

Review

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Animal models of Alzheimer's disease: Current strategies and new directions

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ABSTRACT

Animal models constructed using pathogenic factors have significantly advanced drug development for Alzheimer's disease (AD). These predominantly transgenic models, mainly in mice, replicate pathological phenotypes through gene mutations associated with familial AD cases, thus serving as vital tools for assessing drug efficacy and for performing mechanistic studies. However, the species-specific differences and complex, heterogeneous nature of AD etiology pose considerable challenges for the translatability of these animal models, limiting their utility in drug development. This review offers a comprehensive analysis of widely employed rodent (mice and rats) and non-rodent models (*Danio rerio* (zebrafish), *Drosophila melanogaster*, and *Caenorhabditis elegans*), detailing their phenotypic features and specific research applications. This review also examines the limitations inherent in these models and introduces various strategies for expanding AD modeling across diverse species, emphasizing recent advancement in non-human primates (NHPs) as valuable models. Furthermore, potential insights from the integration of innovative technologies in AD research are discussed, while providing valuable perspectives on the future development of AD animal models.

Keywords: Alzheimer's disease; Animal models; A β ; Tau; Non-human primates

INTRODUCTION

Alzheimer's disease (AD), the most prevalent neurodegenerative disorder, accounts for over 60% of dementia cases (2024 Alzheimer's disease facts and figures, 2024). Clinically, AD manifests initially as episodic and short-term memory impairment, progressing to extensive deficits in both declarative and non-declarative memory functions. Pathological hallmarks include dystrophic neurites, significant

synaptic loss, neuronal degeneration, and gliosis within the brain (Guo et al., 2020; Knopman et al., 2021).

Typical pathological features of AD include extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs) in the cortical and limbic regions (Guo et al., 2020). Targeting β -amyloid (A β), the core protein of amyloid plaques, several monoclonal antibodies (e.g. aducanumab, lecanemab, donanemab) have recently gained approval for AD therapy, marking a significant milestone in the therapeutic landscape (Sevigny et al., 2016; Sims et al., 2023; Van Dyck et al., 2023). Nonetheless, current therapeutics and medications are confined to mitigating cognitive decline, lacking the efficacy to halt or reverse the fundamental neurodegenerative mechanisms. Furthermore, limited translatability of preclinical studies using animal models of AD remains a major issue for drug development (Padmanabhan & Götz, 2023).

Pedigree analyses of familial AD (FAD) and frontotemporal dementia (FTD) have identified mutations in the amyloid precursor protein (encoded by the *APP* gene) and microtubule-associated protein tau (encoded by the *MAPT* gene) (Figure 1), revealing key molecular underpinnings linked to these neurodegenerative disorders (Bugiani et al., 1999; Clark et al., 1995; Levy et al., 1990). This discovery has led to the development of various animal models carrying these mutations, a widely adopted approach in neurodegenerative disease research. The first transgenic mouse model of AD, established in 1995, involved the microinjection of a platelet-derived growth factor (PDGF)-driven construct encoding full-length human *APP* with the V717F mutation (Games et al., 1995). The resulting PDAPP mice exhibited extracellular A β deposition, along with dystrophic neurites and loss of synaptic density in the hippocampus (Dodart et al., 1999; Hartman et al., 2005). However, as designed, these PDAPP mice did not develop tangles or show significant neuronal loss, limiting

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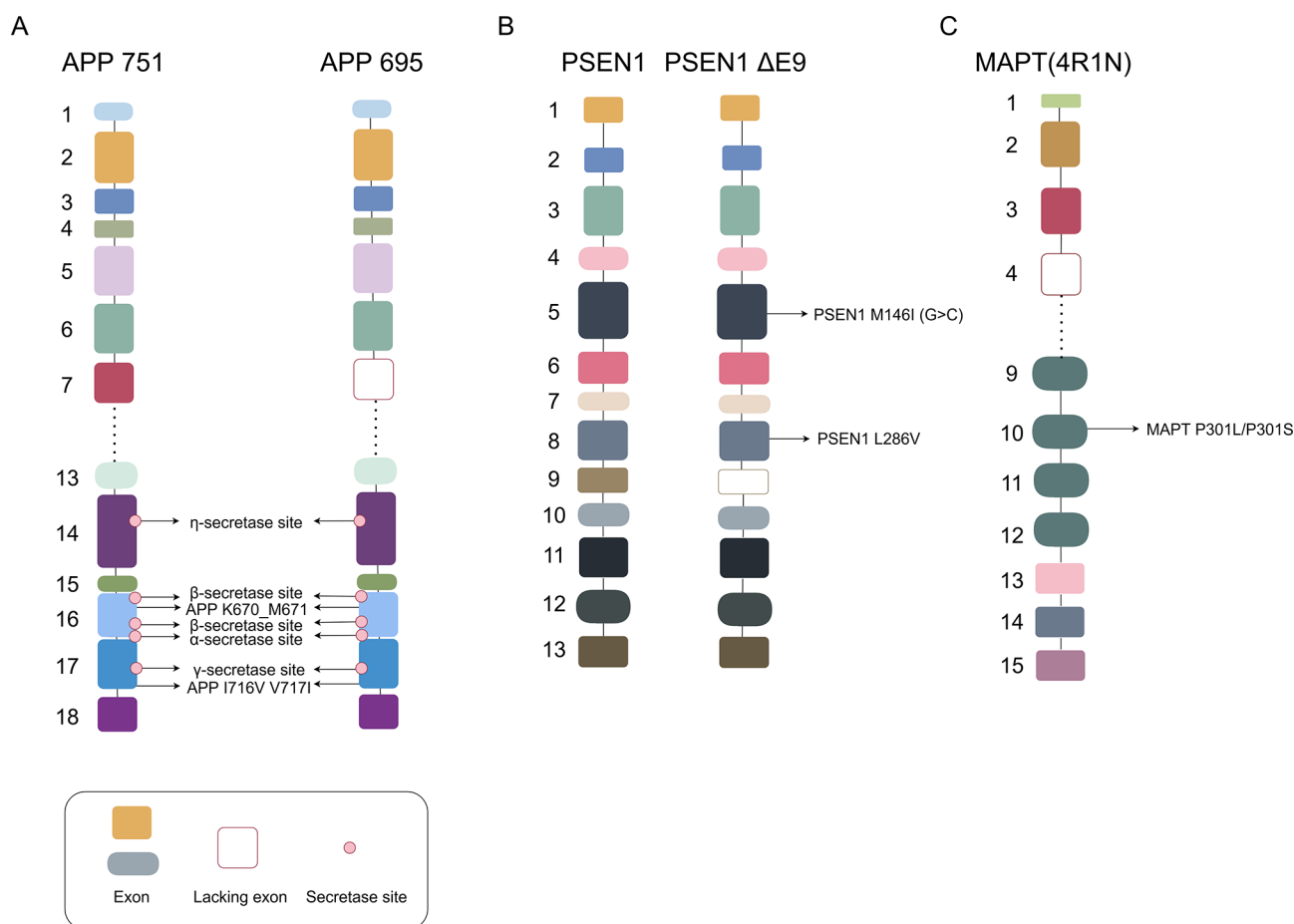


Figure 1 Main pathogenic mutation sites and related secretase sites in FAD associated with *APP* and *PSEN1* and FTD associated with *MAPT*

A: APP isoforms containing 751 or 695 amino acids with main pathogenic mutations, as well as primary secretase cleavage sites: In healthy individuals, α-secretase cleaves APP, producing soluble APP; in disease states, β-secretase and γ-secretase abnormally cleave APP in sequence, initially forming the Aβ peptide fragment. B: Full-length PSEN1 fragments and fragments with exon 9 deletion, as well as main pathogenic mutations. C: Tau 4R1N isoform and its main pathogenic mutations. APP: Amyloid precursor protein; MAPT: Microtubule-associated protein tau; PSEN1: Presenilin-1; FAD: Familial Alzheimer's disease; FTD: Frontotemporal dementia.

their utility in AD research. Currently, widely used transgenic rodent models in AD research encompass several key lines, including Tg2576 (Hsiao et al., 1996), APP23 (Sturchler-Pierrat et al., 1997), APPswe/PS1dE9 (Hsiao et al., 1999), 3xTg (Oddo et al., 2003b), 5xFAD (Oakley et al., 2006), rTg4510 (Berger et al., 2007), and PS19 mice (Santacruz et al., 2005), among others.

In addition to amyloid plaques and NFT pathology, other processes, such as neuroinflammation (activated immune cells and inflammatory mediators), metabolic dysregulation (glucose metabolism and mitochondrial dysfunction), biometal dysregulation (iron and copper accumulation in the brain), and vascular damage (cerebral amyloid angiopathy and microvascular abnormalities), are also highly associated with AD pathogenesis (Graff-Radford et al., 2021), and are often recapitulated in AD animal models. Genes identified through genome-wide association studies, such as *APOE4* and *TREM2*, have been incorporated into transgenic models to explore the pathogenic mechanisms of AD (Kotredes et al., 2021), with models such as *APOE/TREM2* and Thy1-ApoE4/C/EBPβ double transgenic mice serving as pivotal tools in investigating AD-related pathways (Kotredes et al., 2021; Qian et al., 2024). Furthermore, disruptions in

neurotransmitter systems, especially acetylcholine and glutamate, further complicate AD pathophysiology (Hampel et al., 2018; Hsieh et al., 2006; Scott et al., 2011), leading to the development of animal models based on these specific deficits.

While transgenic rodent models have greatly expanded our understanding of AD, species differences and the premature onset of disease symptoms in these models often result in disparities with clinical reality. Naturally occurring AD models, such as those in non-human primates (NHPs), incorporate a wider range of genetic and environmental factors, closely mimicking the complexity of human AD populations (Chen & Zhang, 2022; Yao et al., 2024). These models provide a more comprehensive view of AD heterogeneity, offering potential insights into previously unidentified genetic or environmental contributors to disease development.

This review provides a detailed analysis of the diverse applications of various animal models and examines the three major challenges in AD modeling, namely replicating aging processes, addressing interspecies differences, and capturing sporadic etiology. Additionally, novel animal models designed to overcome these challenges are introduced, offering insights that may enhance future AD model development.

ANIMAL MODELS REPLICATING FAD

Single-transgenic mouse models (*APP* or *MAPT* mutations)

The Tg2576: Tg2576 mouse model, a widely used transgenic model of AD, expresses the *APP*-Swedish mutation (*K670N*, *M671L*) under the control of the *HamPrP* promoter (Hsiao et al., 1996) (Figure 1), resulting in a 5-fold increase in A β 40 peptides and a 14-fold increase in the A β 42/A β 40 ratio.

As early as 2 months of age, Tg2576 mice exhibit intraneuronal soluble A β in the cerebral cortex at detectable pg/mg levels (Manczak et al., 2006). By 3 months, although A β plaques have not yet formed, these mice display hippocampal synaptic dysfunction, increased TUNEL-positive apoptotic cells in dopaminergic neurons, and a marked rise in glial fibrillary acidic protein (GFAP)-positive cells in the ventral tegmental area, findings associated with psychiatric symptoms and suggesting that soluble A β assemblies may impair memory and other brain functions (Nobili et al., 2017). At 6 months, Tg2576 mice show significantly elevated levels of soluble human A β 42 and A β 40, with insoluble A β deposition (plaques) emerging at 7 months (Kawarabayashi et al., 2001). By 12 months of age, A β plaques become more diffuse, forming dense cores within the neocortex and hippocampus (Duffy et al., 2015; Sasaki et al., 2002). Microglial and astrocytic up-regulation of interferon- γ (IFN- γ) and interleukin-12 (IL-12) is observed between 10 and 13 months, indicating microglial activation associated with plaque formation (Abbas et al., 2002; Frautschy et al., 1998). Behavioral changes in Tg2576 mice typically manifest between 8 to 10 months of age (Stewart et al., 2011). While conventional behavioral assays are often employed to assess generalized memory deficits, it is important to acknowledge that specific tests may capture distinct aspects of memory impairment. For example, the forced-choice alternation T-maze test (Deacon & Rawlins, 2006) relies on the natural drive of rodents to explore new environments, providing a measure of spatial working memory sensitive to hippocampal dysfunction, with additional contributions from the prefrontal cortex and basal forebrain (Ito et al., 2018; Lalonde, 2002). In contrast, the spontaneous alternation task in the continuous Y-maze, which assesses working memory in the absence of environmental cues, exhibits reduced sensitivity for detecting memory impairments in Tg2576 mice, potentially masking stereotypic behaviors (Stewart et al., 2011). The Morris water maze (MWM) test (Vorhees & Williams, 2006), which evaluates spatial reference memory—the long-term recall of specific locations in a static environment—is associated with the hippocampal and parahippocampal regions but demonstrates lower sensitivity in Tg2576 mice compared to the T-maze forced-choice alternation test (Cornwell et al., 2008; Stewart et al., 2011).

