top ten
in gastroenterologia
10^ EDIZIONE

8 e 9 MARZO 2019
BERGAMO
HOTEL EXCELSIOR SAN MARCO
Piazza della Repubblica, 6

Responsabile Scientifico: Fabio Pace

Microbiota e IBD
Fatti e suggestioni

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Gut microbiota is the main responsible of the inter-individual differences among humans

3.300.000 Vs 22.000

Microbial genome (microbiome) Vs human genome

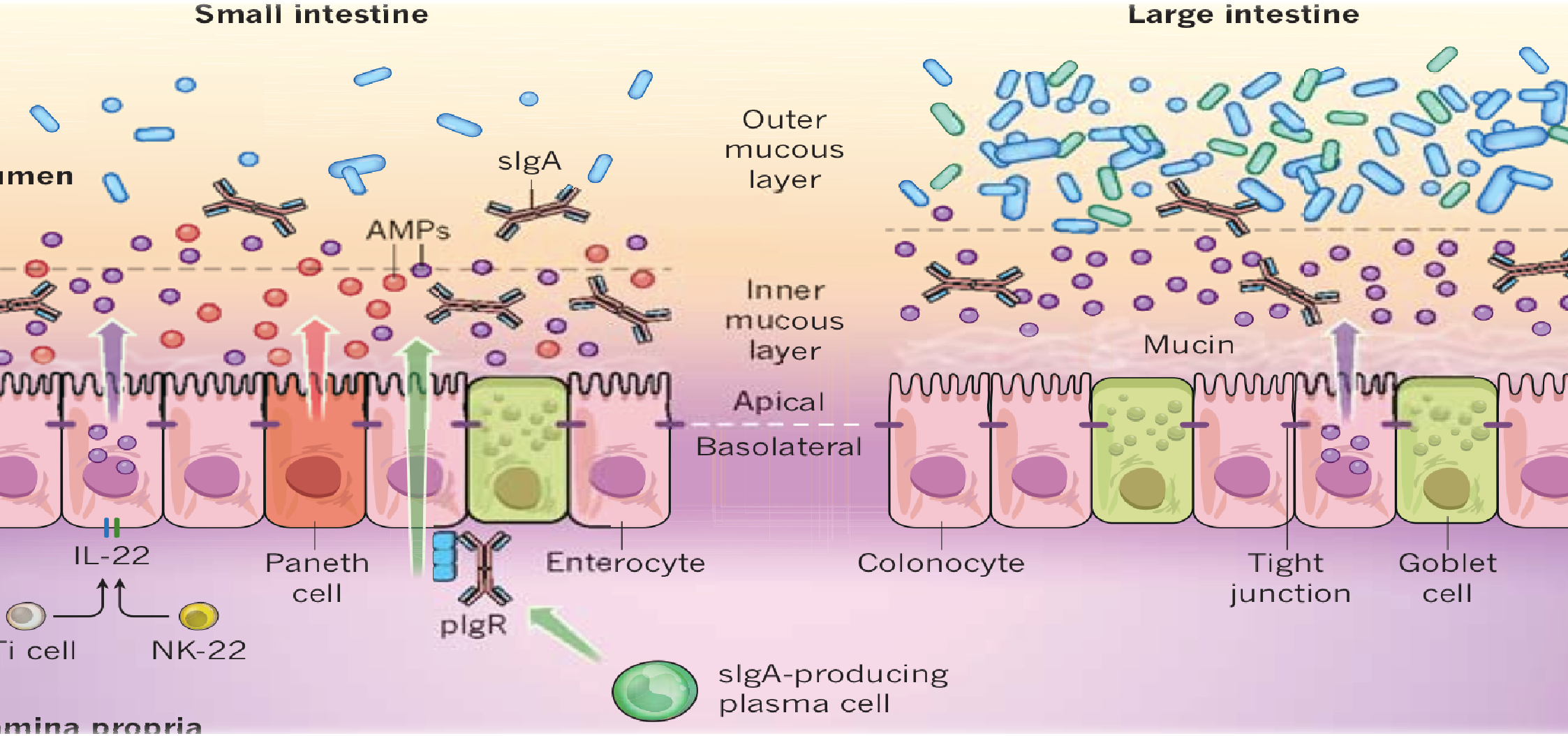
80-90%

er-individual differences of crobial genome

0.01%

Inter-individual differences of human genome

Lifelong immune stimulation by enteric commensal and pathogenic bacteria



Maynard CL et al. Natur

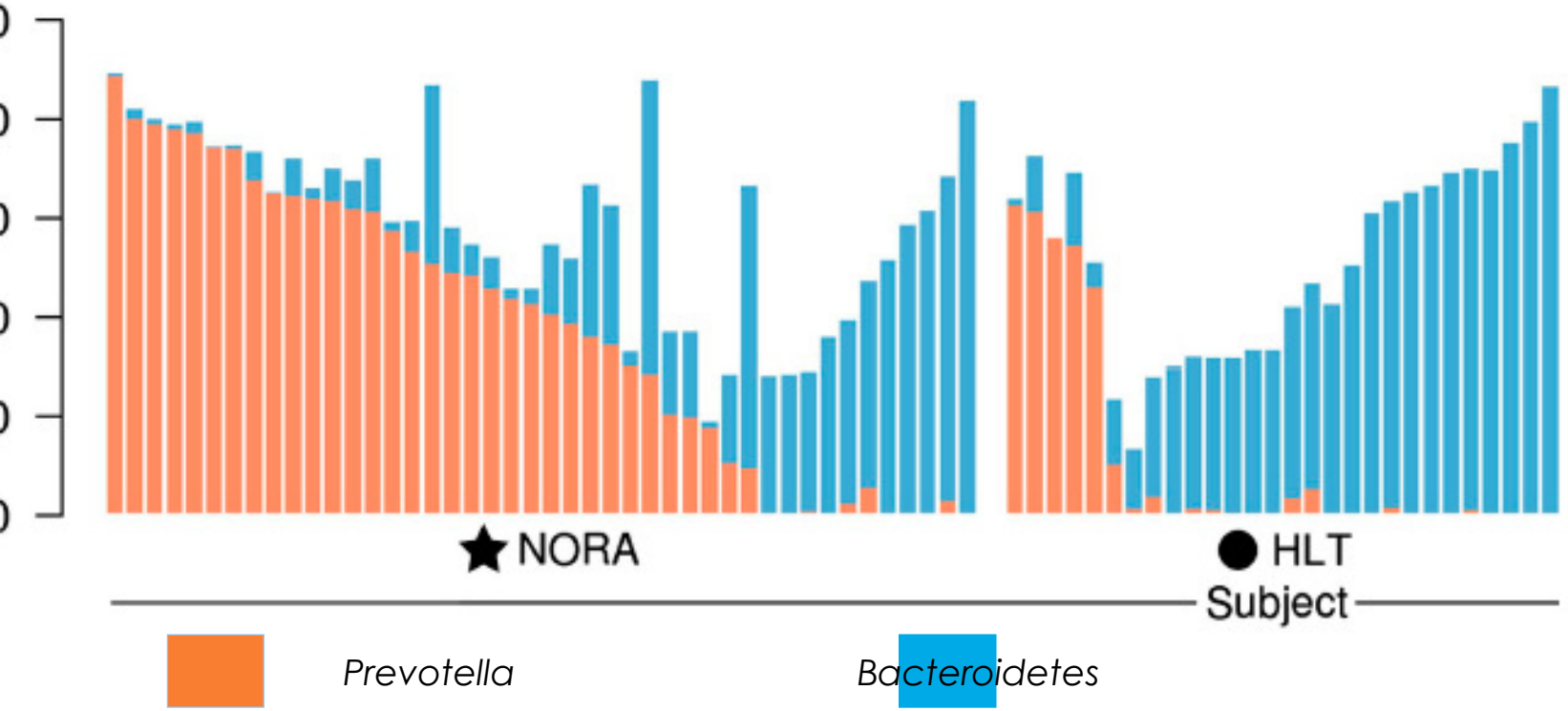
MICROBIAL MOLECULAR MIMICRY

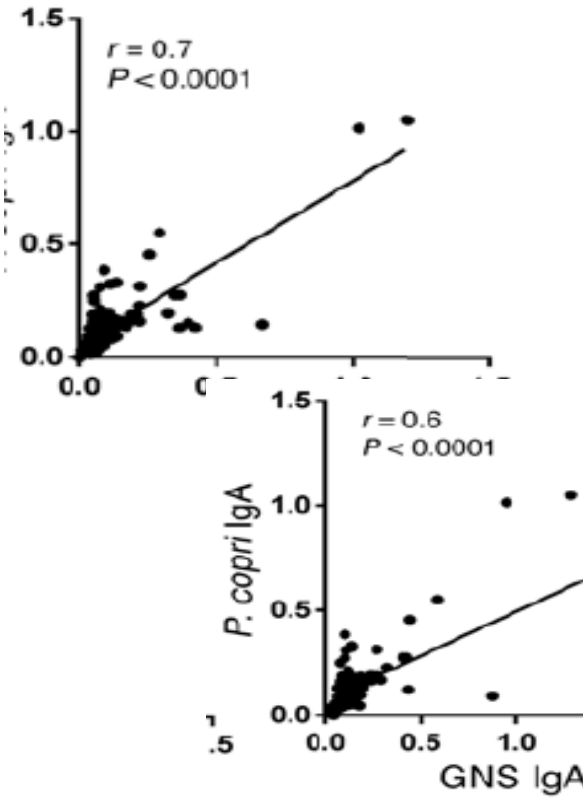
Rheumatoid Arthritis

S sequencing on 114 stool samples from RA patients and controls

evotella copri strongly correlates with disease in new-onset untreated rheumatoid arthritis (NORA)

