

Impact of gut microbiota in immuno-oncology

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GBG

GERMAN
BREAST
GROUP



Agenda

Jahrestreffen

09.-11. März 2022



Microbiota against cancer
International research program



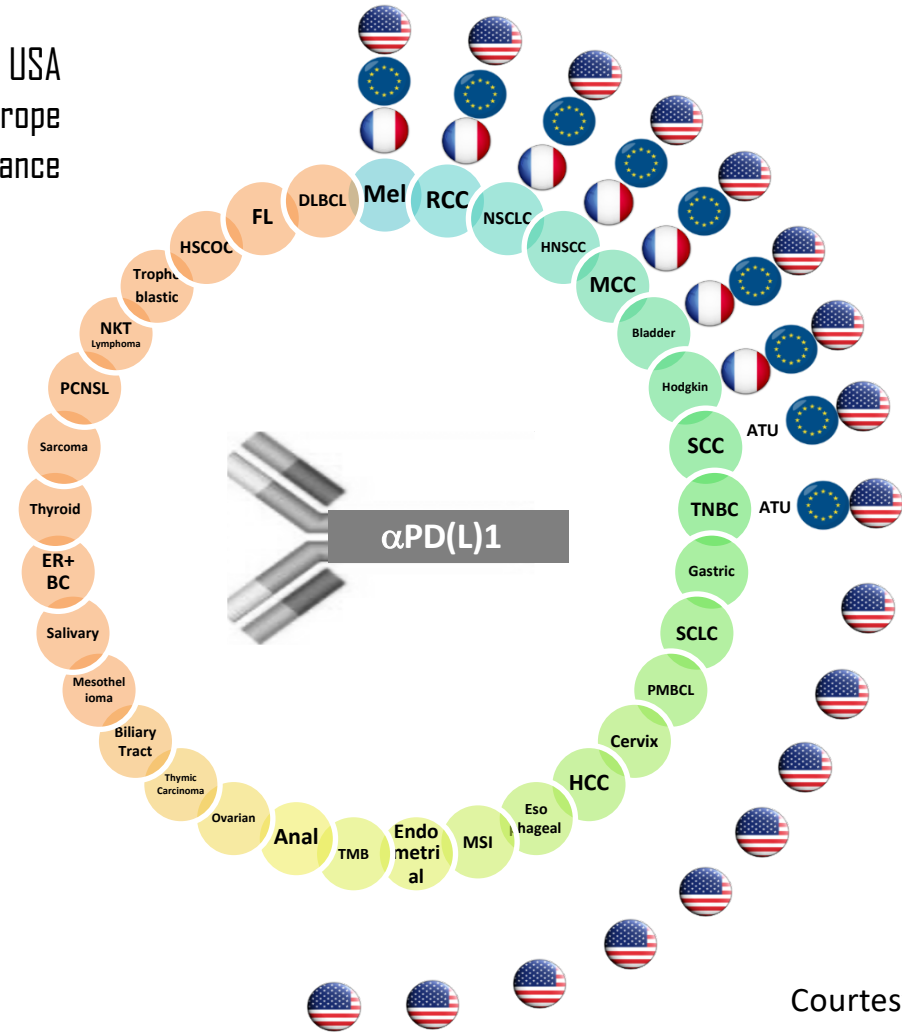
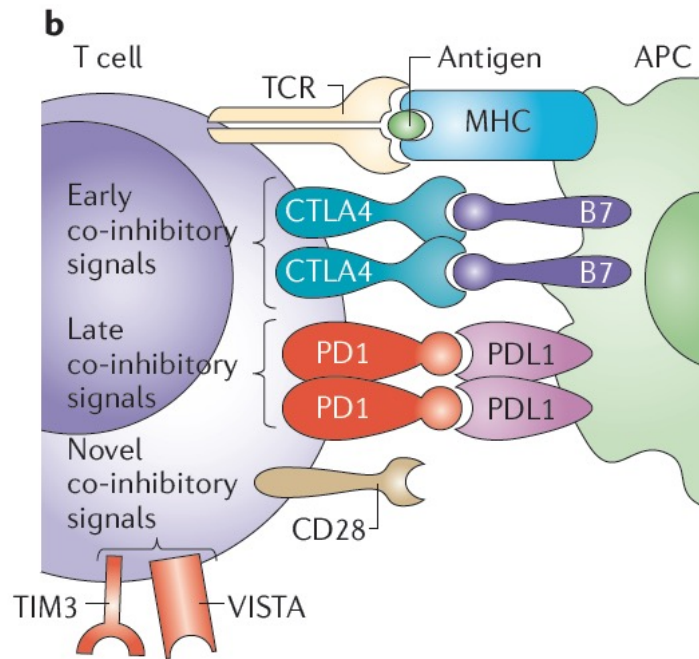
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Institut national
de la santé et de la recherche médicale

THE SUCCESS OF IMMUNE CHECKPOINT BLOCKADE (ICB): EMA-FDA approvals.

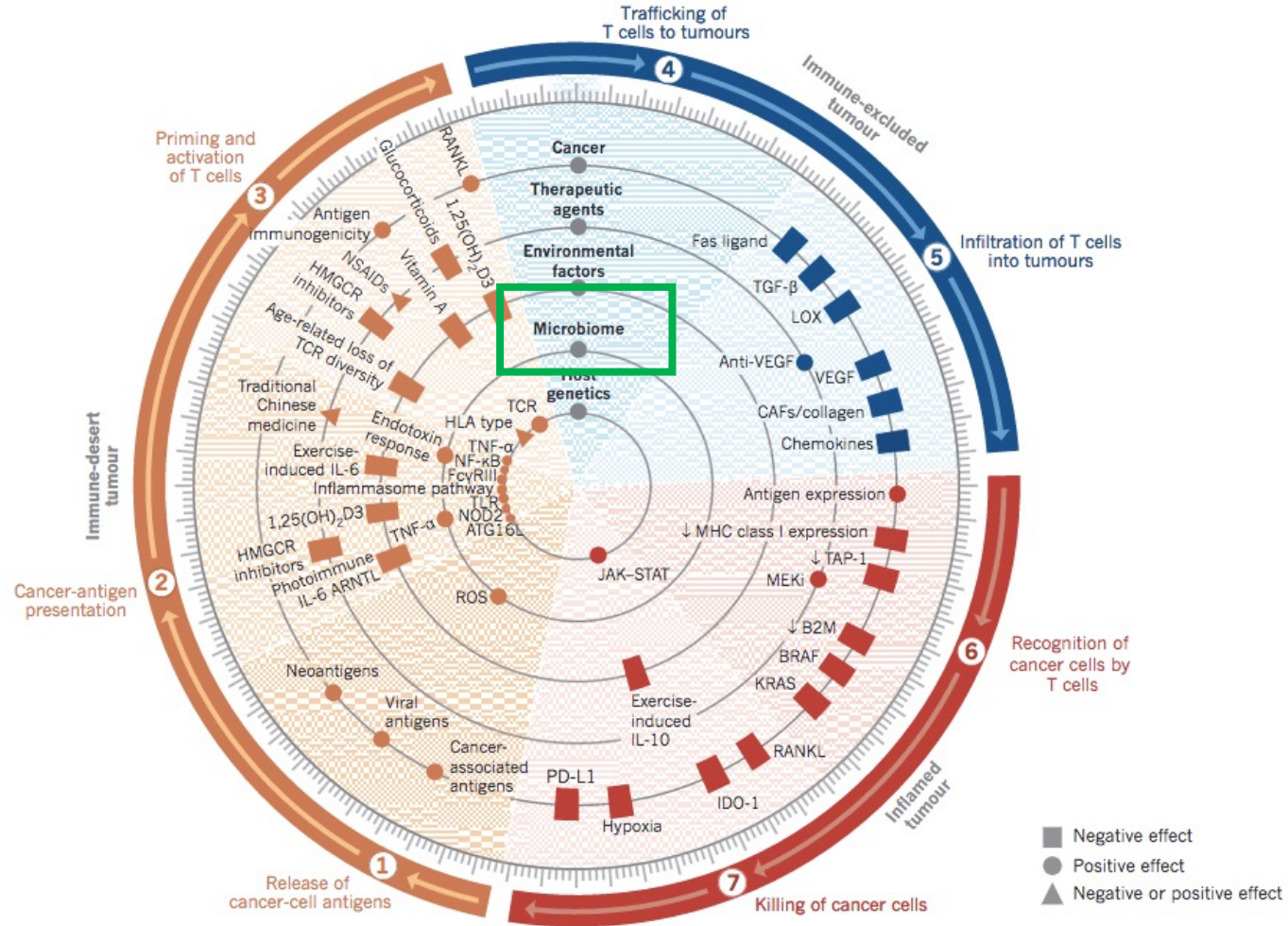
18 Tumor indications approved in the USA
 8 Tumor indications approved in Europe
 8 Tumor indications with reimbursement in France



