FBA417 – Nutrição Humana: Interação Microbioma Nutriente.

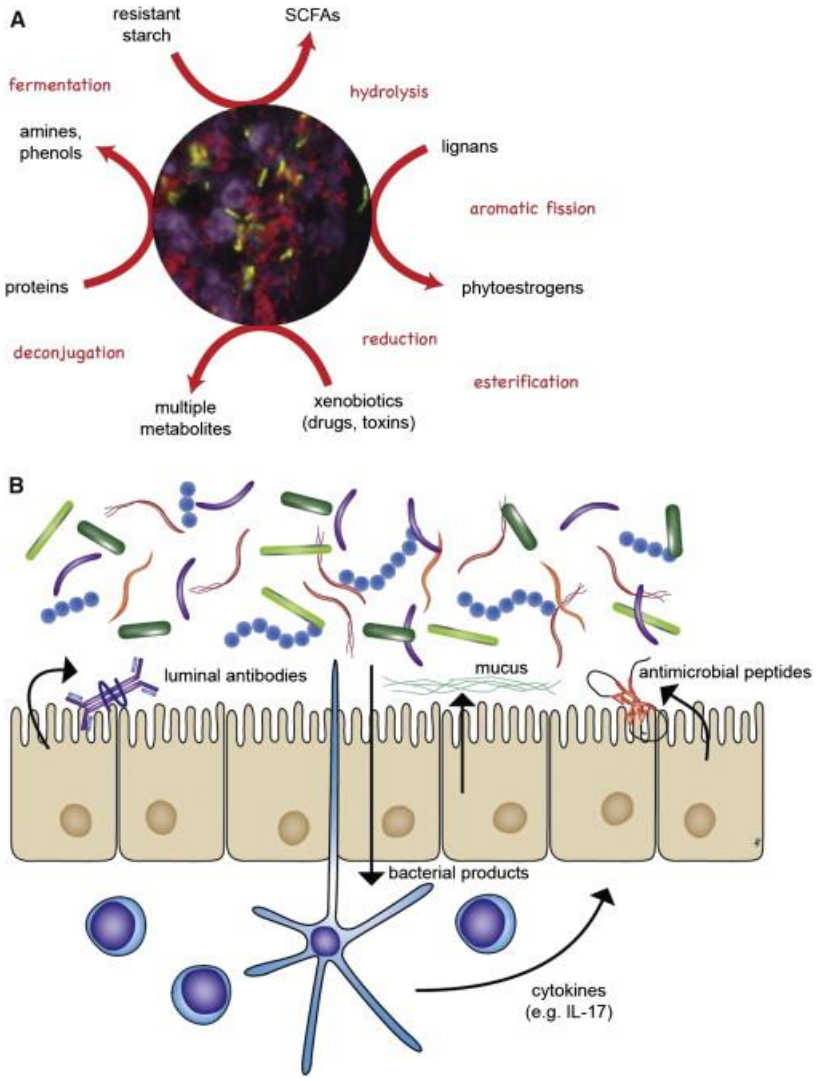
Christian Hoffmann

USP/FCF

Abril 2023.

Efeitos **do** Microbioma

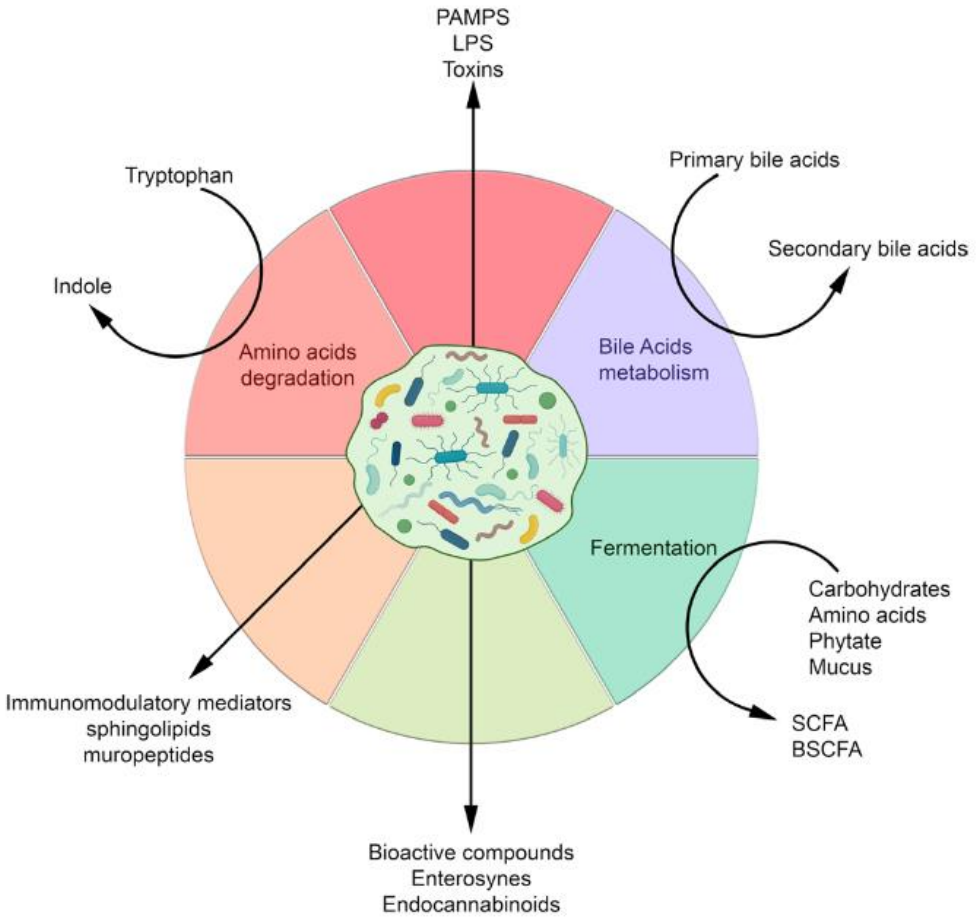
- Proteção ao tecido epitelial
- Regulação do armazenamento de gorduras do hospedeiro
- Estimulação da angiogenese intestinal
- Desenvolvimento do sistema imune
- Digestão
- Etc etc etc



Bäckhed et al. Cell Host & Microbe 2012. 12(5):611–622.

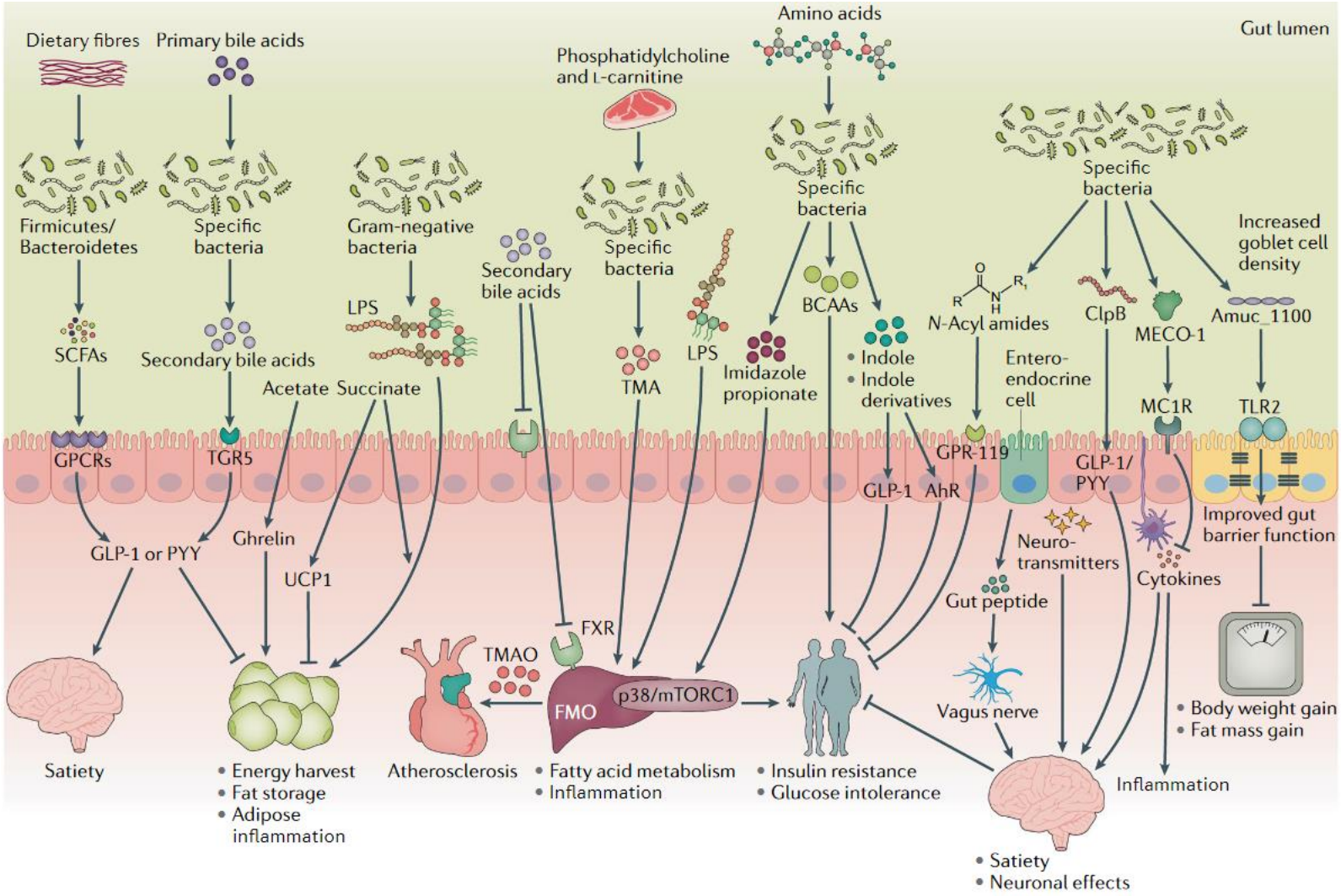
Efeitos **do** microbioma

Algumas moléculas e metabólitos com origem no microbioma e que afetam processos fisiológicos



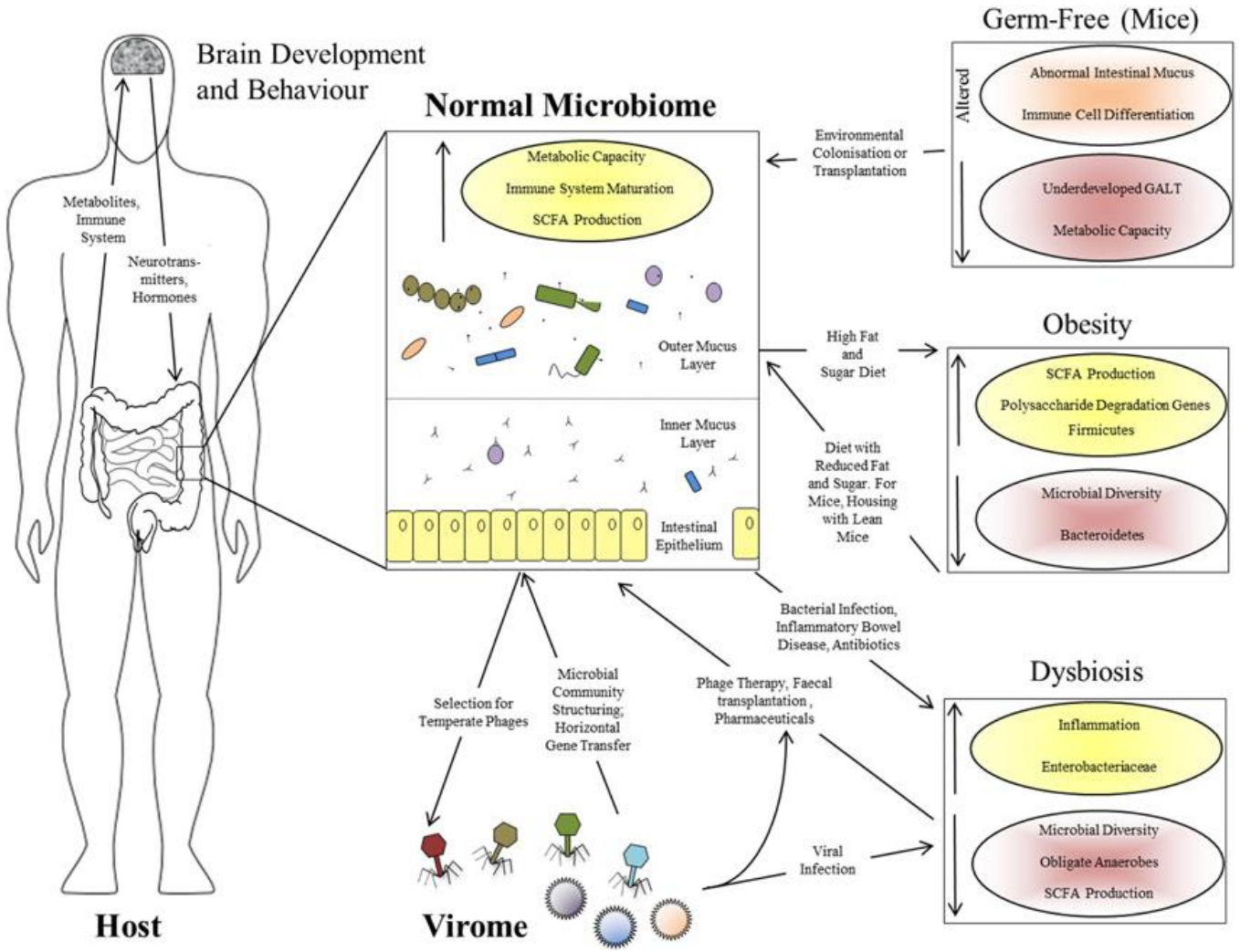
de Vos et al. 2022. *Gut* 71 (5): 1020–32.

Efeitos **do** microbioma



de Vos et al. 2022. *Gut* 71 (5): 1020–32.

O Microbioma e o Organismo Humano: "Simbiose e disbiose"



Glendinning and Free. Front. Cell. Infect. Microbiol. 2014. 4:24.

