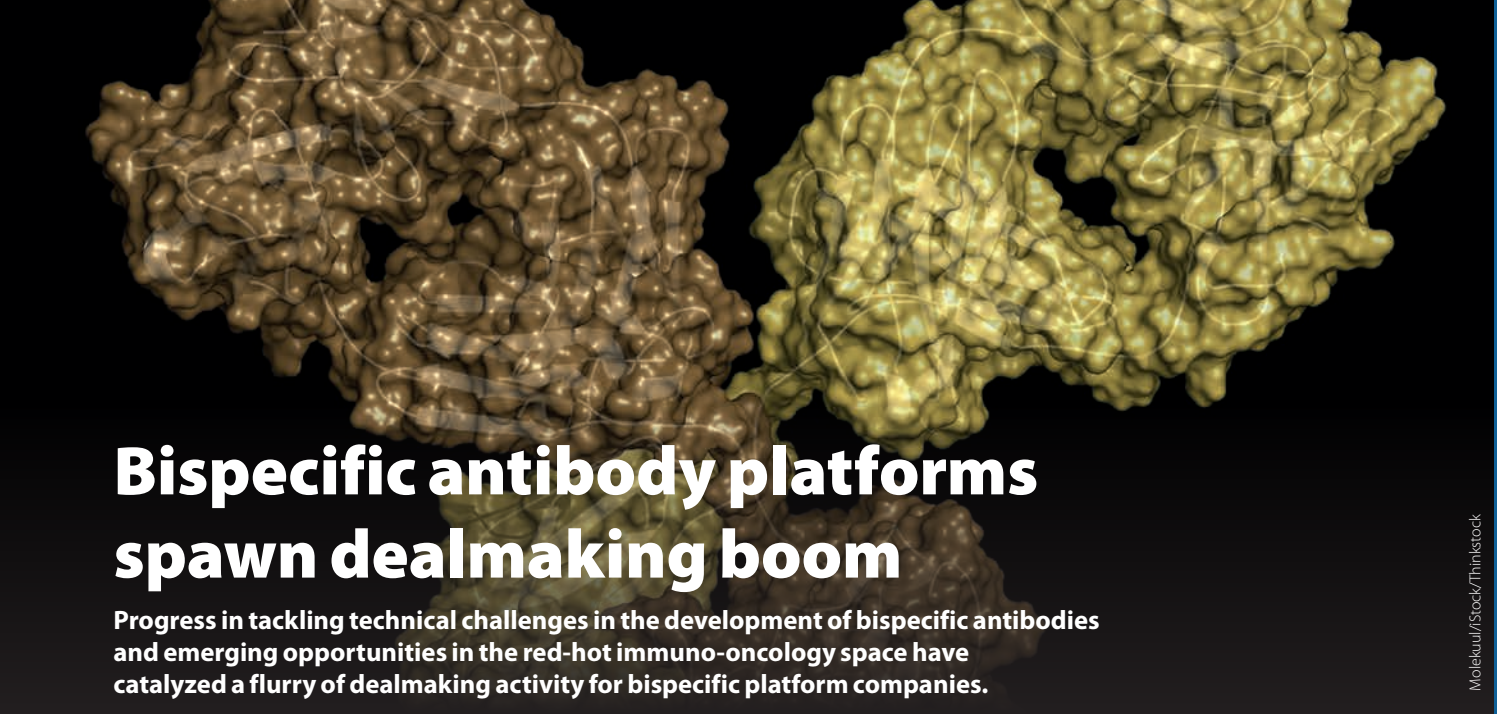

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Bispecific antibody platforms spawn dealmaking boom

Progress in tackling technical challenges in the development of bispecific antibodies and emerging opportunities in the red-hot immuno-oncology space have catalyzed a flurry of dealmaking activity for bispecific platform companies.

Nick Taylor

As with many innovative biotechnology platforms, the progress of bispecific antibodies has been a stuttering affair. Although the format was discovered in the 1960s, only in the past 5 years or so have bispecific antibody platforms matured sufficiently to excite widespread interest in their therapeutic potential.

The first 6 months of 2016 highlight how strong the appeal of bispecific platforms has become for drug developers. GlaxoSmithKline entered into a $908 million deal with Zymeworks, Sanofi struck a $400 million alliance with Innate Pharma, Johnson & Johnson inked a $740 million pact with MacroGenics, and Novartis agreed to pay up to $2.6 billion to Xencor. Each deal saw a large pharmaceutical company commit a significant sum of money to gain access to a platform capable of producing bispecific antibodies, a class of therapeutics designed to interact with two antigens at once.

This dual-targeting capability is particularly attractive to those working on therapeutics for complex conditions such as cancer. "Due to the multifactorial nature of diseases, many patients fail to respond or become refractory to available treatments, even biologics," said Jan van de Winkel, CEO of Genmab. "Bispecific antibodies have great therapeutic potential for designing more efficacious treatments by simultaneously targeting more than one factor."

