

# Drug Hunters

The story of Actelion's genesis  
and the driving force  
behind its success



# “Actelion is a hands-on company”

## Dr. Jean-Paul Clozel

Chief Executive Officer and member of the Board of Directors

Thinking back about the founding of Actelion in 1997, Dr. Jean-Paul Clozel, a French cardiologist and researcher who was heading a Drug Discovery group in the Cardiovascular Department at F. Hoffmann-La Roche, remembers how the idea of the new company hung in the balance.

“I can honestly say that if any one of the founding members had declined, I would not have gone through with it,” he admitted. “That tells you how important each person was and how complementary our skills were in this venture.”

But even with everyone on board, there were imposing obstacles. Potential investors were nervous about committing to a new company without marketable products. Realizing this, the founding members went back to their former employers at Roche and negotiated the licensing in of the compounds they had discovered and developed, tezosentan and bosentan.

“We made the initial investment into the founding of the company and for the licences with our own money,” said Jean-Paul. “It was a frightening moment using a lot of money. We had given up well-paid jobs at Roche, spent our personal savings and we were still without investors.”

The gamble paid off. With the licenses and the financial savvy of CFO André J. Mueller, the needed venture capital was raised. The compound bosentan would later become Actelion’s first product on the market, Tracleer® and lift the company into profitability in record time.

Jean-Paul, who succeeded Dr. Thomas Widmann as CEO when Actelion became a publicly owned company in 2000, takes a pragmatic approach to his job. “There is only one real strategy in the pharmaceutical industry,” he said. “Find as many good drugs as possible and bring them to market as quickly as possible. Everything else follows.”

One of the reasons Jean-Paul believes that Actelion can compete in the biopharmaceutical industry is the shared focus of the employees.

“We are all on the same wavelength about our goals and scientific approach – that saves us an incredible amount of time and energy,” he explained. “There is no head of research here. We take those decisions as a team. That way, we also avoid creating layers of bureaucracy. There are no administrators at Actelion. This is a hands-on company.”

While seeing himself as a facilitator in helping the company make key business decisions, Jean-Paul has never lost his passion as a drug hunter.

“There has always been something magic about discovering new drugs, about developing a small pill that can change someone’s life,” he explained. “Being a medical doctor helps me better understand the impact. It’s not an anonymous disease we are treating – it’s a person, a face.”



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# “Real medicines for real diseases in the real world”

**Dr. Thomas Widmann**, Former CEO

In 1996, a small group of researchers and managers at F. Hoffmann-La Roche began to explore the idea of creating a new biopharmaceutical company. They were drawn together not only by the belief in their scientific work, but also by a proven track record in collaboration and a remarkable complementarity of skills. One of the members of this founding group was Dr. Thomas Widmann, Head of Clinical Development in the Cardiovascular Department.

“We were convinced that we could establish a focused biotech company that could work quickly and efficiently in developing drugs for unmet medical needs,” explained Tom. “And we wanted to be in a position to make our own strategic decisions and make them rapidly.”

Tom, born in Germany and educated in his own country as well as in France, Switzerland and California, had always possessed an entrepreneurial streak. While he was working at the University of California, he launched a company for specialized medical devices. In 1996, he had already decided to leave Roche to start a clinical research company, Hesperion, which became an immediate success. This invaluable experience made him the logical choice to be Actelion’s first CEO.

“One of the founding principles of Actelion was and still is mutual respect and a readiness to accept input from others on the team,” said Tom. “We really tried to put our egos on the shelf and always think of what was best for the company.”

One of the first decisions taken was hiring André J. Mueller as Actelion’s Chief Financial Officer. In addition to appreciating André’s background with venture capital, Tom knew it was vital for the new company to have financial discipline.

“Another important source of balance was provided by our Board of Directors,” he added. “Their broad experience in business and pharmaceuticals served as a reality check and helped us make necessary corrections.”

Based on his years of work at Roche and then Hesperion, Tom established a solid clinical development platform at Actelion for testing drug candidates in man.

“A lot of biotech start-ups fail because people fresh from the university are unable to translate scientific concepts into validated processes,” he emphasized. “Without standard operating procedures that can pass an audit by regulatory authorities, you can’t turn great ideas into new drugs.”

Tom’s experience as a cardiologist also played a formative role in his thinking. “Three of the Actelion’s founding members are medical doctors who know what it means to treat sick patients when there is no sufficient therapy available,” he said. “We want to make real medicines for real diseases in the real world.”

# “I absolutely wanted to find out more”

## Dr. Martine Clozel

Head of Drug Discovery, Pharmacology and Preclinical Development

In the summer of 1987, Dr. Martine Clozel, a French researcher in the Cardiovascular Department of F. Hoffmann-La Roche in Basel, came across scientific data that triggered a cascade of events leading to a remarkable discovery. A previously published research paper on porcine cells had suggested that the endothelium, a thin layer of cells lining the inside of blood vessels, did not play a passive role as previously thought, but secreted an active substance with far-reaching consequences.

