ADDRESSING OCULAR SAFETY CHALLENGES IN ADC DEVELOPMENT

Dr Tina Rogers of WuXi AppTec discusses antibody-drug conjugates and their potential in direct targeting and treatment of cancers, going further to assess the risks of these treatments and how they can be mitigated.

"OVER TIME, THE STABILITY, EFFECTIVENESS AND SAFETY OF ADCs HAVE BEEN SIGNIFICANTLY IMPROVED BY ADVANCEMENTS IN ANTIBODY ENGINEERING, BIOLOGICAL CONJUGATION TECHNOLOGY, LINKER TECHNOLOGY AND OTHER RELATED BREAKTHROUGHS."

Antibody-drug conjugates (ADCs) are among the most promising drugs in the fight against cancer, owing to their unique design and unmatched precision. However, they present ocular safety challenges that can derail development if not addressed, leading to costly delays or regulatory setbacks.

Ocular toxicity can cause a wide range of issues for patients, including blurred vision, night blindness, inflammation of the cornea and other problems of varying severity and incidence. These adverse effects can limit the therapeutic use of ADCs and necessitate close monitoring and management during treatment.

With the appropriate development approach, sponsors can either avoid or mitigate these issues, ensuring that this powerful class of drug is as impactful as possible and reaches the patients who need it most, safely and efficiently.

HOW ADCs WORK

ADCs are designed to selectively deliver a payload, commonly referred to as a "warhead", directly to a target – typically cancer cells – improving treatment efficacy while reducing systemic exposure and off-target effects. An ADC can achieve this because it consists of three main parts: a monoclonal antibody (mAb) with specificity for a tumour cell surface protein, a payload and a linker that connects the first two elements. After the mAb binds to the target, the linker is biochemically cleaved or spontaneously degrades, releasing the payload at a sufficient concentration to act on its target, while the receptor-ADC complex is internalised via endocytosis.

ADCs were first introduced in 1900 by Nobel laureate Paul Ehrlich, who envisioned

"ADCs ARE AMONG THE MOST PROMISING DRUGS IN THE FIGHT AGAINST CANCER, OWING TO THEIR UNIQUE DESIGN AND UNMATCHED PRECISION."

that these drugs could selectively target tumour cells while sparing healthy ones, hence the "magic bullet" term he gave them. Early experimental ADCs emerged in the 1980s and 1990s, but the field reached its first major milestone in 2000, when gemtuzumab ozogamicin was the first ADC approved for clinical use, validating the concept.[1] However, early practices also highlighted safety and design challenges. After the drug reached patients, adverse effects and early mortality resulted in regulators pulling it from the market, later allowing it back at a lower dose given in split portions.

This experience made clear what needed resolving going forwards – the chemical "linker" that holds the drug together must stay intact in the bloodstream and only release inside cancer cells, so that the toxic warhead cannot spill into healthy tissue. Developers must choose the right tumour target and fine-tune how much drug to give and how often. Over time, the stability, efficacy and safety of ADCs have been significantly improved by advancements in antibody engineering, biological conjugation technology, linker technology and other related breakthroughs.

Of the 19 ADCs approved for use as of mid-2025,[2] all are for the treatment of cancers, including lymphoma, specific cases of leukaemia, relapsed or refractory multiple myeloma, and metastatic triple-negative and HER2-positive breast cancer. Future drugs may also treat other conditions, including autoimmune and inflammatory diseases. However, the diverse spectrum of adverse effects in ADCs must be considered in order to prevent delays or discontinuation of treatment, which can adversely affect patient outcomes. This makes the management of off-target effects crucial to maximising efficacy and the number of future applications of ADCs.

THE ADVERSE EFFECTS OF ADCs

Even with all their promise, ADCs by nature are also associated with a number of adverse effects and toxicities, including haematologic side effects such as neuropathy, lymphopenia, neutropenia, thrombocytopenia and more. Payload-specific toxicities and adverse effects may vary based on the drug type and target. Sponsors of ADC drugs should monitor for these conditions during the development and testing process to identify appropriate uses, dosing and labelling. Some examples of ADCs that have toxicity issues include:

- **Monomethyl Auristatin E (MMAE):** ADCs using this payload often cause anaemia, neutropenia, and peripheral neuropathy.
- **Drug Maytansinoid 1 (DM1):** These ADCs are linked to thrombocytopenia and hepatic toxicity.
- **Pyrrolobenzodiazepine (PBD):** Can cause severe myelosuppression, prolonged cytopenias, hepatotoxicity and delayed organ toxicity.
- **Monomethyl Auristatin F (MMAF) and DM4:** Frequently associated with ocular toxicity.

