FORUM
BioEntrepreneur
2015
Belgium - Paris

Conference and Brokerage Event
Thursday, January 29th 2015

CCI Paris Ile-de-France
Bourse de Commerce
2 rue de Viarmes. Paris 1er

The future will be digital and biology but who will lead?

Why do we need to change the discovery paradigm?

Inaugural Presentation (updated 2016)

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 President Centrale-Santé & Adebiotech CEO BMSystems

January 29, 2015 Bio-Entrepreneur 2015

www.centrale-sante.net www.adebiotech.org www.bmsystems.net

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What type of Systems are we talking about?

Complicated Systems

Complex Systems

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

The nightmare of new mums.

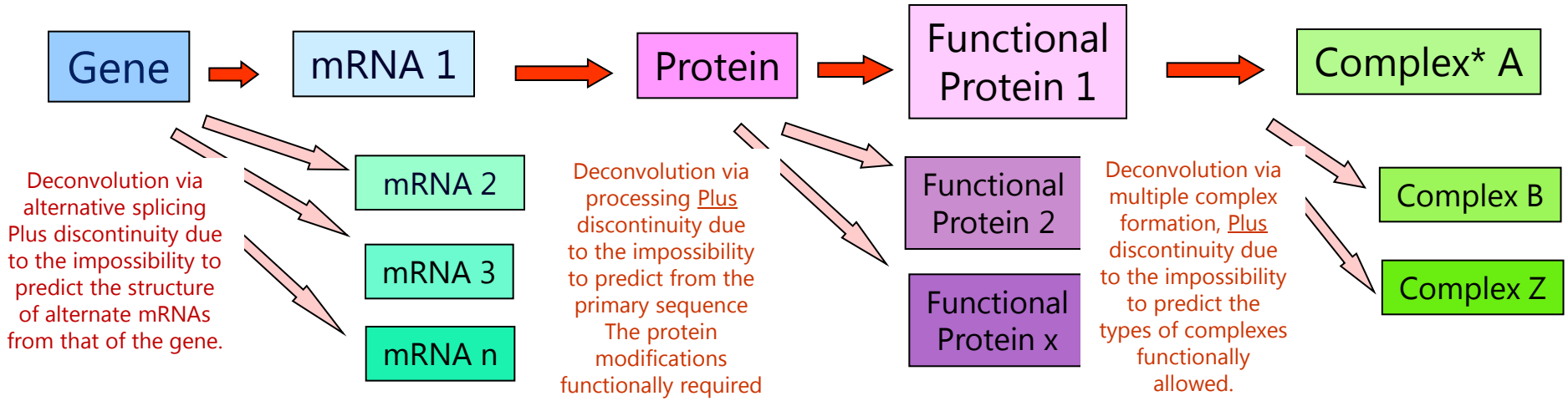
The mission: build a model to simulate the behaviour of spaghettis to prevent stains

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 implementation process

From genes to physiological functions:
Four series of deconvolutions and discontinuities:

One gene = several different physiological functions

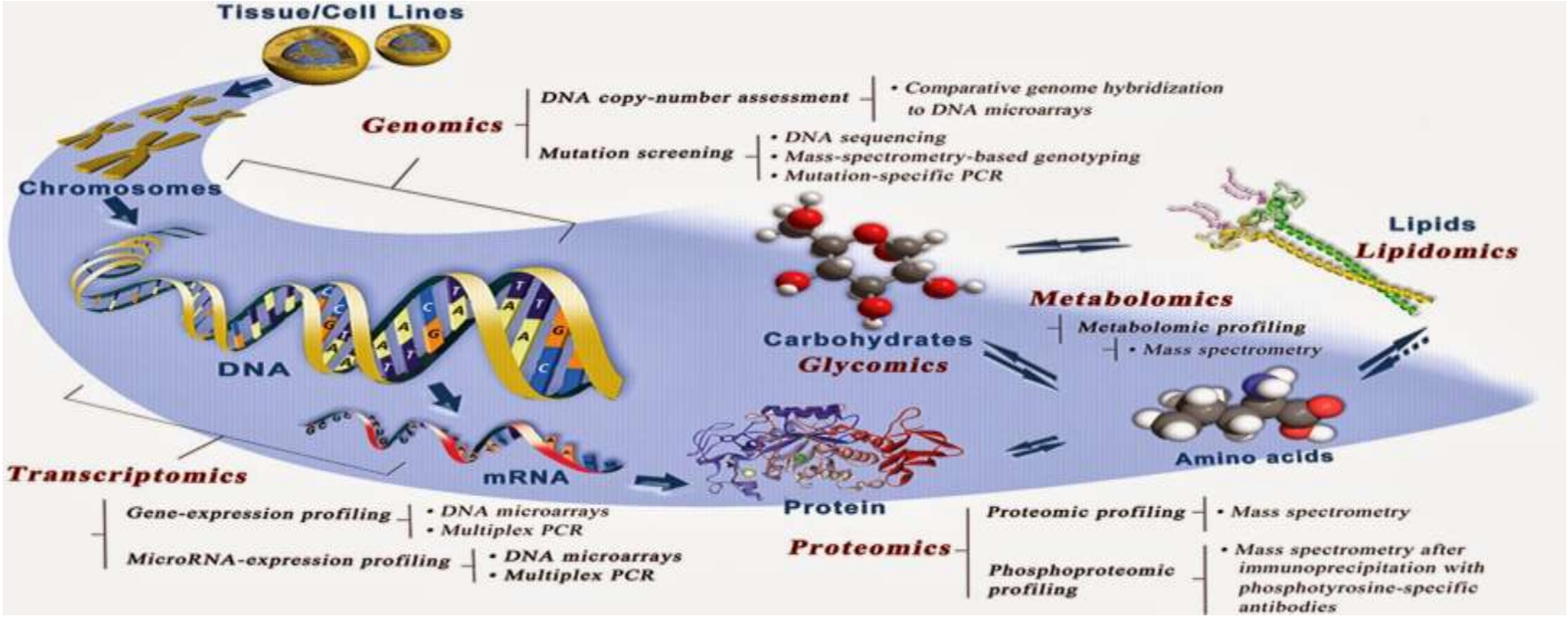


A non-linear integrative system.

