Evaluating CRISPR-Cas13-mediated tau depletion as an Alzheimer's disease therapy

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Tau pathology is a hallmark of several neurodegenerative diseases, including Alzheimer's disease (AD). Accumulation of tau strongly correlates with cognitive decline in patients, yet no tau-targeting therapies are currently FDA-approved. Notably, tau depletion alleviates AD phenotypes in mouse and human induced pluripotent stem cell (hiPSC) models even in the presence of amyloid beta (Aβ), suggesting tau is a critical mediator of Aβ toxicity. To fill this therapeutic gap, we designed a novel CRISPR-Cas13 system to specifically target and deplete human tau expression. Using a predictive algorithm, we identified 25 total tau-targeting guide RNAs (gRNAs) and screened them in SH-SY5Y cells via lentiviral delivery. The 4 most effective gRNAs, each reducing tau levels by over 50%, were cloned into AAV vectors and tested in cortical neurons derived from humanized tau (hTau) mice and hiPSCs. Tau pathology and cell viability will be assessed to identify the optimal gRNA. For *in vivo* validation, we will intravenously administer AAV-CRISPR-Cas13 to hTau mice, which exhibit cognitive impairments, tau aggregation, and neuronal loss. We will evaluate the depletion of tau and whether this improves cognition, memory, behavioral deficits, and survival when received during either early (preventative) or late (therapeutic) stages of disease progression. This study is the first to leverage CRISPR-Cas13 to therapeutically deplete tau in dementia. Our CRISPR-Cas13 strategy may present a promising, non-invasive, and long-lasting gene therapy approach for AD-related cognitive decline.

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