Bio-Modeling Systems

The Mechanisms-Based Medicine Company

We changed the discovery paradigm to create novel medical meanings
from unreliable heterogeneous sources of data

Everything you always wanted to know about Digital Health revolution "*big promises*" but were afraid to ask!

Conference INSEAD Alumni July 4, 2017

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 ?

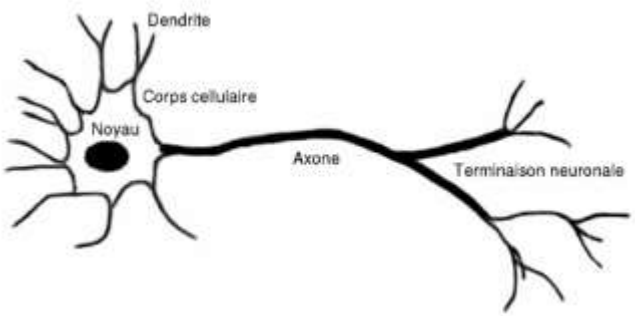
The discovery of the BIB concept by Mum:

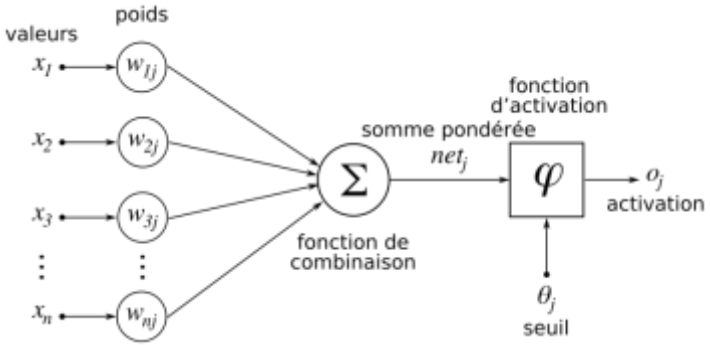
A non-cartesian discovery but a Cartesian production process

The Life-modeling issue

The challenge is clearly not a question of technologies only
Models are Aids to thought NOT a replacement for it!!

