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## The French “Microbial Ecosystems & Meta-omics” (MEM) metaprogram from INRA

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# The French “Microbial Ecosystems & Meta-omics” (MEM) metaprogram from INRA

**Sophie SCHBATH**

MaIAGE, INRA Jouy-en-Josas, France

Thessalonica, Greece — November 16, 2018





# Earth is a microbial world



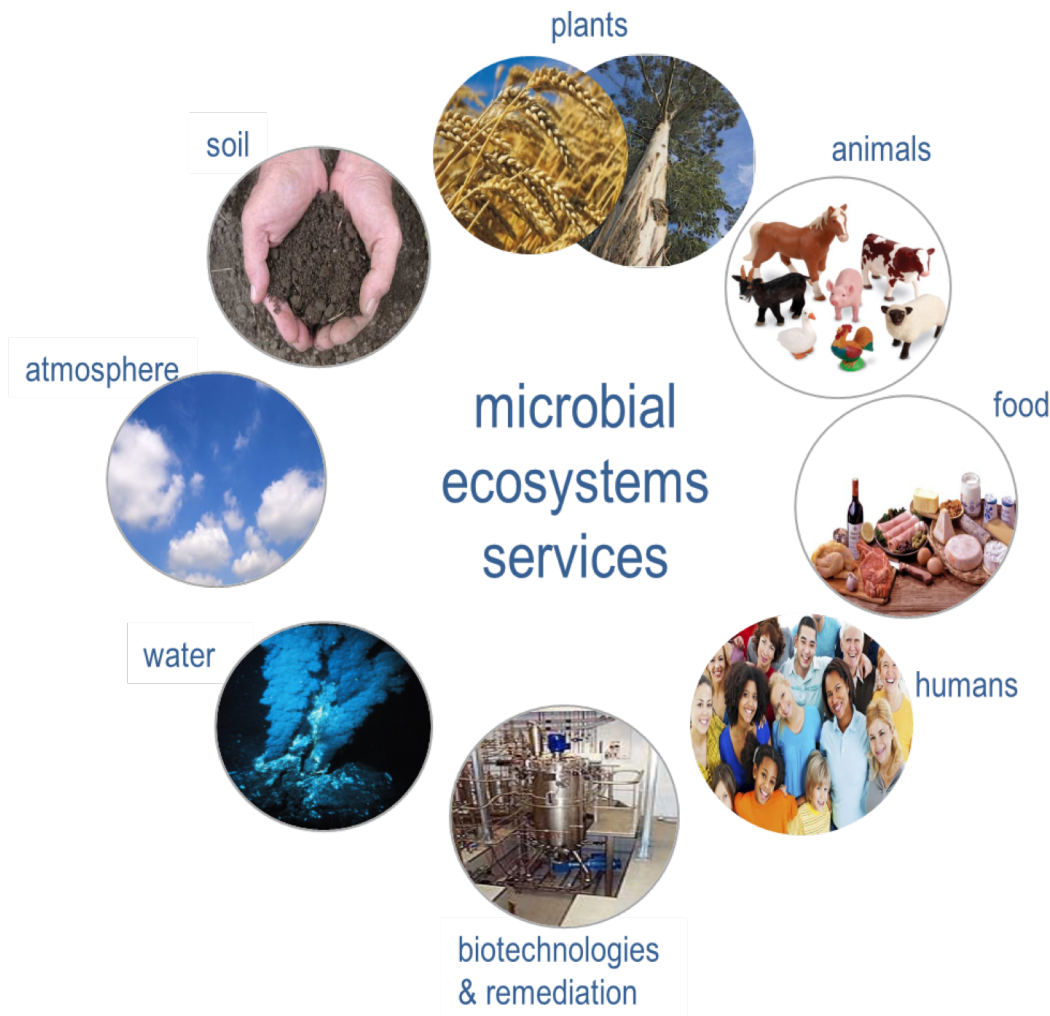
~ 50% of the biomass

~ 95 % of the  
biosphere diversity

Normal microbial life =  
communities i.e.  
ecosystems

# Microbial ecosystems are important

Provide services linked to agriculture, environment, nutrition and health



- **Agriculture** : production and environment
  - Soil, plants, trees microbiomes for production, health & mitigation of climate change
  - Animals microbiomes for production, health and decrease of antimicrobial-use and greenhouse gaz
  - Depollution, recycling, improved sustainability
- **Food chain:** safety and sustainability
  - Food quality, preservation and safety
  - Sustainability, waste reduction and conversion
- **Human:** health
  - Health & disease (chronic non transmissible and infectious ones)
  - Nutrition & preservation of health

# The Human microbiome wave

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**2005** Technological breakthrough: New generation sequencing (C. Venter)

**2005** Paris meeting (INRA sponsored): ~80 scientists including C. Fraser, E. Rubin, J. Weissenbach, J. Doré, S. D. Ehrlich, ... + funding agencies NIH, NSF, EU

**2007** Rockville meeting (co-sponsored by NIH & EU) => creation of IHMC

“Participants agreed that a **consortium** should be formed with membership to **include funding agencies and Principal Investigators** of projects that have an interest in the **comprehensive assessment of the human microbiome and its impact on health and disease.**”

**2007-2008** NIH Human Microbiome Project-NIH Jump start ; EU MetaHIT project

**2008:** Data analysis & coordination center (HMP)

**2009:** Canadian Human Microbiome Initiative (CIHR); Australian Jumpstart Human Microbiome Project

**2010:** Korean Microbiome Diversity using Korean Twin Cohort (NRFK)

**2011:** International Human Microbiome Standards (EU)

...

