Multiple approaches to identify novel and effective treatments for the fragile X syndrome

Fragile X syndrome (FXS) is the most common form of inherited intellectual disability and a leading cause of autism. It is due to the silencing of the FMR1 gene coding for an RNA-binding protein the Fragile X Messenger Ribonucleoprotein (FMRP). This protein is part of ribonucleoprotein complexes associated to polyribosomes and involved in translational regulation. FMRP works mainly as a repressor of translation, but in some cases can also enhance translation. To date no specific treatment is available for this disorder. Thus, the search for new treatments able to modify the lifetime course of FXS and to improve its prognosis is urgent. With this purpose, during the last year, we used different and complementary approaches to identify new effective treatment for FXS. We searched for target mRNAs of FMRP by a CLIP (Cross-Link UV Immunoprecipitation) assay in brain cortex and hippocampus during synaptogenesis. Among the targets we identified, we focused our attention on those involved in the homeostasis of cAMP and cGMP and in the homeostasis of Ca^{2+}. Indeed, pharmacological or genetic modulation of these pathways improves socio-cognitive behavior of the Fmr1-KO mouse. In parallel, we established a stable shFmr1 embryonic stem cell (ES) line depleted of FMRP. We used this cell line to screen a library of biomolecules, anticipating that the molecules revealing an ability to actively revert the phenotype of this cell model would likely be candidates for pharmacological treatment of FXS. We found 4 molecules, called SM1-SM4 and we will present their positive impact on in vitro, ex vivo and in vivo FXS phenotype, thus validating our second approach in the search for FXS treatment.