Translating NAM Innovation into Regulatory Practice

FDA Progress and Collaborative Opportunities

Ksenia Blinova
Associate Director,
Division of Applied Regulatory Science (DARS)
CDER/OTS/OCP

Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's view or policies.

Important Milestones since the Last CiVM Workshop

- ✓FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs - Roadmap published in April 2025
- ✓GAO publishes “Human Organ-on-a-Chip” report in May 2025
- ✓CDER establishes CDER NAMs Coordinating Committee CDERNAMS@fda.hhs.gov in June 2025
- ✓ISTAND becomes a permanent qualification program for innovative approaches in drug review in July 2025

CIVM Qualification Pathway Considerations

FDA'S Development Tools and Programs

Drug Development Tools (DDT) Program

Includes qualification programs for:

- Animal models
- Biomarkers
- Clinical Outcome Assessment
- ISTAND

Medical Device Development Tools (MDDT)

Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program specifically lists tissue chips (i.e., microphysiological systems) as a tool that may advance our understanding of drugs and might be considered for the ISTAND program (along with i.e., use of artificial intelligence (AI)-based algorithms). ISTAND applicability should be stated in the submission (not COA, and not biomarker).

3-Step Qualification Process:

ISTAND Accepted Submissions - 1

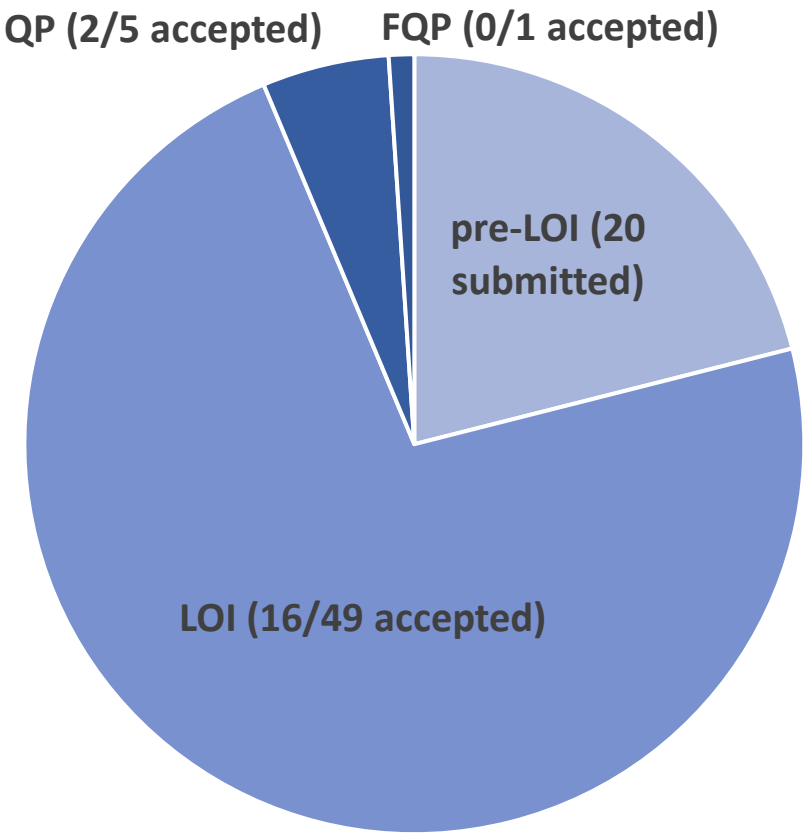
Project #	Acceptance Date (R indicates reviewable date)	Requester	Project Title
DDTIST0006	**QP 2025-01-08** LOI 2022-07-01	Integral Molecular, Inc.	Specificity Screening of Biotherapeutics for Improved Safety Profiling in IND Applications Using the Membrane Proteome Array (MPA)
DDTIST0014	LOI 2023-11-30	Deliberate Solutions, Inc.	AI-COA™ for Automated Depression and Anxiety Severity Measurement
DDTIST0015	LOI 2023-01-23	Fresenius Kabi Deutschland GmbH	Local tolerance of epidurally/intrathecally administered leachables in vitro
DDTIST0016	**QP 2025-07-08** LOI 2024-09-03	Emulate	Human Liver-Chip for Prediction of Drug-Induced Liver Injury
DDTIST0020	**QP 2025-09-16R** LOI 2024-03-08	AstraZeneca	Automating Identification, Detection, and Adjudication (AIDA) of Clinical Events using Artificial Intelligence (AI) and Machine Learning (ML)
DDTIST0027	LOI 2024-12-12	Brigham and Women's Hospital	The Heart Failure Natural Language Processing (HF-NLP) Model
DDTIST0028	LOI 2024-12-27	Dr. Yaoshi Wu	Interval-Specific censoring set adjusted Kaplan-Meier estimator (WKE) to estimate the survival function for the time-to-event endpoints in clinical trials.
DDTIST0032	LOI 2025-01-29	Charles River Laboratoires, Inc., (CRL)	Use of Retrogenix Platform Specificity/Off-target Screening to Enhance Biotherapeutic Safety Assessment
DDTIST0034	LOI 2025-06-23	Organ Pathobiology and Therapeutics Institute, U Pitt	Liver acinus microphysiological system (LAMPS) for determining drug candidate dosing in clinical trials of liver disease.

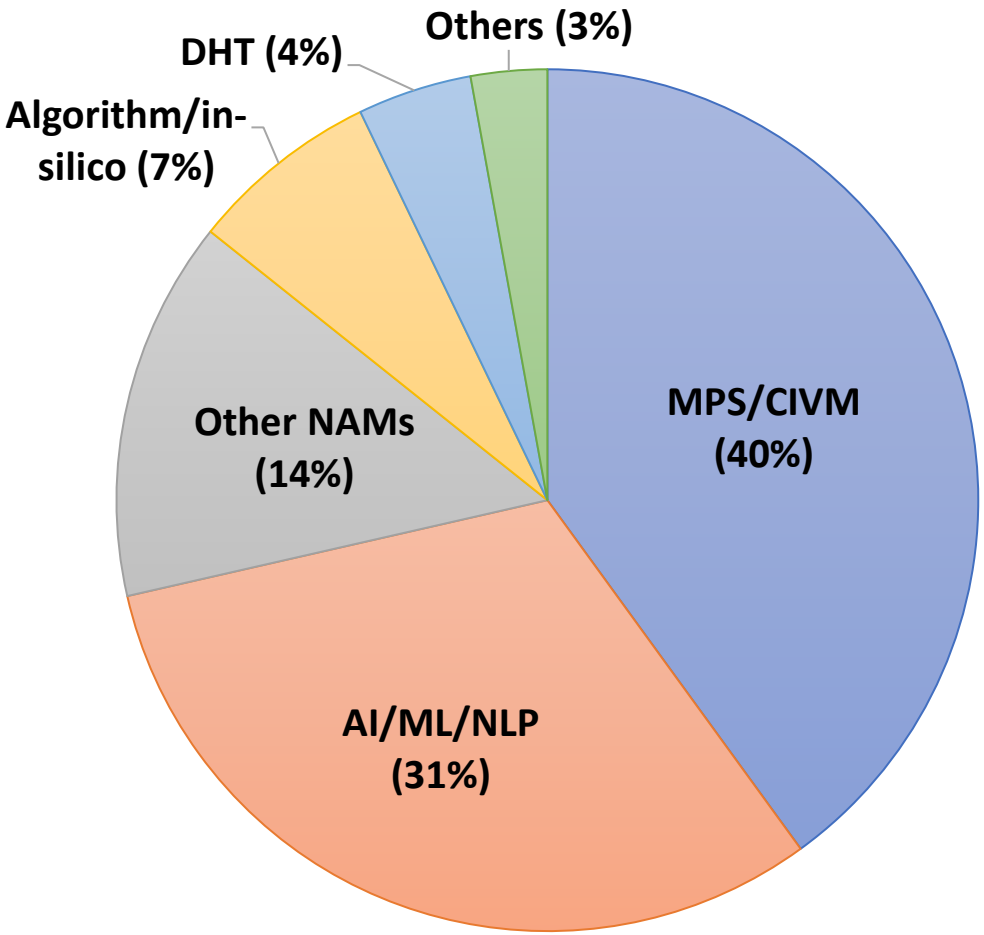
ISTAND Accepted Submissions - 2

Project #	Acceptance Date	Requester	Project Title
DDTIST0043	LOI 2026-01-14	3Rs Collaborative	Microphysiological Systems to Investigate Clinical Drug Induced Liver Injury Risk
DDTIST0044	LOI 2025-11-25	Organ Pathophysiology and Therapeutics Institute	Quantifying hepatotoxicity using the liver acinus microphysiological system (LAMPS) for determining drug candidate dosing in clinical trials of liver disease
DDTIST0045	LOI 2025-11-13	Icahn School of Medicine at Mt. Sinai	Human Kidney Chip for Assessment of Relative Nephrotoxicity
DDTIST0046	LOI 2025-12-19	Johnson and Johnson	Remote Disease Severity Assessment for Psoriasis Drug Clinical Trials: At-Home Image Collection and Artificial Intelligence-Based Scoring Models
DDTIST0047	LOI 2025-11-13	Texas A&M University	Human chorio-decidual interface organ on chip for derisking positive rodent DART studies for new modality investigational new drug candidates
DDTIST0048	LOI 2026-01-21	AIRA Matrix Private Limited	Artificial Intelligence-based solution for automated spermatogenic staging and toxicity assessment in rats. (AIRAToxStage)
DDTIST0049	LOI 2025-12-19	Axion BioSystems	Human iPSC-Cardiomyocyte MEA Assay for Prediction of Clinical Cardiovascular Repolarization Risk

