17e Rencontre Patients de l'Association A.R.Tu.R.

Mercredi 3 avril 2024
À l'Institut Imagine

Marine FIDELLE

Lisa DEROSA
Bertrand ROUTY

Carolina ALVES COSTA SILVA
Toni CHOUIERI

Gut microbiota in the clinical management o[illegible] cancer?

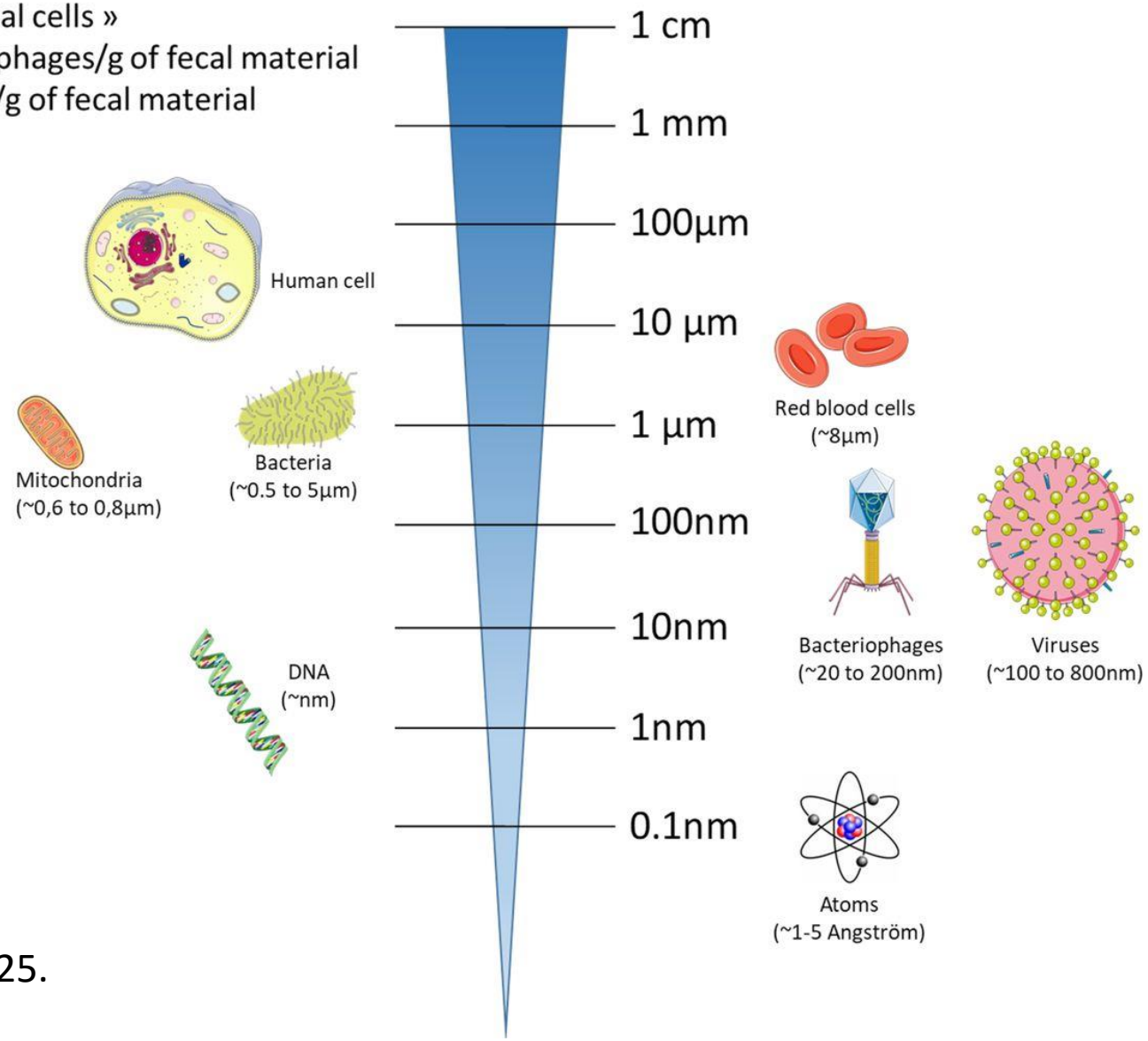
Prof. Laurence ZITVOGEL, Gustave Roussy, Villejuif-Grand Paris, FRANCE


I'M
NOT
DANGEROUS

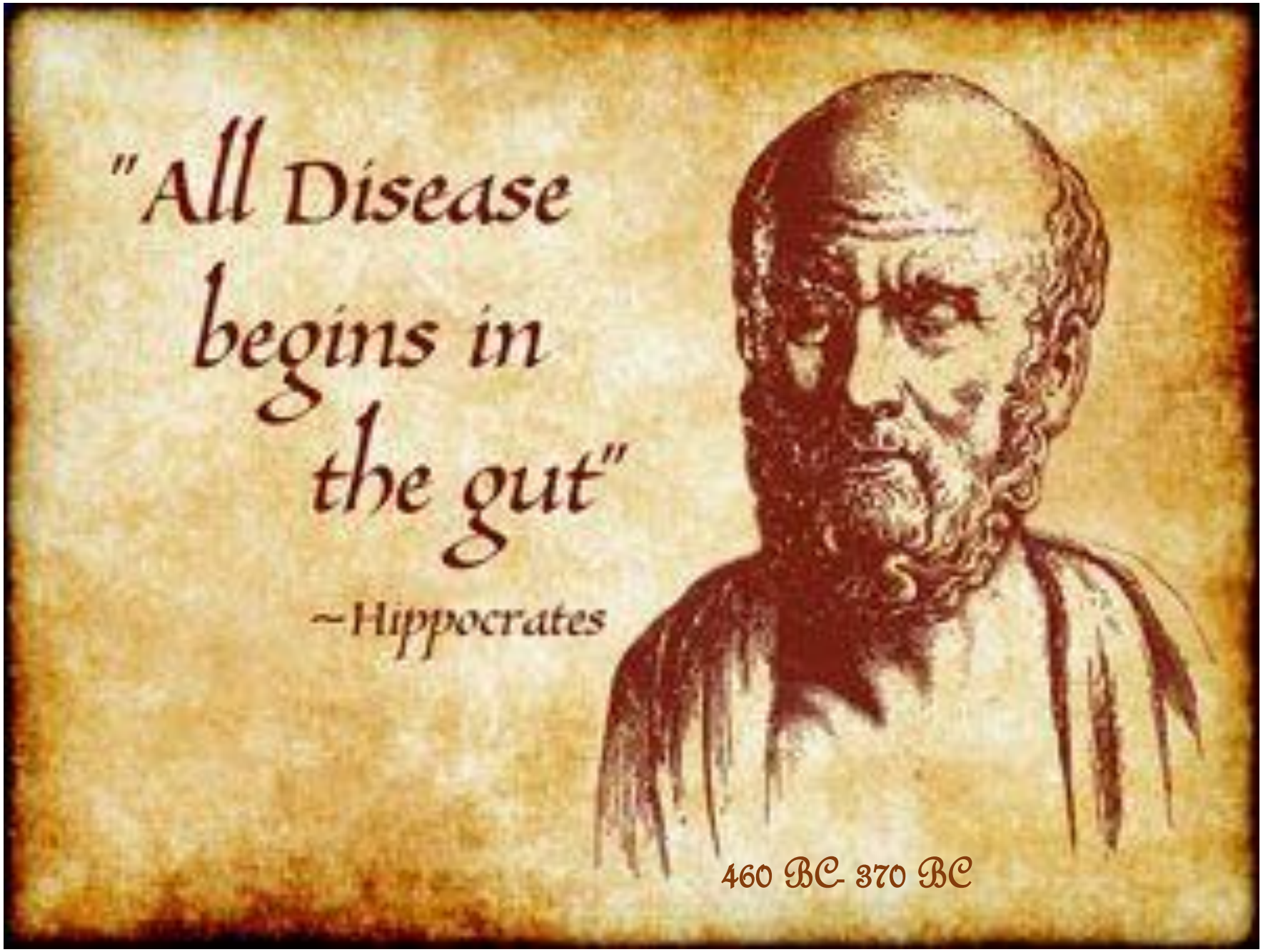
Numbers Matters Not the Size!

In the human body:

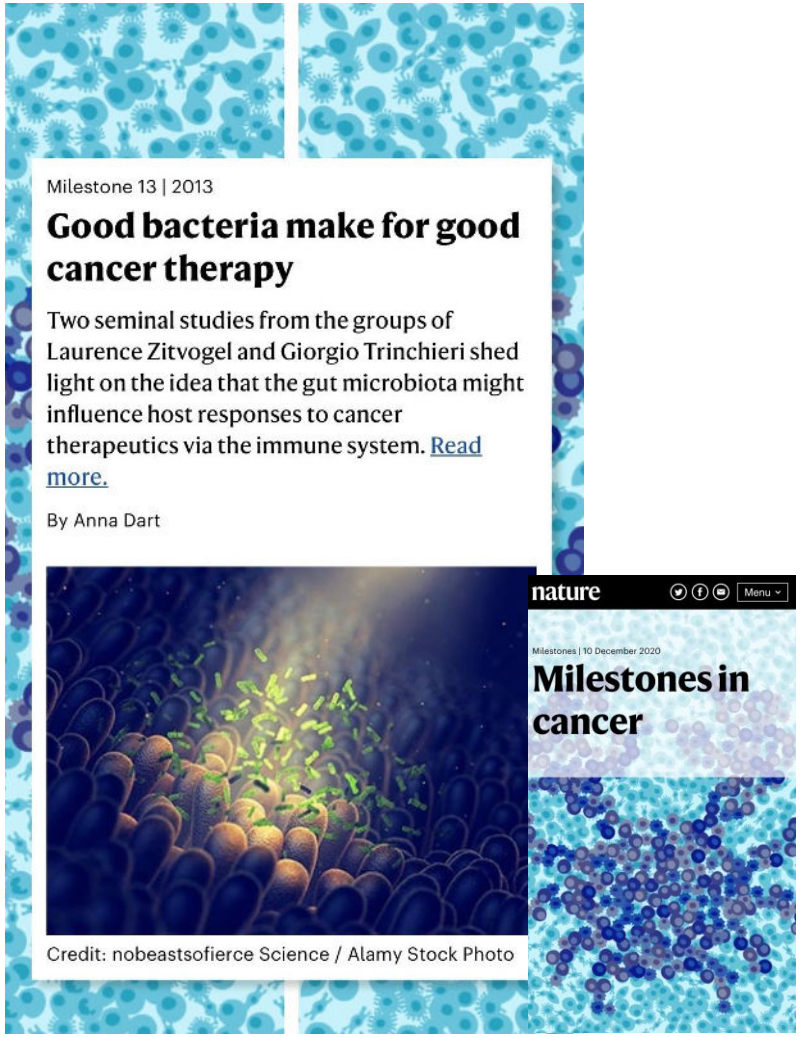
10^{13} « human cells »
10^{14} « microbial cells »
10^{12} bacteriophages/g of fecal material
10^{11} bacteria/g of fecal material

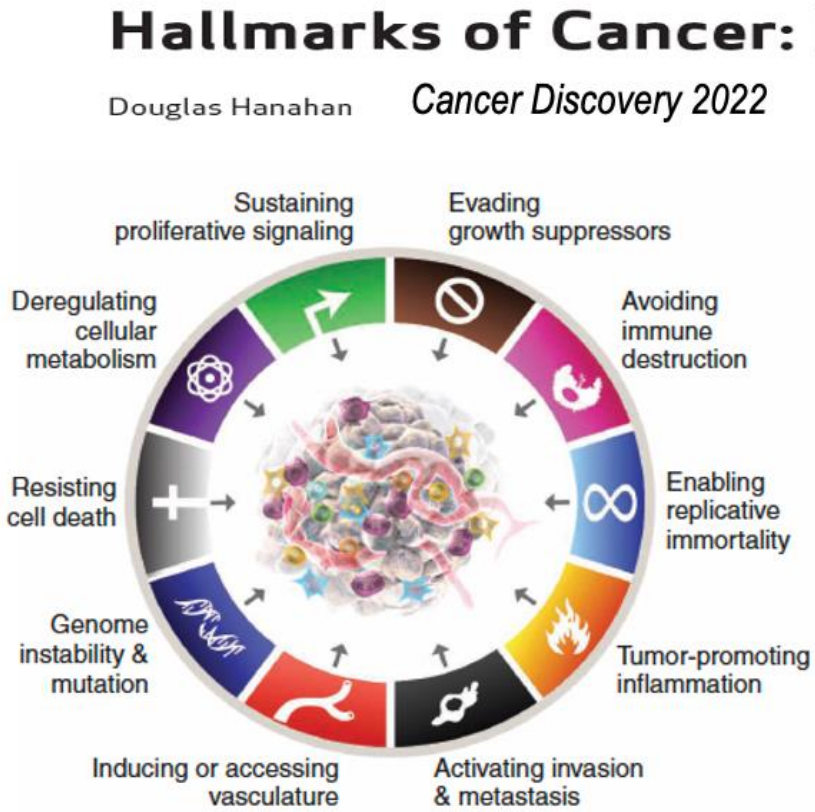


Cani PD. Gut 2018;67:1716–1725.


"All Disease begins in the gut"
~Hippocrates
460 BC- 370 BC

Creating a session on the MICROB is a major FIRST at ASCO 2023 !

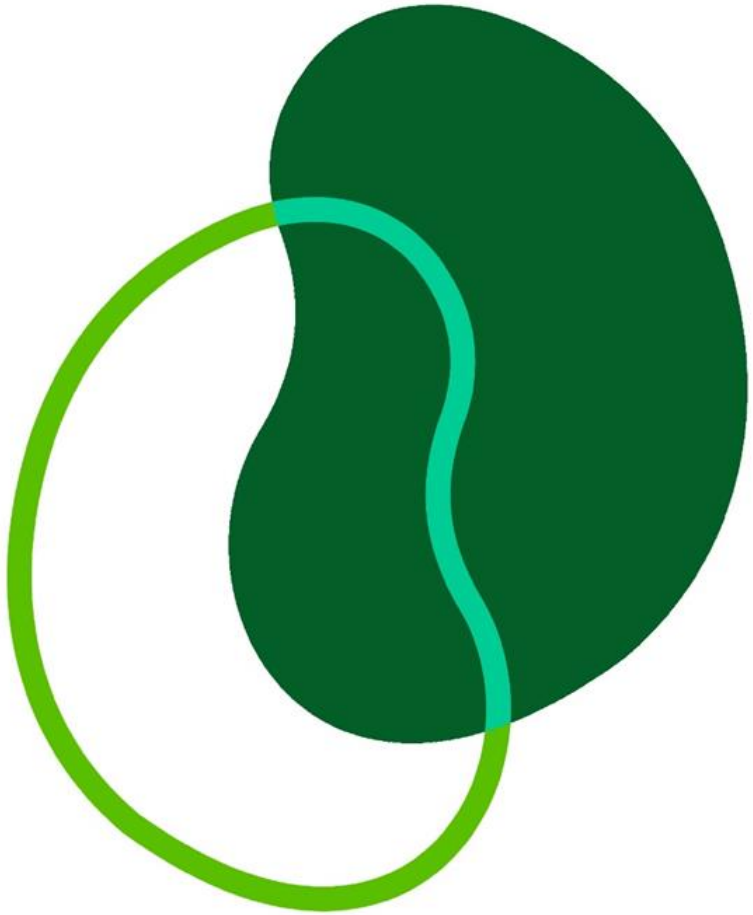




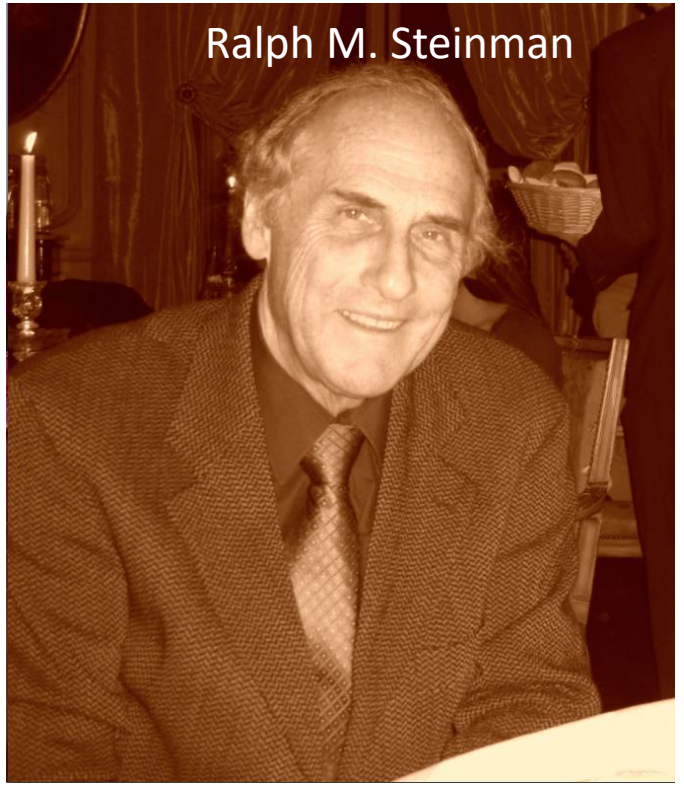
A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

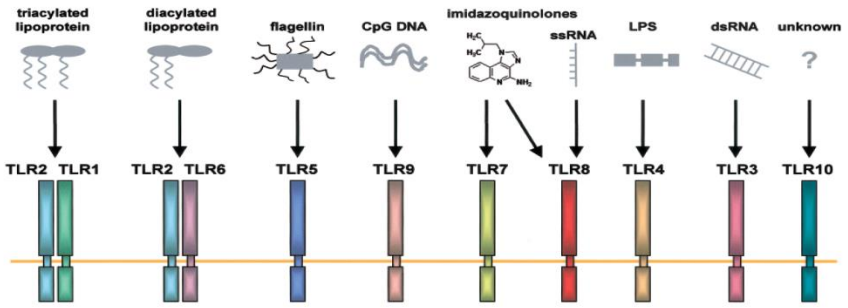
17e Rencontre Patients de l'Association A.R.Tu.R.

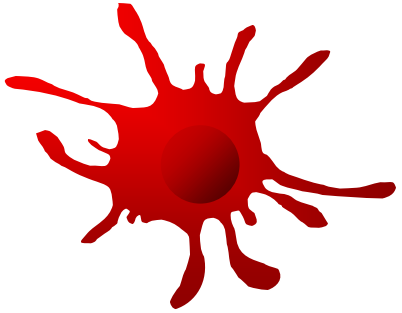
PART1: Immunotherapy: a revolution in oncology



Nobel Prize 2011: Innate Immunity

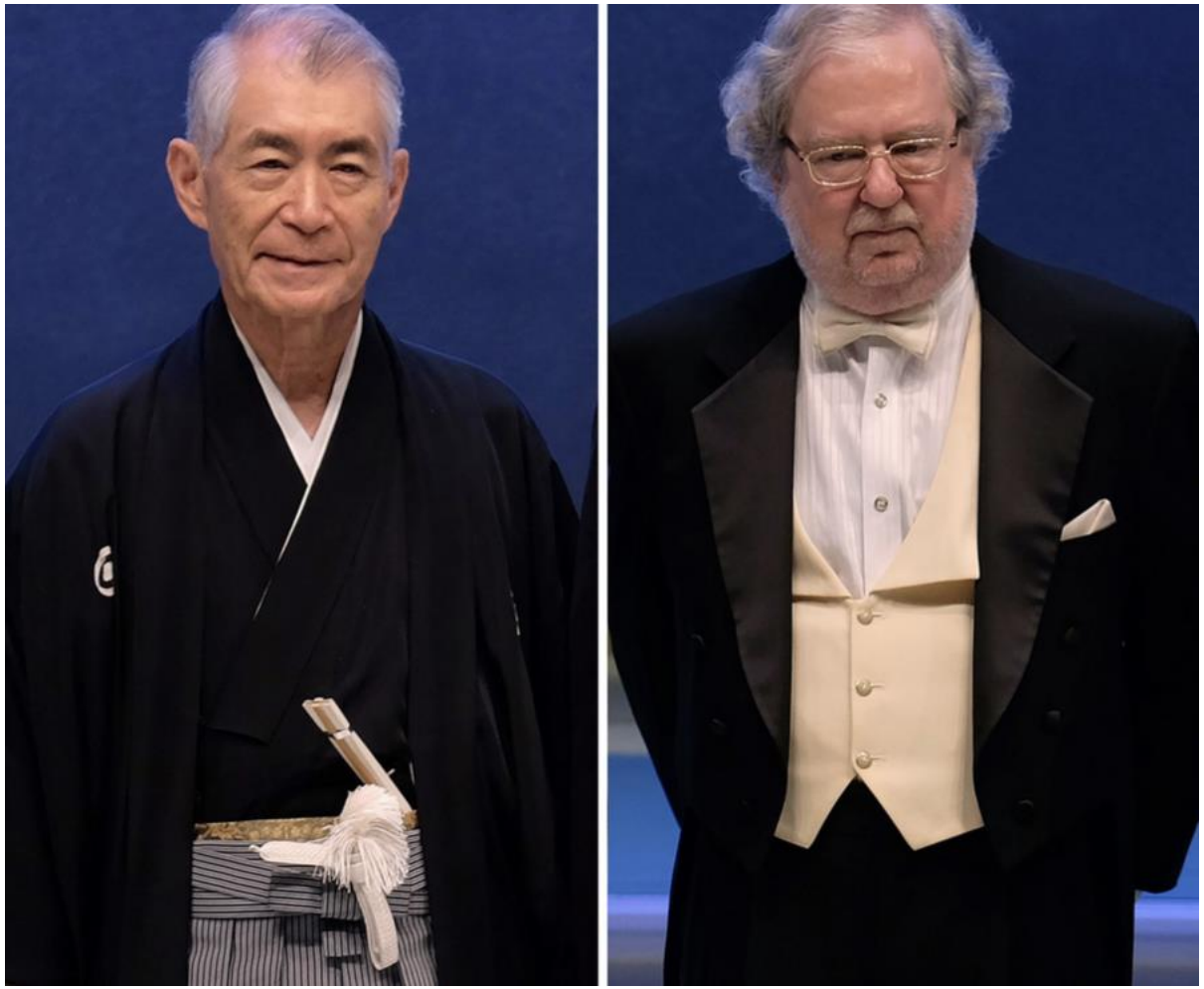




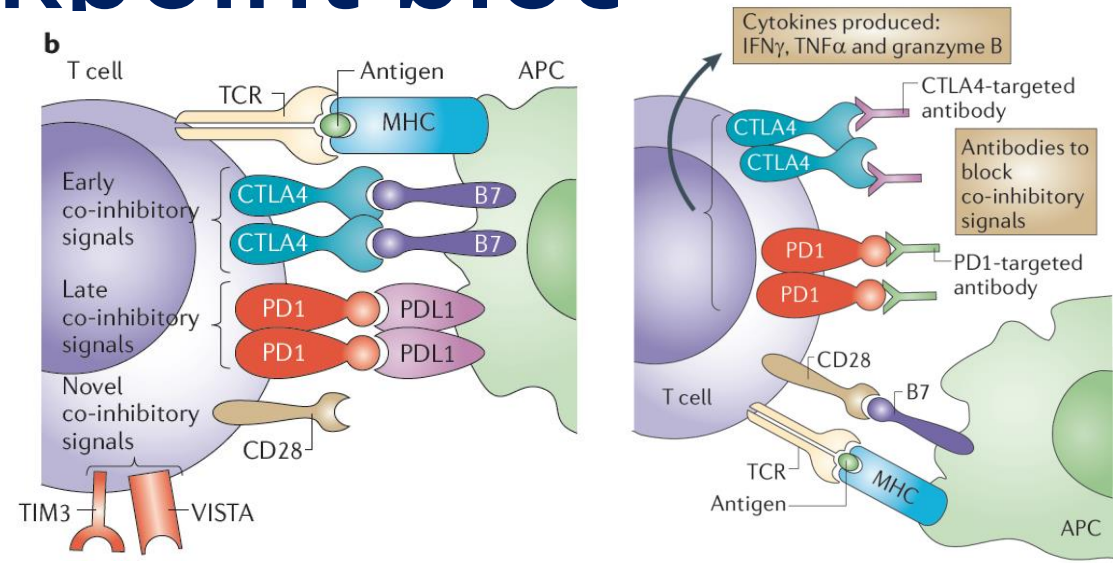


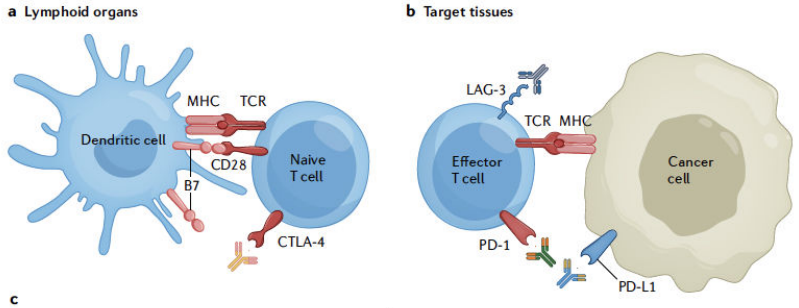
A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

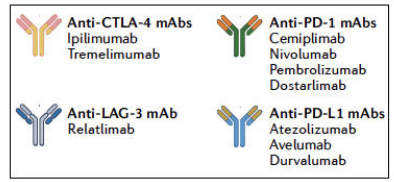
2018: Nobel Prize for the discovery of immune checkpoint blockade



Tasuku Honjo & James P. Allison





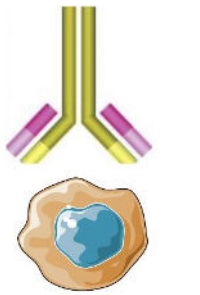


R.Tu.R.
on pour la Recherche
Tumeurs du Rein

EMA & FDA approvals for immune checkpoint inhibitors

ICB: immune checkpoint blockers (antiPD1, PDL-1, CTLA4, LAG3, etc...)

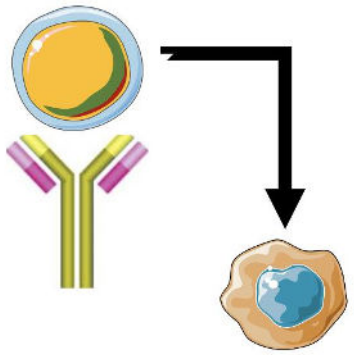
Historical Paradigm: Targeting Tumor Cells



Tumor Cell

New Paradigm: Targeting Immune Cells

Lymphocyte

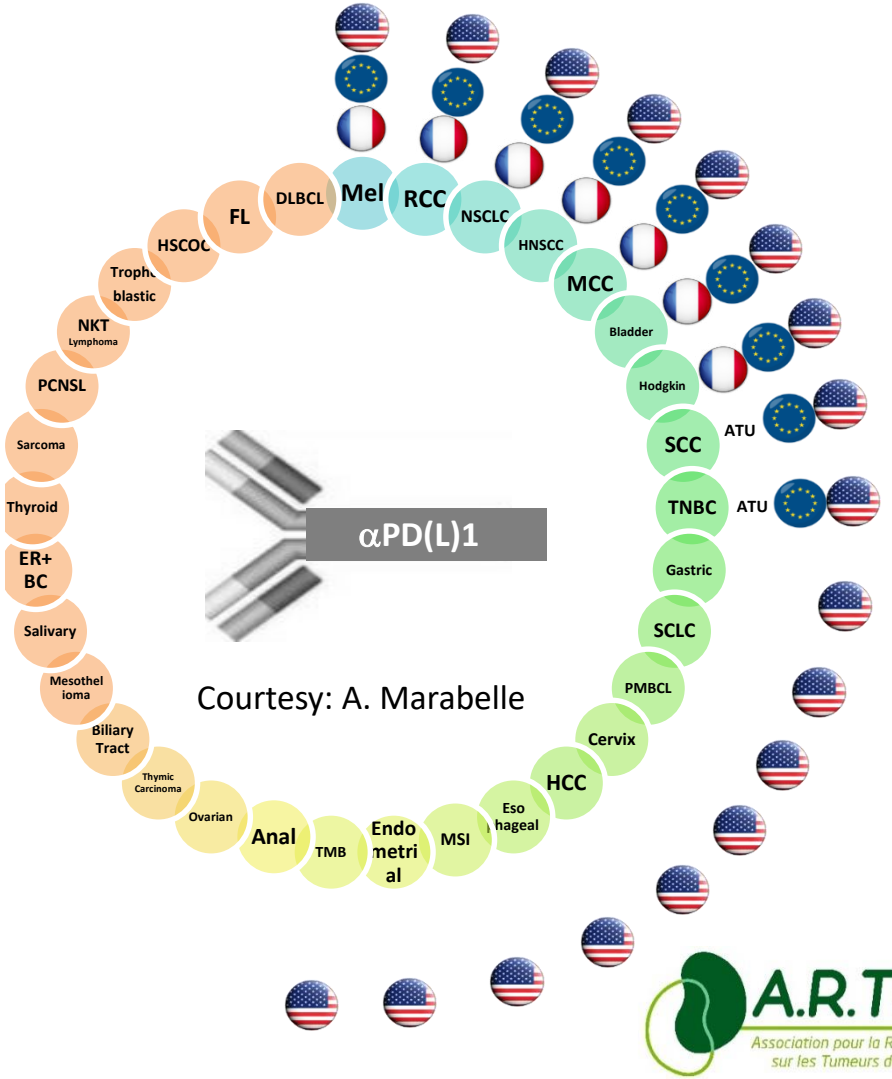


18 Tumor 21 ations approved in the USA
8 Tumor indications approved in Europe
r indications with reimbursement in France

TABLE 1 The approval status of commonly used ICI agents in clinical practice.

