

France's Attractiveness for the Biopharma Industry: Global Ecosystem / Competitiveness Clusters “How to find the right partners in France”

Manuel GEA

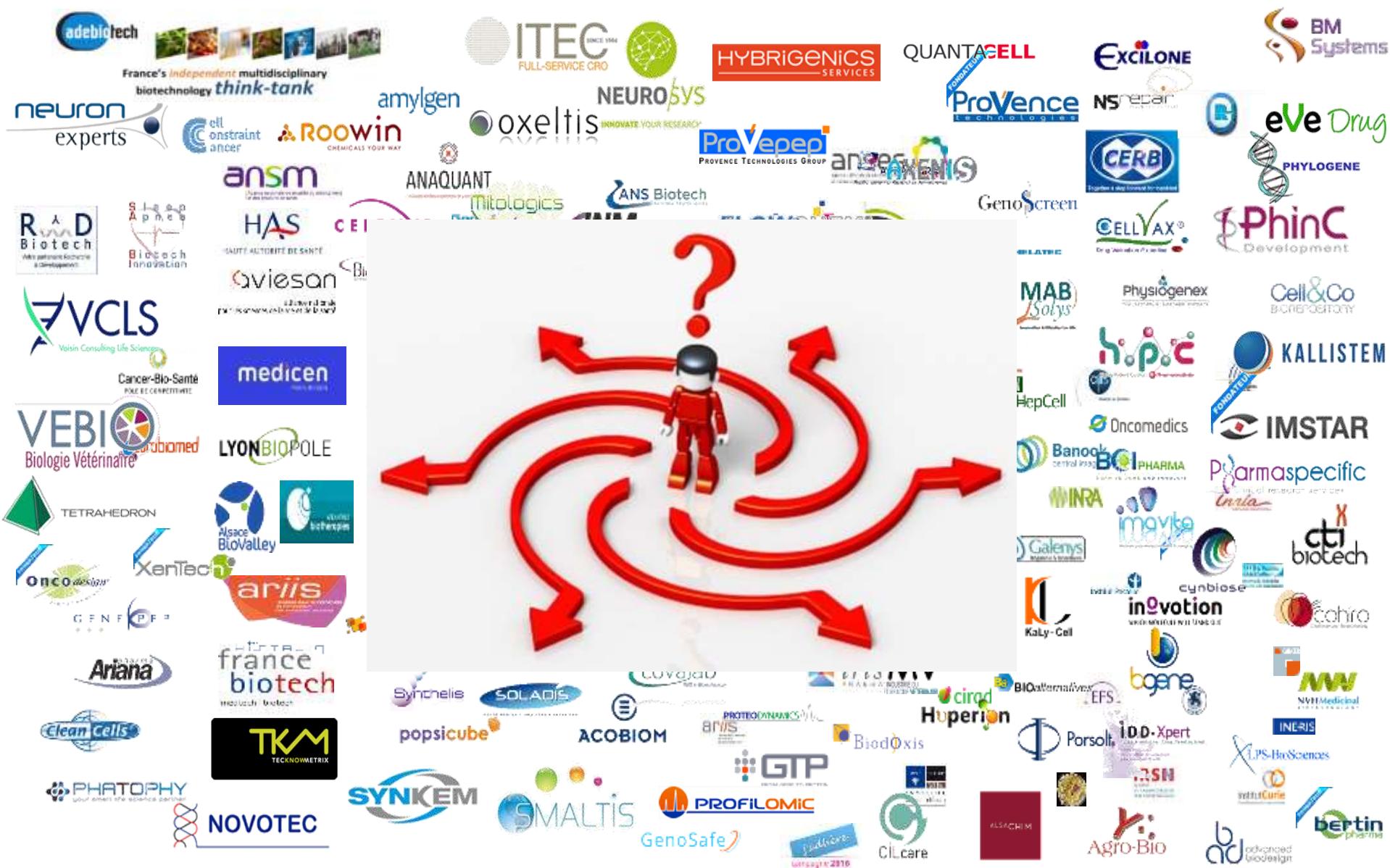
Chairman Adebiotech

