Bio-Modeling Systems
The R&D booster for life Sciences discoveries

CADI™ Discovery Genetic Engineering for Complete & Efficient Human Protein Glycosylation in Yeast for Disruptive BioProduction Programs

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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.*

BMSystems Group addresses *two complementary targets* in Pharma, Biotech, Cosmetics, Nutrition, BioProduction and Digital-Health businesses:

- 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,
- Business Developers, Patients Groups & Investors: We discover novel low-risk, highly effective and cost-effective diagnostics/therapies/nutrition/cosmetics/processes for spin-offs or out-licensing.

Created in 2004, profitable since 2006, thanks to our recurrent clients, CADI™ Discovery already delivered operational outputs.

*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

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				
Hypercholestemia 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	
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 0/I	Phase 2a	Phase 2b	Comp. Use	Phase 3
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
COMBO-DIAGNOSTICS			
CADI-D3041	Alzheimer's Disease Early Diagnostics		Ready

Internal Program Name	Program Domains	Partners	CADI™ vers. 0	Ind. Valid.	Secret or Patent or Co-Patent/Publi.	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		

* New internal classification

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 M€ 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 (Now implemented by Arbuza Regenerate Pvt Ltd) 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. This therapy will also be applied to Gul war Syndrome

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

An experienced Genetic engineering 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™ and of new technologies in molecular biology. MRC Overseas fellow, Member of H.U.G.O., Wellcome Trust; etc.. Inventor of novel technologies, Integrative biologist for the Synthons program and Yeast engineering;

Thanos Beopoulos (PhD), Integrative Biologist – Biology and Yeast genetic engineering expert

Greek Biochemist with a PhD in Biotechnology from INA-PG, France

Integrative biologist at BMSystems; Worked for several years on the metabolic engineering of yeast and bacteria for the production of oleo-chemicals, pharmaceuticals and antibiotics at CNRS and INRA genetic engineering department. 3 patents in recombinant Yeast Cells : WO/2017/108577; BIF1351893; WO2010004141

Active in Key Clusters in the Bio-Production world

POLEPHARMA IAR medicen adebiotech

BMSystems' CADI™ BioProduction programs

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.

Synthons Program: 2006: 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

Complete & Efficient Human Protein Glycosylation in Yeast. The challenge: How to find a way to efficiently overcome the major limitations to the large-scale production of humanized glycoproteins in yeast cells?

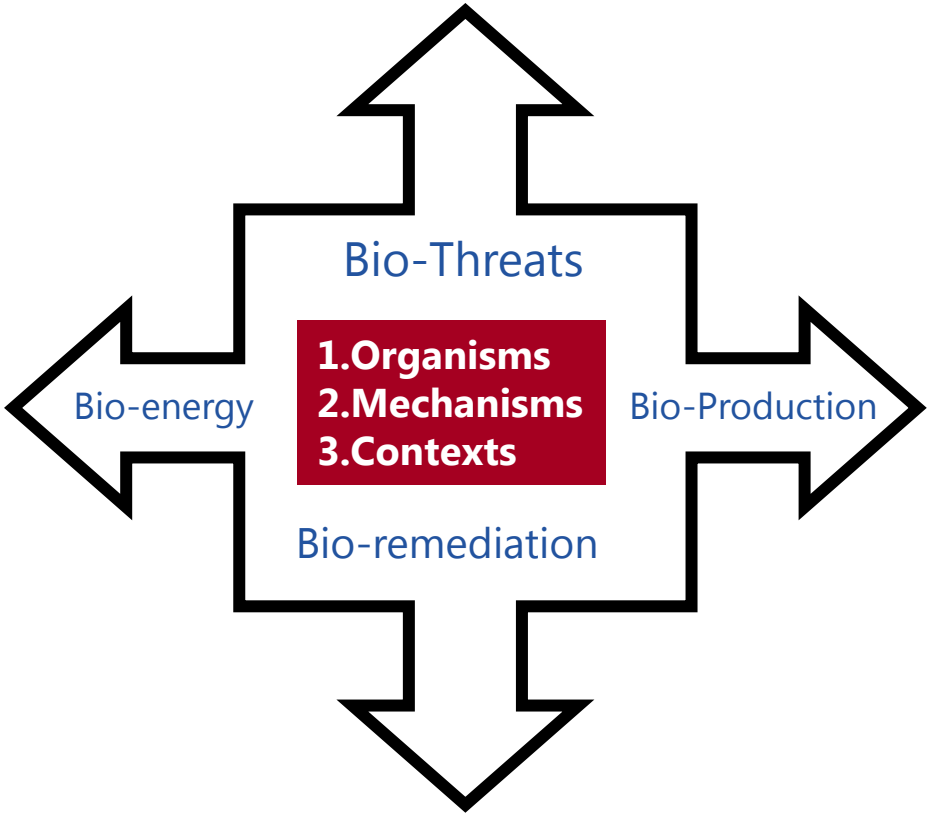
We developed a CADI™ Glycosylation Model that describes the means whereby "human-type, glycosylation pattern-specific tool-boxes" can be constructed and stably harnessed in yeast cells.

