May 31, 2016

CONSIDERING THE MICROBIOME AS PART OF FUTURE MEDICINE AND NUTRITION STRATEGIES: *Challenges and proposed answers*

Bruxelles
Workshop The Microbiome, Diet and Health: Assessing Gaps in Science and Innovation

David Petiteau

AGENDA

1. **INRA and the MetaGenoPolis project**

2. **The currents trends on microbiome research**

1. **Typical business and regulatory questions raised by industry sector involved in the microbiome revolution**

2. **Proposed concepts for regulatory decision-making in order to create a robust framework for the translational applications associed with microbiome science**

INRA'S LABORATORIES – A WORLDWIDE LEADER IN THE MICROBIOME SCIENCE FIELD AND THERAPEUTIC APPLICATIONS

- **INRA has a leading position worldwide on Gut Microbiota**

Scopus

Disciplinary Field	INRA Ranking among the top 1% most-cited Research bodies					
	By Number of Citations			By Number of papers		
	World Ranking	European Ranking	French Ranking	World Ranking	European Ranking	French Ranking
Agricultural Sciences	3/578	2	1	3	2	1
Plant and animal Sciences	4/1060	2	1	5	1	1
Microbiology	18/426	6	3	13	4	3
Environnement /Ecology	29/701	8	2	15	4	1
Biology et biochemistry	124/851	29	5	84	23	5
Molecular biology and Genetics	124/559	30	5	90	21	5

INRA METAGENOPOLIS – MICALIS
20 YEARS OF TOP LEVEL MICROBIOME SCIENCE

metagenopolis mgps.eu

LETTER

doi:10.1038/nature12480

Dietary intervention impact on gut microbial gene richness

Aurélie Cotillard[1,2*], Sean P. Kennedy[3*], Ling Chun Kong[1,2,4*], Edi Prifti[1,2,3*], Nicolas Pons[3*], Emmanuelle Le Chatelier[3], Mathieu Almeida[3], Benoit Quinquis[3], Florence Levenez[3,5], Nathalie Galleron[3], Sophie Gougis[4], Salwa Rizkalla[1,2,4]

ELSEVIER

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Microbiology

Human intestinal metagenomics: state of the art and future

Hervé M Blottière[1,2,3], Willem M de Vos[4,5], S Dusko Ehrlich[3] and

ARTICLE

doi:10.1038/nature09944

Enterotypes of the human gut microbiome

OPEN ACCESS Freely available online

PLOS ONE

High-Throughput System for the Presentation of Secreted and Surface-Exposed Proteins from Gram-Positive Bacteria in Functional Metagenomics Studies

Recent advances in basic science

A metagenomic insight into our gut's microbiome

Patricia Lepage,[1,2] Marion C Leclerc,[1,2] Marie Joossens,[3,4,5] Stanislas Mondot,[6] Hervé M Blottière,[1,2] Jeroen Raes,[3,4] Dusko Ehrlich,[1,2] Joel Doré[1,2]

ARTICLE

doi:10.1038/nature12506

Richness of human gut microbiome correlates with metabolic markers

Emmanuelle Le Chatelier[1*], Trine Nielsen[2*], Junjie Qin[3*], Edi Prifti[1*], Falk Hildebrand[4,5], Gwen Falony[4,5], Mathieu Almeida[1]

OPEN ACCESS Freely available online

PLOS ONE

A Robust and Adaptable High Throughput Screening Method to Study Host-Microbiota Interactions in the Human Intestine

ARTICLES

nature biotechnology

Identification and assembly of genomes and genetic elements in complex metagenomic samples without using reference genomes

RESOURCE

nature biotechnology

An integrated catalog of reference genes in the human gut microbiome

Junhua Li[1–3,19], Huijue Jia[1,19], Xianghang Cai[1,19], Huanzi Zhong[1,19], Qiang Feng[1,4,19], Shinichi Sunagawa[5], Manimozhiyan Arumugam[1,5,6], Jens Roat Kultima[5], Edi Prifti[7], Trine Nielsen[6], Agnieszka Sierakowska Juncker[8], Chaysavanh Manichanh[9], Bing Chen[1], Wenwei Zhang[1], Florence Levenez[7], Juan Wang[1], Xun Xu[1], Liang Xiao[1], Suisha Liang[1], Dongya Zhang[1], Zhaoxi Zhang[1], Weineng Chen[1], Hailong Zhao[1], Jumana Yousuf Al-Aama[10,11], Sherif Edris[11,12], Huanming Yang[1,11,13], Jian Wang[1,13], Torben Hansen[6], Henrik Bjørn Nielsen[8], Søren Brunak[8], Karsten Kristiansen[4], Francisco Guarner[9], Oluf Pedersen[6], Joel Doré[7,14], S Dusko Ehrlich[7,15], MetaHIT Consortium[16], Peer Bork[5,17] & Jun Wang[1,4,6,11,18]

