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Bispecific antibody pipeline moves beyond oncology

The FDA could soon approve the first bispecific antibody for a non-oncology indication, but clinical applications that make full use of the biological opportunity afforded by the nascent modality remain rare.

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The FDA is currently reviewing Roche's bispecific antibody emicizumab for the treatment of haemophilia A, and is set to make a decision by the end of February. If approved, the first-in-class candidate will become the first bispecific to make it to market for a non-oncology indication (and just the second bispecific to gain approval for any indication in the United States, following only Amgen's blinatumomab for acute lymphoblastic leukaemia). Although the FDA might reject the bispecific — especially given the potentially fatal thrombotic adverse events that have occurred in a few patients — the candidate also highlights how the nascent modality can unlock new biology beyond cancer.

"This is a really beautiful example of how you can use bispecifics," says Paul Parren, molecular immunologist at the Leiden University Medical Center and former scientific director at the antibody-focused biotech Genmab. Emicizumab binds to factor IX and factor X, bringing these proteins into proximity with one another and initiating a coagulation cascade — a role that is usually carried out by factor VIII. Although approved factor VIII replacement therapies serve the same purpose, around 30% of patients develop immunogenic responses to these agents and need alternative treatment options. As a so-called obligate bispecific, which has to bind to both of its targets to have an effect, it is the hardest type of bispecific to work on, adds Parren, who was not involved in the discovery of the antibody. "It's very impressive."

But despite growing enthusiasm for the modality, emicizumab stands out from most of the rest of its non-oncology bispecific peers. Of the nearly 20 other non-oncology bispecifics that are advancing towards the market (TABLE 1), most function more like a single-agent combination of two independently acting monovalent antibodies. Just a handful of other candidates push the biological potential of the platform.

By contrast, more than half of the oncology bispecifics in clinical trials are obligate bispecifics that achieve functionality beyond the scope of monovalent antibody combinations. For the most part, these bind to a T cell antigen with one arm and a tumour antigen with the other, recruiting immune cells to cancer cells. Blinatumomab, for example, binds to CD3 on T cells and CD19 on B cells to deplete B cells in acute lymphoblastic leukaemia. "Many people have jumped on that bandwagon because they understand the potency of that system," says Parren. "I hope the same will happen as we find more non-oncology proofs of concept."

New tools need new biology

Interest in bispecifics has grown in recent years, and researchers in industry and academic institutions have come up with more than 100 different antibody formats that can offer bispecificity. The number of bispecifics in clinical trials is on the rise as well, with nearly 60 candidates across all indications. Around 20% of all first-in-human trials of antibodies were of bispecific formats in 2016, up from below 10% 5 years ago. "There is a tremendous amount of interest in this area," says Janice Reichert, executive director of The Antibody Society. But most of this interest is in oncology she adds, which accounts for 68% of the bispecific pipeline. By contrast, oncology accounts for little more than 50% of the overall antibody pipeline.

This underrepresentation of non-oncology indications may stem in part from a need for more proof-of-concept examples of how to apply bispecifics in these settings. If monovalent antibodies are the hammers of the biological world, bispecifics can do so much more than strike two nails. "Bispecifics are very attractive as a tool for carrying out specific jobs; the challenge is to find a use for these tools," says Reichert.

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Imaginative applications are emerging. In the cases of emacizumab and blinatumomab, the bispecifics act like two-headed clamps — bringing two molecules into proximity with one another with therapeutic effect. MacroGenic's MDG-010 shows that this same functionality can also be used to tune immune cell activity for non-oncology indications. The therapeutic targets the checkpoint molecule CD32B and the B cell antigen receptor complex component CD79B, which are both expressed on the surface of B cells. When these proteins bind to one another, they deliver a co-inhibitory signal that dampens B cell activation. MacroGenic's bispecific facilitates this interaction, binding to and co-ligating the target molecules on the surface of B cells. The company hopes that this candidate will offer therapeutic benefits similar or better than those of approved B cell depleting therapies (CD20-targeting rituximab for rheumatoid arthritis, for example), but with faster action and a lower risk of infection.

