

Blueprint for the Development of Remyelination Medicines for Multiple Sclerosis

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In the central nervous system (CNS), oligodendrocytes produce myelin and ensheath individual axons after birth. Demyelination disables saltatory conduction and leads to loss of neural functions. Oligodendrocyte precursor cells (OPCs) are immature and abundant reservoir cells in the adult brain that are capable of differentiating into myelinating oligodendrocytes. Upon demyelination insults, OPCs are spontaneously induced to differentiate in order to remyelinate denuded axons and promote functional recovery. While remyelination is an efficient regenerative process in the CNS, it often fails in the chronic phase of multiple sclerosis (MS) and strategies to promote remyelination are still poorly developed. Clarification of the mechanism of OPC differentiation as well as understanding the molecular pathology of OPC differentiation arrest in chronic MS shall reveal novel drug targets for the remyelination purpose. From our continuous research, we have elucidated that the γ chain of immunoglobu-

lin Fc receptor (FcR γ) is the critical triggering molecule for OPC differentiation, that FcR γ -stimulating antibodies induce OPC differentiation (Nakahara et al., *Dev Cell* (2003)) and provided evidences showing that the molecule is involved in the course of remyelination in MS brains (Nakahara et al., *J Neuropathol Exp Neurol* (2006)). We have also identified an intrinsic factor, TIP30, inhibiting spontaneous OPC differentiation in MS brains (Nakahara et al., *J Clin Invest* (2009)). In addition, a study by the others showed that the *de novo* cholesterol synthesis by oligodendrocytes is a rate-limiting factor for myelination (Saheret et al., *Nat Neurosci* (2005)). Together, we propose that the combined use of: 1) FcR γ -stimulating antibodies, 2) TIP30 antagonists, and 3) lipid precursors for myelin cholesterol synthesis is essential for the promotion of efficient remyelination in chronic MS patients. In the current talk, I will summarize aforementioned findings and our current research status toward the ultimate goal.