Bio-Modeling Systems

The Mechanisms-Based Medicine Company

We changed the discovery paradigm to create novel medical meanings

from unreliable heterogeneous sources of data

Short corporate 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

Manuel GEA : CEO, Co-founder, VP IT R&D
manuel.gea@bmsystems.net

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.
- *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 5 solutions to critical & high impact issues

➢ *GO-NO GO decision before product acquisition or for portfolio risk analysis.*

- ***Why**: With **a failure rate** of 90%-95% in the Pharma industry, be smarter by not investing in the wrong asset, increase your ROI.*
- ***Objective:** Identification and evaluation of the potential hidden issues in acquisitions. **Investment savings. Refine acquisition value**.*
- ***Who is interested**: VCs, Angels, TTO, Corporate funds, Consulting companies and life science industry managers.*

➢ GO-NO GO decision before next development phase.

- ***Why**: When pros and cons are really mitigated and no more robust facts available from existing expertise.*
- ***Objective**: Address the possible safety and efficacy issues before launching the next phase. **Costs and time/resources savings**.*
- ***Who is interested**: Pharma, Diagnostics experts, Biotech, e-Health and cosmetics, preclinical and clinical development managers.*

➢ R&D program Rescue for a program facing critical issues during its lifetime.

- ***Why**: There are multiple reasons for specific problems. Some can be addressed only when functionally understood.*
- ***Objective**: Identify the roots of problems and try to propose a pertinent solution. **Investments & costs savings.***
- ***Who is interested**: Pharma, Diagnostics, biotech, e Health and cosmetics, preclinical, clinical and post-marketing development managers.*

➢ External R&D "B plan" program when the "A plan" cannot be rescued.

- ***Why**: The reasons for failure are systemic, the concepts or the solutions could be wrong.*
- ***Objective**: Propose an alternative solution to secure company's business development. **Business opportunity, new products launch.***
- ***Who is interested**: Pharma, Diagnostics, biotech e Health and cosmetics R&D managers, CEOs.*

➢ Exploratory Discovery program to generate novel causal mechanisms concepts.

- ***Why:** Complex human diseases/disorders need to be revisited to build novel hypotheses.*
- ***Objective**: Propose novel causal mechanisms concepts for cost-effective novel solutions. **Business opportunity, new products launch**.*
- ***Who is interested**: Pharma, Diagnostics, biotech e Health and cosmetics R&D managers, CEOs.*

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' first outstanding POCs completed and 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.

BMSystems' internal & collaborative R&D programs pipeline

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

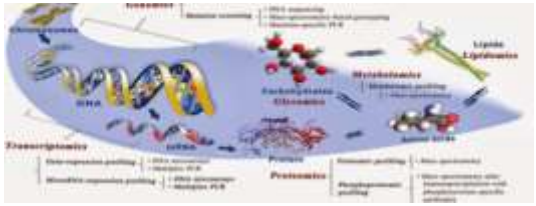
Program Domains	Partners	CADI™ compliance	CADI™ vers. 0	Ind. Valid.	Secret or Patent or Co-Patent/Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.
Infection-Immunology							
Neurology/Psychiatry (CNS-PNS)							
Oncology							
Metabolism							
Dermatology/Cometics							
BioProcesses							

BMSystems' internal & collaborative R&D programs (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						Completed
TAPE (protein improvement)	Open						Completed
Chronic Fatigue Syndrome	Open		high Interest				
Ebola virus ecology	Open						
Hepatitis C	Open						
Auto-immune global concept	Open	high Interest					
Creutzfeldt-Jakob disease's mechanisms	CEA Life Sciences						Completed
Psychiatric Disorders therapeutic strategy	Confidential						
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						
Migraine Mechanisms	Open						
Multiple Sclerosis Mechanisms	Open						
Psychiatric disorders biomarkers	Max Planck Munich						
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					Completed	
Tamoxifen resistance	INSERM				Completed		
Specific Metastasis control	INSERM			Completed			
Encysting Tumour Therapy	Open	high Interest					
Müllerian regression Mechanisms	CNRS				Completed		
Adipocytes growth control	Open						
Skin Contact Allergy Mechanisms	Open		high Interest				
Skin pigmentation Mechanisms	Open		high Interest				
Skin pigmentation Modulation	Open	high Interest					
Skin aging Mechanisms	Open	high Interest					
Modulation of skin hydratation	Open	high Interest					
Modulation of the lipid constituents of the skin	Open	high Interest					
Novel Hair Loss Mechanisms	Open	high Interest					
Program Synthons	ARD-IBT-L'Oréal						Completed
Program Synthons	ARD-IBT-Rhodia			Completed			
Program Synthons	ARD-IBT-Arkema			Completed			
Human Glycosylation with Yeast	Open		high Interest				

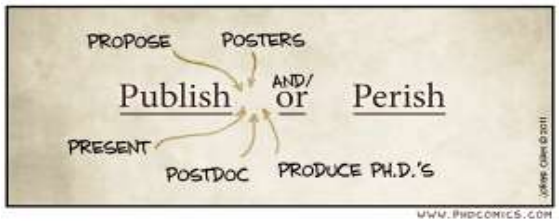
Why did we need to change the discovery paradigm?

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!

