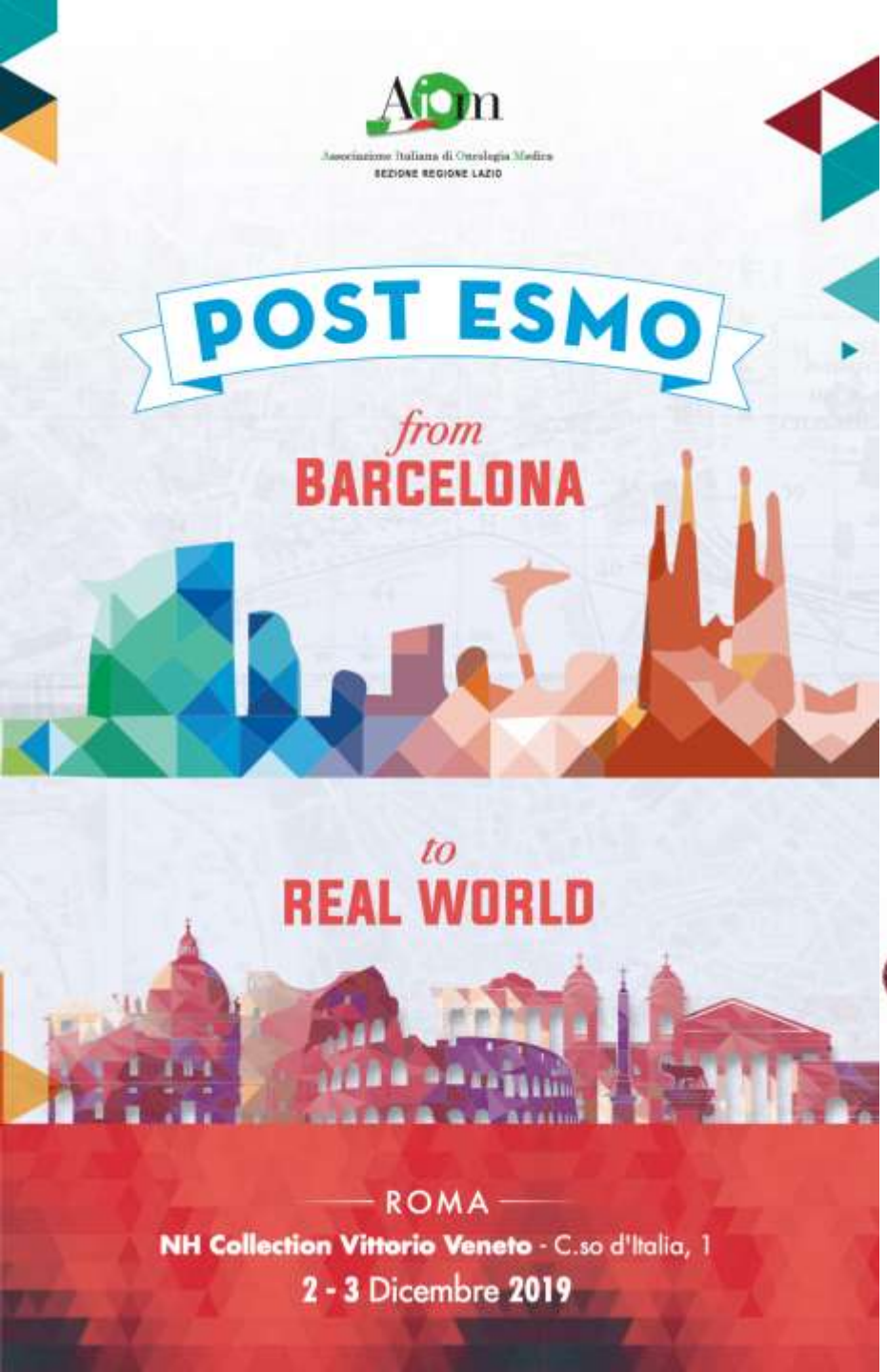


Microbioma
da ospite ad alleato

DIPARTIMENTO DI MEDICINA CLINICA E MOLECOLARE
SAPIENZA UNIVERSITÀ DI ROMA

Paolo Marchetti
paolo.marchetti@uniroma1.it

Di cosa parleremo...

- Within the human body, it is estimated that there are 10x as many microorganisms (10^{14}) as human cells.
  - Our microorganism partners carry out a number of metabolic reactions that are **not encoded** in the human genome and are **necessary** for human health.
- Therefore when we talk about the "human genome" we should think of it as an amalgam of human genes and those of our microorganisms.

S Roy, G Trinchieri, Nature Reviews | Cancer Vol 17, may 2017, 271

Microbiota

- The composition of the microbiota is shaped by host genetics, colonization at the time of birth, type of birth delivery, an individual's lifestyle, incidence of diseases and exposure to antibiotics.

S Roy, G Trinchieri, Nature Reviews | Cancer Vol 17, may 2017, 271

Microbiota

- Microbiota composition evolves during the first few years of human life before maturation into an adult-like microbiota.
- After that, the composition of the microbiota in the gut and other epithelial barriers remains relatively constant throughout adult life, although it could still be affected by diet, changes in lifestyle, disease and disease treatment

S Roy, G Trinchieri, Nature Reviews | Cancer Vol 17, may 2017, 271

Microbiota or Microbioma?

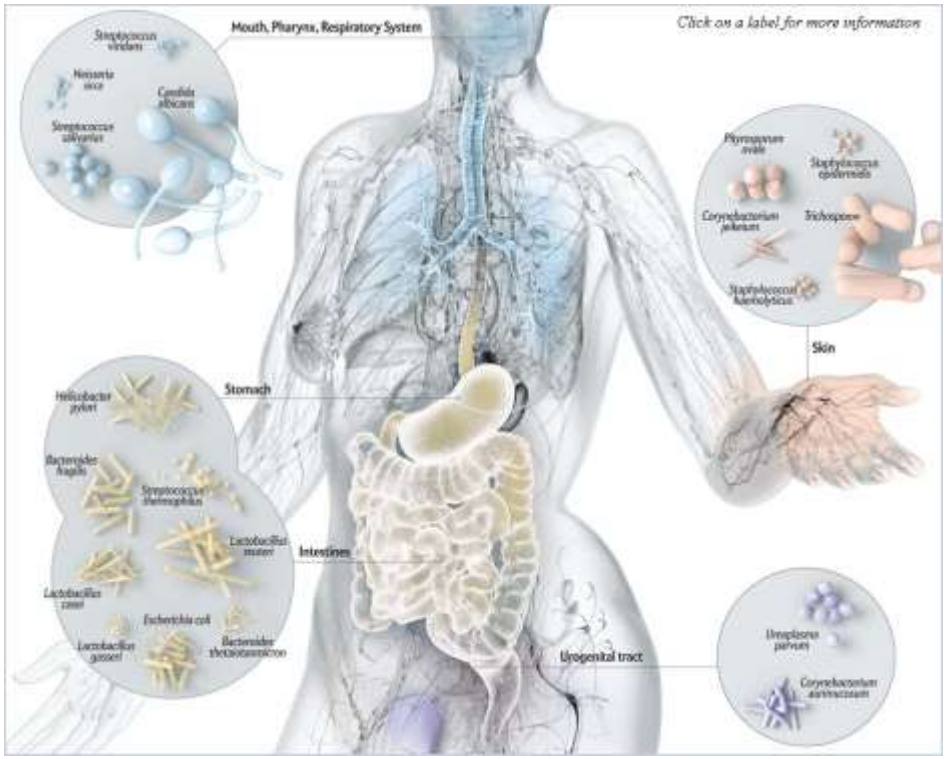
- The terms microbiota and microbiome are often used as synonyms, but express two different meanings:
  - the microbiota refers to the totality of microbes (bacteria, archaea, fungi, viruses and protozoa) in a particular environment, in other words, it refers to taxonomy and abundance of community members,
  - the microbiome is the totality of genomes of a microbiota and it is often used to describe the entity of microbial traits (functions) encoded by a microbiota

