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Drug discovery lies at the heart of Actelion's corporate culture. When the founding members of the team decided to establish Actelion in late 1997, they wanted to harness their knowledge of the endothelium and their experience in medicinal chemistry in order to discover novel, orally available drugs. Actelion's research staff considers itself a group of "drug hunters" and their enterprising spirit permeates the whole Actelion organization.

Actelion's drug discovery unit is guided by a simple, but efficient strategic focus. First, our research focuses on the design and synthesis of novel low-molecular-weight, drug-like molecules. Second, our projects are selected from two molecular platforms of proven utility as drug targets: G-protein-coupled receptors (GPCRs) and aspartyl proteases. Third, we work on innovative drug targets related to the endothelium that have the potential to satisfy important unmet medical needs in cardiovascular, central nervous system and oncology indications.

In June 2002, we held our first R&D Day to showcase our innovative approach to drug discovery and development. We introduced over 100 industry analysts to our research projects on urotensin receptor antagonists, orexin receptor antagonists, renin inhibitors and BACE inhibitors. In all of these projects, we showed that our progress toward identifying drug development candidates is backed by our strong, wholly owned intellectual property positions. The research day also highlighted our unique ability to bridge preclinical and clinical research, by extending our extensive knowledge of the vascular endothelium into new clinical trials and new potential clinical indications for Tracleer® and Veletri™.

### Update on research projects

Urotensin II is a peptide hormone that is extremely potent in constricting certain blood vessels. It also exerts other long-term adverse effects on several target organs. At Actelion, we are pioneering the development of urotensin receptor antagonists for the treatment of certain cardiovascular and metabolic diseases. Our in vivo animal testing laboratories confirmed that we have discovered exciting pharmacological concepts for clinical testing of this new therapeutic principle. In November 2001, we selected an orally active urotensin receptor antagonist for preclinical development. Our in-house preclinical and clinical development groups collaborated closely with external toxicology and manufacturing companies to complete the required studies in the unusually short period of 12 months... and we did it under budget. The urotensin receptor antagonist has passed all hurdles for human clinical studies, which are now in progress. To the best of our knowledge, it remains the most advanced compound of this exciting new therapeutic class.

In 2002 Actelion delivered a pre-clinical compound that Johnson & Johnson is now preparing for human clinical trials. With this accomplishment, we have brought the research term of our collaboration with Johnson & Johnson to a successful conclusion, to the full satisfaction of our partner. Actelion will receive milestone and royalty payments as Johnson & Johnson continues to develop this compound. Its intended clinical indications remain undisclosed.

Our orexin receptor antagonist project is an exciting and innovative approach targeting the GPCRs mediating the actions of orexins. Recently discovered in the brain, orexins are neuropeptides that



play a remarkable role as modulators of sleep/wake states and intake of food and water. In 2002, our research team discovered and patented several classes of potent and selective orexin receptor antagonists. We are optimizing them for their suitability as preclinical development candidates with therapeutic potential for acute or chronic treatment of sleep disorders or obesity.

In the year under review, we also made substantial progress in developing an orally available renin inhibitor. Renin is the

enzyme that initiates formation of the peptide hormone angiotensin II. Angiotensin II plays a major role in the etiology of cardiovascular disease by affecting long-term processes such as arteriosclerosis and remodeling of the heart and kidney. Renin inhibitors provide a novel pharmacological intervention for hypertension, renal failure and vascular diseases. Well-documented clinical trial results with prototypical compounds, which lacked commercial utility, have proven that it is a safe and efficacious principle.

