NEURON-AS-A-SENSOR (NAAS) METHODOLOGY IN COMPARTMENTALIZED MPS TO MODEL CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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BACKGROUND

Drug development suffers from high attrition rates, partly due to the limited predictive power of preclinical models for both efficacy and safety assessment. Rodent models, while widely used, often fail to translate to clinical outcomes, particularly for complex neurological phenotypes such as pain or neurotoxicity, where human-specific mechanisms play a critical role. Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating side effect that remains poorly predicted, insufficiently modeled, and lacks effective preventive strategies in current pipelines.

To address this gap, we developed the Neuron-as-a-Sensor (NaaS) methodology, an integrated platform combining human hiPSC-derived sensory neurons, MEA-integrated microfluidic devices, and advanced electrophysiological analysis. This approach enables the detection of functional changes in neuronal activity over time and captures quantitative electrophysiological signatures that reflect drug-specific effects.

RESULTS

NAAS PLATFORM AND EXPERIMENTAL FRAMEWORK

The NaaS methodology combines human iPSC sensory neurons, microfluidic MEA devices, and advanced analysis to generate a functional map of compound effects. By comparing electrophysiological signatures, the platform enables prediction of neurotoxicity and future classification of unknown compounds.

The methodology combines a device, an optimized cell culture model and an experimental protocol

- Compartmentalized MEA-integrated microfluidic chips
- Human hiPSC-derived sensory neurons and astrocytes in co-culture
- Longitudinal functional recordings under compound exposure
- Metrics are extracted through NETRI UpLink software
- Reference compounds define a discrimination space

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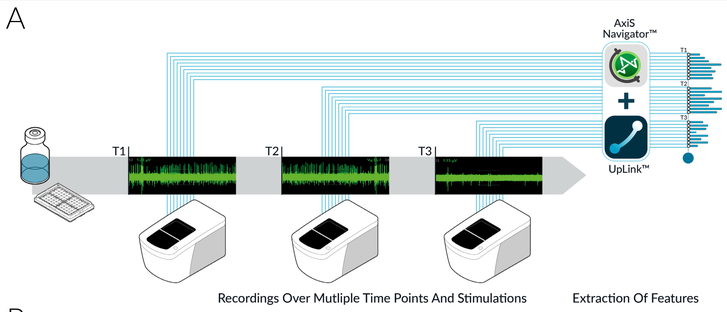

A. Electrophysiological activity is recorded at multiple time points and under different conditions. Signals are processed using AxisNavigator (Axion Biosystems) and NETRI UpLink to extract a wide range of electrophysiological metrics describing the culture's functional state.

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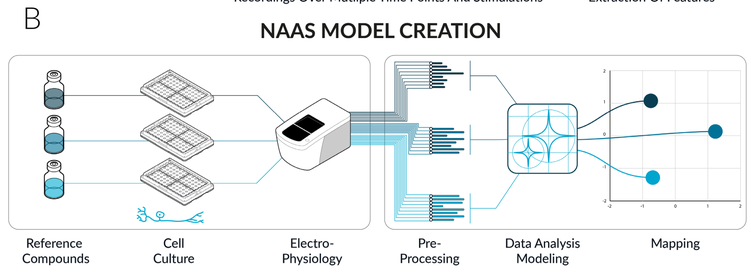

B. Reference compounds are applied to neuronal cell cultures grown in NETRI compartmentalized MEA devices. Electrophysiological responses are recorded using Maestro PRO MEA system.
Extracted electrophysiological features are processed using a dimensionality reduction algorithm to map compound effects within a relevant subspace.

HUMAN SENSORY NEURON MODEL CAPTURES CIPN-RELEVANT PHENOTYPES

The sensory neurons astrocytes co-culture forms a stable, physiologically relevant model. The system exhibits robust spontaneous activity and responds strongly to thermal stimulation, reproducing key nociceptive features for the detection of CIPN clinically relevant functional changes like thermal hyperexcitability.

- Sensory neuron–astrocyte co-culture enhances culture maturation
- Optimal window identified based on the stabilization of culture electrophysiological activity (D21-D24)
- Robust responsiveness to a noxious heat stimulus (42°C)
- Model exhibits functional response consistent with a nociceptive phenotype

