top ten
in gastroenterologia
14^ EDIZIONE

24-25 NOVEMBRE 20**23**

BERGAMO

HOTEL EXCELSIOR SAN MARCO
Piazza della Repubblica, 6

MICROBIOTA E RISPOSTA ALLE TERAPIE

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FARMACOMICROBIOMICA

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Università di Bologna

La sottoscritta Patrizia Brigidi

dichiara

che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- ***Roche***
- ***Alfasigma***

PHARMACOMICROBIOMICS

Pharmacogenomics: how human genome variations affect drug action

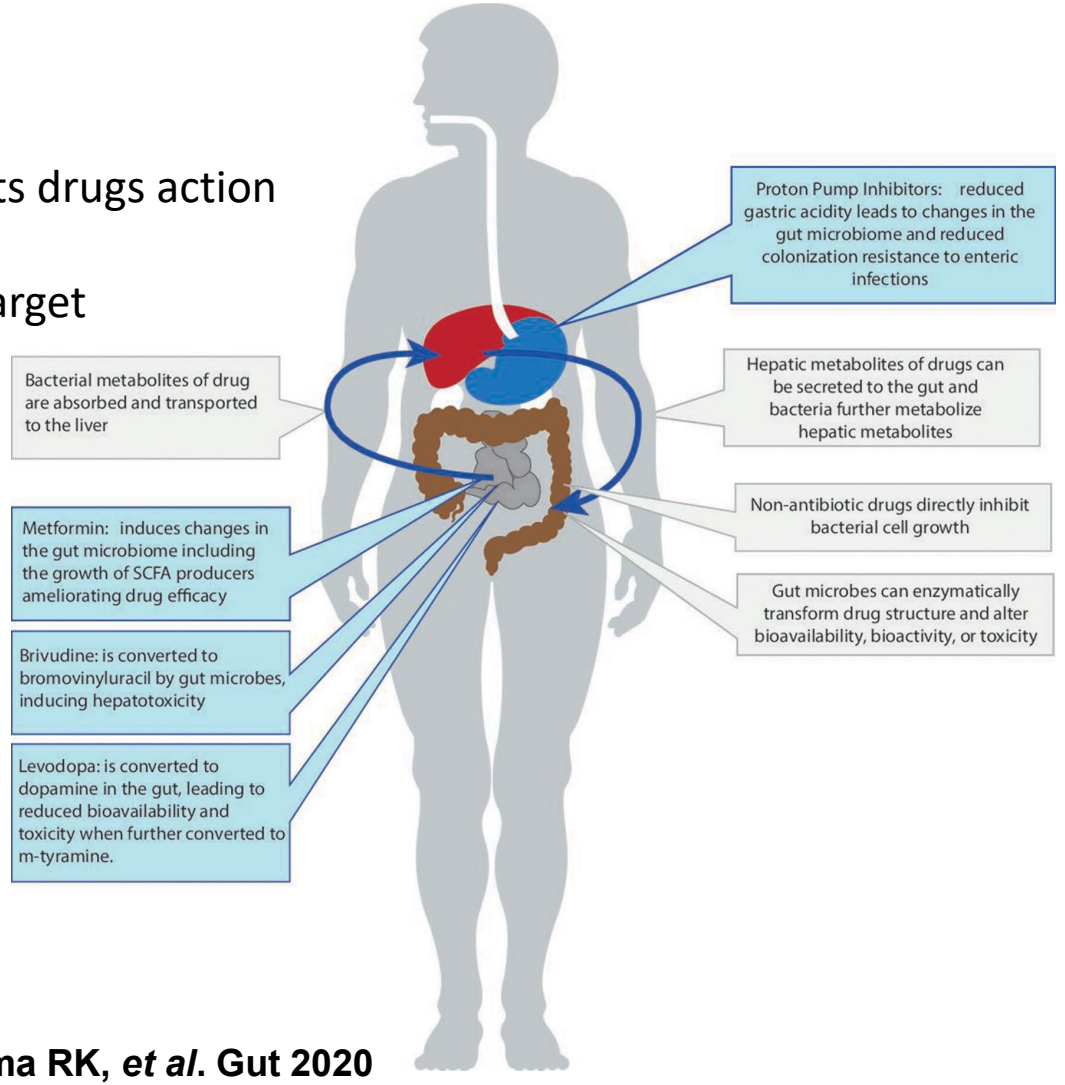
Pharmacomicrobiomics: how GM, as the second human genome, affects drugs action

Unlike human genetics, GM is modifiable ➡ attractive therapeutic target

Bidirectional interaction GM and commonly used non-antibiotic drugs

- **GM composition** can be **influenced by drugs**
- **GM** can **influence an individual's response to a drug** by enzymatically transforming the drug's structure and **altering its bioavailability, bioactivity or toxicity**

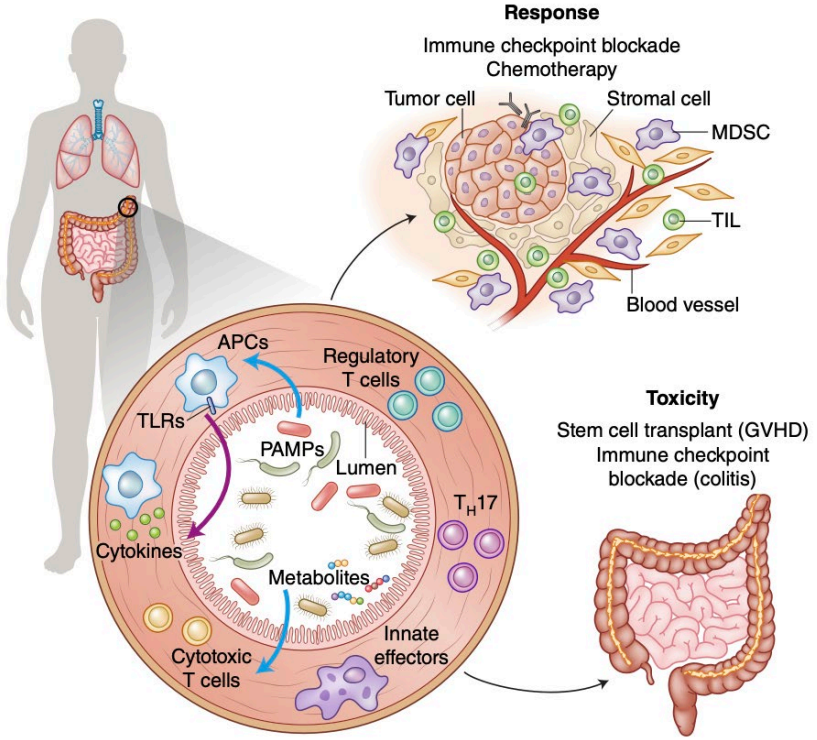
Large human cohort studies: associations between specific drugs and altered GM, including **PPIs, lipid-lowering statins, laxatives, metformin, beta-blockers and ACE inhibitors, and selective serotonin reuptake inhibitor antidepressants**



Weersma RK, *et al*. Gut 2020

PHARMACOMICROBIOMICS: EXPLOITING THE DRUG-GM INTERACTIONS IN ANTICANCER THERAPIES

GM is involved in modulating the clinical response to cancer therapy (chemotherapy and immunotherapy) and associated toxicities (colitis and GvHD)



Chemoresistance: GM metabolizes chemotherapeutic drugs into their inactive forms

Immunotherapy resistance: GM supports the fine-tuning the general host immune status and subsequently antitumour activation of the immune system (immune checkpoint inhibition)

Toxicity: GM alters systemic immune function via local changes within the gut mucosa and gut-associated lymphoid tissue

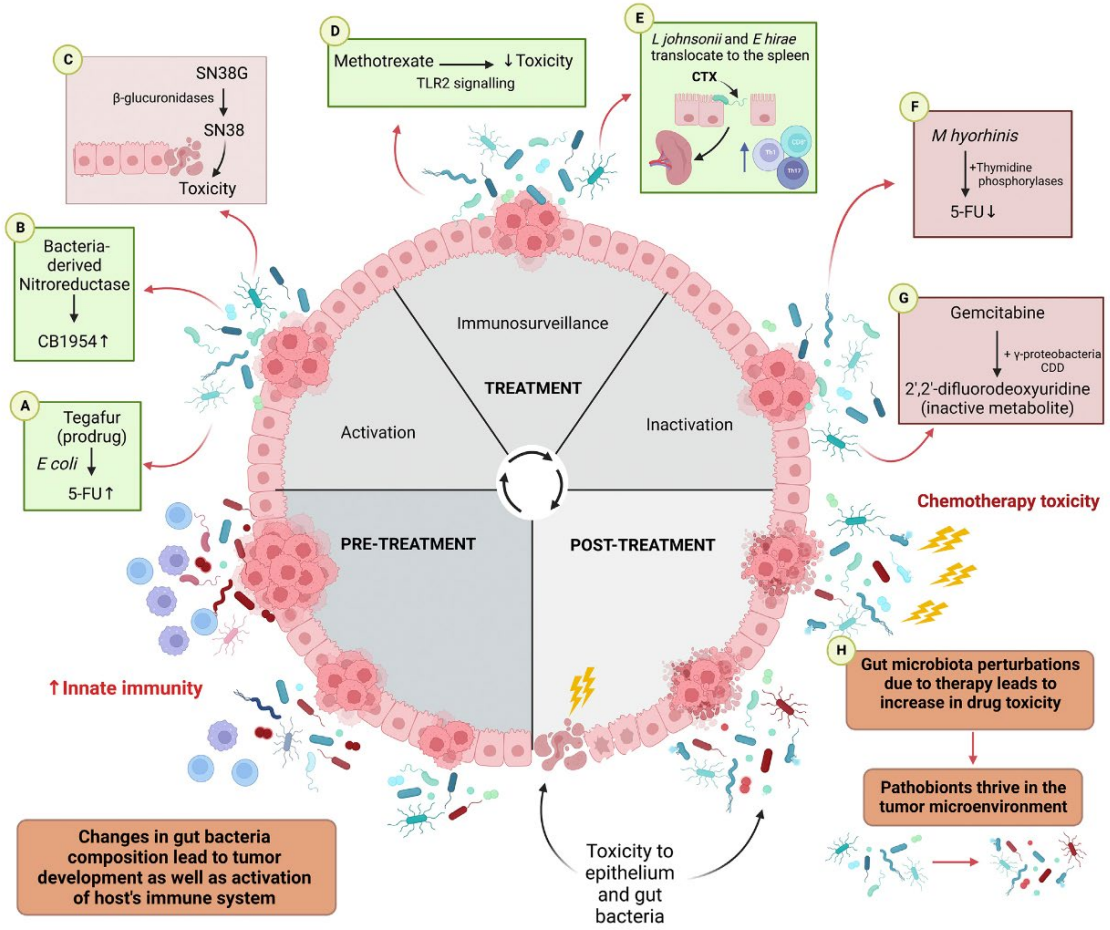
GM SHAPES ONCOLOGIC OUTCOMES

⬇

RESPONDERS NON RESPONDERS????

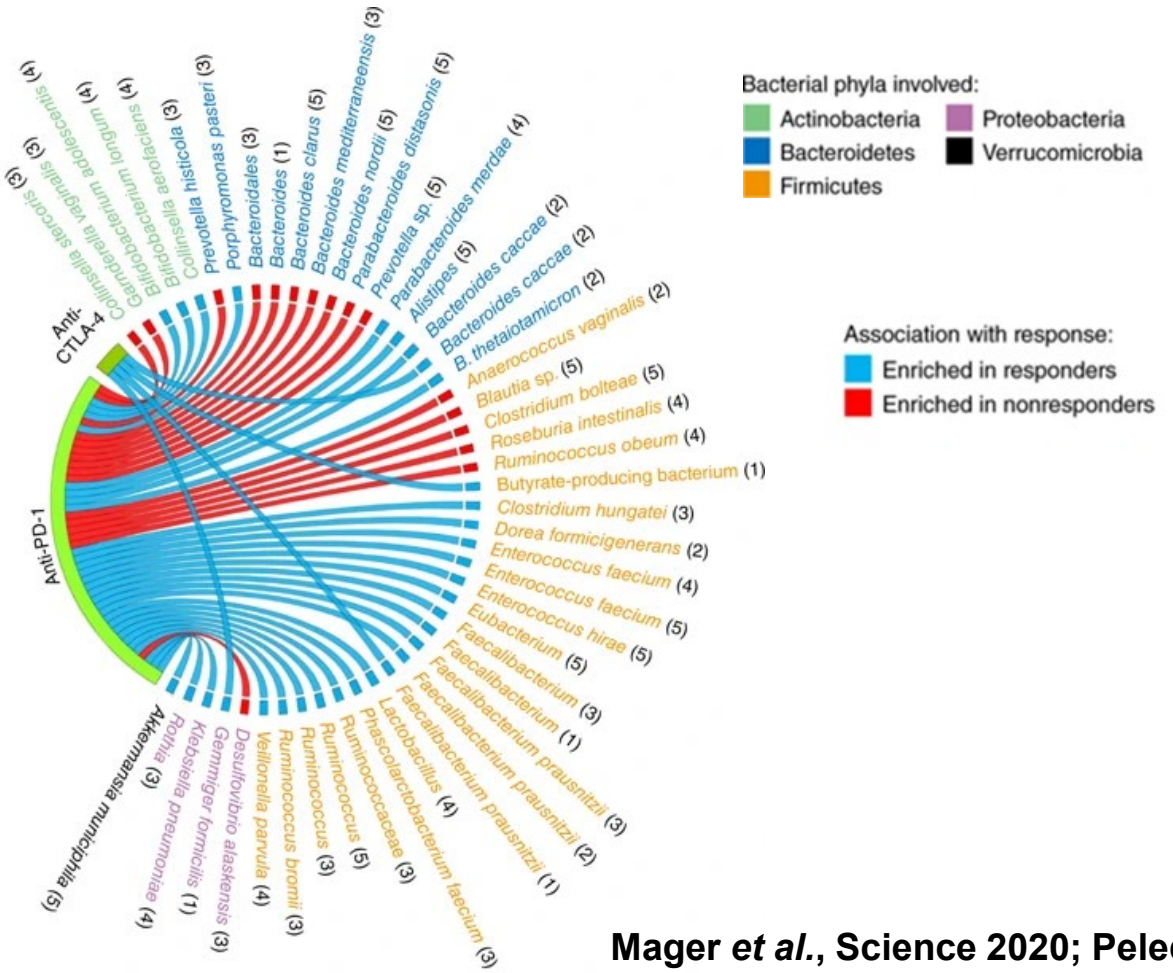
Helmink *et al*. Nat Med 2019; Bullman *et al.*, Science 2017; Spencer *et al.*, Science 2021

