

Applying a versatile, innovative platform to oncology

With its unique Humabody technology platform, Crescendo Biologics is poised to become a significant player in the rapidly progressing immuno-oncology field.

Crescendo Biologics—backed by blue-chip investors including Sofinnova Partners, Imperial Innovations, Astellas Venture Management and EMBL Ventures—is at a pivotal moment in its evolution. The UK biopharmaceutical company made the strategic decision in mid-2015 to focus its drug discovery and development efforts entirely in the oncology space and is now busy building and evaluating an exciting pipeline of highly differentiated therapeutics based on its proprietary, robust Humabody V_H domain technology platform (Fig. 1).

Owing to the exceptional characteristics of Humabody V_H , the team at Crescendo is able to rapidly create an almost limitless number of multispecific constructs. The company can use these to efficiently explore and identify optimal formats for engaging therapeutically valuable targets in a way that is fundamentally different than those using whole antibodies.

Using just this approach, Crescendo is pursuing novel product opportunities, through both in-house development and strategic partnerships in both multispecific immuno-oncology modulators and HDCs (Humabody Drug Conjugates). Humabody formats are set to establish a valuable new class of high-value therapeutics to address substantial unmet medical need.

Crescendo's technology platform is centered on a unique and proprietary transgenic mouse. Using this platform harnesses the benefits of *in vivo* maturation, thereby naturally optimizing the affinity and biophysical properties of Humabodies. Compared with monoclonal antibodies, Humabodies offer a unique combination of benefits owing to their small size and cost-effective production, as well as Crescendo's modular 'Plug & Play' engineering options for generating novel bi- or multispecific formats.

Highly differentiated products in immuno-oncology

Immuno-oncology is an enormously exciting area for the development of new, innovative cancer therapies. Crescendo is developing next-generation immuno-therapies with broad applicability across a range of oncology indications with the aim of re-engaging the body's immune system to recognize and destroy cancer cells.

The company aims to build on the groundbreaking clinical studies with checkpoint inhibitors such as Yervoy (ipilimumab), Opdivo (nivolumab) and Keytruda (pembrolizumab). These products have demonstrated that, by unleashing the power of the immune system, it is possible to achieve durable responses (many of which are now considered 'cures') for a subset of patients in key cancer indications. Importantly, the response to a combined blockade of

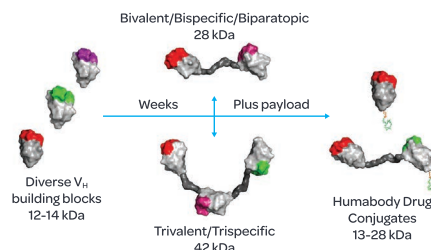


Figure 1: Efficient formatting for differentiated Humabody products.

cytotoxic T lymphocyte-associated antigen 4 (CTLA4) plus programmed cell death protein 1 (PD1) is greater than that to either monotherapy alone, but the proportion of patients and range of tumors that respond to such a checkpoint blockade is still low. Crescendo's goal is to improve on first-generation immune modulators such as these by finding new molecules to increase the number of patients who respond.

The Humabody platform is enabling the team at Crescendo to rapidly engineer highly effective product 'building blocks' targeting a range of key mechanisms in the cancer immunity cycle. These include 'releasing the brakes' on the immune response (blocking inhibitory signals), 'pressing the gas pedal' on the immune response (activating stimulatory pathways), as well as enhancing antigen presentation and inhibiting the immunosuppressive tumor microenvironment.

By leveraging the advantages of the Humabody format, along with substantial in-house expertise in engineering multispecific products, Crescendo is able to rapidly explore numerous multispecific combinations of building blocks in a highly flexible manner. This approach offers a unique way of unlocking new biology through simultaneous engagement of multiple synergistic pathways. Many opportunities such as these are inaccessible to larger, bulkier antibodies (which are sometimes difficult to engineer and develop). Instead, they are ideally suited to the smaller and more flexible Humabody formats, which permit multi-target engagement over a broader range of 3D space.

Crescendo is open about its interest in targeting PD1, but the company is also exploring a range of novel formats (including tumor-specific targeting of immune modulation) with a view to maximizing therapeutic efficacy and product differentiation. The company has already demonstrated that Humabodies are capable of very efficient tumor penetration, maximizing their ability to access the tumor microenvironment where reactivation of T cells that are capable of attacking the tumor is most needed. The serum half-life of all constructs can also be extended by the

addition of a human-serum-albumin-binding domain to optimize treatment scheduling.

Altogether, this combination makes for an extremely efficient, highly selective approach to identifying and delivering exceptionally potent tumor-killing drugs.

Potential for partnerships

At a time when the field of cancer therapy is moving forward at an increasingly rapid pace, Crescendo is firmly focused on establishing itself as a prominent player in the space.

The team is creating a pipeline of novel, highly differentiated in-house assets but makes it clear that there are many additional opportunities that the company is able to pursue in partnerships where the Humabody format would offer substantial benefit.

In particular:

- Mono- and multispecific Humabody constructs would be ideal targeting elements for chimeric antigen receptor (CAR) T cells. The stability of the Humabody format, in which the alternative targeting agent is usually a single-chain variable fragment, which are notorious for unfolding and aggregation, would enhance targeting specificity, facilitate coverage of antigen escape and reduce the potential for nonspecific T cell activation.
- Humabody constructs are ideal immunomodulatory payloads for delivery by an oncolytic virus. Local delivery of Humabody coding sequence for expression directly in the tumor microenvironment with rapid clearance from the systemic circulation owing to its small size would be highly beneficial for maximizing potency and minimizing systemic side effects.

Crescendo is interested in establishing a highly selective portfolio of strategic collaborations with key partners and would be delighted to discuss areas of potential common interest in the oncology space from which to build value for both parties.

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