APRIL 2025

Volume 1 Issue 1

BIOCONJUGATION INSIGHTS

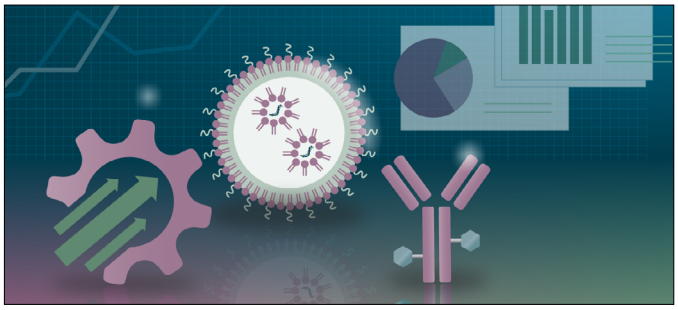
BIOINSIGHTS

LAUNCH ISSUE

BIOCONJUGATION INSIGHTS

CONTENTS VOLUME 1 · ISSUE 1

Launch issue



BIOCONJUGATION INSIGHTS

LAUNCH ISSUE

SPOTLIGHT

Welcome to *Bioconjugation Insights*

Lauren Coyle

FOREWORD

"This new journal marks a significant expansion of BioInsights' mission to provide strategic, technical, and scientific clarity across today's most dynamic therapeutic development frontiers."

Bioconjugation Insights 2025; 1(1), 33–34 · DOI: 10.18609/bci.2025.006

I am delighted to welcome you to the first issue of *Bioconjugation Insights*!

This new journal marks a significant expansion of BioInsights' mission to provide strategic, technical, and scientific clarity across today's most dynamic therapeutic development frontiers. While we have touched on bioconjugation within our other journals, we now recognize the need for a dedicated platform that fully reflects the scope, complexity, and accelerating momentum of this field.

Bioconjugation represents an intersection of biology and chemistry that continues to redefine drug discovery, targeted delivery, and diagnostics. While ADCs may have captured the spotlight in recent years, we are only just beginning to tap into the full potential of this modality-rich area. From antibody-oligonucleotide conjugates to radioconjugates, polymer conjugates, and cutting-edge theranostics, the field continues to rapidly evolve.

Bioconjugation Insights is designed to bring together experts from across the academic, biotech, pharma, and tools sectors to share actionable, up-to-date knowledge. Through this, the journal aims to cover

everything from discovery through regulation and commercialization, supporting those on the front lines of R&D as well as those in the preclinical and clinical settings.

For our launch edition, we have curated a series of contributions that set the scene for key updates in the field and what lies ahead, through the perspectives of some of the foremost thought leaders working in bioconjugation today. This includes viewpoint articles from **Rakesh Dixit** (Cofounder, President and CSO of Regio Biosciences, CEO of Bionavigen, and CSO of Tmab Therapeutics) and **Moein Moghimi** (Professor of Pharmaceutics and Nanomedicine, School of Pharmacy, and Research Professor, Institute of Cellular Medicine, Newcastle University; and Adjoint Professor, Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado-Denver Medical Center) who discuss finding the balance between safety and efficacy in ADCs, and how conjugates can be utilized to address the shortfalls of lipid nanoparticles, respectively.

The issue also includes a series of interviews with **Helen Bright** (CSO, Centauri Therapeutics), **Michelle Morrow** (CSO, Avacta Therapeutics), and **Yu-Tzu Tai** (Associate Director, ADC & Translational Research, Oxford Biotherapeutics). While Bright and Morrow discuss the use of peptide- and small peptide-conjugates in cancer therapies, Tai explores the future of ADCs through the translation of research into therapeutics.

Additionally, the journal also marks the launch of our newest article format, **Industry Insights**. These are concise articles, published once per issue, to highlight key updates in bioconjugations. They will cover the latest developments in collaborations, regulatory changes, marketing trends, and R&D in the field. Additionally, they will provide insights into key clinical trial results and recent innovations in tools and technology, and highlight notable conferences and publications. Going forward, Industry Insight articles will be contributed by our Editorial Advisory Board members.

We extend our sincere thanks to our Editorial Advisory Board and all those who have contributed their time, perspectives, and expertise.

I hope you enjoy this inaugural edition of *Bioconjugation Insights*—and that it becomes your go-to resource as this vital field continues to grow and evolve.

Lauren Coyle is Launch Commissioning Editor of *Bioconjugation Insights*

Bioconjugation Insights 2025; 1(1), 33–34 · DOI: 10.18609/bci.2025.006

BIOCONJUGATION INSIGHTS

LAUNCH ISSUE

SPOTLIGHT

Striking a balance between ADC safety and efficacy

VIEWPOINT

"Continued efforts to educate both clinicians and patients, alongside the adoption of proactive safety management protocols, are essential to advancing the safe and effective use of ADCs in cancer treatments."

On October 9, 2024, **Lauren Coyle**, Launch Commissioning Editor, *Bioconjugation Insights*, spoke to **Rakesh Dixit**, Cofounder, President and CSO of Regio Biosciences, CEO of Bionavigen, and CSO of Tmab Therapeutics, about the application of ADCs in cancer treatment. This article is based on that interview.

Bioconjugation Insights 2025; 1(1), 1–7 · DOI: 10.18609/bci.2025.001

TARGETED THERAPIES OVERVIEW: ADCS IN CANCER TREATMENT

The concept of targeted therapy originated over a century ago when Paul Ehrlich introduced the idea of 'magic bullets'.' His vision was to create therapies that selectively eradicate harmful pathogens while sparing healthy surrounding tissues. While this concept has persisted for decades, the development of truly selective therapies has been gradual and incremental. ADCs represent a step forward as they combine a monoclonal antibody that targets specific tumor antigens with a cytotoxic payload that delivers potent cell-killing agents directly to the tumor site.

ADCs, unlike chemotherapies—which are non-selective and can affect both cancerous and healthy cells—are designed to target antigens expressed on tumor surface cells selectively. This specificity surpasses conventional chemotherapies and radiation therapies by improving the therapeutic index and reducing off-target effects. Thus, ADC therapies have emerged as a potential pillar of cancer treatment.

CHALLENGES AND LIMITATIONS OF ADCS IN CANCER TREATMENT

ADCs are associated with significant safety concerns and limitations despite their targeted nature. One major limitation is their potential to cause off-target toxicities, largely due to the potency of their cytotoxic payloads—similar to chemotherapy agents. Some toxicities of ADCs overlap with those of traditional chemotherapy agents, including hematological toxicities where ADCs cause bone marrow suppression. This suppression can lead to neutropenia, thrombocytopenia, and anemia. These effects arise from ADC payloads targeting rapidly dividing cells, such as those in the bone marrow.

While these effects are not uncommon with chemotherapy, there are key differences in how they manifest with ADCs. Chemotherapy drugs typically have a shorter half-life and, do not remain in the body for extended periods. In contrast, ADCs are designed to remain in circulation longer due to their antibody-based nature and, as a result, can cause prolonged delayed or cumulative adverse effects.

In addition to these shared toxicities, ADCs can also cause unique target-related toxicities. These occur when the target antigen is expressed not only on tumor cells but also on healthy tissues. For instance, Padcev, a nectin-4-direct ADC approved for bladder cancer, is associated with skin toxicities as nectin-4 is also expressed on healthy skin cells. When the ADC binds to these cells, the toxic payload is internalized, leading to cell death and subsequent skin damage.

Other target-related toxicities include interstitial lung disease (ILD), which can occur if the target antigen is present in lung tissue, and ocular toxicities, which are observed with certain ADCs that target tissue factors expressed in eye tissues. The fact that ILD, skin toxicities, and ocular toxicities are all relatively uncommon in traditional chemotherapies serves to highlight the unique safety challenges posed by ADCs.

Despite these challenges, ADCs represent a significant step forward in targeted cancer therapy. Continued efforts to improve their selectivity, minimize off-target binding, and develop less toxic payloads are essential to maximizing their therapeutic potential while reducing adverse effects.

MANAGING ADC TOXICITIES: STRATEGIES AND MONITORING

Beyond hematological effects, ADCs are associated with various toxicities that require careful management. Lung toxicity, for example, can severely impair a patient's respiratory function if not promptly addressed. Peripheral neuropathy is another common adverse effect seen in treatment with ADCs containing microtubule inhibitors, such as auristatin-based payloads like MMAE. Even at lower grades (1 or 2), these toxicities can significantly impair a patient's motor function and overall well-being. Skin toxicities are also reported with ADCs and can further disrupt a patient's quality of life, particularly by interfering with daily activities and mobility.

The prolonged presence of ADCs in the body can exacerbate these challenges, making effective toxicity management essential. Ultimately, developing cancer therapies—whether ADCs, immune-oncology (I-O) agents, or chemo-radiation—involves striking a balance between

therapeutic benefits and the adverse effects patients must endure. While there is hope that advancements will one day eliminate the toxicities associated with ADCs, the current reality is that these complications remain an inherent part of their use. Therefore, balancing the benefits of extended survival against the potential decline in quality of life remains a key consideration in deploying ADC therapy.

Patient monitoring is a significant consideration in the safety management of ADCs and requires careful oversight by physicians to minimize toxicities and ensure optimal patient outcomes. For instance, if patients experience reactions such as shaking or discomfort during drug administration, pre-treatment with steroids can help reduce these reactions. Similarly, hematological toxicity-based neutropenia may require the administration of granulocyte-colony stimulating factors to increase neutrophil counts and prevent life-threatening infections like sepsis. Ocular toxicities, such as blurred vision, eye pain, or opacity, demand a tailored approach, including using steroid eye drops, improved eye hygiene, and regular monitoring to prevent further complications. Lung toxicities require equally vigilant management, with patients undergoing regular chest X-rays and pulmonary assessments to ensure normal lung function. In severe cases, treatment must be paused or discontinued until the patient recovers.

For some patients, particularly those with terminal cancer, the value of prolonged survival may outweigh the associated toxicities, especially if there are personal milestones they wish to achieve. However, for others, the preservation of quality of life may take precedence over extended survival. These decisions are deeply individual and require open communication between patients and their care teams. Ultimately, the role of safety physicians is not only to manage and mitigate toxicities but also to respect patients' individual needs and preferences, ensuring that the balance between treatment efficacy and quality of life is carefully maintained.

