Bio-Modeling Systems

The Mechanisms-Based Medicine Company

We changed the discovery paradigm to create novel medical meanings

from unreliable heterogeneous sources of data

CADI Discovery and 10 POCs Presentation

This is not a pitch presentation

This document is for download only

We added the necessary details and explanations in the slides to help the reader

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BMSystems Group at a glance

- 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%

Our 14 successes to date

Independently validated by our clients/partners

1. Mechanisms of pathogenesis & clinical progression of Creutzfeldt-Jakob Disease;
2. Mechanisms of anti-connexin agents for modulating the therapeutic effect of psychotropic and neurodegenerative drugs;
3. Cellular & metabolic mechanisms associated with chronic anxiety;
4. Mechanisms of N2O-mediated analgesia;
5. Anti-metastatic mechanisms of the RGD15 peptide;
6. Mechanisms of Ras-mediated breast cancer oncogenesis;
7. Mechanisms of breast cancer resistance to tamoxifen;
8. Regression mechanisms of the Müllerian duct;
9. Mechanisms of differential melanosome degradation;
10. Context-dependent functions of OA1 protein;
11. Context-dependent functions OCA2 protein;
12. Context-dependent functions SLC45A2 (MATP) protein;
13. Engineered bacteriophage banks and the control of multi-resistant pathogens;
14. Bioproduction and hemisynthesis of 18-methyl eicosanoic acid;

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): BMSystems' spin-off, (novel M.R. anti-bacterial nano-agents biotherapies), two indications: Multi-resistant Skin infections in Phase I/II. & osteo-articular infections.

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

Our solutions to address Industry critical issues

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.

CADI Discovery: The world’s first operational Computer Augmented Intelligence Platform

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

An experienced multidisciplinary founders' team

Dr. François Iris (PhD), Chairman, CSO-CTO - Heuristic modeling specialist

French-New-Zealander. Geneticist, physiologist & molecular biologist. **40 years of experience in life sciences in academia and industry** : Dept. of Medicine University of Otago, The Christchurch School of Medicine (NZ) Millennium Pharmaceuticals' (USA) collaborator of Nobel Laureate Prof. Jean Dausset. Inventor of CADI™ and of new technologies in molecular biology. MRC Overseas fellow, Member of H.U.G.O., Wellcome Trust; etc..

Manuel Gea, C.E.O & VP R&D I. S. – Operational Research & business development specialist

30 years of experience in IT and life sciences. Scientific Engineering Degree from Ecole Centrale Paris. Various experiences R&D and business from consumer goods Industry to cosmetics, biotechnology & pharmaceutical companies: Colgate-Palmolive McKinsey, Boehringer Ingelheim, HemispherX Biopharma, Pherecydes-Pharma, BMSystems; etc..

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

35 years of experience in clinical and medical research. Head of hospital's Hematology Dept. Former President of the Institute for Sports Medicine; IRMES - Institute for Research in bioMedecine and Epidemiology of Sport, etc..

Paul-Henri Lampe, CIO & Systems Integration Director - Systems Integration specialist

French-American. 20 years of experience in Systems integration in healthcare. Scientific Engineering Degree Ecole Centrale Paris. Former IBM Systems Integration Manager. Former Information Systems Manager, Hospital in Paris.

Pablo Santamaria, IT & Internet Systems Director - Internet technologies specialist

30 years of experience in Internet technologies and life sciences. Scientific Engineering Degree from Ecole Centrale Paris, Founder and President of the computing firm Formitel, Glaxo Pharma (Evreux, France)

Our collaborative R&D programs & their outputs

This list excludes our contractual research programs with our clients

CEA : "Creutzfeld-Jacob Disease CJD" World's first in vivo validation of the mechanisms of Creutzfeldt-Jakob disease pathogenesis & progression. *US, EU & French Awards;* Awards (2009 and 2010) . CEA SEPIA department.
Successfully completed; 1 publication.

CEA: CNS disorders. Collaborative research program that led to a novel therapeutic strategy for the treatment of psychiatric and neurological disorders. Copatent WO/2010/029131– Use of anti-connexin agents for modulating the therapeutic effect of psychotropic drugs. September, 2008 CEA/BMSystems,

Pherecydes-Pharma BMSystems' spin-off created in 2006, novel M.R. anti-bacterial nano-agents biotherapies 3 patents. Two indications: Multi-resistant Skin infections and osteo-articular infections.

Max Planck Institute (Munich): Project "Chronic Anxiety".
Successfully completed; 3 publications & a Reference Book "Biomarkers for Psychiatric disorders" chapter 19.

INSERM: 3 Projects "Tumoral Progression"; "Therapeutic Resistance"; "RGD 15 & Metastasis".
All 3 successfully completed, 3 publications.

CNRS: Project "Müllerian Regression" *Tissue differentiation*
Successfully completed, 1 publication.

Foundation FondaMental: Project "Bipolar Disorders & Schizophrenia".
Immuno-inflammatory hypothesis. On going, 1 publication pending

L'OREAL Arkema, Rhodia/Solvay ARD : "Synthons" Government funded feasibility Program at IAR cluster Industrial Biotech
Feasibility study Completed 16 molecules evaluated, 2 strains built, 1 program with 1 patent (industrial partner only)
- Skin Homeostasis: Reference book "Computational Biophysics of Skin" chapter 15 with Dr. Querleux (L'Oréal)

Centre of excellence in Epigenetics IISER Pune India: Project "Etiology & Epigenetic for metabolic disorders"
Etiology & Epigenetic for metabolic disorders, on going 1 publication pending

BMSystems' R&D programs pipeline

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

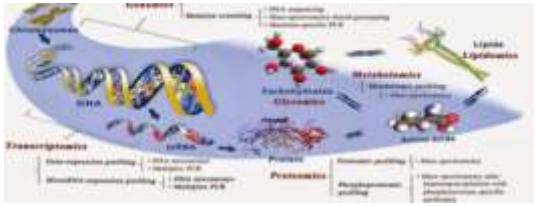
Program Domains	Partners	CADI™ compliance	CADI™ vers. 0	Ind. Valid.	Secret or Patent or Co-Patent/Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.
Infection-Immunology							
Microbiotas (skin, lung, gut, etc)							
Neuroloy/Psychiatry (CNS-PNS)							
Oncology							
Metabolism							
Dermatology/Cometics							
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	Open		high Interest				
Ebola virus ecology	Open						
Hepatitis C	Open						
Auto-immune global concept	Open	high Interest					
Microbiotas ecology, physiology & metabolic mechanisms	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		high Interest				
Alzheimer's Disease Causal Mechanisms	Open		high Interest				
Parkinson's Disease Therapy	Open		high Interest				
Psychiatric inflammatory mechanisms	FondaMental Foundation		high Interest				
Fibromyalgia, facial pain	Open		high Interest				
Pain (Central/Peripheral)	Open		high Interest				
Migraine Mechanisms	Open	high Interest					
Multiple Sclerosis Mechanisms	Open	high Interest					
Metabolic Disorders Therapy	Open		high Interest				
Etiology & Epigenetic in diabetes type 2	IISER Pune		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
Program Synthons	ARD-IBT-Rhodia			Completed			
Program Synthons	ARD-IBT-Arkema			Completed			
Human Glycosylation with Yeast	Open		high Interest				

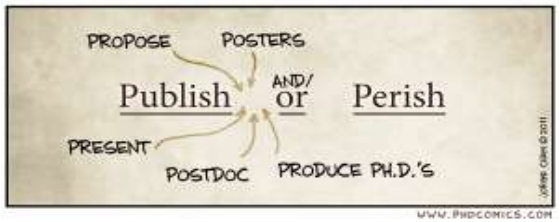
Why did we need to change the discovery paradigm?

1-The industry is under high pressure by too high failure rates and payers no more willing to pay premium therapies with very limited patient benefit.



2-The limits of the big Pharma model. Decades of investments in Omics technologies and Systems Biology programs produced few relevant results due to 3 "side effects" and a conceptual mistake: Life mechanisms are complex not complicated!

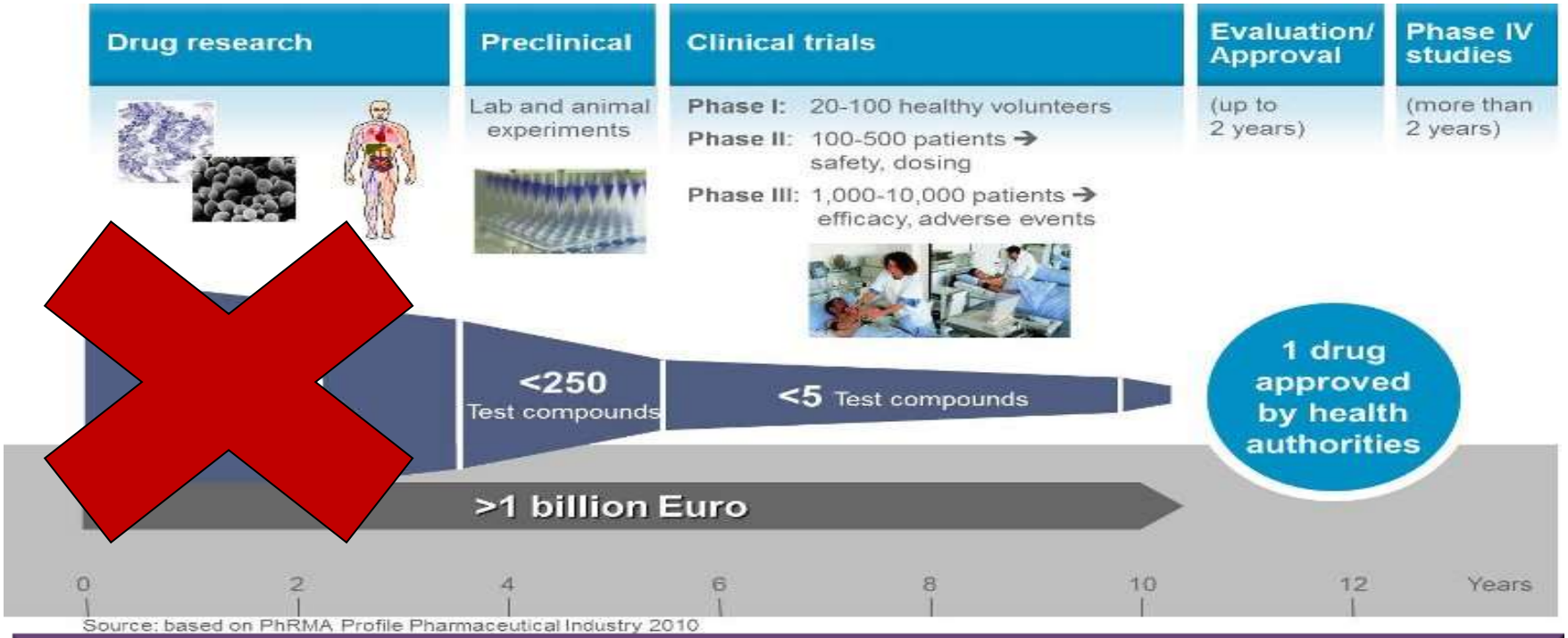
3-The "mirage" of Artificial Intelligence (AI) that MUST follow rules in a world where humans massively do not! Currently the "Garbage in garbage out" reality is not correctly treated by digital giants who consider life as only complicated.



4-The unreliability of scientific and clinical publications is increasing. "Many published research findings are false or exaggerated; an estimated 85% of research resources are wasted." (Stanford university), and the valuable negative results are not published.

So why despite massive investments in technology and IT, the success rate of the industry is still declining? The challenge is not a question of technologies only!

The limits of the Pharma drug discovery process



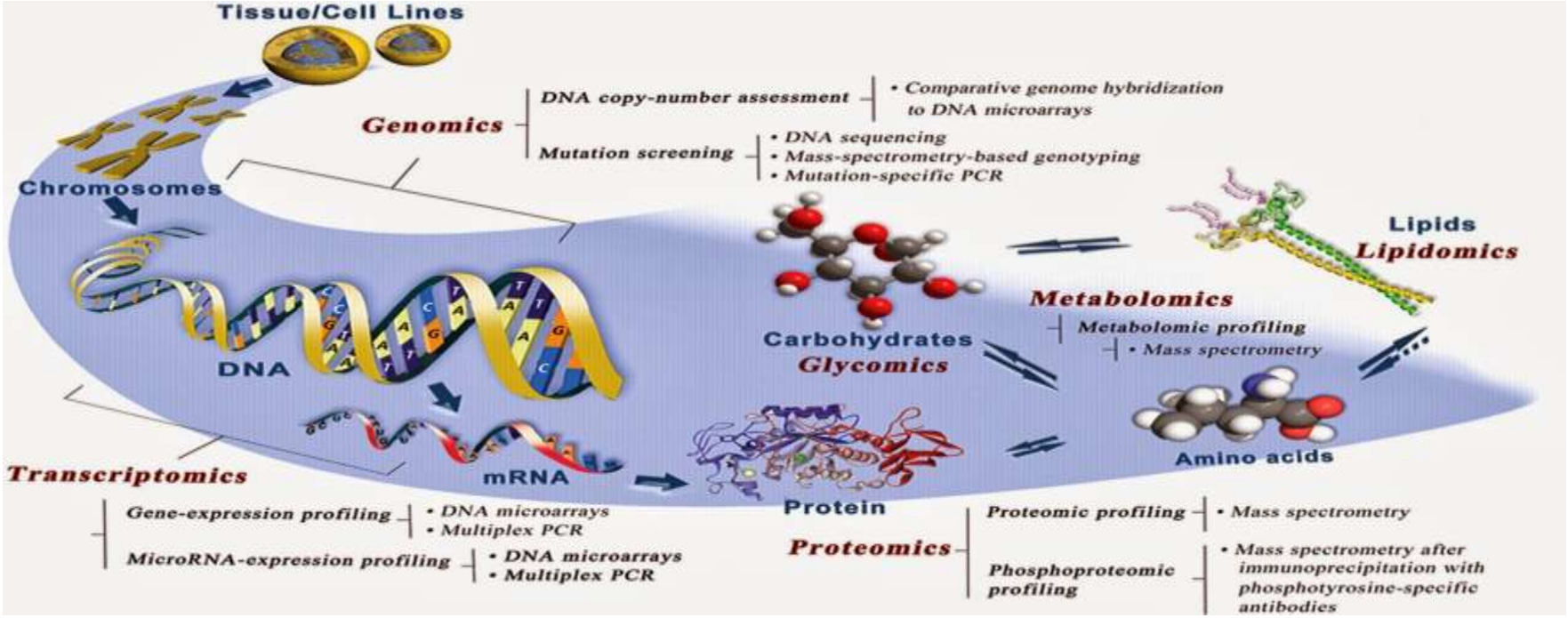
Source: based on PhRMA Profile Pharmaceutical Industry 2010

With a 90%-95% failure rate this Big Pharma R&D model focused on testing new patentable compounds for novel targets based on KOL concepts is not performant!

1. *Is 1 billion € per drug approved a fatality or a Discovery paradigm failure?*
2. *How are KOL concepts generated and evaluated?*
3. *Has Evidence based Medicine reached its limits with chronic complex human diseases?*
4. ***Mechanisms of action/function of a target, drug, gene, .. ARE NOT the mechanisms of a complex disease / disorder***
5. *Are the data produced and the scientific publications reliable and robust enough to feed algorithms that MUST follow rules?*

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 3 major "side effects" of the discovery of molecular biology, and the endless Omics story that began in the 70's



1. Medical research focused on patient's diseases became life sciences research driven by data, technologies and IT outputs.
2. The leadership switched from MDs & biologists to molecular & IT scientists.
3. The discovery issue: Tools, algorithms & concepts from Digital and Technologies giants, valid for complicated systems, cannot address complex systems such as life

The Differences of "Internet" and "Life sciences" worlds

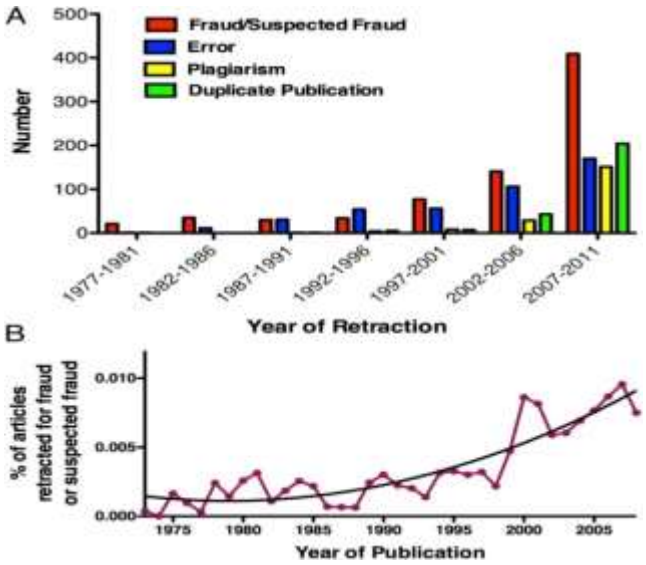
founding basements of the "big data" successes of the digital giants built for "the internet" world:	**Founding basements of Life Sciences R&D that may explain the so far unsuccessful attempts.**
1. The internet world built by humans is only very complicated not complex! 2. Personal data producers do not" know" what these digital giants do with their "big data". 3. Professional data producers do not have a real incentive to lie! 4. Algorithm's recommendations based on rules do not need to be fully validated because there is no vital consequence for the user. 5. Correlations found by "Big Data" Scientists are useful to optimize "personalized" marketing and business outputs. 6. The regulators are aware of the use of the data but the consequences are still limited in the short term.	1. Life's mechanisms are complex and clearly not well described. 2. Personal data producers are still not aware of their data usages and their business value. 3. Professional data producers globally have a strong incentive to lie due to the "publish or perish" dilemma. 4. Algorithms which MUST follow rules are unable to address a complex world where humans do not follow them. 5. Correlations generated by the Data Scientists are misleading and do not make the differences between causes and consequences of the diseases, which is the real issue. 6. The regulators are fully aware of the risks and possible irreversible consequences for patients (insurance issue, wrong diagnostic …)

The founding basements of the two worlds do not obey to the same rules

The unreliability of scientific and clinical publications is unacceptable and increasing

- 85% of research resources are wasted. Currently, many published research findings are false or exaggerated (John P. A. Ioannidis METRICS Institute Stanford University. Published in Plos medicine 2014)
- 90% of 53 studies were not reproducible. Amgen's scientists couldn't reproduce the findings of 53 "landmark" articles in cancer research (C. Glenn Begley ex Amgen. Published in Nature, 2012)
- 79% of 67 projects were not reproduced by Bayer's scientists trying to reproduce the findings of 67 target-validation projects in oncology, women's health, and cardiovascular medicine. (Florian Prinz, Thomas Schlange and Khusru Asadullah Reu Bayer. Published in Nature discovery 2011)