Brought a new vision for health and medicine

# The Human microbiome & INRA

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**2005** Technological breakthrough: New generation sequencing

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**2011**: [International Human Microbiome Standards](#) (EU)

...

=> share with other studied biotopes


# INRA's METAPROGRAMS: overcoming disciplinary boundaries

**AAFCC**  
Adaptation of agriculture and forestry to climate change



2011

**MEM**  
Microbial ecosystems and meta-omics





2011

**SMACH**  
Sustainable management of crop health

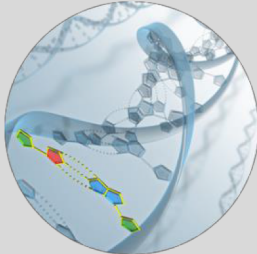


2011

**DIDIT**  
Determinants and impacts of the diets



**ECOSERV**  
Agriculture and forest ecosystem services



**SELGEN**  
Genomic selection (Bovine, Wheat, others)



**GISA**  
Integrated management of animal health



**GLOFOODS**  
Transitions to global food security (CIRAD & INRA)



**OF&F**  
Organic Farming and Food

(becoming a MP in 2018, AgriBio started in 2006)

Pluridisciplinarity – Agronomic issues - International



# Microbial Ecosystems and Meta-omics (MEM)

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- A **multidisciplinary** program built on the strength in microbiology and involving mathematics
- To understand **functioning of the microbial ecosystems of agronomic interest**, from soils to humans, using meta-omics
- And to **optimize their services** through prediction and engineering



# MEM governance & priorities



MEM steering committee

International SAB



Thematic groups

1. Create an interdisciplinary scientific community sharing thoughts, knowledge, resources and working on projects based on both **biology & mathematics**;
2. Develop common & accessible pipelines & analytic methods (for biology & math);
3. Go gradually **beyond descriptive approaches** (who is there) **toward functional** understanding (what do they do, which interactions within & with the environment), modeling, engineering to optimize the ecosystems' services;
4. Encourage and support integrated INRA projects;
5. Enhance visibility and **international positioning of INRA** in these fields of research.

# MEM budget and means

What is it ?

