

Unmasking latent cardiotoxicity: Quantitative proarrhythmic risk prediction via AI-driven modeling of hiPSC-derived cardiomyocytes in regulatory safety pharmacology

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Abstract

Drug-induced cardiotoxicity remains a predominant driver of compound attrition across non-clinical drug development and post-market safety withdrawals. While the Comprehensive *in Vitro* Proarrhythmia Assay (CiPA) initiative shifted regulatory screening from an isolated focus on hERG inhibition toward integrated human-relevant platforms, conventional safety pharmacology still contends with the limitations of cardiomyocyte heterogeneity and univariate analytical thresholds. A recent study by Kim et al. (2026) in Archives of Toxicology addresses these challenges by coupling high-purity (>95% cTnT+), ventricular-dominant (78–84% MLC-2V+) human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) with an Artificial Neural Network (ANN), achieving a reported ROC-AUC of 0.982 across the CiPA 28 reference set. Crucially, this integrated bio-computational platform unmasked 'hidden' functional proarrhythmic liabilities in compounds displaying no detectable impedance-based cytotoxicity specifically the tyrosine kinase inhibitors sunitinib and erlotinib which escape detection in standard structural viability assays yet produce severe, time-dependent electrophysiological perturbations. Simultaneously, it provides a continuous, quantitative Torsades de Pointes (TdP) proarrhythmic risk score for refined risk stratification. This Commentary critically evaluates the methodological and translational implications of these findings within the context of the FDA Modernization Act 2.0 and ICH E14/S7B guidelines, dissects the divergence between structural cytotoxicity and functional proarrhythmic liabilities, identifies technical and dataset-size limitations of current machine-learning models, and outlines key standardization requirements needed before this platform can achieve formal regulatory qualification as an accepted New Approach Methodology (NAM).

Keywords: Cardiac safety, hiPSC-derived cardiomyocytes, Artificial intelligence, Anticancer drugs, Proarrhythmia risk, ICH E14/S7B, FDA Modernization Act 2.0, Context of use qualification

Introduction: The Evolution of Cardiac Safety Pharmacology

Preclinical safety pharmacology has historically been anchored by the International Council for Harmonisation (ICH) S7B and E14 guidelines, which emphasize *in vitro* human ether-à-go-go-related gene (I_{Kr} /hERG) channel block assays and *in vivo* animal telemetry measuring QT-interval prolongation as surrogates for ventricular proarrhythmia [1,2]. While this strategy prevented the clinical introduction of single-target hERG blockers, it lacks optimal predictive translatability due to interspecies electrophysiological differences and an inability to account for multi-channel pharmacodynamics [3,4]. Cardiac repolarization represents an integrated equilibrium between inward depolarizing currents ($I_{Ca,L}$ and $I_{Na,L}$) and outward repolarizing currents (I_{Kr} , I_{Ks} , I_{K1}) [5,6]. Consequently, compounds that simultaneously inhibit inward calcium ($I_{Ca,L}$) or late sodium ($I_{Na,L}$) currents alongside I_{Kr} (e.g., verapamil, ranolazine) mitigate proarrhythmic risk despite repolarization prolongation, counteracting torsadogenic triggers and causing false-positive attrition under single-channel screening paradigms [1,7].

To establish a mechanistic and human-relevant safety framework, international consortia established the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative [8–10]. CiPA integrates high-throughput multiple cardiac ion channel assessments, *in silico* reconstructions of human ventricular electrophysiology, and functional validation in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) [8,11–13]. Concurrently, the enactment of the FDA Modernization Act 2.0 has encouraged the exploration of New Approach Methodologies (NAMs) including human cell-derived microphysiological systems and computational architectures as potential non-animal alternatives [7,14]. However, it is crucial to recognize that the FDA Modernization Act 2.0 merely removes the statutory mandate for animal studies and permits valid non-animal alternatives; it does not confer automatic regulatory qualification on any individual *in vitro* or *in silico* model. Similarly, while the recent ICH E14/S7B Q&A guidelines acknowledge that robust, integrated *in vitro* assays can contribute to non-clinical proarrhythmia risk assessment, formal regulatory adoption requires prospective qualification within a rigorously defined Context of Use (COU). Within this evolving regulatory landscape, the investigation by Kim et al. (2026) provides valuable proof-of-concept evidence regarding the integration of ventricular-enriched cardiomyocyte biology and multi-parametric machine learning [7,15,16].

