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Antisense oligonucleotides for Down syndrome and Tauopathies

Stanford researchers have developed a targeted antisense oligonucleotide (ASO) platform to restore physiological regulation of DYRK1A, a key driver of neurodevelopmental and neurodegenerative pathology in Down syndrome (Trisomy 21) and other tauopathies.

Down syndrome affects approximately 1 in 700 live births and is the leading genetic cause of intellectual disability, with most individuals developing Alzheimer's disease-like pathology by mid-adulthood. A central contributor to these phenotypes is the overexpression of DYRK1A, which disrupts neural progenitor proliferation and promotes tau hyperphosphorylation and neuronal loss. While DYRK1A has been explored as a therapeutic target, direct inhibition strategies have faced significant challenges due to the need for precise control of kinase activity.

This technology introduces a biologically informed alternative by modulating an endogenous regulatory pathway that controls DYRK1A activity. Using an ASO-based approach, the platform enhances the expression of a natural inhibitor of DYRK1A, enabling restoration of kinase activity to physiological levels rather than broadly suppressing it. In preclinical in vitro models, this approach restores neural progenitor proliferation and reduces pathological tau accumulation. In rodent in vivo models, it restores behavioral phenotypes.

By leveraging endogenous regulatory pathways, this ASO-based platform offers a differentiated, target-specific strategy with potential to address both developmental and degenerative components of disease across Down syndrome, Alzheimer's disease, and related tauopathies.

Stage of Development
Research- in vitro, in vivo

Applications

- Targeted therapy for Down syndrome-associated neurodevelopmental and neurodegenerative deficits
- Therapeutic strategy for Alzheimer's disease and other tauopathies
- Precision modulation of kinase signaling in CNS disorders
- Platform for development of targeted ASO-based neurotherapeutics

Advantages

- Restores DYRK1A activity to physiological levels rather than direct inhibition
- Addresses both early neurodevelopmental and neurodegenerative disease mechanisms
- Reduces tau pathology and supports neuronal function
- High specificity through endogenous pathway modulation
- Broad applicability across multiple neurodegenerative and genetic conditions

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