

## **Long-term therapeutic efficacy of intravenous AAV-mediated hamartin replacement in mouse model of tuberous sclerosis type 1**

### **ABSTRACT**

Tuberous sclerosis complex (TSC) is a tumor suppressor syndrome caused by mutations in TSC1 or TSC2, encoding hamartin and tuberin, respectively. These proteins act as a complex that inhibits mammalian target of rapamycin (mTOR)-mediated cell growth and proliferation. Loss of either protein leads to overgrowth in many organs, including subependymal nodules, subependymal giant cell astrocytomas, and cortical tubers in the human brain. Neurological manifestations in TSC include intellectual disability, autism, hydrocephalus, and epilepsy. In a stochastic mouse model of TSC1 brain lesions, complete loss of Tsc1 is achieved in homozygous Tsc1-floxed mice in a subpopulation of neural cells in the brain by intracerebroventricular (i.c.v.) injection at birth of an adeno-associated virus (AAV) vector encoding Cre recombinase. This results in median survival of 38 days and brain pathology, including subependymal lesions and enlargement of neuronal cells. Remarkably, when these mice were injected intravenously on day 21 with an AAV9 vector encoding hamartin, most survived at least up to 429 days in apparently healthy condition with marked reduction in brain pathology. Thus, a single intravenous administration of an AAV vector encoding hamartin restored protein function in enough cells in the brain to extend lifespan in this TSC1 mouse model.

**Keyword:** Brain; Neurology; Tumor suppressor; Gene therapy