GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

UNIVERSITÉ PARIS SUD

INVESTISSEMENTS D'AVENIR

Torino Lumière

Microbiota
and its role for response to immunotherapy

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Inserm
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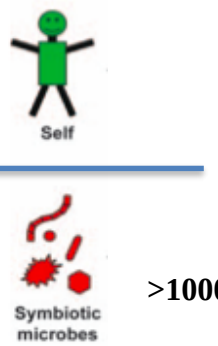
de la santé et de la recherche médicale

FONDATION PHILANTHROPIA
LOMBARD ODIER


I'M
NOT
DANGEROUS

From forgotten to superorganism



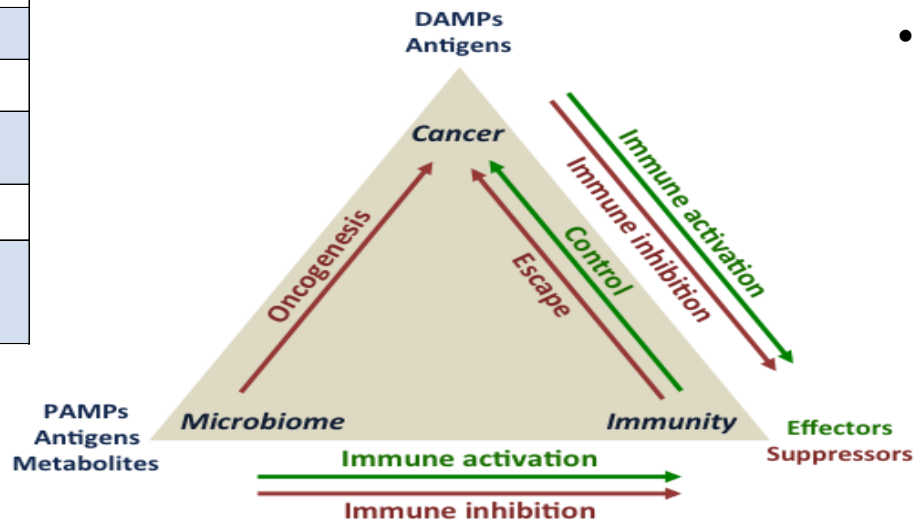
Epithelilal <1 mm

>1000 bacterial species

- Process nutrients
- Produce vitamins
- Protects from new microbes
- Shape the immune system

Epidemiological associations between commensals and cancer

Cancer	Analyzed specimens	Association	Ref (PMID)
HNSCC	Saliva	The total abundance of genus *Streptococcus, Dialister*, and *Veillonella* can be used to discriminate patients with tumor from controls.	27259999
ALL	Feces	Lower abundance of *Anaerostipes, Coprococcus, Roseburia* in the ALL group compared with siblings	27527070
Pancreas	Oral wash	*Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans*, were associated with higher risk of pancreatic cancer	27742762
HPV cancer	Cervical mucus	When comparing CIN2+ vs CIN1: *L. iners* and *unclassified Lactobacillus spp* was associated with CIN 2+	26935422
Breast cancer	Normal (or tumor) breast tissue versus healthy breast	BC healthy tissue associated with higher relative abundances of *Bacillus, Enterobacteriaceae* and *Staphylococcus*	27342554
GU cancer	Urine	Streptococcus abundance was nearly zero in most normal samples but significantly elevated in patient samples	25126590
Lung cancer	Sputum and buccal samples	Burning coal exposed never smoking chinese females in sputum and not in buccal samples compared to controls: Granulicatella (6.1 vs. 2.0%;), Abiotrophia (1.5 vs. 0.085%), and Streptococcus (40.1 vs. 19.8%) were enriched in cases compared with controls	24895247

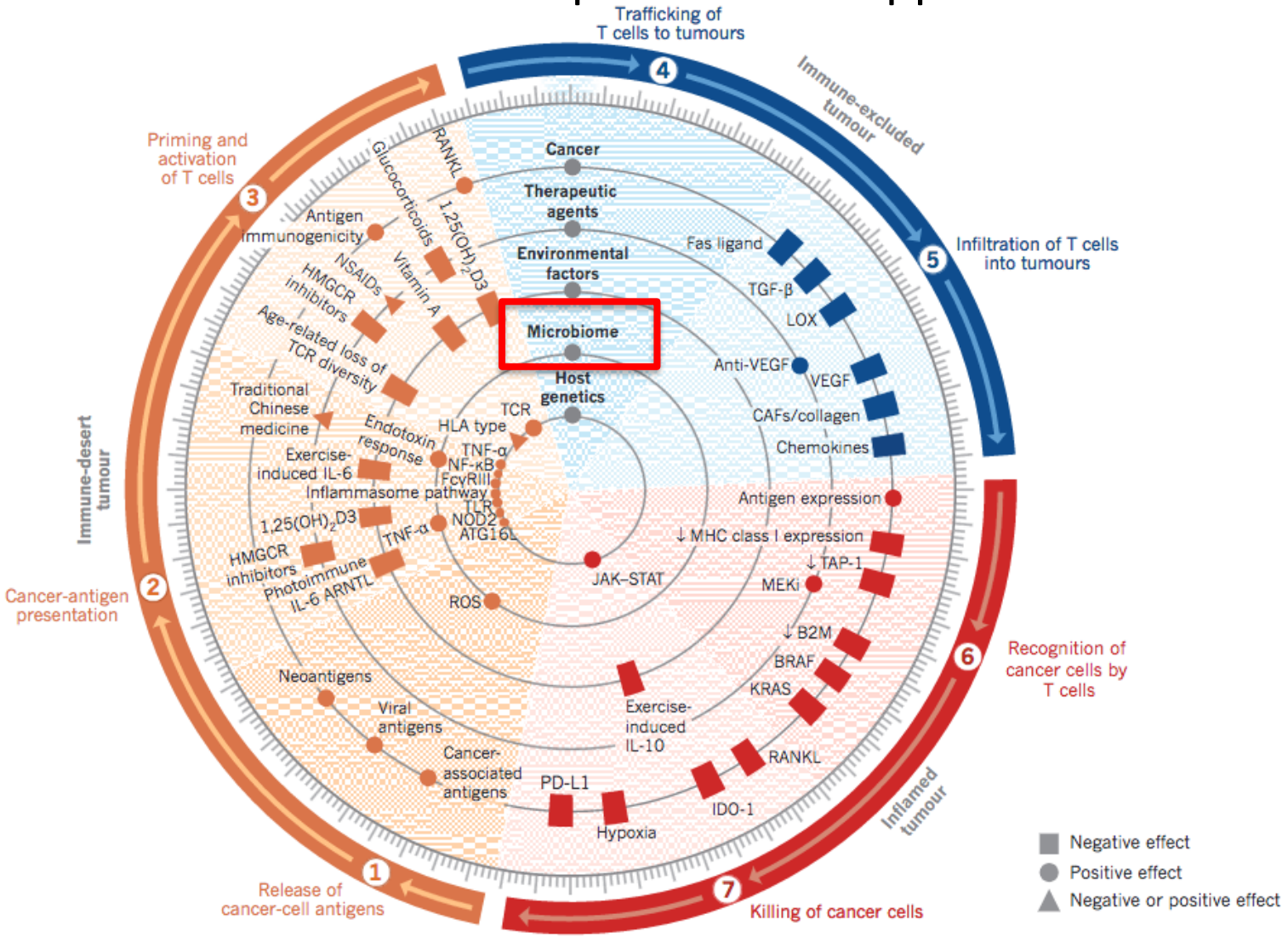


Sender R. BioRxiv 2016

Zitvogel L. Cell 2016 and Nat Rev 2017

The cancer-immune set point:

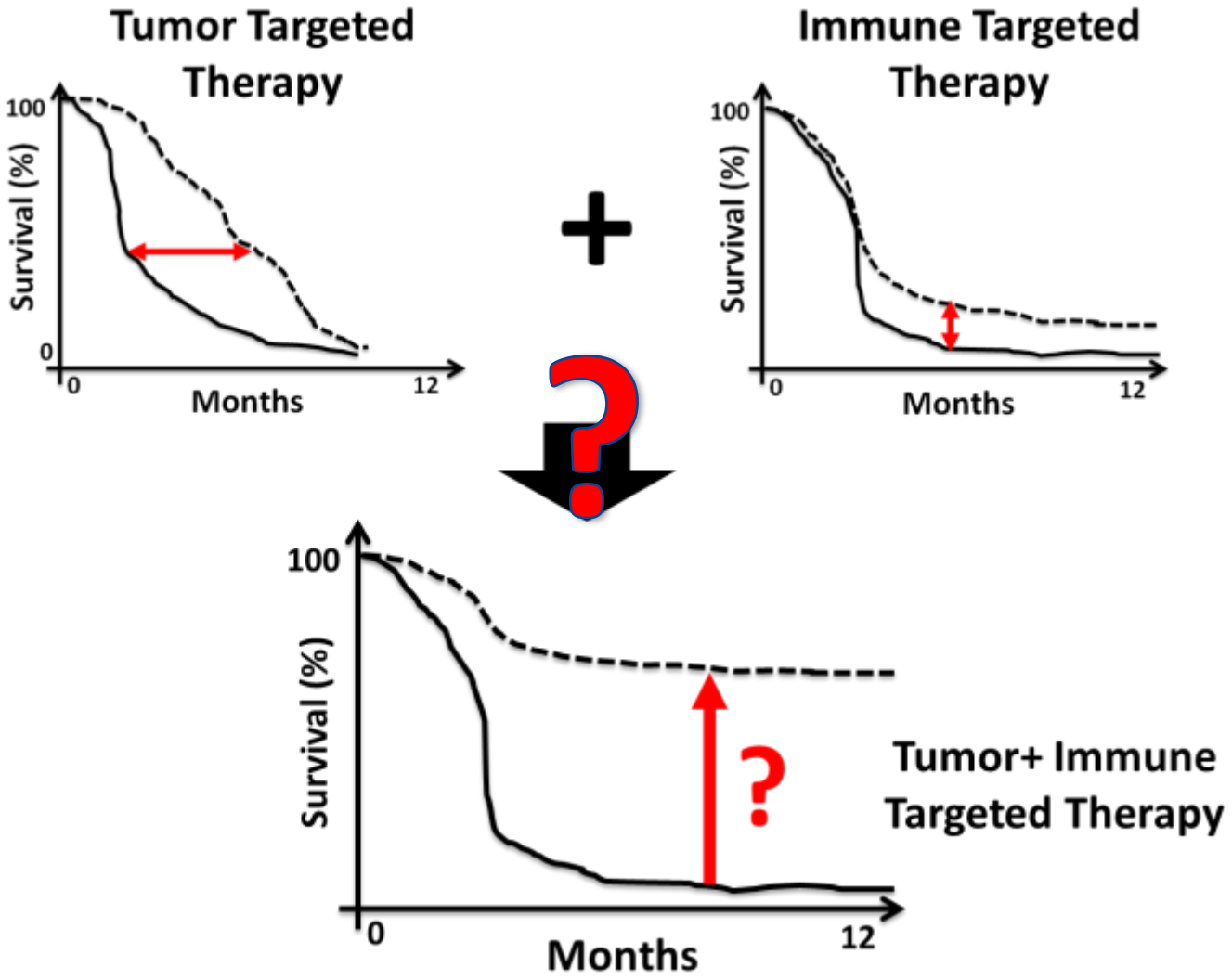
the equilibrium between the factors that promote or suppress anticancer immunity