Targets	Drugs	Approved by	Indications
CTLA-4	Ipilimumab	FDA, EMA, HC, NMPA	Advanced MM, advanced CRC, NSCLC, HL
PD-1	Nivolumab	FDA, EMA, HC, MHLW, NMPA	HNSCC, NSCLC, GC, ESCC, CRC, HCC, RCC, HL, MM, skin cancer
	Pembrolizumab	FDA, EMA, HC, NMPA, NMPA	HNSCC, NSCLC, GC, ESCC, CRC, HCC, RCC, HL, MM, skin cancer, TNBC
	Cemiplimab	FDA, EMA, HC	skin cancer, NSCLC
	Toripalimab	NMPA, EMA	skin cancer, HNSCC, BRCA
	Sintilimab	NMPA, EMA, FDA	NSCLC, HCC, HL
	Camrelizumab	NMPA, FDA	NSCLC, HCC, HL, ESCC, HNSCC
	Tislelizumab	NMPA	NSCLC, HL, BRCA
	Penpulimab	NMPA	HCC, GC, NSCLC, NPC, HL
	Zimberelimab	NMPA	HL
	Serplulimab	NMPA	GC, CRC, NSCLC
	Pucotenlimab	NMPA	CRC, MM
	Dostarlimab	FDA, EMA, HC	UCEC
PD-L1	Durvalumab	FDA, EMA, HC, NMPA	NSCLC, SCLC, BRCA
	Atezolizumab	FDA, EMA, HC, NMPA	skin cancer, NSCLC, SCLC, BRCA, HCC, TNBC
	Envafolimab	NMPA	CRC
	Sugemalimab	NMPA	NSCLC
	Avelumab	FDA, EMA, HC	skin cancer, RCC, BRCA
LAG-3	Relatlimab	FDA, EMA	Metastatic MM

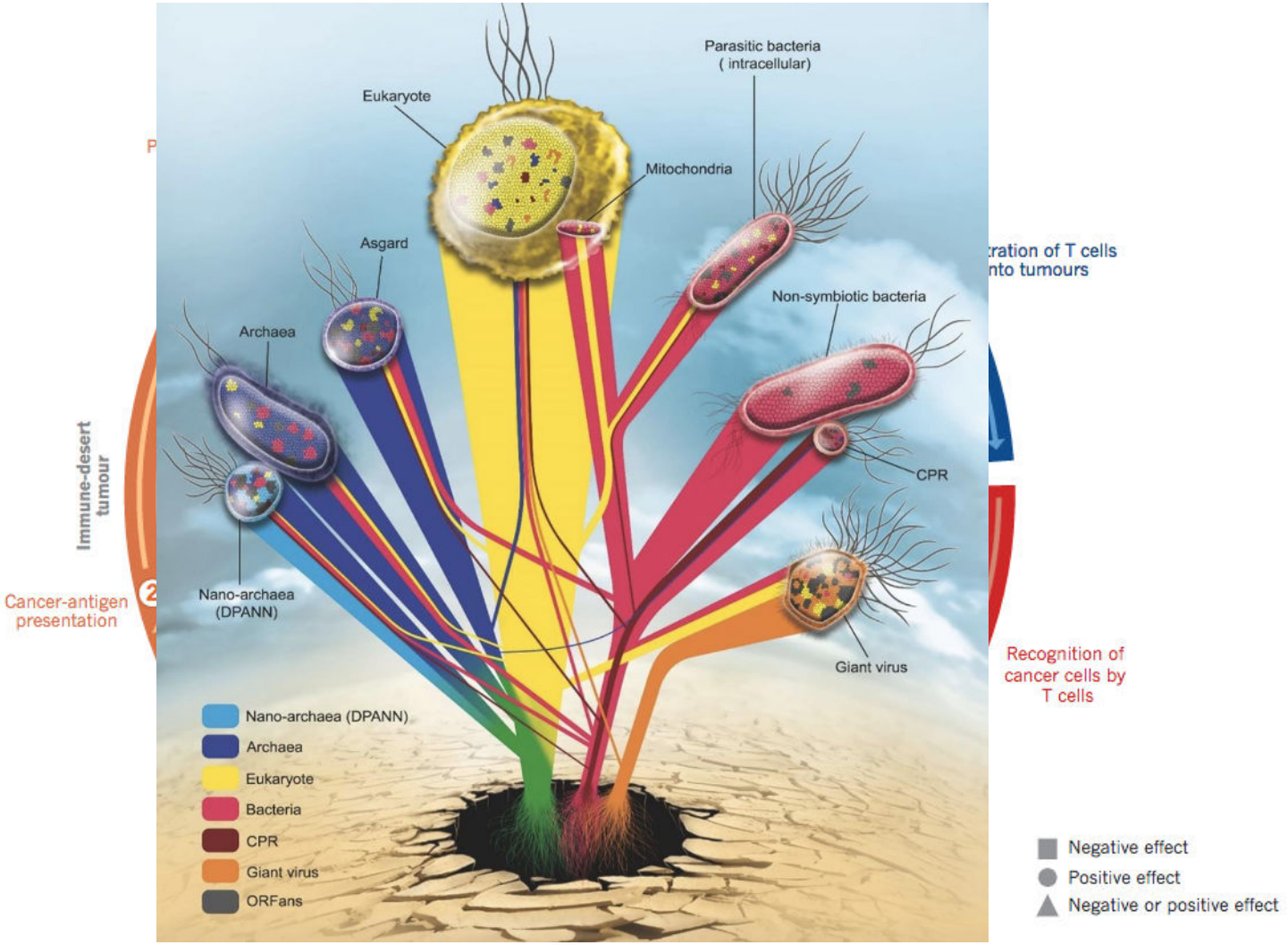
EMA, European Medicines Agency;FDA, United States Food and Drug Administration; HC, Health Canada; MHLW, Ministry of Health, Labour and Welfare of Japan; NMPA, National Medical Products Administration of China; BCC, basal cell carcinoma; BRCA, bladder urothelial carcinoma; CC, cervical cancer; cHL, classical Hodgkin's lymphoma; CRC, colorectal cancer; CSCC, cutaneous squamous cell carcinoma; dMMR, mismatch repair deficiency; EC, endometrial carcinoma; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HL, Hodgkin's lymphoma; HNSCC, head and neck squamous cell carcinoma; MCC, Merkel cell carcinoma; MM, malignant melanoma; MSI-H, high microsatellite instability; MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; PMBCL, primary mediastinal large B cell lymphoma; PMF, primary myelofibrosis; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TMB-H, high tumor mutation burden; TNBC, triple-negative breast cancer; UC, urothelial carcinoma; UCEC, uterine corpus endometrial carcinoma.

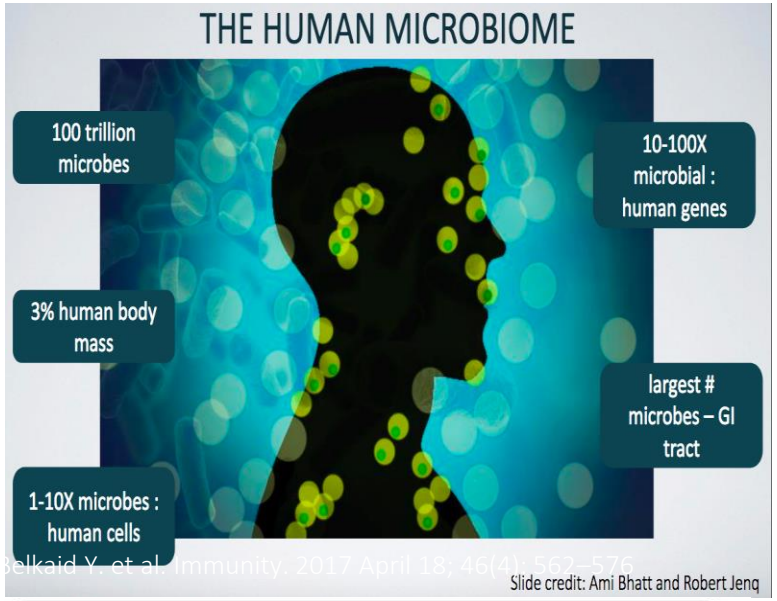


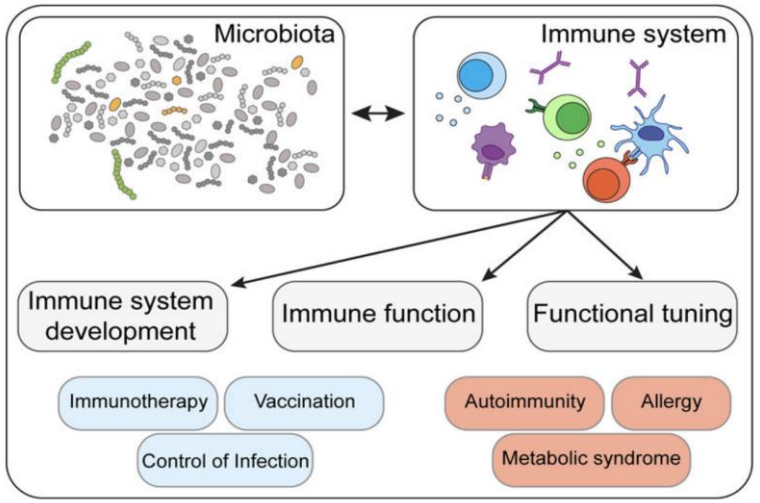
Courtesy: A. Marabelle

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

THE MICROBIOME REGULATES THE CANCER IMMUNE SET POINT

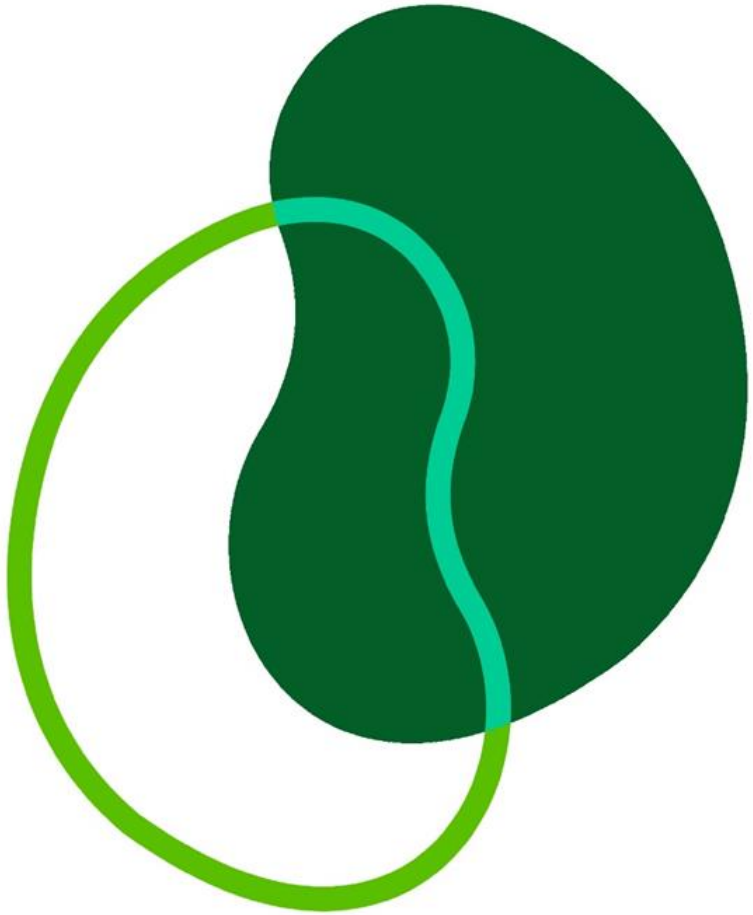




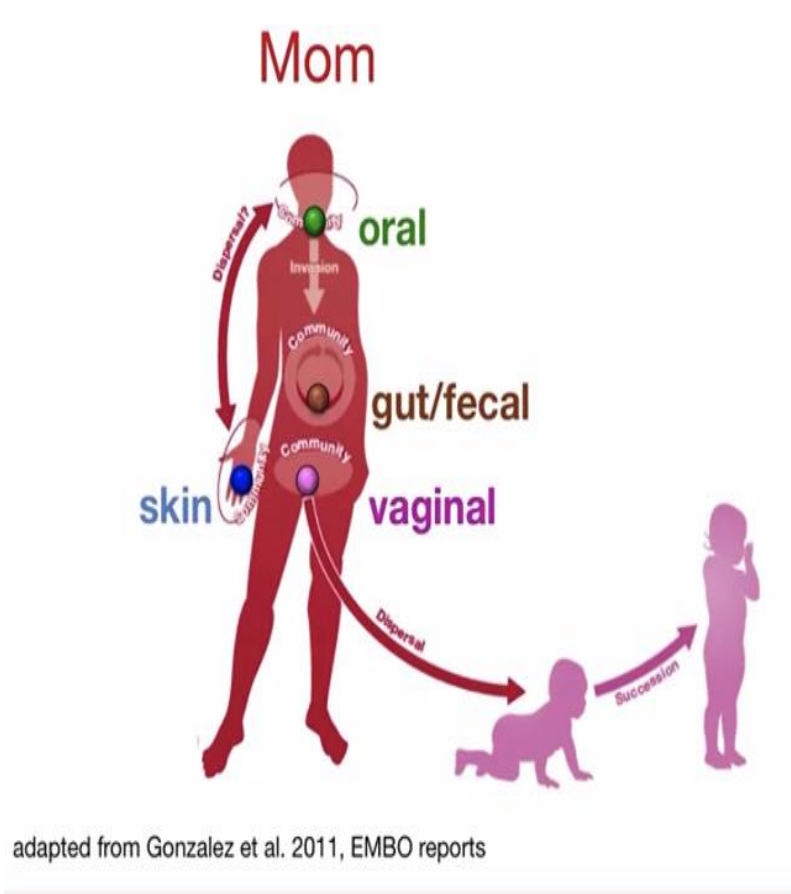


17e Rencontre Patients de l'Association A.R.Tu.R.

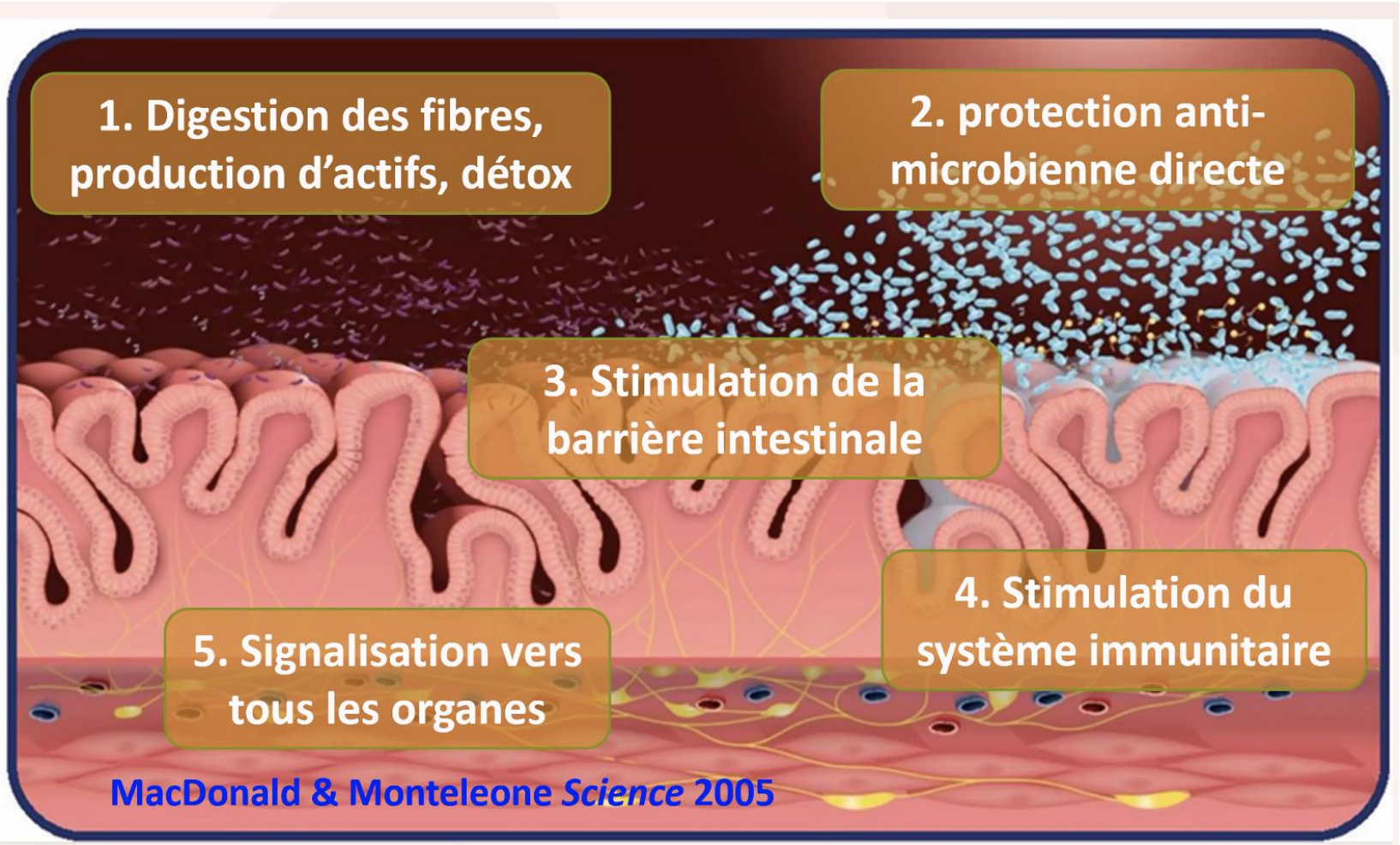
PART2: The links between gut fitness and cancer immunity



THE MICROBIOTA AND THE MICROBIOME: INHERITED ANF IMPRINTED BY MOTHER FROM BIRTH



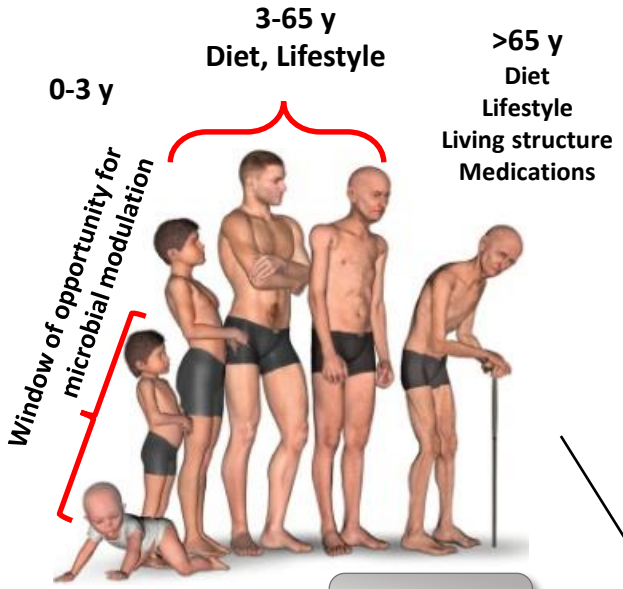
adapted from Gonzalez et al. 2011, EMBO reports



From J. Doré, French Gut, INRAE

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

Changes in our microbiota…



Age

Family

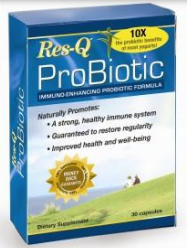
Geographical location

Lifestyle

Nutrition

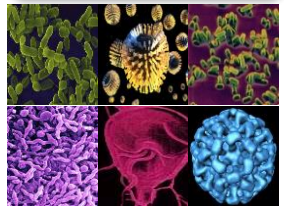
Hygiene

Probiotics

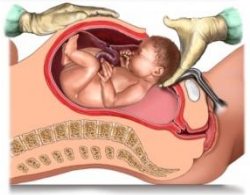


Antibiotics

Infections



Mode of delivery



Mother vaginal and skin microbiota

Mother lifestyle
Peripartum antibiotics

Host Genetics

(genetics accounts for between 1 to 8% of microbiota diversity)

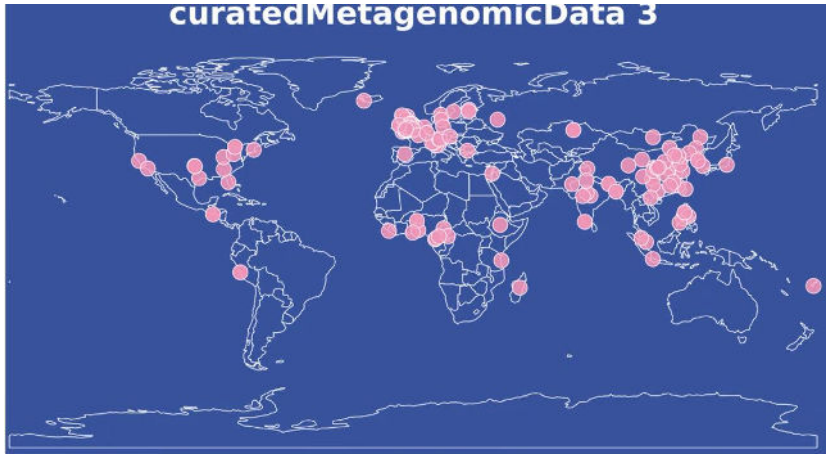
Courtesy: Giorgio Trinchieri, NIH

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

METAGENOMICS OF STOOLS WORDWIDE TO DEFINE THE HEALTHY M

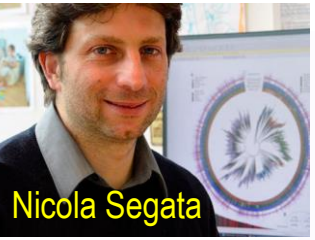
J. Doré &D. Ehrlich

INRA
SCIENCE & IMPACT



86 studies, 90 cohorts and 20,533 metagenomes;
42 countries, 50 clinical conditions, 6 body sites

Meyer, F. BMC Bioinformatics 2008
Wang, M. Nat. Biotechnol 2016
Pasolli, E. Nat. Methods 2017
Gonzalez, A. Nat. Methods 2018
Wu, S. Nucleic Acids Res. 2020
Kasmanas, J. C. Nucleic Acids Res. 2021
Beghini, F. Elife 2021
Ernst, F. G. M. 2022
Wang, P. Nucleic Acids Res. 2022
Dekkers, K. F. Nat. Commun 2022
Dai, D. Nucleic Acids Res. 2022
Xu, Y. Comput. Struct. Biotechnol. J. 2022

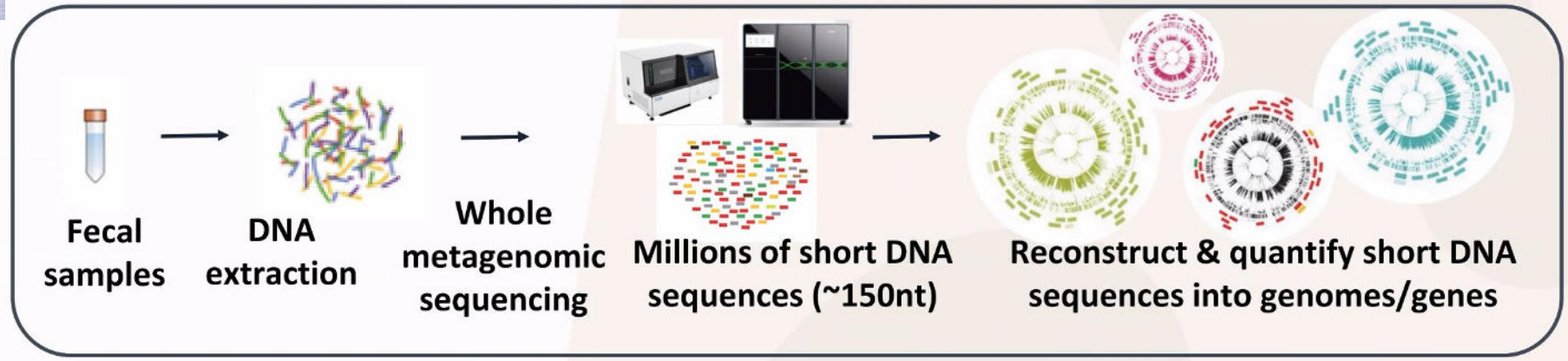


Nicola Segata

V. Iebba

A. Thomas

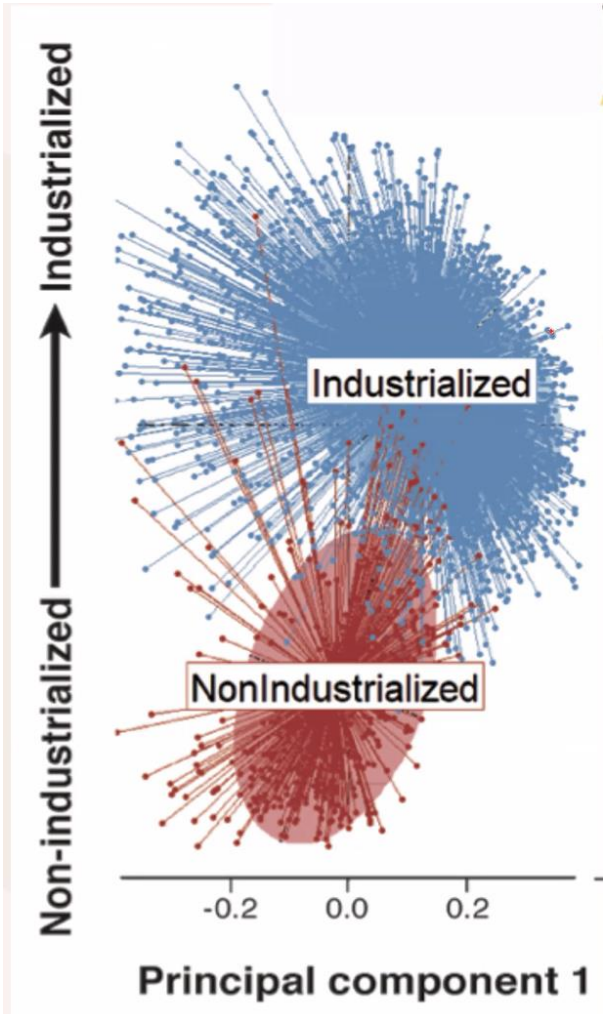
Collect & transfer → Aliquot & Store → DNA Extraction & Sequencing → Functional exploration → Bioinformatic & Statistical analysis

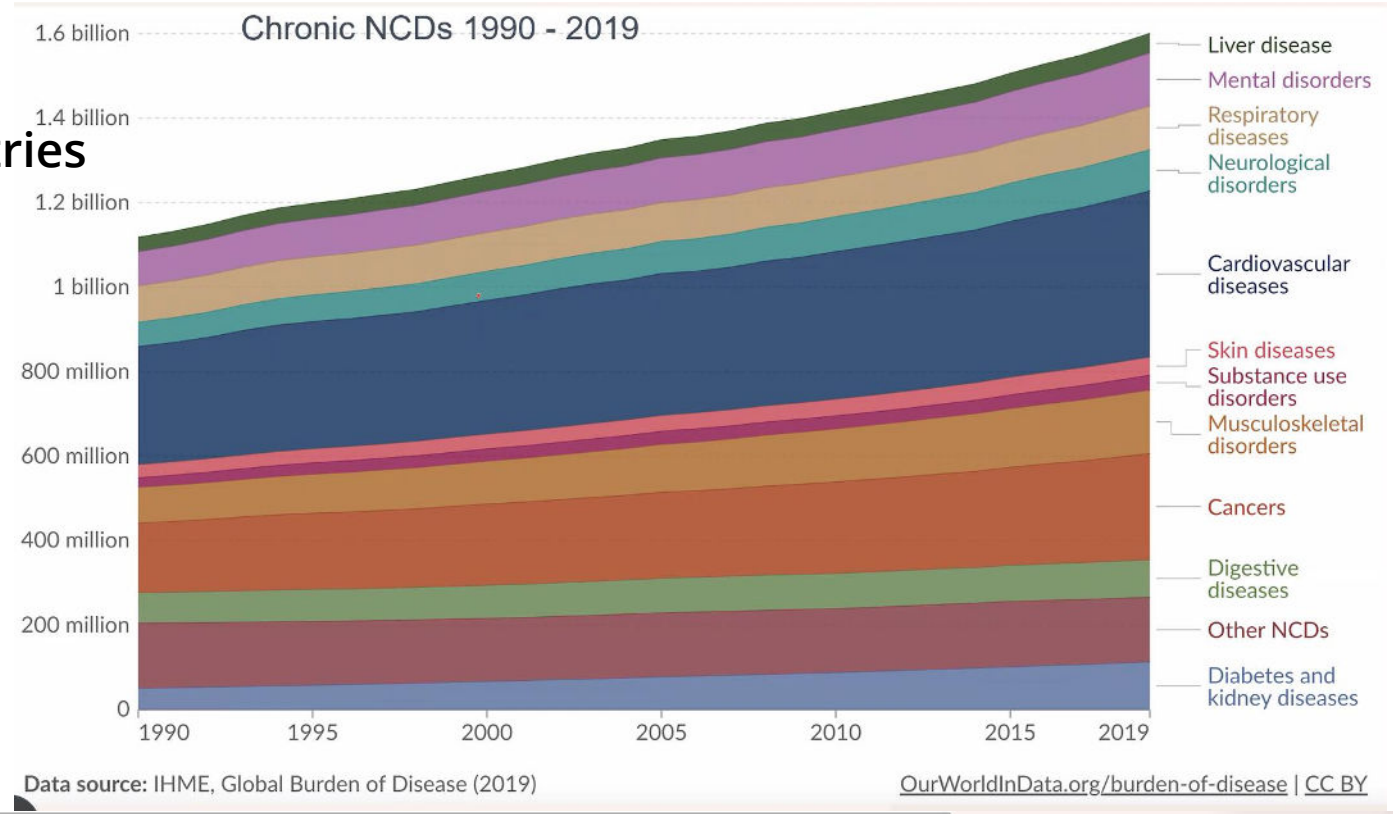


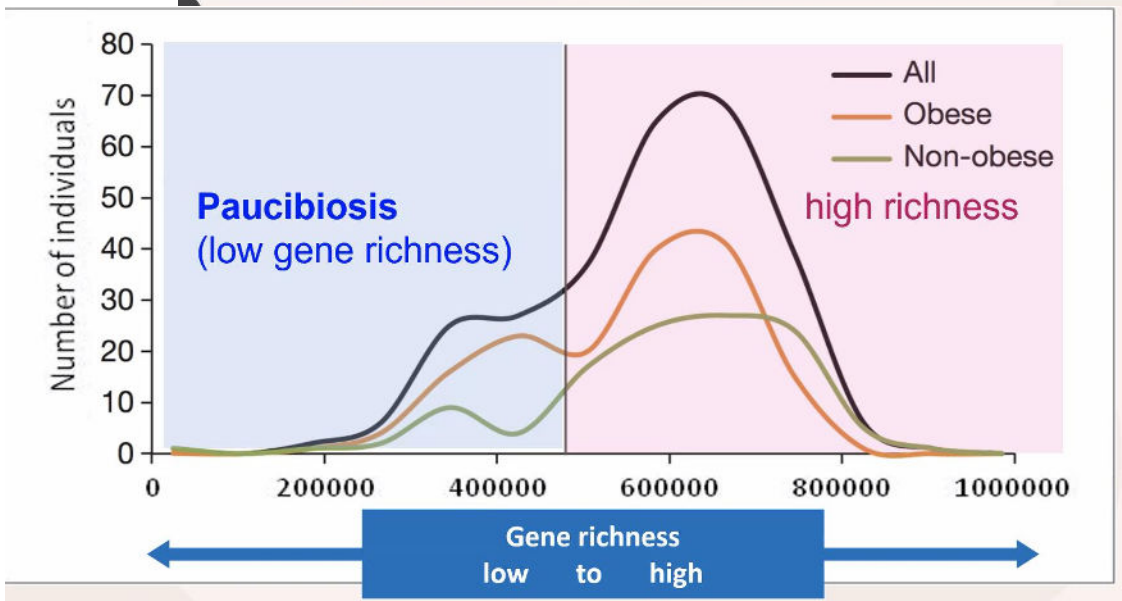
Each step is crucial to a comprehensive and reproducible metagenomic analysis

