

Human Microbiomes and cancer

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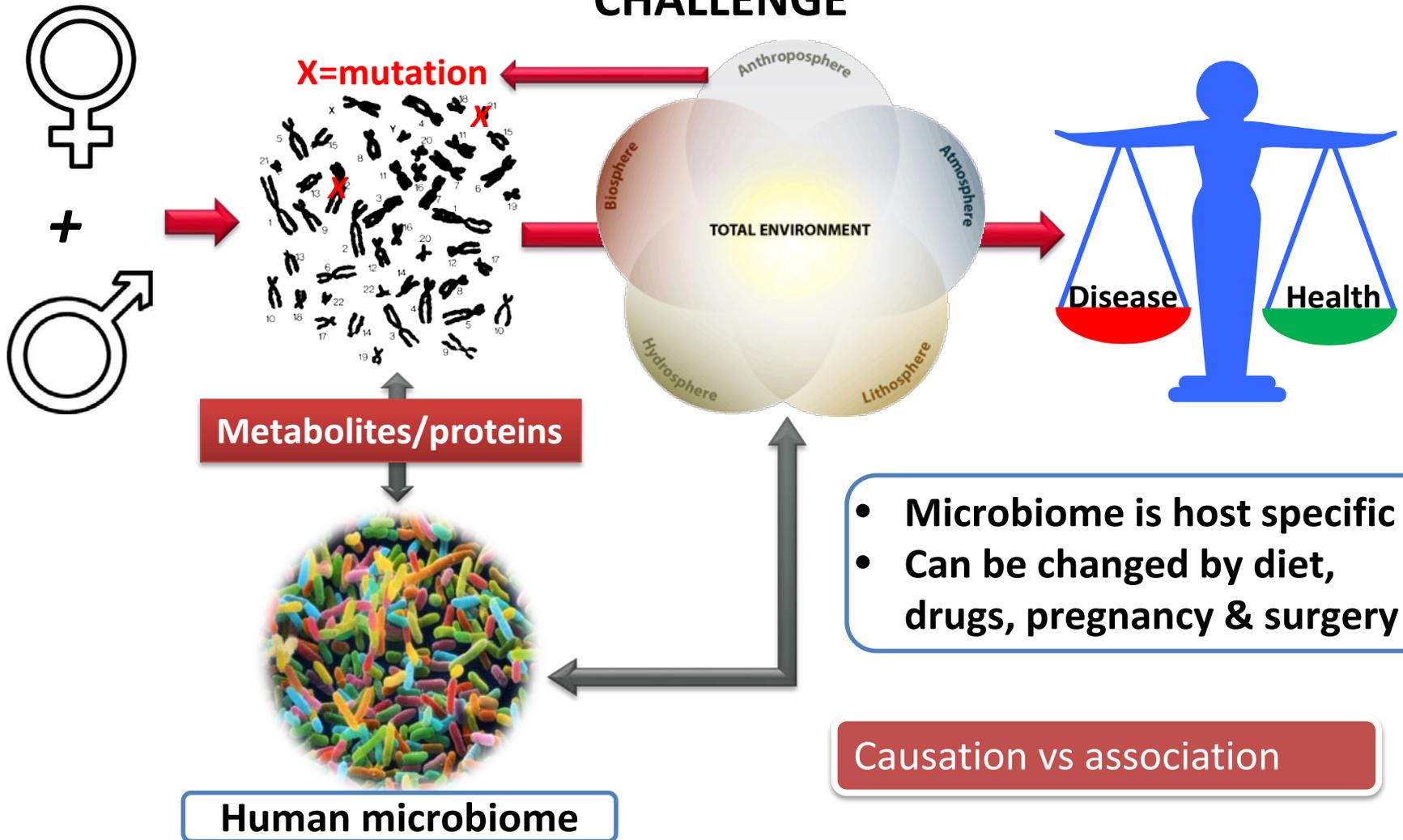
Some definitions¹

- **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.

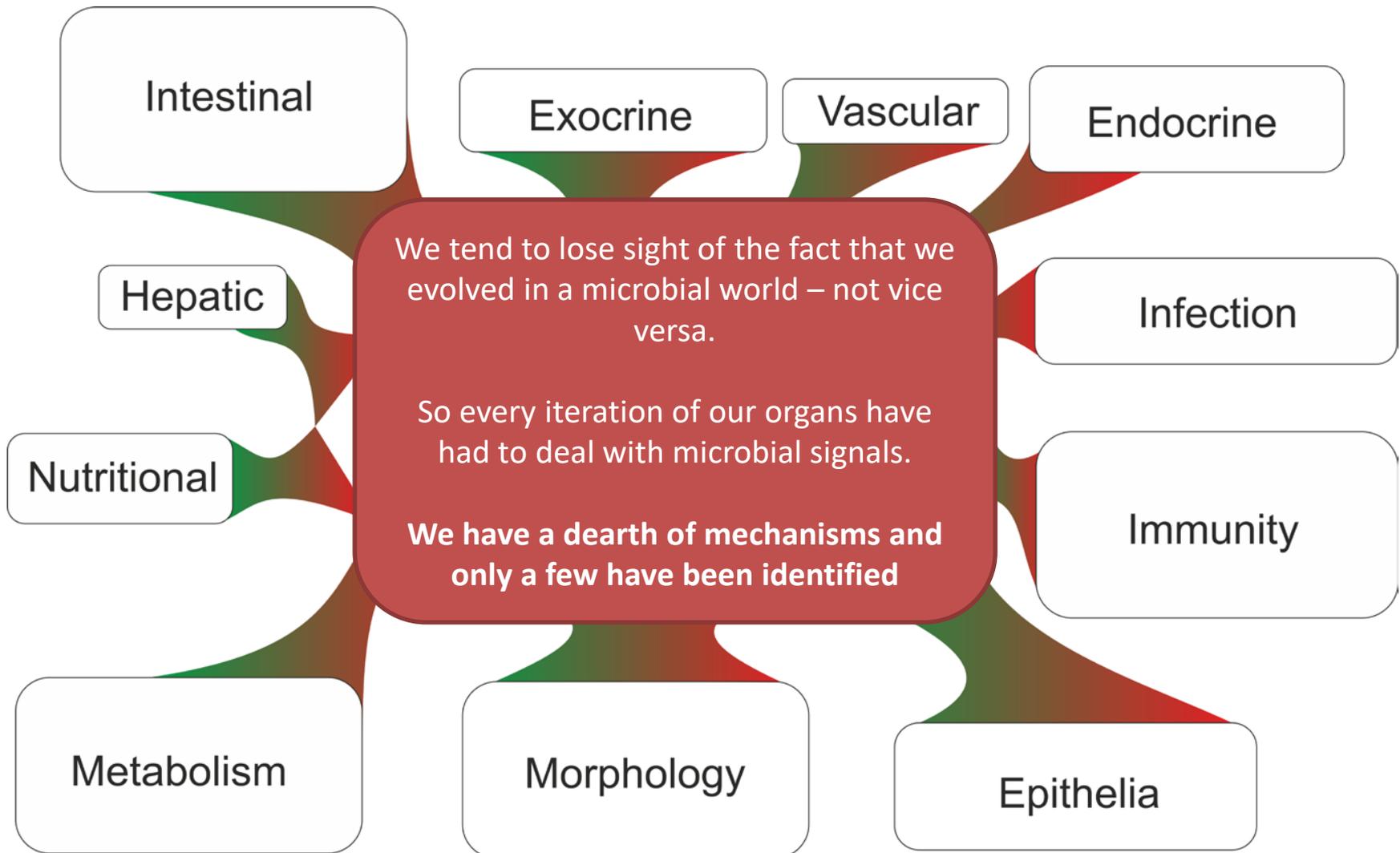
¹ The vocabulary of microbiome research: a proposal Marchesi and Ravel. *Microbiome* 2015 3:31.

A significant focus in human biology has been to explain how it functions in terms of the genome.

