*Emerging Company Profile*

# Bio-Modeling: Negative selection

**By Christopher Maggos**
**Senior Writer**

Bio-Modeling Systems SAS says its in silico drug discovery system, Computer Assisted Deductive Integration (CADI), is working better than previous bioinformatics discovery systems because it is based on the contrarian approach of disproving hypotheses rather than the more traditional method of supporting them, and because the company uses biologists to generate predictions. The company has published its first validated hypotheses and is looking to partner them with drug developers.

"A lot of the issues identified by pharma as being bottlenecks are related to the lack of predictive technologies," said Manuel Gea, co-founder, CEO and vice president of R&D information systems at Bio-Modeling (Paris, France).

Most approaches to improving prediction have focused on positive selection. "In positive selection, you build links between information — for example, data in academic papers — to support a hypothesis," Gea said. "The problem is that sometimes you will include a paper which is wrong or inappropriate, and there's no way to know that beforehand. It becomes very cost-intensive to sort that out."

In Bio-Modeling's negative selection process, "the idea is to find a link between a gene and a disease and then try to prove it wrong," Gea said. "You keep re-building hypotheses until eventually you find one that cannot be destroyed."

For example, finding the link between a gene and a disease is a positive selection process. But where other approaches go on to find and incorporate data supporting that link, Bio-Modeling tries to disprove it.

Specifically, the company uses CADI to comb the scientific literature, public databases and, potentially, the proprietary data of a partner, in the hopes of finding evidence that a theory is wrong, Gea said.

## Bio-Modeling Systems SAS

Paris, France
Technology: CADI, an in silico negative selection process for hypothesis-driven drug discovery
Disease focus: Cancer, neurology
Clinical status: NA
Founded: 2004 by Francois Iris and Manuel Gea
University collaborators: None
Corporate partners: None
Number of employees: 7
Funds raised: ND
Investors: Francois Iris and Manuel Gea
CEO: Manuel Gea
Patents: None issued

Once a hypothesis holds water, Bio-Modeling Systems takes two additional steps to confirm and utilize the finding. First, it talks directly with researchers in the field to see if there are unpublished data that will poke holes in the finding.

If the hypothesis continues to hold up, the company's biologists — not bioinformaticians — then make predictions using CADI's predictive modeling capabilities to organize and structure the data so they can generate visual models of the mechanism of a disease and a corresponding therapeutic strategy.

"For example," Gea said, "if you take the breast cancer paper we published in *Nucleic Acid Research*, we hypothesized that if we combined three molecules, it would be possible to counterattack the Ras mutation, which occurs in 30% of breast cancers."

In the 2003 paper, Bio-Modeling researchers hypothesized that the three molecules together would increase calcium influx and thus exacerbate deregulation of calcium-dependent pathways already present in these cells. The result would trigger the cells' negative feedback mechanisms and induce cell death in breast cancer cells carrying the Ras mutation. Data in the paper showed that the strategy worked in vitro, while cells that did not contain the Ras mutation were spared.

Gea said the objective was not to develop a new therapy, but rather a new strategy. The company disclosed two of the three molecules — a calcium ionophore, which increases calcium influx, and an activator of PKA enzyme called dibutyryl-cAMP. While the molecules can't be used in humans because of toxicity, Gea said, "a pharma company now will know what to look for."

The company is working with potential pharma partners on the idea, and has not disclosed the third compound while it protects the strategy with IP.

The company presented in vitro data validating another CADI model in Creutzfeld Jacob Disease (CJD) at the Euro Prion Conference in Duesseldorf in October 2005 and is preparing a publication.

"We have a possible prophylactic for CJD that could stop the progression of the disease," Gea said. The problem is that there's no test to know if people have CJD prior to death. This molecule is an injectable that would be given only to people at high risk of infection who would have to take it chronically.

"We've decided that as soon as it is validated, the prophylactic strategy will be given to the public domain," Gea said. Instead, the company will pursue Alzheimer's disease on a commercial basis.

Bio-Modeling will avoid fee-for-service deals. "We hope to form collaborative deals with pharma that are success-based. The upside is better," Gea said.