Bio-Modeling Systems

The Mechanisms-Based Medicine Company

GEMMA
Multi-Omics Research in Autism

PHERECYDES PHARMA

Bacteriophages, Genius and success of precision medicine in infections (CU/ATU HCL) and new tracks for microbiote “surgery” control in Autism.

ANTIMIC 2019 CONFERENCE LILLE

Manuel GEA : CEO, Co-founder, VP IT R&D & Chairman Adebiotech
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BMSystems Group description

- Independent Private Company incorporated in 2004. 100% owned by its founders.
- Profitable since 2006, thanks to our recurrent clients.
- We only sell the results of the R&D programs, not our proprietary technologies.
- 100% biology driven company focused on discovery, and critical high impact decisions making
- A unique proprietary CADI™ Knowledge Database of mechanisms & interactions.
- Not domain-dependent, but information-dependent.
- Markets: Pharma, Cosmetics, Nutrition, Health Technologies, Connected health,
- Highly productive 24 vFTE* of which 9 vFTE on CADI™ Discovery programs only.
- Strong & long term strategic R&D collaborations (>100 people collaborating).
- Dual business model : Contractual or Collaborative R&D programs.
- External valorization of our collaborative R&D programs through out-licensing or spin-off.
- Outstanding internal pipeline of programs ready for collaborations.
- *14 successes independently validated by our clients/partners of which: 1 therapeutic spin-off and 1 exclusive out-license, 4 issued patents, 10 publications.*
- *Potential competitors: Key Opinion Leaders, dominant thinking companies or pharma Systems Biology or bioinformatics teams argue they can do the same. We are always open for discussions & comparisons on success rates and outputs for patients.*

The World's first Mechanisms-Based Medicine Company

You have a R&D issue or a decision to make, we may have a solution for you.

*vFTE: variable Full Time Equivalent but variable at 90%

BMSystems' outstanding POCs and our 2 first external outputs

BMSystems/CEA collaborative research in neurodegenerative diseases. World's first in vivo validation of the mechanisms of Creutzfeldt-Jakob disease pathogenesis & progression. Two Awards (Bio IT World Best Practice Award 2009 and European Commission 2010).

Pherecydes-Pharma (2006): First BMSystems' therapeutic spin-off, (novel M.R. anti-bacterial nano-agents biotherapies), two indications: Multi-resistant Skin infections in Phase I/II. & osteo-articular infection compassionate use success.

CEA/BMSystems collaborative research in CNS (psychiatric and neurological disorders) led to the co-owned patent WO201029131 with a worldwide exclusive license to CEA's spin-off currently in Phase II.

5 ongoing BMSystems' outstanding R&D programs

Microbiota & Autism therapeutic H2020 program started with 14 M€ funding. GEMMA program (Genome, Environment, Microbiome and Metabolome in Autism) gathers an international consortium of scientists to study the role of the gut microbiome in the development of Autism Spectrum Disorders (ASD).

Etiology & Epigenetic and therapeutic evaluation for metabolic disorders program self funded. UMANG program How does maternal nutrient restriction coupled with defective one-carbon metabolism alter the foetal development program, leading to enhanced predisposition to T2D in adolescence? Center of Excellence in Epigenetics IISER Pune India

Diagnostic & Therapeutic evaluation program self funded. The French Chronic Fatigue Syndrome Association decides to clinically evaluate the ME/CFS pathogenesis model produced by Bio-Modeling.

Therapeutic evaluation program self funded. Parkinson's disease and metabolic syndrome. The program led to a combinatorial therapeutic approach utilizing two molecules that had long been on the market, neither of which has any known toxicity or undesirable effects. Evaluation status: Discussion with confidential partners

Causal metabolic mechanisms of Alzheimer Disease (AD) model was produced by Bio-Modeling System in 2017-2018. The model in its current state is able to produce biomarkers that could probably predict or increase alertness for identifying AD at its very early stages of progression. Discover the 14 key components explained

Our solutions to address Industry critical issues

- CADI™ Discovery's ***Integrated Descriptions of Biological Systems*** is a valuable tool to generate novel hypotheses and/or challenge existing programs, key opinion leaders and experts recommendations spread all over the departments of the client's company or partner's structure.

We propose to R&D & Translational Medicine Executives, robust alternative decision-making to de-risk, save time, costs, and novel cost-effective diagnostics/therapies for their businesses.

1. GO-NO GO decision before product acquisition or for portfolio risk analysis.
2. GO-NO GO decision before next development phase.
3. R&D program Rescue for a program facing critical issues during its lifetime.
4. External R&D "B plan" program when the "A plan" cannot be rescued.
5. Exploratory Discovery program to discover novel causal mechanisms concepts.
6. Novel Hypotheses for therapeutic and/or diagnostic solutions discovery.

You have a R&D issue or a decision to make, we may have a solution for you.

The Research & Development Answer

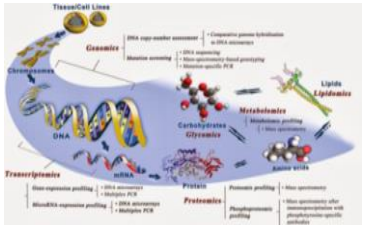
From: Evidence-Based Medicine To: Mechanisms-Based Medicine

- 1-DISEASE/DISORDER
- 2-MECHANISMS
- 3-BIOMARKERS
- 4-TARGETS
- 5-SOLUTIONS
- 6-VALIDATION

Understanding and validating the mechanisms of a disease/disorder becomes the first objective. Finding the most adapted solutions is a necessary consequence of the first objective

The R&D and the reality of Data Answers

The "Cartesian" answers limits



The "garbage in, garbage out" reality demonstrates that a wrong hypothesis, even if generated by top KOLs and/or treated by the best Digital and IT technologies, remain a wrong hypothesis

CADI Discovery Principles

1-Mechanisms-Based Medicine

2-Architechtural Principle

3-Negative Selection Principle

4-4 Steps Validation Principle

5-Integrated Solutions Principle

6-The bridge R&D & Real life data

The objective is to address the complexity of life sciences mechanisms and the digital « garbage in garbage out » reality through CADI™ Discovery

BMSystems' R&D programs pipeline

External valorization of our collaborative R&D programs through out-licensing or spin-off

Program Domains	Partners	CADI™ compliance	CADI™ vers. 0	Ind. Valid.	Secret or Patent or Co-Patent/Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.
Infection-Immunology-Inflammation							
Microbiotas / Inflammation (skin, lung, gut, etc)							
Neuroloy/ Psychiatry/ Inflammation (CNS-PNS)							
Oncology / Inflammation							
Metabolism / Inflammation							
Dermatology/ Cometics/ Inflammation							
BioProcesses							

BMSystems' R&D programs pipeline (details)

