Bispecific antibody development gains momentum

As a concept, the bispecific antibody has been the object of scientific research for decades, but only recently has the clinical pipeline started to fill up. Cancer is the area of greatest activity. Here, the pipeline consists of several candidate products in Phase 3 and one, a product developed by the Janssen Pharmaceutical Companies of Johnson & Johnson Inc, that is in registration for non-small cell lung cancer at the US Food and Drug Administration.

Developers of bispecific molecules say that the FDA approval of blinatumomab (Blincyto) in 2014 was a threshold event for the sector. This is because it showed that an antibody construct could engage the immune system by creating a link between T cells and cancer cells. Blinatumomab came of age just as the entire field was opening up to immunological approaches to cancer with regulatory approvals for checkpoint inhibitors and reports of striking efficacy data for the new chimeric antigen receptor T cell therapies.

As illustrated in the table on pages 8 and 9, a large number of the bispecific antibodies in clinical development are T cell engagers, following the blinatumomab model. They target a T cell receptor in addition to a number of tumour-associated antigens including CD20 and CD33 on haematological malignancies and the prostate-specific membrane antigen in prostate cancer. Among the bispecific antibodies that do not re-direct T cells, there are compounds that target other antigen pairs, in some cases with the intention of influencing an immune pathway. While many of the new molecules are being pioneered by small biotech companies, a growing number of large pharma companies are investing in the field either on their own, or in partnerships with the smaller companies. The table is a representative sample of the nearly 100 compounds in clinical development.

In this article we interview executives from three companies active in the field, two of which are listed on the Nasdaq market in the US and one that is a recent start-up. The two listed companies, Merus NV and Genmab A/S, have substantial portfolios. The start-up, NovalGen Ltd, is due to bring its first product into clinical studies in the first half of this year.

The view from Merus

Merus is a Dutch biotech with a long-standing interest in bispecific antibodies. It originated in the Netherlands, but now has a management presence in the US. In 2013, the company led a European Union consortium investigating bispecifics for cancer, specifically looking at the role of the Wnt signalling pathway in promoting tumour growth. In the years that followed its portfolio grew and in 2016, Merus signed a licensing deal with Incyte Corp giving the US company rights for up to 11 bispecific antibody research programmes, in exchange for cash and an equity investment.

In January of this year, Merus announced a research collaboration and licensing deal with Eli Lilly and Co for up to three CD3 T cell engager therapies in cancer indications. If all three compounds are developed and commercialised, Merus would be due $1.6 billion in milestone payments. This is in addition to an upfront payment and an equity investment from Lilly.

In an interview, Bill Lundberg, Merus' chief executive, said it was the company's ability to screen through thousands of potential antibodies against a T cell component that made the technology so attractive to Lilly. This is possible because the company's platform uses the IgG format as a starting point. "I think the field is coming to appreciate the importance of the fully human format and the ability to evaluate many of these characteristics before you have to decide which one you take into the clinic," he said.

"In essence, we have a freezer full of more than 10,000 different antibodies and we use robotics and automation to do the molecular biology to clone them into the bispecific format," he added. These are then evaluated in assays for their ability to block or to bind or to change cellular behaviour. "We can tease apart all of these different characteristics across a large panel of characteristics," the executive said.

Merus' lead proprietary product, zenocutuzumab, is a bispecific designed to bind to the HER2 and HER3 receptors on cancer cells to block the interaction of HER3 with its ligand, neuregulin 1 (NRG1). The molecule is being studied in pancreatic, lung and a number of other solid tumours. "With our lead molecule Zeno we use the left arm to grab onto the cancer cell with the commonly-expressed antigen HER2, and we use the right arm to grab onto the cancer signalling mechanism and block that. In a population of molecularly-defined cancer cells that signal through the HER3 antigen by virtue of having this NRG1 fusion, we can potentially disrupt the NRG1 fusion pathway," the executive said. This is a 'dock and block mechanism' where one arm of the antibody anchors onto the cancer cells and the other blocks a cancer pathway.

