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BIOCONJUGATION INSIGHTS

SPOTLIGHT

New frontiers

BIOCONJUGATION INSIGHTS

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Exploring advances in bioconjugation: nanozymes, tissue tropism, and the future of responsive systems

INTERVIEW

"ADCs represent a success story for bioconjugation, however, they are also a cautionary tale."

Lauren Coyle (Commissioning Editor, *Bioconjugation Insights*) speaks to **Vincent Rotello** (Distinguished Professor of Chemistry, University of Massachusetts Amherst) about the advantages and limitations of different nanomaterial platforms, and emerging strategies such as tissue tropism and responsive nanozymes that could advance targeted therapeutic and diagnostic delivery.

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Q What initially drew you into bioconjugation research, and how has your focus evolved over the years from your early work to your current research?

VR I began my career in natural product synthesis in 1985, working in this area for five years before shifting to supramolecular chemistry during my

postdoctoral research. I focused on molecular interactions, such as how adenine binds to thymine. As the work became more predictable, I became interested in exploring the effects of repeating specific interactions multiple times, which led me to study multivalency, and ultimately polymers and nanoparticles.

Together with the team, we spent considerable time trying to understand how these nanoparticles and polymers interact with natural compounds. We began our work with proteins and discovered we could create a variety of nanoparticles for denaturing proteins. The particles would be ideal to denature proteins, but it would not be efficient to actually use them.

Later, we focused on designing nanoparticles that could bind proteins, which led us to move into protein and nucleic acid delivery. Our initial *in vitro* studies showed that nanoparticles had promising results for cellular delivery, however, following testing in living organisms, they did not perform as well as *in vitro*. This challenge sparked our interest in using bioconjugation strategies to direct systems *in vivo*. Although *in vivo* work presents some surprising challenges, it remains engaging due to its unpredictability and potential for discovery.

Q While ADCs have captured much of the spotlight, the field extends far beyond these. What other areas of bioconjugation do you see as particularly promising or underappreciated?

VR ADCs represent a success story for bioconjugation, however, they are also a cautionary tale. While effective with low drug payloads, their performance declines as the payload increases, highlighting the sensitivity of the recognition process, also known as the lock-and-key targeting process. Therefore, it is essential to develop systems that can maintain some form of selectivity, or ideally specificity, even at a higher payload-to-carrier ratio. For example, modular self-assembled systems are particularly promising in this regard.

Currently, the design space for bioconjugation remains unclear. While specific approaches, such as ADCs with small payloads, are effective, others, such as nano-delivery systems, are less so—the optimal strategies likely lie between these extremes. Self-assembled systems offer the advantage of modularity, but ultimately, it is crucial that these systems are also degradable and can be efficiently excreted.

Q What unique advantages do nanomaterials offer as platforms for bioconjugation compared to more traditional approaches? What are some key challenges in achieving stable, functional conjugation at nanoscale?

VR There are multiple families of nanoparticles. For example, most people in the field are familiar with lipid nanoparticles (LNPs). These are the 'heart and soul' of the Moderna's and Pfizer's COVID-19 vaccines, meaning most people have been exposed to them physically, if not intellectually. LNPs are highly modular due to the wide range of possible lipid formulations and their ready ability to degrade, which the body can use to

"Currently, the design space for bioconjugation remains unclear. While specific approaches, such as ADCs with small payloads, are effective, others, such as nano-delivery systems, are less so..."

process and excrete their components after delivery. However, a key challenge with LNPs is structural control, as their relatively fluid nature makes it difficult to control the presentation of bioconjugation elements in places such as fluid membranes or to keep them from clustering or distributing on the LNP surface.

In contrast, inorganic particles offer excellent structural control, allowing precise presentation of structural elements. However, the key challenge is that they generally have low payload-to-carrier ratios. Their inorganic nature also raises concerns among patients regarding safety. For instance, gold nanoparticles are generally non-toxic in nature, however, the even the phrasing 'non-toxic' raises some concern among patients.

Lastly, polymer nanoparticles offer self-assembly and, due to their larger size, provide broader capability for structural control and access a broader design space. Polymers can go from flexible to rigid and everywhere in between. Of course this means their behaviour is at present harder to predict.

Regarding the challenges of nanomaterials in nanomedicine, I refer to Dr Warren Chan at the University of Toronto, who has published several papers on nanomaterials. For example, his overview of nanomaterial targeting published in *Nature Materials* (2016) found that only a few nanoparticles end up in the tumor due to protein corona formation [1]. In essence, when making a nanoparticle, they are likely to attract serum proteins onto it once introduced into the bloodstream, leading to two major issues. Firstly, the binding of these proteins effectively masks the intended functionality that was engineered into the nanoparticle. Secondly, the adsorption of serum proteins redirects the nanomaterial towards the reticuloendothelial system where macrophages and monocytes take them up. This major clearance pathway leads nanomaterial to end up in the liver and spleen. Therefore, the biggest challenge is figuring out how to present targeting elements without having them masked by the protein corona and then targeted for degradation.

Q Could you provide some examples of how engineered nanomaterial conjugates are being developed for therapeutic or diagnostic applications?

VR I am particularly excited about nanozymes. These are catalysts that convert inactive materials into active ones, which can be used in diagnostics. For example, when running an ELISA assay, horseradish peroxidase is typically used as the amplifying element. Nanozymes can do the same thing but with greater stability and catalytic activity. The same catalytic process can also be used in imaging. For example, nanozymes can light up a non-fluorescent profluorophore and convert it into a fluorescent dye in tissues and organs.

Perhaps most excitingly, nanozymes have the potential to work as *in situ* drug factories for therapeutics. If you can deliver a small amount of nanozymes to the right site, they can convert inactive prodrugs into active drugs directly at the disease location, leading

to a high local concentration without the high systemic concentrations that cause off-target effects.

Q What emerging nanomaterial platforms or conjugation strategies are you most excited about, and have any recent breakthroughs in surface chemistry opened new possibilities for nanomaterial-based conjugates?

VR One area I find particularly promising is tissue tropism. When thinking about targeting, we usually consider lock-and-key interactions, which the body utilizes. However, the body also utilizes physical properties to partition different substances into various locations. The question is: Can we use surface chemistry to provide that kind of tissue tropism?

A classic example is the blood-brain barrier (BBB). There are few specific lock-and-key targeting mechanisms for it—instead, it is more about the physical process of moving through the tight junctions. Therefore, research is needed to develop improved systems for crossing the BBB and engineer systems capable of targeting the lungs or other organs without relying on traditional molecular recognition.

Tissue tropism-based systems have the potential to revolutionize applications beyond oncology, including inflammation and neurological diseases, thereby broadening the impact of nanomaterial research.

Q Looking ahead, what technological advances or breakthroughs do you think will drive the field forward over the next 5–10 years, and how might this impact research and/or clinical applications?

VR Over the next decade, I believe advances will focus on responsive systems. Recently, these systems have received bad press, with some calling them 'sci-fi' and equating them with turning us into 'grey goo'. It is still an open question, as I am not entirely sure how intelligent we will be able to make them over the next decade. However, I believe we will start seeing systems activated by specific stimuli, which can address the imbalance and disease state at that particular location. For example, developing nanoenzymes with feedback control could enable systems that respond to neurotransmitters, activating prodrugs and releasing analgesics on demand for pain relief.

The concept of on-demand release, as well as release at a desired location, is set to be a significant advancement. It will require bioconjugation, as we must direct molecules to the correct location before they can act intelligently—it will not be useful if they are 'intelligent' in the wrong place.

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BIOGRAPHY

Vincent Rotello is the Charles A Goessmann Professor of Chemistry and a University Distinguished Professor at University of Massachusetts Amherst. He earned his BS from Illinois Institute of Technology (1985) and PhD from Yale (1990), followed by an NSF post-doctoral fellowship at MIT. Since joining UMass in 1993, he has received numerous awards, including the Arthur C Cope Scholar Award (2023) and the Transformational Research and Excellence in Education Award (2016). A Fellow of AAAS and the Royal Society of Chemistry, he is a Highly Cited Researcher (2014–2024). His research bridges synthetic organic chemistry and biology, focusing on nanotechnology, bioconjugation, nanomedicine, and diagnostics, with over 690 peer-reviewed papers published.

Vincent Rotello is Senior Editor of *Bioconjugation Insights*

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You can also listen to the recorded podcast here:

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BIOCONJUGATION INSIGHTS

NEW FRONTIERS: HOW ARE OLIGONUCLEOTIDE, PEPTIDE, AND OTHER EMERGING CONJUGATES EXTENDING THE REACH OF THE FIELD?

