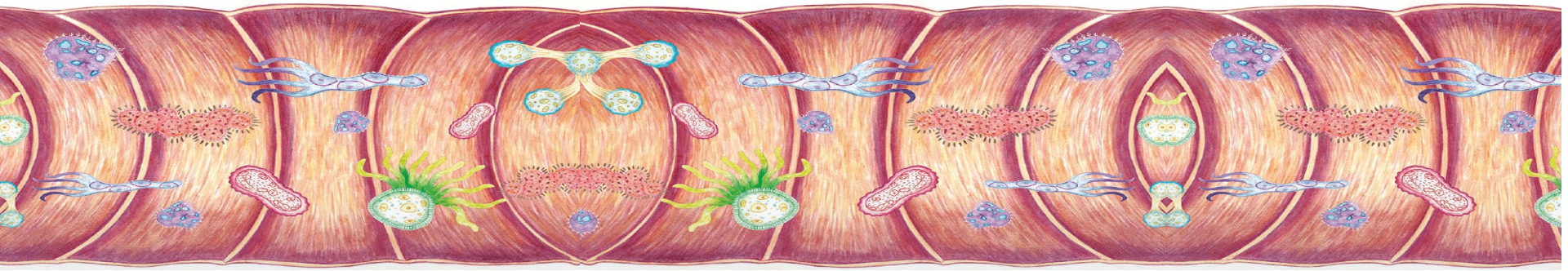
UNIL | Université de Lausanne
Faculty of Biology and Medicine

GSASA «digital» 2020 CONGRESS GENERAL ASSEMBLY



Fecal microbiota transplantation: from facts to fiction

Pr Benoit GUERY
Service des Maladies Infectieuses, CHUV
Lausanne, Suisse

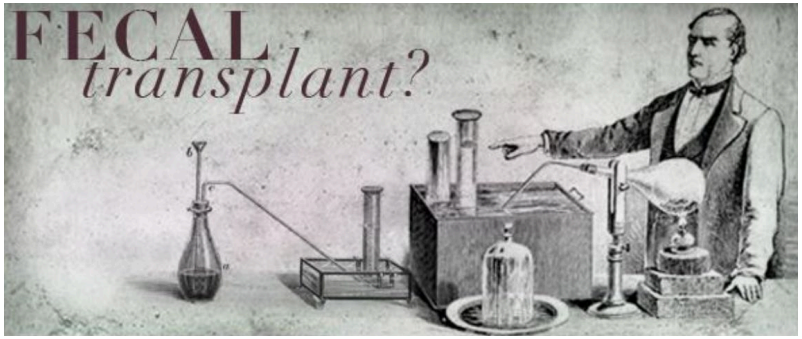
canton de vaud

Disclosures

- ✓ None on the topic

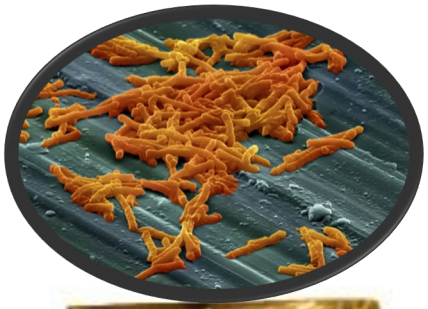
From facts to fiction

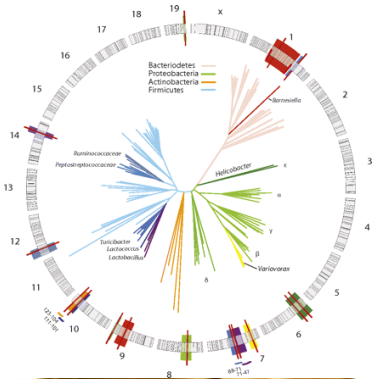
- ✓ History
- ✓ Where do we stand?
- ✓ Where could we go ?
- ✓ One size fits them all?

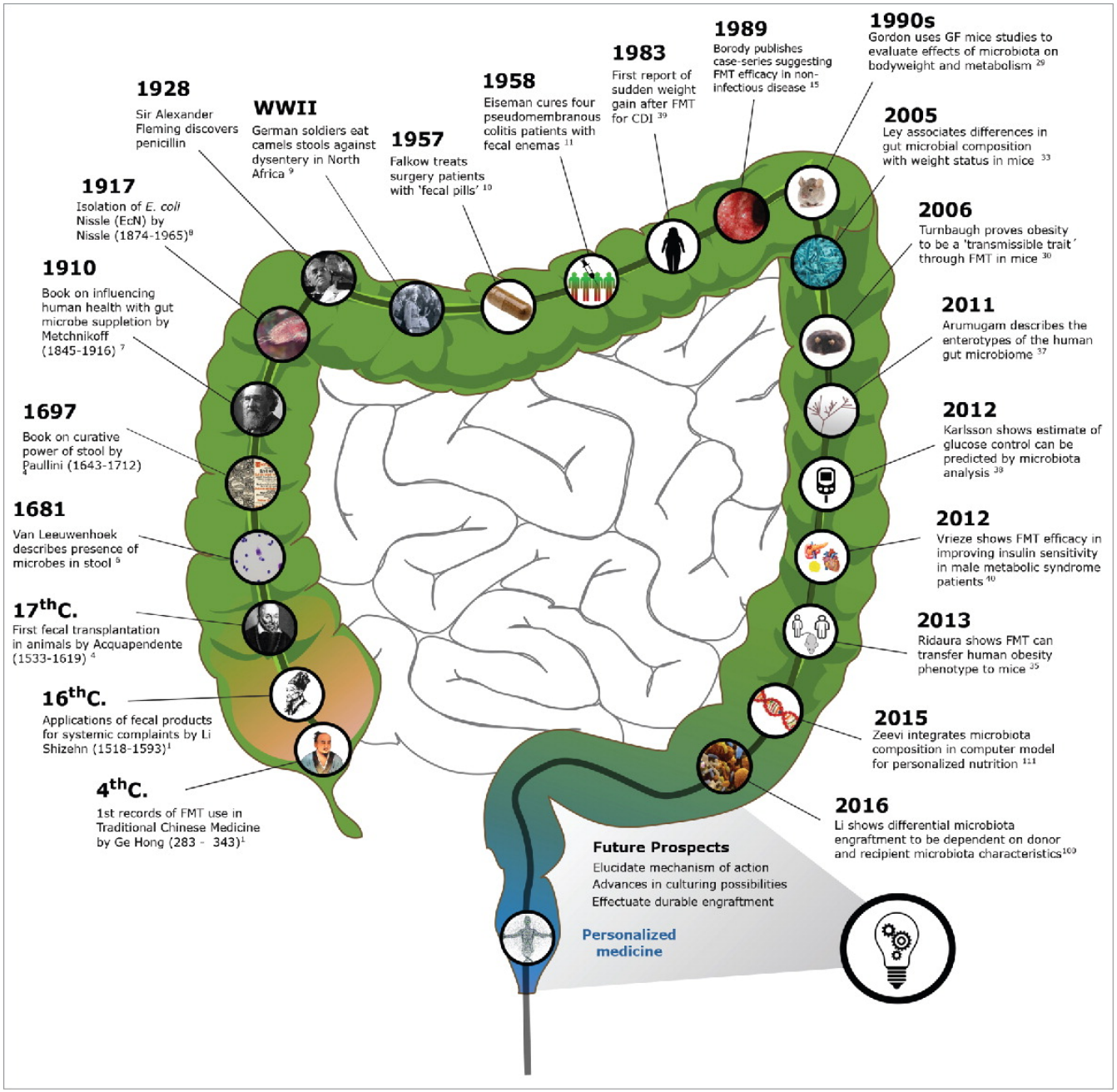


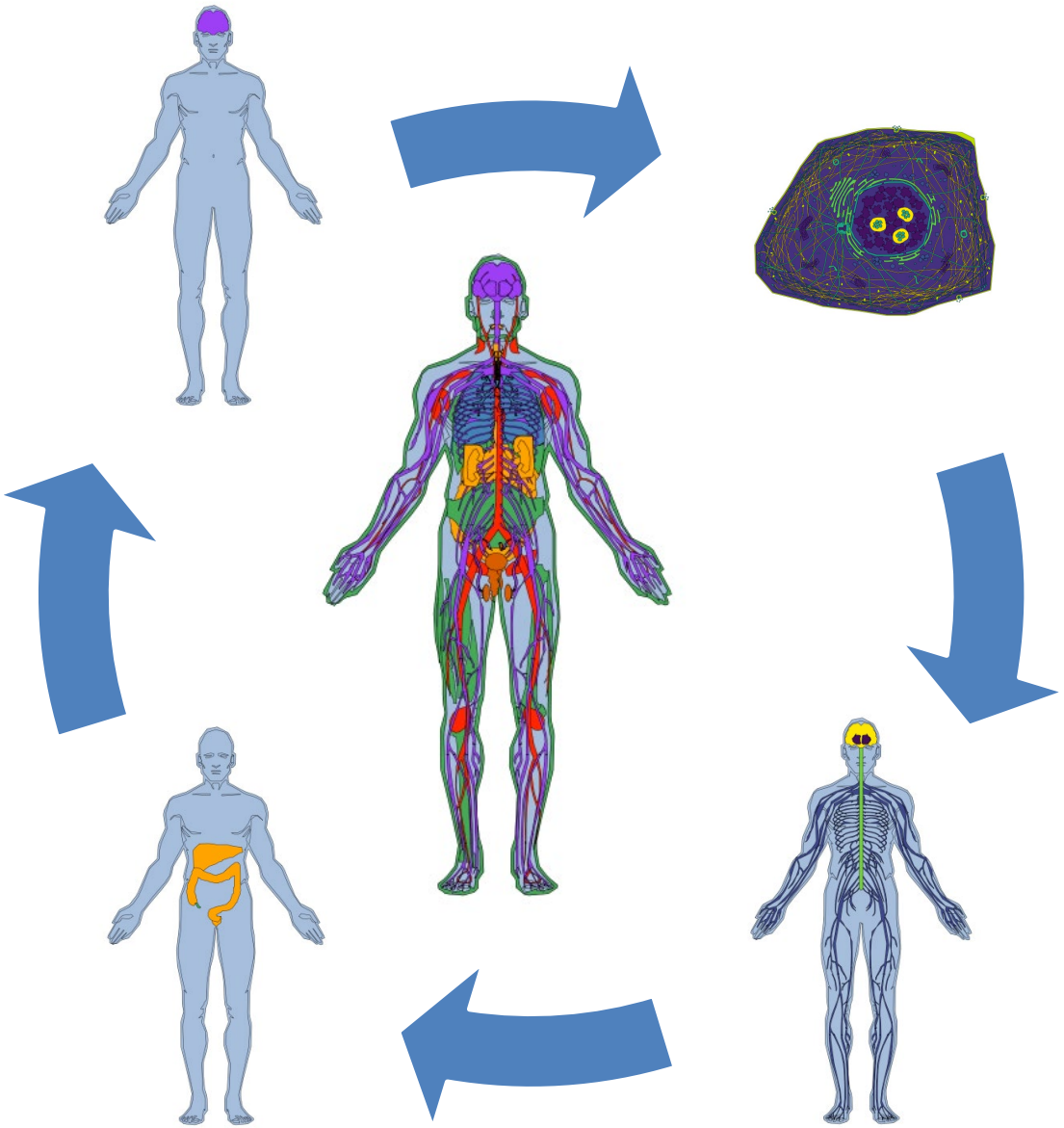
« *Re-establish the balance of nature…* »