THE ROLE OF BIOMARKERS TO PREDICT SAFETY OUTCOMES

The role of biomarkers in predicting the safety outcomes of ADCs remains a challenging area with limited advancements. While some toxicities are relatively straightforward to monitor using measurable parameters such as neutrophil, erythrocyte, or platelet counts, predicting more complex toxicities like lung damage or peripheral neuropathy is far more complicated. For lung toxicity, few, biomarkers can reliably predict issues before the onset of clinical symptoms. Similarly, with peripheral neuropathy, the only reliable indicators are the physical symptoms, such as tremors, motor impairments, or difficulty walking. To date, no measurable protein, DNA marker, or other predictive biomarker has been identified to forecast such adverse effects.

This lack of predictive biomarkers is a significant gap in the safety management of ADCs. The uncertainty surrounding existing biomarkers and their correlation with clinical outcomes is partly the challenge. Physicians may hesitate to rely on biomarkers to guide decisions, if the evidence linking a biomarker to toxicity is inconclusive. This cautious approach often results in a reliance on traditional symptom-based monitoring. For instance, lung toxicity might only be addressed after a patient presents with severe symptoms such as persistent coughing or hemoptysis, while peripheral neuropathy may not be managed until motor impairments or sensory changes become apparent.

Despite incremental progress in the field, the clinical application of safety biomarkers for ADCs remains limited. Predictive biomarkers could enable physicians to take preemptive action, such as

lowering the drug dose, pausing treatment, or discontinuing the therapy altogether for at-risk patients. These measures could prevent the onset of severe toxicities and allow treatment to resume once biomarker levels return to baseline or pre-study values. However, the pace of development and adoption of such tools has been slower than expected, leaving a significant unmet need in the safety management of ADC therapies.

The limited progress in developing safety biomarkers for ADCs appears to be influenced by both funding constraints and a degree of reluctance within the field. The biomarker field has faced significant challenges due to insufficient funding, particularly in the area of safety biomarkers. Identifying meaningful biomarkers requires extensive patient studies to establish clear correlations between biomarkers and clinical outcomes. Unfortunately, much of the focus remains on preclinical studies, which are often not the most effective means of identifying reliable safety biomarkers, thus hindering advancements.

While some progress has been made in identifying biomarkers for tumor efficacy—such as circulating tumor-specific DNA and other soluble markers for tumor growth—safety biomarkers have not received the same level of attention or investment. There is a greater level of acceptance for efficacy biomarkers as they directly correlate with treatment success. However, the development and adoption of safety biomarkers has lagged considerably. Over the past several decades, there has been little innovation, with much of the field relying on traditional approaches to toxicity monitoring rather than exploring novel biomarkers.

A lack of academic funding to support biomarker research, as well as limited interest from pharmaceutical companies in prioritizing safety biomarkers, plays a role in this gap. Companies may focus more on efficacy-related biomarkers that can demonstrate the therapeutic potential of a drug rather than investing in safety biomarkers, which may not yield immediate financial benefits. Ultimately, this combination of inadequate funding, limited academic focus, and a lack of prioritization by industry has slowed progress, highlighting the need for a more concerted effort to advance safety biomarker research.

INTEGRATING THE LATEST SAFETY DATA AND MITIGATION STRATEGIES FOR ADCS INTO CLINICAL PRACTICE

In recent years, prominent oncology conferences such as the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) have presented encouraging data on managing safety events associated with ADCs. These advancements reflect a growing recognition of the importance of addressing and minimizing toxicities that can jeopardize clinical trials or the approval of ADC therapies, particularly in areas such as lung, skin, and gastrointestinal toxicities.

Efforts to integrate safety data into clinical development have become more robust, focusing on preventative strategies, patient education, and patient monitoring. For example, educating patients to report side effects promptly is critical, as patient-reported symptoms often serve as the first indication of an emerging issue. If a patient reports feeling significantly more fatigued post-treatment compared to pre-treatment or if they experience new symptoms such as blurred vision, it is essential to respond swiftly to manage these adverse effects. Addressing such symptoms promptly not only preserves the patient's quality of life but also helps ensure continued adherence to the treatment regimen.

The integration of safety measures in clinical trials has also become increasingly evident in adopting standardized protocols for adverse event monitoring and

management. For instance, companies are more consistently incorporating mitigation strategies such as preemptive treatments for infusion reactions, ocular toxicities, and skin-related adverse effects. These measures are designed to enhance patient comfort and safety, reducing the risk of trial discontinuation or poor patient retention.

However, while progress has been made, these practices remain inconsistent across the industry. Some companies are more proactive than others in prioritizing patient safety and integrating comprehensive safety protocols into their clinical programs. Without these measures, patients may discontinue treatment due to unmanageable side effects, such as severe infusion reactions, debilitating skin toxicities, or other issues that significantly impair their quality of life.

While there has been a significant shift towards better integration of safety data and mitigation strategies in clinical practice, there is still room for improvement. Continued efforts to educate both clinicians and patients, alongside the adoption of proactive safety management protocols, are essential to advancing the safe and effective use of ADCs in cancer treatments.

ADVANCEMENTS TO ENHANCE ADC SAFETY PROFILES

One of the key areas of improvement to advance the safety profiles of ADCs lies in using less-potent cytotoxic payloads. Historically, ADCs have relied on highly potent payloads to achieve efficacy, but these can cause severe adverse effects if even small amounts are prematurely released into circulation. A shift toward using less-potent yet still effective payloads is underway, with some companies demonstrating that strong therapeutic outcomes are possible without relying on highly potent cytotoxins. This approach reduces the risk of systemic toxicity while maintaining the efficacy of the treatment.

Improvements in linker technology also represent a major advancement in ADC safety. The linker is crucial in ensuring the drug's stability and targeted release. Enhancements in linker design have focused on creating stronger, more reliable linkages that prevent the premature release of the payload in circulation. A more robust linker ensures the cytotoxic payload is released only within the tumor environment, minimizing exposure to healthy tissues and reducing off-target toxicities.

Advancements in antibody targeting have improved the specificity of ADCs. Through refined antibody engineering, researchers are developing ADCs that deliver their payload more selectively to tumor cells while sparing healthy tissues. This increased specificity enhances it and reduces collateral damage, thereby improving the overall safety profile.

However, despite these advancements, it is unlikely that the toxicities associated with ADCs can be entirely eliminated. The mechanism of ADCs inherently involves the destruction of tumor cells, which can result in the release of cytotoxic payloads into the circulation. This physiological process makes it unrealistic to expect a toxicity-free ADC. However, by optimizing the design and engineering of ADC constructs—including the payloads, linkers, and antibodies—researchers can significantly mitigate adverse effects.

The future of ADC development will likely focus on fine-tuning these elements to achieve a balance between efficacy and safety. While eliminating toxicity may not be feasible, ongoing innovations pave the way for safer, more tolerable ADC therapies that offer patients both improved outcomes and a better quality of life.

One of the most promising areas of advancement in the field of ADCs is their combination with I-O therapies, particularly agents such as PD-1 and PD-L1 inhibitors. These checkpoint inhibitors have become widely used in cancer treatment,

especially in countries where affordability allows broad patient access. Combined with ADCs, these therapies show promising activity and potential for improved outcomes, as they leverage complementary mechanisms to target and destroy cancer cells effectively.

However, these combinations also pose significant challenges, particularly concerning toxicity. In some cases, the addition of I-O agents to ADCs can enhance the overall toxicity profile, complicating treatment and potentially impacting the patient's quality of life. This raises critical questions about how to strike the right balance between extending survival and preserving a manageable safety profile for patients.

The combination of ADCs with other targeted therapies and agents is likely to become increasingly common. While these combinations hold great promise for advancing cancer care, they also introduce new complexities in managing adverse effects. Ensuring that patients live longer and maintain a good quality of life will remain a central concern. As the field evolves, addressing these challenges through robust safety management strategies and ongoing innovation will be crucial to optimizing the therapeutic potential of these groundbreaking combinations

BIOGRAPHY

Rakesh Dixit is an accomplished executive, inventor, and scientist with over 35 years of success with top biotechnology and pharmaceutical companies, including Merck, Johnson & Johnson, MedImmune and AstraZeneca. He is President and CSO of Regio Biosciences and Bionavigen, LLC. He is a board member of Regio Biosciences and a key member of multiple scientific advisory boards for ADC companies. Dr Dixit is also a chief adviser and consultant for over 20 companies worldwide. From 2006–2019, Dr Dixit was a Global Vice President of the Biologics R&D at MedImmune-AstraZeneca. He has unique expertise in developing biologics (e.g., monoclonal antibodies, bispecific biologics, antibody-drug conjugates, fusion proteins, peptides, gene and cell therapies, etc.) and small-molecule biopharmaceuticals. Dr Dixit conducted extensive graduate and post-graduate training in pharmacology/toxicology–biochemistry with both Indian and USA Institutions (e.g., Case Western Reserve University, Medical College of Ohio, University of Nebraska) and is a Diplomate, Board Certified in Toxicology from the American Board of Toxicology, Inc. since 1992.

Rakesh Dixit PhD DABT, Cofounder, President and CSO, Regio Biosciences, Rockville, MA, USA, and Bionavigen, LLC, Gaithersberg, MD, USA

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author has no conflicts of interest.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

ARTICLE & COPYRIGHT INFORMATION

Article source: Invited. This article is based on an interview.

Revised manuscript received: Feb 12, 2025.

Publication date: Apr 25, 2025.

BIOCONJUGATION INSIGHTS

LAUNCH ISSUE

SPOTLIGHT

Addressing the shortfalls of LNP-based delivery with conjugate modalities

VIEWPOINT

"Good products are born of good science, and good science takes time, patience, and vision."

On April 4, 2025, Lauren Coyle, Launch Commissioning Editor, *Bioconjugation Insights*, spoke to **Moein Moghimi**, Professor of Pharmaceutics and Nanomedicine, Newcastle University and Adjoint Professor, Skaggs School of Pharmacy, University of Colorado Anschutz Medical Campus, about the evolution of conjugates to overcome lipid nanoparticle limitations. This article is based on that interview.

Bioconjugation Insights 2025; 1(1), 35–39 · DOI: 10.18609/bci.2025.007

EVOLUTION AND CHALLENGES OF LIPID NANOPARTICLES (LNPs) IN THERAPEUTIC DELIVERY

LNPs have played a transformative role in vaccine development, particularly during the COVID-19 pandemic, and their success has propelled interest in their broader applications, such as for genetic vaccines targeting infectious diseases and cancer. However, their effectiveness as a delivery vehicle for therapeutics remains hampered by several significant challenges.