Mariana F. Fernández et al., Int. J. Environ. Res. Public Health 2018, 15, 1747

Where is Microbiota?

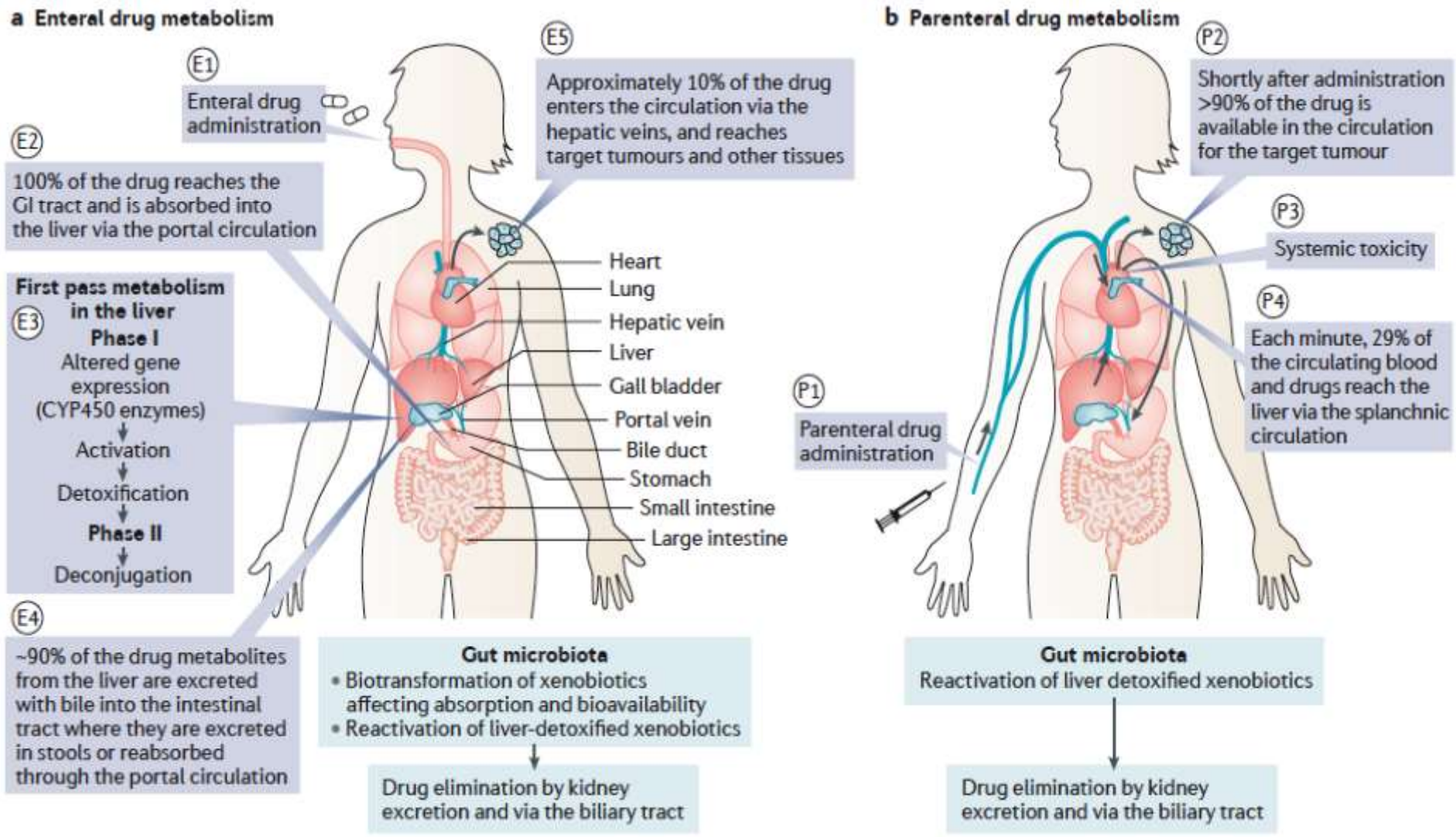
The human microbiota is the term applied to the universe of microbes that live in different habitats of our body (mostly the gut, skin, vagina and mouth, but also the nose, conjunctiva, pharynx and urethra,breast, among others).