Ben Eiseman 1958






1990s
Gordon uses GF mice studies to evaluate effects of microbiota on bodyweight and metabolism [29]
1989
Borody publishes case-series suggesting FMT efficacy in non-infectious disease [15]
1983
First report of sudden weight gain after FMT for CDI [39]
1958
Eiseman cures four pseudomembranous colitis patients with fecal enemas [11]
1957
Falkow treats surgery patients with 'fecal pills' [10]
WWII
German soldiers eat camels stools against dysentery in North Africa [9]
1928
Sir Alexander Fleming discovers penicillin
1917
Isolation of E. coli Nissle (EcN) by Nissle (1874-1965)[8]
1910
Book on influencing human health with gut microbe suppletion by Metchnikoff (1845-1916) [7]
1697
Book on curative power of stool by Paullini (1643-1712) [4]
1681
Van Leeuwenhoek describes presence of microbes in stool [6]
17thC.
First fecal transplantation in animals by Acquapendente (1533-1619) [4]
16thC.
Applications of fecal products for systemic complaints by Li Shizehn (1518-1593)[1]
4thC.
1st records of FMT use in Traditional Chinese Medicine by Ge Hong (283 - 343)[1]
2005
Ley associates differences in gut microbial composition with weight status in mice [33]
2006
Turnbaugh proves obesity to be a 'transmissible trait' through FMT in mice [30]
2011
Arumugam describes the enterotypes of the human gut microbiome [37]
2012
Karlsson shows estimate of glucose control can be predicted by microbiota analysis [39]
2012
Vrieze shows FMT efficacy in improving insulin sensitivity in male metabolic syndrome patients [40]
2013
Ridaura shows FMT can transfer human obesity phenotype to mice [35]
2015
Zeevi integrates microbiota composition in computer model for personalized nutrition [111]
2016
Li shows differential microbiota engraftment to be dependent on donor and recipient microbiota characteristics[109]
Future Prospects
Elucidate mechanism of action
Advances in culturing possibilities
Effectuate durable engraftment
Personalized medicine

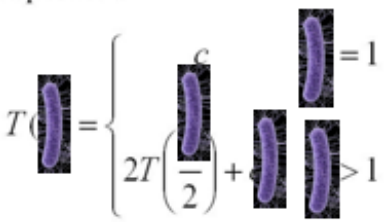


From facts to fiction

- ✓ History
- ✓ Where do we stand?
- ✓ Where could we go ?
- ✓ One size fits them all?

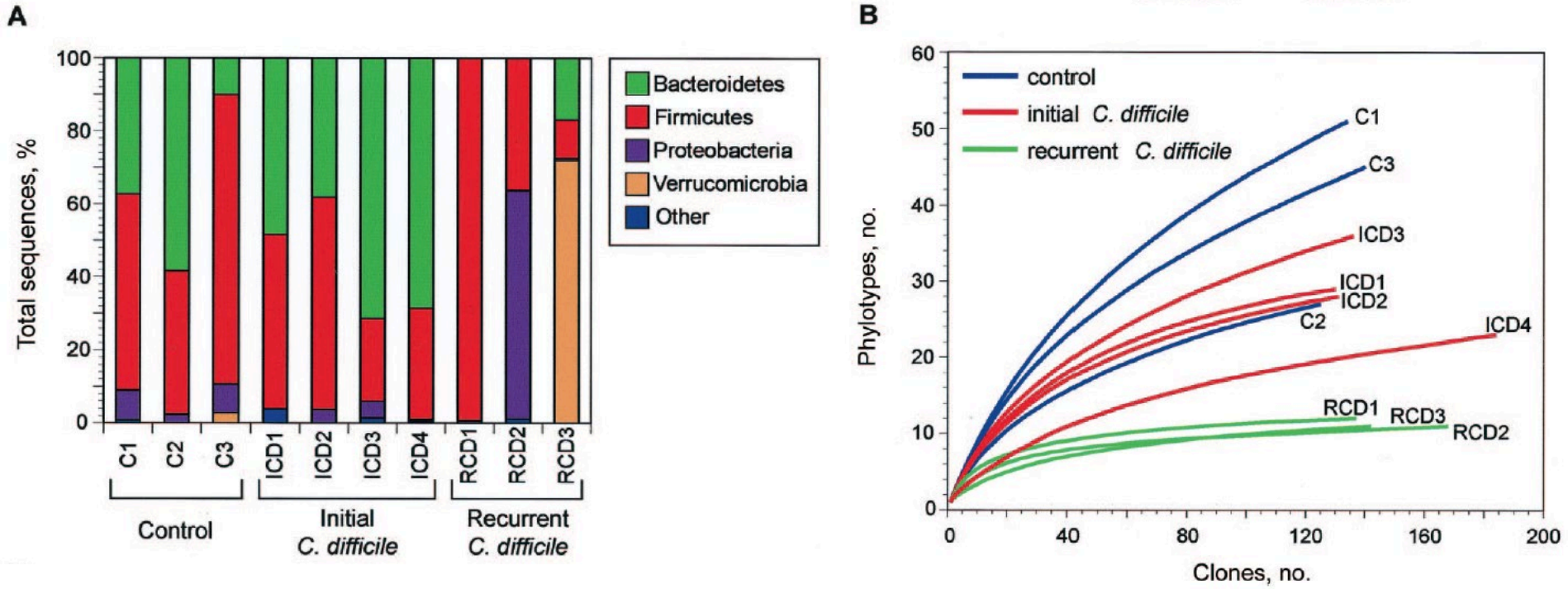
Recurrences

- The expression:



- is a *recurrence*.
  - Recurrence: an equation that describes a function in terms of its value on smaller functions

Decreased Diversity of the Fecal Microbiome in Recurrent *Clostridium difficile*–Associated Diarrhea



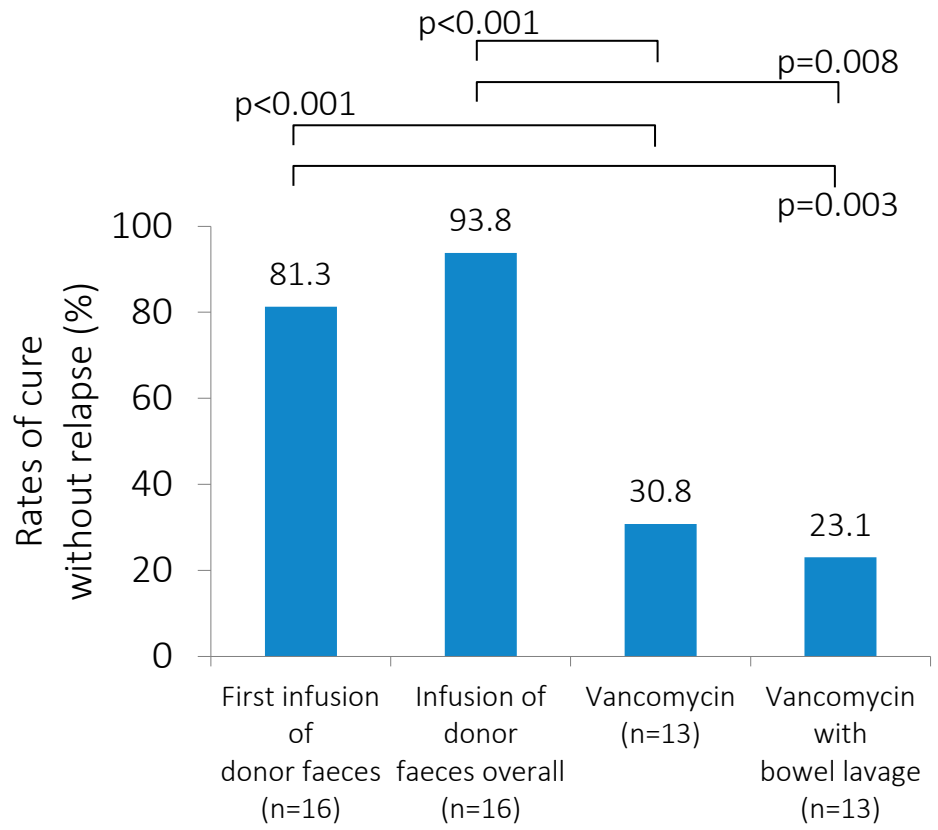
- ✓ Analysis of 16S clone libraries of the fecal microbiota in patients with antibiotic-associated diarrhea due to *Clostridium difficile.*

Chang et al, Journal of infectious Diseases 2008; 197:435-8

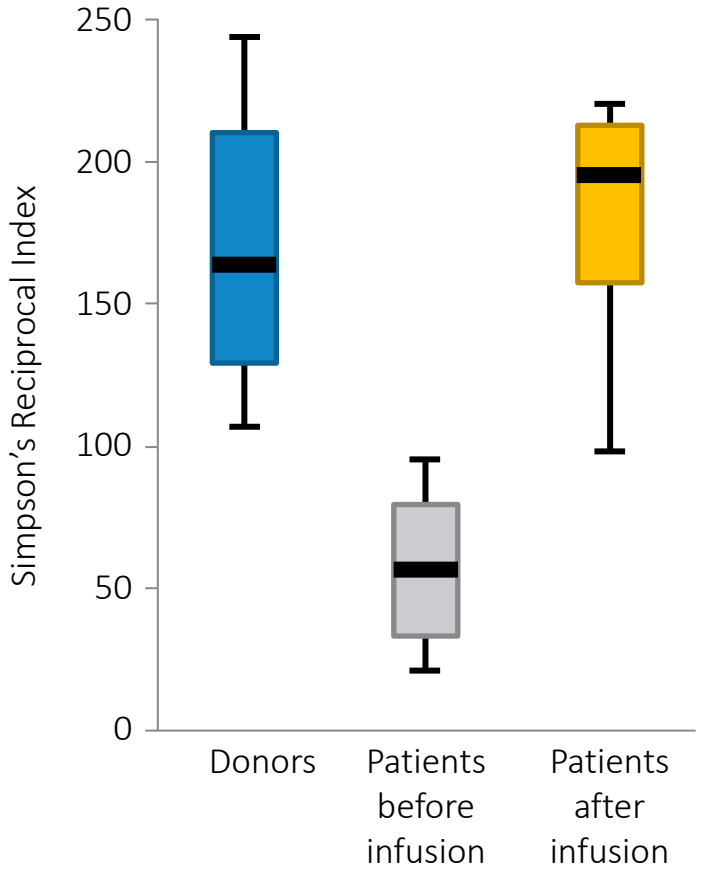
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

UNIL | Université de Lausanne
Faculty of Biology and Medicine

Rates of cure of recurrent CDI without relapse



Microbiota diversity in patients before and after infusion of donor faeces, versus healthy donors



van Nood E, et al. N Engl J Med 2013;368:407–15.