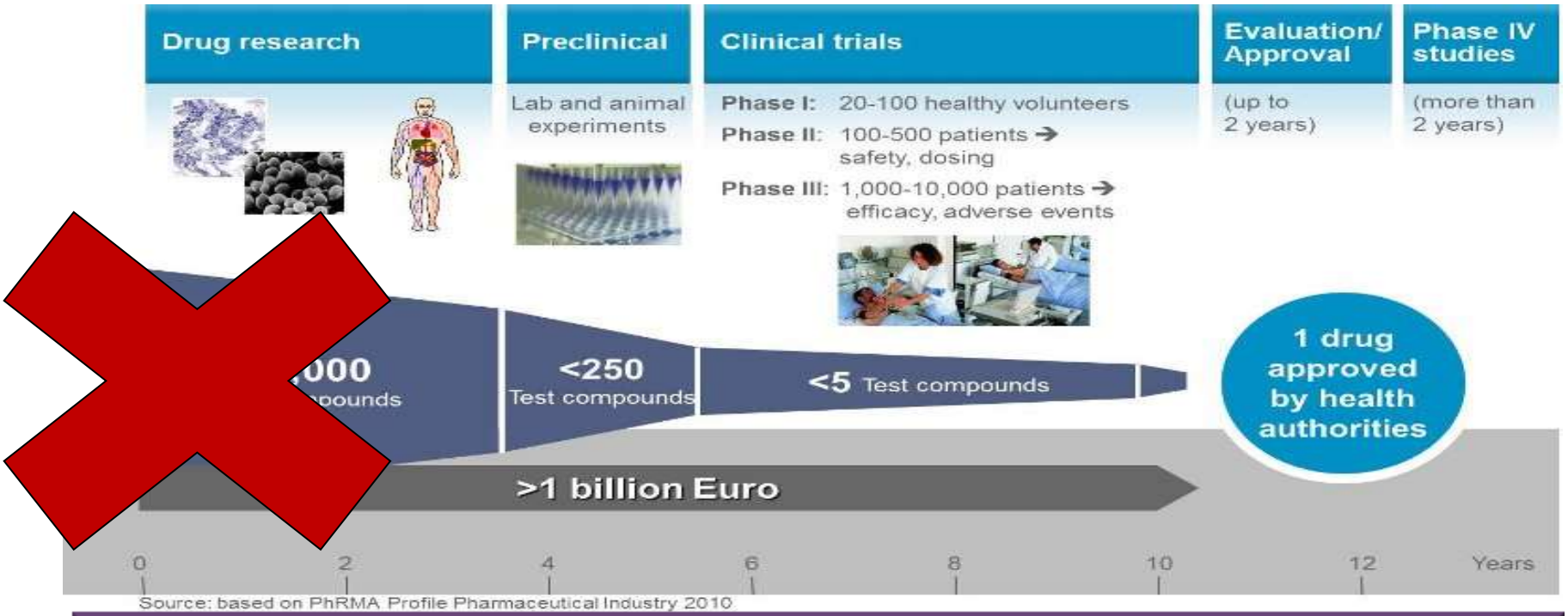
3-The "mirage" of Artificial Intelligence (AI) that MUST follow rules in a world where humans massively do not! Currently the "Garbage in garbage out" reality is not correctly treated by digital giants who consider life as only complicated.



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



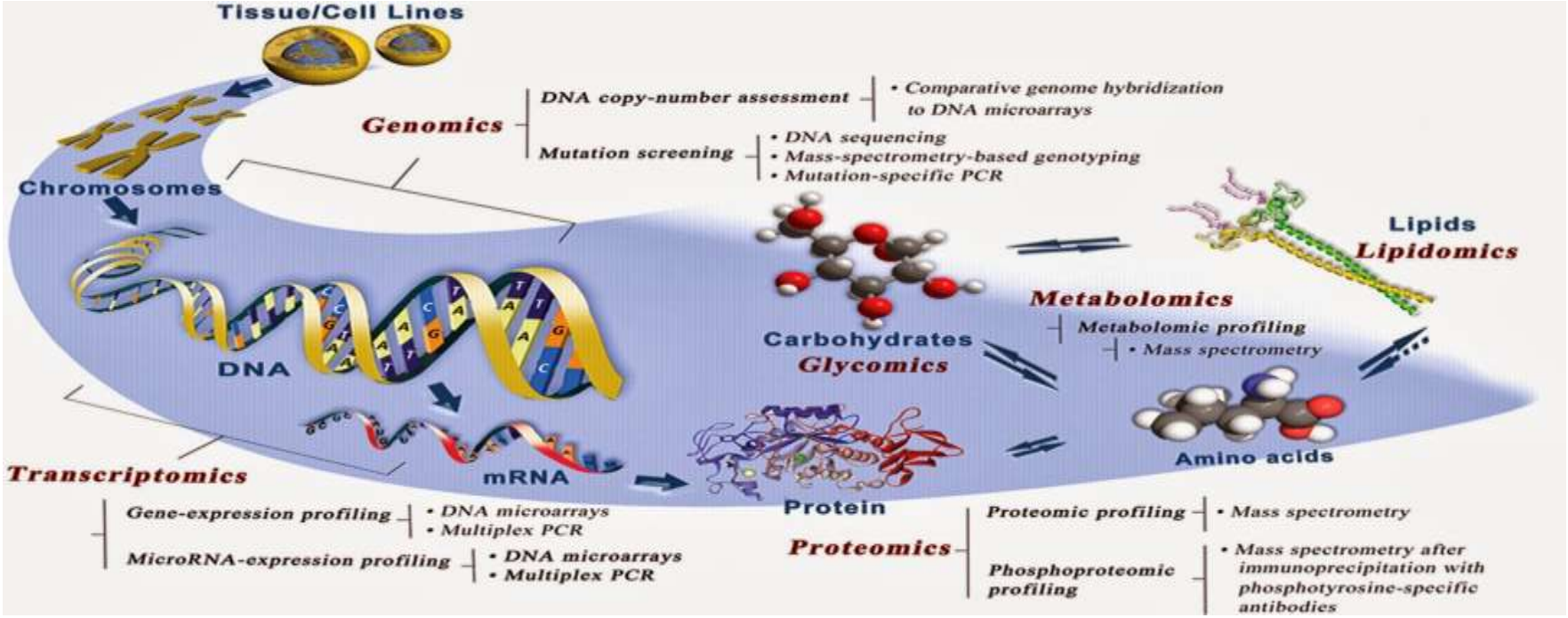
Source: based on PhRMA Profile Pharmaceutical Industry 2010