Key distinction between vaccines and therapeutics are differences in dose and the desired immune response. LNPs exhibit a

pro-inflammatory effect, largely due to ionizable cationic lipids that act as adjuvants. This can be beneficial in vaccination but problematic in therapeutic settings where inflammation must be minimized. This is especially concerning for sensitive tissues or inflamed organs, where repeated—and considerably larger—dosing may trigger systemic toxicity and immune activation.

LNPs also suffer from limited targetability. Systemically administered LNPs are primarily cleared by the liver and spleen, reducing delivery efficiency to other tissues. While engineering with surface ligands can improve specificity, their performance is often inconsistent. Additionally, LNPs suffer from heterogeneity. Their formulations often include multiple particle populations, some with lipid bilayers and others without, resulting in unpredictable biological responses. This variability contributes to instability in blood circulation and complicates control over biodistribution. Products such as ONPATTRO® have revealed such issues through poor stability in the blood and infusion reactions, linked to the complement system.

Moreover, the mechanism of intracellular delivery is still poorly understood, particularly endosomal escape to release cargo into the cytoplasm. Without a solid understanding of this critical step, optimizing LNPs for therapeutic delivery remains speculative and assumption-driven. This knowledge gap limits the rational design of effective LNPs. While artificial intelligence (AI) has been employed to design better ionizable lipids, the underlying models are often based on incomplete or flawed biological assumptions, potentially perpetuating rather than solving core problems.

CONJUGATES AS A TARGETED AND CLINICALLY VALIDATED ALTERNATIVE TO LNPS

In contrast to LNPs, conjugate-based delivery systems have a long history of clinical success and increased targeting capabilities. ADCs, for example, emerged over 40 years ago and now include over 15 FDA-approved therapies, primarily for oncology. Despite early toxicity concerns, advancements in conjugation chemistry have resolved many of these issues, allowing for safer and more effective therapies.

Conjugates, particularly peptides and proteins, offer intrinsic biological specificity. Contrary to the notion that protein and peptide conjugates have been overlooked, these modalities have long been embedded in the therapeutic arsenal. These molecules naturally recognize and bind to receptors on cell surfaces, enabling precise targeting without the need for additional ligands, unlike LNPs, which often rely on conjugated ligands to achieve comparable specificity.

An example of conjugate innovation is the NanoLigand and NanoBlock Carriers. These self-assembled peptide conjugates form core-shell nanoparticles that exploit specific receptors on the blood-brain barrier (BBB), enabling them to bypass the barrier and deliver therapeutic molecules such a nucleic acid medicines to the brain within minutes of intravenous injection. They deliver nucleic acids such as siRNA directly to neurons and microglia, achieving effective gene silencing with minimal toxicity, without triggering immune responses typical of LNPs. These properties make them especially suited for neurological disorders, including pediatric rare diseases.

PEGylated proteins are another mainstay in therapeutic delivery. Although the emergence of anti-PEG antibodies has led to challenges, including clinical trial setbacks and market withdrawals, PEGylation continues to enhance drug stability and circulation time. New alternatives, such as albumin-based scaffolds, are under investigation to circumvent PEG-related immunogenicity while leveraging the body's natural recycling pathways via the neonatal Fc receptor (FcRn).

ADDRESSING DEVELOPMENTAL AND CLINICAL HURDLES IN CONJUGATES

Despite their advantages, conjugates face their own developmental challenges. Bioavailability remains a central issue, particularly for agents with poor natural absorption or distribution. While conjugation can enhance these properties, limitations often persist.

Stability is equally critical. The effectiveness of a conjugate depends on the chemistry of the conjugation process and the choice of linker. Poor stability of conjugates can cause premature degradation while undermining efficacy. However, ongoing advances in chemical methodologies are helping to improve both stability and performance.

The development of conjugates also demands a significant investment of time and resources. Research into new conjugate systems is inherently time-intensive, as it requires a comprehensive understanding of both chemical behavior and biological interactions. For example, while LNPs and cancer nanomedicines have benefited from accelerated product development timelines, this speed has often come at the cost of fully understanding fundamental mechanisms. This lack of understanding can hinder optimization efforts and affect long-term success. In contrast, conjugate development must balance thorough mechanistic insight with efficiency to create optimized and effective products.

Targetability remains another complex challenge. The ability of a therapeutic to selectively reach and act on a specific tissue or cell type is influenced by factors such as plasma half-life and systemic stability. As mentioned, strategies such as PEGylation have shown efficacy but can introduce new complications, such as the generation of anti-PEG antibodies. These immune responses can reduce therapeutic effectiveness and raise safety concerns, further emphasizing the need for careful formulation and long-term evaluation.

Additionally, the clinical development phase presents a substantial bottleneck. Many conjugate therapies progress slowly through clinical trials, limited by regulatory requirements and the need for extensive validation. This slow progression underscores the necessity for a systematic and meticulous approach to research and development. A robust understanding of past challenges—both technical and clinical—can inform better strategies and reduce the likelihood of repeating earlier mistakes.

Nevertheless, conjugates are simpler to manufacture and scale, offer better reproducibility, and shelf life than LNPs. Challenges such as linker selection, maintaining potency without compromising specificity, and ensuring effective distribution across tissues require thoughtful optimization and robust mechanistic understanding.

BALANCING SCIENTIFIC RIGOR AND MARKET TRENDS

The recent surge of interest in LNPs following their pandemic-era success has drawn attention and funding away from other modalities such as protein and peptide conjugates. However, these systems have long played a vital role in modern medicine. The global market for PEGylated proteins, for example, is valued at approximately USD$ 2.4 billion and is expected to exceed USD$ 6 billion by 2034. Peptide-drug conjugates, including radioligand therapies, are also gaining momentum, with a current market valuation of USD$ 5 billion.

The field of drug delivery has historically cycled through phases of intense focus and reinvention. Liposomes, once the center of attention, have evolved through multiple technological waves. Conjugates are now experiencing similar momentum, with emerging innovations such as NanoLigand and NanoBlock Carriers offering multifunctional delivery systems.

Importantly, LNPs and conjugates are not mutually exclusive. Many LNP formulations incorporate conjugated elements, such as PEGylated lipids, to improve performance. As challenges with LNPs become more apparent, the integration of conjugate strategies may prove essential.

REFOCUSING THE FIELD TO PRIORITIZE THE DEVELOPMENT OF CONJUGATES

A recurring theme in therapeutic development is the need to prioritize mechanistic understanding over 'hype-driven' innovation. Accelerated product development, while valuable, must be grounded in biological insight. The rise and fall of cancer nanomedicine, culminating in the closure of major US research centers in 2020, serves as a cautionary tale. LNPs risk following a similar path if their limitations are overlooked in the pursuit of market success.

What is needed instead is a recommitment to fundamental research. The effectiveness of any therapeutic modality depends on a detailed understanding of biological mechanisms, pathophysiological processes, and systemic interactions. Designing a therapy without this insight often results in what some call the 'hit-and-hope' approach: adding targeting ligands or modifying a delivery system based on speculative benefit and then observing whether the outcome is favorable. Understanding disease mechanisms, biological interactions, and delivery pathways is critical. Only with this base can effective, safe, and sustainable therapies be developed.

Young researchers should be encouraged to engage in fundamental science, even if immediate results are lacking. Major breakthroughs, such as gene therapy and molecular diagnostics, emerged from decades of such work. A long-term, interdisciplinary perspective is essential to avoid repeating past missteps and to build a more resilient foundation for therapeutic innovation.

Accelerated development is not inherently flawed, but it must be supported by a solid base of evidence and understanding. Good products are born of good science, and good science takes time, patience, and vision. As the field matures, it must resist the temptation to chase fleeting trends and instead cultivate a sustainable trajectory based on thoughtful inquiry, interdisciplinary collaboration, and a long-term view of impact.

CONJUGATES AND THE FUTURE OF PRECISION MEDICINE

As the demand for precision medicine continues to grow, conjugate-based therapeutics are poised to play an increasingly central role in the future of targeted drug delivery. Technologies such as NanoLigand and NanoBlock Carriers combine active targeting, receptor-mediated transport, and cytoplasmic delivery, setting the stage for multifunctional precision therapeutics across formidable biological barriers such as the BBB.

Conjugates are particularly promising in addressing drug resistance in oncology, modifying cellular pathways, or inhibiting resistance-related enzymes. In chronic conditions such as diabetes and autoimmune disorders, peptide conjugates offer adaptable platforms with low toxicity and sustained efficacy.

Emerging strategies such as 'albumination'—utilizing albumin's natural FcRn interactions—are gaining attention as alternatives to PEGylation. Nanobody-based conjugates are also gaining traction due to their specificity, stability, and ease of production.

Therapeutic fusion proteins, capable of combining multiple biological functions, represent another exciting frontier. For example, fusion proteins integrating complement inhibitors can regulate immune responses while delivering drugs, offering solutions for autoimmune and inflammatory diseases.

Bioconjugation Insights 2025; 1(1), 35–39 · DOI: 10.18609/bci.2025.007

What unites these advancements is the critical need for detailed mechanistic insight. Ultimately, the future of conjugate-based therapeutics will be shaped by a combination of scientific vision, technological innovation, and, perhaps most importantly, patience. The development of robust, targeted therapies takes time and requires collaboration across disciplines and institutions. With continued investment in fundamental research and a commitment to scientific rigor, conjugates can revolutionize the treatment of a broad spectrum of diseases, from cancer and chronic illnesses to viral infections and beyond.

As the field continues to evolve, conjugates are not merely an alternative to existing technologies such as LNPs; they represent a versatile and powerful modality that could redefine the future of personalized medicine.

BIOGRAPHY

Moein Moghimi is a Professor of Pharmaceutics and Nanomedicine at the School of Pharmacy, Newcastle University, UK and an Adjoint Professor at the Skaggs School of Pharmacy, University of Colorado, Denver, USA. He is co-founder of SM Discovery Group Inc. and SM Discovery Group Ltd developing NanoLigand and NanoBlock Carriers for targeted therapeutic delivery across biological barriers, including the blood-brain barrier. He is widely published and reported in the press, and recognised for his extensive contribution to fundamental and translational research in nanomedicine and drug delivery, especially in mechanistic understanding of nanoparticle-mediated complement activation and adverse reactions, and as an inventor of many drug delivery systems for site-specific targeting.