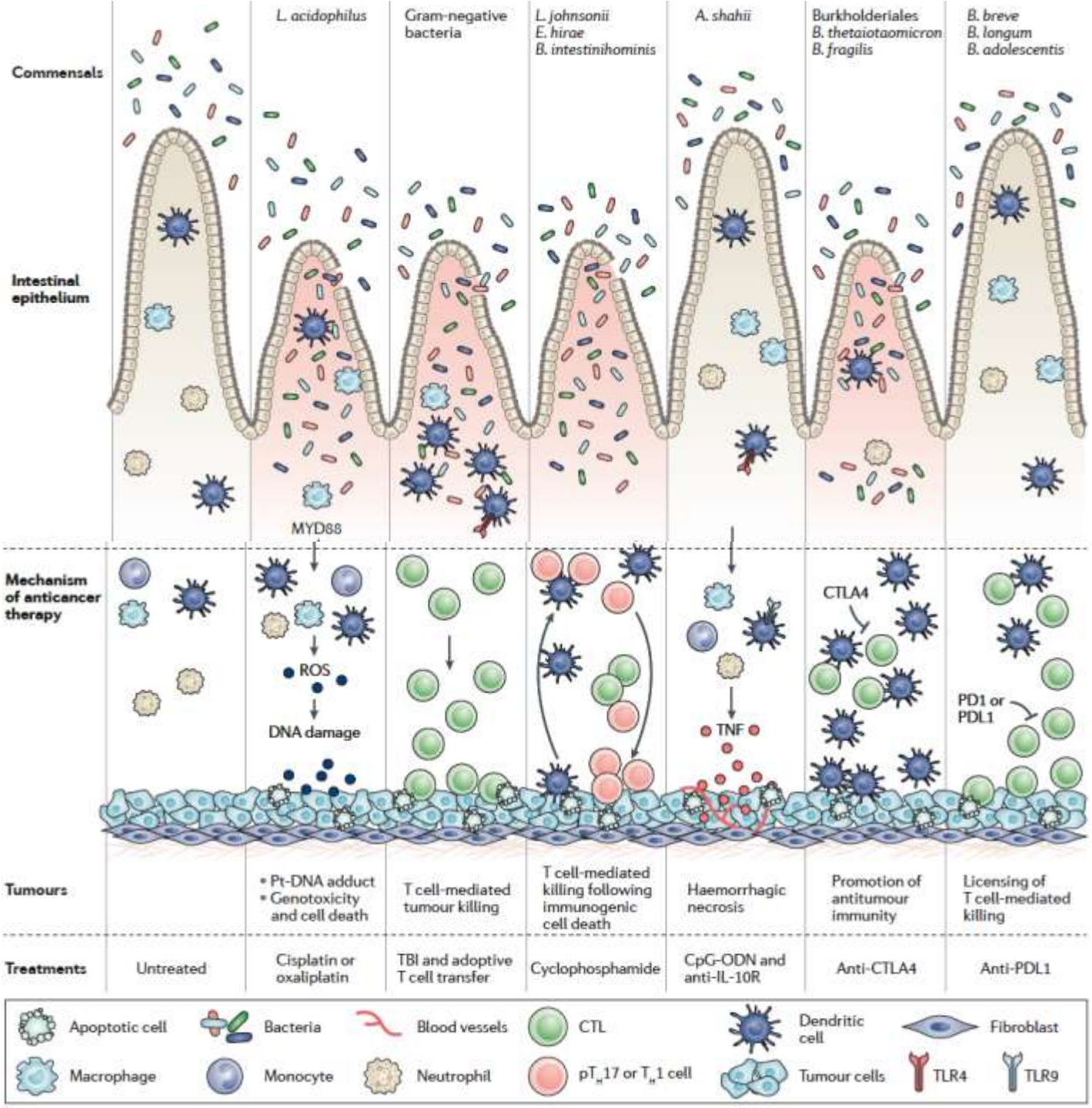
The microbiota of each organ is distinct, and there is an important and functionally relevant inter-individual variability of microbiomes, which makes them a potential determinant of disease (including cancer) development.



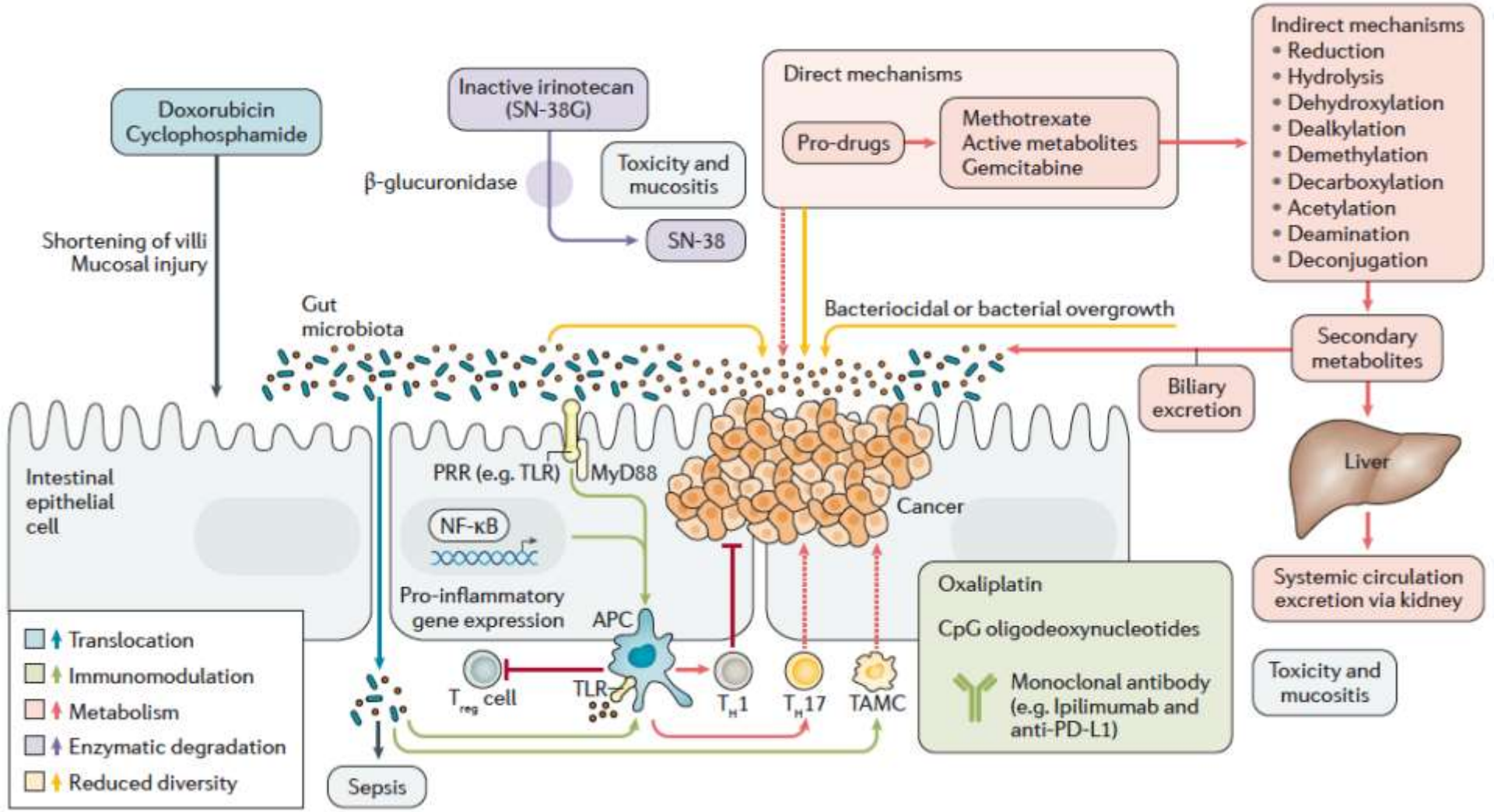
Mariana F. Fernández et al., Int. J. Environ. Res. Public Health 2018, 15, 1747