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

Chronic inflammatory disorders
In Western and Industrialized countries







Gene richness is a health stratifier

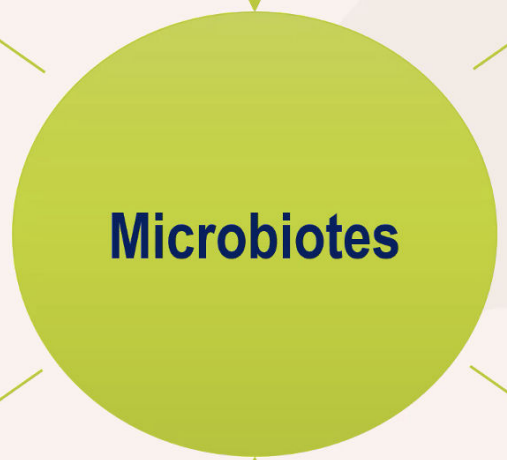
Le Chatelier *et al*, *Nature 2013*

Enjeux de recherche et innovation

Nos microbiotes au cœur d'un système complexe
qui conditionne santé et bien-être

NUTRITION / ALIMENTATION

- Diversité alimentaire
- Modèle alimentaire FR
- Personnalisation
- Prévention



SANTE / BIEN ETRE

- Maladies chroniques
- Prédiction
- « Life-style medicine »
- Prévention

Outils de monitoring et levier d'action
pour la prévention et la santé

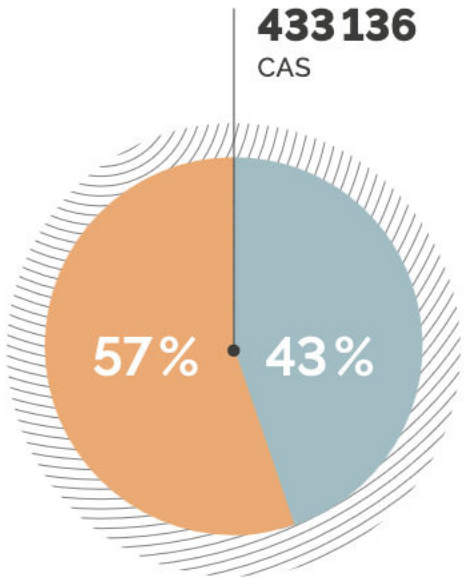
Doré et al. Therapy 2017

Votre logo

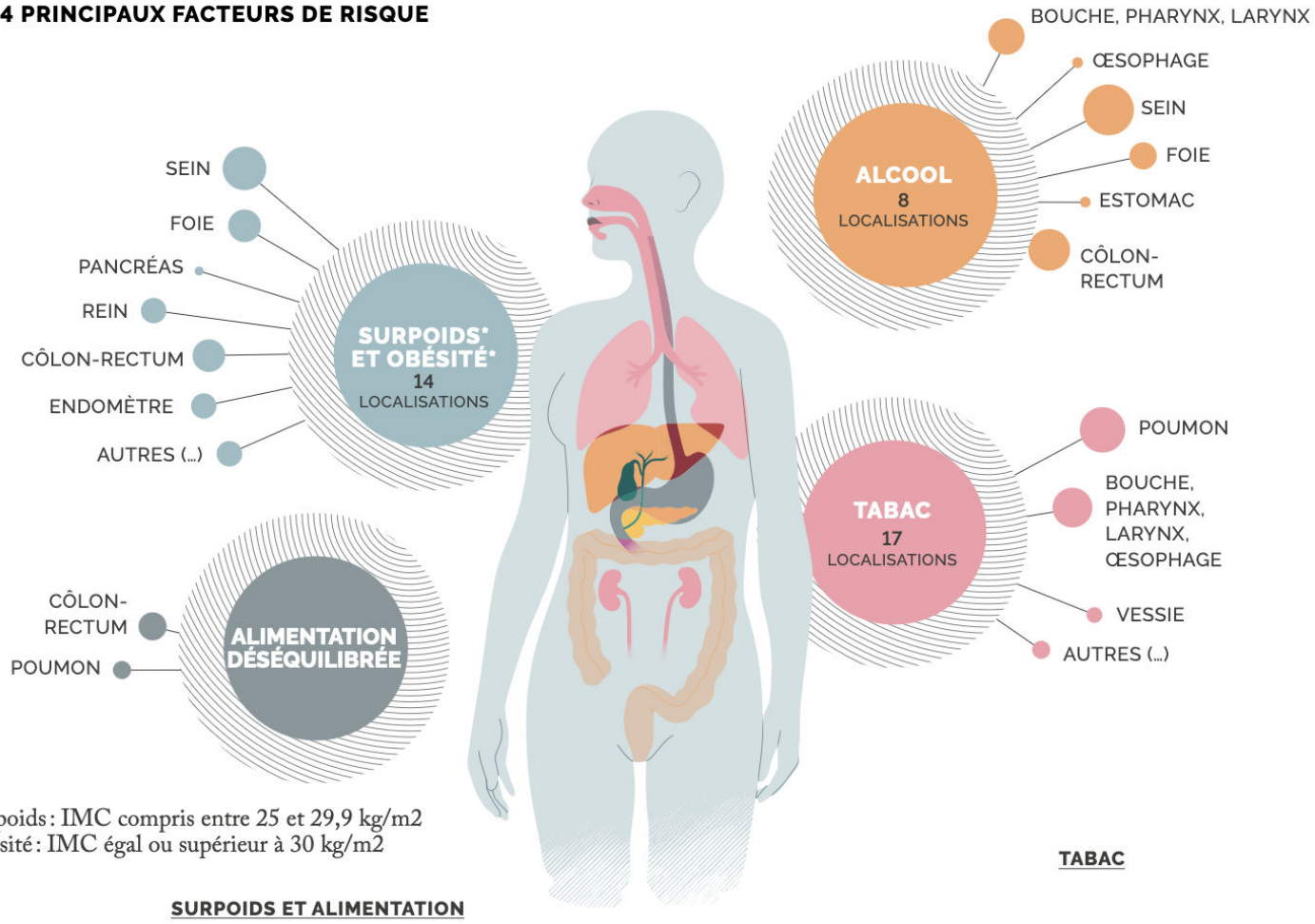
Le microbiote français
Le French Gut

RCC: 15 000 nouveaux cas/an en France =3% totalité des cancers

NOUVEAUX CAS DE CANCER EN 2023



LES 4 PRINCIPAUX FACTEURS DE RISQUE



* surpoids : IMC compris entre 25 et 29,9 kg/m2
* obésité : IMC égal ou supérieur à 30 kg/m2

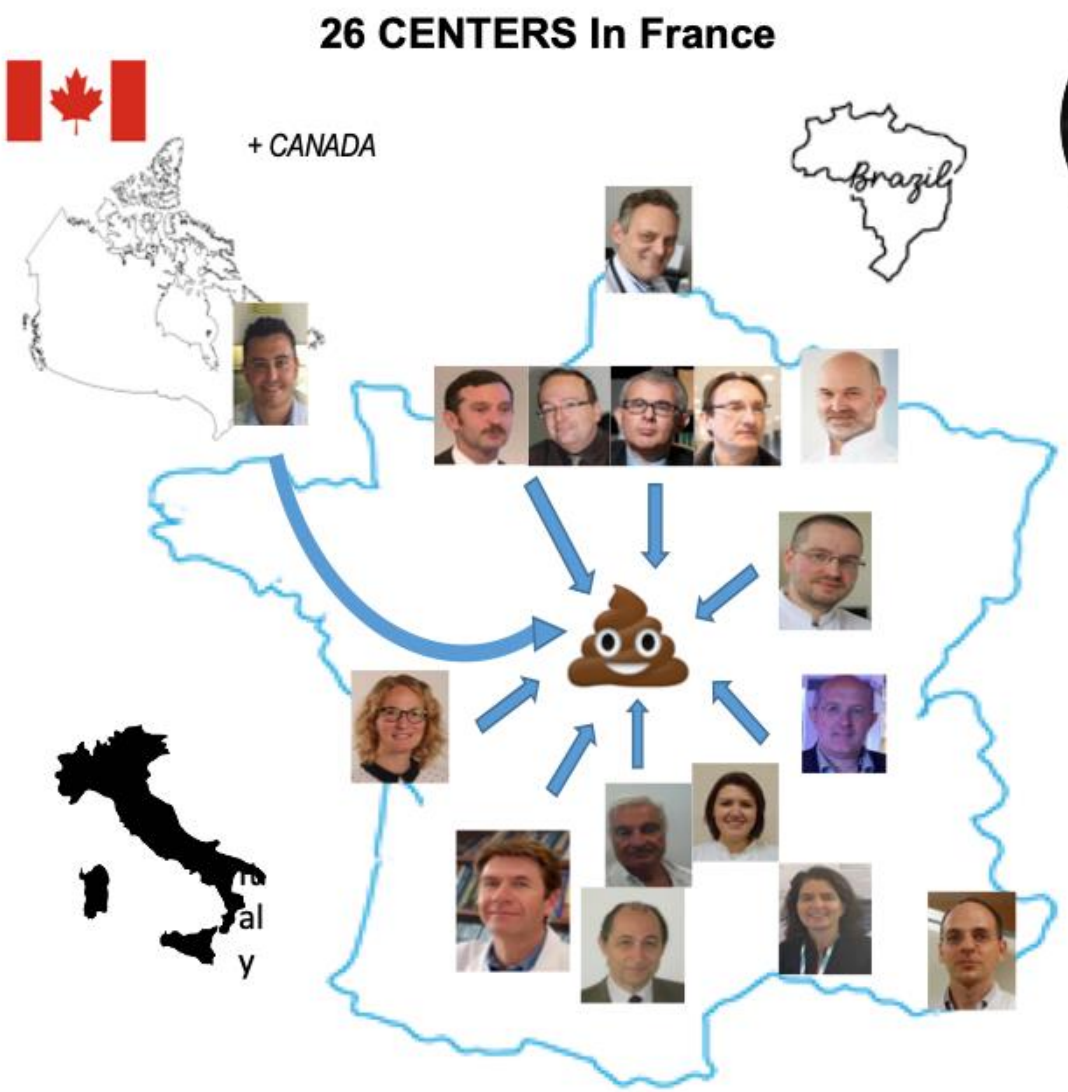
SURPOIDS ET ALIMENTATION

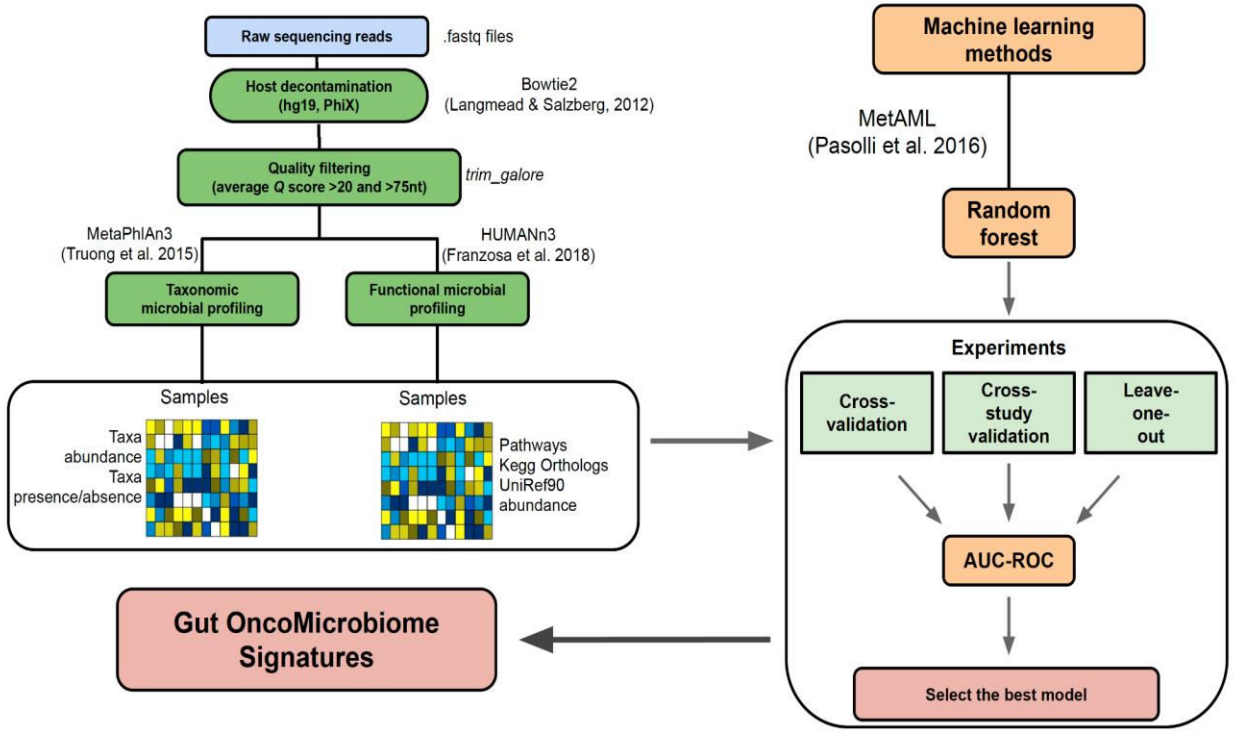
TABAC

TSM: taux standardisé du monde

FRENCH NETWORK: RHU LUMIERE + RHU IMMUNOLIFE

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS





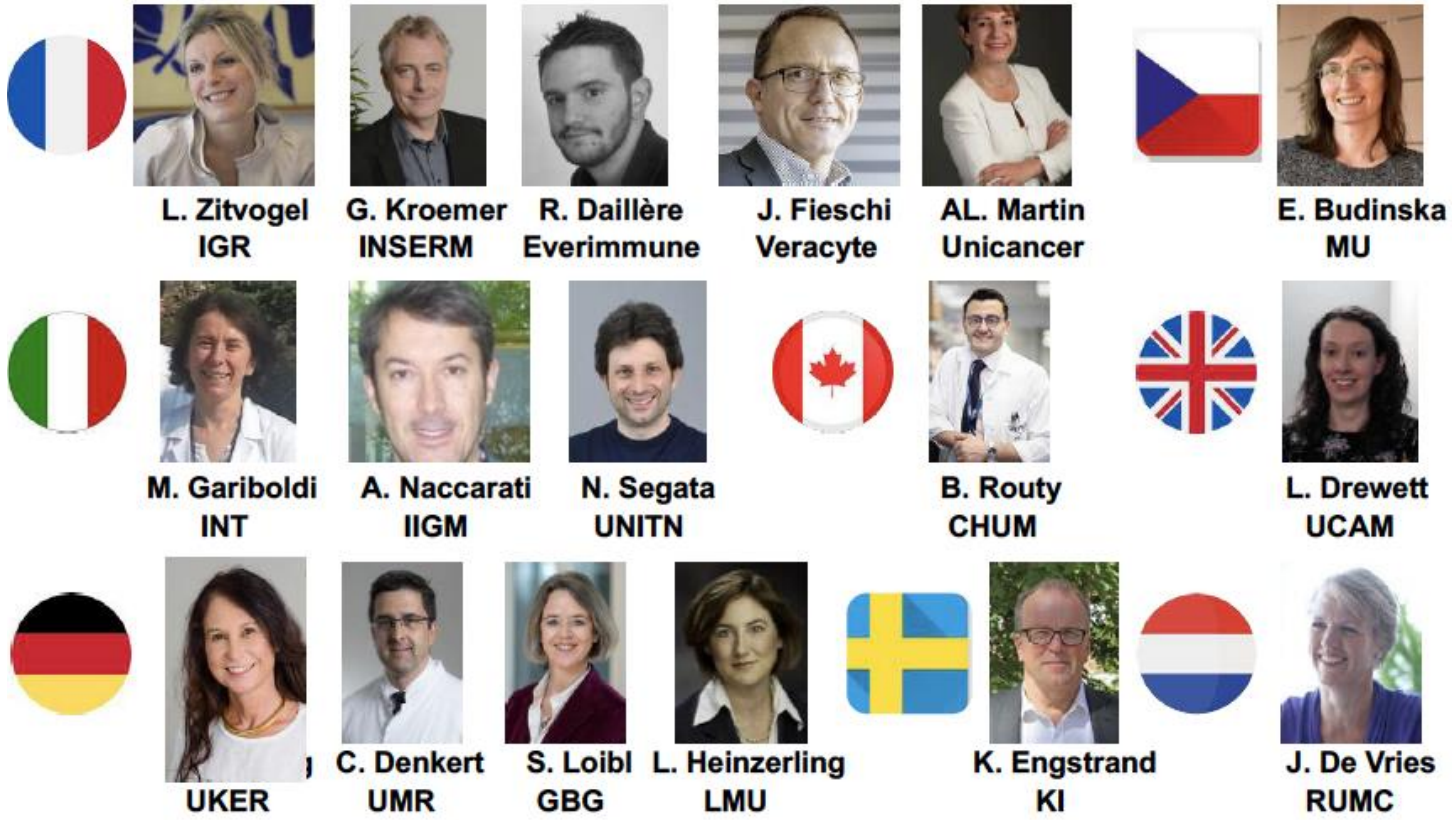
GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

EUROPEAN NETWORK: ONCOB

ONCOBIOME
Microbiota against cancer
International research program

ONCOBIOME: WHAT IS THIS?

A RESEARCH AND INNOVATING ACTION INVOLVING 17 PARTNERS IN 8 COUNTRIES

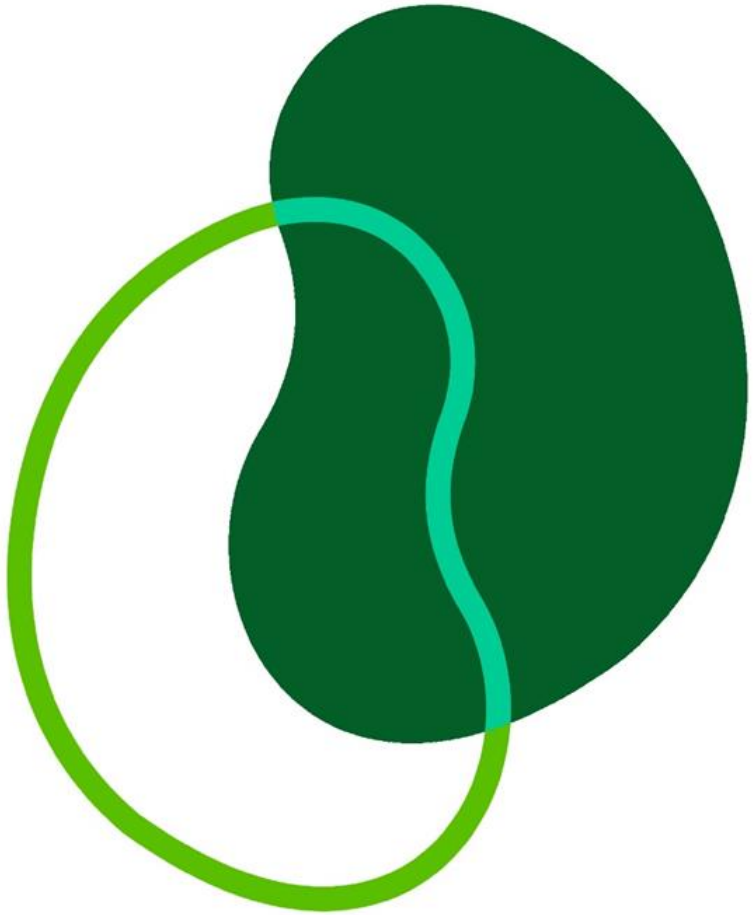


A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein


ONCOBIOME
Microbiota against cancer
International research program
IMMUNOLIFE
SEERAVE
FOUNDATION
2017
Merit Award
Recipient
ASCO
CONQUER
CHUM
GUSTAVE
ROUSSY
CANCER CAMPUS
GRAND PARIS

17e Rencontre Patients de l'Association A.R.Tu.R.

PART3: Antibiotics, and cancer-associated dysbiosis



Rationale for an impact of gut microbiota in cancer immunomodulation

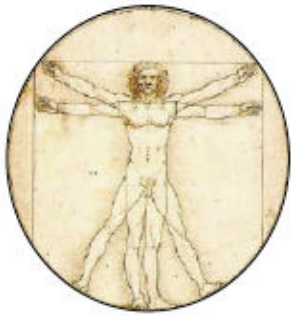
Derosa et al. *Cancer Discovery* **11**, 2396–2412 (2021)

- Blunt ICB efficacy
- **Reduce CAR-T cell efficacy**

ATB

GOMS

- Gut oncomicrobiome signatures predict ICB resistance

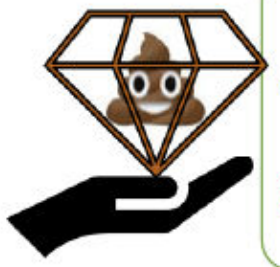


Gopalakrishnan et al. *Science* **359**, 97–103 (2018)

Mechanisms of action

Davar et al. Science **371**, 595–602 (2021)
Baruch et al. *Science 2021 Feb 5;371(6529):602-609.*
Routy et al. *Nat. Med. 2023*

Clinical trials



- **FMT**
  R -> NR to
  Circumvent primary resistance in MM

Avatar mice

Routy et al. *Science* **359**, 91–97 (2018)
Derosa et al. *Eur Urology 2020*

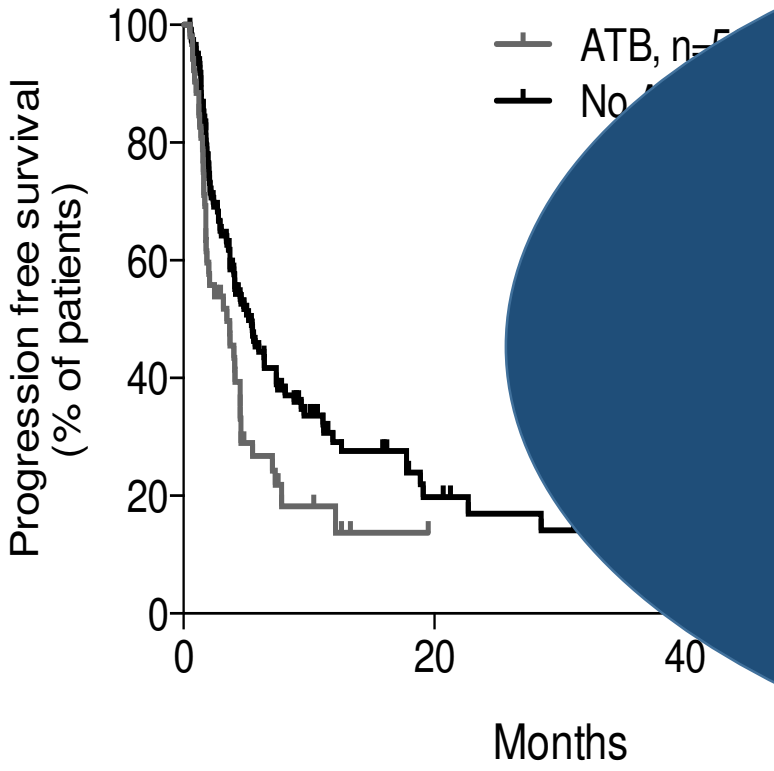
- Humanizing mouse gut microbiota to
- Mirror ICB resistance

GOMS: Gut, NR: non responders

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

META-ANALYSIS: DELETERIOUS EFFECTS OF ANTIBIOTICS FOR THE CLINICAL BENEFIT OF IMMUNE CHECKPOINT INHIBITORS.

ATB:antibiotics



Routy et al; Science, Oct 27, 2017.
Median PFS ATB: 3.5 months
Median PFS No ATB: 5.2 months

ATB NOT ONLY COMPROMISE THE EFFICACY OF IMMUNE CHECKPOINT INHIBITORS

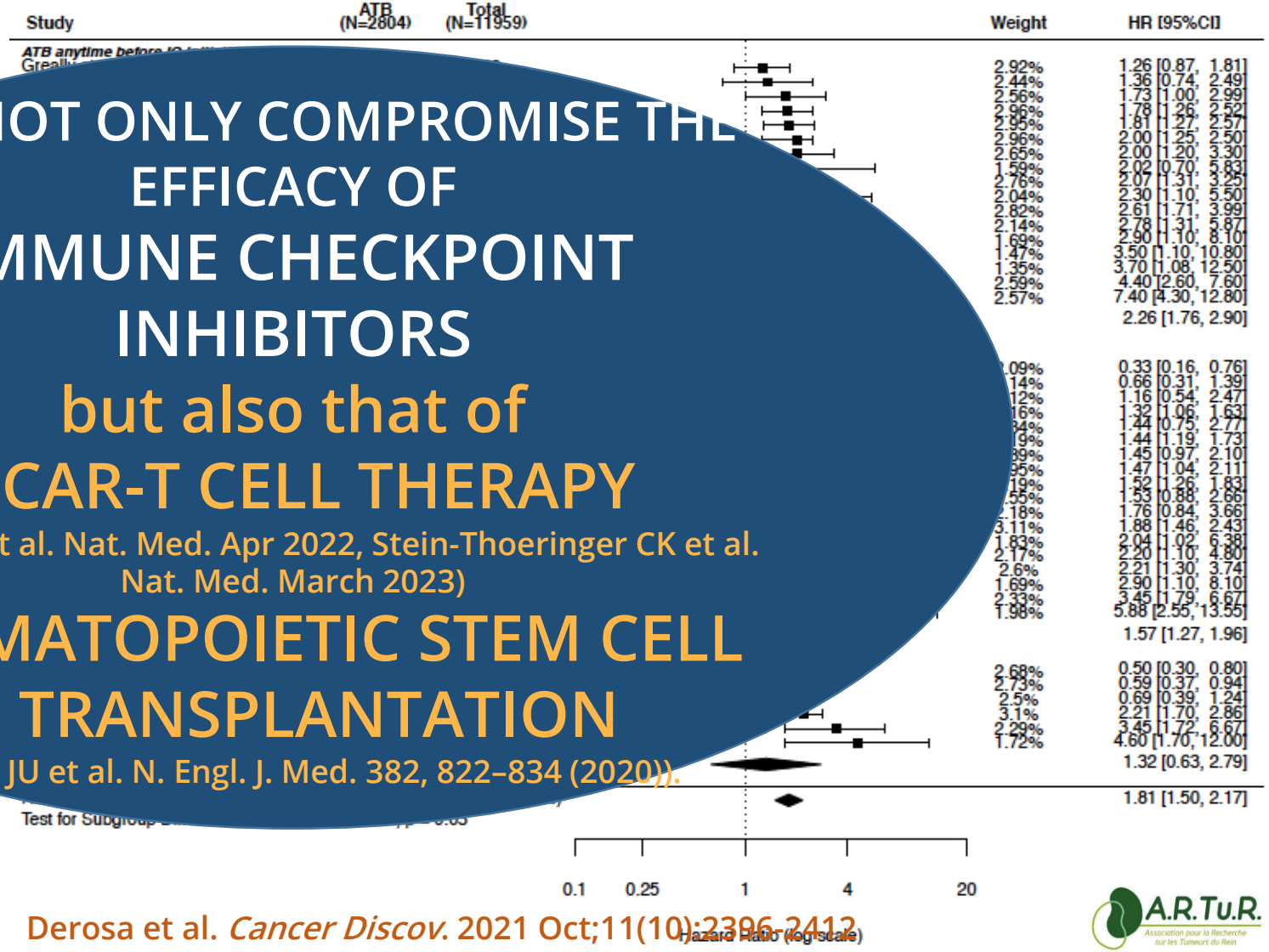
but also that of

- CAR-T CELL THERAPY

(Smith M. et al. Nat. Med. Apr 2022, Stein-Thoeringer CK et al. Nat. Med. March 2023)

- HEMATOPOIETIC STEM CELL TRANSPLANTATION

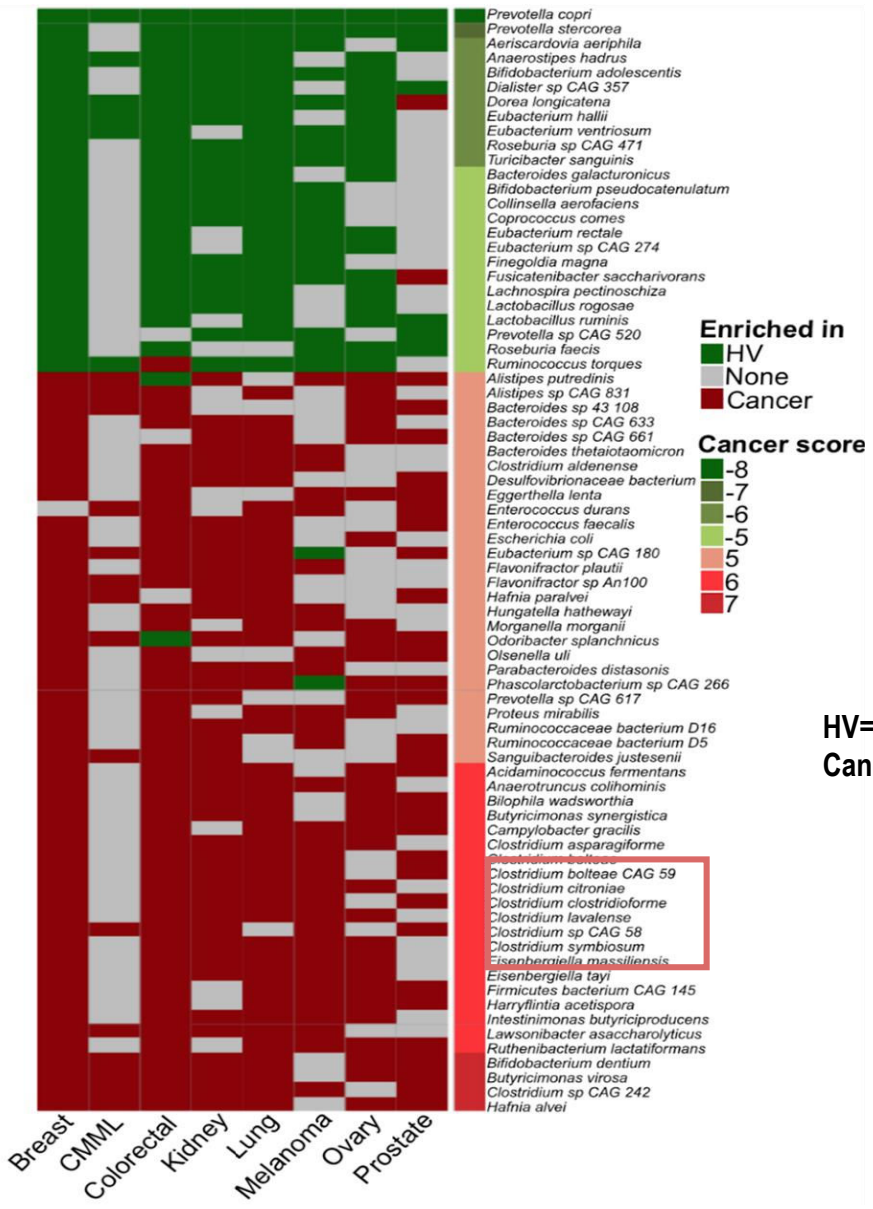
(Peled JU et al. N. Engl. J. Med. 382, 822–834 (2020)).



Derosa et al. *Cancer Discov*. 2021 Oct;11(10):2396-2412.

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

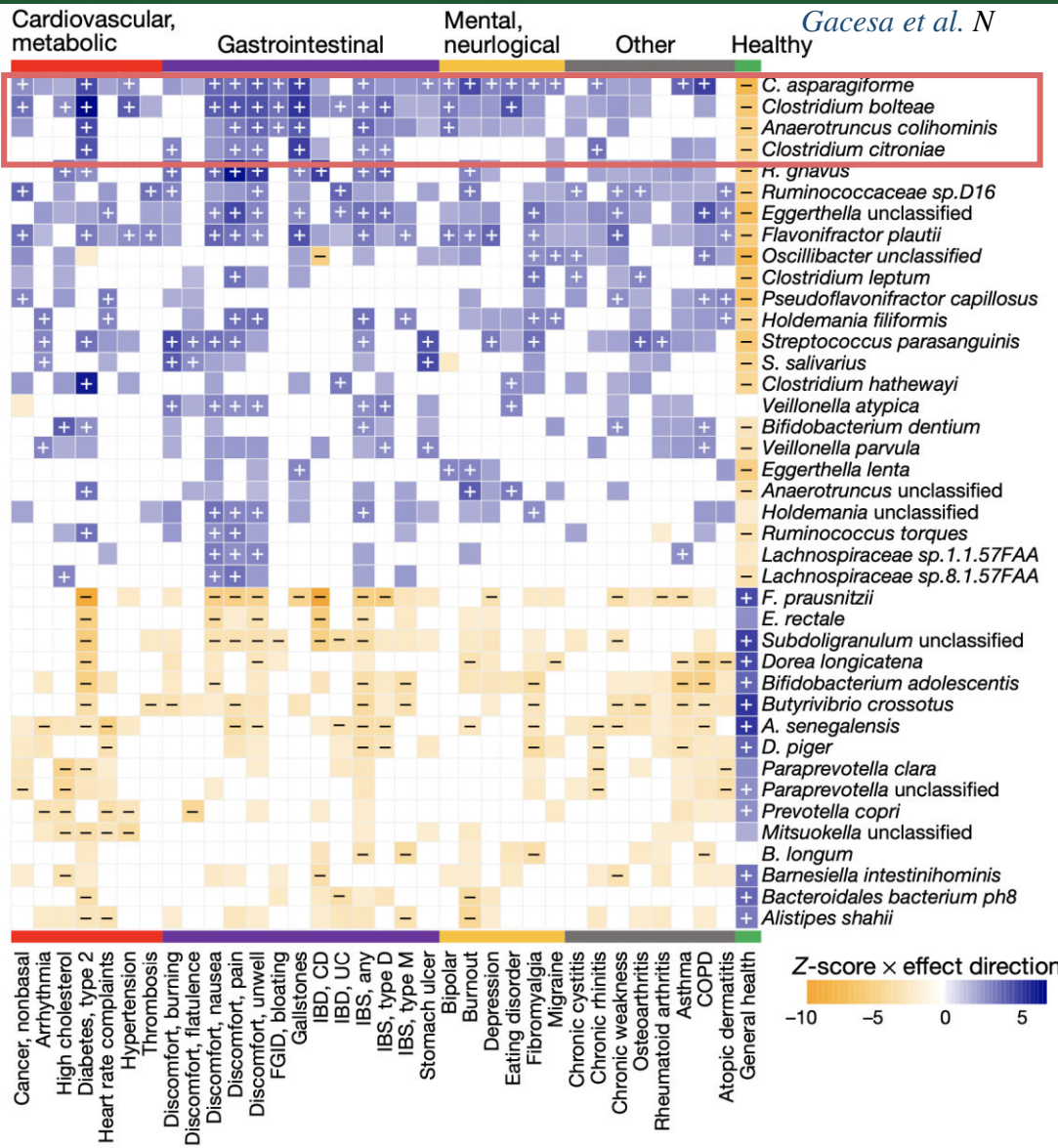
17e Rencontre Patients de l'Association A.R.Tu.R.



