Group name: Sensory transduction and nociception
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Title of the MRP/TFM: **Mast cells in pain signalling: friend or foe?** — Unravelling the role of mast cells in nociception across different neuro-immune scenarios.

Summary of the Project:

Activation of the nervous system is a crucial and significant consequence of immune system function. Indeed, one of the primary effects of inflammatory states is the development of pain. This arises from the activation of specialised 'pain-sensing' neurons, referred to as nociceptors. These sensory neurons express, among others, receptors that recognise immune-derived mediators. Thus, during immune activation, released mediators may disrupt normal nociceptor function, rendering them hypersensitive and ultimately leading to pain.

Mast cells are tissue-resident immune cells classically known for their role in the pathophysiology of allergy and anaphylaxis. Certainly, however, we do not have mast cells so that eating a peanut could make us sick—or kill us! These cells play an important role in host defence. They are equipped with granules containing a wide array of mediators, including histamine, tryptase, prostaglandins, etc., which they can release rapidly upon activation. Mast cells are recruited and activated not only during type 2 immune responses (typically associated with allergic disease), but also during type 1 and type 17 immunity (which protect against intracellular and extracellular microbes, respectively).

Mast cell-derived mediators have consistently been shown to directly activate and/or sensitise nociceptors, leading to increased nociceptive signalling and pain. Notably, recent evidence showed that some of them, such as chymases, can lead to the resolution of inflammatory pain associated with a type 1 immune response. Thus, the activation of mast cells may elicit pain or, conversely, prevent it. Characterising the precise mediators and signalling pathways underlying each of these processes is, therefore, crucial to developing effective therapies for pain conditions associated with specific neuro-immune scenarios.

The overall aim of this project is to characterise the signalling pathways and mediators by which mast cells trigger (or prevent) nociceptive activity in different immunological contexts. To this end, we have designed two integrated but independent objectives:

1. **To evaluate the role of mast cells in the modulation of nociceptor function** under type 1, type 2, and type 17 immune responses.
2. **To assess the effect of mast cell mediators on nociceptive ion channel/receptor expression and membrane translocation** during type 1, 2, and 17 immune responses.

Methods and technology involved in the MRP/TFM Project:

We will use previously generated supernatants from skin biopsies of mice in which type 1, type 2, and type 17 immune responses, respectively, have been induced locally. These supernatants will be applied to cultures of DRG sensory neurons. Then, the following techniques will be used:

- **For objective 1**: Live-cell Ca^{2+}-imaging will be used to evaluate sensory neuron activity.
- **For objective 2:** Immunostaining and confocal microscopy will enable us to evaluate the expression and dynamics of specific ion channels and receptors in sensory neurons**.**

The role of specific mast cell-derived mediators will be assessed by blocking histamine receptors and inhibiting tryptase or chymase activity. Furthermore, the mechanisms underlying channel/receptor sensitisation and/or translocation to the membrane will be evaluated by targeting specific pathways—such as protein kinase A (PKA), protein kinase C (PKC), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), phospholipase C (PLC), and phospholipase A_2 (PLA_2), and by using exocytosis inhibitors.

Member/s of the lab who will act as tutor/co-tutor of the project: **Javier Aguilera-Lizarraga**

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