L'Acadèmia
FUNDACIÓ ACADÈMIA DE CIÈNCIES MÈDIQUES I DE LA SALUT DE CATALUNYA I DE BALEARS

SOCIETAT CATALANA DE FARMÀCIA CLÍNICA

Jornada Microbiota, prebióticos y probióticos: de la teoría a la práctica

Fàrmacs i microbiota

JAVIER MATEU

FARMÀCIA

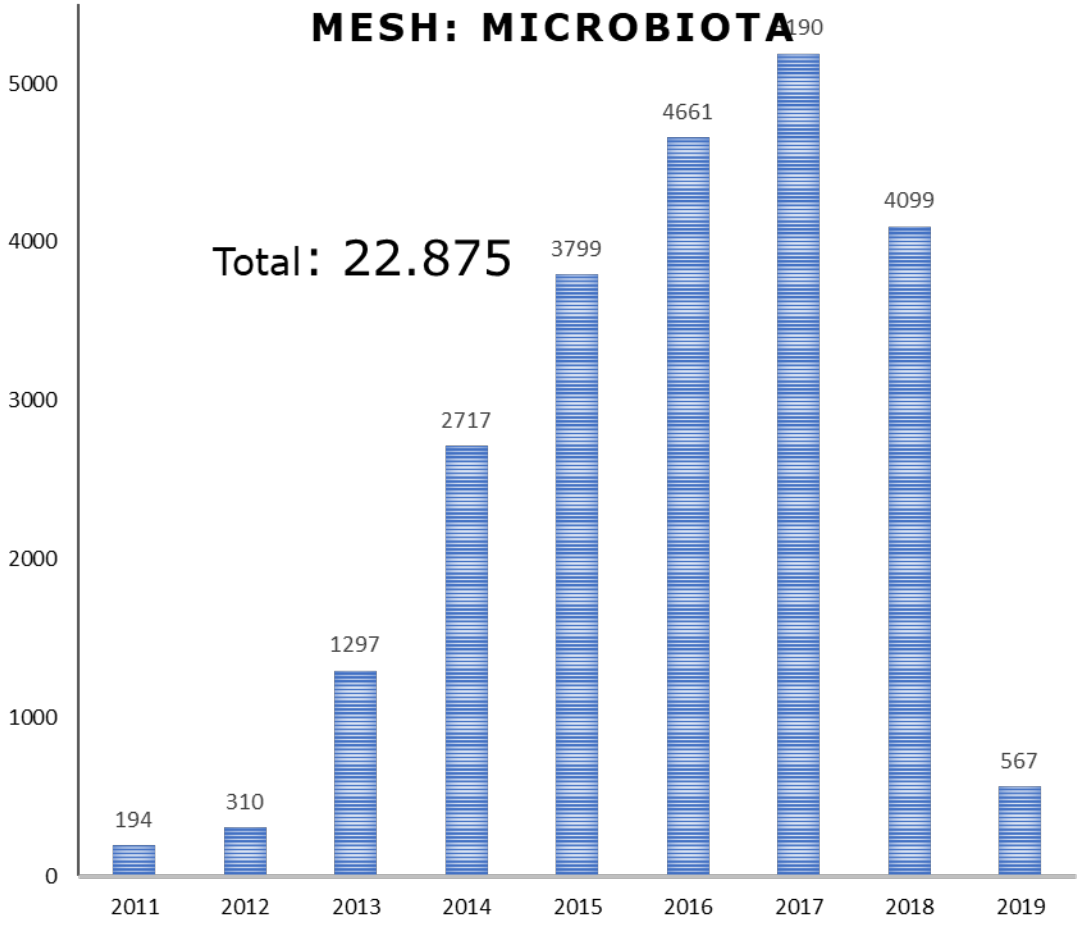
HOSPITAL DEL MAR

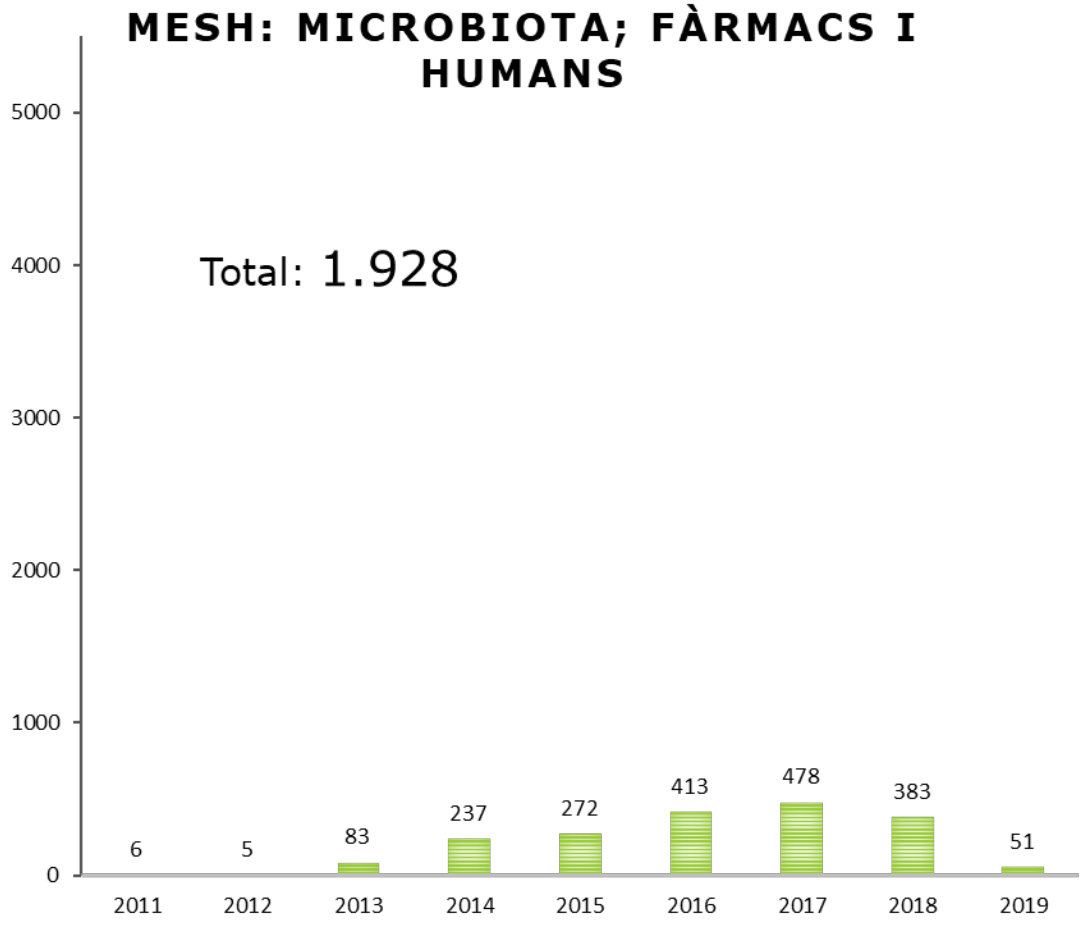
BARCELONA

GNFHC

MAIG 2019

Articles a PubMed

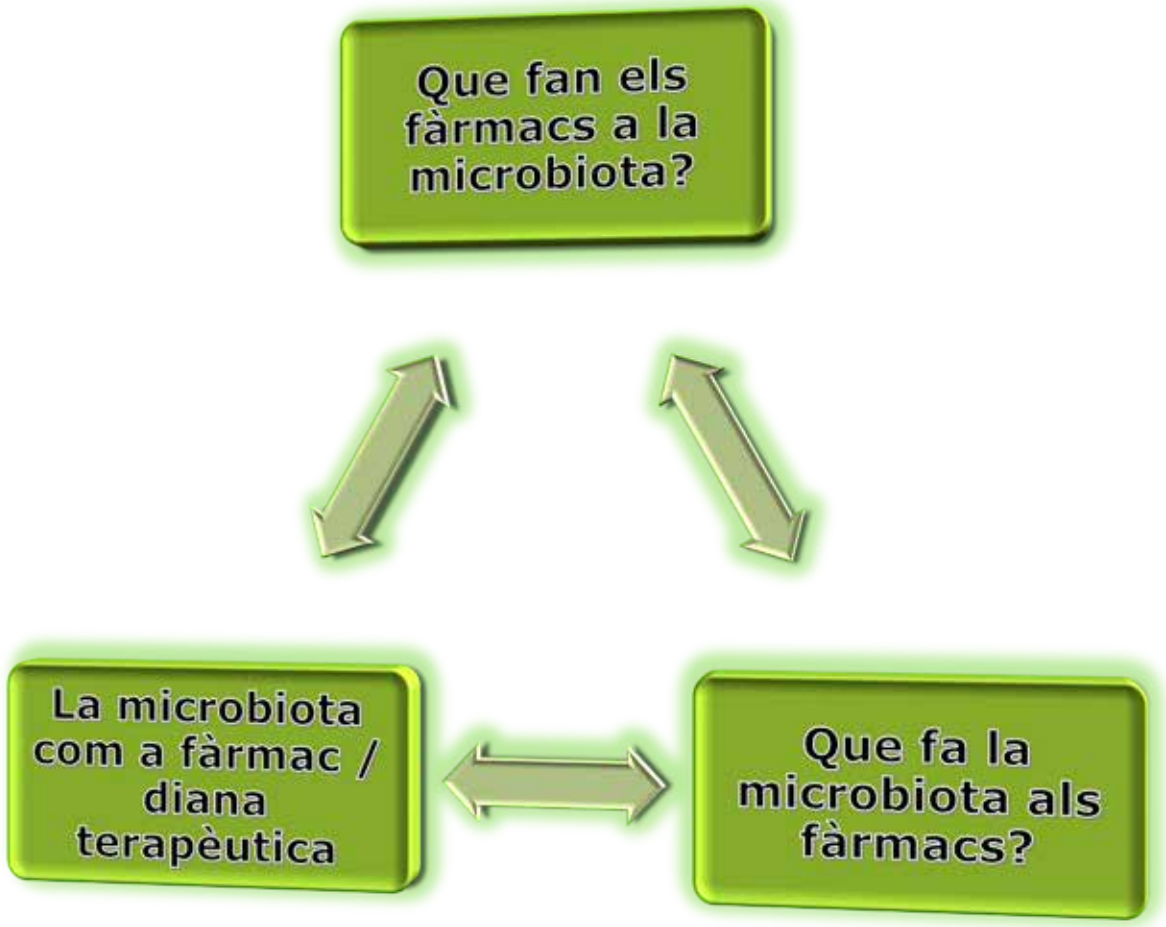




Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina
  - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

Índex


Que fan els fàrmacs a la microbiota?
La microbiota com a fàrmac / diana terapèutica
Que fa la microbiota als fàrmacs?

Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina
  - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

Antibiòtics: Estudi primerenc

Estudi en humans sans:

- 4 **sense** tractament antibiòtic
- 4 **amb** tractament antibiòtic

Tractament: 7 dies de clindamicina 150 mg/6 h

Estudi de PCR a *Bacteroides*

Seguiment a **2 anys**

Jernberg C, Lofmark S, Edlund C, Jansson JK. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. ISME J. 2007;1(1):56-66.

Antibiòtics: Estudi primerenc

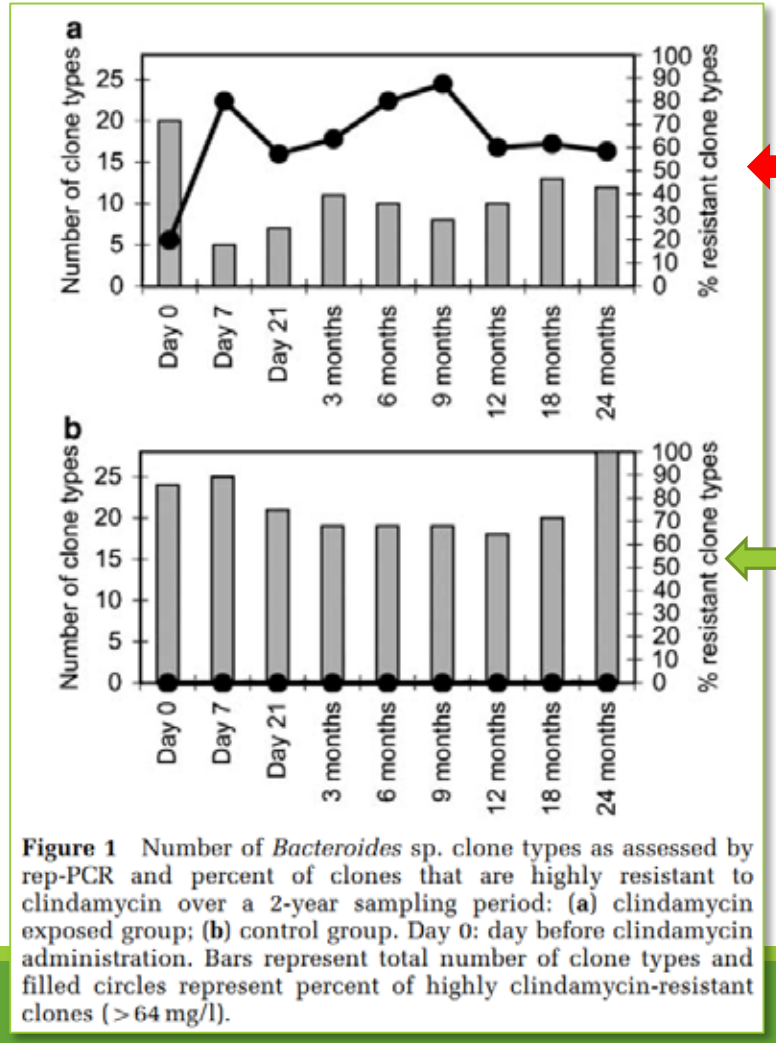


Figure 1 Number of *Bacteroides* sp. clone types as assessed by rep-PCR and percent of clones that are highly resistant to clindamycin over a 2-year sampling period: **(a)** clindamycin exposed group; **(b)** control group. Day 0: day before clindamycin administration. Bars represent total number of clone types and filled circles represent percent of highly clindamycin-resistant clones (>64 mg/l).

Clindamicina

Sense ATB

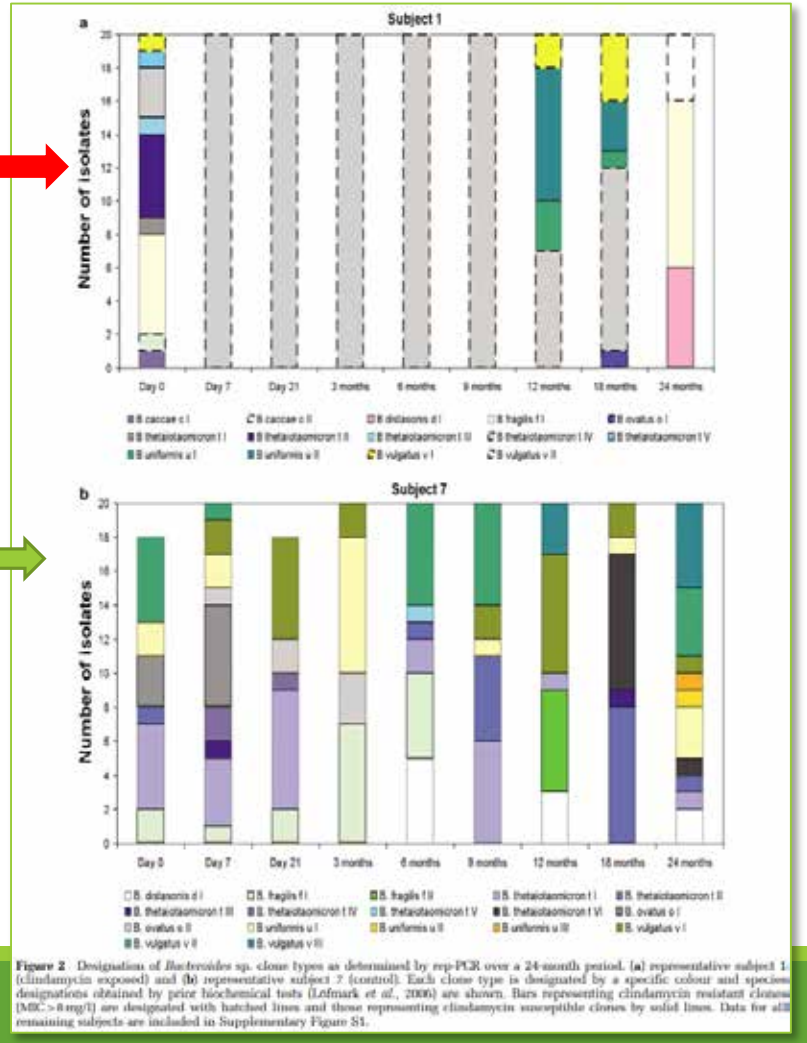


Figure 2 Designation of *Bacteroides* sp. clone types as determined by rep-PCR over a 24-month period. **(a)** representative subject 1 (clindamycin exposed) and **(b)** representative subject 7 (control). Each clone type is designated by a specific colour and species designations obtained by prior biochemical tests (Löfmark *et al.*, 2006) are shown. Bars representing clindamycin resistant clones (MIC > 8 mg/l) are designated with hatched lines and those representing clindamycin susceptible clones by solid lines. Data for all remaining subjects are included in Supplementary Figure S1.

