Evaluating human nerve conduction velocity in vitro as a novel metric for assessing chemotherapeutics-induced peripheral neuropathy

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Overview

Preclinical models for assessment of toxicity and efficacy has consistently failed to deliver, given that a high number (~90%) of clinical trials fail. Animal models do not translate to human success largely because of the inherent differences in the biology of different species, and a bridge which translates to human biology is highly desired. Engineering 3D tissues relevant to the nervous system, especially peripheral nerves, is challenging because of the unique architecture and the necessity of bioelectrical conduction. ***In this study, we have engineered a human 3D nerve in vitro that supports axon growth analogous to PN anatomy and provides a gold standard of clinically relevant metrics such as nerve conduction velocity (NCV) and histological ultrastructure.*** These read-outs represent the gold-standard in preclinical testing. Using this model, we have successfully generated nerve conduction velocity (NCV) dose response curves for several drugs demonstrating that these models can be used for evaluating potential neuropathic side-effects caused by test compounds.

Methods

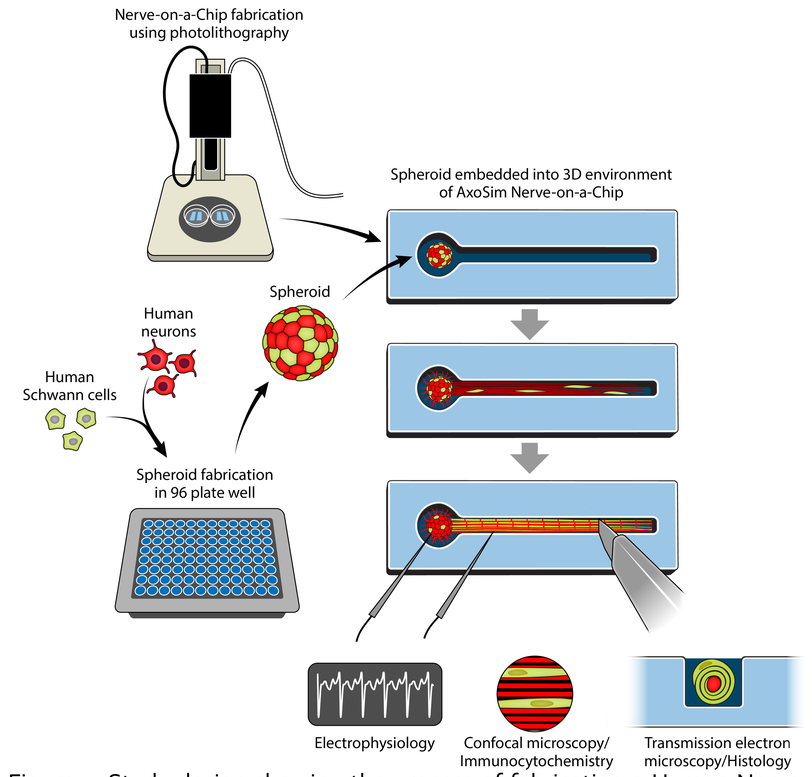
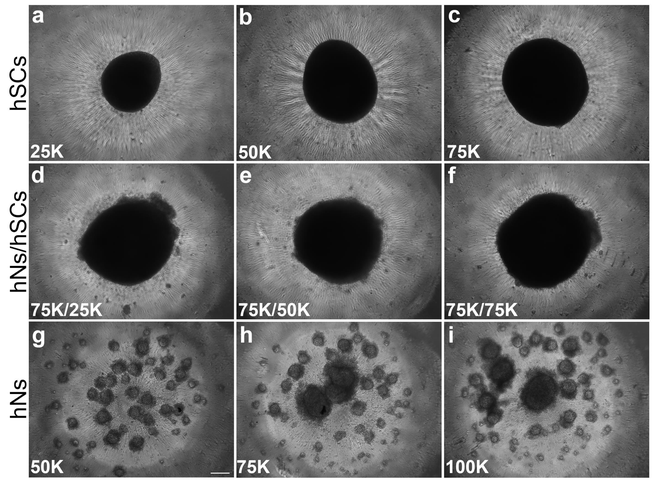


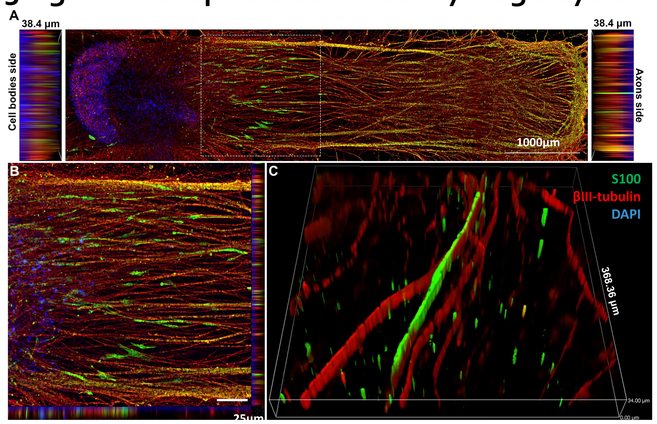
Figure 1. Study design showing the process of fabricating a Human Nerve-on-a-Chip system.