Program Name	Validation / Business Partner(s)	CADI™ compliance	CADI™ vers. 0	Ind. Valid.	Secret or Patent or Co-Patent/Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.
Nano-Bioagents	Pherecydes						Validated
TAPE (protein improvement)	Open						Validated
Chronic Fatigue Syndrome / Gulf War Syndrome	CFS Asso / Open			Started			
Ebola virus ecology	Open						
Hepatitis C	Open						
Auto-immune global concept	Open	high Interest					
Microbiota & Autism H2020 program 14 M€ funded	H2020		Started				
Microbiota ecology, physiology & metabolic mechanisms	Open	high Interest					
Microbiota & inflammation	Open	high Interest					
Creutzfeldt-Jakob disease's mechanisms	CEA Life Sciences						Validated
Cellular & metabolic mechanisms associated with chronic anxiety	Max Planck Munich					Validated	
Psychiatric Disorders therapeutic strategy	Confidential						
Alzheimer's Disease Causal Mechanisms	Open		Produced				
Parkinson's Disease Therapy	Open		Produced				
Psychiatric inflammatory mechanisms	FondaMental Foundation		Produced				
Fibromyalgia, facial pain	Open		Produced				
Pain (Central/Peripheral)	Open		Produced				
Migraine Mechanisms	Open	high Interest					
Multiple Sclerosis Mechanisms	Open	high Interest					
Etiology & Epigenetic in diabetes type 2	IISER Pune			Started			
Metabolic Disorders Therapy	Open	high Interest					
Hypercholestemia Mechanisms	Open						
New global concept for Diabetes type 1	Open						
Metabolic Syndrome	Open						
Breast cancer-Hras	INSERM					Validated	
Tamoxifen resistance	INSERM				Validated		
Specific Metastasis control	INSERM			Validated			
Encysting Tumour Therapy	Open	high Interest					
Müllerian regression Mechanisms	CNRS				Validated		
Adipocytes growth control	Open						
Skin pigmentation Mechanisms	Open			Validated			
Skin pigmentation Modulation	Open			Validated			
Skin Contact Allergy Mechanisms	Open		high Interest				
Skin aging Mechanisms	Open	high Interest					
Modulation of skin hydratation	Open	high Interest					
Modulation of the lipid constituents of the skin barrier	Open	high Interest					
Novel Hair Loss Mechanisms	Open	high Interest					
Program Synthons	ARD-IBT-L'Oréal						Validated
Human Glycosylation with Yeast	Open		high Interest				

Mult-Resistance bacteria Program

Domain: Multi-resistant infectious diseases. Collaborative CADI™ program

Request: How to rapidly (less than 60 min) and efficiently detect and destroy any unknown bacterial pathogen or emerging strain without using:

1. Antibiotics: too many resistant strains, and very rapid resistance acquisition
2. Vaccines: much too slow to act, and small strain variations often lead to inefficacy

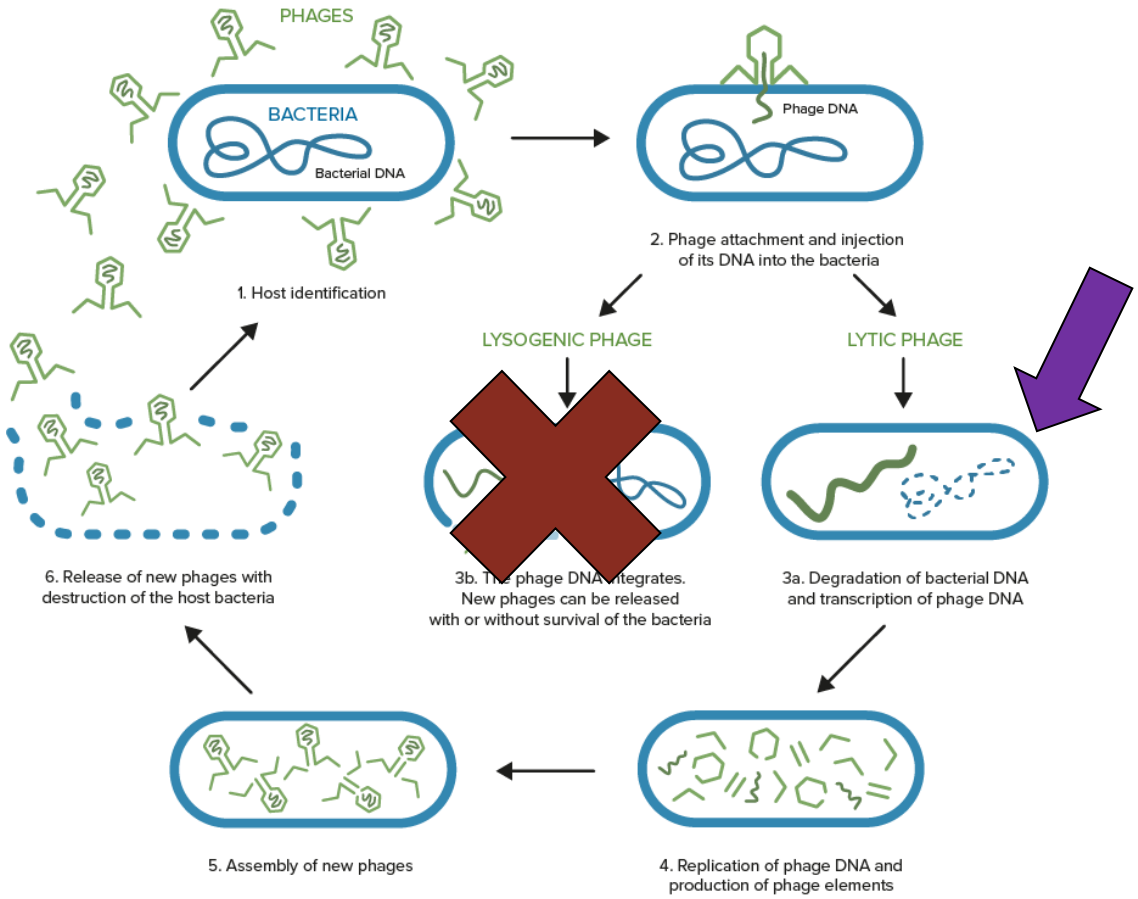
In other words, what could constitute an effective "detector-killer"?

rapid | SME Instrument | HORIZON 2020 | SEVENTH FRAMEWORK PROGRAMME | bpifrance

PhagoBurn | PneumoPhage | PHOSA | PhagoPROD

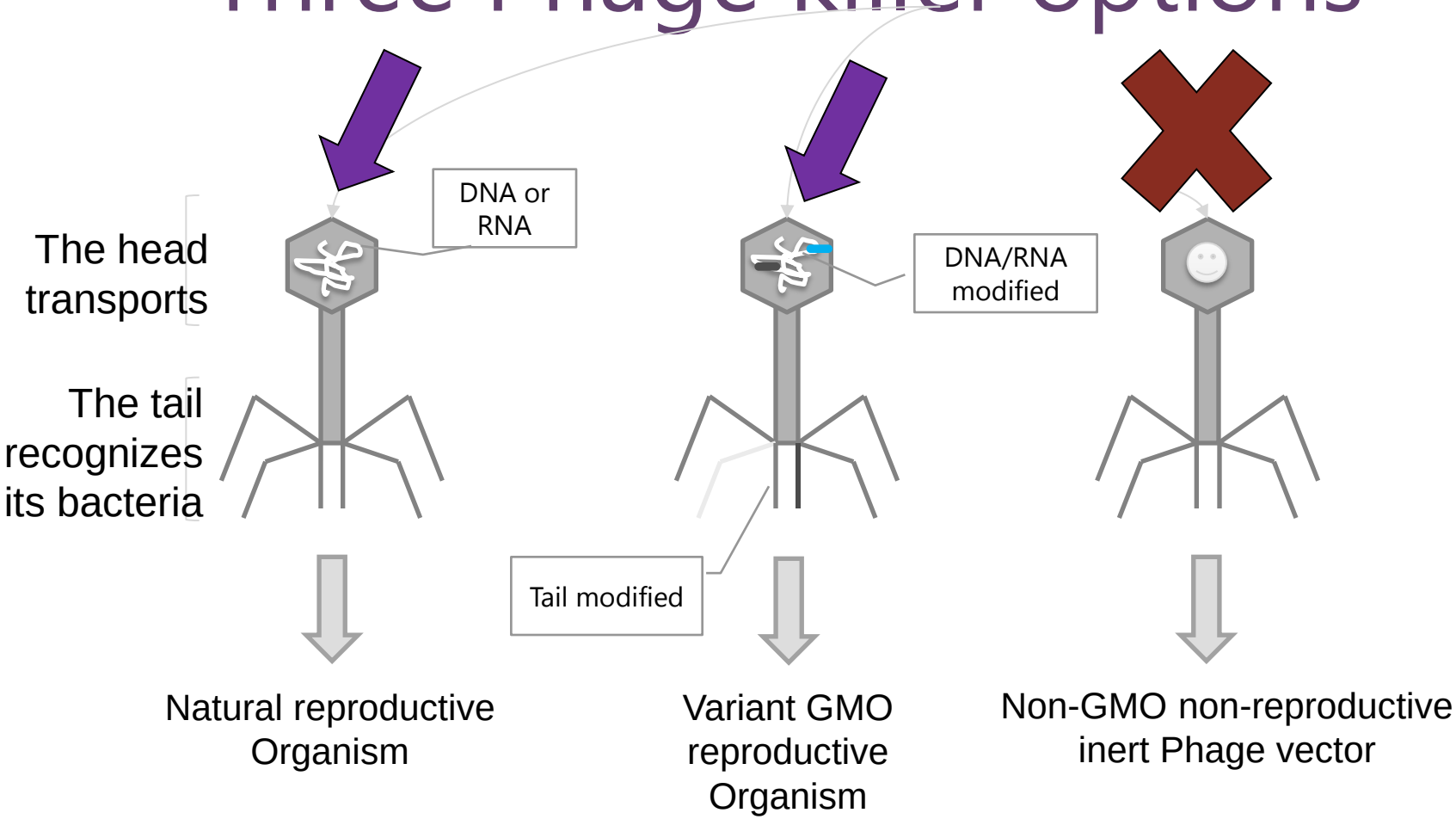
* Important: These engineered phages are equivalent in terms of profile and behavior to natural phages. These program uses natural phages cocktails for GMO regulation issues in Europe, In countries where GMO is not an issue, The engineered phages could be used if interest.

