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PERSPECTIVE

Bridging the rodent to human translational gap: Marmosets as model systems for the study of Alzheimer's disease

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Abstract

Introduction: Our limited understanding of the mechanisms that trigger the emergence of Alzheimer's disease (AD) has contributed to the lack of interventions that stop, prevent, or fully treat this disease. We believe that the development of a non-human primate model of AD will be an essential step toward overcoming limitations of other model systems and is crucial for investigating primate-specific mechanisms underlying the cellular and molecular root causes of the pathogenesis and progression of AD.

Methods: A new consortium has been established with funding support from the National Institute on Aging aimed at the generation, characterization, and validation of Marmosets As Research Models of AD (MARMO-AD). This consortium will study gene-edited marmoset models carrying genetic risk for AD and wild-type genetically diverse aging marmosets from birth throughout their lifespan, using non-invasive longitudinal assessments. These include characterizing the genetic, molecular, functional, behavioral, cognitive, and pathological features of aging and AD.

Results: The consortium successfully generated viable founders carrying *PSEN1* mutations in C410Y and A426P using CRISPR/Cas9 approaches, with germline transmission demonstrated in the C410Y line. Longitudinal characterization of these models, their germline offspring, and normal aging outbred marmosets is ongoing. All data and resources from this consortium will be shared with the greater AD research community.

Discussion: By establishing marmoset models of AD, we will be able to investigate primate-specific cellular and molecular root causes that underlie the pathogenesis and progression of AD, overcome limitations of other model organisms, and support future translational studies to accelerate the pace of bringing therapies to patients.

KEYWORDS
Alzheimer's disease, animal models, biomarkers, cognition, genetic engineering, iPSC, marmoset, multi-omics, PSEN1

1 | INTRODUCTION

Alzheimer's disease (AD) is a devastating neurological disease and the most common cause of dementia.[1] AD is characterized by memory loss, the retardation of thinking and reasoning, and changes in personality and behaviors that ultimately lead to severe disabilities with the patients unable to care for themselves.[1–6] The progression of the disease is lengthy, and there are currently no treatments available to stop or prevent the disease.[1–6] The AD brain exhibits unique pathological alterations, including extracellular deposits of amyloid beta (Aβ) in senile plaques and within the walls of cerebral vessels; filamentous inclusions of the microtubule-associated protein tau in neuronal cell bodies (neurofibrillary tangles [NFTs]) and processes (neurites); marked neuroinflammation and activation of innate immune cells; and synaptic and neuronal cell loss.[1–7] Although understanding the biological pathways underlying these pathological processes has been greatly aided by genetic studies of human AD, how these and other factors act at the molecular and cellular level remains elusive and are crucial for understanding how to stop, prevent, and treat AD. Critically, although model organisms, specifically rodent models, have enabled major advancements in our understanding of AD biology and will continue to be informative, significant gaps in translation have hindered the ability to identify an effective therapeutic. These include the lack of models for spontaneous and early primate-specific cellular and molecular events of the disease; the incorporation of genetic diversity in model organisms to better reflect patient heterogeneity, a comparative primate immune system with intact innate immunity, and the lack of translation of functional, behavioral; and cognitive outcomes in rodents wherein the neuroanatomy of the rodent brain and consequently the major functional connectivity does not equate to that of the human brain.[8–11]

2 | MARMOSETS BRIDGE THE RODENT TO HUMAN TRANSLATIONAL GAP FOR STUDYING AD

Over the past two decades, a major focus for many labs, including our own, has been on the development and characterization of rodent models of AD. Although these models have some translational utility and have provided important insights, in particular into genes implicated in human AD, several notable confounds and limitations have now been well described.[11–13] As a consequence of the limitation of these historical mouse models to recapitulate only a fraction of the full spectrum of AD-related phenotypes associated with disease progression, the National Institute on Aging (NIA) recently established the Model Organism Development for Late-Onset Alzheimer's Disease (MODEL-AD) consortium to develop the next generation of mouse models that can better represent risk factors for sporadic AD and institute standardized and rigorous processes for their characterization, validation, and use in preclinical testing.[10] These rodent models from MODEL-AD and the greater research community will continue to generate insights into the biological mechanisms underlying AD and serve as initial model systems for evaluating therapeutic interventions with respect to pharmacology, pharmacokinetics, in vivo target engagement, and toxicology. However, challenges with mouse models remain. Notably, mice lack the genetic heterogeneity of humans with AD, and their accelerated aging timeline and lack of rodent-to-human translation of cognitive outcomes preclude the ability to study critical facets of disease inception and the beginning of memory loss and cognitive decline. Therefore, there is a critical need to develop improved animal models of AD that incorporate genetic variability, aging, and higher-order cognitive processes that better align with humans (Figure 1).

As our closest relatives in the evolutionary tree, non-human primates (NHPs) have long been considered important model systems. Humans and NHPs share much of the genetic, molecular, cellular, structural, and functional organization of the brain and have remarkable similarities in development, postural, physiological, and immune functions.[14] The genetic similarity to humans also reflects on primates exhibiting cognitive and social behavior representing human behavior and cognition.[8–9,15–17] The common marmoset (*Callithrix jacchus*) is a small New World NHP that has several distinct advantages over other laboratory NHP species, including small size, ready adaptation to life in captivity, minimal husbandry requirements, and prolific breeding.[15–16] As an NHP species, marmosets better recapitulate the human aging process relative to other animal models, including improved genomic sequence homology.[15–17] Based on a survey of the literature and from our own colony, common marmosets have an average lifespan of ≈12 years in captivity and are considered to have a 1:8 equivalent ratio of marmoset human age.[15–17] Thus marmosets are considered middle-aged between 5 and 7 years and aged by 8 years.[15–17] This short lifespan allows longitudinal studies in the same individuals over a reasonable period. It is important to note that marmosets manifest age-related changes in a spectrum of functional and physiological parameters that mirror those in aging humans, including decreases in lean body mass, reduced serum albumin, increased insulin resistance, decreased hippocampal neurogenesis, cognitive impairment, myocardial fibrosis, and age-related AD co-morbidities including cancer, diabetes, and chronic renal disease.[15–17] Of particular relevance as a potential model for AD and similar to other primate species, the sequence homology of Aβ in marmosets is identical to that of humans, with the natural, sporadic presentation of Aβ in marmoset brain that occurs with aging.[16–24] Interestingly, although the sporadic presentation of amyloid plaques has been reported as early as 7 years in normal aging marmosets, experimental studies including Aβ-seeding

