

Neuromuscular models to investigate Charcot-Marie-Tooth disease

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Charcot-Marie-Tooth (CMT) disease is the most common hereditary peripheral neuropathy, leading to symptoms ranging from muscle weakness to sensory loss. While numerous animal models have been developed, their limited success in translating to therapies highlights the need for new disease models derived from human cells. In recent years, several in vitro human stem cell-based models have been developed to investigate the peripheral nervous system. Most of these models are 2D monocultures of motor neurons, which are straightforward to analyze and can mimic some CMT features. Unfortunately, these models are insufficient for studying the complex 3D myelination process, which involves both motor neurons and supporting Schwann cells, as well as crucial neuron-muscle interactions, processes that are disrupted in patients with CMT.

Therefore, within the Peripheral Neuropathy Research group, we are creating various advanced neuromuscular models. On one hand, we are optimizing neuromuscular organoids and assembloids, which are two different 3D stem cell models consisting of multiple cell types. Although, these 3D models are able to mimic important peripheral nerve hallmarks, such as myelination and neuron-muscle interactions, these models are difficult to scale up for high-throughput use. On the other hand, we are developing microfluidic models that will enable easier readouts but currently lack myelinating Schwann cells.

In summary, while we do not yet have a single model that can investigate all CMT hallmarks, we are moving towards the creation of multiple models, each with its own specific application and end goal. The potential value of these models goes beyond CMT and can also be translated to other peripheral nerve diseases.