SPOTLIGHT

INDUSTRY INSIGHTS

Industry insights, September 2025

David Simpson

Bioconjugation Insights is delighted to bring you all the latest news in the bioconjugation space in this new Industry Insights article. Brought to you by one of our esteemed **Editorial Advisory Board** members, David Simpson, it highlights the latest developments in collaborations, regulatory changes, marketing trends, and R&D in the field. Additionally, it provides insights into key clinical trials, innovations in tools and technology, and notable conferences and publications.

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COLLABORATIONS AND PARTNERSHIPS

Sutro Biopharma collaborates with the FDA to advance ADC regulatory standards [1]

Sutro Biopharma announced a research collaboration with the US FDA to develop reference materials that enhance regulatory standards and analytical methods for ADCs. The partnership combines Sutro's cell-free XpressCF® technology, enabling precise ADC engineering, with the FDA's advanced analytical capabilities. Together, they will design studies using representative antigens, payload-linkers, and conjugation sites from approved and investigational ADCs. Findings will be published and are expected to strengthen the FDA's ability to assess ADC quality.

Adagene partners with ConjugateBio to advance novel ADC [2]

Adagene Inc. has entered a collaboration with ConjugateBio Inc. to supply a proprietary antibody for use in ConjugateBio's bispecific ADC programs. The partnership combines Adagene's antibody discovery expertise with ConjugateBio's ADC development platform, aiming to deliver safer, more effective therapies. Adagene will receive upfront, milestone, and royalty payments, while retaining non-ADC rights to the partnered antibody.

Biocytogen and Merck KGaA unite on antibody-conjugated LNP delivery [3]

Biocytogen Pharmaceuticals has entered into an evaluation and option agreement with Merck KGaA, Darmstadt, Germany, to advance antibody-conjugated lipid-based delivery solutions for nucleic acid payloads, including antibody-lipid nanoparticles (LNPs). Biocytogen will provide fully human antibodies from its RenMice® platform for evaluation. Merck KGaA holds an exclusive option to license selected assets in exchange for fees and royalties. The collaboration leverages Biocytogen's antibody discovery capabilities and Merck KGaA's expertise in LNPs to drive innovation in next-generation nucleic acid delivery.

PATENT APPROVALS

Diverse Biotech granted patent for antibody-cannabinoid conjugates [4]

Diverse Biotech, a leader in cannabinoid-based drug innovation, announced the issuance of a fully granted US Patent, covering novel antibody-cannabinoid conjugate molecules. The company's technology integrates antibodies with cannabinoids via a specialized linker, enabling targeted delivery to disease sites while locally releasing cannabinoids such as CBD or CGB. This dual mechanism combines precise antibody targeting with cannabinoid-driven effects, including controlled reactive oxygen species generation to induce cell death in cancer and modulate inflammatory environments.

REGULATORY CHANGES AND UPDATES

Singapore adds PCV20 conjugate vaccine to the National Adult Immunisation Schedule [5]

From September 1, 2025, Singapore's Ministry of Health will include PCV20, a 20-valent pneumococcal conjugate vaccine, in the National Adult Immunisation Schedule (NAIS). PVC20 expands protection to seven more pneumococcal strains than PCV13 and is recommended for adults 65+ and immunocompromised adults 18–59.

MARKET TRENDS

WuXi XDC reports strong 1H 2025 results—expands global bioconjugate leadership [6]

WuXi XDC Cayman, a leading global CRDMO for bioconjugates, reports 62.2% year-on-year revenue growth to RMB 2.7 billion in 1H 2025, with gross profit up 82.2% to RMB 975 million and adjusted net profit before interest up to 69.9% to RMB 733 million. The company expanded its global customer base to 563, signed 37 new iCMC projects, and grew its backlog to $1.3 billion. Key milestones included the GMP release of the DP3 facility in Wuxi and mechanical completion of its Singapore site, on track for GMP release in 1H 2026. WuXi XDC continues advancing frontier technologies to strengthen global leadership in ADCs and bioconjugates.

Pfizer lays off 100 employees at former Seagen HQ [7]

Pfizer is cutting 100 jobs at its former Seagen global headquarters in Bothell, Washington. The site supports R&D and biologics manufacturing, including bladder cancer ADC Padcev. The layoffs follow earlier closures of a 61,000sq. ft. office, and halted construction of a 270,000sq. ft. Everett plant. The job cuts are part of Pfizer's broader $7.7 billion cost-saving plan through 2027, aimed at reducing debt after the $43 billion Seagen acquisition and offsetting declining COVID-19 product sales.

RESEARCH AND DEVELOPMENT HIGHLIGHTS

OBI Pharma initiates Phase I/II trial of TROP2-targeted ADC in advanced solid tumors [8]

OBI Pharma has announced the start of a Phase I/II clinical trial of OBI-902, a novel TROP2-targeting ADC developed with its proprietary GlcoOBI® technology. The study, led by Dr Apostolia M. Tsimberidou at MD Anderson Cancer Center, will evaluate safety, pharmacokinetics, and preliminary efficacy in patients with advanced solid tumors. Preclinical data presented at AACR 2025 showed OBI-902 achieved superior stability, favorable pharmacokinetics, and durable antitumor activity compared with other TROP2 ADCs.

Avenzo Therapeutics receives FDA IND clearance for bispecific ADC, AVZO-103 [9]

Avenzo Therapeutics announced FDA clearance of its IND for AVZO-103, a potential best-in-class Nectin4/TROP2 bispecific ADC. The company also exercised its exclusive option

with VelaVigo, securing global development, manufacturing, and commercialization rights. A Phase I/II trial is planned for later this year to evaluate safety, tolerability, and preliminary activity in advanced solid tumors as monotherapy and in combination.

Duality Bio ADC trial success strengthens BioNTech's oncology pipeline [10]

BioNTech and Duality Biologics reported that their HER2-target ADC, transtuzumab pamirtecan (BNT323/DB-1303), met the endpoint of progression-free survival in a Phase III trial for HER2-positive unresectable or metastatic breast cancer, outperforming Roche's Kadcycla. The 288-patient study drove BioNTech shares up 11%. DualityBio plans regulatory discussions in China, with global expansion also underway. The ADC, licensed by BioNTech in 2023, is additionally being evaluated in the global DYNASTY-Breast02 trial for HER2-low breast cancer.

CLINICAL TRIALS AND RESEARCH

CytomX continues Phase I study despite patient death [11]

CytomX Therapeutics reported a patient death in its Phase I colorectal cancer trial of CX-2051, an EpCAM-targeted, conditionally activated ADC. The fatality, linked to treatment-related acute kidney injury in a patient with a solitary kidney, was reviewed by an independent safety committee, which recommended the study continue. The event was reported to the FDA on July 18, 2025. The trial, with 73 patients enrolled, remains on track for a data readout in Q1 2026. CX-2051 delivers a topoisomerase-1 inhibitor payload.

Abzena's customer MBrace reports positive preclinical data on EphA5-targeted ADC using ThioBridge technology [12]

MBrace has published preclinical data on MBRC-101, an EphA5-targeted ADC designed with Abzena's ThioBridge® conjugation technology. MBRC-101 couples a humanized anti-EphA5 antibody with MMAE, achieving a stable drug-to-antibody ratio (DAR) that enhances efficacy while minimizing off-target effects. Data showed complete tumor regression in multiple xenograft models and favorable tolerability in toxicology studies. EphA5, expressed in several solid tumors, represents a novel therapeutic target. MBCR-101 is now in a Phase I/Ib first-in-hum trial for patients with advanced solid tumors.

ALX Oncology doses first patient in Phase I trial of EGRF-targeted ADC [13]

AXL Oncology announced dosing of the first patient in its Phase I trial evaluating ALX2004, a novel EGFR-targeted ADC for advanced EGFR-expressing solid tumors, including NSCLC, HNSCC, and CRC. ALX2004 combines an affinity-tuned EGFR antibody with a proprietary topoisomerase I inhibitor payload and optimized linker, designed to maximize therapeutic window and reduce toxicity. Preclinical studies demonstrate dose-dependent tumor

activity, favorable safety, and no EGRF-related skin toxicity or payload-related lung toxicity. The study will evaluate dose escalation, dose exploration, and expansion. Initial safety data are expected in the first half of 2026.

Huadong Medicine reports positive early data from Phase I study of ROR1 ADC HDM2005 [14]

Huadong Medicine announced encouraging preliminary results from its Phase I trial of HDM 2005, a receptor tyrosine kinase-like orphan receptor 1 (ROR1)-targeting ADC, in relapsed/refractory B-cell non-Hodgkin lymphoma (B-NHL) and classical Hodgkin lymphoma (cHL). Among 29 patients enrolled, HDM2005 showed a favorable safety profile with no discontinuations due to treatment-related adverse events. In the 1.8 and 2.5mg/kg cohorts, mantle cell lymphoma patients achieved a 50% objective response rate, while two cHL patients achieved complete responses. HDM2005, which received FDA Orphan Drug Designation for mantle cell lymphoma in 2025, is being studied globally in hematological malignancies and solid tumors.

