ANTISENSE OLIGONUCLEOTIDE THERAPY IN A HUMANIZED MOUSE MODEL OF MECP2 DUPLICATION SYNDROME

Yingyao Shao[1], Huda Y Zoghbi[2], Yehezkel Sztainberg[3], Paymaan Jafar-Nejad[4], Frank Rigo[4]

[1] Baylor College of Medicine, Department of Pediatrics, Neurogenetics

[2] Baylor College of Medicine, Pediatrics , NA

[3] Baylor College of Medicine, Genetics, NA

[4] Ionis Pharmaceuticals, NA, NA

Background: Many intellectual disability disorders are due to copy number variations, and to date there have been no treatment options tested for this class of diseases. MECP2 duplication syndrome (MDS) is one of the most common genomic rearrangements in males and results from duplications spanning the methyl-CpG binding protein 2 (MECP2) gene locus. Previously, we have shown that antisense oligonucleotide (ASO) therapy can successfully reduce MeCP2 levels in an MDS mouse model and reverse the disease-like phenotypes. However, our previous MDS mouse model carried one transgenic human allele and one mouse allele, with the latter being protected from human specific MECP2-ASO targeting. In humans, the two MECP2 alleles are identical and because MeCP2 is a dosage-sensitive protein, one must ensure that the ASO is titrated to target the human allele such that MeCP2 levels are reduced from 2X to 1X.

Materials/Methods: We generated a new “humanized” mouse model of MDS, that carries two human MECP2 alleles, and no mouse endogenous allele. Moreover, we tested the effects of a human-specific MECP2-ASO through intracerebroventricular injection in the cerebrospinal fluid, which is a more translatable approach delivery method.

Results: The humanized mouse model of MDS showed elevated MeCP2 levels and recapitulated the majority of the human patient phenotypes through various behavioral tests. We also found that the MECP2-ASO efficiently downregulates MeCP2 expression throughout the brain by quantifying the RNA and protein levels at 7 different brain regions. Furthermore, MECP2-ASO can dose-dependently decrease MeCP2 levels in the brain as well as in the blood. High dose of MECP2-ASO also ameliorates behavioral deficits including exploratory, learning and memory as well as motor coordination behavior, without any dose-limiting toxic effect or safety concern. We characterized the pharmacodynamic effect of the MECP2-ASO on MeCP2 and selected MeCP2-regulated genes during the duration of the treatment.

Conclusions: Taken together, our results demonstrate that central nervous system administration of MECP2-ASO is well tolerated, has beneficial effects, and support a feasible translatable approach for the treatment of MDS.