Co-founder & CEO Bio-Modeling Systems

CMC Strategy Forum Europe 2016

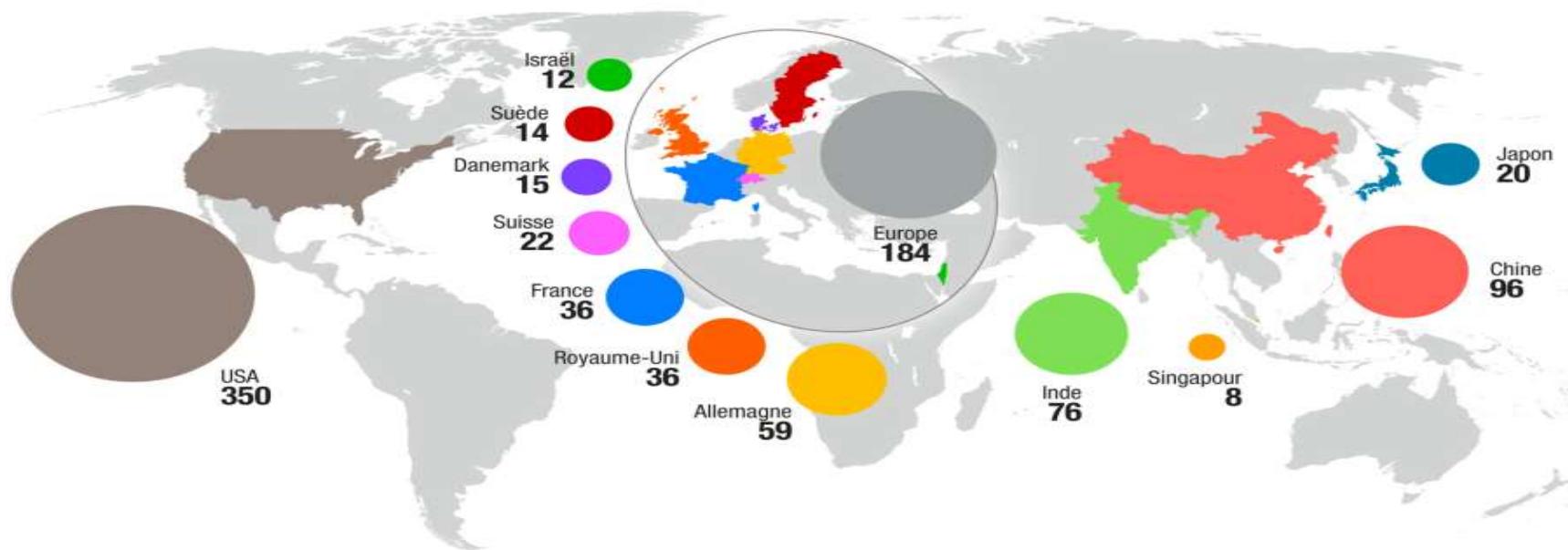
Monday 9, 2016 Paris

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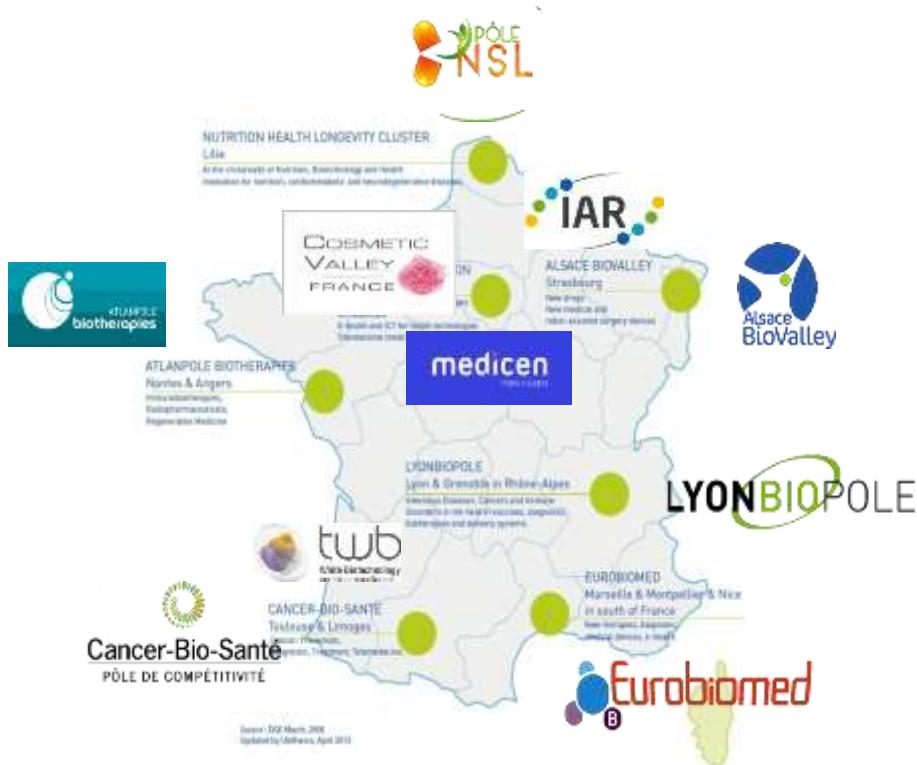