CONFERENCE, EVENTS, AND PUBLICATIONS

Daiichi Sankyo showcases ADC advances in lung cancer at WCLC 2025 [15]

Daiichi Sankyo presented new data across its DXd ADC portfolio at the IASLC World Conference on Lung Cancer (WCLC). A late-breaking oral presentation highlighted results from the Phase II IDeate-Lung01 trial of ifinatamab deruztecan (I-DXd), showing potential as the first B7-H3-directed ADC for patients with pretreated extensive-stage small cell lung cancer (SCLC).

WuXi highlights global CRDMO capabilities at ISPE 2025 Singapore [16]

WuXi XDC participated in the ISPE Singapore Conference, highlighting innovation in ADC development and manufacturing. Dr Jun Hu, VP of WuXi XDC, delivered a keynote on empowering global partners and joined panel discussions on industry challenges and future directions. As part of the event, >20 multinational and regional pharma companies toured WuXi XDC's new Singapore site, offering end-to-end services from antibody intermediates to drug products.

IDEAYA and Hengrui present positive Phase I data for IDE849 in SCLC at WCLC 2025 [17]

IDEAYA Bioscience and Hengrui Pharma reported encouraging Phase I results for IDE849, a DLL3-targeting topoisomerase-1 ADC, at WCLC 2025. Among evaluable SCLC patients treated at doses ≥2.4mg/kg, IDE849 achieved a 73.2% overall response rate (ORR) and 47.9% confirmed ORR. In second-line patients, ORR reached 77.1% with 60% confirmed responses, and in those with brain metastases, confirmed ORR was 66.7%. Median

progression-free survival (PFS) was 6.7 months across all patients, with not-yet-reached PFS in 2L SCLC. Safety was manageable, with Grade ≥3 treatment-related adverse events in 48% of patients and only 2% discontinuations. IDEAYA holds global rights to IDE849 outside China.

SUMMARY

The bioconjugation field continues accelerating with notable partnerships, regulatory updates, and strong clinical progress. Adagene partnered with ConjugateBio to advance bispecific ADCs, while Biocytogen and Merck KGaA entered an agreement to develop antibody-conjugated LNPs for nucleic acid delivery. Sutro Biopharma also announced a collaboration with the FDA to establish new ADC regulatory standards.

Market activity saw WuXi XDC report 62% revenue growth, bolstered by expanding global capacity, while Pfizer implemented cost-saving layoffs at the former Seagen HQ. Regulatory news included Singapore's addition of the PCV20 conjugate vaccine to its immunization schedule.

On the clinical front, OBI Pharma initiated trials for its TROP2 ADC, Avenzo secured FDA clearance for a bispecific ADC, and BioNTech with DualityBio reported Phase III success for a HER2 ADC. Additional highlights included IDEAYA and Hengrui's DLL3 ADC data in SCLC, Huadong's promising ROR1 ADC results, and Daiichi Sankyo's B7-H3 ADC trial updates at WCLC 2025.

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BIOCONJUGATION INSIGHTS

NEW FRONTIERS: HOW ARE OLIGONUCLEOTIDE, PEPTIDE, AND OTHER EMERGING CONJUGATES EXTENDING THE REACH OF THE FIELD?

SPOTLIGHT

Advancing oligonucleotide therapeutics: conjugation strategies for extrahepatic delivery

VIEWPOINT

"A successful conjugate must effectively deliver oligonucleotides while maintaining safety, stability, and manufacturability.."

On August 20, 2025, Lauren Coyle, Launch Commissioning Editor, *Bioconjugation Insights*, spoke to **Sritama Bose**, Associate Director of Chemistry, Orfonyx Bio, about oligonucleotide bioconjugation strategies, delivery challenges, and emerging approaches for tissue-specific targeting. This viewpoint is based on that conversation.

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EXPANDING BIOCONJUGATION BEYOND ADCS

The field of bioconjugation for oligonucleotide delivery represents a rapidly evolving discipline that extends well beyond the established framework of ADCs. Oligonucleotides present distinct hurdles compared to small-molecule drugs, including poor cellular uptake, instability in biological systems, and the critical need for precise tissue targeting. These challenges have driven innovation in oligonucleotide conjugation with diverse delivery vehicles, including but not limited to small molecules, lipids, fatty acids,

N-acetylgalactosamine (GalNAc), and peptides.

The conjugation of oligonucleotides to GalNAc has revolutionized hepatic delivery by targeting the asialoglycoprotein receptor, which is highly expressed on hepatocytes. This targeted approach enables efficient liver-specific uptake and has become the gold standard for hepatic oligonucleotide delivery. Building on this success, researchers are now focusing on extrahepatic delivery, exploring novel ligands that can direct oligonucleotide therapeutics to tissues including the heart, muscle, brain, and kidney.

Recent advances demonstrate the potential for expanding tissue targeting capabilities. Diverse long-chain lipid conjugates have shown functional extrahepatic siRNA delivery *in vivo* to renal, muscular, and cardiac tissues. Similarly, chemically modified carbohydrate conjugates, such as renal tubule-targeting carbohydrate, have shown efficient and selective kidney targeting, illustrating the potential for developing a comprehensive toolkit of targeting ligands.

Peptide-oligonucleotide conjugates represent another promising frontier. Peptides can target numerous cell surface receptors, offering specificity for muscle-targeting or kidney-targeting peptides. Cell-penetrating peptides provide the additional advantage of facilitating cargo transport across cell membranes, significantly enhancing cellular uptake, which is a major bottleneck for oligonucleotide therapeutics.

Beyond delivery enhancement, oligonucleotide-small-molecule conjugates offer synergistic therapeutic effects—the oligonucleotide and small-molecule payload work together to enhance therapeutic outcomes. For example, antisense oligonucleotides (ASOs) conjugated with JQ1, a nuclear importer, have demonstrated superior performance to unmodified counterparts for splice switching and mRNA knockdown in the nucleus.

OPTIMIZING CONJUGATES FOR ENHANCED UPTAKE & SPECIFICITY

Oligonucleotides face significant barriers in reaching intracellular targets due to their large size, often high charge, and susceptibility to nuclease degradation. These properties impede cellular membrane crossing and limit target accessibility. Optimization strategies focus primarily on three objectives: improving cellular uptake, enhancing tissue specificity, and increasing stability.

Ligand conjugation for targeted delivery represents the most direct and successful approach. This strategy involves attaching specific molecules or ligands to oligonucleotides that bind to receptors on target cell surfaces, triggering receptor-mediated endocytosis. The tri-GalNAc conjugate system demonstrates this approach, with optimization involving different linker chemistries and branching patterns to enhance binding affinity and internalization. Oligonucleotide conjugates with lipids such as cholesterol have been used to improve uptake. Cholesterol-conjugated oligonucleotides are associated with lipoproteins such as high-density lipoproteins (HDLs) and low-density lipoproteins (LDLs), enabling cellular uptake through lipoprotein receptors. This approach leverages natural cellular uptake mechanisms to improve oligonucleotide delivery efficiency.

Chemical modifications to the oligonucleotide backbone provide complementary improvements to conjugation strategies. Replacing phosphodiester backbones with phosphorothioate linkages significantly improves resistance to enzymatic degradation, increasing half-life. Neutral backbones, including amide-type linkages, are being extensively explored, with four FDA-approved Duchenne muscular dystrophy drugs containing phosphorodiamidate morpholino oligomers. Additionally,

sugar modifications such as 2′-O-methyl, 2′-O-methoxyethyl, and 2′-fluoro can enhance binding affinity.

Novel conjugation chemistry and linker optimization represent critical components of successful conjugate development. The linker connecting the oligonucleotide with partner compounds must maintain stability to prevent premature cleavage while remaining cleavable under specific intracellular conditions in the presence of certain enzymes or at specific pH levels to release the active oligonucleotide. Pharmacokinetic properties can be optimized by tuning linker length and hydrophobicity to improve absorption, distribution, metabolism, and excretion properties.

STRATEGIC CONSIDERATIONS FOR CONJUGATE SELECTION

Selecting a conjugate type for specific delivery barriers requires a holistic perspective dependent on therapeutic goals. A successful conjugate must effectively deliver oligonucleotides while maintaining safety, stability, and manufacturability.

