

The Synthons Program

Synergic collaboration between integrative biology and industrial biotech

**Integrated research from feasibility study
to industrial demonstration plant.**

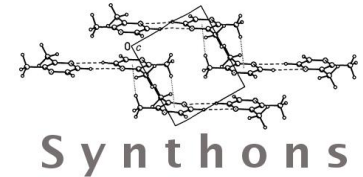
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Summary

- **The industrial biotech challenge**
- **Industrial biotech R&D concept**
- **The Synthons process**
- **Synthons project partners**
- **Three partners: One integrated platform**
- **About ARD.**
- **Evaluation platform : Synthons project.**
- **A red biotech in the kingdom of the Industrial biotech**
- **BMSystems the integrative biology partner**
- **Success factors**
- **Conclusion.**



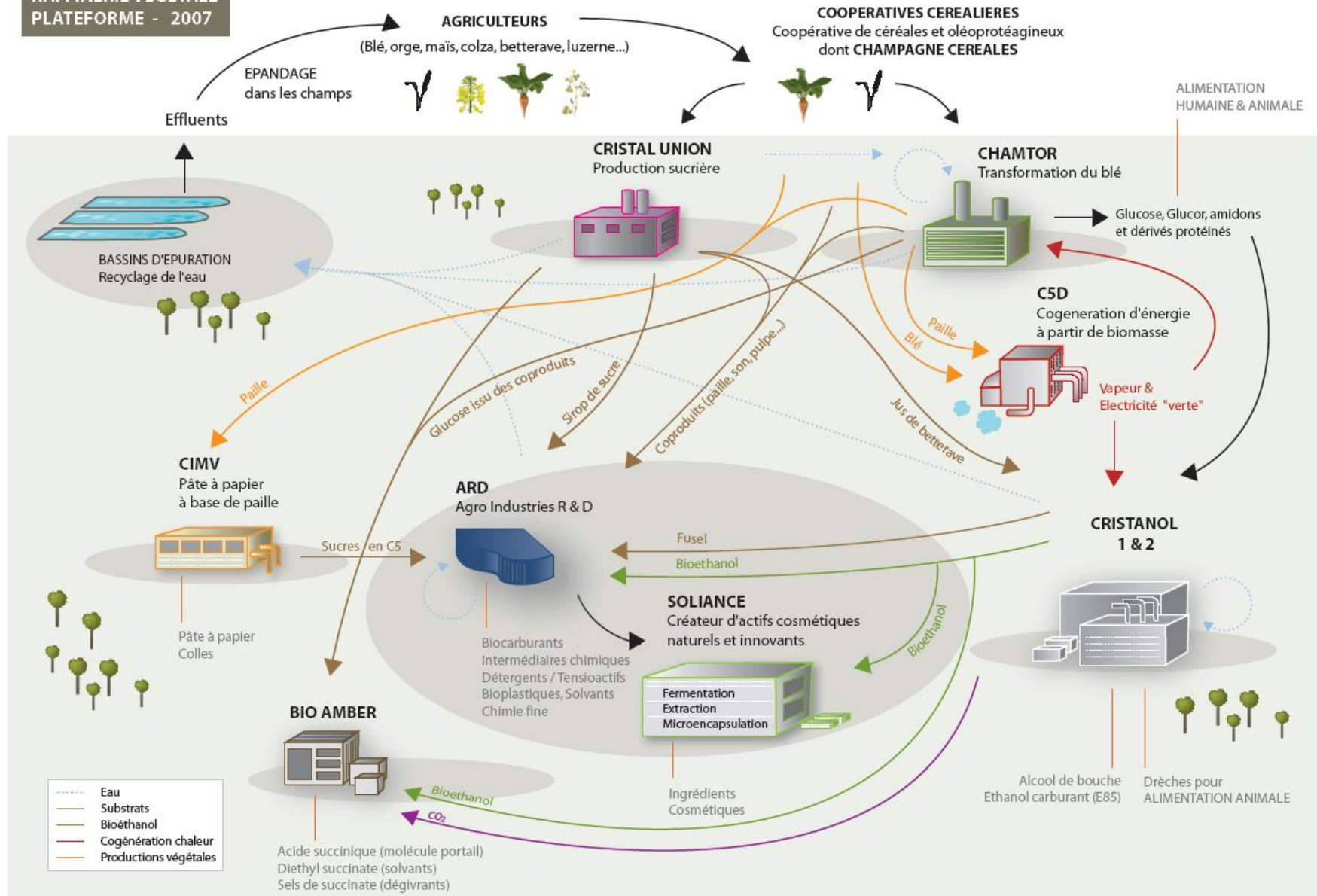
The major chemical industry “tsunami”

- Oil sourcing shortage forecasted.
- Oil cost increases difficult to be totally transferred to clients.

Industrial biotech challenges

- How to help the chemical industry to switch its sourcing from “fossil” carbon from oil to “green” carbon from plants & biomass.
- How to harness the new knowledge, generated by the CADI-mediated modifications of micro-organisms metabolisms to synthesize the required chemicals, in order to produce at industrial scale and supply the market with the chemical compounds at the costs and volumes required.

