How can we regenerate the white matter of the adult human brain?
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Disorders of the white matter of the brain are among the most common and disabling conditions in neurology. They include the traumatic and vascular demyelination, such as white matter stroke, the inflammatory demyelinating disorders like multiple sclerosis (MS), and age-related white matter loss. What all of these disorders have in common is the loss of myelin, the insulating substance of neuronal axons, and a concomitant atrophy of the brain's white matter. This loss of myelin is in large part due to the failure of exhausted resident glial progenitor cells (GPCs), which produce the oligodendrocytes that make myelin, to restore oligodendrocyte production. In this proposal, the labs of Steve Goldman (University of Copenhagen, Denmark) and Gonçalo Castelo-Branco (Karolinska Institutet, Stockholm, Sweden) have joined efforts to better understand the epigenetic basis for the loss of progenitor cell myelination competence that accompanies the chronic demyelination of progressive MS.

In 2020-21, the labs made substantial progress towards this goal. The Castelo-Branco lab mapped the developmental appearance of human oligodendrocyte precursor cells in human fetal development, and used a combination of single-cell RNA-Seq and ATAC-Seq to identify the emergence of a first wave of oligodendrocyte lineage cells as early as week 8 of human brain development. This manuscript was uploaded in BioRxiv in July 2021 and is currently under revision after review. Using the methodologies established in this paper, the Castelo-Branco lab then found that normal oligodendrocytes maintain their genes encoding immune effectors in a primed chromatin state, allowing their rapid transition to immune-competent states in MS. In particular, they identified a subset of immune genes maintained in an epigenetic state that is poised towards activation upon exposure to the cytokine interferon-gamma (IFN-gamma). These data indicate that GPCs and their derived oligodendroglia may be active participants in the immune cascades that lead to both demyelination and remyelination failure in MS – and that these signal cascades may comprise novel therapeutic targets in progressive MS. This paper has been uploaded in BioRxiv and pre-accepted for publication in Neuron.

For its part, the Goldman lab defined the RNA expression patterns of cells extracted from myelin-deficient shiverer mice, that had been neonatally engrafted with human GPCs, resulting in their formation of human white matter. The lab first assessed the bulk RNA expression of human GPCs extracted back from these mice after cuprizone demyelination, as well as controls not subjected to demyelination. They identified pathways involved in the development of replicative senescence – mitotic exhaustion - on the part of these demyelination-mobilized GPCs. This study was published in 2020 in Cell Reports. The lab then assessed the differential gene expression of GPCs derived from young and adult human brain tissue, to define those genes and pathways associated with aging of these cells, so as to correlate those genes – and in particular transcriptional repressors - associated with aging to those induced by sustained demyelination. This work has been submitted for publication, and has been uploaded to BioRxiv as well. Our goal in this work is to use the overlap of these gene sets to identify those genes and pathways leading to senescence after chronic demyelination, and to use that information to abrogate that process, so as to enable remyelination and recovery after white matter loss.