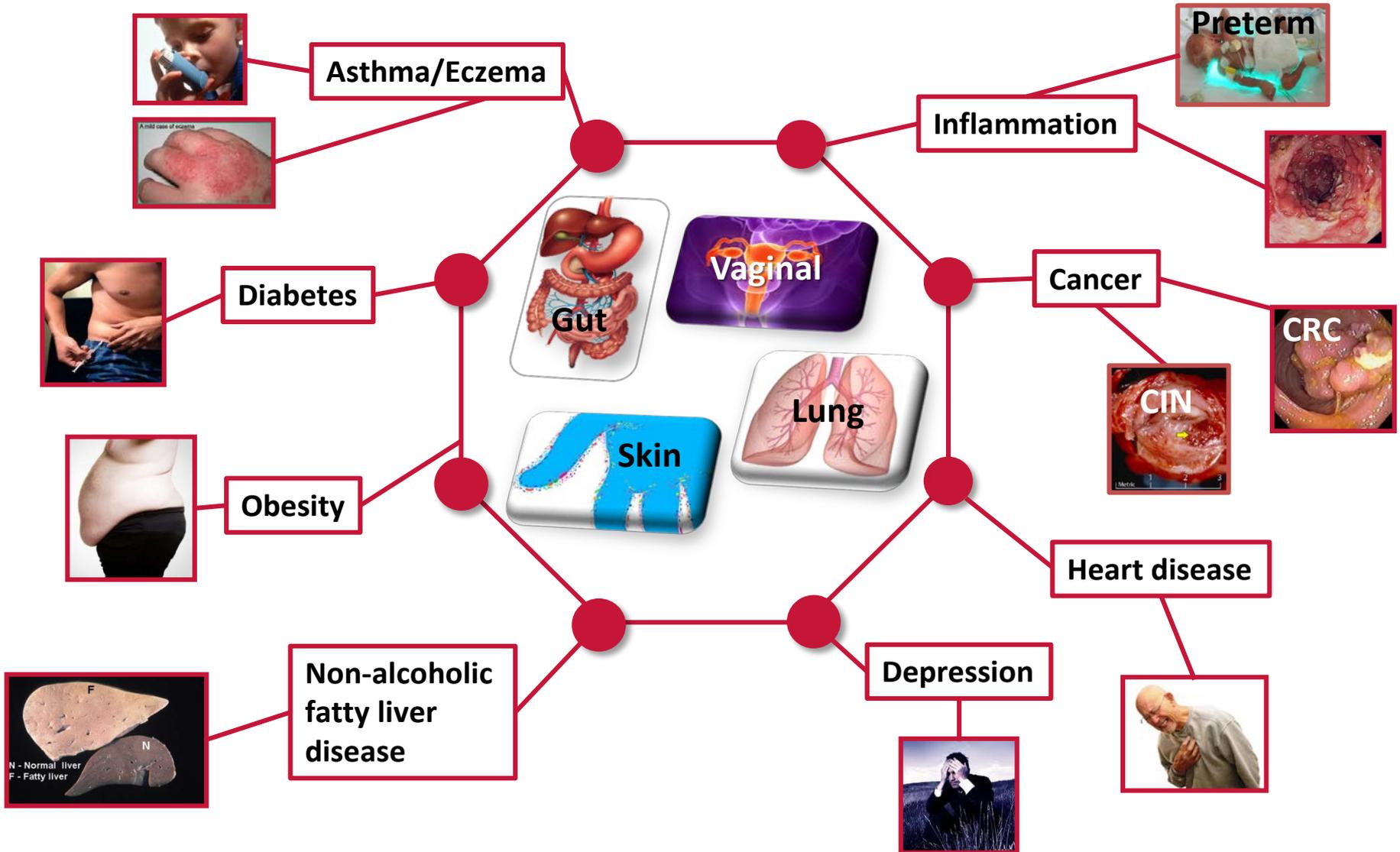
CHALLENGE



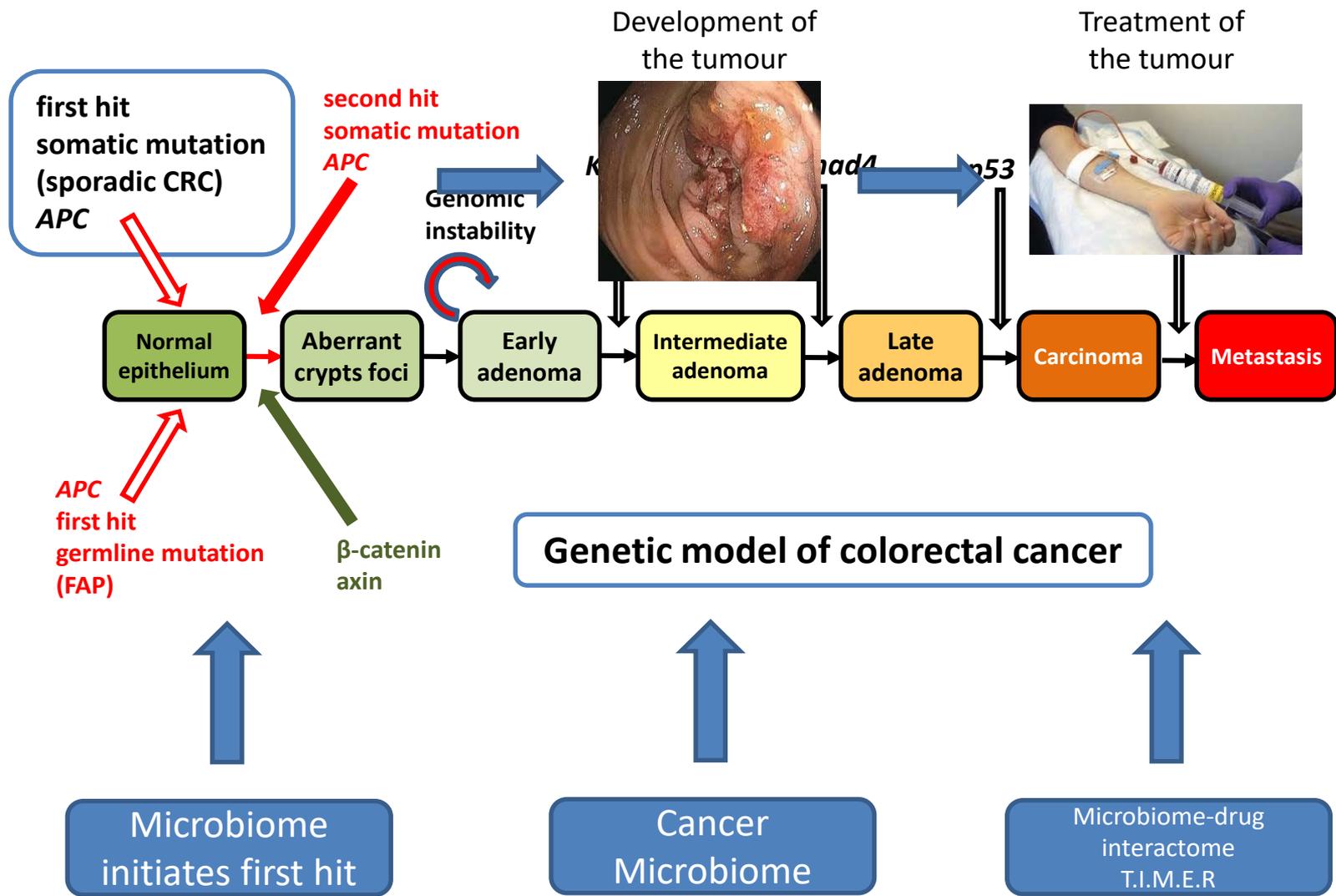
Evidence: The absence of a microbiome impacts the whole host



All these diseases have evidence for a role of a microbiome



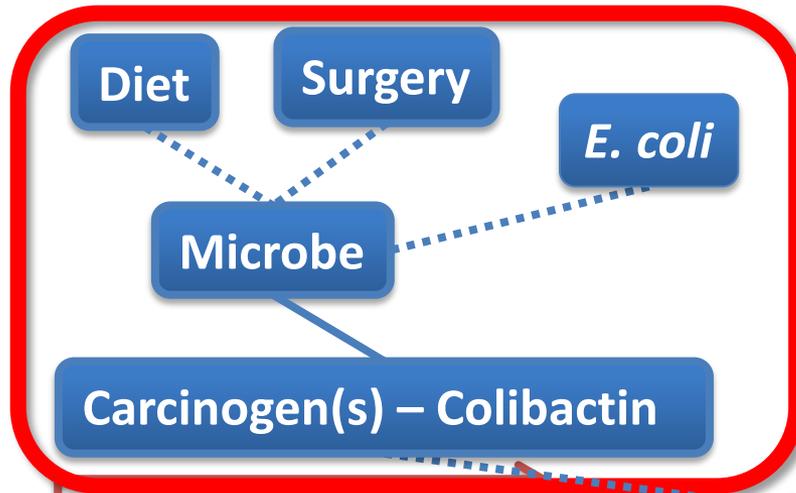
The majority of cancers arise randomly.



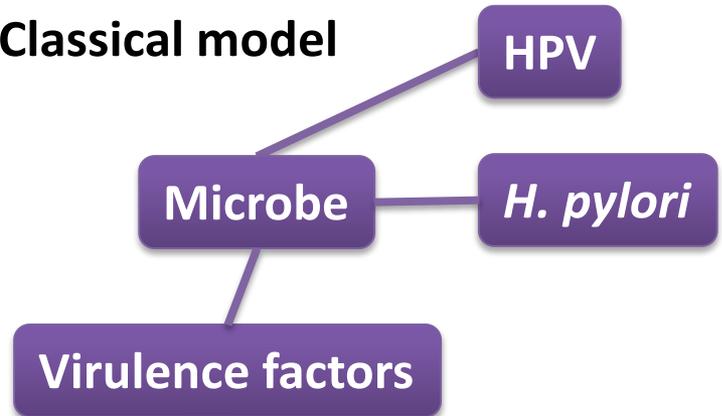
This is why as cancer specialists and oncologists need to think about the microbiome.

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

Who's responsible for the first hit?



