



The human gut microbiome and its influence on drug efficacy

Dennis S. Nielsen

dn@food.ku.dk

COLOTAN 20th of January 2022
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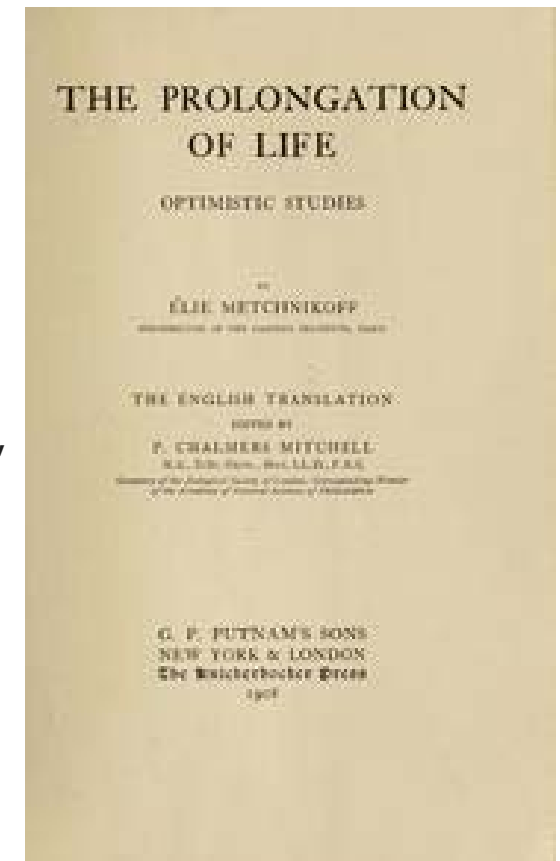
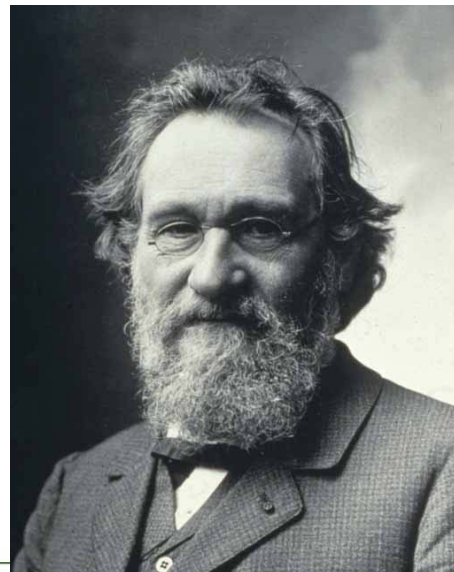
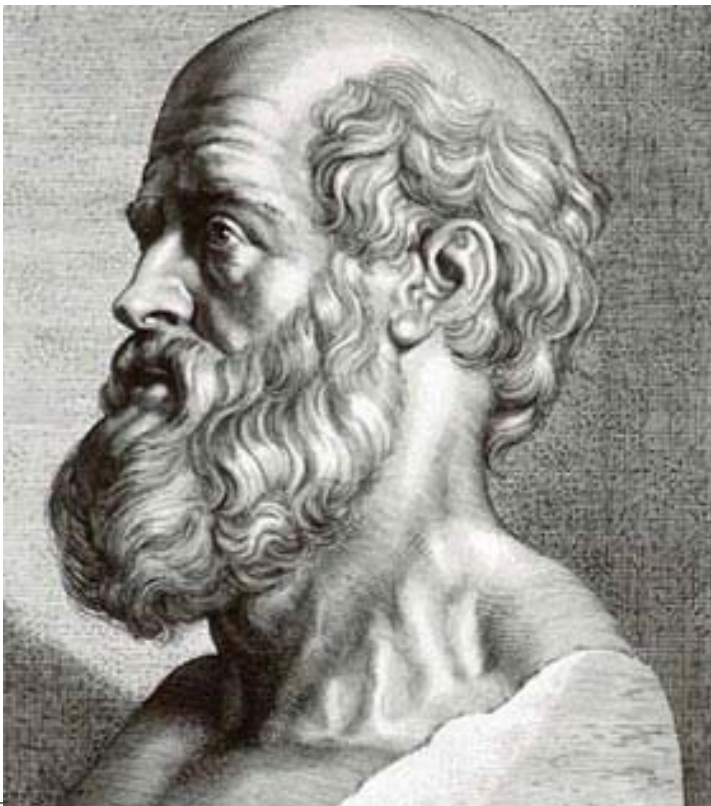


Gut microbiota, health and disease

- “All disease begins in the gut” (Hippocrates, 460-370 BC)
- “A lot of diseases begins in the gut” (Dennis S. Nielsen, 1977-?)
- In his 1910 book “The prolongation of life.

Metchnikoff suggested
to the influence of “bad”

of lactic acid bacteria
effect
on” of
of
bacteria



What do we know today

- We know that the gut is densely populated!

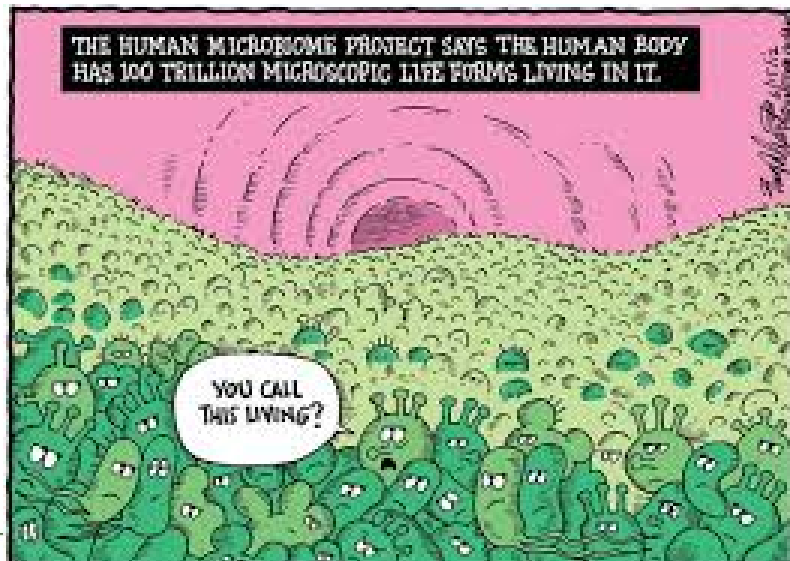
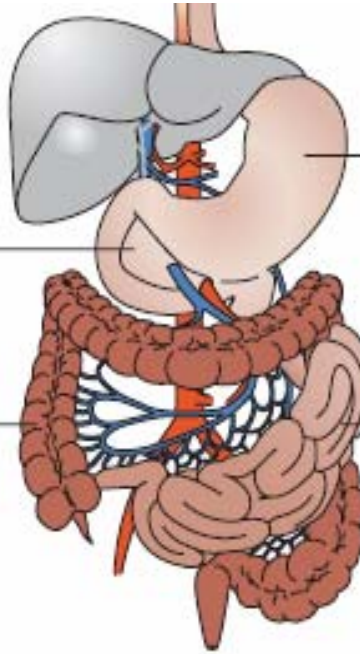
1.000.000.000.000
microbes pr. gram of
faeces!!

Duodenum
 $10^1 - 10^3$ cfu/ml

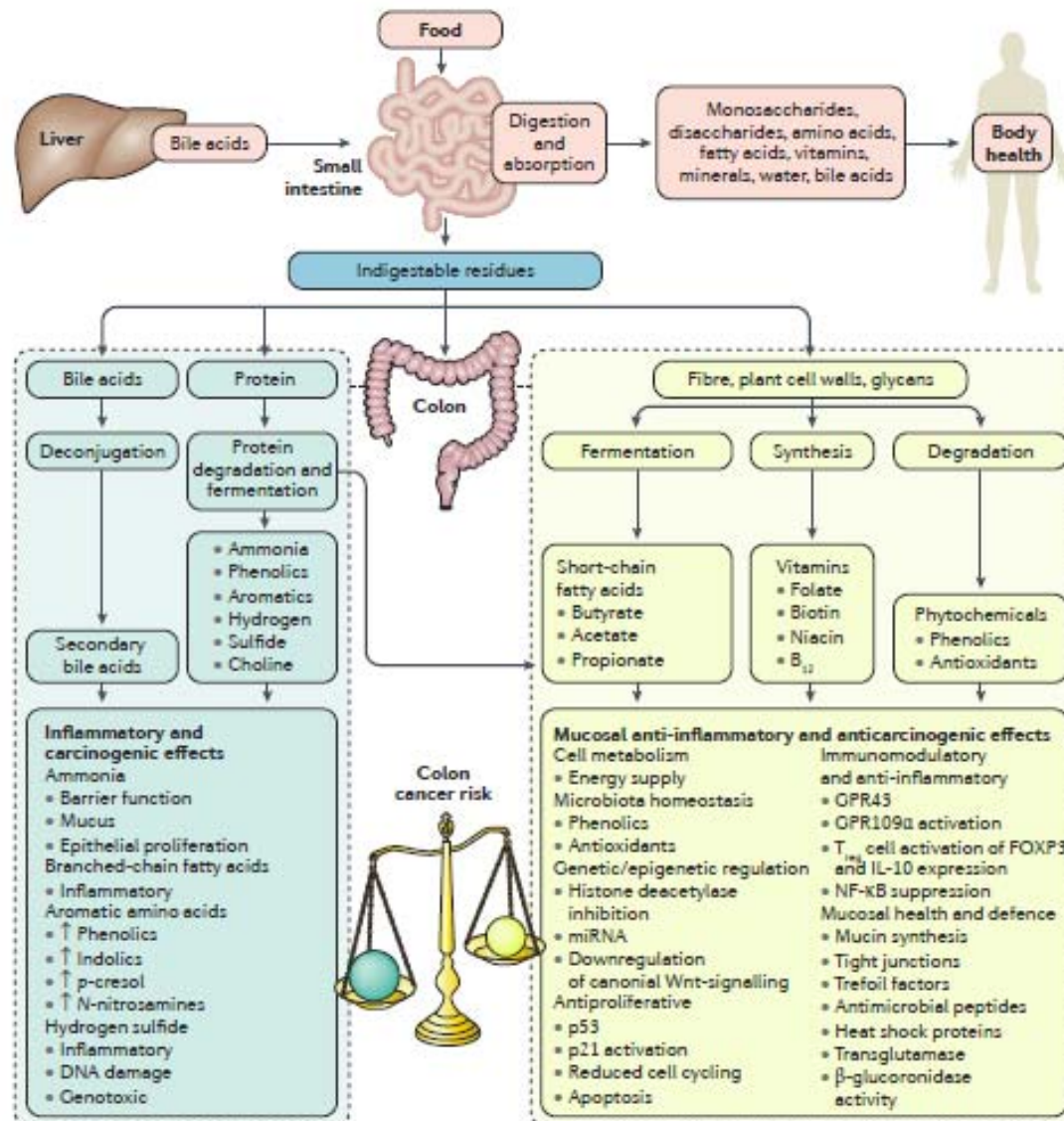
Colon
 $10^{11} - 10^{12}$ cfu/ml

Stomach
 $10^1 - 10^3$ cfu/ml

Jejunum/ileum
 $10^4 - 10^7$ cfu/ml



What do we know today?



