Case Study

Fueling the Future IND-enabling Studies

De-risking biotherapeutics through predictive human-relevant NAMs

Investigational New Drug (IND) applications represent a critical regulatory milestone in therapeutic development, serving as the formal request to initiate clinical trials in humans. At this stage, sponsors must provide a comprehensive package of nonclinical data demonstrating that a candidate is safe for first-in-human administration. This includes pharmacology data to establish biological activity, pharmacokinetic data to characterize exposure and toxicology data to define potential adverse effects. Together, these studies describe the relationship between systemic exposure and biological response, identify adverse effects at high dose levels and establish a safety margin to guide clinical dosing. Traditionally, this framework has relied heavily on in vivo animal models as the primary means of predicting human safety. Animal-based models are an important component of IND-enabling development but often provide results that do not translate to human biology.

For biologics, animal systems frequently fail to capture human-specific targets, immune responses and off-tissue effects, creating structural gaps in safety prediction. Regulatory agencies are increasingly supporting the fit-for-purpose adoption of New Approach Methodologies (NAMs) to improve the human relevance of safety assessments and advance the long-term goal of reducing reliance on animal testing. The US Food and Drug Administration (FDA) has emphasized the importance of these approaches in mAb development, recognizing that many biologics interact with human-specific targets or pathways that cannot be meaningfully assessed in animals. As a result, reliance on animal models alone may not fully capture the safety profile required to support an IND.

NAMs encompass a range of technologies designed to improve predictive relevance and mechanistic understanding. Rather than just modifying the existing pathways, utilizing NAMs-based approaches provides early human-relevant insights to reveal risk, inform mitigation strategies and advance the therapeutic candidates with the greatest probability of clinical success. Advanced in vitro systems such as organoids and organ-on-a-chip platforms can replicate key features of human tissue structure and function. Cellular microarrays and high-content screening approaches enable interrogation of drug effects across diverse cell types and pathways, while in silico models integrate experimental data to generate predictive insights.

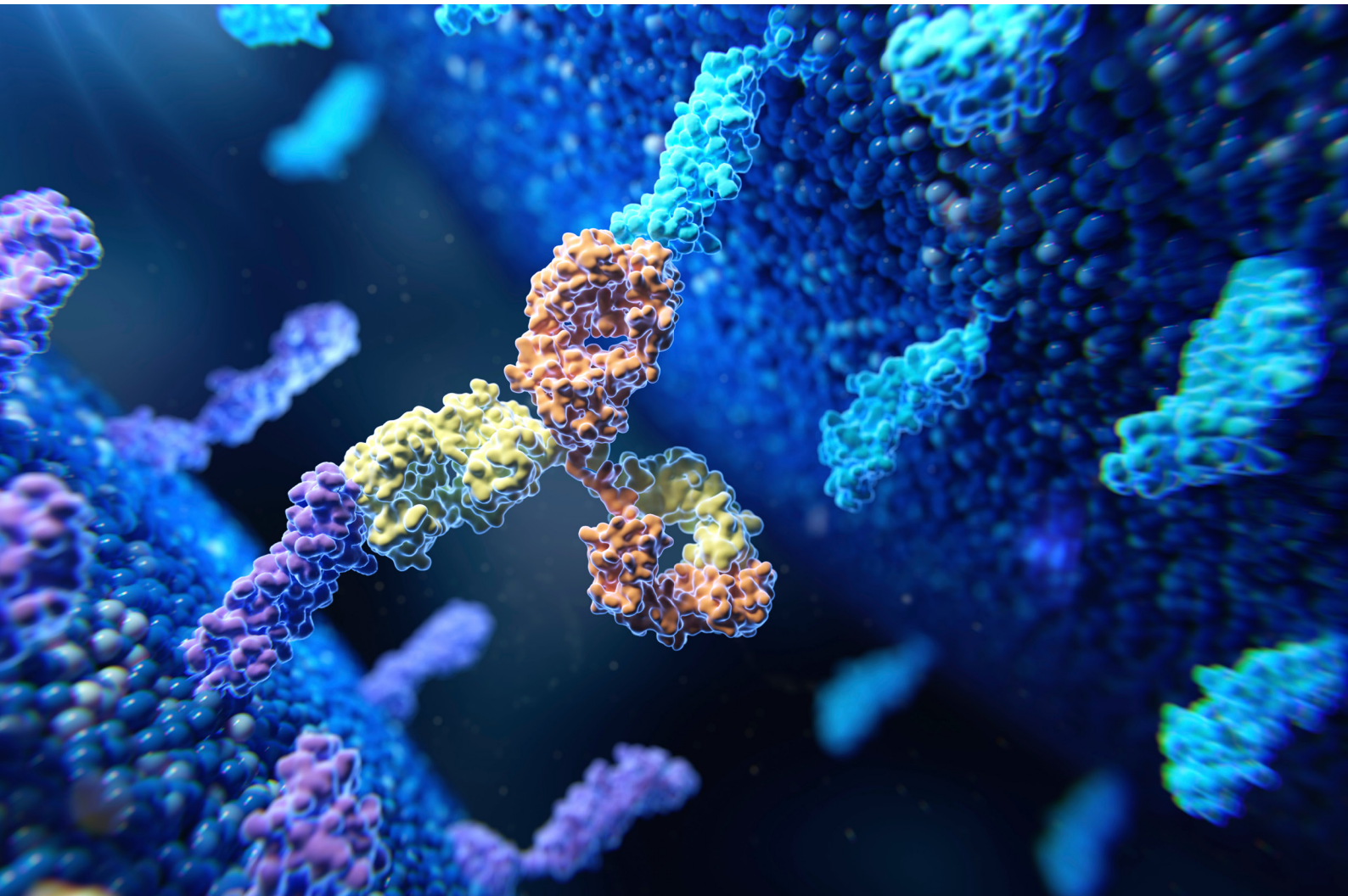
The objective is to use predictive insights to make better decisions before costly failures occur. Human-relevant NAMs support the generation of predictive safety data that improve risk characterization, reducing downstream attrition and increasing confidence

