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Grant Title: Unravelling the role of Heparan sulfates in myelin regeneration in mouse brain

Myelin regeneration has been reported in Multiple Sclerosis patients but these spontaneous repair attempts are not always efficient. Myelin regeneration is due to the mobilization of an endogenous pool of oligodendrocyte progenitors (OPCs) which are maintained in the adult brain. OPCs surrounding the lesion are migrating toward the lesion and differentiating to replace lost myelinating oligodendrocytes. Thanks to a microarray strategy, we have identified a gene regulating heparan sulfate (HS) synthesis that shows a specific up-regulation by adult oligodendrocytes upon demyelination. We have observed that the gene encoding for Ndst1, an enzyme which performs the key step of HS modification, is specifically switched on by mobilized oligodendrocytes in different demyelinating mouse models.

1-Objective:
The objective of the project was to establish the role of HS in cell mobilization during the repair process by modulating HS synthesis combining *in vitro* and *in vivo* approaches.
2. Methods used
We used a combination of in test to assay cell proliferation, migration and differentiation and a model of acute focal demyelination of the corpus callosum (CC) to perform in vivo analysis.
3. Results
Here we show that *Ndst1* is up-regulated by oligodendrocyte population in mouse models of demyelination. We show that, while up regulation of *Ndst1* occurs throughout the demyelination and remyelination processes, lesion-induced *Ndst1* and HS proteoglycans over-expression was found concentrated around the lesion during the demyelination phase and the active phase of OPCs mobilization during the remyelination phase. In this model, conditional deletion of *Ndst1* in Olig2 population results in increased lesion size and a delay in OPC mobilization at early stage during the remyelination process. *In vitro* functional analysis moreover revealed that HS favor OPC proliferation and migration, and prevent OLG differentiation in culture suggesting that their presence maintain the cells in a plastic and immature phenotype.