

Bio-Modeling Systems

The Mechanisms-Based Cosmetics Company



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

R&D conference Cosmetic 306

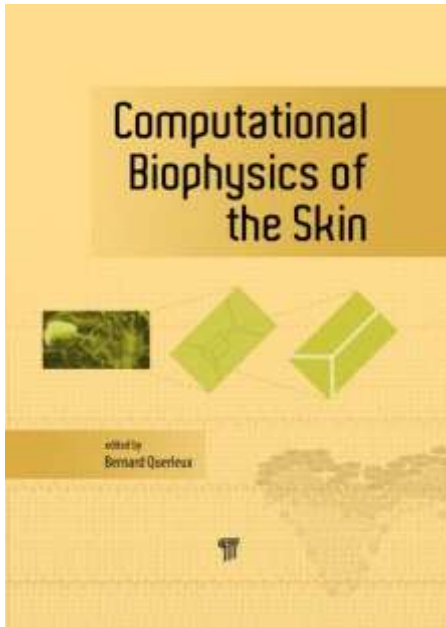
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“Mechanisms-Based Cosmetic”: CADI™ applied to cosmetics

1. Skincare: Strong integrated understanding of the global systems:

1. *The mechanisms associated with constitutive and facultative epidermal pigmentation*
2. *The mechanisms associated with senile/solar lentigines (aging issues)*
3. *Components specific to pigmentation from production to destruction*
4. *Microbiota & Skin Mechanisms*

Contributor to 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. R&I L’Oréal.



Program Name	Validation / Business Partner(s)	CADI™ compliance	CADI™ vers. 0
Skin Contact Allergy Mechanisms	Open		high Interest
Skin pigmentation Mechanisms	Open		high Interest
Skin pigmentation Modulation	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	

Mechanisms-Based Cosmetic : CADI Discovery applied to cosmetics
 A new paradigm qualified for novel solutions in premium personalized marketing strategies

BMSystems Group description

- *Independent Private Company incorporated in 2004. 100% owned by its founders.*
- *Profitable since 2006*, thanks to our recurrent clients.
- We only sell the results of the R&D programs, not our proprietary technologies.
- *100% biology driven company* focused on discovery, and critical high impact decisions making
- *A unique proprietary CADI™ Knowledge Database of mechanisms & interactions.*
- Not domain-dependent, but information-dependent.
- Markets: Pharma, Cosmetics, Nutrition, Health Technologies, Connected health,
- Highly productive 24 vFTE* of which 9 vFTE on CADI™ Discovery programs only.
- *Strong & long term strategic R&D collaborations* (>100 people collaborating).
- Dual business model : Contractual or Collaborative R&D programs.
- *BMSystems values its therapeutics programs through out-licensing or spin-off.*
- Outstanding internal pipeline of programs ready for collaborations.
- *Our Potential competitors: Key Opinion Leaders, dominant thinking companies or pharma Systems Biology or bioinformatics teams argue they can do the same. We are always open for discussions & comparisons on success rates and outputs for patients.*

The World's first Mechanisms-Based Discovery Company
You have a R&D issue or a decision to make, we may have a solution for you.

BMSystems Group at a glance

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

- BMSystems Group addresses two complementary targets in Pharma, Biotech, Cosmetics, Nutrition, Bio-Production and Digital-Health businesses:
 1. **For R&D, Translational Medicine, & Digital Health Executives**, we offer robust alternative **decision-making to de-risk, save time and costs** of R&D and Digital Health programs,
 2. **For Business Developers, Patients Groups & Investors**:, we discover **novel low-risk, highly effective and cost-effective** diagnostic, therapy, nutrition, cosmetic, bioprocess solutions for spin-offs or out-licensing.
- Created in 2004, profitable since 2006, thanks to our recurrent clients, CADI™ Discovery already delivered numerous operational outputs and novel businesses. (See details in next slides).