canton de vaud

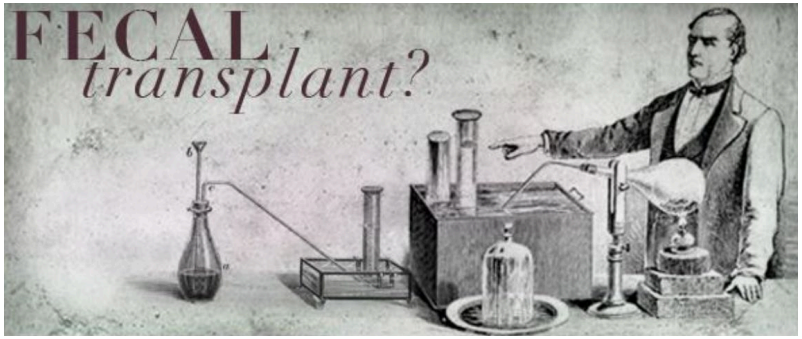
ESCMID
EUROPEAN SOCIETY
OF CLINICAL MICROBIOLOGY
AND INFECTIOUS DISEASES

IDSA
Infectious Diseases Society of America

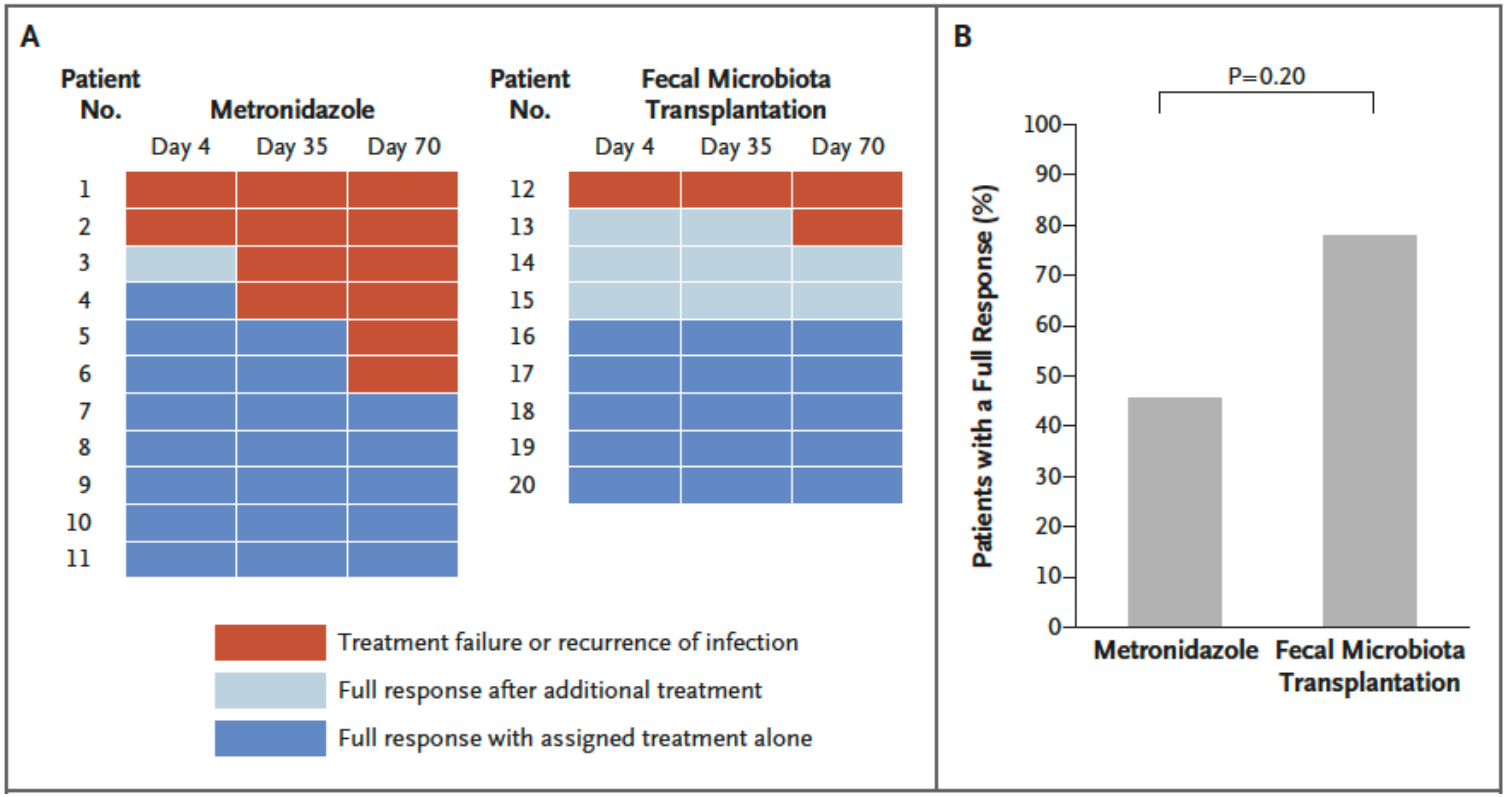
First line in recurrent *C. difficile* infections

From facts to fiction

- ✓ History
- ✓ Where do we stand?
- ✓ Where could we go ?
- ✓ One size fits them all?



Fecal Microbiota Transplantation for Primary *Clostridium difficile* Infection



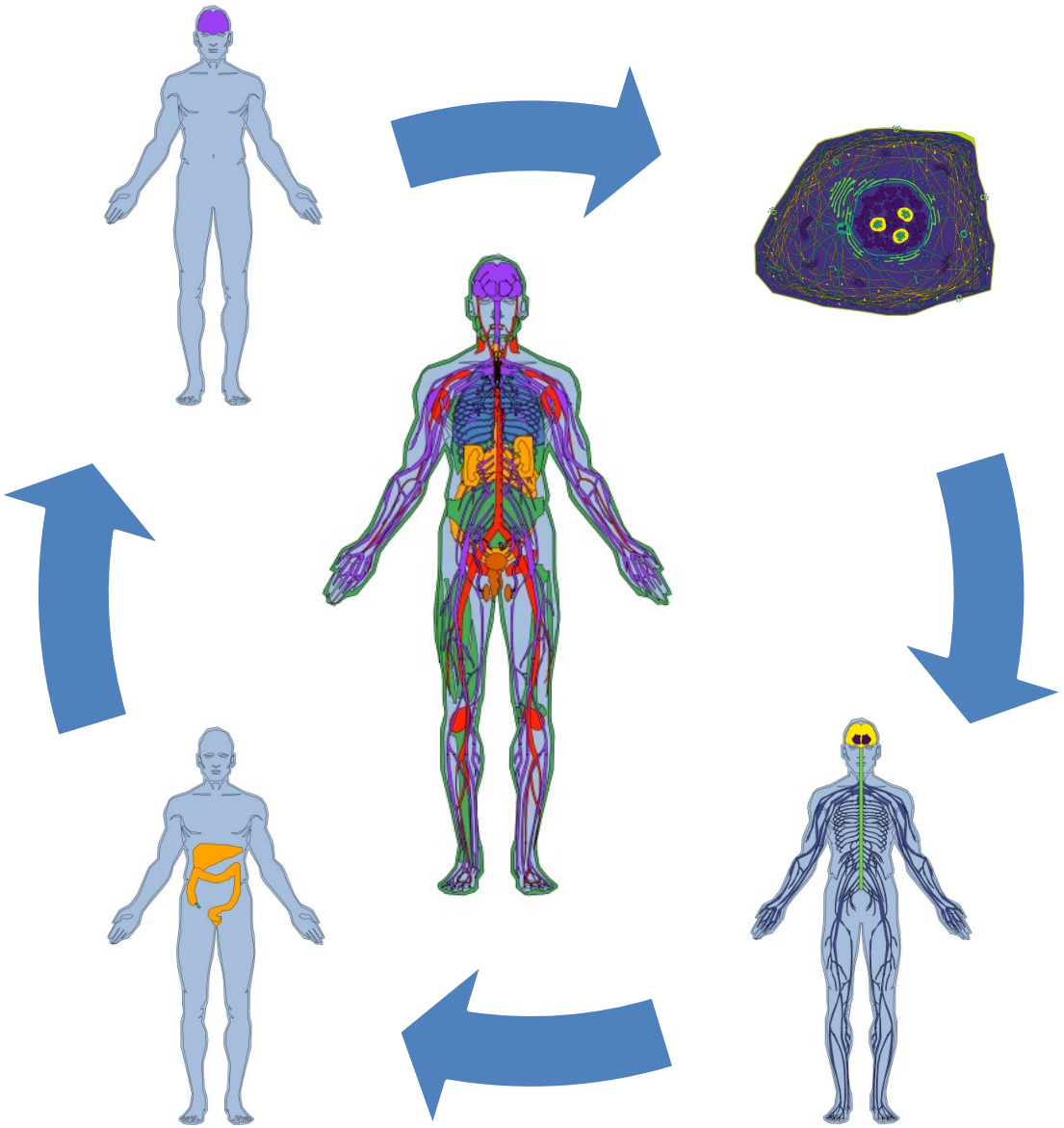
Bretthauer et al, N Engl J Med 2018, 378:26

UNIL | Université de Lausanne
Faculty of Biology and Medicine

FNSNF
FONDS NATIONAL SUISSE
DE LA RECHERCHE SCIENTIFIQUE

Fecal microbiota transplantation
v**E**rsus
va**N**comycin or
fi**D**axomicin in
*Clostridioid**Es** difficile* infection
first **R**ecurrence
A multicenter, pragmatic, randomized superiority trial

canton de vaud



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

UNIL | Université de Lausanne
Faculty of Biology and Medicine

- ✓ Multicentre, double-blind, randomised, placebo-controlled trial at three hospitals in Australia
- ✓ Active ulcerative colitis
  - Placebo
  - Colonoscopic faecal microbiota transplantation followed by enemas 5 days per week for 8 weeks.
- ✓ Primary outcome was steroid-free clinical remission with endoscopic remission or response at week 8.