Yonekura, Cancer Discovery 2022

HV=5570
Cancer=1607

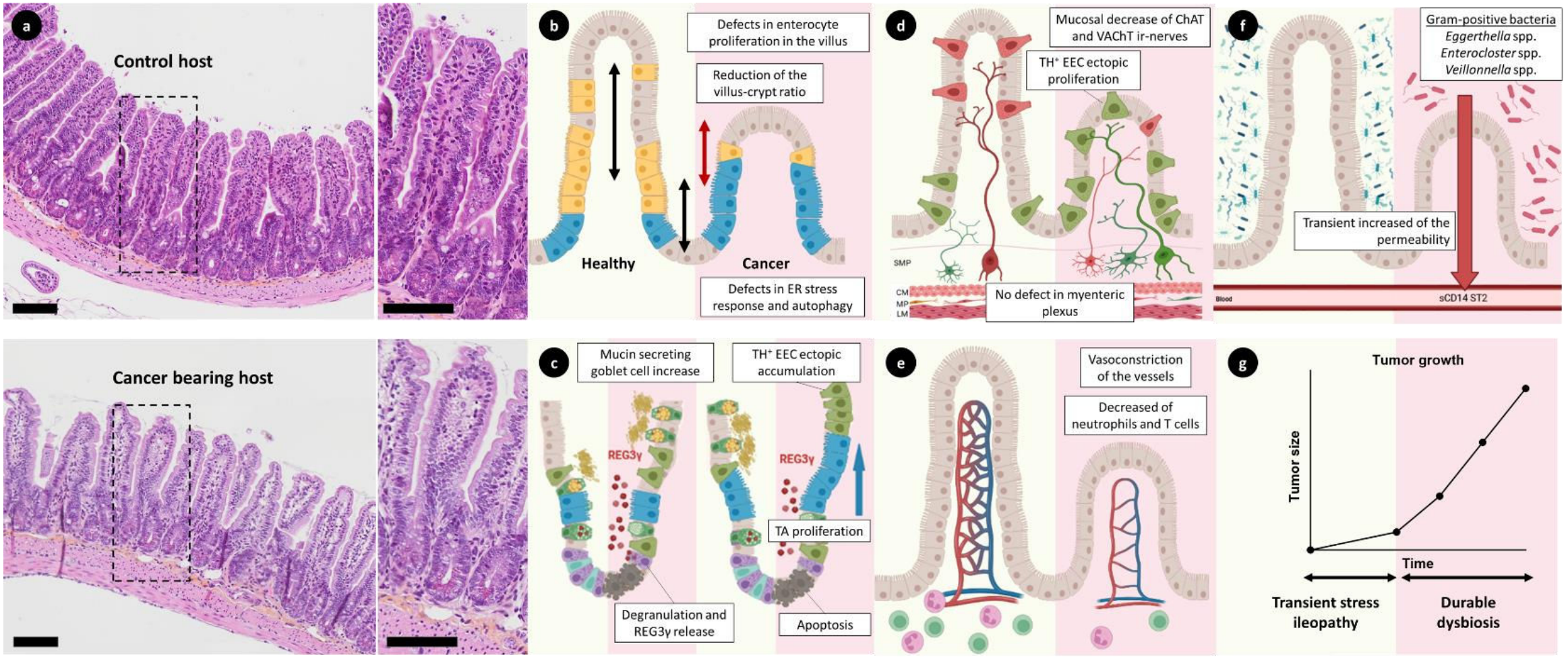
Gacesa et al. N

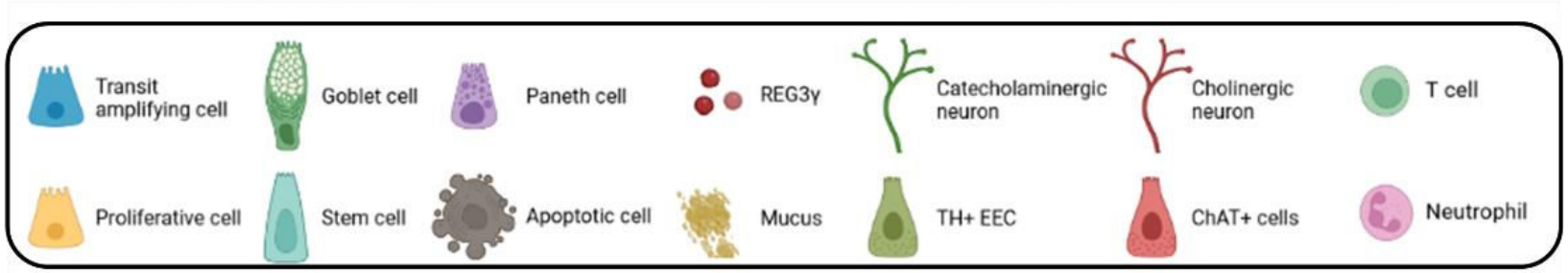


Cancer-associated gut dysbiosis is not cancer-specific

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

17e Rencontre Patients de l'Association A.R.Tu.R.





Yonekura et al.
Cancer Discov. 2022

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

Old papers describing this cancer-associated ileal atrophy

JEJUNAL BIOPSY IN MALIGNANT DISEASE[1]

DONALD J. DELLER,[2] TIMOTHY G. C. MURRELL[3] AND ROMALA BLOWES[4]
From the University of Adelaide Department of Medicine
Royal Adelaide Hospital

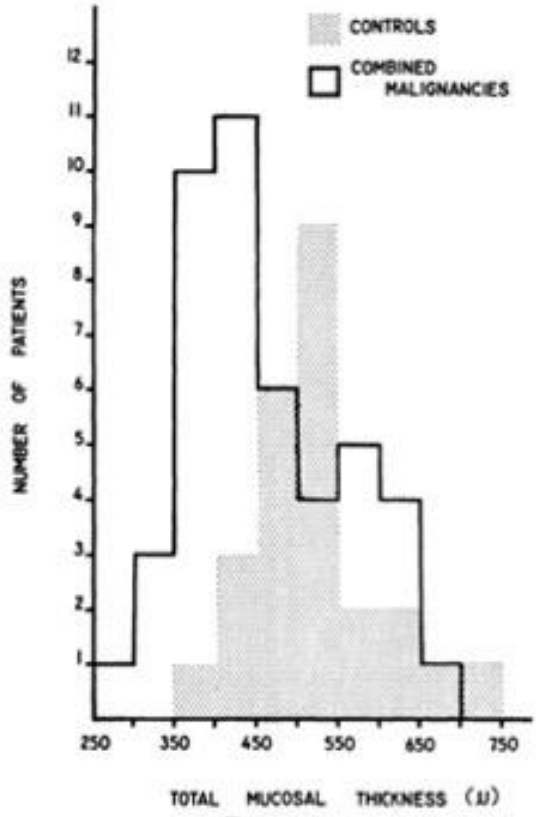


FIGURE 2
Mucosal thickness measurements of biopsy specimens from control subjects and patients with malignant disease

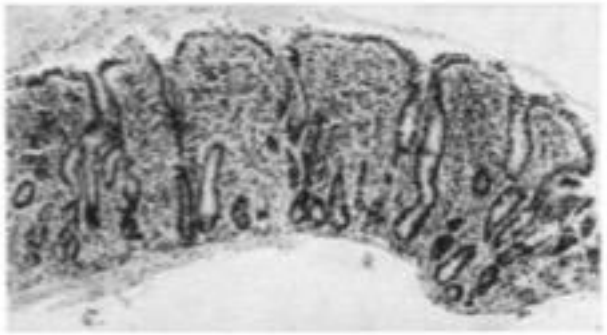


FIGURE 5
Photomicrograph of jejunal biopsy specimen from a patient with bronchial carcinoma showing subtotal villous atrophy. (Original magnification, 170 diameters)

Digestion 7: 147–155 (1972)

Morphology of Small Bowel Mucosa in Malignancy[1]

T. GILAT, B. FISCHEL, J. DANON and M. LOEWENTHAL

Departments of Gastroenterology and Pathology, Ichilov Hospital, Tel Aviv University Medical School, Tel Aviv

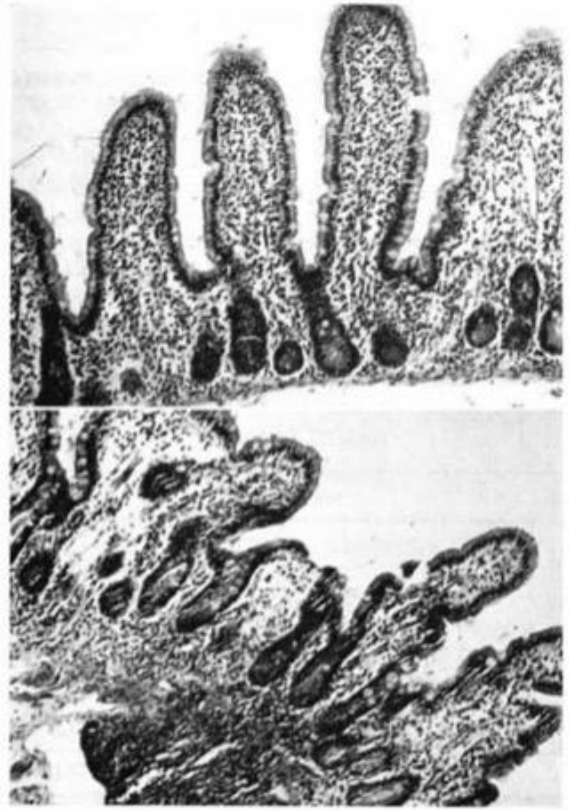
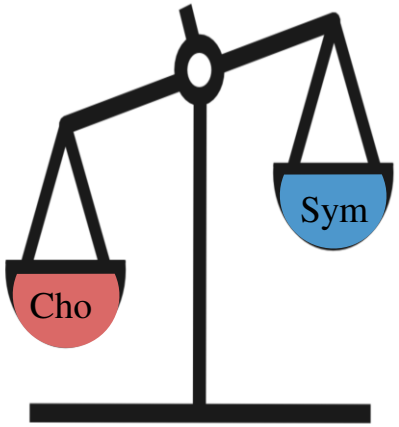
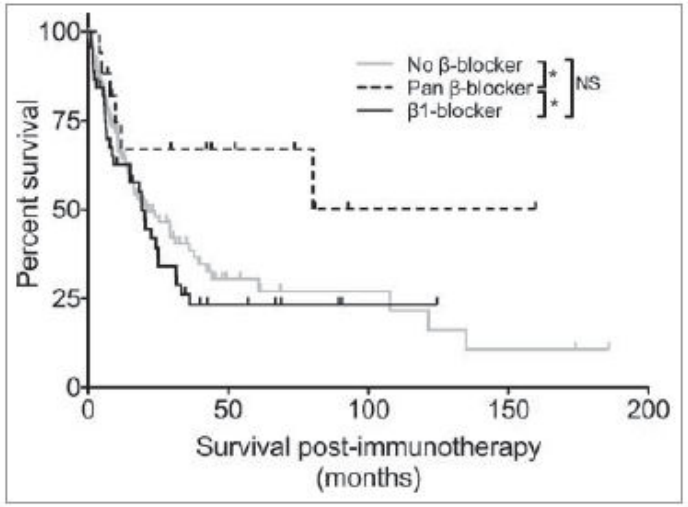


Fig. 1. Mild nonspecific changes. Suction biopsy, jejunum. HE, ×20.
Fig. 2. Marked nonspecific changes. Suction biopsy, jejunum. HE, ×20.

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

Epithelial barrier fitness: β-adrenergic receptors signaling-mediated stress ileopathy

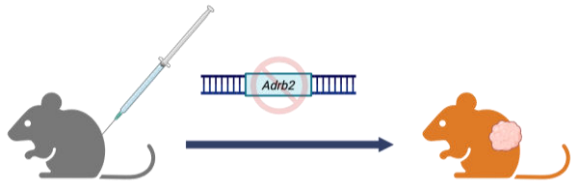


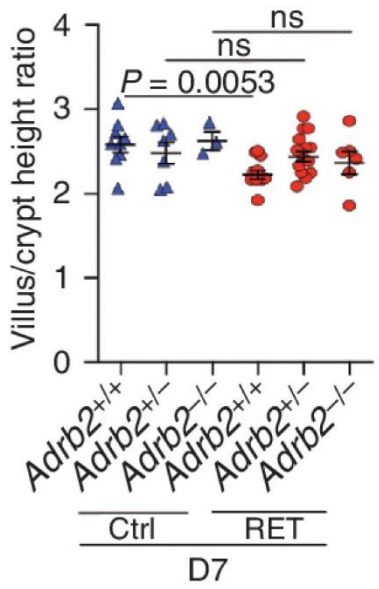


Kokolus et al.

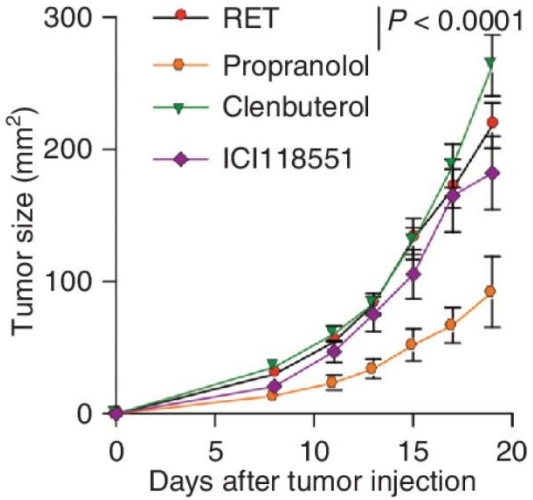
ONCOIMMUNOLOGY
2018, VOL. 7, NO. 3, e1405205 (8 pages)
https://doi.org/10.1080/2162402X.2017.1405205

A Genetic
Adrb2 knockout



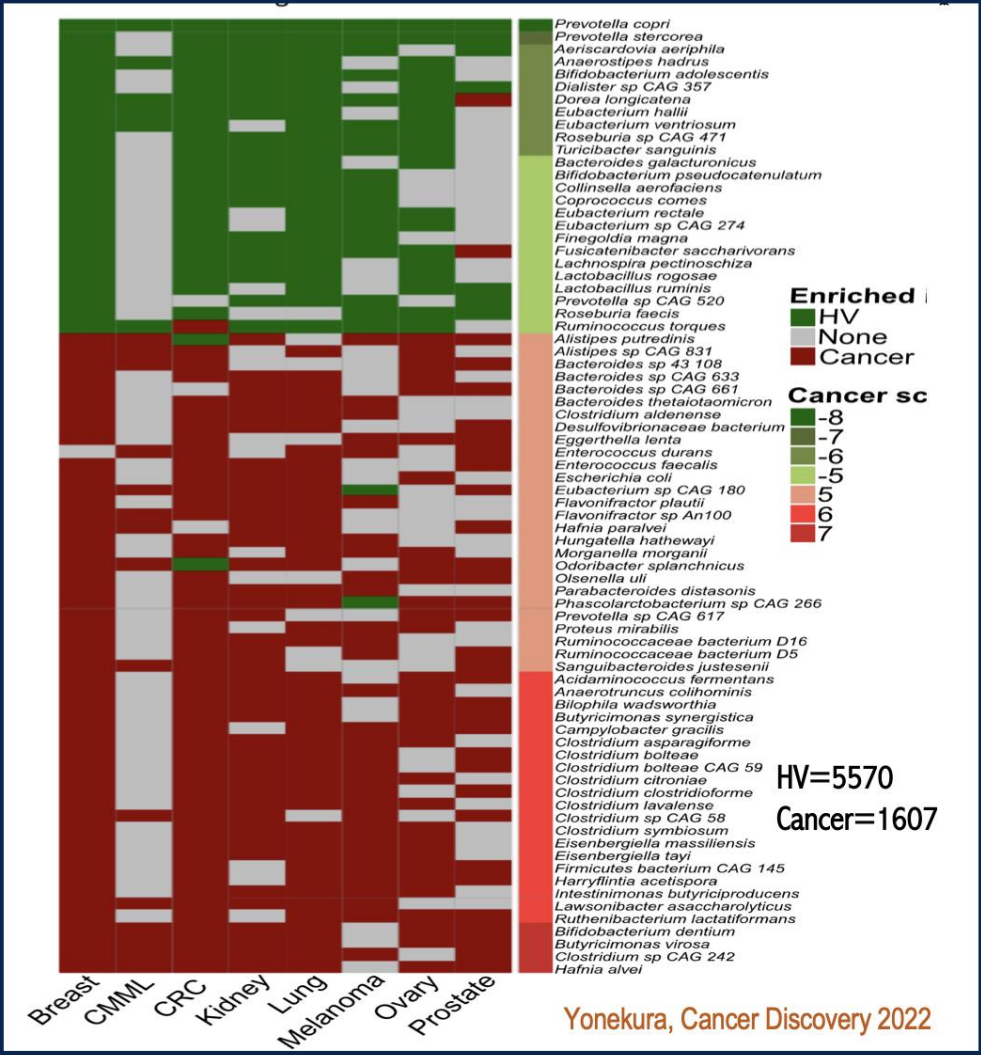


B Pharmacologic
inhibition of β-AR



Propranolol: β1/2-AR blocker
Clenbuterol: β2-AR agonist

GUT DYSBIOSIS IN CANCER PATIENTS: Divergence between healthy volunteers[7] and cancer patients and between responders or non responders to IO



Yonekura, Cancer Discovery 2022

NON RESPONDERS

Gut microbiota composition

- Disease and cancer
- Dysmetabolism
- Immunosuppression
- Chronic inflammation
- Stress ileopathy

- *Actinomyces* spp. and oral taxa
- *Anaerotruncus* spp.
- *Bilophila wadsworthia*
- *Eggerthella lenta*
- *Eisenbergiella* spp.
- *Enterocloster* genus
- *Erysipelatoclostridium* spp.
- *Flavonifractor plautii*
- *Hungatella hathewayi*
- *Veillonellaceae* family members
- *Ruminococcaceae* (SGB15201)
- *Streptococcus* spp.

RESPONDERS

- Health
- Fibre enriched-diets
- Immune fitness
- Epithelial barrier fitness

- *Anaerobutyricum hallii*
- *Akkermansia muciniphila* (SGB9226)
- *Alistipes shahii*
- *Bifidobacterium bifidum* and *B. adolescentis*
- *Blautia* spp.
- *Coprococcus eutactus* and *C. catus*
- *Dorea* spp.
- *Eubacterium* spp.
- *Faecalibacterium prausnitzii*
- *Faecalibacterium* (SGB15346)
- *Lactobacillus vaginalis*
- *Phascolarctobacterium succinatutens*
- *Prevotella copri* clade A (SGB1626)
- *Roseburia* spp.
- *Ruminococcus bicirculans*

Thomas & Fidelle et al. NRCO in press

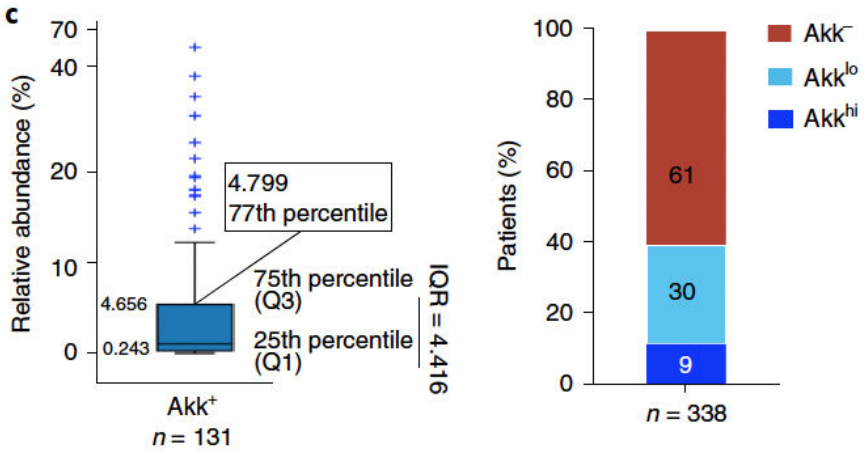
Omics-based identification and design of user-friendly diagnosis tool for gut dysbiosis	Prospective validation of the diagnosis tool across cancer histotypes and stages, and across geographic locations	Prospective validation of predictive value in patients receiving ICIs	• Patient stratification based on dysbiosis • Pharmacodynamics of microbiota-centred interventions

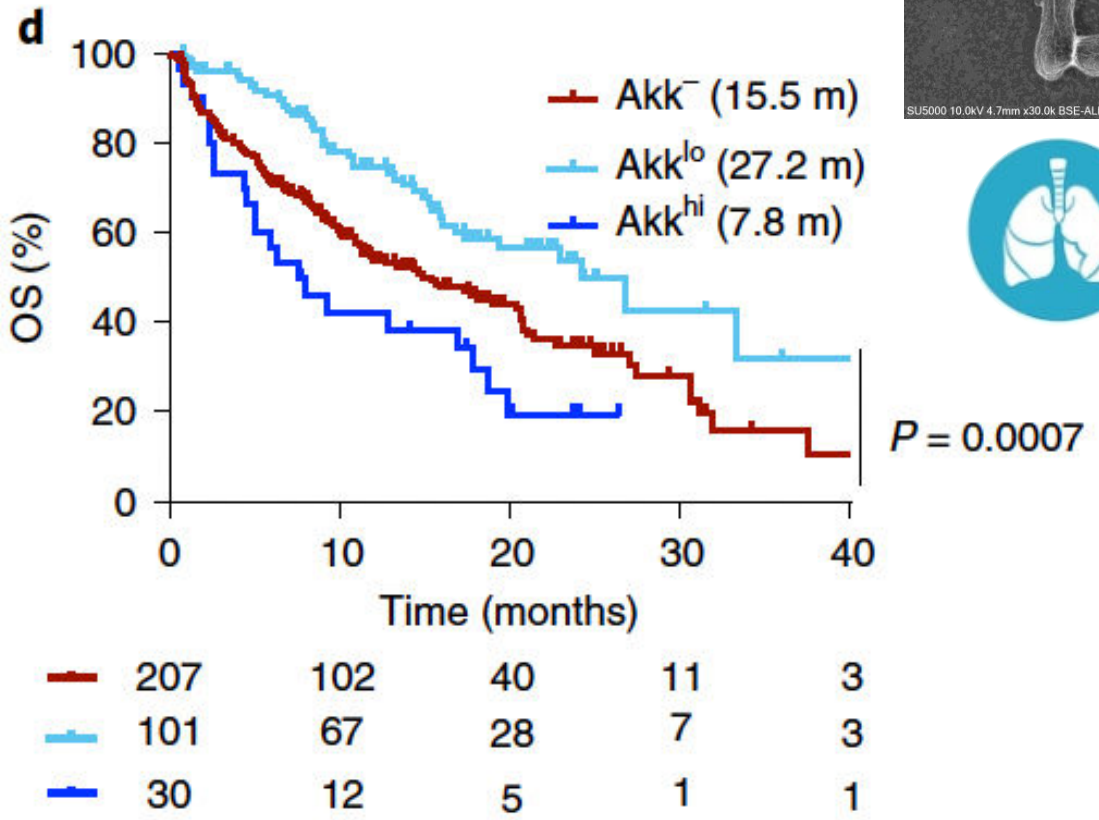
DIAGNOSIS OF INTESTINAL DYSBIOSIS paving the way to I-O resistance in NSCLC.

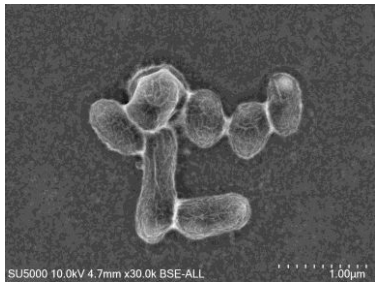
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01655-5
Check for updates

Intestinal *Akkermansia muciniphila* predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer

Lisa Derosa[1,2,3,4,35], Bertrand Routy[5,6,35], Andrew Maltez Thomas[7,8,35], Valerio Iebba[9],





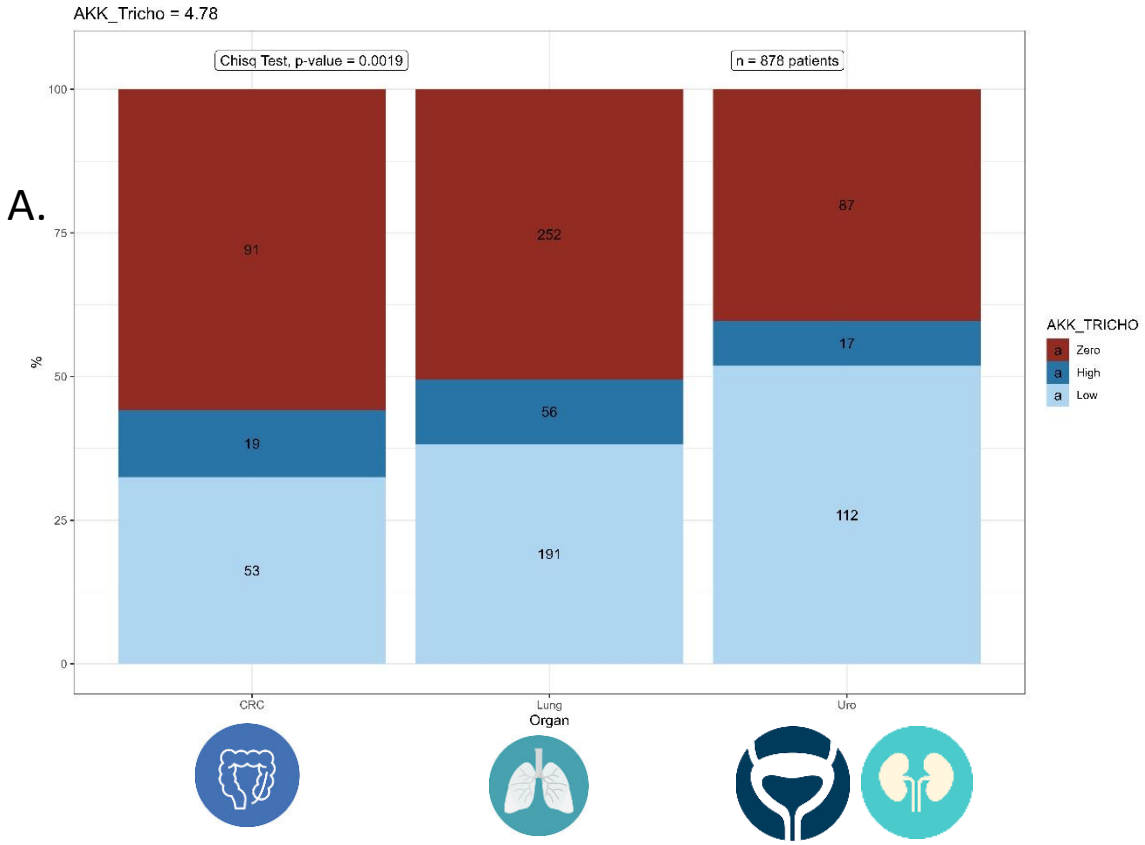


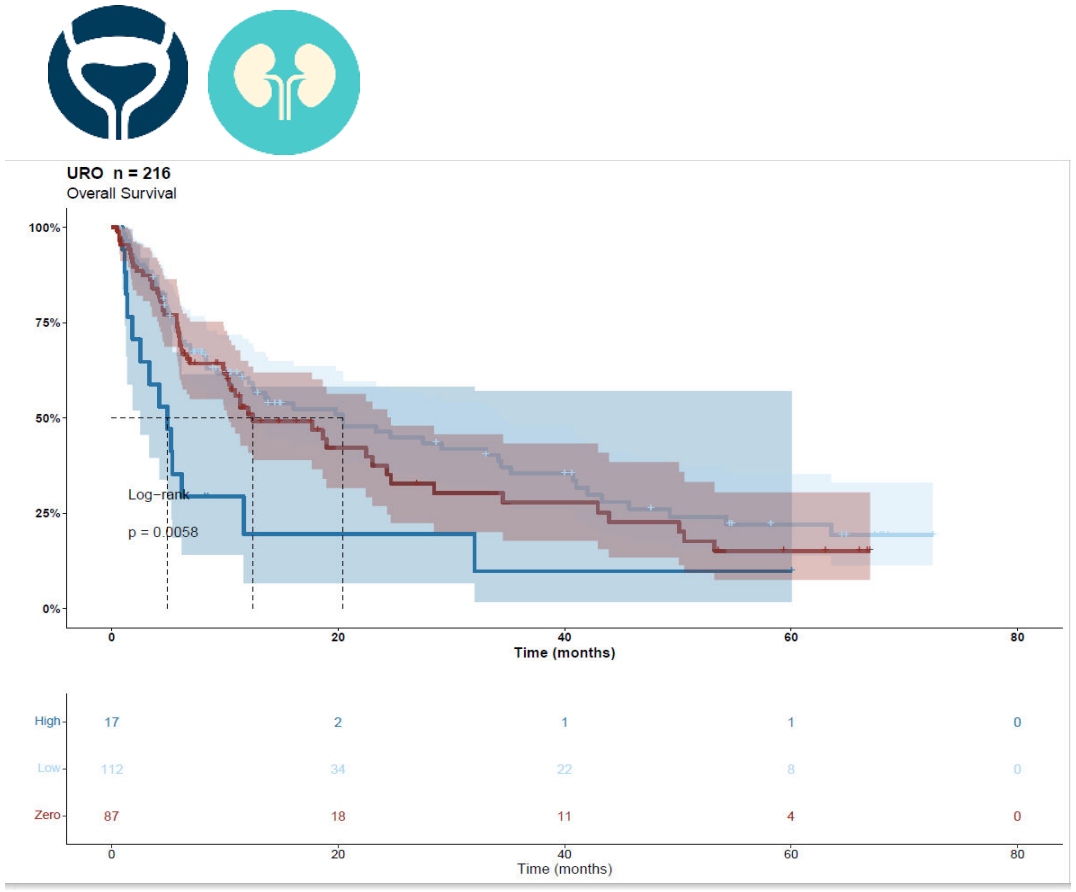
Derosa et al. Nat. Med Feb 2022

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

In urinary tract malignancies, AKK high individuals are at higher risk of mortality

A.





