

Maturing antibody–drug conjugate pipeline hits 30

Driven by recent clinical breakthroughs and technological progress, 30 antibody–drug conjugates against over 24 targets are now in trials for blood cancers and solid tumours.

Asher Mullard

Drug discovery may not be rocket science, but the guided missile concept has nevertheless taken hold. With the US Food and Drug Administration (FDA)'s recent approval of Genentech's trastuzumab-DM1 — which uses a HER2-targeting monoclonal antibody (mAb) to deliver a toxic payload to cancerous cells — drug developers scored their third direct hit with antibody–drug conjugate (ADC) technology. Fuelled by these successes, drug companies are ramping up development of the burgeoning ADC pipeline.

At least 17 ADCs entered the clinic in 2011 and 2012, up from just 8 in 2009 and 2010. “There’s been a big increase in the past few years,” says Jan Reichert, a biotech consultant and unofficial antibody scorekeeper. Thirty ADCs are now in the clinic, accounting for around 15% of the clinical-stage anticancer antibody-based pipeline and outnumbering other modified mAbs such as bispecifics and fragments.

“It is a very exciting time to be involved in this field,” says Charles Morris, Chief Development Officer at ImmunoGen, one of two firms whose technology underpins the growth of the sector.

Unlike in the small-molecule world, where competitors often pursue the same targets, there is minimal overlap in the ADC pipeline (TABLE 1). A few firms are competing on CD19, CD22, CD70 and epidermal growth factor receptor (EGFR), but companies otherwise operate unchallenged on a diverse range of targets. And although some of these are well-established biological nodes, such as HER2 and EGFR, many are as yet ‘undrugged’ antigens. Sanofi’s SAR-566658 against mucin 1 (MUC1), for example, has confounded small-molecule drug developers for years. “ADCs are giving new life to

Table 1 | Clinical-stage ADC pipeline

ADC	Lead	Lead indications	Target	Payload	Phase
Inotuzumab ozogamicin (CMC-544)	Pfizer	Aggressive non-Hodgkin's lymphoma; acute lymphoblastic leukaemia	CD22	Calicheamicin	III
RG-7596	Genentech	DLBCL and follicular non-Hodgkin's lymphoma	CD79b	MMAE	II
Pinatuzumab vedotin (RG-7593)	Genentech	DLBCL and follicular non-Hodgkin's lymphoma	CD22	MMAE	II
Glembatumumab vedotin	Celldex	Breast cancer	GNPMB	MMAE	II
SAR-3419	Sanofi	DLBCL; acute lymphoblastic leukaemia	CD19	DM4	II
Lorvotuzumab mertansine (IMGN-901)	ImmunoGen	Small-cell lung cancer	CD56	DM1	II
BT-062	BioTest	Multiple myeloma	CD138	DM4	II
PSMA-ADC	Progenics	Prostate cancer	PSMA	MMAE	II
ABT-414	AbbVie	Glioblastoma; non-small-cell lung cancer; solid tumour	EGFR	Not disclosed	I/II
Milatuzumab doxorubicin	Immunomedics	Chronic lymphocytic leukaemia; multiple myeloma; non-Hodgkin's lymphoma	CD74	Doxorubicin	I/II
IMMU-132	Immunomedics	Solid tumour	TACSTD2 (also known as TROP2 or EGP1)	Irinotecan metabolite	I
Labetuzumab-SN-38	Immunomedics	Cancer; colorectal cancer	CEA (also known as CD66e)	Irinotecan metabolite	I
IMGN-853	ImmunoGen	Ovarian tumour; solid tumour	Folate receptor 1	DM4	I
IMGN-529	ImmunoGen	B cell lymphoma; chronic lymphocytic leukaemia; non-Hodgkin's lymphoma	CD37	DM1	I
RG-7458	Genentech	Ovarian tumour	Mucin 16	MMAE	I
RG-7636	Genentech	Melanoma	Endothelin receptor ETB	MMAE	I
RG-7450	Genentech	Prostate cancer	STEAP1	MMAE	I
RG-7600	Genentech	Ovarian tumour; pancreatic tumour	Not disclosed	Not disclosed	I
RG-7598	Genentech	Multiple myeloma	Not disclosed	Not disclosed	I
RG-7599	Genentech	Non-small-cell lung cancer; ovarian tumour	Not disclosed	Not disclosed	I
SGN-CD19A	Seattle Genetics	Acute lymphoblastic leukaemia, aggressive non-Hodgkin's lymphoma	CD19	MMAE	I
Vorsetuzumab mafodotin	Seattle Genetics	Non-Hodgkin's lymphoma; renal cell carcinoma	CD70	MMAF	I
ASG-5ME	Agensys	Cancer; pancreatic tumour; stomach tumour	SLC44A4 (AGS-5)	MMAE	I
ASG-22ME	Agensys	Solid tumour	Nectin 4	MMAE	I
AGS-16M8F	Agensys	Cancer; renal cell carcinoma	AGS-16	MMAF	I
MLN-0264	Millennium	Gastrointestinal tumour; solid tumour	Guanylyl cyclase C	MMAE	I
SAR-566658	Sanofi	Solid tumour	Mucin 1	DM4	I
AMG-172	Amgen	Cancer; renal cell carcinoma	CD70	Not disclosed	I
AMG-595	Amgen	Glioma	EGFRVIII	DM1	I
BAY-94-9343	Bayer	Cancer; mesothelioma	Mesothelin	DM4	I