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

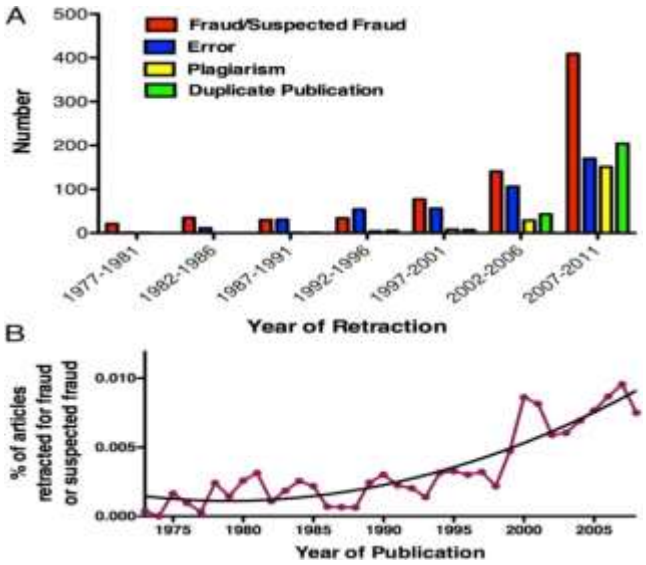
founding basements of the "big data" successes of the digital giants built for "the internet" world:	**Founding basements of Life Sciences R&D that may explain the so far unsuccessful attempts.**
1. The internet world built by humans is only very complicated not complex! 2. Personal data producers do 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

