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Research Article

# Advances and Limitations of Rodent Models in Alzheimer's Disease Pathogenesis and Therapeutics

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## Abstract

Alzheimer's disease (AD) is a neurodegenerative condition characterised by several markers and physiological manifestations. While Alzheimer's disease affects millions of people throughout the world, the intricacy of the condition and the limits of experimental models have slowed the discovery of viable treatments. Rodent models helped researchers identify critical features of Alzheimer's disease pathogenesis and test novel treatment strategies. This chapter gives a detailed summary of rodent models used in Alzheimer's disease research, concentrating on the numerous types of transgenic, knock-in and knock-out models that replicate the genetic alterations linked with familial AD. We look into pharmacological and neurotoxin-induced models as well as infusion models, to imitate particular pathological characteristics of the disease. In these models, pathological assessments are essential for determining the development of amyloid plaque, hyperphosphorylation of tau and neuroinflammatory responses, immunohistochemistry, ELISA as well as synaptic marker investigations, all play significant contributions. Regardless of the benefits they provide, rodent models have substantial limitations in recreating the complete spectrum of human Alzheimer's disease, notable the neurodegeneration and comorbidities present in sporadic AD. As a result, the research is shifting toward more advanced humanised models and gene-editing tools, such as CRISPR/Cas9, to eliminate the disparity between research on rodents and human therapeutic applications. This chapter finishes with a discussion of future AD research paths, highlighting the importance of improved models that combine environmental, genetic, and lifestyle components in order to better portray the complexity of AD. Rodent models are still in an angle to contribute significantly to our understanding of AD and the development of disease-transforming treatments by overcoming these constraints.

## Keywords

Alzheimer's Disease, Rodent Models, Amyloid Plaques, Tau Hyperphosphorylation

## 1. Introduction

Alzheimer's disease is a neurodegenerative condition marked by loss of memory and a gradual deterioration in cognitive function [1]. It is linked to the build-up of neurofibrillary tangles made of hyperphosphorylated tau protein and amyloid-beta (Aβ) plaques. Even after much study, AD is still incurable, posing a serious threat to public health worldwide. The inability of present treatments approaches to translate results in animal models to human effectiveness, in

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particular, emphasizes the need for improved research of disease mechanism and creation of more precise animal models [2].

Since familial AD (FAD) is linked to the overexpression of mutant forms of tau, presenilin-1 (PSEN1), and amyloid precursor protein (APP), these forms have been the main focus of the conventional method for simulating AD in rodents [3]. These models realistically reproduce the hallmarks of Alzheimer's disease—amyloid plaques and tau tangles. Although uncommon, these mutations do not typically cause sporadic late-onset AD [4]. These models considerably underrepresent the detailed complexity of Alzheimer's disease and consequently, many of its immunological and metabolic aspects are insufficiently caught.

Recent research shows that active neuroinflammation considerably effects the development of late-onset Alzheimer's disease. Activated microglia and astrocytes drive neuroinflammation, as well as this neuroinflammation is thought to precede and worsen the core pathological features of Alzheimer's disease, such as tau tangles and Aβ plaques [5]. Rodent models that induce neuroinflammation through several toxin exposures, multiple immunological challenges and multiple metabolic disruptions are therefore in high demand. Their improved representation of the illness's sporadic nature stems from their attempt to reproduce the early inflammation seen in AD [6].

In addition, in view of the potential significance of the biochemical and vascular components of AD in regards to the onset and progression of the disease, there has been heightened interest in AD [7]. To clarify the contribution of individual factors, including insulin resistance, high-fat diet or chronic stress, to the pathogenesis of Alzheimer’s disease, integrated rodent models representing these factors have been developed. These models provide an opportunity to investigate novel treatment targets that tackle the intricate and multifaceted characteristics of Alzheimer’s disease.

However, it has been challenging to implement these findings into clinical practice [8]. Such dollars between human and rodent models of AD pathophysiology, thus contribute to this discrepancy. Important, amyloid pathology does not constitute the entire spectrum of Alzheimer’s disease pathology as described in modelled scenarios. These models need to be further developed in order to increase the translatable nature of study findings.

## 2. Classical Rodent Models of Alzheimer’s Disease

### 2.1. Knock-in and Knock-out Models

Knock-in and knock-out models are genetic techniques that use the introduction or removal of specific genes associated with Alzheimer’s disease to study the disease further. The role of these models is paramount to the molecular dissection of the genetic basis of AD, to the thorough testing, and target-testing of candidate disease-modifying therapies. On the other hand, knock-in and knock-out model creates better genetic modifications and better simulate human condition. In contrast to typical transgenic models, that sometimes include random incorporation of transgenes that may contribute to overexpression and non-physiological consequences [3].

#### 2.1.1. APP Knock-in Models

APP knock-in models, genetically modified rats, also have specific mutations related to AD incorporated into the native APP gene loci. This function is particularly good at not only promoting the pathological features of ad that has been studied in humans, which give researchers a more accurate platform to study the disease [9].

The development of APP knock-in models has been extensively aided by gene-editing technologies especially CRISPR/Cas9. Accurate genome editing allows introducing some point mutations at the APP gene, and it enables the generation of models containing accurate human mutations, without the misleading results sometimes seen in overexpressing animal models and in traditional transgenic animals [10].