Altres Antibiòtics

TABLE 1

Pharmacodynamic and pharmacokinetic overview of select antibiotics and their effect on the microbiota[28–30,32,33,35,37]

	Ampicillin	Clindamycin	Metronidazole	Neomycin	Vancomycin
Classification	Aminopenicillin	Lincosamide	Nitroimidazole	Aminoglycoside	Glycopeptide
Route of administration	Intramuscular Intravenous Oral	Intramuscular Intravenous Oral Topical Vaginal	Intravenous Oral Topical Vaginal	Intravenous Intramuscular Oral Topical	Intraocular Intraperitoneal Intrathecal Intravenous Intraventricular Oral
Spectrum	(1) Gram + (2) Gram – (3) Anaerobes	(1) Gram + (2) Anaerobes	(1) Anaerobes	(1) Gram – (2) Aerobes	(1) Gram + (2) Aerobes
Intestinal absorption by oral administration	Moderate absorption	High absorption	High absorption	Minimal absorption	Minimal absorption
Site of absorption	Small Intestine	Small Intestine	Small Intestine	—	—
Clearance mechanism	Renal[a]	Biliary	Renal[a] Biliary	Renal	Renal[a] Minimal Biliary
Microbiota diversity with oral administration	Long-term changes	Long-term changes	Short-term changes	Long-term changes	Long-term changes
Microbiota diversity with systemic administration	Long-term changes	Long-term changes	Undetermined	Minimal changes	Minimal changes

Kim S, Covington A, Pamer EG. The intestinal microbiota: Antibiotics, colonization resistance, and enteric pathogens. Immunol Rev. 2017;279(1):90-105.

Antibiòtics: “multiomica”

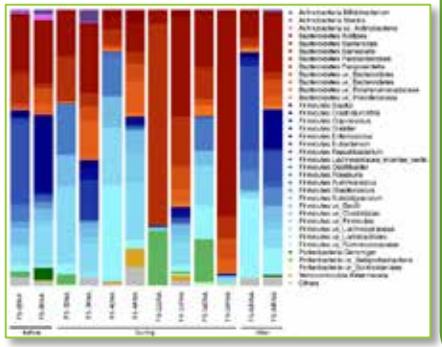
Estudi en 1 pacient, però s’estudia:

- Microbiota
- Metagenoma
- Metatranscriptoma (mRNAs)
- Metametaboloma
- Metaproteoma

14 dies de tractament antibiòtic:

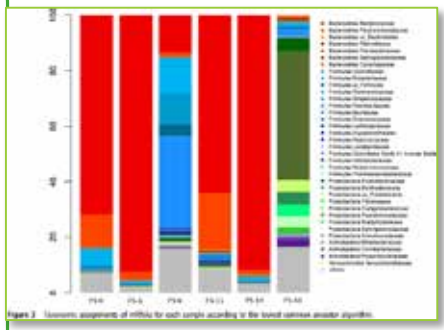
- 1er dia: ampicil·lina/sulbactam + cefazolina
- 13 dies: cefazolina

Perez-Cobas AE, Gosalbes MJ, Friedrichs A, Knecht H, Artacho A, Eismann K, Otto W, et al. Gut microbiota disturbance during antibiotic therapy: a multi-omic approach. Gut. 2013;62(11):1591-601.



- Dia 6: ¯ Gram-
- Dia 11: ¯¯ biodiversitat
- Dia 14: - Gram+ - biodiversitat. Disbalanç màxim
- Dia 40 (post-AB): Tendència a retornar a situació basal. Pèrdua d'espècies de grups minoritaris

- Dia 6: Canvi de bactèries actives. - Firmicutes: Streptococcaceae i Clostridiaceae.
- Dia 11: Recuperació activitat Bacteroidaceae
- Dia 40 (post-AB): -- Burkholderiaceae

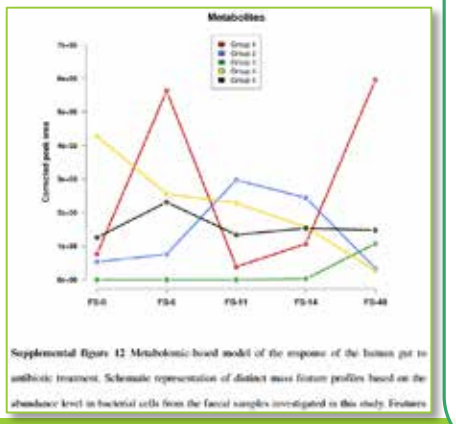


Microbiota

Metatrans-criptoma

Metameta-boloma

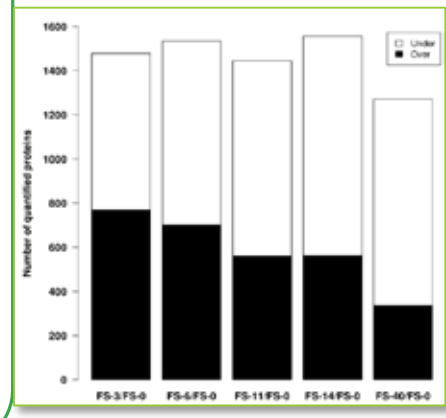
Metapro-teoma

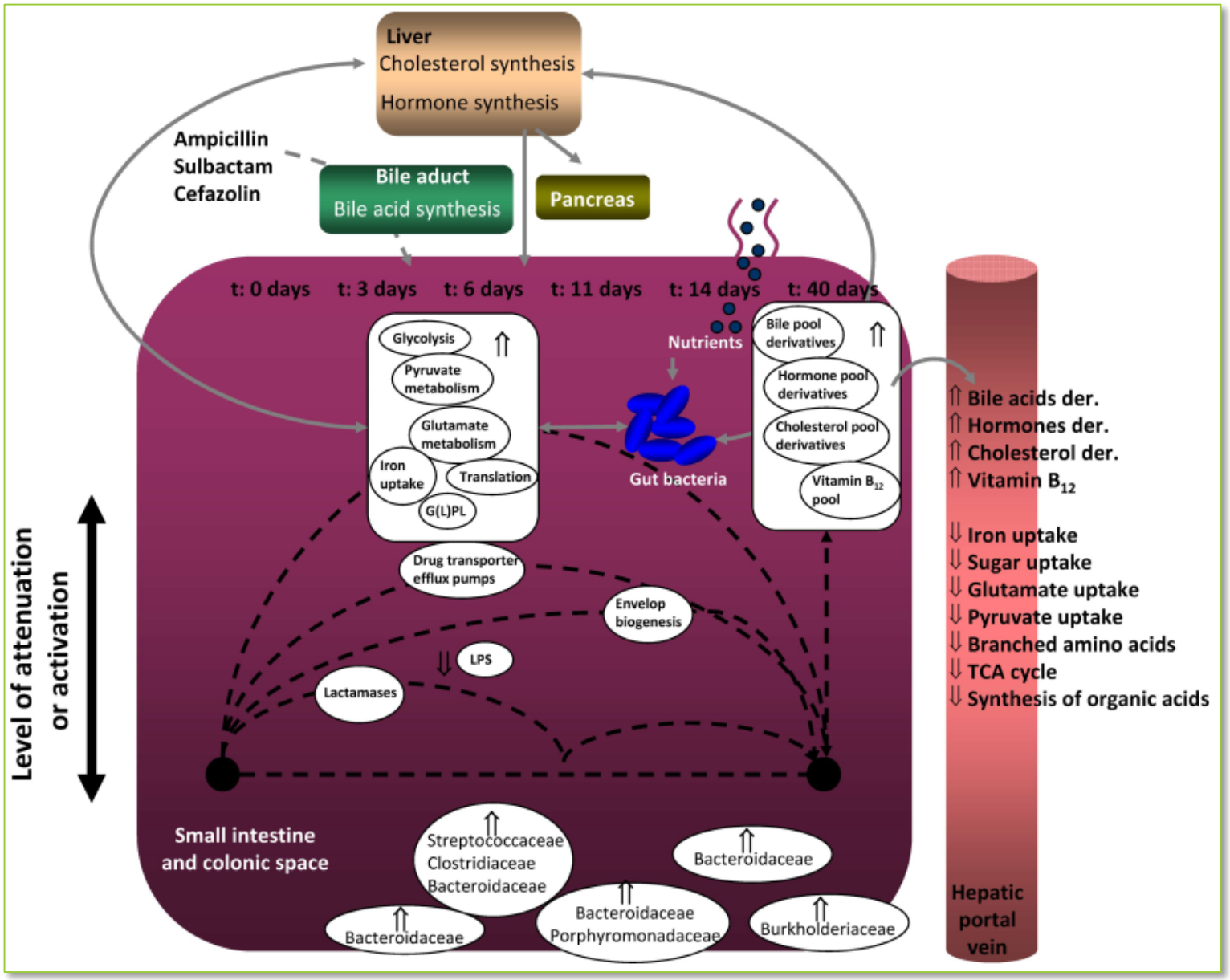


- Dia 6: Augment de LCFA i pèptids
- Disminució de metabòlits interacció hoste – bacteri (B12, colesterol, etc.)
- Dia 40: Reaparició de metabòlits del colesterol, vit. D, etc.

•Durant el tractament: Disminució en el nombre de proteïnes

•Aparició de transportadors peptídics d'antimicrobians i de bombes de flux multifàrmac





Perez-Cobas AE, Gosalbes MJ, Friedrichs A, Knecht H, Artacho A, Eismann K, Otto W, et al. Gut microbiota disturbance during antibiotic therapy: a multi-omic approach. Gut. 2013;62(11):1591-601.

Antibiòtics: Òrgans

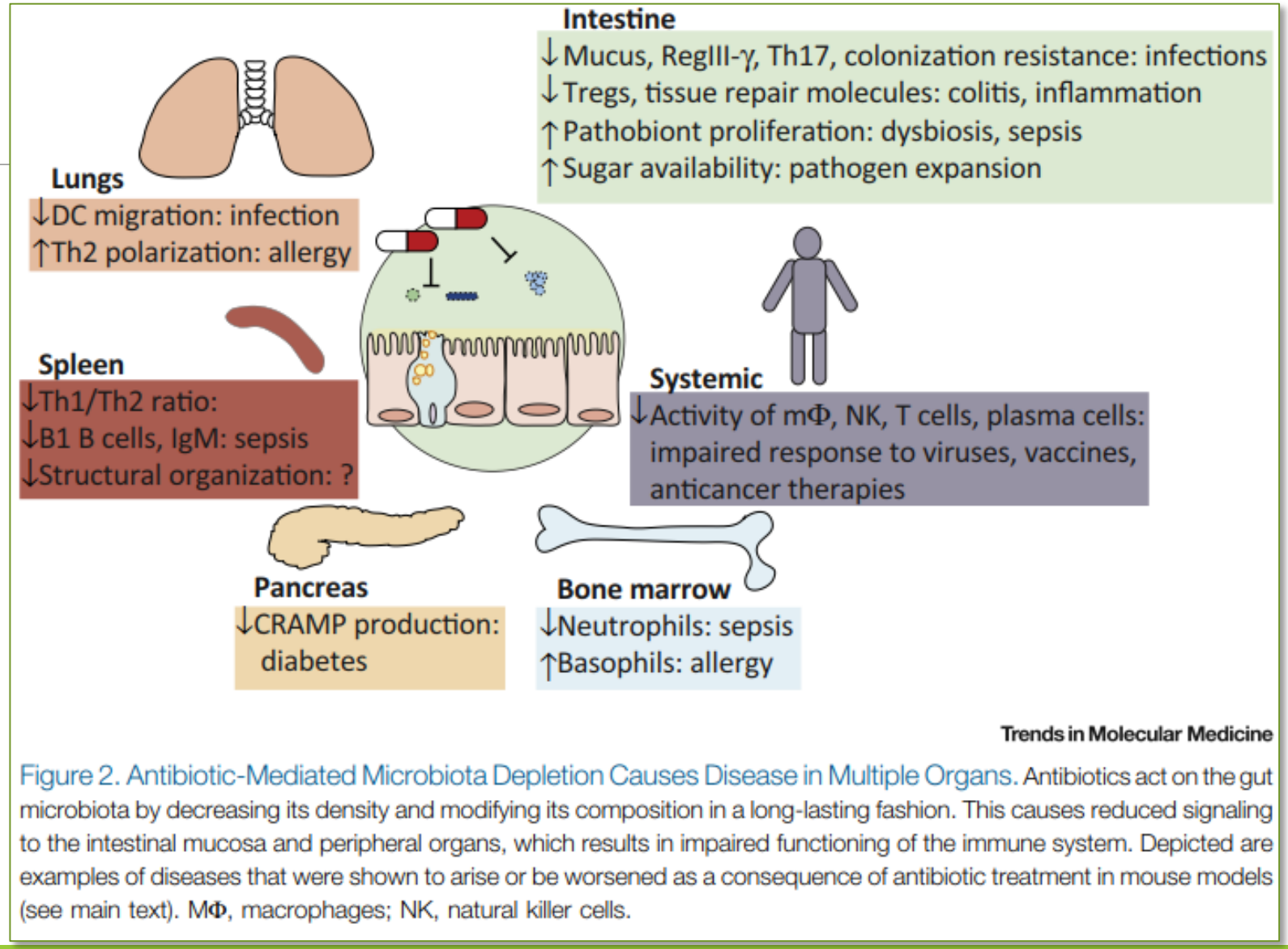
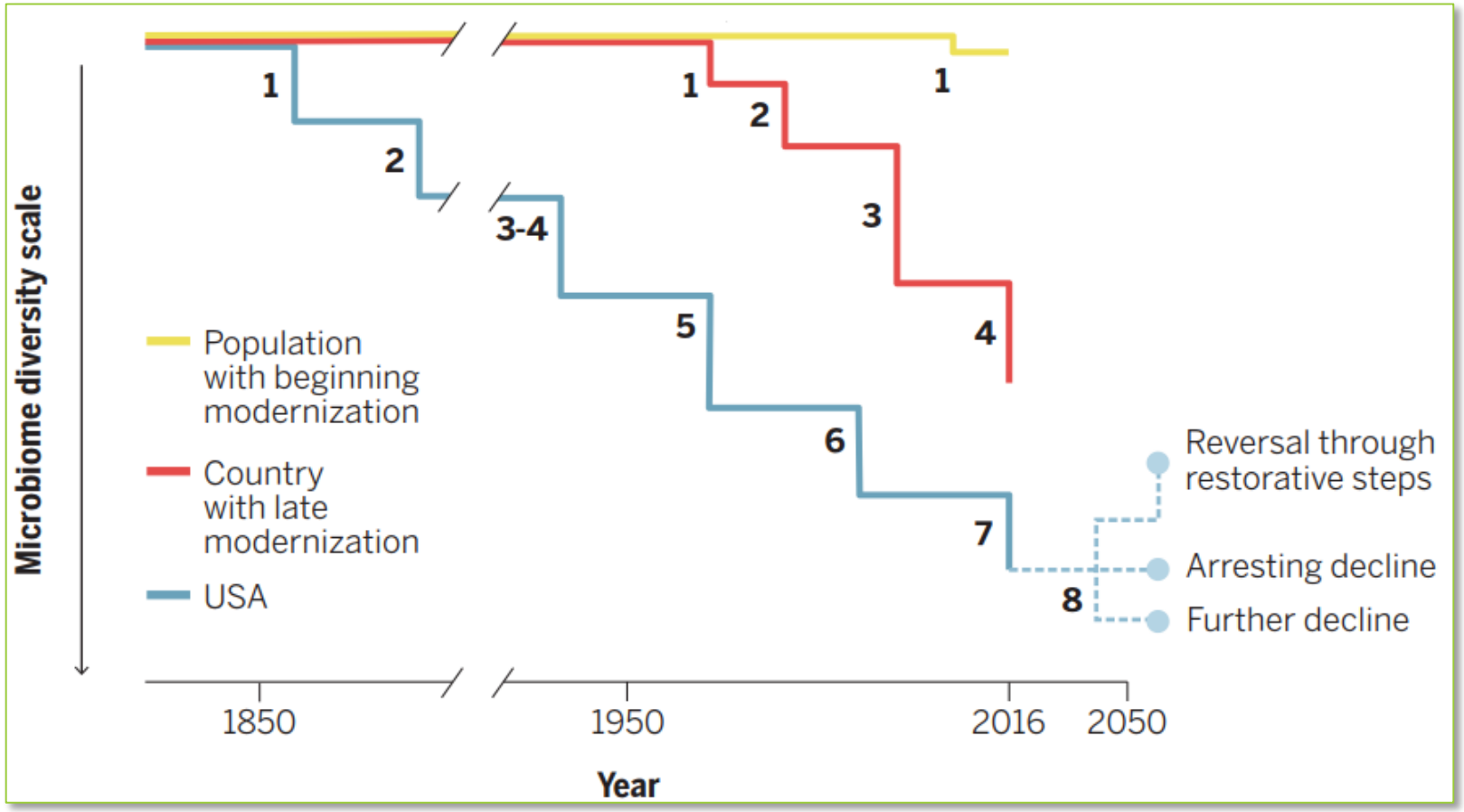


Figure 2. Antibiotic-Mediated Microbiota Depletion Causes Disease in Multiple Organs. Antibiotics act on the gut microbiota by decreasing its density and modifying its composition in a long-lasting fashion. This causes reduced signaling to the intestinal mucosa and peripheral organs, which results in impaired functioning of the immune system. Depicted are examples of diseases that were shown to arise or be worsened as a consequence of antibiotic treatment in mouse models (see main text). MΦ, macrophages; NK, natural killer cells.

Becattini S, Taur Y, Pamer EG. Antibiotic-Induced Changes in the Intestinal Microbiota and Disease. Trends Mol Med. 2016;22(6):458-78.

Antibiòtics: Poblacional/Temporal



Blaser MJ. Antibiotic use and its consequences for the normal microbiome. Science. 2016;352(6285):544-5.

