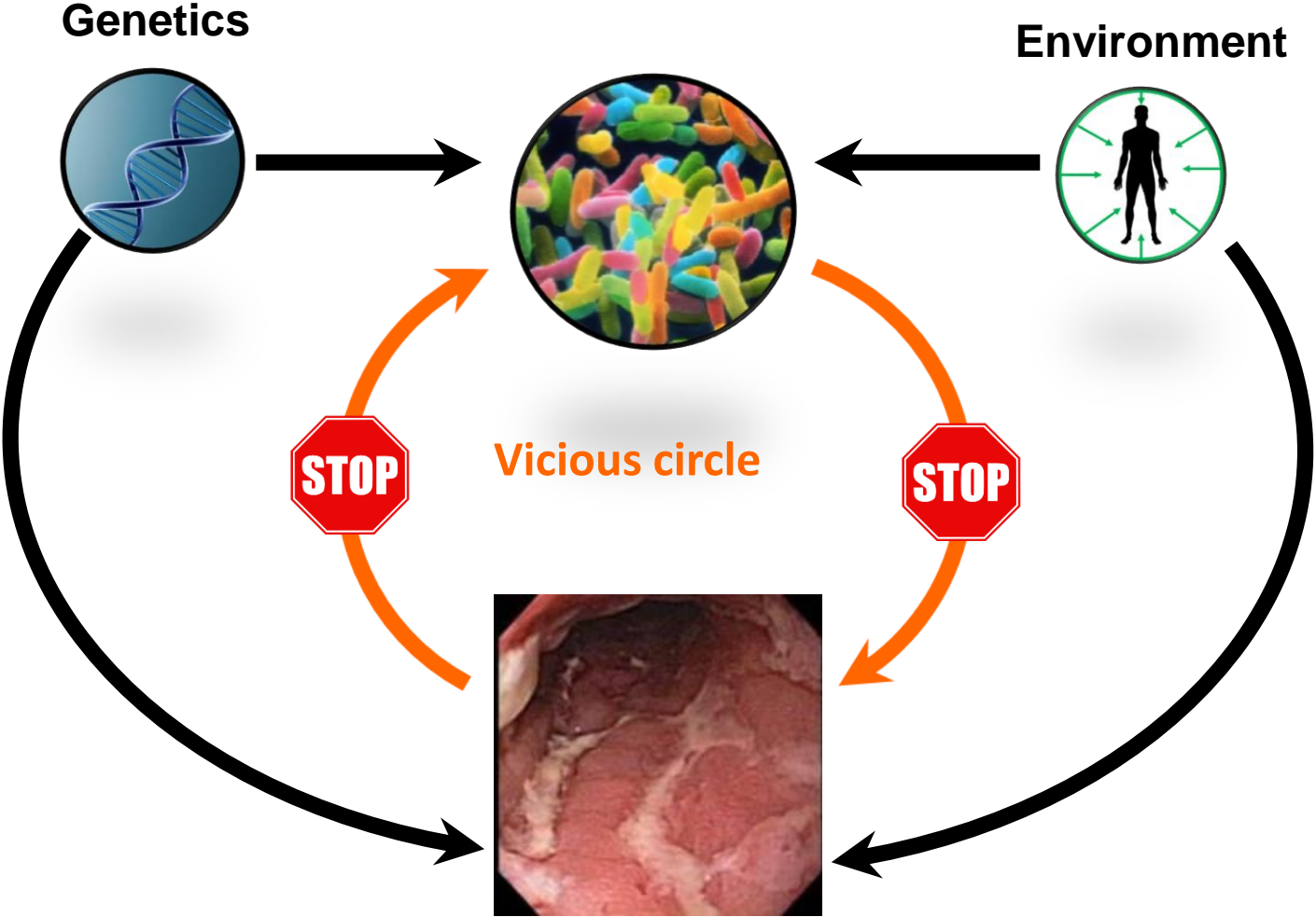


Both!

