# Exploring the Effect of PI-88 on IFN-γ Induced Pathological Quiescence in OPCs

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## Abstract

In Multiple Sclerosis, failure to repair demyelinated lesions results in disease progression and permanent neurodegeneration. Oligodendrocyte precursor cells (OPCs) have the capacity to proliferate and migrate to lesions in response to injury-associated signals and differentiate into oligodendrocytes capable of remyelinating demyelinated axons. However, pro-inflammatory cytokine IFN-γ blocks OPC proliferation by inducing pathological quiescence and likely contributes to remyelination failure. Sulfatase enzymes promote IFN-γ signaling, by removing 6′-sulfate from heparan sulfate proteoglycans. Treatment with PI-88, a sulfatase inhibitor, blocks the negative effects of IFN-γ on OPC proliferation in vitro. This study investigates the ability of PI-88 to partially rescue OPCs from their induced quiescent state in vivo, resulting in increased proliferation and migration of OPCs to lesions. Using a lysolecithin-induced model of focal demyelination in the mouse spinal cord, we demonstrated that IFN-γ significantly reduced the number of Olig2+ migratory OPCs as well as the number of BrdU+ proliferative OPCs in the lesion site at 5 days post lesion, while PI-88 restored OPC cell density in a lesion almost to that of baseline and partially restored the number of OPCs that underwent cell division. Moreover, our data indicated an increase in microglial migration to lesion sites in response to IFN-γ, which was ameliorated by PI-88. This result suggests that PI-88 reduces the inflammatory effect caused by pro-inflammatory cytokine IFN-γ, which could potentially reduce the autoimmune inflammatory effect experienced in MS exacerbations. Our data suggests that the IFN-γ-induced quiescent state does in fact compromise OPC proliferation and migration to lesions, while PI-88 rescues OPCs from their quiescent state, promoting proliferation and migration. Future work will determine the capacity of PI-88 to block the negative effects of IFN-γ on subsequent oligodendrocyte generation and remyelination. This research is important in establishing sulfatase modulation as a therapeutic approach for IFN-γ induced pathological quiescence.

## Introduction

### Demyelination & Myelin Repair

- Demyelination
- Oligodendrocyte precursor cell (OPC) migration
- IFN-γ blockade
- Sulfatase inhibitor (PI-88)
- Remyelination

**Hypothesis**

Hypothesis: IFN-γ induces a pathological quiescent state on OPCs, impairing OPC proliferation and migration following demyelination, and sulfatase modulation mitigates this effect.

**Specific Aim:** Determine the effect of sulfatase inhibitor PI-88 on IFN-γ induced OPC quiescence.

## Experimental Methods

**Kinetics of lysolecithin model of remyelination**

**Direct Injection of Lysolecithin Induces Focal Demyelination Lesions**

- Lesions induced by direct injection of lysolecithin on Day 0. BrdU was injected 48 hr, 24 hr, and 12 hr prior to sac via perfusion. After mice were perfused, their spinal cords were prepared, sectioned, and the tissue was mounted onto slides and analyzed via immunohistochemistry and solochrome cyanine staining.

## Results

### PI-88 decreases IFN-γ induced microglial recruitment in vivo

- Spinal cord tissue stained with IBA1 showed an increase in IBA1+ microglial cell recruitment to the lesion in the IFN-γ condition, with a significant decrease of IBA1+ microglial cell recruitment in the IFN-γ + PI-88 condition.

### PI-88 rescues OPC migration from adverse effects of IFN-γ in vivo

- In spinal cords stained with both BrdU and Olig2, co-localized cells indicate that IFN-γ significantly decreased the number of OPCs that migrated to the lesion, while PI-88 significantly rescued this effect.

### PI-88 rescues proliferating OPCs from adverse effects of IFN-γ in vivo

- In spinal cords stained with both BrdU and Olig2, co-localized cells indicate that IFN-γ significantly decreased the number of OPCs that migrated to the lesion, while PI-88 significantly rescued this effect.

## Conclusions

- IFN-γ impairs proliferation and migration of OPCs to the lesion at 5dp, and treatment with PI-88 rescues this effect.
- IFN-γ induces increased microglial recruitment to the lesion at 5dp, and treatment with PI-88 mitigates this effect.
- Taken together, our data suggests PI-88 may prove to be a novel drug therapy used to promote remyelination in patients suffering from MS by relieving IFN-γ induced pathological OPC quiescence.

## Future Work

**IFN-γ and Remyelination**

- 14 day time point to determine if IFN-γ inhibits remyelination and if PI-88 is able to restore remyelination and functional recovery of axons.

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## References


## Current Work

Preliminary data suggests IFN-γ may impair differentiation of OPCs to oligodendrocytes and induce a shift from M2 to M1 microglia 7dp, and treatment with PI-88 may ameliorate these effects.