Modeling Chemotherapy-Induced Peripheral Neuropathy Using a Nerve-on-a-Chip Microphysiological System

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Overview

We developed a Nerve-on-a-Chip to culture neural tissue that promotes axon growth analogous to mature nerve anatomy[1]. Rat dorsal root ganglia (DRG) were grown for 28 days with a 7-day exposure to 4 neurotoxic chemotherapy drugs. To demonstrate nerve dysfunction we measured electrical signals, metabolic activity, and imaged structural changes in tissue to:

- *Bortezomib (BZ): Proteasome inhibitor*
- *Oxaliplatin (OX): Creates platinum-DNA adducts*
- *Paclitaxel (PTX): Microtubule stabilizer*
- *Vincristine (VN): microtubule inhibitor*

Methods

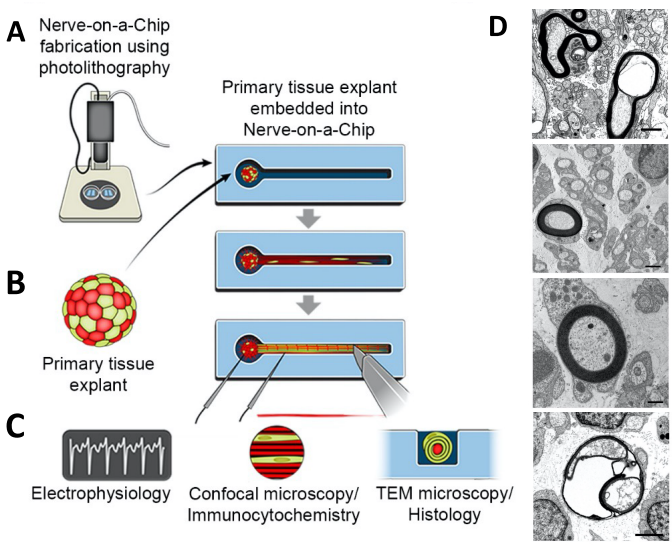


Figure 1. Schematic of Nerve-on-a-Chip. **(A)** Fabrication: PEG hydrogel. **(B)** Tissue culture: DRG explants grown 28 days. **(C)** Results: Robust nerve growth facilitates morphology and electrophysiology. **(D)** TEM show normal and irregular myelin sheaths. Scale bar is 1 µm.

Results

Toxicity screening: CCK-8 metabolic assay for cell viability (red) and electrically evoked nerve conduction velocity (NCV, black).

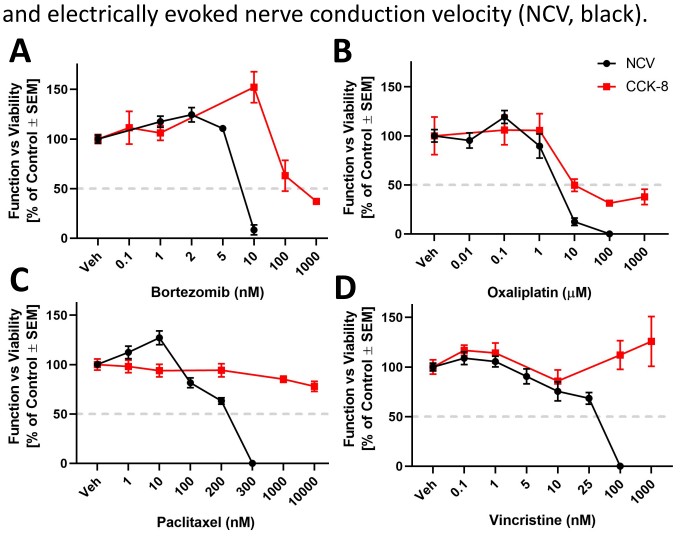
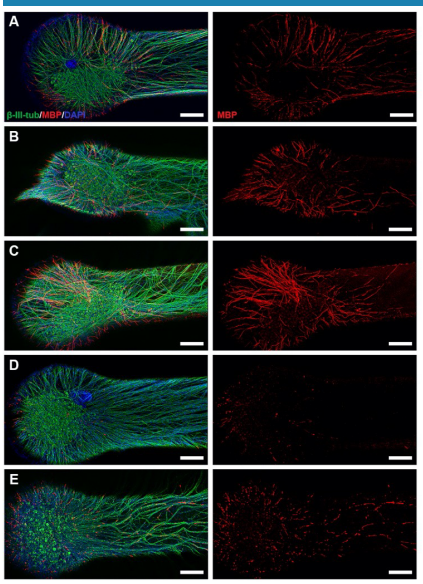