In a project partnered with Betta Pharmaceuticals Co of China, Merus is taking the 'dock and block' strategy one step further. This is to first block the signalling of the EGFR and cMet antigens in order to inhibit tumour growth and survival. Second, it uses an antibody-dependent cellular cytotoxicity mechanism to increase the cancer cell killing potential of the molecule.

Merus' collaboration with Incyte has also produced an early-clinical stage product. This is a bispecific directed against solid tumours that engages PD-L1 on tumour cells and the T cell co-stimulatory molecule CD137. The concept is to activate immune effector cells in the tumour microenvironment while simultaneously blocking PD-L1 in the same immune cell population.

The view from Genmab

Genmab is an established European biotech with a history of successful partnerships. It was founded in 1999 as a spin-out from Medarex with IP for monoclonal antibody development. Through a 2012 licensing deal with Janssen Biotech, Inc for daratumumab, a monoclonal antibody therapy for multiple myeloma, Genmab saw its technology reach the market. It has been receiving substantial royalty income ever since. The

company now has four technology platforms, one of which is called DuoBody for bispecific antibodies.

On 1 March, Tahamtan Ahmadi, previously head of oncology, took over the new position of chief medical officer, head of experimental medicines. Before joining Genmab, Dr Ahmadi was head of experimental medicine at Janssen, where he led the development of daratumumab. In an interview, he discussed some of the programmes in the current Genmab portfolio.

Genmab's lead programme is epcoritamab, a bispecific antibody that targets CD20 on malignant B cells and CD3 on the surface of T cells. The dual targeting redirects a patient's T cells to engage and eliminate the malignant B cells, a mechanism of action pioneered by the developers of blinatumomab. "I think we will see in the near future the true potential of T cell (re)direction through bispecifics. I think that we are just at the very beginning of an era frankly," Dr Ahmadi said.

Epcoritamab is currently in Phase 3 development for diffuse large B cell lymphoma (DLBCL) under a partnership with AbbVie Inc. The molecule is generated from two conventional IgG antibodies in a process called 'controlled Fab-arm exchange.' This allows the binding arms of two distinct antibodies to be exchanged while still keeping the natural immunoglobulin structure and functions. "The Genmab point of view is that if you stay as close as possible to human biology and if you have a discovery process that allows you to interrogate as many epitope combinations as possible, then you are probably in a very iterative process…. and can get to the best possible construct," Dr Ahmadi said.

Epcoritamab is one of three bispecific projects that Genmab is undertaking with AbbVie under a collaboration that was announced in June 2020. The agreement involved an upfront payment of $750 million with total potential milestone payments of up to $3.15 billion. The two other projects are in Phase 1, one of which is a CD37 directed bispecific for haematologic malignancies, and the other is a bispecific targeting CD3 and the tumour antigen 5T4 for the treatment of solid tumours.

In addition to the new collaboration with AbbVie, Genmab has licensing deals with Janssen for multiple bispecific projects, the most advanced of which, amivantamab, has been submitted for a regulatory review in the US. Amivantamab targets tumours with EGFR and Met mutations for patients with non-small cell lung cancer. "This is something that is only just emerging, which is the idea of using [bispecifics] to target mechanisms of resistance and signal pathways," the executive said.

Also in the solid tumour space, Genmab has two early clinical projects underway with BioNTech SE to investigate ways of activating the immune system without generating toxicity. One combines a checkpoint blockade with the conditional stimulation of T cells. "Both programmes are trying to use bispecifics to address very complex biology in the immuno-oncology space," Dr Ahmadi said.

The view from NovalGen

NovalGen Ltd is a privately-held company launched in 2019 on the basis of new technology from University College London (UCL). The company's founder Amit Nathwani is a UCL professor, clinician, and serial entrepreneur. He previously founded and led the gene therapy company Freeline Therapeutics, now a Nasdaq listed company, where he remains a member of the board of directors. NovalGen received Series A funding from Convergys Capital, the UCL Technology Fund and UCL Business.

