Bio-Modeling Systems

CADI™ Heuristic Modeling for Complete & Efficient Human Protein Glycosylation in Yeast

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BMSystems' group at a glance

Dual Business Propositions

BMSystems addresses two complementary Businesses in Pharma, Biotech, Cosmetics, Nutrition, Bio-Processes and Digital-Health businesses:

For R&D, Translational Medicine & Digital Health Executives, we offer **robust alternative decision-making** to de-risk, save time and costs.

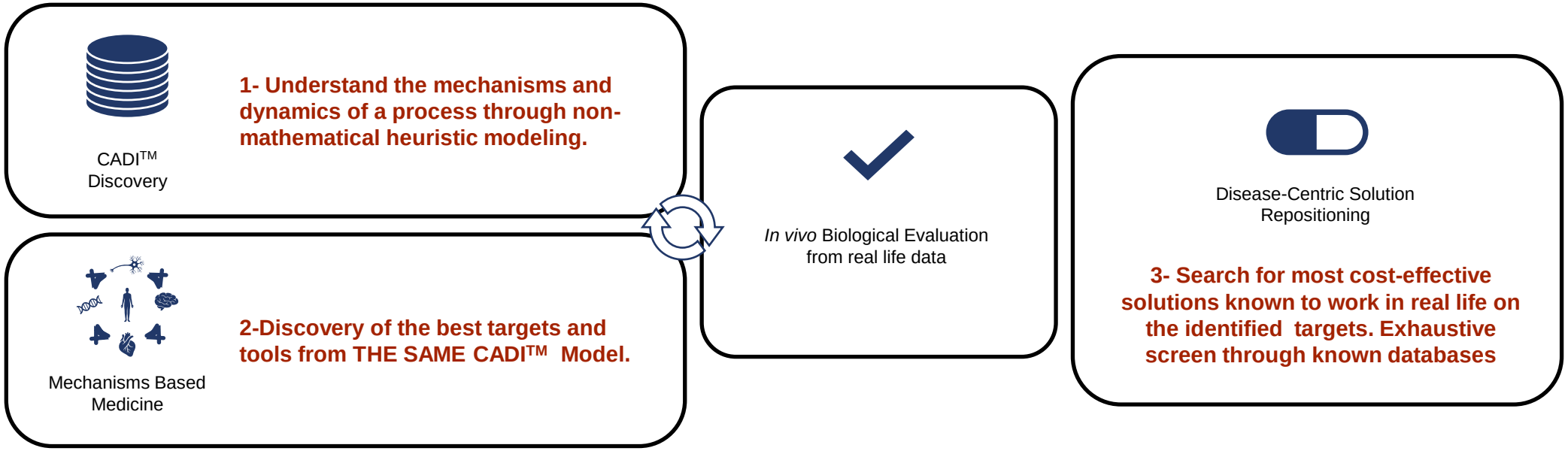
"In other words, we kill hypotheses and programs one phase ahead".

For Business Developers, Patients Groups & Investors, we discover **novel low-risk, highly effective and profitable solutions** in diagnostic, therapeutics, nutrition, cosmetics & bioprocessing for spin-offs or out-licensing.

"In other words, we are a highly productive out-licensing and spin-off factory"

CADI™ Discovery: modeling the processes dynamics and its mechanisms

CADI™ Discovery : domain-independent, readily applicable in biology, medicine, cosmetics, etc.



CADI™ (Computer Assisted Deductive Integration) is the first and only to date operational Augmented Intelligence platform that combines the best of Human and Artificial Intelligences addressing the **complexity** of life sciences mechanisms and the digital "**garbage in garbage out**" reality

CADI™ Discovery: with a proven track record

From modeling to real-life solutions

PHERECYDES PHARMA

BMSystems' spin-off:
Novel M.R. anti-bacterial nano-agents biotherapies with phages.
Phase II, CU

Theranexus
Therapeutic Boosters

CEA's spin-off: CNS disorders, co-owned worldwide patent WO20102913
Listed & Phase II

Telesphore Pharma

Under creation: Low-grade inflammatory disease therapeutic & diagnostic solutions, including Long-Covid & ME-CFS

Bio IT World Best Practices AWARD Honorable Mention 2009

Our CADI™ discovery models were the laureates of two awards:
Bio IT World Best Practice Award 2009 &
European Commission 2010 as "State-of-the-Art Systems Biology applications in Medicine".

BMSystems' collaborative network

A selection of ongoing programs

Autism & Microbiota H2020 therapeutic program-14 M€ funding (2019). International consortium of scientists to study the role of the gut microbiome in the development of Autism Spectrum Disorders (ASD). We built the integrated CADI™ ASD pathology model

Etiology, epigenetics & therapeutic evaluation of metabolic disorders in India. UMANG program R&D Collaboration with the Center of Excellence in Epigenetics IISER Pune India, Arbuza Regenerate and the HCL foundation addressing a 150 million children life threat nutritional problem.