A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

DIAGNOSIS TOOLS FOR DYSBIOSIS TO STRATIFY & ADAPT MICROBIOTA-CENTERED INTERVENTIONS

Early response evaluation:
after therapy initiation
(ORR/RECIST1.1)

αPD-1/CTLA-4 mAbs

SD or PD

Gut dysbiosis-based stratification

Environmental factors
ECOG-PS
BMI
Smoking status
H. pylori

Diet habits

Comedications
Antibiotics
PPIs
Laxatives

Gut microbiota composition
Shotgun/rRNA16S sequencing
Targeted-PCR on specific bacteria

GUT DYSBIOSIS

Microbiota-centered interventions

Antibiotics (-60+42d)

Microbiome protection
Inactivation of ATB in the intestine
(DAV132) (NCT02176005, NCT02917200)

Akk^{NEG}

Single strain
A.muciniphila
(NCT-EV21-01)

Moderate dysbiosis

Prebiotics
Camu-camu or Castalagin
(NCT05303493)

Probiotics or consortia
C.butyricum (CBM588)
(NCT05122546,NCT03829111)

Live bacterial product
(Microbiotica, NCT03637803, NCT03775850, NCT04208958)

Severe dysbiosis or Akk^{HIGH}

FMT or donor-derived microbiome therapeutic
(NCT04116775, NCT05273255,NCT04758507, NCT05251389, NCT04577729, NCT04988841, NCT04975217, NCT05286294, NCT04924374, NCT04729322, NCT04264975, NCT04130763, NCT04521075, NCT04951583, NCT05502913, NCT03686202, NCT03817125)

Pharmacokinetics

Shotgun/rRNA16S sequencing

Targeted-PCR on therapeutic bacteria

End product dosage

Pharmacodynamics

Metabolomics
Metabolite pathways

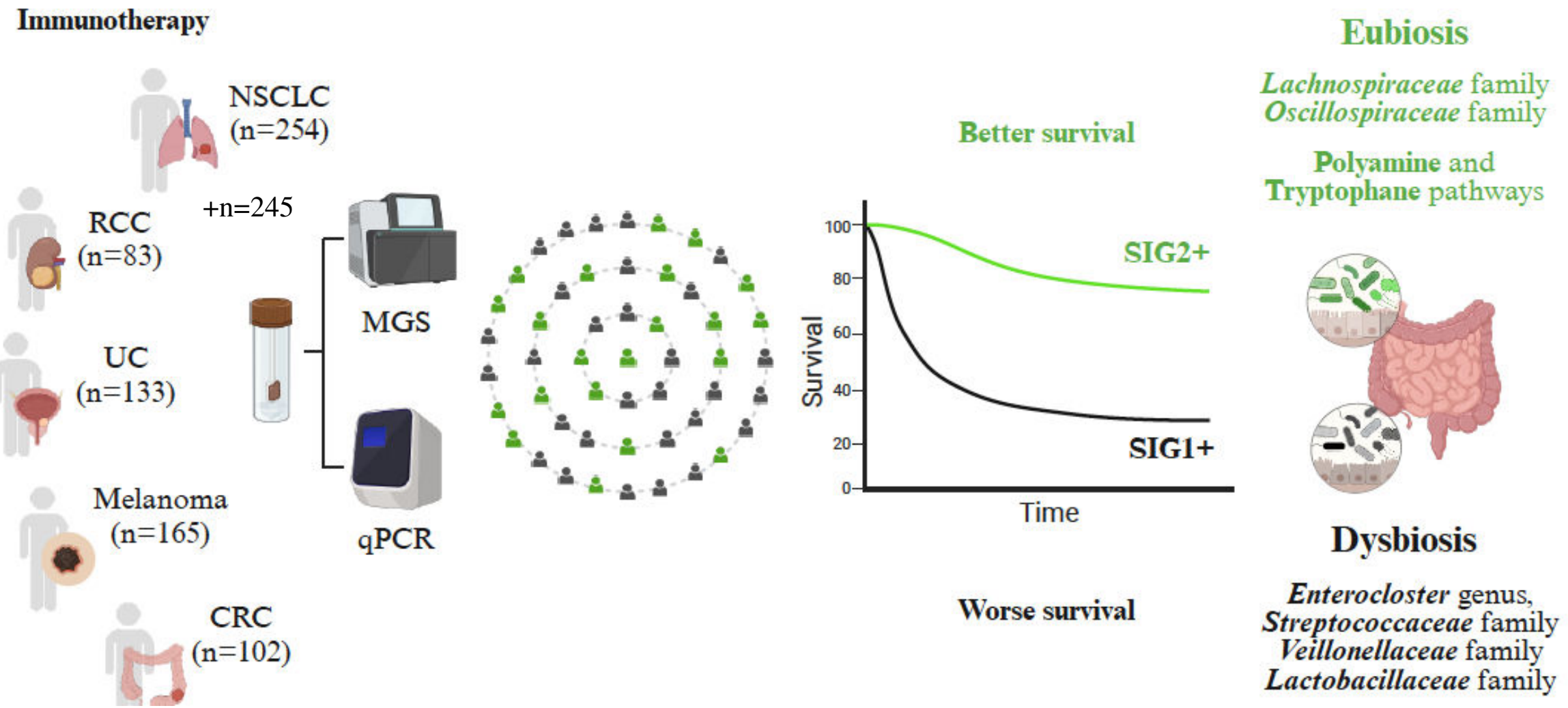
Proteomics
Inflammatory patterns

Immunomics
Therapy-associated IgG/IgA
T cell responses
Flow cytometry, Tumor landscape

Intestinal barrier function
sCD14, ST2, sMAdCAM-1
S100A8/A9

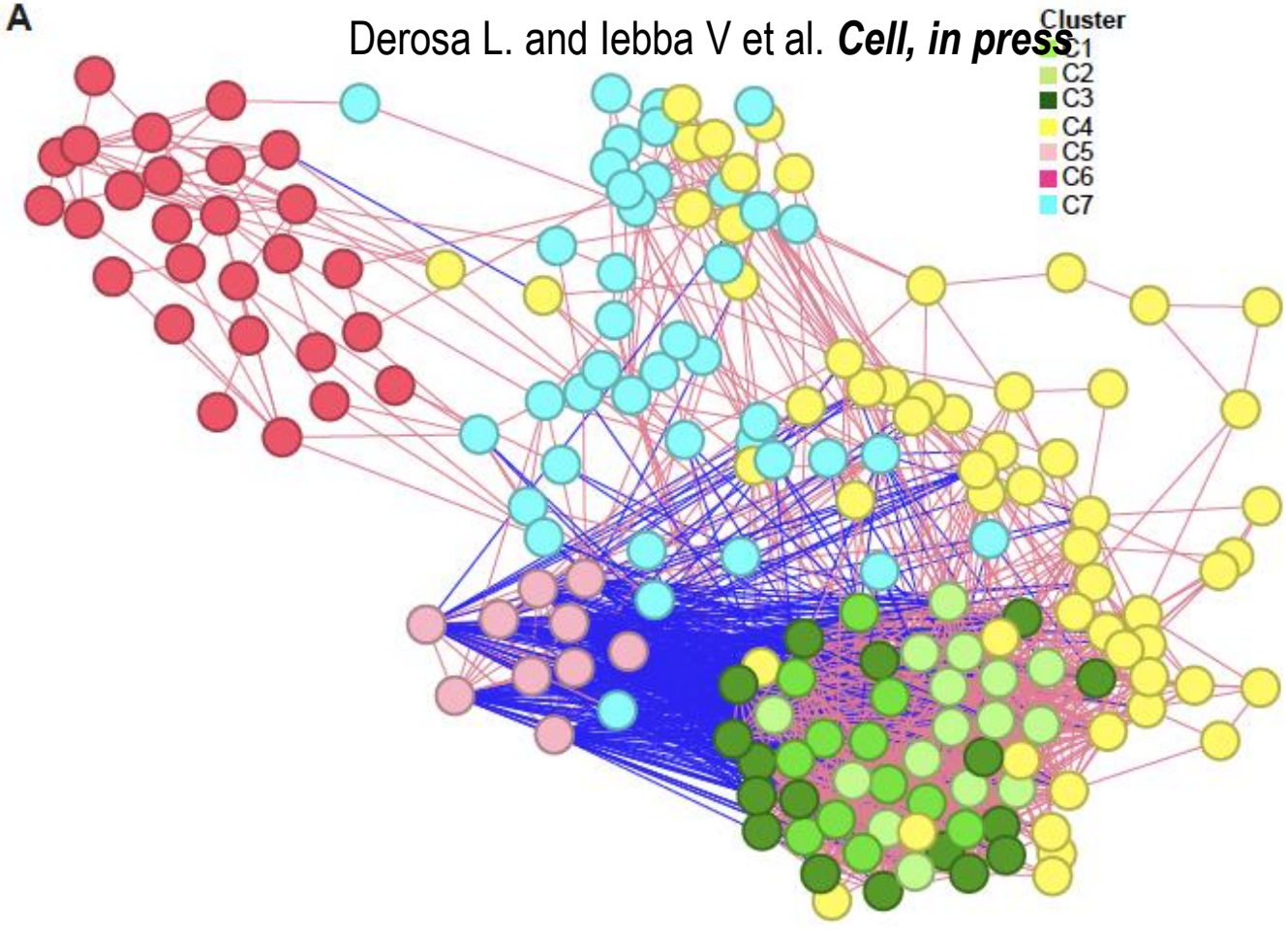
A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

THE TOPOSCORE IS BORN: DEROSA L. and IEBBA V. et al. Cell, in press



ECOSYSTEM COMMUNITY STRUCTURAL ORGANIZATION AND THE DEGREE TO WHICH SUCH FORCES INTERACT IN LONG-TERM RESPONDERS (R) OR NON-RESPONDERS (NR)

Derosa L. and Iebba V et al. ***Cell, in press***



We build intestinal communities (called species interacting groups (SIG)) as follows:

- Each MGS was categorized as either **"low" or "high" based on the median** of its relative abundance in the whole population of 245 subjects. For those MGS that had a majority of null abundances, the MGS were categorized as **"present" or "absent"**
- Cox proportional hazard (CoxPH) models were run to select **MGS associated with an elevated or reduced overall survival (OS)** with a hazard ratio (HR) ≤0.80 or ≥1.25.
- Among the **536 MGS** identified in the discovery cohort, a total of **266 MGS** was retained in the model. Then, **a score proportional to the significance of the interaction between two MGS** ($-log_{10}(p)$) was defined as negative in case of co-exclusion pattern (OR < 1) or positive in case of co-occurrence (OR > 1) ((Fisher's exact test on 2x2 contingency tables based on their absence/presence co-occurrences and scored by the by $-log_{10}(p) \times sign(OR - 1)$ metrics, where p is the Fisher p-value and OR, the Odds Ratio). Interactions with a Bonferroni-corrected p-value ≤ 0.05 were retained for analysis
- A total of **180 connected MGS were then clustered** with Ward's method and Manhattan distance, resulting in the identification of 7 clusters (C1 to C7)
- **Two clusters (C5 and C6) contained 37 MGS**, mostly (95%) **associated with OS<12** (HR ≥ 1.25) that were used to define the SIG1 signature.
- **Three clusters (C1, C2, C3) that contained 45 MGS all associated with OS>12 months** (HR ≤ 0.80) were compounded into the SIG2 signature

Immunotherapy

Enterocloster genus,
Streptococcaceae family
Veillonellaceae family
Lactobacillaceae family

SIG1
37 unfavorable bacteria

Species interacting groups (SIGs)

NSCLC
(n=245)

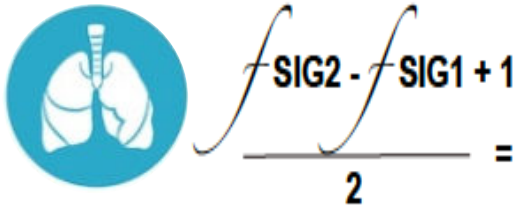
Shotgun metagenomics
sequencing

Lachnospiraceae family
Oscillospiraceae family

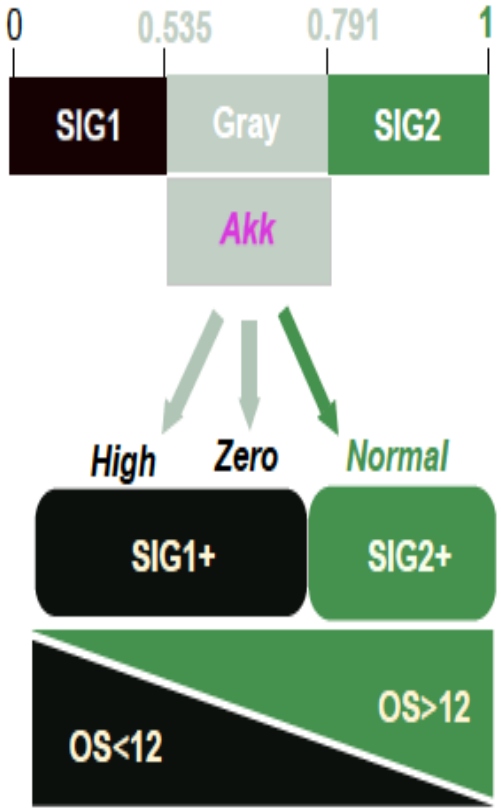
45 favorable bacteria

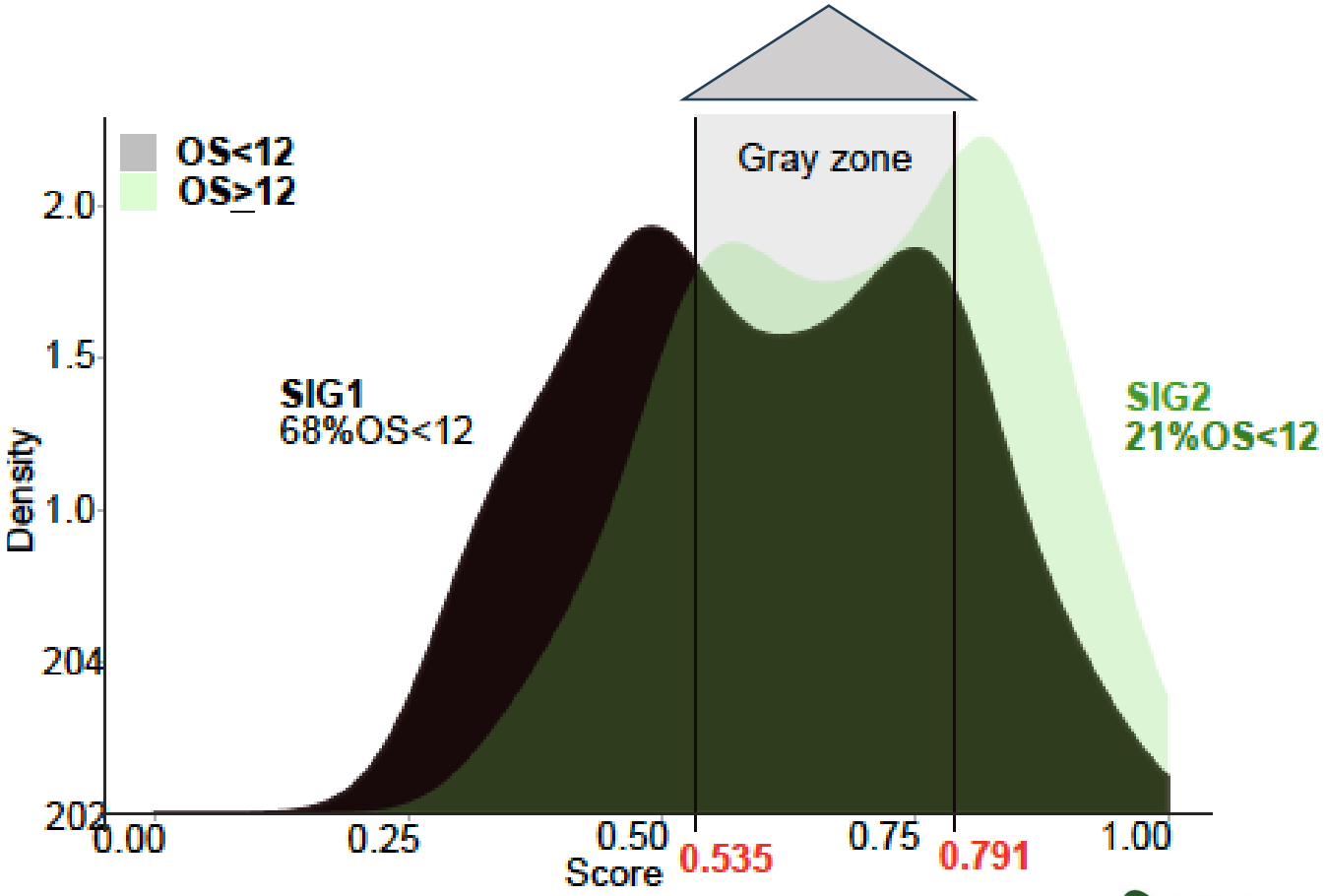
DISCOVERY COHORT OF 245 NSCLC patient-derived stools

The distribution of the S score is depicted by means of Kernel density estimation (KDE). Gray zone teased apart using bacteria with trichotomic distribution (*A. senegalensis, B. caccae, A. muciniphila*)

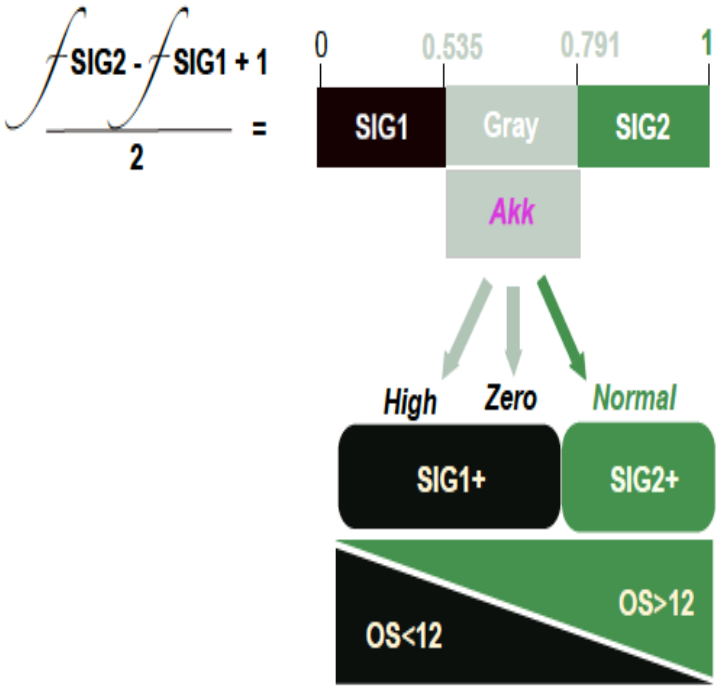


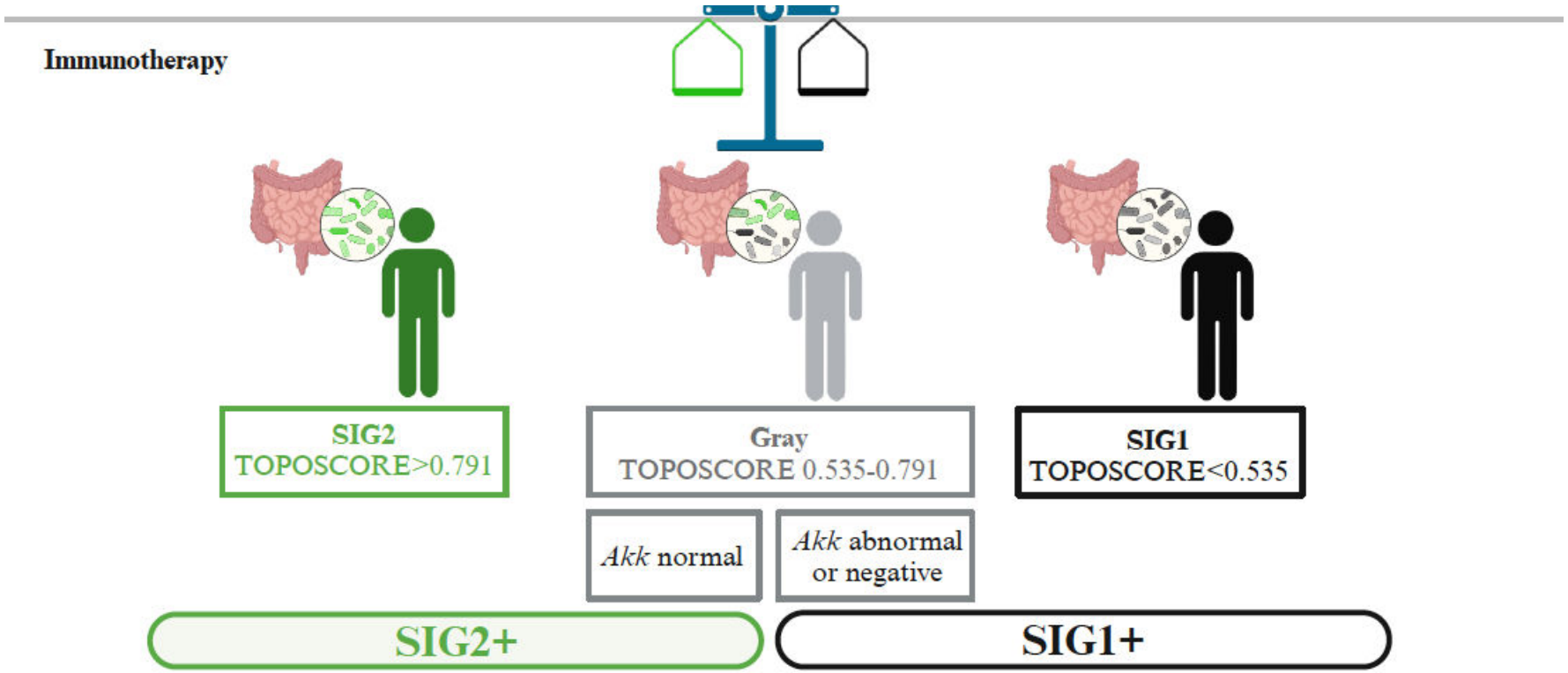
$$\frac{\int SIG2 - \int SIG1 + 1}{2} =$$





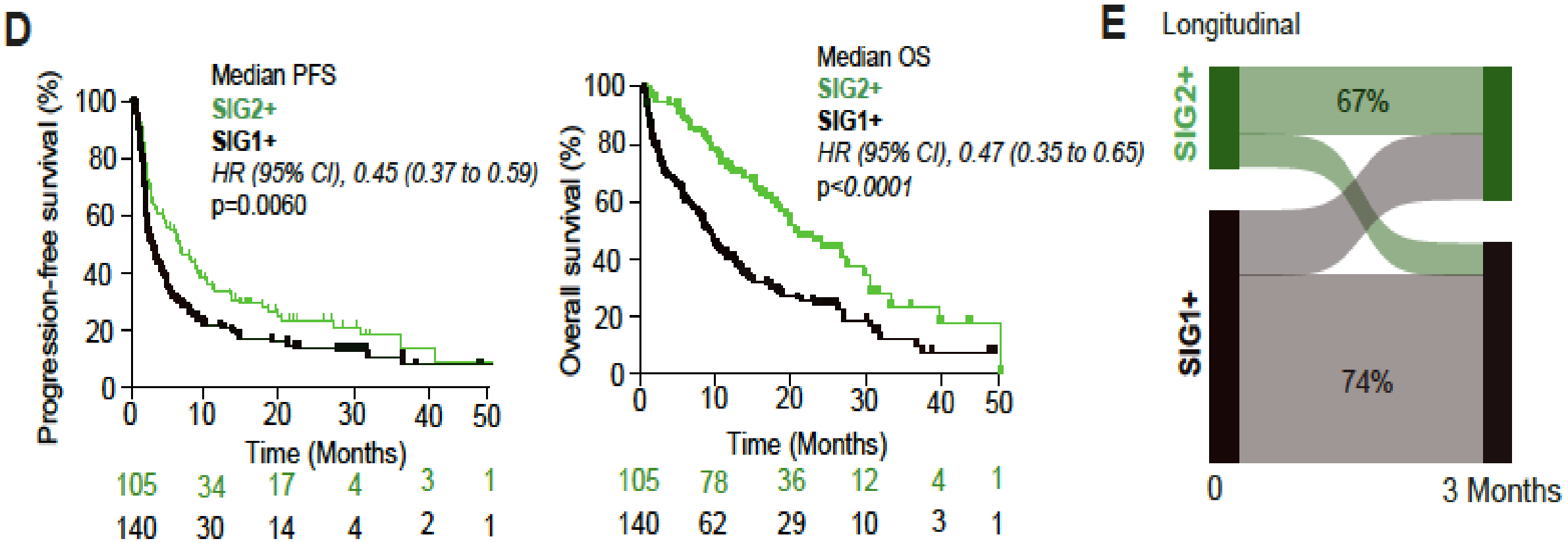
FINAL STOOL CLASSIFICATION BASED ON THE DICHOTOMIC SIG1+ VERSUS SIG2+





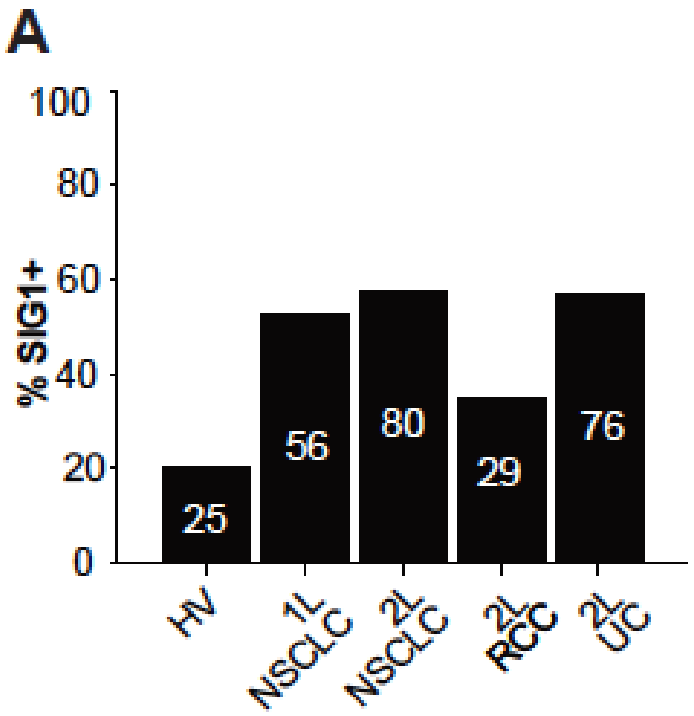
SIG2+ PATIENTS HAVE A BETTER PFS AND OS THAN SIG1+ NSCLC PATIENTS

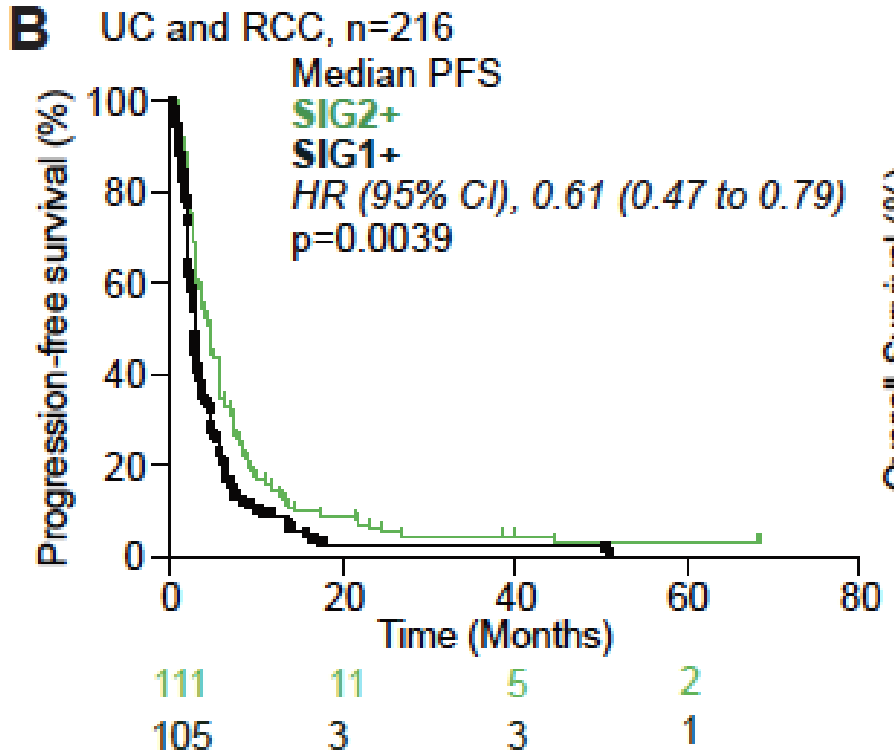
Discovery cohort N=245 but also Validation cohort (N=254)

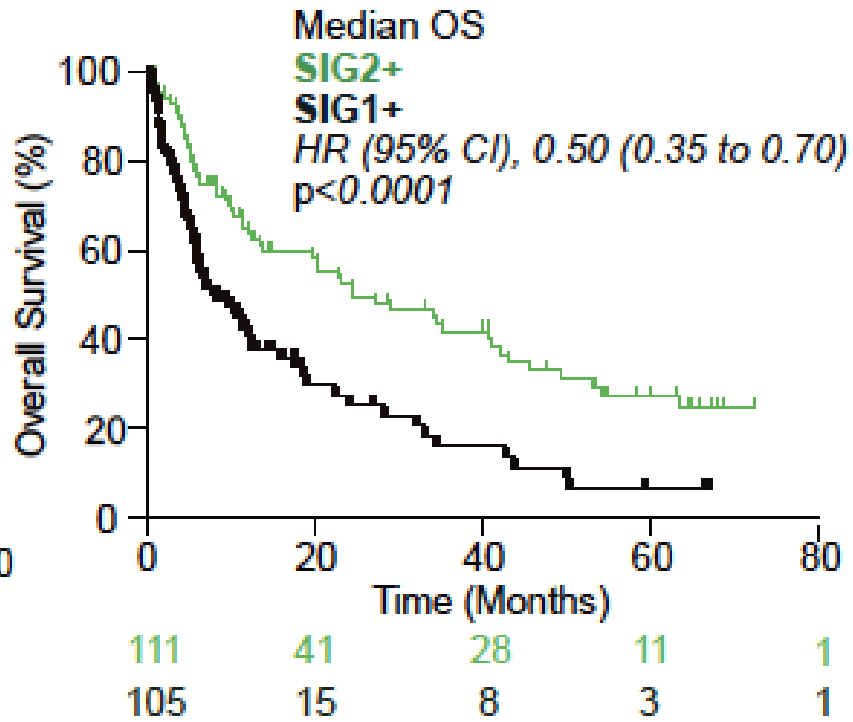


UROTHELIAL CANCER AND KIDNEY CANCER PATIENTS: N=216

Better PFS and overall survival in 1st or 2nd line PD1 blockade in SIG2+ individuals





