Group name: Plasticity and remodeling of neural circuits
IP name: Isabel Pérez Otaño
Group web: https://in.umh-csic.es/en/grupos/plasticity-and-remodeling-of-neural-circuits/#equipo

Title of the MRP/TFM: Targeting non-conventional NMDA receptor and mTOR signaling for resilience to chronic stress

Summary of the Project:

Chronic stress affects brain structure and function and is a well-recognized risk factor for neuropsychiatric disorders including post-traumatic stress disorder, anxiety, and depression. Mounting evidence suggests that chronic stress induces maladaptive plastic changes in glutamatergic neurotransmission that target vulnerable brain circuits and influence specific domains of cognitive and emotional processing. In the last decade, the discovery that ketamine acts as an NMDA receptor antagonist with fast and long-lasting antidepressant effects has stimulated basic research and development of drugs targeting NMDA receptors. In this context, NMDA receptor subunits have been studied intensively on the hope to treat stress-related disorders. Non-canonical GluN3A subunits are gathering momentum because of their selective expression in brain regions critical for stress regulation such as the prefrontal cortex, ventral hippocampus, or amygdala (Perez-Otaño et al, *Nature Reviews Neuroscience* 2016; Murillo et al *Cerebral Cortex* 2021; Bossi et al *Neuron* 2022) and their ability to control signaling by the mammalian target of rapamycin kinase (mTOR). Using several animal models for chronic stress, we recently found that genetic deletion of GluN3A confers resilience to stress implying that GluN3A could be a druggable target to treat stress-related disorders.
By taking advantage of circuit-specific viral manipulations and newly developed negative allosteric modulators (NAM) and positive allosteric modulations (PAM) against GluN3A, the student will test how non-canonical NMDAR signaling modulates cognition, social and emotional behavior of mice in basal conditions and in chronic stress.

During the internship the student will
- become familiar with mice handling, drug injection, behavioral tests
- learn how to apply viral manipulations
- test new pharmacological drugs
- determine how drugs targeting GluN3A modulate synaptic connectivity in brain regions related to stress

Methods and technology involved in the MRP/TFM Project:
-Mice handling and injections; mice behavioral analyses (focusing on emotional behaviors); stereotaxic surgery; viral manipulations; biochemistry and immunohistochemistry; synapse nanobody labeling and reconstruction

A good command of English is needed

Member/s of the lab who will act as tutor/co-tutor of the project (if different from the group IP): Isabel Perez-Otaño/Remy Verhaeghe

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