BMSystems' R&D Partners* at a glance



*Non confidential list of current and past partners of which H2020 GEMMA partners

BMSystems' outstanding POCs and our 2 first external outputs



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



Pherecydes-Pharma (2006): First BMSystems' therapeutic spin-off, (novel M.R. anti-bacterial nano-agents biotherapies with phages), indications: Multi-resistant infections compassionate use success.



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

5 ongoing BMSystems' outstanding R&D programs



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

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

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

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

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



BMSystems' CADI BioProduction programs



Synthons Program: Feasibility study Industrial biotech program for 16 chemical molecules:

Synthons major collaborative industrial biotech research platform funded by the ministry of Industry in the IAR world-class cluster in France. Search for innovative processes non existing patent-dependent

OUTPUTS: A unique significant bacteria metabolic pathways database of strong interest.

- 16 CADI BioProduction models produced
- 2 engineered bacterial strains generated are under evaluation and
- a finalized process under mid-scale validation (patent pending).

The program was funded by the ministry of Industry and supported by IAR world-class cluster

Full Human Glycosylation with Yeast. The challenge: How to found a way to efficiently overcome the major limitations to the large-scale production of humanized glycoproteins in yeast cells?

We develop a CADI Glyco Model that describes the means whereby "human-type, glycosylation pattern-specific tool-boxes" can be constructed and stably harnessed in yeast cells.

1. the control mechanisms which allow *at will* mutual induction / repression of the yeast cells endogenous glycosylation machinery and engineered "human-type, glycosylation pattern-specific tool-box",
2. the means whereby the two systems (yeast cells endogenous glycosylation machinery and engineered "human-type, glycosylation pattern-specific tool-box") can be made to co-exist without interfering upon each other and without jeopardizing yeast cell viability,
3. the complete sets of genes that would allow to specify any given pattern of human-type O-linked or N-linked glycosylation.

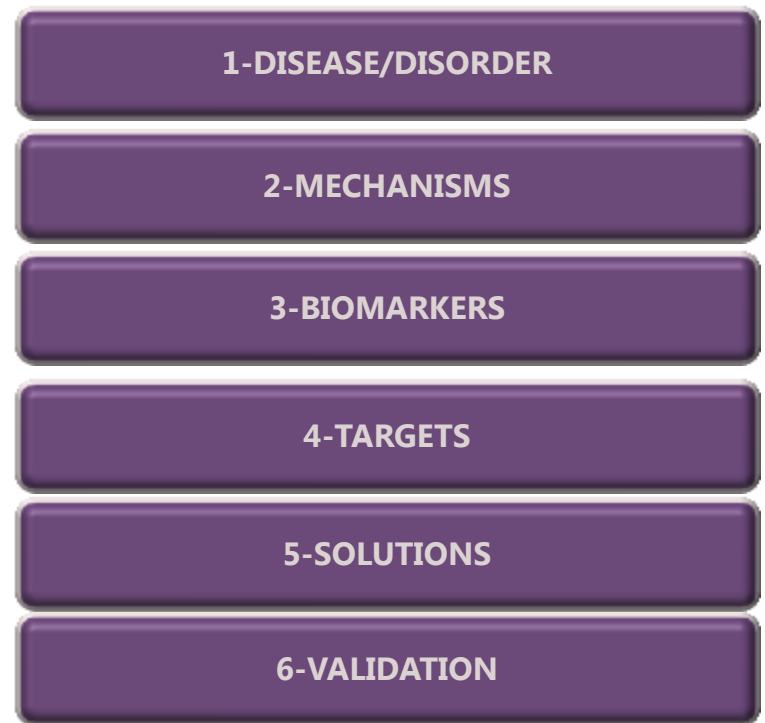
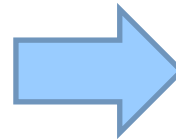
Open for partners: To succeed validation phase, this program needs the synergic collaboration between a correct understanding of the complex yeast's and human's glycosylation mechanisms and the yeast genetic engineering and production processes expertise



To succeed BioProduction programs need collaboration between a correct understanding of the complex mechanisms of strains and a State of the Art engineering, evaluation, and production processes expertise.