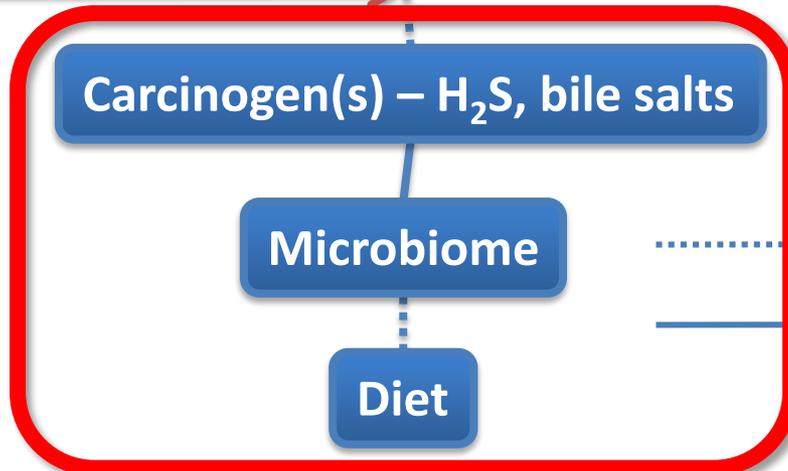
Classical model



first hit somatic mutation
(sporadic CRC) APC

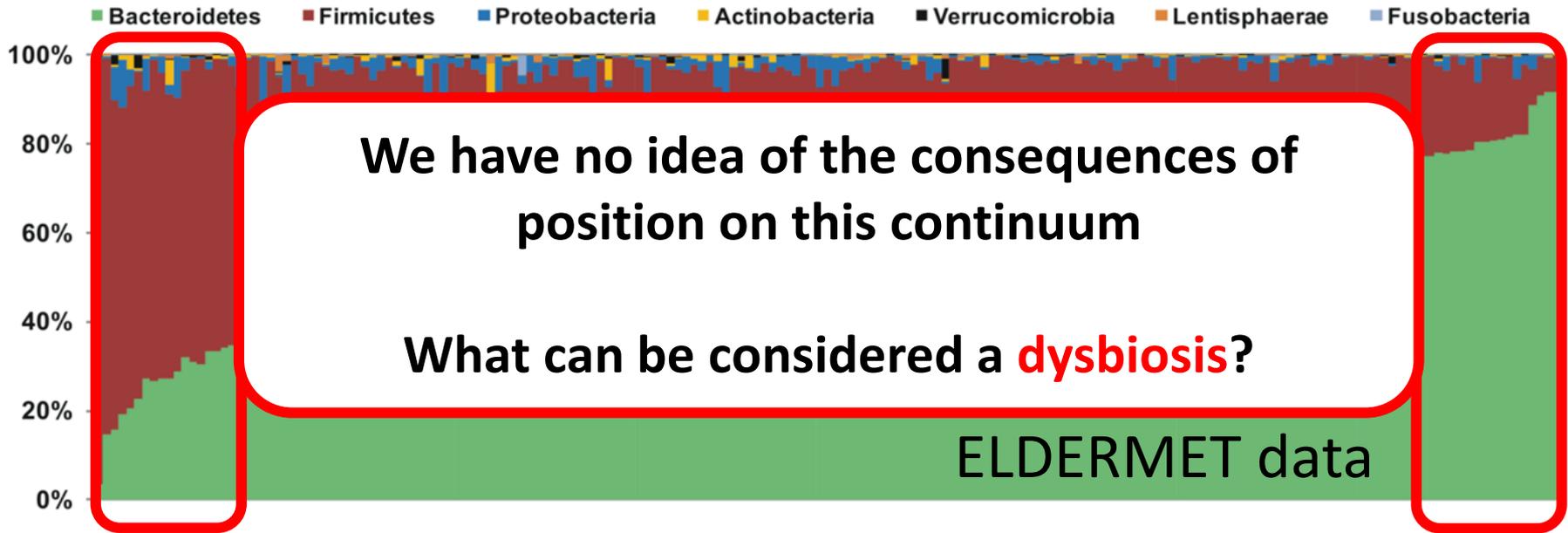
Ammensalistic?

Inflammation

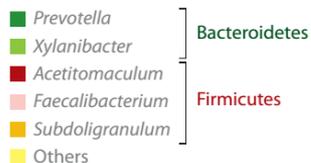
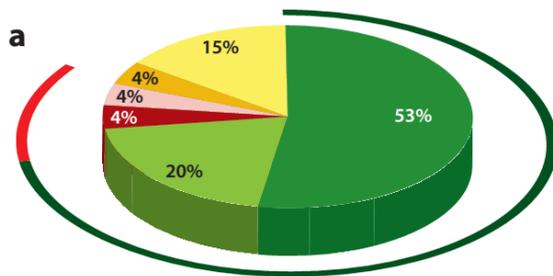


..... Strong associative link
——— Strong causal link

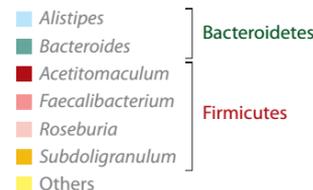
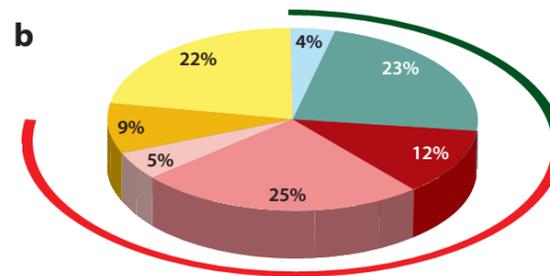
Variability clouds the issue of a healthy vs unhealthy microbiota



Burkina Faso



Italy



& biogeography complicates the story.

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

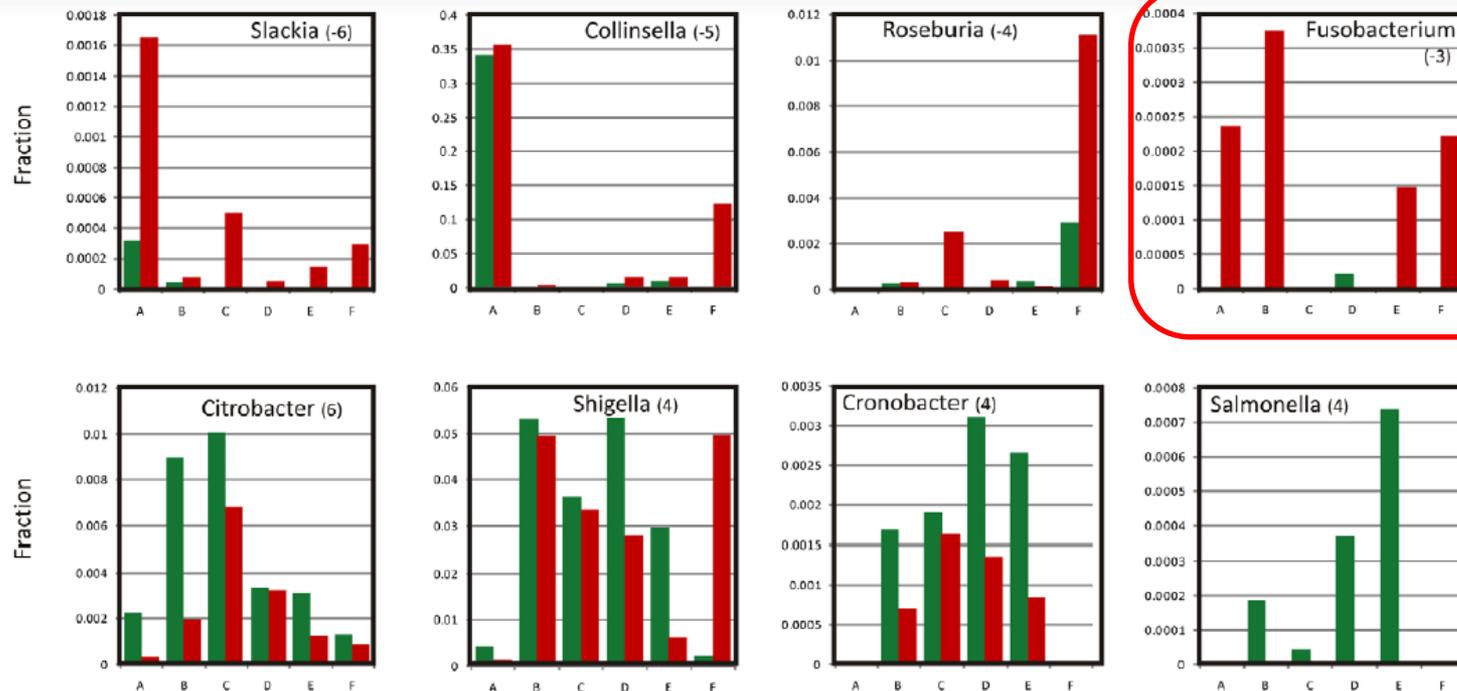
A tumour associated community of bacteria is identified

OPEN ACCESS Freely available online

2011 PLOS one

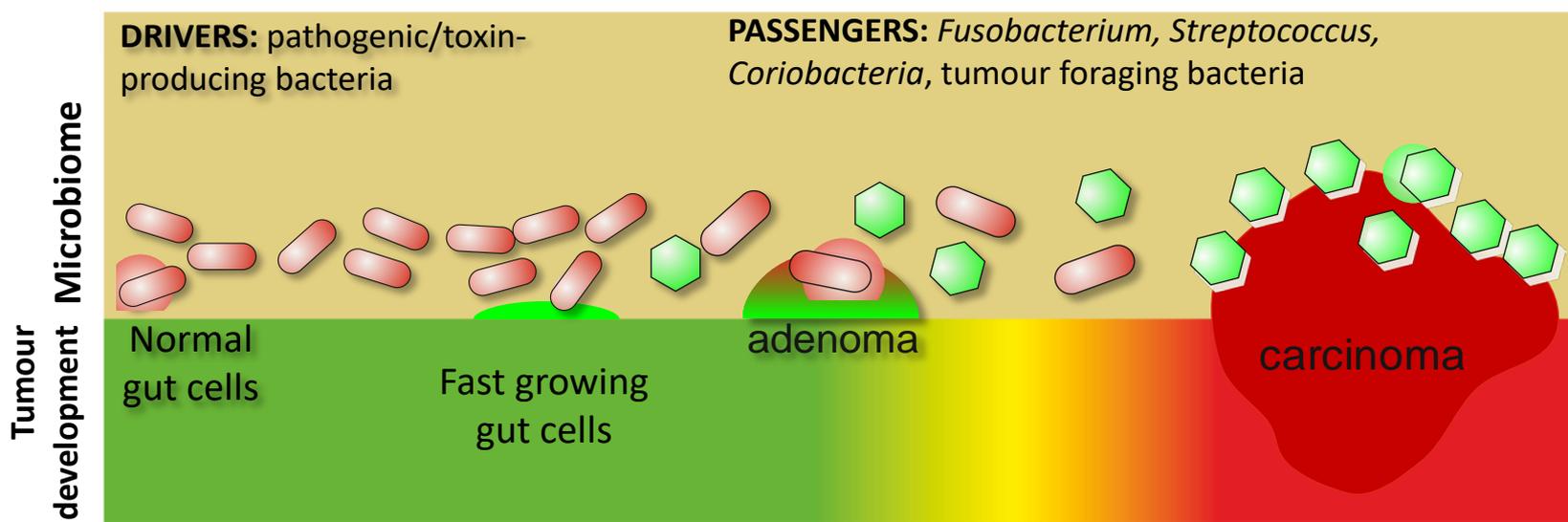
Towards the Human Colorectal Cancer Microbiome