- **MEM budget is based on**
  - Permanent staff salaries (main budget, often forgotten)
  - Functioning: 1M€ to 700 000 € /year
  - 2 cofunded PhD fellowships / year (covering 50% of the PhD salary)
  - Recommendation for permanent positions
- **Support for**
  - Projects : Calls, Key actions, integrated projects (incubated by MEM)
  - Meetings & think-tanks, conferences
  - Training
  - Visits or short stays abroad (started 2017)
  - Management
- **Involves**
  - 70 laboratories /teams from 11 INRA research divisions
  - ~135 scientists

**annual RCAM  
workshop**

=> Examples of achievements...

# Example 1, organize & ease metabarcoding

1. **Enable easy access** to sequencing facilities: SOPs, advices & low cost (20 €/sample)
2. **Development of an analysis pipeline** in a biologist friendly-environment
  - Benchmarking of bioinformatics tools for metabarcoding
  - Pipeline development in a Galaxy environment: **FROGS\***
  - Training sessions from raw reads to (basic) statistical analyses and result interpretation. More than 12 3-days sessions of 10-12 persons.
3. **Expand the choice of microbial barcodes** : understudied phyla and development of functional markers => ongoing project



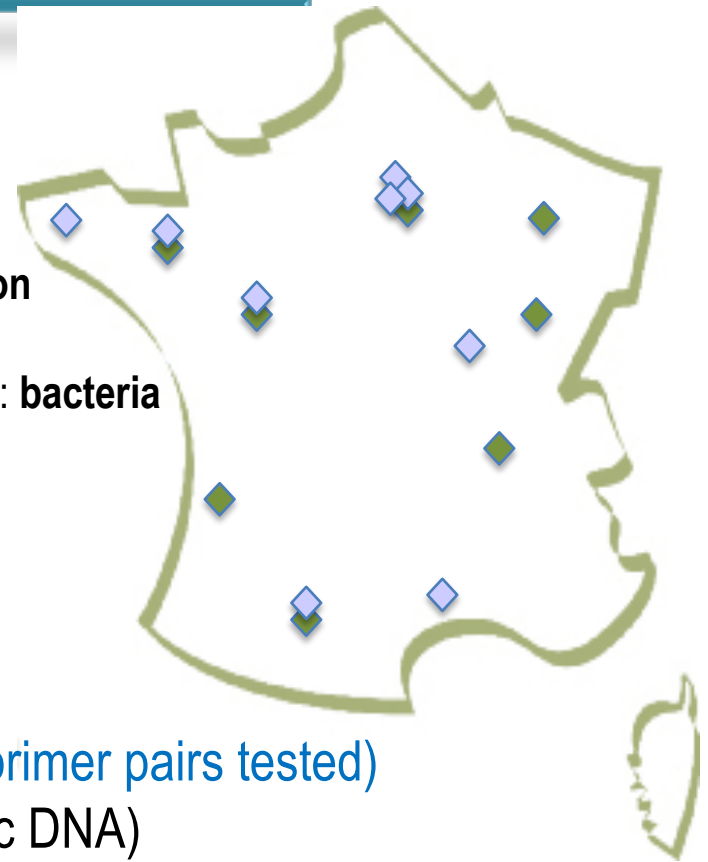
\* Escudié *et al.* (2018) *Bioinformatics* -- [frogs.toulouse.inra.fr](http://frogs.toulouse.inra.fr)

# Example 1, barcodes for understudied species in Agri-systems



C. Mougél  
M. Buée  
C. Vacher  
M. Barret  
S. Schbath

- ✓ IAM unit (Nancy): **Dikarya and Oomycota**
- ✓ IRHS units (Angers): **phytopathogens**
- ✓ CARRETEL unit (Thonon): **eukaryotic microplankton**
- ✓ BioGer Unit, (Versailles): **Fusarium** strains
- ✓ IGEPP (Rennes), LEM (Lyon), Agroecologie (Dijon): **bacteria**
- ✓ Agroecologie (Dijon): **Glomeromycotina**
- ✓ BIOGECO(Bordeaux): leaf **yeasts**
- ✓ MalAGE unit (Jouy): bioinformatics
- ✓ GetPlaGe (Toulouse): sequencing platform