Target tissue and cell type selection represent the most critical starting point, as the desired destination dictates conjugate choice. While liver targeting through GalNAc conjugates serves as the established standard, extrahepatic tissues present greater delivery hurdles. These tissues require alternative approaches, including peptide-oligonucleotide conjugates such as muscle-targeting peptides designed to bind specific receptors on muscle or cardiac cells.

The brain presents particular challenges due to the blood-brain barrier (BBB). Researchers are exploring conjugates with peptides facilitating transport across the barrier or directly targeting neuronal receptors. The nature of the oligonucleotide, whether siRNA, ASOs, or mRNA, influences conjugate choice based on chemical properties.

Larger molecules, such as mRNA, are generally too large for direct conjugation with small molecules and are preferably delivered through nanoparticle systems like lipid nanoparticles. Smaller oligonucleotides, including siRNAs and ASOs, are more amenable to direct conjugation with small molecules, peptides, or antibodies. The distinct mechanisms of siRNAs and ASOs require conjugate and linker designs that facilitate oligonucleotide release in the correct intracellular compartment.

Pharmacokinetics and biodistribution considerations significantly influence absorption, distribution, metabolism, and excretion properties. Some conjugates can extend oligonucleotide half-life in circulation by protecting against nuclease degradation, potentially reducing dosing frequency. Conjugates influence clearance mechanisms, with some cleared renally while others are taken up by the liver or other tissues, impacting off-target effects and toxicity.

Safety profiles require careful consideration, particularly for long-term therapies. Conjugates and metabolic byproducts must be non-toxic, with linkers designed to release payloads without generating harmful metabolites. Production scalability and cost considerations cannot be overlooked, as chosen conjugation chemistry must be scalable for large-scale manufacturing under GMP guidelines.

TARGETING EXTRAHEPATIC TISSUES: OPPORTUNITIES & OBSTACLES

The success of GalNAc conjugates in liver targeting has inspired exploration of other disease-relevant tissues and cell types. Skeletal and cardiac muscles represent promising targets for diseases such as Duchenne muscular dystrophy and cardiomyopathies, which often result from genetic defects suitable for oligonucleotide intervention.

Currently approved oligonucleotide drugs for Duchenne muscular dystrophy are phosphorodiamidate morpholino oligomers that suffer from limited efficacy, necessitating high-dosage regimens. Antibody-oligonucleotide conjugates targeting transferrin receptor 1 (TfR1) have demonstrated successful oligonucleotide delivery to skeletal and cardiac muscles in animal models, achieving effective gene silencing. Peptide-oligonucleotide conjugates offer an alternative approach, with muscle-specific peptides and cell-penetrating peptides being actively screened for high-affinity binding and efficient endocytosis.

The CNS represents another high-priority target, with neurodegenerative diseases such as Huntington's disease, Alzheimer's disease, and amyotrophic lateral sclerosis having strong genetic components suitable for gene silencing therapies. The success of Nusinersen—delivered intrathecally for spinal muscular atrophy treatment—demonstrates oligonucleotide therapeutic potential in the CNS. However, intrathecal injections are invasive, and systemic delivery alternatives are being actively explored.

The BBB represents the foremost hurdle to CNS delivery. Promising approaches include conjugating oligonucleotides to antibodies targeting BBB endothelial cell receptors, such as the transferrin receptor, leveraging natural transcytosis pathways. Brain-penetrating peptides offer another strategy, with short peptides capable of crossing the BBB, potentially enabling systemic delivery with broad CNS distribution.

Kidney targeting presents unique difficulties due to rapid renal clearance, which eliminates drugs from the bloodstream before the therapeutic effect occurs. This issue is compounded by non-specific uptake and passive accumulation in renal tissues, limiting efficacy and potentially causing off-target effects. Renal tubule-targeting carbohydrates have demonstrated selective delivery to proximal convoluted tubules. Long-chain lipid conjugates have also shown selective siRNA delivery to kidney tissues, providing additional targeting approaches.

HYBRID CONJUGATES FOR COMPLEX DELIVERY BARRIERS

Extrahepatic delivery challenges may require multi-component approaches to overcome diverse biological barriers. While single-component conjugates such as GalNAc have succeeded in liver targeting, extrahepatic tissues may benefit from hybrid or combination conjugates that leverage complementary molecular components.

The concept of multi-component conjugates centers on single molecules performing multiple functions, with each component addressing different barriers. For example, oligonucleotides with peptide and lipid conjugates at 5′ and 3′ ends can provide specificity and membrane disruption capabilities. Peptides offer specificity through binding to diverse receptors on extrahepatic cell surfaces, while lipids with amphiphilic properties can disrupt endosomal membranes to facilitate oligonucleotide release into the cytoplasm.

Hybrid conjugates represent a promising strategy for overcoming BBB obstacles and minimizing off-target effects, which remain significant limitations for non-targeted delivery. The future of extrahepatic delivery lies in the intelligent design of hybrid conjugates combining optimal properties from multiple molecular classes. This will enable engineered delivery platforms that overcome complex biological barriers while moving beyond one-size-fits-all approaches.

FUTURE INNOVATIONS IN TISSUE-SPECIFIC DELIVERY

The future of tissue-specific drug delivery represents a convergence of chemistry, engineering, and computational biology. It

is moving toward a highly personalized and programmable era in which delivery systems are as meticulously designed as therapeutic payloads themselves.

Multimodal and tunable conjugates represent a key innovation direction. Current conjugates typically target single tissues, while future developments may bring conjugates addressing multiple delivery challenges simultaneously. Rather than single-targeting ligands, conjugates may incorporate multiple ligands optimized for specific functions, such as a single therapeutic equipped with peptides for cell type targeting and lipids for endosomal escape.

Advanced biocompatible click chemistry techniques will facilitate the synthesis of complex hybrid conjugates, enabling modular approaches to rapidly optimize conjugates for specific therapeutic needs. The development of novel linkers for smart stimuli-responsive delivery systems represents another innovation area, with linkers responsive to biological environments such as pH or specific enzymes.

More precise and diverse options will enhance current enzyme-cleavable and pH-responsive linkers, enabling conjugates that remain stable in circulation but release payloads only upon encountering specific conditions. This on-demand release approach will dramatically improve efficacy while reducing off-target toxicity.

Future approaches may harness endogenous delivery mechanisms rather than introduce foreign substances. Engineering oligonucleotides to associate with specific lipoprotein particles, such as HDLs or LDLs, could enable natural transport to specific tissues.

Machine learning and artificial intelligence will play crucial roles in designing multi-component conjugates. AI-powered algorithms has the potential to analyze vast conjugate structures, chemistry, and preclinical performance datasets to predict *in vivo* behavior. This computational approach will enable screening large numbers of conjugates, accelerating drug discovery and optimization processes.

The next wave of oligonucleotide conjugates will extend beyond liver targeting through targeted and diversified approaches, representing a significant advancement in precision medicine for oligonucleotide therapeutics.

BIOGRAPHY

Sritama Bose is the Associate Director of Chemistry at Orfonyx Bio, where she leads multiple projects on nucleic acid therapeutic development. Previously, she was Head of Chemistry Research & Innovation at Nucleic Acid Therapy Accelerator. She holds a PhD in Synthetic Organic Chemistry from Indian Association for the Cultivation of Science, India with international postdoctoral experiences including a specialization in nucleic acid chemistry at Durham University, UK. Sritama joined Sygnature Discovery, a drug discovery CRO, where she applied her organic synthesis expertise as a Senior Scientist, gaining valuable medicinal chemistry insights that she now brings to her leadership role at Orfonyx Bio.

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BIOCONJUGATION INSIGHTS

NEW FRONTIERS: HOW ARE OLIGONUCLEOTIDE, PEPTIDE, AND OTHER EMERGING CONJUGATES EXTENDING THE REACH OF THE FIELD?

SPOTLIGHT

The promise of antibody-oligonucleotide conjugates for neurological diseases

INTERVIEW

"To fully unlock their potential, there are a few key breakthroughs that are going to be critical."

Lauren Coyle, Launch Commissioning Editor, *Bioconjugation Insights*, speaks with **Kerstin Hofer**, Science and People Lead, Roche, about the evolving application of antibody-oligonucleotide conjugates in neurology. She highlights their design, delivery challenges across the blood–brain barrier, and potential to transform CNS diseases.

Bioconjugation Insights 2025; 1(3), 81–86 · DOI: 10.18609/bci.2025.018

Q You have worked extensively with neurological diseases. What inspired your interest in exploring the translation of ADCs, which are traditionally oncology-focused, and moving them into this field?

KH My interest in translating ADCs into the neurological space was catalyzed by the enormous impact that ADCs have had in oncology over the last decades. In oncology, ADCs have transformed treatment by adding a new level of precision.