Índex

NO antibiòtics

>1000 fàrmacs

- Antibacterians (antibiòtics, antisèptics)
- Antiinfecciosos (protozous, fongs, paràsits o virus),
- Fàrmacs humans (diana cèl·lules humanes)
- Fàrmacs veterinaris (exclusius en animals)
- No fàrmacs (metabòlits farmacològics, fàrmacs d'investigació, o substancies endògenes)

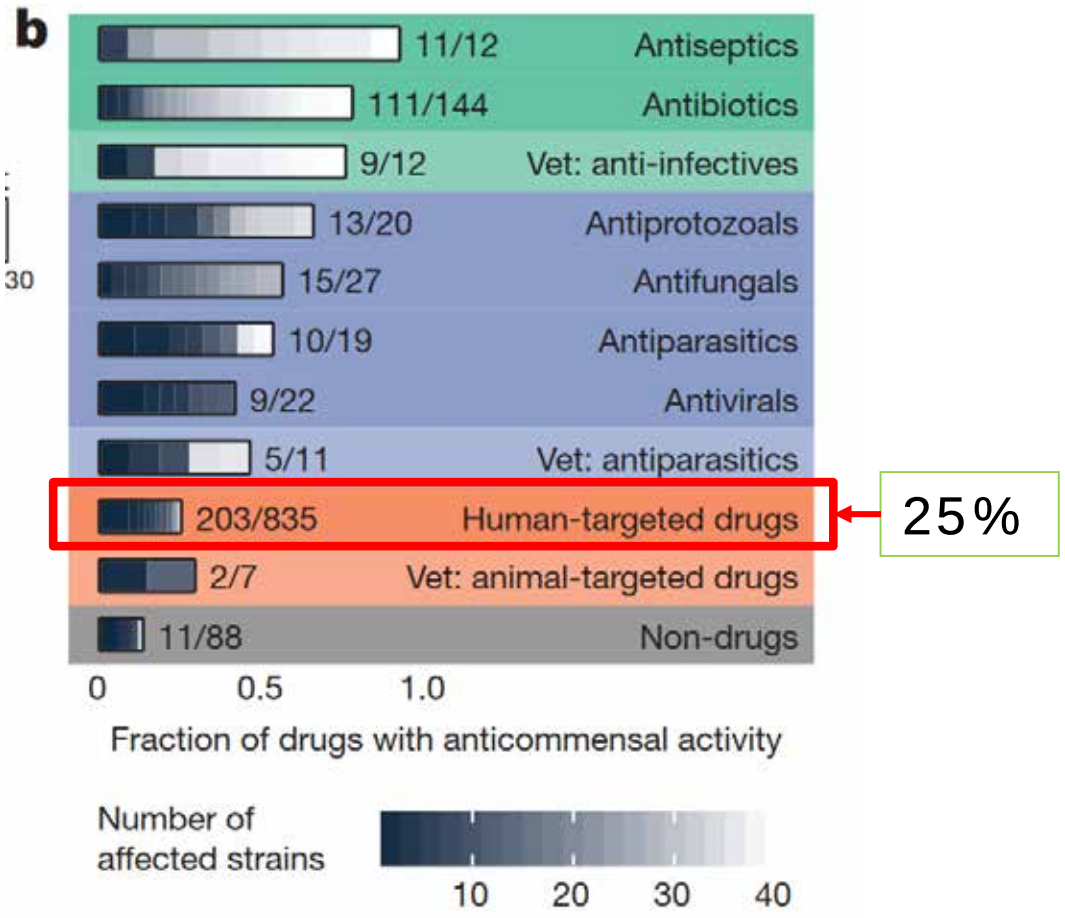
Test a 40 soques bacterianes abundants en microbiomes intestinals d'individus de 3 continents

Correlació amb efectes adversos de medicaments (base de dades SIDER)

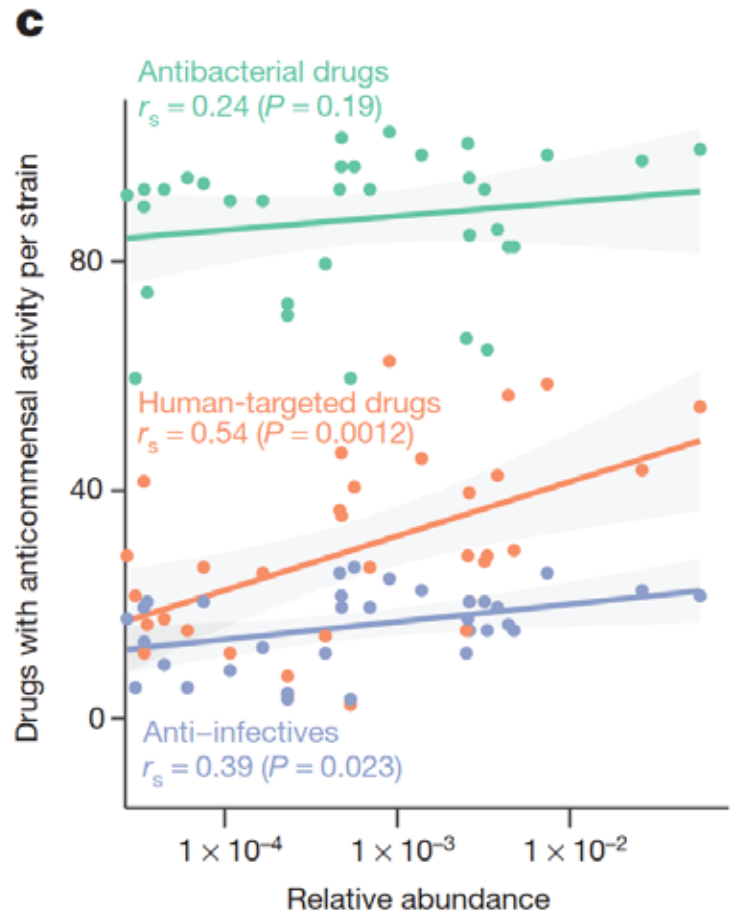
Modelització pK / pD

Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, Brochado AR, et al. Extensive impact of non-antibiotic drugs on human gut bacteri. Nature. 2018;555(7698):623-8.

NO antibiòtics



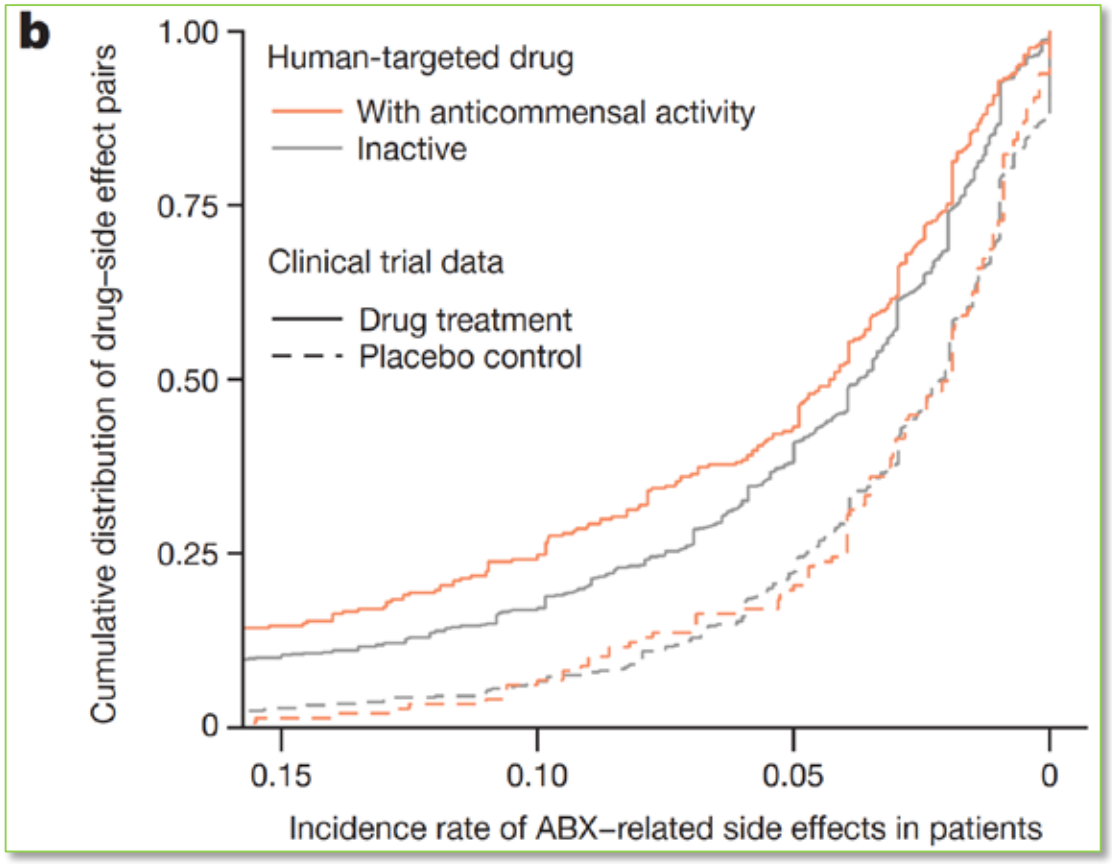
25%



NO antibiòtics

Fàrmacs humans amb inhibició sobre soques de la microbiota:

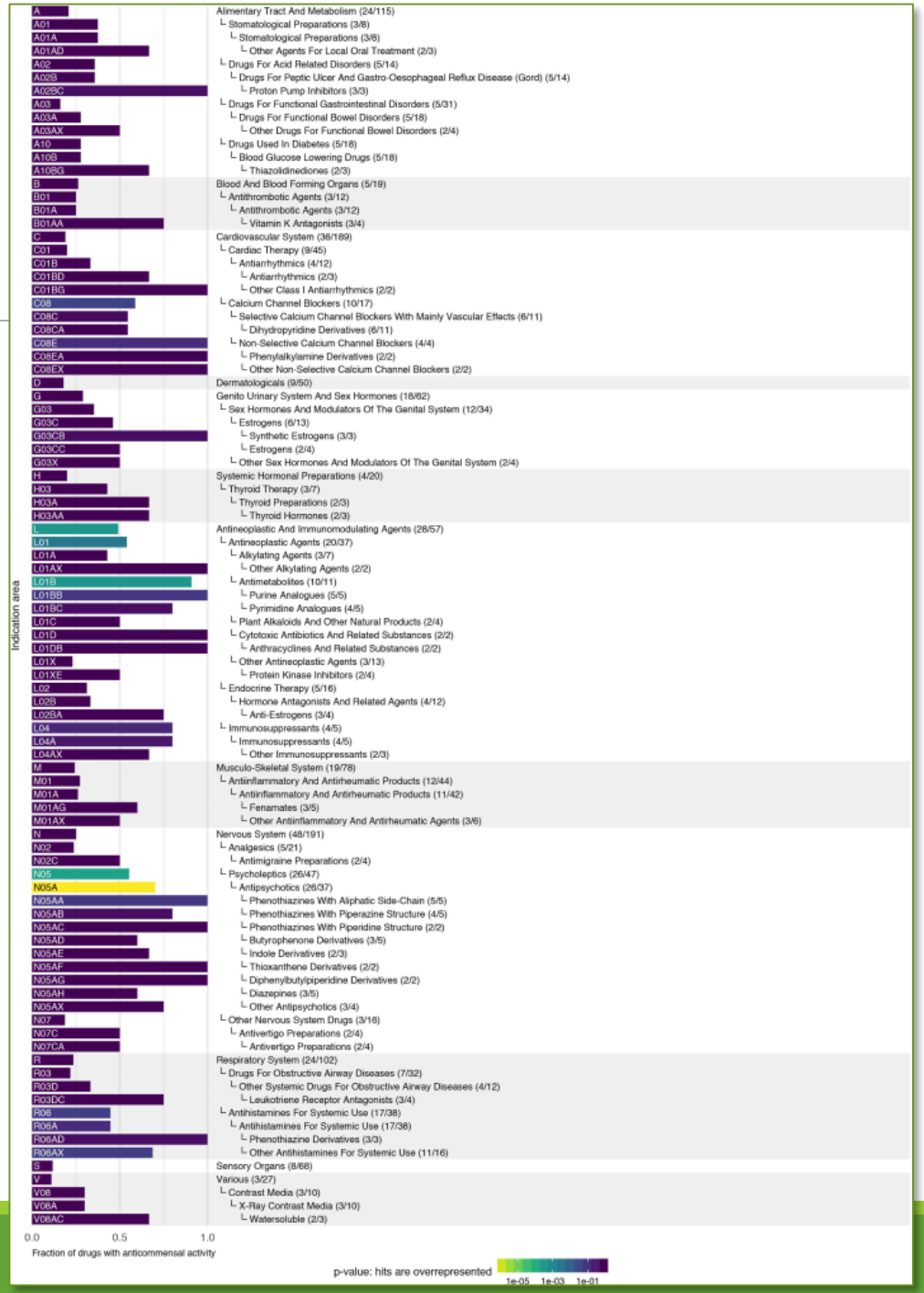
- Tenen efectes adversos semblants a antibiòtics
- Podrien presentar efectes **potenciadors de la resistència a antibiòtics**



NO antibiòtics

Grups amb **MES** fàrmacs alteradors de la microbiota:

- Blocants dels canals del calci
- Agents alquilants
- Anàlegs de les purines i pirimidines
- Immunosupressors
- Antipsicòtics
- Antihistamínics



Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, Brochado AR, et al. Extensive impact of non-antibiotic drugs on human gut bacteri. Nature. 2018;555(7698):623-8.

Índex

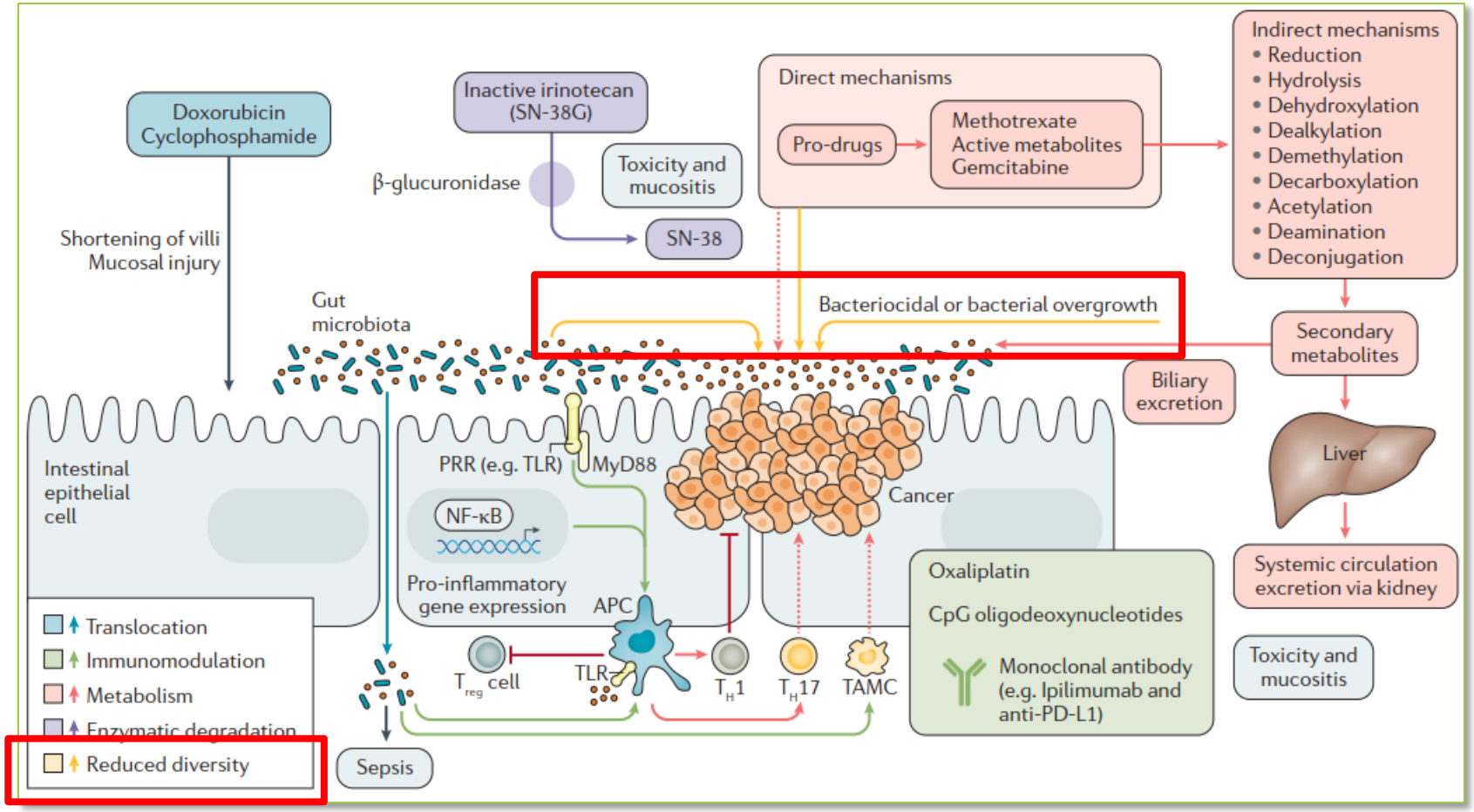
Antineoplàstics

Relació molt complexa (**TIMER**):

- **T**ranslocació
- **I**mmunomodulació
- **M**etabolisme
- **E**nzims degradació
- **R**educció de la diversitat ecològica

Alexander JL, Wilson ID, Teare J, Marchesi JR, Nicholson JK, Kinross JM. Gut microbiota modulation of chemotherapy efficacy and toxicity. Nat Rev Gastroenterol Hepatol. 2017;14(6):356-65.