ADC, antibody–drug conjugate; CEA, carcinoembryonic antigen; DLBCL, diffuse large B cell lymphoma; EGFR, epidermal growth factor receptor; GPNMB, glycoprotein NMB; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; PSMA, prostate-specific membrane antigen; STEAP1, six-transmembrane epithelial antigen of prostate 1; TACSTD2, tumour-associated calcium signal transducer 2.

targets,” says Beverly Teicher, chief of the Molecular Pharmacology Branch at the US National Cancer Institute.

They are also re-energizing sidelined mAbs. Whereas trastuzumab-DM1 incorporated a successful mAb for breast cancer, many of the ADCs in development could rescue preclinical mAbs that failed to deliver sufficient cancer cell killing activity when used on their own — perhaps because the antigens they targeted were not critical for cancer cell viability. If the antigen internalizes, these mAbs are being retested as guidance systems for toxic payloads. “What we see with this first crop of ADCs is a lot of opportunistic use of failed mAbs,” says Teicher.

New mAbs have their uses as well though, adds, Clay Siegall, CEO of Seattle Genetics, another major ADC player. “I don’t think there is a preconceived notion of using old versus new antibodies. Any antibody is potentially usable with ADC technology.”

Haematological ADCs

Much of the initial search for uses of ADCs took place in haematological cancers. The first two approved ADCs — Pfizer’s gemtuzumab ozogamicin (which has since been discontinued) and Seattle Genetics’ brentuximab vedotin — received the green light for leukaemia and lymphoma indications. And five out of eight ADCs in Phase II and III trials are against blood cancers. Partly, this balance was driven by an early view that ADCs would penetrate poorly into solid tumours. Haematological cancers, by contrast, offered accessible cells and, often, homogenous expression of cancer antigens.

Diffuse large B cell lymphoma (DLBCL), which is the most common form of aggressive non-Hodgkin’s lymphoma, and acute lymphoblastic leukaemia (ALL) have become particularly crowded.

Pfizer’s inotuzumab ozogamicin, an antibody against the B cell marker CD22 conjugated to the DNA-damaging drug calicheamicin, is competing in both of these indications, in combination with rituximab, an established mAb that targets CD20, another B cell antigen. Inotuzumab ozogamicin is currently the most advanced of the ADCs and Phase III data are due by December 2014. But clinical progress of this candidate, acquired by Pfizer during the Wyeth merger, has been slow; its first trials were announced in 2003.

“Some of these ADCs have been in trials for a long time, and you start to get worried about them,” says Teicher.

I keep wondering whether there are more mutant proteins on the cell surface that could be used as ADC targets.

Would-be upstarts include pinatuzumab vedotin (RG-7593) and RG-7596, which Genentech advanced into the clinic in 2010 and 2011, respectively. Pinatuzumab vedotin also targets CD22, whereas RG-7596 targets CD79b, an antigen that is expressed only on B cells. “From a cell-type-targeting perspective, these are very attractive targets,” says Stuart Lutzker, vice president of oncology early development at Genentech.

Genentech has initiated a two-arm trial comparing its Phase II ADCs, combined with rituximab, against one another in follicular non-Hodgkin’s lymphoma and DLBCL. “We’ll see if one is clearly superior to the other,” says Lutzker. The trial includes a crossover option; when the disease progresses, patients can start receiving the other ADC. This design and associated biopsy samples will provide Genentech’s scientists with some insight into the mechanisms of resistance. “We haven’t made any decisions as to how we’ll move these ADCs from Phase II to Phase III, but this will provide a nice proof-of-concept study for us,” says Lutzker.

The Phase II trial started in September 2012, and could be completed by the end of 2014.

Sanofi’s SAR-3419, which is also in Phase II trials for ALL and DLBCL, targets the B cell lineage marker CD19. Top-line data were expected late last year, and are anticipated soon.

