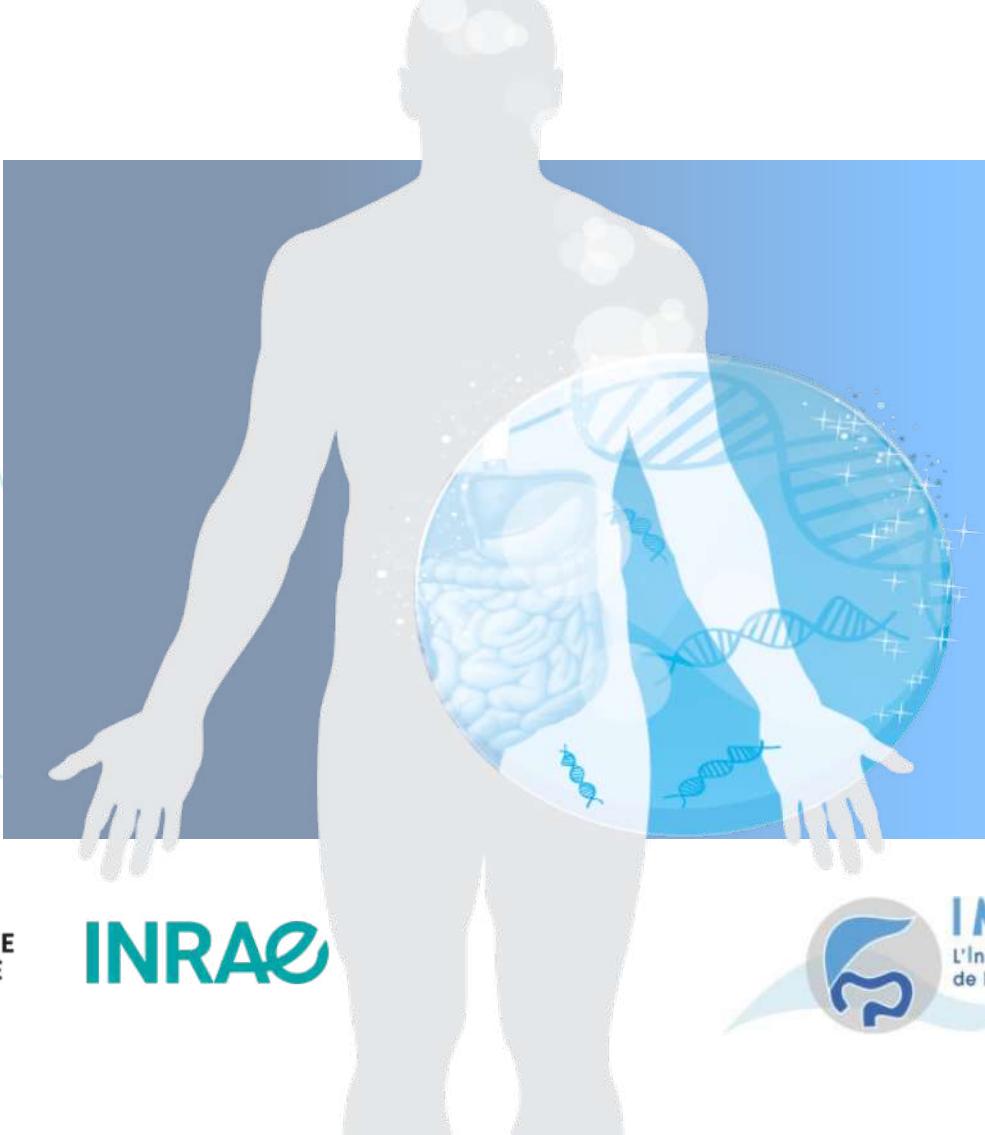


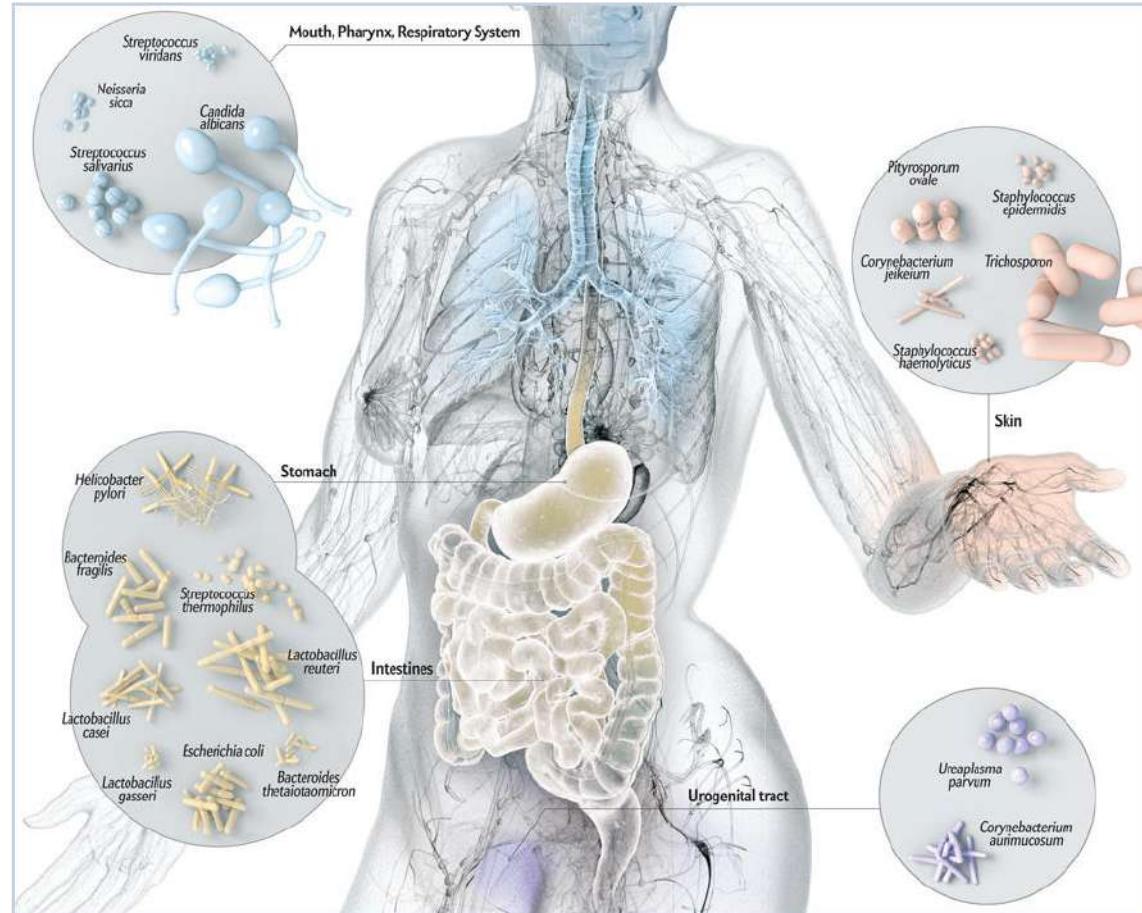
De la flore intestinale à la révolution Microbiome : la découverte d'un organe négligé et de son importance en Santé Humaine



Hervé M. Blotti  re

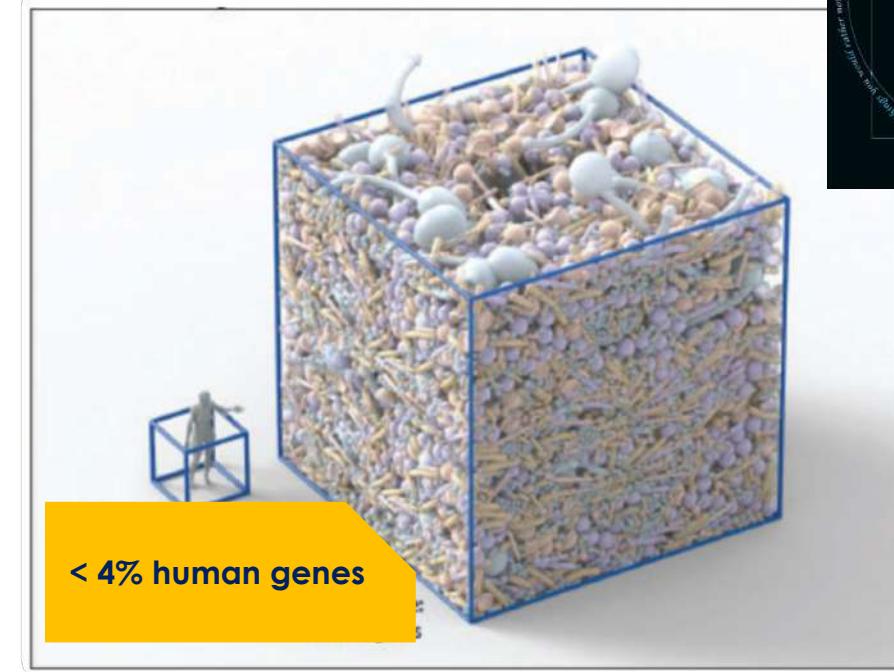
UMR 1280 PhAN, INRAE, Univers  t de Nantes,
«Physiopathologie des Adaptations Nutritionnelles »
&
MetaGenoPolis, INRAE
University of Paris-Saclay
78350 Jouy en Josas

The Human is Microbial, Ecosystem and Symbiosis



23,000
Human
gène

600,000
microbial genes*



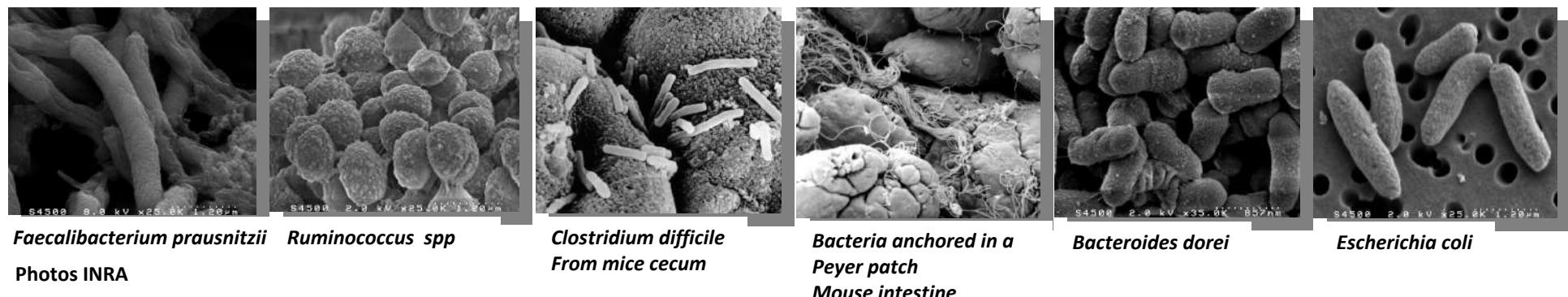
Science of the microbiome is changing the landscape of biology and Medicine

