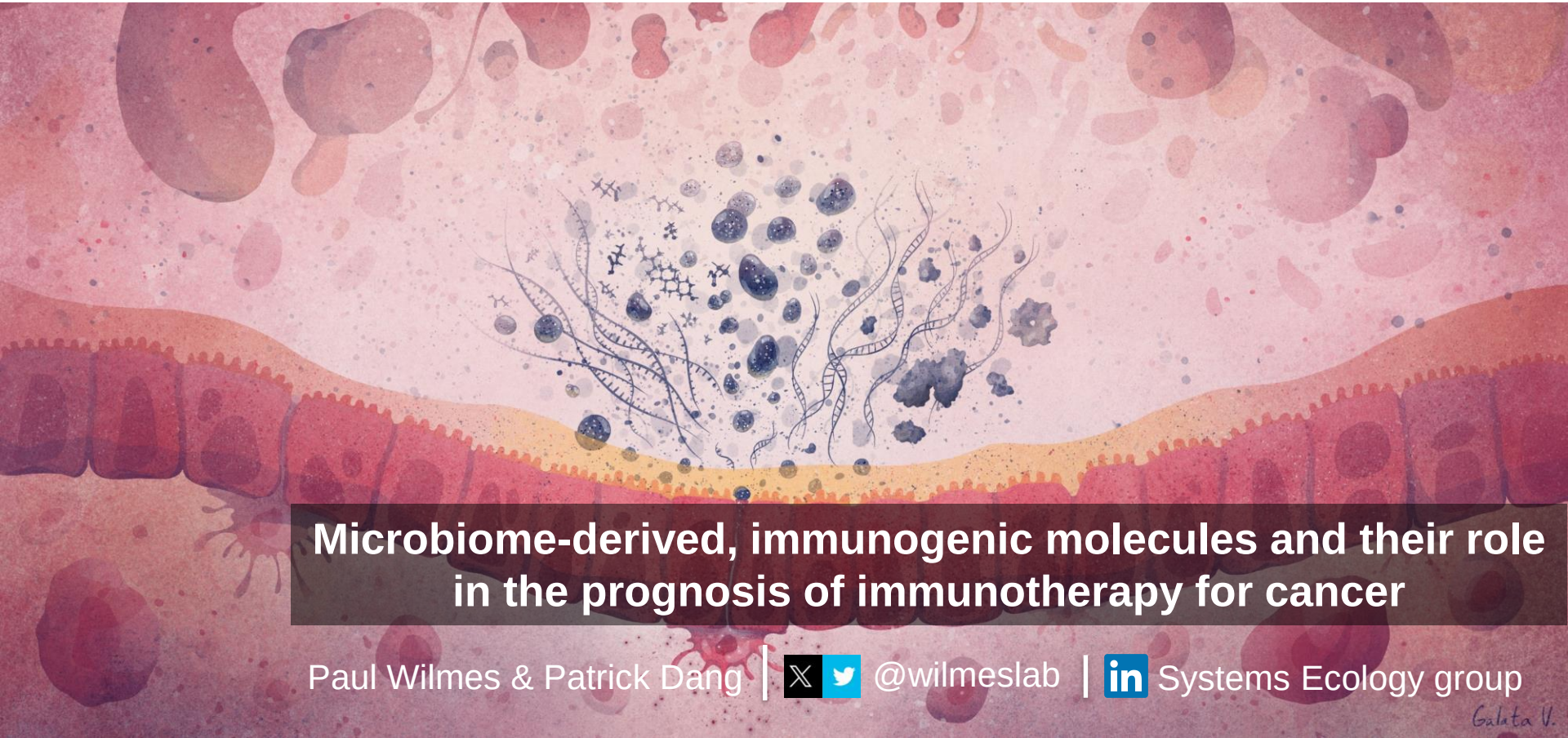
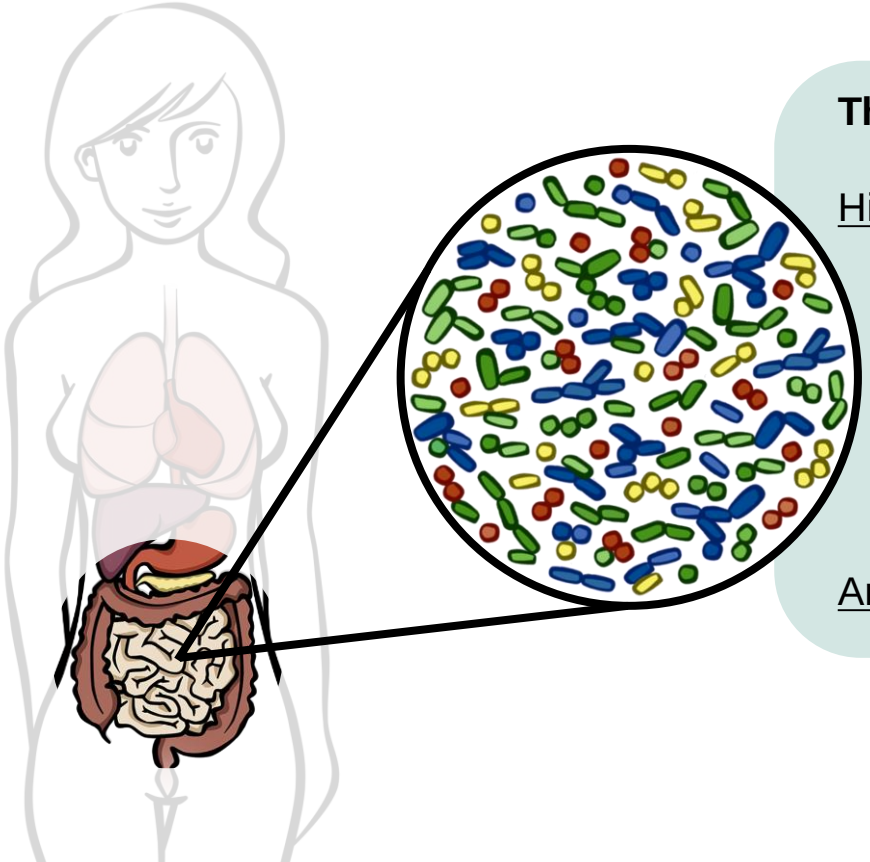
LUXEMBOURG INSTITUTE OF HEALTH | CHL | HÔPITAUX ROBERT SCHUMAN | iTRON | UNIVERSITÉ DU LUXEMBOURG | LCSB | DLSM | DEPARTMENT OF LIFE SCIENCES AND MEDICINE



Microbiome-derived, immunogenic molecules and their role in the prognosis of immunotherapy for cancer