"Reductionism" creates clear misunderstanding

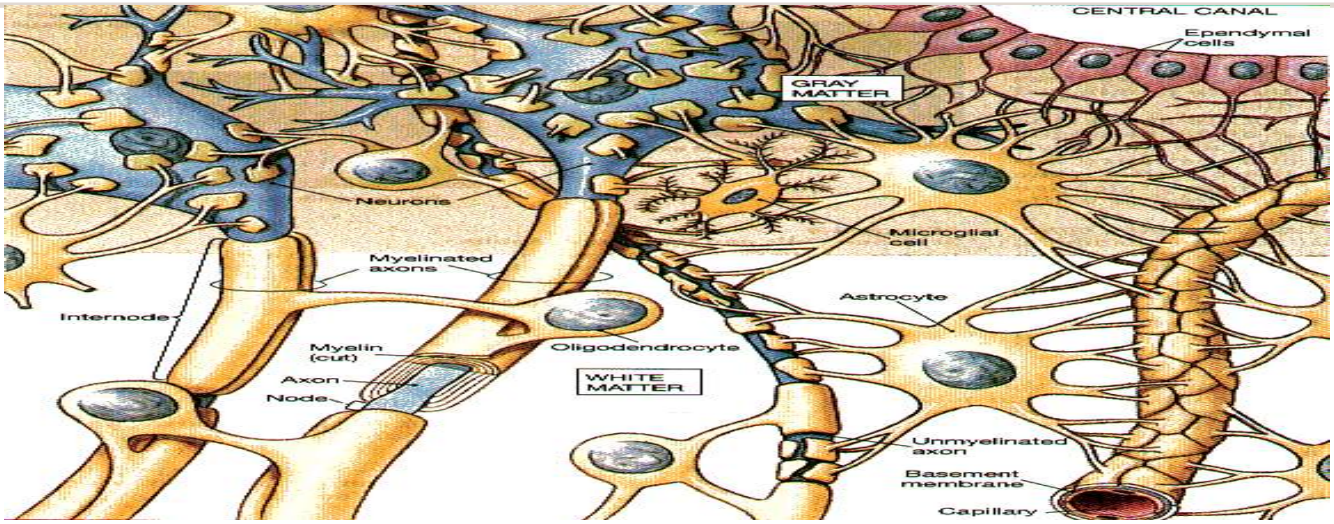




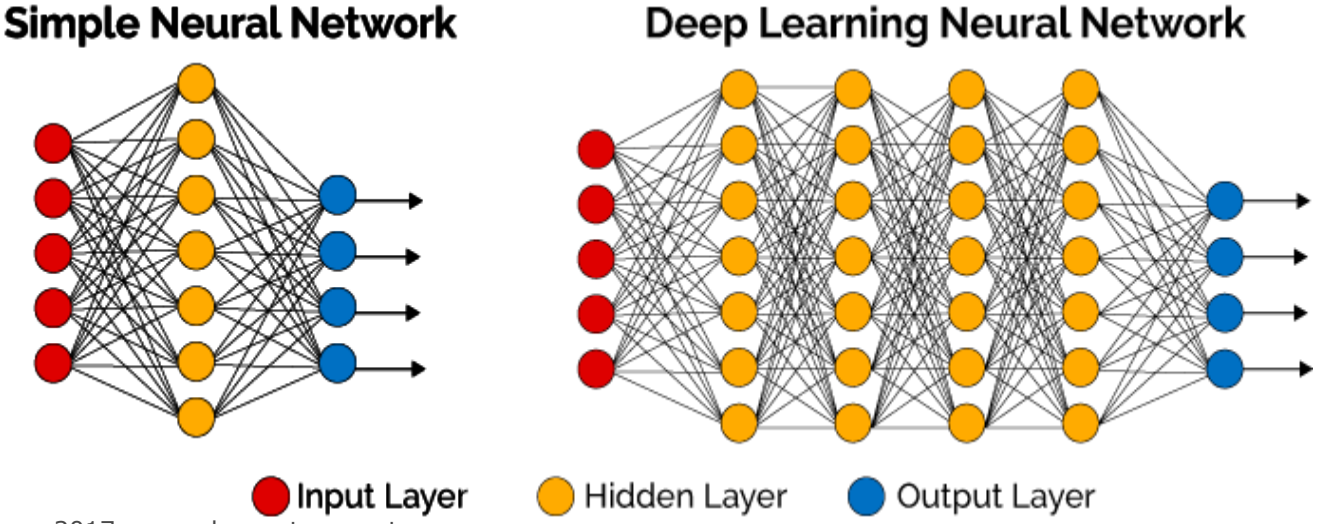
Initially 1 billions € to simulate the complete human brain on supercomputers simulating neurons to better understand how it functions
For more information about the program issue

Which mechanisms ? Is the brain Complex or complicated ?

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



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



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 the same rules.

The Artificial vs Augmented Intelligence Story

"The Singularity" "Transhumanism"

Complicated Systems world

"The big misunderstanding"

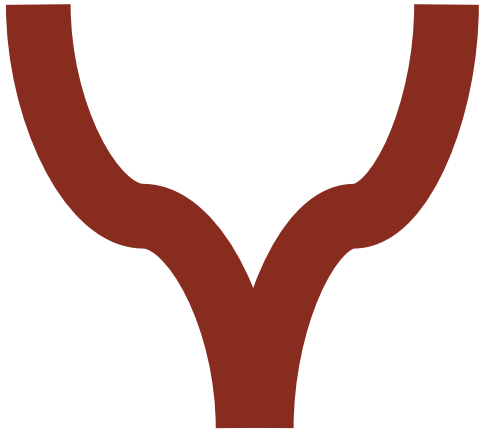
Complex Systems world

Artificial "Non Human" Intelligence

Artificial "Human" Intelligence

Invasive "Augmented" Human Intelligence

Non-invasive "Augmented" Human Intelligence



Artificial "Intelligence"

"Augmented" Human Intelligence

What should be the most productive collaboration?