Phages infection process



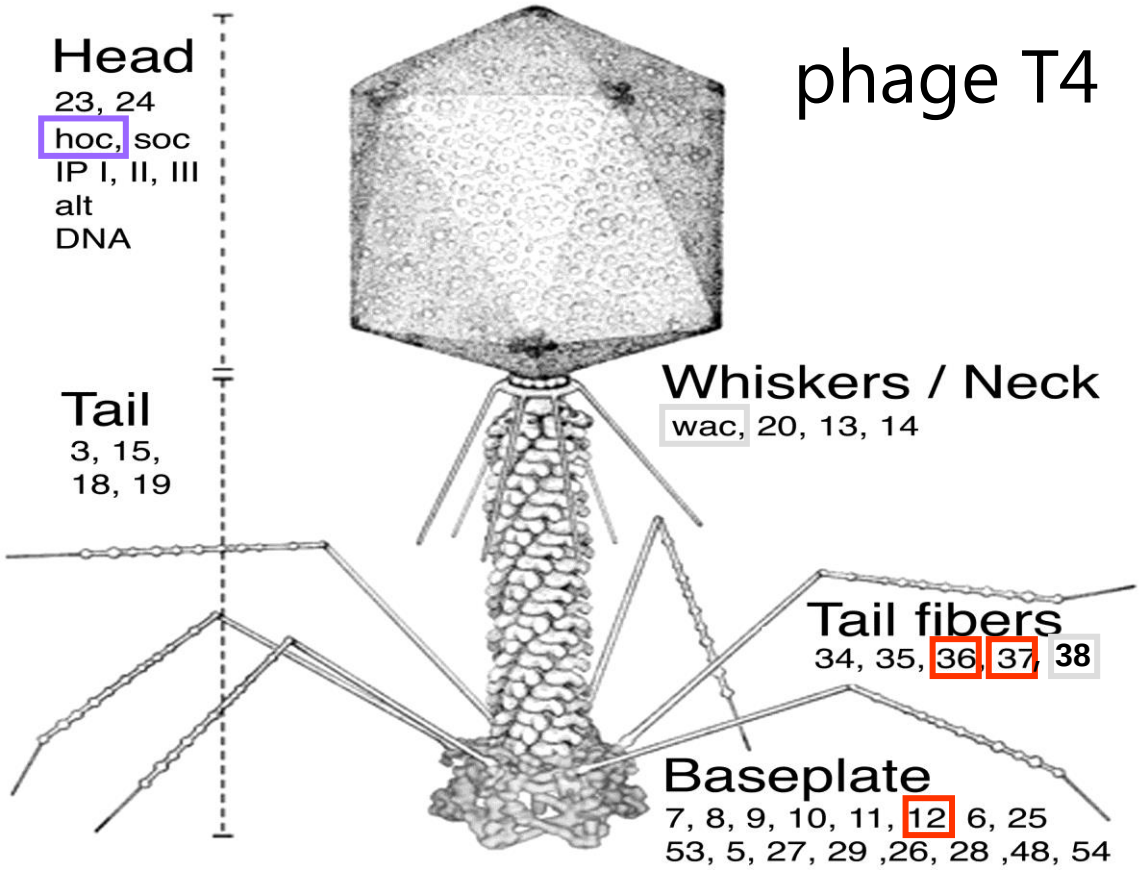
Lytic phage: a virus specific for bacteria. He attaches himself to it and injects his DNA. it multiplies and destroys the bacterium on leaving.

Three Phage killer options



We need at least a phage in advance!.

The detector-killer adaptive tool



phage T4

How to modify any of these proteins in N different regions, at X different sites, in Z different manners, all this simultaneously and then recombine **the multitude of variants** generated into a **population** of **obligate lytic** phages?

The technological answers.

Three proprietary technologies (invented at BMSystems) allowing the production of stochastically engineered phage banks.

TAPE™ Ⓟ (WO 2008/093009):

A technology allowing to rapidly & simultaneously introduce defined densities of random mutations in any number of selected regions within a gene while conserving intact any number of defined coding domains in this same gene.

Applicable to any known coding sequence.

RipH™ Ⓟ (WO 2009/090081):

A technology allowing to reversibly inactivate the genome of an obligate lytic phage within its host and carry out high efficiency homologous recombinations targeting multiple genes simultaneously without adversely affecting the host bacteria and the replicative capacity of the phage.

Ab-ACCUS™Ⓟ (WO 2008/093010):

