**GENOME EDITING THERAPY FOR DUCHENNE MUSCULAR DYSTROPHY-ASSOCIATED CARDIOMYOPATHY**

L. Xu, Y. Lau, Y. Gao, J. Ma, **R. Han**

The Ohio State University, Columbus, OH, USA

**Objective:** Duchenne muscular dystrophy (DMD) is a lethal inherited form of muscular dystrophy caused by mutations in the reading frame of the dystrophin gene disrupting its protein expression. Recent advancement in genome editing technologies offers a promising therapeutic approach in restoring dystrophin protein expression and improving striated muscle function for DMD. However, the long-term impact of this therapy has yet to be evaluated. Therefore, the objective of this study is to assess the long-term therapeutic efficacy and safety of CRISPR (clustered regularly interspaced short palindromic repeats)-mediated genome editing in *mdx* mice.

**Method:** A cohort of 5 *mdx* mice (4 male and 1 female) receiving systemic administration of rAAVrh.74-CRISPR (1x1012 vg) on postnatal day 3, along with 8 control *mdx* and 8 wild-type mice, were analyzed for dystrophin expression, cardiac function, histopathology and off-target events by whole-genome sequencing (WGS) at 19 months of age.

**Results:**By 19 months, two out of 8 control *mdx* mice developed visible sarcoma in their hind limbs, which became immobilized, while all 5 rAAV-treated *mdx* mice did not develop any obvious signs of gross abnormality. On average, about 11% of cardiac muscle fibers were observed to be dystrophin-positive in the treated *mdx* mice. Genome editing significantly reduced cardiac fibrosis and improved cardiac function as assessed by echocardiography. Histological examination of all vital organs did not reveal any pronounced abnormality.

**Conclusion:**These data together suggest that CRISPR-genome editing therapy offers long-term protection for dystrophic heart without eliciting serious adverse consequences.