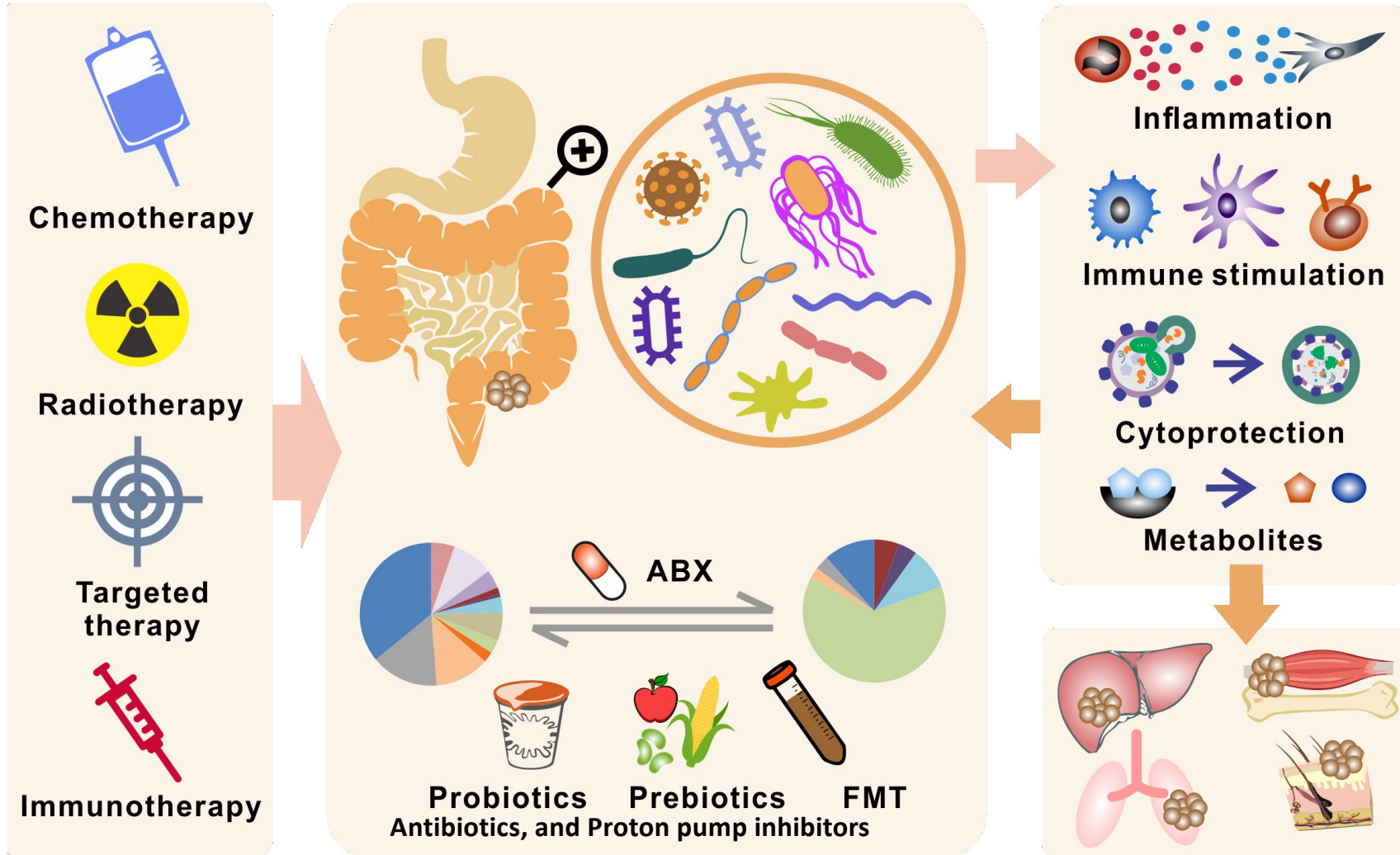
Courtesy: A. Marabelle

THE MICROBIOME REGULATES THE CANCER IMMUNE SET POINT

Chen D. and Mellman I. Nature Jan. 2017



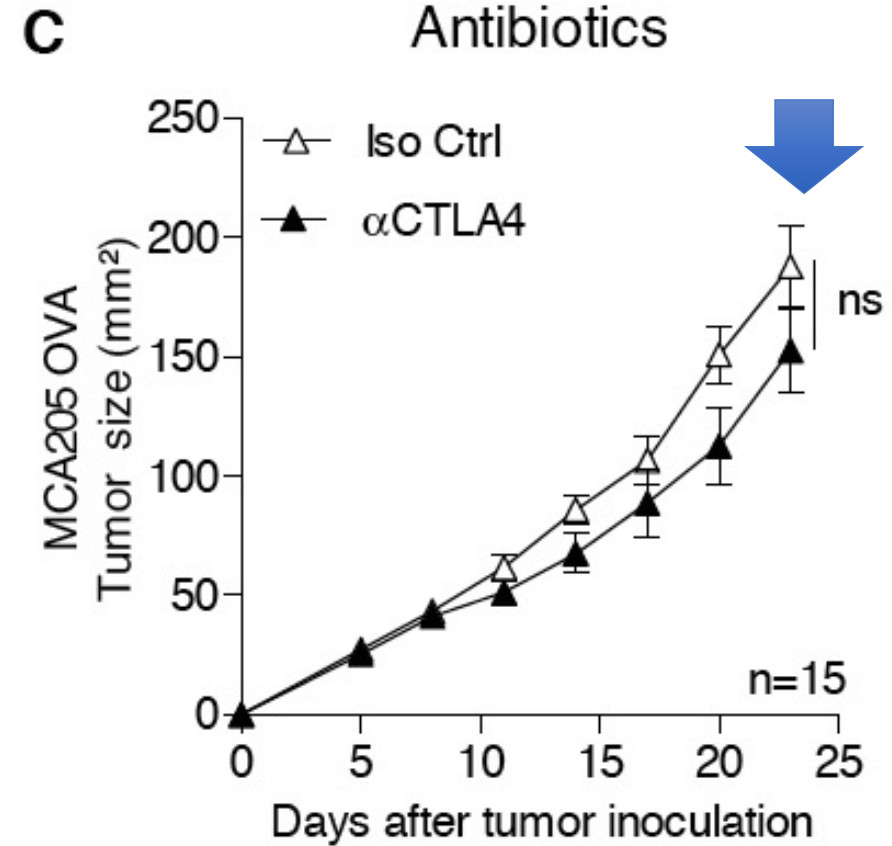
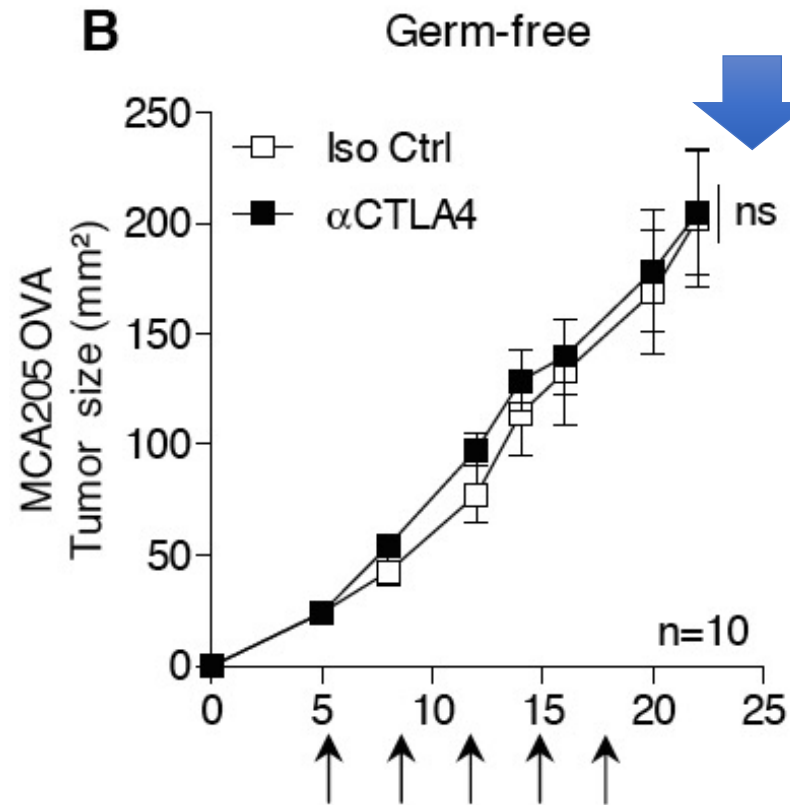
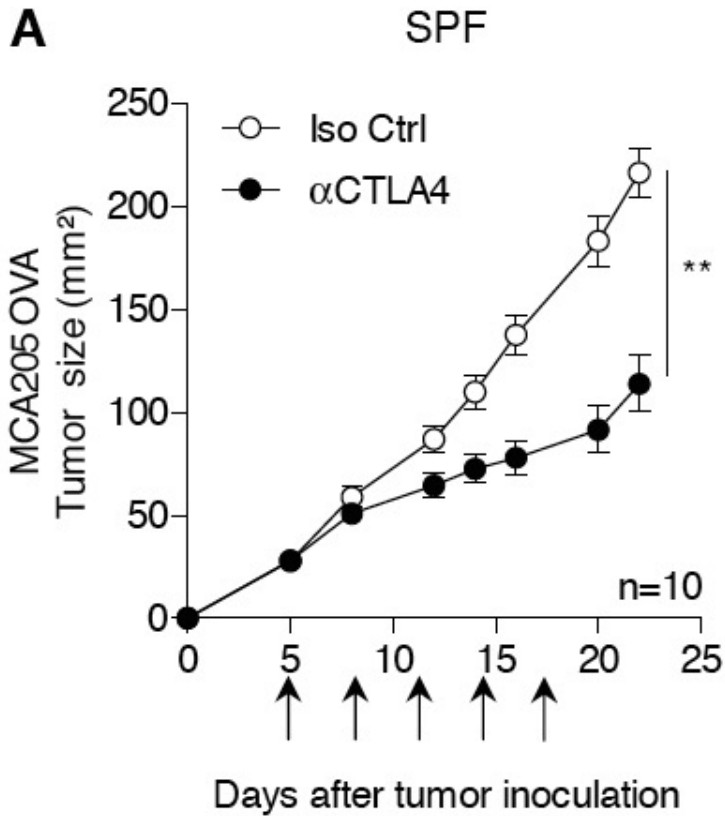
IMPACT OF CANCER THERAPIES ON HOST HOMEOSTASIS.





Cancer immunotherapy (ICB) fails to work in germ free or ATB-treated tumor bearers.

Transplantable subcutaneous and orthotopic tumors
MCA205 sarcoma, MC38 colon cancer and RET melanoma



Similar results using cyclophosphamide, platinum salts, IL-10R and PD1 blockade
(Viaud et al. Science 2013, Iida et al. Science 2013, Vétizou et al. Science Nov 2015, Routy et al. Science 2017).

PROOFS OF CONCEPT of the impact of the gut microbiome in ICB

■ *Four lines of evidence:*

ANTIBIOTICS

Betalactams
Fluoroquinolones
Tetracyclines
Macrolides...except Vanco

PILOT trials

FMT from R into NR pts

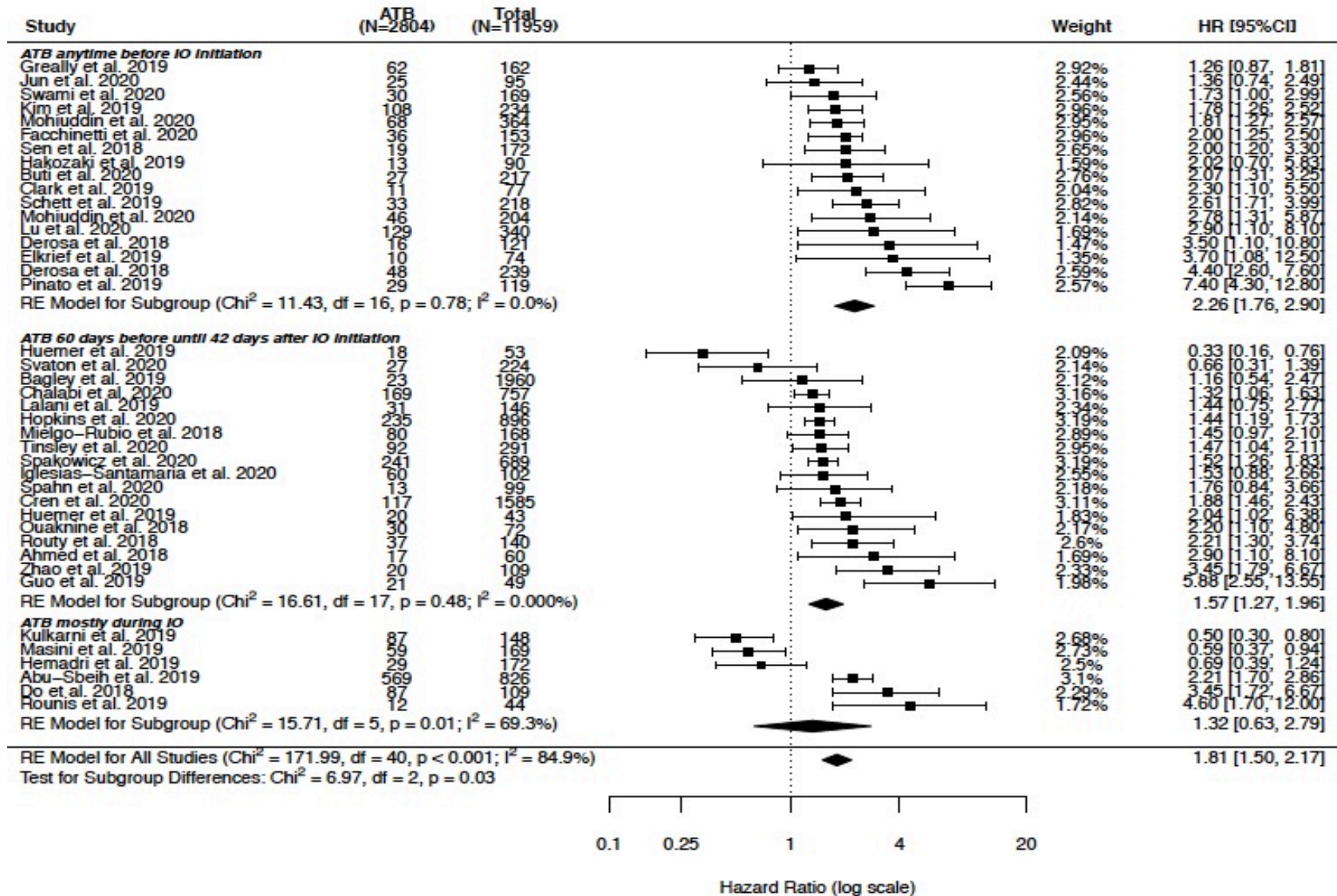
GOMS

MG-based
taxonomic fingerprints

AVATAR mice

Human feces into
murine intestines

META-ANALYSIS: negative effects of ANTIBIOTICS in the clinical benefit to immune checkpoint inhibitors (Derosa, Routy et al. Cancer Discovery 2021)