approaches report an accelerated progression of Aβ deposition as early as 5 years, with a similar spatial-temporal pattern of Aβ deposition to that of humans and similarly with diverse presentation across individuals.[21,24] Furthermore, cerebral amyloid angiopathy (CAA) has also been reported in aging marmosets, which is another important feature of AD that is not observed naturally in rodent models.[24] In addition, the amino acid sequence alignment of tau in marmoset has improved homology over mice, with 94.3% alignment to humans (vs 88.2% mouse to human).[17,22–23] Only a few studies to date have investigated the presence of neurofibrillary tau tangles and neurodegeneration, which are prominent features of human AD, with several reports providing evidence of abnormal tau phosphorylation in aged NHP brains, including that of marmosets.[21–24] We have also now confirmed the natural occurrence of Aβ deposits and hyperphosphorylated tau aggregates in the brain of aged marmosets as well as the presence of both 3R and 4R tau isoforms,[25] suggesting that the pathological hallmarks of AD can form spontaneously during the aging process similar to humans and which has not been demonstrated naturally in rodents. It is notable that marmosets display the typical anatomic and functional organization of the primate brain, offering significant advantages as a translational model of brain diseases.[8–9] Although there has been some general consensus that anatomic regions of the rodent brain map to functional connectivity of that of humans, rodents lack key areas of the cerebral cortex that are critical for higher-order cognitive processes.[8–9] Relatedly, marmosets are excellent at performing cognitive tasks across several domains, including learning, memory, and attention. In addition, marmosets demonstrate age-dependent cognitive decline with impairments associated with synaptic loss and reduced spine density.[16–17,25–31] Of interest, sex differences have also been reported with cognitive impairment in aging marmosets, with worse outcomes in aging females relative to aging males both in task performance and functional connectivity measures.[30,31] Other highly translational features of marmosets include the anatomic similarity of the marmoset cochlea to that of humans, which is relevant for studies of age-related hearing loss.[16–17,32–34] Marmosets have color vision similar to humans, with male marmosets reported as di-chromatic. It is interesting to note that the inability to discriminate color correctly has been reported in patients with AD, which makes color discrimination tasks in marmosets another potential translational feature.[35–36] Similar to humans, marmosets are primarily diurnal with minimal nocturnal activity, which allows for studying alterations in sleep.[16] Marmosets are highly social animals with a broad and sophisticated repertoire of social behavior that includes pair-bonding, cooperative care of young, observational social learning including imitation, and a rich repertoire of vocal communications, including response calling; all of these behaviors are similar to those of humans and can be studied in the laboratory. Marmosets are also excellent translational models for studying emotion regulation and dysregulation. For example, there are individual differences in responses to anxiety stimuli as well as sensitivity to motivational variables, which may have value for assessing anhedonia as a surrogate for depression or increased aggression that corresponds to pathology as a surrogate of irritability.[26,37] At the molecular and cellular level, marmosets share genetic and protein sequences, and protein and biochemical functions that are well beyond that of rodent models and more similar to humans. Finally, marmosets have historically served as essential model organisms in the pharmaceutical industry for drug discovery and development, as well as for pharmacokinetic and toxicology studies, which demonstrate their utility as a model system to enable improved preclinical to clinical translation for the investigation of potential AD therapeutics.[38]

Recently, viable transgenic marmoset lines with germline transmission have been demonstrated for neurological disorders, including

RESEARCH IN CONTEXT

1. **Systematic review**: Using traditional sources (e.g. PubMed, conference abstracts) the authors conducted a thorough search focused on the validation of non-human primates (NHP) as models for translational studies of Alzheimer's disease (AD) to overcome limitations of traditional model organisms.
2. **Interpretation**: Marmosets are an ideal NHP model for studying AD. Here we describe the establishment of a new Open Science consortium aimed at the generation, characterization, and validation of Marmosets As Research Models of AD (MARMO-AD). This consortium will study gene-edited marmoset models carrying genetic risk for AD and wild-type genetically diverse marmosets from birth throughout their lifespan.
3. **Future directions**: By establishing marmoset models of AD, MARMO-AD will be able to investigate primate-specific cellular and molecular root causes that underlie the pathogenesis and progression of AD, overcome limitations of other model organisms, and support future translational studies to accelerate the pace of bringing therapies to patients.

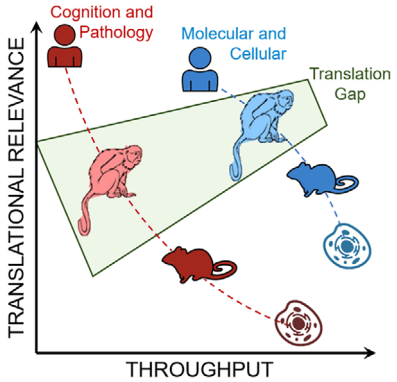

FIGURE 1 Marmoset models bridge the current translation gap between human studies and cell and rodent models of AD. Establishment of marmoset models of aging and genetic risk loci for AD will enable robust and reliable mapping of cognitive and molecular outcomes across species. AD, Alzheimer's disease.

