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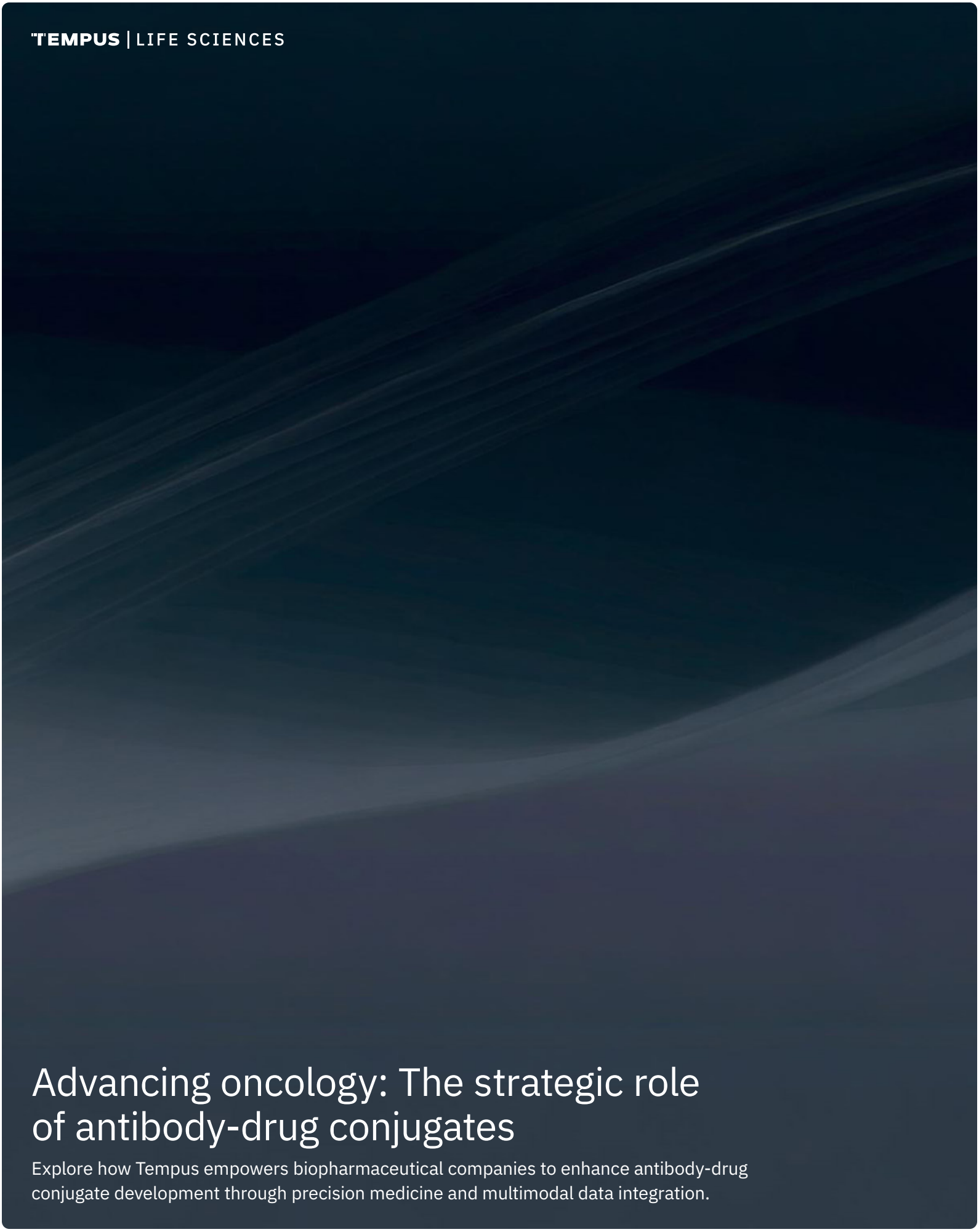


Advancing oncology: The strategic role of antibody-drug conjugates

Explore how Tempus empowers biopharmaceutical companies to enhance antibody-drug conjugate development through precision medicine and multimodal data integration.

What are ADCs and why are they important?

Antibody-drug conjugates (ADCs) are rapidly emerging as a key anti-cancer therapeutic modality across multiple liquid and solid tumor indications. ADCs are composed of an antibody attached to an active payload via a peptide linker. Commonly, cytotoxic chemotherapies are chosen as payloads, with the antibody serving to guide these drugs directly to the tumor.