Bio-Production Sites benchmark

BENCHMARK MONDIAL : NOMBRE DE SITES DE BIOPRODUCTION

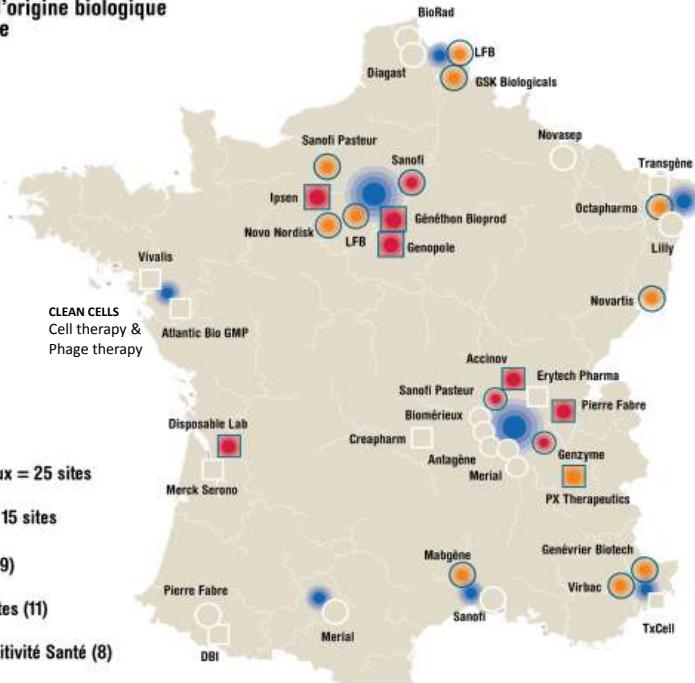


Bio-clusters & Bio-production sites



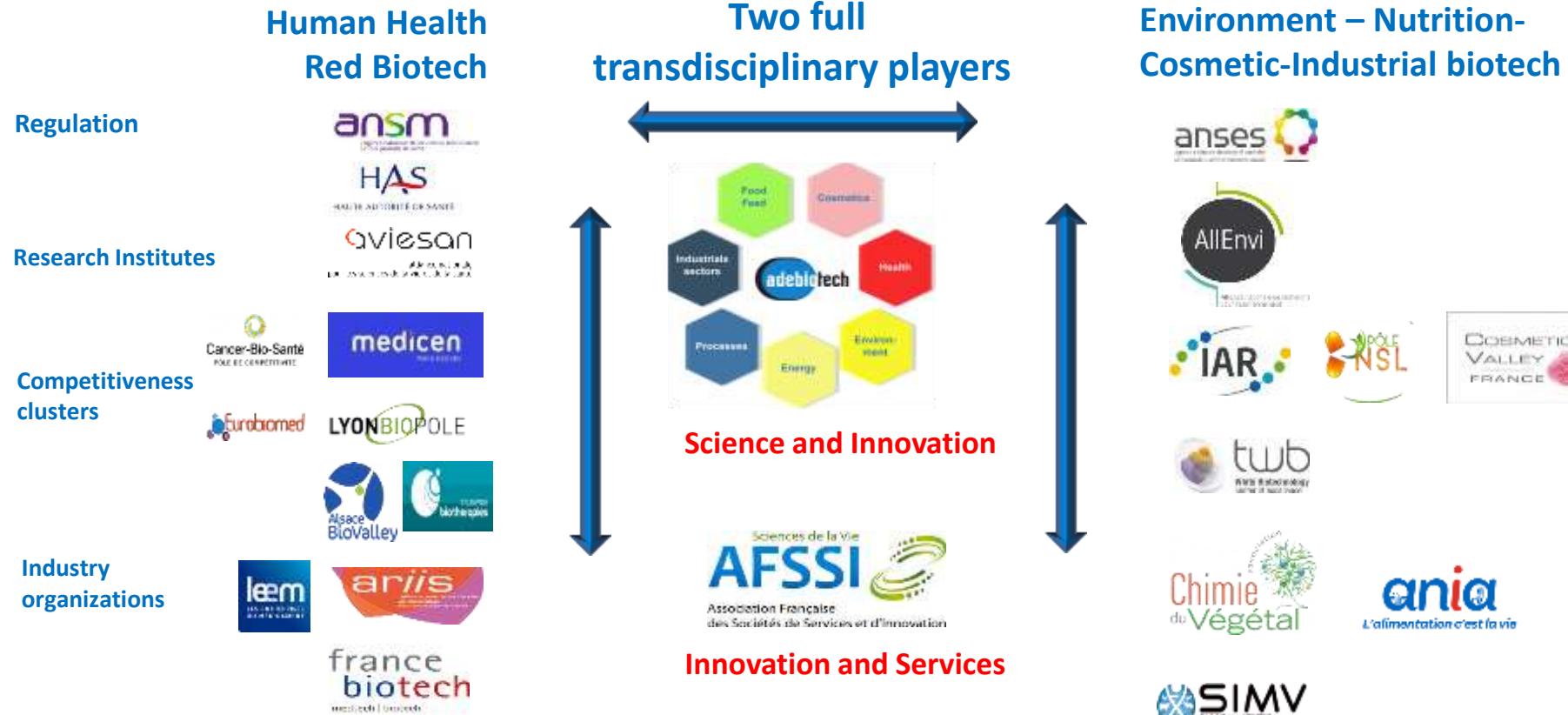
CARTOGRAPHIE DES SITES DE PRODUCTION

Produits de santé d'origine biologique
ou biotechnologique



Who are the “key global contacts”?

The Transdisciplinary map of the “key global contacts” players



Adebiotech: France's independent multidisciplinary biotechnology think-tank

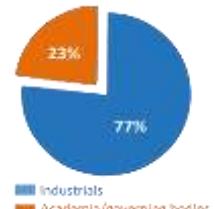
Missions

[Download the 2 pages presentation](#)

- Break down barriers between disciplines or uses
- Support existing industry sectors
- Create new industry sectors and accelerate their development
- Contribute to the dialogue between private and public bodies
- Overcome scientific, technological, regulatory, and ethical hurdles

Represented Members and Partners

- **Industrial**
 - ALGAMA, ARD-IAR, AXIALLY INNOVATIONS, BIOCITECH IMMOBILIER, BIO-MODELING SYSTEMS, BPIFRANCE FINANCEMENT, CARGILL, CSTB, EDF, EFFIASE, EMERTEC GESTION, EUROFINS, FERMENTALG , GENOSCREEN, GENOSTAR, I&IR , IN SITU ENVIRONNEMENT , INGREDIA, INVIVO NSA, KALLISTEM, LCB FOOD SAFETY, LESAFFRE INTERNATIONAL, METABOLIUM, OLYGOSE, PALL LIFE SCIENCES, PHARMA BIOT'EXPERT, PHEREZYDES PHARMA, PROCIDYS, PROFIOMIC, PROTI-FARM NETHERLANDS, RD-BIOTECH, ROQUETTE FRÈRES, SANOFI, SANOFI PASTEUR, SARTORIUS STEDIM FRANCE, SCIENTIS, SOLIANC, SWISSAUSTRAL BIOTECH , TAKARA BIO EUROPE, VEOLIA, WB TECHNOLOGIES, YNSECT...
- **Academia**