CADI v0 program produced

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

BMSystems' Heuristic CADI™ Discovery approach

Pherecydes-Pharma: First BMSystems' therapeutic spin-off, against MR infections diseases, Compassionate Use success,



Program BIO-ENY

Program BIO-REMY
(not active)

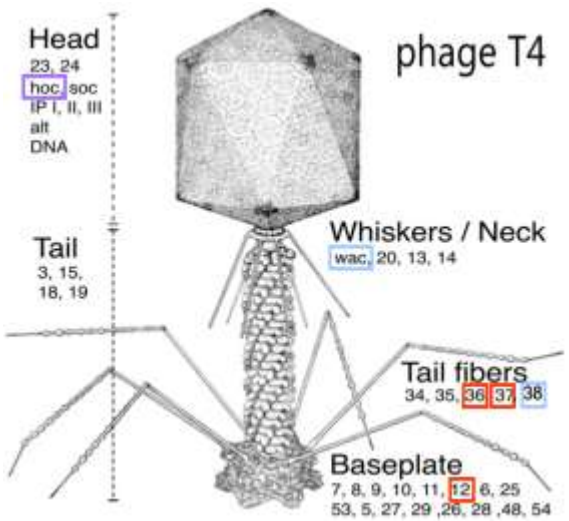
Synthons
Industrial biotech
Partners: ARD, IBT, CVG
L'Oréal, Arkema, Rhodia

'Complete & Efficient Full-Human Protein Glycosylation in Yeast'
CADI™-B8021
Red Biotech

Illustration: Micro-organisms mechanisms and their business applications

CADI™ Discovery program: Pherecydes-Pharma project

A: The challenge / concept



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?

B: The 3 delivered patents

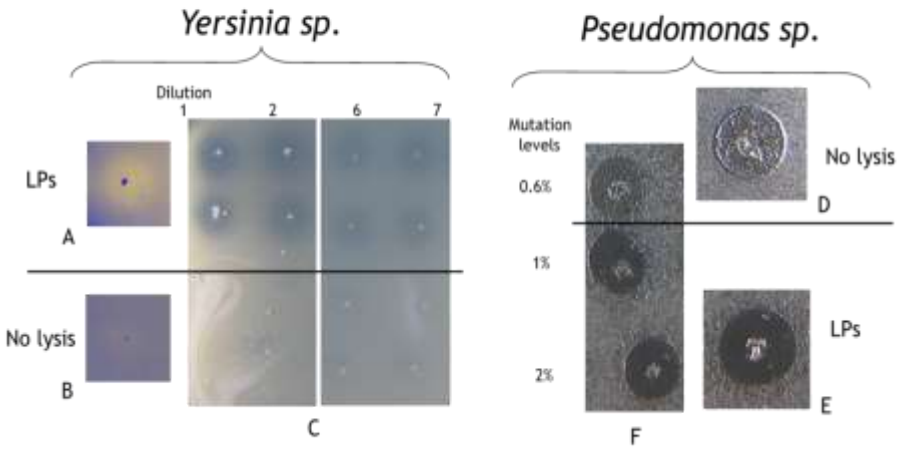
TAPE™ (WO 2008/093009)

Ab-ACCUS™ (WO 2008/093010):

RipH™ (WO 2009/090081)

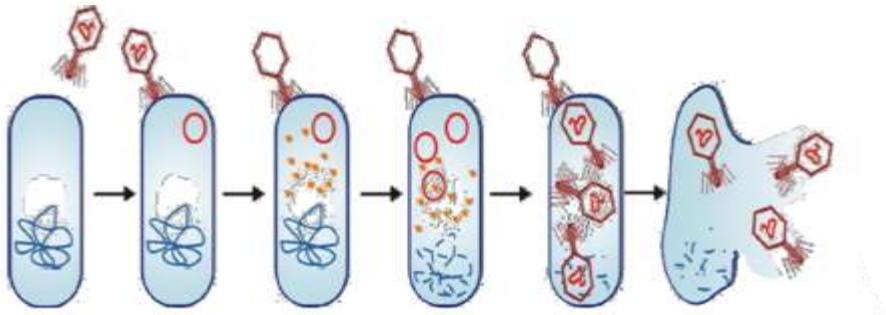
C: The results

While T4 is specific to a narrow range of E. coli strains,



Pouillot F, Blois H & Iris F (2010); Biosecur Bioterror. **8** (2): 155-169.