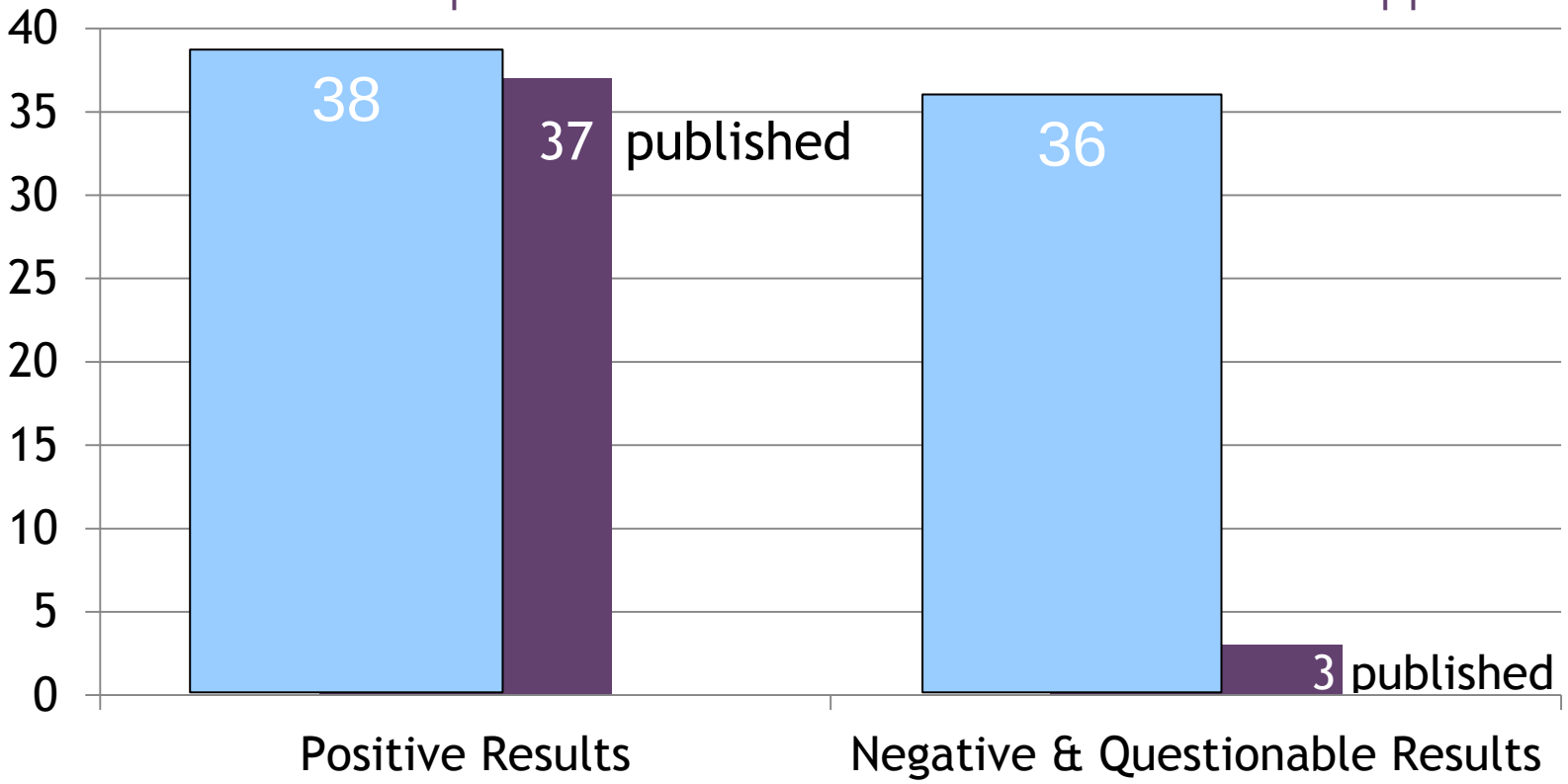


Ferric C. Fang et al. PNAS 2012;109:17028-17033

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"!

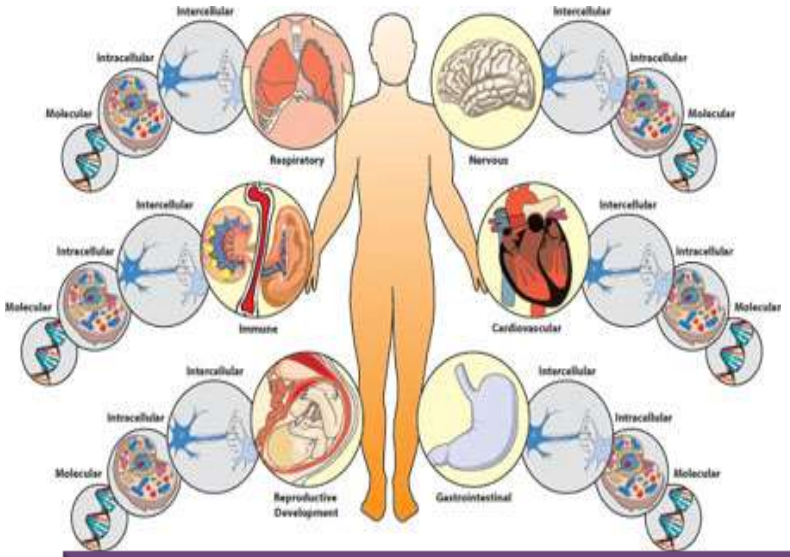
A valid solution must address both the complexity of life's mechanisms and the unreliability of scientific and clinical publications to create novel & pertinent medical meanings

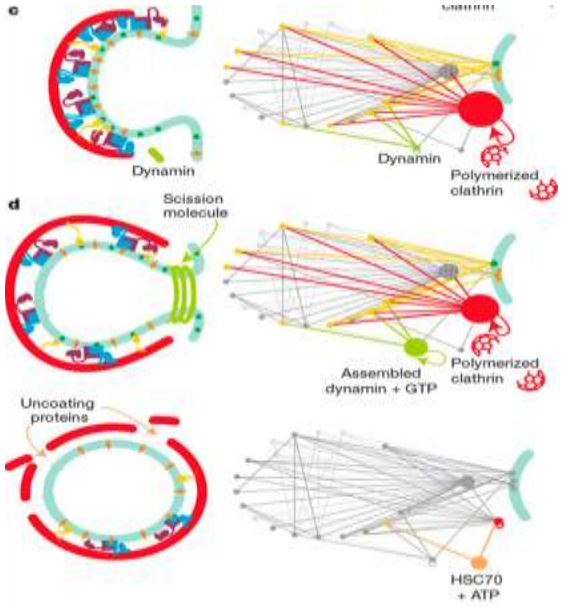
*** Based on this model,1) when birds lay eggs, they explode; 2) the rear end of a bird is extremely hot when it flies; 3) a bird has three legs, etc…. You may think this stupid, but it is what is being done with systems biology.**

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.

** Do not forget but integrate that for a disease/disorder/syndrome, similar symptoms can have very different functional origins, while similar dysfunctions can produce different symptoms. Download the dedicated presentation with the psychiatry case study*

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.

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

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 that addresses life's mechanisms complexity and the unreliability of scientific and clinical publications by combining the strengths of human and artificial intelligences in the right order.