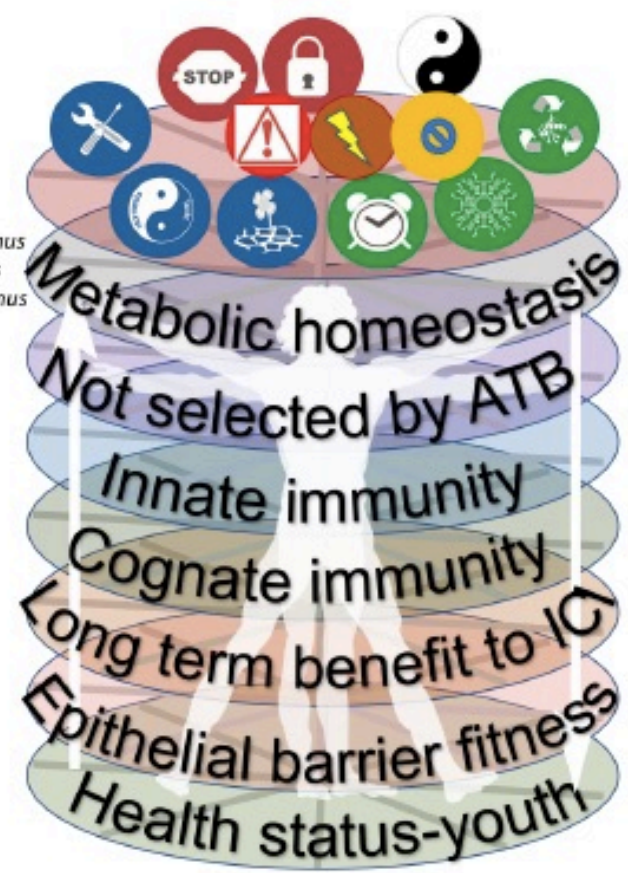
Gut OncoMicrobiome signatures (GOMS) predicting the clinical benefit or resistance to ICB

Derosa et al. Cancer Discovery, 2021

Beneficial bacteria

Harmful bacteria

- Ruminococcus genus** *Faecalibacterium prausnitzii*
- Lachnospiraceae family** *Dorea genus*
Coprococcus genus
Roseburia genus
Eubacterium genus
Blautia obeum
- Actinobacteriaceae family** *Collinsella genus*
Bifidobacterium genus
- Archae** *Methanobrevibacter smithii*
- Verruco-Microbiaceae family** *Akkermansia muciniphila*
- Bacteroidales order** *Prevotella copri*
Barnesiella intestinihominis
Alistipes senegalensis

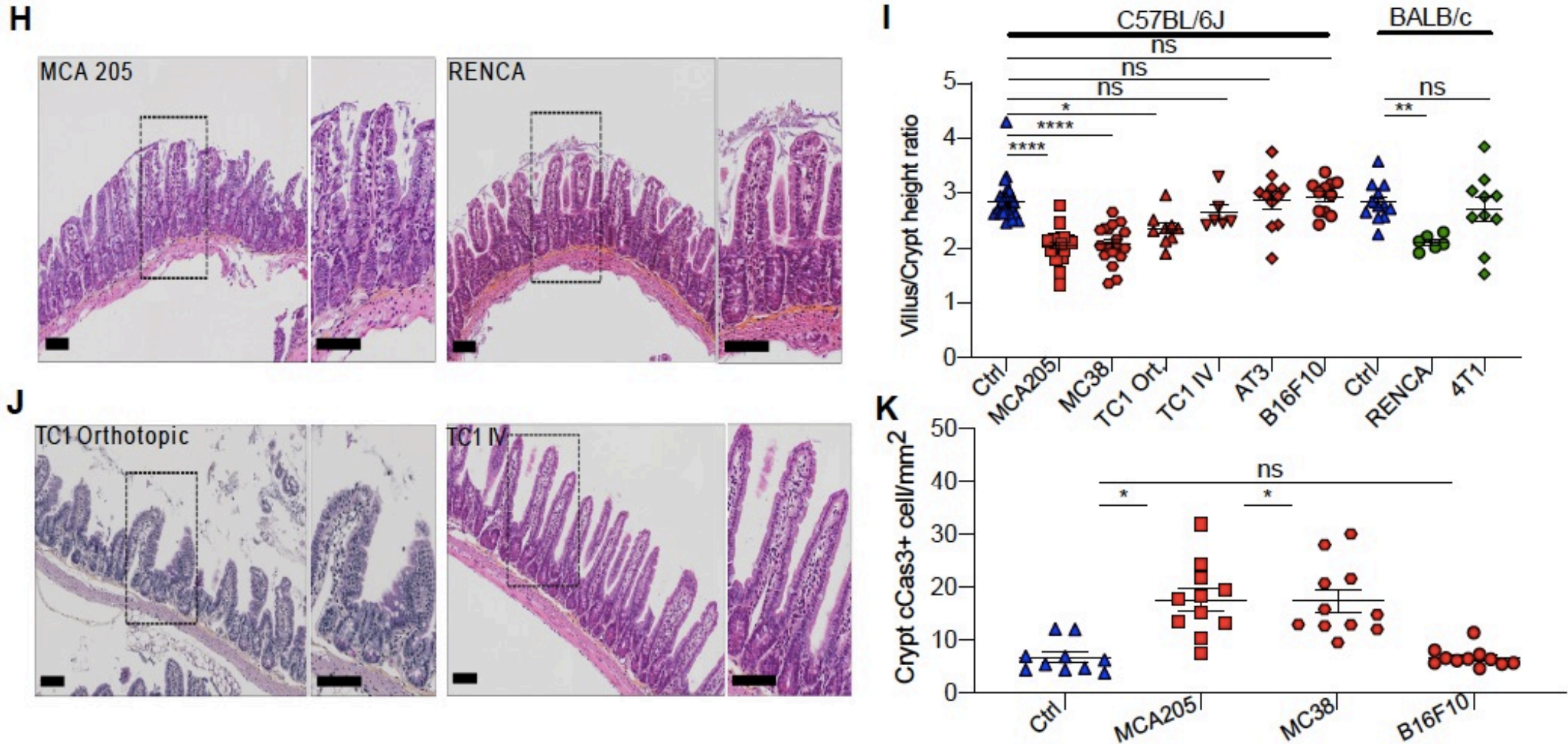


- Enterobacteriales** (E. Coli, Shigella, Klebsiella) **Proteobacteria phylum**
- Bilophila wadsworthia*
- V. parvula* **Veillonella genus**
- B. uniformis* **Bacteroides genus**
- B. distasonis*
- B. nordii*
- Atopobium parvulum* **Actinobacteria phylum**
- Eggerthella lenta*
- Actinomyces spp.*
- C. asparagiforme* **Clostridium genus**
- C. clostridioforme*
- C. citroniae*
- C. boltae*
- C. lavalense*
- C. hathewayi*
- C. symbasium*
- C. aldenense*



Cancer can induce an ileopathy and a protracted intestinal dysbiosis participating in cancer progression.

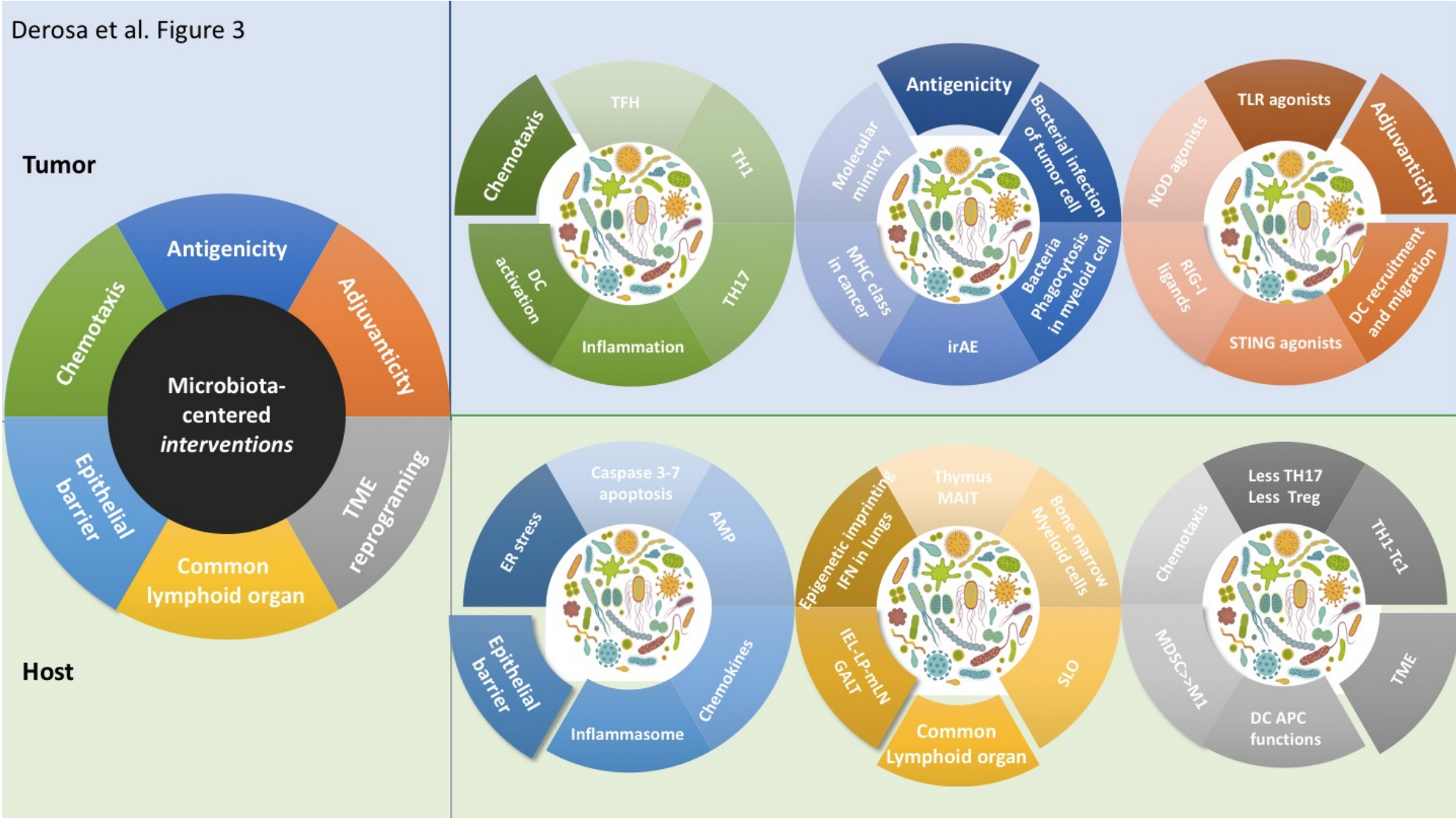
Yonekura et al. Cancer Discovery (Dec 2021)



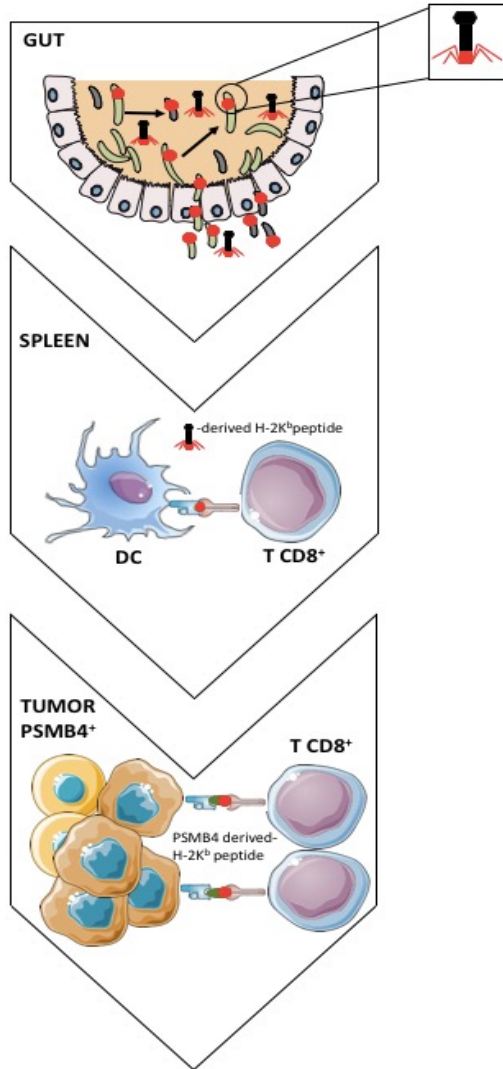


MODES OF ACTION of gut microbes in immuno-oncology (Derosa et al. *Cancer Discovery* 2021).

Derosa et al. Figure 3

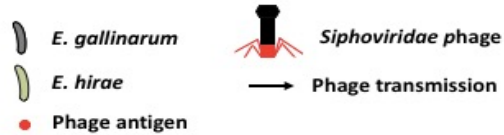


Molecular mimicry between enterophage and oncogene.



