Crescendo Biologics

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Humabody fragments:
Small and perfectly formed

Crescendo Biologics is poised to significantly impact the world of antibody therapeutics with the enormous potential of its Humabody technology and its product-discovery and engineering capabilities.

Monoclonal antibodies represent a hugely important advance in treating life-threatening diseases, heralding new options for many patients. However, new antibody-based formats and products are required to address the medical needs currently not satisfied by treatment with full-length antibodies.

Single-domain \(V_n\) fragments, the smallest antibody fragments that retain the ability to bind antigens specifically and with high affinity, fulfill this requirement. Their properties, compared to whole antibodies, are more akin to those of small molecules, but they have the specificity of monoclonal antibodies, thereby making them highly attractive therapeutic agents.

Until now, \(V_n\) fragments have been generated in llamas or selected from phage display libraries in the lab. Clinically validated, llama-derived \(V_n\) fragments cannot be fully humanized, and human \(V_n\) fragments selected in vitro frequently have suboptimal biophysical properties, causing aggregation that limits their utility for drug development.

Humabody therapeutics

Enter Humabody \(V_n\), robust, fully human \(V_n\) fragments derived from the Crescendo Mouse that bind antigens with a high affinity. Their simplicity, small size and relative ease of manufacture make them attractive, efficient and relatively low cost. The small size and potential for multivalent engineering means that Humabodies are leading to the development of multifunctional products and products with increased tissue and tumor penetration. Other applications include topical and locally active therapeutic biologics.

Through a tour de force of molecular engineering, Crescendo has developed the Crescendo Mouse, a transgenic mouse that produces heavy-chain-only antibodies with fully human \(V_n\) domains in a background devoid of mouse antibodies—a breakthrough in antibody-fragment technology.

The Crescendo Mouse uniquely combines the benefits of producing fully human \(V_n\) fragments with in vivo maturation through the natural process of B-cell development. The key to the platform is its unique triple-knockout (TKO) background, which is completely devoid of endogenous immunoglobulin chains. This characteristic is critical to eliminating light-chain contamination. B-cell development in the Crescendo Mouse is driven from a construct introduced into the TKO background that combines human V, D and J genes with murine constant and regulatory regions to generate high-affinity heavy-chain antibodies (Fig. 1).

As a result, when immunized with target proteins, the Crescendo Mouse yields single-domain \(V_n\) fragments (Humabody \(V_n\)) of exceptional diversity from all human \(V_n\) gene families. In vivo maturation naturally optimizes the potency and biophysical properties of the Humabodies, which do not require subsequent humanization.

Importantly, each mouse yields nonoverlapping diversity. Unlike in other approaches, this diversity can be increased, significantly and easily, through the immunization of multiple mice under different conditions.

Using Crescendo’s expertise, a rapid and efficient process for mining and developing Humabody products from the mouse has been developed. “Mining by phage display means that, in contrast to hybridoma-based screening, we can be confident of capturing the full diversity generated by each mouse,” explained Mike Romanos, Crescendo’s CEO. “Crescendo’s innovative approach means that, in as little as three months from start of immunization, a panel of candidate-quality leads can be identified.”

Humabody \(V_n\) fragments isolated from the Crescendo Mouse are extremely developable, simple to manufacture in microbial systems at low cost and require no humanization.

Highly versatile, Humabodies enable a wide range of product opportunities (Fig. 2). The small size of ‘naked’ Humabodies (12 kilodaltons (kD) versus 150 kD for antibodies) gives them superior tissue-penetration characteristics, making them ideal for oncology applications as well as topical and systemic delivery. Crescendo has the capability to readily engineer them into multivalent formats with excellent biophysical and production properties: Humabody \(V_n\) fragments can be linked in various ways to form multivalent binders, T-cell engagers, antibody-drug conjugates (ADCs) and multivalent checkpoint inhibitors, or to extend drug half-life.

Crescendo is leveraging these advantages to generate high-value differentiated Humabody medicines and products through its in-house pipeline focus on dermatology and oncology and through strategic partnerships.

First topical biologic—psoriasis

The size, robustness and relatively short half-life (5–7 hours) of Humabodies make them ideal for topical delivery to the skin, eye, lung and gut. Crescendo’s lead product, CB001, is a cutting-edge topical biologic in development for psoriasis. The disease affects 125 million people worldwide, with a large and rapidly growing market expected to reach $6.7 billion by 2018. Injectable monoclonal antibodies targeting interleukin-17A (IL-17A) are highly effective for the minority of patients with the most severe disease, but they are expensive and, acting systemically, present safety concerns for long-term therapy. Existing topical therapies, the cornerstone of therapy for psoriasis, are poorly effective and have unacceptable, treatment-limiting side effects. A clear unmet need exists for new topical drugs that have the efficacy of monoclonal antibodies but a better safety profile.