- Anti-GNS/FLNA abs levels correlate with *Prevotella copri* Ab responses

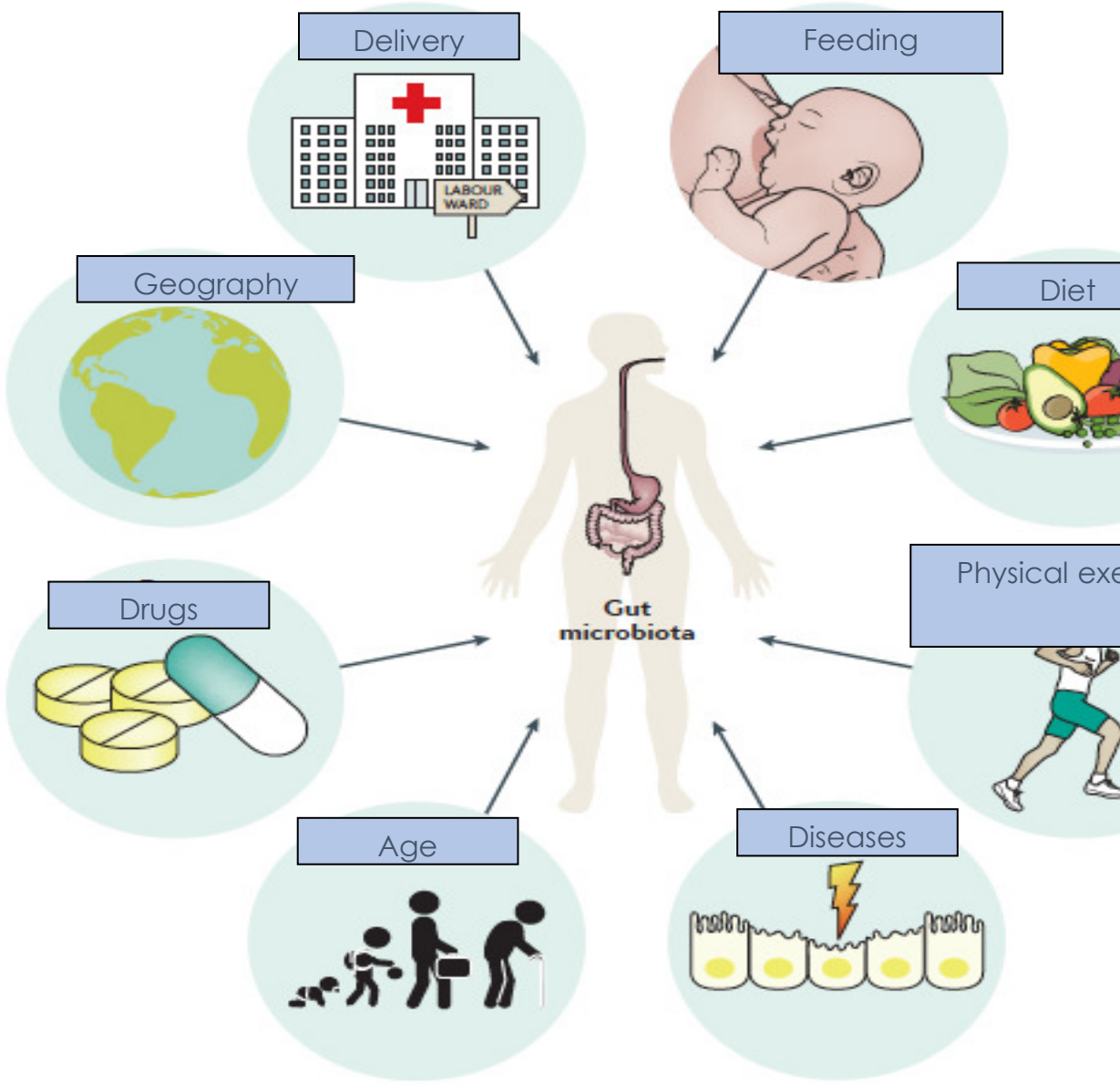




Gemelli

Scher JU, eLife 2013

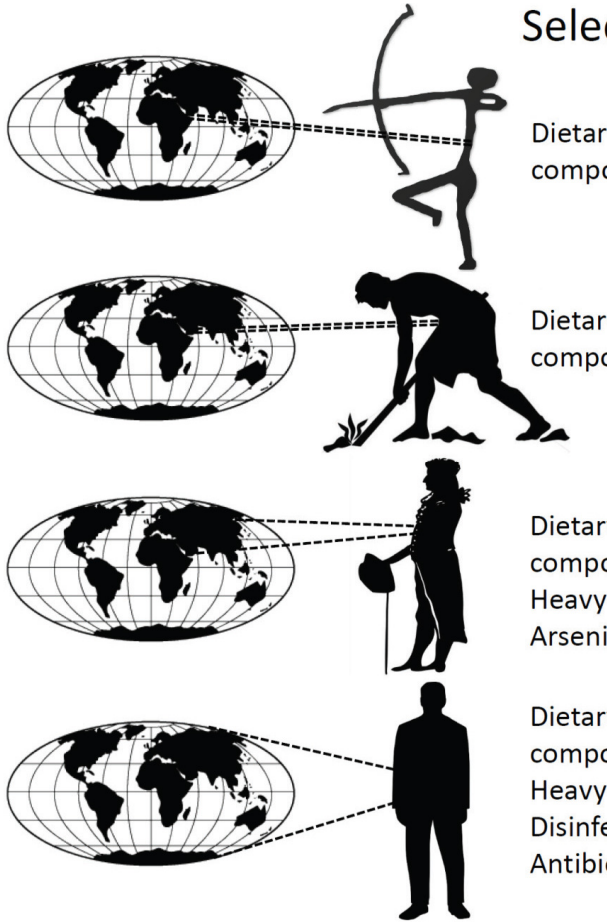
hich
e the
luencers
gut
crobiota?



uman evolution and changes in human microbia cology

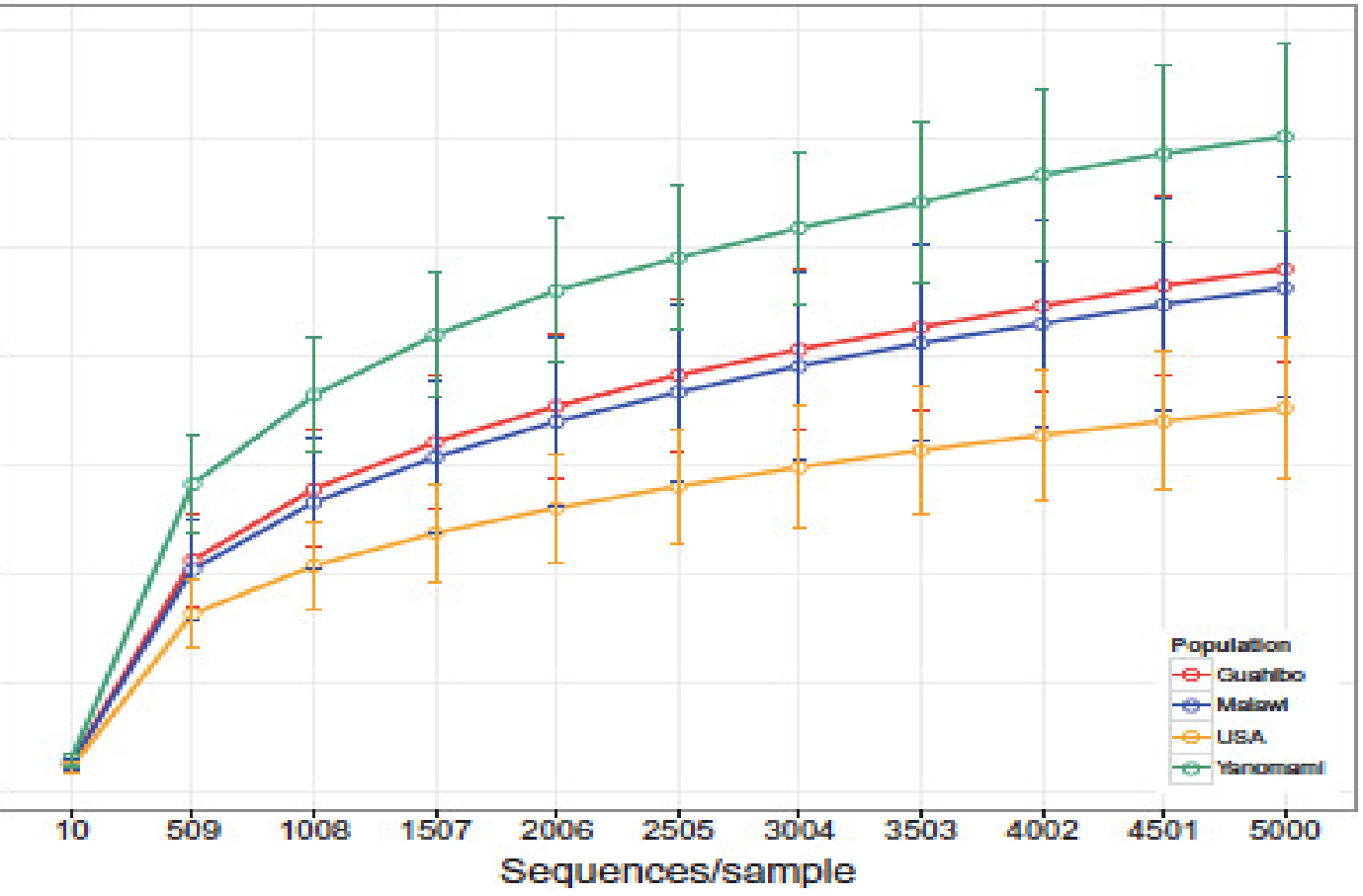
er the last five million years, various olutionary and ecological drivers have ered the composition of the human crobiota

- Fire
- Agriculture
- Processed foods
- Industrial revolution
- Drugs

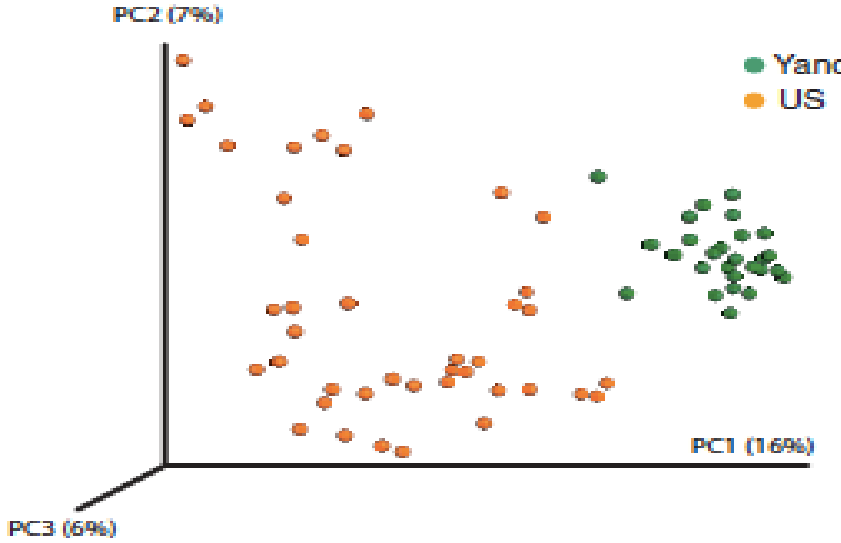


Gillings – Genes

ow westernization is influencing human icrobial ecology



- Yanomami harbor a microbiome the **highest diversity of bacteria a genetic functions** ever reported i human group



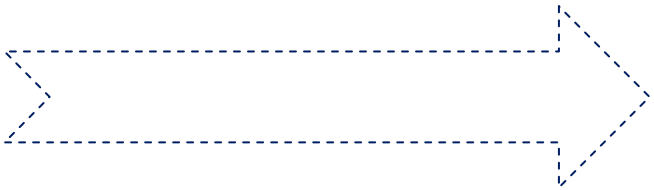
Clemente – Sci Ad

Why microbiota and IBD?

ut microbiota composition is altered in IBD vs controls

ut microbiota composition is altered in active vs non-active IBD

ut microbiota can influence the development of IBD

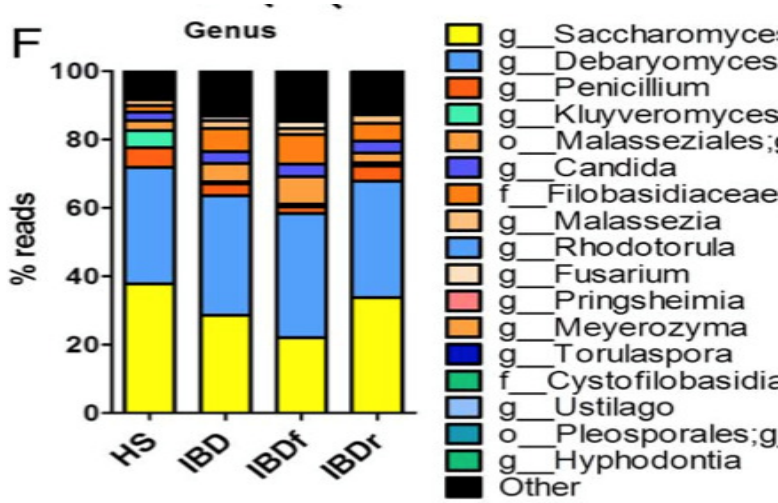
Association  **Causal relationship**

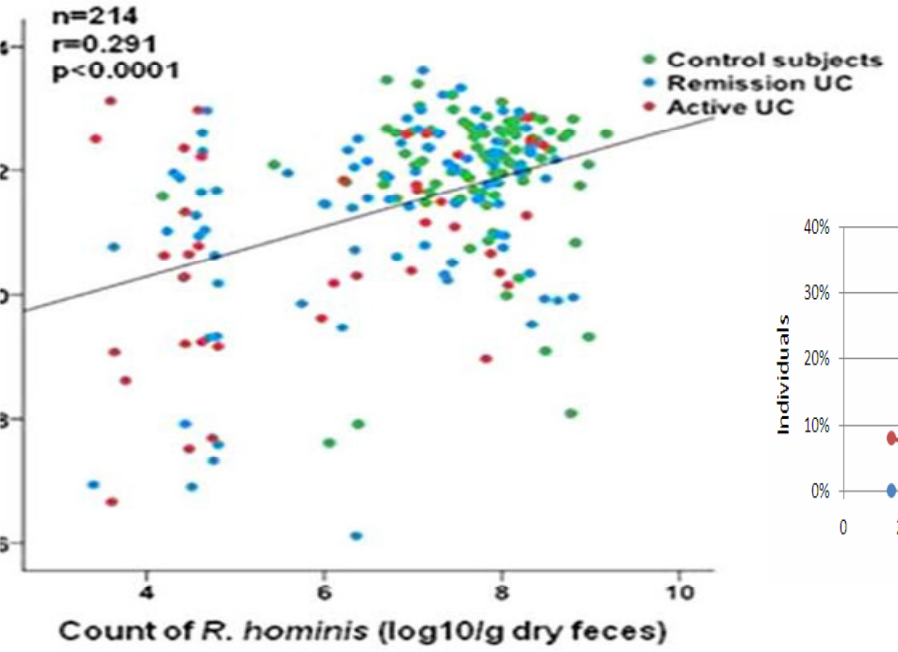
fferences in Bacteria, Fungi and Viruses