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

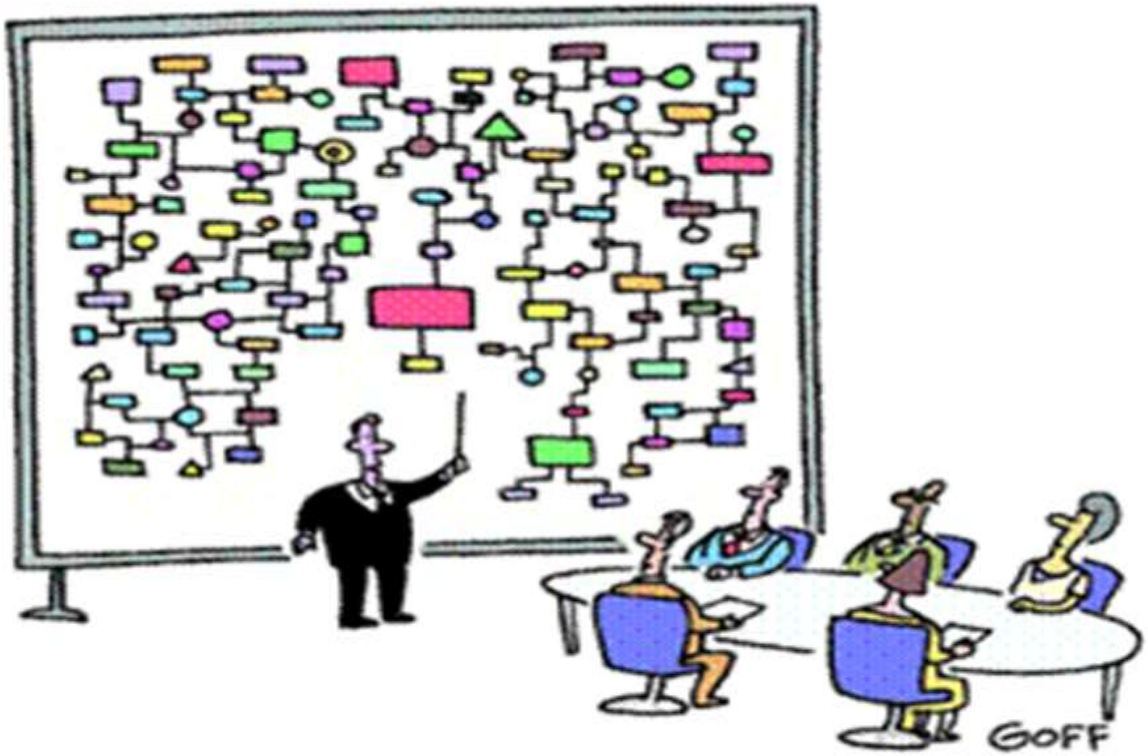
* Complex: is a group of two or more associated proteins or peptides

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 issues: Tools, algorithms & concepts from Digital and Technologies giants, valid for complicated systems, cannot address complex systems such as life

Floods of heterogeneous data under 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?*

* https://www.linkedin.com/pulse/big-data-garbage-6-published-documents-explain-available-manuel-gea?trk=pulse-det-nav_art

Imagine experts trying to understand the mechanisms of this car in a world where electricity is unknown

For « dominant thinking »,
This is a car* and not a great one !

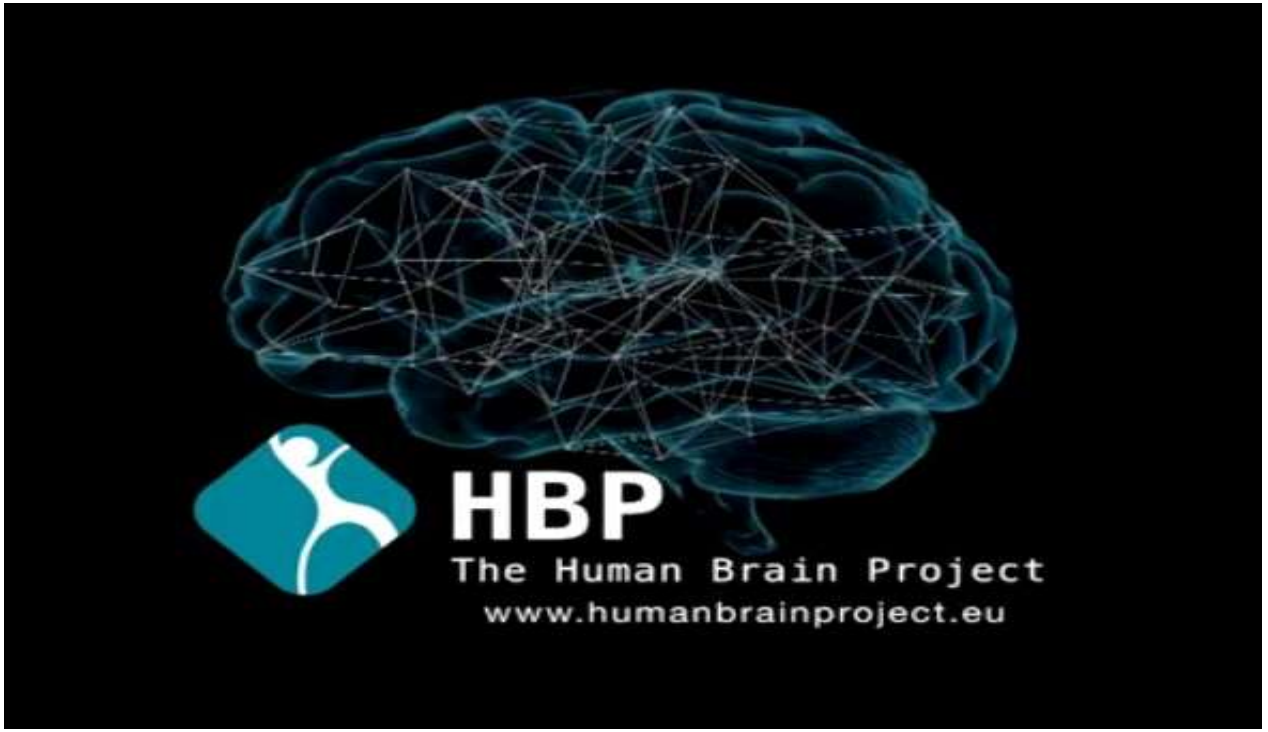
A lot of components
are of obscure**
for the experts.
No real innovation for them!