The Future of Life Sciences & Medicine

Google, Watson, etc… with their Artificial Intelligence

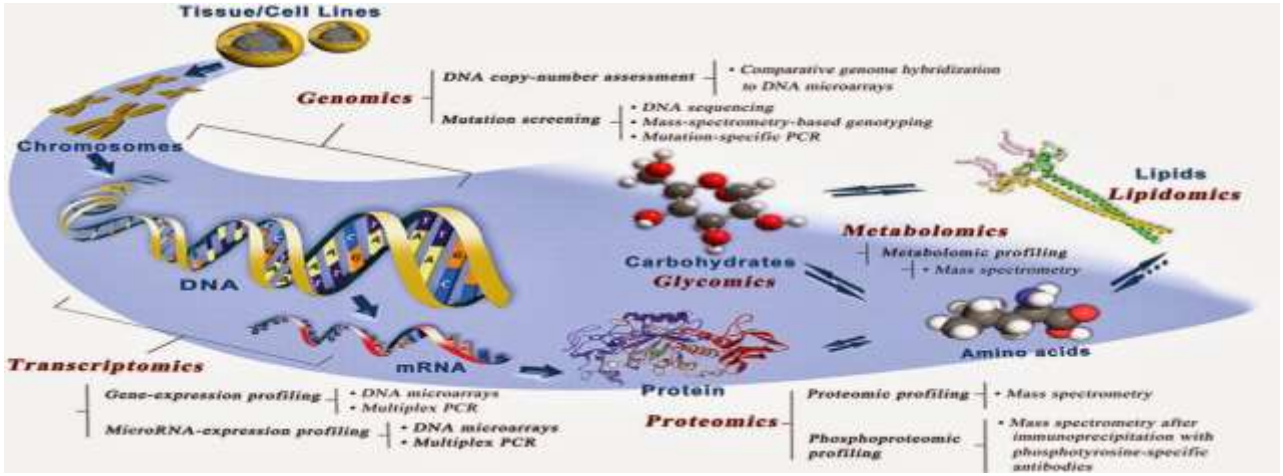
OR

Smart MDs, Biologists, Physiologists educating and mastering them

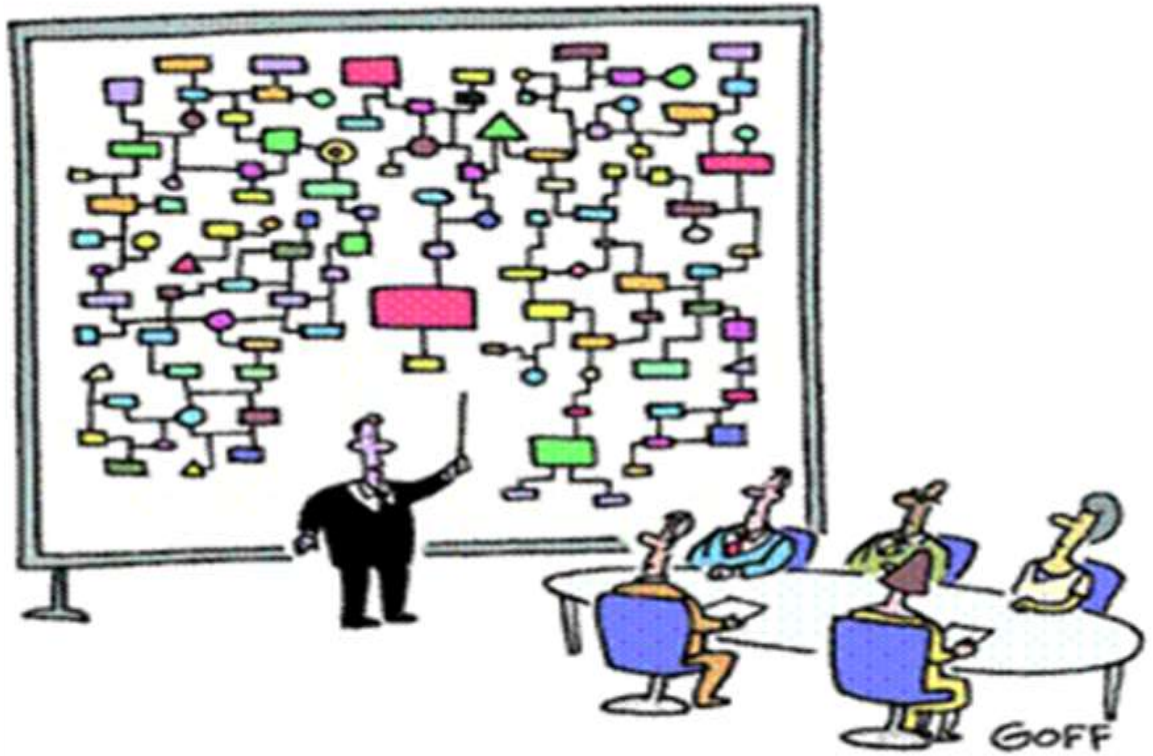
CADI Discovery: Computer Augmented Deductive Intelligence
The best collaboration between the two "complementary intelligences"

