INTERVIEW ARTICLE

Precision oncology released: How innovations in Antibody Drug Conjugate engineering are accelerating the development of smarter cancer therapeutics.

The cancer treatment landscape is undergoing a transformation as Antibody Drug Conjugates (ADCs) emerge as sophisticated "biological missiles" that deliver potent payloads directly to tumor cells while sparing healthy tissue. This rapidly expanding field faces complex challenges, from optimizing dual-payload designs and overcoming resistance mechanisms to developing robust screening methodologies that unlock their therapeutic potential.

In this interview with **Simon Scrace from Revvity's Preclinical Services team,** he discusses the cutting-edge innovations driving ADC development forward and how advanced screening technologies are reshaping the path from promising concepts to life-saving cancer therapies.

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Q What are Antibody Drug Conjugates and what are their main advantages?

A Antibody Drug Conjugates (ADCs) are rapidly emerging as one of the most promising tools in the fight against cancer, blending the precision of immunotherapy with the potency of chemotherapeutics. While traditional chemotherapeutics have long been the cornerstone of cancer treatment, their high cytotoxicity to normal cells limits their therapeutic window, often leading to severe side effects (Wang et al., 2023). ADCs promise a paradigm shift, offering a targeted approach that minimizes collateral damage to healthy tissues.

Often described as "biological missiles" for their precision delivery mechanism, ADCs consist of three core components: a monoclonal antibody that targets specific antigens on cancer cells, a cytotoxic payload that destroys those cells, and a chemical linker that provides payload stability until it reaches the intended target (Tao et al., 2025; Tsuchikama et al., 2024). This innovative design enables ADCs to selectively attack cancer cells while sparing normal tissues, a breakthrough in reducing systemic toxicity.

With 19 ADCs approved globally and over 200 under clinical evaluation targeting more than 50 antigens (biochempeg, 2025), ADCs represent a rapidly growing frontier in oncology drug discovery. Advances in ADC technology, such as bispecific antibodies, dual-payload ADCs, and improved linker chemistries, are further pushing the boundaries of therapeutic possibilities.

Selecting the right antigen is vital for ADC efficacy and safety. Ideal antigens, like HER2, TROP2, and EGFR, are overexpressed on cancer cells and undergo internalization upon antibody binding, ensuring payload delivery to the tumor while reducing off-target toxicity (Beck et al., 2017; Ruan et al., 2023; Tao et al., 2025).

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Moreover, payload optimization plays a critical role in determining antitumor activity and potential adverse effects (Tao et al., 2025). The majority of clinical ADCs utlize tubulin inhibitor payloads (e.g., MMAE, MMAF, DM1, and DM4). DNA damaging agents such as topoisomerase I inhibitors (e.g., SN-38) represent another promising option. These DNA damaging payloads offer the advantage of targeting both proliferating and non-proliferating cells, critical for combating resistant tumor populations.

Linkers are equally crucial, as they control when and where the payload is released (Senter, 2009). Multiple payload chemistries exist, each classified by their mode of cleavage, but the majority take advantage of the differential conditions between the intracellular environment and extracellular environment. For example, linkers that exploit the acidic intra-lysosomal environment ensure payloads remain stable in circulation but are effectively released upon internalization into target cancer cells (Bornstein, 2015). Furthermore, the payload's properties, such as permeability or hydrophobicity, can be tuned for optimal bystander killing effects or reduced off-target interactions (Beck et al., 2017).

These synergistic components make ADCs an exciting innovation, offering improved therapeutic indices, lower effective doses, and reduced systemic toxicity compared to traditional chemotherapeutics (Khongorzul et al., 2020).

Q What are the challenges for ADC development?

A Despite their promise, ADCs face significant challenges. For example, even highly successful ADCs like trastuzumab deruxtecan (Enhertu), co-developed by Daiichi Sankyo and AstraZeneca, are not universally effective. Patients can relapse, highlighting the need for further innovation (Mullard, 2025). One major hurdle lies in the development of resistance, as reliance on a single therapeutic agent may create selection pressure for resistant tumor populations (Dagogo-Jack and Shaw, 2018).

Combination therapies have shown promise in overcoming resistance, with small molecules being paired to enhance antitumor efficacy (Fanale et al., 2014; Younes et al., 2013). However, ADC combination therapies are more complex due to overlapping toxicities and pharmacokinetic differences, making simultaneous delivery of multiple payloads challenging (Wei et al., 2024).

Moreover, administering two ADCs targeting the same antigen could lead to binding competition, reducing overall efficacy (Yamazaki et al., 2021).