1. Lysogenicity of *E. hirae* with phage antigen

Possible transmission of phages between two *E. hirae* or between *E. hirae* and *E. gallinarum*



2. Phage antigen-specific CD8+ T cell priming and activation by antigen presenting cell infected by *E. hirae*/phage or after phagocytosis of dead cells



3. Recognition and elimination of PSMB4 overexpressing tumor cells through cross-reactivity between tumor antigen and phage antigen

78% structural homology between phage and oncogenic antigenic driver

Fluckiger et al. Science 2020
Aug 21;369(6506):936-942.

Enterococcus Phage
sequence harboring antigenic
MHC class I-restricted peptides
sharing molecular mimicry
with an oncogene product
induces or amplifies
memory Tc1 immune responses
beneficial against cancer.



Siphoviridae enterophage



Bacterial epitopes presented by tumor cells to activate TILs.

Bacterial peptides reveal tumours to T cells

Kalaora, S. *et al. Nature*

<https://doi.org/10.1038/s41586-021-03368-8>
(2021).

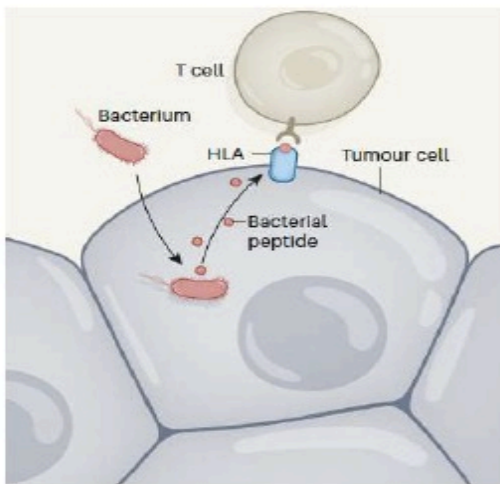


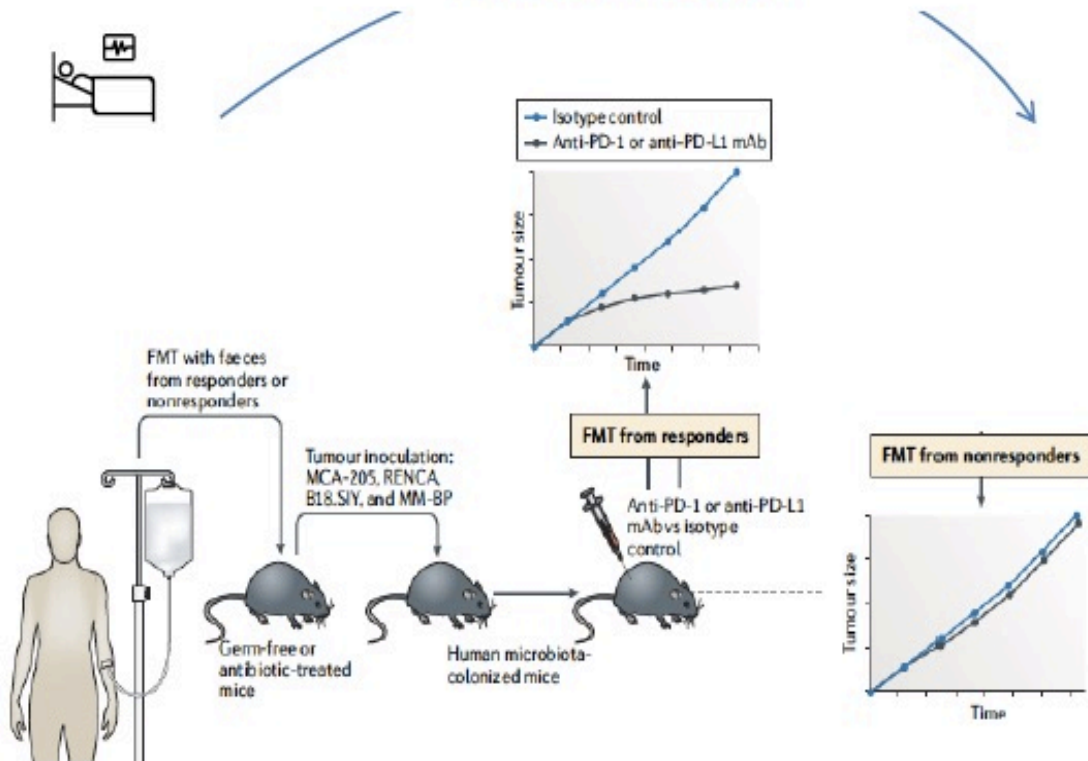
Figure 1 | A route to antitumour immunity triggered by bacteria. Kalaora *et al.*⁴ report that certain bacteria can invade cells from a type of tumour called melanoma. Peptide fragments from bacterium-derived molecules are presented on the tumour cell surface by proteins called human leukocyte antigens (HLAs). Immune cells called T cells recognize and are activated against these presented peptides. Thus, bacterial peptides might be a previously unidentified class of tumour antigen – a type of molecule that enables T cells to distinguish tumour cells from normal tissue.

The analysis of 17 melanoma metastases (derived from 9 patients) revealed 248 and 35 unique HLA-I and HLA-II peptides, respectively, that were derived from 41 species of bacteria. The authors identified recurrent bacterial peptides in tumours from different patients, as well as in different tumours from the same patient.

Nejman, D. *et al.* The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science* 368, 973–980 (2020).

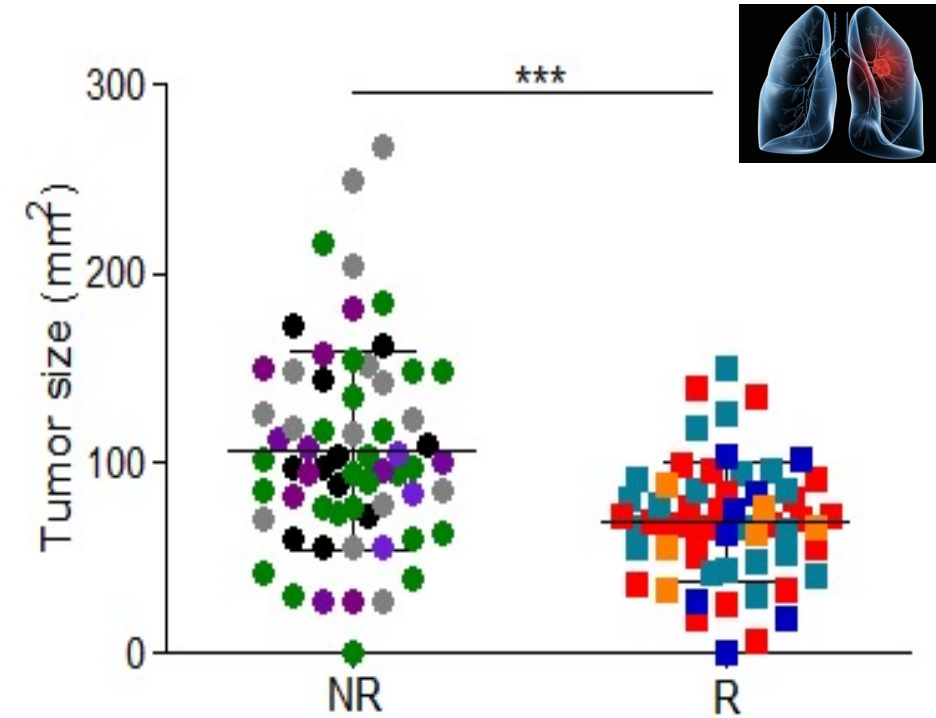
Causality links between GOMS and resistance to ICB: avatar mice (gut humanized)

Demonstrated cause-effect relationship:
The **avatar model**



Routy et al. Nat Rev Clin Oncol. 2018 Jun;15(6):382-396.

Anti-PD1 Ab-treated



Non responders : A, B, E, F, NSCLC pt (RECIST criteria at 3 months)
Responders : C, D, H, I, NSCLC pt (RECIST criteria at 3 months)

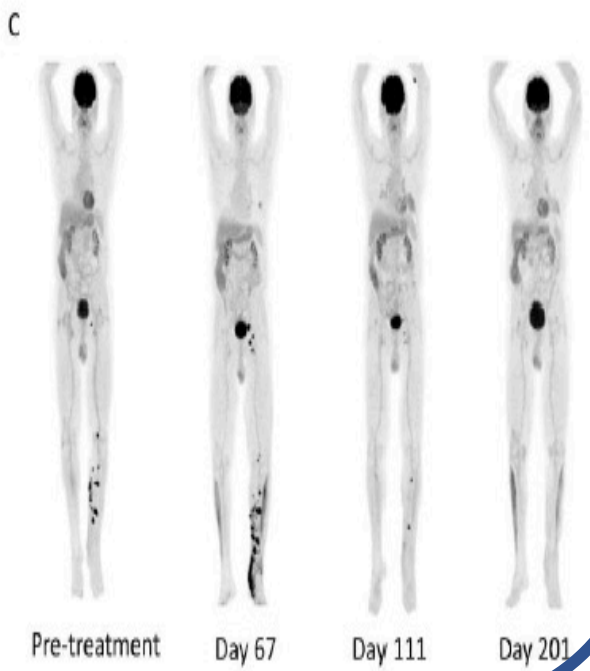
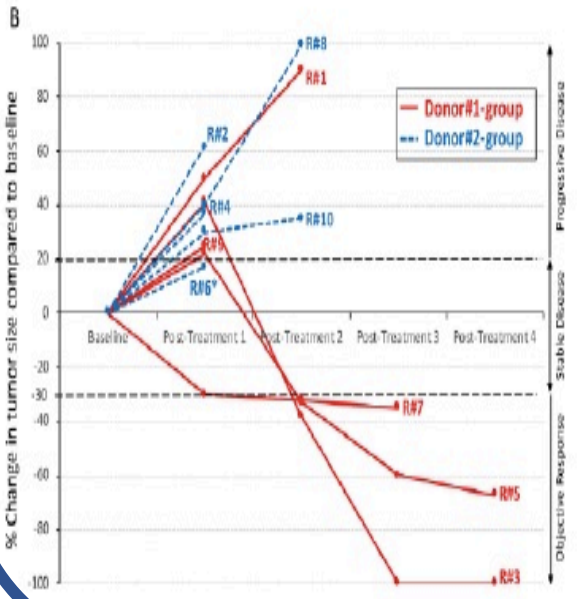
Routy et al; Science, Oct 27, 2017.

Proof of concept of the efficacy of the microbiota-centered therapeutic intervention: FMT from R into NR melanoma patients.

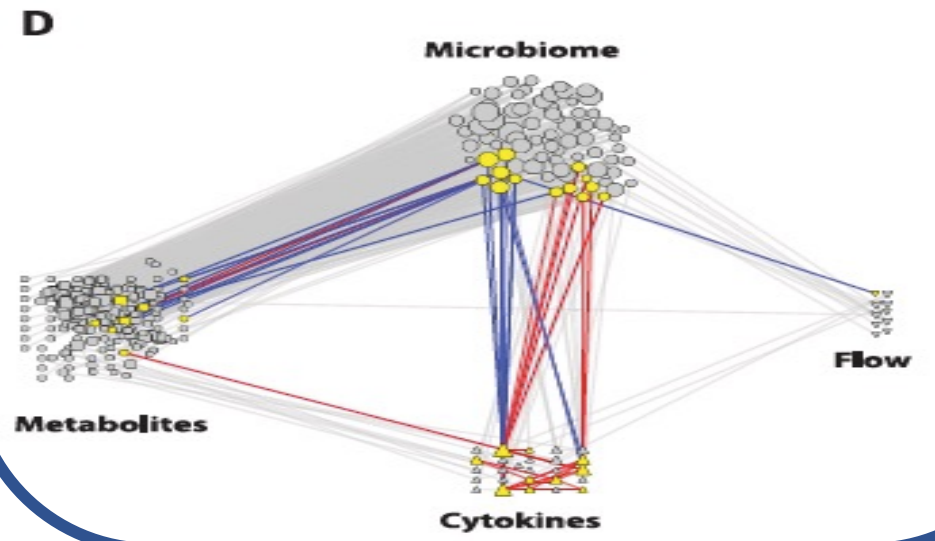
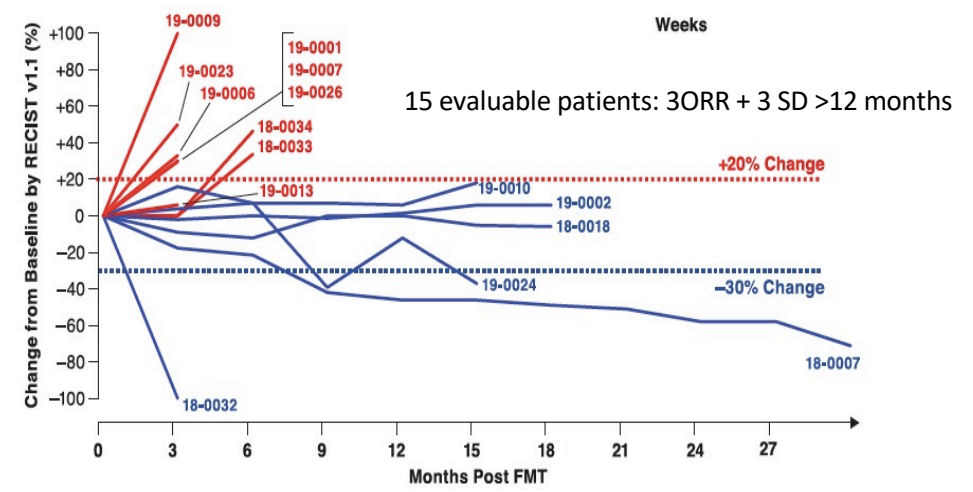
■ *Baruch et al. Science Dec. 2020*



