Bio-Modeling Systems

The R&D booster for life sciences discoveries

Our 4 Case studies & BioXplain Platform

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BMSystems' efficacy

The Proof through operational achievements

CASE 1- BMSystems and its partners produce new knowledge from raw information:
How to understand the mechanisms explaining Tumor Progression in Ras-dependant breast cancer.

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

CASE 2- BMSystems and its partners generate a real business from new Knowledge:
How to rapidly and efficiently destroy any unknown bacterial pathogen or emerging strains without using antibiotics or vaccines in a very limited reaction time (3 hours).

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.

CASE 3- BMSystems and its partners generate real business from their analytical & experimental expertise:
How to successfully enter the fast growing Industrial biotech market in the minimum of time and investment.

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,*

CASE4 – BMSystems and CEA life Sciences team demonstrated how to maximize synergies between experimental and integrative biology. In-vivo validation of CADI models in neurodegenerative & psychiatric diseases.

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 pending).

**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*

(The very first validated model of a complex human pathology ever published)
(Nucleic Acids Research, 2003, Vol. 31, No. 19: 5789-5804)

MCF-7:Breast epithelial cell

- *Latently tumoral and Hormono-dependent*

MCF-7 ras: MCF-7 transfected with constitutively activated h-ras

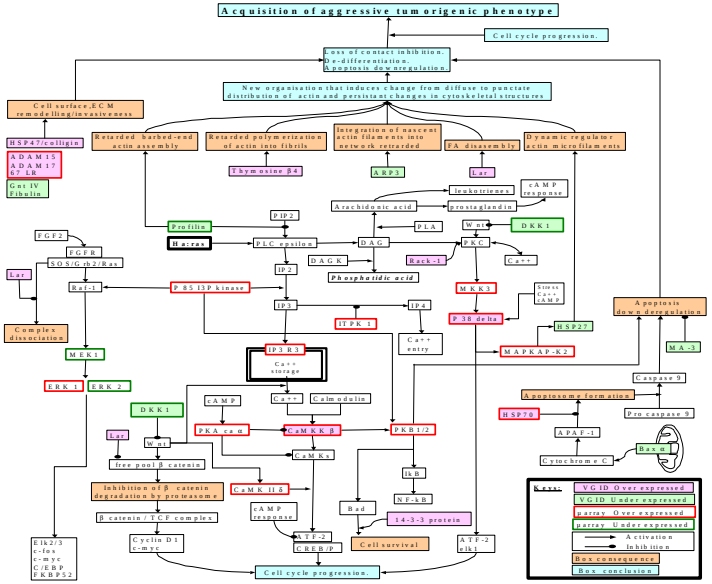
- *Aggressively invasive; Hormonosensitivity but no dependency*

Objectives:

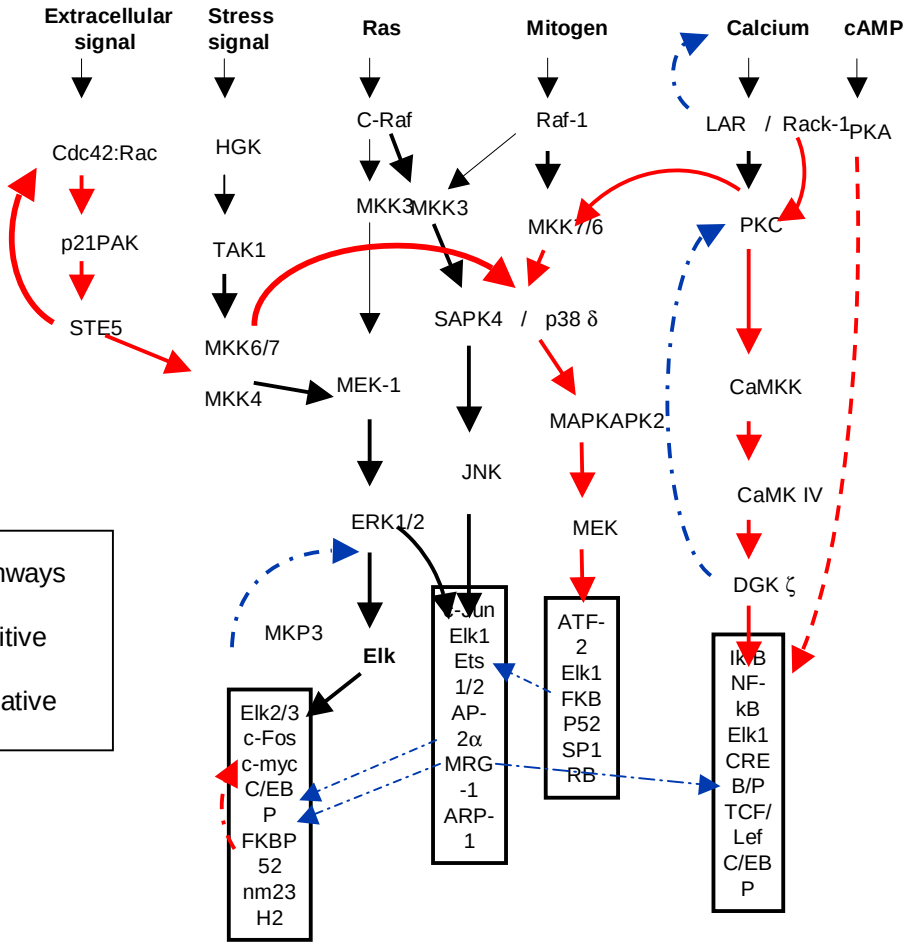
- To discover the mechanisms that explain the different cells behaviors
- To propose, based on the model-derived understandings, a totally new therapeutic strategy that addresses the causes and not the consequences of the deregulated mechanisms.