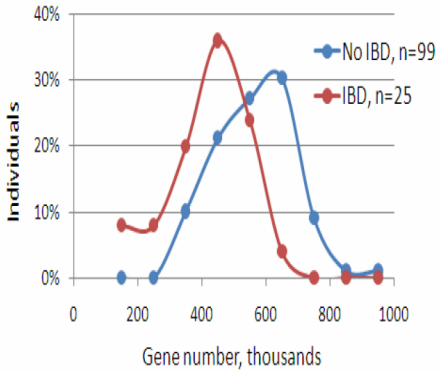
Decrease in bacterial diversity

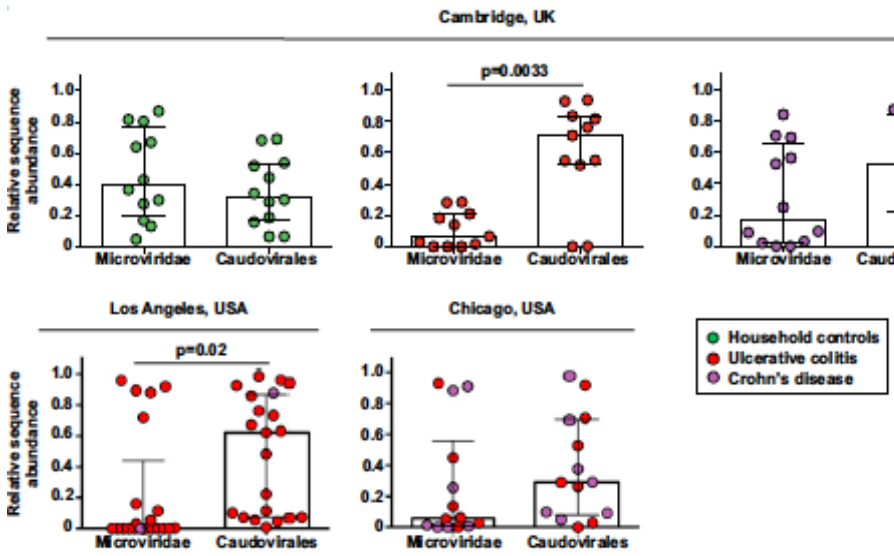
Decrease in SCFAs producers
(R. hominis, F. prausnitzii, etc)

Increase in viral richness & diversity





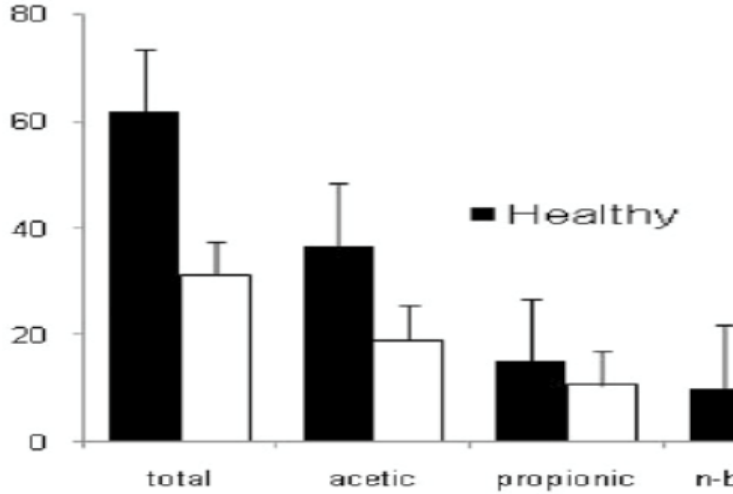




Machiels et al – Gut 2014; Sokol et al – Gut 2016; Norman et al – Cell 2015; Qin et al – Natu

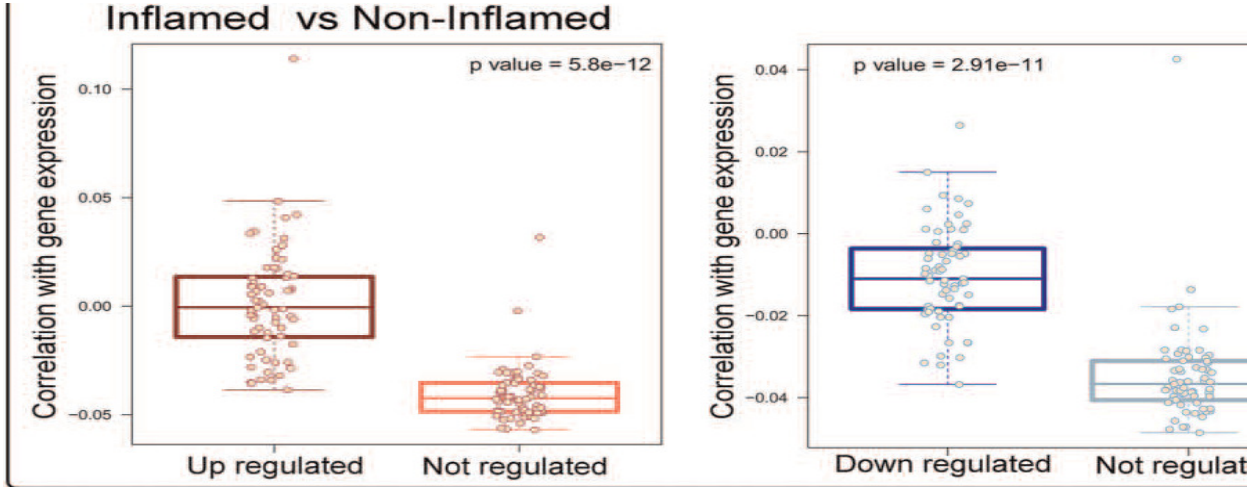
CFAs are reduced in IBD

James SL et al. Gut 2014
Khalil N A, et al. Food Sci Nutr 2014



e interplay between microbiome and host transcriptome is perturbed in I

Hasler et al - Gut 2017



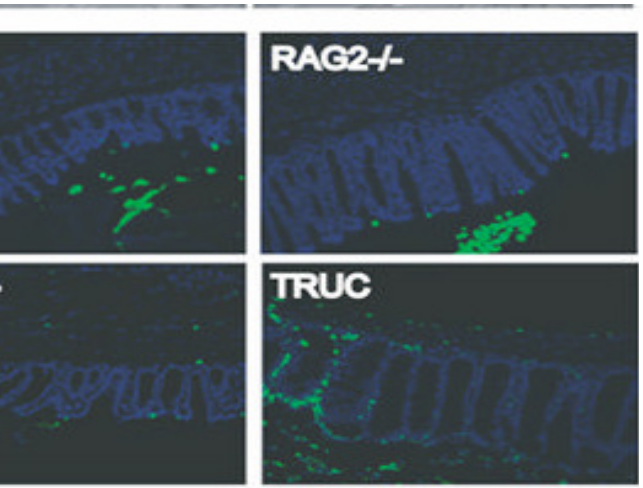
Gut microbiota transmits a colitis phenotype

T-bet controls the response of the mucosal immune system to commensal bacteria by regulating TNF-α production in colonic dendritic cells

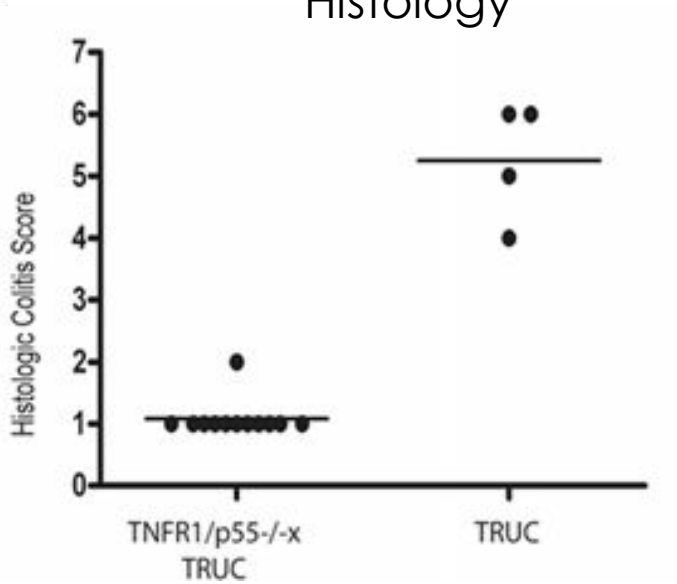
Loss of T-bet influences **bacteria to become colitogenic**

This colitis is **communicable to genetically intact hosts**

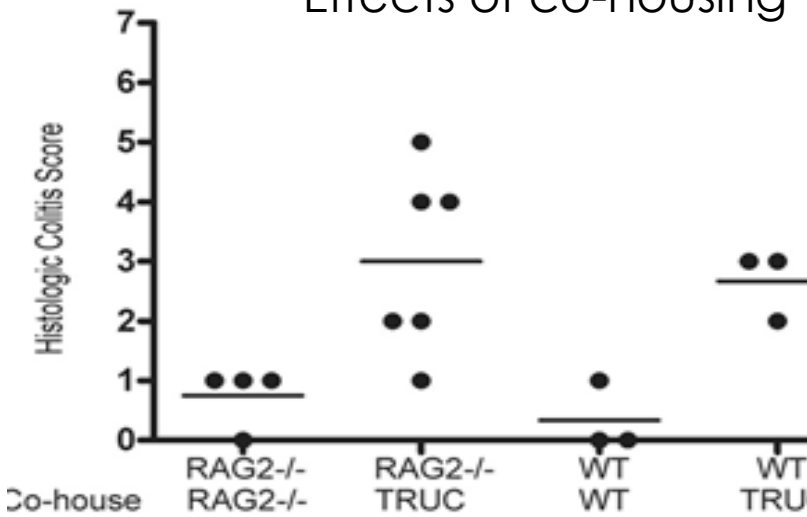
Gut barrier



Histology



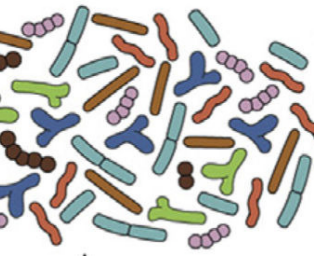
Effects of co-housing



Garrett et al – Science 2007

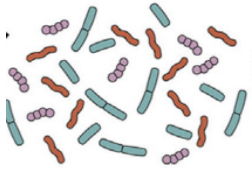
Rationale of microbiota modulation

ny microbiota



Diet & Lifestyle
Drugs
Systemic disorders
Stressful events

Dysbiosis
(Loss of eubiosis)



Quantity

Quality

Diseases

GI infectio

Metabolic dis

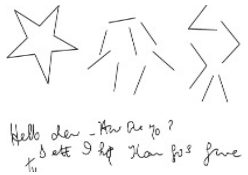
IBD

IBS

Diet
Antibiotics
Prebiotics
Probiotics
FMT

y
ual

Hepatic
Encefalopathy



Other

Probiotics: ECCO recommendations

Maintenance of remissio

ECCO statement 6I
E. coli Nissle is an effective alternative to 5-A
for maintenance [EL1b, RG A]