Submissions and FDA letters are available: https://force-dsc.my.site.com/ddt/s/

ISTAND Submissions as of Feb 25, 2026

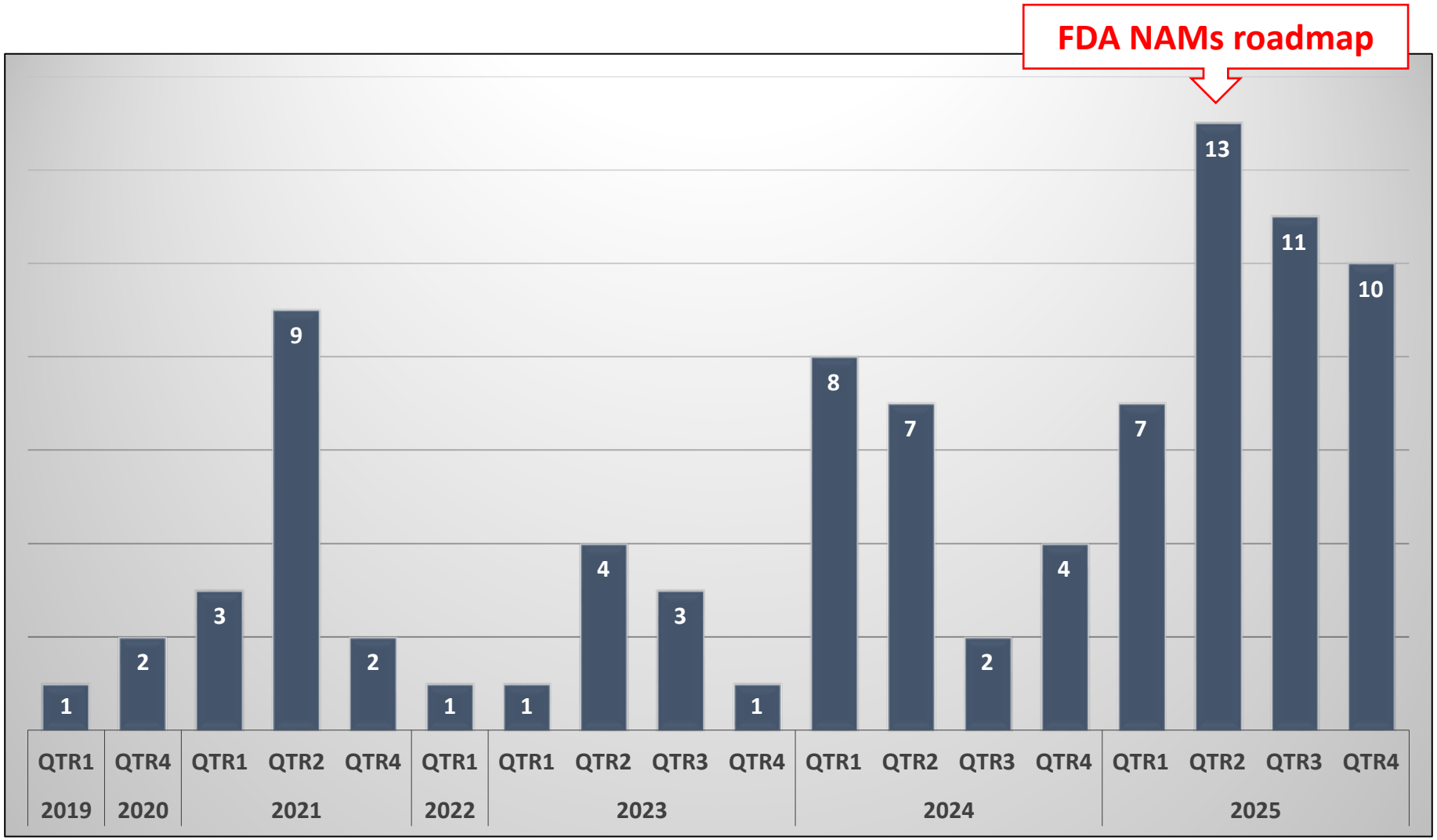




Acknowledgement: York Tamita and the ISTAND and the Biomarker qualification Teams

ISTAND@fda.hhs.gov

Qualification Submissions per Quarter



* As of 12/31/2025

Collaboration Opportunities: Division of Applied Regulatory Science (DARS)

DARS VISION
To move new science into the FDA regulatory process and address emergent regulatory and public health questions

DARS MISSION
To engage stakeholders in mission-critical laboratory, computational, and clinical applied research to inform regulatory decision-making and to address public health

DARS has a multi-disciplinary approach available in a single unit

Computational

Laboratory

Clinical

Complex In Vitro Models Laboratory (CIVM Lab)

The DARS CIVM lab develops in vitro models to assess drug effects on vital organs, toxicity, and drug transfer/pharmacokinetics.

Current Capabilities:

- Nonclinical human NAMs
- hiPSC derived tissues
- Microphysiological systems
- High-content imaging and functional analysis

Cardiac NAMs

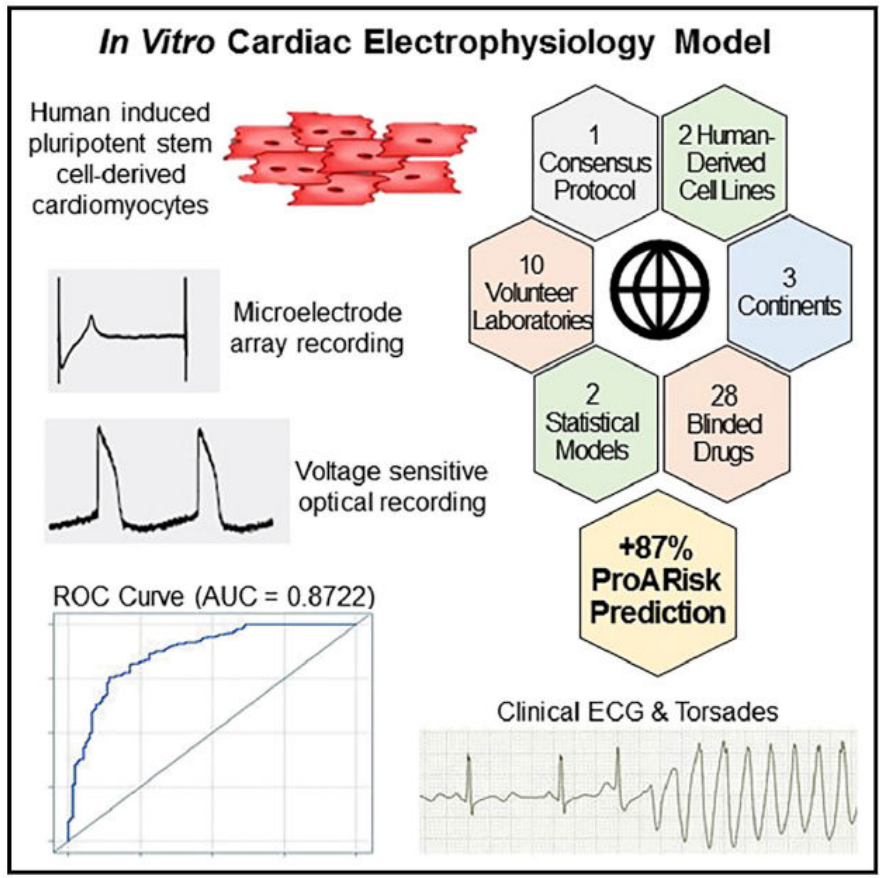
CiPA Paradigm and hiPSC-CM Validation Study