MECHANISMS OF HOST-ONCOMICROBIOME-THERAPY INTERACTIONS



Chrysostomou *et al.*, Gastroenterology 2023

GM STRUCTURE IS PREDICTIVE OF RESPONSE TO IMMUNOTHERAPY



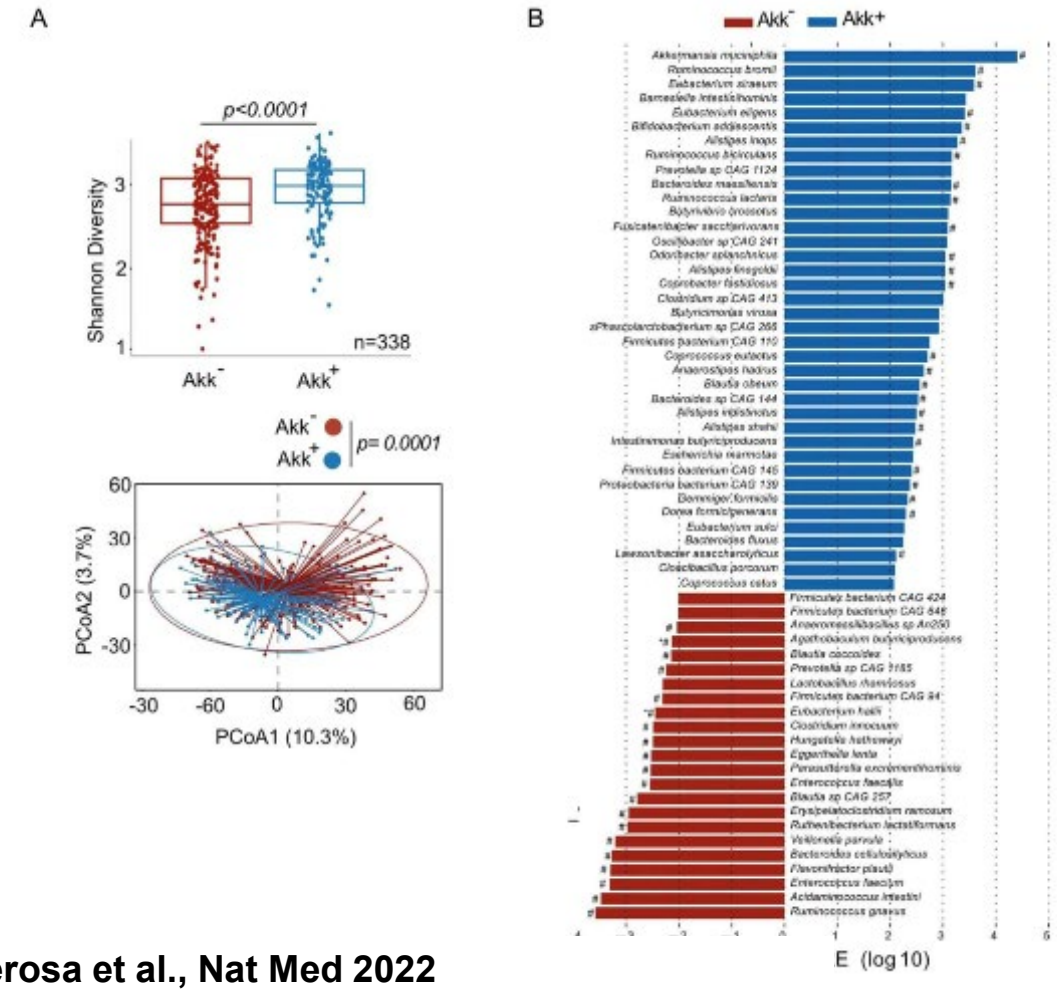
A positive response to mAbs targeting PD-1 is associated with more "favourable" GM:

- **higher diversity**
- **higher relative abundance of health-associated bacteria (*Ruminococcaceae, Lachnospiraceae, Bifidobacteriaceae* and *Coriobacteriaceae*)**

Enhanced systemic and anti-tumour immune responses and improved effector T cell function

Mager *et al.*, Science 2020; Peled et al., New Engl J Med 2020

INTESTINAL *A. MUCINIPHILA* PREDICTS CLINICAL RESPONSE TO mAB ANTI-PD-1 IN NON-SMALL CELL LUNG CANCER PATIENTS



RESPONDERS

⬆ Diversity, *A.muciniphila, Ruminococcaceae* (*R. bromii, R. bicirculans, R. lactaris*), *Lachnospiraceae* (*Eubacterium siraeum, E. eligens*) and *Alistipes* spp. (*A. inops, A. finegoldii, A. indistinctus, A. shahii*)

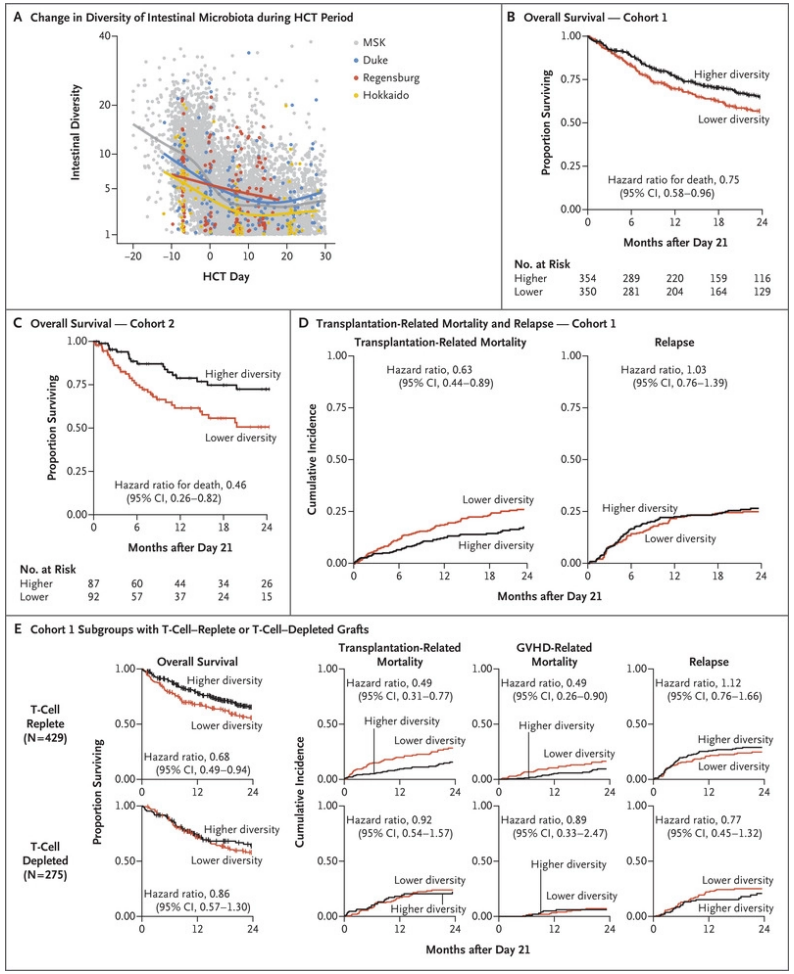
NON RESPONDERS

⬇ *A.muciniphila*

⬆ *Veillonella parvula, Actinomyces* and *Clostridium* (*C. innocuum, Hungatella hathewayi*)

Derosa et al., Nat Med 2022

GM AS PREDICTOR OF MORTALITY IN ALLOGENEIC HEMATOPOIETIC-CELL TRANSPLANTATION

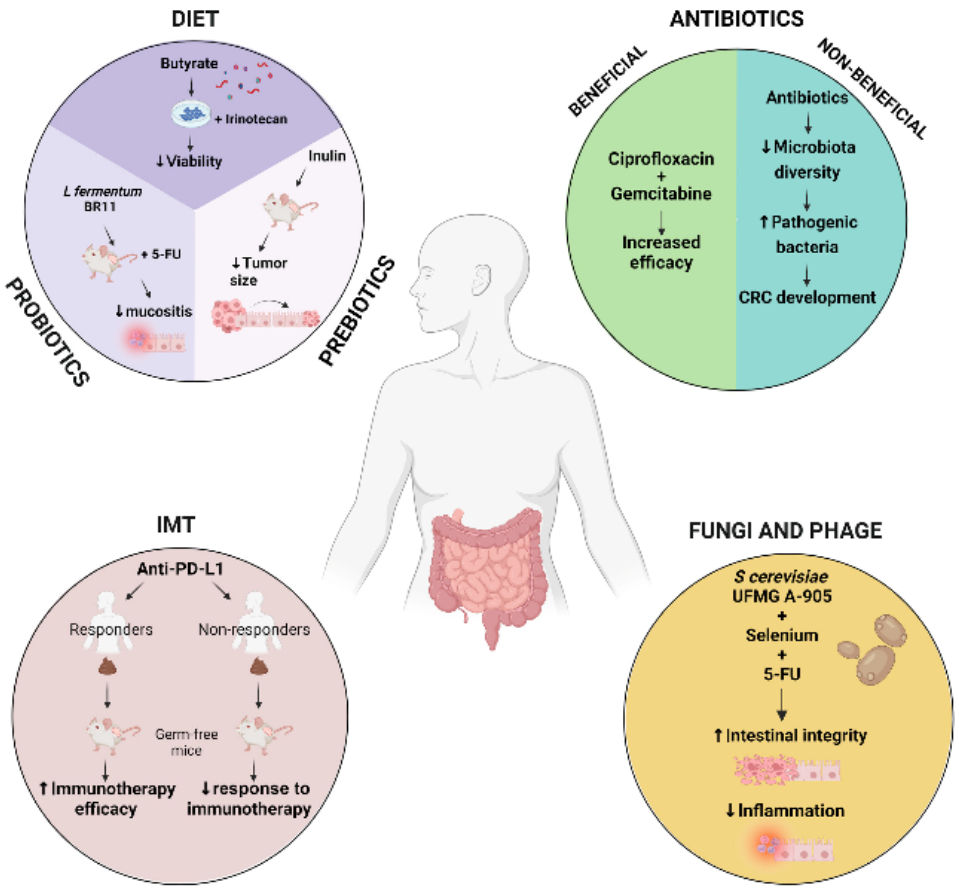


1,362 patients undergoing allogeneic hematopoietic-cell transplantation at four centers (New York, Germany, Japan and North Carolina) (8,767 fecal samples)

- **Patterns of microbiota disruption (diversity loss and domination by single taxa) are similar across transplantation centres**
- **Higher GM diversity at the time of neutrophil engraftment is associated with lower mortality**

Peled *et al.*, New Engl J Med 2020

THERAPY OUTCOMES CAN BE MODULATED BY RESHAPING THE MICROBIOME



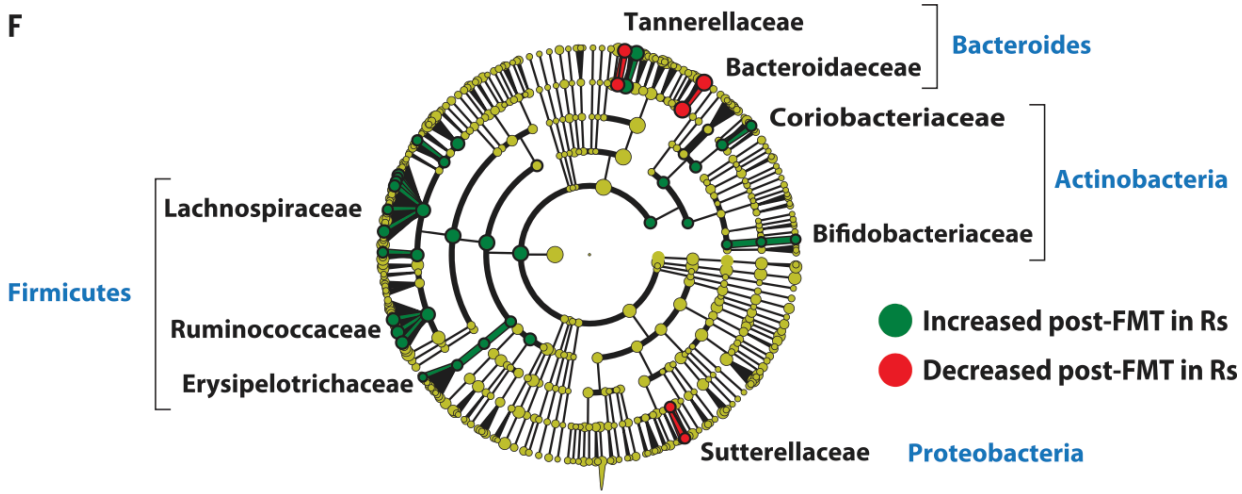
Chrysostomou *et al.*, Gastroenterology 2023

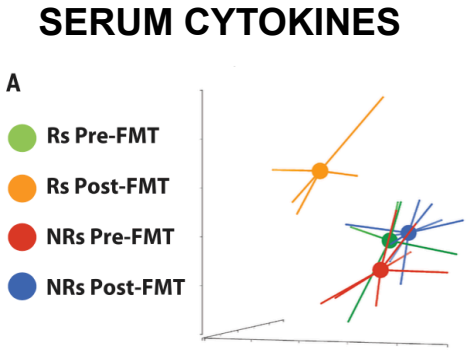
FMT OVERCOMES RESISTANCE TO mAbs anti–PD-1 THERAPY IN MELANOMA PATIENTS

Immune checkpoint blockade with **mAbs anti-PD-1** provides long-term clinical benefits to nearly **40% of patients with advanced melanoma**

15 melanoma patients refractory to anti–PD-1 therapy, received FMT from patients demonstrated durable complete response

FMT: clinical benefit in 6 of 15 patients, and induced rapid and durable GM perturbation





Responders exhibited:

- **increased abundance of taxa** associated with response to anti–PD-1
- **increased CD8+ T cell** activation
- **decreased** frequency of **IL-8**–expressing myeloid cells

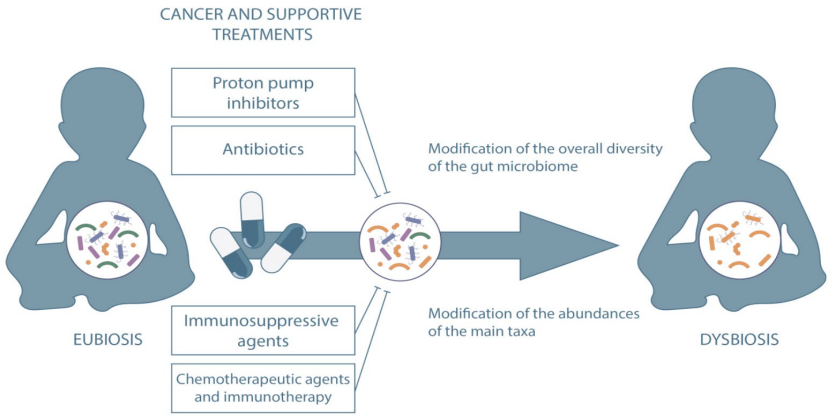
Davar *et al*., Science 2021

HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PEDIATRIC PATIENTS: GM ROLE

