Pharmacological modulation of neuronal activity for the treatment of Rett syndrome

G. De Rocco[1,3], L. Scaramuzza[2], M. Indrigo[3], N. Landsberger[1,3].

1. Department of Medical Biotechnology and Translational Medicine, University of Milan, 20090 Segrate (MI), Italy.
2. Department of Biosciences, University of Milan, Istituto Nazionale Genetica Molecolare "Romeo ed Enrica Invernizzi", 20122, Milan, Italy.
3. San Raffaele Rett Research Unit, Division of Neuroscience, San Raffaele Hospital, 20132 Milan, Italy.

Rett syndrome (RTT) is a neurodevelopmental disorder, representing the most common genetic cause of severe intellectual disability in females. More than 95% of classical RTT cases are caused by mutations in the X-linked *MECP2* gene, and in line with its role as a master regulator of gene expression, null neurons display widespread transcriptional changes, reduced activity, and defective morphology. These elements are linked in a feed-forward cycle where neuronal activity drives transcriptional and morphological changes that increase network maturity. Neuronal activity plays a key role during brain development, thus any variation from physiological ranges leads to severe consequences. We tested the possible causative link between neuronal activity and gene expression in RTT by pharmacologically stimulating *in vitro* and *in vivo Mecp2* null neurons.

We investigated the value of the Ampakines, positive modulators of AMPA receptor. We anticipated the time window of intervention by treating mice from P3 to P9, to prevent or at least alleviate the classic RTT phenotypes. The efficacy of the treatment with CX546 was tested by evaluating the general well-being of mice and by performing behavioral tests.

Although the early time window of treatment suggested a prolonged beneficial effect on *Mecp2* null mice, it was devoid of translational value. So, we decided to study *in vivo* later time points. First results were collected administrating two different ampakines and the efficacy of the treatment was assessed by evaluating the lifespan, the general well-being of mice, and by performing some behavioral tests. Moreover, we tested the value of a prolonged treatment in which animals were injected every other week.

Our results support the value of an early therapeutic approach acting on neuronal activity as a strategy for RTT therapy. More studies are needed to pinpoint the correct time window and to identify the molecular pathways involved in any observed benefits.