- We also know that is kind of complicated – here diet, gut microbiota and risk of colon cancer as an example

Diet, microorganisms and their metabolites, and colon cancer

Stephen J. D. O'Keefe

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

VOLUME 13 | DECEMBER 2016 | 691



What do we know today

- We also know that a (very) long list of diseases are connected (correlation, sometimes also causal link) to gut microbiome (GM) dysbiosis/imbalance
 - Obesity, metabolic syndrome, type 2 diabetes
 - Asthma, eczema, type 1 diabetes (autoimmune diseases)
 - Inflammatory bowel disease
 - Colon cancer
 - Cardiovascular disease
 - Autism
 - Liver disease
 - Behaviour/depression
 - Etc. etc.

A good review:

Gut microbiota in human metabolic health and disease

Yong Fan¹ and Oluf Pedersen^{1,2}

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Gut microbiota and obesity

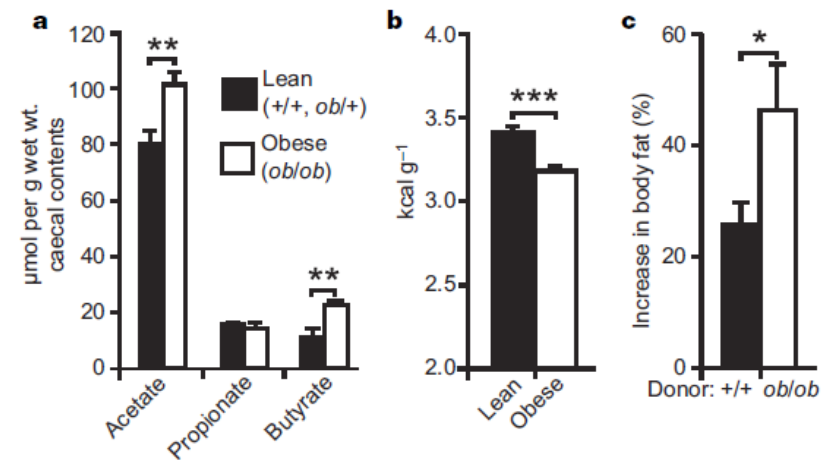
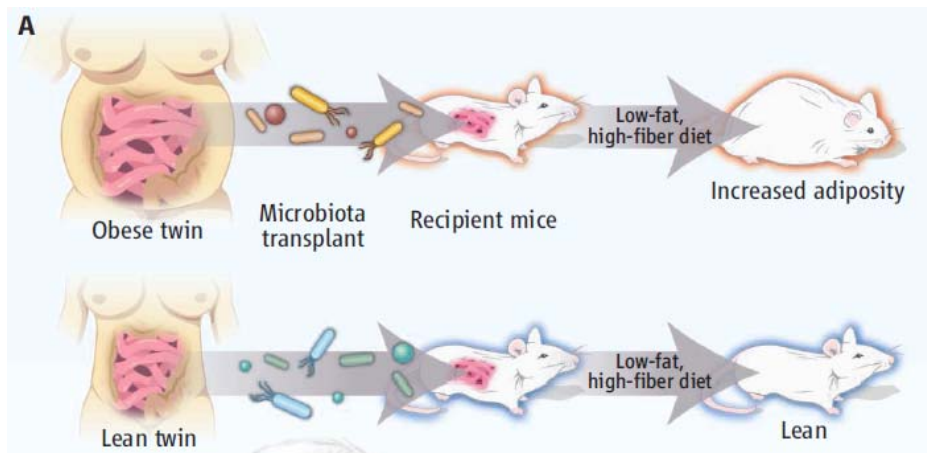
- The fuzz about GM started with some obese mice 17 years ago

Obesity alters gut microbial ecology

PNAS | August 2, 2005 | vol. 102

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

- Then it was shown that the obese GM has an increased capacity for energy harvest
- And that the obese phenotype is transferable with the GM



Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

Vanessa K. Ridaura,¹ Jeremiah J. Faith,¹ Federico E. Rey,¹ Jiye Cheng,¹ Alexis E. Duncan,^{2,3} Andrew L. Kau,² Nicholas W. Griffin,¹ Vincent Lombard,⁴ Bernard Henrissat,^{5,6} James R. Bain,^{6,7,8} Michael J. Muehlbauer,⁶ Olga Ilkayeva,⁶ Clay F. Semenkovich,⁹ Katsuhiko Funai,⁹ David K. Hayashi,¹⁰ Barbara J. Lyle,¹¹ Margaret C. Martin,¹¹ Luke K. Ursell,¹² Jose C. Clemente,¹² William Van Treuren,¹² William A. Walters,¹³ Rob Knight,^{12,14,15} Christopher B. Newgard,^{6,7,8} Andrew C. Heath,² Jeffrey I. Gordon¹⁴

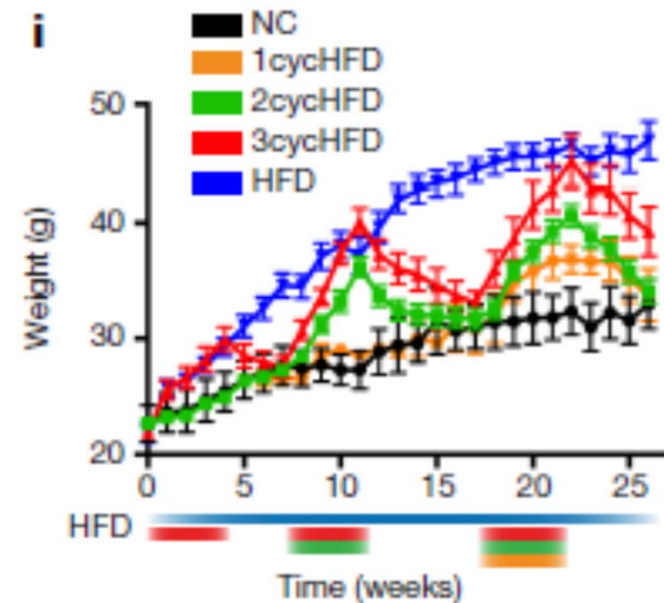
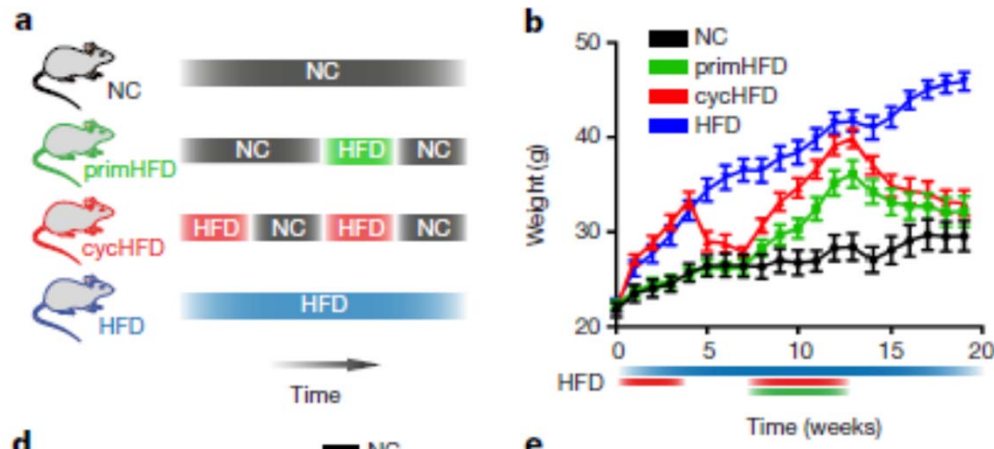
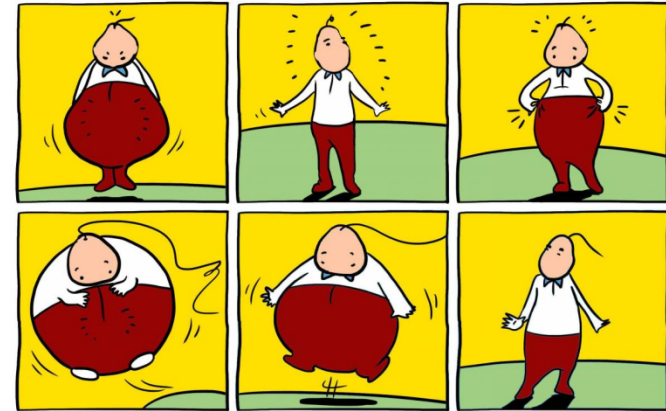
An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh¹, Ruth E. Ley¹, Michael A. Mahowald¹, Vincent Magrini², Elaine R. Mardis^{1,2} & Jeffrey I. Gordon¹



Feel like it is difficult losing the kilos you gained during the Christmas holiday?