Paul Wilmes & Patrick Dang | @wilmeslab | Systems Ecology group

Human microbiome



The gut microbiome

Highly diverse

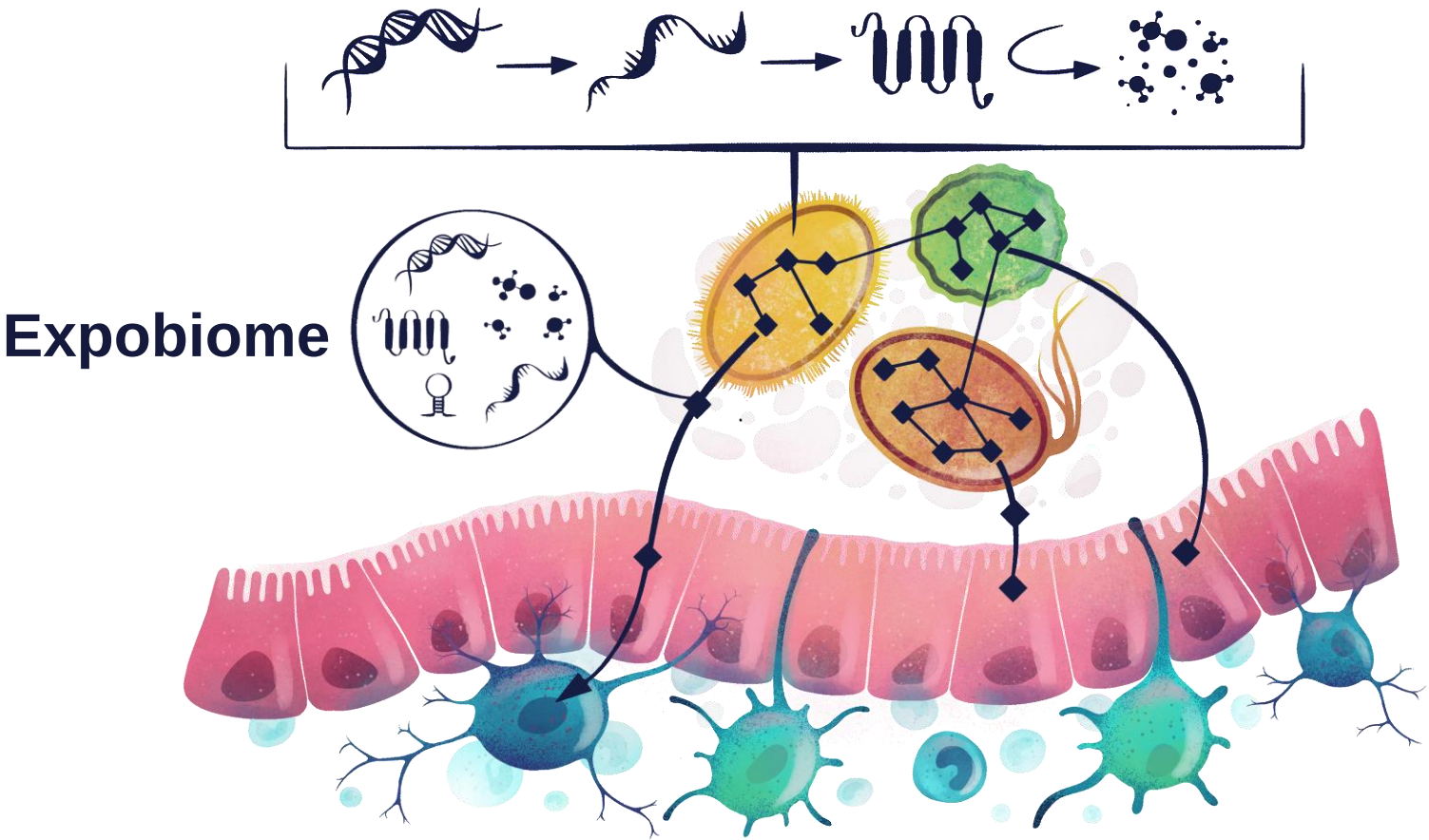
>>100,000s strains

Complex networks

Essential functions

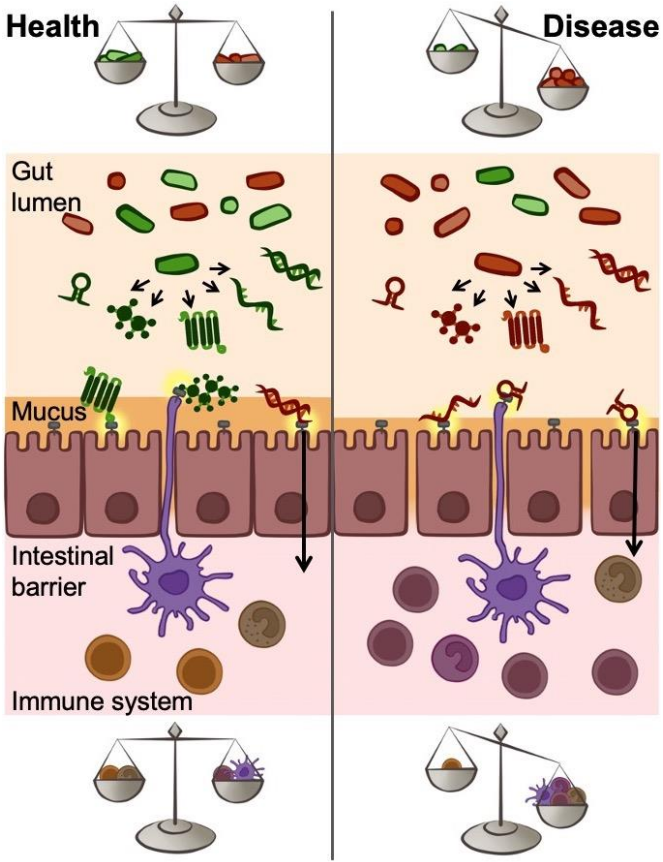
Anthropocene impacts

Microbial Systems Ecology



Wilmes, *et al.* (2022) *Cell Host & Microbe* **30**:1201-1206.
Muller, *et al*. (2018) *Curr. Op. in Systems Biology* **8**:73-80.

Microbiome functions and disease



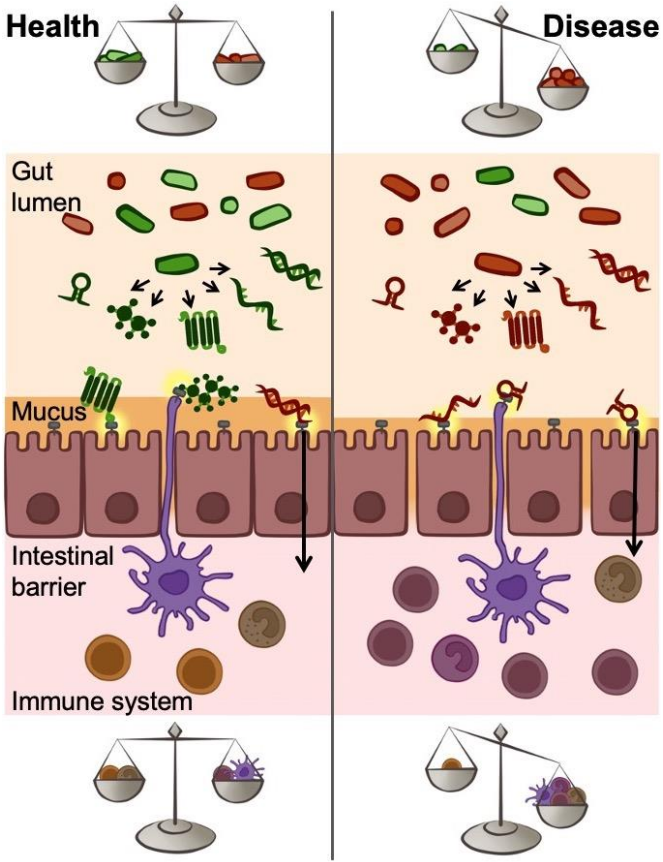
Chronic diseases

- *Autoimmune*
- ***Cancer***
- *Metabolic*
- *Neurodegenerative*

Inflammation

Wilmes, *et al*. (2022) *Cell Host & Microbe* **30**:1201-1206.

Microbiome functions and disease

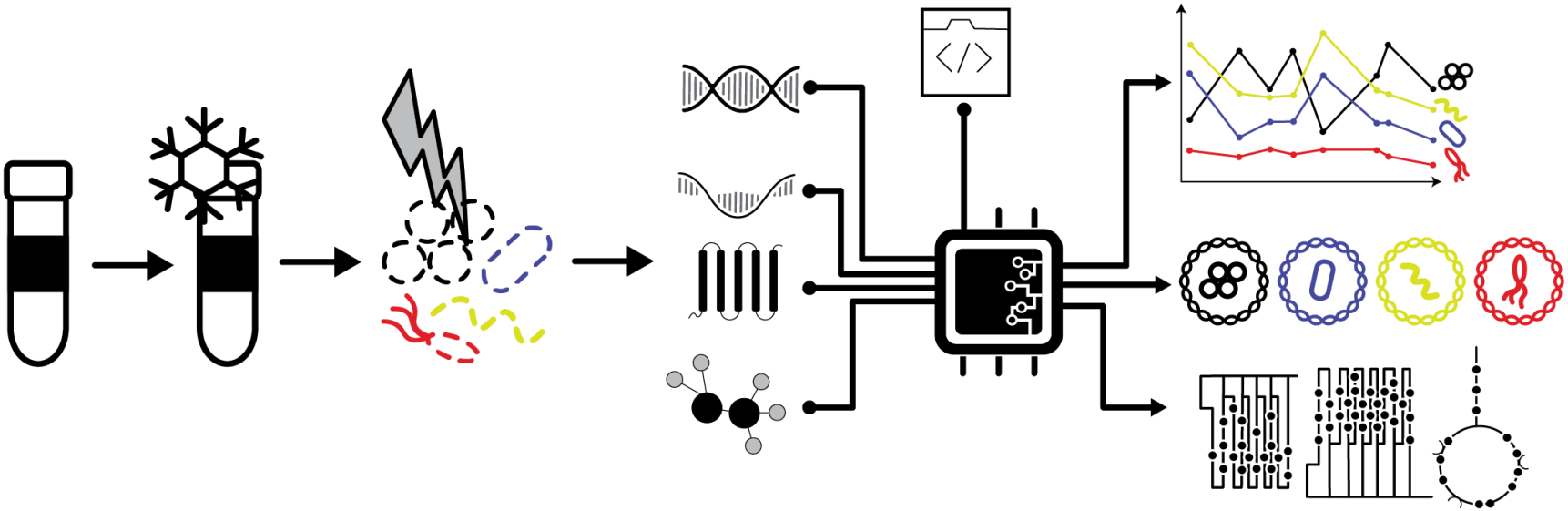


Cause
or
consequence?

MICROBIAL SYSTEMS ECOLOGY

Wilmes, *et al*. (2022) *Cell Host & Microbe* **30**:1201-1206.

Integrated multi-omics



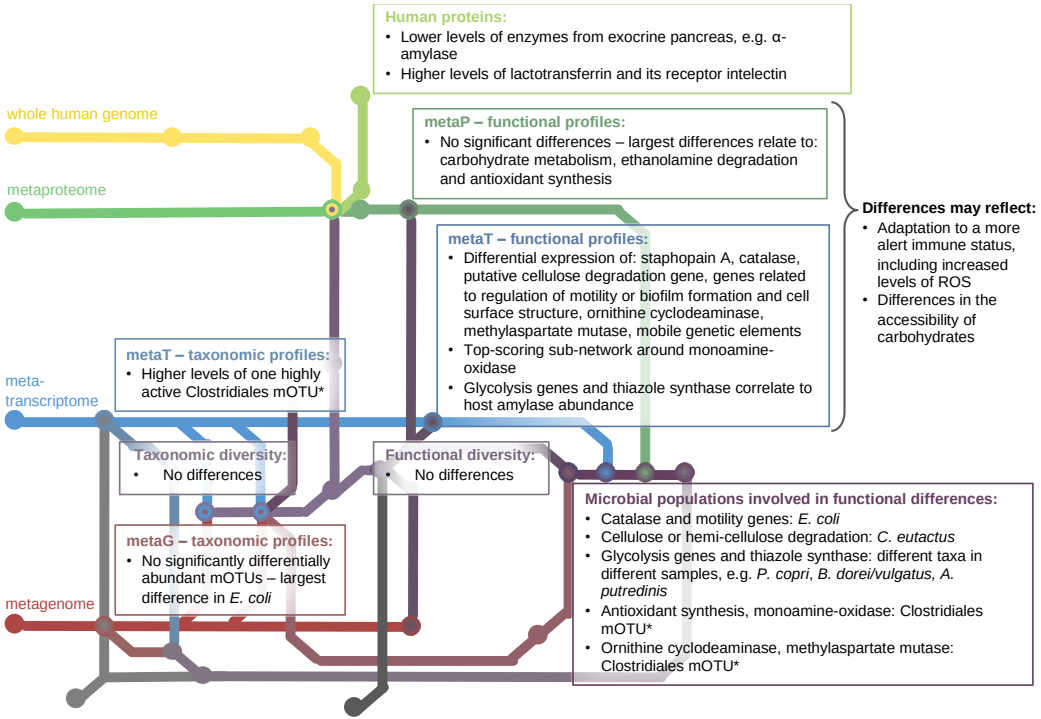
Roume, *et al*. (2013) *The ISME Journal* **7**:110–121.
Muller, *et al*. (2013) *Trends in Microbiology* **21**:325–333.
Roume, *et al*. (2013) *Methods in Enzymology* **531:**219–236.
Muller, *et al*. (2014) *Nature Communications* **5**:5603.
Laczny, *et al*. (2014) *Scientific Reports* **4**:4516.
Laczny, *et al.* (2015) *Microbiome* **3**:1.
Roume*, *et al*. (2015) *npj Biofilms & Microbiomes* **1**:15007.
Narayanasamy, *et al.* (2016) *Genome Biology* **17**:260.
Heintz-Buschart, *et al*. (2017) *Nature Microbiology* **16180**:1-12.
Herold, *et al*. (2020) *Nature Communications* **11**:5281.
de Nies, *et al*. (2021) *Microbiome* **9**:49.
Martinez-Arbas*, Narayanasamy*, *et al*. (2021) *Nature Microbiology* **6**:123–135.
Queirós, *et al*. (2021) *GigaScience* **10**:42.
De Saedeleer, *et al*. (2021) *ISME Communications* **1**:82.
Hickl, *et al*. (2022) *Briefings in Bioinformatics* **23**:431.
de Nies, *et al*. (2022) *eLife* **11**:e81196.
Novikova, *et al*. (2024) *ISME Communications* **4**:ycad014.
Delogu, *et al*. (2024) *Nature Ecology & Evolution* **8**:32-44.

