

Bio-Modeling Systems

The Mechanisms-Based Medicine Company



**Everything you always wanted to know about Digital and AI
Health revolution but were afraid to ask!**

Computer Augmented Intelligence, the other complementary AI Rational

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

Conference INSEAD Alumni at BCG Paris Office July 4, 2017
updated September 2019

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

What type of Systems are we talking about?



Complicated Systems



Complex Systems

Two systems with completely different behaviors
The biggest is not necessarily the most complex!

The nightmare of new mums.

The mission: build a model to simulate the behavior of spaghettis to prevent spots



The right question is: how does she protect clothes from spaghetti sauce ?

The discovery of the BIB concept by Mum:
A non-cartesian discovery but a Cartesian production process

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 ...

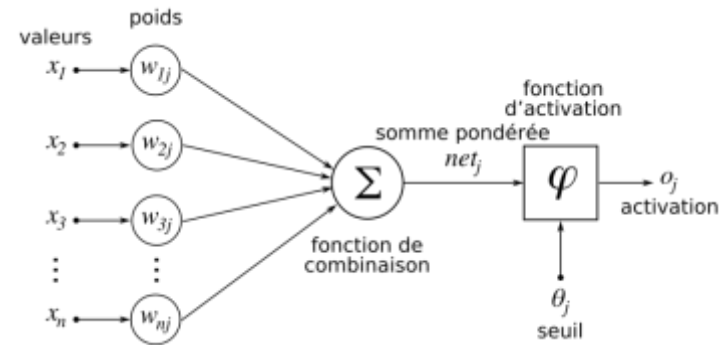
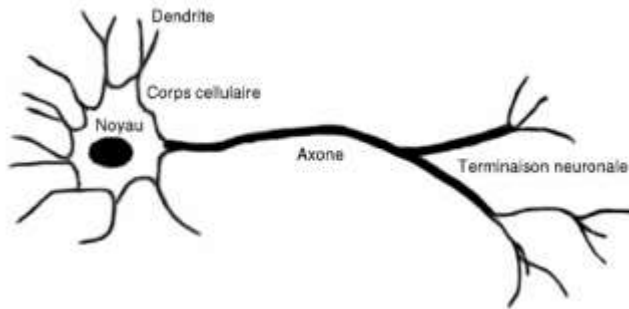


4-...you'll get a Complicated "Cartesian" system. It flies... But the major issue is that, for modelers, this is a bird!*

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.

"Reductionism" creates clear misunderstanding



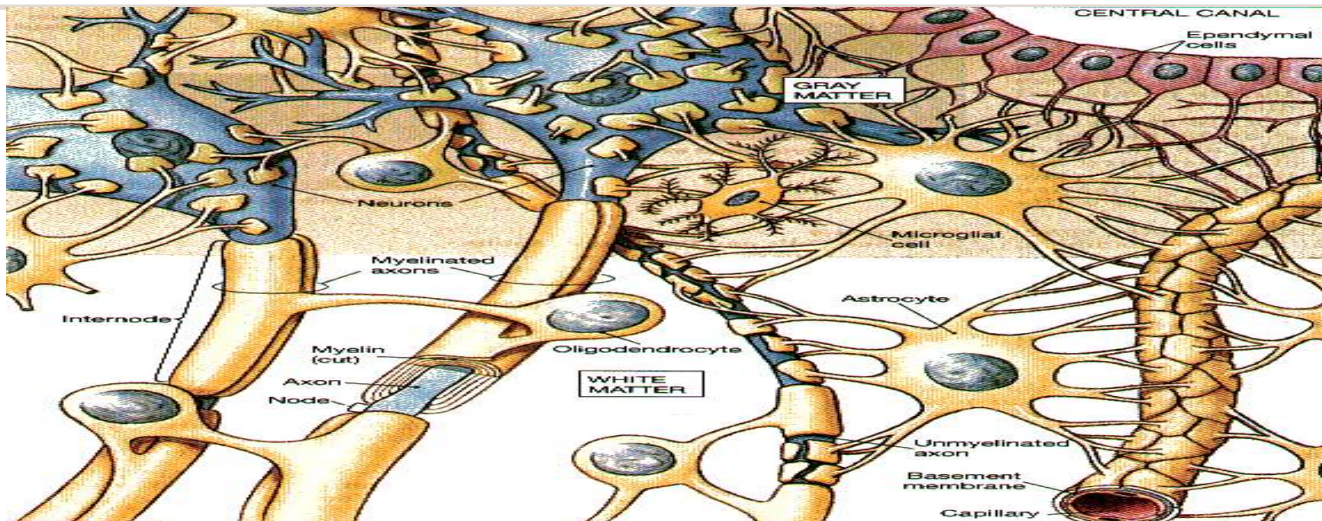
Initially 1 billions € to simulate the complete human brain on supercomputers simulating neurons to better understand how it functions

The program did not delivered and was dramatically reduced:

<https://www.scientificamerican.com/article/why-the-human-brain-project-went-wrong-and-how-to-fix-it/>

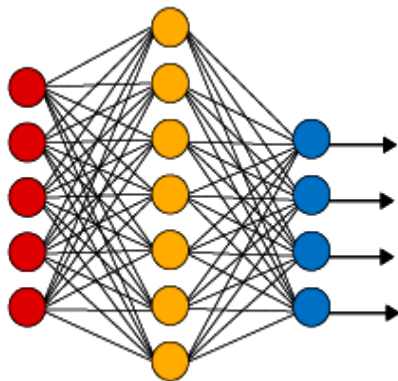
But the brain Complex, the program failed to deliver due to its founders exaggerated ambition

Because the brain can't be reduced to its neurons only!

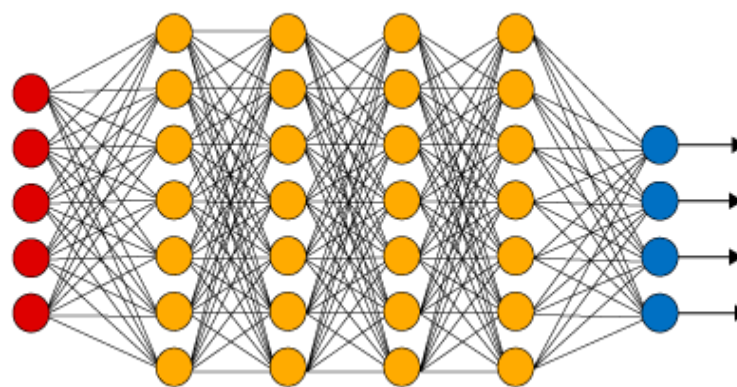


The word "Deep" learning refers to the number of layers only!!!

Simple Neural Network



Deep Learning Neural Network



 **Input Layer**

 **Hidden Layer**

 **Output Layer**

The long AI History: What's next step

AI HAS A LONG HISTORY OF BEING "THE NEXT BIG THING" ...



Timeline of AI Development

- **1950s-1960s:** First AI boom - the age of reasoning, prototype AI developed
- **1970s:** AI winter I
- **1980s-1990s:** Second AI boom: the age of Knowledge representation (appearance of expert systems capable of reproducing human decision-making)
- **1990s:** AI winter II
- **1997:** Deep Blue beats Gary Kasparov
- **2006:** University of Toronto develops Deep Learning
- **2011:** IBM's Watson won Jeopardy
- **2016:** Go software based on Deep Learning beats world's champions

Source: <https://www.actuaries.digital/2018/09/05/history-of-ai-winters/>

The IA and Big Data Giants do not deliver their promises

For The latest and cumulative alerts



Google's Health Moonshot Comes Back to Earth: Verily Life Sciences is beginning a four-year health-tracking study that likely costs eight figures. *Bloomberg April, 19, 2017*
By Caroline Chen and Mark Bergen



Latest news: IBM halting sales of Watson AI tool for drug discovery amid sluggish growth [says STATNews](#)

How IBM Watson Overpromised and Underdelivered on AI Health Care [says IEEE Spectrum!](#)
IBM Has a Watson Dilemma. Big Blue promised its AI platform would be a big step forward in treating cancer. But after pouring billions into the project, the diagnosis is gloomy. [The Aug. 11, 2018 12:19 a.m.](#)

MD Anderson Drops IBM Watson – A Setback For Artificial Intelligence In Medicine ?

AI alert: "IBM's Watson supercomputer recommended 'unsafe and incorrect' cancer treatments" reveal [StatNews](#) & WSJ Forbes