1-Ras-dependent breast cancer

Breast Cancer Progression: *Cellular Mechanisms Model*



CADI™ model extract



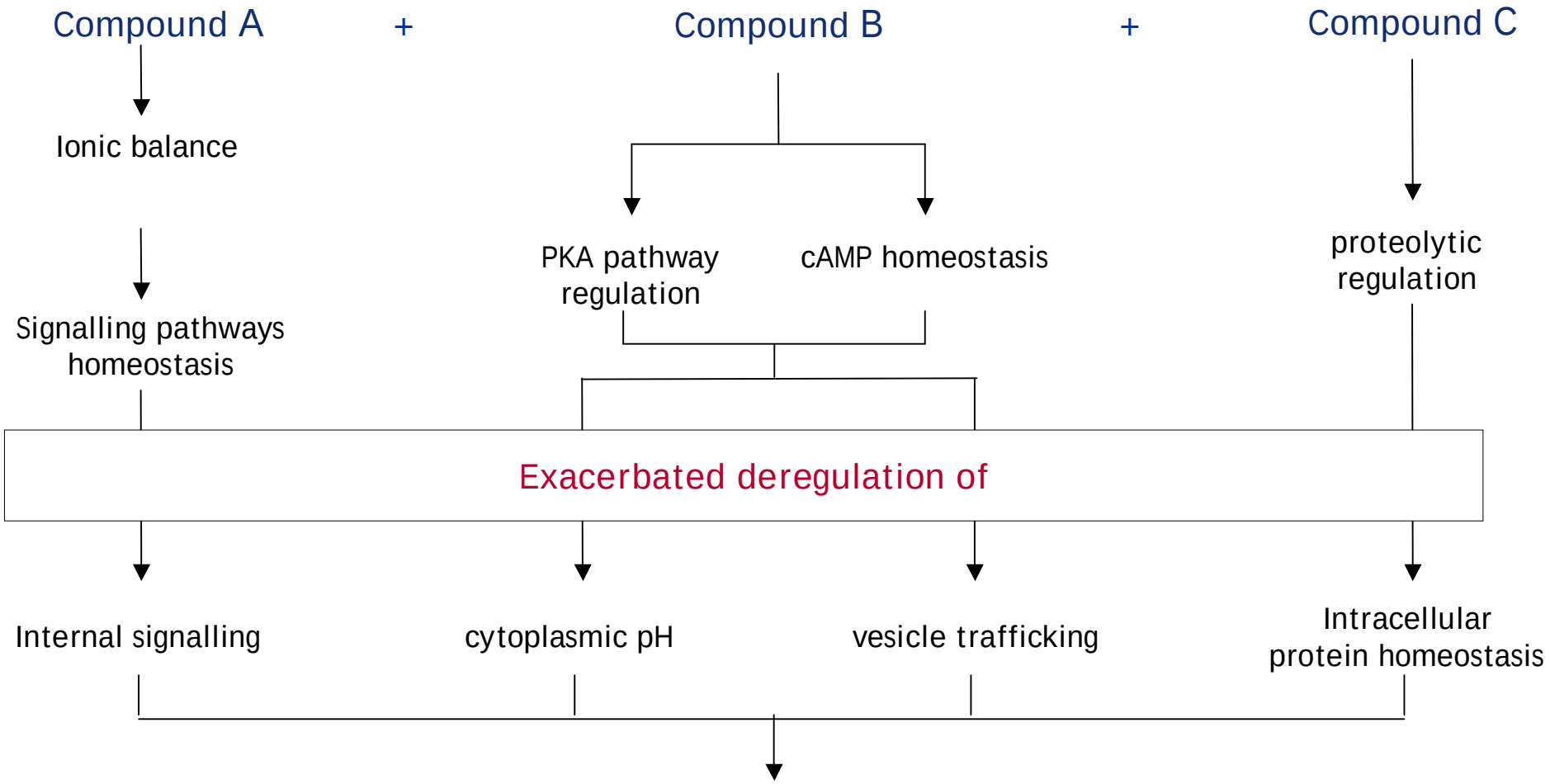
- Standard pathways
- Amplified positive interaction
- Amplified negative interaction

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

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
Forecasts to be validated

The theoretical model made three types of predictions:

-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.

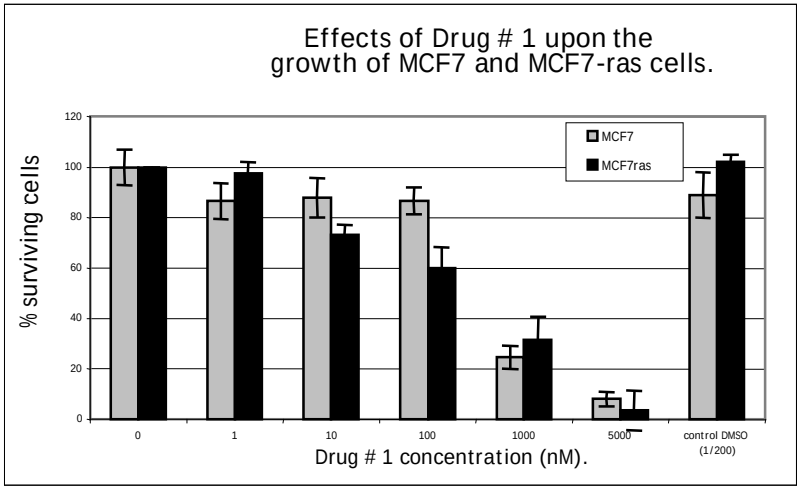
-C) the types of therapeutic interventions required