Obesidade e o Microbioma

Obesity alters gut microbial ecology

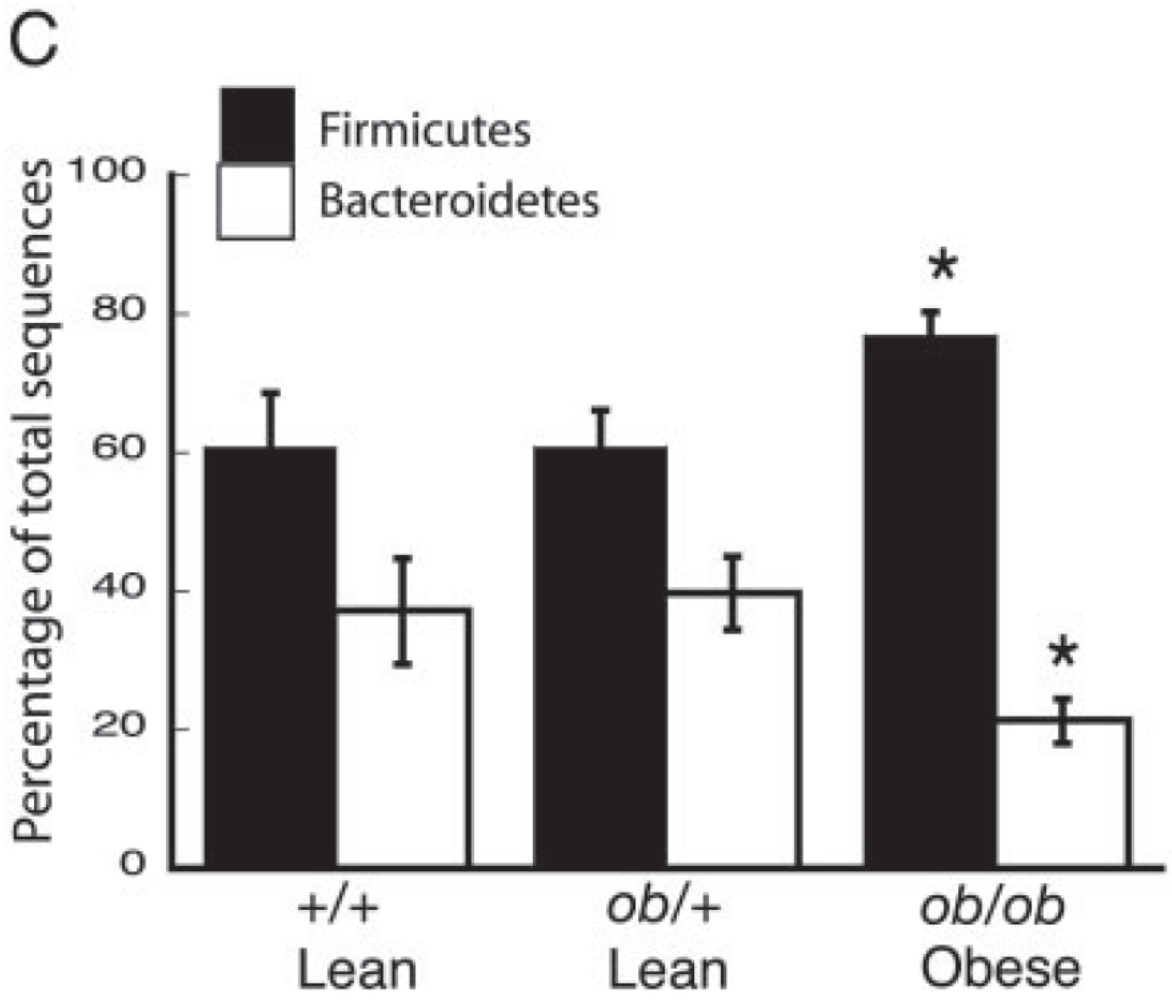
Ruth E. Ley[†], Fredrik Bäckhed[†], Peter Turnbaugh[†], Catherine A. Lozupone[‡], Robin D. Knight[§], and Jeffrey I. Gordon[†¶]

[†]Center for Genomes Sciences, Washington University School of Medicine, St. Louis, MO 63108; and Departments of [‡]Molecular, Cellular, and Developmental Biology and [§]Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309

Contributed by Jeffrey I. Gordon, June 14, 2005

We have analyzed 5,088 bacterial 16S rRNA gene sequences from the distal intestinal (cecal) microbiota of genetically obese *ob*/*ob* mice, lean *ob*/+ and wild-type siblings, and their *ob*/+ mothers, all fed the same polysaccharide-rich diet. Although the majority of mouse gut species are unique, the mouse and human microbiota(s) are similar at the division (superkingdom) level, with Firmicutes and Bacteroidetes dominating. Microbial-community composition is inherited from mothers. However, compared with lean mice and regardless of kinship, *ob*/*ob* animals have a 50% reduction in the abundance of Bacteroidetes and a proportional increase in Firmicutes. These changes, which are division-wide, indicate that, in this model, obesity affects the diversity of the gut microbiota and suggest that intentional manipulation of community structure may be useful for regulating energy balance in obese individuals.

Studies are needed to characterize the rules controlling mic
bial diversity in the human gut. Remarkably, a comprehens
enumeration of the gut microbiota has not yet been reported
Mus musculus, even though this mammalian species provide
very attractive model for systematically exploring the roles
host genotype, maternal exposure, diet, and energy balance
intestinal microbial ecology. Therefore, in this report, we
C57BL/6 mice, homozygous for a mutation in the leptin ge
(*ob*/*ob*) that produces a stereotyped, fully penetrant obes
phenotype (6, 7), and their lean *ob*/+ and +/+ siblings, to sh
that microbial-community composition in the distal intest
changes at a division-wide level in response to increasing a
posity. This finding provides another perspective about the l
between the gut microbiota and host energy balance.


C
Firmicutes
Bacteroidetes
Percentage of total sequences
100
80
60
40
20
0
*
*
+/+
Lean
ob/+
Lean
ob/ob
Obese

Em Humanos

environmental microbiology

Environmental Microbiology (2016) **00**(00), 00–00 doi:10.1111/1462-2920.13463

Pediatric obesity is associated with an altered gut microbiota and discordant shifts in *Firmicutes* populations

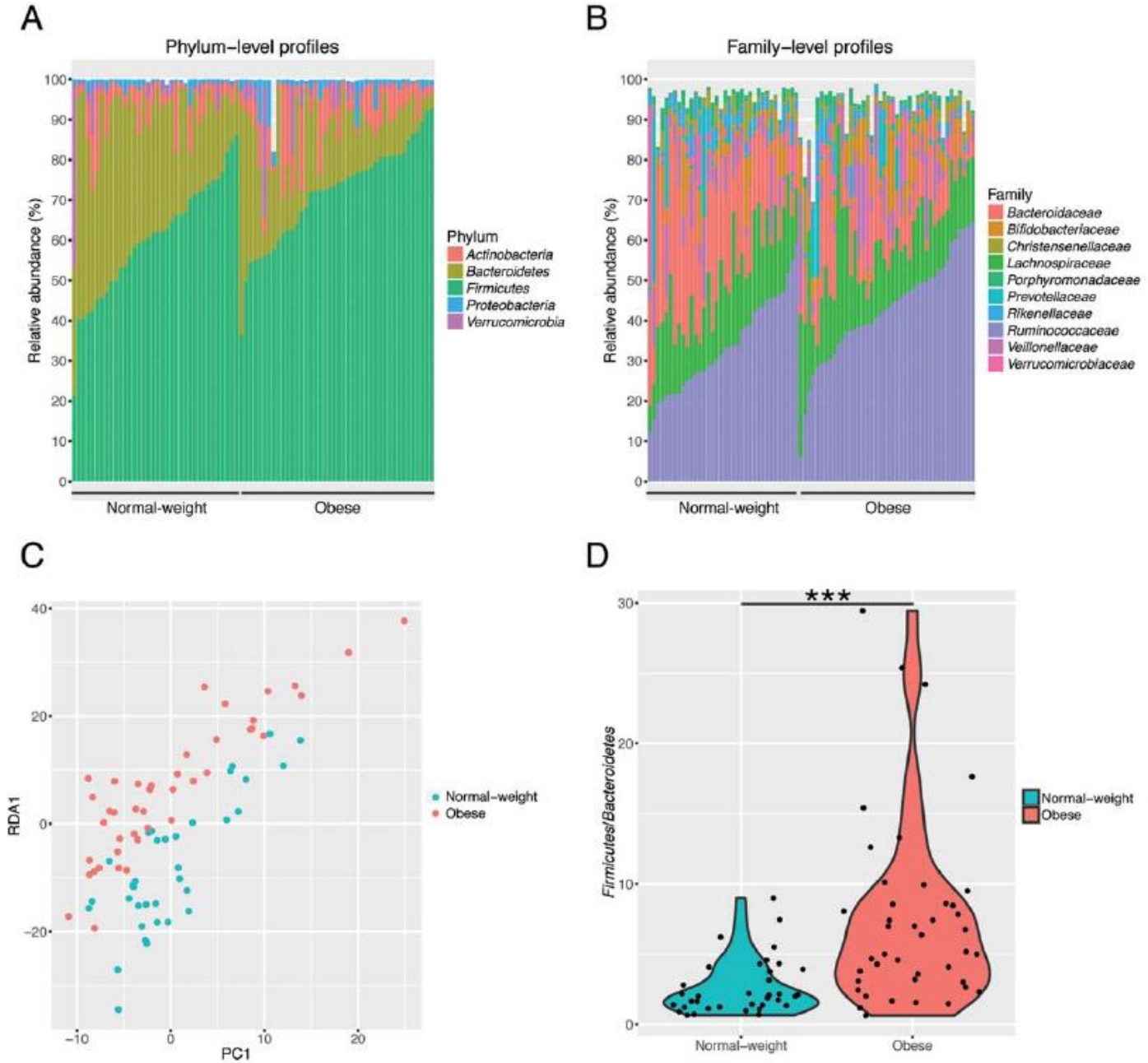
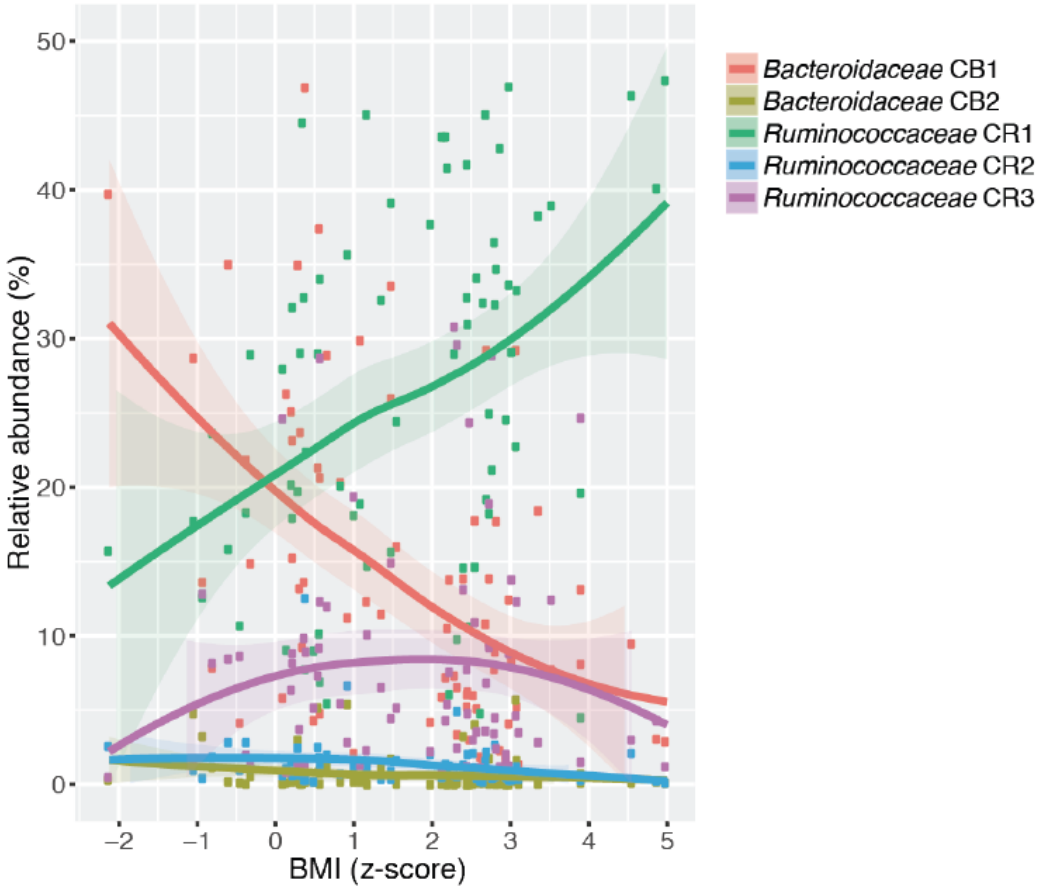
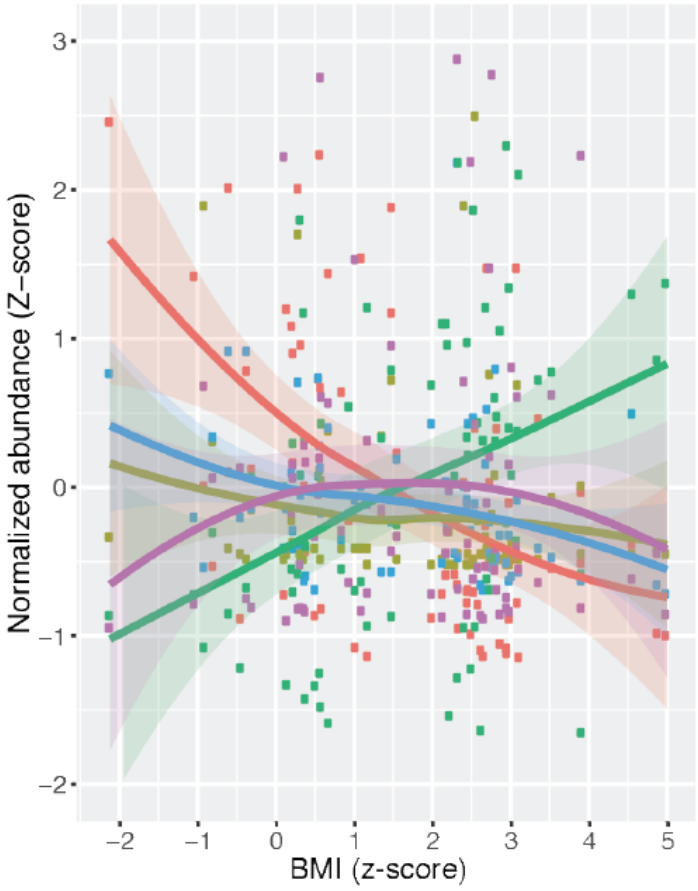


Fig. 1. Abundant bacterial taxa in stool samples of normal-weight ($n = 36$) and obese ($n = 42$) children.
Phylum-level (A) and family-level (B) taxon profiles are shown. Abundant taxa, defined as having a mean relative abundance of >1%, are shown.

A


Relative abundance (%)
50
40
30
20
10
0
−2
−1
0
1
2
3
4
5
BMI (z-score)
Bacteroidaceae CB1
Bacteroidaceae CB2
Ruminococcaceae CR1
Ruminococcaceae CR2
Ruminococcaceae CR3

B


Normalized abundance (Z−score)
3
2
1
0
−1
−2
−2
−1
0
1
2
3
4
5
BMI (z-score)

- **Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice**

- Ridaura, VK, et al. *Science* **341** (6150)
- doi: 10.1126/science.1241214

- Transplante fecal: de humano para murino
- Mostrar relações entre microbiota como possível agente obesigênico

- Gemeos selecionados:

A

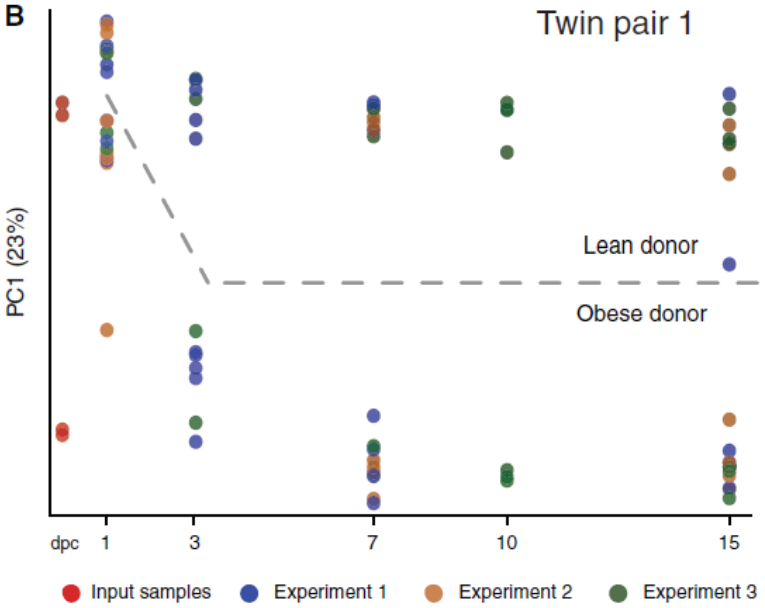
Twin Pair	1 (DZ)		2 (DZ)		3 (DZ)		4 (MZ)	
BMI (kg/m^2)	23	32	25.5	31	19.5	30.7	24	33

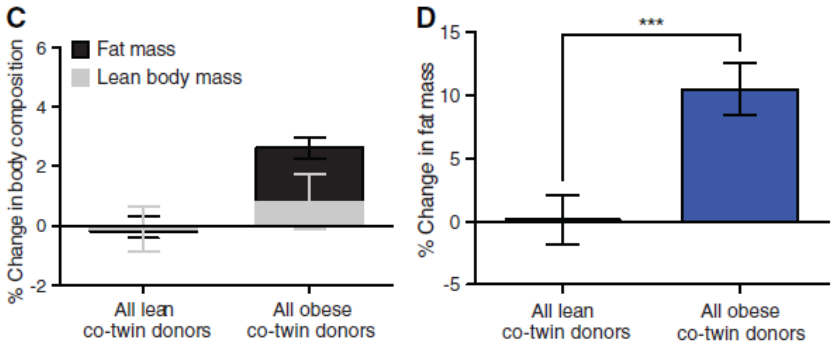
- Transplante fecal para camundongos germ free.

