**The cell-permeable JNK inhibitor peptide (D-JNKI1) prevents motor defects and preserves dendritic spines in Mecp2 and CDKL5 mice models**

Sara Cimini, Eleonora Calcagno, Annamaria Castaldo, Grazia Della Sala, Elena Putignano, Tommaso Pizzorusso, Maurizio Giustetto e Tiziana Borsello

Rett syndrome (RTT) is a progressive neurodevelopmental disorder and one of the most common causes of mental retardation, with a prevalence of 1 in 10000-15000 females. RTT is characterized by normal growth followed by a neurodevelopment regression; the main effect is represented by loss of motor and intellectual abilities. RTT is caused by heterozygous mutations in the X-linked MECP2 gene, encoding methyl-CpG-binding protein-2, a transcription factor. MeCP2 is involved in the regulation of synaptic connectivity and analysis of Rett mice models reported that altered MeCP2 protein level induce important deficits in dendrites. (Johnston et al., 2005, Chapleau et al., 2009). We focused on JNK's role in the mechanism leading to synaptic dysfunction since this protein regulates excitatory synaptic dysfunction. In order to study the modulation of JNK in preventing both motor defects and dysfunction of dendritic spines in MeCP2 mutant mice we used the specific cell permeable JNK inhibitor peptide, D-JNKI1, to inhibit specifically JNK. We performed our research on 2 different RTT mouse model, Mecp2 Jaenisch and Mecp2 Bird. Preliminary data demonstrated that treatment with D-JNKI1 is able to revert motor defects (behavioural data) by improving motor coordination in rotarod test and to stabilize dendritic spines (biochemical data on TIF fraction) by restoring levels of postsynaptic markers in cerebellum. In this study we also performed experiments on CDKL5 mice, responsible for another important mutation of RTT. Data obtained indicates that treatment with the D-JNKI1 induces the formation of dendritic spines, promoting the development of filopodia into mature spine.