- “Yo yo” effect well described phenomenon in relation to weight loss

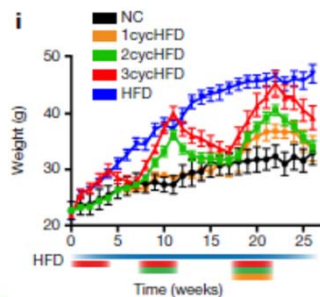
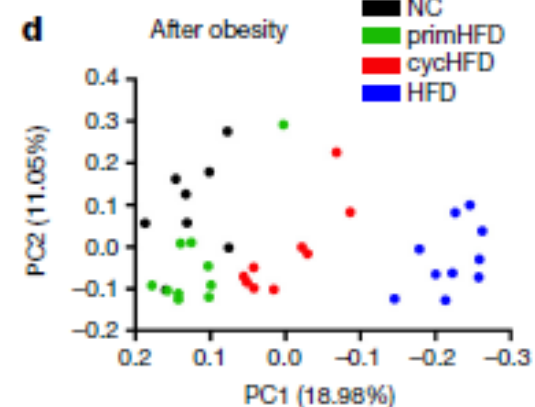
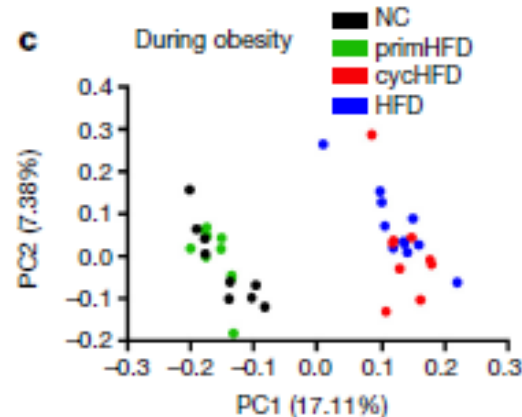
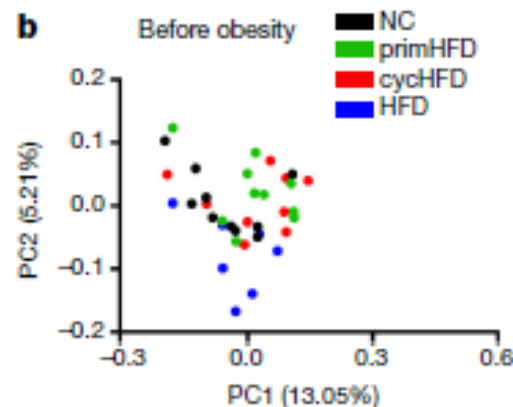
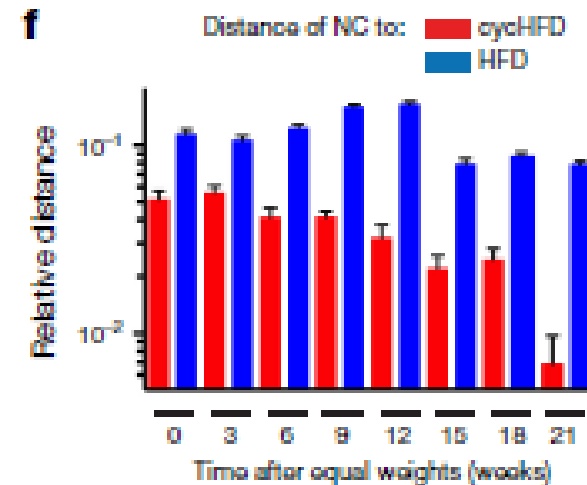


Persistent microbiome alterations modulate the rate of post-dieting weight regain

Christoph A. Thaiss^{1*}, Shlomik Itav^{1*}, Daphna Rothschild^{2,3*}, Mariska T. Meijer¹, Maayan Levy¹, Claudia Moresi¹, Lenka Dohnalová¹, Sofia Braverman¹, Shachar Rozin¹, Sergey Malitsky⁴, Mally Dori-Bachash¹, Yael Kuperman⁵, Inbal Biton⁵, Arie Gertler⁶, Alon Harmelin⁵, Hagit Shapiro¹, Zamir Halpern^{7,8}, Asaph Aharoni¹, Eran Segal^{2,3,9} & Eran Elinav^{1,9}

Feel like it is difficult losing the kilos you gained during the Christmas holiday?

- “Yo yo” effect well described phenomenon in relation to weight loss
- It is not your fault. It’s the GM!



Persistent microbiome alterations modulate the rate of post-dieting weight regain

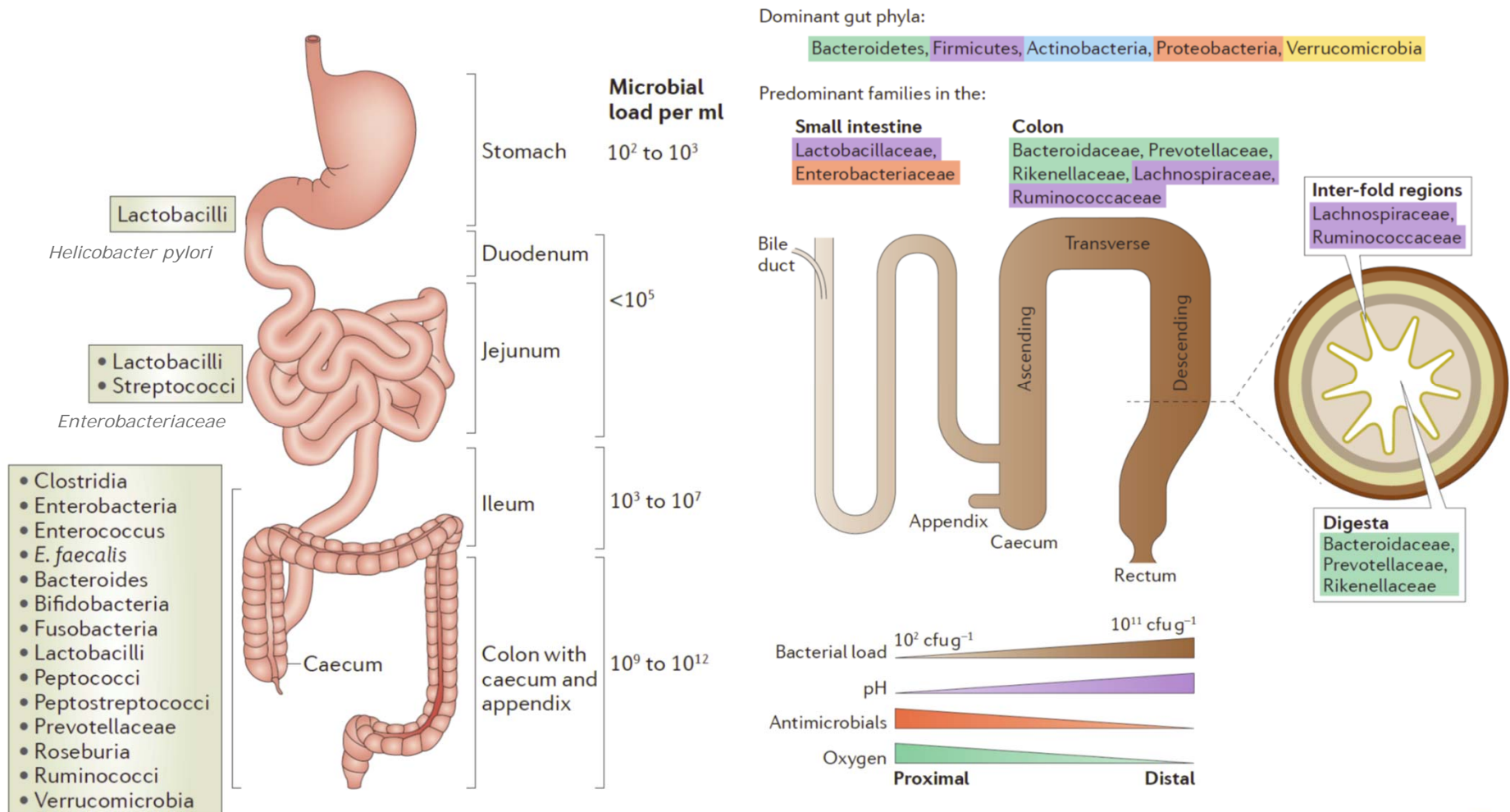
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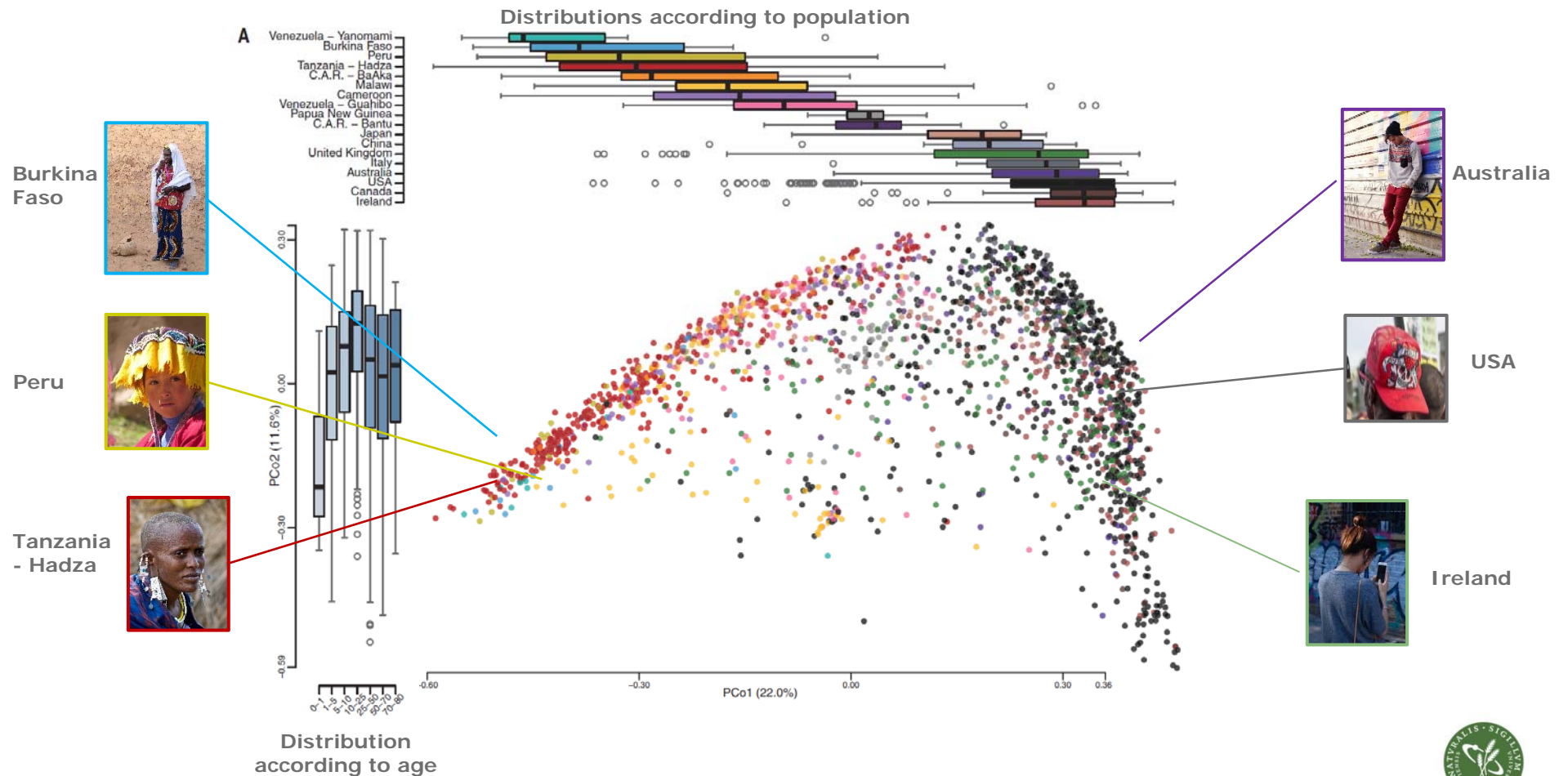
of January 2022