* per individual

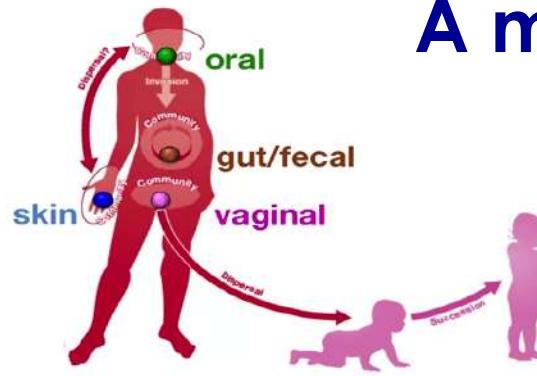
The human intestinal microbiota

- ✓ 39 trillions microorganisms (Sender et al, Cell 2016) ;
- ✓ As many microorganisms as human cells
- ✓ Hundreds of different species predominantly **not yet cultured** (~70% of dominant species);
- ✓ a few dozen species conserved between individuals (core); a stable community.
- ✓ A key organ, interacting with food (fermentation,...); interacting with our cells (immune & nervous systems,...); protecting against pathogens (barrier function);...
- ✓ A true organ, revealed as playing a role in several diseases
- ✓ Thousands of metabolites/molecules with potential functional interest

(Blottière & Doré, médecine/science, 2016)

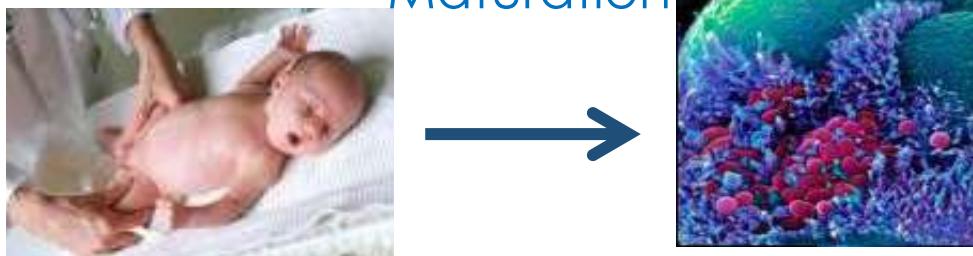


Mom



A man-microbe mutualism that starts at birth

Intestinal & immune
Maturation



Developement
of the microbiota

'unique' symbiosis :
microbiota being
recognized
as an integral part of
the whole organism

Holobiont

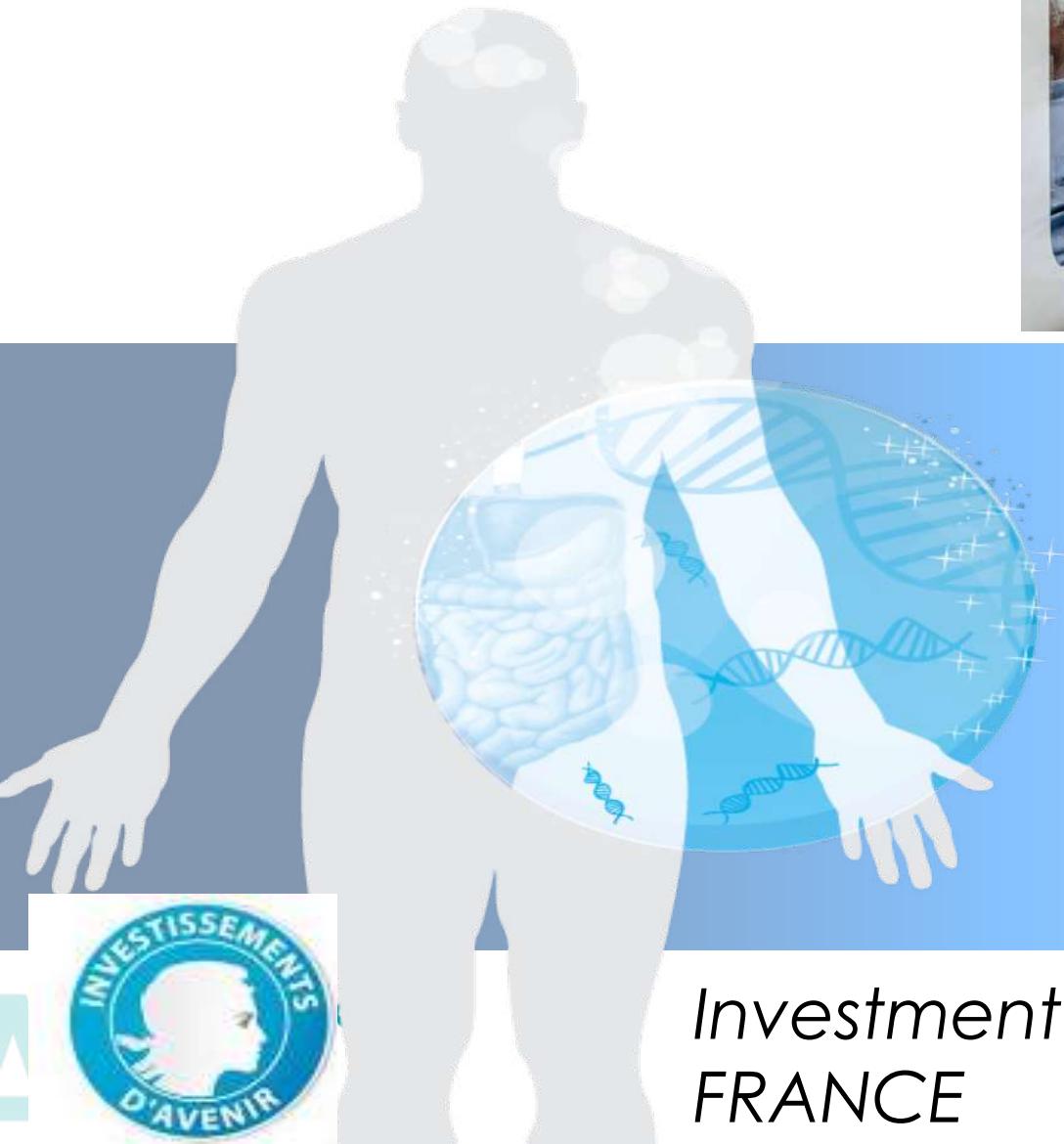
Maintained symbiosis :
health and well-being

Disruption of
ecological balance :
Risk of infection

Disruption of tolerance :
Risk of immune-mediated
disorders

Prevention & Therapy of the
Holobiont : evaluation,
monitoring and treatment

**MetaGenomic tools to characterize
the microbiome**



MetaGenoPolis

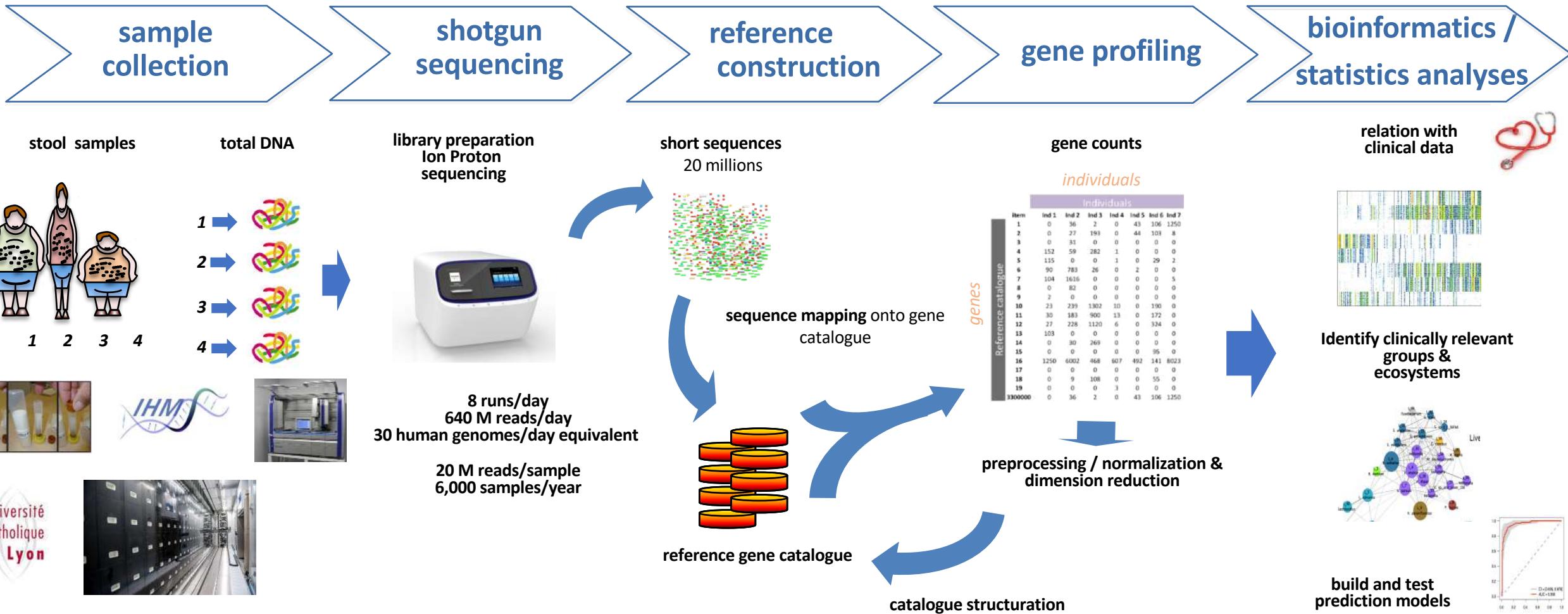
**Platforms dedicated to quantitative
and functional exploration of the
microbiome**

