Predictive In Vitro Safety Profiling of Antibody–Drug Conjugates Using a Fully Human iPSC-Derived Multi-Tissue Panel

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Abstract ID: 16
Poster: #105

Background

Predicting which healthy tissues an antibody–drug conjugate will damage in patients remains one of the most consequential unsolved problems in ADC development. Here we show that a fully human, iPSC-derived seven-tissue panel can reproduce the known clinical toxicity signature of Cetuximab-MMAE — including tissue selectivity, dose-dependency, and the absence of toxicity in tissues where it is not clinically observed — without reliance on animal models or immortalized cell lines. Tissue selection was informed by in silico EGFR mRNA expression profiling across human tissues (GTEx database), yielding a panel of seven iPSC-derived cell types spanning skin (melanocytes), liver (hepatocytes), lung (alveolar epithelial cells), heart (cardiomyocytes), CNS (motor neurons), vasculature (endothelial cells), and intestine (epithelial cells).

Platform overview

Ncardia's safety platform:

- Uses exclusively human iPSC-derived cell types
- Covers seven physiologically relevant tissues
- Enables real-time functional toxicity assessment
- End-point is non-invasive, allowing further optional analysis (i.e. omics)
- Provides mechanistic insight into tissue-specific susceptibility
- Builds upon prior IND-supporting experience in cell therapy programs

This unified system enables early de-risking of ADCs, antibodies, cell therapies, and other biologics.

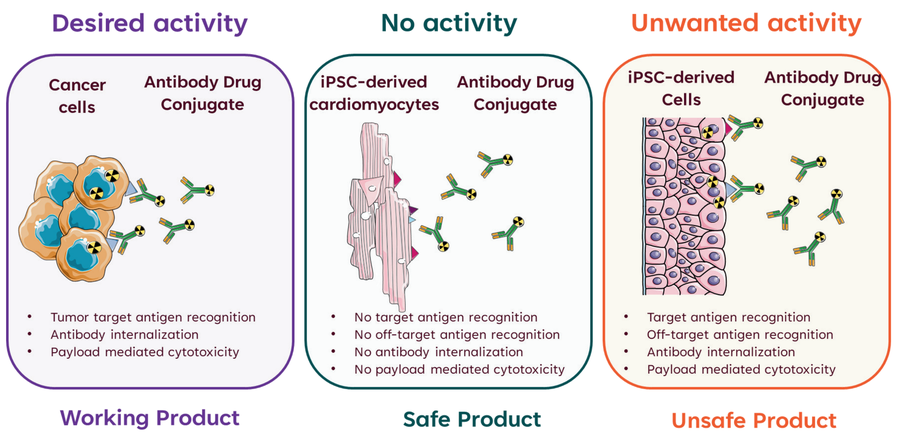

Figure 1. Overview of ADC activity profiles across target and non-target human cell types (Left) Cancer cells express the intended antigen, enabling specific binding of the ADC, internalization, and payload-driven cytotoxicity, representing the desired therapeutic effect. **(Center)** iPSC-derived cardiomyocytes lack expression of the target antigen, resulting in no ADC binding, no uptake, and absence of cytotoxic response, consistent with a safe profile. **(Right)** A panel of iPSC-derived healthy human cells shows unintended interactions including off-target antigen recognition, ADC internalization, and payload-mediated cell damage, reflecting potential safety risks associated with off-tumor toxicity.

Case Study: Cetuximab-MMAE safety profile

To demonstrate proof of concept, we generated an in vitro safety profile for Cetuximab-MMAE — an EGFR-targeting monoclonal antibody conjugated to monomethyl auristatin E (MMAE). Here, we wanted to determine whether our iPSC-derived tissue panel can recapitulate clinically observed toxicity patterns.

Workflow

In silico mRNA expression EGFR

To demonstrate proof-of-concept, we generated an in vitro safety profile for Cetuximab-MMAE — an EGFR-targeting monoclonal antibody conjugated to monomethyl auristatin E (MMAE). Here we wanted to determine whether our iPSC-derived tissue panel can recapitulate clinically observed toxicity patterns.