The Tg2576 model remains a crucial tool in preclinical drug testing due to its stable A β pathology and cognitive impairment profile (Kastanenka et al., 2016). Specifically, A β oligomers (A β o), known for their toxicity, are detectable at a very early age in Tg2576 mice, potentially disrupting memory functions even prior to the appearance of A β plaques (Takahashi et al., 2004). However, certain pathological and behavioral features in Tg2576 mice deviate from clinical manifestations. For instance, plaques in Tg2576 mice exhibit a diffuse, dispersed morphology, contrasting with the dense, stable plaques typically observed in AD patients (Jacobsen et al., 2006). Additionally, psychiatric symptoms, such as

deficits in hippocampal-dependent contextual fear conditioning and alterations in sensorimotor activity, manifest at an early age in Tg2576 mice, differing from the clinical progression of AD symptoms (D'Amelio et al., 2011; King et al., 1999).

The APP23: The APP23 model was designed to express human *APP*751 cDNA with the Swedish (*K670N*/*M671L*) mutation inserted into the *Thy-1* expression cassette, resulting in a 7-fold overexpression of mutant human *APP* (Figure 1). Although APP23 shares the same mutation as Tg2576, it exhibits distinct A β pathology. Unlike the diffuse plaques observed in Tg2576, APP23 mice develop human-like congophilic plaques with a dense, fibrillar amyloid core (Calhoun et al., 1998). This amyloidosis is believed to arise from stochastic formation of A β seeds that subsequently propagate and spread throughout the brain (Eisenberg & Jucker, 2012). Interestingly, A β -containing brain extracts from 22- to 28-month-old APP23 transgenic mice can induce β -amyloidosis in young APP23 mice (Eisele et al., 2009; Heilbronner et al., 2013), suggesting that established amyloid pathology can accelerate amyloid formation in younger animals. Moreover, the seeding activity of APP23 brain extracts reaches a plateau relatively early in the amyloidogenic process (Ye et al., 2017).

Cerebral amyloid angiopathy (CAA), a prominent hallmark of AD, is characterized by the accumulation of A β protein within cerebral blood vessel walls. The APP23 mouse model demonstrates significant CAA pathology, supporting the hypothesis that neuronally derived A β can access and deposit in vessel walls (Calhoun et al., 1999). This CAA pathology in APP23 mice is accompanied by cerebrovascular abnormalities and disruptions in blood flow, with cerebrovascular lesions appearing by 12 months of age, and flow voids detected at the internal carotid artery (Beckmann et al., 2003; Meyer-Luehmann et al., 2008). By 20 months, these mice display flow disturbances in large arteries surrounding the circle of Willis, coupled with cerebral microbleeds (Beckmann et al., 2003; Marazuela et al., 2022). Compared to younger APP23 mice or control groups, aged APP23 mice also show an elevated presence of megakaryocytes in bone marrow and pre-activated platelets, enhancing platelet propensity for thrombus formation under flow and thereby increasing the risk of arterial thrombosis (Jarre et al., 2014). The CAA pathology observed in APP23 mice underscores a potential shared etiological origin between CAA and AD, highlighting the importance of vascular health in AD pathogenesis and pointing to the need for therapeutic strategies that target vascular components.

At 6 months of age, APP23 mice exhibit unique neuropathological features, including distorted neurites with hyperphosphorylated tau—a rare phenomenon among single-gene *APP* mutation models (Sturchler-Pierrat et al., 1997). This observation highlights the potential of A β to trigger excitotoxicity through abnormal tau aggregation, supporting the amyloid cascade hypothesis (Ittner et al., 2010, 2016). Motor and social behavior disturbances also emerge at this age, as evidenced by alterations in cage activity and ambulation in open-field tests (Kelly et al., 2003). By 9 months, APP23 mice also display further signs of AD-related pathology, including immune responses, enlarged dystrophic synaptic boutons in the neuropil, and a breakdown of slow-wave brain activity (Calhoun et al., 1999). An increase in complement component 1q (C1q) mRNA expression is first detected at 9 months, with extensive gliosis, characterized by

hypertrophic astrocytes and activated microglia, closely associated with A β deposits by 12 months (Sturchler-Pierrat et al., 1997). Significant neuritic degeneration and distortion of cholinergic fibers are also evident in regions near amyloid plaques by 9 months of age (Sturchler-Pierrat et al., 1997).

Neuronal damage in APP23 mice progresses subsequent to amyloid plaque pathology, with initial observations in the hippocampal CA1 region occurring at 14 months (Calhoun et al., 1998). By 24 months, an increasing number of neocortical neurons exhibit necrotic-apoptotic phenotypes (Bondolfi et al., 2002). Interestingly, at 8 months, APP23 mice possess approximately 13%–15% more neocortical neurons than their wild-type counterparts (Bondolfi et al., 2002), suggesting that these mice initially maintain elevated neuron counts before experiencing neuronal loss as cerebral amyloidogenesis advances. However, data on long-term potentiation (LTP) in APP23 mice are inconsistent. Roder et al. (2003) found no significant difference in LTP between hemizygous APP23 and wild-type littermates, while Huang et al. (2006) reported reduced LTP in 13–14-month-old APP23 mice, linked with reduced neprilysin activity. These contradictions pose challenges in assessing synaptic function using APP23 mice.

The rTg4510: The rTg4510 mouse model is produced by crossing the 4510-responder line, which carries human *MAPT* P301L cDNA, with an activator line regulated by the forebrain-specific CaMKII α promoter. This cross results in an elevated expression of mutant human tau protein, approximately 13 times higher than that of endogenous mouse tau (Ramsden et al., 2005) (Figure 1).

Tau protein, encoded by the *MAPT* gene, plays a critical role in stabilizing neuronal microtubules. Under pathological conditions, hyperphosphorylated tau detaches from microtubules, leading to cytoskeletal destabilization and impaired neuronal function. The resulting accumulation of hyperphosphorylated tau into NFTs is neurotoxic and a hallmark of neurodegenerative disease. The P301L mutation in the *MAPT* gene, identified across FTD cases globally, poses an increased risk for neurodegeneration (Borrego-Écija et al., 2017; Dumanchin et al., 1998; Gatto et al., 2017; Hutton et al., 1998; Moore et al., 2020; Palencia-Madrid et al., 2019). Although the precise mechanism by which P301L contributes to neurodegeneration remains unclear, studies suggest that the mutated protein may adopt different conformations, contributing to diverse neuropathological outcomes (Daude et al., 2020). Hyperphosphorylated tau with the P301L mutation is more potent in inducing endoplasmic reticulum stress and cytoskeletal damage compared to non-phosphorylated forms, underscoring its role in neurodegenerative diseases (Wang et al., 2023a).

In rTg4510 mice, tau pathology is detectable as early as 6–7 weeks of age, with phosphorylation at Ser202 and abnormal conformations evident in the hippocampus and cortex, identified by CP-13 and MC-1 antibodies, respectively (Ramsden et al., 2005). By later stages, around 10% of cortical neurons become PHF1-positive, closely resembling human tauopathy (Spires et al., 2006). Tau pathology is accompanied by gliosis at approximately 2.5 months of age, as indicated by increased immunoreactivity of GFAP and the microglial marker Iba1 (Helboe et al., 2017). Between 2.5 and 4 months, rTg4510 mice develop a range of cognitive deficits, including impaired spatial memory in the MWM test (Ramsden et al., 2005; Westerman et al., 2002; Yue et al., 2011),

recognition memory deficits in the novel object recognition task (Blackmore et al., 2017; Wes et al., 2014), compromised contextual fear memory in fear conditioning tests (Cook et al., 2014), and hyperactivity in the open-field test (Blackmore et al., 2017; Wes et al., 2014). LTP dysfunction can be observed from 4.5 months of age, followed by declined expression levels of pre- and post-synaptic proteins around 5.5 months, and substantial dendritic spine loss at approximately 9.5 months (Helboe et al., 2017; Hoover et al., 2010; Kopeikina et al., 2013). At 5.5 months of age, hippocampal CA1 neurons show a 60% reduction (Ramsden et al., 2005; Santacruz et al., 2005), while cortical cell loss occurs around 8.5 months (Spires et al., 2006). The rTg4510 mice also exhibit progressive brain weight reduction, which correlates with general body weight loss but may not be specific to tau pathology (Helboe et al., 2017).

Abnormal tau in rTg4510 mice demonstrates a notable capacity for propagation. Thioflavin-S staining reveals tau relocation from axons to soma and dendritic compartments, with spread beyond the entorhinal cortex, correlating with advanced NFT formation in neurons inside the entorhinal cortex (Liu et al., 2012). Phosphorylated high-molecular-weight tau from rTg4510 brain extracts is internalized by neurons and transmitted across synaptically connected neurons (Takeda et al., 2015). These findings highlight the potential of rTg4510 mice for investigating tau-driven neurodegeneration, offering insights into tau spread through neural circuits and degeneration induced by deafferentation.

The rTg4510 mouse model exhibits rapid progression of tau pathology, providing a compressed timeframe to study early tau-related events, including tau seeding. Unlike AD, where NFT pathology typically initiates in limbic structures, rTg4510 mice develop argyrophilic tangle-like inclusions as early as 2.5 months, affecting the cortex by 4 months and hippocampus by 5.5 months (Ramsden et al., 2005; Santacruz et al., 2005). Although tau mutations are not a typical cause of AD, the rTg4510 model serves as a valuable tool for studying tauopathy without the confounding presence of A β pathology, offering insights into the specific mechanisms of tau-driven neurodegeneration.

The PS19: Compared to rTg4510 mice, PS19 mice exhibit slower pathological development (Ramsden et al., 2005). The PS19 model expresses a transgene with the disease-associated P301S mutation, including all four microtubule-binding domains but only one N-terminal domain (4R/1N) (Figure 1). The expression level of mutant human tau is approximately five-fold higher than that of endogenous mouse tau.

Tau seeding activity in PS19 mice is first detected at 1.5 months in the brainstem, neocortex, frontal lobe, and hippocampus, preceding detectable tau pathology by histological methods, suggesting that tau seeding may be an early pathological event (Holmes et al., 2014). By 3 months, misfolded tau is reliably detected in the cortex and hippocampus based on the MC1 marker, while hyperphosphorylated tau becomes evident at 6 months based on the AT8 and PG5 markers (Holmes et al., 2014). Between 3 and 6 months, soluble tau levels decline as insoluble tau deposits, predominantly composed of transgenic human tau, accumulate with age (Yoshiyama et al., 2007). By 6 months, NFT-like inclusions are widely distributed across the neocortex, hippocampus, amygdala, brainstem, and spinal cord (Yoshiyama et al., 2007). However, research has also

reported a delayed appearance of those phenotypes, with prominent hyperphosphorylated tau inclusions and significant neuronal death only emerging at 12 months (Zhang et al., 2012).