Investment for the Future,
FRANCE



Quantitative metagenomic Pipeline at Metagenopolis

Sambo-MetaQuant-InfoBioStat



Scientific excellence: +100 publications in metagenomics



Hervé Blottière
Metafun director
MetaGenoPolis
Scientific director - Micalis
FinE
Functional metagenomic
expert



Stanislav Dusko Ehrlich
Principal investigator
MetaGenoPolis
*Recognized for his
exceptional research
influence in 2019
by web of science group*



Joël Doré
Scientific director
MetaGenoPolis-Micalis
FinE
*Received the Marcel
Dassault prize for research
in mental illnesses in 2017*

Cancer

2018: Routy et al. *Science*, Microbiome and epithelial cancer immunotherapy
2018: Gopalakrishnan et al. *Science*, Microbiome and melanoma cancer immunotherapy

Metabolic disorders

2012: Qin et al. *Nature*, Type II Diabetes
2013: Le Chatelier et al. *Nature*, Richness of gut microbes and metabolic markers
2014: Qin et al. *Nature*, Human gut microbiome alterations in liver cirrhosis
2015: Qin et al. *Nature*, Accurate liver cirrhosis diagnostic
2015: Forslund et al. *Nature*, Drug confounders in microbiome analysis
2016: Pedersen et al. *Nature*, Microbiome & insulin resistance
2020: Viera-Sylva et al. *Nature*, Microbiome & statins

Diet

2011: Arumugam et al. *Nature*, Enterotypes
2013: Cotillard et al. *Nature*, Impact of diet on gut microbiome
2013: Le Chatelier et al. *Nature*, Richness of gut microbes and metabolic markers
2019: Cox et al. *Gastroenterology*, Low FODMAP Diet in Inflammatory Bowel Disease patients

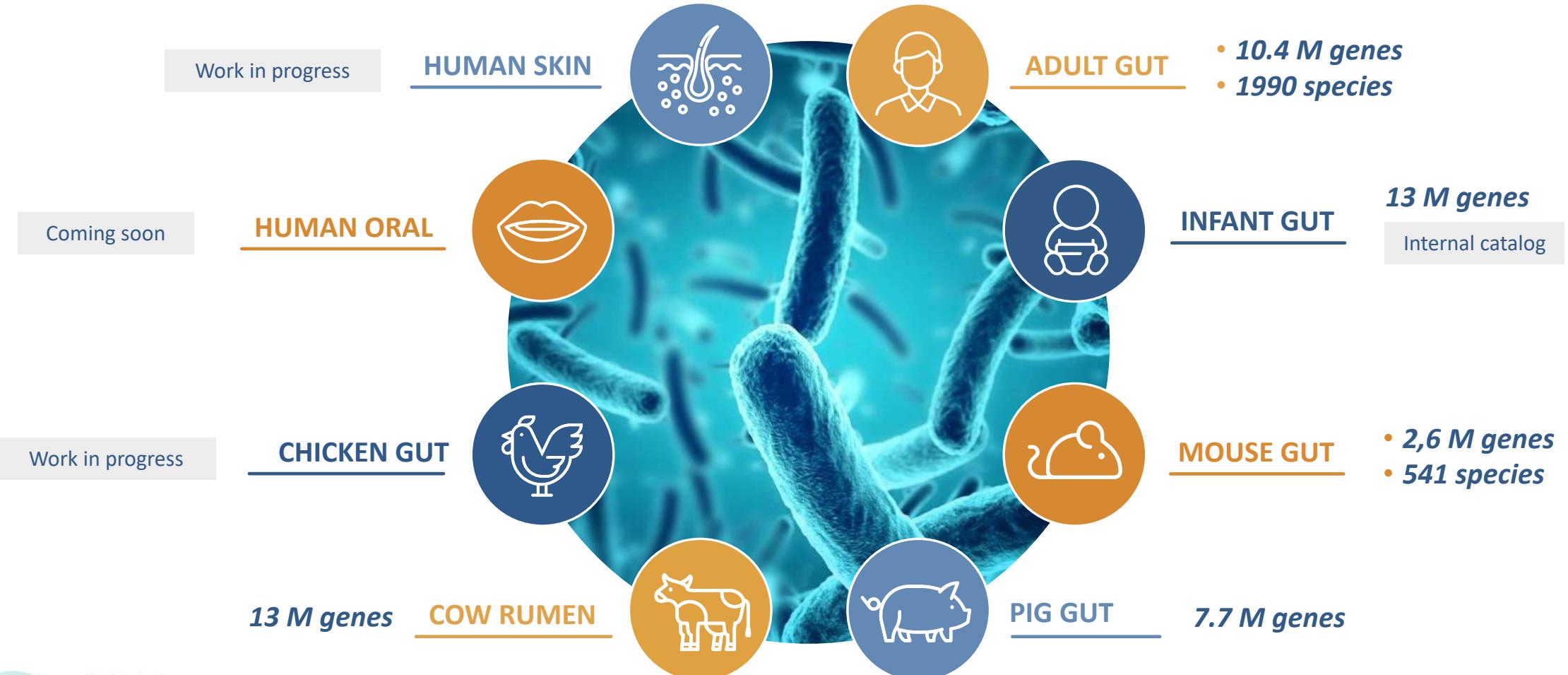
Antibiotic resistance

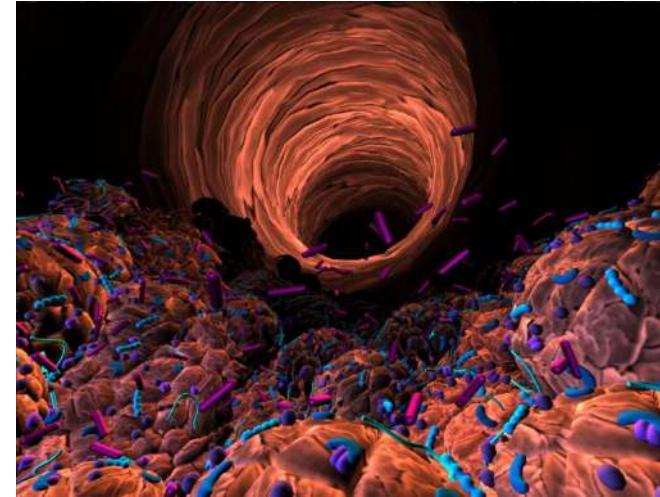
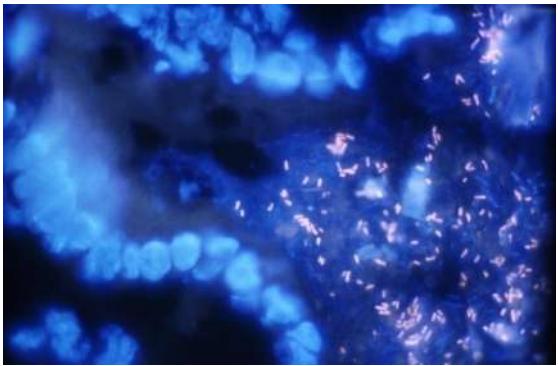
2019: Ruppé et al. *Nature Microbiology*, Prediction of the intestinal resistome

Technologies

2010: Qin et al. *Nature*, The human gut reference catalogue
2013: Sunagawa et al. *Nature Methods*, Universal phylogenetic markers
2014: Nielsen et al. *Nature Biotech*, Method for identifying metagenomic species
2014: Li et al. *Nature Biotech*, 10 millions genes reference catalog
2015: Xiao et al. *Nature Biotech*, A mouse gut gene catalogue
2016: Xiao et al. *Nature Microbiology*, A pig gut gene catalog
2017: Costea et al. *Nature Biotech*, Standards for microbiome studies
2018: Plaza Onate et al., *Bioinformatics*, Reconstitution of metagenomic pangenome species

Gene and species catalogues for various microbiomes





Gut microbiota in healthy individuals

What is symbiosis ?