BMSystems' R&D programs pipeline

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

Program Name	CADI™ Code	Business Partners	CADI™ - v.0	Validation/ PoC	Patent/ Publication	Mid scale/ Preclinical PoC
Nano-Bioagents-Bacteriophages	CADI-R101	Pherecydes	Produced	Yes	Yes	Validated
TAPE (protein improvement)	CADI-R102	Open	Produced	Yes	Yes	Validated
Chronic Fatigue Syndrome/ ME/ Gulf War Syndrome	CADI-R103	Yes/ Open	Produced	Yes	Pending	Validated
Core symptoms of Autism mechanisms	CADI-R201	Confidential	Produced	Yes		Launched
Microbiota & Autism- GEMMA	CADI-R202	H2020	Ongoing			
Creutzfeldt-Jakob disease's mechanisms	CADI-R301	CEA	Produced	Yes	Publication	Validated
Chronic anxiety mechanisms	CADI-R302	Max Plank	Produced	Yes	Publication	
Psychiatric Disorders therapeutic strategy	CADI-R303	Confidential	Produced	Yes	Patent	Validated
Psychiatric inflammatory mechanisms	CADI-R304	Fond. Fnd	Produced			
Alzheimer's Disease Causal Mechanisms	CADI-R305	Open	Produced			
Parkinson's Disease Therapy	CADI-R306	Open	Produced			
Fibromyalgia	CADI-R307	Open	Produced			
Pain (Central/Peripheral)	CADI-R308	Open	Produced			
Malnutrition & Metabolic Disorders	CADI-R402	IISER Pune	Produced	Yes	Pending	
Hypercholestemia	CADI-R403	Open	Produced			
Metabolic Syndrome	CADI-R404	Open	Produced			

Therapeutic, Diagnostic, Bio-processes pipeline

BMSystems' CADI™ pipeline

Program Name	Indication	Pre-clinic	Phase I	Phase 2a	Phase 2b	Comp. Use
COMBO-THERAPIES						
CADI-T1011	Multi-resistance infectious diseases					Started
CADI-T1031	CFS/ME 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
COMBO-DIAGNOSTICS			
CADI-D3041	Alzheimer's Disease Early Diagnostics		Ready

Internal Program Name	Program Domains	Partners	CADI™ vers. 0	Ind. Valid.	Conf/Patent/ Pub.	First Proof of Concept (POC)
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		

BMSystems' CADI™ Bio-production programs

Cell factories for industrial bioproduction

Pherecydes-Pharma(2006): First BMSystems' therapeutic spin-off.
Novel M.R. anti-bacterial nano-agents biotherapies with phages. Compassionate use for multi-resistant infections

Synthons Program (2006): Industrial biotech program for the bioproduction of 16 chemical molecules:

OUTPUTS: Bacterial metabolic pathways database

- **16 CADI™ BioProduction models produced**
- **2 bacterial strains generated**
- **finalized bio-process**

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

Complete & Efficient Human Protein Glycosylation in Yeast.
CADI™ Glycosylation Model v0 describes the means whereby "human-type, glycosylation pattern-specific tool-boxes" can be constructed and stably harnessed in yeast cells.

The Challenge for a Complete & Efficient Human Glycosylation in Yeast

Why therapeutic proteins/ antibodies & peptides need to be properly and consistently glycosylated?

They exhibit higher:

- target specificities
- molecular stability
- pharmacological potencies
- protein-protein binding

With lower side effects

and dramatic half-life increases:

