Prospective Workshop

Eessec Santé – Centrale Santé

"Will the Pharma « bubble » implode within 3 years?"

Why are we in trouble, the bubble deciphered,
new vision, new paradigm , new proposals, novel strategies, operational results
The serial killer of disruptive innovations identified
Key learnings and recommendations

Manuel GEA CEO BMSystems

March 4, 2014
Prospective Workshop
Essec-Santé Centrale-Santé

Non contractual document

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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

If you dream of creating the first operational bird model…

… a "basic" living Complex system that not only flies…

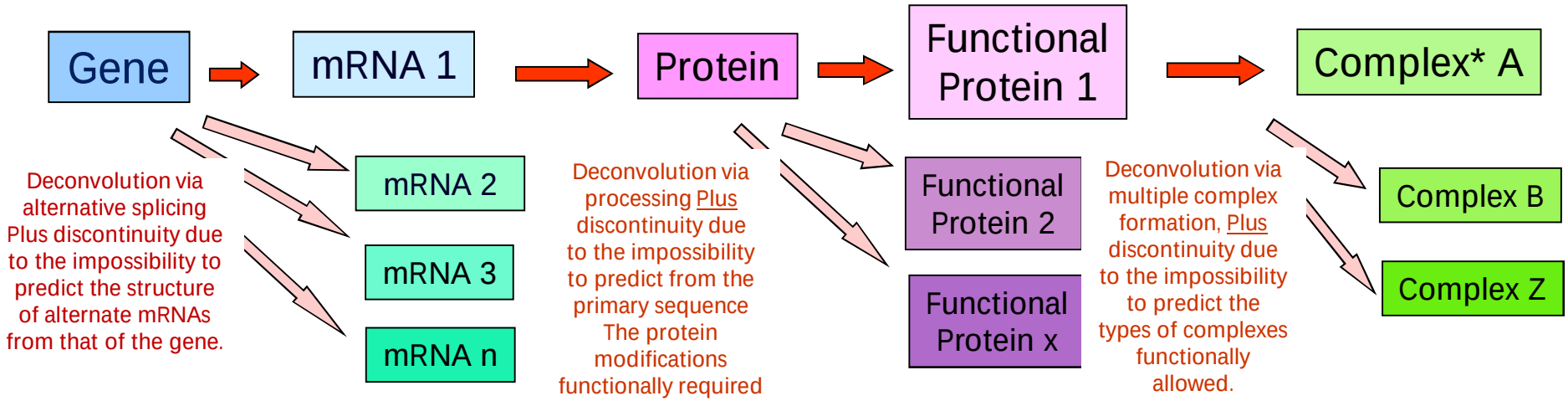
Be sure to use the appropriate modeling concepts & tools. If you don't …

…you get a Complicated "Cartesian" system. It does fly, but… it will never lay eggs! May be bombs!

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

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

One gene = several different physiological functions

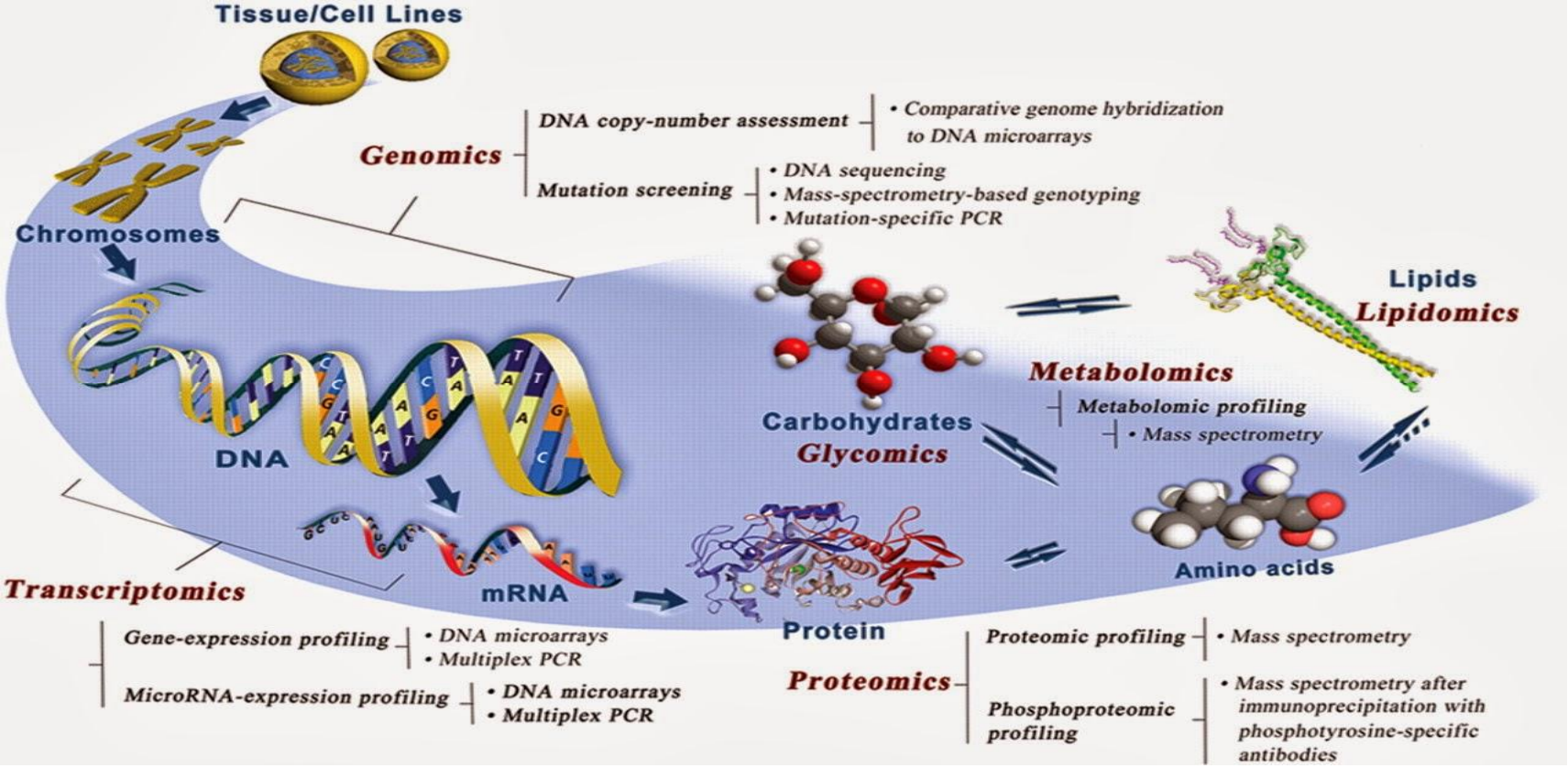


A non-linear integrative system.

At each step, the alternative options are context-dependent AND cannot be directly predicted.
25 000 genes for more than 600 0000 proteins functions
DNA alone cannot explain life functions

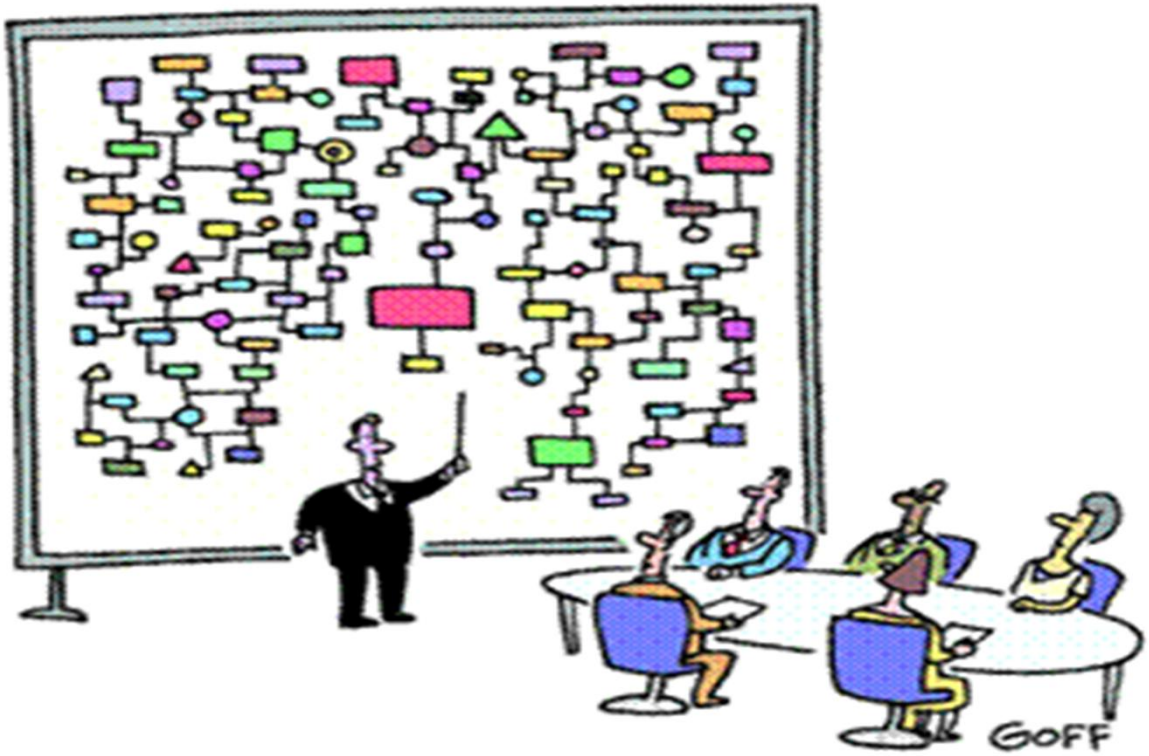
* Complex: is a group of two or more associated proteins or peptides

The Endless Omics Story started in the 70's



Medical research focused on patient's diseases became life sciences research driven by technologies and IT outputs

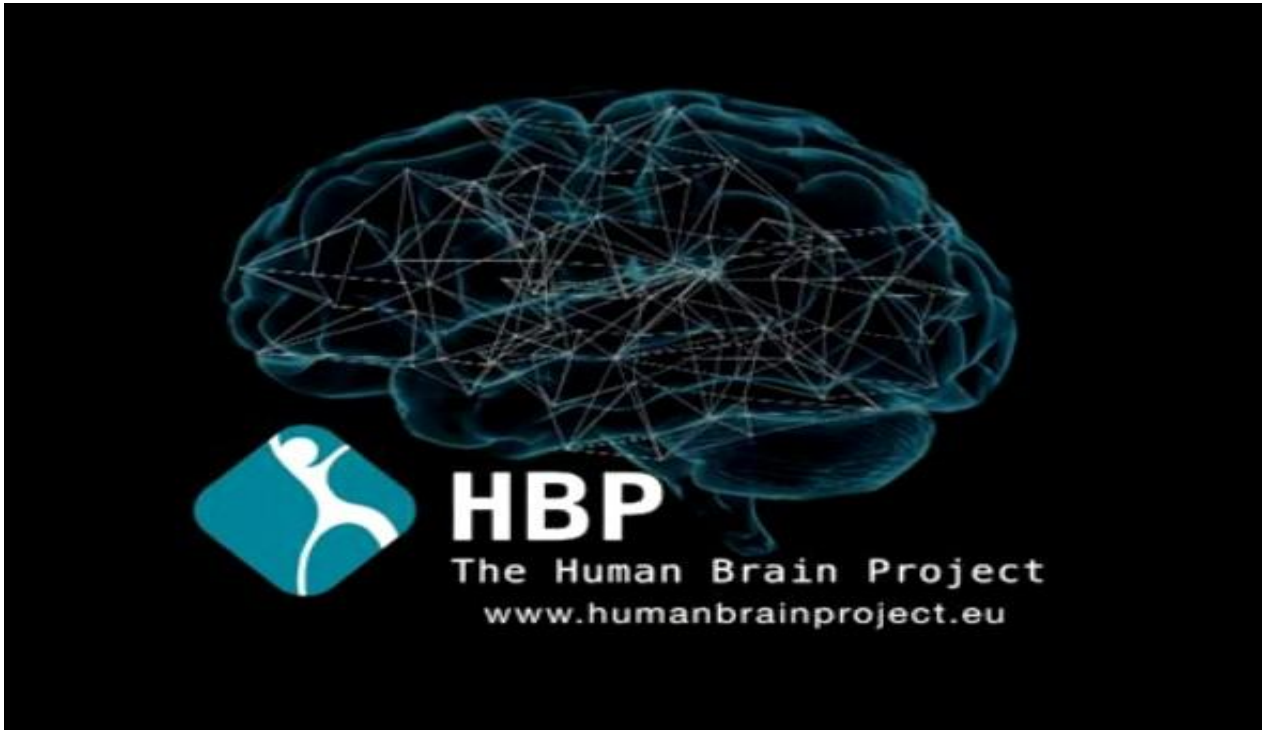
Floods of heterogeneous data under exponential growth



« **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?

