Bio-Modeling Systems

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INNOVATION IN HEALTHCARE, FROM RESEARCH TO MARKET: SMEs IN FOCUS CONFERENCE

European Commission, Brussels may 20-21, 2010 (updated 2012)

A dual disruptive collaborative innovative approach in the field of integrative systems biology deciphered. Issues, first positive results and key learnings.

PHERECYDES PHARMA

cea

Bio·IT World Best Practices AWARD Honorable Mention 2009

Synthons

BM Systems

The Life-modeling issue

If you dream to create the first operational bird model…

… a "basic" living Complex system that not only flies…

Be sure to use the appropriate modeling concepts & tools. If not…

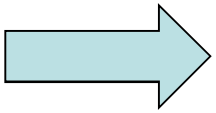
…you get a Complicated "Cartesian" system. It does fly, but…it will never lay eggs

The challenge is clearly not a question of technologies only

The Life science modeling dilemma

1. **The mechanisms of life are *complex, non-linear and integrative***
2. **In "living complex" systems, the functions of *biological components and mechanisms are event and context-dependent*. The same components/networks can produce different biological effects**
3. **Classical "Cartesian" modeling concepts & approaches, valid for the majority of man-made artifacts, imply the concept of a "blue-print". Components are "function-specific" and their assembly pattern determines the final function of the structure they constitute. *But this concept is at the opposite of biological reality***
4. **… While "Cartesian" Bioinformatics and *Mathematical tools have proven to be efficient to* collect, structure, analyze, simulate specific functions to test or to generate innovative hypotheses, yet…**
5. **…The *"garbage in, garbage out" reality*, tells us that the information produced and published (even in leading scientific journals) is necessarily *ALWAYS incomplete, biased and erroneous to unknown extents***

Despite increasing investments in Technology &I.T., major drugs products submissions to FDA are constantly declining



We need to change our point of view

INTERNATIONAL EXPERIENCED TEAM CHALLENGES IN 2004.

- **The challenge: Create the first Integrative Systems Biology company based on a disruptive *"negative selection process"*,**
- **A concept entirely contrary to "dominant" thinking.**

Global critical issue: *How to develop a sustainable research company when all the experts believe it is impossible ?*

Two necessary main proofs of concept to succeed:

- ***Scientific*: Create the 1st *in-silico* model of a complex human disease to be validated *in-vivo*;**
- ***Business*: Set up a 1st spin-off company created from an internal integrative systems biology program.**

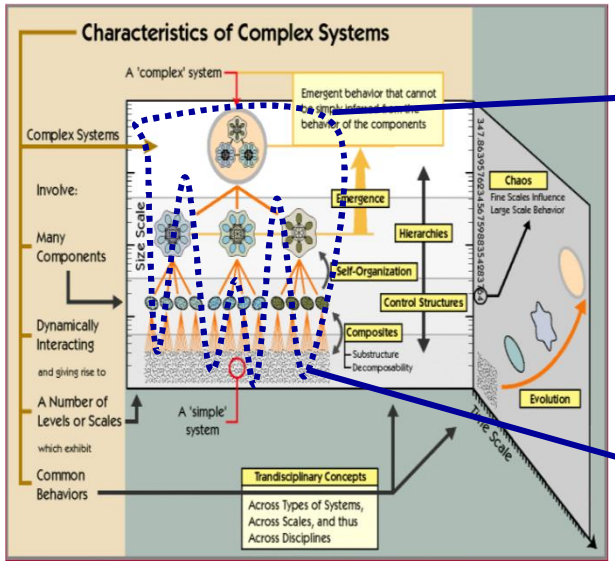
Invent a new "collaborative concept" with networked partners to support the development of CADI*™ disruptive Research & Innovation

**Computer Assisted Deductive Integration*

CADI*™ the first "non-mathematical" modeling approach , successfully applying its 5 principles

1. An *"Architectural Principles"* Approach
2. Our *"Negative Selection"* Process
3. Our *"4 steps validation"* Process
4. Our *"Broad life sciences & IT"* Expertise
5. Our "*synergic collaboration*" with classical IT partners

A complex system to study

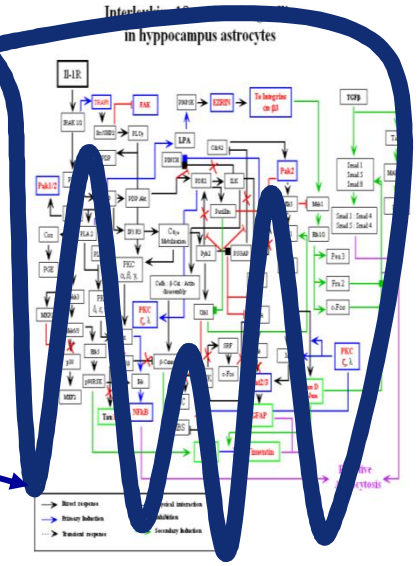


A CADI™ model representing the system in a specific context

Organs level

Cells level

Molecules level

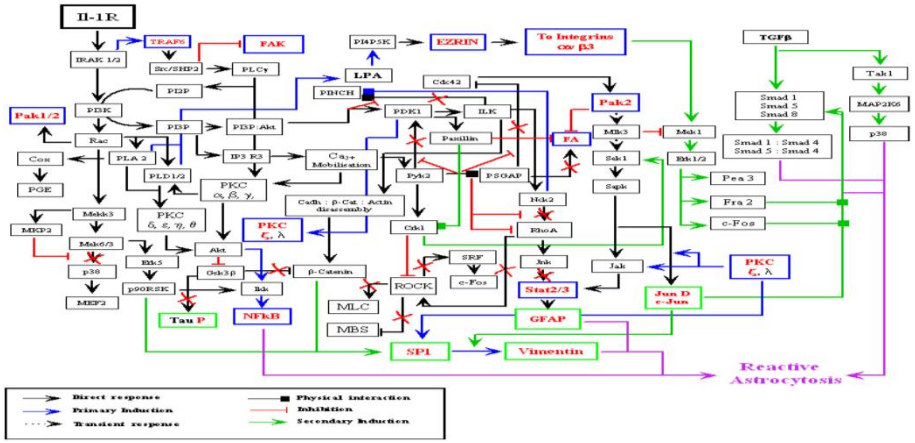


Computer Assisted Deductive Integration

BMSystems CADI™ models

The CADI™ models are detailed maps of inter-cellular and/or intra-cellular mechanisms associated with a biological status.

- CADI™ models are outstanding *"non-mathematical" descriptive in-silico answers* to explain the non-linear mechanisms of life and diseases.
- CADI ™ models can describe *the dynamics of pathological processes and/or pathological mechanisms vs. control.*
- CADI™ models describe *the mechanisms that cause the diseases*, not only the consequences.
- CADI ™ models *create the optimum new knowledge required to identify/explain mechanisms* that can lead to *direct industrial applications*.
- CADI™ models *have repeatedly led to novel patentable discoveries* in highly competitive applications.