Number of retracted articles for specific causes by year of retraction

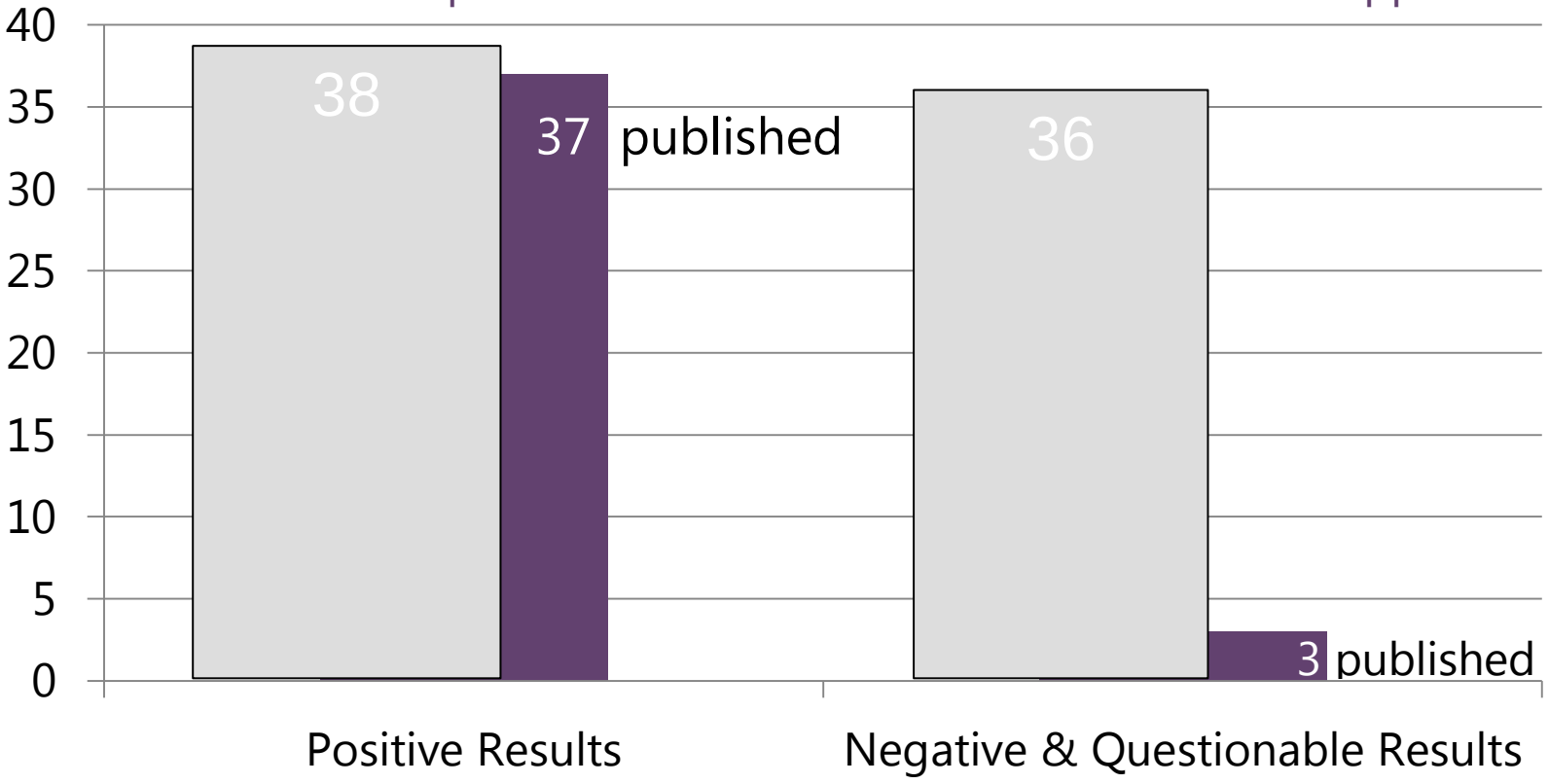


Ferric C. Fang et al. PNAS 2012;109:17028-17033

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

Publications do not represent the real knowledge especially when the results are negative

Based on 74 antidepressant clinical trials submitted to FDA for approval



clinical trials submitted to FDA compared to those published.
An enormous bias. A critically misleading issue if not contextualized

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy, Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D. New England Journal of Medicine 2008

The Life-modeling issue illustrated

1-If you dream of creating the first operational model of a bird…

2-… a "basic" living Complex System that not only flies…

3-Be sure to use the appropriate modeling concepts & tools. If you don't …

4-…you'll get a Complicated "Cartesian" system. It flies… But the major issue is that, for modelers, this is a bird!*

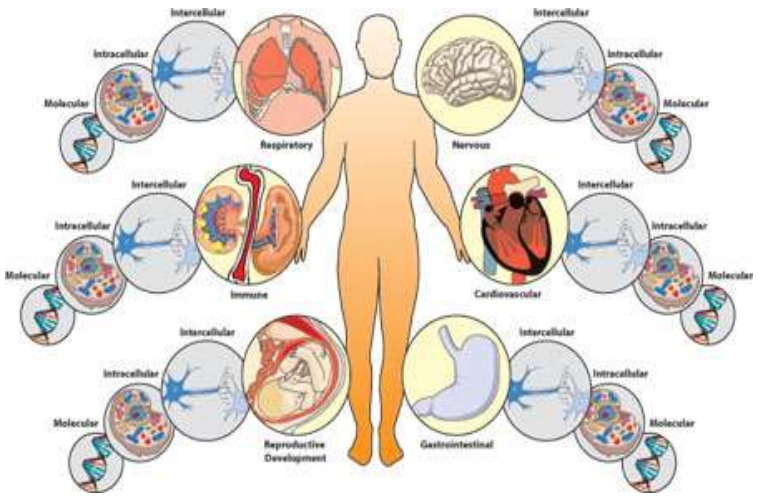
The challenge is clearly not a question of technologies only!
Even with expensive efforts, this model will never become a "bird"!

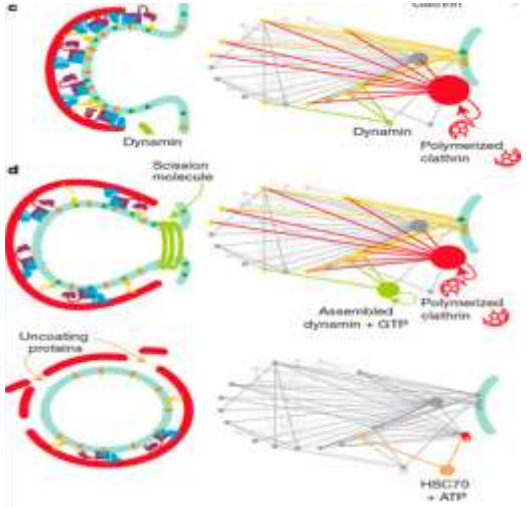
* Based on this model,1) when birds lay eggs, they explode; 2) the rear end of a bird is extremely hot when it flies; 3) a bird has three legs, etc.… You may think this stupid, but it is what is being done with systems biology.

What leads to Therapeutic Success?

The success of a therapeutic approach largely arises from the coherent manipulation of a physiological system as a whole

and not from that of a target in a molecular context.





Therefore, any given medical problem should be approached from a "systems medicine" standpoint

In this context, novel therapies can be combinations of drugs, nutriments, devices, e-health, etc….while targeted therapies belong to the "target in a molecular context" concept)
Do not forget: Mechanisms of action or function of a target, drug, gene, etc.. ARE NOT the mechanisms of a complex disease / disorder

The mechanisms-Based Medicine Principles

The Global Discovery stepwise approach places diagnostic / therapies / prevention solutions & validation processes ***in the right order***:

"1-DISEASE"	❑ *Redefine the definitions and descriptions of the physiopathology of the disease/disorder/syndrome with physiologists, clinicians and patients feedbacks.*
"2-MECHANISMS"	❑ *Discover the causal versus symptomatic mechanisms of the disease/disorder* ❑ *Mechanisms of action or function of a target, gene, etc.. ARE NOT the mechanisms of a complex disease / disorder. It is the same with the mechanisms of action for drugs,*
"3-BIOMARKERS"	❑ *Indirectly based on causal mechanisms, identify relevant biomarkers or specific biomarkers combination/signatures (biological, imagery, physical signals, etc....) that could measure defined mechanistic deregulations at different stages of disease/disorder progression.*
"4-TARGETS"	❑ *based on the causal mechanisms, identify what could be the best targets (not only one) to specifically address the causative deregulations.*
"5-SOLUTIONS"	❑ *We harness the mechanisms to propose the most practical solutions addressing the relevant mechanistic deregulations.* ❑ *It is important to notice that the proposed solutions, integrating diagnostics, therapies & patients follow-up, can be new drugs, combinations of existing drugs, nutriments, devices, e-health, disease prevention tools and services, etc*
"6-VALIDATION"	❑ *Global validation loop at each steps of the process: Integrate the results from e-R&D or e-Health experimentations into the validation process to improve global patient and disease/disorder follow-up.*

The Global Discovery stepwise approach places diagnostic / therapies / prevention solutions & validation processes in the right order:

CADI*™ Discovery Principles

"Mechanisms-Based Medicine Principle"

- *Answers the failures of the pharma Research Process & of the "KOL dominant thinking" by fostering the discovery & selection of novel concepts.*
- *Need to separate causal mechanisms understanding from solutions discovery.*
- *Discovery of lower risk & cost effective multi-technologies and integrated solutions.*

"Architectural Principle"

- *Mechanisms of life are complex, non-linear and integrative .*
- *Heuristic Modeling (the Architects) searches for satisfactory solutions to describe the mechanism of a poorly defined system.*
- *Mathematical Modeling (the Engineers) simulates, when correctly described, the dynamics of the system .*

"Negative Selection Principle"

- *"It is always possible to demonstrate a statement to be false" Karl Popper.1963.*
- *Despite the accumulation of evidence, such as Stanford University with METRICS institute, that 85% research results are false / exaggerated / useless, there still is extractable value.*
- *We eliminate what is impossible ("Negative Selection Process"), what remains may not be true but must be taken into consideration.*

"4 Steps Validation Principle"

- *Only mechanisms that resisted the "Negative Selection Process" are worth testing.*
- *Iterative validation process with the necessary scientists, clinicians, MDs, and patients.*
- *Construction of dedicated experimentations to evaluate the predictions of the model.*
- *Necessary bridge between R&D, clinic and real life.*

"Integrated Solutions Principle"

- *Can be combinations of drugs, diagnostics, medical devices, nutriments, e-health, cosmetics, for treatments, and prevention programs, etc. …*
- *Access to end user is strategic, and digital technologies are essentials to connect all the components of the solutions.*

CADI™ Discovery is the world's first and, to date, only operational platform combining the strengths of human and artificial intelligences in the right order.

*Computer Augmented Deductive Intelligence

CADI™ Discovery process phases

CADI™ Feasibility → CADI™ Construction → CADI™ Validation → CADI™ Exploitation

Phase Objective	• 3-5 weeks • Identify and define what is feasible among the projects submitted. • Define best CADI™ modeling strategy	• Step I : 1-4 months • Preliminary/controls: Simulation of the whole process on a data subset before launching Step II • Step II: 4-10 months • Construction of the CADI™ models version "0" for the complete program. • Novel hypotheses generation	• Timing to be defined • Validation of the CADI™ model using the 4 steps validation process • Model improvement. • Robust hypotheses and mechanisms proposal.	• Timing to be defined • Proposition of robust solutions to solve client's issues. • Answers to the 5 client's R&D and business issues. • Client's team exploits the Model.

Programs costs drivers

1. The company offers "one shot", "first refusal" or "post program exclusivity" deals.
2. In every case, the company offers exclusivity during the execution of the program.
3. The standard deal cost structure can be a combination of access fees, fees and success fees.
4. Domain of analysis, scope of the issues, complexity of the CADI™ model.
5. Availability and ease of access to relevant data.
6. Percentage of CADI™ knowledge database usage. In case of use of existing proprietary CADI™ programs, An additional access fees and success fees are required to compensate previous BMSystems' investments and lower risk for the clients.
7. Reactivity, readiness & willingness of the client/partner's team to contribute.

CADI™ Discovery Principles

CADI™ Discovery in details”

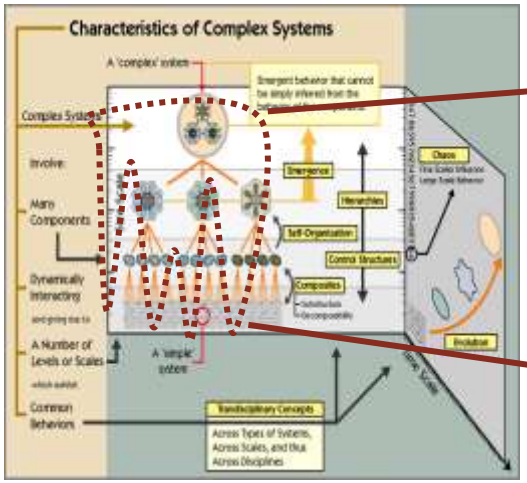
CADI*™models at a glance

Despite the accumulation of evidence, such as Stanford University with METRICS institute, that 85% research results are false or exaggerated or useless, there still is extractable value! Why?

"While the research findings in a publication may be false or exaggerated, this does not preclude some elements of the paper to be very useful, if you know how to identify and deal with them"

- 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 cross-talks within systems and between systems (cells types, organs, etc…) and the dynamics of pathological processes and/or pathological mechanisms vs. control.
- CADI™ models describe the mechanisms that cause the diseases, not only the consequences.

A complex system to study



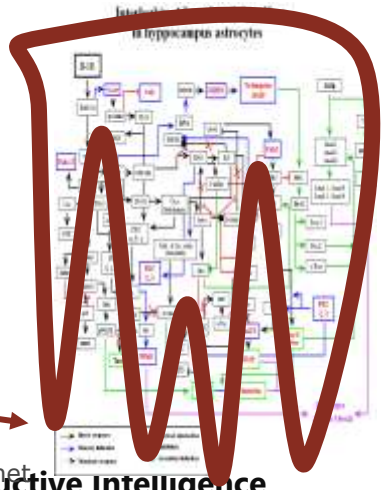
Scale / level

Different organs level

Different Cells level

Molecules level

A CADI™ model representing a multiple systems in a specific context



*Computer Assisted Deductive Integration and Computer Augmented Deductive Intelligence

Mathematical & Heuristic approaches can be complementary, provided they are harnessed in the proper order.

Mathematical approaches are of limited usefulness when applied to poorly defined multicellular physiological systems because they cannot efficiently reveal & define the functional states within such a system (cross-talks alterations, etc…).

→ *But heuristic approaches are very efficient at doing precisely this.*

Heuristic models are of limited usefulness when addressing the dynamics of defined complex physiological pathways structures and cross-talks because they are not open to mathematical manipulations.

→ *But Mathematical models are very efficient at doing precisely this.*

To efficiently address the translation of systems biology to clinical & medical interventions (dominated by patient's data heterogeneity and largely unstructured documents), ways to achieve synergy between Heuristic and Mathematical approaches can be effectively designed.

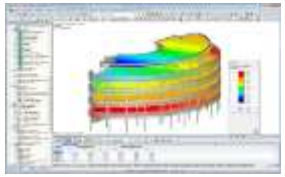
We apply first Heuristic modeling and then propose the outputs for Mathematical modeling when the system is correctly described

The Architectural Principle

- Heuristic Modeling (the Architects) searches for satisfactory solutions to describe the mechanism of a poorly defined system.




- Mathematical Modeling (the Engineers) simulates, when correctly described, the dynamic of the system.




- The net result when they collaborate in the right order



Far from being incompatible, these two different approaches can be complementary.

Negative selection Principle

The reasons why we need to change the conceptual paradigm

- "Mathematical approaches are based on "positive selection": it is assumed that every data-set/statement is actually valid or *ranked following universally obeyed rules*.
- Yet, "an estimated 85% of current published research findings are false or exaggerated" J.P.A Joannidis, 2014 Stanford University [PLoS Med. 11(10): e1001747]; F. Prinz et al., 2011 [Nat Rev Drug Discov. 10 (9):712] . *See other evidences at the end of the document.*
- The "Garbage in Garbage out" of IT technologies cannot change this statement
- "While it is not always possible to demonstrate that a statement is true, it is always possible to demonstrate it to be false" Karl Popper, 1963.
- Following this statement, positive selection principle cannot be used to generate true hypotheses
- But it is possible to use these information to demonstrate that an hypothesis is wrong.

How to identify what is NOT false and/or exaggerated?

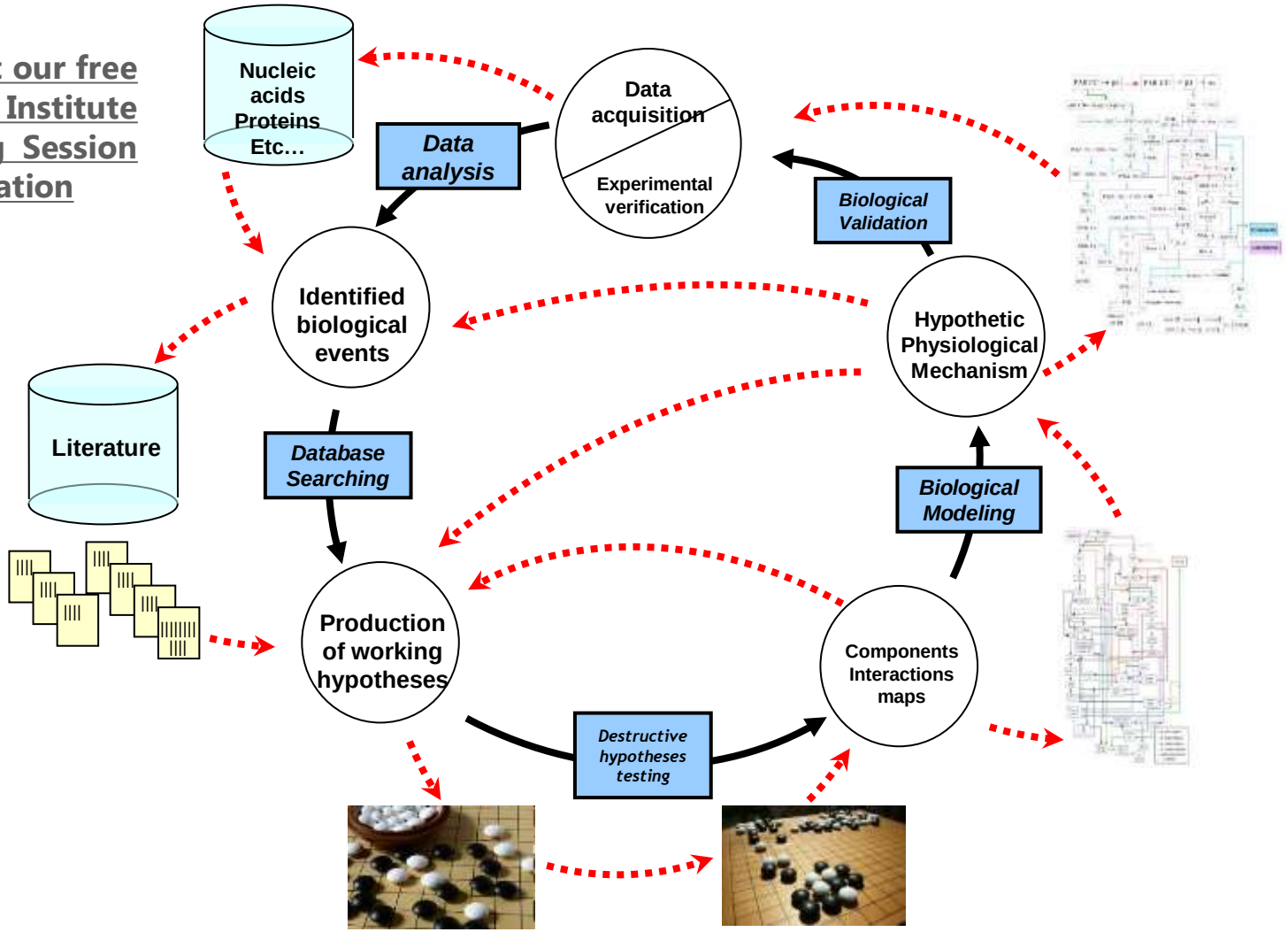
- By doing every thing possible to destroy working hypotheses!
- Only hypotheses that resist destruction are worth retaining.
- And, in any case, remains the experimental validation

Hence, what is demonstrated "False" can now be used to discover what could be "True". We eliminate what is impossible, the remaining questions marks can be addressed during experimental validation phase.

