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ANTIBODY–DRUG CONJUGATES

A TECHNOLOGY UPDATE

Shreeyashi Ojha and Josh Abbott, with Cheryl Scott; William Sanders; and Brian Gazaille wth Robert Petit

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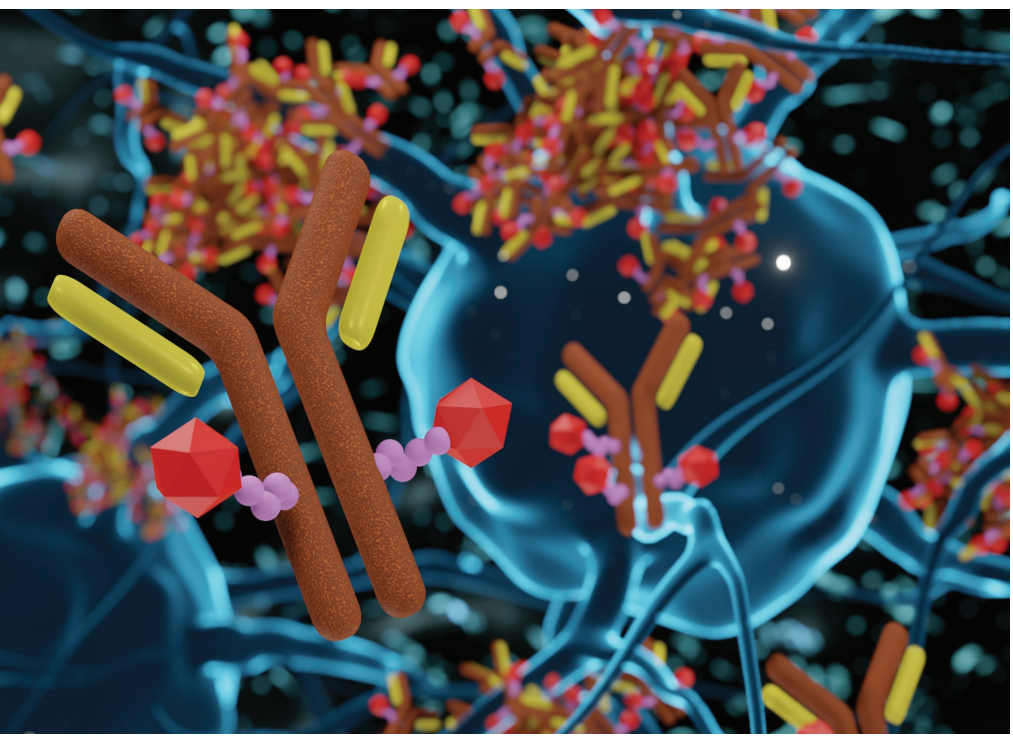
Antibody–Drug Conjugates

A Technology Update

by Shreeyashi Ojha and Josh Abbott with Cheryl Scott; William Sanders; and Brian Gazaille with Robert Petit



The first generation of antibody–drug candidates (ADCs) suffered from instability and systemic drug loss with resulting toxicity. Second-generation ADCs used more potent targeting agents and improved linker chemistries. The third generation introduced site-specific conjugation to produce homogenous ADCs with well-defined drug:antibody ratios (DARs). Now, companies are presenting fourth-generation concepts with new linkers, dual payloads, and bispecific antibodies to expand the modality even farther. This eBook provides a glimpse into the latest technological advances in ADC development.

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Introduction

Business News Reflects Technology Movement

Shreeyashi Ojha and Josh Abbott, with Cheryl Scott

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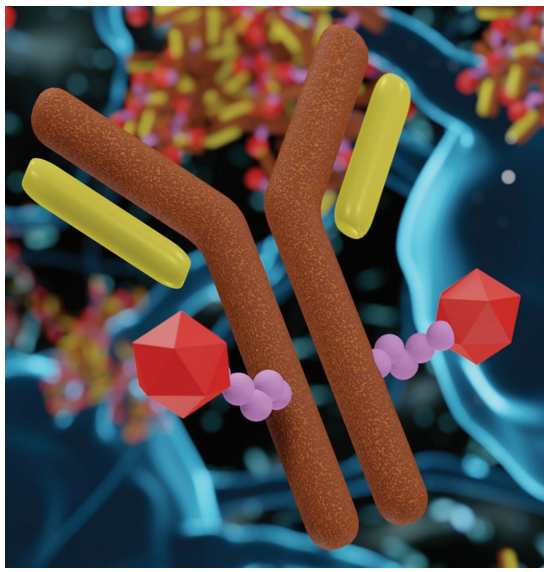

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Antibody–drug conjugates (ADCs) bring together biologic and small-molecule drug substances into powerful but highly complex drug products. Because they demand specialized knowledge from widely disparate segments of the pharmaceutical industry, ADCs most often require collaborative efforts to shepherd their development through connected manufacturing and regulatory pathways. Business partnerships and outsourcing are all but mandatory for success.

