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BIOCONJUGATION INSIGHTS

SPOTLIGHT

Overcoming challenges in the ADC manufacturing and R&D ecosystems

BIOCONJUGATION INSIGHTS

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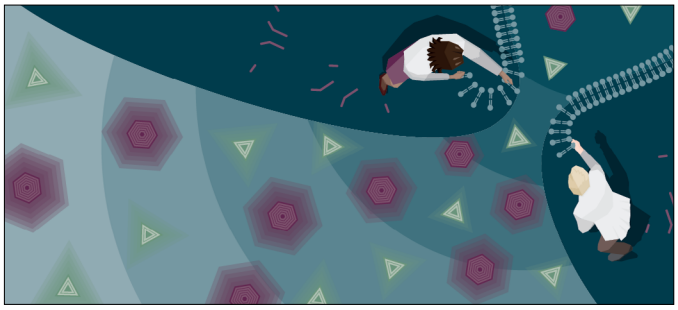

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BIOCONJUGATION INSIGHTS

OVERCOMING CHALLENGES IN THE ADC MANUFACTURING AND R&D ECOSYSTEMS

SPOTLIGHT

REVIEW

Next-generation conjugation technologies fan the ADC flame

Megan Rice and Marcello Marelli

ADCs leverage the specificity of antibodies for tumor-associated antigens to deliver cytotoxins selectively. Despite the conceptual simplicity of ADCs, their clinical development has proven complex. More than 300 ADCs have entered clinical trials, but only sixteen have achieved regulatory approval. So, why is the success rate so low? ADCs are multifaceted drug modalities, with each component—antibody, target, linker, and payload—playing a crucial role in the specificity, stability, efficacy, pharmacokinetics, and tolerability. Growing evidence indicates that conjugation chemistry may also be essential in determining functional properties. Drug developers are increasingly focusing on next-generation technologies that enable stable, site-specific conjugations to improve these properties. Emerging solutions include high-fidelity enzymes, non-natural amino acids, and glyco-engineering for controlled conjugation. These precise engineering tools yield homogenous, stable ADCs with defined DAR and improved biophysical profiles. The results are ADCs with superior pharmacokinetics, increased tumor exposure, controlled drug release, and reduced off-target effects—all of which contribute to greater tolerability and a wider therapeutic index, offering physicians improved dosing flexibility.

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INTRODUCTION

Antibodies for delivering potent cytotoxins in cancer treatment hold immense promise, with ADCs having the potential to enhance treatment efficacy and safety by targeting cytotoxins specifically to tumor cells. Unlike traditional chemotherapies, which expose healthy tissue to systemic toxicity, the antibody component of an ADC aims to confine the activity of a payload to target-expressing cells, improving, in theory, both the efficacy and safety of treatments. However, realizing this potential has proven more challenging in practice than initially anticipated.

Most ADCs that progress through preclinical evaluation never reach the market, and the few successes—currently sixteen ADCs—could be seen as products of circumstance rather than design. These existing ADCs demonstrate an adequate but typically modest therapeutic index (TI), underscoring the need for further refinement.

Several independent factors impact the TI of an ADC: conjugation chemistry, linker design, payload orientation relative to the antibody, and the physicochemical properties of the cytotoxin itself. It is essential to acknowledge that all conjugation strategies possess inherent limitations and that the attachment of typically hydrophobic payloads to an antibody fundamentally influences the molecule's intrinsic biochemical properties and stability. To fully realize the therapeutic potential of ADCs, it is crucial to acknowledge how these molecular factors impact both efficacy and safety, and to develop innovative strategies correspondingly.

CONVENTIONAL ADCS

The earliest and most widespread strategies for ADC construction focused on conjugating cytotoxic payloads to naturally occurring amino acids, primarily lysines and cysteines, within the antibody. These residues are popular targets because they offer accessible functional groups: primary amines on lysines, and sulfhydryl groups on reduced cysteines. This allows for efficient and scalable reactions under relatively mild conditions, supporting manufacturing needs.

LYSINE CONJUGATION

Lysine-based conjugation typically involves ligating the payload to a primary amine using activated esters such as N-hydroxysuccinimide, creating stable covalent bonds. However, antibodies feature up to 80 accessible lysines, resulting in heterogeneous mixtures of ADCs that differ in the number and position of conjugation.

The variability of these products leads to a mixed population of ADCs, each with distinct biophysical and pharmacokinetic properties. This heterogeneity affects *in vivo* behavior, making efficacy and safety unpredictable. Furthermore, exposed conjugation sites can enable non-specific interactions, increasing off-target toxicity and diminishing therapeutic benefit. Despite these limitations, five lysine-conjugated ADCs have reached the market **(Table 1)**.

Therapeutic use of these agents has been constrained by poor tolerability. For instance, the initial dose regimen (9 mg/m^2 or 0.24 mg/kg) for Mylotarg™ led to withdrawal from the market, and subsequent re-approval required substantial dose reduction (3 mg/m^2 or 0.08 mg/kg) **[1]**. Another example comes from Kadcyla™ (T-DM1), which was shown preclinically to target HER2+ tumors effectively, but its efficacy is hampered by the clinical maximum tolerated dose (MTD) **[2–3]**. The MTD of T-DM1 was set at 3.6 mg/kg, but the low dose reduced overall efficacy, leading to objective response rates in only 26–44% of patients **[4–5]**.

Interestingly, Enhertu™ (trastuzumab–deruxtecan (Dxd), **Table 2**) superseded T-DM1 due to its more tolerable profile (6.4 mg/kg) and impressive efficacy **[6]**. Besponsa™ (CD22-Calicheamicin; MTD 0.15 mg/kg; 3 fractionated doses) improves overall survival rates between 6–11 months, however, toxicity prevents more appropriate dosing to improve response rates **[7]**. These early ADCs provide much-needed therapies for patients, but improvements to ADC design to expand the therapeutic index would enable more widespread use of this drug class.

CYSTEINE CONJUGATION

Stochastic conjugation via cysteine residues exploits the eight interchain disulfide bonds of IgG1, which can be reduced to expose sulfhydryl groups for linkage with maleimide-functionalized payloads. While thiol-maleimide ADCs demonstrate improved homogeneity over lysine conjugates, this conjugation chemistry is subject to premature loss of linker-payload through the retro-Michael reaction. With the maleimide intact, the linker-payload can react with free

TABLE 1

US FDA-approved ADCs conjugated via lysine residues.

Name (target)	Manufacturer (date)	Payload (DAR)	ADC clinical maximum tolerated dose/recommended Phase 2 dose (mg/kg)
Mylotarg™ (CD33)	Pfizer (2000, 2017)	Calicheamicin (2–3)	0.08–0.24
Kadcyla™ (Her2)	Genentech (2013)	DM1 (3.5)	3.6
Besponsa™ (CD22)	Pfizer (2017)	Calicheamicin (6)	0.15
Akalux (EGFR)	Rakuten (2020)	IR700 (with Laser activation) (1)	n/a
Elahere™ (FolRa)	Immunogen (2022)	DM4 (4-5)	6

thiols *in vivo*, i.e., unpaired Cys 34 of human serum albumin, a phenomenon known as thiol-exchange that has been shown to drive significant off-target activity [8–10].

Furthermore, conjugating to all available interchain cysteines produces homogenous ADCs (DAR8); however, generating ADCs with lower DARs (2–6) requires partial reduction or partial reoxidation. This creates products with variable drug loading and numerous combinations of conjugation sites (regioisomers). Similar to heterogeneous lysine conjugates, each subset of ADCs may have different stability, hydrophobicity, and therapeutic profiles. Despite these drawbacks, most approved ADCs use stochastic thiol-maleimide conjugations (Table 2).

SITE-SPECIFIC CONJUGATION WITH ENGINEERED CYSTEINES

To address heterogeneity, site-specific conjugation methods have been developed targeting cysteines with very similar

TABLE 2

US FDA-approved ADCs conjugated via interchain cysteine residues.

Name (target)	Manufacturer (date)	Payload (DAR)	ADC clinical maximum tolerated dose/recommended Phase 2 dose (mg/kg)
Adcetris™ (CD30)	Seattle Genetics, Millennium Takeda (2011)	MMAE (4)	1.8
Enhertu (HER2)	AstraZeneca/Daiichi Sankyo (2019)	Trastuzumab–deruxtecan (8)	6.4
Padcev™ (NECTIN-4)	Astellas/Seattle Genetics (2019)	MMAE (3.8)	1.2
Polivy™ (CD79)	Genentech/Roche (2019)	MMAE (3.5)	1.8
Polivy™ (CD79)	Genentech/Roche (2019)	MMAE (3.5)	1.8
Blenrep™ (BCMA)	GlaxoSmithKline (2020)	MMAF (4)	2.5
Tivdak™ (tissue factor)	Seattle Genetics (2021)	MMAE (4)	2.0
Zynlonta™ (CD19)	ADC Therapeutics (2021)	PBD (2.3)	0.15
Aidixi™ (HER2)	Remegen (2021)	MMAE (4)	2.5

chemistry to conventional cysteine conjugation. By substituting a native amino acid for a cysteine at solvent-accessible sites, antibodies can be expressed with minimal functional impact. These engineered cysteines are typically capped with a thiol or glutathione.

The conjugation process involves reducing the antibody completely with mild reducing agents, followed by preferential reoxidation of interchain cysteines (Fab and hinge). This leaves the uncapped, unpaired cysteines available for conjugation with maleimide-bearing linkers. This controlled and stepwise process allowed for site-specific ADCs (THIOMAb®) construction.

While this method allows for the construction of homogeneous ADCs at user-defined sites, not all positions are amenable to efficient thiol-maleimide conjugation, and many result in adducts prone to deconjugation. The context of the site has been shown to alter the reductive properties, conjugatability, and/or the stability of the adduct. Investigations by Seattle Genetics, Genentech, Merck, and others have evaluated various cysteine placements, seeking positions that permit robust conjugation and payload stability, such as S239, S239i, L328, or S442 **[11–15]**. This strategy seemed to improve the overall performance of ADCs.

In 2008, a group from Genentech characterized a MUC16-MMAE (DAR2) ADC using their THIOMAb technology that showed improved homogeneity and better serum stability. *In vivo*, the construct cleared from circulation less quickly, was as effective against tumor xenografts, and was better tolerated than a conventional ADC bearing twice the number of cytotoxins **[15]**. This study demonstrated the feasibility of producing ADC through cysteine engineering and the advantages of site-specific ADCs.

The DMUC5754A ADC was assessed in platinum-resistant ovarian cancer patients in phase I/II trials, where it was found to be generally well tolerated—dosed Q3W, at 0.3–3.2 mg/Kg or Q1W, at 0.8–1.6 mg/Kg—showing typical adverse events for this class of payload. PK analyses showed that the improved stability of the ADC resulted in minimal accumulation of free MMAE, indicating that most of the MMAE remained conjugated to the antibody, a favorable sign for safety and targeted delivery.

In terms of efficacy, the overall response rate was 17% (5/29) at Q3W dosing, with the majority of objective responses in patients with high MUC16 expression **[16]**. However, despite a promising start to the age of site-specific ADCs, Genentech opted not to progress this asset beyond Phase I/II. This raises the question: Does the added complexity and cost of development outweigh their performance improvement?

Since, numerous preclinical studies have been published indicating the advantages of site-specific cysteine conjugates to PK, superior stability and efficacy have been reported **[17–20]**. The site of conjugation has also been reported to impact the stability of the antibody-drug bond, which affects the *in vivo* activity **[21–22]**. As of 2025, two assets are being investigated in clinical phase I (MT-8633 and MYTX-011, Beacon). These highlight the potential of rational protein engineering to drive therapeutic advances. But, given the reported benefits of engineered ADCs, one must ask why we have not seen more successes in the clinic? While these clinical milestones demonstrate the tangible benefits of site-specific cysteine conjugation and underscore advances in antibody engineering, they also reveal persistent limitations. Even with improved site-selectivity and enhanced pharmacological profiles, optimizing the therapeutic index remains an ongoing challenge, as toxicity can still arise from instabilities resulting in systemic payload release. Thus, a compelling need remains to build upon these early successes by systematically re-evaluating how efficacy and safety are balanced and maximized to develop next-generation ADCs

successfully. To this end, we must posit: If site-specific cysteine engineering remedies heterogeneity of ADCs and improves efficacy, but not safety, should we be looking for alternative conjugation chemistries that grant access to new sites and prevent thiol-exchange for superior stability?

RETHINKING EFFICACY & SAFETY IN ADC DESIGN

To improve the therapeutic index of an ADC, we must enhance efficacy, improve safety, or ideally achieve both. Understanding and optimizing the factors that determine these parameters is critical. Efficacy reflects the ADC's capacity to induce a desired response, while potency refers to the drug amount needed to produce that effect. While these terms are related, they are distinct. This has been illustrated with a conceptual example **(Figure 1)** where hypothetical Drugs A and B have different potencies but the same efficacy (same height of the curves).