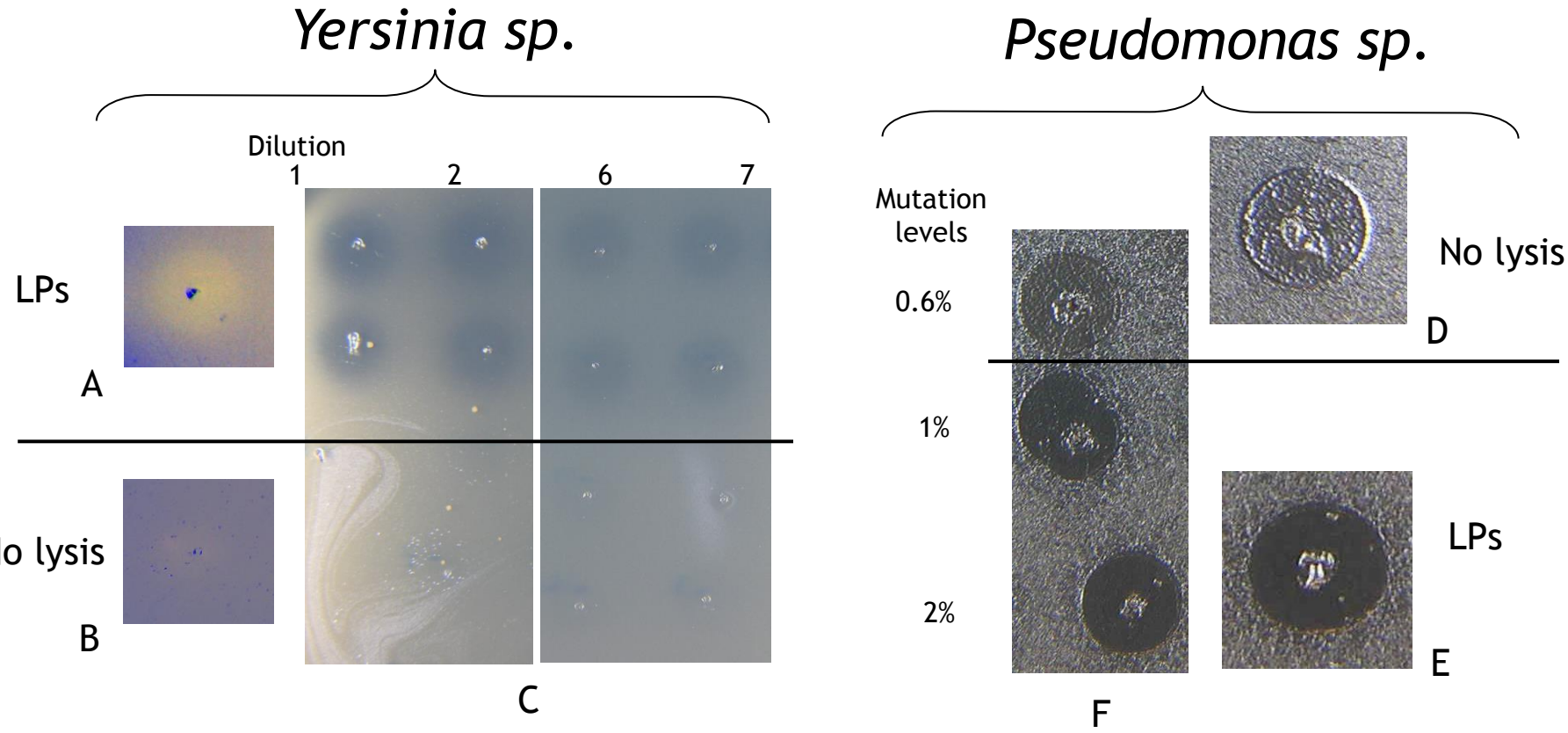
A recombination technology allowing the rapid & efficient production of lytic phage banks in which every individual differs from all others for any number of selected genes or other sequences.

Applicable to any phage and to any known sequence.

The results

While T4 is specific to a narrow range of E. coli strains,

An engineered T4 bank contains variants capable of detecting and killing gram- bacteria far removed from E. coli.



Pouillot F, Blois H & Iris F (2010); Biosecur Bioterror. **8** (2): 155-169.

Since its inception, Pherecydes Pharma benefits of the financial support from regional, national & European organizations.

PHOSA
Ile-de-France Region and Seine-Saint-Denis Department, under the 18th FUI (Unique Interministerial Fund) call; Bpifrance (French public bank of investment), for the future clinical trial planned in humans. PHOSA also benefits from labeling by two French national clusters: Medicen Paris and Lyon Biopôle.

PHAGOGramme
Bpifrance - Innovation Competition of the Programme d'Investissement d'Avenir (PIA)

PHOSAClin
Bpifrance Financement – Aid to innovation

PhagoPROD
European Commission, SME intrument Horizon H2020 program.

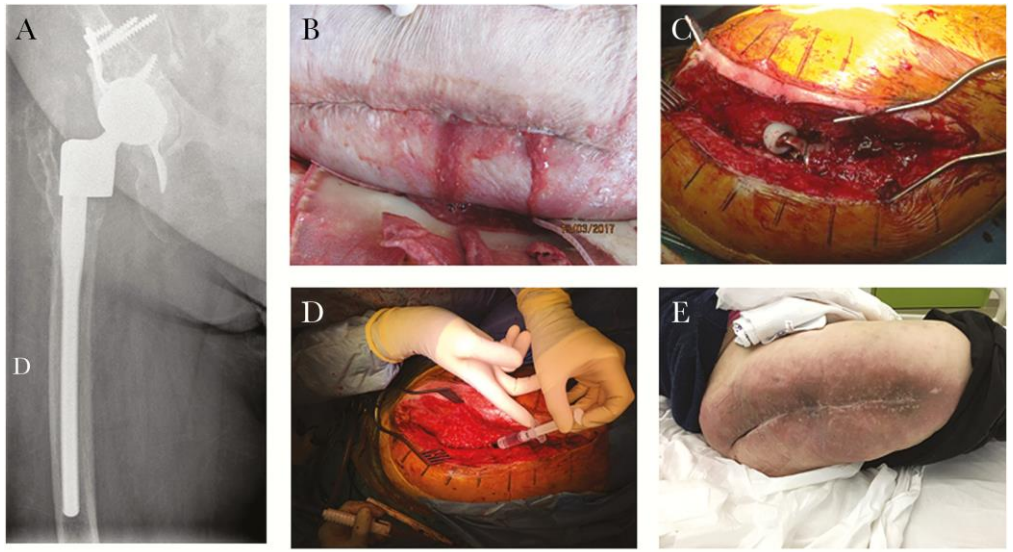
PhagoBurn
European Commission – 7th Framework Program for Research and Development (FP7);
DGA (Directorate General of Armaments) - a first RAPID-Duale grant, for the initial R&D to preclinical steps of the project (PACOBURNS).

PneumoPhage
DGA (Directorate General of Armaments) - a second RAPID-Duale grant for preclinical research up to clinical testing regulatory approval.

PHOSA program at Hospice Civil de Lyon

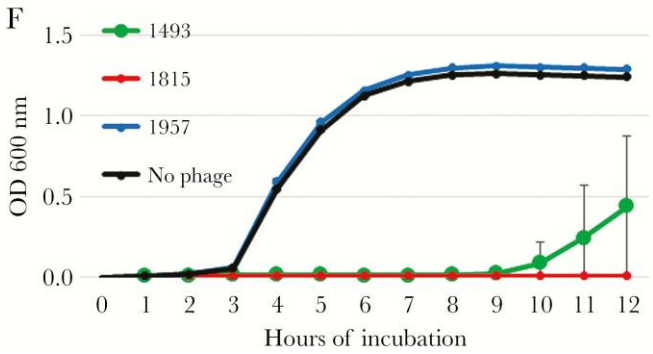
PHOSA

Natural Phages reproductive Organism produced separately. Phages tested before Combination with Antibiotics



PhagoPROD

PHAGO Gramme



Thanks to Precision Medicine

Open Forum Infectious Diseases, Volume 5, Issue 11, November 2018, ofy269, https://doi.org/10.1093/ofid/ofy269

The H2020 GEMMA Autism-microbiota Team

Microbiota & Autism H2020 program selected for 14 M€ funding. GEMMA program (Genome, Environment, Microbiome and Metabolome in Autism) gathers an international consortium of scientists to study the role of the gut microbiome in the development of Autism Spectrum Disorders (ASD). **600 infants followed during 5 years**