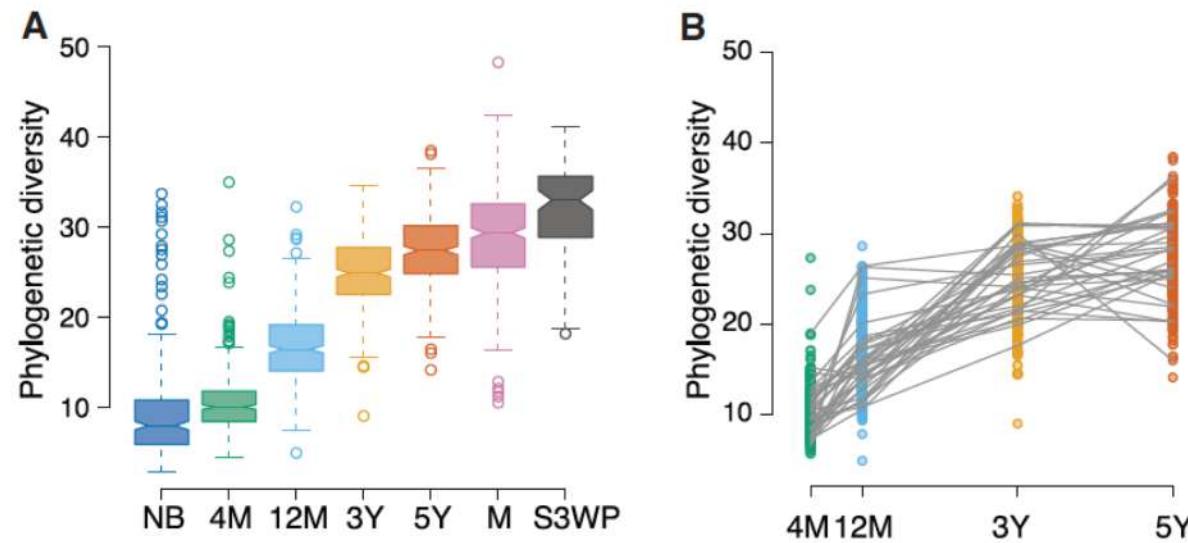


Sterile *in utero*, the intestine is colonized at birth



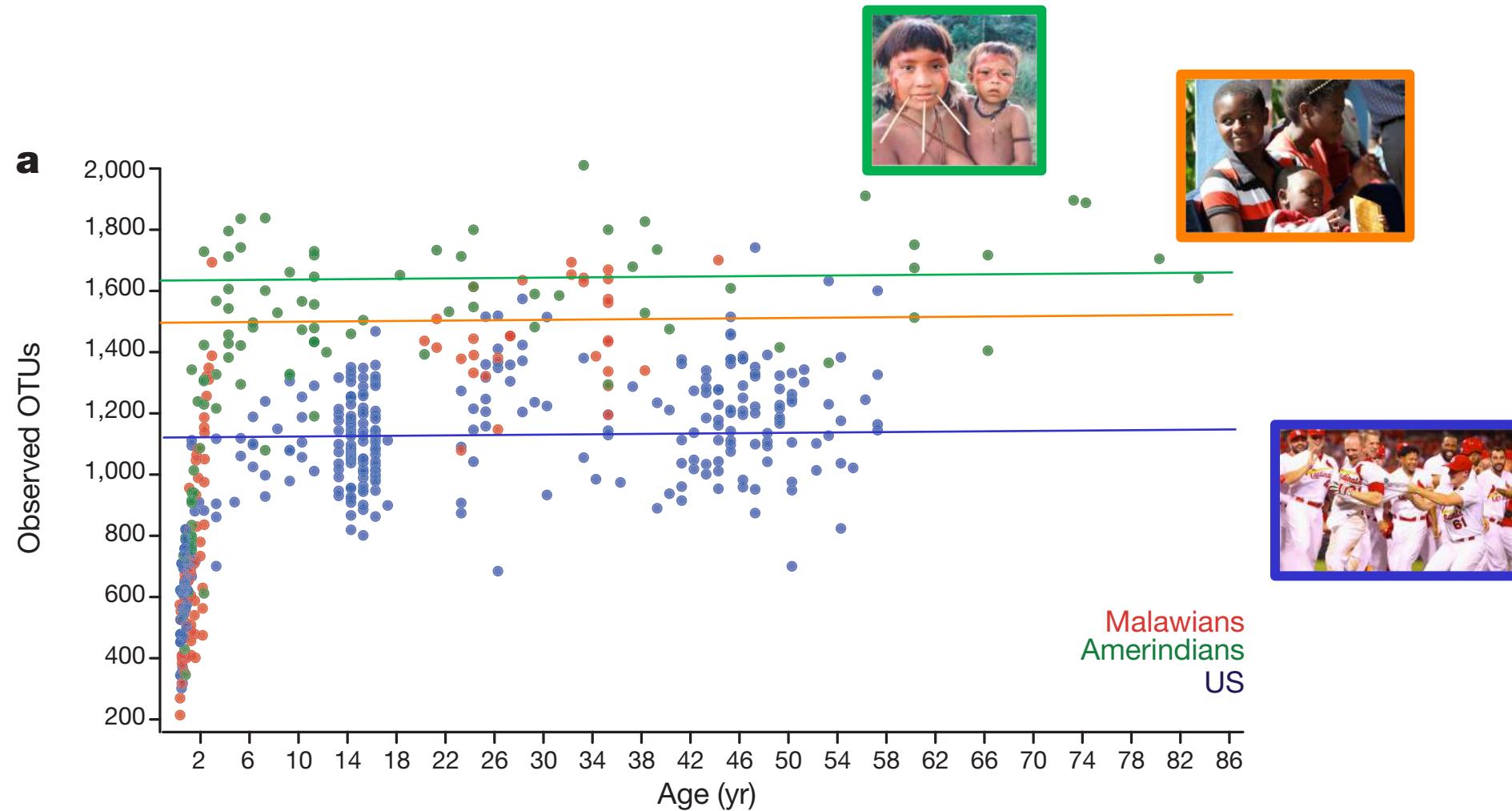
- colonization is affected by :
 - Mode of delivery (vaginal delivery or caesarean section)
 - Hygiene of neonatal environment
 - Drugs administration (antibiotic, PPI, ...)
 - Maternal nutrition and maternal microbiome
 - Mode of feeding (breast milk versus bottled milk; probiotics)
 - Weaning
- early colonization, hygiene hypothesis and DOHaD
 - exposure to **low bacterial diversity** in the neonatal period would prevent or delay maturation of the mucosal immune system and favor aberrant responses to allergens or auto-antigens and onset of associated pathologies

Developmental trajectory of the healthy human gut microbiota during the first 5 years of life



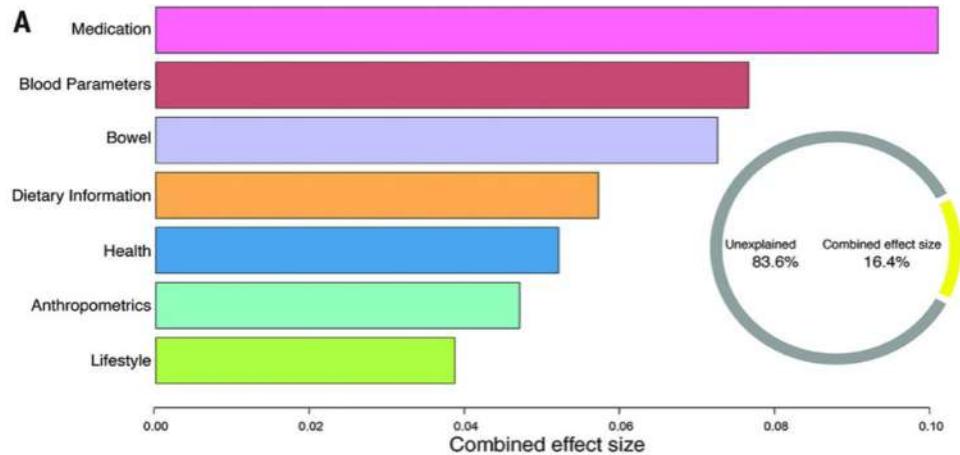
Children gut microbiota mature along similar trajectories but at different speeds
Different microbes follow discrete trajectories in the developing gut microbiota
The effect of c-section on gut microbiota is normalized in 3–5- y.o. children
The gut microbiota has not yet reached adult complexity in 5- y.o. children

Evolution of intestinal microbiota through aging



But What is symbiosis ? Can we really define IT ?

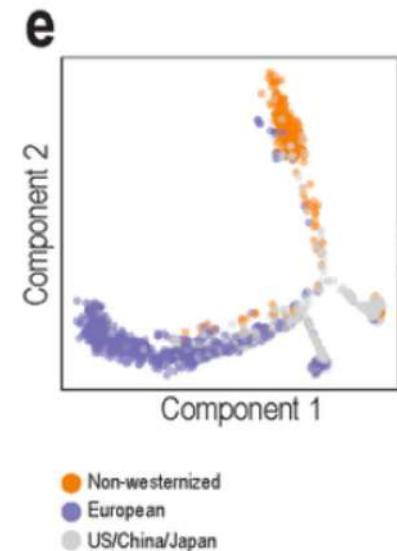
Population-level analysis of gut microbiome variation



1106 Belgium Flemish individuals
16 S sequencing (V4)

Medication explain 10 % of gut microbiota variation
followed by blood parameters, bowel habits, health status,
anthropometric features, and lifestyle.

Global human Gut Microbiome



Introducing Enterotypes

All individuals studied today ($n > 1000$) are clustered in 3 « Entérotypes », each characterized by an ecological context dominated by *Bacteroides*, *Prevotella*, *Ruminococcus/Methanobrevibacter*

