A multi-scale MRI approach to investigate novel drug treatment strategies in mouse models of Alzheimer's disease

Holly Elizabeth Holmes[1], Niall Colgan[1], Ozama Ismail[1], Da Ma[2,3], Jack Wells[1], Nicholas Powell[1,3], James O'Callaghan[1], Ian Harrison[1], Manuel Jorge Cardoso[3], Marc Modat[2], Elizabeth MC Fisher[4], Sebastian Ourselin[3], Michael O'Neill[5], Emily Catherine Collins[6], and Mark F Lythgoe[2]

[1]Centre for Advanced Biomedical Imaging, University College London, London, Greater London, United Kingdom, [2]University College London, London, Greater London, United Kingdom, [3]Centre for Medical Image Computing, University College London, London, Greater London, United Kingdom, [4]Department of Neurodegenerative Diseases, University College London, London, Greater London, United Kingdom, [5]Eli Lilly & Co. Ltd, Windlesham, Surrey, United Kingdom, [6]Eli Lilly & Company, Indianapolis, United States

Introduction: Alzheimer's disease (AD) develops silently decades before the first clinical symptoms appear and as such, it is challenging to develop biomarkers sensitive to the pre-symptomatic or prodromal phase in the wider population. Several emerging therapies are focused on preventing and clearing the accumulation of pathological lesions of tau protein, and as such there is high demand for robust, early biomarkers which are sensitive to the presence of tau pathology *in vivo*. In order to assess the sensitivity of MRI to the suppression of tau, we longitudinally applied MRI biomarkers to the rTg4510 mouse model of tauopathy, which develops tau pathology specifically within the forebrain from 2.5 months [1]. In this model, tau expression can be suppressed with doxycycline [1]. We longitudinally imaged two cohorts of rTg4510 mice, with doxycycline administered from 3.5 months ('early' intervention) and 4.5 months ('late' intervention) to coincide with the development of pathological tau products within the forebrain from 2.5 months. We investigated the exchange of endogenous mobile proteins and peptides in tissue using amide proton transfer (APT), microstructural diffusion using diffusion tensor imaging and morphometric changes using high resolution structural MRI. These techniques were selected for their sensitivity to different aspects of neuropathology, in addition to their clinical relevance.

Methods: 39 rTg4510, and 18 wildtype (WT) litter-matched mice were imaged at baseline (3.5 months for the 'early' intervention study and 4.5 months for the 'late' intervention study) using a 9.4T scanner for structural, APT and DTI data using parameters previously described [2]. 10 rTg4510 were then treated orally with doxycycline hyclate (10mg/kg) and maintained on a doxycycline diet for the remainder of the study to supress tau expression. The doxycycline-treated rTg4510, untreated rTg4510 and WT groups were imaged again at 5.5 and 7.5 months for longitudinal structural, APT and DTI data. During imaging, anaesthesia was maintained using 1.5-2% isoflurane and 1L/min O_2. For analysis, structural, APT and mean diffusivity (MD) measurements were combined for the cortex and hippocampus to quantify changes within high tau pathology regions.

Results: The longitudinal structural, APT and mean diffusivity (MD) results are shown in Figure 1. Atrophy was detectable within the rTg4510s from 5.5 months in both the treated and untreated animals ($p<0.05$ and $p<0.001$ respectively) (Fig. 1A). Volume loss was greater reduced in animals treated with doxycycline from 3.5 months (14.2%) than from 4.5 months (24.83%). APT was able to discriminate between the rTg4510 animals and WTs from 4.5 months ($p<0.05$) (Fig. 1E). Administration of doxycycline, in both early and late intervention, resulted in an increase in APT towards wildtype values by 7.5 months (Fig. 1B, E). Following early treatment at 3.5 months, the APT within the treated rTg4510 animals remained within the range of control values until 7.5 months (Figure 1B). At this timepoint, both the treated rTg4510s and the wildtype controls were significantly different from the untreated rTg4510 ($p<0.01$). MD was able to discriminate between the rTg4510s and WTs at 7.5 months, with increased MD detected within the transgenic animals (Fig. 1C, F). Following treatment from 3.5 months, MD illustrated excellent sensitivity to the effects of doxycycline and was able to readily discriminate between the treated and untreated rTg4510s ($p<0.0001$) as well as the treated rTg4510s and wildtype controls ($P<0.0001$) at 7.5 months (Fig. 1C). MD was not significantly different between groups at earlier timepoints, suggesting it may be sensitive to downstream pathological events.

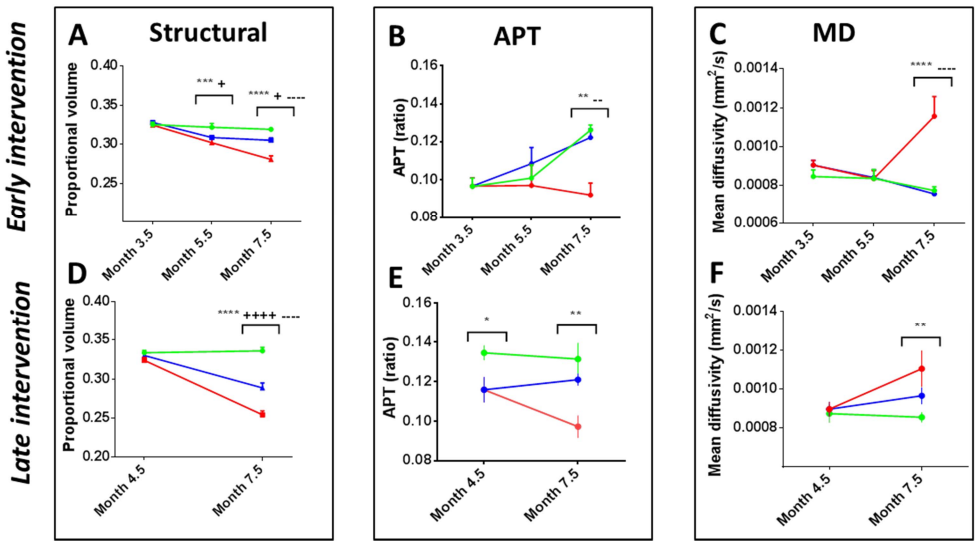

Figure 1 *Multiparametric MRI results following early (A-C) and late (D-f) therapeutic intervention. Results are shown for the high tau pathology regions. Error bars represent the standard error of the mean. WT vs. rTg4510: * = P ≤ 0.05; **=P≤0.01; ***=P ≤0.001; ****=P ≤0.0001. WT vs. rTg4510(+DOX): + = P ≤ 0.05; ++++=P ≤0.0001. rTg4510s. vs. rTg4510(+DOX): --=P≤0.01; ----=P ≤0.0001.*

Conclusions: This study demonstrates the sensitivity of MRI biomarkers to the suppression of pathological tau products, following early and late therapeutic intervention. The longitudinal nature of the study design also enables comparison between the multiparametric methods at different stages of the pathology, which can guide MRI investigation of novel therapies. These techniques could provide valuable insights for the assessment of tau-related pathologies, including diagnosis and prognosis, in addition to assessing the efficacy of tau-targeting therapeutics. This is the first demonstration of clinically relevant MRI biomarkers to tau pathology, following early and late therapeutic intervention.

References: [1] K. Santacruz et al., *Tau suppression in a neurodegenerative mouse model improves memory function* (Science. Jul 15 2005) 309(5733): 476-81. [2] *An Imaging Strategy to Characterise Tau Pathology in vivo in a Model of Alzheimer's disease using Multi-Parametric MRI* (AAIC Proceedings 2014): O4-02-06.