SAN FRANCISCO – There has been a great deal of excitement surrounding the potential use of bispecific antibodies as cancer therapies stemming from the December 2014 accelerated approval of Amgen Inc.’s Blincyto (blinatumomab) to treat patients with relapsed or refractory Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL). Unfortunately, its expected influence in drug development has, as yet, failed to materialize. Why that has been the case was one of the questions posed to company executives in the space during a panel at the BIO Investor Forum last week.

Moderator of the session, Michael King, managing director and senior research analyst, JMP Securities LLC, asked the panelists, given all the knowledge that has been generated to date, why bispecific antibodies haven’t gained more traction and interest from investors.

David Poon, senior director, external R&D and Alliances, at Vancouver, British Columbia-based Zymeworks Inc. said he believed there has been a lull following some challenges faced by the first wave of bispecific antibody therapies. In the intervening period, companies working on novel bispecifics have been fine-tuning their platforms and are now finally moving forward with molecules that are better designed. “We have a better understanding of the biology,” he said.

It is also taken some time for the newer formats, whether they be heterodimers or natural IgG-like molecules, to be developed, noted John Haurum, CEO, F-star Biotechnology Ltd., which is based in Cambridge, U.K. “It is only now that these are reaching the clinic,” and the pace should quicken going forward, thanks to the significant clinical investment that is continuing to be made. Sutro Biopharma Inc. CEO Bill Newell said, “We’re on the cusp of the next wave” in bispecifics. “If investors can be patient there are going to be some exciting investment opportunities as these compounds advance in the clinic.”

Product development

The bispecific antibody product pipeline is also expanding, as exemplified by the panelists’ descriptions of their current progress.

Haurum said F-star had pivoted from being an antibody engineering company five years ago. The priority now is to focus exclusively on immuno-oncology. “We only work outside the I-O space to the extent that our partner brings such a focus.”

For example, in its partnership with neurodegenerative disease-based startup Denali Therapeutics Inc., of South San Francisco, it will use its bispecific antibody platform to develop technology enabling the delivery of therapeutics across the blood-brain barrier.

Denali paid $6 million up front and has the option to acquire exclusive rights to the technology for a total of $450 million, provided it does so before starting phase I development of any products that arise as a result. (See BioWorld Today, Aug. 26, 2016.)

F-star’s Modular Antibody Technology makes it possible to modify both ends of an antibody to generate and rapidly identify the most appropriate bispecific drug candidates for selected targets.

The core of the technology is the generation of Fc fragments of a human antibody with antigen-binding activity, 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, Haurum told BioWorld Insight.

Fcabs with the required properties are identified through screening of large Fcab libraries.

Only a limited number of amino acid modifications are required, and they have no impact on the functionality of the Fc region and, as such, Fcabs possess antigen-binding properties that are similar to those of monoclonal antibodies. F-star 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 mAb2 (mab square).

“We have built what we believe is a reasonably deep biology capability in the I-O space. The philosophy is to try and test a large array of different target permutations in our biological assays both in vitro and animal models,” Haurum said.

The company, both theoretically and empirically, looks for ways in which the bispecific antibody can result in some synergy not observed with the direct comparator combination compound.

In terms of business development, the company employs build-to-buy entities of which it has four currently – F-star Alpha, Beta, Gamma and Delta. The latter encompasses ownership of five bispecific immuno-oncology antibody programs being developed in partnership with Merck KGaA. The pharma
company has paid a €115 million (US$135 million) up-front payment comprising an option fee to shareholders, a license fee to F-star, R&D funding in the option period, and two milestone payments to occur in the near future. In return, Merck KGaA obtained an option to acquire Delta at a certain future milestone point based on results from the program's data package. (See *BioWorld*, June 6, 2017.)

F-star Alpha was created about four years ago and holds all rights to the company's internal program, FS-102 Fcab, an anti-HER2, which has completed a phase I trial in the treatment of HER2-positive breast and gastric cancers.

Ton Logtenberg, CEO, Utrecht, the Netherlands-based Merus NV, said its platform technology is based on full-length human IgG antibodies known as Biclonics. It draws on a range of technologies capable of generating large panels of high-quality human antibodies and rapidly converted into thousands of Biclonics ready for functional screening.

At the end of 2016, the company entered a significant partnership with Incyte Corp. That long-term, oncology-focused pact sees Merus receive $120 million up front, an equity investment of $80 million, and approximately $2.8 billion reserved for potential milestones. In return, Incyte gains the exclusive rights for up to 11 bispecific antibody research programs.

