One agent, two targets

Why industry is investing in bispecific molecules

In the days before the internet became public, the word processor was an enhanced writing instrument. Then electronic messaging came along, and the same box became a tool for creating content as well as delivering it. Could a similar shift be taking place in the field of antibody therapeutics?

The modern antibody therapeutic is a monospecific compound that recognises a single antigen on an invading pathogen and tags it for attack by other parts of the immune system. The tagging job is performed by two arms of the Y shaped molecule called Fabs, while the immune response is generated from the stem of the Y by the Fc region.

The history of the modern antibody therapeutic starts with the discovery by Georges Köhler and César Milstein of a method of producing antibodies that were clones of a unique parent cell. This made it possible for the first time to produce large quantities of monoclonal antibodies specific to a given antigen. A description of this technique was first published in 1975.[1]

It took a little over a decade before the first antibody therapeutic was approved for marketing, and since that time these compounds have significantly improved healthcare. Nevertheless, since the mid-1980s, scientists began looking at different antibody formats in order to increase the molecule's binding capacity, and strengthen its ability to engage the immune system.[2]

This gave rise to the concept of the bispecific monoclonal antibody which is an engineered molecule that binds to two different types of antigen at the same time.

The earliest bispecific molecules were antibodies, and the current growing cohort of bispecifics is still based on the antibody structure albeit in some cases involving elaborate engineering. An exception to this rule is a project announced by Evotec AG on 26 April under which it will investigate *small molecule* bispecifics with a company in Scotland, UK.

What accounts for this interest in bispecifics? "I think what has probably sparked, or triggered, the interest in bispecifics is that people have recognised that monospecific targeting through classical IgG formats as we have known them, for example a Herceptin or an Erbitux-based approach, is not going to be enough for treating diseases and for helping patients in the clinic in the end," said Martin Treder, the chief scientific officer of Affimed NV in an interview.

As the table on page 7 illustrates, there were quite a few large drug companies with bispecific projects in early clinical development as of 30 April. The table lists only oncology compounds. There are other disease areas that are under investigation by bispecific developers as well, but these are outside the scope of this article. An example of the latter is a potential bispecific application in neurology where Genentech is working on a drug that would cross the blood-brain barrier and simultaneously target abnormal amyloid plaques in Alzheimer's disease.[3]

The first approved bispecific was catumaxomab in 2009 for the treatment of malignant ascites, which describes the accumulation of fluid in the abdominal space caused by cancer. This drug did not make much of an impact. The product that really started the current wave of development is blinatumomab, a molecule that activates endogenous T cells when bound to a target cancer cell expressing the CD19 antigen. The molecule was developed by Micromet AG and approved by the US Food and Drug Administration in 2014 for the treatment of relapsed or refractory acute lymphoblastic leukaemia. Amgen Inc acquired Micromet in 2012 when blinatumomab was in pivotal Phase 2 studies. The German company called the compound a bispecific T cell engager because it formed a link between T cells and the tumour cells.

"We knew that T cells for some reason could kill tumour cells if they saw the right antigen on the surface but they weren't doing it. The idea behind blinatumomab was to force the issue, to actually bring T cells into immediate proximity with the tumour cell," said Clive Stanway, chief scientific officer of the UK's Cancer Research Technology.

Blintumomab was a pathfinder because it was developed at a time when pharma companies were still largely sceptical about immunological approaches to cancer. This was related to Phase 3 trial failures, particularly for cancer vaccines. Over the past five years, however, the field has opened up with regulatory approvals for checkpoint inhibitors and striking efficacy data from trials of the new chimeric antigen receptor T (CAR T) cell therapies. This in turn has generated renewed interest in bispecifics. To be clear: not all of the bispecifics in development target an immune cell simultaneously with a tumour cell. Some of the investigational molecules are directed at *two* tumour targets instead.

"The bispecific approaches are going in at least two directions: one is engaging the immune system and the other one is a dual targeting of a tumour cell, a single tumour cell or cells within the tumour, but the malignant cell," Dr Stanway commented.

Table 1 shows the current early-clinical activity for the oncology bispecifics. Most do engage the immune system, but molecules under development by Johnson & Johnson Inc and Eli Lilly and Co involve dual targeting of a tumour cell.

Antibody veteran Genmab

Denmark-based Genmab A/S, one of Europe's oldest biotech companies, won approval from the FDA in November 2015 for daratumumab, a compound that targets CD38 on multiple myeloma cells. Developed with Jansssen Biotech (J&J), it was the first ever monoclonal antibody therapeutic approved for this disease. The single target makes it a monospecific compound, or to be precise, a monospecific monoclonal antibody. This success notwithstanding, the company is turning its attention to bispecific monoclonal compounds in the future.