What is unknown may be of some interest and must be integrated at the beginning to have a chance to really understand the global behavior of the system !
"Billions of investments will never explain why when the engine is off the car still moves!"

* Internal combustion engine

** At the beginning of genomics, the noncoding DNA (80% of the total) was named "junk DNA"

The mechanisms of the brain

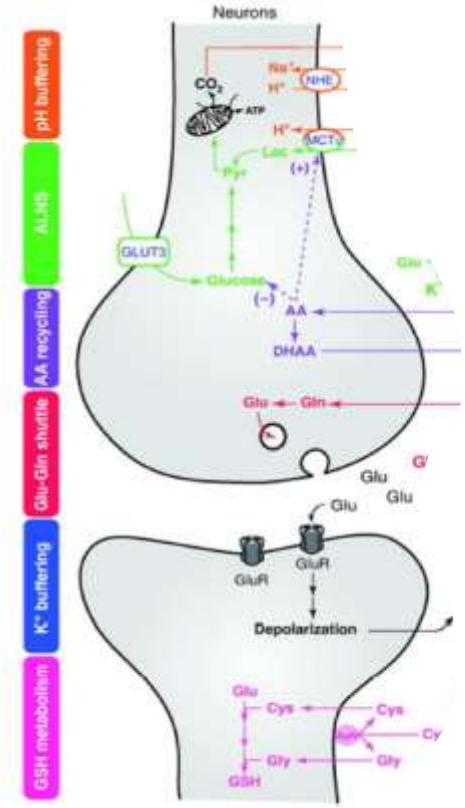


The goal is to simulate the complete human brain on supercomputers to better understand how it functions

Which mechanisms ? Is the brain Complex or Complicated ?

Can HBP, the 1 billion € program, explain Creutzfeldt-Jakob disease?

The classical vision of the brain: The neuron only….

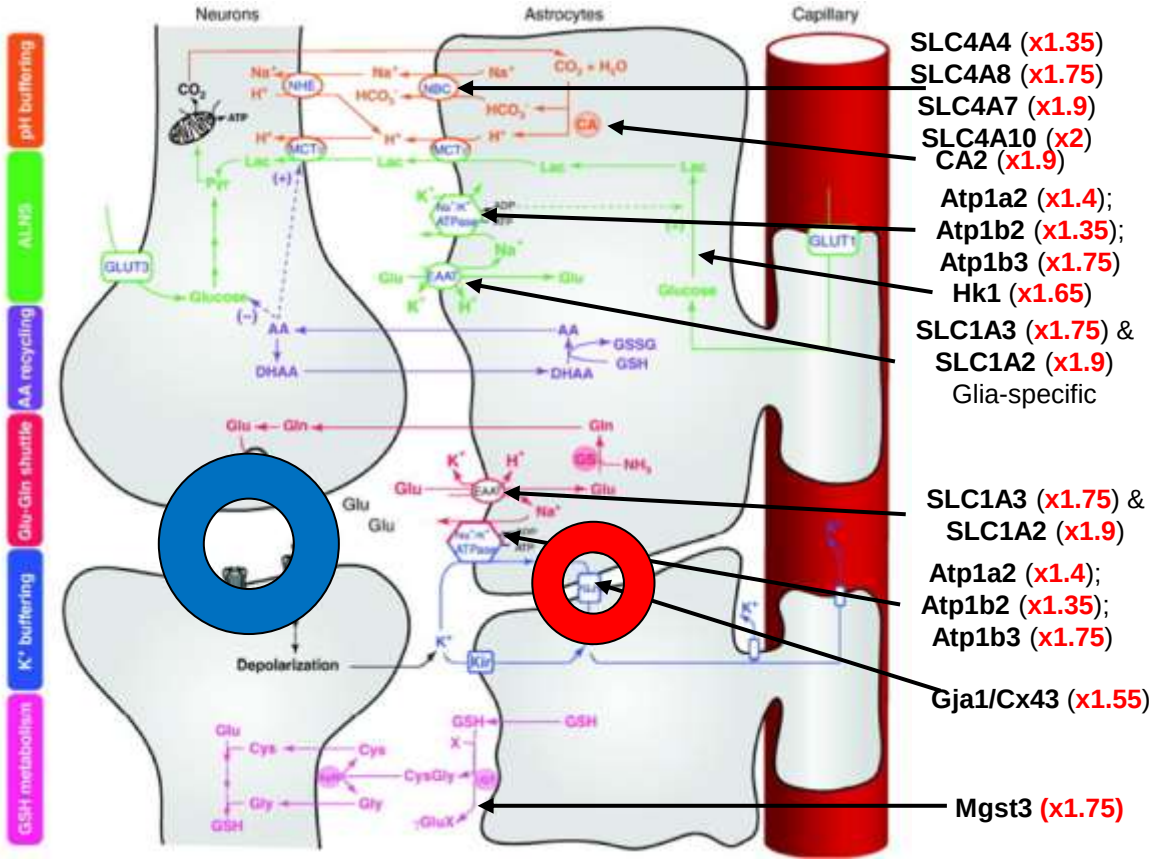


In Chronic Anxiety: Reinforcement (x A.XX) of astroglial-dependent metabolic maintenance of neurotransmission

* 2012, CNS Neurodegenerative & Psychiatry: PharmacoPsychiatry; **WO 2010/29131 A1 - “class” therapeutics patent.

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

Simulating the neurons only will never explain the Creutzfeldt-Jakob Disease*,
nor novel psychiatric treatment** combining an anticonnexin on astrocytes and psychotropic drugs to reduce side effects !