In contrast, Drug C has similar potency to Drug A but less efficacy. Attempts to modulate payload toxicity with conventional conjugation chemistries have generally shifted the therapeutic index without broadening it. Efforts to increase payload potency allow administration at lower absolute doses to achieve equivalent pharmacodynamic effects. However, this is typically associated with a reduced safety margin since both efficacy and toxicity thresholds shift to lower doses proportionally. Conversely, reducing payload potency necessitates higher ADC doses to maintain therapeutic efficacy, but does not inherently increase the safety window, as toxicity also shifts to higher doses in parallel **[23]**. For ADCs, enhancing efficacy is essential. Lasting improvements come from evolving strategies that ensure ADCs are highly stable in circulation—minimizing early payload loss that drives non-specific payload interactions—deliver a consistent and fully loaded drug complement to the tumor to maintain or improve on-target exposure, and limit overall hydrophobicity; factors proven to enhance pharmacokinetics, tumor uptake, and patient tolerability **[10,24–26,27]**. By definition, expanding the therapeutic index involves utilizing robust technologies to achieve equal or better on-target activity and reduce off-target toxicity.

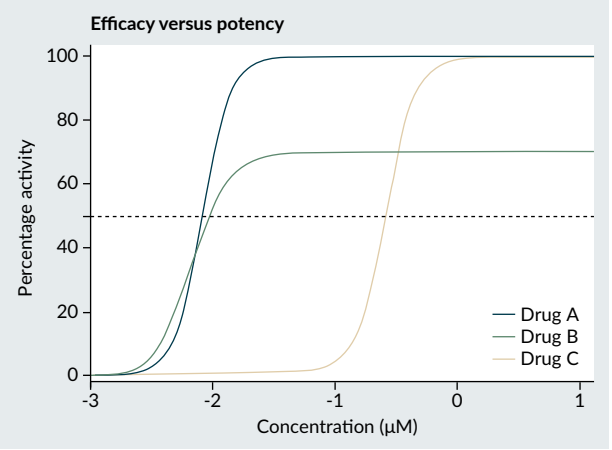
Traditional approaches to bolster ADC efficacy, such as improving the chemical stability of cysteine conjugates, have their limits. Conjugation chemistries that shield the payload from extraneous interactions and premature cleavage remain elusive, highlighting the need for innovative technologies that achieve this balance.

A NEW ERA: NEXT GENERATION TECHNOLOGIES

Increasing evidence of instability-driven toxicities has incentivized the development of next-generation conjugation technologies across the industry **[28]**. These

FIGURE 1

A conceptual demonstration of the difference between efficacy and potency.



Drug A is represented by a curve that achieves 100% activity at a low concentration, while Drug B drives a response at the same low concentration but does not achieve 100% activity. Drugs A & B are therefore equally potent but differ in degree of efficacy. Drug C, like Drug A, achieves 100% activity, but at a much higher concentration. This represents equal efficacy, but lower potency than Drug A.

TABLE 3

Companies utilizing chemoenzymatic conjugation technologies.

Company	Technology	Phase
Catena Bio	Catenase®	Preclinical
GeneQuantum	iLDC® (sortase)	Phase III
Crossbridge Bio	Transglutaminase (MTG)	Preclinical
Catalent	SMARTag	Phase I
LigaChemBio	ConjuAll®	Phase III
Taiho Pharma (Araris)	AraLinQ®	Preclinical
Roche	Transglutaminase (KTG)	Phase III

strategies have produced more stable, homogeneous ADCs by employing irreversible, orthogonal conjugation chemistries. The principal approaches of this new wave are discussed in the following sections.

Enzymatic conjugation

Chemoenzymatic methods harness the high specificity of enzymes such as transglutaminase or sortase, which catalyze conjugation at precise recognition sequences. This enables the construction of ADCs with controlled DAR, excellent stability, and minimal off-target activity. Unlike thiol-maleimide conjugates that are prone to premature payload loss, enzymatically conjugated ADCs have been shown to retain their payload in circulation and more reliably deliver it to the target, driving superior tumor regression with reduced off-target toxicity [26,29,30]. In the wake of these findings several chemoenzymatically conjugated ADCs have entered clinical and preclinical studies (Table 3).

Enzymes such as transglutaminase and sortase must be present during the conjugation reaction to interact with the target residue and the reactive group on the linker-payload. Therefore, the enzyme must be produced as a secondary reagent incorporated into the conjugation scheme. Meanwhile, in some cases, the target residue alone is modified by the enzyme to enable subsequent orthogonal coupling. Formylglycine Generating Enzyme is one example Catalent has exploited with a proprietary production host that co-expresses the target protein and the enzyme to produce a fully functionalized antibody ready for one-step conjugation [31,32]. Catalent's SMARTag® system exemplifies the impact of enzymatic, site-specific conjugation, producing ADCs with precisely defined attachment sites that exhibit improved pharmacokinetics and stability in preclinical models [25,29]. Early-phase clinical ADCs using SMARTag technology have demonstrated favorable safety and biodistribution characteristics, reinforcing the clinical value of truly homogeneous bioconjugation [27].

Non-natural amino acid incorporation

This strategy employs genetic code expansion techniques to incorporate non-canonical amino acids at defined positions. These residues present unique chemical handles for irreversible, orthogonal conjugation, yielding site-specific products with fine-tuned biophysical attributes. Mammalian (e.g., Ambrx/JnJ, AstraZeneca, Veraxa) or cell-free (e.g., Sutro, Brick Bio) expressions are used to achieve this on a manufacturing scale. nnAA-based approaches offer exceptional flexibility, as conjugation can

TABLE 4

Companies utilizing non-natural amino acid technologies.

Company	Technology	Phase
J&J (Ambrx)	pAF	Phase III
Veraxa	Diels-Alder	Preclinical
Sutro	pAF & pAMF	Phase II/III
Brick Bio	eCLIC®	Preclinical
AstraZeneca	Diels-Alder	Preclinical

be engineered at virtually any site to optimize antibody stability, minimize hydrophobicity, or shield the linker-payload [10]. Furthermore, the orthogonal chemistries used for conjugation enable efficient and specific adduct formation that is stable *in vivo*, overcoming the limitations seen with engineered cysteines [33]. While powerful, these methods are not without challenges. Mammalian expression systems may be limited by the yield and incorporation efficiency of nnAAs, while bacterial-based cell-free systems introduce production complexities such as the preparation and storage of the expression medium and endotoxin mitigation strategies [34]. Despite these obstacles, nnAA based ADCs are under development or in clinical studies (Table 4) and many commercial research and manufacturing organizations offer nnAA-enabling services.

Glyco-engineering

Modifying the endogenous N-linked glycan at the conserved asparagine 297 offers a distinct avenue for site-specific conjugation. Typically, the glycan is trimmed and enzymatically modified to create specific reactive sites for payload attachment. An azido-modified sugar enabling azide-alkyne click chemistry is commonly introduced into the glycan. When assessing an IgG1 structure, glycan remodeling seems a logical approach. The sugar group already occupies a hydrophobic pocket between the two heavy chains; by substituting a portion of the carbohydrate with a hydrophobic payload, it leverages the natural hydrophobic region of the antibody Fc domain to shield the payload, potentially reducing hydrophobicity-driven clearance and off-target effects [17,35,36]. Furthermore, the glycan is intrinsically branched, providing multiple conjugation sites for higher DARs without compromising stability or specificity.

Despite these appealing properties, glyco-engineering adds complexity to antibody preparation and often requires specialized reagents for glycoform generation, which increase manufacturing costs and timelines, limiting widespread adoption of this methodology [37]. Regardless, progressive commercial research and/or manufacturing companies have developed processes to accommodate these technologies (Table 5). Regardless, some have developed proprietary chemistries that they license to interested partners (e.g., BioDLink & Genovis).

The common theme amongst these technologies is the move from stochastic conjugations to site-directed methods that enable homogeneous ADCs using biorthogonal chemistry for conjugation to improve the specificity and stability of the adducts. As such, various new methods are now available for site-specific ADC conjugations [38]. Notably, technologies like AJICAP® (Ajinimoto) and AbClick® (AbTis) offer methods for producing

TABLE 5

Companies utilizing glycol-engineering technologies.

Company	Technology	Phase
HoneyBear Bioscience	CoNectar®	Preclinical
Glykos	Undisclosed	Preclinical
T-E Med/ImmuneWorks/CHO Bio	CHOptimax®	Phase I
BioDLink*	DisacLink®	CDMO
Daiichi Sankyo	Undisclosed	Phase I
Genovis*	GlyCLICK®	CDMO
GeneQuantum	iGDC®	Preclinical
OBI Pharma	EndoSymeOBI®	Phase I
Synaffix	GlycoConnect®	Phase III
Chengdu Kanghong	Undisclosed	Phase I
Alphamab Oncology	Undisclosed	Phase III

*Contract development and manufacturing organization with no disclosed internal pipeline.

homogeneous ADCs with consistent DAR and improved stability [39,40]. In these cases, exposed and available lysines (K248 and K288) are modified with a biorthogonal functional group (azide or norbornene) to enable click conjugations at these sites. Both of these technologies are under preclinical evaluation with ADCs or radioconjugates.

TRANSLATIONAL INSIGHTS: BRINGING TECHNOLOGY AND INNOVATION TOGETHER

Günter Blobel explains in his Nobel Lecture that techniques and instruments frequently advance science more than conceptual breakthroughs [41]. The collective impact of these next-generation conjugation technologies can already be seen: improved ADC homogeneity, enhanced stability in circulation, higher tumor specificity, favorable pharmacokinetic profiles, and in several cases, expanded therapeutic indices in preclinical and early clinical trials. GQ1005, for example, is a site-specific DAR4 Dxd HER2 ADC developed by GeneQuantum Healthcare. A stable enzymatic conjugation chemistry (iLDC®, sortase) has achieved comparable preclinical efficacy to Enhertu (DAR8) with half the drug load. This reduction in toxin load has significantly increased tolerability in the clinic. No MTD was established in initial dose-escalation studies despite reaching 8.4mg/kg; subsequent dose expansion studies are ongoing [24]. By maintaining efficacy and improving tolerability, GeneQuantum's next-generation conjugation technology has enabled expansion of the therapeutic index. These are encouraging results, but the technology is in its infancy, and further clinical studies are needed to validate them. As these advances propagate through the industry, expectations are high that they will unlock new frontiers in cancer therapy—validating the promise of ADCs as precision medicines.

Not only have these technologies enabled superior single-payload ADCs, but they are also making multi-payload conjugates possible via branched linkers and/or combined orthogonal chemistries.

Multiple dual-payload ADCs have entered the clinic in 2025, utilizing next-generation conjugation technologies to deliver two drugs with complementary mechanisms of action [42]. Combination therapy, a practice that has long been applied to cancer treatment, has historically relied on dosing two individual therapeutics to overcome heterogeneous tumors and inherent drug resistance. Recently, this has involved the use of ADCs combined with chemotherapies. Hodgkin's lymphoma, for example, is often treated with a cocktail of five drugs including Adcetris™ + CHOP (Cyclophosphamide, Doxorubicin hydrochloride, Vincristine sulfate, and Prednisone) with good clinical effect. However, patients have to endure side effects from these untargeted chemotherapies. Dual-payload ADCs promise to ensure targeted co-delivery of multiple drugs, and preclinical data suggest that this approach has significant biological advantages [43]. Only time will tell if multi-payload conjugates are the future of antibody-targeted delivery. Still, one thing is for certain: technological innovation of new tools and novel methods that repeatedly propel biology and medicine forward. In the evolving landscape of ADC engineering, it is clear that the development of sophisticated conjugation chemistries marks the dawn of a new era with profound implications for patient care.

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BIOCONJUGATION INSIGHTS

OVERCOMING CHALLENGES IN THE ADC MANUFACTURING AND R&D ECOSYSTEMS

SPOTLIGHT

Innovations in process development and manufacturing for scaling ADCs

PANEL

"Future innovation in ADC manufacturing could significantly alter how we manage payloads and conjugation processes."

Bioconjugation Insights hosted a panel of experienced biopharmaceutical leaders to discuss innovations and ongoing challenges in process development and manufacturing of ADCs. **Juma Bridgewater**, **Sunny Zhang**, and **Esohe Idusogie** explore the critical decision points in scaling ADC components, designing comparability studies, managing supply chain complexity, addressing capacity bottlenecks, and balancing speed, cost, and quality in an increasingly competitive field.

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Q When developing ADC manufacturing processes, what are the critical decision points for scaling antibody and linker payloads intermediates, and how do you balance the cost implications with development timelines?

JB When considering the context of how biologics are developed, you start small, aim to move quickly, and then scale up as you see that the molecule is viable and worth further investment. This process is not vastly different for an ADC.

Often, the target on the antibody site is already well validated, sometimes even commercially available, and can be manufactured at large volumes. However, early in development, there is greater benefit in producing small batches, observing variability, and evaluating how different batches of antibody perform when conjugated with different lots of payloads. You also want to obtain those data points quickly, as competitors are likely targeting the same antigen.