CADI™ "Architectural" Principles

The efficient and reliable construction of innovative buildings.

- *The design phase*: Architects conceive and design the building so that it obeys defined functional and structural specifications while integrating within a given environment.

- *The "blueprint" design phase*: The resulting plans are then forwarded to engineering specialists who calculate and/or test components parameters where and as required.

The resulting final blueprint is then forwarded to the contractors who then build the structure according to the blueprint specifications.

- In this analogy, *BMSystems acts as the "Architect"* while mathematical modelers and experimentalists play the complementary role of "engineering specialists".

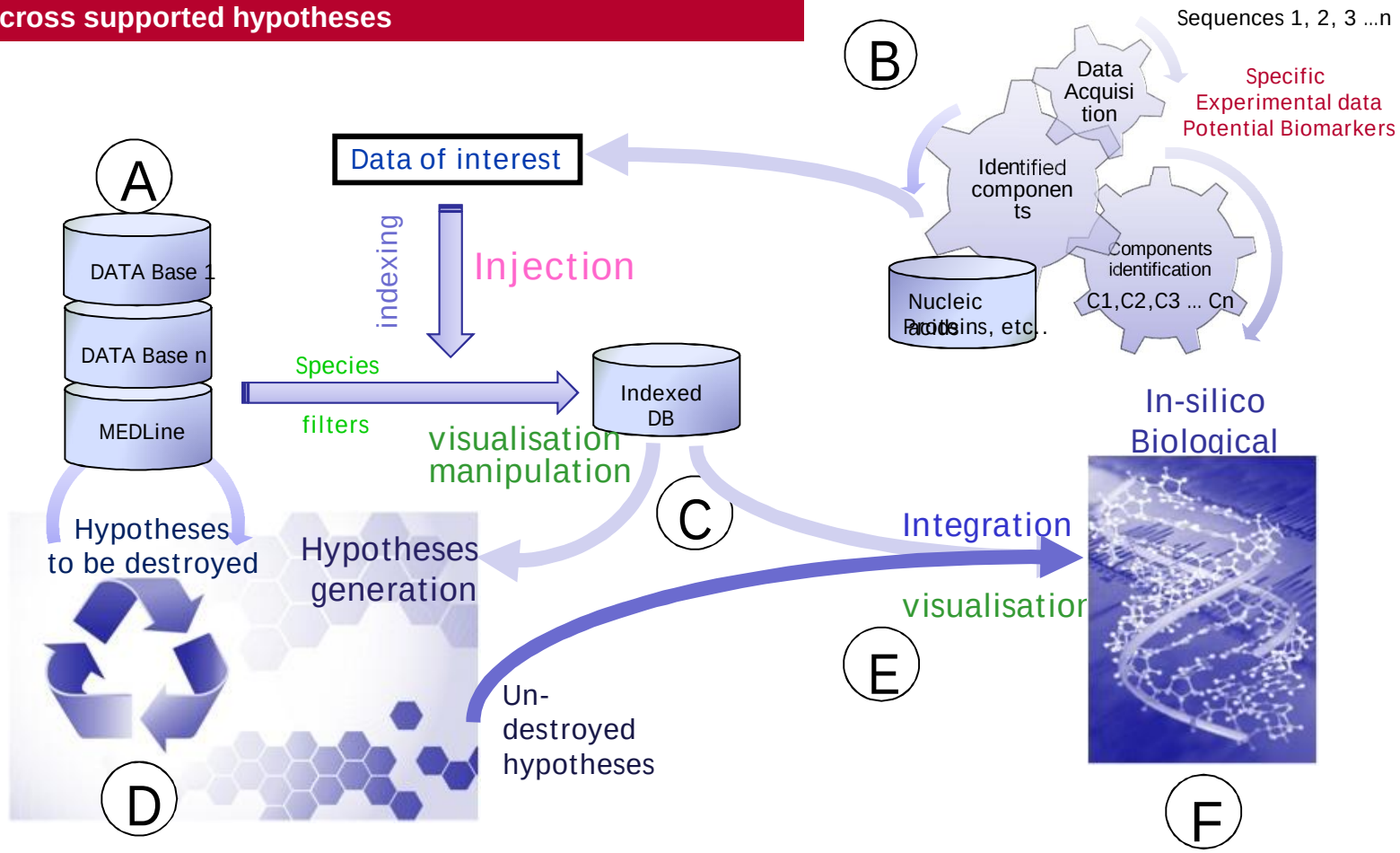
- As with traditional architecture, the results must be solid, useful, convenient and *have intrinsic elegance*.

By keeping to the architect's point of view and overall design attitude, BMSystems' scientists are able to succeed and solve unusual problems where traditional methods fail.

CADI™ negative selection process

The first operational application of the negative selection concept

CADI™ original concept is an operative answer to "the garbage in garbage out issue", and a disruptive innovative way to generate new knowledge from new cross supported hypotheses



CADI™ 4 steps validation process

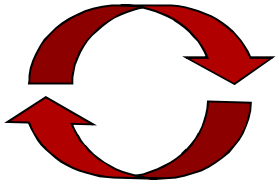
➢The CADI™ 4 steps validation process starts when the integrative biology researchers generate the initial CADI™ model, following the steps from 1 to 4:

CADI™ experimentations design

2

New version of CADI™ map

1



3

Experimentations implementation

4

Analysis of experimental results

➢The CADI™ 4 steps validation process stops when no key unexpected results are reported.

Now we can !

BMSystems "Broad life sciences & IT" Expertise

A strong multidisciplinary & experienced founders team

- *Dr. François Iris (PhD) : Chairman, CSO-CTO. Geneticist, physiologist & molecular biologist.*

Creator of Millennium Pharmaceuticals' (USA) high-throughput DNA sequencing unit. Former collaborator of Nobel Laureate Prof. Jean Dausset. Inventor of new technologies in molecular biology. MRC Overseas fellow, Member of H.U.G.O., Wellcome Trust Systems Biology experts board. Member of the Cambridge Healthtech Institute Scientific Committee, Member of the Evaluation committee for the funding priorities in the "Medical Systems Biology- MedSys" program; German Federal ministry of Research. 14 original articles in international journals including Nature, Cell, Nature Genetics, Genomics, J Mol Endocrinol, J Comp Biochem Physiol. 7 international patents, 3 patent applications currently undergoing examination, 5 book chapters, numerous invited communications at international conferences.

- *Manuel Gea: C.E.O & VP R&D Information Systems. Information systems specialist:*

- Scientific Engineering Degree from Ecole Centrale Paris, Chairman of the Supervisory board of PHERECYDES PHARMA (anti-bacterial bio-agents pharmaceutical company); Former CEO Hemispherx Biopharma Europe. Founder and President of Centrale-Santé. Founding-Administrator of the computing firm Formitel. Former McKinsey executive, creator of Practice Pharma services in France. Former Division Managing Director with Boehringer-Ingelheim France. Former International business manager Colgate-Palmolive Company (US), Co-founder and Vice President of the Biotech Committee of the Association of the Pharma companies operating France (LEEM). Member of the executive board of Medicen Santé, the world-class bio-cluster of Paris region. Vice-President Adebiotech Committee. Co-founder and Evaluation Committee member of Paris Biotech (leading biotech incubator).

