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

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Chairman Adebiotech
Co-founder & CEO Bio-Modeling Systems
CMC Strategy Forum Europe 2016
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Email: manuel.gea@bmsystems.net
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Bio-Production Sites benchmark
Bio-clusters & Bio-production sites

Who are the “key global contacts”?

Source: ODCIE, Horizon 2013 - Leem
The Transdisciplinary map of the “key global contacts” players

Human Health
Red Biotech

Two full transdisciplinary players

Environment – Nutrition-Cosmetic-Industrial biotech

Science and Innovation

Research Institutes

Industry organizations

Competitiveness clusters

Regulation
Adebiotech: France’s independent multidisciplinary biotechnology think-tank

Missions

- 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, PHERECYDES PHARMA, PROCIDYS, PROFILOMIC, PROTI-FARM NETHERLANDS, RD-BIOTECH, ROQUETTE FRÈRES, SANOFI, SANOFI PASTEUR, SARTORIUS STEDIM FRANCE, SCIENTIS, SOLIANCE, 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, CB2 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
FIRST EUROPEAN REGION IN THE FIELD OF LIFE SCIENCE AND HEALTH

- 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)
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

WITH 200 SMES
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.

<table>
<thead>
<tr>
<th>Program Domains</th>
<th>Partners</th>
<th>CADI™ compliance</th>
<th>CADI™ vers. 0</th>
<th>Ind. Valid.</th>
<th>Patents / Publi.</th>
<th>First Proof of Concept (POC)</th>
<th>Mid scale or preclinic. P.O.C.</th>
<th>Business launched</th>
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**BMSystems’ first outstanding POCs completed** (World’s first In-vivo validation, 2 spin-offs)

- **Three technologies patents for a novel M.R. anti-bacterial innovative nano-agents therapy, Phase I/II**
- **Therapeutics CLASS patent, innovative combined therapies for Psychiatric disorders). Phase II entry**
### Cost-effective, lower risk, patentable novel integrated solutions

<table>
<thead>
<tr>
<th>Program Name</th>
<th>Validation / Business Partner(s)</th>
<th>CADI™ compliance</th>
<th>CADI™ vers. 0</th>
<th>Ind. Valid.</th>
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</table>
The Cross-fertilization Process was applied successfully to neurology, psychiatry, dermatology, immunology, cancer, application domains generating novel opportunities and huge time and money savings.

**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.
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)

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™**

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™**

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™**

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.*
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.

The **FP7 Phagoburn** program CMC story

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.
The FP7 Phagoburn CMC story

**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 ...**

<table>
<thead>
<tr>
<th>Strategy definition</th>
<th>Biological material</th>
<th>R&amp;D, Master &amp; Working banks</th>
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<tr>
<td>Optimization</td>
<td>Purified Phages</td>
<td>Culture &amp; purification Process</td>
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<tr>
<td>Validation</td>
<td>Drug Substances</td>
<td>Sterile filtration</td>
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<tr>
<td>cGMP manufacture</td>
<td>Drug Product</td>
<td>Aseptic preparation, fill &amp; finish</td>
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</table>

**Manufacturing**

- Biological material: R&D, Master & Working banks
- Purified Phages: Culture & purification Process
- Drug Substances: Sterile filtration
- 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.

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BMSystems’ CADI™ publications to date


- **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**: Pharmacop Psychiatry publication: Proteome-Based Pathway Modelling of Psychiatric Disorders. Publication with The max Planck Institute of Psychiatry in Munich


- **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


- **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

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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](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

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