A New Humanized Mouse Model for the Study of Peripheral Neuropathies

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PUBLIC ABSTRACT

The peripheral nervous system consists of two components. The sensory component is the part of the nervous system that conveys information about the external environment and the body itself to the spinal cord and brain where reactions to the stimuli are formulated. The motor system on the other hand conveys information from the brain and spinal cord to the muscles, leading to movement. Peripheral neuropathy is the term for disease affecting the peripheral nervous system. It is common, with a prevalence of at least 5 percent in the general population. Peripheral neuropathy significantly increases mortality; its effects are life-altering and the societal costs are overwhelming. In essence, peripheral nerves are composed of two types of cell, neurons that generate electrical impulses that are conveyed along neuronal projections called axons, and supporting cells called Schwann cells. Schwann cells support axons and produce myelin, which provides critical support for the axons and acts as an insulator to increase efficiency of nerve signaling. Schwann cell dysfunction is the key element in many forms of peripheral neuropathy. Nevertheless, attempts to understand and find new therapeutics for human neuropathies are hampered by a lack of adequate models of these conditions. We propose to develop a new humanized mouse, which will provide the scientific community and our laboratories with a novel and critically needed resource for the study of the peripheral nervous system and peripheral neuropathies. To achieve this, we will use genetic techniques to ablate all the endogenous myelin forming Schwann cells and replace them with human Schwann cells derived from human inducible pluripotent stem cells (iPSC).

In the first aim, we will ablate the myelinating Schwann cells and replace them (by direct injection) with human Schwann cells derived from human stem cells. In the second aim, we will characterize these mice by (1) studying the pattern of gene expression (using a group of techniques referred to as RNA sequencing), (2) examining their muscle strength using a grip strength meter, (3) observing the electrical responses of the nerves, (4) observing the quality of myelin produced by out engrafted cells, and (5) examining the fine structure of the nerve produced by the interaction of Schwann cell and axon. In the third aim, we will demonstrate the applicability of our method by applying the same strategy as in Aim 1 to produce a mouse expressing myelinating cells exclusively from iPSC derived Schwann cell expressing a mutation which is associated with the inherited peripheral neuropathy Charcot-Marie-Tooth disease. We will utilize from human inducible pluripotent stem cells derived from a patient with the same mutation as seen in one of our well-established mouse models for CMT1X. Comparison of these two models will increase our confidence in the model and will provide the foundation for myriad future studies in which human mutations that do not have parallel mouse models will be investigated in vivo.