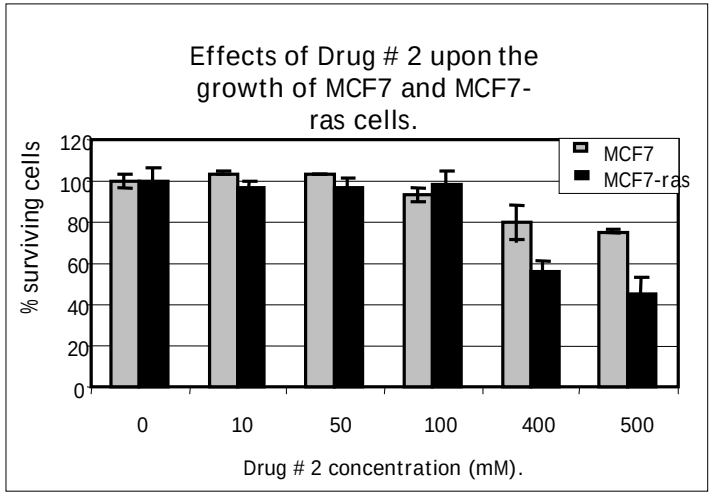
The model indicated three different molecules which, in combination and at sub-optimal concentrations, would have the required effects on the protein targets of cancer cells, leaving non-cancer cells largely unaffected.

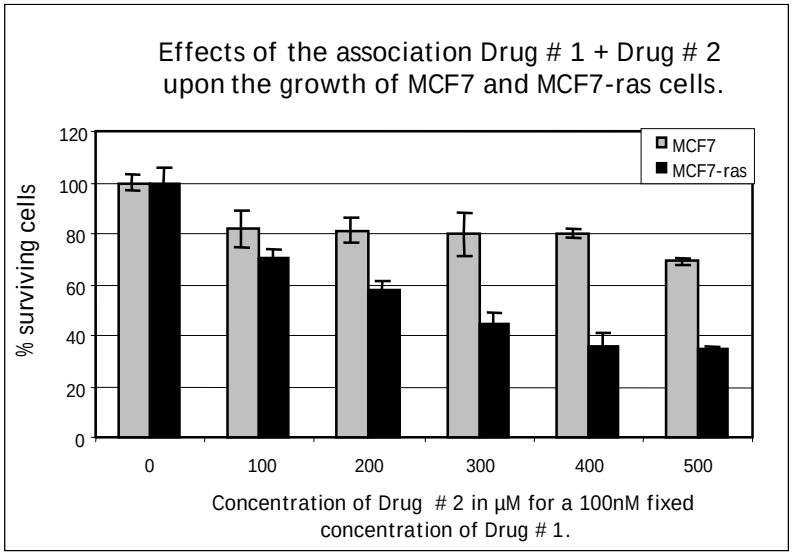
These predictions were directly and independently tested on the cells by cancer specialists INSERM U 553 at Hospital Avicenne (Prof.M.Crépin), and the CEPH Institute (Prof.L.Cazes) in Paris.

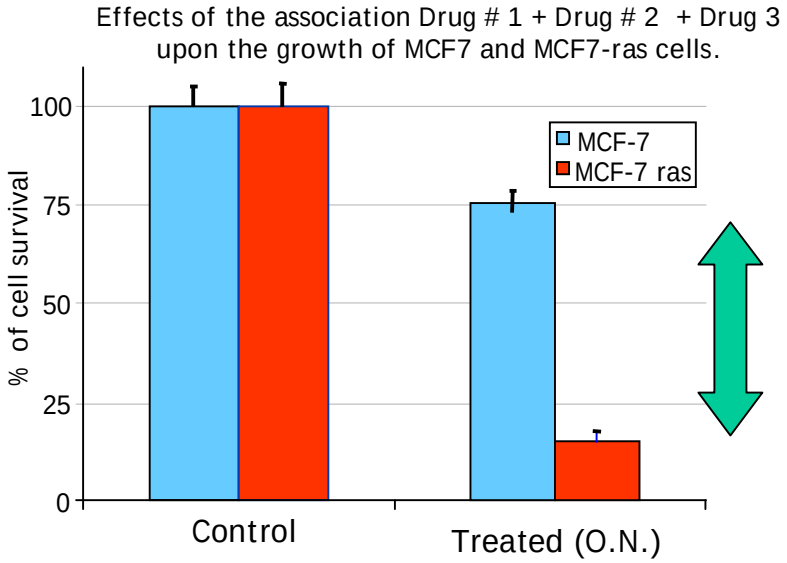
1-Ras-dependent breast cancer

Biological Validation. A significant difference when the three compounds are present









2-Pherecydes-Pharma

A major bio-defense bio-security challenge

The major threat in bacterial infectious diseases:

- Multi-resistant bacteria are increasingly frequent and widely disseminated in a multitude of environments.
- Progress in molecular biology is such that it has become relatively easy to engineer genetically modified pathogens for which there cannot be any immediate counter-measures.

The right question:

How to rapidly and efficiently destroy any unknown bacterial pathogen or emerging strain without using:
- Antibiotics: too many resistant strains, and very rapid resistance acquisition.
- Vaccines: much too slow to act, and small strain variations often lead to inefficacy.