The CADI™ Integration workflow

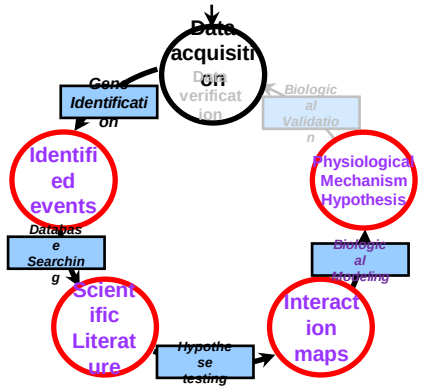
More details in the Full Presentation with CADI full Description, publications and the 10 CADI™ programs & POCS

Request our free Cochin Institute Training Session Presentation



The CADI™ Integration & Modeling Process

More details in the Full Presentation with CADI full Description, publications and the 10 CADI™ programs & POCS

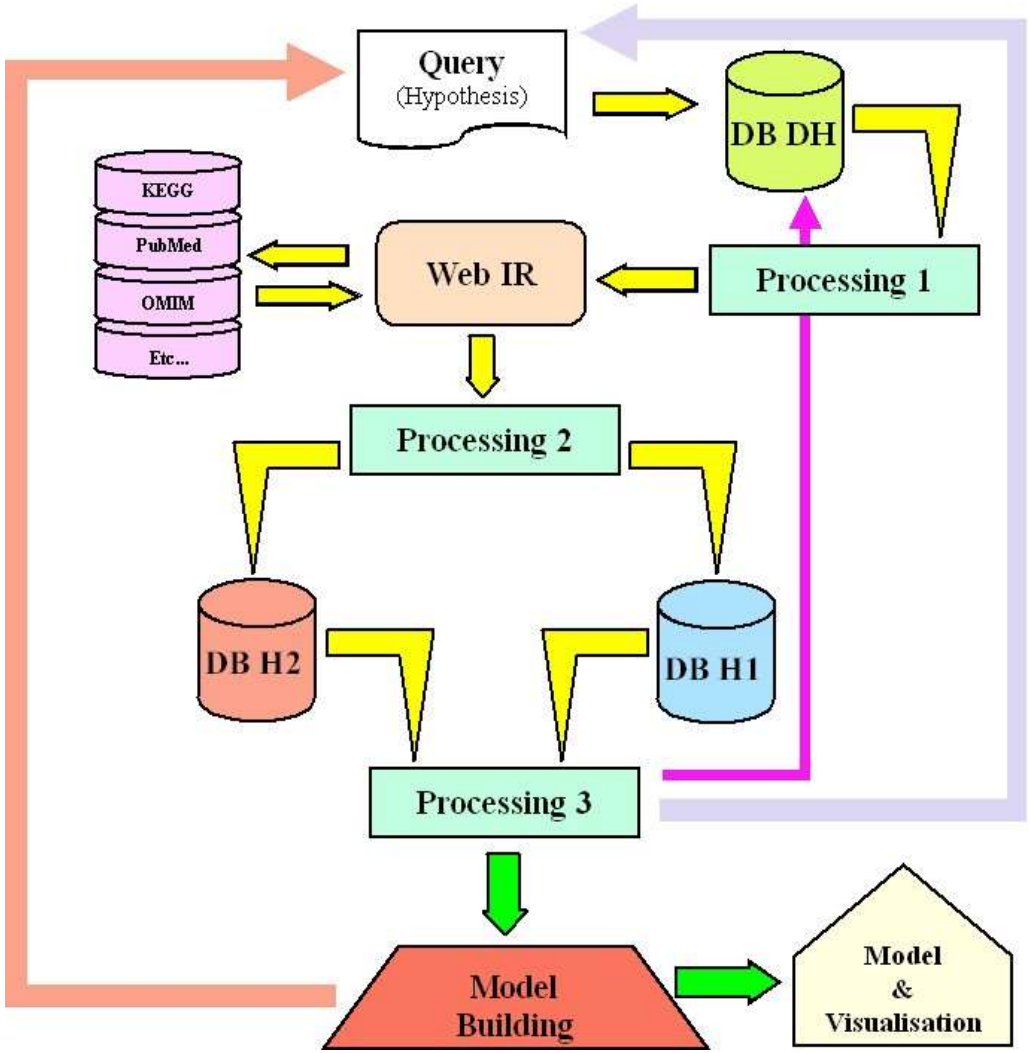


This iterative process does three things:

- It largely resolves the coherence issues attached to the classical approach;

- It reveals hitherto unknown mechanisms/processes, and

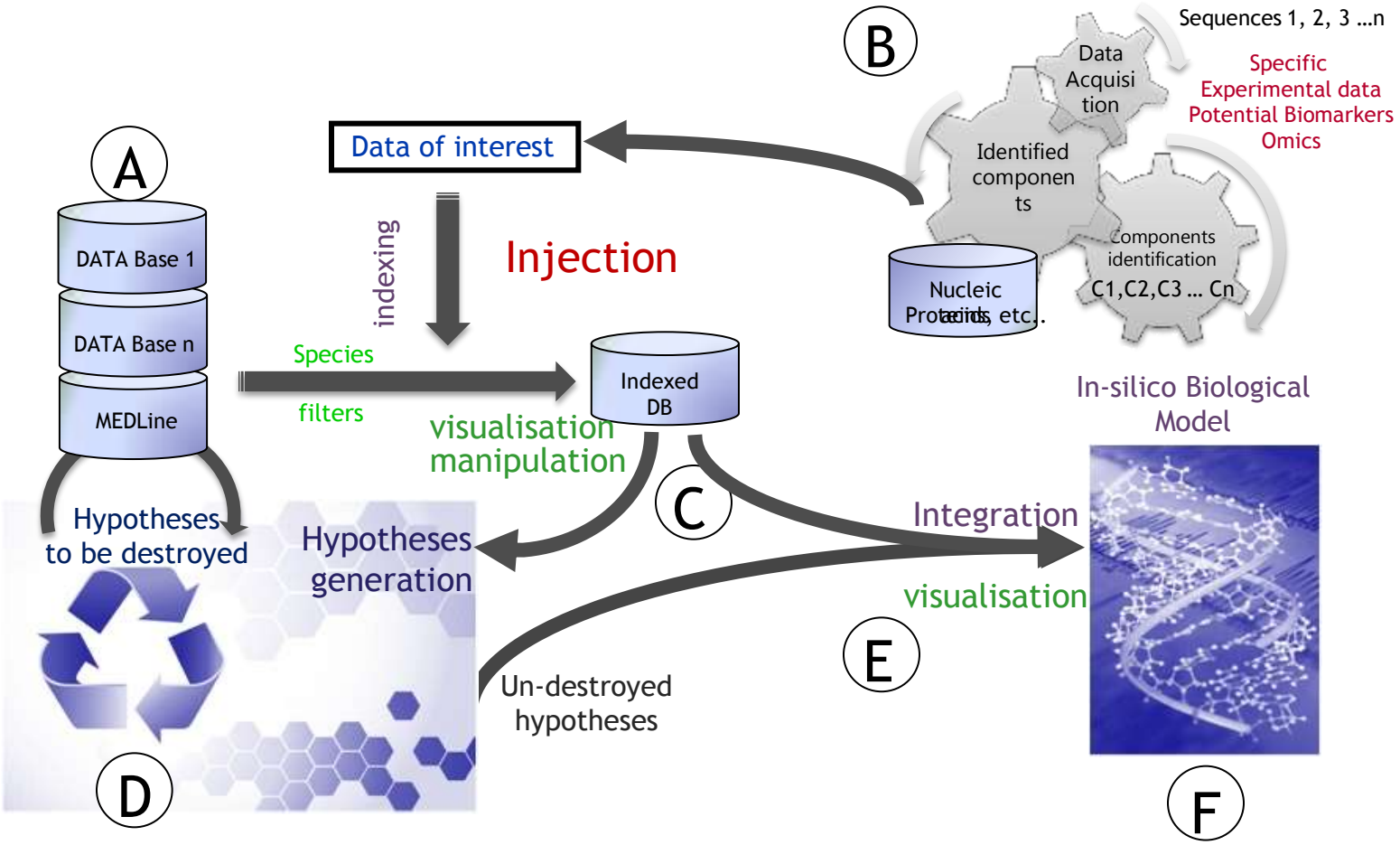
- It allows the translation of systems biology to clinical & medical interventions.



CADI™ Discovery IT structure

The first operational application of the negative selection concept

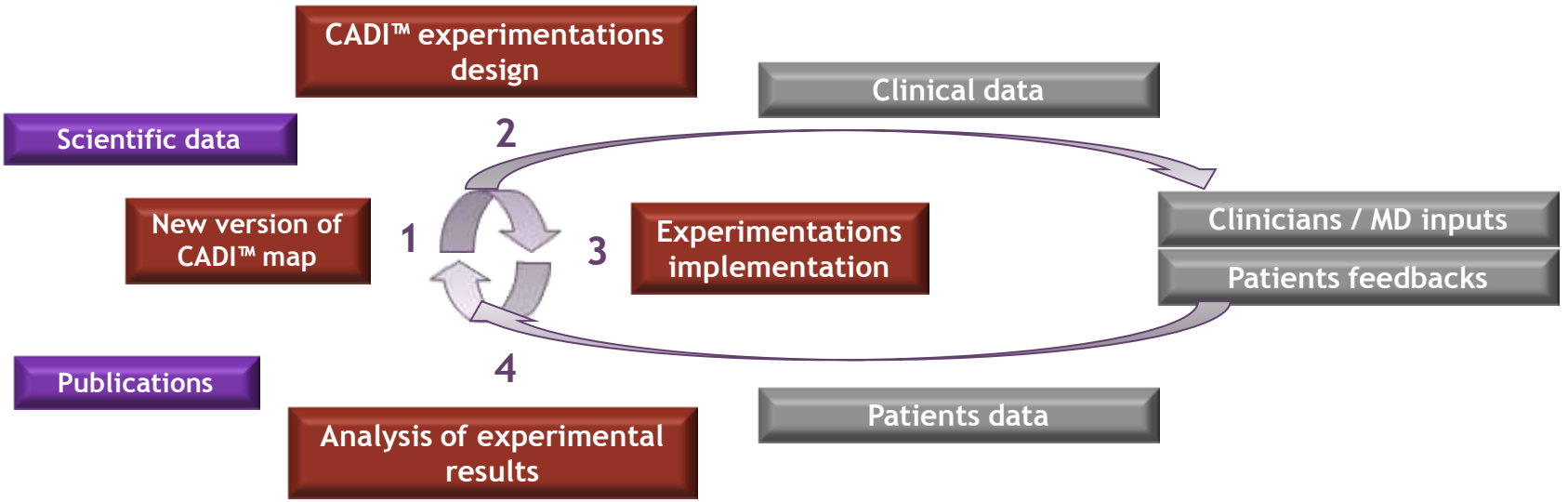
Download our scientific presentation from our website to understand CADI principles and the Differences & Complementarities between "Heuristic" and "Mathematical" approaches - Concepts & Examples



CADI™ Discovery Global validation Principle

exploiting Smart Data (contextualized, with patients based lines, related to mechanisms data)

CADI™ Discovery from bench to bed to real patient health processes



Information technologies

Data acquisition, Simulation, collaborative, data Storage, Big Data, Smart Data, Mobility

CADI™ Smart Data (contextualized, with patients based lines, related to mechanisms)

BMSystems' history

1989 -1993 Dr. Iris is Group Leader at the CEPH in Paris

- The CEPH is a Research Institute founded and lead by Nobel laureate Prof. Jean Dausset.
- He develops methods for high-throughput (HT) sequencing & data integration.
- ➢ *He realizes that the links between genome & biological processes are non-linear.*
- One gene = several proteins = multiple interactions = many context-dependent functions.

1993 -1996 Dr. Iris creates & leads Millennium Pharmaceuticals' (USA) HT Sequencing Unit

- He undertakes the first attempts to carry-out physiological modeling via large scale data integration.
- He invents & develops the basic tools and methods required for Integrative Biology.
- Successful completion of two models, leading to the discovery of the UCP2 and EST1 genes and their roles in obesity and hyperglycemia.
- ➢ *He realizes that since published information is: incomplete (to an unknown extent), slanted (to an unknown extent), and often incorrect (to an unknown extent) methodologies to access/generate complementary unbiased information are required.*

1996-2001 - Dr. Iris is co-founder and C.S.O. of ValiGen SA in Paris

- He invents and develops the computerized data gathering, data mining, clustering and integration tools & technologies necessary for the industrial development of Integrative Biology / Systems Biology (European "Eureka" grant: 18.6 M Euros).
- He finalizes the Bio-Graph™ analytical platform based on the "positive selection" concept.
- He develops the Tamoxifen Resistance model with Bio-Graph™.
- ➢ *He identifies the limitations of this analytical platform that is still the founding concepts of classical systems biology.*

1999-2001 - Dr. Iris meets Mr. M.Gea and Dr. G.Dine

- Dr. Iris meets M.Gea (Pharma and IT) and Prof. G.Dine (MD and biologist), founding members of Centrale-Santé
- ➢ *He decides to abandon the Bio-Graph™ platform* and starts working on a *second Generation analytical platform (CADI™) based and on the negative selection concept* to address the recurrent causes of failures in the "dominant thinking" systems biology programs: the issues of "life mechanisms complexity" and publications unreliability.
- He starts to work on the first version of the Creutzfeldt-Jakob Disease model.

2002-2003 - Dr. Iris, M. Gea and Dr. Dine initiate the BMSystems project

- ➢ *Creation of the world's first "Mechanisms-based Medicine company.* Paul-Henri Lampe, and Pablo Santamaria, IT experts and members of Centrale-Santé Think Tank, decide to join the project.
- ➢ *Development by the multi-disciplinary team of the CADI™ analytical platform.*
- Four new models completed (FGF4-driven fibroblast differentiation, hypercholesterolemia, Chronic Fatigue Syndrome, Creutzfeldt Jakob disease).

2004 - The company is created and starts business operations with a first pharma contract.

CADI™ Discovery Concept and 10 POCs Presentation

Download the presentation for full details

1. Case study A; Domain: CNS neurology and Psychiatry. Collaborative CADI™ program with CEA life sciences (*1 patent, 1 publication 1 out-license),*
2. Case study B; Domain: Metabolism: First disease application: Parkinson's disease. Collaborative CADI™ program (*novel combined therapy proposed for POC in humans*).
3. Case study C; Domain: Infectious diseases. Collaborative CADI™ program with Pherecydes-Pharma (our first spin-off) (*3 patents, 1 publication, 1 BMSystems' spin-off*).
4. Case study D; Domain: Industrial biotech. Collaborative CADI™ program with ARD, IBT, CVG, L'Oréal, Rhodia, Arkema (*1 patent filed by an industrial partner*).
5. Case study E: Domain: Synthetic biology: Yeast-Based Human-Glycoylation Project CADI v0 produced
6. Case study F; Domain: Oncology. Collaborative CADI™ program with Inserm unit 553 (*2 publications, Novel strategy proposed for R&D collaboration*)
7. Case study G; Domain: Dermatology. Contractual program CADI™ for a client (*8 new targets, cosmetic company confidential*).
8. Case study H; Domain: Cosmetics. Collaborative CADI™ program) *(synergistic low allergy mechanisms identified for safety issues).*
9. Case study I; Domain: Type 2 diabetes. Contractual CADI™ program for a client (*NO GO decision for safety issue, pharma company, confidential*).
10. Case study J; Domain: Tissue differentiation/embryogenesis. Collaborative CADI™ program with CNRS (*1 publication*).

A new paradigm qualified for industrial use

BMSystems' CADI™ publications to date

CADI™ Models published in prestigious peer-reviewed journals: (click on the grey links to get the pdf)

- 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.

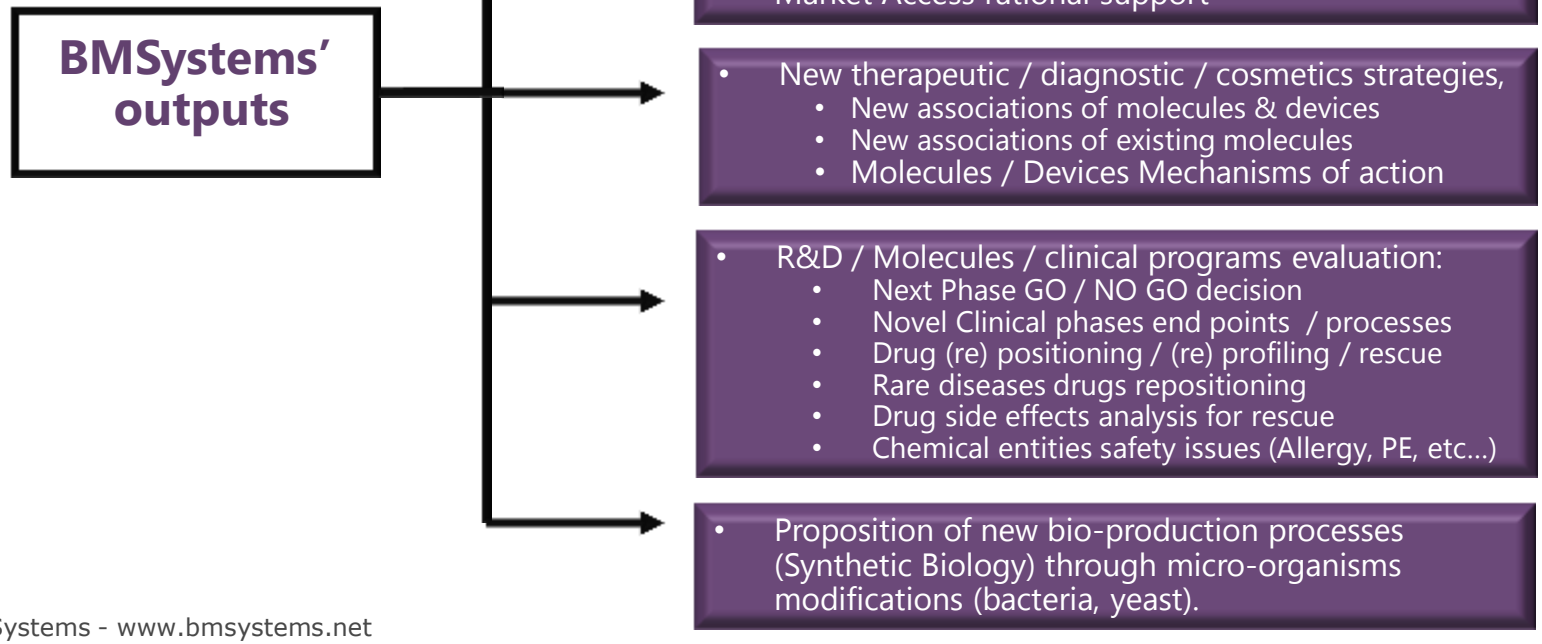
Collaboration to scientific reference books:

- 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

BMSystems' detailed answers to clients/partners issues

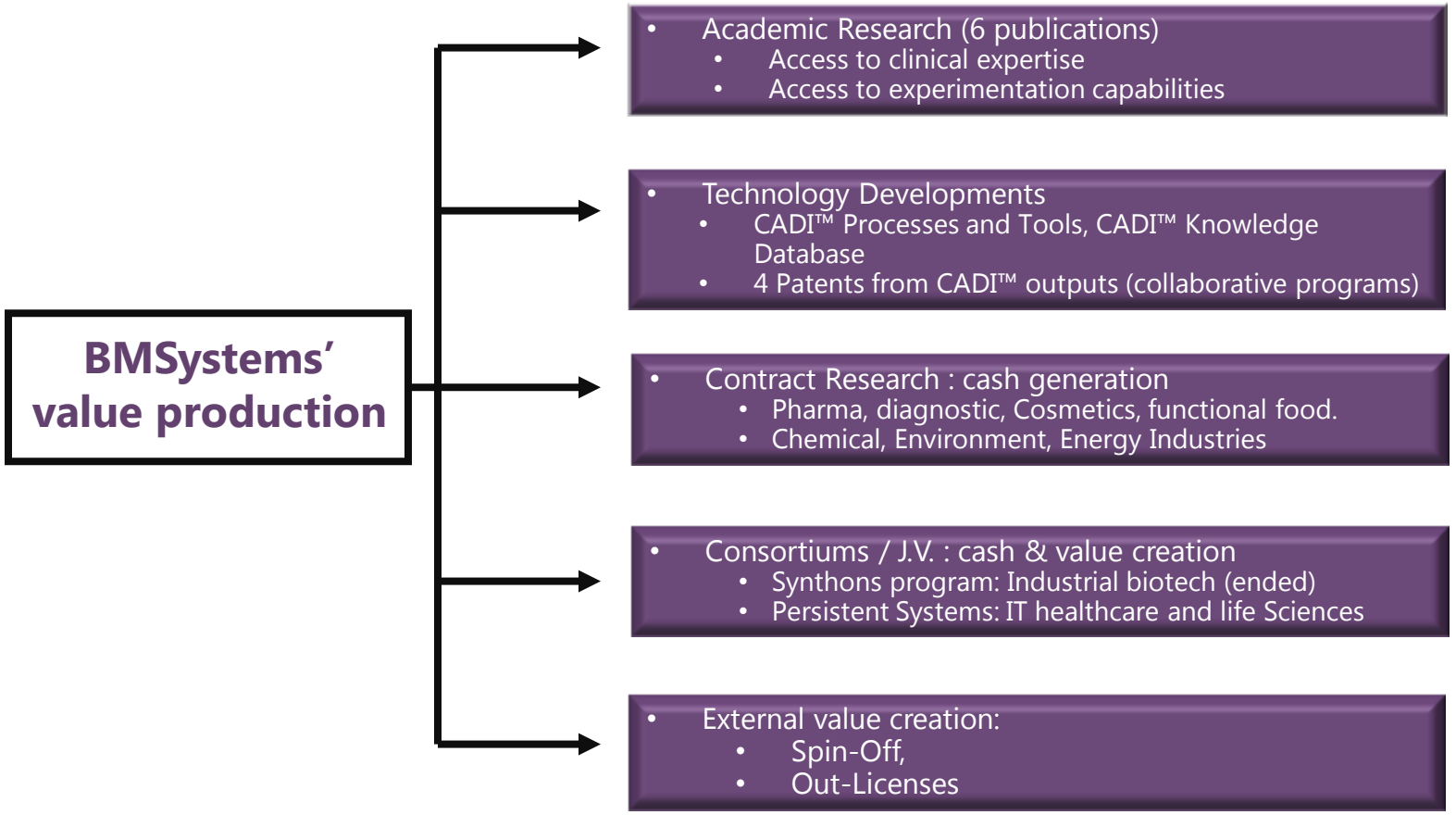
Reduce time to result, improve success rate and reduce development costs to address specific markets:

biomedical, diagnostic, Pharma, cosmetics, nutrition, food, chemistry, environment, energy.



BMSystems' original dual business model

that generates cash through contractual deals & patented novel diagnostic/therapies/prevention solutions through collaborative R&D programs.



Why do we need to change the dominant discovery paradigm? (supporting documents: click on the links for details)

- The *industry is under critical pressure* ***due*** to a too high failure rate and payers no longer willing to pay premium prices.
- The Pharma industry has for decades invested in Omics data production, IT technologies and Systems Biology programs for remarkably few relevant results.
- The consequences of life's mechanisms being complex, as opposed to complicated, are dramatically underestimated by data-treatment scientists and their algorithms.
- "Currently, many published research findings are false or exaggerated, an estimated 85% of research resources are wasted". (John P.A. Ioannidis, MD, DSc PLOS medicine METRICS, Stanford University).
- The unreliability of scientific and clinical publications used by these algorithms is strongly increasing.
- Negative experimental results are seldom published, generating an enormous bias.
- The "garbage in, garbage out" reality demonstrates that a wrong hypothesis, even if generated or treated by the best Digital and IT technologies, remains a wrong hypothesis
- Mathematical models are remarkable validation/fine-tuning tools when applied to well defined processes. They are inadequate discovery tools when applied to multicellular processes poorly understood and/or created form unreliability information.

R&D managers aware of these critical & underestimated issues should ask their suppliers to prove that their operational solutions are really able to address these issues.

CADI™ Discovery

The 10 Programs in details

BMSystems' 10 CADI™ programs & POCs

Selected POCs and their outputs of CADI™ Programs (all details in full presentation):

1. Case study A; Domain: CNS neurology and Psychiatry. Collaborative CADI™ program with CEA life sciences (*1 patent, 1 publication, 1 out license*).
2. Case study B; Domain: Metabolism: First disease application: Parkinson's disease. Collaborative CADI™ program (*novel combined therapy proposed for POC in humans*).
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A new paradigm qualified for industrial use

A: Program objectives and achievements

Domain: Central Nervous Systems. Two Collaborative CADI™ programs

- Context: 2004; Creutzfeldt-Jakob Disease (CJD) is a complex & poorly understood neurodegenerative disease with equivalent animal and human forms.
- Request: Conduct the world's first systems biology program to be validated in-vivo. Understanding and validating the in vivo mechanisms of CJD pathogenesis & progression.

Collaborative work done & rewards, and CEA's start-up creation:

- ***Disease understanding***: CJD is not a neurological disease stricto sensu. It is a disease that primarily affects astrocytes structures and functions which, over time, lethally affects healthy glial & neuronal cells through « bystander effects », leading to widespread CNS disorganization (spongiosis) and functional failure.
- New mechanism Discovery: The program identified the connexins (gap junctions), responsible for neuro-glial communication, as major players in the disease process. It also provided an understanding of key mechanisms associated with psychiatric disorders.
- This word's first was the only European program to receive, in 2009, the prestigious Bio-IT World Best practice Award from the Cambridge Healthtech Institute.
- It also was selected in 2010 as 1 of the 3 pan-European « state of the art examples of systems biology approaches of benefit to medicine » by the European Commission's DG Research, Directorate of Health.

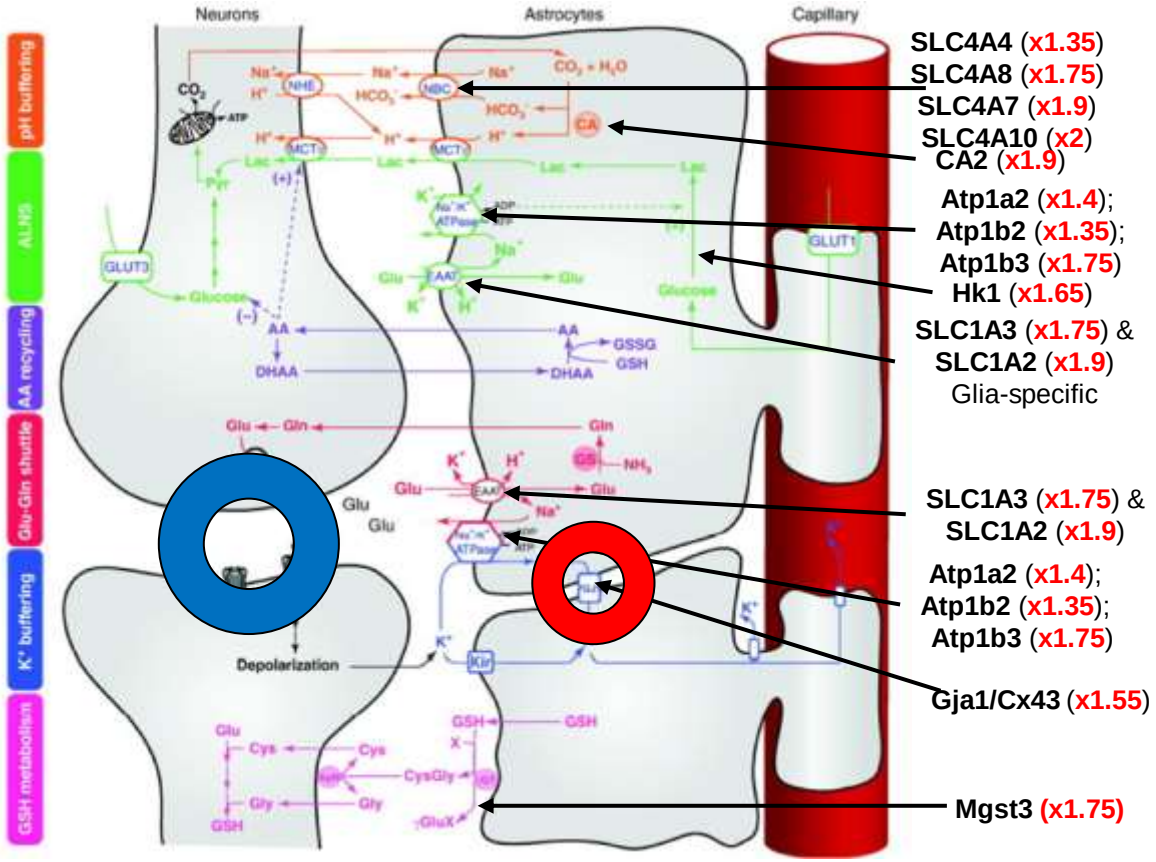
- *This collaborative research between the SEPIA laboratory from the François Jacob Institute of biology par of CEA and Bio-Modeling Systems in the field of prion diseases led to the filing of the co-owned patent WO201029131 (Use of anti-connexin agents for modulating the therapeutic effect of psychotropic drugs). describing a novel therapeutic strategy to treat psychiatric and neurological disorders. This patent is licensed exclusively on a worldwide basis to Theranexus, a CEA spin-off company.*

Theranexus Therapeutic Boosters

Complete BMSystems' "Mechanism-based Medicine" science and business proof of concept

Multiple Systems: clearly the brain can't be reduced to its neurons only!

Simulating the neurons only will never explain the Creutzfeldt-Jakob Disease*,

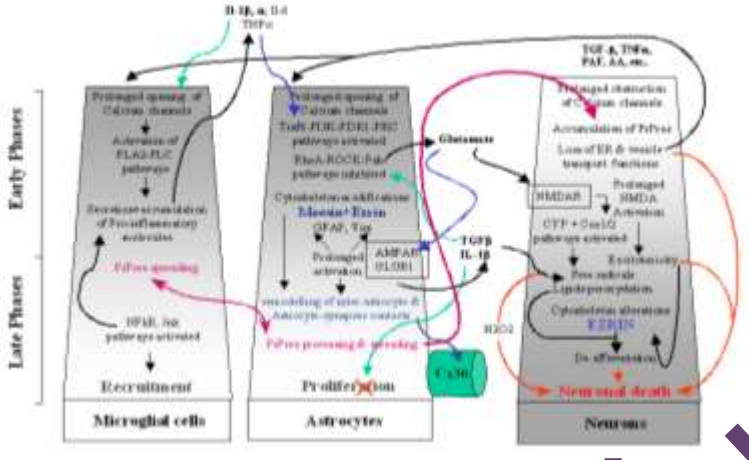


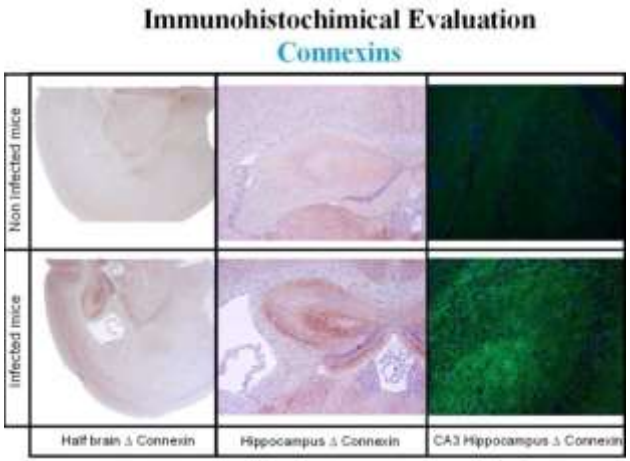
In Chronic Anxiety: Reinforcement (x A.XX) of astroglial-dependent metabolic maintenance of neurotransmission

* 2012, CNS Neurodegenerative & Psychiatry: PharmacoPsychiatry;.

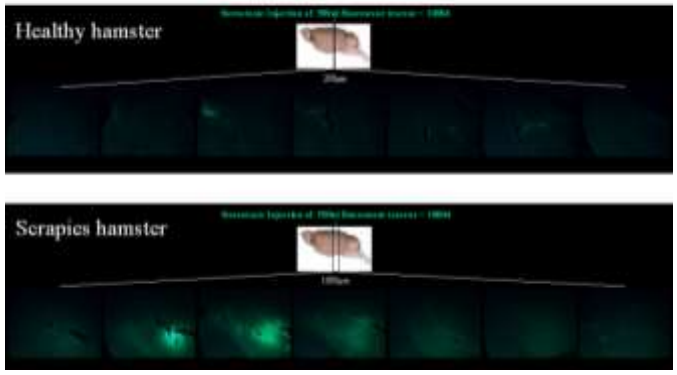
A:The heuristic CJD model finalized in early 2008.

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

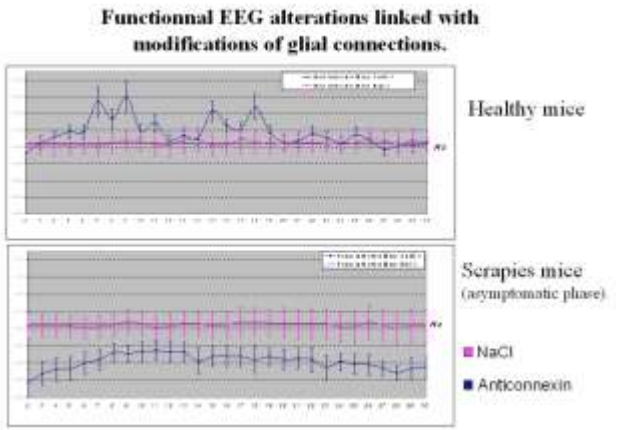




Functional modifications of glial connexions



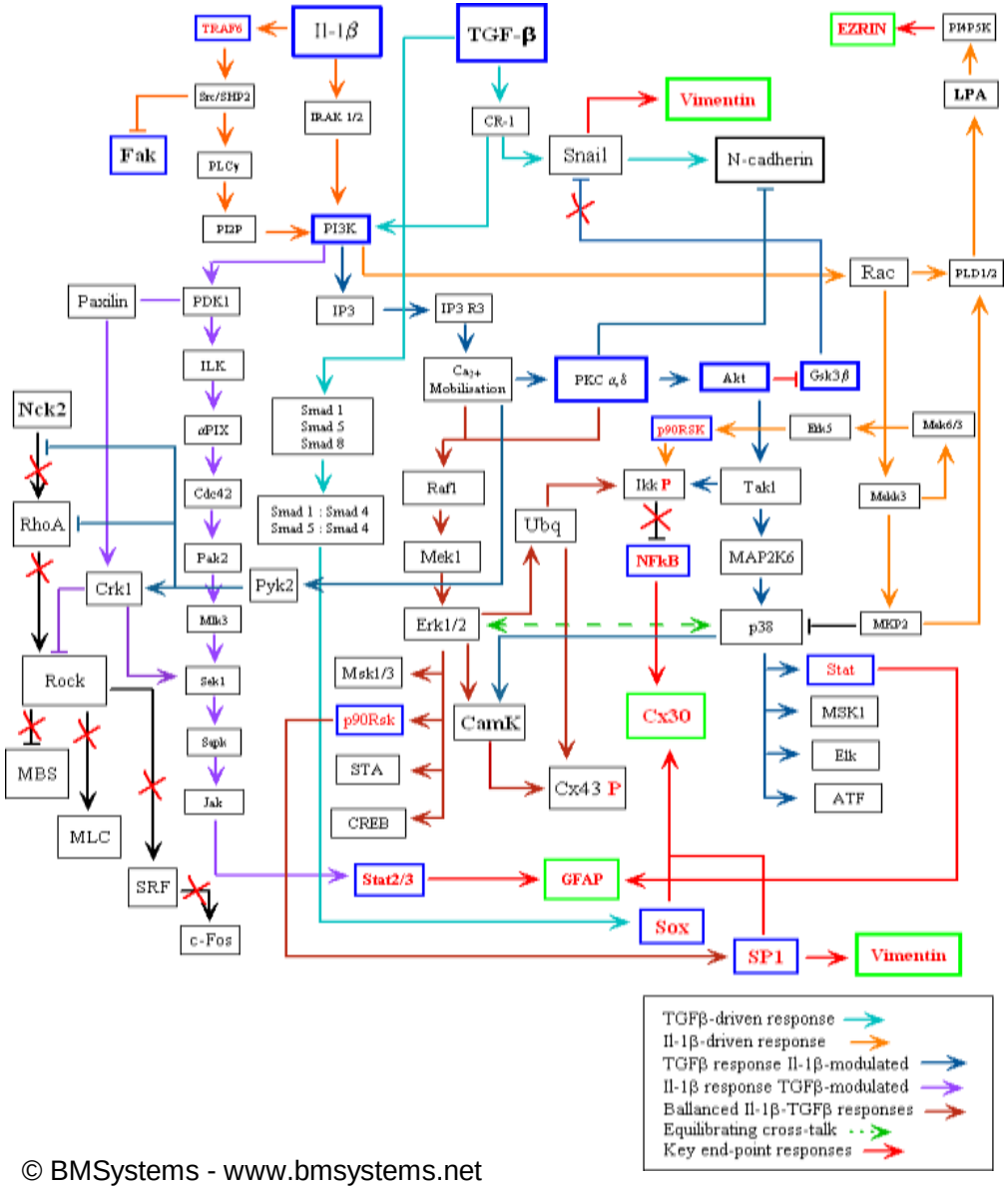
Source: BMSystems & CEA



A: The main driving mechanism

IL-1β & TGF-β-mediated signalling in hippocampus astrocytes

The pathways through which chronic neuronal stress signalling and concurrent glial pro-inflammatory responses lead to reactive astrocyte activation (GFAP + Vim) associated with cytoskeleton reorganisation (ezrin). This leads to a major switch in Cx targeting & distribution, resulting in the formation of a syncytium with massively altered diffusive properties and neurotrophic functions.

