Popko, Brian **Scope of Research** **Rampy MS Research Foundation**

Multiple sclerosis (MS) is the most common chronic neurological disorder to affect young adults. Although the etiology of MS is unknown, it is recognized as an autoimmune disease that is characterized by CNS inflammation, oligodendrocyte loss, demyelination, and axonal degeneration. Recent studies strongly suggest that the progression of disease is driven by irreparable axon loss. Over a dozen immunomodulatory MS therapies exist, but their impact on disease progression appears limited. Attention in the field has thus focused on CNS-specific therapeutic approaches designed to prevent this degeneration. Oligodendrocytes, which not only produce and maintain myelin but also provide trophic support to axons, have entered the spotlight as the primary target cell for potential new MS therapies. The studies being carried out in the Popko laboratory are designed with two main, somewhat overlapping, goals: to protect the oligodendrocytes, myelin and axons against the neuroinflammation that occurs in MS; and to enhance remyelination, which has been shown to restore neuronal function and to protect axons.

Over the past twenty years or so my laboratory has devoted considerable effort to design approaches to protect mature oligodendrocytes, and thus myelin and axons, from inflammatory-mediated cell death. Our studies have centered on an innate cellular protective signaling pathway called the integrated stress response (ISR). Genetic manipulations of the ISR in preclinical models of MS have indicated that the pathway plays an important role in the survival of oligodendrocytes during inflammation. Mouse models with a reduced capacity to mount an ISR response display increased susceptibility to CNS inflammation; whereas, mice genetically modified to experience an enhanced ISR response display increased resistance to CNS inflammation. We are currently exploring pharmacological strategies that will prolong the ISR response in oligodendrocytes, which we believe will limit oligodendrocyte death and demyelination in MS patients.

In MS, the loss of mature, myelin-maintaining oligodendrocytes has been well-documented. Nonetheless, oligodendrocyte progenitor cells (OPCs) have been shown to quickly proliferate, migrate to the areas of damage, and undergo differentiation in order to remyelinate unprotected axons as needed. The remission of symptoms in relapsing-remitting MS patients has been attributed in large part to this effective repair process. As inflammatory events accumulate, however, remissions become less common and less reparative. We are therefore seeking to develop therapeutic strategies that will enhance the CNS remyelination process. Much of our effort centers on obtaining a more complete understanding of the molecular control of oligodendrocyte development from OPCs. Importantly, in MS lesions, the development of oligodendrocytes from OPCs must occur in the harsh CNS inflammatory environment, such that the protection afforded by the ISR described above may also help promote CNS remyelination in MS patients.

The generous funds offered by the Rampy MS Foundation will facilitate all aspects of our research program. Most of our studies are carried out in pre-clinical mouse models of MS, which are expensive to generate and to maintain. Moreover, these funds will be used to offset the costs of laboratory supplies and the use of University core facilities, which provide access to state-of-the-art technologies and equipment. The Rampy MS Foundation funds will also allow scientists in the Popko laboratory to attend conferences relevant to our scientific interests. The receipt of these funds will no doubt have a significant positive impact on our research program. We are extremely grateful that they have been made available for our research efforts.