## Mock communities (10 to 12 barcodes and associated primer pairs tested)

- about 250 strains for Fungi/Oomycota (genomic DNA)
- 54 bacterial strains (gDNA)
- 38 gDNA of EuK plankton

**Extension to food systems** : 10 additional laboratories involved

# Example 2, boosting metagenomic studies

## ☑ Humans: MetaHIT, Chinese and HMP studies



1267

10 Millions genes  
intestinal microbiota

*Li, et al., Nature Biotechnol 2014*

- Stratification of gut microbiota = predicts response to treatment or diet

## ☑ Food – Cheeses: CNIEL



*Almeida et al., BMC genomics 2014*

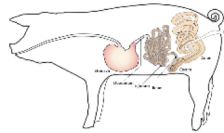


## ☐ Animals; all but one with international consortia



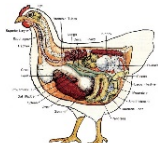
184

2.6 Millions genes *Xiao et al., Nature Biotechnol 2015*



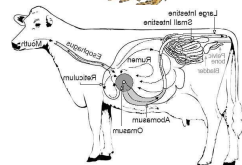
287

7.7 Millions genes *Xiao, Estelle, et al., Nature Microbiol 2016*



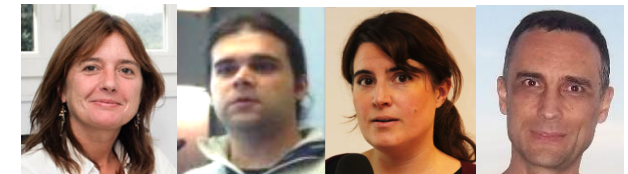
300

9.7 Millions genes *Calenge et al. unpublished*



10

13 Millions genes *Li, ... Morgavi. under revision . bioRxiv*



## Example 3, New statistical methods

- **Latent Block Model for Overdispersed Count Data with Application in Microbial Ecology.** *Aubert, Schbath and Robin. Under revision for JRSS*
  - ➔ a biclustering model-based method allowing to study the interaction between the structure of microorganism communities and environmental samples from an abundance matrix.
  - ➔ **cobiclust** R package available at <https://github.com/julieaubert/cobiclust> and on CRAN
- **Variational inference for probabilistic Poisson PCA.** *Chiquet, Mariadassou and Robin Ann. Appl. Stat., 2018.*
  - ➔ a probabilistic PCA adapted to multivariate Poisson-log normal count data and allowing to account for covariates and offsets.
  - ➔ **PLNModels** R package available at <https://github.com/jchiquet/PLNmodels>

## Example 4, Use of text-mining

Extraction of information from publications thanks to knowledge modelling, ontologies and text-mining approaches :

- Microbes
- Habitat
- Phenotype



- ➔ Ontology : <http://agroportal.lirmm.fr/ontologies/ONTOBIOTOPE>
- ➔ **Florilege** DB and web application <http://migale.jouy.inra.fr/Florilege>
  - Taxon ↔ Habitat : 820 000 relations
  - Taxon ↔ Phenotype : 86 000 relations
  - Direct links with external public DB (PubMed, DSMZ, GenBank ...)

Chaix, Deléger, Bossy & Nédellec (2018). **Text mining tools for extracting information about microbial biodiversity in food.** *Food Microbiology*.