“The data suggested this was the most potent vasoconstrictor known to science,” explained Martine. “I absolutely wanted to find out more about this substance and see if it was the missing link in heart failure, pulmonary arterial hypertension and a number of other diseases.”

Martine went to her colleague at Roche, the experienced Swiss biochemist Walter Fischli, who immediately shared her enthusiasm for the project. Working hand in hand, they purified the substance in question from the human endothelium and realized they were dealing with a yet undiscovered peptide. Then, in March 1988, a Japanese team beat them to the punch, publishing a scientific paper that identified that new peptide in porcine tissue as “endothelin.”

“We were disappointed not to have been first,” recalled Martine, “but it did confirm our research, so we continued our search in human tissue and began looking for antagonists of endothelin receptors. In a series of papers published in scientific journals, including *Nature*, Martine and Walter were not only the first to describe human endothelin and its corresponding cell receptors but also confirmed that endothelin was the culprit in certain diseases. With the human receptors identified, scientists around the world began to look for molecules that would block the effects of endothelin. The race for a new drug was on.

Fast forward to 1996. After years of intense work, Walter, Martine and her husband and colleague at Roche, Dr. Jean-Paul Clozel, had two drug candidates, bosentan and tezosentan, ready to start clinical trials. The experience had welded the small group into a cohesive, focused team that firmly believed in the potential of their discovery. The Clozels, both medical doctors, were also driven by the potential impact on patients.

When Roche decided not to pursue clinical trials, the idea of founding a new company began to grow.

“To realize our vision, we had to become entrepreneurs,” Martine explained. “We discovered whole new areas of business and administration. It was frightening and stimulating at the same time.

We succeeded because we were able to attract talented people to join us. That made all the difference.”



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# “Seeing my research become a reality”

## **Dr. Walter Fischli**

Head of Drug Discovery, Molecular Biology and Biochemistry

“I remember when Martine came to me in 1987 with surprising data on an unknown substance secreted by porcine endothelial cells,” recalled Swiss biochemist Dr. Walter Fischli, then a researcher at F. Hoffmann-La Roche in Basel. “The implications of a similar system in man were tremendously exciting.”

In 1989, Walter and Dr. Martine Clozel became the first scientists to identify the substance, later named endothelin, in human tissue and successfully located its receptors in human tissue. Their priority then shifted to searching for a molecule that would block these receptors and thus the potent effects of endothelin in constricting blood vessels.

New screening approaches quickly identified such a compound. After more than nine months of intense but unsuccessful chemical work to improve the weak biological activity, there were serious doubts about continuing.

“I was convinced that we would find an answer,” said Walter. “I suppose it was the influence of my professor at Stanford, Avram Goldstein, who was absolutely convinced that it should be possible to find potent compounds for any given receptor or binding site.”

But much more time was needed for chemical optimization to find a compound that also had a measurable effect in vivo. Step by step, more effective molecules were synthesized, with Martine exploring the pharmacological effects of each candidate drug. Her husband, Dr. Jean-Paul Clozel, heading a Drug Discovery group in the Cardiovascular Department at Roche, lent his experience in testing new compounds in disease models and his insights as a cardiologist.

Finally, in December 1991, the first milligrams of bosentan were synthesized by Prof. Henri Ramuz at Roche, but moving this potential drug forward to clinical trials was a long and arduous process. Tezosentan, an ideal compound for intravenous use, was also discovered during this period.

“A lot of scientists spend their whole life in the lab without the satisfaction of seeing their research become a reality,” explained Walter. “I knew we were on the right track with bosentan and tezosentan, so when Jean-Paul approached me in 1996 about starting our own company, I knew it was a once-in-a-lifetime chance.”

Nevertheless, deciding to leave the security of a respected pharmaceutical company was anything but easy for the three scientists. All had senior, well-paid positions and families to support. “Sure, it was frightening at times,” admitted Walter. “But at the deepest level, we were convinced Actelion would succeed. We were experienced drug hunters with a clear vision of a new company that would rapidly discover and develop new products. For that kind of opportunity, it was worth taking some risks.”

# “The right place at the right time”

## **André J. Mueller**

Member of the Business Executive Board and Board of Directors

Few things in business and in life are more important than good timing. Just ask André J. Mueller, a former manager for the Swiss pharmaceutical company Sandoz and Chief Financial Officer for the biotech firm Biogen.

“In the fall of 1997, I met Tom Widmann for the first time at the Geneva airport,” explained André. “He told me about the plans to start Actelion and the urgent task of finding investment capital. Thanks to my network as a founder of one of the first Swiss venture capital funds, I was contacted by the same venture capitalists that had been in touch with him. I suppose you could say that I was in the right place at the right time.”

Working first as a consultant, André was soon persuaded by the four other members of the founding team to come on board as Actelion’s first CFO. His experience helped the company find two critical sources of capital in an initial financing round of CHF 18 million. But for a few critical months before the first payment became available, Actelion did not have the necessary funds to buy laboratory equipment.