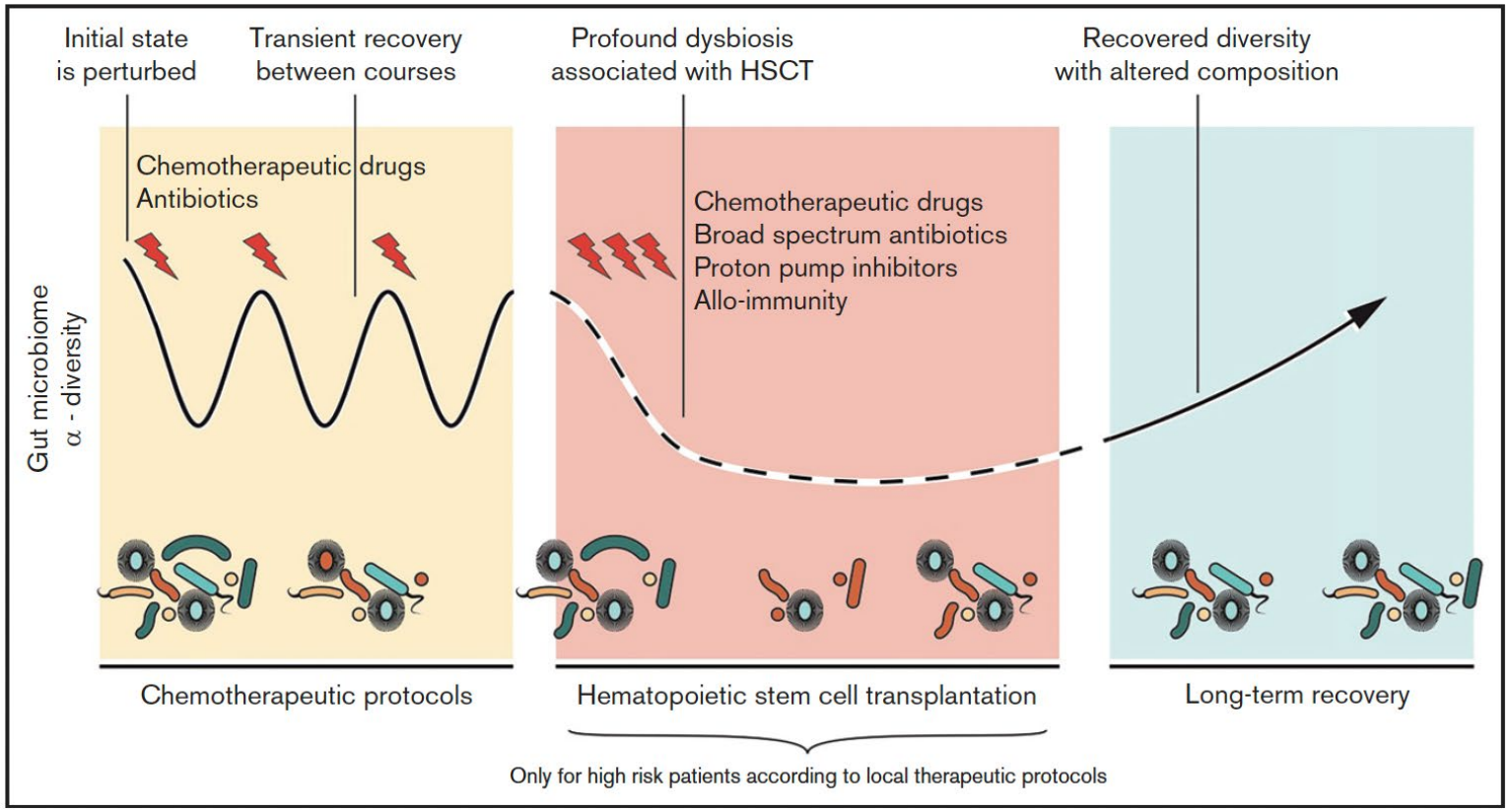
- **Leukemias and lymphomas** are the most frequent type of cancer in pediatric patients (acute leukemia, leading cause of childhood cancer-related deaths worldwide has an incidence rate of 10 to 50 cases per 100 000 per year)
- **These disorders reach the** 80-90% of long-term survival rates thanks to chemotherapy and/or immunotherapies
- **Aggressive treatment with several treatment-related complications**
- **Children GM different ecological properties** compared to adults

Hematopoietic stem cell transplantation (HSCT) is the strongest curative treatment for pediatric hematologic malignancies

In HSCT patients GM is severely injured



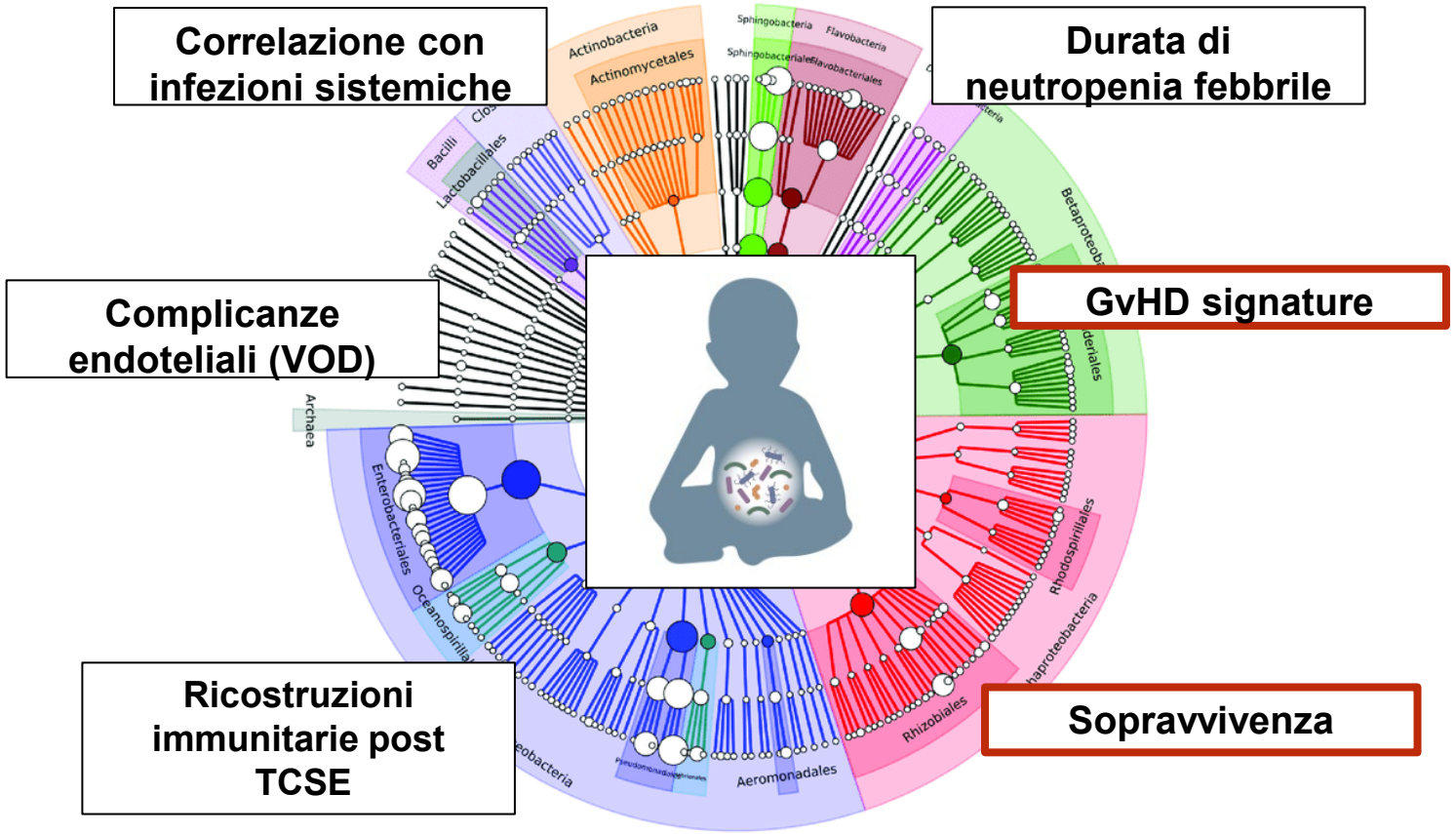
TRAJECTORY OF GM DURING THE THERAPEUTIC COURSE OF HSCT



- **Dramatic decrease of α diversity**
- **Loss of health-associated commensals**
- **Expansion of potentially pathogenic bacteria**, with a predominance of Gram-negative Enterobacteria
- After 2-3 months the ecosystem **partially recovers its initial richness and metabolic capacity**

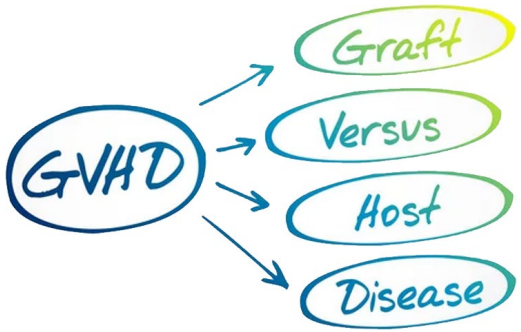
Masetti *et al*., 2021 Blood Adv

DYNAMICS OF GM DIVERSITY AND CLINICAL OUTCOMES IN HSCT



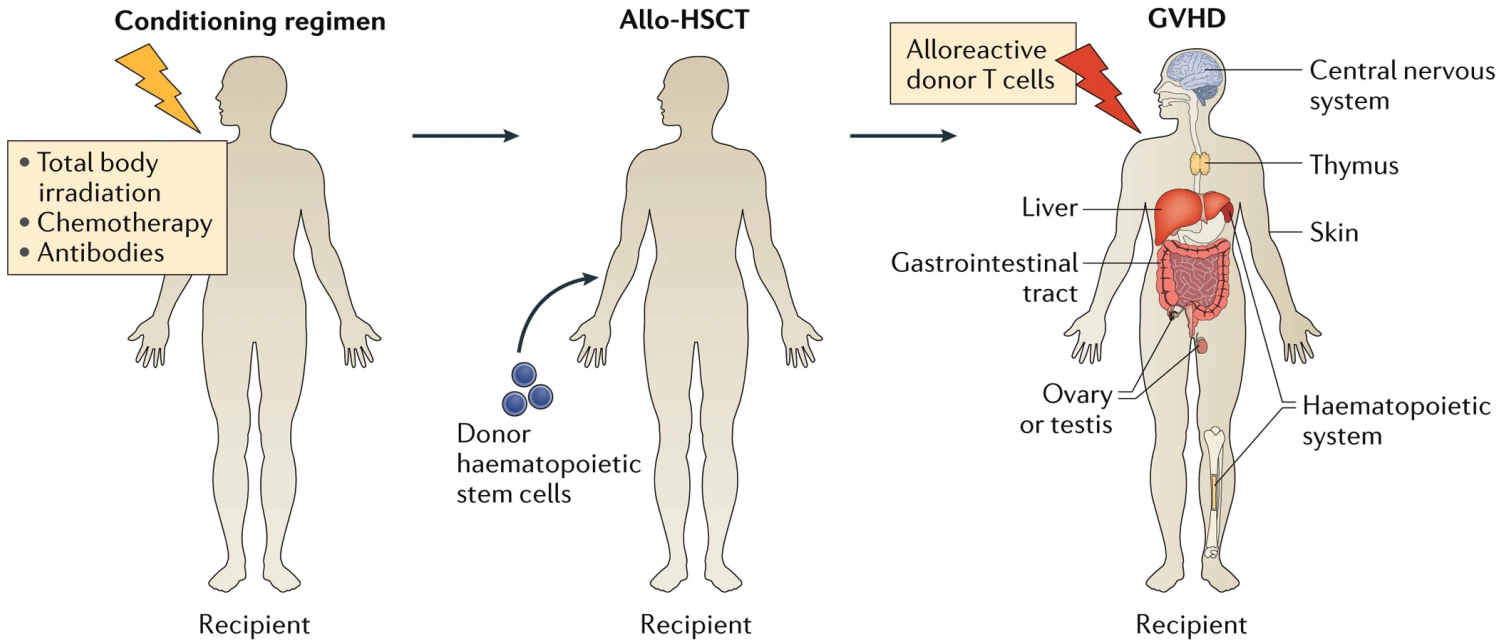
Biagi *et al.* 2015 *Bone marrow transplant*; Simms-Waldrip *et al.* 2017 *Bone marrow transplant*; Biagi *et al.* 2019 *BMC Med Genomics*; Ingham *et al.* 2019 *Microbiome*; Kelly *et al.* 2019 *Bone marrow transplantation* ; D'Amico *et al.* 2019 *Nutrients*; Ingham *et al.* 2021 *Microbiome*; Zama *et al.* 2021 *Transplant Cell Ther*; Masetti *et al.* 2021 *Sci Rep*; Masetti *et al.* 2022 *Cancers*

DYNAMICS OF GM DIVERSITY AND GVHD SIGNATURE



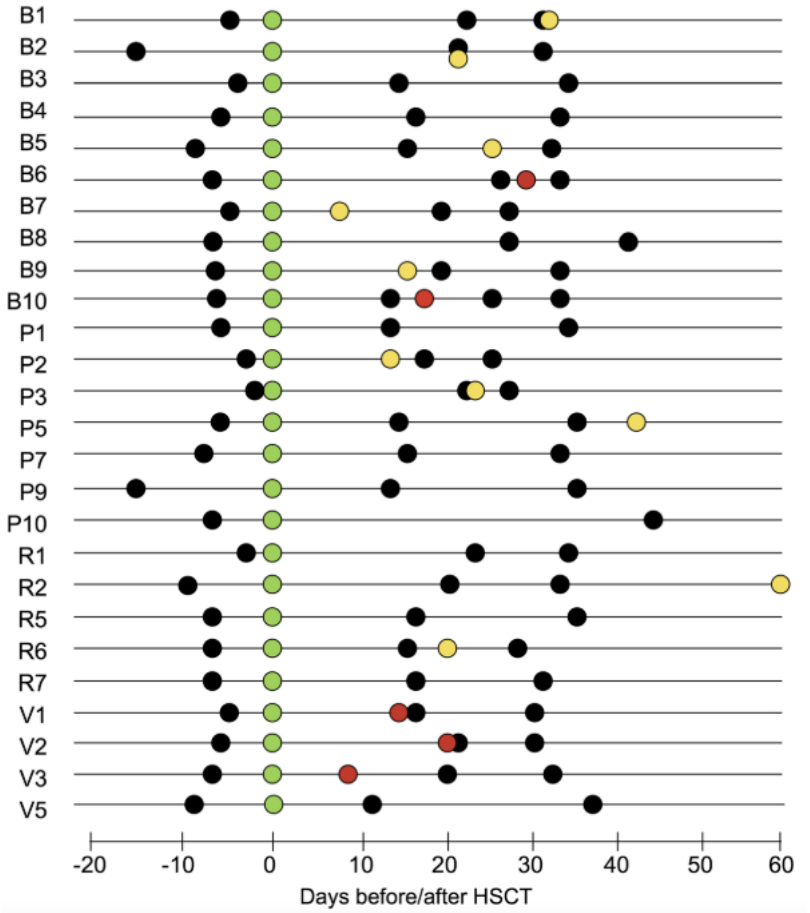
Reactivity of donor derived immune cells against allogenic recipient tissues

GVHD is one of the major complications of allo-HSCT



Nature Reviews | Cancer

EARLY GM SIGNATURES OF aGvHD IN CHILDREN UNDERGOING HSCT



Italian multicentric longitudinal study

36 children undergoing allogeneic HSCT at 4 centers (BO, OPBG, VR, PV)

> 130 samples (pre-HSCT, engrafment, post-HSCT fecal samples)

19/36 patients developed aGvHD

Biagi *et al.*, 2019 *BMC* Medical Genomics

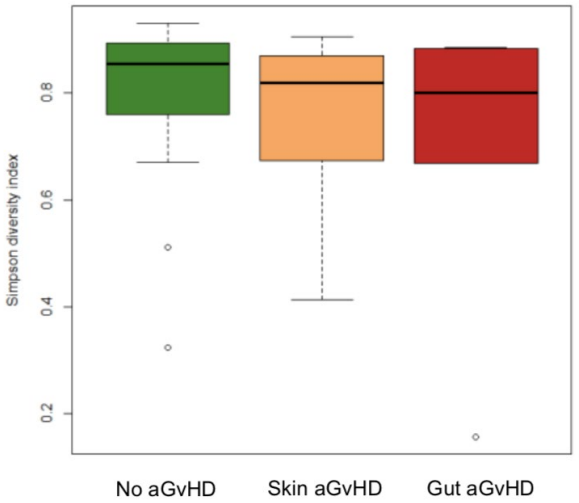
Early gut microbiota signature of aGvHD in children given allogeneic hematopoietic cell transplantation for hematological disorders