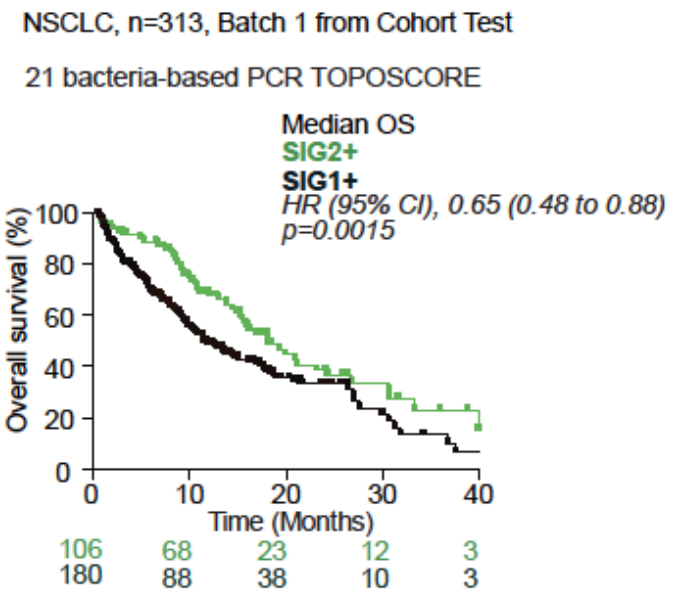


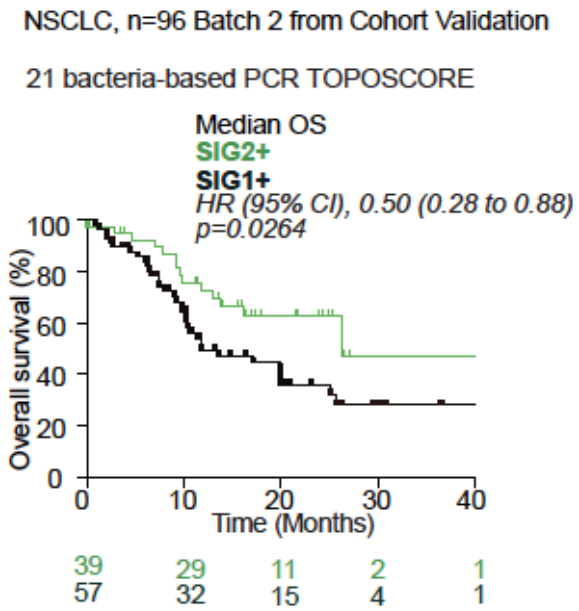
48 hr-turn around diagnosis tool for gut dysbiosis?
DOWNSCALING THE NUMBER OF CLINICALLY SIGNIFICANT BACTERIA PCR_TOPOSCORE

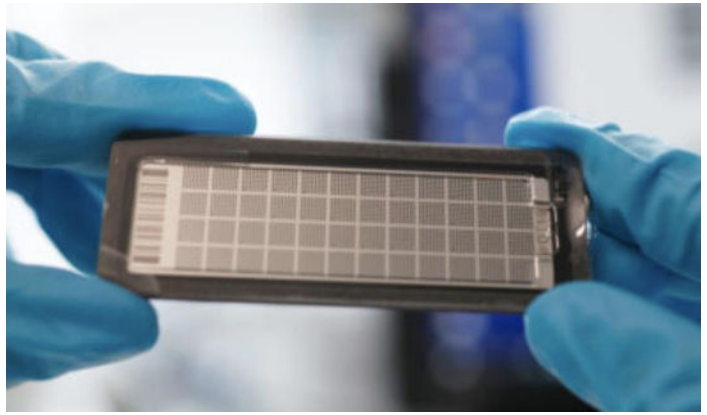
Bio-Me
Microbiome Profiling

To transform the 83 metagenomics-based -TOPOSCORE into a 21 PCR-based **friendly-user test**

- Using the most prevalent MGS species (Park et al. 2022) as well as reliable and robust probe sets (designed by Bio-Me)



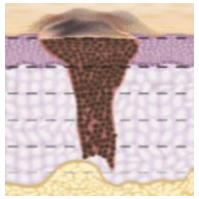


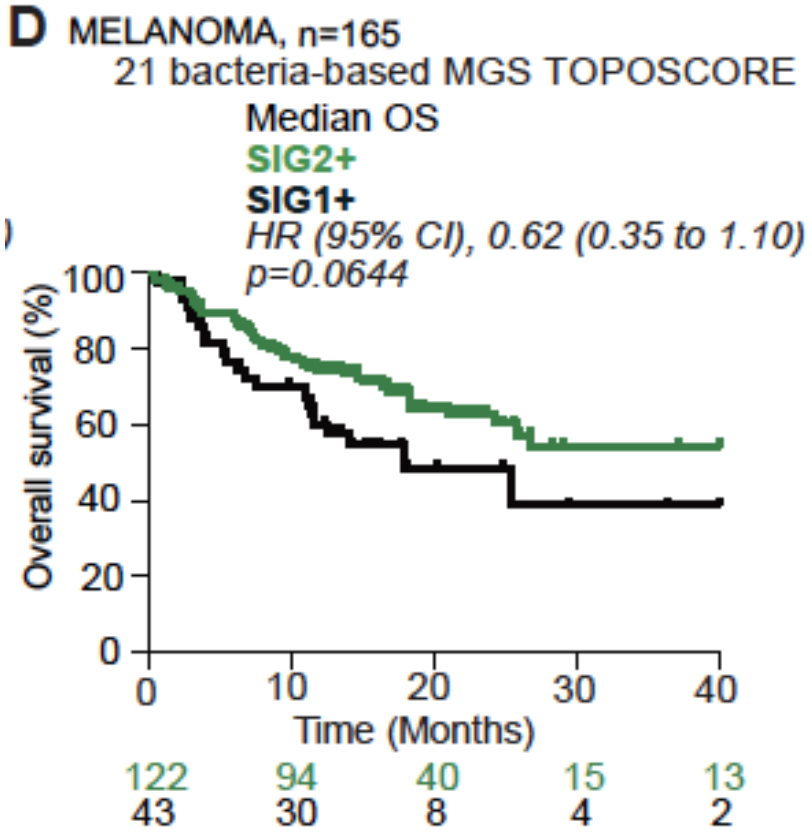


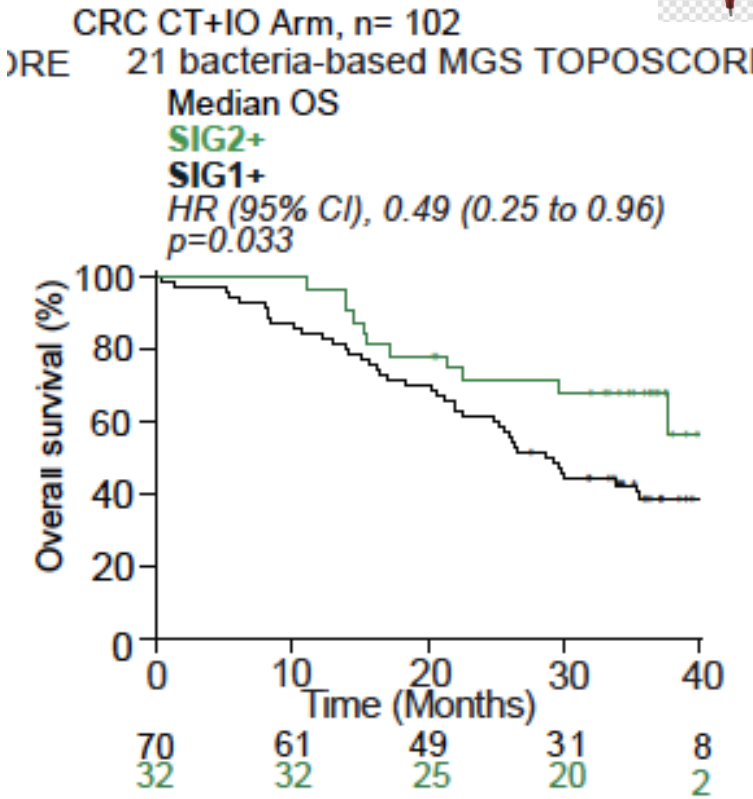
Derosa L. and Iebba V et al. Cell, in press

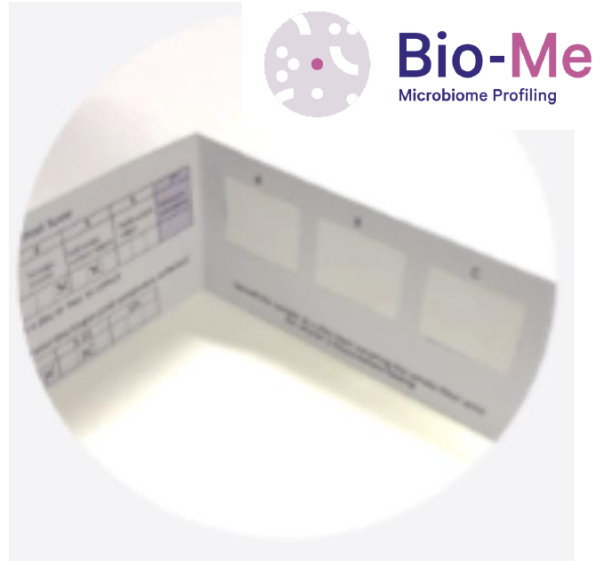
A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

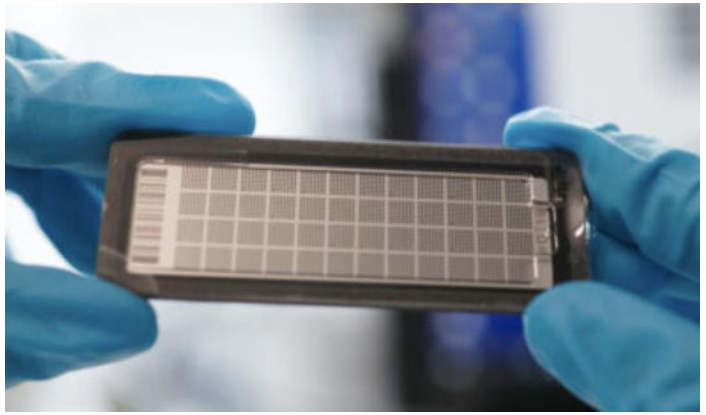
PCR-BASED TOPOSCORE APPLIED TO MELANOMA AND COLORECTAL CANCERS (ATEZOTRIBE TRIAL)





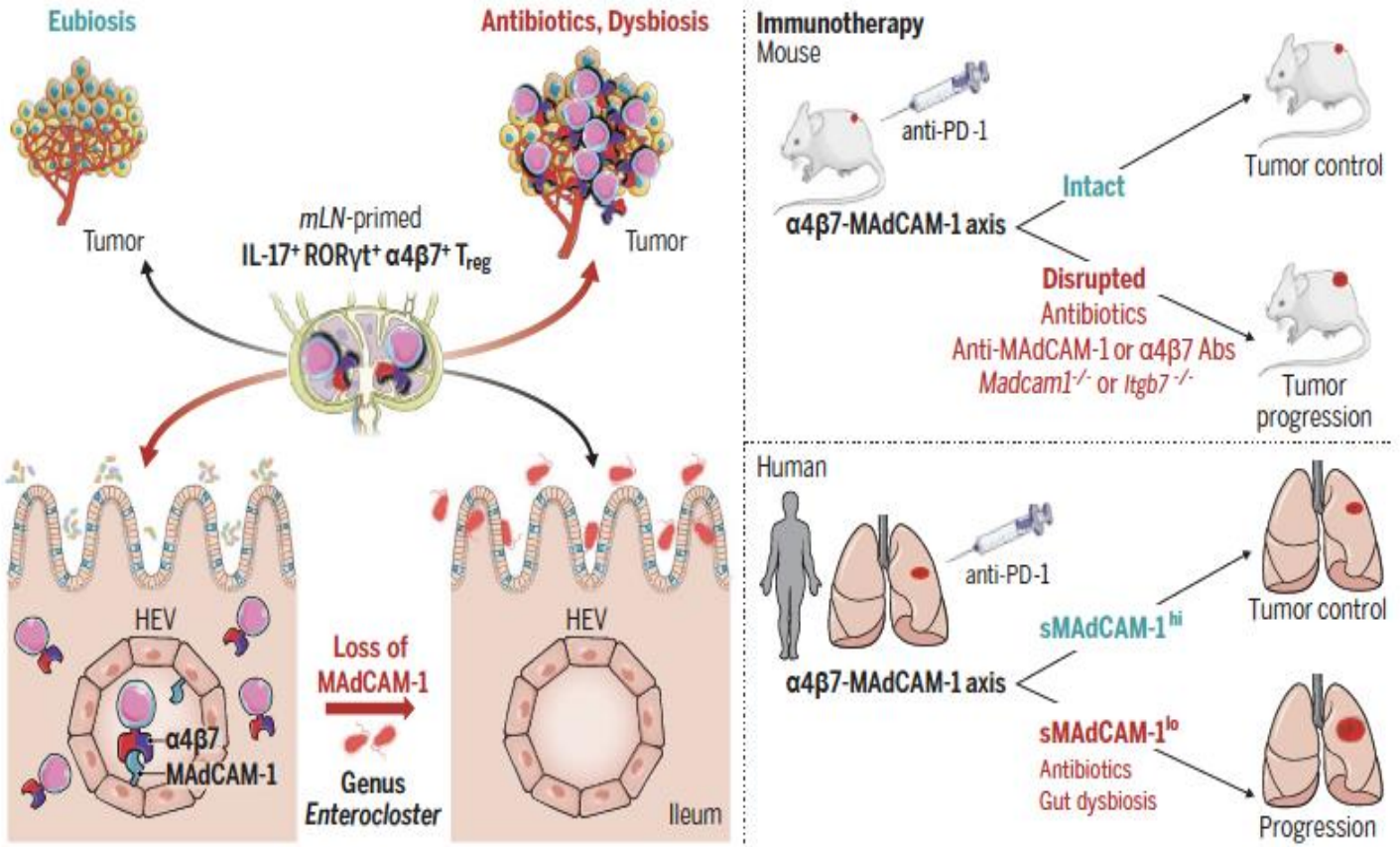




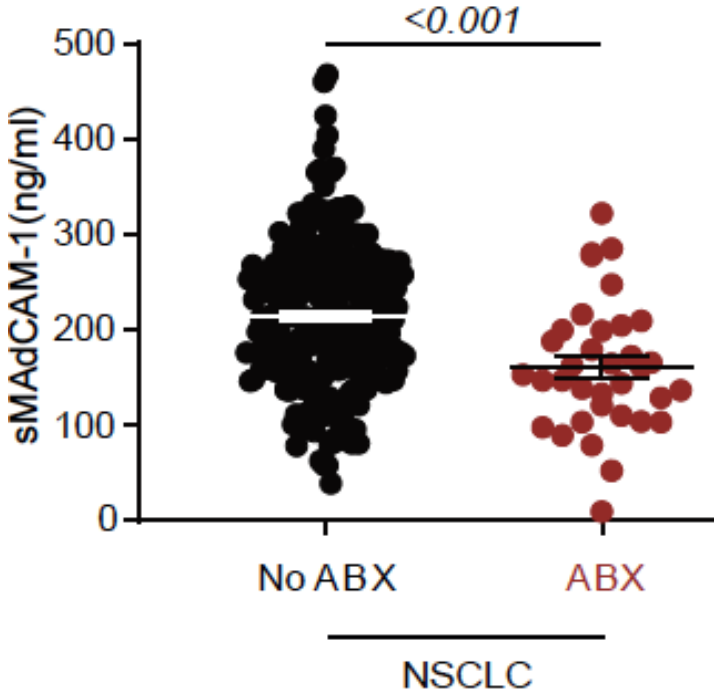


MADCAM-1: GUT IMMUNE CHECKPOINT FOR CANCER IMMUNOSURVEILLANCE

MAdCAM-1 as a gut immune checkpoint for cancer immunosurveillance. Bacteria from the genus *Enterocloster*, for example, after discontinuation of ABX, induce the down-regulation of MAdCAM-1 in the ileal lamina propria and mLNs, inducing the exodus of the immunosuppressive α4β7$^+$ T_{reg}17 cells from the gut to cancers and tdLNs. Disruption of the MAdCAM-1–α4β7 axis compromises the efficacy of immunotherapy in mice and patients.

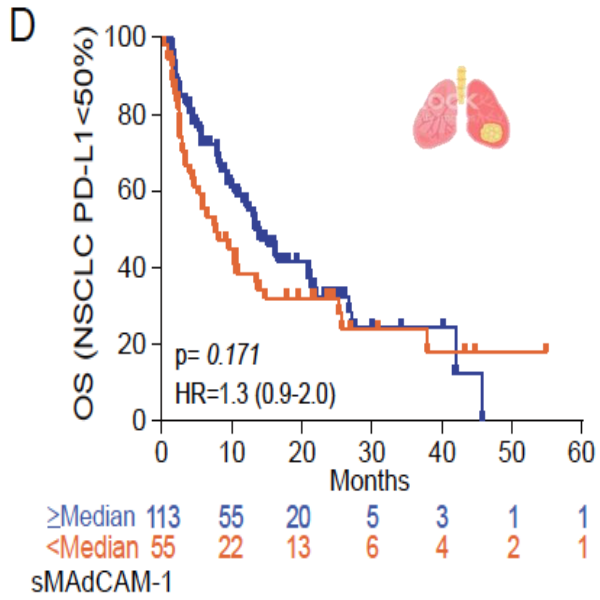


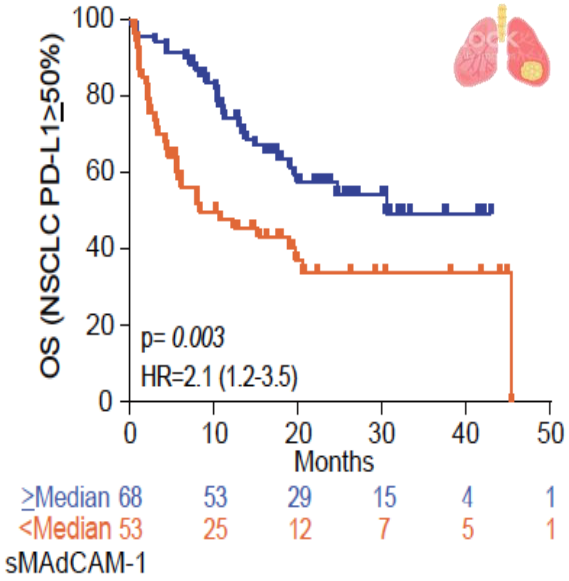
SERUM

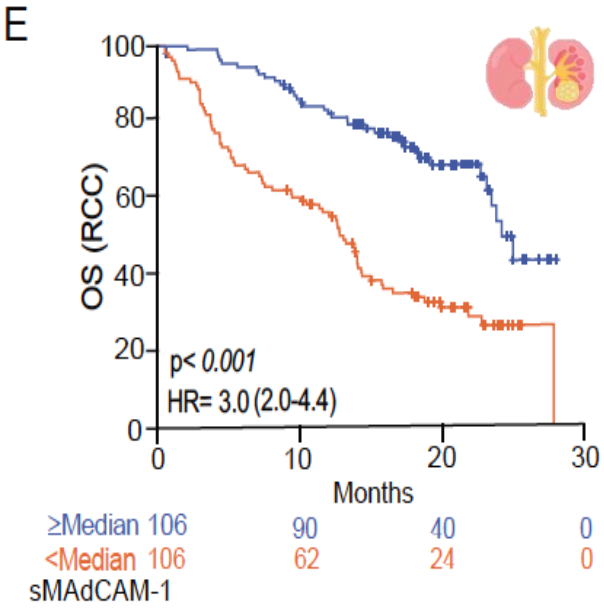


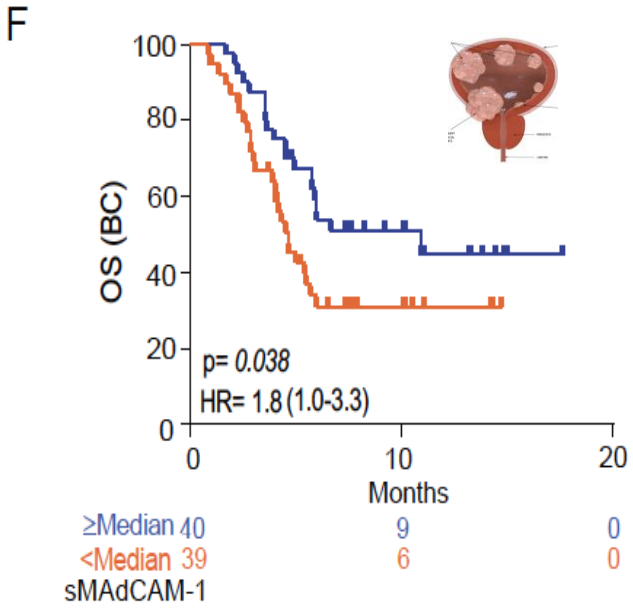
A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

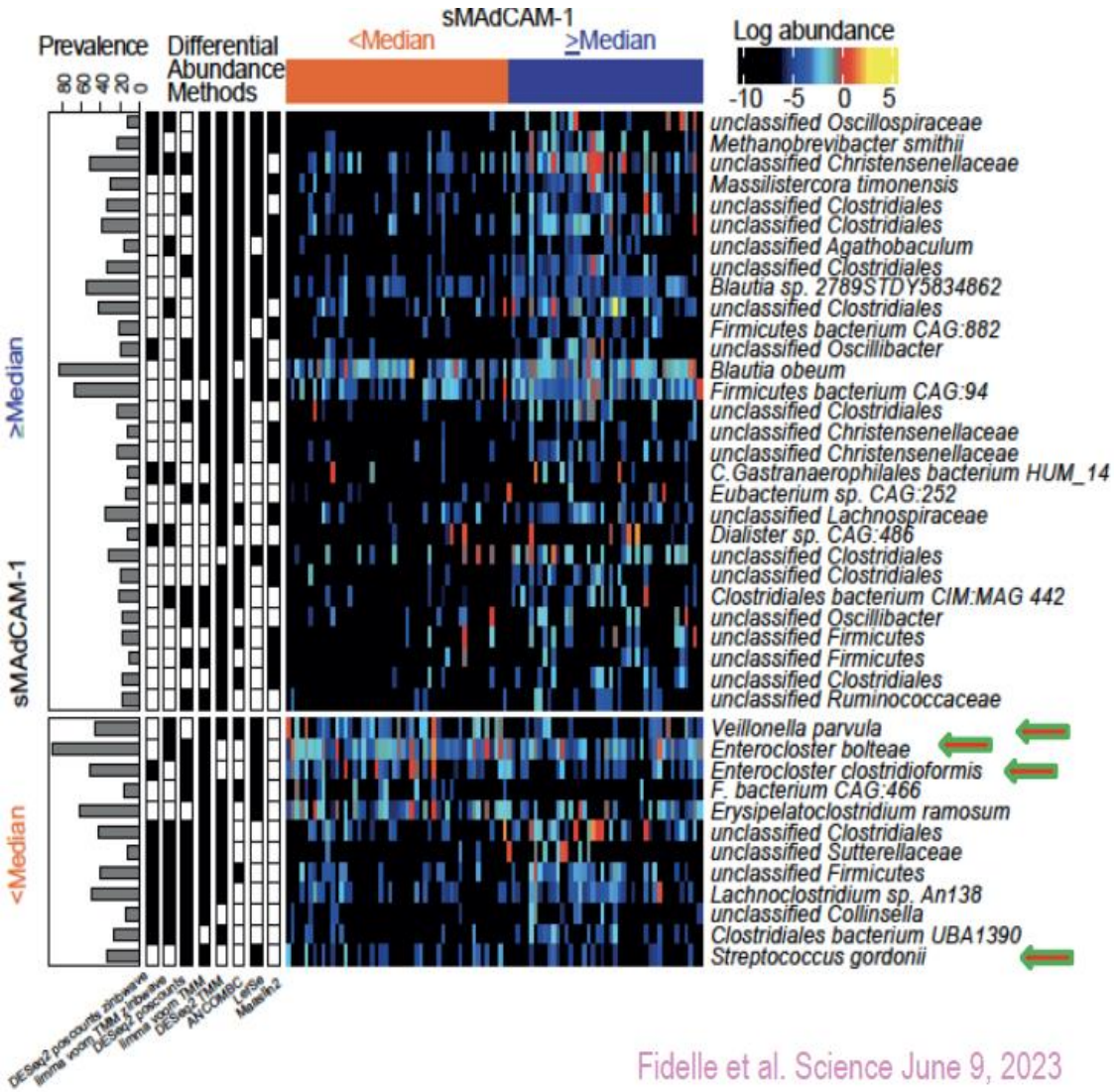
SERUM SOLUBLE MADCAM_1 CORRELATES WITH GUT DYSBIOSIS AND PREDICTS SURVIVAL







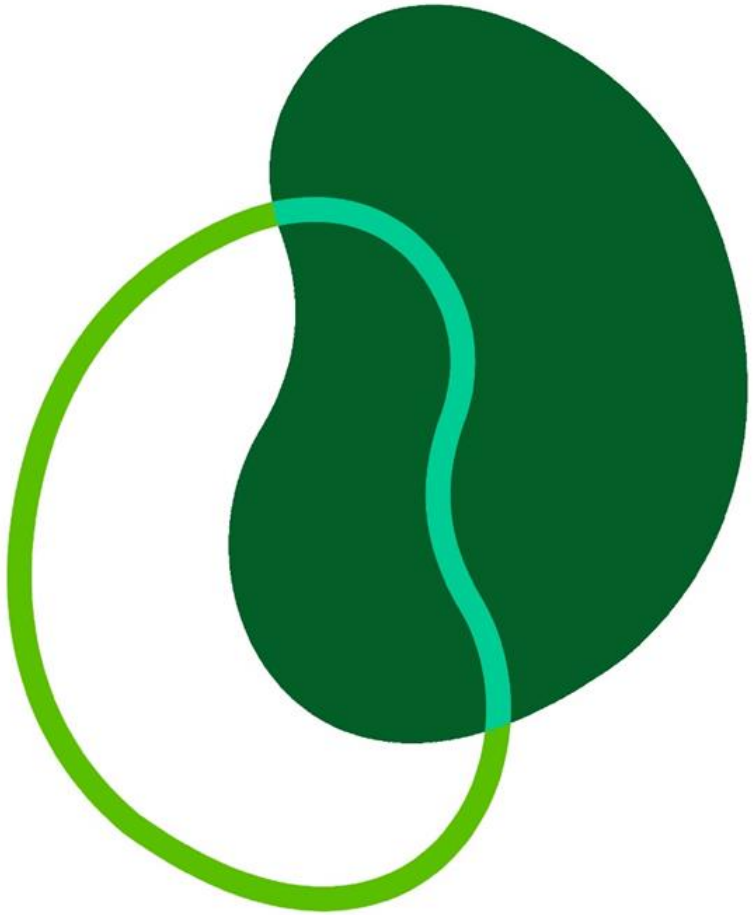




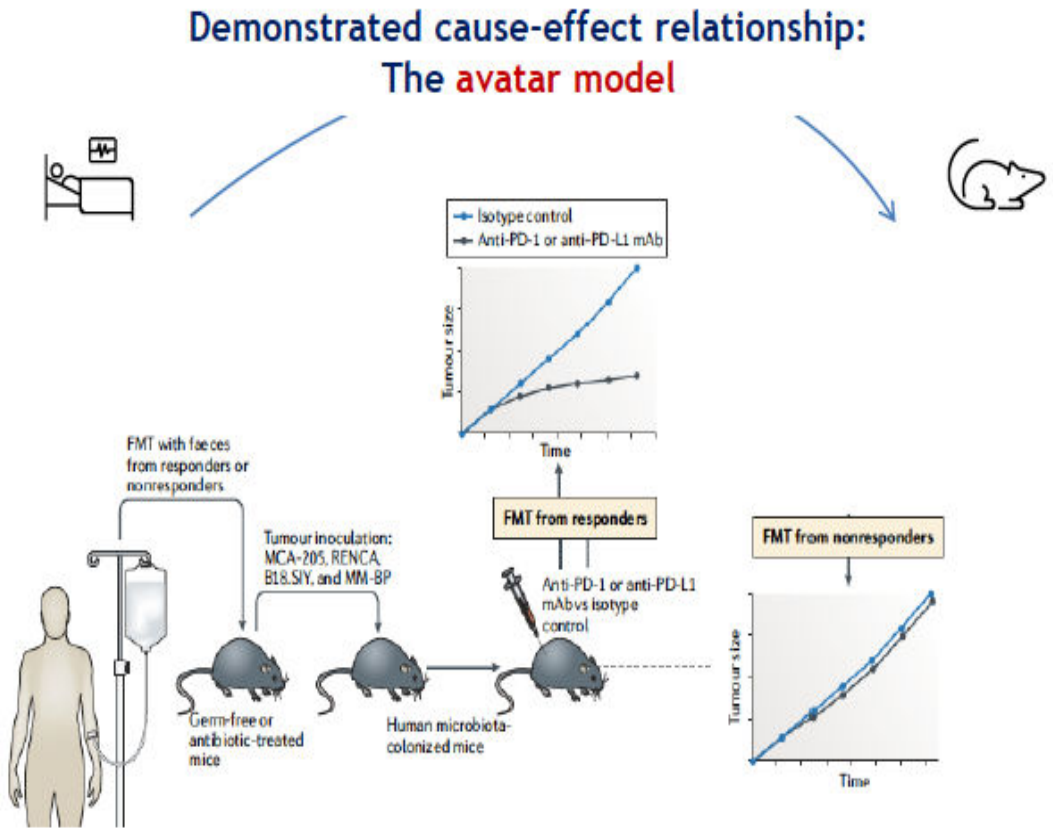
Fidelle et al. Science June 9, 2023

17e Rencontre Patients de l'Association A.R.Tu.R.

PART4: Microbiota-centered interventions

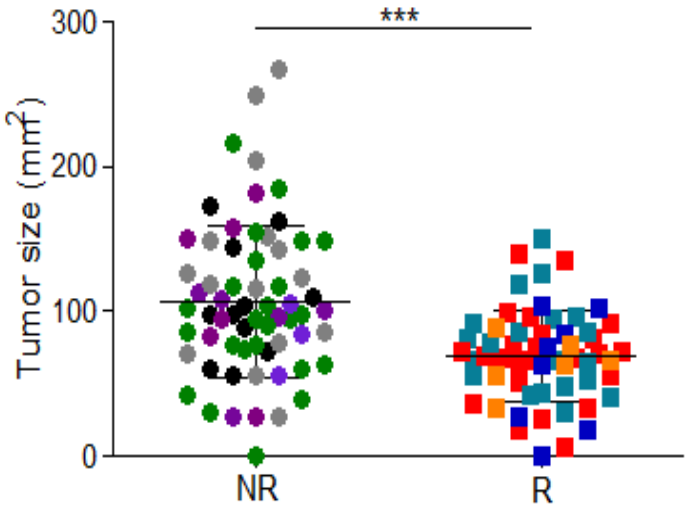


CAUSE-EFFECT RELATIONSHIP: IMMUNOGENIC COMMENSALS
CIRCUMVENT DYSBIOSIS-RELATED RESISTANCE TO PD1



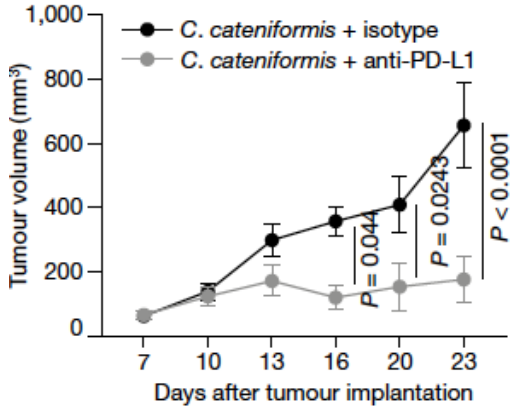
Routy et al. Nat Rev Clin Oncol. 2018 Jun;15(6):382-396.

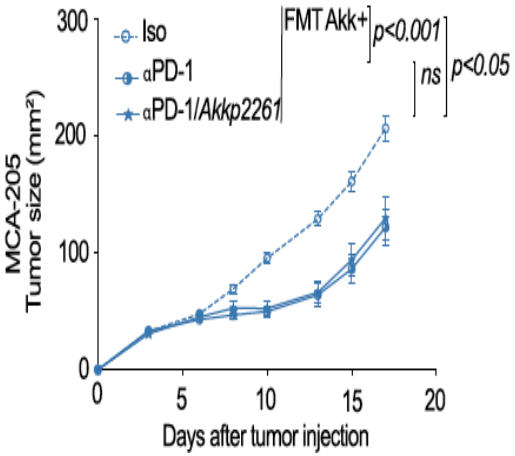
Anti-PD1 Ab-treated



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.