Major pathways of drug metabolism and the role of microbiota




Commensals
L. acidophilus
Gram-negative bacteria
L. johnsonii
E. hirae
B. intestinihominis
A. shahii
Burkholderiales
B. thetaiotaomicron
B. fragilis
B. breve
B. longum
B. adolescentis
Intestinal epithelium
MYD88
Mechanism of anticancer therapy
ROS
DNA damage
CTLA4
TNF
PD1 or PDL1
Tumours
• Pt-DNA adduct
• Genotoxicity and cell death
T cell-mediated tumour killing
T cell-mediated killing following immunogenic cell death
Haemorrhagic necrosis
Promotion of antitumour immunity
Licensing of T cell-mediated killing
Treatments
Untreated
Cisplatin or oxaliplatin
TBI and adoptive T cell transfer
Cyclophosphamide
CpG-ODN and anti-IL-10R
Anti-CTLA4
Anti-PDL1
Apoptotic cell
Bacteria
Blood vessels
CTL
Dendritic cell
Fibroblast
Macrophage
Monocyte
Neutrophil
pT17 or T1 cell
Tumour cells
TLR4
TLR9

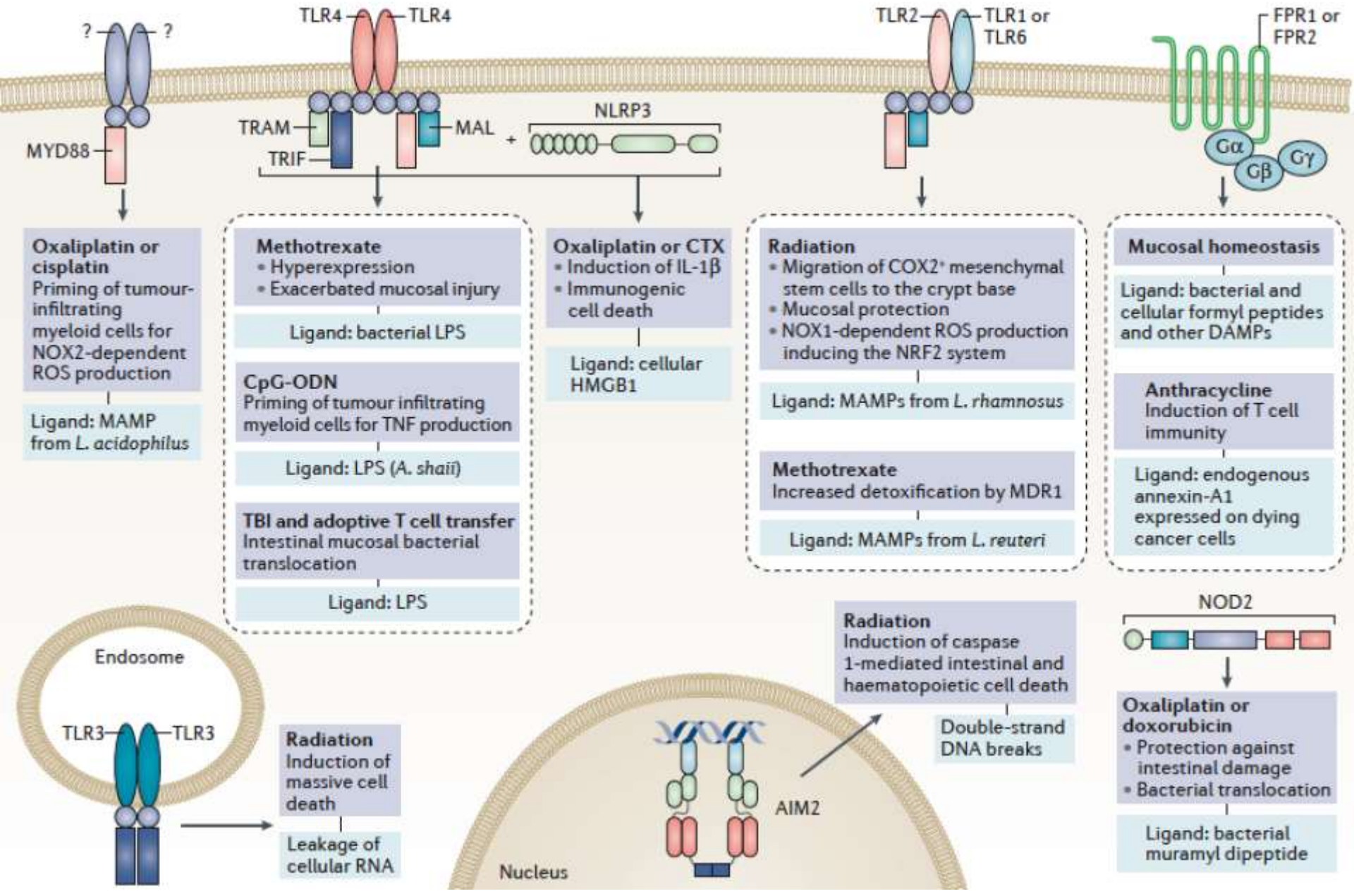
An overview of the microbiota–host interactions that modulate chemotherapy efficacy and toxicity



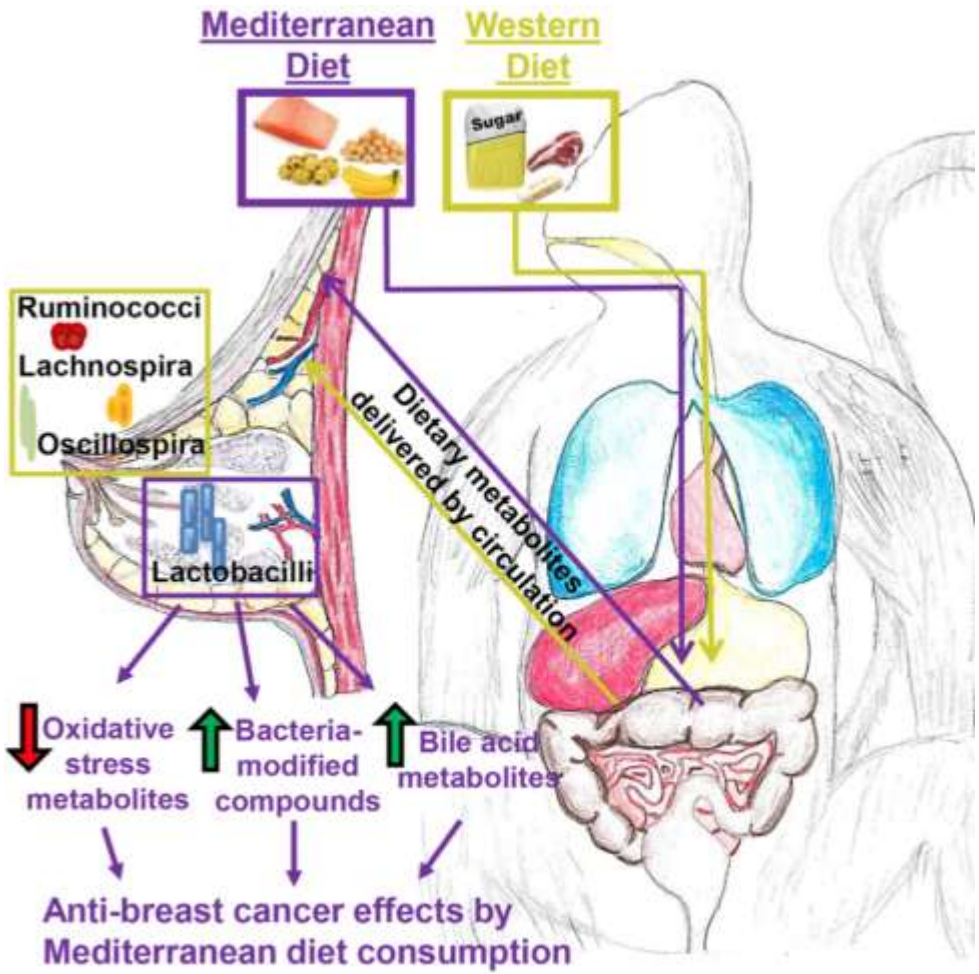
JL Alexander, Nature Reviews | Gastroenterology & Hepatology 14 | 2017 | 357