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

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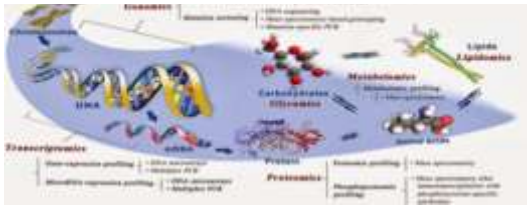
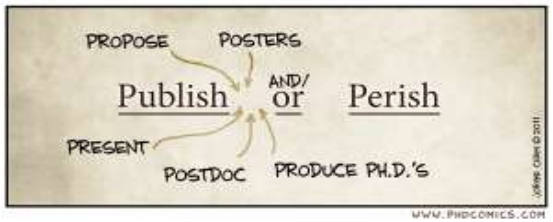
Why did we need to change the discovery paradigm?

1-The industry is under high pressure by too high failure rates (90,4%) 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!

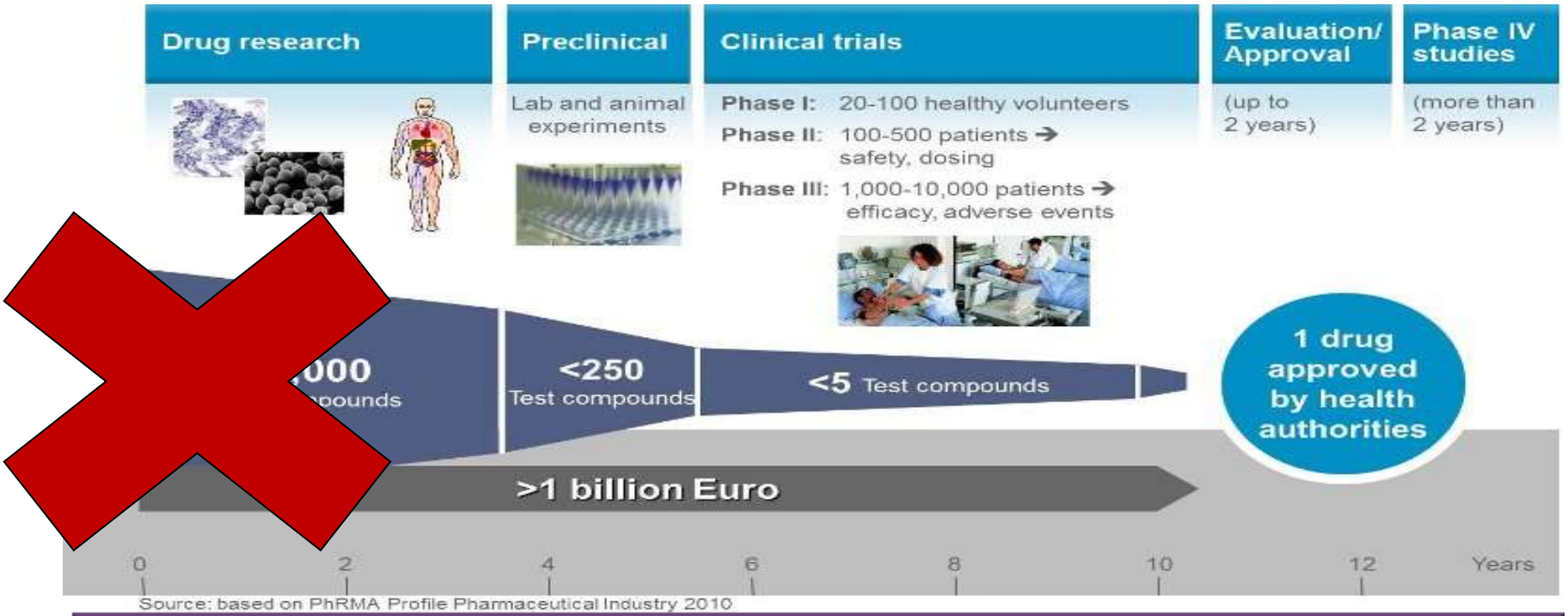
3-The "mirage" of Artificial Intelligence (AI) that MUST follow rules in a world where humans massively do not! Currently the "Garbage in garbage out" reality is not correctly treated by digital giants who consider life as only complicated.



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!

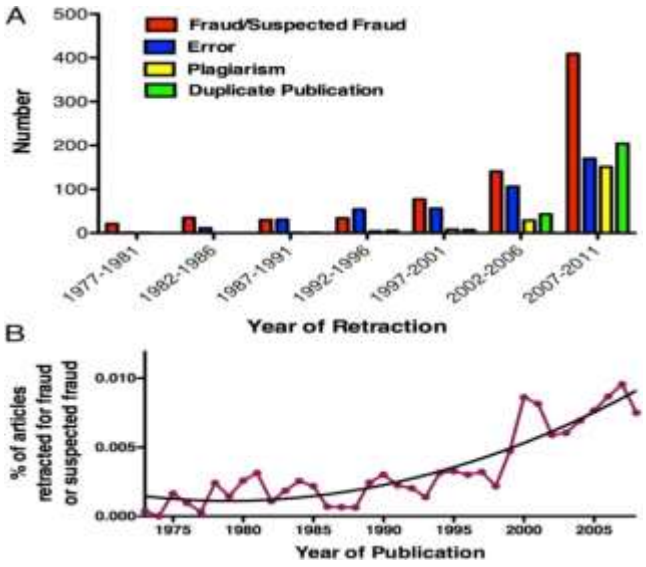
1. Is 1 billion € per drug approved a fatality or a Discovery paradigm failure?
2. How are KOL concepts generated and evaluated?
3. Has Evidence based Medicine reached its limits with chronic complex human diseases?
4. **Mechanisms of action/function of a target, drug, gene, .. ARE NOT the mechanisms 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 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)