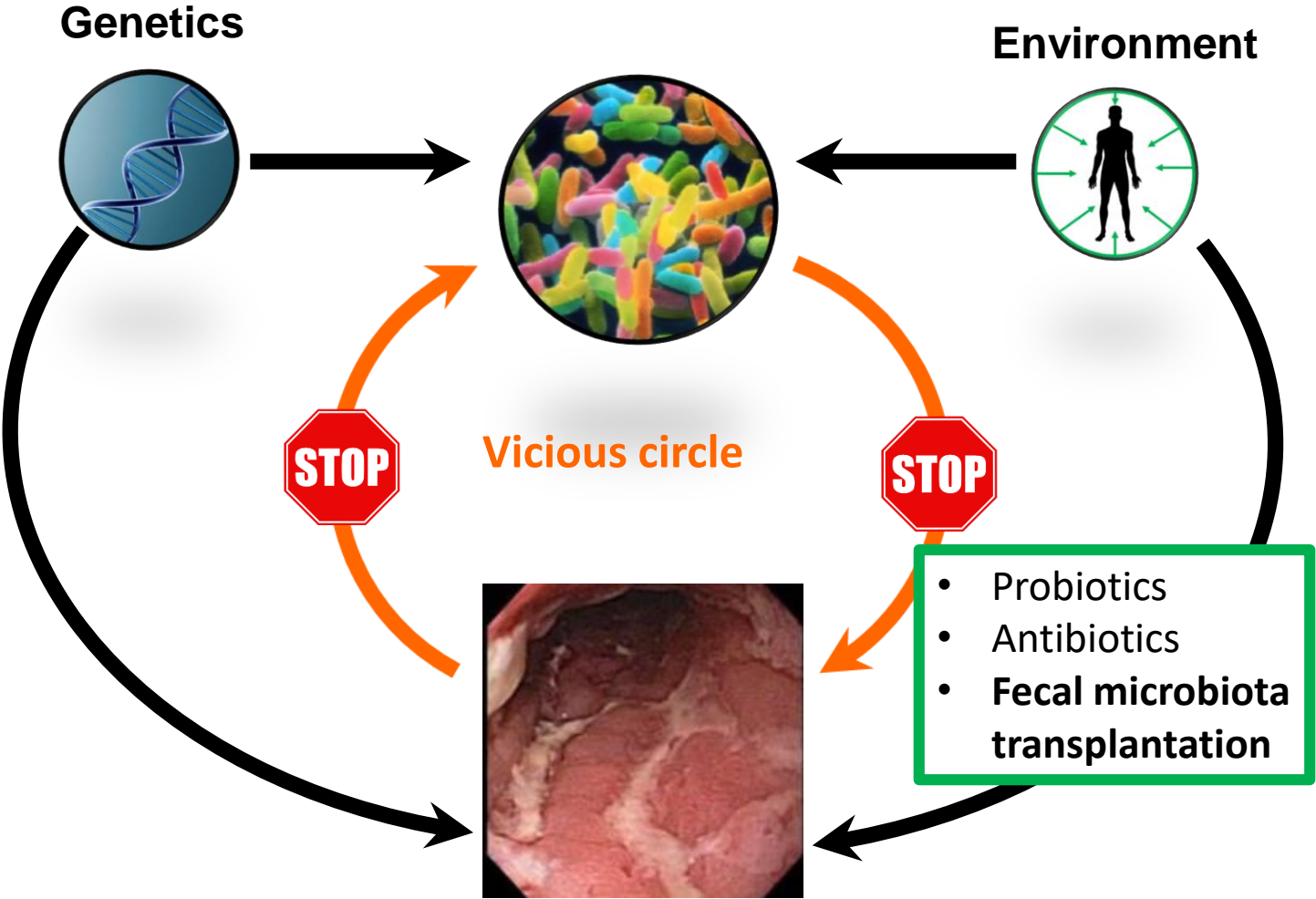
Conclusion 1



Conclusion 1

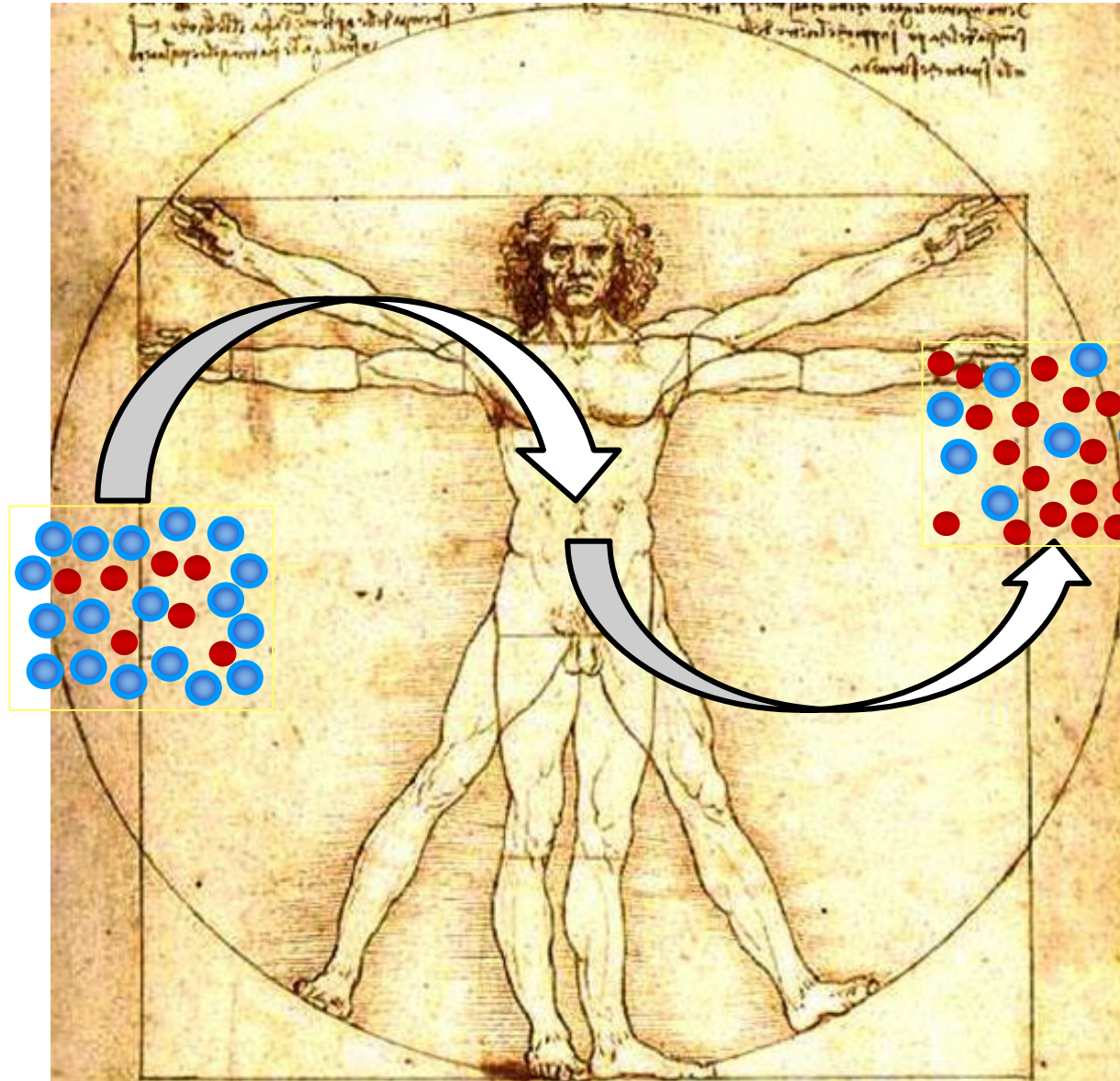


Conclusion 1



Fecal transplantation

Healthy
microbiota



Disease-associated
microbiota

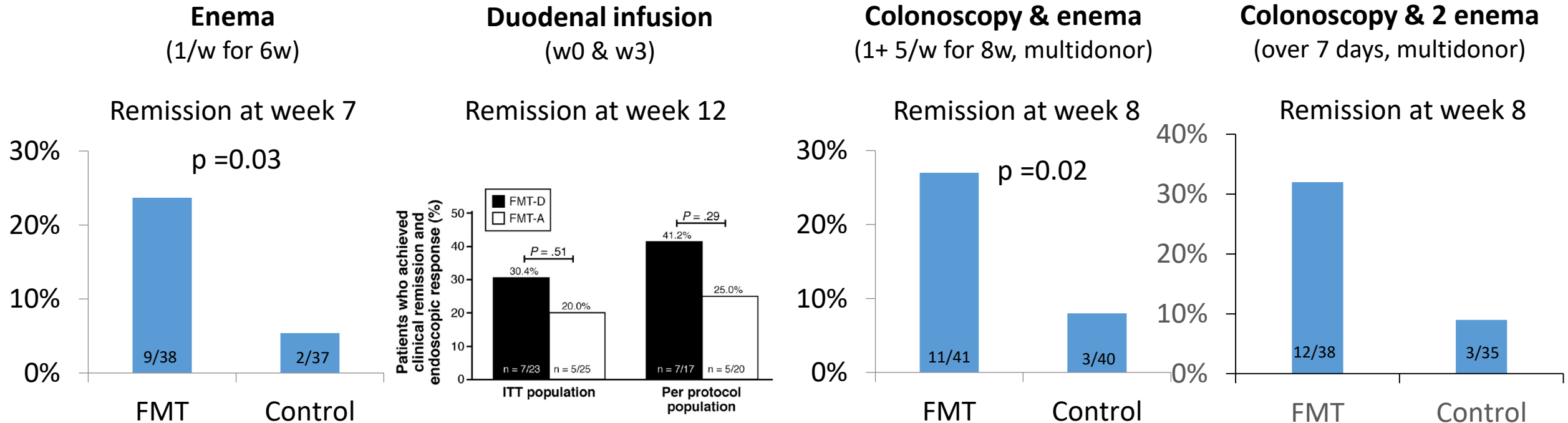
Randomised controlled trials

4 published studies in ulcerative colitis

All performed in active patients and with the aim to induce remission

Randomised controlled trials

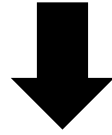
4 published studies in ulcerative colitis



- 3 of 4 trials positive, High heterogeneity
- Small *n*
- Effect size similar to early phase conventional molecules
- No maintenance data

No Randomized controlled trial in CD

No Randomized controlled trial in CD



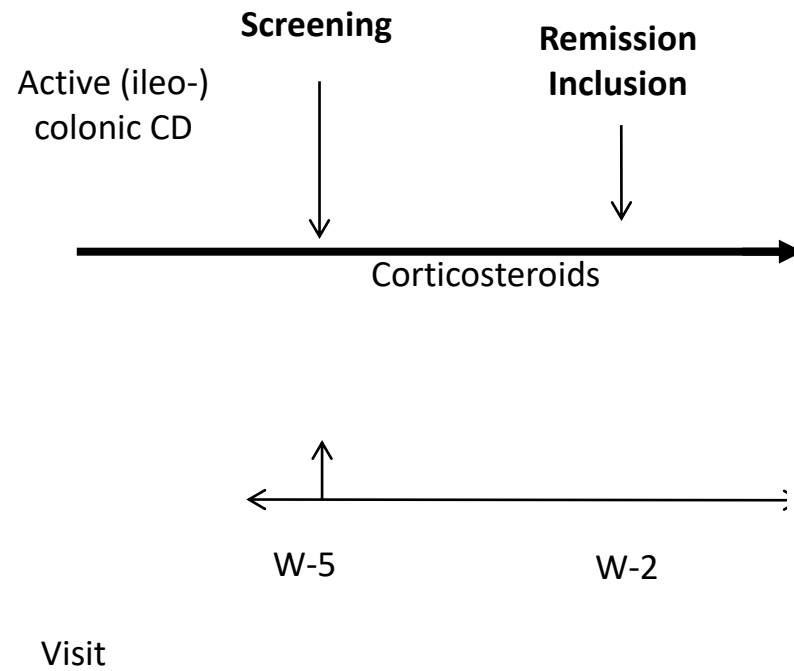
IMPACT-Crohn Study



Original concept and design:

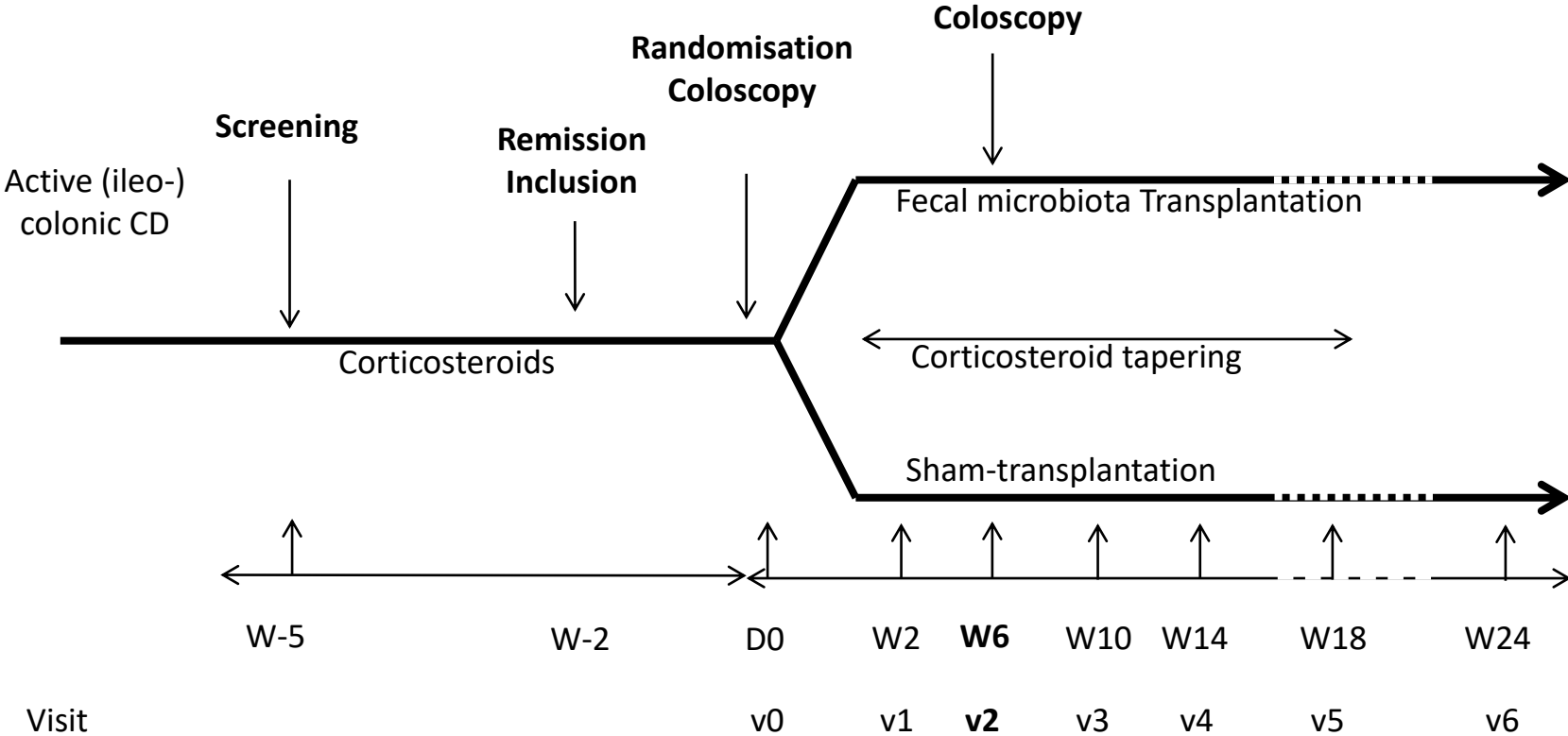
➔ Target both immune system and microbiota