Who, where and how many?

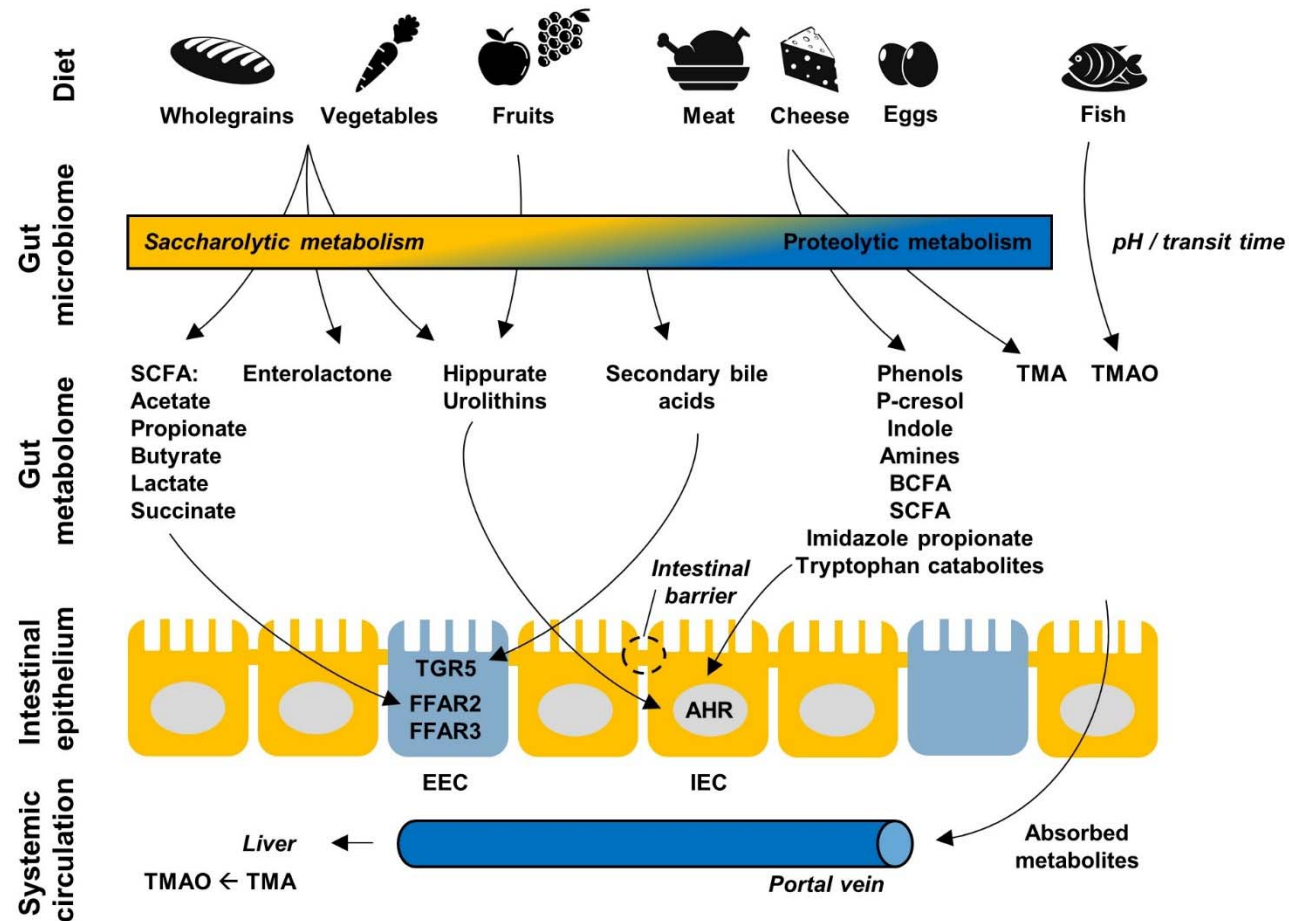


The adult gut microbiome composition across the globe

Bray-Curtis dissimilarity
PCoA based on 2064
microbial community
compositions described at
the family taxonomic level
across populations



The gut microbiome digest our food (and your food strongly influence the GM and its function!)



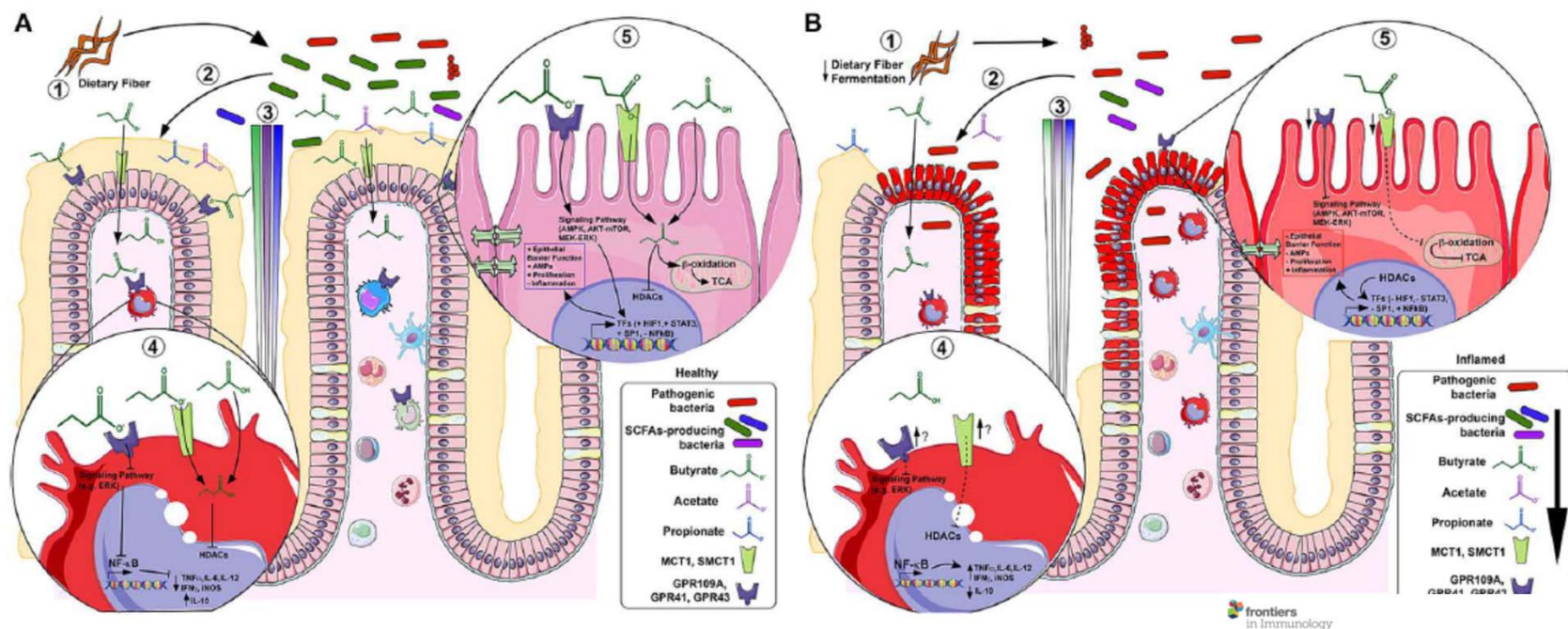
BCFA, branched-chain fatty acids;
SCFA, short-chain fatty acids;
TMA, trimethylamine; TMAO,
trimethylamine-N-oxide
EEC, enteroendocrine cells; IEC,
intestinal epithelial cells



Bacterial fermentation of dietary fibres (polysaccharides) leads to formation of short-chain fatty acids (SCFA)

Colonic fermentation of dietary fibres takes place in the colon

- Leads to formation of SCFA (acetate, propionate, butyrate)