And, the real IA professionals and regulators start to move



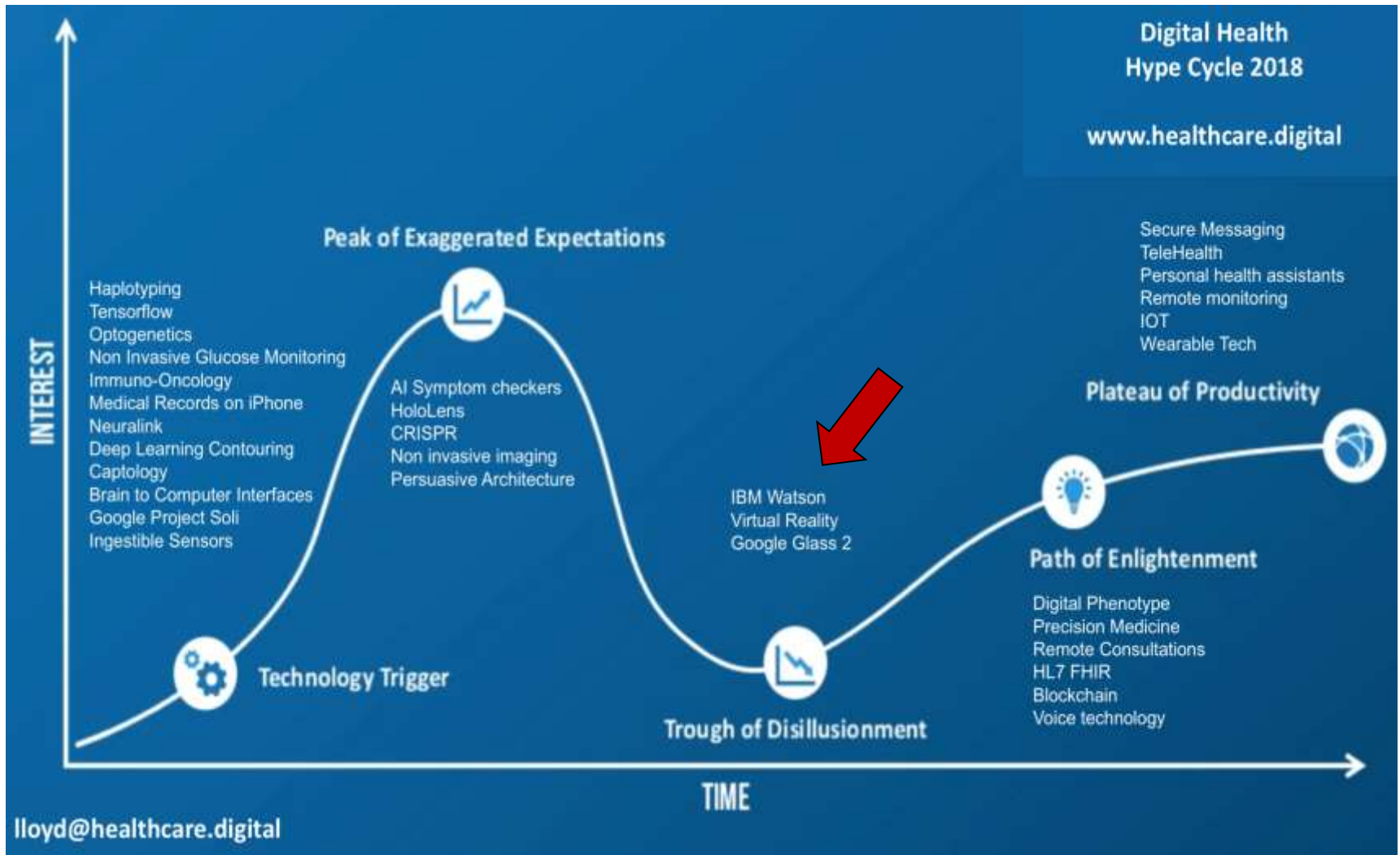
"L'intelligence artificielle a moins de sens commun qu'un rat" Yann Le Cun Dir. Facebook AI Research dans une interview vérité *"Ce qui manque aux machines [pour dépasser l'homme], c'est l'intelligence générale"*



"Artificial Intelligence does not exist" says Luc Julia the Innovation VP Samung (2019). What is called generalized AI does not exist and with current techniques it will never exist. What is called weak AI is the artificial intelligence of today, it is what we do with automatic learning, deep learning and has nothing to do with intelligence.

"La robustesse de la décision et l'explicabilité de la prise de décision algorithmique devront être garanties. La HAS favorable à l'adoption de normes de développement des algorithmes en santé."

Digital Health: uncontrolled marketing vs reality?



The 2 visions of the world: Holism - Reductionism

Holism	Reductionism
1. Complex Systems	1. Complicated Systems
2. Systems Biology	2. Bioinformatics
3. General Semantics	3. Cartesianism
4. Medical Practices, Protocols	4. Machine Learning, Big Data
5. "Mechanisms-based Medicine"	5. Evidence-Based Medicine
6. Human Intelligence.	6. Artificial intelligence
7. Descriptive modeling	7. Mathematical simulation
8. Complete natural products	8. Pure active ingredient
9. Take care of the patient	9. Take care of the disease
10. Sociology, Mechanisms of the living, The nature that surrounds us	10. All the products created by the man the world we built

The objective should be to take the best of the two paradigms

The Differences of “Internet” and “Life sciences” worlds

founding basements of the “big data” successes of the digital giants built for “the internet” world:

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.

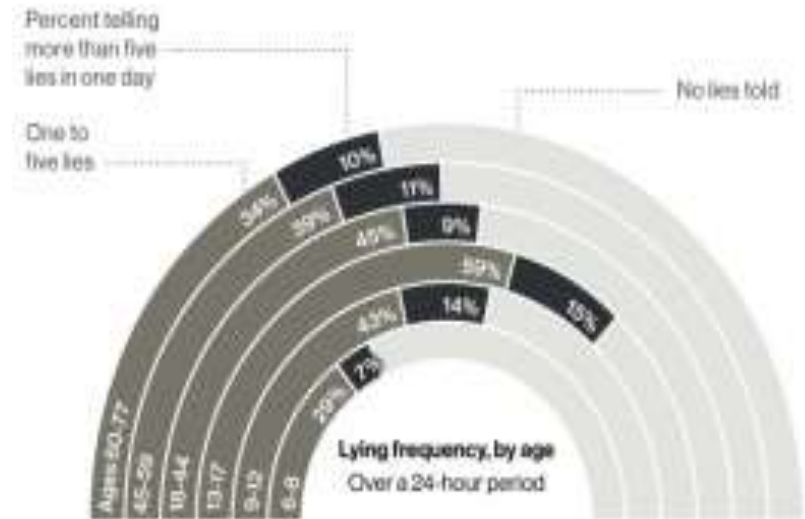
Founding basements of Life Sciences R&D that may explain the so far unsuccessful attempts.

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 the same rules.

Integrity-reliability index

We all lie, but not all lies are the same. People lie and tell the truth to achieve a goal: “We lie if honesty won’t work,” says researcher Tim Levine.



RYAN MORRIS, NGM STAFF; SHELLEY SPERRY

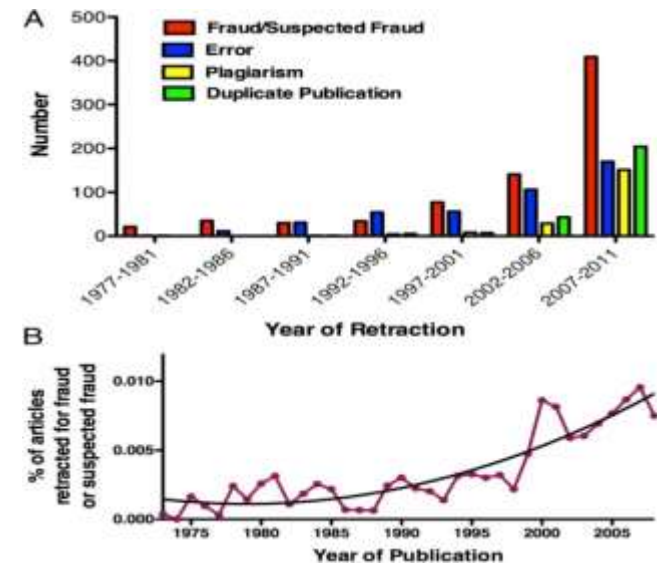
Source: <https://www.nationalgeographic.com/magazine/2017/06/lying-hoax-false-fibs-science/>

We must differentiate “Stochastic” Lies “necessary” for social life with “Systemic” Lies that have sustainable consequences. The objective is to use and combine the right concepts and tools adapted to address the natural nature of human beings for lying. In life sciences and medical research “systemic” liars can lead to death!

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)

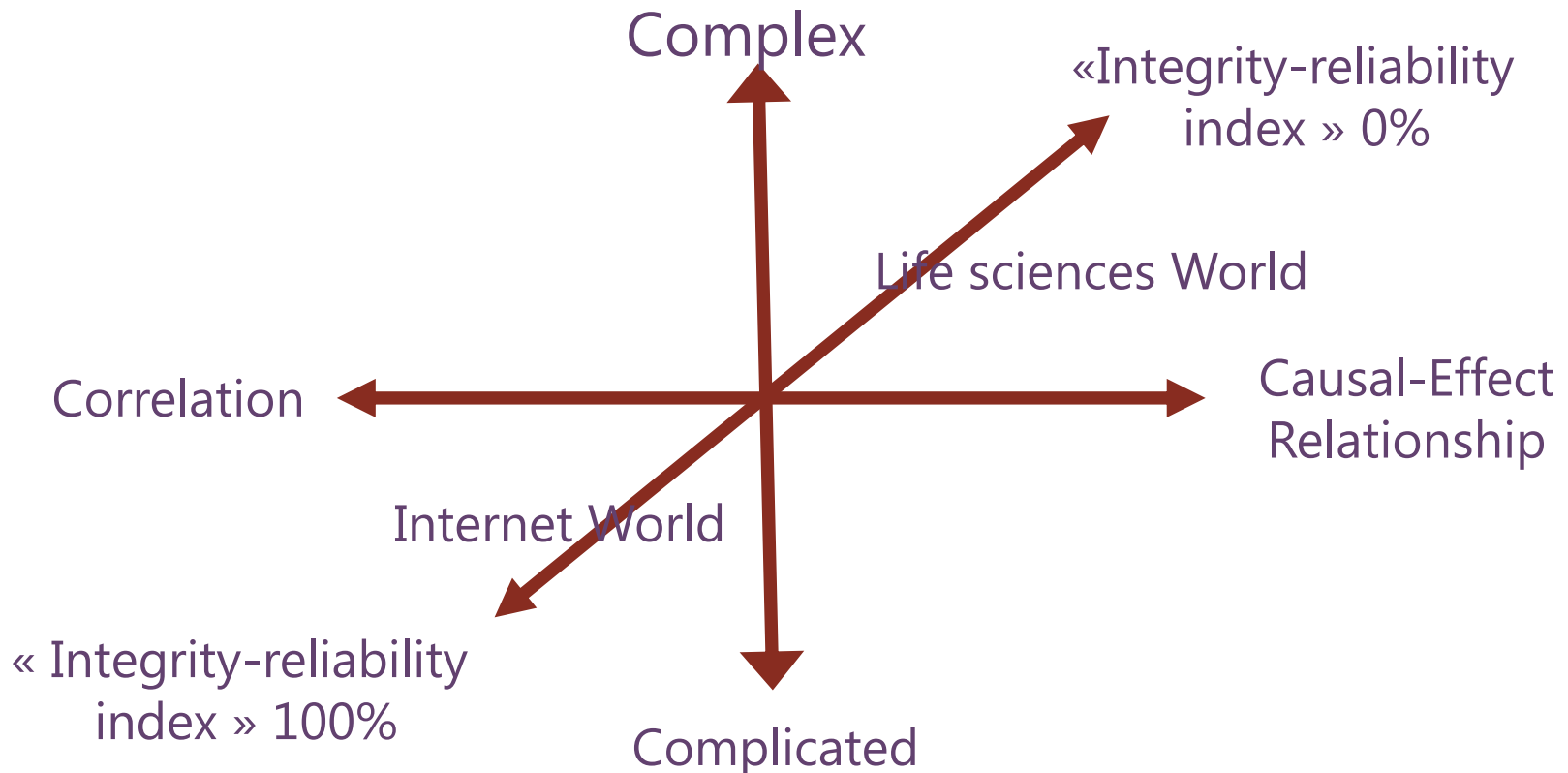
Number of retracted articles for specific causes by year of retraction