The Research & Development Challenge

The Cartesian answer to this complex challenge



Floods of heterogeneous data exponential growth



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

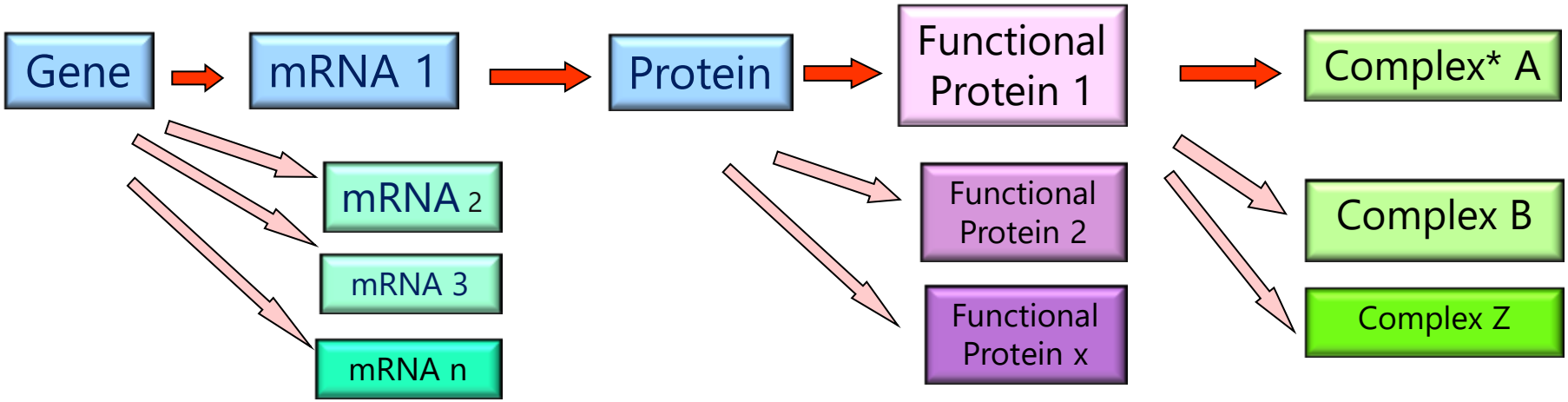
Integrative biology became "bio-informatics"
The new Eldorado for IT and technology sellers
IT, HPC, Big Data ….. Big knowledge or big Garbage?