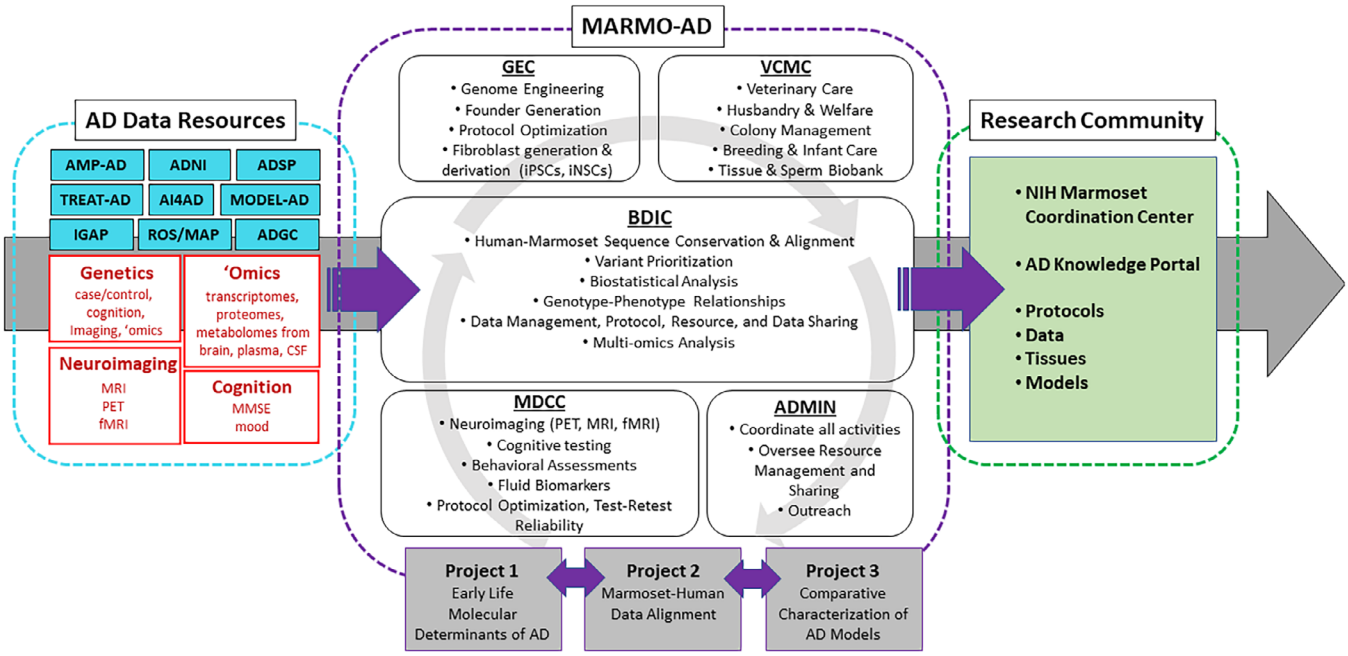

FIGURE 2 Overview of the MARMO-AD Consortium. MARMO-AD will leverage the AD data universe to inform new risk variants for genetic engineering into marmosets as well as alignment of clinical data (genetics, multi-omics, imaging, biomarkers, behavioral measures, cognitive assessments) and mouse model data from MODEL-AD. Projects are supported by experiments executed by technical cores. Animal models will be generated in the GEC, bed and maintained in the VCMC, and characterized in the MDCC. The BDIC will incorporate data from the AD Knowledge Portal, prioritize variants for model generation, and support computation and biostatistical analysis. Finally, the ADMIN Core will ensure that data produces, protocols, tissues, and models will be made available to the research community. AD, Alzheimer's disease; ADMIN, Administrative; BDIC, Bioinformatics and Data Integration Core; GEC, Genetic Engineering Core; MARMO-AD, Marmosets As Research Models of AD; MDCC, Multimodal Disease Characterization Core; VCMC, Veterinary and Colony Management Core; AMP-AD, Acclerating Medicines Partnership Program for Alzheimer's Disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; ADSP, Alzheimer's Disease Sequencing Project; TREAT-AD, Target Enablement to Accelerate Therapy Development for Alzheimer's Disease; MODEL-AD, Model Organism Development for the Evaluation of Late Onset Alzheimer's Disease; AI4AD; Artificial Intelligence for Alzheimer's Disease; IGAP: International Genomics of Alzheimer's Project, ROS/MAP: Religious Orders Study/Memory and Aging Project; ADGC: Alzheimer's Disease Genetics Consortiu.

from our own laboratories,[39–41] opening up novel approaches to understanding neuronal circuitry and function in the primate brain and enabling significant advancements in model organisms for the study of neurological and neuropsychiatric disorders. We are excited that our team has now successfully used CRISPR/Cas9 approaches to genetically engineer single point knock-in mutations in the presenilin 1 (*PSEN1) gene*, including a change in the cysteine 410 codon to tyrosine (C410Y) and a change in the alanine 426 codon to proline (A426P), producing viable founder marmosets[42] which are being studied as part of a recently funded NIA-supported multi-institutional consortium focused on the generation, characterization, and validation of Marmosets as Research Models of Alzheimer's disease (MARMO-AD). The ultimate goal of MARMO-AD is to bridge the rodent to human translational gap and enable detailed studies of the underlying biological mechanisms of AD; and to build the foundational knowledge for the utility of marmoset models with genetic risk for AD. To meet these goals, the consortium consists of three integrated research projects supported by five technical cores focused on project administration, bioinformatics, genetic engineering, multimodal disease characterization, and veterinary and colony management (Figure 2). Project 1 will conduct comprehensive characterization of *PSEN1* mutations in marmosets as a model for the study of early-onset AD (EOAD) and investigate early life molecular determinants of AD disease pathogenesis associated with genetic risk for EOAD. For these studies, the genetically engineered *PSEN1* marmoset founders and their germline offspring will be comprehensively characterized from birth through adolescence and adulthood using multi-modal characterization including integrated assessment of genetic, molecular, functional, behavioral, cognitive, and neuropathological markers in line with clinical staging of AD patients to enable the identification of onset and disease trajectory. In parallel, we will conduct multi-omic profiling in distinct neuronal cell types derived from skin fibroblasts of the living subjects as a surrogate to accessing the brain at the cellular level, in order to investigate the molecular signatures of genes and proteins in these marmosets and their differential expression relative to their respective controls and in comparison to human AD patients. Project 2 will identify and enhance late-onset AD (LOAD)–related signatures in outbred and genetically engineered marmosets by integrating genomic data with multi-omic measures, imaging biomarkers, behavioral assays, and candidate treatments to determine how natural and engineered genetic risk factors in marmosets mimic human LOAD. More specifically, this project will use natural genetic variation and prioritize genetic loci for genetic engineering in outbred

marmosets to model AD risk in humans and rigorously align human and marmoset data with computational analyses. Project 3 will conduct a comparative multimodal phenotypic characterization of marmoset models of AD. This project will develop novel marmoset models engineered with risk variants of LOAD, which we will then be characterized longitudinally to identify emerging phenotypes that precede frank neuropathology. It is important to note that the supporting cores will (1) integrate marmoset and human genomic signatures, (2) establish normative values of AD related biomarkers across normal aging marmosets relative to marmosets with genetic risk for AD, (3) provide data dissemination and resources to the greater research community in line with our commitment to open science, (4) generate novel gene-edited marmoset models of AD and improve methods for their generation, (5) develop optimized protocols for studying disease onset and trajectory in line with clinical protocols, and (6) provide specialized animal care and support, respectively, allowing full characterization of the marmoset models.