	Faecal microbiota transplantation (n=41)	Placebo (n=40)	Risk ratio (95% CI)	p value
Primary outcome				
Steroid-free clinical remission and endoscopic remission or response*	11 (27%)	3 (8%)	3·6 (1·1–11·9)	0·021
Secondary outcomes				
Steroid-free clinical remission†	18 (44%)	8 (20%)	2·2 (1·1–4·5)	0·021
Steroid-free clinical response‡	22 (54%)	9 (23%)	2·4 (1·3–4·5)	0·004
Steroid-free endoscopic remission§	5 (12%)	3 (8%)	1·6 (0·4–6·4)	0·48
Steroid-free endoscopic response¶	13 (32%)	4 (10%)	3·2 (1·1–8·9)	0·016

canton de vaud

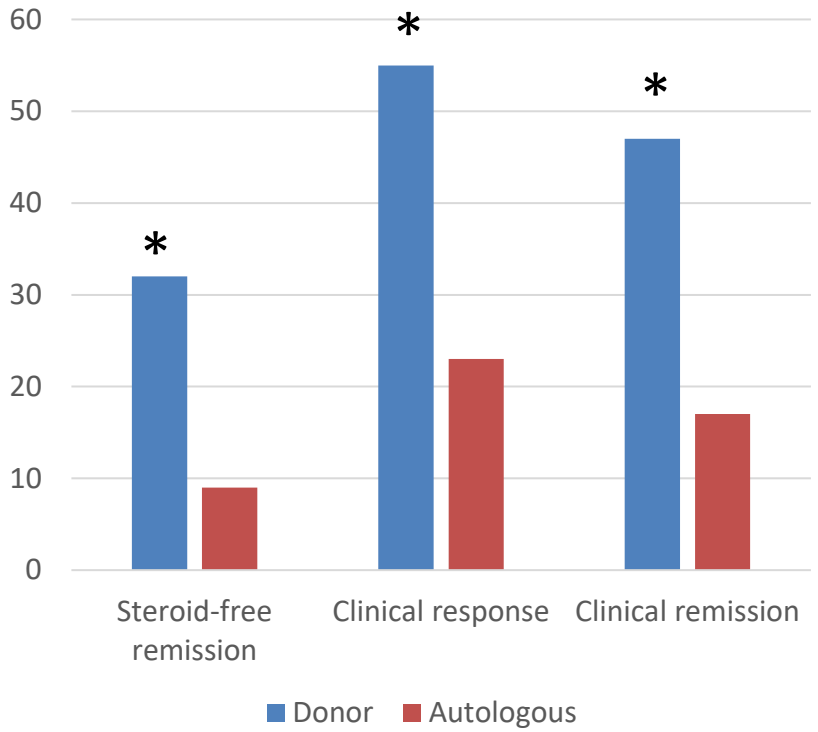
Paramsothy et al, Lancet 2017; 389: 1218

Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis

A Randomized Clinical Trial

UNIL | Université de Lausanne
Faculty of Biology and Medicine

- ✓ 73 adults with mild to moderately active UC
- ✓ Multicenter, randomized, double-blind clinical trial in 3 Australian tertiary referral centers
- ✓ Randomization:
  - anaerobically prepared pooled donor FMT (n = 38)
  - autologous FMT (n = 35) via colonoscopy followed by 2 enemas over 7 days.
- ✓ Primary outcome: steroid-free remission of UC at week 8

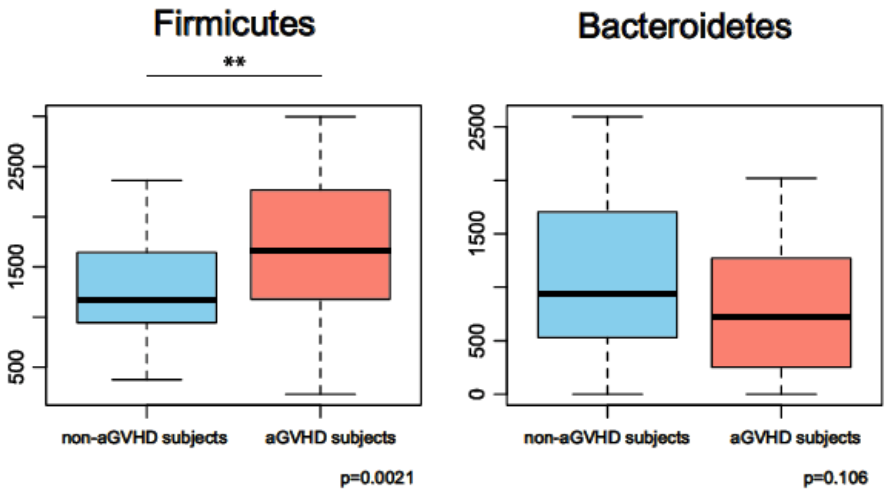


- ✓ FMT associated with a higher likelihood of remission at 8 weeks

Costello et al, JAMA 2019, 32:156

Clinical impact of pre-transplant gut microbial diversity on outcomes of allogeneic hematopoietic stem cell transplantation

- ✓ 107 allo-HSCT recipients between 2013 and 2015
- ✓ Patients were classified into three groups based on the diversity index:
  - low (<2)
  - intermediate (2, 3)
  - high (>3)
- ✓ Endpoint: acute graft-versus-host disease (aGVHD)



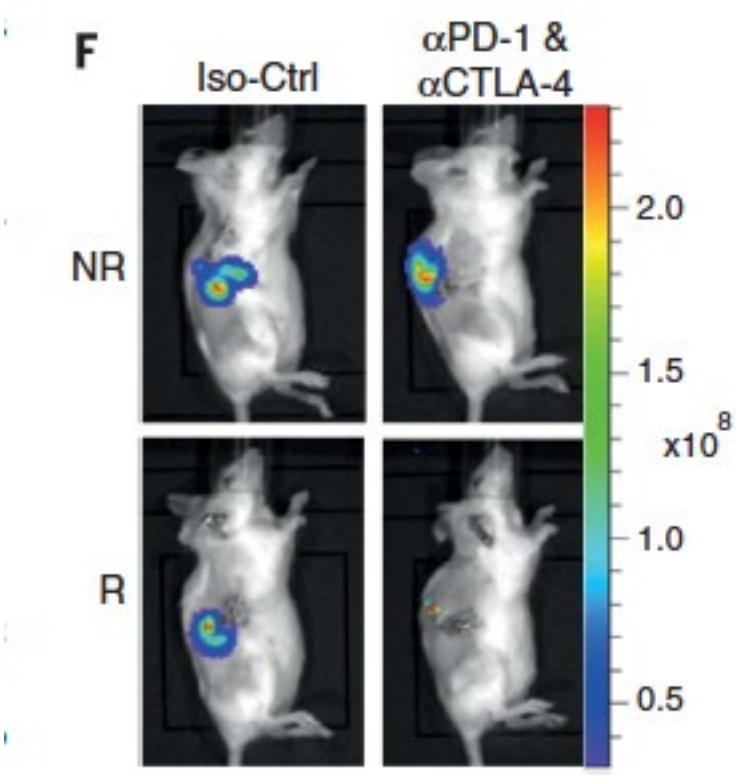
- ✓ The cumulative incidence of grade II to IV acute graft-versus-host disease (aGVHD) was similar among the three groups
- ✓ Composition of microbiota before allo-HSCT, aGVHD patients
  - Significantly higher abundance of phylum Firmicutes ($p < 0.01$)
  - Lower tendency for Bacteroidetes ($p = 0.106$)
- ✓ Maintenance of Bacteroidetes throughout allo-HSCT may be a strategy to prevent aGVHD.

Doki et al, Ann Hematol (2017) 96:1517

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

UNIL | Université de Lausanne
Faculty of Biology and Medicine

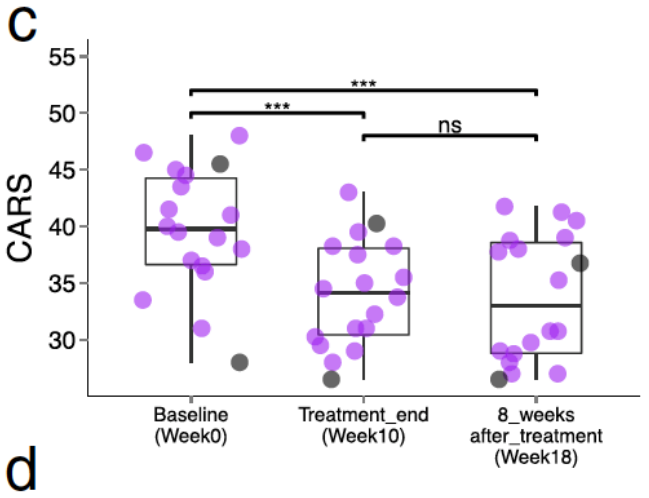
- ✓ Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis induce sustained clinical responses in a sizable minority of cancer patients
- ✓ Primary resistance to ICIs can be attributed to abnormal gut microbiome composition
- ✓ FMT from cancer patients who responded to ICIs into germ-free mice ameliorated the antitumor effects of PD-1 blockade, whereas FMT from nonresponding patients failed to do so
- ✓ Metagenomics of patient stool samples at diagnosis revealed correlations between clinical responses to ICIs and the relative abundance of Akkermansia muciniphila.



Routy et al., Science 359, 91–97 (2018)

Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

- ✓ Goal: impact of Microbiota Transfer Therapy (MTT) on gut microbiota composition and GI and Autism spectrum disorders (ASD) symptoms of 18 ASD-diagnosed children
- ✓ Childhood Autism Rating Scale (CARS): 15 items for diagnosis and severity



Kang et al. Microbiome (2017) 5:10

Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota

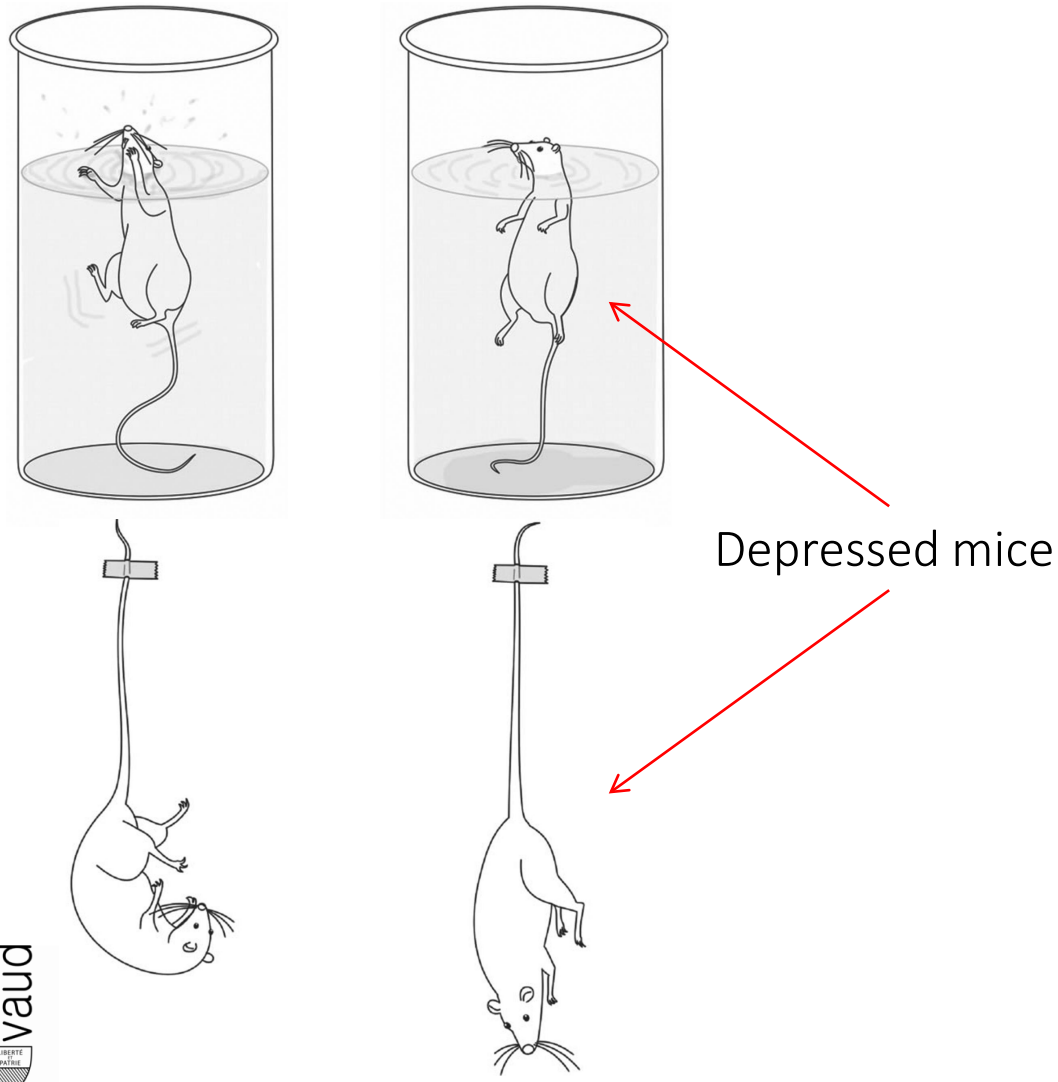
- ✓ Most improvements in GI symptoms maintained (follow up 2 years)
- ✓ Autism-related symptoms improved even more after the end of treatment.
- ✓ At follow-up, increases in bacterial diversity and relative abundances of Bifidobacteria and Prevotella.
- ✓ Long-term safety and efficacy of MTT as a potential therapy to treat children with ASD who have GI problems,
- ✓ Double-blind, placebo controlled trial in the future.