THE METAGENOPOLIS PROJECT – OVERVIEW

THE METAGENOPOLIS PROJECT – IMPACT INDICATORS (1/2)

- S. Dusko Ehrlich, principal investigator of the MGP project and Joël Doré, scientific director of MGP, have played a **leading role in the emergence of metagenomics in Europe** (MetaHIT, MICRO-Obes)

- **Landmark human microbiome publications**: 60+ publications on quantitative & functional Metagenomics

2010 : Qin *et al.* Nature , The human gut reference catalogue
2011 : Arumugam et al. Nature, Enterotypes
2012 : Qin *et al*. Nature, Type II Diabetes
2013 : Cotillard *et al.* Nature, Impact of diet on gut microbiome
2013 : Le Chatelier *et al*. Nature, Richness of gut microbes and metabolic markers

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
2014 : Qin *et al.* Nature, Human gut microbiome alterations in liver cirrhosis
2015 : *Xiao et al.* Nature Biotech, A mouse gut catalogue
2015 : *Qin et al.* Nature, Accurate liver cirrhosis diagnostic,
2015 : *Forslund et al.* Nature, Drug confounders in microbiome analysis

2016 : Pedersen *et al.* Nature in press, Microbiome, metabolome and insuline resistance

- **28 patent applications, 3 registered software**

- MGP has been co-chair of the International Human Microbiome Consortium (2008-09 and 2012-2014) and co-organiser of the International Human Microbiome Congress since 2010

THE METAGENOPOLIS PROJECT – IMPACT INDICATORS (2/2

- MGP project: a team of **80 people**

- With the aim of enabling discoveries of the roles of the gut microbiome in health and disease for **translation of discoveries into applications in nutrition, prevention and therapeutics**

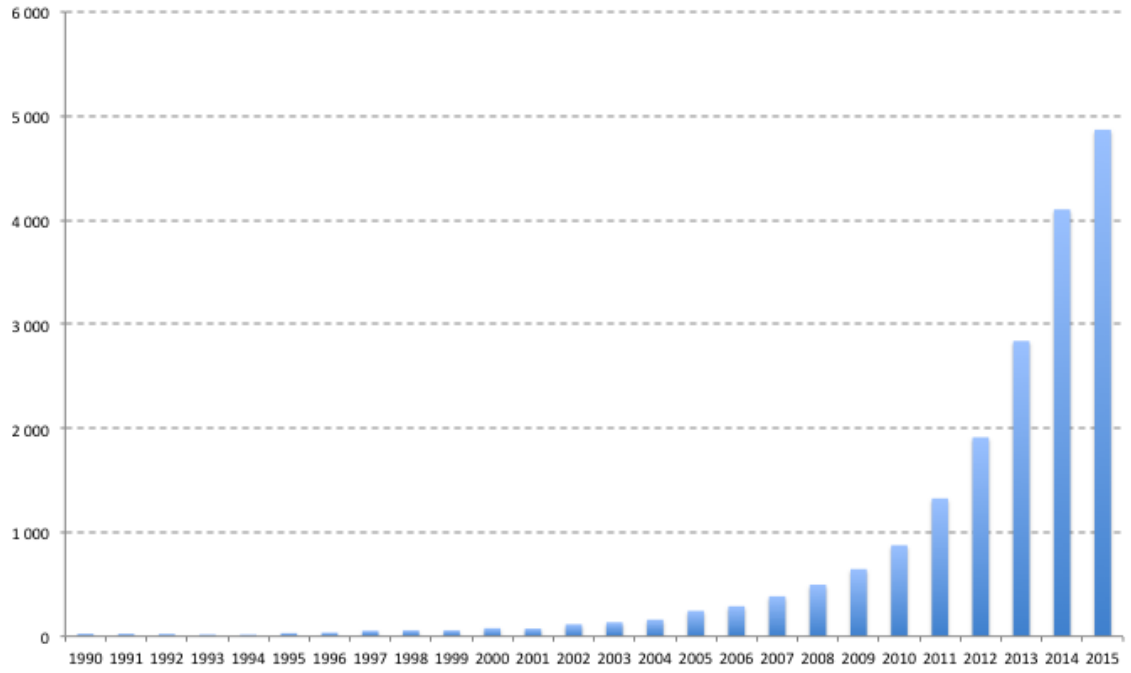
- As a business partnership manager, I am in charge of helping generate (finding a common language and identifying mutual interests) and putting in place research projects with industrial partners