They deliver potent cytotoxic agents directly to tumor cells, which has significantly reduced, although not eliminated, the damage to healthy tissues. This targeted approach has led to significant clinical benefits, such as significantly improved response rates, longer progression-free survival, and, in some cases, turning aggressive cancers into manageable chronic conditions.

As of today, there are 14 FDA-approved ADCs, and hundreds in various stages of clinical development. It is a success story. This success, both scientifically and clinically, has naturally raised the questions: could we apply the same principle in the targeted delivery of potent agents? And, more importantly, can we apply this to other challenging diseases, specifically the central nervous system (CNS) space?

The main hurdle of neurological diseases, such as Alzheimer's disease or ALS, is similar to oncology. It is about delivering therapies precisely to affected cells and tissues. In ADCs, this is solved through the use of antibodies that specifically target tumor cells. For antibody-oligonucleotide conjugates (AOCs), the same delivery strategy is being applied.

The aim is to get oligonucleotide therapies across the blood–brain barrier (BBB) into brain cells. The main difference is the payloads that are needed for neurological diseases. We are not trying to kill cells; we are trying to do the opposite by modulating gene expression. By reducing toxic protein levels or correcting dysfunctional pathways within the brain, that is where the shift from ADCs to AOCs comes in.

It is an evolution of the ADC concept, but with a payload that is specifically suited and tailored to the biology of CNS diseases. In short, I think it was the clinical success of ADCs and how they changed outcomes for cancer patients that made us ask, 'Why can't we apply the same precision approach to the brain?' That question has been with us and at the core of much of what we have done recently.

Q Would you be able to give more details on how these AOCs differ from ADCs and what makes them particularly exciting for neurological applications?

KH ADCs and AOCs share some basic architecture where an antibody is linked to a payload, in essence, but then, the nature and purpose of the payload are almost entirely different.

As mentioned, AOCs are not delivering small-molecule toxins like ADCs—AOCs carry oligonucleotides and modulate gene expression. They are designed to intervene in protein production at the mRNA level. That can be used, for instance, to silence toxic genes, correct splicing errors, or reduce the production of pathogenic proteins within the brain.

This kind of upstream intervention is especially well-suited for neurological diseases, often when dealing with chronic conditions, specifically genetically driven conditions. Many of these CNS disorders, such as Huntington's and certain forms of epilepsy, are driven by genetic mutations or dysregulated transcripts.

Oligonucleotides offer the potential to correct the underlying molecular dysfunctions. They do this rather than just treating symptoms or slowing progression. This is the powerful thing about oligonucleotides, but at the same time, delivery to the brain remains a massive challenge. That is what we are trying to solve with AOCs. In a nutshell, what excites me most in this context is how modular AOCs are and the transferability of the approach across multiple neurological conditions.

Bioconjugation Insights 2025; 1(3), 81–86 · DOI: 10.18609/bci.2025.018

Q One of the biggest challenges in treating brain disorders is the BBB. How are you and your team approaching the challenge of getting AOCs across this barrier, and are there particular delivery technologies or strategies that you have been excited about?

KH The BBB is one of the most defining challenges in the whole field of neurological drug development. This is for good reason, as the BBB has an important biological role as a gatekeeper. That means that it retains the brain homeostasis while also protecting the brain from toxins and pathogens.

Unfortunately, this also means that it prevents the vast majority of therapeutic molecules from entering the brain. This is especially true for large and charged molecules such as oligonucleotides. They do not cross the BBB unassisted, and for that reason, getting oligonucleotides into the brain requires direct administration. Intrathecal and intracerebroventricular injections are often used, but these are invasive techniques that come with a patient burden. They limit the drug distribution, mainly to the spinal cord and the nearby brain regions, but the rest of the brain is not as homogeneously treated by the oligonucleotide.

This is where AOCs get exciting. Oligonucleotides can take advantage of a very natural cellular response, and a process called receptor-mediated endocytosis and transcytosis—a mechanism that the brain uses to import essential molecules. There are specific receptors, such as the transferrin receptor (TfR), and these are expressed on the endothelial cells that are lining the BBB. When a molecule binds to one of these receptors, it can be shuttled across the BBB and reach the inside of the brain.

With AOCs, antibodies are being designed to bind to those receptors at the BBB and attach the oligonucleotide payload to the antibody. The antibody acts as a carrier that allows the whole AOC to be transported across the BBB. In the past, there have been promising preclinical results showing that these AOCs can efficiently reach the brain parenchyma following intravenous administration.

Ultimately, the goal is systemic administration—something that can be given to a patient in a routine setting and will result in meaningful concentrations of a therapeutic oligonucleotide in the brain. When this is achieved, it will be a step forward in making neurological therapies both more patient-friendly and scalable.

Q What do you think are the key design elements, such as conjugation techniques or linker chemistries, that impact success in AOC design and development?

KH Designing an effective AOC is about precision engineering, as it is a multi-component system. You have an antibody, a linker, and an oligonucleotide, and every piece needs to be optimized not only individually but also in terms of how these pieces function together once they are combined into the AOC.

"Oligonucleotides can take advantage of a very natural cellular response, and a process called receptor-mediated endocytosis and transcytosis..."

"...oligonucleotides need to reach the cytoplasm or the nucleus of a cell and be released for them to be effective."

Starting with conjugation, one key lesson learned from the ADC field that can be translated into the AOC field is the value of site-specific conjugation. With ADCs, random conjugation has resulted in heterogeneous products—they have variable pharmacokinetic profiles, unpredictable efficacy, and toxicity profiles. In AOCs, this matters even more. The reason is that oligonucleotides are large, negatively charged molecules, meaning they can significantly affect the antibody's behavior. This is especially true if the oligonucleotide is not attached in the right position within the antibody.

Often, enzyme-mediated methods are used, such as transglutaminase-based conjugation. This way, it can be ensured that the oligonucleotide is attached to a defined location while also being far enough away from the antigen-binding site, so as not to interfere with antigen binding.

The next consideration is the linker. In oncology, both cleavable and non-cleavable linkers have been utilized. This also applies to AOCs, where both types of linkers can be considered. However, there is an added twist—oligonucleotides need to reach the cytoplasm or the nucleus of a cell and be released for them to be effective. One option is to use cleavable linkers that respond to intracellular environments, so the oligonucleotide can be released. The stability in circulation is paramount because if the linker breaks down too early, all of the payload in the circulation is lost before it makes it across the BBB, which is not the desired outcome.

When designing AOCs, the oligonucleotide component also requires careful chemical modification to ensure stability and efficacy. Unfortunately, unmodified oligonucleotides are rapidly degraded, and this happens mostly by nucleases, in the bloodstream and inside cells, for instance, in the lysosomes. Incorporating modifications that assure the stability of the oligonucleotides is essential here.

Finally, the antibodies' target at the BBB has a significant impact. For brain delivery, antibodies that target receptors with good transcytosis behavior, such as TfR, tend to have more of an impact. There are also other factors such as receptor density, expression pattern, also internalization rates. They all influence how well the AOC will be transported across the BBB, but also enter the disease-relevant cells once it is in the brain. This means that the AOC design is highly interdisciplinary.

To effectively achieve this, experts in antibody engineering, oligo chemistry, and linker technology are required. The team at Roche has various experts in many different fields who have to be brought together to work collectively. Building such an effective interdisciplinary team of scientists has been important in this context.

Q Following on from this, what unique hurdles do AOCs face in the neurological space that perhaps aren't as prominent in oncology?

KH Some distinct challenges come along with taking AOCs into the neurological space. There are some biological, but also some practical challenges. As

mentioned, the first and most obvious hurdle is the BBB—it is a level of delivery complexity that just doesn't exist in most oncology applications.

Tumors are more accessible via systemic circulation, and they tend to have leaky vasculature, so it is also not easy to reach tumors effectively. With the brain, it is a completely different level, as the goal is to cross a highly selective barrier. Additionally, specific cell types deep within this complex brain tissue need to be reached, which is a very prominent challenge for AOCs.

There is also the issue of target engagement and pharmacodynamics. In cancer, the goal is often to kill rapidly dividing cells and to do this quickly. This creates a clear readout for preclinical and clinical studies. In contrast, neurological conditions involve chronic or slowly progressing pathologies. Many of the targets, such as RNA transcripts of misfolded proteins or other mRNA targets, are expressed at low levels. This makes it difficult to measure whether the AOC is working and to define clinical trial endpoints, especially as these usually take a long time.

Another hurdle is safety and tolerability, which is also prominent in oncology. The safety hurdle for AOCs has a different nature because the brain has very little regenerative capacity. This means that any unintended off-target effects, whether it is immune activation, gene silencing in the wrong cell types, or the wrong transcript, can have serious consequences, as the brain just cannot recover from these safety effects. This also adds to the regulatory complexity.