Antineoplàstics



Antineoplàstics

Estudi en 28 pacients amb limfoma no-Hodgkin

QT BEAM (Carmustina, Etopòsid, Citarabina i Melfalan)

SENSE antibiòtics

Anàlisi de la microbiota intestinal

Dues mostres fecals:

- Abans de QT
- Abans de transplantament de cèl·lules hematopoètiques

Estudi taxonòmic i funcional (metabòlic) de la microbiota

Montassier E, Gastinne T, Vangay P, Al-Ghalith GA, Bruley des Varannes S, Massart S, Moreau P, et al. Chemotherapy-driven dysbiosis in the intestinal microbiome. Aliment Pharmacol Ther. 2015;42(5):515-28.

Antineoplàstics: Taxonòmic

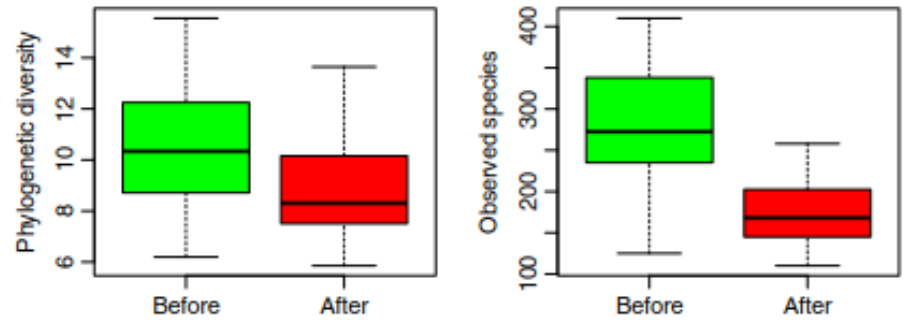


Figure 2 | Alpha-diversity comparisons of the gut microbiomes of the faecal samples collected before chemotherapy and after chemotherapy. Analyses were performed on 16S rRNA V5 and V6 regions data, with a rarefaction depth of 3033 reads per sample. Whiskers in the boxplot represent the range of minimum and maximum alpha diversity values within a population, excluding outliers. Alpha diversity in faecal samples collected after chemotherapy was lower than alpha diversity from samples collected before chemotherapy as observed with both phylogenetic (Faith's phylogenetic diversity (PD), $P = 0.01$) and nonphylogenetic (observed species, $P = 0.001$) richness metrics.

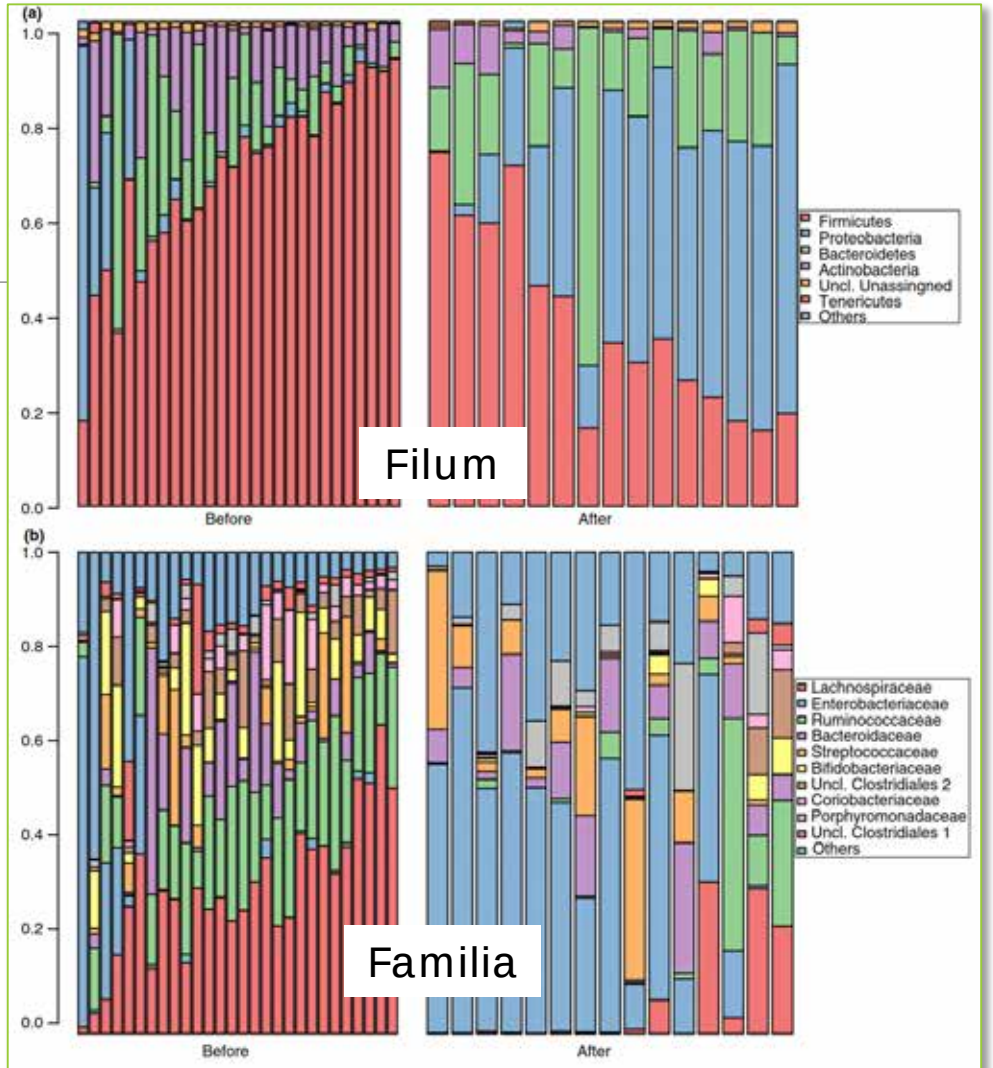


Figure 3 | Taxonomic profile of the gut microbiomes of the samples collected before and after chemotherapy. Analyses were performed on 16S rRNA V5 and V6 regions data, with a rarefaction depth of 3033 reads per sample. (a) Relative taxa abundance plots for individuals from the samples collected before and after chemotherapy, summarised at the phylum level. Individuals are represented along the horizontal axis, and relative taxa frequency is denoted by the vertical axis. (b) Relative taxa abundance plots for individuals from the samples collected before and after chemotherapy, summarised at the family level. Individuals are represented along the horizontal axis, and relative taxa frequency is denoted by the vertical axis.

Montassier E, Gastinne T, Vangay P, Al-Ghalith GA, Bruley des Varannes S, Massart S, Moreau P, et al. Chemotherapy-driven dysbiosis in the intestinal microbiome. Aliment Pharmacol Ther. 2015;42(5):515-28.

Antineoplàstics: Metabòlic

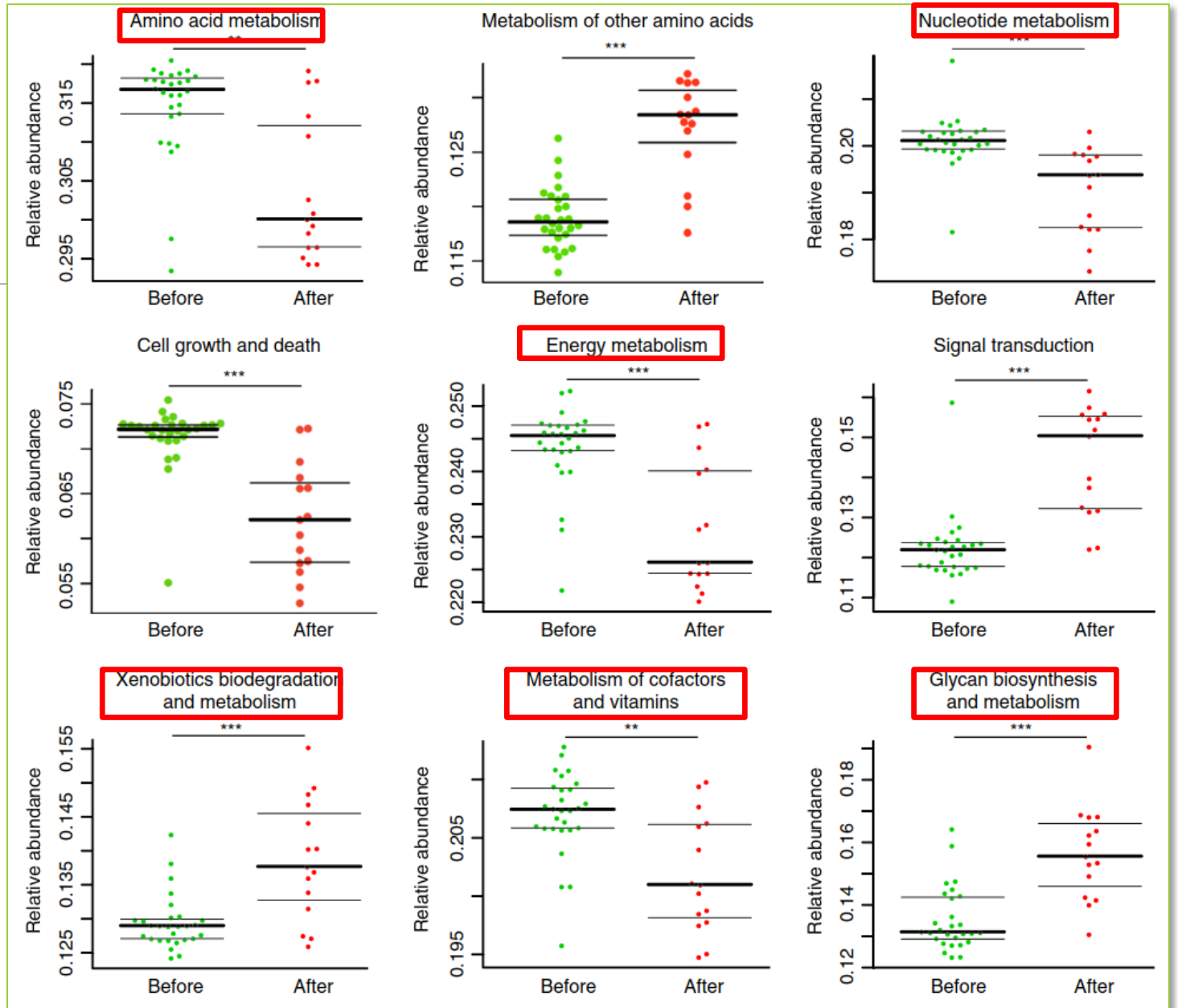


Figure 5 | Relative abundance of the most significant metabolic pathways (L2 KEGG Orthology profiles) in samples collected before (n = 28) and after chemotherapy (n = 15) Mann–Whitney test: *P < 0.05; **P < 0.01 and ***P < 0.001. Boxplots denote top quartile, median and bottom quartile.

Montassier E, Gastinne T, Vangay P, Al-Ghalith GA, Bruley des Varannes S, Massart S, Moreau P, et al. Chemotherapy-driven dysbiosis in the intestinal microbiome. Aliment Pharmacol Ther. 2015;42(5):515-28.

Antineoplàstics

Reducció dràstica de la biodiversitat

Canvi de la composició taxonòmica

- Augment : Enterococcaceae i Enterobacteriaceae
- Disminució: Firmicutes (Ruminococcaceae, Lachnospiraceae) i Actinobacteria (Bifidobacterium)

Canvis del metabolisme de la microbiota:

- Disminució: Metabolisme energètic, nucleòtids i de cofactors i vitamines
- Augment: senyals de transducció, biodegradació de xenobiòtics i metabolisme de glicans

Patró pro-inflamatori à Explicació parcial de mucositis

Montassier E, Gastinne T, Vangay P, Al-Ghalith GA, Bruley des Varannes S, Massart S, Moreau P, et al. Chemotherapy-driven dysbiosis in the intestinal microbiome. Aliment Pharmacol Ther. 2015;42(5):515-28.

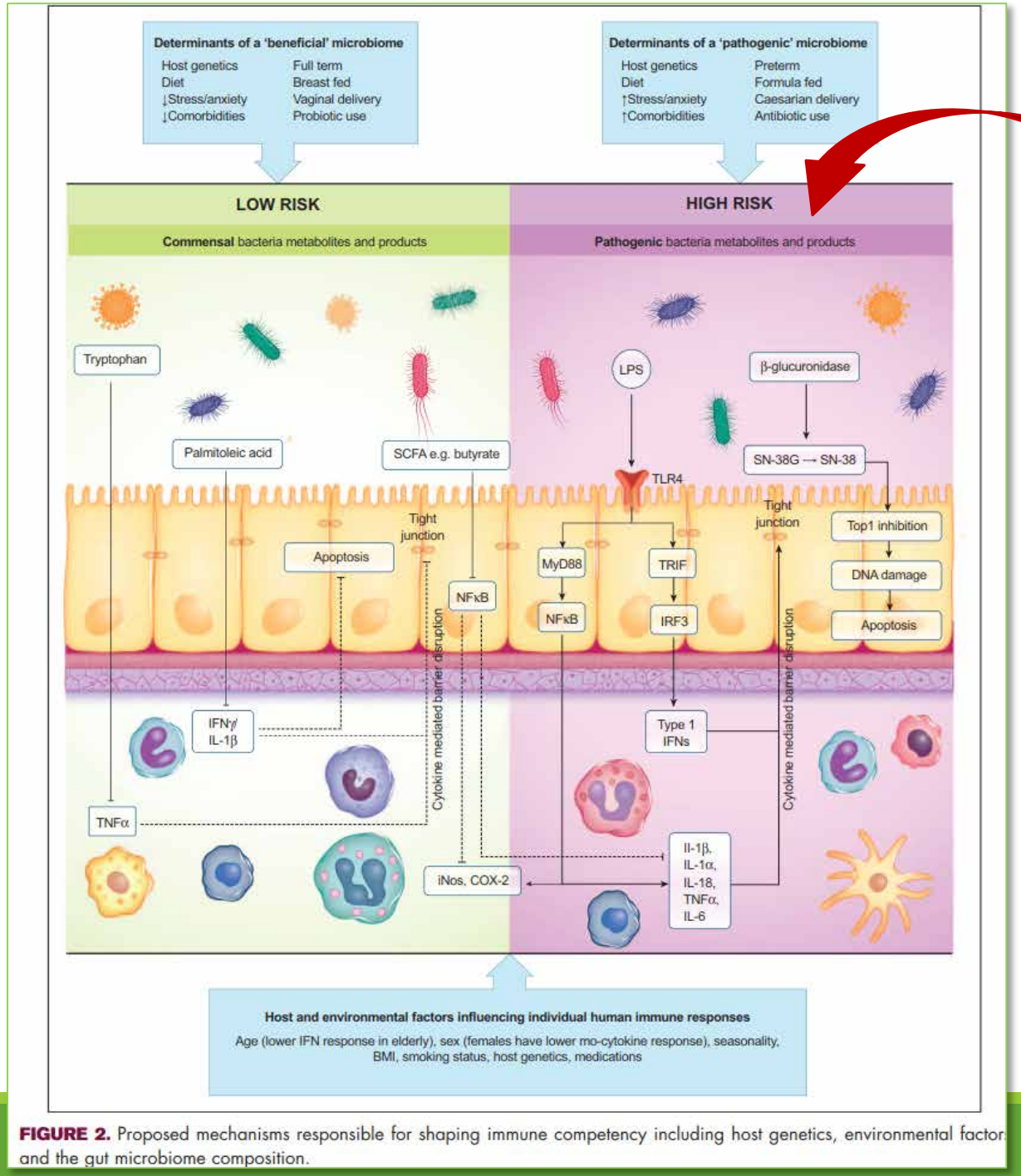


FIGURE 2. Proposed mechanisms responsible for shaping immune competency including host genetics, environmental factor and the gut microbiome composition.

QT (i possiblement RT):

- Disminució de Firmicutes (Lactobaccilus spp.), i Actinobacteria (Bifidobacterium spp.), Bacteroides spp. i Enterococcus spp.
- Augment de Proteobacteria (E. coli) i Staphylococcus spp.
- Metabòlits i substancies pro-inflamatòries

Wardill HR, Tissing WJE. Determining risk of severe gastrointestinal toxicity based on pretreatment gut microbial community in patients receiving cancer treatment: a new predictive strategy in the quest for personalized cancer medicine. Curr Opin Support Palliat Care. 2017;11(2):125-32.

Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina
  - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

Altres

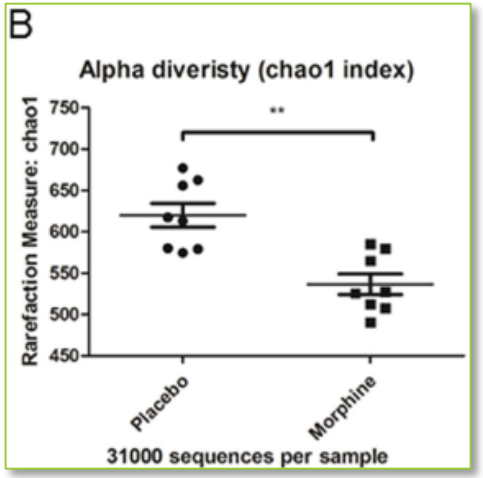
IBP

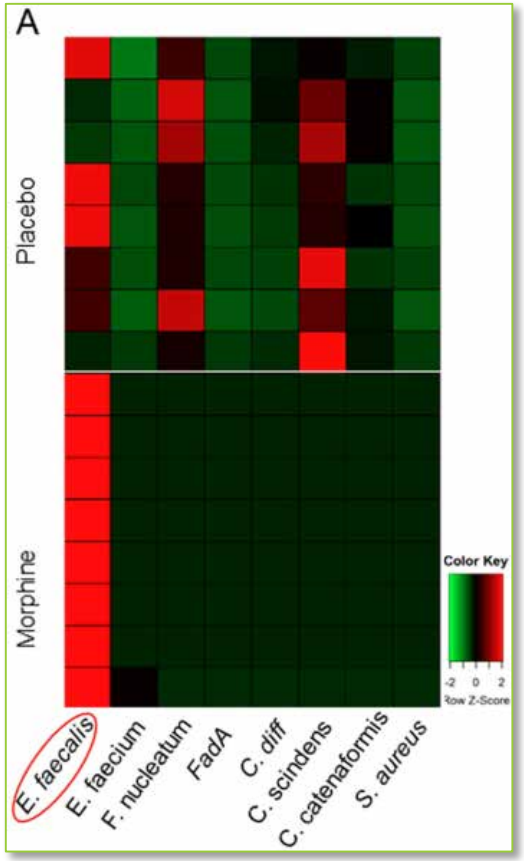
Conclusion

Several meta-analyses using case-control and cohort studies have demonstrated an increased risk of developing infectious and inflammatory diseases in association with gut dysbiosis secondary to long-term use of PPIs. Using 16S rRNA gene sequencing, PPIs were found to significantly increase certain taxa including Streptococcaceae and Enterococcaceae, which are risk factors for CDI, and to decrease *Faecalibacterium*, a commensal anti-inflammatory microbe. Future studies to assess the safety of PPIs and their role in microbiome changes should be encouraged.