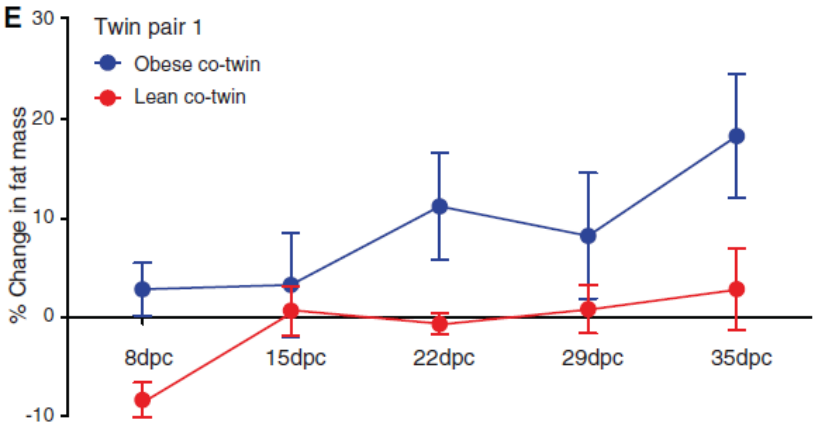
Figura 1: Diferenças em ganho de peso

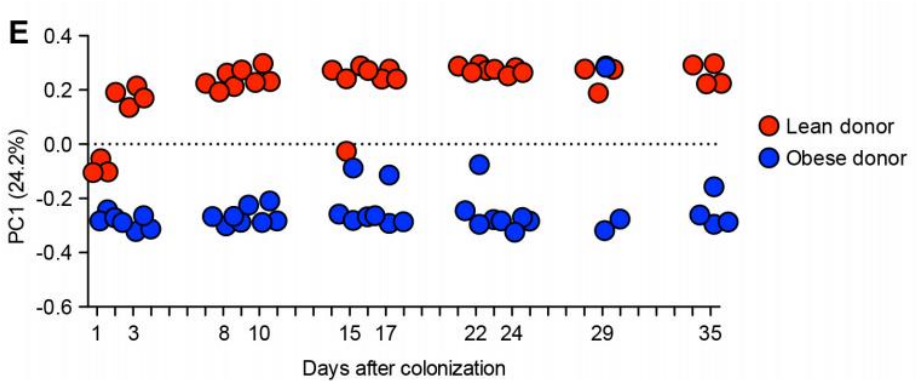
A

Twin Pair	1 (DZ)		2 (DZ)		3 (DZ)		4 (MZ)	
BMI (kg/m²)	23	32	25.5	31	19.5	30.7	24	33









- Fig. 1. Reliable replication of human donor microbiota in gnotobiotic mice.

LF-HPP diet

Figure 2: Co-habitação transfere o fenótipo magro

- Gordos ficam magros, mas magros não ficam gordos

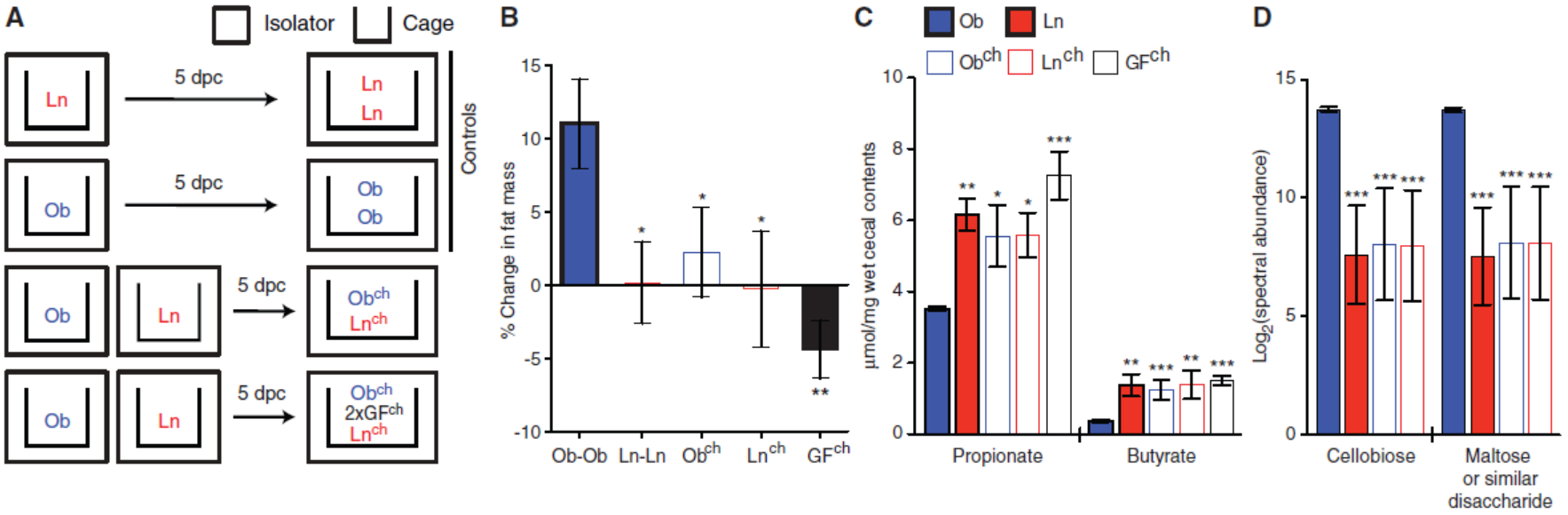
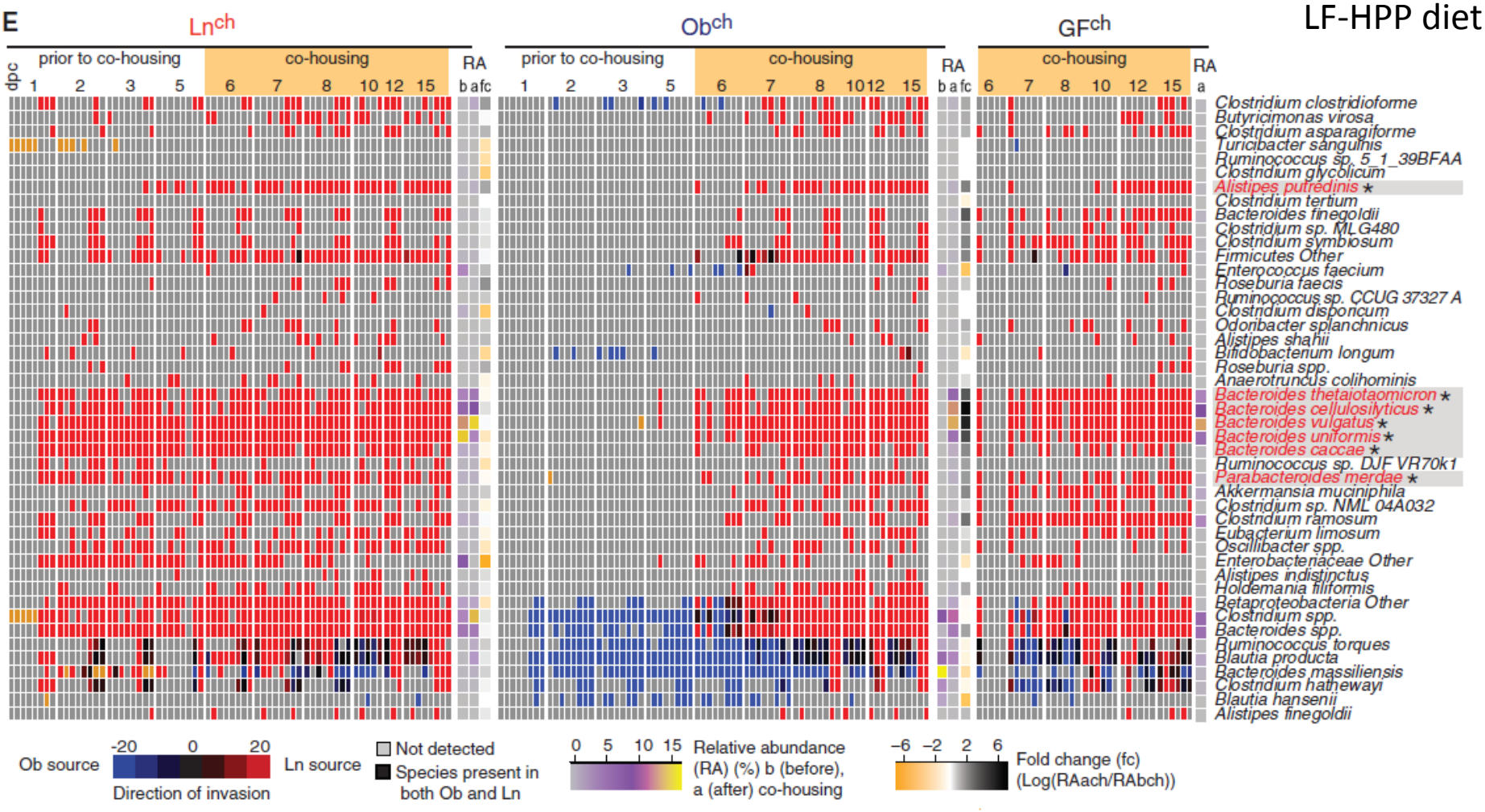


Fig. 2. Cohousing Ob^{ch} and Ln^{ch} mice transforms the adiposity phenotype of cage mates harboring the obese co-twin's culture collection to a lean-like state.

LF-HPP diet

LF-HPP diet



- Red = derived from the Ln^{ch}
- Blue = derived from the Ob^{ch}
- Black = unspecified source (both communities have)
- orange = uncertain origin
  - Resuldato só é obtido com tranferencia da comunidade como um todo, e não com comunidate definida de 39 isolados.

"Microbiota Magra" invade e substitui o SGI dos obesos
- Com a correta manipulação pode-se substituir uam microbiota obesigenica, nesta dieta

LowSatFat-HiFV diet

HiSF-LoFruitsVeg diet

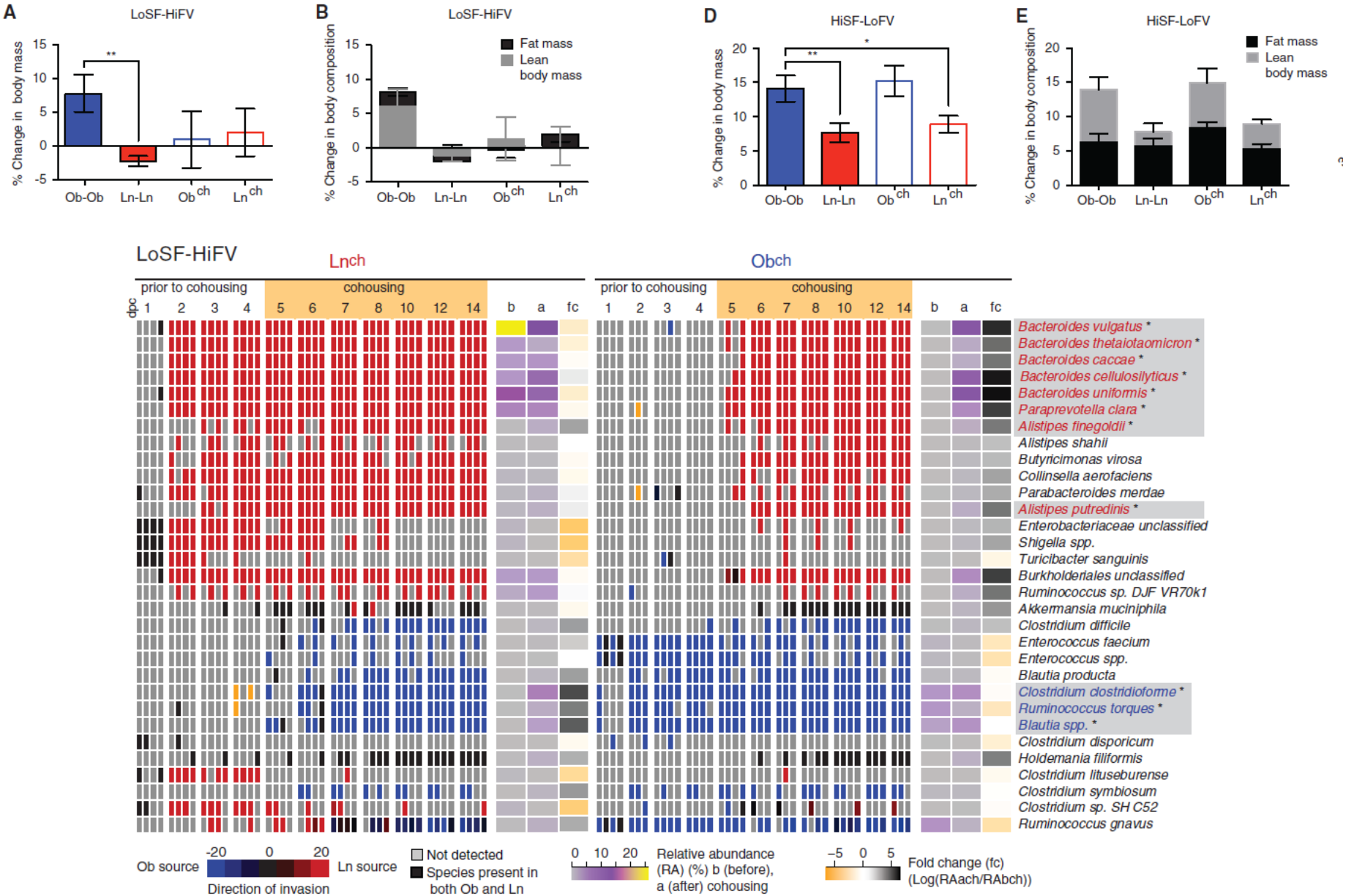
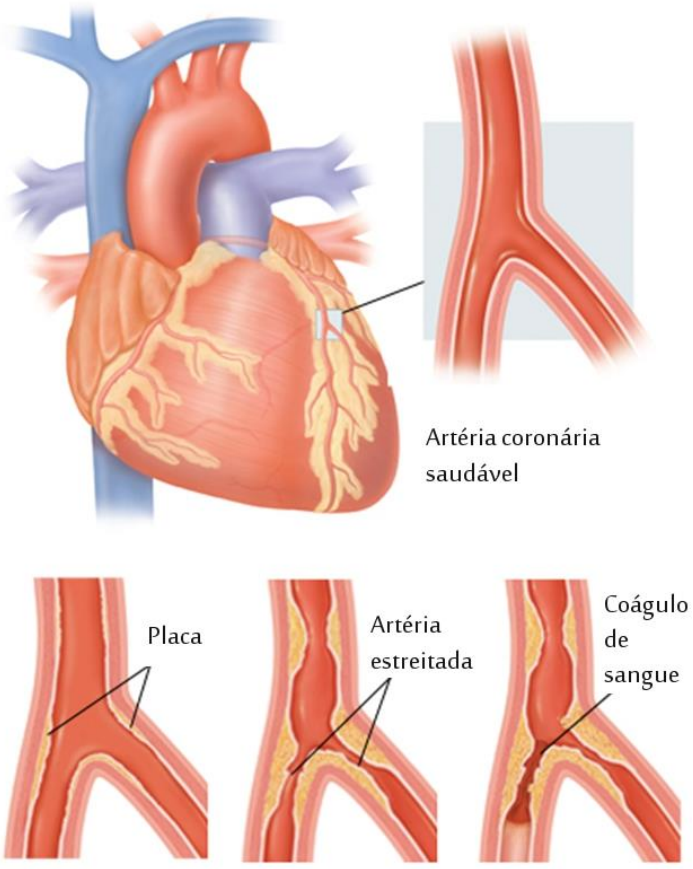