The natural solution forgotten by the industry:

- Bacteriophages, the natural predators of bacteria, could present the best potential to act as detectors-killers.
- But the bacterial host will try anything to escape predation and we have no idea what will be the successful strategy. Furthermore, this strategy is likely to vary between locations (populations) for a same host.

And: Bacteria have existed for nearly 4 BILLION Years.
They have so far resisted to EVERYTHING. And it is certainly NOT for lack of phages!

What should we do to achieve an efficient solution ?

2-Pherecydes-Pharma

Key proposal & success factors

- We must be capable of always preceding the host's escape strategies, no matter what they could be.
- to do so, stochastically engineered phage banks must be constructed in order to produce phage particles capable of targeting anything and everything while maintaining their capacity to replicate in the face of host's evasion attempts.

Natural phages are not enough.

It becomes necessary to abandon all idea of « natural phage pools »

BMSystems' answer: We invented three proprietary technologies allowing the production of stochastically engineered phage banks

TAPE™ : Targeted Accelerated Protein Evolution: 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 all proteins, including antibodies, enzymes, etc..).*

Ab-ACCUS™ (Phage Engineering) : A recombination technology allowing the rapid & efficient production of phage banks in which every individual differs from all others for any number of selected phage-encoded function.

RIPh™ : A process for reversibly stopping phage replication in a host, allowing to extensively modify the phage's genome and restart phage replication and lytic cycle as needed.

Applicable to any phage and to any known sequence.

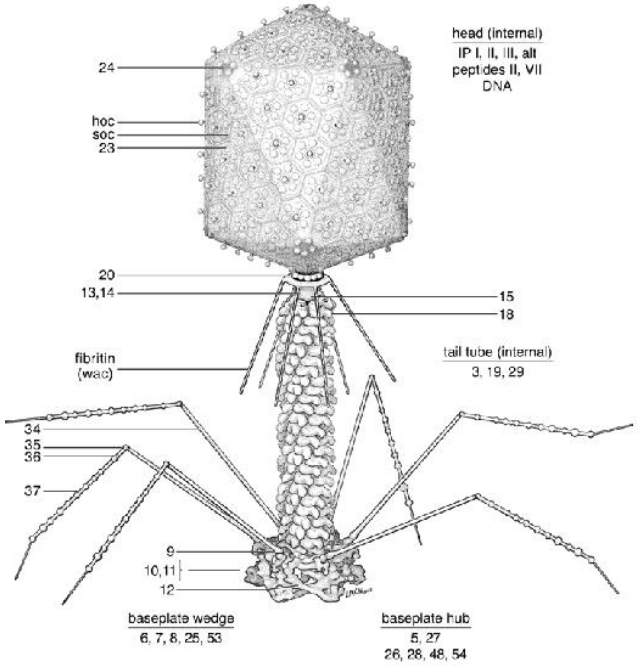
2-Pherecydes-Pharma

The proposed genetic diversity targets

Host recognition is based on tail fibers

- Modify protein tail fibers
- Create huge diversities of tail proteins
- Design banks of phages that recognize:
  - Different bacterial strains
  - Diverse bacterial species

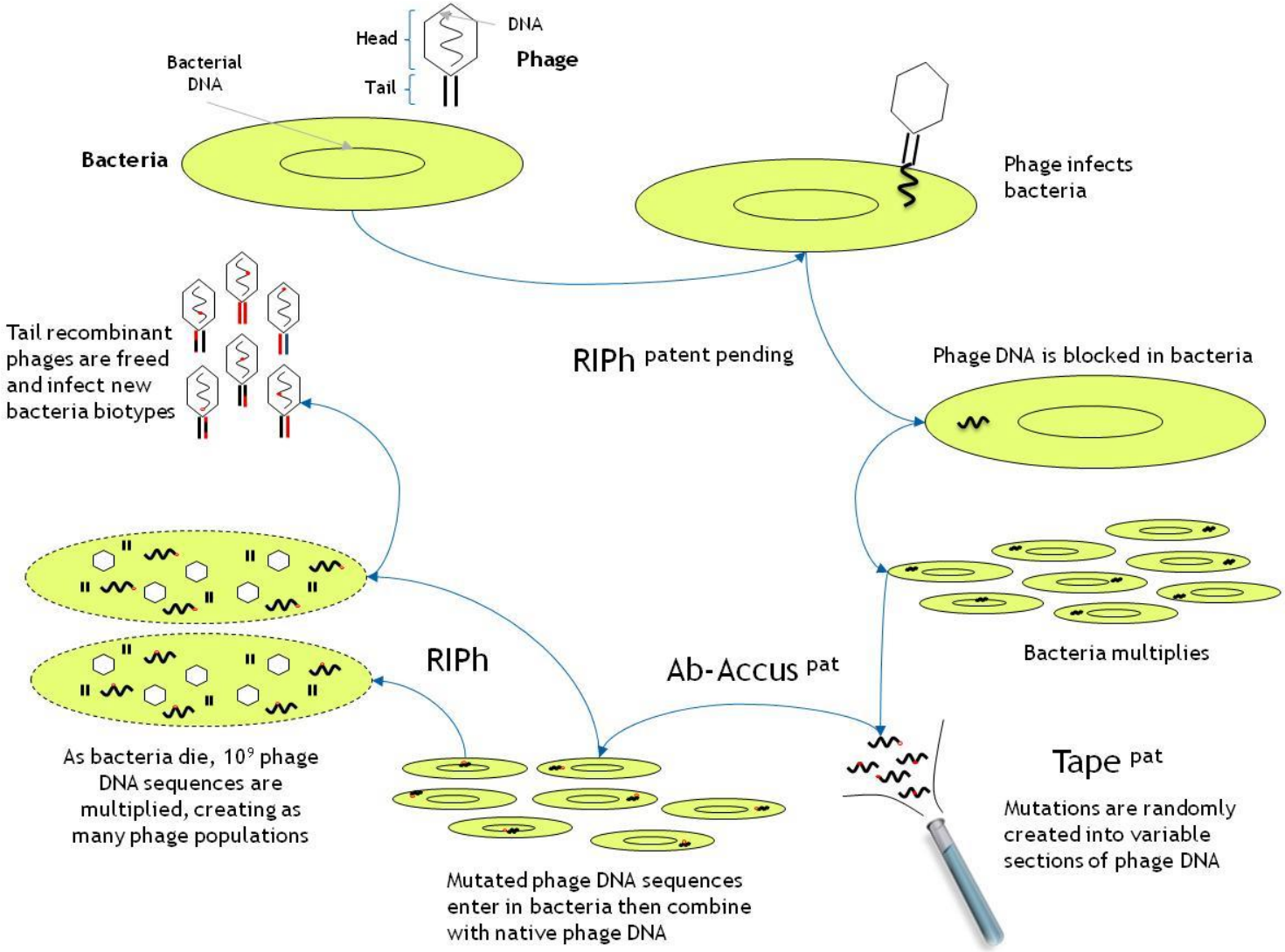
- *Select phage variants to control:*
  - Antibiotic multi resistant bacterial strains
  - Phage resistant bacteria
  - Emerging bacteria



