UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title
Preclinical validation of MT2 receptor modulation as a novel therapeutic approach to Autism-Related Syndromes
2)Abstract (max 500 words)
Fragile X Syndrome (FXS) and Phelan-McDermid Syndrome (PMS) are severe, rare genetic disorders strongly associated with Autism Spectrum Disorder (ASD). They are characterized by a multifactorial etiology and complex clinical phenotype, including core social communication deficits, anxiety, irritability, and severe sleep disturbances. Currently, there are no approved specific treatments for these conditions, highlighting an urgent unmet medical need. Beyond traditional neurotransmitter targets, the melatonergic system, and specifically the melatonin MT2 receptor, has emerged as a critical regulator of sleep architecture and brain function. This melatonin receptor subtype represents a novel, potentially druggable target capable of mechanistically addressing both the behavioral and sleep-related abnormalities characterizing these neurodevelopmental disorders. However, the precise behavioral impact and the underlying neuroanatomical correlates of selectively targeting the MT2 receptor in these specific genetic conditions have not been fully clarified. This PhD project is therefore aimed at further validating the MT2 receptor as a novel therapeutic target by providing a comprehensive preclinical characterization of a first-in-class, selective MT2 agonist (COS01). The project will focus specifically on defining the behavioral efficacy and the associated neuroanatomical modifications induced by this pharmacological modulation. Using established genetic murine models of FXS and PMS (specifically, FMR1 and SHANK3 knockout mice), we will assess the in vivo effects of targeted pharmacological modulation of the MT2 receptor. Extensive behavioral pharmacology testing will be employed to evaluate the rescue of domains relevant to ASD, such as social interaction deficits, anxiety-like behaviors, and cognitive impairments. Furthermore, the underlying neurobiological mechanisms will be investigated ex vivo using advanced immunohistochemical techniques. This will allow us to map neuronal network alterations, assess structural plasticity, and confirm target engagement within specific brain circuits implicated in the pathology. This integrated behavioral and neuroanatomical approach will provide novel insights into the pathophysiology and psychopharmacology of FXS, PMS, and related autism spectrum disorders. By advancing our current understanding of how MT2 receptor activation modulates specific neuronal circuits and behavioral phenotypes, the findings from this project will establish a strong preclinical rationale. Ultimately, this work will support the development and clinical translation of innovative, targeted neuropsychopharmacological strategies aimed at significantly improving clinical outcomes and the quality of life for individuals affected by these debilitating neurodevelopmental conditions.