Microbiome differences in type 1 diabetes

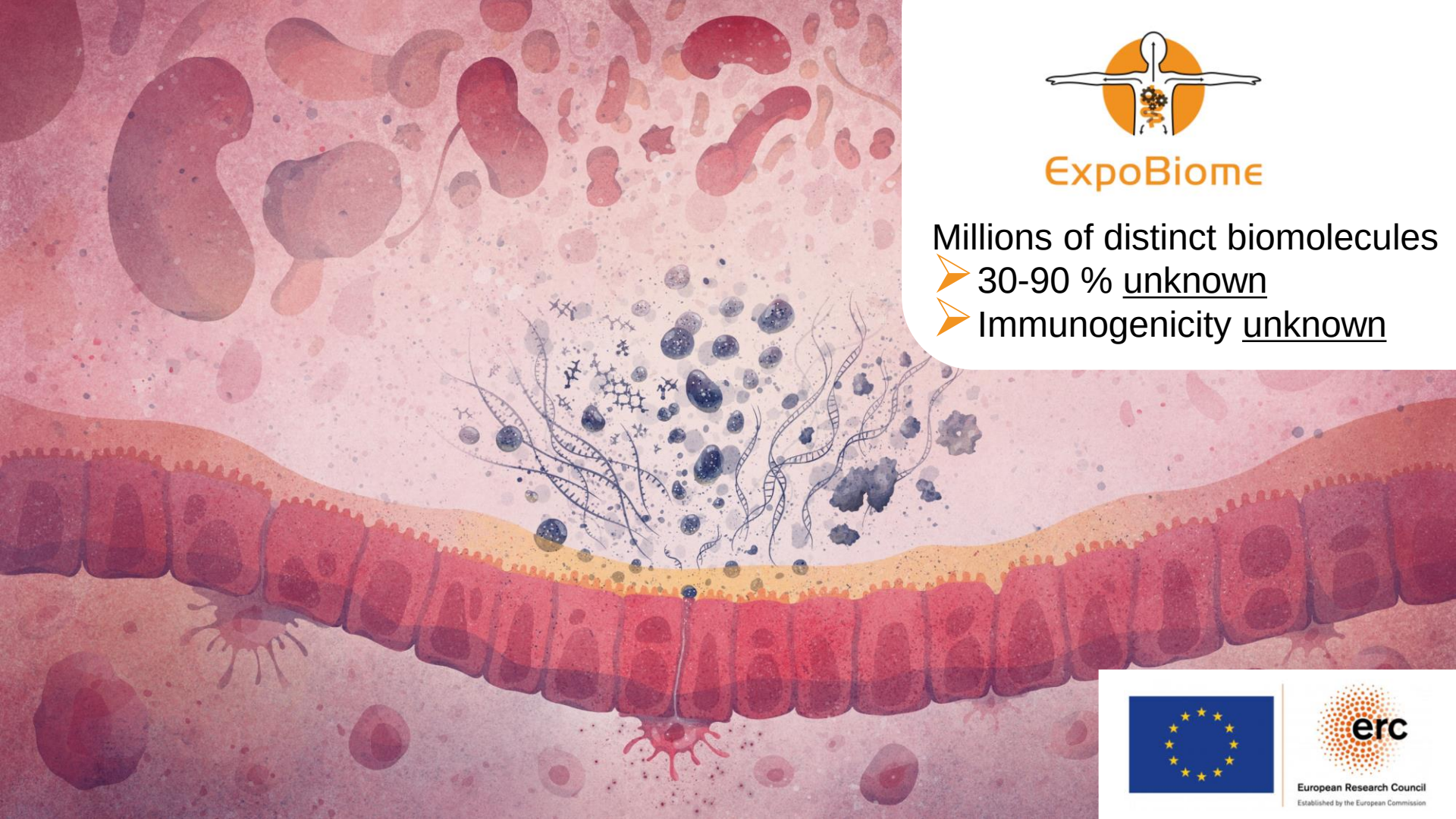
Microbial functions **differentially expressed** in disease:

- **encoded** & **expressed by distinct populations** in distinct individuals
- affected by **endogenous factors** (exocrine pancreatic enzymes)

Ecosystem services!



Heintz-Buschart, *et al*. (2017) *Nature Microbiology* **16180**:1-12.
Heintz-Buschart & Wilmes (2018) *Trends in Microbiology* **26**:563-574.



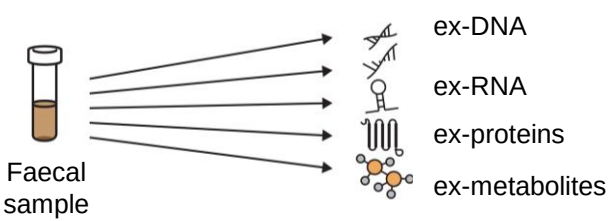
ExpoBiome

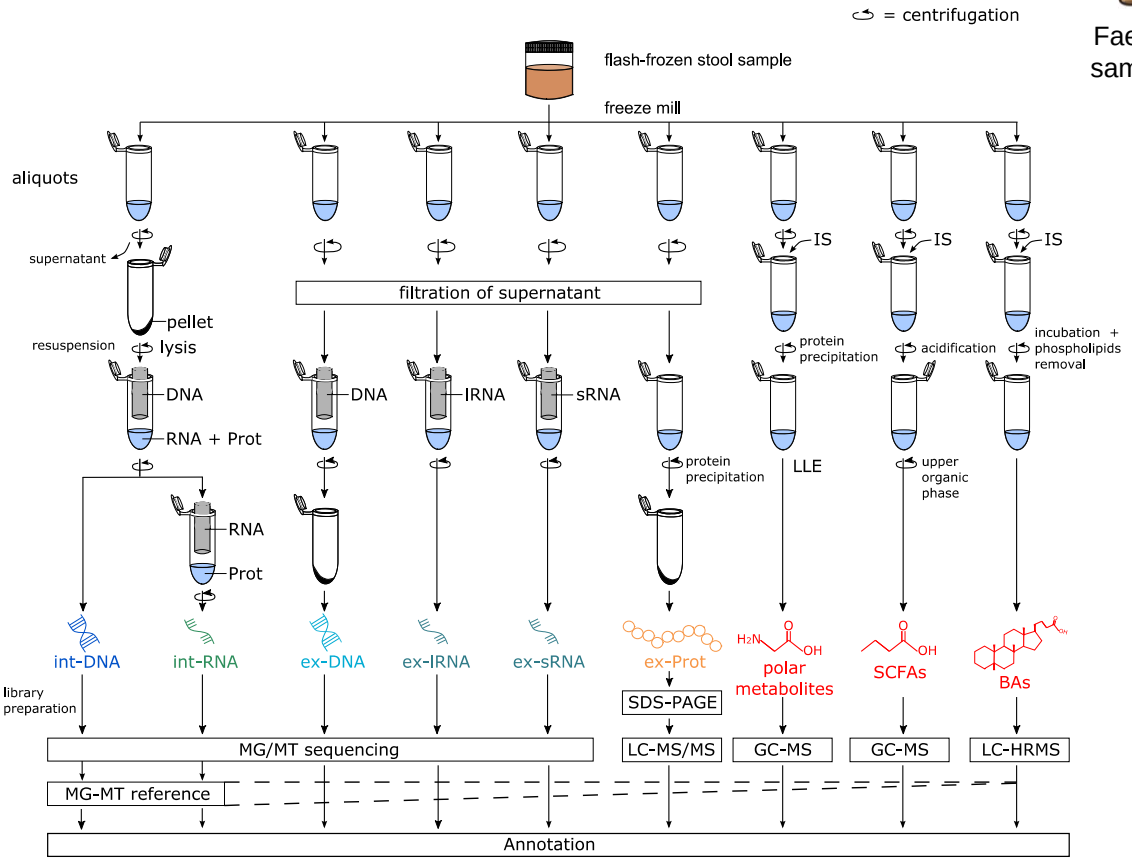
Millions of distinct biomolecules

- 30-90 % unknown
- Immunogenicity unknown

European Research Council
Established by the European Commission

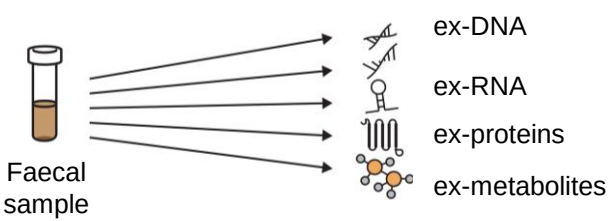
Microbiome-derived omes





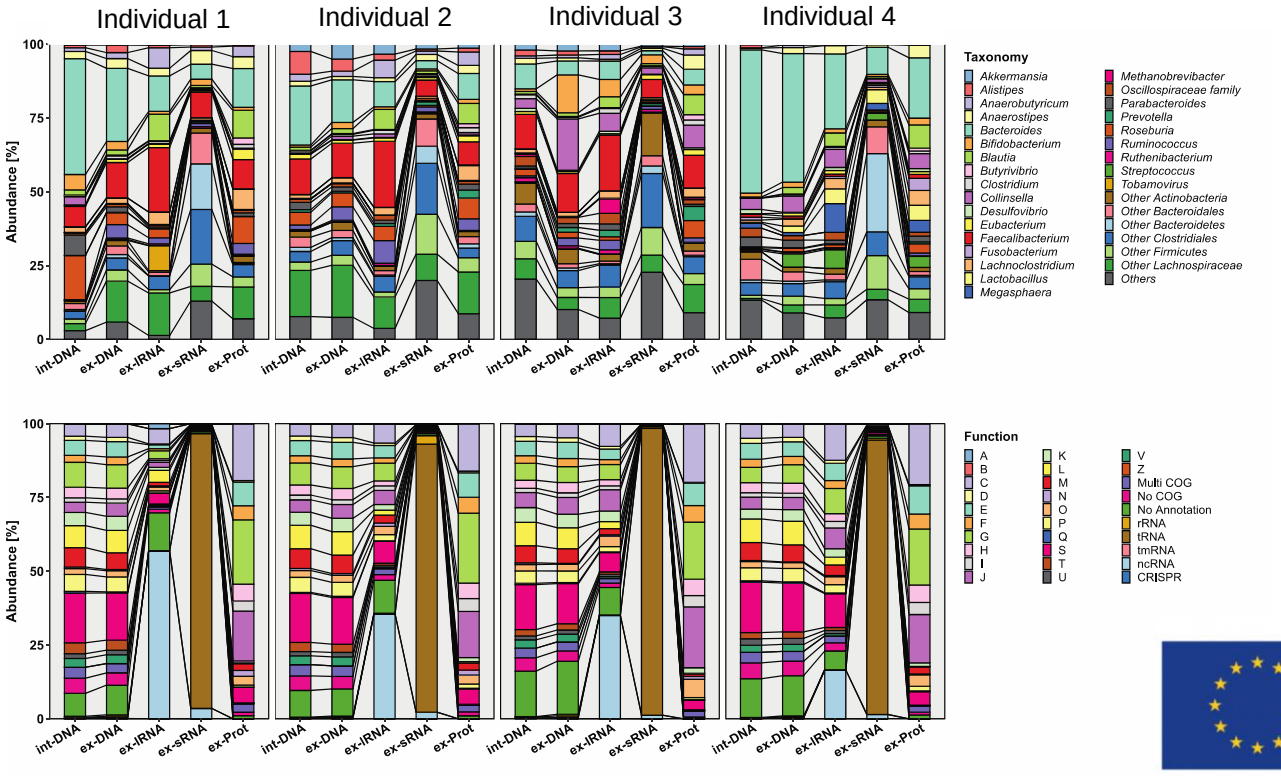
De Saedeleer, …, Wilmes (2021) *ISME Communications* **1**:82.

