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## The world's first Mechanisms-Based Medicine company

### MANAGEMENT SUMMARY

*(Download* the short corporate presentation for details and links to websites)

#### *Overview:*

*"Correct understanding of life mechanisms makes novel integrated diagnostics, therapies & preventive solutions discovery smarter, faster & cheaper for healthcare, diagnostics, health technologies, nutrition, and cosmetics!"*

*Bio-Modeling Systems is the world's first Mechanisms-Based medicine company that changed the discovery paradigm to create novel medical meanings from unreliable heterogeneous sources of data to generate validated & directly exploitable first in class heuristic non-mathematical mechanistic CADI™ Discovery models.*

Created in 2004, profitable since 2006, thanks to our recurrent clients, we confirmed with our partners CADI™ Discovery capability to generate outstanding value through:

- *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*, and
- 14 successes independently validated by our clients/partners of which: *a world's first in neurodegenerative diseases, 1 therapeutic spin-off, 1 exclusive out-license, 4 issued patents, 10 publications* (for all details, visit [BMSystems website](#)).

With CADI™ Discovery, BMSystems *possesses a truly unique competitive advantage*: the ability to address and exploit the two major issues in life sciences

1. the *enormous complexity of life's mechanisms*, and
2. the *significant and growing unreliability* of scientific and clinical publications.

Through its dual contractual & collaborative business model, BMSystems:

1. *proposes robust R&D and Business decision-making support*, and
2. *discovers cost-effective, lower risk, patentable novel integrated solutions*, for medicine, health technologies, nutrition and cosmetics.

You have a question; we may have the ability to generate the answer through one of our 6 BMSystems' solutions to critical & high impact issues.

- *GO-NO GO decision before product acquisition or for portfolio risk analysis.*
- *GO-NO GO decision before next development phase.*
- *R&D program Rescue for a program facing critical issues during its lifetime.*
- *External R&D "B plan" program when the "A plan" cannot be rescued.*
- *Exploratory Discovery program to discover novel causal mechanisms concepts.*
- *Novel Hypotheses for therapeutic and/or diagnostic solutions discovery.*

## 1-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.*
- *14 successes independently validated by our clients/partners of which: a world's first in neurodegenerative diseases, 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.*

## 2-Our 14 successes to date independently validated by our clients/partners

1. Mechanisms of pathogenesis & clinical progression of Creutzfeldt-Jakob Disease;
2. Mechanisms of anti-connexin agents for modulating the therapeutic effect of psychotropic and neurodegenerative drugs;
3. Cellular & metabolic mechanisms associated with chronic anxiety;
4. Novel antiglycemic mechanism;
5. Anti-metastatic mechanisms of the RGD15 peptide;
6. Mechanisms of Ras-mediated breast cancer oncogenesis;
7. Mechanisms of breast cancer resistance to tamoxifen;
8. Regression mechanisms of the Müllerian duct;
9. Mechanisms of differential melanosome degradation;
10. Context-dependent functions of OA1 protein;
11. Context-dependent functions OCA2 protein;
12. Context-dependent functions SLC45A2 (MATP) protein;
13. Engineered bacteriophage banks and the control of multi-resistant pathogens;
14. Bioproduction and hemisynthesis of 18-methyl eicosanoic acid;

### 3-BMSystems' first outstanding POCs completed and 2 first external outputs



BMSystems/CEA collaborative research in neurodegenerative diseases. World's first in vivo validation of the mechanisms of Creutzfeldt-Jakob disease pathogenesis & progression. Two Awards (Bio IT World Best Practice Award 2009 and European Commission 2010).



Pherecydes-Pharma (2006): BMSystems' spin-off, (novel M.R. anti-bacterial nano-agents biotherapies), two indications: Multi-resistant Skin infections in Phase I/II. & osteo-articular infection compassionate use success.