Moein Moghimi, Professor of Pharmaceutics and Nanomedicine, School of Pharmacy, and Research Professor, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK; and Adjoint Professor, Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado-Denver Medical Center, Aurora, CO, USA.

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author is a member of the Advisory Board of SM Discovery Group (SMDG), of which he is the founder, and holds stock in SM Discovery Group Ltd and SM Discovery Holdings Inc. He is a named inventor on issued patents and patent applications on NanoLigand and NanoBlock Carriers.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

ARTICLE & COPYRIGHT INFORMATION

Article source: Invited. **Revised manuscript received:** Apr 23, 2025. **Publication date:** Aug 28, 2025.

LAUNCH ISSUE

SPOTLIGHT

Next-generation conjugates: small peptides to transform targeted cancer therapy

INTERVIEW

"Our mission is to extend the therapeutic index of toxic payloads that effectively target cancer."

Lauren Coyle, Launch Commissioning Editor, *Bioconjugation Insights*, speaks with **Michelle Morrow**, Chief Scientific Officer, Avacta, about a novel drug delivery platform that utilizes a small peptide with a capping group conjugated to a cytotoxic cancer drug. She discusses the advantages of the platform over traditional ADC therapies including the improved precision and safety of cancer treatment.

Bioconjugation Insights 2025; 1(1), 9–14 · DOI: 10.18609/bci.2025.002

Q Can you tell us a bit about your career, specifically your new role as CSO of Avacta?

MM My career has been dedicated to the discovery and development of innovative cancer therapies. I began with an academic research career, earning a PhD in immunology at Cambridge, followed by postdoctoral research into childhood leukemia. This research deepened my interest in cancer biology and its underlying mechanisms.

This approach enables the administration of higher drug concentrations directly to the tumor, enhancing efficacy while reducing systemic toxicity.

During my postdoctoral research on childhood leukemia at Great Ormond Street Hospital, I gained firsthand experience of the impact of cancer on patients and their families. Motivated by a desire to develop new medicines, I transitioned into the pharmaceutical industry which I have been a part of for nearly 18 years.

My industry career began at MedImmune, now part of AstraZeneca, where I worked primarily in immuno-oncology. I contributed to several significant projects, including the invention of Imfinzi, a PD-L1 checkpoint inhibitor. Subsequently, I joined F-star, a biotechnology company based in Cambridge, which provided the opportunity to work in a smaller, more agile environment while gaining insight into business operations. During my tenure, we successfully advanced multiple molecules from research into clinical trials.

I joined Avacta in 2024 and I was drawn to the company for several reasons. First and foremost is the pre|CISION® platform—a differentiated and versatile technology with significant potential, as approximately 90% of solid tumors express its target, presenting an unprecedented market opportunity. Our mission is to extend the therapeutic index of toxic payloads that effectively target cancer. The company is conducting Phase I clinical studies while simultaneously advancing a discovery engine and preclinical pipeline, which I found particularly compelling. Additionally, I am privileged to work alongside a team of passionate scientists dedicated to advancing these projects.

Q Could you describe the pre|CISION platform in more detail and how it works?

MM One of the key challenges in oncology is developing drugs that effectively target cancer cells while minimizing toxicity to patients. Many potent cancer therapies come with significant side effects which can hinder treatment efficacy and allow tumors to regrow. Avacta's pre|CISION technology addresses this challenge by utilizing a small peptide with an engineered capping group that binds in the groove of the fibroblast activation protein (FAP) enzyme, which can be seen in **Figure 1**. The pre|CISION peptide is then conjugated to a cytotoxic cancer drug.

In its intact form, the compound remains inactive and cannot enter cells, enabling systemic distribution without causing toxicity. When the conjugated molecule reaches the tumor, the peptide is cleaved by the enzymatic activity of FAP. This cleavage releases the payload from the pre|CISION peptide, allowing it to act specifically within the tumor. This approach enables the administration of higher drug concentrations directly to the tumor, enhancing efficacy while reducing systemic toxicity.

This technology has been applied to various anti-cancer drugs and consistent results have been observed such as potent cancer cell destruction dependent on FAP activity, leading to a broader therapeutic index. These findings have been validated in preclinical mouse models and are now being extended to additional payloads through our clinical and preclinical programs.

Q Could you tell me what makes FAP strongly attributed to cancer-associated fibrosis (CAF) and why this is so specific?

MM CAFs are non-cancerous cells within tumors, which are influenced by and can influence the tumor itself, creating the tumor microenvironment (TME). FAP is an enzyme expressed on the surface of fibroblasts, particularly at the interface between the tumor and the stroma, which can be seen in **Figure 2**. Additionally, it is present in >90% of human cancers. At Avacta, extensive research is being conducted into FAP expression in collaboration with Tempus AI. This collaboration has involved profiling over 160,000 human cancer samples to gain deeper insights into FAP's role in different cancer types.

The unique advantage of the pre|CISION platform is that it does not only bind to FAP but also leverages its enzymatic activity to release the cytotoxic drug. Avacta is currently the only company utilizing this mechanism to achieve tumor-specific drug activation, making CAFs a crucial component of both tumor biology and the effectiveness of pre|CISION medicines.

Q Could you tell me about the pharmacokinetic (PK) advantages you have observed with pre|CISION when compared to other drug conjugate platforms?

MM pre|CISION molecules are small molecule compounds, with the peptide consisting of only two amino acids. Unlike larger peptide-drug conjugates (PDCs), which can be recognized by the immune system, these micro-peptides are not recognized by immune cells, thus minimizing immunogenicity.

Phase I data from FAP-Dox (AVA6000), a FAP-doxorubicin PDC and the first of Avacta's pre|CISION medicines in clinical trials, has revealed four fundamental changes. First is reduced plasma exposure, ensuring that the payload remains inactive in circulation and minimizing toxicity. Secondly, enhanced tumor exposure allows for more effective drug delivery, with biopsy data from our Phase 1 clinical trial showing a median 100-fold concentration difference between tumors and blood. This is more than what would be expected of an ADC which have reported a three to eight-fold difference. The third and fourth are a reduced volume of distribution and an extended half-life of the released doxorubicin. This lowers active payload exposure in normal tissues and ensures prolonged drug retention in tumors, improving both safety and efficacy through overall reduced cytotoxicity.

The four fundamental changes are based on results seen with FAP-Dox (AVA6000), but this can be applied with other cytotoxic drugs or targeted therapies. Overall, these PK advantages enable a safer, more targeted approach compared to ADCs and traditional chemotherapy.

The unique advantage of the pre|CISION platform is that it does not only bind to FAP but also leverages its enzymatic activity to release the cytotoxic drug.

FIGURE 1

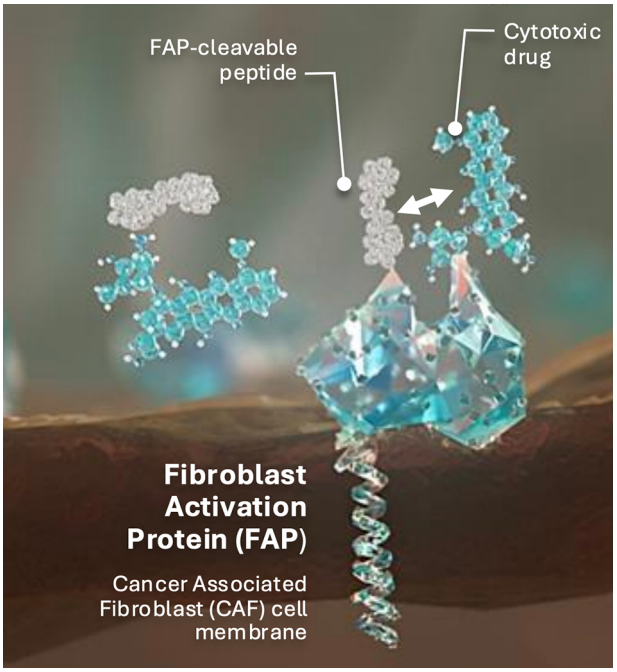
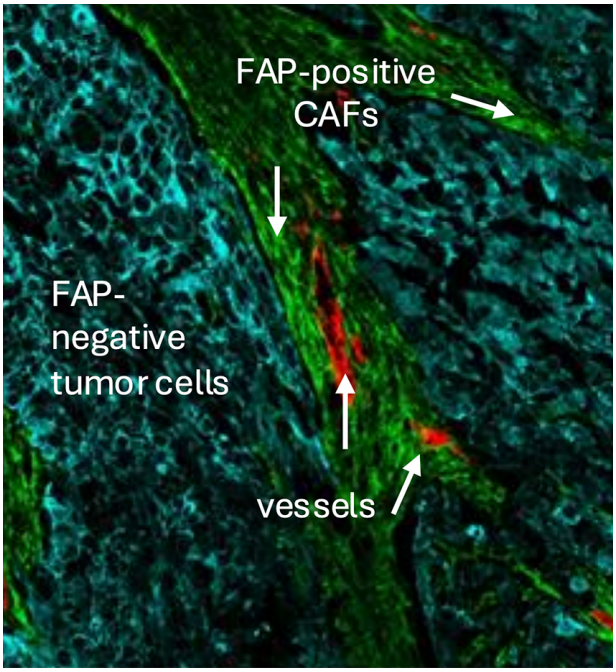


FIGURE 2



Q What have you learned so far from the preclinical and clinical trials about the potential advantages of the pre|CISION platform?

MM **It is exciting to see that these PK differences have also been translated into meaningful clinical outcomes.** One of the most promising findings is the improved safety profile of pre|CISION molecules. These have resulted in a reduction of the toxicities typically associated with chemotherapy, providing clinical validation of the platform. Additionally, early clinical data from our Phase I trials have shown encouraging efficacy signals in tumor types known to be sensitive to doxorubicin. As a result, we are now expanding into Phase Ib cohorts to further investigate these effects, particularly in salivary gland cancer and triple-negative breast cancer.

Another exciting development at Avacta is the FAP-Exatecan project. Exatecan (EXd) is a potent cytotoxic agent and a type I topoisomerase inhibitor, a class of molecules that has already been successfully used in ADCs. The preclinical trials for this project have just been completed and showed highly promising results. Since delivering this class of cytotoxic drugs to tumors has proven effective in patients, there is great potential for the FAP-EXd molecule, AVA6103.