- *Gérard Dine (MD, PhD): Chief Medical Officer: Physician, biologist:*

- Head of the Haematology Dept. at Troye's hospital. Founding member and Head of the Biotechnology Dept. at Ecole Centrale Paris. Founding-President of Troye's Institute of Biotechnologies. Former President of the Institute for Sports Medicine.

- *Paul-Henri Lampe: CIO & Systems Integration Director.Systems Integration specialist* Scientific Engineering Degree from Ecole Centrale Lille. Master Degree in Applied Mathematics from Ecole Centrale Paris. Former IBM Systems Integration Manager. Former Information Systems projects manager in an Acute Care Hospital in Paris.

- *Pablo Santamaria: IT & Internet Systems Director. Internet technologies specialist:* Scientific Degree from Ecole Centrale Paris, Founder and President of the computing firm Formitel (1988) .Founding President of the Centrale-Ethics Think-Tank. Vice-President of Centrale Human Resources Professional group. Former Senior Consultant Information Systems Evaluation (INSEP). Former Industrial Maintenance Manager at Glaxo Pharma (Evreux, France)

BMSystems: a collaborative life sciences company focused on its core know-how to optimize time to market & R.O.I.

- **Independent Private Company incorporated in 2004. Profitable since 2006.**
- **Invented a new paradigm for life science discoveries.**
- ***100% owned by its founders* (no search for external investors).**
- **A "*Biology" driven company* that intensively uses I.T. resources.**
- **Inventor and *exclusive owner of all its technologies.***
- **All non-strategic functions and resources are externalized.**
- **FTE*:24 of which 9 multidisciplinary scientists only focused on CADI™ research for new concepts/mechanisms generation and validation.**
- **Over 100 professionals working on BMSystems' related programs.**
- **BMSystems does not sell its technologies nor give access to them.**
- **Splits its activity between internal (50%) & contractual (50%) research.**
- **Externalizes the outputs of its internal research (spin-offs or out licensing).**
- **Member of BiO (US) , Medicen, IAR (Industrial biotech), Systematic clusters.**
- **Member in France of Leem biotech, Medef, Centrale-Santé Think Tanks.**
- **Founders member of international organizations (HUGO, CHI, etc…)**
- **1 spin-off: Pherecydes-Pharma (2006)**

*FTE: Full time Equivalent

BMSystems' Mission

BMSystems is a the first, and to date the only integrative systems biology company that creates heuristic in-silico CADI*™ models to boost its clients/partners R&D programs with immediate applications generating highly attractive businesses

BMSystems research/business model:

- BMSystems generates robust *innovative concepts/hypotheses* from raw information through the construction of CADI*™ models and,

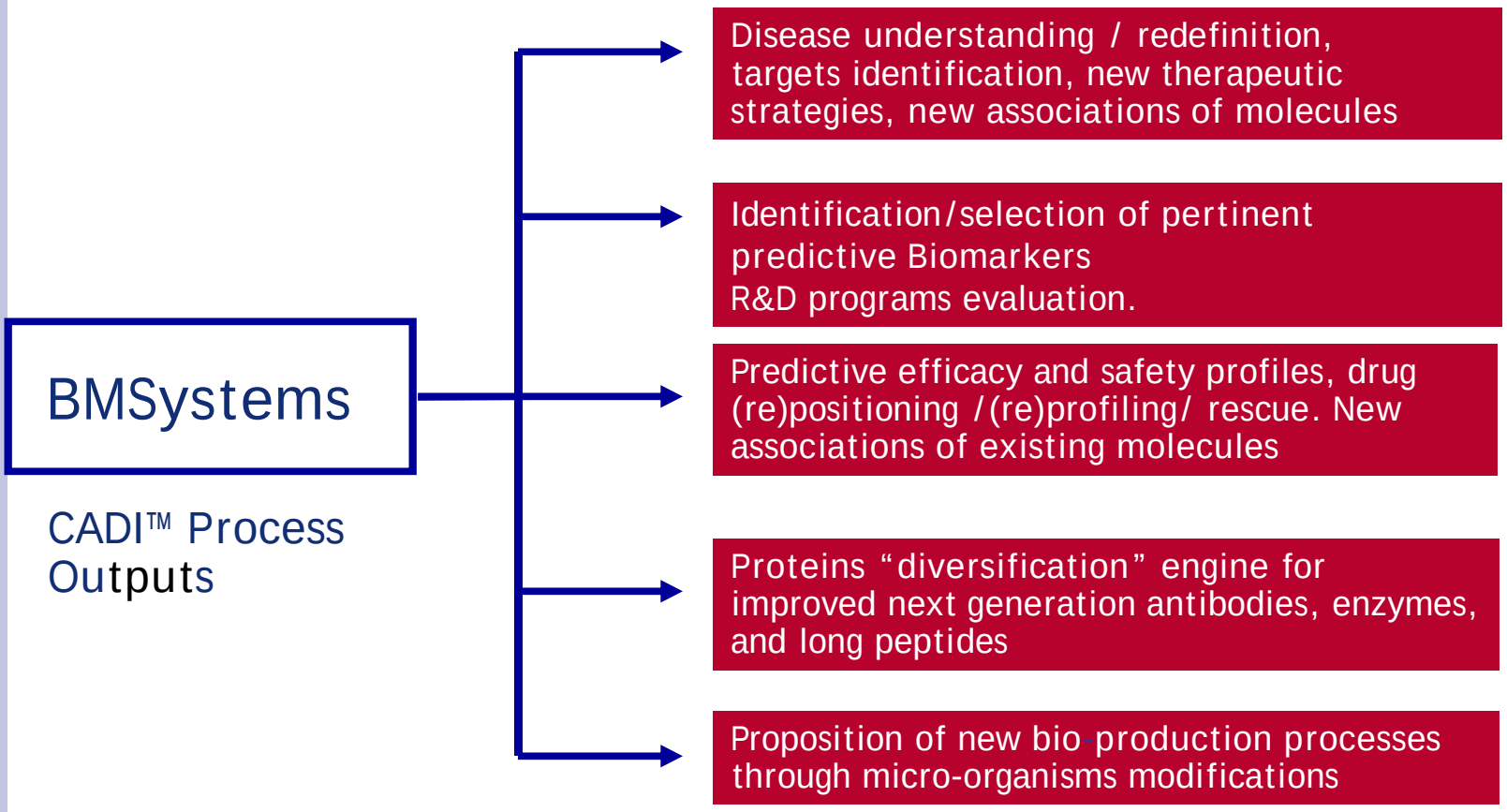
- BMSystems generates *real & attractive businesses* from these innovative concepts/hypotheses through its innovative business model.