- ✓ 10 patients with α PD-1-refractory metastatic melanoma
- ✓ FMT donors = α PD-1-treated MM patients with CR
- ✓ 2PR/1 CR
- ✓ Favoral changes in immune cell infiltrates

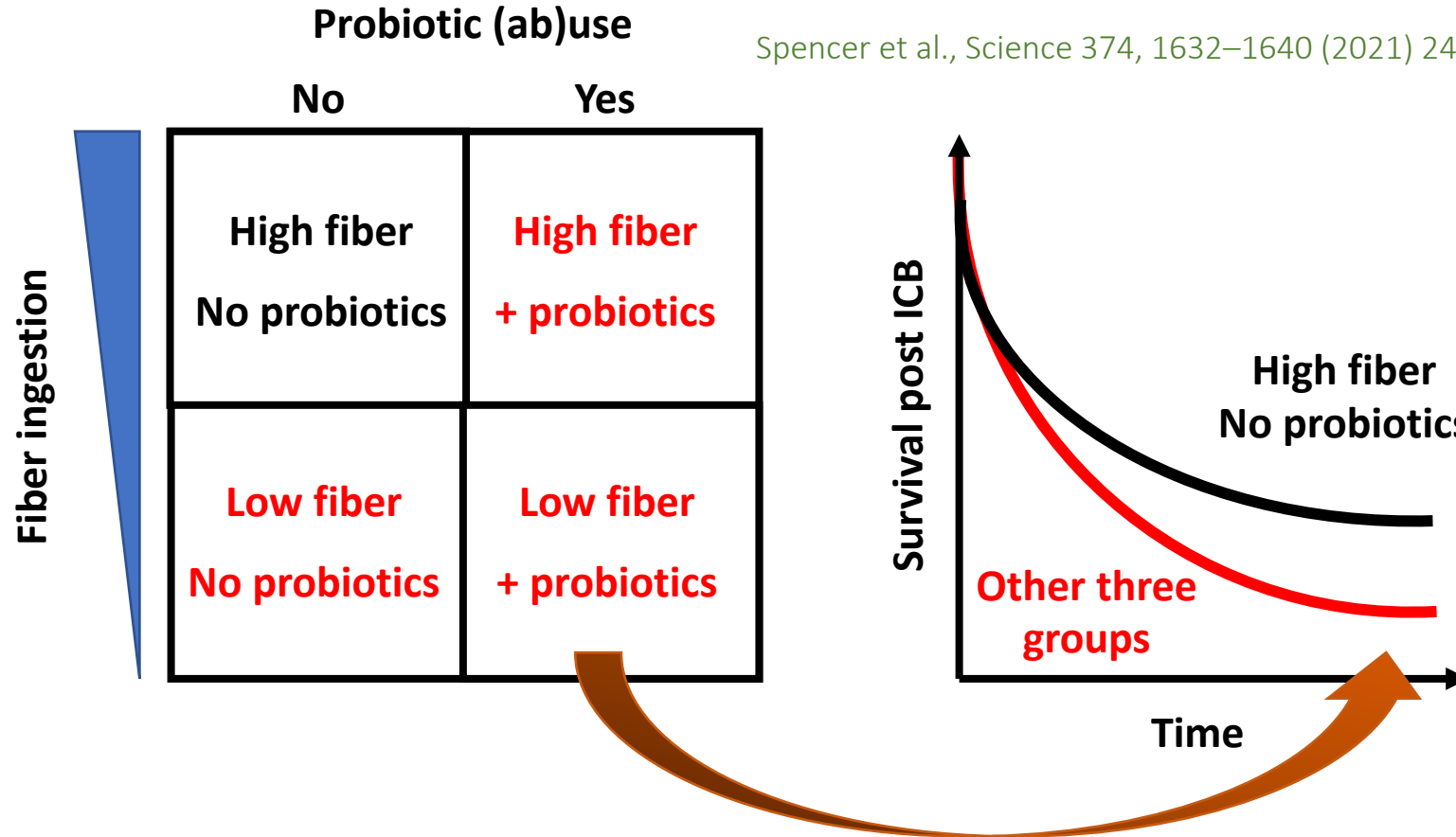


Davar and Zarour, Science Feb 2021



DIET INTERVENTIONS (FIBERS AND PROBIOTICS) INFLUENCE ICB OUTCOME IN MELANOMA

Spencer et al., Science 374, 1632–1640 (2021) 24 December 2021



**Excessive *Bifidobacterium longum* or *Lactobacillus rhamnosus* GG
→ Resistance to ICB**

**Underrepresentation of *Ruminococcaceae* and *Faecalibacterium*
→ Reduced immunostimulation by ICB**



Microbiota against cancer
International research program

Breast cancer gut microbiota

March 18, 2022

Laurence ZITVOGEL, Coordinator

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement N° 825410



Open access Protocol



Check for updates

UNICANCER: French prospective cohort study of treatment-related chronic toxicity in women with localised breast cancer (CANTO)

Ines Vaz-Luis,¹ Paul Cottu,² Christel Mesleard,³ Anne Laure Martin,⁴ Agnes Dumas,⁵ Sarah Dauchy,⁶ Olivier Tredan,⁷ Christelle Levy,⁸ Johan Adnet,⁹ Marina Rousseau Tsangaris,¹⁰ Fabrice Andre,¹ Patrick Arveux⁹



- Institut Gustave Roussy - Villejuif,
- Centre George Francois Leclerc - Dijon .
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- Institut Curie Site - Saint Cloud,
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- Centre Francois Baclesse - Caen,
- Institut Jean Godinot - Reims,
- Institut Bergonié - Bordeaux,
- Institut de Cancérologie de l'Ouest - Angers,
- Institut de Cancérologie de l'Ouest - Nantes,
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- Centre Jean Perrin - Clermont Ferrand,
- Institut Paoli Calmettes - Marseille,
- Centre Eugène Marquis - Rennes,
- Centre Antoine Lacassagne - Nice,
- Hôpital St Louis - Paris,
- Centre Paul Strauss - Strasbourg,
- IUCT O - Toulouse,
- IRCM - Montpellier,
- Institut Sainte Catherine - Avignon,
- CH Blois,
- CHR Orléans,
- Hôpital La Pitié Salpêtrière - Paris,
- Clinique du Parc Dijon

Clinical, pathologic characteristics, treatment details	n=83
Median age (range)	52 (35-75)
Body mass index (BMI), median (range)	20,9 (15,6–45,5)
Histologic grade	
1	6 (7%)
2	23 (28%)
3	26 (31%)
Missing	29 (34%)
Tumor size (p T)	
pT1	29 (35%)
pT2-T3	25 (30%)
Missing	29 (35%)
Node infiltration (pN)	
pN0	31 (37%)
pN+	24 (29%)
Missing	28 (34%)
AJCC Stage	
I	23 (27%)
II	23 (27%)
III	9 (11%)
Missing	28 (35%)
Molecular subtypes	
RH+ HER2-	35 (42%)
HER2+	21 (25%)
Triple negative	13 (16%)
Missing	14 (17%)
(Neo)adjuvant CT type	
Anthracycline based	29 (35%)
Taxane based	36 (43%)
Missing	18 (21%)
HER2 directed therapy	
Yes	21 (25%)
No	48 (29%)
Missing	14 (17%)
Hormonal therapy	
Yes	44 (53%)
No	22 (27%)
Missing	16 (19%)



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QUESTIONS

QUESTIONS TO BE ADDRESSED

- **Primary endpoint: Metagenomics (MG) profiling of CANTO pts**
- **Correlations between stool MG and prognosis of BC**
- **Effects of chemotherapy on MG profiling**
- **Impact of MG profiling on BC/Chemotherapy side effects**
- **Cause-effect relationship tested in preclinical BC tumor models**
- **Dissemination and Publication**