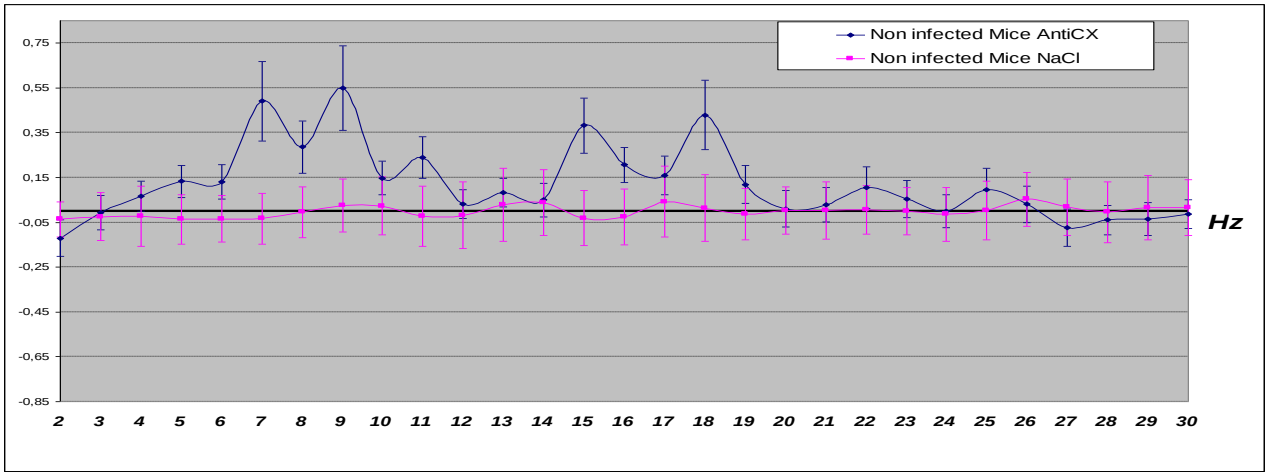


A:The CJD pathological process deciphered.

1. PrPres of external origin interact with neuronal PrPc, producing endogenous PrPres;
2. PrPres fragments (endogenous origin) induce auto-infection waves of ever increasing amplitude, leading to internal neuronal dysfunction, chronic neuronal stress signalling & local microglial activation;
3. The activated microglia secretes IL-1b, inducing TGF-b secretion in astrocytes;
4. Paracrine and autocrine responses of astrocytes to IL-1b & TGF-b induces local astrocytes activation, together with a radical shift in Cx expression and trafficking;
5. This induces the local constitution of a 3D activated astrocyte sheets within which Ca^{2+} waves propagate in an aberrant manner, leading to local failure of neuro-supportive activities;
6. Distant activation foci slowly merge, forming a continuously growing activated astrocyte sheet constitutively secreting pro-inflammatory and cytotoxic molecules while disseminating the infective agent (slow process);
7. Ever more uncoupled neuronal activities exacerbates neuronal stress signalling, reinforcing glia-mediated astrocyte activation & creating a vicious circle of highly toxic responses. These slow processes correspond to approx 2/3ds of the asymptomatic phase;
8. Healthy neurons and glial cells are killed at ever increasing frequencies (spongiosis) through bystander effects: clinical symptoms appear (failure of internal functional redundancies, abnormal, ever deteriorating EEG patterns) followed by death within a few months.

A-Practical consequences

One of the role of connexins is to dampen neuronal synchronization.



Healthy mice

NaCl

Anticonnexin

In healthy animals, pharmacological blockade of Cx activity results in quantitative EEG patterns closely resembling an epileptic crisis (frequency range-specific hyper-synchronisations).

This CEA/BMSystems collaborative research in CNS (psychiatric and neurological disorders) led to the co-owned patent WO201029131 (Use of anti-connexin agents for modulating the therapeutic effect of psychotropic drugs). Sept, 2008 describing a novel therapeutic strategy to treat psychiatric and neurological disorders with a worldwide exclusive license to Theranexus CEA's spin-off currently in Phase II.

B: Program objectives and achievements

Domain: Metabolism: First application disease: Parkinson's disease. Collaborative CADI™ program

- Context: Numerous attempts to utilize low-toxicity metabolic co-factors have been made over the years but all have proven ineffective.
- Objective: Build a CADI™ model that describes the mechanisms which:
  1. could give rise to dysfunctions that would
  2. most severely affect dopaminergic neurons.

Work done or to be done (Confidential program not patented yet):

- The IDUNN program led to a combinatorial therapeutic approach utilizing
  1. two molecules that had long been on the market,
  2. neither of which has any known toxicity or undesirable effects.
- This potential treatment was exposed, under strict confidentiality, to the criticism of internationally respected clinical specialists.
- It received their full approval.
- Implementation of the clinical proof of concept upon Parkinson's disease patients is currently under negotiation.

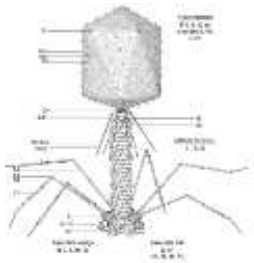
Because the mechanisms are not correctly represented in animal models and the two non-toxic drugs are not given at the same time, the Proof Of Concept will be conducted directly in humans. Savings in time and money

C: Program objectives and achievements

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

Request: How to rapidly (less than 30 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



Work done, BMSystems' start-up creation

- 2005: Two CADI™ models constructed to describe bacterial resistance mechanisms and bacteriophages-bacteria co-evolution mechanisms.
- 3 patented new disruptive technologies invented (TAPE, ABACCUS, RIPH), 3 publications.
- 2006: Successful launch and financing of our first spin-off Pherecydes-Pharma, the first bio-defense and bio-security company in France
- 2009: Creation of the first operational large-scale engineered bacteriophage bank to fight "uncharacterized multi-resistant" bacterial infections.
- 2011: Pherecydes Pharma secures 900 k€ in DGA funding for evaluating the use of bacteriophages on soldiers suffering infected burn-wounds
- 2013: Pherecydes Pharma Phagoburn* consortium granted 3,8 M€ by FP7 program to enter into clinic. This program uses natural phages cocktails for GMO regulation in Europe
- 2014: Pherecydes Pharma Phosa* consortium granted 760 k€ French Ministry of Industry to develop second indication. This program uses natural phages cocktails

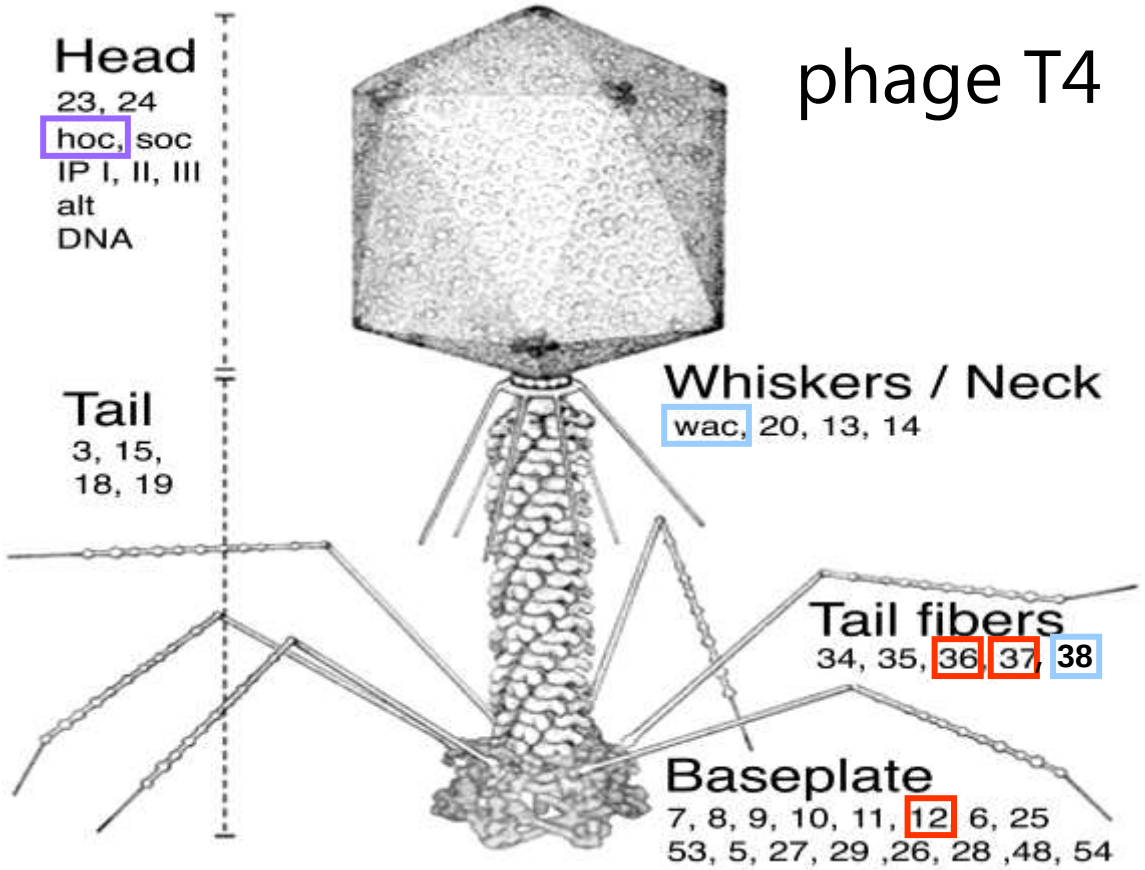
DGA

European Commission

World's 1st company entirely created from a systems biology program

* 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.

C: 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?

C: 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):

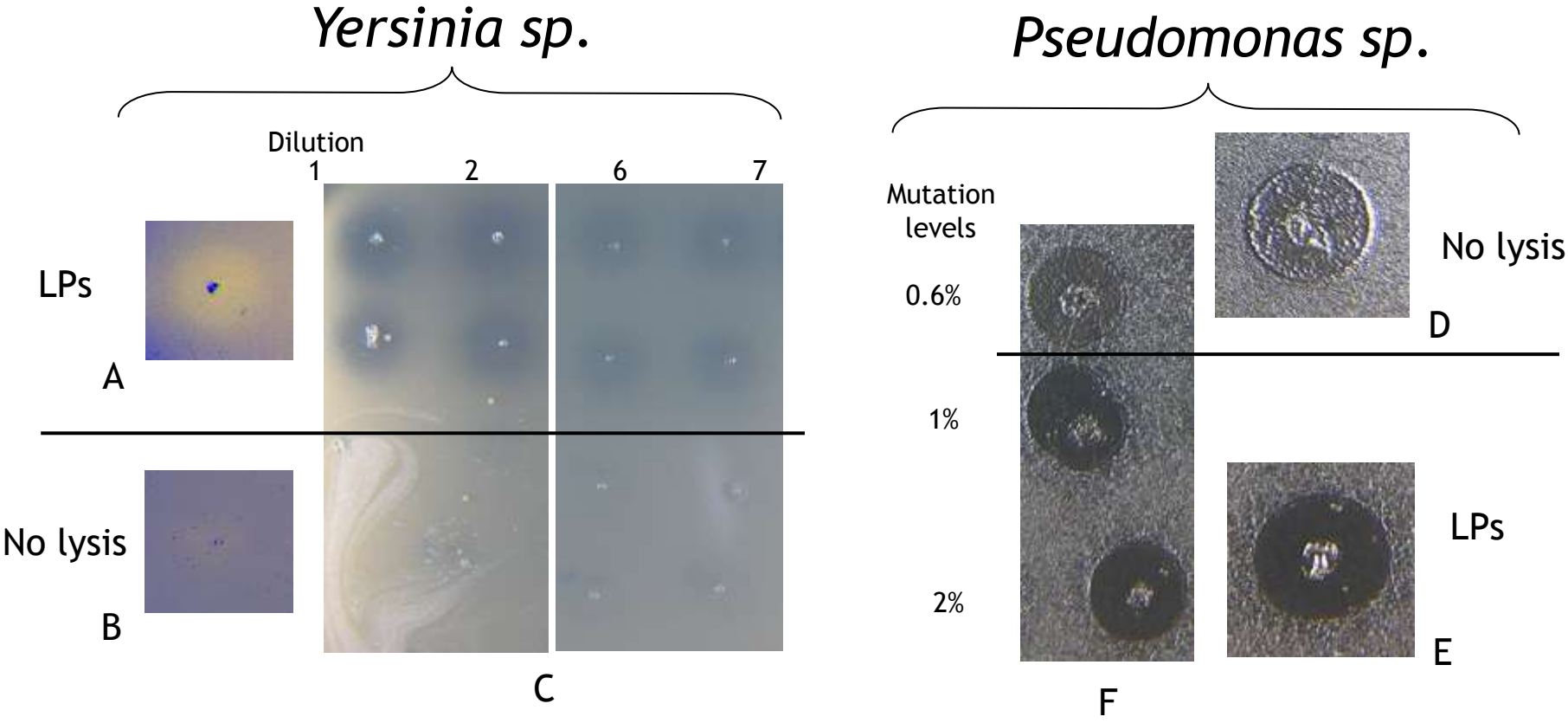
A recombination technology allowing the rapid & efficient production of lytic phage banks in which every individual differs from all others for any number of selected genes or other sequences.

Applicable to any phage and to any known sequence.

C: The results

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

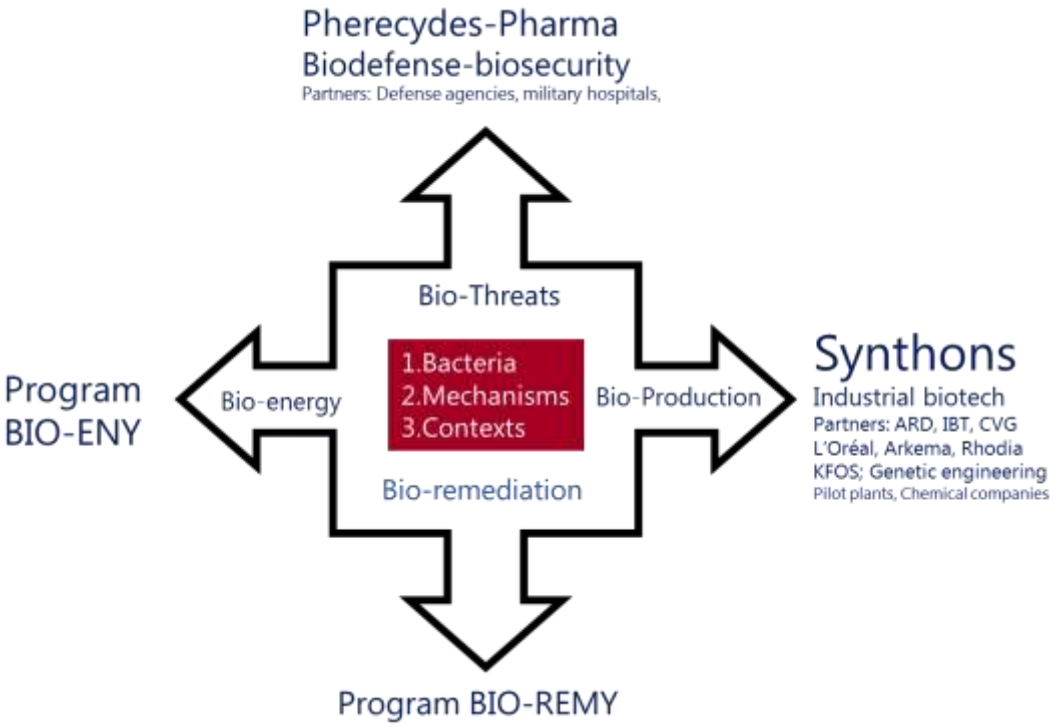
An engineered T4 bank contains variants capable of detecting and killing gram⁻ bacteria far removed from E. coli.



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

BMSystems' CADI™ cross-fertilization business strategy:

Real Illustration: The bacterial mechanisms and their possible business applications



Up to 4 independent possible programs with very different key issues but exploiting the same CADI™ knowledge Database with the best partners

BMSystems' R&D capacity and productivity KFOS

CADI™ knowledge DataBase & CADI ™ Cross-fertilization Process applied successfully to neurology, psychiatry, dermatology, immunology, cancer, application domains generating novel opportunities and huge time and money savings for our programs

D: Program objectives and achievements

Domain: Industrial biotech : Collaborative CADI™ program

Request: Feasibility study Industrial biotech program for 16 chemical molecules:

Synthons major collaborative industrial biotech research platform funded by the ministry of Industry in the IAR world-class cluster in France. Search for innovative processes non existing patent-dependent

A complementary collaborative team:

- A.R.D.: Leading Industrial Biotech research company with experimental capacities, pilot to scale-up plant (2000 Tons), a key factor of success, 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 companies (public information) proposing their molecules to the platform:

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

OUTPUTS: A unique significant bacteria metabolic pathways database of strong interest.
2 engineered bacterial strains generated are under evaluation and
a finalized process under mid-scale validation (patent pending by industrial company).
The program was funded by the ministry of Industry and supported by IAR world-class cluster

D: Synthons Platform: 3 complementary partners

Team Competences gathered	A.R.D.	BMSystems	IBT
• Stat of the art survey, sourcing possibilities,	X		X
• Exploitation freedom	X		X
• **CADI exclusive bacterial pathways proprietary database**		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	X
• Option A: Optimization proposals without genetic modification	X	X	
• Option B: Genetic modifications proposals	X	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	
Teams 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		

E: Yeast-Based Human-Glycoylation Project

Context: Synthetic biology CADI Program open for collaboration

- *The engineering steps implemented to generate human-type glycans irreversibly disrupt the yeast's endogenous glycosylation system, thereby leading to rapid yeast cells dysfunction and growth arrest.*
- *As a result, while proper glycosylation patterns may be achieved on a target protein, the levels produced are very low and a significant proportion of the end product present incomplete glycosylation*
- *Over the past ten years, many academic and industrial laboratories have attempted to overcome these limitations in the production of glycoprotein products by yeast cells, but so far with little success in terms of large-scale production of therapeutic proteins requiring complex glycosylation patterns.*
- *To date, the most efficient means of production remain the milk of transgenic goats, the eggs of transgenic chickens and transgenic plants*
- *We have found a way to efficiently overcome the above major limitations to the large-scale production of humanized glycoproteins in yeast cells using "human-type glycosylation tool-boxes".*

To succeed 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.

F: The Individualized Oncology Therapy Issues

The Individualized therapy mirage vs. novel concept & multi-therapies

Request: Targeted treatment does nothing more than selecting resistant cancer cells;
What alternative solutions could be proposed (full presentation available)

CADI™ past programs

F1-2003, CANCER THERAPEUTIC STRATEGY: Integrated transcriptome analysis of the cellular mechanisms associated with Ha-ras-dependent malignant transformation of the human breast epithelial MCF7 cell line. Nucleic Acids Research. Collaboration with INSERM unit 553. Publication

- Outputs: Identification of 4 differentialy deregulated pathways in malignant cells. Test of a combination of 3 drugs, never used in oncology, that showed synergistic apoptotic activity in-vitro in malignant cells only. Additional outputs: anti-farnesylase can't work!

F2-2004, CANCER METASTASIS MECHANISM : Mechanisms targeted by the ADAM-15 RDG peptide to induce cytostasis in very aggressive breast cancer cells in vitro (MDA-MB 231)and in vivo. Collaboration with INSERM unit 553.

- Outputs: Identification of the ADAM-15RGD mechanism of action and the limits of its therapeutic application. The mechanism is used for normal tissue repair and can't be blocked without dramatic consequences.

F3-2005, UNDERSTANDING OF TAMOXIFEN RESITANCE (CANCER) : Integrative analysis of gene expression patterns predicts specific modulations of defined cell functions by estrogen and Tamoxifen in MCF7 breast cancer cells. Journal of molecular Endocrinology. Collaboration with INSERM unit 553. Publication

- Outputs: explanation for the relapse mechanism: "antibiotic resistance-like" form of selection mechanism identified.