Pouchitis

2007

ECCO Statement 8E
VSL#3 (18×10^{11} of 8 bacterial strains for 9 or 12 months) has shown efficacy for maintaining antibiotic-induced remission [EL1b, RG B]. VSL#3 (9×10^{11} bacteria) has also shown efficacy for preventing pouchitis [EL 2b, RG C]

2016

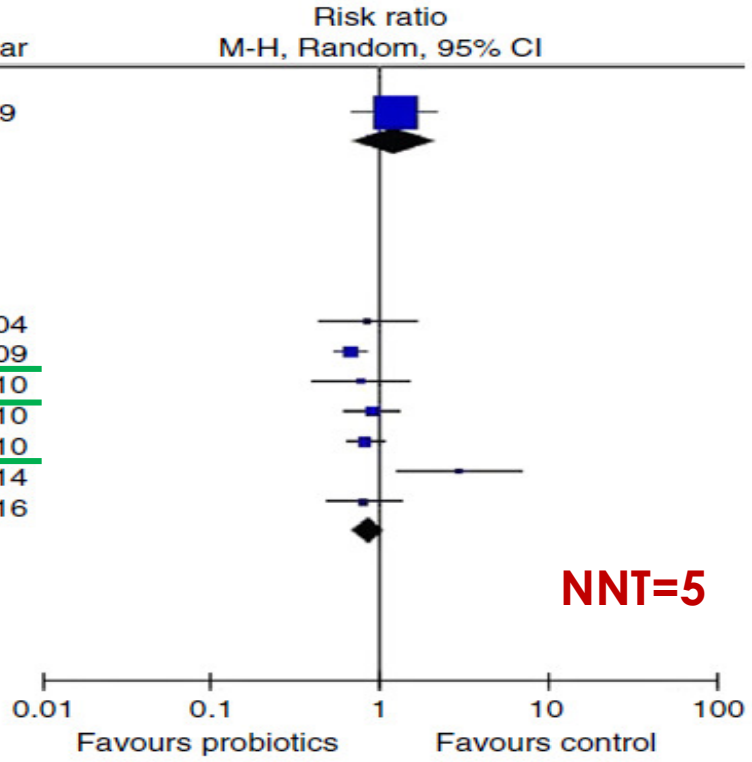
10.3.4. Maintenance of remission: probiotics
Once remission has been achieved in chronic pouchitis, treatment with the concentrated probiotic mixture VSL#3 helps to maintain remission. Two double-blind, placebo-controlled studies have shown the high efficacy of VSL#3 [450 billion bacteria of eight different strains/g] to maintain remission in patients with chronic pouchitis.[722,723] In the Cochrane systematic review, VSL#3 was more effective than placebo in maintaining remission of chronic pouchitis in patients who achieved remission with antibiotics.[703,724]

2016

10.3.5. Prevention of pouchitis: probiotics
The same probiotic preparation [VSL#3] has been shown to pre
pouchitis within the first year after surgery in a randomised, do
blind, placebo-controlled study. Patients treated with VSL#3
a significantly lower incidence of acute pouchitis [10%] comp
with those treated with placebo [40%] [$p < 0.05$], and experie
a significant improvement in their quality of life.[725] A Cochrane
tematic review reports that VSL#3 was more effective than pla
for the prevention of pouchitis.[703,724]

Probiotics in IBD

Study or subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
4.1.1 Probiotics vs. 5-ASA							
Rembacken (1999)	18	57	15	59	100.0%	1.24 [0.70, 2.22]	1999
Subtotal (95% CI)		57		59	100.0%	1.24 [0.70, 2.22]	
Total events	18		15				
Heterogeneity: not applicable							
Test fog overall effect: Z=.73 (P=.46)							
4.1.2 Probiotics vs. placebo							
Kato (2004)	6	10	7	10	9.0%	0.86 [0.45, 1.64]	2004
Sood (2009)	44	77	59	70	24.4%	0.68 [0.56, 0.84]	2009
Ng (2010)	7	14	9	14	8.9%	0.78 [0.40, 1.49]	2010
Matthes (2010)	41	70	13	20	17.0%	0.90 [0.62, 1.31]	2010
Tursi (2010)	40	71	50	73	22.5%	0.82 [0.64, 1.06]	2010
Petersen (2014)	15	25	5	25	6.0%	3.00 [1.29, 7.00]	2014
Tamaki (2016)	13	28	16	28	12.3%	0.81 [0.49, 1.35]	2016
Subtotal (95% CI)		295		240	100.0%	0.86 [0.68, 1.08]	
Test events	166		159				
Heterogeneity: τ^2=.04, χ^2=12.66, df=6 (P=.05), I^2=53%							
Test for overall effect: Z=1.29 (P=.20)							
Test for subgroup differences: χ^2=1.34, df=1 (P=.25), I^2=25.4%							



NNT=5

No benefit of probiotics over placebo in inducing remission in active UC (RR of failure to achieve remission=0.86; 95% CI=0.68-1.08). However, **when only trials of VSL#3 were considered there appeared to be a benefit** (**RR=0.74**; 95% CI=0.63-0.87).

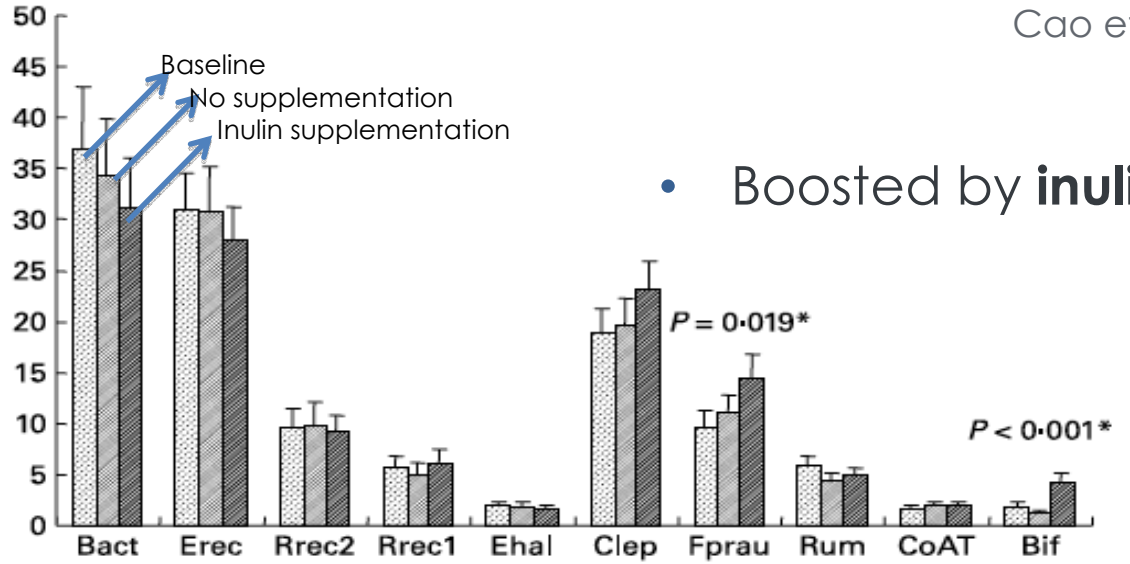
Derwa et al AP&T 2017

Next-generation probiotics: *Faecalibacterium prausnitzii*

eep anaerobe, around 5% of the total bacteria in faeces

rovides **energy to the colonocytes** and maintaining intestinal health

rong **anti-inflammatory effect** both *in vitro* and *in vivo*

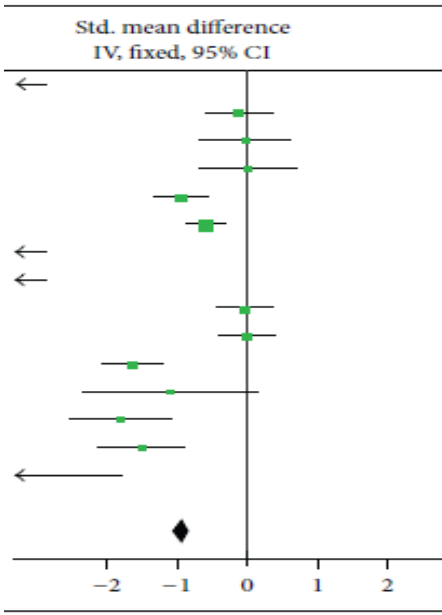


- Depleted in subjects w/**IBD**

  Cao et al – Gastrointest Res Pract 2014

- Boosted by **inulin** intake

  Ramirez-Farias C Br J Nutr 2009



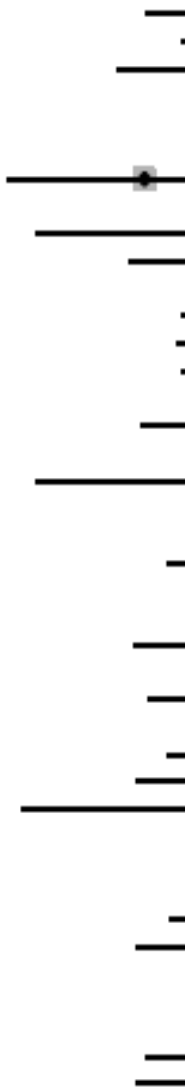
FMT has changed the natural history of rCDI

ar	1st auth	Design	CDI Cure
13	Van nood	RCT (FMT vs vanco)	94%
13	Kassam	Metanalysis	89.7%
14	Cammarota	Syst rev	87%
15	Cammarota	RCT (FMT vs vanco)	90%
15	Drekonja	Syst rev	85%
16	Lee	RCT (fresh vs frozen)	85% vs 83%
16	Kelly	RCT (donor vs autologous)	91% vs 62%
17	Quraishi	Metanalysis	92%
18	Ianiro	RCT (single vs mult. FMT)	75% vs 100%
18	Ianiro	Metanalysis	93% overall

Case Series
Aas 2003 [33]
Agrawal 2016 [44]
Allegretti 2014 [42]
Brandt 2012 [68]
Costello 2015 [69]
Dutta 2014 [43]
Emmanuelson 2014 [70]
Fischer 2016 [59]
Ganc 2015 [34]
Garborg 2010 [35]
Hamilton 2012 [60]
Kassam 2012 [61]
Kelly 2012 [36]
Kelly 2014 [30]
Khan 2014 [62]
Kronman 2015 [45]
Lee 2014 [63]
MacConnachie 2009 [64]
Mattila 2012 [47]
Patel 2013 [46]
Pathak 2014 [65]
Ray 2014 [37]
Rohlke 2010 [38]
Rubin 2013 [39]
Satokari 2015 [40]
Tauxe 2016 [66]
Vigvari 2014 [72]
Yoon 2010 [41]
Youngster 2014 [28]
Zainah 2015 [67]
Subtotal (I^2=64.82%, P=.00)

RCT
Allegretti 2016 [32]
Cammarota 2015 (FMT arm) [23]
Kao 2016 [26]
Kelly 2016 (donor FMT arm) [27]
Lee 2016 (Both FMT arms of RCT) [24]
Van Nood 2013 (FMT arm of RCT) [22]
Youngster 2014 (Both FMT arms) [71]
Subtotal (I^2=.00%, P=.83)

Heterogeneity between groups: P=.790
Overall (I^2=59.70%, P=.00);