- Projects and partnerships :
  - **75 projects, 45 ongoing;**
  - **30 contracts with industry;**
  - **4 EC funded projects, 2 as coordinator;**
  - **€19m+ income from R&D contracts**

- First hand role in facilitating the emergence of a "Microbiome Translational Ecosystem" together with other French/European academic players : S. Dusko Ehrlich is scientific founder and CSO of Enterome and Joël Doré is MaaT Pharma science advisor.

SCIENTIFIC LITTERATURE ON MICROBIOME GROWING FAST

Literature on microbiota – # of articles per year since 1990



Source: Pubmed

- Chronic, immune-mediated diseases have steadily increased in incidence since end of WWII
- Evidence linking to microbiota

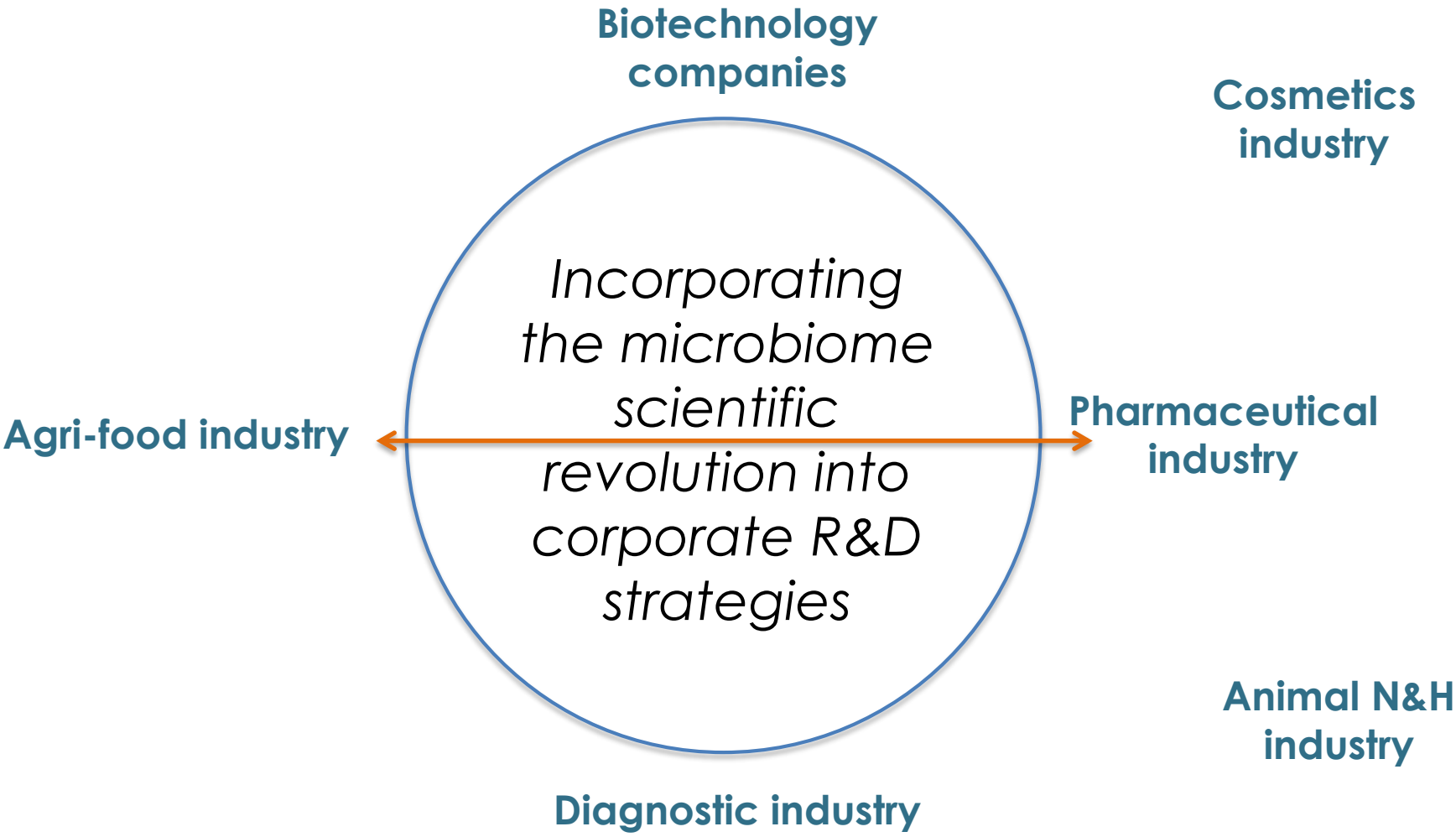
Disorders linked to altered composition of the gut microbiota

