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Transformative bispecific antibody technology

F-star is developing a promising pipeline of immuno-oncology therapies with its innovative bispecific antibody technology, which is ideally suited to uncover novel combinatorial biology.

Recent advances in immuno-oncology research have led to new therapies that leverage the power of the body's natural immune response to fight cancer. Rather than targeting tumors directly, such therapies aim to redirect and focus the immune system to destroy cancer cells through the blockade of immune-system inhibitory signals, the activation of stimulatory pathways, or both. Immuno-oncology therapies may also fight a targeted, tissue-specific battle by identifying cancer cells and recruiting the immune system to eliminate them. More recently, emerging clinical data have demonstrated the advantages of combining immuno-oncology agents, such as Opdivo (nivolumab) and Yervoy (ipilimumab), and attention is therefore increasingly turning to combination therapies.

Another option, however, is to use bispecific antibodies, which are capable of binding to two different targets concurrently, thereby inducing novel biological effects. The advantages of bispecifics over traditional monoclonal antibody technologies include the potential to target therapeutics to particular tissues, as well as the ability to mobilize additional arms of the immune system to fight cancer at the site of a tumor and to cross-link cell-surface receptors to invoke novel biology with powerful therapeutic potential[1]. Bispecific antibody products also have the potential to induce more than one immunotherapy mechanism simultaneously, with a synergy that is not possible with the co-administration of two separate drugs. Finally, bispecifics may offer cost-saving alternatives to combination therapy.

F-star is an immuno-oncology-focused biopharmaceutical company that is using its powerful platform and drug discovery capabilities to develop a promising pipeline of bispecific antibody candidates. "We are developing a large number of bispecific antibodies in the immuno-oncology space to explore and uncover those bispecific products with unique features and novel biology compared with combinations of individual antibodies," said John Haurum, CEO at F-star. The company was founded in 2006 on the basis of the work of Professor Florian Rüker at the University of Natural Resources and Life Sciences (BOKU) in Vienna, Austria, and currently employs over 50 people at its research site in Cambridge, UK.

Modular platform

F-star's development pipeline is based on its proprietary Modular Antibody Technology platform, which exploits both ends of an antibody to generate and rapidly identify the most appropriate bispecific drug candidates for selected targets. Central to this process is the generation of Fc fragments of a human antibody with antigen-binding activity, also known as Fcabs. The antigen-binding sites in an Fcab are introduced by subtle changes to the structural loops at the C-terminal tip of the immunoglobulin heavy chain in the CH3 domain. Fcabs with the required properties are identified through screening of large Fcab libraries using yeast and phage display[2]. Only a limited number of amino acid modifications are required, and they have no impact on the functionality of the Fc region. As a result, Fcabs possess antigen-binding properties that are similar to those of monoclonal antibodies, along with an ability to mobilize immune effector functions, excellent protein stability and simplicity of manufacturing.

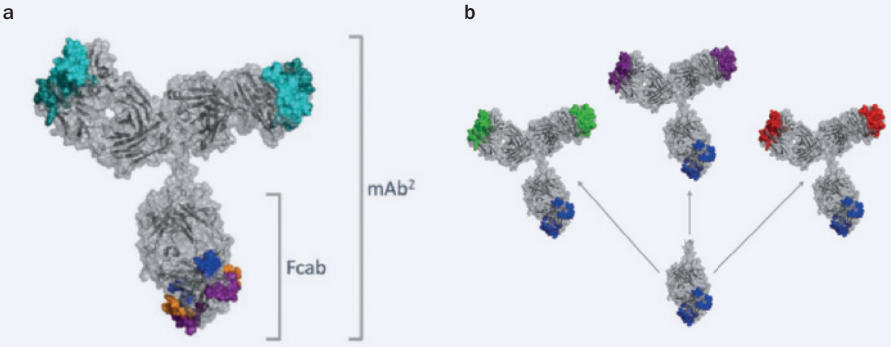

Figure 1: The Modular Antibody Technology at a glance. (**a**) A mAb^2 bispecific antibody comprises an Fcab and a Fab region. The CDRs are highlighted in turquoise. The Fcab carries the second antigen-binding site, which is created by subtle engineering of the Fc CH3 domain; a limited number of amino acid substitutions required in the AB loop residues (orange), CD loop residues (dark blue) and EF loop residues (purple). (**b**) Each Fcab for a particular target can be combined quickly and easily with the Fab region from any existing antibody, providing multiple mAb^2 opportunities.

