Fecal Microbiota Transplantation - Microbiome therapies

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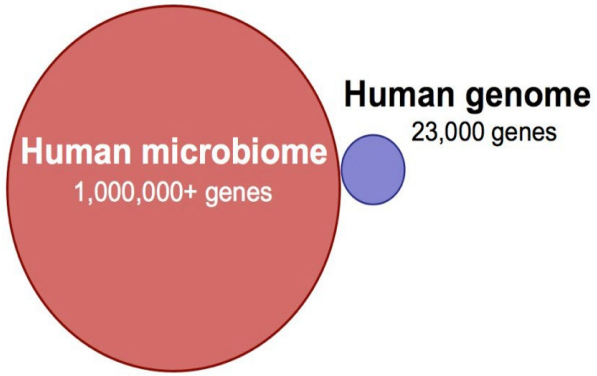
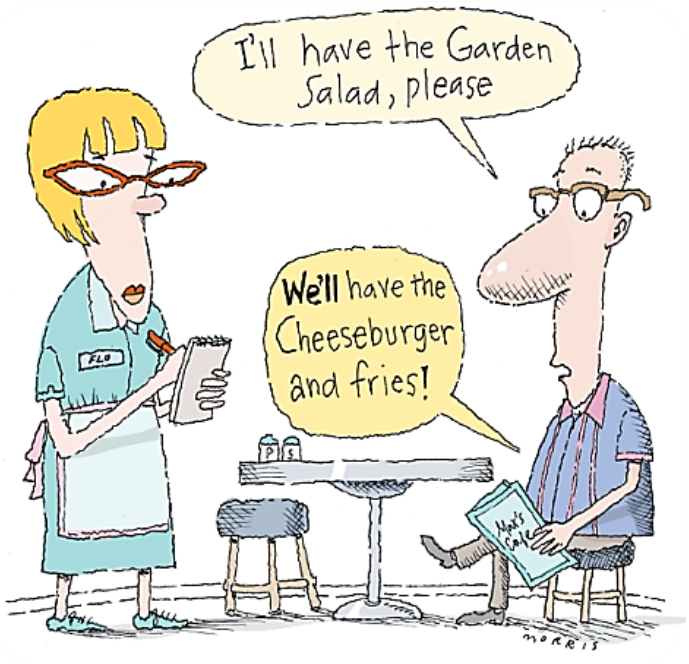
Biological concepts and clinical applications

1. Background: Microbiome and FMT
2. Microbiome therapies for *Clostridioides difficile* infections
   - FMT
   - Microbiota therapies (RBX2660 and SER109) – Phases 1-3
3. Microbiome therapies for IBD
   - FMT for UC
   - Microbiota therapies (SER287) – Phases 1-2
4. Microbiome in cancer
   - FMT studies
   - Microbiome in cancer studies
   - Phase 1 in preparation

The microbiome is of broad interest… rightly so?

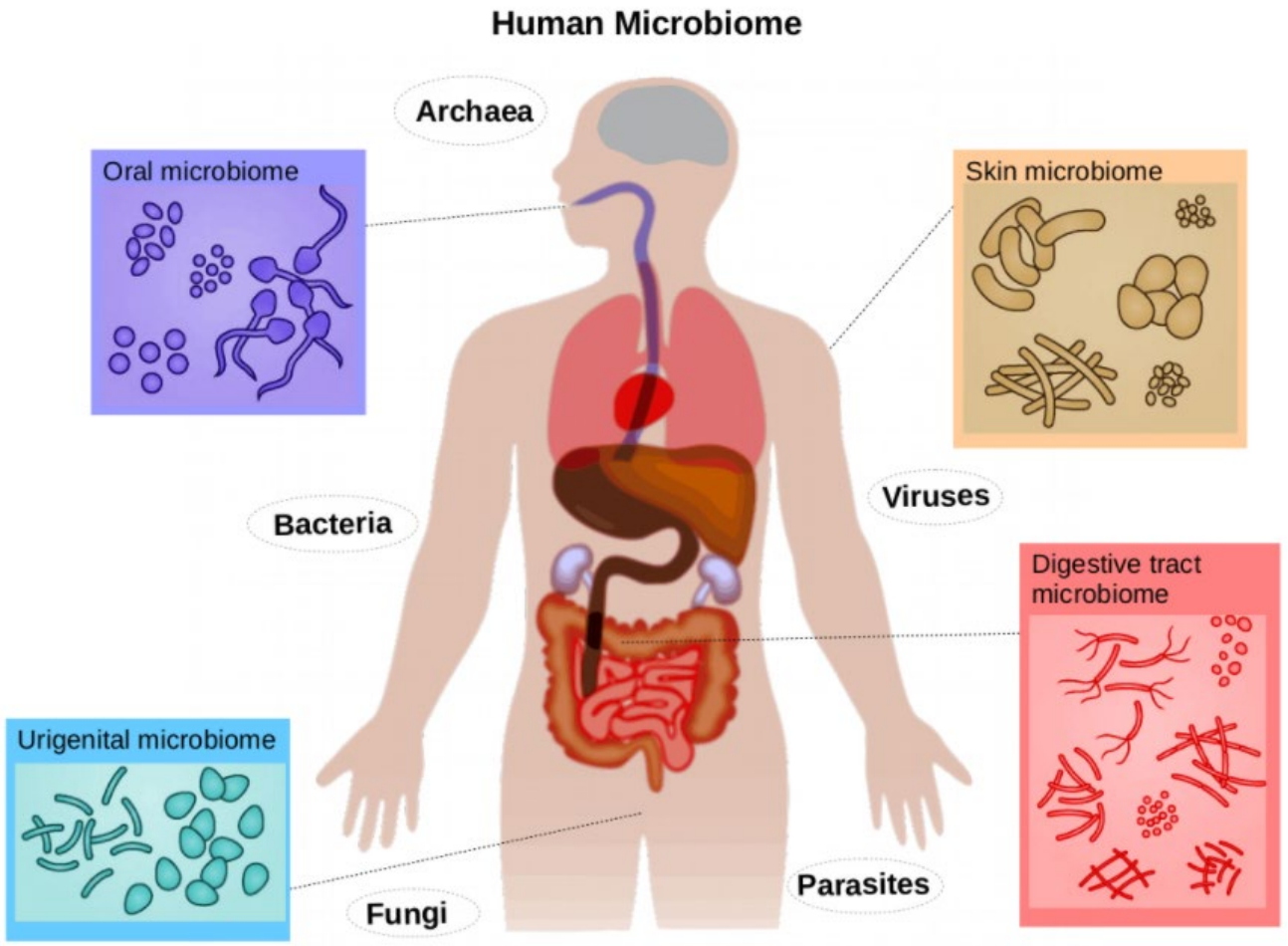
Who are we actually? Some facts regarding the microbiome





- 100x more microbes in our intestine as we have human cells: $10^{14\text{-}15}$ Bacteria
- Total weight: up to 2 kg
- 1000x bigger than the human genome
- Like an individual finger print
- We are great incubators!
- Microbiome as bioreactor – delivers up to 10% of our daily energy needs

Where is the human microbiome located?



95% of the human microbiome is located in the GUT

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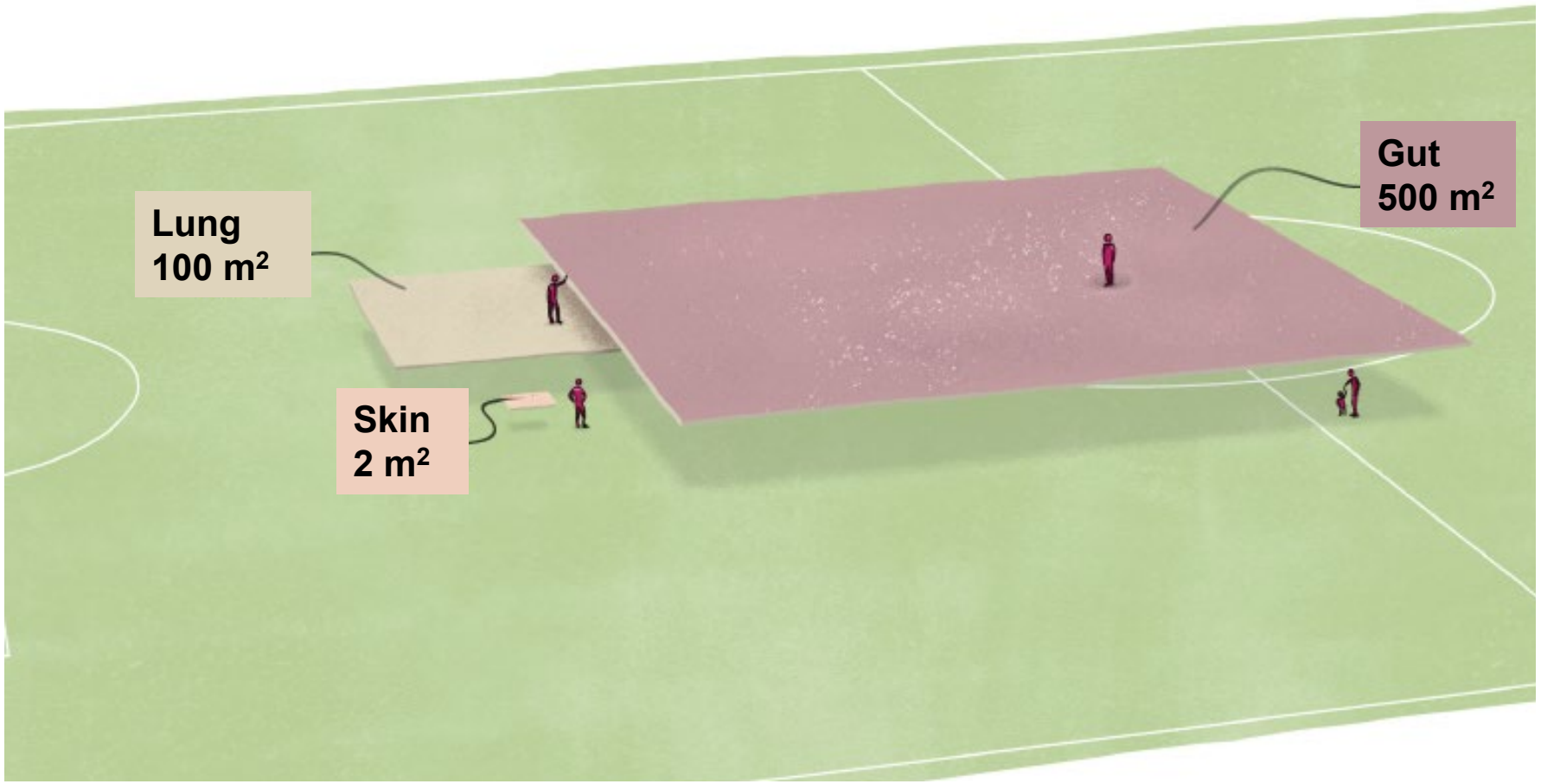
The human microbiome | Summary (whatisbiotechnology.org)

The gut is the main interface with the environment

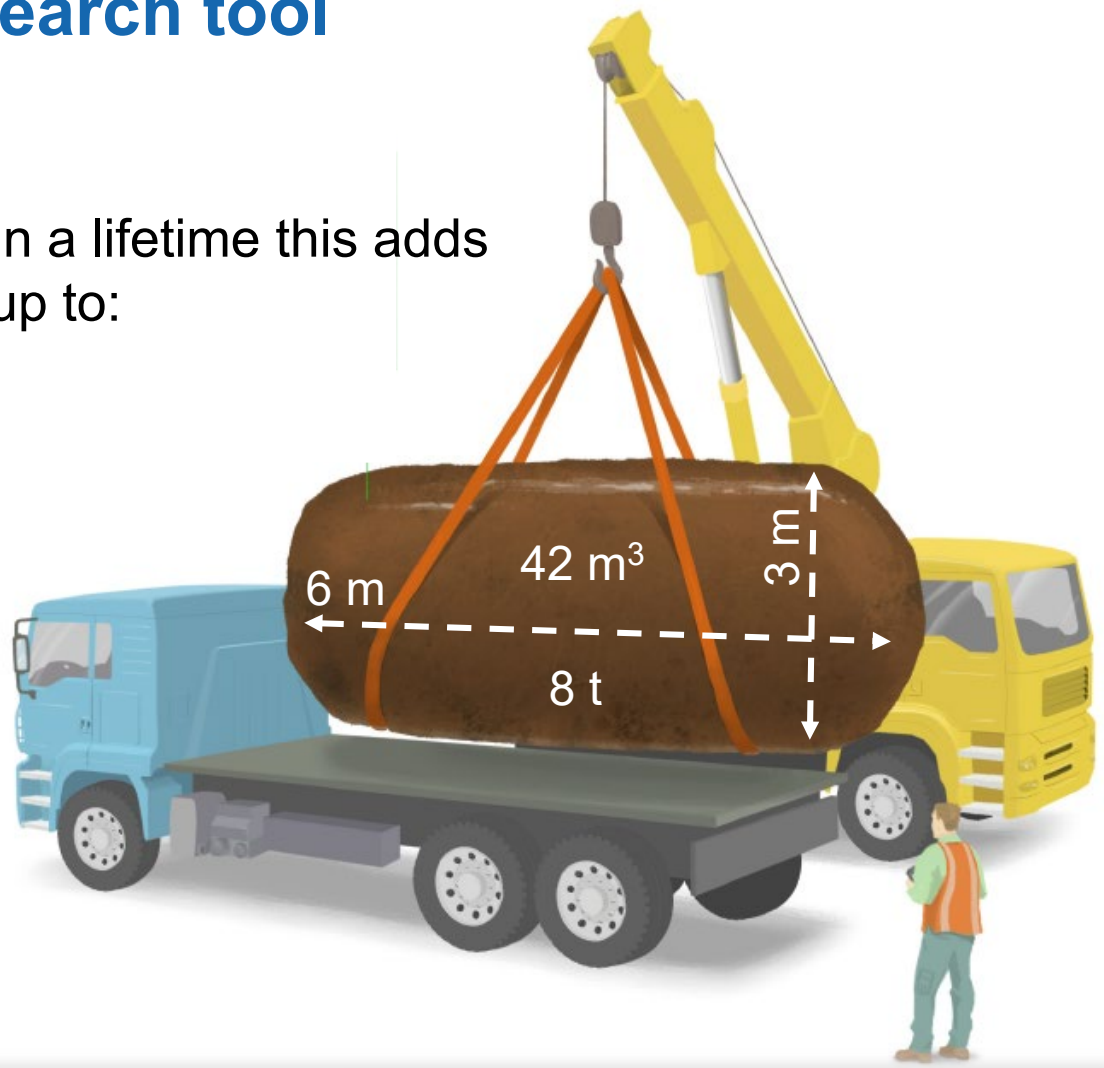


…and home to the biggest number of bacteria

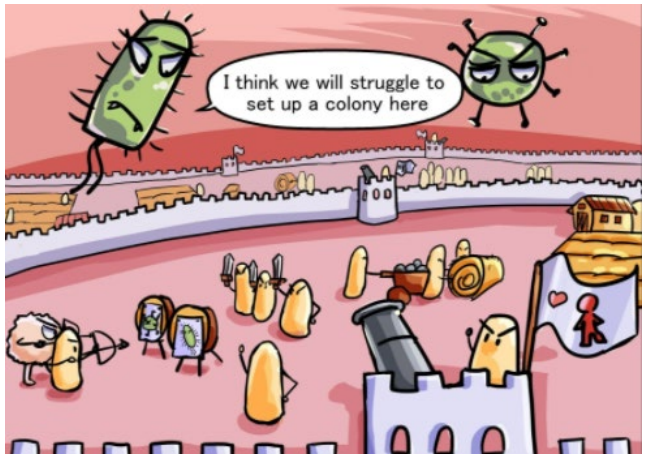
The fecal microbiome: a perfect research tool

Stool per day: ~ 120 g
whereof 40% bacteria

In a lifetime this adds up to:

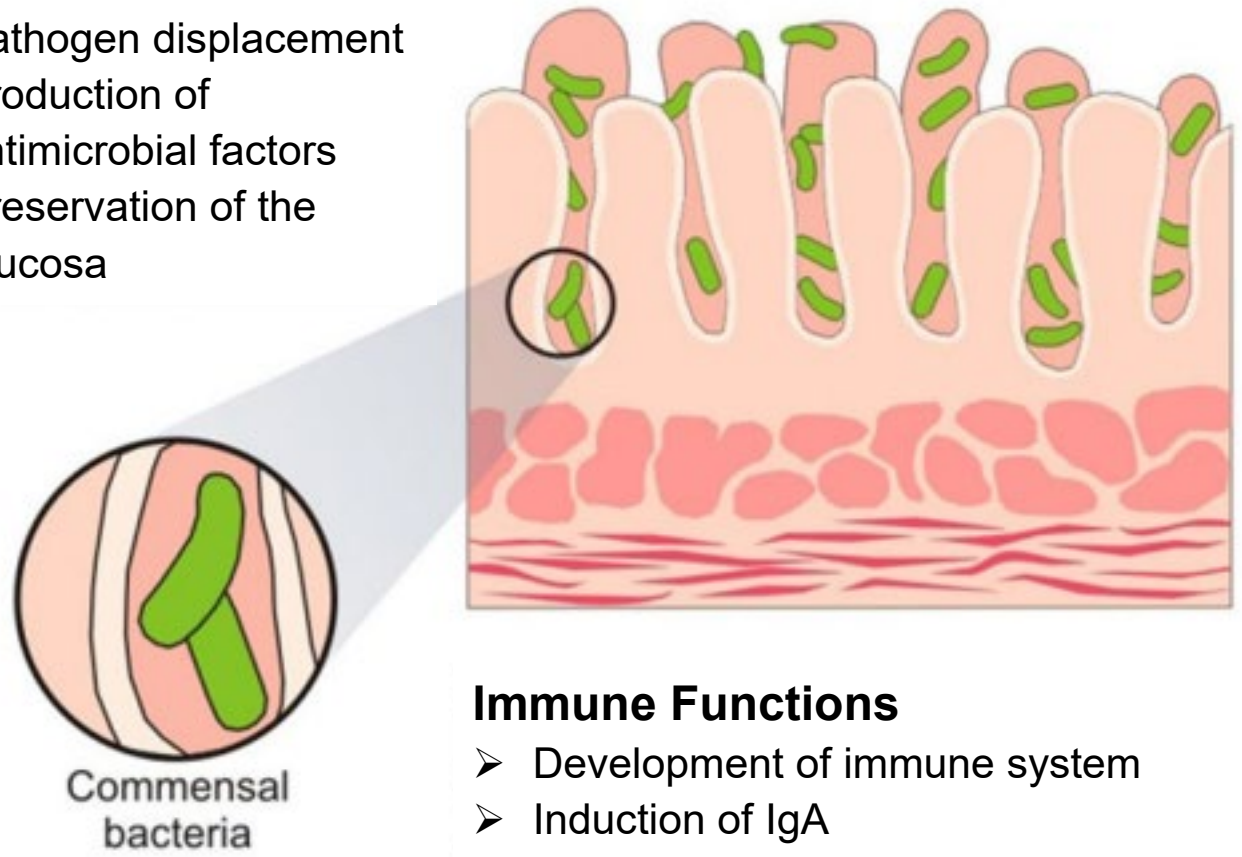


Why is the microbiome important for us?



