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# Friday

## Rescue of FTD-GRN associated phenotypes in a mouse model of PGRN deficiency with the brain penetrant progranulin biologic DNL593

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Loss of function mutations in the GRN gene leading to progranulin (PGRN) haploinsufficiency occur in 5-10% of FTD cases (FTD-GRN). In the brain, PGRN is involved in lysosomal functions including regulation of lysosomal enzymes and loss of PGRN is linked to neuroinflammation and neurodegeneration. We recently characterized novel lysosomal functions of PGRN and demonstrated correction of CNS pathologies in PGRN deficient mice using a brain penetrant, recombinant PGRN fusion protein (DNL593) with 8 weeks of Q1W or Q2W treatment.

Here, we evaluate extended treatment (6 months) with DNL593 in aged, PGRN deficient mice to further uncover treatment-responsive, clinically monitorable, biomarkers. 12-month-old PGRN deficient mice received repeated treatment with either DNL593 at a low or high dose, or saline via intraperitoneal injection. Brain and biofluid samples were assessed for markers of lysosomal function, gliosis, and neuronal degeneration and cross referenced to FTD-GRN patient biomarker data.

DNL593 treatment resulted in dose-dependent correction of several PGRN deficiency mouse brain phenotypes, including lysosomal lipid dysregulation (bis(monoacylglycerol)phosphate and glucosylsphingosine), lysosomal enzymatic activity (glucocerebrosidase, hexosaminidase A), gliosis (CD68, IBA1 and YKL-40), and neuronal degeneration (brain lipofuscin). In addition, we observed DNL593-driven responses in clinically measurable fluid biomarkers, including plasma glucosylsphingosine, and CSF YKL-40 and neurofilament-light.

Our results support that DNL593, systemically delivered in PGRN deficient mice drives: (i) durable correction of brain lysosomal function biomarkers, and (ii) modulation of biomarkers potentially relevant to clinical outcomes in patients.

## Conflicts of interest

All authors are full time employees and shareholders of Denali Therapeutics