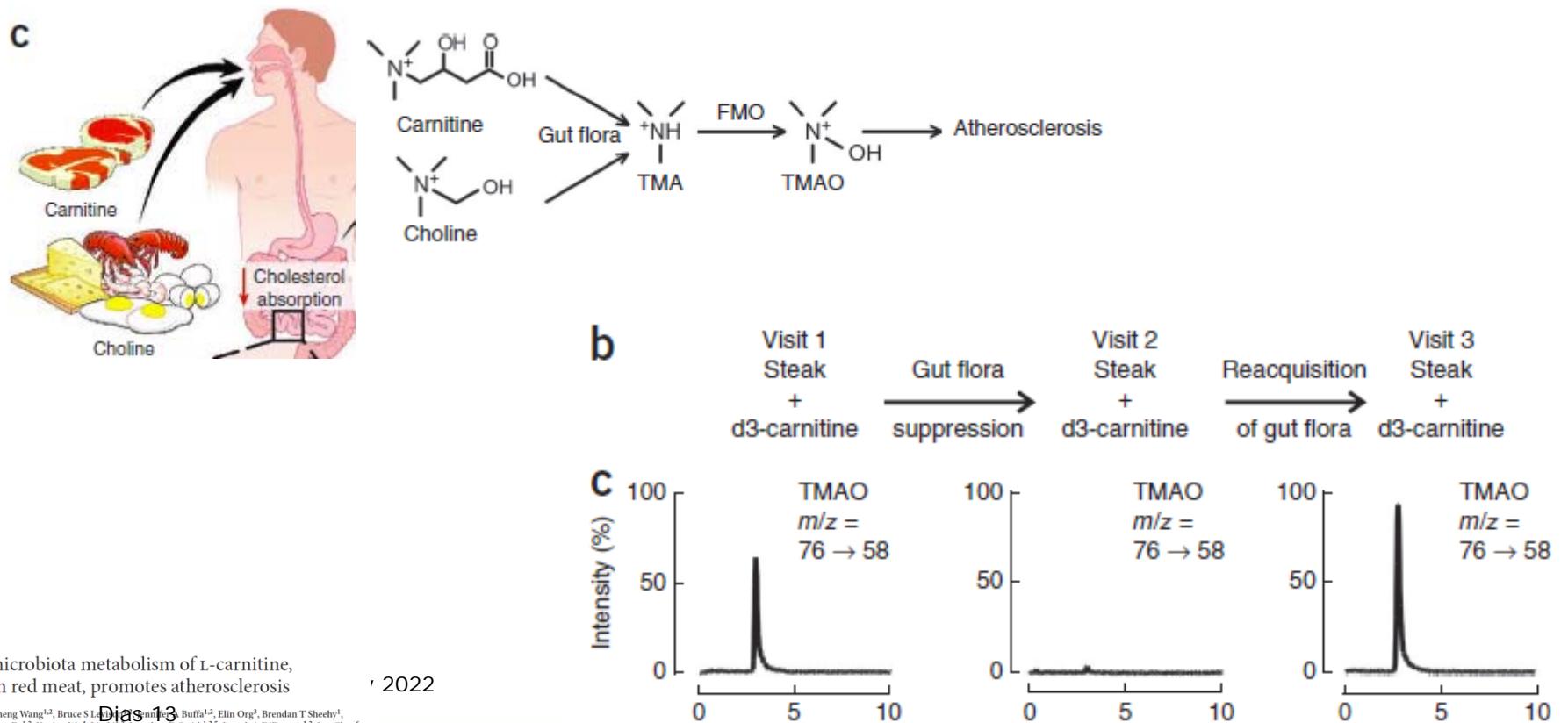


SCFAs not covered in detail in this lecture as Prof. Kristin Verbeke will do this 11.45 today

Du bliver, hvad du spiser (you become what you eat)

High levels of TMAO (trimethylamine-N-oxide) in the blood is associated with increased risk of cardiovascular disease

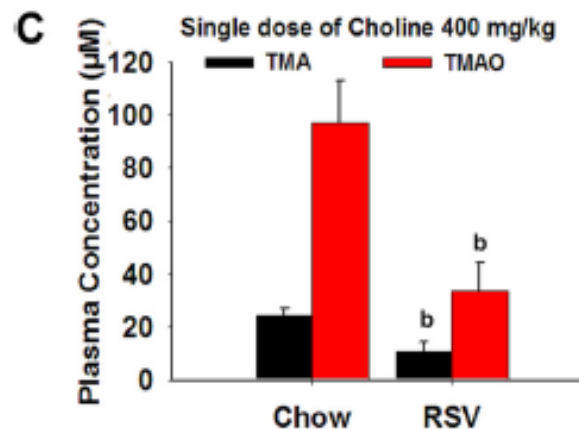
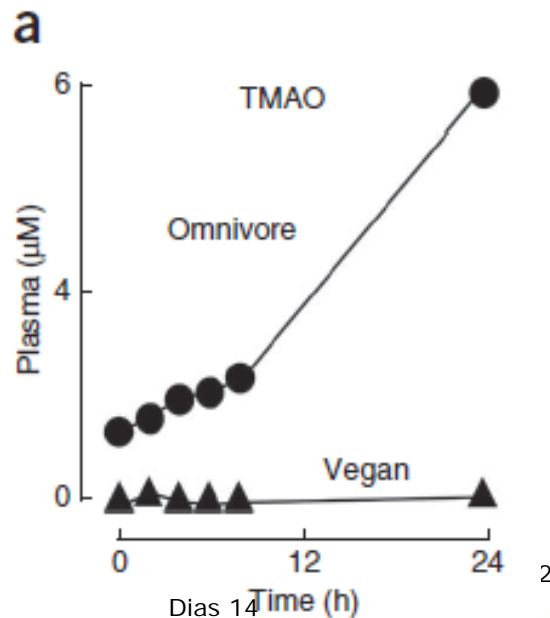
- Driven jointly by diet and GM



Du bliver, hvad du spiser (you become what you eat)

High levels of TMAO (trimethylamine-N-oxide) in the blood is associated with increased risk of cardiovascular disease

- Driven jointly by diet and GM
- Vegetarians and vegans do not form TMAO, as their GM has not been exposed to these substrates for a long time
- Some dietary components are able to limit TMAO-formation, e.g. resveratrol



Resveratrol Attenuates Trimethylamine-N-Oxide (TMAO)-Induced Atherosclerosis by Regulating TMAO Synthesis and Bile Acid Metabolism via Remodeling of the Gut Microbiota

Ming-Hang Chen, Long Yi, Yong Zhang, Xi Zhou, Li Ran, Jining Yang, Jun-dong Zhu, Qian-yong Zhang, Man-tian Mi
Research Center for Nutrition and Food Safety, Institute of Military Preventive Medicine, Third Military Medical University, Chongqing, People's Republic of China

nature
medicine

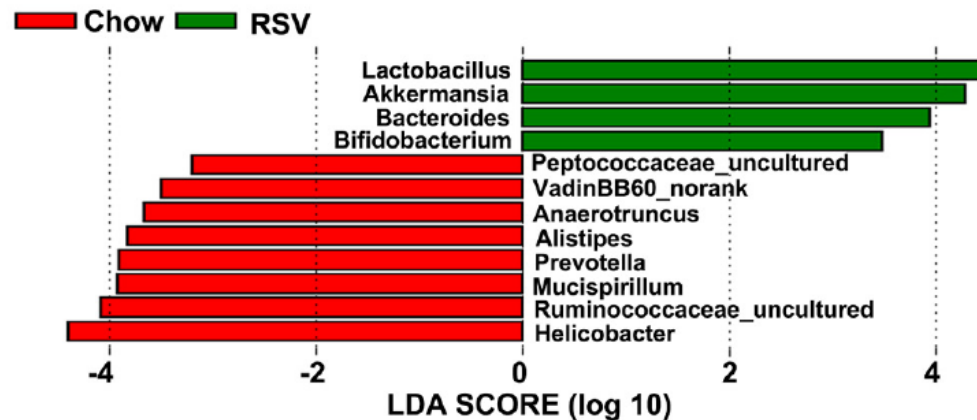
Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis

Robert A Koeth^{1,2}, Zeneng Wang^{1,2}, Bruce S Levison^{1,2}, Jennifer A Buffa^{1,2}, Elin Org³, Brendan T Sheehy¹, Earl B Britt^{1,2}, Xiaoming Fu^{1,2}, Yiping Wu⁴, Lin Li^{1,2}, Jonathan D Smith^{1,2,5}, Joseph A DiDonato^{1,2}, Jun Chen⁶, Hongzhe Li⁶, Gary D Wu⁷, James D Lewis^{6,8}, Manya Warrier⁹, J Mark Brown⁹, Ronald M Krauss¹⁰, W H Wilson Tang^{1,2,5}, Frederic D Bushman⁵, Aidons J Lusis³ & Stanley L Hazen^{1,2,5}



Du bliver, hvad du spiser (you become what you eat)

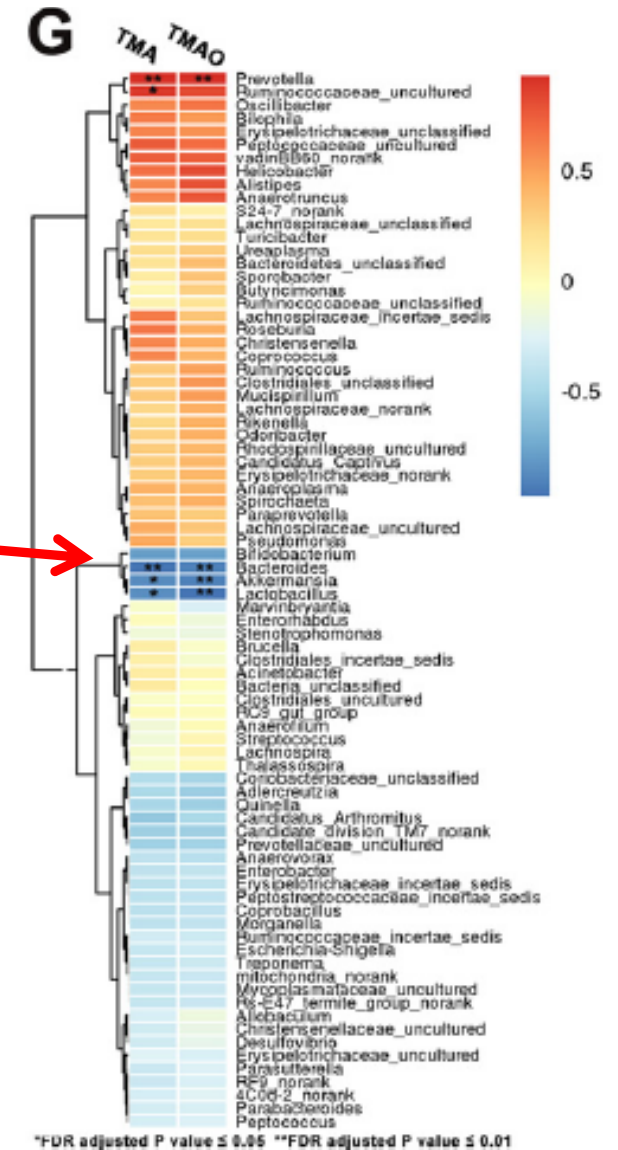
The protective effect of resveratrol against TMAO-formation is associated with GM changes