For the linker or linker-payload, the approach is somewhat different. You can start with a small-scale, non-pivotal process, but this choice may create challenges for comparability. Some components may already be available on the market, and in those cases, using a commercial source initially can simplify development, even if it introduces additional complexity later.

SZ ADCs differ from monoclonal antibodies (mAb), particularly due to their cytotoxic component. When looking at the bigger manufacturing picture, one of the most essential considerations is CDMO capability. From experience, finding a single partner that can handle mAb production, conjugation, and the high-containment manufacturing required for cytotoxics, such as OEB5-level containment or higher, is difficult.

Therefore, every aspect must be considered when planning the development strategy: technology, facility capability, and the interdependencies between process stages.

EI To build on those points, there are at least four major control points in the process. Because few service providers offer end-to-end capabilities, companies must plan carefully to balance cost and timelines. For example, toxicology studies may need to begin while still contracting for mAb or linker-payload GMP manufacturing. This often means running toxicology studies at risk—starting them in parallel with GMP production—to save time later. The decision to take on that risk can make the difference between meeting and missing development milestones.

JB This is a great point, as timing is everything. For many ADC clinical assets, determining the dose is a critical early step. The dose should be as high as possible while continuing to mitigate risks to toxicity, which directly affects when manufacturing decisions must be made.

At the start, it is difficult to know what the final drug product will look like—it is vital configuration, stability profile, or whether it will be lyophilized. Many Phase I studies now also include efficacy endpoints, so when coming out of Phase I, there is the opportunity to start defining the commercial process more concretely.

SZ We recently faced this challenge ourselves around clinical dosing. Initially, the clinical operations team provided a target dose, but as studies progressed,

those assumptions kept changing. Eventually, we decided to move forward with the information available, even knowing it might not be final.

That is part of the reality of Phase I. There will always be uncertainties such as dose, process, and formulation. The key is to document the rationale for every decision, define what could trigger future changes, and move forward confidently, even if not everything is perfect.

Q One of the unique challenges with ADCs is demonstrating comparability when scaling-up multiple components. How do you design and execute comparability studies for such complex multi-step processes, and what are the biggest pitfalls you encounter?

EI Most drugs that reach market undergo comparability at some point. The goal is to demonstrate that pre- and post-change products are comparable, without impacting quality, safety, or efficacy.

It begins with a prospective plan that defines overall strategy—where data will come from, and which assessments are required. It should be reviewed by all key stakeholders: manufacturing, analytical, quality control, regulatory, process development, quality assurance, and sometimes supply chain, depending on the product stage.

The plan must include a risk assessment evaluating all foreseeable consequences of the change. Comparability typically involves analytical testing, biological assays, and sometimes non-clinical or clinical data. For ADCs, there are four major control points: the linker-drug, the mAb, the conjugated drug substance, and the final drug product. Depending on the change, this may need to be evaluated at multiple points.

Testing should cover physical, chemical, and biological attributes affected by the change. This typically includes release, extended characterization, and effector function assays which assess the effect of Fc effector functions. Acceptance criteria must be predefined and realistic—too tight, and it risks unnecessary failure. Analytical methods used must be demonstrated as suitable for their intended purpose. Stability under long-term and accelerated conditions should also be included. Consulting regulators early is always advisable, depending on the organization's experience and the complexity of the change.

Common pitfalls include insufficient development data, over-restrictive acceptance criteria, and reliance on unvalidated methods. Analytical scientists often want to test everything, but excessive testing without a clear link to product quality, safety, or efficacy can cause more confusion than clarity.

In general, we're trying to move as fast as we can, but you need sufficient understanding of whether there will be any product quality impact that needs to be addressed in the plan. It's important to do sufficient development work.

JB Following Esohe's point, understanding the process and its critical quality attributes is key to de-risking. For instance, if changes were made to a raw material or downstream filter, comparability at the antibody level can often be assessed. However, if that same antibody is later conjugated, it raises the question, 'Do you also need to repeat comparability on the ADC?' These nuanced decisions require a deep understanding of process linkages and cytotoxic intermediates.

As scale-up occurs, changes may need to be made to the antibody, linker, and conjugation process simultaneously. Managing each comparability separately while maintaining a holistic view is challenging without a well-defined plan.

EI The exercise becomes expensive and complicated if changes occur at all four control points. You must demonstrate comparability at each stage to ensure there is no impact on the drug's safety, efficacy, or product quality. While complex, a clear, comprehensive plan with stakeholder alignment will streamline execution.

JB The antibody platform is well established, with substantial knowledge and understanding of which changes are significant. Surprises from effects at the antibody level after a minor change are unlikely; however, modifications such as reaction ratio or temperature can have significant impacts for conjugation.

A good scale-down model and robust development data, such as large DoE or QbD studies, are essential to demonstrate reproducibility. While it is difficult to repeat changes at full scale, having extensive development data before implementing changes is highly valuable. Post-change and pre-change batches may be limited, but strong supporting data make a substantial difference. A well-qualified scale-down model for conjugation is crucial.

SZ Given that comparability can be very complex, this highlights the importance of adopting a platform approach. Leveraging prior knowledge and minimizing changes can help achieve greater speed and cost efficiency while maintaining quality.

When considering a platform approach, it is also essential to ensure there is a mechanism within the platform to identify differences and detect potential problems as early as possible.

EI With experience, it can be done correctly and efficiently, saving time and cost. People often say, 'Kick it down the road,' but there is rarely time to fix it later. I always say, do it right from the start.

Q ADCs require coordinating intermediates with vastly different shelf lives and storage requirements, while evolving your testing strategies from early development through commercialization. How do you align batch sizes and analytical approaches across all components while maintaining supply chain efficacy?

EI When considering this, it should be separated into two stages—early development versus late-stage and commercial. In early development, it is critical to work closely with the supply chain and clinical operations to determine the number of vials required for Phase I and II and assess whether resupply will be needed. That information allows manufacturing and analytical teams to plan efficiently.

At this stage, the amount of material used for analytical testing and stability is limited, as full ICH stability testing is not required for intermediates. Stability studies for intermediates such as mAbs and drug linkers can be minimal, conserving precious material.

"Effective inventory management within the supply chain becomes essential—balancing market demand with manufacturing lead times and resupply."
Esohe Idusogie

The process is validated in late-stage and commercial production, and regulatory commitments are fixed. Everything must be on stability following ICH guidelines or per what was filed with the US FDA or other regulatory health authorities. There is much less flexibility here.

Effective inventory management within the supply chain becomes essential—balancing market demand with manufacturing lead times and resupply. On the analytical side, expiry periods are predefined. For example, you may initially have only two years of data at filing, with the opportunity to extend expiry later as more data accumulate.

Overall, there is more flexibility early on, and almost none once you reach the commercial stage.

JB Esohe raises an important point, as I had not initially considered how much the testing strategy evolves across stages. Commercially, the goal is always to lower COGs and minimize waste. The target drug product quantities required to meet market, and patient demand should align well with the amounts of antibody and linker-payload available. This alignment depends on input from marketing teams, who understand market needs and can help define batch size requirements accordingly.

The antibody and drug substance processes may be expanded simultaneously during scale-up, while drug product manufacturing often depends on existing infrastructure. Bottlenecks can arise when fill–finish capacity is constrained. For instance, by lyophilizer size, high-potency filling line capacity, or other equipment limitations. These factors must be carefully considered to ensure efficient coordination across all stages of production.

SZ It is really about alignment and foresight. Managing stability data, inventory, and analytical sampling cohesively across components is a big part of differentiating an efficient ADC program from a chaotic one.

Q The bioconjugation manufacturing capacity is still limited compared with traditional mAb production. What are the biggest bottlenecks in ADC workflows, and how is the industry addressing these capacity constraints?

JB This is one of those areas where perspective is often shaped by the vendors you work with. I would also note that antibody manufacturing capacity itself can be challenging. In several organizations I have worked with, antibody manufacturing is often outsourced, despite internal capabilities, as teams strive to maximize efficiency.

The challenge is even greater for ADCs. High-potency manufacturing requires specialized facilities, and only a limited number of vendors are equipped for this type of work. Large pharmaceutical companies that are not traditional ADC developers typically do not

have dedicated suites for such operations; they may have only one or two ADC programs in their pipeline. As a result, much of this work is outsourced to CDMOs.

The industry has evolved significantly in response to growing demand. Vendors have expanded capacity and developed integrated service offerings as more ADC programs advance, and additional products are approved. Many now operate as 'one-stop shops,' a concept that did not exist 15 years ago. Previously, companies had to source linkers, payloads, antibodies, and ADC conjugation services separately, then secure additional manufacturing slots for the ADC drug substance and drug product fill–finish. Today, CDMOs increasingly provide end-to-end solutions, streamlining timelines, and coordination.

Another key improvement is the availability of trained personnel and enhanced understanding of post-manufacturing handling, storage, and testing requirements. Analytical capabilities have also advanced substantially. For example, determining the DAR, often measured via mass spectrometry, was once a bottleneck, as mass spectrometry was uncommon in many labs. The industry now routinely performs fundamental DAR analyses using mass spectrometry or UV-based assays.

These advances have enabled much faster turnaround times, even allowing for near real-time or at-line DAR assessments during production—something that was not feasible 15–20 years ago. The tools and infrastructure allow for greater analytical agility within quality control operations.

EI A limited number of bioconjugation facilities in the US are capable of handling occupational exposure band (OEB) categories above three. There is a growing emphasis on expanding domestic manufacturing capacity to address this. Offshore manufacturing introduces additional logistical challenges—such as extended lead times, customs delays, and the complexities of shipping materials between continents—all of which can become significant bottlenecks.

JB Another essential factor is the increasing use of single-use manufacturing technologies. Compared with traditional stainless-steel or glass reactors, single-use systems reduce cleaning requirements and allow for safe disposal, improving efficiency and containment, particularly for high-potency compounds. This approach, already common in biologics manufacturing, has also proven tremendously beneficial for ADC production.

Q There is always tension between the speed, the cost, and the quality in biomanufacturing. However, this seems especially true for ADCs, given the multiple components involved. How do you navigate these trade-offs, and are there specific areas where you recommend not cutting corners even when under time constraints?

SZ Navigating the trade-offs between speed, cost, and quality requires strategic prioritization based on risk, regulatory expectations, and long-term product success. Several key levers can be employed to maintain this balance.

The first is the platform approach. Although not a new concept, it continues to prove effective when appropriately implemented. This can include using well-characterized mAb backbones and leveraging the industry's accumulated experience with monoclonal

> "[...] platform-based strategies must incorporate mechanisms to detect and evaluate differences between new and legacy molecules."
> **Sunny Zhang**

antibodies. Conjugation technologies that can be applied across multiple programs are also highly advantageous. Once a proven payload–linker technology is established, it can be adapted to different therapeutic targets with minimal modification.

Formulation is another essential consideration. Establishing a formulation platform, such as a formulation compatible across multiple programs with little or no modification, can reduce development timelines and regulatory risk.

A further component of a robust platform is the CDMO partnership model. Long-term, well-defined relationships with trusted CDMOs enable both organizations to operate efficiently, with a clear understanding of capabilities, limitations, and quality systems. These partnerships streamline technology transfers and ensure greater consistency across projects.

At the same time, platform-based strategies must incorporate mechanisms to detect and evaluate differences between new and legacy molecules. Early identification of potential issues allows for rapid and proactive resolution.

The second lever is phase-appropriate development. This principle remains central to optimizing timelines without compromising quality. Continuous dialogue between industry and regulators defines what constitutes essential data at early, late, and commercial development phases. In early stages, analytical and process methods should be fit for purpose while maintaining scalability and robustness for later stages of development.

The third lever involves integrated CDMO services. Although identifying a truly comprehensive one-stop-shop partner can be challenging, integrated services provide clear benefits. Reduced material transfer, technology transfer, and logistics requirements accelerate development timelines. Fewer external vendors lower transaction costs, minimize audit and communication burdens, and ensure alignment under a consistent technology and quality framework. However, reliance on a single vendor introduces risk, necessitating appropriate contingency planning.

Emerging operational practices are also contributing to improved efficiency. One example is the treatment of specific processes as continuous workflows. For instance, mAb material can be transferred directly to conjugation once it is ready, rather than performing a full release before conjugation. This approach eliminates the need for full release testing and extended stability studies on the mAb, providing substantial savings in both time and cost. The practice has gained regulatory acceptance in multiple R&D programs.

Across all these approaches, product quality remains non-negotiable. Within that boundary, scientifically sound and innovative methodologies can be adopted to enhance speed and cost efficiency without compromising safety or compliance.

EI Key areas where corners should never be cut include those directly impacting product quality. Maintaining development timelines is also vital, as delays can result in losing competitive advantage. Several focus areas are essential to ensuring quality, the first of which is employee training. A robust, ongoing training program should be implemented to maintain staff competence and compliance.

> "Although the drive for speed is strong during early development, early attribute assessment is particularly valuable for ADCs."
> **Juma Bridgewater**

The second area would be talent—recruiting and retaining skilled employees, ensuring efficient task execution and process understanding. There should also be an investment in the consistent quality of raw materials, which remains a critical yet underemphasized focus area.