IMPACT-Crohn Study



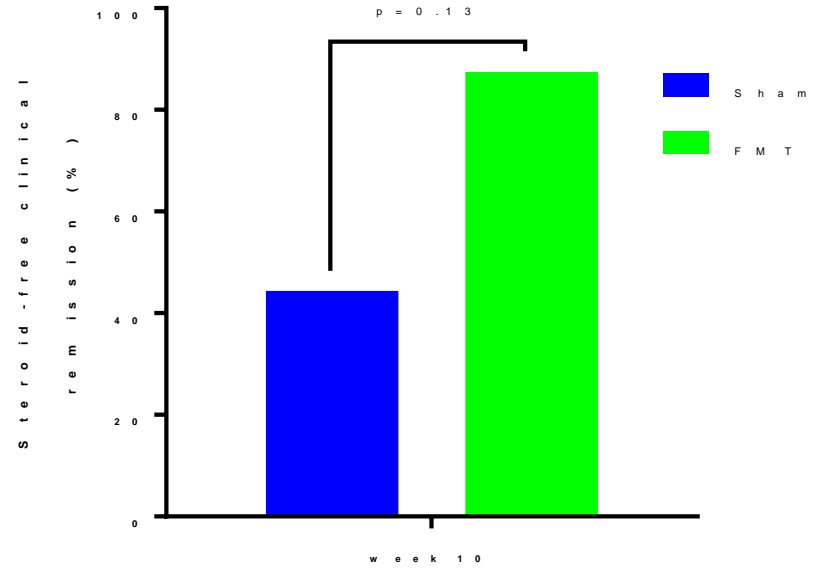
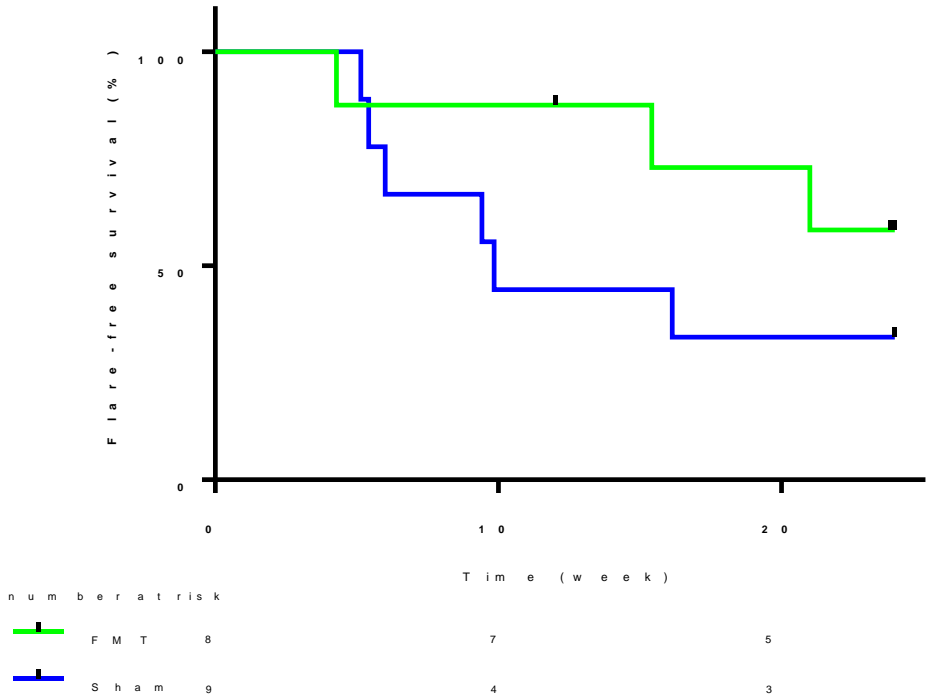
Pilot study, 9 patients /group

IMPACT-Crohn Study



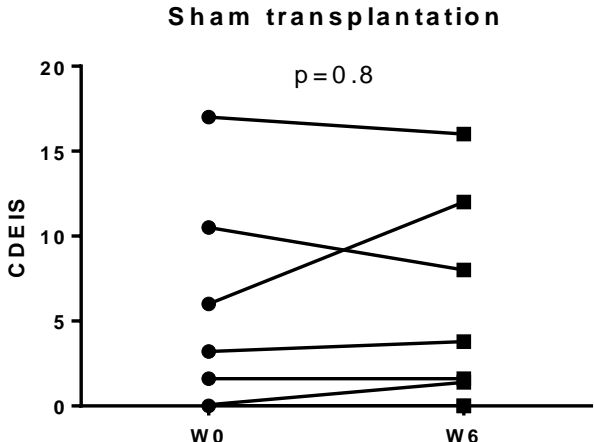
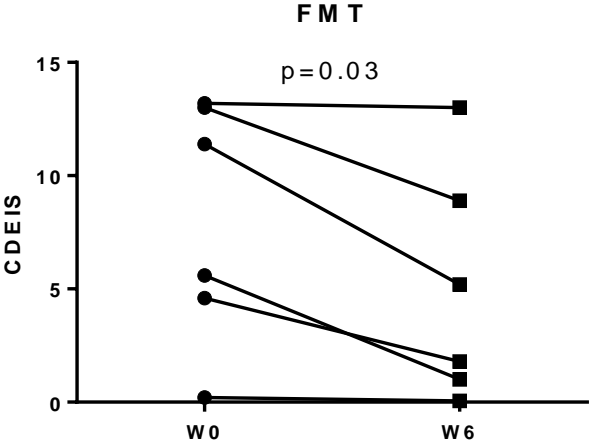
Pilot study, 9 patients /group

IMPACT-Crohn Study



IMPACT-Crohn Study

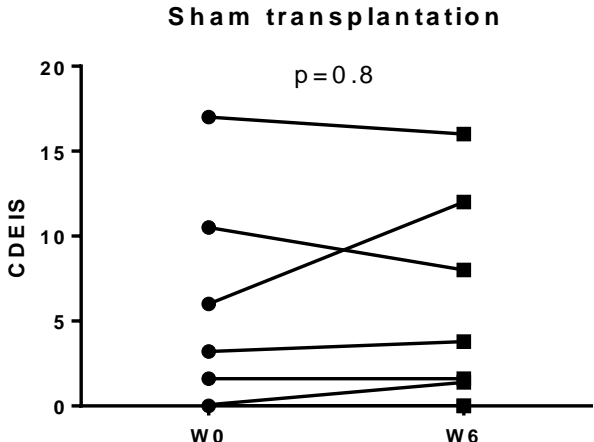
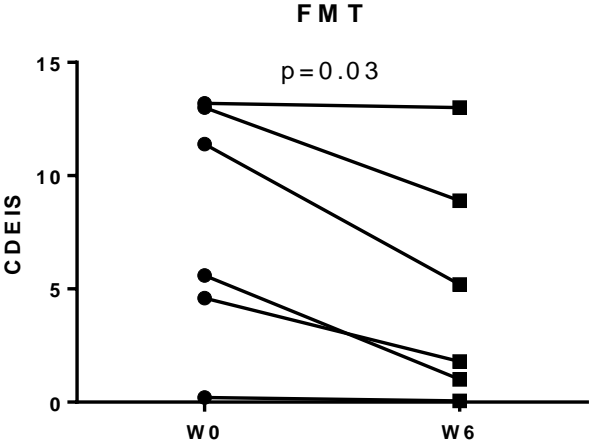
CDEIS



1 patient not evaluable in each group (bowel cleansing problem)

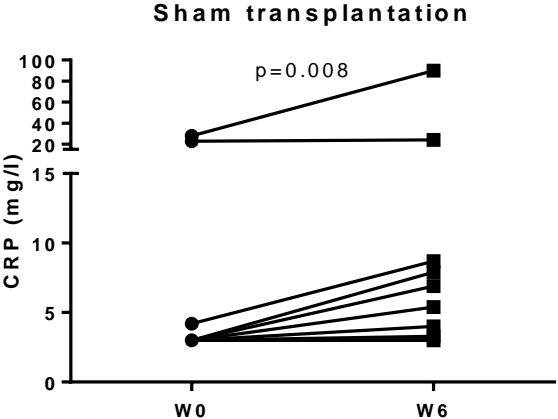
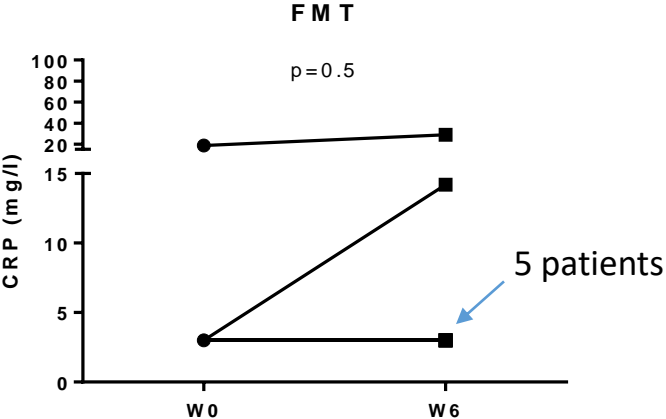
IMPACT-Crohn Study

CDEIS



1 patient not evaluable in each group (bowel cleansing problem)