In an interview, Prof Nathwani said the reason for founding NovalGen was in large part due to his more than 20 years of experience treating patients with chronic lymphocytic leukaemia (CLL). "What is frustrating about this leukaemia is that even though it is the most common leukaemia in adults, the treatment opportunities, particularly when we think about curative therapies, really do not exist for this population," he said.

The bispecific approach attracted him because of the opportunity it provided to target two different antigens and therefore disrupt multiple pathways. "This is a necessity when you're targeting complex disorders like cancer or even when you get into other conditions such as inflammation," he said.

NovalGen has embraced the synthetic route to bispecific antibody development for which there is a growing number of proponents. The company's molecules are composed of two antibody-derived single chain variable fragments (scFv) linked in tandem, but with no Fc region. "In essence, they are different from antibodies in that they are synthesised essentially as a single peptide that falls on itself to form this bispecific format *in vivo*," the executive said. This means the molecules can be produced in a variety of formats depending on the disease.

NovalGen's lead product, NVG-111, follows in the footsteps of blinatumomab as a synthetic T cell engager but with a much broader mandate. The molecule is starting clinical development in patients with CLL and mantle cell lymphoma in the first half of this year, but there are plans to investigate it in solid tumours as well. "We're confident that we can move from haematological malignancies, which is where we're starting our programme, to solid tumours in a seamless fashion without having to further engineer or modify our lead compound NVG-111 in any way whatsoever," Prof Nathwani commented.

The reason for the confidence is the molecule's target. NVG-111 is directed against ROR1, a member of the receptor tyrosine kinase family. ROR1 is a cell surface antigen that is present on a range of malignancies and cancer initiating stem cells but is absent or expressed at low levels in healthy adult tissues.

NVG-111 has two modes of action: as a T cell engager, it brings T cells into proximity with cancer targets. And it also blocks a signalling pathway, the interaction between Wnt5 and ROR1, to limit tumour proliferation. "The fact is, it is the only T cell engager with a dual mode of action," Prof Nathwani said. Just over the horizon, but not yet built into the lead product, are biological sensors that would enable the company's bispecific molecules to turn on and off in response to cues from the environment.

This article was written by the *MedNous* editor on the basis of a literature search and interviews and data provided by the *MedNous* contributing editor Bruno Pagliara.

Bispecific antibodies in clinical development, March 2021				
Drug name	**Sponsor**	**Target**	**Phase**	**Indication**
Amivantamab	Johnson & Johnson Inc	EGFR/cMet	BLA filed in US	NSCLC
AFM-13	Affimed NV	CD30/CD16	2 pivotal	PTCL-CD30+
Glofitamab	Roche	CD20/CD3	3	NHL
KN046	Alphamab Oncology	PD-L1/CTLA-4	3	NSCLC
Flotetuzumab	MacroGenics Inc	CD123/CD3	2 pivotal	AML
Tebentafusp	Immunocore Ltd	gp100/CD3	3	Uveal Melanoma
Epcoritamab	AbbVie/Genmab	CD20/CD3	3	DLBCL
Mosunetuzumab	Roche	CD20/CD3	3	foll NHL
Teclistamab	Johnson & Johnson Inc	BCMA/CD3	2 pivotal	M. Myeloma
REGN5458	Regeneron/Sanofi	BCMA/CD3	2 pivotal	M. Myeloma
Elranatamab	Pfizer Inc	BCMA/CD3	2 pivotal	M. Myeloma
MP0250	Molecular Partners	VEGF/HGF	2	M. Myeloma
Zenocutuzumab	Merus NV	HER2/HER3	2	Breast
MEDI5752	AstraZeneca Plc	PD-1/CTLA-4	2	Kidney
BI 836880	Boehringer Ingelheim	VEGF/ANG2	2	Anal
NVG-111	NovalGen Ltd	ROR1/CD3	1	CLL + Mantle Cell Lymphoma
Navicixizumab	Oncxerna Therapeutics	DLL4/VEGF	1	Ovary
Cibisatamab	Roche	CEA/CD3	1	Solid tumours
AMG 330	Amgen Inc	CD33/CD3	1	AML
Cevostamab	Roche	FcRH5/CD3	1	M. Myeloma
AMG 596	Amgen Inc	EGFRviii/CD3	1	Glioblastoma
AMG 757	Amgen Inc	DLL3/CD3	1	SCLC
Tidutamab	Xencor Inc	SSTR2/CD3	1	Neuroendocrine
FS118	F-star Therapeutics	LAG3/PD-L1	1	Solid tumours
RG6194	Roche	HER2/CD3	1	Breast
GEM333	GEMoaB/BMS	CD33/CD3	1	AML
AMG 427	Amgen Inc	FLT3/CD3	1	AML
REGN4018	Regeneron/Sanofi	MUC16/CD3	1	Ovary
EMB-01	EpimAb Biotherapeutics	EGFR/cMET	1	Solid tumours
XmAb23104	Xencor Inc	PD-1/ICOS	1	Solid tumours
ATOR-1015	Alligator Bioscience	CTLA-4/OX40	1	Solid tumours

