

Julian Marchesi, Prof., PhD.

Current position:

- Deputy Director and Professor of Clinical Microbiome Research at the Centre for Digestive and Gut Health, Imperial College London, UK
- Professor of Human Microbiome Research at the School of Biosciences, Museum Avenue, Cardiff University, Cardiff

Focus of work:

- Role of the gut microbiome in maintaining host health and initiating diseases not only of the gut, but throughout the host system

Specific expertise / current research interest:

- variety of “omic” approaches, e.g. metagenomics, metatranscriptomics, metabonomics, molecular ecology
- The Cancer Microbiome
- Host-microbes interactions in the gut
- Impact of bacterial produced metabolites in the gut and bioactive and biocatalytic agents from the gut



The gut microbiota, inflammation and cancer

Professor Julian R. Marchesi



School of Biosciences

Imperial College
London

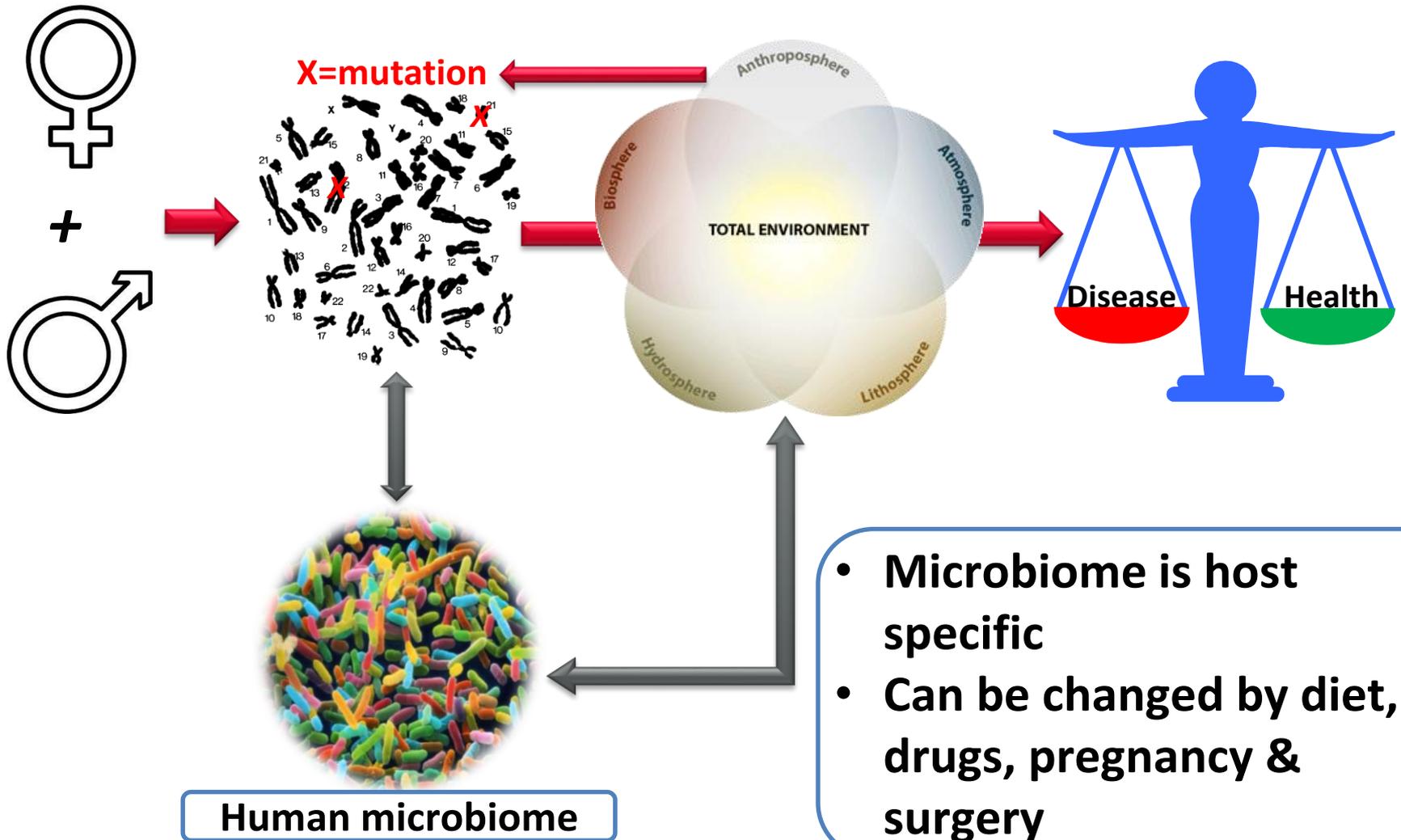
Department Digestive Diseases

Some definitions¹

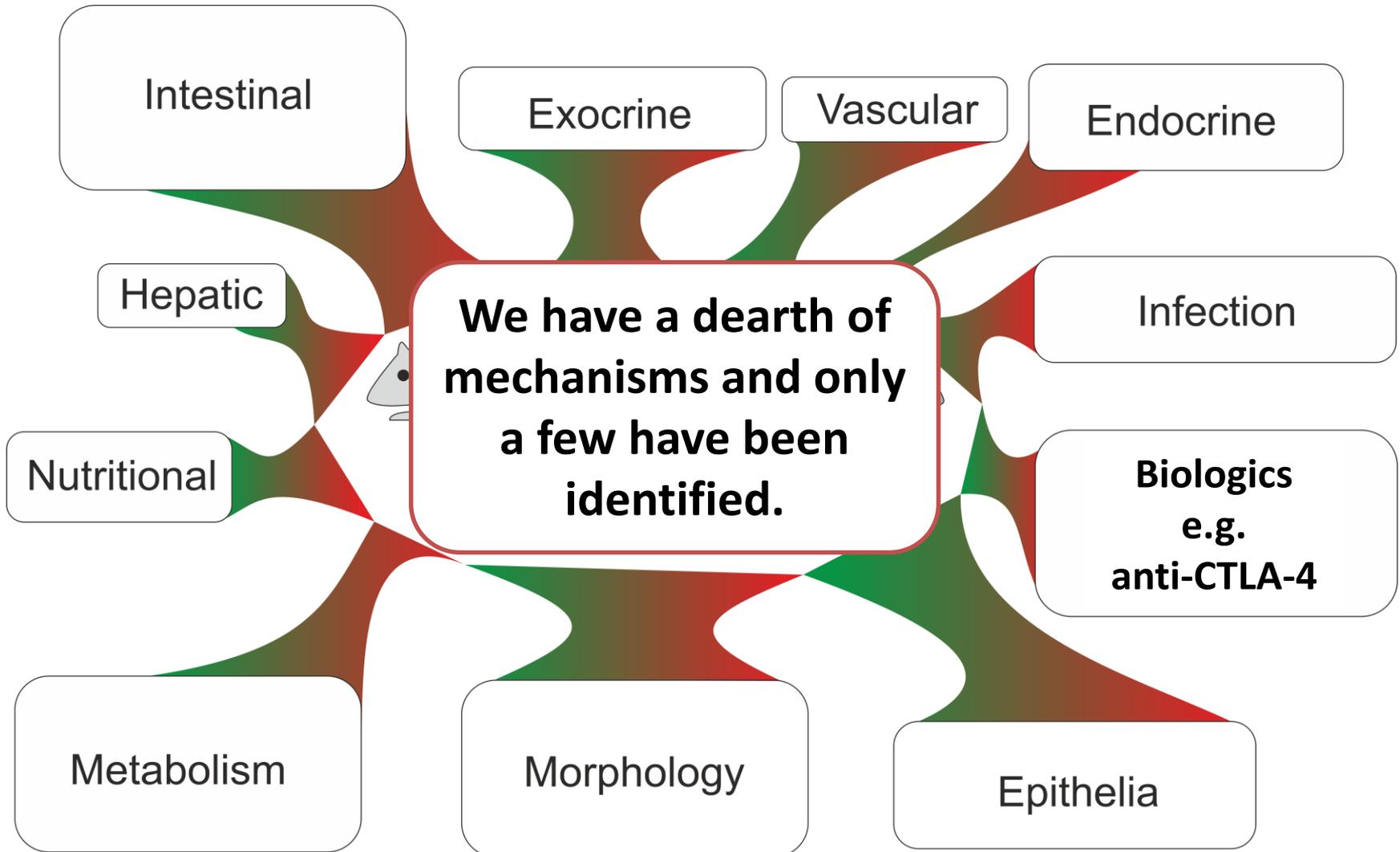
- **Microbiota (microflora)** – the qualitative and quantitative information about the different microbes present in a system – so who is there and how abundant.
- **Microbiome** – the entire habitat, including the microorganisms (bacteria, archaea, lower and higher eukaryotes, and viruses), their genomes (i.e., genes), and the surrounding environmental conditions.
- **Metagenome** – the functions that these microbiota have, e.g. bile metabolism – their gene catalogue.
- **Metaxonome** – a **16S rRNA** gene inventories, used to define the **microbiota**.
- **Metabonome** – a catalogue of the metabolites in a sample.

