Animal Models of Alzheimer's Disease: History of Animal Models for Therapeutic Discovery

Moriah Jacobson, Sarah R. Sterlace, Elisa Giunti, Janell Richardson
Taconic Biosciences, Inc., Rensselaer, New York

Introduction

- Alzheimer's disease (AD), the most common cause of dementia, is characterized by progressive cognitive decline and neuropathologies including amyloid-β (Aβ) plaques, Tau neurofibrillary tangles, neuroinflammation, and synaptic loss.
- Since the 1980s, mouse models have played a central role in advancing our understanding of AD.
- Overexpression of human Amyloid Precursor Protein (APP) mutations linked to familial AD paved the early adoption of mouse models for AD research.
- Newer mouse models have incorporated Tau pathology, presenilin mutations, additional mechanisms, and even humanized immune systems to better mimic disease complexity.
- Despite translational limitations, these models have enabled major breakthroughs in elucidating pathogenic cascades, identifying molecular targets, and guiding preclinical drug development.
- The evolution of AD mouse models—from single-gene transgenics to next-generation knock-ins and humanized chimeric systems—reflects an ongoing effort to generate more pathophysiological and translationally relevant models.

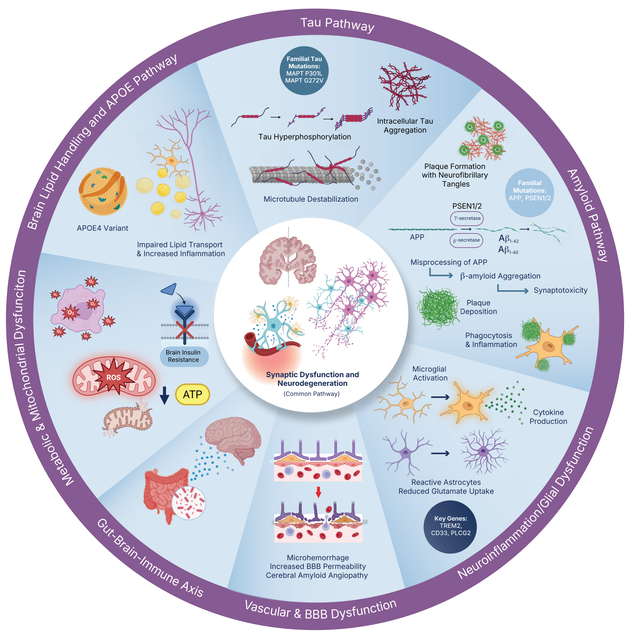


Figure 1. Major Mechanistic Hypotheses in Alzheimer's Disease.

β-amyloid plaque deposition and microglia overlap in hippocampus

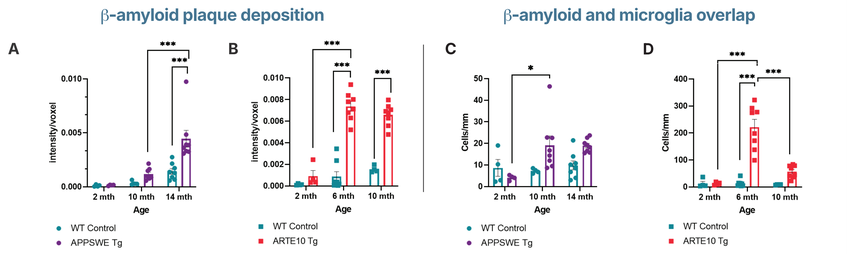
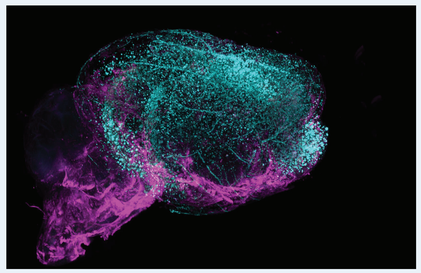


Figure 2. β-Amyloid Plaque Deposition and Microglia Co-localization in APPSWE and ARTE10 mice.
Intensity of plaques per voxel **(A and B)** and density of microglia cells on plaques **(C and D)** calculated for entire hippocampus per animal (n=4-8 per group) for the APPSWE model **(A and C)** and ARTE10 model **(B and D)**. Plaque deposition was significantly increased relative to wild type **(WT)** controls by 6 months of age for ARTE10 mice **(B)**, whereas plaques were not significantly increased in the APPSWE mice until 14 months of age **(A)**. Microglia overlap with plaques differently in the APPSWE and ARTE10 models, following a U shape function in the ARTE10 mice specifically **(D)**. Similar findings were found in the cerebral cortex.

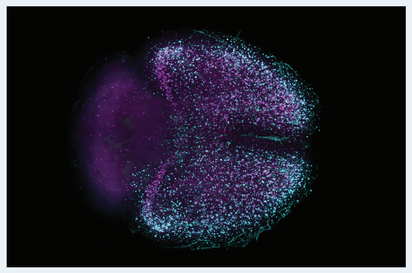
Table 1. Mouse Models for Alzheimer's Research