D: The necessary GMP bio production steps issue



Synthons: Program objectives and achievements

Industrial biotech domain : 2006 Collaborative CADI™ program

Request: 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 unpatented innovative processes:

A complementary collaborative team:

- A.R.D.: Leading Industrial Biotech research company with experimental capacities, pilot to scale-up plant (2000 Tons), a key factor of success, etc.
- I.B.T.: One of France's leading Technology Transfer Institutes.
- BMSystems: integrative Biology & metabolic engineering expertise.
- C.V.G.:"green chemical" sourcing research institute.

3 companies (public information) proposing their molecules to the platform:

- L'Oréal: (world leader in cosmetics)
- Rhodia: (ex. Sanofi Aventis fine chemical entity)
- Arkema: (ex. Total chemical entity

OUTPUTS: A unique significant bacteria metabolic pathways database of strong interest.
2 engineered bacterial strains generated are under evaluation and
a finalized process under mid-scale validation (patent pending by industrial company).
The program was funded by the ministry of Industry and supported by IAR world-class cluster

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

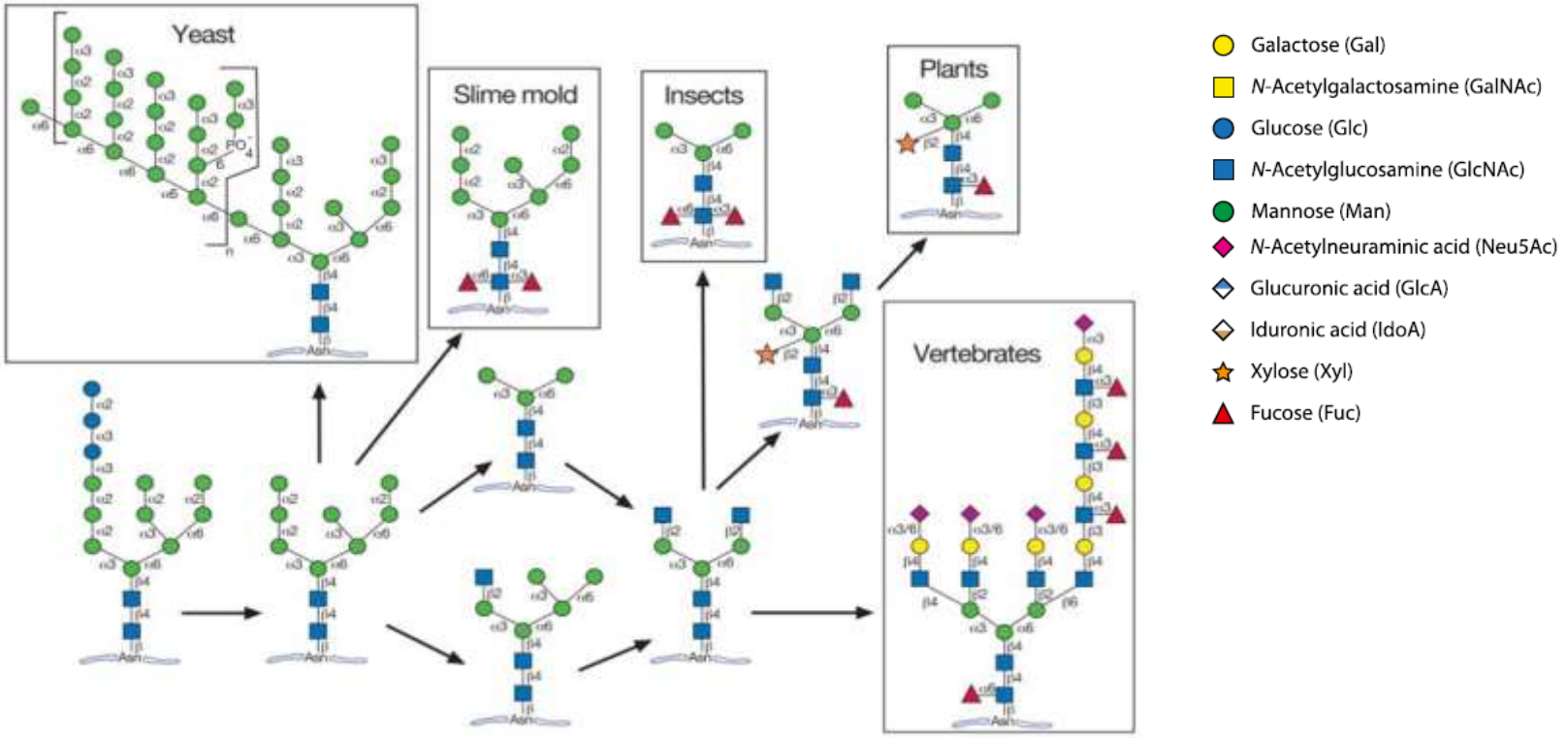
and dramatic half-life increases:

- 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

- 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

- 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

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**.

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

We self-funded the construction of the CADI v0 model ready for experimentation
We are searching for partners to run a POC with a protein of interest

Thank you for your attention

Questions?

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