Microbiome-derived ex-omes



Taxa

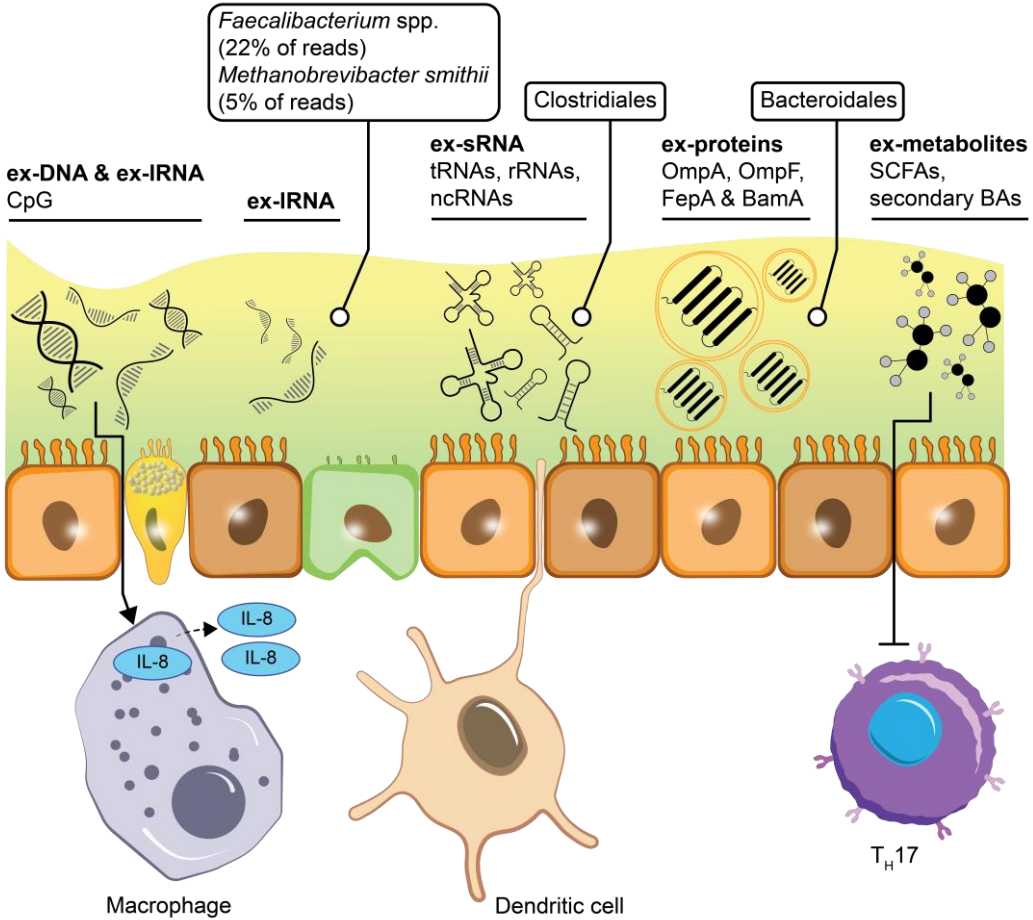
Functions



European Research Council
Established by the European Commission

De Saedeleer, *et al*. (2021) *ISME Communications* **1**:82.

Immunogenicity of biomolecular complement



De Saedeleer, *et al*. (2021) *ISME Communications* **1**:82.

LUXEMBOURG INSTITUTE OF HEALTH

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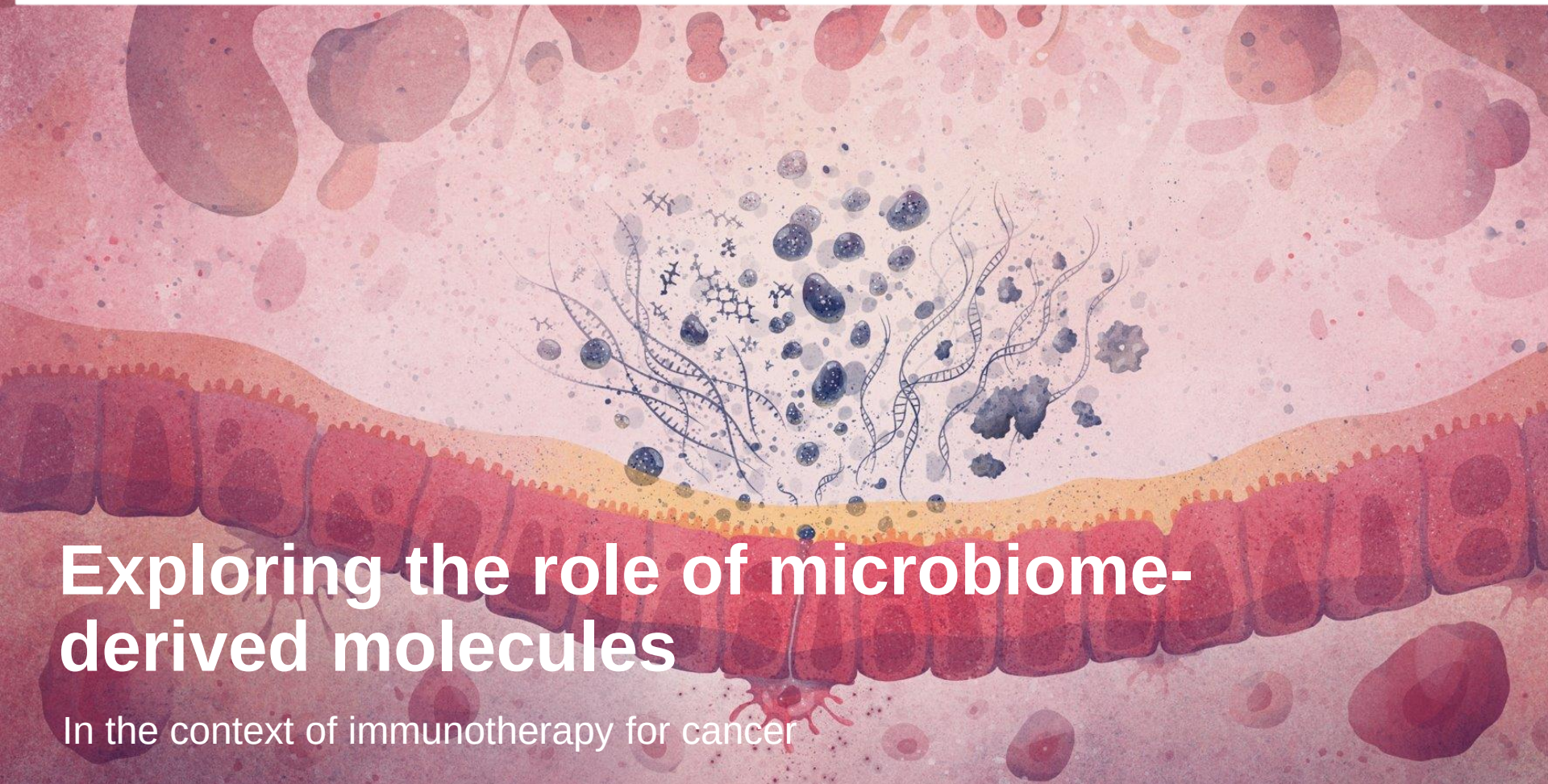
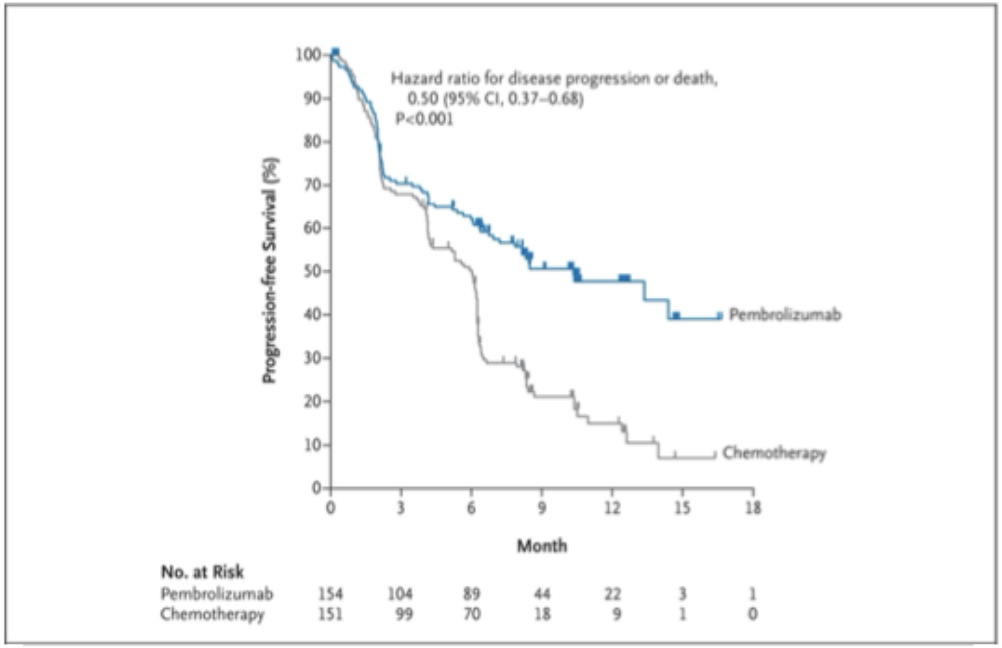