Supplying sufficient budget and resources for in-plant presence when outsourcing manufacturing prevents quality or compliance issues. The final key area is method and process development. Adequate investment early in development minimizes troubleshooting and variability during GMP execution.

JB The alignment of analytical methods and process development is central to establishing a robust control strategy. Ensuring appropriate analytical methods are in place to monitor critical quality attributes is essential.

Although the drive for speed is strong during early development, early attribute assessment is particularly valuable for ADCs. Attributes such as DAR or levels of unconjugated antibody significantly influence molecular performance. Variations that may be acceptable for a naked antibody, such as glycan heterogeneity or oxidation, can have a far greater impact in ADCs.

The area where compromise is unacceptable is characterization. Comprehensive understanding of batch-to-batch variability, identification of changing attributes, and correlation of these changes with molecular function are all critical to maintaining product quality, efficacy, and patient safety.

Q What innovations, process development automation, or analytical technologies are expected to be game changers for ADC manufacturing scalability? How should companies prepare their processes and strategies for the complexities of the next generation of ADCs?

EI Future innovation in ADC manufacturing could significantly alter how we manage payloads and conjugation processes. One area with transformative potential is formulation development for linker–drug payloads, which remains underexplored. Improved formulation strategies could reduce toxicity levels to OEB3 or lower, thereby mitigating risks associated with aerosolization. Lower-toxicity formulations would enable more manufacturing facilities to handle linker–drug intermediates, substantially increasing available capacity.

For mAbs, innovation should focus on upstream and downstream process efficiency to reduce both manufacturing footprint and raw material consumption. Advances in high-density cell culture systems could allow equivalent cell growth in smaller bioreactors, decreasing reliance on large-scale tanks, and lowering overall resource usage. Although

"Advances in analytical technologies are equally vital."
Esohe Idusogie

significant effort has been devoted to productivity improvement, shifting focus toward media and resource efficiency may represent the next frontier in sustainable manufacturing.

Within the ADC workflow, stable, less toxic liquid formulations of linker–drug payloads could allow bioconjugation scientists to handle materials safely within biosafety cabinets rather than isolators. This could further enhance accessibility and safety. Parallel exploration of alternative therapeutic modalities, such as siRNA conjugates, may also reduce dependence on highly cytotoxic payloads while maintaining efficacy.

Then, with respect to automation, a greater emphasis on automating bioassays would have a significant impact. Despite the availability of automation tools for decades, many laboratories still conduct bioassays manually, introducing variability and limiting reproducibility. Broader adoption of QC-compatible liquid-handling platforms would standardize these critical assays and improve data quality.

Advances in analytical technologies are equally vital. Simpler, more quantitative, and robust tools for quality control laboratories would enhance analytical speed, throughput, and cost-efficiency. Examples include QC-compatible LC–NMR for linker–drug identity and impurity profiling, and quantitative LC–MS and SEC–MS systems for routine characterization.

Finally, compact, automated instrumentation for HPLC-based analyses, such as size—exclusion chromatography or DAR measurement, would be transformative. Similar 'breadbox'—type systems already exist for capillary electrophoresis, and extending this capability to SEC and DAR analysis could revolutionize routine ADC testing.

JB Many technological advances established in biologics manufacturing can be directly applied to ADCs, particularly as the field expands beyond cytotoxic oncology applications into new therapeutic areas, including antibacterial and peptide or siRNA conjugates. These developments create opportunities to implement process analytical technologies and at-line testing, especially when handling less potent materials.

Even within high-potency environments, analytical innovation remains essential. For instance, integrating DAR measurement by mass spectrometry with additional molecular analyses can improve characterization efficiency. A single workflow could allow comprehensive whole-molecule assessment alongside targeted analysis of specific liabilities, such as oxidation in complementarity-determining regions. This approach, known as multi-attribute monitoring, offers an opportunity to enhance data richness while reducing analysis time.

SZ A critical area of improvement lies in reducing line losses during manufacturing operations. Despite technological progress in other domains, the physical configuration of manufacturing lines has changed little over time. Losses frequently occur through tubing systems, filters, manifolds, and other hold-up points.

Minimizing tubing length and optimizing flow paths at each stage could yield substantial material savings. Although these changes may appear low-tech compared with other innovations, the practical impact on process efficiency and yield would be considerable. Reducing unnecessary holdup volumes improves recovery and supports sustainability and cost-effectiveness in large-scale ADC manufacturing.

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BIOCONJUGATION INSIGHTS

OVERCOMING CHALLENGES IN THE ADC MANUFACTURING AND R&D ECOSYSTEMS

SPOTLIGHT

Process robustness and quality control in ADC manufacturing

INTERVIEW

"In the future, ADC manufacturing may not even require mAb release testing if it can be integrated."

In this interview, **Lauren Coyle** (Launch Commissioning Editor, *Bioconjugation Insights*), speaks with **Brandon Coyle** (Director Pivotal Purification Process Development, Gilead Sciences), about the scientific and operational challenges that define ADC development and manufacturing. They explore maintaining comparability across scales and sites, the sensitivity of conjugation to equipment and process changes, and strategies for effective tech transfer, including early robustness work and analytical harmonization.

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Q Can you tell us a bit about your work in ADC development and manufacturing, and what initially drew you into the field?

BC What initially drew me to this field was the scientific challenge. ADCs are difficult. You are essentially making three drugs, and every step matters for the final product.

I was also fascinated by how multidisciplinary the work is. You need to understand monoclonal antibodies (mAbs), mAb production, organic chemistry, and complex analytics, all while designing processes that meet stringent quality and regulatory standards.

Additionally, the idea of contributing to therapies that can dramatically improve outcomes for people with cancer was a huge motivator.

Q Comparability remains a critical consideration throughout ADC development scale-up. From your experience, what are the most important parameters to monitor when ensuring product comparability across scales or sites?

BC Comparability for ADCs can be challenging due to simultaneous changes across multiple steps, such as mAbs, drug substance, production line, and drug product. Evaluating impacts not only at the current stage (N) but also downstream (N+1) helps prevent small changes from causing major issues later. For mAbs and small molecules, the industry has established principles for scaling many unit operations, such as maintaining residence time and bed height during chromatography. Many ADC drug substance unit operations mirror mAb purification, allowing similar strategies to be applied.

The key difference lies in conjugation; a reaction step influenced by parameters such as mixing, payload addition rate, location, and temperature control. These factors can vary significantly across scales and sites. For example, one site may use stainless steel reactors while another uses single-use systems. Even with identical reactor volumes, differences in temperature control, impeller design, and inlet port configuration can all impact process performance and product quality.

Q Tech transfer can be particularly intricate for ADCs, where small shifts in process conditions can influence stability or DAR. How do you approach the transfer of ADC processes between R&D and manufacturing settings to maintain control over quality attributes while accommodating differences in equipment and analytical capabilities?

BC One unique aspect is that most ADCs are currently outsourced for conjugation due to the limitations of handling toxic payloads, which adds another layer of communication challenges. Typically, stage-gating the transfer to the CMOs so they get experience at lab, pilot, and at-scale manufacturing has been beneficial. In addition, it allows them to work in their scaled-down systems and provide scale-up tips for their specific manufacturing configurations.

From a process development perspective, doing additional work early to understand process robustness can be very informative. In fact, it is a good idea to stress-test key steps,

"...doing additional work early to understand process robustness can be very informative. In fact, it is a good idea to stress-test key steps, such as conjugation, to try to understand the break points for CQA impact."

"...early and proactive engagement with regulatory authorities is critical to align on implementation and validation strategies for new technologies."

such as conjugation, to try to understand the break points for CQA impact. All this work will significantly improve the risk assessments on both the process and process equipment. In addition to these items, analytical harmonization and timing can improve troubleshooting and help prevent future surprises.

Q Given the pace of innovation in conjugation and analytical technologies, how do you assess when a new technique is sufficiently mature to integrate into an established manufacturing process? What criteria guide that decision?

BC As ADCs mature, the pressure to enhance product and process understanding while reducing costs continues to grow. However, robustness and reproducibility remain paramount, particularly for ADCs, where the complexity of conjugation introduces significantly more variability compared to standard mAb or small-molecule processes. A good example of new technologies being implemented for ADC production is PAT within the conjugation to monitor in real time the reduction and conjugation processes. While this isn't currently used in manufacturing, it can be a powerful tool for development work and could be introduced as the technology develops.

In such a highly regulated environment, early and proactive engagement with regulatory authorities is critical to align on implementation and validation strategies for new technologies. Introducing these innovations early in the product lifecycle is advantageous, as it maximizes the supporting data available for regulatory filings and long-term process control.

When determining readiness for integration, several key factors guide the decision:

- **Technical maturity:** demonstrated robustness, scalability, and reproducibility of the technique
- **Regulatory readiness:** clear validation pathways and precedent for acceptance
- **Risk assessment:** comprehensive evaluation of impact on CQAs and mitigation of potential failure modes
- **Change control complexity:** understanding the operational and compliance implications of implementation

Finally, employing a structured stage-gate approach ensures that each step is supported by data-driven decisions and risk mitigation strategies. This disciplined process is essential for successfully adopting new technologies without compromising quality or compliance.

Q Looking ahead, how do you envision ADC manufacturing evolving over the next decade?

BC ADCs are in a unique position, and we will likely see innovations and medicines coming that are not strictly for cancer or require potent compound handling. This may open the door to new ideas for manufacturing ADCs that can be integrated into the mAb downstream processing. If the conjugation could be performed after viral inactivation but before subsequent purification steps, it could significantly cut costs by reducing unit operations and transfers. In the future, ADC manufacturing may not even require mAb release testing if it can be integrated.

BIOGRAPHY

Brandon Coyle is a Director of Pivotal Process Development at Gilead Sciences, specializing in ADCs. He leads pivotal process development and tech transfers, with expertise in conjugation and purification strategies. Brandon has authored key regulatory submissions, holds multiple patents, and has driven innovations that significantly reduced manufacturing costs. A frequently invited speaker at global bioprocessing and ADC conferences, he has deep experience in CMC and technology transfer. He earned his PhD in Chemical Engineering from the University of Washington, Seattle, WA, USA.

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BIOCONJUGATION INSIGHTS

OVERCOMING CHALLENGES IN THE ADC MANUFACTURING AND R&D ECOSYSTEMS

SPOTLIGHT

Standardizing process development in ADC manufacturing

VIEWPOINT

"ADC production relies on coordination among multiple internal and external partners responsible for antibody supply, linker–payload synthesis, conjugation, and final drug-product manufacturing."

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On October 23, 2025, **Lauren Coyle**, Launch Commissioning Editor of *Bioconjugation Insights*, spoke with **Eric Lacoste**, Global Head of BioProcessing Engineering at Sanofi, about current approaches to ADC manufacturing and the technological and organizational factors that influence process design and scale-up. This article is based on that interview.

EVOLVING PROCESSES IN A DIVERSIFYING FIELD & RECURRING CONSTRAINTS IN ADC MANUFACTURING

Over the past decade, the ADC field has moved from relatively uniform constructs toward a broader range of modalities and chemistries. This diversification has required process scientists to accommodate new payload types, linker designs, and antibody formats while maintaining control of conjugation and purification parameters. Each new construct introduces variables in structure, reactivity, and stability, demanding systematic assessment of how these properties influence process behavior and product quality.

Many technical challenges in ADC manufacturing have persisted despite advances in analytical and process technologies. Diversity in molecular design remains a key source of complexity: every candidate combines a distinct protein, linker, and payload, requiring case-specific optimization. Early-stage attrition rates remain high, meaning that multiple programs must be developed in parallel before a few advance to later stages.

To manage this workload, a structured framework has been established to guide development activities, where a platform-based approach uses defined decision trees that relate molecular characteristics to process routes and analytical requirements. Standardized workflows allow teams to compare data across projects and maintain consistent documentation and risk assessments. Such frameworks support alignment between conjugation, purification, and analytical groups and provide a reference for future optimization rather than prescribing a single method.

HIGH-THROUGHPUT & INTENSIFIED PROCESS STRATEGIES IMPROVING PROCESS PERFORMANCE

Two complementary technological strategies underpin efforts to improve understanding of process performance: high-throughput experimentation and process intensification.

High-throughput tools enable multiple parameters to be examined simultaneously using minimal quantities of material, a particular advantage at early stages when supply is limited. Automated studies of conjugation and purification steps yield quantitative data on reaction kinetics, impurity formation, and stability under different conditions. These datasets inform process definition and reduce the need for repeated scale-up trials.

Process intensification focuses on minimizing production footprint and operator exposure while maintaining containment and reproducibility. Approaches under evaluation include closed or semi-continuous systems that limit manual handling of highly active intermediates. Although not yet routine, such systems are expected to become more common as demand for consistent, lower-exposure operations increases.

INTEGRATING STABILITY, RISK MANAGEMENT, & EMERGING CONJUGATION CHEMISTRIES

Ensuring stability and process robustness requires early evaluation of molecular liabilities and continuous assessment throughout development. Preliminary developability studies characterize the antibody structure and predict aggregation or degradation tendencies, guiding formulation and process decisions.