Finally, manufacturing is also not a small feat, particularly when combining a complex biologic with a highly modified oligonucleotide. These two components are already difficult in themselves. Each component has to be produced with a set of quality control and manufacturing requirements. In addition, conjugation processes must be scaled up for GMP-grade material.

This is still a developing field for AOCs. There are some challenges, however, despite these, the opportunity is enormous. If these challenges are tackled, AOCs could open the door to treating brain diseases in new ways—most importantly, this would increase patient convenience.

Q Finally, as the field of AOCs grows, what advancements or breakthroughs do you think are needed to fully unlock therapeutic potential in the brain?

KH The field is still at the beginning of what's possible with AOCs in the brain. To fully unlock their potential, there are a few key breakthroughs that are going to be critical. First of all, there is a need for better targeting strategies for the BBB. Right now, there are a handful of receptors, such as TfR or CD98, that can be used to carry AOCs. As these receptors are also expressed in peripheral tissues, there is the consequence that only a fraction of the administered dose reaches the CNS. With that, there is a clear need for more BBB-specific targets.

Second, more effective oligonucleotide payloads are needed, and this requires significant working effort. Third, non-invasive biomarkers are critical. They are not only critical in the context of AOCs, but in general for neurological diseases. There is a need for a better target engagement measurements in the brain to fine-tune the dosing and monitor therapeutic responses.

Fourth, is to advance manufacturing technologies. Cost-effectively scaling the production of AOCs remains a challenge. Any technological innovations that could help reduce the manufacturing cost will also be important in the future.

Finally, the regulatory framework must be addressed for it to evolve. AOCs are hybrids, not quite biologics, gene therapies, or traditional oligonucleotides. Guidelines that recognize these unique aspects of AOCs are required to bring them to patients fast and without compromising safety. If a few of these milestones are achieved in the next years, there will be the first wave of CNS targeting AOCs entering the clinic. This means a chance for treating CNS diseases that previously were completely out of reach.

BIOGRAPHY

Kerstin Hofer is a Senior Scientist at Roche Pharma Research and Early Development, where she leads the bioconjugation lab. She has extensive experience in the delivery of oligonucleotide-based therapeutics to target tissues, such as the brain. Prior to joining Roche, Kerstin completed her BSc and MSc degrees in Chemistry and Biochemistry at the University of Munich, Munich, Germany and her DPhil in Chemical Biology at the University of Oxford, Oxford, UK.

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You can also listen to the recorded podcast here:

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EVENT PREVIEW

The 4th Annual Targeted Radiopharmaceutical Summit 2025

Bioconjugation Insights 2025; 1(3), 71–72 · DOI: 10.18609/bci2025.014

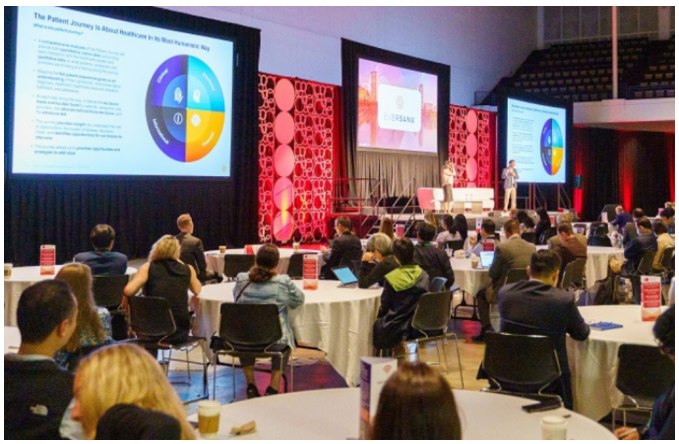
As part of our ongoing coverage of key gatherings in the bioconjugation space, *Bioconjugation Insights* presents an event preview of the 4th Targeted Radiopharmaceuticals Summit 2025. Taking place July 29–31, 2025, in San Diego, the summit will showcase the latest advances, technologies, and collaborative opportunities across the radiopharma pipeline from discovery to commercialization. This preview offers readers a glimpse into the sessions, speakers, and themes that will shape the discussions of this fast evolving therapeutic field.

NOVEL DESIGN APPROACHES

The summit spotlighted innovative strategies in radiopharmaceutical design, with a strong focus on novel targeting molecules and delivery platforms. James Bowman will introduce de novo protein design using AI to create miniproteins with site-specific conjugation handles. Alessandro Mascioni and Guido Wuerth share advances in engineered antibody fragments and Affibody technology for HER2-targeted therapies. Haihong Jin discusses AI-driven medicinal chemistry for peptide-based RLTs. Workshops led by Chris Adams, Keene Wei, Phil Brandish, and Randolf Kerschbaumer explore peptide and mini protein targeting, linker chemistry, and pre-targeting strategies. These sessions collectively emphasized the field's evolution toward precision-engineered biologics and computational design to enhance efficacy and reduce off-target effects.

EMERGING CLINICAL DATA

Emerging clinical insights are a major theme, with speakers presenting early-phase trial data and translational strategies. Manfred Rudgier and Guido Wuerth share updates on first-in-human studies, while Daniel Stevens highlights the role of dosimetry in early go/no-go decisions. Dylan Stoy presented findings from UCLA's FLEX and RE-LuPSMA trials, aiming to optimize fixed dosing schedules. Anna Karmann, Alyssa Vito, and Sudhakar



Chintharlapalli will discuss Phase 0 strategies to accelerate clinical entry. These sessions underscored the growing importance of early clinical signals, imaging biomarkers, and real-world evidence in refining trial design and guiding regulatory and commercial decisions.

BIOCONJUGATION

Bioconjugation will be explored through sessions on antibody-based radiopharmaceuticals, linker technologies, and radiolabeling strategies. Dirk Pleimes, Xueming Qian, and Randolf Kerschbaumer lead a workshop on antibody conjugates and pre-targeting strategies, addressing challenges in radiolabeling and biological half-life alignment. Chris Adams, Keene Wei, and Phil Brandish discuss linker innovations and chelator design in peptide-based targeting. Haihong Jin presents on AI-driven conjugation chemistry for RLTs. These sessions highlighted how bioconjugation is central to improving pharmacokinetics, targeting specificity, and therapeutic index in next-generation radiopharmaceuticals.

SUPPLY CHAIN

The summit will also cover supply chain innovation, addressing isotope availability, manufacturing scalability, and regulatory integration. Kevin Machel and David Bailey will discuss domestic isotope production and supply chain resilience. Kevin Roland and Shaemus Gleasson explore CMC strategies and regulatory frameworks for scalable production. Ashley Mishoe emphasized harmonizing CDMO and sponsor quality systems. Additional insights come from roundtables and panels featuring Max Smock and Luis Rivera, who address funding trends and logistics. These sessions reinforced the need for robust, decentralized supply chains to support the rapid growth of radiopharmaceutical development and commercialization.

From radiochemistry innovators to clinical trial trailblazers, the 4th Annual Targeted Radiopharmaceuticals Summit US 2025 is your gateway to next-generation conjugation strategies, precision alpha therapies, and scalable isotope supply. Bringing together industry-leading pharma, biotech, and academia, this summit delivers the insights, technologies, and partnerships you need to accelerate clinical translation, streamline manufacturing, and lead the radiopharma revolution in oncology.

As a reader of *Bioconjugation Insights*, you're entitled to a **10% discount** on delegate tickets—just use the code **BCIXTRP**! You can find out more about the 4th Annual Targeted Radiopharmaceuticals Summit 2025 events **here**.

Additionally, to find out what other bioconjugate events are upcoming, you can find our online Events Calendar **here**.

EVENT PREVIEW

The 4th Annual Biologics CDMO Asia 2025

Bioconjugation Insights 2025; 1(3), 79–80 · DOI: 10.18609/bci.2025.017

As part of our ongoing coverage of key gatherings in the bioconjugation space, *Bioconjugation Insights* presents an event preview of the 4th Annual Biologics CDMO Asia 2025. The event emerges as the definitive platform to explore contract development and manufacturing innovation across the Asia-Pacific region, uniting C-level executives, manufacturing leaders and regulatory stakeholders to foster partnerships and address challenges in scalability, compliance, and technological integration. From smart tech transfers to CGT manufacturing, this two-day summit delivers the strategies needed to stay competitive in a fast-evolving biomanufacturing ecosystem.