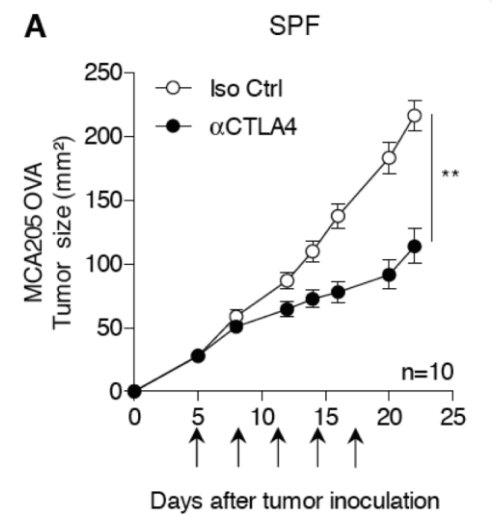
Chen D. and Mellman I. Nature Jan. 2017

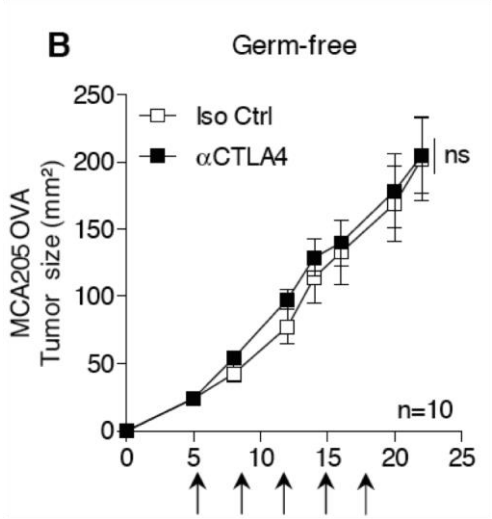
Future of Immuno-Oncology:

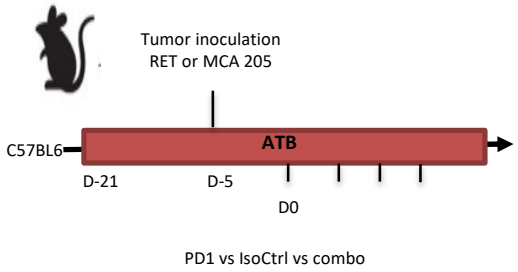
Could a « minimalist microbiome » normalize the cancer-immune set point?

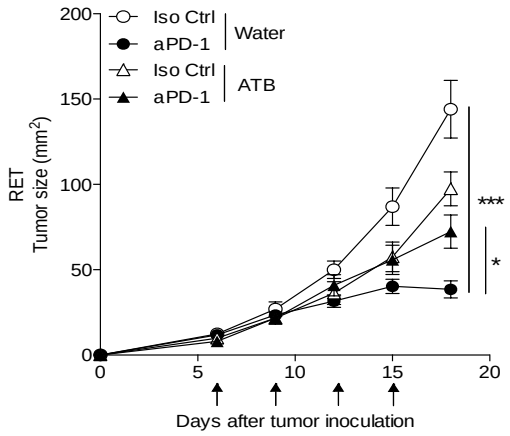


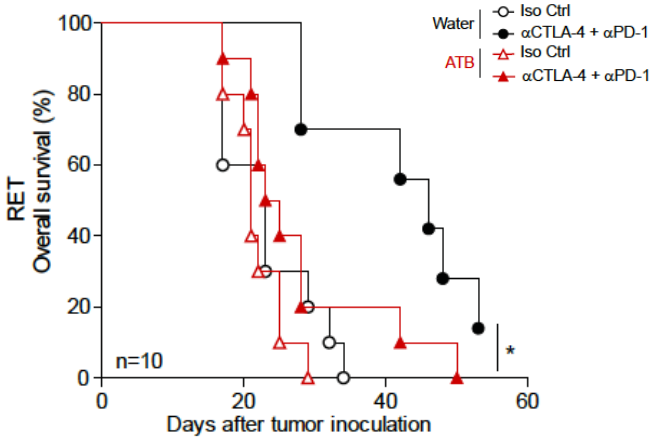
The antitumor efficacy of anticancer immunotherapy requires gut bacteria











Similar results using cyclophosphamide, platinum salts, IL-10R (*Vétizou 2015, Iida Science 2013, Viaud Science 2013,Routy 2017*).

In 2 cohorts of patients, RCC and NSCLC, prior ATB was associated with worse outcomes with ICI

RCC

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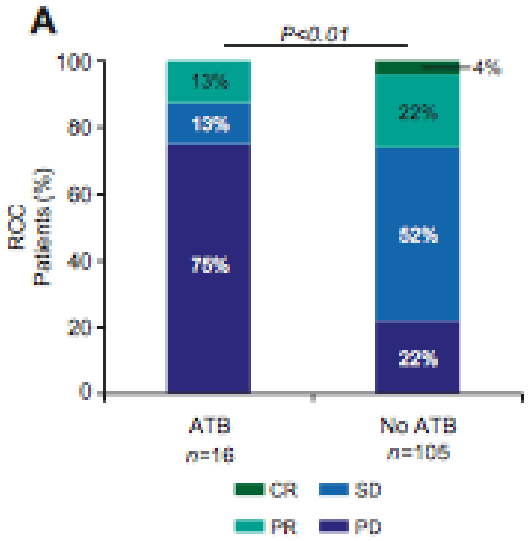
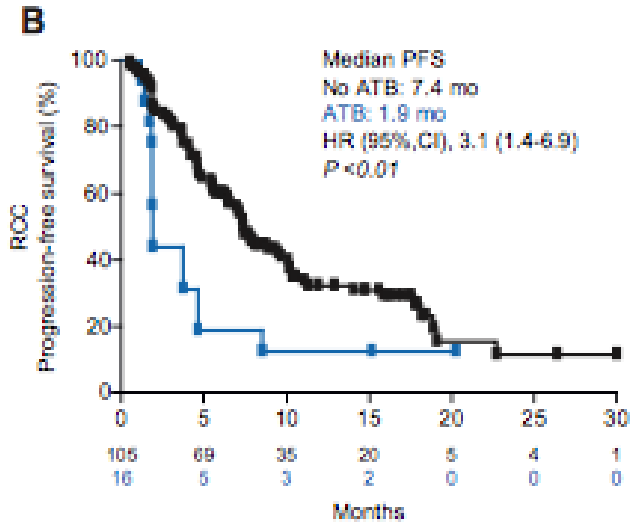
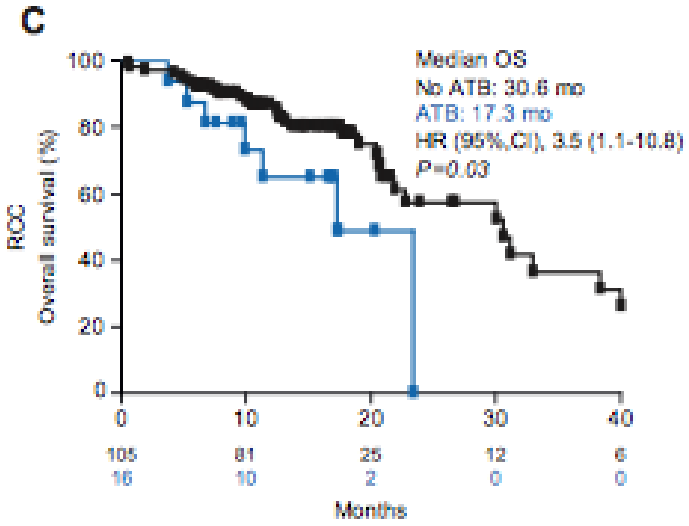
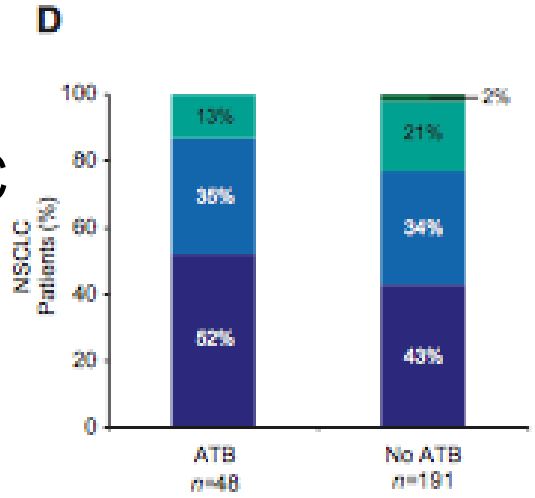


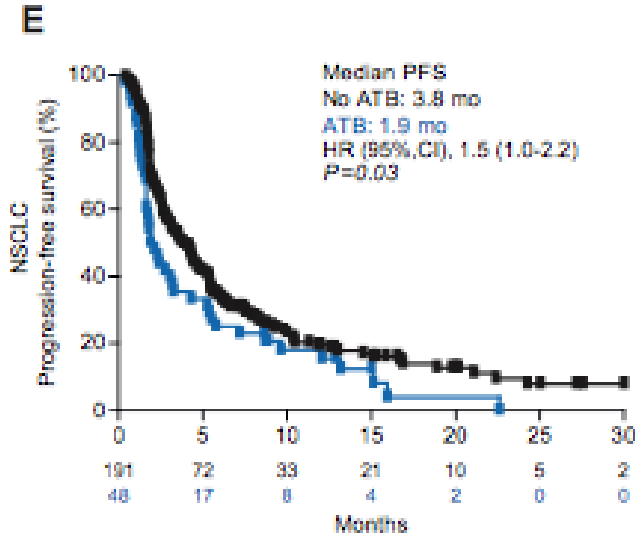


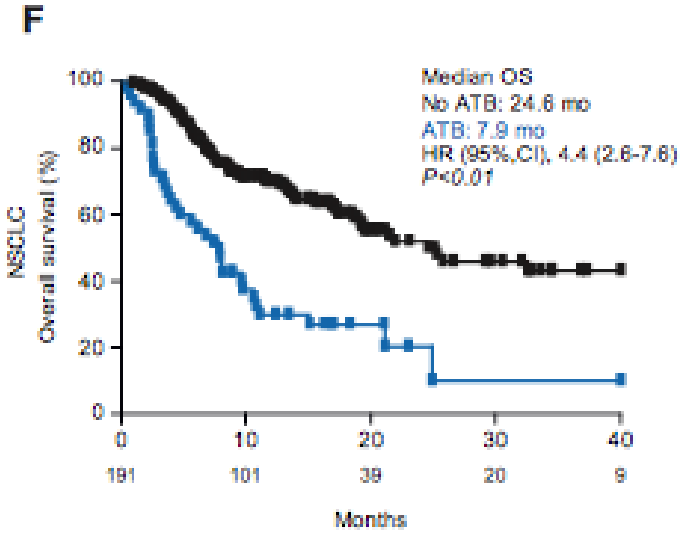


NSCLC

Memorial Sloan Kettering Cancer Center







ATB remained independently associated with worse PFS or OS in multivariate analysis