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



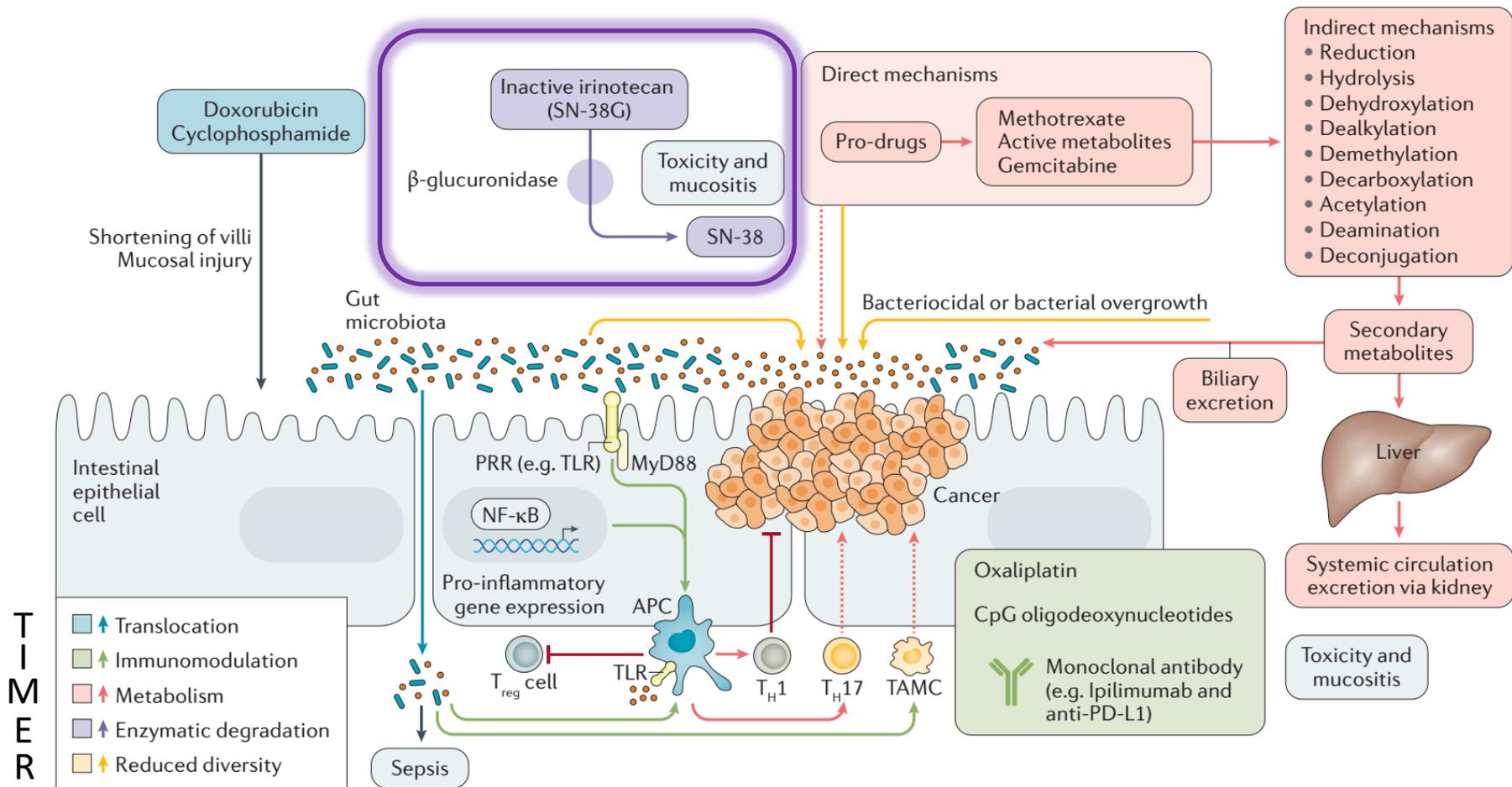
■ ON tumour, ■ OFF tumour

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.

'TIMER' Mechanisms for Microbiome modulation of Chemotherapy



Gut microbiota modulation of chemotherapy efficacy and toxicity

James L. Alexander^{1,3}, Ian D. Wilson³, Julian Teare¹, Julian R. Marchesi¹⁻³, Jeremy K. Nicholson³ and James M. Kinross^{1,3}

356 | JUNE 2017 | VOLUME 14

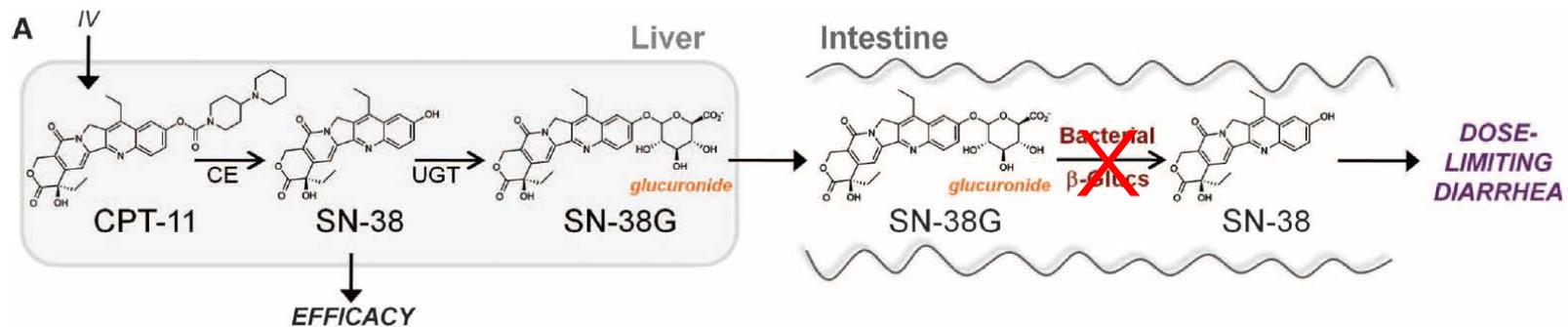
NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

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*}

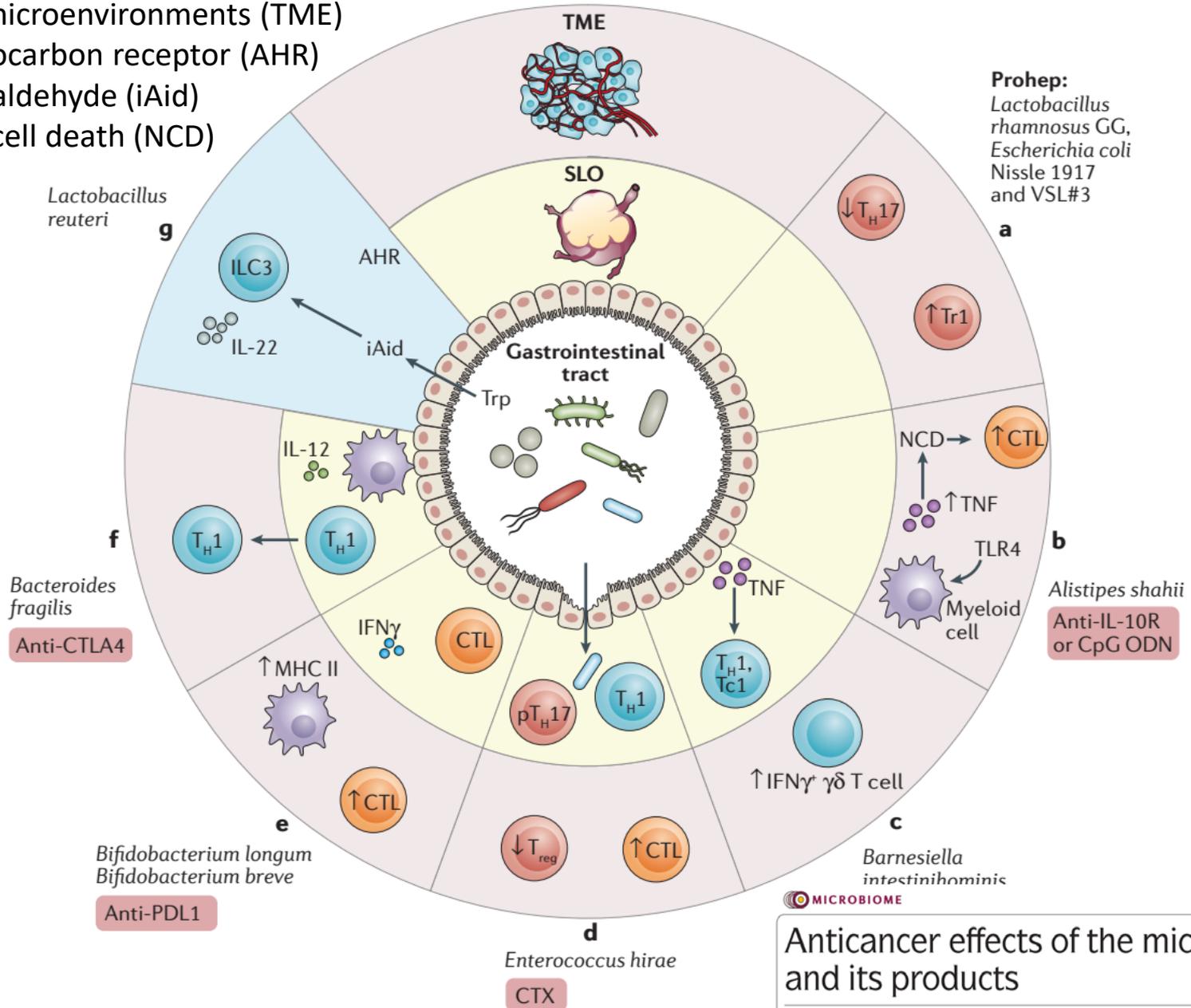
The dose-limiting side effect of the common colon cancer chemotherapeutic CPT-11 is severe diarrhea caused by symbiotic bacterial β -glucuronidases that reactivate the drug in the gut.