¹ The vocabulary of microbiome research: a proposal Marchesi and Ravel. *Microbiome* 2015 3:31.

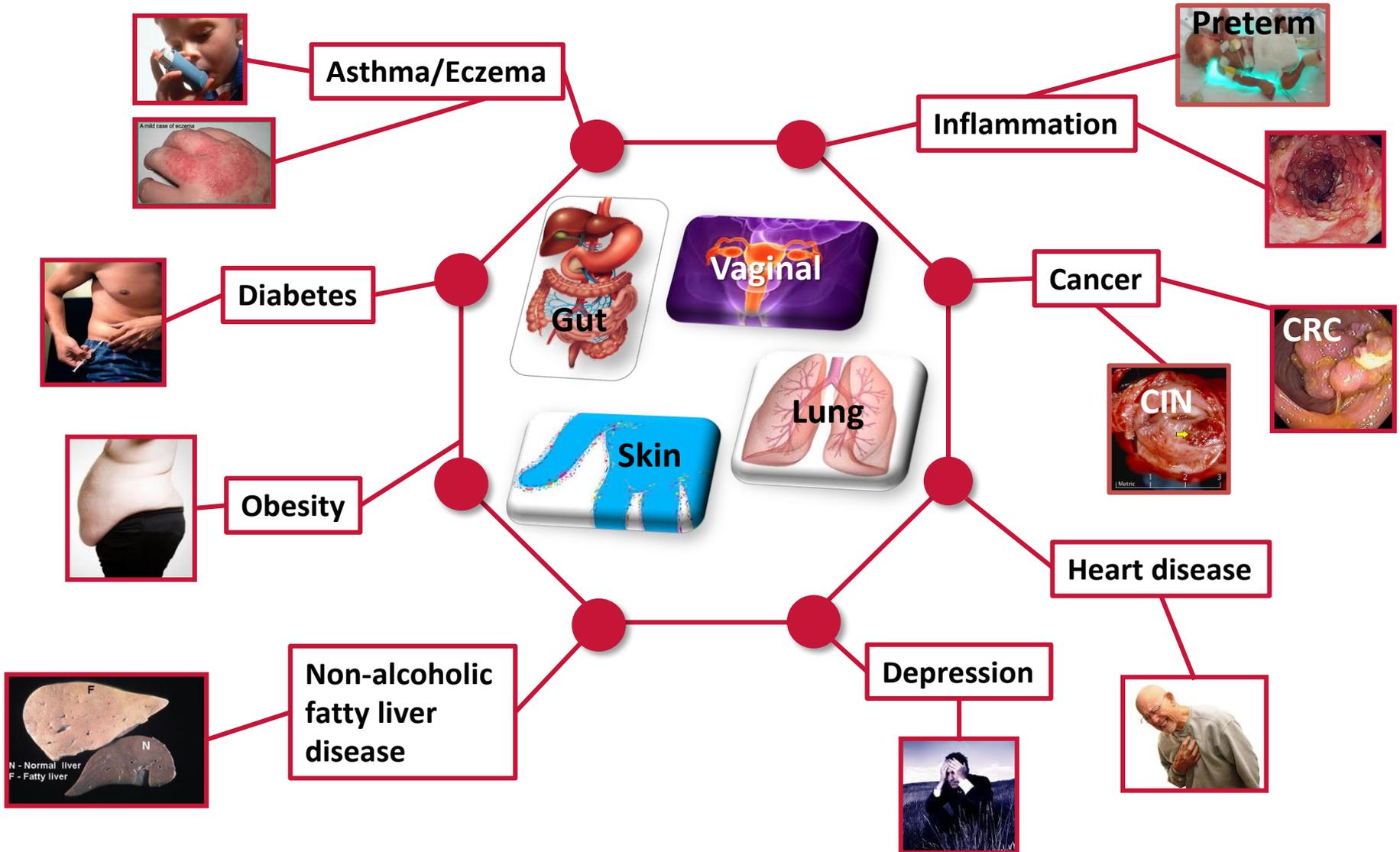
The main focus in human biology has been to explain how it functions in terms of the genome



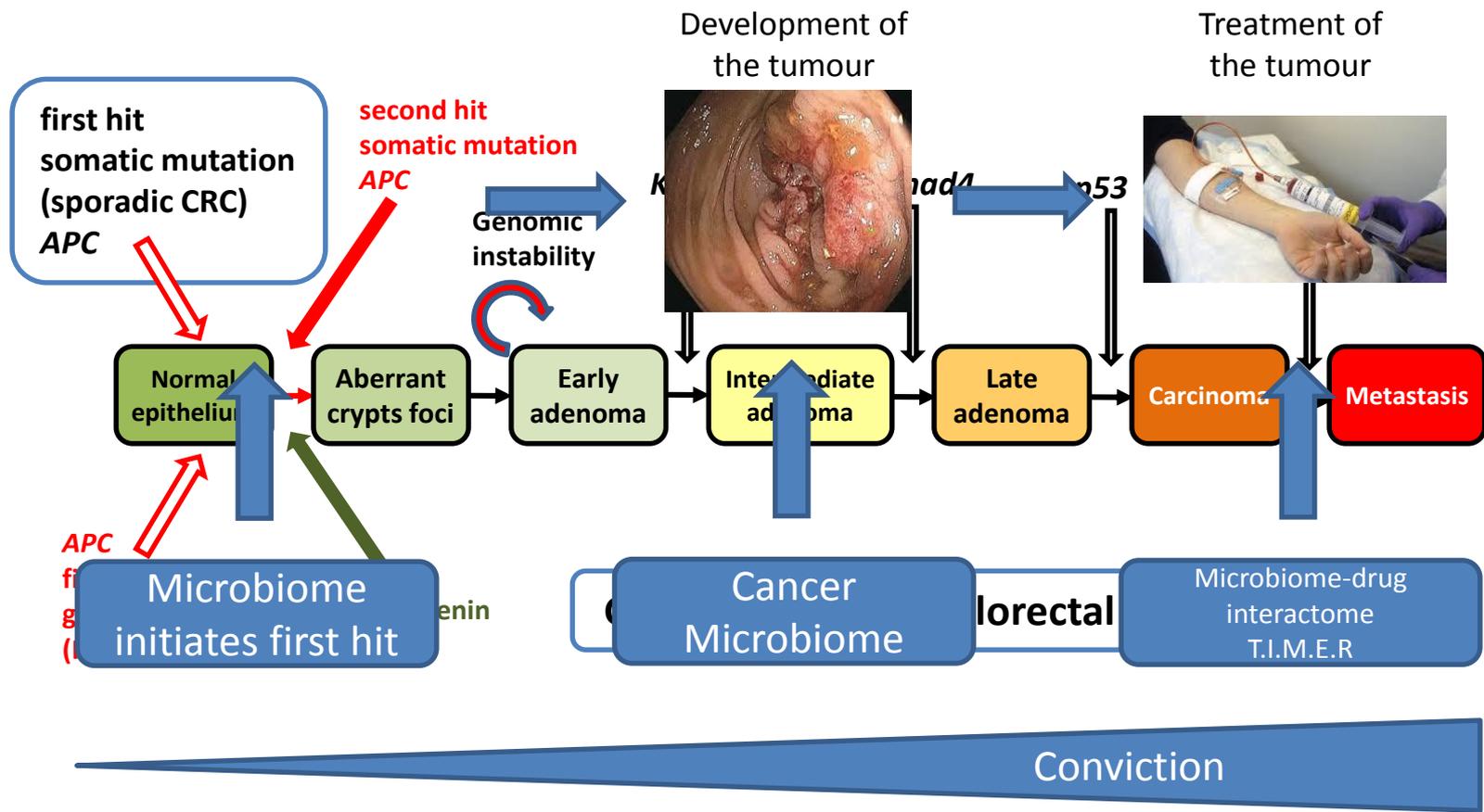
The absence of a microbiome impacts the whole host