The mechanisms of the brain

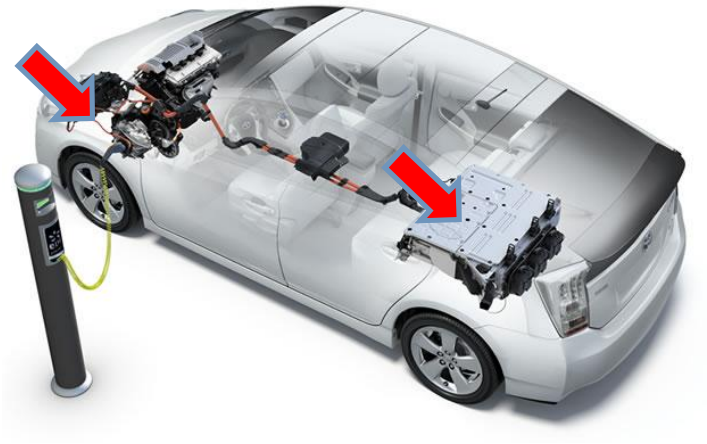


The goal is to simulate the complete human brain functions on supercomputers to better understand how it functions.
They will simulate the neurons only.

Which mechanisms ? Is the brain Complex or Complicated ?
1 billion € invested for which practical end point?

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

For dominant thinking,
This is a car* !



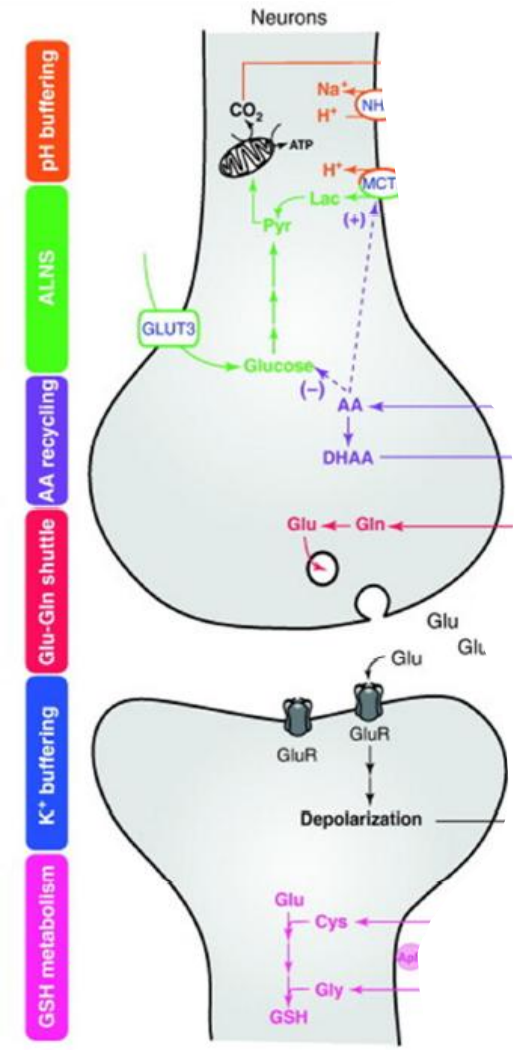
A lot of components
are of no interest**
for the experts.
No real innovation for them!

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 (98% of the total) was named "junk DNA"

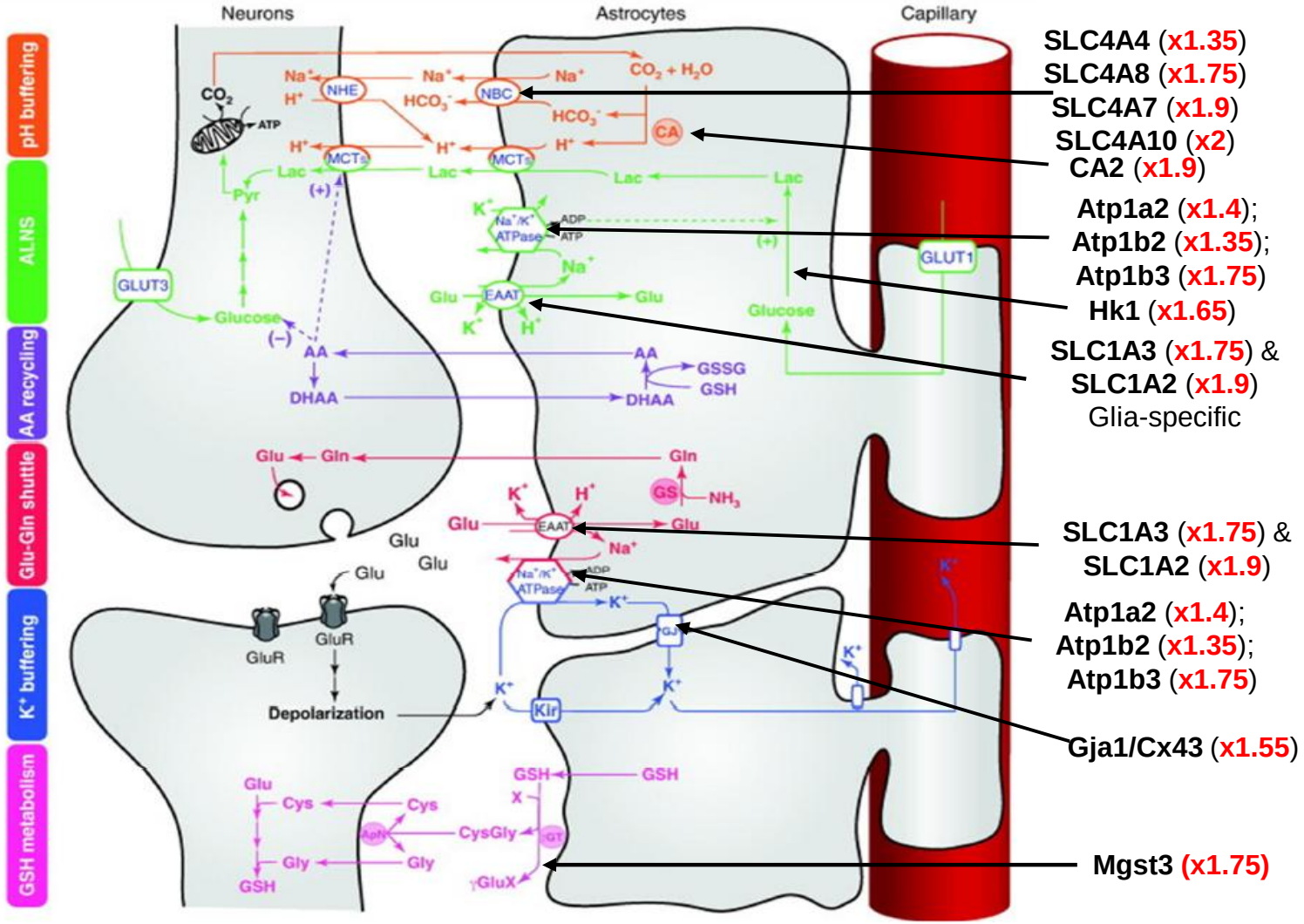
The classical vision of the brain: it's made of neurons …



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

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

The Pharma Industry issues

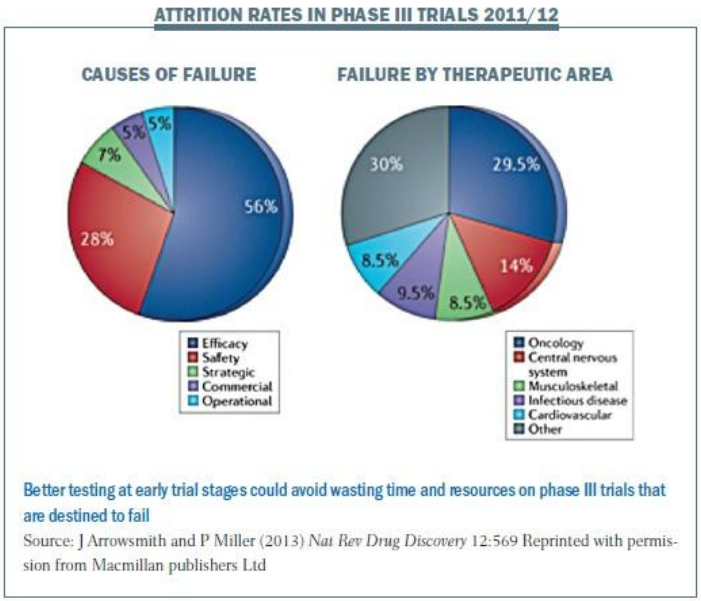
The pharmaceutical industry is facing unprecedented pressure from a combination of factors:

- key product patent expiries,
- an increasingly demanding regulatory environment,
- a declining R&D productivity,
- an exponential increase of R&D costs, and
- payers are no longer willing to pay novel therapeutic drugs at high premium prices.

To combat these threats, the Pharma Industry places a premium on scientific innovation, focusing its efforts on new targets search and new drug discoveries, but innovation itself does not guarantee success.

Net result: an unsustainable attrition rate desperately growing despite
- Massive increases in the production of scientific & clinical information,
- Hundreds of millions invested in state-of-the-art technologies and IT, and
- Massive restructuration efforts to enhance industrial efficacy.

The R&D Attrition rate still unacceptable



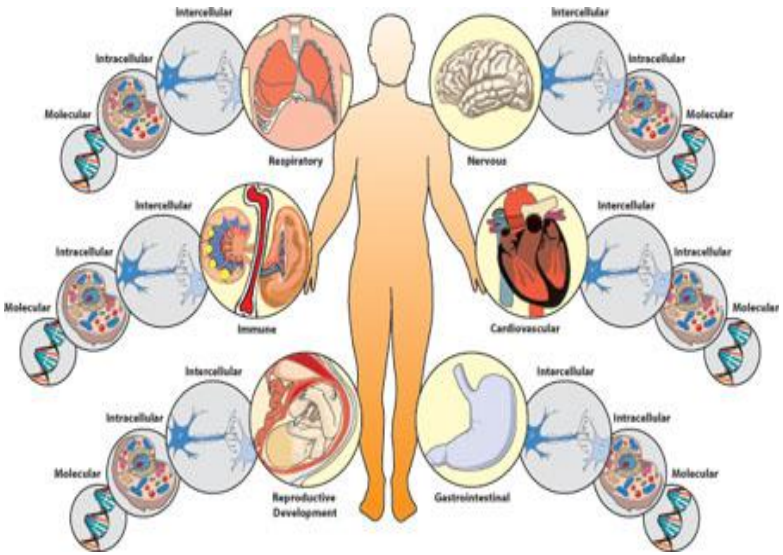
- Efficacy and safety are the major causes of failures in Phase 3
- During decades, multiple reasons and solutions were proposed by the scientific community to address this critical R&D issue.
- But despite huge investments, we must admit that these solutions did not deliver as expected.

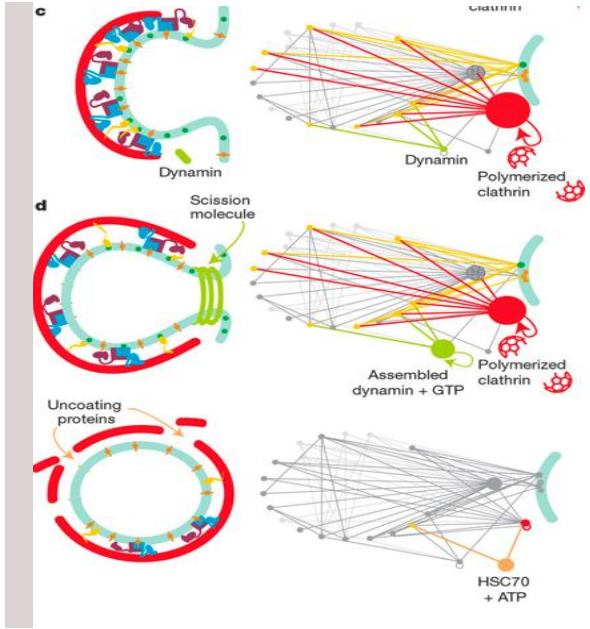
Multiple reasons might explain this attrition rate.
but, in any case, the challenge is clearly not a question of technologies only!
We must not forget that pharmacology addresses complex living systems ....

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)

The mechanisms of life deciphering dilemma

- The mechanisms of life are complex, non-linear and integrative.
- In “living complex” systems, the functions of biological components and mechanisms are event and context-dependent.
- Classical “Cartesian” modeling concepts & approaches, valid for the majority of man-made artifacts, imply the concept of a “blue-print”. But this concept is at the opposite of biological reality.
- While “Cartesian” Bioinformatics and Mathematical tools have proven to be efficient to collect, structure, analyze, simulate specific functions to test or generate innovative hypotheses, yet…
- The “garbage in, garbage out” reality, tells us that the information produced and published (even in leading scientific journals) is necessarily ALWAYS incomplete, biased and erroneous to unknown extents.
- Big Data, due to life sciences reality, does not necessarily means high value Smart Data, if not contextualized, without patients base-lines, and not related to biological mechanisms.
- Finally, statistics, serendipity or big data cannot be the “only” medical research answers to deciphering the mechanisms of complex diseases.