CPT-11 aka Irinotecan



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

Secondary lymphoid organs (SLO)
 Tumour microenvironments (TME)
 Aryl hydrocarbon receptor (AHR)
 Indole-3-aldehyde (iAid)
 Necrotic cell death (NCD)

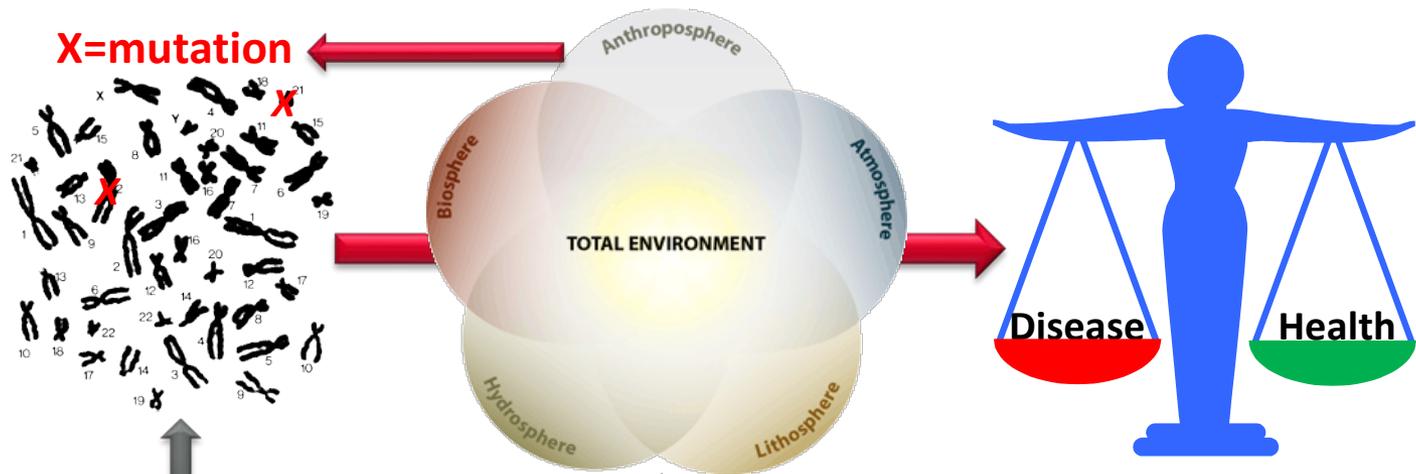


MICROBIOME

Anticancer effects of the microbiome and its products

Laurence Zitvogel¹⁻⁴, Romain Daillère¹⁻⁵, Maria Paula Roberti¹⁻⁵, Bertrand Routy¹⁻⁵ and Guido Kroemer⁴⁻¹⁰

The dialogue between the host and microbiome in a healthy context

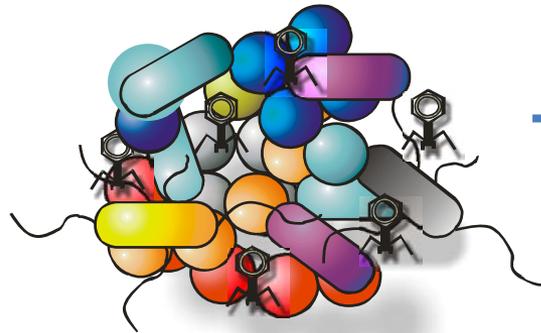


Human microbiome

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

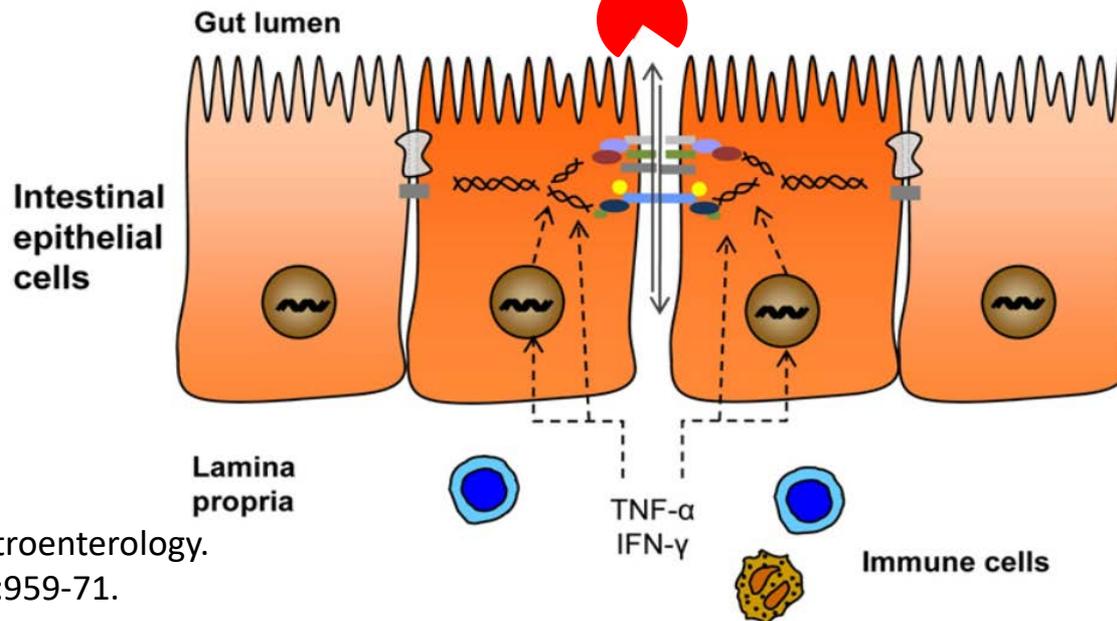
Exploring the gut microbiome via activity – emergent properties

The missing link is the proteome



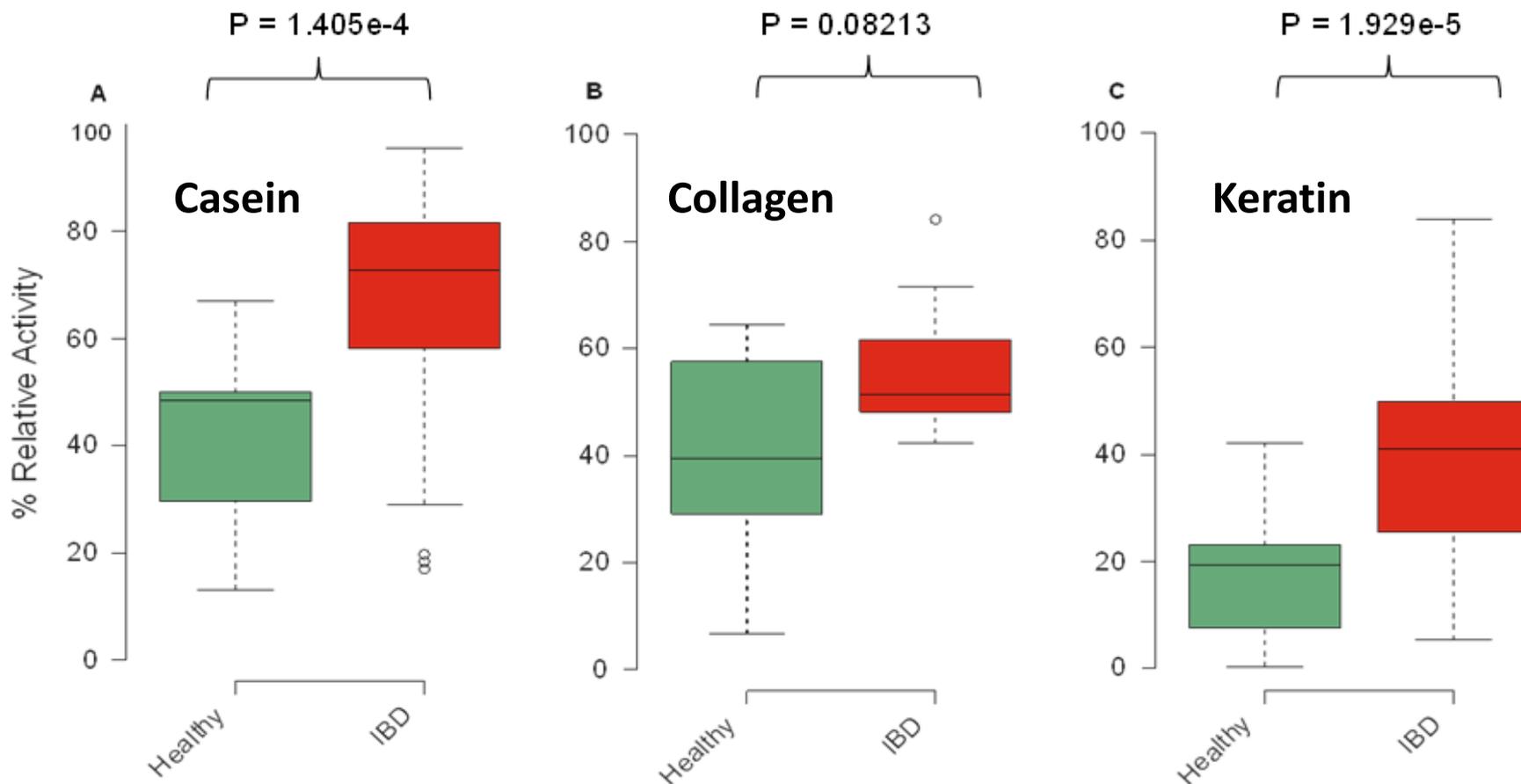
Why?