An efficient process to fight bacteria resistance

2-Pherecydes-Pharma

The combination of the three platforms



2-Pherecydes-Pharma

BMSystems internal research Program (1.5 year)

- Production of two CADI models:
  - Bacterial resistances mechanisms (mid 2005)
  - Phages targeting systems (end 2005)
- Possible strategy to answer the issues identified. First experts validations (2005-2006)
- Two patents filed (end 2006) TAPE and AB-ACCUS

Our partners

- CEA: technological and bio-defense sector expertise
- ACE management team (financière de Brienne & FCPR Security): business expertise, defense& security network, financing.
- Troyes Institute of Biotechnologies: Technological transfer institute. Biological testing of concepts

Pherecydes-Pharma today (after only 3 years)

The first operational bio-defense and bio-security nanobiotech company in France.

- Company created on December 20, 2006, "Young Innovative Company" status.
- 1.15 Million € raised, financed by two ACE management funds
- 500 k € Innovation Program grant from French government.
- TAPE & Ab-ACCUS patents filed December 2006.
- International patents publications August 7, 2008 (TAPE: WO/2008/093010, Ab-ACCUS: WO/2008/093009).
- RIPh patent filed May 2009.
- Fast technological validation process: TAPE, 7 months; AB-ACCUS, 8 months; first validated Industrial Phages bank, June 2009.
- Rapid & Strong international recognition:
  - Ø The only European company invited to present at Biodetection Technologies in Atlanta, June 2008;
  - Ø Invited to present at the Edinburgh International Phages Conference, July 2008, and
  - Ø Invited to present at the 12th annual NSTI Nanotech Conference in Houston, May 2009.
- In discussion with a diagnostic company to produce a specific phage bank.
- New research program launched to address the toxins and virus issues.

3-Synthons Platform

The industrial biotech challenge

The major chemical industry "tsunami"

- Oil sourcing shortage forecasted.
- Oil cost increases difficult to be totally transferred to clients.
- Imperative necessity to turn towards renewable sourcing.

Industrial biotech challenges

- How to help the chemical industry to switch its sourcing from "fossil" carbon from oil to "green" carbon from plants & biomass.
- How to generate the new knowledge necessary to engineer micro-organisms metabolism for the synthesis of the required chemicals, and produce at industrial scale to supply the market at the costs and volumes required.

3-Synthons Platform

The major collaborative industrial biotech research platform

A collaborative complementary team

- A.R.D.: (Agro-industries Research & Development) Industrial Biotech research company (molecular biology, experimental pilot, scale-up, production). The leading structure of the sector, controlled by the major agricultural cooperatives in France.
- I.B.T.: Troyes Institute of Biotechnologies (Biochemistry, molecular biology, intellectual property). One of France's leading Technology Transfer Institutes.
- BMSystems: Predictive integrative Biology & metabolic engineering expertise.
- C.V.G.: Leading chemistry team for "green" sourcing research.

