

SCREEN4PN: Efficient evaluation of therapeutic compounds for Charcot-Marie-Tooth disease using patient-derived induced motor neurons and neuromuscular organoids

Nathan Donies (1), Tamira van Wermeskerken (1), Bieke Bekaert (1), Stijn in 't Groen (1), Vincent Timmerman (1)

(1) Peripheral Neuropathy Research Group, Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium

Charcot-Marie-Tooth (CMT) disease is the most common peripheral neuropathy, affecting over 2.5 million people worldwide. CMT exhibits an exceptionally broad clinical phenotype, complicating research into its pathophysiology. CMT1 primarily involves myelin degeneration, whereas CMT2 is marked by axonal degeneration. Both categories include multiple subtypes with distinct genetic causes, requiring the development of numerous animal models which hinders therapeutic development.

To address this challenge, we developed SCREEN4PN, a service platform that utilizes induced pluripotent stem cells (iPSC) for efficient drug testing on 2D and 3D cell models. We identified several pathological similarities across CMT phenotypes, enabling SCREEN4PN to facilitate therapeutic validations despite disease heterogeneity. Whereby the response to treatment can be evaluated using microscopy, qPCR, and protein biomarkers.

Utilizing patient-derived iPSCs along with isogenic and healthy controls, we can validate drugs, as well as personalized medicine approaches. These cells are differentiated into models tailored to specific subtypes. The 2D motor neuron model assesses axonal degeneration in CMT2, while the 3D neuromuscular organoid model facilitates myelin formation to study the CMT1 phenotype. Additionally, our cell banks undergo rigorous quality control to ensure standardized, high-quality cells for research and therapeutic applications in line with current GCP and industry standards.

So far, we have successfully completed two service contracts aimed at therapeutic compounds for CMT. In the future, we aim to expand SCREEN4PN to other diseases, optimize existing models, and incorporate advanced systems such as assembloids and microfluidics. By reducing the time, cost, and reliance on animal models using innovative approaches, SCREEN4PN offers a more ethical and efficient platform for pharmaceutical companies, clinical research organizations, and academic partners.