FMT in ulcerative colitis: overview

RCTs

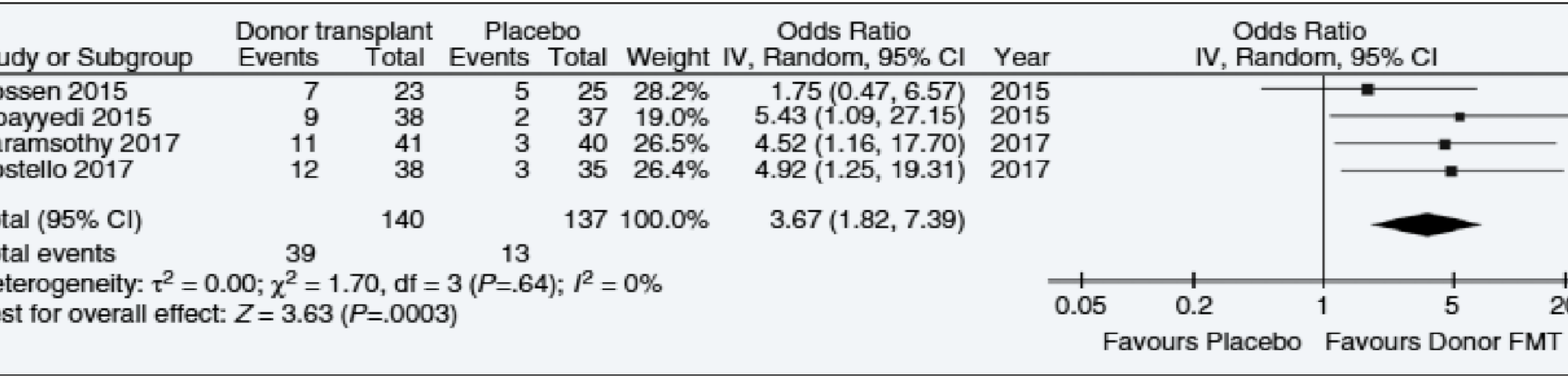
- **Clinical remission 28%** vs 9% placebo (OR 3.67- 95%CI 1.82-7.39, P<0.01)
- **Endoscopic remission 14%** vs 5% plac. (OR 2.89 – 95%CI 1.07-6.74, P=0.04)

cohort studies

- **Clinical remission 24%**

Costello et al – AP&T 2

arked differences between FMT working protocols



FMT in ulcerative colitis: not there yet

Why?

hough they were tested on patients with more severe disease, most recently
proved **biologics** for ulcerative colitis achieved **lower remission rates than FMT** i
eir pivotal trials (golimumab 18%, vedolizumab17%)

why the FMT-based therapeutic approach has not yet becom
treatment option in this disease?

Cammarota & Ianiro – Nat Rev Gastro He

FMT in ulcerative colitis: not there yet

Methods of available studies

ailable FMT trials are **small** (37 to 85 enrolled subjects)
differ with regards to protocols
ossible to draw definitive conclusions in terms of translating efficacy and safety outcomes to clinical settings

s (Year)	***Moayyedi 2015***	***Rossen 2015***	***Paramsothy 2017***	***Costello 2019***
e (number)	70	37	85	73
arator	Water	Autologous stools	Water	Autologous stool
otocol and	1 infusion per week for 6 weeks by enema	2 infusions in 3 weeks by naso-duodenal tube	1 infusion by colonoscopy followed by 5 enemas per week for 8 weeks	1 infusion by colonosco followed by 2 enemas i week
infusates	Fresh, frozen, aerobiosis, single donor	Fresh, aerobiosis, single donor	Frozen, aerobiosis, multiple (3-7) donors	Frozen anaerobiosisi, m (3-4) donors
y outcome	Remission (Mayo score <3 plus endoscopic score of 0) at week 7	Remission (SCCAI≤2) plus 1 point decrease in endoscopic Mayo score at week 12	Steroid-free clinical remission with endoscopic remission or response at week 8	Steroid-free clinical rem at week 8
(primary me)	24% FMT group vs 5% placebo group (p=0.03)	30.4% FMT group vs 20% placebo group (p=0.51)	27% donor FMT group vs 8% autologous FMT group (p=0.021)	32% donor FMT group v autologous FMT group (p=0.03)

FMT in ulcerative colitis: not there yet

FMT-related issues

ite its high efficacy, FMT is underused worldwide as a treatment for recurrent CD
use of several practical difficulties, such as donor recruitment, manipulation of
es, choice of delivery route and lack of regulation.

mising avenues to overcome these barriers include

e use of **sustainable protocols** (e.g. capsules)

nthetic microbial consortia, which could pave the way for a reproducible and
ndardized microbiota-based drug therapy

Cammarota & Ianiro – Nat Rev Gastro He

FMT: as easy as swallowing a pill?

ule FMT has been being used since 2014 to treat CDI, with success

ear	1° author	Design	Sample	Feces/capsule	Single course	CDI Cure rate
014	Youngster	Prospective	20	1.6 g (mean)	**30 capsules**	**70%** (single course); **90%** (multiple courses)
015	Hirsch	Retrospective	19	2.3 g (mean	8-12 capsules	**68%** (single course); **89%** (multiple courses)
016	Hagel	Retrospective	12	NR	NR	**83%** (single course); **92%** (multiple courses)
016	Youngster	Prospective	180	1.6 g (mean)	**30 capsules**	**82% (**single course); **94%** (multiple courses)
017	Staley	Prospective	49	NR	Different n°	**88% (**single course)
017	Kao	Non-inferiority RCT	57 caps. 59 colon	80-100 g per treatment	**40 capsules**	96% (single course): not inferior to colonoscopy

psule FMT restored bacterial diversity and resolved dysbiosis

ts in the fecal microbiome were incremental rather than immediate

Staley et al – Gut micr

Capsule FMT may boost **dissemination of FMT** and ease sustained **cure of chronic disorders** (e.g. UC) through repeated treatment sessions

Need for optimised capsule protocols

FMT 2.0 – Microbiota suspensions

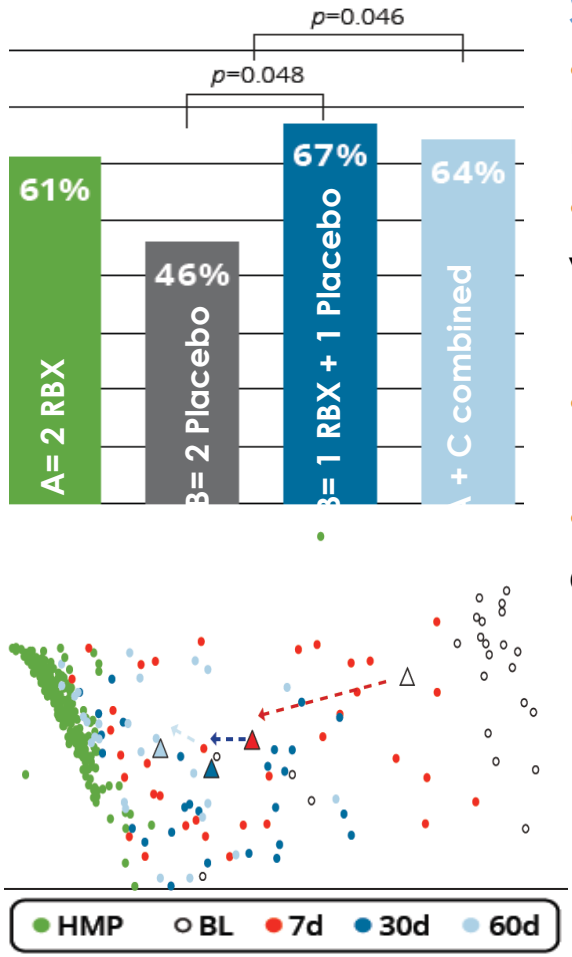
late, only biologically sourced products have been studied, and we have not yet data o
hetic microbial consortia

660

% cure of rCDI + no SAE – pilot study
s

ficant benefit of a single (**67%** rCDI
rates vs placebo 46%), but **not of 2**
doses – 89.2% cumulative cure rate
open-label treatment of all failures -
ts (RCT)

ents' microbiota **shifts towards donor**
es after treatment



SER-109

- **86.7%** cure of rCDI - pilot stu
pts
- Rapid **microbiota diversific**
with **durable engraftment of s**
(both with 1 or 2 SER109 doses)
- No treatment-related SAEs
- **Phase II has failed the pr**
endpoint (interim analysis)

Orenstein et al – Clin Infect Dis 2016
Dubberke et al – Open Forum Infect Dis 2016

Orenstein et al – UEG Week 2016;
Blount et al – ASM Congress 2017

Khanna et al – J Infect Dis 2016

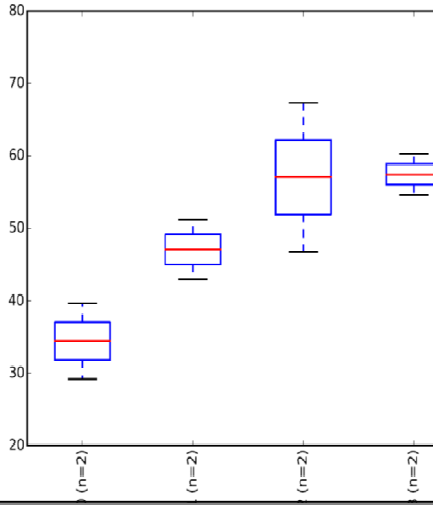
FMT 2.0 – Culturomics-based synthetic microbiota consortium

thetic microbiota consortium composed of **15 bacterial species from a cessful FMT donor, selected from those engrafting the recipients' gut**

rCDI pts

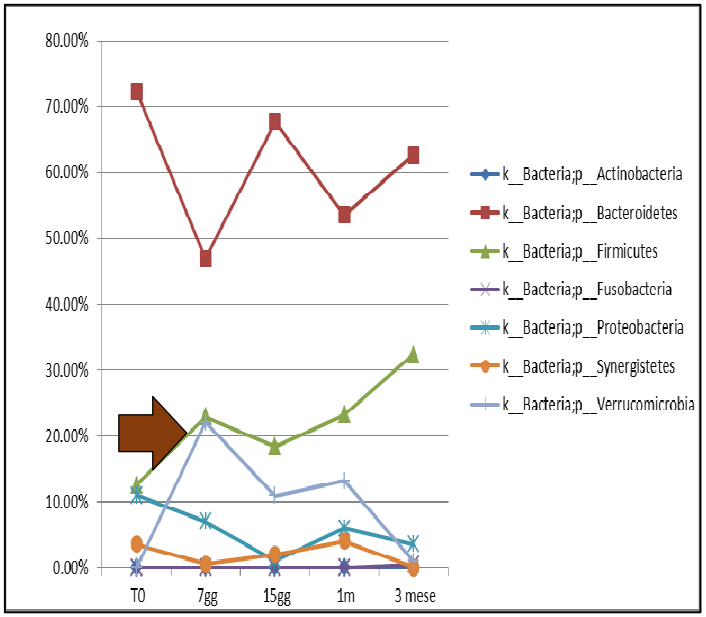
% cure of rCDI

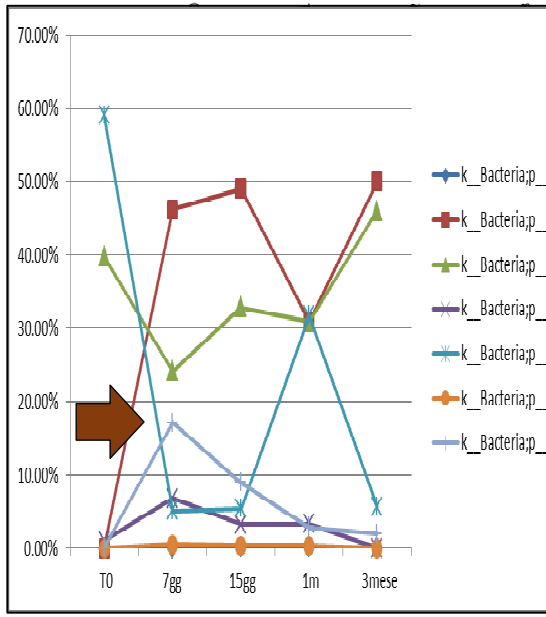
Microbiota richness



Proteobacteria

Verrucomicrobia/
A. muciniphila





FMT in ulcerative colitis: not there yet

Current view of FMT in UC

should be considered as a **chronic treatment to be integrated among other opt**

UC is a chronic disease, and patients need effective and safe therapies not only to induce remission but also to maintain it in the **long-term**

The poor rate of donor–recipient microbial engraftment — which is associated with clin outcomes — achieved by a single faecal infusion suggests that **FMT is unlikely to act as one-time treatment**

Certain donor microbial profiles and bacterial species seem to be **associated with bette nical outcomes, but** there is **no clear evidence of which specific features** the optimal do microbiota should have in terms of bacterial diversity and composition