Naito Y, Kashiwagi K, Takagi T, Andoh A, Inoue R. Intestinal Dysbiosis Secondary to Proton-Pump Inhibitor Use. Digestion. 2018;97(2):195-204.

MORFINA

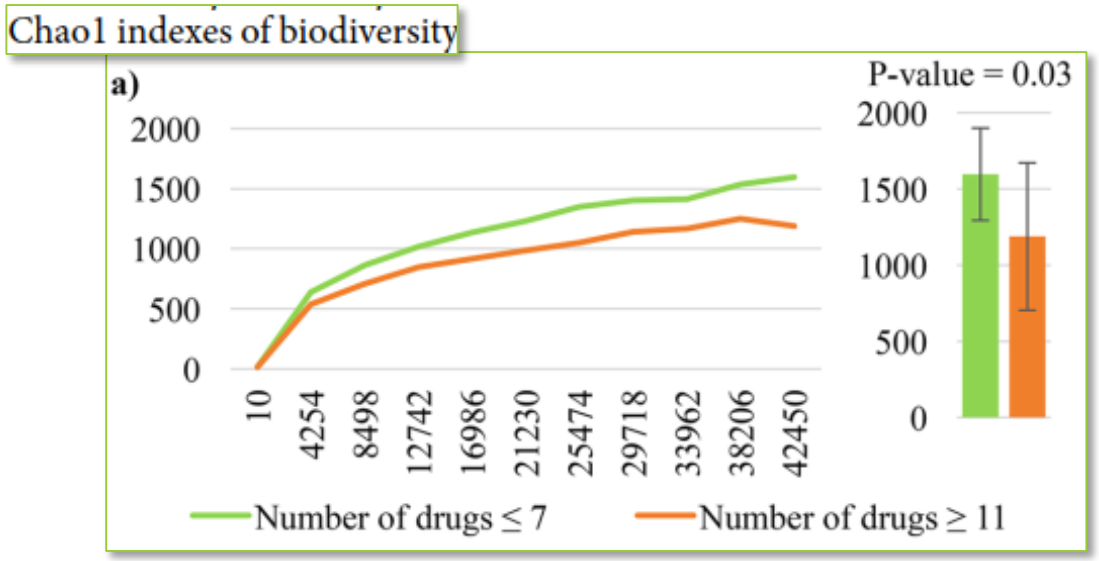




Wang F, Meng J, Zhang L, Johnson T, Chen C, Roy S. Morphine induces changes in the gut microbiome and metabolome in a morphine dependence model. Sci Rep. 2018;8(1):3596.

Índex

Polifarmàcia



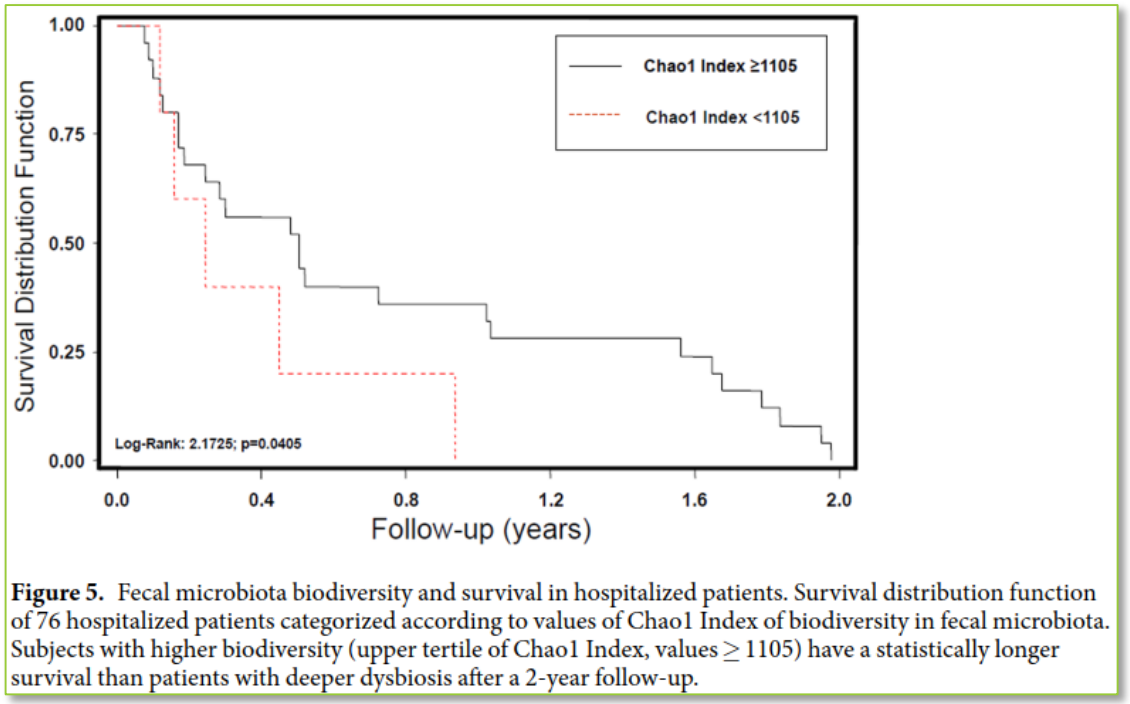


Figure 5. Fecal microbiota biodiversity and survival in hospitalized patients. Survival distribution function of 76 hospitalized patients categorized according to values of Chao1 Index of biodiversity in fecal microbiota. Subjects with higher biodiversity (upper tertile of Chao1 Index, values ≥ 1105) have a statistically longer survival than patients with deeper dysbiosis after a 2-year follow-up.

Ticinesi A, Milani C, Lauretani F, Nouvenne A, Mancabelli L, Lugli GA, Turroni F, et al. Gut microbiota composition is associated with polypharmacy in elderly hospitalized patients. Sci Rep. 2017;7(1):11102.

Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina
  - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

Metformina

Estudi doble cec aleatoritzat amb placebo de 4 mesos de duració, 40 pacients “naives”:

- Milloria IMC
- Milloria control glicèmic
- Lligats a augment de *Bifidobacterium adolescentis* i *Akkermansia muciniphila*
- Augment de metal·loproteïnes i transportadors de metalls bacterians
- Transferència de mostres fecals de ratolins tractats amb metformina a ratolins “germ-free” à Milloria de control glicèmic

- Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Mannerås-Holm L, Ståhlman M, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nature Medicine. 2017;23:850.

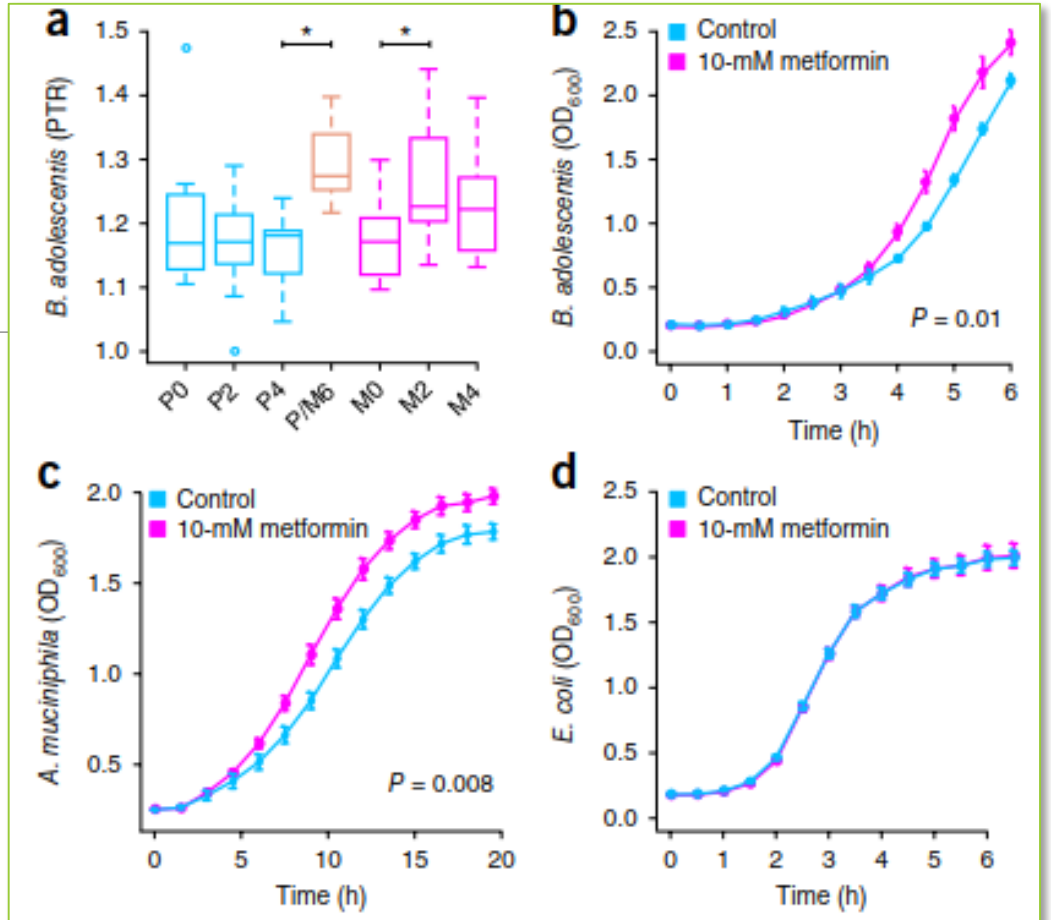


Figure 2 Metformin treatment promotes the growth of gut bacteria. (**a**) Boxplots (with median) showing *B. adolescentis* growth as estimated by peak-to-trough ratio (PTR) before treatment (P0 and M0) and after 2 and 4 months in individuals with T2D randomized to placebo (P2 and P4; $n = 18$) or metformin (M2 and M4; $n = 22$) and 6 months after metformin in a subgroup that switched from placebo to metformin after the randomized study period (P/M6; $n = 13$). Wilcoxon signed–rank test; *FDR < 0.05. (**b**–**d**) Growth of *B. adolescentis*, *A. muciniphila*, and *E. coli* as single cultures in the presence or absence of 10-mM metformin (with six technical replicates). *P* values were determined by two-way analysis of variance (ANOVA) with repeated measurements. Data are shown as means ± s.e.m.

Metformina

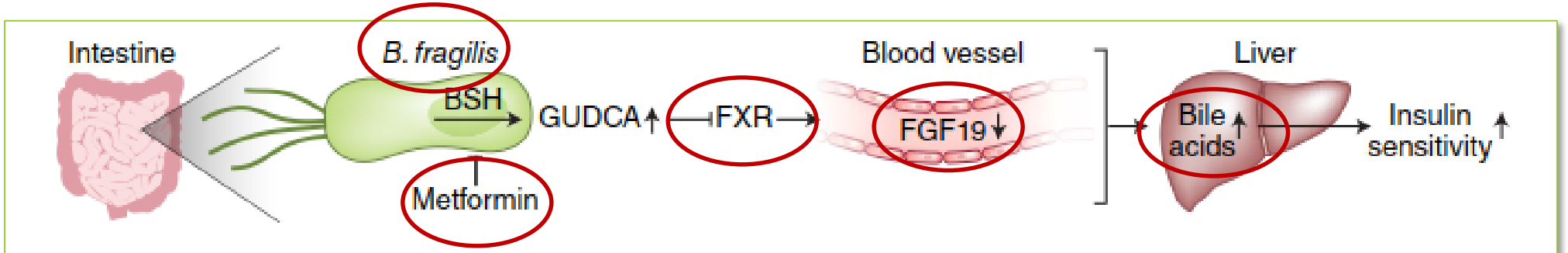


Fig. 1 | Metformin acts through changes in gut *B. fragilis* and bile acid signaling. Sun et al.[4] find that metformin lowers levels of *B. fragilis* in the gut, resulting in a decrease in the enzyme BSH. The subsequent increase in the bile acid GUDCA, which is an antagonist of FXR, increases levels of liver bile acids and through this signaling increases insulin sensitivity.

GUDCA: glycine-ursodeoxycholic acid
BSH: bile salt hydrolase activity
FXR: farnesoid X receptor
FGF19: fibroblast growth factor 19

Guo GL, Xie W. Metformin action through the microbiome and bile acids. Nature Medicine. 2018;24(12):1789-90.
Sun L, Xie C, Wang G, Wu Y, Wu Q, Wang X, Liu J, et al. Gut microbiota and intestinal FXR mediate the clinical benefits of metformin. Nature Medicine. 2018;24(12):1919-29.