**Computer Assisted Deductive Integration*

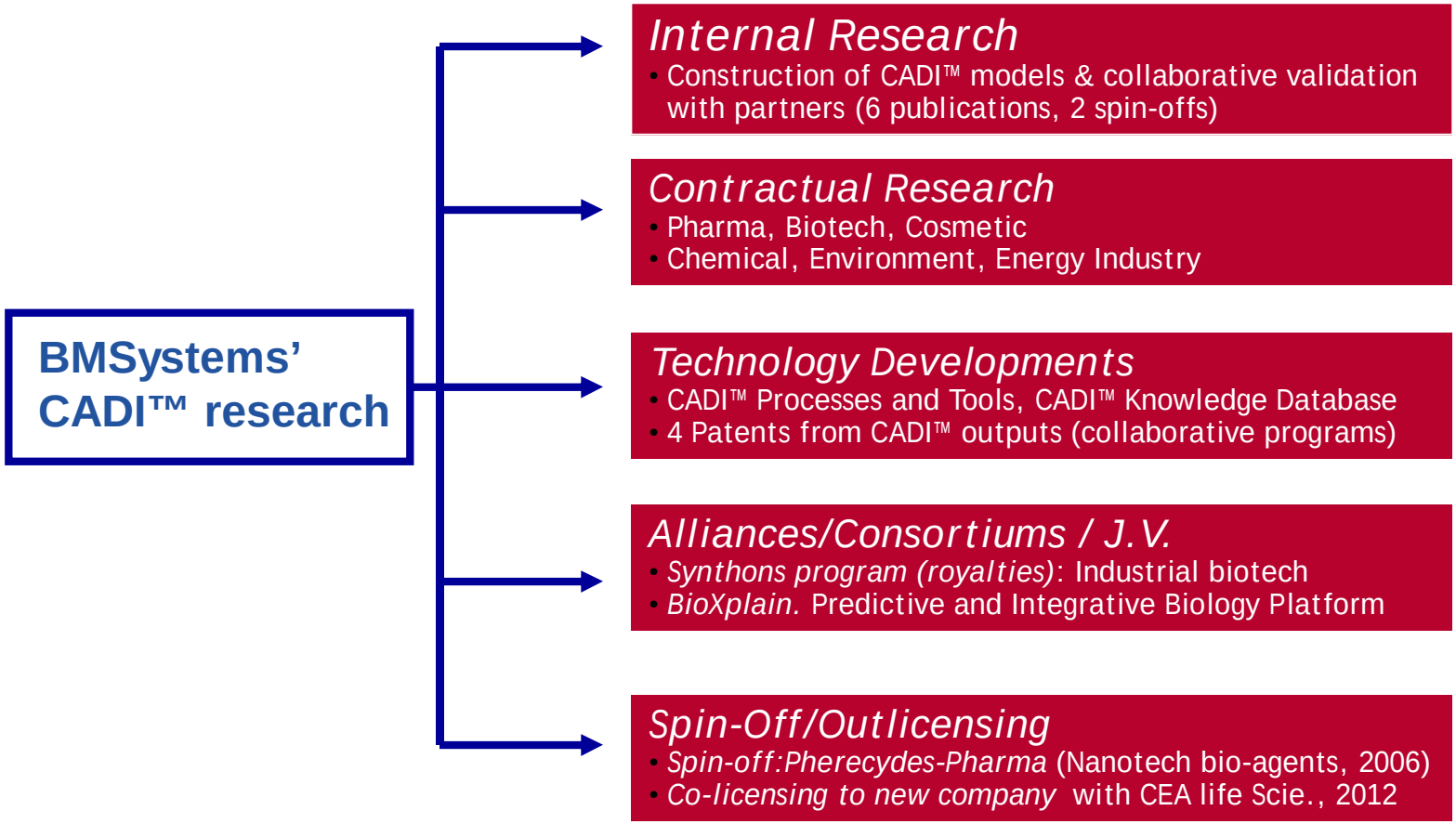
BMSystems outputs

What can we do with CADI™ models?

Reduce time to result, improve success rate and reduce development costs in the following markets, biomedical, chemistry, cosmetics, environment, energy, through:



A new collaborative strategy to optimize capital investments and time to market



BMSystems' CADI™ programs to date

Internal & collaborative programs only

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.	Ready for Business
Nano-Bioagents	Pherecydes							
TAPE (protein improvement)	Pherecydes							
Chronic Fatigue Syndrome	Open							
Ebola virus ecology	Open							
Hepatitis C	Open							
CNS-Psychiatry	CEA Life Sciences							
CNS-Neurodegenerative	CEA Life Sciences							
Alzheimer	Open							
Fibromyalgia	Open							
Pain	Open							
Migraine	Open							
Multiple Sclerosis	Open							
Psychiatric disorders	Open							
Program Synthons	ARD-IBT-L'Oréal							
Program Synthons	ARD-IBT-Rhodia							
Program Synthons	ARD-IBT-Arkema							
Breast cancer-Hras	INSERM							
Tamoxifen resistance	INSERM							
Metastasis mechanism	INSERM							
Müllerian regression	CNRS							
Adipocytes growth control	Open							
Hypercholestemia	Open							
Metabolic Syndrome	Open							

Infection-Immunology	Oncology
CNS-PNS	Tissue Differentiation
Industrial biotech	Metabolism

BMSystems' CADI™ publications to date

Internal & collaborative programs only

CADI™ Models published in prestigious peer-reviewed journals:

- 2012: CNS Neurodegenerative & Psychiatry publication: 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 Ha-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:

- 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
- 2008, CNS: Integrative Biology in the discovery of relevant biomarkers monitoring cognitive disorders pathogenesis and progression. BioTribune Springer publisher Vol. 28, august 2008.
- 2005, Systems Biology: Computer-Assisted Integration into Biological Pathways of Modulated Gene Expressions Patterns. In « Bioinformatics: New Research », Yan PV editor, Chapter IV, pp 81-100; Nova Publishers.

BMSystems'4 case studies

The Proof through operational achievements

New therapeutic strategy: Publication, in 2003, with the INSERM unit 553, of the first independently validated in-silico model of a complex human disease.

Inserm
French Institute of Health and Medical Research

Spin-Off: 3 patented new disruptive technologies & successful launch and financing of Pherecydes-Pharma, the first bio-defence and bio-security company in France to efficiently & reliably address first bacterial threats, next viruses, and then toxin threats.

PHERECYDES PHARMA

Consortium: Co-founder in 2006, *as integrative biology partner, with its key partners A.R.D. , I.B.T. and C.V.G., of the Synthons platform, the major integrated collaborative industrial biotech platform in France,*

Synthons

Industry Award & patent : This collaborative work received a Bio-IT World 2009 Best Practice Award. A second CADI™ modeling program with the same CEA-SEPIA* research team also allowed the discovery of novel therapeutic approaches in the treatment of poorly served CNS diseases (patent filed).