All these diseases have evidence for a role of a microbiome



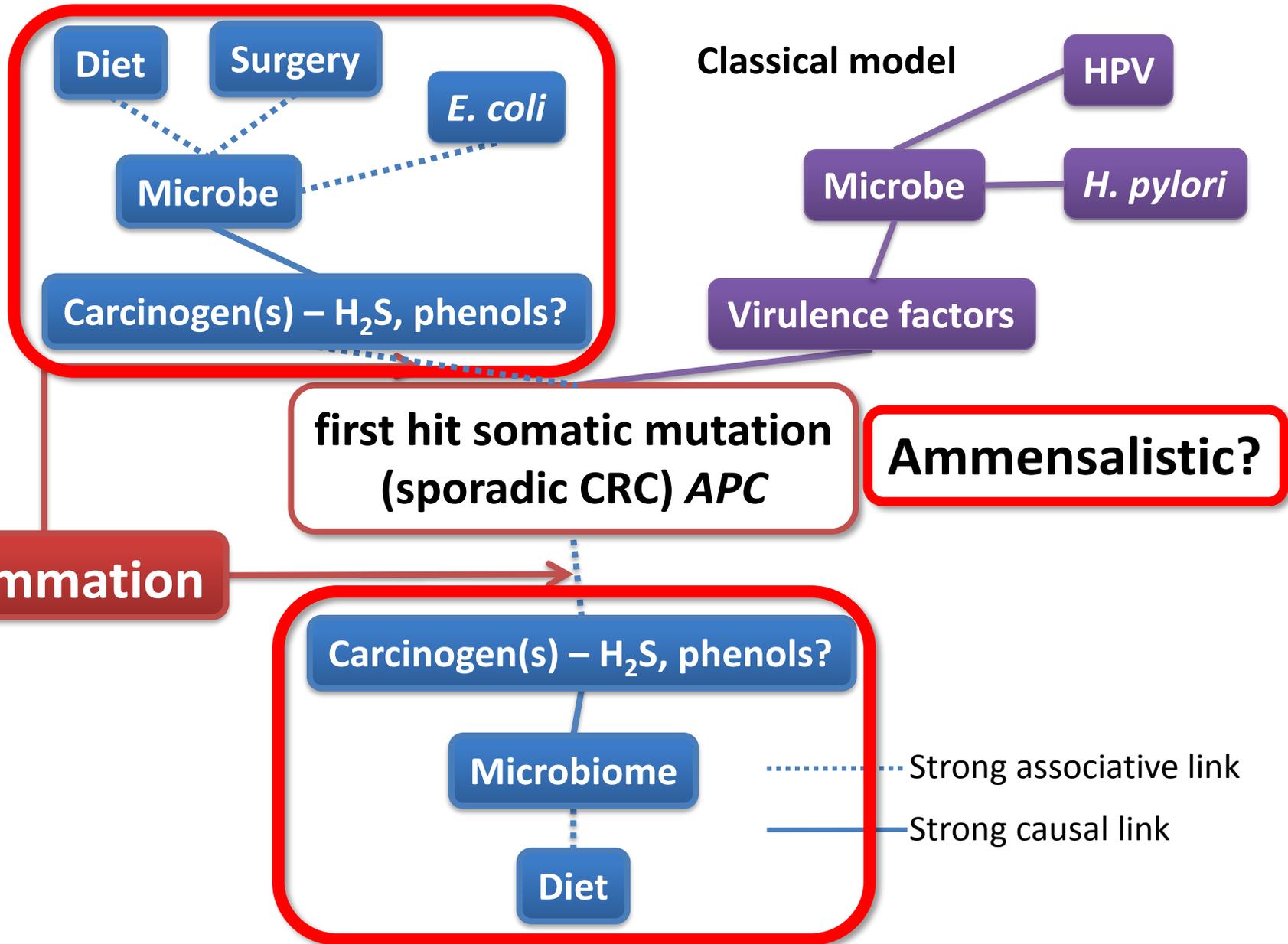
The majority of cancers arise randomly.



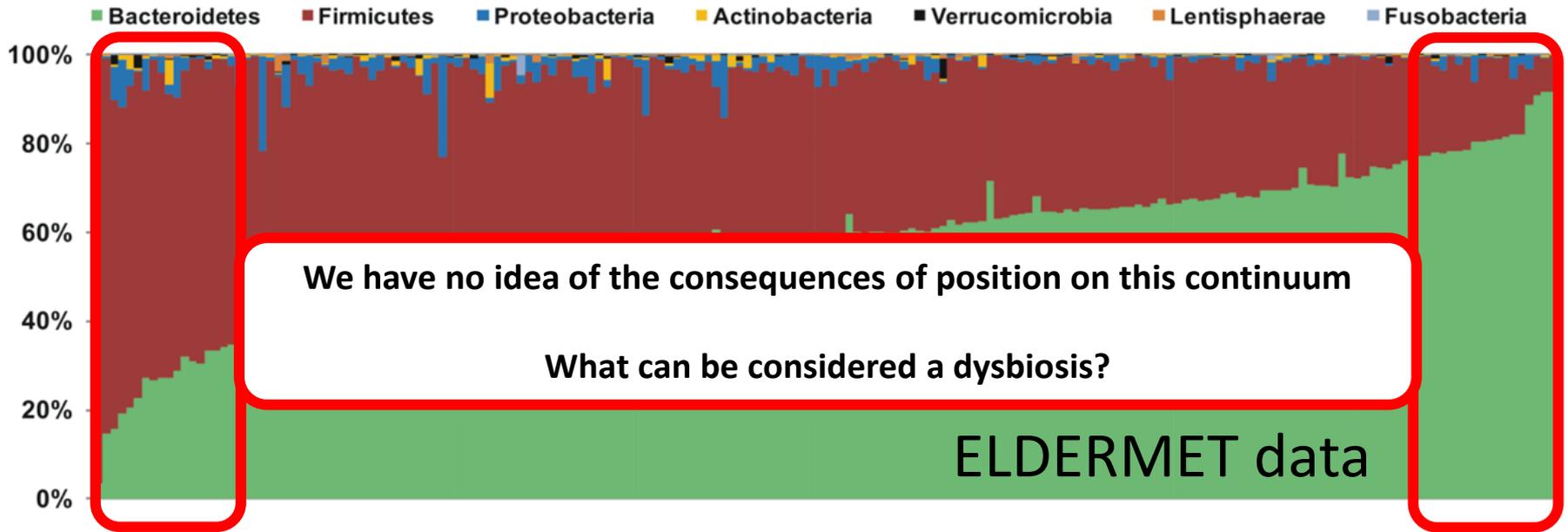
This is why as cancer specialists and oncologists need to think about the microbiome.

It may seem esoteric, but it impacts at all stages of the disease – initiation, development and treatment.

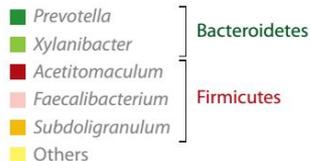
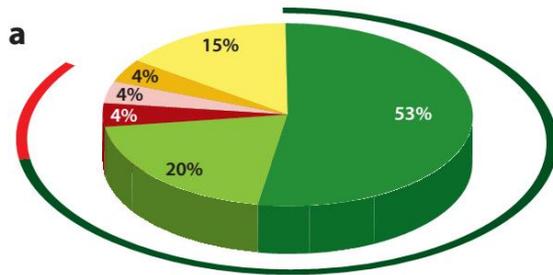
Who's responsible for the first hit?



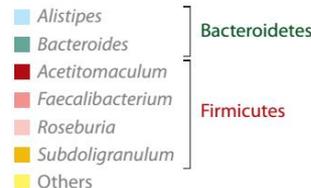
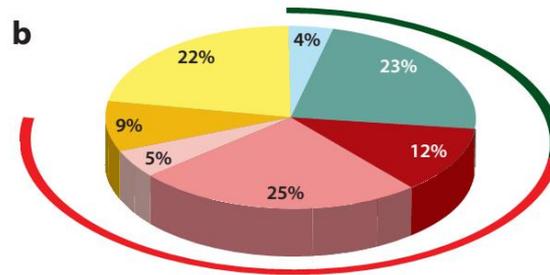
Variability clouds the issue of a healthy vs unhealthy microbiota