Altres ADOs

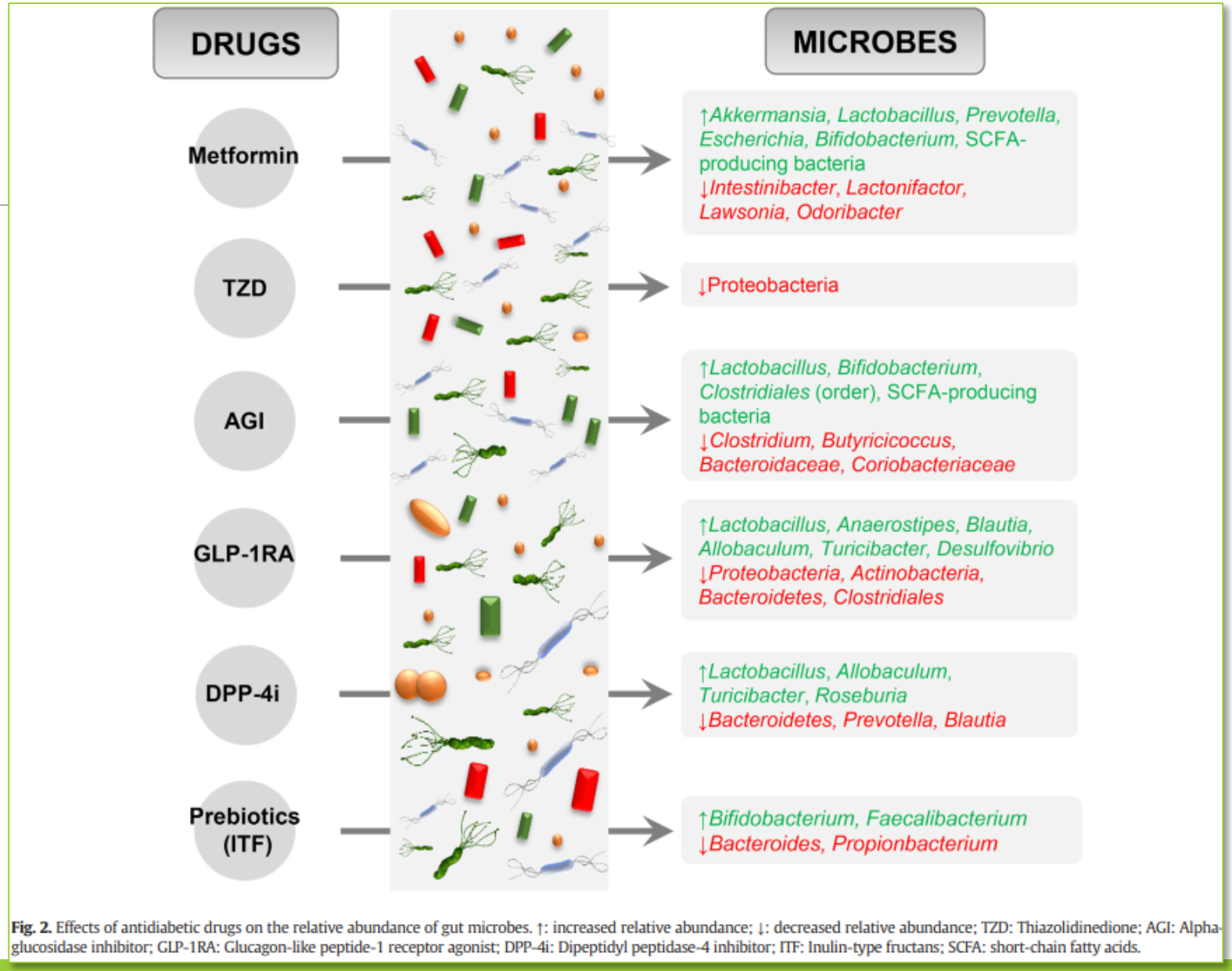


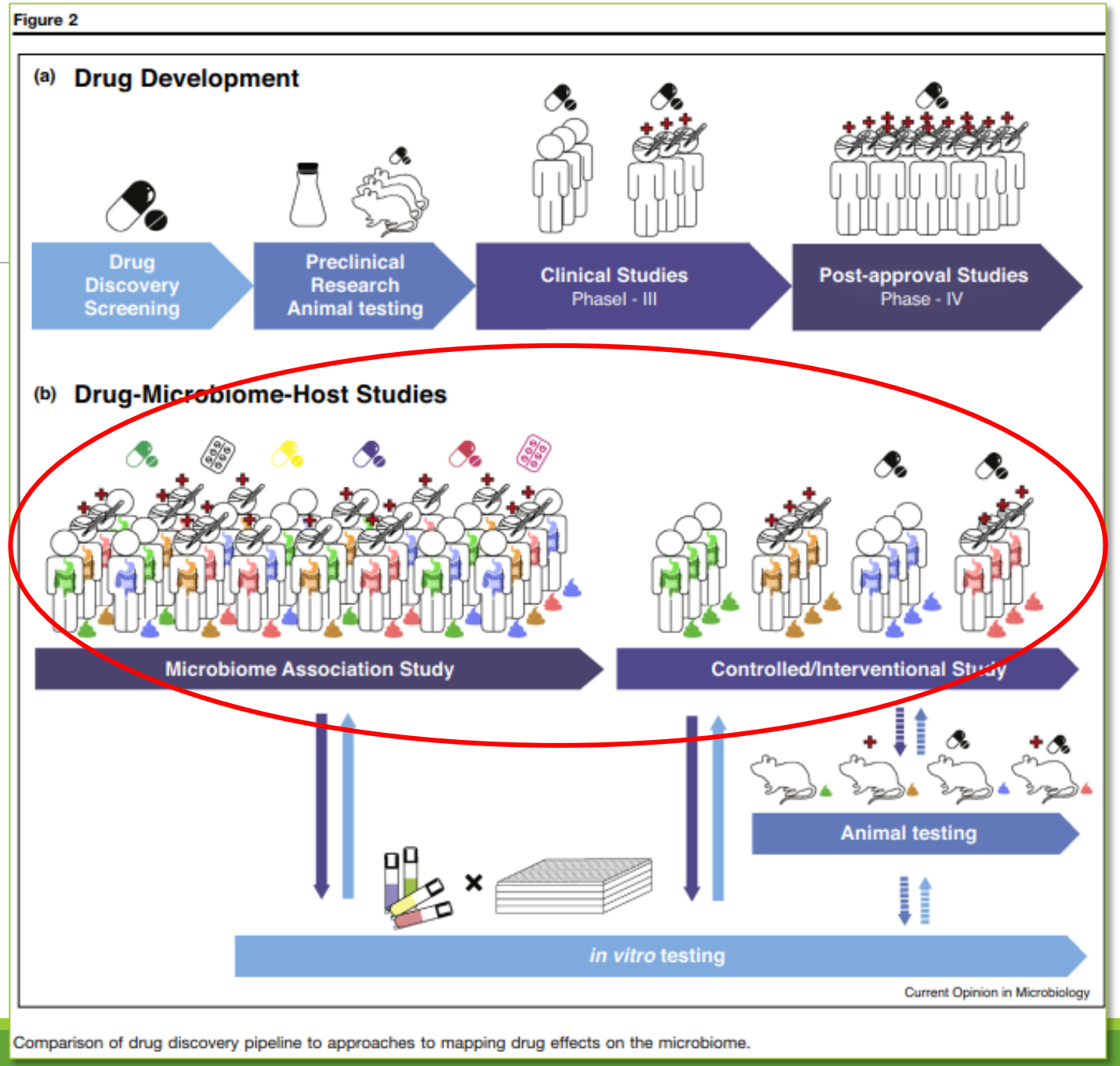
Fig. 2. Effects of antidiabetic drugs on the relative abundance of gut microbes. ↑: increased relative abundance; ↓: decreased relative abundance; TZD: Thiazolidinedione; AGI: Alpha-glucosidase inhibitor; GLP-1RA: Glucagon-like peptide-1 receptor agonist; DPP-4i: Dipeptidyl peptidase-4 inhibitor; ITF: Inulin-type fructans; SCFA: short-chain fatty acids.

Whang A, Nagpal R, Yadav H. Bi-directional drug-microbiome interactions of anti-diabetics. EBioMedicine. 2019;39:591-602.

Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina
  - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

Futurs estudis



Comparison of drug discovery pipeline to approaches to mapping drug effects on the microbiome.

Maier L, Typas A. Systematically investigating the impact of medication on the gut microbiome. Curr Opin Microbiol. 2017;39:128-35.

Índex

Metabolisme: Òrgan microbioma

	Pes (kg)	Taxa metabòlica (Kcal/kg/d)
Fetge	1,39	200
Cervell	1,33	240
Cor	0,31	440
Ronyons	0,29	440
Muscle esquelètic	26,3	13
Teixit adipós	19,4	4,5
Resta	24,7	12
Microbioma	0,2 (1-2?)	??

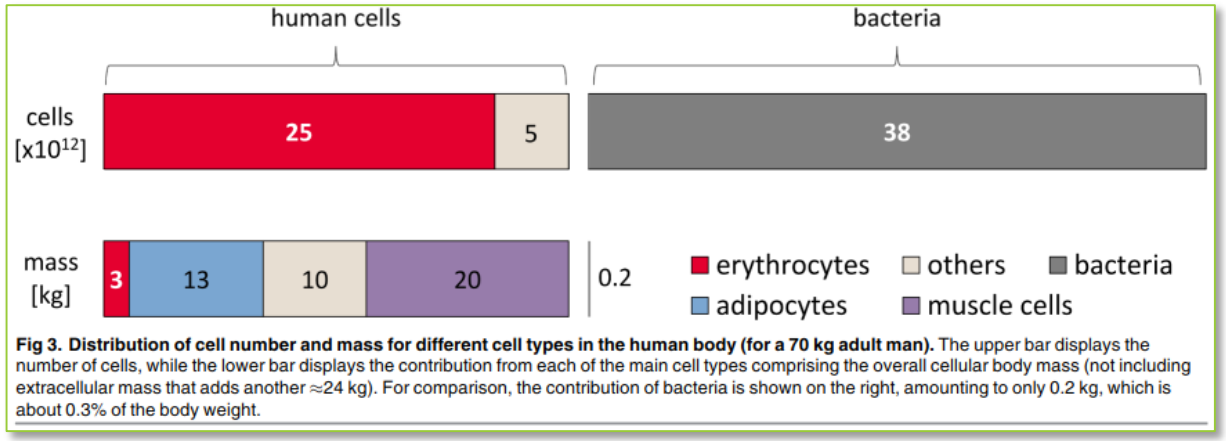
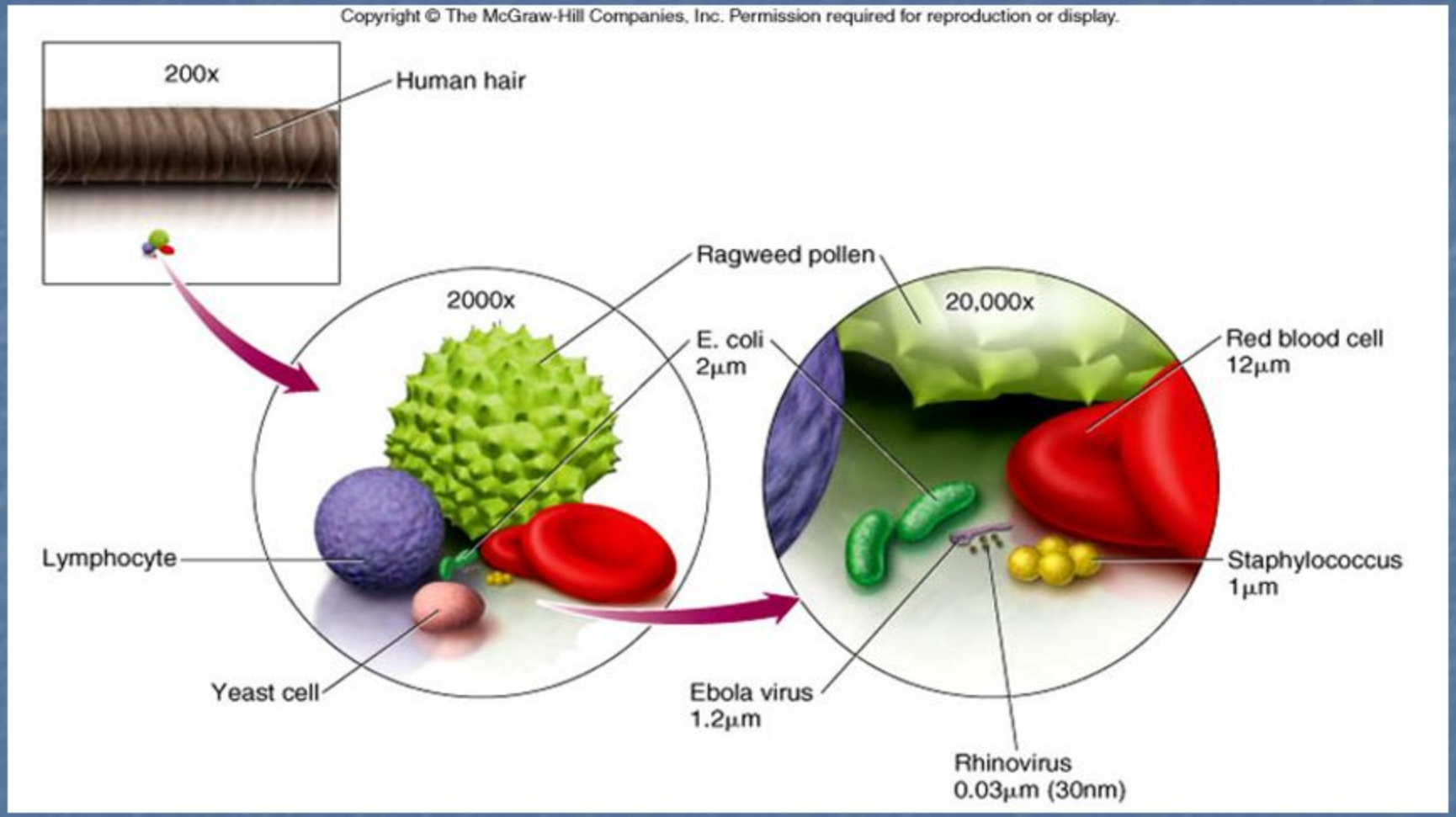


Fig 3. Distribution of cell number and mass for different cell types in the human body (for a 70 kg adult man). The upper bar displays the number of cells, while the lower bar displays the contribution from each of the main cell types comprising the overall cellular body mass (not including extracellular mass that adds another ≈24 kg). For comparison, the contribution of bacteria is shown on the right, amounting to only 0.2 kg, which is about 0.3% of the body weight.

Wang Z, Ying Z, Bosy-Westphal A, Zhang J, Schautz B, Later W, Heymsfield SB, et al. Specific metabolic rates of major organs and tissues across adulthood: evaluation by mechanistic model of resting energy expenditure. Am J Clin Nutr. 2010;92(6):1369-77.

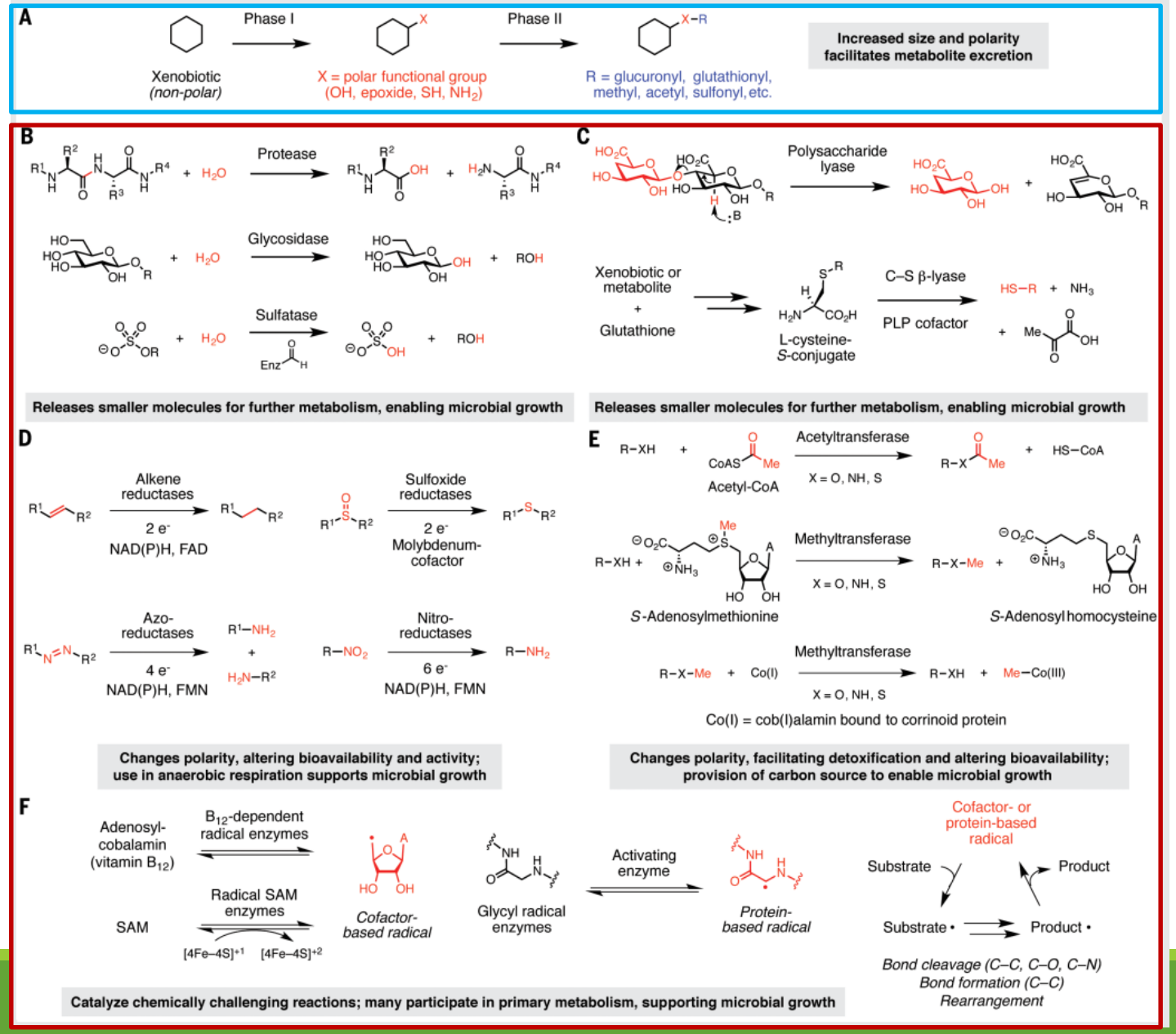
Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol. 2016;14(8):e1002533.

The Dimension of Bacteria



Relative size of a bacterial cell compared to other cells including viruses.

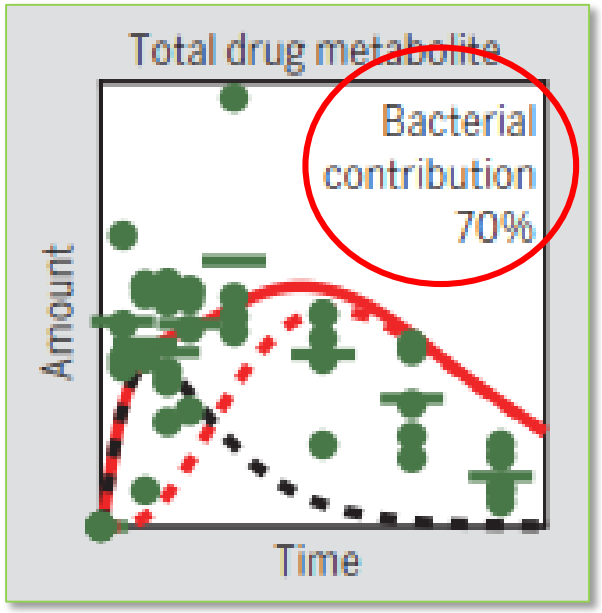
Box 1. The chemistry of gut microbial and host xenobiotic metabolism. (**A**) Chemical logic of host xenobiotic metabolism. Commonly used chemical strategies for microbial xenobiotic metabolism include (**B**) hydrolytic transformations, (**C**) lyase reactions, (**D**) reductive transformations, (**E**) functional group transfer reactions, and (**F**) transformations mediated by radical enzymes. Enz, enzyme; PLP, pyridoxal 5-phosphate; NAD(P)H, NADH or NADPH; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; Me, methyl; CoA, coenzyme A; SAM, *S*-adenosylmethionine.