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

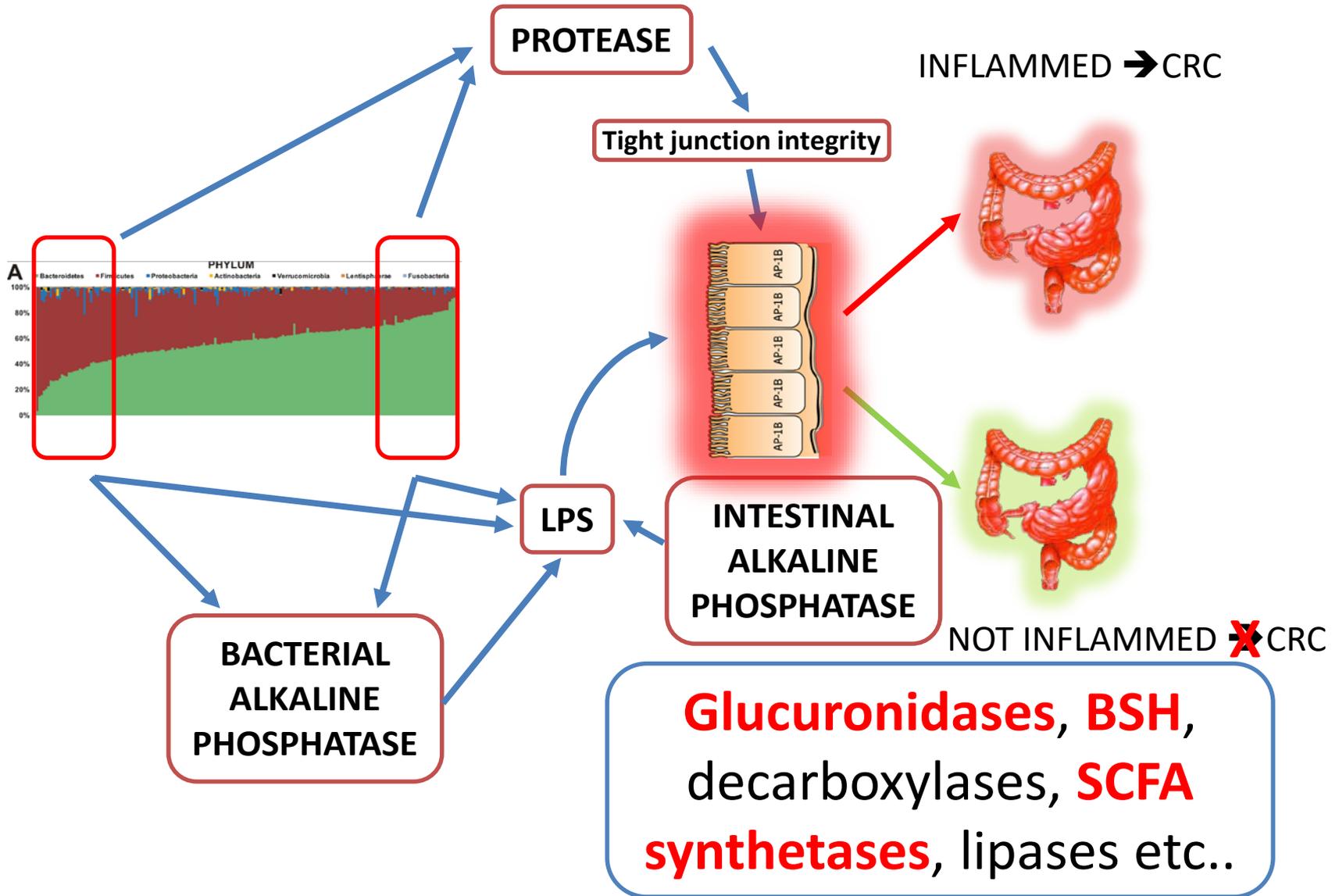
The degradome and degradomics is the study of enzymes which degrade proteins i.e. proteases. So does it play a role in inflammatory bowel disease?



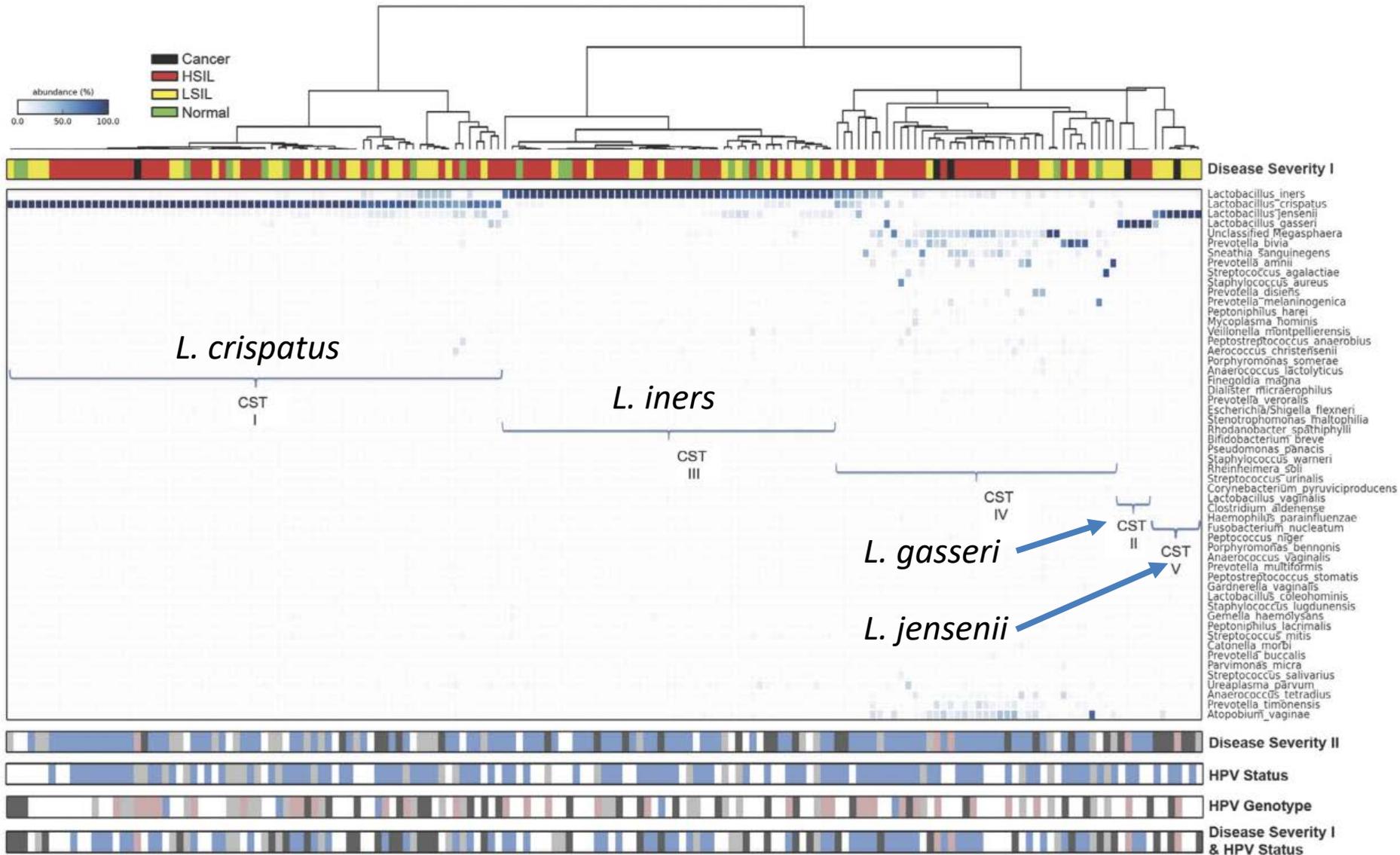
(n=10)