Protective Functions

- Pathogen displacement
- Production of antimicrobial factors
- Preservation of the mucosa



Metabolic Functions

- Synthesis of vitamins, bile acid
- Production of short-chain fatty acids
- Processing of toxins and food components
- Production of energy

Immune Functions

- Development of immune system
- Induction of IgA
- Degradation of toxins

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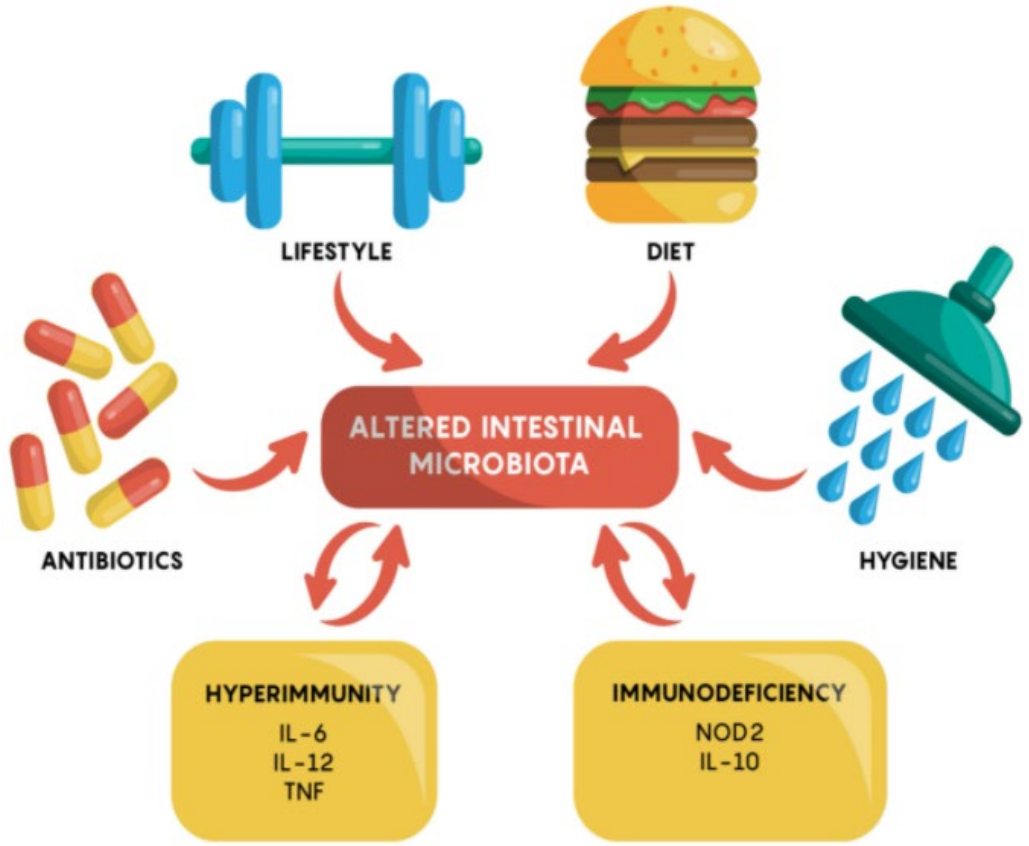
Grenham et al. Front Physiol 2011

The microbiota is influenced by:

- Genes
- Age
- Gender
- Environment
- Stress
- Diet
- Antibiotics
- Drugs
- Immune system

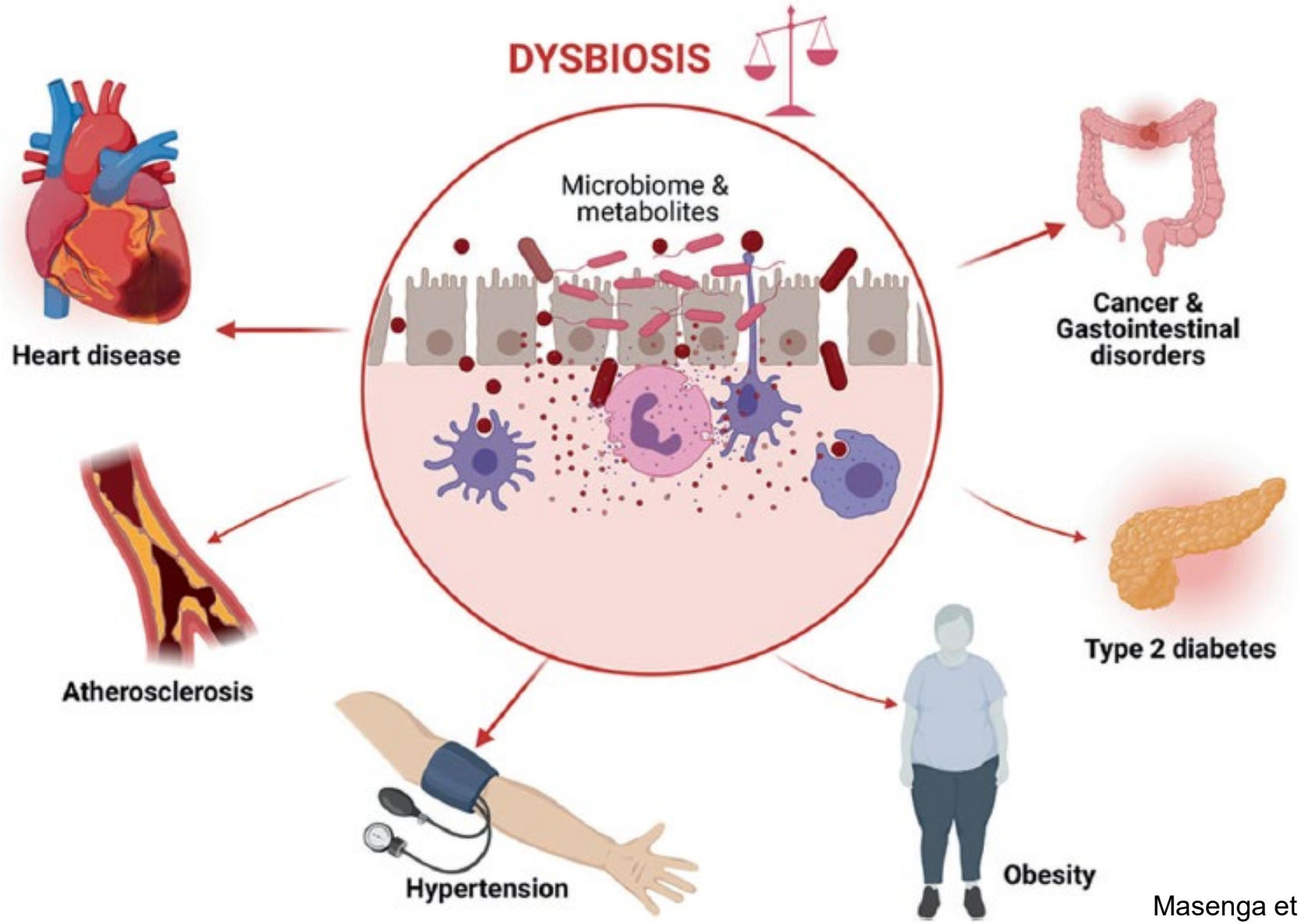


Sommer et al., Nature Reviews 2013

The healthy microbiome– diverse like a big city

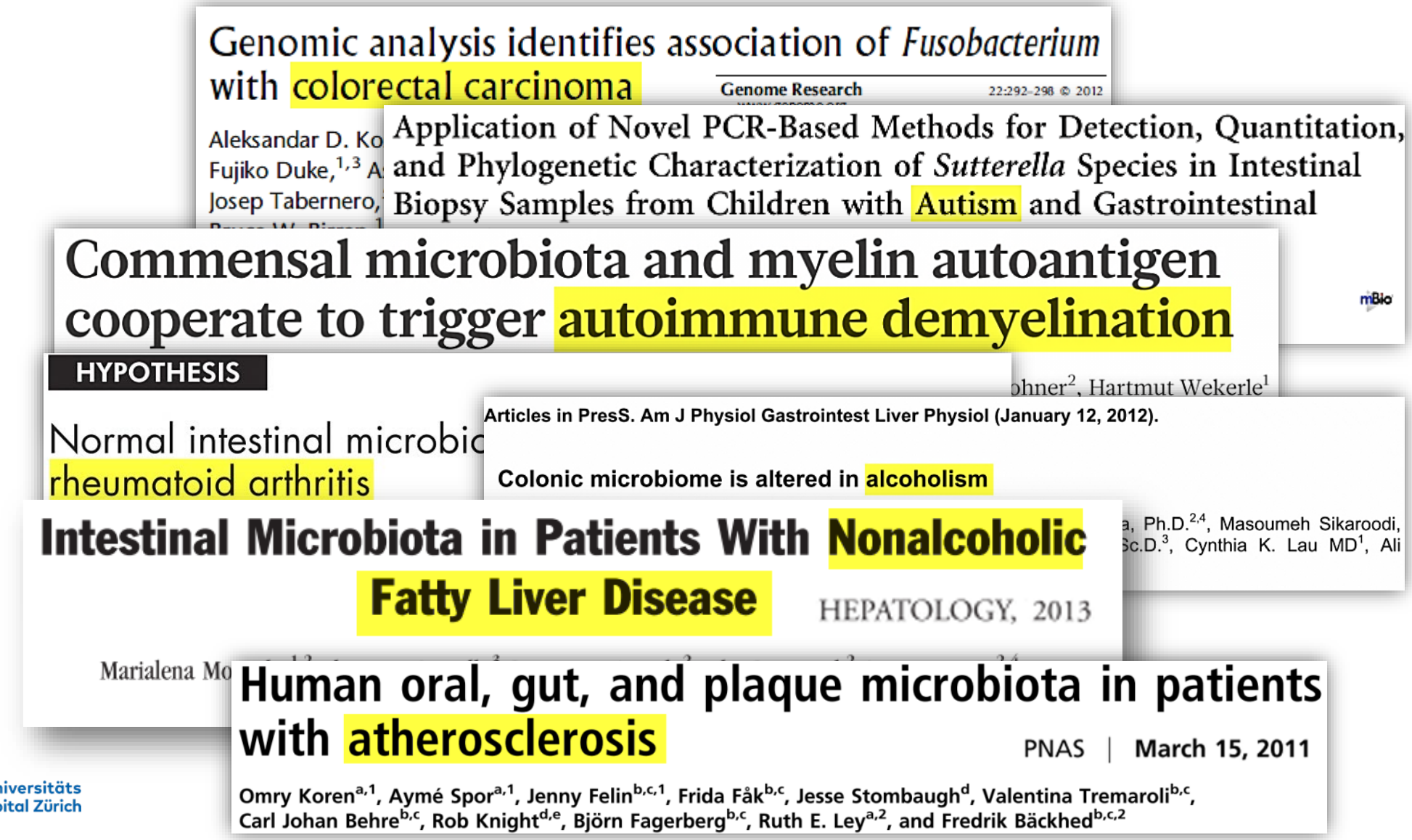
- A healthy microbiome consists in many diverse species (~1’000) that take over specific tasks
- External damage reduces the diversity
- The microbiome can reconstitute itself
- Repetitive damage results in cntnuous aletrations of the microbiome composition:
- Reduced diversity -> Dysbiosis

Dysbiosis favours disease onset

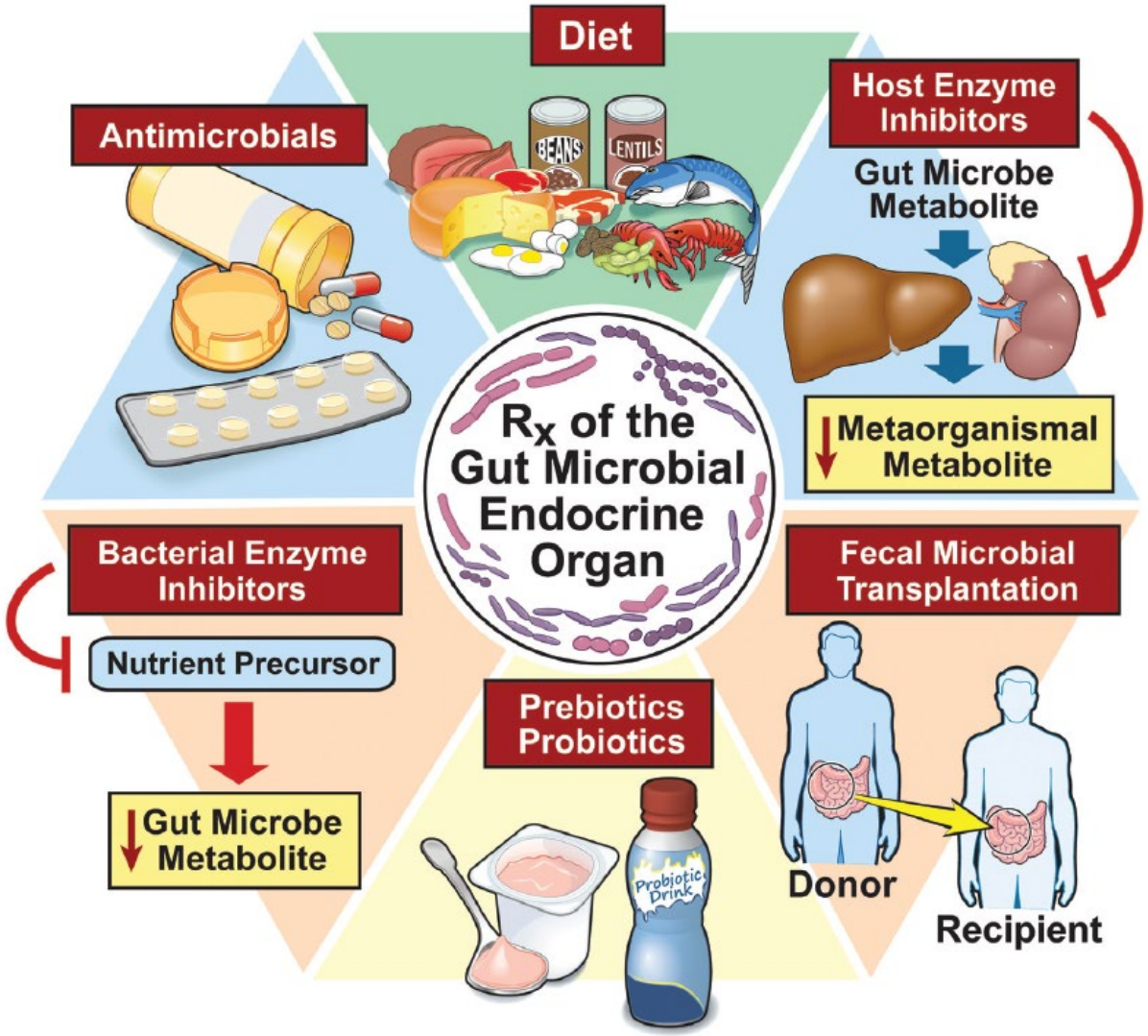


Masenga et al. J Human Hypertension 2022

The role of the Microbiome in the growing list of diseases



Strategies to influence the intestinal microbiome



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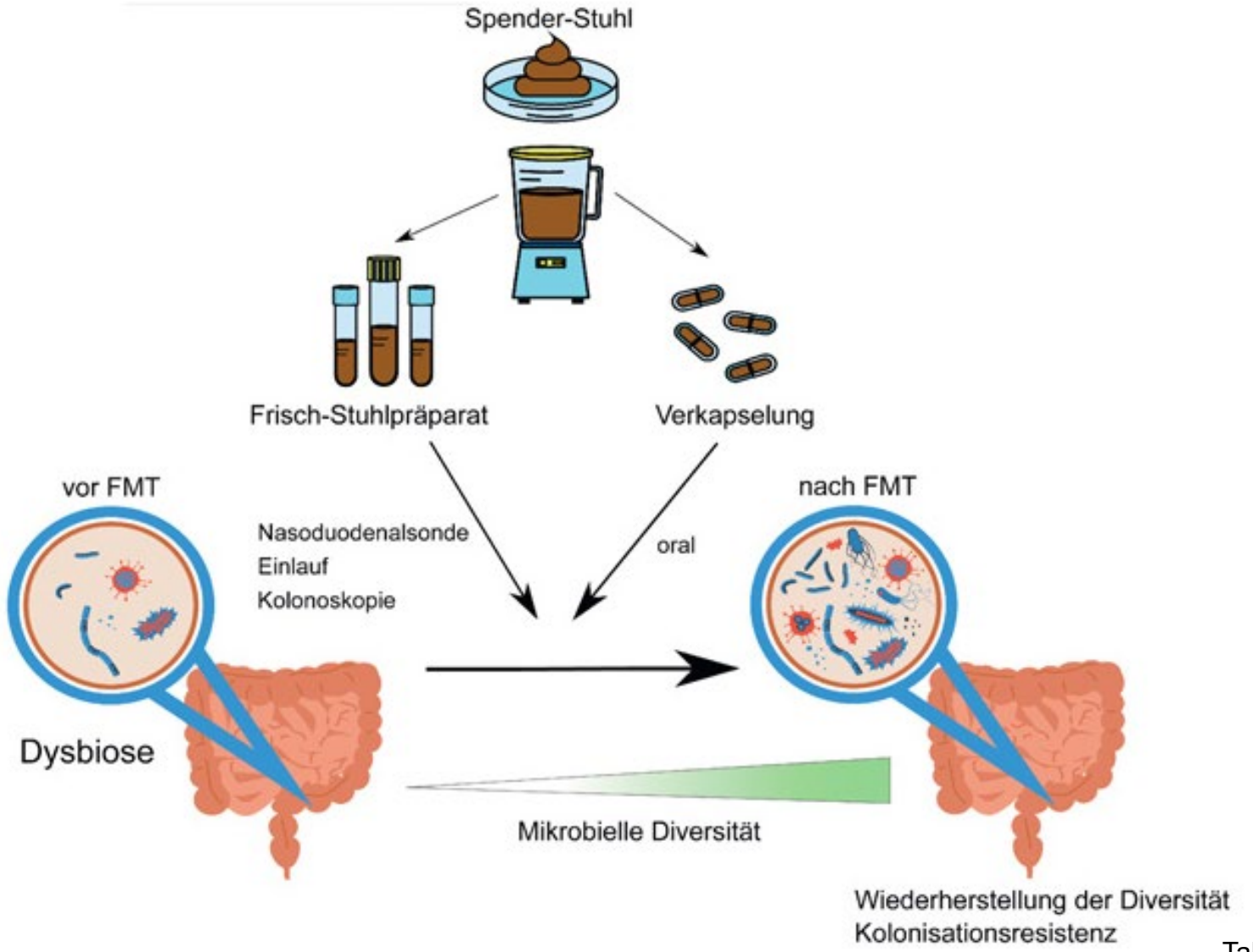
Witkowski et al. Circulation Res 2020; 127,553-570