Derosa L., Annals Oncol 2018
ASCO GU 2017 Merit Award

Several reports are confirming the detrimental impact of ATB

	CANCER TYPE	ATB WINDOW	OUTCOME
Routy Science 2018	NSCLC n =140 RCC n= 67 UC= 32	2 months PRE or 1 month POST	↓ PFS ↓OS
Derosa Annals 2018	NSCLC n=239 RCC n=121	1 month PRE	↑ PD ↓ PFS ↓OS
Huemer Oncotarget 2018	NSCLC n=30	1 month PRE or 1 month POST	↓ PFS ↓OS
Kaderbhai Anticancer Res 2017	NSCLC n=74	3 months PRE	No change in PFS ↓OS (not published)
Elkiref (In press)	Melanoma n=74	1 month PRE	↓ PFS ↓OS
Lalani ASCO GU 2018	RCC n=146	2 months PRE or 1 month POST	↓ ORR ↓PFS
Tinsley ASCO 2018	Melanoma n=201 NSCLC n=58 RCC n=46	14 days PRE or 42 days POST	↓ PFS ↓OS
Do ASCO 2018	NSCLC n=109	1 month PRE or 1 month POST	↓OS
Rubio IASLC 2018	NSCLC n = 168	2 months PRE or 1 month POST	↓ PFS ↓OS
Galli IASLC 2018	NSCLC n=157	ATB for an average of 9 days	↓ PFS ↓OS
Ouaknine IASLC 2018	NSCLC n=72	2 months PRE or 1 month POST	↓OS

n= 1744

Elkief, Derosa et al. submitted to Annals

Working hypothesis

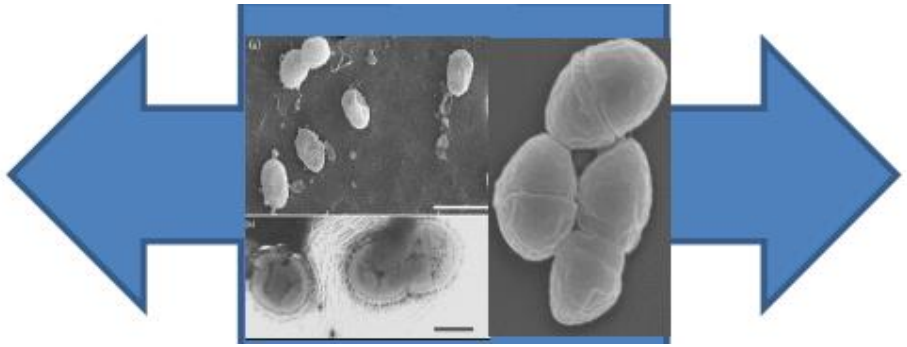
- ATB can change the composition of the gut microbiome (at least in a transient way)

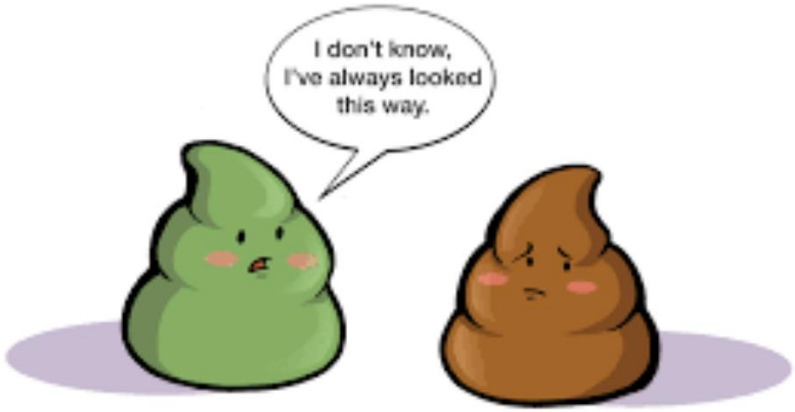
- We speculated that :
- dysbiosis (gut microbiome alteration)
- and ultimately the composition of microbiome might affect the therapeutic efficacy of ICBs

Gut microbiome can predict the efficacy of PD-1/PD-L1 blockade?

How to decipher the clinical relevance of the composition of the gut microbiome?

Avatar platform





NR R

R: responders; NR: non responders

Metagenomics

Shot gun DNA Seq

The “GRCC Cacathèque” – Stoolbank-

a dynamic analyses in a paired fashion (before 1st inj, (after 2 inj.), after 8 inj., after 6 months)

NSCLC

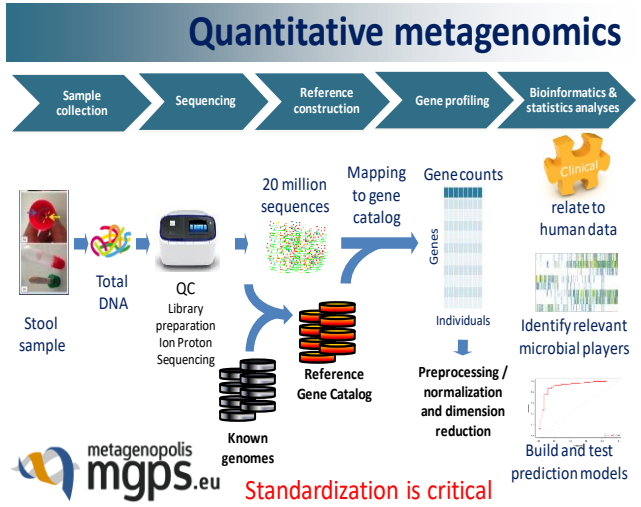


RCC


n=100 Discovery cohort
n=53 Validation cohort

- Clinical data on PD-1
- Toxicities
- Responses (CT scan)

Taking into account ATB uptake



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E. LeChâtelier

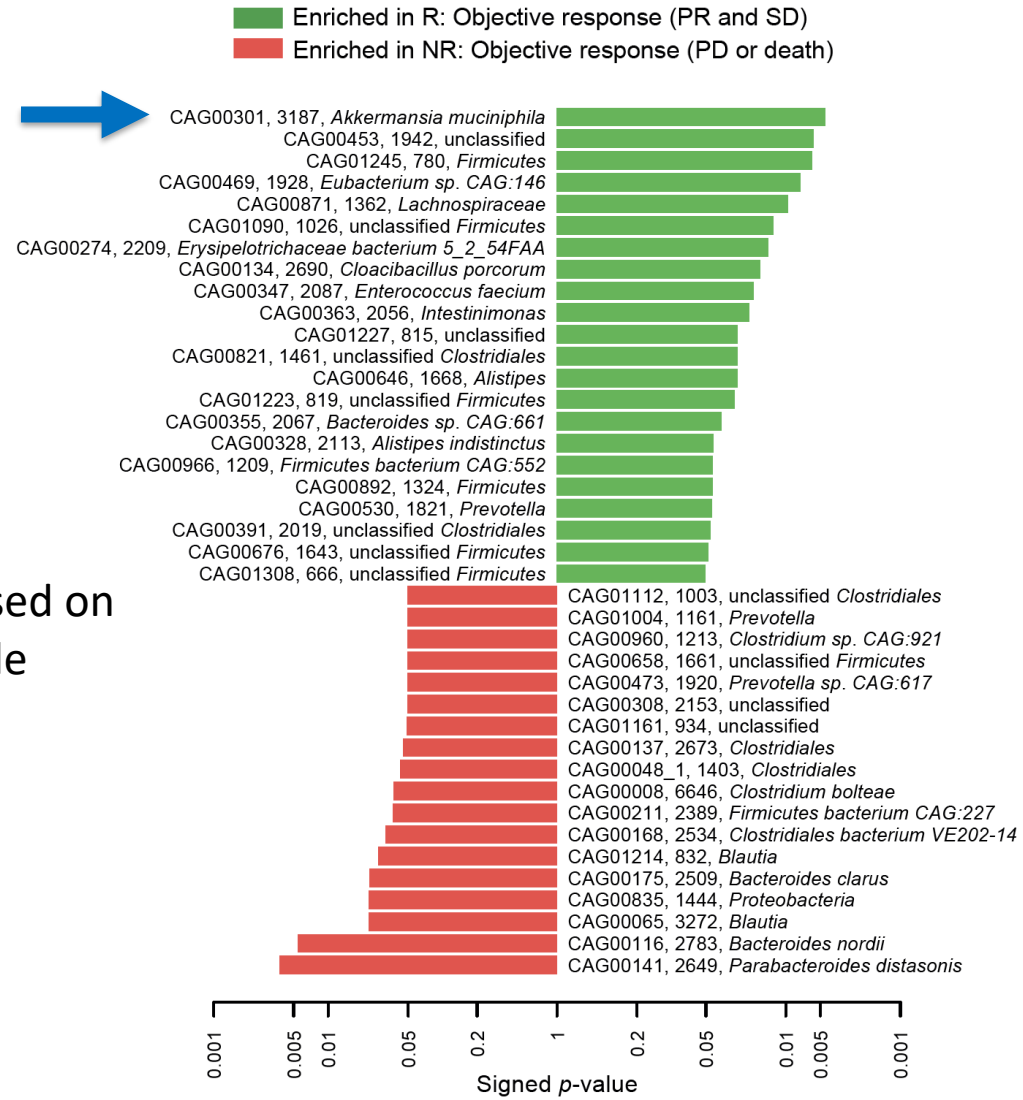
We explored the composition of the gut using quantitative metagenomics analyses by shotgun sequencing

Akkermansia muciniphila : most significantly associated with favorable clinical outcome