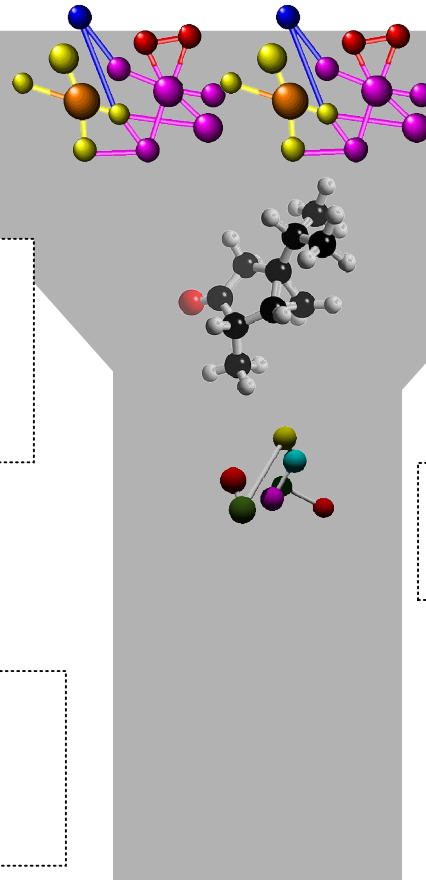
**RAFFINERIE VEGETALE
PLATEFORME - 2007**



Evaluation platform :
SYNTHONS PROJECT

Strain construction
Genetic and metabolic
engineering

Product, process
finalization on industrial
demonstration plant



Laboratory scale fermentation

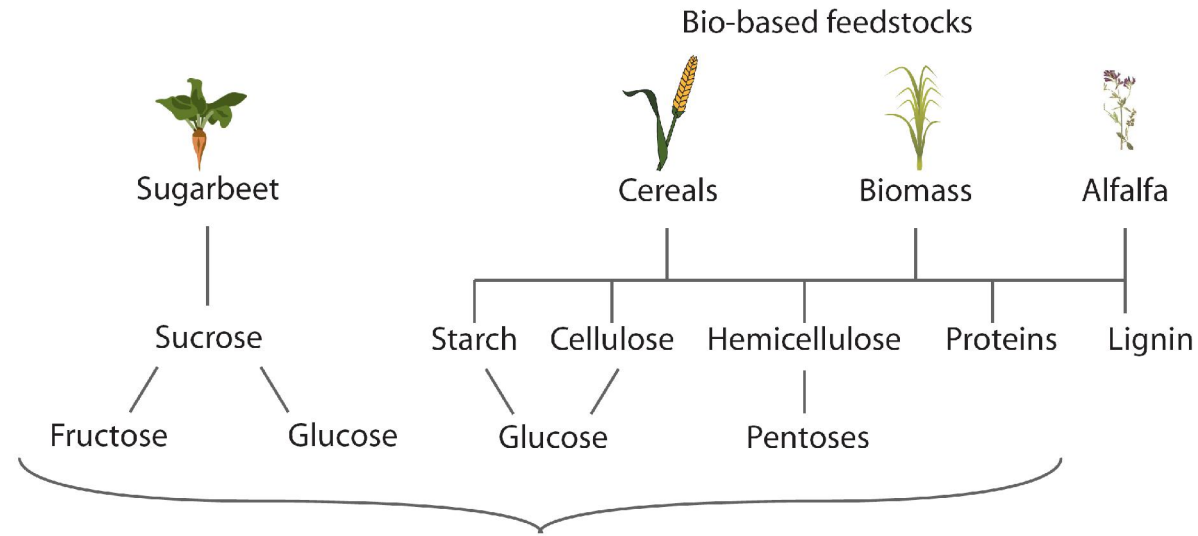
Process definition through pilot
plant test

Complete process for the production of chemical intermediates

PHASE 1

Biorefinery

- Research centers
- Agri businesses



PHASE 2

Definition of molecules of interest

- Input from chemical companies
- Biotech research centers
- Process engineering
- Bio-informatics

Fermentation substrates

Predictive Evaluation

Confirmation in lab

Process Engineering

Evaluation platform

PHASE 3

Development programs

GO / NO GO

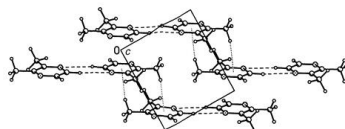
Collaborative research program between white biotech research centers and chemical industry sponsored by French Ministry of Industry and the Champagne Ardenne and Picardie Region.

A collaborative complementary team :

1. **A.R.D.** (AGRO INDUSTRIE RECHERCHES ET DEVELOPPEMENTS)
2. **I.B.T.:** Troyes Institute of Biotechnologies (Intellectual property, biochemical, organism modification). Leading technological transfer institute.
3. **BMSystems:** Predictive integrative Biology expertise.
4. **C.V.G.:** Green chemistry team leader based in Picardie for “green” sourcing research.

3 major European chemical companies proposing their molecules to the platform :

1. **L'Oréal** World leader in the cosmetic market
2. **Rhodia** Major actor in the fine chemicals market (former Aventis fine chemical business)
3. **Arkema** Major actor in the chemistry market (former Total chemical business)



S y n t h o n s

Three partners: One integrated platform

<i>Team Competences gathered</i>	<i>A.R.D.</i>	<i>BMSystems</i>	<i>IBT</i>
<ul style="list-style-type: none"> • Stat of the art survey, sourcing possibilities, • Exploitation freedom • CADI feasibility controls check • Micro-organisms selection • First cost estimation • Production of the initial CADI model • Modification protocols proposition: • Option A: Optimization proposals without genetic modification • Option B: Genetic modifications proposals • Genetic modification realizations • Experimental evaluation protocols design • Optimization of the interesting proposals • Experimentations • Production of the CADI n+1 model and go to Option A or B (above) 	<p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>	<p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>	<p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>
<i>Teams experimental equipments available</i>	<i>A.R.D.</i>	<i>BMSystems</i>	<i>IBT</i>
<ul style="list-style-type: none"> • CADI modeling tools (software, processes, methodology) • Molecular biology • Microbiology • Screening, clones selection, Genetic engineering • Experimental validation: <ul style="list-style-type: none"> –Laboratory scale from 2l to 150l –Scale-up simple pilot up to 5 m³ –Scale-up bio-production pilot from 10m³ to 40 m³ –Works design, Industrial engineering –Estimation and industrial cost fine tuning –Molecules purification 	<p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>	<p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>	<p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p> <p>X</p>