Over the past six months, reporting in the *BioProcess Insider* has tracked movements among partners and service providers that indicate strong interest in next-generation approaches to ADC research and development. Here are a few recent items illustrating the kinds of deals being made and technology/facility expansions in progress. All financial values mentioned are in US dollars.

Making Deals

Sotio Biotech Works Toward Bispecific ADCs: Through a partnership announced in July 2024, Sotio Biotech is accessing Biocytogen's RenLite platform for reducing the complexity of chemistry, manufacturing, and controls (CMC) in developing bispecific antibodies (**1**). The agreement gives Sotio options to license multiple human mono- and bispecific antibodies generated with that platform using its ADC platform. Biocytogen receives an upfront payment and milestone payments totaling up to $325.5 million; commercial rights of the program will lie with Sotio.

"Combining our ADC platform and Biocytogen's RenLite platform will enable us to broaden our portfolio, enabling us to develop ADCs with improved precision targeting and overcome tumor heterogeneity," a Sotio spokesperson told *BioProcess Insider*. "Biocytogen's platform allow us to discover fully human antibodies with high affinity, low immunogenicity, and favorable developability." RenLite technology also enables generation of bispecific antibodies. The spokesperson further explained, "Under the partnership, we will be responsible for non-clinical and clinical development, manufacturing, and commercialization of ADC products."

The RenLite platform involves human antibodies that share a common light chain. "Exploiting the potential of dual targeting in the context of ADC approaches [can] substantially enlarge the therapeutic window and potentially overcome tumor heterogeneity as well as address the challenge of emerging resistance," the spokesperson added. "Bispecific ADCs would be an exciting

expansion of our current portfolio of monospecific ADCs. Our most advanced solid-tumor ADC candidate, SOT102, is now in a phase 1 clinical study in the United States and Europe."

Sotio Biotech is a clinical-stage immunooncology company using multiple partnerships to advance its ADC reach. In 2016, it collaborated with NBE-Therapeutics for next-generation ADCs, gaining access to that company's Transpo-mAb antibody platform and SMAC conjugation technology. A partnership followed with LegoChem Biosciences in 2021, through which Sotio obtained rights to LegoChem's ADC technology for up to five therapeutic programs that target distinct tumor-associated antigens. In 2023, Sotio and Synaffix (part of the Lonza Group) entered a deal worth up to $740 million, giving Sotio access to GlycoConnect, HydraSpace, and toxSYN linker–payload ADC technologies.

Merck Expands ADC Partnership with Daiichi Sankyo: As announced in August 2024, Merck & Co. and Daiichi Sankyo will codevelop and cocommercialize three investigational ADCs, including Merck's MK-6070 (**2**). The companies will cocommercialize the products globally except for one in Japan, where Merck (known as MSD outside of the United States and Canada) will retain the exclusive rights. Merck also will be solely responsible for manufacture and supply of that product, MK-6070, which is an investigational delta-like ligand 3 (DLL3)–targeting T-cell engager.

In October 2023, Merck signed a partnership agreement with Daiichi Sankyo to codevelop the Japanese company's patritumab deruxtecan (HER3-DXd), ifinatamab deruxtecan (I-DXd), and raludotatug deruxtecan (R-DXd) — three ADC candidates that are in phase 3, phase 1–2, and phase 1 clinical trials, respectively. Under that agreement, Merck paid $4 billion up front, with an additional $1.5 billion in contingency payments planned over the following two years.

"We look forward to further evaluating MK-6070 as a monotherapy and in combination with ifinatamab deruxtecan, as well as other potential combinations," a Daiichi Sankyo spokesperson told *BioProcess Insider*. "Expanding our oncology pipeline with a DLL3 T-cell engager further supports Daiichi Sankyo's strategy to create new standards of care for patients with cancer worldwide."

MK-6070 is under evaluation as a monotherapy in a phase 1–2 clinical trial in patients who have advanced cancers associated with expression of DLL3. The study is also evaluating MK-6070 in combination with atezolizumab for patients with small-cell lung cancer (SCLC). The DLL3 target is relevant for 80–96% of SCLCs and also is highly expressed in neuroendocrine neoplasms. Merck gained MK-6070 through the acquisition of Harpoon Therapeutics in a deal worth $680 million in January 2024.

"Daiichi Sankyo looks forward to continuing our relationship with Merck with the addition of MK-6070," the spokesperson said. "It provides potential synergies with our established ADC

In October 2023, Merck signed a partnership agreement to **CODEVELOP** Daiichi Sankyo's patritumab deruxtecan (HER3-DXd), ifinatamab deruxtecan (I-DXd) and raludotatug deruxtecan (R-DXd) — three ADC candidates that are in phase 3, phase 1–2, and phase 1 clinical trials, respectively.

collaboration, particularly ifinatamab deruxtecan, and demonstrates our shared commitment to advancing new medicines for patients."