# And now ?

- **MEM after 7 years**



- ✓ Changes mind and work practices  
(Maths:Bio; 75% MEM project with international partners)
- ✓ Increased % of INRA publications on MEM topics, more collaborative publications, 68% in journals of exceptional & excellent reputations
- ✓ 28 patents, 5 start-ups

- **Assessment of INRA's metaprograms Feb 2018**

- **2018:** institutional reflexion to launch new metaprograms

→ from MEM to « **Holobiont, the host and its microbiota** »

- **No national strategic agenda on Microbiomes**





# European Commission



Food security, sustainable agriculture and forestry, marine, maritime and inland water research and the bioeconomy

- **International Bioeconomy Forum (launched on Nov 2017)**

Flexible **multilateral platform** whereby **European and global R&I partners** would gather **to discuss and act on common challenges** in the bioeconomy, such as the **microbiome**... the IBF will be used as a platform to **share ideas and experiences** on bioeconomy policies, strategies and actions, **fostering collaboration and joint activities** that will promote innovation in key sectors.

➔ Feb 2018: submission of Coordination Support Action projects ↔ Microbiome working group

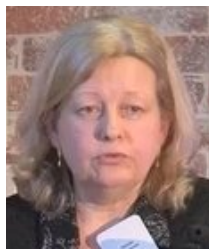
“Towards a **coordinated microbiome R&I activities** in the **food system** to support **(EU and) international bioeconomy goals**”

# Microbiome Support

- Exchange knowledge across the scientific and political community and ensure an efficient use of the available resources
- Improve coherence between national and EU microbiome research and facilitate alignment of international research agendas
- Establish international agreed microbiome definition, best practices and standards
- Improve the international cooperation, creating the basis for joint international partnerships



A. Sessitch



E. Maguin



# More specific European & international initiatives



**epsos** European Plant Science Organization  
<http://www.epsoweb.org/>

- independent academic organization that represents more than 220 research institutes, departments and universities from 31 countries in Europe and beyond.
- EPSO's mission is to improve the impact and visibility of plant science in Europe
- ➔ **Working group on microbiome**

⇒ *2 Leaders from PhytoMic network*



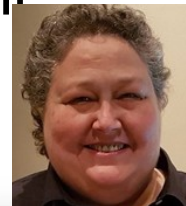
Marc Buée  
Corinne Vacher



**International Alliance for Phytobiomes Research**

<http://www.phytobiomesalliance.org/>

⇒ *2 Leaders from our PhytoMic network*



K. Eversole  
Eversole Associates  
*Enabling Science & Technology*



Corinne Vacher  
Christophe Mougel

# Phytobiomes Conference 2018



4-6 December 2018  
Montpellier – France

[www.phytobiomesconference.org](http://www.phytobiomesconference.org)

## Main Scientific topics

- Microbial community assembly and function
- Impact of microbiota on plant fitness
- Network analyses within the phytobiome system
- Modeling
- Data – framework, tools and resources, big data
- Genetic linkages
- Engineering to improve carbon sequestration
- Interactions within phytobiomes for abiotic stress
- Engineering microbes and microbial communities – including genome/gene editing
- Screening for microbes
- Precision agriculture
- Fertilizer, nutrient, and chemical input efficiency
- Translating complexity into products
- Regulatory requirements (EFSA, EPA, ...)
- Greenhouse & Field trials
- Industry research needs

- ➔ Early bird registration: 15 September 2018
- ➔ Abstract submission for a talk: 31 August 2018



# Conclusion, a time of opportunities

## ✓ INRA's metaprogramm on microbial ecosystems

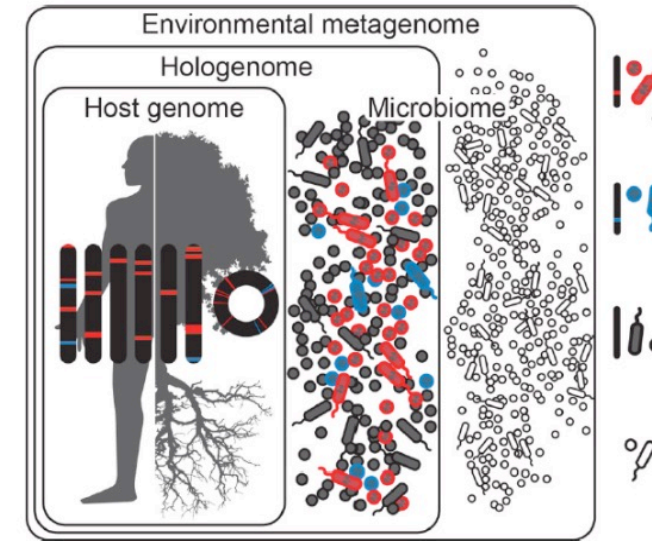
- Create an internal scientific dynamic and ....
- ... foster a pluri-disciplinary community
- Will shift to the more focus **holobiont** concept for next generation of MP