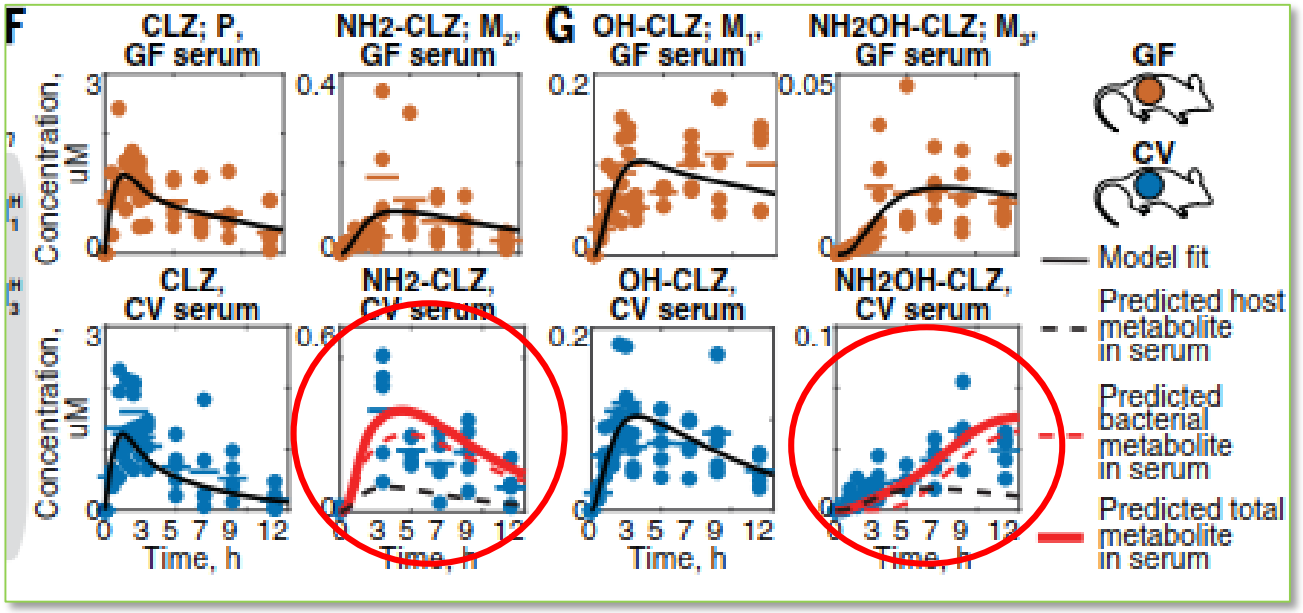
Koppel N, Maini Rekdal V, Balskus EP. Chemical transformation of xenobiotics by the human gut microbiota. Science. 2017;356(6344).

Metabolisme: Contribució microbiota

Brivudine



Clonazepam i els seus metabòlits: 78 % i 66 %



Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Separating host and microbiome contributions to drug pharmacokinetics and toxicity. Science. 2019;363(6427):eaat9931.

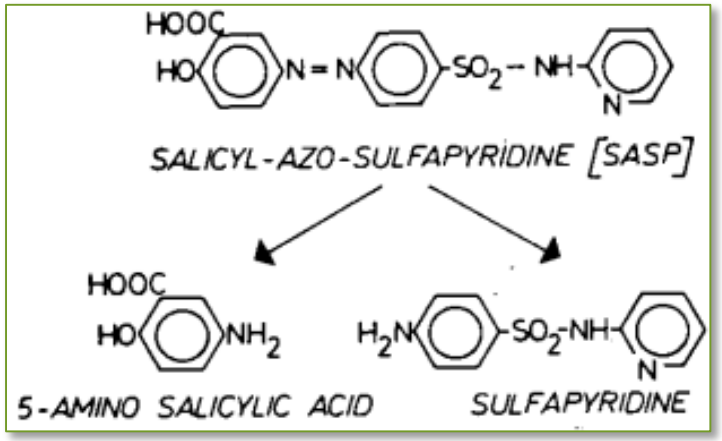
Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

Sulfasalazina

Absorption, metabolism, and excretion of salicylazosulfapyridine in man

Salicylazosulfapyridine (SASP), 4 Gm. daily, was ingested by 9 healthy subjects for 10 days, and the serum concentrations and urinary and fecal excretion of the parent drug and its metabolites were studied. SASP is extensively metabolized by reductive cleavage of the azo linkage, presumably by the action of the gut flora. The sulfapyridine moiety thus formed is subject to N^4-acetylation or ring hydroxylation followed by conjugation to glucuronic acid,



Schroder H, Campbell DE. Absorption, metabolism, and excretion of salicylazosulfapyridine in man. Clin Pharmacol Ther. 1972;13(4):539-51.

Digoxina

DIGOXINA

Digoxin-Inactivating Bacteria: Identification in Human Gut Flora

Abstract. *Digoxin, the most widely used cardiac glycoside, undergoes significant metabolic conversion in many patients to cardioinactive metabolites in which the lactone ring is reduced. This appears to occur within the gastrointestinal tract. An attempt was made to isolate and identify the organisms capable of reducing digoxin from stool cultures obtained from human volunteers. Of hundreds of isolates studied, only Eubacterium lentum, a common anaerobe of the human colonic flora, converted digoxin to reduced derivatives. Such organisms were also isolated in high concentrations from the stools of individuals who did not excrete these metabolites*

Eubacterium lentum = Eggerthella lenta

Saha JR, Butler VP, Jr., Neu HC, Lindenbaum J. Digoxin-inactivating bacteri: identification in human gut flora. Science. 1983;220(4594):325-7.

CORTICOIDES

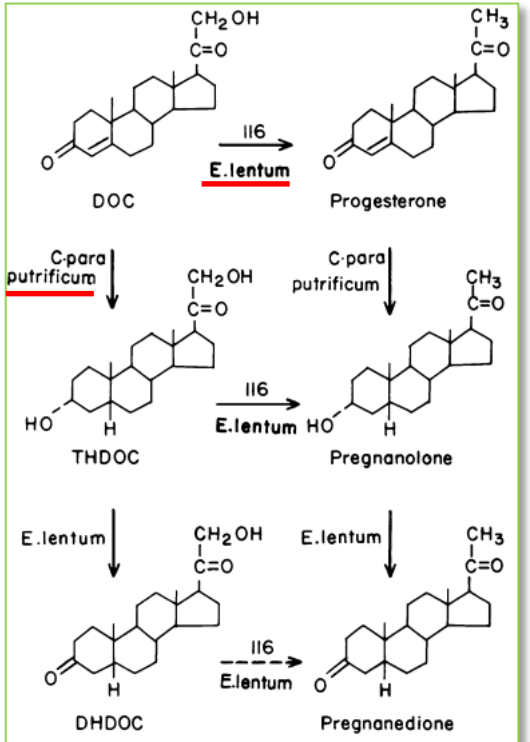


FIG. 1. *Transformation of C_{21} steroids by cultures of C. paraputrificum and E. lentum and culture 116.*

Bokkenheuser VD, Winter J, Dehazya P, Kelly WG. Isolation and characterization of human fecal bacteri capable of 21-dehydroxylating corticoids. Appl Environ Microbiol. 1977;34(5):571-5.

Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

QT

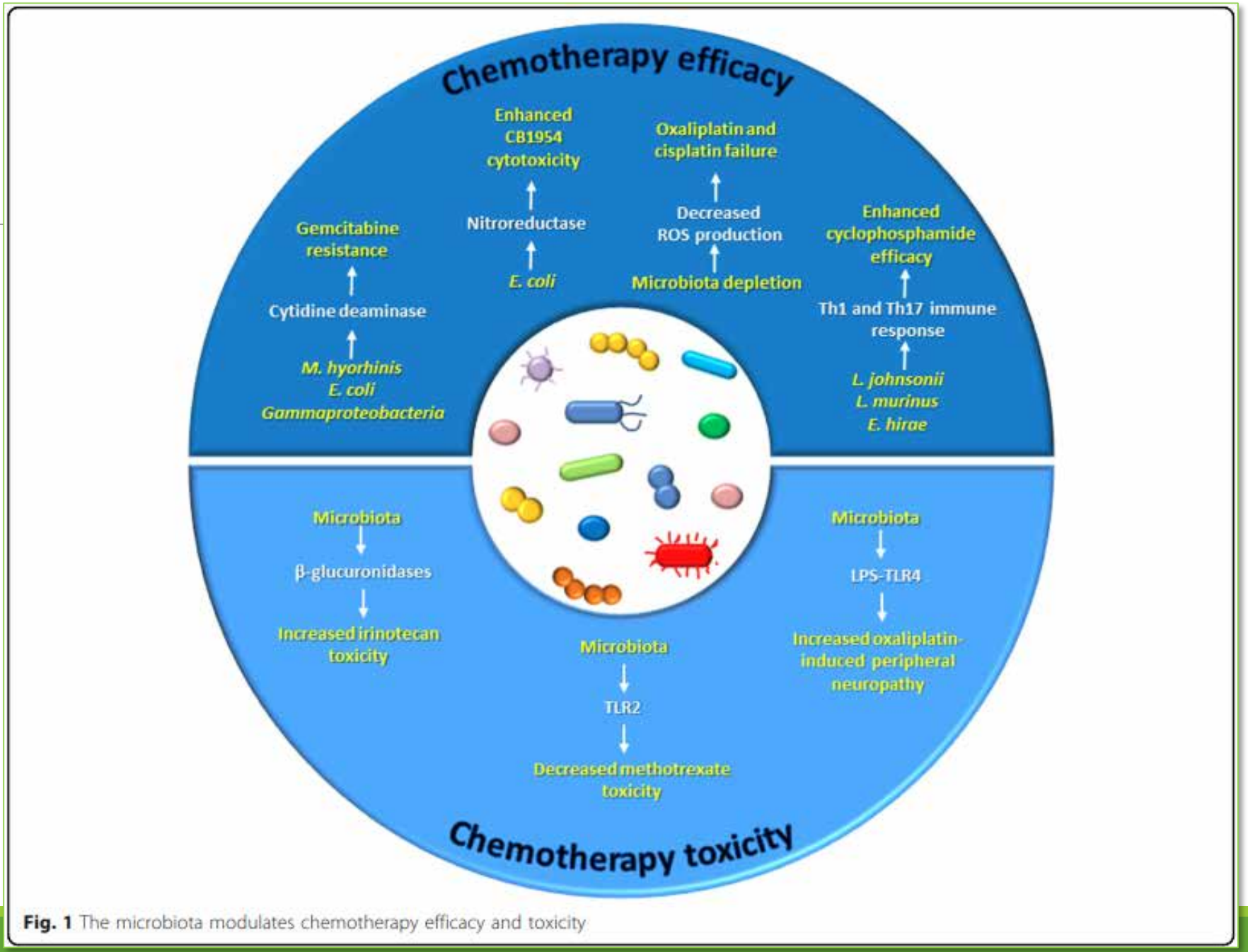
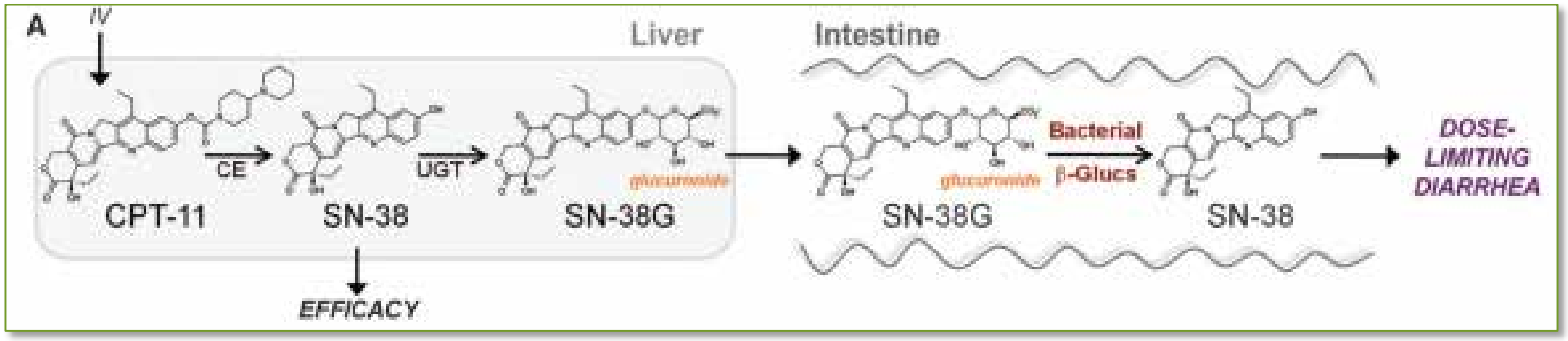


Fig. 1 The microbiota modulates chemotherapy efficacy and toxicity

Panebianco C, Andriulli A, Pazienza V. Pharmacomicrobiomics: exploiting the drug-microbiota interactions in anticancer therapies. Microbiome. 2018;6(1):92.

Irinotecan (CPT-11)



Profàrmac amb greu diarrea com efecte advers limitant

1. Activació hepàtica per carboxilesterases a **SN-38**
2. Posterior glucuronidació hepàtica per la UDP-GT a **SN-38G**
3. Excreció biliar
4. Acció beta-glucuronidasa bacteriana intestinal a **SN-38**

Wallace BD, Wang H, Lane KT, Scott JE, Orans J, Koo JS, Venkatesh M, et al. Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. Science. 2010;330(6005):831-5.

Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina
  - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

Diclofenac

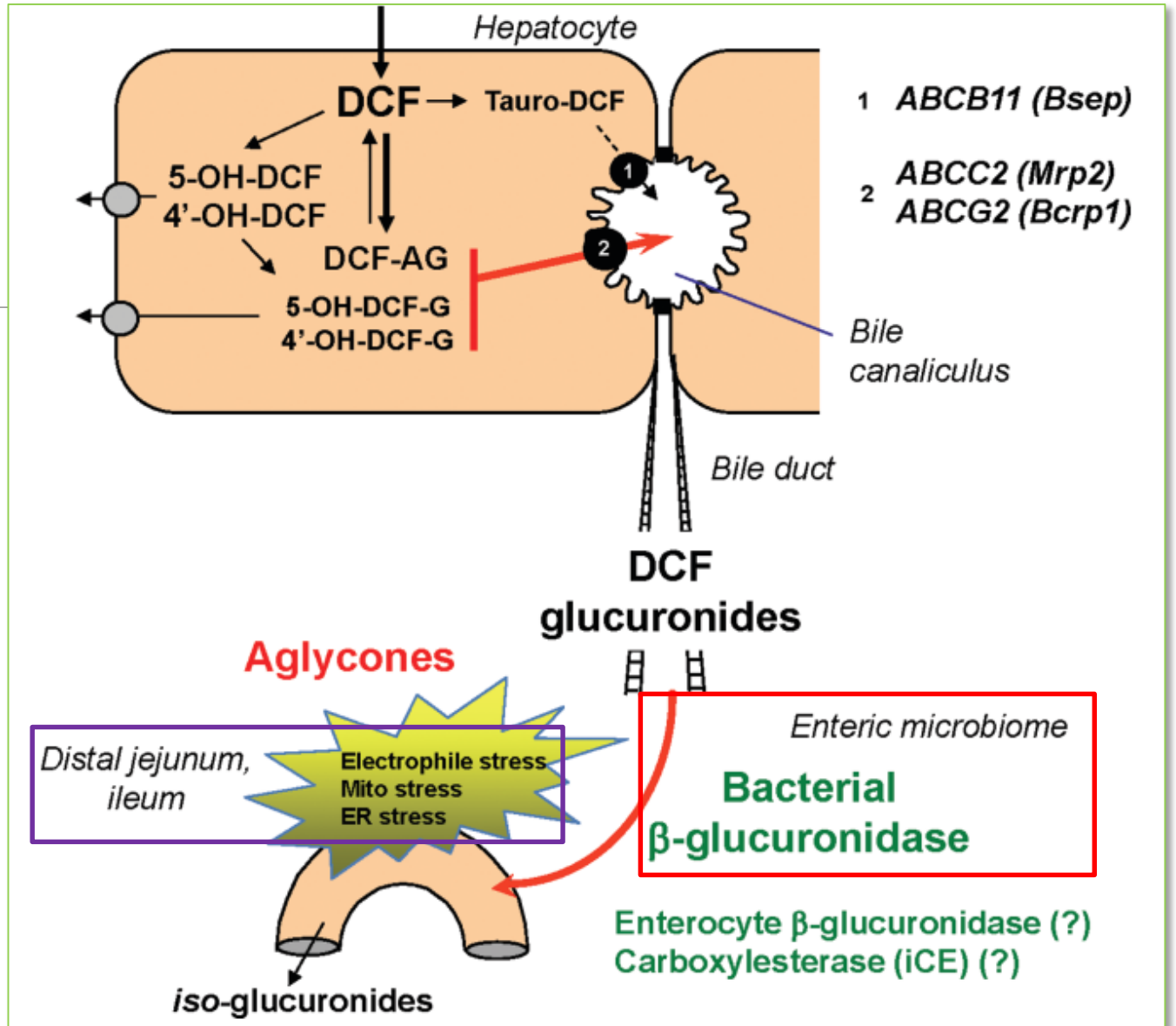


FIG. 2. Hepatic glucuronoconjugation of diclofenac (DCF), biliary export of glucuronides, and site-selective jejunal hydrolysis of glucuronides by bacterial β-glucuronidase. The local release of the aglycones causes electrophile stress and ER/mitochondrial stress. AG, acyl glucuronide; G, ether glucuronide.

Boelsterli UA, Redinbo MR, Saitta KS. Multiple NSAID-induced hits injure the small intestine: underlying mechanisms and novel strategies. Toxicological sciences : an official journal of the Society of Toxicology. 2013;131(2):654-67.

Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina
  - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

Paracetamol

P-CRESOL

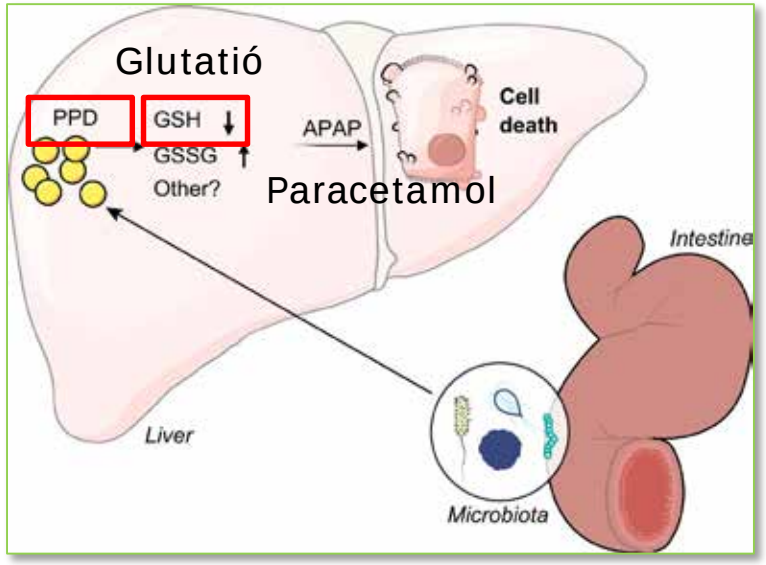
Pacients amb microbiota produint alts nivells de p-cresol a partir de tirosina en les proteïnes de la dieta:

- Disminució de sulfonació humana de paracetamol (depleció GSH)

- **Augment toxicitat**

Clayton TA, Baker D, Lindon JC, Everett JR, Nicholson JK. Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism. Proceedings of the National Academy of Sciences. 2009;106(34):14728.