Researchers have spent more than 50 years trying to realize this potential. An antibody fragment containing two antigen-binding domains with different specificities was created in 1961, but what followed was the first long lull in the progress of bispecific antibodies. The lull was a result of the nature of bispecifics. Whereas developers of standard antibody therapeutics work with a structure that evolved over hundreds of millions of years to be stable and long-acting, bispecific developers have had to force antibody fragments into new configurations that compromise their stability.

"You're trying to do something completely unnatural with an antibody ... which is have it stick to two antigens at once. You have to cook that up and manipulate the structure to do that," said Bassil Dahiyat, CEO of Xencor. "For years, attempts to do that confronted the expected challenges of having the molecules be a lot less stable than a natural molecule ... having them be hard to make, and having them not be terribly persistent in the body ... so they have short half-lives."

Amgen made a breakthrough in 2014 when it won a pioneering US Food and Drug Administration (FDA) approval for a bispecific, the acute lymphoblastic leukemia drug Blincyto (blinatumomab). The approval was a landmark event. "It has provided clinical validation for this concept and generated a lot of interest," Nicolai Wagtmann, CSO at Innate, said. "It proves the point that you can have bispecifics that recruit and engage effector T cells towards tumor cells and then can induce killing and have major clinical benefits."

The clinical-phase bispecific pipeline

Amgen has sought to build on its first-to-market status by creating a pipeline of bispecific programs. The most advanced of these programs are testing blinatumomab in additional indications, but the early-phase pipeline features some new assets. Cancer drugs AMG 211 and AMG 330, based on the same bispecific T cell engager technology as blinatumomab, are in phase 1, as is the AstraZeneca-partnered bispecific antibody–peptide conjugate AMG 570.

Although these programs give Amgen the potential to grow its bispecific business in years to come, analysts at EvaluatePharma predict that the best-selling bispecific in 2022 will belong to Roche. The drug, emicizumab, is a bispecific antibody that recognizes antifactors IXa and X. It is currently being evaluated in hemophilia A patients in a phase 3 trial, and EvaluatePharma analysts think that success in this indication could lead to sales of $1.5 billion in 2022.

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Whereas the pipeline of mid-phase bispecific antibodies covers an array of therapeutic areas, biotechs working on earlier-stage programs have made oncology, particularly immuno-oncology, their primary focus. This has proven to be a fruitful strategy. With large biopharma companies desperate to ensure they have pipelines capable of capturing a slice of the burgeoning immuno-oncology market in years to come, biotechs with bispecific platforms have landed strings of deals.

How platforms are driving deals

The deals struck to date reflect the nature of bispecific platforms. Multiple companies, such as Crescendo Biologics, F-star and Xencor, use descriptors such as 'plug and play' and 'modular' to position their platforms as capable of quickly generating bispecific antibodies against targets selected by their partners.

The details vary from company to company, but Xencor's approach is illustrative of the model in general. "The partner has the two antibody fragment it wants ... to bind the target antigens. We just pop them onto the Fc [domain] and that's it, there's the antibody,"

Dahiyat said. "We don't do anything else. They develop, and they go forward with it. It's a very modular toolkit that lets us have very limited resource allocation to our partnerships on the discovery side."

Armed with such a platform, Xencor has entered into a $1.7 billion deal with Amgen and a $2.6 billion alliance with Novartis while continuing to commit time and resources to its in-house pipeline. Both deals gave Xencor relatively small upfront payments—$45 million from Amgen, and $150 million from Novartis—plus the chance to win big if the fruits of the collaborations come to market.

In return, Xencor is using its platform to generate bispecifics against certain targets. As this process is straightforward, Xencor has the capacity to make lots of deals. Rival bispecific biotechs have a similar appetite for dealmaking. Zymeworks has agreements with Celgene, Eli Lilly, GlaxoSmithKline and Merck & Co., and F-star lists AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb and Merck KGaA among its collaborators.

F-star has also sometimes taken a different approach to dealmaking than its peers, notably by setting up asset-centric vehicles. This entails spinning out an early-stage drug to form a new organization focused solely on its advancement, creating a different way of selling a development-stage product. Notably, whereas money from traditional licensing deals goes into F-star, the proceeds from the sale of an asset-centric vehicle flow more directly to investors.

"It's a way of gradually monetizing the platform," John Haurum, CEO of F-star, said. "We've already returned a fairly significant amount of money to our shareholders. Over the last couple of years we've raised close to $100 million. A significant proportion of that has been returned to the shareholders." Some of that money came from a $475 million deal that gave Bristol-Myers Squibb an option to buy one of the asset-centric vehicles, F-star Alpha.

The future of bispecific dealmaking

The flurry of alliances struck over the past few years is indicative of the advances made in the sector. After decades in which issues with production, persistence and safety held back bispecifics, some biotechs now claim to have overcome these problems. Large companies have responded by inking deals to build pipelines. "Partners want access to multiple programs because they don't know which tumor targets are going to be the right ones in bispecifics," Xencor's Dahiyat said.