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

The 3 dimensions to describe the system type



The objective is to use and combine the right concepts and tools adapted to the nature of the problem (such as heuristic modeling / mathematical modeling)

The Future of Life Sciences & Medicine



Google, Watson, etc... with their Artificial Intelligence

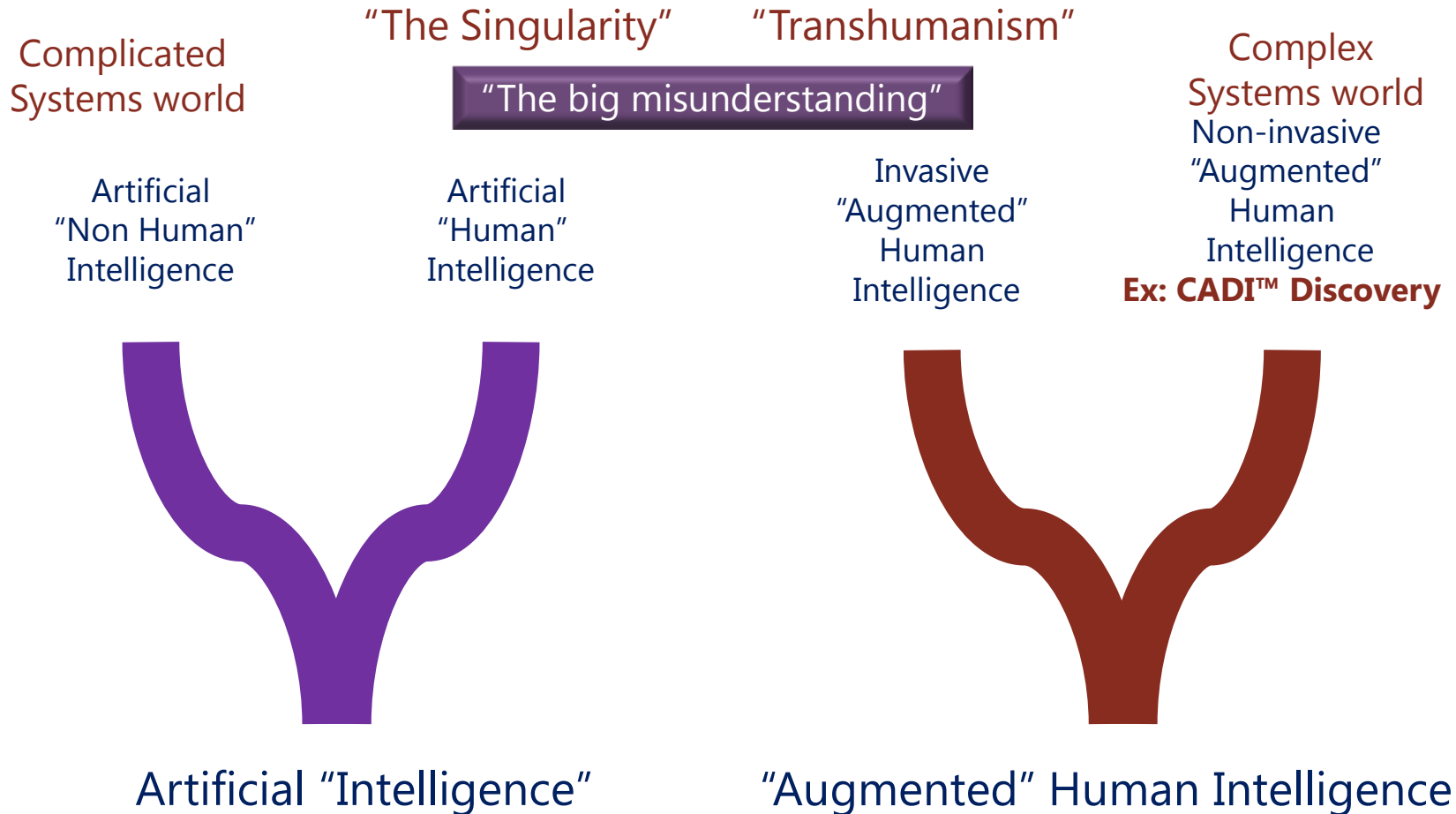
OR

Smart MDs, Biologists, Physiologists, nurses, other Healthcare professionals educating and mastering them



CADI Discovery: Computer Augmented Deductive Intelligence
The best collaboration between the two "complementary intelligences"

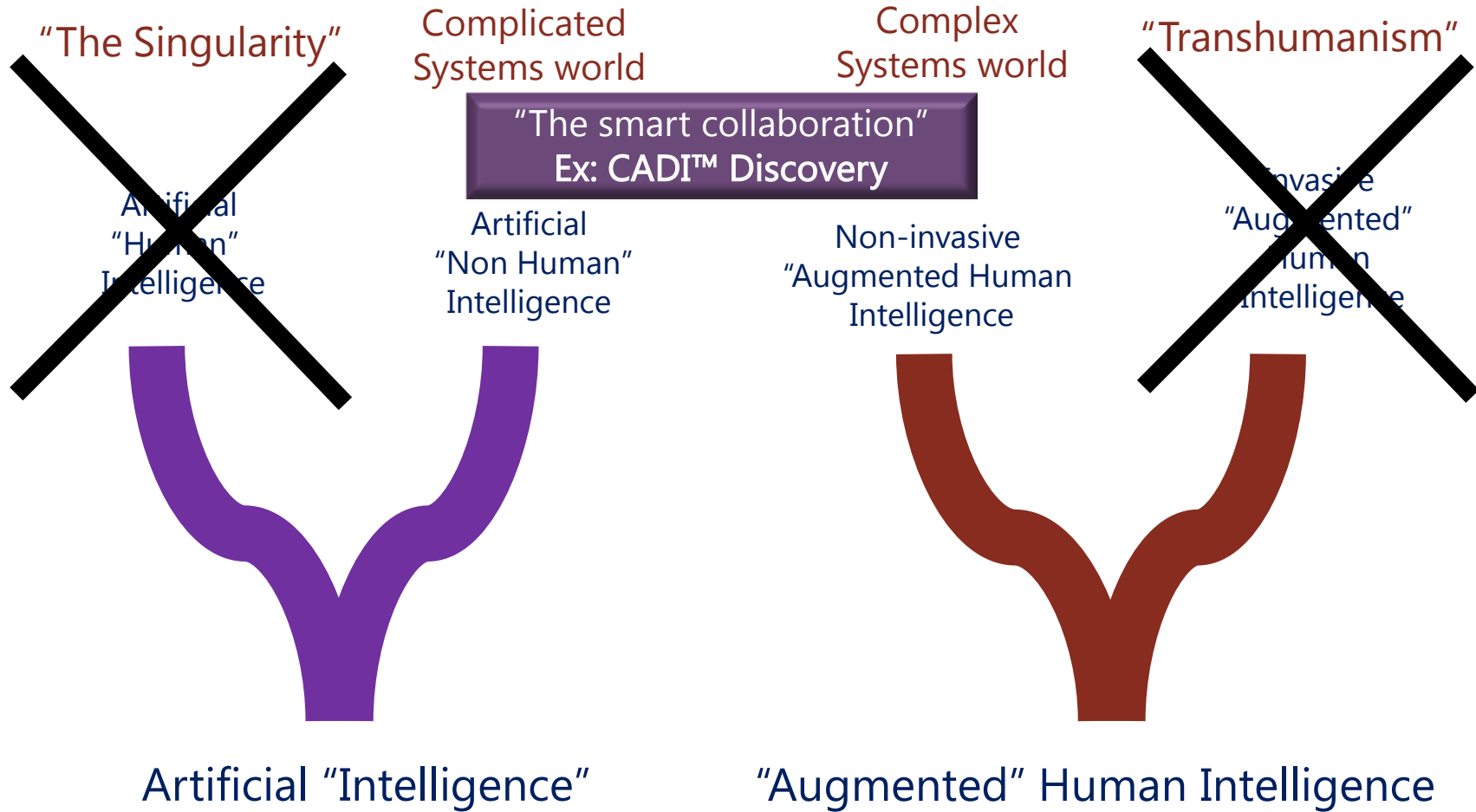
The Artificial vs Augmented Intelligence Story



What should be the most productive collaboration?

CADI Discovery belongs to the Non-invasive "Augmented" Human Intelligence concepts

The smart Collaboration Artificial - Augmented Intelligence



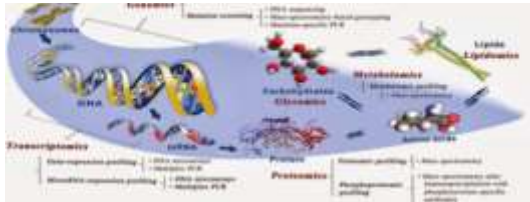
The smart collaboration in the right order

CADI Discovery belongs to the Non-invasive "Augmented" Human Intelligence concepts

Why did we need to change the discovery paradigm?