This targeted delivery strategy minimizes damage to healthy tissue, resulting in more favorable toxicity and therapeutic profiles and earning ADCs recognition as "smart chemotherapies." Excitingly, ADCs are revolutionizing oncologic care with 14 FDA approvals, 12 drugs spanning over 80 open Phase III clinical trials,[1] and sales projected to reach $20–30B per year in the near future.[2]

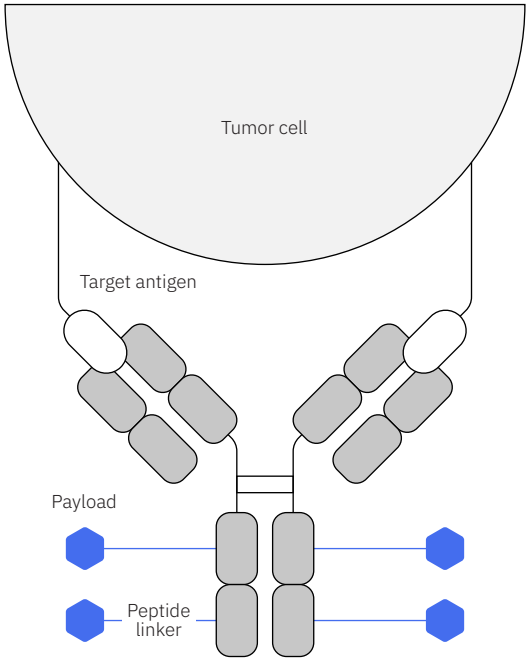


Figure 1 Antibody-drug conjugate depicting specific modality components that can be optimized using Tempus offerings.

By optimizing the individual components of ADCs (antibody, linkers, and payloads), there is significant potential to expand their diversity, leading to a broader and more effective repertoire for cancer treatment.

Clinical success of ADCs can depend on several factors, including:

- Stable expression of **target antigens** by the tumor
- Preferential expression of **target antigens** on **tumor cells** versus healthy cells
- Efficient internalization of the ADC by the **tumor cell**
- Stability of the **peptide linker** when ADC is not proximal to the tumor cell
- Efficient cleavage of the **peptide linker** for adequate release of payload at the tumor site
- Dispersion of the **payload** beyond the targeted tumor cell, otherwise known as the bystander effect, to kill nearby tumor cells
- **Payload** sensitization and resistance mechanisms
- Appropriate clearance/degradation of **payloads** and naked antibodies to minimize off-target effects

Approved ADCs on the market and next-generation ADCs

As of early 2024, the ADC landscape features 14 FDA-approved therapies that target 11 distinct cancer cell antigens, and utilize 9 distinct cytotoxic payloads that share 4 mechanisms of action (MoA). These ADCs have been indicated for use in hematological malignancies such as Hodgkin lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, and multiple myeloma, and more recent approvals seen for solid tumors including breast, gastric, urothelial, and cervical cancers.

Most of these ADCs utilize microtubule inhibitors as their mechanism of action, with monomethyl auristatin E (MMAE) being the most common payload. More significantly, these therapies are marking a significant shift in oncology practices, with ADCs like Enhertu showing remarkable results in clinical trials for pan cancer indications and setting a new standard for precision medicine.

Next-generation ADCs

New ADCs are being designed with enhanced properties. Innovations in antibody design, engineering and target selection offer improved tumor specificity, or employ novel antigens that extend to alternative cell targets within the tumor microenvironment like stromal and vascular components. The more regular use of fully humanized antibodies also results in reduced immunogenicity and improved tissue penetration.[3]

Payload selection is also evolving, including chemotherapy derivatives with optimized potency or membrane permeability, or the incorporation of immunomodulators that can combine the benefits of ADC technology with immunotherapy.[4]

Furthermore, linker technology is improving bond stability, preventing the premature release of cytotoxic payloads thereby minimizing off-target effects and enhancing the delivery of the payload to the tumor cell.[5] Specifically, improvements in site-specific conjugation methods are being utilized to produce homogeneous ADCs with consistent drug-to-antibody (DAR) ratios, improving therapeutic and pharmacokinetic indices.[6] Beyond the engineering of individual components, researchers are seeking to redefine ADC strategies by also exploring dual-targeting methods like bispecific antibodies, dual-payloads, and non-internalizing antibodies to overcome drug resistance and enhance specificity.

