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Emerging Company Profile

Crescendo: Best of both fragments

By Stephen Hansen
Staff Writer

Crescendo Biologics Ltd. believes its transgenic mouse antibody fragment technology combines the best characteristics of the two leading antibody fragment platforms — human origin and *in vivo* maturation — which should allow rapid creation of high affinity fragments. The company hopes to have clinical proof of concept (POC) in about three years.

“The core advantage of our Crescendo mouse over domain antibodies or Nanobodies is that it’s human and it’s matured *in vivo*, with all the advantages that gives in terms of maturation to high affinity and good solubility properties,” founder and CSO Mike Romanos told BioCentury.

Domain antibodies (dAbs) are human antibody fragments created by the Domantis Ltd. unit of **GlaxoSmithKline plc** using phage display. These molecules are human, but according to Romanos require optimization to improve their affinity and solubility because phage display is an *in vitro* system that does not incorporate maturation.

Ablynx N.V. is developing Nanobody therapeutics, which are camelid-derived Fab fragments expressed in llamas. While these have the advantage of *in vivo* matu-

Crescendo Biologics Ltd.

Cambridge, U.K.

Technology: Transgenic mouse antibody fragment technology and ribosome display technology

Disease focus: N/A

Founded: 2008 by Mike Romanos

University collaborators: Babraham Institute

Corporate partners: None

Number of employees: 6

Funds raised: £4.5 million (\$6.7 million)

Investors: Sofinnova Partners; Aitua; Avlar BioVentures; Rainbow Seed Fund

CEO: None

Patents: 5 issued patent families covering the creation and use of a light chain knockout mouse to make human heavy chain antibodies; yeast artificial chromosomes (YACs) for transgenesis; evolution of proteins in a eukaryotic ribosome display library; ribosome display process improvement based on single-primer PCR; and YACs that improve transcription in human constant region of immunoglobulin heavy chain

ration, they require humanization, a process that has the potential to reduce the affinity of the fragment, Romanos said.

Using a transgenic mouse licensed from the **Babraham Institute**, Crescendo is able to produce human antibody fragments that are matured *in vivo*. The mice are created by replacing three regions in the mouse chromosome that control antibody production with a yeast artificial chromosome (YAC) that is engineered to express human heavy chain antibodies.

The antibodies mature naturally *in vivo*, which gives them high affinity and solubility. The heavy chain antibodies then can be isolated, and the variable (VH) fragments cleaved off.

Crescendo also licensed Babraham’s ribosome display platform, which can be used to analyze and further optimize the VH fragments. The technology takes DNA clones from the VH fragment and, after cycles of mutagenesis, produces millions of variants. Variants with the highest affinities can then be selected.

Romanos said ribosome display is useful for analyzing the VH fragments and identifying antigens that the fragments bind.

He said Crescendo can go from immunization to a lead VH fragment in as little as nine months: up to six months to

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produce the VH fragment, and another three to six months for optimization using ribosome display, if required.

“If the transgenic mouse is working in the best possible way, we won’t need the ribosome technology to optimize the VH fragments. But, pragmatically, there is usually an opportunity to improve things further,” Romanos said.

Like other antibody fragments, Crescendo’s VH fragments have a short half-life and lack an effector function. Thus the company will evaluate modification technologies such as pegylation or creation of bi-specifics with a heavy chain constant region.

While Romanos acknowledged that modifying the VH fragments would add time to the development process, he said all antibody fragments require some form of modification for therapeutic use.

Crescendo hopes to raise £20-£30 million (\$29.6-\$44.4 million) in a series A round next year to refine the technologies and get at least one program into the clinic. Romanos said the plan at this early stage is to build the company, although the most likely exit in the antibody space is via acquisition.

“Probably three more years would see us in the clinic. So that could be the kind of time we could see an exit,” he said.

COMPANIES AND INSTITUTIONS MENTIONED

Ablynx N.V. (Euronext:ABLX), Ghent, Belgium

Babraham Institute, Cambridge, U.K.

Crescendo Biologics Ltd., Cambridge, U.K.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.