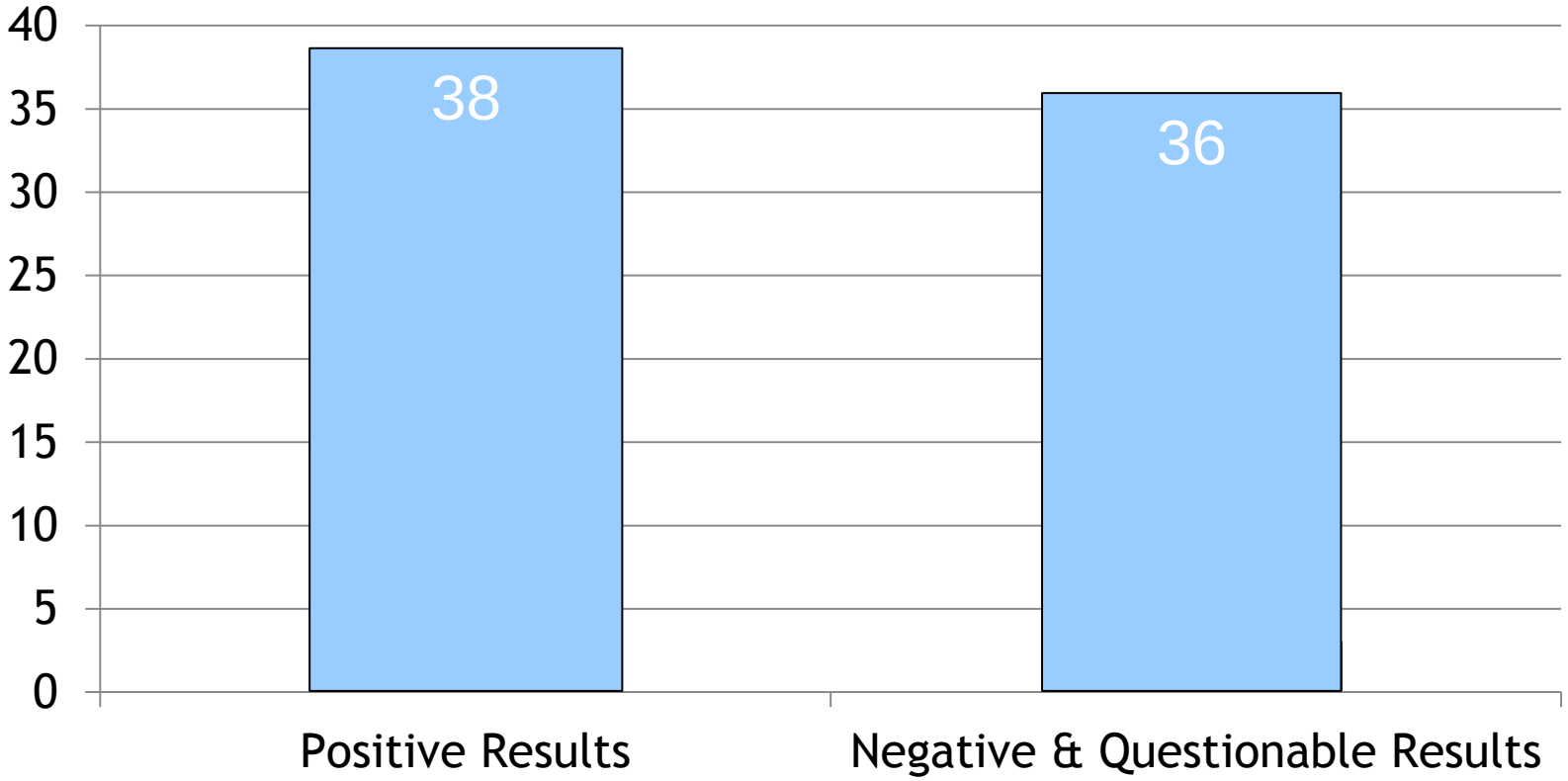
Number of retracted articles for specific causes by year of retraction



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 74 clinical antidepressant trials submitted to FDA for approval