1-PHENYL-1,2-PROPANEDIONE (PPD)



Gong S, Lan T, Zeng L, Luo H, Yang X, Li N, Chen X, et al. Gut microbiota mediates diurnal variation of acetaminophen induced acute liver injury in mice. Journal of Hepatology. 2018;69(1):51-9.

Índex

- Que fan els fàrmacs a la microbiota?
  - Antibiòtics
  - NO antibiòtics
  - Antineoplàstics
  - Altres: IBP / Morfina
  - Polifarmàcia
  - Metformina / ADOs
  - Futurs estudis
- Que fa la microbiota als fàrmacs?
  - Metabolisme
  - Sulfasalazina
  - Digoxina – Corticoides
  - QT: Irinotecan
  - Diclofenac
  - Paracetamol
- La microbiota com a fàrmac
  - Inhibidors de beta-glucuronidases
  - Substancies bioactives
  - Antibiòtics
  - Terapèutica antineoplàstica

Inhibidors de beta-glucuronidases de la microbiota

Fàrmacs d'investigació:

- Inhibitor 1: 1-((6,8-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-(4-ethoxyphenyl)-1-(2-hydroxyethyl)tiourea
- Amoxapina i derivats (Antidepressiu tricíclic)
  - 7-Hydroxyamoxapina
  - 8-Hydroxyamoxapina
- Fenelzina (IMAO)
- Isocarboxazida (IMAO)
- Nialamida (IMAO)
- Loxapina (Antipsicòtic)
- Mefloquina (Antipalúdic)

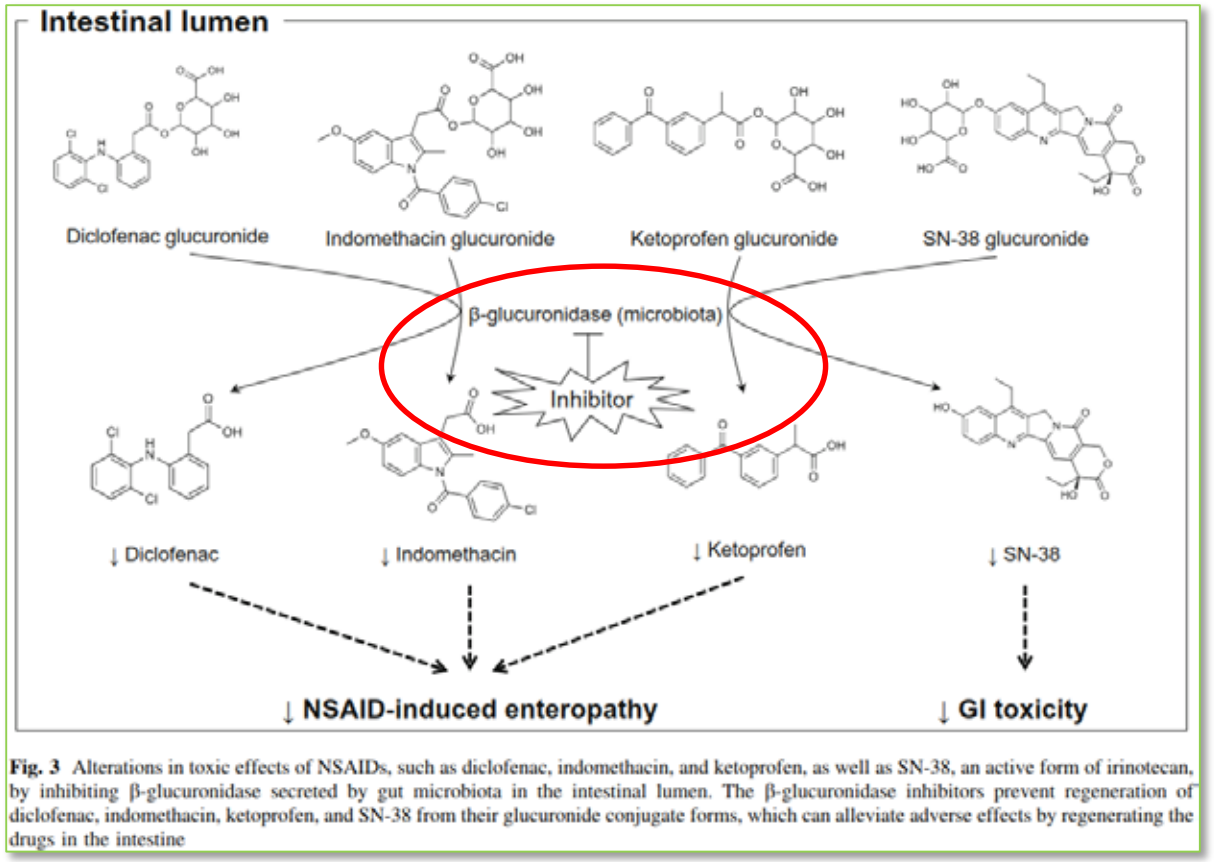


Fig. 3 Alterations in toxic effects of NSAIDs, such as diclofenac, indomethacin, and ketoprofen, as well as SN-38, an active form of irinotecan, by inhibiting β-glucuronidase secreted by gut microbiota in the intestinal lumen. The β-glucuronidase inhibitors prevent regeneration of diclofenac, indomethacin, ketoprofen, and SN-38 from their glucuronide conjugate forms, which can alleviate adverse effects by regenerating the drugs in the intestine

Noh K, Kang YR, Nepal MR, Shakya R, Kang MJ, Kang W, Lee S, et al. Impact of gut microbiota on drug metabolism: an update for safe and effective use of drugs. Arch Pharm Res. 2017;40(12):1345-55.

Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Transl Res. 2017;179:204-22.

Substancies bioactives

Font de substancies bioactives (interacció microbi-hoste i microbi- microbi):

- Reguladors inmunitaris a través G-protein-coupled receptors (GPCRs):
  - Commendamida
  - N-Acylamides i N-Acylserinols
- Antibiòtics:
  - Tiopepetids: Lactocil·lina
  - Humimicines
  - Lugdunin
- Altres substancies amb efectes desconeguts:
  - Pirazinones i dihidropirazinones
  - Derivats de aminoàcids aromàtics
  - Derivats de ac. Piroglutàmic

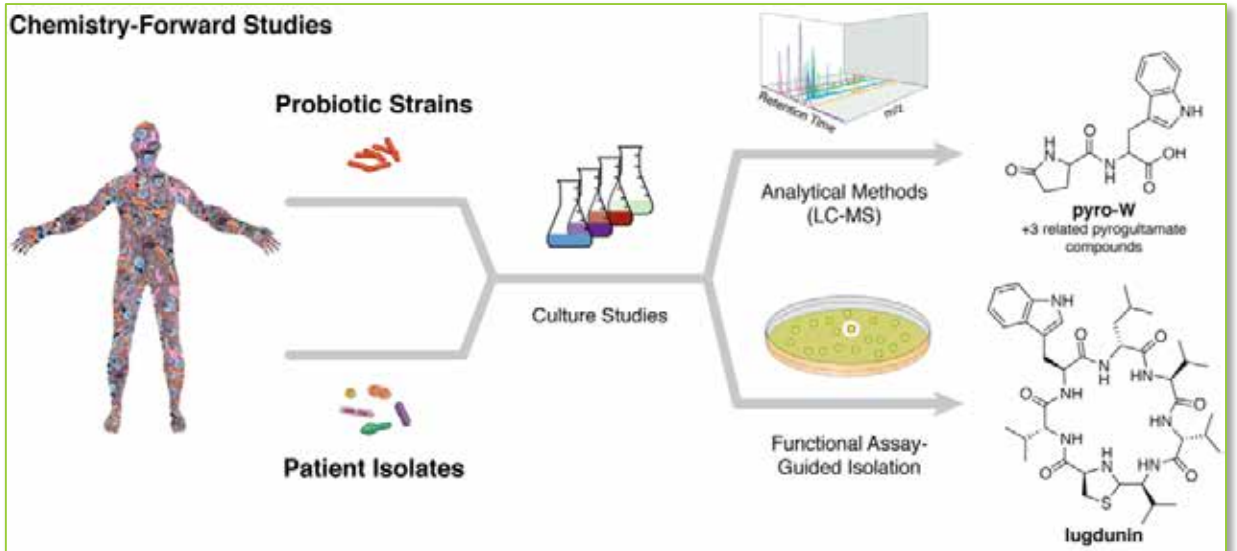


Figure 4. Chemistry-Forward Discovery Workflow
Traditional, chemistry-forward approaches do not rely on biosynthetic gene sequence information but instead use analytical techniques (e.g., pyroglutamate-containing compounds) or functional assays (e.g., lugdunin) to identify metabolites of interest from bacterial strains after laboratory cultivation.

Milshteyn A, Colosimo DA, Brady SF. Accessing Bioactive Natural Products from the Human Microbiome. Cell Host Microbe. 2018;23(6):725-36.

Nous antibiòtics

Antibiòtics produïts per la microbiota contra patògens a diferents nínxols:

- Aurachin
- Epidermina
- Heterobactins
- Humimicins A i B
- Inhibidors síntesis d'aureusimines
- Lactocill·ina
- Lugdunin
- Mutanobactins i mutanamida
- Piro-dipeptids
- Reutericiclina
- Salivaricin

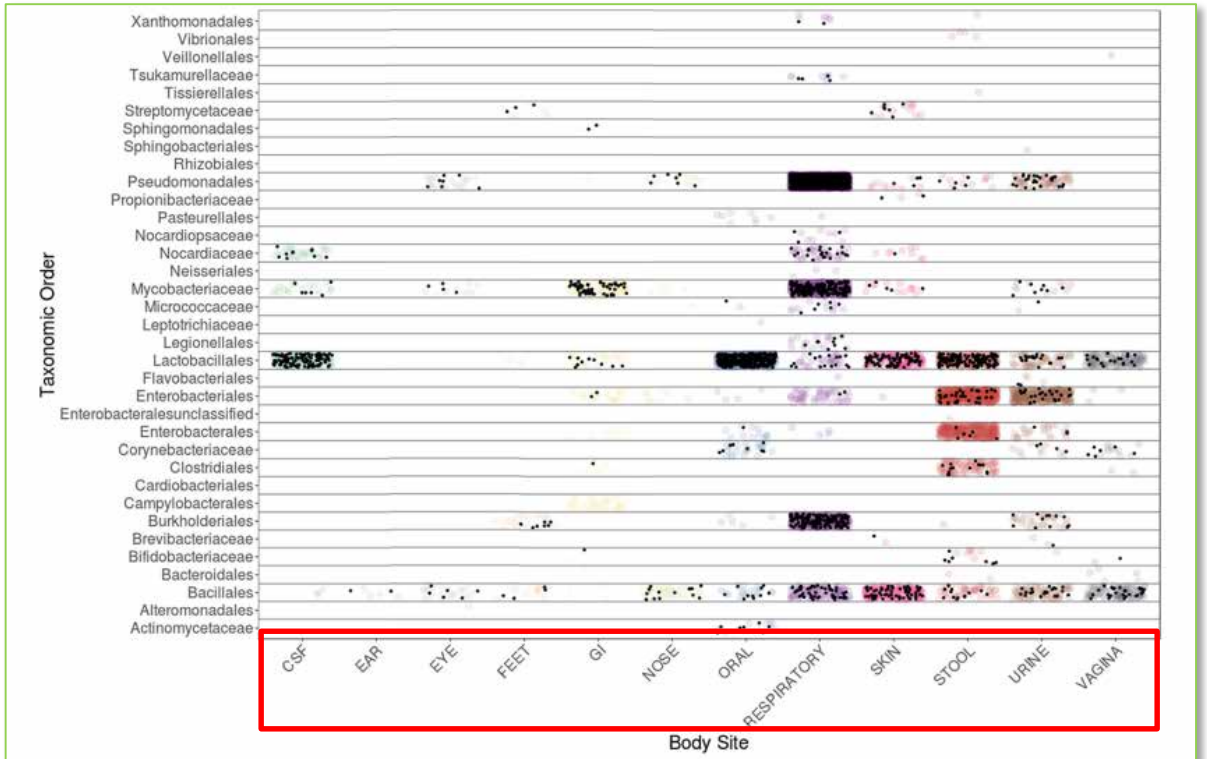


Fig. 10 Distribution of antibiotic-producing taxa over distinct body sites. Points represent biosynthetic clusters predicted from genomes of microbes isolated from human samples (based on NCBI annotation), where black points denote biosynthetic clusters (as predicted by PRISM) with structural similarity to known antimicrobial compounds.

Mousa WK, Athar B, Merwin NJ, Magarvey NA. Antibiòtics and specialized metabolites from the human microbiota. Nat Prod Rep. 2017;34(11):1302-31.

Terapèutica antineoplàstica

Relació complexa

Fase d'investigació incipient

Rol en milloria de resultats de la teràpia antineoplàstica:

- Modulació del microbioma à Modulació de la resposta de la teràpia immunitària
- Biomarcador de la resposta a la teràpia antineoplàstica

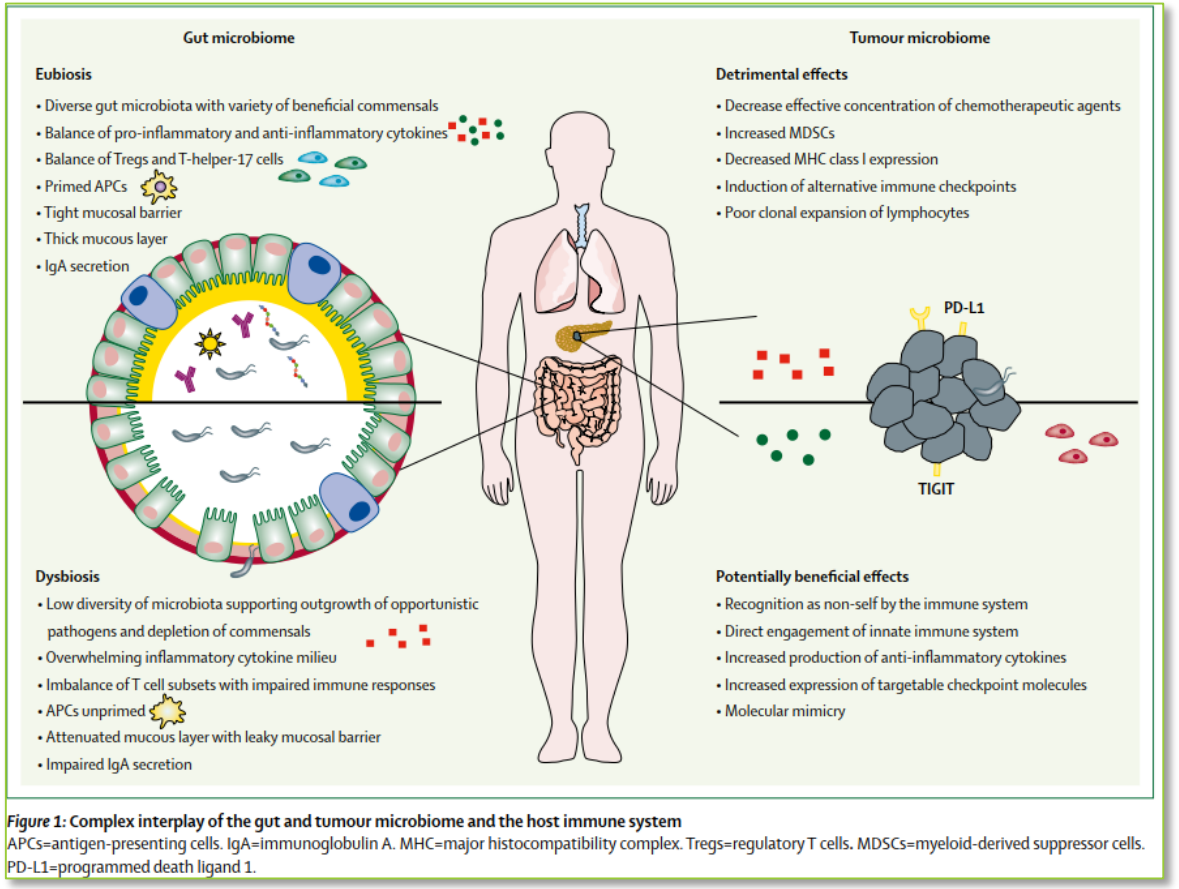


Figure 1: **Complex interplay of the gut and tumour microbiome and the host immune system**
APCs=antigen-presenting cells. IgA=immunoglobulin A. MHC=major histocompatibility complex. Tregs=regulatory T cells. MDSCs=myeloid-derived suppressor cells. PD-L1=programmed death ligand 1.

McQuade JL, Daniel CR, Helmink BA, Wargo JA. Modulating the microbiome to improve therapeutic response in cancer. Lancet Oncol. 2019;20(2):e77-e91.

Gracies per l'atenció!!

GNFHC