CiPA: A shift from reliance on the traditional clinical TQT studies to a mechanistic assessment of proarrhythmic risk

E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential — Questions and Answers

Guidance for Industry

August 2022



hiPSC-CM assay categorized drugs into high and intermediate vs. low TdP risk groups with 0.87 accuracy

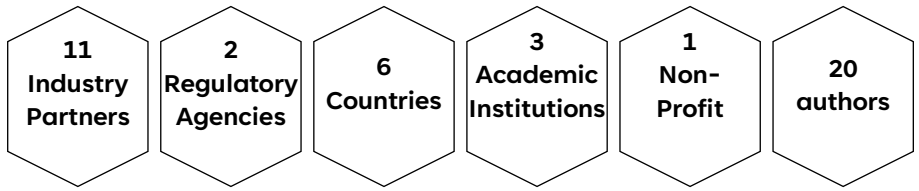
International Multisite Study of Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes for Drug Proarrhythmic Potential Assessment

Ksenia Blinova [1], Qianyu Dang [2], Daniel Millard [3], Godfrey Smith [4], Jennifer Pierson [5], Liang Guo [6], Mathew Brock [7], Hua Rong Lu [8], Udo Kraushaar [9], Haoyu Zeng [10], Hong Shi [11], Xiaoyu Zhang [12], Kohei Sawada [13], Tomoharu Osada [14], Yasunari Kanda [15], Yuko Sekino [16], Li Pang [17], Tromondae K Feaster [18], Ralf Kettenhofen [19], Norman Stockbridge [20], David G Strauss [21], Gary Gintant [22]

Cell Reports, 2018, 24(13):3582-3592

Best Practice Recommendations for hiPSC Assays

Volume 117, November 2020

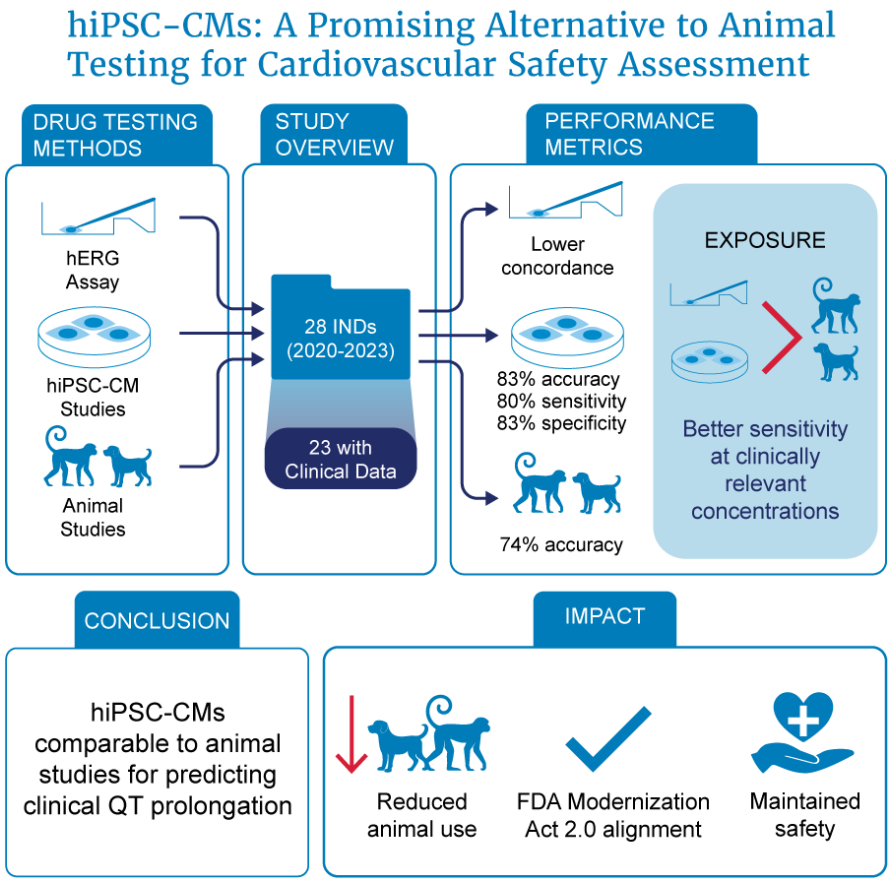


Gintant et al., Reg Tox and Pharm, 2020

hiPSC-CM = human induced pluripotent stem cell derived cardiomyocytes;
CiPA = Comprehensive in vitro Proarrhythmia Assay

hiPSC-CM Assay in Context: Comparison with hERG, In Vivo, and Clinical QT Data

CDER-led hiPSC-derived cardiomyocyte assay for drug-induced QT prolongation assessment

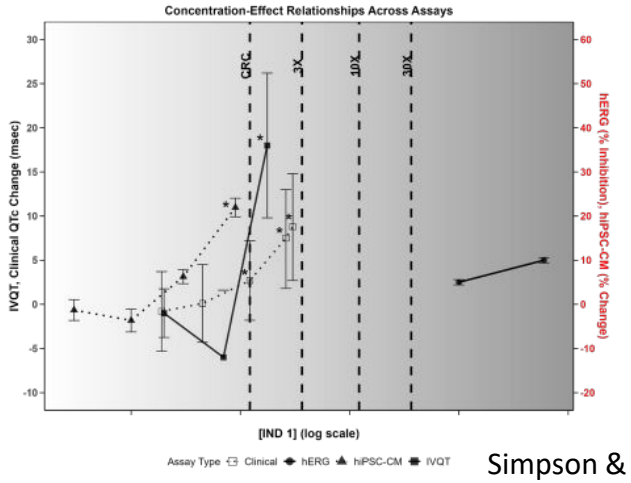


hERG, Animal, and hiPSC assays predictions of Clinical QT prolongation

Nonclinical studies compared to clinical QTc prolongation ≥ 10 msec

Endpoint	Concordance	Sens	Spec	PPV	NPV	MCC	LR+	LR-	PPT	NPT
hERG block at ≤ 10 μM	0.61	0.60	0.61	0.30	0.85	0.18	1.54	0.65	28%	14%
hiPSC-CM	0.83	0.80	0.83	0.57	0.94	0.57	4.80	0.24	54%	6%
hERG+hiPSC-CM	0.57	0.80	0.50	0.31	0.90	0.25	1.60	0.40	29%	9%
IVQT ≥ 10 msec	0.74	0.40	0.83	0.40	0.83	0.23	2.40	0.72	37%	15%
IVQT ≥ 10 msec + Other	0.78	0.80	0.78	0.50	0.93	0.50	3.60	0.26	47%	6%

Pre-Test Probability 20%



Simpson & Feaster et al. 2026 (Under Review)

Increased hiPSC-CM use in drug development and submissions to FDA to support regulatory decision making. 100+ hiPSC-CM study reports submitted. CDER concordance analysis revealed cardiac NAMs are a promising alternative to animal testing for QT prolongation assessment.

hiPSC-CM MEA Assay Review Teaching Tool

Teaching Tool: hiPSC-CM MEA Assay Review

Using this Teach Tool: The following Teach Tool provides an example of a high-quality GRP review for the given topic. Extra hints and tips are referenced (look for highlights) as footnotes. Hints and tips communicate valuable rationale and/or provide helpful explanation where the author deems necessary. While this Teach Tool is one example of expert review, you are encouraged to consult with your team leader/supervisor regarding expectations for review style, focus, and length.

Study Title: Effect of TK123 on Electrophysiological Endpoints in Human Stem Cell-Derived Cardiomyocytes[1]

Study No.:	12345
Study Date:	DATE
GLP Compliance:	No[2]
Testing Facility:	Name of Facility, City, State (or country)
Test article:	TK123 (dihydrochloride salt form, lot # NAM-11-121-BB1-18; purity ≥98.5%)

Objective[3]

To evaluate the functional effects of TK123 on human stem cell-derived cardiomyocytes electrophysiological properties and assess TdP risk potential.

Method/Study Design

Test article was prepared in DMSO[4] and stored frozen and protected from light. Final test article concentrations (0.1, 0.3, 1, 3, 10, 30, 100, and 300 µM)[5] were prepared on the day of testing by diluting the stock solution in assay medium. Final concentrations were selected based on preliminary studies. Samples of the test article formulation solutions collected from each well were analyzed for

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[1] Cell line validation: iCell Cardiomyocytes[2] (iCCM2) are the most common cells used and the only commercially available CiPA validated cells. These cells are normally cryopreserved at approximately day 30 of differentiation and have been extensively validated in Blinova et al. (2018).