in IND-enabling assessments. The use of human-relevant NAMs, either as standalone approaches or in combination with targeted animal studies, can strengthen a weight-of-evidence assessment by providing mechanistic and human-relevant data that support more informed development decisions and a more efficient path to the clinic. Working with a contract research organization (CRO) able to integrate diverse model systems and generate data that is both mechanistically rich and relevant to human biology is an advantage for sponsors.

Modern in vitro systems can leverage primary human cells and induced pluripotent stem cell (iPSC)-derived models across a wide range of tissue types, enabling evaluation of safety risks across major organ systems. These platforms are designed to assess on-target effects in healthy tissues as well as off-target and on-target off-tumor interactions that are particularly relevant for biologics. Mechanistic assays such as cytotoxicity, cytokine release and coculture systems further enhance the ability to characterize potential adverse effects and immune-mediated responses.

The resulting data can contribute directly to IND submissions by strengthening the overall safety narrative and providing human-relevant context for observed effects. Within this shifting paradigm, the role of integrated, human-centric approaches to nonclinical development is expanding, setting the stage for how safety assessment strategies are designed and executed for biologic candidates.

As a pioneering leader in biomedical innovation, we are actively developing and advancing alternatives to animal testing that uphold scientific rigor and patient safety while de-risking and accelerating development. Our comprehensive human-relevant platform encompasses more than 70 different human primary and iPSC-derived cells spanning the majority of physiologically relevant tissue types, providing representative insights into major organ systems. Through close collaboration with regulators, academia and industry, our team translates scientific innovation into practical scalable solutions. This approach shifts safety assessment from confirming observed toxicities to predicting potential liabilities earlier in development, enabling more informed, data-driven decision-making across IND programs.