Fecal Microbiota Transplantation – FMT



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Taken from Gessner, Institutional webpage, University of Regensburg

Microbiome therapies for *Clostridioides difficile (C. diff)* infection

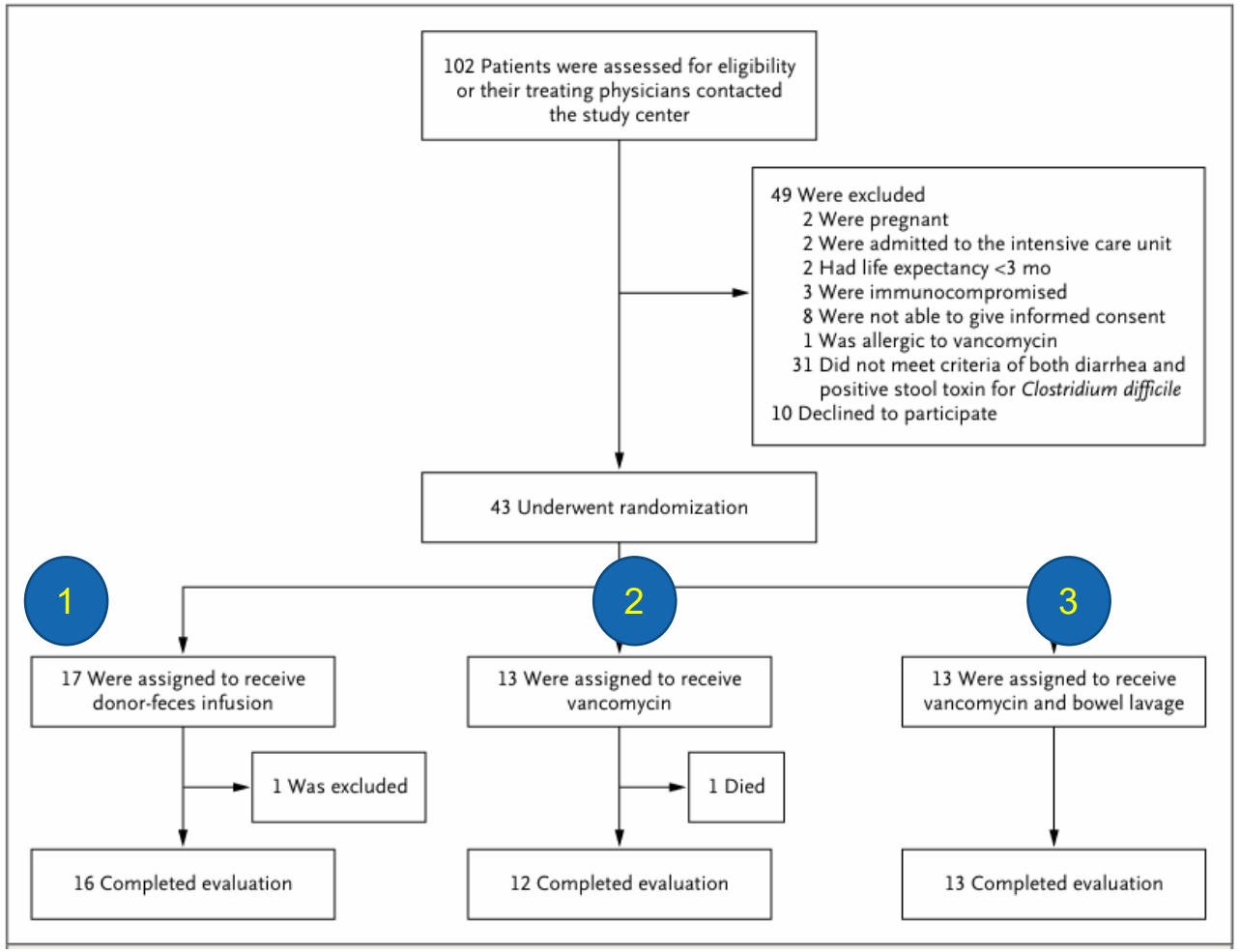
Clostridioides difficile colitis – clinical significance

- Most common form of nosocomial diarrhea[1]
- Estimated costs: > **1.100.000.000** $ per year[2]
- Toxin A: Enterotoxin; permeability, secretion ↑
- Toxin B: Cytotoxin; inflammation
- New, more **virulent strains** (BI/NAP1/027 & Co.), Quinolon-resistence, gene-deletion: toxin-production ↑[3]
- US figures 2008 – **Mortality**: 6x more deaths than all other enteropathogens combined

1) Lipp MJ, J Gastroenterol Hep. 2012
2) Lipp MJ, J Clin Gastroentol. Hepatol. 2012
3) O'Connor JR; Gastroenterology 2009

Randomized controlled trial on FMT for recurrent *C.diff* infection

- 43 patients with relapsed *C. diff.* infections
- → 3 intervention groups:
  1. initial vancomycin + bowel lavage + FMT
  2. vancomycin
  3. vancomycin + bowel lavage
- Primary end point: resolution of diarrhea without relapse after 10 weeks.



Van Nood et al. N Engl J Med, 2013

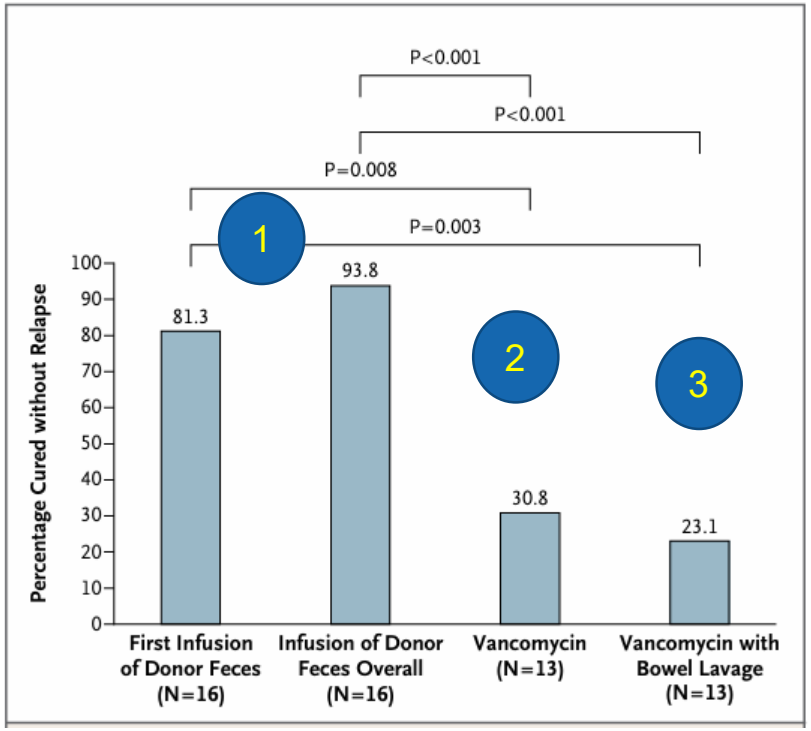
FMT for recurrent *C.diff* infection – more efficient than vancomycin

Resolutions per group

1. 93.8% after first (13/16 pts) or second infusion (2/16)
2. 31% (4/13 pts) after vancomycin alone
3. 23% (3/13 pts) after vancomycin + bowel lavage

➢ As most patients in control groups 2 + 3 relapsed the study was prematurely stopped by the monitoring board.

Rates of cure without relapse

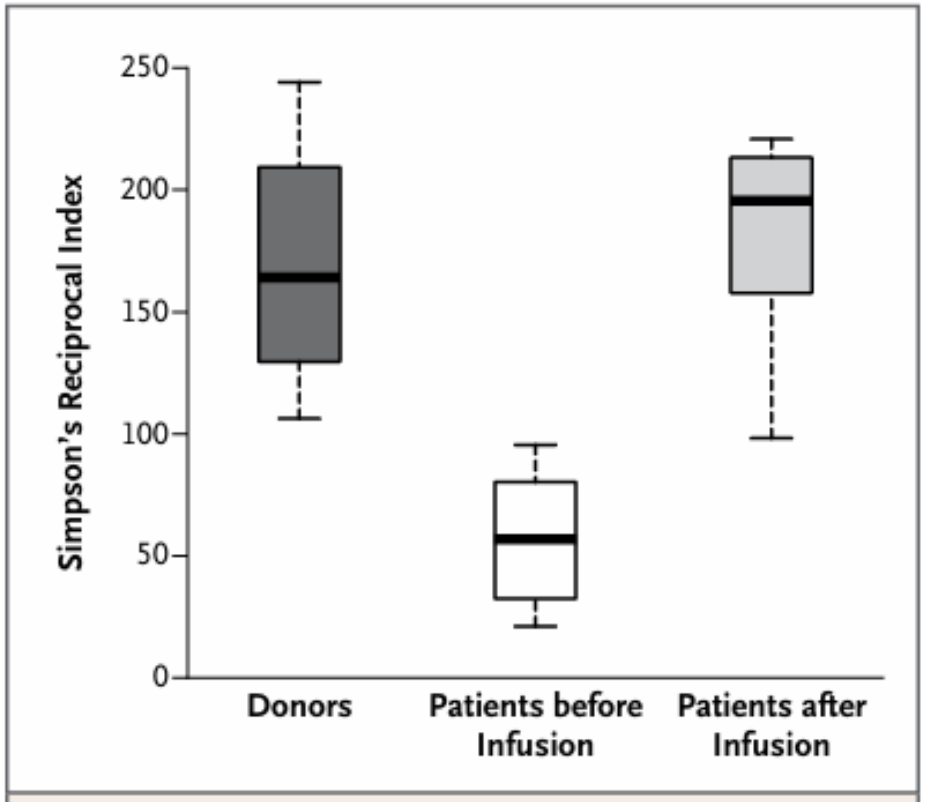


Van Nood et al. N Engl J Med, 2013

FMT for recurrent *C.diff* infection – Analysis of fecal microbiota

Microbiota diversity in patients before/after FMT, as compared to healthy donors

- Fecal bacterial diversity increased after FMT
- Diversity similar to healthy donors
- Increase in *Bacteroidetes* species and *clostridium* clusters IV and XIVa
- Decrease in *Proteobacteria* species



Van Nood et al. N Engl J Med, 2013

FMT for recurrent and refractory *C.diff* infection – effects of different modes of delivery and preparation

- Systematic review and meta-analysis of 37 studies
- FMT was more effective than vancomycin
- Clinical resolution across all studies: 92%
- Significant difference between lower GI & upper GI delivery of FMT (95% vs 88%).
- No difference between fresh and frozen FMT (92% vs 93%)
- Repeated FMT following failure resulted in incremental effects
- SAE were uncommon

Conclusion:

→ FMT is an effective treatment for recurrent and refractory *Clostridium difficile* infection, independent of preparation and route of delivery.

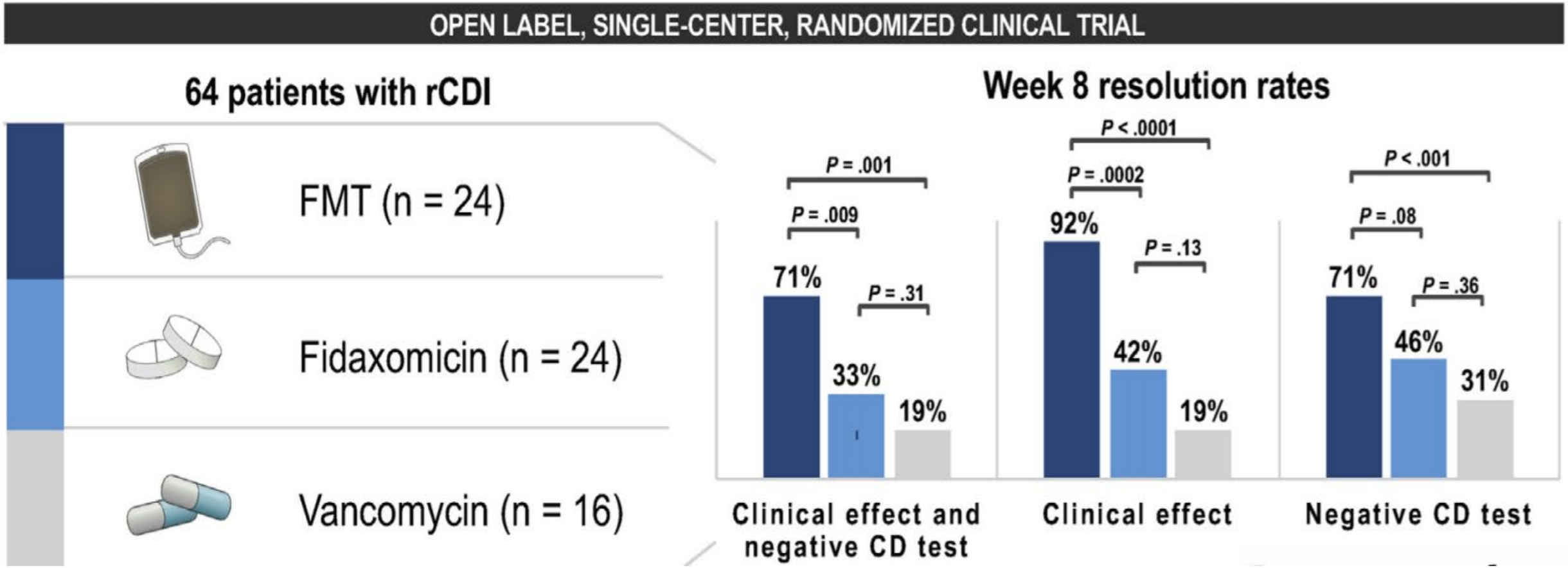
Quraishi et al. Alimentary Pharmacology and therapeutics, 2017

FMT for *C. diff.* infection: the real world experience

- Of the first **259 participants** treated at 20 centers, 222 had completed the short-term follow-up after 1 month and 123 had a follow-up of 6 months.
- **249 (96%) used an unknown donor** (e.g. donor bank).
- Cure at 1 month occurred in **200 patients (90%);** of these 200, **197 (98%) received only 1 FMT**.
- Of **112 patient**s with initial cure who were followed up to 6 months, **4 (4%) had *C.diff*. recurrence**.
- After 6 months, 2 patients (1%) were newly diagnosed with irritable bowel syndrome and 2 patients (1%) with inflammatory bowel disease.

Colleen et al. 2021;160:183–192

FMT OR Fidaxomycin OR Vancomycin for *C. diff*. infection



Hvas et al. Gastroenterology 2019;156:1324–1332

Conclusion on FMT and *C. diff.* Colitis

- FMT prevents a recurrence of *C. diff*. infection by almost 90%
- FMT is more effective than the established antibiotics (vancomycin, fidaxomycin) for recurrent C. diff. infection
- FMT is safe and side effects are rare, however but multidrug-resistant bacteria can be transmitted in rare cases.

Story of the first FDA-approved microbiota therapy - REBYOTA®

- In an open phase 2 study, RBX2660 showed an efficacy of 78.9% after 8 weeks, 91% of responders remained recurrence-free 2 years after treatment. (1)
- A Phase 3 study (PUNCH CD3) showed a sustained clinical response rate of 70,6 % for RBX2660 8 weeks after therapy in comparison to 57,5 % in Placebo (2)
- **RBX2660, (Rebyota®), has been approved by the FDA and is a consortium microbiota-based therapy that is administered as a single-dose rectal enema.**
- A standard antibiotic for *C. diff*. must be administered beforehand.
- Rebyota® is made from donor stools that have undergone extensive screening. (3)

1) *Orenstein et al. Durable reduction of Clostridioides difficile infection recurrence and microbiome restoration after treatment with RBX2660: results from an open-label phase 2 clinical trial. BMC Infect Dis 2022*
2) *Khanna et al. Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent Clostridioides difficile Infection. Drugs 2022*
3) *Feuerstadt et al. Practical Use of Rebyota for the Prevention of Recurrent Clostridioides difficile Infection. Am J Gastroenterol. 2023.*

First FDA-approved microbiota therapy - REBYOTA®

U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125739/0 **BLA APPROVAL**

Ferring Pharmaceuticals Inc. November 30, 2022

STN: 125739
Proper Name: fecal microbiota, live-jslm
Tradename: REBYOTA
Manufacturer: Ferring Pharmaceuticals Inc.
Indication:

- REBYOTA is indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Content current as of:
12/19/2022

Regulated Product(s)
Biologics

U.S. FOOD & DRUG ADMINISTRATION

1) https://www.fda.gov/media/163586/download

2) https://www.fda.gov/vaccines-blood-biologics/vaccines/rebyota

First FDA-approved microbiota therapy - REBYOTA®

INDICATION

REBYOTA (fecal microbiota, live – jslm) is indicated for the **prevention of recurrence** of *Clostridioides difficile* (*C. diff*) infection in individuals 18 years of age and older, following antibiotic treatment for recurrent *C. diff* infection.

Limitation of Use

REBYOTA is **not indicated for the treatment** of *C. diff* infection.

Our own USZ experience:

9 patients treated – 9x success

However, not approved in Europe and will never be according to Ferring!!!

