## Research Line

Small-RNAs in neurodegenerative diseases: identification of deregulated species with neurotoxic activity and biomarker potential

## Group and Scientific Interests

The student will be integrated into the research group "**Functional Genomics of Neurodegenerative Diseases**" (P.I. Eulàlia Martí), at the Department of Biomedical Sciences (Universitat de Barcelona, Campus Clinic). Our group belongs to the **Institute of Neurosciences** that has been awarded with a Maria de Maetzu Excellence Acreditation. At the Institute of Neurosciences diverse researchers, including E. Martí's group are focused on the study of neurodegenerative disorders using multidisciplinary approaches.

Different classes of RNA molecules that do not encode for proteins (non-coding RNAs or ncRNAs) modulate gene expression through diverse mechanisms and constitute a crucial layer of biological regulation. ncRNAs are specially enriched in the nervous system, where their highly specific and dynamic expression is essential in developmental processes and the correct function of the adult brain. The ncRNA repertoire is fundamental for neuron-specific functions and its perturbation is mechanistically related with neuropathological processes.

Our lab has been working for more than 10 years in the understanding of disease-driven deregulation of ncRNAs and their role in neuronal dysfunction. The main research interest in our group is to **identify ncRNA mechanisms contributing to the onset and progression of age-related neurodegenerative disorders**. We aim at understanding disease-driven deregulation of ncRNAs and their role in neuronal dysfunction. Our final purpose is to discover ncRNA-gene expression networks underlying neuro-pathogenic processes with the aim to understand disease mechanisms and identifying pathways for therapeutic intervention.

We are a **multidisciplinary team** including neuroscientists, molecular biologists, bioinformaticians and biostatisticians. We use RNA-seq approaches and data mining strategies to identify deregulated species with neuropathogenic potential. Functional validations, neuropathology and therapeutic approaches are performed *in vivo*, in model organisms and cell culture, using biochemistry strategies and behavioural phenotyping. We have a **wide network of national and international collaborations with clinicians and molecular biologists** that boost our activities

## Proposed Research

Major challenges in translational biomedicine that are the core research of the lab are (i) **to evaluate the potential of ncRNAs as, non-invasive biomarkers** and (ii) to understand the **functional and pathogenic relevance of these species**, which may help to unravel disease mechanisms and identify therapeutic targets. Our activities are currently centered in Huntington's disease and Alzheimer's disease. The proposed research project will be related with any of the following topics:

**1.- Analysis of extracellular RNA (exRNA) as a pathogenic driver in neurodegeneration**. Our most recent data have identified diverse disease specific ncRNAs with neurotoxic potential and additional evidence suggests that ncRNAs are released by various cell types upon inflammatory stimulation. The student will be involved in characterizing exRNA in normal and diseased cells and determine if disease released ncRNAs spread damage in a neurodegenerative condition. Specific candidate ncRNAs, generated in disease will be delivered to cultured neuronal or glial cells (primary cells or cell lines) and diverse readouts of cell dysfunction will be determined, including cell viability, transcriptional deregulation, protein aggregation, stress, and inflammation status.

**2.- Circulating ncRNAs as potential biomarkers.** The student will be involved in the análisis of sRNA sequencing data from human biofluids in paradigms of neurodegeneration. We will use publicly available data and data generated in the lab. This project involves the evaluation of the performance of specific bioinformatic tools generated in the lab in comparison with other commonly used analytical

platforms. In addition to univariant differential expression analysis, machine learning approaches such as Random Forest or Suport Vector Machines will be applied to evaluate weather global patterns of sRNA types can discriminate disease versus control condition. We will evaluate if specific ncRNAs help in identifying the earliest disease alterations, occurring at pre-clinical stages of the disease. We expect to define new biomarkers improving patients' selection, stratification, and inclusion in clinical trials. We aim at opening new avenues in the adoption of a more personalized medicine, allowing the clinician to consider patients' preferences and predisposition for future treatments.

**3.- Brain ncRNA expression dynamics in disease progression.** The student will participate in the identification of ncRNAs whose expression correlates with disease progression and severity. This will involve RNA extraction from diverse brain areas (human samples and model organisms) at different evolutionary stages, ncRNA sequencing, and analysis of sequencing data using bioinformatic and biostatistical tools as described in (2). These studies will be followed by the evaluation of the *in vivo* activity of candidate, disease related ncRNAs as described in (1).

A **training programme** for the student is contemplated, including a follow-up by a Thesis Advising Committee that will discuss results and provide advice on future directions and decisions. Additional training will be provided on **scientific writing and oral presentations**. The candidate will participate in the following activities: **seminars** given by internationally recognized neuroscientists, **journal clubs**, **data seminars** and **neurobiology symposiums**. We expect the candidate to attend at least one international meeting to present results. At least one short stage in the lab of a collaborator will be promoted.