Stability testing is incorporated at defined stages to establish acceptable holding times and storage conditions for intermediates. During technology transfer, a formal package combining gap analysis, risk assessment, and mitigation planning supports collaboration between development and manufacturing teams. This structure identifies parameters that may influence product consistency, such as shear, temperature, or light exposure, and allows mitigation strategies to be implemented before large-scale manufacture.

The introduction of new conjugation methodologies, such as click-chemistry reactions, offers alternative routes for payload attachment. The reaction step itself is well controlled, however, the main challenges lie in impurity management and purification design. Impurities that closely resemble the desired ADC structure can complicate characterization and clearance. Current efforts combine high-throughput screening with computational modeling to better predict reaction behavior and optimize separation conditions during scale-up.

Effective impurity control contributes directly to product quality and regulatory

acceptance. Understanding the relationship between conjugation chemistry, impurity formation, and downstream purification capacity is therefore a central part of process design.

COLLABORATION ACROSS THE MANUFACTURING NETWORK

ADC production relies on coordination among multiple internal and external partners responsible for antibody supply, linker–payload synthesis, conjugation, and final drug-product manufacturing. These relationships function best when structured as scientific partnerships rather than transactional supplier agreements. Shared technical understanding and clear communication pathways facilitate consistent technology transfer and troubleshooting.

Preferred partnerships are established based on complementary expertise and capacity. Joint risk assessments, agreed escalation procedures, and regular site interactions help maintain process continuity. Close scientific dialogue across organizations is considered essential for integrating complex bioconjugation workflows.

LOOKING AHEAD: TOWARD CONSISTENT & SCALABLE MANUFACTURING

As ADC development expands to encompass various payloads and indications, manufacturing strategies are shifting toward intensified and modular processes capable of meeting diverse scale and safety requirements. Continuous or semi-continuous operations can reduce material losses, improve reproducibility, and lower environmental impact by decreasing solvent and waste generation. For compounds with high cytotoxic potential, smaller-volume enclosed systems further minimize operator exposure while maintaining containment and consistency.

The broader objective is to design manufacturing environments that support both niche and large-scale supply within flexible infrastructures. Integration of conjugation technologies with established biologics production systems may enable facilities to efficiently manage multiple conjugate modalities.

Progress in ADC manufacturing will depend on combining standardized development frameworks with data-driven process evaluation and effective collaboration across the supply chain. The transition from empirical to systematic process design is enabling more consistent outcomes and facilitating knowledge transfer between programs.

Continued refinement of conjugation chemistries, impurity control, and process intensification will determine how effectively the field can meet the growing demand for complex bioconjugate therapeutics.

BIOGRAPHY

Eric Lacoste has almost 20 years of experience in ADC Process Development at Sanofi. Currently, he is leading the group manufacturing non-GMP mAb downstream batches and is accountable for DS Tech Transfer to CTM and commercial sites.

Eric Lacoste, Global Head of BioProcessing Engineering, Mammalian Platform, Global CMC Development, Sanofi, Paris, France

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BIOCONJUGATION INSIGHTS

OVERCOMING CHALLENGES IN THE ADC MANUFACTURING AND R&D ECOSYSTEMS

SPOTLIGHT

Small-scale innovation, large-scale ambition: optimizing fragment-drug conjugates

INTERVIEW

"The future of ADCs may be less about choosing one 'perfect' technology and more about combining the best elements of each in a Lego-like way to build truly modular, multifunctional therapies."

In this interview, Ashling Cannon (Assistant Editor, *Bioconjugation Insights*) speaks with Meddy El Alaoui (CEO, AbTx), about the evolution of enzymatic bioconjugation and its role in advancing fragment-based ADC design. They discuss production challenges, scalability, and the promise of plug-and-play bioconjugation technologies for next-generation targeted therapies.

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Q What initially drew you to the ADC field, and how has your approach to design and production evolved?

MEA I first became involved in ADC development shortly following my PhD, during my postdoctoral work. I joined a project focused on demonstrating

"My hope is that in the coming years we will see the first approved ADCs based on transglutaminase or other enzymatic conjugation technologies."

proof of concept that our enzymatic bioconjugation technology could be applied to antibodies and antibody fragments. That was the start of my ADC story, almost 10 years ago.

At that time, few people worked with transglutaminase, the enzyme behind our technology. It has been interesting to see how enzymatic conjugation has grown and evolved over the past decade and is now becoming a genuinely viable technology. Of course, there is still work to do on the CMC side, and GMP production remains complex as enzymatic reactions can be challenging. We are optimistic that the next decade will bring significant progress, and we are proud to be part of that.

Ten years ago, producing ADCs via enzymatic routes was challenging; protocols were much more experimental. Now, with advances and companies such as Araris making deals, the field has gained real momentum. My hope is that in the coming years we will see the first approved ADCs based on transglutaminase or other enzymatic conjugation technologies.

Q What are the most critical considerations in achieving consistency and control across the bioproduction process?

MEA For me, the bioconjugation step itself is essential. It determines much of what follows. During my PhD, I worked in lipidomics, which gave me a useful perspective that ADCs are similar to oil and water: hydrophobic payloads, hydrophilic antibodies, and the challenge of combining them to make something great

For ADC manufacturing, controlling the DAR with precision is essential. Regulatory agencies such as the US FDA now expect homogeneous, batch-to-batch reproducibility with consistent DAR values. Enzymatic conjugation, such as transglutaminase-based methods, offers a clear path to homogeneity. You can precisely control the DAR depending on the therapeutic application.

I also believe simplicity is key. Ideally, we could one day integrate the enzymatic step directly into antibody production, adding the enzyme post-expression, then completing a single purification step to yield the final ADC. That would reduce costs and streamline processing. Since enzymatic reactions can operate efficiently even in complex environments, focusing on a single tag or site, they hold enormous potential to simplify and accelerate manufacturing.

Q You have worked extensively with antibody fragments rather than full-length antibodies. What unique challenges and opportunities do these smaller constructs present?

MEA Producing and purifying antibody fragments is more challenging than working with full-length antibodies, and you cannot reuse the

same process. We focus on fragments because they present a distinct opportunity. The full-length antibody space is already highly developed, with established technologies and many players. In contrast, fragments open new avenues for design and delivery, particularly when paired with site-specific conjugation. Chemical conjugation methods can easily disrupt the fragment's immunoreactivity, so site-specific enzymatic approaches are vital.

One issue with antibody fragments is their lower solubility compared with full-length antibodies. Adding hydrophobic payloads makes that even more complicated. Still, we are convinced fragments can be powerful tools for solid tumor treatment. Their smaller size means faster, deeper tumor penetration. Full-length ADCs often struggle in certain solid tumors, such as pancreatic cancer, so fragment-based ADCs might offer a promising alternative where traditional formats fall short.

Q What are the key advantages and constraints of small-scale ADC production, and how do you balance flexibility and process robustness?

MEA As we are working in a highly innovative area, there is no single, traditional production pathway for fragment-drug conjugates. Our small-scale manufacturing allows us to efficiently screen conditions, optimize reaction parameters, and identify the best-performing processes.

That said, we always think ahead to scalability. Our development mindset is not purely R&D, and we design every experiment with scale and potential CDMO partnership in mind. That means avoiding processes that cannot be scaled or that rely on nonstandard equipment. We work to align our approach with technologies and process capabilities already familiar to major CDMOs in the ADC field.

Q Can you expand on the challenges you anticipate when scaling from small to large-scale production, particularly with fragment-based ADCs? What initial steps are you taking to address this?

MEA Scaling enzymatic reactions is far from straightforward. You cannot simply multiply your quantities and expect the same results. Parameters such as pH, temperature, reaction time, and even mixing or shaking conditions can influence enzyme performance. Reproducibility across enzyme batches, measured as activity per milligram, is also critical.

When moving toward GMP manufacturing, both the antibody and the enzyme must meet GMP standards, which adds complexity and cost. Each step introduces more quality

"As we are working in a highly innovative area, there is no single, traditional production pathway for fragment-drug conjugates."

control and validation requirements. So, while enzymatic conjugation has great promise, scaling it efficiently remains a significant technical and regulatory challenge.

Q How do you see fragment-based ADCs and the supporting bioproduction technologies shaping the next generation of targeted therapies? What developments are you most excited to see over the next 5–10 years?

MEA I think fragment-based ADCs have been somewhat underestimated. They will not replace every ADC format, but they have significant potential in specific contexts. Historically, production complexity and cost were major barriers, but those challenges are now being addressed. Fragment-drug conjugates currently make up only a small fraction of ADC development, around 2%, but I expect that to grow steadily. It is still a niche area, and we have not yet seen a large number of players enter it.

At AbTx, our goal is to make the technology universal and create a 'plug-and-play' enzymatic system that can work with any antibody or fragment. We have already seen that, with transglutaminase-based approaches, we can switch between different antibodies without redesigning the entire R&D process. That is a strong foundation for scalability and flexibility.

Looking further ahead, I believe we will see increasing convergence of these technologies as they are combined in different ways: enzymatic and chemical conjugation working together, multiple payloads, bispecific fragments, and other advanced designs. The future of ADCs may be less about choosing one 'perfect' technology and more about combining the best elements of each in a Lego-like way to build truly modular, multifunctional therapies.

BIOGRAPHY

Meddy El Alaoui earned his PhD in Biochemistry from the University of Lyon, Lyon, France. He worked as a Postdoctoral Researcher at the Centre Léon Bérard and the University of Cambridge, UK, focusing on the development and validation of cross-linking technology for various antibody formats. In 2018, he joined Covalab as Chief Scientific Officer (CSO) and co-founded AbTx in 2023, where he leads the development of the TheranoStick® platform for next-generation antibody and fragment-based ADC treatments.

Meddy El Alaoui PhD, Scientific Director, Covolab and CEO, ABTX, France

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BIOCONJUGATION INSIGHTS

INDUSTRY INSIGHTS • NOVEMBER 2025

Expanding the conjugate landscape through dual-payload breakthroughs, regulatory wins, and pipeline progress

Lauren Coyle

As an editor with extensive experience in bioconjugation (i.e., ADCs, conjugate chemistry, diagnostics and imaging, bi/multi-specifics, targeted delivery, and theranostics), Lauren's focus is on advancing the field by facilitating and disseminating high-impact research on conjugation technologies and their applications. Lauren works closely with researchers, scientists, and industry professionals to publish cutting-edge studies exploring the latest advances in conjugation chemistry, drug delivery systems, and the development and delivery of targeted therapeutics. In addition to her editorial responsibilities, she maintains a strong network within the biopharma industry, staying up to date with emerging trends and breakthroughs in bioconjugation.

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SUMMARY

October through November saw the bioconjugation field broaden on multiple fronts. New alliances, such as **Samsung Bioepis-Phrontline**, **Invenra-Xcellon**, and **SK pharmteco-LOTTE**, strengthened end-to-end capabilities, dual-payload innovation, and linker-payload access. On the regulatory side, momentum continued with US FDA approval of **Blenrep** in combination for relapsed/refactory multiple myeloma, plus Fast Track designations for **Heidelberg Pharma**'s HDP-101 and **Avzeno**'s EGFR/HER3 bispecific.

Market activity featured financing with **Valink** and **NEOK**, strategic updates with **Sutro**, **ArriVent**, and **Bicycle Therapeutics**, and a headline acquisition as **Novartis** moved to buy **Avidity Bioscience** to add antibody-oligonucleotide conjugates.

Clinically, first-in-human studies advanced with **Daiichi Sankyo**'s STING agnostic DS-3610 and **InnoCare**'s B7-H3 asset, and early efficacy signals were reported across multiple programs (ATM-116, JK06, CRB-701, ZW191), while Phase III readouts highlighted potential new standards. Non-oncology applications progressed with **Lifordi'**s

immune-cell-targeting glucocorticoid ADC in rheumatoid arthritis.

Tool and technology innovation remained brisk: **Syngene** added a GMP bioconjugation suite, **Debiopharm** paired AI-guided payload discovery with a dual-payload linker, and **Catalent** unveiled SMARTag enhanced conjugates.

Research and development highlights included kidney-targeting ligand-siRNA conjugates from **Judo Bio**, a resistance-by-passing TOP1i payload from **Immunome**, and a tumor-specific targeting to truncated core 2 O-glycans from **Precision Biologics**.

COLLABORATIONS AND PARTNERSHIPS

Samsung Bioepis and Phrontline Biopharma entered global collaboration to develop bispecific, dual-payload ADCs [1]

Samsung Bioepis and Phrontline Biopharma announced a global collaboration to develop, manufacture, and commercialize two ADC programs, including TJ108, a bispecific, dual-payload ADC targeting EGFR and HER3. This follows Samsung Bioepis' expansion into ADCs after separating from the Samsung Biologics CDMO unit. The agreement also grants Samsung Bioepis an exclusive license to a topoisomerase I inhibitor (TOP1i) payload used in its ADC pipeline. TJ108 incorporates both TOP1i and tubulin inhibitor payloads via Phrontline's dual-linker payload platform, enabling simultaneous delivery of two cytotoxins through a branched-linker architecture. Phrontline will receive upfront and milestone payments tied to development and regulatory achievements. The collaboration supports Samsung Bioepis' expansion into oncology and Phrontline's goal to advance bispecific, dual-payload ADCs as a new class of precision cancer therapeutics.