Microglial activation in PS19 mice is detectable as early as 3–4 months in the hippocampus without obvious gliosis, suggesting that microglial activation precedes astrogliosis (Dejanovic et al., 2018; Yoshiyama et al., 2007). By 9 months, reactive microglia and astrocytes are prevalent in the hippocampus, associated with increased production of proinflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β) (Litvinchuk et al., 2018). Additionally, PS19 mice show reduced synaptophysin immunoreactivity in the hippocampal CA3 region from 3 to 6 months (Yoshiyama et al., 2007), likely resulting from increased microglial engulfment (Litvinchuk et al., 2018). Consistent with this pathology, PS19 mice display reduced maximum field excitatory postsynaptic potential and paired-pulse facilitation by 6 months, indicative of impaired synaptic transmission (Yoshiyama et al., 2007). No significant alternations in paired-pulse ratio and LTP are observed at 4 months, suggesting that synaptic impairments develop as tau pathology progresses (Dejanovic et al., 2018).

PS19 mice exhibit significant behavioral deficits beginning at 6 months of age. Widespread cognitive impairments include deficits in spatial learning and memory in MWM tests (Takeuchi et al., 2011; Zhang et al., 2014), associative learning and memory in cued and contextual fear conditioning tests and working memory in Y-maze tests (Lasagna-Reeves et al., 2016; Takeuchi et al., 2011; Zhang et al., 2014). Motor impairments in the rotarod test are also evident in 6-month-old mice (Caccamo et al., 2013), which progress to severe motor deficits between 7 and 10 months, characterized by a hunched-back posture and feeding difficulties (Yoshiyama et al., 2007). PS19 mice also show reduced anxiety in open-field tests (Caccamo et al., 2013).

PS19 mice begin to show signs of neuronal loss and brain atrophy by 8 months, with marked hippocampal degeneration at 9 months old (Litvinchuk et al., 2018; Yoshiyama et al., 2007). Neurodegeneration extends to other brain regions, such as the neocortex, entorhinal cortex, and amygdala, by 12 months (Yoshiyama et al., 2007). Significant reductions in neocortical and hippocampal volume are also evident by this stage (Dejanovic et al., 2018; Yoshiyama et al., 2007).

Experimental inoculation of recombinant fibrils or tau strains into transgenic PS19 mice rapidly induces tau pathology, initiating within weeks and spreading to distant, synaptically connected regions (Iba et al., 2013; Sanders et al., 2014). Notably, tau strains isolated from inoculated PS19 mice maintain seeding activity upon passage back into cell models (Sanders et al., 2014). Unlike the spontaneously developed tangles in aged PS19 mice, fibril-induced tau inclusions resemble AD NFTs (Iba et al., 2013). This feature establishes PS19 mice as a reasonable model for investigating the spread of tau pathology and its pathological consequences in AD.

Although not traditionally recognized as AD animal models, knockout of the *App* and *Mapt* genes reveals pathologies relevant to AD. APP knockout mice, first developed in 1995, exhibit reduced forelimb grip strength and decreased locomotor activity (Zheng et al., 1995), accompanied by elevated reactive gliosis in the hippocampus and neocortex (Zheng et al., 1995). Over time, these mice also display age-dependent iron accumulation in the brain (Belaidi et al., 2018),

resulting in cell loss within the substantia nigra (Ayton et al., 2015). This pathology implicates APP in iron metabolism, suggesting that loss of APP function disrupts iron regulation and contributes to neurodegeneration (Duce et al., 2010)—a hypothesis supported by successful iron chelation therapy in APP knockout mice (Lei et al., 2017).

Several tau knockout models have been developed in the last few years (Dawson et al., 2001; Harada et al., 1994; Tan et al., 2018; Tucker et al., 2001). While these mice are viable and present minimal phenotypes up to 6 months of age (Roberson et al., 2007), by 12 months they exhibit age-dependent iron accumulation, neuronal loss, and brain atrophy, as well as cognitive and motor deficits, consistent with the features of AD (Lei et al., 2012). In comparative studies, tau knockout mice on a C57BL6/SV129 background show deficits in the Y-maze cognition task, while those on a BL6 background do not (Lei et al., 2014). Additionally, mice on a C57BL6/SV129 background exhibit olfactory deficits prior to behavioral symptoms (Beauchamp et al., 2018), in accordance with early-stage symptoms seen in AD patients (Murphy, 2019). Reductions in tau levels are also implicated in a variety of conditions associated with AD, including diabetes (Mangiafico et al., 2023), traumatic brain injury (Ding et al., 2024), stroke (Bi et al., 2017; Tuo et al., 2017), and Parkinson's disease (Chen et al., 2023; Pan et al., 2022). These findings highlight the significance of tau in a variety of neurodegenerative and systemic conditions, providing valuable insights into the origins and progression of tau pathology in AD.

Double transgenic mouse models

In addition to mutations in *APP*, FAD studies have also identified disease-causing mutations in *PSEN1* and *PSEN2* genetic loci, which encode presenilin 1 (PS1) and presenilin 2 (PS2), respectively. Specifically, an in-frame deletion of exon 9 (PS1 delta9) (Perez-Tur et al., 1995) within the *PSEN1* gene has been found in families affected by FAD (Figure 1). Both PS1 and PS2 affect APP processing (Jiang et al., 2018), leading to the development of double transgenic mice expressing both mutant APP and PS1 as models of AD (Jankowsky et al., 2001, 2004). Since then, various double transgenic mice models have been generated, ultimately becoming important tools for evaluating potential therapeutic interventions.

APP^{swE}/PS1^{dE9}: APP/PS1 double transgenic animal models are based on the Swedish mutation in *APP* combined with specific *PSEN1* variants, such as *M146L* (Duff et al., 1996), *A246E* (Borchelt et al., 1996, 1997), and *L166P* (Radde et al., 2006) (Figure 1). By co-injecting two vectors, one encoding *APP* with the Swedish mutation and another encoding *PSEN1* with the del-E9 mutation, Jankowsky et al. (2001) generated APP^{swE}/PS1^{dE9} (line 85) mice on a C57BL/6J genetic background. Comparative studies confirmed the superior onset time and intensity of the del-E9 mutation, establishing it as one of the most widely used strains. When further backcrossed with C57BL/6J mice, APP^{swE}/PS1^{dE9} hemizygotes exhibit a high incidence of seizures, as detected by video-electroencephalography (Minkeviciene et al., 2008, 2009).

APP^{swE}/PS1^{dE9} mice display an early onset of plaque formation, in contrast to single APP-overexpressing models. By 3 months, small and rare plaques can be detected in the cortex and hippocampus *ex vivo* using thioflavin S or 3D6

(Garcia-Alloza et al., 2006; Unger et al., 2016). At 6 months, levels of insoluble A β 42 increase, with occasional deposits detectable in the cortex and hippocampus (Garcia-Alloza et al., 2006). By 24 months, widespread A β deposition is evident throughout the brain, accompanied by heightened neuroinflammation marked by cortical IL-1 β and TNF- α expression (D'Angelo et al., 2021). In line with the APP23 model, APPswe/PSEN1dE9 mice exhibit prominent and compact congophilic A β deposits, with dense core plaques forming near, rather than inside, blood vessels, implying limited vascular involvement (Meyer-Luehmann et al., 2008). APPswe/PSEN1dE9 mice also show elevated synaptic A β levels, contributing to presynaptic dysfunction (Koffie et al., 2009; Roy et al., 2016; West et al., 2009). Both *in vitro* and *in vivo* studies have revealed that A β 42 monomers and oligomers disrupt SNARE complex assembly in APPswe/PSEN1dE9 mice (Yang et al., 2015), consistent with diminished SNARE complex formation observed in postmortem AD brains (Sharma et al., 2012). Neurons in the hippocampal CA1 region of 6-month-old APPswe/PS1dE9 mice exhibit degeneration, shrinkage, and necrosis, with modest neuronal loss observed near plaques between 8 and 10 months, relative to more preserved neurons in distal regions (Daniels et al., 2016; Shi et al., 2018).

Despite the dual genetic mutations, cognitive decline in APPswe/PSEN1dE9 mice does not manifest substantially earlier than in mice with single genetic mutations. APPswe/PSEN1dE9 mice start to exhibit memory impairment in the contextual fear conditioning task by 6 months (Cramer et al., 2012; Kilgore et al., 2010), with deficits in spatial learning and passive avoidance acquisition becoming evident in the MWM and passive avoidance tests between 8 and 13 months (Ding et al., 2008; Fang et al., 2019; Gimbel et al., 2010; Jo et al., 2014). Additionally, impairments in spatial learning and recognition memory are noted at 9 months in the radial arm water maze and object recognition tasks, coinciding with widespread plaque deposition in the hippocampus and cortex (Cramer et al., 2012; Lewis et al., 2010; McClean et al., 2011).

Neuroinflammatory responses in APPswe/PSEN1dE9 mice have been extensively characterized, revealing plaque-associated reactive gliosis, primarily involving GFAP-positive reactive astrocytes within the cortex by 6 months (Kamphuis et al., 2012). Microgliosis follows 1–2 months later, accompanied by a surge in proinflammatory cytokines. These mice exhibit elevated CD11b- and CD45-positive microglia and increased levels of IL-6 and TNF- α in isolated brain microglia (Fang et al., 2019; Kim et al., 2009). Notably, astrocyte-microglia interactions are thought to influence amyloid pathology, potentially through complement activation mechanisms (Lian et al., 2016).

In APPswe/PSEN1dE9 mice, the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome has also been identified as a crucial factor in sterile neuroinflammation (Milner et al., 2021), mirroring observations in AD patients (Rui et al., 2021). Inhibition of NLRP3 in these mice has been shown to reduce A β load and neuroinflammation and improve synaptic plasticity (Heneka et al., 2013; Venegas et al., 2017), suggesting a role in modulating AD pathology. Based on these findings, novel NLRP3 inflammasome inhibitors have been developed for potential clinical application (Coll et al., 2015).

APPswe/PSEN1dE9 mice serve as a valuable tool in AD

research, particularly for investigating A β pathology, neuroinflammation, and memory decline. However, research on synaptic plasticity within AD mouse models has yielded contradictory findings. Specifically, some studies have reported impairments in high-frequency stimulation (HFS)-triggered hippocampal Schaffer collateral-CA1 LTP following amyloid plaque accumulation (Fu et al., 2014; Ma et al., 2013), while other studies have suggested that A β accumulation during aging does not significantly change synaptic transmission or sustained LTP in hippocampal slices (Volianskis et al., 2010). Considering that AD patients carrying both *APP* and *PSEN1* mutations are rare, the pathology observed in this model may be artificial.

5xFAD: The 5xFAD mouse model exemplifies a rapidly progressing APP/PS1 double transgenic mouse model of AD that co-expresses three human *APP* mutations (Swedish (K670N, M671L), Florida (I716V), and London (V717I) mutations) and two *PSEN1* mutations (M146L, L286V) (Figure 1). This model is characterized by extensive amyloid pathology without notable tau accumulation, providing a robust system for investigating amyloid-driven AD pathology.

Amyloid accumulation in 5xFAD mice is detectable as early as 6 weeks, primarily driven by intraneuronal A β 42 accumulation (Oakley et al., 2006). By 2 months, extracellular amyloid deposition is observed in the subiculum and cortical layer V (Oakley et al., 2006), progressively spreading to the outer cortical layers, hippocampal CA1 region, and eventually to the thalamus, brainstem, and olfactory bulb in an age-dependent manner (Jawhar et al., 2012; Oakley et al., 2006; Youmans et al., 2012). PET imaging has revealed amyloid deposition from 4 months in several cortical regions, including the thalamus and motor cortex. Notably, 5xFAD mice exhibit sex-specific differences in plaque pathology, with females displaying a more pronounced plaque burden (Sil et al., 2022), mirroring sex disparities in human AD.