ARD objective is to develop new products and processes derived from agricultural crops

Our Missions :

- To develop innovative and competitive products and processes that are sustainable and ecologically sound alternatives to petrochemicals.
- To focus on bio-refinery concepts that are designed to process all plant fractions to valuable products.
- To actively promote utilization of bio-based resources in industrial applications and more generally in the economy and the society.

It employs over 75 people.

- 1. Fractionation and Pilot
 - 2. White Biotechnology
 - 3. Green Chemistry
 - 4. Analytical Chemistry
 - 6. Environment
- 3 research teams**
- 2 cross-functionnal teams**



- **Strain construction :**

By coordination of public and private research centers in biotechnology.

- **Adjustment of process parameters (fermentation and downstream processes) :**

- type of carbon source, nitrogen source.
- definition of other nutrients and optimization of the concentration
- definition of physical condition in fermentation (aeration, agitation, temperature, ...)
- definition of preliminary downstream

Process definition through pilot plant test

- Extrapolation of fermentation process from 100 liters fermentors up to 5000 liters pilot fermentor and validation of the lab process parameters.
- Testing on a pilot plant of various type of downstream process including :
 - extraction of molecule from fermentation broth using cross flow filtration, centrifuge, filters, ...
 - purification of extracted molecules with ion exchange resins, activated carbon, electro dialysis crystallization, ...



These tests allow to have a technico-economical GO/ NO GO prior to industrial demonstration.

Product, process finalization on industrial demonstration plant.

- Further to pilot plant process definition and prior to industrialization, an intermediate step is necessary to :
 - validate a comprehensive mass, energy, water balance.
 - establish a realistic environmental balance both on solid, liquid waste and VOC on a representative scale.
 - confirm the cost price of the molecule.
 - validate the quantity of the product on a representative output together with the applicability in industrial uses.

Product, process finalization on industrial demonstration plant.

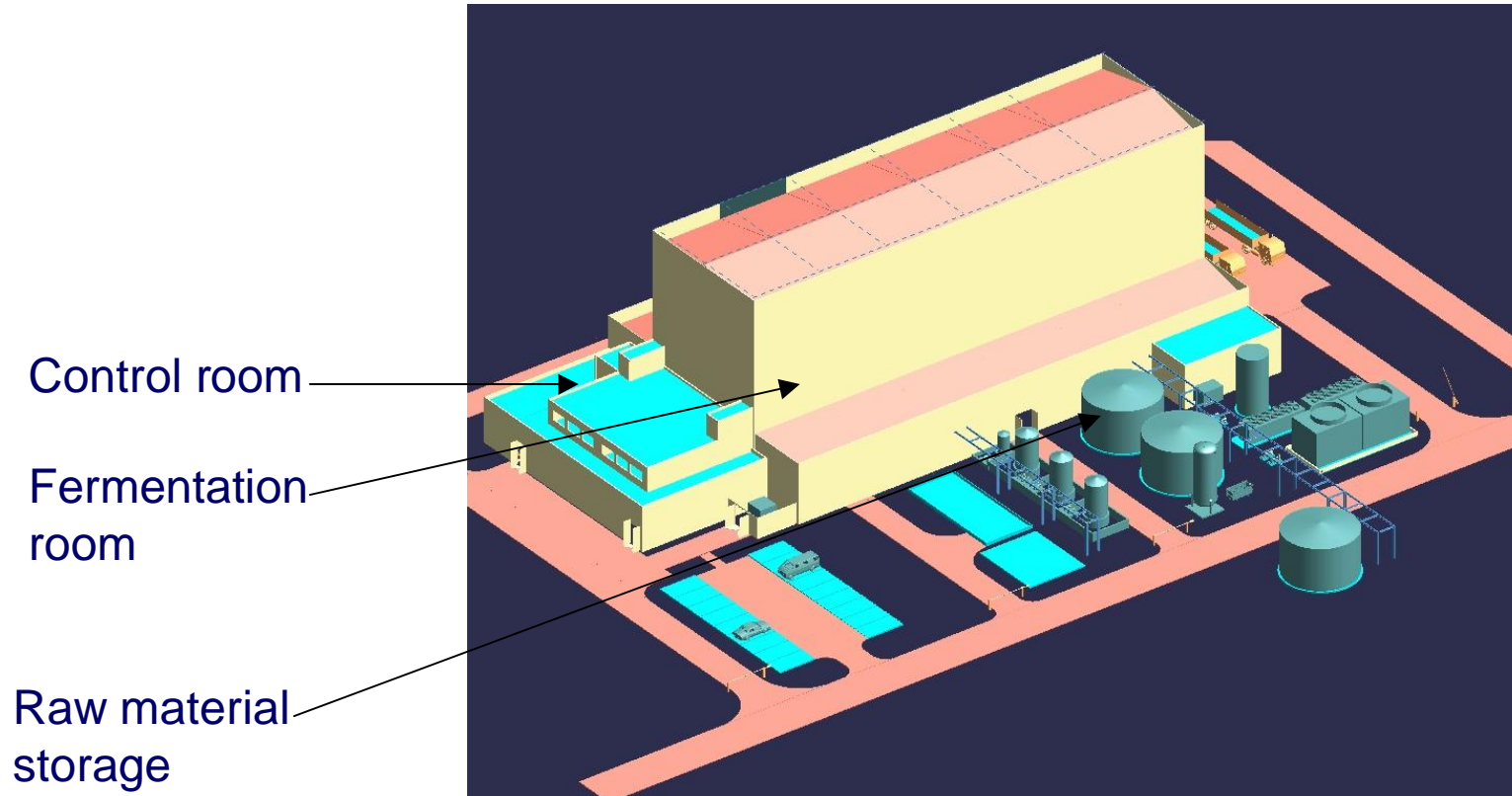
An industrial demonstration plant is under construction for these purposes and will be operational in September 2009

