

## Inside Story

### Orexin antagonists as a potential therapy for sleep disorders

In 1998, scientists at the University of Texas, Dallas, discovered two new peptides in the brain called orexins, which were thought to play a role in sleep-wake balance and the control of feeding behavior. Researchers at Actelion, which had just begun operations as a new company, were intrigued by that discovery. A small team began trying to synthesize small molecules that would function as orexin antagonists. Based on existing scientific literature, three-dimensional computer modeling tools and their own knowledge and instincts, the team members came up with the first leads in a short time.

"In our search for orexin antagonists that were orally available and had low potential for drug-drug interaction, we synthesized some molecules that were absolutely inactive pharmacologically," remembers Ralph Koberstein, Lead Chemist for the orexin project. "Just as a matter of scientific curiosity, we passed them on to the research group in urotensin II receptor antagonists. From those molecules, they found a potent lead compound that would become a promising candidate for clinical development, palosuran. Vice-versa, the urotensin group passed derivative molecules back to us that would become some of our lead candidates as orexin antagonists. This scientific ping-pong game went on for one-and-a-half years."

The fertile period of creativity, however, was followed by years of drought as one potential orexin antagonist after another was eliminated for probable drug-drug interaction or was not active after oral administration. "It was a tough time," remembers Francois Jenck, Head of CNS Pharmacology, "but we believed in the concept, and we don't run out of ideas quickly at Actelion." Then in November 2003, a compound went through the tests and passed with flying colors. The laboratories echoed with the sound of popping champagne corks in both the orexin and urotensin project teams.

"For me, this is proof of the unique culture of Actelion," said Mike Scherz, Vice President, Project Management. "There is a spirit of shared discovery in our research laboratories. We have an open and easy exchange of information; in addition to regular meetings, our scientists discuss the latest lab results when they see each other in the hallway or sit together over a quick sandwich at lunch. There is a real sense of urgency, and we're all pulling together in the same direction. Every decision you take in the lab is important, every hour counts."

"This story and others like it reflect the innovative power of our strategic focus on families of drug targets such as G-protein coupled receptors or aspartyl proteases," said Martine Clozel, Head of Drug Discovery, Pharmacology and Preclinical Development. "Being able to harvest the results is a function of the quality and commitment of our scientists and the dynamic culture that makes us unique as a company."

Work is proceeding at a fast pace on Actelion's new orexin antagonist, which promises to be quite different from traditional sedatives in treating sleep disorders, if it clears the hurdles necessary to become a marketed drug. Animal experiments have shown promising results and the first clinical trials in human volunteers are scheduled for 2005. The original multidisciplinary project team of circa 25 medicinal chemists, biochemists and pharmacologists has grown substantially as the project moves forward.

"The science is compelling," adds Mike, "but for me the best part of working on this project is the people. When I look around the room in a staff meeting and see the brainpower and the dedication, it inspires me. Of course, we all have our own personality quirks and individual ways of working – that's what makes it fun."

