>> Establishing a functional standard for hiPSC-neural models used to screen for seizure liability with the multielectrode array (MEA) assay

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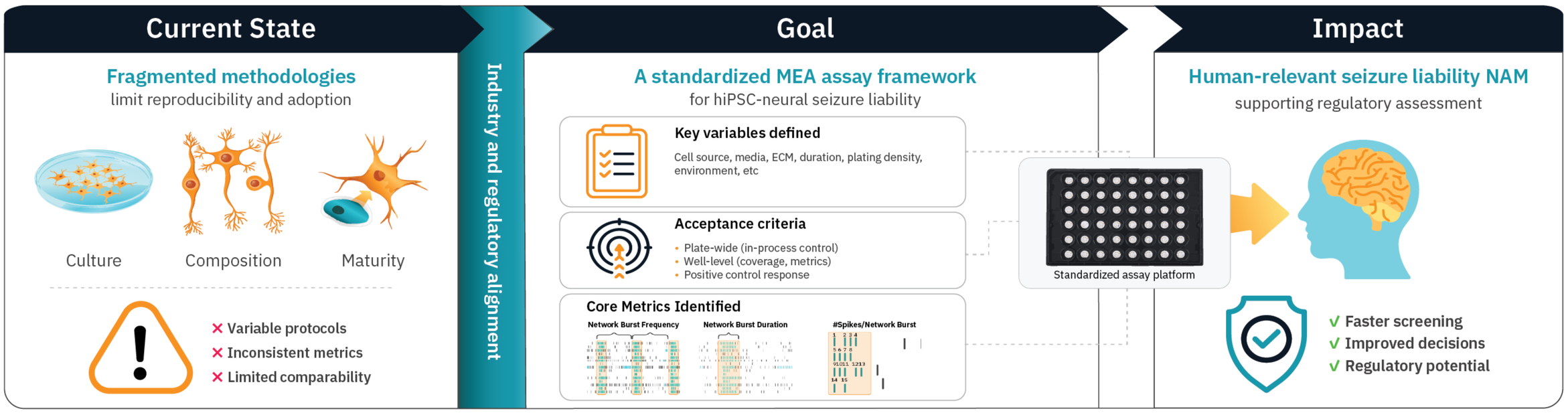


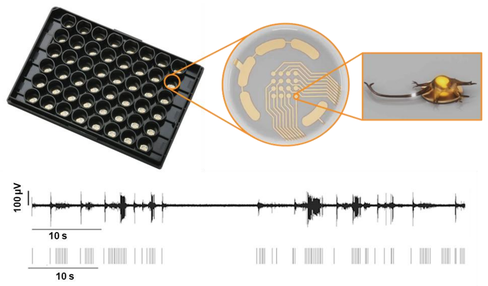
Key Takeaway: The proposed functional standard is to improve reproducibility and cross-laboratory consistency in hiPSC-neural seizure liability MEA assays

Methods

This project establishes a functional framework for hiPSC-neural seizure liability MEA assays through published evidence and expert input.

- >> **Review of 11 published studies**
- >> **Input from 11 experienced laboratories**
- >> **Consensus-derived framework**

MEA Platform



Multiwell MEA plate (CytoView MEA 48-well plate, *left*) with a 4x4 grid of 16 recording electrodes in the base of each well (*middle*). The MEA electrodes are sensitive enough to detect the activity of individual neurons (illustration not to scale, *right*). Spontaneous neural field potential recording from one MEA electrode (*top trace*) and corresponding raster plot (*bottom trace*).

Key Variables Defined

Which factors influence network activity?

Cell Culture
- Cell composition
- Density & distribution
- Days *in vitro*

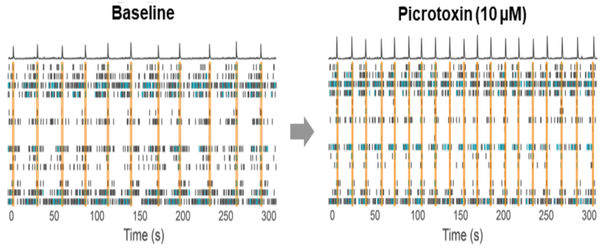
Environmental
- Temperature
- CO_2
- Culture Media & Feeding

Assay
- Recording Time
- Dose Method
- Replicates

Standardizing these variables reduces variability and improves assay comparability.

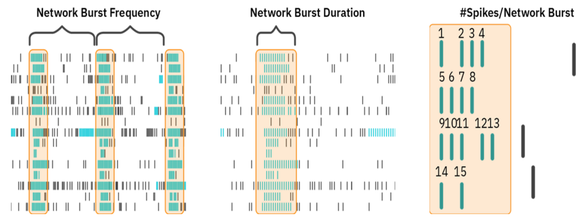
Core Metrics Identified

What does seizurogenic activity look like in the MEA assay?



Raster plot from hiPSC-neuronal cells in a well of a CytoView 48-well MEA plate (16 electrodes per well), recorded on Day 23 before and after exposure to picrotoxin (PTX).

Metrics



Seizurogenic compounds typically increase one or more parameters of network burst activity, including network burst frequency (NBF), network burst duration (NBD), and the number of spikes per network burst (#spikes/NB).

Acceptance Criteria

What should baseline activity look like for a culture to be used in the MEA assay?

Plate-level acceptance:

≥80% of wells meet all baseline acceptance criteria

Well-level acceptance:

Metric	Proposed Threshold
Active electrodes	≥10/well (16-electrode format) ≥6/well (8-electrode format)
Network burst participation	≥40% active electrodes
Network burst frequency	≥0.013 Hz
Synchrony index	≥0.15 and ≤0.85

Positive control response:

PTX (10 µM) produces ≥25% increase in at least one: NBF, NBD, and/or #spikes/NB

Conclusion

This work establishes a pragmatic, evidence-based framework for standardizing hiPSC-neural seizure liability MEA assays. By defining baseline activity thresholds, positive control responses, and recommended reporting practices, the proposed functional standard supports improved reproducibility, cross-study comparison, and broader adoption of the assay as a human-relevant NAM in safety pharmacology.

Why it matters

- Enables cross-lab consistency
- Supports safer and more efficient drug development
- Advances regulatory science and NAMs

Learn more

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