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# Modeling Taxane-Induced Peripheral Neuropathy Ex Vivo Using Patient-Derived Neurons

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**Abstract :** Background: Taxane-induced peripheral neuropathy (TIPN) is the most devastating survivorship issue for patients receiving therapy. Dose reductions due to TIPN in the curative setting lead to inferior outcomes for African American patients, as prior research has shown that this group is more susceptible to developing severe neuropathy. The mechanistic underpinnings of TIPN, however, have not been entirely elucidated. While it would be appealing to use primary tissue to study the development of TIPN, procuring nerves from patients is not realistically feasible, as nerve biopsies are painful and may result in permanent damage. Therefore, our laboratory has investigated paclitaxel-induced neuronal morphological and molecular changes using an ex vivo model of human-induced pluripotent stem cell (iPSC)-derived neurons. Methods: iPSCs are undifferentiated and endlessly dividing cells that can be generated from a patient's somatic cells, such as peripheral blood mononuclear cells (PBMCs). We successfully reprogrammed PBMCs into iPSCs using the Erythroid Progenitor Reprograming Kit (STEMCell Technologies™); pluripotency was verified by flow cytometry analysis. iPSCs were then induced into neurons using a differentiation protocol that bypasses the neural progenitor stage and uses selected small-molecule modulators of key signaling pathways (SMAD, Notch, FGFR1 inhibition, and Wnt activation). Results: Flow cytometry analysis revealed expression of core pluripotency transcription factors Nanog, Oct3/4 and Sox2 in iPSCs overlaps with commercially purchased pluripotent cell line UCSD064i-20-2. Trilineage differentiation of iPSCs was confirmed with immunofluorescent imaging with germ-layer-specific markers; Sox17 and ExoA2 for ectoderm, Nestin, and Pax6 for mesoderm, and Ncam and Brachyury for endoderm. Sensory neuron markers, β-III tubulin, and Peripherin were applied to stain the cells for the maturity of iPSC-derived neurons. Patch-clamp electrophysiology and calcitonin gene-related peptide (CGRP) release data supported the functionality of the induced neurons and provided insight into the timing for which downstream assays could be performed (week 4 post-induction). We have also performed a cell viability assay and fluorescence-activated cell sorting (FACS) using four cell-surface markers (CD184, CD44, CD15, and CD24) to select a neuronal population. At least 70% of the cells were viable in the isolated neuron population. Conclusion: We have found that these iPSC-derived neurons recapitulate mature neuronal phenotypes and demonstrate functionality. Thus, this represents a patient-derived ex vivo neuronal model to investigate the molecular mechanisms of clinical TIPN.

**Keywords :** chemotherapy, iPSC-derived neurons, peripheral neuropathy, taxane, paclitaxel
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