- Which in turn lower TMAO-formation

Resveratrol Attenuates Trimethylamine-N-Oxide (TMAO)-Induced Atherosclerosis by Regulating TMAO Synthesis and Bile Acid Metabolism via Remodeling of the Gut Microbiota

Ming-liang Chen, Long Yi, Yong Zhang, Xi Zhou, Li Ran, Jining Yang, Jun-dong Zhu, Qian-yong Zhang, Man-tian Mi
Research Center for Nutrition and Food Safety, Institute of Military Preventive Medicine, Third Military Medical University, Chongqing, People's Republic of China



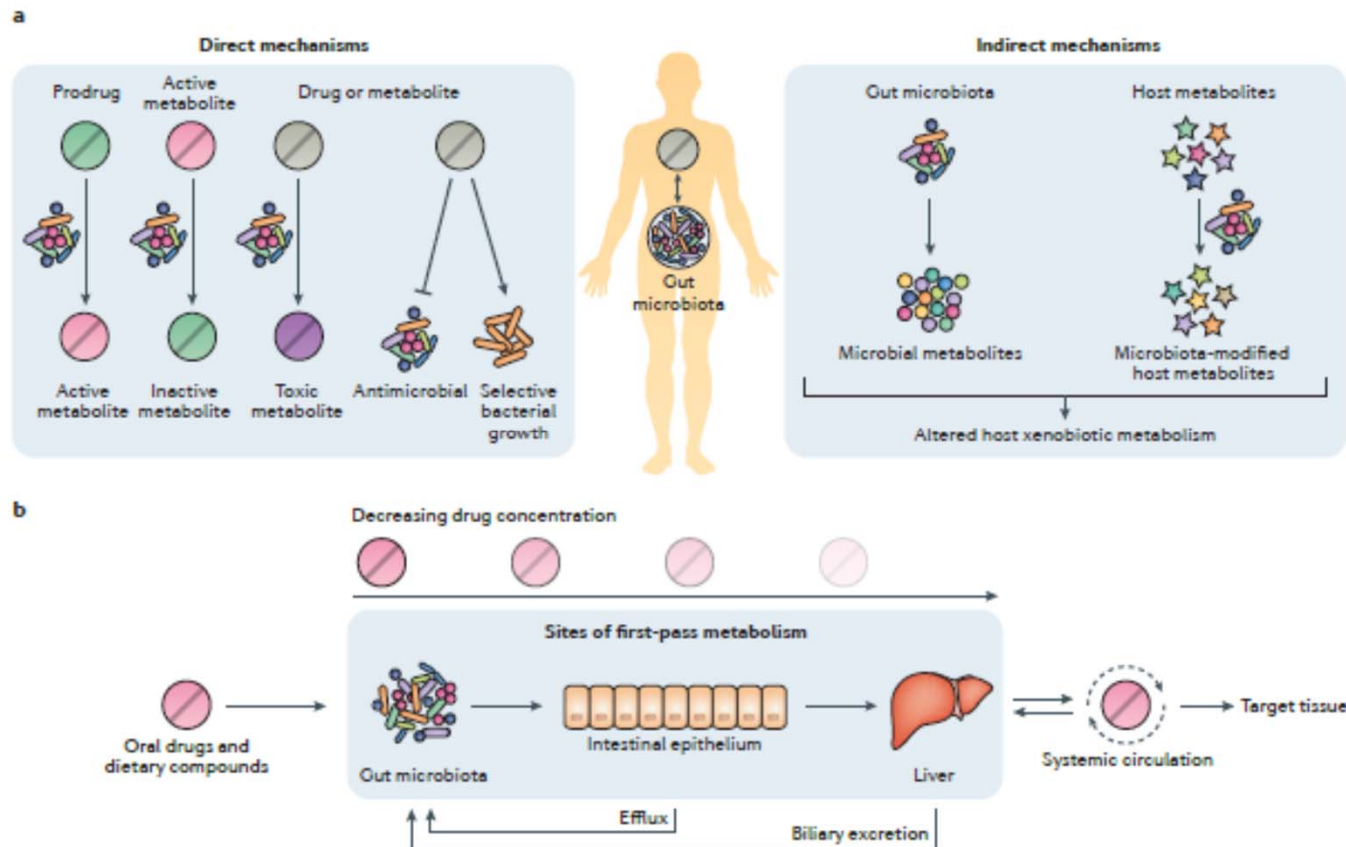
The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism

Peter Spanogiannopoulos, Elizabeth N. Bess, Rachel N. Carmody and Peter J. Turnbaugh

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Drug-gut microbiome interactions

- Similar to food-microbiota interactions, there are also many drug-microbiota interactions

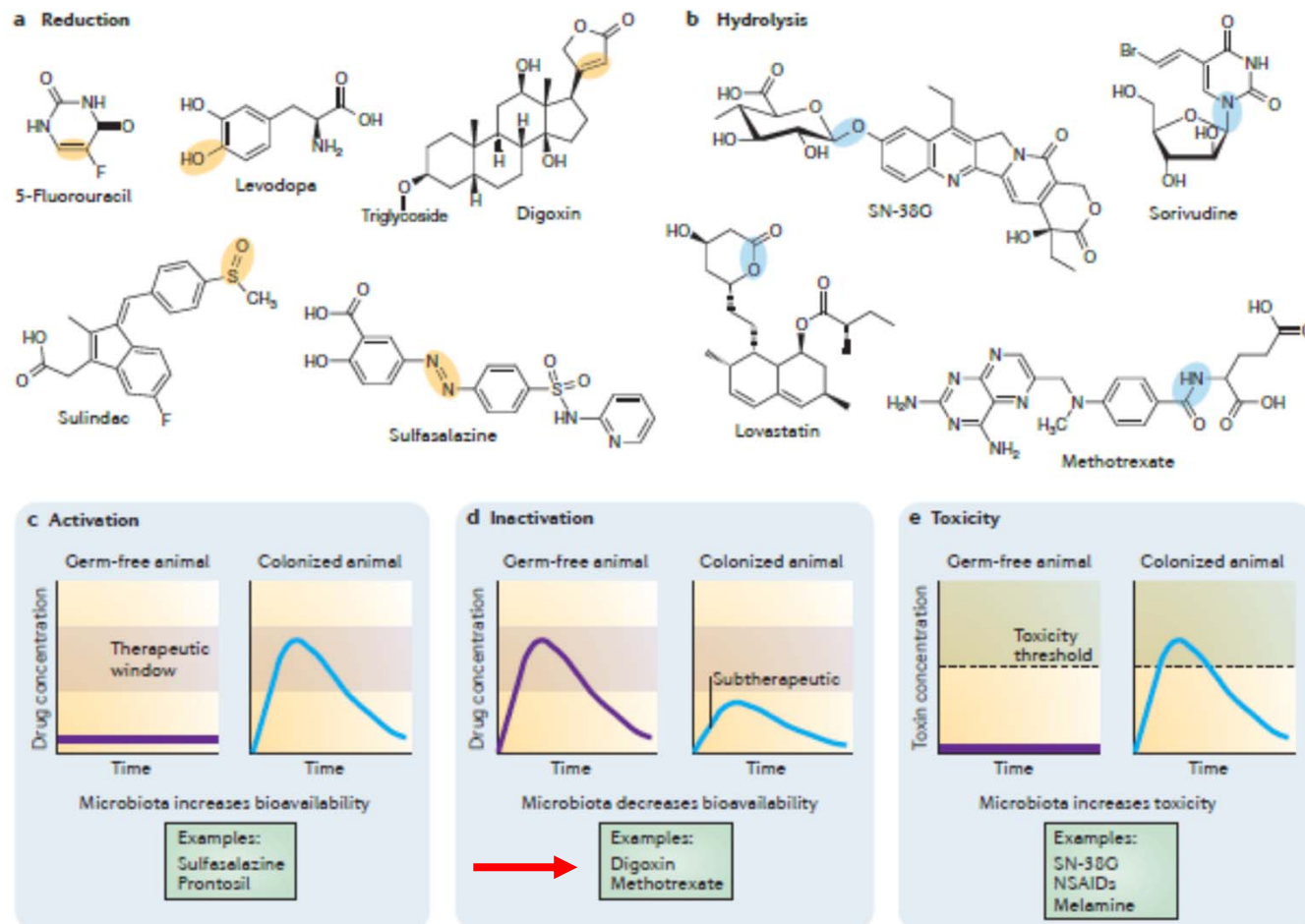


The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism

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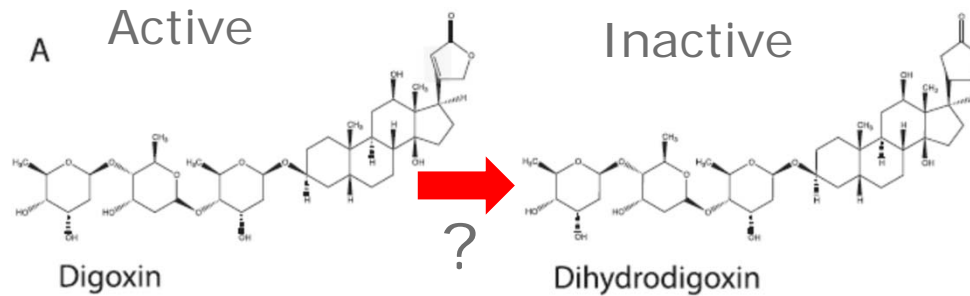
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Drug-gut microbiome interactions



