Docket #: S25-325

Antisense Oligonucleotides Targeting Cryptic Exons for Neurological Disorders

Stanford researchers have developed antisense oligonucleotides (ASOs) that selectively block pathological cryptic exon inclusions in key neuronal genes to treat TDP-43-related neurodegenerative diseases.

TDP-43 pathology is a hallmark of several neurodegenerative conditions, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease. When TDP-43 function is impaired, aberrant "cryptic exons" are incorrectly spliced into mature mRNA transcripts, disrupting normal protein function and contributing to neuronal dysfunction and death. While this mechanism has been identified as a key driver of disease, effective therapeutic strategies to correct these splicing defects have remained elusive.

The inventors addressed this challenge by designing antisense oligonucleotides specifically targeting cryptic exons in three critical neuronal genes: KALRN (involved in nerve growth and function), RAP1GAP (a regulator of cellular signaling), and SYT7 (important for neurotransmitter release). These ASOs function by binding to the aberrant RNA sequences and preventing their inclusion in the final mRNA transcript, thereby restoring normal gene expression patterns. This approach offers a precision medicine strategy that directly addresses the molecular pathology underlying TDP-43-mediated neurodegeneration.

Applications

- Potential therapy for ALS, FTD, and other TDP-43 proteinopathies

Advantages

- Targets the underlying molecular mechanism of TDP-43 pathology
- Applicable across multiple neurodegenerative diseases
- Specific blockade of pathological cryptic exons without affecting normal splicing

Publications

- Caiwei Guo et al. (2026). Cryptic splicing in synaptic and membrane excitability genes links TDP-43 loss to neuronal dysfunction. *Sci. Transl. Med.* 18, eaeb8517(2026). DOI: 10.1126/scitranslmed.aeb8517

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