Clearly, we need to revisit the current R&D paradigm if we want to address the challenge of therapeutic success

BMSystems' answer to address the efficacy & safety issues

A "pragmatic" answer to improve the current situation could be:

1. Efficacy issue: Research should focus on "plausible" diseases causal mechanisms, and "kill" the unlikely ones as soon as possible.
   Objectives: increase robust opportunities, costs savings.
2. Safety issue: The industry should prefer, *when possible*, novel cost-effective therapies using combinations of existing solutions (existing drugs, nutriments, devices, e-health, etc…).
   Objectives: significant safety increase (drugs already given to humans), time & costs savings.

Easy to say, but to succeed we must accept a deep paradigm switch:

1. *From*: New target discovery based on intensive use of "Omics" outputs, and new patented drugs focus,
2. *To*: Novel therapeutic discovery using Mechanisms-Based systems medicine outputs and, *when possible*, novel patented* combinations of therapeutic & prevention solutions, active on the mechanisms (existing drugs, nutriments, devices, e-health, disease prevention tools and services etc…) focus.

**Combinations of existing solutions ARE patentable. They lower short term risks, and provide good starting points for new drug development opportunities. In case of no existing drugs availability, the lead search will be based on well defined targets within causal pathways.*

This new paradigm, The Mechanisms-Based Medicine paradigm, proposed by BMSystems in 2004, led to a fully operational solution that has repeatedly delivered.

The mechanisms-Based Medicine Concept

Global stepwise therapies discovery & validation process in the right order:

1. DISEASE: Describe the physiopathology of the disease with clinicians and patients feedback.
2. MECHANISMS: Discover the causal versus symptomatic mechanisms of the disease.
3. BIOMARKERS: *Indirectly based on causal mechanisms*, identify relevant biomarkers or specific combination, signatures of biomarkers (biological, imagery, physical signals, etc…) that could measure defined mechanistic deregulations at different stages of the disease.
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*. Propose the most practical solutions to address the relevant mechanistic deregulations. It is important to notice that the proposed solutions, integrating diagnostics, therapies & patients follow-up, can be combinations of existing drugs, nutriments, devices, e-health, disease prevention tools and services, etc …
6. FEED BACK LOOP: Integrate the results from e-R&D or e-Health experimentations into the validation process to improve global patient and disease follow-up.

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

Our Mechanisms-Based Medicine Concept

To implement Mechanisms-Based Medicine, BMSystems invented CADI* Discovery platform & know-how protected by industrial secrets:

- A heuristic systems biology approach to addresses complex, non-linear and integrative issues.
- A revised discovery and validation process to address complex diseases issues using necessary mechanisms understanding.
- A novel continuum between e-R&D and e-Health to enlarge and strengthen the translational medicine paradigm and extract the maximum pertinent value from scientific, medical & health data.
- A proactive search of cost-effective solutions with lower failure risks exploiting the growing number of well documented off-patent molecules, multiple devices and e-health tools, disease prevention tools and services.
- A systematic search of synergies between our research domains to optimize our proprietary CADI™ Knowledge database value through cost-effective novel applications.

The CADI™ Discovery platform is a proven operational answer, addressing both efficacy and safety issues, the main culprits for the unacceptable R&D attrition rate in our industry.

*CADI: Computer Assisted Deductive Integration

BMSystems Group at a glance

- Independent Private Company incorporated in 2004, profitable since 2006.
- 100% owned by its founders (no search for external investors).
- The first operational Mechanisms-Based Medicine discovery company for novel therapeutic & prevention solutions.
- Inventor of CADI™ Discovery: A Global therapeutic & prevention solutions discovery & validation process.
- 24 FTE* of which 9 FTE scientists/professionals focused on CADI™ research.
- Long term strategic R&D and business collaborations with more than 100 partners' professionals working on BMSystems' related R&D programs.
- Original dual business model that generates revenues through contractual deals & patented novel therapeutic & prevention solutions through collaborative R&D programs with its partners.
- CADI™ patented novel therapies, already contributed to the creation of two SMEs: Pherecydes-Pharma (2006, M.R. bacteria biotherapies), Theranexus (2013, combined therapies in psychiatry) both about to enter clinical-stage.
- A significant pipeline of internal CADI™ programs ready for collaboration of which IDUNN for Parkinson's disease.
- The digital/biology dual company that created a unique continuum between e-R&D and e-Health to enlarge and redefine the translational medicine paradigm & to extract the maximum pertinent value from health big data and its unique proprietary CADI ™ Knowledge database.
- The largest IT life sciences and healthcare business offer with its strategic IT partner, Persistent Systems (Leading Indian IT company 7000 people, 250 M$, 85% of business in the USA).

What we invented and did for ourselves, we can do for your company:
in the biomedical, diagnostic, Pharma, cosmetics, nutrition, food, chemistry and IT domains

*FTE: Full time Equivalent, CADI: Computer Assisted deductive Integration

The Heuristic Systems biology

Today

Maybe Tomorrow ?!

In any case: The creativity and the integrative capabilities of the brain of open minded, smart biology integrators supported by powerful adaptive IT systems to help them work.

Differences & complementarities between "heuristic" and "mathematical" approaches

HEURISTICS is a problems solving approach evaluating each step in a process, searching for satisfactory solutions rather than for optimal solutions, using all available qualitative information instead of quantitative information.

Thus,

Heuristic modeling starts from accumulated information to produce a model capable of describing the mechanisms that generated the observed outcome / data and predict their modifications associated with a different outcome;

It plays the role of an architect.

While

mathematical (Bayesian) modeling starts from quantitative data to produce models capable of reiterating this data and predict the outcome of a different experimental paradigm.

It plays the role of an engineer.

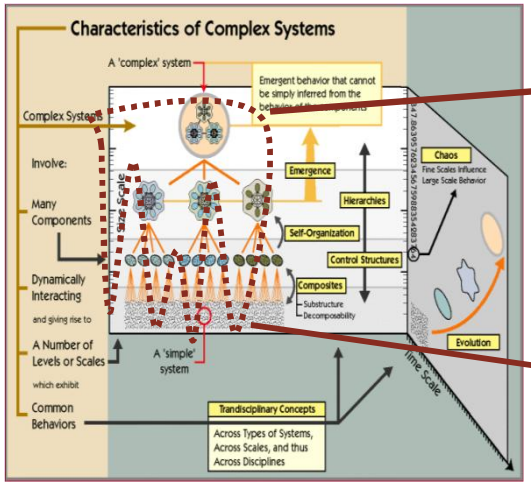
Hence

Far from being incompatible, these two approaches are complementary

CADI*™ the first multiple-scale non-mathematical modeling approach, successfully applying 5 principles more information is available on our website)

- An "Architectural Principles" Approach
- Our "Negative Selection" Process
- Our "4 steps validation" Process
- Our "Broad life sciences & IT" Expertise
- Our "synergic collaboration" with classical IT partners

A complex system being studied



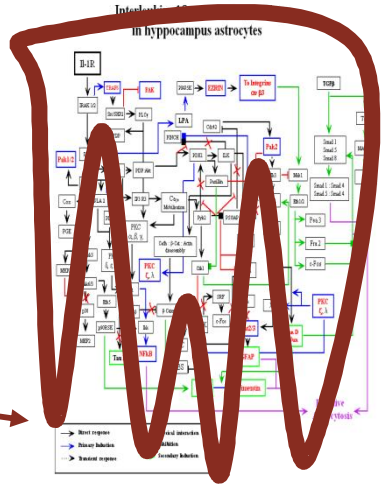
Scale / level

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

Different organs level

Different cells level

Molecules level



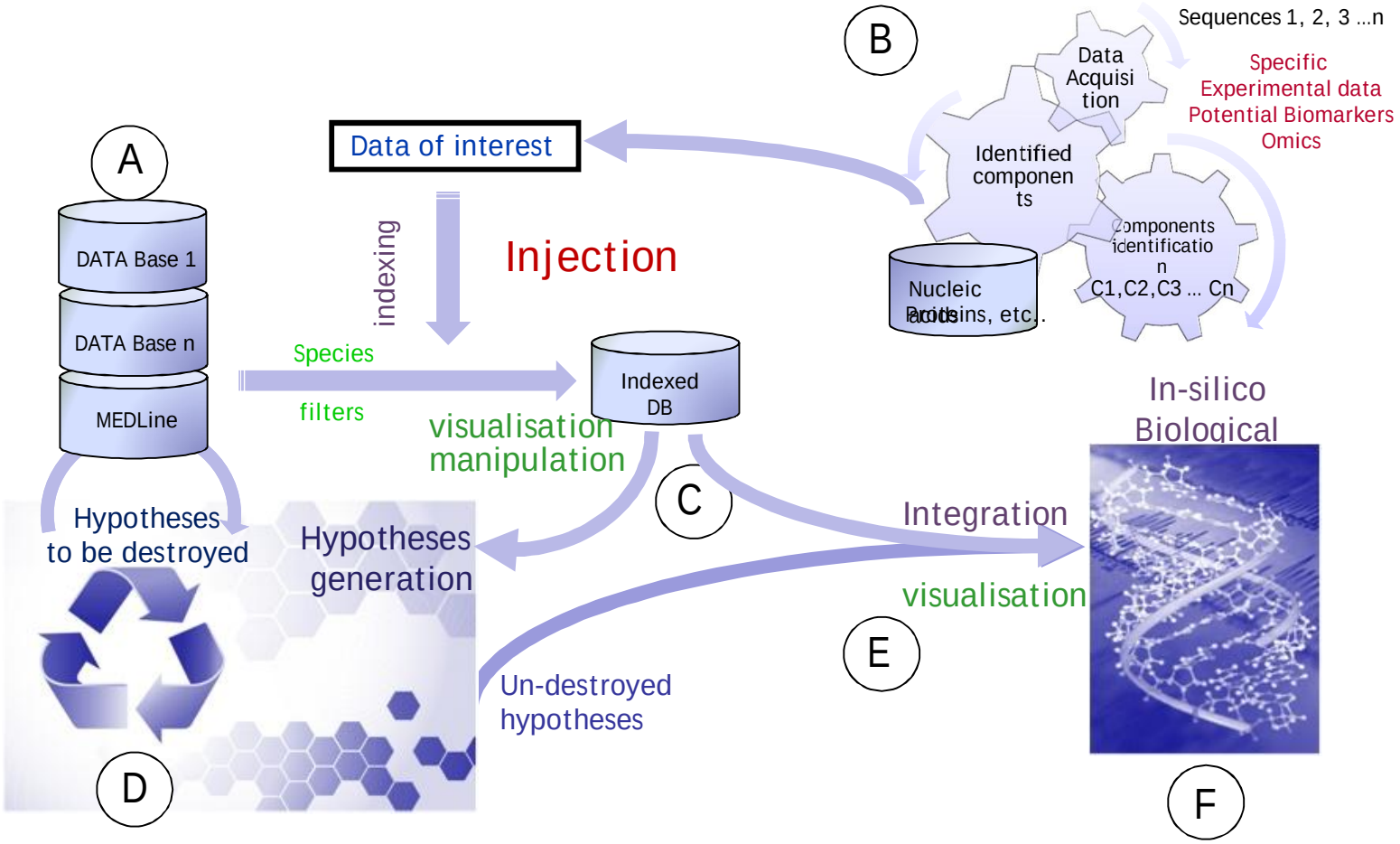
Clearly the challenge is to think out of the box and to ask the right questions!

*Computer Assisted Deductive Integration

CADI™ negative selection process

The first operational application of the negative selection concept

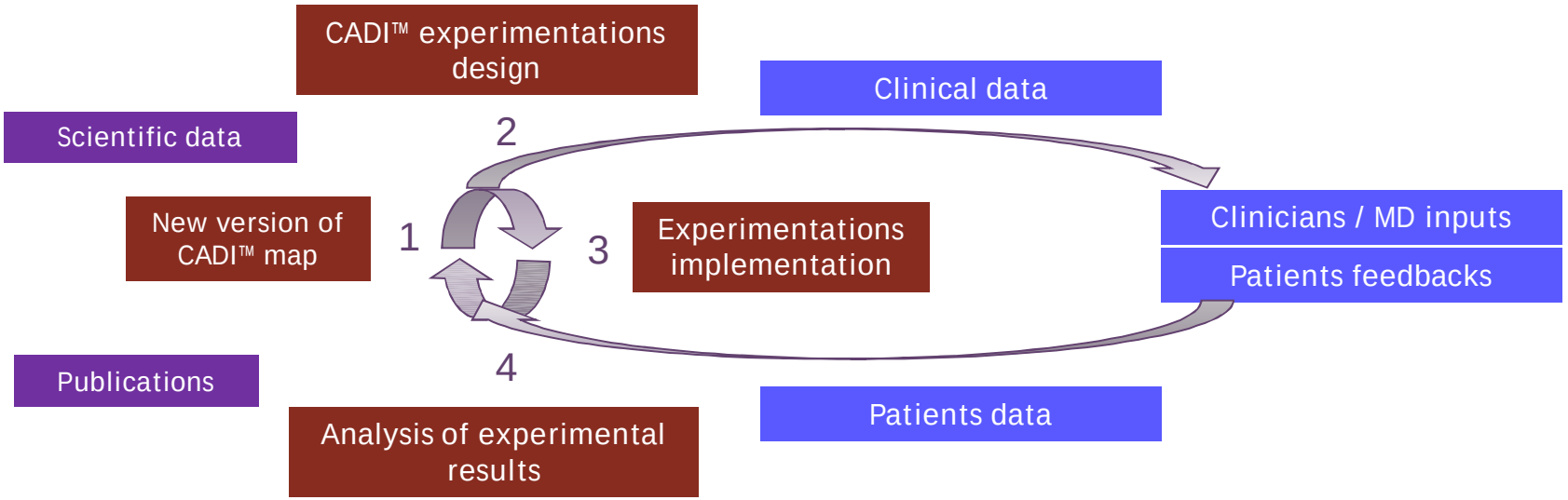
CADI™ original concept is an operative answer to "the garbage in-garbage out" issue, and a disruptively innovative way to generate new knowledge from cross-supported hypotheses.