The project is sponsored by the Champagne Ardenne Region, the Marne department and the FEDER.

Its conception will allow a large range of molecules production, the first one being succinic acid.



General overview of the building



A red biotech in the realm of the Industrial biotech

Our mission : We help our clients and partners to significantly boost the outputs of their R&D programs using our modeling approach.

CADI™: The “first-in-class” answer to explain the non-linear mechanisms of diseases and thus, reveal pertinent biomarkers & therapeutic targets.

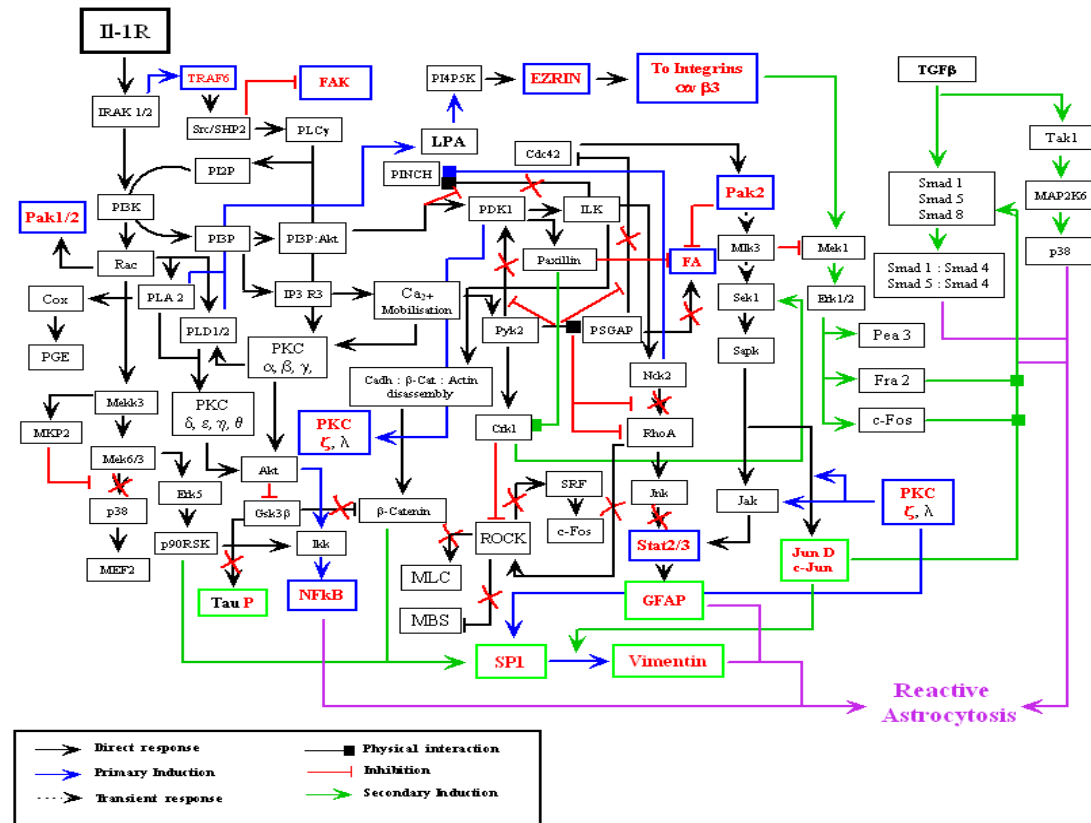
Ø ***2003, CADI™ models “first-in-class”. Publication with INSERM unit 553 of the world’s first successful independently validated model of a complex human disease in Nucleic Acids Research.***

BMSystems’ operational proofs. One approach for multiple validated applications***

- Ø ***At least 7 CADI™ models produced in 5 major medical areas,***
- Ø ***2 publications in “cancer” with INSERM unit 553,***
- Ø ***1 patent in “psychiatric disorders” with CEA** Life Sciences,***
- Ø ***1 scientific publication pending in “neurodegenerative diseases” 2 patents in infectious diseases,***
- Ø ***1 operational spin-off in Biodefense/Biosecurity (infectious threats),***
- Ø ***2 technology platforms (pre-clinical evaluation for psychiatric molecules, industrial biotech),***
- Ø ***2 bacterial strains under development.***

What are/are not CADI™ models ?