Tempus can advance your ADC R&D plans and programs

Tempus is working with pharma and biotech to support ADC development, aiding preclinical discovery groups in designing new ADCs, uncovering biomarkers of response and resistance, and planning clinical trials with enhanced probability of technical success (PTS).

Tempus can reveal insight into key design and investment decisions by leveraging comprehensive multimodal real world data (RWD), which includes over 19K ADC-treated de-identified patient records, plus tens of thousands of records from patients treated with chemotherapies sharing payload target MoA. As the Tempus database spans multiple therapeutic indications with an emphasis on late stage and metastatic tumors we can help companies reveal critical unmet clinical need, allowing for the characterisation of tumor subsets with poor prognosis or resistance to the standard of care. These real-world data insights can inform critical aspects of ADC development including:

01 Selection of the optimal tumor indication

02 Identification of antibody target, payload, linker and biomarker

For example the paired RNA sequencing data for these tumors can provide insight into target expression stratified by tumor indication and stage, and stability of that expression over time, at different lines of therapy, after prior treatments, and at metastatic sites.

Tempus' clinical network can also be leveraged to execute observational studies to assemble truly unique biobanks and data collections. Additionally, Tempus' extensive library of tumor organoids supports the screening of a wide range of tumor indications with well-characterized expression levels of ADC targets, to assess which candidates could be most effective. By combining laboratory research with real-world data insights linked to a live clinical network, Tempus is equipped to help streamline ADC development and enhance clinical trial PTS.

Strategic integration of ADC development and Tempus capabilities

Tempus is uniquely positioned to accelerate the development of ADCs through its advanced platform, which integrates real-world data analytics, organoid modeling, and clinical expertise.

ADC DEVELOPMENT AND VALIDATION

01 Antibody target selection and validation Access Tempus' extensive real-world multimodal data to identify targets overexpressed in specific tumor indications (Fig. 1), where there is an unmet clinical need for either ADC development or in-licensing opportunities. Leverage Tempus' highly characterized tumor organoid biobank to validate ADC performance.

02 Payload selection Identify where biomarkers linked to payload sensitivities track with antibody target expression in Tempus RWD. The efficacy of individual payloads, or combinations/sequences of multiple payloads, can be explored and validated in organoid models.

03 Linker and dose optimization Combine insights from tumor expression dynamics of antibody targets, payload biomarkers, molecular transporters and enzymes, in Tempus' RWD. Employ organoid models to link target expression with levels of payload release, to inform the choice of linker and drug-to-antibody ratios (DAR).

04 Tumor indication selection/expansion Leverage Tempus' real-world data (RWD) to identify optimal tumor indications and entry points in the patient journey, balancing target antigen expression, standard of care biomarkers, and unmet clinical needs. Hypotheses generated can be tested to validate ADC sensitivity/resistance in indication-matched tumor organoids.

05 Insight into current ADC performance Utilize Tempus' RWD to gain a deeper understanding of the current ADC therapies, identifying biomarker and patient clinical profiles that influence patient outcomes. At the same time, clinical trial information can be integrated into the clinical and genomic database, combining Tempus-provided tissue genomics, imaging, and blood-based response monitoring, including minimal residual disease (MRD), to thoroughly characterize the mechanisms and biomarkers of clinical response and resistance.

CLINICAL TRIALS AND OPERATIONS

06 Clinical design strategy Enhance the probability of technical success (PTS) of a clinical study by assessing feasibility of study designs, determining variability of targets and biomarkers, determinants of outcome to standards of care, the impact of potential inclusion/exclusion criteria, and sites and regions with denser eligible populations.

07 Patient selection strategy Refine patient selection for clinical trials based on biomarker discovery facilitated by mapping variability of hypothesized targets and biomarkers in real world data, multi-omic profiling of patient samples, and preclinical validation in patient matched tumor organoids to improve patient outcomes.

08 Clinical biomarker development Validate biomarker hypotheses with Tempus' assay platforms for patient recruitment. Perform observational clinical trials to build biorepositories enabling robust benchmarking of biomarker and assay hypotheses.

09 Clinical trial operation with comprehensive support Benefit from Tempus' regulatory capability, business validation, and ADC response insights to navigate the ADC development landscape successfully.