Microbiota-triggered innate immune receptors

S Roy, G Trinchieri, Nature Reviews | Cancer Vol 17, may 2017, 271



Consumption of Mediterranean versus Western Diet Leads to Distinct Mammary Gland Microbiome Populations



- Diet modulates mammary gland microbiota populations in a non-human primate model
- Consumption of Mediterranean diet elevates mammary gland Lactobacillus abundance
- Mediterranean diet increases breast bile acid and bacterial- modified metabolites
- Consumption of Mediterranean diet decreases reactive oxygen species metabolites

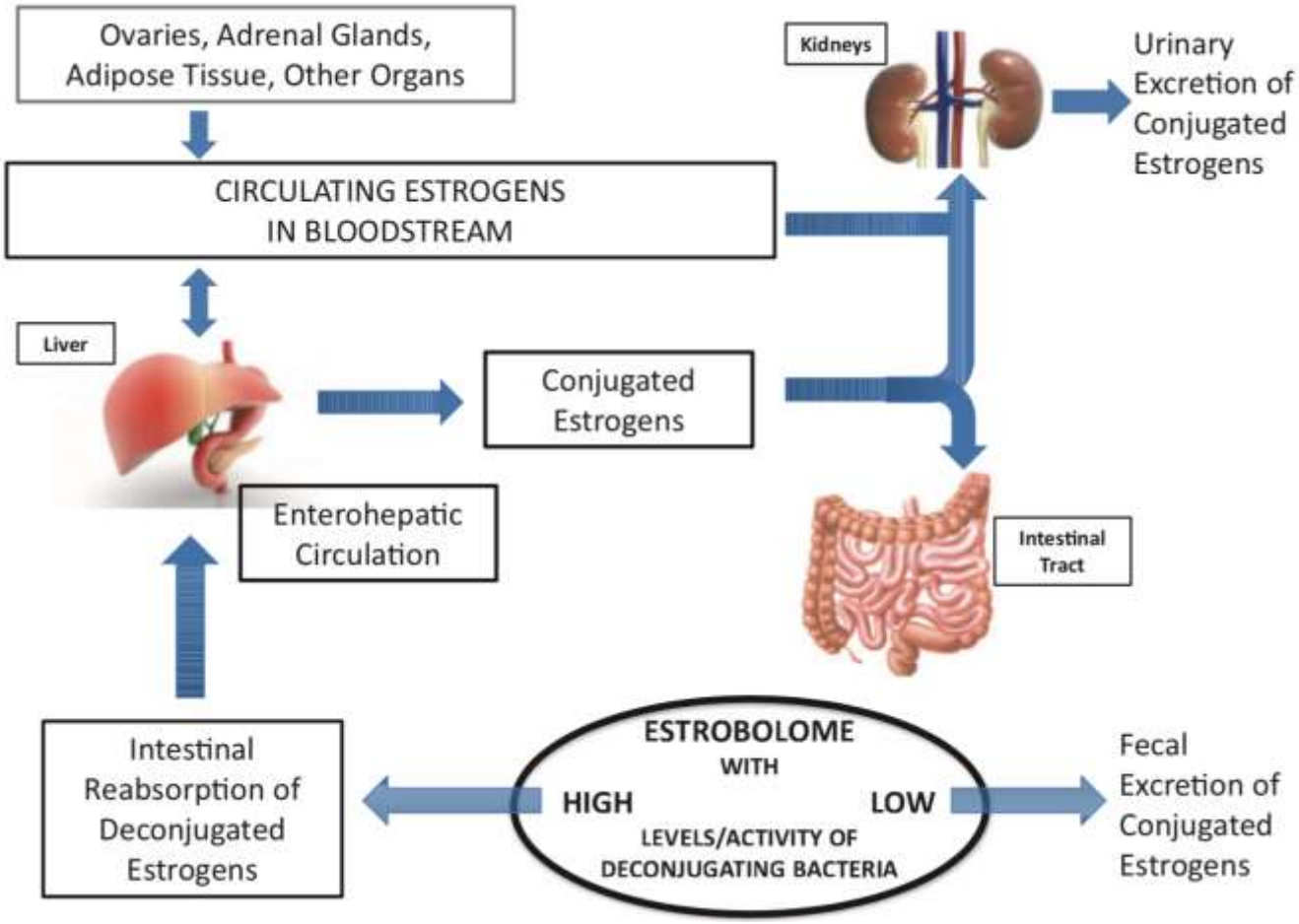
Shively et al., 2018, Cell Reports 25, 47–56 October 2, 2018

Is There a Link between Gut Microbiota and Breast Cancer?

- The studies targeting at the relationship between BC and gut microbiota are quite limited so far.
- The so-called “estrobolome”, the collection of the enteric bacterial genes whose products metabolize estrogen and its metabolites was extensively described.
- Perturbations in the microbiota/estrobolome can therefore lead to elevated levels of circulating estrogens and its metabolites, thereby increasing the risk of BC.

Mariana F. Fernández et al., Int. J. Environ. Res. Public Health 2018, 15, 1747

The estrobolome and enterohepatic circulation of estrogens



M Kwa et al., JNCI J Natl Cancer Inst (2016) 108(8)

Is There a Link between Gut Microbiota and Breast Cancer?

- Microbiota composition
  - Compared with control women, cancer patients had an altered fecal microbiota composition (β-diversity) and a lower α diversity, which was estrogen-independent.
  - Breast microbiome in women with cancer was notably different from the breast microbiome of women with benign disease.
  - The composition and diversity of the gut microbiota were associated with patterns of estrogen metabolism.
  - The triple negative and positive samples showed distinct microbial signature patterns than the ER and HER2 positive breast cancer samples.

M. Mariana F. Fernández et al., Int. J. Environ. Res. Public Health 2018, 15, 1747

Is There a Link between Gut Microbiota and Breast Cancer?