Three major European chemical companies proposing their molecules to the platform

- L'Oréal: World leader in the cosmetics market
- Rhodia: Major actor in the fine chemicals market (former Aventis fine chemicals structure)
- Arkema: Major actor in the chemistry market (former Total chemicals structure)

3-Synthons Platform

Three partners: One integrated platform

Team skills	*A.R.D.*	*BMSystems*	*IBT*
• State of the art survey, sourcing possibilities,	X		X
• Exploitation freedom	X		X
• CADI feasibility controls check		X	
• Micro-organisms selection	X	X	X
• First cost estimation	X	X	X
• Production of the initial CADI model		X	
• Modification protocols proposition:		X	X
• Option A: Optimization proposals without genetic modification	X	X	
• Option B: Genetic modifications proposals		X	
• Genetic modification realizations	X		X
• Experimental evaluation protocols design	X	X	
• Optimization of the interesting proposals		X	
• Experimentations	X		X
• Production of the CADI n+1 model and go to Option A or B (above)		X	
Experimental equipments available	*A.R.D.*	*BMSystems*	*IBT*
• CADI modeling tools (software, processes, methodology)		X	
• Molecular biology	X		X
• Microbiology	X		X
• Screening, clones selection, Genetic engineering	X		X
• Experimental validation:	X		
–Laboratory scale from 2l to 150l	X		
–Scale-up simple pilot up to 5 m3	X		
–Scale-up bio-production pilot from 10m3 to 40 m3	X		
–Works design, Industrial engineering	X		
–Estimation and industrial cost fine tuning	X		
–Molecules purification	X		

3-Synthons Platform

Synthons platform facts and figures

Synthons platform development (3 years)

- Creation of the leading French industrial biotech consortium mid 2006.
- State Competitive Cluster accreditation and financing end 2006.
- Kick-off meeting beginning 2007.
- Construction of the first CADI models mid 2007.
- Identification of new pathways of interest end 2007.
- Start of the construction of the first modified micro-organisms *beginning 2008*.
- Invited to present at the Europabio European forum for industrial biotech in September 2008.
- New potential industrial partners knocking at the door of the Synthons research program.

Synthons platform success factors

- The integrated platform was developed with the best professionals in their respective field.
- Each partner uses its resources to improve its proprietary tools and processes and not to develop competences a partner could provide.
- Each partner finances its own costs but shares with the relevant partners the future returns.
- Within only 3 years, its “intel inside” strategy allowed BMSystems to play a pivotal role in one of the leading platforms in the Industrial biotech market.

BM Systems

Efficient Systems Biology

How to maximize synergies between experimental and integrative biology.

This work received a Bio-IT World « Best industrial Practices » award from the Cambridge HealthTech Institute.

Bio-IT World Best Practices Award

from the Cambridge Healthtech Institute

- BMSystems in 2009, was the only European company to be granted a Bio-IT World Best Practices Award, *recognizing the outstanding contribution made by its innovative CADI™ model building approach* to a collaborative research program, with the CEA*-SEPIA research team, on neurodegenerative disorders.

- Besides leading to *the world's first /in-vivo/ validation of an in-silico model* describing the mechanisms associated with the pathogenesis and the progression of Creutzfeldt-Jakob disease (publication submitted),

- 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 pending). A spin off is under development.*

*CEA-SEPIA: Atomic Energy Council: Department of prion and atypical infections research. Coordinator of the excellence European network Neuroprion

1	BMSystems at a glance
2	CADI™ rational
3	Four operational case studies
3	BioXplain: new integrative platform

BioXplain

The Alliance for Integrative Biology

The First Open Platform for Iterative, Predictive and Integrative Biology

BMSystems enlarges its services proposal to allow the pharmaceutical industry's scientists and clinicians to harness existing models using classical "user friendly" & adapted tools to help them work.

Alliance: Co-founder in 2009 of BioXplain, the First Open Platform for Iterative, Predictive and Integrative Biology, with BioXpr and Kayentis complementary, cutting edge life sciences companies that decided to collaborate to address this challenge.

BIO XPR
Computer science & Biotechnology

BM Systems

kayentis
Technologie & Performance

BioXplain 2009

Let's go a step beyond

The pharmaceutical industry now requires its *scientists and clinicians* to harness & explain the non-linear mechanisms of health and diseases.

But they need *adapted systems and tools to help them work.*

Three complementary, cutting edge life sciences companies decided to collaborate to address this challenge:

ØBio-Modeling Systems: The inventor of CADI™ methodologies and tools, including the collaborative iterative validation process.

ØBioXpr: The most diversified provider of Software solutions built from a versatile library of modules to create real-added value from "OMICS" datasets.

