Universität Basel

Research Project

NCCR Translational Fellowship

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Autism Spectrum Disorders (ASD) are neuro-developmental disorders characterized by altered social communication and repetitive behaviors. ASD appear in the first 2 years of life and affect one in 54 children according to estimates from CDC's Autism and Developmental Disabilities Monitoring Network. Autistic patients will often have a normal life span but with significantly higher medical and social support needs throughout their lives. ASD therefore represents a significant social and economic burden on affected individuals and their families. Current pharmacotherapy does not address the core symptoms of the disease. Recent therapeutic strategies have focused on the neuropeptides oxytocin and vasopressin [1−3] which regulate aspects of social behavior in mammals [4]. However, the vast majority of genetic autism risk factors have no known links to oxytocinergic signaling [5−8]. Studies in rodent models of autism provided evidence that a disruption of translation homeostasis results in impaired plasticity and neurodevelopmental conditions [9−12]. Thus, interventions targeting translational machinery might provide a strategy to treat some forms of autism. In previous studies, we discovered an unexpected convergence of translation homeostasis and oxytocin signaling. We found that pharmacological inhibition of Map Kinase Interacting Kinases (MNKs) restores translational homeostasis, oxytocin receptor responses and social recognition behavior in a rodent model replicating an autism-associated genetic mutation [13]. In the present project, we will seek to extend these findings. We will conduct a comprehensive preclinical evaluation of MNK inhibitors for the treatment of autism. We will examine efficacy in three genetic rodent models of autism and human stem cell-derived neurons in vitro. Specifically, we will focus on a novel, highly specific, brain-penetrant MNK inhibitor (AUM001) which already underwent a phase 1 trial in Healthy Volunteers (ACTRN12620000572965). AUM001 was originally developed for cancer therapy. The goal of this study is to critically evaluate repurposing AUM001 for treatment of autism spectrum disorders and to provide information on suitable biomarkers. Upon successful completion of this project, it should be possible to advance AUM001 to clinical studies in ASD.

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