Synaptic deterioration in 5xFAD mice accompanies plaque accumulation (Oakley et al., 2006; Peretti et al., 2015). Beginning at 4 months, basal synaptic transmission and LTP in the hippocampal CA1 region deteriorate (Crouzin et al., 2013; Kimura & Ohno, 2009). By 6 months, there is a marked loss of mushroom and dendritic spines in CA1 pyramidal and dentate gyrus (DG) granule neurons (Busche et al., 2012). Neuronal density shows a substantial decrease in specific brain regions, such as the ventral horn, by 12 months, coinciding with motor impairment onset (Jawhar et al., 2012). Among AD mouse models, 5xFAD mice demonstrate significant molecular overlap with human AD pathology, encompassing not only amyloid and tau but also neuroinflammation, endolysosomal function, and synapse formation, as revealed through transcriptomic analyses of microglia and bulk brain tissues (Zhong et al., 2024). These findings suggest that the 5xFAD model closely reflects human AD, making it particularly valuable for studying neuroinflammation and endolysosomal dysfunction.

The 5xFAD model also recapitulates amyloid deposition in the spinal cord, paralleling findings in FAD cases (Ogumori et al., 1989). In these mice, spinal cord amyloid pathology becomes evident at 3 months, initially in cervical and lumbar regions and progressively extending along the cord by approximately 5 months (MacPherson et al., 2017).

The 5xFAD mouse model features rapid progression of cognitive impairment, with detectable deficits in spatial working memory in the Y-maze as early as 4–5 months

(Oakley et al., 2006) and further deterioration in memory performance in contextual-fear-conditioning (Kimura & Ohno, 2009). By 6 months, behavioral impairments become pronounced, including deficits in spatial memory assessed via the MWM test (Busche et al., 2012; Ceglia et al., 2015). Starting from 6 months, 5xFAD mice also exhibit abnormal social behaviors, such as excessive social engagement during home-cage observations, with increased sniffing, following, and mounting behaviors indicative of impaired social recognition (Flanigan et al., 2014). Despite conflicting reports on anxiety levels in 5xFAD mice (Flanigan et al., 2014; O'Leary et al., 2018), hyperactivity, an indicator of anxiety, is consistently observed in this model (Merlini et al., 2019; Oblak et al., 2021).

Distinct from other AD models, 5xFAD mice are considered a reliable model for investigating sensory deficits, as they demonstrate reduced acoustic startle responses and impaired olfactory-guided behaviors as early as 3 to 4 months (Ceglia et al., 2015; O'Leary et al., 2017). In addition, deficits in basal synaptic transmission in layer V of the somatosensory cortex emerge at 6 months (Crouzin et al., 2013). Autoradiographic studies have further revealed alterations in glycolysis in 5xFAD mice compared to wild-type controls (Oblak et al., 2021).

Triple-transgenic mouse models

The 3xTg-AD mouse model was developed to closely replicate human AD pathology by combining both A β and tau deposition, two key features that synergistically drive neurodegeneration (Li et al., 2015; Shipton et al., 2022). In conventional rodent models overexpressing mutated APP, tau aggregation is rarely observed, except in the APP23 line, and transgenic tau models typically develop NFTs without amyloid plaques. To address this limitation, the 3xTg model incorporates three mutations associated with AD pathology, namely *APP* Swedish, *MAPT* P301L, and *PSEN1* M146V (Figure 1).

3xTg-AD mice were generated by injecting single-cell embryos from a mouse line carrying the *PSEN1* M146V knock-in mutation with two human transgenes: *APP* with the Swedish mutation and *MAPT* with the P301L mutation. Expression of these transgenes is driven by the Thy1.2 promoter, leading to predominant expression in the central nervous system, as confirmed through protein expression analyses (Oddo et al., 2003b). By 4 months, 3xTg-AD mice exhibit a two-fold increase in tau and APP expression in the brain (Oddo et al., 2003b).

A β accumulation in the 3xTg mice is age-dependent, with a pronounced elevation in A β 42 levels. At 3 months, minimal A β immunoreactivity is detected in the hippocampal CA1 region, where A β primarily exists in a soluble, monomeric form (Oddo et al., 2006; Yao et al., 2009). In this model, A β appears to migrate from intracellular to extracellular compartments, with intracellular A β immunoreactivity in cortical regions the first clear neuropathological manifestation, occurring between 3 and 4 months of age (Oddo et al., 2003a). By 6 months, extracellular A β deposits appear in the frontal cortex, progressing to overt amyloid plaque formation by 12 months (Oddo et al., 2003b, 2006; Yao et al., 2009).

Tau pathology in 3xTg-AD mice also follows an age-dependent progression. Initial signs of tau pathology are visible by 6 months, with HT7-positive tau immunoreactivity accumulating in the somatodendritic compartment of the hippocampal pyramidal neurons in the CA1 region, which

intensifies by 12 months (Oddo et al., 2003a, 2006). Misfolded tau, detectable with the PHF-1 antibody, emerges at about 18 months of age (Oddo et al., 2003a), while neurons with hyperphosphorylated tau and elevated levels of phosphorylated and total tau in the hippocampus are readily apparent between 12 to 15 months (Fang et al., 2019; Oddo et al., 2003a).

Microglial activation in 3xTg mice closely mirrors the age-related increase in amyloid burden, with 15-month-old mice developing intracellular aggregates that resemble small plaques and A β accumulation in lysosomal compartments (Spangenberg et al., 2019). By 24 months, activated microglia colocalize with extraneuronal A β -immunopositive deposits in various brain regions (Kitazawa et al., 2005). Inflammatory processes differentially affect A β and tau, potentially influencing tau pathology onset and development. Notably, IL-1 β overexpression in 3xTg-AD mice significantly promotes tau phosphorylation and exacerbates tau pathology, emphasizing the complex interplay among inflammation, A β , and tau in AD (Ghosh et al., 2013; Kitazawa et al., 2005). Levels of key inflammatory markers, such as CC chemokine ligand 4, CXCL1, and granulocyte-colony stimulating factor, markedly increase between 21 and 24 months (Barber et al., 2024).

With its tau pathology, the 3xTg-AD model can be used to investigate the mechanistic links between A β and tau. A β pathology precedes tau pathology in these mice, consistent with the amyloid cascade hypothesis. Anatomical studies of the hippocampus in 3xTg-AD mice reveal early and prominent colocalization of A β and tau pathologies at CA1 synapses (Takahashi et al., 2010). By 12 months, A β and tau immunoreactivity colocalize within the somatodendritic compartments of the same neurons, further supporting the theory that A β influences tau pathology (Oddo et al., 2003a, 2006). A β oligomers also inhibit proteasome activity, exacerbating age-related accumulation of A β and tau (Tseng et al., 2008). Targeted immunization against A β 42 demonstrates potential in alleviating amyloid and tau aggregation (Oddo et al., 2008; Rosenberg et al., 2018). Notably, while elevated tau levels and hyperphosphorylation do not directly affect A β pathology (Oddo et al., 2007), tau appears to be essential for A β toxicity (Peters et al., 2019). These findings partially substantiate the amyloid cascade hypothesis.

Roberson et al. (2007) developed a double transgenic model by crossing human *APP* transgenic mice with *MAPT* knock-out mice to study the interplay between tau and A β . They found that reducing tau did not impact A β plaque deposition, neuritic dystrophy, or aberrant sprouting, but it effectively prevented water maze deficits, behavioral abnormalities, and premature mortality in mice aged 4–7 months. Tau reduction also increased resistance to excitotoxin-induced seizures (Ittner et al., 2010; Roberson et al., 2007).

Knock-in rodent animal models

All APP-overexpressing mouse models generate elevated levels of C-terminal fragment β (CTF- β), a product of APP cleavage by β -secretase. However, the levels and distribution of these proteins in transgenic mice often do not accurately reflect human AD, limiting their translational relevance (Saito et al., 2014). Moreover, CTF- β has been shown to be potentially more neurotoxic than A β itself (Mitani et al., 2012). Due to shared epitopes near the amino terminus and mid-region of the sequence, CTF- β can bind to many therapeutic

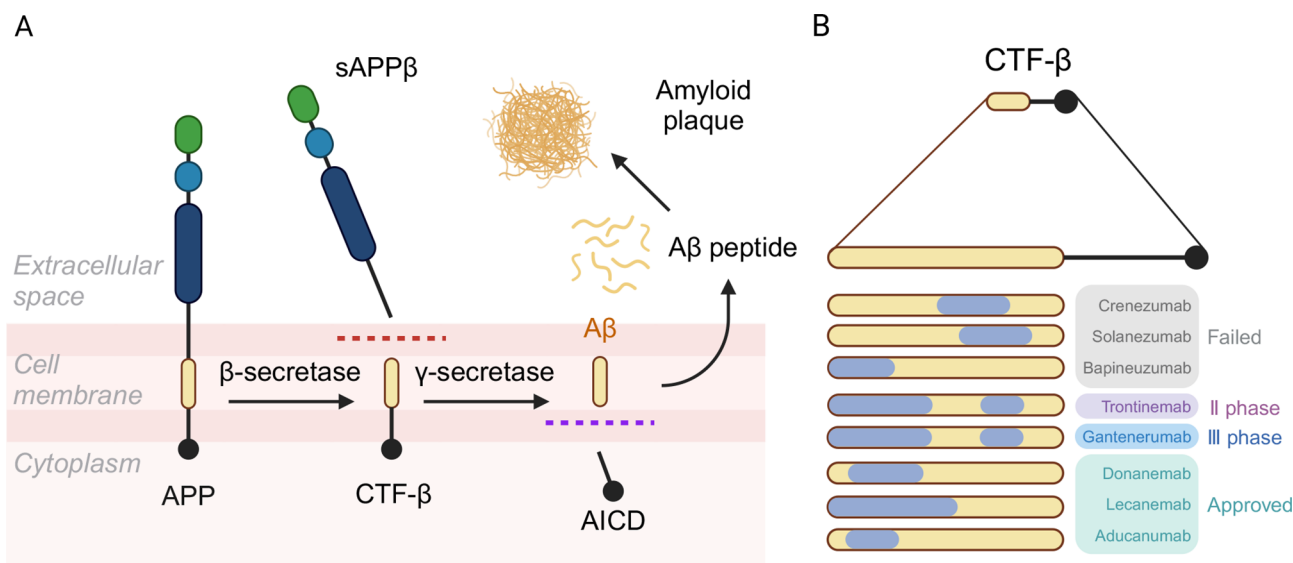


Figure 2 Formation of CTF-β and antibody epitopes

A: After cleavage by β-secretase, APP forms the sAPPβ peptide (extracellular segment of APP in the generation of Aβ) and CTF-β peptide (intracellular segment of APP in the generation of Aβ). B: Correspondence between CTF-β and targets of major pipeline drugs aimed at amyloid plaques, showing that CTF-β can bind to all therapeutic anti-Aβ antibodies (<https://clinicaltrials.gov/>). APP: Amyloid precursor protein; AICD: APP intracellular domain; sAPPβ: Soluble peptide APPβ; CTF-β: Carboxy-terminal fragment β.

anti-Aβ antibodies (Karran & De Strooper, 2022) (Figure 2). Considering that human AD does not require excessive APP or tau protein levels, a model incorporating humanized protein sequences may better replicate disease mechanisms.

App knock-in mice: To address the above limitations, Saito et al. (2014) developed *App* knock-in mice by humanizing the murine Aβ sequence and sequentially introducing Swedish, Beyreuther/Iberian, and Arctic mutations, creating the *App*^{NL/NL}, *App*^{NL-F/NL-F}, and *App*^{NL-G-F/NL-G-F} lines, respectively. These knock-in mice express APP and APP intracellular domain (AICD) in amounts comparable to wild-type mice but generate more Aβ42, resulting in a significantly elevated Aβ42/Aβ40 ratio (Saito et al., 2014). This design makes *App* knock-in models particularly valuable for distinguishing genuine disease processes from artifacts often observed in transgenic *App* mice.