Samsung Bio Extends ADC Contract with LigaChem: Contract development and manufacturing organization (CDMO) Samsung Biologics has extended its partnership with South Korea–based biopharmaceutical development firm LigaChem Biosciences to provide ADC services (**3**). As announced in January 2025, the two companies are working on three ADC projects based on a February 2024 agreement.

A Samsung spokesperson told *BioProcess Insider* that the companies will collaborate on three ADC development projects. The CDMO's service spans late discovery through development and conjugation. The spokeperson said that these projects will commence at a new dedicated ADC facility located near Samsung's Songdo Bio campus. "It is a segregated suite comprised of four floors and equipped with a 500-L reactor and purification line." The company plans to continue investing in its ADC facilities to meet expanding client needs.

These two companies already have worked together in the past on LigaChem Bio's LCB14-19NM oncology candidate for treating solid tumors. "The latest collaboration will further strengthen Samsung Biologics capabilities across all stages of ADC development and manufacturing as part of our commitment to deliver safe and high-quality therapeutics to patients," said John Rim, president and chief executive officer (CEO) of Samsung Biologics. "We look forward to supporting our clients' innovative ADC pipelines, ensuring the highest quality and timelines are met."

LigaChem Bio president and CEO Yong-Zu Kim added, "This collaboration with Samsung Biologics will be an important step toward strengthening the supply chain of high-quality ADC drugs and enhancing the competitiveness of both companies in the global ADC market. By leveraging Samsung Biologics's extensive experience as a CDMO, we will accelerate the development of our pipeline and quickly provide innovative ADC treatments to patients."

Boehringer Ingelheim and Synaffix Collaborate: German pharmaceutical giant Boehringer Ingelheim has licensed ADC technology from Lonza's Synaffix subsidiary (**4**). Under the terms of the agreement, Boehringer's ADC group — NBE Therapeutics, acquired for $1.20 billion in 2020 — will use Synaffix's GlycoConnect, HydraSpace, and toxSYN technologies for an undisclosed number of targets. Along with an upfront payment, Synaffix will receive a milestone payment of $1.3 billion.

"We are building a broad pipeline of ADCs addressing the novel tumor target space to develop next-generation cancer treatments," said Lamine Mbow, global head of discovery research, Boehringer Ingelheim. "By combining our expertise in cancer treatment development with Synaffix's clinical-stage platform technology, we aim to accelerate the delivery of cancer treatments to improve cancer-patient outcomes."

Collaboration will be an important step toward strengthening the **SUPPLY CHAIN** of high-quality ADC drugs and enhancing the competitiveness of both companies in the global ADC market.

Synaffix's clinically validated ADC platform uses an enzymatic modification of native glycan anchor points on antibodies to develop ADCs or bispecifics. The company says its GlycoConnect design easily matches payload potency with drug:antibody ratio (DAR), HydraSpace technology differentiates between efficacy and tolerability, and toxSYN linker–payload systems provide multiple options in tumor biology.

Synaffix CEO Peter van de Sande characterized this agreement as "the culmination of a successful preclinical evaluation of the technology." His Dutch company was acquired by Lonza for $107 million in June 2023. In October 2024, PPF Group's clinical-stage immunooncology company Sotio Biotech partnered with Synaffix to develop up to three products targeting tumor-associated antigens. And Mitsubishi Tanabe Pharma Corporation, the pharmaceutical division of Mitsubishi Chemical Group, also has gained access to the platforms for a single ADC program.

Expanding Capabilities

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MilliporeSigma CDMO Expands ADC Offerings: The life-sciences division of Merck has invested $76 million and tripled the manufacturing capacity for ADCs at a facility in St. Louis, MO (**5**). The added 34,000 ft^2 will house departments for process and analytical development (PAD), quality control, research and development, manufacturing (including buffer preparation), and logistics — including cold storage and a controlled room-temperature (CRT) warehouse compliant with good manufacturing practices (GMPs). The CDMO expects this expansion to create 170 jobs for skilled workers. The PAD laboratories will enable early stage and commercial bioconjugate production for solid cancers.

"ADCs represent a transformative approach to oncology, enabling targeted therapies that minimize damage to healthy tissues," said Benjamin Hein, head of life-science services at MilliporeSigma. "As the market for this novel modality grows and the medical community adopts them as first-line treatments, it may mean that fewer patients need invasive treatments like chemotherapy and radiation that cause significant side effects."

The St. Louis facility is dedicated to downstream conjugation and has been approved by the US Food and Drug Administration (FDA) as a commercial conjugation supplier. Recently, the CDMO opened a $313 million facility in Rockville, MD, consolidating laboratories that were once spread across four buildings into an integrated hub.

Single-Use Reactor Launch: In September 2024, MilliporeSigma launched a single-use reactor for manufacturing ADCs (**6**). The system uses disposable components that are sterile and prevalidated, which the company says will reduce the risk of cross-contamination between batches and increase efficiency by 70%.