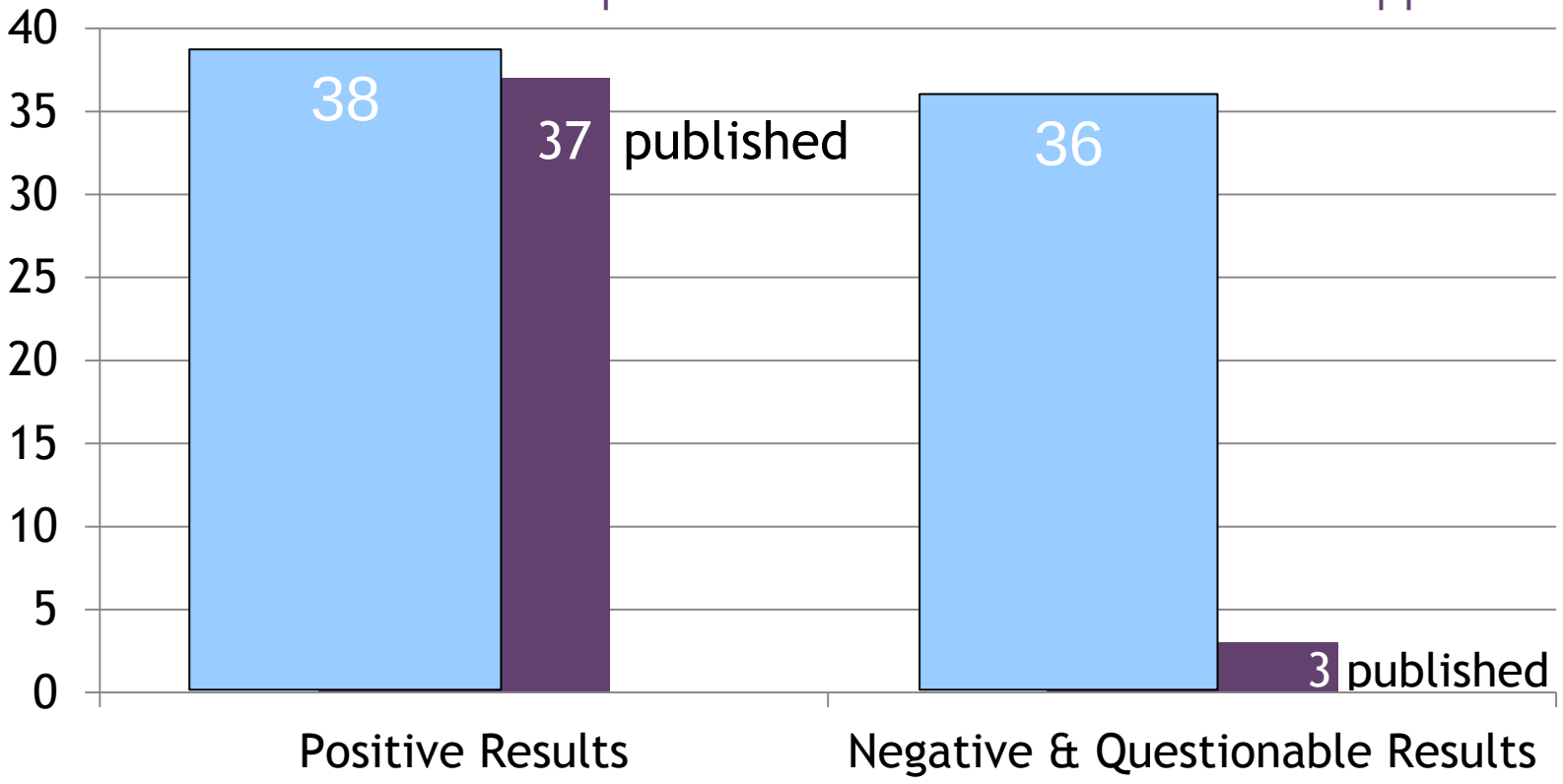


Compared to the clinical trials published. An enormous bias
A critical misleading issue if not contextualized

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

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

Based on 74 clinical antidepressant trials submitted to FDA for approval



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

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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 basement of Life Sciences R&D that may explain the so far unsuccessful**
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 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"!

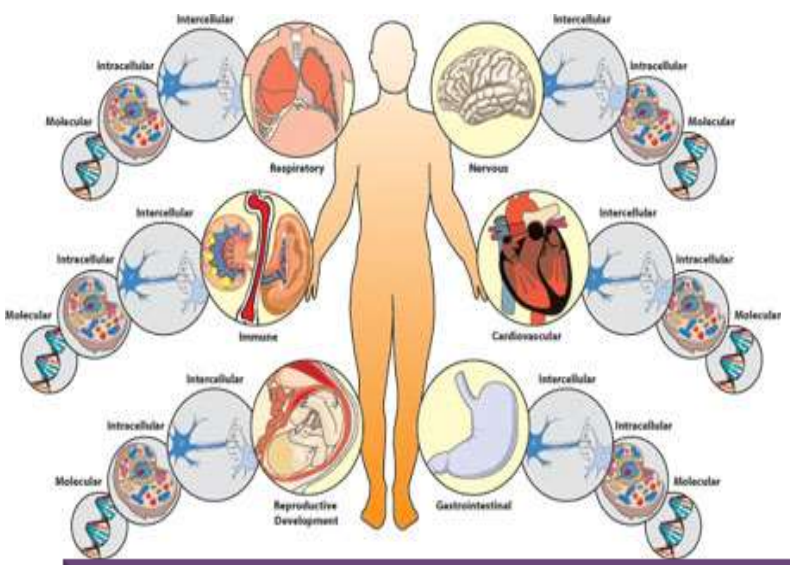
A valid solution must address both the complexity of life's mechanisms and the unreliability of scientific and clinical publications to create novel & pertinent medical meanings

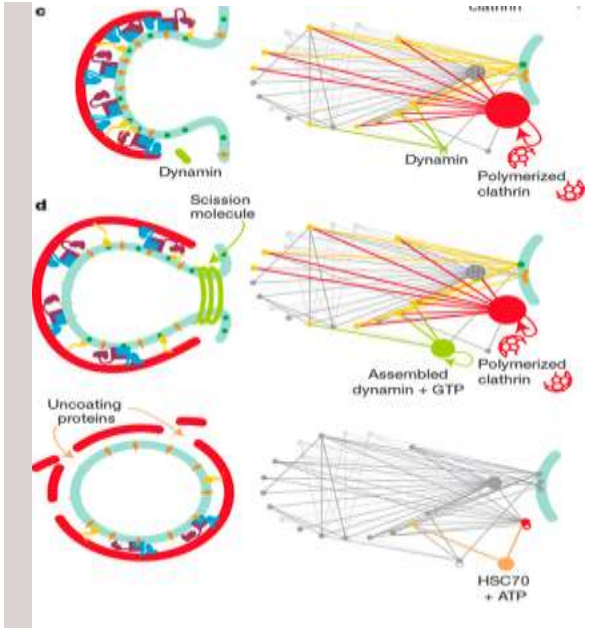
*** Based on this model,1) when birds lay eggs, they explode; 2) the rear end of a bird is extremely hot when it flies; 3) a bird has three legs, etc.… You may think this stupid, but it is what is being done with systems biology.**

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"

- *"An estimated 85% of current published research findings are false or exaggerated" J.P.A Joannidis, 2014 Stanford University [PLoS Med]).*
- *"It is always possible to demonstrate a statement to be false" Karl Popper.1963.*
- *Only working hypotheses that resist destruction are worth retaining.*

"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"

