pT181-Qß VLP-based vaccine against tau pathology shows robust immune response and functional efficacy in the P301S mouse model of tauopathy

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Title: pT181-Qß VLP-based vaccine against tau pathology shows robust immune response and functional efficacy in the P301S mouse model of tauopathy

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**Background:** Tauopathies are progressive neurodegenerative disorders characterized by the hyperphosphorylation of tau and development of intracellular neurofibrillary tangles, collectively referred to as pathological tau (pTau). It is becoming increasingly recognized that the development and spread of pTau accurately predicts and correlates with clinical progression in human tauopathy patients, however there are no FDA-approved drugs that target and reduce pTau. Previously, our lab has developed a virus-like particle (VLP)-based vaccine using a Qß (RNA bacteriophage) platform to multivalently display a 13-mer pTau peptide, with phospho-Thr181 (pT181, a well-established CSF biomarker for tauopathies). pT181-Qß generates a robust and targeted immune response against pTau in a model of tauopathy, rTg4510, resulting in reduced insoluble tau, decreased neurodegeneration and improved delay-dependent and spatial memory. Here, we sought to expand the effects of this vaccine in an additional model of tauopathy, at a more clinically relevant intervention.

**Methods:** We immunized P301S (and non transgenic) mice twice, at 3 and 4 months of age. Next, we assessed anti-pT181 antibody titers at 1-week after the first dose and 5-months following the last injection (9 months). Finally we performed magnetic resonance imaging (MRI) and behavioral analysis prior to biochemical analysis. **Results:** Anti-pT181 antibodies were significantly elevated in all mice treated with pT181-Qß, regardless of genotype, 1 week after the first dose and remained elevated five months after the second injection. In addition to a clear prevention of neurodegeneration in the cortex via T2 MRI, using diffusion tensor imaging, we observed increases in axonal integrity via axial diffusivity in the corpus callosum, a major white matter tract in the brain in the pT181-Qß-vaccinated P301S mice vs. the control treated mice, hinting at an amelioration in tau-mediated axonal damage. Behavioral analysis suggest that pT1818-Qß-vaccinated P301S mice showed gait improvement (as assessed with Catwalk). Finally, P301S mice vaccinated with pT181-Qß had significantly downregulated gene expression of inflammasome components and significantly reduced tau hyperphosphorylation in the hippocampus, hinting at an intimate connection between neuroinflammation and pathological tau accumulation. **Conclusions:** This vaccine represents an efficacious and cutting-edge tool to target and reduce tau pathology in multiple animal models of tauopathy which may have substantial effects on neuroinflammation and white matter integrity.