Burkina Faso



Italy

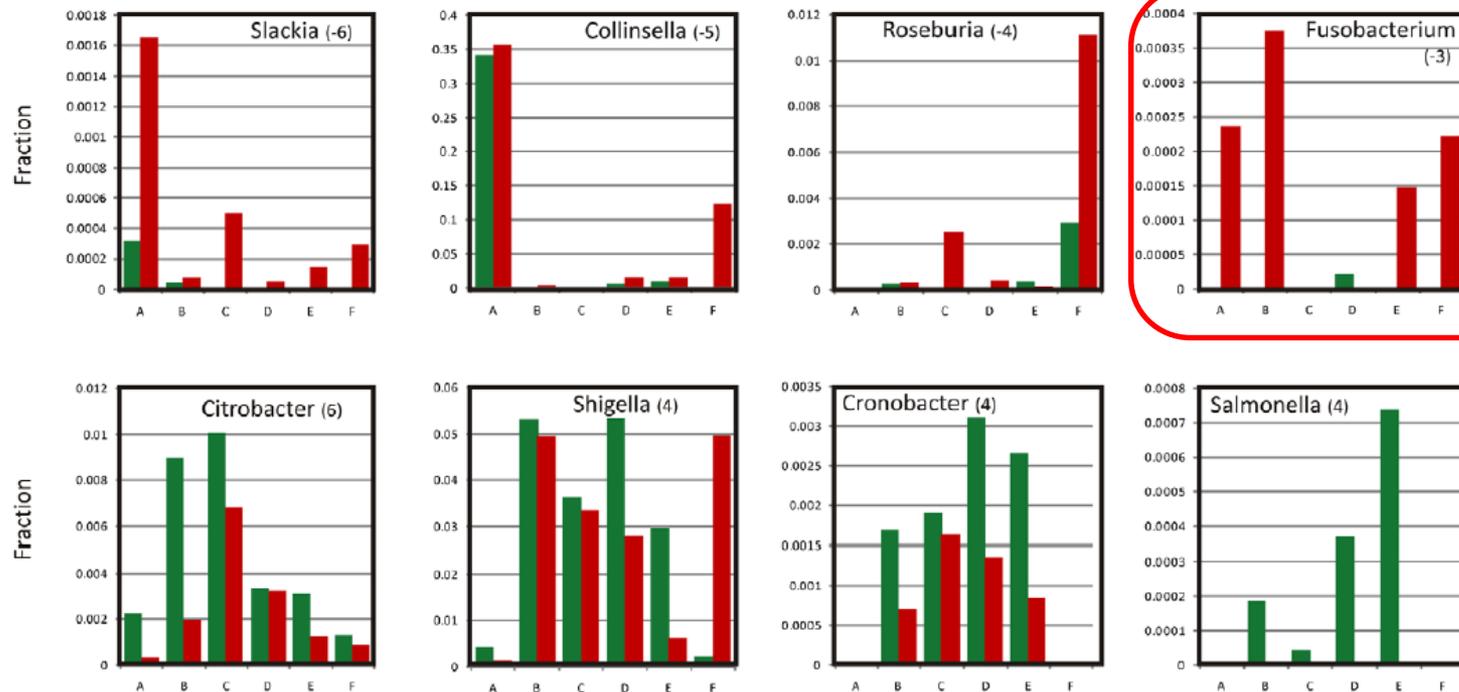


& biogeography complicates the story.

De Filippo et al PNAS
2010,107(33):14691-6

Towards the Human Colorectal Cancer Microbiome

Julian R. Marchesi¹, Bas E. Dutilh^{2,3}, Neil Hall⁴, Wilbert H. M. Peters⁵, Rian Roelofs⁶, Annemarie Boleij⁶, Harold Tjalsma^{6*}



■ ON tumour, ■ OFF tumour

Research

Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma

Aleksandar D. Kostic,^{1,2} Dirk Gevers,¹ Chandra Sekhar Pedamallu,^{1,3} Monia Michaud,⁴ Fujiko Duke,^{1,3} Ashlee M. Earl,¹ Akinyemi I. Ojesina,^{1,3} Joonil Jung,¹ Adam J. Bass,^{1,3} Josep Taberner,⁵ José Baselga,⁵ Chen Liu,⁶ Ramesh A. Shivdasani,³ Shuji Ogino,^{2,3,7} Bruce W. Birren,¹ Curtis Huttenhower,^{1,8} Wendy S. Garrett,^{1,3,4} and Matthew Meyerson^{1,2,3,9}

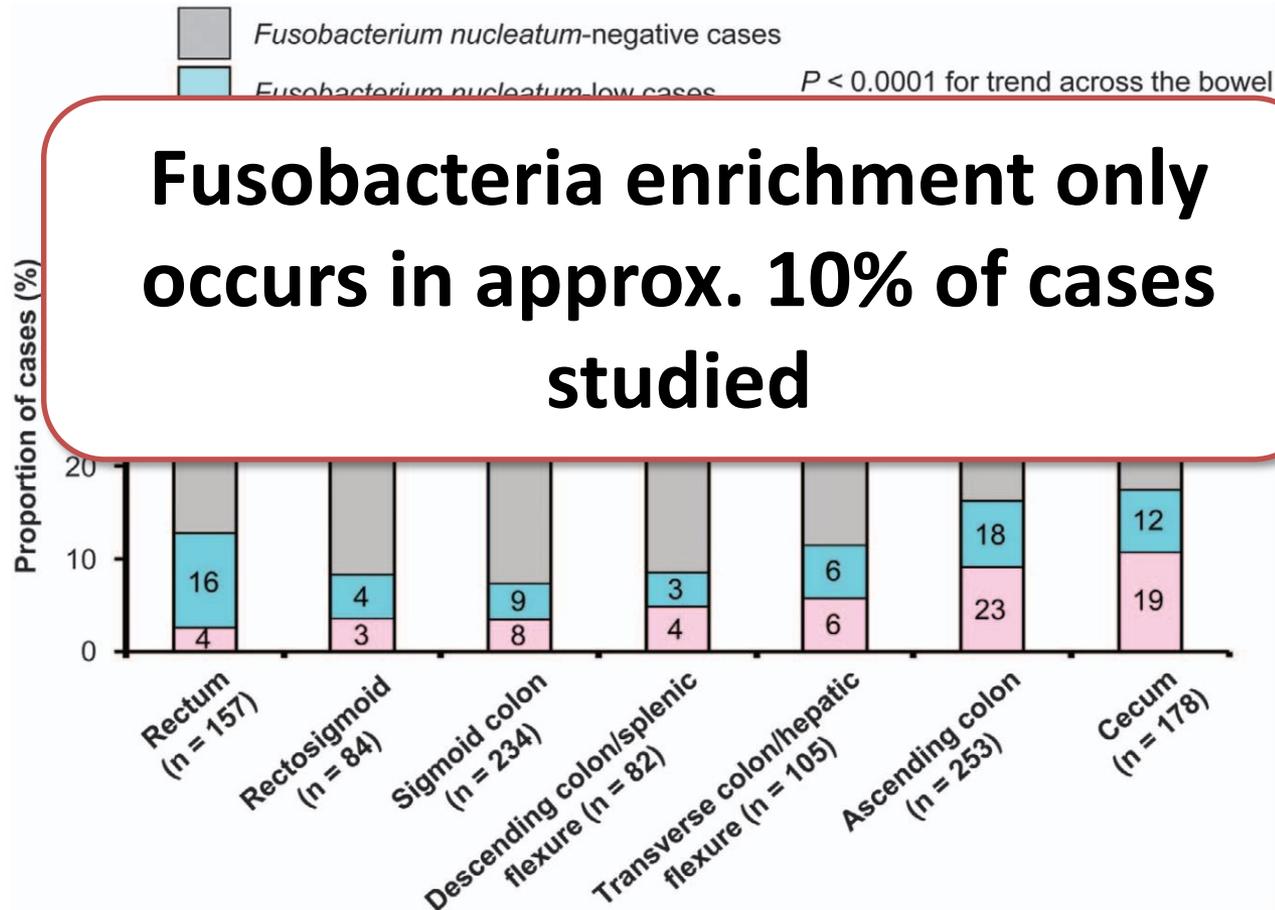
Research

Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma

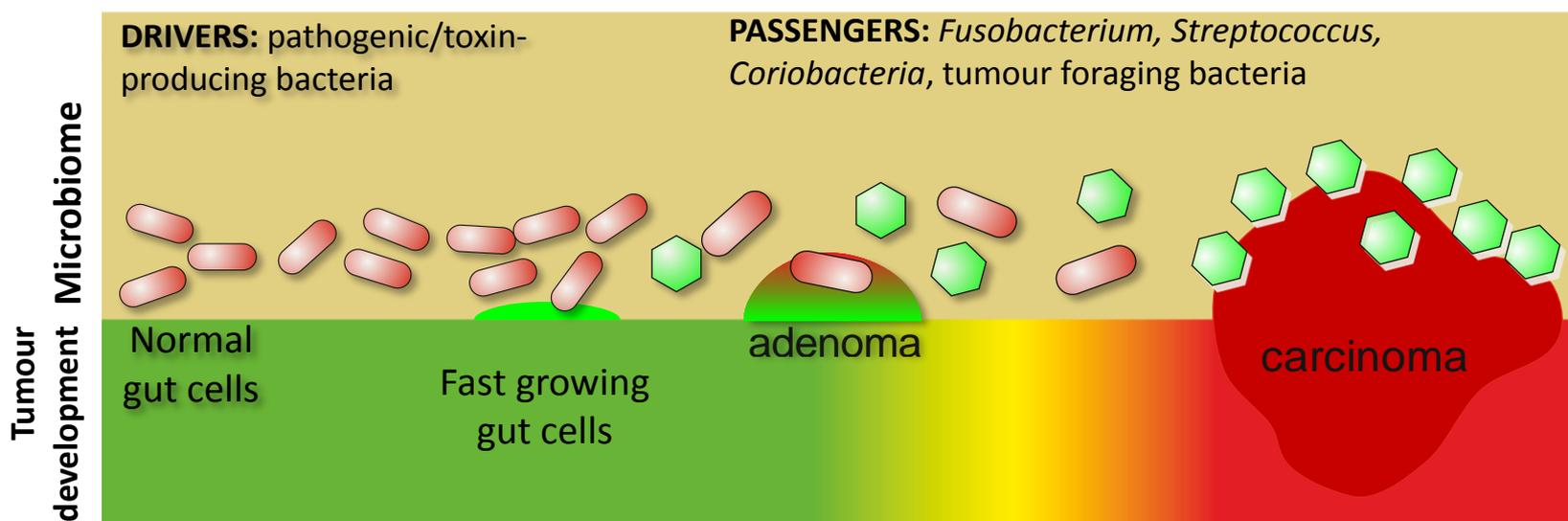
Mauro Castellarin,^{1,2,6} René L. Warren,^{1,6} J. Douglas Freeman,¹ Lisa Dreolini,¹ Martin Krzywinski,¹ Jaclyn Strauss,³ Rebecca Barnes,⁴ Peter Watson,⁴ Emma Allen-Vercoe,³ Richard A. Moore,^{1,5} and Robert A. Holt^{1,2,7}

