

# Selection and Preclinical Testing of DNA Aptamers as Targeted Tau Therapies: A Novel Approach to Slow the Progression of Tauopathies

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Tauopathies are neurodegenerative disorders characterized by the deposition of abnormal tau in the brain. There are over 20 tauopathies that collectively affect millions of people around the world. Alzheimer's disease, Progressive supranuclear palsy, Pick's disease, and Post-encephalitic parkinsonism are some of the most common ones. There are currently no disease-modifying treatments for tauopathies. In these diseases the protein responsible for maintaining the stability of microtubules in neurons, known as tau, becomes hyperphosphorylated, causing the protein to stop functioning properly and leading to neuronal death. This project evaluates whether DNA aptamers can be used to target and alleviate this problem in tauopathies. This study used tau epitopes as the initial target in SELEX to isolate aptamer sequences specific to pathologically relevant sites on the tau protein. The ability of the aptamers to inhibit phosphorylation of the tau protein was evaluated via western blot. Results indicate that the aptamers displayed significant affinity towards tau and were effective in inhibiting phosphorylation of the protein at the selected site (>90% for both monomeric and oligomeric forms of p-tau). Additionally, a microtubule binding protein spin-down assay confirmed that the tau protein could still bind to microtubules in the presence of the aptamer. Furthermore, an in-vivo experiment was conducted to validate the effectiveness of the aptamer-based treatment. The experiment involved testing the aptamers on mutated strains of *C. elegans* that modeled progressive tau toxicity in tauopathies. The aptamer treatment showed promising therapeutic effects on the phenotypic symptoms of *C. elegans* by slowing the rate of decline in locomotor activity in worms that were treated.

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