CRP

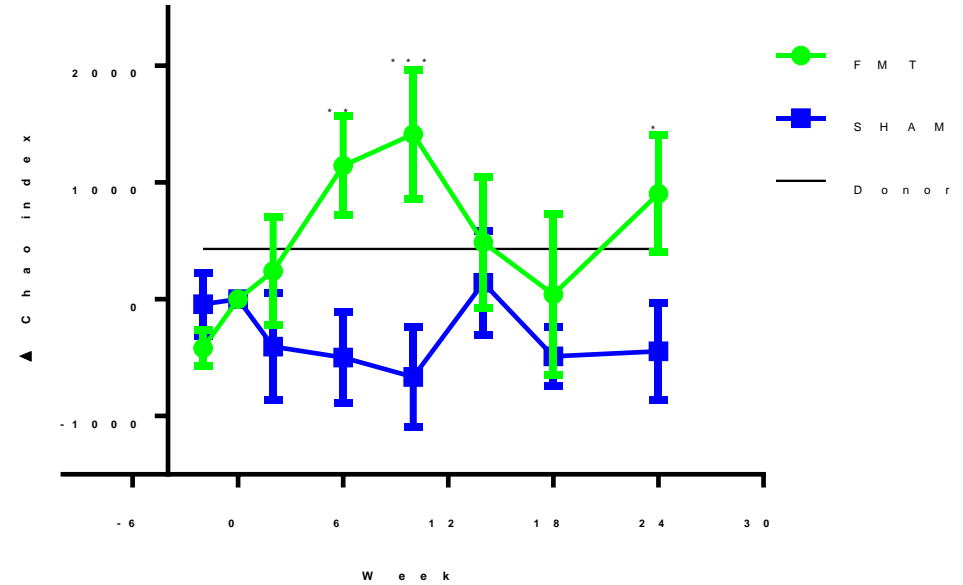
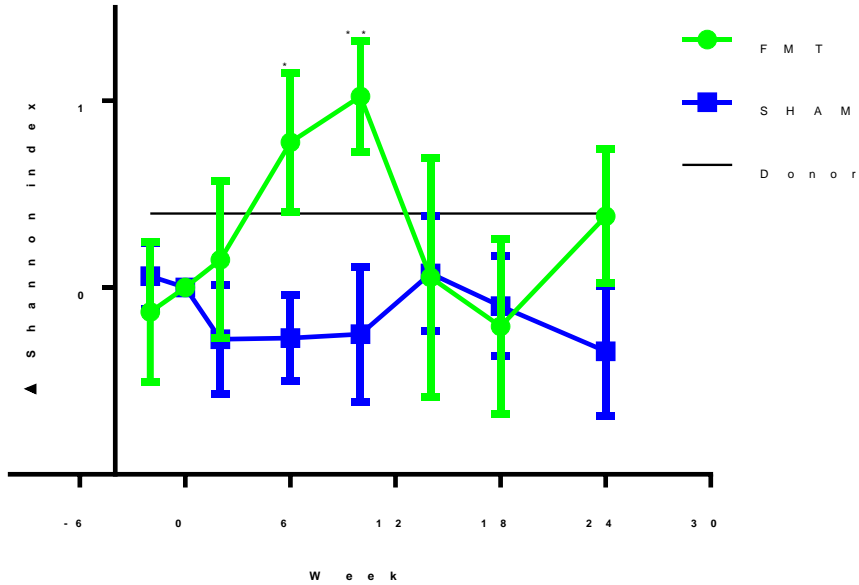


1 patient not evaluable (no sample available)

Paired Wilcoxon test

IMPACT-Crohn Study

Alpha diversity

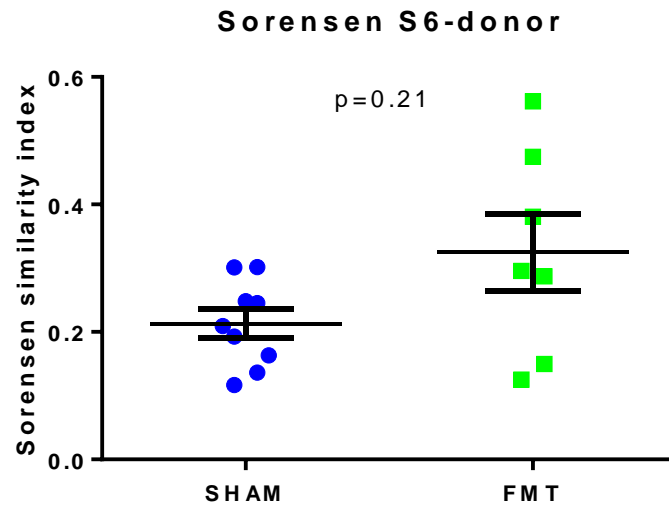


Anova with corrections for multiple comparisons

For donor, delta was calculated with mean of FMT group at D0

IMPACT-Crohn Study

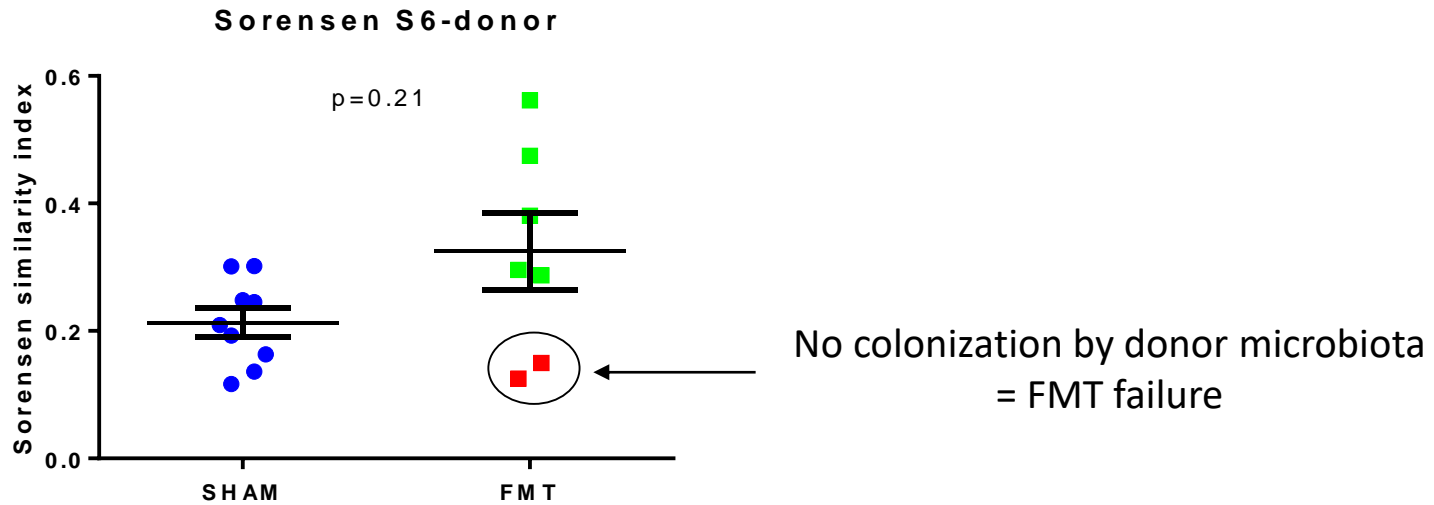
Microbiota similarity between donor and recipient at 6 weeks