THE EFFECTS OF OCULAR TOXICITY

Ocular toxicities are among the most clinically impactful toxicities for many ADCs and control of these requires early planning and active monitoring during ADC therapy. These toxicities often affect the cornea or ocular surface and manifest as a foreign-body sensation and blurred vision. They may also present with clinical symptoms such as corneal fluorescein staining, pseudomicrocysts and conjunctivitis.

> "STRATEGIES TO REDUCE OFF-TARGET UPTAKE ARE EMERGING AND PRESENT A POTENTIAL PATH TO HELP REDUCE OCULAR TOXICITY."

This is most common in ADCs such as enfortumab vedotin and tisotumab vedotin, which have been linked to high incidences of ocular toxicity in clinical trials. Enfortumab vedotin carries a warning for ocular disorders as the incidence of ocular toxicities with the drug can reach as high as 46%, with dry eye the most commonly reported symptom, affecting 36% of patients.[3]

The pathogenesis of ADC-related ocular adverse effects has been attributed to the unique molecular structure of the drug type, the cytotoxic mechanism of its payload and the expression of target antigens on both tumour and healthy ocular cells. However, the precise mechanisms that cause these effects remain elusive to researchers.

Despite this, it is thought that ADCs cause ocular-related adverse effects through both on-target and off-target mechanisms. On-target toxicity can occur when the target antigen of ADCs is also present on healthy eye cells. For example, HER2 is expressed on corneal epithelial cells, allowing HER2-targeting ADCs, such as trastuzumab emtansine or trastuzumab duocarmazine, to be taken up by these cells, causing damage. In contrast, off-target toxicity arises from non-specific uptake of ADCs or their payloads by normal cells, even when the target antigen is absent. An example is belantamab mafodotin, where ocular toxicity occurs despite the absence of target-dependent uptake.

Growing evidence in this area suggests that most ADC-related ocular adverse effects are target-independent and driven primarily by the payload, rather than by antigen expression on normal eye tissue. As a result, strategies to reduce off-target uptake are emerging and present a potential path to help reduce ocular toxicity.

PRECLINICAL TESTING AND STUDY DESIGN FOR MITIGATION OF OCULAR TOXICITY

To meet the safety demands of emerging modalities such as ADCs, toxicology must become more adaptive and integrative, with safety assessments embedded earlier in the development lifecycle. This will allow predictive tools to guide candidate selection and study design. Developers must carefully select the target, antibody, cytotoxic payload and linker to ensure that an ADC realises its therapeutic potential while maintaining safety standards and reducing adverse effects such as ocular toxicity. They must also account for the nuanced characteristics and risks that are not always captured by conventional preclinical assays.

One of the primary and unique concerns in ADC testing is variability in the drug-to-antibody ratio (DAR), which can significantly affect a drug candidate's efficacy, safety and pharmacokinetics. The DAR determines the amount of drug delivered, the duration of ADC circulation and safety. The goal of researchers is not to achieve the highest DAR, but to achieve the appropriate ratio, balancing efficacy, PK and safety. Advanced bioanalytical methods can precisely quantify free and conjugated payloads, as well as antibodies, to characterise the PK profile.

Another crucial step in developing this new modality is determining the maximum tolerated dose (MTD) of each compound.

> "ADVANCED BIOANALYTICAL METHODS CAN PRECISELY QUANTIFY FREE AND CONJUGATED PAYLOADS, AS WELL AS ANTIBODIES, TO CHARACTERISE THE PK PROFILE."

It is essential to set an appropriate preclinical threshold to inform dose selection and risk mitigation strategies. MTD testing can help to establish safety parameters in order to advance therapies into clinical trials and ensure that developers are better equipped to address the intricate balance between safety and efficacy.

BEST PRACTICES FOR OCULAR TESTING IN ADC DEVELOPMENT

Many ADC-related ocular toxicities can be identified and reduced before clinical trials begin by intentionally building eye safety into early development. This includes assessing whether the target antigen is present in healthy eye tissue, testing ADCs and their payloads on human eye-surface cells to determine whether toxicity occurs in the absence of target expression, and examining how the drug enters cells via non-specific uptake.

Developers can also reduce ocular risks by modifying ADC design by, for example, improving linker stability, lowering drug load or reducing hydrophobicity. Furthermore, they can closely study eyes during animal studies using appropriate ophthalmic exams. Together, these steps can help to predict ocular risks early and guide safer dosing, monitoring or redesign decisions prior to human exposure.

Once an ADC drug reaches clinical trials, optimising the dose and treatment schedule can further improve ADC safety. Dose capping, fractionated administration and limiting treatment duration can generally reduce toxicity, while prophylaxis for patients at high risk can further mitigate adverse effects.