“We went to a large Swiss bank for a bridging loan of CHF 400,000 and they turned us down,” André recalled. “A smaller institution, the Basler Kantonalbank, had the foresight to believe in us, and we were in business.”

In addition to his savvy in dealing with bankers and investors, André brought financial discipline to the young company, drawing on his experience at Biogen.

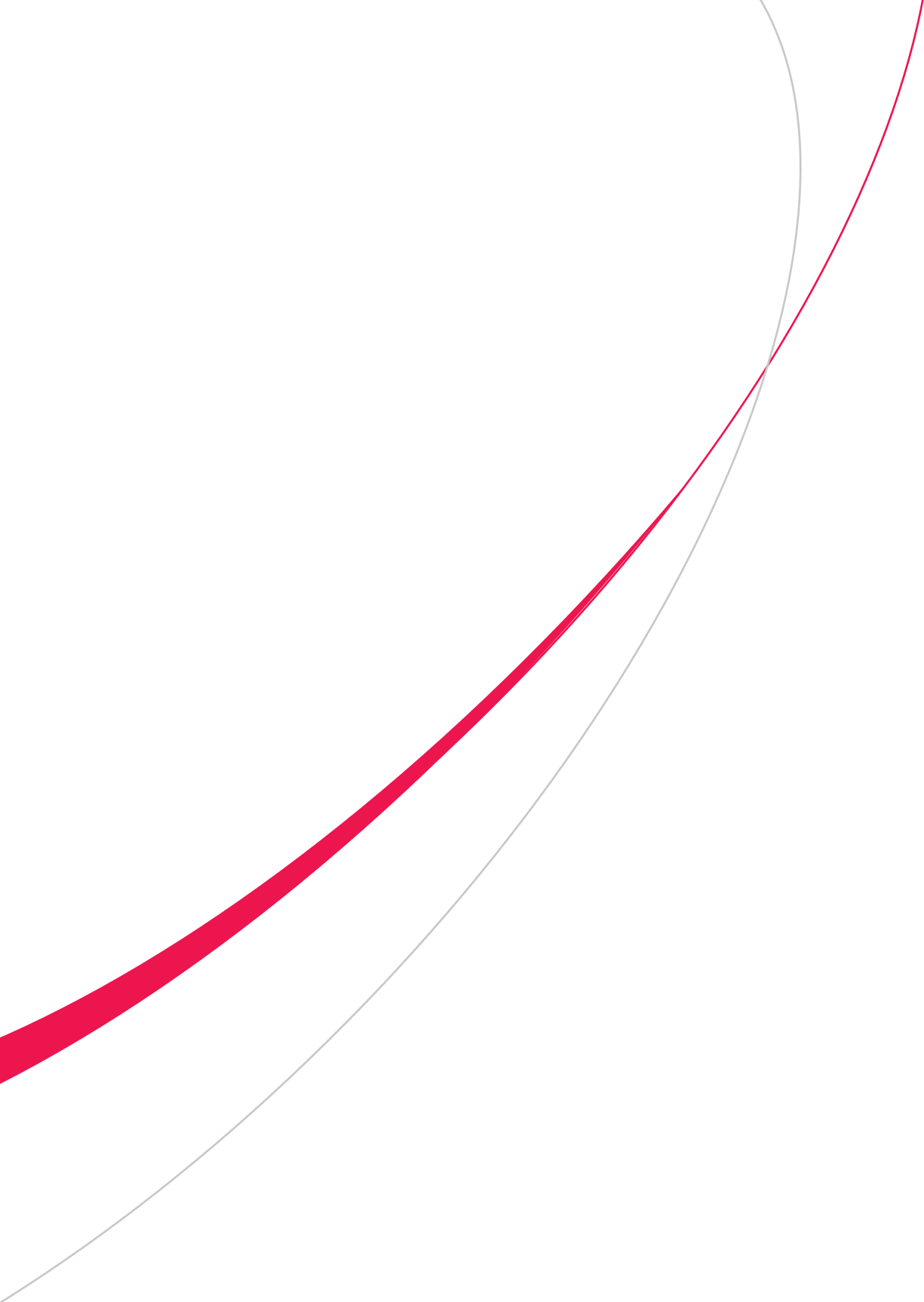
“It’s important to have solid financial reporting on a quarterly basis right from the beginning and to communicate well with the investment community,” emphasized André. “Focus is also a key success factor in a start-up company. Choose the most promising research projects and devote enough resources to realize them, rather than trying to do too many projects, with too few resources for each.”

At the beginning of 2003, after an interim period with another CFO, André turned over the top financial position to Andrew J. Oakley, while continuing to work as a strategic consultant and a member of the Board of Directors. He leaves behind a legacy of a company that is financially sound and respected in the investment community – credit that he insists should be shared with the four other founding members, key members of the Board and Corporate Communications.

“I am optimistic about the future of Actelion,” André concluded. “It has been able to preserve a culture aimed at innovation and bringing solutions to patients with unmet medical needs. The drive of this company is as strong as on the first day.”



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