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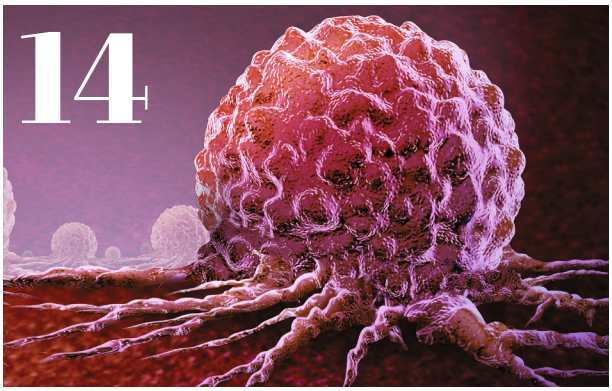

CONTENTS

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Conjugates get cancer in the crosshairs

By Diana Turner

Alongside traditional monoclonal antibodies, antibody-drug conjugates (ADCs) have enjoyed significant success, particularly as innovative, targeted cancer therapies have seen increased adoption. The global antibody-drug conjugates market size was $10.30 billion in 2023, estimated at $11.43 billion in 2024 and is anticipated to reach around $31.96 billion by 2034, expanding at a CAGR of 10.83% from 2025 to 2034, according to predictions from Precedence Research[1].

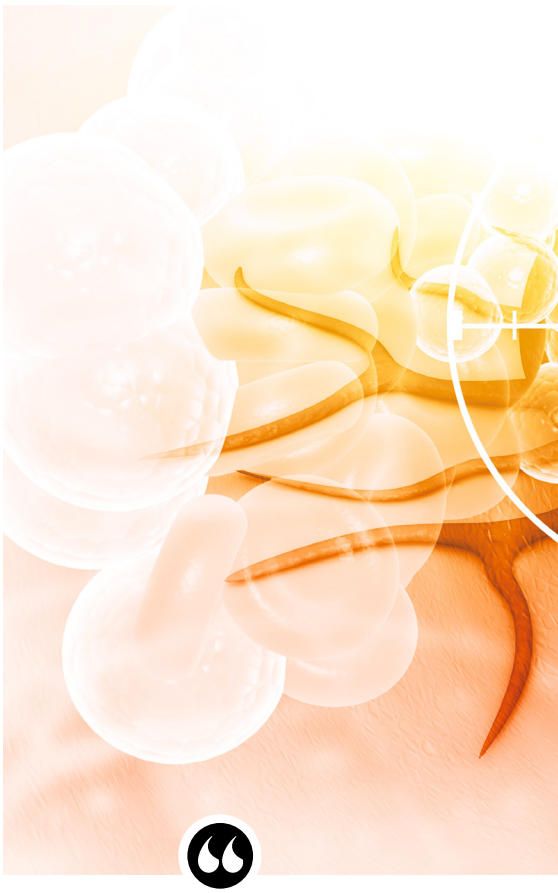
Talking to DDW, Heidelberg Pharma's CEO, Andreas Pahl, thinks that the rise of ADCs as a priority for big pharma companies can be attributed to several factors: "Firstly, the success of recent ADC approvals and their demonstrated clinical benefits have validated the potential of this therapeutic modality. ADCs offer a targeted approach to cancer treatment, combining the specificity of antibodies with the potency of cytotoxic drugs, which has shown promise in improving patient outcomes. Additionally, advancements in ADC technology, such as better linkers and more effective payloads, have addressed some of the earlier limitations, making ADCs more attractive for development."

Targeting cancer

As of May 2025, there were 15 ADCs approved by the US Food and Drug Administration (FDA), the majority of which treat cancers, with over 100 clinical trials ongoing. It is expected that the ageing population and ever-increasing rates of cancer will drive the market's growth into the future. Unsurprisingly, the breast cancer segment dominated the market with 28.9% in 2024, though the ovarian cancer segment is expected to grow at the highest CAGR of 13.2%[1]. Genentech's Kadcyla (ado-trastuzumab emtansine) for human epidermal growth factor receptor (HER) 2-mutated breast cancer held a 22.60% market share in 2024, though its US patent is due to expire in 2026. Another ADC for HER2-positive cancers, AstraZeneca and Daiichi Sankyo's Enhertu (trastuzumab deruxtecan) is expected by Precedence to grow at the fastest CAGR.

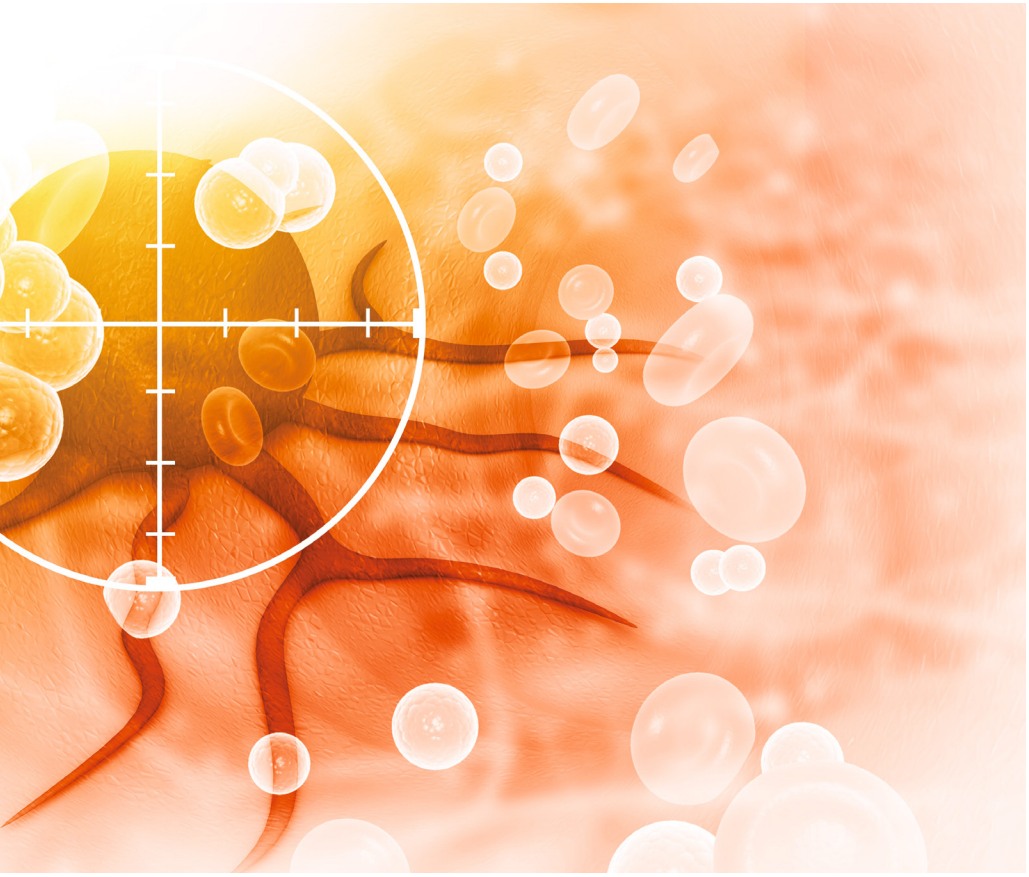
Non-small-cell lung cancer (NSCLC) is a new and expanding market segment for ADCs, with Enhertu first approved by the FDA in this indication in 2022. There are now 29 active Phase III trials of ADCs in NSCLC sponsored by big pharmaceutical companies. The ADC market in NSCLC is projected to grow at a CAGR of 6.8% across the seven major markets and exceed $3.9 billion in 2032, led by AstraZeneca/Daiichi Sankyo's Datroway (datopotamab deruxtecan) and Pfizer's sigvotatug vedotin, according to forecasts by analytics company GlobalData. Datroway is currently being evaluated in five Phase III clinical trials as a first-line therapy in combination with immune checkpoint inhibitors (ICIs), bispecific antibodies, and epidermal growth factor receptor inhibitors.

AstraZeneca is also assessing Datroway's potential in adjuvant settings in combination with its own ICI rilvegostomig (TROPION-Lung12). Datroway is expected to lead the NSCLC ADCs market, accounting for over 32.6% of sales and generating more than $1.2 billion by 2032 across the 7MM, closely followed by Pfizer's sigvotatug vedotin with 27.3% market share and over $1 billion in projected sales.



> **ADCs offer a targeted approach to cancer treatment, combining the specificity of antibodies with the potency of cytotoxic drugs, which has shown promise in improving patient out-comes.**

> **ADCs have the potential to replace chemotherapy, improve safety and efficacy, and prevent resistance mechanisms.**



Biswajit Podder, PhD, Oncology and Hematology Analyst at GlobalData, notes: "Trophoblast cell surface antigen 2-directed ADCs like Merck's and Gilead's Trodelvy (sacituzumab govitecan), HER2-targeting ADC Enhertu, and HER3-directed ADCs such as Datroway are being explored across broad NSCLC populations. Although Enhertu and AbbVie's Emrelis (telisotuzumab vedotin) have received approval, and Datroway is in the pre-registration stage for second-line treatment, companies are increasingly focusing on first-line and even early disease settings, similar to the trajectory of targeted therapies like AstraZeneca's Tagrisso (osimertinib) and immunotherapies like Merck's Keytruda (pembrolizumab) in recent years."

Regional shifts

In 2024, the North America region dominated the global market share with 50%, though emerging market Asia Pacific is predicted to grow at a remarkable CAGR of around 19% from 2025 to 2034[1]. This is due to rising cases of lung, ovarian and stomach cancer in China and India, which have forced researchers to develop advanced cancer treatment options to reduce the mortality rate. Another driver for this growth is degrader-antibody conjugates (DACs), which represent an emerging class of targeted therapy being led by South Korean and Chinese companies, such as Kangpu Biopharmaceuticals, Shanghai Helioson Pharmaceutical, and Primelink Biotherapeutics (Suzhou).

Restraints and limitations

The expansion of ADCs is partially limited by the high cost associated with their research and development, which excludes small-scale pharmaceuticals and biotech companies from taking a share. Low penetration capacity can also be an issue, alongside immunogenicity, lack of stable linkage in blood circulation, drug resistance, uncertain toxicity, poor mechanism of penetration and unusual size of mAbs. However, it is hoped that next-generation antibody drug conjugates like DACs, antibody-oligo conjugates (AOCs) and radioconjugates (RDCs) can combat such limitations by improving the product's overall efficacy.

Podder concludes: "ADCs face several challenges, including resistance to the payload, narrow therapeutic window, molecular heterogeneity, and toxicity, such as interstitial lung disease and thrombocytopenia. However, by identifying novel targets, developing bispecific antibodies, engineering better linkers, using multiple different payloads on one ADC, and identifying suitable patient populations using biomarkers, ADCs have the potential to replace chemotherapy, improve safety and efficacy, and prevent resistance mechanisms by combining ADCs with other treatment modalities such as immunotherapy."

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The rise of the bioconjugates

Diana Turner explores the latest developments in the antibody-drug conjugate (ADC) market and the opportunities presented by the next generation of bioconjugates.

