INTERACTIONS MICROBIOTE/HOTE

APPROCHES FONCTIONNELLES

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MBIO- Adebiotech – 19 juin 2018

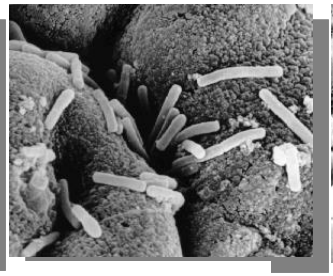
THE HUMAN INTESTINAL MICROBIOTA

- ✓ 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 interest

(Blottière & Doré, médecine/science, 2016)

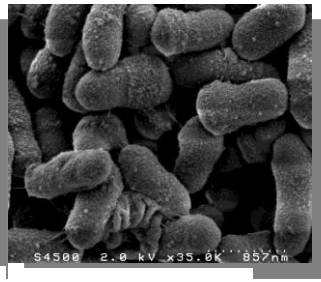
Faecalibacterium prausnitzii

Ruminococcus spp

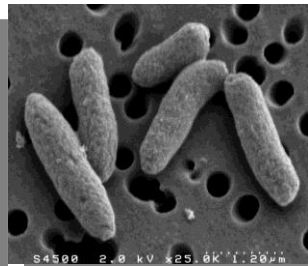


Clostridium difficile
From mice cecum

Bacteria anchored in a Peyer patch



Bacteroides dorei



Escherichia coli

Photos INRA

METAGENOME : genomes of all dominant microbes in an ecosystem

A revolution since the turn of the century

Lessons from early human intestinal tract metagenomics:

- **Qin *Nature 2010*** => 3.3 million gene catalog ; both core metagenome & rare genes
- Arumugam *Nature 2011* => 3 enterotypes, preferred ecological arrangements
- Schloissnig *Nature 2012* => stability at SNPs level (strains)
- Qin *Nature 2012* => metagenomic dysbiosis in T2D
- **Le Chatelier *Nature 2013*** => metagenomic dysbiosis in obesity ; diagnostic signatures
- Cotillard *Nature 2013* => metagenomic dysbiosis in obesity ; low gene count as stratifier
- Qin *Nature 2014* => metagenomic dysbiosis in liver cirrhosis
- Li *Nat Biotech 2014* => 10 million gene catalog ; core metagenome unchanged
- Nielsen *Nat Biotech 2014* => co-abundant gene clustering and metagenomic species
- Xiao *Nat Biotech 2015* => mouse gene catalog ; environment dependent
- Shoaie *Cell Metabol 2015* => nutrition and intestinal metabolome
- Forslund *Nature 2015* => metformin signature in T2D
- Xiao *Nature Microbiol 2015* => A pork gut reference catalog
- Dao *Gut 2016* => *Akkermansia* and obesity/MetS
- Plichta *Nature Microbiol 2016* => metatranscriptomics, niche segregation
- **Pedersen *Nature 2016*** => microbiota affect insulin sensitivity
- Costea, *Nat Biotech, 2017* => SOPs
- Routy, *Science, 2017* => Microbiota and success of cancer therapy

metagenopolis mgps.eu

metagenopolis mgps.eu

How to go further and introduce microbiota in human heath ?

MetaGenoPolis

Platforms dedicated to quantitative and functional metagenomics

Investment for the Future, FRANCE

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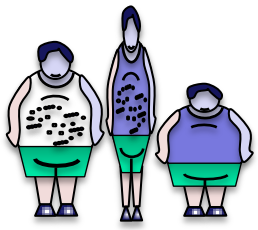
QUANTITATIVE METAGENOMIC PIPELINE AT METAGENOPOLIS

metagenopolis mgps.eu

SAMBO-METAQUANT-INFOBIOSTAT

sample collection → sequencing → reference construction → gene profiling → bioinformatics /statistics analyses



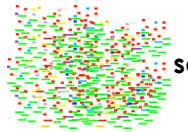
stool sample

total DNA

1 2 3

library preparation SOLiD/Illumina/Proton sequencing

short sequences
30-50 million



sequence mapping onto gene catalogue

reference gene catalogue

catalogue annotation

Known genome

catalogue structuration

gene counts
individuals

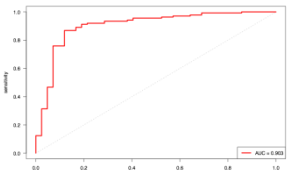
genes

Reference catalogue	Individuals						
item	Ind 1	Ind 2	Ind 3	Ind 4	Ind 5	Ind 6	Ind 7
1	0	36	2	0	43	106	1250
2	0	27	193	0	44	103	8
3	0	31	0	0	0	0	0
4	152	59	282	1	0	0	0
5	115	0	0	1	0	29	2
6	90	783	26	0	2	0	0
7	104	1616	0	0	0	0	5
8	0	82	0	0	0	0	0
9	2	0	0	0	0	0	0
10	23	239	1302	10	0	190	0
11	30	183	900	13	0	172	0
12	27	228	1120	6	0	324	0
13	103	0	0	0	0	0	0
14	0	30	269	0	0	0	0
15	0	0	0	0	0	95	0
16	1250	6002	468	607	492	141	8023
17	0	0	0	0	0	0	0
18	0	9	108	0	0	55	0
19	0	0	0	3	0	0	0
3300000	0	36	2	0	43	106	1250

preprocessing / normalization & dimension reduction

relation with clinical data

Identify clinically relevant groups



build and test prediction models

4000 samples/yr

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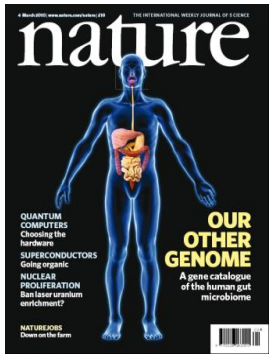
A REFERENCE CATALOG OF 3.3 MILLION GUT GENES



124 MetaHIT subjects
3.3 million gut genes

Rare genes are increasing

Common genes are not

Individuals from MetaHIT, Chinese and HMP studies, n=1267

Qin, Nature 2010
Li et al. Nature Biotechnol, 2014

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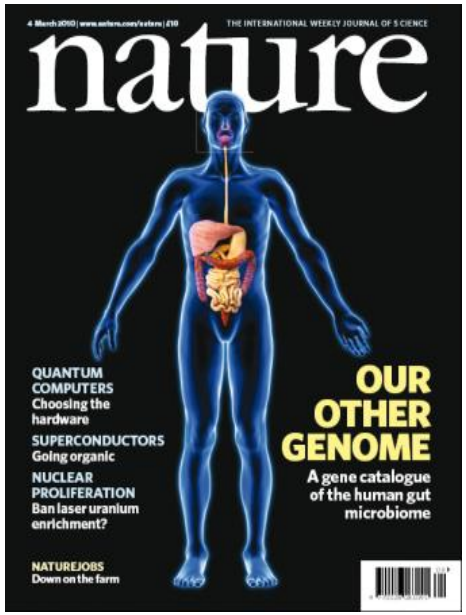
SCIENCE & IMPACT

A REFERENCE CATALOG OF 10 MILLION GUT GENES



124 MetaHIT EU subjects
3.3 million gut genes

Individuals from MetaHIT, Chinese and HMP studies, n=1267

On average, each individual carries ~540 000 genes of the initial catalog. 50 % of the genes of an individual are shared by at least 50 % of individuals = **core metagenome**

Qin, Nature 2010

Li et al. Nature Biotechnol, 2014

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PERTURBATION OF INTESTINAL MICROBIOTA AS A POSSIBLE CHRONIC DISEASE FACTOR