For SHAM group, the mean of the Sorensen with each donor is indicated

IMPACT-Crohn Study

Microbiota similarity between donor and recipient at 6 weeks

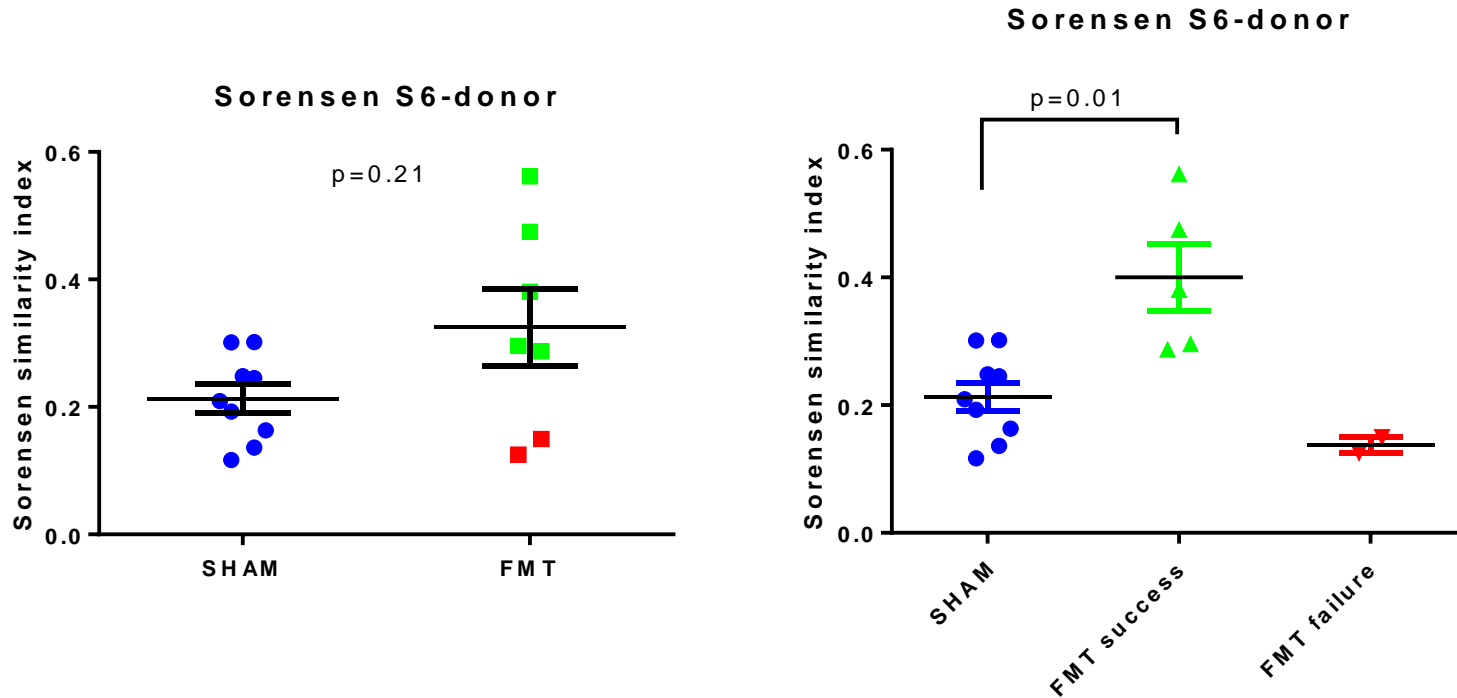


➔ 2 types of microbiota profile following FMT

For SHAM group, the mean of the Sorensen with each donor is indicated

IMPACT-Crohn Study

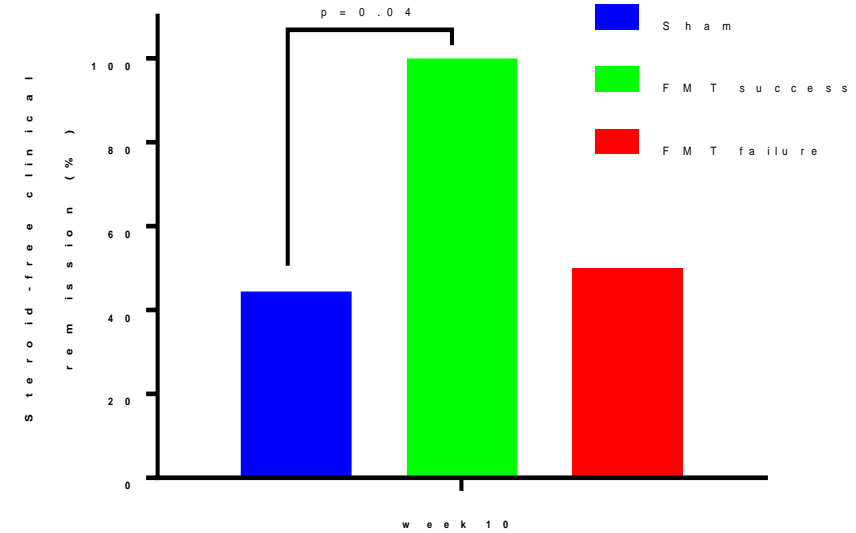
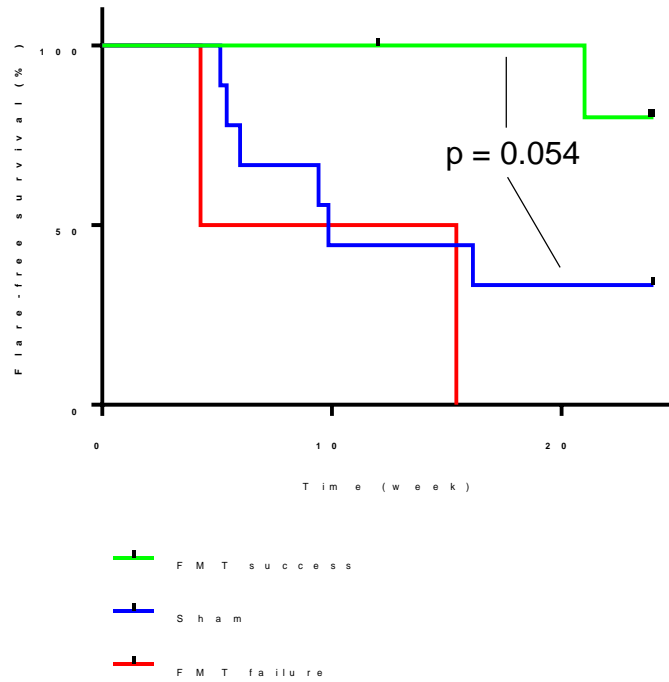
Microbiota similarity between donor and recipient at 6 weeks



➔ 2 types of microbiota profile following FMT

For SHAM group, the mean of the Sorensen with each donor is indicated

IMPACT-Crohn Study



➔ Colonization by donor microbiota is associated with maintenance of remission in CD.

Correlation between IBD activity and Trp metabolites

Randomized controlled trial or fecal
microbiota transplantation in CD

IMPACT-Crohn Study



Correlation between IBD activity and Trp metabolites

Randomized controlled trial or fecal
microbiota transplantation in CD

IMPACT-Crohn Study



Stool and serum samples

- Targeted metabolomics analysis for Trp metabolites
- Pairwise correlations with clinical and biological marker of disease activity

Correlation between IBD activity and Trp metabolites

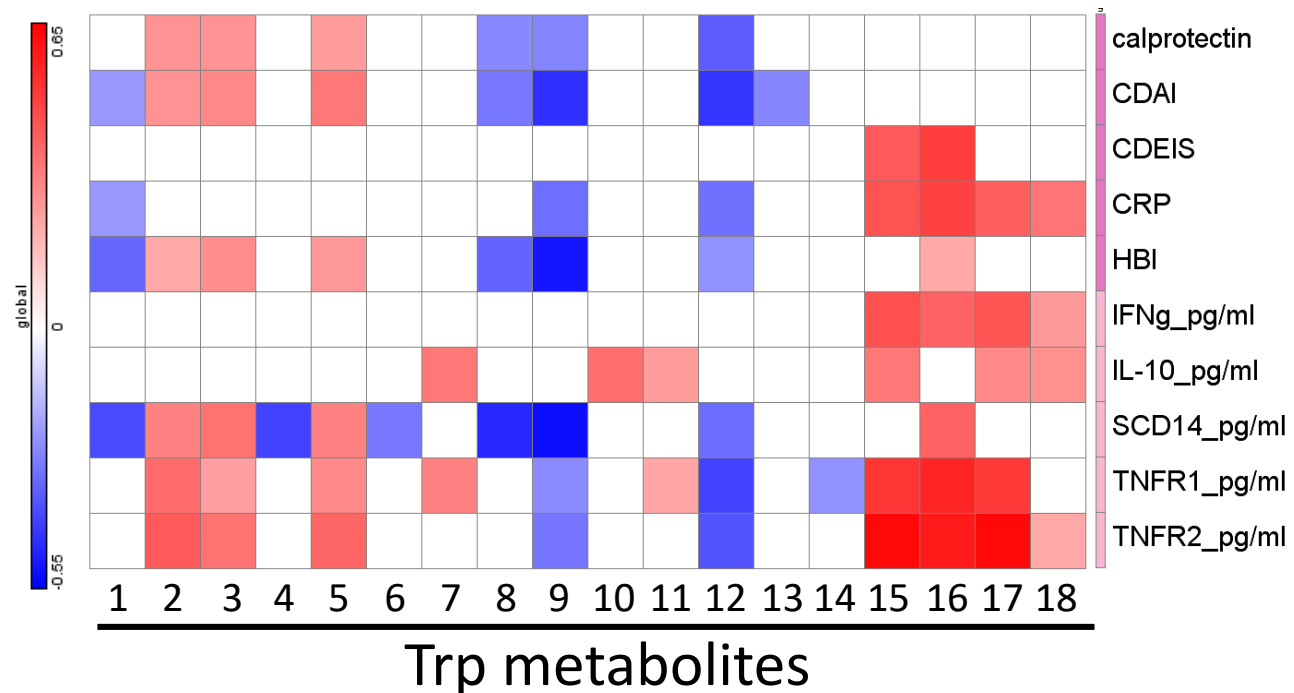
Randomized controlled trial or fecal microbiota transplantation in CD

IMPACT-Crohn Study



Stool and serum samples

- Targeted metabolomics analysis for Trp metabolites
- Pairwise correlations with clinical and biological marker of disease activity



Spearman test (only significant correlations with p value <0.05 and p < 0.1 after FDR correction are displayed).