A notable APP knock-in model is an APP NL-G-F mouse, which contains three humanized mutations: the Swedish mutation, the Iberian mutation and the Arctic mutation [11]. The APP NL-G-F mice develop very significant amyloid pathology and show cognitive abnormalities similar to AD humans. A defining feature of AD pathology in these models includes an increased presence of soluble Aβ oligomers, heightened neuroinflammation, and the progressive formation of amyloid plaques. Crucially, by avoiding the need on APP overexpression, our method guarantees that pathogenic alterations reported, are caused by the introduced mutations and not by an artifact of high protein production.

APP knock-in models are advantageous than traditional transgenic models in several ways. Primarily, these models lessen the possibility of artefactual phenotypes, which might make it more difficult to interpret the data, by not overexpressing APP. In conventional models, overexpression might cause aberrant processing of APP which can rise non-physiological amounts of tau pathology and Aβ, therefore could not fully represent the condition in humans [12]. Conversely, knock-in models preserve endogenous APP expression levels, enabling a more normal course of amyloid disease.

Moreover, disease pathways may be studied in a more controlled genetic environment thanks to knock-in models. Researchers can limit the impact of certain mutations associated with familial AD and examine how they contribute to the development of the illness by including these mutations [2].

In the end, it is more probable that APP knock-in mice will produce data that can be applied to diseases affecting humans. Because they more closely resemble the genetic and clinical features of AD, research findings using such frameworks are more likely to be relevant to the development of therapies for patients in the real world.

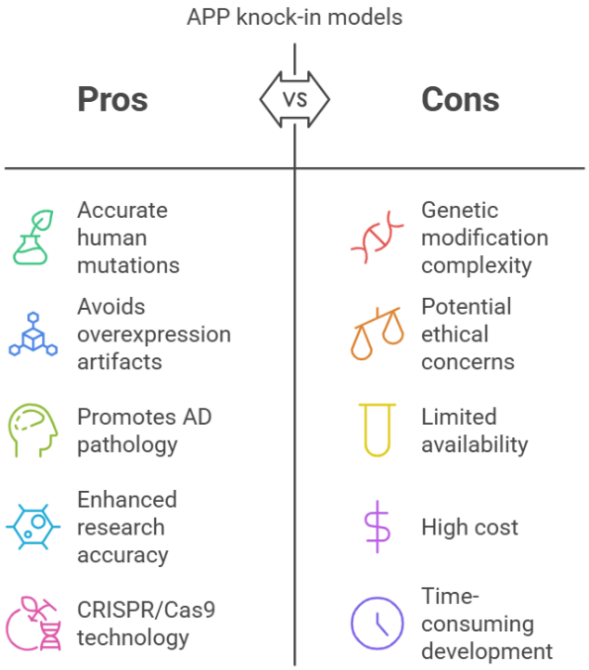


***Figure 1.*** *A pictorial representation of pros and cons of APP Knock-in models— The benefits and drawbacks of APP knock-in models in AD research are contrasted in this graphic. These models improve study quality and translatability by precisely stimulating AD pathophysiology, including human-specific mutations and maintaining physiological expression of genes, as well as, avoiding the overexpression artifacts found in conventional transgenic mice while utilizing CRISPR/Cas9 for precise genomic changes.*

### 2.1.2. PSEN1/PSEN2 Knock-in Models

APP is proteolytically processed into amyloid-beta (Aβ) peptides by the gamma-secretase complex, a multi-subunit enzyme of which presenilin-1 and presenilin-2 are critical constituents. Since familial AD has been closely linked to mutations in the presenilin-1 and presenilin-2 genes, these genes are important targets for creating rodent models that mimic the underlying processes of the illness. In order to do this, scientists have created humanized knock-in models that more closely mimic the pathogenesis of AD by inserting human PSEN1 and PSEN2 genes, or particular mutant variants, into mouse or rat genome [13].

Such animal models offer a useful platform for researching the vulnerable equilibrium between Aβ production and clearance since they closely mimic the human state in terms of Aβ synthesis and accumulation [14]. Furthermore, these humanized mice's alternative splicing may provide information on the intricate relationships linking metabolism of amyloid and decline in cognition.

The ability of knock-in models to incorporate human disease mutations while maintaining the endogenous regulatory systems of mouse genes is a significant advantage over conventional transgenic models. This makes the model more typical of genuine AD pathogenesis by ensuring that gene expression stays under physiological control and lowering the possibility of artificial overexpression.

The gamma-secretase complex, which cleaves APP into peptides Aβ40 and Aβ42, requires the catalytic subunits PSEN1 and PSEN2. The ration of Aβ40 to Aβ42 is a critical determinant in the course of Alzheimer's disease because Aβ42 is more likely to aggregate and constitutes the fundamental element of amyloid plaques [15]. Aβ42 is produced more often than Aβ40 in knock-in modes with PSEN1 or PSEN2 mutations because of altered gamma-secretase activity. One of the hallmarks of AD pathogenesis, especially in familial Alzheimer's dementia (FAD), is this change in the Aβ42/40 ration [16].

These knock-in mice have been used in studies to show that different PSEN1/PSEN2 mutations can affect gamma-secretase activity in different ways. Extended, prone to aggregation Aβ peptides accumulate as a result of some mutations that impair the enzyme's capacity to precisely cleave APP. Others might impact the gamma-secretase complex's assembly or structural integrity, which would further interfere with Aβ processing and hasten the development of amyloid plaque [17].

Through examining humanized PSEN1/PSEN2 knock-in rodents, investigators have learned a great deal about the processes underlying AD pathogenesis. These models have also been crucial in preclinical assessment of possible medical substance meant to lower Aβ generation or alter gamma-secretase activity [18]. Despite the fact that these models accurately depict some of the main features of AD, they fall short in capturing the disease's complexity, especially when it comes to the pathology of tau and neuronal degeneration.