At present, the early-stage nature of many of the platforms means that pipelines, and the deals struck to create them, are focused on discovery and preclinical programs. This is likely to change in the years to come, particularly as drugs developed in-house at bispecific biotechs advance to key value inflection points such as clinical proof of concept. At that stage, the size of the upfront fees associated with bispecific deals is likely to increase considerably.

The past few years may come to be seen as a platform-driven boom period for early-stage bispecific deals, but the flow is unlikely to dry up completely. One possibility is that the therapeutic focus will expand. "I can see, in fact quite easily, that what is being developed in immuno-oncology would be a trendsetter for, in fact, the flip side of the coin ... inflammatory disease," F-star's Haurum said. "You would want to do the opposite in inflammatory disease, but with very similar approaches."

Such a therapeutic expansion could underpin a fresh wave of deals, as could evolution of antibody technology. Such evolution is already happening. The $400 million agreement between Sanofi and Innate is focused on bispecifics that engage natural killer cells (most bispecifics today stimulate T cells). Wagtmann at Innate thinks that this mechanism of action will allow it to deliver high doses without causing cytokine release syndrome, a potentially life-threatening toxicity associated with some cancer immunotherapies.

Other early-stage deals could be driven by technology that broadens the pool of potential targets of bispecifics. CytomX Therapeutics is among the firms working on this problem. "There are great targets out there that are important for oncology but are currently unaddressable because there isn't sufficient differential expression between tumor or healthy tissue," said Debanjan Ray, senior VP, corporate development and strategy at CytomX. The company is in talks about preclinical bispecific partnerships.

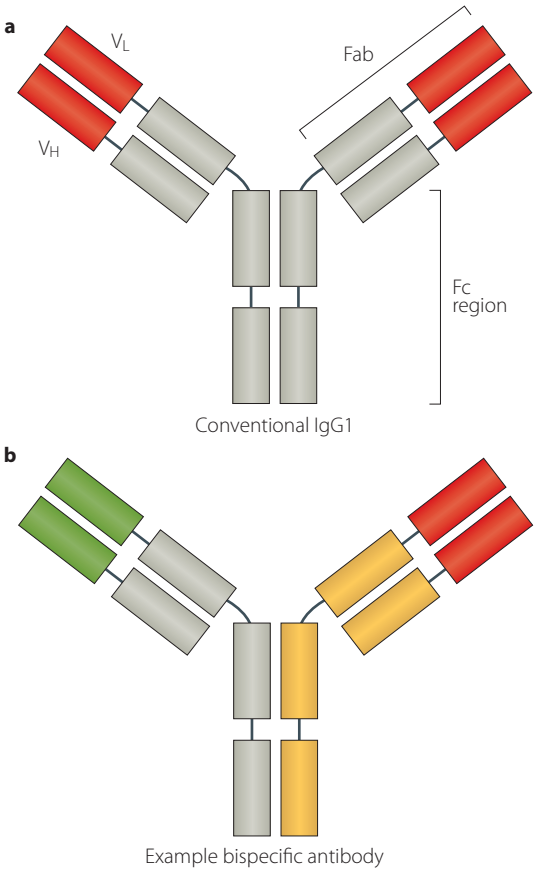

Figure 1: Structure of a bispecific antibody. Bispecific antibodies are artificially engineered from the fragments of two different monoclonal antibodies to create a construct that is able to bind to two types of antigens. Various formats for bispecific antibodies have been developed, some of which are based on the immunoglobulin G (IgG) architecture (**a**), which consists of Fab (fragment antigen-binding) regions connected to an Fc (fragment crystallizable) region. Antigen specificity is provided by the two variable domains (V_H and V_L). An example bispecific antibody format with Fab regions that recognize two antigens is shown in **b**.

Another possible development that could drive dealmaking is the progression from bispecifics to trispecifics or even pentaspecifics. This would create new challenges, but some say these would be manageable. "The more you add [to an engineered antibody-like product], the more complicated it becomes to express, to purify it. It has an effect on stability and all kinds of stuff," said Peter Pack, CEO of Crescendo Biologics, which develops Humabodies, therapeutics based on heavy-chain antibody domains. "Fortunately, we don't have these problems because [a Humabody is] a simple building block [that is] expressed at extremely high yields."

A basis for long-term growth

It now seems more likely than ever in its 50-year history that bispecific technology will have a lasting presence in the drug development toolkit. Some of the platforms that are the subject of deals today may falter when the bispecifics they generate face the more rigorous challenges of late-phase trials. Yet the breadth of approaches now being pursued, many of which have the validation and support of large biopharma companies, suggests that some will succeed. With those successes tipped to yield multibillion-dollar franchises, such companies are increasingly vying to ensure they have stake in the bispecific field.

Nick Taylor is a freelance journalist specializing in the biopharma industry.