Charles River Laboratories and the Francis Crick Institute partnered to accelerate ADC discovery and development [2]

Charles River Laboratories and the Francis Crick Institute announced a collaboration to accelerate ADC discovery and development through an integrated, end-to-end approach spanning antibody generation, conjugation, *in vitro* profiling, and preclinical evaluation. The partnership combines the Crick's antibody discovery capabilities with Charles River's Retrogenix™ platform for off-target interaction profiling to enhance safety and therapeutic index early in development. The jointly managed initiative aims to streamline ADC candidate identification and preclinical validation, reducing timelines and improving translational efficiency.

Xcellon Biologics and Invenra formed partnership to develop multispecific ADCs [3]

Xcellon Biologics and Invenra announced a strategic collaboration to advance multispecific ADC development by combining Invenra's B-Body® bispecific and T-Body™ trispecific antibody platforms with Xcellon's expertise in bioconjugation, ADC development, and manufacturing. The partnership will generate and evaluate novel multispecific ADC candidates to accelerate progression from discovery through preclinical and clinical stages. Invenra's platforms streamline antibody discovery with high developability, while Xcellon provides integrated conjugation and production capabilities for complex biologics. The collaboration

aims to expand the therapeutic reach of targeted ADCs and establish a streamlined framework for developing next-generation bispecific and trispecific antibody-based therapies.

SK pharmteco and LOTTE BIOLOGICS signed LOI to establish integrated global ADC CDMO platform [4]

SK pharmteco and LOTTE BIOLOGICS signed a Letter of Intent (LOI) to collaborate on a strategic initiative to develop a fully integrated global CDMO platform for ADCs. The partnership will combine SK pharmteco's expertise in linker–payload development and manufacturing with LOTTE BIOLOGICS' cGMP bioconjugation and drug substance production capabilities at its Syracuse Bio Campus in the US. The companies aim to deliver one-stop ADC solutions spanning development through commercial manufacturing, minimizing process gaps, and accelerating timelines. Joint marketing and client engagement efforts will target global biopharma partners. At the same time, the collaboration supports supply chain resiliency through established manufacturing infrastructures in the US and Europe.

Piramal Pharma Solutions partnered with IntoCell to enhance ADC development and manufacturing capabilities [5]

Piramal Pharma Solutions signed a Memorandum of Understanding with IntoCell to expand collaboration in ADC development, leveraging IntoCell's proprietary drug-linker technologies and Piramal's integrated CDMO capabilities. Under the non-exclusive agreement, IntoCell may license its OHPAS™ linker, Duocarmycin-based OHPAS payload, Nexatecan-based OHPAS payload, and iso-Nexatecan-based GGFG payload to Piramal's clients. Piramal will provide R&D and GMP manufacturing services for ADCs and other bioconjugates. The partnership strengthens Piramal's ADCelerate™ platform, designed to streamline bioconjugate development from concept to clinic, offering clients faster development timelines, expanded linker–payload options, and enhanced efficiency across the ADC value chain.

Mycenax Biotech licensed RIN Institute's VLK linker technology to enhance global ADC CDMO services [6]

Mycenax Biotech signed a global license agreement with Japan-based RIN Institute, granting rights to integrate RIN's proprietary Val-Leu-Lys (VLK) linker technology into its CDMO services. The VLK linker offers high serum stability and dual antitumor mechanisms, enhancing ADC internalization, promoting cytotoxicity within the TME, and enabling the development of more effective and stable ADCs. The partnership expands Mycenax's technical capabilities and supports the delivery of differentiated ADC solutions for global clients. This agreement follows an LOI signed in April 2025, further solidifying collaboration between the two companies in advancing next-generation ADC therapeutics. the two companies' collaboration to advance.

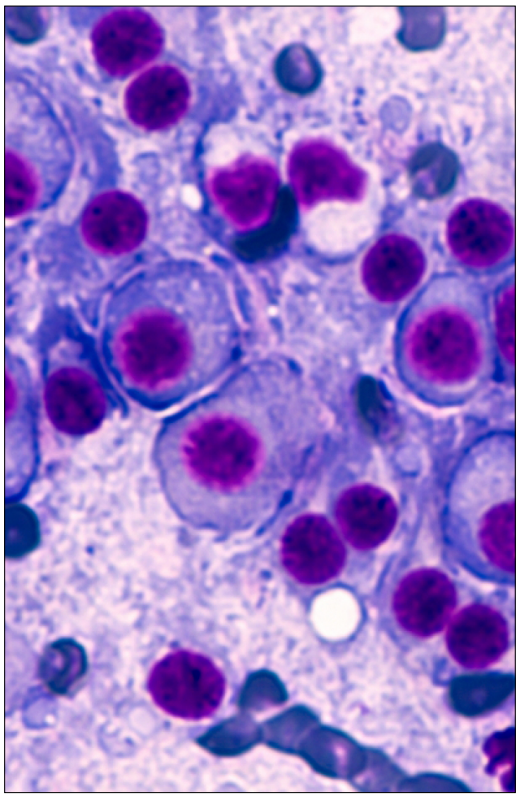
REGULATORY CHANGES AND UPDATES

Heidelberg Pharma received US FDA Fast Track Designation for Amanitin-based ADC HDP-101 in multiple myeloma [7]

Heidelberg Pharma announced that the US FDA has granted Fast Track Designation to HDP-101, the company's lead Amanitin-based ADC, for the treatment of relapsed or refractory multiple myeloma. The designation was supported by preclinical and clinical data from the ongoing Phase I/IIa trial assessing HDP-101's safety and antitumor activity in heavily pretreated patients. HDP-101 remains investigational, with clinical evaluation ongoing to establish its safety and efficacy profile.

GSK received US FDA approval for Blenrep combination therapy in relapsed or refractory multiple myeloma [8]

GSK announced US FDA approval of Blenrep (belantamab mafodotin-blmf), an ADC targeting BCMA, in combination with bortezomib and dexamethasone (BVd) for adults with relapsed or refractory multiple myeloma who have received at least two prior lines of therapy, the risk of death and a 3-fold increase in median progression-free survival to 31.3 months versus 10.4 months with including a proteasome inhibitor and an immunomodulatory agent. The approval is based on Phase III DREAMM-7 results showing a 51% reduction in risk of death and a tripled median progression-free survival of 31.3 months versus 10.4 months for the daratumumab-based comparator. Safety was consistent with known profiles of the individual agents.



US FDA Fast Track designation granted to Avenzo Therapeutics for EGFR/HER3 bispecific ADC AVZO-1418 [9]

Avenzo Therapeutics announced that the US FDA granted Fast Track designation to AVZO-1418 (DB-1418), an EGFR/HER3 bispecific ADC (bsADC), for the treatment of patients with unresectable, locally advanced, or metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 L858R mutations after progression on EGFR tyrosine kinase inhibitor therapy. AVZO-1418 is currently being evaluated in a Phase I/II, first-in-human, open-label trial assessing safety, tolerability, and preliminary efficacy as monotherapy and in combination regimens in patients with advanced solid tumors.

MARKET TRENDS

Valink Therapeutics raised $11.8M to advance bispecific ADC pipeline and expand US operations [10]

Valink Therapeutics closed an $11.8M financing round to support the development of its bsADC pipeline and establish new headquarters in Cambridge, MA, US. The funding, led by redalpine, LongeVC, Oxford Science Enterprises, and existing investors, will advance the company's V-gate discovery platform and oncology programs. Valink's bsADC technology integrates dual-targeting mechanisms with optimized payload delivery to enhance therapeutic precision and safety. The company is also exploring complementary modalities beyond ADCs to address broader oncology indications. The investment strengthens Valink's position in next-generation ADC innovation and supports progress toward upcoming clinical and translational milestones.

Avacta raised £16M to advance peptide drug conjugate and pre|CISION® oncology pipeline [11]

Avacta raised approximately £16M through an oversubscribed share placing to institutional and high-net-worth investors, providing additional working capital to progress its pre|CISION oncology programs into the second half of 2026. Proceeds will support ongoing development of faridoxorubicin (AVA6000) in Phase Ib, initiation of the FAP-EXd (AVA6103) Phase I trial pending US FDA IND approval, and advancement of the Dual Payload Technology (AVA6207) peptide drug conjugate platform. The raise also enables amendments to the company's convertible bond terms, extending repayment timelines. Avacta reported a 91% disease control rate from its faridoxorubicin Phase Ia data presented at the 2025 European Society for Medical Oncology (ESMO) Congress and aims to maintain full ownership of its pre|CISION-based assets while pursuing partnership opportunities.

To learn more about the pre|CISION platform, you can read our interview in *Bioconjugation Insights* with Avacta's CSO, Michelle Morrow **here**.

NEOK Bio launched with $75M Series A financing to advance bispecific ADC pipeline [12]

NEOK Bio emerged from stealth with $75M in Series A funding led by ABL Bio to advance two bsADC programs into clinical development. The financing will support IND filings for NEOK001, targeting ROR1 and B7-H3, and NEOK002, targeting EGFR and MUC1, with both programs expected to enter Phase I trials in mid-2026. NEOK's proprietary SYNtecan E™ linker–payload technology enables high stability and optimized biophysical properties to improve efficacy and safety over conventional ADCs. The company's dual-targeting approach aims to address tumor heterogeneity, enhance internalization, and reduce off-target toxicity.

Novartis to acquire Avidity Biosciences, expanding into antibody–oligonucleotide conjugates for neuromuscular disease [13]

Novartis announced plans to acquire Avidity Biosciences for ~$12B, gaining access to its proprietary antibody

oligonucleotide conjugate (AOC) platform that enables targeted RNA delivery to muscle tissue. The deal, expected to close in the first half of 2026 following the spin-off of Avidity's precision cardiology assets, will integrate Avidity's late-stage neuromuscular programs into Novartis' neuroscience portfolio. AOC programs in development include potential first-in-class therapies for myotonic dystrophy type 1, facioscapulohumeral muscular dystrophy, and Duchenne muscular dystrophy. By combining the tissue specificity of antibodies with the precision of oligonucleotide therapeutics, Avidity's AOC platform offers a transformative approach to genetic muscle diseases and strengthens Novartis' leadership in RNA-targeted conjugate therapeutics.

Bicycle Therapeutics provided 2025 Q3 financial results with pipeline updates and regulatory progress [14]

Bicycle Therapeutics reported third-quarter 2025 financial results, with cash and cash equivalents of $648.3M as of September 30, 2025, compared with $879.5M at year-end 2024. The decrease primarily reflected R&D expenditures supporting its Bicycle Drug Conjugate programs, including the development of zelenectide pevedotin. R&D expenses rose to $58.4M from $48.3M year over year, while general and administrative costs were stable at $18.9M. Net loss was $59.1M compared with $50.8M in Q3 2024. The company remains well capitalized following receipt of a $38.2M UK R&D tax credit, and continues advancing multiple oncology programs toward regulatory milestones in 2026.

Sutro Biopharma reported Q3 2025 results and advanced next-generation ADC portfolio following strategic restructuring [15]

Sutro Biopharma reported third-quarter 2025 financial results which highlighted a strengthened focus on its next-generation ADC pipeline following a corporate restructuring. Cash, cash equivalents, and marketable securities totaled $167.6M as of September 30, 2025, compared with $388.3M a year earlier. Revenue rose to $9.7M, primarily from its collaboration with Astellas, while total R&D and G&A expenses decreased to $48.6M from $76.4M due to cost-saving measures. The restructuring and expected milestone payments extend Sutro's cash runway into at least mid-2027. Key pipeline updates included FDA IND clearance for STRO-004, progress on the ITGB6-targeting ADC STRO-006, and advancement of dual-payload ADC programs, including immunostimulatory collaborations with Astellas.

ArriVent BioPharma advanced ADC pipeline with FDA IND clearance for ARR-217 and reported Q3 2025 financial results [16]

ArriVent BioPharma reported third-quarter 2025 results and key pipeline updates, including FDA IND clearance for ARR-217, a CDH17-targeted ADC being evaluated in an ongoing Phase I study in gastrointestinal cancers. ARR-217, developed in collaboration with Lepu Biopharma, represents a potential best-in-class ADC for solid tumors. The company plans to expand its ADC portfolio across additional solid tumor

indications. ArriVent also highlighted late-stage progress for firmonertinib in EGFR-mutant NSCLC. As of September 30, 2025, ArriVent reported $305.4M in cash and investments, providing operational runway into mid-2027, with R&D expenses totaling $121.2M driven by the $40M ARR-217 licensing payment.