[2] GLP considerations: Given this is considered a safety pharmacology study, it is expected to be conducted according to GLP standards however this is not yet a requirement for the hiPSC-CM assays. Best practices described in Gintant et al. (2020) and E14 Q&A should be followed for experimental design and conduct.

[3] Study objective: The hiPSC-CM MEA cardiac liability assay is a drug development tool used to assess the delayed repolarization risk and TdP risk potential of small molecule candidate drugs in adults to create human-relevant data for the candidate drug's IND submission.

[4] Vehicle specifications: Low DMSO concentration should be used. Vehicle control groups should be included on each plate with time-matched controls. Some sites in Blinova et al. (2018) reported solubility issues requiring sonication, 37°C incubation, or doubled DMSO content (0.2%) for certain compounds.

[5] Concentration range: Test substance should be evaluated at an appropriate concentration range relevant to expected clinical exposure. Suggested concentration range (0 to 100 µM at a minimum) should be below, include, and exceed estimated Cmax. Blinova et al. (2018) used four concentrations per drug with either logarithmic or half-logarithmic intervals.

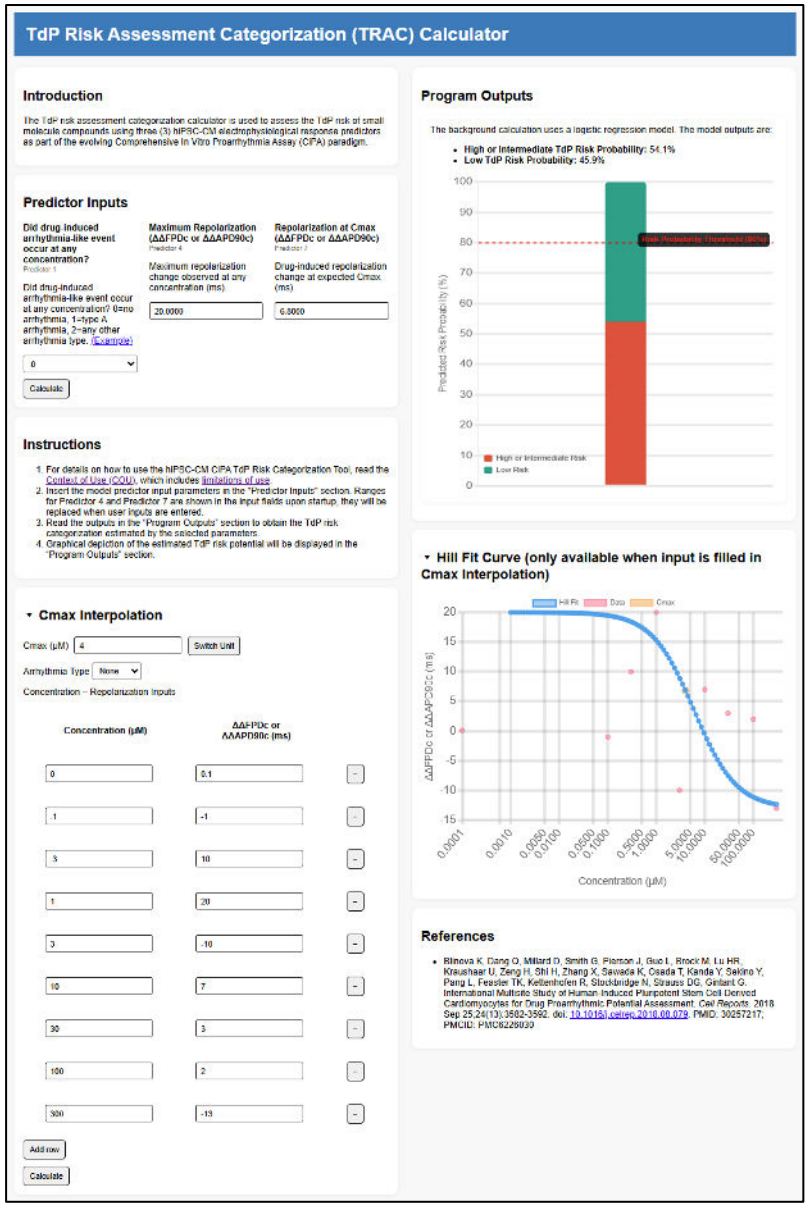
Purpose

This tool outlines how to review and interpret hiPSC-CM repolarization waveform parameters and can be used as a tool to ensure that all required information is present in a study report. This will provide a faster response to sponsors and more consistent review of hiPSC-CM repolarization assay study report submissions, reducing the need for additional consults, animal studies, and re-review rounds.

Context-of-use (COU)

The hiPSC-CM MEA cardiac liability assay is a drug development tool used to assess the delayed repolarization risk and TdP risk potential of small molecule candidate drugs in adults to create human-relevant data for the candidate drug's Investigational New Drug (IND) submission, providing greater evidence of safety assurance for regulatory decision making that enables Phase I clinical trials.

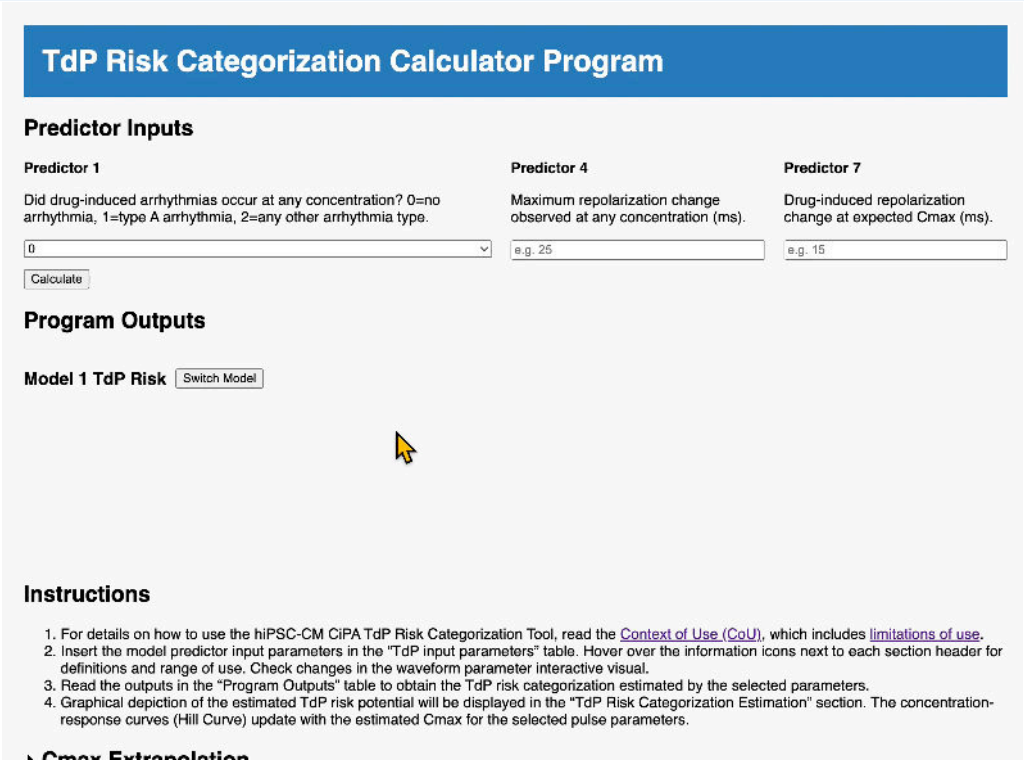
TdP Risk Assessment Categorization (TRAC) Calculator



TRAC Calculator

Open-source web-based online tool for quick evaluation of Torsades de Pointes (TdP) risk for in vitro hiPSC cardiomyocytes models. Streamlines TdP risk estimation for routine regulatory use