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 Microb**es 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, Angerobe 2010*

also

- ✓ Multiple sclerosis
- ✓ Alzeimer disease
- ✓ Parkinson disease

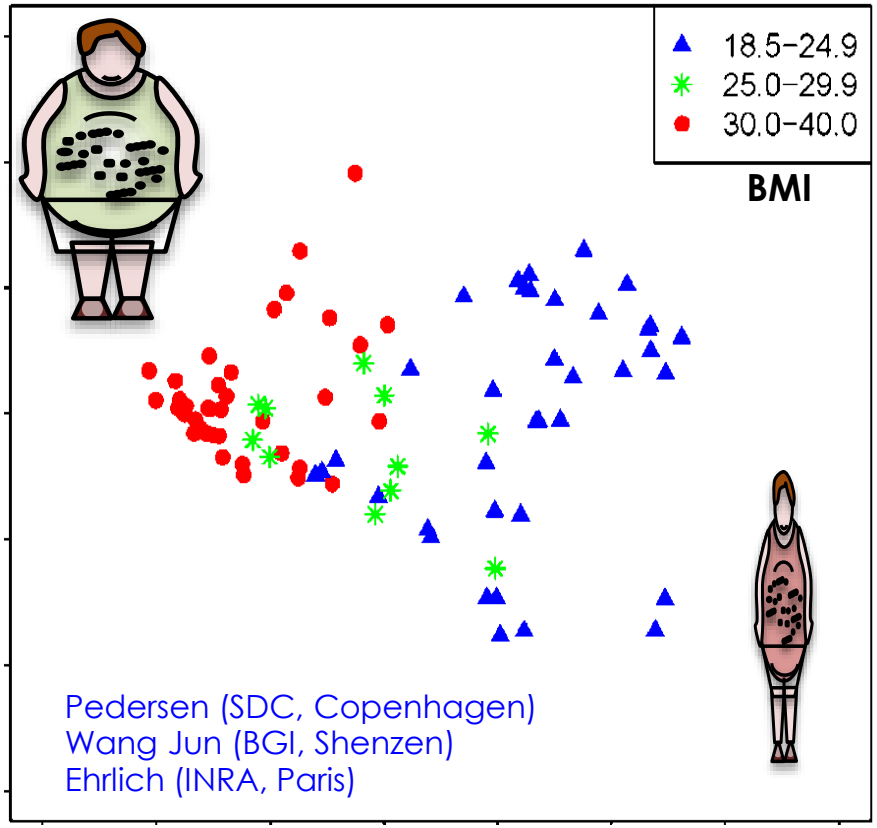
- ✓ Hypertension
- ✓ Bone
- ✓ Kidney diseases
- ✓ …

Human clinical studies :
Shotgun sequencing
16S sequencing

Blottière & Doré, médecine/science, 2016

METAGENOMIC SIGNATURES OF DYSBIOSIS IN OBESITY

Animal studies demonstrated a link between obesity and gut microbiota



Bacterial genes and genomes specific of the microbiome of patients

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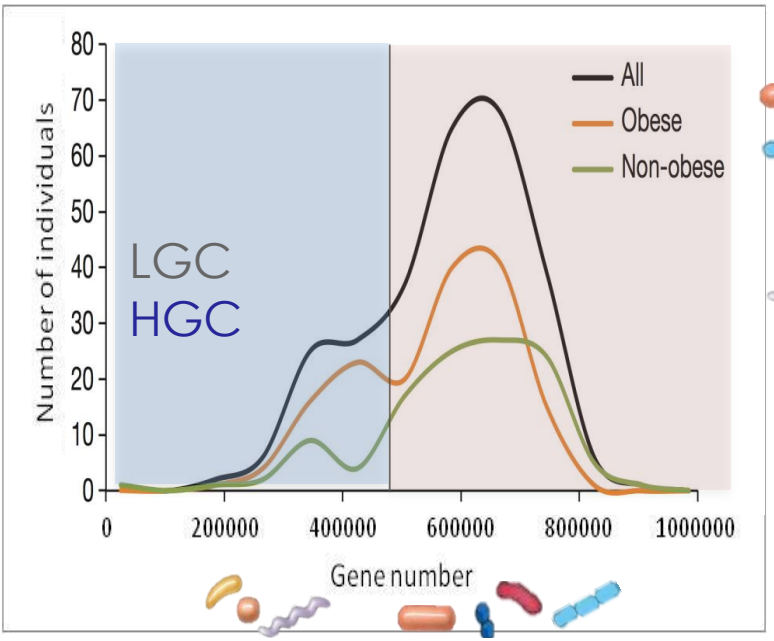
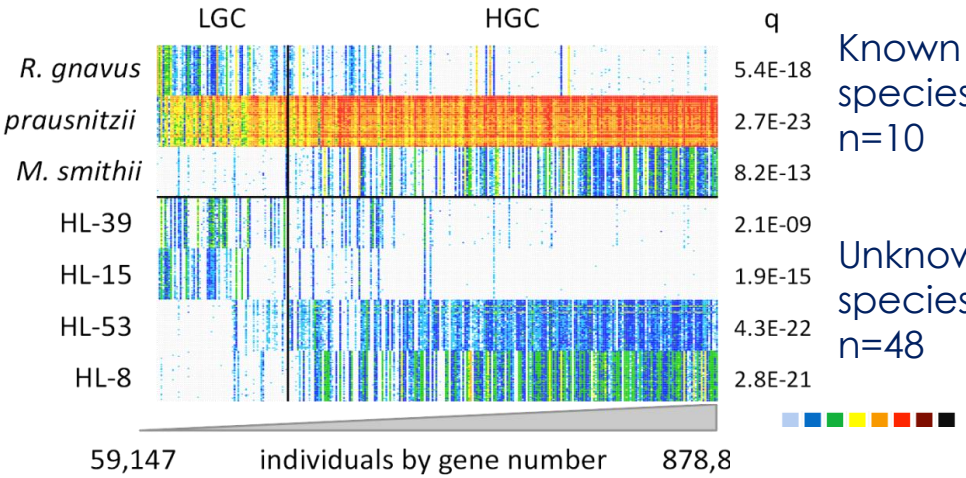
MICROBIOTA GENE COUNT / DIVERSITY IS A HEALTH-ASSOCIATED STRATIFIER

Low to High
gene count (French or Danes)



Signature species (n= 58)



LGC associates with CMD risks

- dyslipidemia
- adiposity
- insulin resistance
- inflammation (circulating and adipose tissue)

and healthier diet

LGC: ↗ Pro-inflammatory
- *Cl. bolteae*
- *Cl. symbiosum*
- *Cl. clostridioforme*
- *Cl. ramosum*
- *R. gnavus*

HGC: ↗ Anti-inflammatory
- *F. prausnitzii*
- *R. inulinivorans*
- *Co. eutactus*
- *M. smithii*

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

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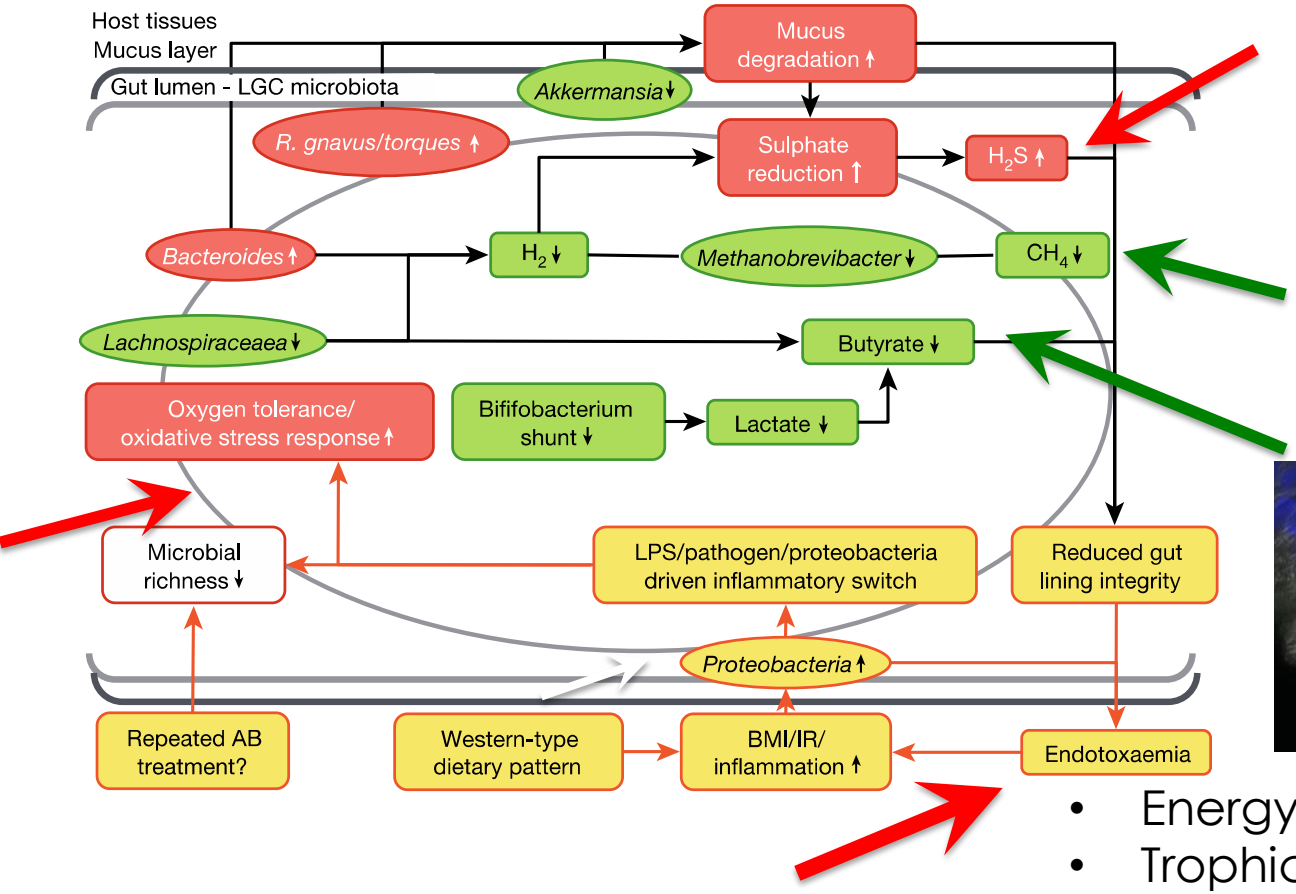
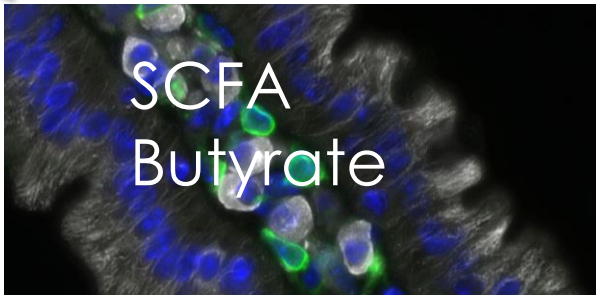
FUNCTIONAL SHIFTS IN THE LGC MICROBIOME