CADI™ Global discovery & validation process

Mechanisms-Based Medical Research

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



E-R&D Continuum/Synergies E Health

Information technologies

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

PERSISTENT

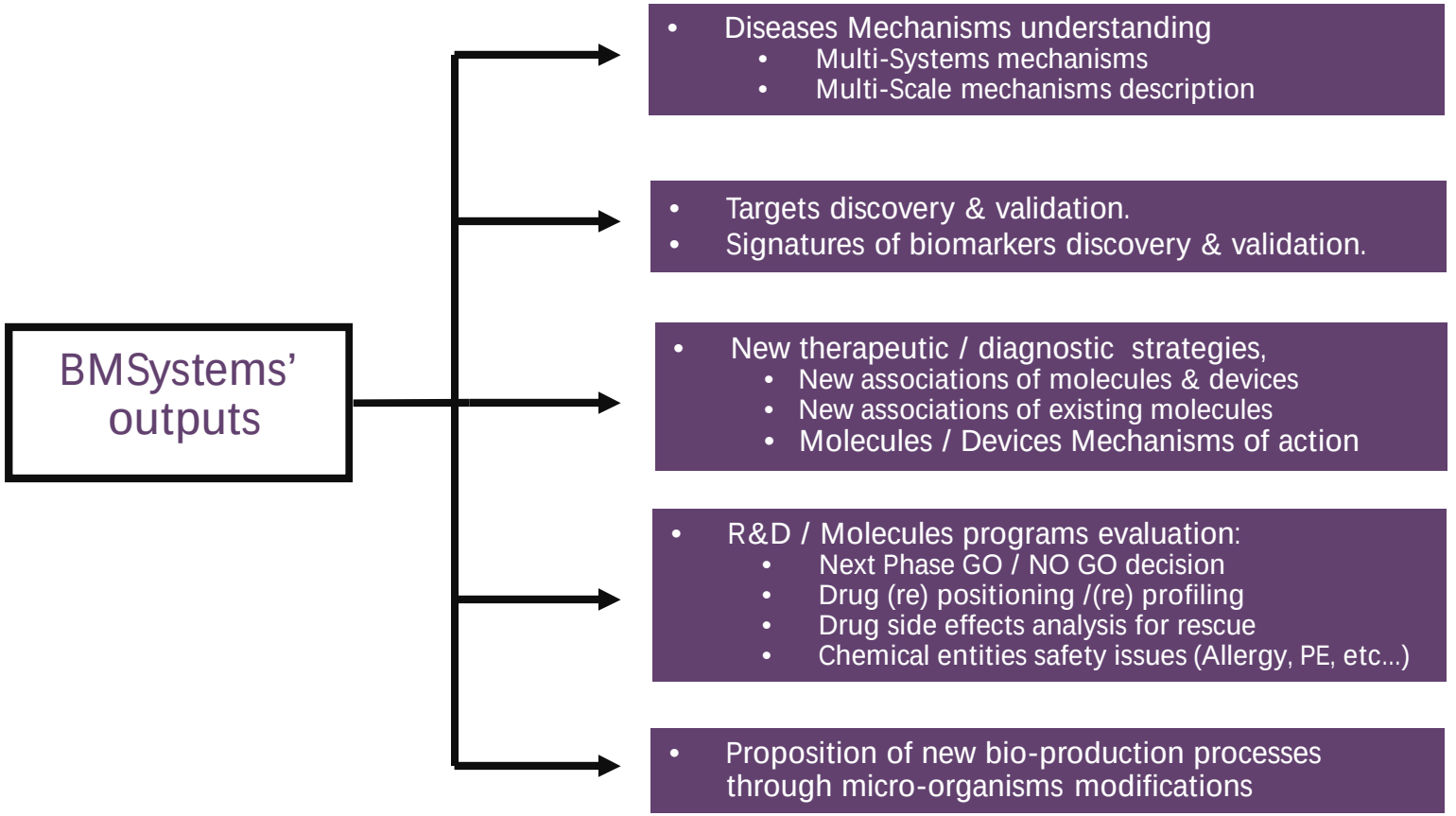
Persistent Systems Ltd worldwide IT partner

Leading Indian IT company 7000 people, 250 M$, 85% of business in the USA

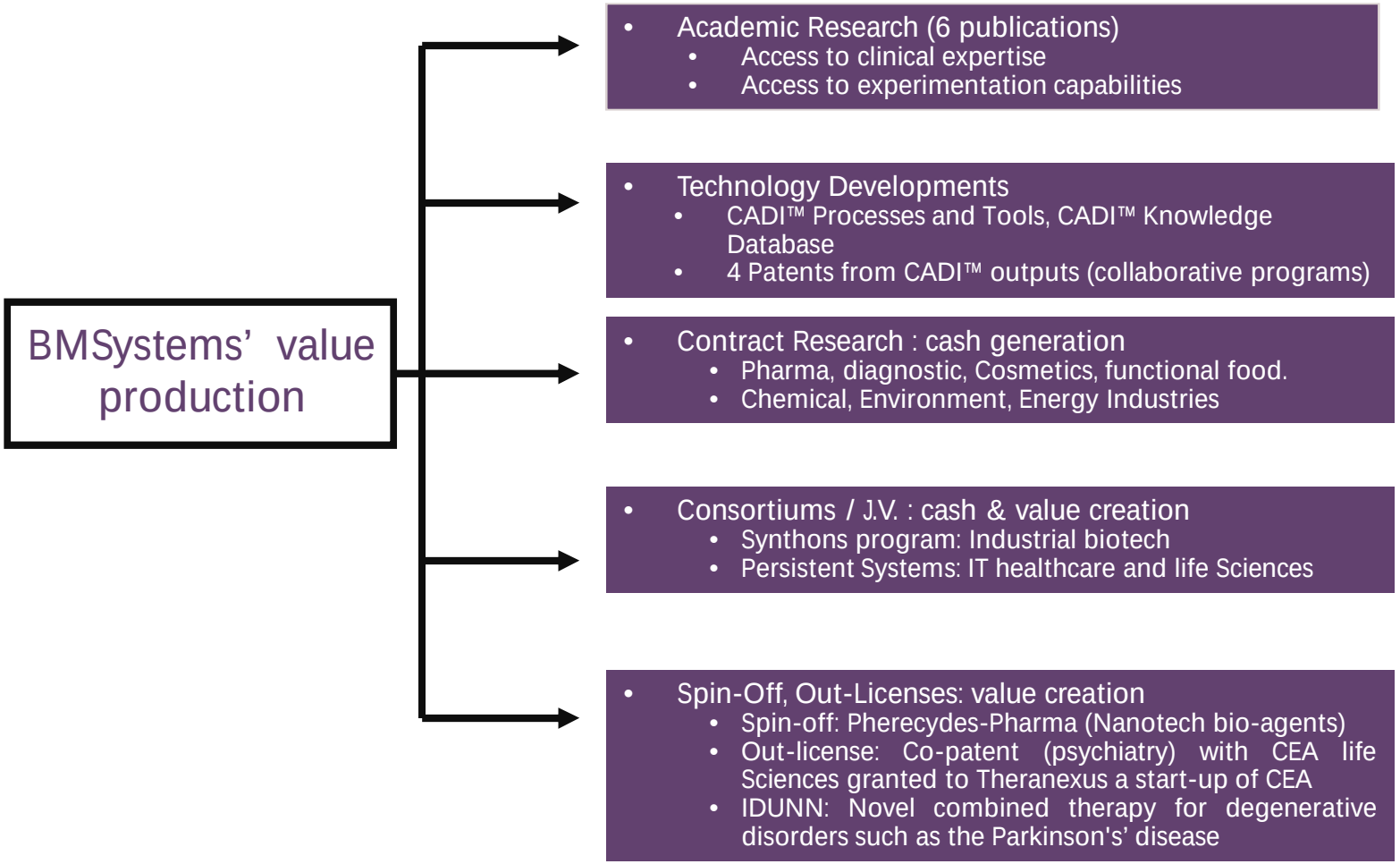
BMSystems' answers to clients/partners needs

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

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



Original dual business model that generates cash through contractual deals & patented novel therapies through collaborative R&D programs.



BMSystems' CADI™ programs: Internal & collaborative programs only

Program Name	Validation / Business Partner(s)	CADI™ compliance	CADI™ vers. 0	Ind. Valid.	Patents / Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.	Business launched
Nano-Bioagents	Pherecydes							
TAPE (protein improvement)	Pherecydes							
Chronic Fatigue Syndrome	Open							
Ebola virus ecology	Open							
Hepatitis C	Open							
Auto-immune global concept	Open							
Psychiatric combination treatment	CEA Life Sciences							
Creutzfeldt-Jakob disease mechanisms	CEA Life Sciences							
Alzheimer Disease Mechanisms	Open							
Parkinson's Disease Treatment	Confidential							
Psychiatric inflammatory mechanisms	FondaMental Foundation							
Fibromyalgia, facial pain	Aepodia							
Pain (Central/Peripheral)	Open							
Migraine Mechanisms	Open							
Multiple Sclerosis Mechanisms	Open							
Psychiatric disorders biomarkers	Confidential							
Program Synthons	ARD-IBT-L'Oréal							
Program Synthons	ARD-IBT-Rhodia							
Program Synthons	ARD-IBT-Arkema							
Human Glycosylation with Yeast	Open							
Breast cancer-Hras	INSERM							
Tamoxifen resistance	INSERM							
Specific Metastasis control	INSERM							
General Metastasis control	Open							
Müllerian regression Mechanisms	CNRS							
Adipocytes growth control	Open							
Skin Contact Allergy Mechanisms	Persistent Systems							
Skin immunology mechanisms	Open							
Hypercholestemia Mechanisms	Open							
New global concept for Diabetes type 1	Open							
Metabolic Syndrome	Open							

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

BMSystems "Broad life sciences & IT" Expertise team

A strong multidisciplinary & experienced core founders' team

- **Dr. François Iris (PhD), Chairman, CSO-CTO - Geneticist, physiologist & molecular biologist**
  - Creator of Millennium Pharmaceuticals' (USA) high-throughput DNA sequencing unit. Former collaborator of Nobel Laureate Prof. Jean Dausset. Inventor of new technologies in molecular biology. MRC Overseas fellow, Member of H.U.G.O., Wellcome Trust Systems Biology experts board. Member of the Cambridge Healthtech Institute Scientific Committee, Member of the Evaluation committee for the funding priorities in the "Medical Systems Biology-MedSys" program; German Federal ministry of Research. 14 original articles in international journals including Nature, Cell, Nature Genetics, Genomics, J Mol Endocrinol, J Comp Biochem Physiol. 7 international patents, 3 patent applications currently undergoing examination, 5 book chapters, numerous invited communications at international conferences.
- **Manuel Gea, C.E.O & VP R&D Information Systems - Information systems specialist**
  - Scientific Engineering Degree from Ecole Centrale. Dregree in sosiology Paris IX Dauphine University. Chairman of the Supervisory board of PHERECYDES PHARMA (anti-bacterial bio-agents pharmaceutical company); Former CEO Hemispherx Biopharma Europe. Founder and President of Centrale-Santé. Founding-Administrator of the computing firm Formitel. Former McKinsey executive, creator of Practice Pharma services in France. Former Division Managing Director with Boehringer-Ingelheim France. Former International business manager Colgate-Palmolive Company (US), Co-founder and Vice President of the Biotech Committee of the Association of the Pharma companies operating France (LEEM). Member of the executive board of Medicen Santé, the world-class bio-cluster of Paris region. Vice-President Adebiotech Committee. Co-founder and Evaluation Committee member of Paris Biotech (leading biotech incubator).
- **Gérard Dine (MD, PhD), Chief Medical Officer - Physician, biologist**
  - Head of the Haematology Dept. at Troye's hospital. Founding member and Head of the Biotechnology Dept. at Ecole Centrale Paris. Founding-President of Troye's Institute of Biotechnologies. Former President of the Institute for Sports Medicine.
- **Paul-Henri Lampe, CIO & Systems Integration Director - Systems Integration specialist**
  - Scientific Engineering Degree from Ecole Centrale Lille. Master Degree in Applied Mathematics from Ecole Centrale Paris. Former IBM Systems Integration Manager. Former Information Systems projects manager in an Acute Care Hospital in Paris.
- **Pablo Santamaria, IT & Internet Systems Director - Internet technologies specialist**
  - Scientific Degree from Ecole Centrale Paris, Founder and President of the computing firm Formitel (1988). Founding President of the Centrale-Ethics Think-Tank. Vice-President of Centrale Human Resources Professional group. Former Senior Consultant Information Systems Evaluation (INSEP). Former Industrial Maintenance Manager at Glaxo Pharma (Evreux, France)

