

P024 Memory impairment in a novel mouse model of human tauopathy
Ramsden, M.¹, Kotilinek, L.¹, Paulson, J.¹, Guimaraes, A.¹,
Forster, C.², SantaCruz, K.², Ashe, K.H.¹.

¹*Department of Neurology,* ²*Department of Lab Medicine and Pathology, University of Minnesota, Medical School, Minneapolis, MN 55455 USA.*

Neurofibrillary tangles (NFT) are composed of detergent-insoluble fibrils of hyperphosphorylated tau protein. In human disease, tangles correlate closely with cognitive deficits and neuronal loss. To study the relationships between NFT pathology, tau biochemistry and cognitive performance, we created a novel transgenic mouse model expressing a human tau variant. Using a version of the conventional Morris water maze modified for mice, spatial reference memory was measured in 31 rTg(tau_{P301L})4510 mice (+/+) and 27 transgenic control littermates. As early as 2.5 months of age, mean target quadrant occupancy was significantly lower in +/+ mice when compared to control littermates. Importantly, we observed a wide range of cognitive impairment which preceded both NFT pathology and the expression of hyperphosphorylated sarkosyl-insoluble 64kD tau. Thus, our data suggest that subtle alterations in tau biochemistry may compromise neuronal function and induce cognitive impairment in the absence of overt neuropathology. Furthermore, we hypothesize specific forms of tau are responsible for generating functional versus structural phenotypes. Current investigations focus on correlating changes in tau phosphorylation, solubility state and subcellular distribution with behavioural deficits. If successful, these novel and exciting findings may identify a specific molecular target for the treatment and prevention of tau-related neurodegenerative disorders.