NEUROSCIENCE
CONFERENCE
SERIES

Institut de Neurociències
UNIVERSITAT DE BARCELONA

EXCELENCIA
MARÍA
DE MAEZTU

SOMATIC CAG EXPANSIONS AS A THERAPEUTIC TARGET FOR HUNTINGTON'S DISEASE

Targeting the DNA mismatch repair pathway to prevent somatic repeat expansions constitutes a promising therapeutic strategy for HD and other trinucleotide repeat expansion disorders

Ricardo Mouro Pinto, M.Sc., Ph.D.

Center for Genomic Medicine, Massachusetts General Hospital. Instructor in Neurology, Harvard Medical School. Associated Scientist, Program in Medical and Population Genetics, Broad Institute at MIT and Harvard

Huntington's disease (HD) is a rare neurodegenerative disease caused by an expanded CAG repeat in the HTT gene, with larger alleles being associated with earlier disease onset and more severe clinical phenotypes. Despite this being a single gene disorder, where the underlying genetic mutation has been known for just over 30 years now, there remains no cure or disease-modifying therapy, indicating that novel approaches are critical. A hallmark of HD, and most repeat expansion disorders, is that the repeats are highly unstable, both intergenerationally (parent to child) and in somatic tissues, where the repeat expands progressively over time in a cell-/tissue-specific manner. Notably, in HD, medium-spiny neurons of the striatum, which succumb most severely to the effects of the HTT mutation, exhibit the most dramatic CAG expansions. These observations, together with growing genetic evidence from genome-wide association (GWA) studies in HD patients, support the hypothesis that progressive repeat length increases in somatic tissues contribute to the pathogenic process.

Consequently, the HD disease process can be viewed as two components: 1) a rate driver mechanism (somatic CAG expansion) that determines the timing of disease onset, and 2) a toxicity mechanism (as yet not unequivocally defined) that triggers the damage caused by a CAG repeat expanded above a critical threshold. To date, we have primarily implicated the DNA mismatch repair pathway as the critical driver of somatic repeat expansions. We have developed novel methods to facilitate the study of somatic CAG instability and an in vivo CRISPR/Cas9-based platform to test novel genetic candidates in HD mice. We are currently developing genome editing therapeutics that target somatic instability as a therapeutic for HD and potentially many other repeat expansion disorders.

Hosted by: **Verónica Inés Brito**

January 24th
Wednesday at 11:00h

Faculty of Medicine and Health Sciences
Campus Clinic | Aula Magna