## 2.2. Transgenic Mouse Models

Transgenic models have been essential in advancing our knowledge of AD because they allow scientists to investigate the molecular and cellular mechanisms underlying the condition. These models usually involve transferring human genes associated with AD into rodents, usually mice, in order to replicate key aspects of the disease's pathophysiology. These models were developed in response to the identification of genetic variants linked to FAD, including those affecting PSEN1, PSEN2, tau and APP [19].

### 2.2.1. Tau Transgenic Models

The tau protein is vital for the stability of microtubules in neurons, which in turn, are necessary for preserving cell function and structure. Numerous studies have demonstrated that aberrant hyperphosphorylation of tau causes neurofibrillary tangles, a crucial indicator of AD. Tau transgenic models is essential for researching tau-related neurodegeneration in AD, whereas APP and PSEN transgenic models are mostly focused on amyloid pathology [20].

The rTg4510 mouse model, which produces a mutant version of human tau (P310L) pursuant to the oversight of tetracycline-responsive promoter, is among the majority of renowned tau

transgenic models [21]. These mice show neurofibrillary tangles, neuronal degeneration and severe cognitive abnormalities by the time they are five or six months old. Understanding the causes of tau-driven neurodegeneration and developing research on tau-targeted therapeutics have both benefited greatly from the use of the rTg4501 model [22].

The JNPL3 mouse, which expresses the P310L mutation in tau via the prion promoter, is another significant model. Tau builds up in the central nervous system of these model animals, causing neuronal degeneration and motor deficits. The JNPL3 framework is especially helpful for researching the connection between pathology of tau and motor manifestations as well as for assessing possible therapies meant to lessen tau aggregation [7].

The particular mutation and promoter employed in these models determine the degree and course of tau ailments. Neuronal loss, synaptic dysfunction and tau inclusions are common in tau transgenic mice [7]. These models are useful for examining a wide range of signs of Alzheimer's in addition to amyloid anomalies, such as impairments in memory and dysfunction of motor control, because these pathological alterations are linked to behavioural deficiencies.

#### 2.2.2. Combined APP/PSEN/Tau Transgenic Models

Both amyloid and tau abnormalities are crucial in human AD, even though unique APP, PSEN and tau transgenic models offer insightful information on certain facets of AD pathogenesis [9]. Mutations in APP, tau and PSEN are included into combined transgenic mice to better reproduce the disease's complexity and enable a more thorough investigation of their interactions.

The 3xtg-AD mouse, which has mutations in tau (P310L), PSEN1 (M146V) and APP (Swedish), is one of the most well-known models. Key clinical characteristics of AD in humans are mirrored in this model, which shows gradual cognitive decline and the formation of neurofibrillary tangles and amyloid plaques [23]. It is especially useful for researching how tau and amyloid diseases interact, and it is a crucial instrument for evaluating treatment approaches that focus on various facets of the illness [24]. Furthermore, because of their propensity to acquire cognitive impairments at a rather quick pace, these mice are frequently employed in translational studies concerning disease-modifying therapies, which makes them valuable for assessing possible interventions.

***Table 1.*** *Key Transgenic Rodent models in Alzheimer's disease research.*

| | | | | | |
|---|---|---|---|---|---|
| Tg2576 | APPswe (Swedish Mutation) | Amyloid plaques, synaptic loss | Memory deficits (Morris Water Maze, Novel Object Recognition) | Early-stage amyloid pathology, synaptic dysfunction | [25] |
| PDAPP | APP (Indiana Mutation) | Early amyloid deposition, neuroinflammation | Severe cognitive impairments | Role of amyloid in neurodegeneration | [26] |
| 3xTg-AD | APP (Swedish), PSEN1, Tau | Amyloid plaques, tau tangles, neurodegeneration | Memory impairments, deficits in spatial learning | Interaction between amyloid and tau pathologies | [27] |
| 5xFAD | APP (Swedish, Florida), PSEN1 | Rapid amyloid plaque deposition, synaptic dysfunction | Cognitive decline, LTP/LTD impairments | Early-onset model, role of Aβ in synaptic toxicity and memory loss | [28] |
| Tau P310L | Tau (P310L mutation) | Neurofibrillary tangles, neuronal loss | Motor and cognitive impairments | Role of tau in neurodegeneration and cognitive deficits | [29] |

## 3. Novel and Emerging Rodent Models

### 3.1. Humanized Rodent Models

A significant advancement in biomedical research has been made possible by humanized rodent models, which offer a priceless platform for researching human conditions and evaluating possible treatments in a live system that closely resembles physiology in humans [30]. By implanting human genes, organs, tissues or cells, into mice pr rats, these models enable researchers to study biological processes that are exclusive to humans [31].

Humanized models come in several forms, such as genetically humanized models, which include human genes into the animal's genome and engrafted models, which involve transplanting human cells or tissues into the rodents [32]. Human genes frequently take the position of their rodent counterparts in genetically humanized models, which in turn, makes them especially helpful for researching disease processes unique to humans [33]. These models are crucial for pharmaceutical discoveries and toxicological evaluation because they also aid researchers in understanding how human genes affect metabolism and response of drugs [34].

Adding human PSEN1, PSEN2 and APP genes is one of the main strategies for creating humanized AD models. These transgenic mice acquire amyloid-beta plaques in addition to

displaying cognitive deficits resembling those observed in AD humans. Because they mimic the aggressive and early onset characteristics of FAD, models that express mutant variants of these genes – APPswe. PSEN1De9 and PSEN2N1l – are especially useful [35].

