

## BIOTECHNOLOGY

## arGEN-X BV

### Looking to llamas for potent human antibodies

Tim Van Hauwermeiren, the CEO of arGEN-X BV, is well aware of drugmakers' growing interest in antibody fragments. As business development manager for Ablynx NV from 2003 through 2007, he was part of a team responsible for boosting pharmaceutical industry interest in that company's heavy-chain scaffolds and orchestrating deals around them. Job well done: Ablynx signed numerous deals involving its *Nanobodies* technology platform during Van Hauwermeiren's tenure, with companies including Procter & Gamble, Centocor, Novartis, Wyeth and Boehringer Ingelheim AG buying in. The deals helped Ablynx launch its IPO on the Euronext exchange in November 2007.

These days, as CEO of arGEN-X BV, which is based in Rotterdam but recently opened an R&D facility in Belgium, Van Hauwermeiren is promoting the potential of a technology platform that generates whole antibodies. But why? Who needs solid antibodies, large molecules that must always be injected, when fragments also bind disease targets and can be formulated in many ways, including as oral, inhaled and topical drugs?

This biotech executive believes his company's new *SIMPLE Antibody* platform, which relies on active immunization of llamas, will appeal to pharmaceutical companies that are "under-served" by existing technologies or unconvinced of fragments' potential for potency. The acronym *SIMPLE* stands for *Superior Immunodiversity with Minimal Protein Lead Engineering*. Because no antibody fragments, or "scaffolds" as they are also known, have yet emerged from Phase III trials, some drug industry executives remain reticent

about their potential for clinical success.

"Big Pharma is indeed conservative. Unless they know they cannot fix a clinical problem with a monoclonal antibody, they won't go to a scaffold," Van Hauwermeiren declares. Also, he says, because antibody platform developers in the past often granted partners exclusive rights to work with specific targets, others today are still being thwarted by those "black-outs." Corporate acquisitions of recent years have also blocked access to certain proven whole-antibody platforms, even for those willing to pay.

The discovery platform arGEN-X is developing could let latecomers to popular clinical areas develop monoclonals that don't violate anyone else's patents and won't evoke fat royalty stacks. "We won't license the technology to just anybody who wants it. We plan to build a few deep, strategically compelling partnerships," Van Hauwermeiren declares. Ideally, the company's backers would like to see this start-up acquired outright, for its intellectual property and for a selection of drug candidates the team is preparing now but has no intention of taking into the clinic. "We will stick to what we are good at: running our discovery engine as efficiently as possible," Van Hauwermeiren asserts, adding, "It is not our business plan to invest in manufacturing or clinical trials."

By now, more than 20 years since the first monoclonal antibody won regulatory approval, arGEN-X believes this class of drugs is so well-established and understood that preclinical data alone should attract partners or spur an acquisition. Van Hauwermeiren

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**Contact:** Tim Van Hauwermeiren, CEO

**Business:** Antibody discovery platform

**Founded:** April 2008

**Founders:** Hans de Haard, PhD; Torsten Dreier, PhD

**Employees:** 15

**Financing to Date:** €12.5 million

**Investors:** Erasmus MC Biomedical; Thuja Capital; Forbion Capital Partners; Life Sciences Partners; Crédit Agricole Private Equity; KBC Private Equity; BioGeneration Ventures; Vlaams Instituut voor Biotechnologie (VIB)

**Supervisory Board:** Peter Verhaeghe, LL.M (Vermulst Verhaeghe & Graafsma); Christina Takke, PhD (Forbion Capital Partners); John de Koning, PhD (Life Sciences Partners); Philippe Guinot, MD, PhD (Crédit Agricole Private Equity); Harrold van Barlingen, PhD (Thuja Capital); Johan Cardoen, PhD (CropDesign)

points out that 90% or more of monoclonal antibodies that enter clinical trials pass Phase I tests for safety, so arGEN-X itself will not spend its time and money building capacity that other companies already have.

The *SIMPLE Antibody* platform is the brainchild of Professor Hans de Haard, a co-founder of the company and former senior director of discovery research at Ablynx. He was one of the first researchers to recognize that llamas produce whole antibodies with variable regions almost identical to human antibodies, and to see the potential therein for creating new human therapeutics.

arGEN-X aims to show its technology can yield "multiple gold-standard antibodies" against targets that have proved

troublesome for some conventional mouse-based platforms. Membrane-bound surface proteins are where the company will focus first. “We think our technology is an ideal starting point for cell-surface targets including trans-membrane receptors, because we make use of active immunization,” Van Hauwermeiren asserts.

The company immunizes llamas with cells or cell fragments, then collects blood samples and screens them for antibodies against the injected antigen. The animals are “out-bred,” as opposed to in-bred laboratory specimens. “There are big herds we can access,” Van Hauwermeiren explains, adding, “Europeans think they are really nice animals, like ponies.”

Although llamas are quite far from man from an evolutionary point of view, it turns out that the antibodies they produce are “unbelievably identical in terms of genetic sequence and molecular structure,” he says. The variable region of the antibodies, that is, the portion that actually binds to the antigen, is so close to and often perfectly matching human antibodies that arGEN-X scientists need do little more than swap the constant region of the llama antibody for a human component. Anyone making “human” or “humanized” antibodies in mice does the same, substituting at least the constant region and often engineering the variable region as well, Van Hauwermeiren says.

It’s not only the genetic similarity between llama and human antibodies that distinguishes arGEN-X’s platform, Van Hauwermeiren says. He believes a great deal of the platform’s strength derives from its ability to access functional diversity that inbred laboratory mice do not possess. Just as individual humans mount unique immune responses to antigens, individual llamas also fight infection and disease in their own way. Van Hauwermeiren explains why this unique response is of practical value: “One of our collaborators used a classic mouse model to generate an antibody against a really small target. The molecule did go into the clinic, but there was really no other choice. The mouse model produced only one strong antibody and one weak one.” By contrast, he says, when arGEN-X immunized four llamas with the same antigen, between them “they generated 65 highly potent antagonists, all completely different.” Immunizing more transgenic mice would not have generated more diversity, because all siblings are genetically identical to each other, their parents, their aunts and uncles and grandparents.

“Diversity matters,” Van Hauwermeiren insists, and so too the robustness inherent in molecules produced by a real, live immune system. “One gains confidence by knowing that once there was a B cell that made this antibody and the B cell survived,” he says. He believes antibodies that have been heav-

ily manipulated in vitro to enhance target binding are “more difficult to manufacture and more risky as drug candidates.”

arGEN-X aspires to build a preclinical portfolio of antibodies, and to that end Van Hauwermeiren says the company will be “validating the platform with targets that ring bells.” He declines to share any details of his “very appealing lead project,” however, because the company has yet to file patents on its discoveries.

For now, Van Hauwermeiren and other members of the management team are busy talking to drug developers of all kinds and sizes, those that already have antibody platforms in-house as well as those that have come late to the game and are still looking for basic technology. The concept of functional diversity is resonating well with everyone, he says, but the deep partnerships arGEN-X seeks will be struck only with those who appreciate this company’s value proposition.

To date, arGEN-X has raised €12.5 million from investors including Erasmus MC Biomedical, Thuja Capital, Forbion Capital Partners, Life Sciences Partners, Crédit Agricole Private Equity, KBC Private Equity, Bio-Generation Ventures, and Vlaams Instituut voor Biotechnologie (VIB).

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—DEBORAH ERICKSON