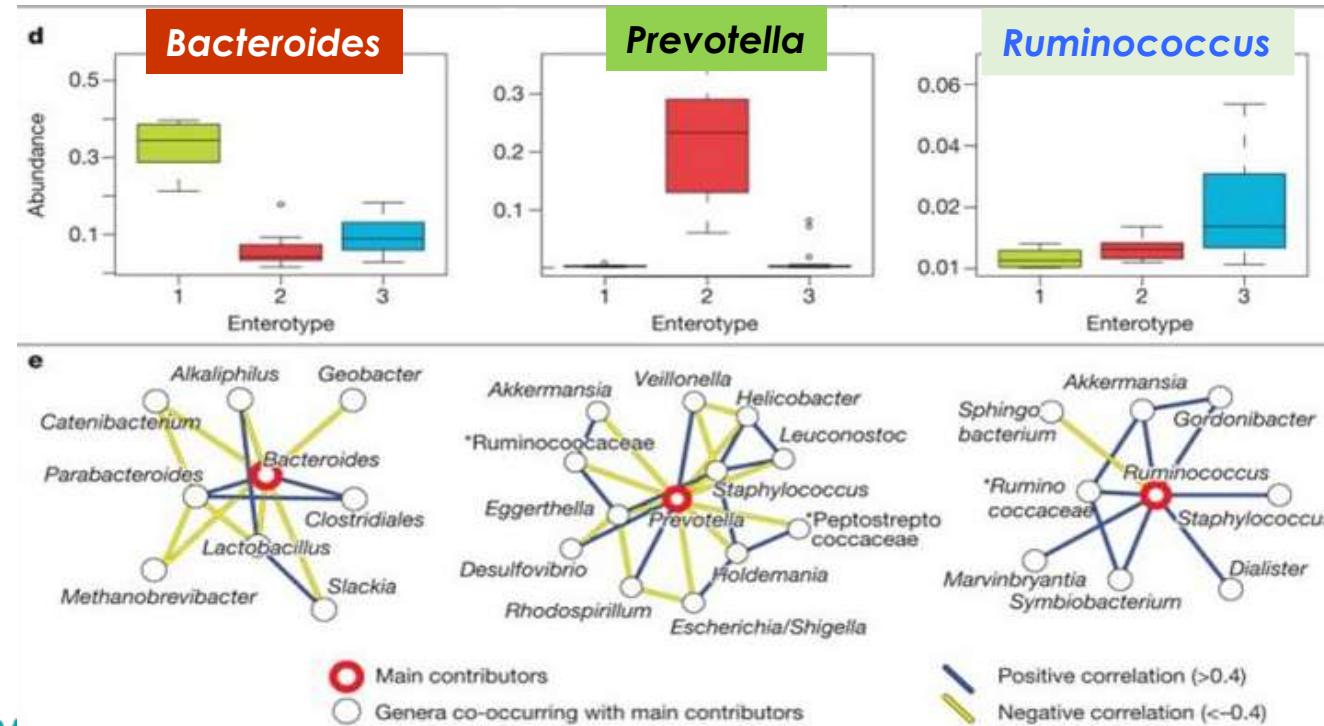
ARTICLE

doi:10.1038/nature09944

Enterotypes of the human gut microbiome

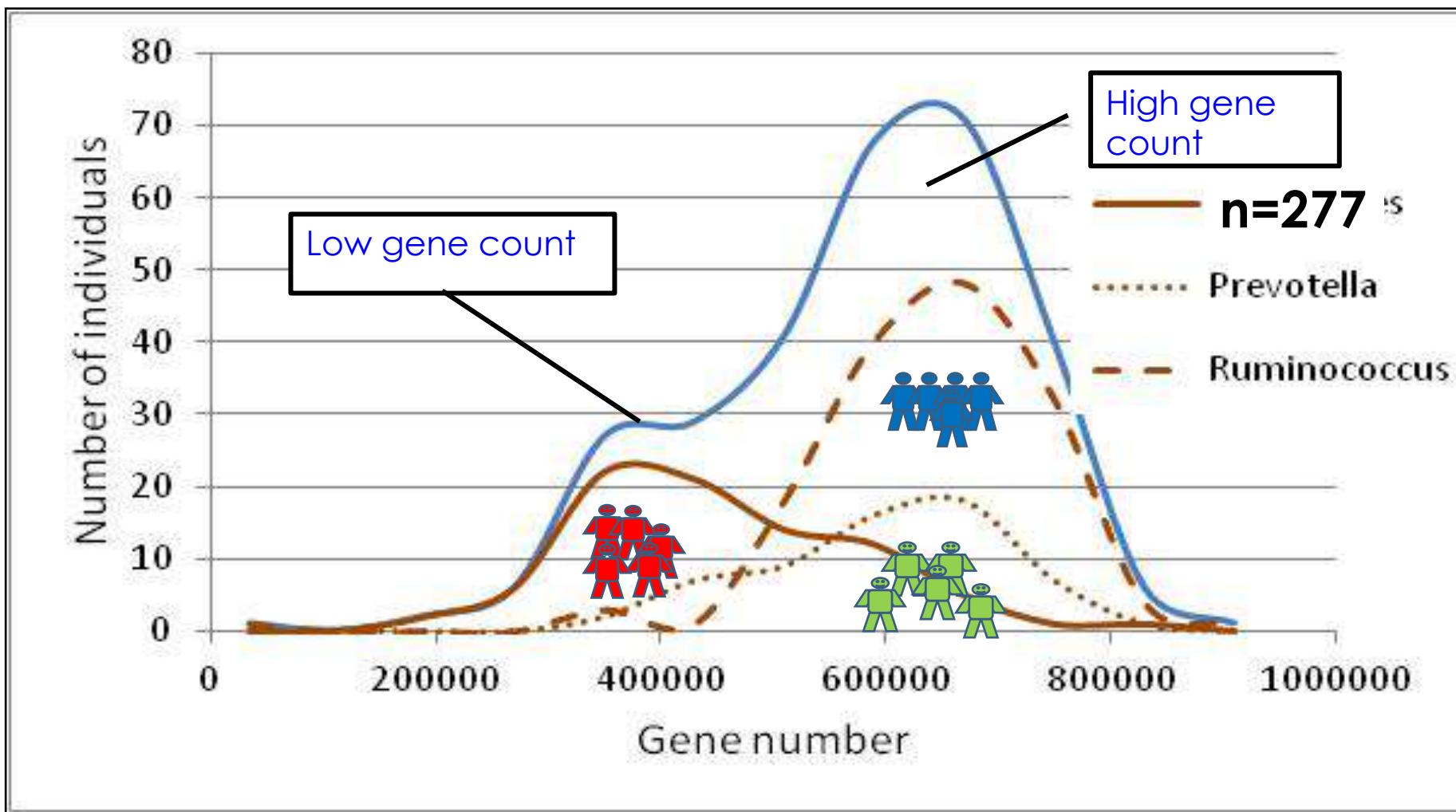
Manimozhiyan Arumugam^{1*}, Jeroen Raes^{1,2*}, Eric Pelletier^{3,4,5}, Denis Le Paslier^{3,4,5}, Takuji Yamada¹, Daniel R. Mende¹, Gabriel R. Fernandes^{1,6}, Julien Tap^{1,7}, Thomas Bruls^{3,4,5}, Jean-Michel Batto⁷, Marcelo Bertalan⁸, Natalia Borrue⁹, Francesc Casellas⁹, Leyden Fernandez¹⁰, Laurent Gautier⁸, Torben Hansen^{11,12}, Masahira Hattori¹³, Tetsuya Hayashi¹⁴, Michiel Kleerebezem¹⁵, Ken Kurokawa¹⁶, Marion Leclerc⁷, Florence Levenez⁷, Chaysavanh Manichanh⁹, H. Bjorn Nielsen⁸, Trine Nielsen¹¹, Nicolas Pons⁷, Julie Poulaert³, Junjie Qin¹⁷, Thomas Sicheritz-Ponten^{8,18}, Sebastian Timm¹⁵, David Torrents^{10,19}, Edgardo Ugarte³, Erwin G. Zoetendal¹⁵, Jun Wang^{17,20}, Francisco Guarner⁹, Oluf Pedersen^{11,21,22,23}, Willem M. de Vos^{15,24}, Søren Brunak⁸, Joel Dore⁷, MetaHIT Consortium†, Jean Weissenbach^{3,4,5}, S. Dusko Ehrlich⁷ & Peer Bork^{1,25}

Link with food habits



Ecology underlying enterotypes should be better understood

Human gut microbiomes differ on gene (and species) richness

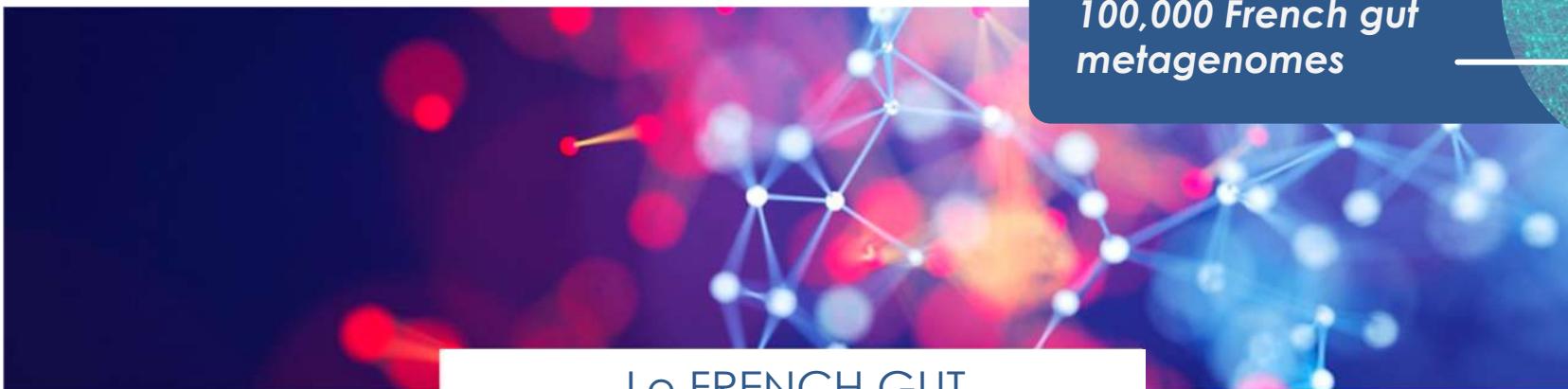


LGC
≈ 15 % of lean individuals
≈ 40% Overweight-moderate obese
≈ 75% Morbid obese before bypass surgery

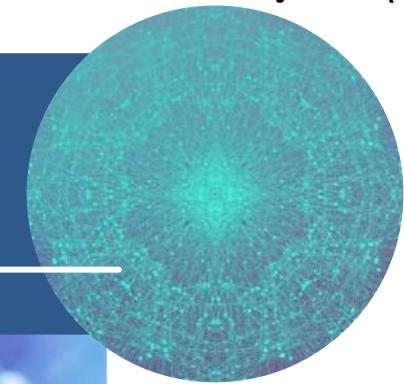
58 « species » significantly linked to gene count