Fig 4 and 5

LoSF-HiFV diet

Doênça Cardiovascular – Aterosclerose

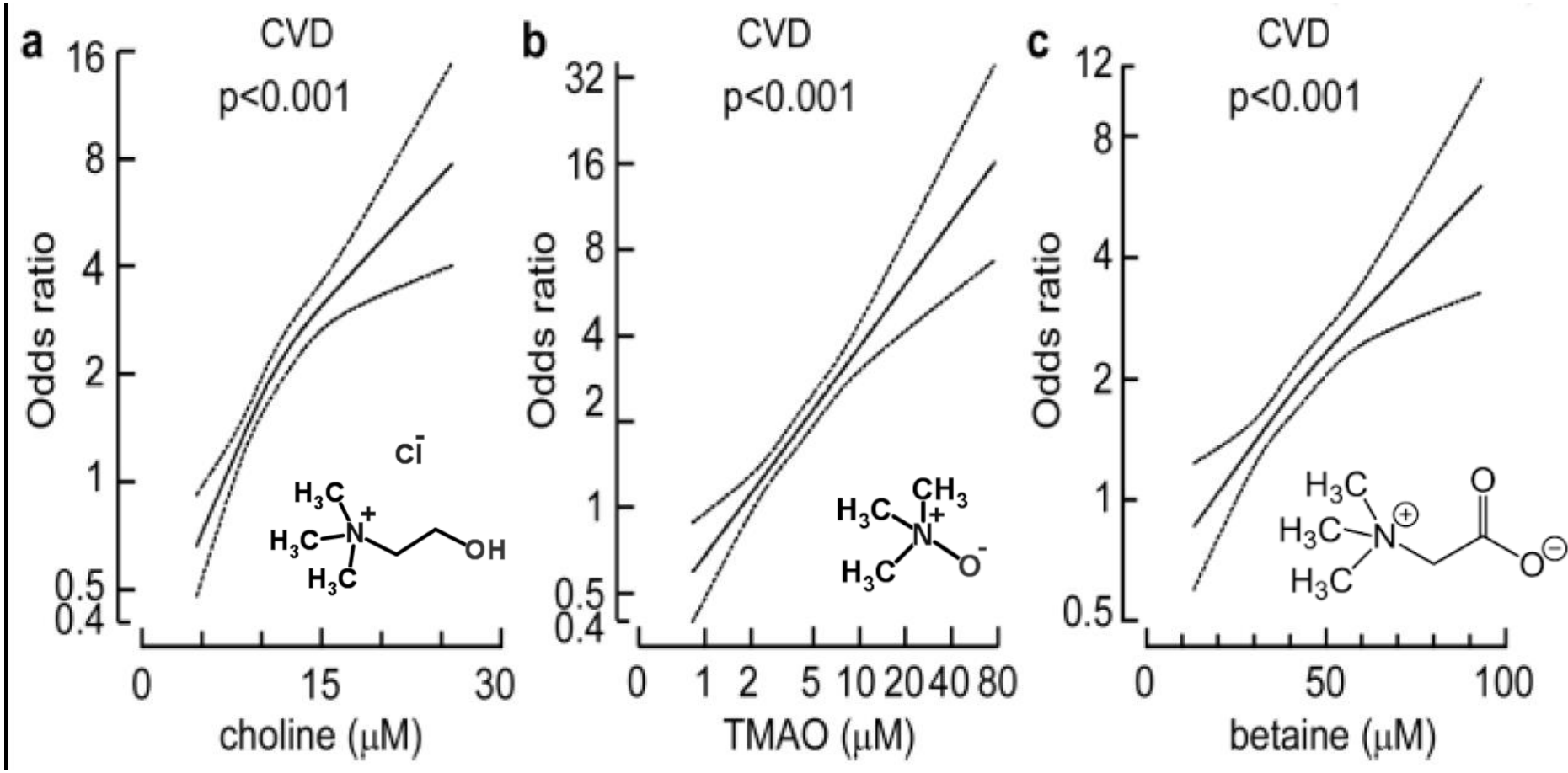
- O que é a aterosclerose?
- Fatores de risco:
  - Colesterol alto
  - Obesidade
  - Diabetes
  - etc



Wang et a. Nature 2011. 472:57-63.

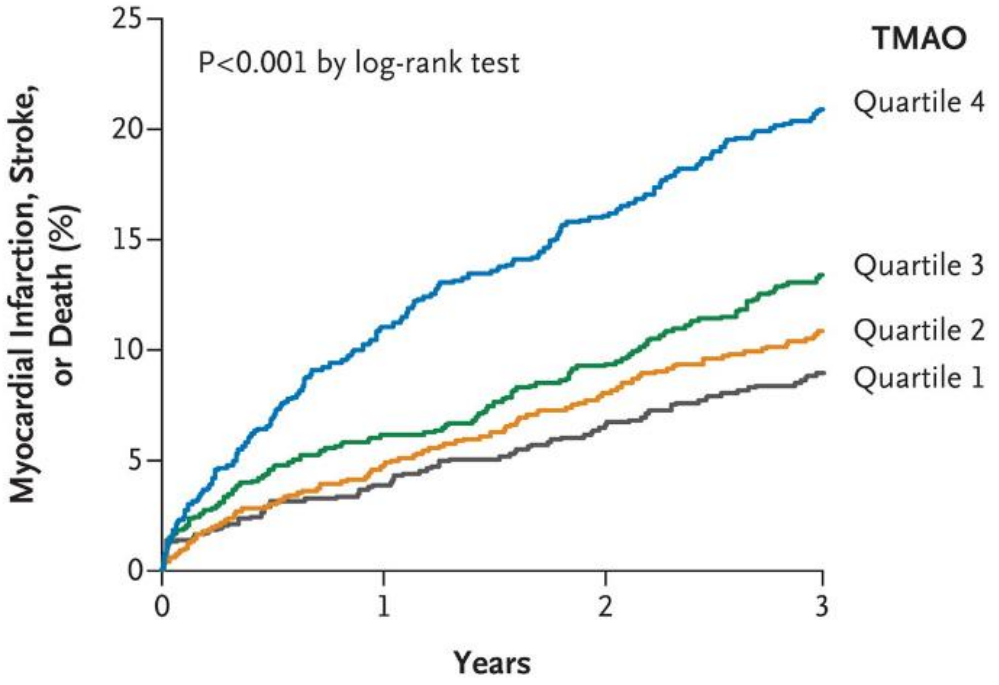
Risco doença cardiovacular

- N = 1865
- Níveis séricos humanos



Wang et al. 2011. Nature 472:57–63

- TMAO
- N=4007
- Seguidos por 3 anos.

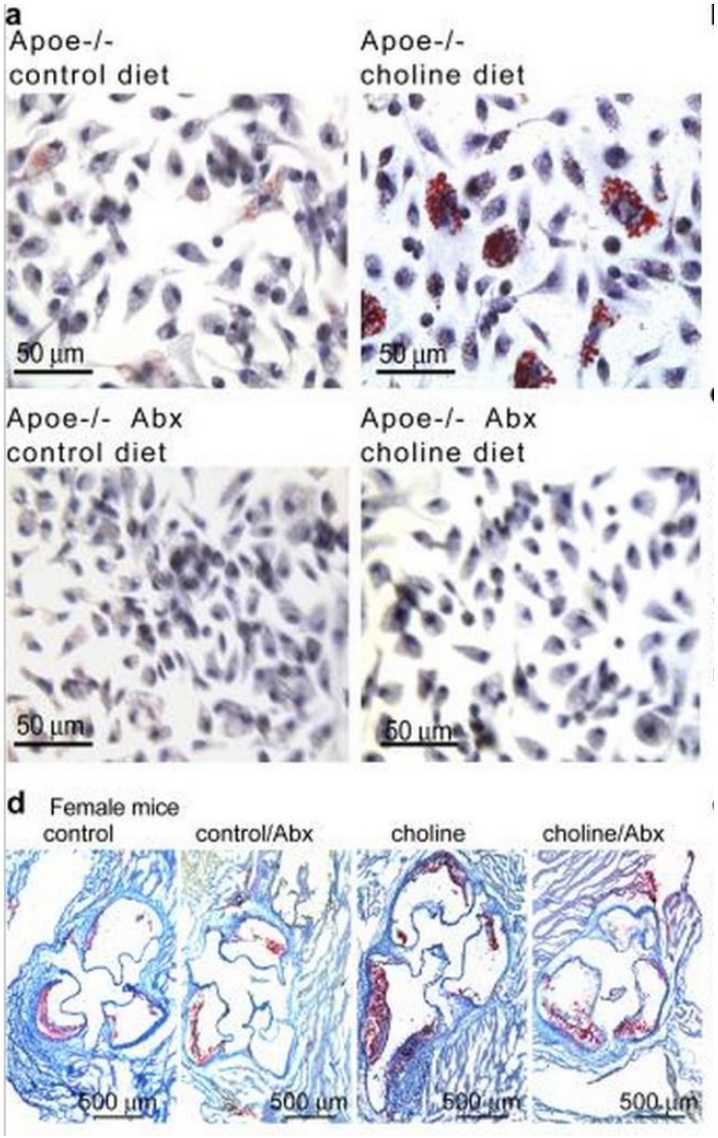


No. at Risk				
Quartile 1	1001	933	869	827
Quartile 2	998	940	884	843
Quartile 3	1003	938	888	835
Quartile 4	1005	913	849	791

Tang et al. 2013. NEJM 368:1575-1584

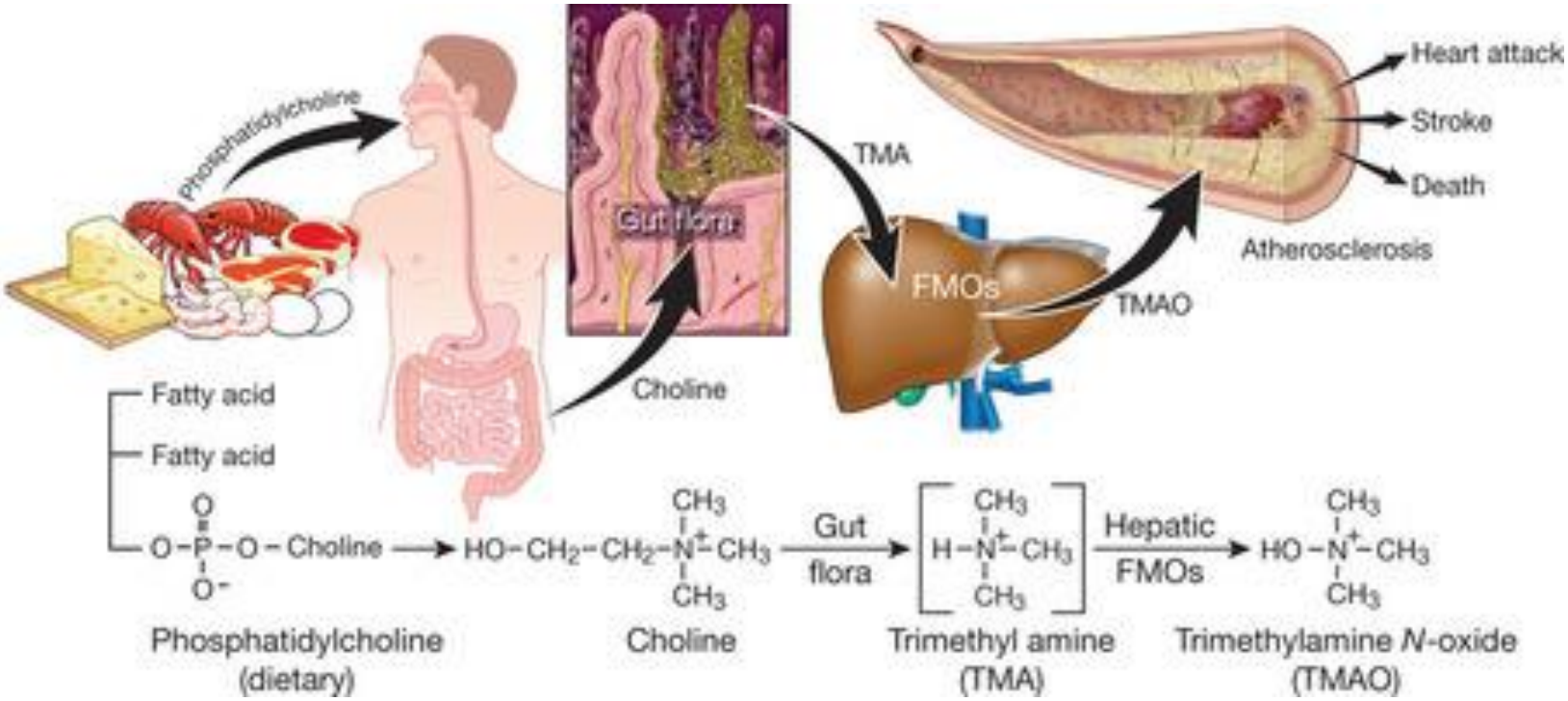
Aterosclerose

- Modelo animal:
  - Colina
  - células espumosas (macrófago), com e sem antibiótico



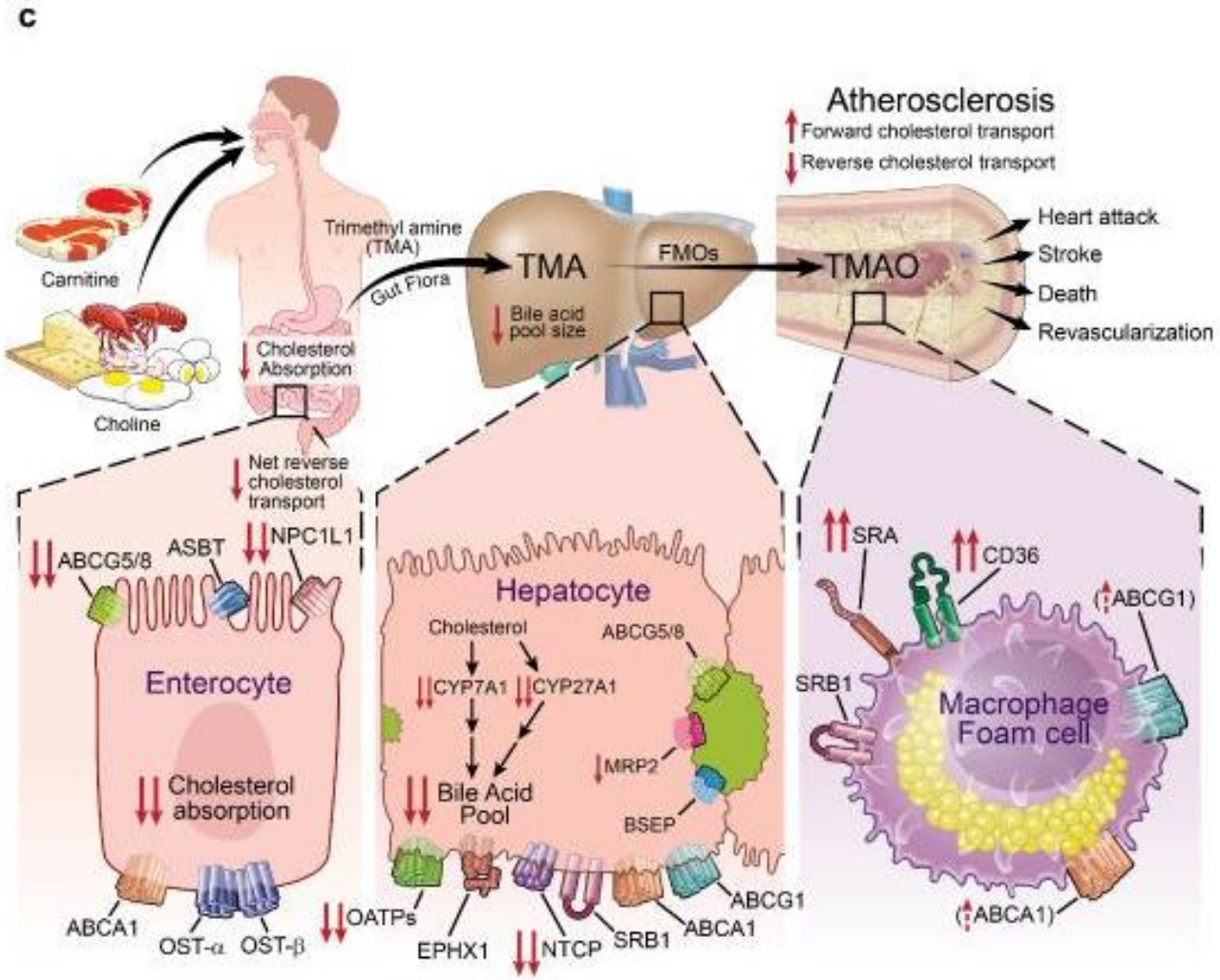
Wang et a. Nature 2011. 472:57-63.