In an interview with *MedNous*, Jan van de Winkel, the chief executive, disclosed that more than 75% of the company's preclinical portfolio consists of bispecific compounds.

"I can tell you that it is increasingly [the case] for companies

like Genentech and Regeneron as well. I think bispecifics are going to drive over 60% of the growth in the antibody therapeutics field in the coming years," he commented.

Moreover, there are grounds for considering the bispecific antibody as "an analogue to CAR T cell technology, but a much safer analogue and we think much more druggable," the executive added.

The Genmab technology, which it calls DuoBody, involves combining two halves of two human immunoglobulin G (IgG) antibodies, each with its own binding site, into one engineered molecule with two binding sites. The molecules all have normal Fc regions. The company says the way the bispecific molecule has been created is modelled after nature.

Genmab has nine partnerships around its bispecific technology five of which are full commercial licenses. The largest of these is with Janssen which has two bispecific molecules in the clinic, and is poised to launch more clinical programmes this year and next. The other four licensing deals are with Novartis, Novo Nordisk A/S, Aduro Biotech Inc and BioNTech, a privately-owned company in Mainz, Germany.[4] Apart from the Novo agreement, the licensing deals focus on cancer, and in particular on immuno-oncology.

In the agreement with Aduro, Genmab is exploring bispecifics that would target checkpoint molecules on T cells that inhibit the immune system, and in the deal with BioNTech, bispecifics targeting checkpoint molecules that would directly activate the immune system. "We are very, very interested in the potential of using the bispecifics in the immuno-oncology area," Dr van de Winkel commented.

A different angle

F-star Biotechnology Ltd of Cambridge, UK has a different angle on bispecific development. It has created an antibody structure which mostly incorporates the conventional features of an IgG including the Fab antigen binding region. But uniquely, the molecule also has an additional binding site in the constant, or Fc region. Specially designed antibody fragments called Fcabs, each targeting different antigens, can be plugged into the Fc region depending on the developer's therapeutic requirements. The Fcabs can be part of the bispecific antibody, or they can be stand-alone products.

F-star has research agreements with Merck Serono (Merck KGaA) and Boehringer Ingelheim GmbH. And in 2014 it signed its first major commercial deal – an option agreement with Bristol-Myers Squibb Company to acquire a product targeting human epidermal growth factor receptor 2 (HER2) for breast and gastric cancers. The therapy is an Fcab – not a bispecific antibody. But it could become part of a bispecific antibody if the company chooses to do so, John Haurum, the F-star chief executive, told *MedNous* in an email. Called FS102, the molecule is currently in a Phase 1 study being conducted by BMS. The US company can exercise its option to acquire the drug prior to the start of a Phase 2b trial.

In January of this year, F-star signed a licensing deal, this time with AbbVie Inc, to research and develop bispecific antibodies in immuno-oncology. Under the agreement, F-star will make Fcabs against two immuno-oncology targets after which AbbVie may make bispecific antibodies based on these Fcabs. One Fcab target is exclusive to AbbVie, while the other is co-exclusive to AbbVie and F-star.

Meanwhile, F-star has its own portfolio of products, the most advanced of which is FS118, a dual checkpoint inhibitor in preclinical development. This is a bispecific antibody directed against two immune checkpoint antigens. Like Genmab, the approach could involve any combination of immune checkpoint targets.

These could be checkpoint inhibitor antigens, or checkpoint stimulator pathways, or the approach could be one of each. The company's strategy is to develop Fcabs against each target and then test the Fcabs in antibodies directed against other targets. The host antibodies could be marketed compounds like ipilimumab or nivolumab, or new antibodies that haven't yet been marketed. Altogether, it will be investigating more than 75 target combinations, Dr Haurum said.

In the blinatumomab tradition

Table 1 shows that as of 30 April, there were three Phase 2 bispecific antibody programmes in development of which one is from Affimed NV of Heidelberg, Germany. Like Micromet before it, Affimed is looking to improve the traditional antibody by engaging the immune system directly. Its lead product for Hodgkin lymphoma, AFM13, targets both CD30, an antigen on Hodgkin lymphoma cells, and CD16A, a receptor on natural killer (NK) cells.

In the interview, Dr Treder said AFM13 is designed to engage NK cells and induce a stronger immune response than a conventional monospecific antibody would do. The parallel with blinatumomab is that immune cell recruitment is the goal.

"The advantages that the bispecific approaches have is that they are targeting specific molecules on the tumour cells and then they are recruiting the effectors. And that is something that a straight IgG cannot do," he commented. "So you are engaging the effector cells for a longer period of time as well as compared even to an Fc-enhanced IgG," he added.