Biological Fidelity: Resolving Ventricular Lineage and Phenotypic Consistency

A foundational requirement for computational modeling is the biological reproducibility of the empirical input substrate [14,17]. A historical challenge with hiPSC-CM platforms has been phenotypic heterogeneity arising from uncontrolled mixtures of ventricular-, atrial-, and nodal-like cells which introduces signal variability and dampens mechanistic clarity [18–20]. Because Torsades de Pointes (TdP) is fundamentally a ventricular pathology driven by delayed repolarization and early afterdepolarizations (EADs), subtype-specific purity is critical for electrophysiological assays [7,21,22].

Kim et al. addressed this baseline requirement through the rigorous characterization of cryopreserved Cardiosight-S across multiple manufacturing batches [7]:

- **Pan-cardiac purity:** Flow cytometry demonstrated consistent differentiation efficiency, with cardiac troponin T (cTnT+) expression exceeding 95% across three independent lots (95.13%, 97.92%, and 96.63%) [7].
- **Ventricular lineage enrichment:** Subtype quantification confirmed a dominant ventricular-like identity, with MLC-2V+ populations ranging from 78.46% to 84.91% [7]. Nevertheless, it should be noted from a critical analytical perspective that an MLC-2V+ fraction of 78–84% indicates that 16–22% of the cellular population consists of non-ventricular subtypes (e.g., atrial-like, pacemaker-like, or non-cardiac cells). In an electrically coupled syncytium, this residual subpopulation can subtly influence resting membrane potentials, spontaneous firing automaticity, and syncytial wavefront propagation, representing a potential biological source of baseline variability across independent preparations.
- **Structural and syncytial integrity:** Immunofluorescence staining verified organized sarcomeric alpha-actinin striations and dense expression of the gap junction protein Connexin 43

(CX43), establishing functional electrical syncytial coupling [7,23,24].

- Culturing these cells through a standardized 7-day stabilization period post-thawing established stable spontaneous rhythmicity and reproducible baseline field potential durations (FPD), providing a dependable human-relevant platform for Multi-Electrode Array (MEA) signal acquisition [7,17].

Machine Learning Architecture: Deconstructing Multi-Parametric MEA Signals

Traditional MEA evaluations have predominantly relied on univariate thresholding of Fridericia-corrected field potential duration (FPDcF) [4,25]. However, rate-corrected duration metrics alone can be confounded by severe chronotropic shifts, dynamic repolarization morphologies, or uncoupled conduction delays [7,17,26]. To overcome these constraints, Kim et al. extracted five distinct MEA-derived electrophysiological parameters across 28 CiPA reference compounds [7]:

- **Beat period (BP):** Marker of chronotropic kinetics and intrinsic automaticity [7,26].
- **Field potential duration (FPD):** Uncorrected repolarization duration [7,25].
- **Corrected FPD (FPDcF):** Fridericia-normalized repolarization time [7,25]. Notably, because Fridericia's formula assumes an empirical cube-root relationship established in clinical surface ECGs, it can lose correction accuracy under extreme compound-induced bradycardia or tachycardia, a physiological caveat that multi-parametric modeling helps mitigate.
- **Depolarization spike amplitude:** Reflecting local field depolarization magnitude [4,7]. While often interpreted as an indicator of inward sodium current (I_{Na}) conductance, it is essential to emphasize that extracellular spike amplitude is simultaneously governed by physical electrode-cell interface impedance, local monolayer confluence, and multi-cellular conduction velocity across the electrode array, rather than purely isolated channel conductance.
- **Beating irregularity:** Defined quantitatively as the coefficient of variation of the beat-to-beat interval (CoV_{BP} = standard deviation / mean of beat period) [7,15,22]. This metric serves as a direct quantitative marker of arrhythmogenic instability, temporal dispersion, and beat-to-beat variability.