Case study 1: Translating safety insights into IND confidence

Background

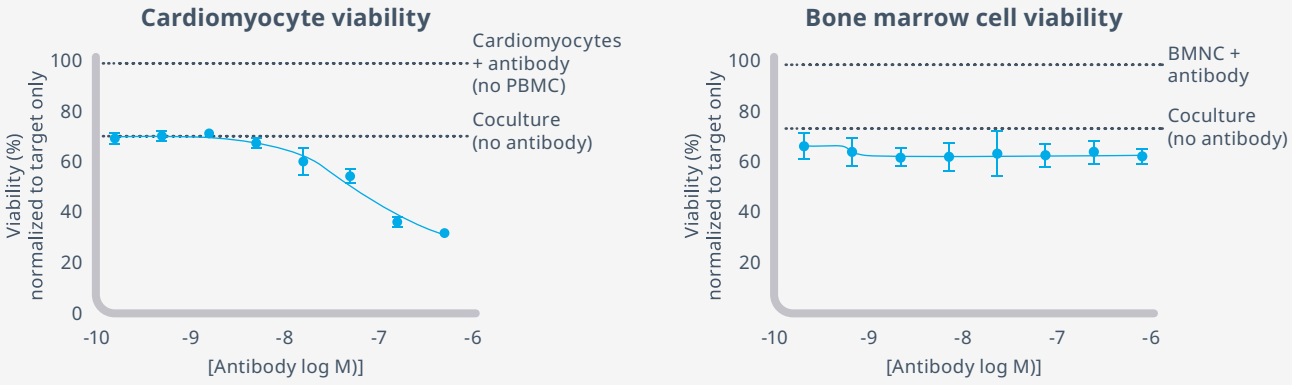
Human epidermal growth factor receptor 2 (HER2) overexpression occurs in approximately 20% of breast cancers, driving tumor development and disease progression.[1] HER2-targeted therapies, including mAbs and antibody-drug conjugates (ADCs), have markedly improved treatment outcomes for patients with HER2-positive breast cancer. However, these therapies are associated with a high risk of cardiotoxicity, particularly among patients also treated with anthracycline chemotherapies. HER2 signaling plays a key role in myocardial homeostasis, activating survival pathways and reducing oxidative stress. Disruption of HER2 signaling through targeted therapies induces cardiomyocyte apoptosis and contractile dysfunction.[2]

Early assessment of on-target effects in human cardiomyocytes is thus a vital source of safety data during the development of HER2-targeted modalities. In this study, researchers sought to evaluate the cardiac risk of a HER2 bispecific antibody using a human-relevant in vitro platform.

Approach

iPSC-derived cardiomyocytes (HER2+) and bone marrow cells (HER2–) were exposed to a HER2/NKG2D bispecific antibody across a range of concentrations. Cytotoxicity was measured in real time using the Agilent xCELLigence Real-Time Cell Analysis multielectrode array platform. Loss of viability was demonstrated in HER2+ cardiomyocytes across increasing antibody concentrations, while HER2- bone marrow cell viability remained stable (Figure 1).

Figure 1: Viability of iPSC-derived HER2+ cardiomyocytes (left) and HER2- bone marrow mononuclear cells (BMNCs, right) across concentrations of HER2/NKG2D bispecific antibody



Insights

Loss of viability in HER2+ cardiomyocytes cocultured with peripheral blood mononuclear cells (PBMCs) but not HER2- bone marrow cells cocultured with PBMCs confirmed on-target cardiac risk while demonstrating therapeutic selectivity for HER2+ tissues. Early identification of on-target cardiotoxicity enabled risk mitigation strategies prior to clinical progression, supporting more informed development decisions and more precise IND positioning.

Case study 2: Assessing on-target/off-organ cytokine risk

Background

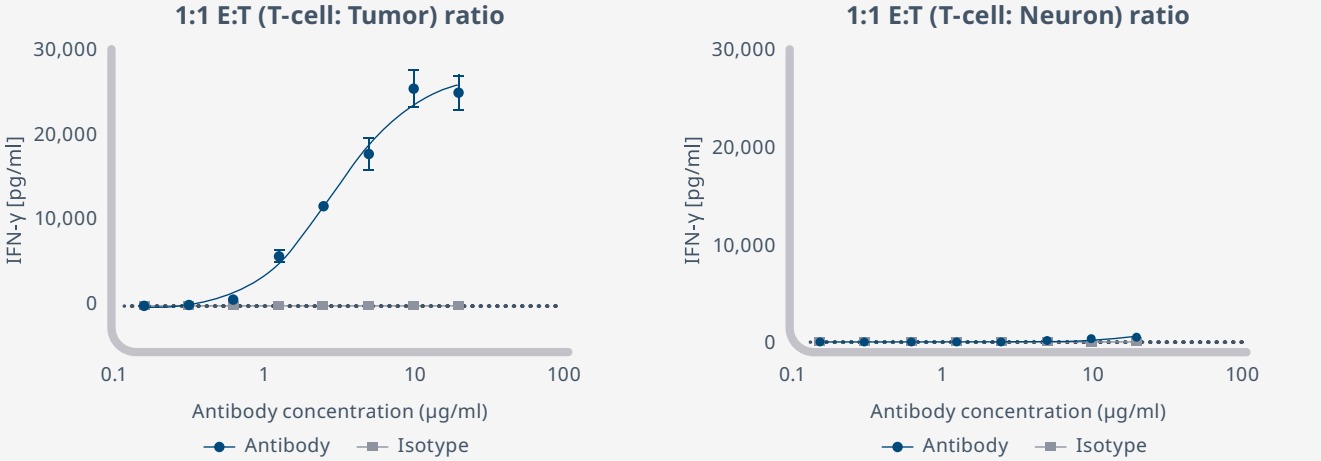
T-cell engagers (TCEs), including bispecific T-cell engagers (BiTEs) and chimeric antigen receptor (CAR) T cells, represent a new frontier of opportunity in cancer immunotherapy. Although these therapies depend on localized immune activation to effectively kill target cancer cells, this mechanism presents a risk of excessive proinflammatory activity and systemic cytokine release. This overactivation can affect any organ system and results in a range of harmful symptoms, including possible neurotoxicity.[3]