The partnership is progressing well and in its second-quarter financial results the company reported it had advanced the first candidate into an IND-enabling study. MCLA-145 is designed to bind to PD-L1 and to a second undisclosed immunomodulatory target to treat various solid tumors. Merus has full rights to develop and commercialize MCLA-145 in the U.S., and Incyte is responsible for its development and commercialization outside the U.S.

Merus is also advancing several bispecifics in the clinic, including MCLA-128, an ADCC-enhanced Biclonic that bind to HER2 and HER3-expressing solid tumor cells.

During this quarter, Merus expects to initiate a phase II trial to evaluate MCLA-128-based combinations in two metastatic breast cancer (MBC) populations: confirmed HER2-positive MBC patients (progressing on two to four anti-HER2 therapies, including TDM-1), who will receive MCLA-128 in combination with trastuzumab with and without chemotherapy; and confirmed ER+/HER2-low MBC patients progressing on one or more prior endocrine therapies and CDK4/6 inhibitors, who will receive MCLA-128 in combination with endocrine therapy. The trial is expected to enroll approximately 120 patients in total, with approximately 60 patients targeted in each cohort.

**Plenty of partner interest**

Edgardo Baracchini, chief business officer at Xencor Inc., said its initial bispecific antibody programs are tumor-targeted antibodies that contain both a tumor antigen-binding domain and a cytotoxic T-cell-binding domain (CD3). Those bispecific antibodies activate T cells for highly potent and targeted killing of malignant cells. XmAb-14045 is currently in a phase I study for the treatment of acute myeloid leukemia (AML) and other CD123-expressing hematologic malignancies, and XmAb-13676 is currently in a phase I study for the treatment of B-cell malignancies. Trial readouts are expected next year.

The technology has also attracted the attention of biopharma players, including Novartis AG and Amgen Inc.

The Novartis partnership involves sharing development costs for the worldwide development of XmAb-14045 and XmAb-13676, with Xencor maintaining U.S. commercialization rights and Novartis having commercialization rights in the rest of the world. Novartis will receive worldwide rights to Xencor's bispecific technology to develop and commercialize four additional targets selected by Novartis, one of which Xencor may elect to co-detail in the U.S. The bispecific collaboration will include molecular engineering by Xencor. Additionally, Novartis will receive a worldwide nonexclusive license to use Xencor's XmAb Fc technologies in up to 10 molecules. (See *BioWorld Today*, June 29, 2016.)

Sutro's Newell stressed the importance of partnerships in helping manage technology and product portfolio risks. “We partner in a synergistic way and rely on our partners’ understandings of the biology.”

The company has multitarget partnerships with Celgene Corp. and Merck KGaA, which include antibody-drug conjugates as well as bispecifics and lever the company's cell-free synthesis platform.

Zymeworks' Poon explained that protein engineering remains at the core of his company's business. It does not grant target exclusivity to its partners, but they can in-license Zymeworks’ technology platform. The up-front payments and subsequent milestones help drive the firm's own internal programs.

For example, in July, Zymeworks and Daiichi Sankyo Co. Ltd. reported the successful achievement of a research milestone for an immuno-oncology bispecific antibody therapeutic candidate in their collaboration, for which Zymeworks received a milestone payment of $1 million.

Under the terms of their 2016 agreement, Zymeworks granted Daiichi Sankyo a license to its Azymetric and EFECT platforms to develop a bispecific antibody therapeutic for which it is eligible to receive preclinical, clinical and commercial milestone payments, as well as up to double-digit tiered royalties on global product sales.

The company has one Azymetric bispecific antibody in the clinic – ZW-25 targeting two distinct domains of the HER2 receptor. The results from a dose-escalation portion of the first-in-human study of ZW-25 showed it was well-tolerated at all dose levels evaluated, with single-agent antitumor activity in patients with advanced HER2-expressing cancers that had progressed after multiple lines of therapy, including HER2-targeted agents.

**Watch this space**

It is clear that the full potential of bispecific antibodies is just beginning to be seen. However, it is still early days for many of the therapies in development. The interest is building and we will certainly see more dealmaking going forward as biopharma companies look to exploit the evolving knowledge from immuno-oncology research.

“Watch this space,” King aptly said as the session concluded.