BMSystems' CADI™ publications to date

CADI™ Models published in prestigious peer-reviewed journals:

- 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 Ha-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
- 2008, CNS: Biomarkers for Psychiatric Disorders. (Ref. ISBN: 978-0-387-79250-7, November 2008). Dr. François Iris, is the author of the Integrative Biology chapter of the book. The editor, Prof. Christoph W. Turck, is head of the Proteomics and Biomarkers branch at the Max Planck Institute for Psychiatry

BMSystems' 9 scientific & businesses proof of concepts

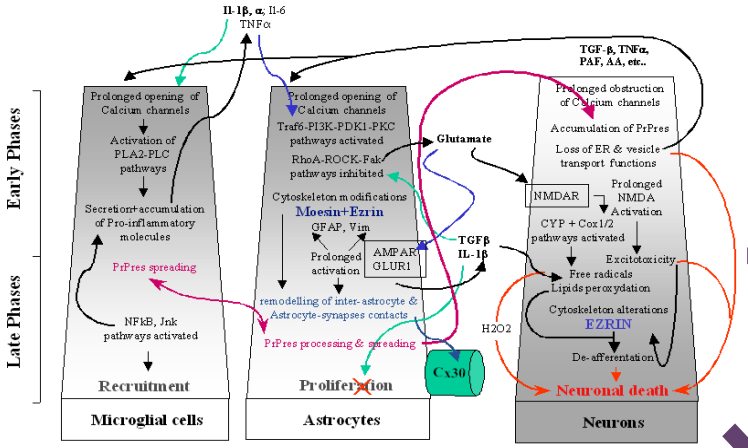
Selected POC and their related outputs of CADI™ Programs:

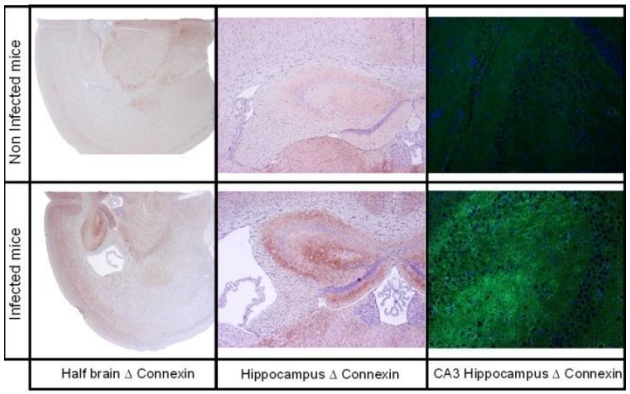
1. Case study A: Domain: CNS neurology and Psychiatry. Collaborative CADI™ program with CEA life sciences (*1 patent, 1 publication, 1 spin-off*).
2. Case study B: Domain: Dermatology. Contractual program CADI™ for a client (*8 new targets, cosmetic company confidential*).
3. Case study C:. Domain: Cosmetics. Collaborative CADI™ program with Persistent Systems Labs (India), Institute for Genomic and Integrative Biology (India) *(low allergy mechanisms identified for safety issues).*
4. Case study D: Domain: Type 2 diabetes. Contractual CADI™ program for a client (*NO GO decision for safety issue, pharma company, confidential*).
5. Case study E: Domain: CNS neurology/Parkinson's disease. Collaborative CADI™ program with Belgium partners (*novel combined therapy proposed for POC in humans*).
6. Case study F: Domain: Infectious diseases. Collaborative CADI™ program with Pherecydes-Pharma (our first spin-off) (*3 patents, 1 publication, 1 spin-off*).
7. Case study G: Domain: Industrial biotech. Collaborative CADI™ program with ARD, IBT, CVG, L'Oréal, Rhodia, Arkema (*1 patent filed by an industrial partner*).
8. Case study H:. Domain: Tissue differentiation / embryogenesis. Collaborative CADI™ program with CNRS (*1 publication*).
9. Case study I: Domain: Oncology. Collaborative CADI™ program with Inserm unit 553 (*2 publications, Novel strategy proposed for R&D collaboration*)

Mechanisms-Based Medicine: 9 proofs of concept:
A new paradigm qualified for industrial use

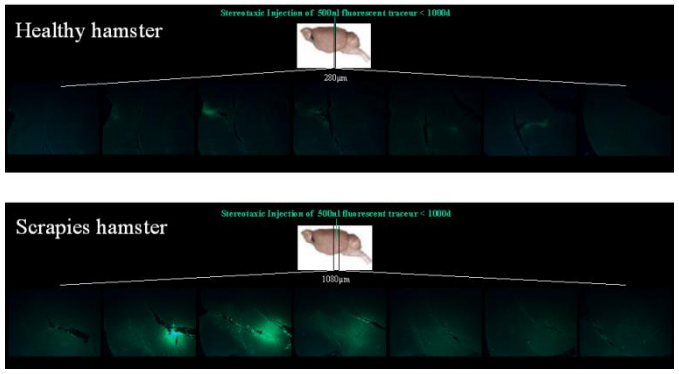
The heuristic CJD model finalized in early 2008.

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



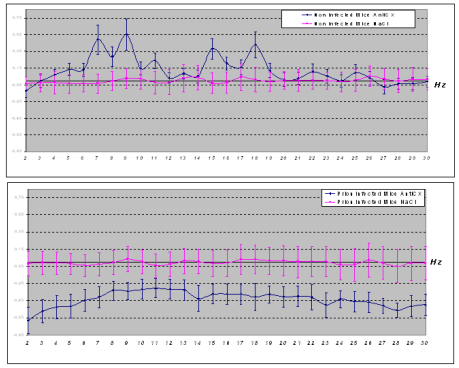


Functional modifications of glial connexions



Source: BMSystems & CEA

Functionnal EEG alterations linked with modifications of glial connections.



Healthy mice

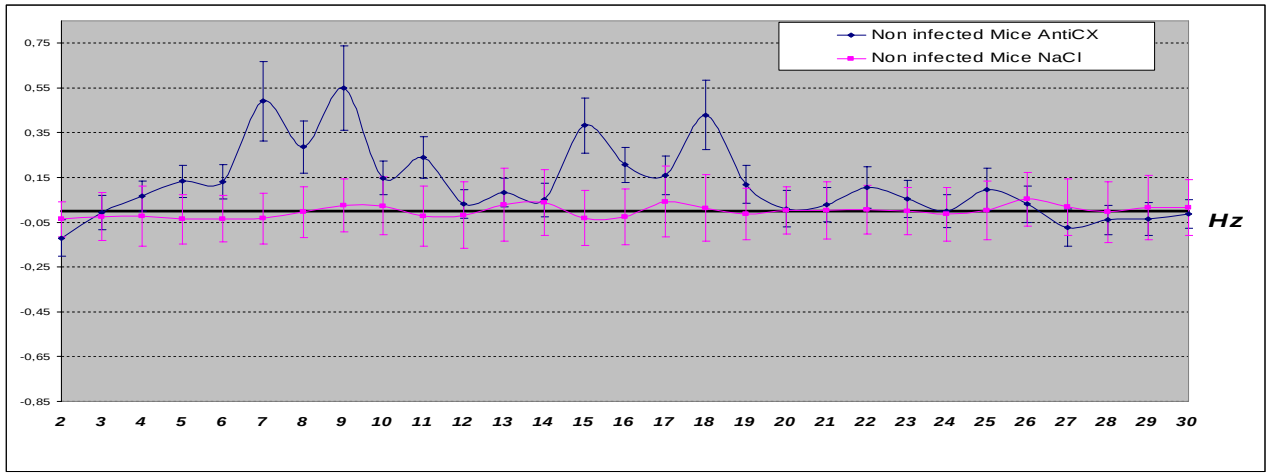
Scrapies mice
(asymptomatic phase).

NaCl

Anticonnexin

Practical consequences

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



Healthy mice

NaCl

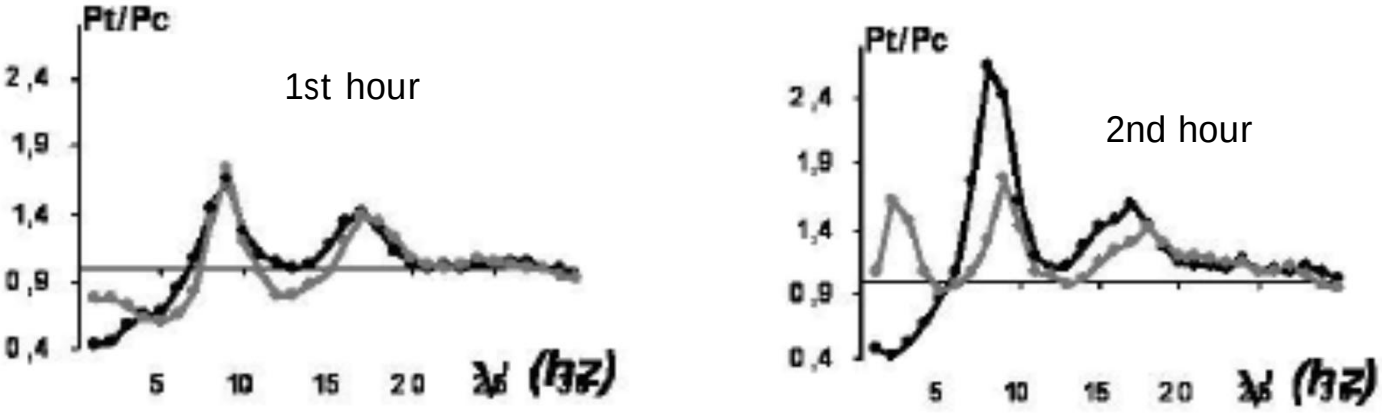
Anticonnexin

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

Hence, in cases where the aim of treatment is to affect synchronization, the adjunction of Cx modulators could potentiate current drugs therapeutic effects (allow to decrease doses while preserving activity) thereby reducing unwanted side effects.

A new model was constructed and the predicted approach tested in vivo.

Effects Cx modulator adjunction to Paroxetin treatment



Paroxetin 1 mg/kg (2 to 5-fold below usual doses)

Paroxetin 0.5 mg/kg + Cx modulator 0.4 mg/kg

Similar boosting effects of Cx modulators are seen with Clozapin; Modafinil, Diazepam; Venlafaxin; Escitaloprame; Bupropion; Sertralin; etc.

The dose-reducing effects are in the order of 5 to 20-fold (depending on the therapeutic molecule) without any loss of therapeutic effects.

NB: one of the molecules utilized as Cx modulator is already on the market for a completely different indication and is used here at 1/x th of its approved dosage (the predicted dose-dependent effects were observed).

The net results

CJD is not a neurological disease stricto sensus. It is a disease that primarily affects astrocytes structures and functions which, over time, lethally affects healthy glial & neuronal cells through « bystander effects », leading to widespread CNS disorganization and functional failure.

But this model also provides an understanding of key mechanisms associated with psychiatric disorders.

An entirely new approach for their effective treatment was designed, tested in vivo and validated.

- Patent covering novel therapeutics for cognitive disorder (CEA/BMSys).
  Delivered in Europe: WO 2010/29131 A1 - “class” therapeutics patent.
- Exclusive co-license signature to a start-up of CEA
  Neither of which have much to do with CJD per se…

This work received a Bio-IT World “Best Practices” award from the Cambridge HealthTech Institute (USA),

and was selected as 1 of the 3 pan-European “state of the art examples of systems biology approaches of benefit to medicine” by the European Commission’s DG Research, Directorate of Health (June 2010).

Case Study B: CADI™ Standard Full program

Domain: Dermatology. Contractual CADI™ program

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

- Build a strong integrated understanding of the global systems to redefine the R&D strategy and portfolio programs;
- Review coherence of existing Expert's requests, and pertinence of Expert's answers;
- GO/ NO GO decision for two existing programs;
- Identify new pertinent targets with mechanisms of action;
- Suggest potential molecules for new targets;
- Propose a validation strategy and assist client's team in experimentation outputs analyses.

