The accelerating rise of bispecific antibodies outside of oncology

In the wake of the surge of interest in bispecific antibodies for cancer therapy, bispecifics are now being pursued in a wide range of other disease areas, driving further dealmaking.

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The Food and Drug Administration (FDA) made a landmark approval in November 2017, when Roche's hemophilia A treatment Hemlibra (emicizumab) became the first bispecific antibody to get the green light for a noncancer indication. Now, other companies are applying the bispecific format to the treatment of infections, autoimmune conditions and neurological diseases.

Bispecific antibodies are single constructs designed to interact with two targets. The modality came to prominence in 2014 when the FDA approved Amgen's Blincyto (blinatumomab) in acute lymphoblastic leukemia. One arm of blinatumomab interacts with T cells while the other binds to cancer cells, triggering an immune attack on the tumor.

Blinatumomab showed that it is possible to create bispecifics that are stable enough to be effective. A surge in interest followed, leading companies such as GlaxoSmithKline, Johnson & Johnson, Novartis and Sanofi to commit billions of dollars to biotechs in exchange for the rights to anticancer bispecific antibodies (see *Biopharma Dealmakers* B21–B22, September 2016). More quietly, companies explored the use of bispecifics in other diseases.

These noncancer programs are garnering increased interest and Roche's emicizumab is leading the way. The pharma company used the bispecific format to mimic the function of factor VIII (FVIII), a blood-clotting protein that is deficient in patients with hemophilia A. Similar to FVIII, emicizumab promotes interactions between FIXa and FX by using its dual-target design to bring the proteins together. In clinical trials, emicizumab reduced the bleeding rate by 87%.

Analysts see that efficacy translating into blockbuster sales, catching the attention of other companies in the area. Shire, anticipating a threat to its hemophilia franchise, has licensed a preclinical bispecific program targeted to the same proteins as emicizumab from Novimmune in return for an undisclosed financial package.

By using a dual-target design to enable the interaction of two different targets, the approved and experimental hemophilia A medicines work in a similar way to Amgen's blinatumomab. However, this is just one of the ways to use bispecifics.

"It was thought that it was a matter of taking the best antibody against target A, and then the best antibody against target B, putting them together, and then you have a great new drug as a bispecific antibody," said John Haurum, CEO of F-star Gamma. "This is a bit of a fallacy. In reality, you need to have a very thorough discovery phase to determine which are the different specificities."

This makes the development of bispecifics harder than initially thought, but also encourages the development of candidates that make full use of the modality. Applied creatively, bispecifics do far more than just provide the independent effects of two antibodies.

Addressing autoimmune diseases

The breadth of possibilities unlocked by bispecifics is evident in the autoimmune and inflammatory disease field. Bispecifics in development in these indications use the dual-target format to improve specificity, extend half-life and trigger coinhibitory signals. The potential for such mechanisms to drive novel biology and thereby address major diseases has made these areas among the most active and advanced outside of oncology.

Takeda moved into the sector in 2014 when it paid MacroGenics $15 million upfront for an option to license the CD32B–CD79B bispecific MGD010. The drug is designed to trigger an immune checkpoint loop to inhibit B cell function, preventing autoimmune attacks. MGD010 coligates CD32B, a checkpoint molecule, and CD79B to deliver a coinhibitory signal (**Table 1**).

The mechanism of action of MGD010 provides another example of how bispecifics can unlock novel biology, but the drug has suffered setbacks. Takeda handed back the rights to the asset in September 2016. MacroGenics, a cancer-focused biotech, offloaded MGD010 to Provention Bio in return for a stake in the biotech in May. Provention plans to run a phase 1b/2a trial in lupus.

Elsewhere, bispecifics against autoimmune diseases have been progressing in clinical development while attracting deals. In 2008, Merck KGaA paid Ablynx €10 million to codevelop single-domain antibodies against oncology and immunology targets. ALX-0761, a bispecific that blocks interleukin (IL)-17A and IL-17F, entered human testing in 2013 and was licensed by Merck the same year. Merck put the drug through a phase 1b psoriasis trial before striking a deal of its own. The second agreement saw Merck transfer responsibility for running and funding phase 2 and 3 trials of the bispecific to Avillion, a company that takes on clinical-stage drug candidates from pharma firms that have more drugs than they can develop internally.

By the time Avillion became involved, there was clear evidence of the importance of IL-17 and a rationale for targeting receptors other than IL-17A. "Prior to entering the deal, we had seen data with brodalumab demonstrating the benefit of broader inhibition via blocking the IL-17 receptor," said Mark Weinberg, CMO at Avillion. "Both IL-17A and IL-17F drive the disease and there is a clear logic to increasing the effect of IL-17 blockade by expanding beyond IL-17A."

Avillion is now testing this idea in a 300-patient psoriasis phase 2b trial. Some patients in the study will take Novartis's anti-IL-17A monoclonal antibody secukinumab, allowing Avillion a chance to gauge the effect of also targeting IL-17F.

