EPFL LAIDLAW FOUNDATION

<u>Research proposal:</u> Comm2 regulation of synaptic arborization at the neuromuscular junction (NMJ) and its impact on the locomotor system of *Drosophila Melanogaster*

To what extent does the lack of Comm2 protein impact the locomotion of adult flies?

Summary of the research project that you will be working on *(Description, goals and why you are interested in working on it)*

The fundamental organization of motor synapses is key to understanding locomotion in health and disease. Commissureless 2 (Comm2), is expressed in the Nervous System (NS) glia of *Drosophila Melanogaster* and is part of the 'Comm' protein family (Sarro J et al., 2013). In contrast to Comm1, Comm2 has not been extensively studied.

In adult flies, a nerve fibre divides and connects with a specific muscle fibre (Soler et al., 2004; Baek and Mann et al., 2009) which is reminiscent of the human NMJ organization (Ross A. Jones et al., 2017). Studies conducted by Prof. McCabe's Lab has revealed that the loss of function of Comm2 causes extensive branching at the larval NMJs (unpublished) leading to the hypothesis that the mutant flies would present an aberrant level of muscle activity and less efficient motor neuron circuitry.
To investigate our hypothesis, we will record adult flies on a treadmill to analyze kinematics of the *Drosophila Melanogaster*'s legs, representative of motor neuron activity.

Thus, the goal of this experiment is to characterize how synaptic arborisation regulation by Comm2 at the NMJ affects the locomotion of adult flies. It should enable us to gain a better understanding of locomotor systems, fundamental to our comprehension of motor neuron diseases.

Description of the work that you will be specifically undertaken in this project *(Description and intended outcomes of your work)*

<u>My project will consist of five main stages:</u>

1. Learning how to maintain fly husbandry and understand the basis of genetic crossing to obtain the desired genotype.
2. Raising stocks of homozygous comm2 null mutant flies mutants and of the control group (wild type *w1118*).
3. Recording of 10 days old and 20 days old flies locomotion on the treadmill.
4. Analyzing the data obtained using DeepLabCut (a software for 2D and 3D markerless pose estimation) to quantify the phenotypic differences between the groups.

At the end of this experiment, we will be able to quantify the kinematics associated to extensive synaptic arborization by Comm2 loss of function, hence its repercussions on flies' movement and behaviour.

Expected planned research impact *(How this research will positively impact society and how this will be measured)*

Even though Comm2 orthologs haven't been identified in the mammalian CNS (Sarro J. et al, 2013), understanding how the protein impacts the locomotion of *Drosophila Melanogaster* should broaden our understanding of neurodevelopmental diseases with defects in motor neurons branching and therefore movement disorders.
In fact, the way synapses organize themselves into branches and interact in the NMJ is a great concern for all motor disorders. Depending on the results that we will obtain, we could even promote the design of gene therapies aiming at mimicking the Comm2 pathway in mammals.

Its effectiveness could be measured through clinical trials, which would evaluate if the patients present any improvements in their fine motor movements in comparison with patients who didn't receive the therapy.

References

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