The life mechanisms reality

From genes to physiological functions:

Four series of deconvolutions and discontinuities:[2]

One gene = several different physiological functions

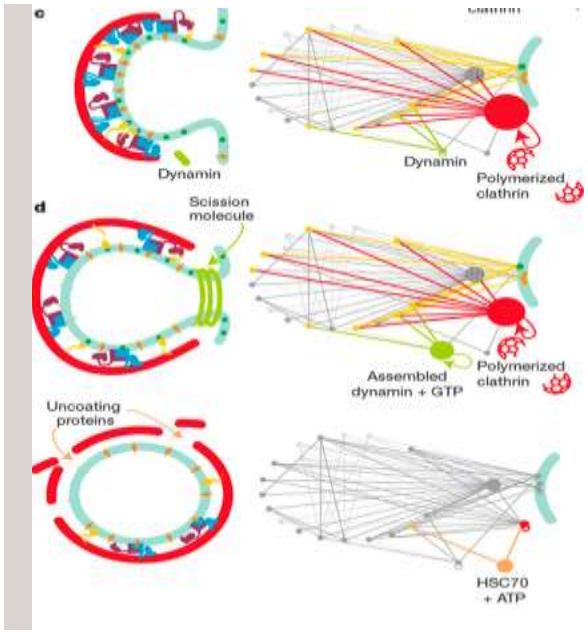


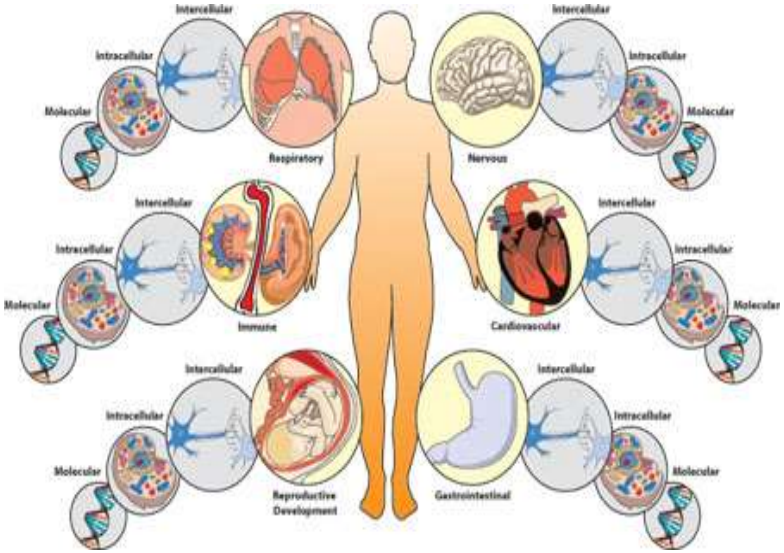
A non-linear integrative system.

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: is a group of two or more associated proteins or peptides

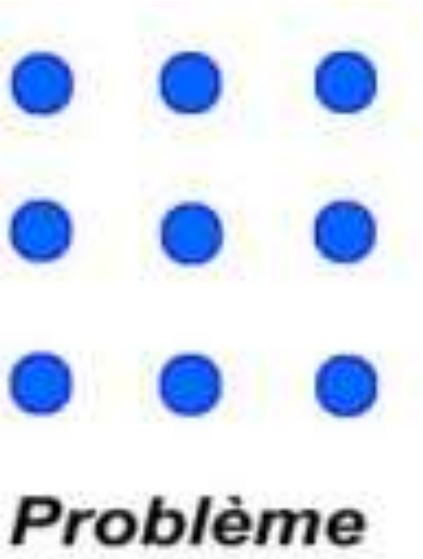
What is a Therapeutic success?





