The integrated Strategy for Cardiac Safety Liability Assessment to Improve the clinical translation value

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Introduction

Cardiac safety liability assessment is essential in drug development to prevent arrhythmias like torsades de pointes (TdP), which can cause sudden death. Traditional ICH S7B and E14 guidelines focus on hERG blockade and QT prolongation, but these lack specificity, leading to high attrition or missed risks. The Comprehensive in vitro Proarrhythmia Assay (CiPA), launched in 2013 by FDA, academia, and industry, shifts to a mechanistic paradigm. It integrates in vitro ion channel assays, in silico modeling, hiPSC-CM evaluations, and clinical ECGs to predict proarrhythmia accurately, reducing animal use and improving efficiency. Validated with 28 reference compounds, CiPA enhances specificity.

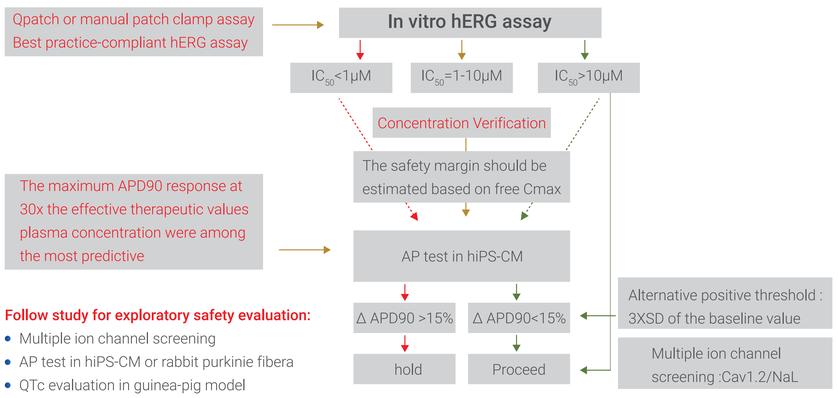
1. Translational Value of Combining hERG Assay and hiPSC-CM Action Potential Assay

The hERG assay detects IKr potassium channel blockade, a key cause of delayed repolarization, but overestimates risks by ignoring multi-channel interactions, causing false positives. hiPSC-CM action potential (AP) assays use MEA or optical methods to measure integrated responses in human-like cardiomyocytes, capturing repolarization, depolarization, and arrhythmogenic events like early afterdepolarizations. Combining them bridges molecular (hERG potency) and cellular (hiPSC-CM) levels, improving translational relevance. Studies show this reduces false positives by 30-50%, correlates strongly with clinical QT/TdP, and outperforms hERG alone in predicting human outcomes. It enables early derisking, aligns with ethical standards, and supports efficient discovery.

2. Integration of CiPA

CiPA's tiered approach directly assesses torsadogenic potential via four components: (1) Multi-ion channel assays (hERG, Nav1.5, Cav1.2) for potency; (2) In silico simulations of AP and TdP metrics; (3) hiPSC-CM validation of cellular effects; (4) Phase 1 ECG biomarkers for clinical translation. This quantifies channel interactions (e.g., compensatory effects), refines risk stratification, and validates across drugs. It minimizes attrition, animal testing, and accelerates therapeutics. Ongoing refinements, like open data and pharmacology models, promote regulatory adoption.

Integrated Assessment Strategy in ICE

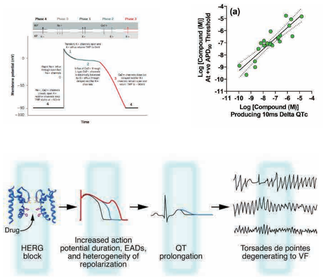


Follow study for exploratory safety evaluation:

- Multiple ion channel screening
- AP test in hiPS-CM or rabbit purkinie fibera
- QTc evaluation in guinea-pig model

How to design the in vitro assay combinations that could provide more clinically translatable assessments

A Basic reasoning



1. in vitro hERG assay
   - hERG block and TdP: positive correlation but not absolutely causality
   - More and earlier hERG test, more safety and less cost

2.In vitro hiPS-CM action potential assay
   - A good correlation between increase in hIPS-CM APD90 and clinic QTc prolongation or TdP risk prediction

B "Double-Negative" Scenario

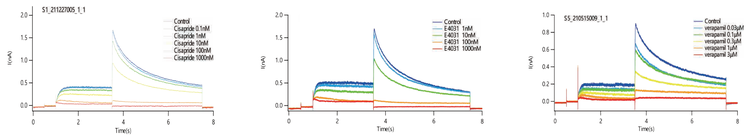
QT prolongation risk category	hERG assay[a]	In vivo QT Assay[b]	Probability of clinical QTc prolongation (%)[c]	Probability of TdP liability (%)[c]	ICH S7B follow-up studies for consideration	Potential early clinical QTc testing
High	Negative	Negative	3.8	0.1	None	Collect safety ECGs.[d]
LOW	Positive	Positive	84.1	93.5	Potential use of proarrhythmia model, e.g., CIPA paradigm.	Quantitative assessment of OT and other intervals.
Intermediate	Negative	Positive	31.1	22.0	Consider (i) characterizing potential for hERG-blocking metabolite, (ii) other evidence of indirect QT effects e.g. temperature or hypokalemia, (iii) use of proarrhythmia model (e.g., CIPA paradigm).	Rigorous Quantitative assessment of OT and other intervals as indicated by followup studies.
	Positive	Negative	31.4	4.7	Consider heart rate effects. Consider additional ion channels or kinetics of hERG block. Consider use of proarrhythmia model (e.g., CIPA paradigm).	Rigorous quantitative assessment of QT and other intervals as indicated by follow-up studies.

