Auteurs
Matagne V, Villard L, Roux JC.

Improvement in Rett syndrome-like symptoms in Mecp2-deficient male and female mice after administration of a self-complementary AAV9 (scAAV9) construct expressing a codon-optimized *Mecp2* transgene.

Rett syndrome (RTT) is an X-linked neurodevelopmental disorder primarily affecting CNS functions. Most RTT cases are due to mutations in the methyl CpG binding protein 2 (MECP2) gene, a global transcriptional modulator. There is currently no cure for the disease and drugs alleviating symptoms are the only available therapies.

Recently, two different research teams reported that gene therapy in the Mecp2-deficient RTT mouse model partially cured the disease (Gadalla et al 2013; Garg et al 2013). Although both studies reported a beneficial effect of gene therapy, they also showed that there was still room for improvement.

In order to try and improve vector delivery and expression, we designed a plasmid construct expressing a codon-optimized version of *Mecp2* that was used to generate a scAAV9 virus. Thirty day-old Mecp2 KO male (KO) and 5 month-old Mecp2-heterozygous (Hz) female mice were injected with the virus through the tail vein ($2*10^{11}$vg/mouse).

Despite a low percentage of Mecp2-expressing cells in AAV9-treated KO mice (10-24% of WT levels), we did find an improvement in spontaneous locomotor activity and sensorimotor coordination, as well as normalization of the number of apneas (145±68 in treated vs 4,5±3,2 in untreated KO, $p<0,001$) that are characteristic RTT symptoms. A decrease in apnea occurrence was also observed in female Hz mice 4 weeks post-injection.
Further studies will be aimed at optimizing the dose administered and investigating the long-term effects (therapeutic benefits and/or side effects) of gene therapy in Hz female mice.

Support: AFM