Most active areas

- GI diseases
- Metabolic disorders
- Cancer
- Skin disorders and conditions
- Neuro-psychiatric disorders

Based on # of publications in last ten years

INDUSTRY SECTORS INVOLVED IN THE MICROBIOME SCIENTIFIC REVOLUTION



QUESTIONS FOR AGRI-FOOD INDUSTRY

Immediate microbiome-based applications	Typically associated regulatory questions
Leveraging microbiome knowledge to optimize nutrition strategies ▪ Development of personalised diets and specific food for specific target groups ▪ Development of "healthy" food products for general population Mixes of probiotics, fibres, prebiotics	▪ What is dysbiosis? ▪ What is a healthy microbiome? ▪ Which "glasses" should we use to characterize healthy and unhealthy states and hence substantiate a nutritional / -biotic product?

- **HGC / LGC individuals based on microbial reference gene catalogs, highlighting both core metagenome & rare genes**
- **Standard operating procedures developed by the International Human Microbiome Standards (IHMS) project**

QUESTIONS FOR AGRI-FOOD INDUSTRY – PROPOSED ANSWERS
REFERENCE GENE CATALOGS

- Human microbiomes differ by bacterial gene counts
- **Microbiota gene count / diversity is a health-associated stratifier**
- Low gene count (low bacterial richness) individuals (c.1/4) have less healthy metabolic and inflammatory traits
- Low bacterial richness associated with:
  - increased adiposity
  - insulin resistance
  - dyslipidaemia
  - inflammation
  - higher risk for type 2 diabetes
  - cardio-vascular and hepatic complications
- 6 MetaGenomic Species (MGS) identify at risk individuals that are microbe poor with 95% accuracy

3.3M genes Qin *Nature* 2010
Richness Le Chatelier *Nature* 2013
10M genes Li *Nature Biotech* 2014