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

### 4-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<sup>TM</sup> 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 develop. 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 bioMedicine 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)

## 5-Collaborative and Academic R&D programs



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 in Phase I/II in 2015 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. Ongoing, 1 publication pending*



Centre of excellence in Epigenetics IISER Pune India: Project "Etiology & Epigenetic for metabolic disorders" *Etiology & Epigenetic for metabolic disorders, 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)

## 6-BMSystems' internal and collaborative R&D programs

Not domain dependent, we already conducted R&D programs in the fields of neurology, inflammation, metabolism, immunology, addressing neurodegenerative diseases (Creutzfeldt-Jakob's, Parkinson's & Alzheimer's diseases), psychiatry, autism, cancer, diabetes, longevity/aging, infections, dermatology, skincare and cosmetics

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 predinic. P.O.C.
Nano-Bioagents	Pherecydes						Validated
TAPE (protein improvement)	Open						Validated
Chronic Fatigue Syndrome	Open		high Interest				
Ebola virus ecology	Open						
Hepatitis C	Open						
Auto-immune global concept	Open	high Interest					
Microbiotas ecology, physiology & metabolic mechanisms	Open	high Interest					
Creutzfeldt-Jakob disease's mechanisms	CEA Life Sciences						Validated
Cellular & metabolic mechanisms associated with chronic anxiety	Max Planck Munich					Validated	
Psychiatric Disorders therapeutic strategy	Confidential		high Interest				
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		high Interest				
Migraine Mechanisms	Open	high Interest					
Multiple Sclerosis Mechanisms	Open	high Interest					
Metabolic Disorders Therapy	Open		high Interest				
Etiology & Epigenetic in diabetes type 2	IISER Pune		high Interest				
Hypercholestermia Mechanisms	Open						
New global concept for Diabetes type 1	Open						
Metabolic Syndrome	Open						
Breast cancer-Hras	INSERM						Validated
Tamoxifen resistance	INSERM				Validated		
Specific Metastasis control	INSERM			Validated			
Encysting Tumour Therapy	Open	high Interest					
Müllerian regression Mechanisms	CNRS				Validated		
Adipocytes growth control	Open						
Skin pigmentation Mechanisms	Open			Validated			
Skin pigmentation Modulation	Open			Validated			
Skin Contact Allergy Mechanisms	Open		high Interest				
Skin aging Mechanisms	Open	high Interest					
Modulation of skin hydration	Open	high Interest					
Modulation of the lipid constituents of the skin barrier	Open	high Interest					
Novel Hair Loss Mechanisms	Open	high Interest					
Program Synthons	ARD-IBT-L'Oréal						Validated
Program Synthons	ARD-IBT-Rhodia			Completed			
Program Synthons	ARD-IBT-Arkema			Completed			
Human Glycosylation with Yeast	Open		high Interest				

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

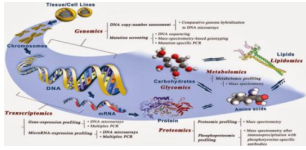
Of which 4 strategic programs of high interest open for partners or clients.

- *Parkinson's disease*: Novel combinatorial therapeutic approach utilizing two molecules that had long been on the market, neither of which has any known toxicity or undesirable effects.
- *Alzheimer's disease*: Alternative concept (3 novel mechanisms) to the dominant "Aβeta & Tau" hypothesis as causes to the disease (Aβeta & Tau should be unspecific consequences).
- *Cancer*: Complementary therapy: Peri-tumoral tissue could be induced to "encyst" the tumor, preventing metastases while starving the cancer cells.
- *Bio-Pharma production*: Yeast-Based Full Human-Glycoylation CADI program that describes the means whereby "human-type, glycosylation pattern-specific tool-boxes" can be constructed and stably harnessed in yeast cells.
- *Skin contact allergy (reduction of animal testing) and skin pigmentation mechanisms*.

## 7-Why did we need to change the discovery paradigm?



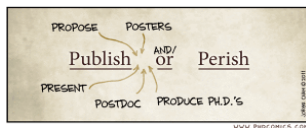
1-The industry is under high pressure by too high failure rates and payers no more willing to pay premium therapies with very limited patient benefit.



2-The limits of the big Pharma model. Decades of investments in Omics technologies and Systems Biology programs produced few relevant results due to 3 "side effects" and a conceptual mistake: Life mechanisms are complex not complicated!



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



4-The unreliability of scientific and clinical publications is increasing. "Many published research findings are false or exaggerated; an estimated 85% of research resources are wasted." (Stanford University), and the valuable negative results are not published.

## 8-The Mechanisms-Based Medicine Concept:

*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.*

1. **DISEASE/DISORDER:** Describe the physiopathology of the disease/disorder with clinicians and patients feedback.
2. **MECHANISMS:** Discover the causal versus symptomatic mechanisms of the disease/disorder.
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/disorder
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. **FEEDBACK LOOP:** Integrate the results from e-R&D or e-Health experimentations into the validation process to improve global patient and disease/disorder follow-up.