Wave Life Sciences reported Q3 2025 results and advanced RNAi and RNA editing therapeutics into clinical development [17]

Wave Life Sciences reported third-quarter 2025 results emphasizing the advancement of its GalNAc-conjugated RNA medicines platform, which enables targeted delivery to hepatocytes for RNA editing and RNAi therapies. Clinical data for the GalNAc-siRNA WVE-007 showed potent, durable INHBE silencing for obesity, while GalNAc-AIMer WVE-006 achieved physiologic AAT restoration in patients with alpha-1 antitrypsin deficiency. The company also introduced WVE-008, a GalNAc-conjugated RNA editor targeting PNPLA3 I148M for liver disease, and unveiled a bifunctional oligonucleotide construct that simultaneously edits and silences RNA. These advances underscore Wave's leadership in conjugate-enabled RNA therapeutics, integrating precise chemical design with ligand-directed delivery to achieve durable, tissue-specific gene modulation across metabolic and genetic diseases.

RESEARCH AND DEVELOPMENT HIGHLIGHTS

Judo Bio presented preclinical data on megalin-STRIKER ligand-siRNA conjugates for kidney-targeted gene silencing [18]

Judo Bio presented preclinical results at the 21st Annual Meeting of the Oligonucleotide Therapeutics Society, demonstrating that its megalin-STRIKER ligand–siRNA conjugates achieved potent, kidney cell-selective gene silencing in rodents and non-human primates. The conjugates target megalin receptors on proximal tubular epithelial cells (PTECs), enabling precise delivery and mRNA knockdown within renal tissue. A single administration resulted in approximately 70% target gene silencing sustained for two months, with dose-dependent effects in rodents and clear translation to primates. The data underscore the modularity of the STRIKER platform and its potential to enable kidney-specific oligonucleotide therapies addressing disease-modifying genes expressed in PTECs.

Immunome presented preclinical data showing HC74 ADC payload overcomes resistance mechanisms [19]

Immunome presented preclinical data demonstrating that its proprietary TOP1i-payload, HC74, can overcome multiple mechanisms of resistance to ADCs, including drug efflux and target heterogeneity. HC74, used in the ROR1-targeting ADC IM-1021, currently in Phase I trials, and other preclinical candidates showed strong cytotoxicity and bystander activity due to its high membrane permeability. ADCs incorporating HC74 achieved efficacy in preclinical models of colorectal cancer resistant to trastuzumab-DXd and irinotecan, as well as in NSCLC with heterogeneous target expression. The findings, presented at the 2025 AACR-NCI-EORTC Conference, support HC74's potential as a next-generation ADC payload designed to address multidrug resistance and improve therapeutic durability.

Precision Biologics presented preclinical data demonstrating efficacy and safety of tumor-specific ADC [20]

Precision Biologics reported preclinical data for PB-vcMMAE-5, a tumor-specific ADC targeting truncated core 2 O-glycans, at the 2025 Society for Immunotherapy of Cancer (SITC) Annual Meeting. PB-vcMMAE-5 combines the monoclonal antibody PB-223 with a cleavable mc-vc-PABc linker and monomethyl auristatin E (MMAE) payload, with DAR 3.92, showing selective binding to tumor tissues and no reactivity with normal tissues. The ADC demonstrated potent *in vitro* cytotoxicity across nine human cancer cell lines, including triple-negative breast, prostate, ovarian, and lung cancers. *In vivo*, PB-vcMMAE-5 produced dose-dependent tumor inhibition in ovarian xenograft models, achieving complete tumor necrosis at 9mg/kg with no observable toxicity or weight loss. These findings support its potential as a targeted therapeutic for core 2 O-glycan–expressing malignancies.

CLINICAL TRIALS AND RESEARCH

Daiichi Sankyo initiated first-in-human trial of DS-3610, a first-in-class STING agonist ADC for solid tumors [21]

Daiichi Sankyo announced dosing of the first patient in a Phase I first-in-human trial evaluating DS-3610, an investigational STING agonist ADC, in patients with advanced, metastatic, or unresectable solid tumors. DS-3610 combines precise tumor targeting with an immunomodulatory payload that activates innate immune pathways and may overcome resistance to current immunotherapies. The global, multicenter, open-label study will assess safety, tolerability, pharmacokinetics, and preliminary efficacy, including objective response rate and disease control rate. DS-3610 represents the first STING agonist ADC to enter clinical development and a new frontier within Daiichi Sankyo's ADC portfolio, expanding its exploration of immune-modulating payloads to enhance anti-tumor responses in refractory solid tumors.

Multitude Therapeutics reported early clinical data for CD44v9-directed ADC AMT-116 in advanced solid tumors [22]

Multitude Therapeutics presented initial results from its ongoing Phase I/II dose escalation and expansion study of AMT-116, a CD44v9-targeting ADC, in patients with EGFR wild-type NSCLC and other advanced solid tumors. Across 164 patients treated at 1.5–5.0mg/kg every two weeks, AMT-116 demonstrated a manageable safety profile and promising efficacy. In heavily pretreated EGFR wild-type NSCLC, overall and disease control rates were 40% and 93%, respectively, increasing to 80% and 100% at the 5.0 mg/kg dose. Objective responses were also seen in nasopharyngeal, anal, and salivary gland cancers. The ADC showed reduced mucosal and skin toxicities compared with other TOP1i-based ADCs, supporting continued dose expansion.

Salubris Biotherapeutics reported Phase I/II dose escalation data for 5T4-targeted ADC JK06 in advanced solid tumors [23]

Salubris Biotherapeutics presented results from the dose-escalation phase of its

ongoing Phase I/II trial evaluating JK06, a 5T4-directed ADC with an MMAE payload, in patients with advanced, relapsed, or refractory solid tumors. Among 29 response-evaluable patients, six achieved confirmed partial responses (21%), including five of 13 with NSCLC (overall response rate (ORR) 38%) and one of seven with breast cancer. JK06 was generally well tolerated, with predominantly low-grade adverse events; isolated Grade 3 events included peripheral neuropathy, keratitis, fatigue, and ALT elevation, and one Grade 5 pneumonitis at higher doses. Pharmacokinetics supported doses up to 4.5mg/kg. Dose expansion is ongoing in NSCLC and breast cancer cohorts.

Corbus Pharmaceuticals presented Phase I/II data for Nectin-4-targeting ADC CRB-701 in advanced solid tumors [24]

Corbus Pharmaceuticals presented data from its ongoing multicenter Phase I/II trial evaluating CRB-701 (SYS6002), a next-generation Nectin-4-targeting ADC, in 167 patients with advanced solid tumors, including head and neck squamous cell carcinoma (HNSCC), cervical cancer, and metastatic urothelial carcinoma. The trial, conducted in the US and Europe, reported no dose-limiting toxicities, with 2.7mg/kg and 3.6mg/kg selected for optimization. CRB-701 showed a favorable safety profile, with Grade 3 treatment-related adverse events in 18% of patients and no Grade 4 or 5 events; peripheral neuropathy was limited to 8.4% (all Grade 1–2). Clinical responses were observed across varying levels of Nectin-4, PD(L)-1, and HPV expression. Corbus plans to meet with the US FDA and initiate registrational studies by mid-2026.

Sichuan Kelun-Biotech reported Phase III results for HER2-directed ADC trastuzumab botidotin versus T-DM1 in metastatic breast cancer [25]

Sichuan Kelun-Biotech presented Phase III data from a randomized study comparing the HER2-targeting ADC trastuzumab botidotin (A166) with trastuzumab emtansine (T-DM1) in 365 patients with unresectable or metastatic HER2-positive breast cancer previously treated with anti-HER2 therapy. Median progression-free survival was 11.1 months with trastuzumab botidotin versus 4.4 months for T-DM1 ($p<0.0001$), with consistent benefit across subgroups. The ORR was 76.9% versus 53.0%, and a trend toward improved overall survival was observed. Grade ≥3 adverse events occurred in 69.8% of patients with trastuzumab botidotin versus 63.7% with placebo, with ocular events the most frequent with trastuzumab botidotin. No on-treatment deaths occurred amd the data support trastuzumab botidotin as a potential new therapy for pretreated HER2-positive breast cancer.

SystImmune reported positive Phase III results for bispecific ADC iza-bren in metastatic nasopharyngeal carcinoma [26]

SystImmune announced positive topline results from the Phase III BL-B01D1-303 trial evaluating iza-bren, a bispecific ADC targeting EGFR and HER3, in recurrent or metastatic nasopharyngeal carcinoma (NPC) following at least two prior lines of therapy, including platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. Iza-bren achieved a BICR-assessed ORR of 54.6% versus 27.0% for chemotherapy ($p<0.0001$), with median duration of response and progression-free survival of 8.5 and 8.38 months, respectively, compared with 4.8 and 4.34 months. The ADC was well tolerated, with mainly manageable hematologic toxicities and limited cases of interstitial lung disease.

Zymeworks reported preliminary Phase I results for FRα-targeting ADC ZW191 in advanced solid tumors [27]

Zymeworks presented preliminary data from its ongoing Phase I trial evaluating ZW191, a folate receptor-alpha (FRα)-targeting ADC incorporating the proprietary payload ZD06519, in patients with platinum-resistant ovarian, metastatic endometrial, and NSCLC. Among 27 response-evaluable patients, ZW191 achieved an ORR of 44% across doses and 53% at 6.4–9.6 mg/kg; gynecologic cancer patients achieved an ORR of 50% and 64% at higher doses. Responses occurred even in tumors with low or negative FRα expression. ZW191 was well tolerated, with no treatment-related deaths or discontinuations and low rates of Grade ≥3 events. Dose optimization at 6.4 and 9.6mg/kg will proceed further to evaluate efficacy and safety in advanced solid tumors.

Lifordi Immunotherapeutics initiated Phase I trial and presented nonclinical data showing immune cell–targeted glucocorticoid delivery [28]

Lifordi Immunotherapeutics presented nonclinical results and announced initiation of a Phase I SAD/MAD study of LFD-200, an ADC designed to deliver a glucocorticoid payload selectively to immune cells for the treatment of rheumatoid arthritis. Data presented at ACR Convergence 2025 showed that in non-human primates, LFD-200 achieved sustained glucocorticoid exposure in immune tissues for seven days, reduced TNFα and IL-1β levels, and did not affect cortisol, bone formation, or bone mineral density after 13 weekly doses. The ADC's VISTA-targeted approach achieved anti-inflammatory activity without systemic toxicity. Preliminary clinical data from healthy participants are expected by the end of 2025, supporting translation of immune cell–selective glucocorticoid delivery into first-in-human studies.

InnoCare dosed first patient with novel B7-H3–targeting ADC in solid tumors [29]

InnoCare announced the first patient dosing of ICP-B794, a novel B7-H3–targeting ADC developed using the company's proprietary platform. ICP-B794 combines a humanized anti-B7-H3 monoclonal antibody with a potent cytotoxic payload via a protease-cleavable linker, enabling precise tumor targeting and minimized off-target toxicity. In preclinical studies, the ADC demonstrated superior antitumor activity and strong efficacy even in large tumor models. The therapy is being investigated in patients with solid tumors, including lung, esophageal, nasopharyngeal, HNSCC, and prostate cancer. As no B7-H3–directed therapy has yet been approved, ICP-B794 represents a first-in-class opportunity.

BioAtla reported improved survival with AXL-targeting ADC in treatment-refractory sarcomas [30]

BioAtla presented Phase II clinical data for Mecbotamab vedotin (Mec-V), an AXL-targeting ADC, at the 2025 SITC Annual Meeting. In 44 patients with treatment-refractory leiomyosarcoma, liposarcoma, or undifferentiated pleomorphic sarcoma, Mec-V achieved a median overall survival of 21.5 months, 22.9 months in combination with anti–PD-1 therapy, and 18.4 months as monotherapy when compared with the median overall survival of 21.5 months, 22.9 months in combination with anti–PD-1 therapy, and 18.4 months as monotherapy, compared with a historical median survival of approximately 12 months. The 12-month overall survival rate was 73%, with a disease control rate of 52% and two partial responses. Adverse events were manageable, with no treatment-related deaths or ocular or pulmonary toxicities reported. Mec-V uses BioAtla's Conditionally Active Biologic (CAB) technology to bind AXL selectively in acidic TME, minimizing off-target toxicity while maintaining potent antitumor activity.

PDS Biotech presented new data highlighting immune mechanisms and biomarker correlations for PDS01ADC and PDS0101 [31]

PDS Biotechnology reported new translational and clinical data at the 2025 SITC Annual Meeting, demonstrating strong immune activation with its investigational HPV16-targeted immunotherapy, PDS0101, and its novel immunocytokine, PDS01ADC. In analyses of 50 patients with advanced HPV16-positive cancers treated with PDS0101, PDS01ADC, and a checkpoint inhibitor, the combination induced broad pro-inflammatory cytokine responses and measurable T cell recruitment associated with improved clinical outcomes. Serum proteomic profiling identified predictive biomarkers correlating with anti-tumor activity, supporting future biomarker-guided patient selection. These findings, developed under PDS Biotech's CRADA with the National Cancer Institute, validate the immunologic basis of its platforms and reinforce the clinical potential of PDS01ADC in combination immunotherapy for advanced HPV-associated cancers.