Work done:

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

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

Case Study C: CADI™ Standard Limited program

Domain: Dermatology/cosmetics. Collaborative CADI™ program

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

- May 2013, the European Unions bans the import and sale of cosmetics containing ingredients tested on animals.
- Objective of the program: Offer to the industry a highly effective, competitive and reliable alternative to detect & characterize the potential for irritant contact dermatitis and/or allergic contact dermatitis complex formulations could have in normal skin in vivo, using reconstructed skin, in-vitro and in-silico tools.
- Develop a range of products/services to fit clients' needs.

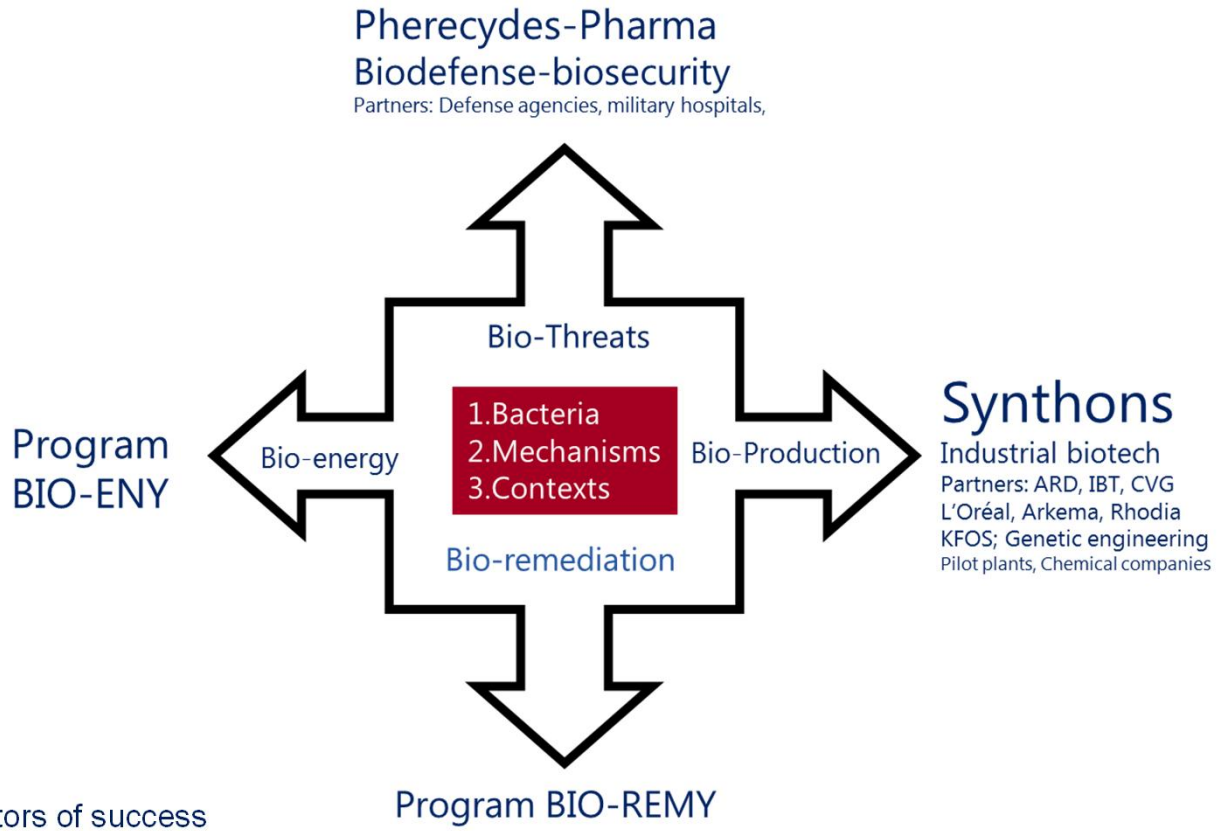
Work completed under progress or to be done:

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

The operational solution combining heuristic modeling and mathematical modeling

BMSystems' cross-fertilization business strategy:

Illustration: The bacterial mechanisms and their possible business applications



KFOS: Key factors of success

The BMSystems' R&D productivity KFOS

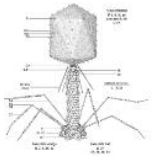
Up to 4 independent possible programs with very different key issues but exploiting the same CADI™ knowledge database and same BMSystems' skills without changing its core-business and avoiding any massive additional investment.

CADI™ Multi-resistance infectious diseases program

Domain: Multi-resistance infectious diseases. Collaborative CADI™ program (BMSystems created the partner)

Request: How to rapidly (less than 30 min) and efficiently detect and destroy any unknown bacterial pathogen or emerging strain without using:

1. Antibiotics: too many resistant strains, and very rapid resistance acquisition
2. Vaccines: much too slow to act, and small strain variations often lead to inefficacy

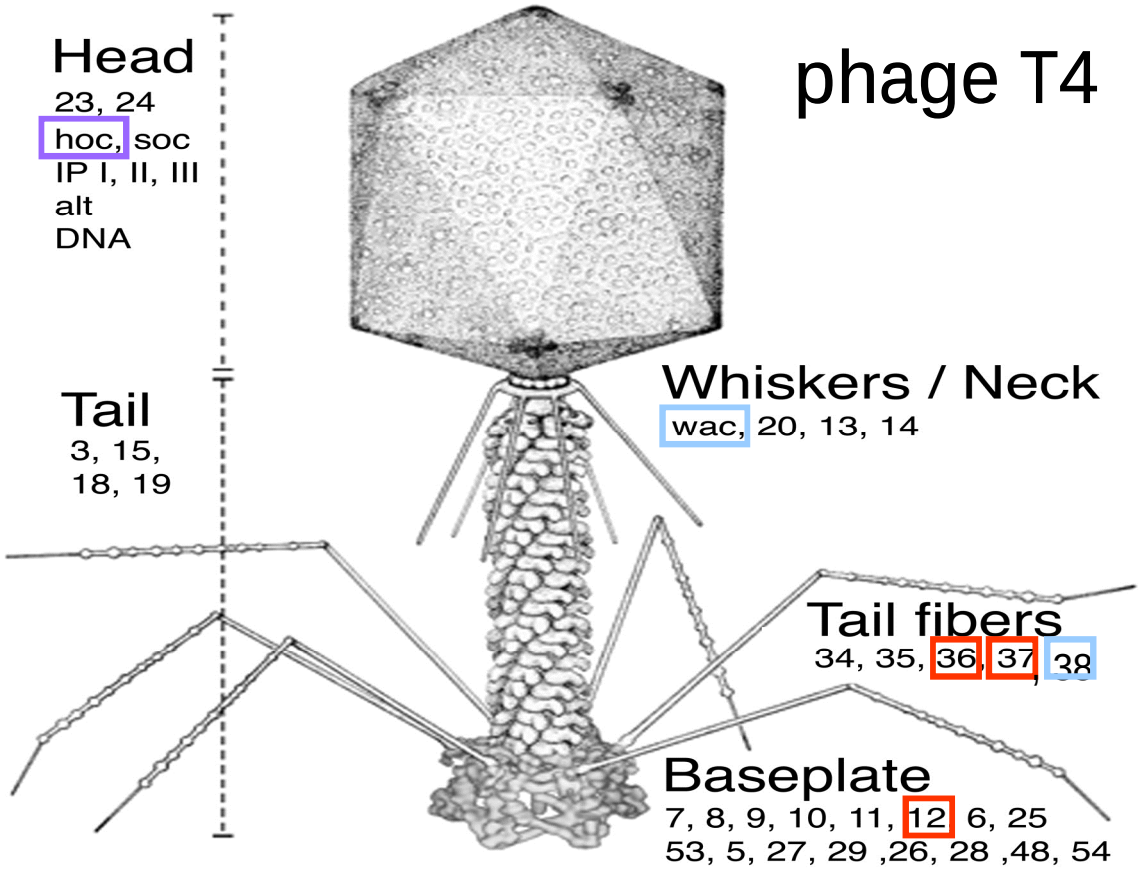


Work done, start-up creation

- 2005: Two CADI™ models constructed to describe bacteria resistance mechanisms and bacteriophages-bacteria co-evolution mechanisms.
- 3 patented new disruptive technologies invented (TAPE, ABACCUS, RIPH), 3 publications.
- 2006: Successful launch and financing of Pherecydes-Pharma, the first bio-defence and bio-security company in France
- 2009: Creation of the first operational large-scale engineered bacteriophage bank to fight against “unknown multi-resistant” bacterial infections.
- 2011: Pherecydes Pharma secures 900 k€ DGA funding for evaluating the use of bacteriophages on infected burnt soldiers
- 2013: Pherecydes Pharma consortium granted 3,8 M€ by FP7 program to enter into clinic.

World’s 1st company entirely created from an integrative systems biology program

The detector-killer adaptive tool



How to modify any of these proteins in N different regions, at X different sites, in Z different manners, all this simultaneously and then recombine the multitude of variants generated into a population of obligate lytic phages?

CADI™ Parkinson's disease program

Domain: Parkinson's disease. Collaborative CADI™ program

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

Work done or to be done:

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

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

The oncology Individualized therapy bubble

The Individualized therapy mirage vs. multi-therapies novel concept

CADI™ past programs and novel therapeutic strategy

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

- Outputs: Identification of 4 differently deregulated pathways between the 2 types of cells. Test of combination of 3 drugs, never used in oncology, that showed synergistic apoptotic activity in-vitro. Additional outputs: anti-farnesylase can't work!

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

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

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

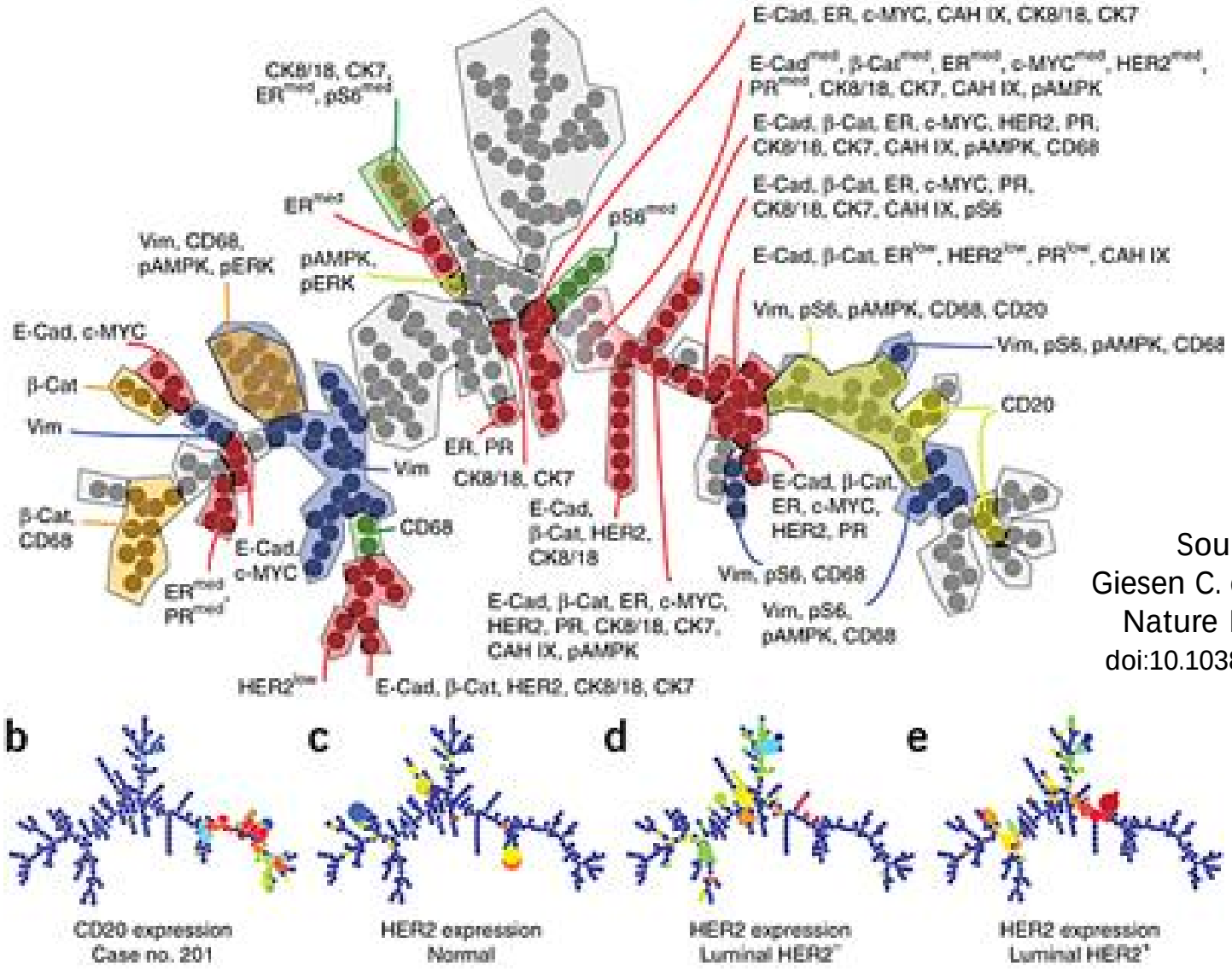
- Outputs: explanation for the relapse mechanism: "antibiotic resistance-like" form of selection mechanism identified.

