EFFICACY OF RAA7 TREATMENT IN rTG4510 MOUSE MODEL OF ALZHEIMER´S DISEASE

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1 INTRODUCTION

Tauopathies are neurodegenerative characterized by the accumulation of abnormal phosphorylated and aggregated forms of Tau protein in the brain. rTg4510 (MAPT*P301L) mouse model is a widely used tauopathy model for studying therapeutic intervention that target neurodegeneration and tau pathology. Here we demonstrated efficacy of RAA7, a monoclonal antibody highly specific to human aggregated AD-tau species (APNmAb005) in the treatment of rTg4510 mouse.

2 METHODS

In this study rTg4510 mice (n=13-15/group) were treated with RAA7 (10 mg/kg and 50 mg/kg) or vehicle (PBS) for 12 weeks starting at 3.5-4 months of age. At 7 months of age tau pathology and neurodegeneration was characterized using cresyl fast violet staining (CFV) and NeuN for neurodegeneration, total human Tau (HT7) and phosphorylated human Tau (AT8). Sections were analyzed as % of area of positive signal. Four regions of interest were examined: cortex, CA1 and dentate gyrus regions and whole hippocampus. All animals in the study were used following national and international regulations.

3 RESULTS

Our results showed that RAA7 treatment diminish neurodegeneration and affect tau pathology. In Cresyl Fast Violet (CFV) and NeuN staining, RAA7 10 mg/kg increased % of stained area in all analyzed brain regions, whereas RAA7 50 mg/kg in the CA1 region when compared to PBS group. In addition, high dose treatment showed neuroprotective effect in the DG regions of hippocampus as well. NeuN/CFV ratio was decreased by RAA7 10 mg/kg treatment in all analyzed areas. Assessment of tau expression revealed that RAA7 10 mg/kg decreased level of total Tau in CA1 region and phosphorylated Tau in cortex when compared to PBS group. Unexpectedly, RAA7 50 mg/kg showed significantly higher total tau level in the whole hippocampus when compared to PBS group, and no effect on the tau phosphorylation level.

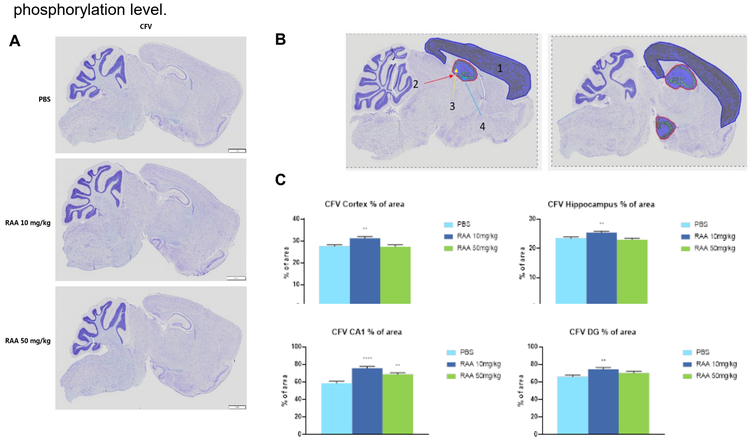

Figure 1. Cresyl Fast Violet Staining. **A**) Example images from CFV staining PBS, RAA 10 and 50 mg/kg. **B**) Example images of analyzed Areas (CFV staining) 1. Cortex; 2. Whole hippocampus; 3. CA1; 4. DG. **C**) Quantitative analysis of CFV staining as % area in cortex, whole hippocampus, CA1 and dentate gyrus (DG) of hippocampus. Data is presented mean + SEM, n=13-15 per group. **p<0.01; ***p<0.001 RAA 10 mg/kg and RAA 50 mg/kg vs PBS (One-way ANOVA, Dunnett's post hoc).

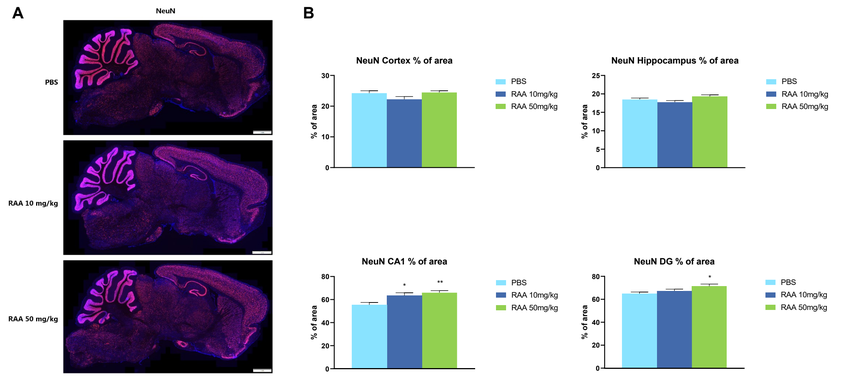

Figure 2. NeuN Staining. **A**) Example images from neuronal marker, NeuN, staining (red fluorescence) and nuclear counterstain, DAPI is shown in blue fluorescence; PBS, RAA 10 and 50 mg/kg treatment groups. **B**) Quantitative analysis of NeuN staining as % area in cortex, whole hippocampus, CA1 and dentate gyrus (DG) of hippocampus. Data is presented mean + SEM, n=13-15 per group. *p<0.05; **p<0.01 RAA 10 mg/kg and RAA 50 mg/kg vs PBS (One-way ANOVA, Dunnett's post hoc).