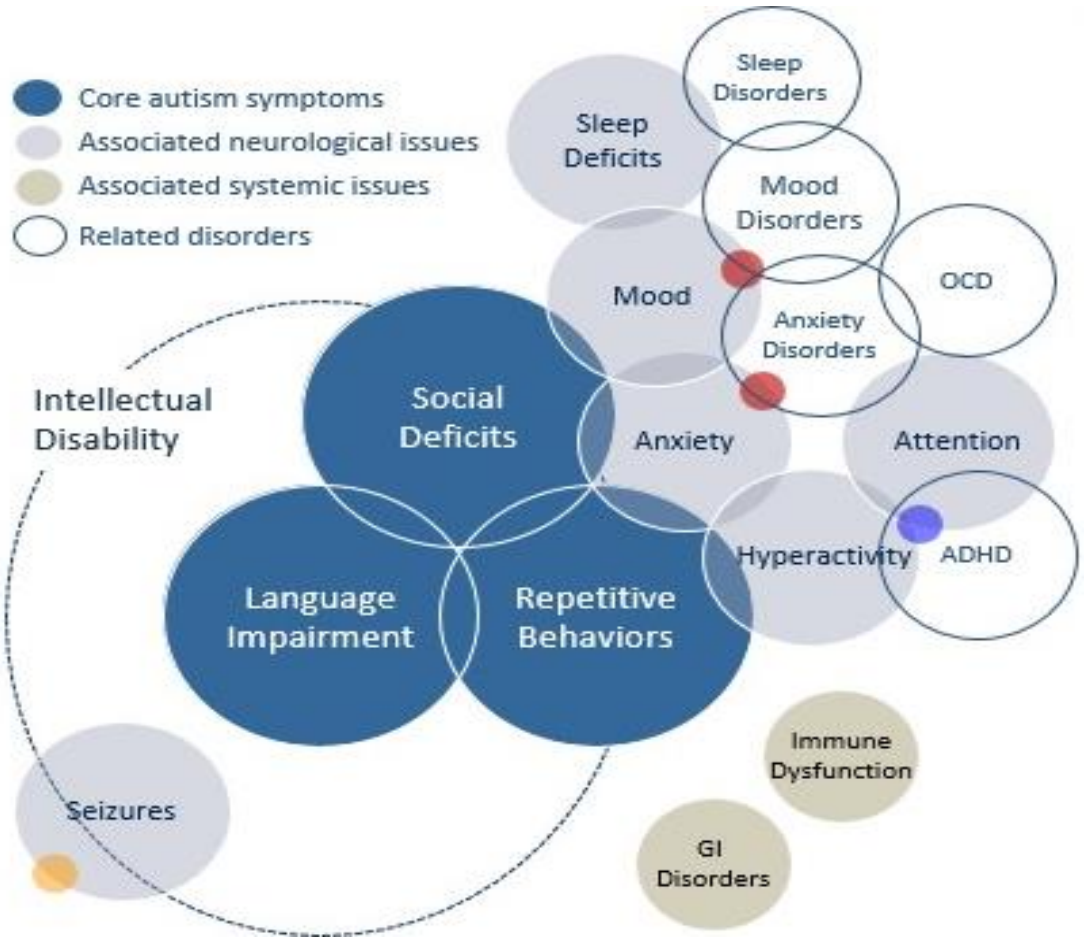
Advisory Board

Finally the consortium has assembled an Advisory Board, who will provide advices and recommendations on strategy and implementation of the project, and help the consortium disseminate the project results

- **Elaine Y. Hsiao**: Research Assistant Professor in the Division of Biology and Biological Engineering at the California Institute of Technology (USA)
- **Sarkis Mazmanian**: Professor of Microbiology, Division of Biology & Biological Engineering at the California Institute of Technology (USA)
- **Saskia van Hemert**: Senior scientist at Winclove Probiotics (Netherlands)
- **Paul Ashwood**: Professor, Department of Medical Microbiology and Immunology, M.I.N.D. Institute at the University of California Davis (USA).
- **Catherine Lord**: Director of the Center for Autism and the Developing Brain, New York (USA)
- **Daniel Coury**: Professor of Paediatrics and Psychiatry in the College of Medicine at the Ohio State University (USA) and Medical Director for the Autism Speaks Autism Treatment Network (ATN).
- **James Adams**: Director of the Autism/Asperger's Research Program at Arizona State University (USA)
- **John Cryan**: Professor, Professor & Chair, Dept. of Anatomy & Neuroscience, University College Cork (Ireland)
- **Paul Wang**: Senior Vice-President and Head of Medical Research, Autism Speaks (USA)

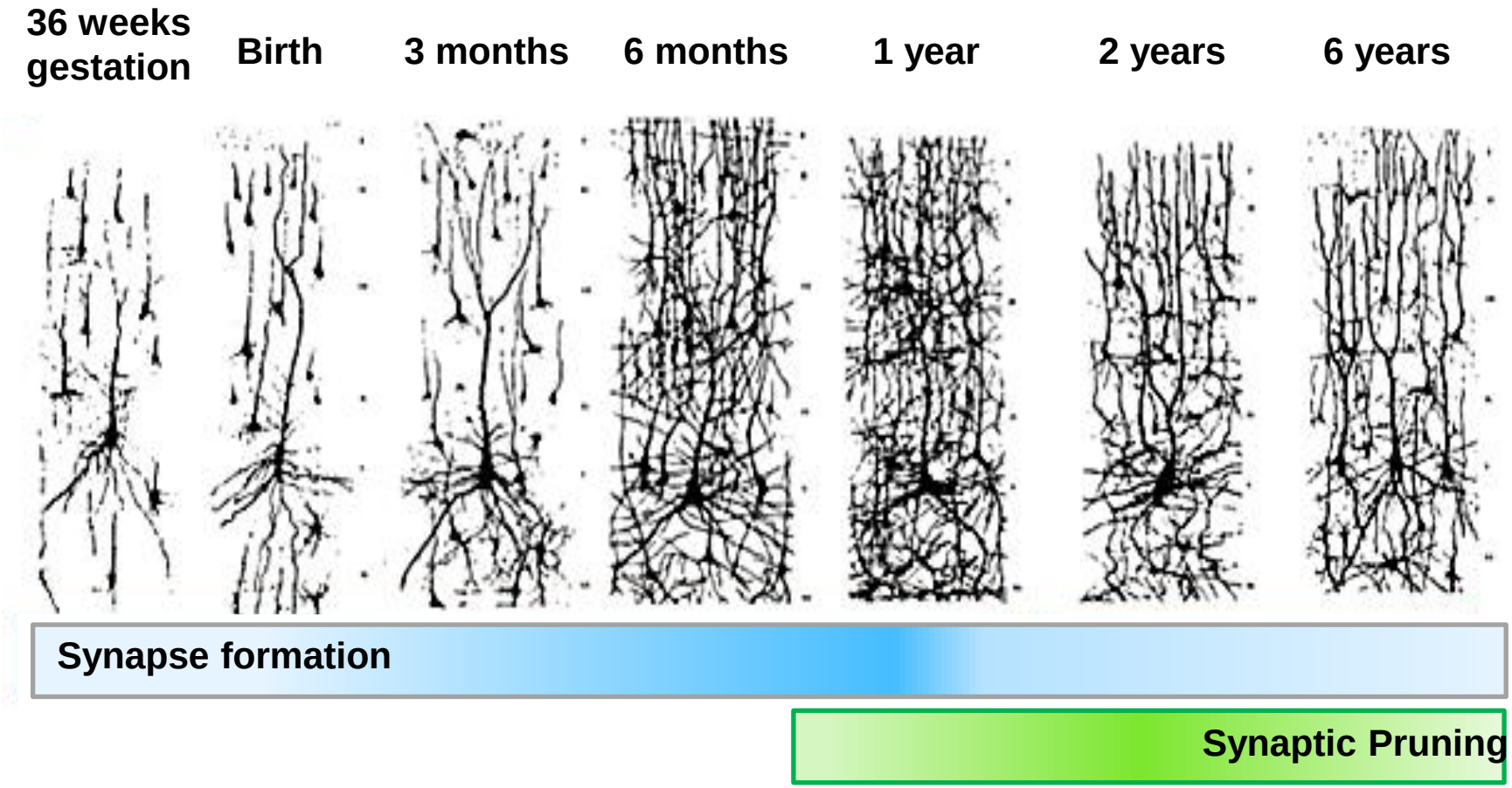
Autistic Spectrum Disorders (ASD)

Autistic Spectrum Disorders (ASD) are a major concern for healthcare systems as they now affect **1 in 68 children** around the world (a 35-fold increase since 1960) and carry **larger societal costs than cancer, heart disease and stroke combined**.