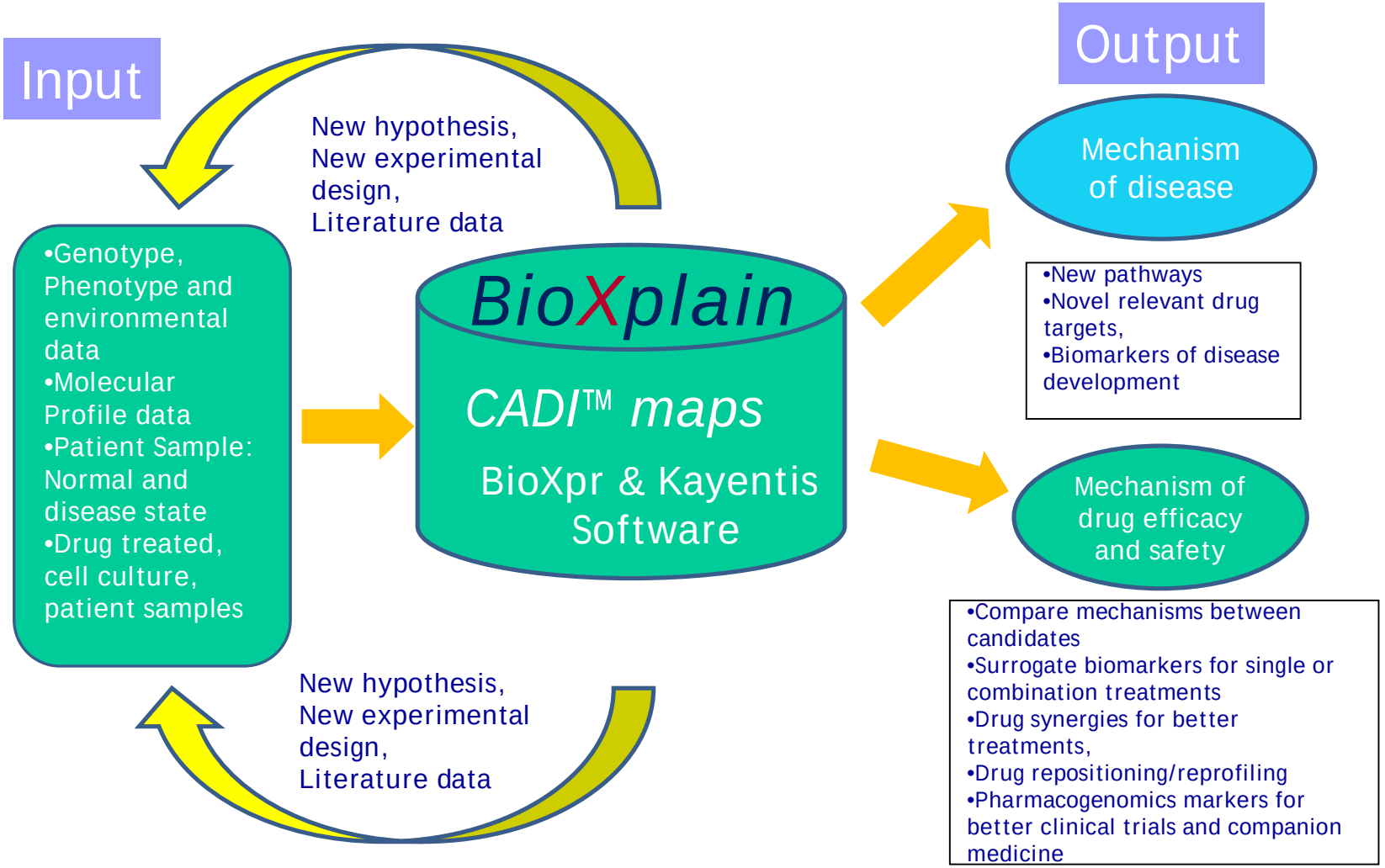
ØKayentis: The provider of the first "Digital Pen and Paper technology 2.0", the universal platform delivering "contextualized" information .

The first Open Platform for Iterative Predictive and Integrative Biology.

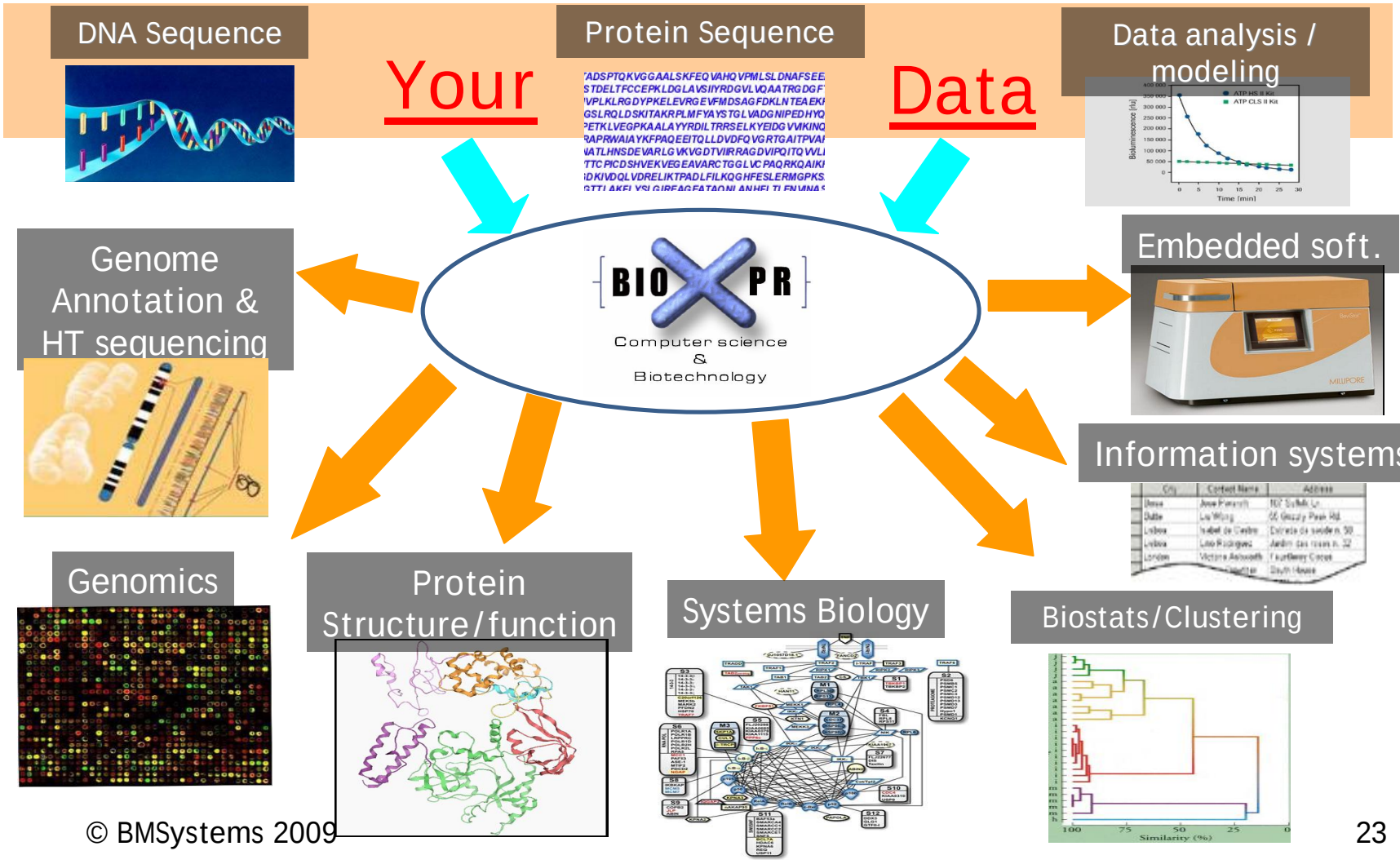
Now we can Bio-eXplain!