Exploring the role of microbiome-derived molecules

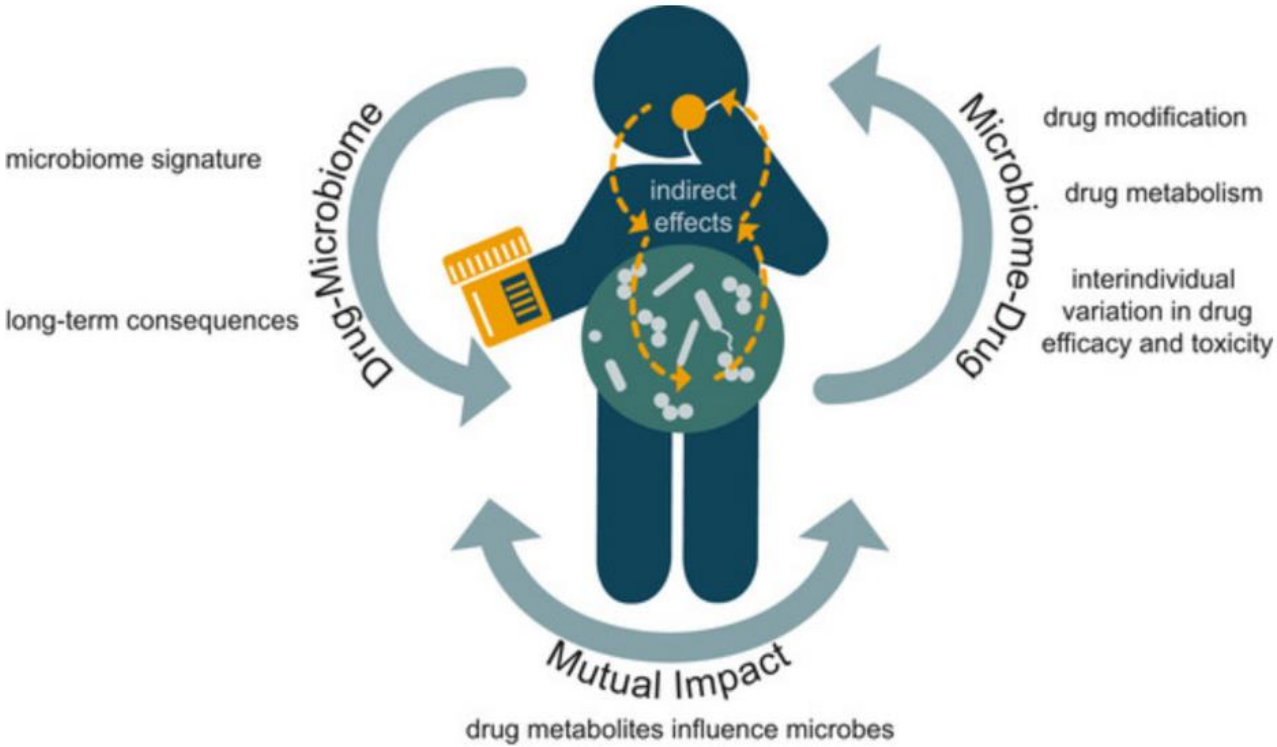
In the context of immunotherapy for cancer

Why Immunotherapy?

- Treatment that uses a person's own immune system to fight cancer
- A small proportion of patients actually see long-lasting benefits
- **A deeper understanding** of the relationships between immunotherapy and treatment resistance **is needed**



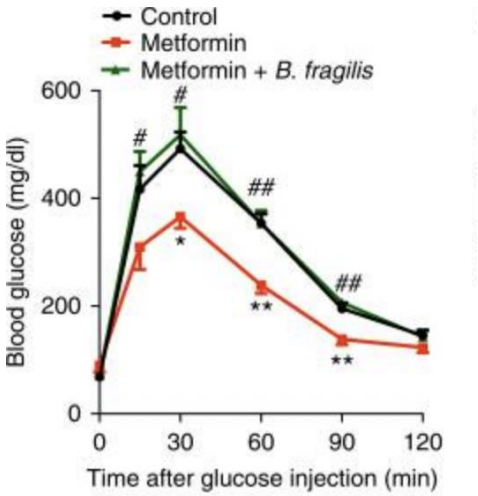
Martin Reck and al. **Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer**

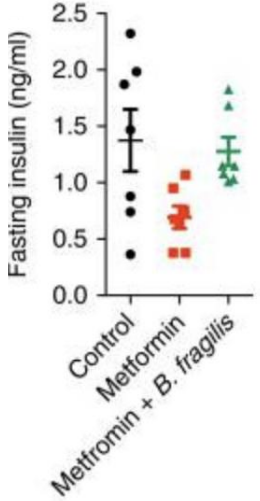


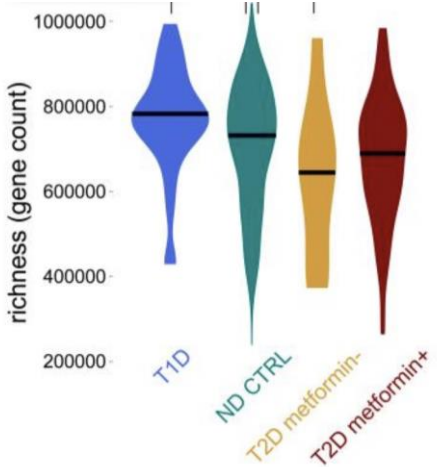
Zimmermann *et al*. (2020) *Molecular Systems Biology* **17**.

Metformin

- Limited oral bioavailability, resulting in a **high concentration** of the drug in the **intestines**
- Discovery of a **direct link between taxonomic changes** in the bacterial population of the microbiome **and the improvement of metabolic dysfunctions and hyperglycemia**

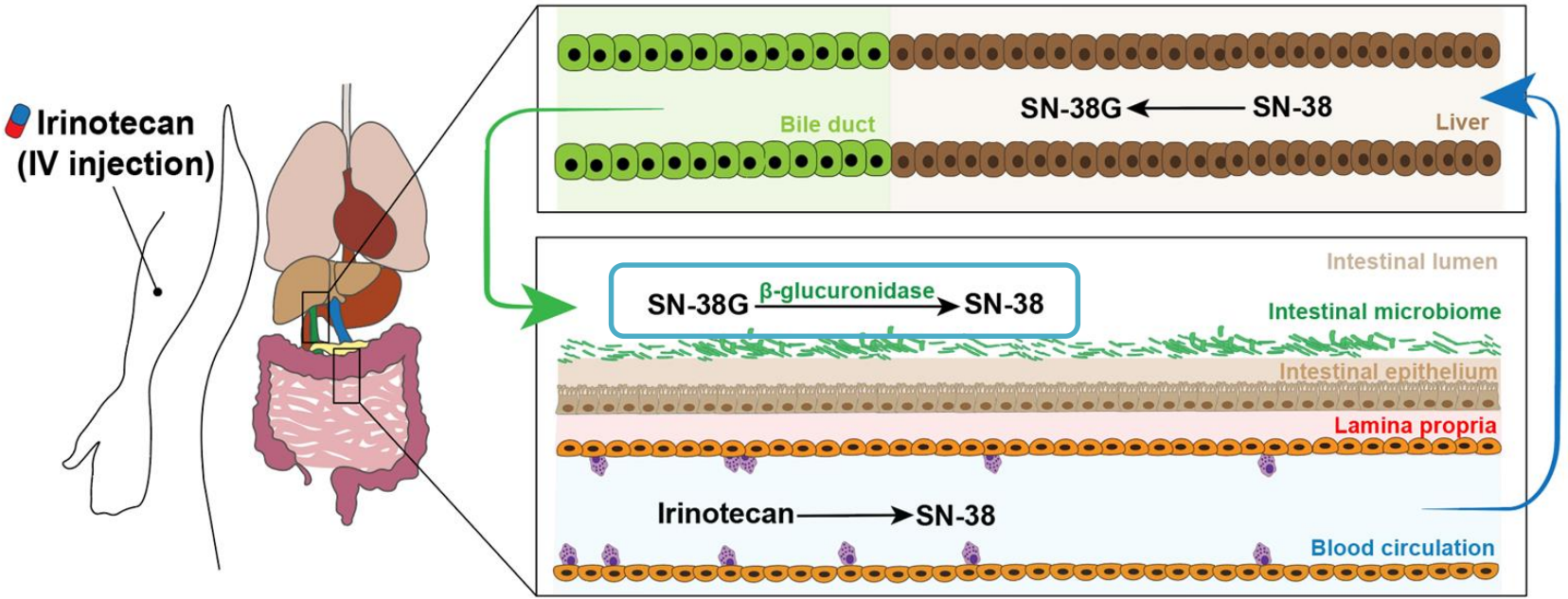






Wu *et al*. (2017) *Nature Med*icine **23**:850-858.

Irinotecan bioactivation & metabolism

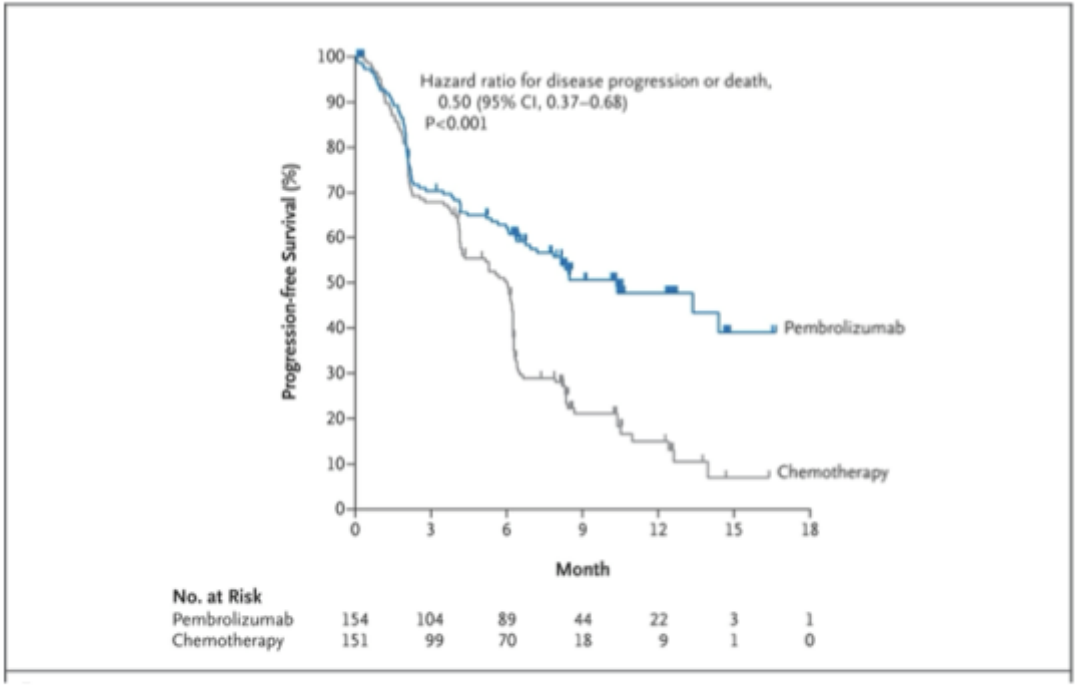


SN-38G reactivation by the gut bacterium *Escherichia coli*
Side effects: **diarrhea**, neutropenia