Human tau protein mutations, notably P310L and P310S mutations linked to frontotemporal dementia, may also be expressed in humanized mice. Researchers may investigate the intricate relationship between tau and amyloid anomalies by using these animals to create neurofibrillary tangles [36]. Inducible genetic expression systems, which offer chronological regulation of the activation of AD related genes, are a relatively recent development in humanized models. Researchers may now examine the disease at various stages and evaluate the impact of possible therapies as it develops thanks to this breakthrough [37].

Conversely, in engrafted simulations, human tissues or cells are transplanted into immuno-compromised rodents, which do not mount a response of the immune system to the transplanted material, guaranteeing the survival functionality of the human cells [38]. Recognizing that they enable researchers to examine tumor development, metastasis and treatment responses in a live organism, these models are very helpful in the study of cancer. Furthermore, immunological research, particularly the creation of novel immunotherapies, frequently employs engrafted models [18].

Advanced gene-editing technologies like CRISP/Cas9, which enable the exact insertion of human genes into the mouse genome, are being used to create humanized models [10]. Significant obstacles must be overcome for this procedure to be successful, such as species-specific variations in genetic control, maintaining appropriate gene expression, and reducing unwanted side effects. Notwithstanding these difficulties, humanized rodent models remain a vital resource for researching Alzheimer's disease as well as other illnesses, helping to close the gap between fundamental research and practical implications.

## 3.2. CRISPR/ Cas9 and Gene Editing Approaches

Genetic engineering has been transformed by CRISPR/Cas9, which provides an unparallel degree of accuracy and versatility in altering the genomes or living things. This method, which was initially inspired by a bacterial immune defense mechanism, enables researchers to create extremely precise DNA incisions at specified sites. Once these targeted breaks occur, the cell's natural repair processes take over, either fixing the cut or enabling the introduction of desired genetic modifications. This breakthrough has opened new frontiers in genetic research, therapeutic interventions, and biomedical advancements [39]. Genes can be deleted, mutations can be introduced, or new genetic material can be inserted using this procedure.

CRISPR/ Cas9 is used to insert human counterparts into particular mouse or rat genes in order to create humanized models. Typically, guide RNAs (gRNAs) that target the appropriate site in the genome are designed to do this. At this point, the Cas9 enzyme causes a double-strand break that may be fixed by homologous recombination, which substitutes the human gene for the original animal gene using the human gene as a template [10].

In AD research, CRISPR/Cas9 has been utilized to create knock-in models that produce humanized versions of tau, PSEN1/2 and APP. Scientists have used CRISPR/Cas9 to directly insert certain point mutations linked to familial AD into the endogenous loci of important genes in mice, in order to create models that more accurately represent the genetic landscape of Alzheimer's disease in people [40]. Along with illuminating their more general impacts on functions of neurons and decline in cognition, these models offer important insights into how specific mutations impact amyloid and tau-related diseases.

Creating knockout models, in which particular genes are completely deactivated, is another potent use of CRISPR/Cas9 in Alzheimer's research. These models aid researchers in understanding how certain genes contribute to the pathophysiology of AD [41]. For instance, the loss of microglial genes linked to AD risk, such as TREM2, has shed important light on how neuroinflammation contributes to the development of the illness [42].

Among the increasingly exciting areas of Alzheimer's research, is gene therapy with CRISPR/Cas9. This technique has the potential of both lessening the symptoms of AD as well as stopping its progression by accurately detecting and fixing damaging mutations in living things. According to preclinical research in neurodegenerative models, CRISPR/Cas9-based gene editing can successfully lower hyperphosphorylation of tau and buildup of amyloid-beta plaques, which would ultimately enhance cognitive functions [43].

In addition to CRISPR/Cas9, other gene-editing methods such as transcription activator-like effector nucleases (TALENs) and zinc finger nuclease (ZFN) have been employed to generate AD models and explore possible therapeutic approaches These techniques have contributed to the advancement of the field even if they are not as flexible as CRISPR/Cas9 [44].

Single nucleotide polymorphisms (SNPs) have been identified by genome-wide association studies (GWAS) as potential genetic risk factors for Alzheimer's disease. Researchers are using gene-editing techniques to alter these SNPs in humanized models in order to gain a better understanding of their effect on the expression of genes, function of proteins, and pathology of the disease [42].

Furthermore, new gene-editing techniques are being investigated to control or inhibit the expression of genes linked to AD. Base editing is one method that allows for accurate point mutation repair without breaking double-stranded DNA. This method has great therapeutic potential, especially for monogenic types of AD, in which the development of the illness is

caused by a single nucleotide change [19].

Another new tactic that changes the epigenetic control of genes associated to AD to change their expression is epigenome editing. Researchers can rewire gene expression patterns linked to Alzheimer's disease by fusing a deactivated form of Cas9 (dCas9) with epigenetic modifiers. This might possible reverse detrimental molecular alterations and open up new treatment avenues.