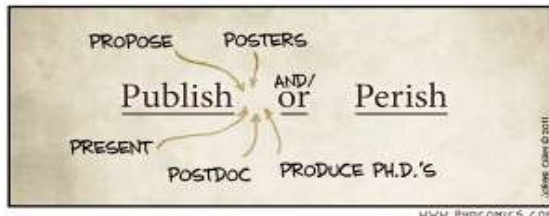
1-The industry is under high pressure by too high failure rates (90%-95%) and payers no more willing to pay premium therapies with very limited patient benefit.



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!



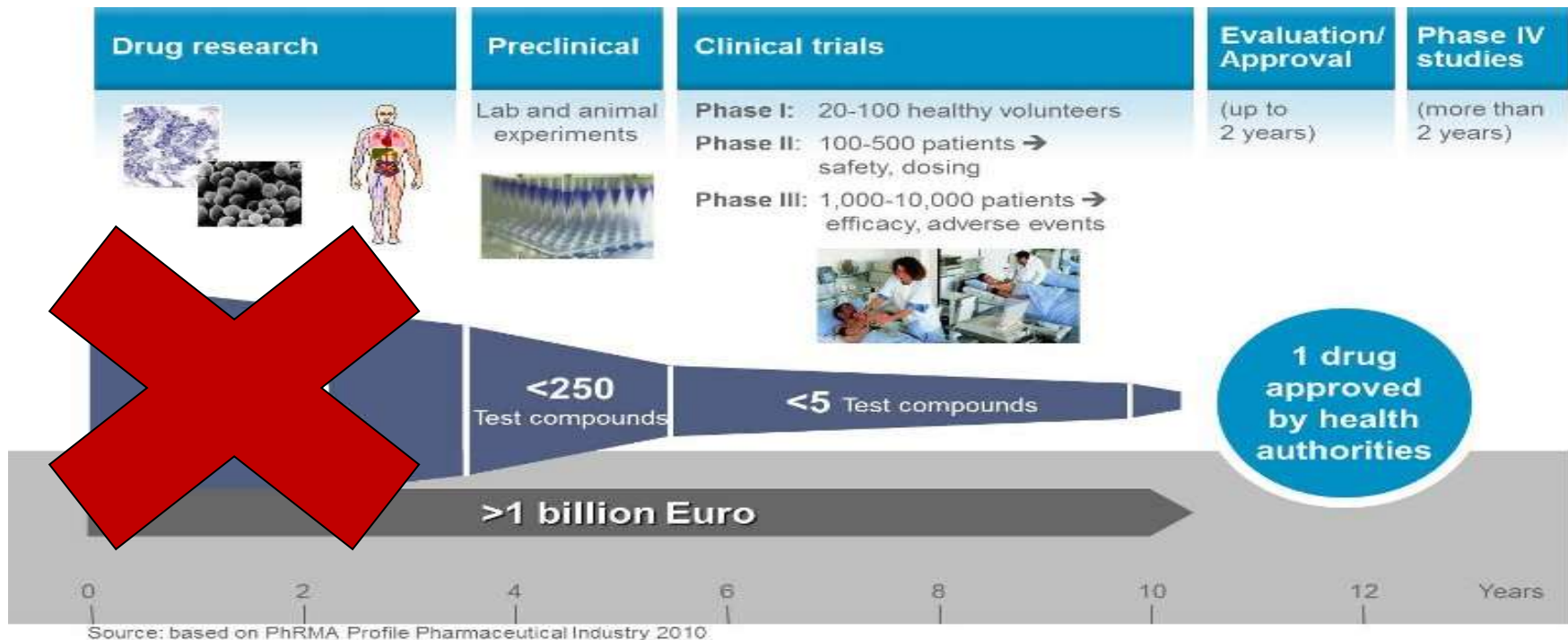
3-The "mirage" of Artificial Intelligence (AI) that MUST follow rules in a world where humans massively do not! Currently the "Garbage in garbage out" reality is not correctly treated by digital giants who consider life as only complicated.



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

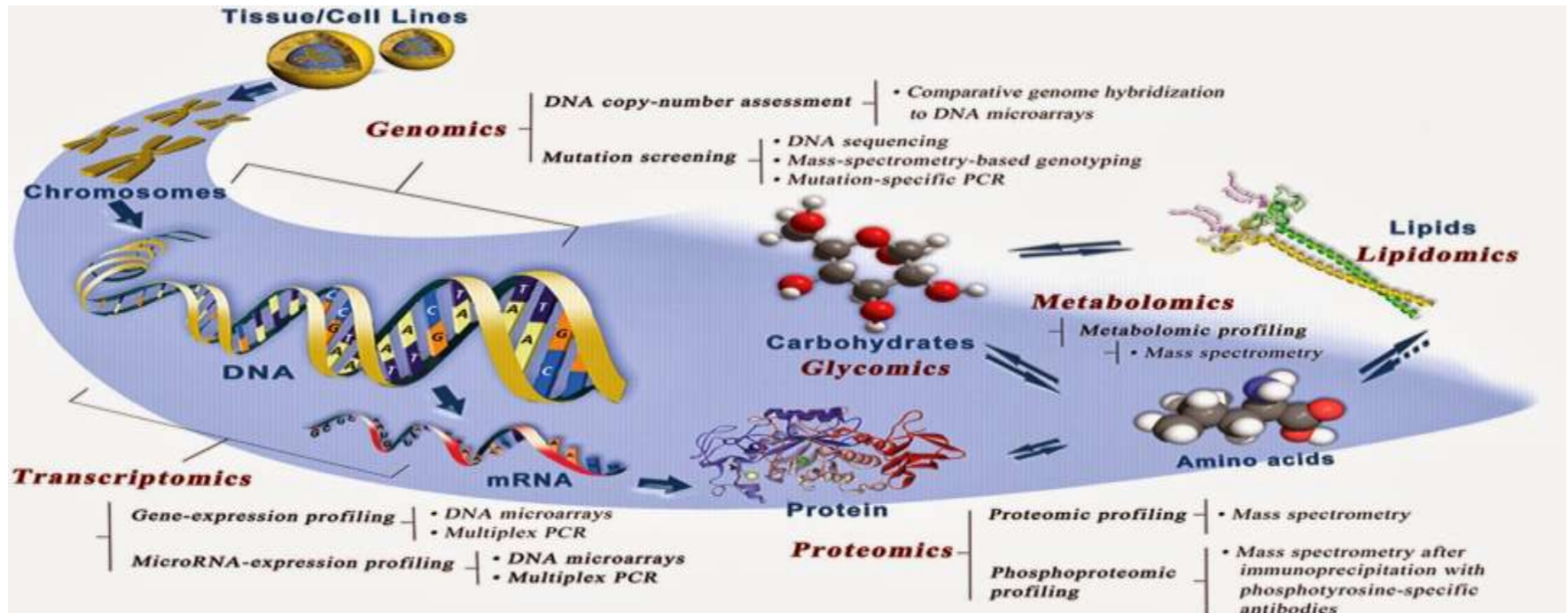


With a 90%-95% failure rate this Big Pharma R&D model focused on testing new patentable compounds for novel targets based on KOL concepts is not performant!

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?

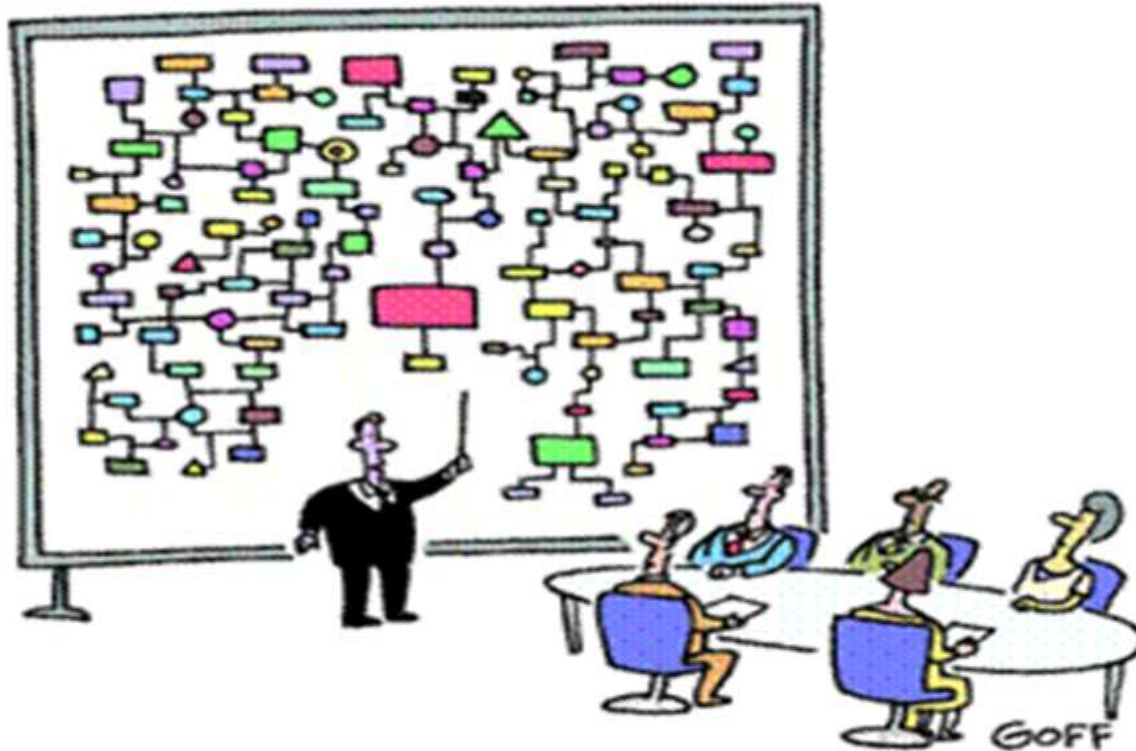
Understanding and validating the mechanisms of a disease/disorder becomes the first objective.
Finding the most adapted solutions is a necessary consequence of the first objective