Fusobacterium nucleatum in Colorectal Carcinoma Tissue According to Tumor Location

Kosuke Mima, MD, PhD^{1,15}, Yin Cao, ScD^{2,3,4,15}, Andrew T. Chan, MD, MPH^{2,3,5,15}, Zhi Rong Qian, MD, PhD^{1,15},

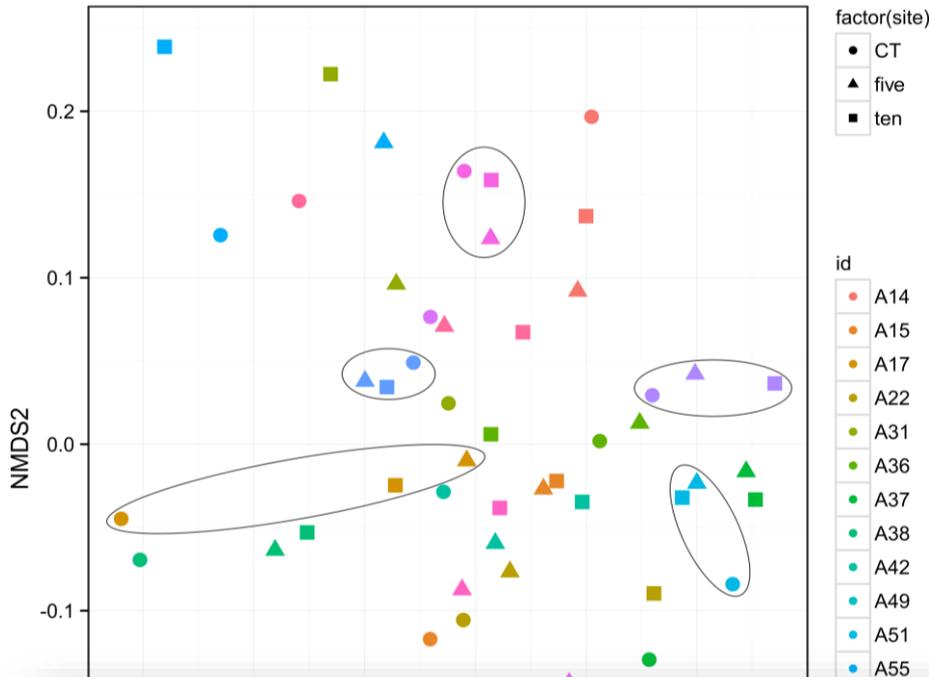


This led us to hypothesize that we had a driver:passenger model



But we had derived this model from a small group (6) individuals who had been prepared for endoscopy.

Extending the dataset



NMDS of weighted UNIFRAC distances from 38 patients

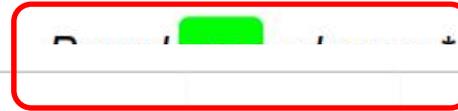
Samples on tumour (CT) and at 5 and 10 cm from the tumour

No bowel prep

Next stage is to examine the metabotypes of CRC and look for bacterial metabolites as biomarkers of tumour development and progression

Co-occurrence of driver and passenger bacteria in human colorectal cancer

Confirmation of driver – passenger hypothesis



PI S-DA model

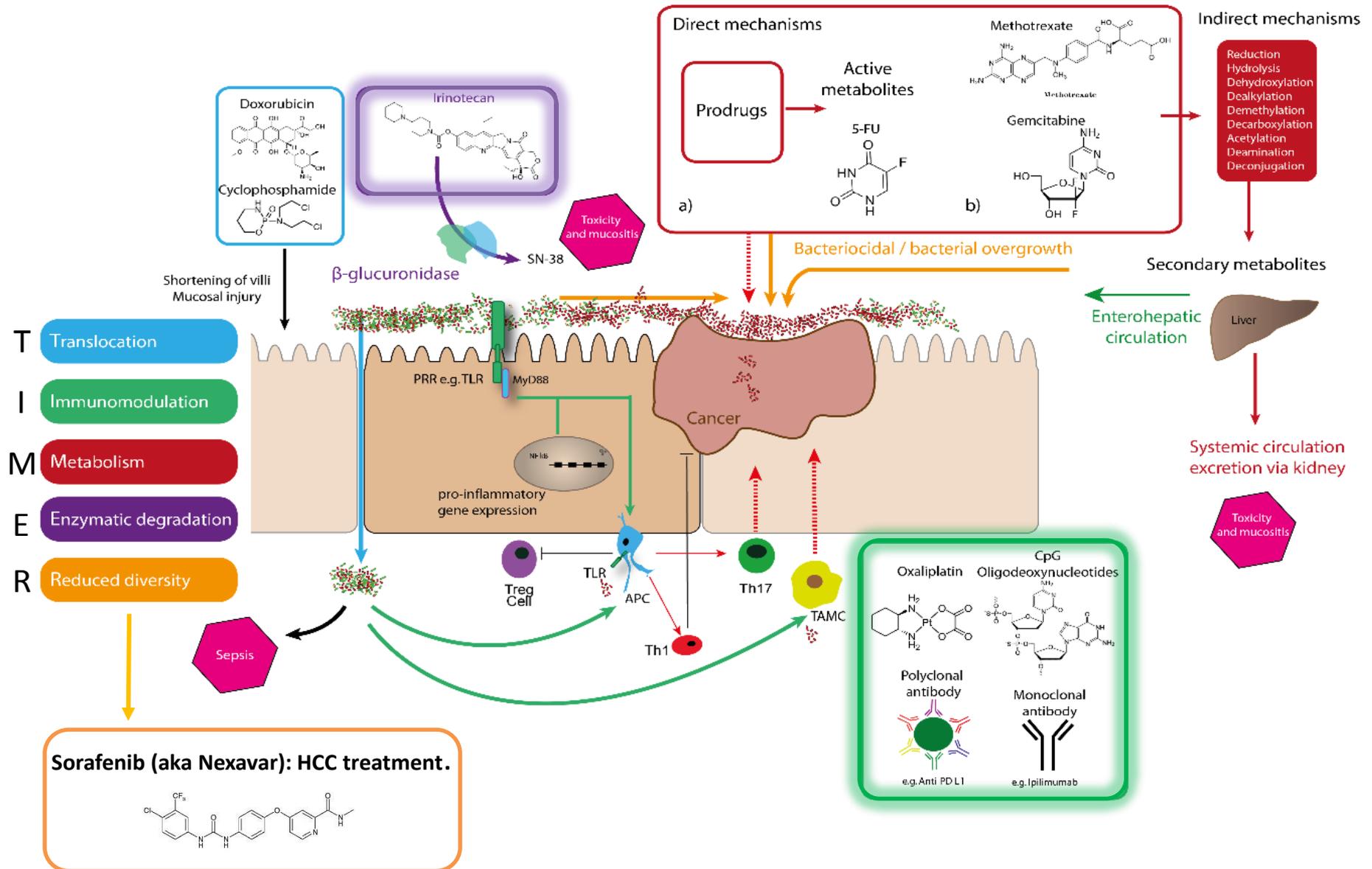


No fusobacteria in Chinese cohort

er
-inflammatory
enger

1. The *Fusobacterium* phyla are over abundant in European and US colon cancer, irrespective of bowel prep, but only on late stage tumours – **passengers?**
2. The β , γ and ϵ -proteobacteria are present in advanced disease
3. The CRC microbiome may be of prognostic importance