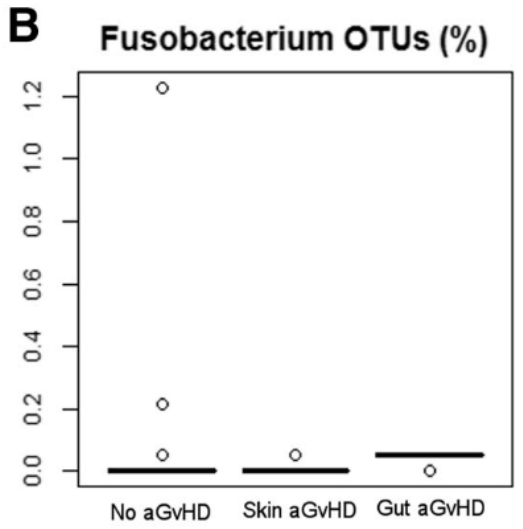
Elena Biagi[1*†], Daniele Zama[2†], Simone Rampelli[1], Silvia Turroni[1], Patrizia Brigidi[1], Clarissa Consolandi[3], Marco Severgnini[3], Eleonora Picotti[2], Pietro Gasperini[2], Pietro Merli[4], Nunzia Decembrino[5], Marco Zecca[5], Simone Cesaro[6], Maura Faraci[7], Arcangelo Prete[2], Franco Locatelli[4], Andrea Pession[2], Marco Candela[1†] and Riccardo Masetti[2†]

Higher pre-HSCT GM diversity associated to a lower incidence of intestinal aGvHD

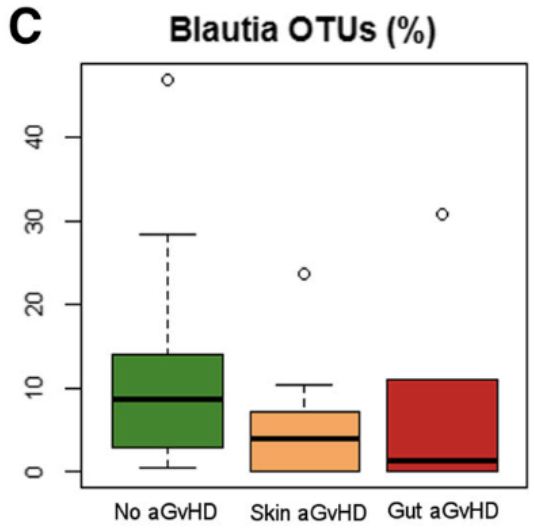
High relative abundance of *Blautia* in pre-HSCT samples of NO aGvHD patients

High relative abundance of *Fusobacterium nucleatum* associated to severity of intestinal aGvHD



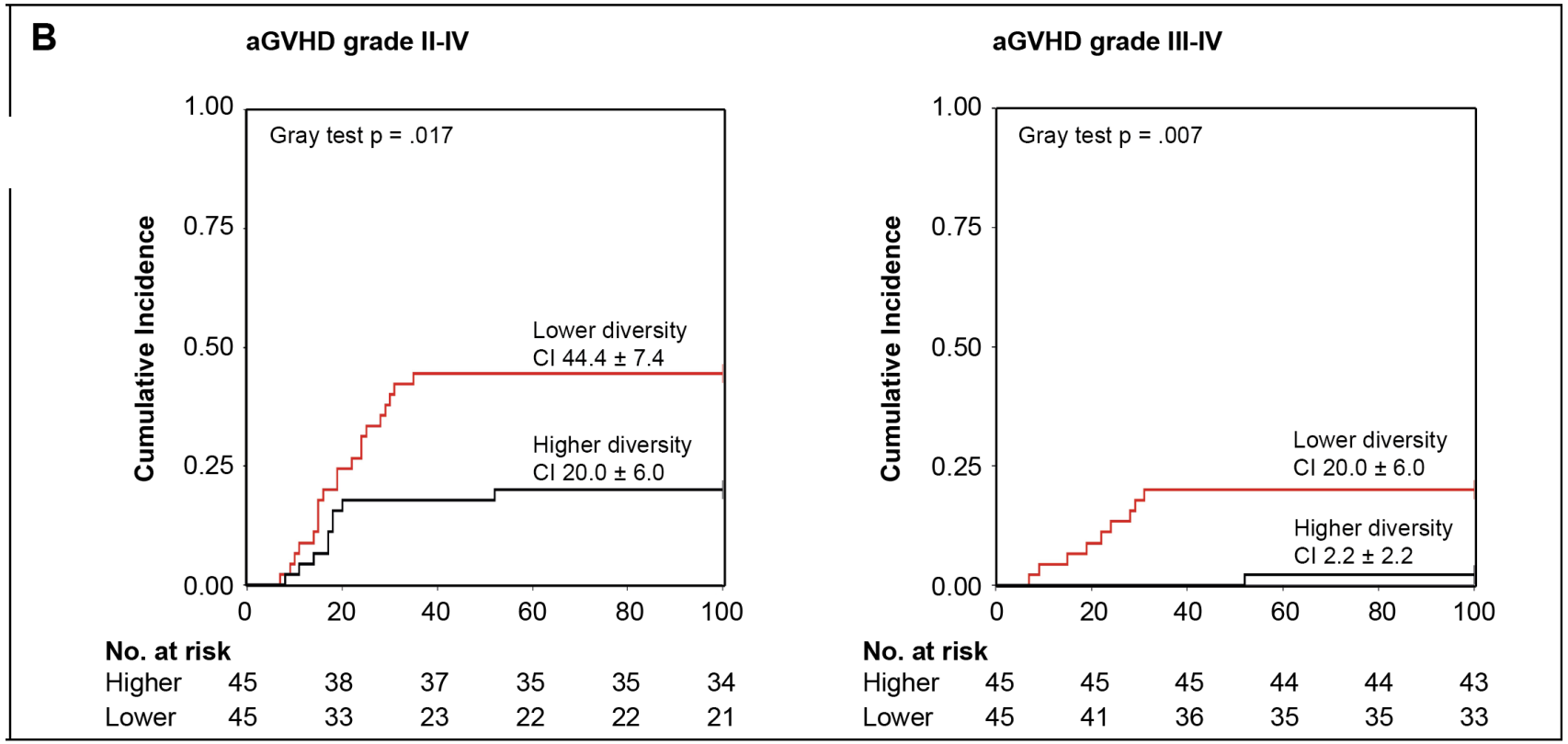


Pathobionts



SCFA producer:

- trophic effect on the intestinal barrier
- crosstalk between GM and host immune cells



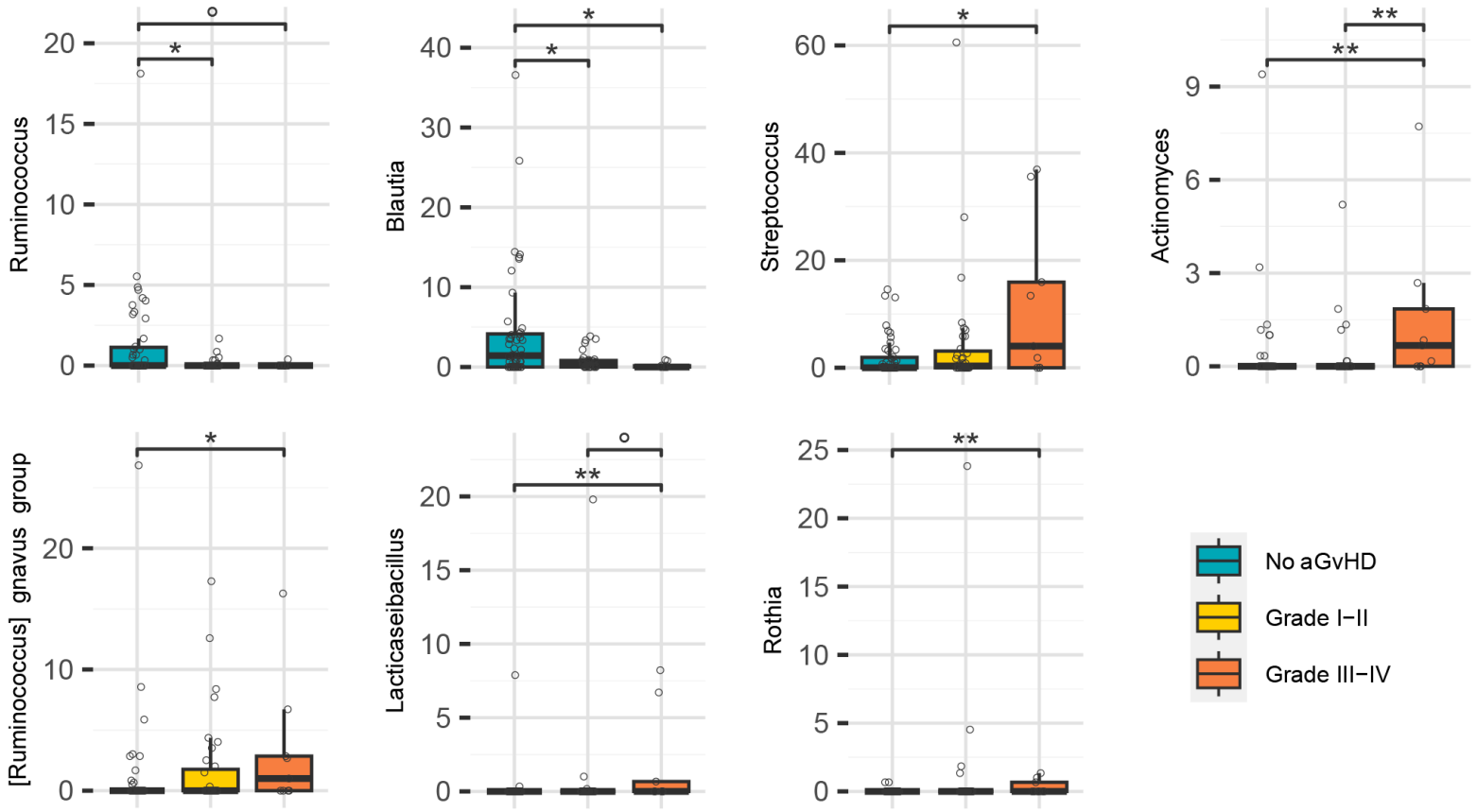
Multicentric longitudinal study

90 patients undergoing HSCT at 5 centers (BO, OPBG, VR, PV, Wroclaw) (>300 fecal samples)

Higher pre-HSCT **GM diversity** associated to **a lower incidence of grade II-IV and grade III-IV aGVHD**

GM diversity of pre-HSCT of fecal samples predicts cumulative incidence of acute GvHD

Masetti *et al.*, 2023 *Blood*



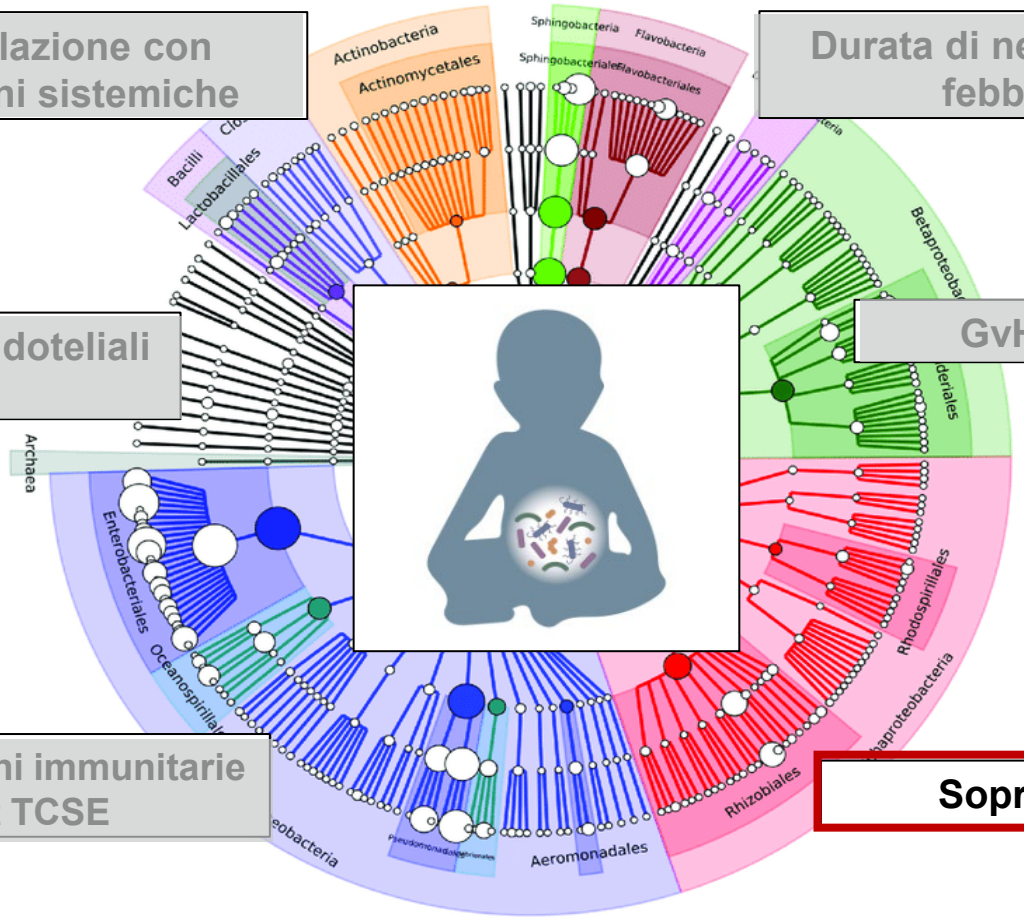
High abundance of *Blautia* and *Ruminococcus* (p ≤ 0.05) in pre-HSCT is protective for the subsequent development of acute GvHD

Increased abundance of facultative aerobic pathobionts in pre-HSCT is associated with increased acute GvHD

Masetti *et al.*, *Blood* 2023

Correlazione con infezioni sistemiche

Durata di neutropenia febbrile



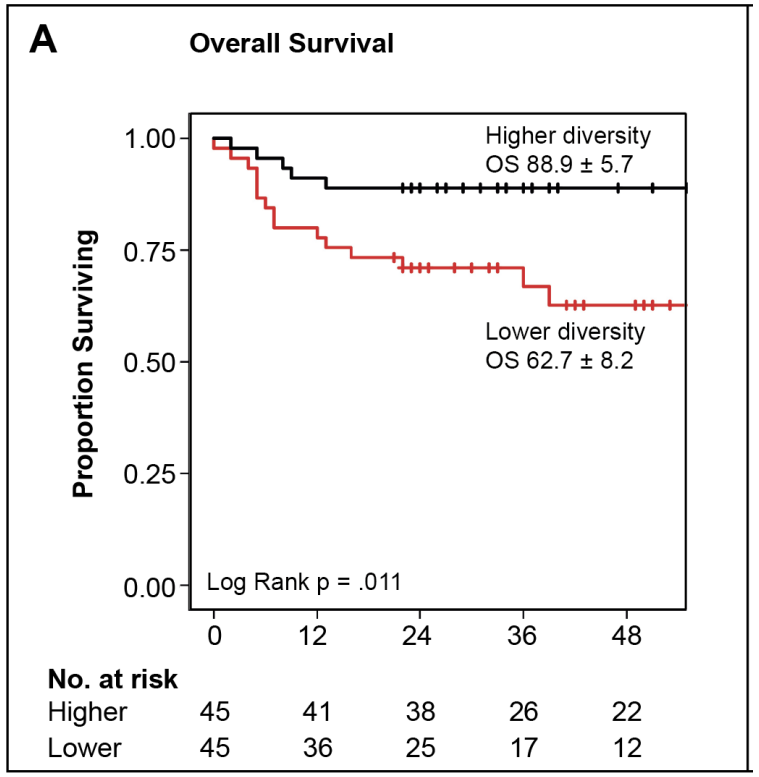
Complicanze endoteliali (VOD)