When assessing TCE candidates, it is thus critical to distinguish tumor-specific immune activation from off-organ effects in healthy tissues to minimize the risk of excessive cytokine release. In this study, researchers assessed this risk using cocultures of target (tumor) and nontarget cells along with CD8+ T cells to measure response to TCE.

Approach

Researchers cocultured primary neurons and target tumor cells with CD8+ T cells in the presence of TCE antibody and isotype control across a range of concentrations. Cytokine levels were quantified using a Meso Scale Discovery (MSD) panel to compare immune activation profiles between target cells and primary neurons, which display low levels of target but represent a distinct population from the tissue of interest (off-organ/on-target). Results demonstrated a strong cytokine response in tumor cell coculture (on-target) and a minimal response in neuronal coculture (off-organ).

Figure 2: Changes in cytokine levels of TCE and isotype control in a coculture of tumor cells (target, left) or neurons (nontarget, right) and CD8+ T cells



Insights

Comparison of cytokine profiles across primary neurons and tumor cocultures enabled confirmation of target-specific immune activation and revealed minimal risk of off-organ neurotoxicity. Distinguishing tumor-specific immune activation from off-organ effects enabled early de-risking of cytokine release liability, supporting confident progression while minimizing unforeseen clinical risk.

Fueling the future of IND-enabling studies

IND-enabling strategies are shifting from reactive risk assessment to predictive safety design. As development timelines compress and biologic complexity increases, reliance on traditional models alone creates unacceptable uncertainty. Human-relevant NAMs enable earlier identification of risk, supporting faster, more confident decision-making before critical milestones.

In this context, human-relevant in vitro models are central to this transition. By enabling detailed characterization of on-target and off-target effects in systems that more closely reflect human biology, these platforms provide critical data that enhances predictive relevance and strengthens the overall regulatory narrative. Their integration into IND-enabling strategies supports earlier identification of potential liabilities and more informed decision-making as candidates progress toward the clinic.

As expectations continue to evolve, the ability to effectively deploy these methodologies is becoming a key differentiator. CROs operating at the forefront of NAMs are uniquely positioned to help sponsors navigate this shift, offering both the scientific insight and operational capabilities required to generate robust, regulator-ready data packages. With deep expertise across in vitro and in vivo systems, our Discovery Sciences team provides the strategic guidance to design IND-enabling programs and the technical infrastructure to execute them efficiently, supporting partners in advancing biologics with greater confidence.

Partner with integrated scientific teams applying predictive, human-relevant strategies to enable earlier, more confident safety decisions.

Get in touch with an expert.

References

1. Pamungkas RP, Pratiwi L, Sutanto H. HER2-targeted therapies and cardiotoxicity: from major concern to manageable risk. *Curr Probl Cardiol*. 2025;50(11):103168. doi:10.1016/j.cpcardiol.2025.103168
2. Slavcheva SE, Angelov A. HER2-targeted therapy — from pathophysiology to clinical manifestation: a narrative review. *J Cardiovasc Dev Dis*. 2023;10(12):489. doi: 10.3390/jcdd10120489
3. Cosenza M, Sacchi S, Pozzi S. Cytokine elease syndrome associated with T-cell-based therapies for hematological malignancies: pathophysiology, clinical presentation, and treatment. *Int J Mol Sci*. 2021;22(14):7652. doi: 10.3390/ijms22147652

IQVIA LABORATORIES

CONTACT US
labs.iqvia.com