'TIMER' Mechanisms for Microbiome modulation of Chemotherapy

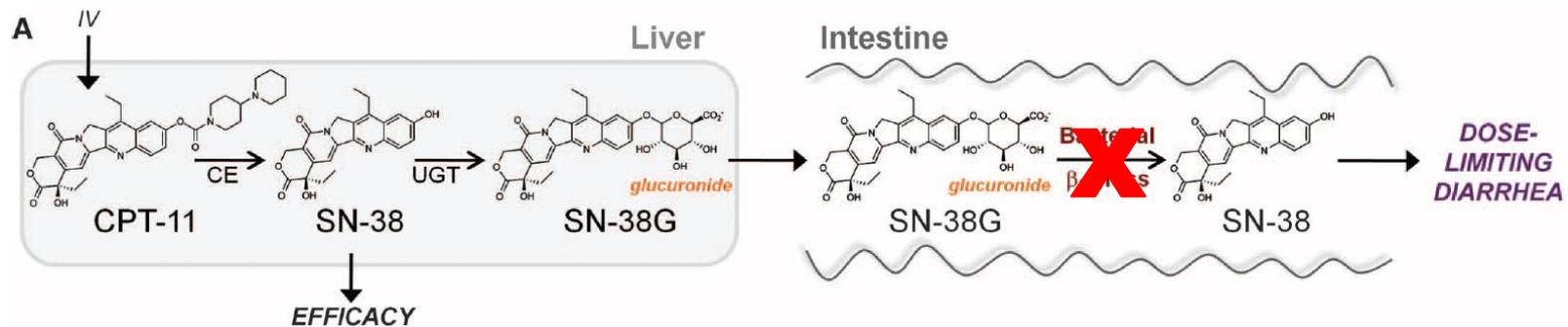


Alleviating Cancer Drug Toxicity by Inhibiting a Bacterial Enzyme

Bret D. Wallace,¹ Hongwei Wang,² Kimberly T. Lane,¹ John E. Scott,³
Jillian Orans,¹ Ja Seol Koo,⁴ Madhukumar Venkatesh,² Christian Jobin,⁴ Li-An Yeh,³
Sridhar Mani,² Matthew R. Redinbo^{1,5,6*}

The dose-limiting side effect of the common colon cancer chemotherapeutic CPT-11 is severe diarrhea caused by symbiotic bacterial β -glucuronidases that reactivate the drug in the gut.

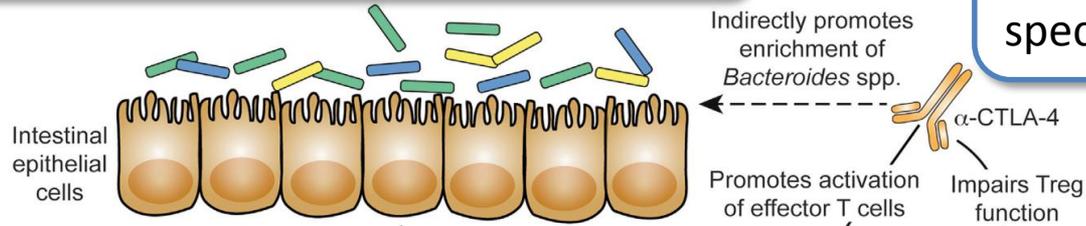
CPT-11 aka Irinotecan



Key: carboxylesterases (CE), UDP-glucuronosyltransferase (UGT) enzymes and glucuronidases (b-glucs)

1: Gut colonization by immunostimulatory bacteria e.g. bifidobacterial or *Bacteroides* spp.

2: Anti-CTLA-4 enriches *Bacteroides* species



3: Factors from these bacteria stimulate DCs

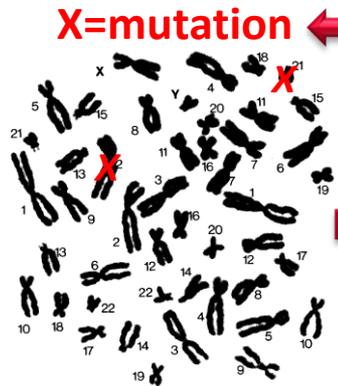
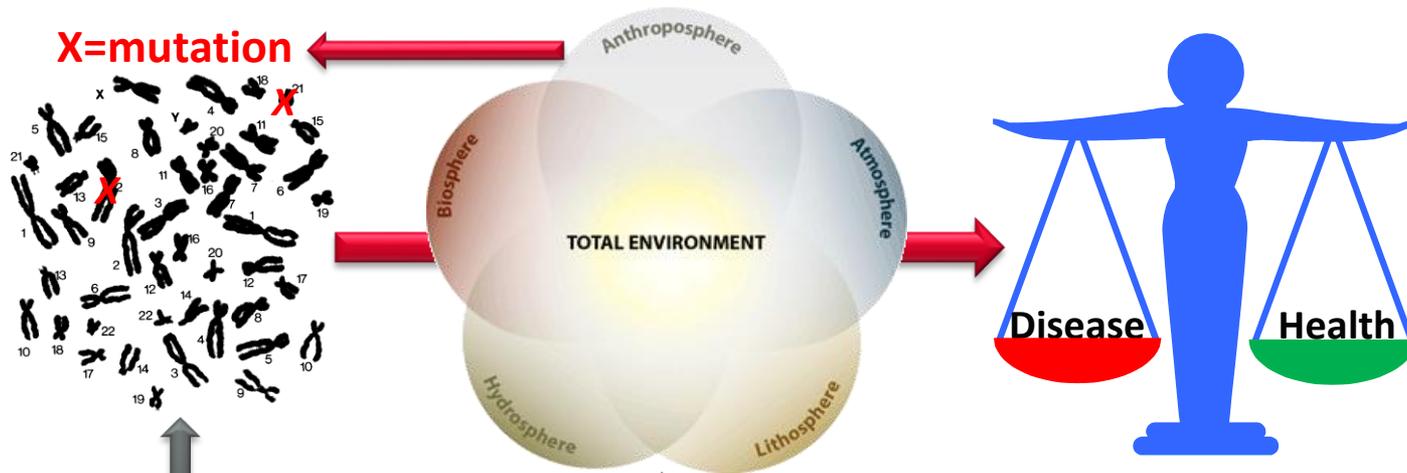
4: These DCs present tumour antigens to anti-tumour T cells.

Immunotherapy Not Working? Check Your Microbiota

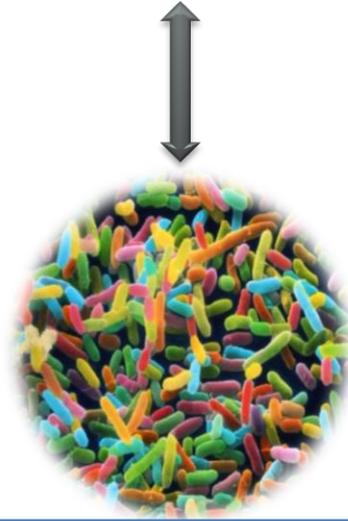
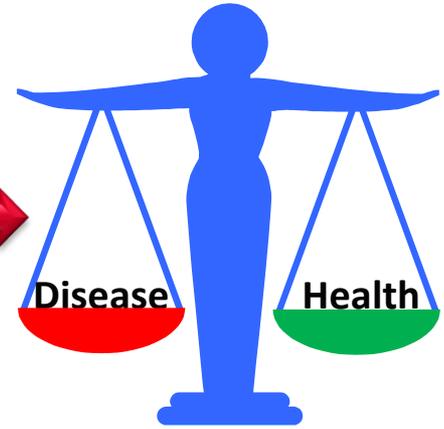
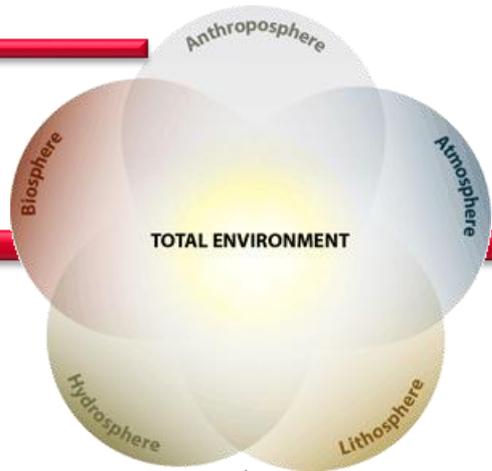
Nathan R. West¹ and Fiona Powrie^{1,2,*}

Cancer Cell 28, December 14, 2015 ©2015 Elsevier Inc.