Serum CK

Unpublished data

Correlation between IBD activity and Trp metabolites

Randomized controlled trial or fecal microbiota transplantation in CD

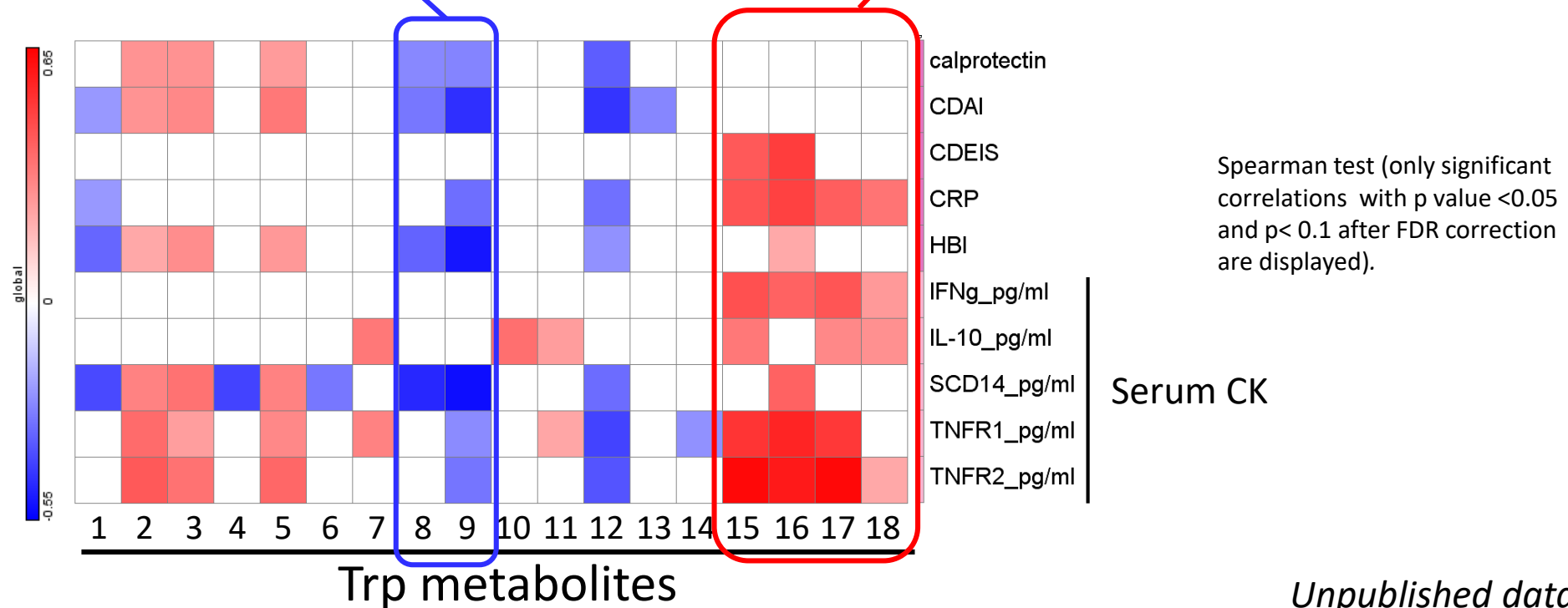
IMPACT-Crohn Study

Metabolites negatively correlate with disease activity

Metabolites positively correlate with disease activity

→ Targeted metabolomics analysis for Trp metabolites

→ Pairwise correlations with clinical and biological marker of disease activity



Correlation between IBD activity and Trp metabolites

Randomized controlled trial
microbiota transplantation

IMPACT-Crohn Study

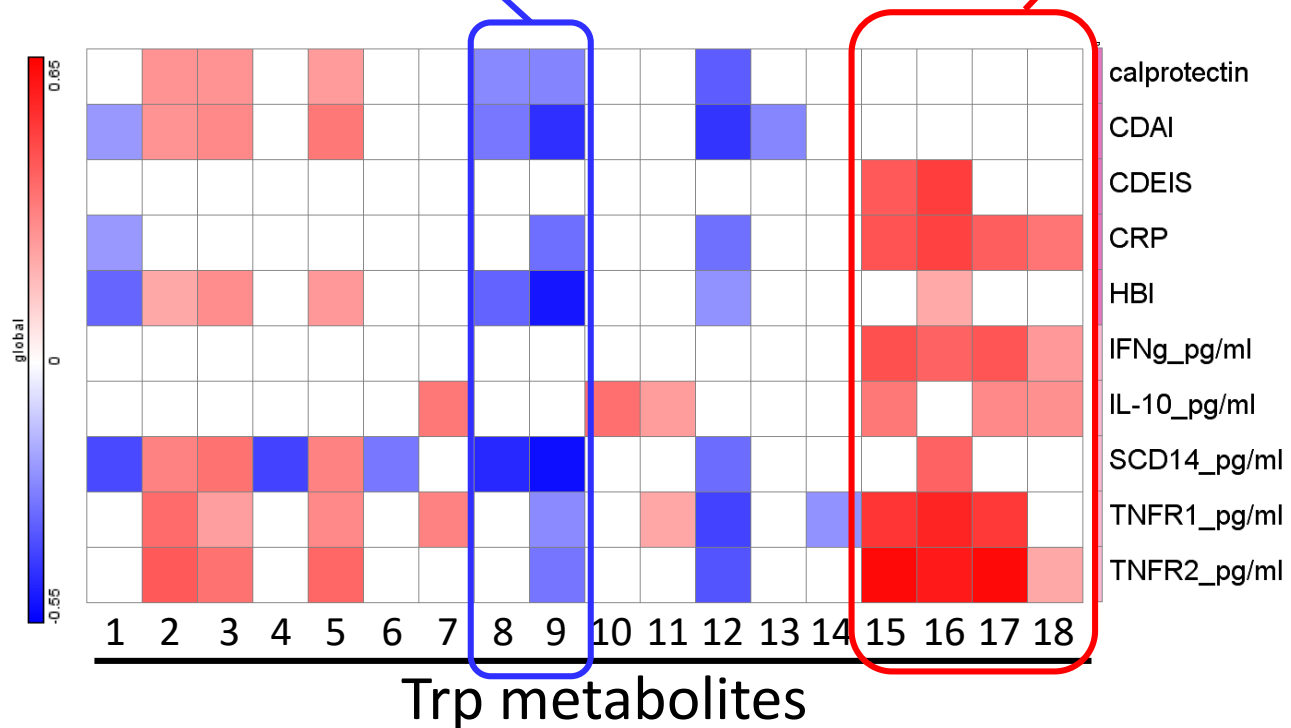
Only secondary to inflammation or actors in the inflammatory process?

Metabolites negatively correlate with disease activity

Metabolites positively correlate with disease activity

→ targeted metabolomics analysis for Trp metabolites

→ Pairwise correlations with clinical and biological marker of disease activity



Spearman test (only significant correlations with p value <0.05 and p < 0.1 after FDR correction are displayed).



Serum CK

Unpublished data

Correlation between IBD activity and Trp metabolites

In mice submitted to DSS-induced colitis:

→ Administration of:

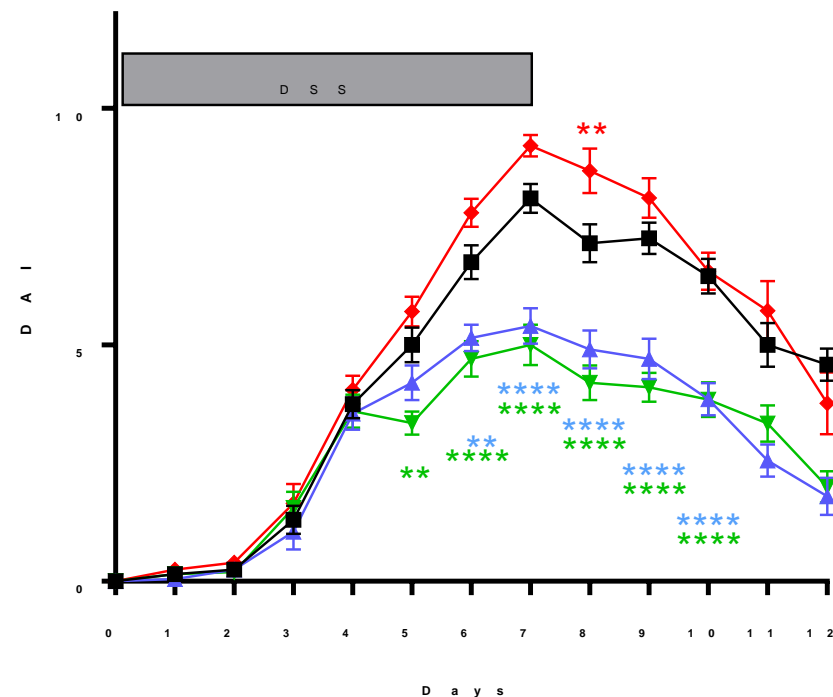
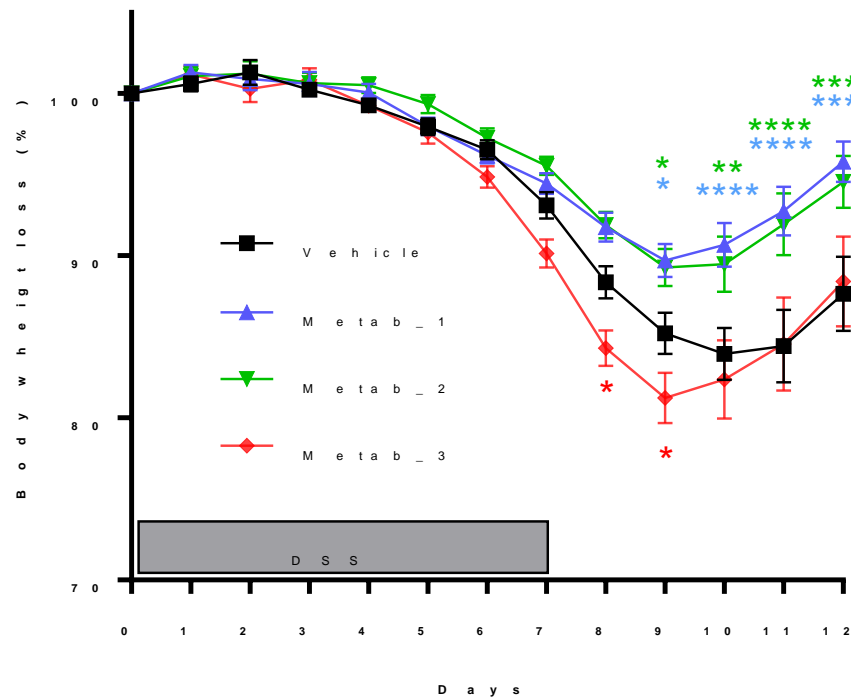
- 2 metabolites that correlate negatively with inflammation 
- 1 metabolite that correlate positively with inflammation 

Correlation between IBD activity and Trp metabolites

In mice submitted to DSS-induced colitis:

➔ Administration of:

- 2 metabolites that correlate negatively with inflammation ▲ ▼
- 1 metabolite that correlate positively with inflammation ◆