Cammarota & Ianiro – Nat Rev Gastro He

FMT: the key role of engraftment

pient-donor engraftment is the key for therapeutic success in UC and other chro
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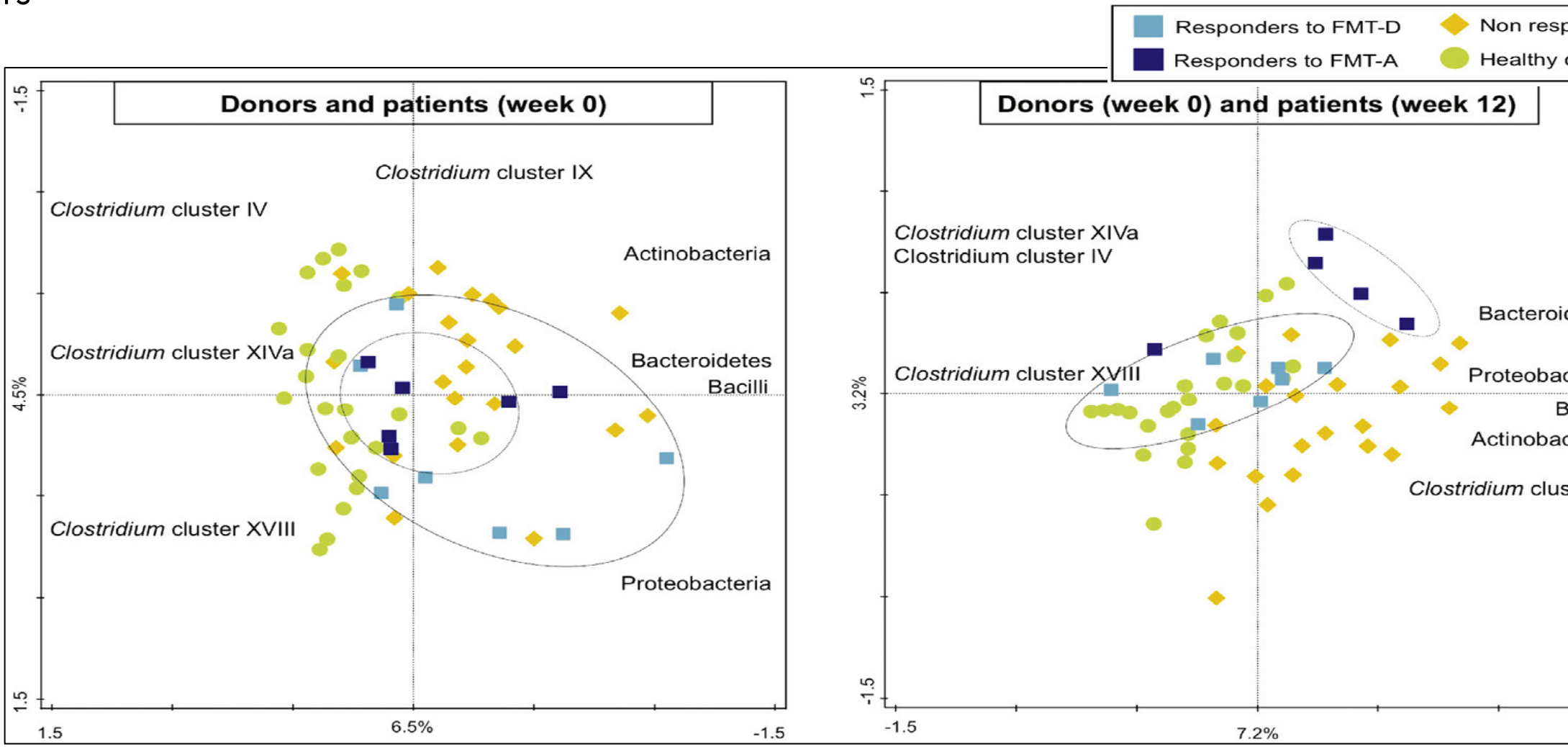
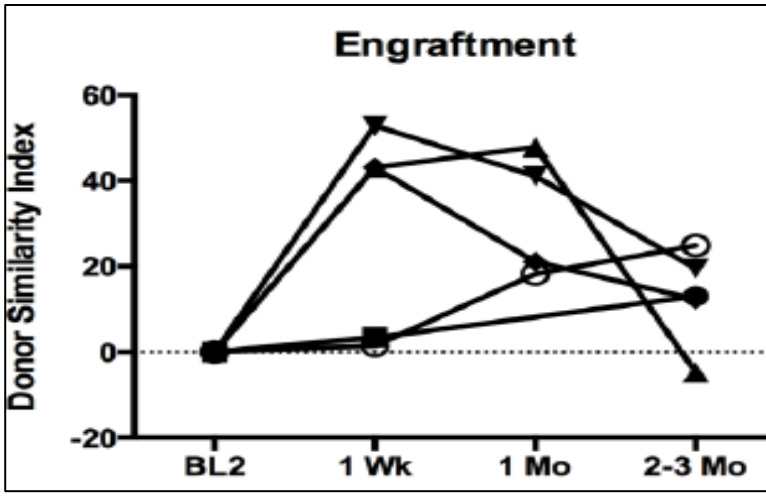


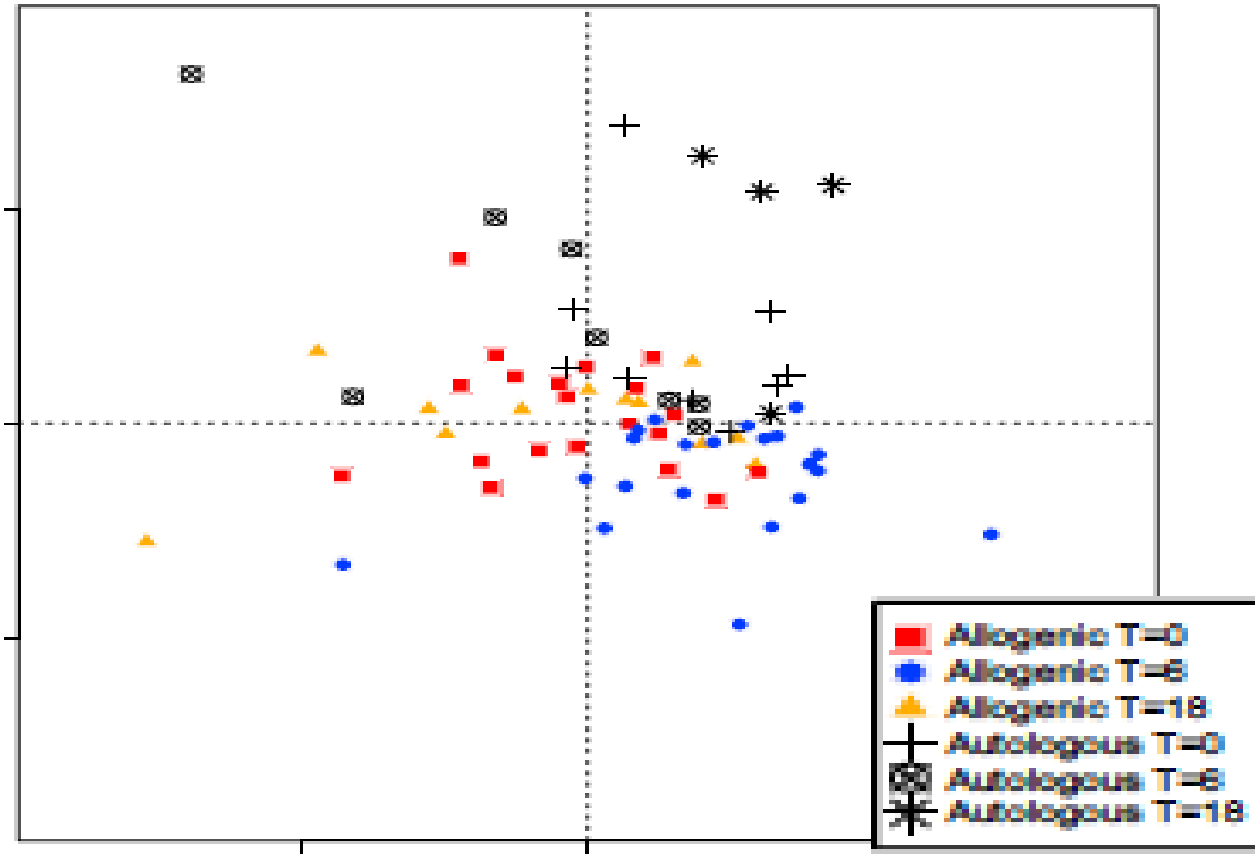
Rossen et al – Gastroenterology 2015; Moayyedi et al – Gastroenterology 2015; Kootte et al – Cell Metabo

FMT: the key role of engraftment

Single FMT provides only **low level of** donor-recipient microbiota **engraftment**

Angelberger et al – Am J Gastro 2013;
Kump et al – UEGW 2013 (abstract





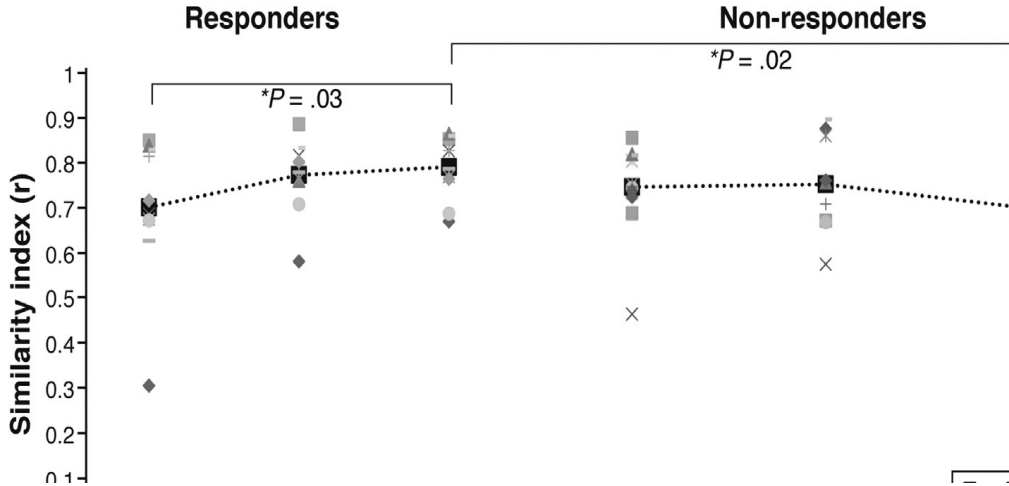
- **Engraftment** goes lost after FMT the mid-term

Kootte et al – Cell Metabolism 20

FMT in UC: the issue of donors

or-recipient track in the TURN trial

At 12 weeks after treatment, **responders** in the FMT group had a significantly **higher similarity to their donors** than nonresponders (P 0.02)

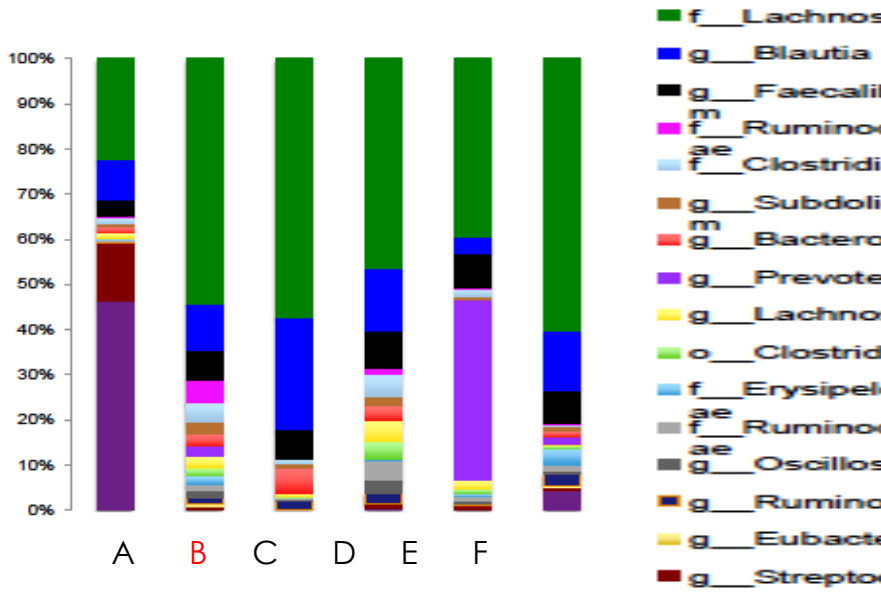


uper-donor" in the Moayyedi trial

onor B recipients were **more likely to achieve clinical mission** than others
9% vs 10%, p=0.06)

onor B showed significant enrichment for **achnospiraceae** and **Ruminococcus**

onors B and F had similar profiles and both were ssociated with successful FMT



Conclusions #1

microbiome modulation appears to be deeply involved both in the pathogenesis and
potential therapeutic management of IBD