Antibody-drug conjugates (ADCs) are biopharmaceutical products in which a monoclonal antibody (mAB) is linked to a small molecule drug with a stable linker. They have enjoyed considerable success, particularly in treating cancer, and as a result various different types of bioconjugates are now in development, including bispecific ADCs, dual payload ADCs, antibody-oligo conjugates (AOCs) and radioconjugates (RDCs).

Continued investment in ADCs

The level of investment in ADCs in recent years points to this being a growing trend in the therapeutic antibodies market. This can be seen in the 2025 launch of ADC company Callio Therapeutics with a $187 million Series A financing round to achieve clinical proof-of-concept for its HER2-targeted dual-payload ADC and a second undisclosed ADC programme. The company also entered into an exclusive worldwide license agreement with Hummingbird Bioscience for its multi-payload ADC platform in oncology, and associated intellectual property and pipeline assets.

"The multi-payload ADCs being developed at Callio Therapeutics have the potential to address large unmet medical needs by overcoming many of the limitations of existing ADCs," says Adam Simpson, Executive Board Chair of Callio Therapeutics and Venture Partner at investor Frazier Life Sciences. "With the expertise of the Callio Therapeutics team, together with access to the innovative multi-payload ADC technology, we believe that Callio Therapeutics will be the first company to show the clinical benefit of this exciting new multi-payload ADC approach and is well positioned to transform cancer therapy."

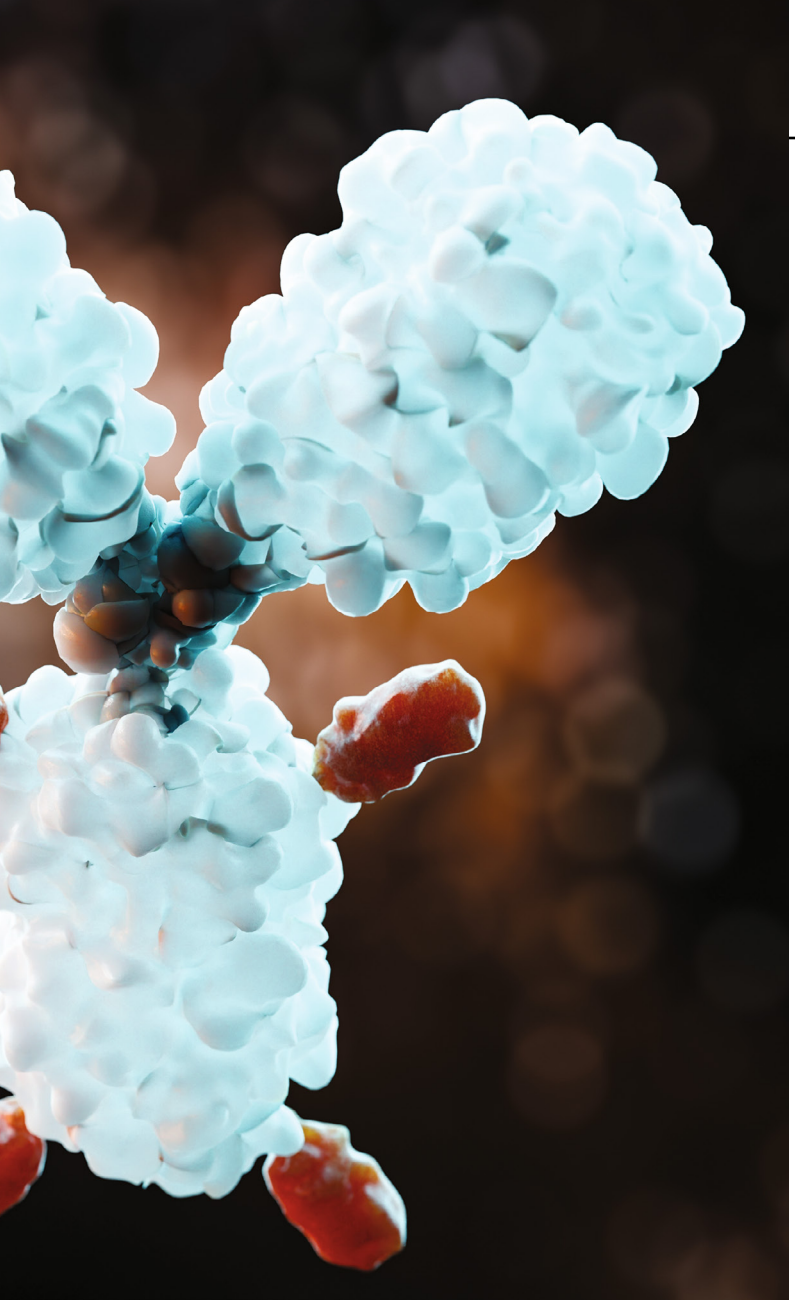
In another large financing,

> **We continue to deliver on our ambition for antibody-drug conjugates to improve upon and replace conventional chemotherapy for the treatment of multiple cancers.**

biotech company Adcendo raised $135 million in a Series B round, which it plans to use to accelerate the development of its ADC pipeline, including the ADCE-T02 (Tissue Factor ADC), ADCE-D01 (uPARAP ADC), ADCE-B05 and A0401 programmes. Michael Pehl, Chief Executive Officer of Adcendo, comments: "The excitement in the ADC space paired with our team's experience and passion for the underlying science motivates us to continue pushing our programmes forward into the clinic."

In late 2024, ADC manufacturer Allink Biotherapeutics successfully completed a $42 million Series A financing to support the clinical development of its pipeline of next-generation ADCs and bispecific antibodies targeting oncology and immunology diseases. The company also announced that the US Food and Drug Administration (FDA) had cleared its application for ALK201, and the first patient has been successfully dosed in Australia. ALK201 is an ADC candidate targeting FGFR2b, an oncogenic driver that has demonstrated clinical validation in solid tumours.

Big pharma is also keen to share in the success of the new generation of ADCs. In January 2025, Roche and Innovent Biologics agreed an exclusive license agreement for Roche to purchase ADC IBI3009 for advanced small cell lung cancer following the early phases of development, in return for $80 million up front and up to $1 billion in commercial milestone payments. IBI3009 targets DLL3, an antigen with low expression in normal tissues but significantly overexpressed in certain cancers, particularly small-cell lung cancer and other neuroendocrine tumours. "This partnership builds on Roche's long history of innovation in the area of ADCs, to address the unmet needs of patients with solid tumours with transformational medicines," states Boris Zaïtra, Head of Corporate Business Development at Roche.



Extended regulatory approvals for ADCs

There have been a number of important regulatory approvals of ADCs over the last year. The European Commission followed the FDA's example and granted marketing authorisation for Pfizer and Astellas' ADC Padcev (enfortumab vedotin) in combination with PD-1 inhibitor Keytruda (pembrolizumab) for urothelial cancer. The approval was based on results from the Phase III EV-302 clinical trial (KEYNOTE-A39) which showed that enfortumab vedotin in combination with pembrolizumab resulted in a median overall survival (OS) of 31.5 months compared to 16.1 months with platinum-containing chemotherapy. The median PFS of 12.5 months with the combination compared to 6.3 months with just chemotherapy.

Dr Thomas Powles, Barts Cancer Institute Biomedical Research Centre, UK, says: "Having an effective new first-line treatment for advanced urothelial cancer is opening a long-awaited new chapter in the management of this usually fatal disease. The impressive effects of the treatment combination were clearly seen during the Phase III clinical trial programme, with enfortumab vedotin in combination with pembrolizumab significantly extending overall survival and progression-free survival compared to platinum-containing chemotherapy. I look forward to seeing the treatment combination implemented as a first-line regimen in the clinical setting."

There has also been considerable success for AstraZeneca and Daiichi Sankyo's Trop-2-directed antibody and topoisomerase inhibitor conjugate datopotamab deruxtecan-dlnk (Datroway). In January 2025, the FDA approved Datroway for HR-positive, HER2-negative metastatic breast cancer based on the results of the Phase III TROPION-Breast01 trial, which showed a 37% reduction in the risk of disease progression or death vs. chemotherapy. In the trial, median progression-free survival was 6.9 months in patients treated with Datroway versus 4.9 months with chemotherapy. Dave Fredrickson, Executive Vice President, Oncology Hematology Business Unit, AstraZeneca, expands: "With this first approval of Datroway in the US, we continue to deliver on our ambition for antibody-drug conjugates to improve upon and replace conventional chemotherapy for the treatment of multiple cancers."

Then in June, Datroway was approved in the US for locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC), following Priority Review and Breakthrough Therapy Designation based on results from a subgroup analysis of the TROPION-Lung05 Phase II trial and supported by data from the TROPION-Lung01 Phase III trial. Datroway demonstrated a confirmed overall response rate (ORR) of 45% in patients with previously treated locally advanced or metastatic EGFR-mutated NSCLC as assessed by blinded independent central review (BICR). Complete responses were seen in 4.4% of patients and partial responses were seen in 40% of patients. The median DoR was 6.5 months.

New bioconjugate modalities

Following the success of ADCs, new modalities like antibody-oligonucleotide conjugates (AOCs) and radioconjugates are demonstrating promise. AOCs use a linker to attach different drug modalities – small molecules, peptides, antibodies, etc – to direct the oligonucleotide to the tissue of interest. Similarly, radioconjugates are designed to bind specifically to tumour associated antigens on the surface of cancer cells, allowing for more stable and prolonged tumour uptake of the radioactive payload, such as actinium-225.

AstraZeneca is one company leading development of these new therapies. In 2024, the company acquired radioconjugates developer Fusion Pharmaceuticals for $2 billion, including its lead programme alpha-emitting radiopharmaceutical FPI-2265, a small molecule targeting prostate cancers expressing PSMA (Prostate-specific membrane antigen). The pharma giant also has a long-standing agreement with Aptamer Group to evaluate the potential of using Optimer-based strategies to target renal cells and explore the feasibility of developing next-generation drug delivery vehicles, Optimer-drug conjugates.

"Oligonucleotide conjugates offer the potential to reach a specific cell or tissue, and have the potential to have a real impact for new drug targets identified in renal disease. By working together with Aptamer Group and leveraging their Optimer-based strategies we aim to identify novel targeting aptamers to deliver drug molecules to the kidney," explains Regina Fritsche Danielson, Senior Vice President and Head of Research and Early Development, Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals R&D at AstraZeneca.

Market potential for AOCs

AOCs are showing potential as treatments in oncology, autoimmune diseases, and genetic disorders, driven by key players Avidity Biosciences, Dyne Therapeutics, and Tallac Therapeutics, alongside

AstraZeneca. By 2035, according to analysts ResearchAndMarkets.com, the market is projected to see exponential growth to $5.26 billion per year by 2035, fuelled by the increasing adoption of oligonucleotide-based therapies, advances in genomic technologies, and the growing use of small interfering RNA (siRNA) and antisense oligonucleotides[1].

The growing prevalence of cancer and genetic disorders is also a key driver for the antibody conjugate oligonucleotide market. As the global cancer burden continues to rise, with an estimated 18 million new cancer cases and 9.6 million cancer deaths reported annually according to the World Health Organization (WHO), there is an increasing demand for targeted therapies that offer more effective treatments with fewer side effects.

