Human iPSC-derived oligodendrocytes and organoids to identify promyelinating drugs

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Multiple Sclerosis (MS) is the most frequent demyelinating disease of the central nervous system (CNS), affecting 2.5 million people worldwide. MS is characterized by focal inflammation and demyelination caused by autoreactive lymphocytes that cross the blood-brain-barrier (BBB) and enter the CNS, resulting in axonal injury and loss. Remyelination, the process that counteracts the destruction of myelin sheaths, occurs in MS but declines with disease progression and age. Impaired oligodendroglial progenitor cell (OPC) migration and differentiation as well as myelin sheath formation may contribute to remyelination failure in MS. Therefore, promotion of remyelination is a promising new treatment strategy to prevent neurodegeneration in MS and other CNS diseases. The identification of such compounds is challenging, since access to primary human oligodendrocytes is heavily limited due to the inaccessibility of the human CNS and hits identified in mouse models often show no effect on human remyelination in subsequent clinical trials.

Here we establish a drug screening system using human iPSC-derived oligodendrocytes to identify compounds, which promote the differentiation into mature oligodendrocytes. We use this system inter alia to compare the effect of siponimod with fingolimod as well as selective S1P1 and S1P5 modulators with regard to oligodendroglial differentiation, migration and myelination.

Furthermore, to overcome limitations of 2D models and to be able to investigate the effects of compounds on a more systemic level, we develop a protocol to generate myelinating human midbrain organoids in a fast and reproducible manner. Using these myelinating organoids, we analyse the effect of compounds on oligodendrocytes influenced by various cell types including astrocytes and neurons.

In summary, we developed a fast and reproducible drug-screening system in 2D and 3D, providing an attractive tool for the identification of promyelinating compounds and hitherto the most rapid generation of complete approximation of human neural tissue *in vitro*.

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