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Morphological Insights into Bortezomib-induced Peripheral Neurotoxicity Using hiPSC-Derived Schwann Cell Precursors and Sensory Neurons

ELISA TONELLI¹, FEDERICO ISEPPO¹, ALESSIO MALACRIDA¹, LAURA TAPELLA², VIRGINIA RODRIGUEZ-MENENDEZ¹, MARTINA SANTEUSANIO¹, SARA PALERMO³, DANIELE CARTELLI⁴, ARIANNA SCUTERI¹, CRISTINA MEREGALLI¹

¹ School of Medicine and Surgery, Experimental Neurology Unit and Milan Center for Neuroscience, University of Milano-Bicocca, Monza, Italy

² Department of Pharmaceutical Sciences, Università degli Studi del Piemonte Orientale, 28100 Novara, Italy

³ Department of Biosciences, Università degli Studi di Milano, 20133 Milan, Italy

⁴ Neuroalgology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milan, Italy

Chemotherapy-induced peripheral neurotoxicity (CIPN) remains a severe dose-limiting side effect of several anticancer agents, such as the proteasome inhibitor bortezomib (BTZ). While *in vitro* platforms offer a controlled environment to dissect specific neurotoxic pathways, their clinical predictability is often limited by a lack of human-centric architectural relevance. To bridge this translational gap, current neurobiology is shifting towards more advanced, human-based models. In this context, a detailed morphological and structural characterization of these platforms is an absolute priority to ensure they can accurately replicate the complex neuro-glial alterations typical of human CIPN pathology [1].

To achieve this, we performed a comprehensive morpho-functional evaluation of human induced Pluripotent Stem Cell (iPSC)-derived sensory neurons (RealDRG™) and compared them against primary cultured mouse Dorsal Root Ganglion (DRG) neurons upon exposure to different doses of BTZ [2,3]. Meanwhile, we conducted a preliminary characterization of human iPSC-derived Schwann Cell Precursors (SCPs). Cellular morphology together with the expression of specific population markers were characterized in detail using immunofluorescence. To capture early architectural changes and neurite alterations in real time, label-free live imaging was performed using holotomography microscopy (Nanolive SA, Tolochenaz, Switzerland). This morphological assessment was complemented by multiple functional assays evaluating proteasome inhibition, cell viability, mitochondrial morphology and network analysis as well as axonal degeneration.

Our results showed successful differentiation toward a broader peripheral neuron phenotype with several specific markers for neuronal subpopulations in RealDRG™ neurons, together with specific cellular markers expression in SCPs. Proteasome inhibition and cell viability assays showed similar dose/response curves between RealDRG™ and their murine counterpart, while label-free microscopy enabled the observation of early morphological alterations due to BTZ-induced neurotoxicity. Additionally, immunofluorescence studies revealed an early impact of BTZ on axonal degeneration that

was successfully replicated. Mitochondrial morphology and network analysis also revealed good correspondence in the BTZ-induced dysfunctions among all models.

Taken together, these findings elucidate the potential of these cellular models and strongly suggest that the translational gap in CIPN research is being bridged by our successful alignment of human sensory neurons with already characterized models. Finally, the early results provided on human-derived SCPs ultimately aim to pave the way for the establishment of a co-culture model that better mimics the physiological landscape.

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