Moreover, the integration of oligonucleotide conjugates with gene editing technologies such as CRISPR/Cas9 is expected to impel the market growth. This combination enables not only the precise delivery of genetic material but also targeted gene modification, creating new possibilities for gene therapies. For instance, Avidity Biosciences is leveraging this integration to enhance the delivery and efficacy of genetic therapies for rare diseases like Duchenne muscular dystrophy (DMD). Similarly, Editas Medicine is utilising CRISPR/Cas9 technology in combination with oligonucleotide conjugates to develop treatments for genetic conditions like Leber congenital amaurosis, a rare inherited eye disorder.

However, a major constraint in the antibody conjugate oligonucleotide market is the high cost of development and production associated with these therapies. The synthesis of oligonucleotides and the creation of effective antibody conjugates demand substantial capital investment in both R&D and specialised manufacturing infrastructure.

ResearchAndMarkets.com cautions that these elevated costs can restrict the affordability and accessibility of such treatments, especially in low-income regions, which could hinder their wider adoption and limit their impact on global healthcare[1].

AOCs and neuromuscular disorders

The rising incidence of genetic disorders, such as DMD, which affects about 1 in 3,500 male births according to the Muscular Dystrophy Association (MDA), and cystic fibrosis, which impacts around 70,000 people worldwide as reported by Cystic Fibrosis Foundation, is further driving the demand for therapies that can directly target the underlying genetic causes of these diseases.

In July 2025 Avidity Biosciences received FDA Breakthrough Therapy designation for delpacibart zotadirsen (del-zota) for the treatment of DMD in people living with mutations amenable to exon 44 skipping (DMD44). The therapy has previously been granted orphan designation by the FDA and the European Medicines Agency (EMA) and Rare Pediatric Disease and Fast Track designations by the FDA for the treatment of DMD44.

> **Oligonucleotide conjugates offer the potential to reach a specific cell or tissue, and have the potential to have a real impact for new drug targets identified in renal disease.**

Del-zota is currently being assessed in the Phase II EXPLORE44 Open-Label Extension (EXPLORE44-OLE) trial for people living with DMD44 and is the first of multiple AOCs the company is developing for DMD, including for del-desiran in myotonic dystrophy type 1 (DM1) and del-brax in facioscapulohumeral muscular dystrophy (FSHD). In the completed Phase I/II EXPLORE44 trial for people living with DMD44, del-zota demonstrated statistically significant increases in exon skipping, a substantial increase in dystrophin production, a significant and sustained reduction in creatine kinase levels to near normal and consistent favourable safety and tolerability.

"Breakthrough Therapy designation further underscores the FDA's appreciation for the significant potential of del-zota to address the underlying cause of DMD44 and the urgent need to bring innovative treatment options to the DMD community," says Steve Hughes, Chief Medical Officer at Avidity. "With the remarkable, consistent improvements we've seen in multiple biomarkers including dystrophin in the Phase I/II EXPLORE44 trial, we are focused on bringing del-zota to people living with DMD44 as quickly as possible and remain on track for our planned BLA submission at year end 2025."

Another therapy for DMD, Dyne Therapeutics' DYNE-251, received FDA Breakthrough Therapy Designation in 2025, following previous Fast Track, Orphan Drug and Rare Pediatric disease designations by the FDA and Orphan Drug designation by the European Medicines Agency (EMA). It is being evaluated in the Phase I/II global DELIVER clinical trial for individuals with DMD who have mutations in the DMD gene that are amenable to exon 51 skipping. DYNE-251 consists of a phosphorodiamidate morpholino oligomer (PMO) conjugated to an antigen-binding fragment (Fab) that binds to the transferrin receptor 1 (TfR1). It is designed to enable the production of near full-length dystrophin in muscle and the central nervous system (CNS) to provide functional improvement. In the trial so far, meaningful and sustained improvements from baseline in multiple functional endpoints were observed in both the 20mg/kg (selected registrational dose) and 10mg/kg DYNE-251 Q4W cohorts, through 12 and 18 months, respectively. DYNE-251 also demonstrated unprecedented near-full length dystrophin expression as measured by Western blot.

In addition to DYNE-251, Dyne's DYNE-101 was granted Breakthrough Therapy Designation in DM1 in the same year. According to company reports, in the randomised, placebo-controlled MAD portion of the DYNE-101 ACHIEVE trial, DYNE-101 demonstrated robust and sustained improvement in myotonia, as well as sustained improvements across multiple other endpoints. Treatment with DYNE-101also led to an improvement in video hand opening time (vHOT) of 3.3 seconds as compared to placebo at six months. The mean improvements at six months were sustained at 12 months for vHOT, 10MWR, 5xSTS, MDHI and QMT, which demonstrated a 10% improvement in strength at six months, increasing to 20% at 12 months relative to baseline.

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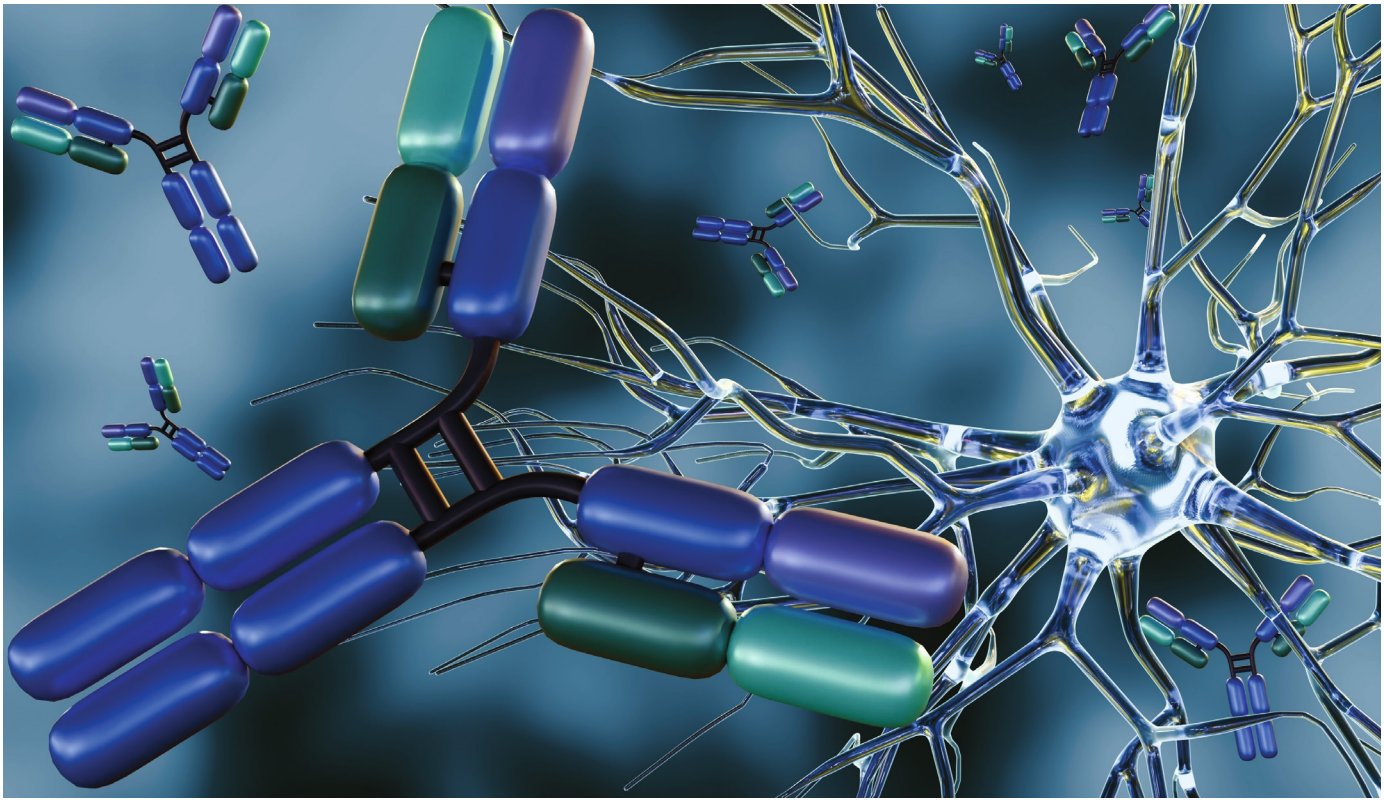


The challenges in solid tumour targeting with bispecific ADCs

Czech biotechnology company SOTIO recently started preclinical development of its first two bispecific antibody drug conjugates (ADCs). **Megan Thomas** speaks with SOTIO's Chief Scientific Officer, **Martin Steegmaier**, about the company's pipeline.

MT: Bispecific ADCs are a promising frontier in drug discovery. What specific challenges in solid tumour targeting is SOTIO aiming to overcome with its approach?

MS: Unlike standard ADCs targeted to a single tumour antigen, bispecific ADCs can be targeted to two antigens simultaneously. This dual-targeting format could improve the precision of ADC delivery — ensuring it gets to the cancerous tissue and not other, normal tissues — and could also help ADCs overcome the challenge of tumour heterogeneity, which is a key challenge in treating some of the solid tumours SOTIO is focused on. By targeting two distinct antigens, bispecific ADCs can more effectively target and kill a wider range of cancer cells within a heterogeneous tumour.

Furthermore, targeting two distinct tumour antigens bares the potential to prevent or to overcome potential emerging resistances. If one target were to be downregulated by the tumour (or its associated molecular mechanism of internalisation), the cytotoxic payload could still be delivered to the tumour cell via the second internalising tumour antigen.

MT: What considerations go into selecting and validating the two targets for your bispecific ADCs, and how do you ensure they synergise rather than interfere?

MS: Selecting two targets for a bispecific ADC approach may sound straightforward but this is substantially more complex than the selection of a tumour antigen for a monotargeting ADC approach. At SOTIO, we invest great thought and lots of resources in this key innovation step. The below mentioned questions are just some of the ones that need to be tackled in this process:

1. It starts with the question which tumour indication we would like to address and whether for this tumour indication (or indications) there are at least to some extent validated internalising tumour targets.
2. Equally important is the question whether there is underlying biology that hints that the potential target pairs physically interact or at least are colocalising on the surface of the tumour cell and whether the two target molecules are abundantly expressed on the surface of the tumour cells but ideally not or to a substantially lesser extent on the surface of any normal or vital healthy tissue to avoid added toxicities.
3. There are the more mechanistical and technical questions. Things like spatial consideration such as proximity and subcellular colocalisation of targeted epitopes and whether such pairs of targets (or monomers of one target) actually do get efficiently internalised and then end up in the lysosome to release the payload. Needless to say that all these questions will need to be answered by detailed expression and localisation analysis on tumour and healthy tissue via multiple approaches including mRNA and protein expression (proteomics, immunohistochemistry), often guided by big data and AI approaches. Equally important are mechanistic and proof-of-mechanism investigations in vitro (2D and 3D systems) and in vivo.