Pathway	Model	Genetic alteration (short)	Typical pathology	Supporting use for FDA-approved Drugs
Amyloid	APPSWE (Tg2576)	APPswe overexpression (PrP promoter)	Aβ plaques by ~11–13 mo; gliosis; memory deficits	"Aducanumab Lecanemab"
	PDAPP (J20)	APP V717F (Indiana) overexpression (PDGF-β promoter)	Aβ plaques; synaptic/memory deficits	Donanemab
	APPArcSwe (Arc/Swe)	APP E693G (Arctic) + KM670/671NL (Swedish) overexpression	Aβ protofibrils; plaques	Lecanemab
	AppNL-G-F (KI)	APP KI: Swedish (NL), Arctic (G), Iberian (F)	Robust Aβ pathology without overexpression	—
	AppNL-F (KI)	APP KI: Swedish (NL) + Iberian (F)	Aβ pathology (later than NL-G-F)	—
	APP23	APPswe overexpression (Thy1 promoter)	Aβ plaques; neuron loss (older ages)	—
Combination	ARTE10 (aka APP/PS1 (line 85))	APPswe + PS1dE9 overexpression	Aβ plaques; synaptic deficits	—
	3xTg-AD	APPswe + PS1(M146V) KI + Tau(P301L)	Aβ plaques + tau pathology	—
	5xFAD (Tg6799)	APP (Swedish, Florida, London) + PSEN1 (M146L, L286V) overexpression	Early, aggressive Aβ plaques; cognitive deficits	—
Tau	Tau (JNPL3)	Carries the transgene for the human P301L mutation of the microtubule-associated protein Tau gene (MAPT) and expresses mutant human TAU protein	Aggregates of filaments of TAU resultin Neurofibrillary tangles (NFT). Develops behavioral and motor disturbances related to development of NFT	—
	PS19 (tau P301S)	MAPT P301S overexpression	Taupopathy; neurodegeneration	—
	rTg4510 (tau P301L)	Tet-off MAPT P301L overexpression	Tau tangles; neuron loss	—
APOE	hAPOE2/3/4 (KI)	Targeted replacement with human APOE2, APOE3 or APOE4 allele	LOAD risk modeling; lipid & neuroinflammation phenotypes	—
	hAPOE3 x ARTE10	—	Characterization pending	—
	hAPOE4 x ARTE10	—	Characterization pending	—

Development of Refined Techniques



Sagittal view of whole-brain imaging of β-amyloid (cyan) and astrocytes (GFAP, magenta) in ARTE10 mice.



Horizontal view of whole-brain imaging of β-amyloid (cyan) and microglia (IBA1, magenta) in ARTE10 mice.

Figure 3a. Whole-brain 3D Light Sheet Microscopy of β-Amyloid, Astrocytes and Microglia in Aged ARTE10 Brains.

Figures 2-3 generated in collaboration with LifeCanvas Technologies.

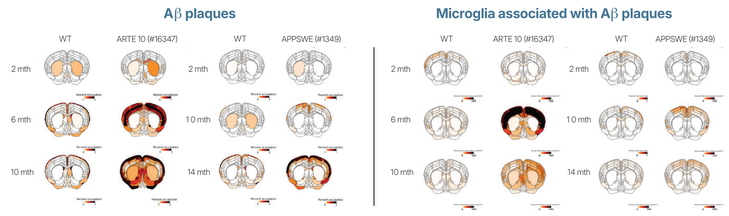


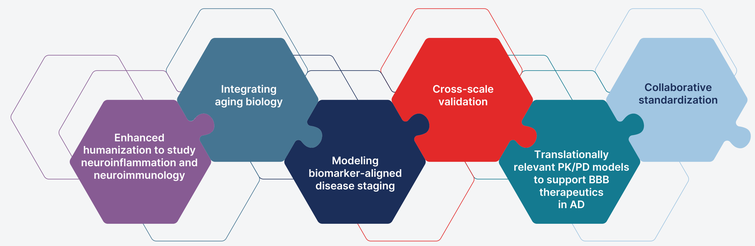
Figure 3b. Whole-brain 3D Light Sheet Microscopy of β-Amyloid, Astrocytes and Microglia in Aged ARTE10 Brains.
Heatmaps (25 m sections) generated from image registration to the Allen Brain Atlas and segmentation analyses of plaque deposition (SmartAnalytics) for control wild type (WT) and APPSWE and ARTE10 transgenic mice highlight increased plaque deposition in cortical regions in ARTE10 mice >6 mo and at >14 mo in the APPSWE mice. Similar findings were found in the hippocampus.

Discussion

- While decades of Alzheimer's disease (AD) research in mouse models have yielded invaluable mechanistic insights, translation to successful clinical therapies remains limited. A key contributor to this gap is the physiological divergence between current models and the human disease trajectory. Many established transgenic lines exhibit early and aggressive amyloid deposition or Tau pathology, often driven by supraphysiological overexpression of mutant human genes that represent rare familial forms of AD. These models accelerate pathology for experimental practicality but fail to capture the gradual, age-dependent progression and heterogeneous staging observed in sporadic, late-onset AD—the form that predominates in patients.
- Moreover, current models frequently lack important comorbid features such as cerebrovascular dysfunction, metabolic impairment, and microglial and astrocytic diversity that evolve over the human disease course. As clinical diagnostic frameworks increasingly emphasize biomarker-based staging (e.g., A/T/N systems reflecting amyloid, Tau, and neurodegeneration status), preclinical models must evolve to reflect these dynamic, overlapping pathological phases.
- Future efforts should prioritize physiologically relevant systems that integrate humanized immune and glial components, age-appropriate gene regulation, and progressive pathology across molecular and functional domains. Knock-in models, induced pluripotent stem cell (iPSC)-derived chimeras, and multi-omic longitudinal mapping in rodents offer promising avenues to align preclinical staging with clinical phenotypes. By developing models that more faithfully mirror disease initiation, propagation, and symptomatic progression, the field can improve predictive validity and ultimately enhance the translational success of Alzheimer's therapeutics.

Future Directions

To advance translational relevance, next-generation Alzheimer's disease models should move beyond single-pathway paradigms toward systems that reflect the temporal and biological complexity of human disease. **Key priorities include:**



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