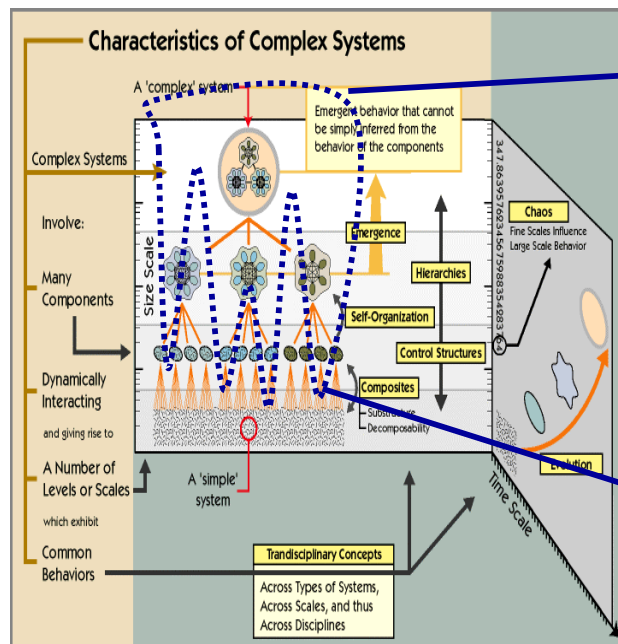
The CADI™ (Computer Assisted Deductive Integration) models are detailed maps of inter-cellular and/or intra-cellular mechanisms associated with a biological status.



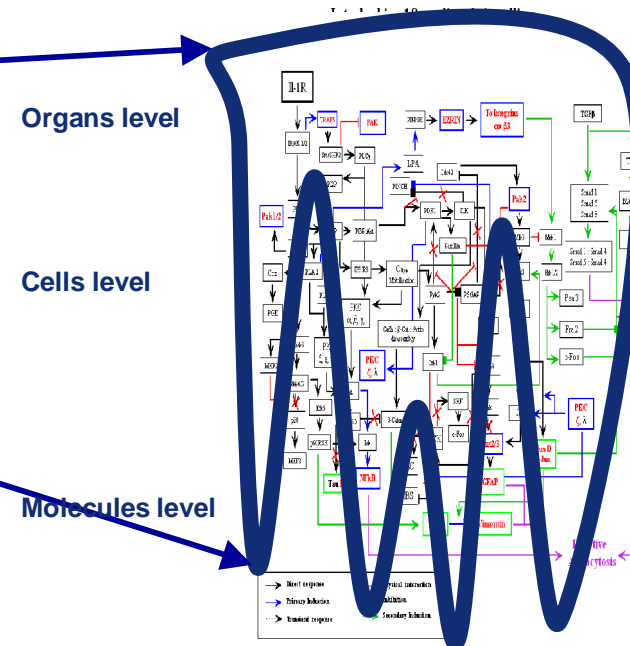
Predictive Integrative Biology: The CADI™ models

- The CADI™ (Computer Assisted Deductive Integration) to build validated biological interaction maps. CADI™, based on negative selection concept, was invented in 2002 by Dr. François Iris, founder, Chairman and CSO of the company.
- The CADI™ models, belong to the non-mathematical holistic and heuristic class of models.

The complex system to study



A CADI™ model representing the system in a specific context



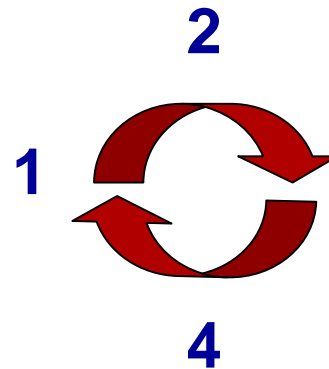
The unique CADI™ 4 steps validation process

∅ The CADI™ 4 steps validation process starts when the integrative biology researchers generate the initial CADI™ model, following the steps from 1 to 4:

CADI model's forecasts are defined by both experimental and integrative biology researchers
The experimental biology researchers define and invent new innovative experimentations to test the model's forecasts

1 The initial CADI™ Ver.0 model is constructed by integrative biology researchers.

2 For each loop, integrative biology researchers integrate the experimental results to generate the next CADI™ Ver.n+1 model



