

Title: Comparison of novel virus-like particle vaccines against tau in a mouse model of Alzheimer's disease.

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Abstract: Alzheimer's disease (AD) is characterized by the accumulation of tau tangles and amyloid- β plaques in the brain with accompanied neurodegeneration. Phosphorylation of tau at specific sites occurs early in the disease process and has been shown to drive tau pathology which correlates with disease progression. Promoting the clearance of pathological tau may be a useful therapeutic strategy. Previously, we developed Q β bacteriophage virus-like particle (VLP) vaccines displaying phosphorylated Thr181 tau peptides that promoted robust immune response, tau clearance, and improved memory. Here we report characterization and comparison of a Q β -PHF-1-VLP and a Q β -AT8-VLP vaccine. Transgenic rTg4510 mice were administered three bi-weekly intramuscular injections of Q β control or Q β conjugated to peptides corresponding to the tau PHF-1 site or the tau AT8 site. Serum antibody titers were assessed using ELISA. Cognitive function was assessed using Morris Water Maze (MWM) and Novel Object Recognition (NOR) tasks. Western blot and immunohistochemical analyses were performed to assess the levels of phosphorylated and aggregated tau. Both Q β -PHF-1 and Q β -AT8 vaccination induced a robust antibody response compared to Q β control. Q β -PHF-1 significantly reduced phosphorylated and Sarkosyl-insoluble tau in the brain compared to Q β control while Q β -AT8 did not. Q β -PHF-1 vaccination ameliorated delay-dependent memory deficits assessed by NOR but did not rescue spatial memory deficits assessed by MWM (unlike Q β -pT181 which also rescues spatial memory-PMID: 31428463). Q β -AT8 failed to rescue any deficits in delay-dependent or spatial memory. Q β -PHF-1 also reduces inflammatory microgliosis observed by immunohistochemistry compared to Q β control. In summary, Q β -PHF-1 vaccine outperforms the Q β -AT8 vaccine, but both are less efficacious than Q β -pT181.

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Non-Expert Summary: Alzheimer's disease (AD) is the 7th leading cause of death in the United States. AD is driven in part by the accumulation of toxic proteins in the brain including the tau protein. We are developing vaccines against tau that will use the immune system to fight the disease by removing tau from the brain. We are testing these vaccines using mice that were bred to develop AD. These vaccines could provide lifelong protection against AD.