3 | COMPREHENSIVE NON-INVASIVE MULTIMODAL DISEASE PHENOTYPING IN MARMOSETS IN LINE WITH THE NIA–AA (ALZHEIMER'S ASSOCIATION) RESEARCH FRAMEWORK

AD is a progressive disease that undergoes a continuum evolution, from preclinical AD to mild cognitive impairment (MCI), to dementia.[1–6] The phenotypic characterization of AD was unified under a biological construct research framework based on the assessment of biomarkers for Aβ, pathologic tau, and neurodegeneration (ATN).[43–44] The ATN classification system allows combining OF biomarkers obtained by multimodal methods. For example, positron emission tomography (PET) imaging and bioassays of blood or cerebral spinal fluid (CSF) can assess Aβ and pathological tau deposition. Behavioral testing, structural and functional magnetic resonance imaging (MRI), and blood or CSF bioassays for neurofilament light (NfL) chain can evaluate neurodegeneration. Applying the NIA-AA Research Framework to marmosets will attain a more accurate characterization and understanding of the etiological sequence of events that lead to AD development, in line with the currently used framework in AD patients (Figure 3). In this respect, the testing battery for MARMO-AD has been developed in collaboration with the veterinary team to ensure the health, welfare, and minimal stress to the marmosets. Before initiating the longitudinal MRI and PET neuroimaging pipeline, marmosets are acclimated to be comfortably restrained in an MRI/PET-compatible bed under awake conditions.[45] The ability to conduct neuroimaging in fully conscious animals is critical to avoid the confounds introduced by anesthesia on neural activity, neurovascular coupling, and hyperphosphorylated tau.[46] For example, we found that anesthesia significantly reduces the connectivity strength in resting-state functional networks.[47] MRI and PET imaging will be conducted twice annually at 6-month intervals. Pittsburgh compound B (11C-PiB) is being utilized for Aβ plaque burden and 18F-fluorodeoxyglucose (FDG)-PET for brain metabolism. Longitudinal MRI sessions include structural (anatomic) whole-brain T1-, T2- and T2*-weighted and diffusion MRI with a target isotropic spatial resolution of 250 μm.[45] The functional MRI (fMRI) protocol includes resting-state functional connectivity (rsFC) measurements of the default mode network (DMN) in awake marmosets[9,47] and task-based blood oxygen level–dependent (BOLD) fMRI of the visual system.[9,47–48] Given that vascular integrity is compromised in AD, we will also obtain quantitative MRI measures of cerebral blood flow using the continuous arterial spin labeling (ASL) technique with a separate labeling coil and blood-brain barrier integrity[49] (Figure 4). In addition, given that it is increasingly recognized that vascular dysfunction is prominent in sporadic, late-onset AD and AD-related dementias, arterial stiffness, a proxy for vascular dysfunction, will be measured with an ultrasound imager.[50]

As part of the multi-modal characterization, a behavioral and cognitive testing battery has been established with outcome measures that align to those studied in AD patients. Although the primary symptom for AD has historically been memory loss, such memory decline occurs in both normal healthy aging and AD, albeit at an accelerated pace and more pronounced severity in AD. Intact memory function relies on the precise integration of several sensory and motor function processes, which also progressively decline or become altered with age, including hearing, vision, olfaction, gustation, motor activity, strength, sleep, and balance.[34] Relatedly, it is likely that the progression in these multisensory and motor functions that subserve cognitive function are also accelerated and possibly begin years before the emergence of memory impairment. We have established these cognitive and non-cognitive outcome measures as analogs to the clinical assessments in patients, which comprise many of the composite scores that evaluate disease progression in AD patients. These include for example, Clinical Dementia Rating (CDR), Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Mini-Mental State Exam (MMSE), Neuropsychiatric Inventory (NPI) [52] (Figure 3). Behavioral observations begin at birth during standard veterinary health checks to track developmental milestones via weekly tests using the methods described previously.[53] Observations are recorded with anonymous IDs, and a trained analyst blinded to genotype scores the videos using a qualitative assessment. During the adolescent period, reward preferences for positive reinforcement are established with motor, fine motor, and sensory assessments conducted beginning at 6 months of age and annually. This includes activity and sleep monitoring non-invasively conducted in the home cage via monitoring of Actiwatch devices attached to collars.[54] Because marmosets are primarily diurnal and sleep with minimal activity during the dark cycle, abnormal sleep patterns can be quantified readily and would be an essential phenotype given abnormal sleep patterns reported in AD patients.[34] Quantitative grip strength, social behavior, and measures of olfaction, gustation, vision, and hearing, which are critical sensory functions that contribute to cognition, are also measured longitudinally similar to the methods described previously.[16,24] The extensive cognitive testing battery was established based on translational cognitive outcomes and, therefore, takes advantage of the analogous paradigms of the CANTAB testing battery using the same modality of visual cues and