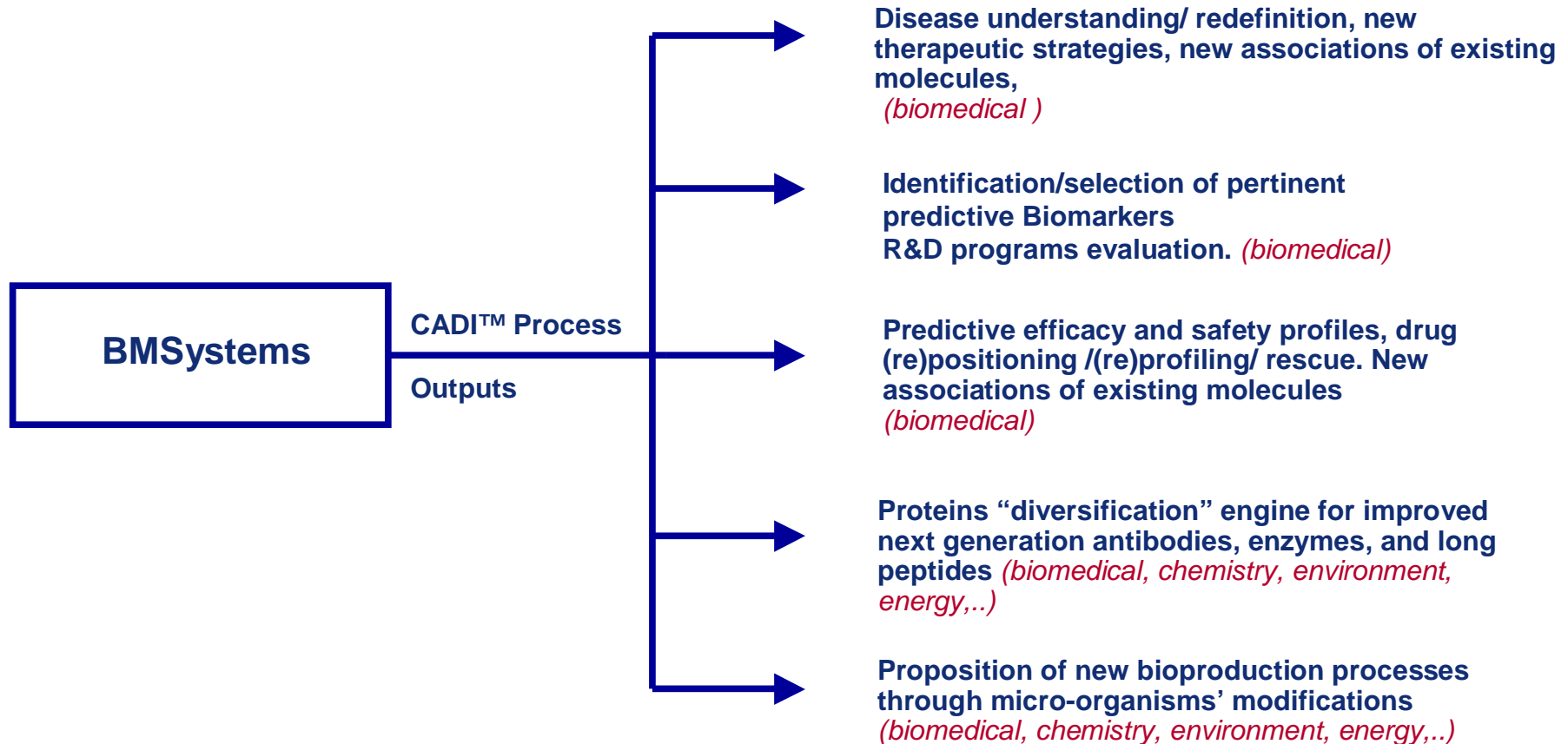
3 Experimental biology researchers implement the innovative experimental approaches to test the model's forecasts

4 Unexpected experimental results are analyzed and interpreted by both experimental and integrative biology researchers

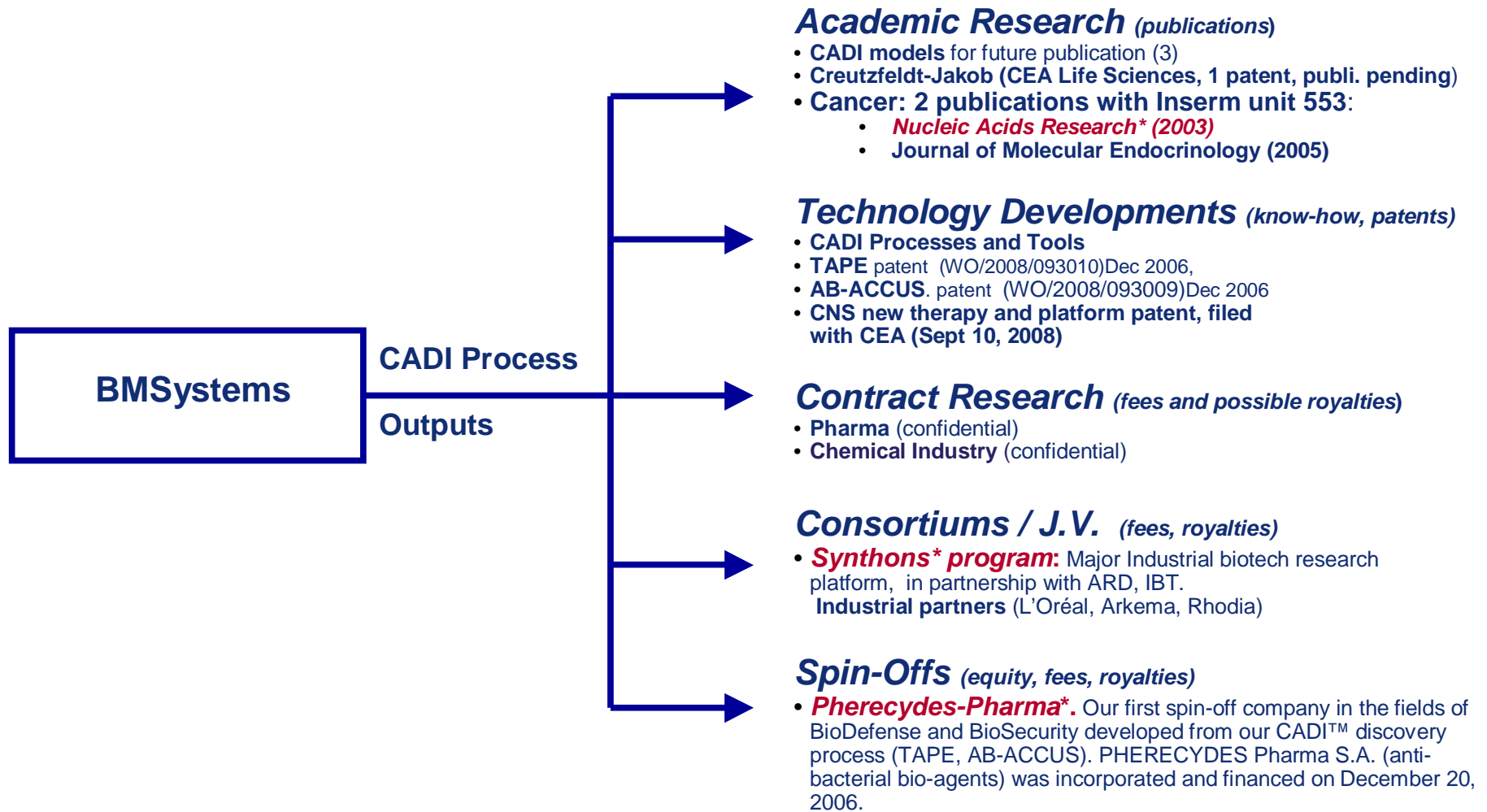
∅ The CADI™ 4 steps validation process stops when no key unexpected results are reported.