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

Floods of heterogeneous data exponential growth



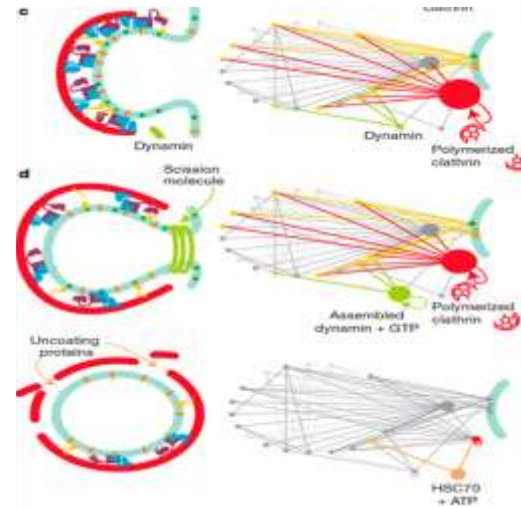
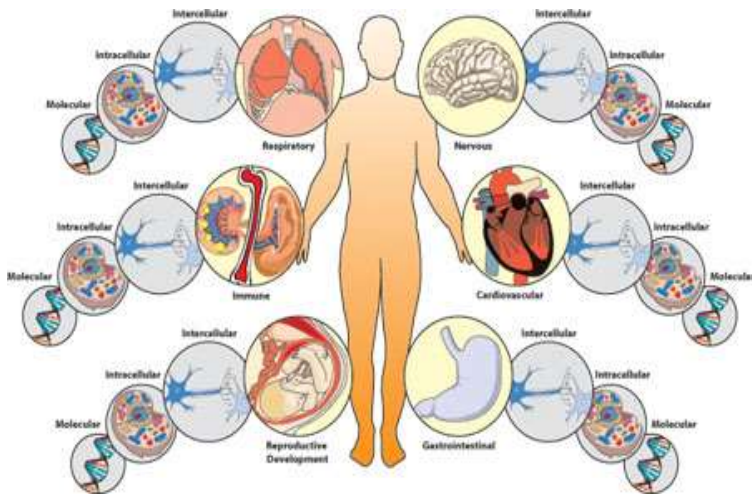
« **And that's why we need a computer.** »

Integrative biology became "bio-informatics"
The new Eldorado for IT and technology sellers
IT, HPC, Big Data Big knowledge or big Garbage?

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, nutriment, 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

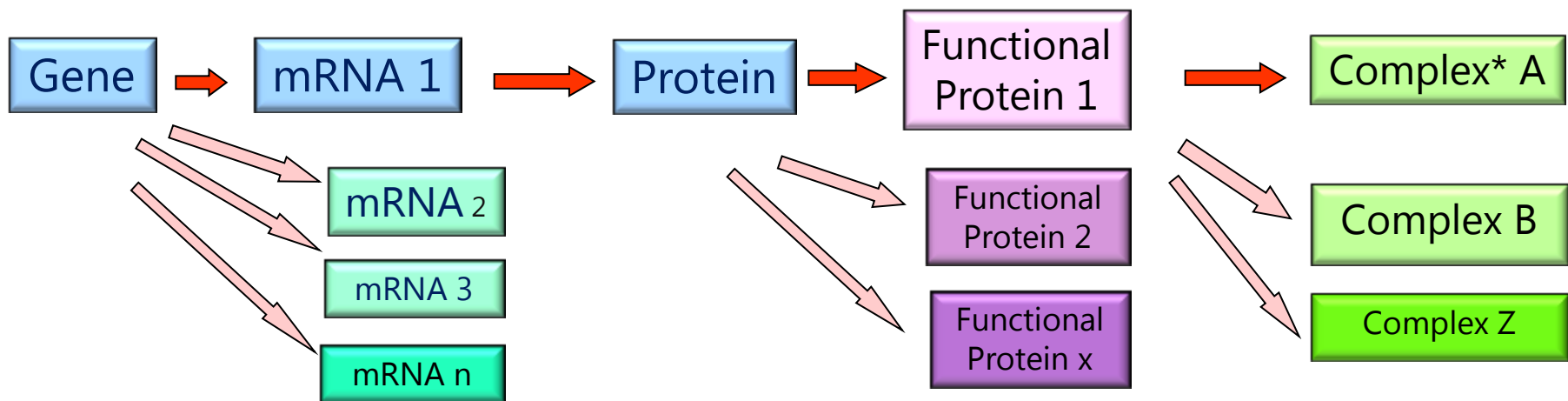
The life mechanisms reality

From genes to physiological functions:

Four series of deconvolutions and discontinuities:

At each step, the alternative options are context-dependent AND cannot be directly predicted

One gene = several different physiological functions



A non-linear integrative system.

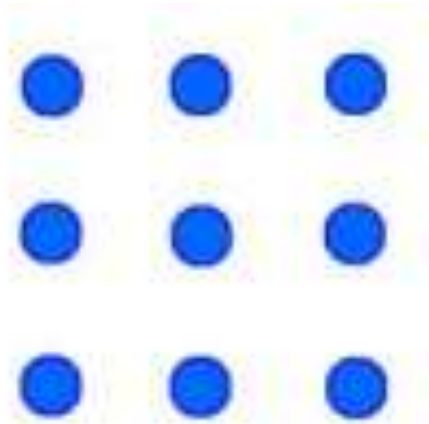
At each step, the alternative options are context-dependent AND cannot be directly predicted.

25 000 genes for more than 1 000 000 proteins functions.

DNA alone cannot explain life functions

Complex Problems Solving with a simple example

Complex Problems Solving



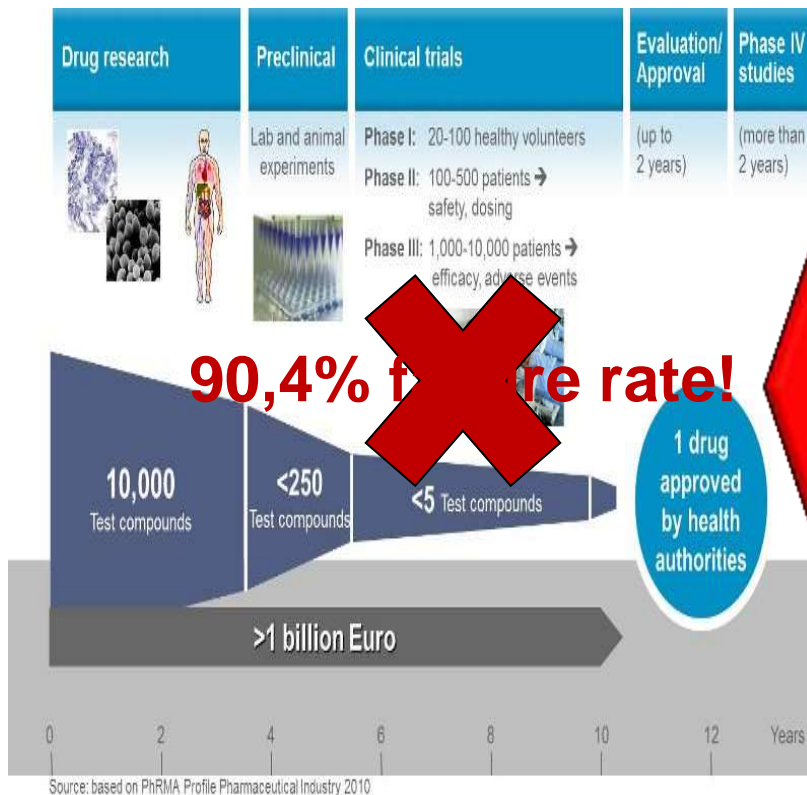
Problème



Think and do out of the box!

The Global Health dilemma

Evidence-Based Medicine



Real life Medicine

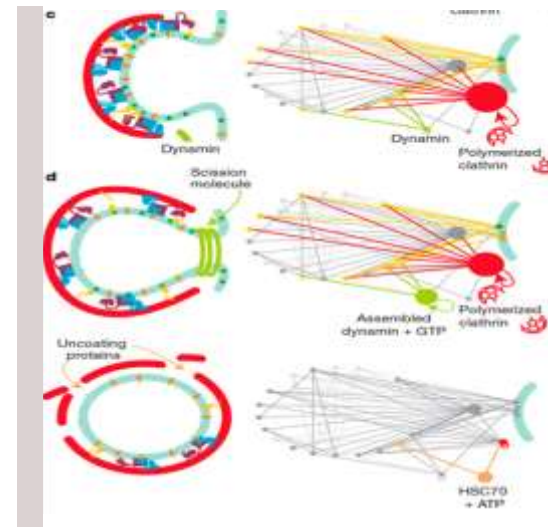
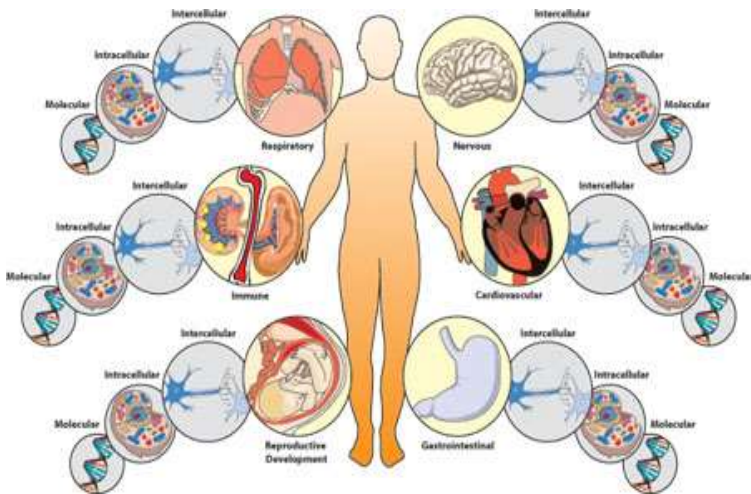


90,4% failure rate! And “usages” that still need to prove their long run ROI
Cartesian solutions for Complex Systems issues can improve?

What leads to Therapeutic Success?