Le Chatelier, et al, Nature 2013; Cottillard et al, Nature, 2013

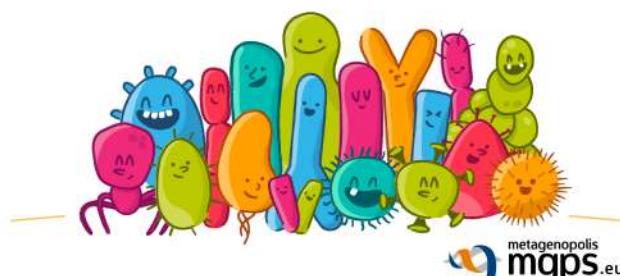
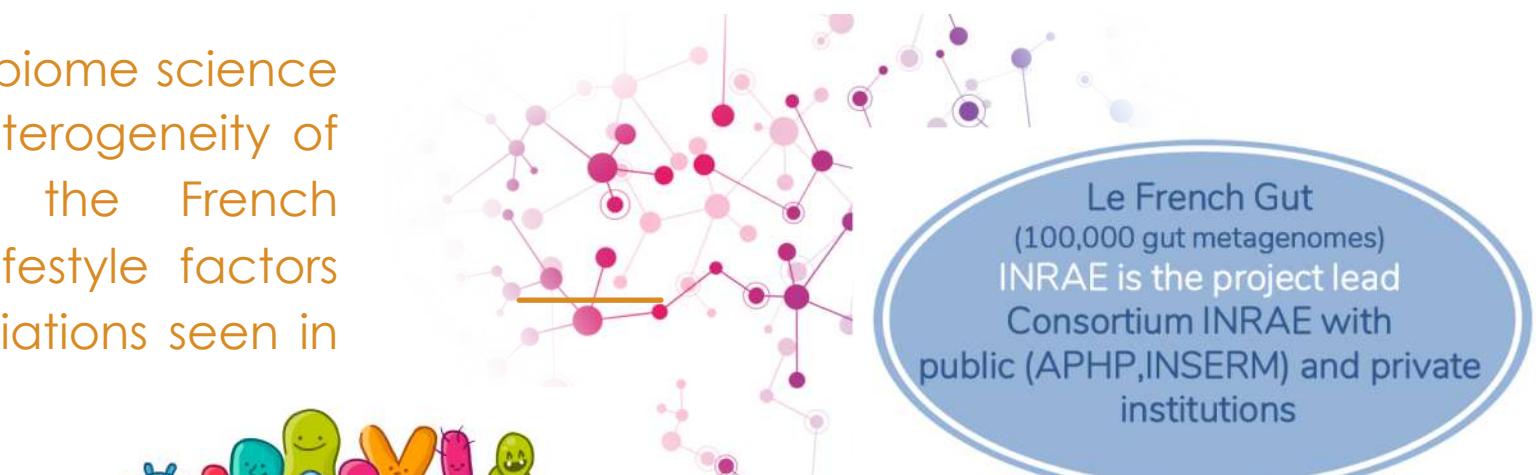
Introducing « Le French Gut » project



MGP participates to MMHP by bringing 100,000 French gut metagenomes



National citizen contribution to microbiome science with the ambition of defining the heterogeneity of healthy gut microbiomes within the French population, the environmental and lifestyle factors impacting them, as well as their deviations seen in chronic diseases



Perturbation of intestinal microbiota and diseases

also

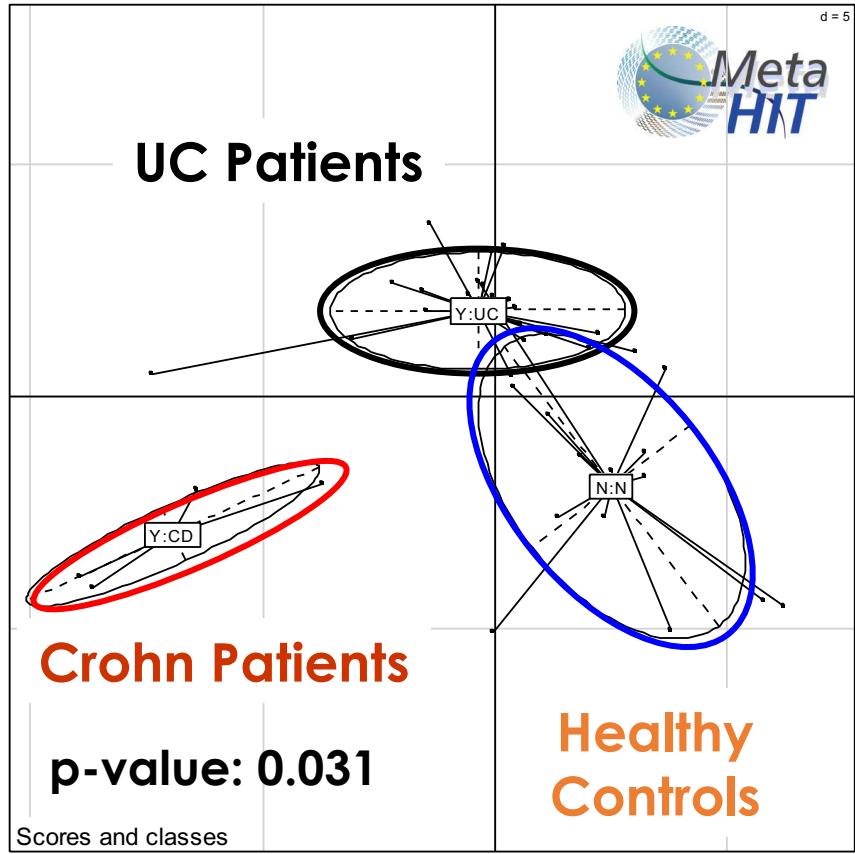
- ✓ Multiple sclerosis
- ✓ Alzheimer disease
- ✓ Parkinson disease
- ✓ Hypertension
- ✓ Spondyloarthritis
- ✓ Bone
- ✓ Kidney diseases
- ✓ Cancer
- ✓

From Human clinical studies

Blottière & Doré,
médecine/science, 2016

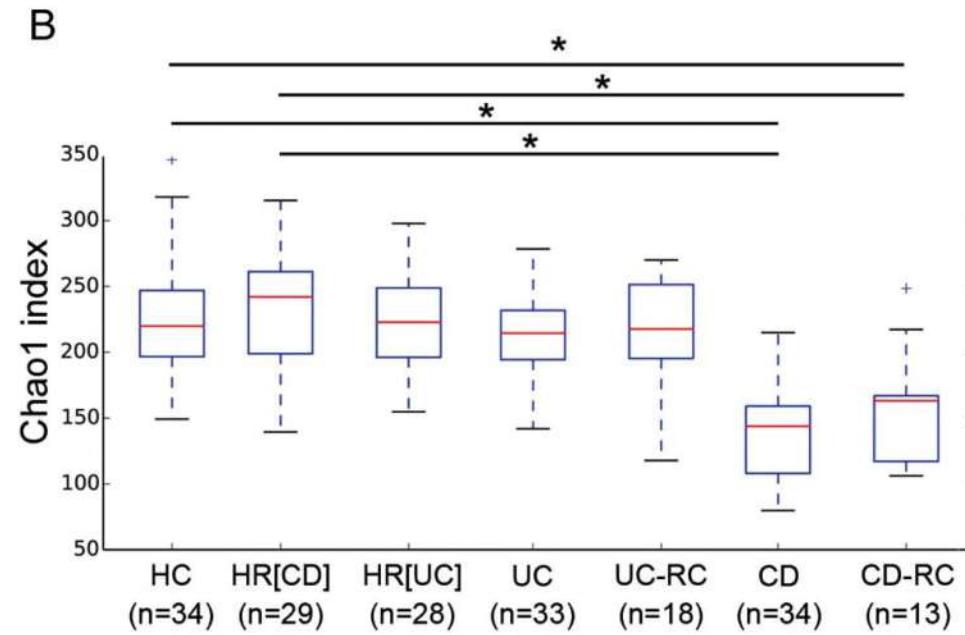
Pathologies	References
Crohn's disease	Qin, Nature 2010 Gevers, Cell Host Microbe 2014
Ucerative colitis	Qin, Nature 2010 Lepage , Gastroenterology, 2011
Celiac disease	D'Argenio, Am J Gastroenterol 2016
Irritable bowel syndrome	Saulnier, Gastroenterology 2011 Rajilic-Stojanovic, Gastroenterology 2011
Colorectal cancer	Zeller, Mol Syst Biol 2014 Sobhani PLoS one 2011
Obesity	Le Chatelier, Nature 2013 Ley, Nature 2006
Type 1 diabetes	Kostic, Cell Host Microbes 2015 Murri, BMC medicine 2012
Type 2 diabetes	Forslund, Nature 2015
Seniors frailty	Claesson Nature 2012
GVHD	Taur, Blood, 2014
Allergy	Abrahamsson, J Allergy Clin Immunol 2012
Liver pathologies	Qin, Nature 2014
Cardiovascular diseases	Karlsson Nat Commun 2012 Projet MetaCardis
Autism, Depression,	Finegold, Anaerobe 2010 Naseribafrouei Neurogastroenterol Motil 2014

Human Inflammatory Bowel Diseases



Qin et al *Nature*, 2010

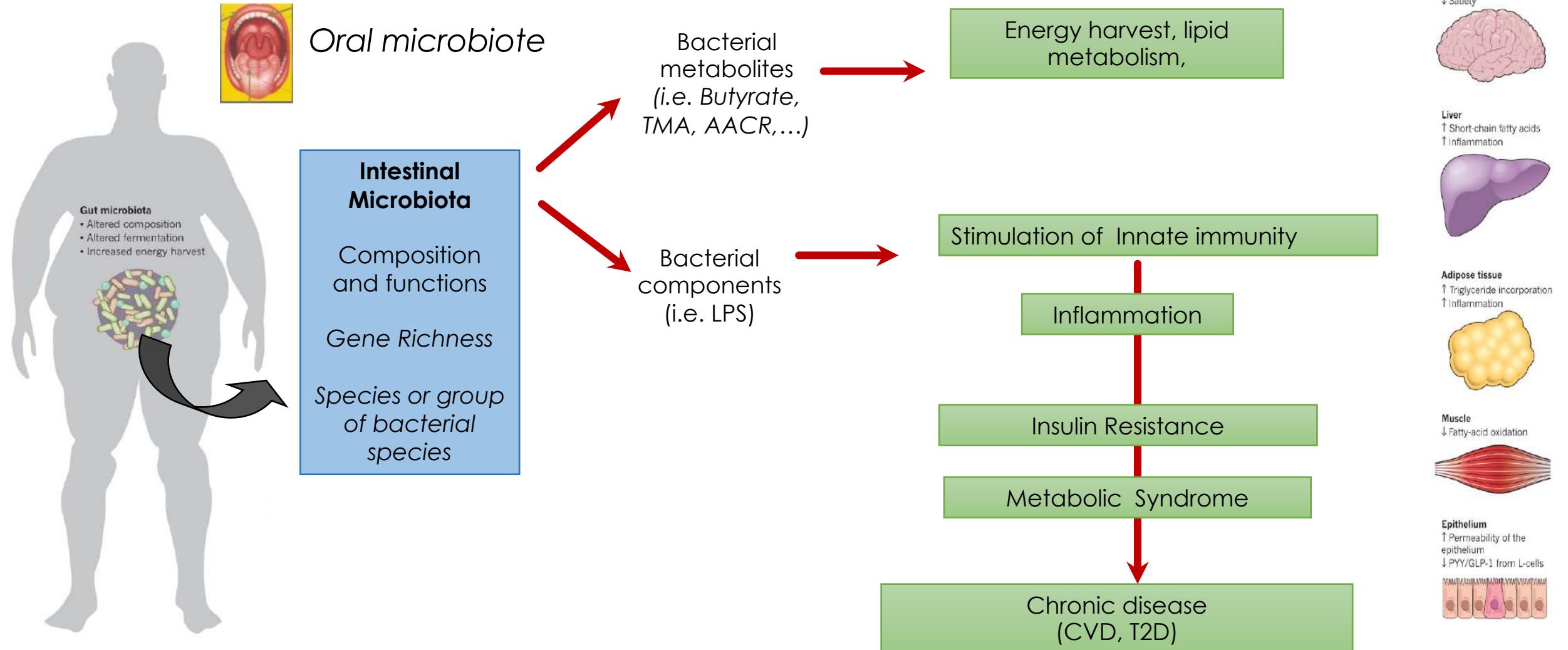
Reduced richness



Eight groups of microorganisms including *Faecalibacterium*, could be used to discriminate CD from non-CD