Software Available: https://github.com/FDA/TRAC-Calculator

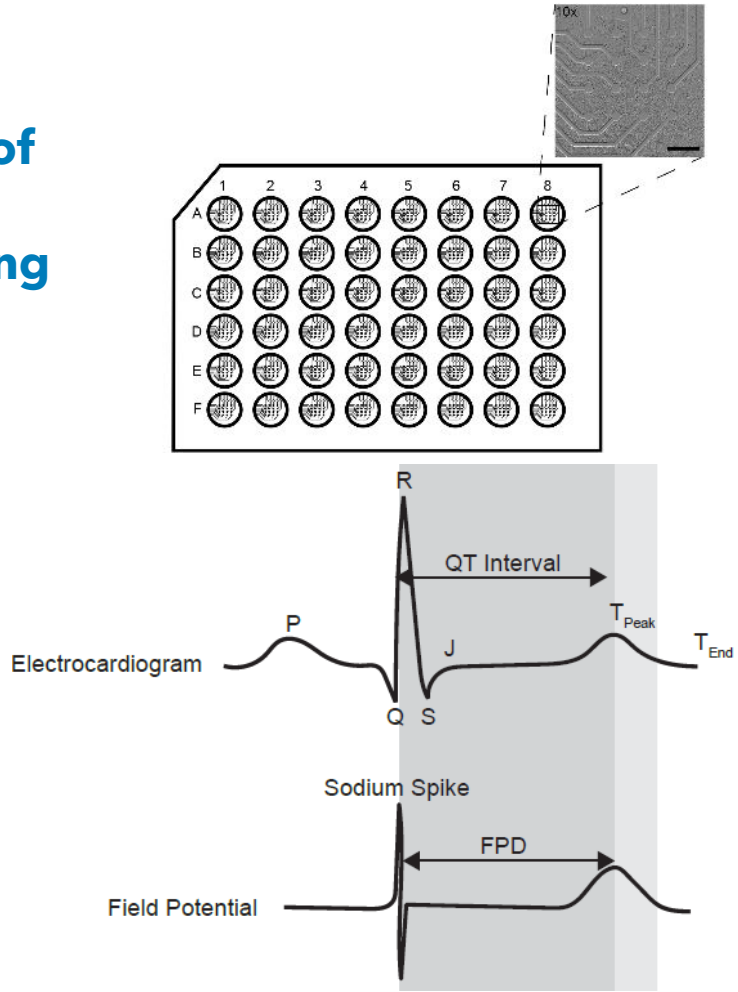


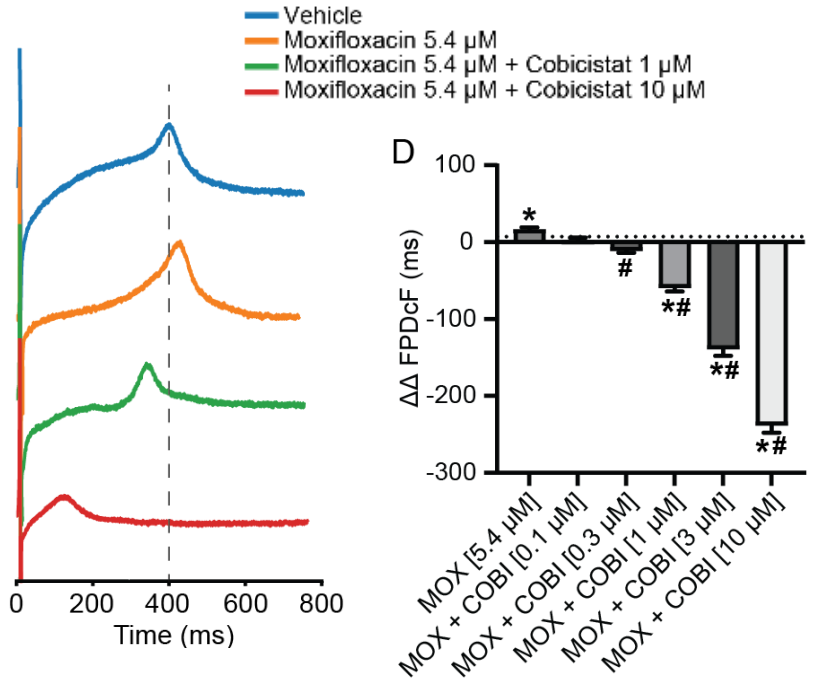
Feaster & Ma et al. 2026 (Under Review)

Cardiac NAMs for Assessing Proarrhythmic Risk of Drug Combinations: A Case Study

CDER led project evaluating the use of a cardiac NAM to assess the safety of moxifloxacin (a drug known to prolong repolarization) and cobicistat (a drug known to shorten repolarization).

- hiPSC-CM are plated onto a multielectrode array. Drug induced changes in the field potential duration (FPD) are measured.
- Studies have shown that the FPD measured in vitro correlates well with the QT interval measured in the clinic.





Geiger et al. 2025, *Frontiers Drug Discovery.*

This assay can be used to understand the net electrophysiological effect of a drug combination prior to clinical trials.

Human Cardiac Microphysiological System for Drug Testing

Ensuring Reproducibility in Cardiac MPS Models and Functional Evaluation of Vanoxerine Using Cardiac MPS

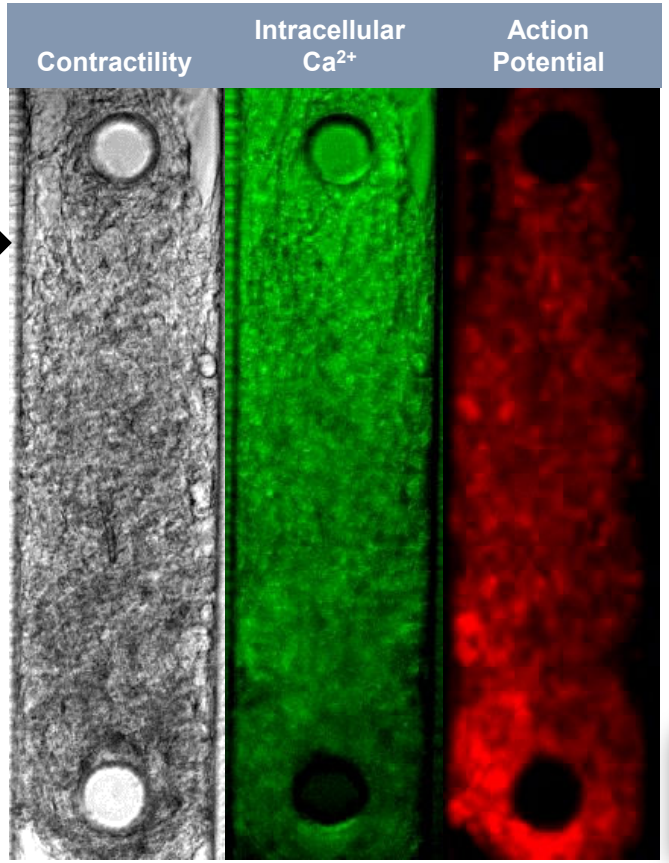
Overview

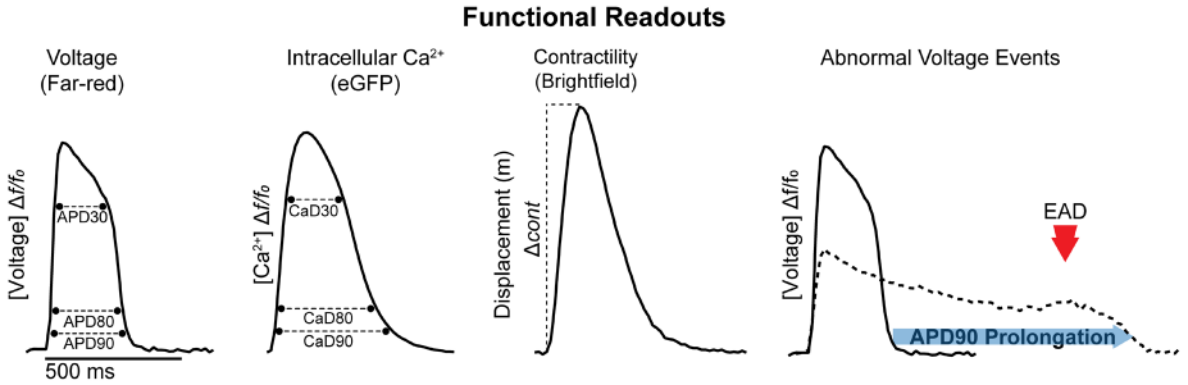
- Organ-on-a-chip platform mimicking human cardiac tissue.
- Integrated media inlet/outlet for nutrient/drug exchange.
- Central cell chamber loaded with in-house derived iPSC-CMs.
- Enables assessment of drug-induced cardiac function changes.

