

# Potential therapy of phosphacan in demyelinating disease

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## Laboratory

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## Subjects / Tools-Methodologies

- 1 : Tyrosine Phosphatases/KO mice and various constructions
- 2 : Myelination/lesions by cuprisone and MOG in collaboration
- 3 : repair/Fusion proteins constructs ready for proteins

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## Summary of lab's interests

Protein Tyrosine Phosphatases in myelination and demyelinating diseases In the laboratory of signaling of physiopathology neural directed by Dr. Sheila Harroch, we focus our research in molecules involved in the development of myelinating cells and in repair of non-inflammatory demyelinating disease. We aim to develop animal model of neurodegenerative disease to research potential therapies. As a part of this, we dissect the role of receptor protein tyrosine phosphatase  $\zeta$  (RPTP $\zeta$ ) in the developing nervous system in physiological and pathological contexts. We have made use of cell culture systems, the yeast two hybrid system, and knockout animals to dissect the role of RPTP $\zeta$  and RPTP $\beta$  (Lamprianou et al, 2006) in neural development. We have demonstrated that RPTP $\zeta$  plays a critical role in recovery from demyelinating illness, highlighting its potentially important role in multiple sclerosis (Harroch et al, 2002). We also provided evidence that the oligodendrocytes in the RPTP $\zeta$ -deficient animals were more susceptible to apoptosis in the demyelinating/remyelinating process. We have identified a novel player in remyelination, RPTP $\zeta$ , which constitutes a non-immune pathway that drives oligodendrocyte proliferation and remyelination. We expect that understanding the molecular mechanisms behind these physiological changes will uncover novel signaling pathways that can be targeted for the therapy of demyelinating diseases.

## Summary of project

Demyelinating lesions present in multiple sclerosis, for instance, are characterized by demyelination, oligodendroglia cell death, axonal damage, and a failure to remyelinate. Remyelination is believed to protect axons and thus prevent a further accumulation of axonal damage.

The processes of myelination and remyelination have received great attention during the last years, and factors governing oligodendrocyte precursor cell (OPC) proliferation and differentiation have been identified. However, to date, the precise governing of remyelination is not well understood.

We could recently identify the receptor protein tyrosine phosphatase  $\zeta$  (RPTP $\zeta$ ) as regulator of remyelination in non-inflammatory and inflammatory disease models and that RPTP $\zeta$  is an important regulator of myelin repair. Furthermore, preliminary data suggest that phosphacan (soluble RPTP $\zeta$ ) influences oligodendroglia proliferation and acts as an

oligodendrocyte progenitor cell (OPC) differentiation factor in vitro. We propose to study the role of phosphacan (soluble RPTP $\beta$ ) in promoting remyelination.

We will :

1. dissect the biological function and signaling pathways of soluble RPTP $\beta$  in vitro (some aspects will be done in Israel using the Weizmann institute microarrays platform) and
2. assess the therapeutic efficacy of phosphacan therapy for remyelination in demyelinating animal models in collaboration with Christine Stadelman in Gottingen, a known pathologist of demyelinating diseases.

The goal of our project is thus to explore the remyelinating capacity of phosphacan, the soluble isoform of RPTP $\beta$ , in demyelinating mouse models and to determine its signaling pathways. This will hopefully pave the way to its use as a pro-remyelinating therapy in human demyelinating diseases.