Pearson correlation analysis demonstrated that while FPD and FPDcF showed expected collinearity ($r = 0.95$), correlations between FPDcF and the other parameters remained low ($|r| < 0.30$) [7]. Although low correlation with FPDcF does not formally prove mathematical orthogonality across all possible parameter combinations, it confirms that spike amplitude, beat period, and beating irregularity supply partially independent, non-collinear biophysical information that captures multi-channel electrophysiological shifts not discernible from repolarization duration alone [7,15].

Evaluating four machine learning architectures (Logistic Regression, Artificial Neural Network [ANN], Random Forest [RF], and Extreme Gradient Boosting [XGBoost]) across repeated-sampling test iterations demonstrated the advantage of multi-

parametric modeling over univariate analysis [7,27]. To clarify the model configurations evaluated by Kim et al., the authors compared multiple input feature subsets: Scenario 1 combined four complementary electrophysiological parameters (FPDcF, spike amplitude, beat period, and beating irregularity), whereas alternative scenarios evaluated sub-combinations (such as FPDcF alone or subsets excluding irregular beating). Feature selection was guided by removing highly collinear pairs (such as uncorrected FPD in the presence of FPDcF) to minimize dimensionality. In the 28-compound benchmarking phase, models were evaluated via 10,000 repeated random sub-sampling validation runs (70% training, 30% testing split). Under Scenario 1, the ANN achieved a reported median ROC-AUC of 0.982 (with XGBoost at 0.964 and Logistic Regression at 0.964) [7], showing improved discriminative metrics compared to historical single-parameter logistic regression benchmarks (ROC-AUC ~0.87 across 28 CiPA compounds reported by Blinova et al., 2018) [7,25] (**Table 1**).

For prospective risk scoring in unknown compounds (such as the oncology panel), Kim et al. implemented a soft-voting ensemble classifier that computes the unweighted average of predicted probabilities across all four trained machine-learning algorithms.

An empirical decision threshold of 0.5 was established based on standard logistic decision boundaries, categorizing compounds with an ensemble predicted probability > 0.5 as high-to-intermediate proarrhythmic risk, and < 0.5 as low risk [7]. This dual-stage methodology effectively leverages individual model architectures for benchmarking while employing ensemble aggregation to enhance classification stability against test variance.

Decoupling Structural Cytotoxicity from Functional Proarrhythmic Liabilities in Anticancer Therapeutics

The translational utility of the integrated AI-hiPSC-CM platform was evaluated using 12 clinically established anticancer agents, comprising anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin), tyrosine kinase inhibitors (sunitinib, sorafenib, erlotinib, vandetanib, crizotinib), and conventional chemotherapeutic agents (cisplatin, carboplatin, cyclophosphamide) [7,27–35]. These therapeutic classes frequently trigger chronic cardiomyopathies, heart failure, or electrophysiological disturbances through diverse cellular mechanisms, including topoisomerase II beta inhibition, reactive oxygen species generation, AMPK signaling disruption, and off-target mitochondrial impairment [36–41].

Table 1. Comparative evaluation of non-clinical proarrhythmic cardiotoxicity screening paradigms.

Evaluation Metric / Feature	Conventional hERG Assay (ICH S7B)	Single-Parametric hiPSC-CM MEA (Blinova et al., 2018)	Multi-Parametric hiPSC-CM + AI Platform (Kim et al., 2026)
Biological Substrate	Recombinant heterologous cell lines (HEK293, CHO)	Commercial hiPSC-CMs (Mixed lineages, variable purity)	High-purity (>95% cTnT+), ventricular-dominant (78–84% MLC-2V+) hiPSC-CMs
Electrophysiological Target	Isolated potassium current (IKr inhibition only)	Multi-channel syncytial repolarization (I_{Kr} , $I_{Ca,L}$, I_{Na})	Integrated syncytium with quantified functional gap junctions (CX43)
Analyzed Biomarkers	Single parameter: IC50 (50% block concentration)	Single parameter: Rate-corrected duration (Δ FPDcF)	Multi-parametric suite: BP, FPD, FPDcF, Spike Amplitude, and Beating Irregularity (CoV_BP)
Confounding Liabilities	Cannot resolve multi-channel balance (false positives: verapamil, ranolazine)	Confounded by severe chronotropic shifts, dynamic morphology, and conduction blocks	Mitigates rate/conduction biases via multi-parametric non-collinear feature integration
Computational Architecture	Empirical safety margin calculation (ETP_unbound / IC50)	Univariate logistic regression (Binary thresholding)	Multi-model comparison (ANN, XGBoost, RF, LR) with soft-voting ensemble for continuous risk scoring
Predictive Performance	Low clinical specificity (~60–70%; risk of false compound attrition)	Moderate multi-site accuracy (ROC-AUC ~0.87 across 28 CiPA compounds)	Reported median ROC-AUC 0.982 (ANN; Scenario 1 combining FPDcF, spike amplitude, beat period, and beating irregularity) across 28 CiPA compounds; prospective validation pending
Structural vs. Functional Decoupling	Not applicable (Acellular/heterologous system)	Limited (Typically short-term acute electrophysiology)	Decouples label-free 120-h impedance (structural viability) from MEA electrophysiology (functional liability)
Regulatory Qualification Status	Established standard guideline (ICH S7B / E14)	Empirical validation model (Early CiPA multi-site pilot)	Candidate NAM framework; formal Context of Use (COU) regulatory qualification pending multi-site validation