Aterosclerose



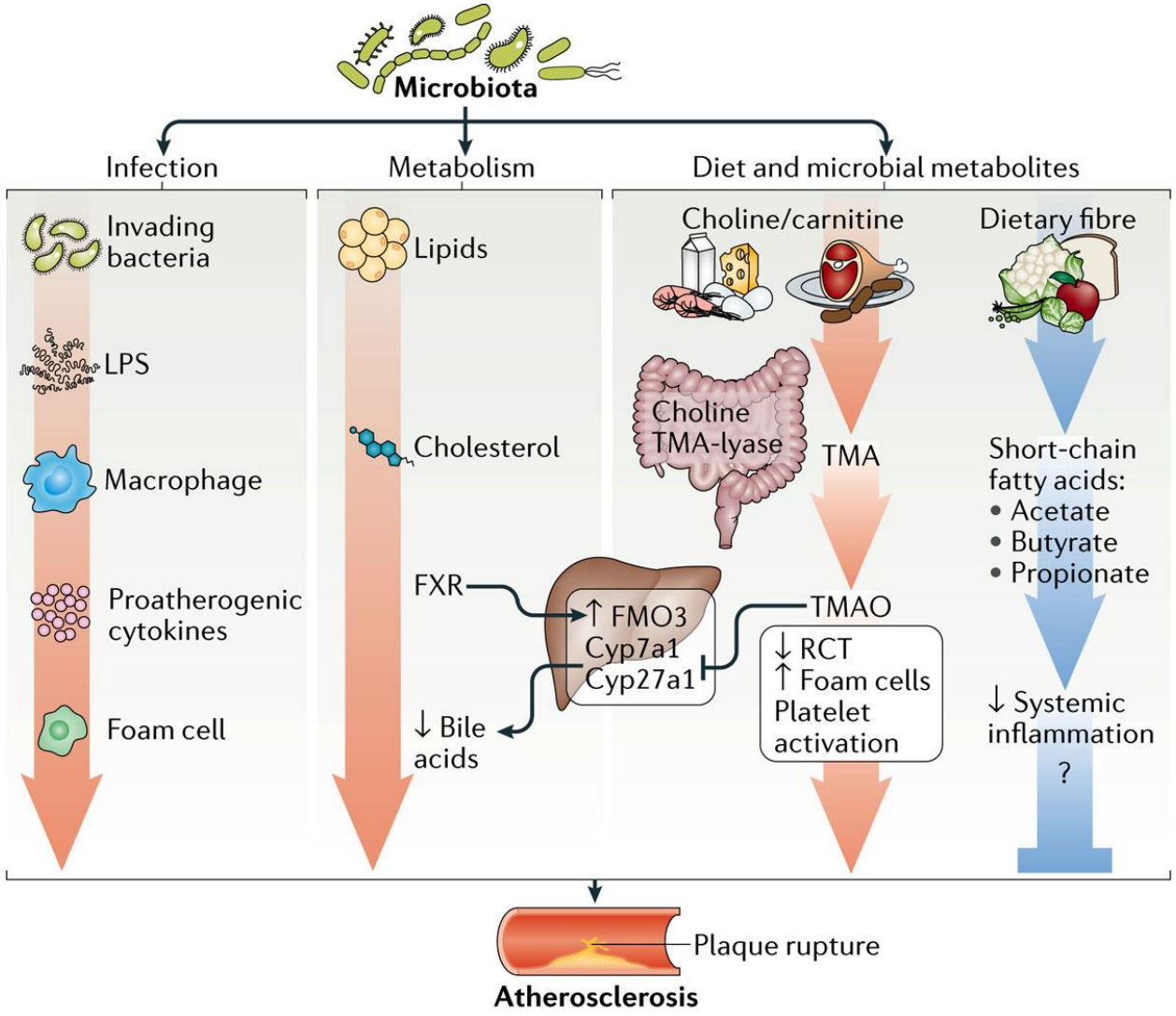
Wang et a. Nature 2011. 472:57-63.

Aterosclerose



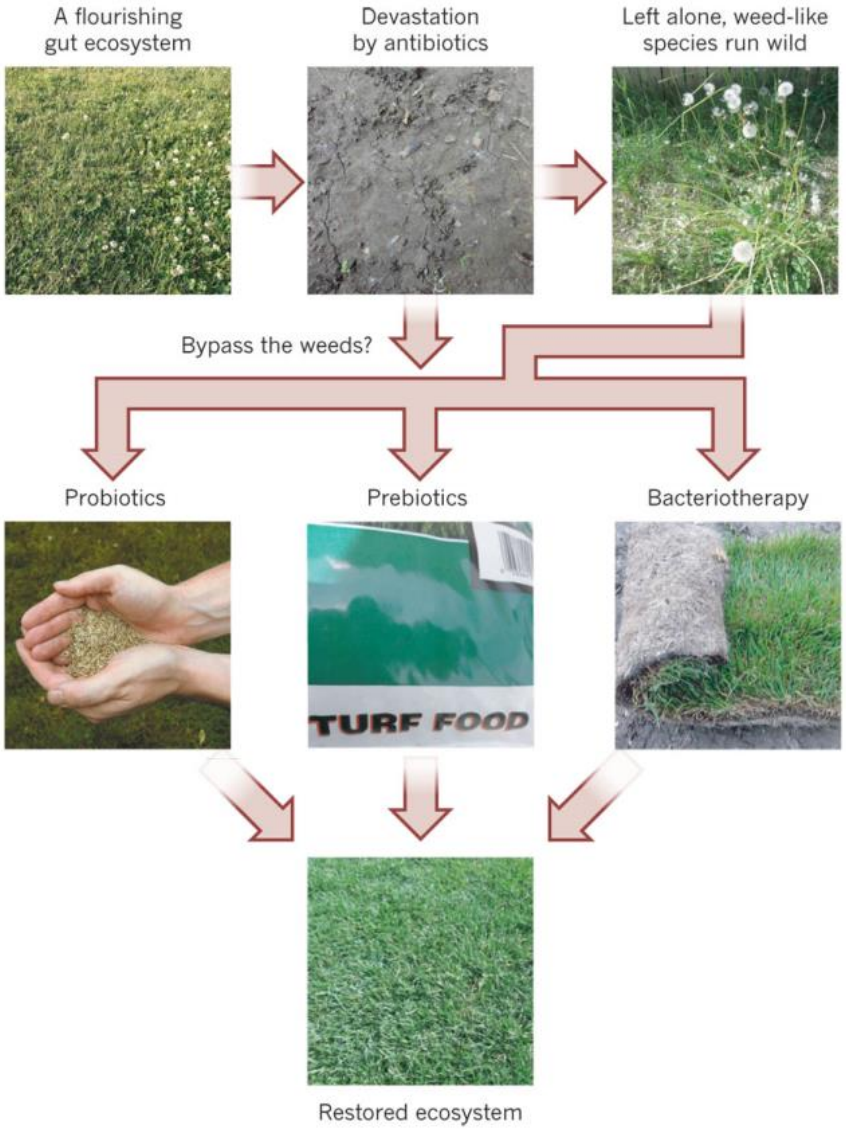
Koeth et al 2013. Nat Med. 2013 May; 19(5): 576–585.Published online 2013 Apr 7

Microbiota e Aterosclerose



Jonsson & Bäckhed. (2016) Nat. Rev. Cardiol. 14: 79-87

Manipulando o Microbioma Intestinal



Lozupone et al. Nature 2012. 489:220–230

Manipulando o Microbioma Intestinal

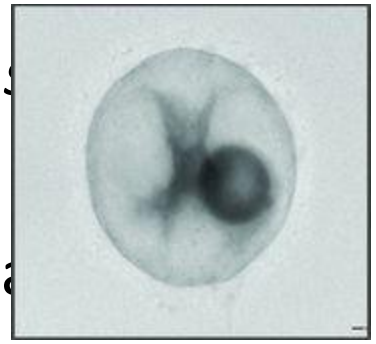
4D Pharma, AOBiome, APC Microbiome Institute, AbbVie, ActoGeniX, Admera Health, Advanced Technology Ventures, Advancing Bio, AgBiome, Assembly Biosciences, Avid Biotics, Azitra, BioAster Technology Research Institute, BioBalance Corporation, BioConsortia, BioGaia, Biocartis, Biomecite Diagnostics, C3 Jian, Center for Biologics Evaluation and Research (CBER), Cipac Therapeutics, Companion PBx, Concorde Medical Group, Da Volterra, Dairy Innovation Australia Limited (DIAL), Danisco, Debiopharm, Dermala, Enso Ventures, Enterologics, Enterome BioScience, Epibiome, Epiva Therapeutics, Evelo Therapeutics, Evolve Biosystems, Evotec, ExeGi Pharma, FUJIFILM Diosynth Biotechnologies, Flagship Ventures, GMU Microbiome Analysis Center (MBAC), GT Biologics, Gallinee, Genetic Analysis, Genewiz, Gustave Roussy, Human Longevity, Hy Laboratories, Igen Biotech Group, Illumina Accelerator, Immune Biologics, Immuron, Inocucor Technologies, Inserm, Institut Merieux, Intrexon, Janssen, Johnson & Johnson Innovation Center, KOLUPOHAKU TECHNOLOGIES (KPT), Kindstar Global, Lundbeckfond Ventures, MBcure, MaaT Pharma, Manzo Pharmaceuticals, Matatu, Merck, Metabiomics, Metabogen, Metabolon, Metanome, Metrodora Therapeutics, MiOmics, MicroBiome Therapeutics, Microbiome, Microbiome Diagnostics, Microbiota Company, Miyarisan Pharmaceutical, Monarch Labs, Morgenthaler, MyBiotics, NIZO Food Research, Novartis, OmniBiome Therapeutics, One Way Liver, OpenBiome, OptiBiotix Health, Oragenics, Osel, OxThera, Pfizer, Pivot Bio, Prev AbR, Procarta Biosystems, PureFlora, Quorum Innovations, Rebiotix, Ritter Pharmaceuticals, Second Genome, Sen Nuo Wei Biotechnology, Seres Therapeutics, Servier, Seventure, Shire, Shoreline Biome, SigmaTau Pharmaceuticals, SporeGen, Swecure, Symberix, Symbiota, Symbiotix Biotherapies, Synlogic, Synthetic Biologics, TargEDys, Therapeutic Solutions International, TriPhase Pharmaceuticals, UAS Labs, Universal Stabilisation Technologies, VSL Pharmaceuticals, Vaiomer, Vedanta Biosciences, ViroPharma Incorporated, Vithera Pharmaceuticals, Wavepoint Ventures, Whole Biome, Xycrobe Therapeutics, Yakult Honsha, cLECta

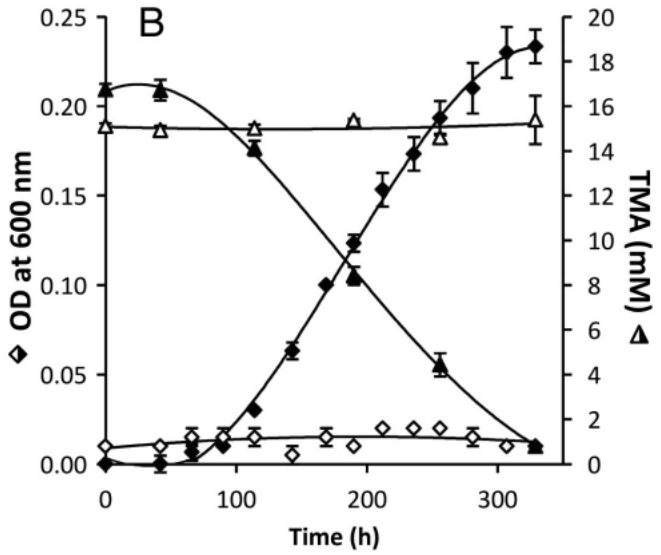
Microbiome Therapeutics Market to 2030. http://www.researchandmarkets.com/

Private Companies Working In The Microbiome		
Company	**Description**	**Total Funding (M)**
C3 Jian	Biotech company focusing on diagnosing, treating, and preventing diseases relevant to the human microbiome (with a focus on oral health)	$113
Eligo Bioscience	Developing ultra-precise antibiotics to target harmful bacteria and sparing beneficial ones	$2.2
Enterome	Focusing on microbiome-related diseases such as Irritable Bowel Syndrome and metabolic diseases (diabetes and obesity)	$23.8
EpiBiome	Precision microbiome engineering, creating therapies for humans and agriculture without the use of antibiotics	$5.7
Evelo Therapeutics	Company that seeks to create microbiome therapies for the treatment of cancer	$35
Evolve BioSystems	Working to develop products that maintain healthy microbiomes in infants	$9
Vedanta Biosciences	Fecal transplantation substitutes	$50
Kallyope	Cutting-edge technologies in sequencing, bioinformatics, neural imaging, cellular and molecular biology, and human genetics to provide an understanding of gut-brain biology	$44
Rebiotix	Creating “Microbiota Restoration Therapy” to deliver live microbes into intestinal tracts to treat disease	$30
Second Genome	Clinical-stage company discovering and developing therapies for microbiome related diseases, focusing on inflammatory bowel disease	$43
uBiome	Sequences, stores, and analyzes data related to the human microbiome	$4.9

Arqueobiótico X Aterosclerose

- *Uma propostaMethanomassiliicoccus luminyens*
- Metanogênica
- Isolada do microbioma intestinal de uma pessoa na França
- Cresce usando TMA e produz Metano

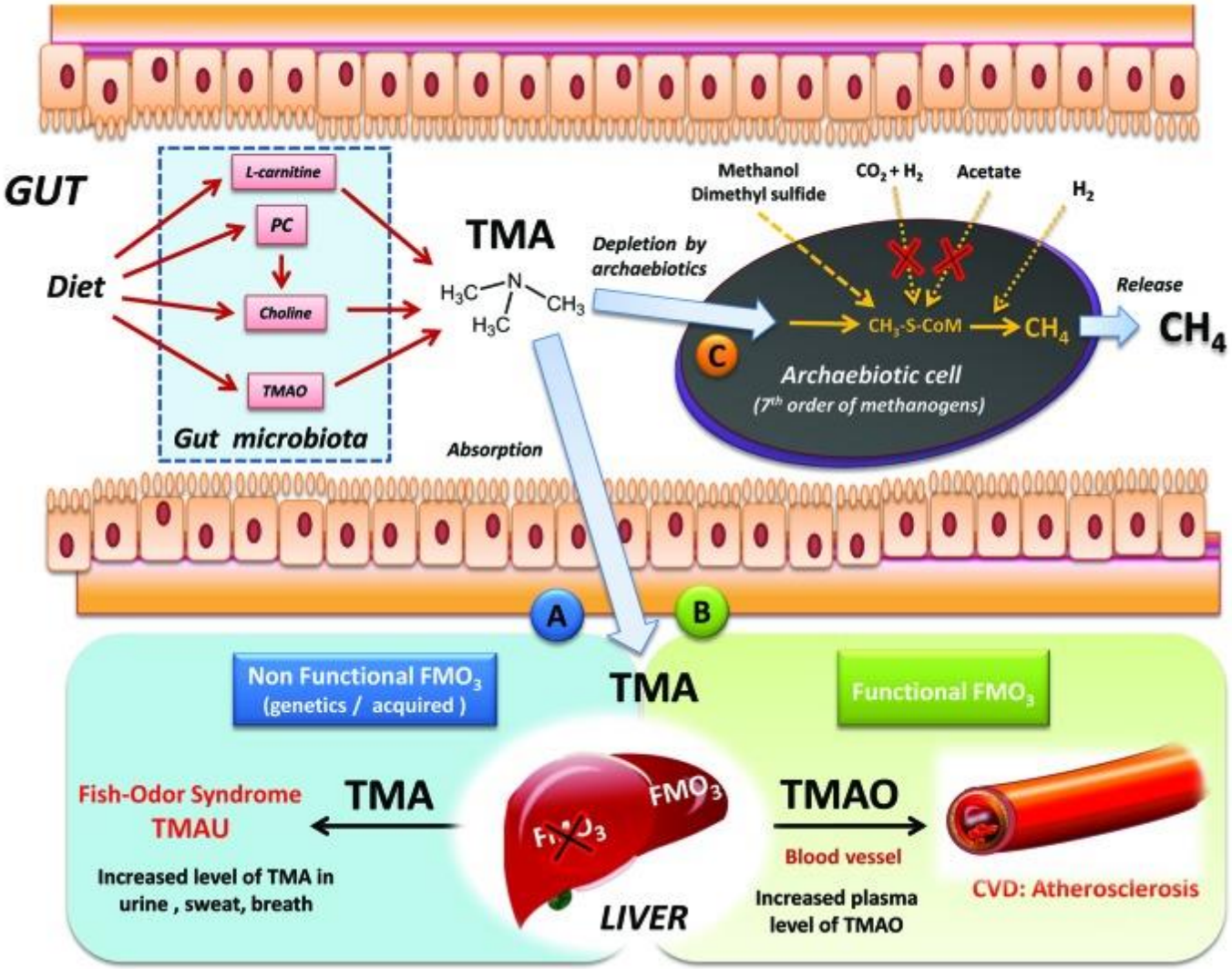




▲ [TMA] com TMA e H2
△ [TMA] com TMA sem H2
◆ Crescimento da *M.lum.* com TMA e H2
◇ Crescimento da *M.lum*. sem TMA e H2