Key Features

- Real-time imaging of cardiac function
- Calcium handling via genetically encoded fluorescent indicator.
- Membrane potential changes via non-toxic voltage-sensitive dye.
- Cardiac contraction

Garcia et al. 2025, *Nature Protocols*





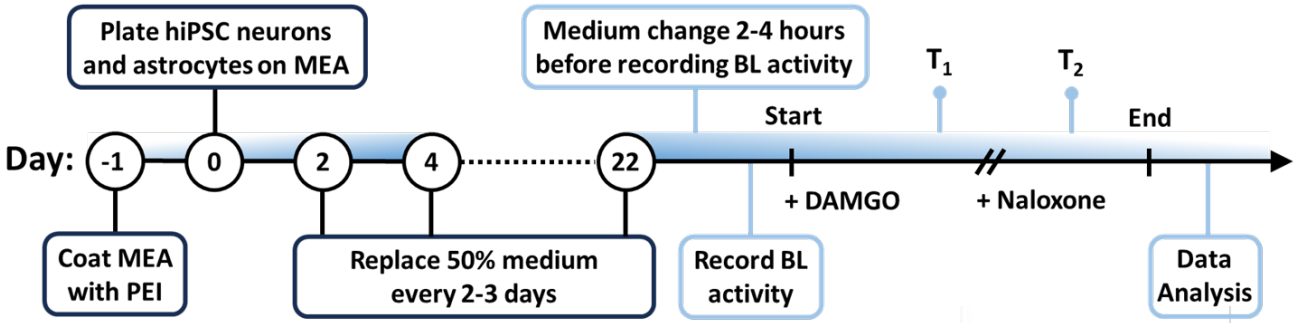
Garcia et al. 2025, *J. Cardiovasc. Dev. Dis.*

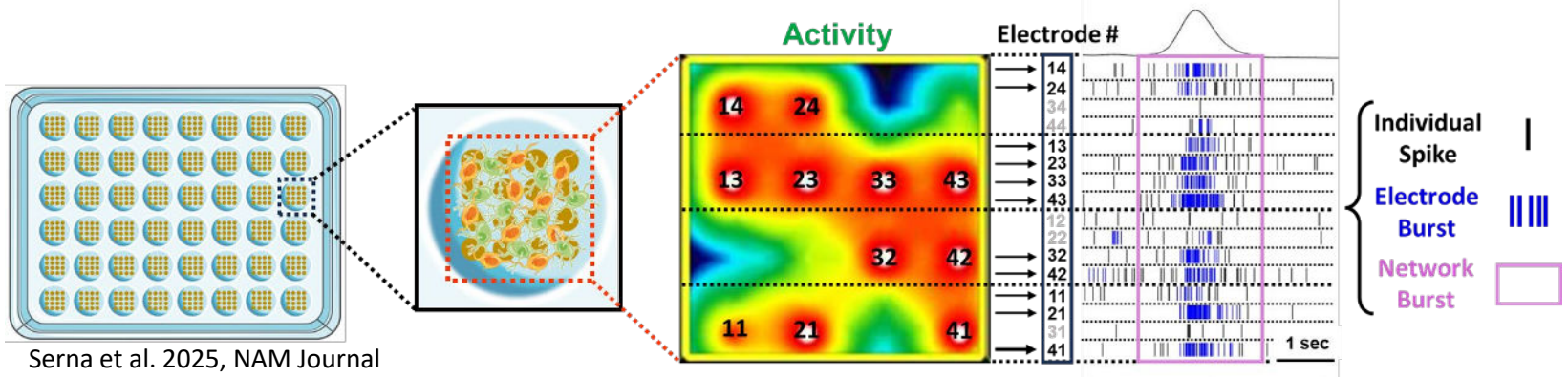
This work evaluated human-based NAMs to assess how drugs affect heart function. Using this model, vanoxerine was shown to cause delayed repolarization and irregular heart rhythms. This shows NAMs can be used to assess whether multi-channel blockers are proarrhythmic or not, supporting their use for safer and more predictive drug testing.

Neural NAMs

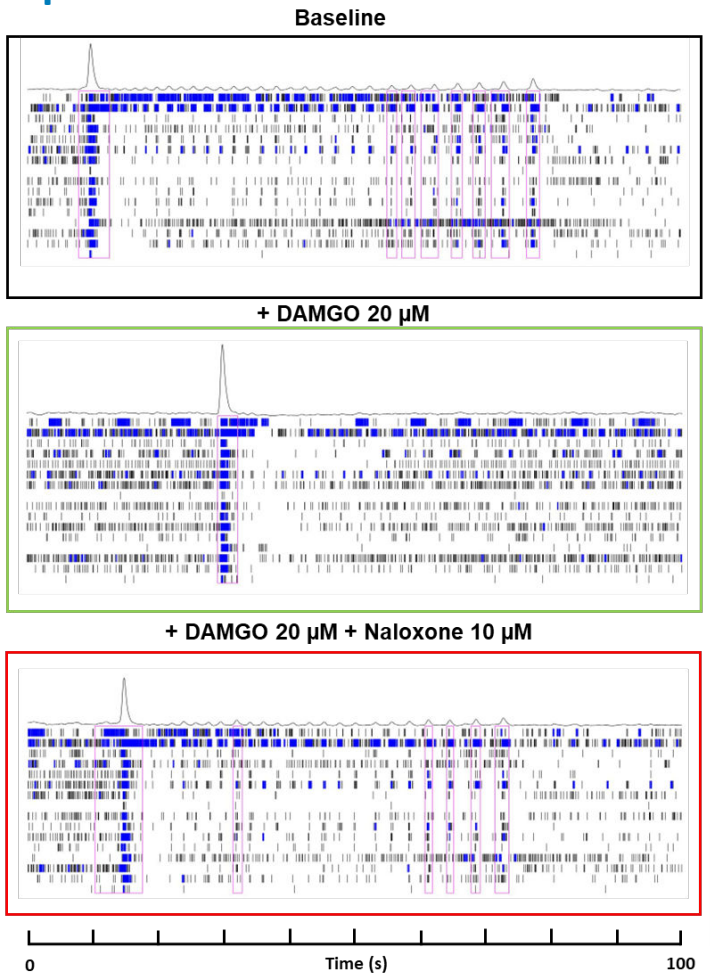
Neural NAM for Electrophysiological Assessment of Opioid Agonist and Antagonist Combination

CDER-led hiPSC-derived neural co-culture assay using MEA platform to assess CNS opioid interactions in combination with rescue antagonist (Naloxone)