BioXplain

The first Open Platform for Iterative Predictive and Integrative Biology

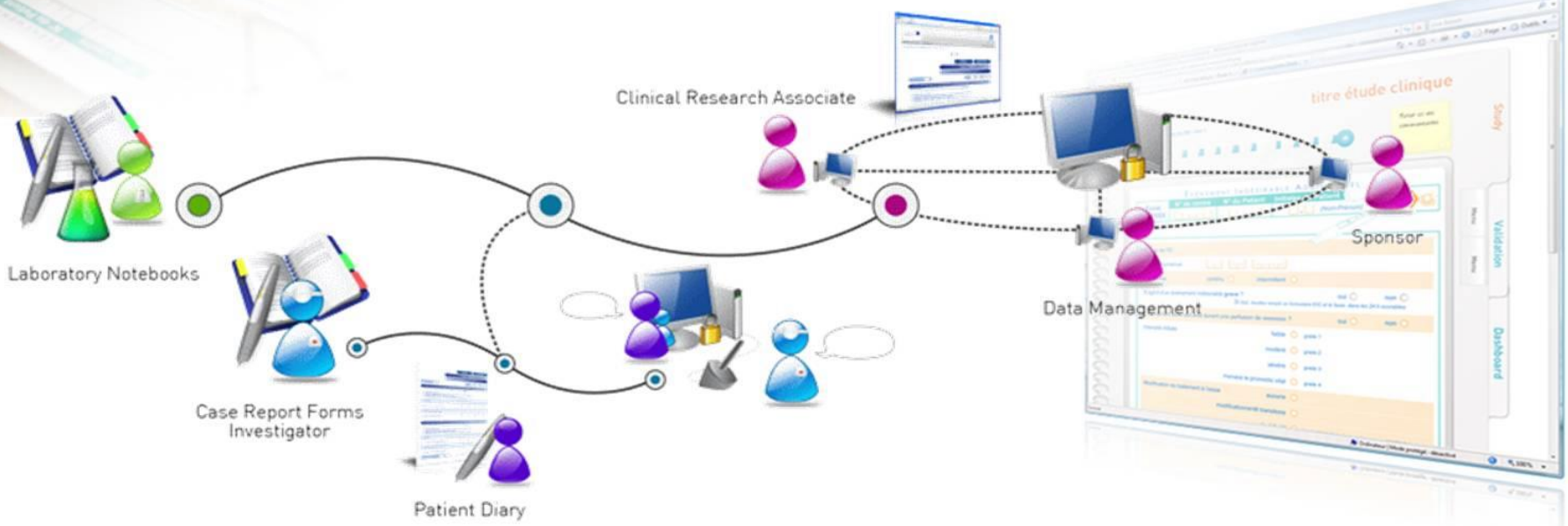


BioXpr: The Integrative Software & Services Platform



The «Digital Pen and Paper 2.0» universal solution platform

45 countries, 5 continents, 10 000 users
3 Millions pages captured from pharma, hospitals, Research centers , patients …



BioXplain

Three partners sharing same values and history

Company	Company specificities	Company information
BM Systems	• Created by senior scientists and engineers. • Inventor of CADI™ methodologies and tools • Research-based biotech company • *The company does not sell its technologies* nor access to its technologies • 1 spin-off Pherecydes-Pharma	• The R&D booster for life sciences discoveries, Member of BiO • Established : 2004 • 9 FTE based in France, 100 people working on BMSystems research programs • Active in the pharma, Industrial biotech and biosecurity businesses
BIOXPR Computer science & Biotechnology	• Created by senior scientists and biologists. • Collect, format, store, integrate, analyze and interpret from literature and experimental data ("OMICS", "environmental" data ,…) • Technology based on a library of powerful software modules that can be easily combined to create specific custom tools.	• A State of the Arts software solutions company. • Established 2003. • 10 people based in Namur Belgium. • Namur University Spin-off. • Numerous clients in the pharma, red and green biotech industries.
kayentis Technologie & Performance	• Created by senior scientists and clinicians • Collect, carry and share research, pre-clinical, clinical and post-marketing data using Digital Pen and Paper technology, DPP. • Full, un-biased and complete data capture in real-time ensure the completeness and integrity of the data.	• A software provider with strong growth • Established in 2004. • 40 staff based in France (Gif-sur-Yvette, Grenoble, Reims) and in the United States (Philadelphia). • More than 10 000 users in 44 countries on 5 continents.

BioXplain clients and partners

Diversified complementary network

Comparative R&D
Program value generation