The success of a therapeutic approach

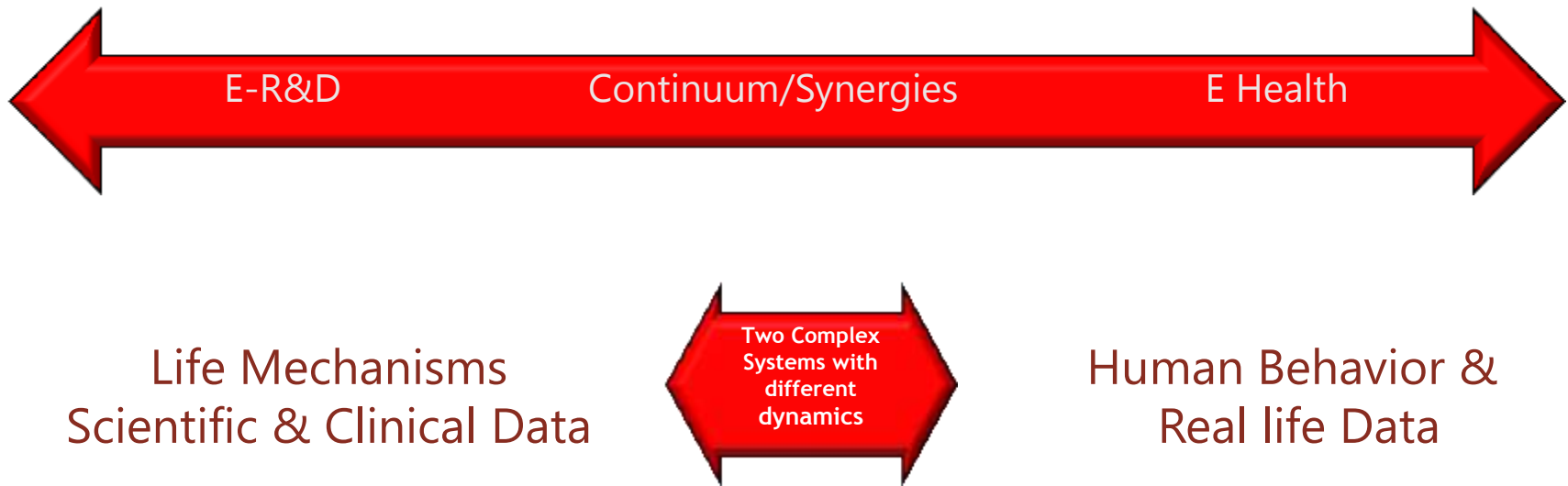
and not from that of a target in a molecular context.



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

The Holy Grail of the Healthcare industry

From bench to bed to real patient health processes



Information technologies

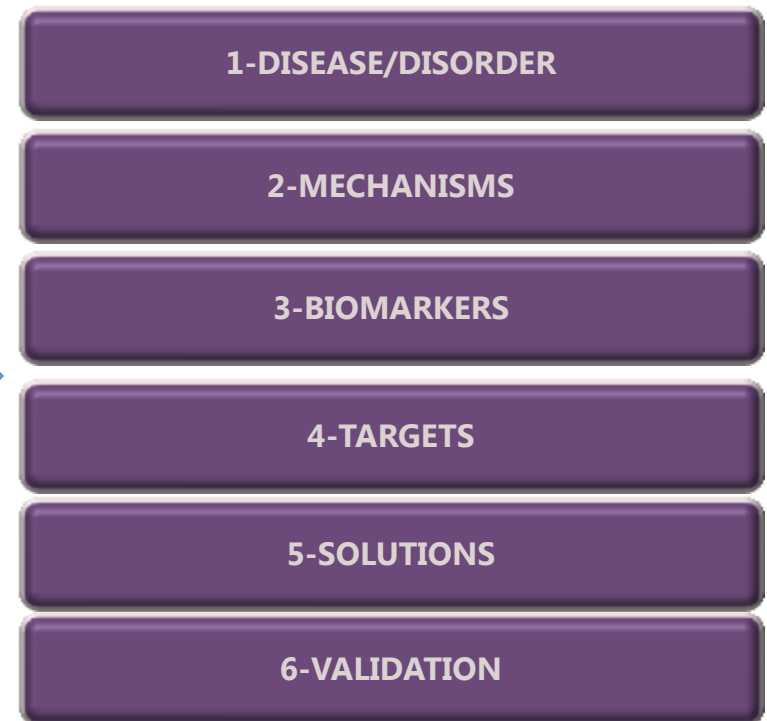
Data acquisition, Simulation, collaborative, data Storage, Big Data, Smart Data, Mobility
Smart Data (contextualized, with patients based lines, related to mechanisms)

The Research & Development Answer

Evidence-Based Medicine

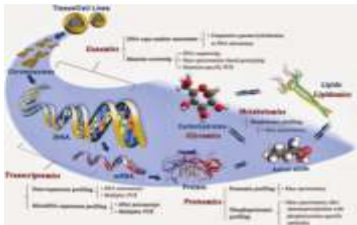


Mechanisms-Based Medicine



The R&D and the reality of Data Answers

The "Cartesian" answers limits



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

CADI Discovery Principles

1-Mechanisms-Based Medicine

2-Architectural Principle

3-Negative Selection Principle

4-4 Steps Validation Principle

5-Integrated Solutions Principle

6-The bridge R&D & Real life data

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"

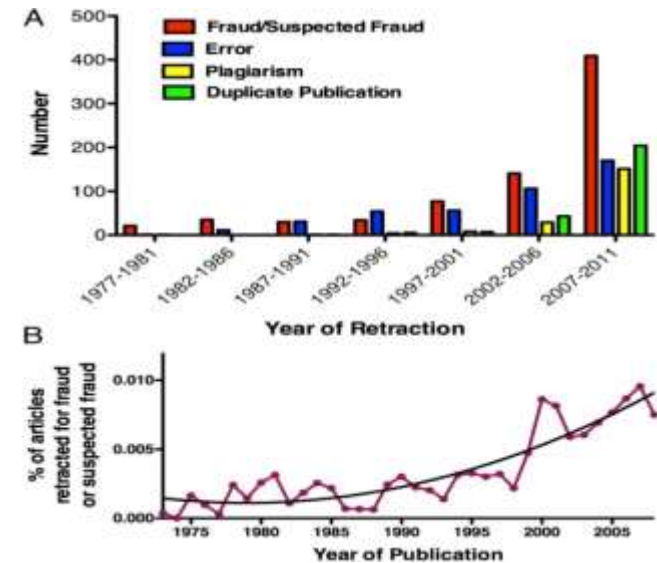
- ❑ *Global validation loop at each steps of the process: Integrate the results from e-R&D or e-Health experimentations into the validation process to improve global patient and disease/disorder follow-up.*

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

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

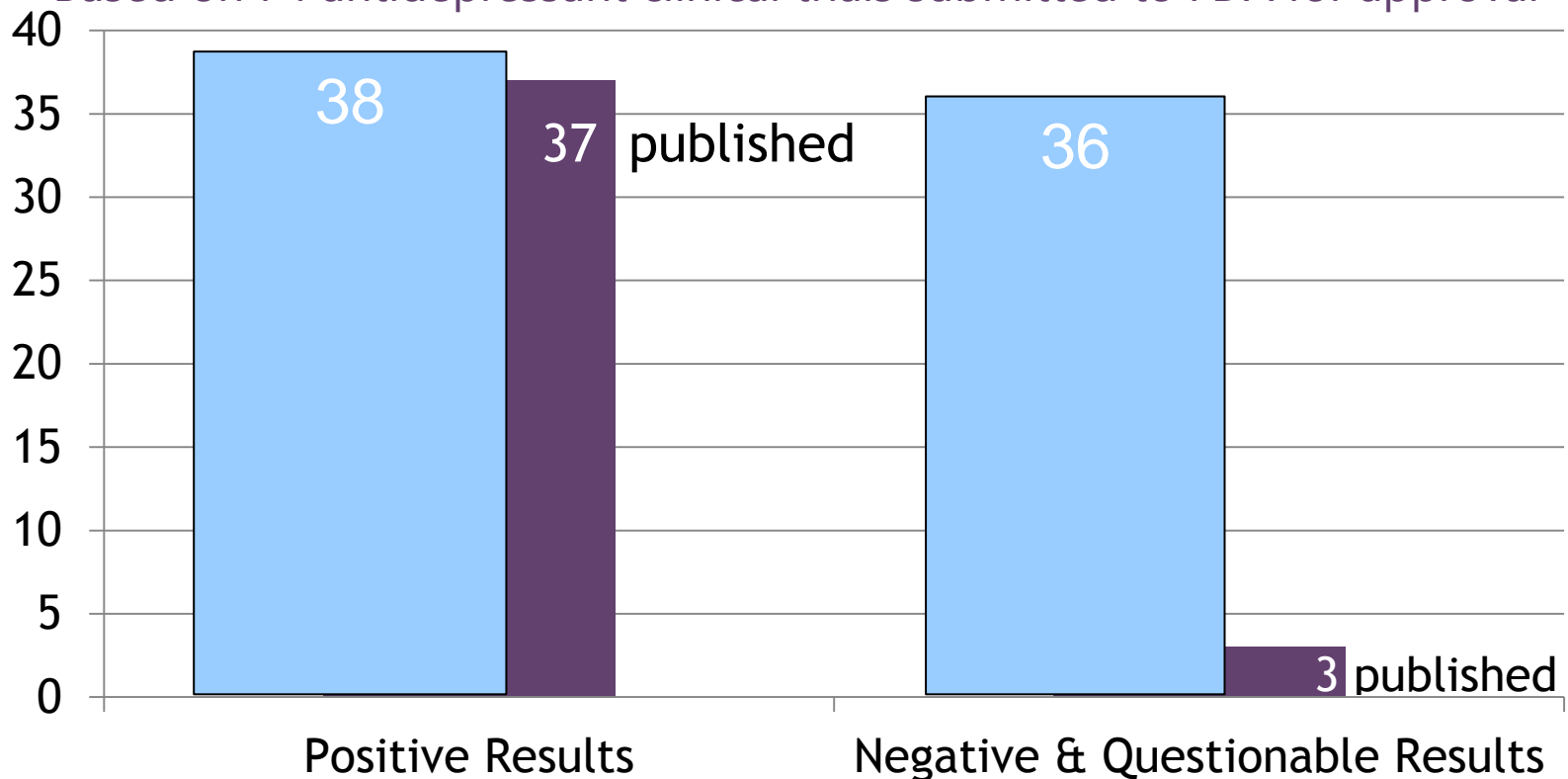


Ferric C. Fang et al. PNAS 2012;109:17028-17033

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

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.