NAVIGATING REGULATORY GUIDELINES

A careful and proactive approach to monitoring and mitigating ocular toxicity risks also aligns with global regulatory guidelines. By integrating this approach early in the process, drug sponsors can demonstrate that the risk is anticipated, understood and managed, rather than being unexpected. This means leveraging a preclinical pathway that explains a likely mechanism, linking it to a defined monitoring plan and specifying in advance how dose interruptions, reductions or discontinuations will be handled if toxicity occurs.

Starting early in trials, using established assessment tools, documenting mitigation

"BY INTEGRATING THIS APPROACH EARLY IN THE PROCESS, DRUG SPONSORS CAN DEMONSTRATE THAT THE RISK IS ANTICIPATED, UNDERSTOOD AND MANAGED, RATHER THAN BEING UNEXPECTED."

measures and being transparent about severity and reversibility all help to build regulatory confidence. It is also crucial to align teams early on, ensuring that there is no miscommunication among those working on each stage of the regulatory process. Ultimately, regulators are not seeking to eliminate risk completely, they just want to ensure that it is predictable, measurable and controllable.

EFFECTIVE OCULAR ASSESSMENTS

Due to the high incidence of adverse effects, consistent monitoring is required at the clinical stage and beyond. Diagnosing ocular toxicity in ADCs involves a thorough cadence of clinical assessment, imaging and functional testing throughout the treatment period. Slit-lamp biomicroscopy is recommended to establish a baseline in a patient. This baseline should capture any pre-existing dry eye, corneal disease, cataracts, glaucoma and contact lens use, as these factors can confound disease grading and management.

Once in the clinic, a few key tests performed regularly are critical for the efficient and responsible monitoring of side effects and ocular toxicity. Fluorescein and lissamine green staining are used to identify corneal and conjunctival epithelial damage, and corneal confocal microscopy provides high-resolution imaging of microcysts and nerve alterations. Schirmer's Test and tear breakup time can help to evaluate any ADC-induced dry eye. Finally, optical coherence tomography can detect changes in the corneal and retinal structure. Early diagnosis of ocular issues enables dose adjustments, temporary treatment interruptions and other strategies to manage ocular toxicity.

A FINAL WORD ON ADC-RELATED OCULAR TOXICITY

ADCs are one of the most popular drug modalities being developed in the world today. They hold considerable potential for treating cancers and could make a significant difference to countless lives. However, adverse effects – ocular toxicity in particular – may dampen their impact or cause avoidable issues that impact health and quality of life. Even when adverse effects are mild, they can derail treatments and reduce their effectiveness.

For the many sponsors working in this area, ocular safety should be considered at the forefront of the development process and should continue beyond the point at which drugs reach patients. This can ensure that ADCs are delivered to market in the most efficient and safe manner possible, while adhering to regulatory standards.

ABOUT THE COMPANY

WuXi AppTec is a partner and contributor to the pharmaceutical and life sciences industries, providing R&D and manufacturing services that help advance healthcare innovation. With operations across Asia, Europe and North America, WuXi AppTec offers integrated, end-to-end services through their unique CRDMO platform. WuXi AppTec works alongside nearly 6,000 partners across over 30 countries, supporting their efforts to bring breakthrough treatments to patients. Guided by a vision that every drug can be made and every disease can be treated, they are committed to advancing breakthroughs for patients – one collaboration at a time.

REFERENCES

1. *Wang R et al, "Antibody-Drug Conjugates (ADCs): current and future biopharmaceuticals". J Hematol Oncol, 2025, Vol 18(1), art 51.*
2. *Wu D et al, "Antibody-drug conjugates in cancer therapy: current advances and prospects for breakthroughs". Front Cell Dev, 2025, Vol 13, art 1669592.*
3. *Cheng Y et al, "Overview of antibody-drug conjugates nonclinical and clinical toxicities and related contributing factors". Antibody Therapeutics, Vol 8(2), 2025, pp 124–144.*

Dr Tina Rogers

Tina Rogers, PhD, Senior Technical Director, joined WuXi AppTec's Laboratory Testing Division in 2022. Her past leadership positions include Vice-President of Preclinical Sciences at Altasciences, Executive Vice-President and Director of Research at M.P.I. Research, and Vice-President of Drug Development at Southern Research Institute.

E: tina.rogers@wuxiapptec.com

WuXi AppTec

288 Fute Zhong Road, Waigaoqiao Free Trade Zone,
Pudong District, Shanghai, China
labtesting.wuxiapptec.com