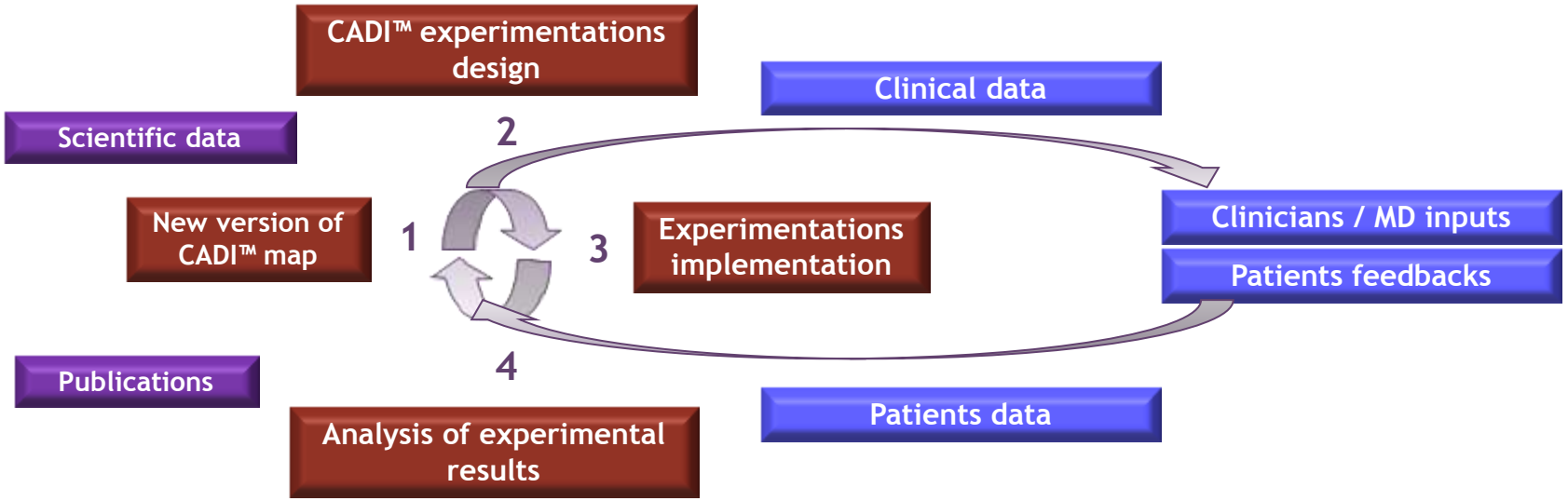
- *Can be combinations of drugs, diagnostics, medical devices, nutriments, e-health, cosmetics, for treatments, and prevention programs, etc. …*
- *Access to end user is strategic, and digital technologies are essentials to connect all the components of the solutions.*

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.

Global discovery & validation process

Mechanisms-Based Medical Research

Discovery from bench to bed for real patient health processes



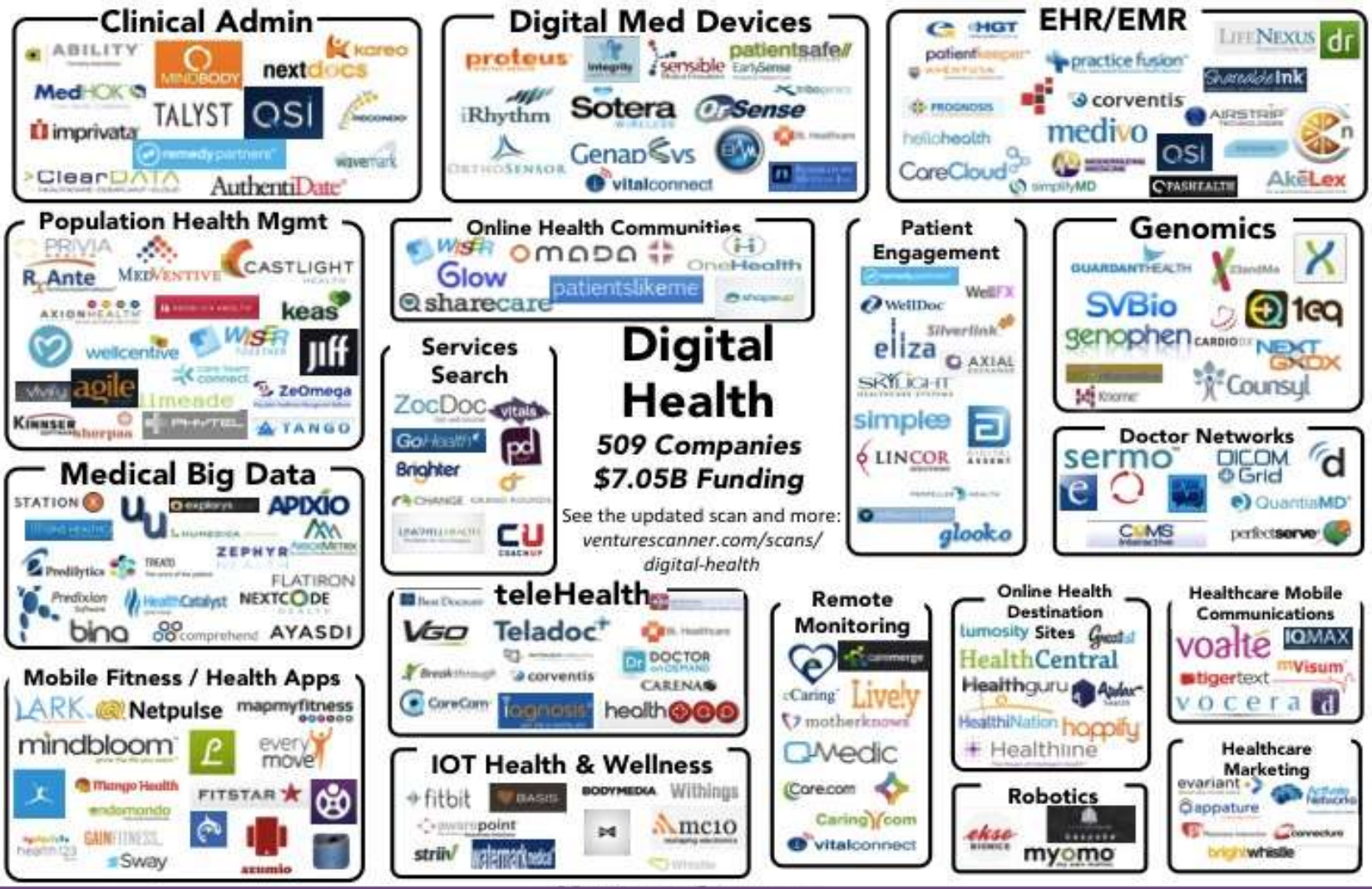
E-R&D — Continuum/Synergies — E Health

Information technologies

Data acquisition, Simulation, IT Networks, Data Storage, Big Data, Smart Data, Mobility, etc.

Remember: Big Data, due to life sciences reality, does not necessarily means high value Smart Data,
We need data contextualized, with patients base-lines, and related to biological mechanisms.