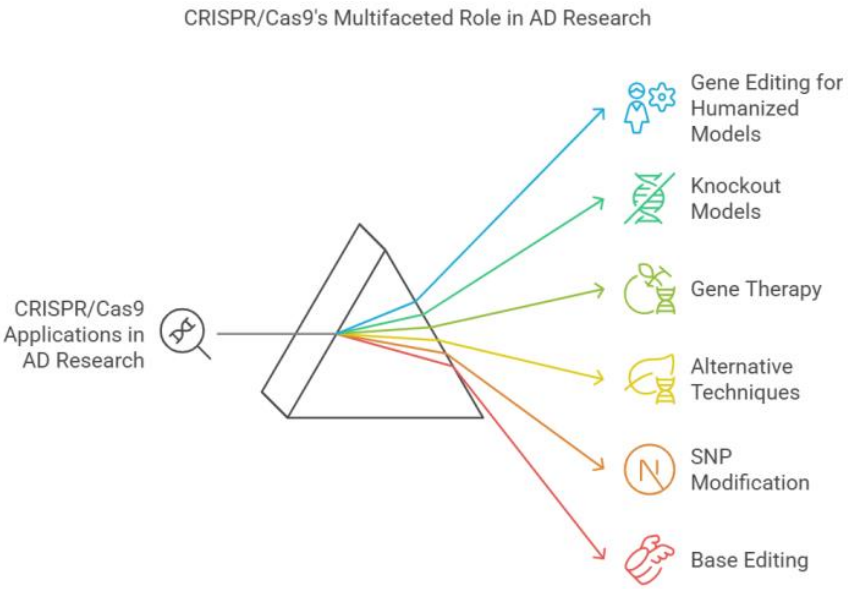


***Figure 2.*** *CRISPR/Cas9 Application in AD research – The many uses of CRISPR/Cas9 in AD research is depicted in this figure. Gene editing for humanized models is made possible by CRISPR/Cas9, which introduces genetic variations unique to humans, improving translational accuracy. By specifically deactivating AD-related genes, it makes it easier to crate knockout model as well as used in gene therapy applications to fix mutations linked to the pathology and potentially implement therapeutic treatments. Alternative methods investigate changes such as epigenetic regulations that go beyond traditional gene editing and Base editing offers accurate, permanent nucleotide modifications without double-strand breaks.*

# 4. Pathological, Behavioural, and Cognitive Assessments

## 4.1. Pathological Assessments

### 4.1.1. Techniques for Assessing Amyloid Plaques

Both quantitative and qualitative methods are used to analyse amyloid beta plaque distribution and existence in the brain.

#### (i). Immunohistochemistry

One of the most used techniques for identifying amyloid plaques in the brain tissue is immunohistochemistry (IHC). This method makes use of antibodies like 6E10 or 4G8, which bind to distinct Aβ sequence regions. By labelling these antibodies chromogenically or fluorescently, researchers may then see the number and location of amyloid plaques in the brain slices. IHC is frequently used in conjunction with stereological methods to further measure plaque load across various rain areas and provide observations regarding the pattern of distribution of amyloid pathology [45].

#### (ii). Enzyme-linked Immunosorbent Assay

The enzyme-linked immunosorbent assay (ELISA) is a very sensitive and quantitative method for determining the amounts of soluble and insoluble Aβ in brain homogenates. This technique uses a secondary antibody coupled to an enzyme that generates a detectable signal to identify Aβ peptides after they have been initially trapped by certain antibodies. Understanding the development of amyloid pathology and assessing the effectiveness of prospective therapeutic approaches that target Aβ aggregation and generation depend on the ability of ELISA to differentiate between Aβ species, such as Aβ40 and Aβ42 [46].

#### (iii). Thioflavin-S and Congo Red Staining

Given that dyes selectively adhere to beta-sheet structures, which are a characteristic of amyloid plaques, histological dyes like Thioflavin-S and Congo Red are frequently employed to view amyloid fibrils. A fluorescent dye called thioflavin-S makes it easier to see fibrillar Aβ aggregates, which are indicative of mature plaques. In animal models of AD,

Congo Red is a valid marker for differentiating amyloid amyloid plaques due to its distinctive apple-green birefringence when viewed under polarized light [47].

### (iv). Silver Staining

Silver staining, which includes techniques like the Gallyas or Bielschowsky processes, is another way to find amyloid plaques. These methods use the diverse ways that silver salts attach to aggregated amyloid fibrils to create a staining pattern that ranges from dark brown to black. Silver staining is still a useful method for evaluating total plaque deposition, although being less specific than IHC. It may be used in conjunction with other histopathological markers to provide a more thorough assessment of pathology of amyloid [48].