Human-animal model assays	• identical	∘ similar	- analog	x N/A	
NIA-AA, AMP-AD, ADNI etc.				Marmoset	Mouse
Omics	Whole Genome Sequencing			•	•
	Transcriptomics (RNAseq)			•	•
	Proteomics			•	•
Fluid Biomarkers	Aβ40, Aβ42			•	•
	pTau181, pTau217, pTau231, tTau			•	•
	NFL, GFAP			•	•
Neuroimaging	Amyloid PET (^{18}F-AV45 or ^{11}C-PIB)			•	•
	Glucose Metabolism (^{18}F-FDG-PET)			•	•
	Cerebral Blood Flow (ASL-MRI)			•	•
	Tau PET			•	x
	Structural, Anatomical MRI, Morphometric Analysis			•	-
	Task-Based Functional fMRI (Visual Stimulation)			•	x
Behavior (Non-cognitive)	Developmental Milestones			•	•
	Motor, Fine Motor, Activity and Sleep			•	•
	Social behavior			•	-
	Neuropsychiatric (Social, anxiety, motivation, appetite)			•	-
	Sensorimotor (vision, hearing, olfaction, gustation)			•	-
Cognitive (Touchscreen*)	Working Memory (Delayed Match to Position)*			•	•
	Attention (sustained, selective, divided); Speed of Processing*			•	-
	Reversal Learning & Behavioral Flexibility (Delayed Non-Match to Position)*			•	-
	Recognition Memory (Trial Unique Delayed Match to Sample)*			•	-
	Spatial Navigation (Egocentric)			•	-

FIGURE 3 Application of the NIA-AA Research Framework to marmosets. A comprehensive evaluation of marmosets via measures of cognitive and behavioral outcomes, neuroimaging, and fluid biomarkers per the ATN research framework is being conducted as part of the MARMO-AD consortium. Measures are listed as identical, similar, analogous, or not applicable in marmosets and mice relative to the human measures. For example, awake fMRI is not plausible in mice and currently available Tau PET ligands require both 3R and 4R tau isoforms which are not present naturally in mice. Aβ, amyloid-beta; ATN, Aβ, pathologic tau, and neurodegeneration; NFL, neurofilament light chain; GFAP, glial fibrillary acidic protein; PET, positron emission tomography; MRI, magnetic resonance imaging; fMRI, functional MRI; ASL-MRI, arterial spin labeling-MRI; MARMO-AD, Marmosets As Research Models of AD; NIA-AA, National Institute on Aging–Alzheimer's Association; AMP-AD, Accelerating Medicines Partnership for AD; ADNI, Alzheimer's Disease Neuroimaging Initiative.

touch, and with outcome measures that have been demonstrated sensitive for detecting cognitive impairments in AD and MCI.[55] Like humans, the marmosets will not be subjected to water maze or fear conditioning tasks that have been used traditionally in rodents, especially given the limited translational relevance of those tests in addition to the significant stressors required of those paradigms.[56] The current cognitive testing battery includes measures of motivation (progressive ratio), spatial working memory (Delayed Match to Position task), spatial flexibility (Delayed Non-Match to Position task), recognition memory (Trial Unique Delayed Match to Sample task), and indices of attention including sustained, selective, and divided attention as well as speed of processing (Continuous Performance/Serial Reaction Time Task) (Figure 3). Each task is trained during adolescence with a priori advancement criteria, and peak performance is established for each subject across multiple outcome measures for each test (e.g., accuracy, trials to criteria, response latencies, reward latencies, etc.) from adolescence through adulthood. Given the genetic heterogeneity and phenotypic diversity in marmosets, like humans, individuals are tracked longitudinally throughout the course of their lifespan for changes in behavior and cognitive outcomes. Performance typically improves from adolescence with peak performance during adulthood. Decline is tracked at the individual level relative to each subject's peak performance during annual longitudinal testing. It is important to note that the population of male and female marmosets to be studied will exceed $n = 200$ across the project with annual longitudinal measures over the lifespan (≈12 years) of an individual subject.

4 | GENETIC STUDIES PROVIDE IMPORTANT CLUES TO THE EARLIEST CELLULAR AND MOLECULAR EVENTS THAT LEAD TO DISEASE PATHOGENESIS

Traditionally, AD is generally classified into two categories: the more common sporadic, late-onset AD (LOAD) form that makes up the majority of AD diagnoses (≈95% of cases) and the familial form (FAD),