Kang et al, Scientific Reports | (2019) 9:5821

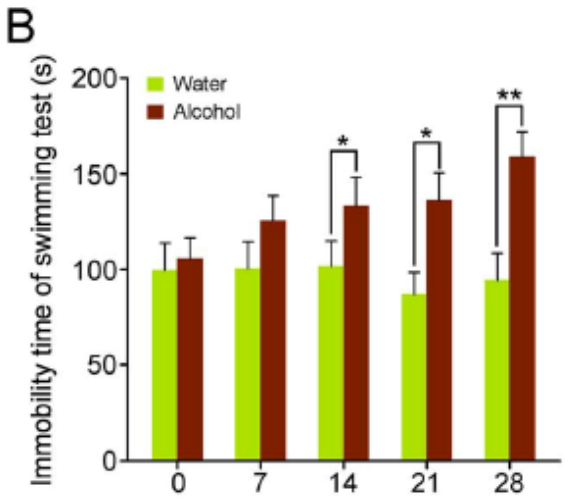
Gut microbiota modulates alcohol withdrawal-induced anxiety in mice

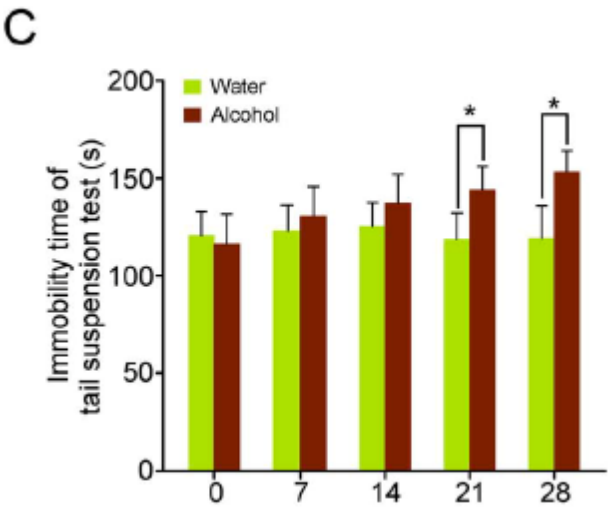
Hui-wen Xiao[a,1], Chang Ge[a,1], Guo-xing Feng[a,1], Yuan Li[a], Dan Luo[a], Jia-li Dong[a], Hang Li[a], Haichao Wang[b], Ming Cui[a,*], Sai-jun Fan[a,*]

UNIL | Université de Lausanne
Faculty of Biology and Medicine



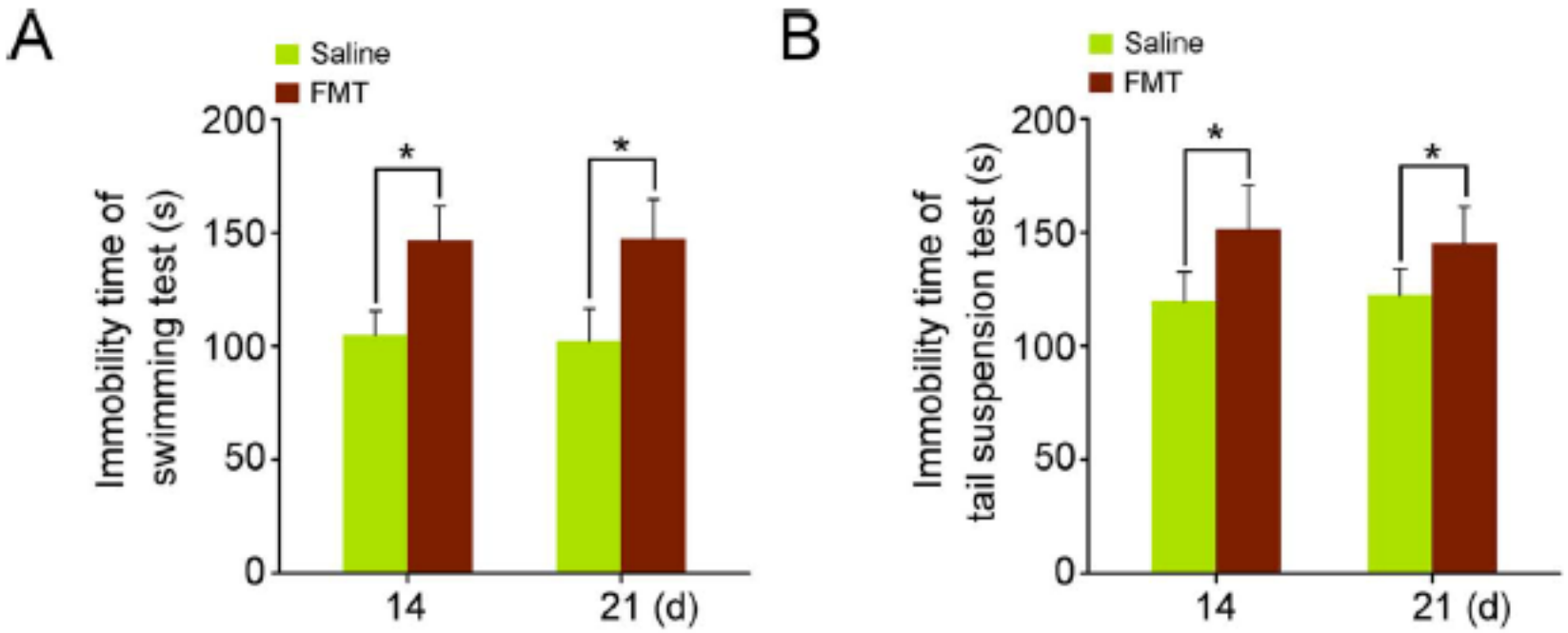
Depressed mice





Toxicology Letters 287 (2018) 23–30

Transplantation of the gut microbiota from alcohol-fed mice facilitated the development of depressive behavior in the recipients



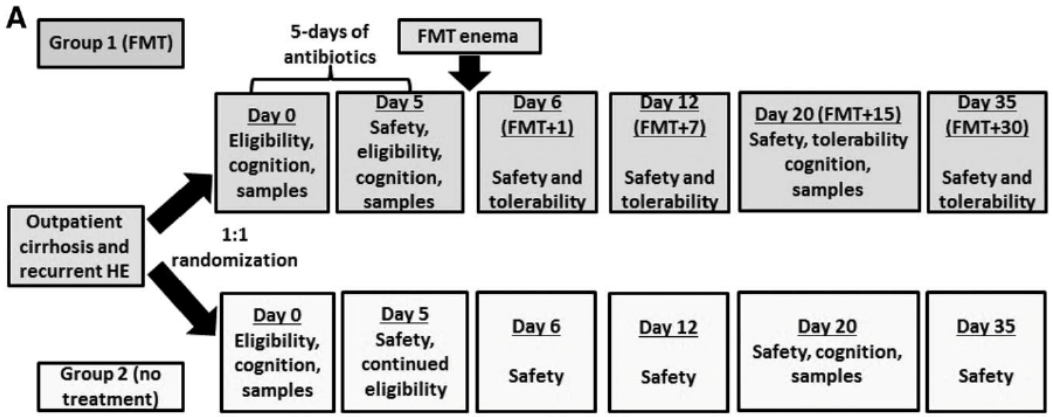
- ✓ Alterations of gut microbiota composition might contribute to the development of alcohol withdrawal-induced anxiety,

Toxicology Letters 287 (2018) 23–30

Fecal Microbiota Transplant From a Rational Stool Donor Improves Hepatic Encephalopathy: A Randomized Clinical Trial

UNIL | Université de Lausanne
Faculty of Biology and Medicine

- ✓ Open-label, randomized clinical trial with a 5 month follow-up in outpatient cirrhotic men with recurrent HE
- ✓ Follow up at D5, 6, 12, 35, and 150 post- randomisation
- ✓ 10 patients/group

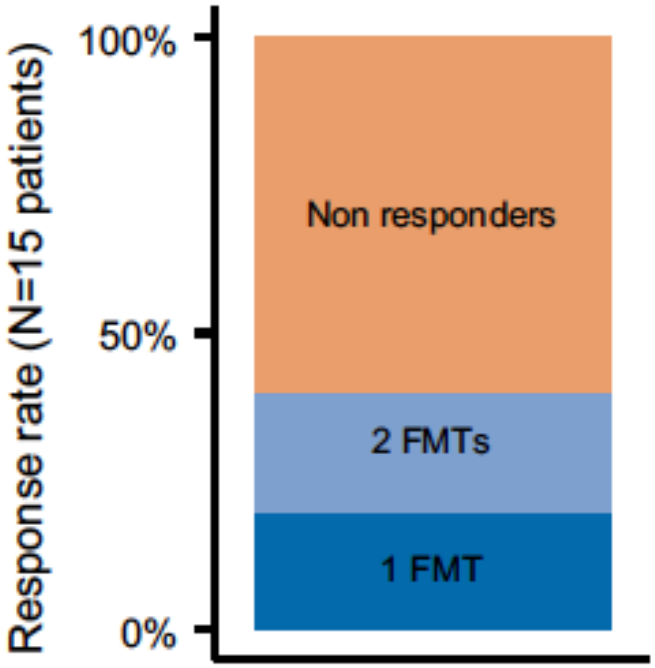


- ✓ Five SOC and no FMT participants developed further HE (p=0.03)

Bajaj et al, HEPATOLOGY, VOL. 66, NO. 6, 2017

Fecal microbiota transplantation against intestinal colonization by extended spectrum beta-lactamase producing *Enterobacteriaceae*: a proof of principle study