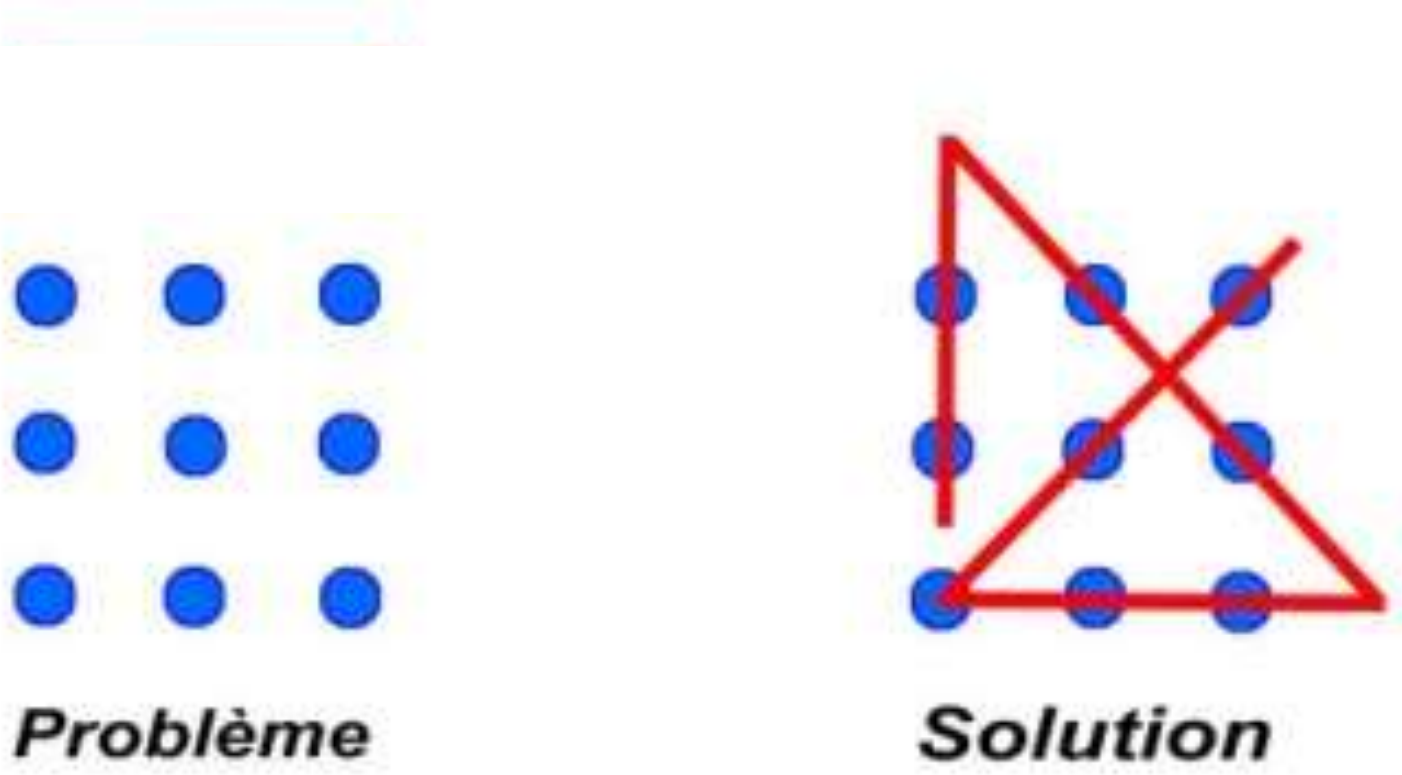
The need of an integrative "systems medicine" approach

Complex Problems Solving with a simple example



Problème

Complex Problems Solving with a simple example



The power of "General Semantic" to address complexity

If you don't understand "Data Scientists", maybe you are right!

