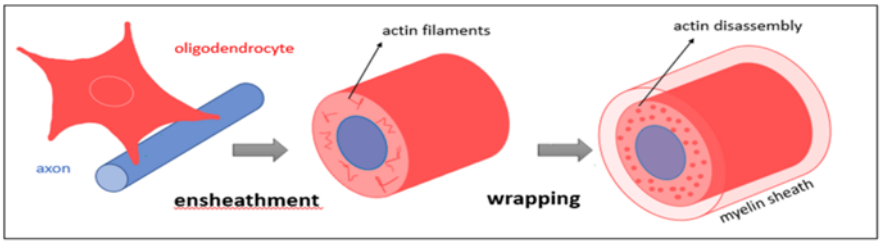
Experimental thesis project in Neurobiology



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We are seeking an highly motivated student to undertake a laboratory experimental study for Master Thesis discussion (LM in Molecular, Cellular and Biomedical Science, LM in Biotechnology) starting from March-April 2019.

Project Title: Study of the molecular mechanism of action of drugs promoting remyelination using 2D and 3D cell culture.

Background: Myelination starts during embryogenesis and terminate during adolescence in humans. Adult myelination is associated with adaptive learning. Several types of pathologies can lead to central nervous system (CNS) demyelination among which Multiple sclerosis, viral infection, injury and genetic diseases. Demyelination of axon is the main cause of neurodegeneration in patients after axonal demyelination. Remyelination is the natural process that restores myelin of damaged axons. CNS remyelination is often incomplete in Multiple Sclerosis (MS) patients, and it declines during aging.

Understanding of how remyelination occurs in adult CNS in normal and pathological conditions will open knew views on how adult myelin plasticity occurs, as we know little on how neuronal stem cells are reactivated, migrate and differentiate into linage specific oligodendrocyte precursor cells (OPC) and how they mature in myelinating oligodendrocyte (OLs) in adult brain. These knowledge has enormous medical implications as remyelination therapies might contribute to restore lost function and impair neuronal degeneration in demyelination disease, among which multiple sclerosis (1).

WHAT WE DO: Pharmacological intervention in CNS remyelination became feasible only in the recently years, thanks to the development of suitable phenotypical drug screens (2-3). Our group has successfully repurposed three classes of compounds out of the 1,200 clinically bioactive drug tested for their ability to promote myelin basic protein expression using phenotypical screening (2). One drug we selected, Clobetasol, was proven in EAE (3) and Neuromyelitis optica (4) animal models for remyelination. The next challenge will be to clarify their mechanism of action and understand the main cellular pathways leading to engagement of synthetic axons. We have set up an in vitro system to study OL/synthetic axon myelination in collaboration with Prof.Ing Alberto Rainer (University Campus Biomedico,Rome), that now we use for deciphering drug mechanism of action.

References **1.** Kremer D, Göttle P, Hartung HP, Küry P. Pushing Forward: Remyelination as the New Frontier in CNS Diseases. Trends Neurosci. 2016 Apr;39(4):246-263. **2.** Porcu G, Serone E, De Nardis V, Di Giandomenico D, Lucisano G, Scardapane M,Poma A, Ragnini-Wilson A. Clobetasol and Halcinonide Act as Smoothened Agonists to Promote Myelin Gene Expression and RxRγ Receptor Activation. PLoS One. 2015, 10:e0144550. **3.** Najm FJ, Madhavan M, Zaremba A, Shick E, Karl RT, Factor DC, Miller TE, Nevin ZS, Kantor C, Sargent A, Quick KL, Schlatzer DM, Tang H, Papoian R, BrimacombeKR, Shen M, Boxer MB, Jadhav A, Robinson AP, Podojil JR, Miller SD, Miller RH, Tesar PJ. Drug-based modulation of endogenous stem cells promotes functional remyelination in vivo. Nature. 2015, 522:216-20. **4.** Yao X, Su T, Verkman AS. Clobetasol promotes remyelination in a mouse model of neuromyelitis optica. Acta Neuropathol Commun. 2016, 4:42.