IHMS - FP7-HEALTH-2010-261376

International Human Microbiome Standards

Grant Agreement: HEALTH-F4-2010-261376

Coordinator: S. Dusko Ehrlich

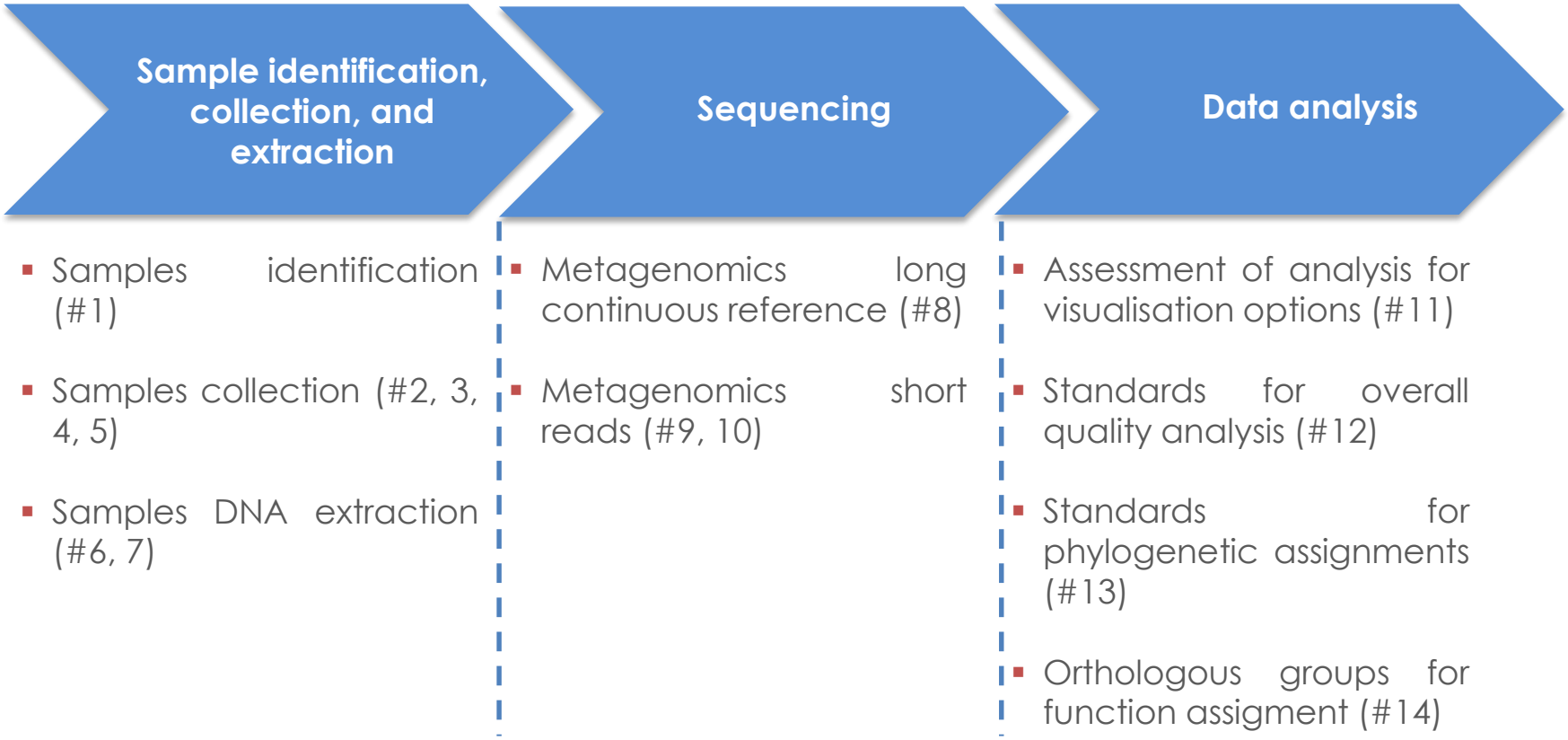
Start date: Feb 01, 2011 duration: 4 years

- **Web : http://www.microbiome-standards.org/**
- **Partners & PI:**

1	INRA	SD Ehrlich
2	HUVH	F Guarner, Barcelona
3	BCM	J Versalovic, Houston, Texas
4	SJTU	L Zhao, Shanghai
5	CEA Genoscop	J Weissenbach, Evry
6	BGI Shenzhen	W Jun, Shenzen
7	EMBL	P Bork, Heidelberg
8	Western Ontario	B Singh, London, Ontario