> **Due to the increased complexity, timelines from project start to clinical candidate selected tend to be longer.**

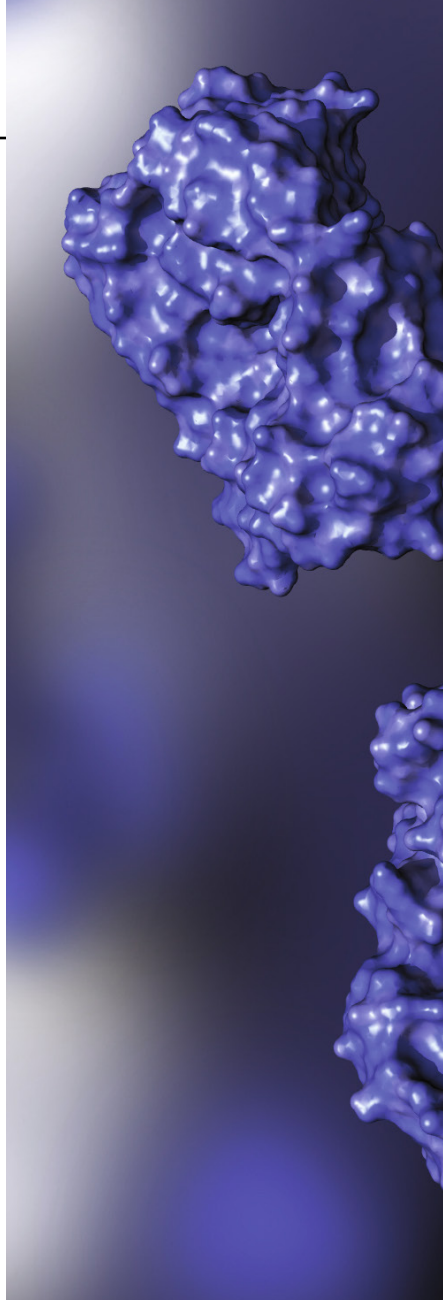
MT: From a discovery and development standpoint, how do bispecific ADCs complicate or accelerate the preclinical pipeline?

MS: Due to the increased complexity, timelines from project start to clinical candidate selected tend to be longer. In the case of a bispecific ADC, two binders that match or fit together in terms of affinities and epitopes need to be identified or engineered. There is another layer of complexity that needs to be tackled. The number of molecules that need to be tested and profiled multiplies. Instead of testing molecules on low or high target expression cells, all of a sudden one needs to look at all permutations of target 1 and 2 high and low. Needless to say that not only the discovery phase becomes more complex. Complexity is also added to the development aspects. Often one needs to develop two companion diagnostic tools instead of one. What is the expression level cut-off for target 1 and 2 to select or include patients in a trial? This complexity in most approached extends the timelines to the clinical candidate selected milestone and possibly even beyond, but if done right it will deliver highly differentiated drug candidates.

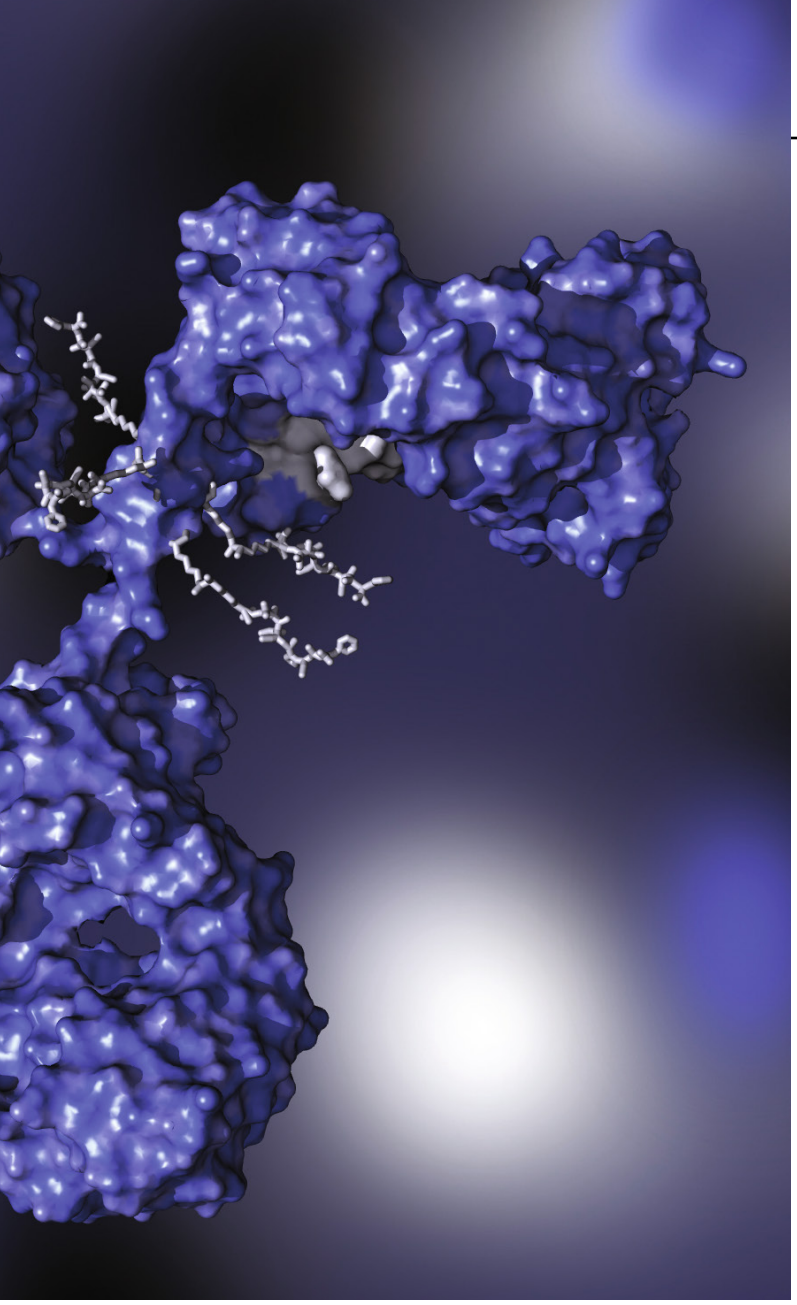
MT: Can you describe the technology platform or engineering strategy SOTIO is using to construct its bispecific ADCs, and how it supports scalability and manufacturability?

MS: We are utilising multiple technology platforms to construct our bispecific molecules, depending on the antibody binders we use or have available. The most straightforward technology is the so called common light chain approach combined with KiH (knob-into-hole) technology to ensure correct heavy chain pairing but in case our selected binders do not carry matching light chains, we rely on other, more sophisticated approaches. But in every case, we are ensuring good physico-chemical properties of the molecules and thereby ensure good manufacturability and scalability of the production process.

MT: Heterogeneity of tumour antigen expression is a major hurdle in oncology. How do your designs help mitigate this, and what data supports that promise so far?



MS: You are probably familiar with the terms 'AND' or 'OR' gate approaches. In addition, we are (for some projects) also applying a so called 'AND/OR' gate approach. This combines the best of both worlds. This allows us to combine a relatively clean target (but maybe more heterogeneously expressed target), with a somewhat 'dirtier', more broadly expressed target. By combining this more heterogeneously expressed but clean target with a somewhat dirty but highly internalising target, one can overcome the heterogeneous expression for this clean target and, if the design of the molecule in terms of affinities and binding valency is right, one still has a highly



internalising and clean (safe) molecule. In preclinical tumour models we could indeed show improved activity on tumours that display a heterogenious antigen expression. We are about to start safety studies in nonhuman primates to demonstrate that the more 'promiscuous' nature of the targeting antibody that allows us to overcome the tumour heterogeneity is nevertheless clean and well tolerated.

MT: What are the major learnings from the development of your first two bispecific ADC candidates, and how will they shape the next generation in your pipeline?

MS: We experienced that a simple so called 1+1 molecular design of the bispecific targeting antibody often is not sufficient to translate into an improved and differentiated profile of the drug in comparison to already existing monotargeting approaches. The majority of the bispecific ADC projects today are such 1+1 approaches but tumour and target biology is more complicated or complex and more sophisticated designs are needed. For all our bispecific projects we are nowadays not only testing antibody pairs in the standard 1+1 format, but we also include a format screen including 2+2 or asymmetric bispecific formats such as 2+1. This ensures that we can indeed address such often more complex target biologies and distributions.

> **Bispecific ADCs can be targeted to two antigens simultaneously.**

MT: For drug discovery researchers working on ADCs or multispecific formats, what will differentiate clinical success from failure?

MS: Many of the bispecific ADC approaches are built on simply combining two 'available' binders for at first sight obvious target combinations in a 1+1 format, but biology is much more complex than that. Just look at how many 1+1 bispecific ADCs targeting EGFR and HER2 or similar combinations are seen in the drug development pipelines. We have to go beyond such first generation bispecific approaches! This is of course technically much more challenging and consequently more lengthy and resource intensive but putting in more thought and molecule optimisation cycles will in the long term pay off, ensuring a really differentiated molecule and not only one that only caries the label 'bispecific' but is otherwise not truly differentiated and improved versus a monotargeting approach.

MT: Looking ahead, how does SOTIO envision the role of bispecific ADCs within the broader oncology therapeutic landscape? Will they complement or compete with existing modalities like cell therapies or immune checkpoint inhibitors?

MS: In contrast to cell therapies, bispecific ADCs can be developed as 'off-the shelf' precision medicines. This will allow them to not only get approval in late line settings but we eventually will see them moving into earlier lines of therapies offering differentiated treatment options for many more patients. Considering the logistical complexity of (at least autologous) cell therapy approaches and the associated high cost of such a treatment, (in contrast) a bispecific ADC approach for me can develop into a standalone regiment even in earlier line settings. Combining this with CAR-T approaches are less likely to be seen. Mechanistically, this makes lesser sense. In contrast, combinations with CPIs are indeed to be considered for the potential biological synergies such combinations can and will create.

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Biography:

Martin Steegmaier has held leadership roles at Boehringer Ingelheim, Roche, and MorphoSys, focusing on oncology drug discovery and antibody-based therapeutics. In 2022, he became Chief Scientific Officer at SOTIO. He earned a PhD in biochemistry from the University of Basel and an MBA from Edinburgh Business School.

What drug developers need to be aware of with ADC innovation

Abzena's VP, **Dr Ian Glassford** and VP of Regulatory Strategy, **Dr Jeffrey Mocny**, share ten critical aspects of ADC development and highlight the factors shaping the future of targeted therapies.

Antibody-drug conjugates (ADCs) have emerged as a groundbreaking advancement in oncology, promising improved patient outcomes and quality of life. However, developing these complex therapeutics involves numerous challenges and considerations. As we venture further into this field, it is essential to consider the many challenges and the evolving nature of ADC development. With the promise of ADCs comes many scientific, regulatory, and clinical considerations that must be navigated to transform these biopharmaceuticals from a concept into a cure.

Here Abzena's VP and Bristol, PA Site Head, Dr Ian Glassford and VP of Regulatory Strategy, Dr Jeffrey Mocny, dive into ten critical aspects of ADC development and bring to light the indispensable factors that are shaping the future of targeted therapies. From the therapeutic window to market demands, clinical efficacy, and beyond, each element underscores the importance of innovation and patient-centricity in forging the path forward.

1. Understanding the therapeutic window: data is reshaping our understanding of the ADC therapeutic window – the range of dosages of a drug or a treatment that provides effective therapy with minimal to acceptable side effects. It's crucial to balance safety and efficacy in drug design, a task that requires ongoing analysis and data-driven refinement. The goal is to create a dynamic therapeutic window that adapts to emerging clinical data, ensuring personalised treatment strategies that can significantly improve patient outcomes.

