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AAVrh10 based progranulin delivery to the central nervous system for the treatment of frontotemporal dementia caused by *GRN* mutations

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Upto 10% of frontotemporal dementia (FTD) is caused by dominantly inherited loss-of-function mutations in the granulin (*GRN*) gene (*GRN*-FTD), marked by > 50% reduction of progranulin (PGRN) in patients. Progranulin is a highly conserved secreted protein that is believed to play critical roles in multiple cellular processes, including lysosomal function, neuronal growth, and inflammation. Adeno-associated virus (AAV) gene therapy to booster the levels of progranulin may represent a promising strategy to treat *GRN*-FTD.
Methods: Progranulin is expressed in central nervous system (CNS) utilizing an AAV vector encoding a human *GRN* gene driven by a neuron-specific promoter packaged in AAVrh10 capsid and directly delivered to cerebrospinal fluid (CSF) via intracisternal magna (ICM) injection in mouse models of progranulin deficiency and in non-human primates..
Results: The results show that a single ICM injection of AAVrh10-*GRN* results in a fair amount and CNS-specific expression of human progranulin (hPGRN) in mouse models and non-human primates. Using genetic mouse models of progranulin deficiency, we show that AAVrh10-*GRN* restores the phenotypes associated with PGRN deficiency including lysosomal pathology and lipofuscinosis. In NHP, ICM administration of AAVrh10-*GRN* resulted in a dose-dependent expression of progranulin and achieved levels above the CSF progranulin level in normal humans and was not associated with any vector-associated adverse effects, demonstrating an appreciable safety profile.
Conclusion: Collectively, these preclinical results support the feasibility of augmenting progranulin expression via AAV-*GRN* gene therapy for treating FTD caused by *GRN* mutations and suggest that our approach may provide an effective and safe treatment.

Conflicts of interest

All co-authors are employees of AGTC