 - BRGM, CBSO, CEA-DSV, INSERM, CNRS, INSTITUT PASTEUR, CNRS-DIRE, ICBMS-UMR 5246, INERIS, INSTITUT CHARLES VIOLETTE, INSTITUT PASTEUR, LABORATOIRE DE TOXICOLOGIE-FACULTÉ DE PHARMACIE (UNIV PARIS DESCARTES), UNIVERSITÉ DE CORSE PASQUALE PAOLI, UNIVERSITÉ DE LA ROCHELLE...
- **Institutional, Clusters, Partner associations**
 - ACCINOV, AGROPARISTECH, BIOPÔLE CLERMONT-LIMAGNE, CBB CAPBIOTEK, ICCF, ID2SANTÉ, IMPROVE, LISBP-INSA, POLEPHARMA, SUP'BIOTECH, TOULOUSE WHITE BIOTECHNOLOGY...



Extract of Adebiotech Working Groups Contributions

[**Download all Adebiotech conferences, position papers, recommendations**](#)

- **2016:** Allergenicity and Immunogenicity impacts of Proteins processes
- **2015:** The lipids of the future: lipases in the heart of scientific and industrial developments
- **2015:** Stability and formulation of proteins and peptides: issues and applications
- **2014:** Enzymes Innovations Industries
- **2014:** Endocrine Disruptors: Industrial, health and environmental issues
- **2013:** Technological innovation in industrial protein separation
- **2012:** Peptides derived from the hydrolysis processes: industrial chains
- **2010:** Algae – an industry for the future

Ministries and Agencies partners of our symposia





medicen

PARIS REGION

innovation
for
health



MAIRIE DE PARIS * îledeFrance



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en France

LES PÔLES DE
COMPÉTITIVITÉ
NOTRE DÉVELOPPEMENT ET D'EMPLOI

► FIRST EUROPEAN REGION IN THE FIELD OF LIFE SCIENCE AND HEALTH

medicen
PARIS REGION

- 1st for pharmaceuticals
- 2nd in medtech
- 3rd in biotechnology
- 1st in public-sector research
- Europe's largest hospital network
(the AP-HP, Paris Public Hospitals Group)