In our preclinical mouse tumor models, FAP-EXd (AVA6103) has demonstrated remarkably strong responses, including complete tumor regression at well-tolerated levels. The molecule has been shown to be tolerated at doses up to 75 times higher than conventional EXd alone. This suggests a significantly improved therapeutic window, giving us confidence in its potential clinical benefits. We are now initiating IND-enabling studies for this program and are eager to move it forward, as we believe it could have a transformative impact on patient treatment in the future. We anticipate the Phase 1 trial beginning in the first quarter of 2026

Bioconjugation Insights 2025; 1(1), 9–14 · DOI: 10.18609/bci.2025.002

Q Overall, what are the main differences between PDC and traditional ADCs, and what advantages and/or challenges have you seen so far?

MM The platform shares common goals with ADCs, aiming to deliver toxic drugs to tumors while minimizing side effects. However, the two differ significantly in their molecular composition. The pre|CISION molecules are small, allowing for better tumor penetration compared to antibodies. This enhanced penetration can potentially lead to higher drug concentrations in tumors than what is achievable with conventional ADCs.

There are some key advantages of pre|CISION PDCs over conventional ADCs. Avacta has the ability to fine-tune the kinetics how the cytotoxic payload is released in a FAP-dependent manner. For instance, with AVA6103, modifications to the technology were introduced by incorporating additional linker groups, which enables the control rate at which FAP cleaves the molecule to achieve a sustained release of EXd in the tumor microenvironment.

pre|CISION molecules also exhibit a bystander effect as the warheads are released in the TME rather than inside individual cancer cells. This means that they can effectively kill neighboring cancer cells unlike conventional ADCs, which rely on antigen expression on tumor cells for direct intracellular delivery. ADCs also face challenges related to resistance, which may be a limitation of their mechanism of action.

Immunogenicity is another major consideration. Antibodies inherently carry the risk of triggering anti-drug antibody responses, which can impact both the efficacy and PD of the drug while causing side effects for patients. With pre|CISION, this is not a concern as it does not involve antibody-based delivery.

Finally, from a manufacturing perspective, the platform benefits from small-molecule synthesis, which is significantly less expensive and time-consuming compared to the complex production processes required for ADCs. This streamlined manufacturing allows for a more rapid transition from research to clinical application. While there are similarities between pre|CISION and ADCs, the differences present clear advantages that we believe make it a highly promising platform.

Q Finally, what are your overachieving goals for the next year or two?

MM My primary focus is advancing the FAP-Exatecan program (AVA6103) through IND-enabling studies. We aim to submit the IND later in the year and initiate clinical trials in early 2026, marking a significant milestone for Avacta. Additionally, we are expanding our discovery efforts to explore new payloads that could be optimized using the platform.

We are also refining the technology to enhance its performance further. Looking ahead, we are excited to continue generating clinical data with key data readouts from our Phase 1b cohorts in 2025. It will be an exciting few years for Avacta and we look forward to sharing further progress.

BIOGRAPHY

Michelle Morrow is the Chief Scientific Officer at Avacta Therapeutics, a biotech company focused on developing cancer treatments using its pre|CISION® peptide drug conjugate platform. Previously, Morrow was SVP and Head of InvoX Therapeutics Innovation at InvoX Pharma, after its acquisition of F-star Therapeutics. At F-star, she led teams that advanced several bispecific antibody therapeutics from discovery to clinical trials. Earlier, she held leadership roles at Medimmune (AstraZeneca), where she contributed to the development of Imfinzi® (an approved anti-PD-L1 antibody) and volrustomig (an anti-PD-1/CTLA-4 bispecific antibody). Morrow earned a PhD in Immunology from the University of Cambridge, Cambridge, UK and conducted post-doctoral research on childhood leukemia at the Institute of Child Health in London.

Michelle Morrow PhD, Chief Scientific Officer, Avacta Therapeutics, London, UK

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author has no conflicts of interest.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

ARTICLE & COPYRIGHT INFORMATION

Article source: Invited.

Revised manuscript received: Mar 21, 2025.

Publication date: Apr 25, 2025.

BIOCONJUGATION INSIGHTS

LAUNCH ISSUE

SPOTLIGHT

Harnessing peptide conjugates strategies for cancer immunotherapy and infectious disease

INTERVIEW

"Early engagement with regulatory bodies is essential to clarify how peptide conjugates will be evaluated."

Lauren Coyle, Launch Commissioning Editor, *Bioconjugation Insights*, speaks to **Helen Bright**, CSO, Centauri Therapeutics, about an immune-stimulating platform that leverages peptide conjugation to enhance immune responses. She discusses the challenges and advantages of this conjugate platform, from achieving regulatory body approval to therapeutic efficacy.

Bioconjugation Insights 2025; 1(1), 15–19 · DOI: 10.18609/bci.2025.003

Q Could you tell me a bit about what you're currently working on?

HB I am the Chief Scientific Officer at Centauri Therapeutics, where I oversee the scientific development of our immune therapy Alphamer® platform and progression of its lead program. The platform leverages natural anti-sugar antibodies that are inherently present in the human body. These antibodies are polyclonal, exhibit high titers, and are profusely distributed throughout all tissues.

Centauri's technology is based on a conjugation platform, incorporating a binding moiety at one end, which targets the intended site, and a conjugated sugar at the other. This

sugar facilitates the recruitment of anti-sugar antibodies, thereby activating Fc immune functions such as complement-mediated killing and phagocytosis. Between the binding moiety and the effector sugar, proprietary linkers are strategically designed to optimize balance based on the conjugation context.

Q Could you explain the key differences in conjugation when working with peptides compared to larger molecules and are there any specific advantages?

HB **The binding moiety of the platform varies depending on the application.** In our lead program, it is a cyclic peptide, however, depending on the target, monoclonal antibodies (mAbs) and antigen-binding fragments (Fabs) can also be utilized. Considerable attention is given to linker design as its purpose differs between large biologics and smaller peptides. For larger biologics, such as mAbs and Fabs, the linker's primary role is to maximize the number of rhamnose sugars that can be attached, thereby increasing the drug-to-antibody ratio (DARs). In this context, the linker ensures optimal rhamnose display while maintaining surface exposure to anti-rhamnose antibodies.

In contrast, when conjugating smaller molecules such as peptides, the linker must maintain the physicochemical balance of the entire molecule. Peptides often possess specific charges and some degree of lipophilicity, whereas the effector sugar is more polar. Consequently, linkers are designed to preserve binding affinity and overall molecular stability. Unlike larger biologics, where linker chemistry is more standardized, peptide conjugation requires greater customization due to its influence on molecular properties.

The primary advantage of our technology for peptide conjugation lies in the nature of the rhamnose effector moiety. Unlike traditional bioconjugations that involve cytotoxic payloads, rhamnose is a stable, non-toxic, and polar molecule, making it significantly easier to handle chemically at scale. Rhamnose conjugate manufacturing is relatively straightforward compared to the cytotoxic payloads of traditional ADCs, which require stringent production conditions and higher costs.

Q What regulatory and/or commercial challenges have emerged in peptide conjugation research and development following advancements in ADC regulatory approvals?

HB **The regulatory landscape is constantly evolving.** While agencies have well-defined guidelines for ADCs and synthetic peptides—which can be viewed as small molecules—peptide conjugates occupy a regulatory gray area, borrowing requirements from both ADC biologics and small-molecule drug classifications. Early engagement with regulatory bodies is essential to clarify how peptide conjugates will be evaluated.

Regulatory agencies often assume that linkers are designed for payload release, which directly impacts toxicological assessment. For our platform, however, linkers are non-cleavable and stable, meaning the molecule behaves as a single entity rather than a payload-releasing conjugate. In such cases, regulatory expectations shift toward metabolite analysis and small-molecule pharmacokinetics rather than traditional ADC assessments.

Bioconjugation Insights 2025; 1(1), 15–19 · DOI: 10.18609/bci.2025.003

Q How does your immune stimulatory platform differ from traditionally linked chemistry found in other conjugates, such as ADCs, and what are the key advantages?

HB **One of the fundamental differences of the platform is its stable, non-cleavable linker design.** Unlike ADCs, where linkers are engineered to release cytotoxic payloads inside target cells, our approach maintains molecular integrity. This stability enables our platform to align with established small-molecule regulatory guidelines, focusing on metabolic and clearance studies rather than fragmented component analysis.

Another major difference is the retention of our effector molecule at the cell surface. Our targeting moieties function solely as high-affinity binders. We prioritize stable conjugation that ensures the effector sugar remains exposed on the cell surface. In contrast, ADC linkers are typically designed to conceal their toxic payloads within antibodies and release is triggered at the cell surface or even within the cell. The stable nature of our linkers allows for a fundamentally different immune activation strategy, leveraging surface-bound effector molecules rather than intracellular payload release.

Q Further, what are the key challenges associated with developing an immune stimulatory peptide conduit?

HB **Developing an immune-stimulatory platform introduces specific challenges, particularly with respect to immune safety risks.** Any drug designed to enhance immune responses requires a rigorous and extensive immunotoxicity assessment. Key considerations include the selection of appropriate nonclinical species and the development of tailored immunotoxicity assays. Unlike conventional immunotherapies that modulate T cell activity, our mechanism operates earlier upstream than the T cells, engaging complement pathways and neutrophils. As a result, standard immunotoxicity assays require modification and advice from regulatory agencies to accurately evaluate immune safety in relevant assays for our platform's mode of action.

Additionally, regulatory requirements mandate the evaluation of anti-drug antibodies (ADAs), even for small peptides. ADA assessments extend beyond the peptide itself to include linker components, necessitating comprehensive immunogenicity studies despite the molecule's relatively small size.

Q What challenges exist in peptide conjugate R&D for infectious diseases compared to an oncology setting?

HB **Infectious disease research presents significant challenges, particularly due to the complexity of bacterial cell surfaces.** Unlike human cells, bacteria have complex and highly variable membranes, often featuring two layers packed with components such as peptidoglycan, lipid A, and dense layers of lipopolysaccharides. These unique structural features make bacterial surfaces difficult to target effectively.

As the field continues to evolve, innovations in conjugation chemistry will be essential to fully harness the potential of smaller biologics in both oncology and infectious disease applications.

Additionally, bacteria are highly adept at immune evasion as their rapid replication enables them to quickly evolve resistance mechanisms. Many bacterial species deploy immune evasion strategies, such as inhibiting complement activation and releasing decoy membranes to misdirect neutrophils, making them formidable adversaries in drug development. However, we believe that our immunostimulatory mechanism will tip the balance back in favor of the host.

