INTRAVENOUSLY ADMINISTERED GENE THERAPY FOR THE TREATMENT OF NEURONOPATHIC GAUCHER DISEASE

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Gaucher Disease is caused by mutations in the *GBA* gene encoding the enzyme glucocerebrosidase. Acute neuronopathic Gaucher Disease (nGD) is characterised by neuronal loss, astrocytosis and microglial proliferation. nGD is untreatable since enzyme replacement therapy cannot cross the blood-brain barrier.

AAV9 has been demonstrated to be able to efficiently transduce the Central Nervous System and visceral organs following intravenous administration to mice and non-human primates.

In this study, I tested the hypothesis that neonatal intravenous injection of adeno-associated viral vector serotype 9 (AAV9), carrying functional *GBA* gene, would improve lifespan, behavior, brain and visceral pathology in a mouse model of nGD.

Untreated KO mice die 12-14 days after birth. Treated mice showed a >10-fold increase in their lifespan. Neuropathological markers such as microglia-mediated inflammation, astrogliosis and lysosomal accumulation were ameliorated and some of the most affected areas of the brain, like thalamus, brain stem and cerebellum were partially rescued. Histologic analysis, enzymatic assay and blood test revealed improvement in the visceral pathology; in the lung, spleen and liver the presence of Gaucher cells is significantly reduced and tissue architecture is preserved.