The Mobius ADC system is a scalable, single-use reactor specifically designed for ADC manufacturing. A spokesperson for MilliporeSigma told *BioProcess Insider* that the technology meets the requirements of linking the necessary components, enabling

biopharmaceutical companies to produce their critical therapies quickly and safely. The reactor's single-use assemblies are made of Ultimus film technology, which provides enhanced bag strength, improved durability, and leak resistance.

"Current ADC production methods use stainless-steel or glass reactors, which require labor-intensive and costly cleaning procedures," said Sebastian Arana, head of process solutions at MilliporeSigma. "Our new Mobius ADC reactor is the first scalable single-use mixer specifically designed for ADC manufacturing." He cited bag leaks as a "top pain point" for users. A single leak can cost $50,000–564,000 in biomanufacturing. "Our Ultimus single-use process-container film has 10 times greater abrasion resistance compared to other single-use bioprocessing films, minimizing product loss."

Proponents of single-use bioprocessing equipment tout many benefits for its use: high energy efficiency, low water use, floor-space efficiencies, reduced installation costs, decreased cross-contamination risk, shortened product-development time, and rapid implementation.

Arana said that ADCs present considerable challenges. "Their development is complex in both composition and supply chain. Each ADC construct is unique, [and such drugs] typically contain highly cytotoxic compounds." He said that the many process steps involved can give rise to product loss/contamination and high costs while extending execution time. "Our technology offers faster turnaround times and fewer cross-contamination risks, all while maintaining high product quality."

Sterling Doubles ADC Capacity at UK Facility: Sterling Pharma Solutions has invested over $12.8 million to expand its ADC manufacturing facility in Deeside, Wales (**7**). The CDMO has upgraded its GMP bioconjugation capacity, adding a 2,300-ft^2 suite that includes 500-L bioreactors for clinical-scale manufacturing and a 1,400-ft^2 grade C cleanroom. The latter will use both flexible and hard containment technologies for safe handling of highly potent molecules with exposure limits down to 0.01 µg/m^3, the company said. This facility should open in early 2026.

"The expansion will share some facilities with the existing suite," a spokesperson told *BioProcess Insider,* "but the cleanroom will be equipped with capabilities to enable scale-up manufacture and conjugation of ADCs. This will allow the suites to be used in tandem for complex processes or handle two individual projects simultaneously."

"The existing suite is 430 m^2 and includes a grade C cleanroom with supporting infrastructure such as a water for injection (WFI) plant and separate areas for buffer preparation." Manufacturing operations using disposable canopy isolators can use either disposable or glass reactors. With dedicated chromatography and tangential-flow filtration (TFF) equipment, the suite is designed to handle manufacturing of up to 1-kg batches.

ADCs present considerable **CHALLENGES**. "Their development is complex in both composition and supply chain. Each ADC construct is unique; they typically contain highly cytotoxic compounds." —Sebastian Arana, MilliporeSigma

Sterling says the expanded suite will use both hard containment and flexible isolators to accommodate an array of processes. Disposable equipment will reduce risk by eliminating potential cross-contamination between projects. Citing feedback from customers and market intelligence, the spokesperson said that clinical-scale ADC manufacturing currently has the lowest available global capacity but the highest demand.

The spokesman said, "The team at the facility has great expertise in bioconjugation, and this has historically been associated with oncology treatments and the conjugation of highly toxic payloads. However, the scope of ADCs is now changing, with other molecules such as peptides, immunocytokines, and proteolysis targeting chimeras (PROTACs) being conjugated to antibodies to allow the development of treatments for nononcology related diseases."

Based in Cramlington, UK, Sterling entered the ADC space with the acquisition of ADC Bio in 2021. That deal brought with it the 6,500-m^2 Deeside site. The CDMO invested $1.3 million in that site in 2022, increasing laboratory space from 275 to 419 m^2 and installing a new mass spectrometer, and reconfigured the layout to accommodate future services. The facility gained authorization for investigational medicinal products from the UK Medicines and Healthcare products Regulatory Agency (MHRA) in April 2023, enabling GMP manufacture of ADCs for clinical use.

Clinical-scale ADC manufacturing currently has the **LOWEST** available global capacity but the **HIGHEST** demand.

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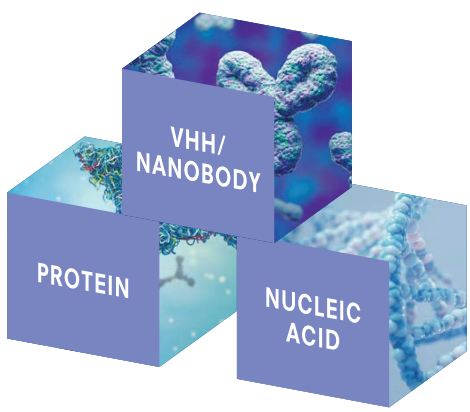

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Exploring Linker Chemistry

Understanding the Critical Role of Linkers in Advancing ADCs

William Sanders

Antibody–drug conjugates (ADCs) represent the cutting edge of precision medicine, combining targeted therapeutic delivery with potent cytotoxic agents to address some of the most challenging cancer types. Since the US Food and Drug Administration (FDA) approved the first ADC for acute myeloid leukemia in 2000, these innovative therapies have advanced rapidly. Today, 13 ADCs have received FDA approval, with >100 more currently in clinical trials (**1**).