GvHD signature

Ricostruzioni immunitarie post TCSE

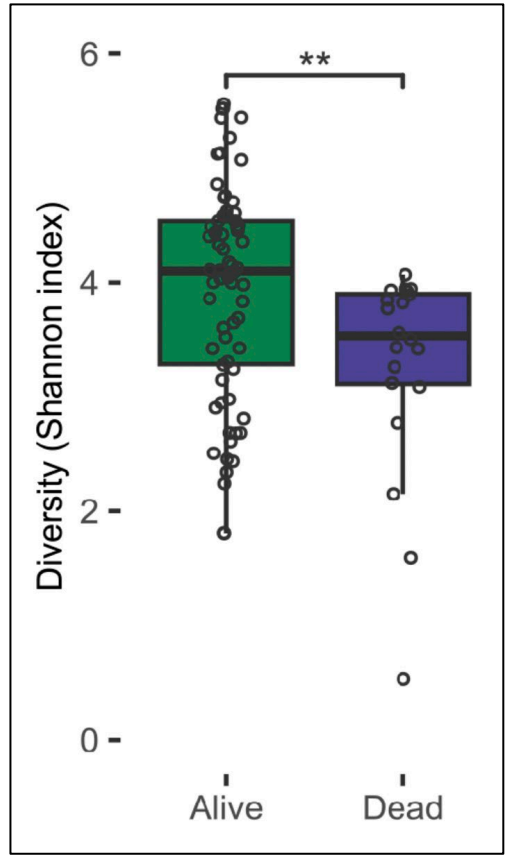
Sopravvivenza

GM DIVERSITY AND SURVIVAL IN CHILDREN RECEIVING HSCT



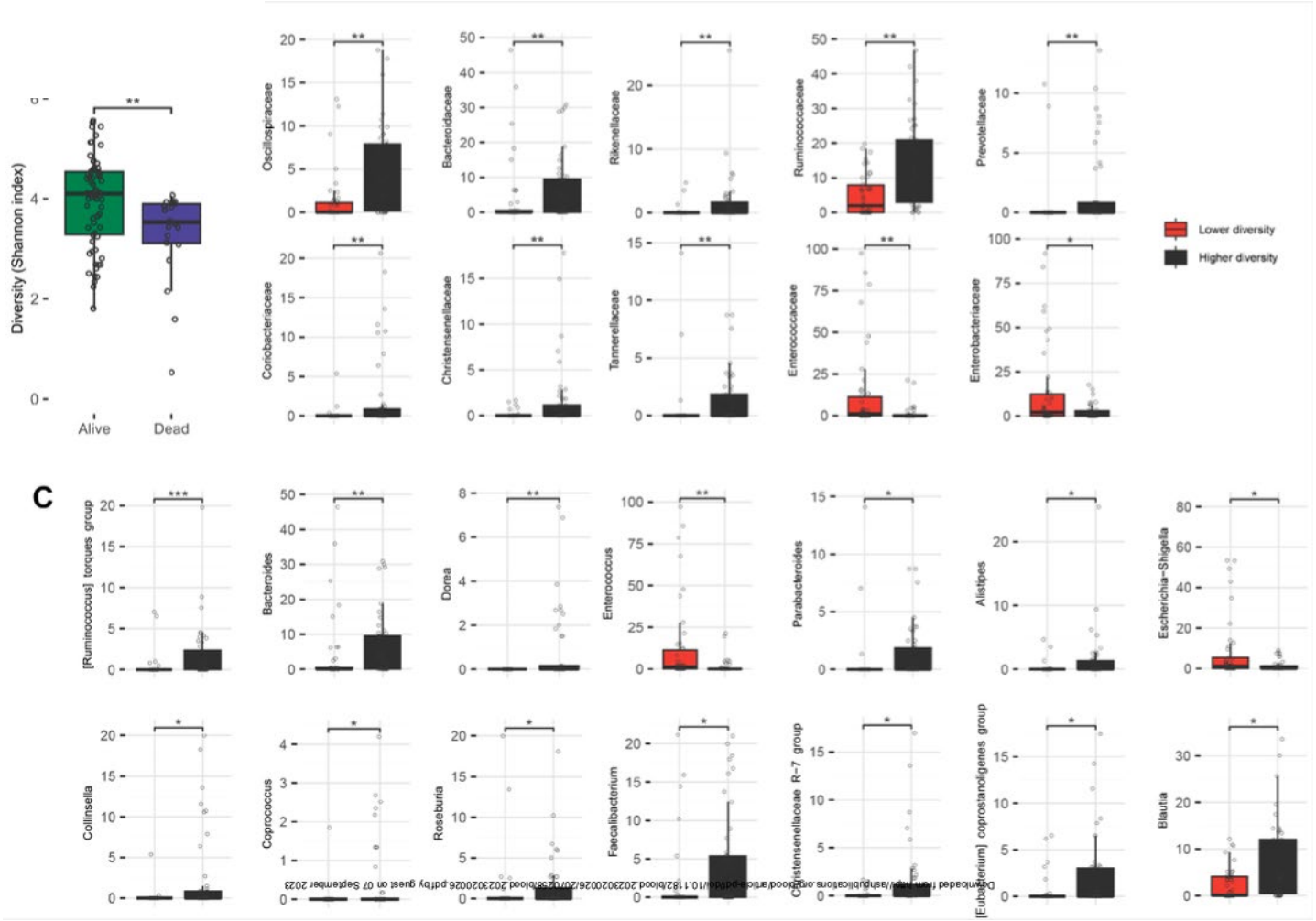
- **90 patients** undergoing HSCT at 5 centers (the **largest pediatric cohort studied for GM composition in HSCT**)
- Evaluation of **GM diversity before HSCT and at engraftment**
- Evaluated the impact of GM diversity on the survival post HSCT

GM diversity before HSCT



First evidence of an association between pre-transplantation lower GM diversity and poorer outcome in children undergoing allo-HSCT

Masetti *et al.*, 2023 *Blood*



Higher-diversity group composition:
> abundances of health-related families, such as *Ruminococcaceae* and *Oscillospiraceae, Bacteroidaceae*, *Rikenellaceae*, *Prevotellaceae*, *Coriobacteriaceae*, *Christensenellaceae*, (**SCFAs producer genera** such as *Blautia*, *Faecalibacterium*, *Roseburia*, *Bacteroides*, ..)

Lower-diversity group composition:
overabundance of *Enterococcaceae* and *Enterobacteriaceae,* including **many facultative aerobic pathobionts** (*Enterococcus*, *Escherichia-Shigella* and *Enterobacter*)

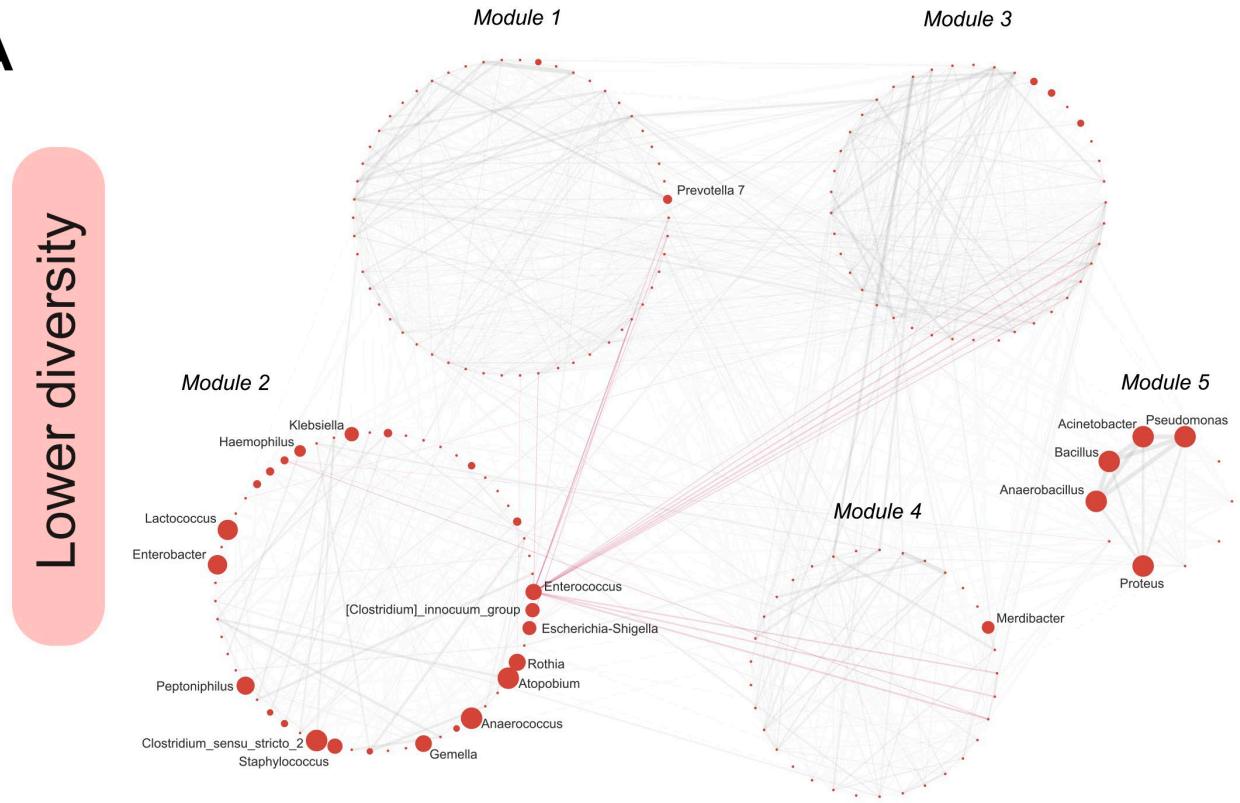
GM diversity and composition before transplantation correlate with survival

GM NETWORKS OF THE LOWER-DIVERSITY GROUP

Differences between the higher- and lower-diversity groups in terms of network topology and network properties linked to potential ecological interactions within GM communities.

5 modules were detected , which were clearly differently populated in the two diversity groups.

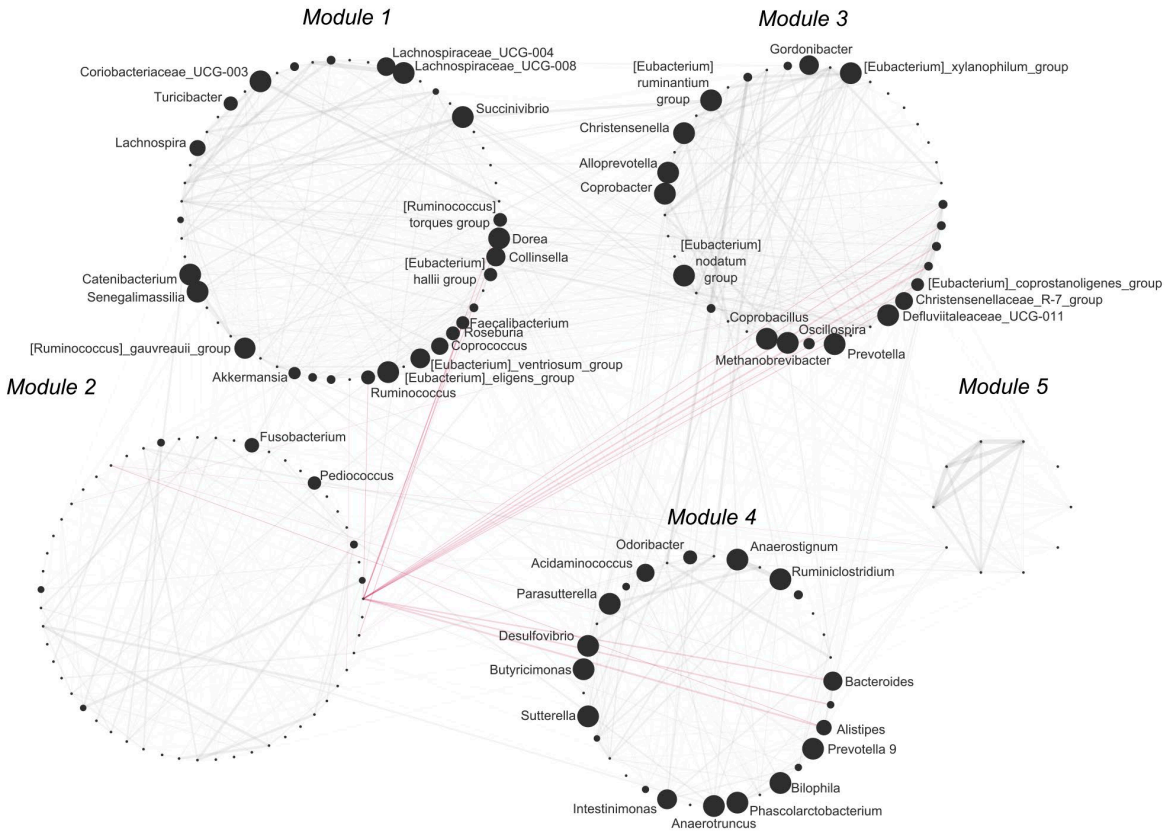
A



Before HSCT, GM network of patients belonging to the lower-diversity group showed **enrichment in network modules:**
#2, represented by *Enterococcus*, *Escherichia-Shigella*, *Rothia, Enterobacter, Anaerococcus* and *Klebsiella*
#5, with *Pseudomonas, Anaerobacillus, Bacillus, Proteus*, and *Acinetobacter*

GM NETWORKS OF THE HIGHER-DIVERSITY GROUP

Higher diversity



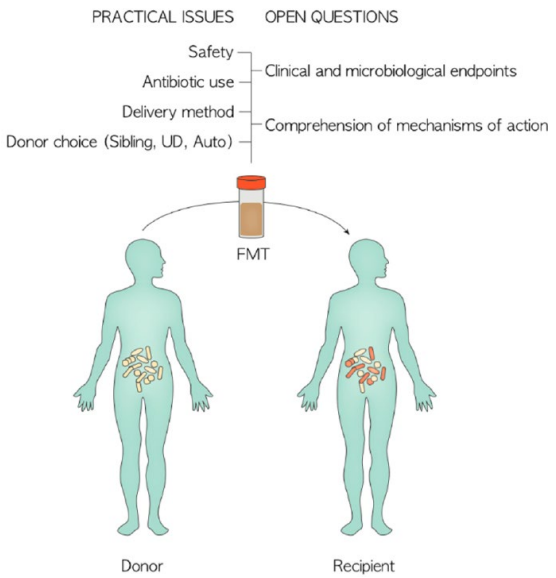
Before HSCT, GM network of patients belonging to the higher-diversity group showed enrichment in modules **#1, #3 and #4** containing several SCFAs producers (*i.e.*, *Bacteroides*, *Coprococcus*, *Roseburia*, *Oscillospira*, *Faecalibacterium*, *Ruminococcus,* and [*Eubacterium*] spp)

NEXT STEPS….

