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Intrathalamic delivery of AVB-101 rescues pathology in progranulin deficient mice and achieves widespread cortical expression in two large animal models.

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State of the art: Mutations in *GRN* encoding progranulin (PGRN) cause frontotemporal dementia (FTD-GRN). PGRN deficiency leads to lysosomal dysfunction, resulting in the accumulation of neuronal TDP-43 and exaggerated microglial reactivity accelerating neurodegeneration. Effective vector delivery to treat central nervous system disorders remains challenging.

Methodology: We developed an adeno-associated viral vector expressing PGRN under a neuronal-specific promoter (AVB-101). Using bilateral intra-thalamic infusions of low-dose AVB-101, we sought to rescue pathology in a mouse model of PGRN deficiency and investigate brain PGRN biodistribution in sheep and non-human primates (NHPs).

Results: Our studies demonstrate that (1) in *Grn* null mice, AVB-101 suppressed neuronal lipofuscinosis and reactive microgliosis, key hallmarks of FTD-GRN. (2) intrathalamic infusion of AVB-101 in sheep achieved vastly superior biodistribution compared to infusion into the cerebrospinal fluid (CSF) within the cisterna manga, even though the vector dose was 500-fold lower. (3) Dose-dependent increases in sheep cortical PGRN levels were mirrored by increases in the CSF. (4) Widespread cortical PGRN expression in sheep was achieved without evidence of significant glial activation or neuronal loss. (5) In NHPs, AVB-101 resulted in widespread cortical PGRN levels, particularly in the areas affected by FTD-GRN.

Conclusion: Collectively, the data suggest that intrathalamic infusion of AVB-101 constitutes a novel and promising approach to supplement PGRN in FTD-GRN patients and a novel gene delivery method for neurological disorders.

Conflicts of interest

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