4TH ANNUAL BIOLOGICS CDMO ASIA

EVENT HIGHLIGHTS

The 4th Annual Biologics CDMO Asia 2025 features a dynamic agenda focused on aligning biomanufacturing strategies with Asia's accelerating demand for biologics. The event opens with strategic insights from Christopher Pawlak, Bayer, Daniel Hurni, Bristol Myers Squibb, and Hu Jun, WuXi XDC in a high-level panel on global CDMO partnerships, emphasizing how multinational companies are aligning capabilities with the region s biomanufacturing boom. Further to the panel, keynote speaker Christopher Pawlak presents a compelling roadmap for strategic supplier management, integrating performance metrics, cultural alignment, and digital tools to futureproof external manufacturing operations. Day 1 sessions will explore the full CDMO lifecycle, with insights on global network design and supplier positioning. Jennifer Kuan, Bora Biologics, will outline how regional site specialization supports faster, more flexible tech transfers from early-stage to commercial production.

In the digital sphere, Nora Pataut, GSK, reveals how standardized digital frameworks are revolutionizing CMC tech transfers, and Kamyar Sadri, Novo Nordisk, discusses AI s transformative potential in CDMO ecosystems. Zach Pang, ASTAR Bioprocessing Technology Institute (BTI), offers a deep dive into computational workflows for optimizing culture media, especially for new modalities.

Day 2 kicks off with Bi Xuezhi, ASTAR Bioprocessing, examining mass spectrometry s growing role in real-time biologics quality control. Jimmy Chang, TaiMed Biologics, recounts lessons from developing and commercializing the world s first FDA-approved HIV monoclonal antibody an inspiring look at R&D-to-commercial translation through CDMO partnerships.

The regulatory spotlight features a robust panel discussion with experts Sudeep Srivastava, TechInvention Lifecare, Jimmy Chang, TaiMed,, Rakesh Kumar Sinha, Biological E. Limited, and Akhil Prakash Chincholikar, Naprod Life Sciences, tackling APAC-specific compliance challenges. Follow-up sessions examine how CDMOs are adapting to the evolving landscape through precision medicine, biologics, and strategic approaches like smart manufacturing and total quality management to enhance regulatory compliance, cost efficiency and capacity realisation.

Asia's innovation potential is further spotlighted through case studies on scaling CDMO capacity, technology adoption, and strategic biotech partnerships. The agenda concludes with a strong focus on next-generation modalities: Warren Chan, WTU, explores mRNA, cell, and gene therapies, while Andy Tan, A*STAR showcase case studies on cell-based immunotherapies.

Whether you're optimizing tech transfer, expanding capacity, or adopting AI for regulatory efficiency, the 4th Annual Biologics CDMO Asia 2025 is your gateway to scalable biomanufacturing, strategic CDMO partnerships, next-generation therapies, and Asia-Pacifics booming biologics ecosystem uniting innovation, compliance, and collaboration under one roof.

As a reader of *Bioconjugation Insights*, you're entitled to a **15% discount** on delegate tickets—just reach out to **kingsley.chukwura@imapac.com**! You can find out more about the event here.

Additionally, to find out what other bioconjugate events are upcoming, you can find our online Events Calendar **here**.

EVENT PREVIEW

Biologics CDMO Europe 2025

Bioconjugation Insights 2025; 1(3), 87–88 · DOI: 10.18609/bci.2025.019

As part of our ongoing coverage of key gatherings in life sciences, BioInsights presents a preview of Biologics CDMO Europe 2025. Scheduled for November 19–20, 2025, in Munich, Germany, this summit will unite up to 300 senior manufacturing and external supply-chain experts from across Europe. Focusing on agile, tech-enabled biologics manufacturing, regulatory alignment, and strategic CDMO partnerships, the agenda features off-the-record case studies, executive roundtables, and deep-dive sessions.

OUTSOURCING STRATEGY AND CDMO PARTNER EVALUATION

A strategic panel including Suyamburam Sathasivam (Associate Vice President, SUN PHARMA), Ulrich Rümenapp (Head of Launch Preparation and Coordination, Bayer), and Daniel Hurni (Former Director of Manufacturing Network Strategy and Business Intelligence, Bristol Myers Squibb) will discuss outsourcing trends toward 2030. Additionally, Christopher Pawlak (External manufacturing Lead, Bayer) will outline practical tools for CDMO partner evaluation, while Andreas Schaaf (Managing Director/CSO, Eleva) will highlight innovations in biomanufacturing technologies. Key sessions will also explore risk allocation in CDMO agreements and resilient partnership models, setting a collaborative tone for navigating Europe's evolving biologics landscape.

TECH TRANSFER AND GLOBAL REGULATORY HARMONIZATION

The summit will also focus on tech transfer and regulatory compliance for advanced therapies. Christian Simon (Head of Technical Transfer External Manufacturing, Sanofi) will explore how AI-driven predictive maintenance can reduce downtime and improve equipment performance. Jenny Prange (CTO, Muvon Therapeutics) will present strategies for navigating tech transfer in regenerative therapies. Furthermore, a panel on global regulatory harmonization will follow, featuring Pavan Beleyur Narayanaswamy (Head of CMC and Regulatory Affairs, AATec Medical) and Eoin McGrath (Executive Director, ICCBBA).

COST OPTIMIZATION AND EVOLVING CONTRACT MODELS

Ulrich Rümenapp (Head of Launch Preparation and Coordination, Bayer) will address strategic approaches to outsourcing CMC development and manufacturing, including IP protection and building effective CDMO partnerships. Giulio Cavalli (Principal Lead, External Manufacturing, Johnson & Johnson Innovative Medicine) will share best practices for managing cross-border tech transfers in a globalized production landscape. The summit will also include a panel discussion on the evolution of contract models in biomanufacturing, featuring Ralf Huss (Managing Director, Biom Biotech Cluster) and Chris Baldwin (Vice President, Manufacturing and Supply, Resolution Therapeutics), who will explore shifting trends and collaborative opportunities in outsourcing agreements.

Biologics CDMO Europe 2025 will convene key stakeholders from across the biologics manufacturing landscape to address the most pressing challenges and innovations shaping the industry, from evaluating CDMO capabilities and optimizing outsourcing strategies to simplifying tech transfer and scaling single-use technologies.

As a reader of the BioInsights journals, you're entitled to a **15% discount** on delegate tickets—just use the code **CDMO-Insights**! You can find out more about the Biologics CDMO Europe 2025 events **here**.

To learn about other events coming up in your field, you can find our online Events Calendars here:

Bioconjugation Insights, ***Cell & Gene Therapy Insights***, ***Nucleic Acid Insights***, and ***Vaccine Insights***

EVENT PREVIEW

The 3rd Annual ADC Linker & Conjugation Summit

Bioconjugation Insights 2025; 1(3), 73–75 · DOI: 10.18609/bci.2025.015

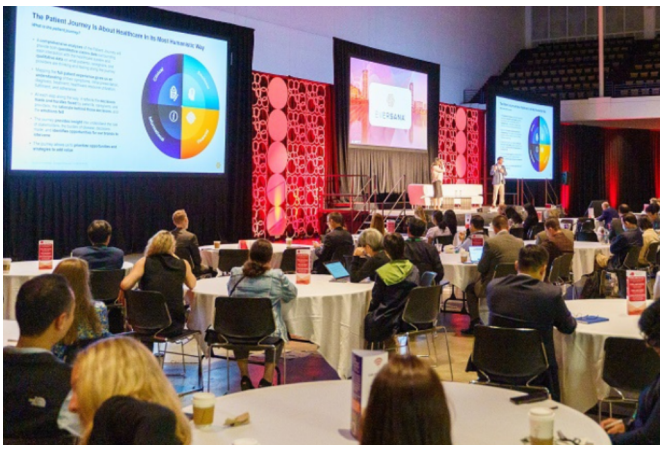
As part of our ongoing coverage of key gatherings in the bioconjugation space, *Bioconjugation Insights* presents an event preview of the 3rd Annual ADC Linker & Conjugation Summit. Taking place August 19–21, 2025, in Boston, Massachusetts, US, the summit will showcase the latest advances, technologies, and collaborative opportunities in innovative linker design, optimized conjugation strategies, and breakthroughs that are driving safer, more effective next-generation ADCs. This preview offers readers a glimpse into the sessions, speakers, and themes that will shape the discussions of the 3rd Annual ADC Linker & Conjugation Summit.

LINKER DESIGN STRATEGIES

The summit showcases groundbreaking approaches to linker design aimed at improving stability, controlled payload release, and accommodating new formats and highly hydrophobic payloads. Arnaud Tiberghien, Bicycle Therapeutics, will present the architectures of Bicycle® constructs, highlighting differences from traditional antibody-based systems and how these bicyclic peptide linkers enhance therapeutic properties. Tatiana Novobrantseva, NextPoint Therapeutics, shares the development of the proprietary NPX125 linker for B7-H7 targeting ADCs, specifically designed to address a broad patient population while ensuring linker compatibility with complex tumor biology. Marc Robillard, Tagworks, introduces click-cleavable linkers, which promise to expand payload release mechanisms, improve targeting scope, and offer enhanced safety profiles by reducing premature cleavage. The summit also includes a roundtable on balancing stable versus unstable linkers to optimize efficacy and toxicity outcomes.