The dialogue between the host and microbiome in a healthy context



X=mutation



Human microbiome

These arrows really depict the movement of proteins and metabolites - in other words the communication is via the proteomes and metabonomes

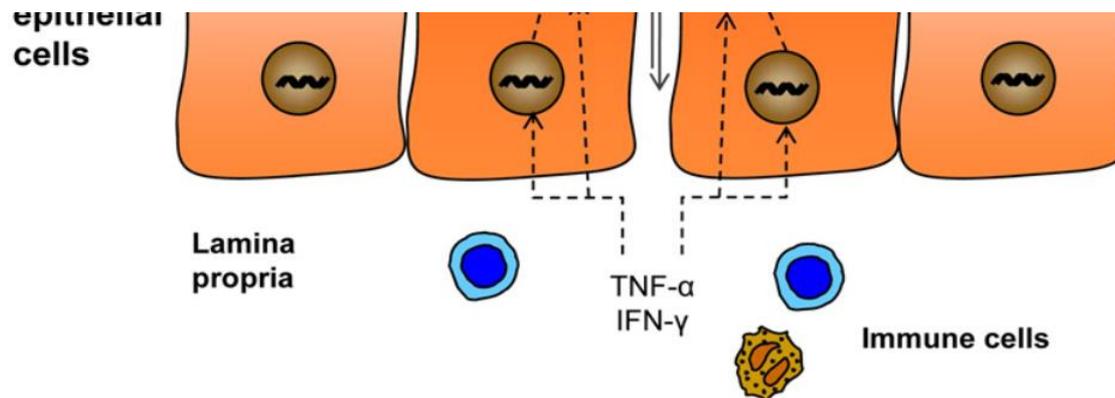
Exploring the gut microbiome via activity – emergent properties

The missing link is the proteome



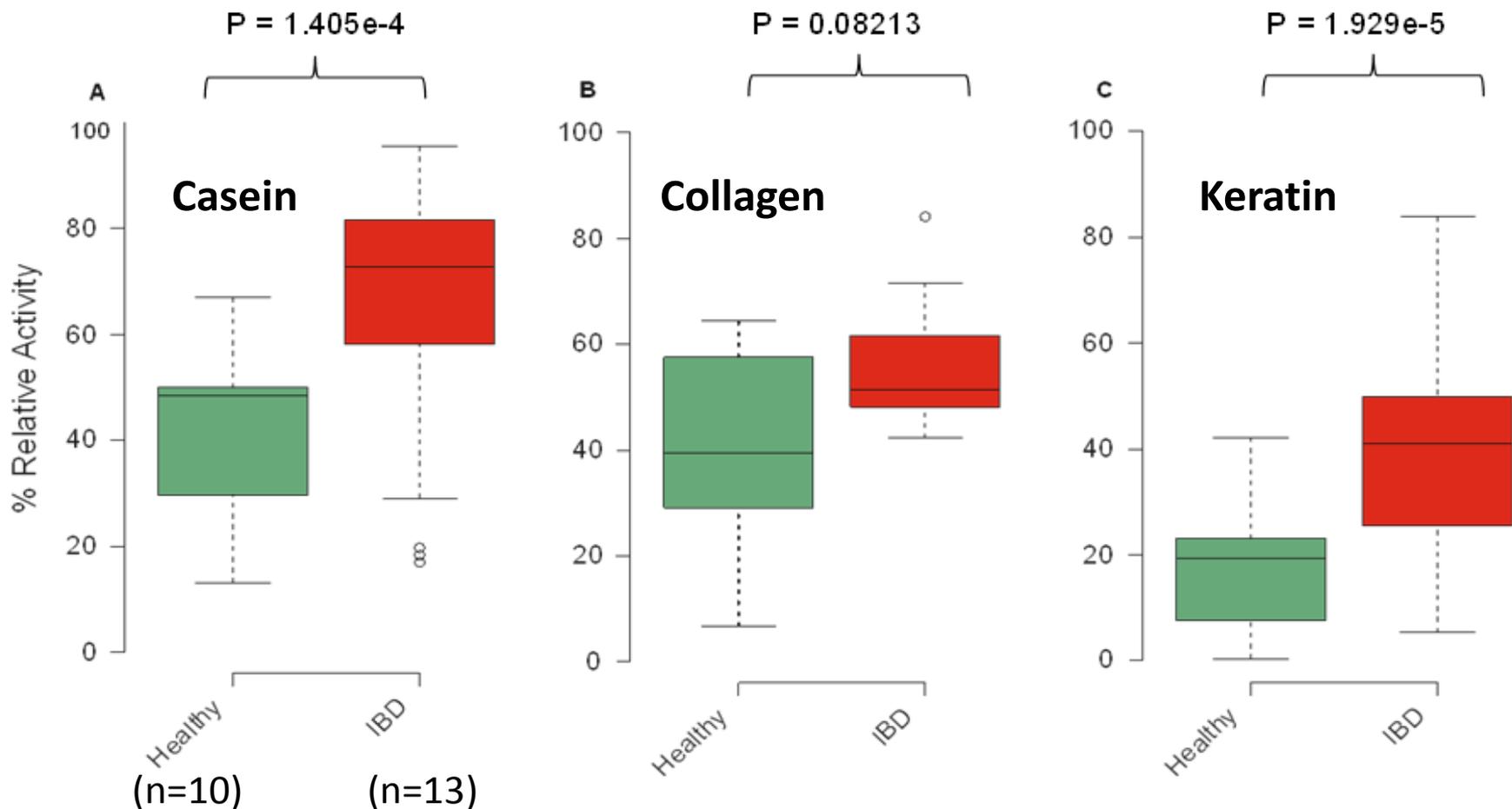
Why?

Bacterial proteases are a potential virulence factor in colorectal cancer and IBD. They have also been shown to compromise tight junction integrity.



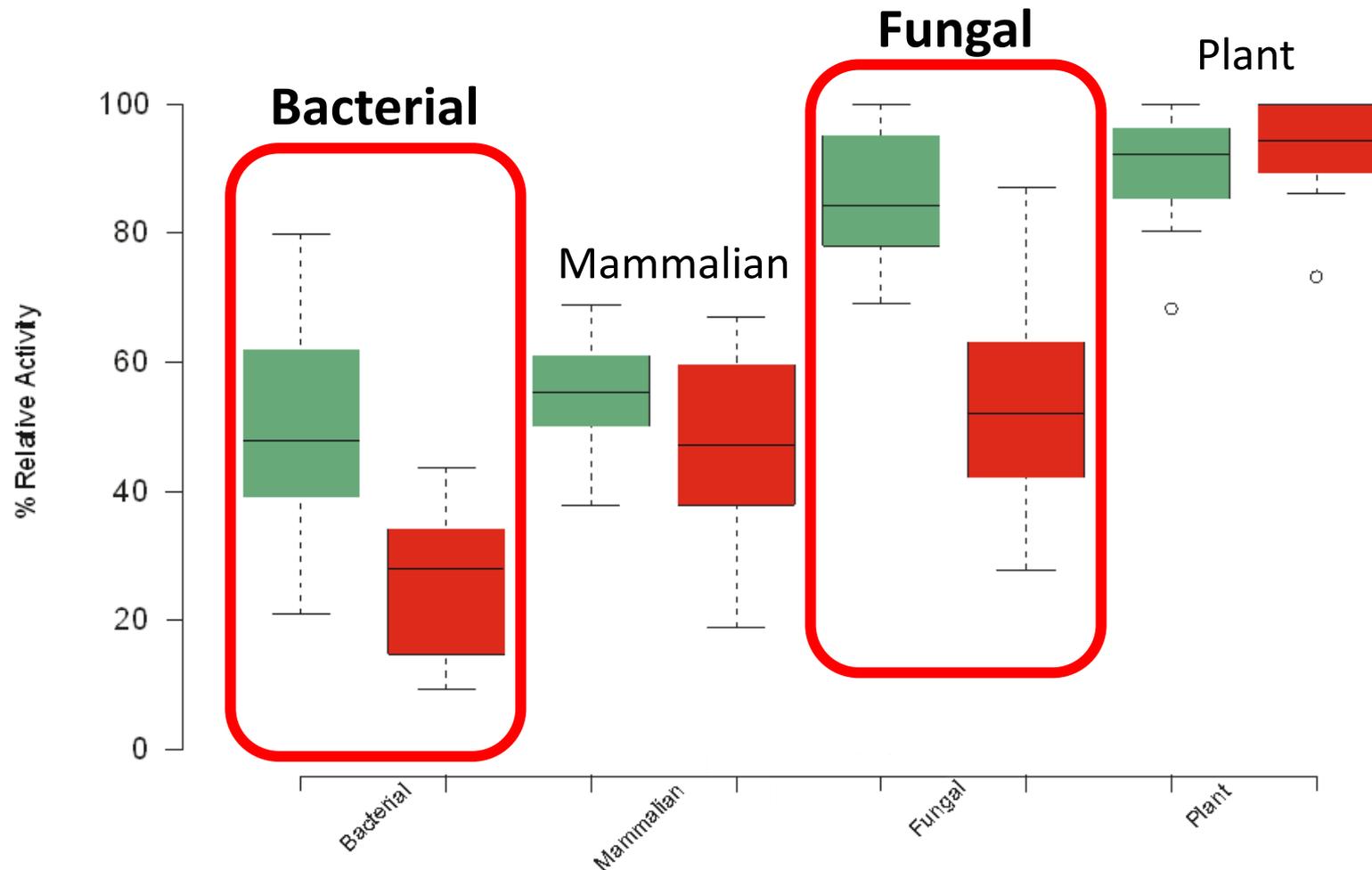
IBD and the degradome

The degradome and degradomics is the study of enzymes which degrade proteins i.e. proteases. So does it play a role in inflammatory bowel disease?