What can we do with CADI™ models?

Reduce time to result, improve success rate and reduce costs to exploit:



What kind of “Value” can we generate?



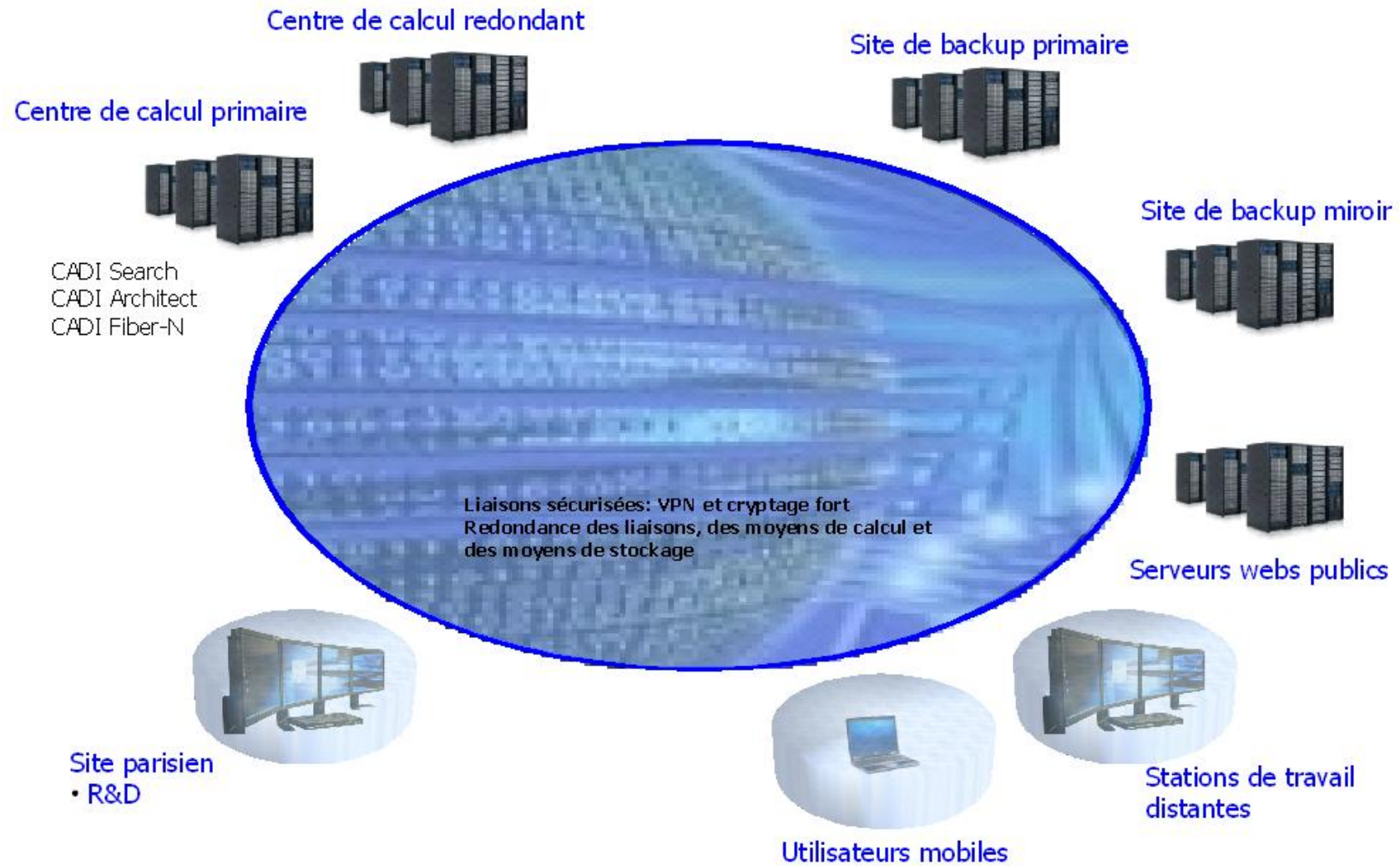
* See the details of the three case studies in this document