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.

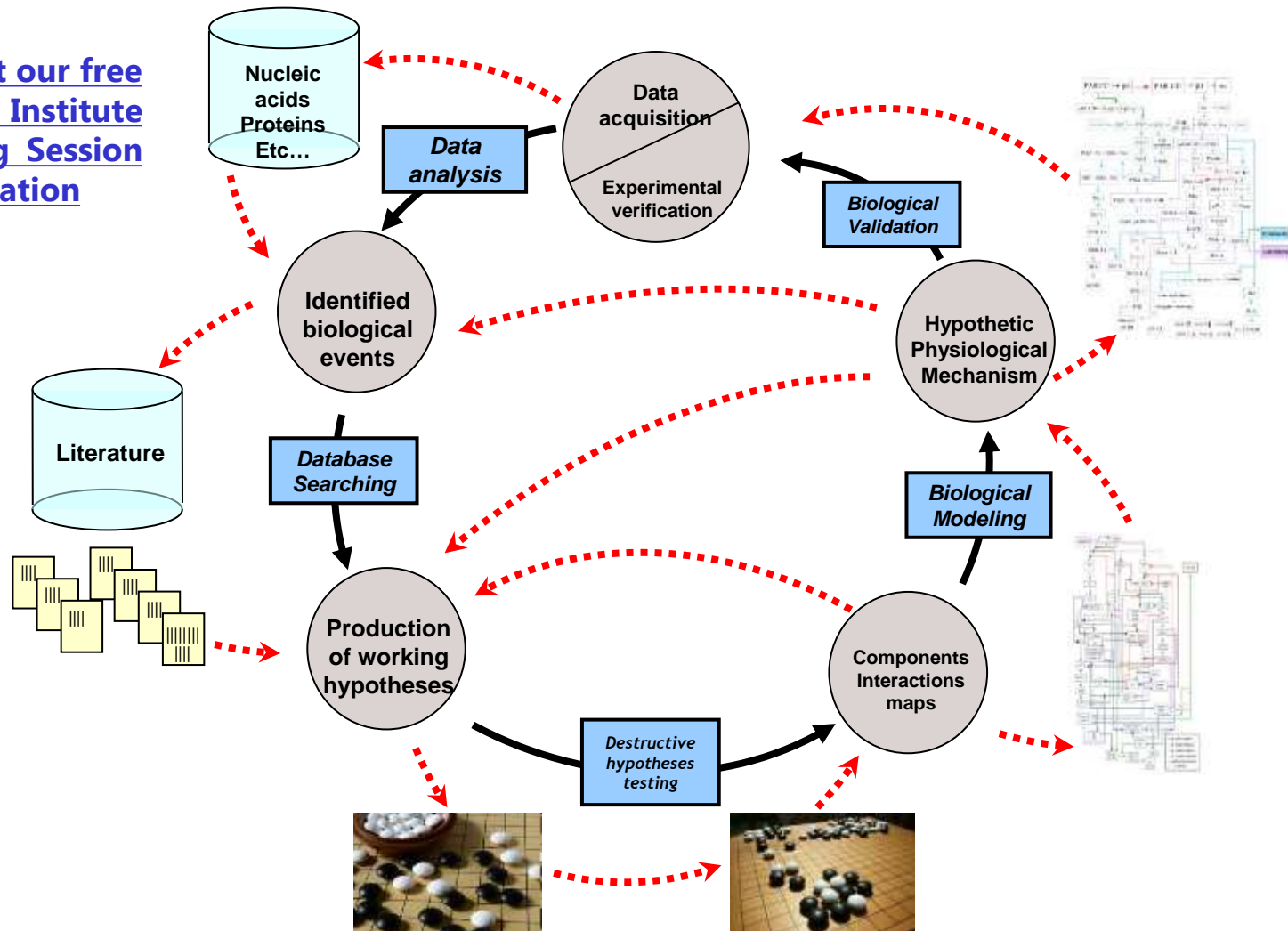
To efficiently address the translation of systems biology to clinical & medical interventions (dominated by patient's data heterogeneity and largely unstructured documents), ways to achieve synergy between Heuristic and Mathematical approaches can be effectively designed.

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

The CADI™ Integration workflow

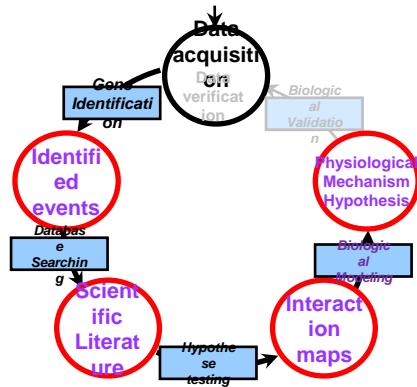
More details in the Full Presentation with CADI full Description, publications and the 10 CADI™ programs & POCS

**Request our free
Cochin Institute
Training Session
Presentation**



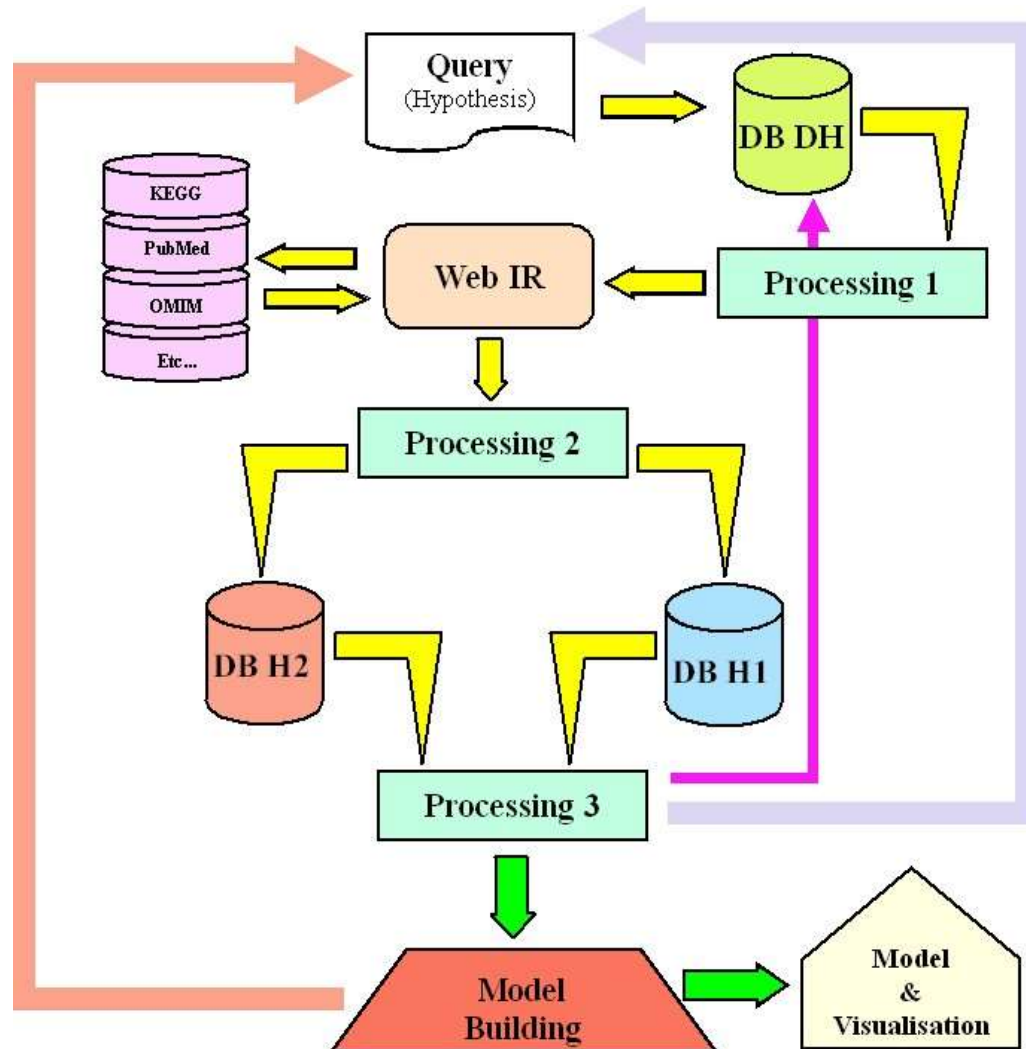
The CADI™ Integration & Modeling Process

[More details in the Full Presentation with CADI full Description, publications and the 10 CADI™ programs & POCS](#)



This iterative process does three things:

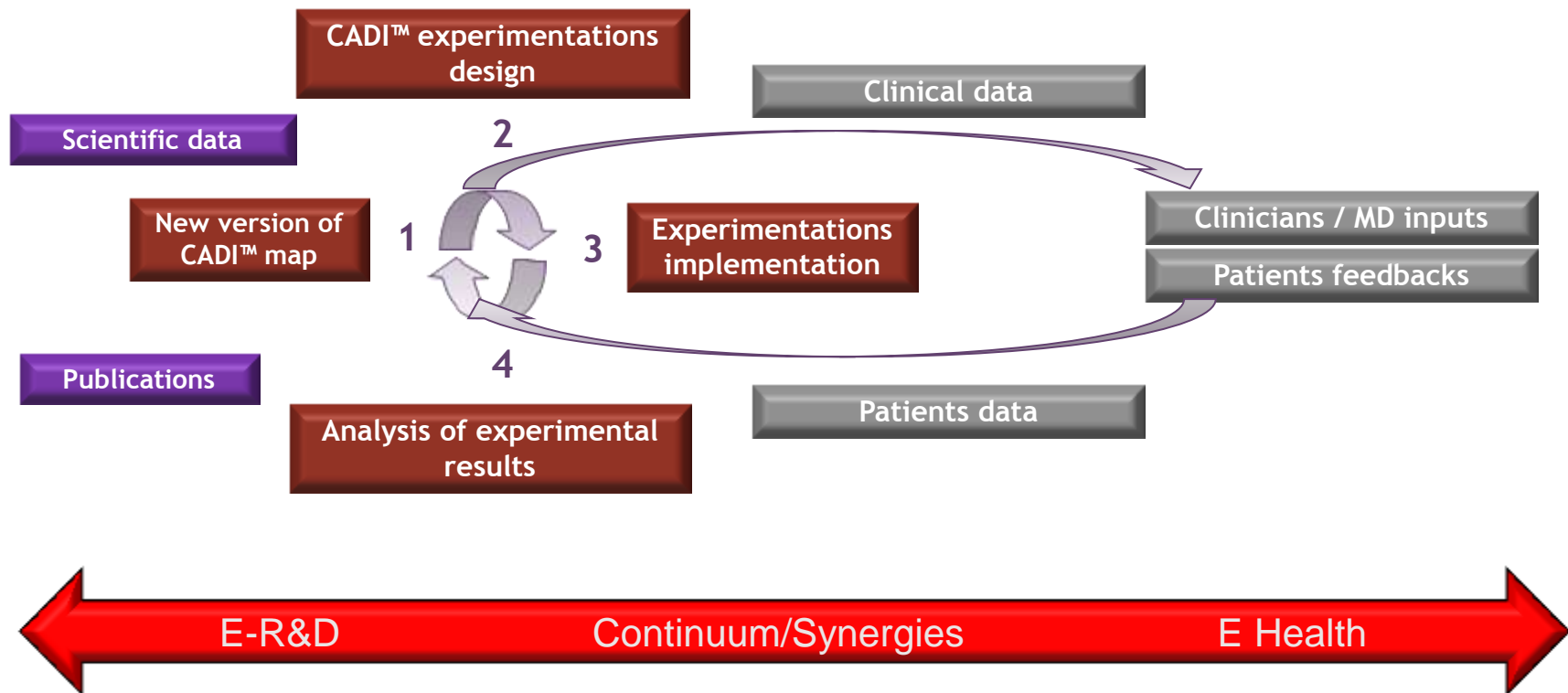
- It largely resolves the coherence issues attached to the classical approach;
- It reveals hitherto unknown mechanisms/processes, and
- It allows the translation of systems biology to clinical & medical interventions.



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 Group at a glance

Bio-Modeling Systems is the world's first Mechanisms-Based Medicine company that successfully changed the discovery paradigm, addressing the complexity of life sciences mechanisms and the digital "garbage in garbage out" reality through CADI™ Discovery based on Augmented Intelligence, the other complementary AI, for complex systems.*

BMSystems Group addresses *two complementary targets* in Pharma, Biotech, Cosmetics, Nutrition and digital-Health businesses:

1. *R&D, Translational Medicine, & Digital Health Executives:* We offer **robust alternative decision-making to de-risk, save time and costs** of R&D and Digital Health programs,
2. *Business Developers, Patients Groups & Investors:* We discover **novel low-risk, highly effective and cost-effective diagnostics/therapies** for therapeutic spin-offs or out-licensing.

Created in 2004, profitable since 2006, thanks to our recurrent clients, CADI™ Discovery already delivered operational outputs:

1. A world's first in CNS diseases with CEA: 2 awards (US & Europe),
2. Pherecydes-Pharma: First BMSystems' therapeutic spin-off, against MR infections diseases, Compassionate Use success,
3. CEA/BMSystems collaborative research success in CNS that led to a co-owned therapeutics class patent with a worldwide exclusive license to a CEA's spin-off,
4. 14 R&D validated successes, 8 novel combo-therapies & combo-diagnostics ready for development,
5. Mechanisms-Based Cosmetics developed to address Cosmetics business,
6. GEMMA (Autism & Microbiota) H2020 program with €14.2M funding. BMSystems is the Integrative Biology Partner.

BMSystems Group description

- *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.
- *BMSystems values its therapeutics programs through out-licensing or spin-off.*
- Outstanding internal pipeline of programs ready for collaborations.
- *Our 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.

BMSystems' R&D Partners* at a glance



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): First BMSystems' therapeutic spin-off, (novel M.R. anti-bacterial nano-agents biotherapies with phages), indications: Multi-resistant infections compassionate use success.



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

5 ongoing BMSystems' outstanding R&D programs



Microbiota & Autism therapeutic H2020 program started with 14 M€ funding. GEMMA program (Genome, Environment, Microbiome and Metabolome in Autism) gathers an international consortium of scientists to study the role of the gut microbiome in the development of Autism Spectrum Disorders (ASD).



Etiology & Epigenetic and therapeutic evaluation for metabolic disorders program self funded. UMANG program How does maternal nutrient restriction coupled with defective one-carbon metabolism alter the foetal development program, leading to enhanced predisposition to T2D in adolescence? Center of Excellence in Epigenetics IISER Pune India



Diagnostic & Therapeutic evaluation program self funded. The French Chronic Fatigue Syndrome Association decides to clinically evaluate the ME/CFS pathogenesis model produced by Bio-Modeling.



Therapeutic evaluation program self funded. Parkinson's disease and metabolic syndrome. The program led to a combinatorial therapeutic approach utilizing two molecules that had long been on the market, neither of which has any known toxicity or undesirable effects. Evaluation status: Discussion with confidential partners



Causal metabolic mechanisms of Alzheimer Disease (AD) model was produced by Bio-Modeling System in 2017-2018. The model in its current state is able to produce biomarkers that could probably predict or increase alertness for identifying AD at its very early stages of progression. Discover the 14 key components explained

Our solutions to address Industry critical issues

- CADI™ Discovery's ***Integrated Descriptions of Biological Systems*** is a valuable tool to ***generate novel hypotheses and/or challenge existing programs, key opinion leaders and experts recommendations*** spread all over the departments of the client's company or partner's structure.

We propose to R&D, Translational Medicine & Digital Health Executives, robust alternative decision-making to de-risk, save time, costs, and novel low-cost, highly effective, and cost-effective diagnostics/therapies for their businesses.

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.

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. Former 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)

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-Inflammation

Microbiotas / Inflammation
(skin, lung, gut, etc)

Neurology/ Psychiatry/ Inflammation
(CNS-PNS)

Oncology / Inflammation

Metabolism / Inflammation

Dermatology/ Cometics/ Inflammation

BioProcesses

Infection-Immunology	Oncology/Inflammation
CNS-PNS/Inflammation	Tissue Differentiation
Industrial biotech	Metabolism/Inflammation
Dermatology/Inflammation	Microbiotas

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						Completed
TAPE (protein improvement)	Open						Validated
Chronic Fatigue Syndrome / Gulf War Syndrome	CFS Asso / Open			Started			
Ebola virus ecology	Open						
Hepatitis C	Open						
Auto-immune global concept	Open	high Interest					
Microbiota & Autism H2020 program 14 M€ funded	H2020		Started				
Microbiota ecology, physiology & metabolic mechanisms	Open	high Interest					
Microbiota & inflammation	Open	high Interest					
Creutzfeldt-Jakob disease's mechanisms	CEA Life Sciences						Completed
Cellular & metabolic mechanisms associated with chronic anxiety	Max Planck Munich					Completed	
Psychiatric Disorders therapeutic strategy	Confidential						
Alzheimer's Disease Causal Mechanisms	Open		Produced				
Parkinson's Disease Therapy	Open		Produced				
Psychiatric inflammatory mechanisms	FondaMental Foundation		Produced				
Fibromyalgia, facial pain	Open		Produced				
Pain (Central/Peripheral)	Open		Produced				
Migraine Mechanisms	Open	high Interest					
Multiple Sclerosis Mechanisms	Open	high Interest					
Etiology & Epigenetic in diabetes type 2	IISER Pune			Started			
Metabolic Disorders Therapy	Open	high Interest					
Hypercholesteremia 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 pigmentation Mechanisms	Open			Completed			
Skin pigmentation Modulation	Open			Completed			
Skin Contact Allergy Mechanisms	Open		high Interest				
Skin aging Mechanisms	Open	high Interest					
Modulation of skin hydration	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						Completed
Human Glycosylation with Yeast	Open		high Interest				

BMSystems' CADI™ Therapeutics pipeline*

Internal Program Name	Indication	Pre-clinic	Phase I	Phase 2a	Phase 2b	Comp. Use	Phase 3
-----------------------	------------	------------	---------	----------	----------	-----------	---------

COMBO-THERAPIES

CADI-T1011	Multi-resistance infectious diseases						Started
CADI-T1031	CFS low-grade chronic inflammation		Ready				
CADI-T1032	Gulf War Syndrome	Ready					
CADI-T2011	Attenuation of the Core Symptoms of Autism		Ready				
CADI-T3021	Parkinson's Disease		Ready				
CADI-T4021	Attenuation of Developmental Consequences of Children Malnutrition		Ready				
CADI-T4031	Metabolic Syndrome		Ready				

Internal Program Name	Indication	Pre-clinic	Clinic
-----------------------	------------	------------	--------

COMBO-DIAGNOSTICS

CADI-D3041	Alzheimer's Disease Early Diagnostics		Ready
------------	---------------------------------------	--	-------

Our 14 CADI 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. Novel antiglycemic mechanism;
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 of OCA2 protein;
12. Context-dependent functions of SLC45A2 (MATP) protein;
13. Engineered bacteriophage banks and the control of multi-resistant pathogens;
14. Bioproduction and hemisynthesis of 18-methyl eicosanoic acid;