- ✓ Goal: Can FMT be an effective treatment in patients carrying ESBL-EB?
- ✓ 15 patients carrying ESBL-producing Enterobacteriaceae (ESBL-EB)
- ✓ Seven patients underwent a second FMT after 4 weeks when ESBL-EB remained

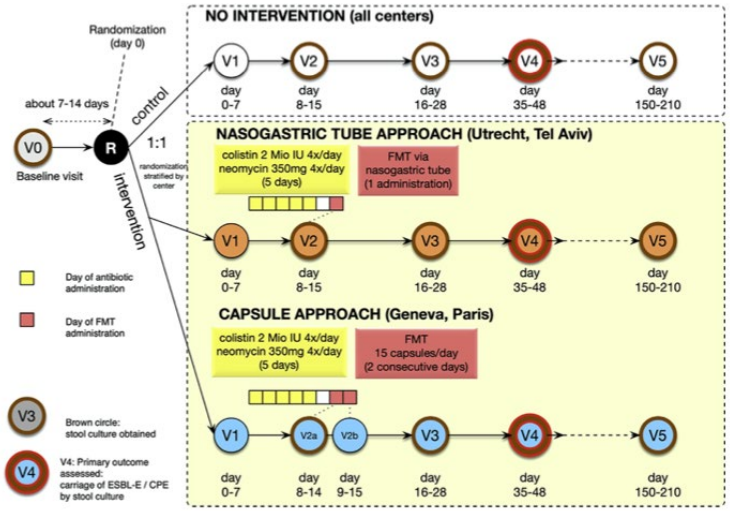


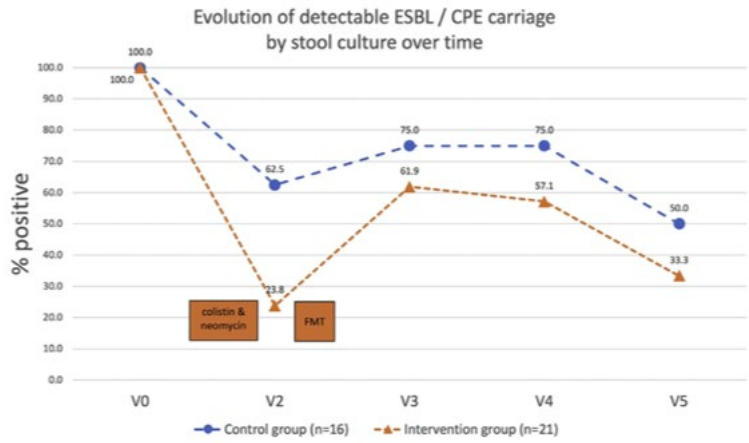
- ✓ FMT be an effective treatment in patients carrying ESBL-EB.

Singh et al. BMC Res Notes (2018) 11:190

A 5-day course of oral antibiotics followed by faecal transplantation to eradicate carriage of multidrug-resistant *Enterobacteriaceae*: a randomized clinical trial

- ✓ Randomized, open-label, superiority trial (Geneva, Paris, Utrecht, Tel Aviv).
- ✓ Non-immunocompromised adult patients randomized 1: 1 to
  - no intervention (control) (17)
  - 5-day course of oral antibiotics (colistin sulphate, neomycin sulphate) followed by frozen FMT from unrelated healthy donors (22)
- ✓ Primary outcome was detectable intestinal carriage of ESBL-E/CPE by stool culture 35-48 days after randomization (V4).
- ✓ Non-absorbable antibiotics followed by FMT slightly decreased ESBL-E/CPE carriage compared with controls; this difference was not statistically significant





B.D. Huttner et al. Clinical Microbiology and Infection 25 (2019) 830e838

Gut microbiota and obesity: implications for fecal microbiota transplantation therapy

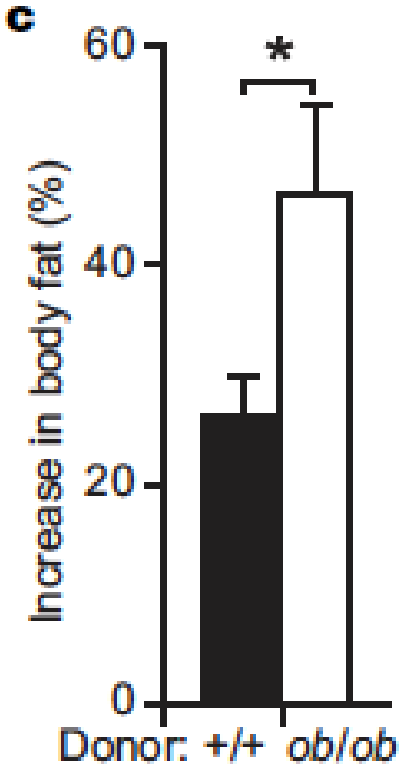
Table 1 Changes in microbiota composition associated with obesity.

Models	Disease	Implicated microbiota	Reference
Rat	Obesity	Altered gut microbiota	29,30
Rat	Obesity	*Firmicutes* ↑, *Bacteroidetes* ↓	31,32
Human	Obesity	*Firmicutes* ↑, *Bacteroidetes* ↓	37, 38, 39, 40, 41
Human	Obesity	*Proteobacteria* ↑, *Bacteroidetes* ↑, *Campylobacter* ↑, *Shigella* ↑, *Lactobacillus* ↑, *Clostridium coccoides* ↑, *Bifidobacterium* ↑, *Akkermansia muciniphila* ↓, *Clostridium leptum* ↓, *Bacteroides fragilis* ↓, *Bifidobacterium catenulatum* ↓	43,44
Human	Obesity	H2-producing *Prevotellaceae* ↑, H2-utilizing methanogenic *Archaea* ↑	46
Human	Obesity	*Enterobacter* ↑	48

Kang and Cai, HORMONES 2017, 16(3):22

An obesity-associated gut microbiome with increased capacity for energy harvest

- ✓ Obesity is associated with changes in the relative abundance of the two dominant bacterial divisions, the Bacteroidetes and the Firmicutes
- ✓ Colonization of germ-free mice with an 'obese microbiota' results in a significantly greater increase in total body fat than colonization with a 'lean microbiota'



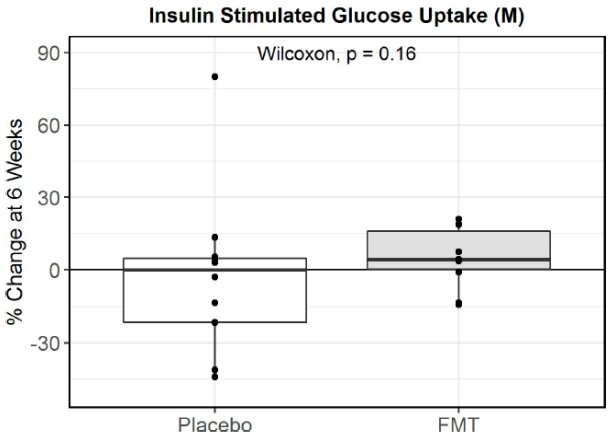
Turnbaugh et al, Nature, Vol 444, 21/28 December 2006

Fecal microbiota transplantation for the improvement of metabolism in obesity: The FMT-TRIM double-blind placebo-controlled pilot trial

UNIL | Université de Lausanne
Faculty of Biology and Medicine

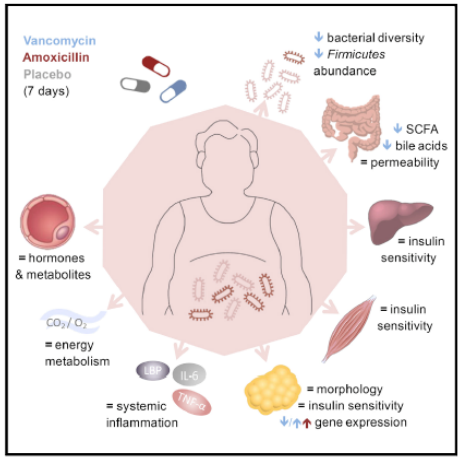
- ✓24 adults with obesity and mild–moderate insulin resistance
- ✓Weekly healthy lean donor FMT versus placebo capsules for 6 weeks.

- ✓Despite engraftment, we did not observe clinically significant metabolic effects during the study



Yu et al, PLoS Med 2020 17(3): e1003051

Effects of Gut Microbiota Manipulation by Antibiotics on Host Metabolism in Obese Humans: A Randomized Double-Blind Placebo-Controlled Trial



- ✓a 7-day antibiotic treatment (amoxicillin/ vancomycin) has no clinically relevant impact on host metabolism in obese humans

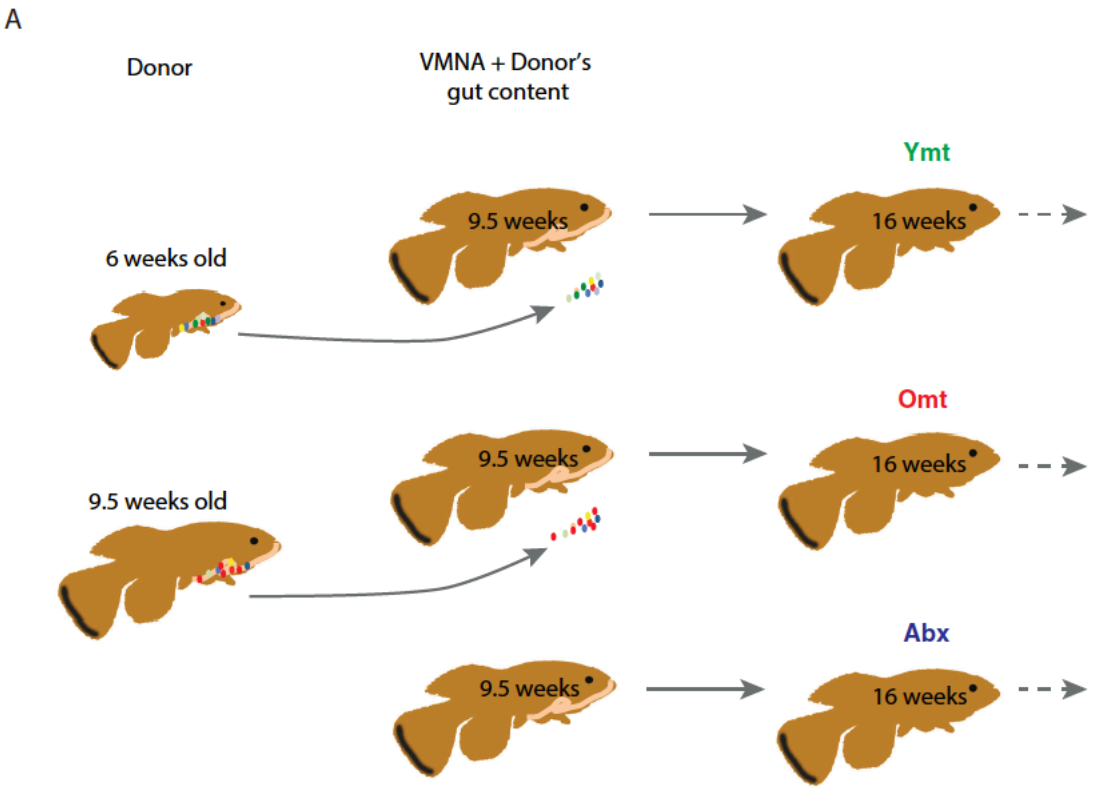
Reijnders et al., 2016, Cell Metabolism 24, 63–74

canton de vaud

Regulation of life span by the gut microbiota in the short-lived African turquoise killifish

