P2-07

Neuroimaging of New and Novel Alzheimer's Disease (AD) Mice from the MODEL AD Consortium

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MODEL-AD
Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease

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Introduction

The Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (**MODEL-AD**) Consortium is developing the next generation of AD models based on human genomic and imaging data. Preclinical studies have the advantage of being able to directly correlate findings to the observed neuropathology. The MODEl-AD imaging cores utilize existing state of the art translationally relevant medical imaging methodologies as well as ascertain feasibility of emerging imaging methods for increased diagnostic sensitivity.

Methods

Two primary imaging modalities will be utilized: high-field MRI (9.4T and 17.6T) and PET/CT. Deep MRI phenotyping is based on the accepted human-AD standards like ADNI (Structural T2W, FLAIR, diffusion, perfusion (PWI), susceptibility, and functional MRI and MR spectroscopy). Novel histological vessel painting combined with PWI will assess vascular modifications. PET imaging will evaluate brain metabolism (18F-FDG), regional perfusion (64Cu-PTSM), amyloid (18F-AV45), tau (18FAV1451), neuroinflammation (18F-CPPC and 18F-GSK1482160), and astrogliosis (18F-FEBU) markers in new mouse models.

MODEL AD Consortium Platform Mice

- hAβ-KI^{loxP} / hTAU / hAPOE4 (MODEL-AD1)
- hAβ-KI$^{SWE/IB/loxP}$ / hTAU / hAPOE4 (MODEL-AD2)
- B6.APOE4.TREM2^{R47H}(LOAD1)
- LOAD1.hAβ (LOAD2)
- LOAD2.Plcg2^{M28L}
- LOAD2.Mthfr^{C677T}
- LOAD2.ABCA7^{A1527G}

PET/CT Scanner

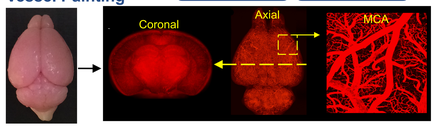
MOLECUBES β-CUBES
Preclinical PET Scanner
0.4-0.7m^3 Resolution
10-20 min/bed

MOLECUBES X-CUBES
Preclinical CT Scanner
0.05-200 m^3 Resolution
1-3 min/bed

MRI (9.4T)

Bruker Avance 9.4T
30cm bore
Mini- and Microgradients
Min. Resolution: 50u

Vessel Painting



Typical MRI and PET Workflows

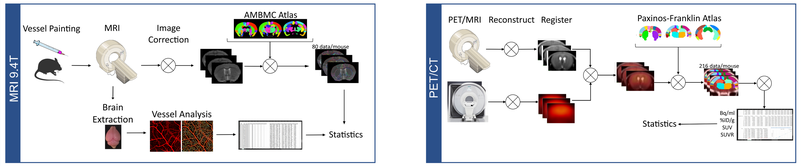


Figure 1: MODEL-AD imaging cores utilized standardized acquisition and data analysis processing workflows. These workflows are updated as new and improved methods are validated.

MR Imaging Modalities

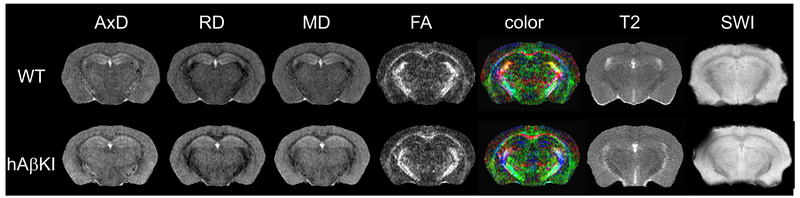


Figure 2: MRI diffusion tensor (DTI) acquisitions for axial (AxD), radial (RD) and mean (MD) diffusivities with fractional ansiotropy (FA) and its pseudo-colored (color) maps provide quantitative information about the underlying tissue microstructure. Multi-echo T2 images and data show anatomical structure and reports water content. Susceptilibity-weighted imaging (SWI) is sensitive to tissue iron and potential location of tissue microbleeds. MODEL-AD uses these imaging metrics to phenotype new and emerging models. Images are from 18mo old males mice.