In June, the company presented phase I data from the bispecific at the European Congress of Rheumatology. "These results provide compelling rationale for further development of this therapeutic modality for autoimmune disorders," said Scott Koenig, CEO of MacroGenics.

AstraZeneca's MEDI-3902 provides an altogether different functionality, attacking *Pseudomonas aeruginosa* bacterium and neutralizing its defences at the same time. One arm binds to the exopolysaccharide Psl, increasing the ability of neutrophils to recognize and phagocytose the bacterium; the other binds to the type III secretion system virulence factor PcrV, preventing the release of bacterial factors that would otherwise neutralize the phagocytic process. In 2014, AstraZeneca reported that MEDI-3902 has synergistic benefits over a combination of the parental antibodies. In part, this is because the strong attraction of the bispecific to the abundant Psl antigen increases the local concentration and residence time of the antibody around the bacterium, enabling better neutralization of the PcrV defences.

Results from an ongoing trial of the bispecific in mechanically ventilated patients for the prevention of *P. aeruginosa* infection are expected next year.

Roche/Genentech's RG-7992 shows how bispecificity can also provide a means of achieving high levels of selectivity against a target. The researchers had previously worked

Table 1 | **Selected non-oncology bispecific pipeline**

Drug name	Sponsor	Targets	Indication	Properties	Status
Emicizumab	Roche	Factor IX; factor X	Factor VIII deficiency	Two-factor dimerization	BLA
MEDI-3902	AstraZeneca	PcrV; Psl	*Pseudomonas aeruginosa* infection	Two-antigen inactivation	Phase II
MDG-010	MacroGenics	CD32B; CD79B	Autoimmune disorders	B cell modulation	Phase I
RG-7992	Roche/Genentech	FGFR1; KLB	Type 2 diabetes	Hormone mimetic	Phase I
RG-7716	Roche	VEGF-A; angiopoietin-2	Wet AMD and DME	Two-ligand inactivation	Phase II
SAR-156597	Sanofi	IL-4; IL-13	Idiopathic pulmonary fibrosis	Two-ligand inactivation	Phase II
Lutikizumab (ABT-981)	AbbVie	IL-1α; IL-1β	Osteoarthritis	Two-ligand inactivation	Phase II
MEDI-7352	AstraZeneca	NGF; TNF	Osteoarthritis	Two-ligand inactivation	Phase I
MEDI-0700	AstraZeneca/Amgen	BAFF; ICOS ligand	RA, SLE	Two-ligand inactivation	Phase I
RG-7990	Roche/Genentech	IL13; IL17	Asthma	Two-ligand inactivation	Phase I
NA	Eli Lilly & Company	BAFF; IL-17	Inflammatory arthritis	Two-ligand inactivation	Phase I
M1095/ALX-0761	Merck KGaA/Ablynx	IL-17A; IL-17E	Psoriasis	Two-ligand inactivation	Phase I
JNJ-63823539	Johnson & Johnson	IL-17; TNF	RA	Two-ligand inactivation	Phase I
BCD-121	BIOCAD	IL-17; TNF	RA	Two-ligand inactivation	Phase I
JNJ-61178104	J&J/Genmab	NA	RA	NA	Phase I
NA	Novartis/Ablynx	CXCR2	Inflammation	Biparatopic mAb*	Phase I
Vobarilizumab	Ablynx/AbbVie	IL-6R; albumin	RA, SLE	PK-modulated receptor antagonist	Phase II
Ozoralizumab	Ablynx	TNF; albumin	RA	PK-modulated ligand antagonist	Phase II

AMD, age-related macular degeneration; BAFF, B cell activating factor; BLA, Biologics License Application; DME, diabetic macular oedema; FGFR1, fibroblast growth factor receptor 1; ICOS, inducible co-stimulator; IL, interleukin; KLB, β-klotho; mAb, monoclonal antibody; NGF, nerve growth factor; PK, pharmacokinetic; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor; VEGF-A, vascular endothelial growth factor A.*Biparatopic antibodies target two epitopes of a single antigen. Sources: Janice Reichert; MAbs **9**, 182–212; 2017.

