ANALYSIS OF GENE EXPRESSION IN THE HIPPOCAMPAL SUBFIELDS OF THE TG4510 TAUOPATHY MODEL

P.D. Wes¹, A. Easton², M.A. Seager², N.X. Barrezaeta¹, C. Bourin², J. Hogan², A. Truong², A. He³, D. Barten², A.M. Cacace¹

¹Applied Genomics, ²Neuroscience, Bristol-Myers Squibb, Wallingford, CT, ³Applied Genomics, Bristol-Myers Squibb, Hopewell, NJ, USA

Introduction: Neural network dysfunction has been implicated in the pathophysiology of Alzheimer’s disease. The transgenic Tg4510 mouse model over-expresses mutant human Tau(P301L), providing a model to study AD and other Tauopathies. Tg4510 mice comprise a transcriptional activator (tTA) that drives Tau(P301L) expression from a second transgene. Tg4510 mice display age-dependent deficits in hippocampal-mediated behavioral tasks and neuronal loss in the cornu ammonis 1 (CA1) hippocampal subfield.

Aims: Our aim was to determine transcriptional changes in the hippocampal network of Tg4510 mice.

Methods: We laser microdissected various hippocampal subfields from the hippocampus of Tg4510 mice and littermate controls at various ages. mRNA from these subfields was subjected to Affymetrix transcriptional profiling.

Results: Neuronal and synaptic markers were downregulated in the CA1 of Tg4510 mice compared to littermate controls, indicative of neuronal loss. Inflammatory markers were dramatically upregulated in all subfields. Interestingly, markers of GABAergic inhibitory interneurons were upregulated in the CA1 and dentate gyrus of Tg4510 animals. Of note, tTA mice that lack the Tau transgene displayed expression changes predicted to have profound impacts on behavior and neuronal function. Indeed, while Tg4510 mice showed some cognitive deficits relative to tTA, tTA animals also showed cognitive deficits relative to wild-type littermates.

Conclusions: Transcriptional alterations in Tg4510 mice are consistent with known pathology in this line (neuronal loss and inflammation) and suggest increased inhibitory tone in the dentate gyrus and CA1.