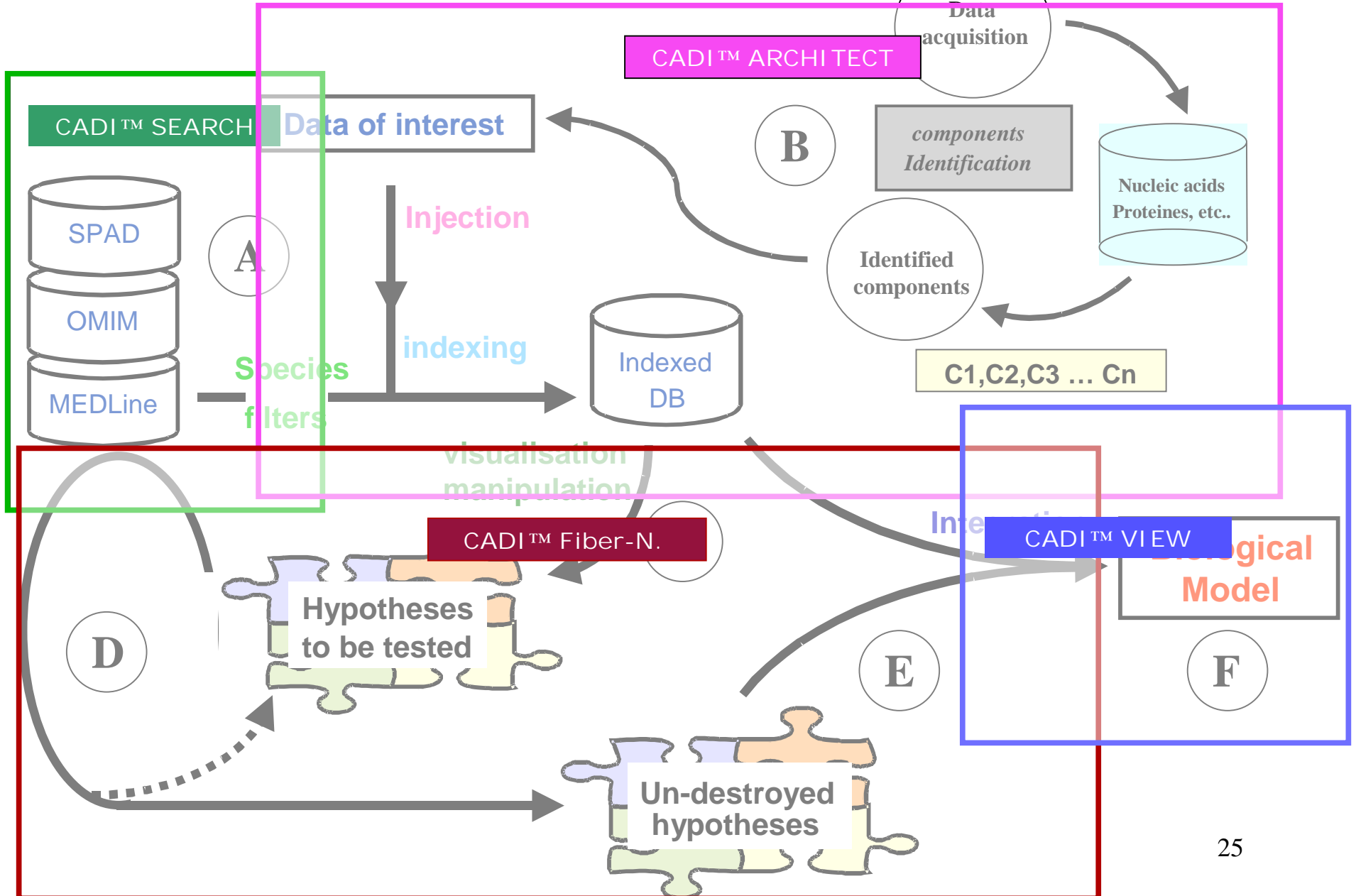
CADI™ models and proto-models already built

Bio-Modeling Systems R&D team has already made seven CADI™ models & four « proto-models », in 5 major medical areas for optimization of the drug development process and the diversification of drugs applications. CADI™ models for Industrial biotech and the generation of “improved” proteins were recently developed

- § **CNS** → *Creutzfeldt-Jakob^{2*}, Alzheimer disease^{1*}*
- § **Systemics** → *Breast cancer^{3*}, Tamoxifen resistance^{3*}, Metastasis^{2*}*
- § **Infection / Immunology** → *Antibacterial bio-agent^{4*}, Hepatitis C¹, CFS¹*
- § **Tissue differentiation** → *Adipocytes growth control¹, Müllerian regression^{2*}*
- § **Metabolism** → *Hypercholesterolemia¹,*
- § **Industrial biotech** → *Program Synthons: Collaborative research platform*
- § **Proteins “diversification” engine** → *CADI™-TAPE Process³
(antibodies, enzymes, long peptides etc..)*

1 : Models ready for experimental evaluation; 2 : Experimentally validated models; 3: Experimentally validated and published models; 4 Experimentally validated and industrially exploited * CADI Models, the others being proto-models (feasibility study done)





Synthons platform success factors

- The integrated platform was developed with the best professionals in their respective field.
- Each partner spends its resources to improve its proprietary tools and processes and not to develop complementary competences a partner could provide.
- Each partner finances its costs and shares with the relevant partners the future returns.
- The “intel inside” strategy allowed BMSystems to become an active member of the leading platform in the Industrial biotech market within only 2 years.

***And as my personal conclusion
Thanks to ARD for this opportunity
to enter the white biotech business***

Conclusion

At this stage, on the same biorefinery site of Pomacle-Bazancourt in France,

- 12 chemical intermediates are under evaluation under the Synthons project
- for 2 chemical intermediates strain and laboratory scale fermentation are under competition
- for 1 chemical intermediate, the process is under definition on a pilot plant
- for succinic acid, the process will be finalized on an industrial demonstration unit to start in September 2009

All the R&D concept is opened at any stage for any industrial partners.

Thanks for your attention !!

For more information

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