Despite such progress, developing an effective ADC remains a highly complex endeavor that demands detailed understanding of the product's three primary components: an antibody, a payload, and a linker (Figure 1, next page). Among those features, the linker plays a central but often underappreciated role in determining the safety, efficacy, and manufacturability of a final ADC product. As the bridge connecting the antibody to the cytotoxic payload, the linker directly influences drug release mechanisms, stability, and solubility.

What's the Link?

Since early ADC development efforts in the late 20th century, linker chemistry has advanced dramatically. An appropriate linker between an antibody and cytotoxic drug forms a specific and stable bridge, enabling precise delivery of the payload to tumor cells and subsequently ensuring selective release. Linkers also maintain ADC stability during preparation, storage, and systemic circulation.

First- and second-generation ADCs used linkers that were unstable in the bloodstream, resulting in limited efficacy, severe side effects, and termination of several clinical trials. To address those challenges, third-generation ADCs incorporate more-stable linkers and leverage advanced conjugation technologies, designed with a well-defined drug:antibody ratio (DAR) (**2**). Such improvements have enhanced ADC safety and therapeutic performance significantly.

Considering growing interest in ADCs, understanding how to design and select optimal chemical linkers is essential to developing safe and effective therapies. For ADCs to achieve both selectivity and potency, linkers must exhibit three critical properties:

- high stability in circulation to prevent premature release of cytotoxic payloads
- high water solubility to facilitate bioconjugation and prevent formation of inactive ADC aggregates

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A scientist at contract development and manufacturing organization (CDMO) Veranova handles materials for antibody–drug conjugation under a fumehood.

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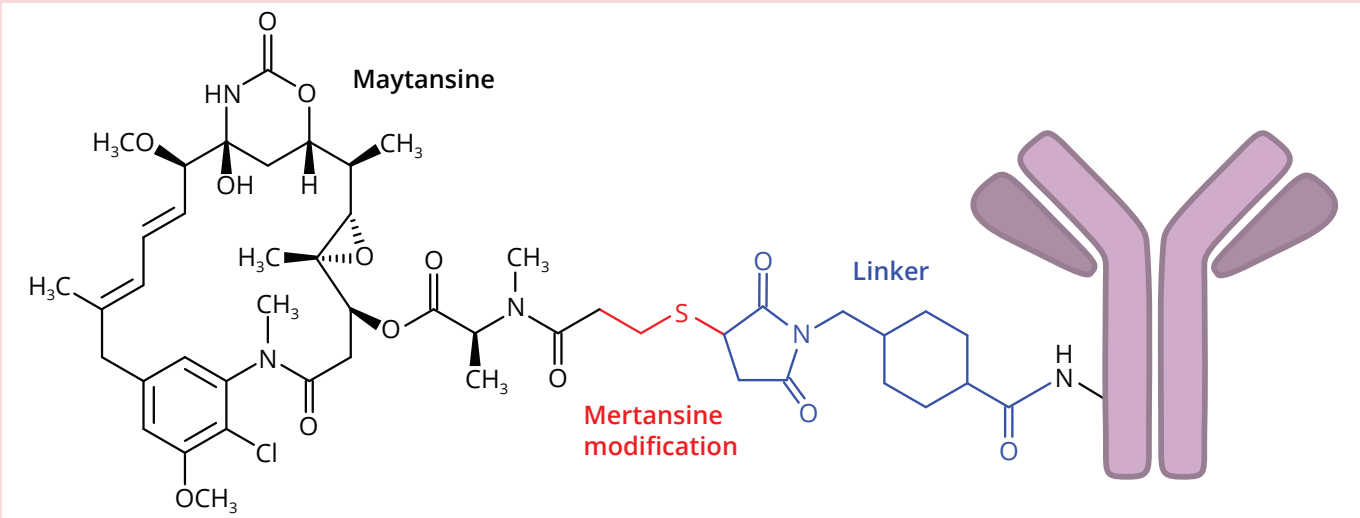
Figure 1: Chemical structure of an emtansine (mertansine + linker molecule) conjugated to a monoclonal antibody (mAb); emtansine is a chemotherapy agent featured in products such as Kadcyla (trastuzumab emtansine). (ADAPTED FROM **3**)



• efficient payload release to ensure effective cytotoxic-drug delivery at a tumor site.

Examining those three factors provides an understanding of the role of linkers in ADC development and further insights into optimizing linker selection, ensuring stability, and contributing to the overall success of these groundbreaking therapies.

High Stability in Circulation

A linker's stability is its resistance to premature cleavage during systemic circulation. An unstable linker risks releasing cytotoxic molecules before reaching a target site, diminishing therapeutic efficacy and generating systemic toxicity.