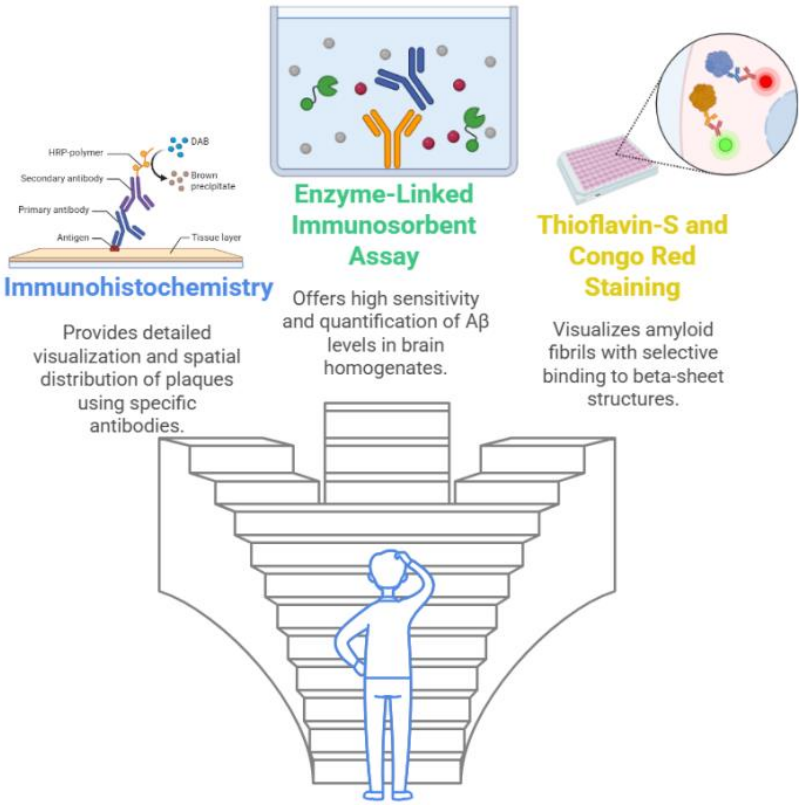


***Figure 3.*** *Possible techniques which can be used to assess amyloid plaques in Alzheimer's disease – Three main methods for assessing Aβ plaques in AD research are shown in this illustration. Using particular antibodies, immunohistochemistry helps with histopathological investigation by providing a comprehensive visual representation and geographical distribution of plaques. ELISA is an essential instrument for biochemical evaluation because of its outstanding sensitivity and quantification. The Congo Red enables the detection of aggregates via refraction and fluorescence.*

### 4.1.2. Assessing Tau Pathology

Tau pathology, which includes the buildup of hyperphosphorylated tau protein as well as the consequent development of neurofibrillary tangles (NFTs), is a hallmark of AD [49]. Tau pathology is evaluated in rodent models using a variety of methods.

### (i). Paired Helical Filaments (PHFs) - Tau Detection

Hyperphosphorylated tau makes up paired helical filaments (PHFs), which are the ultrastructural element of NFTs. PHF-specific antibodies, such AT100, are frequently utilized for PHF-tau detection because they specifically target PHF-tau epitopes. PHF-tau antibody-based immunohistochemistry makes it possible to see NFTs and pre-tangles in the brain tissue. In transgenic rodent models, that express mutant human tau, this method is very useful for examining the development of tau-related disease [48].

### (ii). AT8 Staining

For identifying hyperphosphorylated tau at serine 202 and threonine 205, AT8 is one of the most used antibodies. NFTs, neuropil threads and other early as well as mature tau diseases may all be successfully identified with this staining method. AT8 staining is frequently used in conjunction with other tau-specific antibodies to provide a thorough evaluation of tau phosphorylation patterns and their dispersion throughout the brain. Important markers of the severity of tau disease include the abundance of AT8-positive neurons and the magnitude of

AT8 staining in certain brain areas, such as the hippocampus and cerebral cortex [49].

### (iii). Western Blotting for Phosphorylated Tau

Another popular technique for analysing tau pathology is Western blotting, which measures the amount of phosphorylated tau in brain homogenates. Using this method, proteins are separated using electrophoresis and then phosphorylated tau-specific antibodies are used for detection. Western blotting offers vital cues into the biochemical alterations linked to tau disease in rodent models by evaluating several tau phosphorylation species and tracking aggregation of tau [50].

### (iv). Tau Aggregation Assay

Biochemical tests that assess tau's ability to develop into filaments in vitro can also be used to investigate tau aggregation. In these investigations, aggregation-inducing substances are frequently introduced to recombinant or brain-derived tau and the development of fibrils is seen by Thioflavin-S fluorescence or electron microscopy. These tests are especially helpful in identifying the molecular processes behind tau aggregation and in screening possible therapeutic drugs that targets tau disease [51].

### 4.1.3. Assessing Neuroinflammation and Gliosis

As AD advances, neuroinflammation – which is fuelled by astrocyte and microglia activation – becomes increasingly significant. Several indicators linked to glial activation are used by researchers to evaluate neuroinflammation in rodent models.

### (i). Iba1 Staining for Microglia

Ionized calcium-binding adaptor molecule 1 (Iba 1), a frequently used marker for evaluating microglial activation in AD models, is expressed by microglia, the immune cells that dwell in the brain microenvironment. Activated microglia are frequently seen assembling around amyloid plaques in reaction to these deposits, which aids in neuroinflammatory processes [52]. Researchers can get important views into the involvement of microglia in the course of AD by analysing their shape, density and geographic distribution in connection to pathology of amyloid and other disease characteristics using Iba 1 immunohistochemistry [53].

### (ii). GFAP Staining for Astrocytes

In reaction to AD-related brain injury, astrocytes – another important component of neuroinflammation – increase glial fibrillary acidic protein (GFAP). Using immunohistochemical labelling, reactive astrocytes may be identified by their hypertrophy and elevated GFAP expression [54]. In rodent AD models, GFAP staining is frequently used to measure astrogliosis, especially in areas with tau pathology or amyloid plaque deposition. The degree and duration of neuroinflammatory reactions are frequently associated with the GFAP staining intensity [42].

### (iii). Cytokine Profiling

Finding pro and anti-inflammatory cytokines in the CNS requires the use of cytokine profiling. Multiple cytokines may be quantified simultaneously using methos like multiplex ELISA and cytokine bead arrays, providing a thorough understanding of the neuroinflammatory milieu. In AD rodent models, heightened quantities of cytokines that trigger inflammation, such as TNF, IL-1 and IL-6, are commonly seen and associated with astrocytes and microglial activation [55]. Clarifying the contribution of neurological inflammation in AD etiology and assessing possible anti-inflammatory treatment approaches depend on understanding of these molecular indicators.