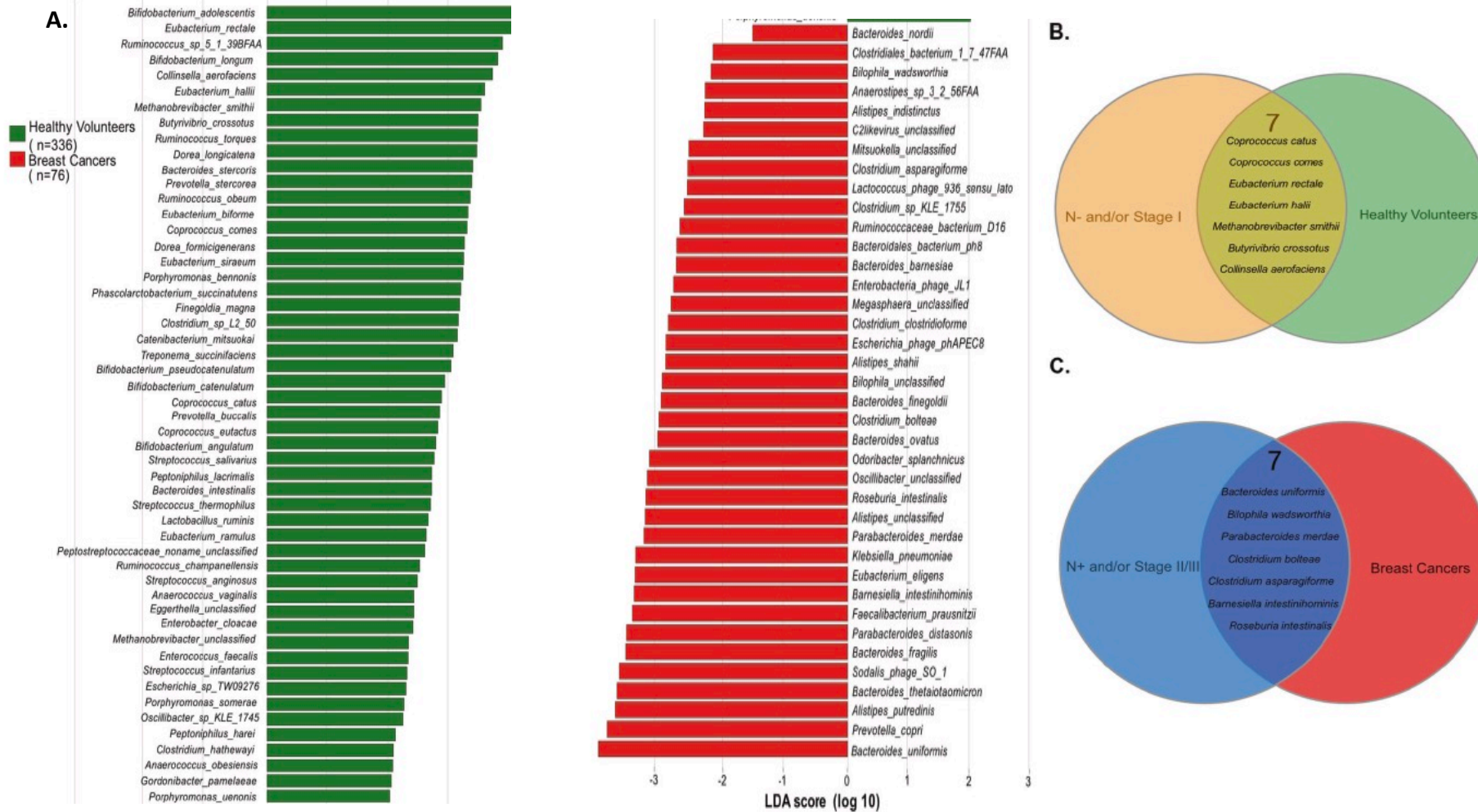


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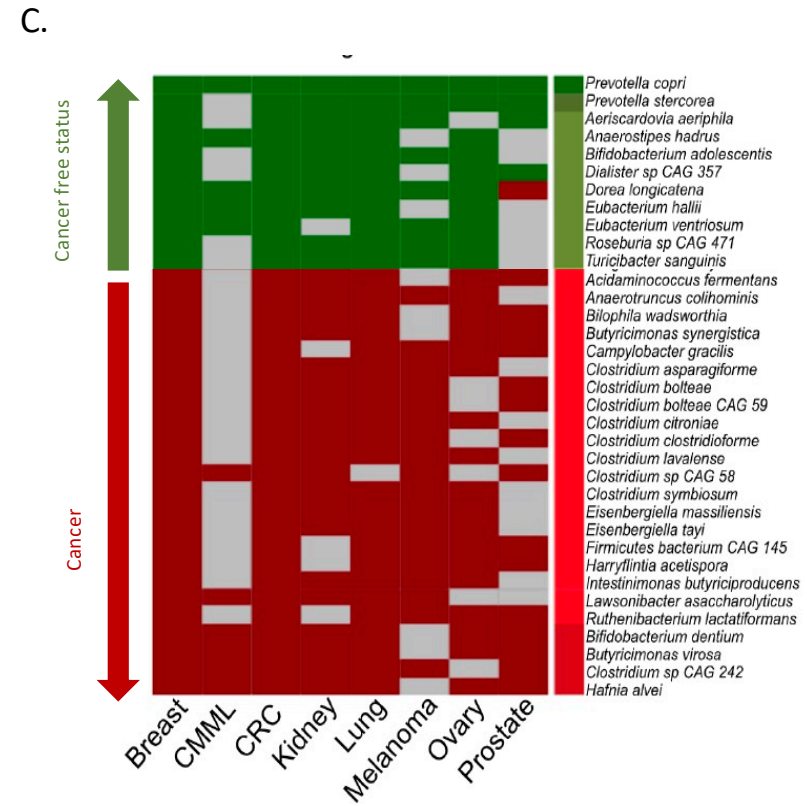
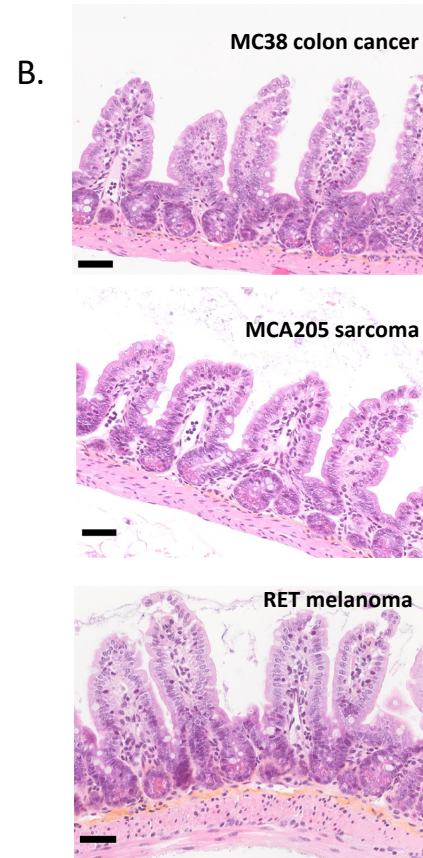
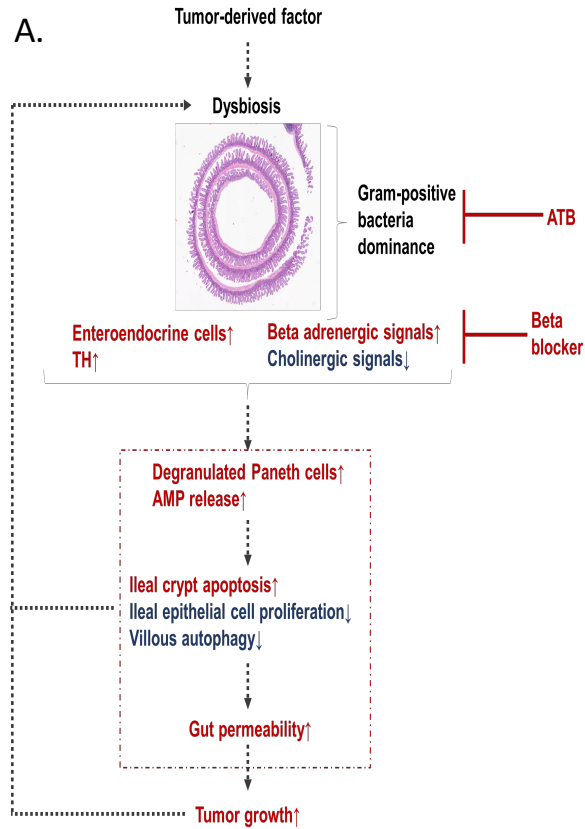


DESCRIPTION OF BC-RELATED DYSBIOSIS

FECAL TAXONOMIC COMPOSITION DIFFERS BETWEEN HV VS EARLY BC.



Cancer can induce an ileopathy and a protacted intestinal dysbiosis participating to cancer progression.



Extracted from Yonekura et al. Cancer Discov. 2021 Dec 20;candisc.0999.2021.
doi: 10.1158/2159-8290.CD-21-0999. Online ahead of print. PMID: 34930787
To be redone changing colors and order of cancer in X axis.

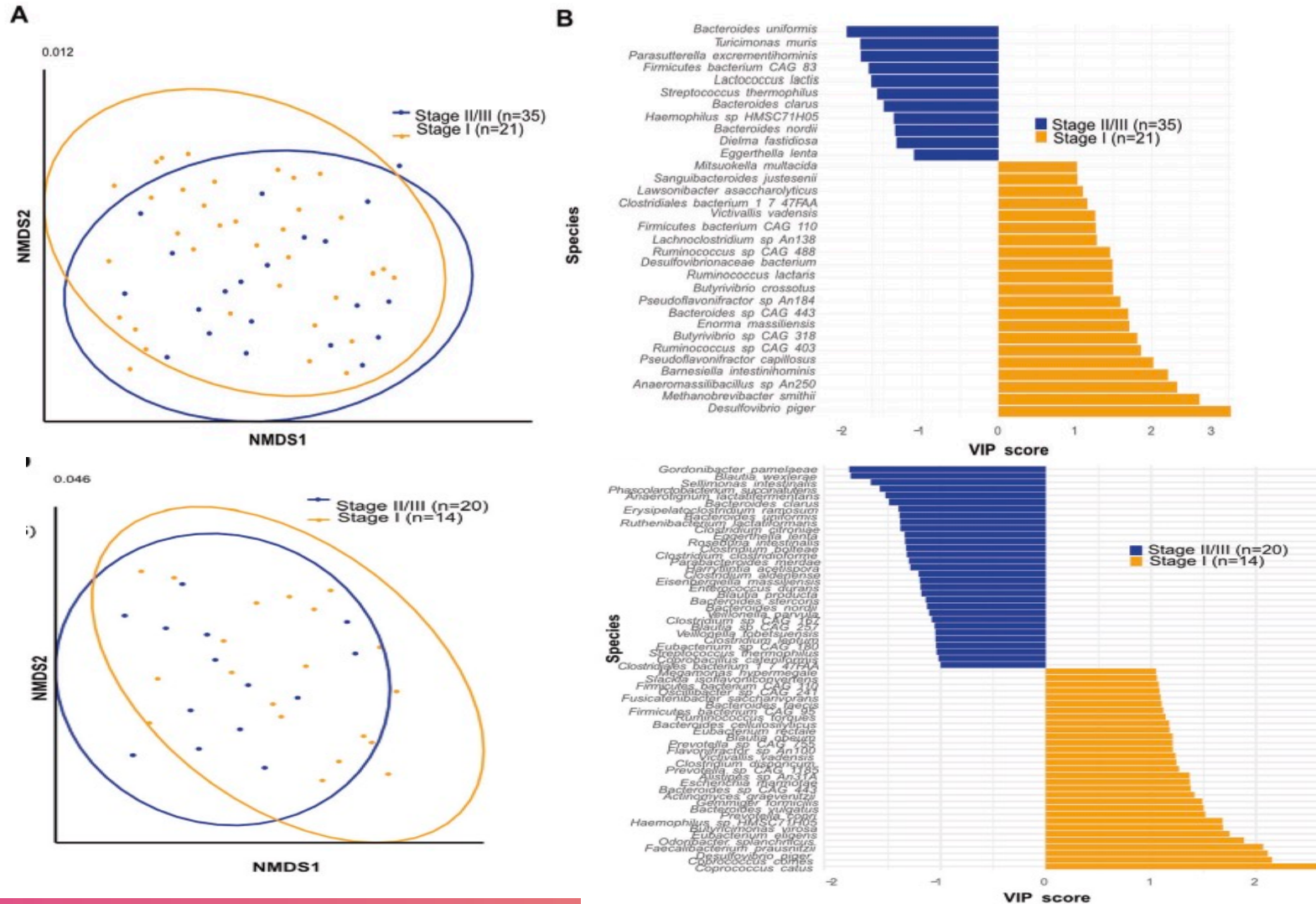


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IMPACT OF DYSBIOSIS ON BC PROGNOSIS

FECAL TAXONOMIC COMPOSITION PRE- AND POST CHEMOTHERAPY AND EARLY BC STAGING



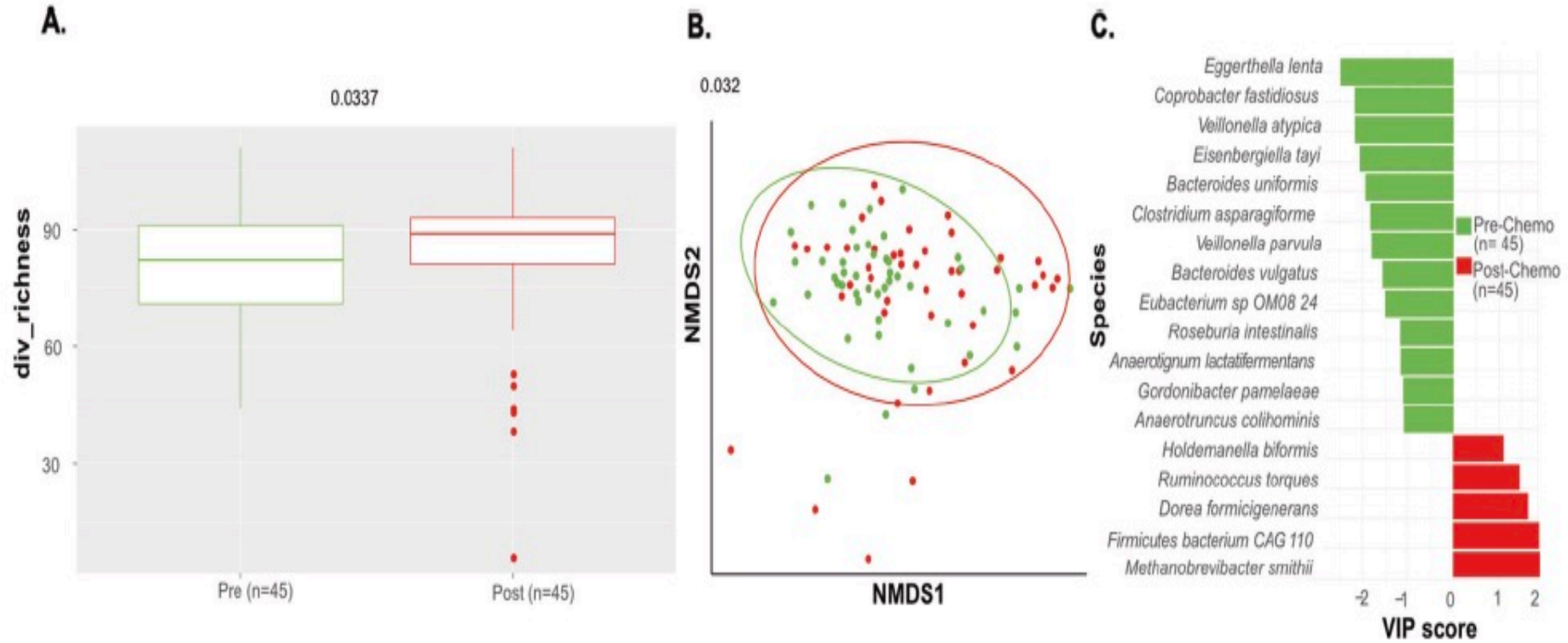


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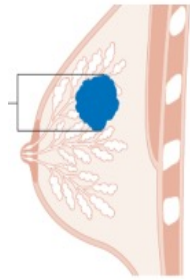


EFFECTS OF CHEMOTHERAPY ON MG COMPOSITION

FECAL TAXONOMIC COMPOSITION IS CHANGING AFTER CHEMOTHERAPY: ELIMINATION OF HARMFUL BACTERIA

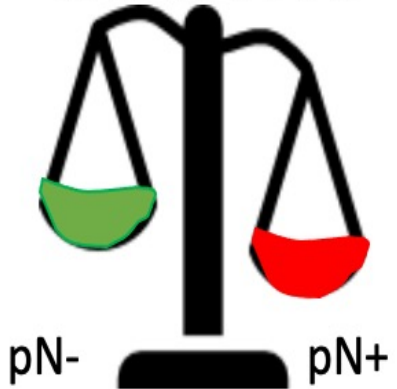


NEOADJUVANT OR ADJUVANT CHEMOTHERAPY RESTORE GUT INTESTINAL MICROBIOTA TOWARDS EUBIOSIS



A.