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date, there is a **gap between microbiome basic scientists and clinicians** involved in dysbiosi
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Time for a translational figure: the **MICROBIOME CLINICIAN**
Time for a breakthrough in clinical practice: the **MICROBIOME CLINIC**

CROBIOME CLINICIAN

ntinuous up-to-date on microbiota research

owledge of different dysbiotic profiles of GI and a-GI Disorders

erpretation of gut microbiota profiling

plication of microbiome research data in ical practice

pertise in microbiota modulation (anti-pre-biotics, FMT)

MICROBIOME CLINIC

- **Multidisciplinary team** (microbiome clinician microbiologists, immunologists, nutricians, etc
- **Availability of microbiota sequencing tools**
- **Availability of stool bank/FMT Centre**
- **Hotspot for microbiota research**
- **Networking and teaching centre**

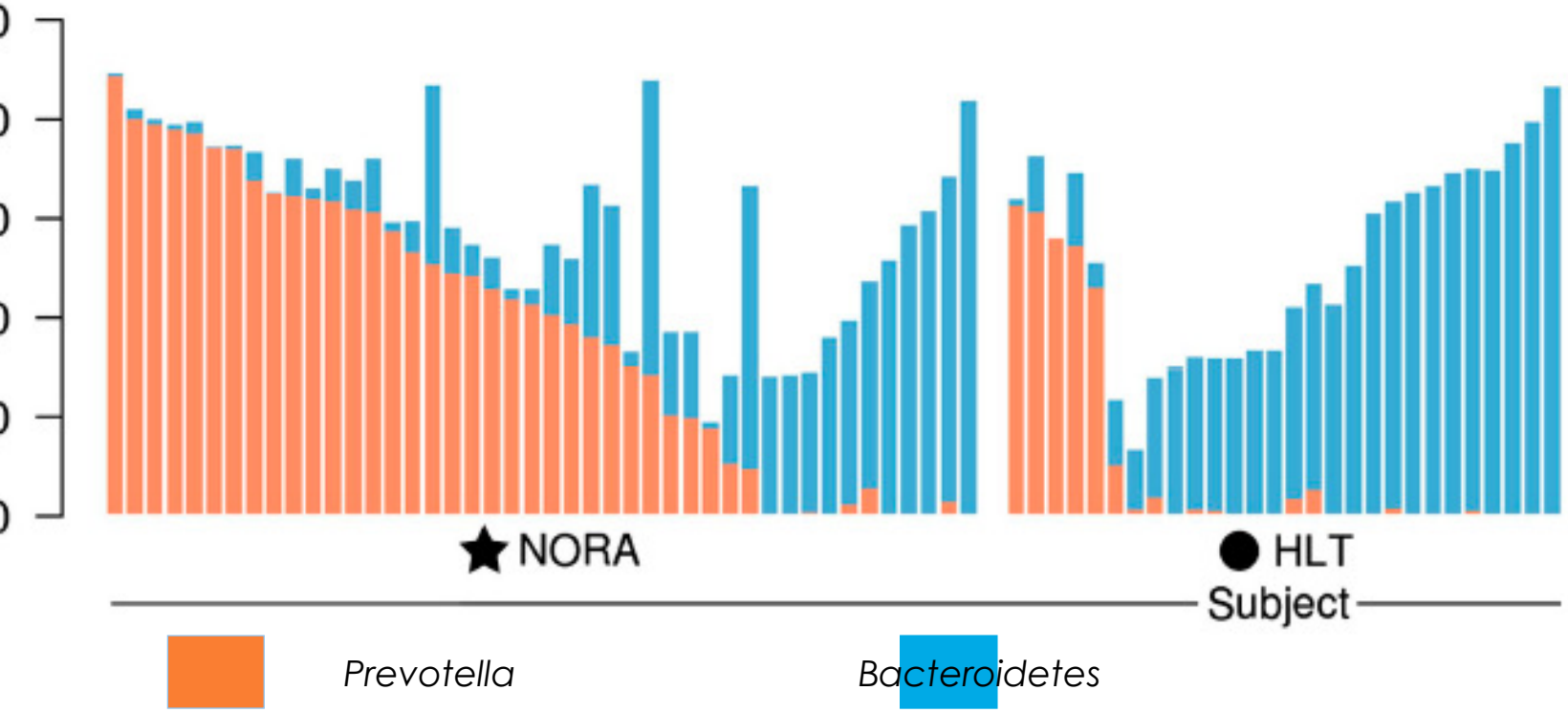
MICROBIAL MOLECULAR MIMICRY

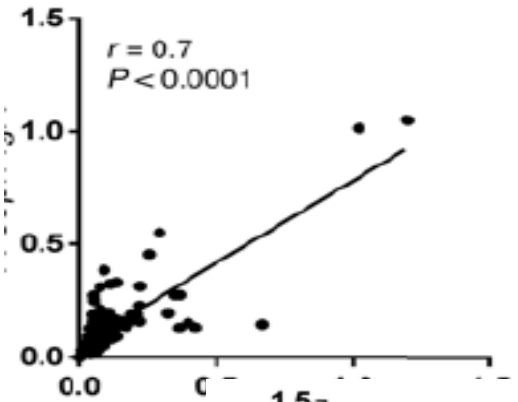
Rheumatoid Arthritis

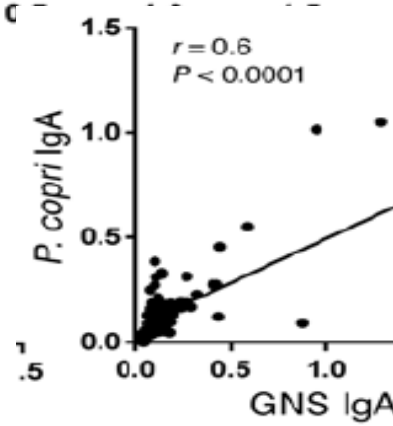
S sequencing on 114 stool samples from RA patients and controls

evotella copri strongly correlates with disease in new-onset untreated RA

- Anti-GNS/FLNA abs levels correlate with *Prevotella copri* Ab responses







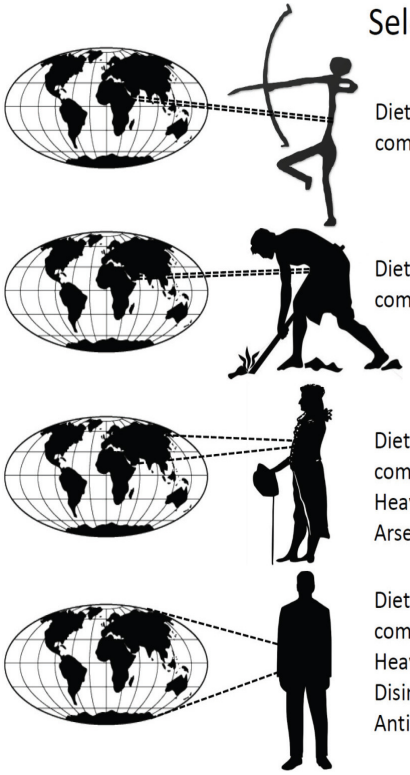
Scher JU, eLife 2013

2

Human evolution and changes in human microbial ecology

er the last five million years, various olutionary and ecological drivers have ered the composition of the human crobiota

- Fire
- Agriculture
- Processed foods
- Industrial revolution
- Drugs

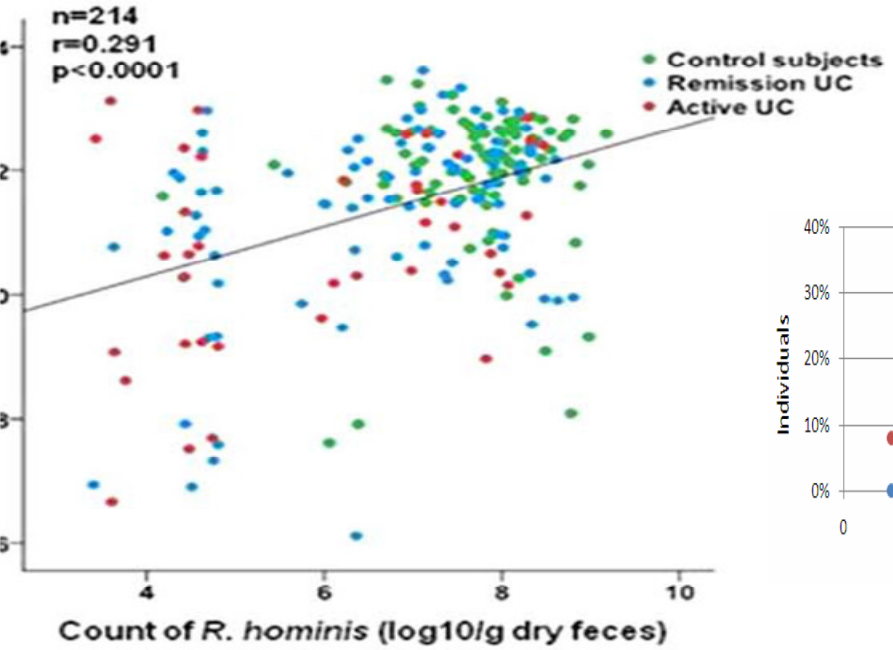


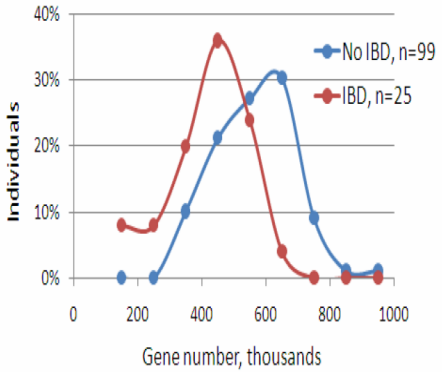
Gillings – Genes

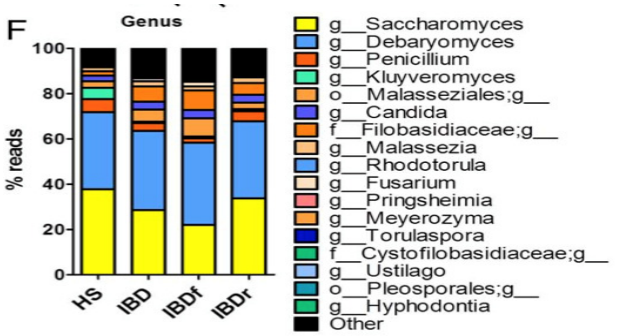
3

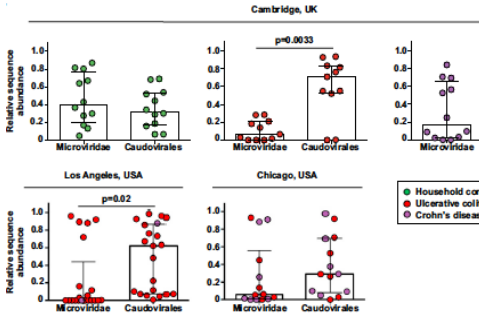
• Differences in Bacteria, Fungi and Viruses

- **Decrease in bacterial diversity**
- **Decrease in SCFAs producers**
  (R. hominis, F. prausnitzii, etc)
- **Increase in viral richness & diversity**