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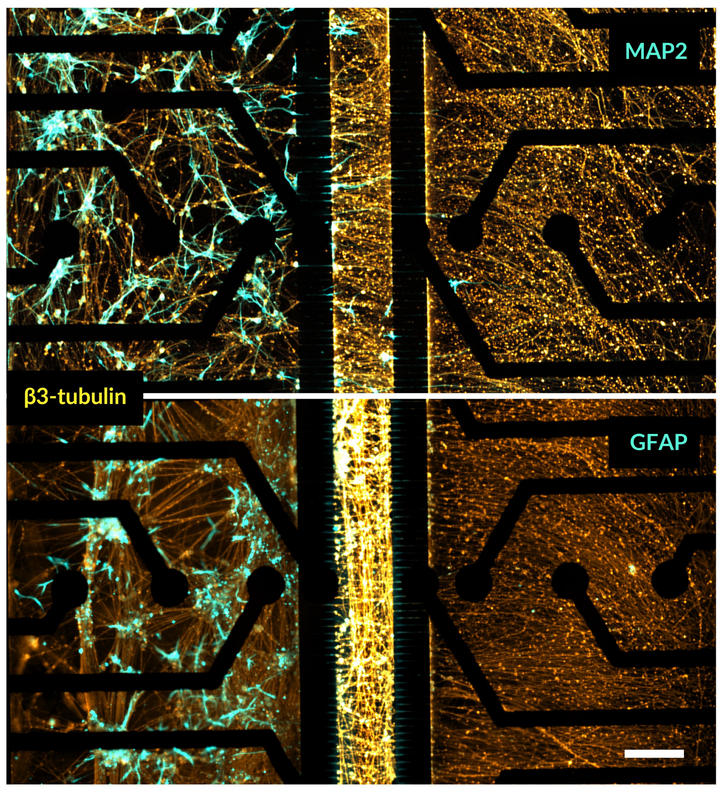

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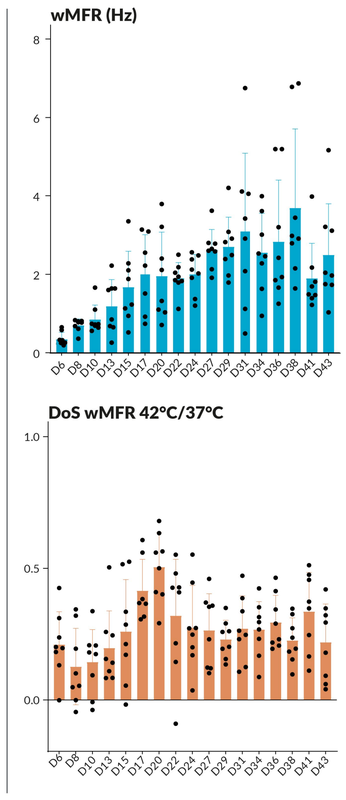

A. Representative immunofluorescence image of a sensory neuron–astrocyte co-culture at DIV 24, showing β3-tubulin (orange), MAP2 and GFAP (cyan) staining. Scale bar = 200 µm.
B. Electrophysiological recordings of co-cultures were performed three times per week at 37°C and 42°C. Top: Weighted Mean Firing Rate (wMFR) over time. Bottom: Difference of Signal (DoS) between wMFR at 37°C and 42°C.

FUNCTIONAL SIGNATURES DISCRIMINATE NEUROTOXIC COMPOUNDS

Electrophysiological recording protocol, including thermal stimulation, revealed distinct activity profiles induced by paclitaxel 1µM and oxaliplatin 10µM. Dimensionality reduction (PCA) allows clear separation of compound-specific signatures, demonstrating that NaaS captures subtle, drug-dependent functional differences beyond basic toxicity.

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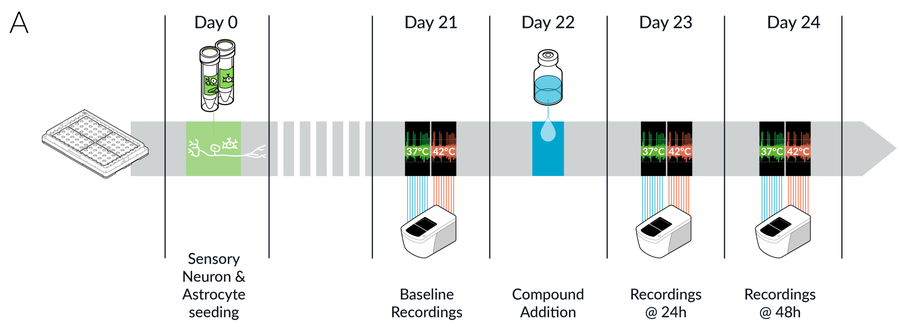