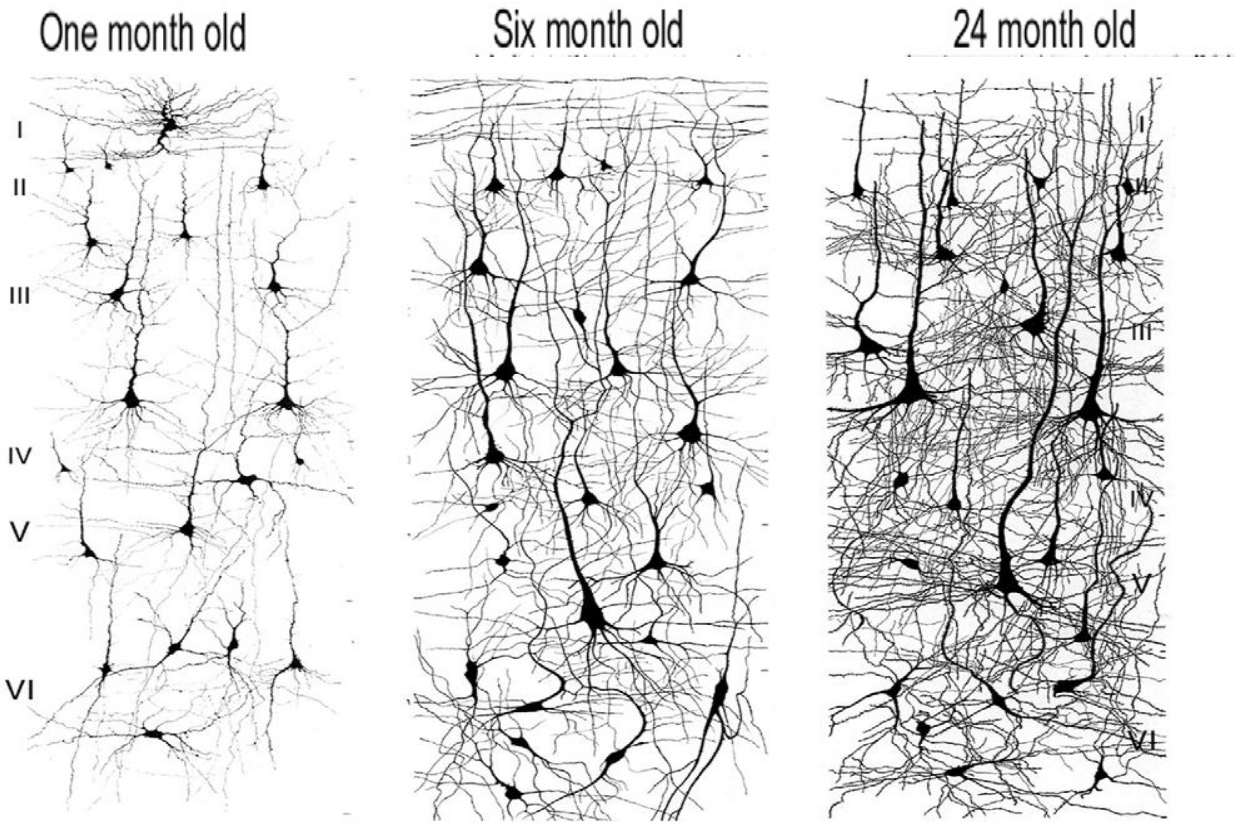
The anatomical characteristics of brain development

Normal development of the brain in many mammals including humans is governed by a synaptic overgrowth, followed by selective synaptic pruning.

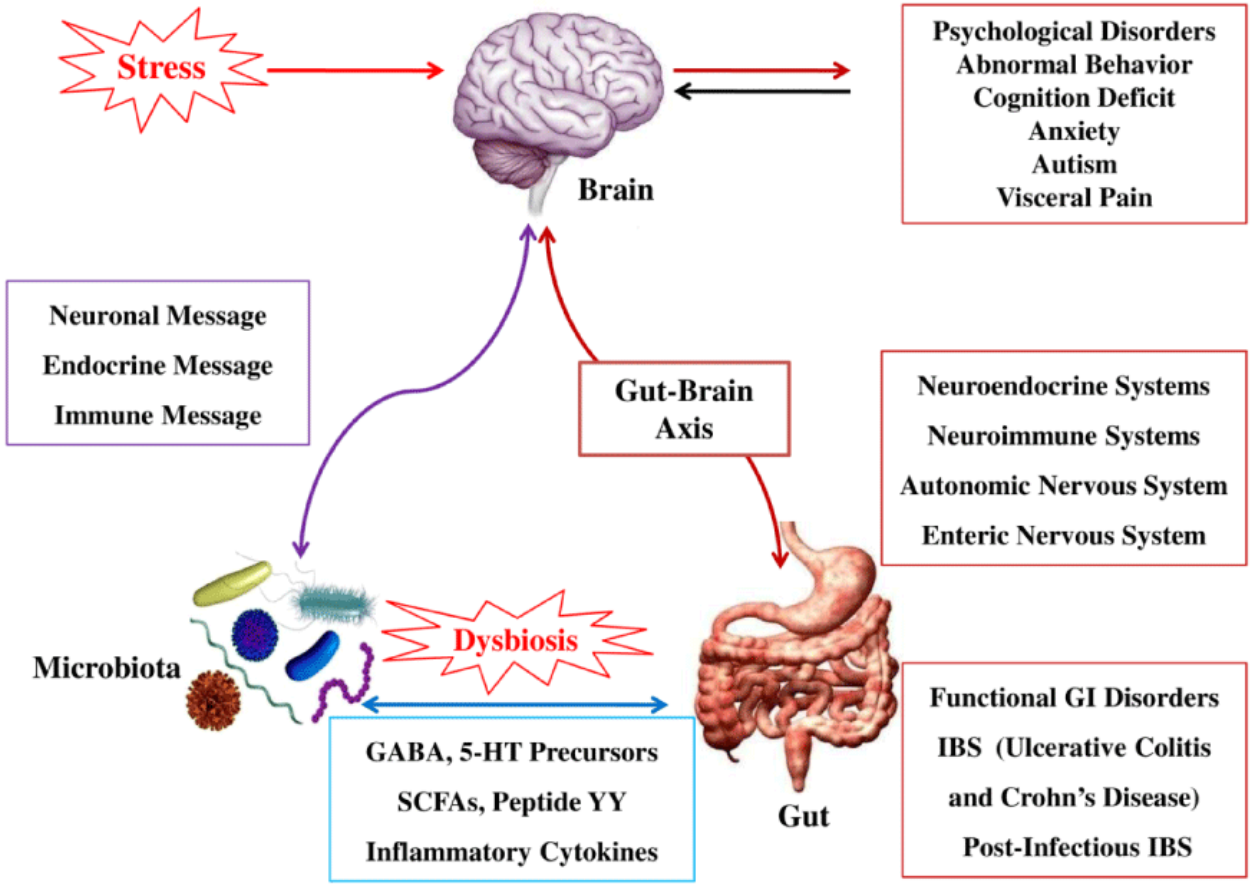


The extent of synaptic pruning defects in ASD

The extent of dendritic growth in the BA9 cortical area of ASD brains at 1, 6 and 24 months of age.