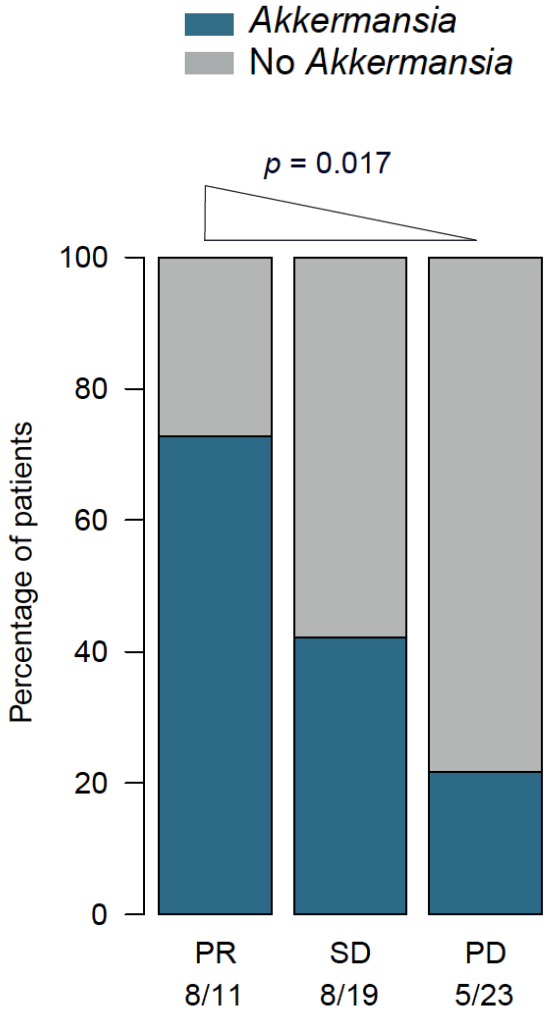
R

NR

2 different signatures, based on baseline sample



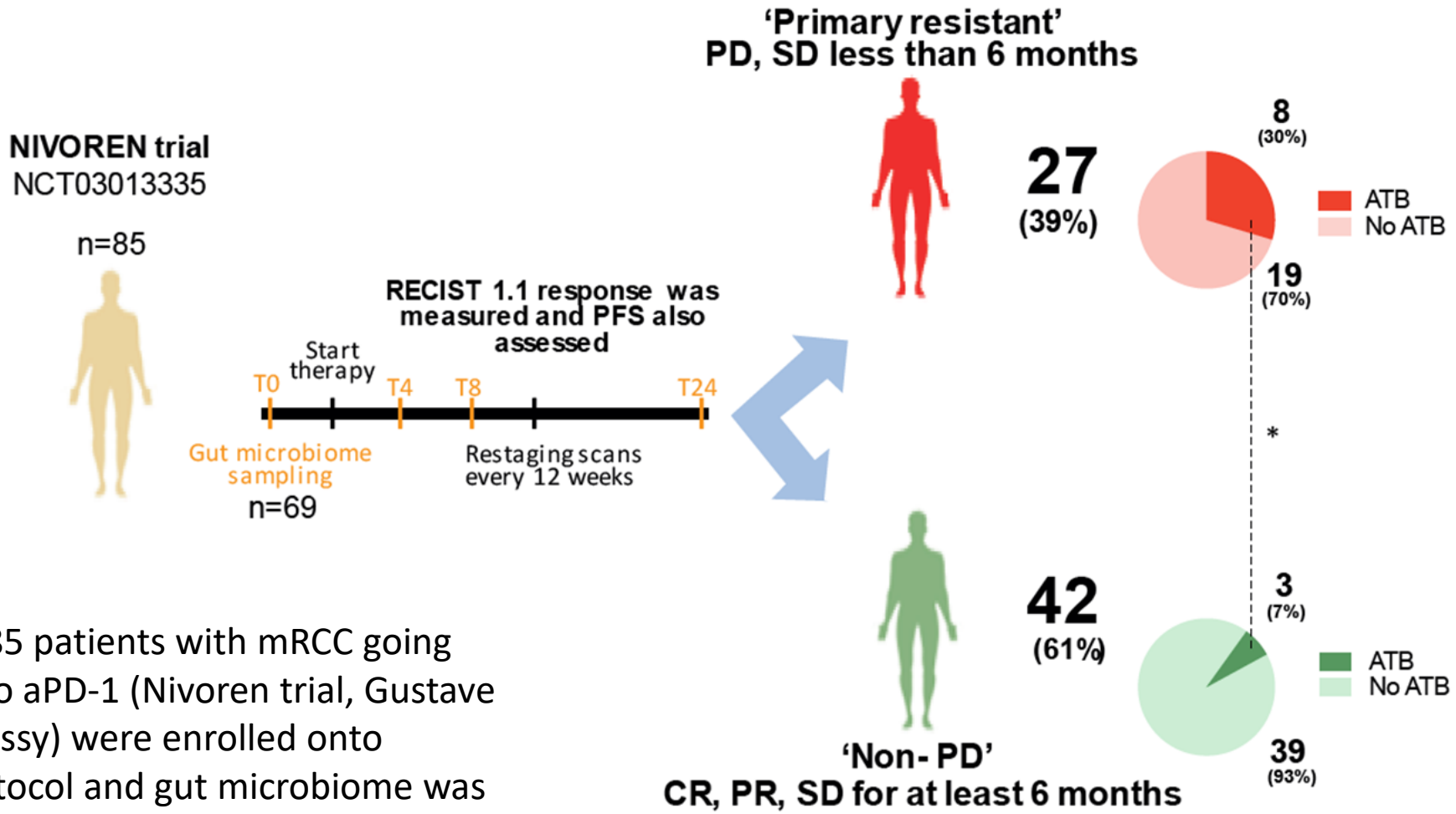
Discovery cohort n =100 (60 NSCLC + 40 RCC)



Validation cohort n=53 (27 NSCLC +26 RCC)

(Routy, Le-Chatelier, Derosa et al; Science, 2018).

Specific microbiota fingerprint signature in RCC

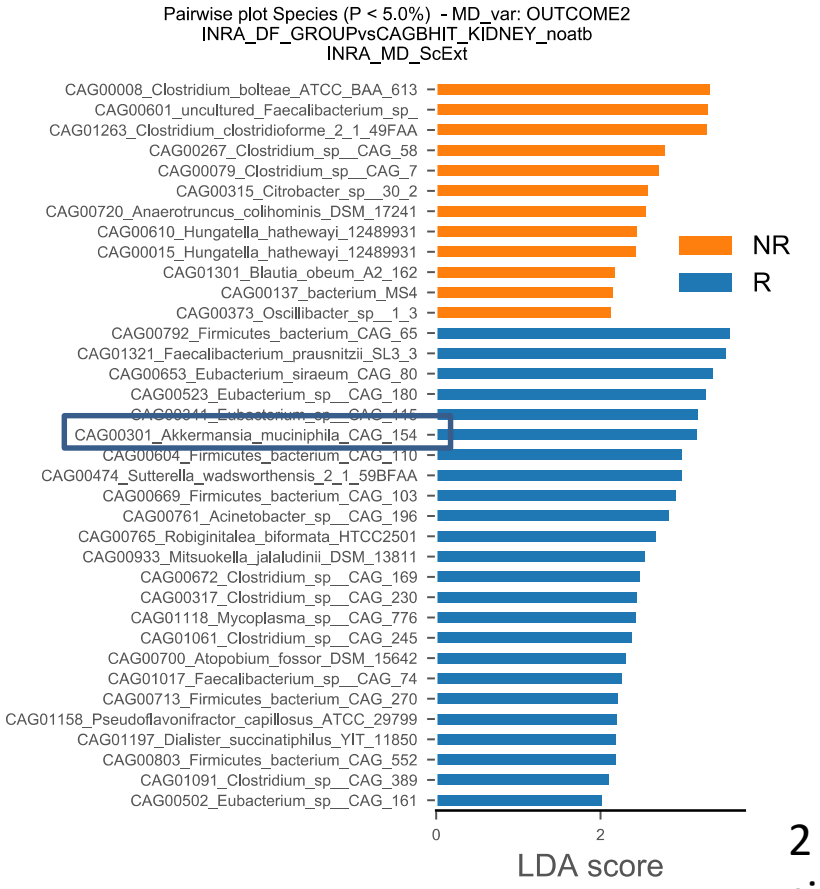


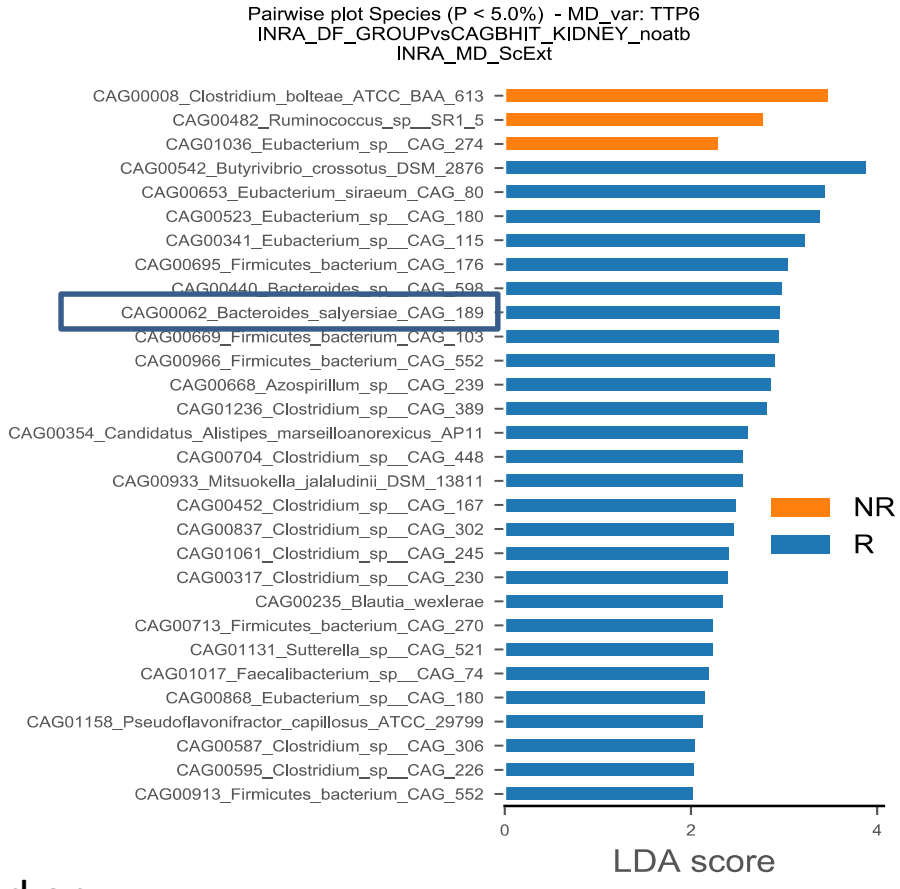
Recent ATB was associated with increased rate of primary PD

N=85 patients with mRCC going onto aPD-1 (Nivoren trial, Gustave Roussy) were enrolled onto protocol and gut microbiome was profiled (n=69)

Derosa L. ASCO 2018 Merit Award

A. muciniphila and *B. salyersiae* were more abundant in R (FR of 2.65 (p = 0.01) and 27.09 (p = 0.05), respectively)

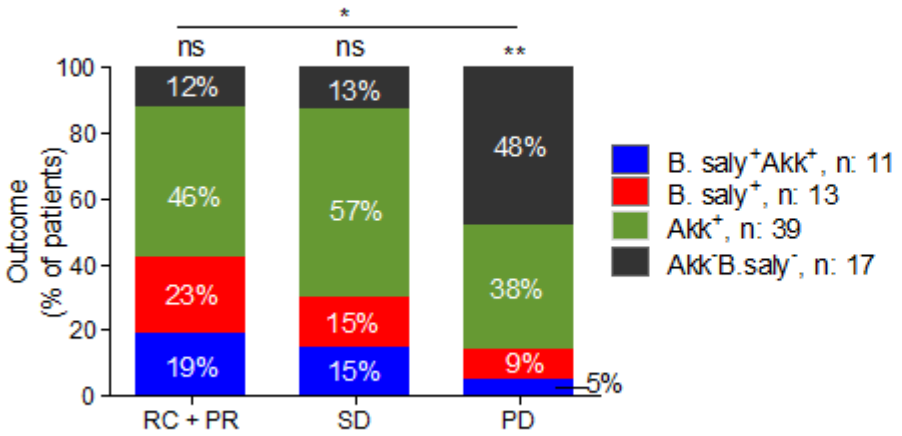


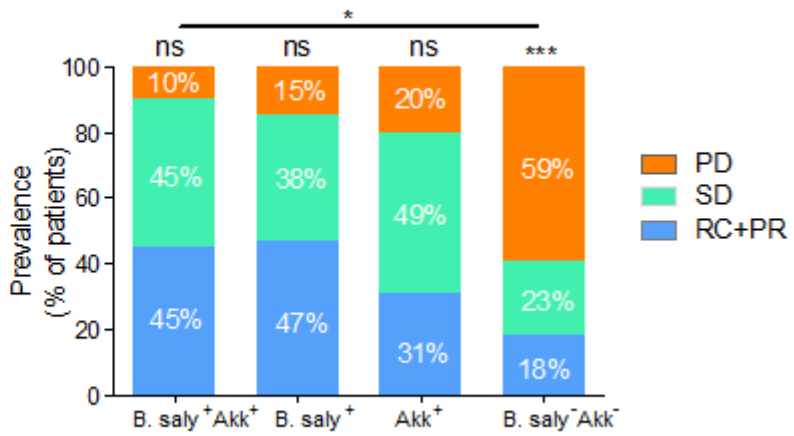


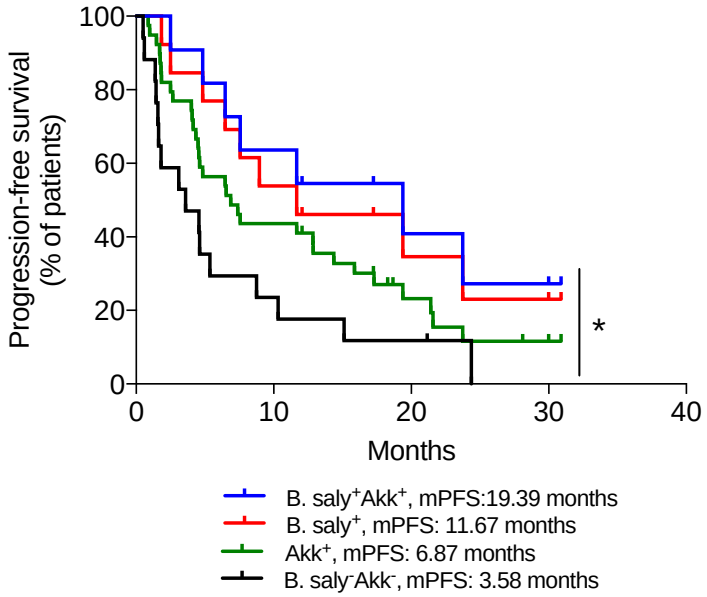
2 different signatures, based on baseline sample