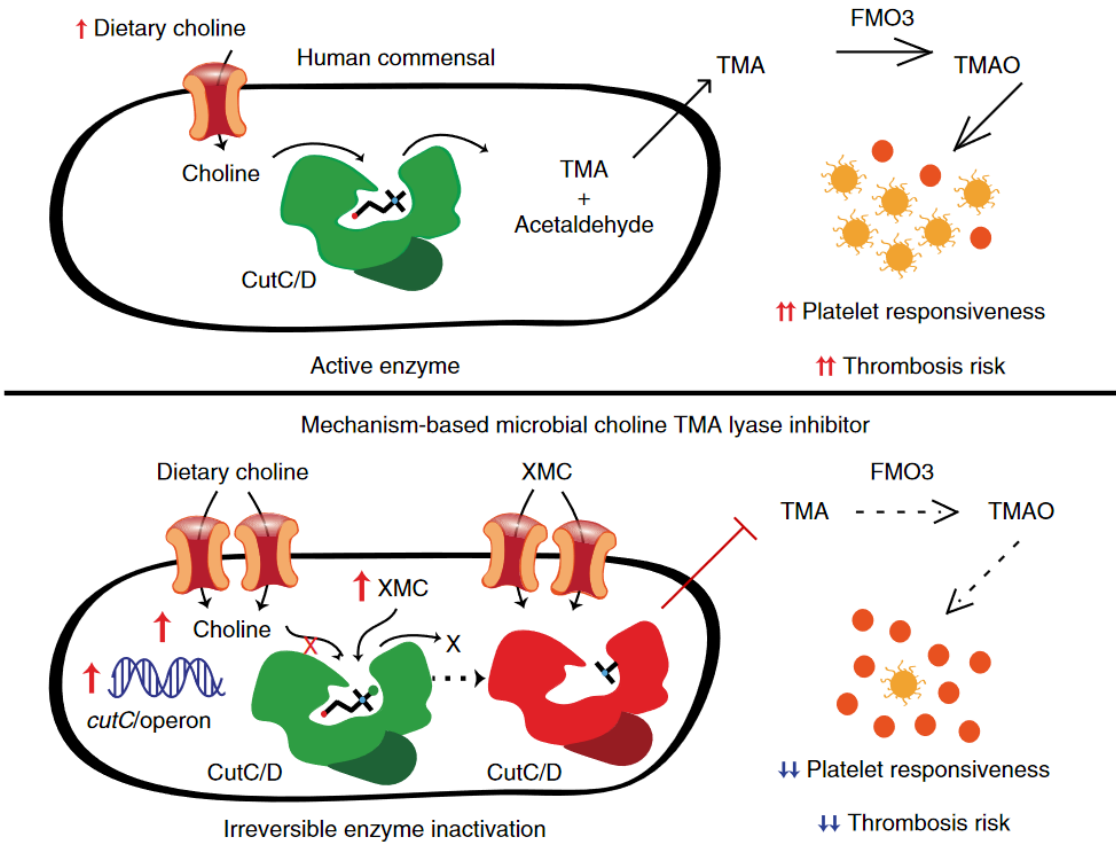
Brugere et al. Gut Microbes 2014. 5(1):5-10.

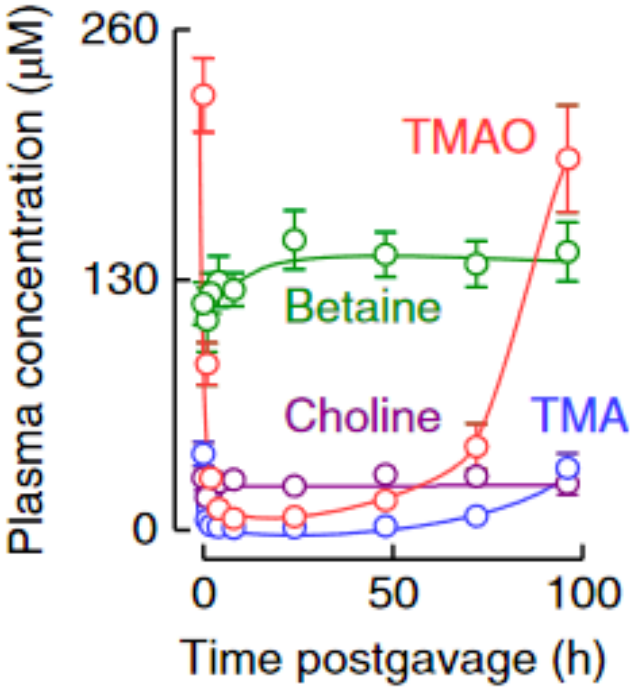
Arqueobiótico X Aterosclerose



Brugere et al. Gut Microbes 2014. 5(1):5-10.

Inibidores de atividade presente no microbioma





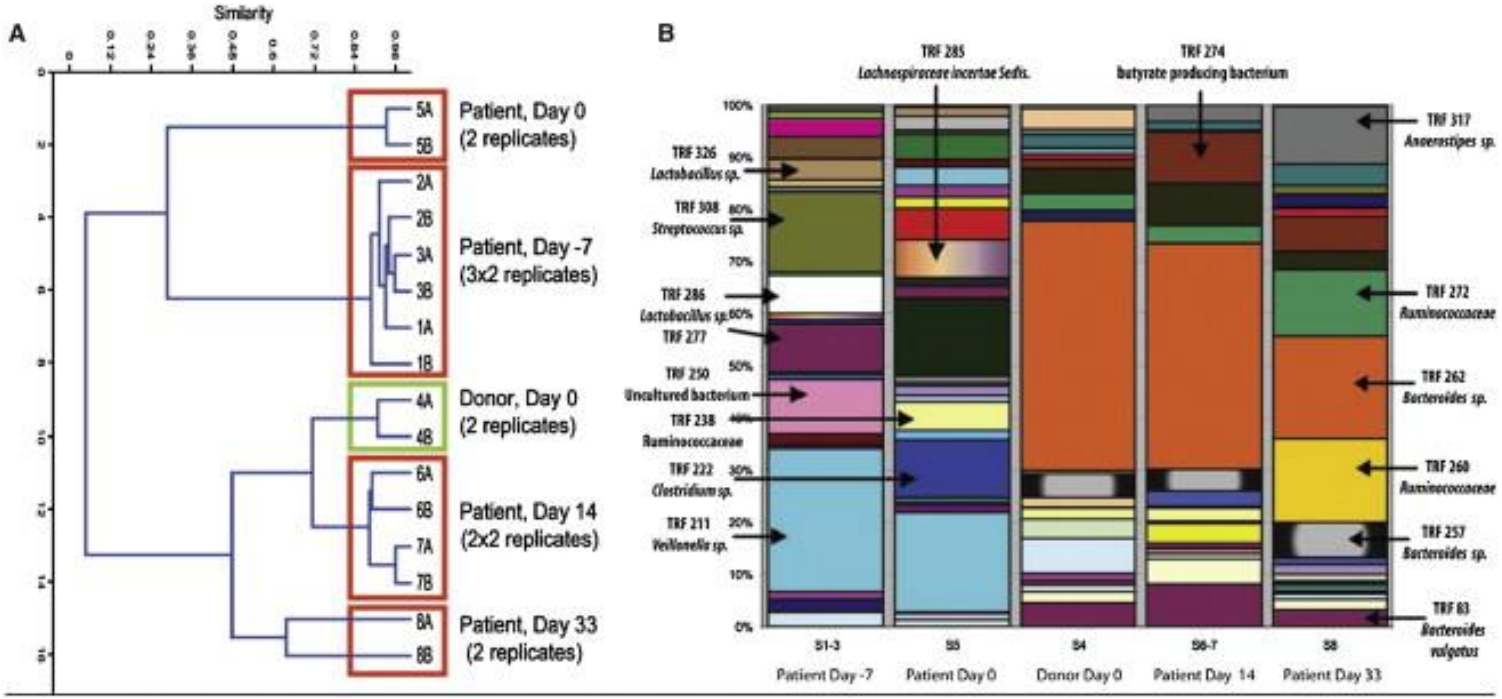
Roberts et al. 2018. *Nature Medicine* 24 (9): 1407.

Transplante fecal

- Infecção por *Clostridium difficile*
  - Diarréia decorrente do uso de antibióticos: ~10% dos casos, dos quais: *C. difficile* Responsável por 20%.
  - Geralmente adquirida em contexto hospitalar
  - Nos EUA: estimado que 12% das IH são causadas por C.diff.
  - Até 16% de mortalidade (1 ano do diagnóstico)

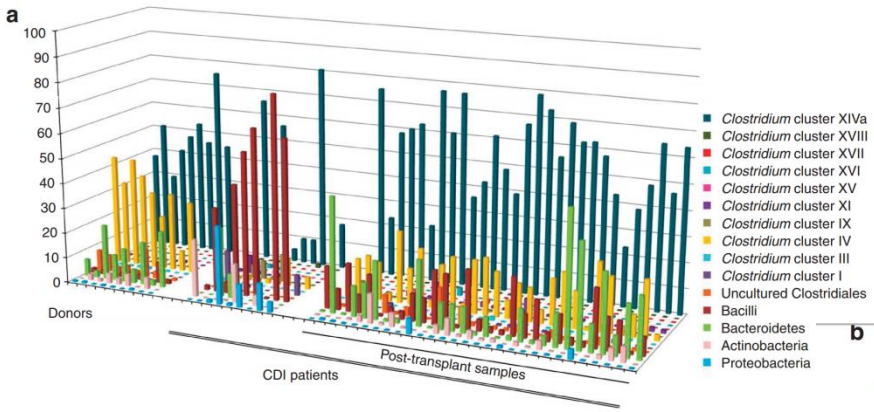
Transplante fecal

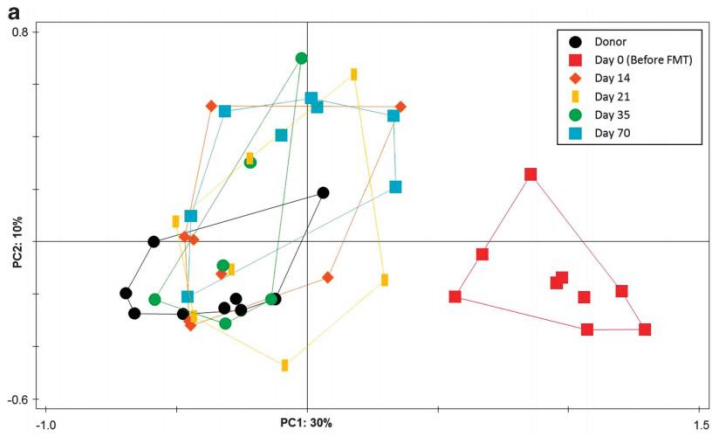
- Exemplo em um paciente, mudança após o transplante

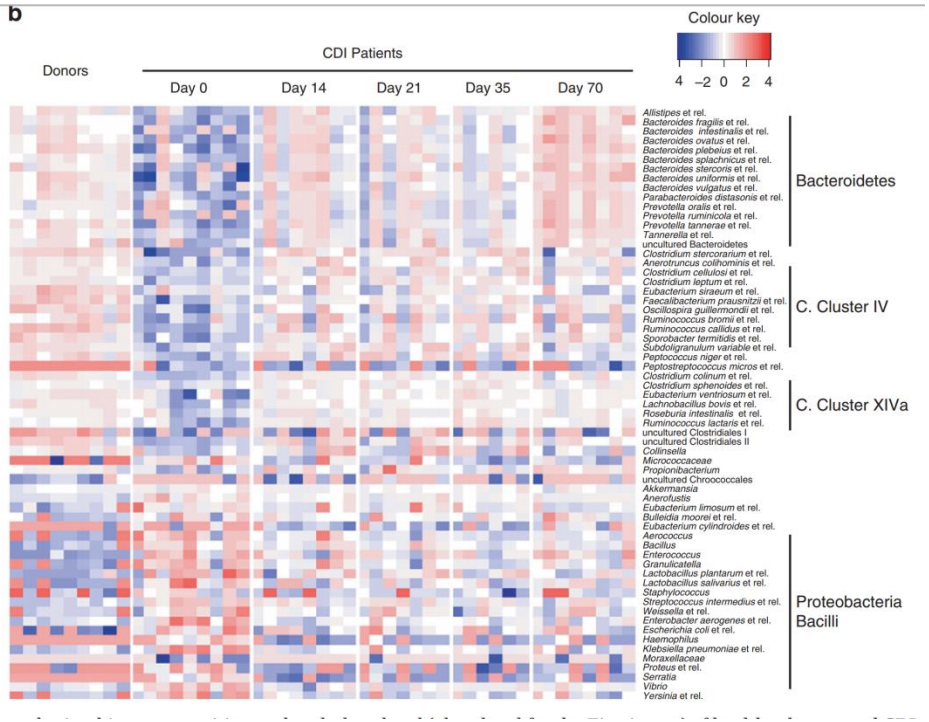


Bäckhed et al. Cell Host & Microbe 2012. 12(5):611–622.

Transplante Fecal







Fuentes et al. The ISME Journal 2014. 8(8):1621-1633.

Transplante Fecal

- Vancomicina (n=13)
- Vancomicina e lavagem intestinal (n=13)
- Vancomicina, lavagem e transplante (n=16)

- O comite ético discontinuou o teste por causa dos resultados nos controles

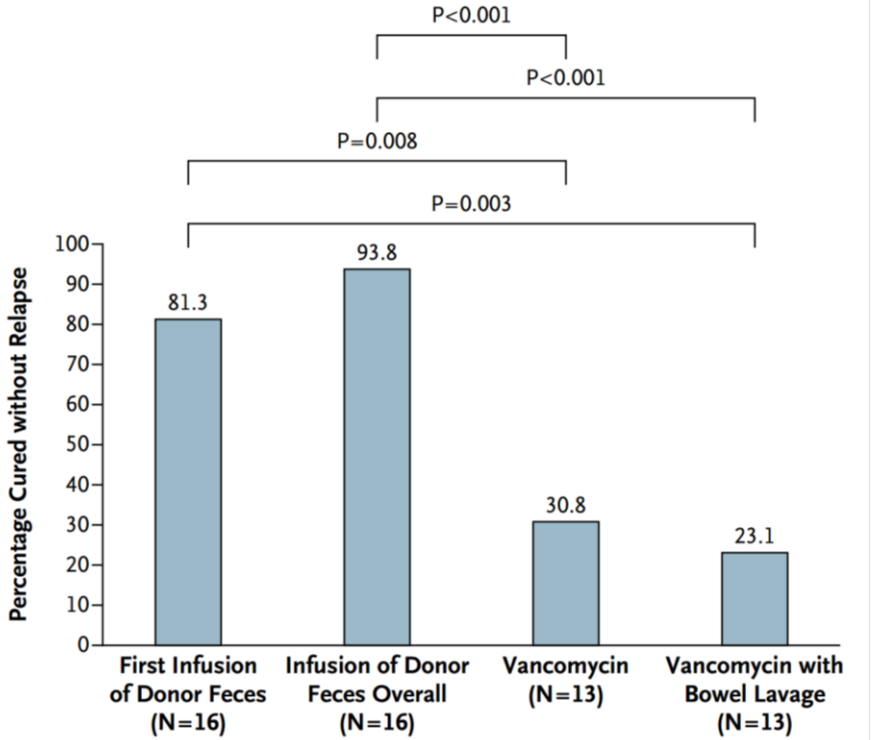


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

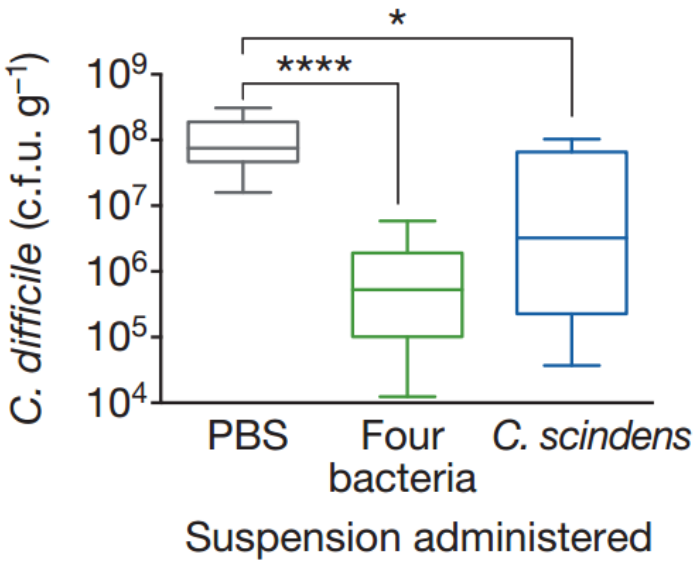
Van Nood et al. NEJM 2013. 368(5):407-415.