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*).
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

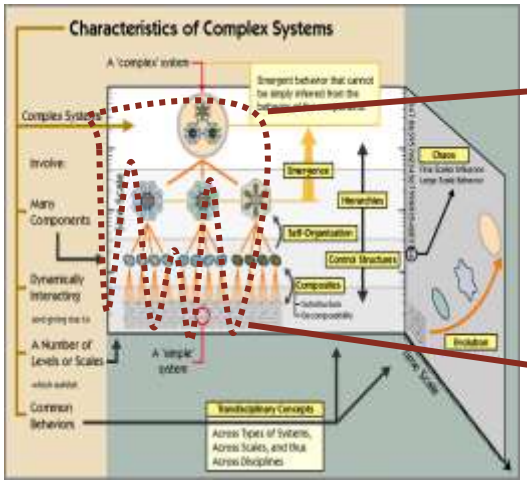
CADI*™models at a glance

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"

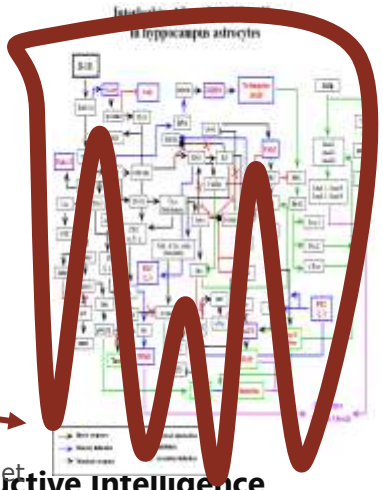
- CADI™ models are outstanding "non-mathematical" descriptive in-silico answers to explain the non-linear mechanisms of life and diseases.
- CADI ™ models can describe the cross-talks within systems and between systems (cells types, organs, etc…) and the dynamics of pathological processes and/or pathological mechanisms vs. control.
- CADI™ models describe the mechanisms that cause the diseases, not only the consequences.

A complex system to study



Scale / level

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



Different organs level

Different Cells level

Molecules level

*Computer Assisted Deductive Integration and 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.

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.*

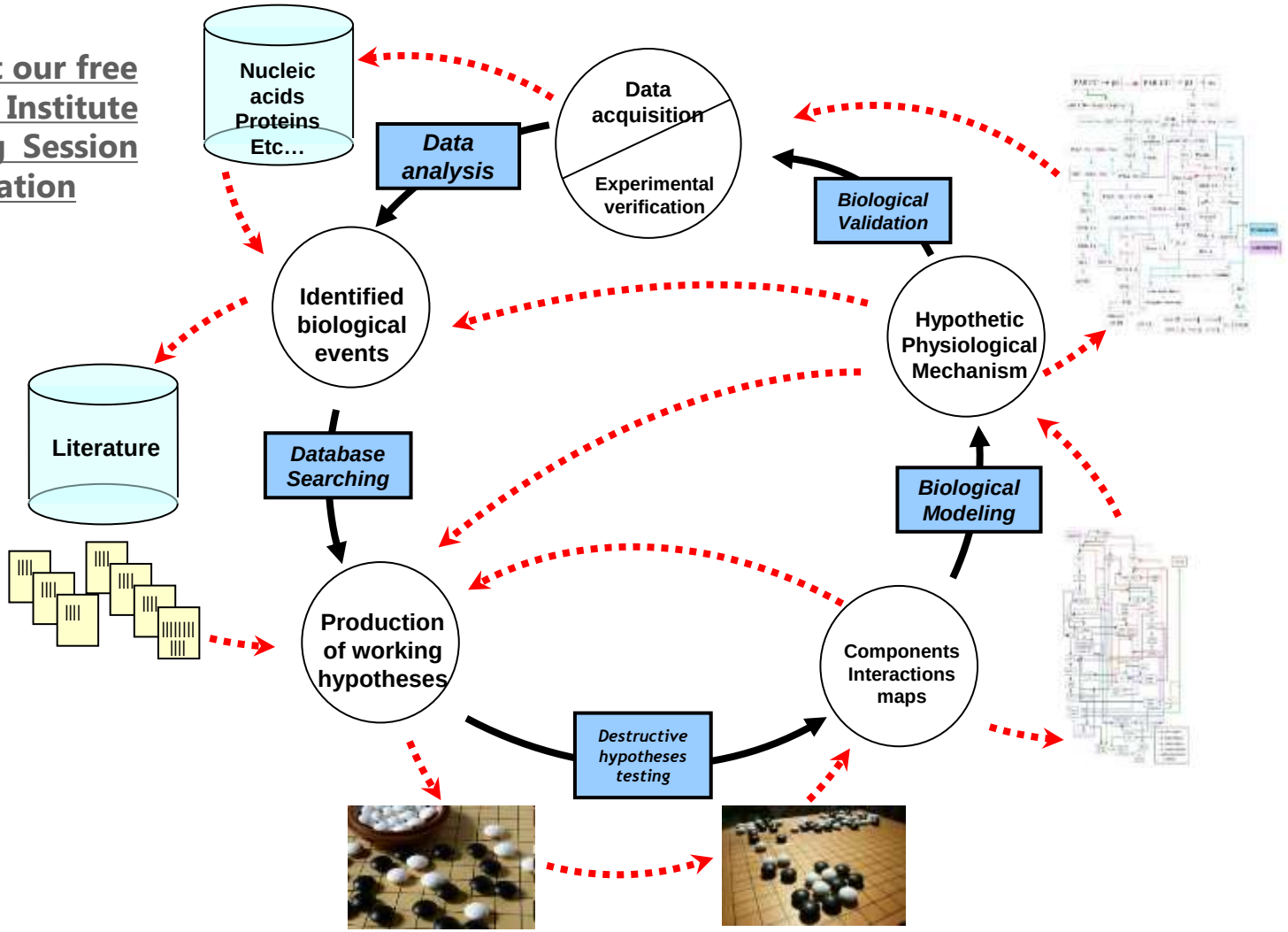
To efficiently address the translation of systems biology to clinical & medical interventions (dominated by patient's data heterogeneity and largely unstructured documents), ways to achieve synergy between Heuristic and Mathematical approaches can be effectively designed.