Serna et al. 2025, NAM Journal

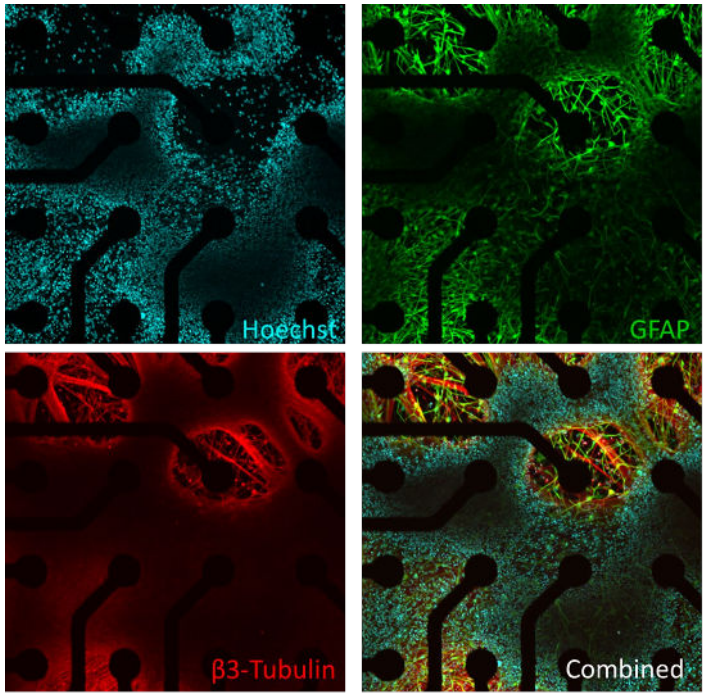


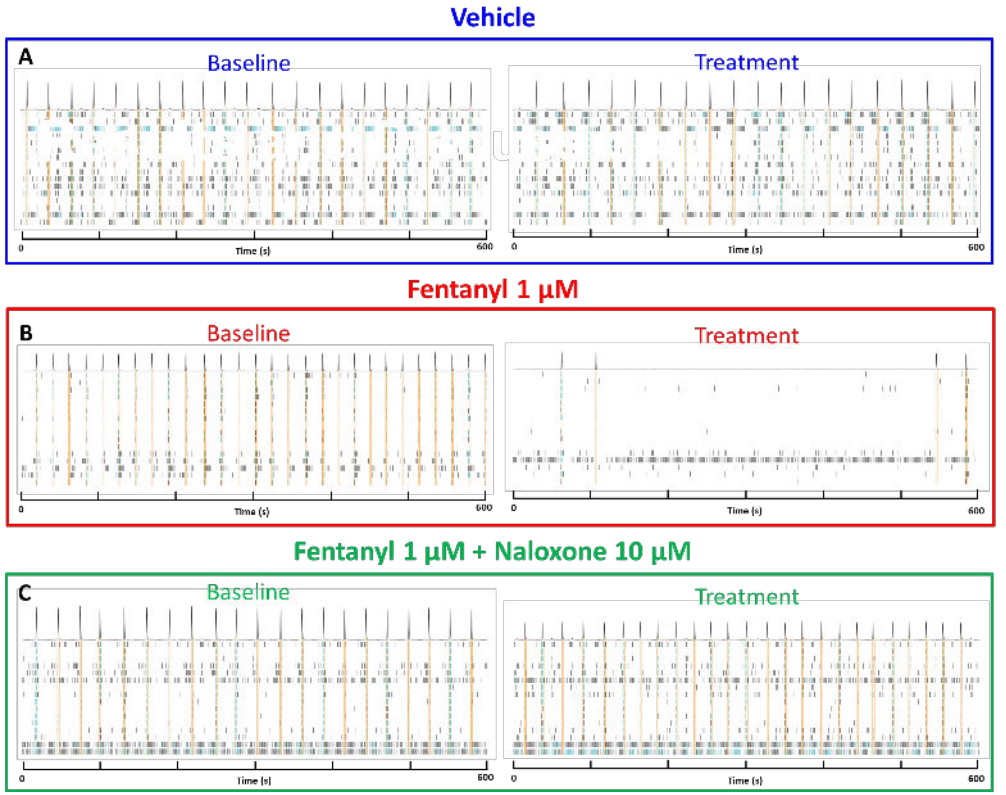
Analysis of MEA output metrics show neural co-culture responding to opioid agonist DAMGO and reversion towards baseline behavior through application of antagonist Naloxone.

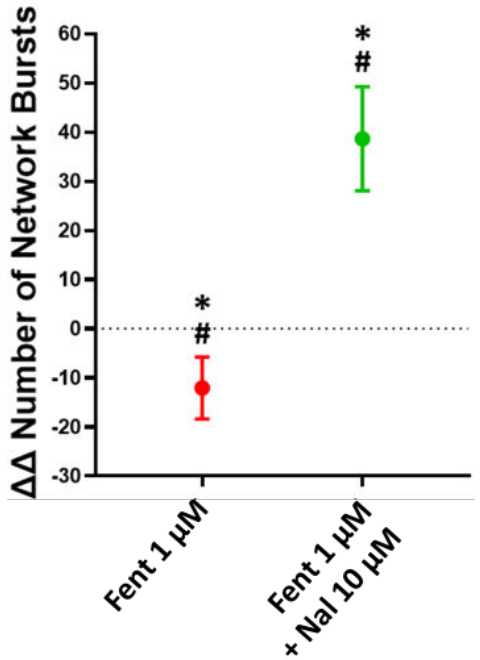
This study provides a foundation for the nonclinical evaluation of opioid agonist and antagonist on human neuronal electrophysiological activity to support safety and efficacy assessment.

Clinically Relevant Opioid Agonist and Antagonist Combination in Neural NAM

Fentanyl significantly reduced network burst activity, while co-administration with naloxone reversed opioid-induced network suppression







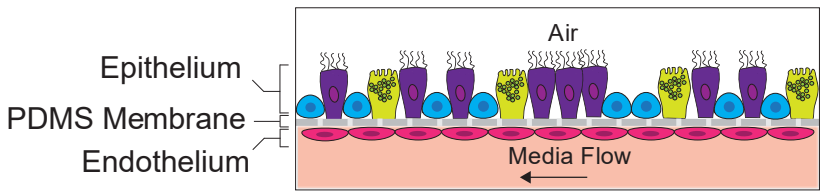
Serna et al. 2026, (In preparation)

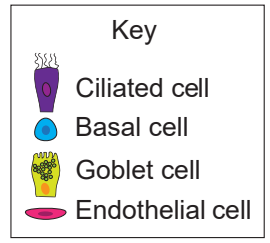
These findings contribute to addressing the opioid epidemic by providing a nonclinical platform to evaluate expanded treatment options for opioid overdose reversal.

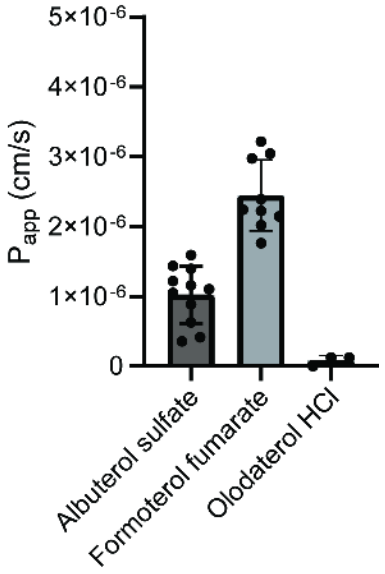
Respiratory NAMs

Small Airway MPS Assessment of Apparent Permeability for Inhaled Drugs

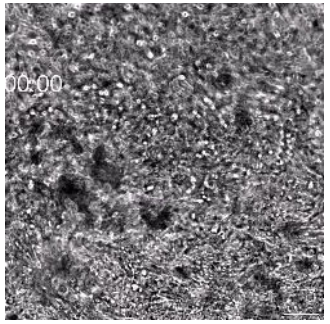
CDER-led project evaluating human lung MPS for relevant cell types and potential to measure the apparent permeability of inhaled drugs

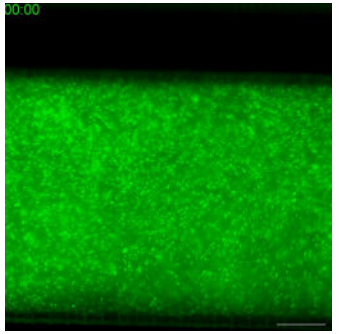






Geiger et al. 2025, *Frontiers Pharmacology*





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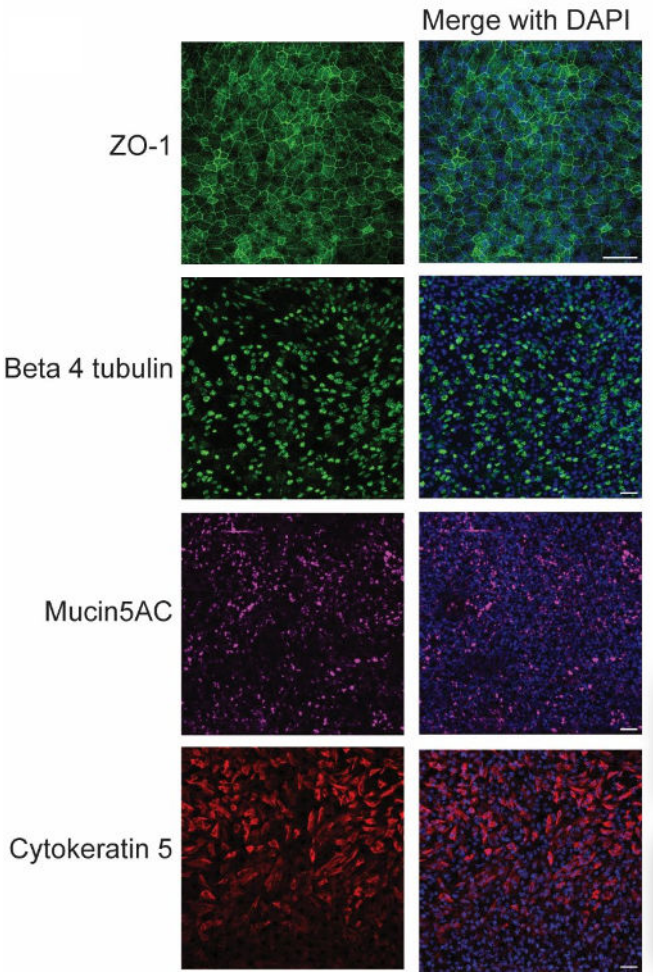