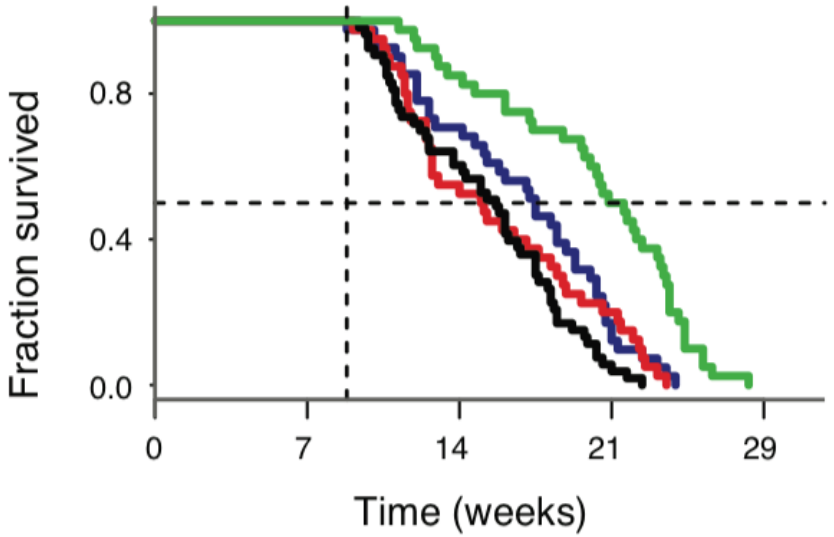
UNIL | Université de Lausanne
Faculty of Biology and Medicine

Life span: 21 weeks

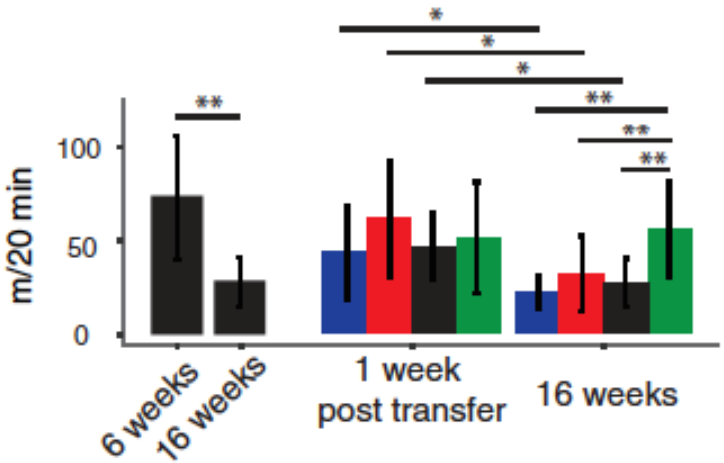


Smith et al. eLife 2017;6:e27014

Regulation of life span by the gut microbiota in the short-lived African turquoise killifish



	Abx	Omt	wt	Omt
Abx	-			
Omt	n.s.	-		
wt	*	n.s.	-	
Ymt	***	***	***	-



- ✓ Abx: antibiotic treatment at 9.5 weeks without direct recolonization
- ✓ Omt: same-age GM transfer after antibiotic treatment at 9.5 weeks.
- ✓ Wt: wild-type, untreated fish.
- ✓ Ymt: 6- week-old fish GM transfer after antibiotic treatment at 9.5 weeks

Smith et al. eLife 2017;6:e27014

From facts to fiction

- ✓History
- ✓Where do we stand?
- ✓Where could we go ?
- ✓One size fits them all?

Legal environment

Country	Drug	Human tissu
Switzerland, France	x	
Belgium, UK, Denmark		x
Austria, Estonia, Germany, Ireland, Malta, Netherlands, Portugal, Slovenia,…	?	?
USA , Canada	Investigational new drug	
Australia, New Zealand	Unapproved	
Hong Kong	… Refused comment…	

Perfect donor

Screening questionnaire (specific items for stool donation).

Information	Exclusion criteria	Selection criteria with personal assessment
Co-morbidities	Digestive disorders (acute or chronic diarrhoea) within 3 months prior to donation Known chronic disease History of typhoid fever	Donors with family history of: – Inflammatory bowel disease (relation) – Autoimmune diseases (relation) – Colon cancer (relation and age at onset) Donors with personal history of uncomplicated hypertension or hypercholesterolaemia
Drug treatment	Donor under long term medical treatment[a] Antibiotic intake within 3 months[a]	Treatment of uncomplicated hypertension or hypercholesterolaemia
Travels	Living in tropical areas during the 3 months prior to donation Long-term residence in tropical areas Hospitalizations abroad longer than 24 hours in the 12 months prior to donation (including members of the donor's entourage)[b]	Game consumption (trichinosis screening mandatory)
Age	Minor donor[c]	Aged donor (>65 years)[d]
Weight status	Non limiting	Donor with Body mass index > 30[e]

Sokol, Galperine et al. Digestive and Liver Disease 48 (2016) 242–247

Agent	FDA	van Nood	Austria	France
Blood				
HIV 1/2	x	x	x	x
HBV,HAV, HCV	x	x	x	x
HEV				
HTLV ½		x	x	x
TPHA VDRL	x	x	x	x
CMV		x		x
EBV		x		x
Toxoplasma				x
Strongyloides stercoralis		x		x
Trichinella				x
Entamoeba histolytica		x		x
Stool				
Standard	x	x	x	x
C. Difficile	x	x	x	x
Salmonella, shigella, yersinia, campylobacter	x	x	x	x
L monocytogenes				x
MDR				x
Vibrio cholorae/parahemolyticus				x
Adenovirus				x
Astrovirus				x
Norovirus				x
Picornavirus			x	x
Rotavirus	x			x
Parasites	x	x	x	x

Perfect donor

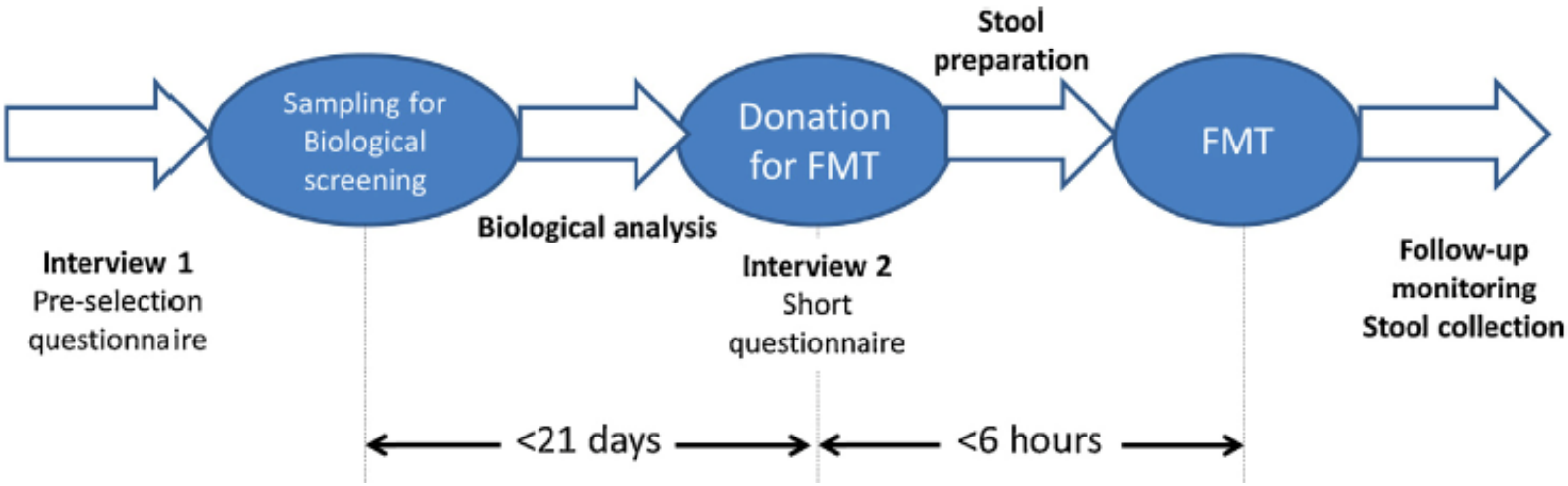
Screening questionnaire (specific items for stool donation).

Information	Exclusion criteria	Selection criteria with personal assessment
Co-morbidities	Digestive disorders (acute or chronic diarrhoea) within 3 months prior to donation Known chronic disease History of typhoid fever	Donors with family history of: – Inflammatory bowel disease (relation) – Autoimmune diseases (relation) – Colon cancer (relation and age at onset) Donors with personal history of uncomplicated hypertension or hypercholesterolaemia
Drug treatment	Donor under long term medical treatment[a] Antibiotic intake within 3 months[a]	Treatment of uncomplicated hypertension or hypercholesterolaemia
Travels	Living in tropical areas during the 3 months prior to donation Long-term residence in tropical areas Hospitalizations abroad longer than 24 hours in the 12 months prior to donation (including members of the donor's entourage)[b]	Game consumption (trichinosis screening mandatory)
Age	Minor donor[c]	Aged donor (>65 years)[d]
Weight status	Non limiting	Donor with Body mass index > 30[e]

Screening questionnaire/events since the screening visit.

Exclusion criteria	Selection on the basis of individual assessment
Diarrhoea (>3 loose or liquid stools/day) **Situations at risk of contamination:** – Travel in tropical areas – Contact with human blood (sting, wound, showing, piercing[a], tattoo[a]) – Sexual high-risk behaviour – Presence of anal lesions caused by Human papilloma virus or Herpes Simplex Virus	**Specific events to be investigated:** Medical consultation (reason) Contracted disease (type, date and duration) Medication (type, date of last intake) Travel abroad Diarrhoea (>3 loose or liquid stools/day) among members of the entourage (including children) within 4 weeks of donation.