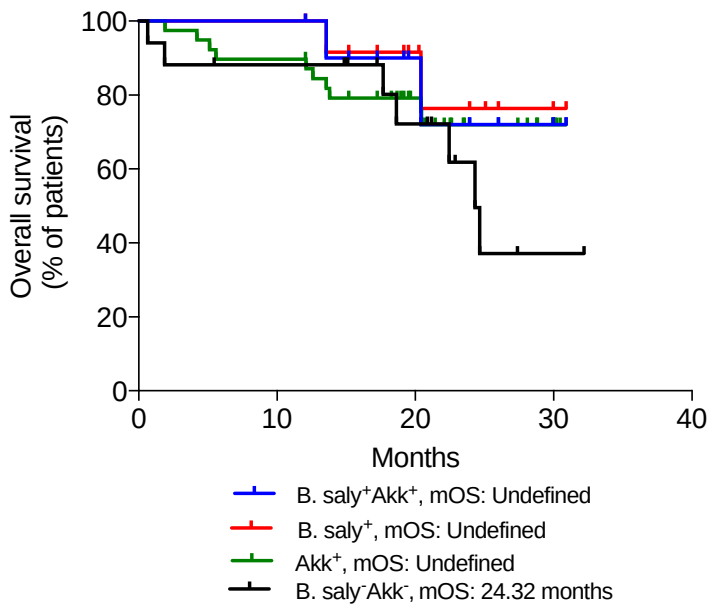
Derosa L., Poster discussion ASCO 2018

The co-absence of *A. muciniphila* and *B. salyersiae* was a predictor of primary resistance





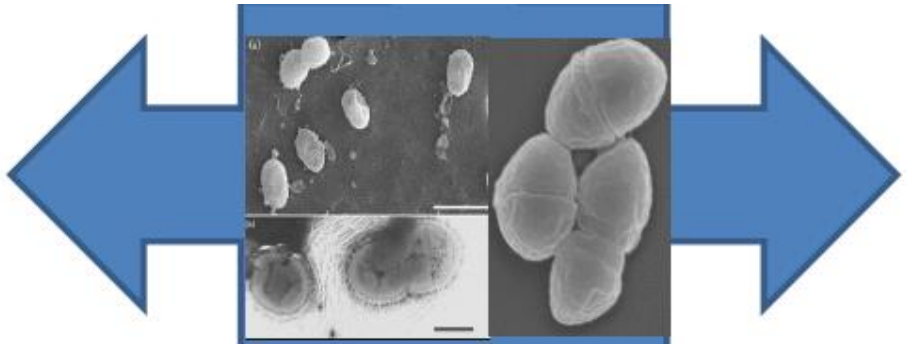


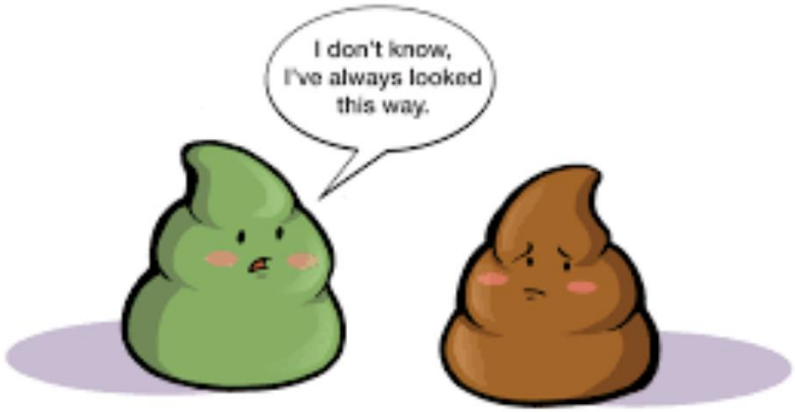


NB: random bacteria from Lefse
Butyvibrio crossotus or Eubacterium spp
did not increase PFS

How to decipher the clinical relevance of the composition of the gut microbiome?

Avatar platform



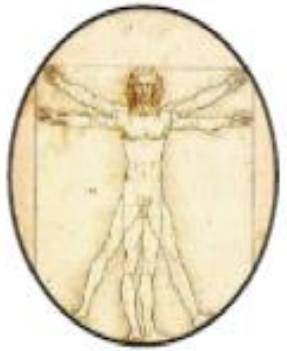


NR R

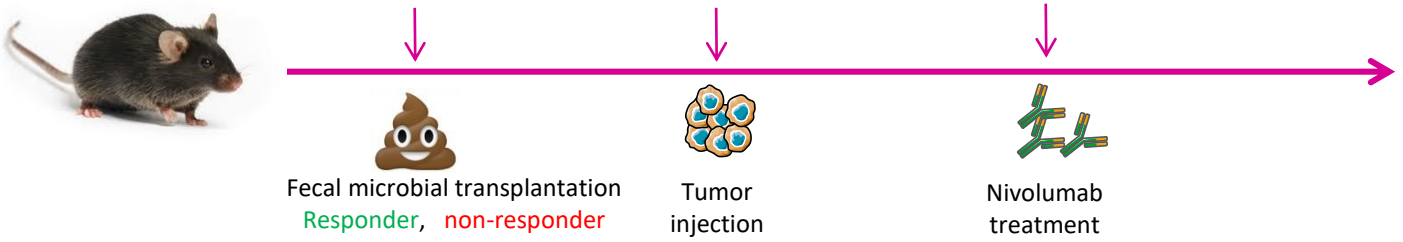
R: responders; NR: non responders

Metagenomics

Shot gun DNA Seq



NSCLC Fecal microbial transplantation in « Avatar » mice
We recolonized ATB treated mice with FMT of stools from lung cancer patients

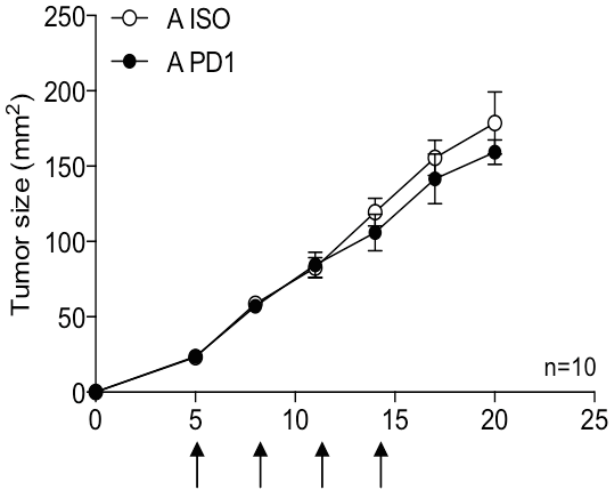


FMT	Patient characteristics							
All patients (n=7)	Non responders				Responders			
	A	B	E	F	C	D	H	I
Age-yr	67	76	77	48	61	73	66	53
Gender	Male	Male	Female	Male	Male	Male	Female	Male
Smoking status	Former	Former	Former	Current	Current	Former	Non smoker	Former
Histology	Non-squamous	Non-squamous	Non-squamous	Squamous	Non-squamous	Non-squamous	Non-squamous	Non-squamous
Mutation status	KRAS positive	Negative	Negative	Negative	Negative	Negative	EGFR positive	Negative
Number of metastatic sites	3	1	1	1	1	1	1	2
Brain metastasis	Yes	No	No	No	No	No	No	No
Number of prior systemic regimens	2	2	1	2	1	4	3	1
Time to Progression-months	2,4	1,3	1,6	1,4	4,5	5	4,3	5,1

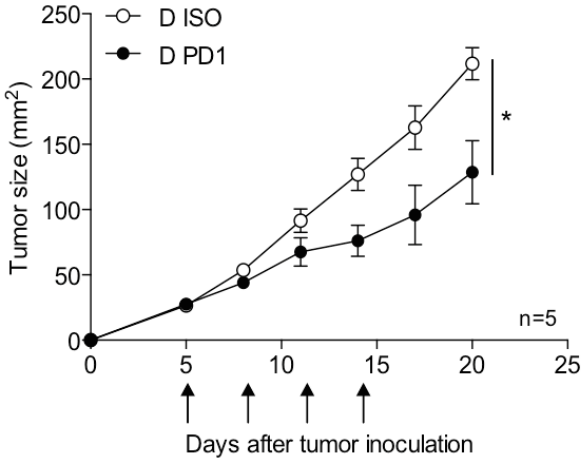
(Routy, Le-Chatelier, Derosa et al; Science, 2018).

Feces composition influences the antitumor efficacy of anti-PD1 Abs in avatar mice

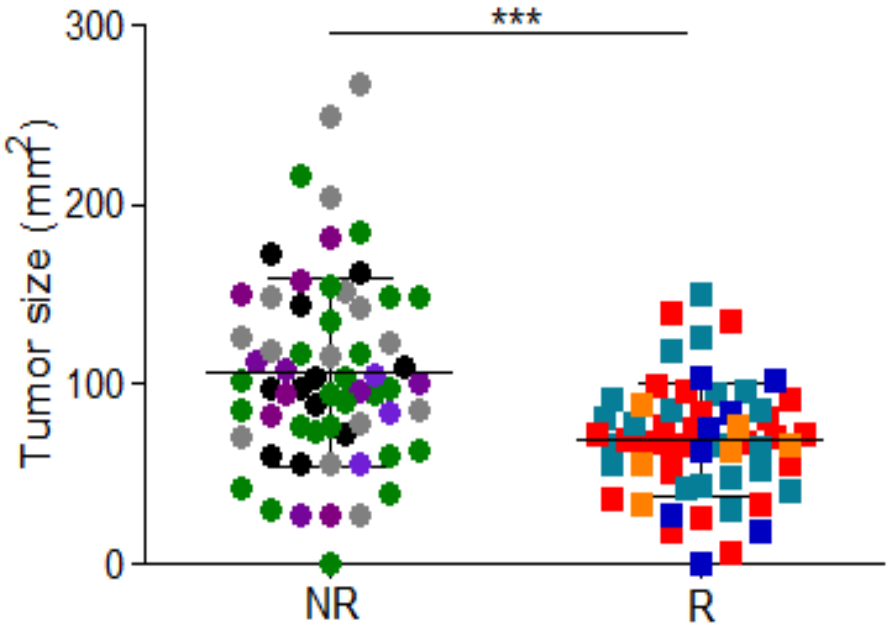
PROGRESSOR FMT



RESPONDER FMT



Anti-PD1 Ab-treated



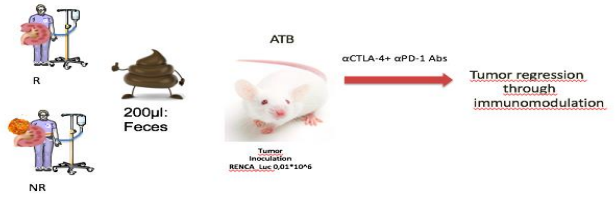
Non responders : A, B, E, F, NSCLC pt (RECIST criteria at 3 months
Responders : C, D, H, I, NSCLC pt (RECIST criteria at 3 months