“Not all of these ADCs will succeed,” cautions Bertrand Coiffier, a haematologist at the Hospices Civils de Lyon, in France, who has worked on clinical trials of various ADCs. Once a first ADC is approved in DLBCL in particular, for which around 30% of patients are refractory to the chemotherapeutic standard of care, the market for the others may fall off. Experimental naked mAbs and small molecules in Phase III development provide another layer of uncertainty.

The bigger question though, says Coiffier, is whether ADCs can be combined with chemotherapeutics, targeted small molecules, mAbs and maybe even other ADCs? Drug hunters are starting to develop such combination regimens, but preliminary data demand pause for thought, says Coiffier. ADCs, although less toxic than chemotherapies, are more toxic than naked mAbs and may induce thrombocytopenia, neutropenia and other adverse events. “It may not be possible to combine the ADCs with standard chemotherapies,” he says. If this is the case, their use may remain restricted to palliative settings in refractory patients.

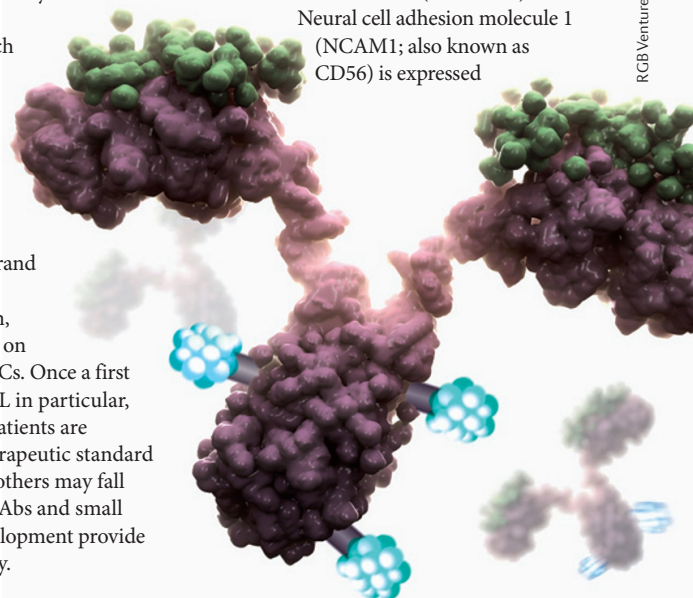
Solid tumour ADCs

The success of trastuzumab-DM1 in metastatic breast cancer has done away with the view that ADCs are only useful against blood cancers. In terms of solid tumours, the field is pursuing a broader suite of targets and indications, and making more use of companion diagnostics. “For the solid tumours, we see much more variable antigen expression. It behoves you to have a diagnostic strategy in place to look at the tumours that have the highest expression levels,” says Lutzker.

Celldex’s experience with its Phase II candidate glembatumumab vedotin backs this up. Celldex reported in December that its glycoprotein NMB (GPNMB)-targeting ADC doubled progression-free survival and overall survival in patients with advanced triple-negative breast cancer and high GPNMB expression. Celldex plans to initiate pivotal trials on the ADC by the end of the year.

ImmunoGen is taking a different tack with its mid-stage small-cell lung cancer candidate lorvotuzumab mertansine (IMGN901).

Neural cell adhesion molecule 1 (NCAM1; also known as CD56) is expressed



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Box 1 | Immunotoxins fall behind

While antibody–drug conjugates have surged, the related immunotoxin approach has languished.

Immunotoxins similarly use a monoclonal antibody (mAb) guidance system to deliver a toxic payload, but replace the small-molecule cell-killing agent with a larger biological poison. A first generation of these agents, which used chemical linkers to combine a mAb and a protein toxin, were immunogenic, cleared rapidly from the bloodstream and induced systemic toxicity at low doses. Hopes for later iterations of the immunotoxin technology — some of which used recombinant DNA to express antibody fragments linked to truncated toxins — has fared little better. “There is still concern about the immunogenicity of immunotoxins,” says Beverly Teicher, chief of the Molecular Pharmacology Branch at the US National Cancer Institute.

The field got a small boost earlier this year, however, when AstraZeneca announced plans to advance MedImmune’s moxetumomab pasudotox into pivotal trials for hairy cell leukaemia. Moxetumomab pasudotox consists of a CD22-targeting mAb covalently bound to a fragment of *Pseudomonas aeruginosa* exotoxin A. In a Phase I trial in which 48 patients received the immunotoxin, 26 patients experienced a complete response, the company reported last year.

Other immunotoxins in development include Helix Biopharma’s Phase I/II lung cancer candidate L-DOS47, which combines a carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6)-specific antibody fragment with a urease derivative, and Angimmune’s Phase I/II T cell lymphoma candidate A-dmDT390-bisFv (UCHT1), which combines a CD3-targeting antibody fragment with truncated diphtheria toxin.

in around 90% of small-cell lung cancers, says Morris, and so there isn’t much need for a patient selection tool. Preliminary results from an ongoing Phase II trial of the ADC in small-cell lung cancer are expected later this year. (ImmunoGen did use a patient selection tool to test the ADC in a Phase I trial in multiple myeloma, in which around 70% of patients have CD56 expression.)