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

The CADI™ Integration workflow

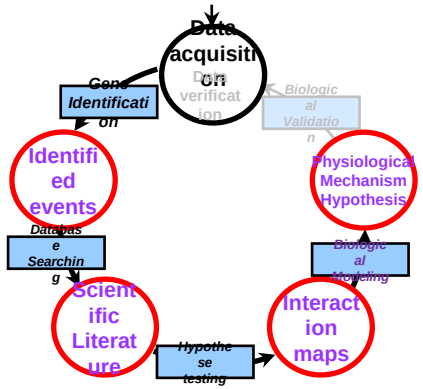
More details in the Full Presentation with CADI full Description, publications and the 10 CADI™ programs & POCS

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

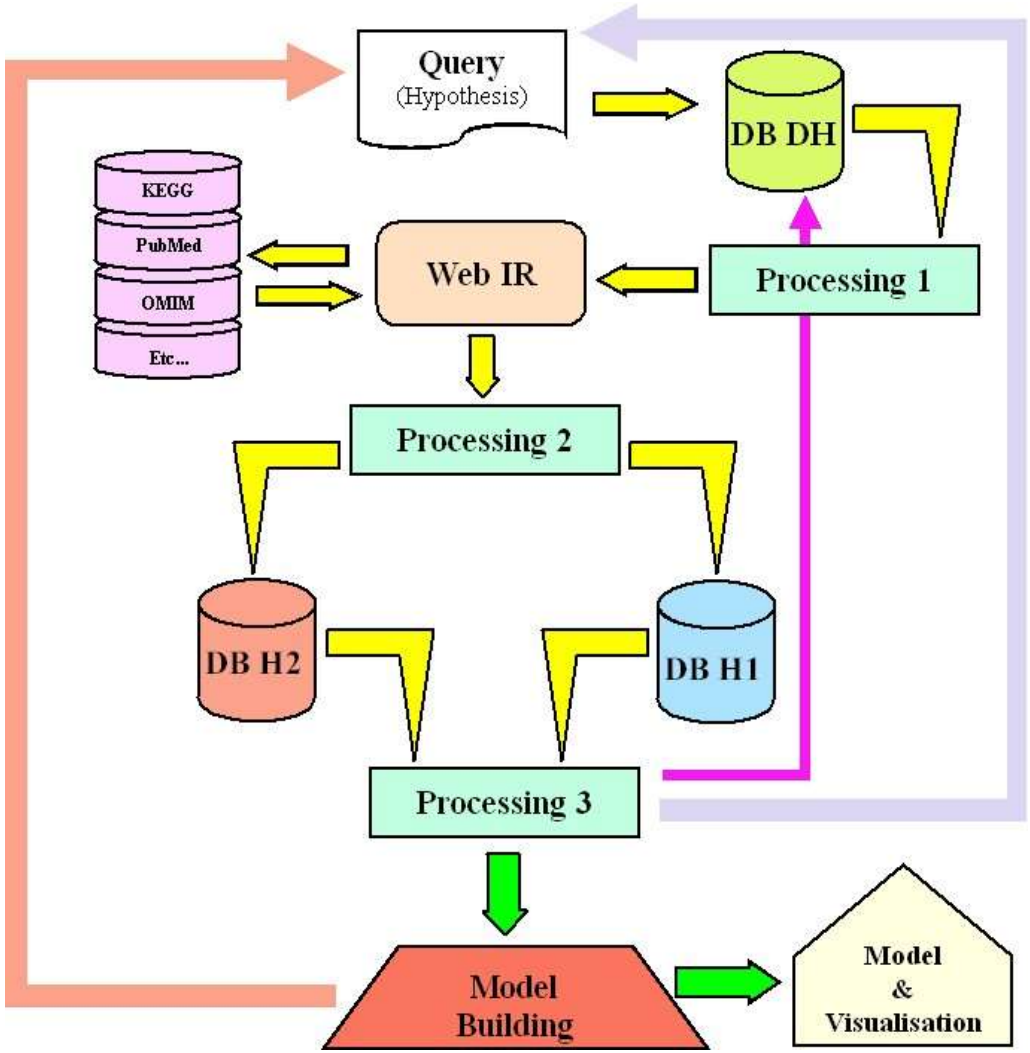


This iterative process does three things:

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

- It reveals hitherto unknown mechanisms/processes, and

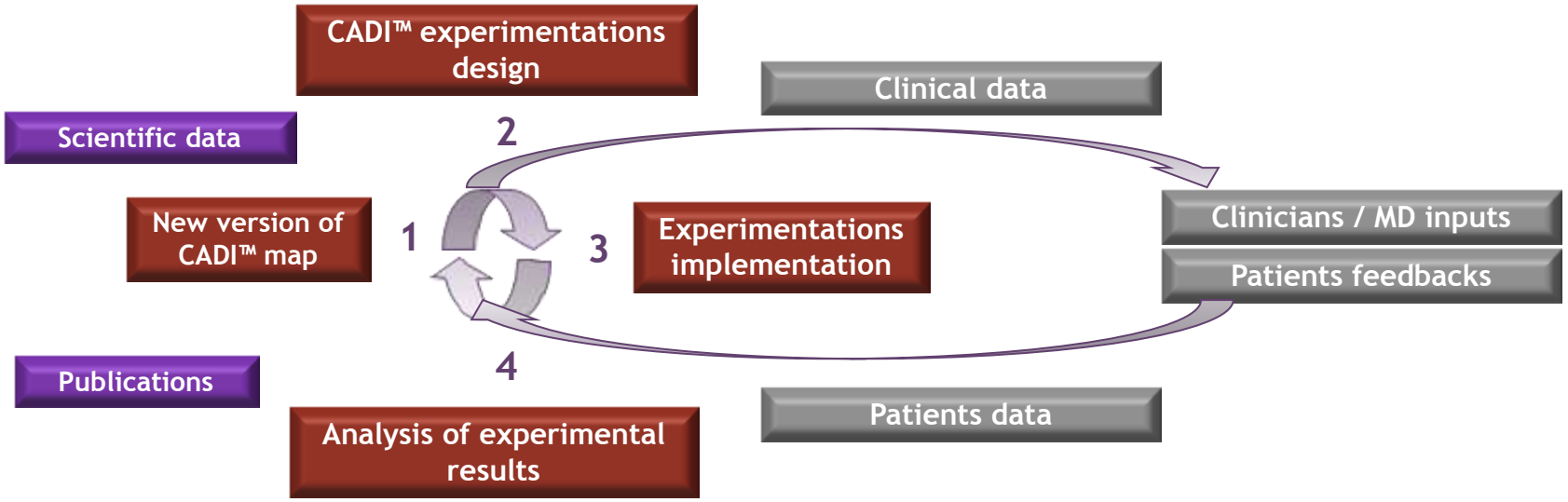
- It allows the translation of systems biology to clinical & medical interventions.



CADI™ Discovery 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' science at a glance

- Correct understanding of disease/disorder/syndrome mechanisms is the first objective. Finding the most pertinent biomarkers and therapeutic solutions is the necessary consequence of the first objective.
- We check the "CADI™ compliance" of requests in novel domains for GO NO GO decision before launching the full CADI™ Discovery program. We are information-dependent not domain-dependent.
- CADI™ Discovery was invented in 2002 by Dr. François IRIS, geneticist, physiologist & molecular biologist. Our IT people, from the digital world, developed the platform to "help" our biologists work.
- CADI™ Discovery addresses the recurrent causes of failures in the "dominant thinking" systems biology programs: the issues of "life mechanisms complexity" and publications unreliability.
- CADI™ Discovery is operated by biologists to generate and destroy the maximum of working hypotheses before starting the experimental validation phase.
- Our biologists build heuristic non-mathematical holistic models to generate novel disruptive physiological/ medical meanings from scientific, medical & health smart data.
- CADI™ Discovery, our proprietary CADI™ Knowledge Database of mechanisms & interactions and our CADI™ domains cross-fertilization process cannot be compared to classical systems biology or bioinformatics. Only discovery processes already delivering novel therapies should be the benchmarks.
- Highly productive, we successfully conducted R&D programs in the fields of neurology, inflammation, metabolism, immunology, addressing neurodegenerative diseases (Creutzfeldt-Jakob's, Parkinson's & Alzheimer's diseases), psychiatry, autism, cancer, diabetes, longevity/aging, infections, dermatology, skincare and cosmetics.

Whatever the technologies: The final objective remains developing cost-effective solutions for patients