Stools from responders conferred sensitivity

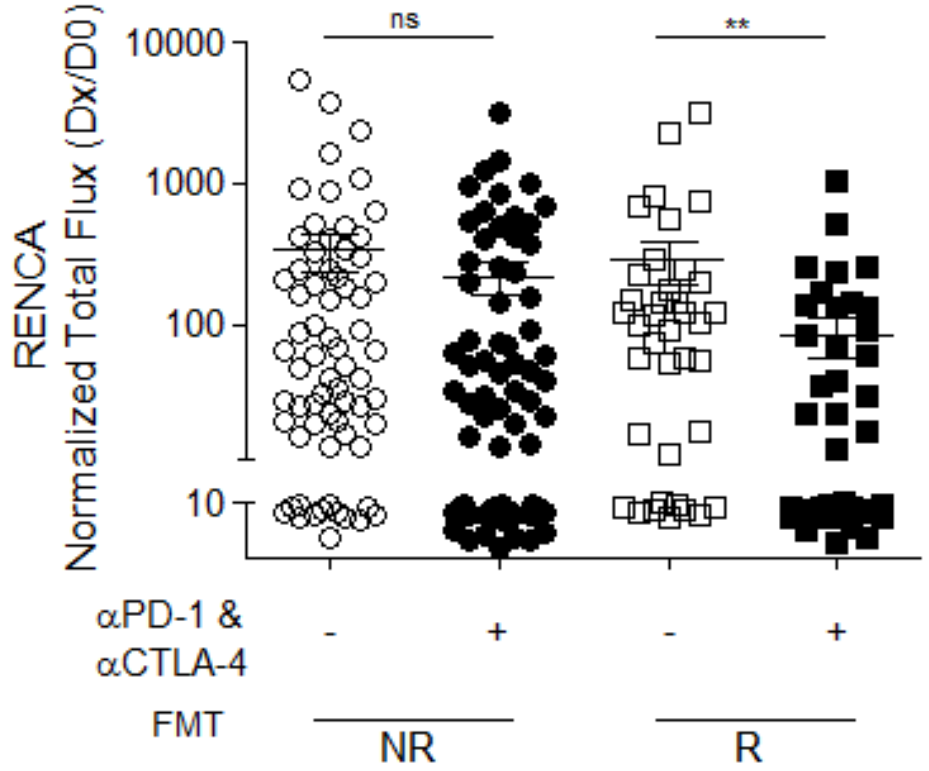
(Routy, Le-Chatelier, Derosa et al; Science, 2018).

Fecal microbial transplantation in the context of kidney cancer:

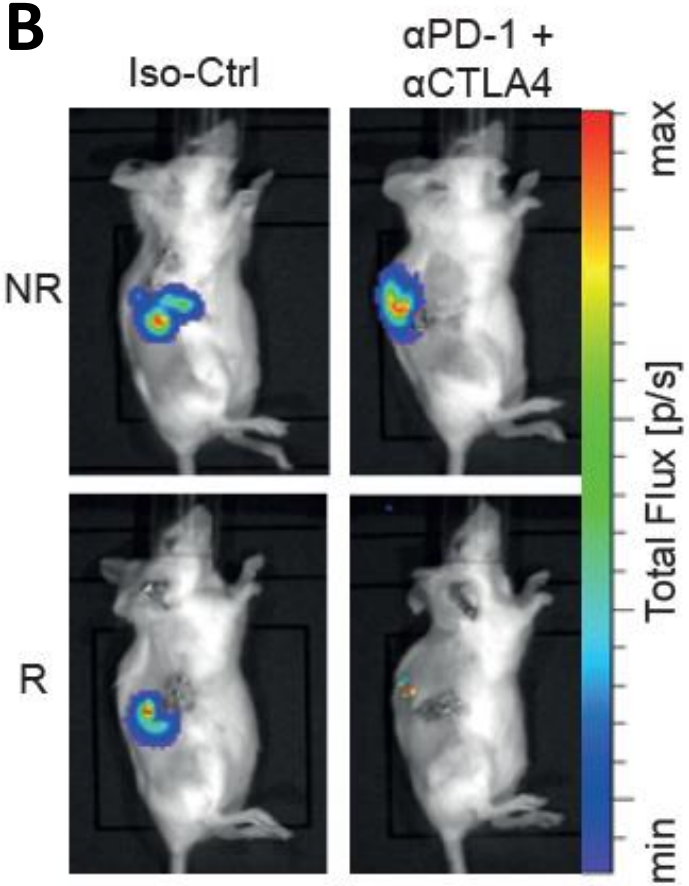
RCC cancer feces into ATB avatar RENCA mice



A



B

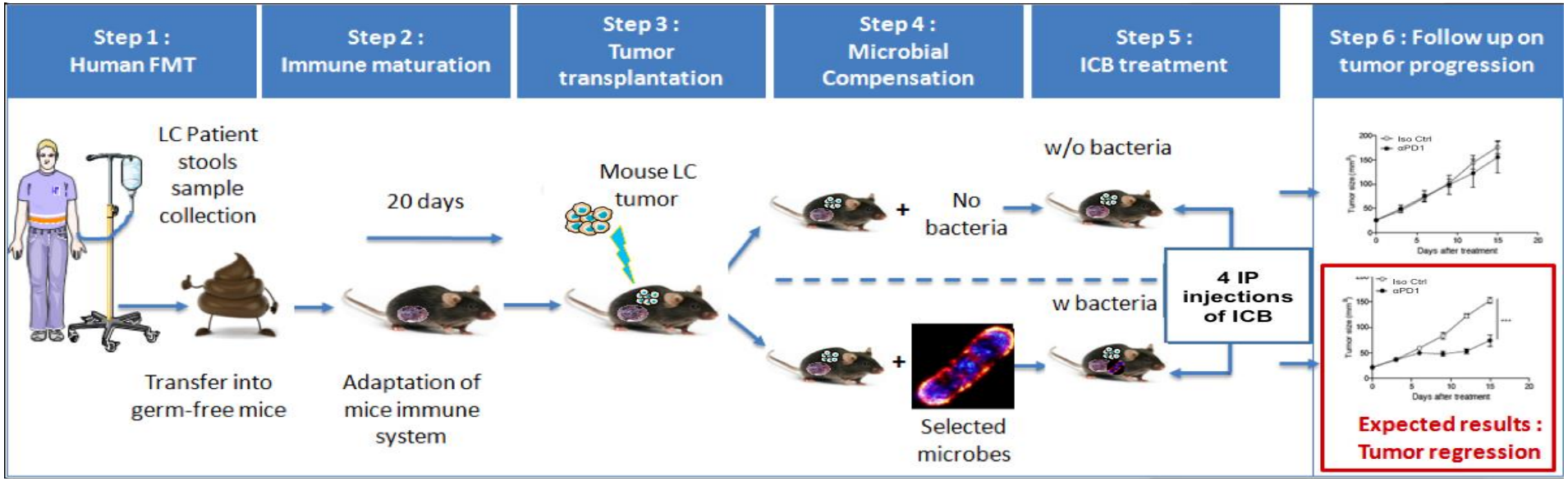


n: 131
FMT of 5 RCC NR and 5 RCC R

R: responders; NR: non responders

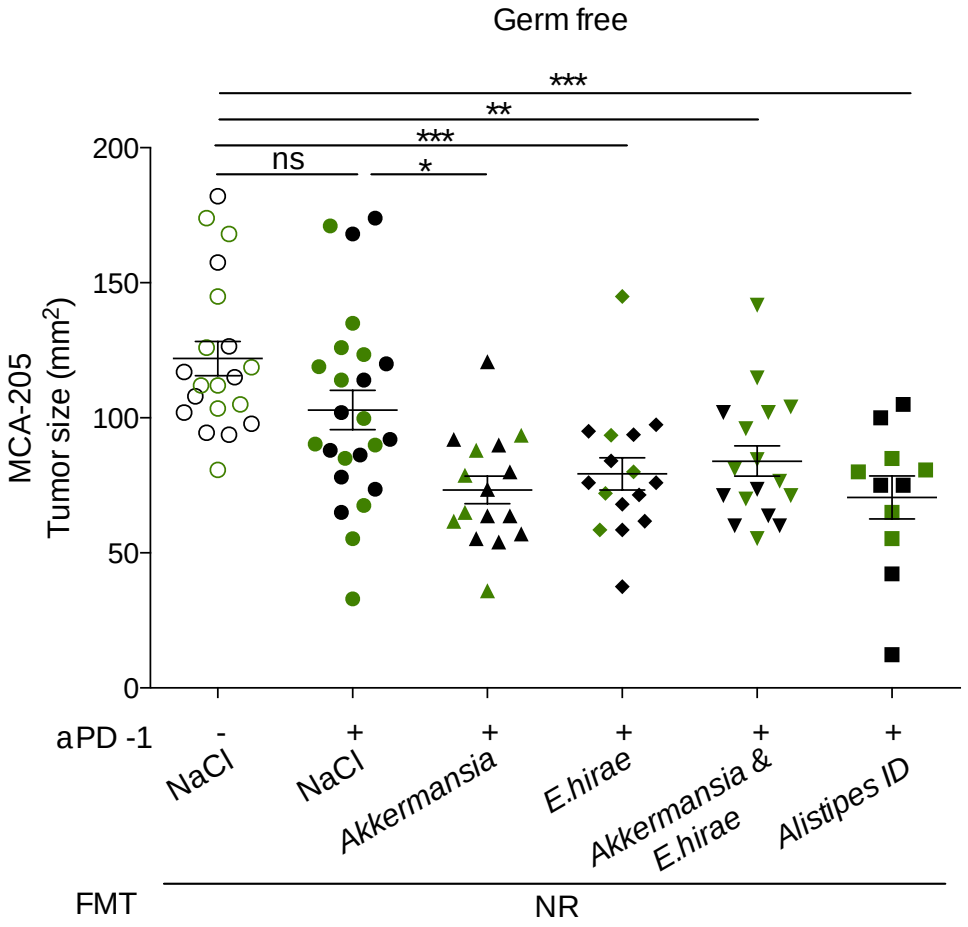
(Modified from Routy, Le-Chatelier, Derosa et al; Science, 2018).