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*https://*www.rebyota.com/

Further microbiome therapies for *C. diff.* infection – SER-109 Phase 3

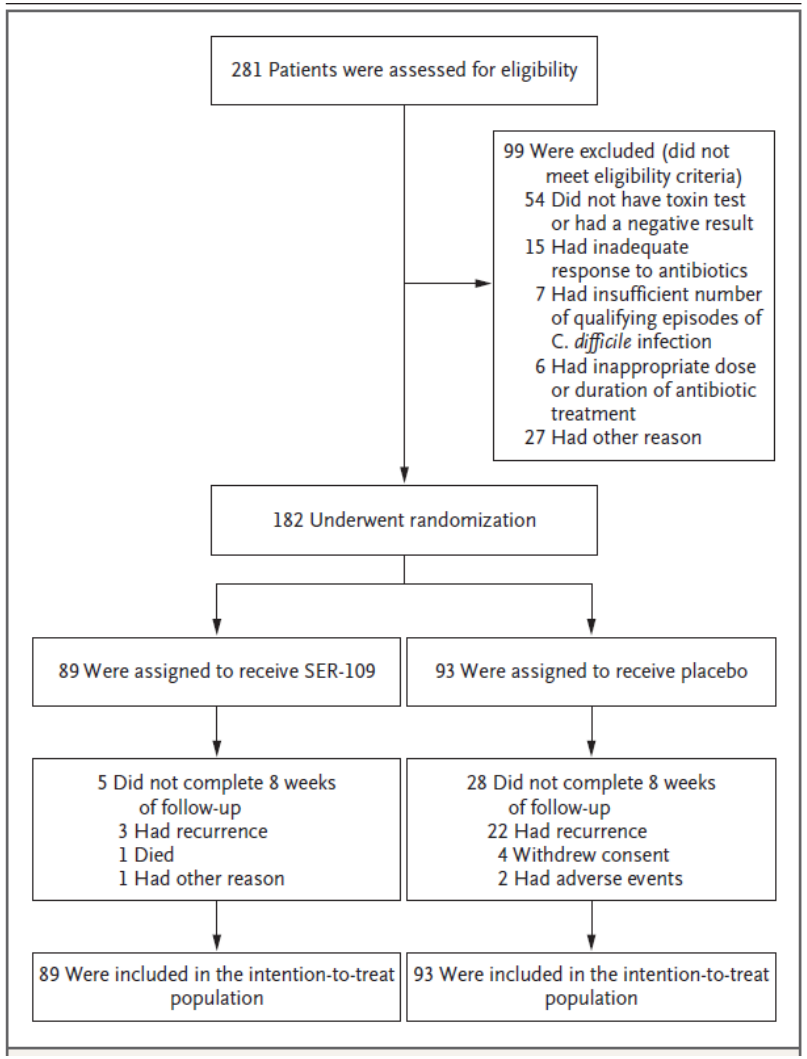
Randomized, double-blind, placebo controlled phase 3 trial

Inclusion: >3 *C. diff.* infections

Treatment: SER-109 or placebo (4 capsules daily for 3 days) after standard-of-care antibiotic treatment.

Primary objective: efficacy up to 8 weeks after treatment.

Analyses of safety, microbiome engraftment, and metabolites were also performed.



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Feuerstadt et al. SER-109,. N Engl J Med. 2022 Jan 20;386(3):220-229.

Further microbiome therapies for *C. diff.* infection – SER-109 Phase 3

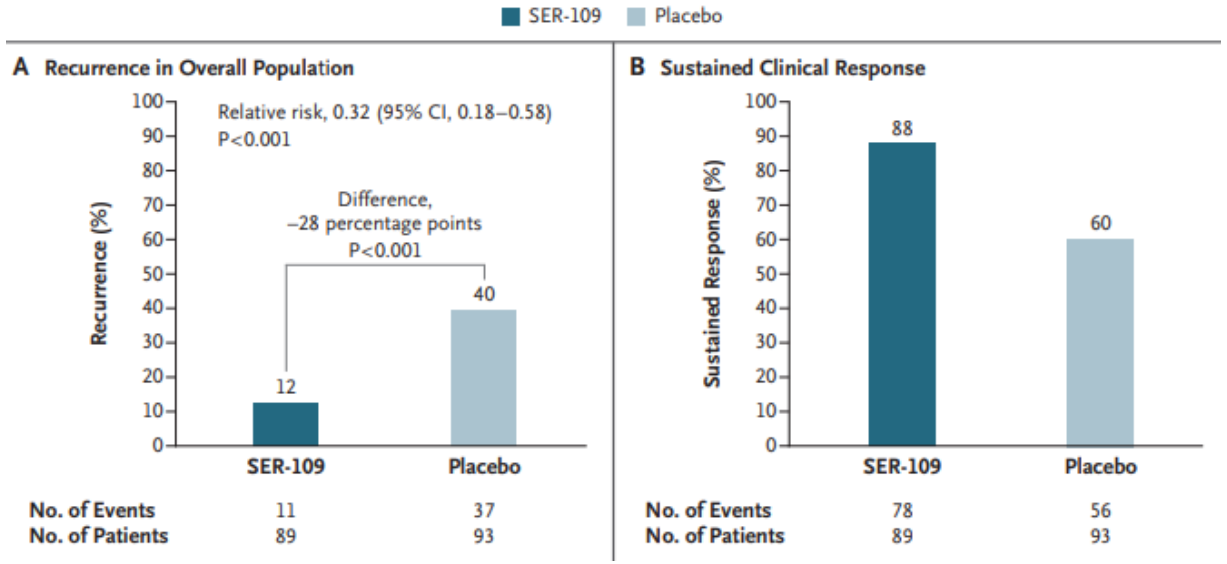
Results

- recurrence was 12% in the SER-109 group and 40% in the placebo group
- Sustained clinical response (absence of recurrence treated with antibiotics) through 8 weeks was 88% in the SER-109 group, 60% in the placebo group

Conclusions:

→ Oral SER-109 administration was superior to placebo

→ Safety profile of SER-109 similar to placebo



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Feuerstadt et al. SER-109. N Engl J Med. 2022 Jan 20;386(3):220-229.

Further microbiome therapies for *C. diff.* infection - SER-109 Phase 3

Conclusions:

→ SER-109 is well tolerated by patients with recurrent *C. diff* infections and prevalent comorbidities

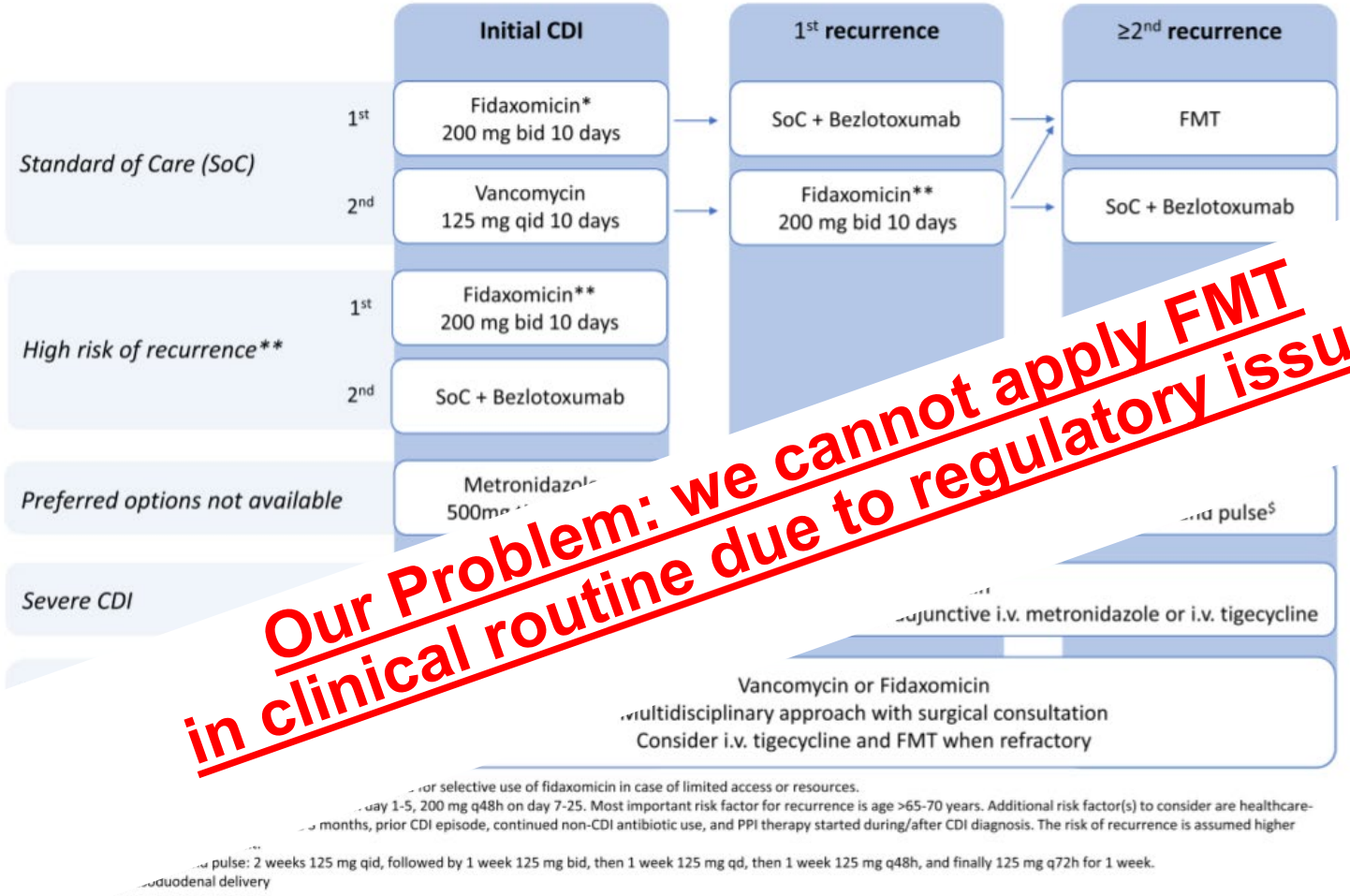
→ Low recurrence rate regardless of prior recurrence, demographics or diagnostics approach

Our own USZ experience: not existing

Not approved in Europe and will never be according to Seres!!!
Even embargo to ship outside of US.

Sims et al. JAMA Netw Open. 2023 Feb 1;6(2):e2255758.

Latest treatment guidelines for *C. diff* infections (2021 update)



Our Problem: we cannot apply FMT in clinical routine due to regulatory issues

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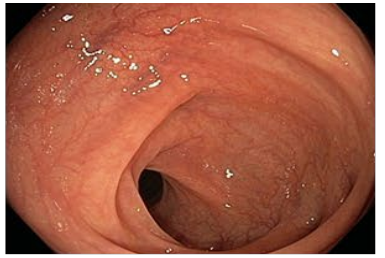
Prehn et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 (2021)

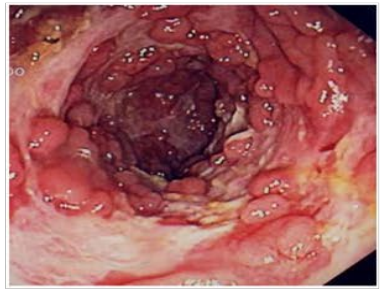
Microbiome therapies for Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD)

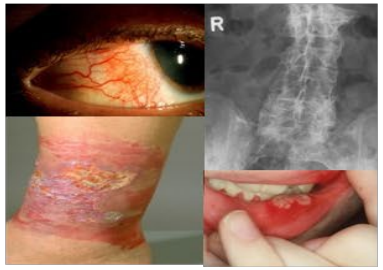
- Crohn's disease (CD) and ulcerative colitis (UC)
- About 15'000 patients in Switzerland
- Chronic and relapsing intestinal inflammation
- CD: segmental, transmural inflammation of the whole gastrointestinal tract
- UC: continuous mucosal inflammation of the colon always starting in the rectum
- Systemic inflammation: eyes, joint, skin, liver



Healthy colon



Crohn's disease

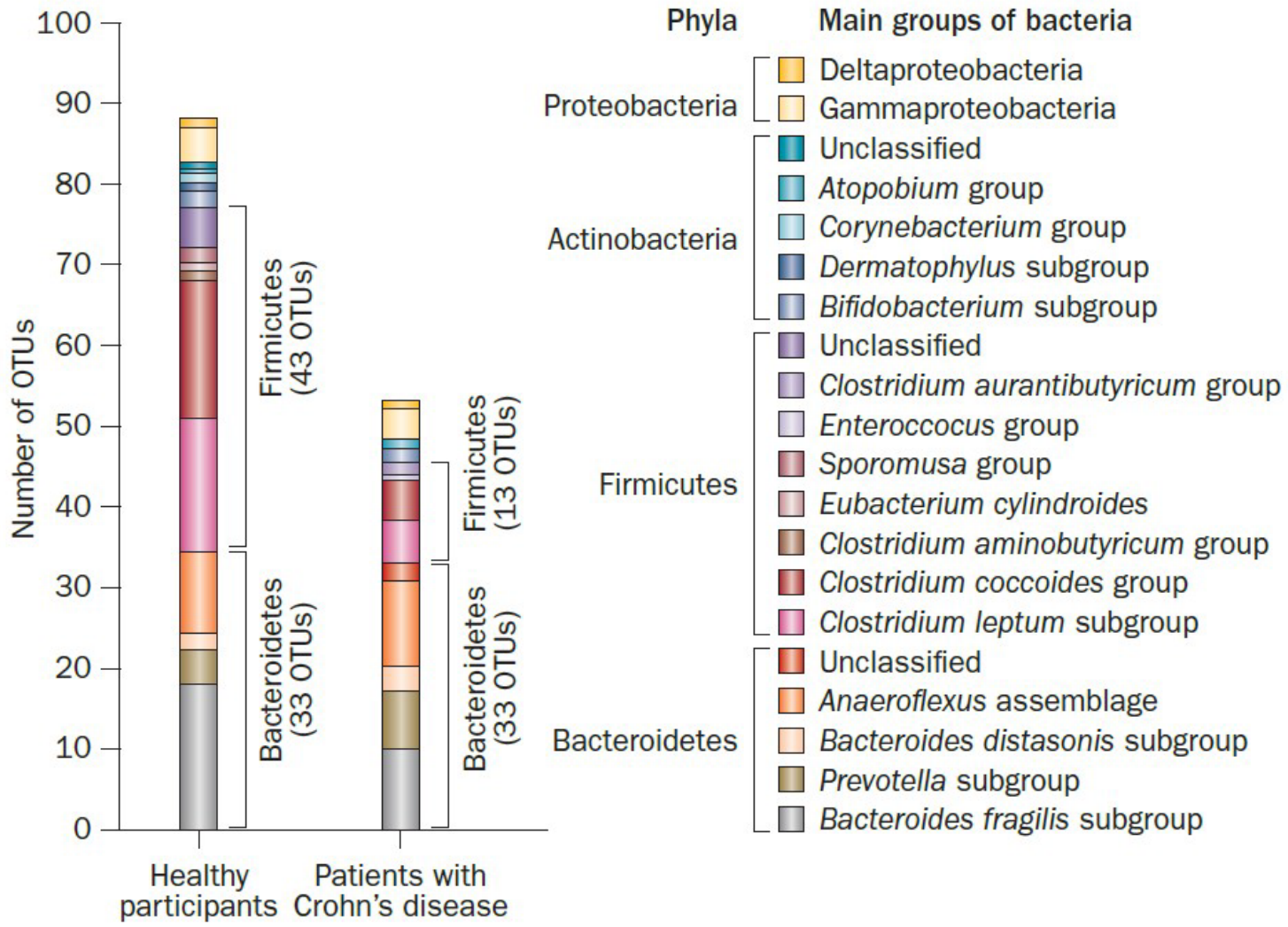


Extraintestinal manifestations

Symptoms of IBD

	CD (n = 279)	UC (n = 113)
Diarrhea	**89.5 %**	**96.4 %**
Bloody stools	27.3 %	89.3 %
Pain (severe)	**86.9 %**	**81.3 %**
Fatigue	81.7 %	40.2 %
Weight loss	59.6 %	38.4 %
Arthralgia/Arthritis	**29.2 %**	**27.7 %**
Fever	24.7 %	20.5 %
Skin manifestations	14.2 %	15.2 %

“Dysbiosis” in IBD: reduced “diversity”



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Manichanh, C. et al. Nat. Rev. Gastroenterol. Hepatol. 9,599–608 (2012)

Microbiota and FMT for Colitis ulcerosa

TREATMENT OF ULCERATIVE COLITIS BY IMPLANTATION OF NORMAL COLONIC FLORA

SIR,—One of us (J. D. B.) has proposed that bacterial metabolites of bile acids or cholesterol are involved in the actiology of ulcerative colitis.[1] Using himself as a subject he found that alpha-tocopherylquinone (α-TQ) suppressed disease activity in ulcerative colitis, possibly due to its ability to interfere with bacterial oxidation of bile acids by an anti-vitamin K activity.[2] He report a further experiment implicating colonic flora in the pathogenesis of ulcerative colitis.

J. D. B. had continuously active, severe ulcerative colitis for 7 years, confirmed endoscopically and histologically. The condition was refractory to standard management including steroids and sulphasalazine and every time daily prednisone dosage was reduced below 30 mg severe symptoms (bloody diarrhoea, cramping, tenesmus, skin lesions, and arthritis) recurred. For the past 4 years disease activity has been well controlled with α-TQ (4·2 g per day) and a very low fat diet. Although this regimen was effective at reducing the severity of symptoms the underlying disease process remained active—when α-TQ was discontinued or reduced in dosage severe symptoms recurred in 1–2 days.

THE LANCET, JANUARY 21, 1989

FMT for the treatment of Colitis ulcerosa

Gastroenterology 2015;149:102–109

Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

Paul Moayyedi,[1] Michael G. Surette,[1] Peter T. Kim,[2,3] Josie Libertucci,[1] Melanie Wolfe,[1] Catherine Onischi,[3] David Armstrong,[1] John K. Marshall,[1] Zain Kassam,[4] Walter Reinisch,[1] and Christine H. Lee[3]

→ Randomized trial demonstrating efficacy of FMT in UC (9 of 38 (24%) patients in the FMT arm vs 2 of 37 (5%) in the placebo arm in remission at the end of treatment

→ Fecal donor and time of UC appear to affect outcomes

Moayyedi et al. Gastroenterology 2015;149:102–109

FMT for the treatment of Colitis ulcerosa

Gastroenterology 2015;149:110–118

Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis

Noortje G. Rossen,[1] Susana Fuentes,[2] Mirjam J. van der Spek,[1] Jan G. Tijssen,[3] Jorn H. A. Hartman,[2] Ann Duflou,[1] Mark Löwenberg,[1] Gijs R. van den Brink,[1] Elisabeth M. H. Mathus-Vliegen,[1] Willem M. de Vos,[2,4] Erwin G. Zoetendal,[2] Geert R. D'Haens,[1] and Cyriel Y. Ponsioen[1]

→ Single-center, double-blind, placebo-controlled, randomized, proof-of-concept phase 2 trial on efficacy of FMT in UC.