Negative or positive hERG outcome is defined by high (≥ 30-fold) or low (< 30-fold) margin,; hERG margin= hERG IC50/EFTPC
In vivo QT negative: No QT effect (<10 ms) and expected clinical exposure ≥ 10 times
Positive QT in vivo: with QT impact and expected clinical exposure <10 times

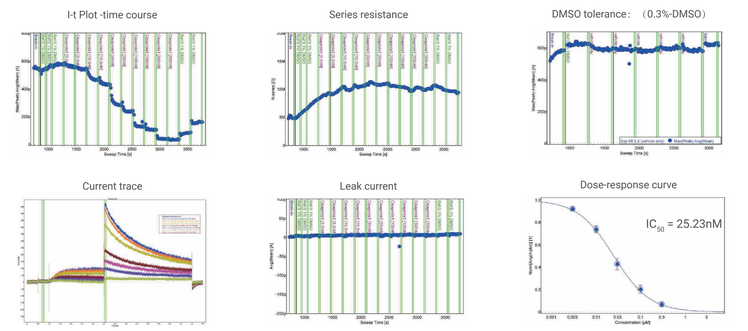
Comprehensive CiPA Ion Channel Panel

Electrophysiological assay for hERG

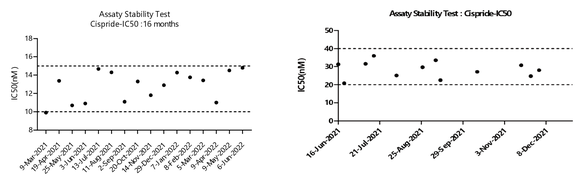
A Manual patch clamp assay for hERG



B Qpatch assay for hERG

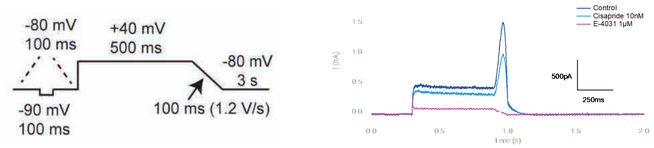


C The robustness of hERG assay



Drugs	Manual patch clamp IC_{50}	Automated patch clamp $1C_{50}$
Cisapride	14.4nM	28.8nM
Amitryptyline	3700nM	5732.3nM
E4031	11.0nM	24.3nM
Quinidine	596.6nM	1124.9nM
Mexiletine	55900nM	50174.7nM
Verapamil	169.6nM	636.7nM
Ranolazine	8000nM	8811.6nM
Nifedipine	170500nM	133655.9nM

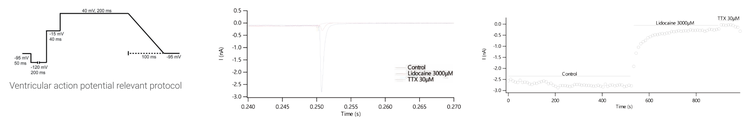
hERG assay at at physiological condition



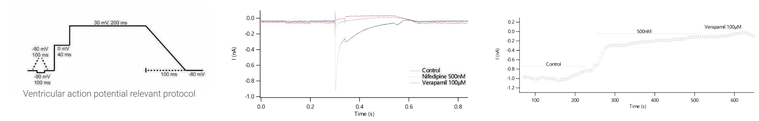
	Room Temperature (IC_{50})	Physiological Temperature (IC_{50})
Erythromycin	>900 μM	105.5μM
E-4031	20.38nM	10.58nM
Terfenadine	16.64nM	27.69nM
Cisapride	16.37nM	18.16nM

Cav1.2 and Nav1.5 assay

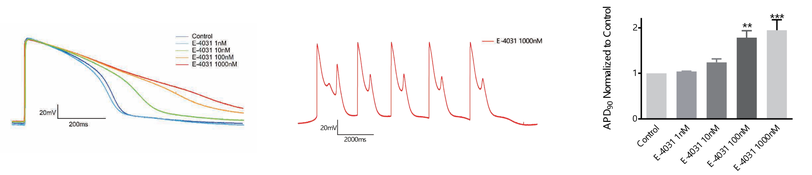
The Effect of Lidocaine on Nav1.5-Peak at PT with Protocol Relevant to Ventricular AP



The Effect of Nifedipine on Cav1.2 at PT with Protocol Relevant to Ventricular AP



Action potential assay



Other follow-up study

Action Potential Assay in Rabbit Purkinje Fiber Prep.

The isolated heart perfusion-- Langendorff

Summary

This integrated platform enables rapid identification of cardiac safety liability using a couple of in vitro assay in early phase with a good clinical translational value.