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Table 1 | Selected bispecifics in clinical development for diseases outside of oncology

Company	Candidate	Development stage	Targets	Indication
Provention Bio	PRV 3279 (formerly MGD010)	Phase 1	CD32B and CD79B	Autoimmune disorders
Xencor	XmAb5871	Phase 1/2	CD19 and CD32B	Autoimmune disorders/ Rheumatoid arthritis/SLE
Covagen/Johnson & Johnson	COVA322	Phase 1/2	TNF and IL-17A	Psoriasis
Sanofi	SAR156597	Phase 2	IL-4 and IL-13	Systemic scleroderma
AbbVie	ABT-122	Phase 2	TNF and IL-17	Rheumatoid arthritis
AbbVie	ABT-981	Phase 2	IL-1α and IL-1β	Osteoarthritis
AstraZeneca (MedImmune)	MEDI3902	Phase 2	Psl and PcrV	*Pseudomonas aeruginosa* infection
Avillion/Ablynx/Merck KGaA	ALX-0761	Phase 2	IL-17A and IL-17F	Psoriasis

IL, interleukin; SLE, Systemic lupus erythematosus; TNF, tumor necrosis factor.

Breaking antibiotic resistance

Bispecifics that target infectious diseases have also advanced into the clinic, albeit in small numbers and without generating as many deals as the autoimmune field. AstraZeneca's MEDI3902 is leading the way (**Table 1**). MEDI3902 is designed to kill the *Pseudomonas aeruginosa* bacterium. One specificity allows white blood cells to identify and engulf the bacteria, while the other disrupts a bacterial defense mechanism that prevents phagocytosis.

Pursuing two targets reduces the likelihood that the bacterium's evasion and subversion mechanisms will protect it from immune attacks. This could enable MEDI3902 to better prevent and treat infections compared with single-target antibodies, which have failed to protect patients against bacteria in clinical trials.

AstraZeneca had originally hoped to complete a phase 2 trial of MEDI3902 in July 2018 but pushed back the target date twice in 2017. The trial is now due to end in 2021.

Other bispecific anti-infective programs have stumbled earlier in development. Cidara Therapeutics was developing a bispecific antibody, CD201, that used one specificity to bind to a target on bacteria and another to recruit the immune system to attack the pathogen. In 2017, Cidara received a $6.9 million grant from CARB-X to put CD201 through phase 1 trials. However, data from preclinical animal infection models persuaded Cidara to switch its attention to an antibody–drug conjugate (ADC) based on the same platform as CD201.

"In addition to killing bacteria directly, our ADC bispecifics mediate bacterial killing via engagement of the innate immune system. By adding a second killing mechanism, our ADC bispecifics further reduce the potential for resistance development," said Les Tari, VP of discovery research at Cidara.

Crossing the blood–brain barrier

The anti-infective and autoimmune applications of bispecifics are among the more mature uses of the modality outside of oncology. However, while these drugs could establish bispecifics outside of cancer, the preclinical prospects of targeting diseases of the central nervous system may deliver the biggest wins for patients and drug developers.

Bispecifics that target conditions such as Alzheimer disease are yet to progress into human testing but, despite that, the field has already seen its first major deal. In May this year, Denali Therapeutics paid $24 million upfront and committed up to $447 million in milestones to acquire F-star Gamma, an asset-centric vehicle founded in 2016 to develop bispecifics that cross the blood–brain barrier.

Denali is a neurodegenerative disease biotech founded by ex-Genentech employees that has raised almost $350 million in venture funding. In 2016, the biotech approached F-star about the use of the latter company's bispecific platform to cross the blood–brain barrier, which stops unwanted substances—including antibodies—from accessing the brain. The idea is to have one specificity bind to the transferrin receptor, which shuttles materials across the barrier. Once the transferrin receptor transports the bispecific across the barrier, the other arm can interact with targets in the brain. Denali is developing one bispecific in Parkinson disease and two in Alzheimer disease.

Groups at companies including AstraZeneca's MedImmune and Biogen have also researched the idea of using the bispecific format to cross the blood brain–barrier. However, F-star thinks its platform is particularly well-suited to the task.

"A lot of what has conventionally been deployed are what is called the heterodimer half antibodies, where you have one specificity on one half of the antibody and then you have the second specificity on the other half of the antibody," F-star's Haurum said. "If you use that format, it would be a half antibody that you had in the brain."

Denali wanted to get a full antibody into the brain and therefore approached F-star, which has a platform that makes bispecifics with independent specificities. Using F-star's platform, the specificity targeting the transferrin receptor should not affect the performance of the specificity targeting the receptor in the brain, and vice versa.

Other companies tout the potential of different approaches. In 2017, Lundbeck teamed up with Ossianix to develop multiple candidates. Ossianix's technology attaches a shark variable new antigen receptor (VNAR) antibody to a therapeutic antibody. The VNAR antibody targets transporters in brain capillaries to transfer the therapeutic antibody across the blood–brain barrier.

Overall, given the biological complexity of the remaining unmet medical needs and rising rates of comorbidities in aging populations, bispecifics look well-suited to today's therapeutic challenges. After a slow start, interest in bispecifics outside of cancer could be about to take off.

Nick Taylor writes about the biopharmaceutical industry.