Derosa et al. Nat. Med Feb 2022

THE FUTURE IS BRIGHT

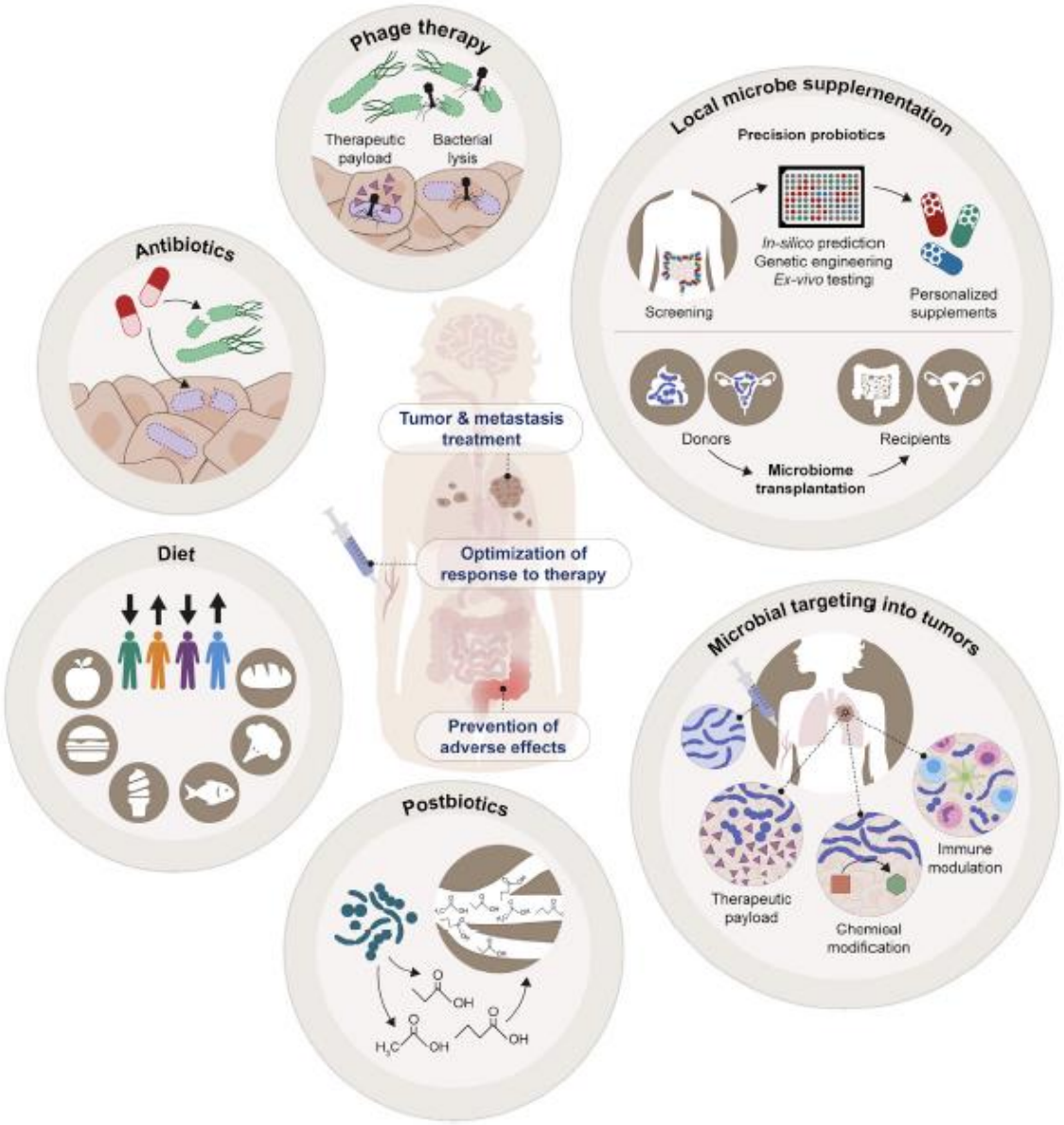


Table 1. Overview of current clinical studies investigating the effects of microbiome modulations in cancer therapies

Intervention	Cancer therapy	Cancer entity	Study phase	Endpoint	Reference
Fecal microbiota transfer (FMT)	Immune checkpoint inhibition	NSCLC, melanoma	Phase II	Therapy response	NCT04951583
	Immune checkpoint inhibition	Prostate cancer	Phase II	Therapy response	NCT04116775
	Immune checkpoint inhibition	CRC	Phase I	Therapy response	NCT04729322
	Immune checkpoint inhibition	RCC	Phase II	Therapy response	NCT04758507
	Immune checkpoint inhibition	Melanoma, NSCLC, GU cancer	Phase I	Toxicity	NCT03819296
	Immune checkpoint inhibition	GU cancer	Phase I	Toxicity	NCT04038619
	Immune checkpoint inhibition	Melanoma	Phase II	Response	NCT04577729
	Allo-HCT	Hematologic cancer	Phase II	Toxicity (GVHD)	NCT03812705
	Allo-HCT	Hematologic cancer	Phase II	Toxicity (infections)	NCT03678493
Microbial ecosystem therapeutics (MET-4)	Immune checkpoint inhibition	Solid tumors	Phase I	Response	NCT03686202
Probiotic (Bifidobacteria)	Immune checkpoint inhibition + chemotherapy	NSCLC	Phase I	Toxicity, surgical complications	NCT04699721
	Chemotherapy	CRC	Phase II	Therapy response	NCT04131803
Probiotic (*Clostridium butyricum*)	Immune checkpoint inhibition	RCC	Phase I	Safety	NCT03829111
	Allo-HCT	Hematologic cancer	Phase I	Toxicity	NCT03922035
Prebiotic (Fiber)	Immune checkpoint inhibition	Melanoma	Phase II	Safety	NCT04645680
	Chemotherapy	Gastrointestinal cancers	Phase II	Toxicity	NCT04447443
	Radiotherapy	Gastrointestinal and GU cancers	Phase III	Toxicity	NCT04534075

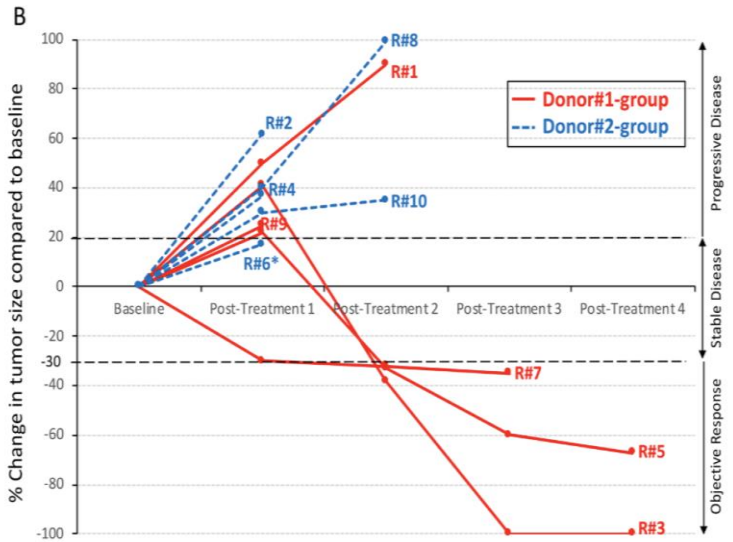
Derived from clinical trials registry of the NIH Library of Medicine. allo-HCT, allogeneic hematopoietic cell transfer; CRC, colorectal cancer; GU, genitourinary; RCC, renal cell carcinoma; MET, defined mixture of pure live cultures of intestinal bacteria isolated from a stool sample of a healthy donor; NSCLC, non–small-cell lung cancer.

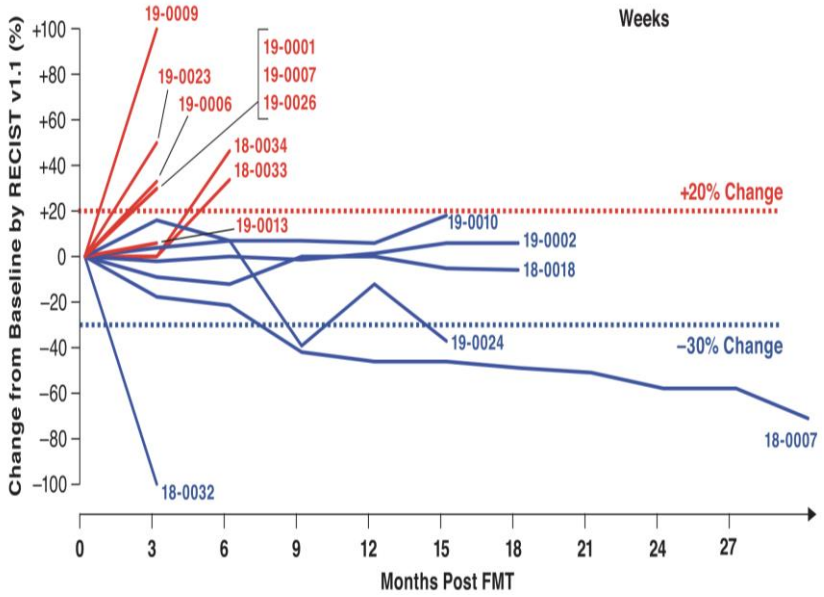
A.R.Tu.R. Association pour la Recherche sur les Tumeurs du Rein

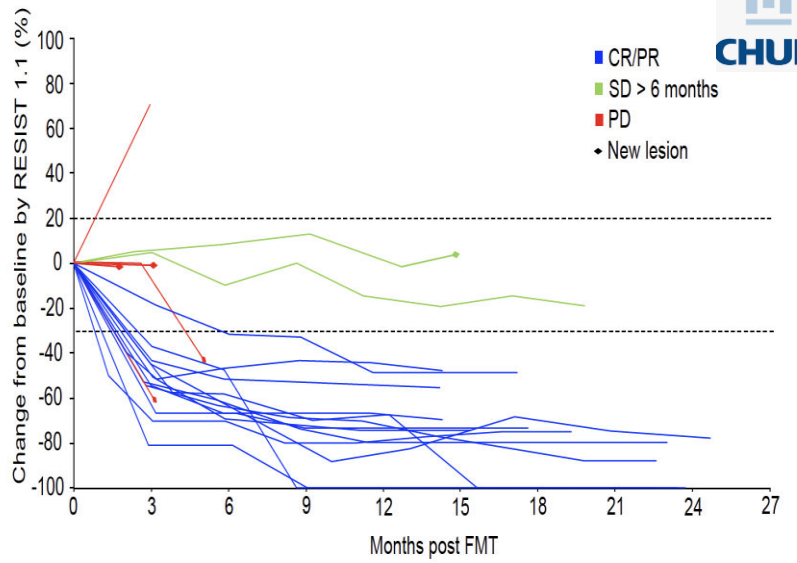
FECAL MICROBIAL TRANSPLANTATION ameliorates 1L objective response rates (by 20%) and circumvent primary resistance to PD1 blockade in about 30% MM.

Feces from cancer patients benefiting from αPD1 Ab

Feces from healthy voluntee







EN Baruch et al.
Science 2021 Feb 5;371(6529):602-609.
N=10 patients with anti-PD-1-refractory metastatic melanoma
1CR+ 2PR

D. Davar et al.
Science 2021 Feb 5;371(6529):595-602.
N=15 patients with anti-PD-1-refractory metastatic melanoma
1CR+2PR+3SD

Routy et al.
Nature Med. In press
N=20 naïve metastatic melanoma
Disease control rate = 15/20 (75%
ORR: CR + PR =13/20 (65%)

FIRST PROOF OF CONCEPT OF THE EFFICACY OF THE MICROBIOTA-CENTERED THERAPEUTIC INTERVENTION: FMT FROM R INTO NR MELANOMA PATIENTS

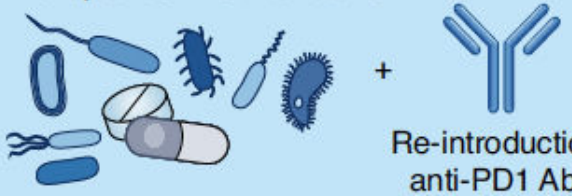
Bullman S et al. Nature Cancer 2021

CHUM

LUMINATE TRIAL

NATURE CANCER | VOL 2 | DECEMBER 2021 | 1301–1304 | www.nature.com/natcancer

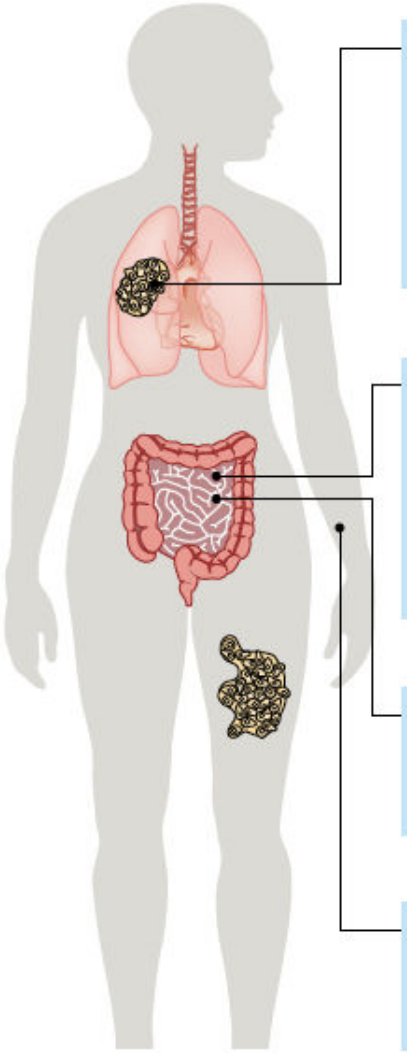
Therapeutic interventions



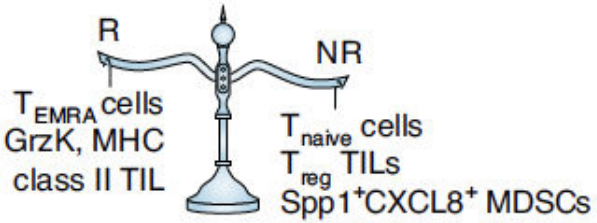
Re-introduction: anti-PD1 Abs

Pharmacokinetics of the MCI
Immunomics and single-cell transcriptomics
Serial metagenomics
Metabolomics
Serum cytokine/chemokine multiplex ELISA

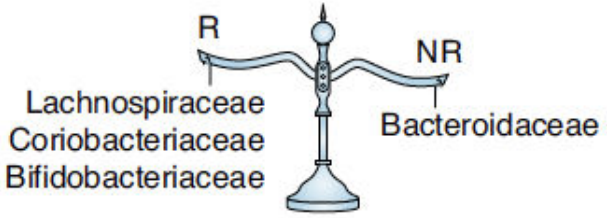
Clinical data
n = 26 patients (1 excluded), stage IV, 2nd- to 4th-line therapies
Resistant to PD-1 + CTLA-4 blockade
Safety (23 grade 1-2; 3 grade 3)
Efficacy (1 CR, 5 PRs, 3 SDs)



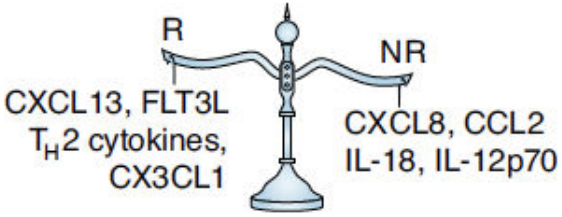
Reprogramming systemic immunity and TME
TILs and CTLs (lytic machinery, innate receptors, IFNγ, CD74, MHC class II…)
Myeloid cells (IL-8$^+$)
CTL/T_{reg} cell ratio
Blood CD56$^+$CD8$^+$TIGIT$^+$Lag3$^+$T-bet$^+$T cells



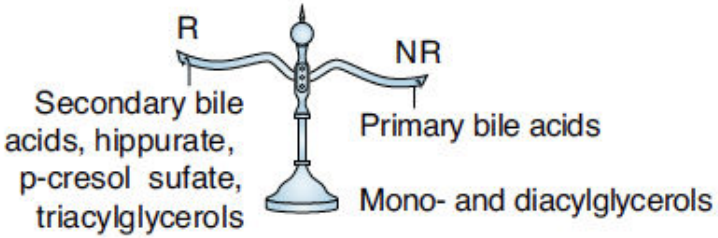
Recipient intestine
Infiltration of lamina propria by CD68$^+$ M2 macrophages GrzB$^+$ MAIT cells in blood
Rise in donor bacteria–specific IgG serum titers
Metagenomics-based shift in the taxonomic composition toward donor stool



Intestinal barrier dysfunction
Reduction in serum inflammatory mediators
Rise in TLS-associated chemokines



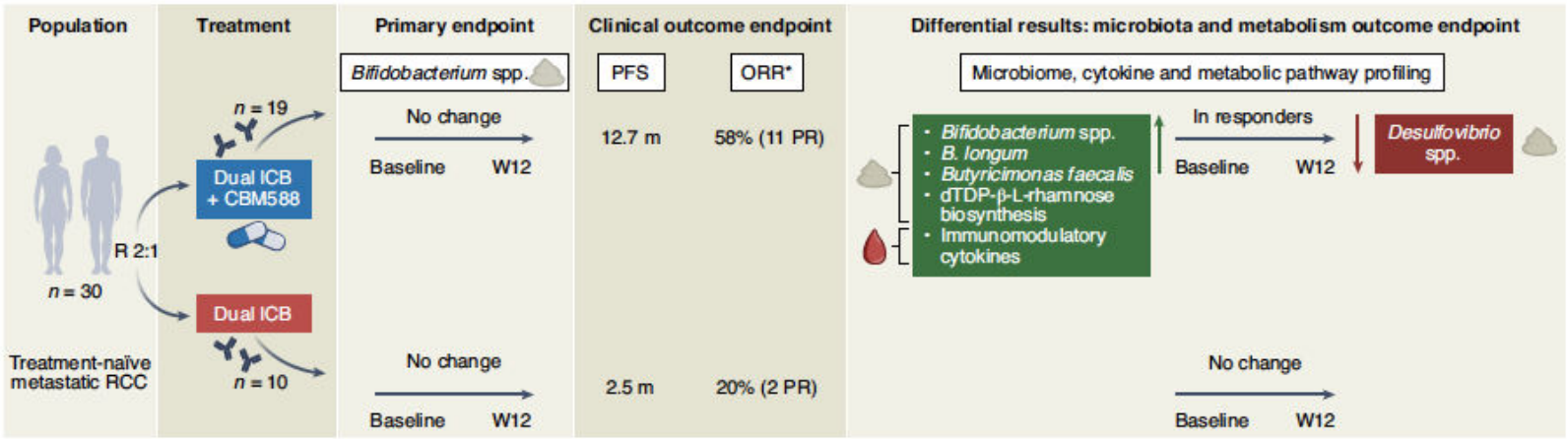
Host metabolism
Metabolomics of plasma
Specific metabolites and lipids



RANDOMIZED PHASE I TRIAL IN ADVANCED RCC: Clostridium butyricum MYAIRI

Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial

Nazli Dizman[1,2,8], Luis Meza[1,8], Paulo Bergerot[3,8], Marice Alcantara[4], Tanya Dorff[1], Yung Lyou[1],



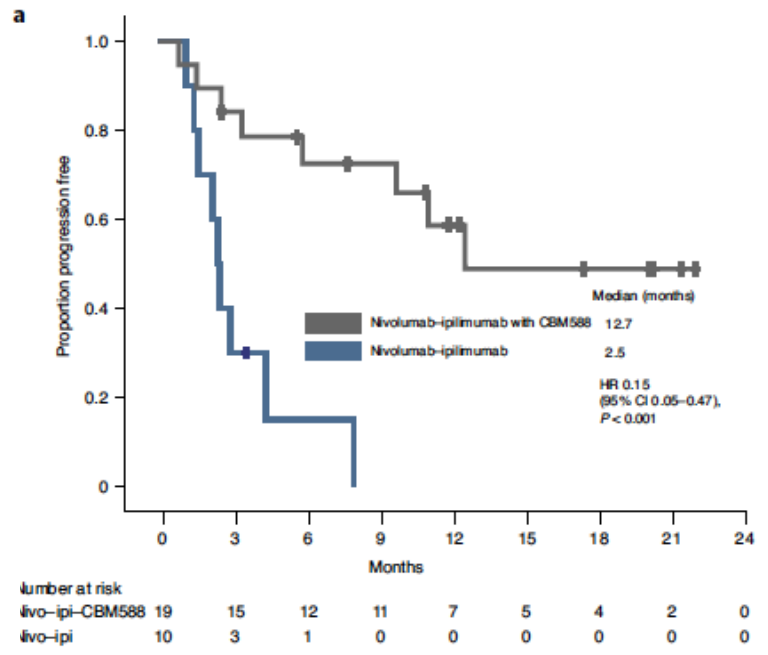
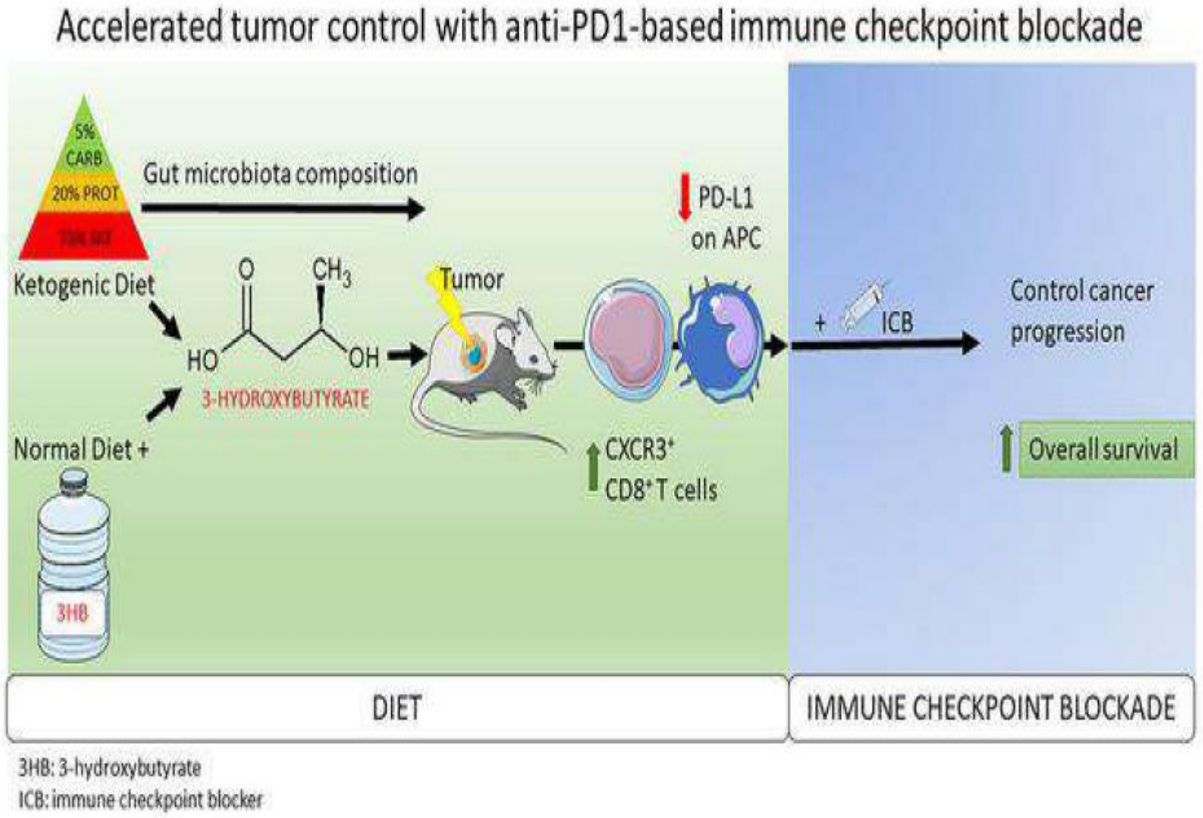


Fig. 1 | First randomized phase 1 trial combining a probiotic strain (*C. butyricum* CBM588) with a nivolumab plus ipilimumab regimen in metastatic kidney cancer. Primary endpoints were change in Shannon index and metagenomics-based enrichment in *Bifidobacterium* strains; secondary endpoints were change in median progression-free survival (PFS), objective response rates (ORR), and metabolic and immunological changes between baseline and week 12 (W12). m, months; PR, partial response; *, no significant difference.

A. ESMOR.
Association pour la Recherche sur les Tumeurs du Rein

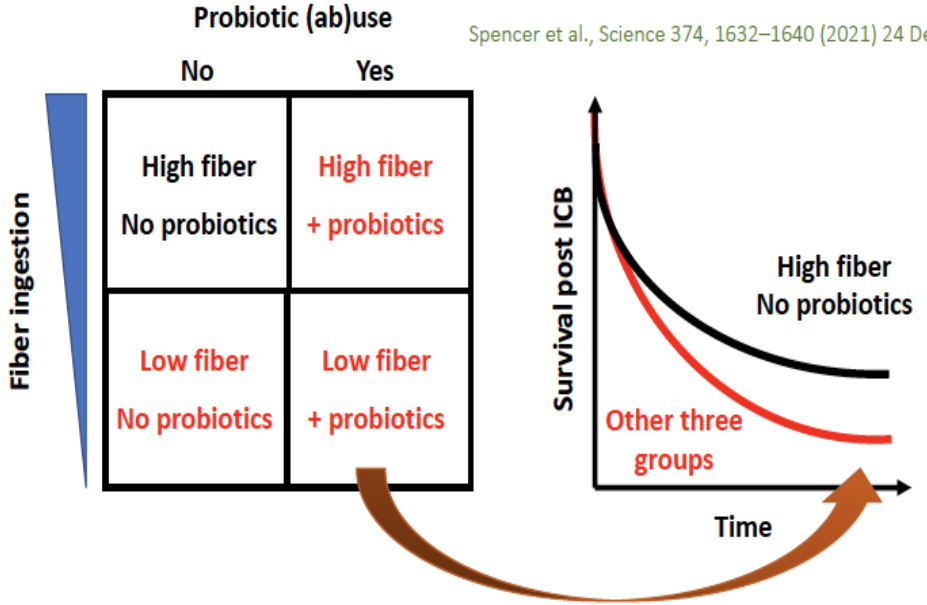
KETOGENIC DIET AND 3OH BUTYRATE OR FIBER ENRICHED DIETS : IMMUNE PRIMING AND SYNERGY WITH IMMUNE CHECKPOINT BLOC

JCI Insight. 2020. https://doi.org/10.1172/jci.insight.145207.



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

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

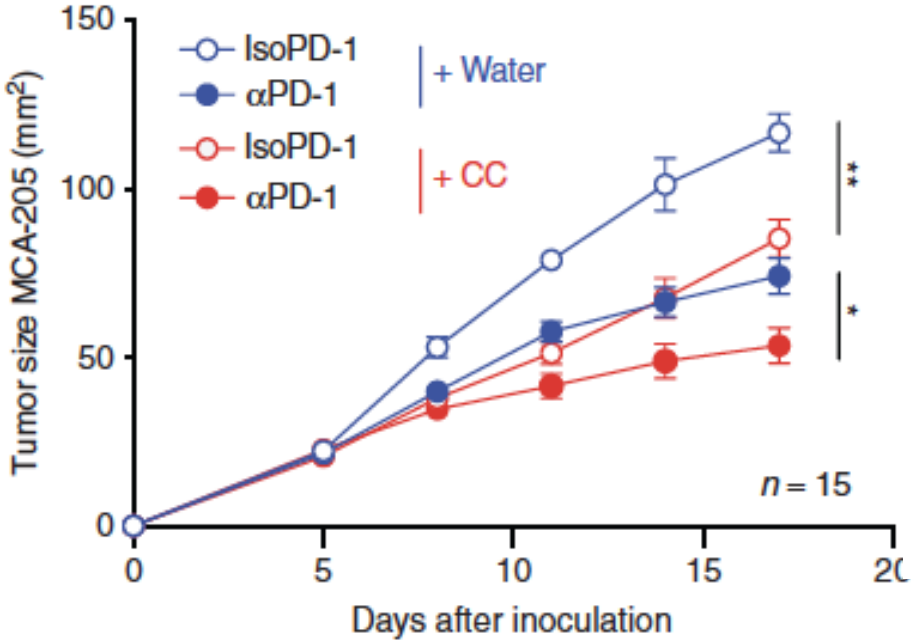


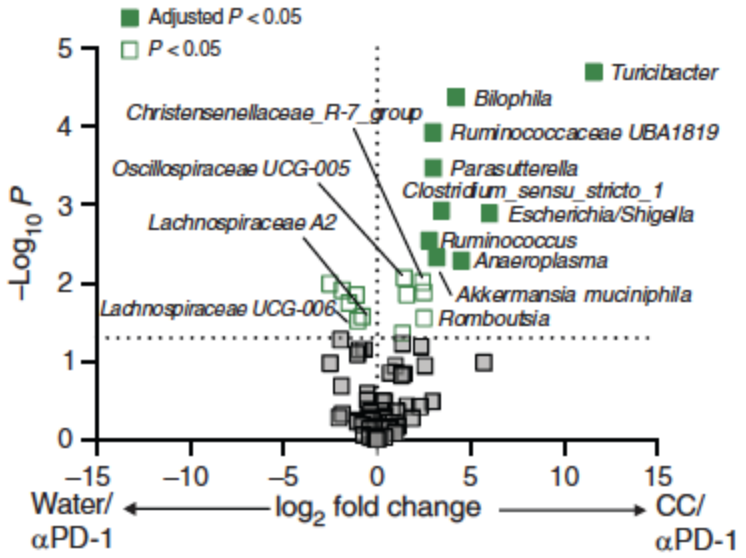
Excessive *Bifidobacterium longum* or *Lactobacillus rhamnosus GG*
→ Resistance to ICB

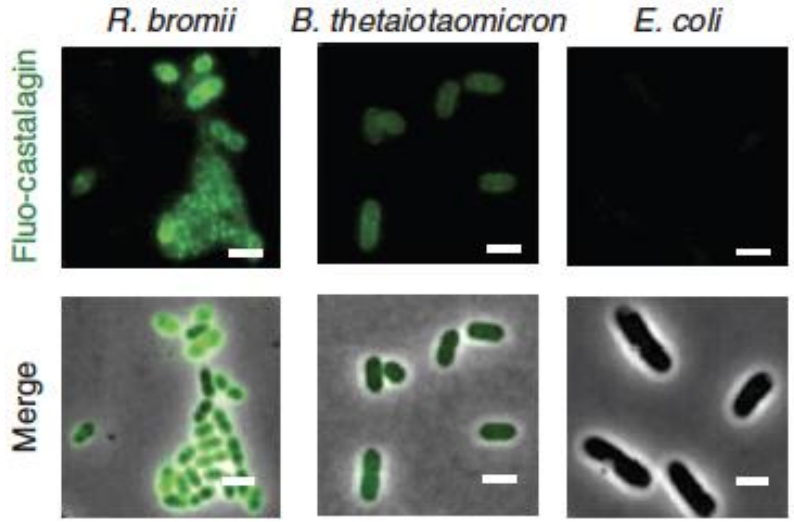
Underrepresentation of *Ruminococcaceae* and *Faecalibacterium*
→ Reduced immunostimulation by ICB

PREBIOTICS WITH IMMUNOSTIMULATORY PROPERTIES: POLYPHENOL CASTALAGIN FROM CAMU-CAMU

Camu-Camu and Castalagin (Cancer Discovery, Apr 2022, 1071)