This complexity has led to the exploration of dual-payload ADCs, a single molecule delivering two therapeutic agents. This approach can harness synergistic effects, minimize resistance, and overcome barriers associated with combination therapies.

Beyond this, opportunities for tailoring the linker region can allow staggered or locational release of each payload to tailor the ADC mechanism of action further. For instance, Chengdu Kanghong have used distinct linkers that release one payload intracellularly and another in the tumor microenvironment, enabling spatial and temporal control over drug action, enhancing efficacy while targeting multiple pathways simultaneously through direct action on the target cell line and via the bystander effect (Mullard, 2025).

Q How can cell panel screening help identify novel combinations for ADCs?

A Cell panel screening (CPS) is a valuable tool for identifying novel drug combinations and assessing ADC efficacy across diverse cancer models.

Whilst the complex chemical properties of ADCs created some initial challenges for screening ADCs using CPS, these have been addressed with advanced dispensing technologies, making comprehensive cell panel screening more accessible and efficient for ADC development.

By screening ADCs or ADC payloads across a large cell line panel, CPS enables researchers to pinpoint tissue types or specific mutations that respond to a given treatment.

For dual-payload ADCs, CPS is invaluable for identifying additive or synergistic combinations of payloads at ratios suitable for conjugation to the targeting antibody. The ability to evaluate combinations that target a diverse range of pathways across effective dose ranges and target cell lines ensures that payload combinations that target different pathways, which reduce the tumor's ability to develop resistance, are selected.

Beyond viability readouts like measurement of ATP levels (e.g., ATPlite™ assays), CPS can incorporate additional datasets, for example high content imaging or high throughput transcriptomics such as MERCURIUS™ DRUG-seq, to answer a wide range of ADC-specific development questions.

For ADCs, understanding target protein expression on the cell surface is important for selecting cell populations for screening, or for understanding how ADC efficacy is impacted by differential expression of the target. Evaluation of surface expression of the target protein using qualitative methods such as mRNA expression, e.g. from public datasets, or quantitative methods like quantitative flow cytometry analysis can be combined with traditional CPS techniques to answer these questions.

Additionally, understanding ADC uptake kinetics is critical for optimizing payload delivery. Innovative assays leveraging antibodies labelled with pH-sensitive dyes enable analysis of endocytosis rates, providing insights into intracellular processing and payload release. These tools help refine ADC designs for maximal therapeutic impact.

Q Are there ways to identify novel combinations without needing to systematically test a large panel of compounds?

A CPS is a powerful tool for identifying novel synergistic combinations of compounds, but if a more agnostic approach to identifying potential synergistic partners is required then Functional Genomic Screening (FGS) using CRISPR-Cas9 technology offers a powerful approach. Pooled FGS, for example, enables genome-wide evaluation of gene ablation (CRISPRko, CRISPRi) or overexpression (CRISPRa), identifying genes that confer resistance or sensitivity to ADCs. These findings shed light on the mechanisms of ADC processing and resistance, potentially leading to novel drug development programs.

FGS traditionally focuses on simple endpoints like viability, but advancements in single-cell analysis and co-culture systems are expanding its scope. These innovations allow researchers to explore complex biological phenomena, such as bystander effects or immunogenicity, further enhancing ADC development strategies.

Q How can Revvity help in the development of ADCs?

A Revvity offers a comprehensive suite of products and services tailored to accelerate ADC research and development. Its OncoSignature™ Cell Panel Screening platform features a diverse panel of 300 cell lines representing 18 tissue types, providing rapid insights into ADC efficacy. CPS can be performed in 2D or 3D spheroid models by our Preclinical Services team, with flexible endpoints ranging from viability assays to advanced imaging techniques.

For ADCs, dosing challenges are addressed through Revvity's FlexDrop™ technology, which provides accurate dosing with reduced variability and improved cell health in both 2D and 3D spheroid culture versus traditional high-throughput dosing methods. The resultant improved data quality increases confidence in the data and improves decision-making.

Revvity's pHSense™ assay offers a high-throughput solution for measuring ADC uptake, leveraging plate-reader compatibility for scalability. This assay is particularly valuable for studying endocytosis kinetics and optimizing linker designs for payload release.

Beyond primary screening, Revvity supports downstream functional analysis of ADC effects through advanced assays like DRUG-seq for transcriptomic profiling and PhenoVue™ reagents such as high content DNA damage readout kits for detailed mechanistic understanding of ADC action.

Finally, Revvity's expertise in Functional Genomic Screening has enabled researchers to uncover key mechanisms of ADC action and resistance, helping stratify patient populations, identify novel drug targets, and discover synergistic combinations. These capabilities offered through our Preclinical Services empower scientists to drive innovations in ADC development and maximize therapeutic outcomes.