Robust analytical methods are essential for evaluating linker integrity and resilience under diverse in vivo and in vitro conditions. Advanced analytical techniques such as high-performance liquid chromatography (HPLC), mass spectrometry (MS), and nuclear magnetic resonance (NMR) spectroscopy can provide detailed characterization to that end.

Moreover, DAR profiling provides critical insights into ADC stability. An ADC typically contains multiple drug molecules attached to a single antibody, and the DAR serves as a key metric for assessing ADC potency and efficacy. Advanced analytical tools, including liquid chromatography–mass spectrometry (LC-MS) and capillary electrophoresis (CE), are indispensable for accurately determining the DAR.

High Water Solubility

ADCs often pose significant solubility challenges due to the hydrophobic nature of their payloads. Cytotoxic drugs can aggregate because of "sticky" interactions with similar moieties. Coupling such molecules with hydrophobic linkers exacerbates that issue.

The resulting aggregation can have several serious implications for ADC stability, therapeutic performance, and manufacturability.

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For example, aggregated ADCs are more likely than unaggregated ones to be sequestered by the liver and rapidly cleared by the reticuloendothelial system, increasing risks of hepatotoxicity. Moreover, protein aggregates are immunogenic, triggering unwanted immune responses during systemic circulation and reducing therapeutic efficacy (**4**).

Reducing DARs can mitigate such difficulties. However, although lower DAR values decrease aggregation propensity, they also can reduce therapeutic efficacy and the size of an ADC's therapeutic window, triggering unintended side effects. Alternatively, developers can leverage hydrophilic linkers, such as those containing sulfonates or poly(ethylene glycol) (PEG). Such linkers can provide a "shielding effect" that counters payload hydrophobicity. Thus, they enable higher DARs without increasing aggregation levels; however, the increased structural complexity significantly increases challenges in their preparation.

No one solution will fit all ADCs. Thus, developers should work with experts who have years of experience with multiple ADC linker–payload systems. Such help can facilitate preclinical evaluation through synthesis of custom payload–linker constructs.

Efficient Payload Release

For ADCs to achieve their full potential, they must be tailored for accurate release of cytotoxic payloads at tumor sites. The choice of linker, which governs the release mechanism, is critical for ensuring both the safety and efficacy of ADCs. Linkers are categorized broadly into cleavable and noncleavable types, each offering distinct advantages depending on the therapeutic context.

Cleavable linkers leverage specific physiological differences between the tumor microenvironment and healthy tissues to enable selective payload release. Such mechanisms include

- acidic environments, with linkers exhibiting sensitivity to low pH — e.g., maleimide linkers such as those used in Trodelvy (sacituzumab govitecan, Gilead Sciences), which includes a short PEGylated unit
- enzymatic activity — e.g., enzyme-cleavable linkers designed to respond to proteases such as cathepsins
- reducing conditions — e.g., linkers using disulfide bonds that cleave in the presence of reducing agents.

Cleavable linkers exploit such mechanisms to allow for the bystander effect, enabling payload diffusion to neighboring cells. That strategy is particularly advantageous for solid tumors and for heterogeneous tumors with diverse antigen expression.

Noncleavable linkers remain intact until an ADC is internalized and degraded within a target cell's lysosome. Thus, payload release occurs only at intended sites. Noncleavable linkers are highly stable during systemic circulation, reducing risk of off-target toxicities. However, this mechanism negates the bystander effect, making noncleavable linkers most effective against tumors in which most cells express a target antigen and against circulating tumor cells.

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For ADCs to achieve their full potential, they must be tailored for **ACCURATE RELEASE** of cytotoxic payloads at tumor sites.

The decision of whether to use cleavable or noncleavable linkers depends on several factors (**5**). For instance, developers should consider characteristics of the tumor microenvironment. Cleavable linkers are well suited for tumors with distinct microenvironmental traits (e.g., acidity or enzymatic activity). Payload properties are equally important to evaluate. Cytotoxic or highly hydrophobic payloads might benefit from the stability of noncleavable linkers. Finally, developers must identify their therapeutic goals. Improved efficacy resulting from the bystander effect might favor application of cleavable linkers, whereas a focus on stability might lean toward noncleavable linkers.

A comparison between Enhertu (trastuzumab deruxtecan, AstraZeneca) and Kadcyla (ado-trastuzumab emtansine, Genentech/Roche) demonstrates the impact of linker choice. The former product, which uses a cleavable linker, has shown higher efficacy in tumors with heterogeneous human epidermal growth factor receptor 2 (HER2) antigen expression. But that choice of linker requires balancing the increased risk of off-target toxicities with the drug's therapeutic potential. On the other hand, noncleavable linkers such as that used in the Kadcyla ADC are effective in treating hematological cancers or tumors with high antigen expression, in which the majority of tumor cells must be eradicated to achieve remission.

