

**Group Name:** Sensory Transduction and Nociception  
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**Title of the MRP:**

**Functional sensitization of MrgprD+ nociceptors in oxaliplatin-induced neuropathy**

**Summary of the MRP:**

Our group has recently identified Piezo2 as a key mediator of mechanosensitivity in a specific population of mechanonociceptors (MrgprD+) under both physiological and neuropathic conditions<sup>1</sup>. Interestingly, these neurons show only minimal responses to innocuous mechanical stimulation despite Piezo2 being widely recognized as a detector of low-intensity mechanical forces. One possible explanation is that Piezo2 activity may be restrained by a voltage-dependent inhibitory mechanism in these cells. Under sensitizing conditions that depolarize the membrane, this “voltage lock” could be relieved, thereby increasing the responsiveness of MrgprD+ nociceptors to low-threshold mechanical stimuli<sup>2</sup>.

This Master’s Research Project (MRP) aims to test this hypothesis using a mouse model of chemotherapy-induced peripheral neuropathy (CIPN) triggered by oxaliplatin administration, which produces both mechanical and thermal hypersensitivity. Specifically, the project will investigate whether acute oxaliplatin treatment alters the activity and/or recruitment of MrgprD+ nociceptors in response to innocuous and noxious mechanical stimulation.

To address this question, *in vivo* calcium imaging experiments will be performed in dorsal root ganglia (DRG) neurons from transgenic mice expressing GCaMP6f selectively in MrgprD+ nociceptors. During imaging recordings, controlled mechanical stimuli of different intensities will be applied to the hindpaw in order to characterize neuronal response profiles before and after oxaliplatin treatment.

If oxaliplatin-induced sensitization is confirmed, additional experiments will be conducted using voltage-gated and purinergic channel modulators to explore the molecular mechanisms underlying this hypersensitivity. In particular, these studies will assess the possible involvement of P2X3 receptor signaling and potassium channel modulation in the functional unmasking of Piezo2-mediated mechanosensitivity.

To begin the project, the student must either hold certification in animal handling or be performing the TBS.

1. <https://doi.org/10.1097/j.pain.0000000000003954>

2. <https://doi.org/10.1093/brain/awae290>

**Methods and technology involved in the MRP:**

The project will combine pharmacological, behavioural, and *in vivo* imaging approaches:

- Intradermal injections into the hindpaw will be performed using oxaliplatin to induce acute CIPN, as well as ATP and SK channel modulators to investigate the contribution of purinergic signaling and potassium channel activity to neuronal sensitization.
- Behavioural assessment of mechanical hypersensitivity: Mechanical sensitization will be evaluated using the von Frey assay to quantify changes in paw withdrawal.
- *In vivo* DRG calcium imaging: Functional activity of sensory neurons will be monitored through *in vivo* calcium imaging of dorsal root ganglia (DRG) neurons in transgenic mice expressing GCaMP6f in MrgprD+ nociceptors. This technique will include: DRG exposure surgery, real-time fluorescence image acquisition, and simultaneous application of controlled mechanical stimuli to the hindpaw.
- Data analysis will be performed using specialized software and custom-written scripts.

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