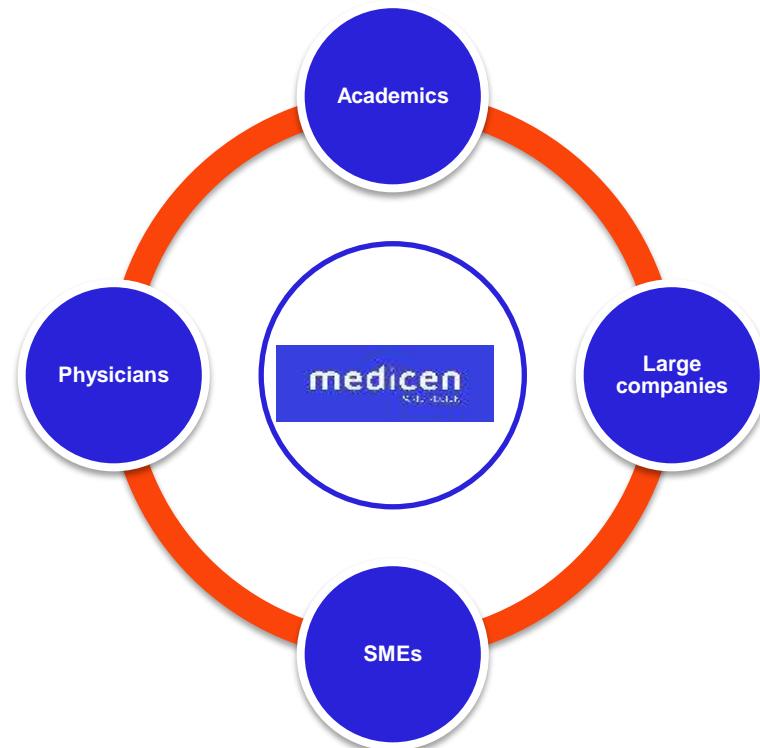
► MEDICEN PARIS REGION CONNECTING THE STAKEHOLDERS

Paris Region Assets

- 45% of the Academic Research in Life sciences, chemistry, and ICT in France
- Europe's largest hospital network

Medicen Paris Region Assets:

- One of Europe's biggest life sciences' clusters
- A unique forum connecting ALL of the stakeholders that INNOVATE in Health:
 - 249 members
 - 24 large companies
 - 189 innovative SMEs
 - 272 funded projects / 1,1 billions € in total investment
- Unique Collaboration in Connected Health



YOUR BEST GATEWAY TO EUROPEAN INNOVATION AND MARKETS



Academia

Large companies

Territorial collectivities



Case study CMC phages bioproduction Bio-Modeling Systems at glance

- Founded in 2004, **profitable** since 2006. Independent private company.
- The **world's first Mechanisms-based Medicine** Company that invented CADI™ Discovery.
- Dual business model** : Contractual and/or Collaborative R&D programs.
- Construction of **in-silico non-mathematical heuristic** models to describe the causal mechanisms of the diseases.
- Industrial biotech** player in both red and white biotech with experimental and scale-up partners.

Program Domains	Partners	CADI™ compliance	CADI™ vers. 0	Ind. Valid.	Patents / Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.	Business launched
Infection-Immunology (6 programs)								Phase I/II
CNS-PNS (10 programs)								Phase II entry
Oncology (4 programs)								
Metabolism (5 programs)								
Dermatology/Cosmetics (4 programs)								
BioProcesses / Synthetic biology (4 prog.)								

BMSystems' first outstanding POCs completed (World's first In-vivo validation, 2 spin-offs)



World's first in vivo validation of the mechanisms of Creutzfeldt-Jakob disease pathogenesis & progression.
Two Awards (2009 & 2010)



Three technologies patents for a novel M.R. anti-bacterial innovative nano-agents therapy, Phase I/II