TOOLS AND TECHNOLOGIES

Syngene International expanded capabilities with new GMP bioconjugation suite for end-to-end ADC services [32]

Syngene International announced the addition of a GMP bioconjugation suite at its commercial biologics' facility in Bengaluru, enabling fully integrated end-to-end services for ADCs from discovery through GMP manufacturing. The OEB-5-rated suite will enable monoclonal antibody production and bioconjugation at a single site, supported by in-house payload, linker, analytical, and bioanalytical capabilities. Expected to be operational within the financial year, the facility will streamline ADC development timelines and reduce supply chain complexity. Building on over a decade of ADC experience, Syngene will also provide process development, analytical characterization, and scale-up for early- and late-stage programs, enhancing its position as a full-service CDMO partner for ADC development.

Debiopharm partnered with NetTargets to integrate AI-driven drug discovery with dual-payload ADC linker technology [33]

Debiopharm announced a research collaboration with NetTargets to accelerate the development of next-generation ADCs by combining AI–driven discovery with precision linker engineering. NetTargets' AI-Powered Discovery Engine integrates multi-omics data and neural network modeling to identify synergistic compound combinations, which will be incorporated into Debiopharm's proprietary MLINK Duo platform. MLINK Duo enables the attachment of two distinct payloads to a single antibody, supporting coordinated intracellular release and a high DAR (up to DAR 8+8). This integration of AI-guided payload selection with Debiopharm's modular MultiLINK platform aims to rationally design dual-payload ADCs that overcome tumor resistance while minimizing systemic toxicity, thereby representing a convergence of computational biology and advanced conjugation technology for oncology innovation.

CONFERENCES, EVENTS, AND PUBLICATIONS

Sacituzumab govitecan improved progression-free survival in PD-L1-negative triple-negative breast cancer [34]

Results from the global Phase III ASCENT-03 trial presented at the 2025 ESMO Congress showed that ADC sacituzumab govitecan significantly improved progression-free survival compared with standard chemotherapy in patients with previously untreated, PD-L1-negative triple-negative breast cancer (TNBC). Conducted across 229 sites with 558 participants, the study reported median progression-free survival of 9.7 months versus 6.9 months for chemotherapy, and a median duration of response of 12.2 months versus 7.2 months, respectively. Overall survival data remain immature. The ADC's safety profile was consistent with prior studies and manageable with standard supportive care.

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Akari Therapeutics presented preclinical data showing immune activation and synergy of spliceosome-targeting PH1 ADC payload [35]

Akari Therapeutics presented preclinical data at the 2025 SITC meeting demonstrating that its novel spliceosome-targeting ADC payload, PH1, drives both tumor cytotoxicity and multi-faceted immune activation. In preclinical HER2-positive colon cancer models, a Trastuzumab-PH1 ADC combined with anti-PD1 therapy achieved complete tumor regression in 74% of cases, compared with 42% with Kadcyla® plus anti-PD1 ($p<0.05$). PH1 disrupted RNA splicing to increase neoantigen generation, inducing macrophage polarization, neutrophil infiltration, B cell expansion, and γδ T cell activation—effects not seen with traditional microtubule payloads. The data highlight the potential of PH1-based ADCs to synergize with checkpoint inhibitors, expanding immuno-oncology applications beyond cytotoxic mechanisms. Akari's lead Trop2-PH1 ADC, AKTX-101, is entering IND-enabling studies.

Catalent showcased SMARTag® Enhanced Conjugates and new MUC1-targeting ADC data at World ADC San Diego [36]

Catalent presented innovations from its SMARTag technology platform at the 16th World ADC San Diego conference, including preclinical data for CAT-09-833, a MUC1-targeting ADC for platinum-resistant ovarian cancer, and the debut of SMARTag Enhanced Conjugates. This new ADC class integrates both cytotoxic and non-cytotoxic payloads on a single antibody to amplify efficacy while maintaining safety. Enabled by site-specific aldehyde tag and HIPS chemistry, the platform allows tunable DAR and controlled payload release via a tandem-cleavage linker. These developments expand SMARTag's modular capabilities for designing dual- and triple-payload ADCs tailored to complex tumor biology.

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23. Salubris Biotherapeutics. ESMO 2025 poster presentation: a Phase 1/2 study of JK06, a 5T4-targeted antibody drug conjugate (ADC), in patients with unresectable locally advanced or metastatic cancer.
24. Corbus Pharmaceuticals. Corbus Pharmaceuticals presents CRB-701 robust clinical responses in HNSCC and cervical cancers at ESMO25. Oct 18, 2025.
25. Sichuan Kelun-Biotech. Kelun-Biotech presents positive Phase 3 data for trastuzumab botidotin compared to T-DM1 at 2025 ESMO. Oct 19, 2025.
26. Systimmune. SystImmune announces iza-bren meets one of the dual primary endpoints in the BL-B01D1-303 trial in recurrent or metastatic NPC patients with results presented as a late-breaking oral presentation at ESMO. Oct 19, 2025.
27. Zymeworks. Zymeworks presents initial clinical data from the Phase 1 trial of ZW191, an antibody-drug conjugate targeting folate receptor-α at AACR-NCI-EORTC Conference. Oct 23, 2025.
28. Lifordi Immunotherapeutics. Lifordi Immunotherapeutics presents nonclinical data on glucocorticoid antibody drug conjugate LFD-200 at ACR 2025 and initiates Phase 1 study in rheumatoid arthritis. Oct 27, 2025.
29. InnoCare. InnoCare Pharma's novel ADC drug ICP-B794 has been successfully administered to its first patient. Oct 30, 2025.
30. BioAtla. BioAtla's mecbotamab vedotin (Mec-V), an AXL-targeting ADC, demonstrates a median overall survival (OS) of 21.5 months in subtypes of refractory soft tissue sarcomas. Nov 7, 2025.
31. PDS Biotech. PDS Biotechnology announces translational data showing strong immunological and clinical activity of PDS0101 and PDS01ADC presented at SITC 2025. Nov 10, 2025.
32. Syngene International. Syngene International announces plans to add bioconjugation suite for end-to-end antibody-drug conjugates development. Oct 22, 2025.

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34. Dana Farber Institute. ADC improves outcomes for patients with advanced triple-negative breast cancer who are ineligible for immune checkpoint inhibitors. Oct 19, 2025.

35. Akari Therapeutics. Akari Therapeutics presents promising immuno-oncology data for its novel splicing-targeted ADC payload driving immune activation, both as single agent and in combination with anti-PD1 checkpoint inhibitors. Nov 10, 2025.

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BIOCONJUGATION INSIGHTS

EVENT PREVIEW

The 2nd Annual ADC Pharmacokinetics & Clinical Pharmacology Summit

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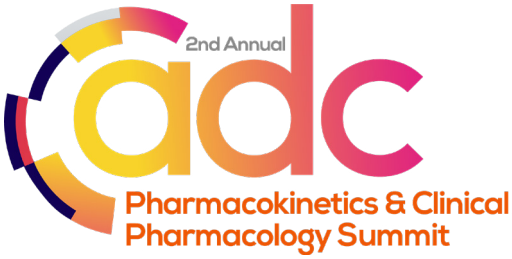
As part of our ongoing coverage of key gatherings in the bioconjugation and ADC development space, *Bioconjugation Insights* presents a preview of the 2nd Annual ADC Pharmacokinetics & Clinical Pharmacology Summit, taking place December 9–11, 2025, in Boston, MA. The meeting will convene leaders in drug metabolism and pharmacokinetics, pharmacokinetics/pharmacodynamics, bioanalysis, pharmacometrics, and clinical pharmacology to address some of the most pressing translational challenges in ADC development, from first-in-human dose prediction to the complexities introduced by novel conjugation formats and emerging payload classes.

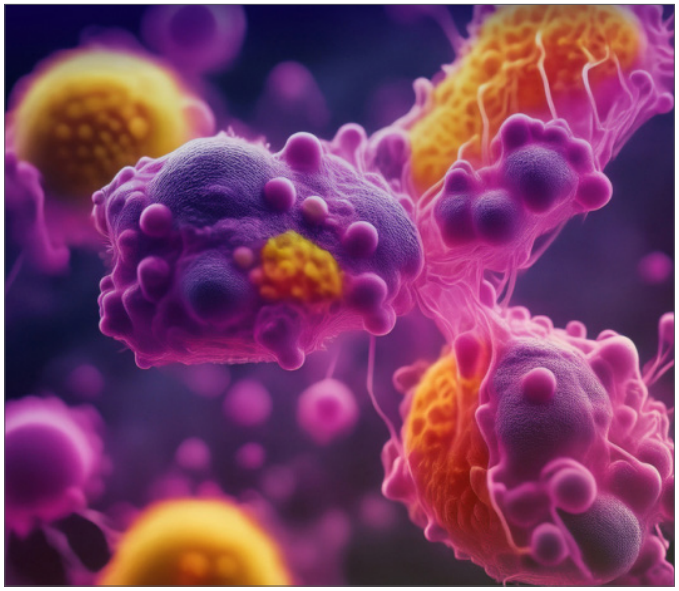


TRANSLATING PRECLINICAL INSIGHTS INTO CLINICAL DOSE PREDICTION

A major focus of this year's summit is strengthening pharmacokintetics-pharmacodynamics (PKPD) translation to inform clinical projections and reduce uncertainty in early development. Christina Vasalou (AstraZeneca) will discuss 'Defining the therapeutic index in early ADC development: considerations from design parameters to clinical translation,' outlining how consistent translational strategies can support the integration of preclinical efficacy and safety data into early-stage decision-making.

This presentation is part of the 'Bridging the translational gap for PKPD: preclinical approaches for improved translation of PK and reduced reliance on animal models' section, which will examine approaches designed to strengthen PK translation and inform clinical studies while reducing dependence on animal model data.

Additional perspectives on translational prediction come from Zuzana Antošová (SOTIO Biotech), who will explore how species-specific differences in ADC stability and degradation influence human PK prediction, and Werner Rubas (Sutro Biopharma), who will outline AI-based methods to efficiently identify ADC candidates with unfavorable PK profiles.



DOSE OPTIMIZATION & EXPOSURE–RESPONSE ANALYSIS

Dose selection continues to be a central challenge for ADC developers. Salaheldin Hamed (Astellas Pharma) will open the main program with 'Dose optimization of antibody-drug conjugates & exploring the relevance of exposure–response relationships,' addressing the integration of PKPD and exposure–response data in refining dose-finding strategies, including a case example focused on enfortumab vedotin.

The agenda includes further discussions on dose optimization for emerging ADC modalities. Hongmei Xu (Bicycle Therapeutics) will describe considerations for dose evaluation in bispecifics, incorporating preclinical and clinical datasets alongside quantitative system pharmacology (QSP) modelling. Amit Khatri (Daiichi Sankyo) will present on applying cross-ADC exposure–response learnings to streamline development where candidates share common payloads.

Later in the program, Souvik Bhattacharya (Astellas) will examine enfortumab vedotin exposure in patients with urothelial carcinoma through population PK modelling, exposure–response analyses, and clinical evaluation of dose modification.

ADC STABILITY, TUMOR DISPOSITION, & BIOANALYSIS

The summit will also explore the analytical and mechanistic factors that influence ADC behavior in both preclinical and clinical settings, with Marcel Hop (Genentech) presenting on 'Tumor disposition of ADCs & implications for efficacy'. He will focus on ADC design principles guided by understanding mechanisms of cellular uptake and payload release, along with key drivers influencing ADC efficacy.

Bioanalytical complexity is further addressed in several sessions. Christopher Beaver (Daiichi Sankyo) will highlight the impact of *in vivo* biotransformation on the suitability of bioanalytical assay formats and strategies for managing these effects, while Yuting Wang (AbbVie) will explore analytical approaches for novel ADC modalities, including techniques for assessing structural integrity, DAR, and conjugation site characterization.

These sessions collectively reflect increasing attention to stability, biotransformation, and characterization challenges as ADC formats diversify.

MODELLING-ENABLED DECISION-MAKING

Modelling and simulation will feature prominently across both mechanistic and clinical applications. Prabhas Jagdale (GSK) will present on using advanced modelling to understand how ADC format, target binding, and payload dynamics inform dose decisions. Eshita Khera (Novartis Biomedical Research) will describe QSP-guided design considerations for selectively targeted payloads, including degraders.

Roundtable discussions will address how clinical pharmacology assessments, including organ impairment studies and drug-drug interaction evaluations, can be used strategically to support clinical trial planning and regulatory alignment.

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The 2nd Annual ADC Pharmacokinetics & Clinical Pharmacology Summit brings together a focused community of ADC developers committed to improving the predictability, efficiency, and safety of next-generation conjugates. With deep dives into PKPD translation, dose optimization, stability assessment, tumor disposition, and advanced modelling frameworks, the meeting offers a rich platform for data-driven discussion across early discovery and clinical development. Attendees can expect rigorous scientific exchange and practical insights that reflect the increasing complexity of ADC design and the growing need for integrated, mechanistically informed development strategies.

For more information, visit **the conference webpage**.