Abbreviations: I_{Kr} : Rapid Delayed Rectifier Potassium Current; $I_{Ca,L}$: L-type Calcium Current; I_{Na} : Peak Inward Sodium Current; ETP: Unbound Effective Therapeutic Plasma Concentration; hiPSC-CMs: Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes; MEA: Multi-Electrode Array; cTnT: Cardiac Troponin T; MLC-2V: Myosin Light Chain 2 Ventricular Isoform; CX43: Connexin 43; BP: Beat Period; FPD: Field Potential Duration; FPDcF: Fridericia-corrected Field Potential Duration; CoV_BP: Coefficient of Variation of Beat Period; ANN: Artificial Neural Network; XGBoost: Extreme Gradient Boosting; RF: Random Forest; LR: Logistic Regression; ROC-AUC: Receiver Operating Characteristic Area Under the Curve; CiPA: Comprehensive *in Vitro* Proarrhythmia Assay; NAM: New Approach Methodology; COU: Context of Use.

A critical feature of the experimental design was the explicit decoupling of structural cytotoxicity from functional electrophysiological perturbations [7]:

- **Impedance-Based cytotoxicity profiling:** Continuous label-free impedance monitoring over 120 hours using the Nanion AtlaZ platform (at an optimized 9.6 kHz frequency) revealed marked, dose- and time-dependent cell index declines for eight compounds [1]. However, four agents—idarubicin, erlotinib, sunitinib, and cyclophosphamide—exhibited no detectable impedance-based cytotoxicity under the acute testing window, displaying an absence of overt cell detachment or lysis [7].
- **Electrophysiological deconvolution:** Subsequent MEA functional assays on these four agents with negative impedance profiles revealed pronounced, time-dependent electrophysiological perturbations [7]. Sunitinib (0.3 and 1.0 μ M) induced rapid FPDcF prolongation exceeding 20% within 24 hours, accompanied by a ~40% reduction in beat rate and spike amplitude and severe beating irregularities [7,36,42]. Erlotinib exhibited delayed FPDcF prolongation (>20%) emerging after 72 hours alongside progressive rhythm irregularity [7,28,43]. Conversely, idarubicin and cyclophosphamide induced isolated FPDcF lengthening without triggering severe conduction depression or rhythm breakdown [7,21,32].

When analyzed by the soft-voting ensemble classifier, sunitinib and erlotinib were classified as high-to-intermediate proarrhythmic risk (risk scores >0.5) [7]. It is important to emphasize that sunitinib and erlotinib are already clinically documented to carry cardiovascular and electrophysiological toxicities, including QT prolongation and ventricular arrhythmias [35,42,43]. The fundamental scientific novelty of the Kim et al. platform is therefore not the initial clinical discovery of sunitinib/erlotinib cardiotoxicity, but rather demonstrating that high-content MEA-AI modeling successfully captures functional proarrhythmic liabilities that completely evade detection by label-free cellular viability and impedance assays.

