The Human Microbiome in Medicine

IMI Stakeholders Forum
October 19, 2017, Brussels, Belgium

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The human intestinal microbiome is a neglected organ

- 100 trillion microorganisms; more cells than the human body; up to 2 kg of mass!
- Interface between food and epithelium
- In contact with the 1st pool of immune cells and the 2nd pool of neural cells of the body

An organism can function well when all its organs function well
Multiple functions of the neglected organ
The gut microbiome appears altered in many chronic diseases.

Seven of the top 10 causes of death in 2010 were chronic diseases. Two of these—heart disease and cancer—accounted for nearly 48% of deaths in the US. (Centers for Disease Control and Prevention, 2013)
A common alteration is loss of microbial richness.

Atrophy of the neglected organ.
Microbial richness can be lost even in healthy people.

Low gene count individuals (1/4) have increased adiposity, insulin resistance, dyslipidaemia & inflammation – a risk for chronic diseases.

Microbe-poor gut microbiome is less healthy

Low butyrate, high LPS, high $H_2S$, oxidative stress

Microbiome richness is associated with health and well-being

It is better to be rich than poor

We need more gut bacteria!
Standardization is critical for quantitative metagenomics. Costea et al. NatBiotech 2017

http://www.microbiome-standards.org/#SOPS
An integrated 9.9 M genes reference catalog

March 2010
124 individuals
3.3 M genes

Rare genes are increasing
- Transient species ?
- Strain differences ?

Pan-metagenome

Common genes are not
They may be most clinically useful for common diseases

Individuals from MetaHIT, Chinese and HMP studies, n=1267
Sequenced reference gut genomes

Li et al. Nature Biotech, 2014
Improving microbiome description
Infant gut microbial catalog containing 13 M genes

2006 individuals
739 kids, 1 week to 6 yrs
1267 adults

Gene detection in 6 weeks old infants is greatly augmented

- Metahit 9.9M : 53,151 genes
- Infant 13M : 128,750 genes

Anne Sophie Alvarez et al, in preparation
Towards a common gut gene catalog

- Rheumatoid arthritis catalog
- Liver cirrhosis catalog
- Vegan catalog
- Atherosclerosis catalog

Comparability of studies requires a common catalog – we should cooperate to make it and update it!
Other human sites

- Oral gene catalog – 300+ individuals, ~13 M genes (Cabrero et al. in preparation)

Animal models

- Mouse gut - 184 animals, different providers, housing institutions and diets, 2.5 M genes
  5% overlap with the human gene catalog (Xiao et al., Nat Biotech 33, 1103-1108, 2015)
- Pork gut – 287 pigs from France, Denmark and China, 7.7 million genes (Nat Microb, 2016)
  12% overlap with the human gene catalog
- Bovine, chicken, rabbit gut – under construction
Gene catalog clustered in MetaGenomic Units by co-abundance binning

741 large MGU (>700 Genes) correspond to bacterial species (MetaGenomic Species; 85% previously unknown)

238 high quality genomes reconstructed

6640 small MGU: phages, plasmids, virulence islands, CRISPR...

Improving knowledge of human associated microbial species

- By systematic culturing, enabling characterization of players
- By computational means, enabling strain and pangenome assessment

Empowering reasoned microbiome modulation
Diagnostics
Liver cirrhosis

123 patients
Liver cirrhosis diagnosis
• by biopsy in 46
• by clinical symptoms or imaging in 77

114 controls
Healthy volunteers who visited the hospital for annual physical examination

AUC = 0.943
AUC = 0.935

Discovery
• 98 patients
• 83 controls

Validation
• 25 patients
• 31 controls

Zhejiang University, Hangzhou, China & MGP, Jouy en Josas, France
Parkinson disease

Bedarf ... Bork et al., Genome Biology, 2017

Rich and poor microbiome

Atherosclerosis

Zhie ... Karstensen et al., Nat Comm, 2017
Microbiome-based biomarkers can accurately detect a disease and even a risk of a disease

6 MGS identify at-risk individuals that are microbe-poor with 95% accuracy

Cotillard et al. Nature 2013, doi: 10.1038/nature12480.39
Severity of the disease – liver cirrhosis

MELD
p<1e-5

CTP
p<3e-4

LC MGS load

Invasion of the gut by oral bacteria

Overproduction of NH$_3$ & GABA; impact on Mn$^{2+}$

Qin N. et al. Nature 2014
Current concepts in the assessment and treatment of Hepatic Encephalopathy


Pathophysiology – impacted by the microbiome?
✓ The ammonia theory
✓ GABA/benzodiazepine receptor complex theory
✓ Manganese theory

Treatments – impact the microbiome?
✓ Oral laxatives
✓ Enemas
✓ Antibiotics
Treatments to improve the microbiome more permanently - FMT?

*Hepatology*

**Fecal Microbiota Transplant from a Rational Stool Donor Improves Hepatic Encephalopathy: A Randomized Clinical Trial**

*Bajaj et al 2017, DOI: 10.1002/hep.29306*

FMT, n=10; Standard of care, n=10, Follow-up 150 days

Conclusions: FMT ... reduced hospitalizations, improved cognition and dysbiosis in cirrhosis with recurrent HE.
Advent of toxic microbiome in liver cirrhosis

Trigger:
Virus infection, alcohol, obesity, autoimmunity...

