Abstracts

GABAergic-selective AAV Gene Therapy for SLC6A1-related Disorder

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Rationale:
SLC6A1-related disorder is a severe developmental epileptic encephalopathy with an urgent need for an effective disease-modifying therapy. It is caused by loss of function in GAT1, a primary GABA transporter in the brain, leading to impaired GABA clearance and widespread neural circuit dysfunction. Endogenous GAT1 neuronal expression is restricted to inhibitory neurons, where it plays a crucial role in synaptic and extra-synaptic GABA uptake. AAV-mediated gene delivery of *SLC6A1* has the potential to provide a one-time curative treatment for this disease, yet the importance of targeting expression to defined brain cell types remains unknown. This study aims to determine the significance of cell-type specificity in gene therapy for *SLC6A1*-related disorder.

Methods:
We developed AAV-based therapeutics to express human *SLC6A1* either selectively in inhibitory neurons or in all neurons to test whether cell-type selectivity is essential for the safe rescue of phenotypes. AAV vectors were delivered via retro-orbital injection into a mouse model of *SLC6A1*-related disorder at a juvenile age (postnatal day 21). Therapeutic efficacy was assessed through multifaceted analyses, including hippocampal synaptosome GABA uptake assays, acute slice electrophysiology recording, chronic video EEG/EMG recordings, and behavioral tests assessing motor function and short-term learning and memory.

Results:
Inhibitory neuron-specific expression of *SLC6A1* was well tolerated in diseased mice and led to significant improvements across major disease-relevant phenotypes. Treated mice showed restored GABA uptake function in hippocampal synaptosomes, normalized kinetics of evoked inhibitory postsynaptic currents, and reduced epileptiform activities, including decreased spike-and-wave discharges (absence seizures), spike trains, and interictal spikes, and restored FFT features. Behavioral testing revealed rescue of failure-to-thrive phenotype, tremor, hindlimb clasping, rotarod performance, and short-term learning deficits in contextual and cued-induced fear conditioning. In contrast, pan-neuronal expression of *SLC6A1* led to increased mortality, convulsive seizures, and limited rescue of disease phenotypes.

Conclusions:
Our findings demonstrate that targeting *SLC6A1* expression specifically to inhibitory neurons is necessary and sufficient for safe and efficacious gene therapy in a mouse model of *SLC6A1*-related disorder. The inhibitory-specific strategy improves a wide range of phenotypes in juvenile mice, including epileptiform activity, motor dysfunction, and cognitive deficits. Pan-neuronal expression, while partially effective, introduces significant safety concerns. These results support inhibitory neuron-selective gene therapy as a promising approach for *SLC6A1*-related disorder.

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Translational Research