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Progranulin upregulation by antisense oligonucleotides targeting regRNAs for treatment of FTD-GRN

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State of the Art:
Regulatory RNAs (regRNAs) are a class of noncoding RNAs that modulate gene transcription. We have developed an RNA Actuating Platform that identifies regRNAs and enables tunable upregulation of genes by specific targeting of regRNAs with antisense oligonucleotides (ASOs). Here, we describe the development of oligonucleotide drug candidates that target regRNAs to upregulate *GRN* expression as a therapeutic approach for GRN-related frontotemporal dementia.

Methodology:
We utilized next generation sequencing techniques to identify regRNAs associated with human and mouse GRN gene. ASOs targeting these RNAs were screened in immortalized cells lines and confirmed to upregulate PGRN levels in patient iPSC derived cells or FTD-GRN preclinical mouse models.

Result:
Our platform identified shared *GRN* regRNAs in human neurons and microglia. ASOs targeting shared regRNAs were screened in a human cell lines to identify lead ASOs that upregulate *GRN*. We showed that the lead ASOs upregulate *GRN* in both FTD-GRN patient neurons and microglia cells, and rescue staurosporine-induced toxicity in FTD-GRN patient neurons and alleviate interferon gamma-induced immune response of iMGL cells.

Furthermore, we identified mouse *Grn* regRNA-targeting ASOs that upregulate *Grn* transcription *in vitro*. We tested these ASOs for efficacy in an FTD-GRN mouse model (*Grn+/tm1.1Far*) by intracerebroventricular injection. *Grn* upregulation is observed across disease-relevant brain regions, including cortex in the *Grn* haploinsufficient mice.

Conclusion
Camp4's strategy to target shared GRN regRNAs in neurons and microglia restores PGRN levels in both cell types. We are developing these oligonucleotides as a disease modifying treatment for patients with FTD-GRN.

Conflicts of interest

I am a paid employee of Camp4 Therepeutics.