Bio-IT World Best Practices AWARD Honorable Mention 2009

**CEA-SEPIA: Atomic Energy Council: Department of prion and atypical infections research*

1-Ras-dependent breast cancer

Tumour Progression: *MCF-7 vs MCF-7 ras*

Inserm
French Institute of Health and Medical Research

The theoretical model made three types of predictions:

Published in: *Nucleic Acids Research*, 2003, Vol. 31, No. 19: 5789-5804

-A) the cellular mechanisms.

The model predicted the expression patterns of 13 key genes associated with the physiological changes revealed during the model-building process.

These predictions were independently tested, using RNA-chip technologies, at Hospital Tenon.

-B) the therapeutic targets

The model indicated three different cellular processes as being key to the maintenance of the hormono-sensitive malignant state. In each case clearly defined protein targets (isoforms level) were identified.

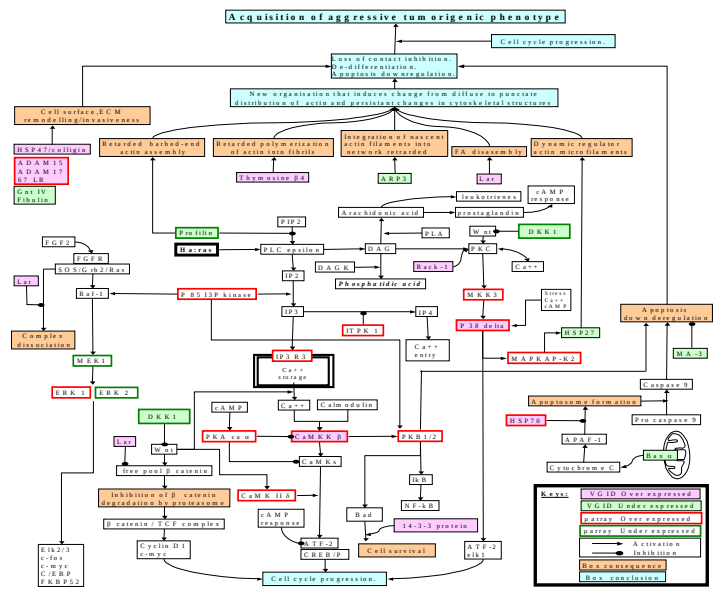
-C) the types of therapeutic interventions required

The model indicated three different molecules which, in combination and at sub-optimal concentrations, would have the required effects on the protein targets of cancer cells, leaving non-cancer cells largely unaffected.

These predictions were directly and independently tested on the cells by cancer specialists INSERM U 553 at Hospital Avicenne (Prof.M.Crépin), and the CEPH Institute (Prof.L.Cazes) in Paris.

1-Ras-dependent breast cancer

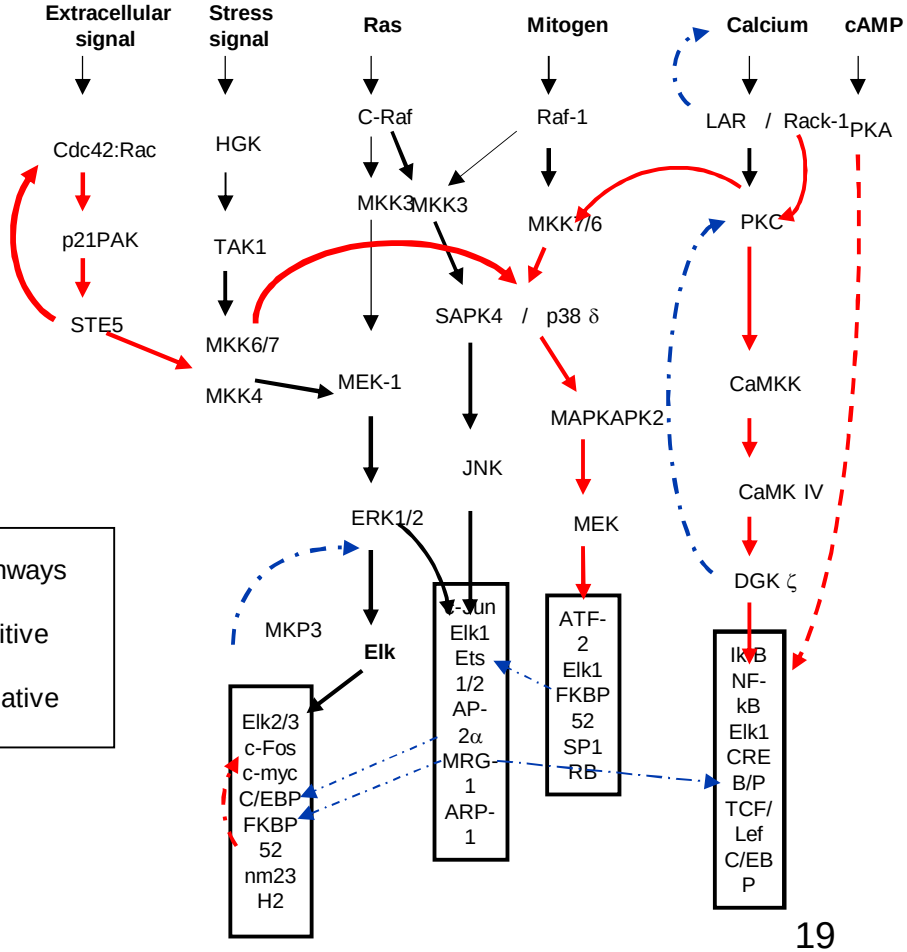
Breast Cancer Progression: *Cellular Mechanisms Model*



Published in:
Nucleic Acids Research, 2003, Vol. 31, No. 19: 5789-5804

- Standard pathways
- Amplified positive interaction
- Amplified negative interaction