→ 2 duodenal infusions of feces from a healthy donor did not result in a statistically significant difference in clinical remission and endoscopic improvement.

→ FMT in UC is not "one size fits all"

Rossen et al. Gastroenterology 2015;149:110–118

Multidonor FMT for the treatment of Colitis ulcerosa

Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial

Sudarshan Paramsothy, Michael A Kamm, Nadeem O Kaakoush, Alissa J Walsh, Johan van den Bogaerde, Douglas Samuel, Rupert W L Leong, Susan Connor, Watson Ng, Ramesh Paramsothy, Wei Xuan, Enmoore Lin, Hazel M Mitchell, Thomas J Borody

→ Multicentre, double-blind, randomised, placebo-controlled trial at three hospitals to establish the efficacy of intensive-dosing, multidonor, faecal microbiota transplantation in active UC.

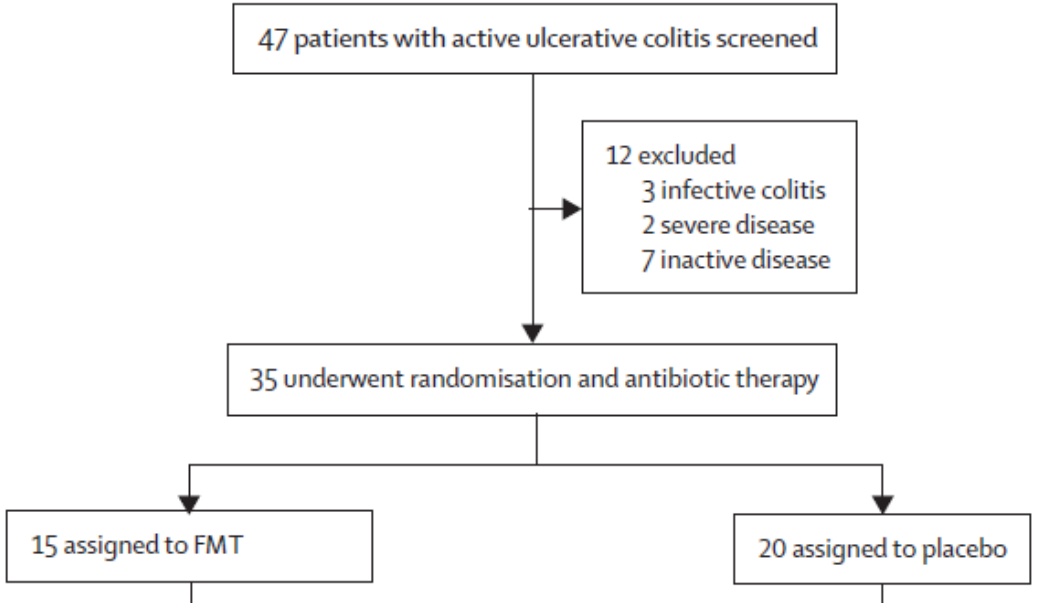
→ FMT or placebo colonoscopic infusion, followed by enemas 5 days per week for 8 weeks.

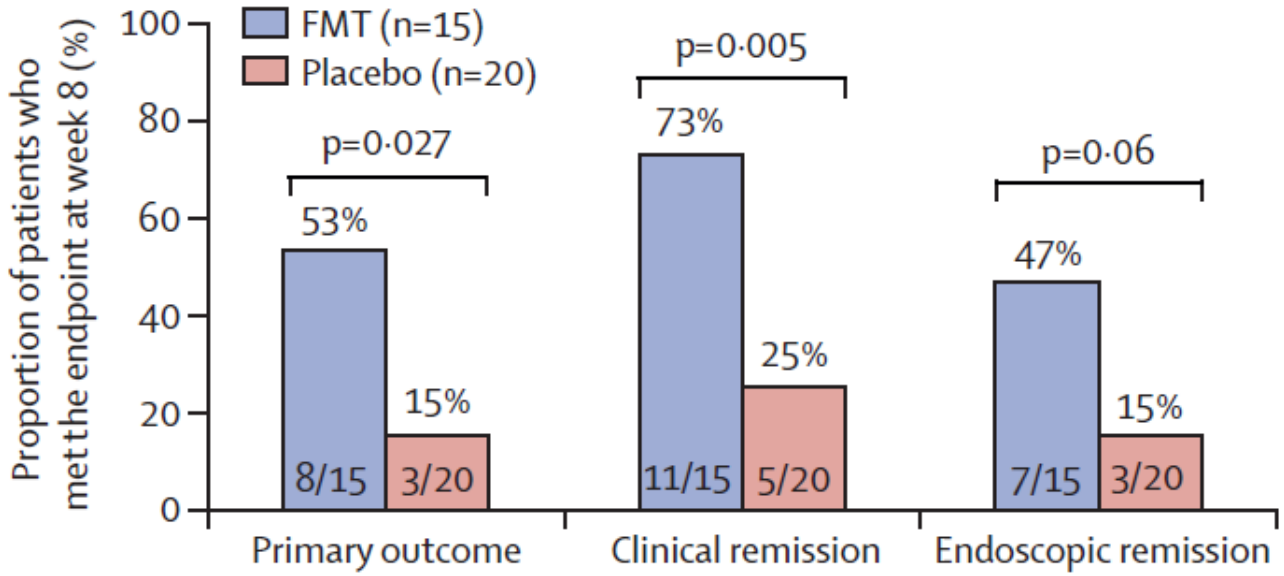
→ Intensive-dosing, multidonor, FMT induces clinical remission and endoscopic improvement in active UC and is associated with distinct microbial changes that relate to outcome. FMT is a promising new therapeutic option for UC.

Paramsothy et al. Lancet 2017; 389:1218-1228

LOTUS Study: Lyophilised oral faecal microbiota transplantation for ulcerative colitis (LOTUS)

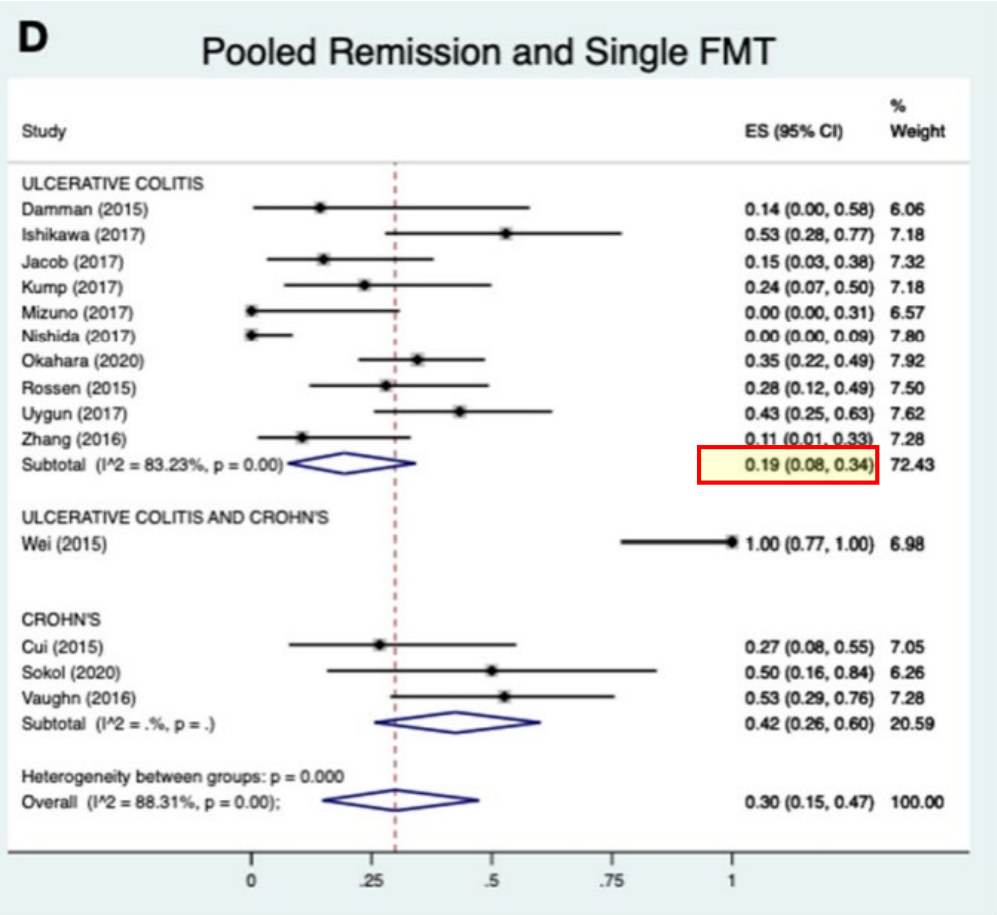
Randomised, double-blind, placebo-controlled trial

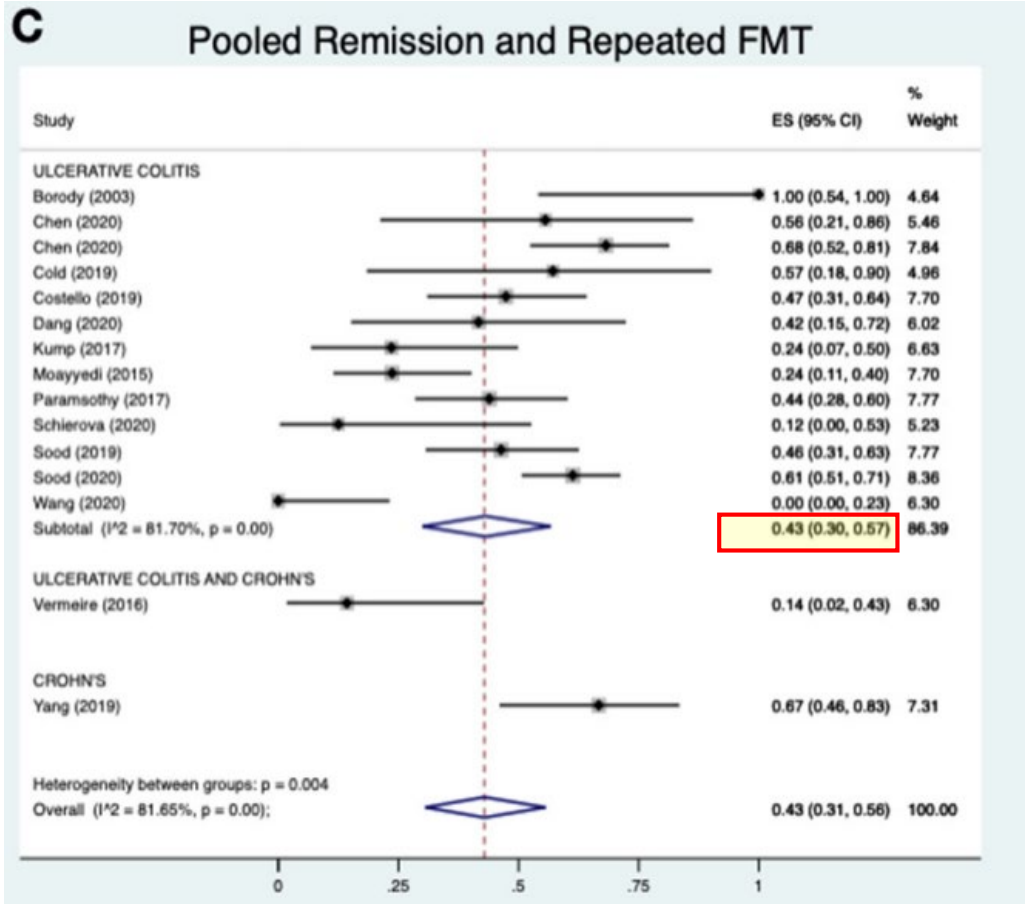




Haifer et al. Lancet Gastroenterol Hepatol 2022; 7: 141–51

Repetitive FMT in Colitis ulcerosa: Systematic Meta-Analysis





Single FMT: 10 studies, Remission rate 19%, CI 8-34%

Repeated FMT: 13 studies, remission rate 43%, CI 30-57%

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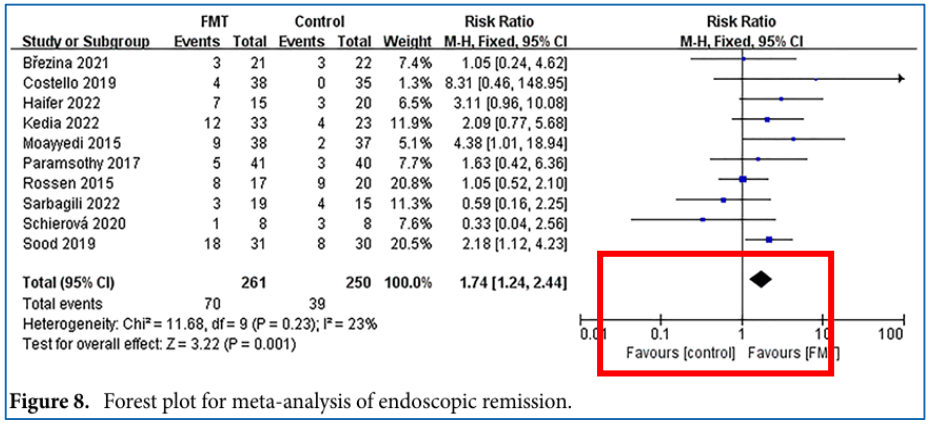
Mocanu V, et al. J Clin Med. 2021 Mar 1;10(5):959.

Further indication - Preclinical/clinical studies
Acute, mild-to-moderately active, refractory ulcerative colitis

Systematic review and meta-analysis of 13 randomized controlled trials[1]:

- FMT is effective in patients with active ulcerative colitis (UC)
- Very good safety profile

Endoscopic remission



Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Březina 2021	3	21	3	22	7.4%	1.05 [0.24, 4.62]
Costello 2019	4	38	0	35	1.3%	8.31 [0.46, 148.95]
Haifer 2022	7	15	3	20	6.5%	3.11 [0.96, 10.08]
Kedia 2022	12	33	4	23	11.9%	2.09 [0.77, 5.68]
Moayyedi 2015	9	38	2	37	5.1%	4.38 [1.01, 18.94]
Paramsothy 2017	5	41	3	40	7.7%	1.63 [0.42, 6.36]
Rossen 2015	8	17	9	20	20.8%	1.05 [0.52, 2.10]
Sarbagili 2022	3	19	4	15	11.3%	0.59 [0.16, 2.25]
Schierová 2020	1	8	3	8	7.6%	0.33 [0.04, 2.56]
Sood 2019	18	31	8	30	20.5%	2.18 [1.12, 4.23]
Total (95% CI)		**261**		**250**	**100.0%**	**1.74 [1.24, 2.44]**
Total events	70		39			

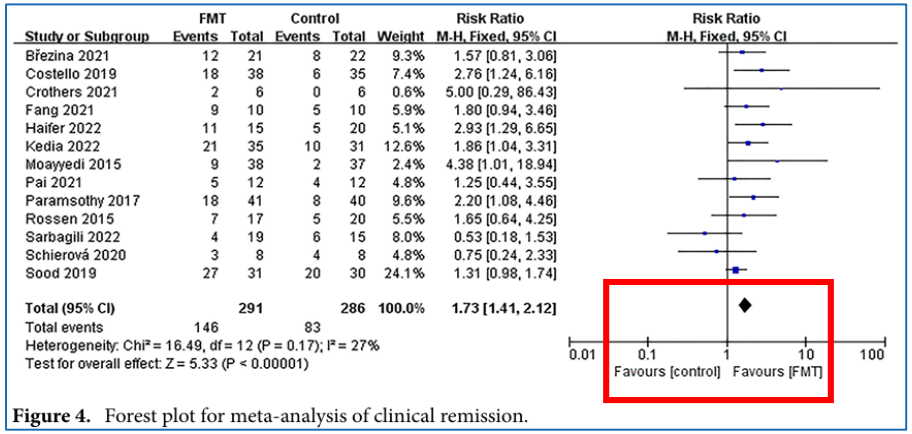
Heterogeneity: Chi² = 11.68, df = 9 (P = 0.23); I² = 23%
Test for overall effect: Z = 3.22 (P = 0.001)

Risk Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours [control] Favours [FMT]

Figure 8. Forest plot for meta-analysis of endoscopic remission.

Conclusion: FMT is an effective and safe therapy for the treatment of active UC

Clinical remission



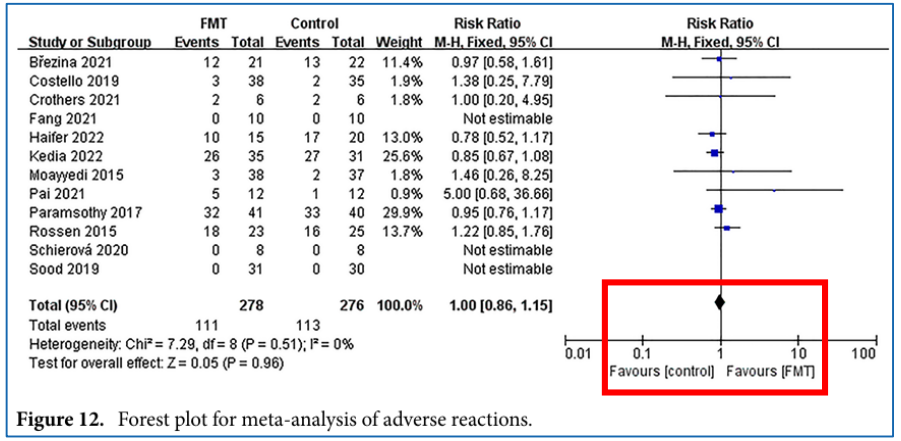
Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Březina 2021	12	21	8	22	9.3%	1.57 [0.81, 3.06]
Costello 2019	18	38	6	35	7.4%	2.76 [1.24, 6.16]
Crothers 2021	2	6	0	6	0.6%	5.00 [0.29, 86.43]
Fang 2021	9	10	5	10	5.9%	1.80 [0.94, 3.46]
Haifer 2022	11	15	5	20	5.1%	2.93 [1.29, 6.65]
Kedia 2022	21	35	10	31	12.6%	1.86 [1.04, 3.31]
Moayyedi 2015	9	38	2	37	2.4%	4.38 [1.01, 18.94]
Pai 2021	5	12	4	12	4.8%	1.25 [0.44, 3.55]
Paramsothy 2017	18	41	8	40	9.6%	2.20 [1.08, 4.46]
Rossen 2015	7	17	5	20	5.5%	1.65 [0.64, 4.25]
Sarbagili 2022	4	19	6	15	8.0%	0.53 [0.18, 1.53]
Schierová 2020	3	8	4	8	4.8%	0.75 [0.24, 2.33]
Sood 2019	27	31	20	30	24.1%	1.31 [0.98, 1.74]
Total (95% CI)		**291**		**286**	**100.0%**	**1.73 [1.41, 2.12]**
Total events	146		83			

Heterogeneity: Chi² = 16.49, df = 12 (P = 0.17); I² = 27%
Test for overall effect: Z = 5.33 (P < 0.00001)

Risk Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours [control] Favours [FMT]

Figure 4. Forest plot for meta-analysis of clinical remission.