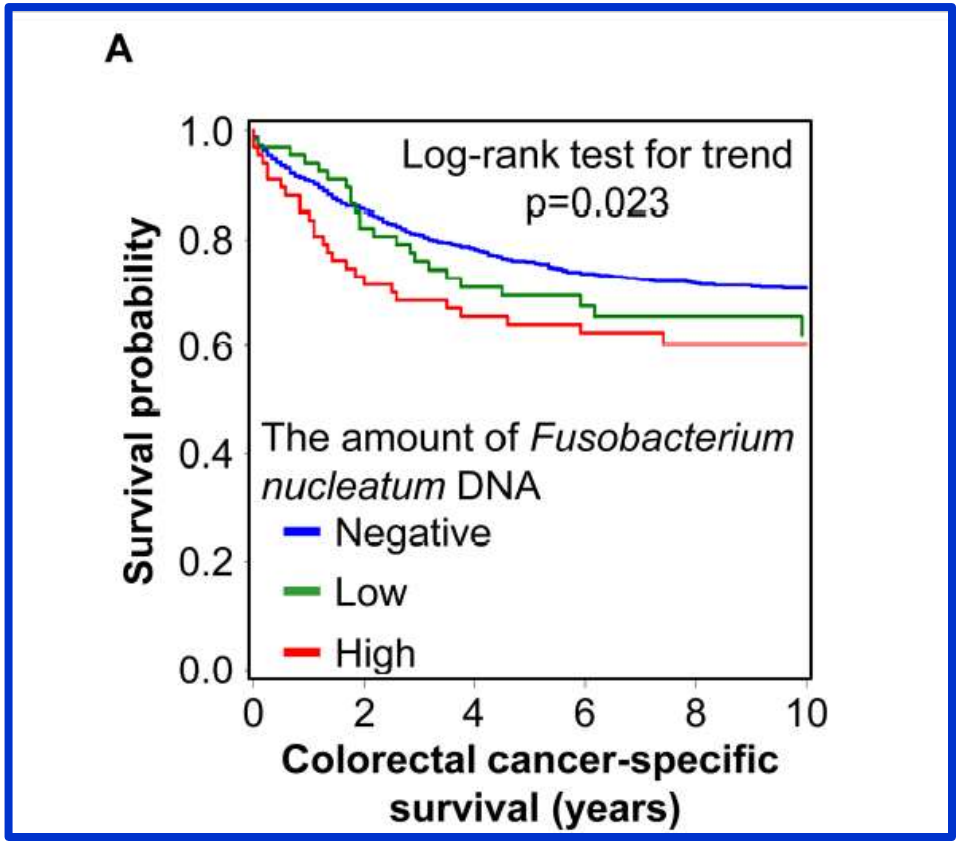
- Functional Pathways
  - Regulation of Chronic Inflammation and Immunity
  - Expression of TILs in patients with BC.
  - Genomic Stability and DNA Damage
  - Metabolic Function

M. Mariana F. Fernández et al., Int. J. Environ. Res. Public Health 2018, 15, 1747

FUSOBACTERIUM AND PROGNOSIS IN mCRC

Published in final edited form as:
Gut. 2016 December ; 65(12): 1973–1980. doi:10.1136/gutjnl-2015-310101.

Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis



Regorafenib

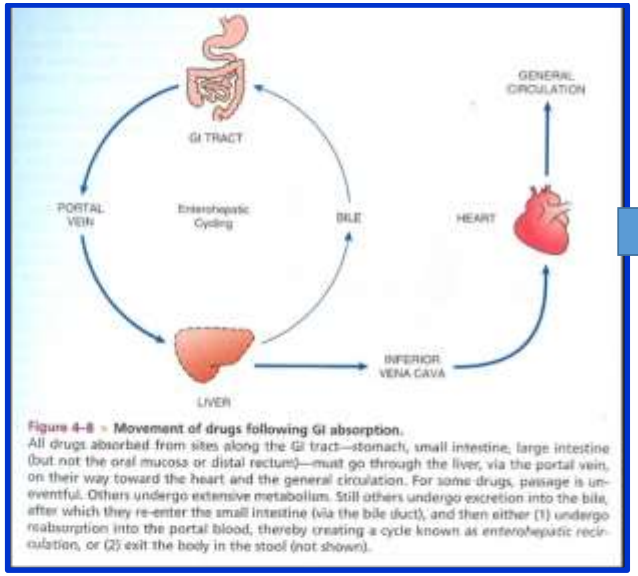
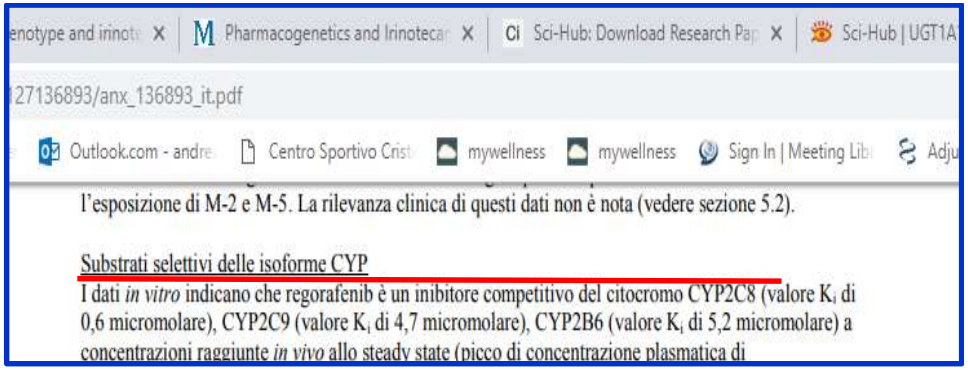


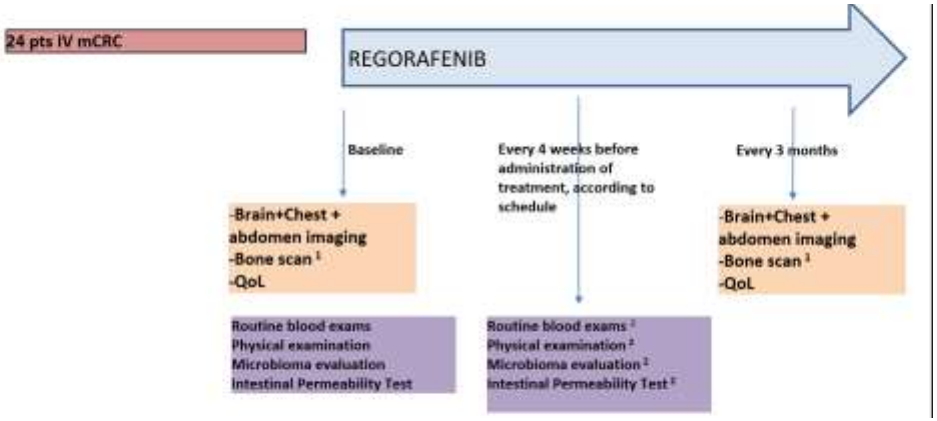
Figure 4–8 • Movement of drugs following GI absorption.
All drugs absorbed from sites along the GI tract—stomach, small intestine, large intestine (but not the oral mucosa or distal rectum)—must go through the liver, via the portal vein, on their way toward the heart and the general circulation. For some drugs, passage is uneventful. Others undergo extensive metabolism. Still others undergo excretion into the bile, after which they re-enter the small intestine (via the bile duct), and then either (1) undergo reabsorption into the portal blood, thereby creating a cycle known as *enterohepatic recirculation*, or (2) exit the body in the stool (not shown).



l'esposizione di M-2 e M-5. La rilevanza clinica di questi dati non è nota (vedere sezione 5.2).