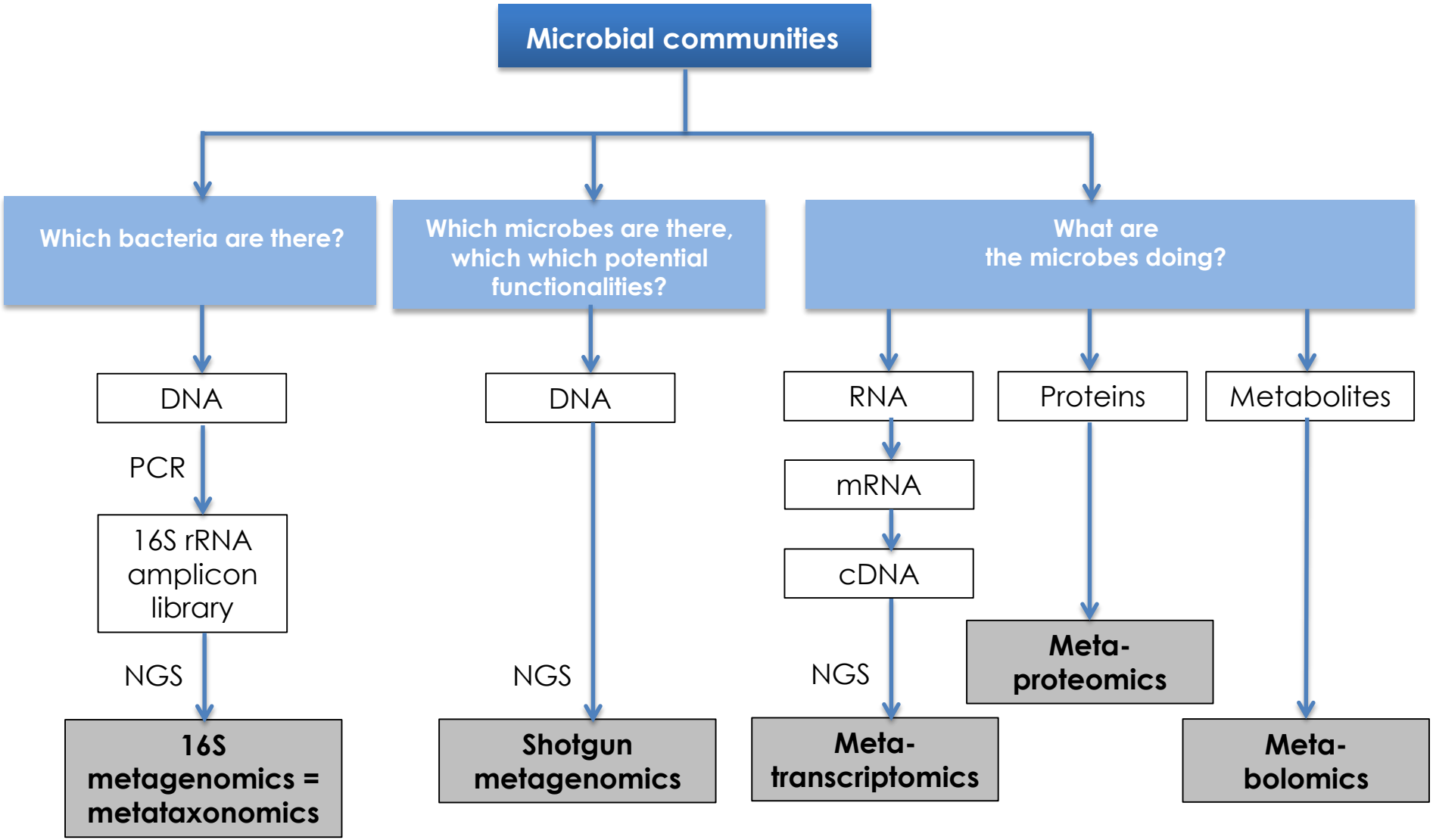
QUESTIONS FOR AGRI-FOOD INDUSTRY – PROPOSED ANSWERS STANDARDS IN METAGENOMICS (2/2)

- **Standard operating procedures and recommendations, designed to optimize data quality and comparability in the human microbiome field, covering the whole chain:**



- **SOPs downloadable under www.microbiome-standards.org since April 2015**

WHICH "GLASSES" SHOULD WE USE?



QUESTIONS FOR BIOTECHNOLOGY COMPANIES

Immediate microbiome-based applications	Typically associated regulatory questions
▪ Microbiome as a target for modulation => Microbial ecosystem therapeutics ▪ Microbiome as a treatment of its own => Faecal microbiome transfer	▪ What is dysbiosis? ▪ What is a healthy microbiome? ▪ Strain approach vs keystone species vs ecosystemic approach ▪ Which glasses should we use to characterize healthy and unhealthy states and hence substantiate an ecobiotic product? ▪ For FMT companies: what is a healthy donor (heterologuous FMT) / a healthy state (autologous FMT)?

MICROBIOME THERAPEUTICS – SPECTRUM AND LANDSCAPE

metagenopolis mgps.eu

Live Bacterial Products (LBPs)

Drugs

Broad activity

Narrow activity

Consortium

Non–defined consortia
Faecal microbiota transfer

Rebiotix
Microbiota Restoration Therapy

WHOLE BIOME

Autologous FMT

MaîâT

Defined consortia

VEDANTA BIOSCIENCES

SERES THERAPEUTICS

Single bacterium

Single strain native

TargEDys
TARGETING EATING DYSFUNCTIONS

4D pharma plc

Single strain modified
Synthetic biology

ELIGO BIOSCIENCE

synlogic

Derived matter

Molecule

enterome bioscience

TargEDys
TARGETING EATING DYSFUNCTIONS

LNC
RESEARCH & DEVELOPMENT

SECOND GENOME
THE MICROBIOME COMPANY

QUESTIONS FOR DIAGNOSTIC INDUSTRY

Microbiome as a source of competitive biomarkers on certain pathologies?