(n=13) we have now > 500 samples assayed

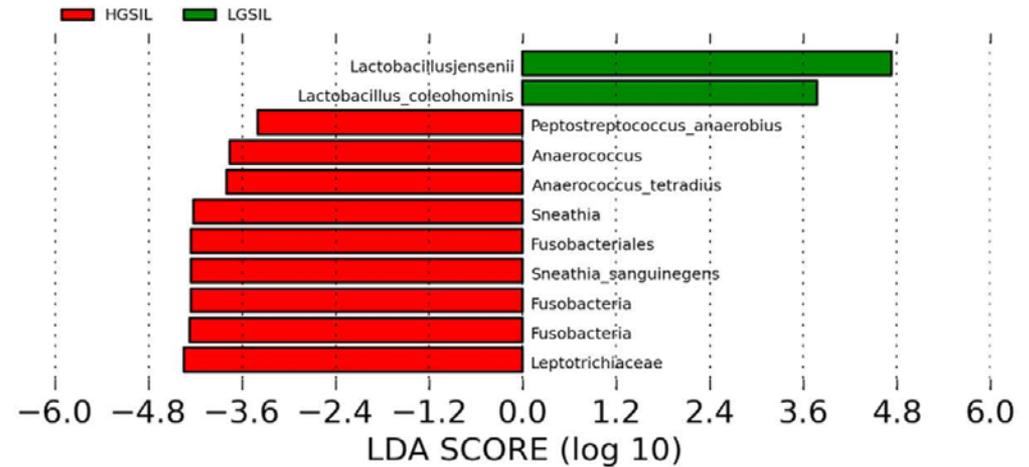
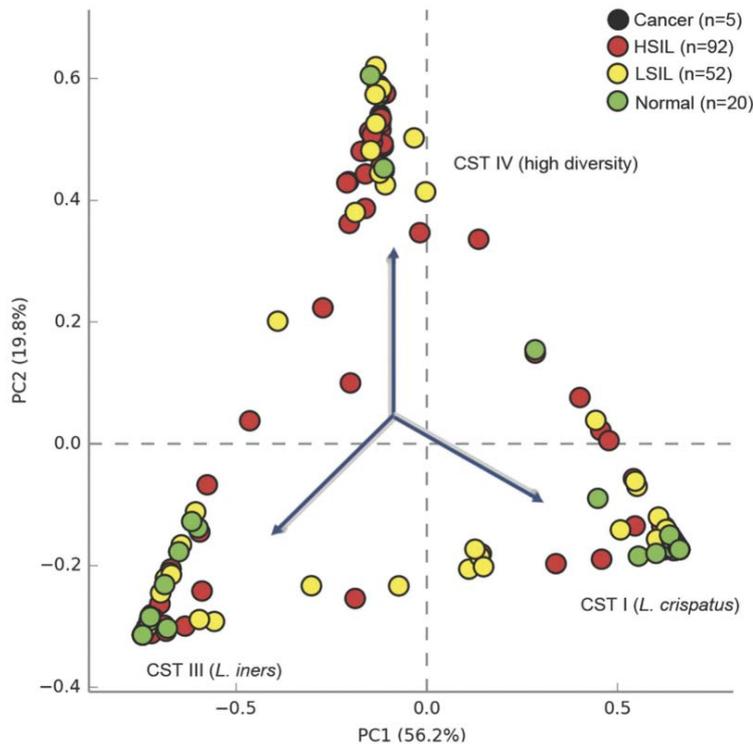
The microbiome and the healthy person



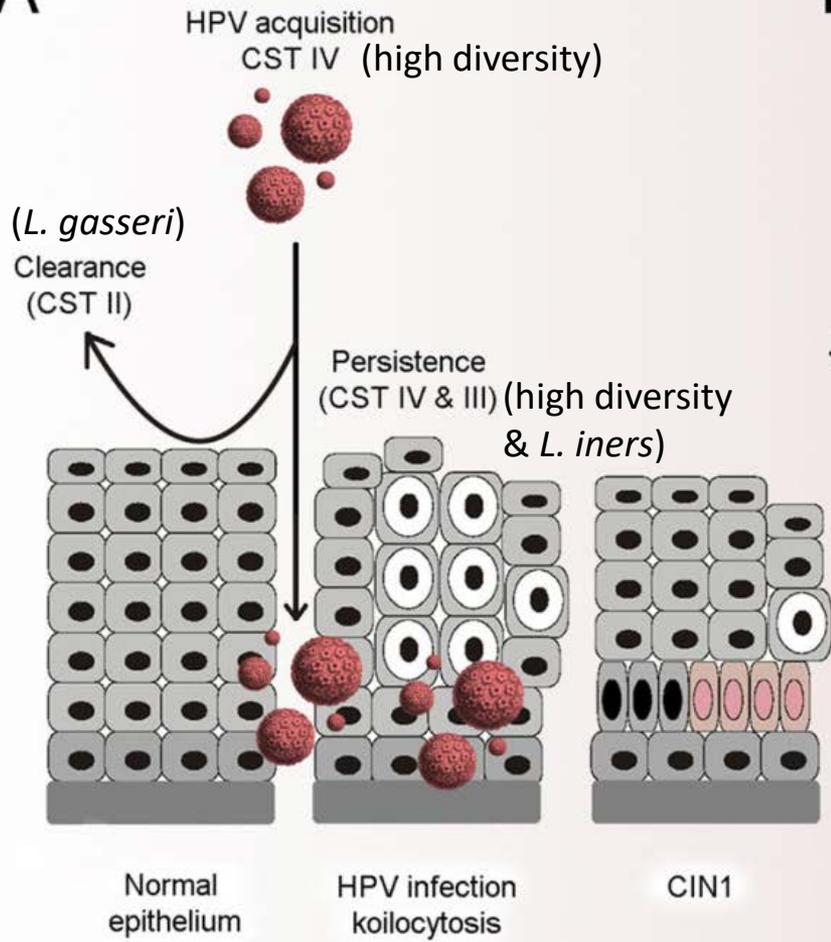
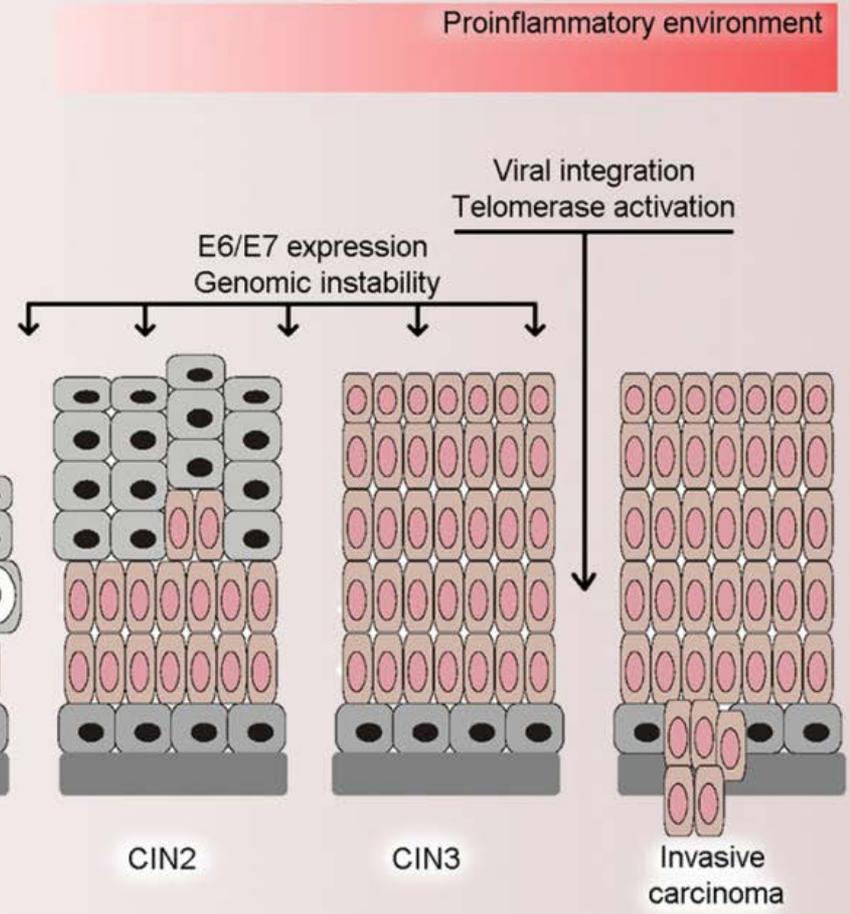
Vaginal microbiome CSTs in our UK population



Vaginal microbiome CSTs in our UK population



High-grade squamous intra-epithelial lesions (HSIL or HGSIL)
Low-grade squamous intra-epithelial lesions (LSIL or LGSIL)

A**B**

5 years from now?

- The infrastructure of a Global atlas of the gut microbiome-cancer drug/therapy landscape.
 - Already populated with data and recruiting trials and inception cohorts
- Robust tools for manipulating the gut microbiota
- Clear set of mechanisms for microbiota-immune interactions and how they drive adverse affects and drug response.
- Exploitation of bacteria as sentinels and therapies – mainly in animal models.
- Clearer epidemiological data for gut and vaginal microbiota in cancer initiation.