The third ADC in Phase II trials for a solid tumour is Progenics’ PSMA–ADC, which is being developed for prostate cancer. Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is nearly ubiquitously expressed in prostate cancer. Progenics initiated a Phase II trial of the drug in September 2012, and anticipates primary completion of the trial in May 2014.

Phase I candidates, meanwhile, highlight several other facets of the changing ADC landscape. Amgen’s Phase I candidate AMG-595, for example, binds EGFR variant III (EGFRvIII), a mutated form of the cell surface receptor that can be highly expressed in glioblastoma multiforme and other cancers. By targeting the mutated rather than wild-type receptor, Amgen hopes to achieve increased cancer-tissue specificity, an approach that appeals to Teicher. “I keep wondering whether there are more mutant proteins on the cell surface that could be used as ADC targets. It seems like a natural,” she says.

Under optimistic assumptions, just 1.5% of an ADC’s small-molecule payload reaches its intended destination. So in addition to hunting for mAb targets that are highly

expressed on the cell surface and offer some tissue specificity, both of which can improve successful delivery, drug developers are also taking care to ensure that the mAbs in their ADCs bind to the best antigen epitope.

As a case in point, Lutzker points to Genentech’s recently disclosed Phase I candidate RG-7458. When Genentech was preclinically testing ADCs against MUC16, an ovarian cancer antigen, it compared the effects of targeting a repeating epitope of MUC16 versus a non-repeating epitope. The ADC against the repeating epitope delivered more toxin into cancer cells, making it clear which ADC to advance.

Payloads and linkers

Beyond target selection and antibody optimization — which can endow ADCs with antibody-associated cell-killing activity — payload selection and conjugation chemistry are also key. Payloads need to have picomolar potency. Linkers need to be stable enough to survive in circulation and labile enough to break down in the cell. “ADCs are non-trivial to develop. There are a lot of moving parts,” says Reichert.

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Currently, most ADCs use auristatins (monomethyl auristatin E (MMAE) and MMAF; Seattle’s Genetics’ weapons of choice) or maytansines (DM1 and DM4; ImmunoGen’s favourites) as toxins, which block tubulin polymerization and inhibit cell division. An upside of these payloads is that they provide a buffer against adverse events: ADCs that misdeliver their payload have relatively low toxicity in tissues where cells are not dividing.

But powerful DNA-damaging chemotherapeutics have demonstrated strong efficacy in many cancer types, and so the chase is on to incorporate these in ADCs as well. The discontinued gemtuzumab ozogamicin and the Phase III candidate inotuzumab ozogamicin both deliver DNA-damaging calicheamicin, but a newer payload that is generating more excitement is Spirogen’s pyrrolobenzodiazepines (PBDs). “Those are exquisitely, extremely potent toxins,” says Teicher. The first clinical test of these payloads should come soon, with Seattle Genetics planning to push an anti-CD33–PBD ADC called SGN-CD33A into the clinic later this year for the treatment of acute myeloid leukaemia.

Other firms, including Nerviano Medical Sciences and Mersana Therapeutics, are developing their own cytotoxic payloads that could add to the ADC arsenal. Given the importance of multidrug cytotoxic regimens for the treatment of cancer, says Lutzker, progress with payloads will be a “leap forward”. (Drug developers are also attaching mAbs to biological toxins to create ‘immunotoxins’, but have had difficulty overcoming immunogenicity issues; see BOX 1.)

Linker technology is also on the move. Seattle Genetics’ SGN-CD33A will showcase an engineered cysteine linker that uniformly delivers two drugs per antibody. Most clinical-stage ADCs, by contrast, deliver on average four drugs per antibody. By reducing the drug load, and increasing the drug–mAb homogeneity of ADCs, Seattle Genetics may improve the pharmacokinetics and pharmacodynamics of some of its mAbs and achieve manufacturing efficiencies.

Companies like Allozyne, Ambrx and Sutro are introducing unnatural amino acids into mAbs so that they can develop new linker chemistries. And Mersana is developing polymer tails that may tag up to 20 cytotoxics onto each mAb.

“ADCs, we believe, are the future of cancer care,” summarizes Jonathon Drachman, vice president of research and translational medicine at Seattle Genetics. “Not only are they working well now, but they are also rapidly evolving.”

ERRATUM

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PDB has been corrected to PBD, and the text has been updated to clarify Stuart Lutzker's affiliation.