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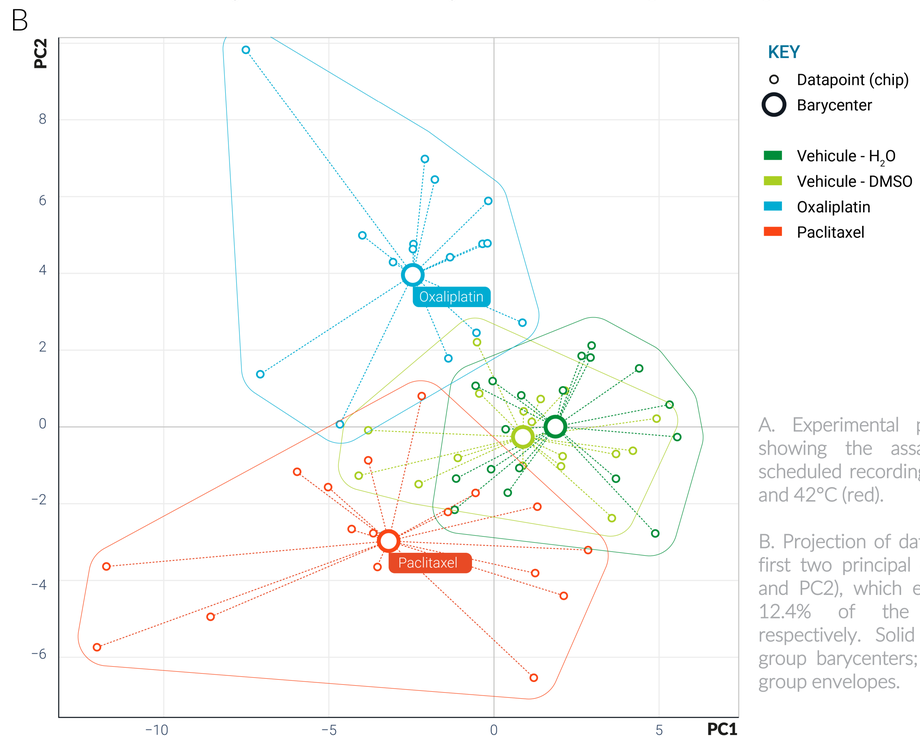


A. Experimental paradigm diagram showing the assay timeline with scheduled recordings at 37°C (green) and 42°C (red).

B. Projection of data points onto the first two principal components (PC1 and PC2), which explain 19.2% and 12.4% of the total variance, respectively. Solid circles represent group barycenters; plain lines depict group envelopes.

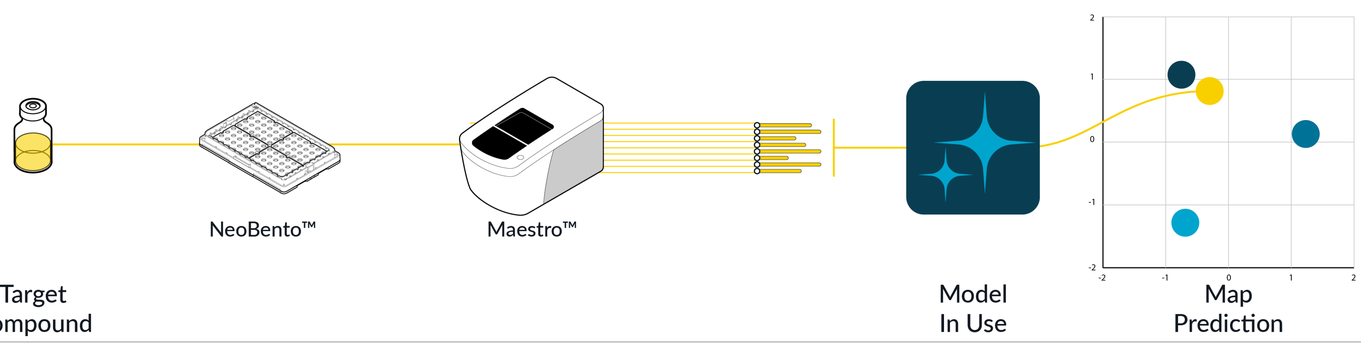
CONCLUSION & PERSPECTIVES

The NaaS methodology provides a scalable and human-relevant platform to detect and classify compound-induced functional neurotoxicity. By combining electrophysiological profiling with dimensionality reduction, it captures subtle and clinically relevant neuronal alterations beyond cytotoxicity. The successful discrimination of paclitaxel and oxaliplatin demonstrates its relevance for modeling CIPN and predicting adverse effects.

Future work will focus on expanding the reference compound library to better represent diverse drug classes, as well as integrating additional functional stimuli to enrich phenotypic profiling. Compounds with unknown clinical effects will also be evaluated to assess their functional signatures relative to established references.

Beyond CIPN, the NaaS platform holds strong potential for broader applications in neurotoxicity screening, drug discovery, and multi-organ innervation models.

NAAS MODEL PREDICTION



To assess an unknown compound, the same experimental protocol can be applied. Electrophysiological features will be extracted and projected into the reference space to infer the compound's functional profile.

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