- Energy source for IEC
- Trophic & barrier functions
- HDAC inhibitor (gene regulation)
- GPR agonist – PYY & GLP1
- Immunomodulatory effects

Le chatelier et al, Nature, 2013

Blottière et al, PNS 2003;
Segain et al, Gut, 2000

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SCIENCE & IMPACT

LETTER

doi:10.1038/nature12721

Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells

Yukihiro Furusawa[1,2]*, Yuuki Obata[1,2,3]*, Shinji Fukuda[1,4]*, Takaho A. Endo[1], Gaku Nakato[1], Daisuke Takahashi[1], Yumiko Nakanishi[4], Chikako Uetake[1], Keiko Kato[1,5], Tamotsu Kato[1], Masumi Takahashi[1], Noriko N. Fukuda[4], Shinnosuke Murakami[4], Eiji Miyauchi[1], Shingo Hino[6], Koji Atarashi[1,7], Satoshi Onawa[1], Yumiko Fujimura[2], Trevor Lockett[8], Julie M. Clarke[8], David L. Topping[8], Masaru Tomita[4], Shohei Hori[1], Osamu Ohara[1], Tatsuya Morita[6], Haruhiko Koseki[1,3,5], Jun Kikuchi[5,9], Kenva Honda[1,10], Koii Hase[1,2,7]* & Hiroshi Ohno[1,3,5]

LETTER

doi:10.1038/nature12726

Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation

Nicholas Arpaia[1,2], Clarissa Campbell[1,2], Xiying Fan[1,2], Stanislav Dikiy[1,2], Joris van der Veeken[1,2], Paul deRoos[1,2], Hui Liu[3], Justin R. Cross[3], Klaus Pfeffer[4], Paul J. Coffer[1,2,5] & Alexander Y. Rudensky[1,2]

19/26 DECEMBER 2013 | VOL 504 | NATURE | 451

Cell PRESS

Immunity

Article

Activation of Gpr109a, Receptor for Niacin and the Commensal Metabolite Butyrate, Suppresses Colonic Inflammation and Carcinogenesis

Nagendra Singh,[1,2,*] Ashish Gurav,[1] Sathish Sivaprakasam,[1] Evan Brady,[1] Ravi Padia,[1] Huidong Shi,[1,2] Muthusamy Thangaraju,[1,2] Puttur D. Prasad,[1,2] Santhakumar Manicassamy,[2] David H. Munn,[2,3] Jeffrey R. Lee,[4] Stefan Offermanns,[5] and Vadivel Ganapathy[1,2,*]

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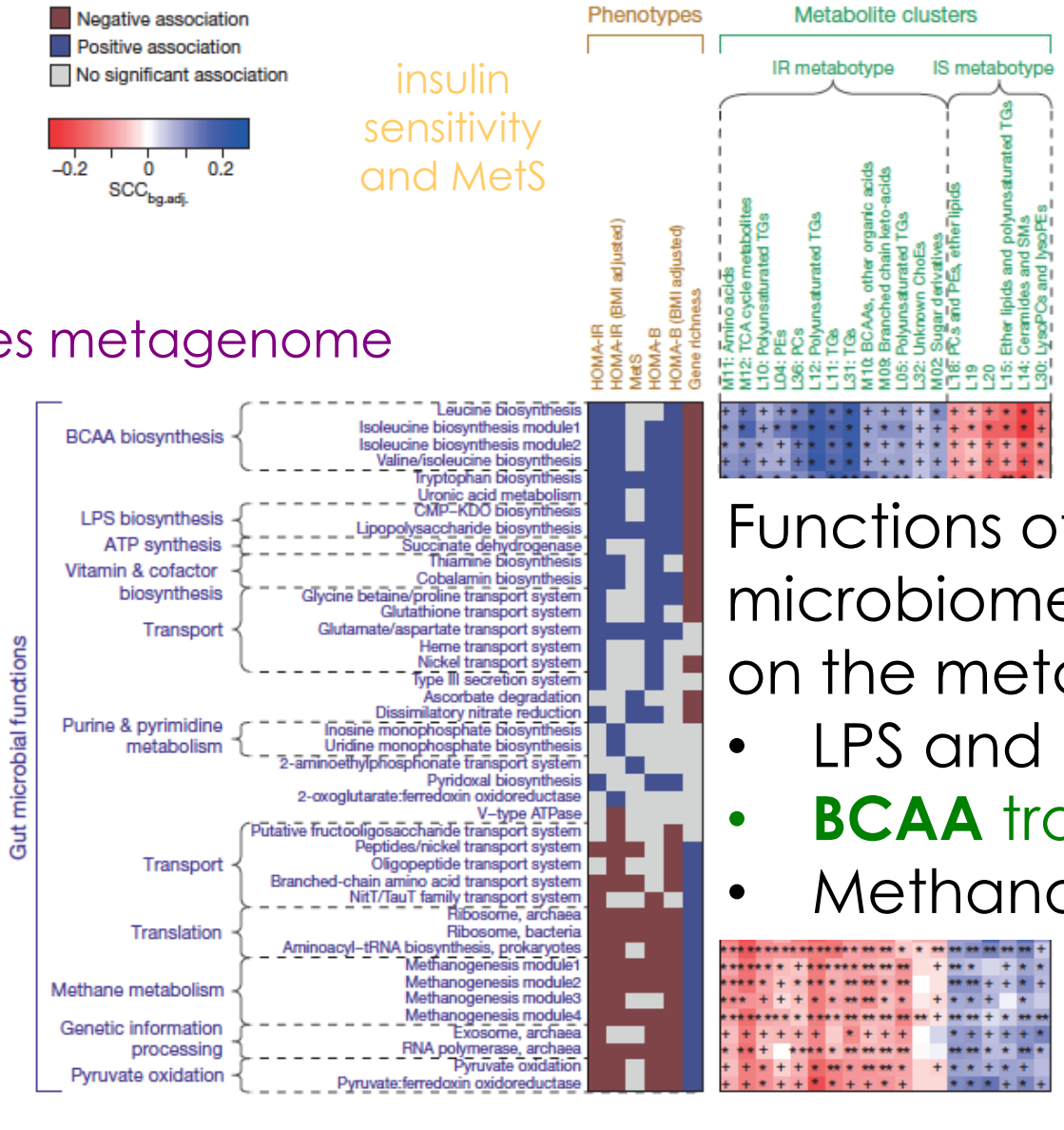
GUT MICROBIOME, SERUM METABOLOME & INSULIN RESISTANCE



insulin sensitivity and MetS

277 non-diabetic individuals (164 obese, 113 non-obese)

fasting serum metabolome

Feces metagenome

Functions of IR-associated microbiome have an impact on the metabolome :

