Evaluation of AAV9-BDNF treatment in two mouse models of RTT

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Rett syndrome (RTT) is characterized by motor, cognitive and autonomic deficits in patients as well as in mouse models. Several of these abnormalities are strongly associated with alterations of Bdnf levels (Chen et al, 2003; Martinowich et al, 2003). Our team also demonstrated that Bdnf trafficking is affected in the brain of the Mecp2-deficient mouse model of RTT (Roux et al, 2012). Finally, increased Bdnf expression in the Mecp2 mutant brain with a conditional Bdnf transgene extends lifespan, rescues locomotor defects and reverses electrophysiological deficits (Chang et al, 2006). This last result demonstrates the physiological significance of altered Bdnf expression and signaling in RTT disease progression and the possibility of using Bdnf as a therapeutic tool. However, Bdnf is not able to cross the blood brain barrier avoiding its direct use. Alternatively, several scientific teams are trying to identify pharmacological compounds able to stimulate indirectly the brain Bdnf expression. In the past 5 years, we and other have developed gene therapy for RTT using AAV9 vectors (Gadalla et al, 2013, 2017; Garg et al, 2013; Matagne et al, 2017, Simmonett et al, 2017). The goal of these projects was to express Mecp2 in the brain of the Mecp2-deficient mice. These different promising works have brought hope for a definitive treatment of the pathology. However, one of the major problems encountered with RTT is still the fine regulation of the Mecp2 dosage and the resulting neurological defects when this dosage is unbalanced. Many research teams around the world are working to find a pharmacological way to directly or indirectly modulate BDNF levels. Surprisingly, and to the best of our knowledge, no project was developed using AAV-mediated Bdnf-expressing vectors while this type of treatment has recently shown its efficacy in other models of neuropathology (Igarashi et al, 2016; Connor et al, 2016, Kells et al, 2004). Therefore, our objective will be to evaluate in vivo and in vitro the effect of AAV9-Bdnf treatment in two mouse models of RTT. The first one is the knockout one and the second the knocking T158M.