ABSTRACT
Alzheimer’s disease (AD) is an irreversible, progressive brain disorder that slowly destroys memory and cognition, and eventually the ability to carry out the simplest tasks. In most people with Alzheimer’s, symptoms first appear in their mid-60s. Estimates vary, but data suggest that more than 5 million Americans may have AD. Most of diagnosed cases (>95%) are late-onset AD (LOAD). One of the obstacles to developing compounds to treat AD may be that models currently used for preclinical testing are based on familial mutations, which account for less than 5% of all AD cases. The Model Organization Development and Evaluation for Late-onset AD (MODEL-AD) Center has been established as a consortium consisting of Indiana University, The Jackson Laboratory, University of California-Irvine and Sage Bionetworks with the purpose of generating animal models of AD. Therefore, MODEL-AD aims to: identify and prioritize novel genetic variants, genes and biomarkers from AD patient data; generate and validate new animal models based on these, 24 will be characterized at a high capacity level, with female mice, to assess the variation that may occur due to sex.

Disease Modeling Project DMP
Aim: To generate and characterize the next generation of mouse models for LOAD.

Model Production
Over the period of this grant the MODEL-AD consortium aims to generate at least 50 new mouse models for LOAD. Of these, 24 will be characterized at a high capacity level, with the most promising models being further phenotyped in the deep phenotyping pipeline. All studies will use male and female mice, to assess the variation that may occur due to sex.

Phenotyping Pipelines
To develop effective testing pipelines, familial AD models (5xFAD, TItau, and 3xTg) will be used to determine the most informative approach. To further validate this pipeline, our newly developed APOE4/Trem2 KO mouse strain will be subject to the same testing paradigm as the familial models. This will enable us to ensure robust and rigorous results, along with comparing data generated at multiple institutions on the same strains of mice.

Primary high capacity phenotyping will determine the initial perturbations in these new strains. Those strains with promising LOAD relevant phenotypes will be moved onto the deep phenotyping phase of characterization. Deep phenotyping will include functional studies (behavior and electrophysiology) of memory/cognition, but also genomic/RNA-seq data, blood and CSF biomarkers, and in vivo imaging. Some strains will be assessed at multiple sites using standardized protocols to ensure reproducibility. Models developed at UCI will undergo the same testing paradigm as IU/JAX to further corroborate experimental reproducibility.

Preclinical Testing Core PTC
Aim: To validate the next generation of mouse models of LOAD and develop a best practice preclinical testing pipeline.

The PTC aims to establish best practice protocols for novel compound testing in animal models for LOAD. To develop the pipeline, compounds that have been (BACE inhibitor, clinical trials will be used with a familial model of AD (5xFAD), Pharmacokinetic (PK)-/dynamic (PD) studies will be carried out in males and females to determine sex specific dosing differences, whether the compound is penetrant, and the efficacy of the compound.