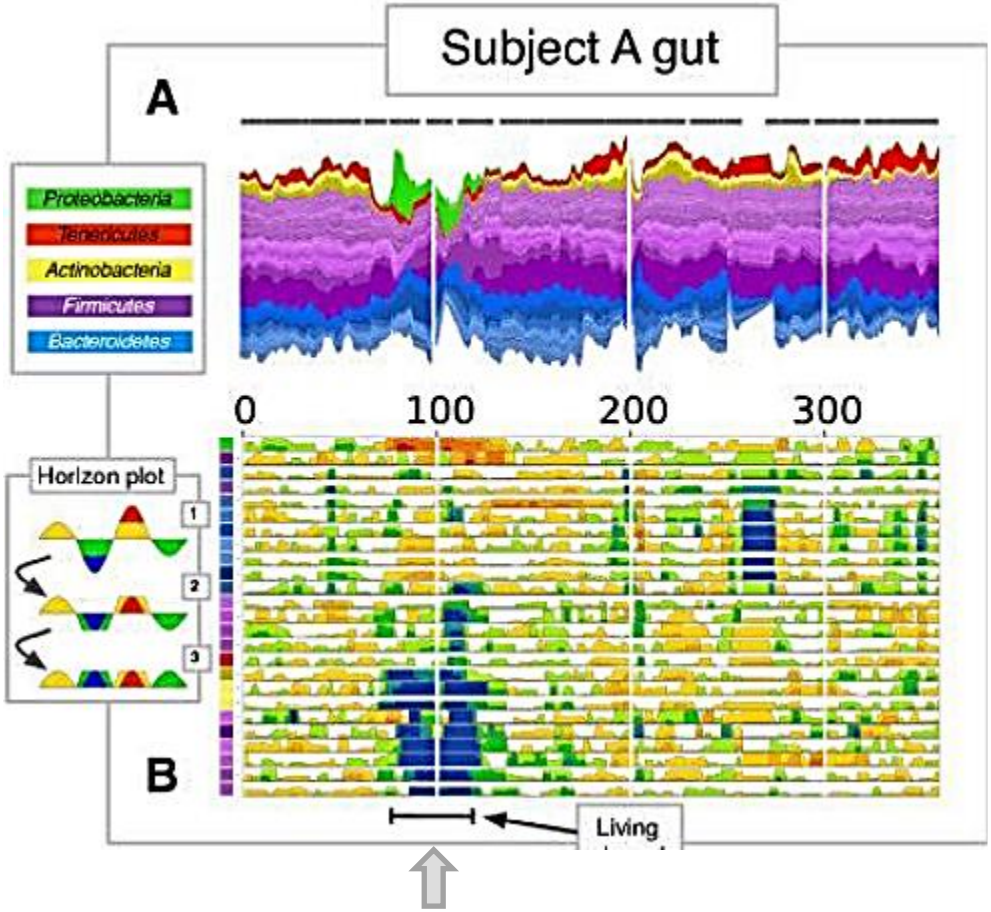
There are well established links between microbiota and psychiatry



Microbiota dysbiosis is a primary source of low grade systemic inflammation.

But, what constitutes a medically relevant dysbiosis?

Although over a year human-associated microbial communities appear relatively stable, they can be quickly and profoundly altered by common human actions and experiences.

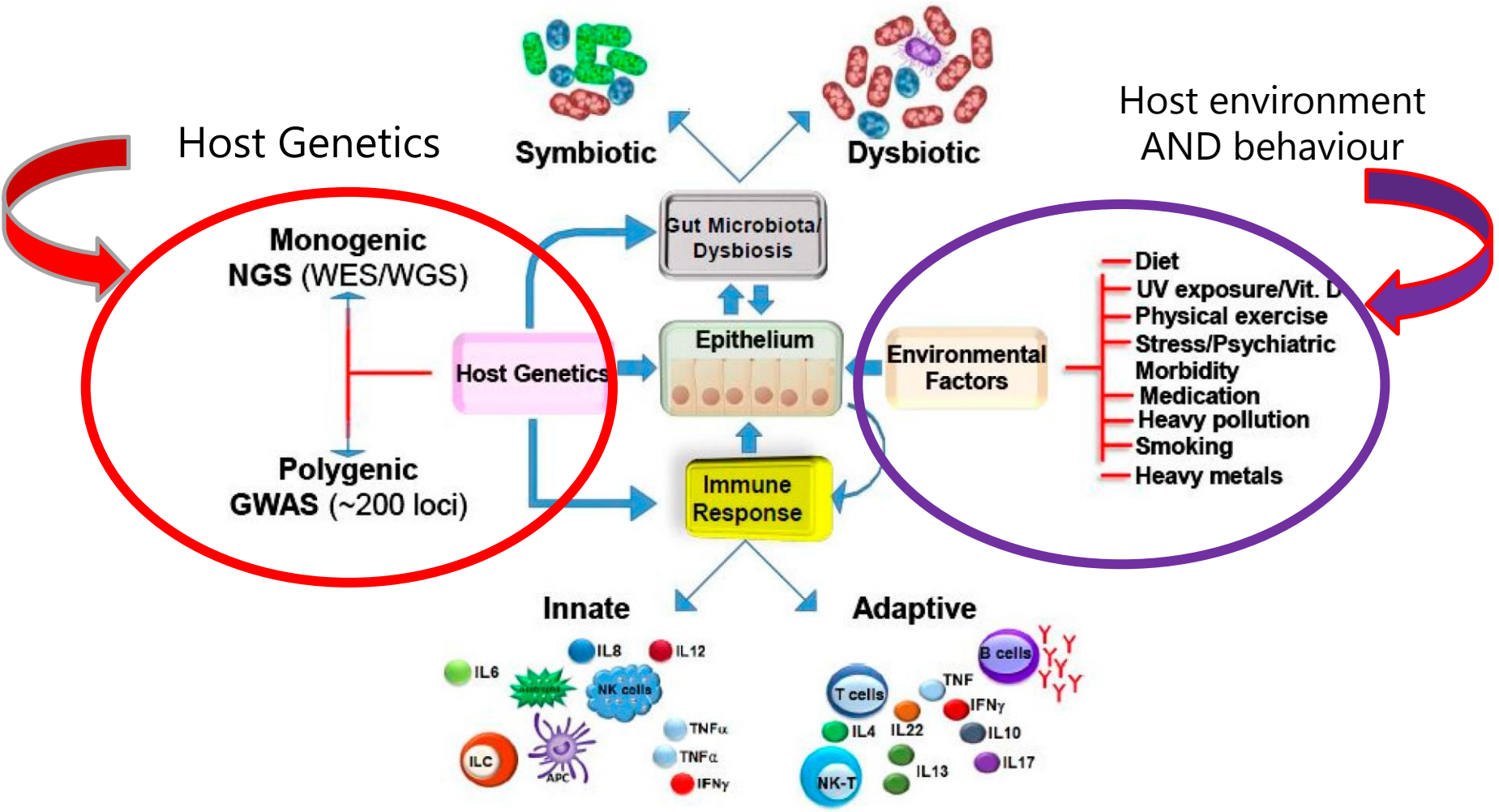


Travel episode

Furthermore, microbial communities composition and populations dynamics differ significantly not only between subjects but also seasonally within a same subject.