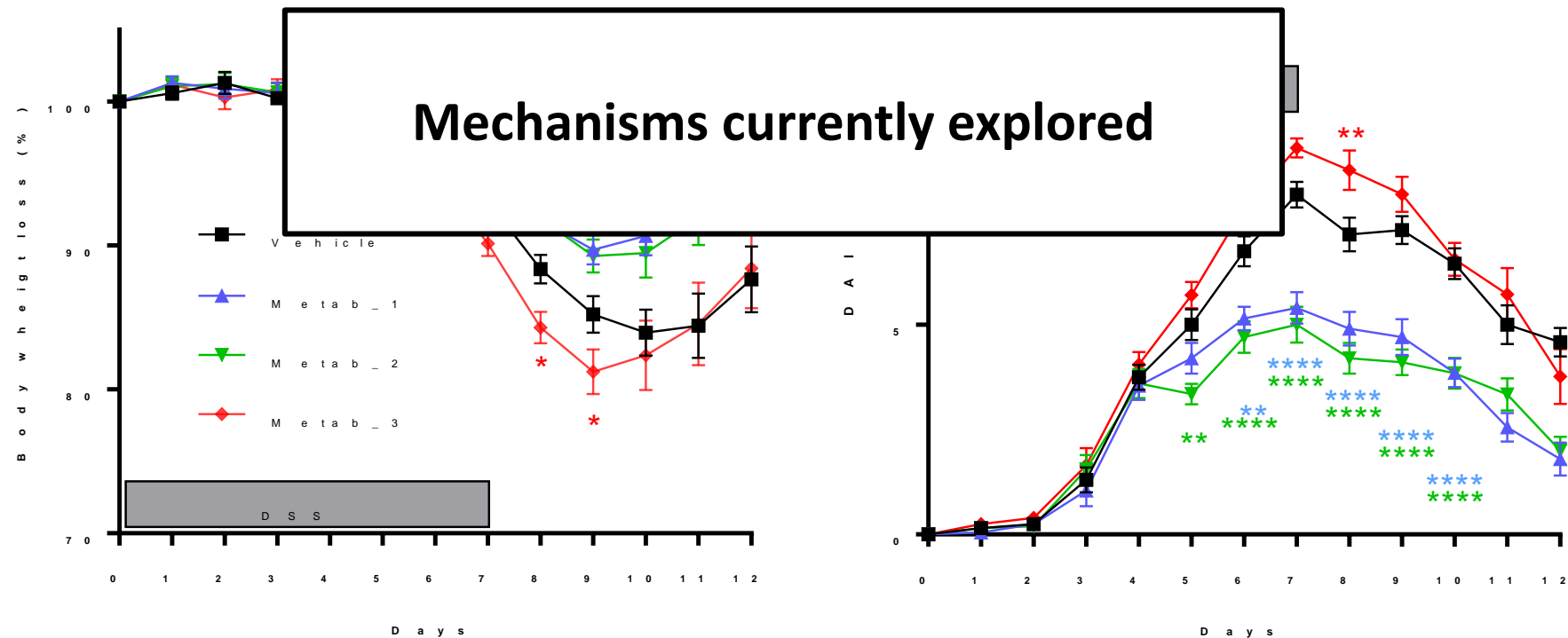
Unpublished data

Correlation between IBD activity and Trp metabolites

In mice submitted to DSS-induced colitis:

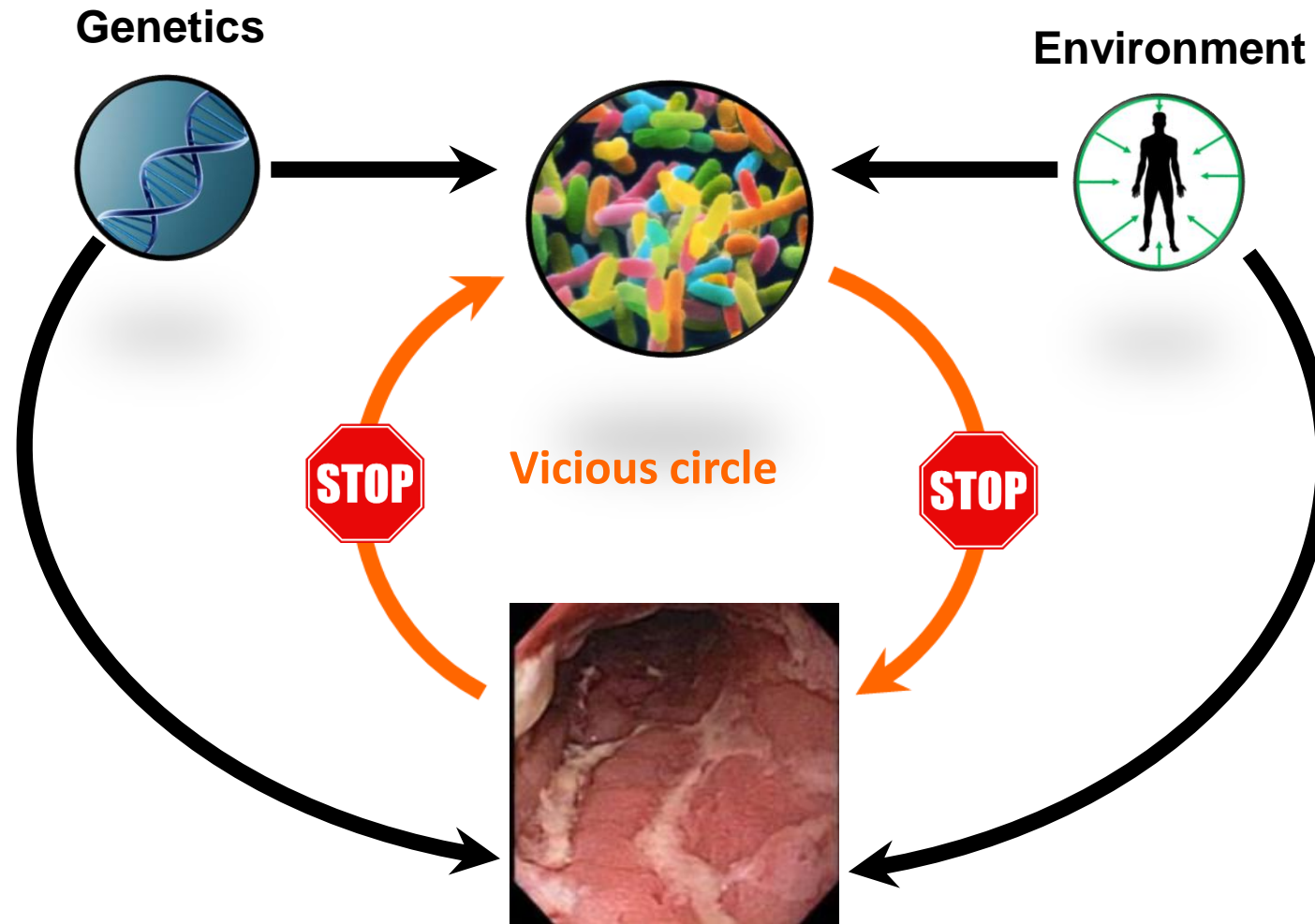
→ Administration of:

- 2 metabolites that correlate negatively with inflammation ▲ ▼
- 1 metabolite that correlate positively with inflammation ◆