2. Comparing ADCs and small molecules: when looking at oncology trials, ADCs often show higher objective response rates (ORR) – the proportion of patients whose cancer reduces or disappears after treatment – compared to their small molecule counterparts. This indicates a potential for greater patient benefit but requires careful data analysis for accurate comparisons.

3. Dose optimisation: for effective ADC development, there's a heightened focus on fine-tuning dosing regimens to maximise the therapeutic index – the ratio of drug efficacy to its toxicity. This trend toward precision dosing is exemplified by the case of Sotorasib, a targeted therapy for a specific mutation in non-small cell lung cancer. After its initial approval, the FDA required further studies to explore dose optimisation, comparing the approved dosage to lower doses used in earlier trial phases. These studies aim to identify the most effective dose that minimises side effects, ensuring a better balance between treatment benefits and patient safety.

4. Maximum tolerated doses (MTD) and payload-linker stability: contrary to expectations, ADCs do not necessarily increase the MTD compared to equivalent small molecules. Factors like payload-linker stability and deconjugation in plasma play a crucial role here. A stable payload-linker ensures that the drug remains attached to the antibody until it reaches the target cancer cells, minimising premature release and reducing toxic side effects in non-target cells. This stability is key to maximising the therapeutic efficacy of the ADC while keeping the side effects within the tolerable range.

At Abzena we employ a matrix evaluation and developability approach to determine the optimal design of the linker payload architecture. This process includes in silico, in vitro, and ex vivo activity and safety assessments to support candidate ranking and lead selection. Such comprehensive evaluation and development strategies streamline and de-risk the scaling and manufacturing of linker payloads, ensuring that our ADCs not only meet the therapeutic goals but also adhere to safety standards.

5. Innovative conjugation technologies: the shift towards site-selective conjugation in ADC development aims to produce more uniformly structured ADCs, enhancing their efficacy and safety. By attaching the cytotoxic payload to specific sites on the antibody, these technologies ensure a more predictable drug release and interaction with cancer cells. This uniformity reduces the risk of overdosing and minimises off-target effects, thereby enhancing the safety profile.

Abzena's ThioBridge™ platform exemplifies the advancements in this field, overcoming limitations of earlier conjugation methods. ThioBridge™ employs site-specific conjugation to antibody interchain disulfides, leading to a more uniform Drug-to-Antibody Ratio (DAR) and offering stable attachment. This technology also allows for optimised pharmacokinetic profiles with flexibility in payload and spacer design providing an innovative approach to ADC development enhancing both the efficacy and safety of ADCs.

6. Clinical data and efficacy: recent clinical findings have prompted an evaluation of ADC maximum tolerated doses (MTD), which appear to align more closely with those of traditional small molecule drugs than previously anticipated. This realisation has pivotal implications for the design and optimisation of ADCs, underscoring the necessity for rigorous clinical trials to investigate efficacy at varying dosages.

7. Optimising downstream development: manufacturing ADCs becomes more challenging as their complexity increases. Streamlining downstream development is crucial for timely market entry. Advancements in artificial intelligence and machine learning are accelerating the development timeline by automating manufacturing processes.

8. Increasingly potent compounds: the use of highly potent active pharmaceutical ingredients (HPAPIs) in ADCs is a growing trend. HPAPIs enable lower dosages with reduced side effects. However, their potency also brings heightened safety risks during manufacturing. These challenges are addressed by implementing strict safety procedures, conducting extensive risk assessments, and using specialised equipment for safe handling.

9. Market growth and demand: the ADC market is rapidly expanding, driven by a demand for more targeted oncology treatments. This growth is a testament to the confidence in ADCs' ability to offer safer, more effective treatments with reduced side effects, meeting the needs of a patient population seeking more sophisticated and less invasive treatment options.

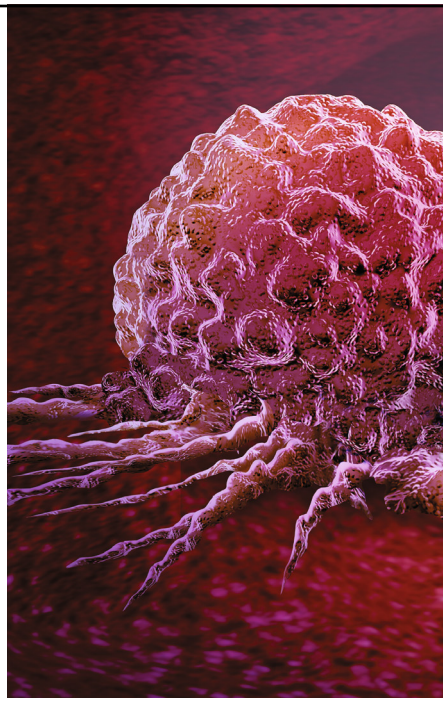
10. Patient-centric approach: at every stage of ADC development and manufacture, the patient journey is paramount. From ensuring the drug meets patient needs to considering the administration and dosing, a holistic understanding of the patient's experience is essential. The ultimate goal is to accelerate the delivery of the drug to the patients without compromising on quality or efficacy.

With over a dozen ADCs already licensed, the future of this field is bright. Innovations in linkers, payloads, and targeting mechanisms are expanding the reach of ADCs beyond oncology to other therapeutic areas. Realising the full potential of ADCs requires ongoing innovation, particularly in targeting strategies and linker technologies.

The growth trajectory of ADCs suggests a future where individual patient needs are met with treatments as unique as their conditions. The path to realising the full promise of ADCs is charted through relentless innovation and an unwavering commitment to patient-centric care. In this rapidly evolving field, remaining agile, informed, and ready to embrace new technologies and strategies is key. It is through this dedication to innovation and adaptability that ADC development will continue to break new ground, offering hope with unparalleled precision and efficacy.

Are you trying to develop a new ADC? Find out about Abzena's advanced capabilities in ADC development and manufacturing and how our experts can help accelerate your bioconjugate from concept to commercialisation.

ADCs: the next generation of targeted therapies



Megan Thomas explores what's to come from antibody-drug conjugates (ADCs) and speaks with experts in the industry.

Antibody-drug conjugates (ADCs) are among the hottest properties in pharma, powerful anticancer drugs that target tumours and deliver a lethal payload that destroys them, while leaving healthy tissues untouched.

Early days of ADC drug development

The first ADC was approved around the turn of the century, with Pfizer's Mylotarg (gemtuzumab ozogamicin) becoming the first such drug approved by the FDA for acute myeloid leukaemia in 2000. Nearly a quarter of a century later, ADCs are among the hottest properties in the cancer drug market following some notable successes after a difficult start for Mylotarg, which failed to live up to its potential because of concerns over its safety.

Mylotarg was ahead of its time in many ways: its novel structure of an antibody to target diseased cells, plus a cancer-killing payload attached via a special linker, is the blueprint for the antibody-drug conjugates (ADCs) that followed.

AstraZeneca and Daiichi Sankyo's Enhertu (trastuzumab deruxtecan) is a blockbuster-level success, combining the antibody trastuzumab found in Roche's HER2-targeting cancer drug Herceptin, attached via a special linker to the cancer-killing drug deruxtecan.

Approved in indications including HER-2 expressing breast cancer, Enhertu's payload is only offloaded once the antibody is bound to the target, where it is absorbed by the cancer cell, which it destroys.

Enhertu is now one of 13 ADCs approved by the FDA, with hundreds of others in development, some of which have been snapped up by big pharma in substantial deals, as is evident in the figures below.

These include Johnson & Johnson's $2 billion purchase of ADC specialist Ambrx in January, Genmab's $1.8 billion buy of ProfoundBio in April, and Ipsen's $900 million deal with Sutro for anticancer ADC STRO-003, also in April. Medilink's $1 billion ADC licensing deal with Roche, signed in January 2024, also caught the eye, three months after a $1 billion deal ADC deal with BioNTech.

Challenges for ADCs

There are, of course, challenges for ADCs. They are technically demanding to develop and finding new targets that are expressed only on the surface of cancer cells is a tough task. Development is also, perhaps, hindered by the troubles Pfizer experienced with Mylotarg.

Mylotarg was cleared by the FDA's accelerated approval process, allowing it to be marketed on the basis of early data in the expectation that a larger trial would confirm its benefits. But Pfizer voluntarily withdrew it from the market in 2010, after post-marketing data failed to confirm its benefits and a lackluster sales performance, although it was reintroduced in 2017 following a reformulation and some further data from investigator-led trials.

Getting new targets for ADCs is a high priority as it could lead to therapies that are more likely to hit cancer cells, allowing for higher doses and greater efficacy with fewer trade-offs needed to ensure an acceptable safety profile.

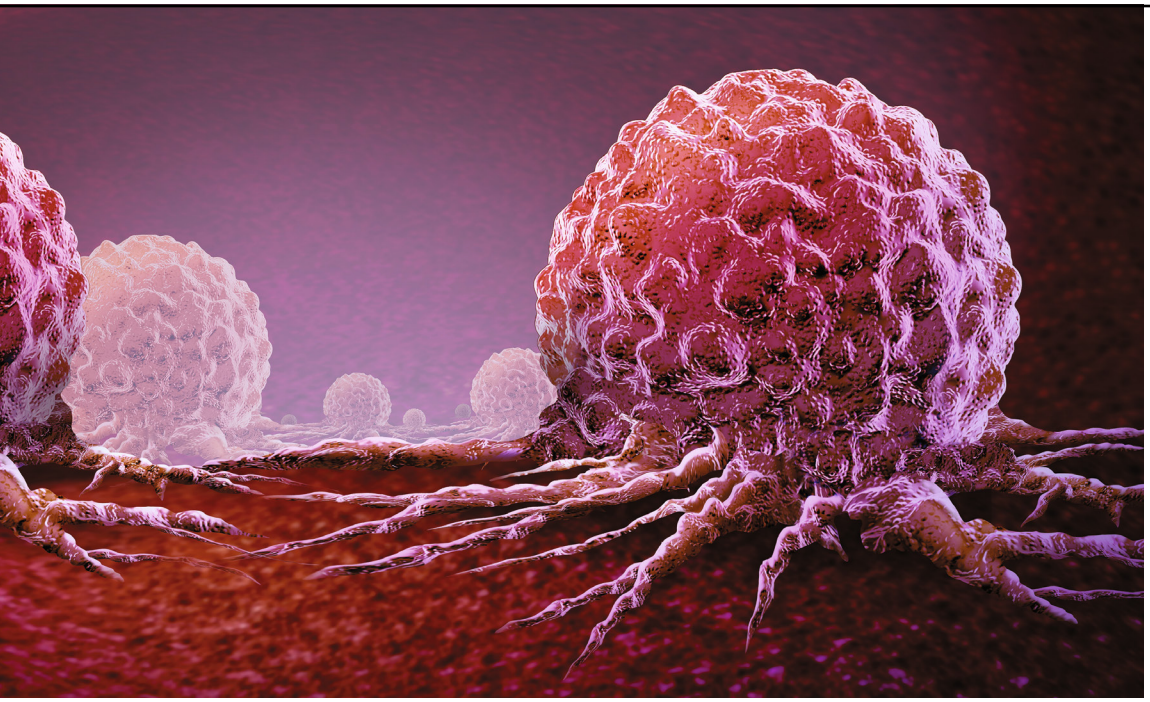
New targets

Professor Andreas Pahl, CEO of Germany-based ADC specialist Heidelberg Pharma, says: "Finding new targets for ADCs involves several significant challenges. Firstly, identifying tumour-specific antigens that are highly expressed on cancer cells but have limited or no expression on healthy cells is crucial to minimise on-target off-tumour effects and toxicity.