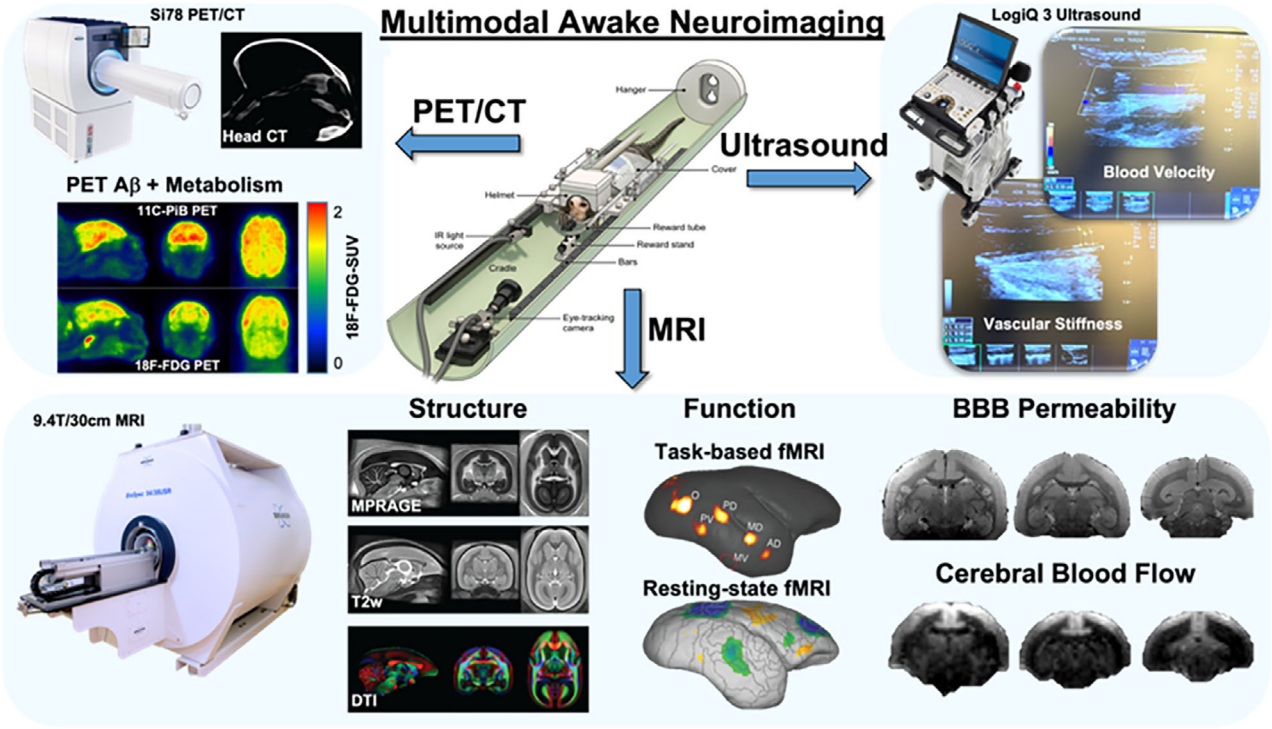

FIGURE 4 Multimodal Marmoset Neuroimaging Pipeline. Marmosets will be acclimated to restraint in a compatible imaging holder. The awake neuroimaging pipeline includes CT, PET-amyloid, and PET-metabolism in a PET/CT scanner, structural and functional MRI protocols in a 9.4T MRI, and vascular stiffness and blood velocity by ultrasound. All protocols will exceed the ADNI-3 standards. PET/CT, positron emision tomography/computerized tomography; MRI, magnetic resonance imaging; fMRI, functional MRI; BBB, blood brain barrier.[51]

which comprises ≈5% of AD cases and arises from genetic mutations in one of three genes: the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) genes, which are all involved in Aβ production.[1–6] Although the sporadic form of AD results in the emergence of AD symptoms typically presenting well into the sixth decade of life and beyond, patients with FAD mutations have an early onset of AD symptoms (EOAD; typically between the ages of 30 and 50 years). A much smaller proportion of FAD patients (<1%) comprise autosomal dominant AD (ADAD), which results in nearly 100% penetrance of EOAD.[1–6] Approximately 80% of ADAD cases comprise mutations in *PSEN1*,[1-6] which was our initial impetus for developing our first marmoset models of AD. Indeed, studies of ADAD have been critical in revealing that the pathological features of AD are not only similar between FAD and LOAD with respect to the spatial temporal progression of neuronal loss, NFTs, Aβ plaques, and presence of CAA, but also the presentation of behavioral, cognitive, and clinical changes that are shared in EOAD and LOAD.[1–6] Given the limitations of Aβ-targeted therapies to fully treat disease, despite their effectiveness for lowering Aβ, the question remains whether Aβ deposition is indeed the genesis of disease, or more likely it is a consequence of earlier events that lead to Aβ seeding; and whether therapeutic interventions would be required prior to the initial seeding event.[1–6,57] It is notable that studies of ADAD such as those ongoing through the Dominantly Inherited Alzheimer's Network (DIAN),[58–60] as well as the studies planned through the efforts of MARMO-AD by comprehensive characterization of *PSEN1* marmosets, will play an essential role in elucidating the earliest cellular and molecular changes that lead to AD pathogenesis, particularly as these animal models of ADAD are studied at the cellular and molecular level from birth through aging. In addition, the ability to study these subjects from birth will also allow us the potential for conducting true prophylactic studies aimed at preventing the earliest Aβ-seeding events. More specifically, our rationale for choosing the C410Y and A426P mutations in *PSEN1* is in part to align with studies of several human families with this mutation that are enrolled in a longitudinal natural history study led by our clinical colleagues at the University of Pittsburgh Alzheimer's Disease Research Center, thereby providing a roadmap to align the phenotypes of the AD marmoset models with.[61] Therefore, the early-onset disease trajectory of the PSEN1 phenotype will provide a platform to optimize the research tools and protocols for model characterization in line with human disease staging, which will further enable studies aimed at creating and characterizing marmoset models genetically engineered with risk variants of late-onset AD (LOAD) (Figure 5).

5 | INVESTIGATING THE MOLECULAR AND CELLULAR EVENTS THAT PRECEDE FRANK NEUROPATHOLOGY IS CRUCIAL FOR UNDERSTANDING HOW TO PREVENT DISEASE

In the absence of a cure or preventative treatment for AD, there will continue to be a need to understand and identify the mechanisms that

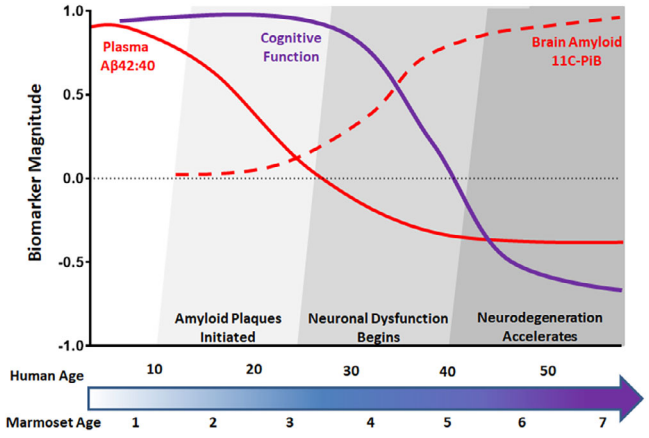

FIGURE 5 Predicted phenotypic trajectory of *PSEN1* marmosets. To illustrate the predictive phenotypic trajectory of the *PSEN1* marmosets aligned to human ADAD patient trajectory based on a marmoset to human age ratio of 1:8.[16] Based on our observations of increased plasma Aβ42:40 in our adolescent *PSEN1* founder marmosets that are <1 year of age,[42] we predict that by 4 years of age in marmosets (equivalent to 32 years of age in human) we will begin to observe Aβ accumulation in brain by PET imaging and consequent reduced plasma Aβ and cognitive decline in the *PSEN1* mutation carriers relative to contemporaneous non-carrier controls.