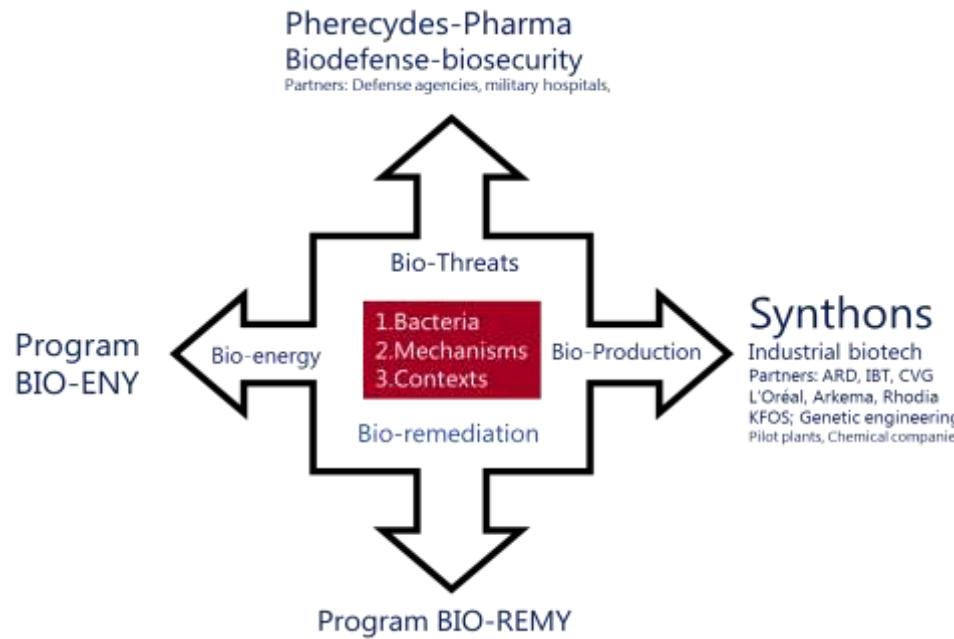
Theranexus
Therapeutic Boosters

Therapeutics CLASS patent, innovative combined therapies for Psychiatric disorders). Phase II entry

Cost-effective, lower risk, patentable novel integrated solutions

Program Name	Validation / Business Partner(s)	CADI™ compliance	CADI™ vers. 0	Ind. Valid.	Patents / Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.	Business launched
Nano-Bioagents	Pherecydes							Phase I/II
TAPE (protein improvement)	Pherecydes							Completed
Chronic Fatigue Syndrome	Open							
Ebola virus ecology	Open							
Hepatitis C	Open							
Auto-immune global concept	Open	high Interest						
Psychiatric combination treatment	CEA Life Sciences							Phase II entry
Creutzfeldt-Jakob disease mechanisms	CEA Life Sciences							Completed
Alzheimer Disease Mechanisms	Open			high Interest				
Parkinson's Disease Therapy	Open			high Interest				
Psychiatric inflammatory mechanisms	FondaMental Foundation							
Fibromyalgia, facial pain	Aepodia							
Pain (Central/Peripheral)	Open							
Migraine Mechanisms	Open							
Multiple Sclerosis Mechanisms	Open							
Psychiatric disorders biomarkers	Max Planck Munich							
Metabolic Disorders Therapy	Open		high Interest					
Etiology & Epigenetic for metabolic disorders	IISER Pune		high Interest					
Hypercholesterolemia Mechanisms	Open							
New global concept for Diabetes type 1	Open							
Metabolic Syndrome	Open							
Breast cancer-Hras	INSERM						Completed	
Tamoxifen resistance	INSERM						Completed	
Specific Metastasis control	INSERM			Completed				
Encysting Tumour Therapy	Open	high Interest						
Müllerian regression Mechanisms	CNRS					Completed		
Adipocytes growth control	Open							
Skin Contact Allergy Mechanisms	Open		high Interest					
Skin pigmentation Mechanisms	Open		high Interest					
Skin aging Mechanisms	Open							
Program Synthons	ARD-IBT-L'Oréal						Completed	
Program Synthons	ARD-IBT-Rhodia							
Program Synthons	ARD-IBT-Arkema							
Human Glycosylation with Yeast	Open			Completed				
				Completed				

Discovery cross-fertilization strategy and implementation

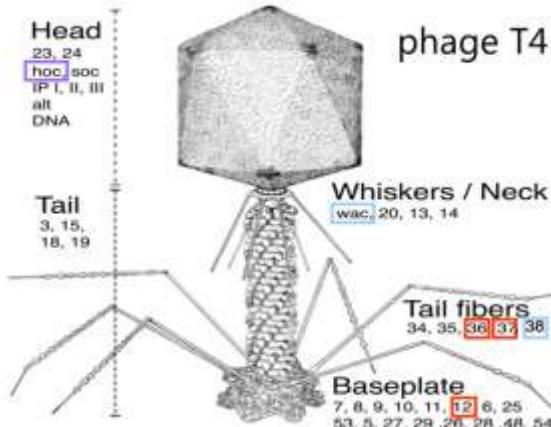


Synthons: Most important Industrial Biotech program in France funded by the government. A feasibility study was conducted for **16 molecules** were analyzed. ARD provided a 2000 T pilot plant .

The Cross-fertilization Process was applied successfully to neurology, psychiatry, dermatology, immunology, cancer, application domains generating novel opportunities and huge time and money savings

CADI™ Discovery program: Pherecydes-Pharma project

A: The challenge / concept



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?