- LPS and **BCAA** biosynthesis
- **BCAA** transport
- Methanogenesis

Pedersen et al, Nature 2016

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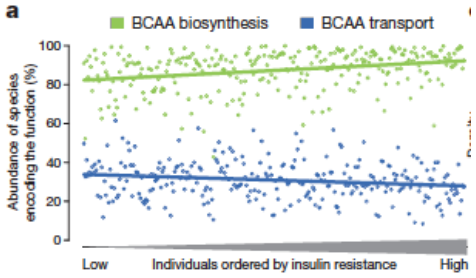
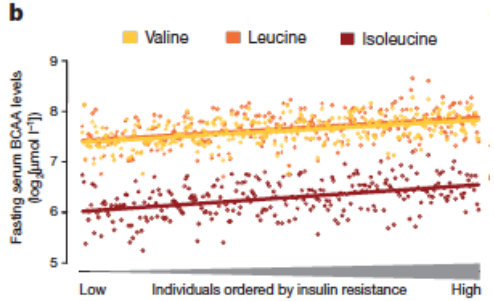
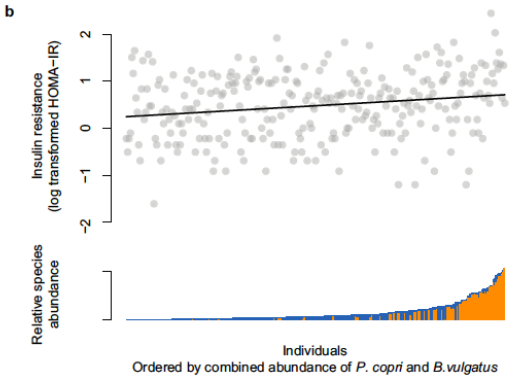
BRANCH CHAIN AMINO-ACIDS & INSULIN RESISTANCE

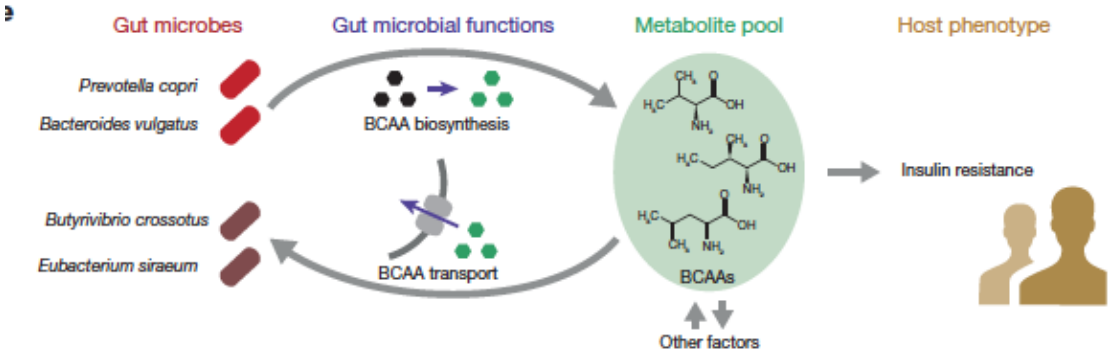
Microbiome functions

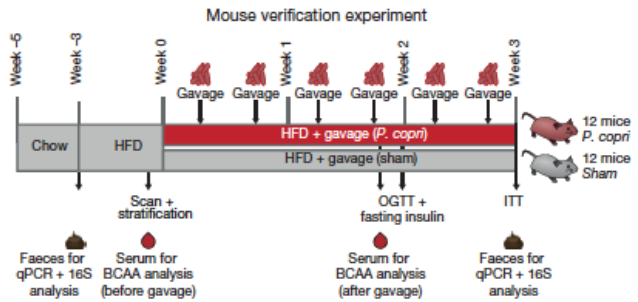


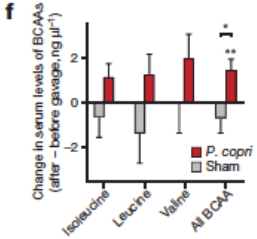
Metabolome

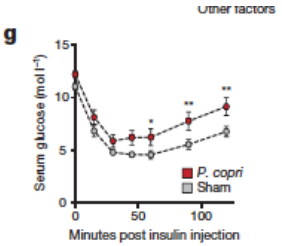


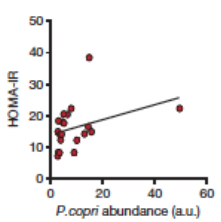












Pedersen et al, Nature 2016

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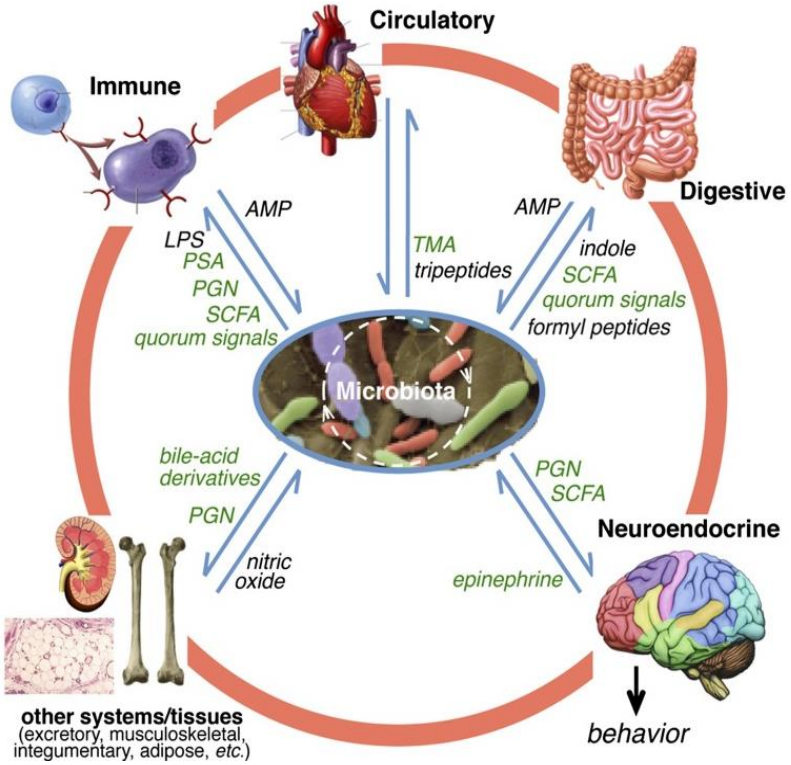
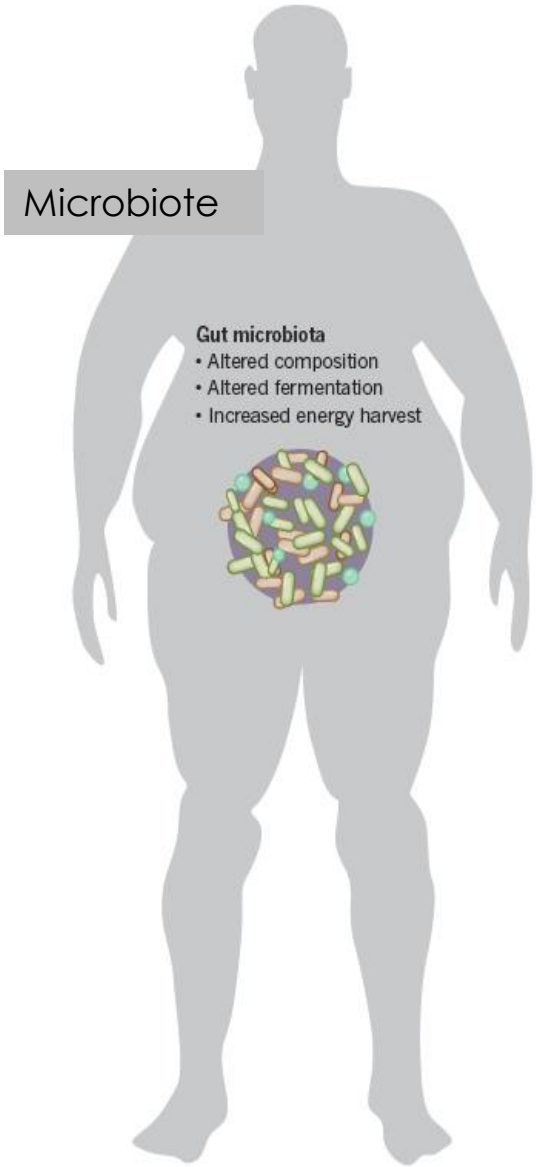
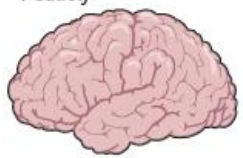
MECHANISMS LINKING DYSBIOSIS AND DISEASES