NEXT-GENERATION CONJUGATION CHEMISTRY

Day two focuses on cutting-edge conjugation technologies beyond traditional maleimide chemistry, which often limits its stability. Manel Merabet, Skymab



Therapeutics, reveals preclinical insights into a next-generation site-specific conjugation platform that overcomes maleimide limitations, while Marcello Marelli, AstraZeneca, outlines how stable chemistries and optimized sites can significantly improve therapeutic indices. Martijn Verdoes, Leiden University Medical Center, introduces Ubi-tagging, a ubiquitin-based modular platform enabling precise, iterative conjugation steps and potent immune activation. Mark Distefano, University of Minnesota, explores prenyltransferases as tools for installing biorthogonal functionalities, broadening applications from targeted cell killing to diagnostic imaging. Wei Lu, OnCusp Therapeutics, highlights the T1000-exatecan platform, demonstrating stable, target-specific antitumor activity with a clean safety profile, while Philipp Ochtrop, Tubulis GmbH, discusses the Alco5 strategy for delivering hydroxyl-linked payloads with high DAR and excellent PK profiles.

OPTIMIZING CONJUGATION SITE SELECTION

The pre-conference workshops provide a deep technical dive into selecting optimal conjugation sites, a crucial step for maximizing ADC stability and payload release. Ganapathy Sarma, Exelixis, Tero Satomaa, Glykos, and Lea Rochet, ADC Therapeutics, lead sessions on how the chemical environment influences site choice and how structural modeling and analytical tools, such as hydrophobic interaction chromatography, guide site accessibility decisions. Andrea North, CSIRO, contributes expertise on balancing linker exposure to prevent premature cleavage while ensuring efficient payload delivery. A complementary focus is optimizing the drug-to-antibody ratio (DAR), a critical balance for efficacy and safety. Strategies include integrating hydrophilic moieties like PEGs, phosphate prodrugs, and charged amino acids to offset hydrophobic payload limitations and achieve higher DAR without compromising solubility or stability. Participants will explore solvent selection and payload design in tandem with conjugation chemistry, gaining practical insights into tuning DAR and site selection to extend ADC half-life, reduce aggregation, and improve clinical outcomes.

DUAL PAYLOAD ADCS

A major highlight is the exploration of new linker and conjugation technology for unlocking success in dual payload ADCs. Marco Lobba, Catena Biosciences, will discuss site-selective conjugation technologies such as the CysTyr platform, enabling the efficient manufacturing of multi-payload ADCs with improved potency and stability.Romain Bertrand, , Araris Bio, presents an innovative approach utilizing bacterial transglutaminase combined with Diels-Alder cycloaddition to attach two payloads via diene-containing linkers, demonstrating robust *in vitro* and *in vivo* performance. Juhani Saarinen, Glykos, delves into the chemical engineering of branched linkers designed to provide tumor-specific cleavage mechanisms, maintaining payload stability while ensuring effective release. The session also covers hydrophilic linker designs that facilitate dual payload incorporation without increasing hydrophobicity or aggregation.

Whether you are advancing early research, refining conjugation platforms, or exploring novel ADC formats, the 3rd ADC Linker & Conjugation Summit 2025 is your gateway to novel linker designs, optimized conjugation chemistry, dual-payload innovations, and next-generation ADC strategies.

As a reader of *Bioconjugation Insights*, you're entitled to a **10% discount** on delegate tickets—just use the discount code **BCI10**! You can find out more about the event **here**.

Additionally, to find out what other bioconjugate events are upcoming, you can find our online Events Calendar **here**.

EVENT PREVIEW

Antibody & TIDES Summit 2025

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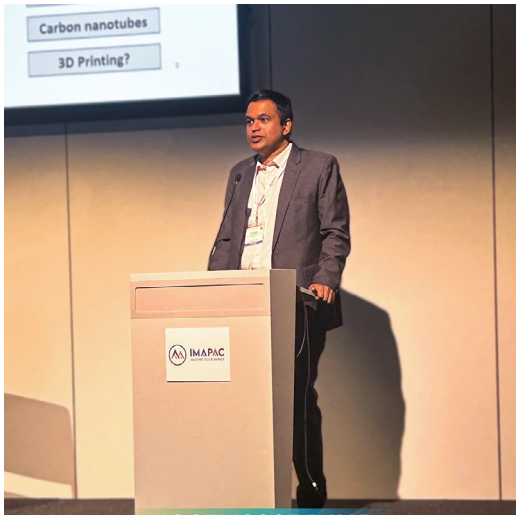
IMAPAC's Antibody & TIDES Summit 2025, taking place from September 9–10, in Amsterdam brings together the TIDEs and Antibody & ADC agendas. Designed for biopharma professionals driving innovation in biologics, the summit offers a comprehensive platform to explore cutting-edge developments in antibody therapeutics, ADCs, and peptide and oligonucleotide-based drugs. Attendees will gain insights into emerging modalities, manufacturing optimization, regulatory strategies, and next-generation delivery systems.

ANTIBODY & ADC AGENDA

The Antibody & ADC agenda offers a dynamic, two-day program spanning cutting-edge antibody engineering, AI in discovery, and next-generation ADC platforms. Day 1 opens with keynote insights into the evolving antibody therapeutics landscape, followed by sessions on bispecific antibody design from Peter Ellmark, Alligator Bioscience, and therapeutic antibody humanization from Nathan Robertson, LifeArc. A standout panel featuring leaders from Genmab, Step Pharma, and LifeArc delves into biomarker integration to bridge preclinical and clinical success. Sessions also explore AI and machine learning in antibody development, including innovations from Michael Mullin, LabGenius, and Barry Duplantis, Ailux. Functional antibody platforms gain the spotlight with presentations on IgE/IgA therapeutics from Kevin Fitzgerald, Epsilogen, and autoregulating T cell engagers from Vincent Muczynski, NovalGen.

On Day 2, Kerstin Hofer, Roche, presents a breakthrough in CNS delivery of conjugated oligonucleotides, which you can read more about in her recent *Bioconjugation Insights* podcast article **here**. Manel Kraiem, Skymab, Dominik Brücher, CIS BIOPHARMA, and Philipp Spycher, Araris Biotech, showcase advances in multi-payload and anti-GPCR ADCs. Joost Uitdehaag, Crossfire Oncology, adds further insight into payload innovation and site-specific conjugation chemistry. Strategic panels



and roundtables focus on regulatory navigation, manufacturing scale-up, and global market readiness. From discovery to clinical translation, the agenda provides a comprehensive look at the technologies redefining antibody and ADC therapeutics.

TIDES AGENDA

The TIDES session offers a robust exploration of peptide and oligonucleotide therapeutics across discovery, development, and delivery. The agenda spans cutting-edge topics including mRNA vaccine delivery, peptide immunogenicity, and regulatory impacts on innovation. Highlights include Vusala Ibrahimova, CureVac, on mRNA stability innovations, and Bernard Maillere, The CEA, examining immunogenic responses in endogenous peptides.

Technical session delves into peptide synthesis, with Fernando Alberico and Walter Cabri discussing greener and cost-efficient approaches in SPPS and LPPS. Thought-provoking roundtables tackle delivery bottlenecks, regulatory hurdles, sustainability. And AI adoption across therapeutic pipelines. Jean Ge and Rafael Grochot address regulatory frameworks and CMC complexities, with David Gilot, AstraZeneca, share strategies for safety monitoring in clinical oligonucleotide development.

Clinical advancements are also spotlighted, with Anders Gabrielsen, Ribocure, presenting siRNA delivery breakthroughs and AiCuris sharing Phase I trial data. Sessions on circular RNA therapeutics, supply chain, digitization, and GLP-compliant logistics round out this future-focused program. Together, these sessions offer a panoramic view of the scientific, regulatory, and operational factors shaping the next wave of oligonucleotide and peptide-based medicine.

Whether you're engineering next-generation antibodies or advancing oligonucleotide and peptide therapeutics, the Antibody & TIDES Summit 2025 is your gateway to cutting-edge antibody design, ADC innovation, AI-driven discovery, scalable synthesis, and regulatory-ready strategies shaping the future of precision biologics and RNA-based medicines.

As a reader of *Bioconjugation Insights*, you're entitled to a **15% discount** on delegate tickets—just reach out to **bronwyn.westmore@imapac.com**! You can find out more about the event **here**.

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