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Review Article

Induced Pluripotent Stem Cell-Derived Cardiomyocytes as a Model for Drug Cardiotoxicity Screening

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Abstract

Background: Cardiomyocytes derived from human induced pluripotent stem cells offer a human cardiac substrate for safety pharmacology, and have been adopted faster than they have been validated.

Objective: To review what these cells have been shown to predict, the assay platforms used, and the limitations that qualify the result.

Methods: Narrative review of differentiation and maturation studies, assay development, and the blinded multisite validation work.

Findings: A ten-site blinded study of 28 drugs separated low-risk from higher-risk compounds with an area under the curve of 0.872, and a consortium study reported 81% sensitivity and 87% specificity. Against this, the cell line contributed more variance than the testing site, and monolayer cells carry roughly half the sodium current density of adult myocardium.

Conclusions: The cells detect repolarisation delay reliably. Specificity, not sensitivity, is the unresolved problem, and the regulatory framework treats them as confirmatory rather than primary.

Keywords: induced pluripotent stem cells; cardiomyocytes; cardiotoxicity; proarrhythmia; safety pharmacology

Introduction

Drug-induced arrhythmia has removed more compounds from development than almost any other toxicity, and the assay used to predict it has for two decades been a hERG channel block measurement in a non-cardiac cell line. That assay is sensitive and poorly specific: it flags compounds that block the channel without producing arrhythmia in patients, and a human cardiac readout has been sought for as long as the deficiency has been recognised.

Reprogramming supplied one. Human somatic cells were induced to pluripotency with four defined factors [1], functional cardiomyocytes were derived from the resulting lines [2], and differentiation became efficient and defined through temporal modulation of canonical Wnt signalling [3] and then in chemically defined medium [4]. By 2015 a laboratory could generate large numbers of contracting human cardiomyocytes on a predictable schedule, and the question moved from whether the cells could be made to what they could be trusted to tell you.

This review considers that second question.

Materials and Methods

Studies were retrieved from Crossref, Europe PMC and publisher records for the terms *induced pluripotent stem cell*, *cardiomyocyte*, *cardiotoxicity*, *proarrhythmia*, *CiPA* and *multielectrode array*, without date restriction. Priority was given to blinded or multisite validation studies, since single-laboratory reports of predictive accuracy are not comparable. Every bibliographic record was confirmed at source, and quantitative values were taken from the source rather than from secondary citation.

Differentiation and the immaturity problem

The cells are not adult cardiomyocytes and no one claims otherwise; the disagreement is over whether the difference matters. They resemble fetal myocardium in sarcomere organisation, in electrophysiology and in metabolism, and

the position has been reviewed repeatedly [5]. The most useful framing asks directly whether this is a fatal flaw or a soluble problem [6], and the honest answer depends on which property the assay depends on.

Maturation strategies work, and the quantitative gains are substantial. Engineered heart tissue raises sodium current density from -10.3 ± 1.2 pA/pF in monolayer to -18.5 ± 1.9 pA/pF, against -20.2 pA/pF in adult human ventricle, and upstroke velocity in that format (219 ± 15 V/s) does not differ significantly from adult left ventricle (253 ± 7 V/s) [7]. Electromechanical conditioning of early-stage tissue produces adult-like gene expression, a sarcomere length of $2.2 \mu\text{m}$ and 30% mitochondrial density after four weeks [8]. Substituting galactose and fatty acids for glucose raises estimated ATP production 2.7-fold, from 687 to 1843 nmol/h [9].

The difficulty is that almost none of the screening data were generated in these formats. The cells that have been validated are monolayer cells.

Assay platforms

Four readouts dominate. Microelectrode arrays record the field potential and its duration, and were applied to arrhythmia screening early [10]. Voltage-sensitive dyes give an optical action potential, with ratiometric measurement correcting for motion artefact [11]. Calcium and contractility can be extracted from video [12]. Engineered heart tissue reports force directly, and blinded contractility analysis in that format has been compared against human atrial trabeculae [13].

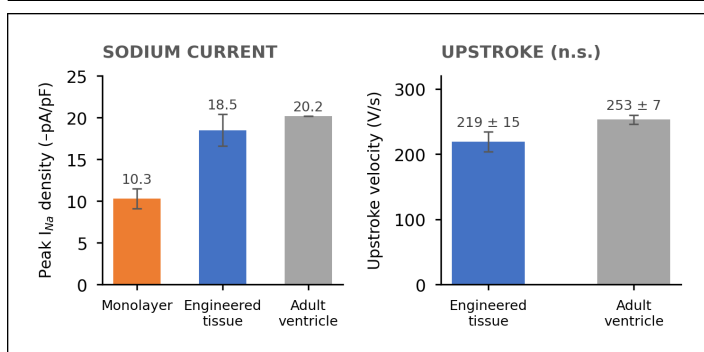


Figure 1: Sodium current density and upstroke velocity in monolayer culture, engineered heart tissue and adult human ventricle. Engineered tissue closes most of the gap; monolayers, in which nearly all screening is done, do not. Data from Lemoine et al. [7].

Each measures something different, and a compound may prolong field potential duration without altering contractility or vice versa. The choice of platform is therefore part of the claim being made.