Adverse reaction



Study or Subgroup	FMT Events	FMT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Březina 2021	12	21	13	22	11.4%	0.97 [0.58, 1.61]
Costello 2019	3	38	2	35	1.9%	1.38 [0.25, 7.79]
Crothers 2021	2	6	2	6	1.8%	1.00 [0.20, 4.95]
Fang 2021	0	10	0	10		Not estimable
Haifer 2022	10	15	17	20	13.0%	0.78 [0.52, 1.17]
Kedia 2022	26	35	27	31	25.6%	0.85 [0.67, 1.08]
Moayyedi 2015	3	38	2	37	1.8%	1.46 [0.26, 8.25]
Pai 2021	5	12	1	12	0.9%	5.00 [0.68, 36.66]
Paramsothy 2017	32	41	33	40	29.9%	0.95 [0.76, 1.17]
Rossen 2015	18	23	16	25	13.7%	1.22 [0.85, 1.76]
Schierová 2020	0	8	0	8		Not estimable
Sood 2019	0	31	0	30		Not estimable
Total (95% CI)		**278**		**276**	**100.0%**	**1.00 [0.86, 1.15]**
Total events	111		113			

Heterogeneity: Chi² = 7.29, df = 8 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

Risk Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours [control] Favours [FMT]

Figure 12. Forest plot for meta-analysis of adverse reactions.

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[1]Feng et al. Scientific Reports, 2023

Further indication - Preclinical/clinical studies
Acute, mild-to-moderately active, refractory ulcerative colitis

- FMT is as **efficient as corticosteroids** in UC patients with mild to moderate disease[1]
- FMT is **efficient** in patients with active disease while being **under thiopurines, mesalazine or corticosteroids**[1,2,3,4,5,6,7,9]
- FMT is **efficient** in patients with active disease while being **under anti-TNF** antibody therapy[4,9]
- FMT induces **steroid-free** clinical and endoscopic **remission**[3,4,5,6,9]
- FMT is successful for **maintenance of steroid-free remission**[8]

Conclusions: based on existing clinical data

→ no further preclinical studies necessary

→ no further clinical trial necessary

→ the approval for FMT in this further indication as non-standardizable medicinal therapeutic can be requested

→ FMT will be applied in UC patients with mild-to-moderately active disease who have not responded to standard therapy (mesalazine, thiopurines) **and** at least 1 biological and/or have steroid-refractory disease

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[1]Huang et al. Journal of Translational Medicine, 2022, [2]Rossen et al. Gastroenterology 2015, [3]Paramsothy et al. Lancet 2017, [4]Moayyedi et al. Gastroenterology 2015, [5]Kedia et al. Gut 2022, [6]Haifer et al. Lancet Gastroenterol Hepatol 2022, [7]Fang et al. Microb Cell Fact 2021, [8]Sood et al. J Crohns Colitis 2019, [9]Costello et al. JAMA 2019

Can we possibly identify the “Super-Donors”

Standardized faecal microbiota transplantation with microbiome-guided donor selection in active UC patients: A randomized, placebo-controlled intervention study

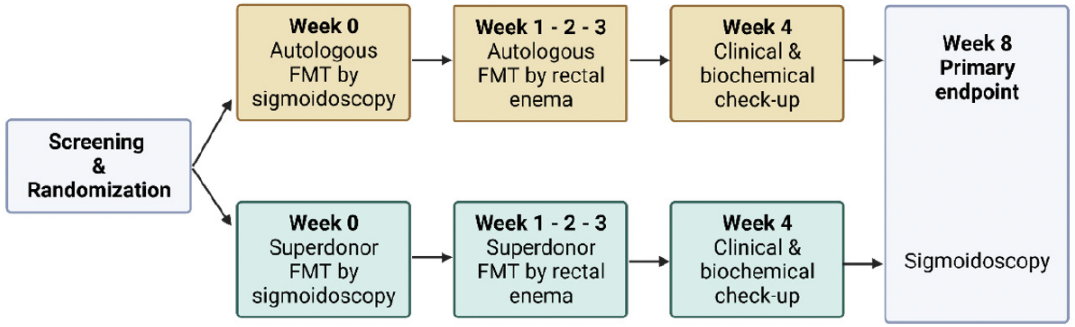

Table 2: Primary and secondary endpoints at week 8.

Outcome	Autologous FMT (n=36)	Superdonor FMT (n=30)	*p*
Primary outcome			
Steroid-free clinical remission*	5 (13.9%)	3 (10.0%)	0.72
Secondary outcomes			
Steroid-free PRO-2 remission†	10 (27.8%)	7 (23.3%)	0.78
Steroid-free PRO-2 response‡	12 (33.3%)	9 (30.0%)	0.80
Steroid-free endoscopic remission§	7 (19.4%)	5 (16.7%)	1.00
Steroid-free endoscopic responseΔ	7 (19.4%)	5 (16.7%)	1.00

*Total Mayo score ≤2, with all subscores ≤1.

†Combined Mayo subscores of ≤1 for rectal bleeding plus stool frequency.

‡Decrease of ≥3 points or ≥50% reduction from baseline (or both) in combined Mayo subscores for rectal bleeding plu stool frequency.

§Mayo endoscopy subscore ≤1.

ΔMayo endoscopy subscore ≤1, with ≥1 point reduction from baseline.

Conclusions

→ no significant difference in steroid-free remission rates at week 8 btw repeated anaerobic-prepared super donor (S) FMT and autologous (A) FMT

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Caenepeel et al., Abstracts of the 17th Congress of ECCO - European Crohn’s and Colitis Organisation, February 2022

Improved microbiome therapies for UC – SER-287 phase 1

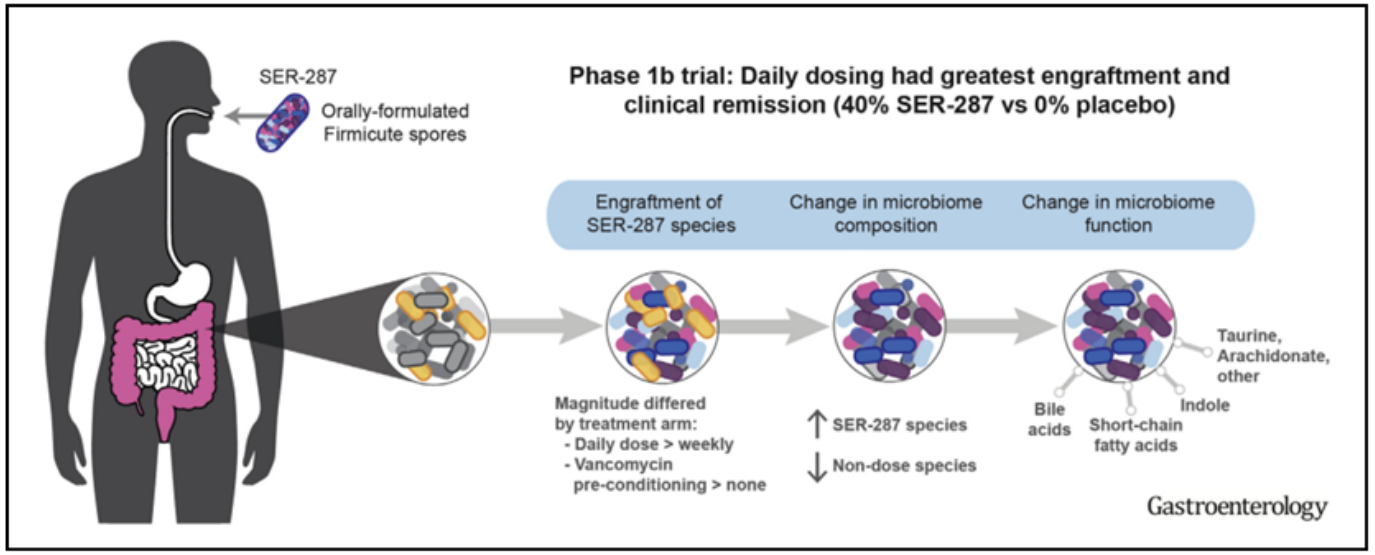
A Phase 1b Safety Study of SER-287, a Spore-Based Microbiome Therapeutic, for Active Mild to Moderate Ulcerative Colitis

Matthew R. Henn,[1] Edward J. O'Brien,[1] Liyang Diao,[1] Brian G. Feagan,[2] William J. Sandborn,[3]

→ Safety and tolerability of SER-287 were similar to placebo in phase 1b

→ SER-287 after vancomycin was more effective than placebo for induction of remission

→ Engraftment of dose species was facilitated by vancomycin preconditioning and daily dosing of SER-287



Henn et al. Gastroenterology, 2021;160:115-127

SER-287 failed to improve outcomes in a phase 2 trial in UC

nature reviews drug discovery

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NEWS IN BRIEF | 06 August 2021

Failure of Seres's phase II ulcerative colitis programme renews microbiome concerns

→ SER-287 failed to improve outcomes in phase II trial in UC.

→ Phase 2 b (203 patients) clinical remission rates were around 10–11% on two different doses of SER-287, and 11% on placebo.

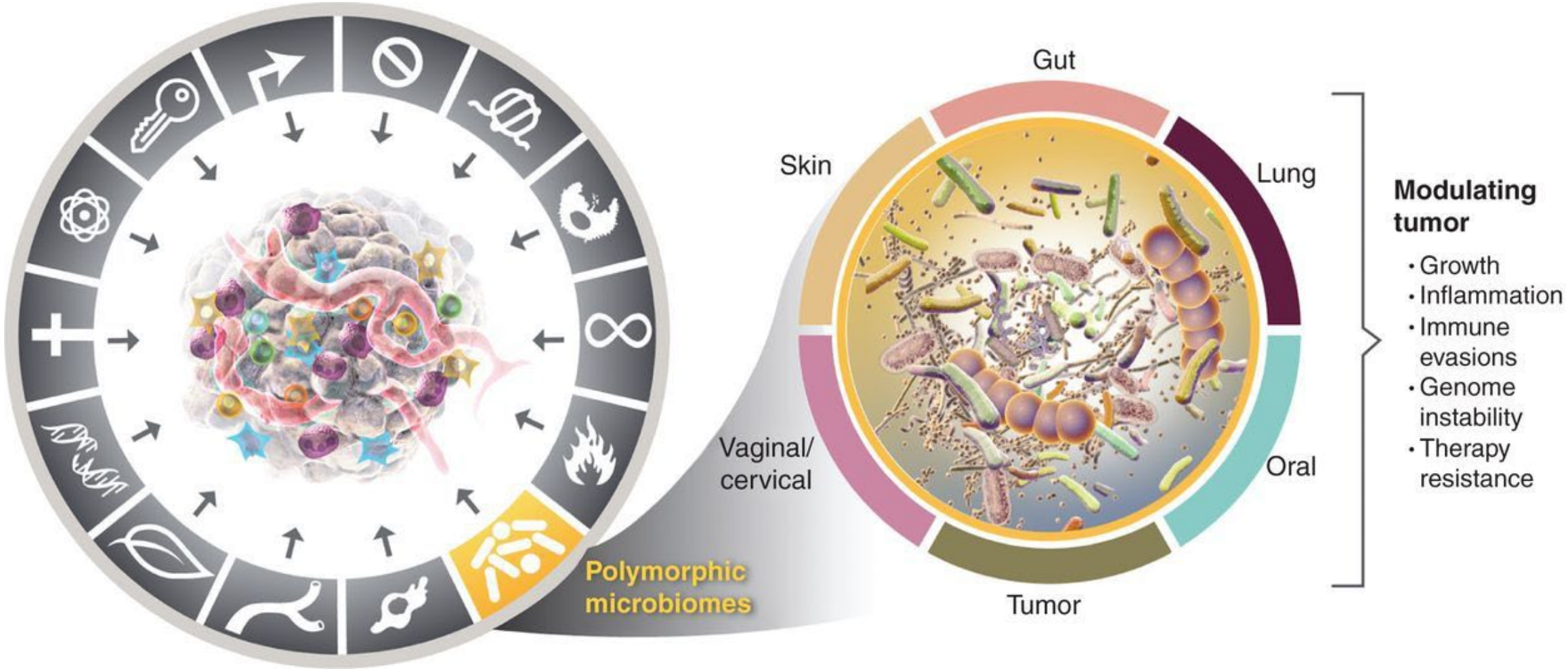
Mullard, Nature, 2021; 20, 358

Summary of FMT studies for UC

- The 20 cohort studies and 6 RCTs on FMT in UC used very different protocols.
- Meta-analyses show clinical remission in 39 of 140 (28%) patients versus 13 of 137 (9%) patients with placebo (OR 3.67 (95% CI: 1.82-7.39, P<.01).
- Antibiotic pretreatment and repetitive FMTs are associated with higher success rates.
- There are still "super donors" (even when pooling multiple donors), but these cannot yet be selected or identified.
- Oral therapy approaches are now also showing potential success.
- **There are many unanswered questions and FMT in UC colitis should only be carried out in the context of studies**.

Microbiome in Cancer

Microbiome impacts on carcinogenesis



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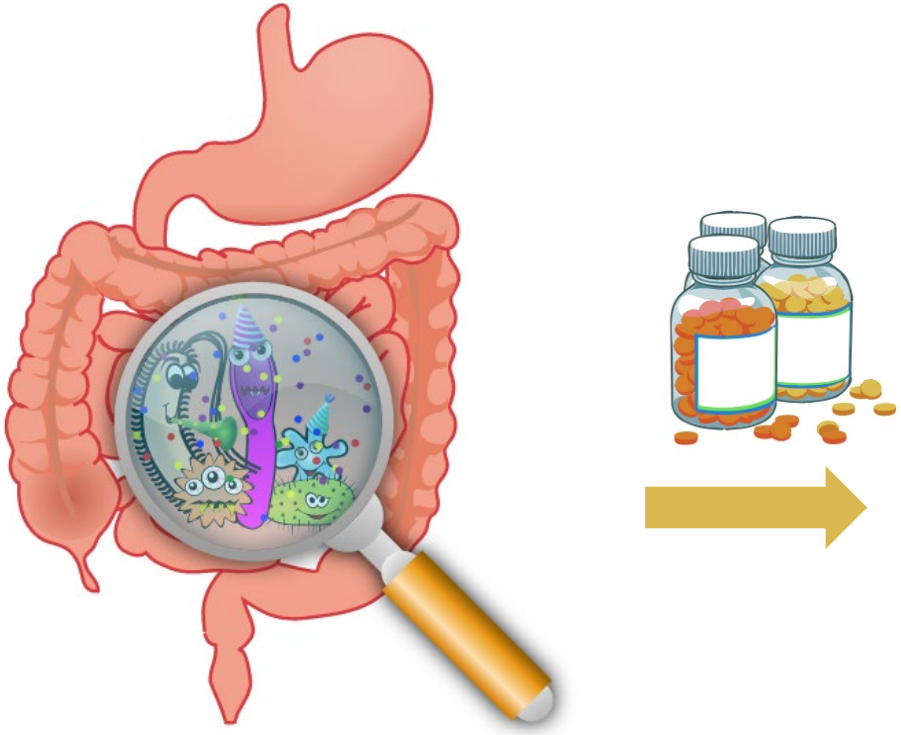
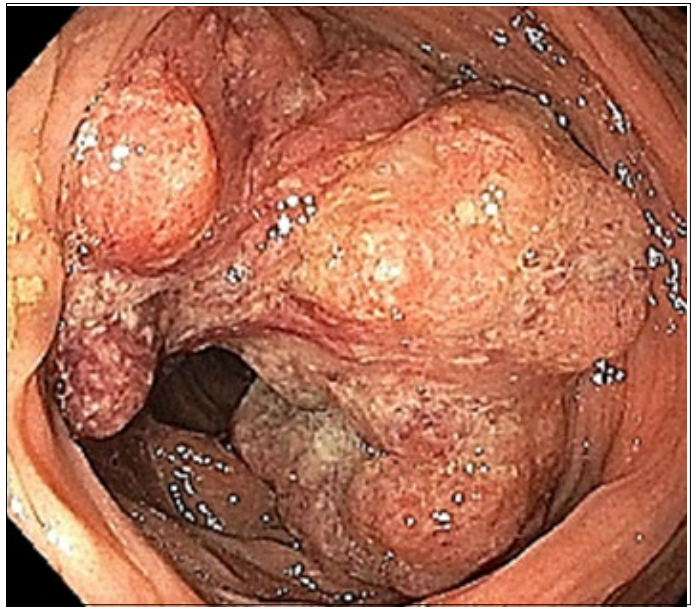
Hannahan et.al. *2022*