The Research & Development Answer

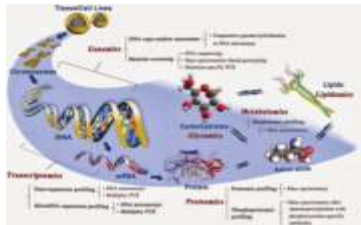
From: Evidence-Based Medicine To: Mechanisms-Based Medicine



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 R&D and the reality of Data Answers

The "Cartesian" answers limits



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

CADI Discovery Principles

1-Mechanisms-Based Medicine

2-Architectural Principle

3-Negative Selection Principle

4-4 Steps Validation Principle

5-Integrated Solutions Principle

6-The bridge R&D & Real life data

The objective is to address the complexity of life sciences mechanisms and the digital « garbage in garbage out » reality through CADI™ Discovery

BMSystems' R&D programs pipeline

External valorization of our collaborative R&D programs through out-licensing or spin-off

Program Domains	Partners	CAD™ compliance	CAD™ vers. 0	Ind. Valid.	Secret or Patent or Co-Patent/Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.
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Infection-Immunology

Microbiotas (skin, lung, gut, etc)

Neurology/Psychiatry (CNS-PNS)

Metabolism

Cardiovascular Diseases

Oncology

Dermatology/Cosmetics

BioProcesses

Infection-Immunology	Oncology/Inflammation	Dermatology/Cosmetics
CNS-PNS/Inflammation	Tissue Differentiation	Cardiovascular Diseases
Industrial biotech/ bioprocesses	Metabolism/Inflammation	Microbiotas

BMSystems' R&D programs pipeline

External valorization of our collaborative R&D programs through out-licensing or spin-off

Program Name	PROG CADI™ CODE	Validation / Business Partner(s)	CADI™ compliance	CADI™ vers. 0	Ind. Valid.	Secret or Patent or Co-Patent/Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.
Nano-Bioagents-Bacteriophages	CADI-R101	Pherecydes						Validated
TAPE (protein improvement)	CADI-R102	Open						Validated
Chronic Fatigue Syndrome / Gulf War Syndrome	CADI-R103	CFS Asso / Open			Started			
Ebola virus ecology	CADI-R104	Open						
Hepatitis C	CADI-R105	Open						
Autoimmunity : Global concept	CADI-R106	Open	high Interest					
Core symptoms of Autism mechanisms	CADI-R201	Confidential			Produced			
Microbiota & Autism H2020 program 14 M€ funded	CADI-R201	H2020			Started			
Microbiota ecology, physiology & metabolic mechanisms	CADI-R202	Open	high Interest					
Microbiota & inflammation	CADI-R203	Open	high Interest					
Creutzfeldt-Jakob disease's mechanisms	CADI-R301	CEA Life Sciences						Validated
Cellular & metabolic mechanisms associated with chronic anxiety	CADI-R302	Max Planck Munich					Validated	
Psychiatric Disorders therapeutic strategy	CADI-R303	Confidential					Ready	
Alzheimer's Disease Causal Mechanisms	CADI-R304	Open			Produced			
Parkinson's Disease Therapy	CADI-R305	Confidential			Produced			
Psychiatric inflammatory mechanisms	CADI-R306	FondaMental Foundation			Produced			
Fibromyalgia, facial pain	CADI-R307	Open			Produced			
Pain (Central/Peripheral)	CADI-R308	Open			Produced			
Migraine Mechanisms	CADI-R310	Open	high Interest					
Multiple Sclerosis Mechanisms	CADI-R311	Open	high Interest					
Etiology & Epigenetics in Diabetes type 2	CADI-R402	IISER Pune			Produced			
Metabolic Syndrome	CADI-R403	Confidential			Produced			
Hypercholesteremia Mechanisms	CADI-R404	Open						
New global concept for Diabetes type 1	CADI-R405	Open						
Metabolic Disorders	CADI-R406	Open	high Interest					
Atherosclerosis mechanisms	CADI-R901	Open			Produced			
Breast cancer-Hras	CADI-R601	INSERM					Validated	Validated
Tamoxifen resistance	CADI-R502	INSERM				Validated		
Specific Metastasis control	CADI-R503	INSERM			Validated			
Tumor Encysting Therapy	CADI-R504	Open	high Interest					
Müllerian regression Mechanisms	CADI-R601	CNRS					Validated	
Adipocytes growth control	CADI-R602	Open						
Skin pigmentation Mechanisms	CADI-R701	Open				Validated		
Skin pigmentation Modulation	CADI-R702	Open				Validated		
Skin Contact Allergy Mechanisms	CADI-R703	Open			Produced			
Skin aging Mechanisms	CADI-R704	Open	high Interest					
Modulation of skin hydratation	CADI-R705	Open	high Interest					
Modulation of the lipid constituents of the skin barrier	CADI-R706	Open	high Interest					
Novel Hair Loss Mechanisms	CADI-R707	Open	high Interest					
Program Synthons	CADI-R801	ARD-IBT-L'Oréal						Validated
Full Human Protein Glycosylation in yeast	CADI-R802	Open			high Interest			

