APPLICATION NOTE

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Discovery of pharmacodynamic biomarkers to **advance antibody-drug conjugate (ADC) development**

Introduction

Antibody-drug conjugates (ADCs) have emerged as a promising class of targeted therapeutics, leveraging the unique cell-specific binding abilities of monoclonal antibodies to deliver cytotoxic drugs directly into cancer cells. The chemical "linkers" that attach drug to antibody are designed to create a stable connection until the ADC binds to and is internalized into the cancer cell, thus destroying the tumor while minimizing damage to healthy tissues.

This combination of specificity and potency supports the accurate, efficient delivery of anticancer drug "payloads" to their site of action for enhanced therapeutic effect with less side effects. To date, however, ADC drug response still varies widely across patients. This challenge stems largely from the inherent heterogeneity of ADCs and their targets. ADCs can have varying drug-to-antibody ratios which may affect efficacy, and dynamically change by decoupling as they infiltrate the cancer cell. There may also be variations in antigen expression levels across cancer cells which can affect target binding, cell internalization, and delivery of the ADC to lysosomes. Pharmacokinetic (PK) assays can be used to characterize intact ADCs before they reach the tumor, and to quantify the released payload in blood after, but they do not effectively capture the biological effects occurring at the tumor site.

Assessments of target engagement (TE) and pharmacodynamic (PD) response can provide insight into the payload's interaction at the tumor to better understand drug response and identify patients in which a given ADC therapy would be most efficacious. Continued success in ADC development will depend on the ability to discover dynamic TE and PD biomarkers.

Why small molecule biomarkers are suited for TE/PD assessment of ADCs

Small molecule biomarkers, inclusive of metabolites and lipids, are reflective of the dynamic physiologic changes that occur in response to drug exposure. As such, they can be used to read out target engagement to confirm if an ADC is effectively binding to its intended target. Small molecule biomarkers can also associate with the pharmacological activity of the payload upon cellular uptake and trafficking to lysosomes, providing a measure of PD response following TE. Given that small molecule biomarkers are sensitive indicators of real-time cellular and organ function, they may serve as early indicators of TE and treatment response, well before clinical signs are observed. Their dynamic nature makes them ideal for assessing TE at different drug doses, helping to dial in dosing strategies that optimize ADC target binding for efficacy while minimizing potential toxicities. Additionally, small molecule biomarkers are released from cells into blood, a readily accessible matrix that allows for efficient longitudinal sampling to monitor changes in TE and/or PD over time.

How Sapient identifies biomarkers of response to ADC therapies

Sapient leverages a unique, nontargeted approach to enable discovery of critical biomarkers. Our rapid liquid chromatography-mass spectrometry (rLC-MS) systems are capable of measuring >15,000 small molecule biomarkers per biosample in very rapid order, supporting discovery of the most biologically relevant biomarkers – even those yet to be characterized. This enables identification of robust, specific TE and PD biomarkers that are changed in blood from pre- to post-ADC treatment.

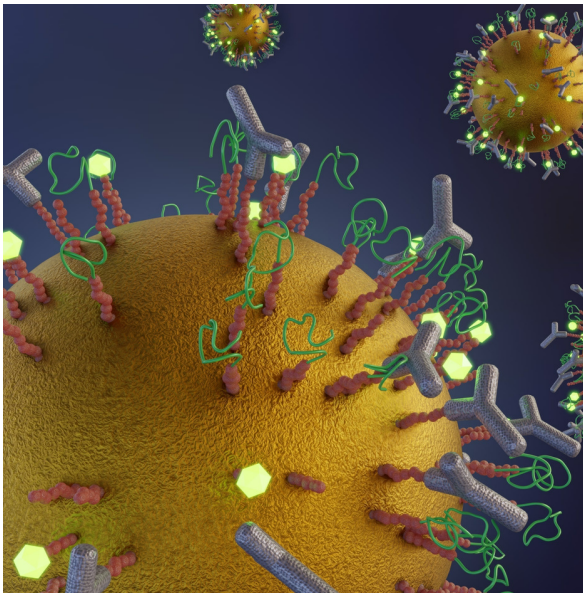
Sapient can then leverage its Human Biology Database, which is comprised of mass spectrometry data collected from 100,000+ human biosamples and paired with phenotypic and other -omics measures, including genetics information, to perform genome-wide association studies (GWAS). This allows us to map the relation of identified circulating TE and PD biomarkers with genetic variants of the drug target and its related pathways. Robust associations with those genes can provide evidence that the ADC is in fact engaging its intended target.

The same biomarker(s) can also be evaluated in individuals within the Human Biology Database that have received similar ADC therapies, to confirm whether the biomarker changes similarly with drug exposure in these patients and to assess whether it associates with increased drug response. In an effort to rapidly translate these key discoveries, Sapient can leverage its on-site CAP-accredited, CLIA-certified laboratory to develop clinical assays that can be used to advance and enrich ADC clinical trials.

Applications of small molecule biomarkers throughout ADC development

Sapient has supported a number of top pharma sponsors in their pursuit to advance ADC-based therapeutics. This work spans *in vitro* studies, preclinical models, and early clinical phases to identify dynamic TE and PD biomarkers of drug response.

The studies have allowed us to identify novel circulating biomarkers in the periphery that read out the activity of ADCs, both in cellular systems as well as *in vivo*. Through these efforts, we have found that the heterogeneity present in target engagement is a key determinant of overall disease progression, survival, and response to ADC therapeutics. The discoveries are now being advanced to the clinic as tools to optimize deployment of these exciting new therapeutic modalities.



Conclusion

Metabolite and lipid biomarkers can help decipher the heterogeneity of ADCs and their targets so that the potential of these highly potent, specific therapies can be further realized. They provide insight into the dynamic biological effects occurring at the tumor site as the ADC binds to and releases its payload into the cancer cell. Sapient's nontargeted approach supports identification of the most biologically relevant biomarkers that read out dynamic responses to drug exposure, supporting assessment of TE and early efficacy as well as enabling dose optimization and ongoing treatment response monitoring. When paired with Sapient's Human Biology Database, these TE and PD biomarkers can be rapidly validated in independent human samples, and may serve as predictive markers of treatment response or resistance to guide patient selection for ADC clinical trials.

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