are the root cause of AD and precede the known cascade of events. A major impetus for this project is the repeated failure of therapeutics to prevent or fully treat disease, despite their effectiveness at lowering Aβ.[57] Consequently, the lack of efficacy may also be due to initiating therapeutic interventions too late in the disease process, raising the questions of when does disease inception begin in order to identify the optimal timeframe to initiate preventative treatment, and more importantly what is the optimal target if not Aβ.[57] Therefore, studies as early in life as possible in those with genetic risk for AD will be critical for identifying the root molecular causes and biochemical changes that precede disease. To date, the most comprehensive studies reported in the youngest mutation carriers with the highest risk for developing AD are those ongoing in the Colombian FAD kindred of *PSEN1* mutation carriers (E280A) and non-carrier relatives. These studies have provided critical insights into AD trajectory in mutation carriers as young as 6 years of age.[58–59] Of interest, even as adolescents, plasma Aβ42 levels and plasma Aβ42:40 ratio were significantly increased in *PSEN1* carriers relative to age-, sex-, and education-level matched non-carriers from the same kindred.[55] These findings are consistent with the studies of this mutation in young adults where plasma Aβ42 levels are elevated prior to detection of Aβ on brain via PET.[58] More recently, a study found that male children with the *PSEN1* variant had reduced cognitive abilities compared to female children with the variant and relative to age- and sex-matched non-carriers, although the later-life implications of this require further investigation.[60] Together these studies demonstrate some of the earliest reported phenotypes in ADAD mutation carriers and implicate evidence for events that emerge well before Aβ-plaque deposition and notably before adulthood. In this respect, access to the brain prior to disease onset is critical for identifying cellular and molecular pathways that may lead to disease pathogenesis, especially in the context of genetic risk. The challenge, of course, is obtaining brain cells from living subjects, and the practical and ethical considerations for studies involving children.

Recent advances using induced pluripotent stem cell (iPSC) technologies offers an innovative approach to potentially bridge the gap between clinical studies of those living with genetic risk and their postmortem tissues many years later. Throughout the last several years, multiple studies have reported the utility of fibroblasts and iPSC-derived neurons to recapitulate processes specific to neural cells.[62–63] These include increased levels of Aβ and phosphorylated tau from fibroblasts and fibroblast-derived neurons of ADAD patients including *PSEN1* mutation carriers, and differential gene expression profiles in carrier cell lines versus non-carriers including mechanistic insights beyond the amyloid cascade hypothesis (e.g., neuroinflammation, vascular dysfunction), which provides opportunities for target identification of potential novel therapeutic interventions.[63] More recently, neurons derived from iPSCs of AD patients have shown near-identical molecular signatures that align to post-mortem brains from the same individuals, which supports the potential of this approach for using iPSCs in living individuals as a proxy for brain tissue.[62] This provides an exciting, innovative, and opportunistic approach for us to use these same methods in living marmosets with genetic risk for AD to identify molecular signatures that diverge from normal healthy aging in non-mutation carriers prior to Aβ deposition in brain. More specifically, the current proposal aims to employ differentiated neurons from fibroblasts generated from our *PSEN1* marmosets and their age-matched wild-type controls from infancy with longitudinal samples evaluated to investigate changes with aging, and profile these using multi-omics strategies. This innovative approach has the potential to identify early molecular events that emerge prior to Aβ aggregation in brain, at the cellular level, using the proxy of derived neurons. In contrast to the considerations needed to allow for such studies in pediatric mutation carriers from infancy, our marmoset models that incorporate genetic risk for AD, can be studied in a highly controlled environment from infancy through lifespan with corresponding and comprehensive documentation of AD-related disease phenotypes and systematic behavioral and cognitive assessments.

6 | DIVERGENT MECHANISMS OF EOAD AND LOAD

Although genetics is the primary risk factor for developing EOAD, for most cases of LOAD, a multitude of risk factors including genetics, environmental/lifestyle exposure factors, and co-morbidities, on top of the primary risk factor of age confers conversion to AD.[1–6] Unlike EOAD, the genetic underpinnings and relatively predictable disease trajectory are not as conclusive of LOAD, and currently it is impossible to provide patients with a reliable prediction of the course of the disease. Current AD biomarkers have been useful for early AD detection including ATN.[43–44] However, ATN biomarkers have a high degree of variability in their presentation and severity as well as a

limited sensitivity for predicting cognitive decline.[43–44] Indeed, up until several years ago, only the apolipoprotein E (*APOE*) gene on chromosome 19, and particularly the inheritance of the ε4 allele, had been identified as a significant genetic risk factor in AD. However, it is estimated that *APOE* accounts for only ≈30% of the LOAD genetic risk[1] and ε4 risk is highly variable across human populations.[1] With respect to marmoset *APOE*, the marmoset reference genome is *APOE* ε4 at the two typing polymorphisms, consistent with primate ancestral *APOE*. Although we will conduct whole genome sequencing in our genetically diverse marmoset population, we have not observed *APOE* variation at the ε2/ε3/ε4 genotype variants in 25 marmosets sequenced to date. However, there is abundant genetic variation at the locus, including non-coding regions, which may be of translational relevance. Recent, large genome-wide association studies and exome sequencing studies of rare variants in addition to continually emerging data from large-scale sequencing studies including the Alzheimer's Disease Sequencing Project (ADSP) and the Integrative Genome Analysis Pipeline (IGAP) have provided evidence for dozens of additional genetic loci as contributing to AD risk that have been replicated in multiple independent patient populations.[64–65] Many of the genes and pathways implicated in LOAD are also supported by systems biology analysis of transcripts from postmortem human brain.[64–65] Notably, these genes implicate alternative pathways in the development of AD, including immune response and inflammation, lipid transport, endocytosis, and others. Consequently, these genes and pathways confer genetic risk for LOAD co-morbidities including vascular diseases such as hypertension, metabolic dysfunction, and diabetes, among others.[66–70] It is important to note that sequence homology of many of these LOAD risk genes in marmosets have improved homologies for human relative to mouse. As part of the goals of MARMO-AD, there is a comprehensive plan to evaluate the natural variation and presentation of these associated risk factors that may lead to LOAD, as well as AD-related systems biology outcomes and co-morbidities including hypertension in our marmoset colony that can be studied independently and combined with genetic risk for LOAD.