Consequence:
Loss of hepatocytes, impaired bile production – gut ecosystem becomes permissive to bile-intolerant microbes

Result:
Invasion of the gut by oral bacteria & food-borne pathogens - advent of a toxic microbiome

Avenues for new treatments:
FMT to restore a healthy microbiome
Administration of bile salts (or equivalents) to protect it!? 
Treating the human and the microbial parts of our body to optimally preserve health and cure the disease.
Alterations of the microbiome can aggravate the disease; restoration of the microbiome should be beneficial
Microbiome restoration

- Diet, nutritional interventions
- Molecules
  - Promoters of “good” species (prebiotics, fibers)
  - Inhibitors of “bad” species (narrow spectrum AB, bacteriocins)
- Microbes
  - Bacteriophages
  - Probiotics
  - Communities
  - Transplantation
Nutritional intervention can impact richness
Dietary intervention improves simultaneously gene richness and risk phenotypes

Risk mitigation by intervention

The communities of the gut microbiome
Enterotypes of the human gut microbiome

Based on genus-level analysis
Named after the dominant genus

Europeans, Americans, Asians, n=33.

Danes n=85
US n=154
Quest for mechanisms – single species or communities?
Integration of clinical phenotypes, microbiome and metabolome data reveals microbial species important for a disease

Microbiome and insulin resistance

- 277 non-diabetic individuals
- 75 T2D patients

The IR-associated metabolome was associated with the gut microbiome-encoded functions:

- Higher potential for LPS and BCAA biosynthesis
- Reduced potential for BCAA transport into bacterial cells

A few species drive the association

Positive correlations between microbial functions and IR are largely driven by a few species, notably *Prevotella copri* and *Bacteroides vulgatus*, suggesting that they may directly impact host metabolism. We tested this hypothesis in mice on a high-fat diet, and found that a challenge with *P. copri* led to increased circulating serum levels of BCAAs and insulin resistance.

A single species can play an important role but many are likely to contribute
Is microbiome alteration a cause, a consequence or a contribution to a chronic disease?
Contribution of the microbiome to the disease – two examples

- Liver cirrhosis gut microbiome may be toxic
  - Ammoniac, manganese, GABA (encephalopathy)
- Low richness gut microbiome may be less healthy
  - Low butyrate producers (gut health)
  - Abundant pro-inflammatory species (systemic inflammation)

The advent of vicious cycle: inflammation selects for resistant species, which are pro-inflammatory.
We should strive to restore or preserve health by modulating unhealthy/toxic microbiome and treating the host, to break the vicious cycle...

...while attempting to unravel the mechanisms which underlie its advent and its effects on our bodies.
Understanding mechanisms

- Cell lines, high throughput screens for microbe-derived effectors
- Organoids
- Artificial organs (gut) to characterize microbial interactions
- Animal models to study host-microbe dialogue
- Interventional longitudinal studies

...will take time
Impact of human microbiome research on health

A tremendous potential of human microbiome

- diagnostics
- prognostics
- patient monitoring
- target for modulation to improve health

To better preserve health and better treat the disease

Industry-academia partnering
MetaGenoPolis

Pre-industrial Demonstrator
Grant P.I.: S. Dusko Ehrlich
Director of the INRA Unit: Florence Haimet
Director of Research: Joël Doré

Microbiome in health & disease

Funding: 19M€ for 2012-2020 by Investissements d’Avenir
Budget for the period: 60+ M€
A set of ISO9001-2015 certified platforms
Landmark human microbiome papers

► 60+ publications on quantitative & functional Metagenomics

2012 : Qin et al. Nature, Type II Diabetes
2013 : Le Chatelier et al. Nature, Richness of gut microbes and metabolic markers
2013 : Sunagawa et al. Nature Methods, Universal phylogenetic markers
2014 : Li et al. Nature Biotech, 10 millions genes reference catalog
2015 : Xiao et al. Nature Biotech, A mouse gut catalogue
2015 : Qin et al. Nature, Accurate liver cirrhosis diagnostic,
2017 : Costea et al. Nature Biotech, Standards for microbiome studies

► 29 patent applications, 70% licensed
► 24 M € research contracts, 54% private sources
Beyond discovery: impact on the society – engaging industry

enterome bioscience

http://www.enterome.com/

To fix IBD... look at the Microbiome
THE FIRST NONINVASIVE GUT MICROBIOME BIOMARKER surrogate marker of mucosal healing

Gut bacterial richness scan on a Q-PCR & nanostring platforms
Acknowledgments

MetaHIT Consortium

Micro-Obese: K. Clement, JD. Zucker, J. Doré
The team

InfoBioStat
Nicolas PONS
Anne-Sophie ALVAREZ
Ariane BASSIGNANI
Kevin DA SILVA
Magali BERLAND
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Véronique LEJARD
Parfait EVOUNA-MENGUE
Amélie GOUDET
Aline LETUR

Transversal services
Florence HAIMET
Anne Bonin
Anthony DOBEZ
Marine FRAISSANGE
Damien TOTY
Merci beaucoup,
Thank you very much!
And take good care of your microbiome...

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