Equally vital is clarifying the interpretation of compounds classified as ‘low risk.’ Idarubicin and cyclophosphamide are well known to exhibit potent clinical cytotoxicity and long-term cardiotoxicity (e.g., anthracycline-induced dilated cardiomyopathy and fatal cyclophosphamide-induced myocarditis/pericarditis). The fact that they received low risk scores (<0.5) in the Kim et al. model should not be misconstrued as evidence of overall cardiac safety. Rather, it highlights that this platform is specifically calibrated to predict ventricular proarrhythmic and torsadogenic liability (TdP risk), rather than all modes of non-electrophysiological or structural cardiotoxicity [7,13,15]. Maintaining this conceptual distinction is essential for appropriate preclinical safety interpretation.

Methodological Limitations and Translational Perspectives

Critical appraisal and machine-learning limitations

While the findings by Kim et al. present a compelling bio-computational paradigm, several critical limitations must be objectively acknowledged before the platform can be considered for generalized drug screening:

- **Sample size and overfitting risk:** The model was trained and benchmarked on only 28 CiPA reference compounds and

evaluated on 12 anticancer agents. In machine learning, training high-capacity non-linear architectures (such as deep ANNs) on small datasets creates a substantial risk of overfitting and optimistic performance estimates. Although repeated random sub-sampling (10,000 iterations) mitigates split bias, it is not mathematically equivalent to true independent prospective validation on blind, external compound cohorts.

- **Model calibration and decision curves:** The study reported classification accuracy primarily via ROC-AUC (0.982). However, high discrimination does not guarantee clinical calibration. In safety pharmacology, calibration analysis (e.g., Brier score, calibration curves) and decision-curve analysis are critical to ensure that a predicted probability of 0.6 genuinely corresponds to a 60% empirical proarrhythmic event rate, avoiding misleading risk categorizations around the 0.5 threshold.
- **Single-Site and platform specificity:** The reported data were derived from a single laboratory utilizing a single hiPSC-CM commercial line (Cardiosight-S) and specific MEA hardware. The true translational viability of any non-clinical assay hinges upon inter-laboratory reproducibility, multi-operator transferability, and platform agnosticism across diverse commercial cell lines and MEA instruments.

Roadmap toward regulatory context of use (COU) qualification

To transition this promising prototype into an accepted, qualified New Approach Methodology (NAM) under ICH E14/S7B and FDA Modernization Act 2.0 frameworks, future international efforts should focus on four coordinated initiatives:

- **Independent multi-centre blinded ring trials:** Executing formal multi-site studies across independent academic, industrial, and regulatory laboratories using blinded compound sets (including prospective non-CiPA positive and negative proarrhythmia controls) to quantify inter-laboratory coefficient of variation and classification robustness.
- **Adherence to AI/ML reporting standards:** Aligning model development with emerging regulatory standards for artificial intelligence in safety evaluation, such as the OECD Good *In Vitro* Method Practices (GIVIMP) and AI/ML reporting guidelines (e.g., TRIPOD-AI), ensuring transparent feature weighting, code accessibility, and reproducible hyperparameter tuning.
- **Physiological maturation in 3D systems:** Implementing metabolic maturation (fatty-acid supplementation) and 3D engineered heart tissue (EHT) platforms to enhance adult-like electrophysiological traits such as resting membrane potential hyperpolarization via IK1 density while enabling concurrent measurement of inotropic contractility alongside electrophysiology [44–48].
- **Mechanistic explainable AI (XAI) and biophysical modeling:** Coupling multi-parametric MEA-AI outputs with explainable attribution frameworks (e.g., SHAP values) and biophysical mathematical simulations (e.g., the Dutta-modified O’Hara-Rudy *in silico* model) [5,6,11,12]. This integration provides mechanistically interpretable ionic justifications to support non-clinical regulatory dossiers.

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Conflict of Interest

J.-M.K. and D.-H.W. are full-time employees of NEXEL Co., Ltd., a biotechnology company commercializing human induced pluripotent stem cell-derived cardiomyocytes (Cardiosight-S) and related cardiac safety testing services. Cardiosight-S was utilized as the primary biological substrate in the focal research article by Kim et al. (2026, *Archives of Toxicology*) evaluated in this Commentary. The authors declare that this Commentary was drafted to provide an objective, critical, and balanced academic discussion of the underlying bio-computational methodologies, their scientific limitations, and the necessary regulatory qualification requirements. NEXEL Co., Ltd. had no role in the editorial commissioning, drafting, or decision to submit this Commentary.

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