Closing thoughts from Simon

Antibody Drug Conjugates are redefining cancer treatment, combining precision targeting with potent payloads to overcome the limitations of traditional therapies. While challenges like resistance persist, innovations such as dual-payload ADCs offer exciting new possibilities. With cutting-edge tools and services, Revvity is uniquely positioned to help researchers unlock the full potential of ADCs and transform cancer care.

Biography

Simon Scrace, MBA (Open), DPhil (Oxon), is a director in the Revvity Preclinical Services team. He leads a team of scientists specialising in the use of functional genomic screening and cell panel screening technologies for target identification, target validation, and patient stratification studies. His team has been using these technologies to help clients understand ADC mechanism of action and how payload combinations may increase ADC efficacy and overcome cancer resistance.

References

1. Beck, A., Goetsch, L., Dumontet, C. and Corvaia, N. (2017) Strategies and challenges for the next generation of antibody-drug conjugates, *Nature Reviews Drug Discovery,* 16, pp. 315-337.
2. Biochempeg (2025) *ADC Market 2025: Rising sales and growing phase III pipelines.* www.biochempeg.com/article/447.html#:~:text=Global%20Phase%20III%20ADC%20Pipeline,to%20Phase%20III%20clinical%20trials.
3. Bornstein, G.G. (2015) Antibody drug conjugates: Preclinical considerations, *The AAPS Journal,* 17(3), pp. 525-534.
4. Dagogo-Jack, I. and Shaw, A.T. (2018) Tumour heterogeneity and resistance to cancer therapies, *Nature Reviews Clinical Oncology,* 15, pp.81-94.
5. Fanale, M.A.., Horwitz, S.M., Forero-Torres, A., Bartlett, N.I., Advani, R.H., Pro, B., Chen, R.W., Davies, A., Illidge, T., Hueber, D., Kennedy, D.A. and Shustoc, A.R. (2014) Brentuximab vendotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase 1 study, *Journal of Clinical Oncology.: Off. J. Am. Soc. Clin. Onocol.,* 32, pp. 3137-3143.
6. Khongorzul, P., Ling, C.J., Khan, F.U., Ihsan, A.U. and Zhang, J. (2020) Antibody-drug conjugates: a comprehensive review, *Molecular Cancer Research,* 18, pp. 3-19.
7. Mullard, A. (2025) Dual-payload ADCs move into first oncology clinical trials, *Nature Reviews Drug Discovery,* 24, pp. 573-576.
8. Ruan, D-Y., Wu, H-X., Meng, Q. and Xu, R-H. (2023) Development of antibody-drug conjugates in cancer: Overview and prospects, *Cancer Communications,* 44(3), pp. 3-22.
9. Senter, P.D. (2009) Potent antibody drug conjugates for cancer therapy, *Current Opinion Chemical Biology,* 13(3), pp. 235-244.
10. Tao, J., Gu, T., Zhou, W. and Wang, Y. (2025) Dual-payload antibody-drug conjugates: taking a dual shot, *European Journal of Medicinal Chemistry,* 281, pp. 1-23.
11. Tsuchikama, Y., Anami, Y., Ha, S.Y.Y. and Yamazaki, C.M. (2024) Exploring the next generation of antibody-drug conjugates, *Nature Reviews Clinical Oncology,* 21, pp. 203-223.
12. Wang, Z., Li, H., Gou, L., Li, W. and Wang, Y. (2023) Antibody-drug conjugates: Recent advances in payloads, *Acta Pharmaceutica Sinica B,* 13(10), pp. 4025-4059.
13. Wei, Q., Li, P., Yang, T., Zhu, J., Sun, L., Zhang, Z., Wang, L., Tian, X., chen, J., Ju, C., Xue, J., Ma, L., Shimura, T., Fang, J., Ying, J., Guo, P. and Cheng, X. (2024) The promise and challenges of combination therapies with antibody-drug conjugates in solid tumors, *Journal of Hematology and Oncology,* 17(1).
14. Yamazaki, C.M., Yamaguchi, A., Anami, Y., Xiong, W., Otani, Y., Lee, J., Lee, N.T. Ueno, N.T., Zhang, N., An, Z. and Tsuchikama, K. (2021) Antibody-drug conjugates with dual payloads for combating breast tumor heterogeneity and drug resistance, *Nature Communications,* 12, pp. 3528.
15. Younes, A., Connors, J.M., Park, S.I., Fanale, <., O'Meara, M.M., Hunder, N.N., Hueber, D. and Ansell, S.M. (2013) Brentuximab vendotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study, *Lancet, Oncology,* 14, pp.1348-1356.