What has been validated

The early demonstrations were encouraging and single-site: proarrhythmia risk was estimated from field potential recordings [14], and the Maestro platform was assessed against a blinded compound set [15]. That second study is worth reading carefully, because it found the readout sensitive but unable to distinguish low-risk from high-risk torsadogens, and said plainly that the model would carry a false-positive rate.

The Comprehensive in Vitro Proarrhythmia Assay initiative was the field's structured response to exactly this problem. Its rationale and progress were set out by the consortium that ran it [16]. The stem cell component was assessed in a translational study [17] and then in the study that matters most: ten sites, 28 drugs, two commercial cell lines, blinded, with standardised protocols [18]. A three-endpoint model separated low-risk from combined intermediate and high-risk compounds with an area under the receiver operating characteristic curve of 0.872, falling to 0.826 for a three-category outcome. A parallel consortium study of 60 drugs reported sensitivity of 81%, specificity of 87% and accuracy of 83% [19]. Cross-site

reliability across three microelectrode array platforms was examined separately [20].

One number from the ten-site study deserves more attention than it receives. When site was treated as a fixed effect, the mean squared error introduced by site was 170 ms, while that introduced by the cell line was 245 ms [18]. The reagent, not the operator, is the noise floor.

Patient-derived models and oncology

Where the cells have been least equivocal is in modelling variation between people rather than between drugs. Long QT syndrome was reproduced in patient-derived lines [21], and lines from breast cancer patients recapitulated their own predilection to doxorubicin cardiotoxicity [22]. Tyrosine kinase inhibitors have been screened at scale in the same way [23], and the approach in oncology drug development carries a scientific statement from the American Heart Association [24].

That variation cuts both ways. Common genetic variation drives molecular heterogeneity between lines [25], and batch variation between commercial suppliers has been characterised [26].

Discussion

Three conclusions follow. First, the sensitivity claim is well supported and the specificity claim is not. Every study that has looked has found the cells good at detecting repolarisation delay; the studies that report specificity rely on bespoke scoring paradigms rather than a generic readout.

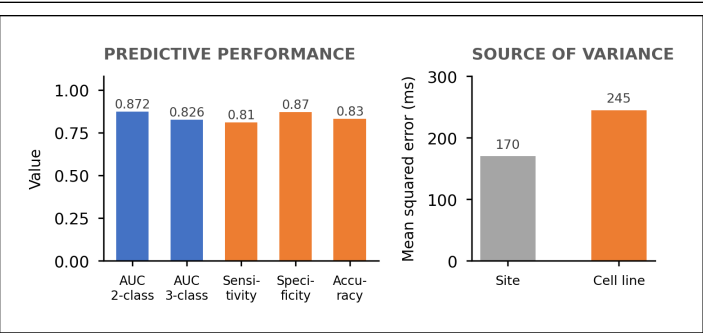


Figure 2: Predictive performance reported by the two largest blinded studies, with the variance decomposition from the ten-site study shown alongside. The cell line contributed more variability than the testing site. Data from Blinova et al. [18] and Ando et al. [19].

Second, the dominant source of variability is the cells themselves. That is uncomfortable, because it cannot be fixed by better laboratory practice, and it sets a ceiling on what standardisation can achieve.

Third, the regulatory position is more modest than the field’s enthusiasm. The evolving strategy places these cells as one input among several [27], and the ICH E14/S7B revision frames them within a package built on in silico ion channel modelling [28]. CiPA demoted the stem cell assay to a confirmatory check rather than the primary discriminator, which is a quieter verdict than the literature usually admits.

This is a narrative review without systematic search or risk-of-bias assessment. Predictive accuracy figures are not comparable across studies because compound sets, risk categorisations and endpoints differ.

Conclusion

Cardiomyocytes derived from induced pluripotent stem cells are a genuine advance over a channel assay in a non-cardiac cell, and the blinded multisite evidence supporting their sensitivity is stronger than that available for most preclinical models. The unresolved problems are specificity, line-to-line variability that exceeds site-to-site variability, and the gap between the mature formats in which the cells behave most like myocardium and the monolayer formats in which nearly all screening is done.

Studies should report cell line and lot, culture format and platform alongside any predictivity claim, and should state which risk categorisation was used, since that choice alone moves the reported accuracy.

Table 1: Blinded and multisite studies of proarrhythmia prediction, and what each actually tested.				
Study	Drugs	Sites	Platform	Headline result
Guo 2011	Not blinded	1	Field potential	First risk estimate from hiPSC-CMs [14]
Qu 2015	15 blinded	1	Maestro MEA	Sensitive; specificity low [15]
Blinova 2017	26 + 3 combinations	Multi	Voltage dye and MEA	Translational assessment [17]
Ando 2017	60 (57 risk-classified)	Consortium	MEA	Sensitivity 81%, specificity 87% [19]
Blinova 2018	28 blinded	10	MEA and optical	AUC 0.872 (two-class) [18]
Millard 2018	8 blinded	13	Three MEA platforms	Cross-site reliability [20]

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Conflict of Interest

The authors declare that they have no competing interests relevant to the content of this review.

Ethics Statement

This article reviews previously published studies and contains no new studies with human participants or animals performed by any of the authors. Ethical approval was therefore not required.

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