Bacterial Synthetic Engineering improves 5-FU Efficacy

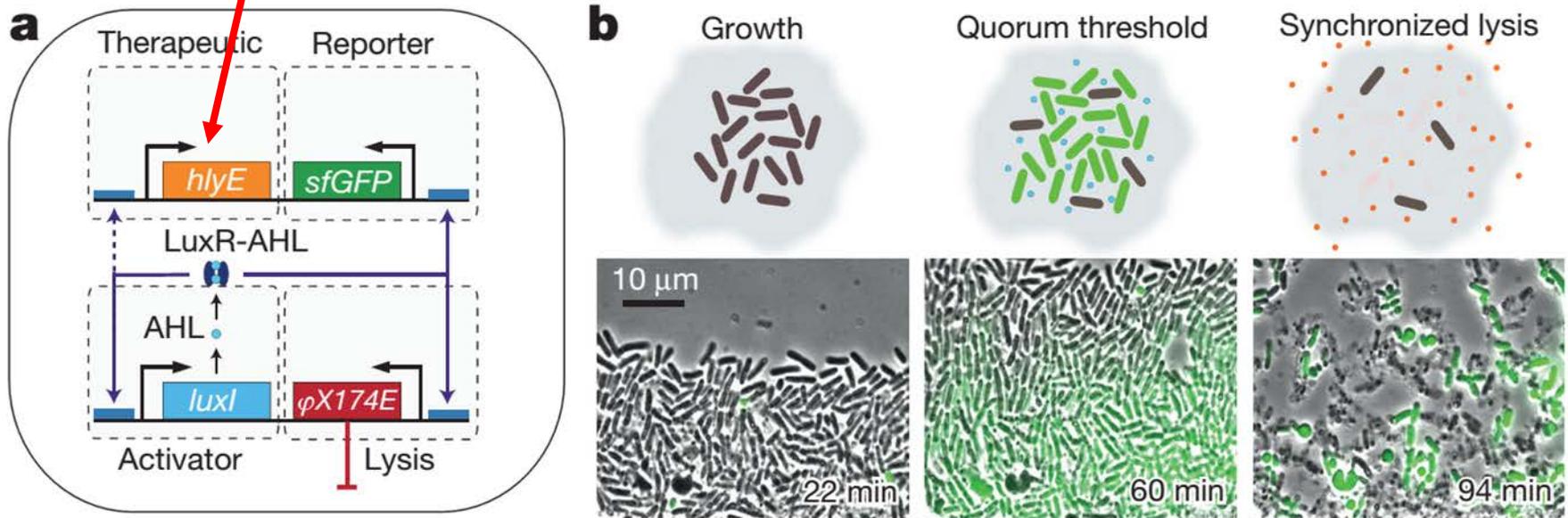
LETTER

doi:10.1038/nature18930

Synchronized cycles of bacterial lysis for *in vivo* delivery

M. Omar Din^{1*}, Tal Danino^{2,3*}, Arthur Prindle¹, Matt Skalak², Jangir Selimkhanov¹, Kaitlin Allen², Ellisix Julio¹, Eta Atolia², Lev S. Tsimring³, Sangeeta N. Bhatia^{2,4,5,6,7,8} & Jeff Hasty^{1,3,9}

Haemolysin E, encoded by *hlyE* is a pore-forming anti-tumour toxin



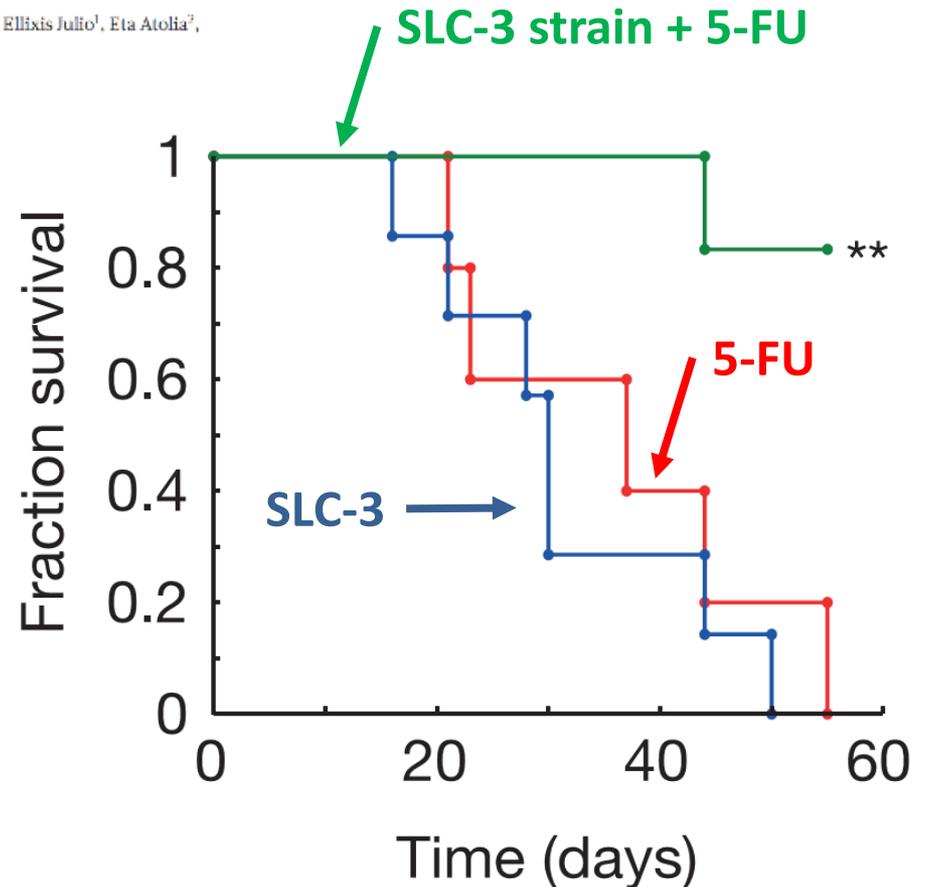
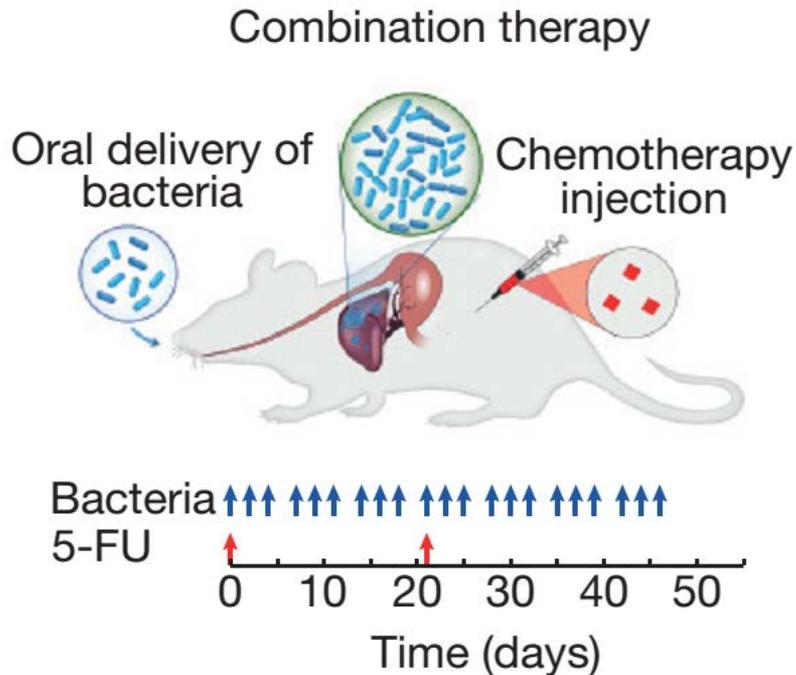
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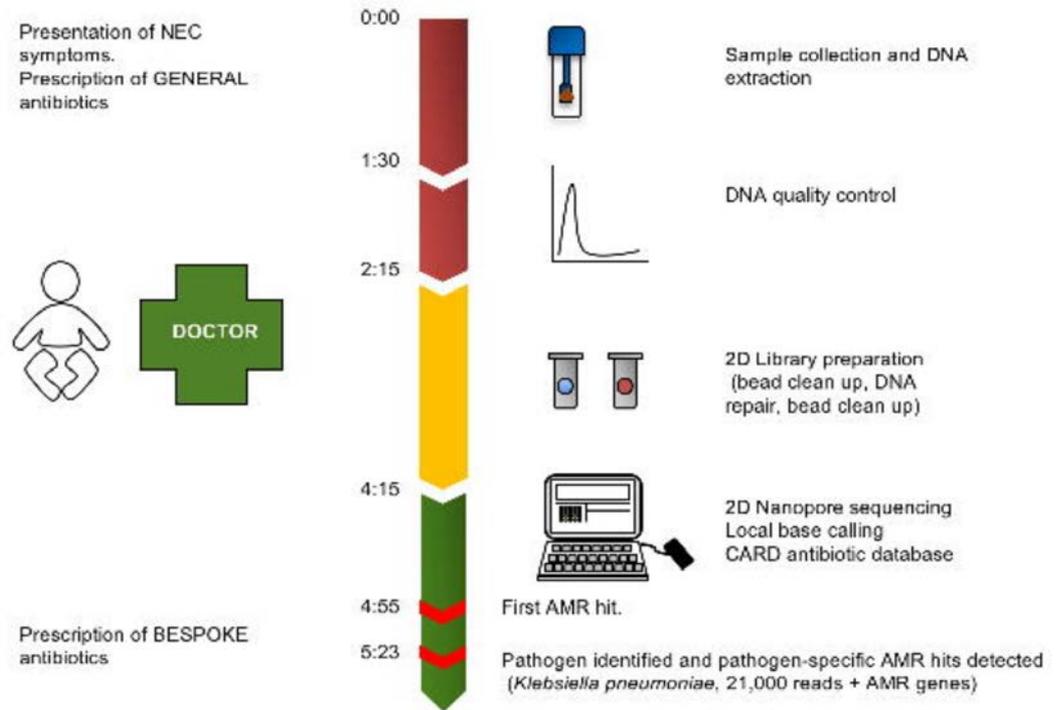
M. Omar Din^{1*}, Tal Danino^{2,3*}, Arthur Prindle³, Matt Skalak², Jangir Selimkhanov¹, Kaitlin Allen², Ellis Julio¹, Eta Atolia², Lev S. Tsimring³, Sangeeta N. Bhatia^{2,4,5,6,7,8} & Jeff Hasty^{1,3,9}



Transplantation model of hepatic colorectal metastases

10 years from now

- Routine screening of the gut microbiota, as a clinical variable, when undertaking chemo- and immunotherapy
- Screening of the exo-proteome will become more routine.



Dr Lindsay Hall Quadram Institute

- Precision medicine and cancer therapy will start to merge in terms of diagnosis and treatment – we will see some tangible integration of the microbiome in oncology

In summary

- Application of multi modal “omic” tools is definitely helping us to determine the roles of the gut bacteria in IBD, cancer, general inflammation, auto-immune disease and other NCDs.
- Newer ecologic concepts, such as ammensalism will help guide us to a better understanding of the role of the microbiome.
- The microbiome will need to be considered in relation to drug efficacy
- Can we harness knowledge of the microbiome to treat and understand NCDs?
- Thank you and I wish to thank my labs at Imperial and Cardiff and the funders of my research.