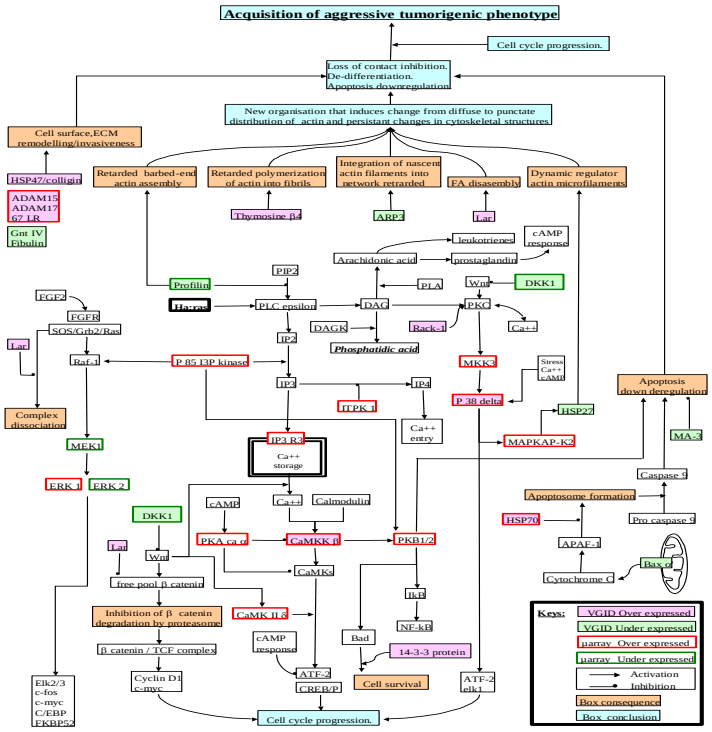
These three programs show that the interpretation of cancer as a chronic disease raises numerous long term efficacy issues due to the "antibiotic resistance-like" behavior of tumor cells.

Poor efficacy and too high prices of treatments only reinforce payers reluctance to reimburse them. Based on HIV experience, a new paradigm, simultaneously addressing different targets combined with a novel metastasis control strategy, must be investigated.

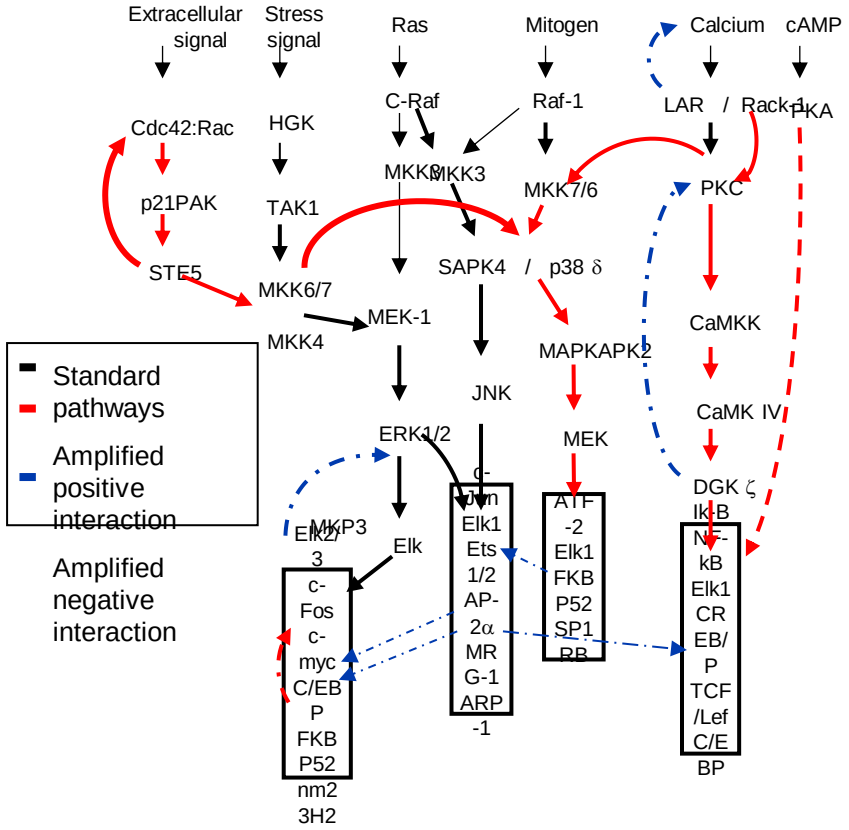
A tumor is rarely composed of one type of malignant cells. BMSystems, through his 3 programs, identified the narrow limits of mono-targeted therapies and proposes a new approach to oncology, based on a therapeutic strategy that does not only target the tumor itself but uses the possibilities of surrounding tissue to control metastatic processes while starving cancer cells.

F1: CADI™ Ras-dependent breast cancer model

1-Ras-dependent breast cancer
Breast Cancer Progression: Cellular Mechanisms Model



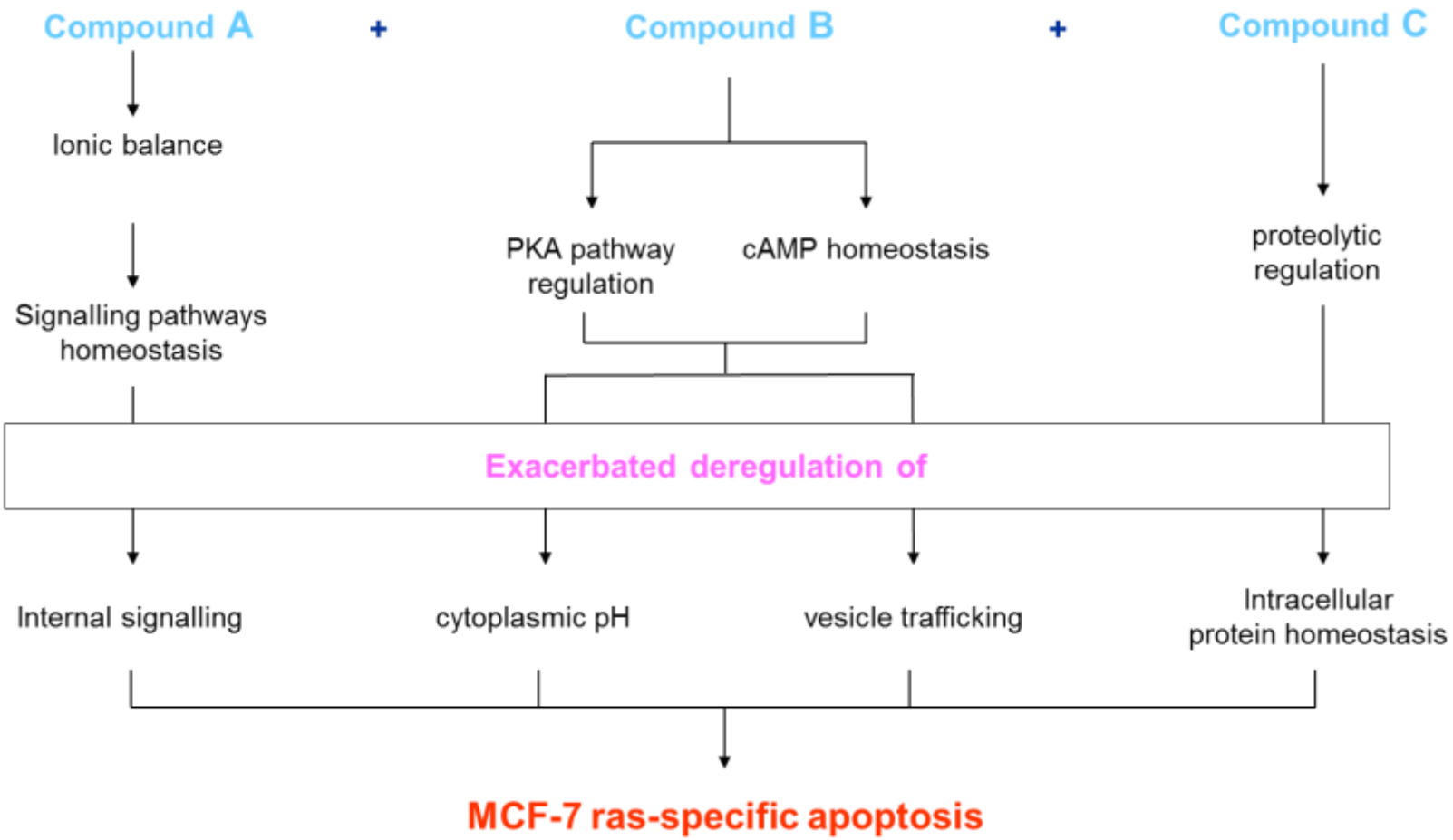
CADI™ model extract



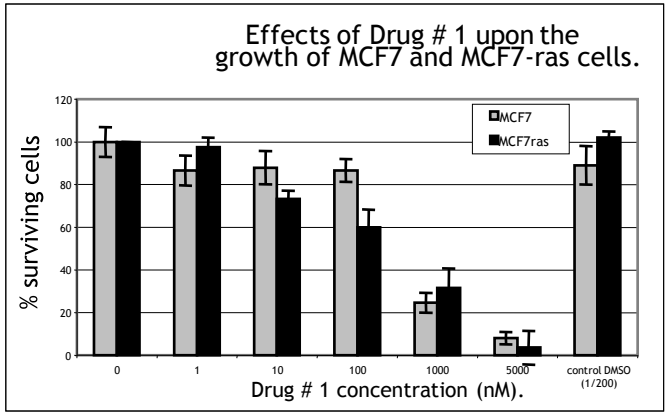
Published in: *Nucleic Acids Research*, 2003, Vol. 31, No. 19: 5789-5804

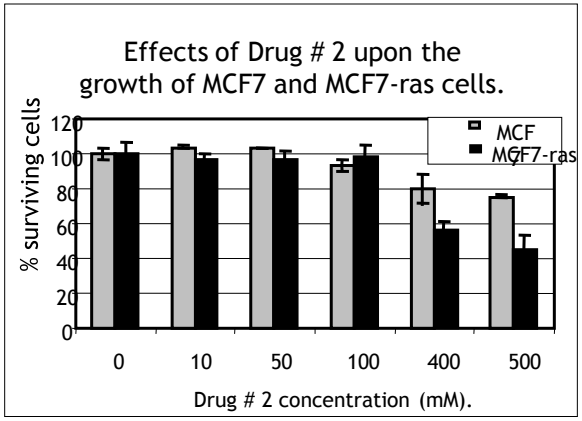
Identification of 4 differently deregulated pathways in malignant.
Additional outputs: anti-farnesylase can't work!

F1: Anti MCF-7 ras intervention using sub-optimal doses (nM)

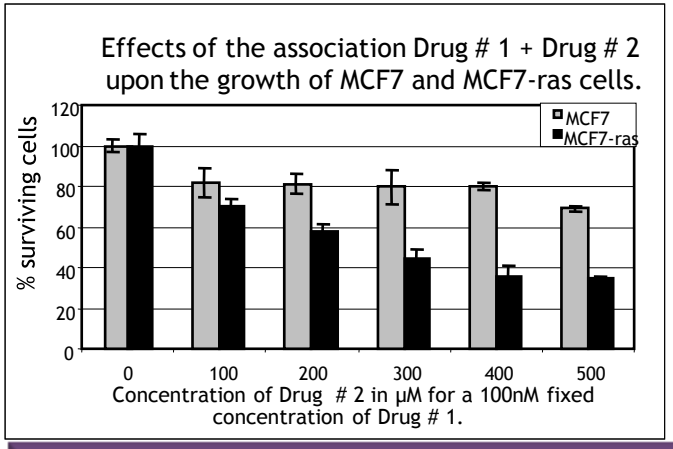


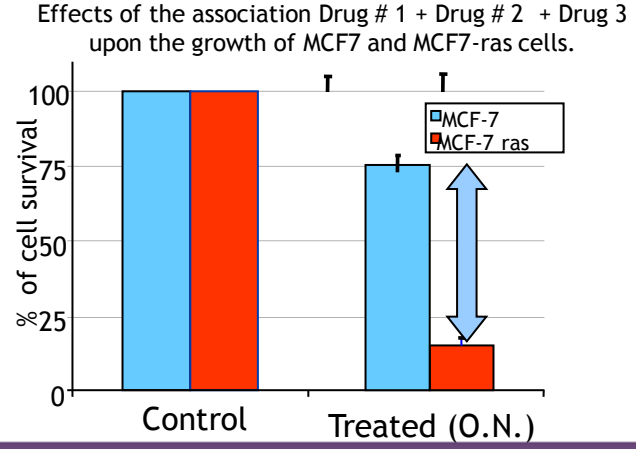
F1: CADI™ Ras-dependent breast cancer





Biological Validation.
A significant difference when the three compounds, NEVER USED IN ONCOLOGY, are concurrently used.





Test of a combination of 3 drugs, never used in oncology, that showed synergistic apoptotic activity in-vitro in malignant cells only.
This is not a treatment, but this gives novel hypotheses

F2: CADI™ Cancer Metastasis

ADAM-15 RGD peptide mechanisms model

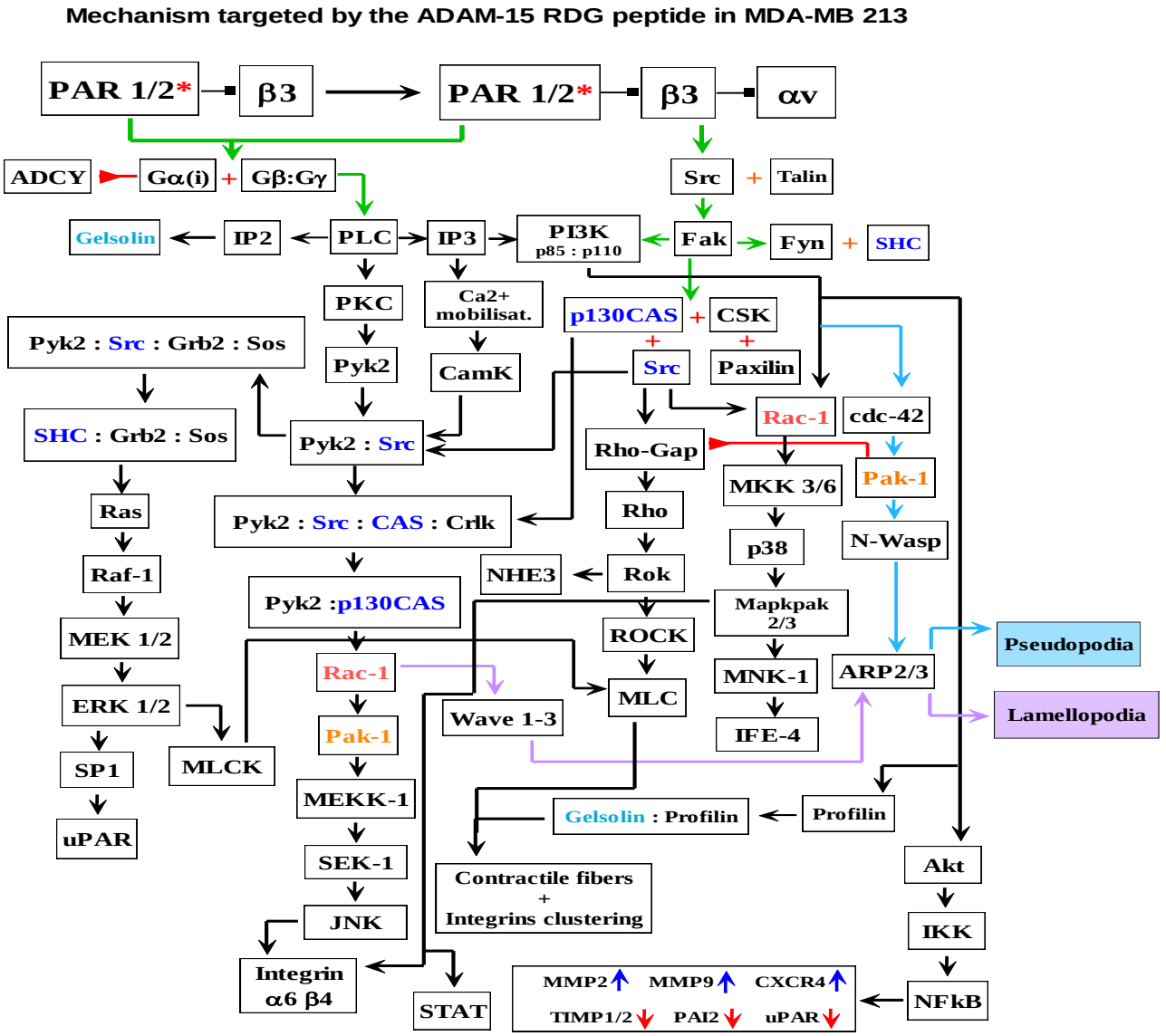
- *10 amino acids fragment (GCGGRGDGGC) derived from the metaloprotease Adam 15.*
- *Induces cytostasis (dormancy) in very aggressive metastatic breast cancer cells both in vitro and in vivo.*
- *The target of this peptide appears to be integrin-containing structures (cell adhesion) but not integrins alone (anti-integrins antibodies have no such effects).*

  - What is (are) the target (s) of this peptide?
  - What mechanisms does if affect? and
  - Why does it induce cytostasis?