Figure 2. In silico profiling of EGFR expression across human tissues (GTEx).
To evaluate potential on-target/off-tumor risk, we first performed an in silico analysis of EGFR expression across human tissues using publicly available transcriptomic data from the GTEx database. This analysis combined with known high-risk organs for toxicity, resulted in a representative 7-tissue panel covering major organ systems (Figure 3).

Selected human seven-tissue iPSC derived panel

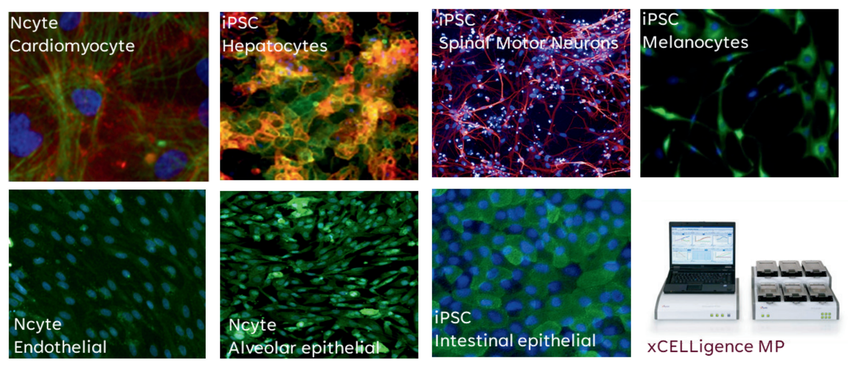

Figure 3. Characterization of the seven iPSC-derived human cell models selected for ADC safety assessment.
All cells representing a tissue derived from human iPSCs, providing:

- Lineage-appropriate receptor expression
- Physiological functional properties
- Human-specific biology

Cytotoxicity was measured using real-time impedance-based analysis on the xCELLigence MP platform.

In vitro functional safety profile

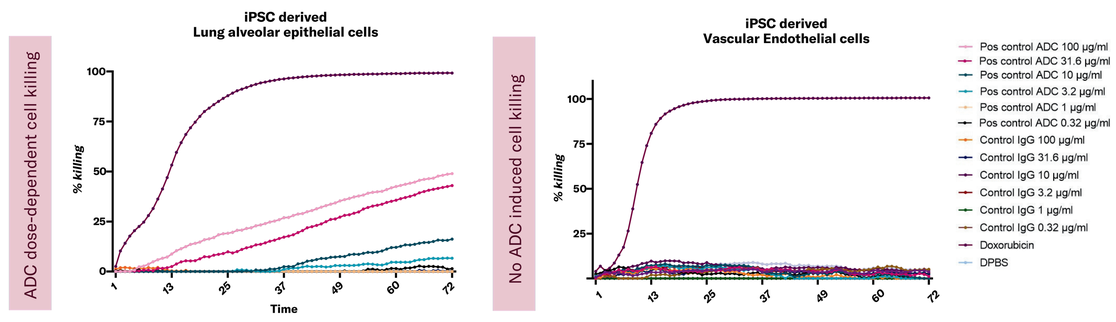

Figure 4. iPSC-derived lung alveolar epithelial cell.
(A.) and iPSC derived vascular endothelial cell **(B.)** susceptibility to Cetuximab-MMAE over 72 hours.as toxicity control and quantifiable dose-dependent effects where a response was observed.