BMSystems' Therapeutics-Diagnostics-BioProduction CADI™ pipeline*

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

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

Internal Program Name	Indication	Pre-clinic	Clinic
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COMBO-DIAGNOSTICS

CADI-D3041	Alzheimer's Disease Early Diagnostics		Ready
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Internal Program Name	Program Domains	Partners	CADI™ vers. 0	Ind. Valid.	Secret or Patent or Co-Patent/Publi.	First Proof of Concept (POC)
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CADI™-BIOPRODUCTION

CADI-B8011	Program Synthons (16 molecules study)		ARD-IBT-L'Oréal-Arkema-Solvay			Completed
CADI-B8021	Full Human Protein Glycosylation in yeast	Open		Ready		

* New internal classification

CADI™ Discovery process phases



Phase Objective	CADI™ Feasibility	CADI™ Construction	CADI™ Validation	CADI™ Exploitation
	<ul style="list-style-type: none"> • 3-5 weeks • Identify and define what is feasible among the projects submitted. • Define best CADI™ modeling strategy 	<ul style="list-style-type: none"> • Step I : 1-4 months • Preliminary/controls: Simulation of the whole process on a data subset before launching Step II • Step II: 4-10 months • Construction of the CADI™ models version "0" for the complete program. • Novel hypotheses generation 	<ul style="list-style-type: none"> • Timing to be defined • Validation of the CADI™ model using the 4 steps validation process • Model improvement. • Robust hypotheses and mechanisms proposal. 	<ul style="list-style-type: none"> • Timing to be defined • Proposition of robust solutions to solve client's issues. • Answers to the 5 client's R&D and business issues. • Client's team exploits the Model.

Programs costs drivers

1. The company offers "one shot", "first refusal" or "post program exclusivity" deals.
2. In every case, the company offers exclusivity during the execution of the program.
3. The standard deal cost structure can be a combination of access fees, fees and success fees.
4. Domain of analysis, scope of the issues, complexity of the CADI™ model.
5. Availability and ease of access to relevant data.
6. Percentage of CADI™ knowledge database usage. In case of use of existing proprietary CADI™ programs, An additional access fees and success fees are required to compensate previous BMSystems' investments and lower risk for the clients.
7. Reactivity, readiness & willingness of the client/partner's team to contribute.

BMSystems' CADI™ publications to date

CADI™ Models published in prestigious peer-reviewed journals: (click on the grey links to get the pdf)

- [2018: Current Opinion in Pharmacology](#): How scientific literature analysis yields innovative therapeutic hypothesis through integrative iterations. CADI Discovery addresses the complexity of life sciences mechanisms and the digital « garbage in garbage out » reality
- [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 H-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
- [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