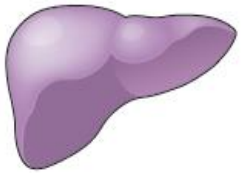
Brain

↓ Satiety



Liver

↑ Short-chain fatty acids
↑ Inflammation



Adipose tissue

↑ Triglyceride incorporation
↑ Inflammation

Muscle

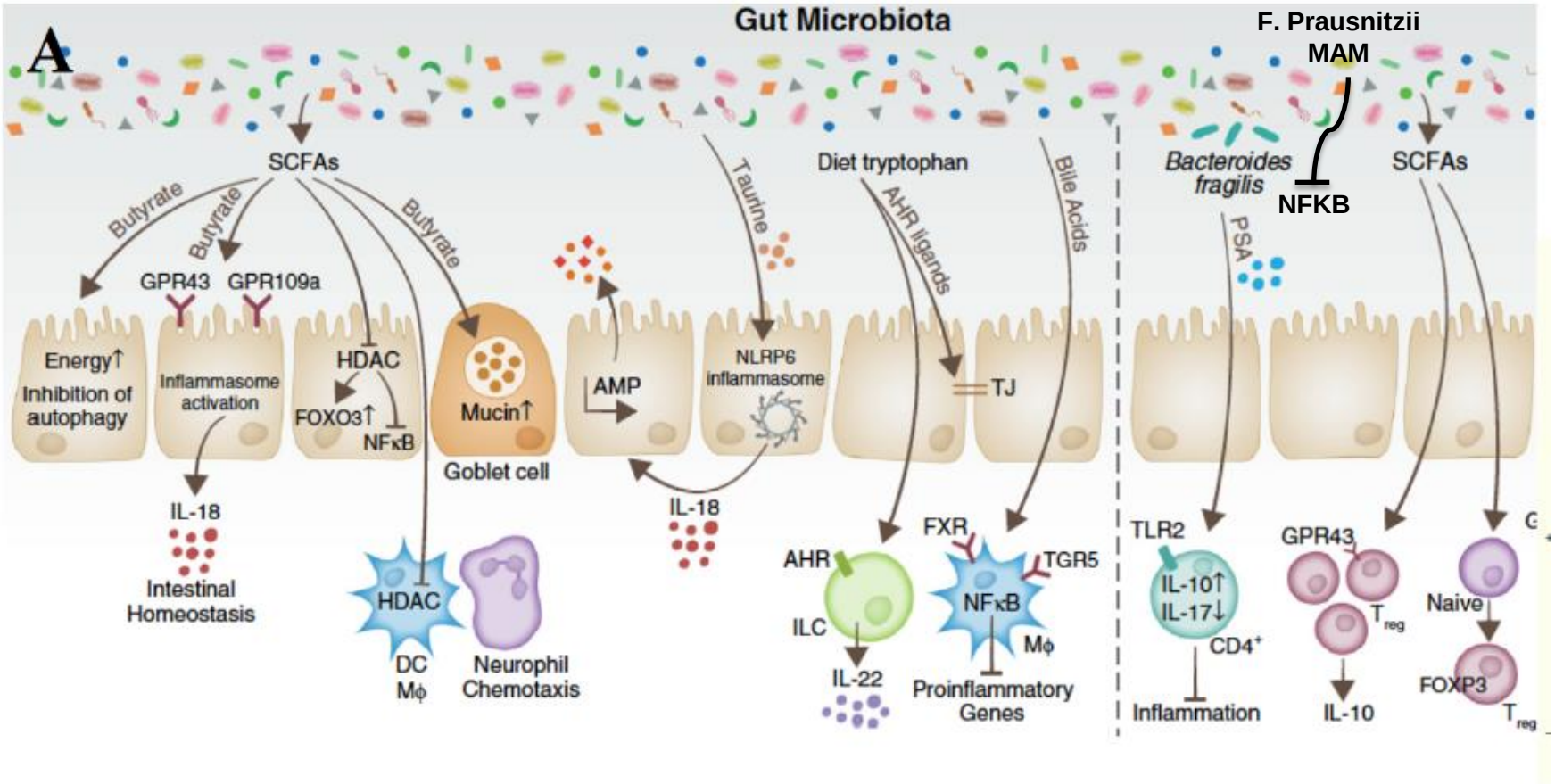
↓ Fatty-acid oxidation

Intestine

↑ Permeability of the epithelium
↓ PYY/GLP-1 from L-cells

Tremaroli et Bäckhed, Nature 2012;
McFall-Ngai et al, 2013

HOST-MICROBIOTA INTERACTIONS. FEW MOLECULES IDENTIFIED



Ligand for AhR

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MICROBIOTA HOST-INTERACTIONS

USE OF ANIMAL MODELS

- ✓ The intestinal microbiota plays a key role on Human Health, but how ?
- ✓ Few bacterial metabolites are known to control/modulate host cell response, i.e. SCFA, TMA, indols, … only few are known
- ✓ Can we learn from animal model ?

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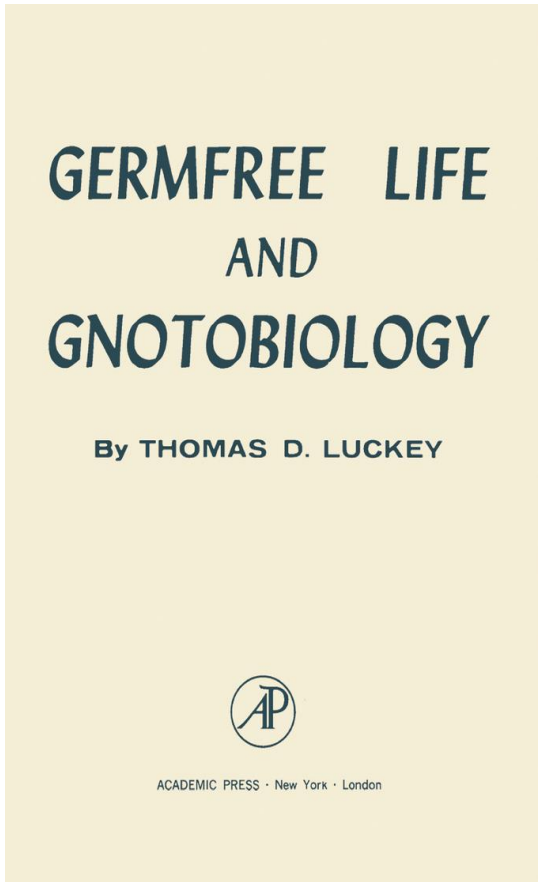
GUT MICROBIOTA AND IMMUNE SYSTEM
LESSON FROM GERM-FREE ANIMALS



1963

Glimstedt G. Bakterienfrei Meerschweinchen. Aufzucht, Lebensfähigkeit und Wachstum, nebst Untersuchung über das lymphatische Gewebe. Acta Pathol Microbiol Scand. 1936;S30:1–295.

Bacteria free guinea pigs. Rearing, viability and growth, as well ***as investigation of the lymphatic tissue.***

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MAIN IMMUNE SYSTEM ABNORMALITIES DESCRIBED IN GERM-FREE MICE COMPARED TO CONVENTIONAL ANIMALS

Immunological deficiency	Site	Phenotype in axenic mice
Development of the small intestine	Peyer's patches	Decrease in number and size
	Lamina propria	Thinner, fewer lymphocytes
	Germinal centers	Fewer plasmocytes
	Isolated lymphoid follicles	Smaller
Development of mesenteric lymph nodes	Germinal centers	Smaller with fewer plasmocytes
CD8+ T cells	Intraepithelial lymphocytes	Less numerous and less cytotoxic
CD4+ T cells	*Lamina propria*	Reduced cell number, decrease in Th17 in the small intestine but not in the colon
MAIT cells		Absent
CD4+ and CD8+ T cells	Spleen	Reduced cell number, reduced cytokine production
CD4+CD25+ T cells	Mesenteric lymph nodes	Decreased expression of FoxP3 and reduced suppressive capacities
Expression of antimicrobial peptides	Paneth cells	Reduced
IgA production	B cells	Reduced, and fewer serum Ig
IgG and IgM	Serum	Strongly reduced levels
ATP level	Gut	Reduced
Expression of class II MHC	Intestinal epithelial cells	Reduced
Expression of TLR2, TLR4 and TLR9		
IL-25 level		Reduced

Martin-Gallausieaux, Lapaque et Blottiere, 2017

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THE INNATE IMMUNE SYSTEM AND GUT MICROBIOTA

Cell *145*, 745–757, May 27, 2011 ©2011 Elsevier Inc. 745

Cell

NLRP6 Inflammasome Regulates Colonic Microbial Ecology and Risk for Colitis

Eran Elinav,[1,8] Till Strowig,[1,8] Andrew L. Kau,[4,5] Jorge Henao-Mejia,[1] Christoph A. Thaiss,[1] Carmen J. Booth,[2] David R. Peaper,[3] John Bertin,[6] Stephanie C. Eisenbarth,[1,3] Jeffrey I. Gordon,[4] and Richard A. Flavell[1,7,*]

Cell

1428 Cell *163*, 1428–1443, December 3, 2015 ©2015 Elsevier Inc.

Article

Microbiota-Modulated Metabolites Shape the Intestinal Microenvironment by Regulating NLRP6 Inflammasome Signaling

