UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

Tutor's Name	Prof. Stefano Comai
Cotutor's Name	

1) Project title

Targeting the kynurenine pathway in schizophrenia: a translational approach to identify novel therapeutics and biomarkers

2)Abstract (max 500 words)

Schizophrenia is a severe mental illness and a leading cause of disability worldwide. The disease is characterized by a multifactorial etiology and complex clinical phenotype, and its underlying pathophysiological mechanisms and biological correlates remain only partially understood. Beyond dopaminergic hyperfunction, which represents the primary target of all currently available antipsychotic drugs but often fails to adequately address negative and cognitive symptoms, schizophrenia has also been associated with other central dysfunctions. At the neurochemical level, these include glutamatergic hypofunction and an altered inflammatory profile. Patients also show dysregulation of the kynurenine pathway of tryptophan metabolism, which lies at the crossroad between inflammation and glutamatergic signaling. This pathway represents a novel, potentially druggable target capable of mechanistically linking these disparate dimensions. At the neurophysiological level, EEG alterations in both resting state and task-related oscillations have been consistently observed in individuals with schizophrenia, and abnormalities in sleep architecture are now considered an integral correlate of schizophrenia pathology and a potential endophenotype of the disease. However, the mechanisms by which these alterations are individually and collectively associated with the psychopathology and cognitive impairments characterizing the illness have not been clarified yet. This PhD project is therefore aimed at further validating the kynurenine pathway as a novel therapeutic target by providing a more profound and comprehensive characterization of the interaction between these domains, with a particular focus on the intersection between inflammation, kynurenine pathway metabolism, glutamatergic dysfunction, and sleep abnormalities. Using established murine models of schizophrenia based on pharmacologically induced glutamatergic hypofunction (e.g., MK-801), we will assess the effects of inflammation and targeted pharmacological modulation of the kynurenine pathway (specifically, via the administration of targeted enzyme inhibitors such as KAT inhibitors) on sleep-wake patterns and neural activity. In vivo electrophysiology and EEG analyses will be employed to characterize neurophysiological correlates, while behavioral testing will be used to assess domains relevant to positive, negative, and cognitive symptoms. The underlying neurobiological mechanisms and potential therapeutic efficacy will be further investigated by testing whether this specific pharmacological modulation of the kynurenine pathway can effectively rescue neurophysiological and behavioral abnormalities associated with glutamatergic hypofunction, thereby establishing a strong preclinical rationale for this novel pharmacological approach.

Finally, preclinical findings will be complemented by analyses in patients with schizophrenia, by examining the associations between psychopathology, cognitive performance, sleep parameters, circulating inflammatory mediators and tryptophan-kynurenine metabolites, as well as related genetic biomarkers to guide future potential targeted therapies. This integrated and multidisciplinary approach will provide novel insights into the pathophysiology and psychopharmacology of schizophrenia. By advancing our current understanding of the interplay between inflammatory, neurochemical and neurophysiological processes, the findings from this project can contribute to identify novel biological markers for patient stratification, and support the development of innovative neuropsychopharmacological strategies centered on kynurenine pathway modulation aimed at improving clinical outcomes and quality of life in individuals with schizophrenia.

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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.