App knock-in mice exhibit progressive, age-dependent Aβ pathology, neuroinflammation, and cognitive decline. Aβ deposition begins at 6 months in the *App*^{NL-F/NL-F} model (Saito et al., 2014) but at 3 months in the *App*^{NL-G-F/NL-G-F} model (Chen et al., 2020; Saito et al., 2014). Both *App*^{NL-F/NL-F} and *App*^{NL-G-F/NL-G-F} mice demonstrate cognitive impairments, including reduced spatial reversal learning, enhanced impulsivity, and increased compulsivity (Masuda et al., 2016; Saito et al., 2014). Consistent with extensive Aβ deposition, *App*^{NL-G-F/NL-G-F} mice exhibit evident memory impairment by 6 months, while *App*^{NL-F/NL-F} mice show similar abnormalities at 10 months (Masuda et al., 2016). Memory impairments are observed in place avoidance learning tasks in both models, with enhanced compulsive behaviors detected in delay-discounting tasks (Masuda et al., 2016). Notably, deficits in reversal learning and attention emerge later than compulsivity, indicating distinct regional brain involvement underlying these behavioral changes.

Tau seeding studies in *App*^{NL-F/NL-F} mice have demonstrated the formation of NFTs and other tau pathologies following injection with AD-derived tau from a human case of AD. In 15-month-old AD-*App*^{NL-F/NL-F} mice, initial tau pathology appears

within one month post-infection, and progressively spreads across the hippocampus and various cortical regions over a period of one to six months. The pathology begins as tau deposits within neuronal processes and later develops into widespread NFTs, likely due to secondary seeding events that drive the expansion of tau aggregates (He et al., 2018).

Given their humanized Aβ sequence, *App*^{NL-F/NL-F} mice serve as an effective tool to investigate the molecular mechanisms underlying Aβ deposition (Saito et al., 2014). For instance, a deficiency in autophagy-related gene 7 disrupts Aβ secretion, leading to intracellular Aβ accumulation and neurodegeneration in the absence of tau pathology (Nilsson et al., 2013). This finding suggests the existence of a pathway that directly links intracellular Aβ to neurodegeneration, bypassing tauopathy.

APP knock-in rats: Gene manipulation in rats remains less advanced than in mice, resulting in fewer rat models of AD. However, due to their closer genomic similarities to humans, rats may provide a more relevant model for studying AD (Pang et al., 2022). To leverage these advantages, *App*^{NL-G-F} rats carrying three human FAD mutations have been developed. This model exhibits Aβ plaque deposition in key brain areas, accompanied by microglial activation and proliferation, progressive synaptic degeneration, and cognitive impairments, closely mirroring the symptoms of AD observed in humans. Interestingly, *App*^{NL-G-F} rats also display tau pathology, neuronal cell death, and brain atrophy—phenotypes rarely observed in other APP-based models.

In *App*^{NL-G-F} rats, Aβ plaques predominantly accumulate in the neocortex, followed by the thalamus, brainstem, striatum, and other brain regions, with minimal vascular-related deposition observed in early AD stages (Chen & Zhang, 2022). Both apoptosis and necroptosis are evident in neuronal populations, resulting in severe cerebral cortex atrophy. This model is the first to demonstrate ventricular enlargement in an AD animal model. When directly compared to the *App* knock-in mice constructed by Saito et al. (2014), *App*^{NL-G-F} rats show tau pathology, sustained neuronal death, and resulting brain

atrophy, suggesting closer alignment with human AD pathology (Pang et al., 2022).

The complex pathology displayed by *App*^{NL-G-F} knock-in rats provides an opportunity to study interactions between different disease mechanisms. This model also enables direct comparisons of molecules targeting various pathways within a single preclinical system. Similar to APP23 mice, *App*^{NL-G-F} rats are particularly useful for investigating the impacts of A β on tau pathology in AD, addressing the crucial question of whether tau aggregation is a consequence of A β deposition or an independent factor causing neurodegeneration. Furthermore, compared to mouse models, rats offer advantages in genetic homology and brain structure similarity, making them well-suited for drug testing, biomarker discovery, and omics-based research. However, *App*^{NL-G-F} rats have yet to be widely distributed and evaluated across multiple research laboratories.

MAPT knock-in mice: Although studies have noted an abnormal increase in 4R-tau isoforms in AD and tau pathologies, tau splicing analysis remains challenging in existing mouse models due to the lack of models expressing all human tau isoforms without overexpression. To address this, a *MAPT* knock-in mouse model was developed as early as 2005 through homologous recombination, replacing all murine tau isoforms with wild-type human tau-4R/2N to create Tau-KOKI mice (Terwel et al., 2005). These mice express normal levels of tau protein, allowing researchers to investigate the underlying mechanisms of tau pathogenesis. For example, while tau-4R/2N in Tau-KOKI mice exhibits greater phosphorylation compared to tau in Tau-P301L mice, Tau-KOKI mice live a normal lifespan, showing only minor motor deficits in old age without significant tau pathology (Terwel et al., 2005). This finding suggests that tau phosphorylation alone does not necessarily induce pathological changes; instead, conformational changes in tau may also contribute to the development of pathology. In P301S mice, tau exhibited abnormal dendritic mislocalization, whereas both *MAPT*- and P301L-knock-in mice maintain correct axonal localization, implying that excessive tau expression, rather than specific mutations, may drive mislocalization (Benderradji et al., 2022; Hashimoto et al., 2019; Saito et al., 2019). Despite these insights, overt tau pathology is rarely observed in *MAPT* knock-in models. However, PLB2Tau mice, which express two tau mutations, show increased levels of phosphorylated tau, neuroinflammation, and early-set behavioral changes, including heightened anxiety, depressive/apathetic behavior, and reduced exploratory activity (Koss et al., 2016). By 8 months, these mice also develop hyperglycemia, indicative of a diabetic phenotype (Hull et al., 2020), similar to observations in the P301L-knock-in model with impaired glucose-stimulated insulin secretion in pancreatic β -cells (Benderradji et al., 2022).

To investigate the interaction between A β and tau pathologies, Hashimoto et al. (2019) and Saito et al. (2019) developed double knock-in (*App*^{NL-G-F}/*MAPT* dKI) mice by cross-breeding *MAPT* knock-in mice with single *App*^{NL-G-F} mice and found that A β amyloidosis intensifies tau accumulation and is closely associated with dystrophic neurites, underscoring its role in tau pathology. Cognitive deficits, such as those in object-place association tasks, emerge as early as 4 months, accompanied by tau pathology in the medial temporal cortex and increased c-Fos activation, suggesting

early perirhinal-entorhinal involvement. The pathology appears to progress through regions, including the claustrum, medial prefrontal cortex, and ultimately the retrosplenial hub, linking frontal and temporal brain areas (Benskey et al., 2023).

Overall, AD models with APP or tau mutations replicate essential AD characteristics, including neuroinflammation, synaptic damage, neuronal loss, and cognitive decline. Transgenic models based on APP and tau mutations exhibit clear early-onset symptoms and show evidence of protein seeding. However, there is no definitive pattern regarding the onset timing or specific morphology of these phenotypes, as shown in Figure 3. Intriguingly, although APP mutant mice rarely form tau tangles, elevated tau phosphorylation levels have been observed sporadically, with each model reflecting the pathologies associated with their respective mutations.

Non-rodent genetic models

In addition to the widely used rodent models, classical model organisms such as *Danio rerio* (zebrafish), *Drosophila melanogaster*, and *Caenorhabditis elegans* offer valuable systems for mimicking AD (Chen & Zhang, 2022). Their advantages, including low cost, short life span, and easy genetic manipulation, make them highly suitable for preliminary drug screening and investigations into AD pathogenesis (Figure 4).

Zebrafish have proven effective in drug screening due to their accessible delivery methods (Kalueff et al., 2014) and exhibit AD-like behaviors, such as avoidance and impaired habituation to startling stimuli (Best et al., 2008). *Drosophila melanogaster* is highly amenable to genetic manipulation, enabling the development of diverse AD models through mutations in genes such as *APP*, *MAPT*, and *BACE1*. For example, models co-overexpressing APP and BACE1 show age-dependent neurodegeneration and deposition of A β plaques (Ogunsuyi et al., 2022). *Caenorhabditis elegans*, which retains functional synapses, demonstrates significant responses to external stimuli, making it a valuable model for studying neuronal decline. For instance, AD models overexpressing A β 42 exhibit intracellular A β accumulation, chemotaxis deficits, and hypersensitivity to serotonin, mimicking aspects of AD pathology (Link, 2006; Wu et al., 2006).

Despite their utility, these models have notable limitations due to significant differences in brain structures compared to humans. As lower-order species, their capacity to assess cognitive functions, a clinical endpoint of AD, remains limited. Consequently, these models are better suited for drug screening and mechanistic studies rather than for validating the clinical efficacy of therapeutic interventions. Nevertheless, they can serve as effective models for preliminary identification of potential therapeutic targets, providing important insights that can inform and guide subsequent research efforts.

ANIMAL MODELS FOR LATE-ONSET SPORADIC AD

Transgenic AD animal models commonly rely on the expression of alleles that induce A β aggregation, typically manifesting pathology during adolescence or early adulthood (Sasaguri et al., 2017). However, AD is fundamentally an age-related disorder, characterized by the gradual accumulation of pathological changes over time, a core aspect of its etiology. Given the age equivalence between mice and humans, the early onset of cognitive impairment in these classical AD

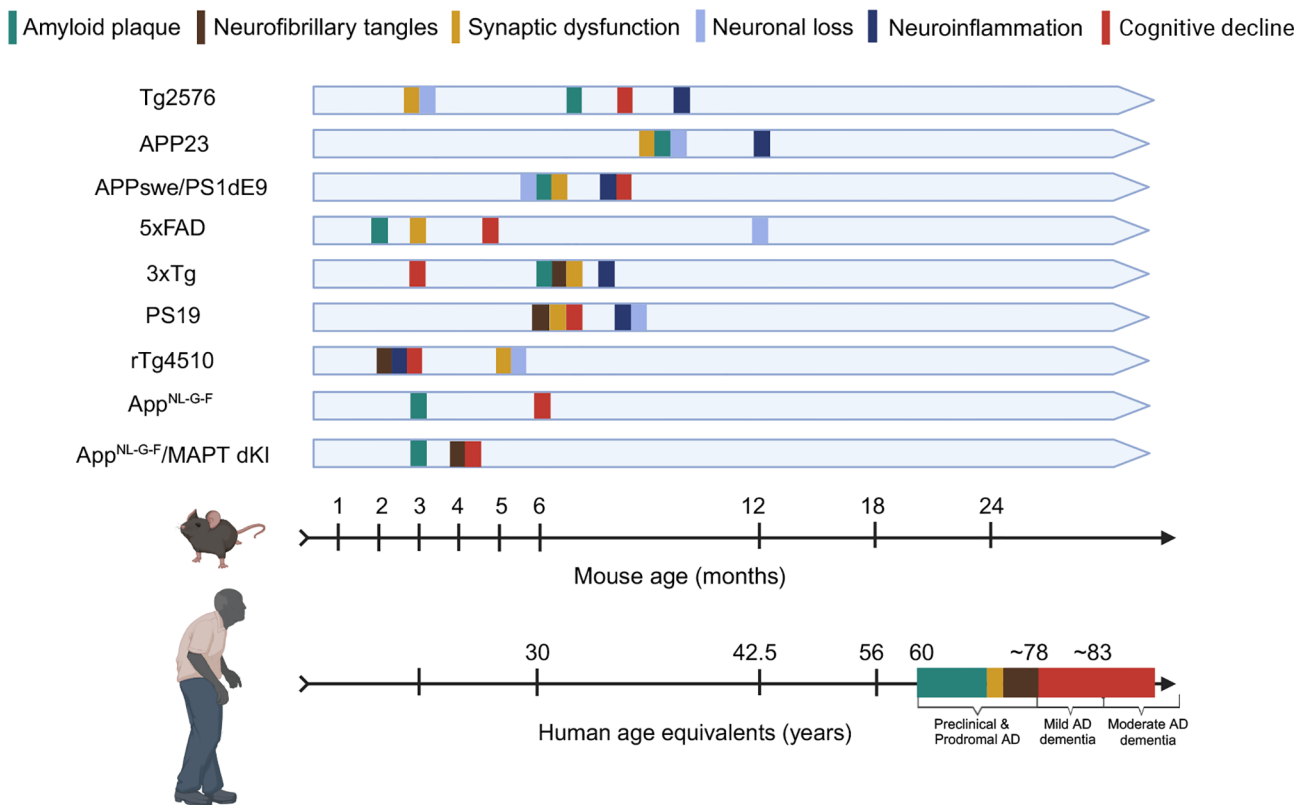


Figure 3 Timeline of pathological progression in AD transgenic mouse models with reference to human age

Timeline illustrates age at which various pathological features emerge in different transgenic mouse models for AD. Specific transgenic models (Tg2576, APP23, APPswe/PS1dE9, 5xFAD, 3xTg, PS19, rTg4510, APP knock-in mice) are listed for clarity. Mouse Age (Months) vs. Human Age (Approximate Correspondence) (Vermunt et al., 2019) (Preclinical & Prodromal AD; Mild AD dementia; Moderate AD dementia) (Johnson et al., 2023).

models does not align with the typical onset age of 65 years in most sporadic cases. Consequently, these models may not fully represent the complexity of the disease, particularly in elderly individuals, and fail to replicate critical aspects such as the inflammatory response and changes in neurotransmitter systems (Krauthausen et al., 2015).