## 4.2. Behavioural Assessments

AD rodent models are crucial for researching the behavioural abnormalities and cognitive decline linked to the illness. Researchers may assess memory loss, learning challenges and behavioural impairments that closely mimic those observed in actual AD patients using these models. Scientists can monito the development of impairments and evaluate the efficacy of possible therapies by using behavioural and cognitive tests [8].

The most widely used behavioural examinations in AD rodent models are examined in this part, along with their use in measuring cognitive decline and examining the relationship between cognitive impairment and underlying disease pathology.

### 4.2.1. Commonly Used Behavioural Assays

### (i). Morris Water Maze

One of the most popular examinations for evaluating spatial learning and memory in rodent models of AD is the Morris water maze (MWM). In order to find a concealed platform under the surface of a circular pool of water, rats must be able to navigate the pool utilizing distant visual clues. In example, escape latency – the amount of time it takes the rodent to locate the platform – is one of the important performance factors that researchers analyse through repeated trials.

Long escape latencies are frequently seen in rats with tau hyperphosphorylation or buildup of amyloid, which are characteristics of AD and may indicate problems with spatial memory. The MWM is particularly useful for researching hippocampus- dependent learning and memory since AD largely affects the hippocampus. Research on AD models, including 3xTg-AD mice, has shown severe impairments in motor function and spatial learning, which are directly linked to the development of Alzheimer's related neurodegeneration [56].

### (ii). Novel Object Recognition

The Novel object recognition test (NOR) assesses recognition memory by using rodents' innate interest to explore novel

objects. In order to test the rodents, two comparable things are initially presented to them and then one of those objects is replaced with a different one. Healthy recognition memory is defined as a deeper exploration of the unknown items. Deficits in this task have been shown in rodent models of AD with mutations in tau as well or APP over expression. As demonstrated by their incapacity to distinguish between familiar and new objects, mice with amyloid-beta accumulation, for instance, commonly have cognitive impairment typical of AD [6].

#### (iii). Y-maze and T-maze Spontaneous Alteration

Y-maze and T-maze tasks, called spontaneous alteration, is used to assess working memory. It is the natural tendency of rodents to investigate new sections of the going back to previously explored sections. Reduced alterations rated in AD rodent models, especially those harbouring FAD mutations, suggest impaired working memory. Because these abilities are compromised early in AD, this test is especially helpful for evaluating short-term memory and flexibility in cognition [57].

### 4.2.2. Assessing Cognitive Decline in Rodent Models

One of the primary signs of AD is cognitive decline, and rodent models show abnormalities in several cognitive regions that correspond with the course of AD in humans. In AD rodent models, working memory, recognition memory, as well as spatial memory are frequently compromised. These deficits may be identified using a variety of behavioural tests, including the MWM, NOR, and Y-maze. Amyloid plaques and tau tangles appear in transgenic models such as the 5XFAD, APP/PS1, and 3xTg-AD mice, as early as 3-6 months of life, and they are frequently accompanied by detectable cognitive deterioration [58].

Similar to the gradual deterioration in cognition observed in AD patents, longitudinal studies of these models demonstrate a consistent reduction in cognitive ability. For instance, the APP/PS1 paradigm states that while issues with spatial memory initially appear at six months of age, working memory deficits become more severe at nine months of age. Rodent models are very helpful for understanding the temporal aspects of cognitive decline linked to AD since these deficits are progressive [55].

## 4.3. Electophysiological and Synaptic Studies

### 4.3.1. Electrophysiological Assessments

Two examples of synaptic plasticity that are believed to represent significant brain mechanisms governing learning and memory – both of which are significantly impaired in AD – are long-term potentiation (LTP) and long-term depression (LTD). Learning and memory are significantly impacted by the basic mechanisms of LTD and LTP, which control synaptic strength. While LTP is linked to the building and consolidation of synapses in response to repetitive activity, LTD entails the weakening of synaptic connections. These processes, especially in the hippocampus, are critical for formation of memory and are intimately related to the cognitive deficits shown in Alzheimer's disease [59].

Even before amyloid plaques or NFTs show up, electrophysiological research on rodent models of AD indicated that one of the first processes to be compromised, is synaptic plasticity. Learning and memory problems are associated with diminished hippocampus LTP and increase LTD in several transgenic AD models, including Tg2576 and 5xFAD mice [60]. The buildup of Aβ oligomers, that interfere with normal synaptic function by changing NMDA and AMPA receptor activation, is primarily responsible for these deficiencies [61].

According to research, Aβ oligomers cause synaptic dysfunction by inhibiting LTP and encouraging excessive LTD, which causes AD patients to gradually lose their synapses. Age-dependent LTP deficiencies, for instance, are shown in Tg2576 mice and are closely linked to elevated Aβ buildup. Additionally, electrophysiological recordings have shown that Aβ increases synaptic depression through LTD that is reliant on the NMDA receptor. Aβ's function in AD related cognitive decline is further supported by in vitro research employing hippocampus slices treated with Aβ oligomers, which demonstrated that Aβ directly impairs synaptic plasticity [62].

### 4.3.2. Synaptic Marker Analysis

Analysing synaptic markers like postsynaptic density protein 95 (PSD95) and synaptophysin is necessary to determine synaptic integrity and function in AD rodent models. While synaptophysin is a presynaptic vesicle protein that is commonly used as a measure for synaptic density, PSD95 is a postsynaptic scaffolding protein that is crucial for synaptic transmission [18]. With techniques like Western blotting and IHC, both markers are commonly analysed to assess synaptic degeneration, a characteristic of AD pathophysiology.