"The heterogeneity of tumours further complicates this process, as different patients, and even different cells within the same tumour, may exhibit varying antigen profiles. Additionally, the dynamic nature of tumour biology means that these targets can change over time, or under treatment pressure, necessitating continuous

Figure 1: Major deals involving ADCs – 2024

Buyer	Acquired company	Month	Value
Johnson & Johnson	Ambrx	January	$2bn
Genmab	ProfoundBio	April	£1.8bn
Ipsen	Sutro Biopharma	April	$900m
Merck & Co	Abceutics	April	$208m



research and adaptation."

Stefan Ries is Chief Scientific Officer at DISCO Pharmaceuticals, a German company specialising in finding targets for targeted therapies such as ADCs. DISCO's approach is to analyse the "surfaceome" of cancer cells – the totality of all proteins expressed on the cell surface – looking for ways that diseased tissue is differentiated from normal tissue. Ries noted that there are other things to think about aside from finding targets expressed only on tumour cells.

He adds: "The target must be internalised efficiently upon antibody binding to ensure the cytotoxic payload is delivered into the cancer cell to trigger cell death. Also, off-target effects of ADCs have to be taken into consideration when selecting the right cytotoxic payloads. This requires extensive preclinical research and validation."

Advanced genomics and proteomics technologies are being used to discover and validate new targets, Pahl noted, including high-throughput screening techniques and bioinformatics tools. "Collaborative efforts between academic institutions and industry are also accelerating the discovery process," Pahl said.

According to Ries, one approach is to find targets that tend to be clustered on the surface of cancer cells, allowing for development of bispecific ADCs. These have different binding sites on the tips of the antibody's "Y-shaped" structure, allowing them to bind with two different targets at once. This increases their chances of hitting a target on the surface of a tumour while reducing side-effects caused by the drugs accidentally killing healthy tissue.

ADC risks

There are risks associated with ADCs, including off-target toxicity, limited efficacy due to drug resistance and complex manufacturing processes.

Pahl explains: "On-target toxicity can arise from the ADC affecting healthy cells that express low levels of the target antigen, whereas off-target toxicity can arise from premature release of payload in circulation or from unspecific uptake of the ADC in healthy cells. Drug resistance may develop as cancer cells adapt to the ADC treatment, reducing its effectiveness over time."

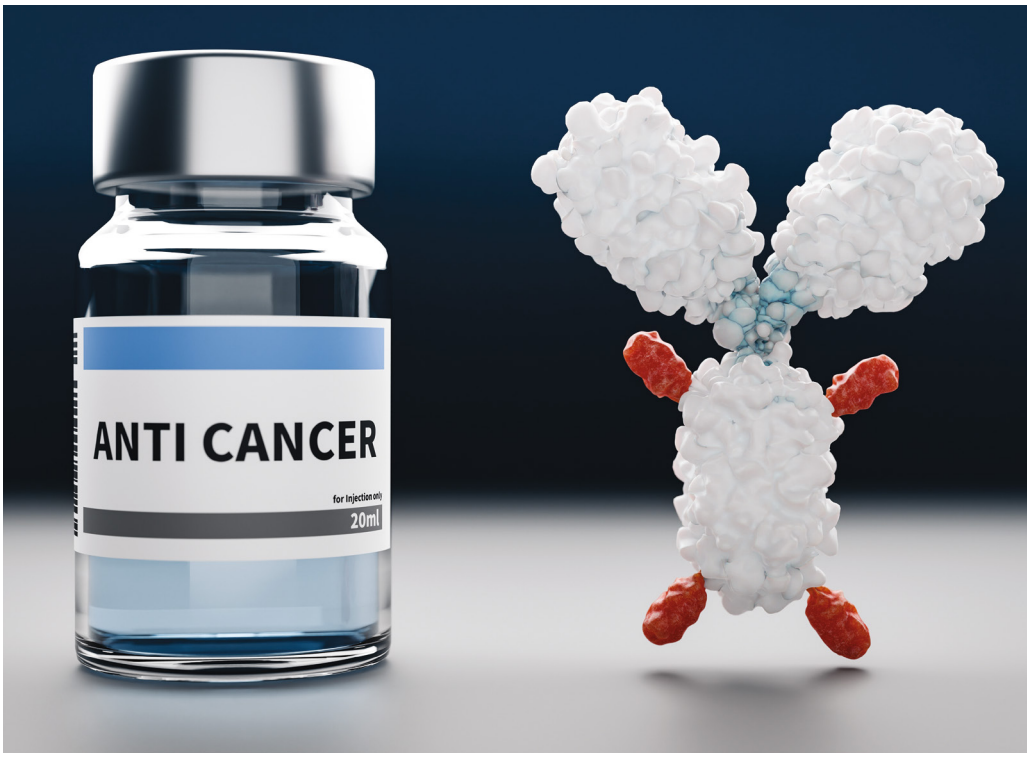
Heidelberg Pharma wants to exploit the destructive power of alpha-Amanitin to attack cancer cells, by attaching it to an antibody that binds to tumours, while leaving healthy tissues unaffected. Known to modern science as an inhibitor of RNA polymerase II, alpha-Amanitin is a poison that, when ingested by eating mushrooms such as the death cap (Amanita phalloides), destroys liver cells. The compound targets the transcription process at the heart of all cells, with the accurately antibody section of the drug preventing the poison from damaging healthy tissues.

Pahl says there is a bright future for ADCs, citing the string of high-profile, high value deals where big pharma companies have snapped up rights to pipeline assets. He adds: "The rise of ADCs as a priority for big pharma companies can be attributed to several factors. Firstly, the success of recent ADC approvals and their demonstrated clinical benefits have validated the potential of this therapeutic modality. ADCs offer a targeted approach to cancer treatment, combining the specificity of antibodies with the potency of cytotoxic drugs, which has shown promise in improving patient outcomes.

Figure 2: Examples of FDA-approved ADCs – 2024

Drug	Trade name	Manufacturer	Condition	Target	Approval Year
Gemtuzumabozogamicin	Mylotarg	Pfizer/Wyeth	Relapsed acute myelogenous leukaemia (AML)	CD33	2017,200
Brentuximab vedotin	Adcetris	Seattle Genetics, Millennium/Takeda	Relapsed HL and relapsed sALCL	CD30	2011
Trastuzumab emtansine	Kadcyla	Genentech, Roche	HER2-positive met-astatic breast cancer after treatment with trastuzumab and maytansinoid	HER2	2013
Trastuzumab deruxtecan	Enhertu	AstraZeneca/ Daiichi Sankyo	Adults with unresectable or metastatic HER2-positive breast cancer who have received two or more anti-HER2 regimens	HER2	2019

"Additionally, advancements in ADC technology, such as better linkers and more effective payloads, have addressed some of the earlier limitations, making ADCs more attractive for development. And, last but not least, therapy with ADCs offers physicians the decisive advantage that it can be administered on site at the hospital. Many other new treatment methods, such as CAR-Ts or radio-conjugates, can only be carried out in a few specialised centres."



Combination therapies

There's also a growing body of clinical evidence that ADCs could be used in combination with other therapies to enhance their potency.

Combining ADCs with chemotherapy is a well-accepted strategy, with clinical trials showing it can help overcome drug resistance. Many chemotherapies work by damaging DNA in cancer cells, leading to effective combinations with ADCs that target certain parts of the cell cycle. Chemotherapy may also increase the levels of surface antigens targeted by ADCs – for example combining gemcitabine can increase expression of HER2, making it a good choice for combination with ADCs that bind to this receptor.

However, there are issues with overlapping-side effects with chemotherapy, and clinicians have more confidence in the safety profile when used in combination with other drug classes, such as endocrine therapy. It's also possible to use ADCs in combination with radiotherapy, which can induce cancer cells to produce neoantigens that could be targeted by ADCs, although this has yet to be explored in the clinic[1].

Combining ADCs with drugs targeting DNA damage response mechanisms such as poly (ADP-ribose) polymerase (PARP) inhibitors could be another option. The combination approach could be made possible because of fewer overlapping toxicities between these two therapeutic approaches. As our knowledge of cancer biology expands, so does the list of potential targets, with receptors such as Claudin18.2, ROR1, poliovirus receptors (PVR) coming into the frame[2].

Immunotherapy potential

An exciting potential combination is with immunotherapy, due to an oft-overlooked property of antibodies. Their Y-shaped structure allows for many different functions: while the tips of the "Y" engage with the surface receptor, the "tail" (Fc) interacts with immune cells.

This includes important interactions with white blood cells and the immune system, encouraging them to destroy cancer cells through a range of mechanisms. These include cytotoxicity, phagocytosis, and attacks from the complement system. This also means that using ADCs in combination with immunotherapy has been shown to create synergies, as immune checkpoint inhibitors.

For example, Astellas and Pfizer's Padcev (enfortumab vedotin) was FDA approved in April 2023, in combination with Merck & Co's PD-1 checkpoint inhibitor Keytruda (pembrolizumab), for patients with locally advanced or metastatic urothelial carcinoma, particularly those who could not receive cisplatin-based chemotherapy.

Heidelberg's Pahl says: "As precision medicine continues to advance, ADCs represent a logical extension of targeted therapies, aligning with the broader trend towards more personalised cancer treatments. Moreover, the substantial commercial potential of ADCs, driven by their high efficacy and the unmet medical needs they address, has incentivized big pharma companies to invest heavily in this area, ensuring a robust pipeline of next-generation ADCs."

DISCO's Stefan Ries points out that as our understanding of cell surface proteins increases, there could be the potential to expand ADCs into therapy areas beyond oncology.

ADCs could be used to carry payloads other than cytotoxic drugs, such as anti-inflammatory compounds, antibiotics and siRNAs, Ries said. Any disease where there is a target that clearly differentiates it from healthy tissues could be eligible, he added.

He says: "Infectious diseases, autoimmune disorders, and certain neurological conditions could benefit from the targeted approach of ADCs. By harnessing the precision of the ADC technology, we can develop therapies that more specifically target pathogenic cells or disease-causing proteins."