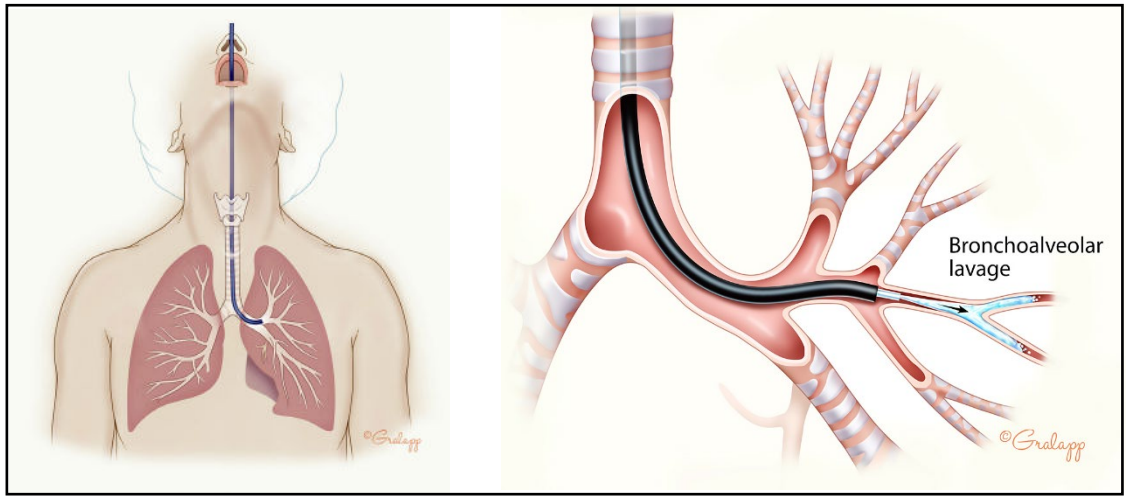
Rahman et al. 2025, *ACS Pharmacol Transl Sci*

Scale bar = 50 μm

This project establishes quality control criteria for the small airway MPS and is consistent with the 3Rs as the ex vivo rat lung is often used to assess to evaluate inhaled drug permeability.

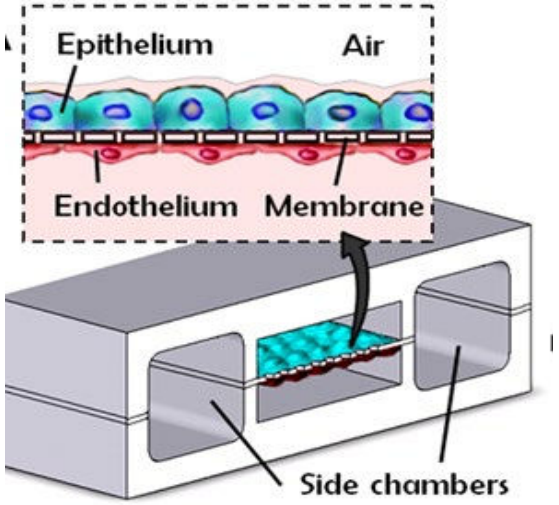
Lung MPS for Predicting Anti-Infective Drug Penetration

CDER-led project evaluating human lung MPS for relevant cell types and potential to measure the apparent permeability of inhaled drugs



https://psnet.ahrq.gov/web-mm/one-bronchoscopy-two-errors

Phase 1 epithelial lining fluid (ELF) studies use bronchoscopy and bronchoalveolar lavage (BAL), which is labor-intensive, unpleasant, and yields lung penetration results with high variability



Huh et al., Science, 2012

Emulate MPS for modeling lung alveoli

The model includes:

- Alveolar cells
  - Type 1
  - Type 2
- Endothelial cells
- Interstitial space

This study will compare lung MPS data with existing clinical data to evaluate whether MPS could serve as an alternative or supplementary approach to current methods. The results may influence FDA regulatory decision making for anti-infective drugs and could encourage pharmaceutical companies to increasingly adopt MPS technology in their nonclinical testing and regulatory submission processes.

Blood-Milk Barrier NAMs (Lactation)

Application of MPS to Predict Drug Transfer Across the Blood-Milk Barrier

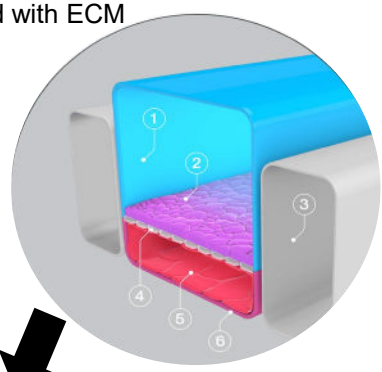
Objectives

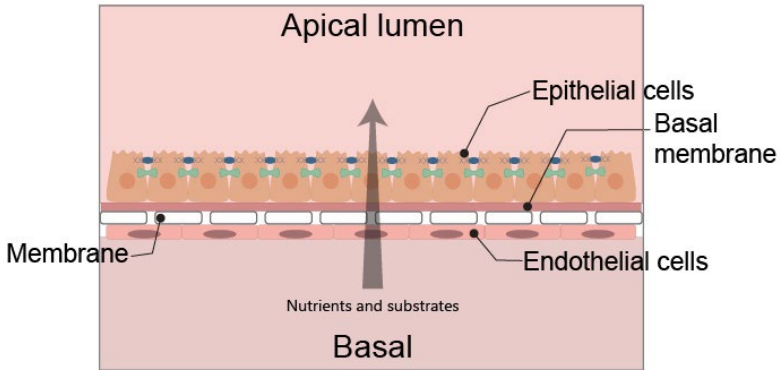
- Evaluate a MPS model that mimics the human blood-milk barrier.
- Validate model predictions by comparing to existing clinical data on drug transfer into breast milk.

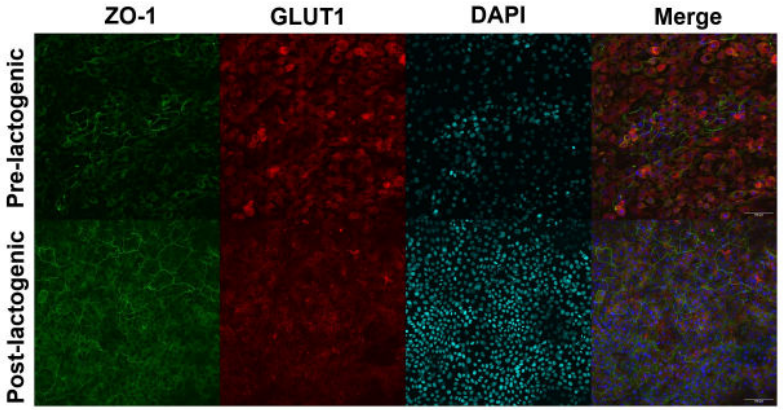
Key Features

- Breastfeeding is vital, but medication safety knowledge is limited.
- Traditional methods struggle to predict drug transfer into milk accurately.
- The MPS model mimics human mammary tissue function and structure.
- MPS technology provides a novel tool to support safety assessments of medication use during breastfeeding.

1. Blood (mother side)
2. Mammary endothelial cells
3. Porous membrane coated with ECM
4. Mammary epithelial cells
5. Breast milk (infant side)







Garcia et al. 2026, (In preperation)

The development of MPS to model drug transfer across the blood-milk barrier addresses a critical knowledge gap in medication safety for breastfeeding mothers and infants. Providing a human-relevant model that mimics mammary epithelium physiology, offer a powerful tool to better predict infant drug exposure during lactation. This advancement supports informs regulatory guidance on medication use in breastfeeding populations and promotes the inclusion of lactating women in drug development. Ultimately, MPS have the potential to accelerate regulatory decisions while enhancing maternal and infant health by ensuring safer medication use during breastfeeding.

Conclusions

- **Commitment to Modernization:** FDA is committed to phasing out animal studies where scientifically valid alternatives exist, advancing more predictive, human-relevant methods.
- **Coordinated Leadership in NAMs:** CDER has established the **CDER NAMs Coordinating Committee** to serve as a central point of contact for FDA and external stakeholders, ensuring alignment, transparency, and strategic integration of NAMs.
- **Growing Momentum in ISTAND:** Uptake of ISTAND submissions continues to increase, with approximately 40% focused on MPS and CiVM technologies — demonstrating strong innovation in this space. Workshops like this one are critical to accelerating scientific exchange and regulatory readiness.
- **Collaborative Regulatory Research:** DARS regulatory science initiatives provide meaningful opportunities for collaboration to generate the evidence needed to support qualification, adoption, and implementation of novel methods.