Crescendo Biologics
www.crescendobiologics.com

Developing differentiated, multifunctional immuno-oncology products

Attracting the interest of large biopharma companies, the Crescendo Biologics Humabody platform and product candidates are targeting immuno-oncology and beyond.

Crescendo Biologics is an innovative biotech company developing drugs for the clinic in-house while also forming a small number of strategic partnerships to deliver novel products into partner pipelines. Underpinned by a gold-standard transgenic mouse platform, Crescendo has established a pipeline of multifunctional Humabody-based oncology products that are capable of dual-target blockade and targeted immuno-oncology (IO) modulation and are optimally configured to engage targets for maximum therapeutic benefit by driving novel biology.

The proprietary Crescendo mouse platform generates Humabody building blocks. These small, highly diverse and exceptionally stable molecules are made up of fully human antibody heavy chain variable (V_H) domains that mature *in vivo*, thereby optimizing their potency and biophysical properties. The superior biophysical properties of Humabodies stem from the fact that the Crescendo mouse is deficient in all antibody light chains. This means the mice act as natural filters for V_H domains that are stable in the absence of a partner light chain.

Comprising constructs containing more than 20 V-genes covering all the human germline families, the Crescendo mouse delivers a diverse array of Humabody building blocks that the company can configure into an almost limitless range of multifunctional molecules. Such molecules are capable of simultaneously engaging multiple therapeutic targets and mechanisms of action, thereby accessing novel biology. Crescendo's technology lacks the constraints of traditional monoclonal antibodies, enabling the assembly only of what is required in a molecule to achieve maximal therapeutic benefit from optimal target engagement. Humabody-based therapeutics are therefore highly differentiated molecules (**Fig. 1**).

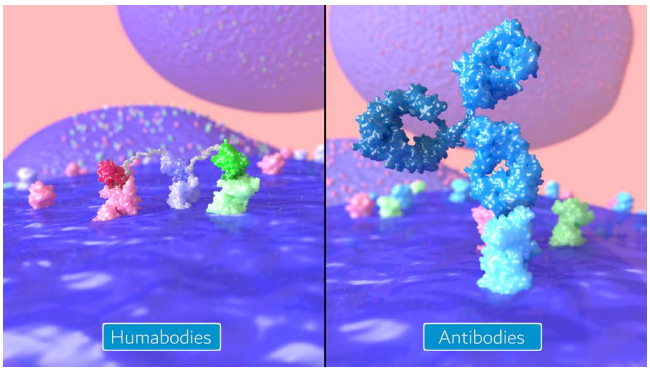

Figure 1: Humabody characteristics. These stable molecules are optimally configured to engage therapeutic targets.

Moving toward clinical trials

Crescendo is planning to take two proprietary Humabody product candidates into clinical trials and to out-license an additional two programs earlier.

The first of Crescendo's proprietary programs is a PD1–LAG3 bispecific Humabody. The immune-checkpoint receptors targeted by the Humabody collaboratively regulate T cell activity to help tumors evade the immune system. PD1 antibodies such as Merck's Keytruda (pembrolizumab) have shown the power of disrupting one component of this regulatory process in some patients. However, other patients show no response or show initial responses that are not durable. Crescendo's bispecific molecule targets both components simultaneously to drive dual-checkpoint blockade in highly exhausted T cells expressing both targets in a way that simply combining monospecific monoclonal antibodies is unable to achieve.

Crescendo's second proprietary program in development is in the area of targeted IO. The lead molecule is a bispecific Humabody targeted to tumors that express PSMA, a transmembrane protein important in prostate cancer and other solid tumors. Designed to deliver highly potent T cell costimulatory activity only in the tumor microenvironment (TME), this molecule rapidly accumulates in tumors, activating tumor-specific T cells in the TME but clearing quickly from systemic circulation. Costimulatory activity is therefore localized to the TME, resulting in maximum therapeutic effect with minimum systemic exposure and thus reducing potential toxicity.

Already, data from this exciting approach suggest that the targeted costimulatory molecule has potential as a platform in its own right. Crescendo can use different tumor markers to target this potent mechanism to cancers with high unmet medical need.

Crescendo is also working on two programs that it will out-license after candidate nomination.

One of these candidates is a PD1–PD1 biparatopic molecule. The way this asset engages PD1 sets it apart from standard bivalent monoclonal antibodies. Crescendo's molecule 'handcuffs' PD1: one domain binds and blocks PD1 from engaging with its ligands, while the other binds a nonblocking epitope on the other side of the PD1 molecule.

This mechanism gives the molecule high avidity and very specific localization to PD1-expressing cells, resulting in a highly potent product that drives novel biology *in vitro* and efficacy *in vivo* in models that are insensitive to marketed antibody PD1 antagonists.

The second program that Crescendo plans to out-license is a PSMA-targeted Humabody–drug conjugate (HDC). HDCs eliminate many of the problems associated with antibody–drug conjugates. HDCs deliver latest-generation small-molecule payloads very efficiently into tumors and clear rapidly from circulation, which substantially enhances their therapeutic index. Crescendo will develop further HDCs solely as deliverables for strategic partnerships.

Partnering the platform

The characteristics of Humabodies have attracted the interest of large biopharma companies. Last year, Crescendo and Takeda Pharmaceuticals—through its subsidiary Millennium Pharmaceuticals—entered into a $790 million multitarget collaboration and licensing agreement. Crescendo is using its transgenic platform to discover and configure IO modulators and HDCs against targets chosen by Takeda.

Crescendo is now looking to enter into a limited number of additional strategic collaborations. These deals will further validate Crescendo's platform and put novel, differentiated products into the pipelines of its partners. Crescendo would be happy to discuss potential collaboration opportunities with interested parties in both IO or other therapeutic areas with a view to building value for both parties.

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