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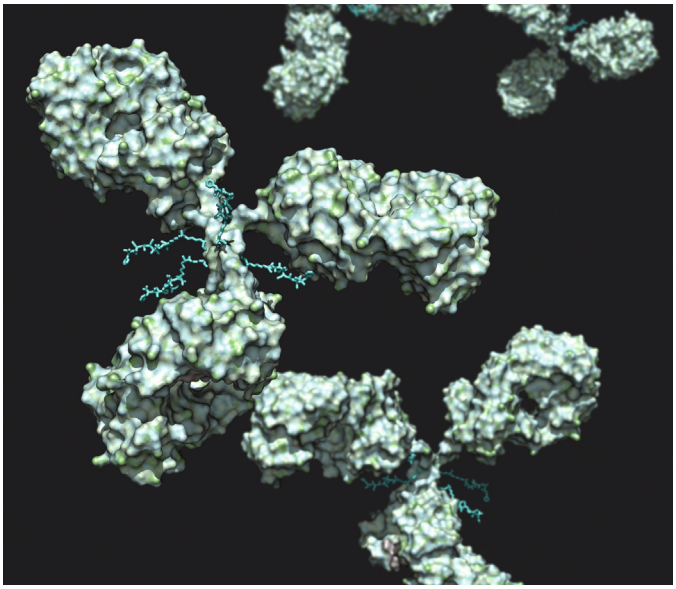
Finding protein therapeutics for cancer treatment

At the 2024 American Association of Cancer Research (AACR) Annual Meeting, **Megan Thomas** spoke with **Dr Paul Moore**, Chief Scientific Officer at Zymeworks and **Dr Nina Weisser**, Director of Multispecific Antibody Therapeutics at Zymeworks, about the future of cancer research.

MT: Can you give a topline summary of the new data presented at AACR?

We had five presentations at AACR this year (2024) providing new details on Zymeworks' preclinical pipeline, including an update on ZW191, our FRa targeted ADC which we anticipate filing an IND application on this year, and progress on one of our trispecific T cell engager (TCE) platforms. Collectively, the data presented highlighted the strength of the company's preclinical pipeline and our potential to develop novel antibody-drug conjugates (ADCs) and multispecific antibody therapeutics (MSATs) using complementary, antibody-based technologies.

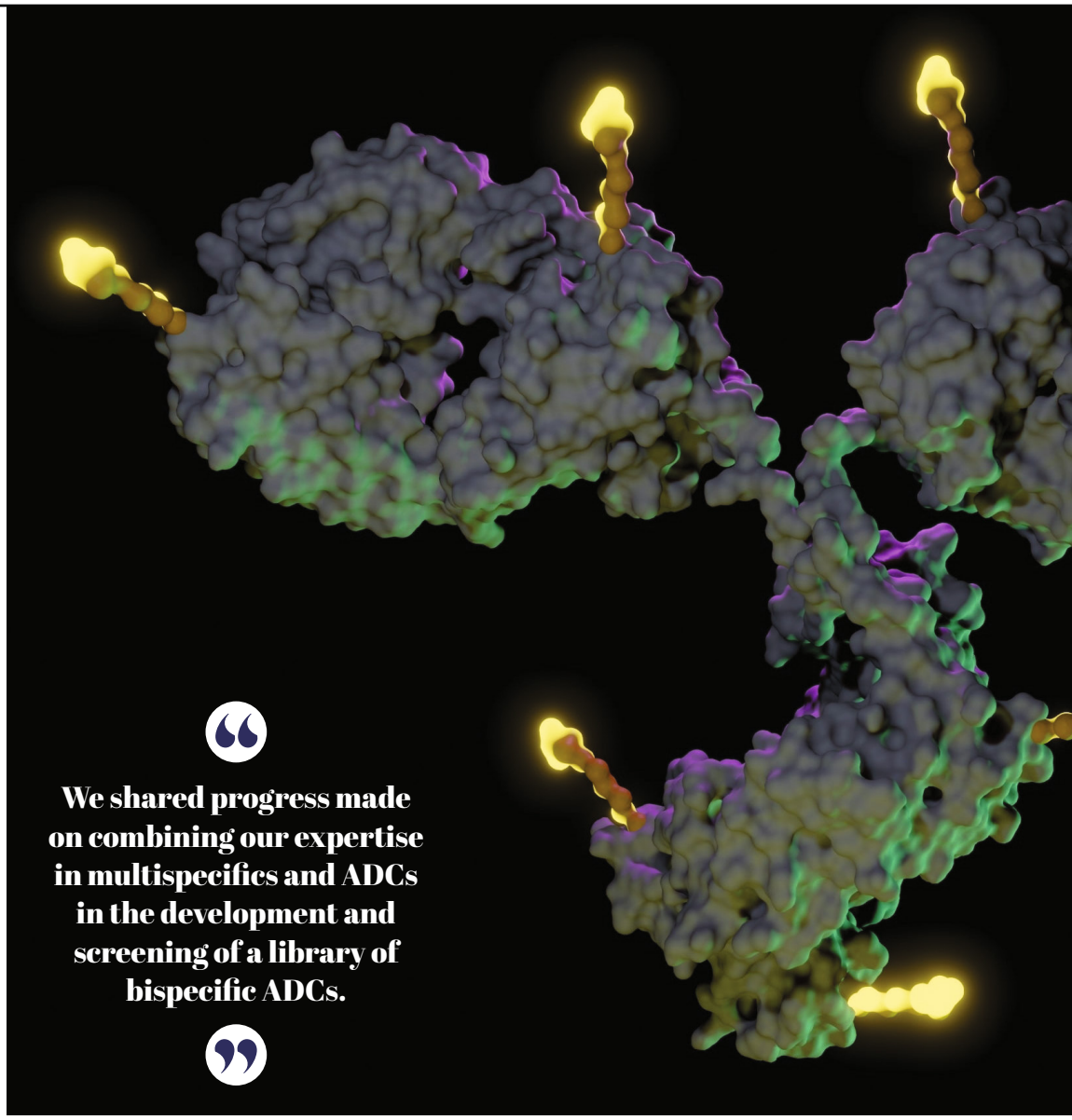
The ZW191 presentation included new data demonstrating the superior internalisation, payload delivery and spheroid penetration of the parental FRa antibody incorporated in ZW191 compared to other FRα-targeted antibodies being developed as ADCs. Expanded preclinical anti-tumour activity of ZW191 across multiple FRa expressing tumour types including ovarian, lung, endometrial, and triple-negative breast cancer (TNBC) was also presented, in addition to repeat dose safety studies in non-human primates (NHP) demonstrating its favourable tolerability profile. Beyond the ZW191 poster, our ADC team also presented on the development of novel 3D cancer cell model systems, that are more predictive of in vivo anti-tumour efficacy in xenograft and PDX models, that support functional screening and characterisation of our ADC molecules. Finally, we shared progress made on combining our expertise in multispecifics and ADCs in the development and screening of a library of bispecific ADCs. Specifically in the generation and screening of a library of bispecific ADCs, to identify those optimally formatted to overcome challenges associated with targeting a single antigen.



Overall, the presented data highlighted the attention to design and functionality of our multispecific and ADC platforms, that is also reflected in the favourable preclinical profile of our molecules to benchmark comparators. Importantly we believe the approaches shared can also be extended to additional cancer types and associated targets.

MT: How will these developments influence the landscape of the development space for antibody drug conjugates (ADCs) and T cell engagers (TCEs)?

Our team's goal is to develop a diverse pipeline of novel therapeutics that can improve the standard of care for cancers and other diseases that are currently labeled as "difficult-to-treat." In the ADC treatment space, we chose to develop therapeutic candidates that have the potential to address challenges associated with the existing ADC treatment space, including high discontinuation rates, off-target toxicities and issues related to maximum tolerated doses. In the T cell engager treatment space, we are focused on developing therapeutic candidates that have the potential to overcome challenges that have plagued TCE treatment, including limited success against solid tumours as a result of a narrow therapeutic window due to dose-limiting toxicities associated with cytokine release syndrome (CRS), neurotoxicity, on-target-off-tumour effects or poor anti-tumour activity.



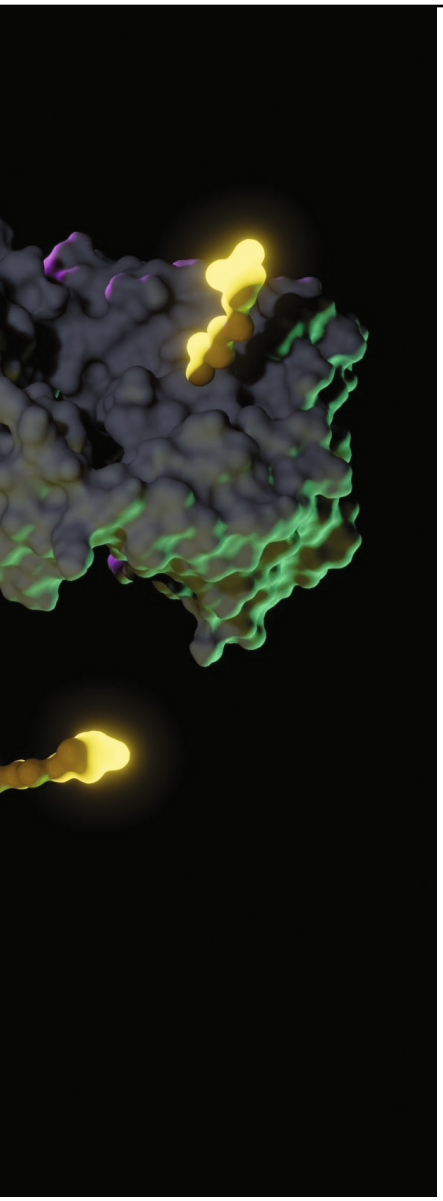
> We shared progress made on combining our expertise in multispecifics and ADCs in the development and screening of a library of bispecific ADCs.

MT: What are some key takeaways from your time at AACR

Progress was reported across all aspects of oncology, from basic biology to clinical studies with informative updates on various therapeutic modalities, including targeted small molecules, immune and cellular therapies, and cancer vaccines. As researchers dig deeper into cancer mechanisms at the cellular level, both within the tumour microenvironment and the host macroenvironment, the level of complexity and multitude of factors controlling tumour growth and metastases is becoming more apparent, albeit still not fully understood. Importantly, the various deep-data multiomics approaches being applied across the spectrum of tumour types are being paced with advances in computational biology and artificial intelligence (AI) that should accelerate our understanding of the data and contribution of various pathways. This is already yielding new insights to molecular targets and cellular mechanisms to leverage in the design of next generation cancer therapeutics. While there has been remarkable progress in the last 5-10 years with immune based therapeutics including checkpoint inhibitors, CAR-T cells and antibody-drug conjugates, results from clinical trials presented at the meeting clearly show the need for further advancements, to increase the breadth of patients that respond, to improve the depth of responses, to limit side effects and to better select patients that will benefit from particular treatment regimens.

MT: What do you think is the most exciting opportunity for global cancer research?

With increasing knowledge of the fundamental pathways and mechanisms driving cancer, and learnings from existing cancer therapeutics – both approved and in development – the opportunity to build next generation multi-functional therapeutics that incorporate these learnings into their design is here. The critical cancer signalling pathways to either block or leverage, the cell populations to eradicate or mobilise, and the targets to select for those populations are becoming increasingly apparent from deep profiling and advancements in tools to interpret. Advances in AI to drive more rapid and effective design of therapeutics to leverage this knowledge should translate into better therapeutics, while advances in individual patient profiling should aid in patient selection. The ability to also combine multiple mechanisms of action into a single multi-functional therapeutic layered with therapeutic combination strategies should further advance benefit to cancer patients across the globe.



MT: Where are the challenges in cancer research and how is the work Zymeworks is doing going to influence them?

Two challenges that Zymeworks is focused on addressing include challenges associated with the biology of the tumour that play a role in treatment resistance and failure, and challenges associated with the optimisation of drug design that maximise the therapeutic window to enable delivery of safe and effective therapies. Both the biology of the tumour and tailored drug design are considered in the development of our ADC and multispecific therapies.