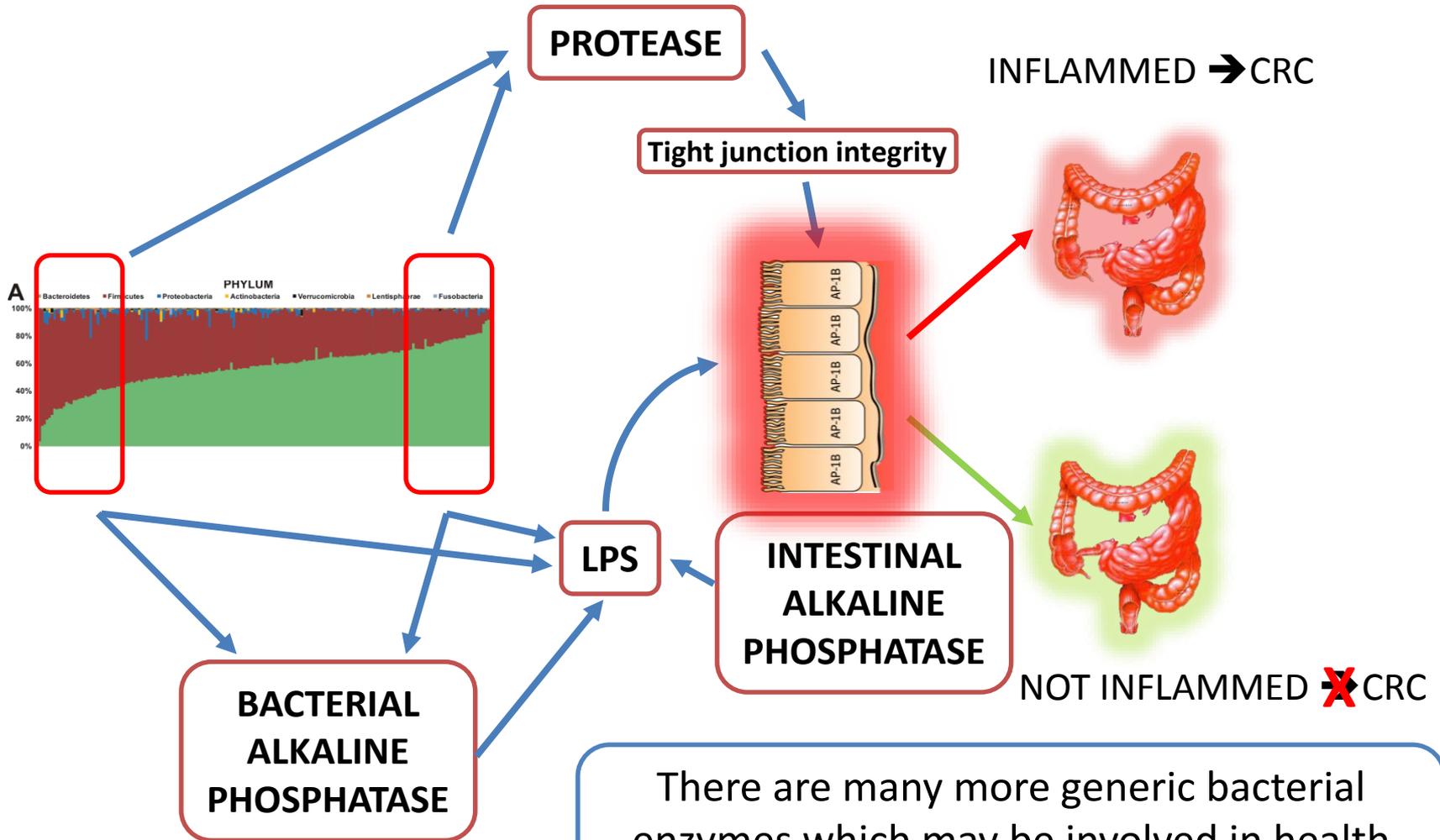


IBD and the degradome cont.

Use of targeted proteases inhibitors to understand the degradome in **IBD** and **healthy** samples

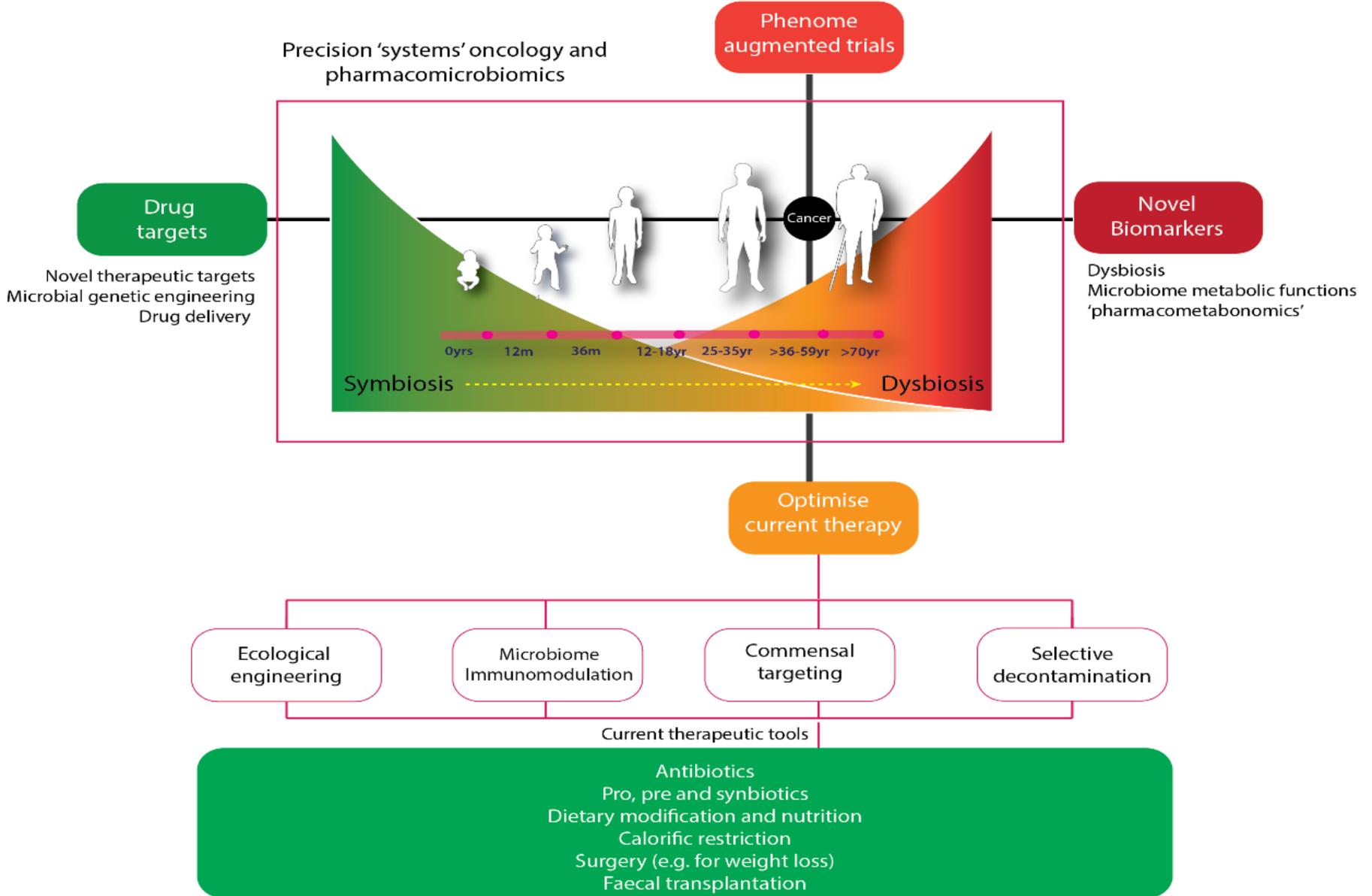


The microbiome and the healthy person



There are many more generic bacterial enzymes which may be involved in health and disease – **Bile processing enzymes**.

Future Analysis of the 'Oncomicrobiome'



In summary

- **Application of multi modal “omic” tools is definitely helping us to determine the roles of the gut bacteria in health and disease – for example cancer, IBD and general inflammation.**
- **Newer ecologic concepts, such as ammensalism will help guide us to a better understanding of the role of the microbiome.**
- **The gut does influence the host, but we are a long way from determining the true significance of this influence e.g. SCFA, bile metabolism and glucuronidases are all core functions, with roles to play in cancer initiation and development.**
- **The metabolic axis is the other arm of the microbiome-inflammation interactome.**
- **Can we harness the microbiome to treat and understand cancer in the gut?**