

BIOTECHNOLOGY

Crescendo Biologics Ltd.

Aiming to optimize antibody fragments

Over the past two decades, therapeutic monoclonal antibodies have taken a proud place within the pharmaceutical armamentarium. Some 30% of all drugs marketed today are members of this biological class, together generating over \$32 billion in annual sales. Given the success of therapeutic antibodies, it's not at all surprising that many, many companies have been looking for ways to make them better, faster, or cheaper.

Crescendo Biologics Ltd. is one of a growing number of outfits seeking to develop antibody fragments, which in theory will combine the virtues of now-conventional monoclonal antibodies with the charms of small molecules. Antibodies work as well as they do because they are biological compounds created by the immune system to find and bind specific antigens. Scientists have figured out various methods for making therapeutic antibodies, and companies owning those key technology platforms have made fortunes by broadly licensing the methods. But regardless of the means of manufacture, therapeutic antibodies are prized for their ability to recognize and tightly bind to antigens or "targets" such as proteins expressed on the surface of tumors. The bound targets thus become marked for destruction by the patient's own immune system, and sometimes antibodies also carry radioactive payloads designed to wipe out their target. For all their power, monoclonal antibodies have some drawbacks as drugs: manufacturing biologicals in living animals and cells is far more expensive than stirring

up a batch of chemicals. Also, antibodies are large molecules that need to be given by injection or infusion and thus are much less convenient than pills, topical gels or inhalation therapies.

Scientists and clinicians alike are hoping that antibodies can be trimmed down to fragments that will still hit their desired targets, but that will be able to be manufactured inexpensively and delivered to the body without needles. Some organizations, like **Micromet Inc.** in Munich with its *BiTE* platform, are betting that antibody fragments can be "bi-specific": binding targets and also rousing T cells to action. Although firms large and small presently have antibody fragments in preclinical and clinical testing, as yet none of these drug candidates has passed the final hurdle: generating Phase III data proving fragments can help or halt disease in humans.

Crescendo Biologics is betting it can gain commercial advantage over the many companies competing in this space from a pair of antibody-oriented technology platforms invented at **Babraham Institute**, an institute of the Biotechnology and Biological Sciences Research Council (BBSRC) in Cambridge, UK. Crescendo was founded in December 2008, and its six employees are currently occupying offices on the Babraham campus. As yet the company has no CEO, but its CSO Mike Romanos emphasizes that he had the opportunity to see and test a variety of antibody discovery technologies while holding senior research positions at Glaxo SmithKline PLC.

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Business: Antibody fragment technologies
Founded: December 2008
Founder: Michael Romanos
Employees: 6
Financing to Date: £4.5 million
Investors: Sofinnova Partners; Avlar BioVentures Ltd.; Rainbow Seed Fund; Aitua Ltd.
Board of Directors: Graziano Seghezzi (Sofinnova Partners); Alan Goodman (Avlar BioVentures Ltd.)

"Our whole focus is on single-domain antibodies and in particular VHs, or heavy-chain antibodies, which we intend to generate in transgenic mice." The fragment-production technology Crescendo seeks to leverage was developed at the Babraham Institute by Marianne Brüggemann, PhD, credited along with Michael Neuberger, PhD, for creating the first "human" antibody in a transgenic mouse. The research that gave rise to the intellectual property that Crescendo has in-licensed attracted funding support as far back as the 1980s from British government entities including the Medical Research Council (MRC) and AFRC, the forerunner of BBSRC. Key elements of the work were first published in 1989, but Crescendo's investors feel the time is now ripe for it to be put to commercial use—likely at least in part because in the wake of patent expiry, licensing fees can no longer be imposed on the technology.

The Crescendo platform that originated in Brüggemann's lab centers on mice that have had three of their native genetic loci

involved in antibody production functionally deleted, to make room for human versions. Other antibody developers, including Medarex, acquired in July 2009 by Bristol-Myers Squibb Co., have relied on a similar maneuver to make their patented transgenic animals produce human antibodies. But Romanos believes Crescendo's method for removing all three loci is "a unique asset," as is the company's method for transferring into the mice human DNA coding for human heavy-chain IgG, or immunoglobulin gamma.

Romanos maintains there are a number of design features in the human DNA constructs Crescendo makes that are "important," but he declines to explain what these are other than to say that swapping mouse genes for human ones involves stitching together large pieces of DNA. Given the nature of the task, it's not surprising that Crescendo is "working with experts on YAC construction." Researchers involved early on with the Human Genome Project relied heavily on yeast artificial chromosomes, or YACs, to help them assemble contiguous segments of DNA in proper order.

Romanos anticipates that the YACs and transgenic animals Crescendo presently has will give rise to "improved animals which we believe will yield class-leading human VH antibody fragments." While other outfits are also working to make human IgG fragments lacking the so-called light chain found in native human antibodies, Romanos is betting that producing fragments in a living animal's B cells will result in more potent therapeutics than, say, fragments assembled in vitro. He says, "Because of the way our fragments come into being, we think they will function properly, as high-affinity antibodies that can also be selected for solubility."

Like every other would-be drug developer, Crescendo is seeking ways to optimize its initial drug candidates. Romanos believes the second technology platform in-licensed from Babraham can help with this aspect of the company's challenge. Michael Taussig, PhD, and Mingyue He, PhD, experts in protein display and array

systems, are credited as the inventors of the platform Crescendo has licensed. Taussig and He have authored many publications about display technology.

Romanos says Crescendo is pleased to have rights to a ribosome-display technology that promises to allow creation of "an enormously diverse library of antibodies, entirely in vitro." Long-established antibody companies including Cambridge Antibody Technology Ltd. (CAT) and Med-

Immune LLC, now part of **AstraZeneca PLC**, already utilize ribosome expression systems based on prokaryotic cells, but Crescendo is banking on one that leverages eukaryotic cells. Both methods share similarities with and arguably proceed from the phage-display technology that CAT pioneered and protected with a network of patents.

Proponents of ribosome-display technologies appreciate that the method allows individual proteins (phenotypes) to be linked physically to their corresponding mRNA (genotypes) in stable protein-ribosome-mRNA complexes. These complexes can then be screened en masse, to see which bind best to a given target. The protein, in

this case the antibody fragment, is what binds to the antigen, but in this kind of system the stand-out binder comes conveniently attached to its coding sequence. "Because you have the RNA in hand, you also have the DNA in hand for the best binding sequence," Romanos declares. From there it's easy to make new iterations, test *their* binding affinity, and so speed a fragment's evolution as a drug candidate.

"We think it's great to have this combination of in vivo and in vitro platform technologies." Romanos asserts: "With a potent optimization technology, we can maximize the value of the antibody fragments created in transgenic animals." He says Crescendo plans to spend "the next two years or so" working in-house to improve its transgenic mice and optimizing the ribosome-display technology for single-domain antibody fragments. Once the platforms are optimized, the company will seek strategic partnerships to maximize their value.

Two years from now, the first wave of antibody fragments could be emerging from their final clinical trials. If and as fragments start making their way to market, Romanos believes Crescendo will be well-positioned to ride the wave. By then, the start-up could have some preclinical candidates of its own ready to move into human trials. Just as good and arguably better, Crescendo could also license the platforms it is now perfecting to drugmakers that have been holding back, waiting to see if antibody fragments actually can become successful drugs.

To date, Crescendo has raised £4.5 million from investors including Sofinnova Partners, Avlar BioVentures Ltd., Rainbow Seed Fund and Aitua Ltd.

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—DEBORAH ERICKSON

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