Maayan Levy,[1,13] Christoph A. Thaiss,[1,13] David Zeevi,[2,3] Lenka Dohnalová,[1] Gili Zilberman-Schapira,[1] Jemal Ali Mahdi,[1,4] Eyal David,[1] Alon Savidor,[5] Tal Korem,[2,3] Yonatan Herzig,[1] Meirav Pevsner-Fischer,[1] Hagit Shapiro,[1] Anette Christ,[6,7] Alon Harmelin,[8] Zamir Halpern,[9,10] Eicke Latz,[6,7] Richard A. Flavell,[11,12] Ido Amit,[1] Eran Segal,[2,3,14,*] and Eran Elinav[1,14,*]

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CAUTION WITH ANIMAL MODEL

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Immunity

Article

Nlrp6- and ASC-Dependent Inflar Do Not Shape the Commensal Gut Microbiota Composition

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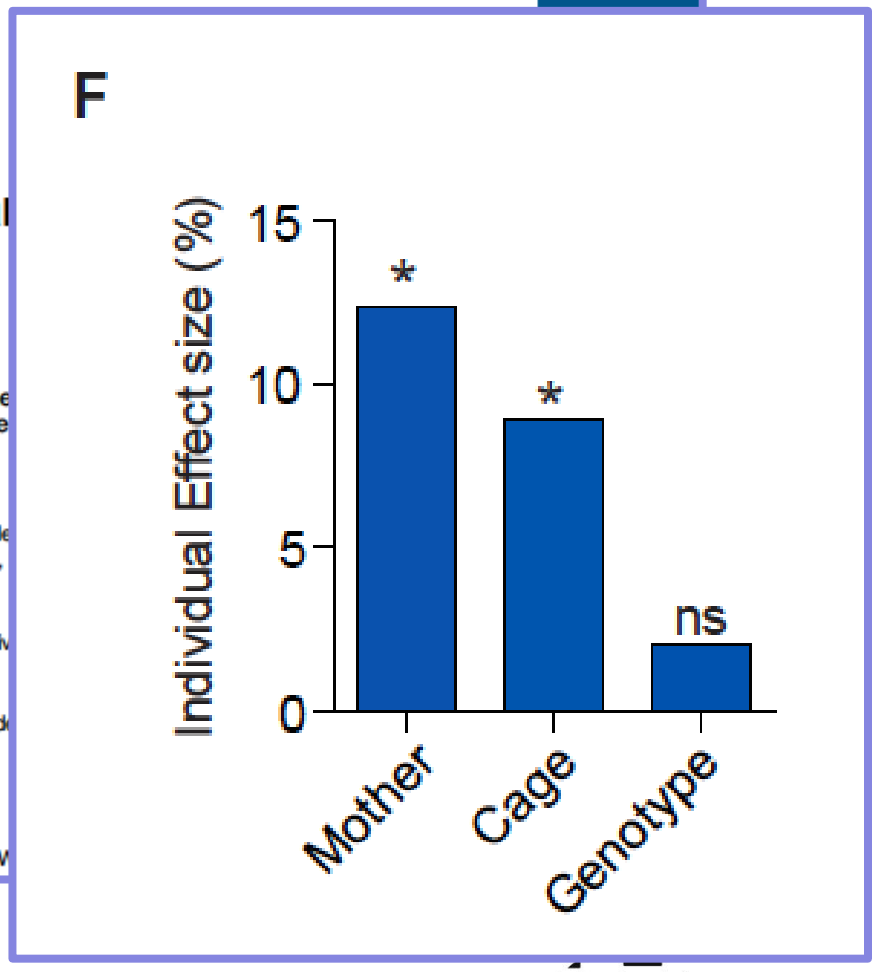

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CAUTION WITH ANIMAL MODEL

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Article

Cell

Wild Mouse Gut Microbiota
and Improves Disease Resi

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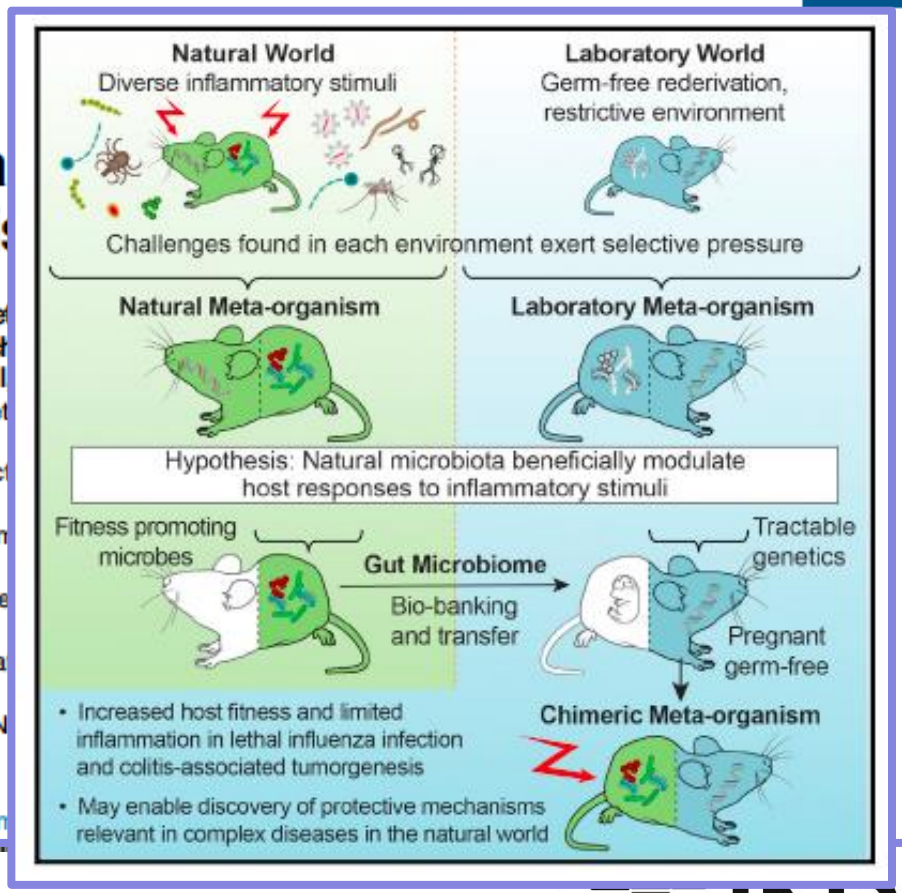

WORK WITH CHIMERIC MICE

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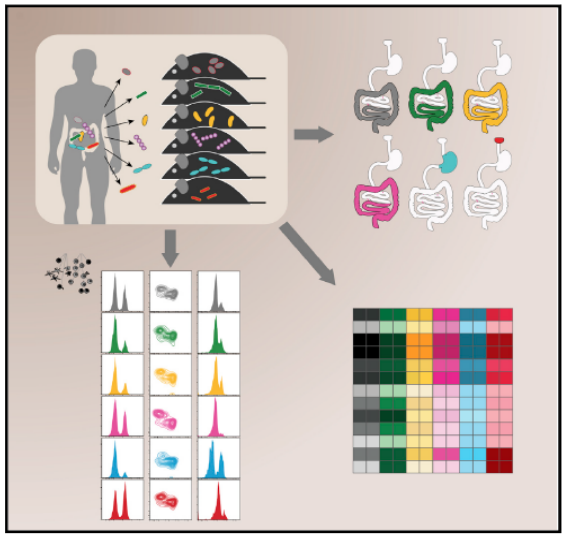
INTERACTION WITH IMMUNE SYSTEM IS SPECIES SPECIFIC ?

Resource

Cell

Mining the Human Gut Microbiota for Immunomodulatory Organisms

Graphical Abstract



Authors

Naama Geva-Zatorsky, Esen Sefik, Lindsay Kua, ..., Diane Mathis, Christophe Benoist, Dennis L. Kasper

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In Brief

Each of 53 human-resident bacterial species studied in monoculture in mice modulates the host immune system, providing a baseline for investigating how consortia of gut microbes interact with their host.

Highlights

- Human gut microbiota comprises a treasure trove of immunomodulatory bacteria
- Diverse and redundant immune and transcriptional responses follow monocolonization
- Immunologic and transcriptional changes are not related to microbial phylogeny
- Following monocolonization, immune recalibration varies to strains within a species

Cell, february 2017

Mediators ?

Mechanisms ?