Irinotecan → prodrug
SN-38 → active drug
SN-38G → inactive drug

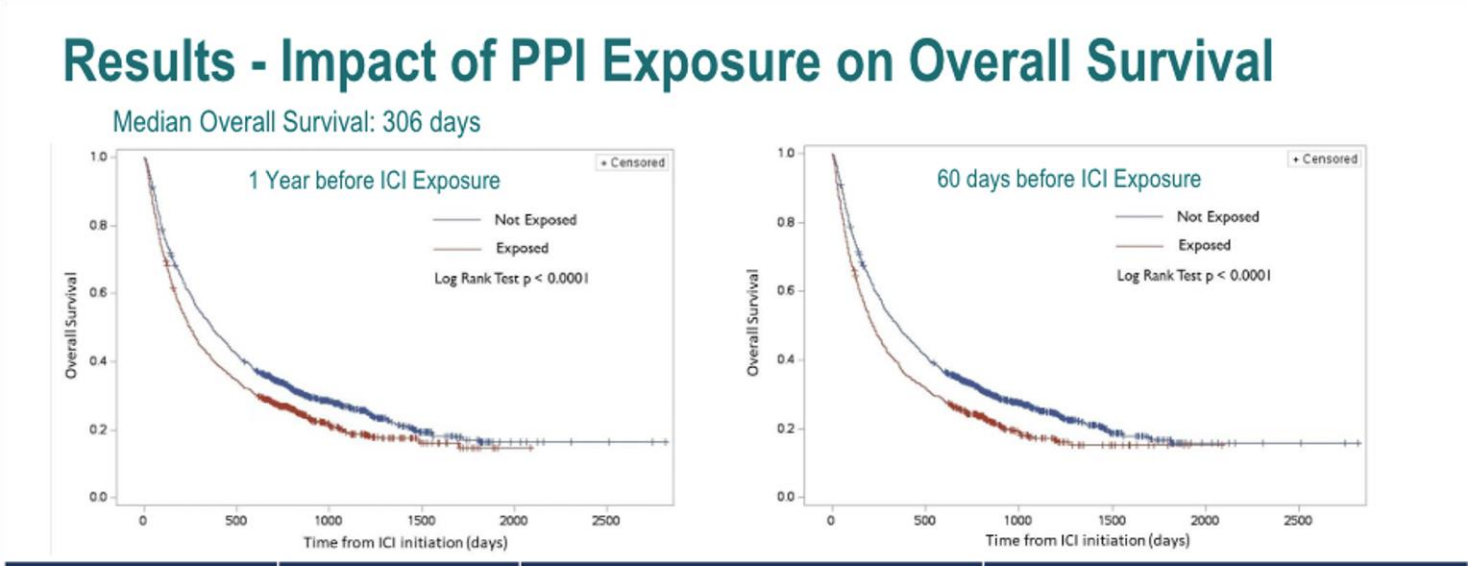
Lucchetti, *et al*. (2024) *Advanced Healthcare Materials* **7**:2303943.

What influences immunotherapy response?



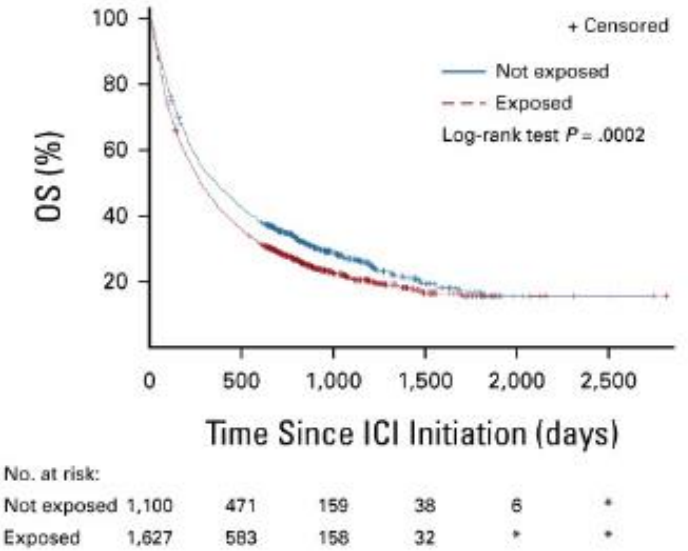
Martin Reck and al. **Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer**

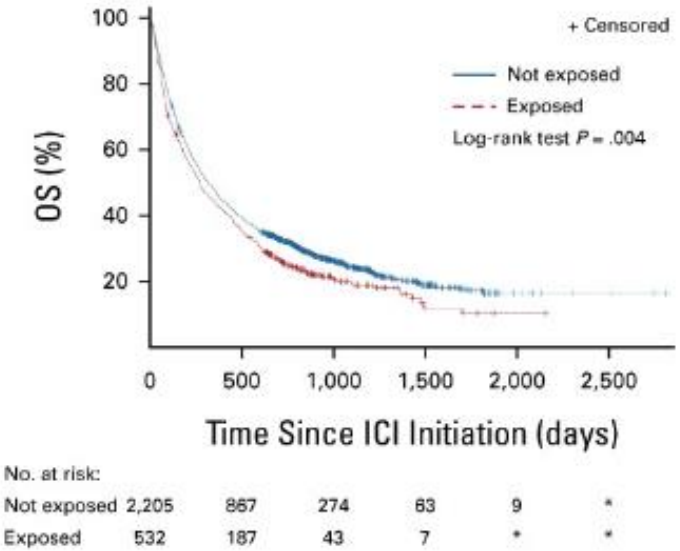
The impact of proton pump inhibitor (PPI) exposure before immune checkpoint inhibitor



2033MO The impact of proton pump inhibitor (PPI) exposure before immune checkpoint inhibitor (ICI) therapy on overall survival (OS): A population-based study
Eng, L. et al.
Annals of Oncology, Volume 34, S1079

Administration of antibiotics





Eng L, Sutradhar R, Niu Y, *et al.* Impact of Antibiotic Exposure Before Immune Checkpoint Inhibitor Treatment on Overall Survival in Older Adults With Cancer: A Population-Based Study. *JCO*; Published online 24 February 2023. DOI: 10.1200/JCO.22.00074

Pinato DJ, Cortellini A. Antibiotic Therapy: The Cornerstone of Iatrogenic Resistance to Immune Checkpoint Inhibitors. *JCO*; Published online 24 February 2023. DOI: 10.1200/JCO.23.00049

REPORT

CLINICAL TRIALS

Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients

Erez N. Baruch[1,2*†], Ilan Youngster[3,4], Guy Ben-Betzalel[1], Rona Ortenberg[1], Adi Lahat[5], Lior Katz[6], Katerina Adler[7], Daniela Dick-Necula[8], Stephen Raskin[4,9], Naamah Bloch[10], Daniil Rotin[8], Liat Anafi[8], Camila Avivi[8], Jenny Melnichenko[1], Yael Steinberg-Silman[1], Ronac Mamtani[11], Hagit Harati[1], Nethanel Asher[1], Ronnie Shapira-Frommer[1], Tal Brosh-Nissimov[12], Yael Eshet[4,8,13], Shira Ben-Simon[10], Oren Ziv[10], Md Abdul Wadud Khan[14], Moran Amit[15], Nadim J. Ajami[14], Iris Barshack[4,8], Jacob Schachter[1,4], Jennifer A. Wargo[14,16], Omry Koren[10], Gal Markel[1,2,17*‡], Ben Boursi[4,18,19‡]

The gut microbiome has been shown to influence the response of tumors to anti–PD-1 (programmed cell death–1) immunotherapy in preclinical mouse models and observational patient cohorts. However, modulation of gut microbiota in cancer patients has not been investigated in clinical trials. In this study, we performed a phase 1 clinical trial to assess the safety and feasibility of fecal microbiota transplantation (FMT) and reinduction of anti–PD-1 immunotherapy in 10 patients with anti–PD-1–refractory metastatic melanoma. We observed clinical responses in three patients, including two partial responses and one complete response. Notably, treatment with FMT was associated with favorable changes in immune cell infiltrates and gene expression profiles in both the gut lamina propria and the tumor microenvironment. These early findings have implications for modulating the gut microbiota in cancer treatment.

nature medicine

Article

https://doi.org/10.1038/s41591-023-02453-x

Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial

Received: 9 February 2023

Accepted: 8 June 2023

Published online: 6 July 2023

Check for updates

A list of authors and their affiliations appears at the end of the paper

Fecal microbiota transplantation (FMT) represents a potential strategy to overcome resistance to immune checkpoint inhibitors in patients with refractory melanoma; however, the role of FMT in first-line treatment settings has not been evaluated. We conducted a multicenter phase I trial combining healthy donor FMT with the PD-1 inhibitors nivolumab or pembrolizumab in 20 previously untreated patients with advanced melanoma. The primary end point was safety. No grade 3 adverse events were reported from FMT alone. Five patients (25%) experienced grade 3 immune-related adverse events from combination therapy. Key secondary end points were objective response rate, changes in gut microbiome composition and systemic immune and metabolomics analyses. The objective response rate was 65% (13 of 20), including four (20%) complete responses. Longitudinal microbiome profiling revealed that all patients engrafted strains from their respective donors; however, the acquired similarity between donor and patient microbiomes only increased over time in responders. Responders experienced an enrichment of immunogenic and a loss of deleterious bacteria following FMT. Avatar mouse models confirmed the role of healthy donor feces in increasing anti-PD-1 efficacy. Our results show that FMT from healthy donors is safe in the first-line setting and warrants further investigation in combination with immune checkpoint inhibitors. ClinicalTrials.gov identifier NCT03772899.