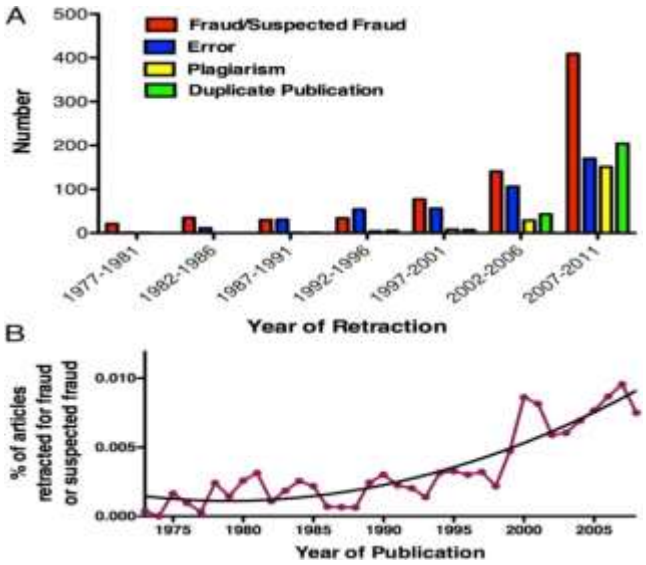
Think and do out of the box!

The mechanisms-Based Medicine Principle

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)

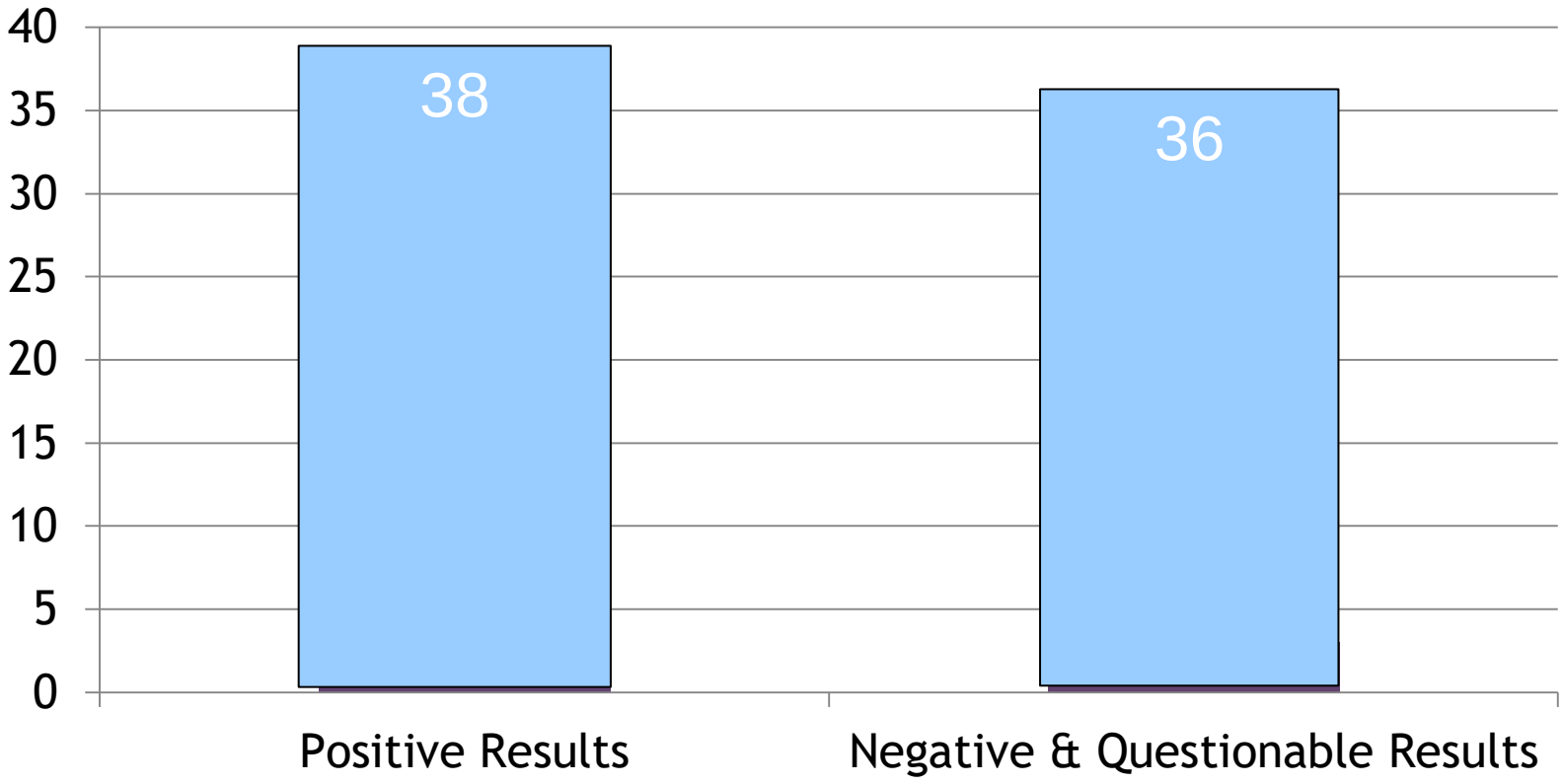
Number of retracted articles for specific causes by year of retraction