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MICROBIOTA HOST-INTERACTIONS

- ✓ The intestinal microbiota plays a key role on Human Health, but how ?
- ✓ Few bact … te host cell response,
- ✓ Animal mo … k
- ✓ How to ic … onal interest and poter … when 80 % of the cor … stool/tissue microbiom …

Functional Metagenomics

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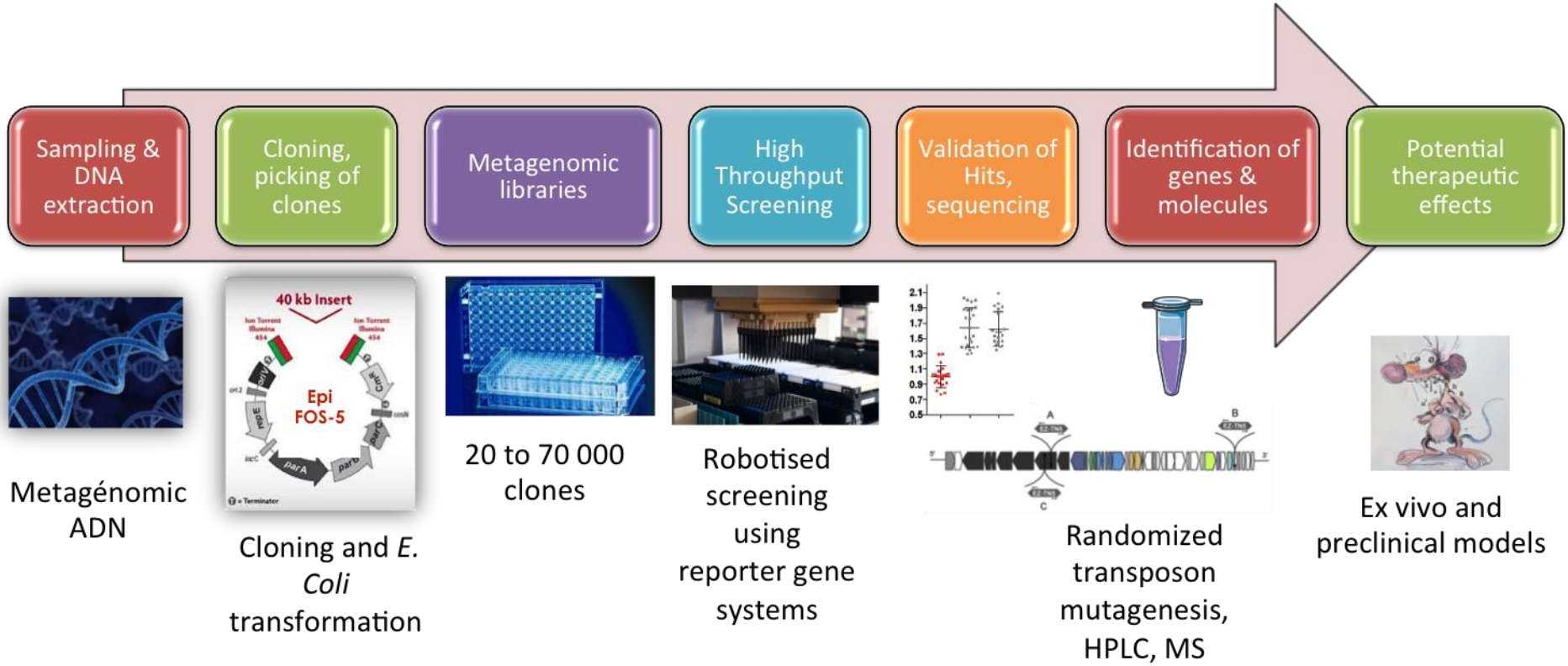
FUNCTIONAL METAGENOMICS TO STUDY MICROBIOTA – HOST CROSSTALK



Gloux et al., AEM, 2007
Lakhdari et al., Plos one, 2010; de Wouters et al., Plos one, 2014
O'Cuiv et al, anaerobes, 2017, 6 patents

From Blottière & Doré, m/s médecin/Sciences, 2016

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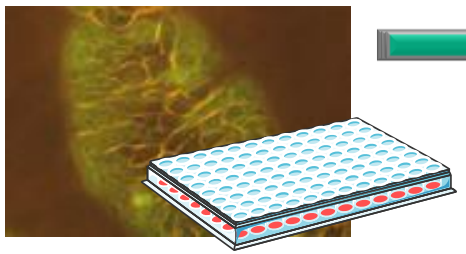
FUNCTIONAL METAGENOMICS STRATEGY

Sampling & DNA extraction → Cloning, recombinants selection → Homogenous DNA library → Screening

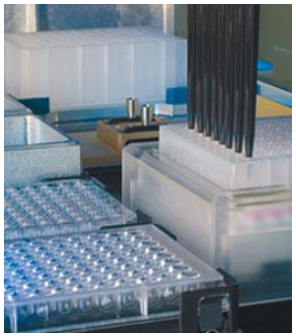
Metagenomic libraries

18 libraries
From healthy, obese, Crohn's, CRC,
Ileum/ mucosal
= 575 000 clones

→ ***23 millions genes***



HTS



Identification of
- Clones
- Genes
- Molecules

Reporter human intestinal epithelial cells

Luciferase or fluorescent probes/genes

metagenopolis mgps.eu

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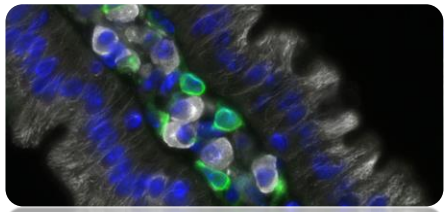
TARGETED INTESTINAL FUNCTIONS



Functions linked to several diseases

Endocrine | **Metabolism** | **Gut barrier** | **Immunity**

Enteroendocrine cell

Focusing on functional bacterial genes…

PYY, GLP-1 → Ca^{2+}

Fiaf/Angptl4
Choline metabolism → PPARγ

Muc2, Cyclin D1
autophagy → AP1, p53, hsf1

TSLP, TGF-β, IDO,
IL-10, RALDH1,… → NF-κB, AP1, AhR

… and metabolic pathways

Epithelial cell

ROBOTIC EQUIPMENTS FOR HTS

metagenopolis mgps.eu

Development of MetaFun

Castor 1 & 2 – Human cells
Pollux 1 & 2 – Bacteria culture
Qpix – colony picker
Cell sorter FACS ARIA III
Automated Image Xpress confocal HCA

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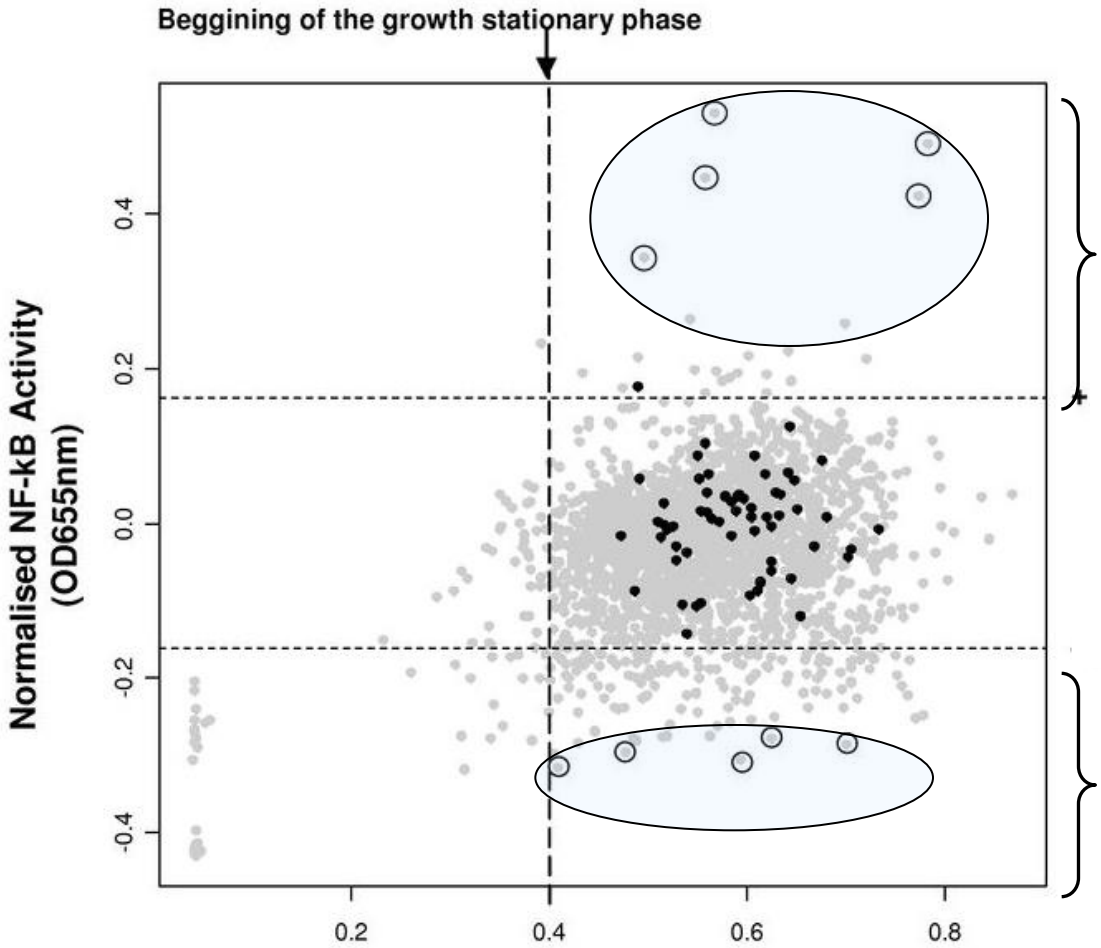
HTS OF METAGENOMIC CLONES