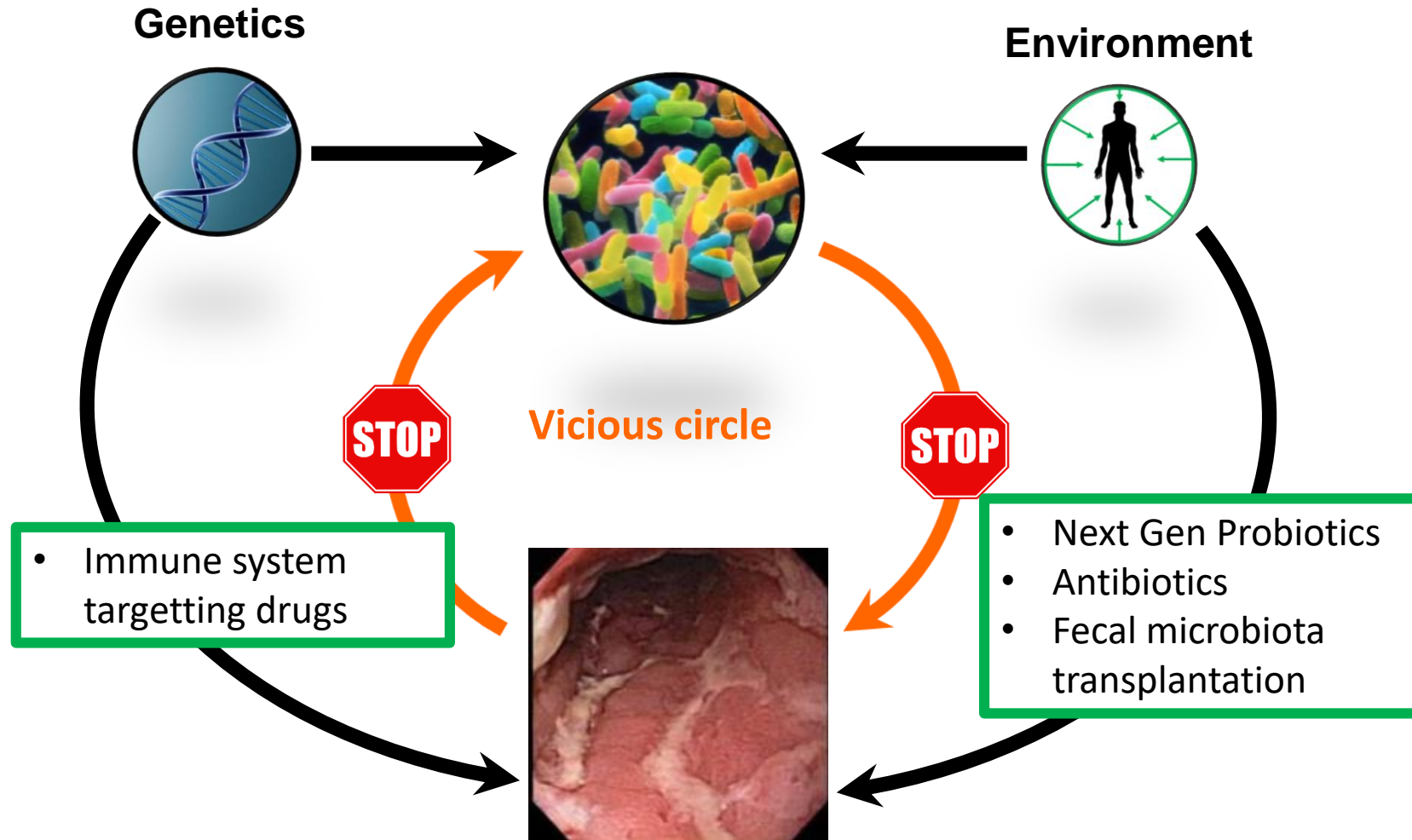


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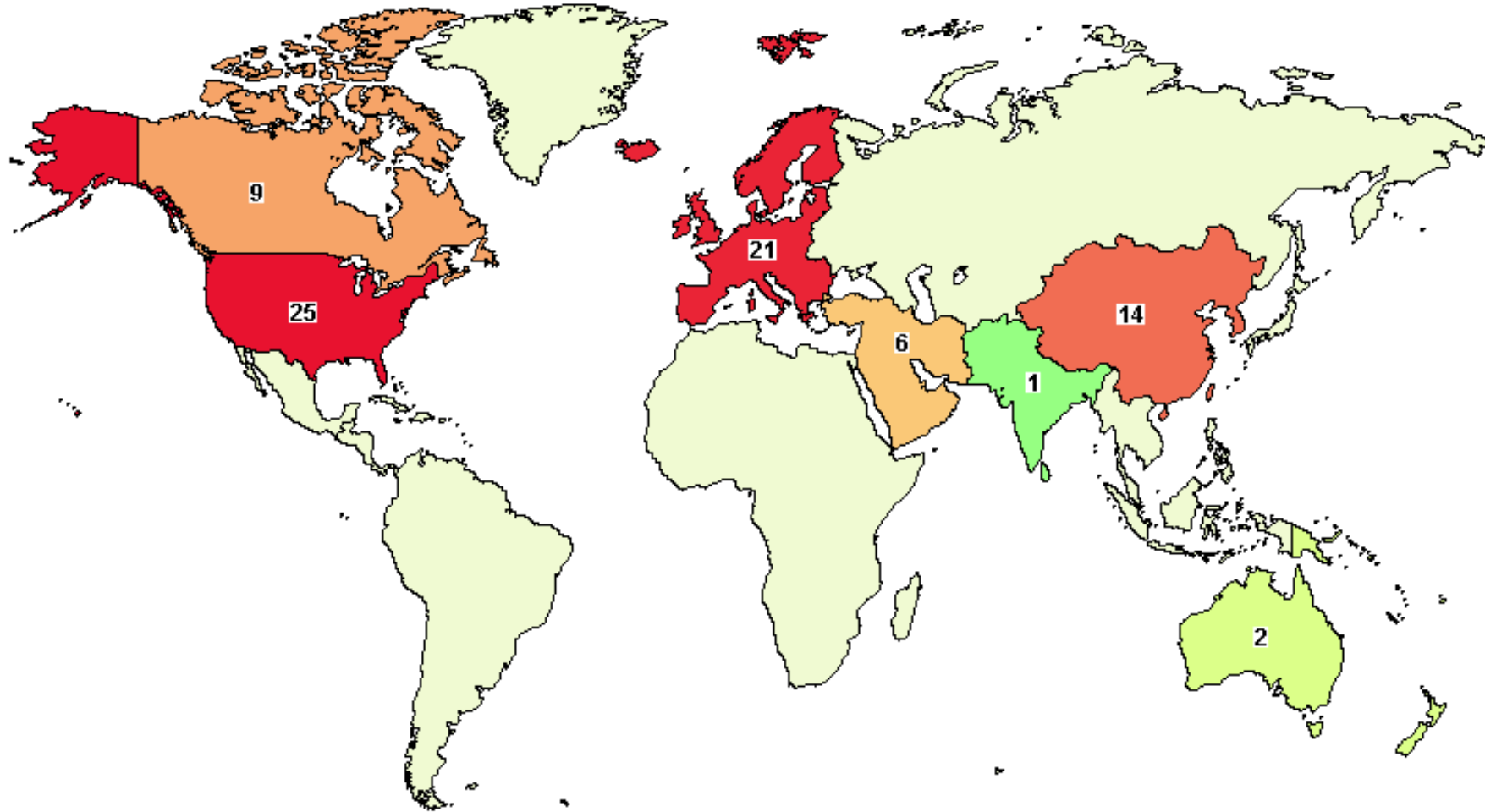
Conclusion



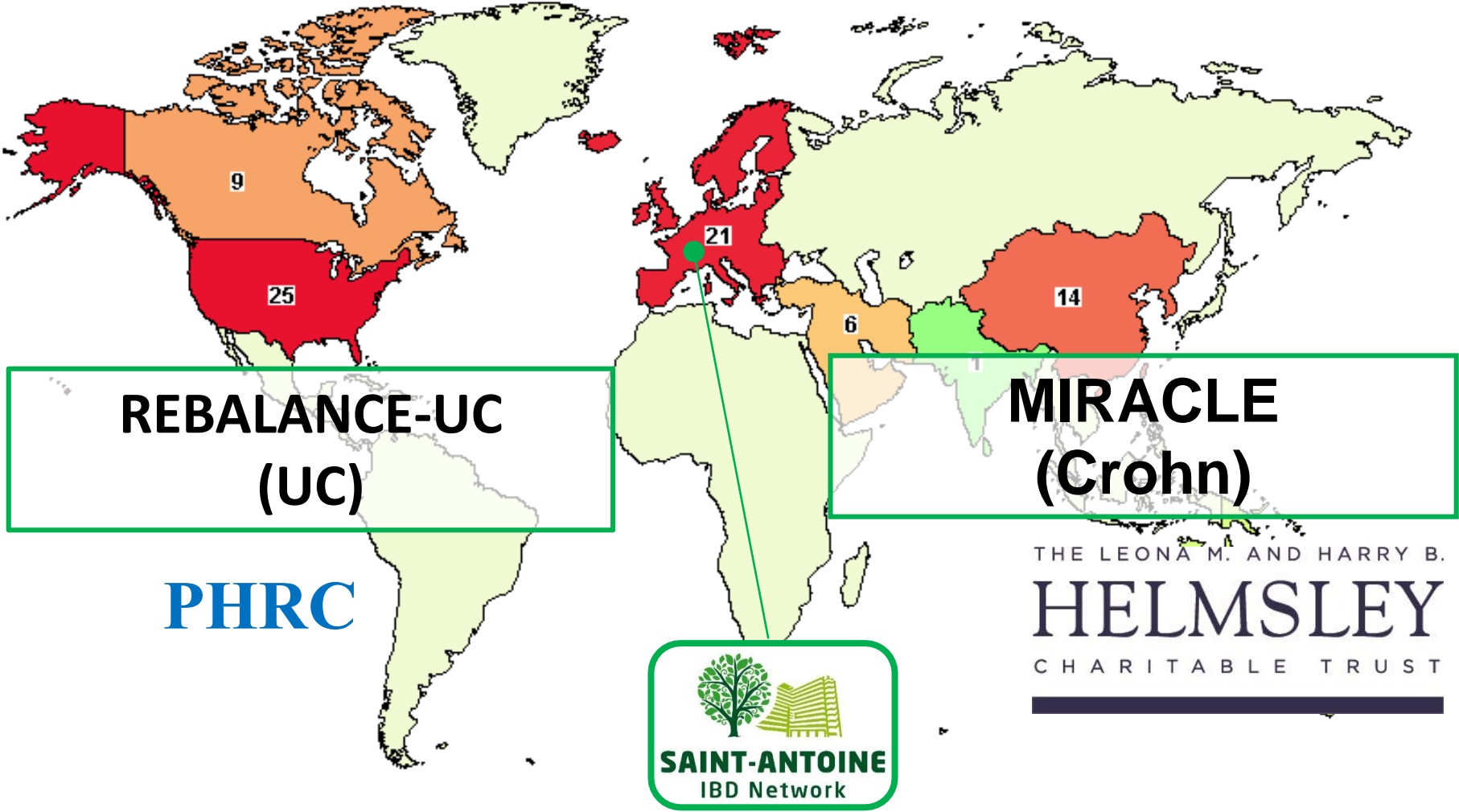
Conclusion



FMT studies in IBD

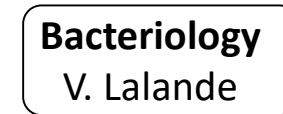


FMT studies in IBD



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H Sokol	A Bourrier
P Seksik	C Landman
J Kirchgesner	C Martineau
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 RJ Xavier Broad /Harvard
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N Rolhion	ML Michel
S Touch	G Da Costa
A Lavelle	A Magniez
M Straub	J Planchais
L Dupraz	J Glodt
C Oeuvray	A Agus
M Modoux	C Michaudel
C Danne	



P Langella