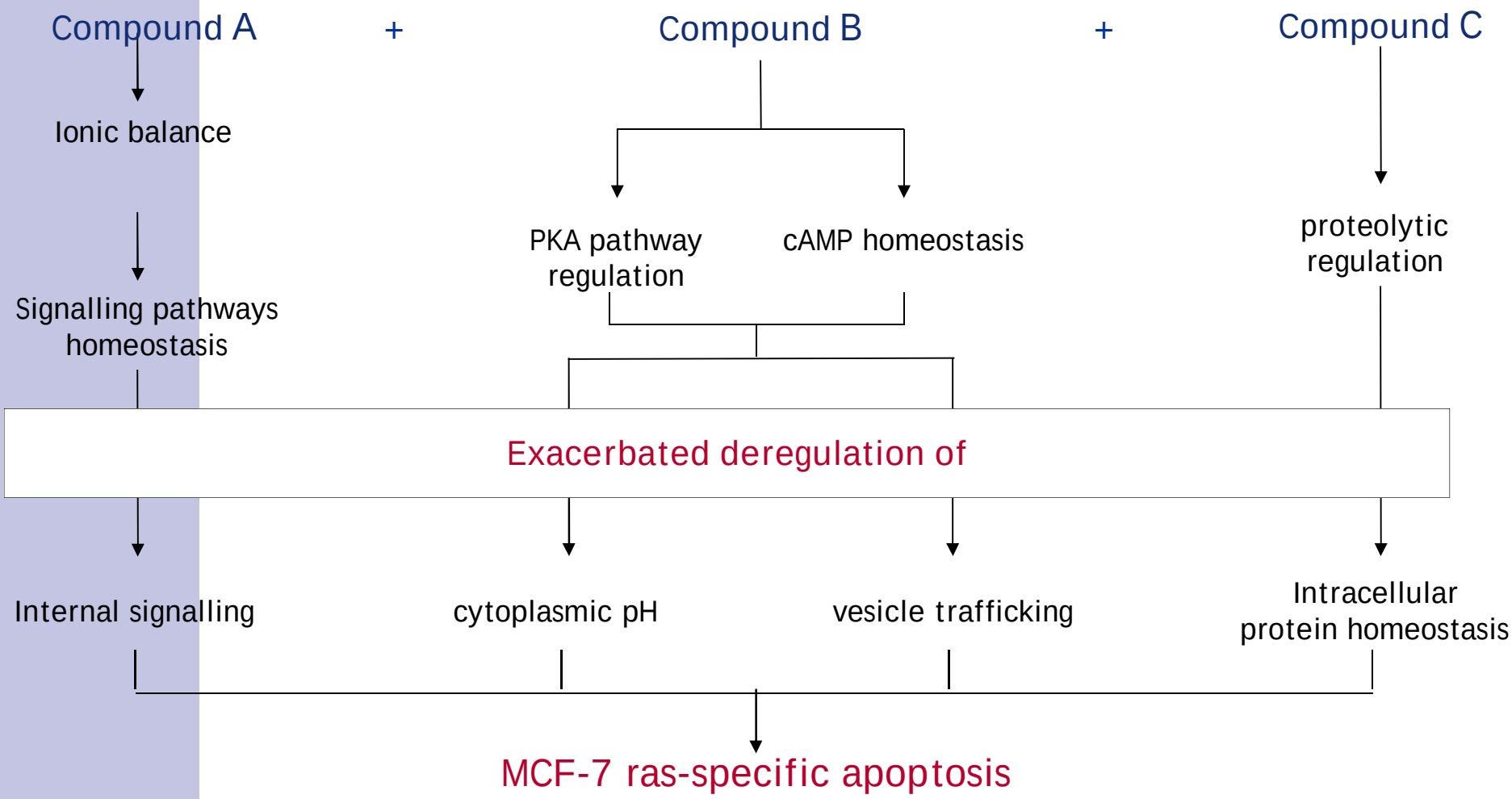
CADI™ model extract



1-Anti MCF-7 ras pharmacological

intervention using sub-optimal doses (nM)

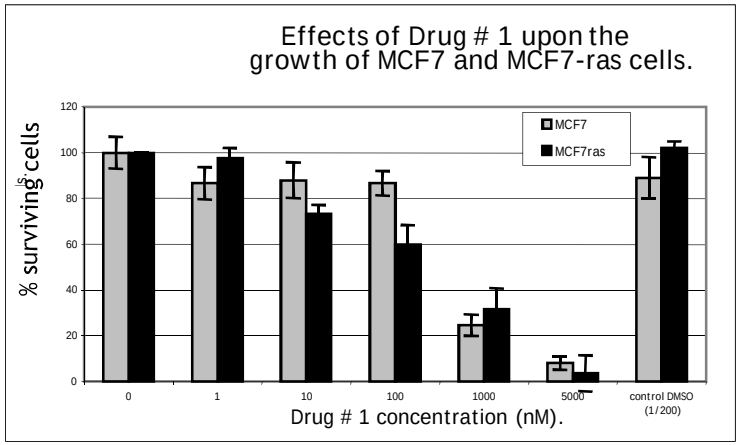
Important: Three compounds never used in cancer treatments*

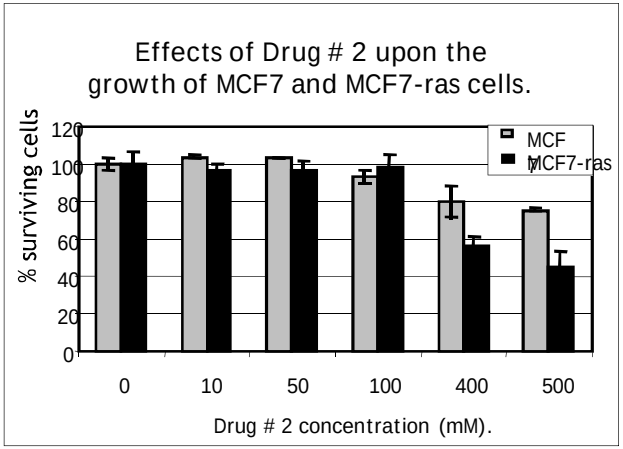


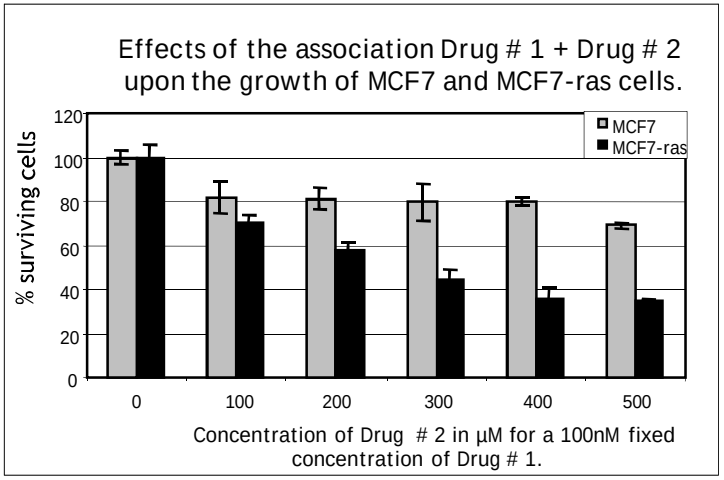
** Rational: We are not fighting against the mechanisms leading to cancer, we are using compounds known to exacerbate the imbalances induced in cancer cells by the pathways identified as causative.*

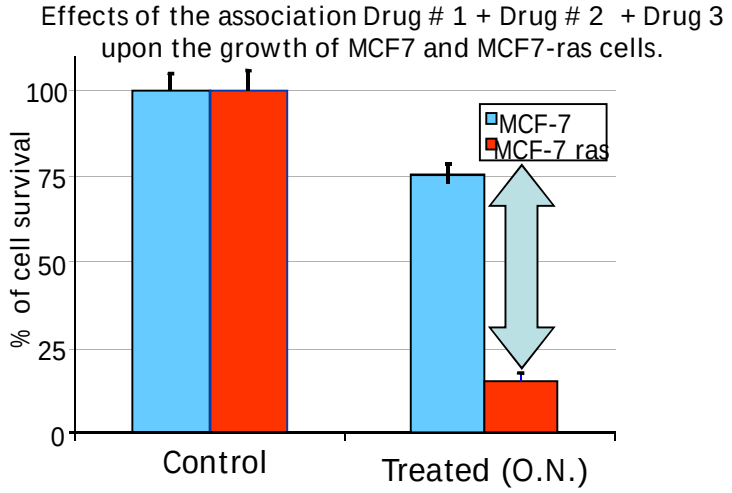
1-Ras-dependent breast cancer

Biological Validation. A significant difference when the three compounds, NEVER USED IN CANCERS, are present