- ✓ SOPs defined
- ✓ ISO 9001

Growth of metagenomic clones (DO 600nm)

Lakhdari et al, PLoS One, 2010; de Wouters, PLoS one, 2014

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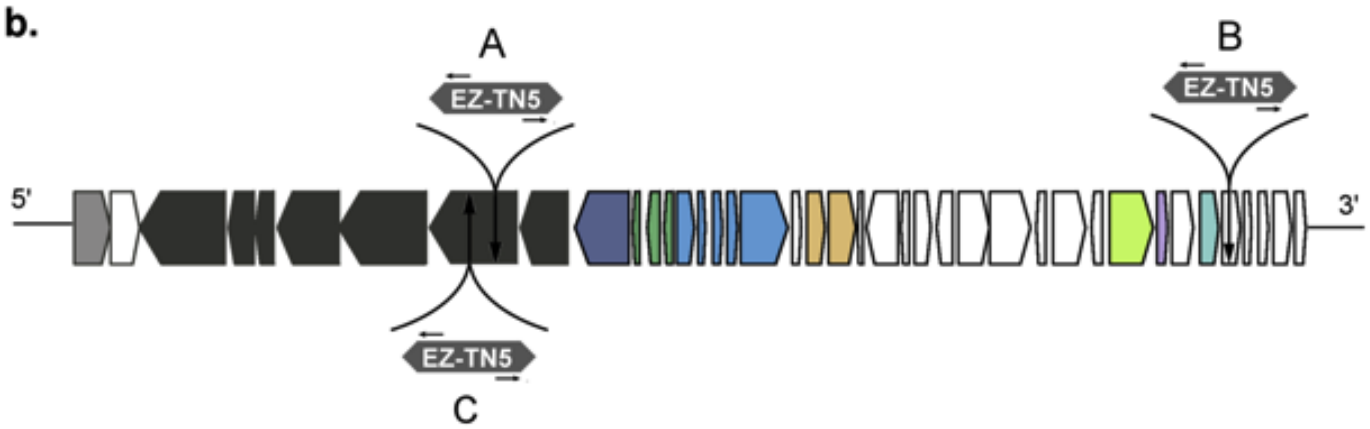
AN EXEMPLE : CLONE 52B7 *(from Crohn 's Disease library)*

Stimulates NF-κB in several cell lineages and **IL-8** secretion in IEC
Secreted in the supernatant, size 50 KD, Trypsin sensitive
From ***Bacteroides vulgatus***



- ✓ The 2 targeted genes code for : a lipoprotein and a lipoprotein transporter
- ✓ Bacterial genes found more often in Crohn disease patients

Lakhdari et al, PLoS one, 2010, O'cuiv et al, Anaerobe, 2017

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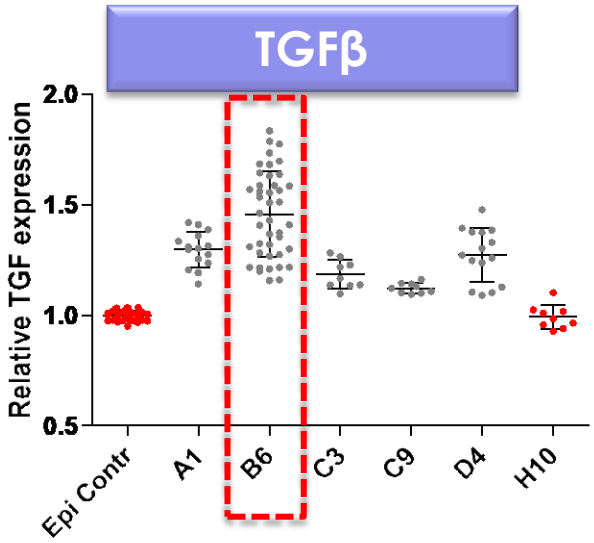
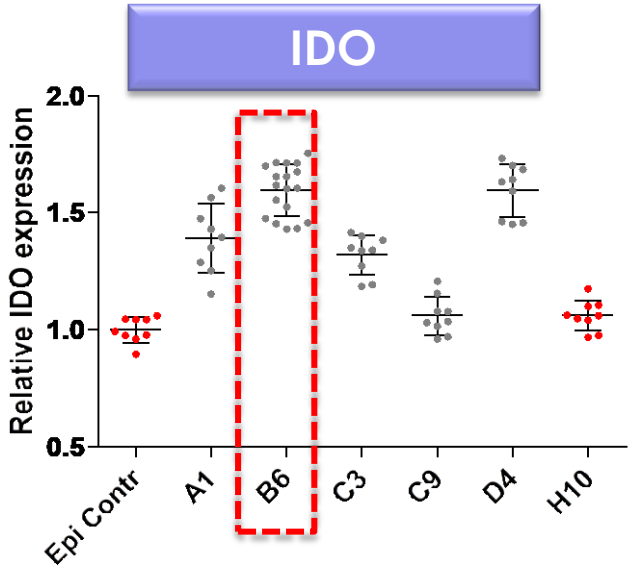
ANOTHER EXEMPLE : CLONE B6 (*from healthy's library*)

- **Stimulates NF-κB** (MyD88 independent), **IDO and TGFβ** on colonocytes
- Secreted in the supernatant by a ABC transporter
- size < 1 kD
- Firmicutes: *related to Blautia (Clostridium XIVa))*





- ✓ One gene , Mate efflux family protein
- ✓ Mutagenesis on this gene: loss of function
- ✓ Metabolomic : NEW compound

- ✓ NEW PATHWAY/TARGET

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FUNCTIONAL METAGENOMIC : A FRUITFUL STRATEGY

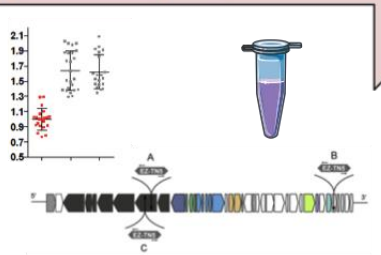
Sampling & DNA extraction → Cloning, picking of clones → Metagenomic libraries → High Throughput Screening → Validation of Hits, sequencing → Identification of genes & molecules → Potential therapeutic effects

Metagénomic ADN

Cloning and *E. Coli* transformation

20 to 70 000 clones

Robotised screening using reporter gene systems

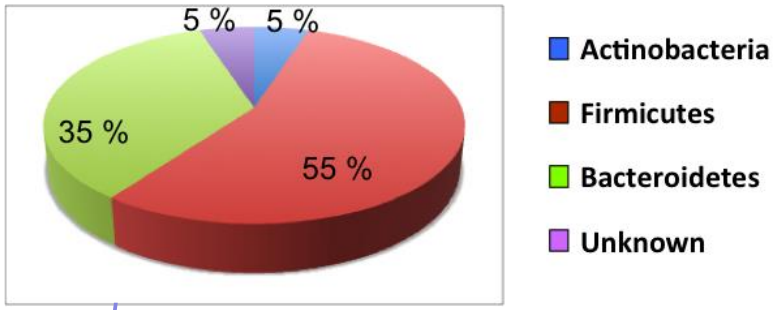


Randomized transposon mutagenesis, HPLC, MS

Ex vivo and preclinical models

>30 bioactive clones, identified with screens based on cell-assays on :

- *Immunity*
- *Proliferation*
- *Metabolism*



New molecules, new pathways discovered
6 patents in 2015, licenced to

enterome bioscience

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TAKE-HOME MESSAGES

- ✓ Quantitative metagenomic allows functional understanding of microbiota host-interaction
- ✓ Animal models are useful tools but should be used with caution
- ✓ Functional metagenomics : A new strategy to study the molecular mechanisms of cross-talk between (uncultivated) gut microbiota and its host
- ✓ We are far from fully understanding microbiota-host cross-talk

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FInE/Blottière lab,
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Catherine Juste,
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Florence Haimet
Nicolas Pons
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Véronique Lejard

Merci

Nous sommes prêts à travailler avec vous

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Anne Jarry (INSERM, Nantes)

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