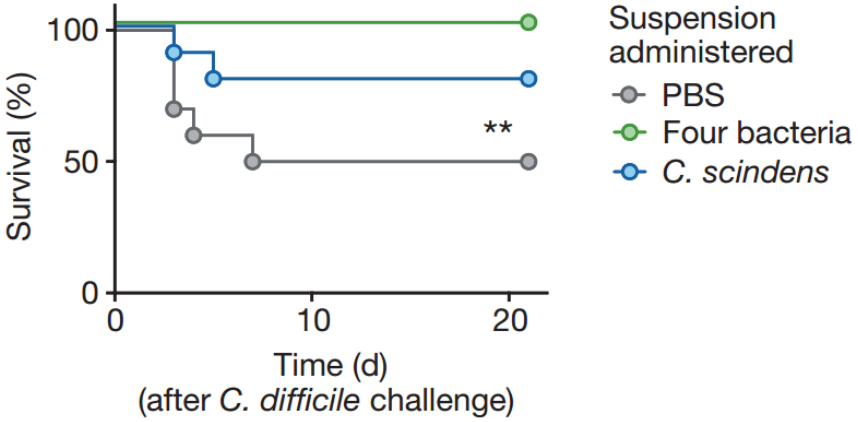
Introdução de “novas” espécies

- Probiótico
  - Proteção contra *C. dificile*
  - “Proteção” contra alergia

Clostridium difficile

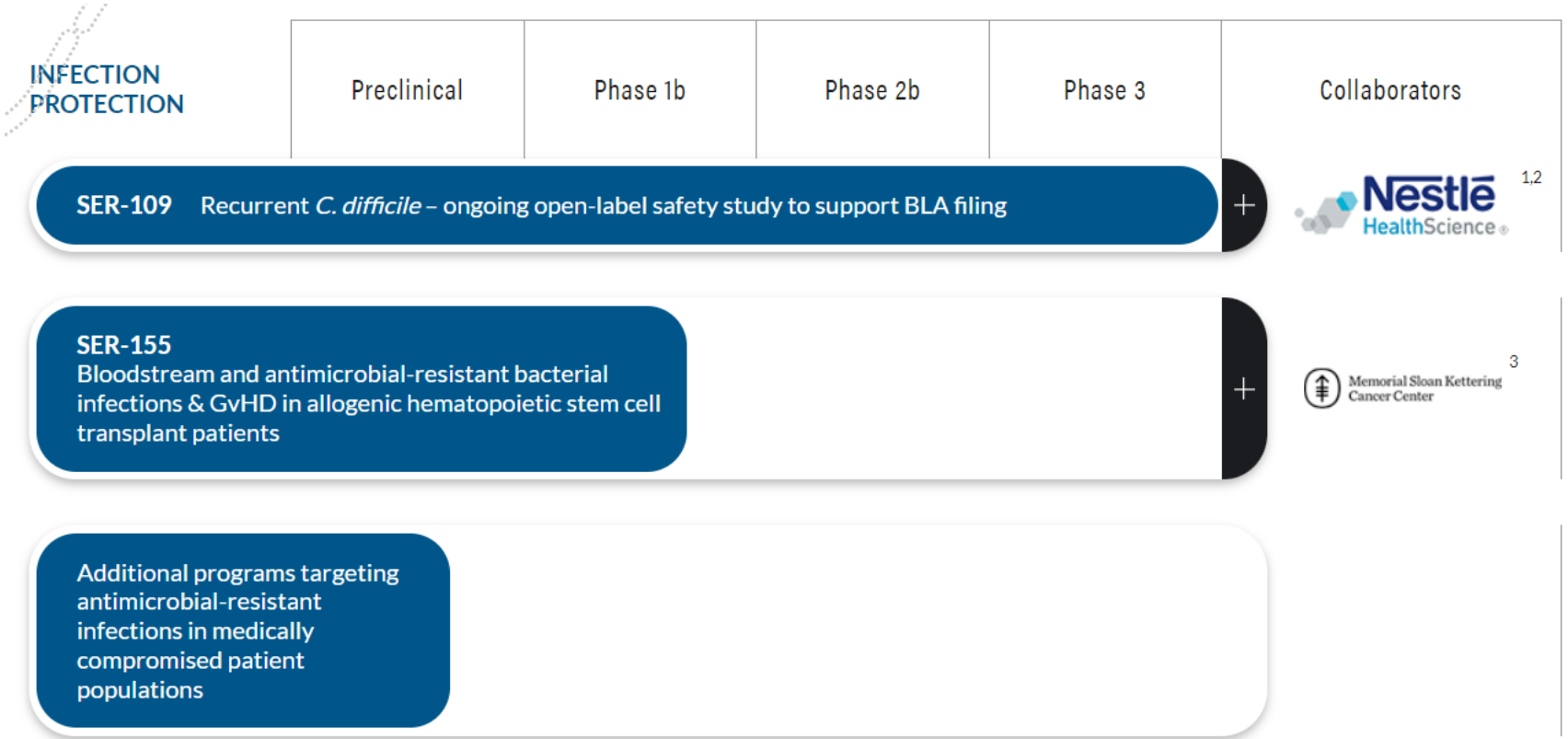
- Modelo em camundongos
- Infecção por *C. Difficile*
- Consorcio bacteriano proteje contra infecção
- Espécie protetora usa metabólito derivado de ácido biliar do hospedeiro





Buffie et al. Nature 2014.

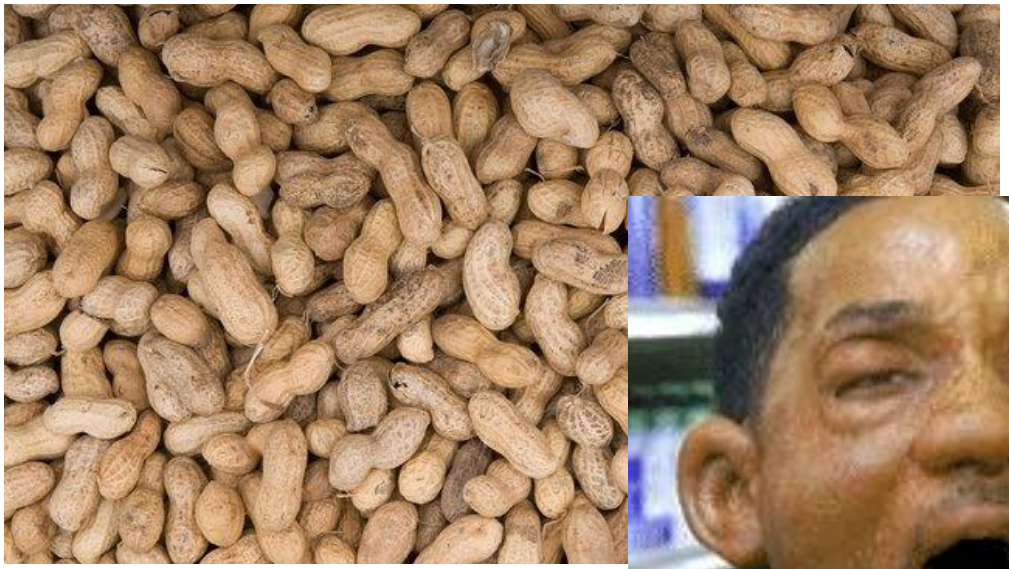
Human clinical trials



https://www.serestherapeutics.com/

Alergia Alimentar

- Alergia ao amendoim



Alergia Alimentar

PNAS

Commensal bacteria protect against food allergen sensitization

Andrew T. Stefka[a,1], Taylor Feehley[a,1], Prabhanshu Tripathi[a], Ju Qiu[b], Kathy McCoy[c], Sarkis K. Mazmanian[d], Melissa Y. Tjota[e], Goo-Young Seo[a], Severine Cao[a], Betty R. Theriault[f], Dionysios A. Antonopoulos[e,g], Liang Zhou[b], Eugene B. Chang[e], Yang-Xin Fu[a], and Cathryn R. Nagler[a,e,2]

Departments of [a]Pathology, [e]Medicine, and [f]Surgery, The University of Chicago, Chicago, IL 60637; [b]Departments of Pathology and Microbiology-Immunology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611; [c]Department of Clinical Research, University of Bern, 3010 Bern, Switzerland; [d]Department of Biology, California Institute of Technology, Pasadena, CA 91125; and [g]Argonne National Laboratory, Argonne, IL 60439

Stefka et a. PNAS 2014. 111(36):13145-13150.

The NEW ENGLAND JOURNAL of MEDICINE

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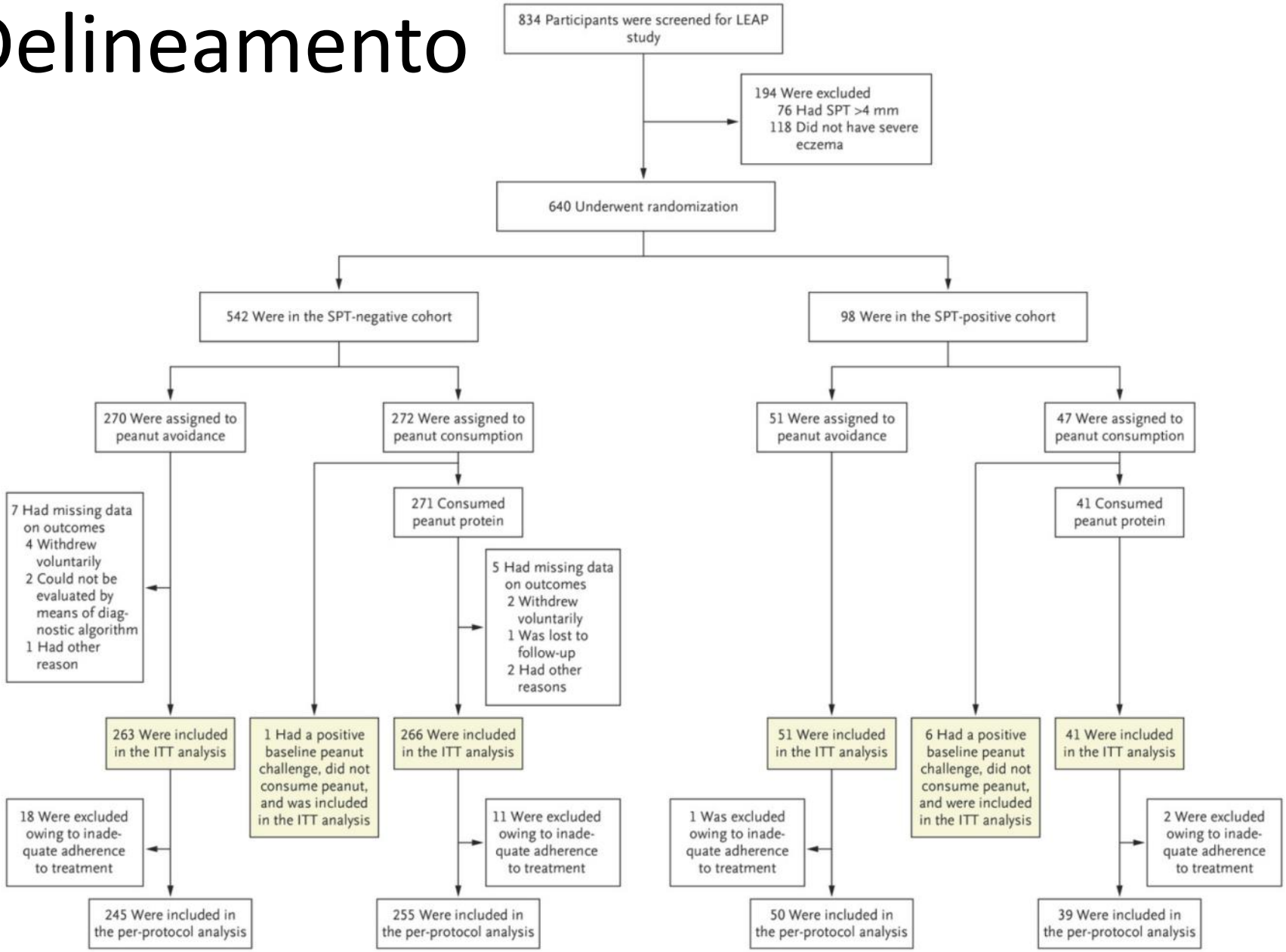
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

Du Toit et al. NEJM. 2015.372(9):803-813.

Delineamento

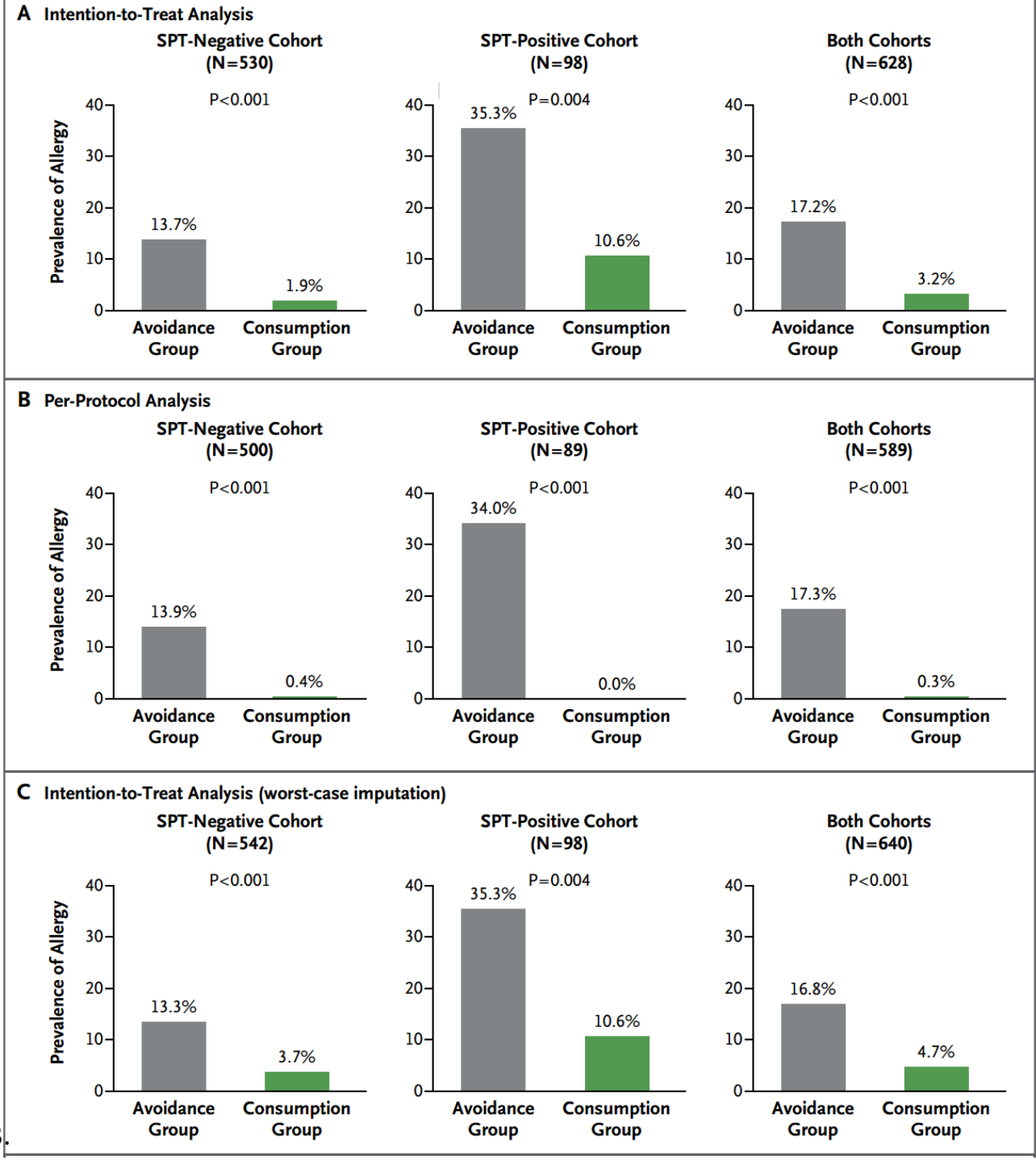


Du Toit et al. NEJM. 2015.372(9):803-813.