By contrast, tumor cells present a more stable and predictable landscape for targeting. The oncology field benefits from well-characterized tumor-associated antigens and the availability of high-affinity binders like monoclonal antibodies. Many of these targets have been clinically validated, making them more accessible for drug development. However, tumors pose a different set of challenges, particularly in terms of penetration. Tumors often exist in immune-suppressed environments, which lack immune surveillance and are difficult to treat.

As mentioned, one of the key advantages of our mechanism is its ability to work upstream of T cells, potentially converting cold tumors into 'hot' tumors by activating complement pathways and releasing pro-inflammatory chemokines. This process recruits neutrophils and macrophages, leading to tumor cell destruction and subsequent antigen release, which can enhance T-cell responses.

From a drug development perspective, the field is shifting from traditional mAbs toward smaller formats such as Fabs, single-domain antibodies (VHHs), and peptides. This transition introduces new pharmacokinetic considerations, particularly regarding conjugation strategies. In smaller biologics such as Fabs and VHHs, cysteine engineering is commonly used for conjugation, but it can sometimes destabilize these molecules. A key area for advancement lies in developing new conjugation methods that preserve stability while enabling effective payload delivery.

Peptide conjugation, by contrast, is more straightforward as peptides can be synthetically designed with built-in conjugation sites. However, for smaller biologics, optimizing conjugation strategies remains a critical challenge. As the field continues to evolve, innovations in conjugation chemistry will be essential to fully harness the potential of smaller biologics in both oncology and infectious disease applications.

Q Looking towards the future, what are your key goals for the next year or two?

HB Our primary goal is advancing our lead molecule. A recent press release announced the selection of our clinical candidate, which is progressing through nonclinical development. Our goal is to achieve first-in-human trials by the end of this year. This milestone will not only validate our platform but also address a critical unmet need in broad-spectrum gram-negative bacterial pneumonia.

Beyond our lead program, we are focused on pipeline expansion. As a novel platform, our technology offers extensive therapeutic potential. Selecting the next indications for

development presents both an opportunity and a challenge, given the diverse applications of our mechanism. Identifying the optimal pathways for future exploration remains a key strategic initiative.

BIOGRAPHY

Helen Bright is an esteemed immunologist with 30 years of experience in infectious diseases within the biopharmaceutical industry. As CSO, she leads the research and development for Centauri's Alphamer immunotherapy platform, guiding the company's pipeline programs which focus on indications within the anti-infectives space.

Prior to this, Bright held senior scientific and operational leadership positions at AstraZeneca, Pfizer, and GSK. Bright holds a PhD in Virology and Immunology from Newcastle University and is a Fellow of the Royal Society of Medicine.

Helen Bright PhD, Chief Scientific Officer, Centauri Therapeutics Ltd, Alderley Park, Nether Alderley, Cheshire, UK

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author is an employee of Centauri Therapuetics Ltd and a director at Bright Pharma Consulting Ltd.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

ARTICLE & COPYRIGHT INFORMATION

Article source: Invited.

Revised manuscript received: Apr 4, 2025.

Publication date: Apr 25, 2025.

BIOCONJUGATION INSIGHTS

LAUNCH ISSUE

SPOTLIGHT

Translating research into therapeutics: the future of ADCs in cancer therapy

INTERVIEW

"ADCs have demonstrated significant success in solid tumors, largely due to our deep understanding of tumor biology and target antigens."

Lauren Coyle, Launch Commissioning Editor, *Bioconjugation Insights*, speaks with **Yu-Tzu Tai**, Associate Director, ADC and Translational Research, Oxford Biotherapeutics about the advancements in ADC development for therapeutic use in multiple myeloma and solid tumors. She discusses future directions in overcoming resistance and off-target toxicity through novel targeting and combination strategies.

Bioconjugation Insights 2025; 1(1), 27–32 · DOI: 10.18609/bci.2025.005

Q You recently transitioned into your first industry role after spending your career in academic research. What motivated this shift, and how has your academic background influenced your current work?

Y-TT My transition from academia to industry was driven by several key factors. First, I wanted to broaden my impact by contributing directly to biotech

innovations. Industry is highly specialized in technological development, and working here allows me to play a more immediate role in advancing new products and therapies.

Second, resource availability and funding were considerations. In industry, projects are often better supported, whereas academia faces funding constraints despite having the benefit of research freedom. Third, I saw an opportunity for career growth. My experience at Dana-Farber exposed me to industry-academic collaborations aimed at translating biotech innovations into clinical applications. By moving into industry, I hope to bridge this gap and accelerate the development of novel therapeutics.

Work-life balance was also a factor, as industry roles tend to have more structured schedules. However, I remain committed to the competitive nature of this field, especially in areas such as ADCs.

My academic background brings a unique perspective to biotech, particularly in disease and target biology. By integrating this expertise with industry's technological strengths, I aim to help accelerate the development of innovative drugs for patients with unmet medical needs. This transition marks an important milestone in my career, allowing me to merge academic insights with industry-driven innovation while continuing to learn and adapt.

Q ADCs and multiple myelomas (MM) are advancing rapidly. What factors are driving this progress, and what do you see as the next major milestone?

Y-TT Currently, MM treatments have been heavily focused on bispecific T-cell therapies and CAR-T cell therapies. While bispecific antibodies may be off-the-shelf, ADCs are fully off-the-shelf therapies, requiring fewer logistical challenges. Looking ahead, the next generation of ADCs will likely be more personalized to enhance therapeutic efficacy and durability of response. Unlike CAR-T therapies, which require patient-specific manufacturing, ADCs offer broader accessibility, making them easier for cancer centers to implement.

Future advancements will continue to focus on targeted therapies, and ADCs align well with this approach. They reduce the non-specific toxicity associated with traditional chemotherapy while allowing for continued innovation in linker and payload technology. There is still significant room for improvement, leveraging discoveries from academic research to refine ADC design through medicinal chemistry, linker optimization, and payload development. These foundational studies will drive the next wave of ADC innovation.

A key goal is ensuring that newly developed ADCs succeed in clinical trials and ultimately receive regulatory approval to make them available to patients. Additionally, ADCs hold significant potential for combination therapies and not just in MM but also in solid tumors, which is my current area of focus. In myeloma, standard treatment already involves multiple drug combinations, and ADCs have characteristics that make them strong candidates for integration into these regimens. Their ability to function like small molecules while also inducing immune-mediated effects provides a compelling rationale for their inclusion in 'treatment cocktails'. The goal is to enhance patient outcomes and quality of life, particularly for those who are severely ill or immunocompromised, as the ADCs do not require the patients to have an effective immune system.

Bioconjugation Insights 2025; 1(1), 27–32 · DOI: 10.18609/bci.2025.005

If CAR-T and bispecific T-cell therapies have achieved such success, ADCs should also have a promising future. While challenges remain, ongoing advancements in ADC design, manufacturing, and clinical application suggest a bright future for this therapeutic approach.

Q Monomethyl auristatin F (MMAF) has shown specificity, cytotoxicity in in vitro studies, but it hasn't yet led to an approved drug. What challenges remain and bringing this technology to clinical use?

Y-TT My work with MMAF dates back to a publication in 2014. At the time, MMAF was a novel payload, following the development of monomethyl auristatin E (MMAE). Seattle Genetics—now part of Pfizer—pioneered both compounds, and early clinical trials demonstrated promising efficacy. However, despite this potential, MMAF, which induced even more specific anti-tumor effect than MMAE in MM, failed to gain FDA approval due to concerns about its ability to outperform the standard of care in clinical trials, as well as safety considerations.

Several challenges remain in bringing MMAF to clinical use, though significant progress has been made. One major issue identified during trials was ocular toxicity, an off-target effect that was not fully understood at the time. Over the years, through studies such as DREAMM-1, DREAMM-2, and now DREAMM-8, clinicians have developed better strategies for managing this toxicity, which has been a critical advancement.

Another challenge is drug delivery. To maximize therapeutic benefit while minimizing harm to healthy tissues, optimizing linker technology and antibody specificity is essential. Advances in delivery mechanisms could help ensure that MMAF reaches tumor cells more selectively, reducing off-target toxicity. Additionally, resistance mechanisms also pose a significant hurdle. Cancer cells continuously evolve, and one common resistance mechanism is the downregulation of target antigens, leading to reduced drug efficacy. Ongoing research is focused on understanding and overcoming these resistance pathways to enhance MMAF's long-term effectiveness.

Clinical trial design is another key factor. Determining the optimal dosing schedule, treatment duration, and patient selection criteria is crucial for maximizing efficacy while minimizing side effects. Advances in AI and genomics now allow for more precise patient stratification, which could improve trial success rates compared to earlier studies. Further, regulatory hurdles play a role as gaining FDA approval requires rigorous testing and extensive documentation to meet safety and efficacy standards. Navigating this regulatory landscape efficiently is essential for bringing MMAF to market.

Moving forward, improving targeting strategies and reducing off-target toxicities—potentially through combination therapies—will be critical. Lowering the required drug concentration while maintaining efficacy could also help mitigate side effects. With ongoing advancements in clinical trial design and cancer biology, I am confident that MMAF has the potential to be revived as a viable treatment option for MM and solid tumors. Ensuring that clinicians have access to a broader range of therapeutic options will ultimately improve patient care and outcomes.

Q In your work with solid tumors, ADCs have shown more success compared to other immunotherapies. What makes ADCs a more promising approach for solid tumors?

Y-TT ADCs have demonstrated significant success in solid tumors, largely due to our deep understanding of tumor biology and target antigens. For example, HER2 has been extensively studied, particularly in breast cancer, where high expression levels have made it a key therapeutic target. This foundational knowledge paved the way for the success of HER2-targeted therapies like Trastuzumab, Kadcyla (T-DM1), and Enhertu (T-DXd). Similarly, while EGFR-targeted therapies have been more effective with small molecules, ADCs targeting HER2 and other well-characterized antigens have shown great promise.

One critical factor contributing to ADC efficacy is target specificity. The antibodies used in ADCs can induce strong internalization upon binding, ensuring efficient drug delivery into cancer cells. While internalization remains a key mechanism for ADC function, newer technologies are emerging that allow ADCs to be effective even when internalization rates are lower. These advancements are expanding ADC applicability and driving further innovation.

Another important consideration in solid tumors is antigen heterogeneity. Unlike hematologic malignancies, where target expressions are often uniform, solid tumors exhibit heterogeneous antigen expression. This makes the bystander effect a key factor in ADC success. Achieving an optimal bystander effect can enhance ADC efficacy, particularly in bulky, tissue-based tumors where drug penetration is a challenge.