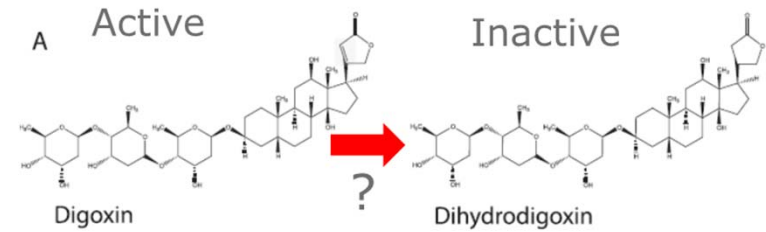
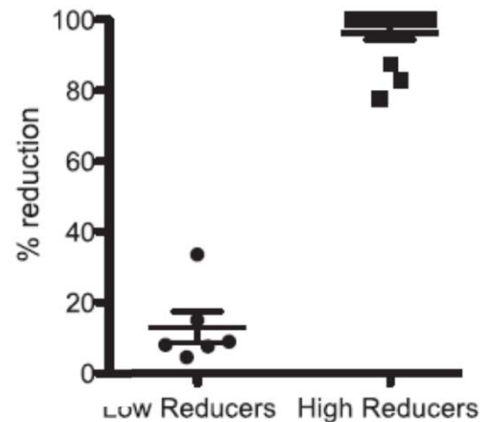
Digoxin and the GM

- Digoxin used treat atrial fibrillation and congestive heart failure.
- Mediated through binding of digoxin to a Na^+/K^+ ATPase transporter in cardiac myocytes...but:



Digoxin and the GM

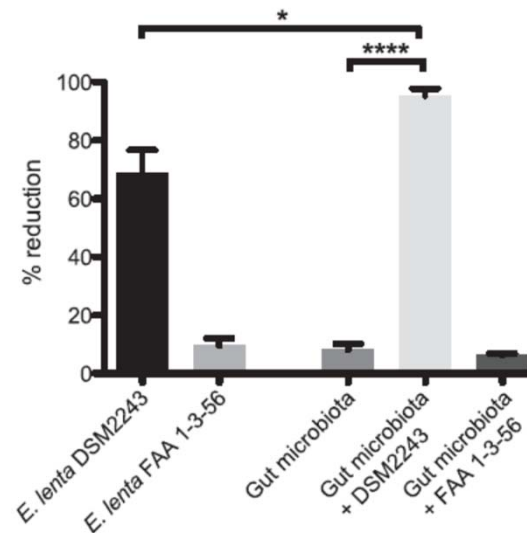
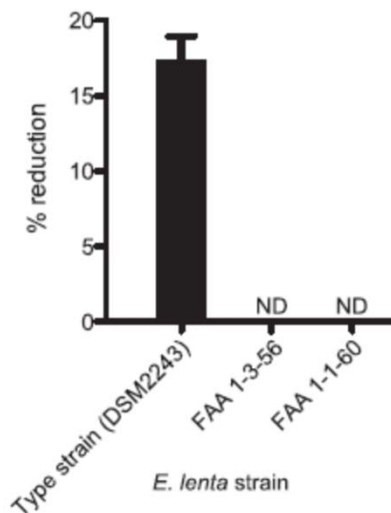
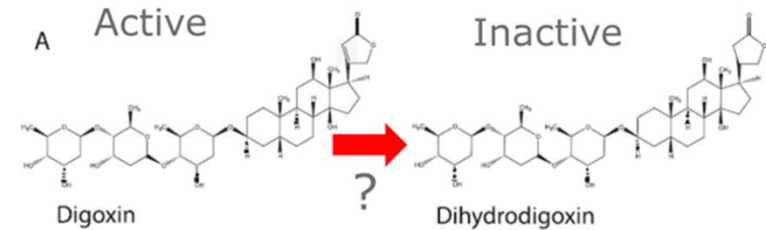
- Digoxin – a cardiac drug
- Inactivation is person-specific



- And broad-spectrum antibiotics abolish inactivation => Inactivation is due to gut microbial activity

Digoxin and the GM

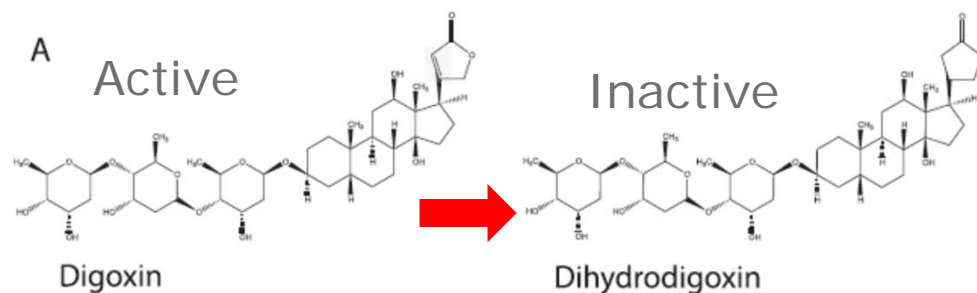
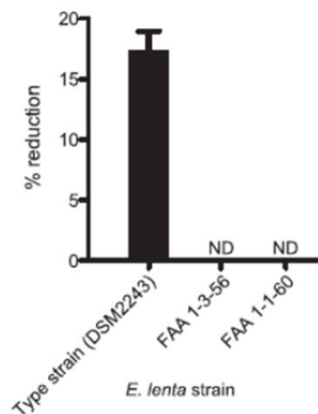
- Digoxin – a cardiac drug
- Inactivation is person-specific
- Broad-spectrum antibiotics abolish inactivation => Inactivation is due to gut microbial activity
- *Eggerthella lenta* identified as the “guilty”
 - But strain specific



Faeces from low-reducing spiked with different *E. lenta* strains

Digoxin and the GM

- Digoxin – a cardiac drug
- Inactivation is person-specific
- Broad-spectrum antibiotics abolish inactivation => Inactivation is due to gut microbial activity
- *Eggerthella lenta* identified as the “guilty”
 - But strain specific
- RNAseq identified a specific operon (cardiac glycoside reductase, *cgr*) where expression was +100-fold increased in faeces from individuals inactivating the drug *in vitro* and *in vivo*



If your GM is inhabited by *cgr*-positive *E. lenta* you need a much higher digoxin dose

Treatment of colon cancer – the influence of the GM

- GM dysbiosis might lead to disease
- And influence the efficacy of certain types of medicine
- "Immune check-point inhibitors" (ICI) are a promising class of new drugs for treatment of certain types of colon cancer
 - But ICIs only benefit a fraction of the patients

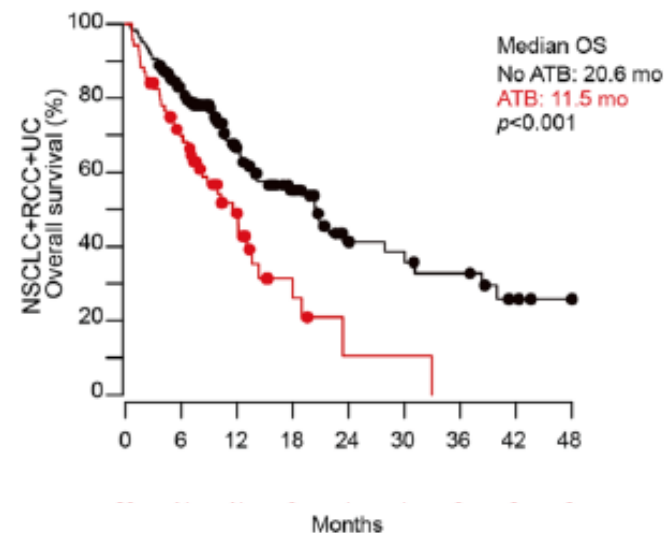
Science

REPORTS

Cite as: B. Routy *et al.*, *Science*
10.1126/science.aan3706 (2017).

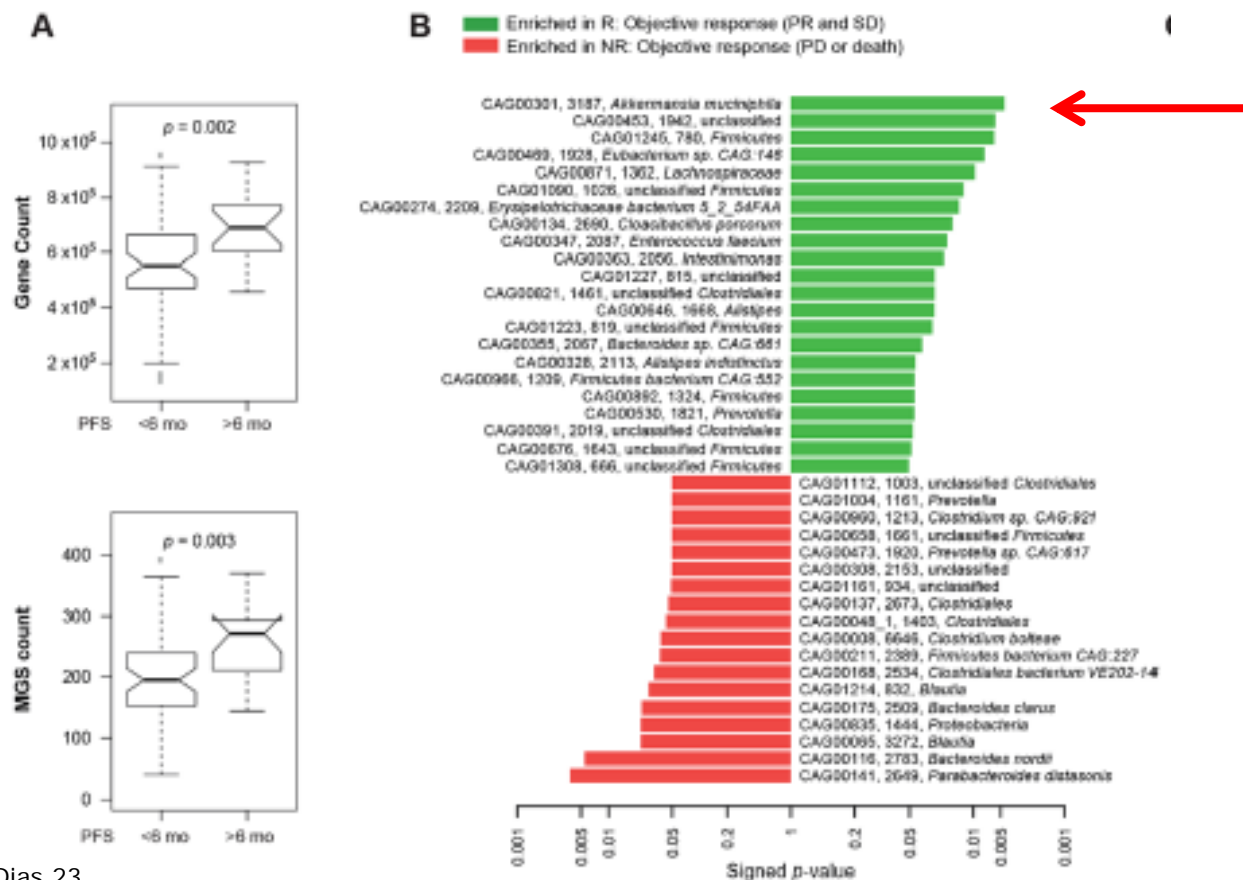
Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