Pascal et al *Gut*, 2017

Concept in metabolic diseases

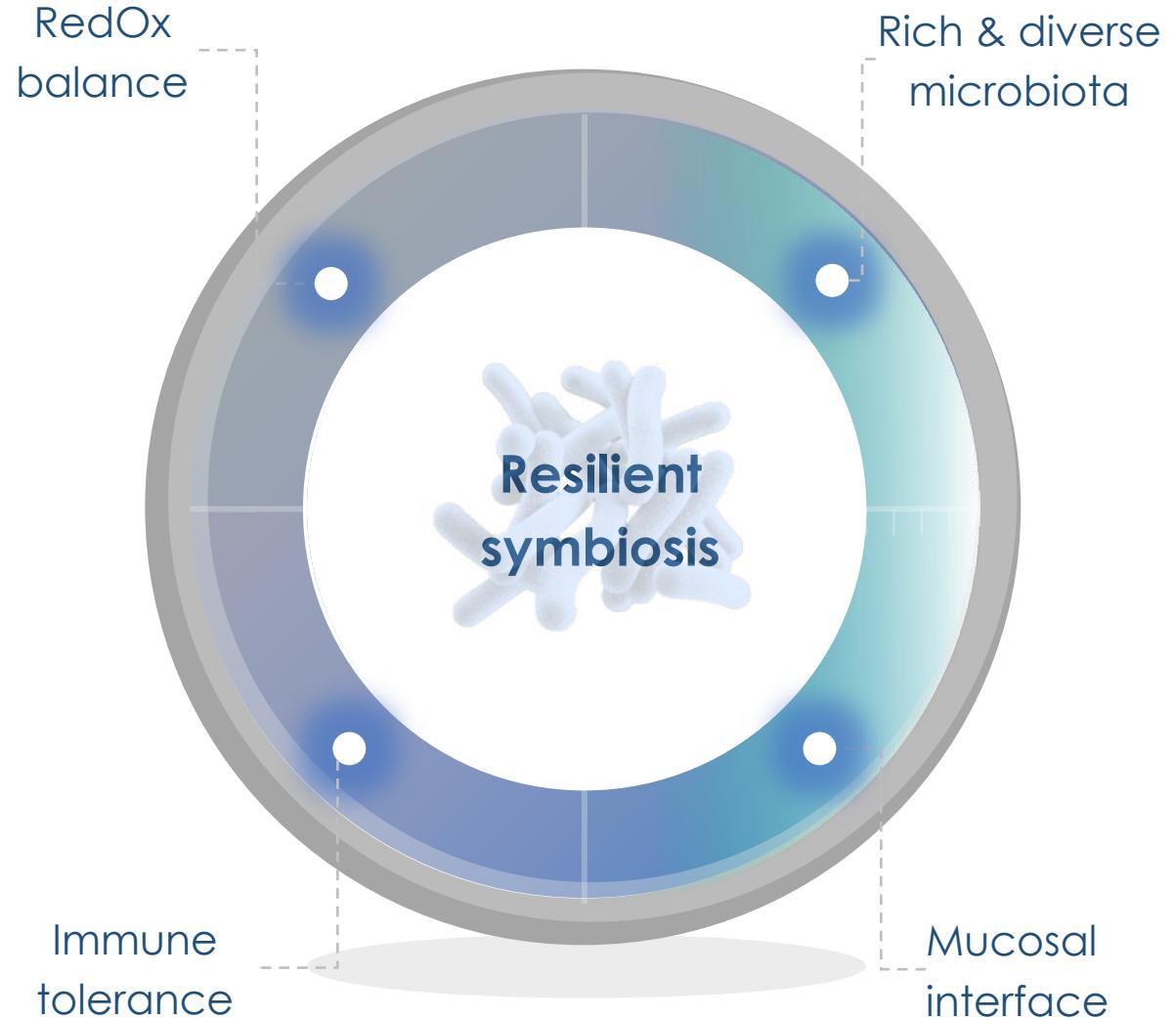


INRAe

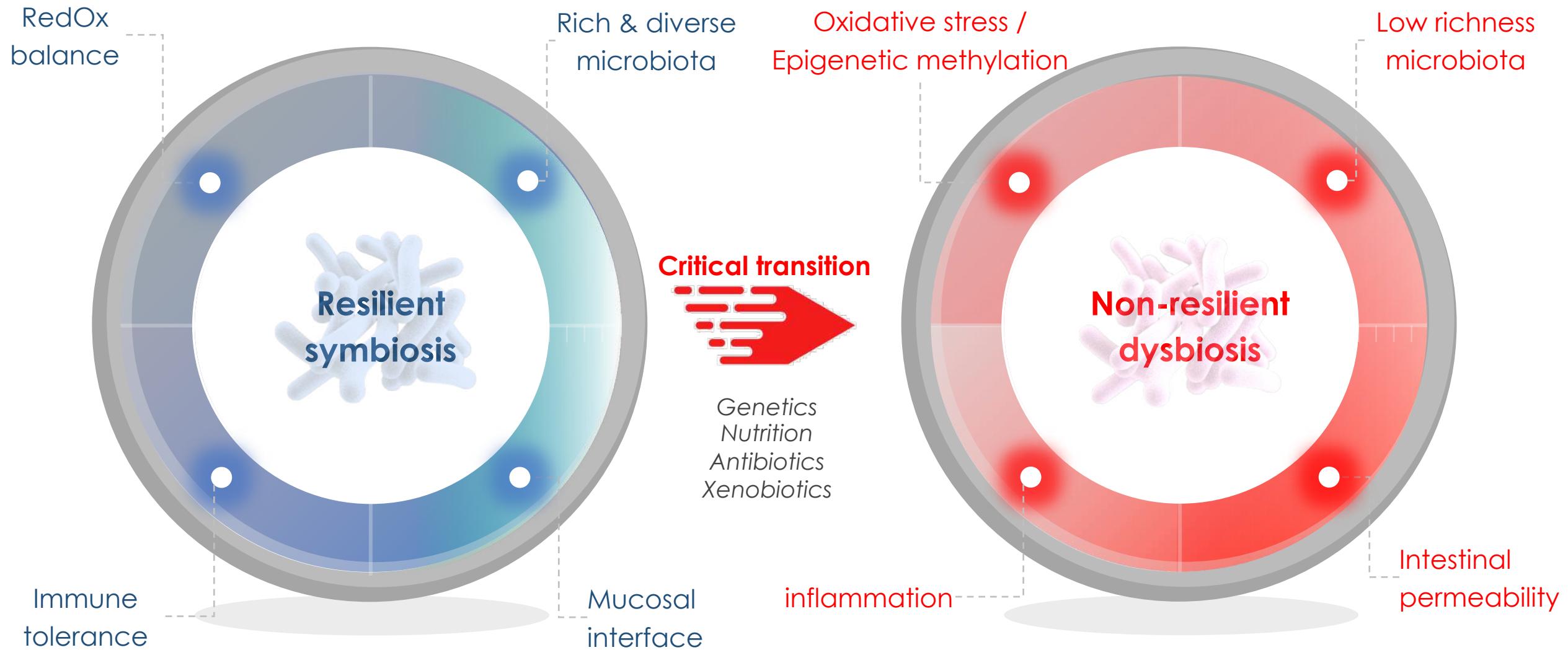
Tremaroli et al. Nature 2012

Adapted from Harris et al. J Obes 2012

Critical transitions of the ecosystem



Critical transitions of the ecosystem



van de Guchte, Blottière, Doré, Microbiome, 2018 ;
van de Guchte et al, Microbiome, 2020



Microbiome can predict anti-PD1 response IN Cancer patients



B. Routy
L. Zitvogel

Science



Cite as: B.
10.1126/scie

Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

Bertrand Routy,^{1,2,3} Emmanuelle Le Chatelier,⁴ Lisa Derosa,^{1,2,3} Connie P. M. Duong,^{1,2,5} Maryam Tidjani Alou,^{1,2,3} Romain Daillère,^{1,2,3} Aurélie Fluckiger,^{1,2,5} Meriem Messaoudene,^{1,2} Conrad Rauber,^{1,2,3} Maria P. Roberti,^{1,2,5} Marine Fidelle,^{1,3,5} Caroline Flament,^{1,2,5} Vichnou Poirier-Colame,^{1,2,5} Paule Opolon,⁶ Christophe Klein,⁷ Kristina Iribarren,^{8,9,10,11,12} Laura Mondragón,^{8,9,10,11,12} Nicolas Jacquelot,^{1,2,3} Bo Qu,^{1,2,3} Gladys Ferrere,^{1,2,3} Céline Clémenson,^{1,13} Laura Mezquita,^{1,14} Jordi Remon Masip,^{1,14} Charles Naltet,¹⁵ Solenn Brosseau,¹⁵ Coureche Kaderbhai,¹⁶ Corentin Richard,¹⁶ Hira Rizvi,¹⁷ Florence Levenez,⁴ Nathalie Galleron,⁴ Benoit Quinquis,⁴ Nicolas Pons,⁴ Bernhard Ryffel,¹⁸ Véronique Minard-Colin,^{1,19} Patrick Gonin,^{1,20} Jean-Charles Soria,^{1,14} Eric Deutsch,^{1,13} Yohann Loriot,^{1,3,14} François Ghiringhelli,¹⁶ Gérard Zalcman,¹⁵ François Goldwasser,^{9,21,22} Bernard Escudier,^{1,14,23} Matthew D. Hellmann,^{24,25} Alexander Eggermont,^{1,2,14} Didier Raoult,²⁶ Laurence Albiges,^{1,3,14} Guido Kroemer,^{8,9,10,11,12,27,28*} Laurence Zitvogel^{1,2,3,5*}