TIME Combine data, technology, and operations to power real-time patient matching, and increase site engagement for your clinical trials.

Genomic sequencing Comprehensive genomic profiling services; solid tissue, liquid biopsy, DNA, whole transcriptome RNA, and MRD for ADC development.

(continued)

10 Tempus Next Improve adherence to guideline-based care by creating awareness of care gaps and identifying patients who may benefit from these guideline-based suggestions, including those pertinent to ADCs.

"Next" delivers customized and targeted notifications to treating physicians during the course of care and at the point of care. Ongoing performance across care pathways is tracked through routine reports delivered to health systems and life sciences partners to understand effectiveness of the notifications and emerging trends.

Summary

In the evolving landscape of targeted therapeutics, antibody-drug conjugates (ADCs) represent a significant advancement in oncology treatment modalities. Tempus, a leader in precision medicine and artificial intelligence, offers comprehensive partnership opportunities for companies at any stage of ADC development.

Whether your organization is in the early discovery phase, engaged in clinical trials, or advancing towards commercialization, Tempus provides a suite of services tailored to enhance and expedite your ADC development process.

References

1 Based off of Citeline clinical trial query, pulled May 2, 2024

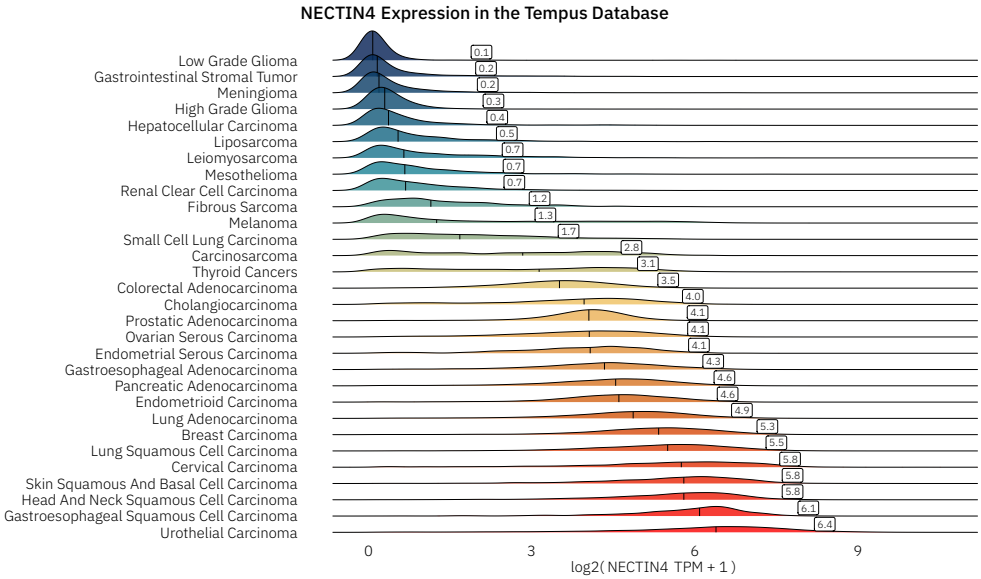
2 Flynn et al, Nature Reviews Drug Discovery 2024, The Antibody-Drug Conjugate Landscape.

3 Abdollahpour-Alitappeh, M. et al. Antibody–drug conjugates (ADCs) for cancer therapy: Strategies, challenges, and successes. J. Cell. Physiol. 234, 5628–5642 (2019).

4 He, Lei, et al. "Immune modulating antibody–drug conjugate (IM-ADC) for cancer immunotherapy." Journal of Medicinal Chemistry 64.21 (2021)

5 Doronina, Svetlana O., et al. "Novel peptide linkers for highly potent antibody– auristatin conjugate." Bioconjugate chemistry 19.10 (2008)

6 Matsuda, Y. & Mendelsohn, B. A. An overview of process development for antibody-drug conjugates produced by chemical conjugation technology. Expert Opin. Biol. Ther. 21, 963–975 (2021).



Sample ridge plot for NECTIN4 expression across multiple tumor indications Leveraging Tempus' expansive genomics data, we can quantify the relative expression of different markers like NECTIN4 across multiple cancers, enabling a) NECTIN4 targeting ADCs to be developed for indications with higher relevant marker expression and b) stratification of patient populations more likely to benefit from NECTIN4 targeted interventions.