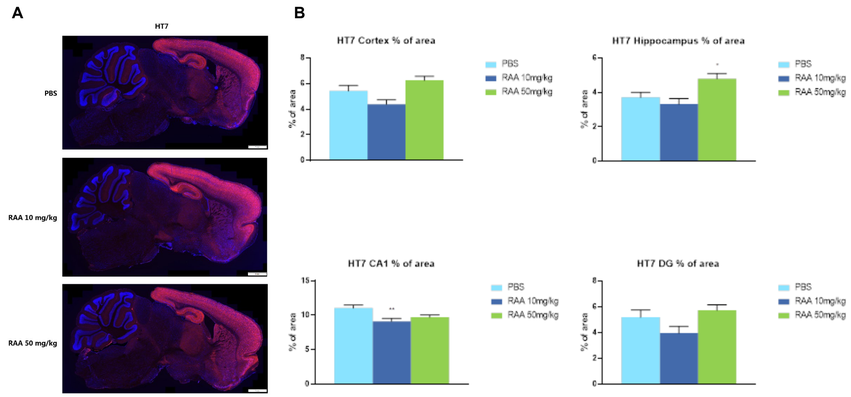

Figure 4. Total human tau HT7 Staining. **A**) Example images from total human tau, HT7, staining (red fluorescence) and nuclear counterstain, DAPI is shown in blue fluorescence; PBS, RAA 10 and 50 mg/kg. **B**) Quantitative analysis of HT7 staining as % area in cortex, whole hippocampus, CA1 and dentate gyrus (DG) of hippocampus. Data is presented mean + SEM, n=13-15 per group. *p<0.05; **p<0.01 RAA 10 mg/kg and RAA 50 mg/kg vs PBS (One-way ANOVA, Dunnett's post hoc).

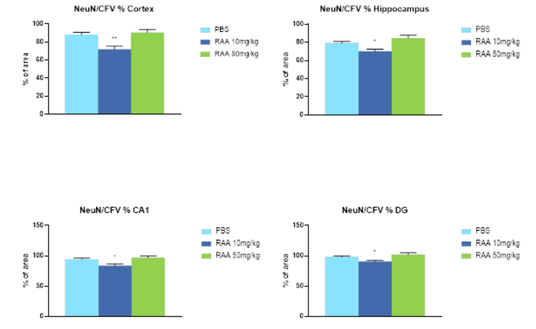

Figure 3. The ratio of NeuN/CFV staining (NeuN % of area / CFV % of area) in cortex, whole hippocampus, CA1 and dentate gyrus (DG) of hippocampus. Data is presented mean + SEM, n=13-15 per group. *p<0.05, **p<0.01; RAA 10 mg/kg and RAA 50 mg/kg vs PBS (One-way ANOVA, Dunnett's post hoc).

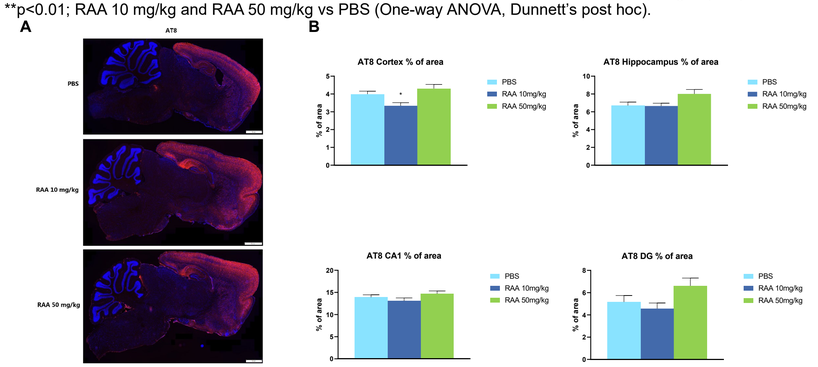

Figure 5. Human phospho tau AT8 Staining. **A**) Example images from human phospho tau AT8, staining (red fluorescence) and nuclear counterstain, DAPI is shown in blue fluorescence; PBS, RAA 10 and 50 mg/kg. **B**) Quantitative analysis of HT7 staining as % area in cortex, whole hippocampus, CA1 and dentate gyrus (DG) of hippocampus. Data is presented mean + SEM, n=13-15 per group. *p<0.05; **p<0.01 RAA 10 mg/kg and RAA 50 mg/kg vs PBS (One-way ANOVA, Dunnett's post hoc).

4 CONCLUSION

As a summary, treatment with anti-tau species mAb RAA7 (APNmAb005) showed neuroprotective effect in rTg4510 mice demonstrated by reduced tau accumulation and tau phosphorylation driven inhibition of neuronal cell death. RAA7 is raised against aggregated tau highly specific for those tau species found in tauopathy patients' brains including Alzheimer's Disease. The rescue of neuronal loss found in the hippocampal formation of rTg4510 mice brains suggesting a therapeutic effect of RAA7 for Alzheimer's Disease.