Pietro Merli,[1] Lorenza Putignani,[2*] Annalisa Ruggeri,[1] Federica Del Chierico,[3] Livia Gargiullo,[4] Federica Galaverna,[1] Stefania Gaspari,[1] Daria Pagliara,[1] Alessandra Russo,[3] Stefania Pane,[5] Luisa Strocchio,[1] Mattia Algeri,[1] Francesca Rea,[6] Erminia Francesca Romeo,[6] Paola Bernaschi,[7] Andrea Onetti Muda,[8] Bruno Dallapiccola[9] and Franco Locatelli[1,10]*

Decolonization of multi-drug resistant bacteria by fecal microbiota transplantation in five pediatric patients before allogeneic hematopoietic stem cell transplantation: gut microbiota profiling, infectious and clinical outcomes

Pietro Merli[1], Michele Massa[1], Alessandra Russo[2], Francesca Rea[3], Federica Del Chierico[2], Federica Galaverna[1], Francesca Del Bufalo[1], Stefania Pane[2], Mattia Algeri[1], Erminia Francesca Romeo[3], Luca Masucci[4], Paola De Angelis[3], Lorenza Putignani[2] and Franco Locatelli[1,5]



Fecal microbiota transplantation for the treatment of steroid refactory GvHD in pediatric patients

PNRR BBMRI
Microbiome Biobank

BBMRI.it
Biobanking and BioMolecular Resources Research Infrastructure of Italy

Harnessing the Gut Microbiota to Potentiate the Efficacy of CAR T Cell Therapy

HemaSphere

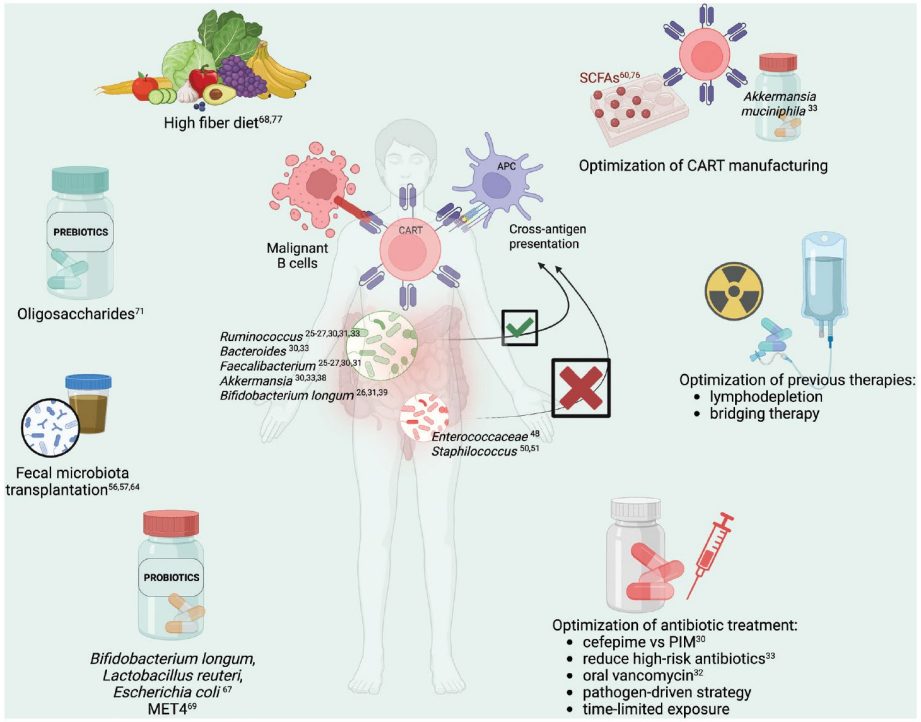
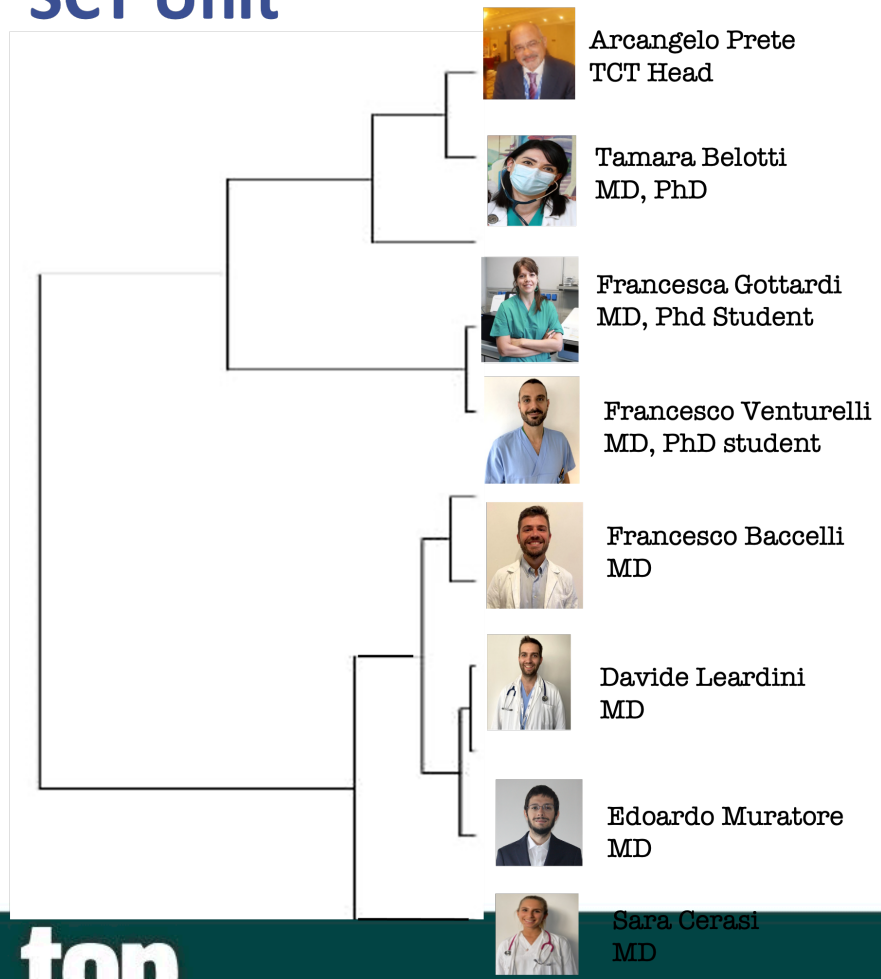


Figure 1. Possible strategies to enhance CART immunotherapy by modulating the gut microbiota. CART = chimeric antigen receptor T cell therapy; MET4 = Microbial Ecosystem Therapeutics; PIM = piperacillin-tazobactam, imipenem, meropenem; SCFAs = short-chain fatty acids.

GRAZIE PER L'ATTENZIONE

Aknowledgments: dai diamanti non nasce niente……

SCT Unit



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Francesca Gottardi
MD, Phd Student

Francesco Venturelli
MD, PhD student

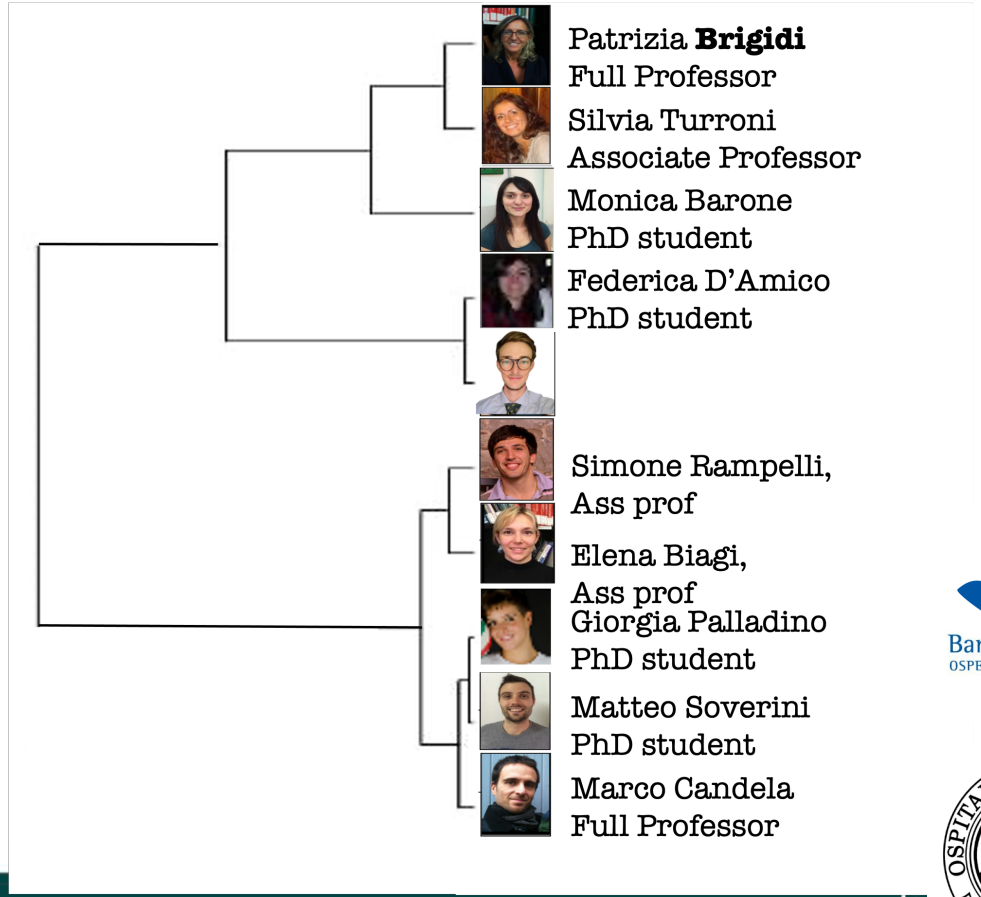
Francesco Baccelli
MD

Davide Leardini
MD

Edoardo Muratore
MD

Sara Cerasi
MD

Micro Unit



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Matteo Soverini
PhD student

Marco Candela
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Dott. Simone Cesaro

Bambino Gesù
OSPEDALE PEDIATRICO

Dott. Pietro Merli
Prof. Franco Locatelli

Ospitale di S. Matteo Pavia

Dott. Marco Zecca

TOP TEN Slides

1

PHARMACOMICROBIOMICS

Pharmacogenomics: how human genome variations affect drug action

Pharmacomicrobiomics: how GM, as the second human genome, affects drugs action

Unlike human genetics, **GM is modifiable** ➡ **attractive therapeutic target**

Bidirectional interaction GM and commonly used non-antibiotic drugs

- **GM composition** can be **influenced by drugs**
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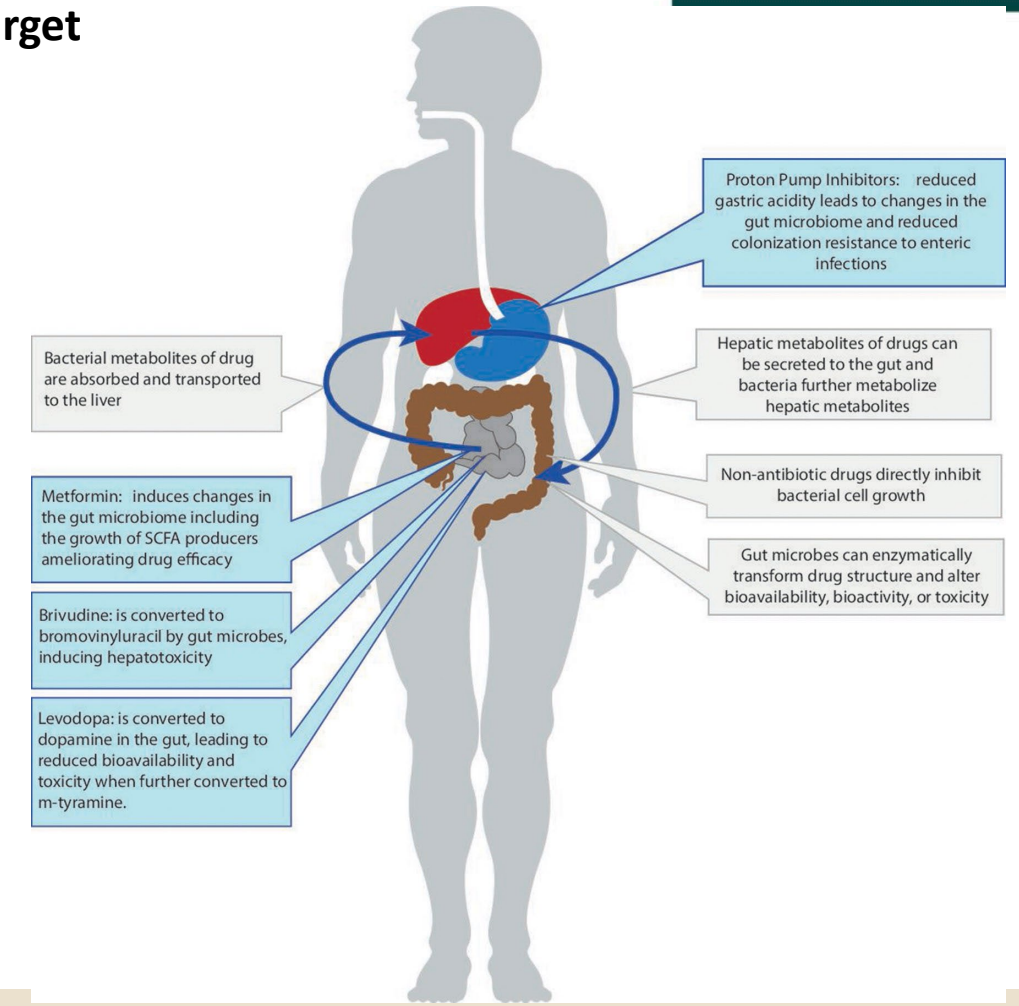
Large human cohort studies: associations between specific drugs and altered GM, including **PPIs, lipid-lowering statins, laxatives, metformin, beta-blockers and ACE inhibitors, and selective serotonin reuptake inhibitor antidepressants**



Weersma RK, *et al*. Gut 2020

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PHARMACOMICROBIOMICS: EXPLOITING THE DRUG-GM INTERACTIONS IN ANTICANCER THERAPIES

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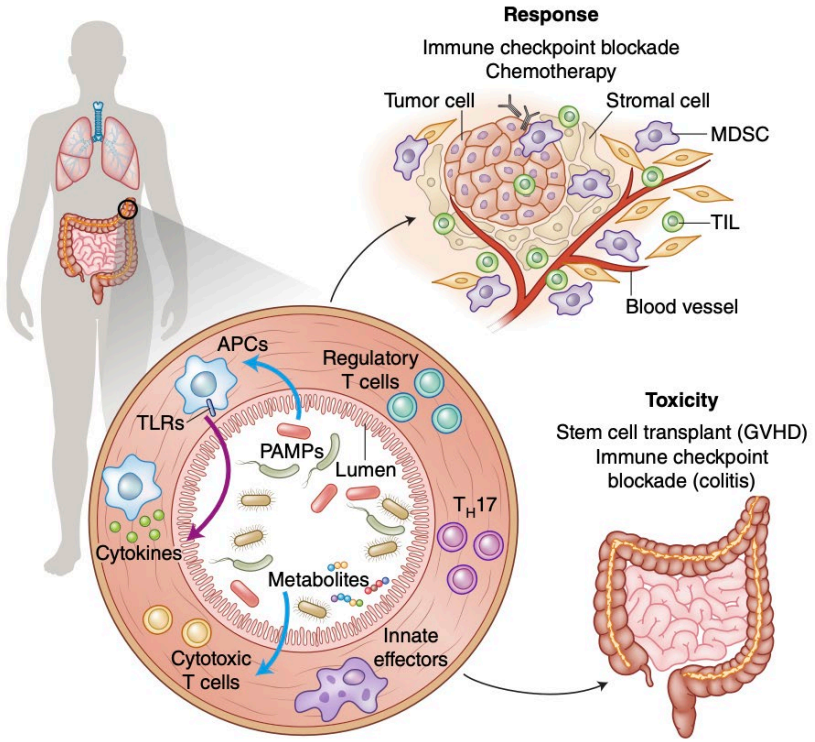
GM is involved in modulating the clinical response to cancer therapy GM (chemotherapy and immunotherapy immune checkpoint inhibitors**) and associated toxicities (colitis and GvHD)**