Synaptophysin and PSD95 quantities have been shown to significantly decline in transgenic animals as the illness progresses. This loss of synapses is thought to be caused by the detrimental impacts of tau and Aβ protein clumps. For example, APP/PS1 transgenic mice displays accumulation of Aβ plaques which are associated with decreased synaptophysin levels, suggesting synaptic dysfunction. A decrease in PSD95 expression also indicated an expense of postsynaptic frameworks, which worsens synaptic transmission dysfunction and decline in cognition [35].

# 5. Limitations of Rodent Models

Our comprehension of AD has greatly benefited from the use of rodent models, especially when it comes to investigating the pathophysiology, disease causes and possible therapies. They cannot, however, precisely mimic the pathology and neurodegeneration of AD in humans due to a number of constraints. These restrictions affect the translational significance of research conducted on rodents and are cause by genetic,

physiological and neuroanatomical variations between humans and rodents.

### 5.1. Genetic Limitations

The genetic difference between humans and rodents is one of the main drawbacks of using them as models. AD is a complicated neurological illness that, especially in its sporadic form, frequently involves interactions between numerous genes. Nonetheless, FAM mutations, such as those in PSEN1 or APP genes, constitute the basis for the majority of rodent models that are employed. These models cannot fully capture sporadic AD, that is more common in the human population, because these mutations only account for 1-5% of all AD cases [42].

### 5.2. Incomplete Replication of AD Pathology

While transgenic rodent models are successful in stimulating some components of AD, such as tau pathology and Aβ plaque development, they are unable to replicate other important parts of the pathology of AD in humans. In this regard, the majority of rident models do not show the development of neurofibrillary tangles or extensive neurodegeneration observed in human AD, moreover, although tau tangles and amyloid plaques are frequently employed as indicators of the disease, rodent models never exhibit the same level of neuronal death and atrophy as is seen in human brains.

### 5.3. Limited Lifespan and Disease Progression

Rodents live far shorter lives than humans do, which has an impact on how AD-like symptoms develop naturally. In people, AD can develop over decades, starting with moderate cognitive impairments and progressing to severe dementia. The delayed development and course of AD seen in humans is not precisely mirrored by rodent models, which are usually investigate over a considerably shorter duration and frequently result in accelerated disease progression. The protracted prodromal phase of the illness, which is crucial for early identification and management in human AD, is less well-represented in the models due to this constraint [18, 32].

### 5.4. Lack of Comorbidities

AD patients frequently have a number of comorbidities that can have a substantial impact on the course of the illness, including hypertension, diabetes and cardiovascular problems [8]. On the other hand, rodent models usually lack these extra elements, which can restrict how broadly outcomes from such models are capable of being leveraged in human situations. The value of these models in reflecting the complete spectrum of the illness is further diminished by the difficulty of reproducing environmental and lifestyle variables that influence sporadic Alzheimer's disease in humans [47].

## 6. Conclusion

Despite decades of research, Alzheimer's disease remains a global health crisis without a definitive cure. Rodent models have been foundational in deconstructing the mechanisms of the disease, particularly in clarifying the roles of amyloid-beta deposition, tau hyperphosphorylation, and neuroinflammation. While transgenic models have provided a window into familial AD pathogenesis, they often fail to capture the full clinical spectrum of the human condition, most notably the widespread neuronal death and the metabolic comorbidities characteristic of sporadic AD.

The future of AD research lies in closing this translational gap. By integrating CRISPR/Cas9 gene editing and humanized genomic sequences into rodent lines, we can move beyond simplistic overexpression models toward systems that more accurately mirror human gene expression and sporadic disease etiology. Combining these advanced genetic tools with more sophisticated behavioural and environmental assessments will refine the predictive value of preclinical trials. Ultimately, the transition from successful rodent studies to meaningful human therapies depends on this shift toward integrated, multi-factorial models that reflect the true complexity of the aging human brain.

## Abbreviations

| | |
|---|---|
| Aβ | Amyloid-beta |
| AD | Alzheimer's Disease |
| AMPA | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid |
| APP | Amyloid Precursor Protein |
| CNS | Central Nervous System |
| CRISPR | Clustered Regularly Interspaced Short Palin-dromic Repeats |
| dCas9 | Deactivated Form of Cas9 |
| ELISA | Enzyme-linked Immunosorbent Assay |
| FAD | Familial Alzheimer's Disease |
| GFAP | Glial Fibrillary Acidic Protein |
| gRNAs | Guide RNAs |

| | |
|---|---|
| GWAS | Genome-wide Association Studies |
| Iba1 | Ionized Calcium-binding Adaptor Molecule 1 |
| IHC | Immunohistochemistry |
| IL-1 | Interleukin-1 |
| IL-6 | Interleukin-6 |
| LTD | Long-term Depression |
| LTP | Long-term Potentiation |
| MWM | Morris Water Maze |
| NFTs | Neurofibrillary Tangles |
| NMDA | N-methyl-D-aspartate |
| NOR | Novel Object Recognition Test |
| PHFs | Paired Helical Filaments |
| PSD95 | Postsynaptic Density Protein 95 |
| PSEN1 | Presenilin-1 |
| PSEN2 | Presenilin-2 |
| SNPs | Single Nucleotide Polymorphisms |
| TALENs | Transcription Activator-like Effector Nucleases |
| TNF | Tumor Necrosis Factor |
| ZFN | Zinc Finger Nuclease |

## Author Contributions

**Abhinav Singh:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft

**Lena Duerner:** Resources, Software, Validation, Visualization, Writing - review & editing

## Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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