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Gene Therapy for Familial ALS Using AAV9 Mediated Silencing of Mutant SOD1

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Background. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder resulting in death of brain and spinal cord motor neurons. Some familial cases are caused by missense mutations in the gene encoding the Cu/Zn superoxide dismutase 1 (SOD1) conferring a toxic gain of function to this protein. We hypothesised that specifically silencing expression of the mutant form of the human SOD1 gene would alleviate SOD1-linked ALS symptoms.
Objectives. Evaluate the therapeutic efficacy of AAV9-shRNA mediated SOD1 silencing in the SOD1G93A mouse model.
Methods. Animals were treated either at postnatal day 1 (P1, pre-onset) or P40 (onset). scAAV9-hSOD1si or scrambled control scAAV9-hSOD1ssi were delivered using 2 routes of delivery, facial vein or cisterna magna. Mice were then tested using behavioural tests including weekly rotarod runs, neurological scoring and CatWalk gait analysis. Weekly body weight was also collected.
Results. We observed an improvement in rotarod performance in mice treated with scAAV9-hSOD1si vs. scAAV9-hSOD1ssi and untreated controls in all studies. Survival analysis revealed that scAAV9-hSOD1si delivery via cisterna magna at P1 and P40 extended SOD1G93A mouse life span by 67 days and 16 days, respectively. The P1 cisterna magna study is still ongoing**. So far the longest survival has been 241 days.** SOD1 silencing at P40 also improved motor function as revealed by CatWalk gait analysis.
Conclusions. AAV9-shRNA mediated SOD1 silencing through cisterna magna improved motor performance and led to remarkable life span extension in the SOD1G93A mouse model. Our gene therapy approach offers promising strategy for clinical application in SOD1-linked familial ALS.