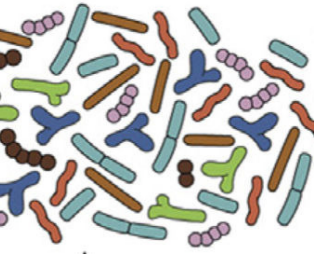




Machiels et al – Gut 2014; Sokol et al – Gut 2016; Norman et al – Cell 2015; Qin et al – Natu

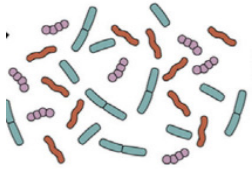
Rationale of microbiota modulation

ny microbiota



Diet & Lifestyle
Drugs
Systemic disorders
Stressful events

Dysbiosis
(Loss of eubiosis)



Quantity

Quality

Diseases

GI infectio

Metabolic dis

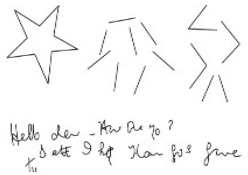
IBD

IBS

Diet
Antibiotics
Prebiotics
Probiotics
FMT

y
ual

Hepatic
Encefalopathy



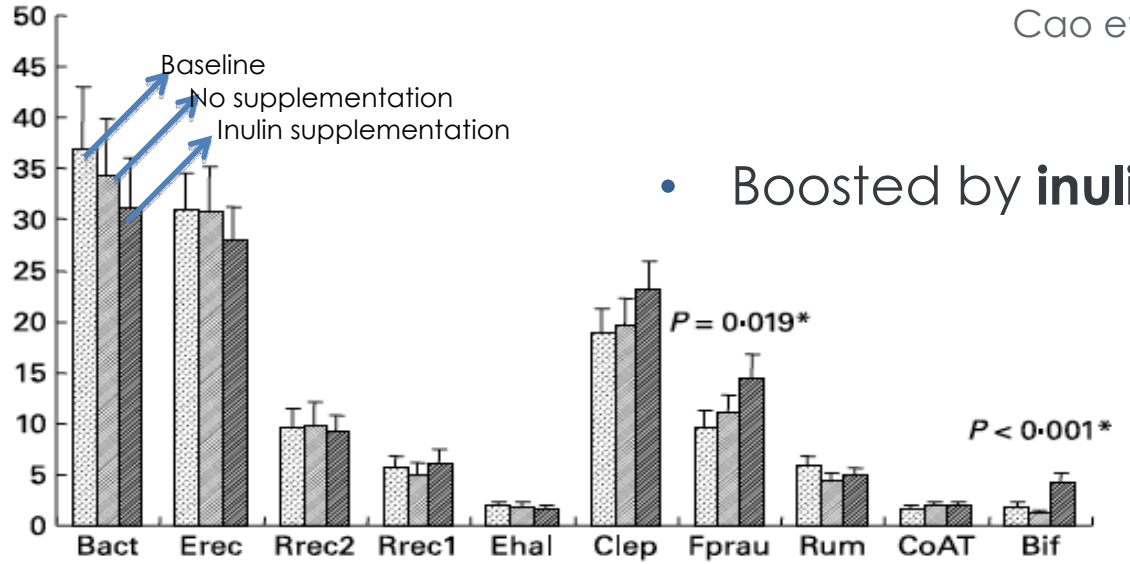
Other

Next-generation probiotics: *Faecalibacterium prausnitzii*

eep anaerobe, around 5% of the total bacteria in faeces

ovides **energy to the colonocytes** and maintaining intestinal health

rong **anti-inflammatory effect** both *in vitro* and *in vivo*

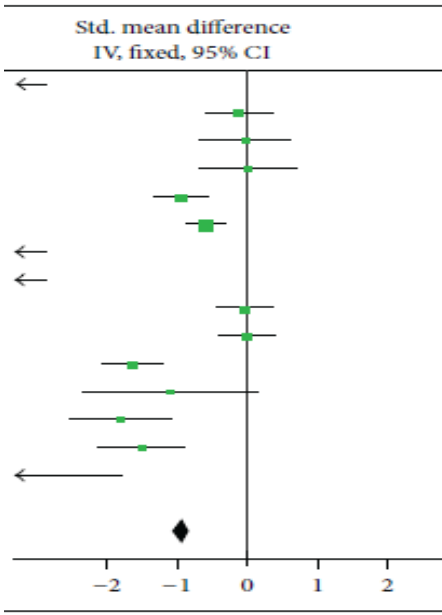


- Depleted in subjects w/**IBD**

  Cao et al – Gastrointest Res Pract 2014

- Boosted by **inulin** intake

  Ramirez-Farias C Br J Nutr 2009



FMT in ulcerative colitis: overview

RCTs

- **Clinical remission 28%** vs 9% placebo (OR 3.67- 95%CI 1.82-7.39, P<0.01)
- **Endoscopic remission 14%** vs 5% plac. (OR 2.89 – 95%CI 1.07-6.74, P=0.04)

cohort studies

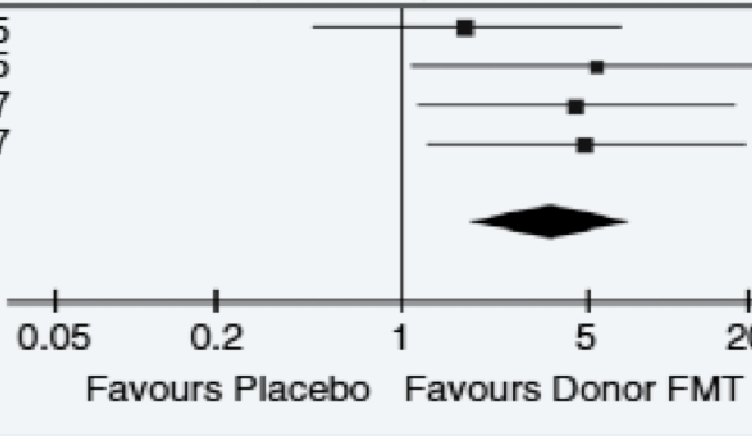
- **Clinical remission 24%**

Costello et al – AP&T 2

arked differences between FMT working protocols

udy or Subgroup	Donor transplant Events	Total	Placebo Events	Total	Weight	Odds Ratio IV, Random, 95% CI	Year
ssen 2015	7	23	5	25	28.2%	1.75 (0.47, 6.57)	2015
ayyedi 2015	9	38	2	37	19.0%	5.43 (1.09, 27.15)	2015
ramsothy 2017	11	41	3	40	26.5%	4.52 (1.16, 17.70)	2017
stello 2017	12	38	3	35	26.4%	4.92 (1.25, 19.31)	2017
tal (95% CI)		140		137	100.0%	3.67 (1.82, 7.39)	
tal events	39		13				

Odds Ratio IV, Random, 95% CI



eterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.70$, df = 3 (P=.64); $I^2 = 0\%$

st for overall effect: $Z = 3.63$ (P=.0003)

FMT in ulcerative colitis: not there yet

Methods of available studies

ailable FMT trials are **small** (37 to 85 enrolled subjects)
differ with regards to protocols
ossible to draw definitive conclusions in terms of translating efficacy and safety outcomes to clinical settings

s (Year)	***Moayyedi 2015***	***Rossen 2015***	***Paramsothy 2017***	***Costello 2019***
e (number)	70	37	85	73
arator	Water	Autologous stools	Water	Autologous stool
otocol and	1 infusion per week for 6 weeks by enema	2 infusions in 3 weeks by naso-duodenal tube	1 infusion by colonoscopy followed by 5 enemas per week for 8 weeks	1 infusion by colonosco followed by 2 enemas i week
infusates	Fresh, frozen, aerobiosis, single donor	Fresh, aerobiosis, single donor	Frozen, aerobiosis, multiple (3-7) donors	Frozen anaerobiosisi, m (3-4) donors
y outcome	Remission (Mayo score <3 plus endoscopic score of 0) at week 7	Remission (SCCAI≤2) plus 1 point decrease in endoscopic Mayo score at week 12	Steroid-free clinical remission with endoscopic remission or response at week 8	Steroid-free clinical rem at week 8
(primary me)	24% FMT group vs 5% placebo group (p=0.03)	30.4% FMT group vs 20% placebo group (p=0.51)	27% donor FMT group vs 8% autologous FMT group (p=0.021)	32% donor FMT group v autologous FMT group (p=0.03)

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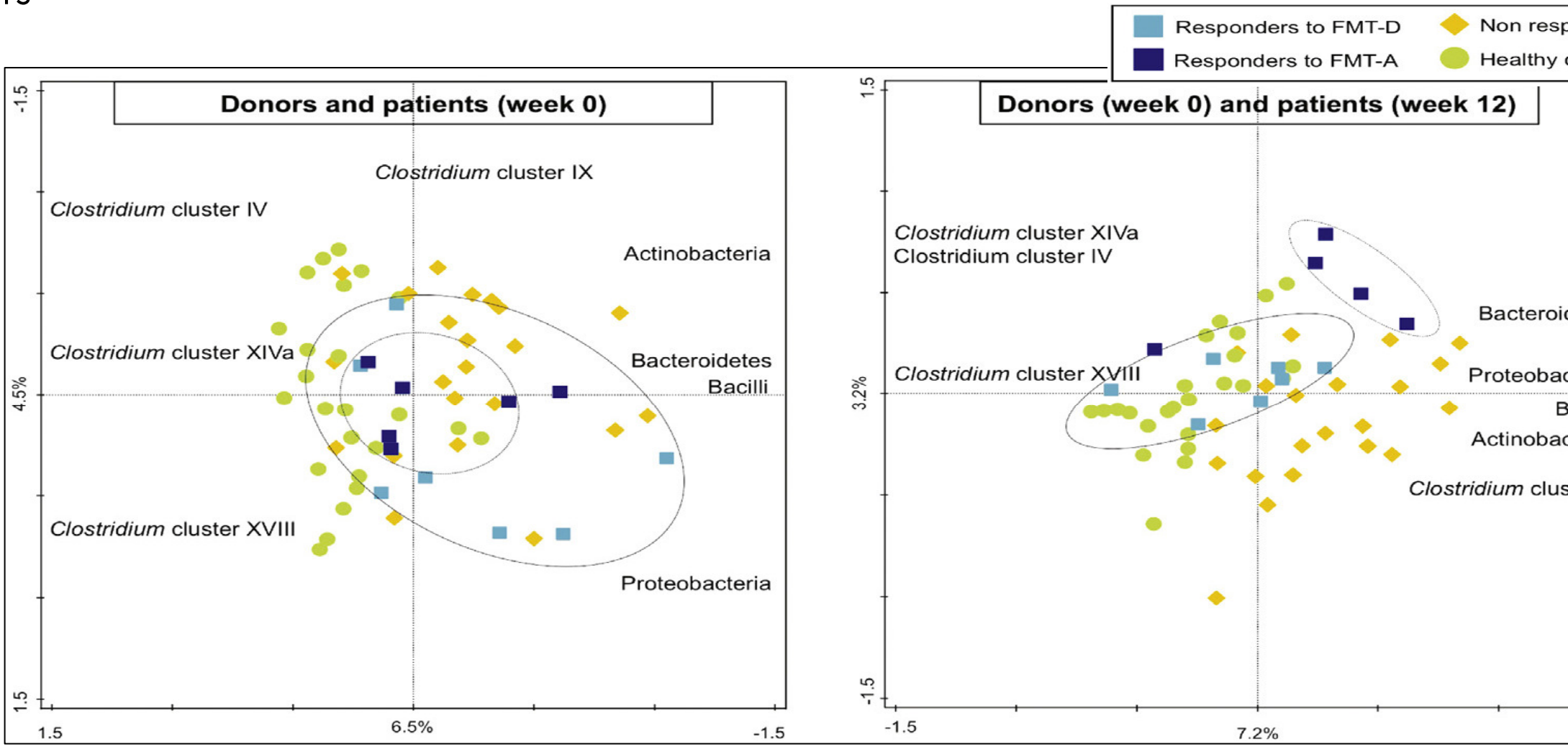

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