ADCs also offer a significant advantage over traditional chemotherapy by reducing systemic toxicity. Their targeted approach aligns with the early vision of monoclonal antibodies as 'magic bullets' capable of delivering treatment directly to cancer cells without harming healthy ones. Further, ADCs have demonstrated synergy with standard chemotherapy and immunotherapy. Beyond their direct cytotoxic effects, ADCs can modulate the immune system, enhancing anti-tumor immune responses. The success of ADCs such as T-DM1 (Kadcyla), T-DXd (Enhertu), and TROP2-targeting ADCs further reinforces their potential. The recent FDA approvals of new ADCs highlight their growing role in cancer treatment, providing potent and effective options with manageable toxicity profiles.

Ultimately, ADCs represent a promising approach for solid tumors, and continued advancements in linker technology, payload optimization, and drug penetration strategies will further enhance their clinical impact.

Q Ten years ago, you published a paper that focused on the therapeutic use of ADCs in MM, however, there were only a handful of clinical trials at that time. What has surprised you most about how the field has evolved since then?

Y-TT One of the most notable developments has been the evolution of B-cell maturation antigen (BCMA)-targeting ADCs, particularly belantamab mafodotin (Blenrep). As previously mentioned, ocular toxicity has been a distinct challenge with MMAF-based ADCs, and belantamab remains the only MMAF payload

ADC in myeloma to date. The drug was withdrawn from the market around 2022 following the results of the DREAMM-3 trial. However, the field has made significant progress in understanding how to better manage its side effects, and the latest DREAMM-8 trial results suggest renewed optimism.

A key learning from DREAMM-8 has been the ability to achieve comparable, or even improved, progression-free survival by adjusting dosing strategies. By reducing the drug concentration and extending the treatment cycle from three weeks to four weeks, researchers have found a way to maintain efficacy while improving the safety profile. These findings, presented at the American Society of Hematology Annual Meeting and discussed among leading clinicians, have fueled hopes of reintroducing belantamab to the market.

Looking ahead, once the challenges surrounding MMAF toxicity are addressed, there is strong interest in moving BCMA-targeting ADCs into earlier lines of treatment. The DREAMM-8 trial, which investigated belantamab (B) in combination with pomalidomide and dexamethasone (PD) —both standard-of-care agents— showed promising safety and efficacy results when compared to Velcade (bortezomib) combination (VPD). Given Velcade's pivotal role as the first proteasome inhibitor in MM treatment, seeing ADCs demonstrate comparable or improved outcomes is highly encouraging. This progress suggests that ADCs could soon be incorporated into earlier treatment settings, even following initial diagnosis.

In terms of future directions, personalization of ADC therapy is an exciting area of research. Technologies such as single-cell sequencing could help refine patient selection and optimize ADC treatment strategies. Additionally, novel payloads are emerging as potential alternatives to MMAF. For example, Heidelberg Pharma has developed a payload that inhibits protein translation, offering a distinct mechanism of action from traditional MMAF-based ADCs. This approach has shown promising results in Phase 1 trials, and another company has already developed a similar candidate with encouraging in vitro data.

Q Lastly, what do you hope will be the key breakthroughs in ADC fields over the next few years, specifically in overcoming challenges with off-target toxicity and resistance?

Y-TT One of the most critical challenges in ADC development, as mentioned, is preventing resistance. A common mechanism of resistance is the downregulation of target antigens, which reduces the drug's effectiveness. To address this, bispecific ADCs could offer a promising solution. Not only would this enhance tumor specificity, but it could also mitigate resistance by ensuring that the drug remains effective even if one target is downregulated.

Several clinical trials are already exploring bispecific ADCs, including those targeting prostate cancer and EGFR. The key challenge will be identifying the most effective antigen combinations, leveraging existing platforms such as HER2 and TROP2 as backbones while incorporating additional tumor-specific targets.

Additionally, an area of advancement that will hopefully see a breakthrough is the linker and payload technology. The stability of ADCs in circulation remains a challenge as premature payload release can contribute to off-target toxicity. Future research should focus on developing highly stable linkers that ensure payload release occurs exclusively within tumor cells. This could also lead to more homogenous ADCs, optimizing drug-to-antibody ratios for improved efficacy and reduced toxicity.

In terms of enhancing ADC effectiveness, combination therapies will play an essential role. In addition to the emerging class of protein translation inhibitors, researchers are now exploring immunomodulatory ADCs. For example, the STING pathway has been identified as a potential target for ADC payloads. STING agonists can activate the immune system, potentially creating a dual mechanism of action where ADCs not only kill tumor cells directly but also stimulate an immune response for a more sustained anti-tumor effect.

Personalized medicine will also be fundamental in refining ADC therapies. Biomarker-driven research can help identify which patients will benefit most from specific ADCs. For example, differentiating between HER2 and EGFR expression levels can guide treatment selection, ensuring that ADCs are used in the most responsive patient populations. Additionally, advancements in single cell sequencing and AI are already being utilized by major pharmaceutical companies to optimize target selection. AI and machine learning can help analyze vast datasets, pinpoint specific patient subsets, and refine clinical trial designs to develop more precise and effective ADC-based therapies.

BIOGRAPHY

Yu-Tzu Tai joined Oxford Biotherapeutics in 2022, bringing expertise in cancer and immune oncology research. Her translational work has led to FDA-approved therapies including small molecules (BTK, XPO1, IMiDs, PIs) and biologics (CD38, SLAMF7, BCMA). Tai has authored over 210 scientific articles and spent 25 years at Dana-Farber Cancer Institute, holding patent publications. She is a long-term member of AACR and actively serves on the editorial board of *Clinical Cancer Research*. At Oxford Biotherapeutics, she oversees ADC programs and preclinical studies for ongoing OBT076 trials while supporting external partnerships, all aimed at developing innovative immunotherapies for unmet medical need.

Yu-Tzu Tai PhD, Associate Director, ADC and Translational Research, Oxford Therapeutics, Inc., San Jose, CA, USA

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given his approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author has no conflicts of interest.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

ARTICLE & COPYRIGHT INFORMATION

Article source: Invited.

Revised manuscript received: Apr 15, 2025.

Publication date: Apr 25, 2025.

BIOCONJUGATION INSIGHTS

LAUNCH ISSUE: INDUSTRY INSIGHTS

SPOTLIGHT

Industry insights, April 2025

Lauren Coyle

Welcome to the first in this new article series, exclusive to the *Bioconjugation Insights* journal—Industry Insights!

These concise articles, published once per issue, will spotlight key updates in bioconjugation. They will cover the latest developments in collaborations, regulatory changes, marketing trends, and R&D in the field. Additionally, they will highlight key clinical trials, innovations in tools and technology, and notable conferences and publications.

Subsequent articles in the series will be contributed by our Editorial Advisory Board members.

Bioconjugation Insights 2025; 1(1), 21–26 · DOI: 10.18609/bci.2025.004

COLLABORATIONS AND PARTNERSHIPS

Partnership between WuXi and AbTis to advance next-generation ADC therapeutics with novel conjugation technologies [1]

On March 11, 2025 WuXi XDC, a global leader in CDMO for ADCs and XDC bioconjugates, has signed a Memorandum of Understanding (MOU) with AbTis, a South Korean biotechnology company specializing in ADCs. This partnership combines AbTis' proprietary AbClick® site-selective conjugation platform with WuXi XDC's integrated discovery, development, and manufacturing services to accelerate innovation in ADC therapeutics.

WuXi XDC will integrate AbClick, which employs affinity peptide-assisted linkers for precise and efficient antibody-drug conjugation, into its service offerings. Additionally, WuXi XDC will connect AbTis with its extensive global client network, expanding opportunities for collaboration and market growth. Both companies aim to enhance bioconjugate drug development, streamline CMC processes, and support clients in advancing next-generation ADC therapies.

GV20 Therapeutics and Mitsubishi Tanabe Pharma Corporation partner to develop first-in-class ADC using AI-driven antibody discovery [2]

GV20 Therapeutics (GV20), a clinical-stage AI-driven biotherapeutics company, has entered a strategic research collaboration with Mitsubishi Tanabe Pharma Corporation (MTPC) as of March 2025. MTPC will utilize GV20's proprietary antibodies, targeting

novel tumor antigens identified through its STEAD AI platform, to develop potentially first-in-class ADCs. This partnership with utilize MTPC's expertise in linker-payload technology and drug-development.

Under the agreement, GV20 will receive an upfront payment and is eligible for milestone payments. MTPC gains exclusive negotiation rights for licensing these antibodies during the collaboration period.

Frazier Life Sciences launches Callio Therapeutics with $187M in partnership with Hummingbird Bioscience to develop dual-payload ADCs [3]

Frazier Life Sciences launched Callio Therapeutics with $187 million in Series A funding to develop clinical data for a HER2-targeted, dual-payload ADC in an undisclosed cancer. The biotech is also working on a second ADC program, though details are not yet available. The financing round was supported by Jeito Capital, Novo Holdings A/S, Omega Funds, ClavystBio, Platanus, Norwest, Pureos Bioventures, SEEDS Capital, and EDBI.

Callio is led by Piers Ingram, CEO of Hummingbird Bioscience. The company has secured a global licensing deal to utilize Hummingbird's multi-payload ADC technology for oncology and other pipeline assets, in exchange for equity, potential milestones, and royalties.

MARKET TRENDS

WuXi XDC reports strong growth, big pharma partnering success, and capacity expansion plans [4]

WuXi XDC, a leading contractor, reported strong growth, partnering with 13 of the top 20 global pharmaceutical companies by 2023 revenue on projects at various stages. Last year, the company completed 177 integrated ADC projects and 17 broader bioconjugate projects. WuXi XDC is expanding its business with planned capacity increases in 2025 and 2027, along with a new manufacturing site in Singapore set to open by the end of the year. This site will include manufacturing lines for monoclonal antibody intermediates, drug substances, and products, as well as quality control labs and warehouse space. Although the company did not provide formal guidance for the remainder of 2025, CEO Jimmy Li expressed confidence that WuXi XDC will continue to attract customers and grow its market share.