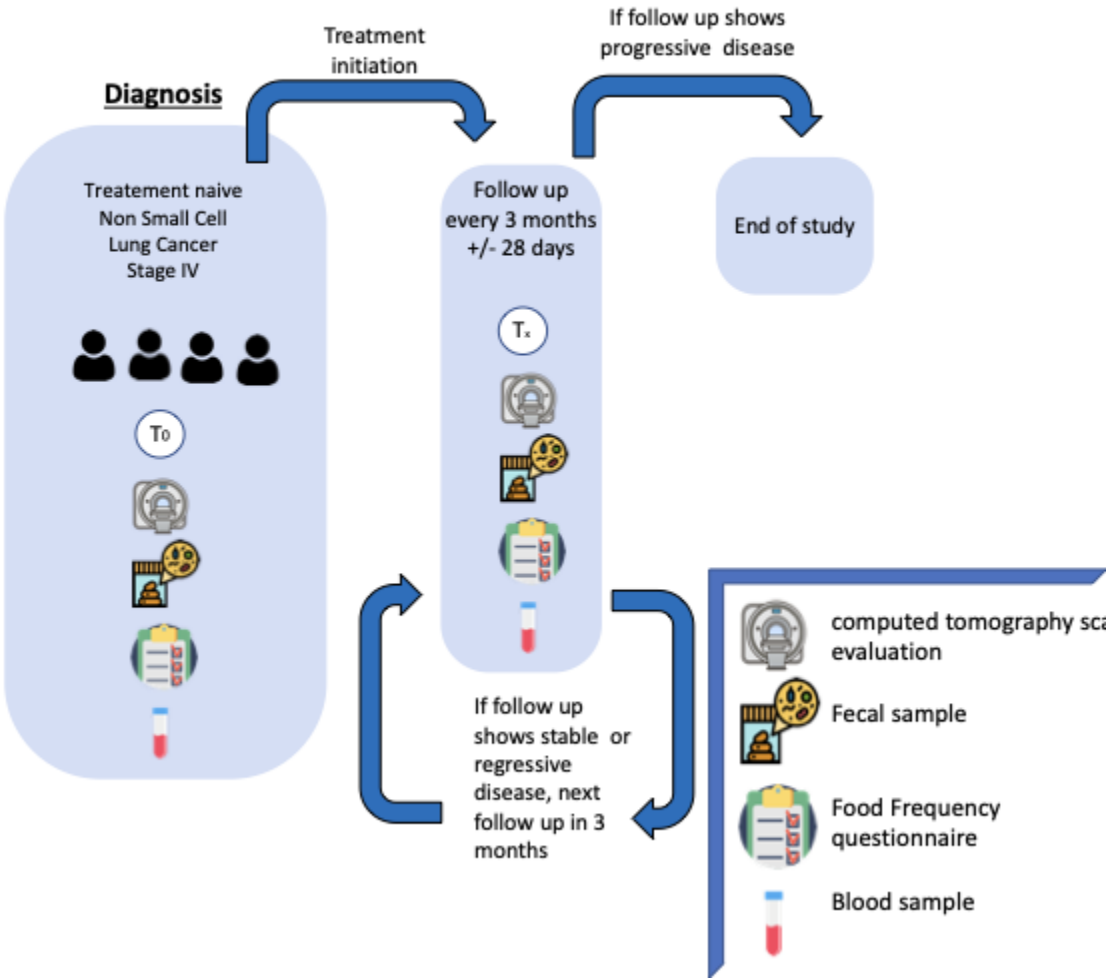
Study design

This is a multicentric prospective study including 60 patients diagnosed with unresectable NSCLC

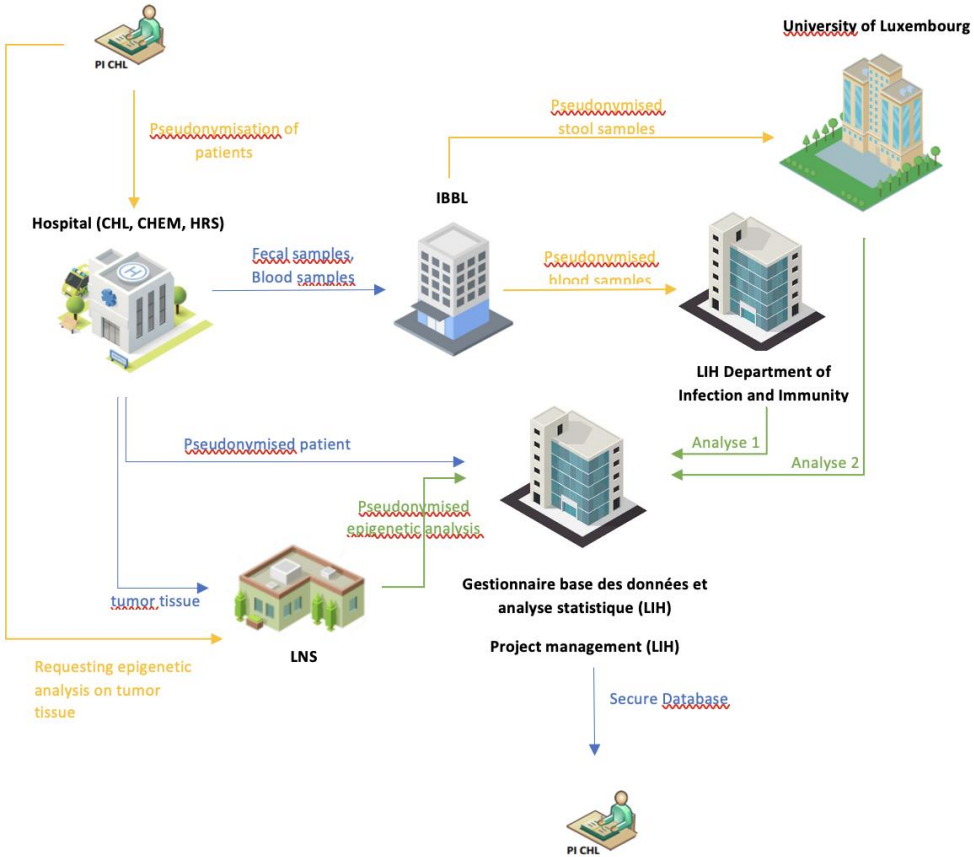
Planned to start treatment with either standard of care immune checkpoint inhibitors in monotherapy or combined with platinum-doublet chemotherapy.

Enrolled patients will be assigned retrospectively to either the "responders" or "non responders" cohort.

Response status is defined 12 weeks (+/- 28 days) after initiation of standard of care treatment, through computed tomography scan evaluation



Translational Research Ecosystem: Key Players

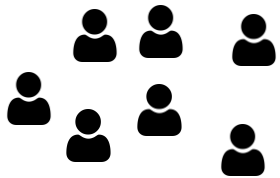


Study design

- **Unresectable stage 3 or stage 4 NSCLC** planned to start treatment with either standard of care immune checkpoint inhibitors in monotherapy or combined with platinum-doublet chemotherapy.
- Approximately **60 patients** will be enrolled in this study.
- **Multicentric** (CHL & HRS)

Diagnosis

Treatement naive
Non Small Cell
Lung Cancer
Stage III/IV



Study design

Diagnosis

Treatement naive
Non Small Cell
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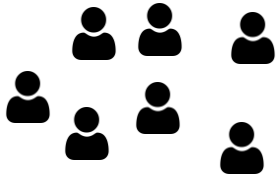
Stage III/



Treatment
initiation

Follow up
after 3 months

Retrospective assignment into cohorts

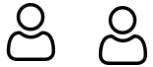
Non-responders to ICI

Responders to ICI

Retrospective assignment into cohorts

Non-responders to ICI

Responders to ICI



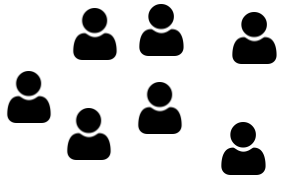
Objective:

- To identify microbiome biomolecular signature differences between responders *vs*. nonresponders.

Retrospective assignment into cohorts

Diagnosis

Treatement naive
Non Small Cell
Lung Cancer
Stage III/



Retrospective assignment into cohorts

Diagnosis

Treatement naive
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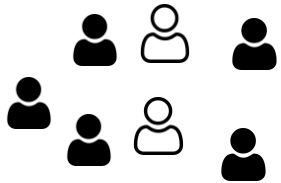
Lung Cancer
Stage III/



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nature medicine

Article | Open access | Published: 16 February 2024

Longitudinal gut microbiome changes in immune checkpoint blockade-treated advanced melanoma

Johannes R. Björk ✉, Laura A. Bolte, Andrew Maltez Thomas, Karla A. Lee, Niccolo Rossi, Thijs T. Wind, Lotte M. Smit, Federica Armanini, Francesco Asnicar, Aitor Blanco-Miguez, Ruth Board, Neus Calbet-Llopart, Lisa Derosa, Nathalie Dhomen, Kelly Brooks, Mark Harland, Mark Harries, Paul Lorigan, Paolo Manghi, Richard Marais, Julia Newton-Bishop, Luigi Nezi, Federica Pinto, Miriam Potrony, ... Rinse K. Weersma ✉ + Show authors

Fig. 2: A longitudinal balance of microbial taxa (SGBs) predicts OS at baseline.

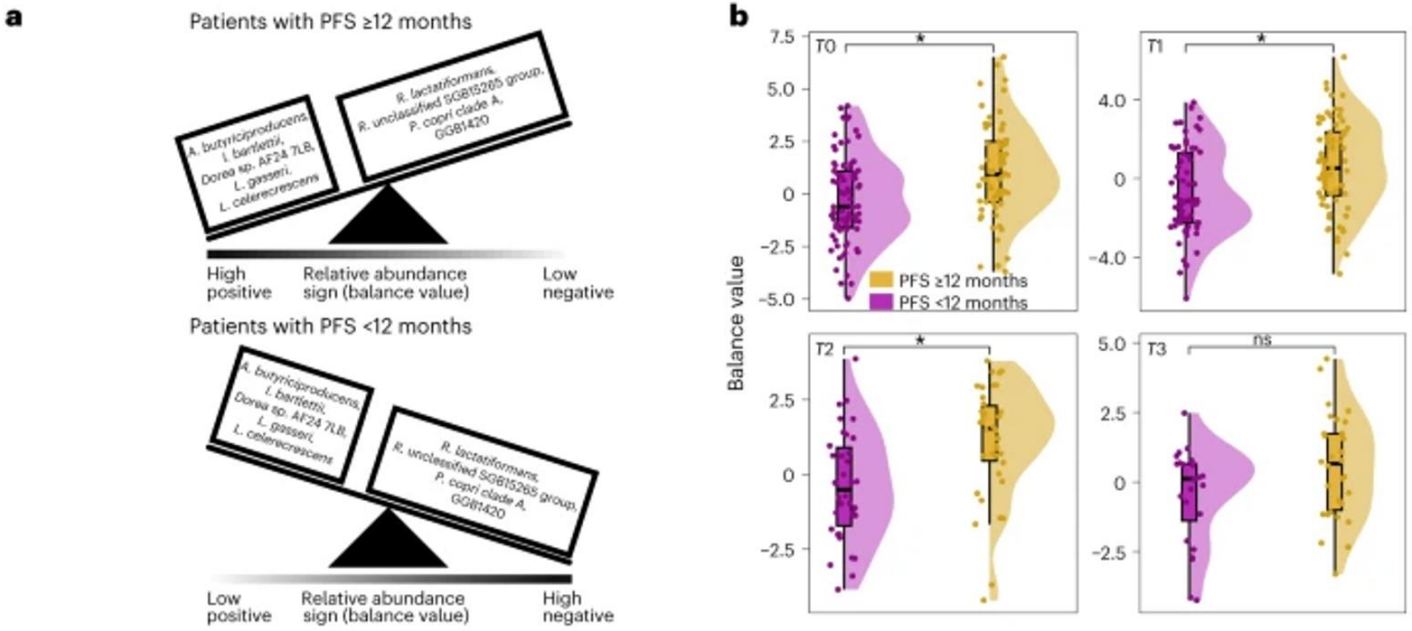
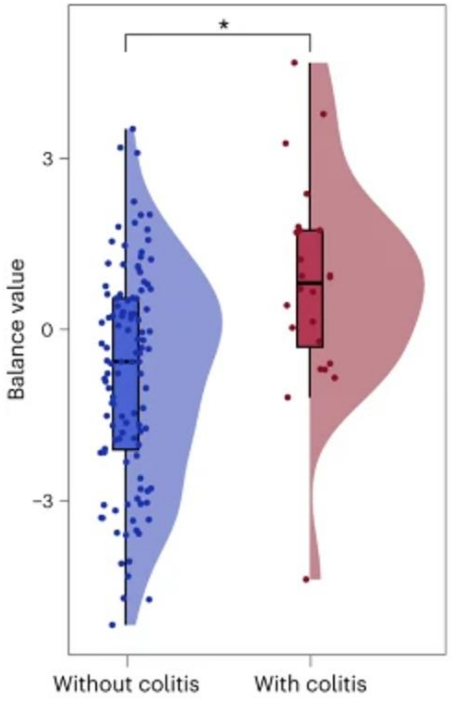