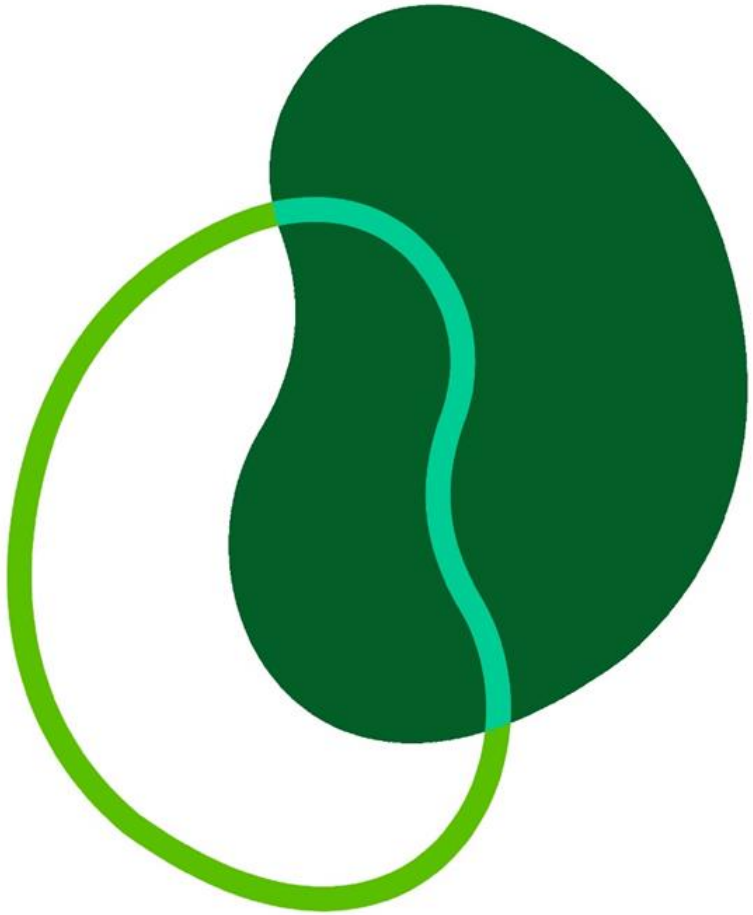






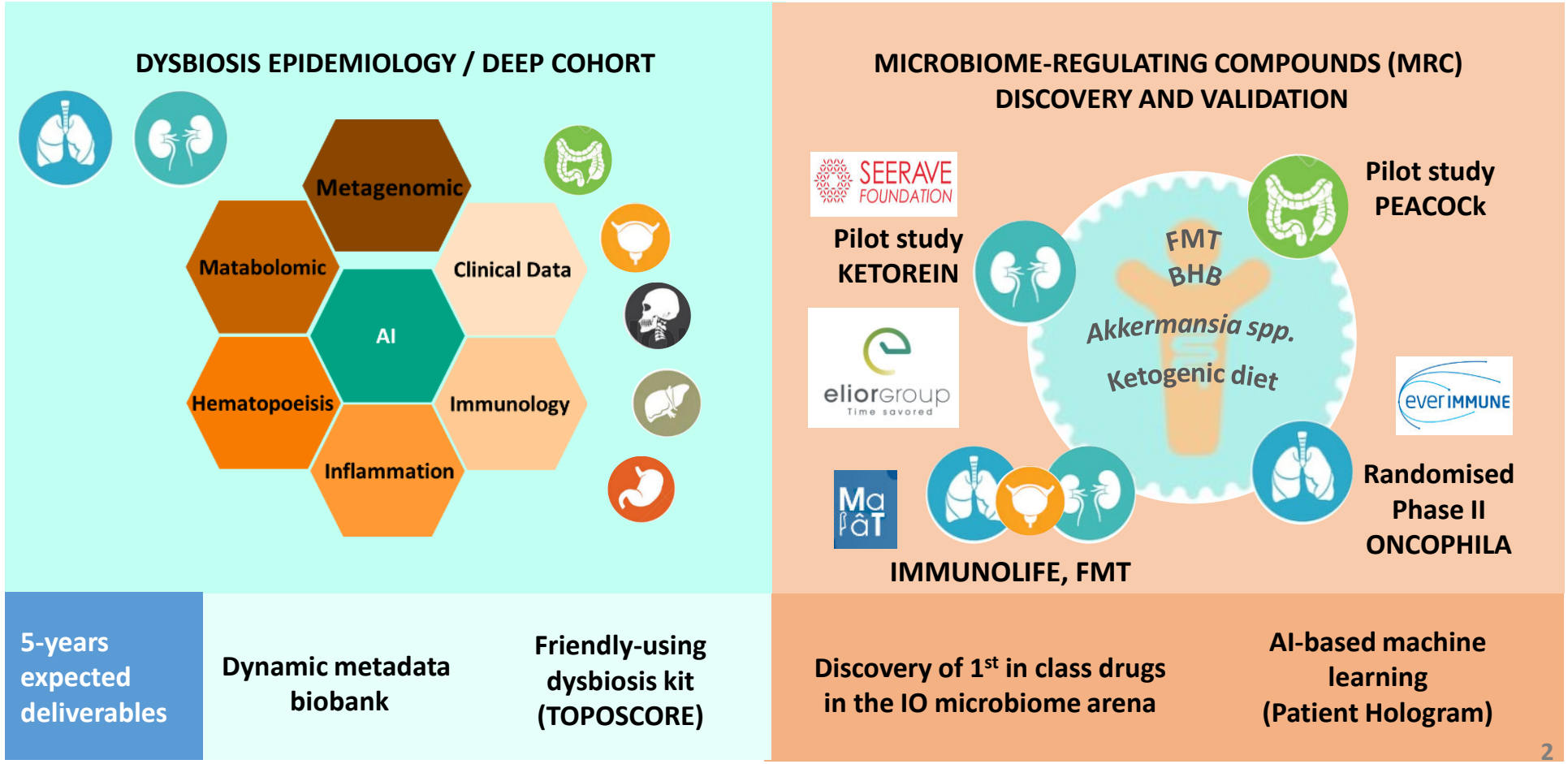
17e Rencontre Patients de l'Association A.R.Tu.R.

PART5: The clinicobiome at Gustave Roussy



AMBITION: Gustave Roussy ClinicObiome

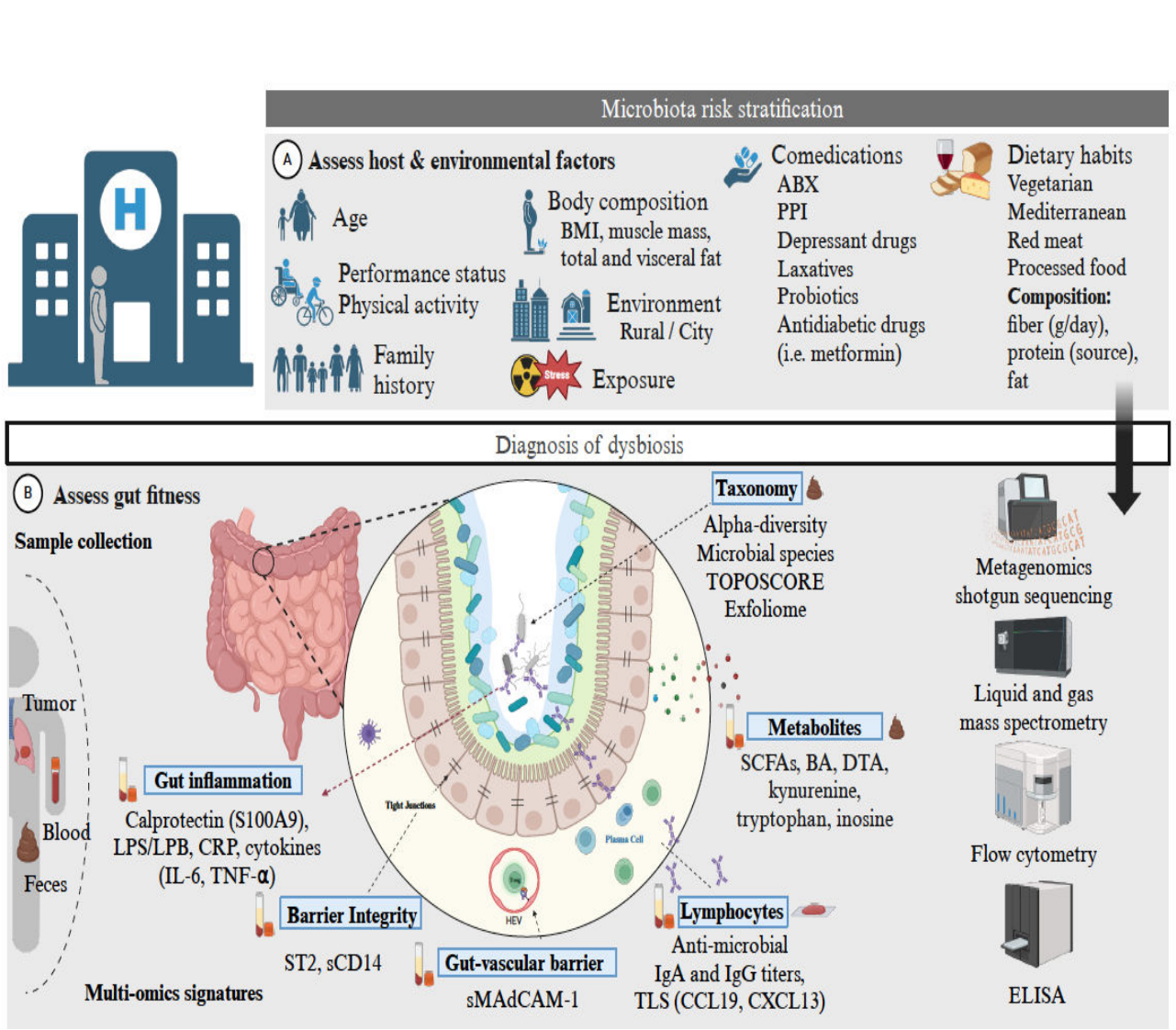
L. Zitvogel & L. D

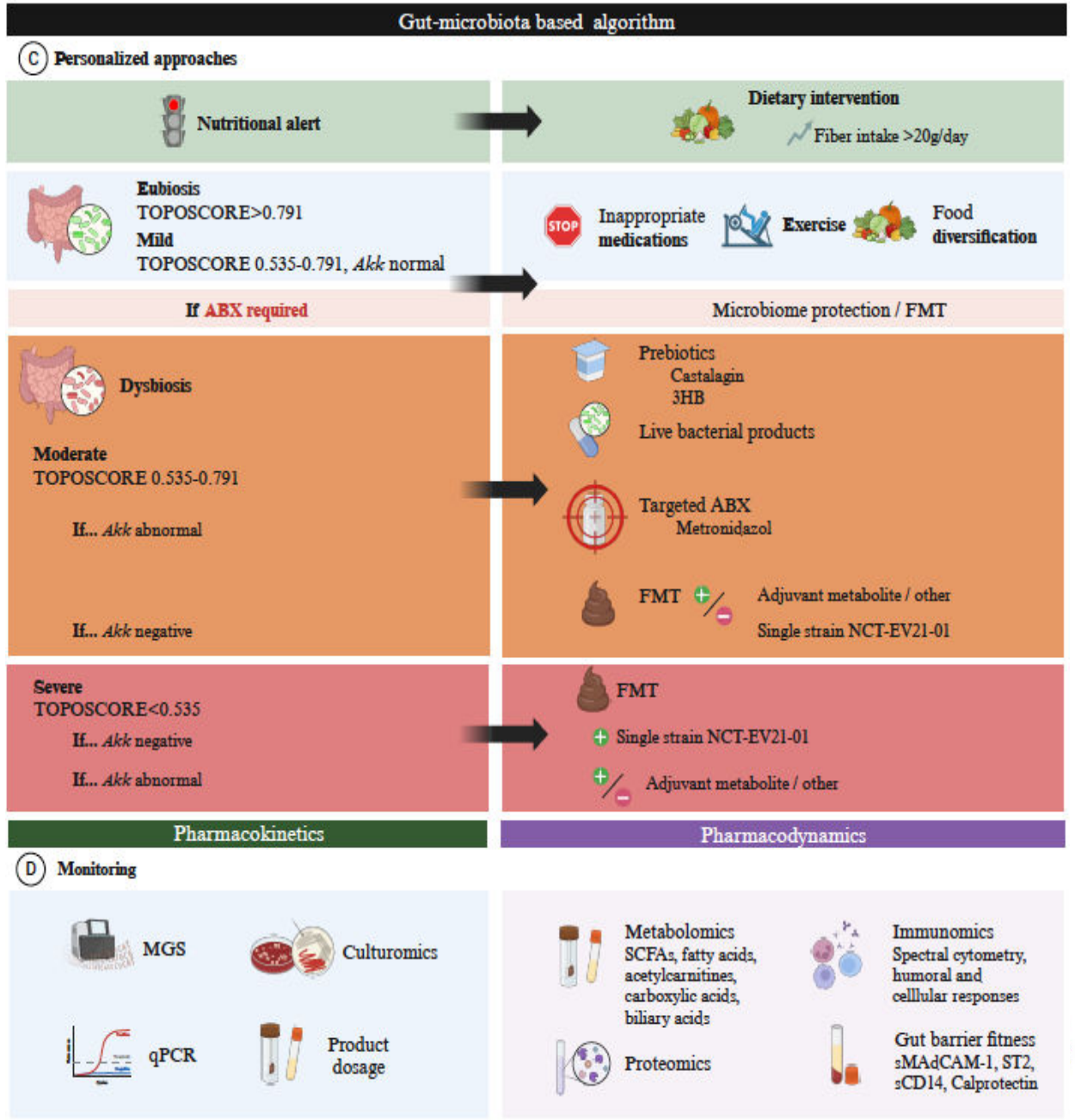


Clinic biome

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

17e Rencontre Patients de l'Association A.R.Tu.R.





Alves Costa Silva C. et al. Annu. Rev. Pharmacol. In press

17e Rencontre Patients de l'Association A.R.Tu.R.

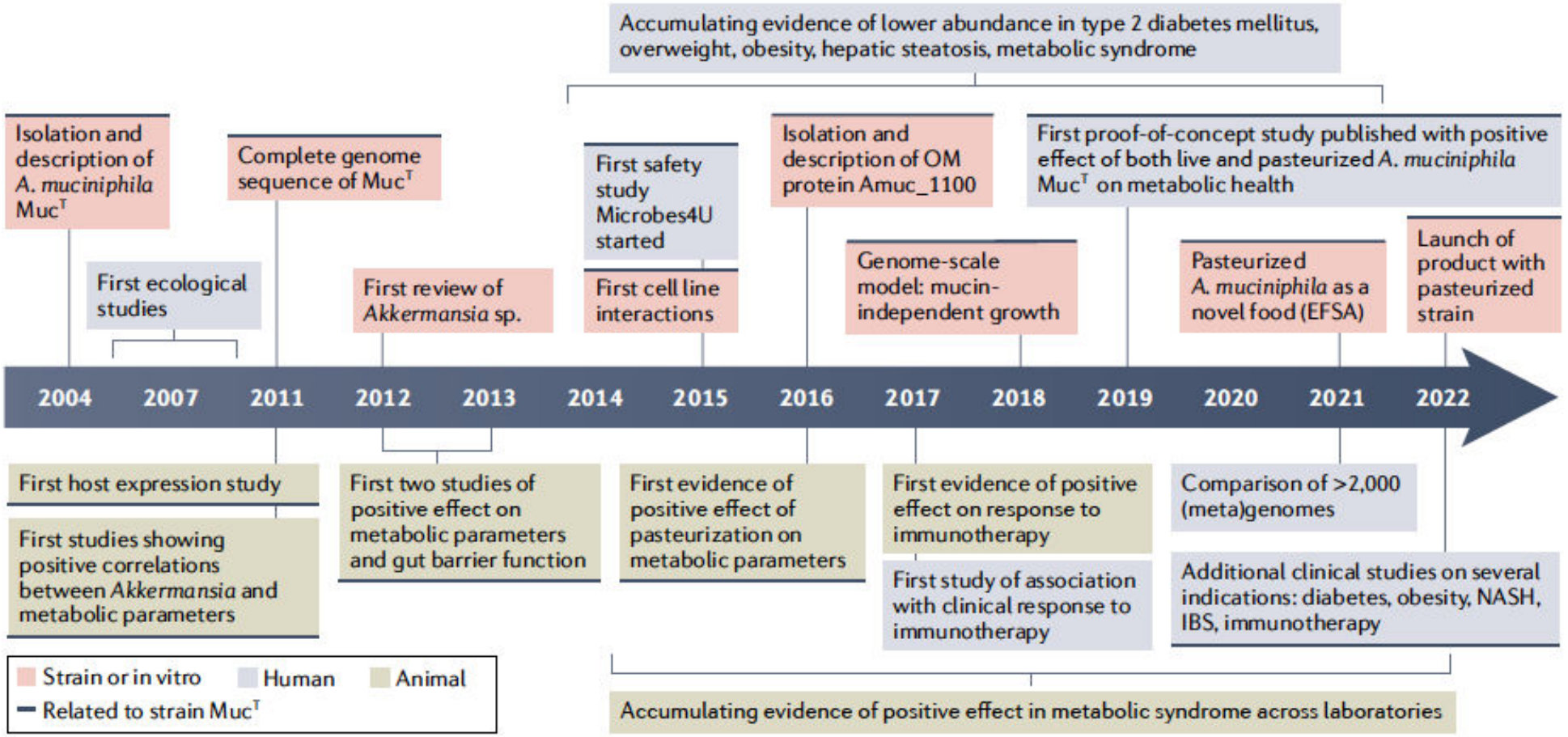
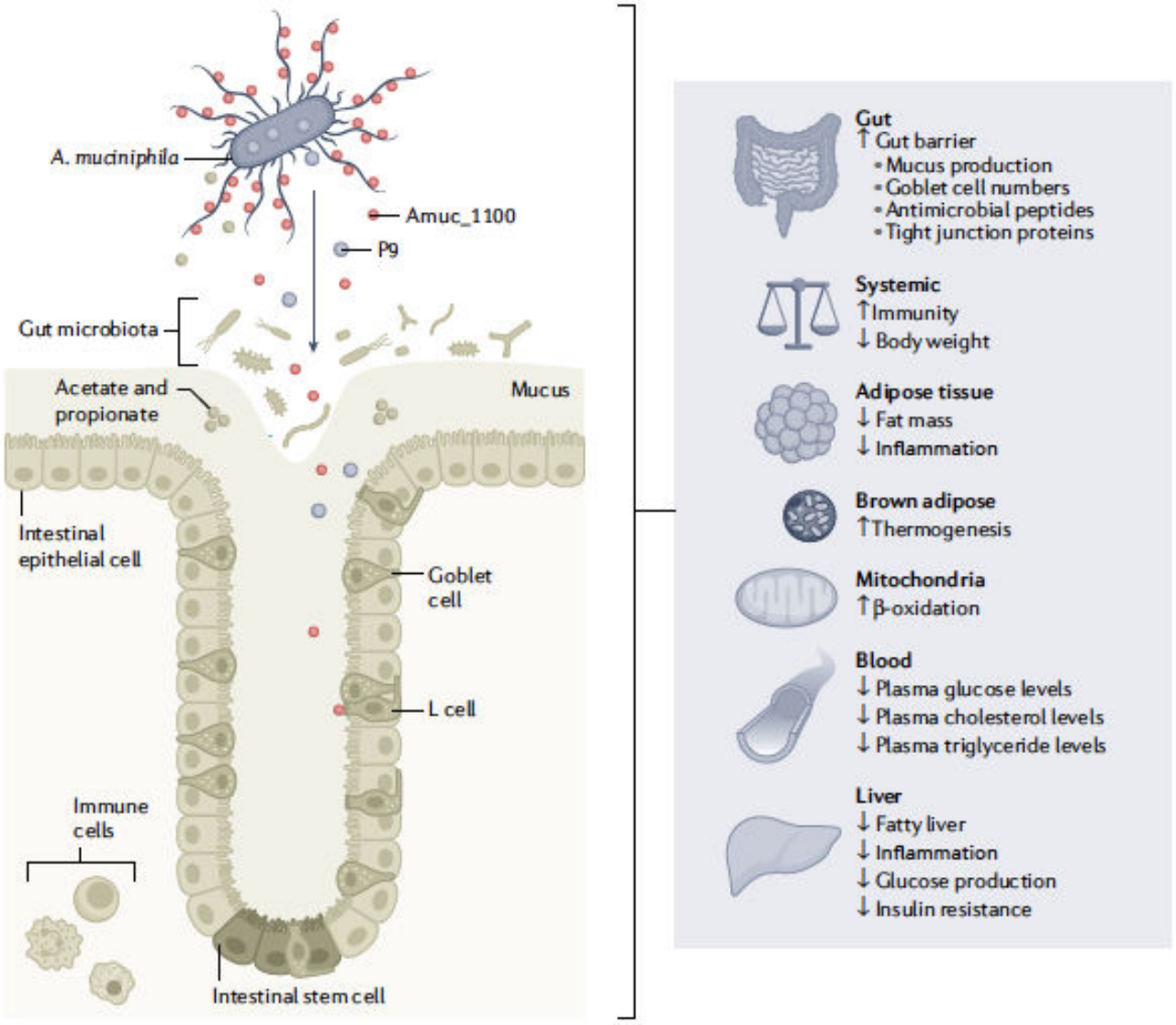


Fig. 1 | **Timeline of major advances related to *Akkermansia muciniphila*.** Colours of the boxes depict the model: in vitro, animals, humans. Discoveries related to the type strain or other strains are also indicated with a bold line. EFSA, European Food Safety Authority; IBS, irritable bowel syndrome; NASH, nonalcoholic steatohepatitis.

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein



Cani PD et al. Nat Rev GastroEnterol & Hepatol 2022

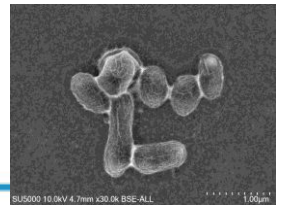
Fig. 2 | **Metabolic effects and major factors involved in *Akkermansia muciniphila* in the context of metabolic health.** *Akkermansia muciniphila* targets host intestinal cells and contributes to the regulation of gut barrier function, antimicrobial peptide production, immune regulation, mucus layer thickness and the regulation of inflammation. *A. muciniphila* regulates mitochondrial activity, thermogenesis, inflammation, and lipid and glucose metabolism, which influences metabolic health. P9, protein 9.

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

17e Rencontre Patients de l'Association A.R.Tu.R.

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

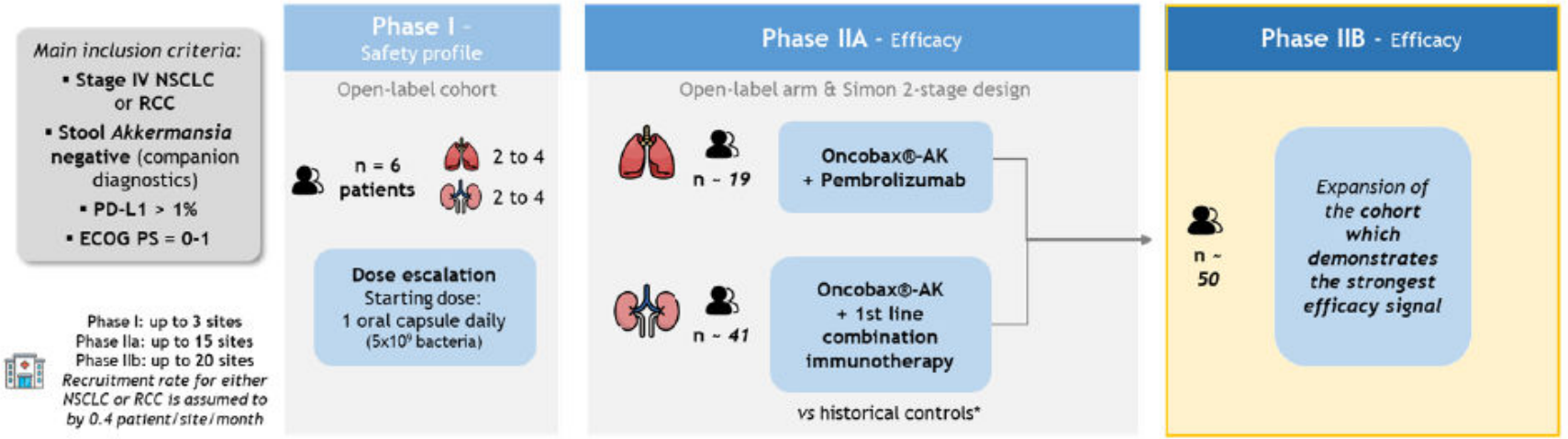
Oncobax®-AK will be administered in combination with ICIs to advanced NSCLC or RCC patients



Akkermansia massiliensis

Dr B. Escudier
Pr. L. Albiges
Pr. P. Barthelemy
Pr F. Ghiringhelli
Dr S. Ladoire

Pr. L. Albiges



** Prospective comparative observational studies conducted at leading institutions in Europe*

NSCLC: Oncobax®-AK + pembrolizumab (Keytruda®)
Primary endpoints: 10% ORR

RCC: Oncobax®-AK + combination immunotherapy (ipilimumab (Yervoy®) / nivolumab (Opdivo®))
Primary endpoints: 20% improvement in ORR

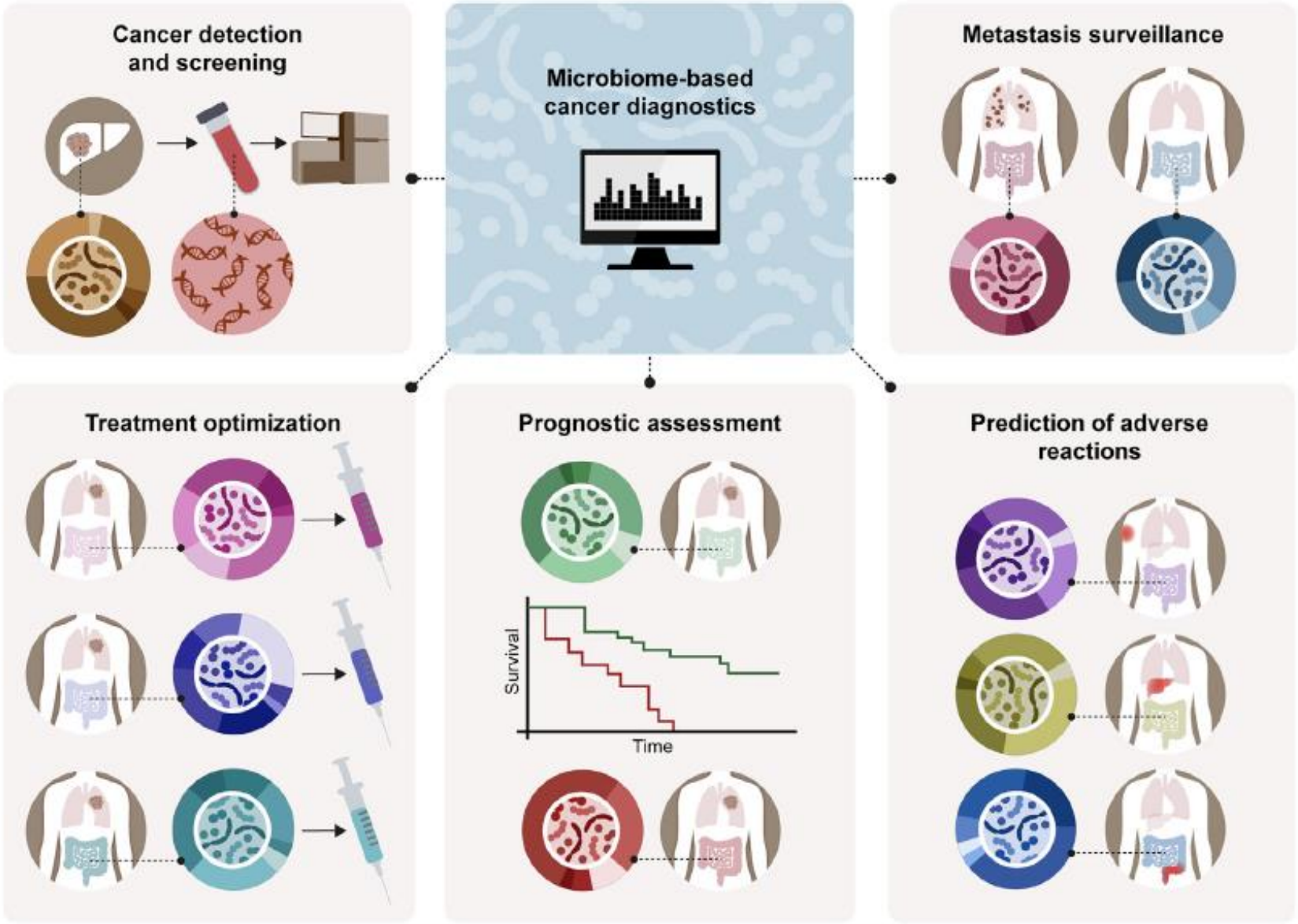
everIMMUNE

Clinical trial Phase I/IIA

EVERIMMUNE

A.R.Tu.R.
Association pour la Recherche sur les Tumeurs du Rein

CONCLUSION: the potential of the microbiome in cancer



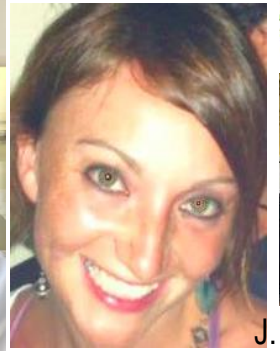

IMMUN LIFE
OCTO
MASCOTTE IMMUNOLIFE

SEERAVE FOUNDATION

contre

D. Raoult
G. Kroemer

B. Routy



L. Derosa

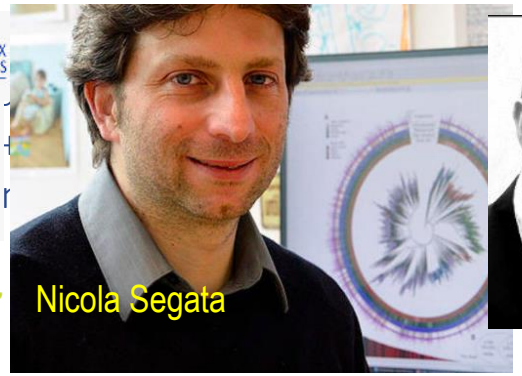
INRA SCIENCE & IMPACT

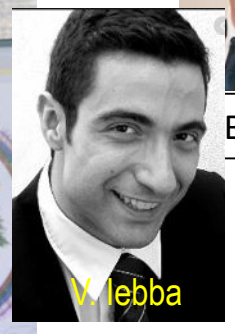
J. Doré &D. Ehrlich

Besse

F. Goldwasser G. Zalcman JC Soria

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
CHUM
GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS





A. Thomas

ONCOBIOME
Microbiota against cancer
International research program

THANKS to U1015 INSERM

ONCOBIOME

SEERAVE Foundation

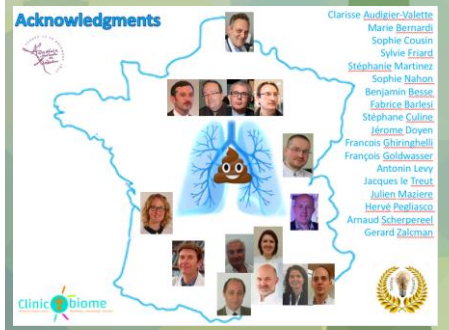
INRAE

AP-HP

IHU Méditerranée Infections

EVERIMMUNE

Inserm
Institut national de la santé et de la recherche m



Clarisse Audigier-Valette
Marie Bernardi
Sophie Cousin
Sylvie Friard
Stéphanie Martinez
Sophie Nahon
Benjamin Besse
Fabrice Barlesi
Stéphane Culine
Jérome Doyen
Francois Ghiringhelli
François Goldwasser
Antonin Levy
Jacques le Treut
Julien Maziere
Hervé Pegliasco
Arnaud Scherpereel
Gerard Zalcman

R. Daillère, AG Goubet, M. Vétizou

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

université
PARIS-SACLAY

Merci de votre attention !

17e Rencontre Patients de l'Association A.R.Tu.R.

A.R.Tu.R.

Association pour la Recherche
sur les Tumeurs du Rein