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Abstract 30

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Introduction: Autoimmune diseases of the central nervous system, like multiple sclerosis (MS), result from autoreactive immune cells attacking myelin. Although numerous therapies targeting the immune system are effective for slowing the progression of MS, there are no therapies to promote remyelination. Therefore, we developed DUOC-01, a first-generation macrophage cell-therapy product manufactured from banked cord blood to promote remyelination. Using mouse models of demyelination, we determined that DUOC-01 blocked progression of disease and enhanced remyelination.

Objectives: Although preclinical data using DUOC-01 are promising, shortfalls in manufacturing and an unknown mechanism of action limits their use for MS. Here, we examined the effects of DUOC-01 on oligodendrocyte precursor cells (OPCs) to develop a second generation product that promotes the maturation of OPCs.

Methods: We first developed an ex vivo system, using organotypic brain slices treated with lysophosphatidylcholine (LPC), to measure remyelination by imaging the co-localization of myelin basic protein (MBP), a marker for myelin, and neurofilament, a marker for neuronal axons. Next we developed a primary OPC differentiation assay and measured maturation through markers of proliferation and differentiation. Using these assays, we set out to determine the ability of DUOC-01 and a second generation product to promote remyelination.

Results: In culture, our brain slices maintained well-preserved cytoarchitecture and myelinated axons, indicating a healthy three-dimensional system. Treating the slices with LPC caused massive demyelination of neuron processes three days post exposure. After washing out LPC, we treated cultures with vehicle or DUOC-01 and determined that DUOC-01 promoted remyelination when compared to controls. Using primary OPC cultures, we determined that DUOC-01 skewed OPC cultures to a more mature phenotype, demonstrated by the increased expression of the mature oligodendrocyte marker MBP. When treating OPC cultures with DUOC-01 conditioned media or separating DUOC-01 from OPCs using a transwell, OPC cultures still upregulated expression of MBP, indicating that bioactivity was due to factors released by DUOC-01.

Discussion: Overall, our data demonstrated that DUOC-01 promoted remyelination, and the factors released by DUOC-01 drive the maturation of oligodendrocytes. Thus, these remyelination factors released by DUOC-01 have the potential to work as a cell-free therapeutic for treating MS and other diverse neurological demyelinating diseases.