Chemoresistance: GM metabolizes chemotherapeutic drugs into their inactive forms

Immunothreapy resistance: GM supports the fine-tuning the general host immune status and subsequently antitumour activation of the immune system on checkpoint inhibition

Toxicity: GM alters systemic immune function via local changes within the gut mucosa and gut-associated lymphoid tissue

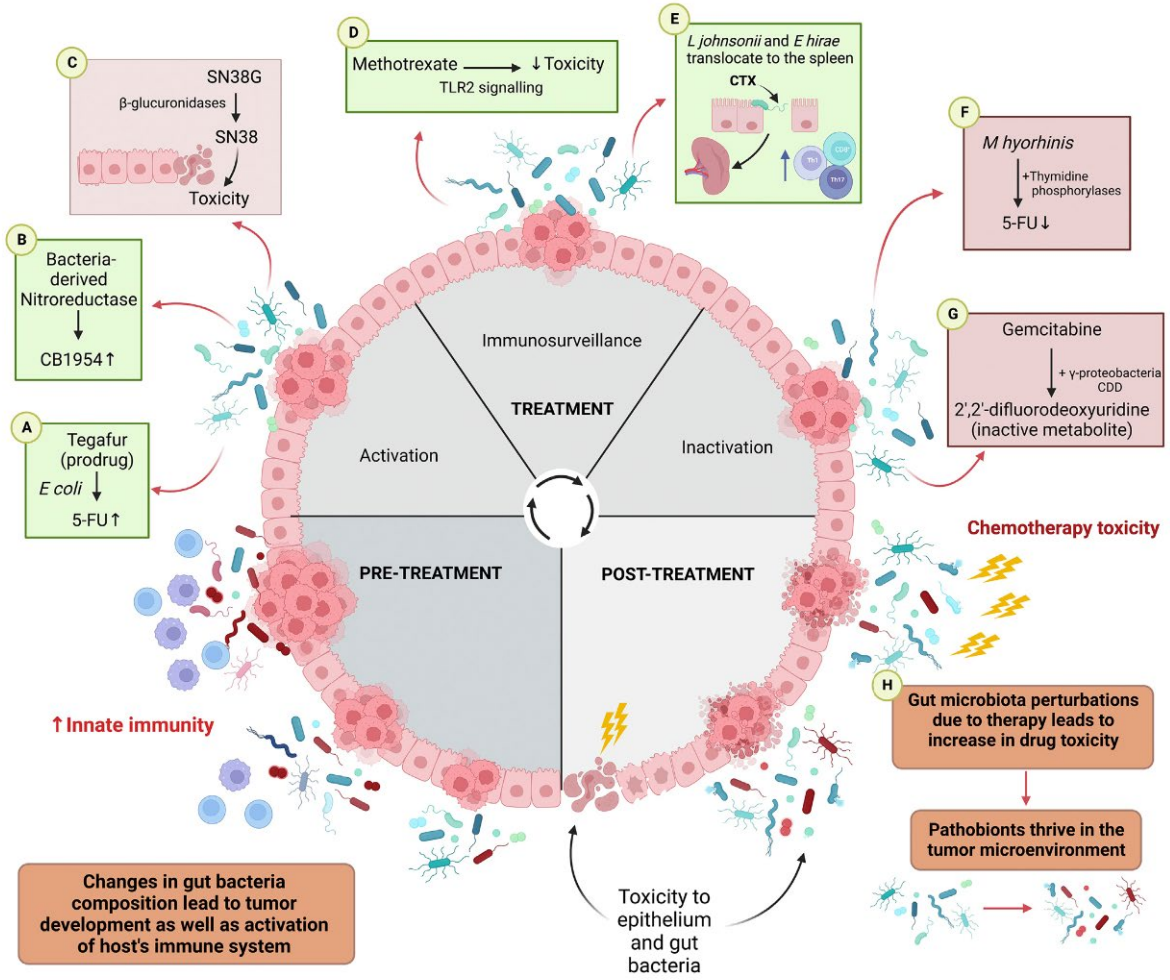
GM SHAPES ONCOLOGIC OUTCOMES

⬇

RESPONDERS NON RESPONDERS????

Helmink *et al*. Nat Med 2019; Bullman *et al.*, Science 2017; Spencer *et al.*, Science 2021

MECHANISMS OF HOST-ONCOMICROBIOME-THERAPY INTERACTIONS



Chrysostomou *et al.*, Gastroenterology 2023

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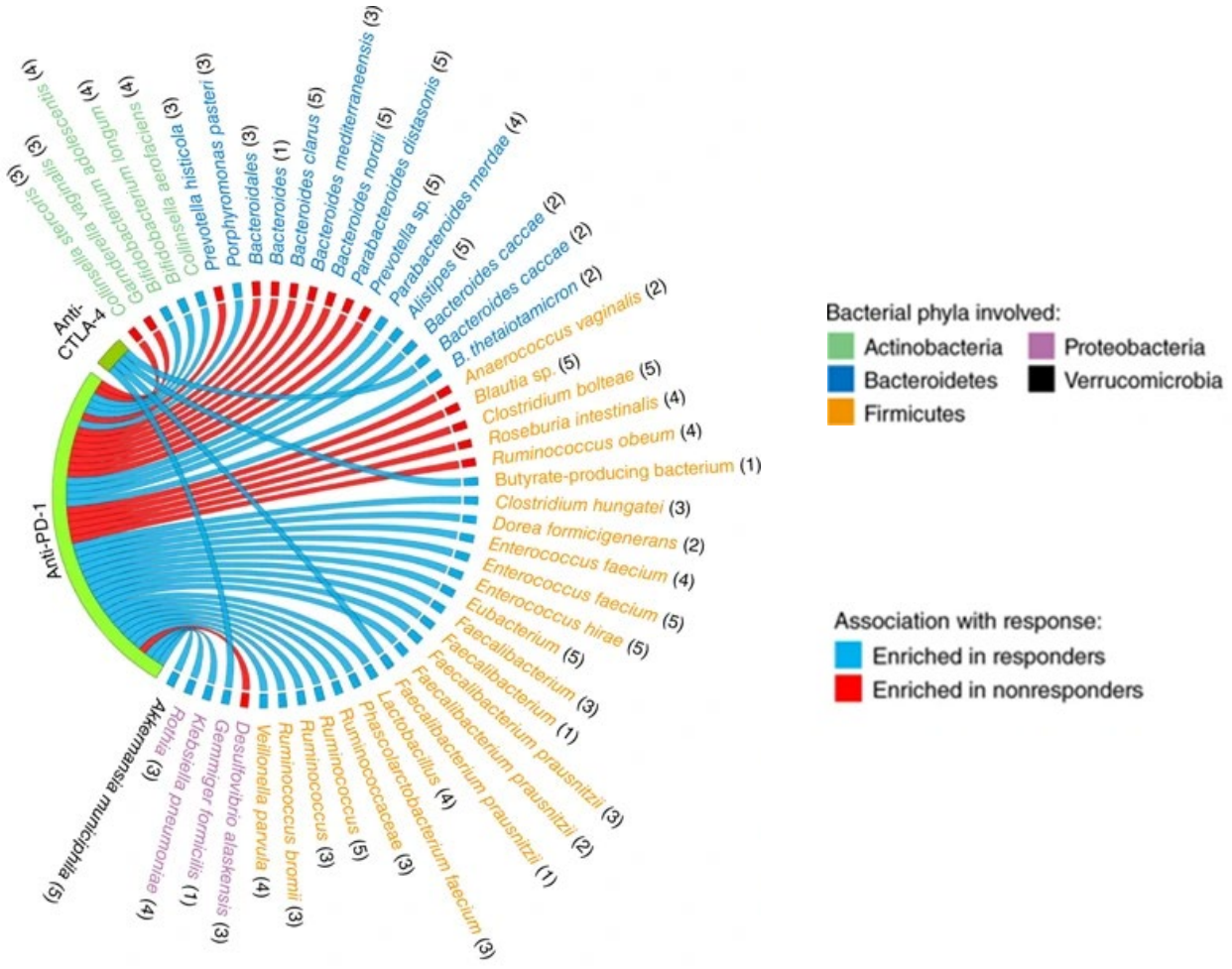
GM STRUCTURE IS PREDICTIVE OF RESPONSE TO IMMUNOTHERAPY



A positive response to mAbs targeting PD-1 in metastatic melanoma patients is associated with more "favourable" GM:

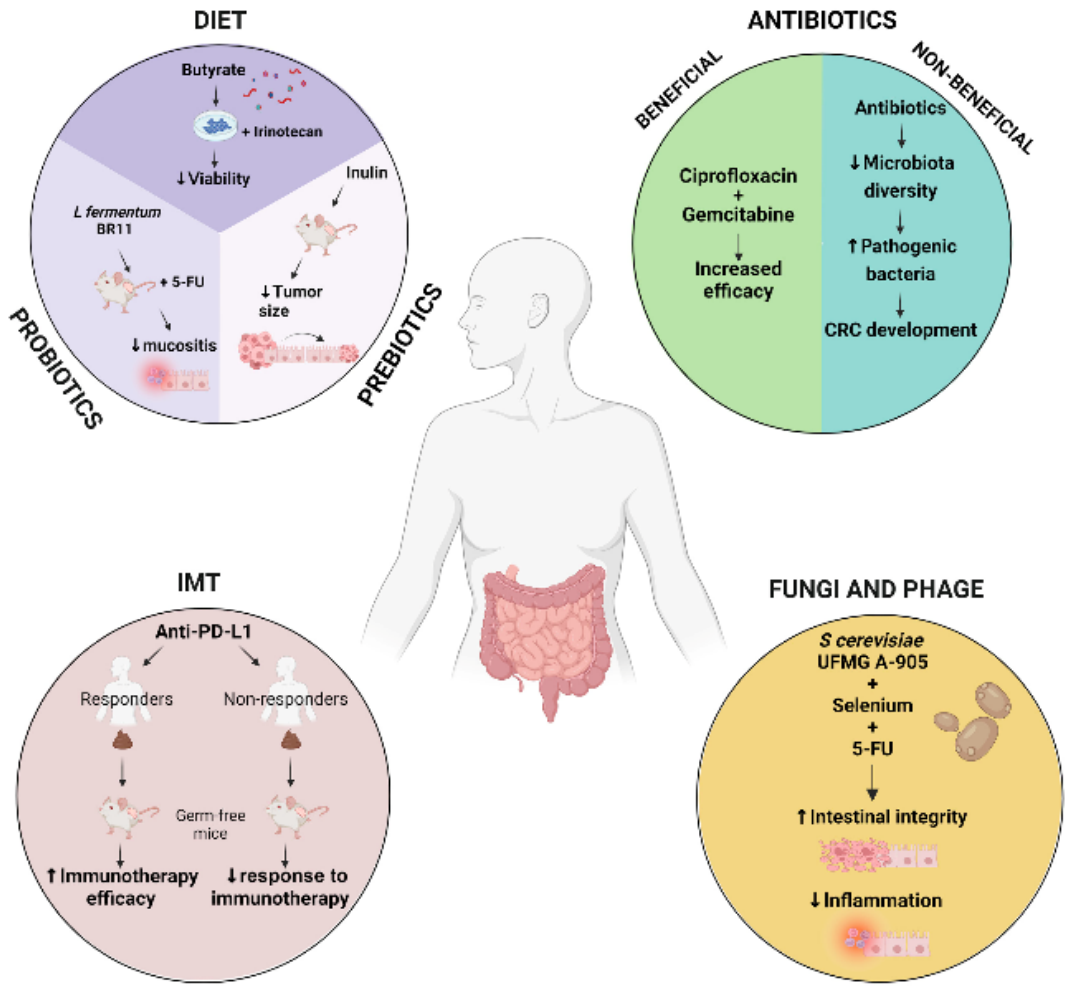
- **higher diversity**
- **higher relative abundance of health-associated bacteria (*Ruminococcaceae, Lachnospiraceae, Bifidobacteriaceae* and *Coriobacteriaceae*)**

Enhanced systemic and anti-tumour immune responses and improved effector T cell function

Mager *et al.*, Science 2020; Peled et al., New Engl J Med 2020

5

THERAPY OUTCOMES CAN BE MODULATED BY RESHAPING THE MICROBIOME



Chrysostomou *et al.*, Gastroenterology 2023

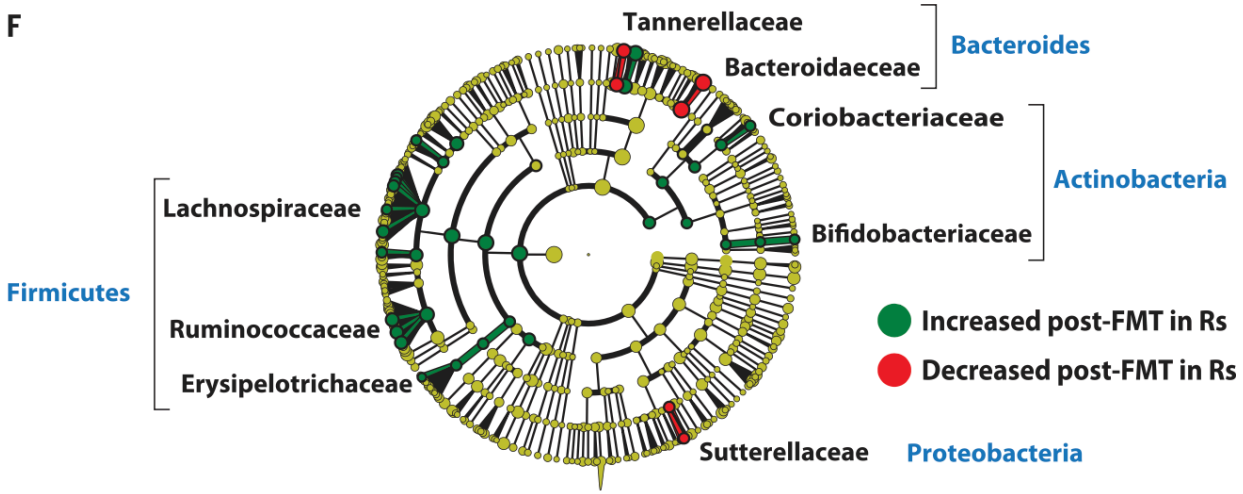
6

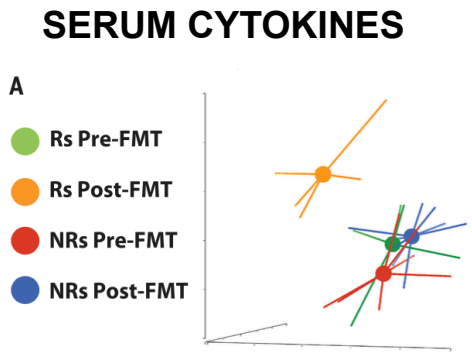
FMT OVERCOMES RESISTANCE TO mAbs anti–PD-1 THERAPY IN MELANOMA PATIENTS

Immune checkpoint blockade with **mAbs anti-PD-1** provides long-term clinical benefits to nearly **40% of patients with advanced melanoma**

15 melanoma patients refractory to anti–PD-1 therapy, received FMT from patients demonstrated durable complete response

FMT: clinical benefit in 6 of 15 patients, and induced rapid and durable GM perturbation