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

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

Based on 74 antidepressant clinical trials submitted to FDA for approval



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

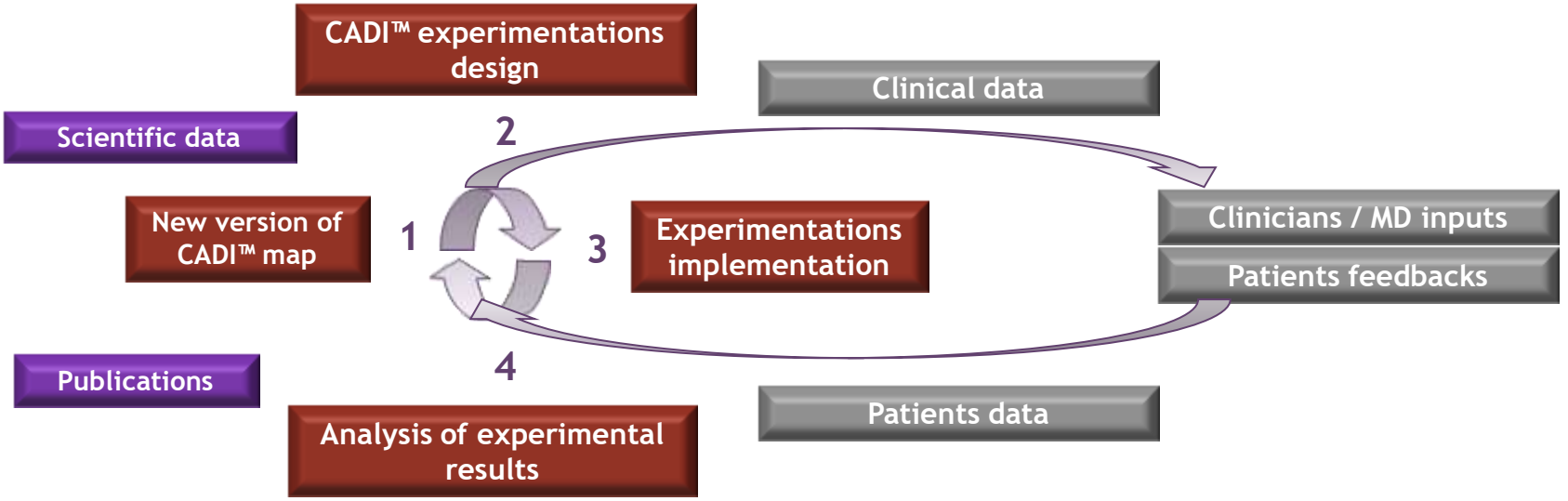
CADI™ Discovery Principles

- "Mechanisms-Based Medicine Principle"
- "Architectural Principle"
- "Negative Selection Principle"
- "4 Steps Validation Principle"
- "Integrated Solutions Principle"

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)

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 (**combined therapies**) for the treatment of psychiatric and neurological disorders**.** Copatent WO/2010/029131 **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' 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	Closed						
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 aging 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				

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%