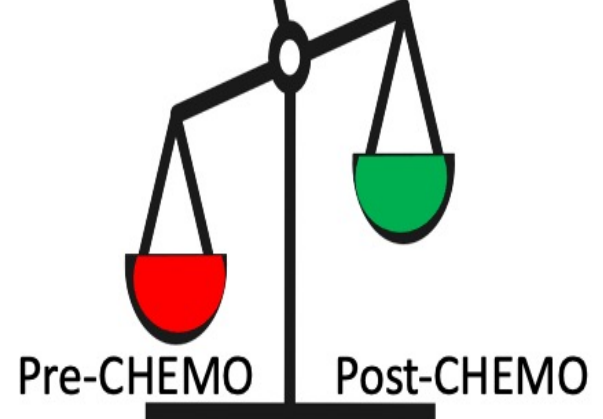
NEOADJUVANT



*Fusicatenibacter
saccharivorans
Dorea formicigenerans*

*Enterocloster gen.nov.
(E. bolteae, E. citroniae, E. clostridioforme
E. asparagiforme, E. aldenense), C. symbosium
Eisenbergiella massiliensis*

ADJUVANT



*Eggerthella lenta
Veillonella spp.
Eisenbergiella tayi
B. uniformis
E. asparagiforme*

*Dorea formicigenerans
Methanobrevibacter smithii
Holdemania biformis
Ruminococcus torques*

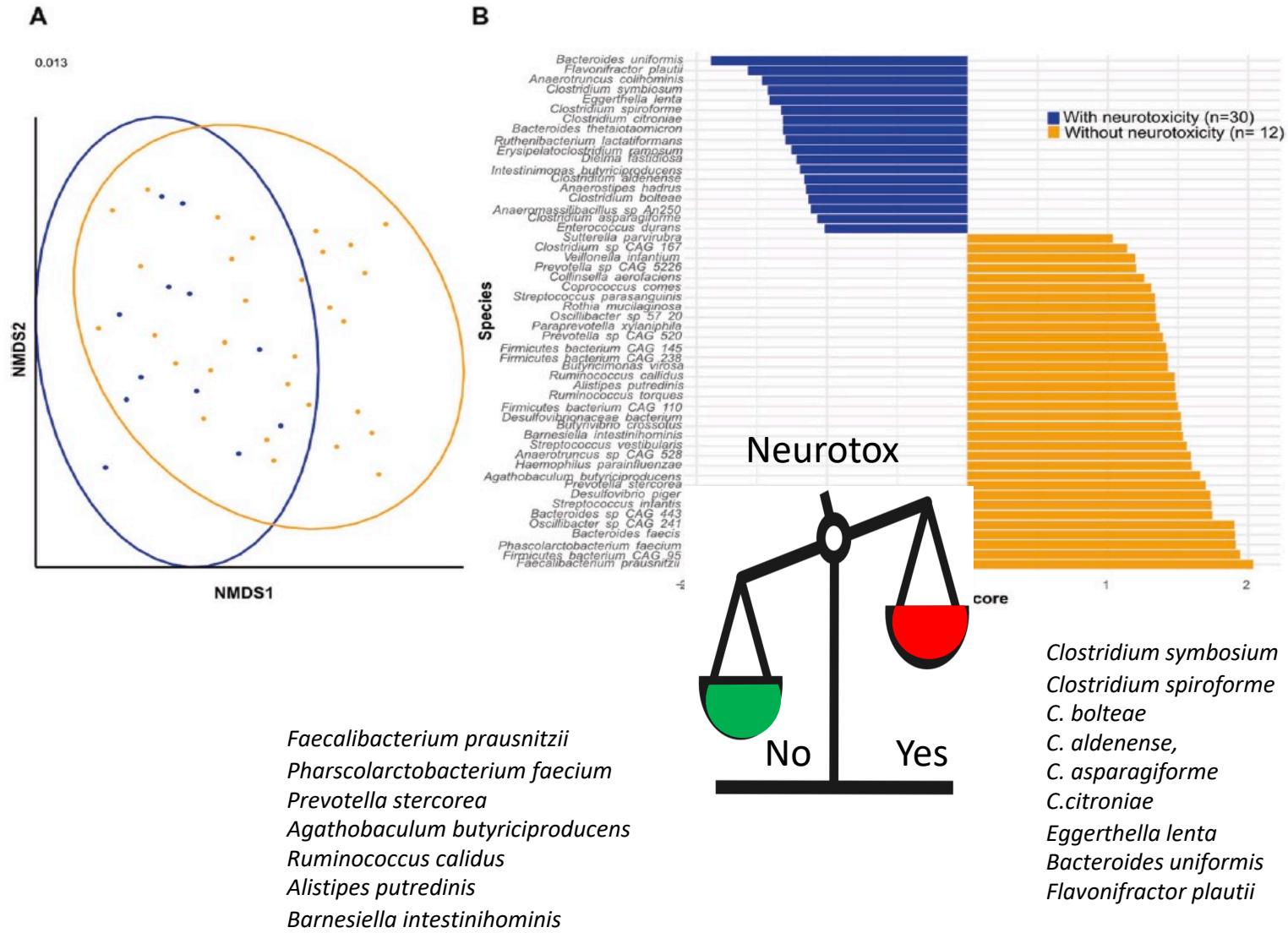


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IMPACT OF MG COMPOSITION ON BC TREATMENT SIDE EFFECTS

DYSBIOSIS IS ASSOCIATED WITH NEUROTOXICITY

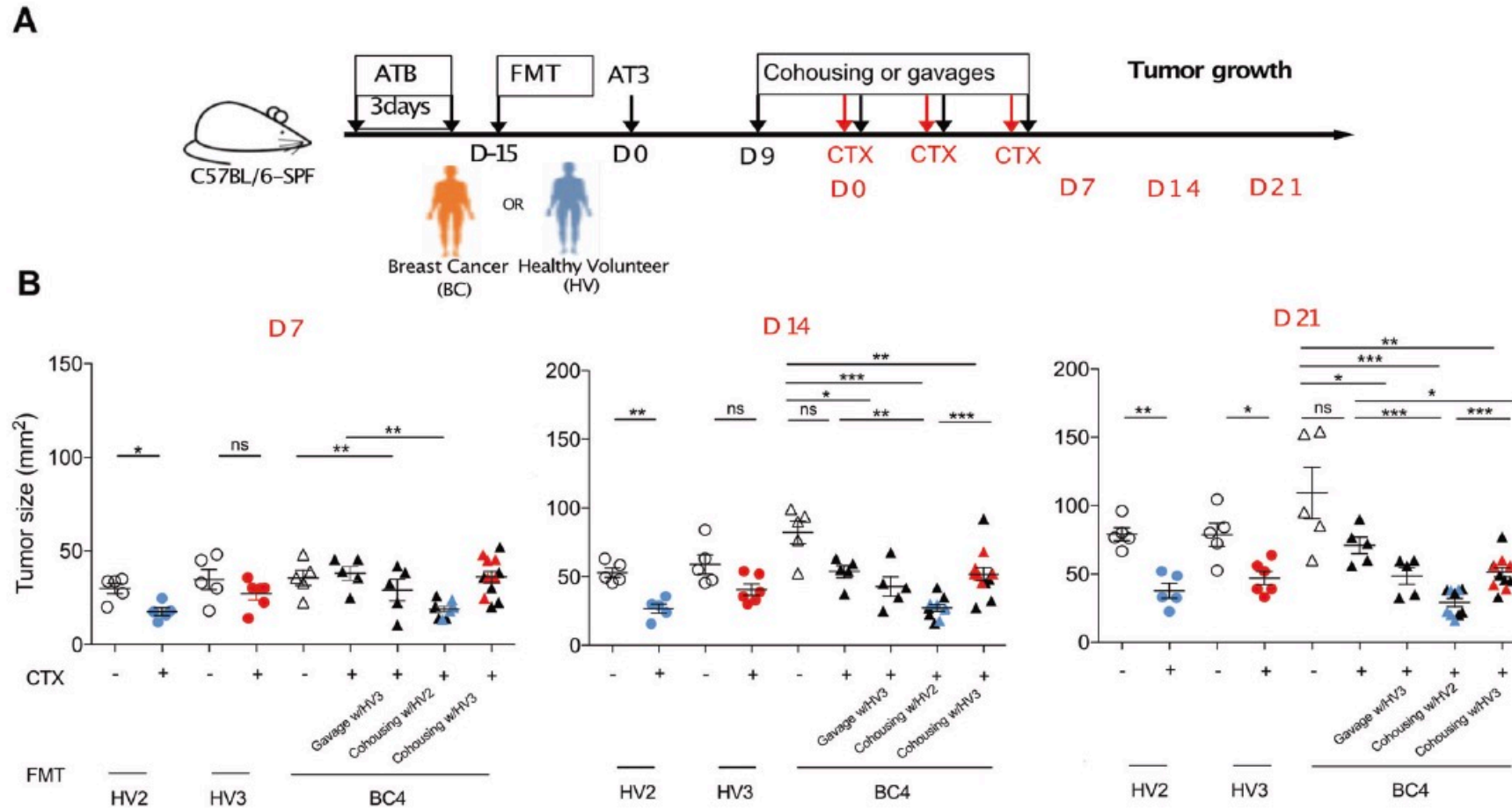




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ANIMAL MODELS: CAUSE-EFFECT RELATIONSHIPS BETWEEN DYSBIOSIS AND RESPONSE TO CHEMOTHERAPY

