

Jean-Paul Clozel

When Merck KGaA purchased the Geneva-based giant Serono SA in September, Actelion Pharmaceuticals became Switzerland's largest biotech firm. That capped off a hot streak over which Jean-Paul Clozel—the firm's CEO—has presided since he cofounded Actelion in 1997.

Clozel and Actelion owe their success to a combination of work, timing and geography. The drug that fueled their rise, Tracleer (bosentan), is a treatment for pulmonary arterial hypertension, which affects 145,000 patients in the US and Europe, and the product had sales in 2005 exceeding \$480 million across more than 30 countries. To a degree, the Swiss biotech environment helped propel the drug's global reach, says Clozel, a French cardiologist.

"I really don't think Actelion could have become what it is in another country," he says. "Switzerland is too small to support companies with local sales, so our orientation is global. We're based in Basel, where we border three countries and where a third of the population makes its living from the drug industry. There's a lot of international expertise here."

Clozel and his Actelion colleagues leveraged those resources when they launched Tracleer in 2001. But the story began in the 1980s, when he and his wife, Martine, a pediatrician, were working at the University of California at San Francisco (UCSF). From his spot in UCSF's Cardiovascular Research Institute, Clozel recalls, he watched with admiration the emergence of Genentech and California's biotech industry. "My dream was always to discover new drugs," he says. "All my medical and research training was directed at that one goal."

Clozel recollects that the life-science culture in California seemed "absolutely adapted" to innovation in drug development. But being European, the couple left for Switzerland and both secured research positions with F. Hoffmann-La Roche (Basel). Soon after, while studying thrombosis, Martine began investigating endothelin, which causes severe constriction of blood vessels. It was a Japanese team, led by Masashi Yanagisawa, that determined endothelin's structure in 1988, but Martine made the crucial clinical advance of discovering an endothelin receptor antagonist (ERA). This compound was subsequently developed into a pair of therapeutic small molecules, one of which became Tracleer.

Meanwhile, Clozel led a research team working on inhibiting renin, a hormone-like enzyme that increases blood pressure under certain conditions. But after seeing his wife's discovery, he and a group of Roche scientists, including Walter Fischli and Thomas Widmann, began to focus exclusively on drug development opportunities based on the ERA pathway.

Shortly thereafter, the group split off from Roche to form Actelion, although the pharma firm kept developing the two compounds that Martine had worked so hard to produce. But then, in a stroke of luck, Roche's management suddenly terminated several cardiovascular research projects, thereby liberating the molecules for licensing.

The rest, as they say, is history. Actelion linked up with Andre Mueller, a prior CFO at Biogen-Idex, who helped secure Actelion's initial public offering in 2000, raising CHF1.2 billion (\$960 million). Tracleer, a twice-daily oral medication with an annual, per-patient cost of roughly \$40,000 (less than half the \$100,000 annual cost of competitor Flolan [epoprostenol sodium] from GlaxoSmithKline), entered US markets soon after and grew steadily to dominate the pulmonary arterial hypertension (PAH) market worldwide. Clozel says the company now has several new drugs in its pipeline, the leader being a sleep aid in phase 2 trials that apparently enhances the dream phase, an indication of its advantage over comparable products, he claims.

The pressure for Actelion to diversify is growing, as competitors look to knock Tracleer off its perch. David Luckenbach, a lead analyst with Datamonitor America, says a small molecule called ambrisentan, developed by Myogen (recently purchased for US\$2.5 billion by Gilead Sciences, headquartered in Foster City, CA, USA) is due to enter the PAH market in the US and Europe in the second half of 2007 and 2008, respectively. Luckenbach says the drug offers two advantages over Tracleer at roughly the same price: once-daily dosing, and a lower risk of elevated liver enzymes that indicate toxicity.

"I think, at least in the US, ambrisentan has the potential to pass Tracleer in terms of sales," he says. "But that shouldn't affect sales in the rest of the world, where Tracleer has a huge head start. Other companies chasing that market are going to be playing catch-up for a long time."

In November, Actelion purchased CoTherix, a California-based biopharmaceutical company that manufactures small molecule Ventavis (iloprost), the only inhalable PAH therapy approved in the US. That acquisition helps solidify Actelion's hold on the PAH space and could add more than \$100 million in annual revenue, the company claims.

In many ways, Actelion has its Swiss base to thank for its global presence. John Hodgson, *Nature Biotechnology's* editor-at-large and director of Oxford-based consultancy Critical I, which has studied the European

"All my medical and research training was directed at that one goal" of making drugs, says Clozel.



sector in depth, points out that Switzerland has a population of just 8 million to 9 million people. "They have to be international to be successful," he says. "And then Switzerland offers all the contacts and global infrastructure inherited from their pharma outreach, which is where many of the biotech executives come from."

With 138 domestic biotech companies—an unmatched per-capita concentration—the Swiss life science industry is growing. Hodgson says Switzerland devotes 0.8% of its gross domestic product to pharmaceutical activities, compared with France, Germany and the UK, each of which devote about 0.2%. What's more, the Swiss go about their business quietly, which Hodgson attributes in part to the success of their industry.

Although a lack of finances hinders the global biotech scene, that isn't a problem in Switzerland—the country's per-capita density of millionaires is unmatched worldwide. Hodgson notes that much of the venture capital raised in Switzerland since the turn of the millennium has been invested in a relatively few companies, Actelion being an obvious example. "The companies Swiss investors back, they back well," he says.

Clozel takes a modest view of Switzerland's place in biotech. "We have good companies [here], but our global role is still small," he says. "Hopefully, we're making some gains. It's an incredible adventure to have this job. I feel very lucky to be in this industry."

Charlie Schmidt, Portland, Maine