Clotilde Lagier-Tourenne, MD PhD **Research Description**

Overview

The long-term goal of my laboratory lay in identification of molecular mechanisms crucial for neuronal function and how errors in that drove the major human **neurodegenerative diseases**. We are particularly interested in the role of **RNA processing alterations** in neuronal health and dysfunction. This work finds its relevance in the increasing recognition that RNA processing alterations are crucial in the pathogenesis of neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Indeed, mutations and/or cellular mislocalization of several RNA binding proteins have been identified as central components in the pathogenesis of ALS and FTD, as well as in an increasing number of neurodegenerative diseases.

A focus on altered RNA processing as a central component of neurodegeneration is also supported by the realization that the most common cause of inherited ALS and FTD is an hexanucleotide expansion in the C9orf72 gene accompanied by RNA foci that may sequester one or more RNA binding proteins. Indeed, the causative mutation in the C9orf72 gene is remarkable with the presence of hundreds to thousands of GGGGCC repeats in an intronic region, while the motif is repeated only 2 to 30 times in unaffected individuals. The pathogenic mechanisms of this expansion are not understood, but initial observations point to either a loss of function of the C9orf72 gene, and/or a toxic gain of function of the expanded RNA through sequestration of RNA binding protein(s) that may provoke RNA misprocessing.

With my young team, I pursue efforts to unravel the role of RNA processing alterations in the pathogenesis of neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). We use **genomic approaches** in animal models and patient samples to investigate two main questions:

1) How do aggregation-prone RNA binding proteins influence the processing of their RNA targets to maintain normal neuronal function?

2) What are the mechanisms triggering neurodegeneration in patients with C9orf72 repeat expansions?

We use innovative genomic strategies to attacking these difficult problems. Indeed, rather than singlehandedly cause, I strongly believe that a combination of multiple splicing or expression alterations is one of several contributors to neuronal dysfunction in ALS and FTD. Therefore, rather than focusing on one specific target, we use the combination of changes as a direct indicator of disease state to answer essential questions about **disease mechanisms**. After establishing **RNA profiles** linked to specific ALS/FTD mutations, we determine what conditions may recapitulate or reverse disease-related RNA alterations. Importantly, the molecular signature may also serve as a **functional readout** to screen therapeutic compounds, and one part of my rationale is that uncovering which RNAs are abnormally processed in ALS/FTD will open opportunities for **interventional strategies**.