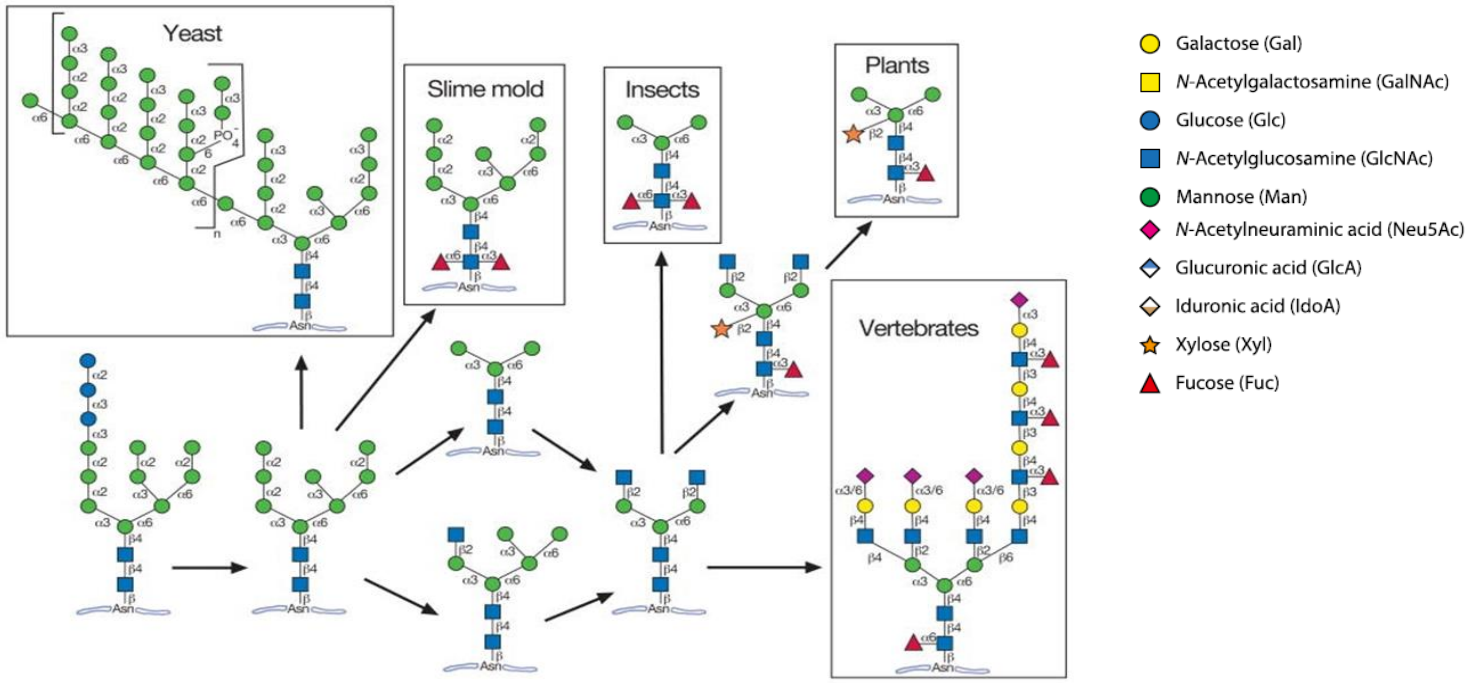
- natively glycosylated protein (sialic acid terminated glycans; t1/2: ~ 56 hrs) and
- partially glycosylated variant (galactose terminated glycans; t1/2: < 30 min)

Protein pharmaceuticals need to be properly glycosylated (human-type glycosylation patterns) to exhibit optimum therapeutic efficacy.

Why bacterial / yeast protein production systems fail

Yeasts lack the key components necessary for the production of human-type N-glycosylated patterns

- Most prokaryotic expression systems cannot carry out post-translational modifications.
- Eukaryotic expression hosts, have different glycosylation patterns.



- Different glycosylation patterns (i.e. high-mannose glycans) are often immunogenic
- Additional epitopes may induce allergies
- Only human cells produce sialyated glycoproteins containing N-acetylneuraminic acid

Why approaches addressing these drawbacks also fail

Little or no success over the years

- The engineering steps implemented to generate human-type glycans irreversibly **disrupt** the yeast's endogenous glycosylation system, thereby leading to rapid yeast cells dysfunction and growth arrest.
- As a result, while proper glycosylation patterns may be achieved on a target protein, the levels produced are very **low** and a significant proportion of the end product present **incomplete** glycosylation
- Over the past ten years, many academic and industrial laboratories have attempted to overcome these limitations in the production of glycoprotein products by yeast cells, but so far with little success in terms of large-scale production of therapeutic proteins requiring **complex** glycosylation patterns.
- To date, the most efficient means of production remain the milk of transgenic goats, the eggs of transgenic chickens and transgenic plants

The **challenge**: How to find a way to efficiently overcome the major limitations to the large-scale production of humanized glycoproteins in yeast cells?

CADI™ Solution for Complete & Efficient Human Glycosylation in Yeast

All genes, patterns and technology identified: ready for **POC** with a protein of interest

Glycosylation Toolbox Concept:

Human-type, glycosylation pattern-specific tool-boxes can be constructed and stably harnessed in yeast cells.

The proposed CADI™ technology includes:

1. the control mechanisms that allow ***at will*** the 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.

The system is able to produce **any given human-type glycosylation pattern** without being metabolically compromised by the yeasts housekeeping functions, hence ensuring **constancy of glycosylation patterns** and **proper protein folding**, while maintaining **high and sustainable production yields** and **end-product quality**.

Thank you for your attention

Open for Partners

To succeed the validation phase, the program needs the synergic collaboration between a correct understanding of the complex yeast's and human's glycosylation mechanisms. Expertise in yeast genetic engineering and production processes is essential.

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