Fcabs are incredibly versatile, as they can serve as the starting point for creating different classes of biologics depending on the therapeutic need. For example, Fcabs can be used as monospecific antibodies in their own right, or they can be used as building blocks to create bispecific antibodies, as well as antibody-drug conjugates.

Bispecifics with properties similar to those of monoclonal antibodies

The generation of bispecific antibodies traditionally has involved the addition of a second antigen-binding site in the Fab arms. These types of bispecific products are based on highly engineered antibody constructs, which can be associated with problems such as poor stability, immunogenicity and challenges in the manufacturing process. In contrast, F-star simply replaces the Fc region of an existing antibody with an Fcab that binds to a second target of interest to create a full-length bispecific monoclonal antibody known as a mAb^2 (pronounced "mAb square") (**Fig. 1a**).

The resulting mAb^2 not only outperforms traditional monoclonal antibodies, by binding two different antigens at the same time, but also benefits from all the well-established characteristics of those antibodies. These include favorable pharmacokinetics, antibody-dependent cellular cytotoxicity, and excellent stability and ease of manufacturing. Because of its strong intellectual property estate, F-star is the only biopharmaceutical company able to create and produce bispecific antibodies by introducing additional binding sites to the constant region of an existing antibody.

A key advantage of F-star's combinatorial approach is that it enables efficient and broad exploration of the distinctive biology associated with dual targeting. "Identifying the biologically optimal bispecific antibody drug candidate in immuno-oncology requires a modular platform where you can essentially use our 'plug and play' approach to mix the different specificities systematically and test a large number of bispecifics empirically in a relatively high-throughput manner, both in cell-based assays and *in vivo*," said Haurum.

In essence, each Fcab creates multiple mAb^2 opportunities because it can be combined with the Fab regions of any antibody to make it bispecific (**Fig. 1b**). This modularity gives F-star the ability to leverage existing monoclonal antibodies along with Fcabs to rapidly create a large portfolio of novel bispecific products for biological screening.

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BISPECIFIC. BY DESIGN.

Rapid pipeline generation

F-star has been able to rapidly generate a pipeline of clinically relevant differentiated products, thanks to the efficiency of the technology and the versatility of the Fcabs it creates. Fcabs have been created for numerous immune-checkpoint targets, and programs are now under way to test an array of mAb[2] antibodies *in vivo*. In addition, activities to support investigational new drug (IND) applications have been initiated.

F-star has assembled an immuno-oncology advisory board of leading international scientific and clinical advisors to provide expert advice during each step of the development process. For example, at the outset of programs to generate Fcabs to particular immuno-oncology targets, the board helps to select the most promising targets. The board also provides advice on which antibodies to combine with the Fcabs to create mAb[2] antibodies, which bispecific pharmacology screening models to use and which translational settings to test the products in. "We also ask the board to review the data, in order to understand which are the most promising compounds in terms of creating a clinically and commercially differentiated product, which we may then take forward for clinical development," said Haurum.

F-star is well funded and has major product alliances with Bristol-Myers Squibb, Boehringer Ingelheim and Merck Serono. Two asset-centric vehicles have been established, creating a flexible corporate structure, which further enhances F-star's ability to attract leading biopharmaceutical companies to join forces with the company; F-star Alpha Ltd. was formed in 2013 and holds all rights to FS102 (see below), whereas F-star Beta Ltd. was formed in 2014 and holds an exclusive license to certain targets in oncology and immuno-oncology for Fcab and mAb[2] products.

"We currently have a rich array of immuno-oncology programs that we are progressing ourselves, some of which will potentially be partnering assets at a later stage," said Haurum. "However, given the breadth of opportunity in this area, we are planning on executing a limited number of value-creating partnerships over the coming years. We are particularly interested in working with companies that can bring key assets to the table, including novel pharmacology screening models, valuable internal understanding of relevant biology, and exciting new antibodies to explore the bispecific space."