MCLA-145	Merus NV	PD-L1/CD137	1	Solid tumours
TG-1801	TG Therapeutics Inc	CD47/CD19	1	Lymphomas
XmAb22841	Xencor Inc	CTLA-4/LAG3	1	Solid tumours
AMG 160	Amgen Inc	PSMA/CD3	1	Prostate
Hu3F8-BsAb/nivatrotamab	Y-mAbs Therapeutics	G2/CD3	1	Neuroblastoma
GS-1423	Gilead Sciences Inc	CD73/TGFbeta	1	Solid tumours
HPN536	Harpoon Therapeutics	Mesothelin/CD3	1	Solid tumours
JNJ-67571244	Johnson & Johnson	CD33/CD3	1	AML/MDS
BNT-311	BioNTech/Genmab	PD-L1/CD137	1	Solid tumours
GEM3PSCA	GEMoaB/BMS	PSCA/CD3	1	Solid tumours
REGN5678	Regeneron	PSMA/CD28	1	Prostate
AK112	Akesobio	PD-1/VEGF	1	Solid tumours
HX009	Waterstone	PD-1/CD47	1	Solid tumours
AMG 199	Amgen Inc	MUC17/CD3	1	Gastric
BI 905711	Boehringer Ingelheim	TRAILR2/CDH17	1	Gastrointestinal
RG6139	Roche	PD-1/LAG3	1	Solid tumours
AFM24	Affimed NV	EGFR/CD16A	1	Solid tumours
IBI315	Innovent	PD-1 /HER2	1	HER2+ solid tumours
AMG 509	Amgen Inc	STEAP1/CD3	1	Prostate
PF-07062119	Pfizer Inc	GUCY2C/CD3	1	Gastrointestinal
FS120	F-star	CD137/OX40	1	Solid tumours
AMG 910	Amgen Inc	CLDN18.2/CD3	1	Gastrointestinal
ABBV-184	AbbVie Inc	Survivin/CD3	1	AML, NSCLC
SAR442257	Sanofi SA	CD38/CD28/CD3	1	M. Myeloma
Gen-1044	Genmab/AbbVie	5T4/CD3	1	Solid tumours
RG6296	Roche	BCMA/CD16a	1	M. Myeloma
CDX-527	Celldex Therapeutics	PD-L1/CD27	1	Solid tumours
JNJ-75348780	Johnson & Johnson	CD22/CD3	1	Hematologic malign.
RO7293583	Roche	TYRP1/CD3	1	Melanoma -TYRP1+
REGN5668	Regeneron	MUC16/CD28	1	Ovary
REGN7075	Regeneron	EGFR/CD28	1	Solid tumours
M1231	Merck KGaA	EGFR/Mucin 1	1	Solid tumours
TAK-186	Takeda	EGFR/CD3	1	Solid tumours