One approach to bridge this gap is to construct natural aging models through phenotype screening and selective breeding, which can better capture the delayed onset of cognitive decline associated with sporadic AD. NHPs may be particularly valuable in this area, offering closer physiological parallels to human aging. Simultaneously, advances in next-generation sequencing have uncovered novel AD risk factors and molecular pathways implicated in disease pathogenesis. With sophisticated genome-editing tools like CRISPR, researchers can now efficiently generate specific genetic mutations in mice, accelerating the production of models that better mirror the genetic complexity and gradual progression of late-onset sporadic AD.

APOE/TREM2 mouse models

In a landmark 1993 study, Strittmatter and colleagues identified a strong association between the *APOE4* allele and an elevated risk of developing sporadic AD (Corder et al., 1993), a discovery subsequently confirmed by multiple genome-wide association studies (Beecham et al., 2009; Bertram et al., 2008; Coon et al., 2007; Grupe et al., 2007; Lambert et al., 2013; Li et al., 2008). Carriers of the *APOE4* genotype often show signs of systemic metabolic dysfunction years before the emergence of AD. A single *APOE4* allele, characterized by a Cys112-to-Arg112 amino acid substitution,

increases AD risk by 3–4 times, while homozygous carriers face an 8–12 times greater risk (Corder et al., 1993).

To investigate the effects of *APOE* in an AD context, researchers have developed mouse models with humanized *APOE* alleles inserted into the mouse genome (Foley et al., 2022; Huynh et al., 2019; Mann et al., 2004), resulting in mice with distinct phenotypes related to neuronal function, mitochondrial dysfunction, and impaired insulin signaling. However, despite these phenotypic similarities to humans, these mice do not develop hallmark amyloid plaques or tau tangles (Hauptmann et al., 2009; Johnson et al., 2017).

TREM2, a surface receptor expressed on microglia, initiates intracellular protein tyrosine phosphorylation pathways and plays a pivotal role in regulating microglial function. A rare mutation of *TREM2*, involving the substitution of histidine for arginine at position 47 (*R47H*), is strongly associated with an increased risk of developing AD (Guerreiro et al., 2013; Jonsson et al., 2013). *TREM2 R47H* knock-in mice exhibit reduced Trem2 expression and a decreased density of microglia in the hippocampus, indicating impaired microglial function (Liu et al., 2020). Studies using siRNA-mediated Trem2 knockout in microglia have shown that *TREM2* facilitates a shift in microglial activity from an inflammatory cytokine-producing phenotype to one that is phagocytic and anti-inflammatory (Liu et al., 2020). This mechanism may underlie the heightened microglial density surrounding amyloid plaques observed in AD.

To better model sporadic, late-onset AD, researchers developed the B6.*APOE4*.Trem2^{R47H} mouse model, which features a humanized ApoE knock-in mutation, encoding for

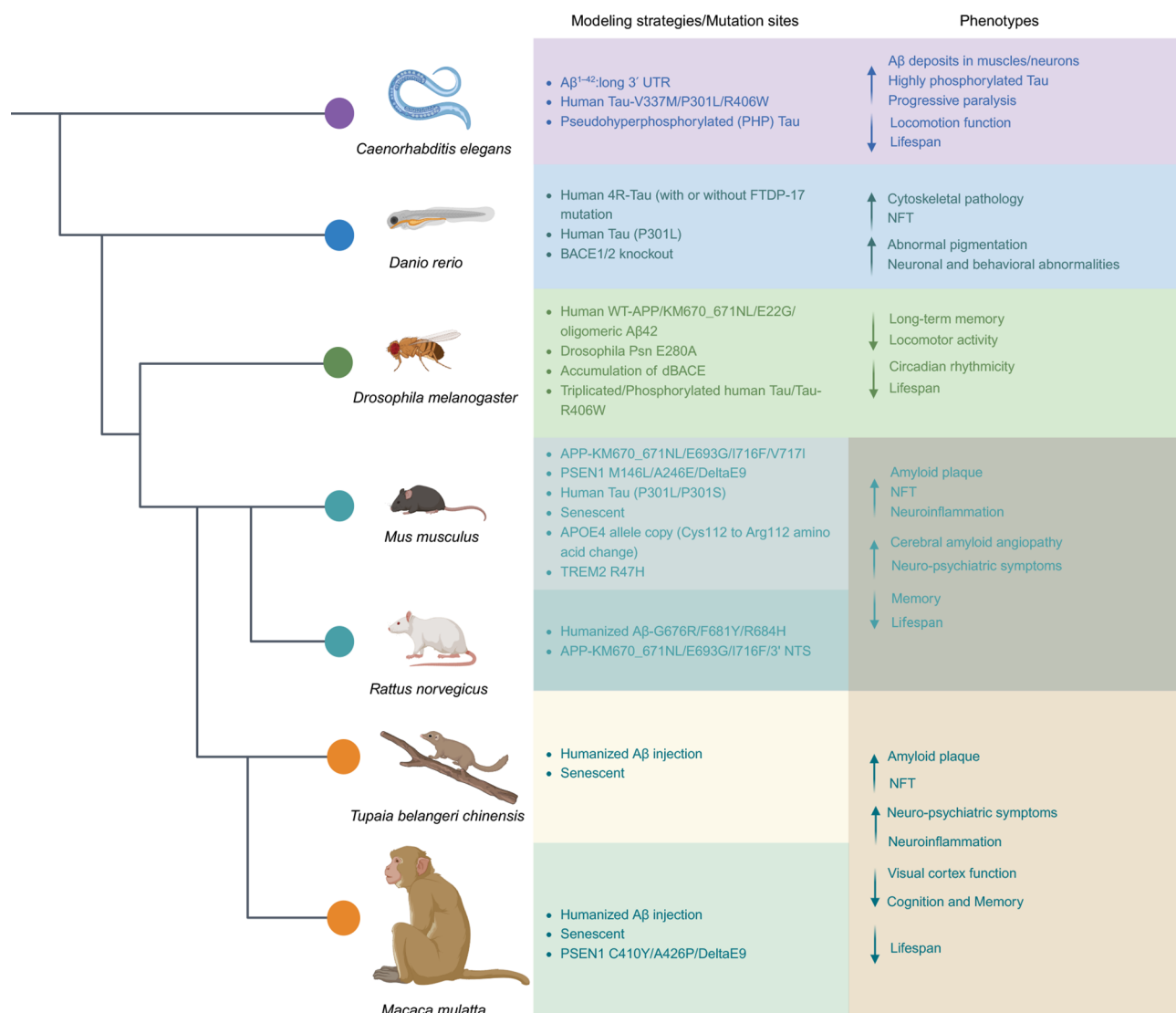


Figure 4 Modeling strategies/mutation sites and main phenotypes of principal model organisms used in AD research

Principal model organisms include *Caenorhabditis elegans*, *Danio rerio* (Zebrafish), *Drosophila melanogaster*, *Mus musculus* (mice), *Rattus norvegicus* (rats), *Tupaia belangeri chinensis* (Chinese tree shrews), and *Macaca mulatta* (macaques). BACE1: beta-secretase 1; UTR: untranslated regions; FTDP-17: frontotemporal dementia with Parkinsonism-17; NFT: neurofibrillary tangle; TREM2: triggering receptor expressed in myeloid cells 2; PSEN1: presenilin 1.

the E4 isoform, and a CRISPR/Cas9-generated R47H point mutation in the *Trem2* gene. These mice exhibit decreased survival probability by 24 months (Kotredes et al., 2021), with both B6.Trem2*R47H and B6.APOE4.Trem2*R47H mice displaying disruptions in multiple immune-related processes at this age, highlighting the significant connection between aging, Trem2 function, and AD.

B6.APOE4.Trem2*R47H mice do not develop amyloid plaques or hyperphosphorylated tau, nor do they exhibit pronounced age-related behavioral changes (Kotredes et al., 2021). However, between 4 to 24 months of age, they display progressive age-related deficits in locomotor activity, motor coordination, and wheel-running activity, while spatial working memory remains unaffected until 24 months.

Metabolic and functional imaging studies using 18F-FDG and 64Cu-PTSM have revealed that B6.APOE4.Trem2*R47H mice show reduced brain perfusion and increased glycolysis in key regions associated with sensory, cognitive, and motor functions compared to controls (Kotredes et al., 2021). Molecular profiling has also identified genotype- and age-

dependent alterations in cytokine expression, including variations in IL-6 and KC/GRO levels in both blood and brain tissues (Kotredes et al., 2021). Given their characteristics, these mice may serve as valuable models for studying AD, lipoproteins, arteriosclerosis, and coronary heart disease, offering insights into age-related pathologies beyond classical AD hallmarks.

Thy1-ApoE4/C/EBPβ double transgenic mouse models

CCAAT/enhancer-binding protein β (C/EBPβ) is a crucial transcription factor in adipocyte differentiation and maturation, mediating the expression of inflammatory cytokines (Cardinaux et al., 2000). Notably, its levels gradually increase in neurons with age (Cortes-Canteli et al., 2011), suggesting a potential link in age-related neurodegenerative diseases. Recent research identified C/EBPβ as a key regulator of ApoE, modulating its mRNA levels in an age-dependent manner and selectively promoting the expression of ApoE4 in human neurons, with overexpression of C/EBPβ in 3xTg and 5xFAD mouse models shown to accelerate AD pathology (Xia

et al., 2021). These findings implicate C/EBP β in the regulation of ApoE4 and its broader effects on tau and A β pathologies (Xiong et al., 2023a).

Building on this understanding, researchers engineered the Thy1-ApoE4/C/EBP β neuron-specific transgenic mouse model (Qian et al., 2024). In this model, neuronal ApoE4 drives C/EBP β expression, triggering a cascade of AD-like pathological changes. By 12 months, these mice exhibit hallmark features of AD, including memory deficits, brain volume reduction, A β and tau aggregation, and PET signal alterations. Thy1-ApoE4/C/EBP β transgenic mice represent a promising tool for studying sporadic AD, providing valuable insights into the molecular mechanisms underlying disease progression and offering a platform for evaluating therapeutic interventions.

Senescence-accelerated mouse models

Senescence-accelerated mouse-prone 8 (SAMP8) is a naturally occurring mouse line characterized by accelerated aging, derived from the inbred AKR/J line. In the 1970s, Takeda and colleagues observed accelerated aging traits, including reduced activity, hair loss, and early mortality, in certain progeny. This led to the development of senescence-accelerated mice (SAM), categorized by survival curves and phenotypic features. SAMP8, which exhibits memory and learning disorders, emerged as a prominent outcome of this selective breeding process (Takeda et al., 1991).

