THE HARTWELL FOUNDATION

2022 Individual Biomedical Research Award

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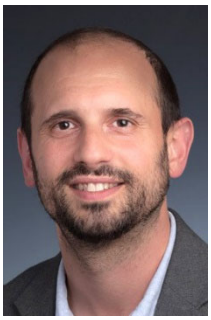

Reviving Brain Myelination as a Curative Therapy for Leukodystrophy

Leukodystrophies are a group of devastating childhood disorders characterized by a progressive loss of neurological function. They are caused by degeneration of brain white matter due to defects in myelin, the fatty covering that insulates nerves (neurons) in the brain and spinal cord. Much like insulation on an electrical wire, myelin is critical for neurons to properly transmit electrical signals. Leukodystrophies are considered rare, yet at least one in every 7600 children born in the United States will be diagnosed with the disorder. Genetic mutations account for only half of the diagnoses, while the remainder are identified based on symptoms and brain imaging. There is no cure and, tragically, there are no approved therapies for improving myelination. Targeting the specialized brain cells (oligodendrocytes) that wrap myelin around neurons in order to stimulate remyelination has proved to be a challenging strategy. Previously published work has demonstrated that macrophages derived from umbilical cord blood (rich in oligodendrocyte precursor cells) can increase myelination when injected directly into the brains of immunocompromised mice that have been treated with a metal-chelating agent known to induce demyelination. While the mechanism of myelin repair is not completely understood, it is apparent that soluble factors released by blood borne macrophages stimulate differentiation of oligodendrocyte precursor cells, which form oligodendrocytes that create new myelin sheaths on demyelinated axons. There is also evidence that cerebral spinal fluid (CSF) is dysregulated in leukodystrophy, where transplanting CSF from a young mouse into an old mouse improves myelination. Considering these observations, I speculate that, instead of targeting single brain cells directly, CSF can serve as a means to modify the internal environment of the brain and spinal cord. To promote remyelination, I propose to use released myelination factors derived from umbilical cord blood macrophages. Using Krabbe disease (KD), an inherited leukodystrophy that is fatal by 2-3 years of age, as a model system, I will explore rejuvenating the toxic CSF with my cell-based-derived therapy to promote desired remyelination. To characterize the CSF dysregulation in individuals diagnosed with the disease, I will use mass spectrometry to identify toxic molecules that could be used as novel biomarkers, enabling early diagnosis, and expanding the treatment window for thousands of children. If I am successful, it will be possible to collect vital preclinical data needed to proceed into a Phase I clinical trial in children diagnosed with KD, and, potentially develop the first US approved product to promote a curative therapy not only for this devastating, fatal neurological disease, but other leukodystrophies with similar, yet distinct pathologies.