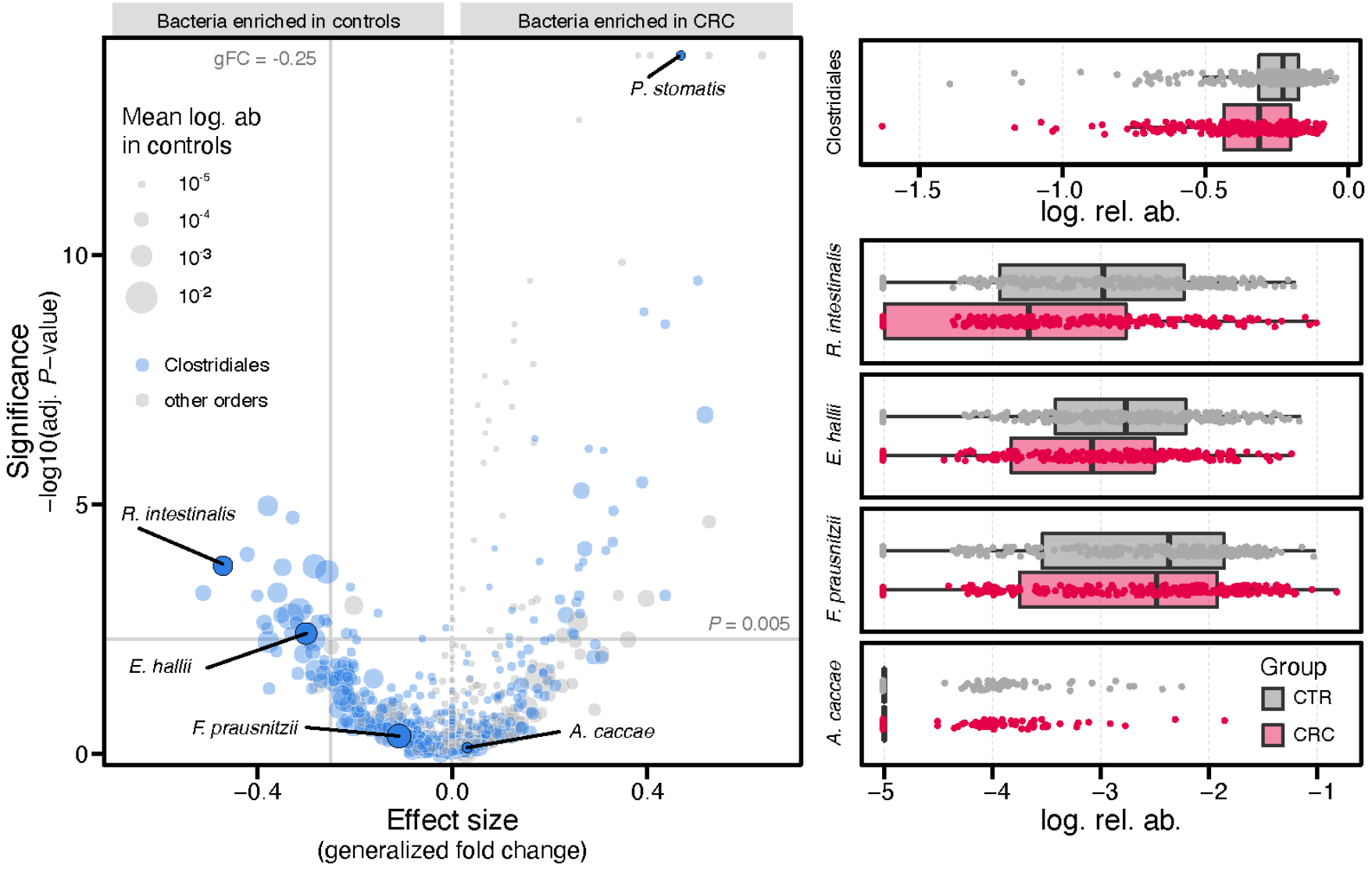
Cancer Immunotherapies have limited efficacy in colorectal carcinoma





Can bacteria be used as monotherapy for tumor treatment?

Clostridiales bacteria are underrepresented in the colon of CRC patients



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Montalban-Arques et al. Cell Host & Microbes 2021

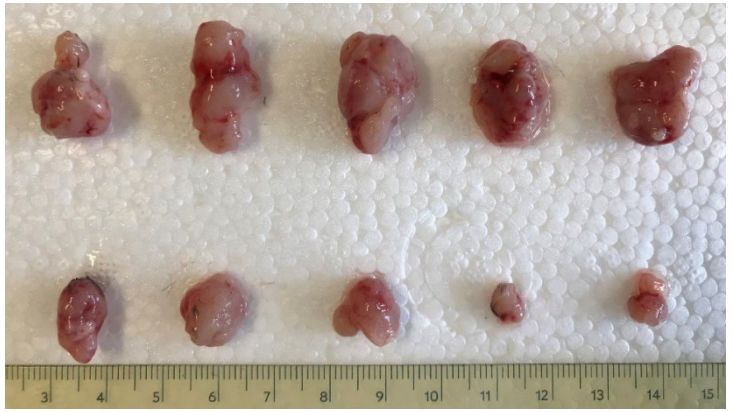
4 *Clostridiales* bacteria mix (CC4) acts as a systemic immunotherapy *in vivo*

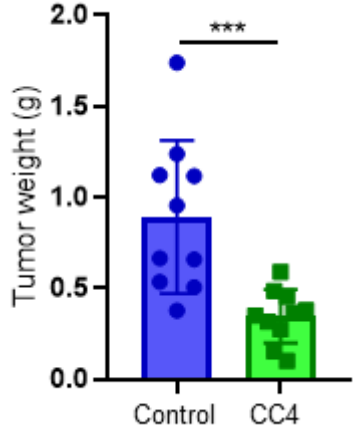
MC-38 tumors

Sc injection

Control

CC4

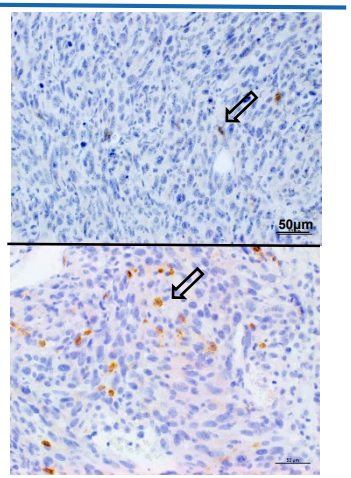


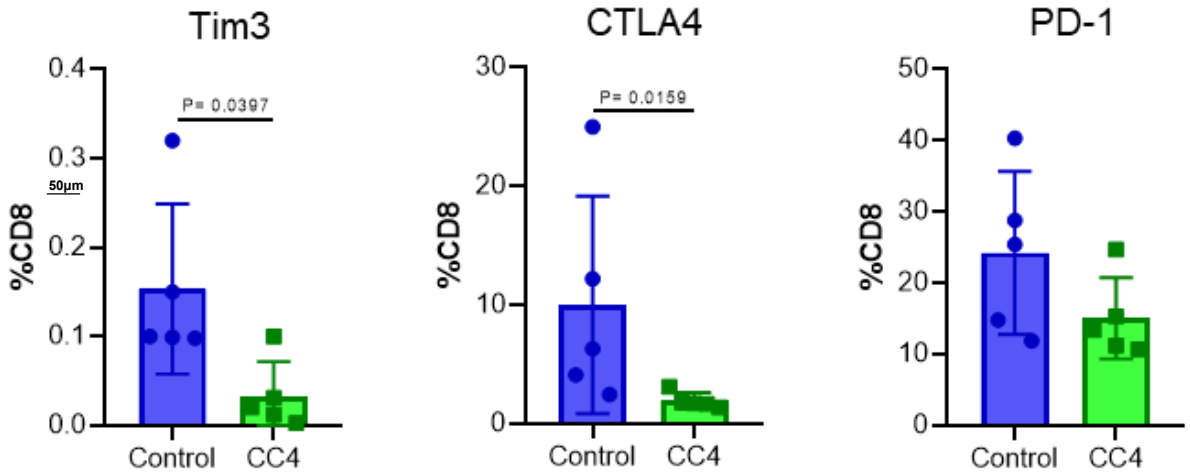


CD8 staining

Control

CC4





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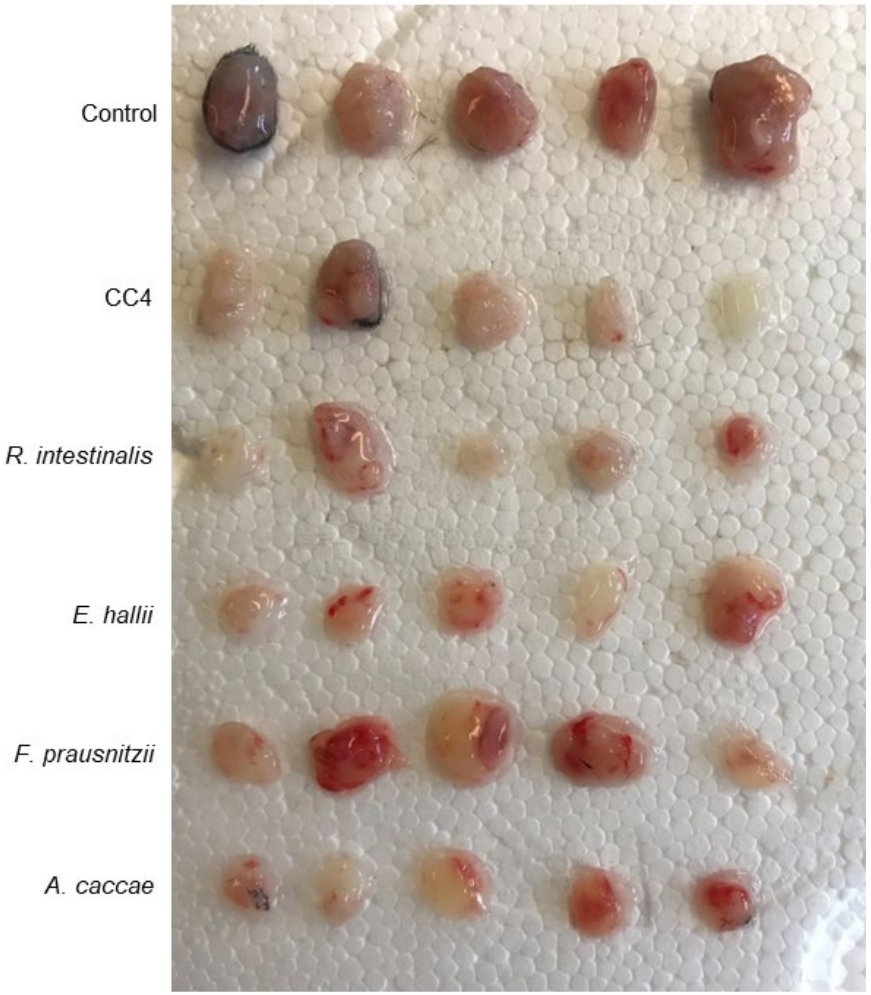
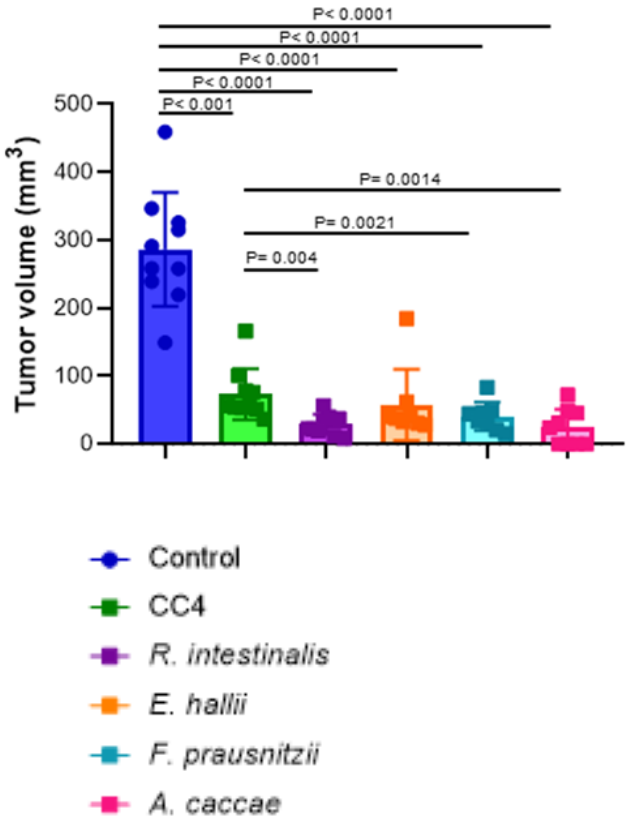
Montalban-Arques et al. Cell Host & Microbes 2021

Single bacterial strains are more efficient than CC4 mix





Subcutaneous injection of MC38 cells

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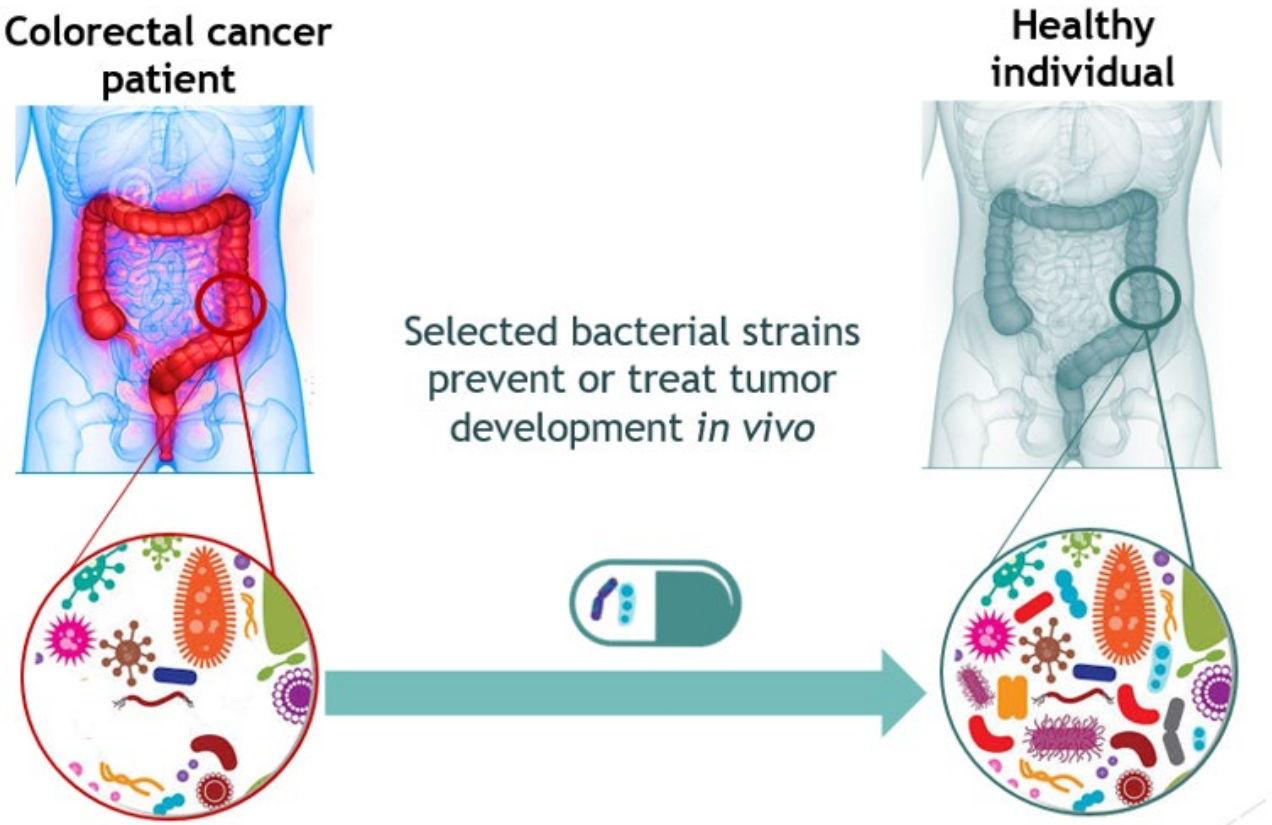
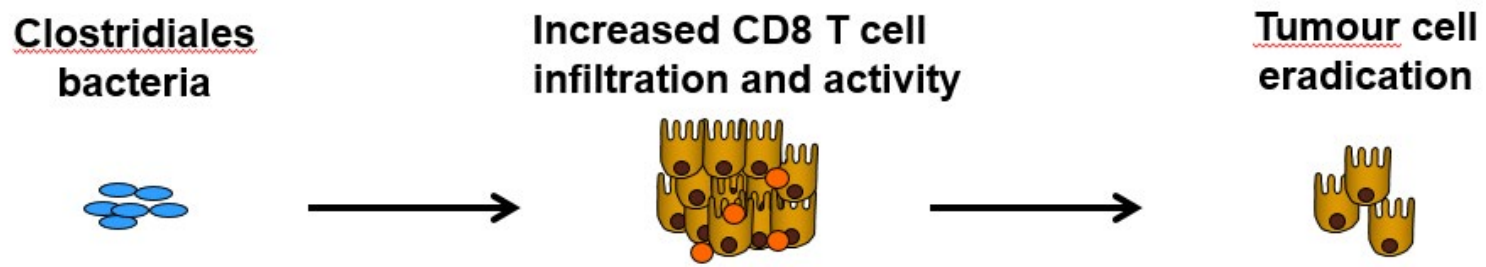
Montalban-Arques et al. Cell Host & Microbes 2021

Specific bacteria as a novel cancer immunotherapy approach



RE+ COLONY

Wyss Zurich
Translating Science into Life



Montalban-Arques et al. Cell Host Microbes 2021

Bacteria as cancer therapy in humans?