Fig. 5: A balance predictive of ICB-induced colitis at baseline.



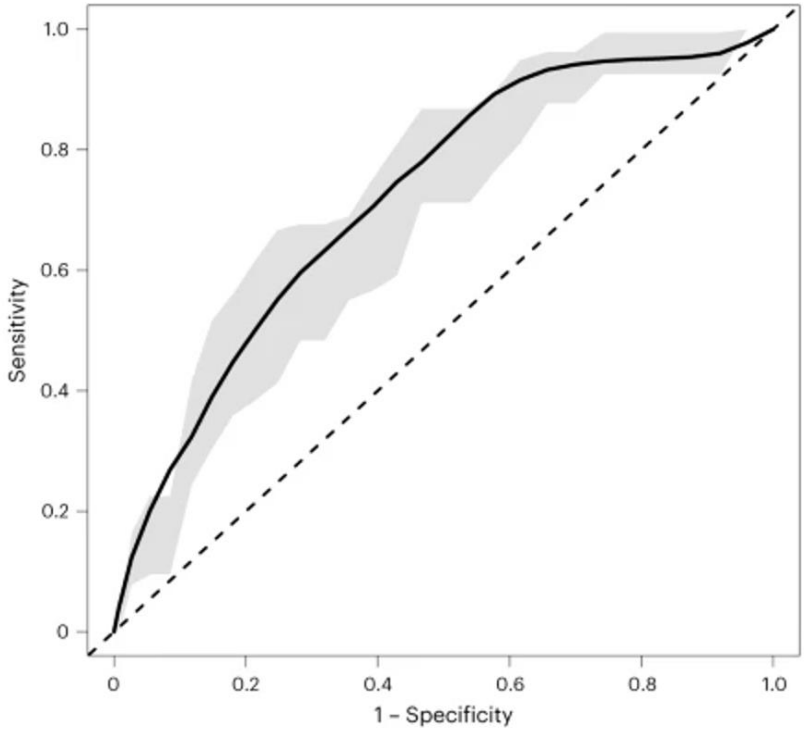
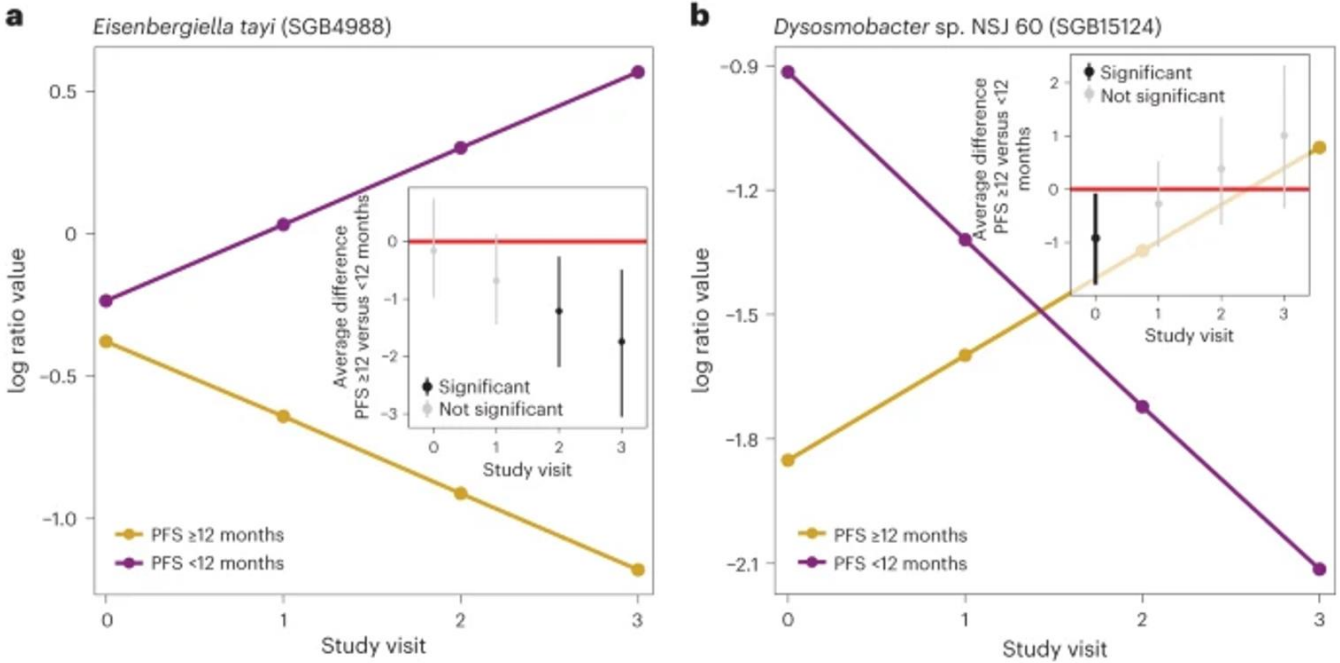


Fig. 3: Different taxon dynamics in patients with PFS ≥12 and PFS <12 months.



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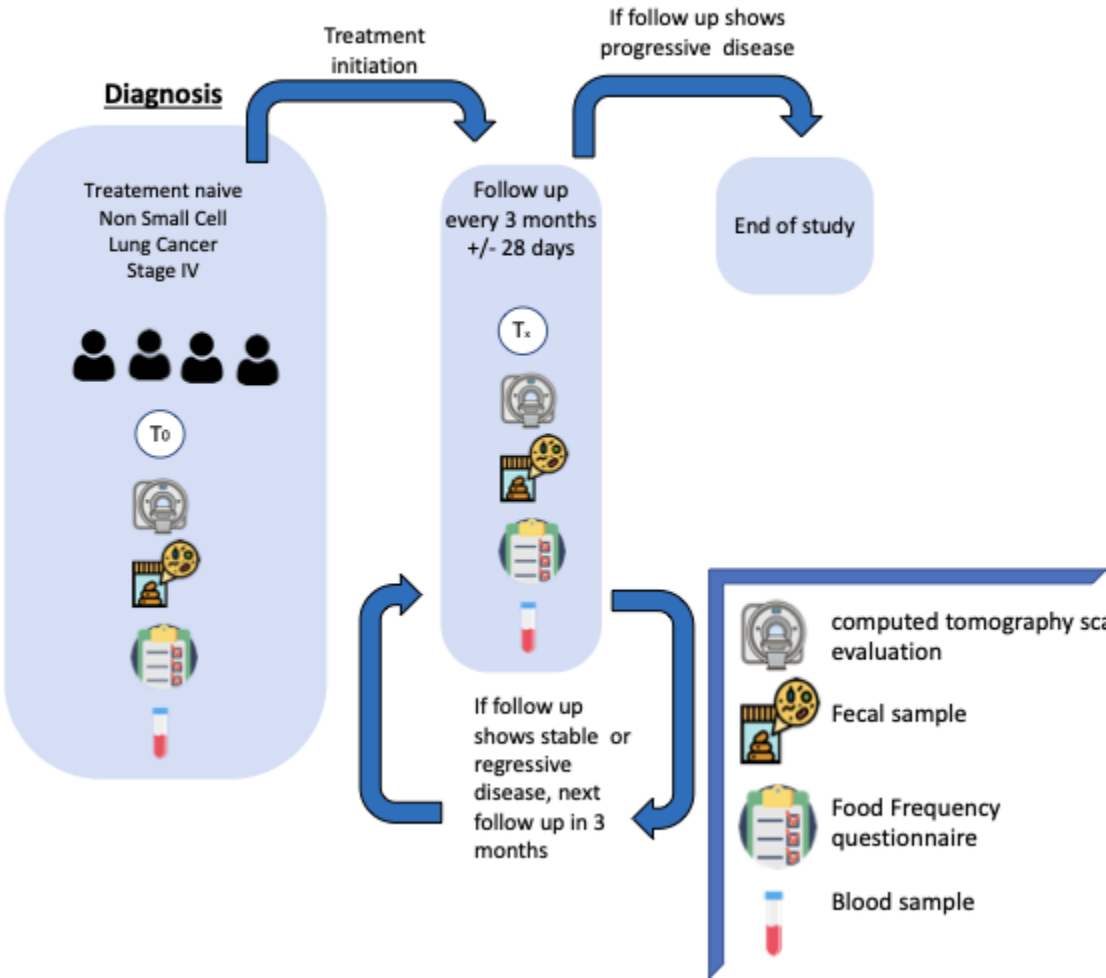

Conclusion

- Wet- and dry-lab methodologies for systematic integrated multi-omics of microbial communities
- Expobiome as a complex mediator of the immune system
- Gaining new mechanistic insights into microbiome-immune system interactions in the context of immunotherapy
- Predictive biomarkers for personalised cancer therapy
- Potential for novel therapeutic interventions

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