RESEARCH AND DEVELOPMENT HIGHLIGHTS

Avidity's antibody-oligonucleotide conjugate, Del-zota, shows positive results in Duchenne muscular dystrophy [5]

Avidity Biosciences announced positive data from the Phase 1/2 EXPLORE44® trial of Del-zota, an antibody-oligonucleotide conjugate (AOC) for Duchenne muscular dystrophy (DMD) with exon 44 skipping (DMD44). The data demonstrated consistent, statistically significant improvements in dystrophin production, exon skipping, and creatine kinase levels, with favorable safety and tolerability across two dose cohorts. Del-zota significantly reduced serum creatine kinase levels to near normal after just three doses.

Del-zota targets the dystrophin gene using phosphorodiamidate morpholino oligomers (PMOs) to enable near-full-length dystrophin production. It has received Orphan Drug and Rare Pediatric Disease designations from the FDA. Avidity plans to submit a Biologics License Application (BLA) for Del-zota by year-end, based on these results and safety data from the ongoing EXPLORE44 Open-Label Extension trial.

MD Anderson researchers develop novel antibody-toxin conjugate to

stimulate immune-mediated tumor eradication [6]

Researchers at The University of Texas MD Anderson Cancer Center have developed a new antibody-toxin conjugate (ATC) aimed at stimulating immune-mediated tumor eradication. Unlike traditional ADCs, this ATC design triggers the immune system to attack tumors, potentially reducing side effects and preventing recurrence. It targets CD47, a protein that helps tumors evade immune detection, and delivers a bacterial toxin rather than chemotherapy. This prompts immune cells to engulf the tumor and release the toxin, activating tumor DNA and protein fragments which then help the immune system recognize and fight cancer more effectively.

In preclinical models of breast cancer and melanoma, this approach enhanced immune responses and provided long-lasting immunity, with T cells remaining active for up to two months. The team plans to expand this strategy to target other tumor-specific receptors, with clinical testing expected in the next 3-5 years.

Researchers at Mount Sinai develop blood-brain barrier-crossing conjugate for neurological disease treatment [7]

Researchers at the Icahn School of Medicine at Mount Sinai have developed a groundbreaking blood-brain barrier-crossing conjugate (BCC) system to deliver therapeutics into the brain, offering new treatment possibilities for neurological and psychiatric diseases. The BCC platform utilizes γ-secretase-mediated transcytosis to allow for the crossing of the BBB.

In preclinical studies, including mouse models and human brain tissue, the system successfully delivered large therapeutic molecules, such as oligonucleotides and proteins, directly into the brain through an intravenous injection. The BCC10 compound, linked to antisense oligonucleotides, reduced harmful gene activity in ALS and Alzheimer's disease models by silencing disease-causing genes. The treatment was well tolerated in mice, causing minimal organ damage. Further studies in large animal models are planned to expand its therapeutic potential.

CLINICAL TRIALS AND RESEARCH

OASIS project: a new European research program for enhancing ADCs [8]

The OASIS project is a European research initiative focused on advancing ADCs for cancer treatment, led by Dr Barbara Pistilli at Gustave Roussy. It aims to improve ADC selection for patients by adressing challenges such as resistance mechanisms and reducing toxic side effects.

OASIS addresses these challenges through multicentric clinical trials using advanced technologies, including nuclear medicine, digital pathology, liquid biopsies, and patient-derived organoids. Data collected will inform the development of a next-generation ADC to enhance efficacy and minimize resistance. A key outcome is the OASIS Score, an AI-based model combining clinical, biological, and radiological data to predict ADC effectiveness and toxicity, enabling more personalized treatment.

Launched in January 2025, OASIS unites 12 European partners and is funded by a €9.9 million Horizon Europe grant.

CONFERENCES, EVENTS, AND PUBLICATIONS

Data from Heidelberg Pharma's ADC technology platforms are to be presented at the AACR Annual Meeting 2025 [9]

Heidelberg Pharma AG, a clinical-stage biotech company specializing in ADCs, will

present its latest research on Exatecan-based ADC technology at the AACR Annual Meeting 2025 (Chicago, April 25-30).

Beyond its proprietary Amanitin-based ADCs, Heidelberg Pharma has developed an advanced ADC toolbox to overcome tumor resistance through multiple mechanisms, enabling targeted treatment across various cancer types.

Dr Sarah-Jane Neuberth will present preclinical findings on HDP-201, an Exatecan-based multimeric linker ADC (ETAC technology) for colorectal cancer. Results show strong target-specific potency, anti-tumor efficacy, and high tolerability.

Dr Pablo Ruedas Batuecas will highlight the role of computational modeling in optimizing NAMPT inhibitors (NAMPTi) as ADC payloads and as a mechanism of action. This novel approach could overcome current cancer therapy limitations by effectively targeting both dividing and non-dividing cancer cells.

Cantargia to present promising preclinical data on novel IL1RAP targeting ADC at AACR Annual Meeting 2025 [10]

Cantargia will present preclinical data on IL1RAP-targeting ADCs at the AACR Annual Meeting (April 25-30, 2025). These ADCs leverage IL1RAP expression in tumor cells and the TME to deliver cytotoxic drugs directly to cancer cells.

Preclinical studies demonstrated strong anti-tumor efficacy, safety, and tolerability of IL1RAP-targeting ADCs across multiple cancer models. The selected IL1RAP-binding antibody, conjugated to a tubulin-targeting cytotoxic payload, maintained binding specificity and induced IL1RAP-dependent tumor cell killing while effectively suppressing tumor growth in animal models.

Developed in collaboration with ImmunoGen (now part of AbbVie), IL1RAP ADCs are designed to selectively target IL1RAP-expressing cells, minimizing harm to healthy tissues. Cantargia aims to optimize and advance this technology for broader cancer applications.

SUMMARY

In March 2025, the ADCs field saw significant advancements and strategic collaborations aimed at enhancing cancer therapies. Notable partnerships included WuXi XDC's collaboration with AbTis to integrate the AbClick conjugation platform for improved ADC development, and GV20 Therapeutics' agreement with Mitsubishi Tanabe Pharma to develop novel ADCs targeting new tumor antigens. Additionally, Callio Therapeutics launched with $187 million in funding, aiming to develop multi-payload ADCs and leveraging Hummingbird Bioscience's technology.

In marketing trends, WuXi XDC reported strong performance in 2024 and announced the expansion of its operations and plans to build new manufacturing sites to support ADC production. In clinical advancements, Avidity Biosciences demonstrated positive results for its Del-zota ADC in treating DMD, while MD Anderson developed a new ATC that stimulates immune responses against tumors.

Meanwhile, the OASIS project in Europe is focused on optimizing ADCs for cancer treatment, addressing resistance and toxicity through advanced technologies like digital pathology and patient-derived organoids. These collaborations and innovations reflect a continued push toward more targeted, effective, and personalized therapies in the bioconjugation space.

Lauren Coyle is Launch Commissioning Editor of *Bioconjugation Insights*

REFERENCES

1. WuXi XDC. WuXi XDC and AbTis announce strategic partnership to advance next-generation ADCs. Mar 11, 2025. https://wuxixdc.com/wuxi-xdc-and-abtis-announce-strategic-partnership-to-advance-next-generation-adcs.
2. FirstWorld PHARMA. GV20 Therapeutics announces collaboration agreement with Mitsubishi Tanabe Pharma Corporation to develop novel antibody-drug conjugates. Mar 26, 2025. https://firstwordpharma.com/story/5945165.
3. Hummingbird Bioscience. Callio Therapeutics launches with US$187 million Series A to advance multi-payload antibody-drug conjugate platform through clinical proof-of-concept. Mar 3, 2025. https://hummingbirdbioscience.com/callio-therapeutics-launches-with-us187-million-series-a-to-advance-multi-payload-antibody-drug-conjugate-platform-through-clinical-proof-of-concept.
4. WuXi XDC. WuXi XDC achieved another remarkable year with extraordinary business performance and financial results for 2024. Mar 24, 2025. https://wuxixdc.com/wuxi-xdc-achieved-another-remarkable-year-with-extraordinary-business-performance-and-financial-results-for-2024.
5. Avidity Biosciences. Avidity Biosciences announces positive topline del-zota data demonstrating consistent, statistically significant improvements in dystrophin, exon skipping and creatine kinase in people living with Duchenne muscular dystrophy amenable to exon 44 skipping in Phase 1/2 EXPLORE44® trial. Mar 17, 2025. https://aviditybiosciences.investorroom.com/2025-03-17-Avidity-Biosciences-Announces-Positive-Topline-Del-zota-Data-Demonstrating-Consistent,-Statistically-Significant-Improvements-in-Dystrophin,-Exon-Skipping-and-Creatine-Kinase-in-People-Living-with-Duchenne-Muscular-Dystrophy-Amenable-to-Exon-44.
6. MD Anderson Cancer Center. MD Anderson researchers develop novel antibody-toxin conjugate. Feb 25, 2025. https://www.mdanderson.org/newsroom/md-anderson-researchers-develop-novel-antibody-toxin-conjugate.h00-159774078.html.
7. Mount Sinai. Study reveals new way to unlock blood-brain barrier, potentially opening doors to treat brain and nerve disease. Nov 25, 2024. https://www.mountsinai.org/about/newsroom/2024/study-reveals-new-way-to-unlock-blood-brain-barrier-potentially-opening-doors-to-treat-brain-and-nerve-diseases.
8. Gustave Roussy. OASIS, a new European research programme to optimise antibody-drug conjugates. Feb 6, 2025. https://www.gustaveroussy.fr/en/oasis-new-european-research-programme-optimise-antibody-drug-conjugates.
9. Heidelberg Pharma. Heidelberg Pharma to present data from its ADC technology platforms at AACR Annual Meeting 2025. Mar 26, 2025. https://heidelberg-pharma.com/en/press-investors/announcements/press-releases-and-ad-hoc-announcements/pr-heidelberg-pharma-to-present-data-from-its-adc-technology-platforms-at-aacr-annual-meeting-2025.
10. Cantargia. Cantargia presents promising preclinical results on a novel IL1RAP-targeting antibody-drug conjugate at AACR 2025. Mar 25, 2025. https://cantargia.com/en/press-releases/cantargia-presents-promising-preclinical-results-on-a-novel-il1rap-targeting-antibody-drug-conjugate-at-aacr-2025.

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given their approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author has no conflicts of interest.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

ARTICLE & COPYRIGHT INFORMATION

Article source: Lauren Coyle is Launch Commissioning Editor of *Bioconjugation Insights*,

Revised manuscript received: Apr 4, 2022.

Publication date: Apr 28, 2025.