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Rescue of FTLD-associated TDP-43 pathology and neurodegeneration by peripheral AAV-mediated expression of brain-penetrant progranulin

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Abstract

Background: Progranulin (PGRN) haploinsufficiency is a major risk factor for frontotemporal lobar degeneration with TDP-43 pathology (FTLD-*GRN*). Multiple therapeutic strategies are in clinical development to restore PGRN levels in the CNS, including gene therapy. However, a limitation of current gene therapy approaches aimed to alleviate FTLD-associated pathologies may be their inefficient brain exposure and biodistribution.

Method: We therefore developed an adeno-associated virus (AAV) targeting the liver (L) to achieve sustained peripheral expression of a transferrin receptor (TfR) binding, brain-penetrant (b) PGRN variant (AAV(L):bPGRN) in two mouse models of FTLD-*GRN*, namely *Grn* knockout and *GrnxTmem106b* double knockout mice. This therapeutic strategy avoids potential safety and biodistribution issues of CNS-administered AAVs while maintaining sustained levels of PGRN in the brain following a single dose.

Result: AAV(L):bPGRN treatment reduced several FTLD-*GRN* associated disease pathologies including severe motor function deficits, aberrant TDP-43 solubility and phosphorylation, dysfunctional protein degradation, lipid metabolism, gliosis and neurodegeneration in the brain. Translatability of our findings was confirmed in a novel human *in vitro* model using co-cultured human induced pluripotent stem cell (hiPSC)-derived microglia lacking PGRN and TMEM106B and wild-type hiPSC-derived neurons. As in mice, aberrant TDP-43, lysosomal dysfunction and neuronal loss were ameliorated after treatment with exogenous TfR-binding protein transport vehicle fused to PGRN (PTV:PGRN).

Conclusion: Together, our studies suggest that peripherally administered brain-penetrant PGRN replacement strategies can ameliorate FTLD-*GRN* relevant phenotypes including TDP-43 pathology, neurodegeneration and behavioral deficits. Our data provide preclinical proof of concept for the use of this AAV platform for treatment of FTLD-*GRN* and potentially other CNS disorders.

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