

Technology Briefing

New Huntington clue

Mutant forms of huntingtin protein have long been known to play a role in Huntington's chorea, but the exact molecular mechanism of the disease is still far from being understood. French scientists think they have identified a crucial mechanism and that tacrolimus, a marketed drug, may be able to interfere with this process.

While studying the mechanism that leads to neural death in Huntington's patients, Frederic Saudou and his group at the Institut Curie in Paris discovered that phosphorylation at serine 412 in mutant huntingtin can slow disease progression in vivo. This means that compounds enhancing phosphorylation are of therapeutic interest.

"Huntington's disease is caused by an abnormal expanded polyglutamine repeat in the huntingtin protein," Saudou told BioCentury. "This so-called polyQ huntingtin, when cleaved in the cytoplasm, moves into the nucleus where it forms certain aggregates and induces transcriptional dysregulation and cell death."

Saudou added it also is known that several posttranslational modifications, such as proteolysis, ubiquitination and sumoylation (modification by the small ubiquitin-like modifier, or SUMO), can modify toxicity of polyQ huntingtin. "In particular, phosphorylation at serine 421 abolishes polyQ toxicity in a cellular model of Huntington's disease," Saudou said. "However, it was not clear whether this plays a role in vivo."

The group then focused on phosphatases acting on serine 421 (S421). Among these phosphatases, calcineurin (CaN) is ubiquitous in the brain, and the researchers therefore decided to test inhibitors of CaN, such as cyclosporine A and tacrolimus (FK506), in animal models of HD. They focused on tacrolimus, which is marketed as an immune suppressant by Astellas Pharma Inc. (Tokyo:4503, Tokyo, Japan), because "this compound and ligands derived from it can readily cross the blood-brain barrier, while cyclosporine cannot," Saudou said.

The researchers found that phosphorylation of polyQ at S421 is neuroprotective in vivo. They also demonstrated that CaN dephosphorylates phosphorylated S421 in vivo and that inhibition of CaN leads to increased levels of phosphorylation in polyQ at S412 and prevents polyQ-induced death of neurons.

According to Institut Curie, IP based on the research is available for license. The results were published in the February issue of *The Journal of Neuroscience*. — *Ludger Wess*

Better ubiquitin screening

The ubiquitin proteasome pathway is involved in many cell processes, including apoptosis, immune response, cell cycle progression, gene expression regulation and DNA repair. But its complexity makes it difficult to build assays to gauge the effect of compounds in the pathway.

Cytomics Systems SA says its Ubiscreen yeast-based screening assay is more useful than non-cell-based in vitro methods because it more closely mimics the actual pathway. The company was

expected to announce this week that it has raised €10 million (\$11.9 million) in the first closing of a series B round led by Edmond de Rothschild Investment Partners, which will enable it to start developing compounds derived from its screens.

"It is known that perturbations in this pathway are tightly linked to several diseases, such as neurodegenerative diseases, inflammatory diseases and cancer," said CEO Dominique Thomas.

For example, he said, "depending on the type of cancer, you can

have an over-function of the ubiquitin pathway or an under-function. An example is over-degradation of the p53 protein, so you have no more apoptosis response."

It's the pathway's complexity that makes a cell-based assay important, according to Thomas. "The ubiquitin pathway is very complicated and is impossible to replicate in its totality in a test tube," he said. "We decided to emulate it in Baker's yeast cells, where every aspect of human cell biology is present."

The technology, which is high throughput, is being used to discover drugs for the company's own account. Cytomics (Gif sur Yvette, France) has no plans to offer Ubiscreen in fee-for-service deals.

One project is the development of next-generation proteasome inhibitors that would improve on Velcade bortezomib from Millennium Pharmaceuticals Inc. (MLNM, Cambridge, Mass.), which is marketed for multiple myeloma (MM).

"We can isolate catalytic and non-catalytic inhibitors of the proteasome," Thomas said. "We think we could isolate a new chemical family that would work in Velcade-resistant cell lines."

The company's proteasome inhibitors are in in vitro testing, with animal studies expected to start in the first half of 2007. It expects to look for a partner after showing preclinical proof of principle.

A more advanced program is its CYS001 series, which targets a ubiquitin ligase enzyme responsible for degradation of an undisclosed fungal protein that is critical for fungal survival. Cytomics plans to develop CYS001 for hospital-acquired fungal infections.

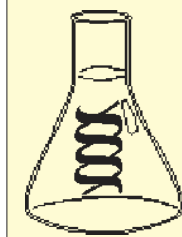
"Our lead compound protects mice from death from *Candida albicans* infection at very low doses — about 1 mg/kg," Thomas said. "We had less toxicity in mice than amphotericin B," with similar efficacy.

Cytomics is starting preclinical toxicology testing of the series and hopes to enter Phase I in the first half of 2007. The company plans to complete Phase IIa studies before partnering these molecules.

Cytomics also was expected to announce this week that it has hired Jean Thebault as director of clinical development and chairman of the supervisory board. Thebault is founder and former CEO of Aster-Cephac SA, a CRO that specializes in Phase I trials.

The series B round, which included Truffle Venture and pre-existing investor Societe General Asset Management Alternative Investments (SGAM AI), should give Cytomics enough cash to complete Phase IIa testing of CYS001 and establish preclinical proof of principle for its proteasome inhibitor, according to Gilles Nobecourt, a director at Rothschild. — *Christopher Maggos*

This week's briefing



Institut Curie: New Huntington clue

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Cytomics: Better ubiquitin screening