Substrati selettivi delle isoforme CYP

I dati *in vitro* indicano che regorafenib è un inibitore competitivo del citocromo CYP2C8 (valore K_i di 0,6 micromolare), CYP2C9 (valore K_i di 4,7 micromolare), CYP2B6 (valore K_i di 5,2 micromolare) a concentrazioni raggiunte *in vivo* allo steady state (picco di concentrazione plasmatica di



The impact of chemotherapeutic treatment on the oral microbiota of patients with cancer

- During chemotherapeutic treatment, patients with cancer have a higher proportion of gram-negative bacteria of the Enterobacteriaceae family and gram-positive Streptococcus, which can cause different general pathologies (septicemia or localized infections) at the level of the oral cavity (e.g., acute oral infections, oral mucositis).

Kelly Rocio Vargas Villafuerte et a., Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:552–566

Ipilimumab

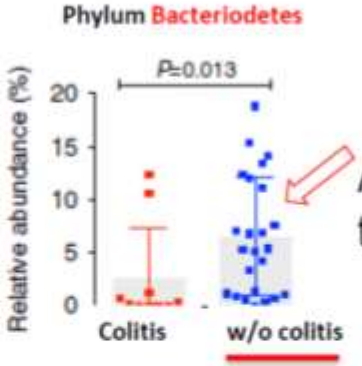
BASELINE MICROBIOTA COMPOSITION IS ASSOCIATED TO IPILIMUMAB-INDUCED COLITIS IN MM PATIENTS IN INDEPENDENT COHORTS

nature COMMUNICATIONS

Dubin et al. 2016

ARTICLE

Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis

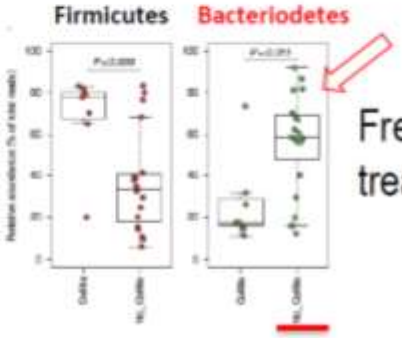


American MM patients treated with ipilimumab

ESMO

ORIGINAL ARTICLE

Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab



French MM patients treated with ipilimumab

A Comparison of the Gut Microbiome Between Long-term Users and Non-users of Proton Pump Inhibitors

- Long-term PPIs use has an effect on the gut microbiome.
- Proton pump inhibitor (PPI) use is associated with an increased risk of Clostridium difficile infection, though the mechanism is unclear.

BEYOND MICROBIOME …

nature genetics

LETTERS

The fecal metabolome as a functional readout of the gut microbiome

NEOPLASIA

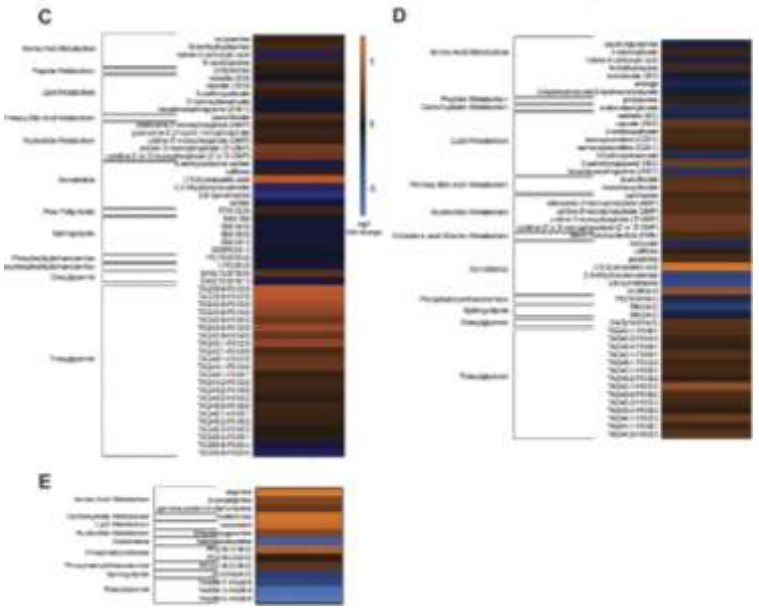
Volume 19 Number 10 October 2017 pp. 848–855

Metagenomic Shotgun Sequencing and Unbiased Metabolomic Profiling Identify Specific Human Gut Microbiota and Metabolites Associated with Immune Checkpoint Therapy Efficacy in Melanoma Patients

Arthur E. Frankel, Laura A. Coughlin, Jiwoong Kim, Thomas W. Froehlich, Yang Xie, Eugene P. Frenkel and Andrew Y. Koh

…The fecal metabolome provides a functional readout of microbial activity and can be used as an intermediate….

phenotype mediating host–microbiome interactions…

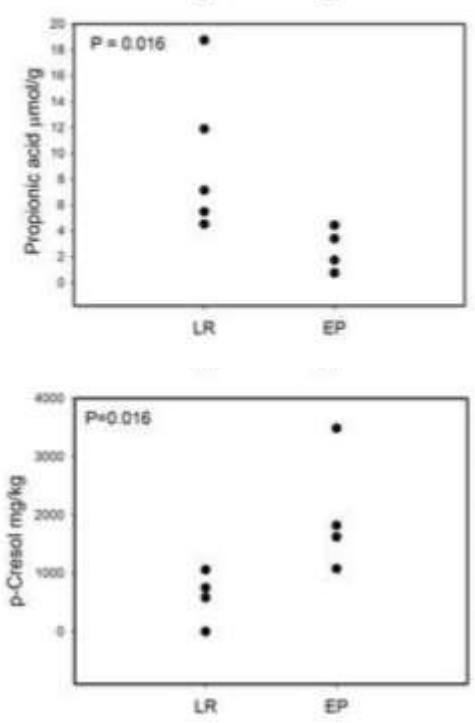


Gut metabolomics profiling of NSCLC patients under immunotherapy treatment

Botticelli A. … Marchetti P. e al. submitted

HIGH ALCOHOLS,ESTERS AND PHENOLS:
Associated with ***fast progressor***

ORGANIC ACID AND SHORT CHAIN FATTY ACIDS:
Associated with ***long term benefit***



Abstract

» Background

Although immunotherapy with immune checkpoint inhibitors (ICIs) has been remarkably effective across multiple cancer types. Several reports showed the gut microbiome is a possible factor proposed to impact the efficacy of ICI. The relationship between gut microbiome and immune status in tumor microenvironment remains unclear. Short-chain fatty acids (SCFAs) are major end products of gut microbiota metabolites and are known to wide-ranging impacts on host physiology. The objective of this study was to evaluate the fecal SCFA (fSCFA) in solid cancer patients treated with anti-programmed death-1 inhibitor (PD1i).