These three programs show that the aim of the Industry to transform cancer into a chronic disease raises a lot of issues on long term efficacy due to the "antibiotic resistance-like" behavior of tumor cells.

The poor efficacy and too high prices of treatments proposed by the industry decided more and more payers to refuse reimbursing them. Based on HIV experience, a new paradigm, addressing simultaneously different targets combined with a novel metastasis control strategy, must be investigated.

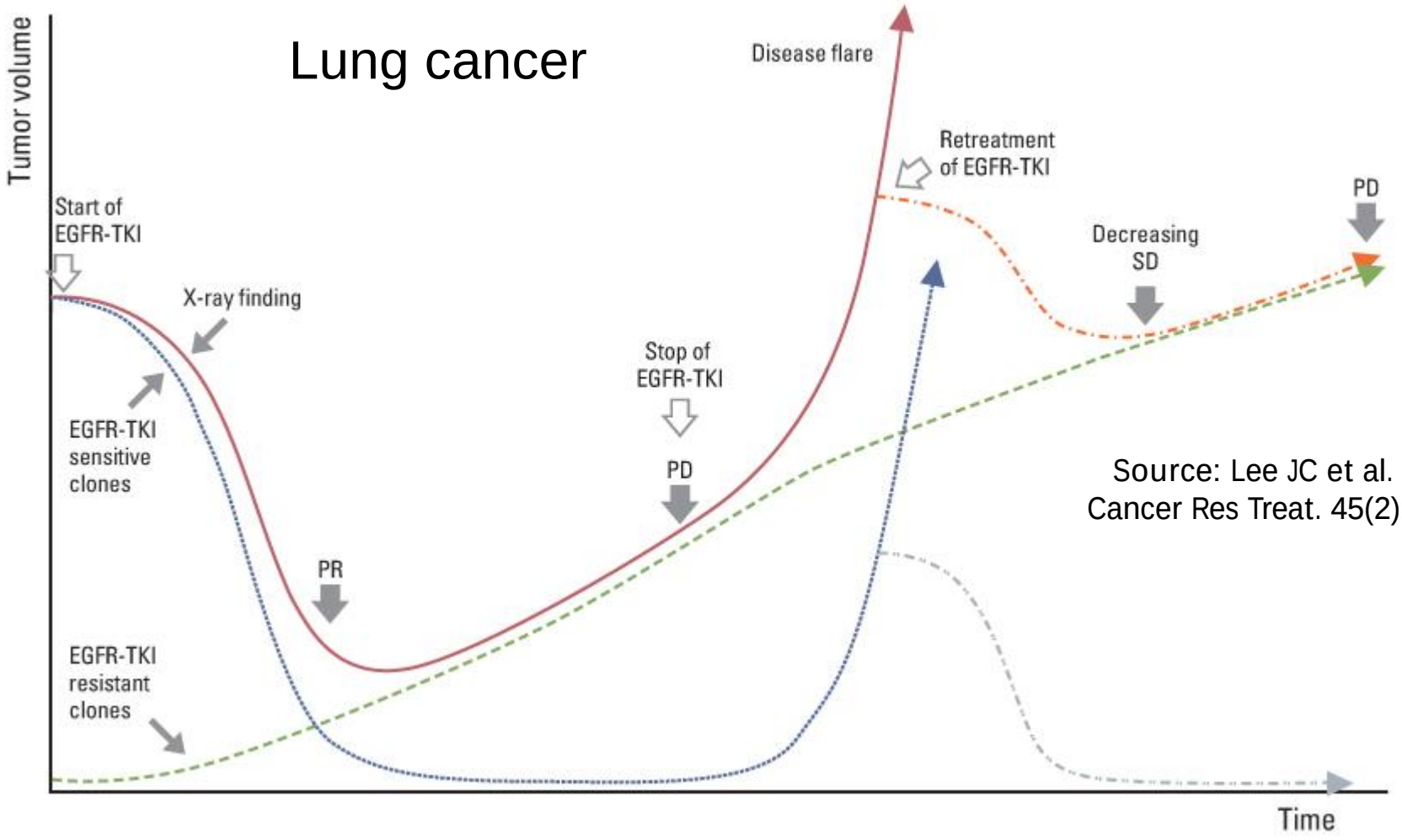
A tumor is rarely composed of one type of tumor cell. BMSystems, through his 3 programs, identified the narrow limits of mono-targeted therapies and proposes a new approach to oncology research, based on a therapeutic strategy that does not only target the tumor inside but uses the possibilities of surrounding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

Brest cancer: multiple types of cancer cells within the same tumour



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

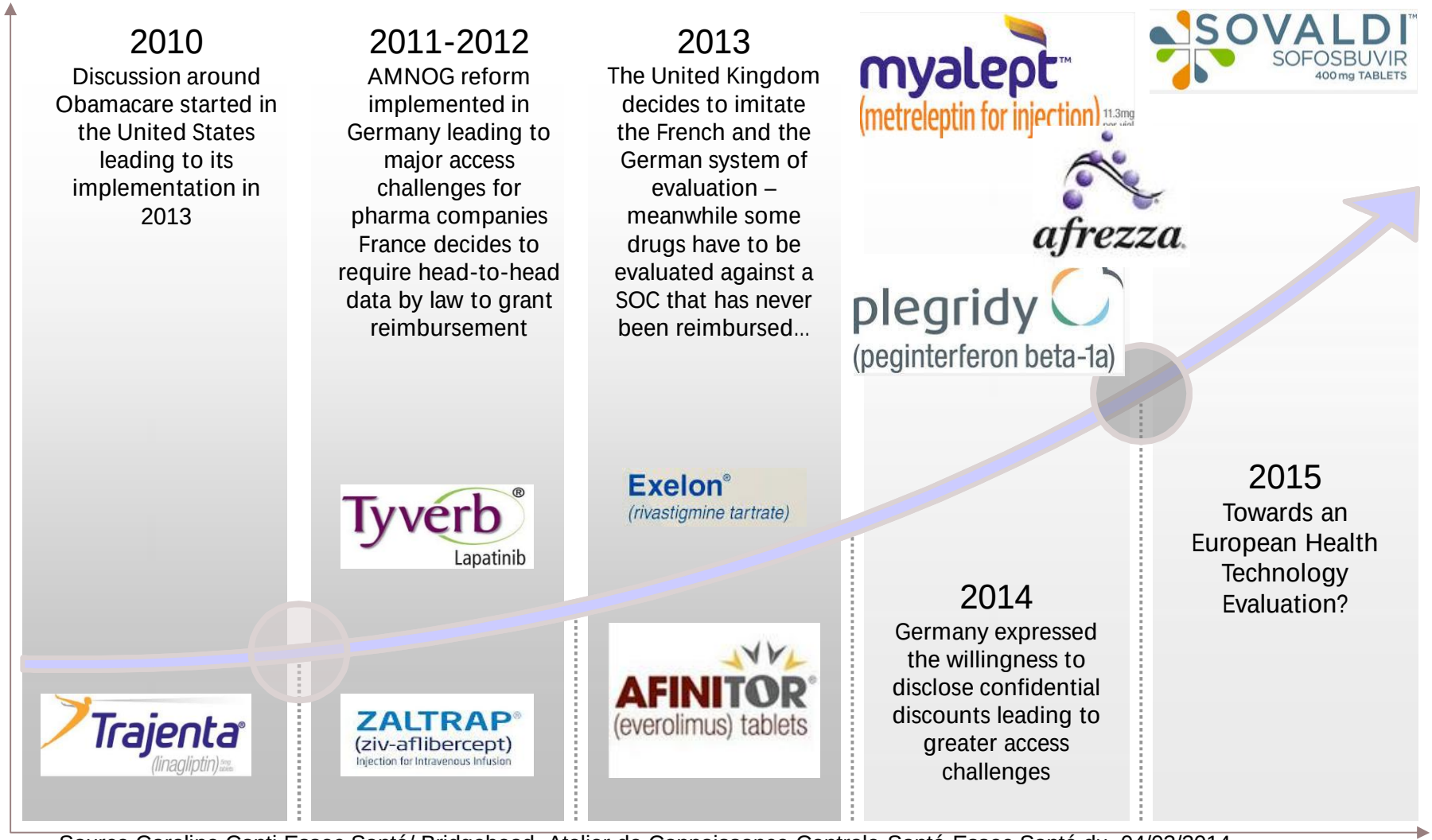
Targeted treatment does nothing more than selecting resistant cancer cells: The cancer first diminishes & then starts again and cannot be stopped.



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

In a nutshell…What may happen in the coming 3 years ? Will the bubble implode?

New drugs coming to the market have faced significant access challenges – are these artefacts or signals? We will see in no time

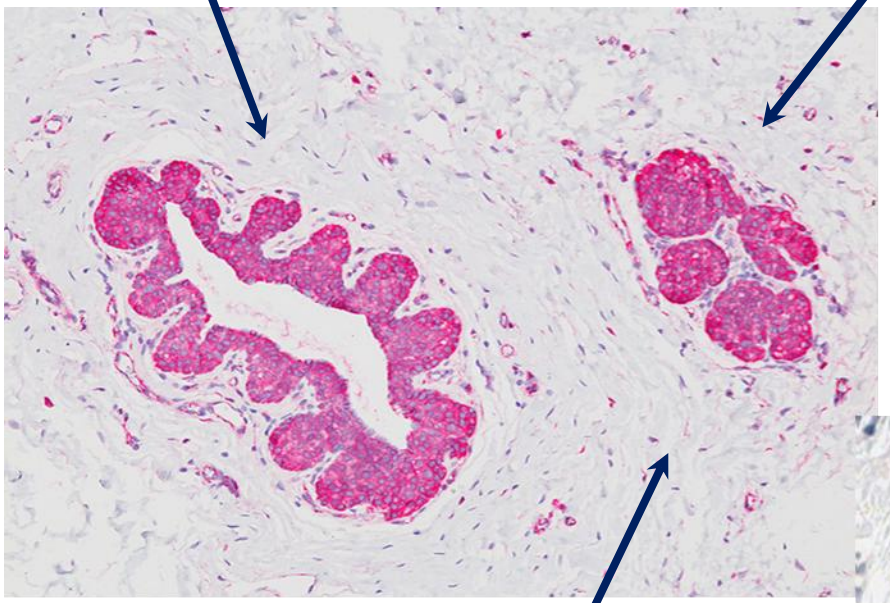


Source Caroline Conti Essec Santé/ Bridgehead Atelier de Connaissance Centrale-Santé Essec Santé du 04/03/2014

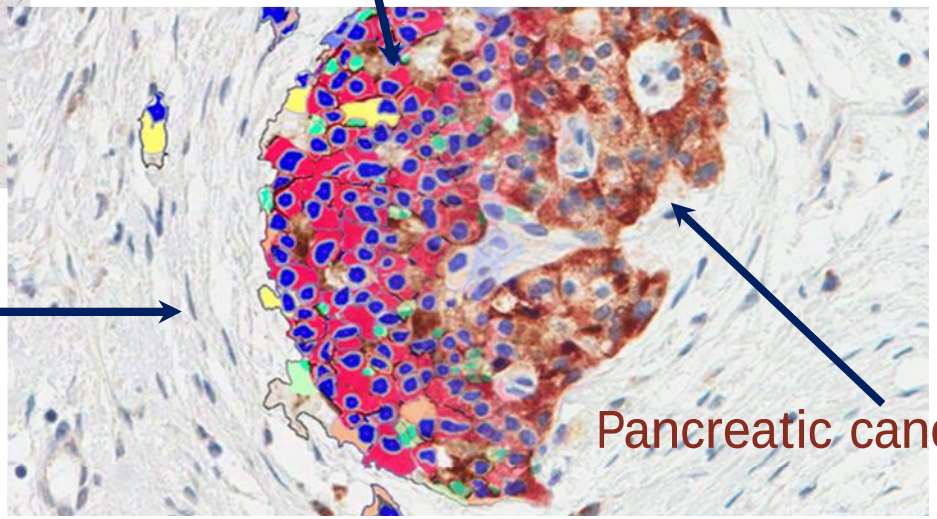
A novel approach to cancer therapy.