## ✓ European Commission level

- International Bioeconomy Forum / WG microbiome / **Microbiome Support**
  - Common strategic agenda
  - Work on standards
  - Recommendations for future actions

## ✓ European & international initiatives

- EPSO & International phytobiomes Alliance
- ERA-Net INTIMIC : Diet-microbiota-health => 11 projects, knowledge PF





Thank you !



# Bi-clustering of overdispersed count data: LBM

## Latent Block Model:

### Assumptions

$(\mathbf{Z}_i) \sim \mathcal{M}(1, \pi = (\pi_1, \dots, \pi_K))$   $(\mathbf{W}_j) \sim \mathcal{M}(1, \rho = (\rho_1, \dots, \rho_G))$   
Latent variables  $(\mathbf{Z}_i)$  and  $(\mathbf{W}_j)$  are independent  
The random variables  $Y_{ij}$  are independent conditionally on labels

### Model

$(Y_{ij}), i = 1, \dots, n$  et  $j = 1, \dots, m$  matrix of observations.

$$Y_{ij} | (Z_{ik} = 1, W_{jg} = 1) \sim f(\cdot; \mu_i \nu_j \alpha_{kg})$$

- $\mu_i$  : mean level of presence of one particular bacteria
- $\nu_j$  : scale factor correcting for sampling effort (around 1)
- $\alpha_{kg}$  : interaction level between bacteria and sampling units within the  $(k, g)$  group

## Poisson-Gamma Latent Block Model:

$$Y_{ijr} | (Z_{ik} = 1, W_{jg} = 1) \sim \mathcal{P}(\mu_i \nu_{jr} U_{ijr} \alpha_{kg})$$

with  $U_{ijr} \sim \text{Gamma}(a, a)$

# Probabilistic PCA for multivariate Poisson-log normal counts

## Hierarchical Model

$$\mathbf{z} \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma})$$

$$\lambda_j | \mathbf{z} = e^{z_j}$$

$$\mathbf{Y}_j | \mathbf{z} \sim \mathcal{P}(e^{z_j})$$

Basis

Average count of species  $j$

Observed count of species  $j$



# Example 4, Pathobiome concept

2013 Think tank => multidiscipline to address animal and plant health taking into account the biotic environment of pathogens (pathologists, infectiologists, microbial ecologists, mathematics, etc).