B: The 3 delivered patents

TAPE™ (WO 2008/093009)

Ab-ACCUS™

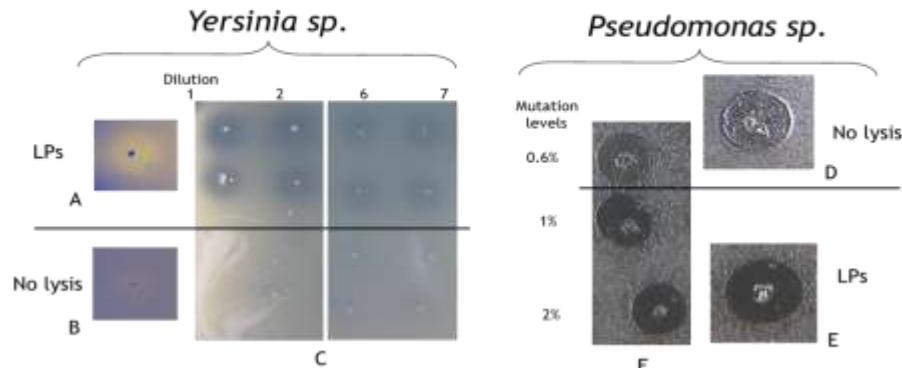
(WO 2008/093010):

RipH™

(WO 2009/090081)

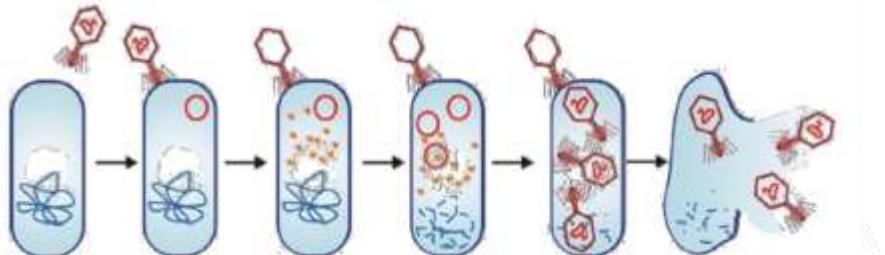
C: The results

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



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

D: The necessary GMP bio production steps issue



The technological answers.

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

TAPE™ P (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™ P (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™ P (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 FP7 Phagoburn* program CMC story



**PHERE CYDES
PHARMA**

PHERECYDES-PHARMA STORY....

- Founded in 2006, in **Paris**, France
- A Biopharma **spin-off of BMSystems** Discovery
- 2013: **FP7 grant to conduct the world's first metacenter clinical trial.**
- A 3 products pipeline under development
- **AdebioTech member**

PHERECYDES-PHARMA MISSION...

- Pherecydes Pharma is focused on the development of therapeutic products.
- Objective: **treat infections acquired in the hospital** (nosocomial), antibiotic-resistant germs and viruses responsible for the production of biofilm, the structure is often a barrier to the action of antibiotics.



CLEAN-CELLS STORY ...

- Founded in 2000, near **Nantes**, France
- Team of 48 qualified persons : 50 % PhD/MSc
- 50% of service dedicated to R&D
- Experience in all domains
- **AFSSI member**

CLEAN CELLS MISSION ...

- To play a key role in the development and optimization of novel therapies in human medicine and animal health
- Biosafety testing of biopharmaceutical products
- Manufacturing of biological products for clinical trials
- ... in accordance with regulatory requirements



STATITEC STORY ...

- Founded in 1996, near **Toulouse**, France
- Expertise in rare malignancies & ATU
- Expertise in adaptive studies
- Experience in FDA submission
- **AFSSI member**

STATITEC MISSION ...

- To design the clinical study. In this context STATITEC will implement the clinical program , will carry a e-CRF and will assess product efficacy.
- STATITEC finalized the clinical protocol with medical physicians involved in this innovative project .

At this time, nothing was existing in Europe. It was critical to set up a team of companies for a European Phagoburn FP 7 program able to create world's firsts necessary regulatory, clinical trial and GMP bio-production frameworks for this novel therapy. They did it!

* For Regulations and OGM issues in Europe, the Phagoburn Program uses natural phages cocktails. The phages form the banks are exactly like the natural phages The processes developed during the program can be adapted easily in countries where it is possible.

CLEAN CELLS' INNOVATION ...

- ❑ Development of specific bioprocessing methods :
 - ❑ To ensure potency and quality of phage productions
 - ❑ To meet the requirements of European regulatory agencies

CLEAN CELLS' ANSWERS ...