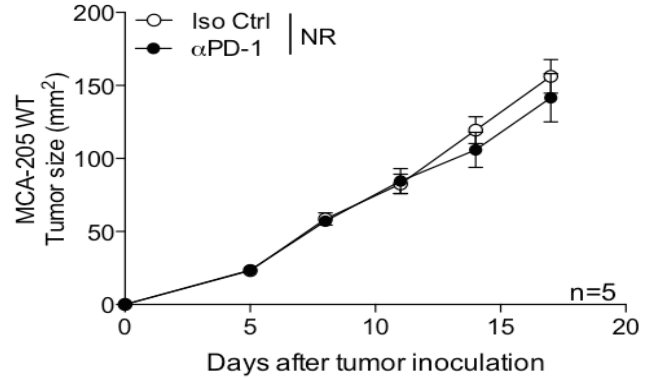
Avatar model to compensate non responder feces into good feces with oncomicrobiotics

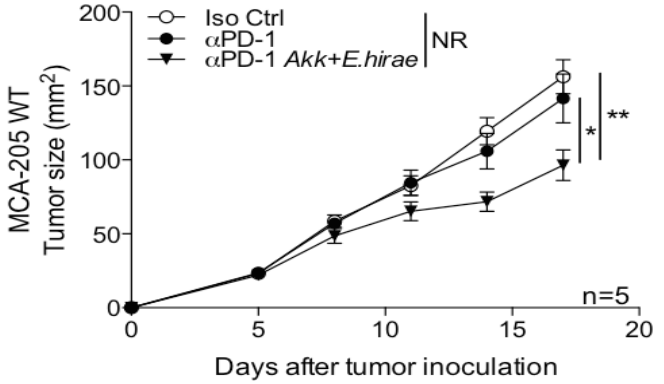


To validate the biological significance of the commensal species identified in the metagenomic analysis of patients with a favorable clinical outcome, we mono- or bi-colonized mouse intestines with A. muciniphila alone or combined with other commensals (oncoBax) in several conditions of gut dysbiosis

FMT-induced dysbiosis: Restoration of aPD1 Abs efficacy with anticancer probiotics



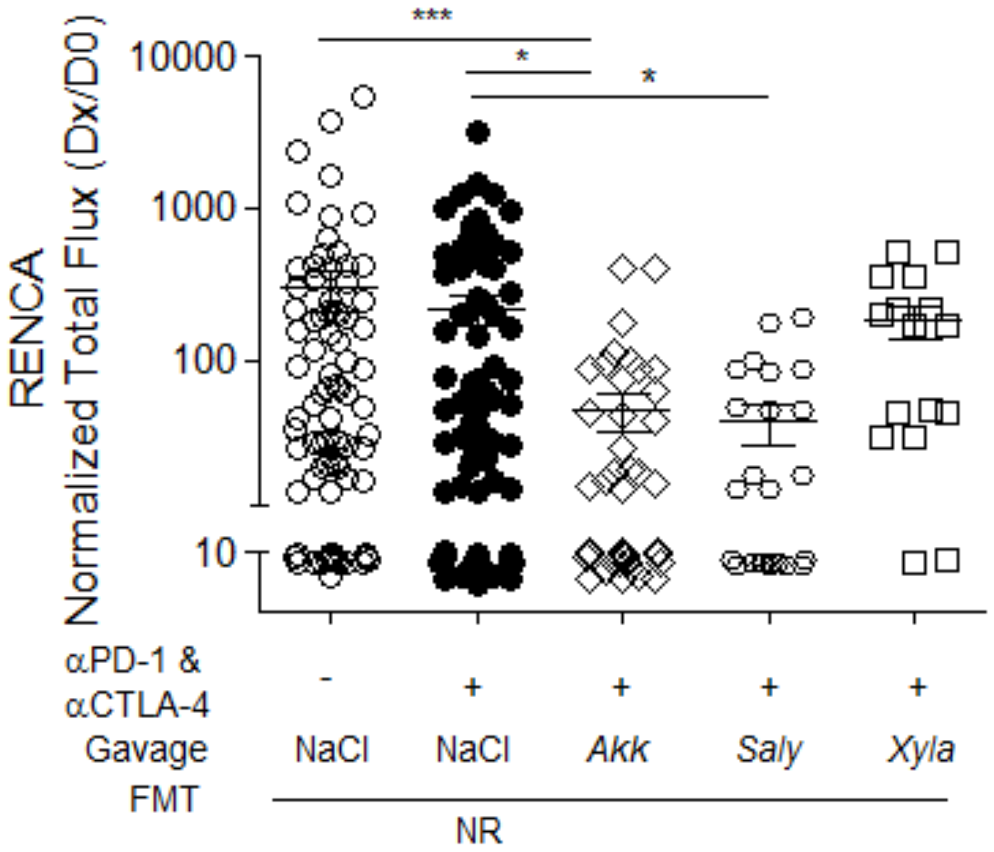


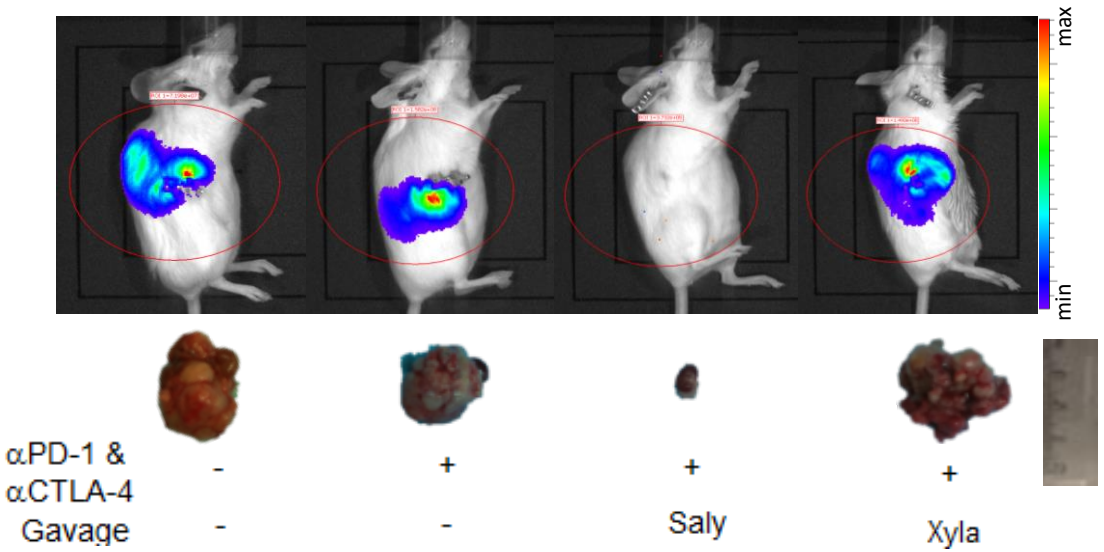


NB: random bacteria *E. faecalis or B. nordii* did not compensate the dysbiosis

(Modified from Routy, Le-Chatelier, Derosa et al; Science, 2018).

Next, in RENCA model oral supplementation with *A. muciniphila* or *B. salyersiae* (but not *B. xylanosolvens*) post-FMT with NR feces restored the efficacy of PD-1/CTLA-4 co-blockade

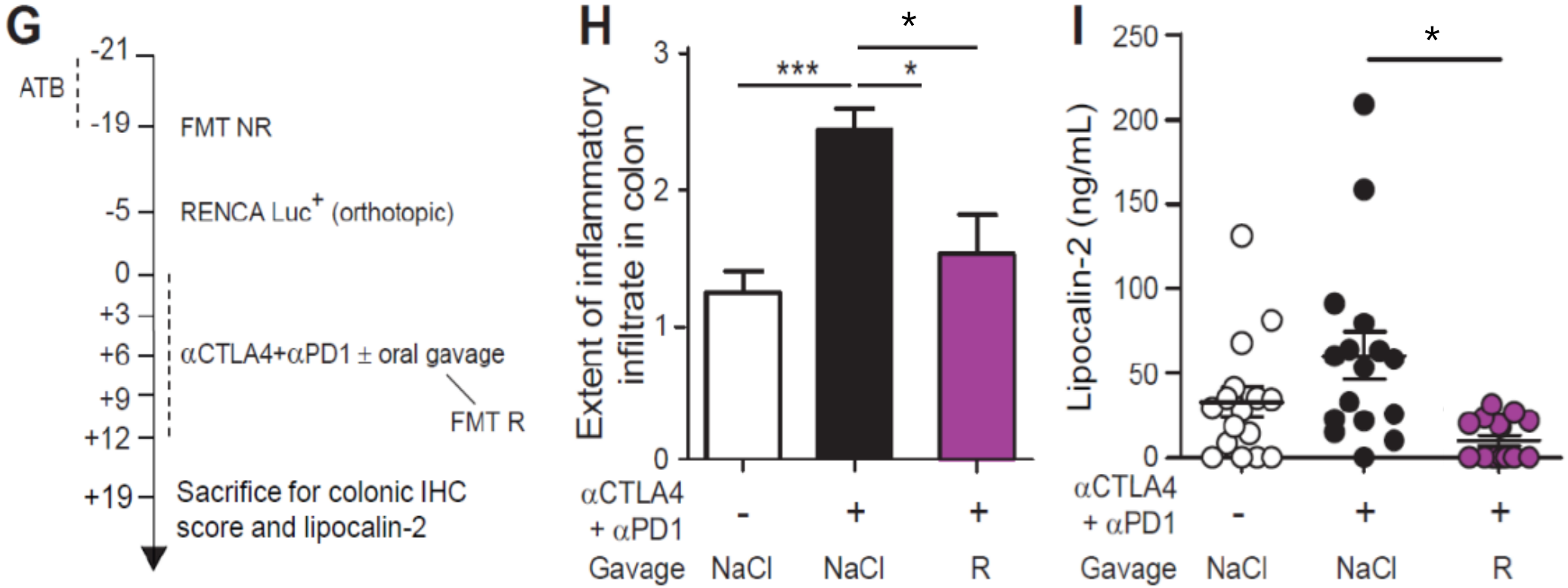




Tumor free: Dx/D0 < 10

Modified from Derosa L. ASCO 2018 Merit Award

Combo treatment results in gut toxicity but oral gavage with R feces conferred protection against toxicity

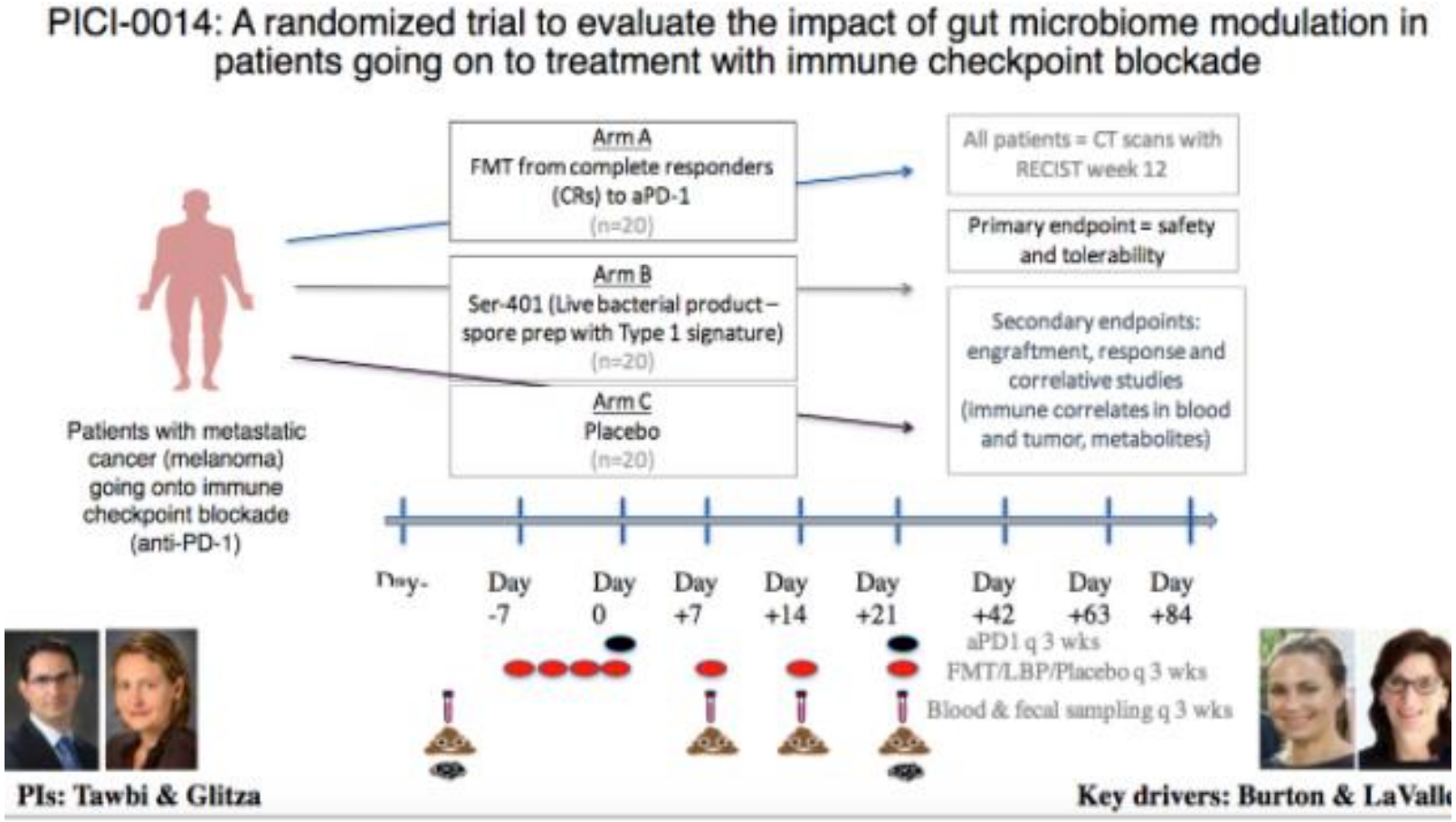


Gavage with R feces:

48,5% increase in the prevalence of tumor free mice

Andrews M and Derosa L (Jenny Wargo's lab) in preparation

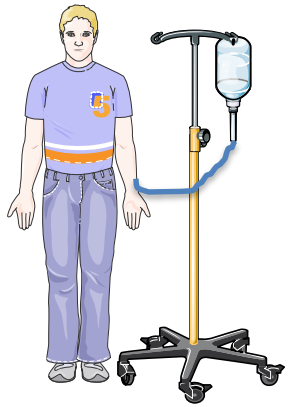
Fecal microbiota transplant and administration of bacterial consortia are being used experimentally in cancer



There are considerable question regarding the selection of the most appropriate donor or the optimal composition of bacterial formulation

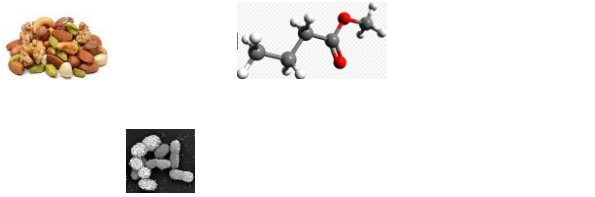
J. Wargo lab

Modulating the microbiome to improve therapeutic resonse: Ready for clinical trials?



Diagnostic Kit

Unfavorable feces



Favorable feces

Modalities that may modify the patient microbiome:

- Fecal transplant (R or HV stools?)
- Diet
- Bacteria (single vs consortia)
- Antibiotics
- Prebiotics
- Metabolites

GRCC Cacathèque

Network 1 (RHU): LUMIERE

H&N
-Nivo 2nd line

Chemotherapy
CANTO (Breast)
Standard Chemo 1st line
92 (150)

OvBiomark (Ovarian)
Standard Chemo 1st line
34 (100)

Healthy Volunteers
-Metacardis
-Italy
54(100)

Melanoma
-Nivipit

NSCLC
ABimmune
Durva+RadioTx +/- Treme
7(40)

Oncobiotics
Nivo 2nd line
380(400)

Oncobiotics
Pembro 2nd line
4(50)

PRINCEPS
Neoadj Atezo
7(40)

Oncobiotics
Pembro 1st line
4(50)

GU

RCC

Nivoren
Nivo 2nd line
76(76)

TiTan
Nivo+Ipi
2nd line (75)

Prostate

Oncobiotics
Enzalutamide
or
ODM205
5 (30)

Oncobiotics
Ipi + Nivo
7 (10)

Oncobiotics
Abiraterone
7 (30)

Bladder

PANDORE
Neoadj Pembro
2 (40)

Oncobiotics
CMML
10(50)

Basket trials

Pembib
Nintedanib+Pembro 2nd line
13(250)

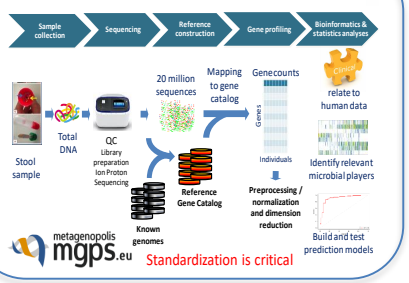
SABR-PDL1
RadioTx + Atezo 2nd line
28(55)

Digestive

Gastric/GEJ
Nivo adj
8(80)

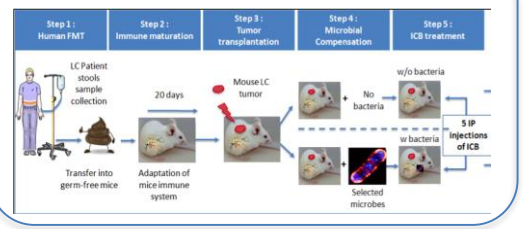
Oesogastric/GEJ
Pembro +CT (neo)adj
(100)

Metagenomics

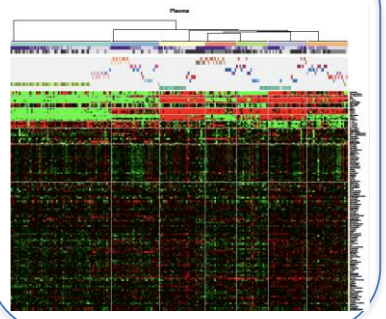


Standardization is critical

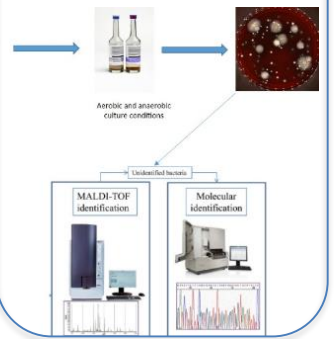
FMT



Metabolomics



Culturomics



Network 2: (H2020): ONCOBIOME

ACRONYM: ONCOBIOME

‘European’ Cacathèque

List of participants

Participant No	Participant organisation name	Country
1 (Coord)	Gustave Roussy Cancer Center (GRCC)	France
2	National Institute for Health & Medical Research (INSERM)	France
3	University of Trento (UNITN)	Italy
4	Fondazione IRCCS Istituto Nazionale dei Tumori (INT)	Italy
5	Masaryk University (MU)	Czech Republic
6	Universitätsklinikum Erlangen (UKER)	Germany
7	Radboud University (RU)	Netherlands
8	Italian Institute for Genomic Medicine (IIGM)	Italy
9	University of Cambridge (UCAM)	UK
10	Karolinska Institute (NKI)	Sweden
11	University Hospital of Montreal (CRCHUM)	Canada
12	Unicancer (UNI)	France
13	La Charité-UniversitätsMedezin Berlin (CHA)	Germany
14	German Breast Group (GBG)	Germany
15	HalioDx (HDX)	France
16	EverImmune (EVI)	France
17	Algoé Consultants (ALG)	France

ONCOBIOME project has received funding from the European Union’s Horizon 2020 research and innovation programme

ONCOBIOME endpoints

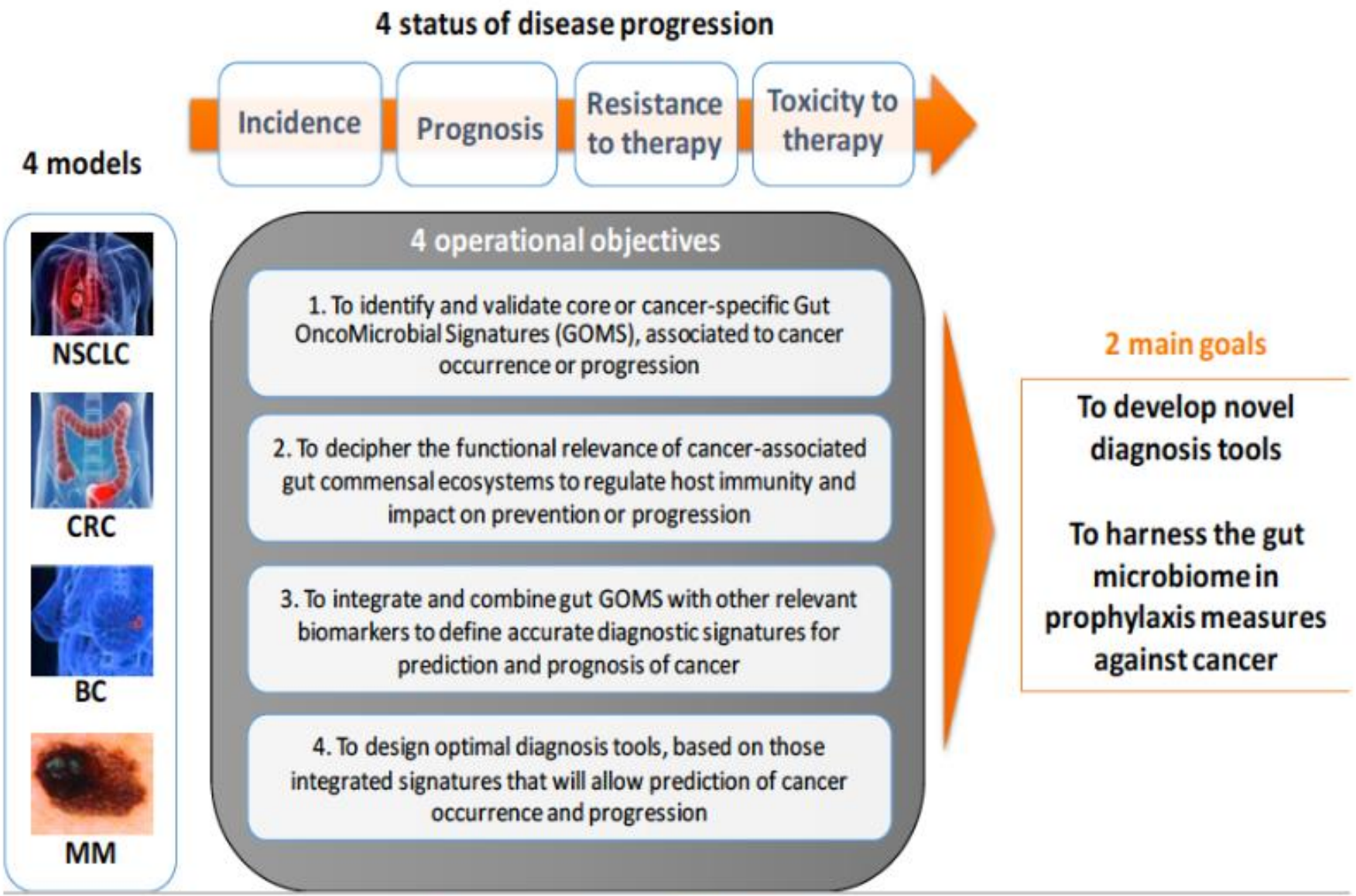


Figure 1: ONCOBIOME objectives

Conclusion and future perspectives

- Microbiota affects immunity and therapeutic response in cancer
- Mouse model suggest that modulation of the microbiome can enhance responses to ICI and prevent toxicity
- Ready for interventional studies?
  - Life stile/diet randomized trial are challenging!
- Paradigm shift in oncology
  - From tumor cells
  - To immune system
  - To host and its environment

In GUT (bacteria), we trust!





CRCHUM


McGill University Health Centre Research Institute

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS




INRA SCIENCE & IMPACT


1884
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Institut Pasteur de Lille
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metagenopolis mgps.eu
Instituts thématiques Inserm Institut national de la santé et de la recherche médicale
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS
université PARIS-SACLAY

If You Trust Gut (Microbiota), Please Contact Me For Collaborations

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