- *This model addresses the mode of action of a potential treatment.*

Collaboration BMSystems-INSERM U 553 (Hôpital St Louis)

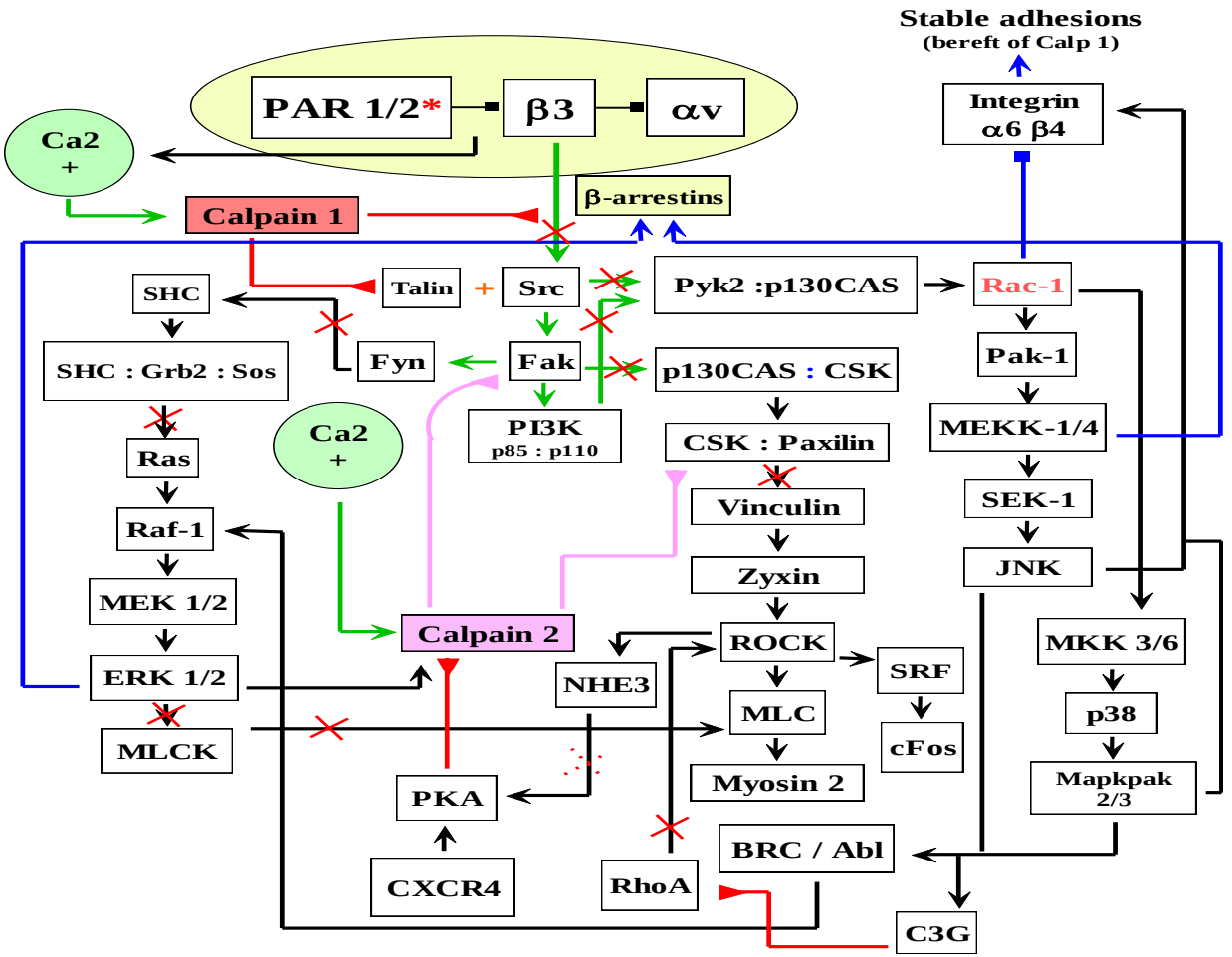
F2: CADI™ Cancer Metastasis



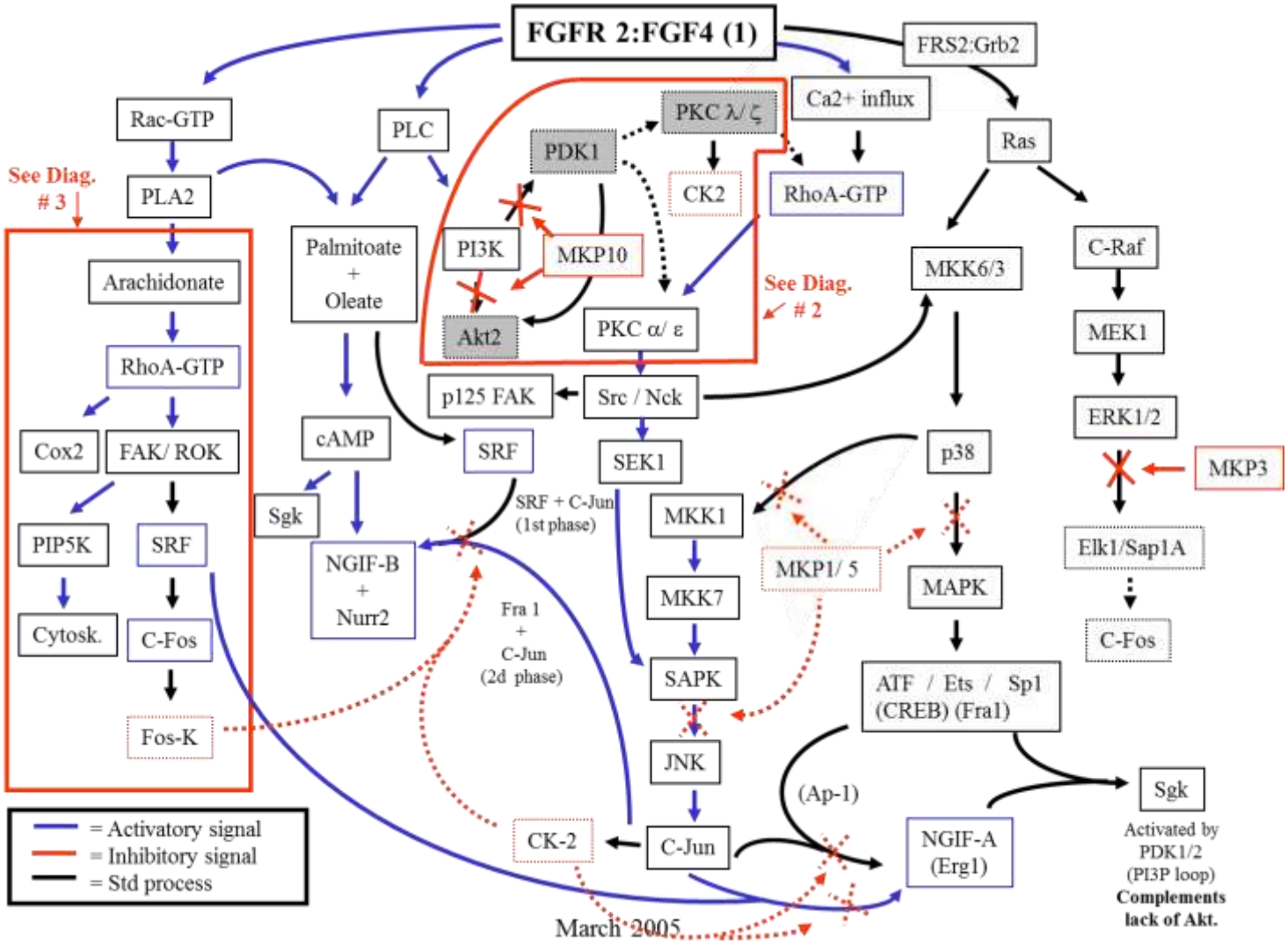
F2: CADI™ Cancer Metastasis

Consequences of ADAM-15 RDG peptide binging

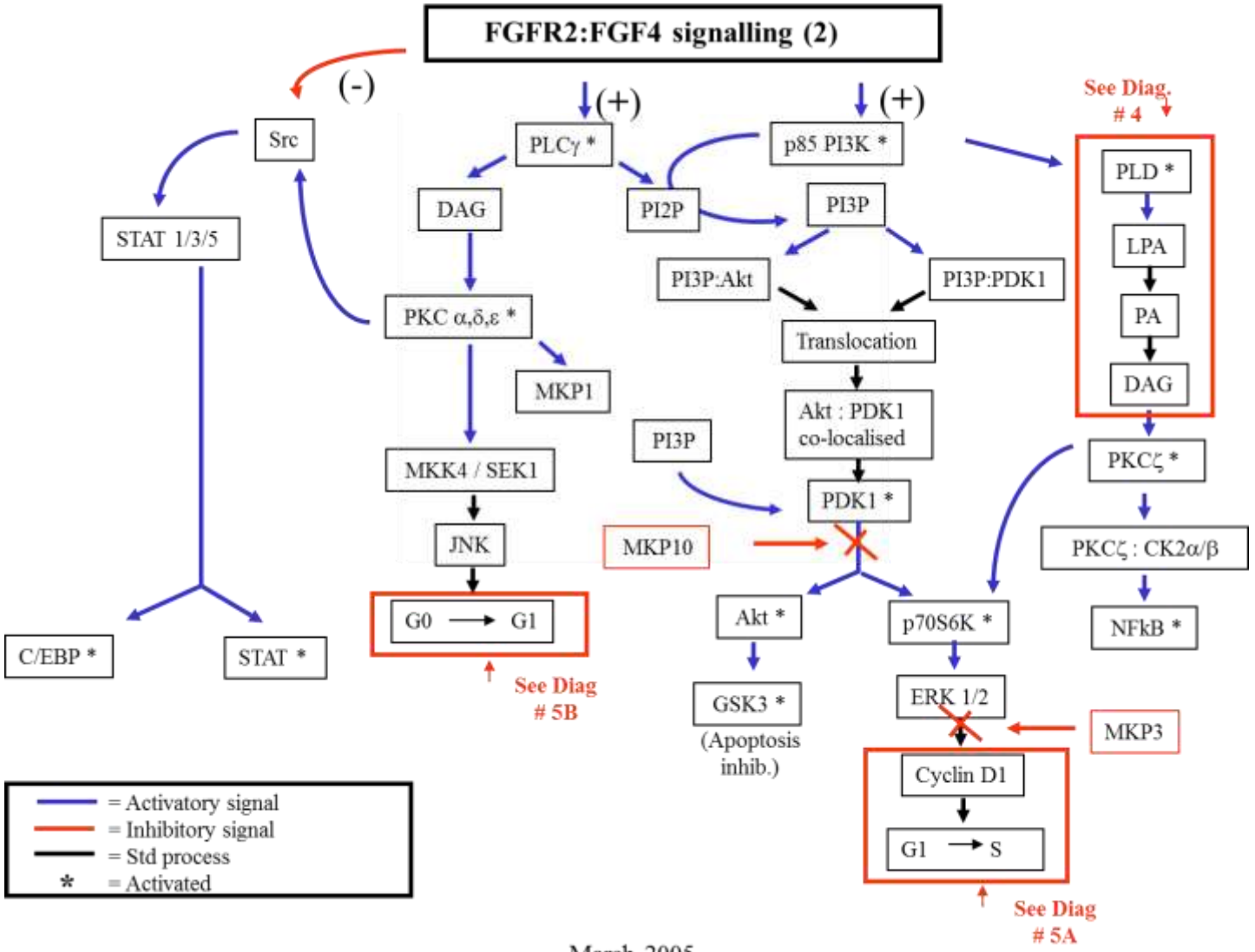
β-arrestins-mediated endocytosis of PAR : Integrin complexes & cytoplasmic segregation of ERKs & MEKKs 1/4



F2: CADI™ Cancer Metastasis



F2: CADI™ Cancer Metastasis



F2: CADI™ Metastasis: Practical outcome.

- Treatment with the ADAM-15 RGD peptide massively triggers the integrins-associated, β-arrestin-dependent endocytotic mechanisms.
- This effectively abolishes integrins-dependent cytokinesis mechanisms while inducing cytostasis in cells where these mechanisms are being implemented.
- But this does NOT solely address metastasis, where integrin-dependent mechanisms are inappropriately activated.
- It will also address and inhibit physiologically coherent integrins-dependent cytokinesis mechanisms, such as fibroblasts migration during wound healing, or repair of damaged capillaries.
- Thus, the potential therapeutic benefits of ADAM-15 RGD (inhibition of integrin-dependent metastasis) are annihilated by direct, highly undesirable effects (failure of wound healing and thus serious risks of gangrene; failure of vascular repair and thus serious risks of multiple organ failures; etc.).

In spite of high efficacy, the therapeutic potential of the ADAM-15 RGD peptide is extremely low.

Reconsider therapeutic development.

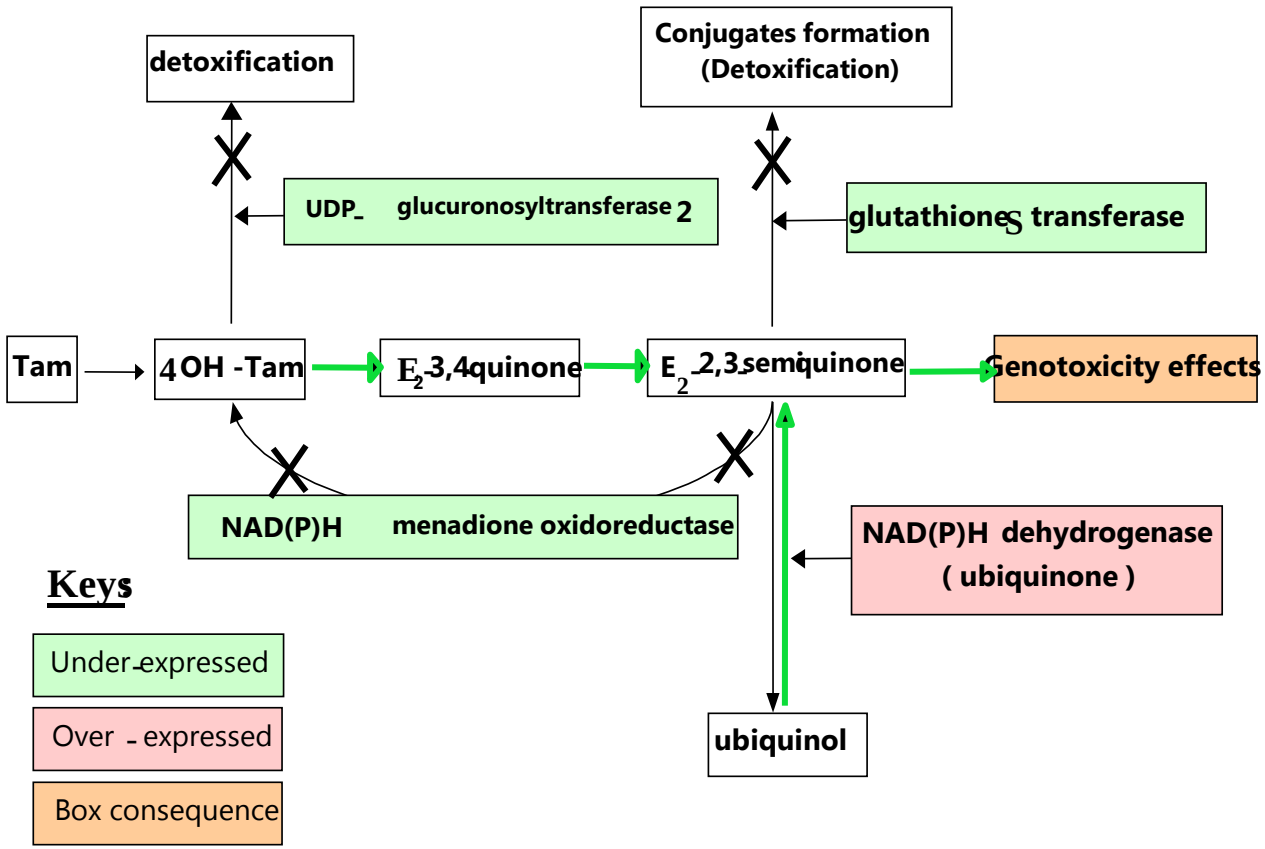
Ouputs: The mechanism is used for normal tissue repair and can't be blocked without dramatic consequences.

F3: CADI™ tamoxifen-resistance model.

Validation:

RNA-chip technology (9 independent assays) + Enzyme activity assays.

Induction of Quinone-resistance



F. Gadal *etal*. *J. Molecular Endocrinology*, 2005, Vol.34, 61-75.

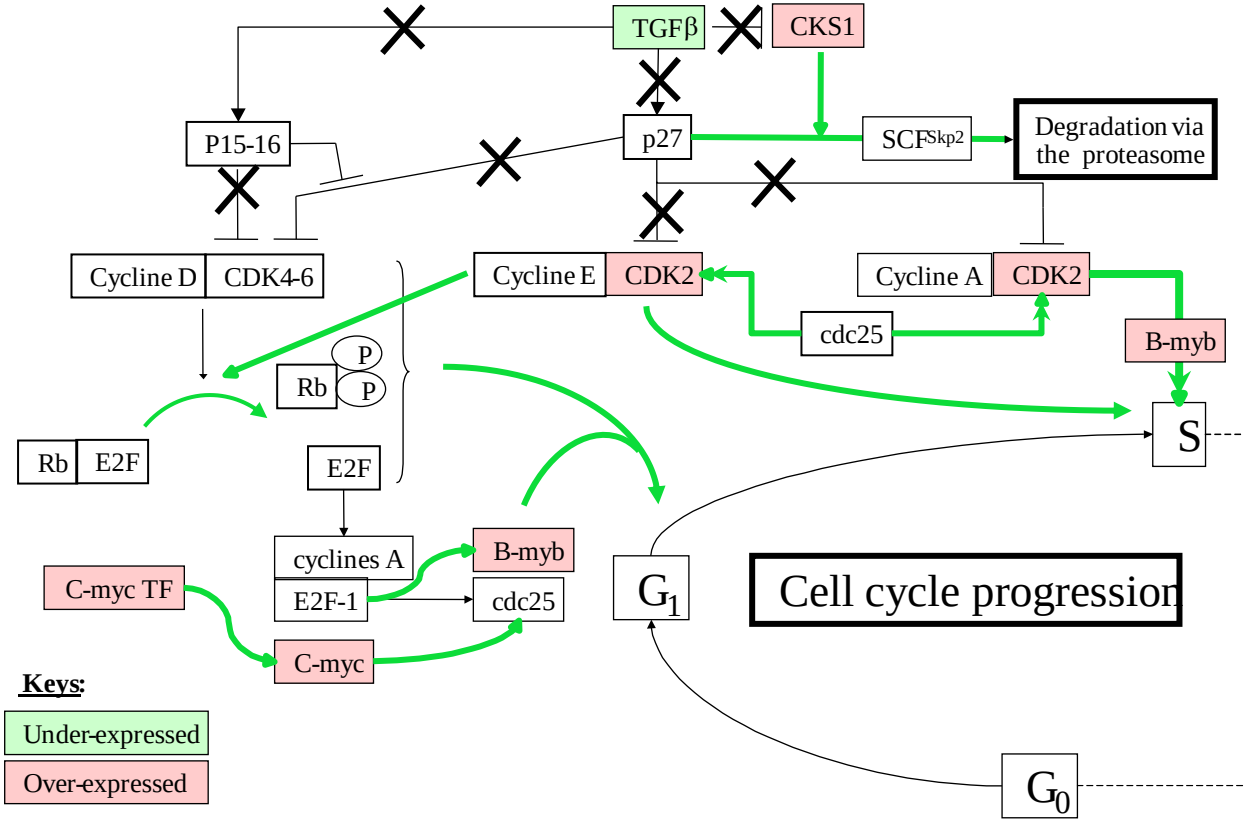
March 2005

F3: CADI™ tamoxifen-resistance model.

Validation:

RNA-chip technology (9 independent assays) + Enzyme activity assays.

Quinone-mediated suppression of negative feed-back on cell-cycle control mechanisms.



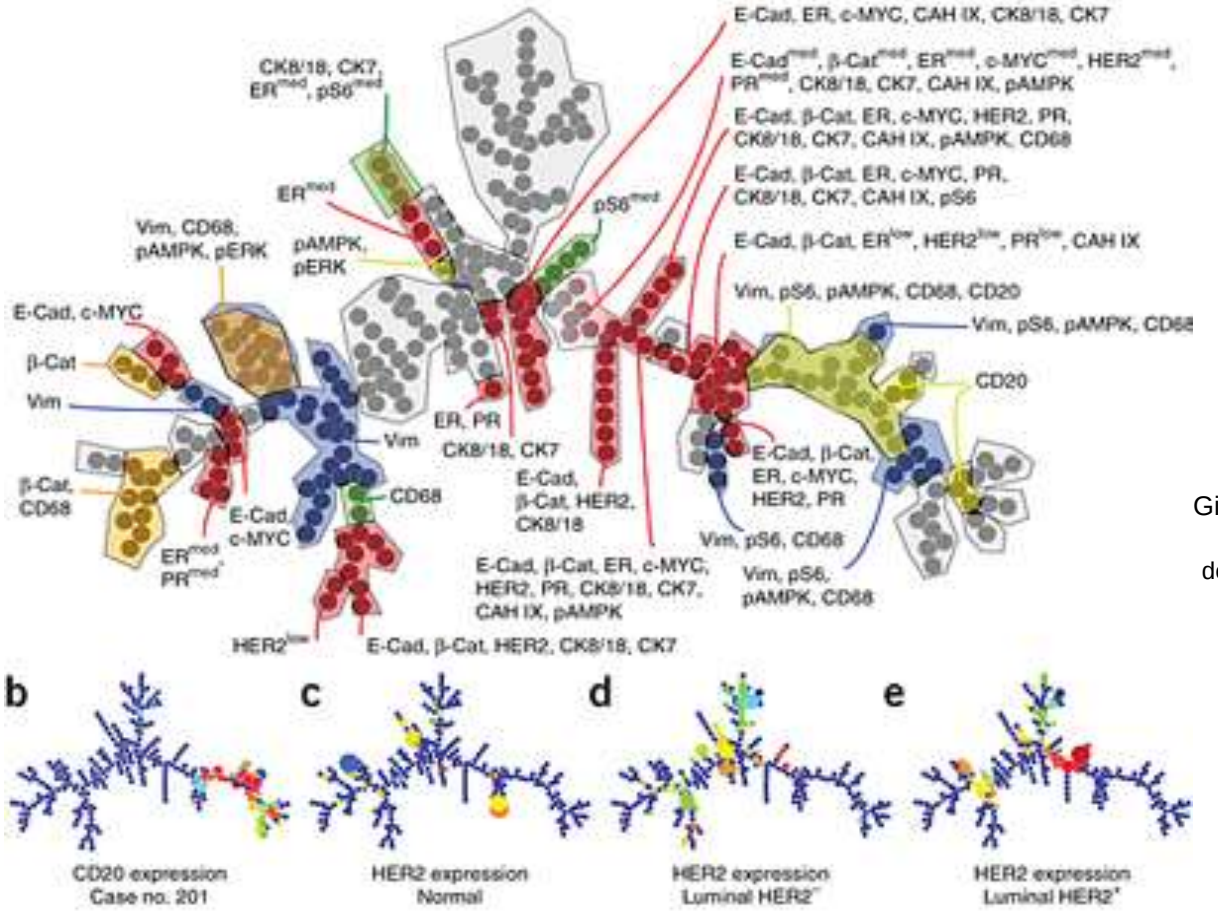
F. Gadal *etal.* *J. Molecular Endocrinology*, 2005, Vol.34, 61-75.