E. Le Chatelier

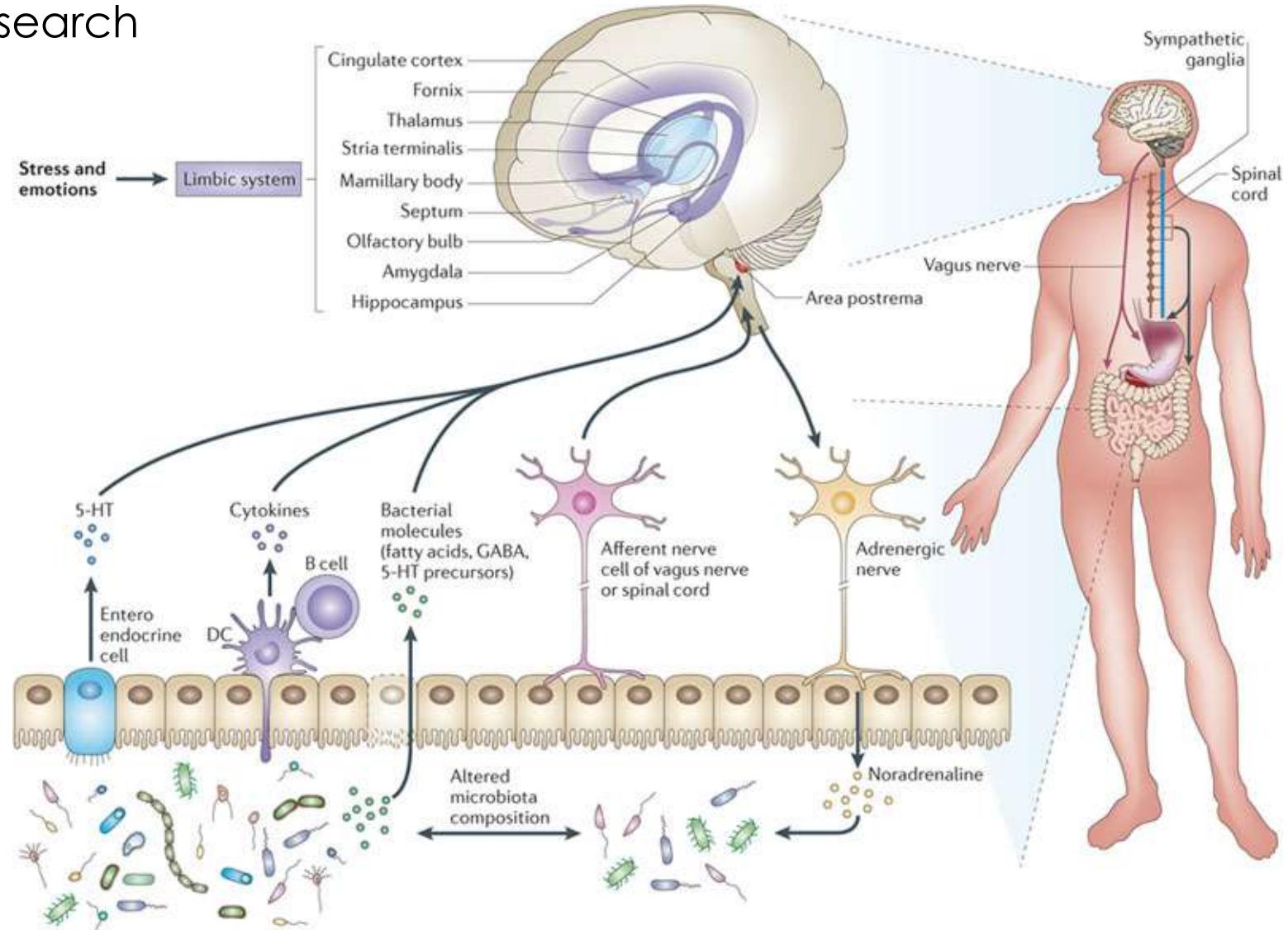


Routy et al Science, 2018

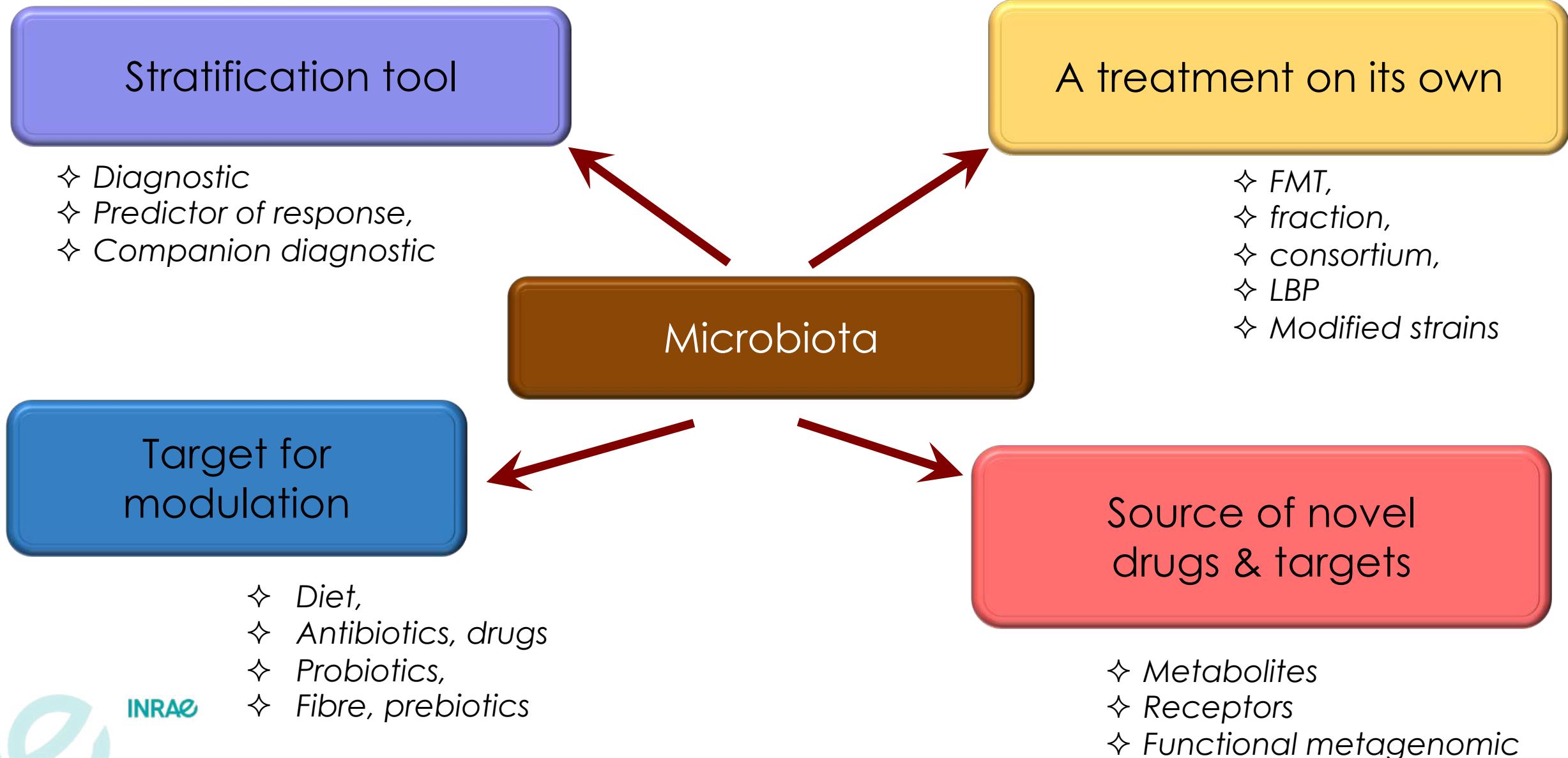
Deciphering the Microbiome - Gut - Brain axis

A new promising area of research

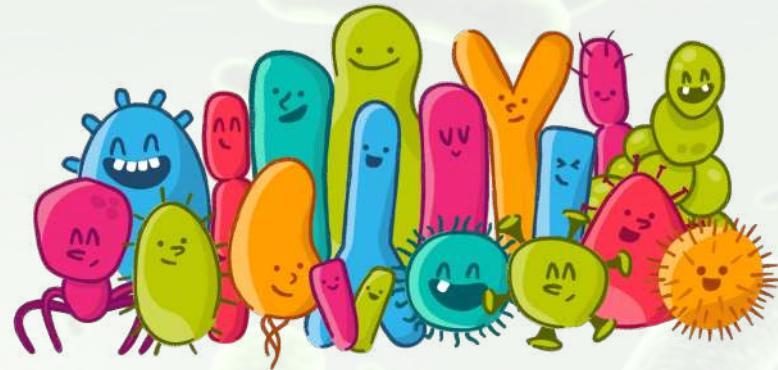
- ✓ Mood disorders
- ✓ Depression
- ✓ Anorexia
- ✓ Autism
- ✓ Alzheimer disease
- ✓ Parkinson disease
- ✓ ...



The microbiota useful for human health ?



We need more knowledge, larger cohorts
of healthy people and patients
but it's promising



We must keep on working

Future will tell us



herve.blottiere@inrae.fr