Age-related neuropathological changes in SAMP8 mice include the accumulation of periodic acid-Schiff (PAS)-positive granular structures within astrocytes in the hippocampus and brainstem, indicative of misfolded protein accumulations associated with amyloid plaques (Akiyama et al., 1986). This is accompanied by prominent astrogliosis in the hippocampus as the mice age (Han et al., 2010). Additionally, the brainstem reticular formation contains numerous vacuoles of varying sizes, surrounded by clusters of activated microglia (Kawamata et al., 1998; Yagi et al., 1989). These features resemble changes in aging human brains and reflect specific glioneuronal reactions, where glial cells play an essential role in the brain's response to neurodegeneration. Behavioral tests have revealed that SAMP8 mice experience marked declines in spatial working memory between 6 and 10 months of age, as assessed by the Y-maze test (Del Valle et al., 2012; Lin et al., 2014; Pačesová et al., 2022). Moreover, SAMP8 mice show increased mobility with age compared to senescence-accelerated mouse resistant 1 (SAMR1) controls (Sawano et al., 2013; Tsumagari et al., 2021; Yanai & Endo, 2016).

SAMP8 mice show elevated levels of phosphorylated tau at multiple epitopes, including Ser396, Thr231, and Ser214, by 6 to 9 months of age (Pačesová et al., 2022). However, hallmark tau structures, such as NFTs, have not been conclusively observed in this model. These mice also demonstrate age-dependent increases in A β -like protein production, with some studies reporting the presence of amyloid granules containing both A β 42 and A β 40 peptides in the hippocampus of 6-month-old mice (Del Valle et al., 2010). However, these findings are inconsistent across studies, as other antibody-based analyses have failed to confirm such deposits, and the observed A β increases are minor compared to transgenic mice. Notably, no evidence of A β deposition is evident in 12-month-old SAMP8 mice, indicating that plaque formation may not be crucial for amyloid-induced memory loss and brain damage (Morley et al., 2012).

Chemically induced rodent models

Chemically induced rodent models have been established to investigate the role of specific neurotransmitter pathways in the pathophysiology of AD. These models, created by administering chemical agents, replicate certain symptoms of AD, such as impaired cholinergic function and deficits in learning ability (Hampel et al., 2018). While these models effectively demonstrate cognitive defects, they do not replicate key pathological features of AD, such as amyloid plaques and NFTs, with the exception of the A β -injection model.

The A β -injection model, where A β monomers or oligomers are directly injected into the hippocampus, is widely used to investigate the mechanisms by which A β peptides contribute to neuronal dysfunction and cognitive decline. This model provides insights into the mechanisms underlying A β -induced toxicity and serves as a platform to evaluate the effectiveness of drugs aimed at reducing A β aggregation, preventing plaque formation, and alleviating associated neuroinflammation and neurodegeneration. A β injections in the hippocampus have been shown to induce memory impairment, impair long-term potentiation, and activate microglia in mice (Hyun Yi et al., 2023), as well as impair cholinergic function and learning ability without progressive neurodegeneration (Nakamura et al., 2001). Increasingly, this model is used to explore the interactions between A β and other prion proteins, such as tau and α -syn (Bassil et al., 2020; Chen et al., 2024).

Other chemicals have also been used to induce AD-like pathologies by targeting specific neuronal or neurotransmitter pathways. For example, scopolamine impairs cholinergic function (Wang et al., 2023b), L-methionine activates NMDA receptors (Sain et al., 2011), and okadaic acid promotes tau phosphorylation (Kamat et al., 2013). These compounds mimic aspects of AD-related dementia, providing tools to study specific mechanisms underlying cognitive impairment and evaluate potential therapeutics. However, these models cannot be considered true representations of AD, as they lack hallmark pathologies like amyloid plaques and NFTs, reflecting only partial disease phenotypes.

NHP MODELS WITH VALID PREDICTIVITY OF LATE-ONSET SPORADIC AD

The evolutionary divergence between rodents and humans results in significant genetic and neuroanatomical differences, hindering the translational applicability of rodent models to human AD (Perlman, 2016). Behavioral assays widely used in mice often fail to predict clinically relevant outcomes in humans (Wan et al., 2020), while species-specific variations in drug metabolism further complicate pharmacokinetics and therapeutic responses (Seeley & MacDougald, 2021). These challenges highlight the need for more predictive models to bridge the gap between animal studies and human AD research.

NHPs

NHPs, owing to their closer genetic and neuroanatomical similarities to humans, provide an essential avenue for studying late-onset sporadic AD. Their well-developed brain structures, extended lifespans, and cognitive abilities make them uniquely suited for specific age-related neurodegeneration. Aging NHPs exhibit a broad range of cognitive, physical, and sensory declines, along with comorbid illnesses such as cancer, cardiovascular disease, and neurodegeneration.

Nearly all studied NHP species develop amyloid-related pathology with age, although the onset, quantity, distribution, and appearance of amyloid pathology vary. Furthermore, given their similarity in brain structure, NHPs can be utilized to study the neocortical-to-allocortical expansion of AD-like pathology. While amyloid plaques are typically limited to the hippocampus in NHPs, their progressive spread within the brain mirrors aspects of human AD progression (Poduri et al., 1994; Sani et al., 2003). However, the frequent sacrifice of NHPs for pathological testing prior to cognitive assessments poses a significant challenge in correlating pathological changes with cognition decline (Stonebarger et al., 2021). Recent studies provide compelling evidence that aging NHPs may spontaneously develop AD-like conditions. Li et al. (2022b) reported that aged rhesus monkeys with cognitive impairments display hallmark clinical and pathological features of AD, including memory decline, intracellular NFTs, extracellular amyloid plaques, and significant neuronal loss. These findings suggest that NHPs may naturally recapitulate sporadic AD-like conditions upon aging, similar to humans.

However, rhesus macaques, one of the most common NHP species used in research, typically exhibit amyloid coverage limited to 5%–6% in regions of interest, even in advanced age (Zhang et al., 2019). To enhance the utility of NHP models in AD research, various strategies have been engineered to accelerate the progression of AD pathology through targeted plaque and NFT induction in species with extended lifespans, such as rhesus macaques. Exogenous administration of A β oligomers has been shown to induce A β accumulation in key brain regions associated with higher-order cognition, such as the prefrontal cortex and hippocampus, closely mirroring human AD pathology (Beckman et al., 2019). This approach has revealed hallmark AD features, including synaptic degeneration, heightened tau phosphorylation, and activation of astrocytes and microglia in A β -enriched macaque brain areas (Forny-Germano et al., 2014). Additionally, studies on middle-aged female monkeys demonstrated that A β oligomers selectively target vulnerable dendritic spines in the neocortex and hippocampus, eliciting neuroinflammatory responses comparable to those observed in humans (Beckman & Morrison, 2021). Genetic approaches have further advanced NHP modeling of AD. The introduction of mutated tau into rhesus monkey brains has been shown to trigger the spread of misfolded tau proteins, accompanied by TREM2-positive microglial activation and significant alterations in cerebrospinal fluid (CSF) and plasma biomarkers indicative of AD (Beckman et al., 2021; Beckman & Morrison, 2021; Jiang et al., 2024). The transgenic cynomolgus macaque model expressing tau (P301L), developed through lentiviral embryo infection, shows age-related neurodegeneration, motor impairments, and spinal cord A β oligomer production induced by embryonic transgenic tau expression or stereotactic intracerebral injection of AAV-Tau (Tu et al., 2023). This suggests that tau accumulation can trigger A β oligomer formation, demonstrating that tau plays a causal role in endogenous A β formation and toxicity. Moreover, since A β oligomers induced by mutated tau are stable in the spinal cords of NHPs, targeting this form of A β may be beneficial for treating pathologies induced by both tau and A β , at least in the spinal cord.

Longitudinal studies of neurocognitive functions in NHPs are necessary for understanding both healthy and pathological aging in humans. Short-lived primates, such as gray mouse lemurs and common marmosets, provide a unique opportunity

to observe natural age-related changes in brain structure and behavior, offering potential predictors of neurodegenerative diseases. These species serve as ideal primate models due to their naturally short lifespans, ease of handling, rapid reproduction, availability of neuroanatomy atlases, and brain organization comparable to larger NHPs and humans. At middle age (approximately 5 years old for gray mouse lemurs and 8 years for marmosets), these animals demonstrate a decline in psychomotor capacities and cognitive performance, respectively (Chaudron et al., 2021; Rothwell et al., 2021). In certain instances, these animals exhibit spontaneous pathological aging, displaying age-related deficits similar to humans, including severe cognitive decline, brain atrophy, amyloidosis, and glucoregulatory imbalance (Chaudron et al., 2021; Tardif et al., 2011). As such, they provide a suitable bridge between rodent and larger NHP models for neuroscience and aging research (Tardif et al., 2011).

Recent advancements in genomics have enabled the development of genetically modified NHPs to model AD more effectively. Genetically engineered marmosets and cynomolgus monkeys (*Macaca fascicularis*) carrying mutations associated with AD have been successfully established. For example, *PSEN1* Δ 9 founder marmosets have been generated (Sato et al., 2020), as well as two founder lines carrying knock-in point mutations such as *PSEN1* C410Y and A426P (Rizzo et al., 2021). These mutations lead to a progressive increase in plasma A β 42 levels and an elevated A β 42-to-A β 40 ratio with age. In 17-month-old marmosets with the homozygous *PSEN1* C410Y mutation, A β 42 (detected by NAB228 antibody) accumulates in both intracellular and extracellular compartments within various brain regions, including the sensorimotor cortex and globus pallidum (Homanics et al., 2024). In cynomolgus monkeys, the dual-guide CRISPR/Cas9 system has been employed to successfully emulate the *PSEN1*- Δ E9 mutation through the genomic excision of exon 9, leading to a groundbreaking presentation of tau-related pathology, including phosphorylated tau in CSF. Blood transcriptome and proteome profiling of juvenile *PSEN1* mutant cynomolgus monkeys has revealed early dysregulation of inflammatory and immune molecules, underscoring the complex interplay of molecular mechanisms in the early stages of AD (Li et al., 2024b). These models are particularly promising for testing preventive therapies before the onset of overt symptoms.

In conclusion, NHPs represent powerful models for studying brain aging and AD-related pathology. Their genetic and physiological similarities to humans, combined with emerging genomic tools, provide critical insights into the mechanisms underlying neurodegeneration and offer platforms for evaluating novel therapeutic approaches.

Chinese tree shrews

Chinese tree shrews, small mammals of the order Scandentia, are phylogenetically close to NHPs. Recent genomic and nuclear DNA analyses place them within the Euarchonta branch, alongside primates and colugos. Their small size, brief reproductive cycle, relatively short lifespan, and low maintenance costs make them a promising alternative to NHPs in biomedical research (Meng et al., 2016). The third edition of the tree shrew brain atlas, developed with single-cell RNA sequencing (scRNA-seq) and advanced multiomics technologies, provides detailed insights into brain region delineation and cellular composition, further affirming their

close evolutionary relationship with NHPs (Yao et al., 2024). Notably, their high brain-to-body mass ratio and developed frontal cortex make them suitable for studying clinical features related to advanced brain functions.

Chinese tree shrews have been used in various neurological disorder models, including depression (Meng et al., 2016; Wang et al., 2012), glioma (Tong et al., 2017), and Parkinson's disease (Wu et al., 2019). Genes involved in A β production and NFT pathways exhibit higher sequence identity with humans than those of rodents. In particular, the A β 42 peptide sequence in tree shrews is identical to that of humans, unlike that in mice and rats, which differs by three residues (Pawlik et al., 1999). Aging tree shrews display a substantial increase in 4G8-positive deposits and an elevated A β 42-to-A β 40 ratio in hippocampal and cortical tissues (Li et al., 2024a). Behaviorally, tree shrews demonstrate superior memory performance compared to rodents, particularly in tasks involving novelty preference (Khani & Rainer, 2012; Nair et al., 2014). They have also been utilized in preclinical drug development studies (Shen et al., 2018; Wang et al., 2013).