7 | CHALLENGES AND OPPORTUNITIES OF MARMOSETS AS MODELS FOR AD

As highlighted in this *Perspective*, marmosets provide a unique opportunity to overcome a number of the limitations that are present with other model organisms for AD research. This includes improved sequence homology of AD-related pathological proteins and risk genes, as well as key anatomic and functional features of the primate brain and relatedly higher order cognitive functions that cannot be studied in lower species. That being said, marmosets will not replace other model organisms per se, but rather be carefully selected among other model systems to address specific questions where gaps remain in our understanding of AD and translation to human. On balance, as one of the shortest living NHP species relative to longer-lived laboratory NHPs, marmosets allow for the study of primate-specific mechanisms that may underlie the conversion from healthy aging toward the inception and progression of AD within a more feasible timeframe and cost. Although similar in size to larger laboratory rodent species, marmosets require elevated levels of care and behavioral considerations similar to other NHPs, including a housing environment with significant space to accommodate their natural behaviors, as well as a formalized enrichment and breeding programs. Unlike rodents, marmosets are selective in their breeding partners and this requires careful management under the care of highly trained and dedicated husbandry and veterinary staff, which is provided for within the dedicated Veterinary and Colony Management Core (VCMC) as part of our MARMO-AD consortium. Although many studies can be de-risked in lower species including rodents, certain avenues of research such as the role of adaptive and acquired immunity require NHP species with a comparative primate immune system. Consequently, with the recent regulatory approval of immunotherapies for AD (e.g., aducanumab, lecanemab), the trajectory of disease in patients prescribed with such therapies will be altered, and marmosets are well positioned to study this consequence and potentially how intervention with adjunct treatment of alternative mechanisms of action in the presence of these new standard of care therapies may provide therapeutic benefit. This type of study that requires longitudinal measures can be easily designed and executed in marmosets using non-invasive methods as described as part of MARMO-AD, and with the same non-invasive approaches and identical reagents including fluid and imaging biomarkers that are used in the clinic. Indeed, there are a number of notable limitations of marmosets as models for AD. For example, certain active areas of AD research that may not be suitably addressed in marmosets include the role of menopause, as frank menopause does not occur in aging female marmosets despite follicular depletion and anovulation. This does not preclude the use of marmosets for studying the biological role of sex on AD risk per se, but rather re-emphasizes the need to carefully select the most appropriate model to address the specific question. Other limitations of marmosets include the challenges of importation and limited availability due to recent increase in demand, which if not addressed can ultimately result in a genetic bottleneck in the ability to maintain outbred populations.[71] Recognizing this potential impact as a future limitation, MARMO-AD has put in place a robust breeding program that will not be impacted by this for several years. In addition to the financial commitment and significant regulatory requirements to ensure appropriate use of marmosets in biomedical research, there is an ethical responsibility that cannot be understated and remains at the forefront of discussion in the research community.[71] In recognition of our ethical responsibilities, MARMO-AD has focused on establishing non-invasive measures, analogous to those used in the clinic, to comprehensively study the marmosets throughout their lifespan, and with no planned terminal studies with the exception of welfare concerns that require humane euthanasia. Although arguments are often made that NHP studies take too long, are too expensive, and that alternative species can be used, this can be countered by emphasizing the cost of investing in a continuous cycle of experiments in other animal models that have failed to translate to humans (e.g., drugs that improve cognition in mice), which only further delays the goal of advancing treatments to patients while continuing to waste resources.

8 | DISCUSSION

MARMO-AD is expected to have a lasting impact on the study of AD biology. The MARMO-AD consortium will sit at a natural nexus point that leverages the knowledge from other NIA-funded open-science resource programs including the Accelerating Medicine Partnership program for Alzheimer's Disease (AMP-AD), Model Organism Development for the Evaluation of Late onset Alzheimer's Disease (MODEL-AD), and Target Enablement to Accelerate Therapy development for Alzheimer's Disease (TREAT-AD). Specifically, insight from variant prioritization including successes and failures in mouse model creation and translational phenotypes from MODEL-AD efforts will be used to inform MARMO-AD variant selection for future genetic engineering of new models of late onset Alzheimer's disease (LOAD). In addition, compounds screened from the MODEL-AD Preclinical Testing Core and TREAT-AD through rigorous screening pipelines in the mouse models that are deemed to be safe and have potential efficacy, may be advanced into MARMO-AD models for confirmation (e.g., in vivo target engagement, pharmacokinetics [PK]/pharmacodynamics [PD]) and specifically extend to the evaluation of cognitive assessments. All resources generated from this program including the marmoset models, protocols, methods, and data will be shared with the greater AD research community (Figure 2). Data will be integrated with human, mouse, and cellular outcomes on the AD Knowledge Portal. The consortium will deliver new insights by identifying early emerging primate-specific mechanisms that precede the pathogenesis of AD. Many biologists will benefit from the genetic analysis and marmoset to human genomic alignment. It is important to note that the early-onset disease trajectory of the PSEN1 phenotype will provide a platform to optimize the research tools and protocols for model characterization in line with human disease staging, which will further enable studies aimed at creating and characterizing marmoset models genetically engineered with risk variants of LOAD (Figure 5). In addition to sharing the marmoset models of AD with qualified investigators from the research community, our comprehensive phenotyping of these models will serve as a resource and essential field guide for AD researchers planning to employ these models in their laboratories. Building on our success with the generation of our founder *PSEN1* marmosets, the MARMO-AD consortium will allow the study of the pathogenesis of AD by comprehensive evaluation from birth through aging and will provide model organisms that will more faithfully recapitulate the spectrum of primate-specific behavioral, functional, cognitive, genetic, molecular, and cellular phenotypes of AD that will enable improved translational studies of potential therapeutic interventions.

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CONFLICT OF INTEREST STATEMENT

S.J.S.R. has served as a consultant for Sage Therapeutics. G.W.C. has served as a consultant for Astex Pharmaceuticals. N.T.S. is a co-founder and board member of Emtherapro Inc. G.E.H., D.J.S., L.S., J.E.P., J.U., T.Z., A.H., B.P., A.G., T.M., S.H.C., H.H., J.K., P.L.S., and A.C.S. report no competing interests to declare at the time of submission. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

No human subjects were used in these studies, and, therefore, consent was not necessary.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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