Delineamento: muito simples!

- 640 pacientes
  - 4 - 11 meses
  - Eczema severa, alergia a ovo (albumina), ou os dois.
- Dois grupos de pacientes:
  - Alergicos a amendoin
  - Não alergicos
- Dois tratamentos
  - Consumir amendoin
  - Nao consumir amendoin
- Medidas objetivas de alergia aos 60 meses de idade

Resultados



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E o Microbioma?

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PNAS

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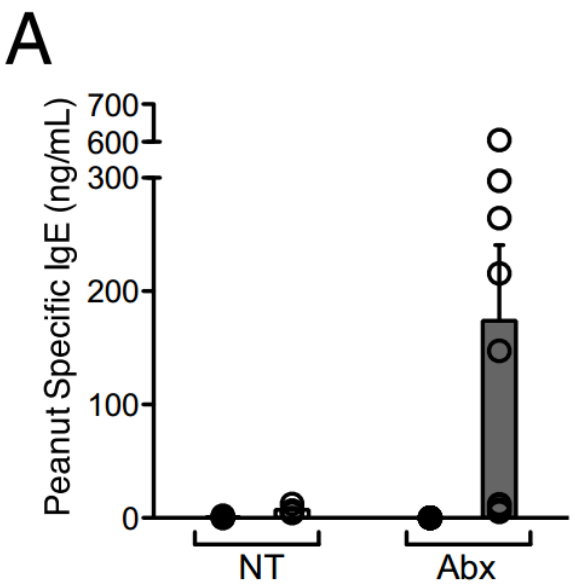
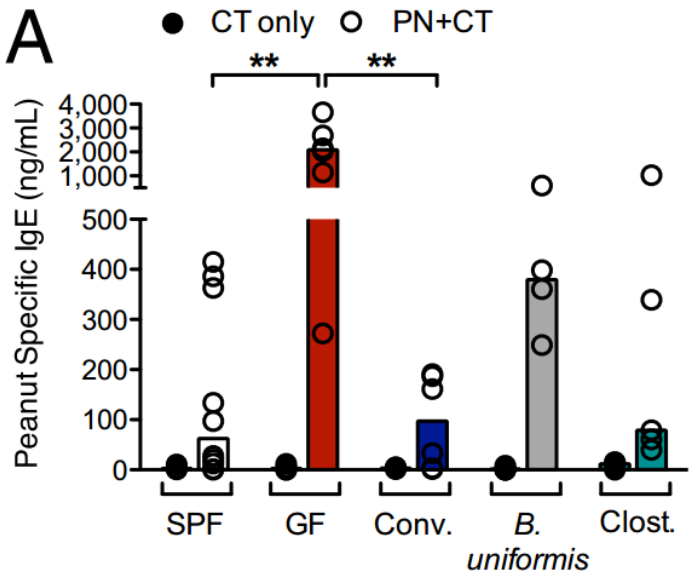
Stefka et a. PNAS 2014. 111(36):13145-13150.

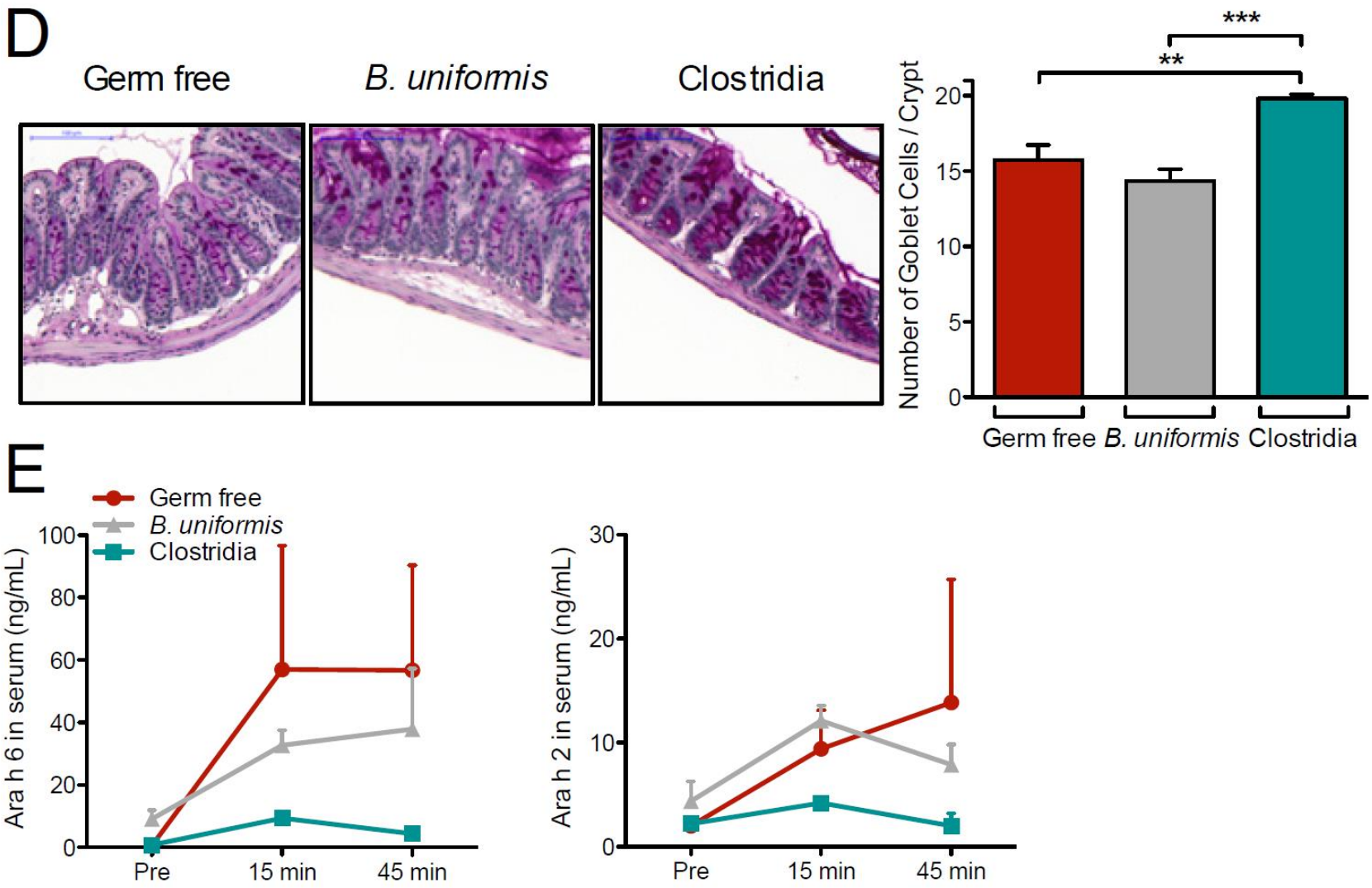
Modelo murino

- Testes em camundongos
- Tratamento com proteina do amendoin
- Tratamento com antibiótico
- Introdução de microrganismos





Stefka et a. PNAS 2014. 111(36):13145-13150.



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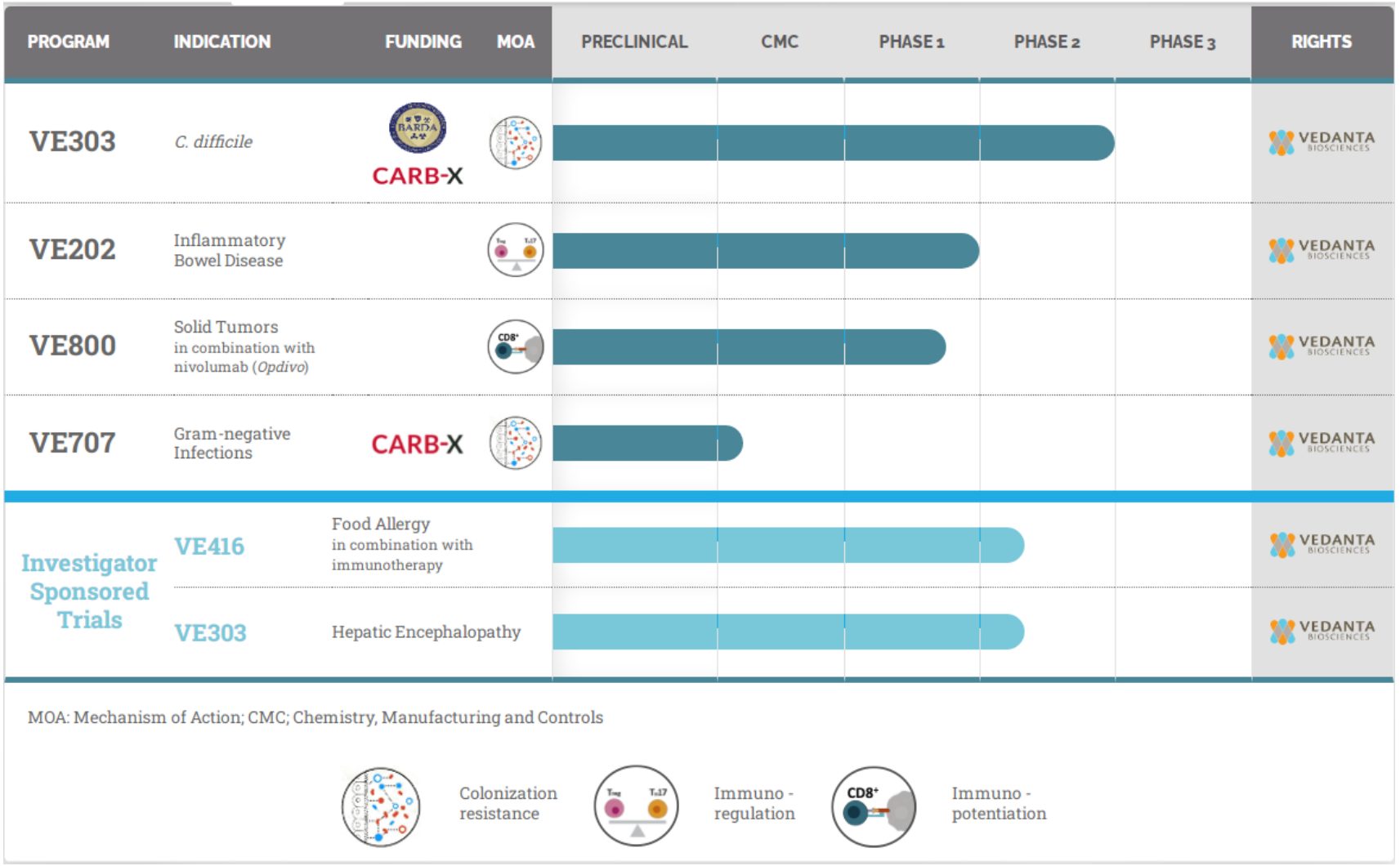


Bioterapeuticos vivos, uma nova geração de “probióticos”

	Akkermansia	Metabolic Daily	Glucose Control
What it's for	**Enhances** gut health	**Optimizes** sugar and carb metabolism	**Helps manage** blood sugar levels in type 2 diabetes
Key benefits	Supports a healthy weight Strengthens gut lining Boosts GLP-1 production Keystone strain	Reduces sugar cravings & energy slumps Increases butyrate & GLP-1 Supports a healthy weight	Supports gut health Helps reduces A1C Helps lower glucose spikes Clinical-grade formula
Strains in the formula	*Akkermansia muciniphila*	*Akkermansia muciniphila* *Clostridium butyricum* *Anaerobutyricum hallii* *Clostridium beijerinckii* *Bifidobacterium infantis*	*Akkermansia muciniphila* *Clostridium butyricum* *Anaerobutyricum hallii* *Clostridium beijerinckii* *Bifidobacterium infantis*
Amount of Akkermansia	Medium amount	Lowest amount	Highest amount
Usage instructions	1 capsule per day with food	1 capsule per day with food	1 capsule in the morning, 1 at night, with food

BMJ Journals

BMJ Open Diabetes Research & Care

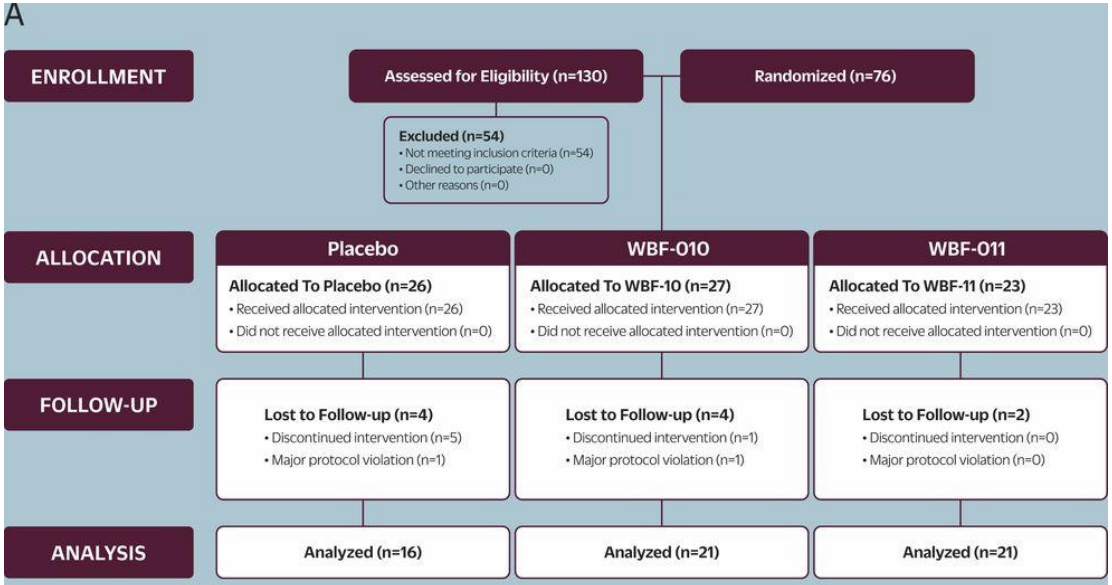
Improvements to postprandial glucose control in subjects with type 2 diabetes: a multicenter, double blind, randomized placebo-controlled trial of a novel probiotic formulation

Fanny Perraudeau , Paul McMurdie , James Bullard , Andrew Cheng , Colleen Cutcliffe , Achal Deo , John Eid , Jessica Gines , Mohan Iyer , Nicholas Justice , Wesley T Loo , Madeleine Nemchek , Marcus Schicklberger , Michael Souza , Brendon Stoneburner , Surabhi Tyagi , Orville Kolterman

Correspondence to Dr Orville Kolterman; orville.kolterman@pendulum.co

Perraudeau et al. *BMJ Open Diabetes Research and Care. 2020.* **8:**e001319.
doi: 10.1136/bmjdrc-2020-001319

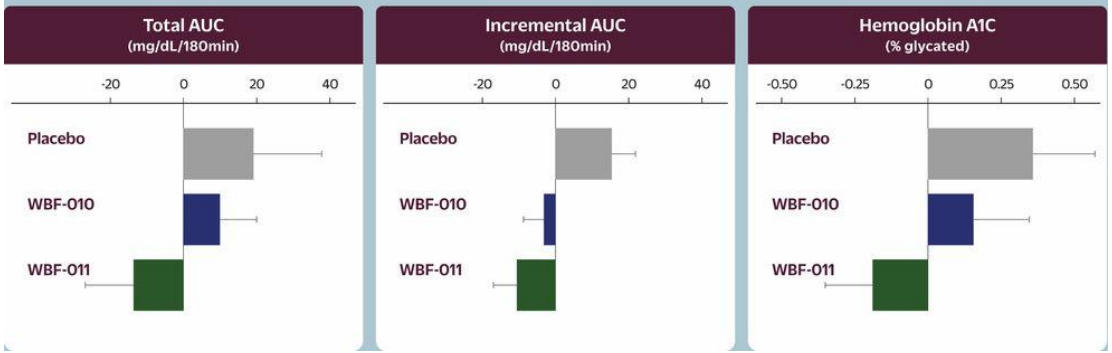
A



B

Ingredients	Placebo	WBF-010	WBF-011
Colloidal silicon dioxide	●	●	●
Inulin		●	●
Clostridium beijerinckii (CBEI)		●	●
Clostridium butyricum (CBUT)		●	●
Bifidobacterium infantis (BINF)		●	●
Akkermansia muciniphila (AMUC)			●
Anaerobutyricum hallii (EHAL)			●

C



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Tempus fugit!