Chinese tree shrews possess 131 AD-related genes, demonstrating a high degree of similarity to humans in both protein sequence identity and expression patterns (Fan et al., 2018). Age-dependent increases in total A β levels have been documented in the cortical tissue, correlating with intracellular amyloid deposition that exhibits diffuse and dense patterns (Fan et al., 2018; Yamashita et al., 2010, 2012). Astrocytes, identified through GFAP-positive staining, also show A β immunoreactivity (Fan et al., 2018). While the manifestation of NFTs in the aging process is not yet well understood, key genes implicated in the NFT formation pathway share a high degree of protein sequence identity with their human counterparts. Elevated phosphorylated tau (pTau-181) levels in the hippocampus further underscore the similarity between Chinese tree shrews and humans in their respective NFT formation pathways (Fan et al., 2018). In addition, aged tree shrews show progressive cognitive decline in maze-based tests, paralleling impairments observed in human AD patients.

Despite current limitations in the use of tree shrews for research, significant advancements have enhanced their utility. Publicly available resources, including brain anatomical MRI templates, atlases of white matter, striatum, pallidum, and cerebellum (Dai et al., 2017; Ni et al., 2018a, 2018b), and fine anatomical features of the primary visual cortex and hippocampus (Dai et al., 2018), provide essential tools for advanced investigations. Additionally, comprehensive maps of c-Fos expression in the forebrain and genome annotations derived from large-scale RNA sequencing have expanded the scope of genomic and transcriptomic studies in tree shrews (Ni et al., 2020). The integration of advanced artificial intelligence (AI) and deep learning motion recognition technologies has further facilitated detailed behavioral studies, establishing the tree shrew as a valuable model for neuroscientific research (Yao et al., 2024). These resources collectively enable further exploration of the Chinese tree shrew as a potential model for AD, supporting investigations into disease pathogenesis and potential therapeutic targets.

LIMITATIONS OF CURRENT ANIMAL MODELS

The development of animal models of AD faces significant challenges due to the complexity of the disease pathology and poorly understood pathogenesis. Currently, no animal model can fully replicate the intricate neurodegenerative processes

observed in human AD brains.

Models incorporating mutations or knock-ins of pathogenic genes have inherent limitations. First, these models predominantly simulate early-onset FAD, which represents less than 5% of the AD population. The rapid and severe pathology observed in these models does not align with the slow and progressive nature of the disease in most AD patients. Second, while AD patients with diverse genomic variations often exhibit similar pathology, animal models with distinct genomic variations display inconsistent pathological features (Sierksma et al., 2020). This genotype-phenotype discrepancy undermines the translatability of findings to clinical trials. Third, in AD patients with *APP* or *PSEN1* mutations, tau pathology typically arises subsequent to A β pathology. However, existing animal models fail to recapitulate tau pathology under conditions of *APP* or *PSEN1* overexpression.

Conversely, animal models without pathogenic gene mutations or knock-ins primarily simulate late-onset sporadic AD, which accounts for over 95% of the AD population. The multifactorial nature of sporadic AD involves genetic risk factors, aging, and environmental effects. Current models of sporadic AD predominantly focus on risk genes and the aging process, while neglecting environmental factors and their interactions with genes, such as the impacts of diet, exercise, and air quality (Zhang et al., 2023).

NHPs exhibit greater similarity to human AD in brain anatomy, pathological features, and behavioral patterns. Their extended lifespan allows for the study of gradual cognitive decline, better mirroring the slow progression of AD. However, the limited reproductive capacity and high costs associated with NHPs significantly restrict their extensive use in research, a common challenge to many biomedical studies. A possible solution to address this issue involves using NHP models to identify key disease processes, which can be subsequently validated in rodent animals.

In addition to the respective limitations of each animal model, there are overarching challenges associated with using animal models for AD research. First, the heterogeneity observed among AD patients—including variations in genetics, sex, physical health, and lifestyle—profoundly affects disease progression and therapeutic responses. However, preclinical trials typically use male animals with a uniform genetic background and maintained on identical diets in identical pathogen-free environments. This lack of diversity may contribute to the limited predictive validity of these models in clinical settings. Second, aging, an important risk factor in AD, is often inadequately addressed. Many studies focus on a narrow age range, failing to account for the slow, progressive nature of the disease. Third, behavioral symptoms are frequently selected as primary therapeutic endpoints in preclinical studies. However, behavioral testing paradigms in animal models often yield inconsistent and unstable results, poorly predicting clinical trial outcomes (Wan et al., 2020). Additionally, differences in drug metabolism between species lead to variable responses to therapeutic candidates, further complicating the translation of preclinical findings to human trials (Seeley & MacDougald, 2021). Despite recent efforts to address these issues, many challenges remain unresolved, emphasizing the need for more refined and representative models to advance AD research.

FUTURE PERSPECTIVES

The fundamental biological differences between species contribute significantly to the poor predictive validity of animal models in preclinical trials. However, refining experimental design and leveraging novel technologies can help bridge this translational gap, providing more powerful tools for AD research.

To address the impact of heterogeneity within the AD population on preclinical testing, controlled variables, such as sex, age, and housing conditions, should be systematically varied (Viaud-Delmon et al., 2011). Moreover, instead of increasing the number of animals in a single experiment, conducting parallel studies across multiple independent laboratories can introduce controlled variability. Although this approach may increase variability within individual studies, it can reduce variability across studies, potentially minimizing false-positive results and increasing reproducibility (Viaud-Delmon et al., 2011).

The aging process, a critical factor in AD progression, remains challenging to replicate in short-lived animal models. Expanding age ranges or incorporating progressive pathological stages into experimental designs could improve the translational relevance of these models, even if the human aging process cannot be fully simulated. Additionally, investigating environmental factors and their interplay with genetic and pathological mechanisms requires a more diverse array of animal models and research methods. Developing crossover models that combine AD with comorbid conditions such as diabetes, cerebrovascular disease, and depression, or directly subjecting animal models to specific environmental factors under standardized conditions, represent viable avenues for future research.

In consideration of the fundamental biological differences between humans and animal models, *in vitro* human cell systems offer a promising strategy for AD research. Recent advances in induced pluripotent stem cell (iPSC) technology have enabled the generation of CNS cell types derived from healthy individuals or AD patients, facilitating the development of *in vitro* models (Arber et al., 2017; Israel et al., 2012; Kwart et al., 2019). For example, organoid systems composed of iPSC-derived neurons with APP mutation replicate A β accumulation characteristic of amyloid plaques (Choi et al., 2014; Park et al., 2018). Similarly, human cerebral organoid models with APP^{NL-G-F} knock-in illustrate the sequential development of A β aggregates, tau pathology, astrogliosis, and cell death, closely resembling the full spectrum of pathological and pathophysiological events in the human AD brain (Liu et al., 2024). Despite these advancements, replicating the complex microenvironment of the human brain within iPSC-derived human cell systems remains challenging. Emerging xenograft models, where iPSC-derived human cells are grafted into mouse brains, provide a novel platform for investigating human cell behavior *in vivo* (Hasselmann et al., 2019). For instance, iPSC-derived human microglia grafted into mouse brains display distinct transcriptomic profiles compared to mouse microglia when exposed to AD-related amyloid pathology (Mancuso et al., 2024). Additionally, neurons derived from fibroblasts of both healthy and AD patients exhibit signature AD traits. In neurons derived from patients with late-onset AD (LOAD), A β accumulation drives neurodegeneration, which can be alleviated by early secretase inhibitor treatment (Sun et al., 2024). Single-cell analyses have further advanced our understanding of AD by unraveling gene expression and structural heterogeneity across various

neural cell populations. These insights enhance our comprehension of AD pathogenesis, aiding marker gene identification for early diagnosis and timely intervention in neurodegenerative diseases with pathogenesis preceding clinical manifestation. One notable example is the discovery of disease-associated microglia (DAMs) through scRNA-seq in 5xFAD mice (Keren-Shaul et al., 2017), which transition into activated response microglia (ARMs) and IFN response microglia (IRMs) in App^{NL-G-F/NL-G-F} mice (Keren-Shaul et al., 2017). Integrating data from multiple cohort studies on AD has also refined our understanding of disease trajectories, allowing for the stratification of subjects based on baseline gene expression and disease subtype. By comparing differentially expressed genes in 5xFAD and APP/PS1 mice, researchers identified significant enrichment patterns consistent with microglial changes observed in humans (Wang et al., 2022).

Beyond transgenic mice, recent progress in single-cell and single-nucleus transcriptomic technologies have significantly expanded our understanding of AD pathogenesis. Notably, studies in NHPs and humans have provided critical insights into the cellular and molecular mechanisms underlying AD. For example, single-cell analyses of aged *Macaca fascicularis* identified a subpopulation of excitatory neurons (ExNs subpopulations) with heightened susceptibility to AD (Li et al., 2022a). Similarly, a single-nucleus transcriptomic atlas of the human prefrontal cortex in elderly individuals revealed key cellular and molecular determinants of high cognitive function, dementia, and resistance to AD pathology (Mathys et al., 2023). Further investigations into human microglia through single-nucleus transcriptomic and epigenomic profiling uncovered dynamic changes in microglial states across different pathological stages of AD, as well as the transcription factor networks regulating these transitions (Sun et al., 2023). Additionally, analyses of the human brain revealed epigenomic erosion and loss of cellular identity in late-stage AD (Xiong et al., 2023b). Comprehensive examination of six brain regions in aged individuals, with and without AD, demonstrated region-specific neuronal vulnerabilities and distinct genetic expression profiles, including a decrease in certain neuronal subtypes, an increase in reelin pathway-related genes, and alterations in astrocyte gene expression linked to cognitive resilience, underscoring their impact on AD susceptibility (Mathys et al., 2024). These findings highlight the potential of single-cell molecular data to redefine existing paradigms of AD pathogenesis and uncover novel therapeutic avenues. Considering the accessibility of research subjects, further investigation of AD animal models is essential to translate these findings into meaningful advances in understanding and treatment.

Single-cell analysis primarily focuses on clustering and differential gene expression analyses, which rely heavily on similarities in expression profiles. However, it has limitations in accurately capturing developmental trajectories and lineage structure (or “fate”) of cells. In contrast, lineage tracing offers distinct advantages by enabling the tracking of cell fate through the labeling of stem and progenitor cells during embryonic stages. This is achieved by sequencing inherited DNA sequences or “barcodes” across subsequent stages (Kalhor et al., 2018; McKenna et al., 2016). For example, MRI data from 71 patients showed that lower levels of A β 42 and higher concentrations of total tau, pTau-181, sAPP β , and their ratios with A β 42 are closely linked to reduced brain myelin. These findings suggest that age-related myelin decline,

influenced by CSF biomarkers, may serve as an early indicator of AD pathology in white matter, particularly in myelin content (Dean III et al., 2017). Mouse models, such as APPswe/PS1dE9 and 5xFAD mice, exhibit demyelination phenotypes. Lineage tracing and cell labeling have further clarified the relationship between A β morphology, demyelination, and remyelination in APPswe/PS1dE9 mice, suggesting that soluble A β may not significantly alter myelin formation.

CONCLUSIONS

While AD animal models remain indispensable, acknowledging their limitations is crucial for advancing the field. Recognizing the species-specific nature of AD pathology has prompted a greater shift towards the use of NHPs in research. Their closer biological resemblance to humans offers a promising platform for exploring AD mechanisms and evaluating potential therapeutic strategies. By addressing these challenges through technological innovations and biologically relevant models, researchers can bridge the translational gap, improving the predictive accuracy of preclinical findings and accelerating the development of effective therapies for AD.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

P.L. provided ideas and outlines. Q.W. and B.T.Z. collected references and prepared the original manuscript and figures. P.L. supervised and revised the manuscript and figures. All authors read and approved the final version of the manuscript.

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