Responders exhibited:

- **increased abundance of taxa** associated with response to anti–PD-1
- **increased CD8+ T cell** activation
- **decreased** frequency of **IL-8**–expressing myeloid cells

Davar *et al.*, Science 2021

7

DYNAMICS OF GM DIVERSITY AND GVHD SIGNATURE IN CHILDREN UNDERGOING HSCT

Early gut microbiota signature of aGvHD in children given allogeneic hematopoietic cell transplantation for hematological disorders

Elena Biagi[1*†], Daniele Zama[2†], Simone Rampelli[1], Silvia Turroni[1], Patrizia Brigidi[1], Clarissa Consolandi[3], Marco Severgnini[3], Eleonora Picotti[2], Pietro Gasperini[2], Pietro Merli[4], Nunzia Decembrino[5], Marco Zecca[5], Simone Cesaro[6], Maura Faraci[7], Arcangelo Prete[2], Franco Locatelli[4], Andrea Pession[2], Marco Candela[1†] and Riccardo Masetti[2†]

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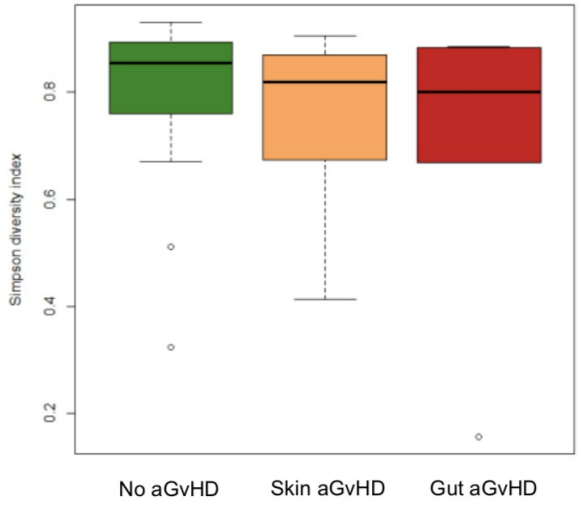
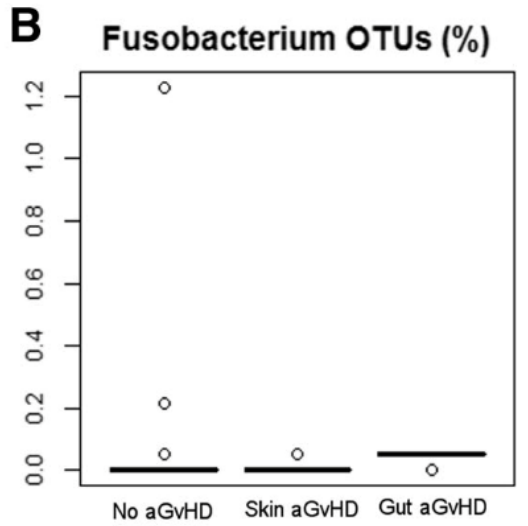
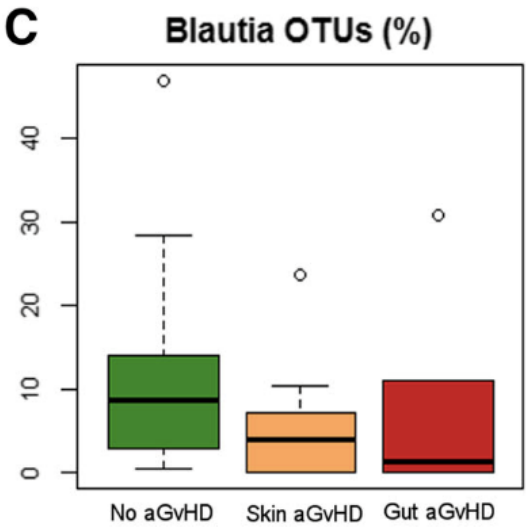
Higher pre-HSCT GM diversity associated to a lower incidence of intestinal aGvHD

High relative abundance of *Blautia* in pre-HSCT samples of NO aGvHD patients

High relative abundance of *Fusobacterium nucleatum* associated to severity of intestinal aGvHD





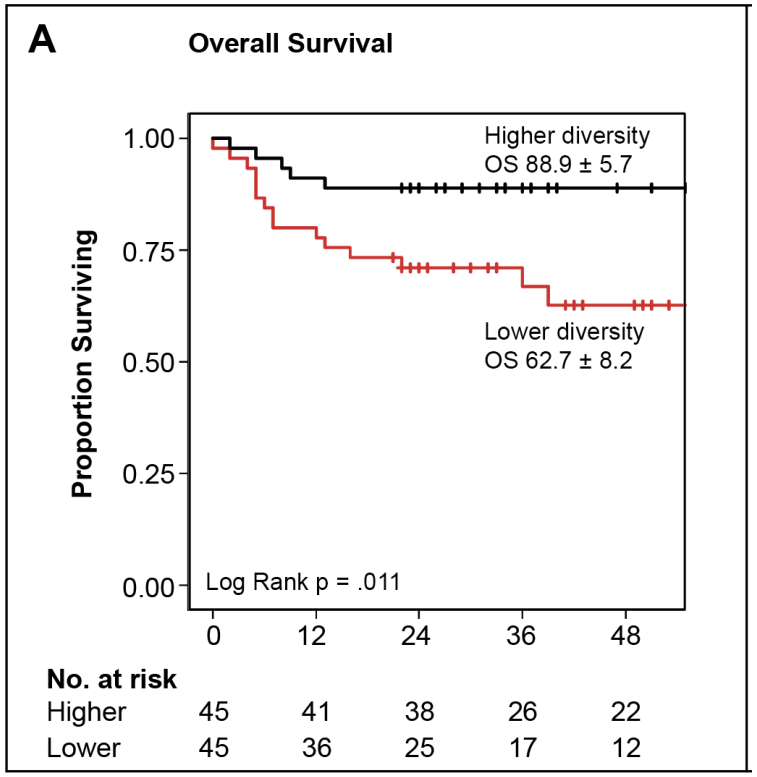


Pathobionts

SCFA producer:

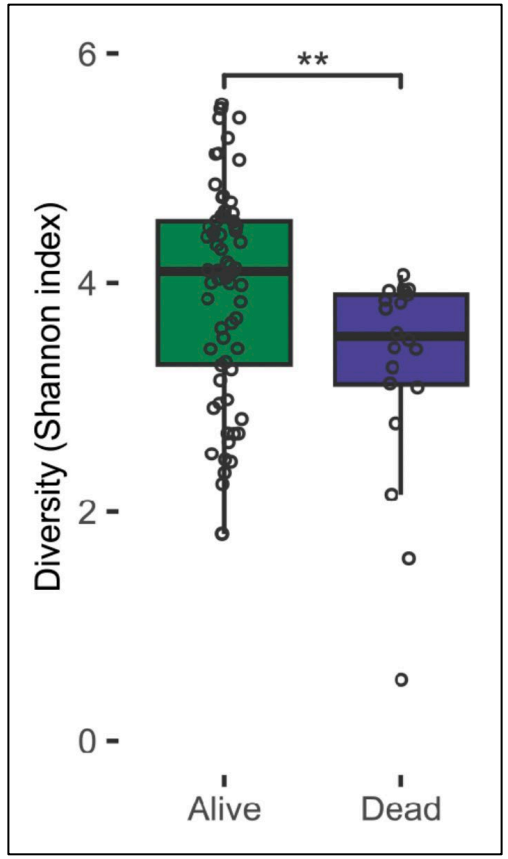
- trophic effect on the intestinal barrier
- crosstalk between GM and host immune cells

GM DIVERSITY AND SURVIVAL IN CHILDREN RECEIVING HSCT



- **90 patients** undergoing HSCT at 5 centers (the **largest pediatric cohort studied for GM composition in HSCT**)
- Evaluation of **GM diversity before HSCT and at engraftment**
- Evaluated the impact of GM diversity on the survival post HSCT

GM diversity before HSCT



First evidence of an association between pre-transplantation lower GM diversity and poorer outcome in children undergoing allo-HSCT

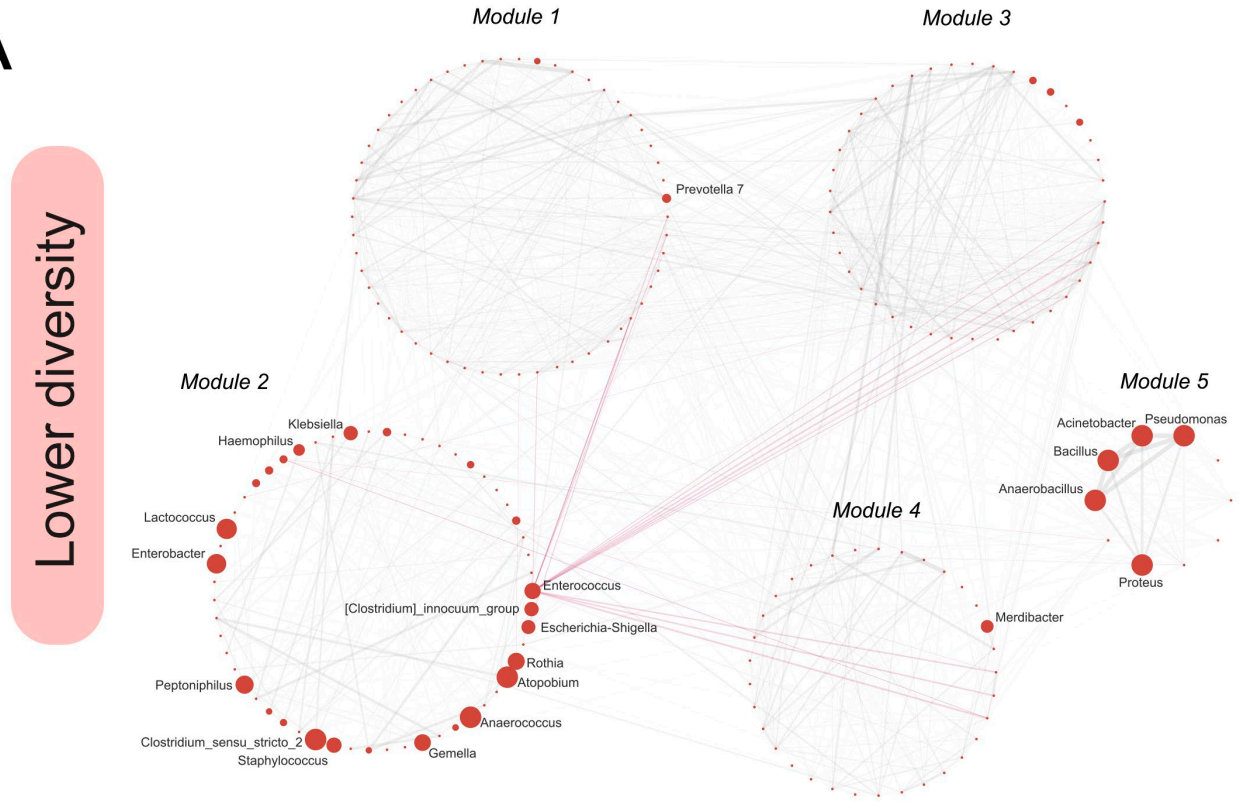
Masetti *et al.*, 2023 *Blood*

GM NETWORKS OF THE LOWER-DIVERSITY GROUP

Differences between the higher- and lower-diversity groups in terms of network topology and network properties linked to potential ecological interactions within GM communities

5 modules were detected , which were clearly differently populated in the two diversity groups

A



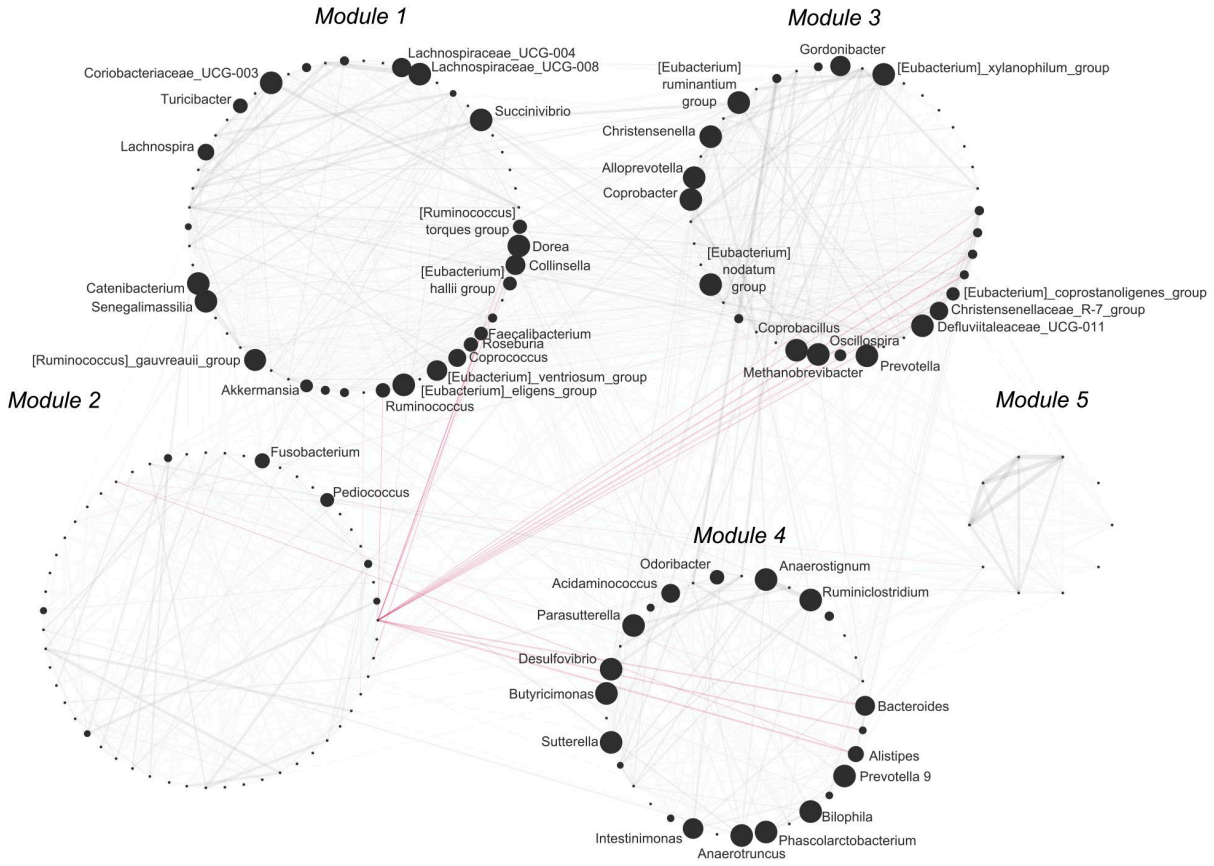
Before HSCT, GM network of patients belonging to the lower-diversity group showed **enrichment in network modules:**

#2, represented by *Enterococcus*, *Escherichia-Shigella*, *Rothia, Enterobacter, Anaerococcus* and *Klebsiella*

#5, with *Pseudomonas, Anaerobacillus, Bacillus, Proteus*, and *Acinetobacter*

GM NETWORKS OF THE HIGHER-DIVERSITY GROUP

Higher diversity



Before HSCT, GM network of patients belonging to the higher-diversity group showed enrichment in modules **#1, #3 and #4** containing several SCFAs producers (*i.e.*, *Bacteroides*, *Coprococcus*, *Roseburia*, *Oscillospira*, *Faecalibacterium*, *Ruminococcus,* and [*Eubacterium*] spp)