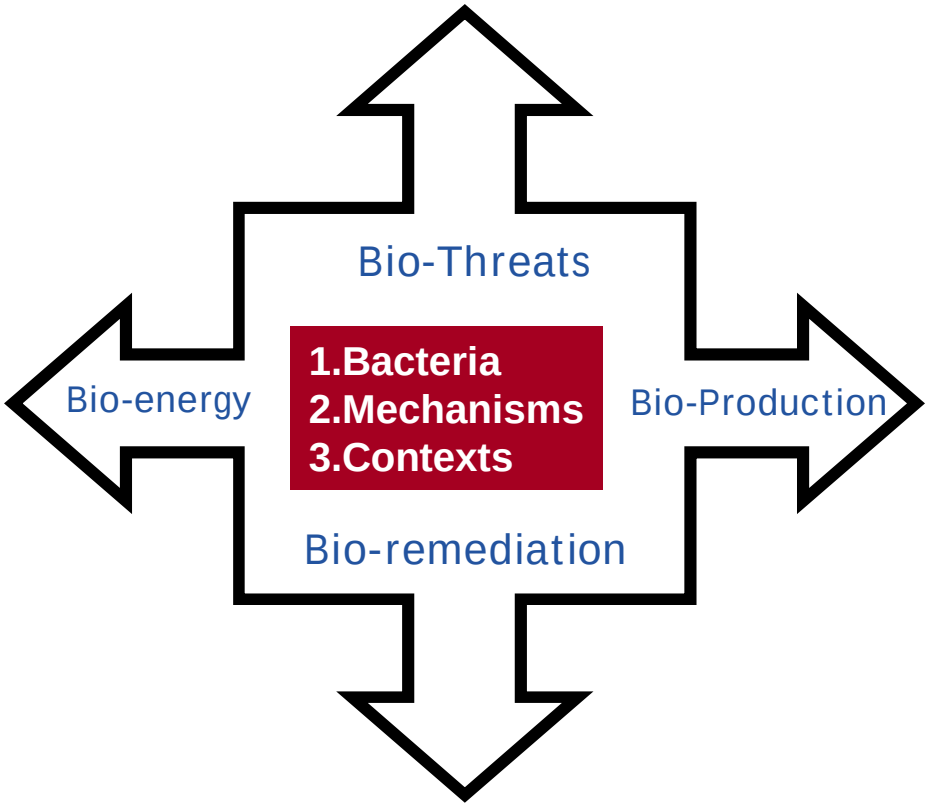


This is not a treatment, but this work gives new patentable ideas to develop new therapeutic strategies using a combination existing and/or new drugs.

BMSystems' Heuristic CADI™ approach

Illustration: The bacterial mechanisms and their business applications

Pherecydes-Pharma
Biodefense-biosecurity
Partners: ACE management, CEA

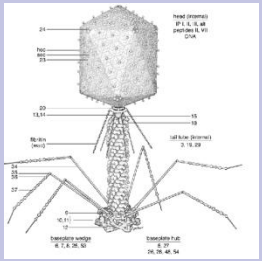


Program
BIO-ENY

Synthons
Industrial biotech
Partners: ARD, IBT, CVG
L'Oréal, Arkema, Rhodia

Program
BIO-REMY

2. Pherecydes-Pharma



PHERECYDES-PHARMA: Less that 5 years from concept to industrial proof in the field of biodefense /biosecurity.

- ***World's 1st company created from an integrative systems biology program***
- **Creation of the *first operational large-scale engineered bacteriophage bank* to fight against *"unknown multi-resistant" bacterial infections*.**
- ***Outstanding support from CEA Fontenay-aux Roses* (founding member of Medicen cluster), including IMETI* Institute's scientific team.**
- **Creation Dec. 2006: *1.15 Million € raised*, from ACE management funds.**
- ***500 k € Innovation Program grant* from Oséo Innovation Agency.**
- **Rapid international recognition in the USA *(4 invitations to present*).**
- ***3 fully owned international patents* invented by BMSystems.**
- ***Industrial proof of concept:* Sept. 2009.**
- **2011: DGA funding 1M€**
- **April 2010: signs its *first international collaboration with BAC (Bio Affinity Company) BV* to develop improved antibodies and is negotiating 2 others in N. America.**

Clearly, the outstanding collaboration & support from CEA life Sciences Fontenay-aux-Roses, led to Pherecydes-Pharma being located in France

*Pr. Leboulch, Jean-Philippe Deslys, Franck Mouthon and Pierre Chagvardieff

3. Synthons Program

Synthons program, major collaborative industrial biotech research platform in the IAR world-class cluster

A complementary collaborative team:

- **A.R.D.: Leading Industrial Biotech research company with experimental capacities, pilot scale-up, pilot plant (2000 Tons), etc.**
- **I.B.T.: One of France's leading Technology Transfer Institutes.**
- **BMSystems: integrative Biology & metabolic engineering expertise.**
- **C.V.G.:"green chemical" sourcing research institute.**

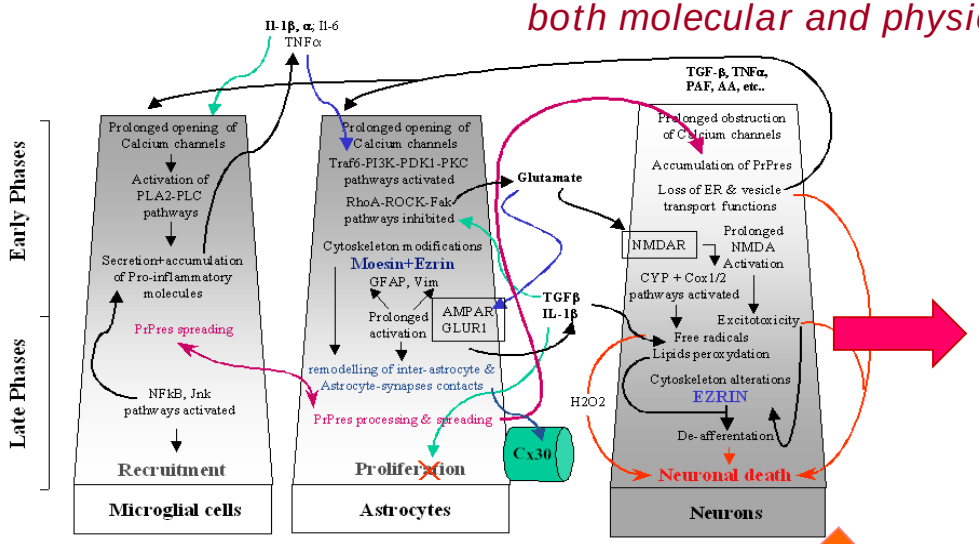
3 EU chemical companies proposing their molecules to the platform:

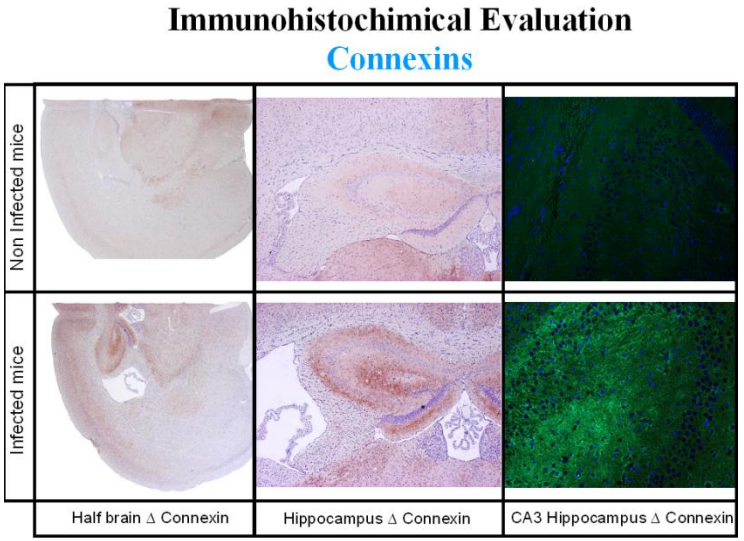
- **L'Oréal: (world leader in cosmetics)**
- **Rhodia: (ex Sanofi Aventis fine chemical entity)**
- **Arkema: (ex Total chemical entity)**

2 engineered strains generated are under evaluation and a finalized process under mid-scale validation. The program is funded by the ministry of Industry and supported by IAR world-class cluster

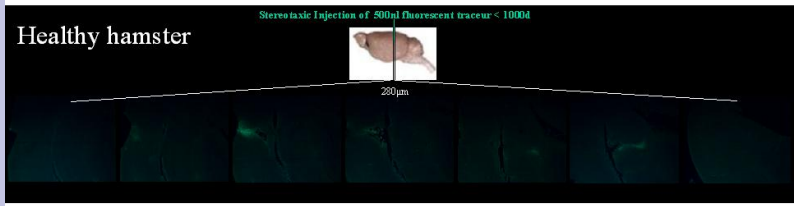
2-Creutzfeldt-Jakob/prion disease

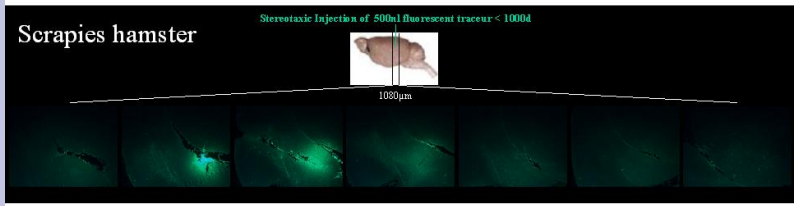
Which predicts and explains the pathological mechanisms at both molecular and physiological levels.



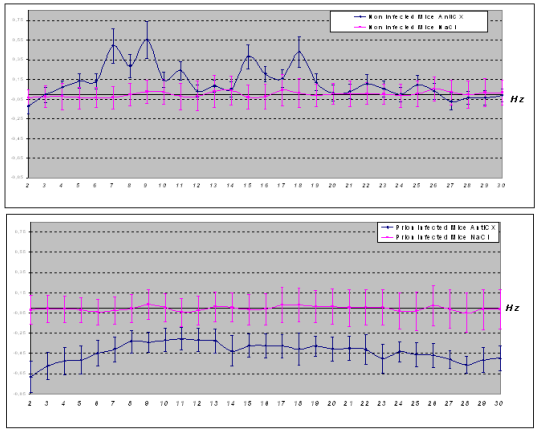


Functional modifications of glial connexions





Functionnal EEG alterations linked with modifications of glial connections.



Healthy mice

Scrapies mice
(asymptomatic phase).

NaCl

Anticonnexin

Source:
BMSystems & CEA

2-CADI™ programs outputs

The double take win-win CNS programs

1. 2008: *World's first in-vivo validation of a CADI™ in-silico model* of a complex human disease (Creutzfeldt-Jakob/prion disease) with CEA SEPIA, coordinator of the European NeuroPrion Network of Excellence. Discovery of a new regulation system in the brain. (publi. Pending)

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1. Prestigious US Industry Award: Bio-IT World 2009 Best Practice Award.The only EU team rewarded in 2009.
2. Best Systems biology program by the D.G.Research of the Eu. Com. in 2O1O.

2. 2009: *New industrial application*: A 2nd CADI™ model with the same research team, exploiting one discovery of the 1st CADI™ model, led to the discovery of novel therapeutic approaches in the treatment of poorly served psychiatric diseases (*patent filed Sept 2008, PCT 2009**)

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In 2009, BMSystems and CEA Life Sciences decided to license the patent to a new CNS company under creation by the research team.

• Dose reduction: USE OF ANTI-CONNEXIN AGENTS FOR MODULATING THE THERAPEUTIC EFFECT OF PSYCHOTROPIC DRUGS

Possible businesses with partners or clients

Neurodegenerative diseases:

1. *Alzheimer*: CADI™ compliance ok: (3 mechanisms already identified). Search for partners or clients ready to work on new causal hypotheses.

Psychiatric disorders:

1. *Psychiatric disorders: Drug combination.*
2. *Multiple Sclerosis*: CADI™ compliance ok. Search for clients.

Pain diseases

1. *Pain:* CADI™ compliance ok. Search for clients
2. *Migraine:* CADI™ compliance ok. Search for clients
3. *Fibromyalgia*: CADI™ compliance ok (first mechanisms already identified). Search for partners or clients.

Key learnings to really support disruptive innovative SMEs

- **Be aware that SMEs can "also" generate disruptive R&D paradigms, but they need open minded partners to have access to costly equipments and/or complementary academic expertise.**
- **The expertise issue: The "classical" experts, well adapted to "incremental" progress, represent the major issue in the evaluation of disruptive innovations. We appreciate that it is difficult to objectively evaluate something you can't understand!**
- **Based on our experience, the first impulse of the expert may be to state that "it is impossible" and then, when the first results are observed, to try obtaining the "secrets" in order to understand or, failing that, to claim "other reasons".**
- **The SMEs managers know that the value of "secret agreements" and patents protecting innovations are directly proportional to the amount of money they are ready to spend to defend them!**

SMEs are ready to participate to Collaborative European Programs, they are attractive, but the evaluation rules must be "more transparent", and the selection of experts and their briefing need to be adapted to the type of innovation presented and integrate an understanding of SMEs factual life.

Conclusions / Questions

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