on a monovalent anti-fibroblast growth factor receptor 1 (FGFR1) antibody that would stimulate brown adipose tissue activity, increasing energy expenditure and clearing excess calories for the treatment of type 2 diabetes. But because FGFR1 is widely expressed in a range of tissues, this antibody induced unintended side effects including hypophosphataemia and hypophagia in mice. By developing a bispecific that has to bind to both FGFR1 and its co-receptor β-klotho to elicit downstream signalling, the team was able to advance an experimental candidate with a more promising selectivity profile. Phase I trials of this bispecific, which mimics the activity of endogenous FGF21, are ongoing.

"The bispecific antibodies that create new biology, these are the most innovative," says Parren.

Many of the other bispecific candidates in the pipeline, by contrast, function more like two-headed hammers. These antibodies circulate in the bloodstream to take out two ligands at the same time — most commonly pro-inflammatory IL-17 and tumour necrosis factor (TNF). "These could turn out to be very good drugs," says Parren. "But I'm not sure that you need a bispecific to achieve the effect they are after. You could also likely use two antibodies in combination." Many of these bispecific candidates instead address patent problems or improve drug administration profiles for patient ease.

"If you have the choice between a bispecific and a combination of two parent antibodies, personally I would go for the parent combination because you have much more flexibility in combining the two," he says.

Two clinical candidates from Ablynx use one arm of a bispecific to bind to albumin, showing how bispecificity can also be used to extend an antibody's half-life.

Preclinical promise

A few other innovative applications of bispecifics could soon be entering clinical trials.

Last year, F-star partnered with Denali Therapeutics to harness bispecificity to shuttle antibodies into the brain. Drug developers have long been working on antibody therapies for central nervous system (CNS) indications — especially anti-amyloid antibodies for Alzheimer disease — but have struggled with poor antibody penetration across the blood–brain barrier (BBB). By using one arm of a bispecific to bind membrane receptors that actively shuttle molecules across the BBB, Denali hopes they can smuggle the targeted activity of the other arm into the CNS.

"The opportunity for antibodies to treat CNS disorders, if successful, is enormous," says F-star CEO John Haroum. The partners have yet to disclose their targets or indications, but Denali's focus is on neurodegenerative disease including Alzheimer disease, Parkinson disease and amyotrophic lateral sclerosis.

"Our partnership with Denali is an ideal opportunity to validate our modular antibody technology outside of immuno-oncology," says Haroum. The firm's plug-and-play technology is therapy-area agnostic he adds, and could one day also address other emerging opportunities in immunology and inflammation, infectious diseases, ophthalmology and respiratory disorders.

Roche is also interested in using bispecifics to cross the BBB. In 2014, they showed that an antibody fragment that binds to the transferrin receptor could serve as a brain

shuttle module to get anti-amyloid antibody activity into the brain.

Last year, academic researchers reported in *Science* that bispecificity can also improve antibody ingress to another difficult-to-access area — endosomes. Ebola virus uses a viral glycoprotein to gain access to host cells; a receptor binding site on this glycoprotein interacts with the host endosomal transporter protein Niemann–Pick C1 (NPC1) to enable access. Antibody blockage of this receptor binding site therefore offers an opportunity to prevent the virus from entering host cells, but the virus only exposes this epitope when it is engulfed in a host endosome. The researchers therefore developed a bispecific that hitches a ride into the endosome; one arm binds to an epitope on the glycoprotein that is always exposed, and then once the virus is engulfed in an endosome the second arm binds and blocks the newly exposed viral receptor binding site.

This antibody offered post-exposure protection against multiple Ebola viruses in mice, the team reported last year. A similar strategy might also offer protection against Marburg virus and Lassa virus, they wrote.

After decades of optimization of bispecific formats, screening platforms and manufacturing processes, the technology of obligatory bispecific antibodies is at last ready to deliver, wrote Parren and his colleague Aran Labrijn, at Genmab, in a perspective piece about this anti-Ebola antibody. The invention of interesting therapeutic applications for these new tools "may only be limited by our imagination," they concluded.