## 9-The 5 CADI™ Discovery Principles (see *full* presentation for details)

*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.*

1. Mechanisms-Based Medicine
2. Architectural Principle
3. Negative Selection Principle
4. 4 Steps Validation Principle
5. Integrated Solutions Principle

## 10-CADI™ Proprietary Technologies and Know-how:

*Industrial secrets to protect the CADI™ platform:*

- CADI™ Search (data acquisition & mining),
- CADI™ Framework (data organization & structuring),
- CADI™ Fiber-N (integrative engine),
- CADI™ View (model representation & visualization),
- CADI™ knowledge Database.

*Patents produced during the collaborative research programs for spin-offs or out-licensing:*

- TAPE Patent: WO/2008/093010- December 2006,
- AB-ACCUS patent: WO/2008/093009 - December 2006,
- RPh patent: PCT/FR2010/050796 – May 2009,
- CNS patent: WO/2010/029131 - September, 2008

## 11-The 6 BMSystems' solutions to critical & high impact issues.

- GO-NO GO decision before product acquisition or for portfolio risk analysis.
- GO-NO GO decision before next development phase.
- R&D program Rescue for a program facing critical issues during its lifetime.
- External R&D "B plan" program when the "A plan" cannot be rescued.
- Exploratory Discovery program to discover novel causal mechanism concepts
- Novel Hypotheses: therapeutic and/or diagnostic solutions discovery.

## 12-CADI™ Models published in prestigious peer-reviewed journals:

- 2014: CNS Psychiatry publication: American Journal of Psychiatry and Neuroscience. Second publications with the Max Planck Institute of Psychiatry in Munich: Differential proteomics analyses reveal anxiety-associated molecular and cellular mechanisms in cingulate cortex synapses. The first output of the DECIUS CNS research program.
- 2012. CNS NEURODEGENERATIVE & PSYCHIATRY: PharmacoPsychiatry publishes the first review describing a productive vision of Systems Medicine that will change R&D organization and interactions between clinicians & researchers & reveals how the world's first explanation of the mechanisms of the Creutzfeldt-Jakob disease led to the discovery of a truly innovative psychiatric treatment.
- 2011. CNS PSYCHIATRY: Pharmaco Psychiatry publication: Proteome-Based Pathway Modelling of Psychiatric Disorders. Publication with The max Planck Institute of Psychiatry in Munich

- 2010, INFECTIOUS DISEASES: Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science : Genetically Engineered Virulent Phage Banks in the Detection and Control of Emergent Pathogenic Bacteria. Publication with Pherecydes-Pharma.
- 2009, TISSUE DIFFERENTIATION: Médecine & Sciences: Müllerian duct regression explanation. Integrative systems biology & experimental Biology. Publication with CNRS experimental data.
- 2005, CANCER: Journal of molecular Endocrinology: Integrative analysis of gene expression patterns predicts specific modulations of defined cell functions by estrogen and Tamoxifen in MCF7 breast cancer cells. Publication in collaboration with INSERM unit 553.
- 2003, CANCER: Nucleic Acids Research: Integrated transcriptome analysis of the cellular mechanisms associated with 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.

### 13-Collaboration to scientific reference books:

- 2014, Dermatology Cosmetics. The first reference book on “Computational Biophysics of the Skin” edited by Prof. Bernard Querleux , scientific chairperson of the International Society for Biophysics and Imaging of the Skin
- 2011: Phage Nano Technology book published by Valery Petrenko. Chapter 8: Genetically Engineered Virulent Phage Banks for the Detection and Control of Bacterial Biosecurity Threats.
- 2008, CNS: Biomarkers for Psychiatric Disorders. (Ref. ISBN: 978-0-387-79250-7, November 2008). Dr. François Iris, is the author of the Integrative Biology chapter of the book. The editor, Prof. Christoph W. Turck, is head of the Proteomics and Biomarkers branch at the Max Planck Institute for Psychiatry

### 14-Useful links:

- BMSystems' Management Summary
- BMSystems' short presentation
- BMSystems' CADI™ Discovery presentation *with the 10 POCs and the publications.*
- BMSystems' scientific presentation
- Why we need to change the R&D paradigm
- Author's LinkedIn Posts

### 15-Contacts

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