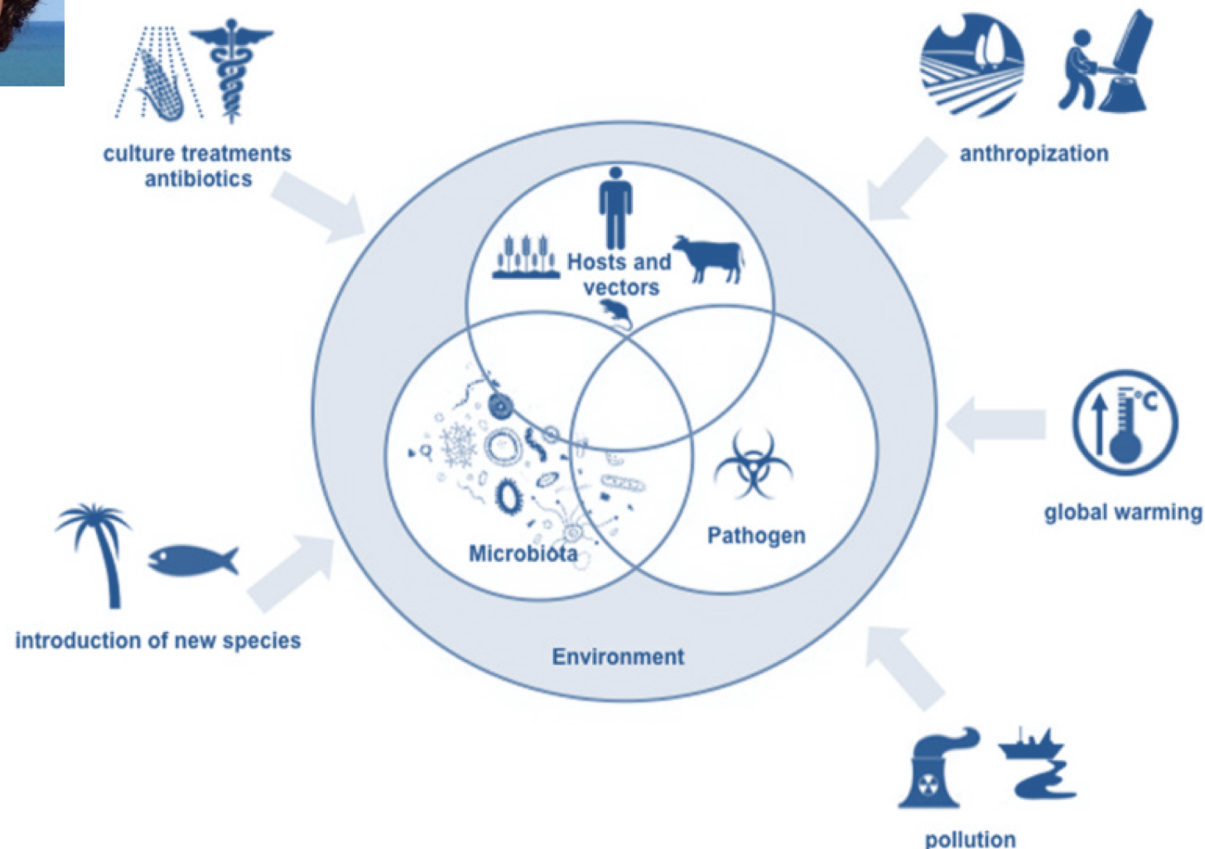
Muriel Vayssier  
Animal Sc Div.

frontiers in  
CELLULAR AND INFECTION MICROBIOLOGY

REVIEW ARTICLE  
published: 05 March 2014  
doi: 10.3389/fcimb.2014.00029

## Shifting the paradigm from pathogens to pathobiome: new concepts in the light of meta-omics

Muriel Vayssier-Taussat<sup>1\*</sup>, Emmanuel Albina<sup>2,3,4</sup>, Christine Citti<sup>5</sup>, Jean-François Cosson<sup>6</sup>, Marie-Agnès Jacques<sup>7</sup>, Marc-Henri Lebrun<sup>8</sup>, Yves Le Loir<sup>9,10</sup>, Mylène Ogliastra<sup>11</sup>, Marie-Agnès Petit<sup>12</sup>, Philippe Roumagnac<sup>13</sup> and Thierry Candresse<sup>14</sup>



 @gr\_pathobiome  
2 international meetings  
2015, march 2018

# MEM activities

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## Scientific impetus

- INRA think tank: 6 (pathobiome and phytoMic emerged)
- INRA, National & international meetings : 20
- Networks: 5 on going
- Continuing education: bioinformatics & microbial ecology
- Science popularization: 5

## Research projects

- Call for projects : 35 funded projects (all maths & biology)
- Key actions : 20
- PhD fellowships : 14 (directly supported by MEM)
- Short international missions : 10 (2017 & 2018)