Figure 2. CCK-8 and NCV normalized to the vehicle. NCV decreased before decreased cell viability for all drugs **(A-D)**, demonstrating early functional deficit of neuropathologies before cell death.

1. Huval RM, et al. Lab Chip 2015 May 21;15(10):2221-32
2. Kramer L, et al. ALTEX 2020;37(3):350-364.

Results



βIII-tubulin – Neural marker
MBP – Myelin basic protein
DAPI – Nuclear stain

Figure 4. Confocal images of DRGs in hydrogel constructs. Samples were exposed for 7 days to **(A)** vehicle control, and IC50 concentrations of **(B)** BZ 9 nM, **(C)** OX 2.9 µM, **(D)** PTX 245 nM, and **(E)** VN 32 nM. PTX and VN show MBP reduction while cell number was constant for all tissues.

Scale bar=250 µm

Summary

Data suggest e-phys tracks subtle pathological changes in function, with distinction from cytotoxicity. E-phys reveals BZ and OX reduce electrical activity and viability after 7-day exposure whereas PTX and VN reduces activity but not viability. Histology reveals that PTX and VN do not reduce mitochondrial activity but cause demyelination, while BZ and OX have the opposite effects. Additional data in Kramer et al. 2020[2].

Future Work

Custom embedded electrode arrays have been designed for automated, longitudinal electrophysiology studies. With closed loop system of multiple recording sites, additional clinically relevant metrics are enabled, providing higher content metrics and further mechanistic insights. Additional validation ongoing.

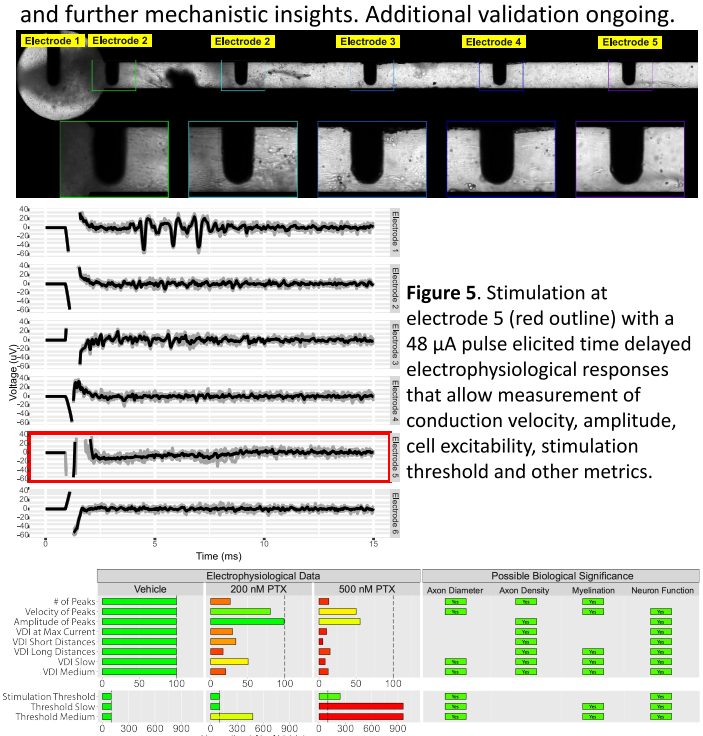


Figure 5. Stimulation at electrode 5 (red outline) with a 48 µA pulse elicited time delayed electrophysiological responses that allow measurement of conduction velocity, amplitude, cell excitability, stimulation threshold and other metrics.

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