Overcoming ADC Complexity with Confidence

Over recent years, advancements in ADC development have been driven by significant scientific innovations, particularly in linker chemistry. As these therapeutics become increasingly complex and targeted, linker selection and optimization will continue to play a pivotal role in their success. By addressing linker-related challenges, such as heterogeneity and stability, during early development, innovators can mitigate risks, streamline timelines, and ensure that ADCs meet regulatory and therapeutic expectations.

Given the complexity of linker characterization, partnering with contract development and manufacturing organizations (CDMOs) that offer advanced analytical expertise and state-of-the-art technologies is essential. Such partnerships enable precise design and optimization of linkers, ensuring a balance between stability during circulation and efficient payload release at tumor sites. Working with an experienced contract partner could accelerate development timelines and mitigate the risk of costly setbacks during the late stages of ADC development.

My company, Veranova, offers >18 years of experience in developing and manufacturing ADC constructs. We apply a deep understanding of unique challenges in linker–payload development and manufacturing to support our partners in creating innovative, high-quality therapeutics that drive positive patient outcomes.

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Tuning ADC Targeting with Silicon Chemistries

Brian Gazaille with Robert Petit

Antibody–drug conjugates (ADCs) are among the latest biopharmaceuticals to reach cancer patients. As of January 2025, 13 such products have received US Food and Drug Administration (FDA) approval, primarily for blood, breast, and urinary indications (**1**). Another >100 candidates are wending their way through clinical evaluation (**1**). Despite the relative novelty of the modality, drug developers already are composing variations on the ADC theme, seeking to improve upon safety, efficacy, and manufacturing limitations that beset initially commercialized products.

Robert Petit (chief medical and scientific officer of OS Therapies, OST) explained to me late in 2024 that many candidate ADCs and even some currently available products "have had difficulties with targeting, including on-target off-tumor binding, unexpected or undesired cleavage by serum proteases, thiol reduction, and hydrolysis of carbohydrates." By some estimates, only about 0.1% of an injected ADC dose reaches a targeted cell population; much of the remaining material undergoes off-site catabolism in nontargeted cells (**2–6**). Thus, although ADCs are generally well tolerated, some patients have experienced unexpected toxicity events. Petit highlighted adverse vision changes observed with products such as Blenrep (belantamab mafodotin, GSK) and Elahere (mirvetuximab soravtansine, ImmunoGen/AbbVie) and cases of interstitial lung disease associated with ADCs targeting human epidermal growth factor 2 (HER2), including Kadcyla (trastuzumab emtansine, Genentech/Roche), Enhertu (trastuzumab deruxtecan, AstraZeneca and Daiichi Sankyo), and Jivadco (trastuzumab doucamazine, Byondis) (**3**). He said, "Solving some of those issues" with targeting "will help to improve the therapeutic index of future ADCs."

Drug developers now are poised to improve ADC safety and efficacy. "I believe that the current landscape is in a 'second wave,'" Petit continued. "We have gained understanding from the first generation of ADCs, and now we are working on improvements that can make such drugs even more effective." Recent efforts in that area have focused on conjugation and linker chemistries, with developers "exploring methods beyond lysine- or cysteine-residue–directed conjugation and linker technologies that go beyond conventional cleavable options."

OST is one such drug developer seeking to fine-tune the capabilities of ADCs. During our conversation, Petit described his company's interventions in the field, including development of the

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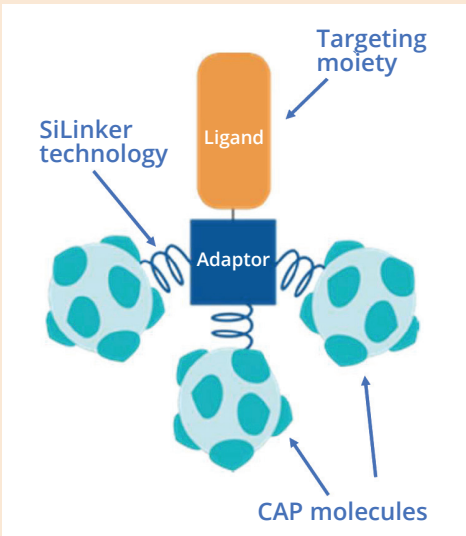
Figure 1: Design of OS Therapies' tunable antibody–drug conjugate (tADC) technology, which features SiLinker cleavable payload linkers and Conditionally Active Payload (CAP) molecules



proprietary tunable ADC (tADC) technology platform, which features diverse candidates based on OST's silicon-based linkers and payload coatings (Figure 1, previous page) (**7, 8**). He explained how those advances could improve ADC efficacy, reduce toxicity potential, and ultimately expand the types of payloads that can be applied in conjugated modalities.

A seasoned biopharmaceutical executive, entrepreneur, and medical scientist, Petit has been integral to new-drug application/biologics license application (NDA/BLA) filings for six immuno-oncology products, and he has devised and executed development plans for dozens of therapeutics. His industry experience includes executive roles at Advaxis Inc., Aesgen, and RGP Biotech, as well as tenures at Adria-Pharmacia, Pharmacia Upjohn, and Bristol Myers Squibb, where he was US medical lead for the Yervoy (ipilimumab) immune-checkpoint inhibitor. He holds a PhD in immunology and viral oncology with medical training from the Ohio State University College of Medicine.