- Potentially yes!
- Fecal microbiota transplantation (FMT) induces response in immunotherapy-refractory melanoma patients
- FMT induces accumulation of cytotoxic CD8+ T cells in tumor tissue

CLINICAL TRIALS

Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients

Diwakar Davar[1]*, Amiran K. Dzutsev[2]*, John A. McCulloch[2], Richard R. Rodrigues[2,3], Joe-Marc Chauvin[1], Robert M. Morrison[1], Richelle N. Deblasio[1], Carmine Menna[1], Quanquan Ding[1], Ornella Pagliano[1], Bochra Zidi[1], Shuowen Zhang[1]†, Jonathan H. Badger[2], Marie Vetizou[2], Alicia M. Cole[2], Miriam R. Fernandes[2], Stephanie Prescott[2], Raquel G. F. Costa[2], Ascharya K. Balaji[2], Andrey Morgun[4], Ivan Vujkovic-Cvijin[5], Hong Wang[6], Amir A. Borhani[7], Marc B. Schwartz[8], Howard M. Dubner[8], Scarlett J. Ernst[1], Amy Rose[1], Yana G. Najjar[1], Yasmine Belkaid[5], John M. Kirkwood[1], Giorgio Trinchieri[2]‡§, Hassane M. Zarour[1,9]‡§

Davar *et al.*, *Science* **371**, 595–602 (2021) 5 February 2021

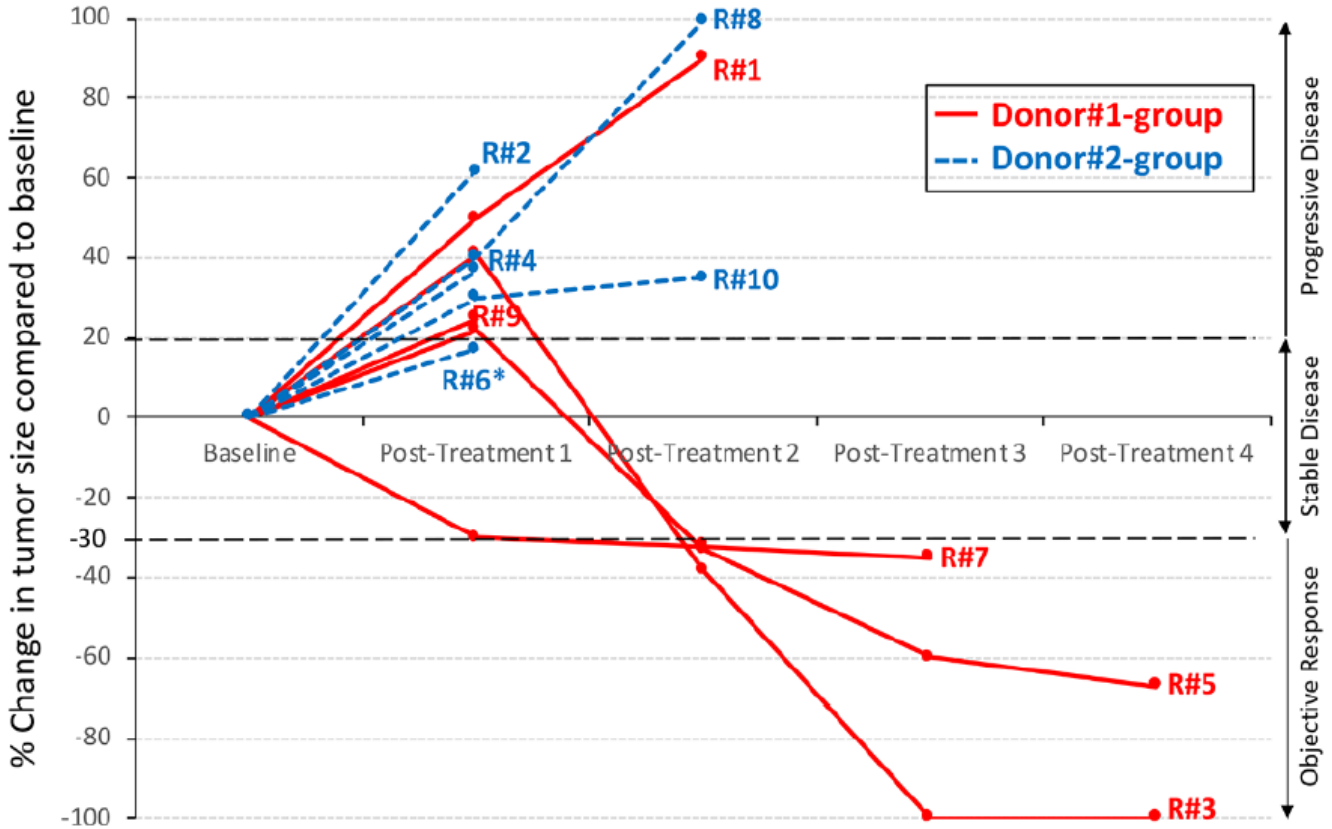
CLINICAL TRIALS

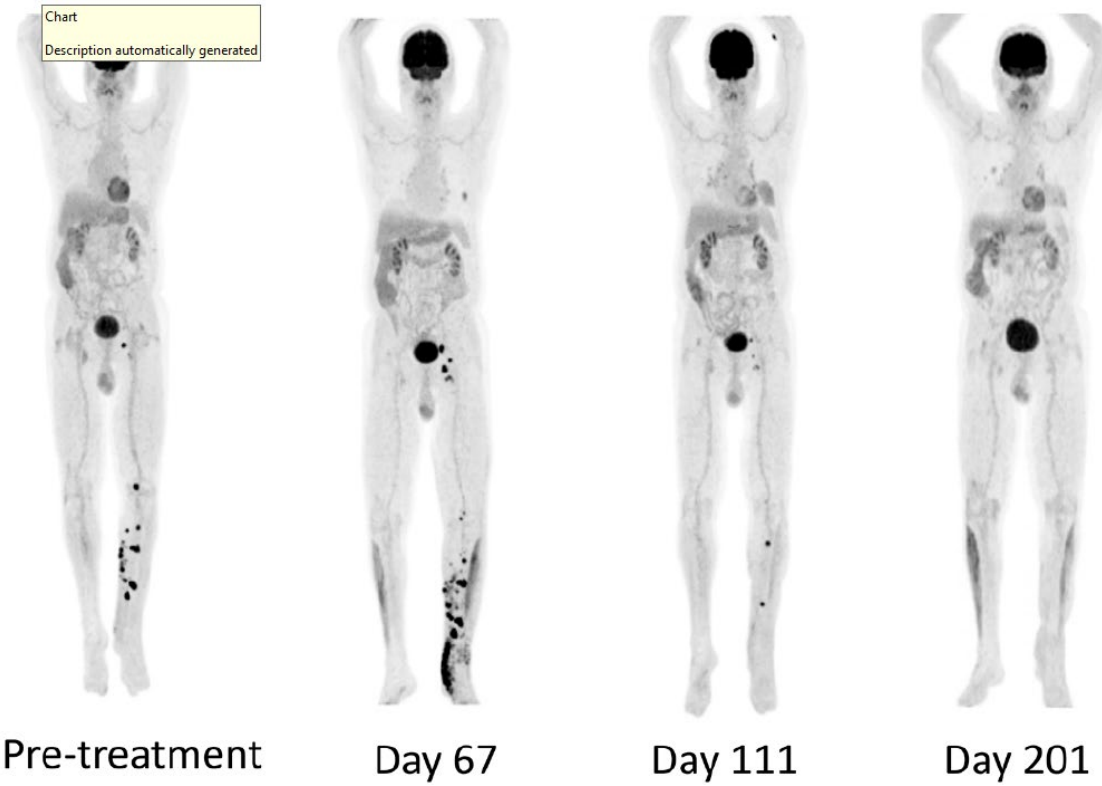
Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients

Erez N. Baruch[1,2]*†, Ilan Youngster[3,4], Guy Ben-Betzalel[1], Rona Ortenberg[1], Adi Lahat[5], Lior Katz[6], Katerina Adler[7], Daniela Dick-Necula[8], Stephen Raskin[4,9], Naamah Bloch[10], Daniil Rotin[8], Liat Anafi[8], Camila Avivi[8], Jenny Melnichenko[1], Yael Steinberg-Silman[1], Ronac Mamtani[11], Hagit Harati[1], Nethanel Asher[1], Ronnie Shapira-Frommer[1], Tal Brosh-Nissimov[12], Yael Eshet[4,8,13], Shira Ben-Simon[10], Oren Ziv[10], Md Abdul Wadud Khan[14], Moran Amit[15], Nadim J. Ajami[14], Iris Barshack[4,8], Jacob Schachter[1,4], Jennifer A. Wargo[14,16], Omry Koren[10], Gal Markel[1,2,17]*‡, Ben Boursi[4,18,19]‡

Baruch *et al.*, *Science* **371**, 602–609 (2021) 5 February 2021

FMT-induced therapy response in initially therapy-resistant patients





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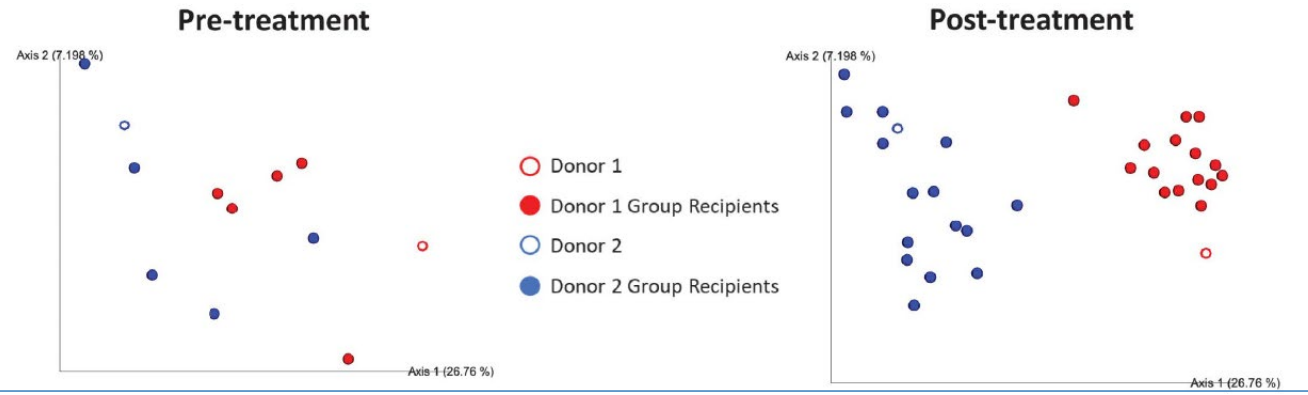
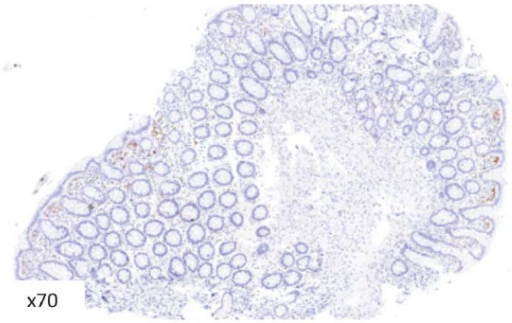
Baruch et al. Science 2021

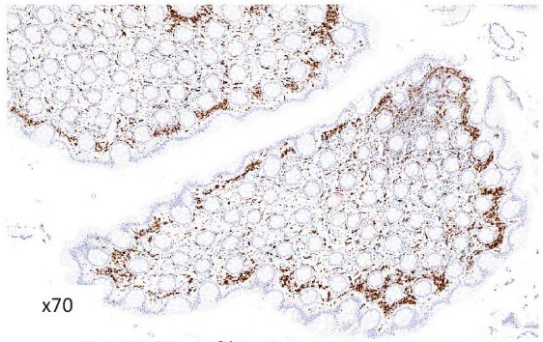
FMT alters the microbiome composition and induces CD8+ cytotoxic T-cells in the tumor tissue



Intestinal Microbiota composition

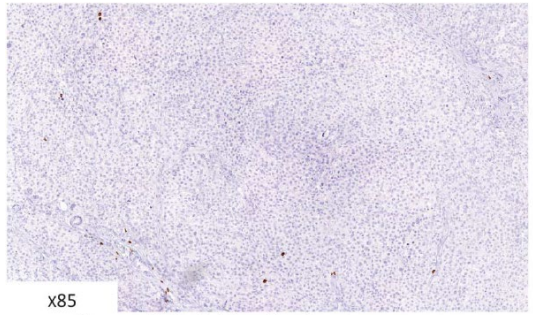


Gut CD68+ Infiltration Pre-treatment

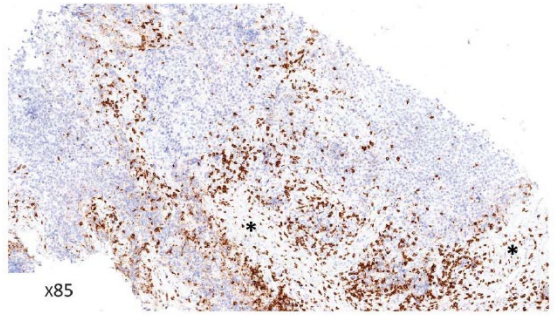


Gut CD68+ Infiltration post-treatment

Intestinal Tissue



Tumor CD8+ Infiltration Pre-treatment



Tumor CD8+ Infiltration post-treatment

Melanoma Tumor tissue

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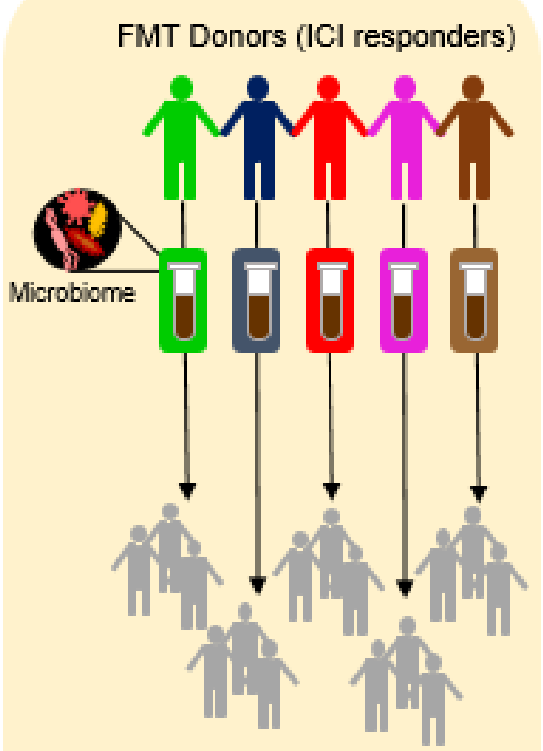
Bacteria promote the efficacy of cancer immunotherapy

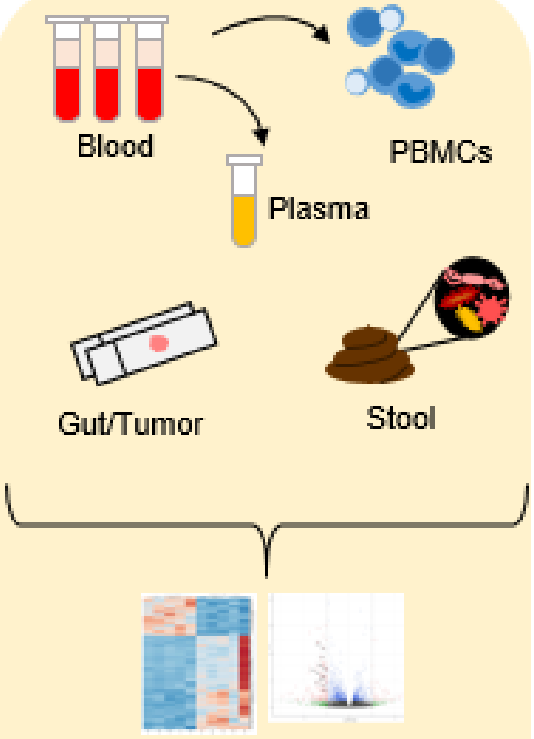
Comprehensive Cancer Center Zürich Lighthouse Project

Exploratory FMT trial



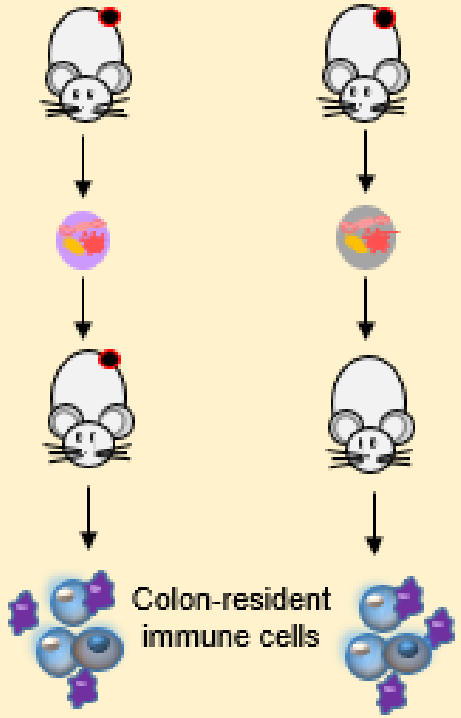
Changes in intestinal microbiome

Biomarkers



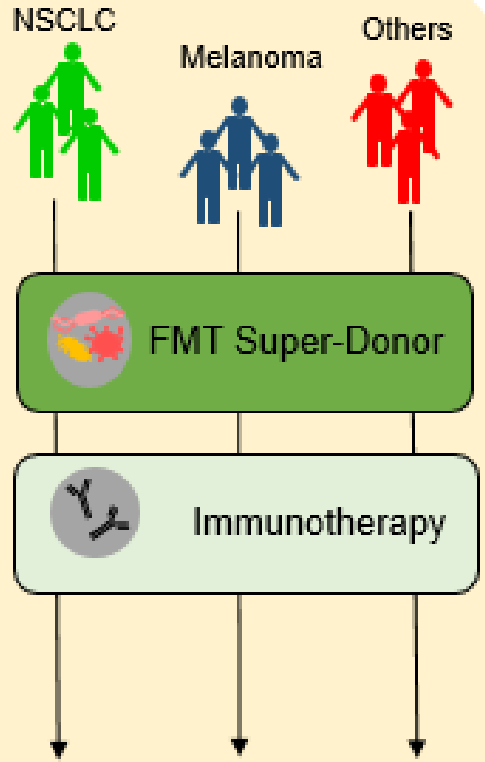
Predictive biomarkers

Mechanistic analysis



Immune features driving anti-tumor response

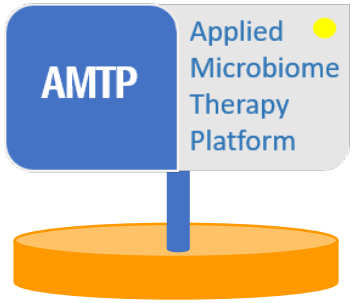
Precision FMT trial



Overall response rate (ORR)

Identification of Super-Donor

Bring FMT as Standard-Therapy into the clinical setting – we collaborate with ZüriPharm AG



- **FMT in die Klinik bringen**
- **GMP-Produktion der FMT etablieren**
- **Kooperation mit ZüriPharm AG** (ehemals Kantonsapotheke Zürich)

Klinische Studien erweitern

- Therapie-Refraktäres Melanom/Krebs
- Colitis Ulcerosa
- Kardiovaskuläre Erkrankungen
- Antibiotikaresistente Bakterien
- Depression
- Graft-versus-Host Disease
- Etc. etc.

Präzisionsmedizin

- Identifikation von Biomarkern
- Molekulares Verständnis
- Neuartige Mikrobiom-Therapieziele

Nationaler «Outreach»

- Nationale Stuhlspenderbank
- Schweizweite Verteilung von FMT-Produkten

Kurzfristige Ziele der AMTP

Mittel- und langfristige Ziele der AMTP

Herzlichen Dank für Ihre Aufmerksamkeit!