» Methods

This was a prospective study of patients with cancer who were treated with nivolumab (2 mg/kg, every 3 weeks; 3 mg/kg, every 2 weeks; or 240 mg/body, every 2 weeks) or pembrolizumab (200 mg/body, every 3 weeks) at Kyoto University Hospital between July 2016 and April 2018. Patients were classified into two groups: responder (R) with an objective response and non-responder (NR) according to the Response Evaluation Criteria in Solid Tumors version 1.1. Fecal samples were collected before administration of PD-1 inhibitor and were analyzed by the ultra-high performance liquid chromatography-tandem mass spectrometry system.

» Results

A total of 40 patients (melanoma 19; head and neck cancer 7; gastrointestinal cancer 7; genitourinary cancer 4; other 3) were enrolled. The response rate was 22.5%. The fSCFAs in R patients (n = 9) were significantly higher than that in NR patients (n = 31) ($p < 0.001$). Progression-free survival (PFS) was significantly longer in patients with high fSCFAs than patients with lower fSCFAs (median 5.5 vs. 1.4 months, hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.17-0.72). In melanoma patients, PFS was also significantly longer in patients with high fSCFAs than that with lower fSCFAs (median 6.1 vs. 1.4 months, HR 0.30, 95% CI 0.10-0.89).

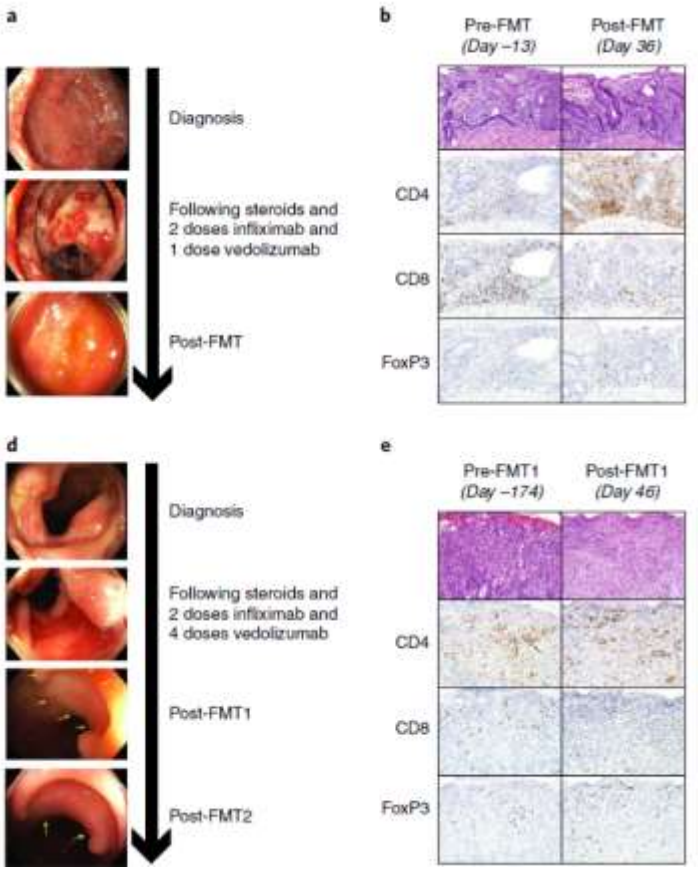
NOVEL FRONTIERS

nature medicine

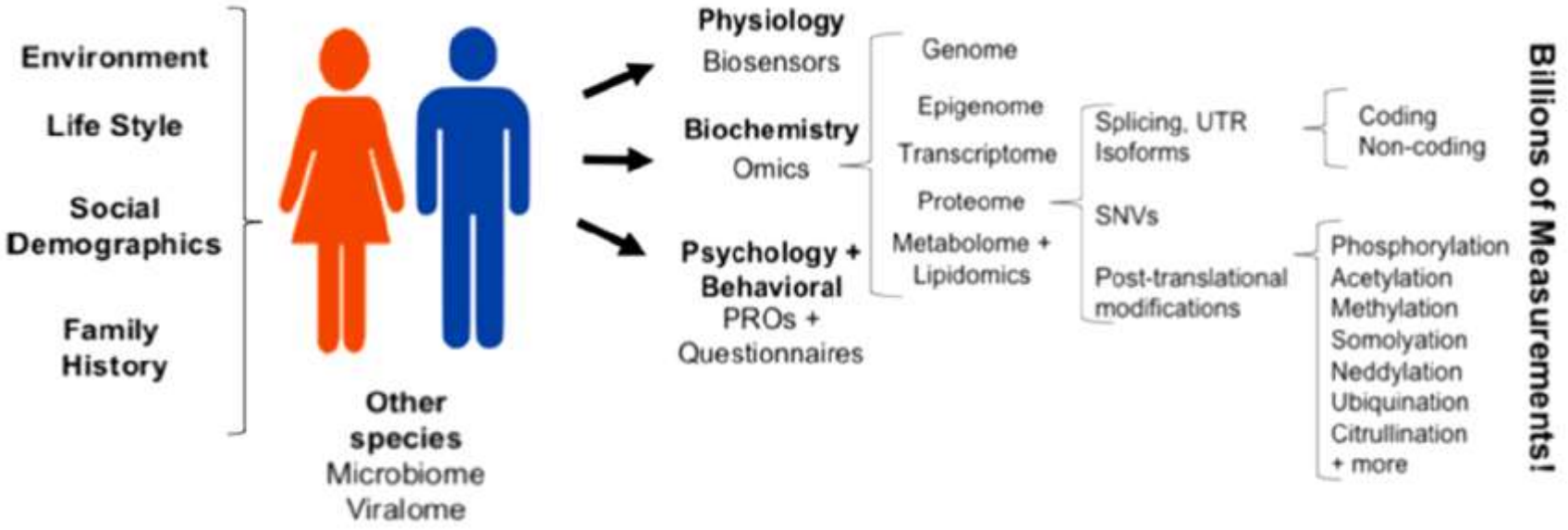
BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-018-0238-9

Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis



Multifactorial influences dictate the individual's phenotype and proteome.



J E Van Eyk, M P Snyder Proteome Res. 2019, 18, 1−6

Conclusions

- The resilience and stability of the gut microbiota and its responsiveness to physiological, pathological and environmental changes are characteristics that would enable us to use the microbiota composition as
  - a biomarker,
  - a diagnostic tool
  - a therapeutic target
  - a therapeutic allied

mod. S Roy, G Trinchieri, Nature Reviews 2017