Different categories of biomarkers:
diagnostic, susceptibility/risk, prognostic, therapy-predictive, PD, surrogate

Criteria for successful biomarkers

- **High analytical validity** (i.e. reproducibility, Limit of Detection, measures what it is supposed to measure)
- **Appropriate sensitivity and specificity** (i.e. appropriate for the condition being assessed)
- **Clinical validity / Clinical utility** (i.e. clinical relevance)
- **Ability to influence treatment plan** (i.e. impact on therapeutic choices or outcomes)
- **Ethical and social acceptance** (i.e. ethical and socially pertinent and acceptable)

Typically associated regulatory questions

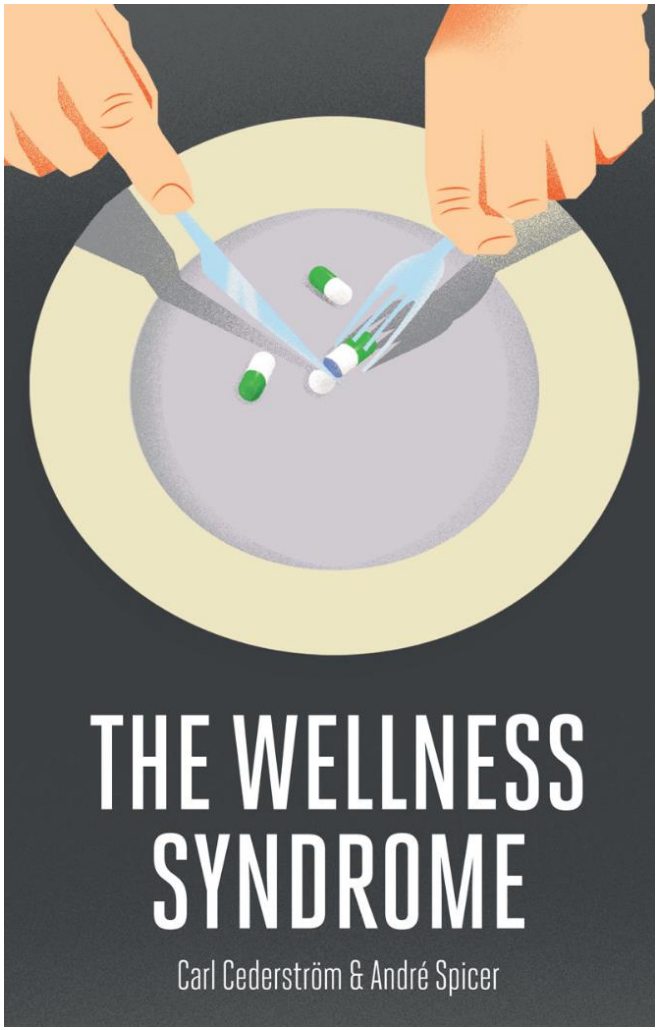
- **Health authorities (Food/Medicines) pro-actively asking for microbiome-based stratification?**

Metagenomic signatures (potentially coupled with other -omics approaches) as a source of competitive biomarkers and CDx