Strategy definition	Manufacturing	Biological material	R&D, Master & Working banks
Optimization		Purified Phages	Culture & purification Process
Validation		Drug Substances	Sterile filtration
cGMP manufacture		Drug Product	Aseptic preparation, fill & finish
Quality Controls			Potency, Identity, Purity, other characterizations

Yeast-Based Human-Glycosylation Project

The challenge: How to found a way to efficiently overcome the major limitations to the large-scale production of humanized glycoproteins in yeast cells?

We develop a CADI Glyco Model that describes the means whereby “human-type, glycosylation pattern-specific tool-boxes” can be constructed and stably harnessed in yeast cells.

1. the control mechanisms which allow *at will* mutual induction / repression of the yeast cells endogenous glycosylation machinery and engineered “human-type, glycosylation pattern-specific tool-box”,
2. the means whereby the two systems (yeast cells endogenous glycosylation machinery and engineered “human-type, glycosylation pattern-specific tool-box”) can be made to co-exist without interfering upon each other and without jeopardizing yeast cell viability,
3. the complete sets of genes that would allow to specify any given pattern of human-type O-linked or N-linked glycosylation.

Open for partners: To succeed validation phase this program needs the synergic collaboration between a correct understanding of the complex yeast's and human's glycosylation mechanisms and the yeast genetic engineering and production processes expertise.

BMSystems' CADI™ publications to date

- [**2014: CNS Psychiatry publication:**](#) American Journal of Psychiatry and Neuroscience. Second publications with the Max Planck Institute of Psychiatry in Munich: Differential proteomics analyses reveal anxiety-associated molecular and cellular mechanisms in cingulate cortex synapses. The first output of the DECIUS CNS research program.
- [**2012, CNS NEURODEGENERATIVE & PSYCHIATRY:**](#) PharmacoPsychiatry publishes the first review describing a productive vision of Systems Medicine that will change R&D organization and interactions between clinicians & researchers & reveals how the world's first explanation of the mechanisms of the Creutzfeldt-Jakob disease led to the discovery of a truly innovative psychiatric treatment.
- [**2011, CNS PSYCHIATRY:**](#) Pharmaco Psychiatry publication: Proteome-Based Pathway Modelling of Psychiatric Disorders. Publication with The max Planck Institute of Psychiatry in Munich
- [**2010, INFECTIOUS DISEASES:**](#) Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science :Genetically Engineered Virulent Phage Banks in the Detection and Control of Emergent Pathogenic Bacteria. Publication with Pherecydes-Pharma.
- [**2009, TISSUE DIFFERENTIATION:**](#) Médecine & Sciences: Müllerian duct regression explanation. Integrative systems biology & experimental Biology. Publication with CNRS experimental data.
- [**2005, CANCER:**](#) Journal of molecular Endocrinology: Integrative analysis of gene expression patterns predicts specific modulations of defined cell functions by estrogen and Tamoxifen in MCF7 breast cancer cells. Publication in collaboration with INSERM unit 553.
- [**2003, CANCER:**](#) Nucleic Acids Research: Integrated transcriptome analysis of the cellular mechanisms associated with H-ras-dependent malignant transformation of the human breast epithelial MCF7 cell line. Publication in collaboration with INSERM unit 553. World first. First in-silico model of a complex human disease validated in-vitro and published.
- **Collaboration to scientific reference books:**
- [**2014: Dermatology Cosmetics.**](#) The first reference book on "Computational Biophysics of the Skin" edited by Prof. Bernard Querleux , scientific chairperson of the International Society for Biophysics and Imaging of the Skin
- [**2011: Phage Nano Technology**](#) book published by [Valery Petrenko](#). Chapter 8: Genetically Engineered Virulent Phage Banks for the Detection and Control of Bacterial Biosecurity Threats.
- [**2008: CNS:**](#) Biomarkers for Psychiatric Disorders. (Ref. ISBN: 978-0-387-79250-7, November 2008). Dr. François Iris, is the author of the Integrative Biology chapter of the book. The editor, Prof. Christoph W. Turck, is head of the Proteomics and Biomarkers branch at the Max Planck Institute for Psychiatry

Useful links

- Important: **To help the readers, the logos in this presentation** are linked to their corresponding website.
- The Pharma Academy official [dictionary](#) for translations.
- [Adebiotech](#) knowledge and conferences database.
- [Afssi](#) cartography database
- [ARIIS](#) cartography database
- Author's LinkedIn Posts: <https://www.linkedin.com/today/author/871235>
- BMSystems' [5 pages management summary](#)
- BMSystems' [short presentation](#)
- BMSystems' [full presentation with the 10 POCs and the publications.](#)
- BMSystems' [scientific presentation](#).
- [The 7 critical issues](#) R&D managers should urgently address to secure their decision making process & the future of their company!

Thank you