But we also affect the components of the zoo

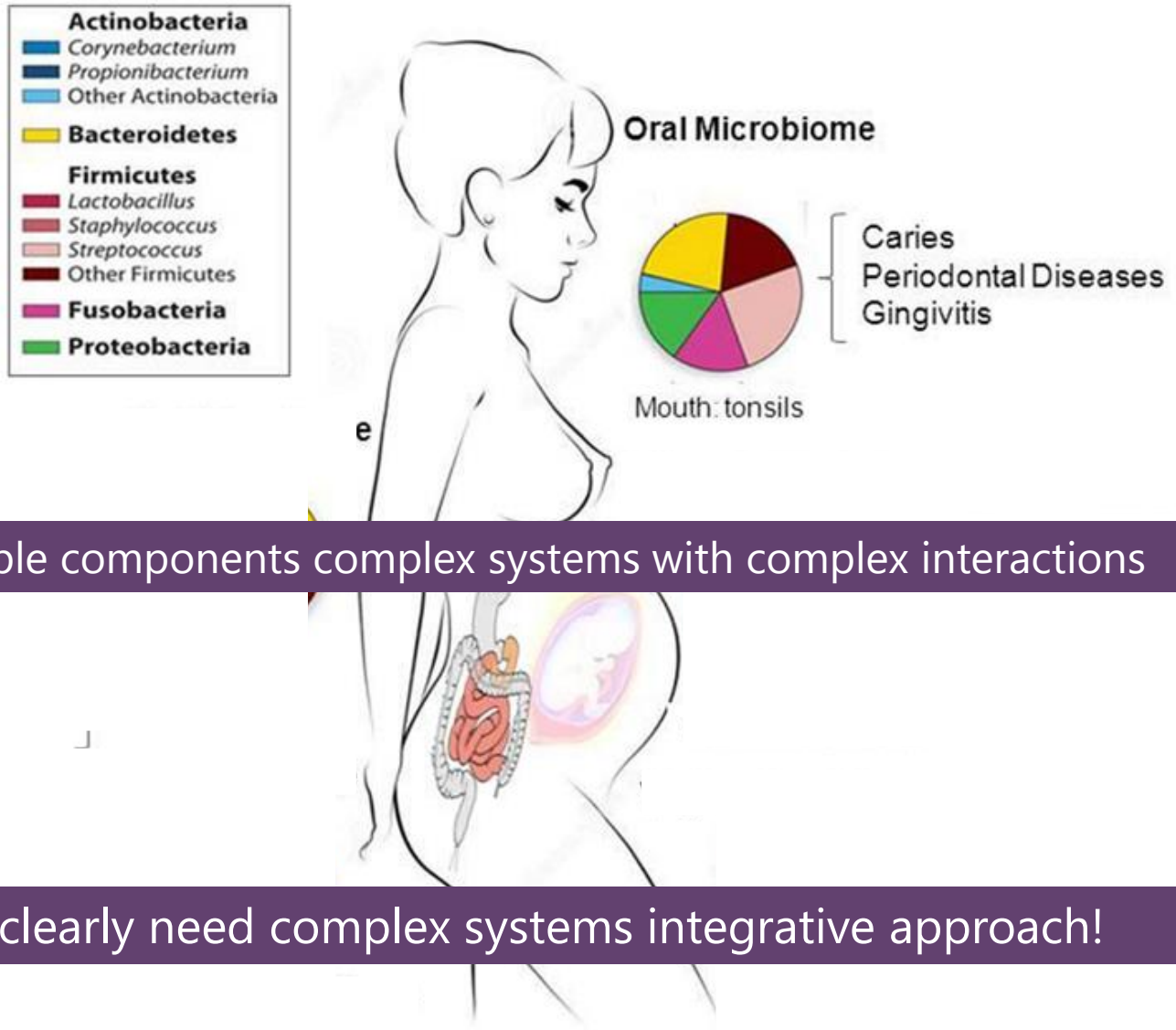
The cross-talks between microbiota, host and environment



Multiple components complex systems with complex interactions

NGS: next-generation sequencing;WES/WGS: whole-exome (mRNA)/whole-genome sequencing; GWAS: genome-wide association study

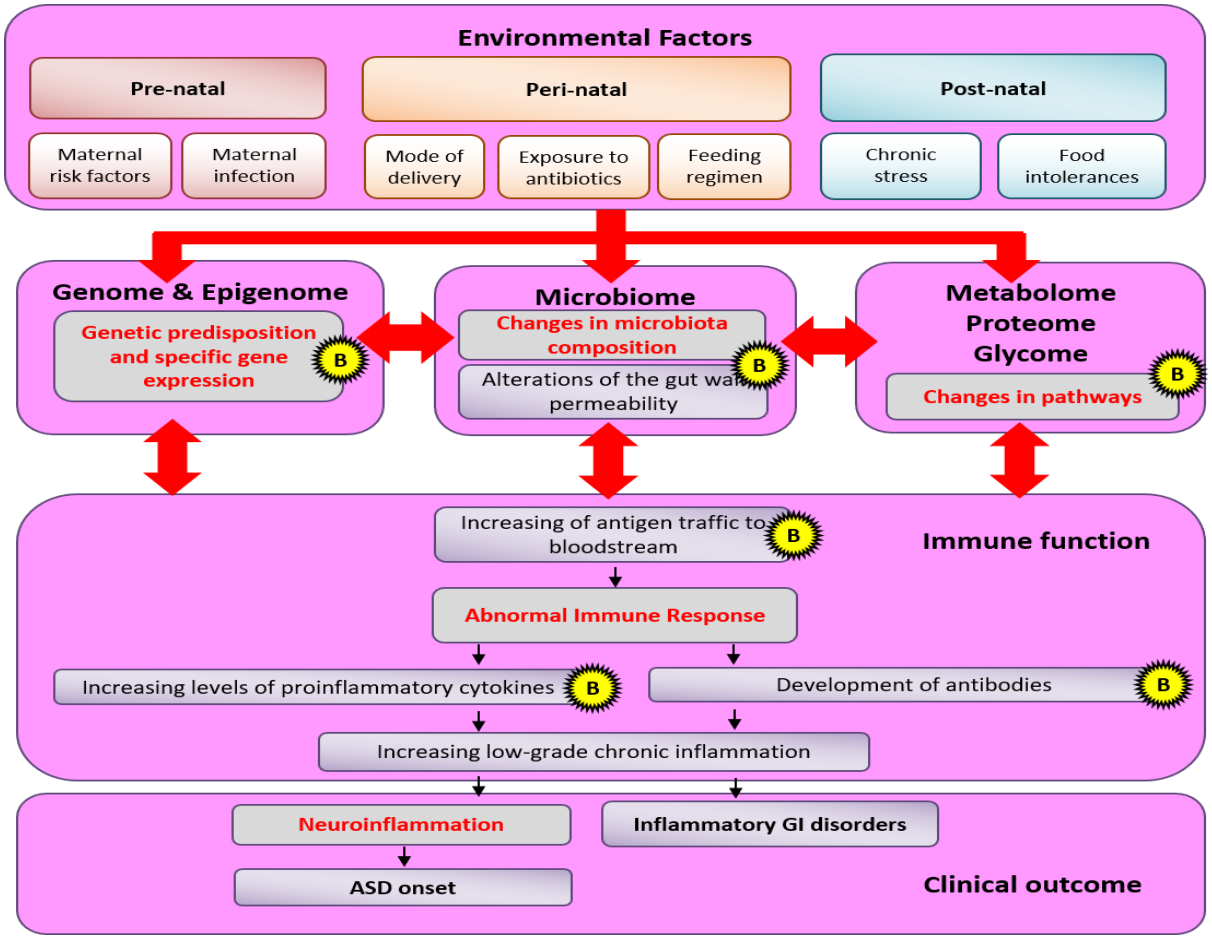
We are walking zoos and the zoo inmates affect us



Multiple components complex systems with complex interactions

We clearly need complex systems integrative approach!

GEMMA Global 5 years Program



Interplay between environment, genome, epigenome, microbiome, metabolome, proteome, glycome and immune function

B

Biomarkers targeted by the pre-clinical and clinical studies

Controlling inflammation suppose to control precisely microbiota. Phages are a possible option

Thank You!