Outputs: explanation for the relapse mechanism: "antibiotic resistance-like" form of selection mechanism identified

2005

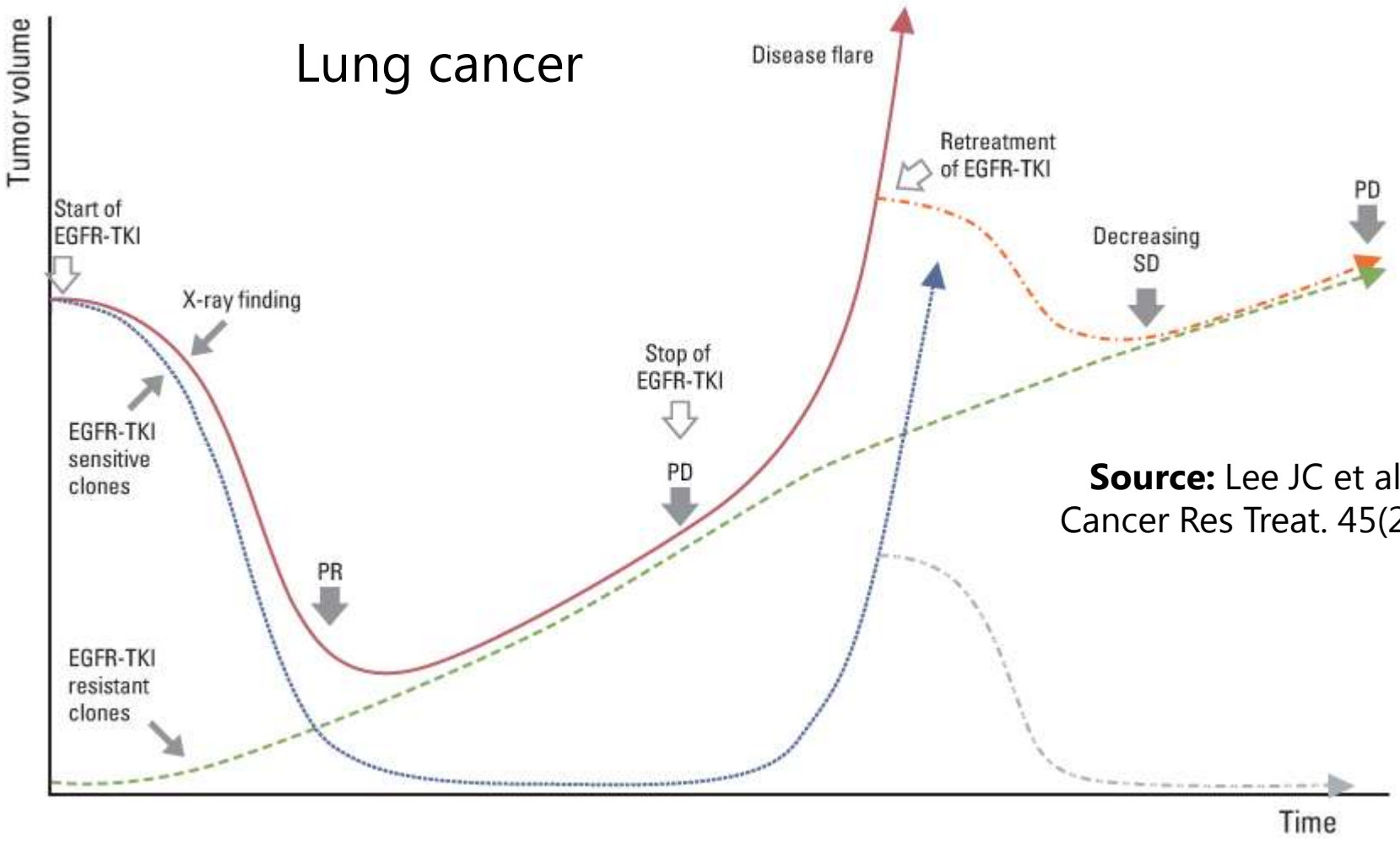
F4: Precision medicine applied to cancer issues

1-Cancer: multiple types of cancer cells within the same tumour



Source:
Giesen C. et al. 2014
Nature Methods
doi:10.1038/nmeth.2869

2-F4: Targeted treatment does nothing more than selecting resistant cancer cells: The cancer first diminishes & then starts again and cannot be stopped.

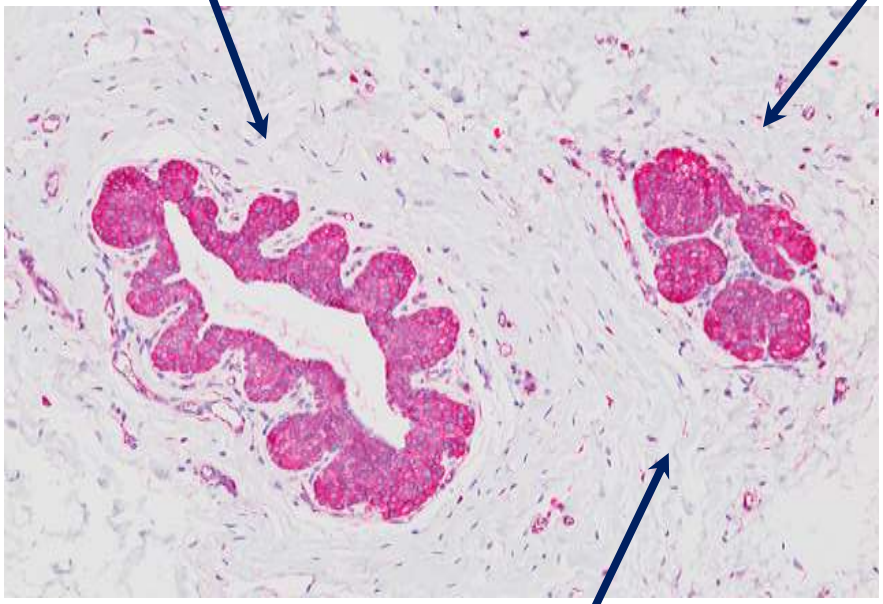


Source: Lee JC et al. 2013 Cancer Res Treat. 45(2):79-85.

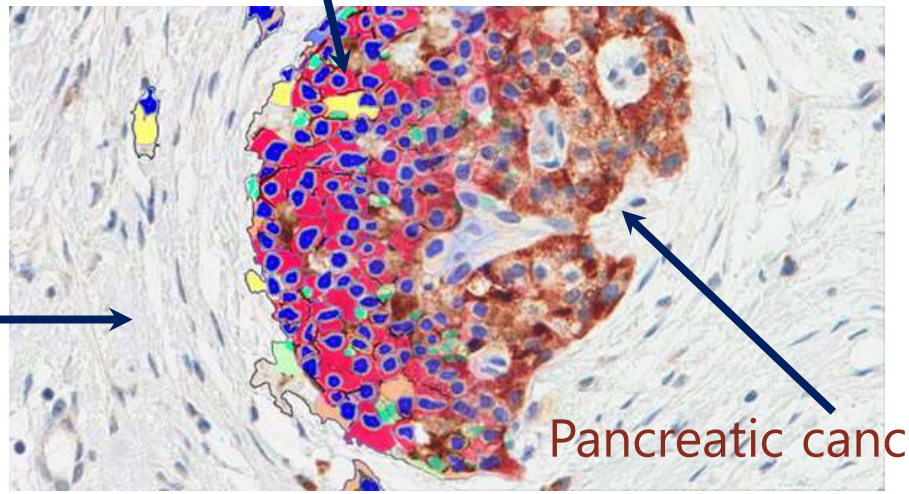
F4: A novel approach to cancer therapy.

Ductal breast cancer

Non-ductal cancer off-shoot



Multiple types of cancer cells within the same tumour
(each colour indicates a different type of cancer cell)



Pancreatic cancer

Complementary therapy:
Peri-tumoural tissue could be induced to "encyst" the tumour, preventing metastases while starving the cancer cells.

Source: http://flagshipbio.com/pancreatic-cancer-drug-development/

F4: A novel approach to cancer therapy

CANCER MESTASTASIS CONTROL PROGRAM:

Concept

Complementary therapy: Peri-tumoural tissue could be induced to "encyst" the tumor, preventing metastases while starving the cancer cells.

We propose to investigate the "grey zone" between tumor boundary and so-called healthy tissue.

- Objective: To develop a therapeutic strategy that does not target the tumor but the possibilities of surrounding tissue to control metastatic processes.
- I.P. competitive advantage: The possible mechanisms and corresponding therapeutic strategies that will be discovered (surely never used to treat cancers) should be patentable.

Work done and to be done

- Feasibility Study completed
- CADI v0 to be initiated
- Search for partners for future validation phases

G: BMSystems' applications focus in dermatology and cosmetics

1. Skincare: Strong integrated understanding of the global systems:
   1. *The mechanisms associated with constitutive and facultative epidermal pigmentation*
   2. *The mechanisms associated with senile/solar lentigines (aging issues)*
   3. *Components specific to pigmentation from production to destruction*
2. Domain: Tissue differentiation / embryogenesis. Collaborative CADI™ program with CNRS (*1 publication*).
3. 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.
4. Skincare Project 1 : Offer to the industry a highly effective, competitive and reliable alternative to detect & characterize the potential for irritant contact dermatitis and/or allergic contact dermatitis complex formulations could have in normal skin in vivo, using reconstructed skin, in-vitro and in-silico tools. *Provide in a second step a possible "weak allergens/sensitizers effect suppression" formulation strategy* combining interesting raw materials (weak allergens/sensitizers ex: full plant extract, mixture of components) with their corresponding inhibitors for the development of innovative cosmetic/skin-care products.
5. Skincare Project 2: Personalized, "physiological mechanisms-Based" prevention, diagnostic, treatment and follow-up to support *premium marketing strategies proposing innovative solutions (services, products)* to address targeted populations issues (aging, skin/timing/ treatment adaptation, etc…).

Mechanisms-Based Medicine applied to cosmetics and dermatology
A new paradigm qualified for novel solutions in premium personalized marketing strategies

G: Program objectives and achievements

Domain: Dermatology. Contractual CADI™ program

Request: Review of a complete domain, R&D strategy and programs

- Build a strong integrated understanding of the global systems to redefine the R&D strategy and portfolio programs;
  - *The mechanisms associated with constitutive and facultative epidermal pigmentation*
  - *The mechanisms associated with senile/solar lentigines (aging)*
  - *Components specific to pigmentation from production to destruction*
- Review coherence of existing Expert's requests, and pertinence of Expert's answers;
- GO/ NO GO decision for two existing programs;
- Identify new pertinent targets with mechanisms of action;
- Suggest potential molecules for new targets;
- Propose a validation strategy and assist client's team in experimentation outputs analyses.

Work done:

- Global integrated set of 6 CADI™ sub-models describing the mechanisms and cross-talks between sub-systems at different maturation & differentiation status for an organ composed of 3 main cell types;
- NO GO decision for two existing programs;
- Identification of 8 new targets of interest, 5 of which went to the Phase 2 (validation);
- Identification by BMSystems of 5 tool-molecules to test the 5 targets (3 of which arose from our internal "CNS CADI™ Knowledge Database");
- 3 targets/tool-molecules couples validated in-vitro;
- 4 not-anticipated additional questions answered at marginal cost;
- Identification of a screening test issue and explanation of the problem;
- Contribution to client's team behavior and dynamic evolution (some difficulties due to resistance to research paradigm changes).

Clearly, investing in a CADI™ Standard Full Multi-Scale/Systems program is a better investment than "spreading" expenses through independent experts' requests and their inconsistent answers

H: Program objectives and achievements

Domain: Dermatology/cosmetics. Collaborative CADI™ program

Request: Eliminate as much as possible the Use of Animals in Contact Allergy Testing for cosmetic products

- May 2013, the European Unions bans the import and sale of cosmetics containing ingredients tested on animals.
- Objective of the program:
- Offer to the industry a highly effective, competitive and reliable alternative to detect & characterize the potential for irritant contact dermatitis and/or allergic contact dermatitis complex formulations could have in normal skin in vivo, using reconstructed skin, in-vitro and in-silico tools.
- Provide in a second step a possible "weak allergens/sensitizers effect suppression " formulation strategy combining interesting raw materials (weak allergens/sensitizers ex: full plant extract, mixture of components) with their corresponding inhibitors for the development of innovative cosmetic/skin-care products..
- Develop a range of products/services to fit clients' needs.
- R&D Partners: Open for complementary partners (research, industry, etc.…)

Work completed under progress or to be done:

- CADI™ model under construction.
- Identification of the parameters characterizing pathway-specific & cross-talk inductions.
- Construction of the complementary mathematical in-silico model.
- Identification of appropriate program validation tests.
- Development of the future tools and software to run and exploit the tests.
- Contact Allergy Testing solution evaluation by Cosmetics partners.

The operational solution combining heuristic modeling and mathematical modeling

I: Program objectives and achievements

Domain: Type 2 diabetes. Contractual CADI™ program

Request: GO / NO GO decision for "lead A"

- Mechanisms whereby "Lead A" produces anti-glycemic effects;
- Understand the drug's potential mechanisms of action that could explain pre-clinical results;
- Identify the side-effects mechanisms;
- Assist client's team in experimentation outputs analyzes.

The information we were provided with were:

- the 2D chemical structure of this molecule (confidential),
- the fact that it had "strong anti-glycemic effects in the rat", and
- Some receptor-binding data.

Work done:

- We proposed & fully documented the mechanisms of action of the molecule;
- We identified potential deleterious side-effects;
- We explained why "lead A" couldn't be improved;
- At least 2 of the predicted undesirable effects (induction of hypothermia and decreased nociception) turned out to be correct in vivo;
- Development of this particular "Lead" was abandoned (NO GO decision);
- Financial consequence for Client: significant Clinical Trial costs savings + new mechanisms to exploit.

Robust consensus that generated significant savings of time and money for the Pharma company

J: Program objectives and achievements

Domain: Tissue differentiation/embryogenesis. Collaborative CADI™ program

Request: Build a CADI™ model that could explain an organogenesis mechanism that had remained obscure for over 60 years.

- Context: In early embryos, the male & female genital tracts are initially identical. Then in males (AMH) the organ degenerates while in females (no AMH) it continues development.
  - Only mesenchymal cells (majority) express the AMH receptor.
  - Only epithelial cells (minority) visibly respond to AMH (most undergo an EMT and some enter apoptosis).
  - The regression (transformation of the duct into a fibrous mensenchymal cord) begins at the posterior end while the anterior end continues to grow normally.
  - Regression progresses as a wave that propagates along the duct much faster than the rate of growth of the structure.

Work done

- Detailed functional understanding of the mechanisms.
- Discovery of a 3 phases response to AMH signaling.
- In-vivo validation of the key discoveries in collaboration with CNRS.
- One of the key, hitherto largely obscure mechanisms (EMT) may be associated with malignant transformation (cancer).
- 1 publication.

A CADI™ model explained a major organogenesis mechanism involved in embryogenesis and led to new hypothesizes in malignant transformation mechanisms.

Why do we need to change the dominant discovery paradigm? **(supporting documents: click on the links for details)**

- The *industry is under critical pressure* *due* to a too high failure rate and payers no longer willing to pay premium prices.
- The Pharma industry has for decades invested in Omics data production, IT technologies and Systems Biology programs for remarkably few relevant results.
- The consequences of life's mechanisms being complex, as opposed to complicated, are dramatically underestimated by data-treatment scientists and their algorithms.
- "Currently, many published research findings are false or exaggerated, an estimated 85% of research resources are wasted". (John P.A. Ioannidis, MD, DSc PLOS medicine METRICS, Stanford University).
- The unreliability of scientific and clinical publications used by these algorithms is strongly increasing.
- Negative experimental results are seldom published, generating an enormous bias.
- The "garbage in, garbage out" reality demonstrates that a wrong hypothesis, even if generated or treated by the best Digital and IT technologies, remains a wrong hypothesis
- Mathematical models are remarkable validation/fine-tuning tools when applied to well defined processes. They are inadequate discovery tools when applied to multicellular processes poorly understood and/or created form unreliability information.

R&D managers aware of these critical & underestimated issues should ask their suppliers to prove that their operational solutions are really able to address these issues.

Useful Downloads

Download the Full Presentation with CADI Description, publications and the 10 CADI POCS

For more information about published results quality & reliability

- New evidence published in "Science" confirms the poor reproducibility (less than 1/3) of peer-reviewed published studies.
- An estimated 85% of current published research findings are false or exaggerated: How to Make More Published Research True. Article in "PLOS Medicine" by John P. A. Ioannidis, Meta-Research Innovation Center at Stanford (METRICS), Stanford University.
- Diagnosing the decline in pharmaceutical R&D efficiency. Published in "Nature Review Drug Discovery". The diagnostic is clear for our industry.
- Only 21% of the results (14 out of 67 experimentations) could be reproduced: Believe it or not: how much can we rely on published data on potential drugs targets? Published "Nature Review Drug Discovery". This title is crystal clear.
- Only 10% of the results published in 53 "landmark" papers in top journals could be replicated: Cancer research at Amgen, C. Glenn Begley. Published as comments in the journal "Nature".

Heuristic modeling principles and case studies

- **Request our Cochin Institute Paris "Integrative Analyses" Training Session Presentation**
- The discovery of Innovative Therapeutic Approaches: Under the street light is not the right place to search BIT's 10th Annual Congress International Drug Discovery Science and Technology 2012 November 8-10, 2012, Nanjing, China
- The Differences & Complementarities Between « Heuristic » and « Mathematical» approaches. The scientific presentation given by Dr. François IRIS (CSO BMSystems) during the EPA (European Psychiatric Association) conference in 2011.

Author's LinkedIn Posts : https://www.linkedin.com/today/posts/manuelgea

- The future will be digital & biology, but who will lead?
- Therapeutic innovation is moving faster than it may appear and this may be of interest to you.
- Alzheimer drugs failures. Why not a good news for patients!
- Big Data = Big garbage? An estimated 85% of research resources are wasted! 6 documents to read.
- Who is the number 1 serial killer of disruptive innovations in biomedical research?

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