Bertrand Routy,^{1,2,3} Emmanuelle Le Chatelier,⁴ Lisa Derosa,^{1,2,3} Connie P. M. Duong,^{1,2,5} Maryam Tidjani Alou,^{1,2,3} Romain Daillère,^{1,2,3} Aurélie Fluckiger,^{1,2,5} Meriem Messaoudene,^{1,2} Conrad Rauber,^{1,2,3} Maria P. Roberti,^{1,2,5} Marine Fidelle,^{1,2,5} Caroline Flament,^{1,2,5} Vichnou Poirier-Colame,^{1,2,5} Paule Opolon,⁶ Christophe Klein,⁷ Kristina Iribarren,^{8,9,10,11,12} Laura Mondragón,^{8,9,10,11,12} Nicolas Jacquilot,^{1,2,3} Bo Qu,^{1,2,3} Gladys Ferrere,^{1,2,3} Céline Clémenson,^{1,13} Laura Mezquita,^{1,14} Jordi Remon Masip,^{1,14} Charles Naltet,¹⁵ Solenn Brosseau,¹² Coureche Kaderbhai,¹⁶ Corentin Richard,¹⁶ Hira Rizvi,¹⁷ Florence Levenez,⁴ Nathalie Galleron,⁴ Benoit Quinquin,⁴ Nicolas Pons,⁴ Bernhard Ryffel,¹⁸ Véronique Minard-Colin,^{1,19} Patrick Gonin,^{1,20} Jean-Charles Soria,^{1,14} Eric Deutsch,^{1,15} Yohann Loriot,^{1,5,14} François Ghiringhelli,¹⁶ Gérard Zalcman,¹⁵ François Goldwasser,^{9,21,22} Bernard Escudier,^{1,14,23} Matthew D. Hellmann,^{24,25} Alexander Eggermont,^{1,2,14} Daniel Risché,²⁶ Laurence Albiges,^{1,5,14} Guido Kroemer,^{8,9,10,11,12,27,28*} Laurence Zitvogel^{1,2,3,5*}



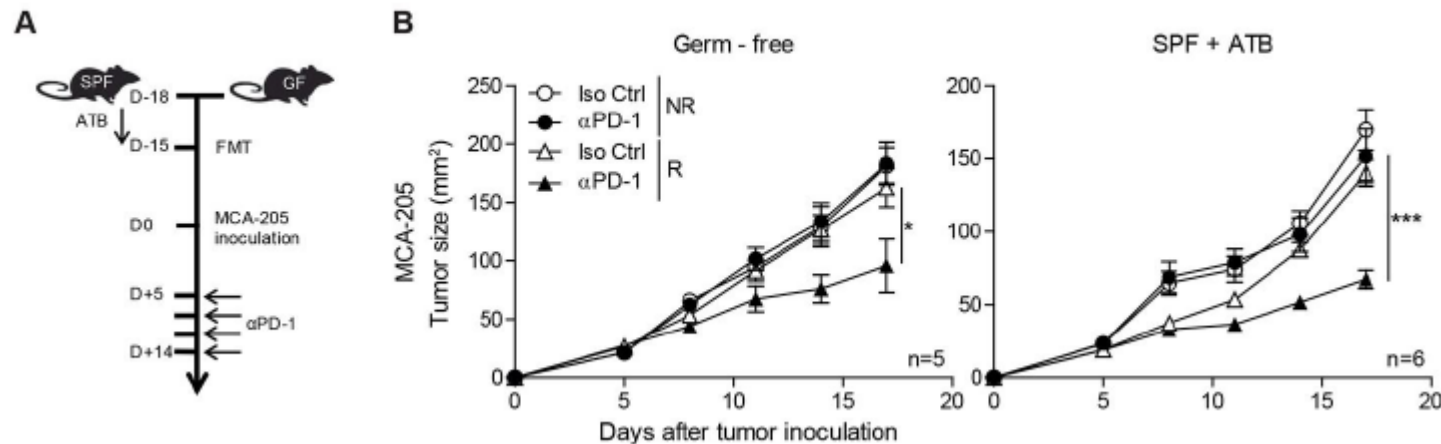
Treatment of colon cancer – the influence of the GM

- If certain species (*A. muciniphila* among others) there is a much higher chance, that the drug (ICI) works



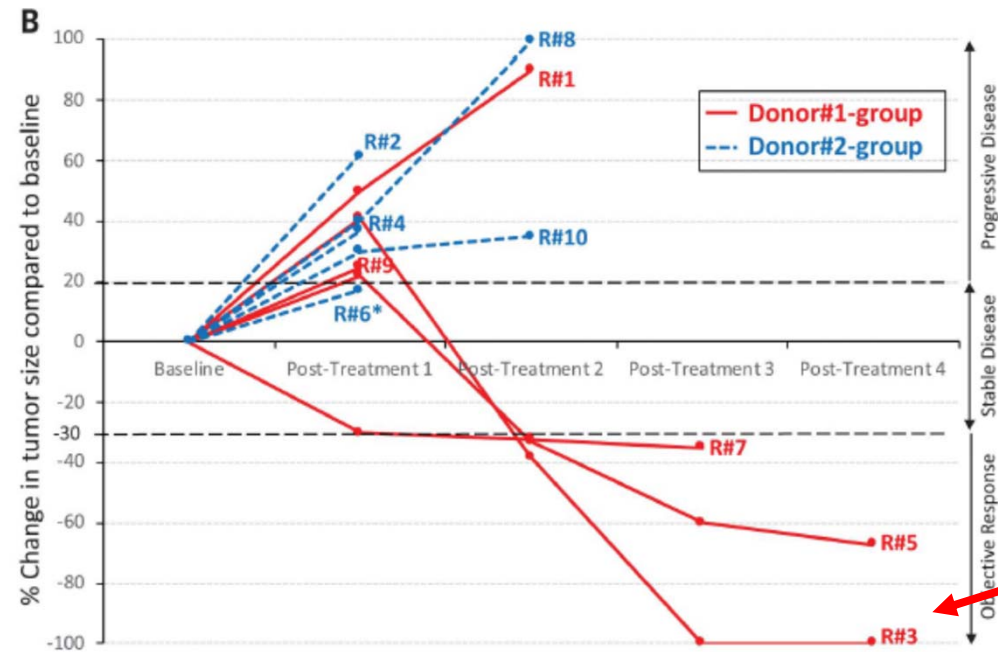
Treatment of colon cancer – the influence of the GM

- If certain species (*A. muciniphila* among others) there is a much higher chance, that the drug (ICI) works
- In mice the “responder” (drug works) and the “non-responder” (drug does not work) phenotypes are transferable with GM



Latest news from the ICI-frontier

- Fecal microbiota transplant saves the day again (for some)



A pretty lucky guy!!

CLINICAL TRIALS

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

Diwakar Davar^{1,2}, Amiran K. Dzutsev^{2,3}, John A. McCulloch², Richard R. Rodrigues^{2,3}, Joe-Marc Chauvin¹, Robert M. Morrison¹, Richelle N. Deblasio¹, Carmine Menna¹, Quanquan Ding¹, Ornella Pagliano¹, Bochra Zidi¹, Shuowen Zhang^{1,†}, Jonathan H. Badger², Marie Vetizou², Alicia M. Cole², Miriam R. Fernandes², Stephanie Prescott², Raquel G. F. Costa², Ascharya K. Balaji², Andrey Morgun⁴, Ivan Vujkovic-Cvijin⁵, Hong Wang⁶, Amir A. Borhani⁷, Marc B. Schwartz⁸, Howard M. Dubner⁸, Scarlett J. Ernst¹, Amy Rose¹, Yana G. Najjar¹, Yasmine Belkaid⁵, John M. Kirkwood¹, Giorgio Trinchieri^{2,§}, Hassane M. Zarour^{1,9,†§}

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

CLINICAL TRIALS

Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients

Erez N. Baruch^{1,2,*,†}, Ilan Youngster^{3,4}, Guy Ben-Betzalel¹, Rona Ortenberg¹, Adi Lahat⁵, Lior Katz⁶, Katerina Adler⁷, Daniela Dick-Necula⁸, Stephen Raskin^{4,9}, Naamah Bloch¹⁰, Daniil Rotin⁸, Liat Anafi⁸, Camila Avivi⁸, Jenny Melnichenko¹, Yael Steinberg-Silman¹, Ronac Mamtani¹¹, Hagit Harati¹, Nethanel Asher¹, Ronnie Shapira-Frommer¹, Tal Brosh-Nissimov¹², Yael Eshet^{4,8,13}, Shira Ben-Simon¹⁰, Oren Ziv¹⁰, Md Abdul Wadud Khan¹⁴, Moran Amit¹⁵, Nadim J. Ajami¹⁴, Iris Barshack^{4,8}, Jacob Schachter^{1,4}, Jennifer A. Wargo^{14,16}, Omry Koren¹⁰, Gal Markel^{1,2,17,*,†}, Ben Boursi^{4,18,19,†}

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

To sum up

- The gut microbiome plays an important role in health and disease
- Diet is the most important driver of GM development, composition and function
 - But also other environmental factors important
- There are numerous drug-microbe interactions, that we are only beginning to understand
 - But which you need to take into account, when developing new drugs, delivery systems etc. etc.