Ductal breast cancer

Non-ductal cancer off-shoot



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



Pancreatic cancer

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

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

Key learnings about life sciences issues

- The mechanisms of life are complex, non-linear and integrative. They are "built" to survive.
- In "living complex" systems, the functions of biological components and mechanisms are event and context-dependent.
- Classical "Cartesian" modeling concepts & approaches, valid for the majority of man-made artifacts, imply the concept of a "blue-print". But this concept is at the opposite of biological reality
- … While "Cartesian" Bioinformatics and Mathematical tools have proven to be efficient to collect, structure, analyze, simulate specific functions to test or to generate innovative hypotheses, yet…
- …The "garbage in, garbage out" reality, tells us that the information produced and published (even in leading scientific journals) is necessarily ALWAYS incomplete, biased and erroneous to unknown extents.

What must be clarified to change the R&D paradigm

- In life sciences, with less than 10% success rate, a dominant recurrent thinking that fails may be “false”!, even if supported by Key opinion leaders.
- The Academic World is not “the only” source of innovations.
- “Discovery” means finding “unknown” facts.
- Simulating a system supposes to have understood and described it before beginning with.
- In life sciences, Big Data may lead to Big Garbage if the data produced are not correctly contextualized.
- “New therapies” do not necessarily mean new drugs.
- Combinations of existing drugs are patentable!
- The cost of drug development is not 1 billion € per drug for a SME. It is around 250 M €, but in case of failure the SME is “dead”.
- Scientific Proof of concept on humans does not mean clinical trials.
- Nevertheless, it MUST be remembered that Models are Aids to thought, NOT a replacement for it!!

Proposals to develop Integrative Biology teams

- Develop new training programs for the future integrators through smart selection processes and open minded educational organizations.
- Develop multidisciplinary training programs for both IT integrators and biology Integrators to build complete Integrative biology teams.
- Create for these “generalists” “successful” job evolutions adapted to their specificities and profiles.
- Introduce “general semantic” and other “soft” knowledge in life sciences and technologies educational programs to train people think “out of the box”.
- Re-introduce physiology in the educational cursus.
- Support and protect people who think different.
- Systems biology must be considered as a biology driver research process supported by IT tools to help them work.
- We could say, being a little provocative, that we need more “Dr. House” type MDs and biologists in our medical research teams !

Key learnings and proposals for innovation

- The experts' consensus evaluation process, well adapted for incremental innovation evaluation, is clearly the number one serial killer of disruptive innovation.
- Disagreement amongst experts should be considered a necessary, but not sufficient, condition to detect disruptive innovations.
- The great disruptive discoveries come from challengers such as Pasteur who discovered that most infectious diseases were caused by germs against the medical establishment since Felix Pouchet in 1859 had published a prevailing work in favor of spontaneous generation theory.
- Similarly the Australian scientists Barry Marshall and Robin Warren were obliged in 1984 to infect themselves with Helicobacter pylori to prove that it was the gastric ulcers cause.
- Three types of Innovations are complementary: technology, organizational and usage innovations must be equally supported and evaluated.
- A specific evaluation track could be defined : evaluation of the innovation by experts of the domains where the technology comes from, and by open minded potential users of the innovation applications.
- 25% of institutions/companies R&D budgets should be dedicated to this specific track.
- Research "supposed of no interest" for industry or VCs should be supported and funded to prepare the future and regenerate diversity of concepts and ideas.
- Develop multidisciplinary team spirit and training built on already existing prototypes that can gain support (example: Alliance of Essec Santé, Centrale-Santé and FSM).

More information and downloads

- Our publications and our contribution to reference books
- Our Press-releases
- BMSystems Scientific Presentation (IDDST conference China 2012)
- What are the differences & synergies between Heuristic and Mathematical approaches? (EPA conference Europe 2011)
- Case study: Mechanisms-Based Medicine applied to Psychiatric disorders
- BMSystems selected in the Europe-wide inventory of industry involved in Systems Medicine by the EC Directorate of Research network “Coordinating Action Systems Medicine” (CASyM) (see page 31-32)
- Persistent Systems Corporate website
- Persistent Systems SAS France
- Foundation FondaMental
- Aepodia

Do not hesitate to contact us: Manuel Gea: manuel.gea@bmsystems.net

www.bmsystems.net

Key learnings for disruptive innovation support

Nevertheless, it MUST be remembered that Models are Aids to thought, NOT a replacement for it!!

Questions

Contact: www.bmsystems.net
Email: manuel.gea@bmsystems.net

Our strategic IT Partner at a glance

PERSISTENT

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

Bio-Modeling Systems SAS
Dr. François Iris (PhD), Chairman & CSO
Manuel Gea, Chief Executive Officer
Paul-Henri Lampe CIO Integration Systems Director
Dr. Gérard Dine (MD, PhD), Chief Medical Officer

To contact us
Bio-Modeling Systems SAS
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manuel.gea@bmsystems.net
www.bmsystems.net

Persistent at a Glance

Experience

- 350 Customers
- 3000+ Product releases in last 5 years
- 14 of Top 20 technology companies in the world are our customers
- 24 Years in business

Growth

- Publically listed (BSE, NSE)
- $237.8M FY13 revenue
- Rs 1,294.51 crore FY13 revenue
- 23% CAGR

The Practice

- U.S., APAC and EMEA regions
- 7000+ Employees
- ISO 9001:2008
- ISO 27001:2005
- ISO 14001:2004
- OSHAS 18001:2007
- ISO 13485:2003

Named a "Leader" in the IAOP 2013 Global Outsourcing 100 service providers list

– *IAOP*

"2013 Computerworld Honors Laureate"

– *ComputerWorld*

Leading vendor in Global OPD & Specialty Application Development & Management (ADM)

– *Global Services Media*

Top 3 player in Smartphone Application Development

– *Forrester Research, 2011*

Leading Player in Software/ ISV R&D & Consumer Software Segments. Ranked Highly in Cloud & Enterprise Mobility Segments

– *Zinnov Management Consulting*

…With a Global Footprint

PERSISTENT

…and more than 7000 employees.

Our Business Strategy

We work in a

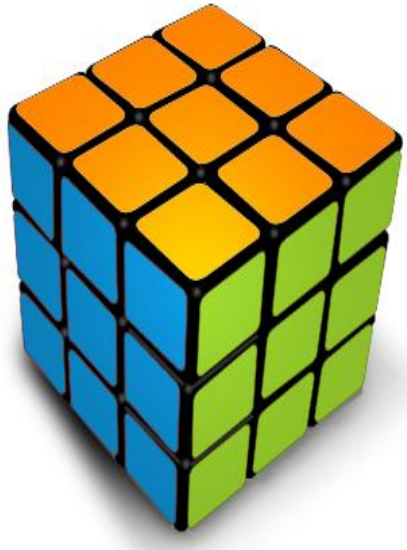
4 x 4 x 4

matrix

giving us a comprehensive outlook

- IP-led Business
- Technology Consulting
- Strategic Alliances
- Product Engineering (OPD)

- Technology
- Telecom
- Life Sciences & Healthcare
- Banking & Financial Services



- Cloud
- Mobility
- Analytics
- Collaboration

Life Sciences expertise




Research

- Biomarker Research, Marker mining
- Pharmacogenomics
- Algorithms for microarray, proteomics, sequencing, spectroscopic data
- Componentizing the life sciences analysis apps

Preclinical & Translational

- Sanger and Next Generation Sequencing, Genotyping, Mutation Profiling
- Gene Expression Analysis
- Analytics & Decision

Clinical Trials

- Clinical Trial Management System (CTMS)
- Clinical Data Management System (CDMS)
- Regulatory Submissions

Manufacturing

- Custom solution for tracking of samples, reagents, chips, gels and lab animals
- Reusable components for quick solution implementation on top of the LIMS framework
- Integration modules
- Transportation Management

Packaging & Distribution

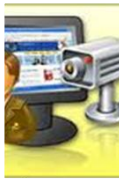
- Packaging workflows
- Business Process Management
- Mobile enablement
- Analytics

Connected Healthcare

- Portal Development, Healthcare Cloud, AppStore
- Medical devices & Diagnostic imaging
- EMR, Hospital & Pharmacy Management
- Accountable care
- Payer & Cycle revenue Management
- m-Health & Gamification
- Healthcare Interoperability & Integration

Mobile Healthcare services

Mobilizing workflow for healthcare application services to any mobile device.



Remote Patient Monitoring:

Capture patient data and share it with care team via monitoring devices

Patient Mobile Services:

Consultation, Diagnosis, Prescription, Medication, First aid, Emergency Services, Medication alarm & monitoring, Telemedicine, Order Entry, Alerts

Clinician Mobile Solutions:

Patient/ Practitioner Search, Dictation, Imaging, Results Reporting, Change Capture, Task List, Initiate/ track referrals, Patient registration, Appointments management, Reports & Lab results display etc.

Health & Wellness:

Capture and transmit general well being information for the purpose of wellness and fitness, Personal health tracking/ coaching

Homecare:

Mobilizing home healthcare applications provides real-time communication with care team to ensure proper treatment

Collaboration:

Mobile-supported co-operation between all sections and professions in a general and comprehensive health care process

Reduction of documentation:

Reducing and digitization of documentation for invoicing, insurance, gathering of medical and nursing-relevant data

In-Clinic Solutions:

Asset Management, Sales support-intranet extension, Hospital bed management, Communication and Training for Healthcare Workers

Supply Chain Management:

Drug quality authentication, inventory management,

HealthCare Connected Platform

Mobile and Monitoring Devices generating Data







Health Telemetry Data

Connect APIs

Web Portal

Services


Monitor


Connect

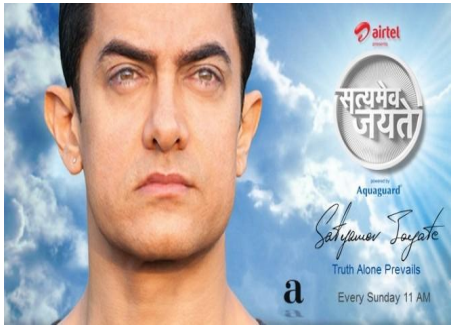

Plan


Healthcare Providers and Payor

Patients

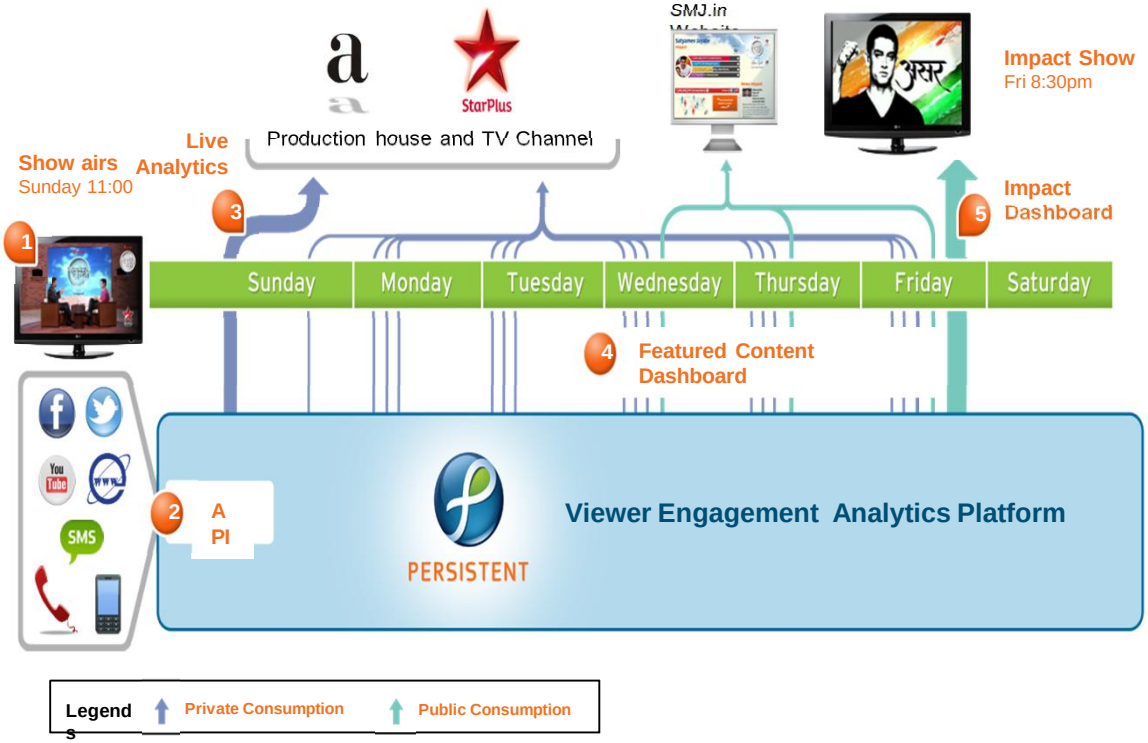
Pharma

Big Data POC: About Satyamev Jayate–TV Show–14 weeks



Bring a positive change to every individual watching the show

Stimulate a public debate on sensitive issues which are usually brushed under the rug



2,25 Billion Impressions

14 Million Responses

1 Billion Respondents

3 different formats

15 Languages

9 Data Channels

165 Countries

5435 Cities

Understand the pulse of the viewers
Gauge the appreciation for the show
Spread the message
Harness the truth from the viewer response data
Understand the comments about sponsors