Digital health universe

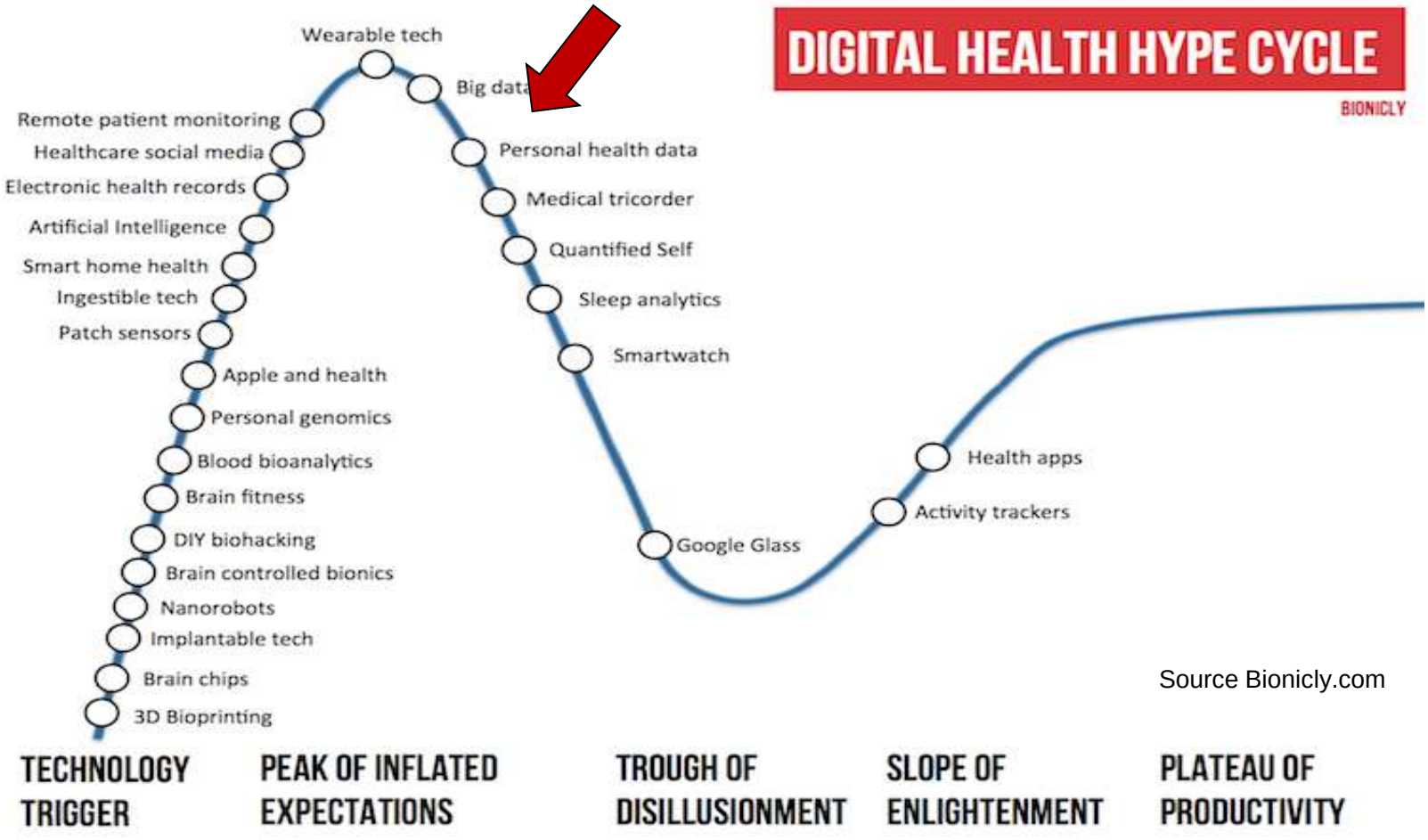


The digital health universe is already full of companies

A MUCH More Diversified Market Than Investors Realize

CREDIT SUISSE

Big Data: Bubble or not bubble: That's the question!



Source Bionicly.com

The future will be digital and biology, but who will lead!

Google? Watson? alone, or MDs, Physiologists, Biologists "educating "and "mastering" them

The Future of Medicine

Google, Watson, etc… with their Artificial Intelligence

OR

Smart MDs, Biologists, Physiologists educating and mastering them

In any case, we do need cost-effective novel therapies and prevention solutions combining diagnostics, therapies, connected devices and IT technologies.
Who will be the smartest leaders to answer industry's critical issues?

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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.

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The key 5 solutions to critical & high impact issues

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

- ***Why***: *With a success rate around 10%-15% 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.*

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Forum agenda

09:00 am - 09:30 am	What are the major trends of our industry? What are the new limits of our industry? Why do we need novel therapies and prevention solutions combining diagnostics, therapies, connected devices and IT technologies?
09:30 am - 10:45 am	**Belgium :** Presentation of the Belgium environment and the specificities of its three regions: Brussels, Flanders and Wallonia. Novel strategies and programs. Collaborations: how does it work? The contributions of the state, the regions and the clusters. Case studies of companies collaborating to propose cost effective global solutions.
11:15 am - 12:00 pm	**France :** Presentation of French environment and the specificities of its national and regional levels. Novel strategies and programs. Collaborations: how does it work? The contributions of the state, the regions and the clusters. Case studies of companies collaborating to propose cost effective global solutions.
12:00 pm - 12:45 pm	3 Belgium clusters: Biowin, Fédéric Druck - Flanders Bio, Veerle De Colvenaer - lifetech.brussels, Azèle Mathieu 1 success story from the last edition of the Forum Bio-entrepreneur: PHYSIP, Marie Brandewinder and eClinica, Vincent Wautelet 1 representative of Enterprise Europe Network: Isabelle POTTIER
12:00 pm - 12:45 pm	**Closing session** Gilles Dabezies, Directeur général adjoint en charge des actions internationales et européennes, Chambre de commerce et d'industrie de région Paris Île-de-France

Buffet lunch Offered by BioWin, FlandersBio and lifetech.brussels

Questions

It is may be time to think out of the box.
We need open minded professionals working in multidisciplinary teams
in direct contact with patients and solutions providers

For more information

Author's LinkedIn Posts: https://www.linkedin.com/today/author/871235

- The future will be digital & biology, but who will lead?
- BMSystems a pragmatic answer to this major industry challenge
- 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

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