BMSystems' detailed answers to clients/partners issues

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

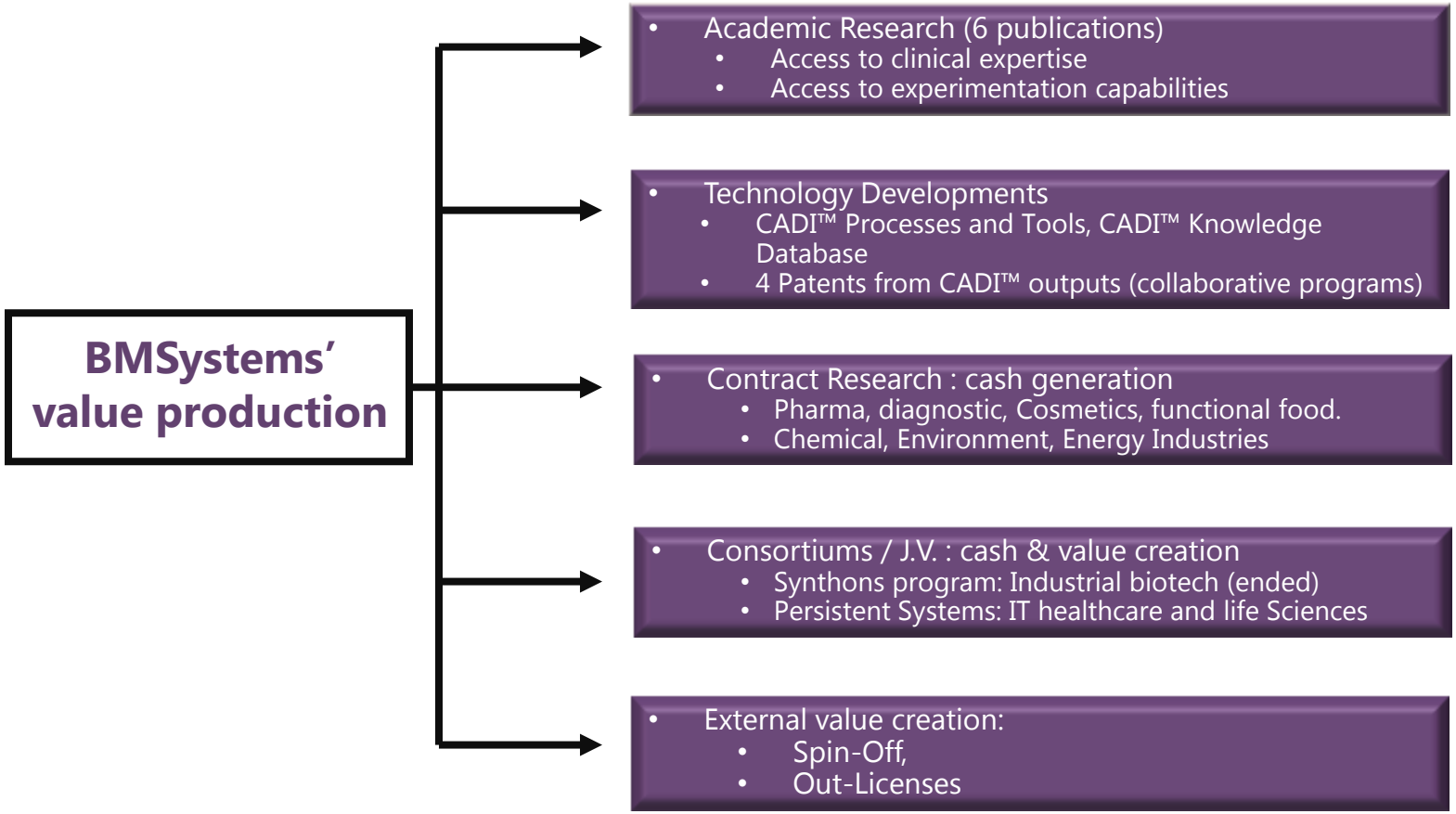
biomedical, diagnostic, Pharma, cosmetics, nutrition, food, chemistry, environment, energy.

BMSystems' outputs

- Physiological / Diseases Mechanisms understanding
  - Multi-Systems mechanisms
  - Multi-Scale mechanisms description
  - CADI™ knowledge Data Base
  - CADI ™ Cross-fertilization Process
- Targets discovery & validation.
- Signatures of biomarkers discovery & validation.
- Marketing strategies rational support
- Adaptive clinical trials rational support
- Market Access rational support
- New therapeutic / diagnostic / cosmetics strategies,
  - New associations of molecules & devices
  - New associations of existing molecules
  - Molecules / Devices Mechanisms of action
- R&D / Molecules / clinical programs evaluation:
  - Next Phase GO / NO GO decision
  - Novel Clinical phases end points / processes
  - Drug (re) positioning / (re) profiling / rescue
  - Rare diseases drugs repositioning
  - Drug side effects analysis for rescue
  - Chemical entities safety issues (Allergy, PE, etc…)
- Proposition of new bio-production processes (Synthetic Biology) through micro-organisms modifications (bacteria, yeast).

BMSystems' original dual business model

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



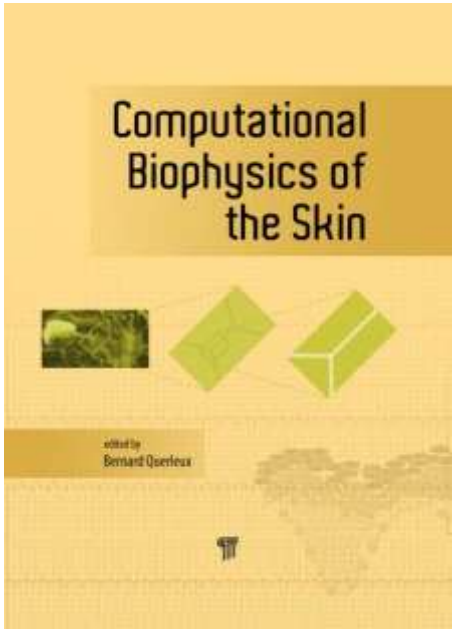
Why do we need to change the dominant discovery paradigm? **(supporting documents: click on the links for details)**

- 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.

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*



Contributor to 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. R&I L'Oréal.

Program Name	Validation / Business Partner(s)	CADI™ compliance	CADI™ vers. 0
Skin Contact Allergy Mechanisms	Open		high Interest
Skin pigmentation Mechanisms	Open		high Interest
Skin pigmentation Modulation	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	

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

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?

Email: manuel.gea@bmsystems.net Join my networks