Whereas monoclonal antibodies cannot penetrate skin, a rigorous study undertaken by Crescendo shows that Humabody \(V_n\) in contrast, can be delivered efficiently into the skin. Capitalizing on this and the proven efficacy of the IL-17–targeting monoclonal antibodies, the company is developing CB001, a highly potent IL-17A antagonist designed to be a safe, topical drug for mild to moderate psoriasis. Combining the...
potency and specificity of systemic monoclonal antibodies with the potential for a benign side-effect profile suitable for chronic use, CB001 is likely to be transformative for the majority of psoriasis patients while significantly reducing healthcare costs. Clinical proof-of-concept data for CB001, which would be the first topical biologic on the market, is anticipated in 2016.

CB001 pushes the boundaries of current science and technology and opens the door to dermatological applications in other major areas of unmet need, such as atopic dermatitis, which affects up to 3% of adults worldwide.

**Multivalent products**

There is increasing recognition of the advantages that small biologics have in tumor penetration, resulting in potential improvement in therapeutic efficacy and safety. At the same time, there is growing demand for product modalities with multiple functions. Humabodies, with superior biophysical properties that make them highly amenable to modular engineering, address both of these needs (Fig 3).

Through its oncology pipeline, Crescendo is exploring bispecific T-cell engagers. Such biologics have demonstrated excellent clinical efficacy and are of high interest as novel cancer treatments, but there have been significant engineering challenges to producing them elsewhere. The superior biophysical characteristics of Humabody Vₕ will enable Crescendo to create products that bind T cells and multiple tumor targets concurrently for greatly increased efficacy and tumor specificity.

Through collaboration, Crescendo is also exploring next-generation ADCs, Humabodies linked to a cytotoxic payload of drugs or radioisotopes. Because Humabodies are so small, they not only target and penetrate solid tumors rapidly but also are cleared swiftly from systemic circulation by kidney filtration. This results in a high tumor-to-blood ratio and the potential for reduced systemic side effects, thereby enhancing therapeutic index and facilitating continuous high dosing. “Humabodies have real potential in this dynamic field,” said Romanos. “Although this work is at an early stage, we’re very excited.”

Another area ideally suited to Humabody products is that of checkpoint inhibitors, a particularly promising class of immunotherapeutic agents aimed at reengaging the body’s immune system to recognize and destroy a range of tumor types. There is enormous excitement around these molecules, which represent a potentially curative oncology treatment.

Checkpoints in our immune system are important in containing the immune response to protect the body from attacking itself. However, many cancers actively corrupt these checkpoints to avoid immune detection. Checkpoint inhibitors overcome this by modulating the activity of T cells by taking the brakes off or ramping up their activation. Checkpoint inhibitors antagonizing single targets to date (CTLA-4 or PD-1) have been successful in some patients but have had many adverse effects. Crescendo is leveraging the advantages of Humabody Vₕ and its expertise in engineering multivalent products with the aim of exploring and developing multivalent checkpoint inhibitors that block several targets simultaneously, potentially increasing both therapeutic efficacy and safety. In December 2014, Crescendo received additional funding enabling it to do just that—recognition of the potential of the Humabody approach to develop best-in-class therapeutics in this field. “We are now in a strong position to discover and develop high-value, innovative immune checkpoint product candidates within our in-house pipeline leveraging the unique advantages of Humabodies,” said Romanos.

Additionally, for systemic applications requiring a longer half-life, Crescendo can make use of Humabodies that bind to human serum albumin (HSA). In addition to conferring long half-life after injection, binding HSA has the extra advantage of concentrating products at sites of inflammation and in tumors, providing additional drug selectivity.

Combining the huge potential of Humabody technology with the company’s product-discovery and engineering capabilities to enable topical, systemic and multivalent products, Crescendo will significantly impact the world of antibody therapeutics.

### Partnering strategy

Through partnership opportunities, Crescendo will apply its discovery and development capabilities to a partner’s targets in discovery collaborations to generate leads, preclinical or investigational new drug (IND)-ready clinical candidates. This can be achieved quickly through a customized program to develop the best products. The company is also open to licensing its own pipeline programs through strategic partnerships, including its development candidate in psoriasis and its oncology programs (particularly ADCs and checkpoint inhibitors).

“We can leverage the advantages of Humabodies to rapidly generate multiple different molecules and thereby probe design space for optimal therapeutic products,” explained Romanos. “We are eager to explore and fully realize the potential of Humabody technology through collaborative partnerships.”

Crescendo Biologics, based in Cambridge, UK, was founded in 2009 around seminal intellectual property from Marianne Brüggemann, pioneer of transgenic antibody technology. The company, which has assembled management and scientific teams with exceptional industry experience, is backed by a consortium comprising Sofinnova Partners, Imperial Innovations, Astellas Venture Management and EMBL Ventures.

**CONTACT DETAILS**

Brian McGuinness, Vice President, Discovery
Crescendo Biologics
Cambridge, UK
Tel: + 44 (0)1223 497142
Email: bmi@crescendobiologics.com

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**Figure 3: Product opportunities.** Crescendo’s Humabody platform yields multiple high value product opportunities in different disease indications through its in-house pipeline and strategic partnerships.

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