Hippocampal DTI Metrics

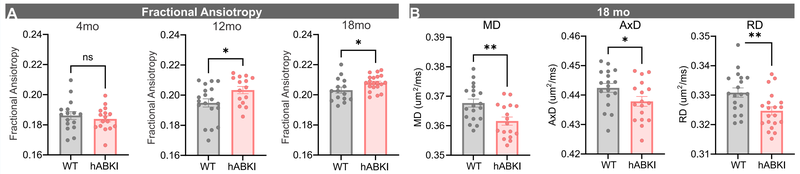
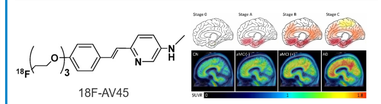


Figure 3: MRI diffusion tensor imaging (DTI) of WT and hAβKI mice in the hippocampus. A) Temporal changes in FA (fractional ansiotropy) with significant elevations at 12 and 18 mo of age in hAβKI mice compared to WT. B) Mean (MD), AxD (axial) and RD (radial) diffusion was reduced within the hippocampus at 18 mo of age relative to age-matched WT Mice. Data includes both male and female mice from each genotype.

PET Tracers

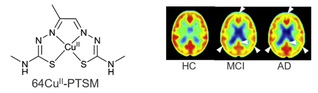
β-Amyloid



Target binding: tracers targeting Aβ aggregates

Off-target binding: minimal to no off-target binding

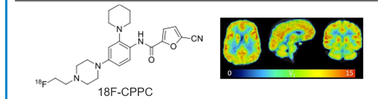
Perfusion



Target activity: 70% first pass extraction and cytosolic trapping via glutathione-reductase oxidation of 64Cu^{II}

Off-target activity: no off-target binding, PTSM has high albumin binding, and 64Cu-ETS is used instead

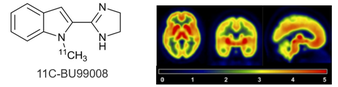
Inflammation



Target activity: Isotopolog of the selective CSF1R Inhibitor CPPC, 11C (Kd 1.1); 18F (Kd 3.4) nM

On/Off-target activity: 100x increase in CSFR1 protein expression, and 1.8x increase in an LPS model, with 75% specific binding post-blockade at 45min

Astrogliosis (I$_2$BS)



Target binding: Binds to imidazoline-2 binding site which is expressed during astrogliosis (Kd1 0.05); (Kd2 35.2) nM

On/Off-target binding: 52% specific binding post-blockade at 45min

Figure 4: MODEL-AD PET tracers. A variety of PET tracers will be utilized by the MODEL-AD imaging cores. Additional tracers include those for metabolism (FDG), synaptic proteins (S2VA), neuroinflammation (P2X7R) and tau (PHF-Tau). As new tracers become available, these will be incorporated into PET imaging protocols.

Metabolic Effects of a High Fat Diet

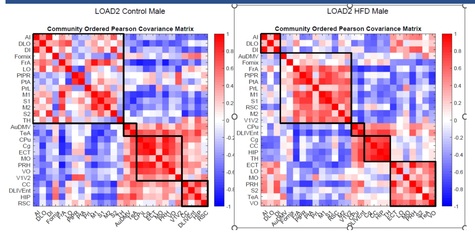


Figure 5: Individual community ordered adjacency matrices of 18F-FDG PET for 12mo male LOAD2 mice on control diet (left) compared to high fat diet (HFD, right) illustrating significant regional metabolic differences due to HFD.

Conclusions

The MODEL AD consortium continues to develop new and novel AD mouse models and the imaging cores will deeply phenotype these models using existing and emerging neuroimaging methods and analytic approaches. All data will be made available via the Sage Knowledge Network (https://adknowledgeportal.synapse.org/).

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Additional Information

MODEL-AD: model-ad.org ; AMP-AD Knowledge Portal: ampadportal.org
AlzForum Research Models: alzforum.org/research-models