FMT FROM BC WOMEN INTO AVATAR MICE INFLUENCE THE EFFICACY OF CYCLOPHOSPHAMIDE





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DISSEMINATION

PUBLICATION

Cell Death & Differentiation
<https://doi.org/10.1038/s41418-021-00784-1>



ARTICLE

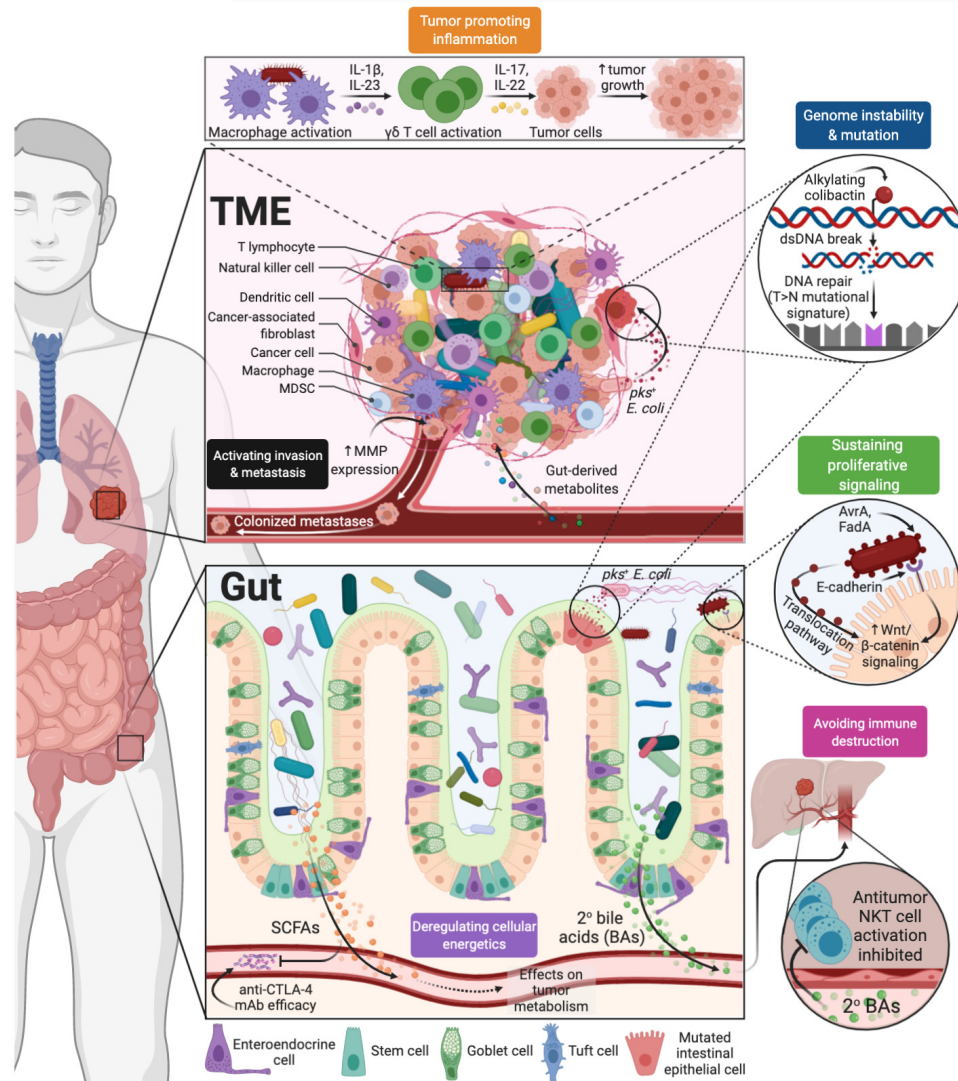


Intestinal microbiota influences clinical outcome and side effects of early breast cancer treatment

Safae Terrisse^{1,2,3,4} · Lisa Derosa^{1,2,5} · Valerio Iebba^{1,2} · François Ghiringhelli^{6,7,8,9} · Ines Vaz-Luis^{10,11} · Guido Kroemer^{12,13,14,15} · Marine Fidelle^{1,2,3,5} · Stergios Christodoulidis^{16,17} · Nicola Segata^{18,19} · Andrew Maltez Thomas¹⁹ · Anne-Laure Martin²⁰ · Aude Sirven²⁰ · Sibille Everhard²⁰ · Fanny Aprahamian¹³ · Nitharsshini Nirmalathasan¹³ · Romy Aarnoutse^{21,22,23} · Marjolein Smidt^{21,22,23} · Janine Ziemons^{21,22,23} · Carlos Caldas²⁴ · Sibylle Loibl^{25,26} · Carsten Denkert²⁷ · Sylvere Durand¹³ · Claudia Iglesias¹³ · Filippo Pietrantonio²⁸ · Bertrand Routy²⁹ · Fabrice André^{1,10,11,16} · Edoardo Pasoli^{30,31} · Suzette Delaloge^{1,11} · Laurence Zitvogel^{1,2,3,5}

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Microbes are involved in most “cancer hallmarks”

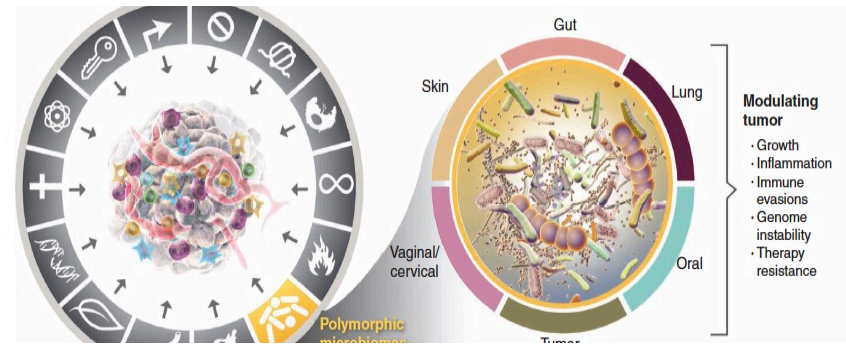


REVIEW SUMMARY

CANCER MICROBIOME

The microbiome and human cancer

Gregory D. Sepich-Poore, Laurence Zitvogel, Ravid Straussman, Jeff Hasty, Jennifer A. Wargo, Rob Knight*



The Hallmarks of Cancer²

¹Graphic on left: Sepich-Poore *et al.* *Science*. March 2021

²Hanahan D (2021). *Cancer Discovery*

• PUBLIC AWARENESS

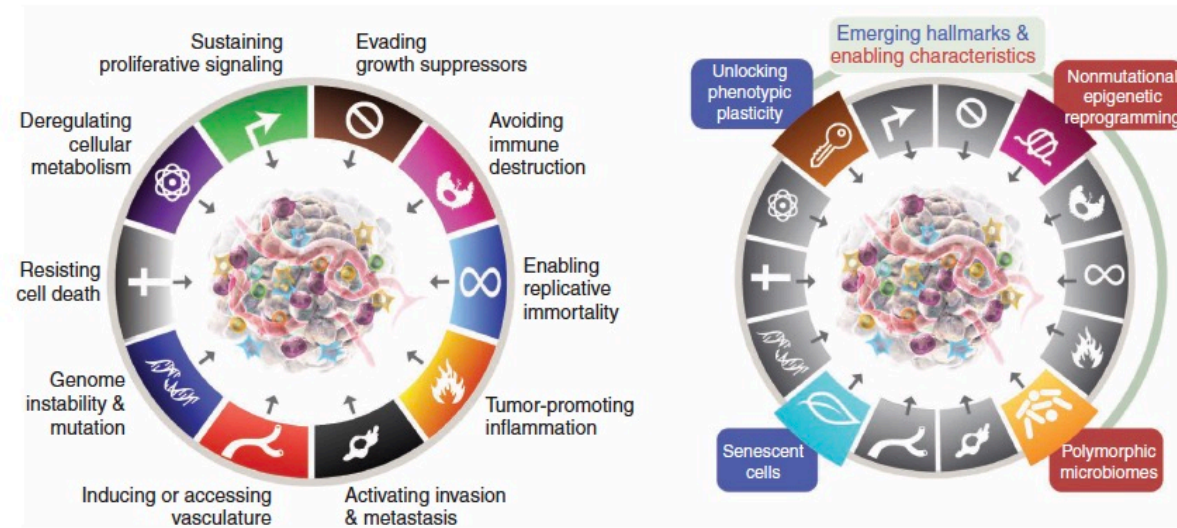
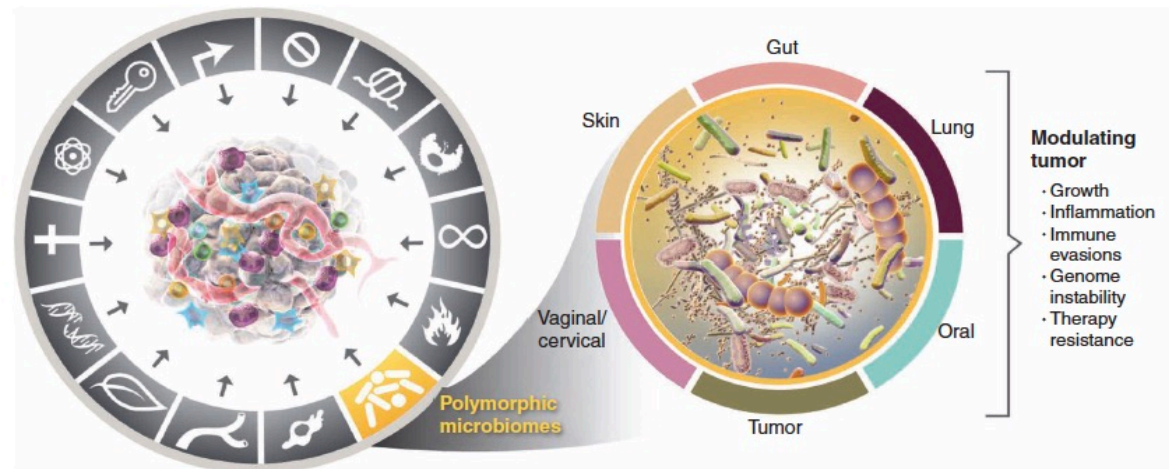


Figure 1. In essence: the Hallmarks of Cancer, circa 2022. Left, the Hallmarks of Cancer currently embody eight hallmark capabilities and two enabling characteristics. In addition to the six acquired capabilities—Hallmarks of Cancer—proposed in 2000 (1), the two provisional “emerging hallmarks” introduced in 2011 (2)—cellular energetics (now described more broadly as “reprogramming cellular metabolism”) and “avoiding immune destruction”—have been sufficiently validated to be considered part of the core set. Given the growing appreciation that tumors can become sufficiently vascularized either by switching on angiogenesis or by co-opting normal tissue vessels (128), this hallmark is also more broadly defined as the capability to induce or otherwise access, principally by invasion and metastasis, vasculature that supports tumor growth. The 2011 sequel further incorporated “tumor-promoting



Hallmarks of Cancer: New Dimensions

Thanks!



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 François Goldwasser
 Antonin Levy
 Jacques le Treut
 Julien Mazières
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 Arnaud Scherpereel
 Gerard Zalcman

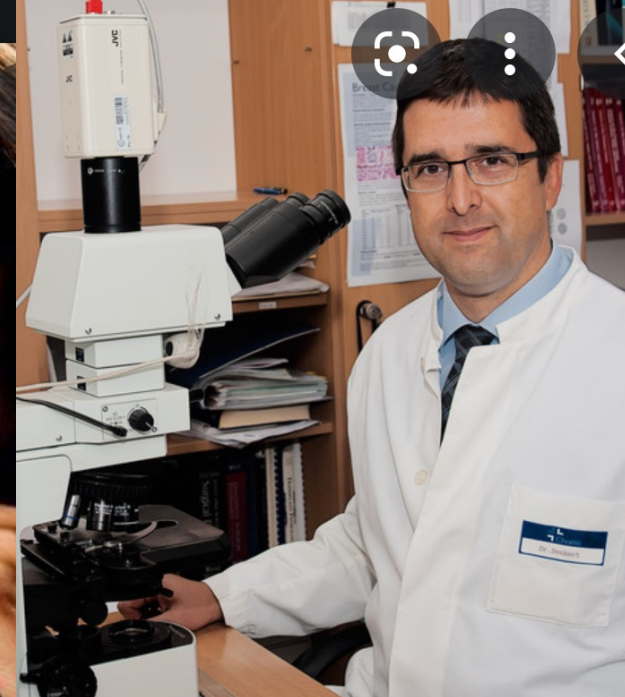
Clinic biome



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Institut national
de la santé et de la recherche médicale



Pr. Dr Sibylle LOIBL

Pr. Dr. Carsten DENKERT



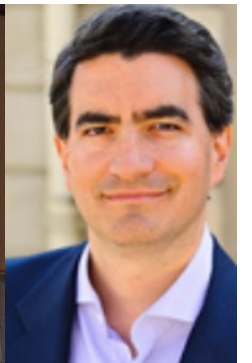
B. Besse



F. Goldwasser



G. Zalcman



JC Soria



L. Derosa



B. Routy



B. Routy



L. Derosa



C. Duong



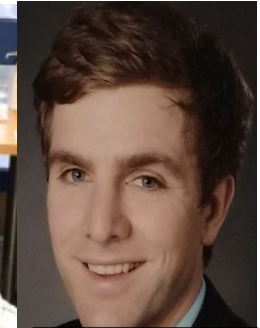
M. Tidjani



Sato Yonekura



M. Fidelle



C. Rauber



B. Besse

F. Goldwasser G. Zalcman JC Soria



D. Raoult



G. Kroemer

R. Daillère
M. Vétizou & P. Roberti



A. Fluckiger



B. Escudier L. Albigès

E. LeChâtelier J. Doré



Jean Eudes Fahrner



Fabrice André



Suzette DELALOGUE

Safae Terrisse
AG Goubet



G. Gorochov



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