Affimed conducted preclinical research on AFM13 with Stanford University. In addition to the Phase 2 trial underway in Hodgkin lymphoma, the company is poised to start a Phase 1b study in the same disease that combines AFM13 with pembrolizumab, Merck & Co's marketed checkpoint inhibitor. The two companies announced the collaboration in January. Affimed's pipeline also includes bispecifics that, in the tradition of Micromet, also engage T cells.

Left field coming center?

As proof that the field is ever expanding, Evotec AG announced in late April that it had started a collaboration to discover bispecific compounds based on small molecules – rather than antibodies. The research will be carried out with *Ex scientia,* a small company in Scotland that has computational capabilities suited to new small molecule design. In an interview Cord Dohrmann, chief scientific officer, said the goal is to discover molecules that would be directed against two targets in intracellular space. Antibodies, because of their size, cannot penetrate the cell membrane.

"The most likely scenario is that these are targets may stem from the same target family," he commented.

There are many precedents for dual-targeting small molecules including the cancer medicine imatinib (Gleevec). But Gleevec acquired its new indications largely through a process of serendipity. Technology has now advanced to a point where the drug candidate can be designed with these

TABLE 1 BISPECIFIC ANTIBODIES IN CLINICAL DEVELOPMENT

Drug name	Phase	Sponsor	Targets	Type of cancer
AFM-13	2	Affimed NV	CD30/CD16A	Hodgkin lymphoma
RG-7221	2	Roche	Ang2/VEGF	Colorectal
MM-141	2	Merrimack Pharmaceuticals Inc	IGF-1R/HER3	Pancreatic
MEDI-565	1	AstraZeneca Plc	CEA/CD3	Gastrointestinal
BAY2010112	1	Bayer AG	PSMA/CD3	Prostate
MGD006	1	MacroGenics Inc	CD123/CD3	Acute myeloid leukaemia
AFM-11	1	Affimed NV	CD19/CD3	Haematological malignancies
MP0250	1	Molecular Partners AG	VEGF/HGF	Solid tumours
MGD007	1	MacroGenics Inc	GPA33/CD3	Colorectal
LY3164530	1	Eli Lilly and Company	MET/EGFR	Solid tumours
OMP-305B83	1	Oncomed/Celgene	DLL4/VEGF	Solid tumours
REGN1979	1	Regeneron Pharmaceuticals Inc	CD20/CD3	Haematological malignancies
AMG211	1	Amgen Inc	CEA/CD3	GI malignancies
RG-7802	1	Roche	CEA/CD3	Solid tumors
MOR209	1	MorphoSys AG	PSMA/CD3	Prostate
JNJ64052781	1	MacroGenics/J&J	CD19/CD3	B-cell malignancies
M7824	1	Merck KGaA	PD-L1/TGF	Solid tumours
OXS-1550	1	Oxis International Inc	CD19/CD22	Haematological malignancies
GBR-1302	1	Glenmark Pharmaceuticals	HER2/CD3	Breast cancer
MGD-009	1	MacroGenics Inc	B7-H3/CD3	Solid tumours
JNJ-61186372	1	Johnson & Johnson	EGFR/cMET	Solid tumours
PF-06671008	1	Pfizer Inc	P-cadherin/CD3	Cervical, head & neck
BI 836880	1	Boehringer Ingelheim GmbH	VEGF/Ang2	Solid tumours
JNJ-63709178	1	J&J /Genmab A/S	CD123/CD3	Acute myeloid leukaemia
ERY974	1	Chugai Pharmaceutical	GCP3/CD3	Solid tumours

Source: On-kòs Pharma Consulting

features in advance. "What is really important here is when you are doing your lead optimisation, being able to predict with some certainty that a certain molecule will hit two targets. That is the crucial part of what *Ex scientia* will bring to the table," the executive commented.

The project will look at immuno-oncology applications. Like the bispecific antibodies, the goal will be to achieve better efficacy with a single molecule, than the existing monospecific compounds deliver. As small molecules are less expensive to produce, the ultimate product may also be more affordable, he said.

References:
1. Kohler G, Milstein, Continuous cultures of fused cells secreting antibody of predefined specificity, *Nature*, 1975.
2. Chames, Patrick, Baty, Daniel, Bispecific antibodies for cancer therapy, *MAbs*, Nov-Dec 2009.
3. Sheng, Morgan How to get into the brain, 1 Dec 2015, www.gene.com.
4. Genmab also has four research agreements with Gilead Sciences Inc, Agenus Inc, Humabs BioMed AG and Pierre Fabre SA.

This article is based on interviews and a literature search by the *MedNous* editor. Interviews were conducted with senior executives at Cancer Research UK, F-star Biotechnology Ltd, Genmab A/S, Affimed NV and Evotec AG.