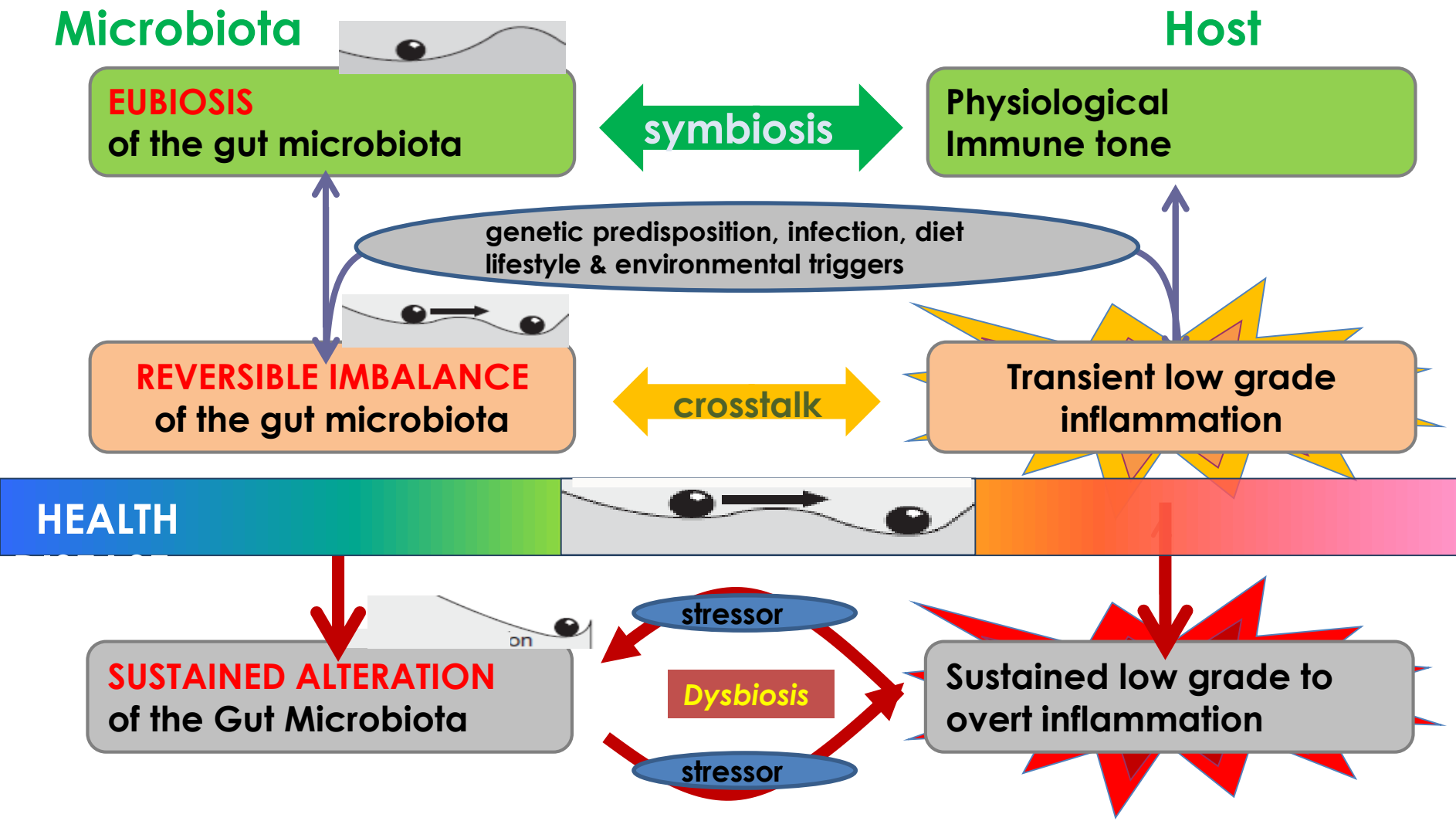
QUESTIONS FOR PHARMA INDUSTRY

Immediate microbiome-based applications	Typically associated regulatory questions
Mining the human microbiota for new drugs	**Metabolites based / pharmabiotic approach**
Predicting the influence of xenobiotics on the human microbiota	**Impact on microbiomes to be taken into account in safety and efficacy guidelines by Food and Safety and Medicines Agencies**
Protecting the gut microbiota from collateral damage during antibiotic exposure	

ASSOCIATED ETHICAL QUESTIONS TO BE TAKEN INTO ACCOUNT BY THE REGULATOR



- To which point shall we modulate the microbiome?
- "Meta-eugenics"



Doré, Scheffer 2001, Kefi 2014

POTENTIAL ANSWERS (2/2)

Proposed *concepts* for regulatory perspective	Founding regulatory pillar for… (notional)
MAN-MICROBE SYMBIOSIS	**Nutrition to stay healthy**
***REVERSIBLE* IMBALANCE**	**Food for Special Medical Purposes**
***SUSTAINED* ALTERATION**	**Microbiome therapeutics**

TAKE-HOME MESSAGES

- **Significant investments** into drug discovery and human trials are underway in the microbiome field across a variety of therapeutic areas
- **Richness in gut microbiota is key for health**
- Usual taxonomic approaches do not provide an accurate view of the **functional composition of the microbiome**
- Development of microbiome-based products will be helped by regulatory definitions in the following fields:
  - Definition of **MAN-MICROBE SYMBIOSIS** and its boundaries
  - Definitions of levels of **DYSBIOSIS: REVERSIBLE IMBALANCE** vs **SUSTAINED ALTERATION**
- Basis for innovative microbiome-based solutions
  - MAN-MICROBE SYMBIOSIS => **PREVENTIVE NUTRITION PRODUCTS** (EFSA)
  - REVERSIBLE IMBALANCE => **FSMP** (EFSA)
  - SUSTAINED ALTERATION => **MICROBIOME THERAPEUTICS** (EMA)
- Multi-national collaboration essential for generalization and validation of relevant standards. Define together **the relevant common denominator** for further studies, which will enable capitalization (e.g. via microbiome meta-analyses) of these studies


THANK YOU!
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