For example, biological challenges associated with tumour heterogeneity – which is thought to limit treatment responses and drive resistance – is being address with the design of our bispecific ADCs that can target two different tumour targets both simultaneously and independently may overcome challenges associated with target heterogeneity and the reliance on target co-expression associated with bivalent bispecific antibodies. Additionally, biological limitations associated with tumours with poor immune function are being address with our trispecific TriTCE Co-Stim molecules that provide balanced and target-dependent T cell activation of both Signal 1 (through CD3) and Signal 2 (through CD28) in a single molecule. TriTCE Co-Stim have the potential to induce more sustainable T cell responses in the tumour microenvironment to treat tumours with low T cell infiltration and poor T cell function that are under-served by existing immune based therapies.

In terms of challenges associated with optimising drug design, both our ADC and multispecific candidates build on the learning within the field and employ tailored engineering of each molecule component to maximise the therapeutic benefit to patients. With ADC-based treatments, our team is focused on addressing a number of ADC associated challenges including high discontinuation rates, maximum tolerated doses and severe off-tumour toxicities such as nausea, anaemia, interstitial lung disease, neutropenia, and gastrointestinal effects. We have seen in emerging clinical data that treatment-related off-target toxicities and maximum tolerated doses are primarily related to ADC payloads while the efficacy of ADC-based treatments is likely driven by a combination of targeted payload delivery, free payload exposure and tumour sensitivity to the molecule's components. With these insights in mind, our candidates are chosen and developed while keeping all properties of the ADC in mind, including the target, antibody, linker and payload. This approach allows us to maximise the clinical efficacy of a candidate while balancing the risk of off-tumour toxicity. By coordinating the design of ADC candidates, our hope is to provide unprecedented clinical benefit to patients and afford them the best possible chance of a positive outcome. Similarly, with our T cell engaging-based multispecific treatments, our team is focused on addressing design limitations associated with TCE. TCE have exhibited clinical utility against haematological malignancies but have shown limited success against solid tumours as a result of a narrow therapeutic window due to dose-limiting toxicities associated with CRS, neurotoxicity, on-target-off-tumour effects or poor anti-tumour activity. Our team is addressing these limitations through the optimisation of paratope affinities including low affinity binding to CD3 and CD28 to reduce cytokine release, and antibody format and geometry engineering to drive tumour selective binding and activity to limit on-target-off-tumour effects and enhanced anti-tumour activity.

> **With ADC-based treatments, our team is focused on addressing a number of ADC associated challenges...**

Originally published on the DDW website – June 2024

Biography: Dr Paul Moore is Chief Scientific Officer at Zymeworks. He has more than 25 years of US-based experience in biologics drug discovery and development in biotechnology research. His career efforts have led to the discovery and development of a range of FDA-approved and clinical-stage biologics for patients with difficult-to-treat cancers and autoimmune conditions. Dr Moore received a PhD in molecular genetics from the University of Glasgow. He has an exten-sive research record, co-authoring more than 75 peer-reviewed manuscripts and is a named co-inventor on over 50 issued US patents.

Biography: Dr Nina Weisser is the Director of Multispecific Antibody Therapeutics at Zymeworks. She has more than 20 years of experience in biologics and anti-body engineering and has spent more than 12 years on the Zymeworks multi-specific antibody team, where she now leads the preclinical programmes group and plays a key role in the development of the company's lead clinical candi-dates and preclinical research programmes. Dr Weisser received a PhD in anti-body engineering from the University of Guelph.

Reducing cancer side effects through targeted therapies

Harry Palmer, Royal Commission of 1851 Industrial Fellow and PhD at University of Strathclyde, shares with DDW's **Megan Thomas** how antibody-drug conjugates (ADCs) are revolutionising cancer treatment by offering targeted therapies with improved efficacy and reduced side effects, while addressing challenges in their development and paving the way for future innovations.

ADCs vs chemotherapy

Though Palmer acknowledges that traditional chemotherapy has had significant clinical benefits for patients, and that currently around 25% of cancer patients receive some form of chemotherapy, he also references the side-effects patients receiving chemotherapy can suffer from, which stems from the medicine's inability to

distinguish cancer cells from healthy cells.

"Where ADCs can change this downside of cancer treatment is by tethering, or 'conjugating', chemotherapeutic medicines to antibodies. These antibodies can recognise and bind to antigens - specific protein structures present on the surface of cancer cells. By leveraging the antibody's selectivity for cancer cells, the chemotherapeutic medicine can be released at the site or even inside the cancer cell. This drives the chemotherapeutic medicine, or 'payload', towards the cancer cell with excellent selectivity, which can lead to improved tolerability and better patient outcomes."

Advantages and challenges

"ADCs represent a new approach for targeted therapy, through combining existing chemotherapeutics with antibodies that selectively recognise cancer-cells", says Palmer. "ADCs are more effective at targeting and killing cancer cells, and this greater efficacy allows for a lower dosage compared to traditional chemotherapy, leading to reduced side-effects."

> **ADCs represent a new approach for targeted therapy.**

In addition to using existing chemotherapeutics, Palmer says the reduction in side-effects provided by ADCs has opened the door for the use of anti-cancer medicines with excellent anti-cancer activity but high rates of side effects when not administered as ADCs. He provides the example of 'auristatins', which inhibit cell division mechanisms and are now the most commonly used class of payload in clinically approved ADCs.

He concludes: "As patients' cancers are understood better, ADCs offer an opportunity for a personalised treatment option, employing ADCs that target specific antigens present on a patient's cancer cells and increasing the chances of a successful treatment."

While ADCs have already shown great performance in clinical practice, Palmer acknowledges that there is still plenty of research to be done. He says: "In particular, developing and optimising methods to attach the payload to the antibody can be a lengthy process. The nature of the chemical linker between the drug and the antibody, as well as the number of payload drugs conjugated to the antibody, the drug-to-antibody ratio (DAR), are key features of ADCs which underpin many of their resulting pharmacological properties. Given the complexity of ADCs, exploring the impact of each individual component can be a lengthy process and can require making and testing hundreds of ADCs to understand which combination offers the best balance of safety and efficacy."

Palmer says that scientists

are now learning to understand better the process of conjugation, developing techniques to exert greater control over parameters such as the DAR, as well as understanding how the choice of linker structure can tune the properties of the resultant ADC. "Further research in these areas could enable greater chances of success for ADCs to reach and succeed in clinical practice", he confirms.

Looking forward

"ADCs are one of the fastest growing drug modalities," Palmer says. "It is always exciting to think where this growth will lead."

One area which particularly excites Palmer is in developing novel techniques to control the conjugation process. He explains that the DAR is a key property to consider during the development of ADCs, but of growing significance is the precise site of payload conjugation on the antibody. "Research is beginning to unpick how the sites of conjugation can affect the properties of the resultant ADC, such as stability of the conjugation in the blood plasma and payload release rate once inside the cell. My own research is developing new strategies to enable site-selective payload conjugation, to fine-tune both the DAR and site of conjugation and produce ADCs with improved pharmacological properties."

Another area Palmer hopes to see grow over the next decade is the expansion of ADCs into novel payload formats, such as multi-payload ADCs. He says: "By incorporating two or more payloads with distinct mechanisms of action into a single ADC, multi-payload ADCs could offer greater effectiveness of treatment. For example, by combining traditional payloads with immune-stimulating payloads, the body's own immune response could be locally boosted at the cancer to work alongside the chemotherapeutic payload. Simultaneously benefitting from multiple different payload mechanisms of action may allow factors such as tumour resistance to be overcome."

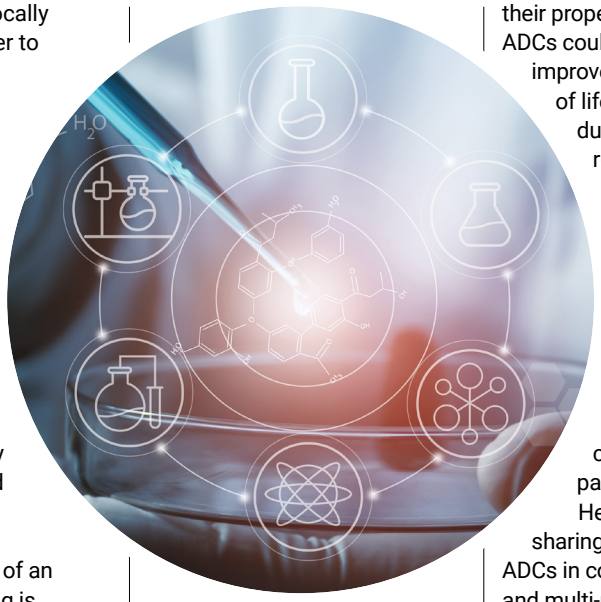
ADCs are also beginning to diversify into payloads beyond cytotoxic molecules, Palmer confirms. He provides an example of an area currently growing is degrader-antibody conjugates (DACs), a class of ADCs which feature PROTAC (proteolysis-targeting chimera) or molecular glue payloads conjugated to the antibody. He says: "Rather than causing cell death directly, these payloads lead to the targeted degradation of specific proteins within the cell, and expansion into novel classes of payload could allow ADCs to treat disease indications beyond oncology."

Cancer indications

ADCs have already received approval for several different cancer indications. Palmer says: "The great benefit of ADCs as a modality is that by selecting different antibodies, different cancer types can be targeted."

One form of cancer which has been successfully treated are haematological cancers such leukaemia and lymphoma, which Palmer says is in part due to a greater exposure of these cancers to ADCs circulating in the blood stream. He says: "ADCs have also been clinically approved for several solid tumour indications, and in particular have shown success in treating breast cancer, with three of the thirteen FDA-approved ADCs approved for its treatment."

According to Palmer, a key target for the field will be the development of new antibodies targeting a wider range of antigens over-expressed by cancer cells, expanding the range of cancers which are treatable by ADCs.



> **ADCs are one of the fastest growing drug modalities.**

Quality of life

As the development of new ADCs accelerates, and with greater research into understanding how to optimise their properties, Palmer says ADCs could offer a great improvement in the quality of life for patients both during and after receiving treatment.

"Targeting cancer cells leads to more effective killing of the cancer cell, and could reduce the risk of long-term tumour relapse through enabling the use of more potent chemotherapeutic payloads."

He elaborates on this, sharing that the use of ADCs in combination therapies and multi-payload formats offers further opportunities to improve remission rates by treating the cancer through multiple pathways at once, and overcoming cancers resistant to other treatment options.

He continues: "Additionally, selective targeting cancer cells reduces systemic toxicity to healthy cells, and can lead to a large reduction in the adverse effects for patients compared to traditional chemotherapeutics. As the field develops further, the long-term complications and chronic side-effects associated with traditional chemotherapy could be reduced further through improving the selectivity of ADCs for cancer cells, sparing healthy cells in vital organs."

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Biography:

Harry Palmer is an Industrial Fellow of the 1851 Royal Commission at the University of Strathclyde. He holds a first-class BA and MSci in Natural Sciences from the University of Cambridge, where he won multiple awards, including the Gordon Wigan Prize for his research dissertation with Professor Robert Phipps.

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