Results

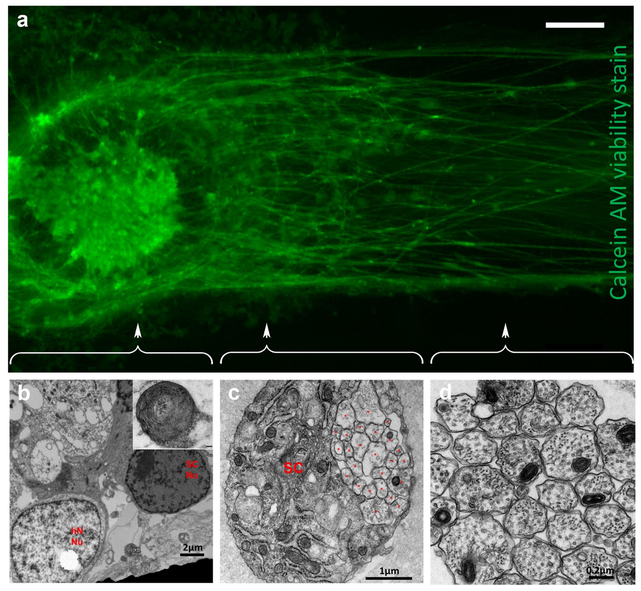
Spheroid formation



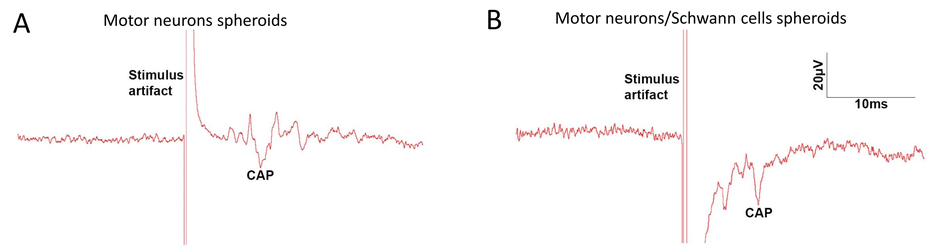
3D growth of spheroids in dual hydrogel system



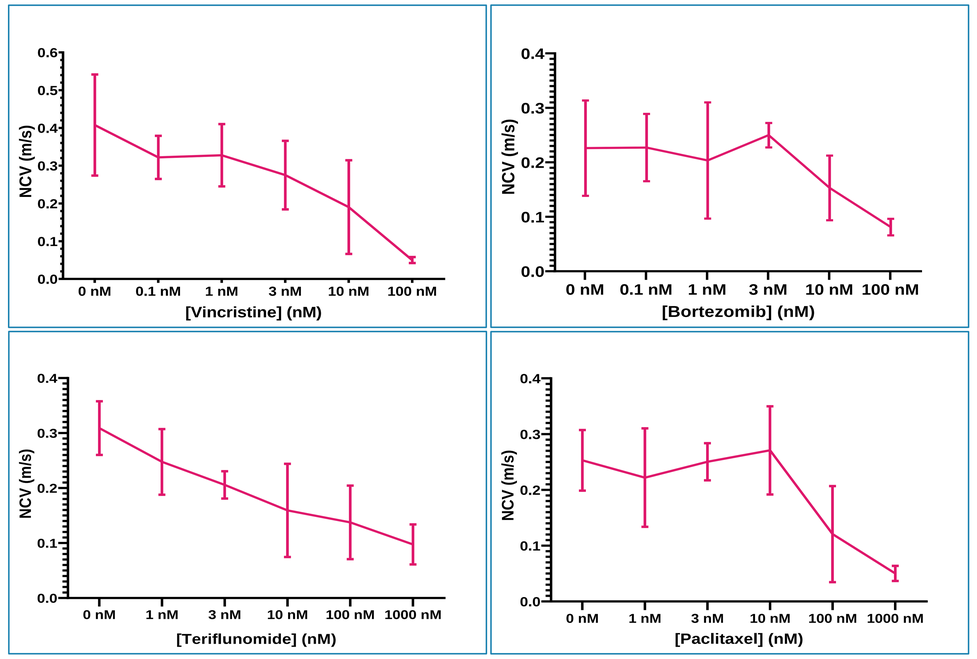
Ultrastructure of *in vitro* human nerve



Nerve conduction velocity testing



Test compounds screening (Avg. NCV)



Summary & Conclusion

- Schwann cells facilitated the spheroid fabrication process
- Evidences of both Schwann cells migration & myelination was detected
- Nerve conduction velocity was successfully evaluated for both mono and co-culture spheroids
- Monoculture nerve-on-a-chip constructs exhibited sensitivity to various test compounds
- Teriflunomide and Vincristine showed a slow reduction of NCV with increasing dosing concentration
- Paclitaxel and Bortezomib showed a sudden reduction in NCV after a specific dosing concentration

Acknowledgements

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