Lead program validation

F-star's discovery engine has already generated one clinical-stage product, FS102, a human epidermal growth factor receptor 2 (HER2)-targeting Fcab. "Preclinically, FS102 validates that the Fcab may serve as an antibody-like product in its own right, with favorable pharmacokinetic and manufacturing-related properties," said Haurum.

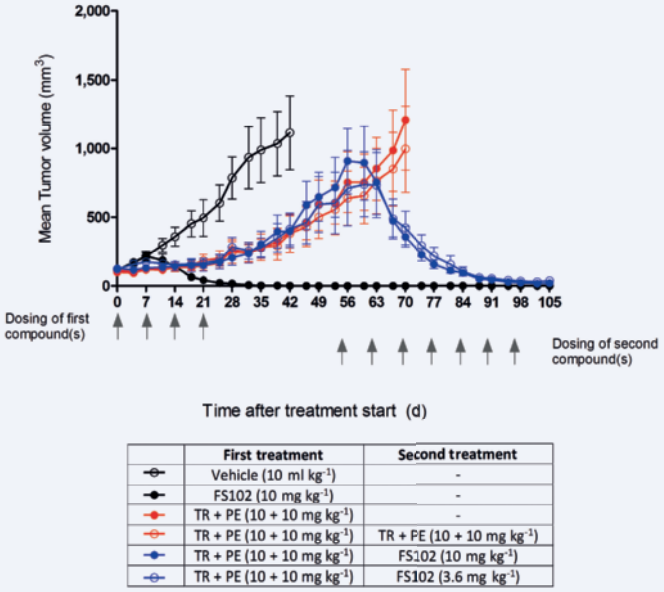

Figure 2: In preclinical studies, FS102 caused complete tumor regression in a patient-derived xenograft model that had progressed after combination treatment with Herceptin and Perjeta[3] (TR + PE). Animals were subjected to four cycles of treatments with vehicle, FS102, or TR + PE and tumor volumes were measured (mean ± s.e.m.). After a 31-d recovery period, they were subjected to seven additional cycles of treatments as indicated. The treatment-administration times are shown by arrows.

Preclinical studies have shown that FS102 has the potential to eliminate cancer cells through a novel mechanism of action in a biomarker-defined population and to overcome resistance that has developed to other HER2-targeted drugs. It binds to HER2 with high affinity and recognizes an epitope that does not overlap with those of Herceptin (trastuzumab) or Perjeta (pertuzumab). It causes profound HER2 internalization and degradation leading to apoptosis in tumor cells that overexpress HER2. In preclinical studies, FS102 has demonstrated encouraging efficacy against certain HER2-positive cancers and has induced major regression in tumors, including those that are refractory to combination treatment with Herceptin and Perjeta[3] (**Fig. 2**).

In October 2014, Bristol-Myers Squibb and F-star Alpha Ltd. entered into an agreement that provided Bristol-Myers Squibb with the exclusive option to acquire F-star Alpha Ltd. and gain worldwide rights to FS102. Under the terms of the agreement, Bristol-Myers Squibb made an initial payment of $50 million, comprising an option fee for the right to acquire F-star Alpha Ltd., payment for certain rights and licenses from F-star Alpha Ltd. and a clinical milestone payment upon initiation of the phase 1 trial. Bristol-Myers Squibb is responsible for conducting and funding development of FS102 during the option period and can exercise the option to acquire F-star Alpha Ltd. at its sole discretion prior to commencement of a phase 2b clinical trial. Total aggregate consideration may reach $475 million, which includes the $50 million initial payment, the option exercise fee and milestone payments upon the commencement of a phase 3 clinical trial and regulatory approvals in the United States and Europe.

In December 2014, a phase 1 clinical trial of FS102 was initiated for the treatment of HER2-positive breast and gastric cancer. "FS102, if approved, has the potential to become an important addition to the treatment of several types of HER2-positive solid tumors, including breast, gastric and colorectal cancers," said Haurum. "As the company's first program to enter human clinical trials, this novel, targeted therapy not only represents a significant milestone for F-star but, more importantly, has the potential to be of great value to patients."

References

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