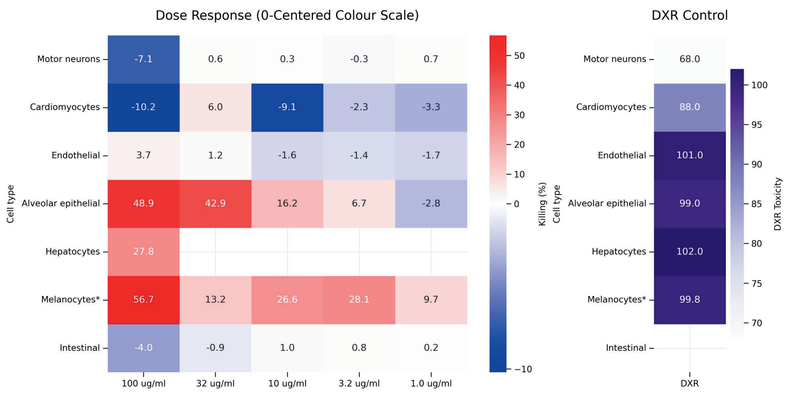

Figure 5. Cetuximab-MMAE cytotoxicity across a fully iPSC-derived multi-tissue panel.
*Due to confluency, the iPSC-derived Melanocytes were measured at 62 hours

At non-clinically relevant dose (100 µg/mL, Supratherapeutic)

- High cytotoxicity in melanocytes (skin-derived cells)
- Moderate effects in lung and liver models
- Minimal to no toxicity in cardiac, CNS, vascular, and intestinal models
- This pattern aligns with known EGFR expression distribution.

Clinically Relevant Dose (1 µg/mL)

- Toxicity was largely reversed across tissues
- Low residual sensitivity observed only in melanocytes

This demonstrates the platform's ability to distinguish between supratherapeutic hazard and clinically meaningful exposure risk — supporting translational relevance rather than nonspecific cytotoxicity detection.

Clinical Correlation

Clinically, cetuximab therapy is strongly associated with dermatologic adverse events (>80% of patients)[4]. Large real-world pharmacovigilance datasets from FAERS and VigiAccess consistently identify skin as the dominant toxicity class[5]. Our in vitro findings mirror this clinical signature.

Tissue	EGFR Expression	In Vitro Toxicity (100 µg/mL)	In Vitro Toxicity (1 µg/mL)	Clinical AE Signal
Skin (Melanocytes)	High	High	Low residual	High
Liver (Hepatocytes)	Moderate	Moderate		Low–Moderate
Lung (Alveolar epithelial)	Moderate	Moderate	None	Moderate
Heart (Cardiomyocytes)	Low	Minimal	None	Minimal
CNS (Motor neurons)	Low	Minimal	None	Minimal
Vascular (Endothelial)	Low	None	None	Minimal
Intestine (Epithelial)	Low	None	None	Minimal

Notably, absence of intestinal epithelial toxicity aligns with clinical evidence that gastrointestinal events during cetuximab therapy are typically inflammation-driven rather than due to direct epithelial injury[6]. Moderate cytotoxicity observed in lung and liver at supratherapeutic exposure reflects tissue susceptibility associated with EGFR expression and MMAE payload sensitivity. Importantly, these effects were not observed at clinically relevant concentrations, consistent with regulatory expectations for hazard identification in human in vitro safety models.

Conclusions

Importantly, the use of a fully iPSC-derived, multi-tissue panel provides a unique advantage by enabling mechanistically relevant, human-specific interrogation of ADC off-target or on-target liability within a unified platform. iPSC-derived tissues recapitulate key physiological features—including lineage-appropriate receptor expression, barrier properties, and functional responsiveness—offering a biologically coherent system that surpasses traditional immortalized cell lines. Together, these results suggest that fully human iPSC-derived multi-tissue systems can move safety pharmacology beyond hazard detection toward genuine prediction of clinical toxicity patterns, with broad applicability across immunotherapy modalities and direct relevance to IND-enabling study design

Predictive iPSC-based safety profiling of your immunotherapies

Questions? Contact us at: support@ncardia.com, www.ncardia.com

1. Tan et al., J Hematol Oncol, 2025
2. Hwang et al., JAMA Intern Med, 2016
3. FDA Roadmap, FDA, 2025

1. Onufer et al., PLOS ONE, 2020
2. Human Protein Atlas, 2024
3. Tito et al., J Biomed Sci, 2025

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