Antibody Therapy Against Tau Pathology Improves Neuronal Transport as Assessed In Vivo by Tract-Tracing Manganese-Enhanced MRI.

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Introduction: Alzheimer's disease (AD) is the most common cause of progressive dementia and is associated with extensive deposition of amyloid-beta peptide and hyperphosphorylated tau protein. Immunotherapies to target both pathologies have been developed in recent years, but so far amyloid-beta centric approaches that reached Phase III clinical trials have shown limited efficacy, leading to a shift in focus of the pharmaceutical industry to tau-based immunotherapies aimed at clearing pathological tau protein **[1,2]**. Our group has demonstrated that Tract-Tracing Manganese-Enhanced Magnetic Resonance Imaging (TT-MEMRI) is a very sensitive method in evaluating the deleterious effect of tau pathology on neuronal transport in transgenic mouse models of tauopathy. Our multisession imaging method proved very successful in monitoring the progression of tauopathy with minimal risks to mice evaluated over a period of several months with multiple MR examinations [**3,4**]. In this study, we used TT-MEMRI to determine how early and effective an immuno-based passive treatment recently developed by our group can potentially modify the disease progression and the associated impairment in neuronal transport that we previously documented in an aging transgenic mouse model of tauopathy.

Methods: Fifteen homozygous JNPL3 transgenic mice modeling tauopathy **[5]**, aged 13 months, underwent our TT-MEMRI protocol prior to treatment to establish the baseline and 4 weeks after being subjecting to immunotherapy on a weekly basis (10 mg/kg of mAb injected intraperitoneally). Eight of these mice received a tau monoclonal antibody targeting the tau 396-404 region, while the other seven mice received immunoglobulin G as a control. Imaging studies were performed on a 7-T micro-MRI, using a 3D T1-SPGR sequence. Mice were imaged pre-injection, then intranasally instilled with of 1.5 ul of 5M $MnCl_2$, under isoflurane anesthesia. Image sets were acquired at 1, 4, 8, 12, 24, 36, 48 hours, and finally at 7 days for a total of nine time points. Image datasets were registered with Amira 5.0 and predefined ROI's for the glomerular layer were processed using ImageJ. Normalized measurements for each mouse were plotted and fitted to a tract tracing bolus using MATLAB. This time-curve fitting allows for the estimation of the time to peak of intensity, peak intensity value of the bolus of Mn, and maximal value of the ascending slope of uptake.

Results: The mouse control group subjected to IgG injections demonstrated a significant decline in the peak value of manganese uptake after 4 weeks reflecting a progression of transport impairment expected in this mouse model based on our prior findings **[3]** (**Figure 1.A**; *p<0.05, paired t-test). On the other hand, the same peak value parameter did not decay in the transgenic mouse group treated during the four week period with the tau mAb and resulted in a significant difference compared to the IgG treated group (**Figure 1.A**; ## p<0.01, unpaired t-test). A significant decrease in the time to peak (*p<0.05, paired t-test; **Figure 1.B**) and an increase in maximal slope of manganese uptake (*p<0.05, paired t-test; **Figure 1.C**) were observed in the glomerular layer of the tau mAb-treated mice after the same four week period. These results taken together with our previous TT-MEMRI-based characterization of the same JNPL3 Tau transgenic mouse model indicate that the four weeks of treatment against tau pathology can lead to effective improvement in neuronal transport detectable by our protocol.

Conclusions: Antibodies targeting tau pathology can restore neuronal transport in advanced stage of the disease within a period of four weeks. Our *in vivo* and noninvasive TT-MEMRI protocol proved to be a sensitive technique to assess the improvement in neuronal transport resulting from the treatment. Olfactory sections from these mice are currently being analyzed to assess the correlation of the improvement in axonal transport seen in our in vivo results with the load of tau lesions in both groups.

Acknowledgements: This work was supported by: NIH AG020197, AG032611, NS077239 E.M.S.; the Alzheimer's Association IIRG-08-91618 to Y.Z.W.; the American Health Assistance Foundation A2008-155 to Y.Z.W and the NYU Applied Research Support Fund to Y.Z.W. as well as funding from NIH/NCI 5P30CA016087-32 & NIH P41 EB017183. NYU technology on tau immunotherapy is licensed to and is being co-developed with H. Lundbeck A/S. E.M.S. is an inventor on relevant tau immunotherapy patents assigned to NYU and licensed to H. Lundbeck A/S.

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Clinical Relevance: This study provides evidence that TT-MEMRI is a useful, noninvasive tool to assess the efficacy of novel antibody therapies in the preclinical setting. Tau monoclonal antibody targeting the Tau396-404 region shows promise as a candidate for therapy to clear tau pathology.

Figure 1

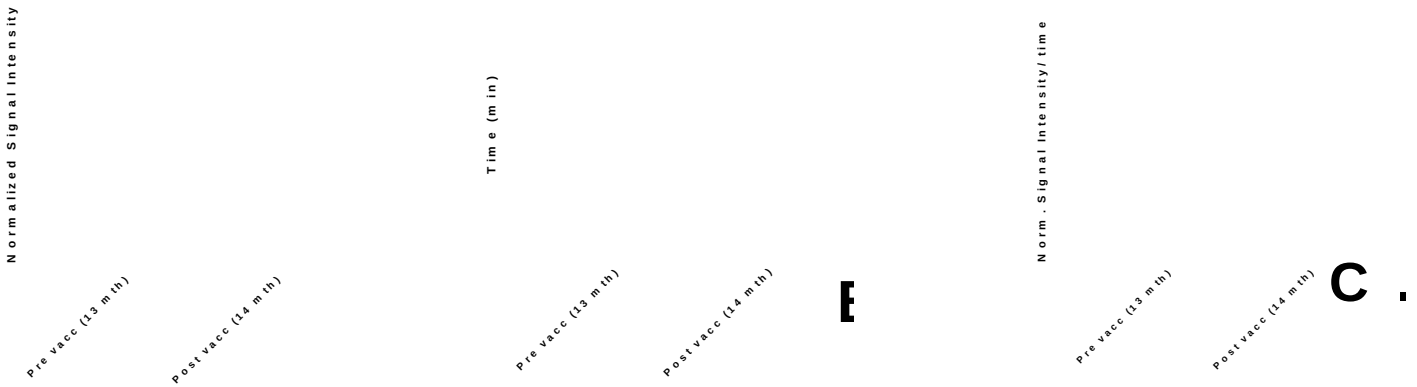

Fig. 1A. A decrease in Peak Value was observed in Tg mice following 4-week IgG treatment (red) indicating an expected decline in neuronal transport with statistical significance (* $p < 0.05$, paired t-test).

When comparing both group IgG treated mice (serving as contro, red) and mAb treated mice (blue), a significant difference was observed (## $p<0.01$, unpaired t-test) suggesting a slowing down of the decline in mAb treated mice.

Fig. 1B. A decrease in Time-to-Peak was observed in Tg mice following 4-week treatment with mAb (blue) with statistical significance (* $p < 0.05$, paired t-test).

Fig. 1C. An increase in maximal slope was observed in Tg mice following mAb treatment (blue) that was statistically significant (* $p < 0.05$, paired t-test).