Shifting into ADC Development

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A relatively new entrant to the ADC space, OST has its roots in cancer-vaccine development. The company's primary goal, as stated on its website, has been "to bring to market the first new treatment for osteosarcoma (OS) in over 30 years" (**9**). OS is a rare bone cancer that usually affects children and adolescents. Because the disease is particularly aggressive and has high rates of recurrence after treatment, significant medical needs remain. OST's initial research has resulted in an anti-HER2 vaccine, which delivers HER2-bearing *Listeria monocytogenes* vectors to patient antigen-presenting cells (APCs). Those, in turn, stimulate cytotoxic T cells to target HER2-expressing bone tumors. Currently, the company is concluding a phase 2b clinical trial of its OST-HER2 candidate. Depending on data from that study, the company plans to seek accelerated approval for the immunotherapy sometime in 2025 (**9**).

When asked about how OST moved from cancer vaccines into ADCs, Petit said, "We find those two classes of agents to be complementary." ADCs can "debulk tumor masses and provide extended activity by freeing up tumor antigens that the immune system can pick up and target." Cancer vaccines, on the other hand, are "well suited to identifying and controlling micrometastases and to cleaning up potentially resistant cells after tumor-debulking treatments." Because of their complementary mechanisms, Petit continued, such classes of therapeutics "might be used best in sequence." It was natural, then, for his company to explore both approaches to treating OS — and perhaps other solid-tumor indications. Thus, in addition to its OST-HER2 program, the company has initiated preclinical work for three tADC candidates, for ovarian cancer, breast cancer, and other solid-tumor indications, respectively.

Silicon Chemistry

OST has turned to silicon chemistries to avert toxicity concerns observed with previous ADCs. "As a biologically inert material," Petit explained, "silicon is not susceptible to interference from protonolysis, protease attack, thiol reduction, or hydrolysis of carbohydrates." Thus, silicon-based materials should be "more stable than alternatives" often used in ADC linkers. To that end, OST developed its proprietary SiLinker technology. Petit added that the company's approach to ADC design "doubles down on safety" because it incorporates both silicon-chemistry linkers and Conditionally Active Payload (CAP) drugs capped with silicon.

As the tADC moniker suggests, the primary advantage of using silicon caps and linkers is the ability to "tune" drug delivery. SiLinker technology is designed to deconjugate in low pH levels that occur only in phagolysosomes and tumor microenvironments. Meanwhile, Petit said, the silicone capping "is biologically inert and only melts away when an ADC is within a targeted cell or necrotic tumor." Together, such components could minimize unintended deconjugation, on-target off-tumor effects, and off-target toxicity.

SiLinker technology also could provide flexibility for future ADC programs. Petit highlighted that the silicon linkers can accommodate drug:antibody ratios (DARs) of six to 24. Moreover, "their targeting moieties are small, facilitating entry into cells; and they can deliver a diversity of payloads from small-molecule cytotoxics to nucleic acids."

OST has designed several prototypes to demonstrate that principle. "In one iteration," Petit reported, "we developed a therapy with a high DAR to target folate receptor alpha (Frα), which is overexpressed in ovarian cancer and related malignancies." Frα represents an established ADC target, serving as the mechanism of action for several candidates and marketed drugs, including the Elahere product. Other OST prototypes are exploring immunomodulating agents and mRNA as payloads. In keeping with the industry trend to expand upon conventional drug designs, the tADC platform also could provide for different targeting molecules. For instance, OST plans to study antigen-binding fragments (Fabs) and single-chain antibodies in addition to standard monoclonal antibodies (mAbs). Although OST's tADC programs are still in preclinical development, the company is encouraged by preliminary results. "We have found that we can create targeted, high-DAR ADCs that show excellent antitumor activity in animal models," Petit reported.

Toward Targeted Cancer Treatment

Building on drug-design strategies embodied by currently available ADC products, developers such as OST are fine-tuning their constructs for optimal delivery of cytotoxic agents. Petit observed that developers' efforts are bolstered by continuing investment in ADC technologies. As an example, he cited AbbVie's US$10 billion

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> As a **BIOLOGICALLY INERT** material, silicon is not susceptible to interference from protonolysis, protease attack, thiol reduction, or hydrolysis of carbohydrates.
>
> —R. Petit

acquisition of ImmunoGen in February 2024, a move hastened by the clinical success of the latter company's Elahere program (**10**).

With the support of ample funding, industry interest, and rapid innovation, ADC developers very well could revolutionize cancer treatment in the coming years. "The hope," Petit said, "is that chemotherapy someday will be replaced completely by ADCs that are more effective and better tolerated by patients. OST hopes to be part of that future."

The hope is that chemotherapy someday will be **REPLACED COMPLETELY** by ADCs that are more effective and better tolerated by patients. OST hopes to be part of that future.

—R. Petit

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