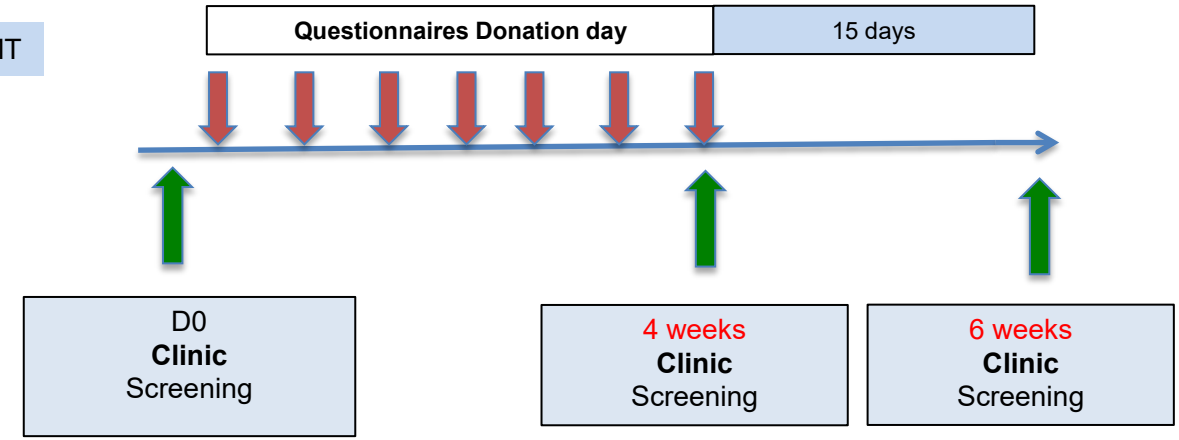
Sokol, Galperine et al. Digestive and Liver Disease 48 (2016) 242–247



Sokol, Galperine et al. Digestive and Liver Disease 48 (2016) 242–247

Multiple donations for frozen formula

Questionnaires FMT



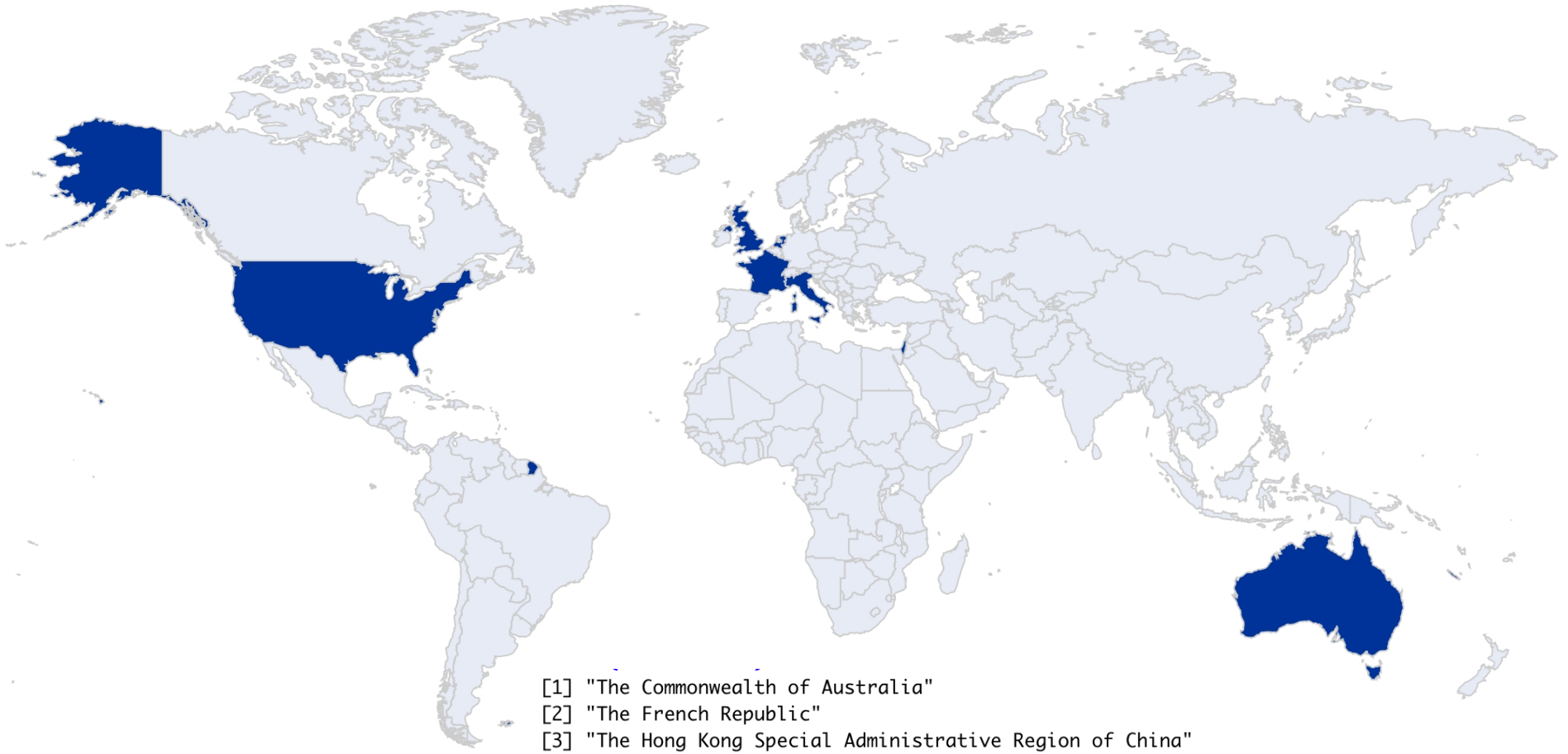
swissmedic

Approval of our center since October 2019


BACKPACKER'S
PANTRY
Beef Stroganoff
MAKES TWO 13 OZ SERVINGS

The Dutch Are Opening Europe's First Donor Bank ... for Poop

Countries with stool bank

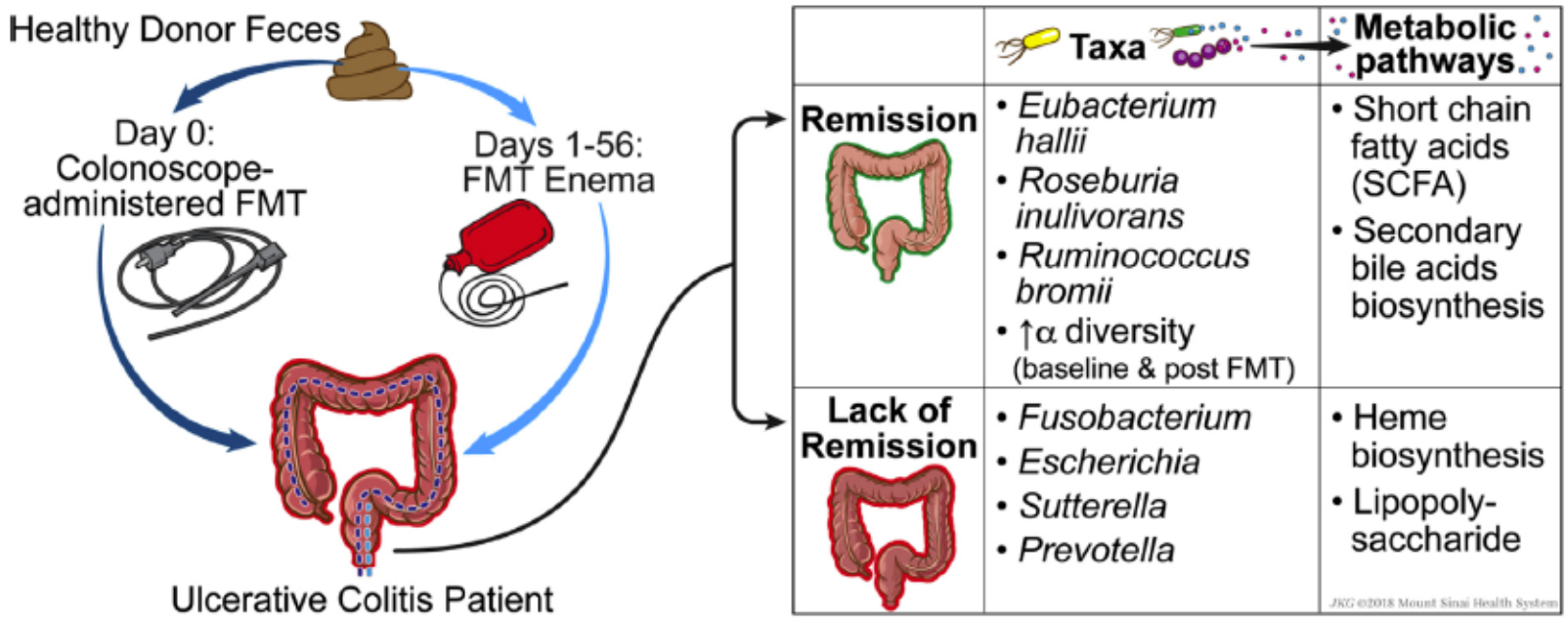


[1] "The Commonwealth of Australia"
[2] "The French Republic"
[3] "The Hong Kong Special Administrative Region of China"
[4] "The Italian Republic"
[5] "The Kingdom of the Netherlands"
[6] "The State of Israel"
[7] "The United Kingdom of Great Britain and Northern Ireland"
[8] "The United States of America"

Highcharts.com © Natural Earth

Specific Bacteria and Metabolites Associated With Response to Fecal Microbiota Transplantation in Patients With Ulcerative Colitis

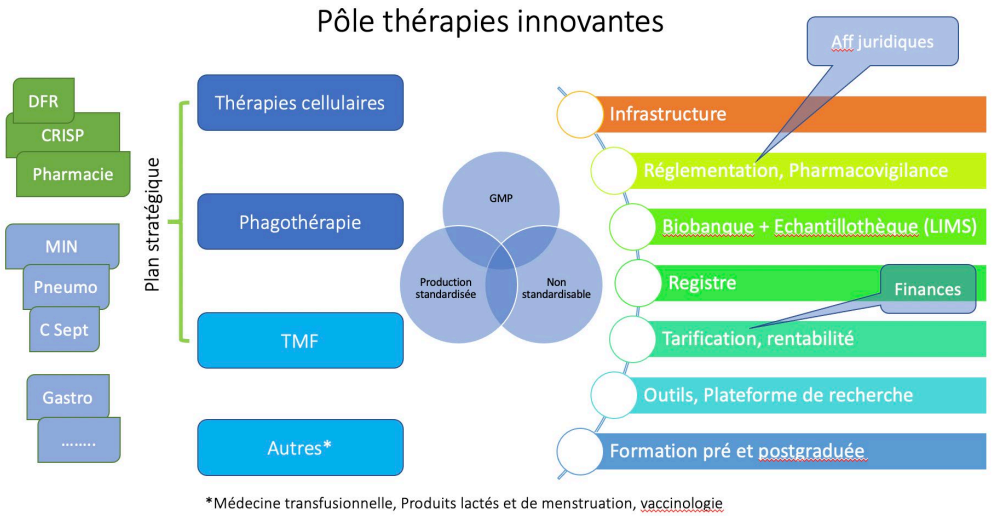
Double-blind trial of 81 patients with active UC randomly assigned to groups that received an initial colonoscopic infusion and then intensive multidonor FMT or placebo enemas, 5 d/wk for 8 weeks.



Paramsothy et al, Gastroenterology 2019 Apr;156(5):1440-1454

Conclusions

- ✓ Highly efficient in reccurent CDI
- ✓ A lot of potential indications
- ✓ Regulation in constant evolution
  - Discussion with SwissMedic
  - Modulation regarding sanitary crisis
- ✓ Necessity to be associated to a research platform
  - Inovative treatments
  - Microbiota analysis
  - Research protocols



*Médecine transfusionnelle, Produits lactés et de menstruation, vaccinologie