



Published in final edited form as:

Neurobiol Dis. 2020 June ; 139: 104811. doi:10.1016/j.nbd.2020.104811.

Alzheimer's Disease Pathology in ApoE Transgenic Mouse Models: The Who, What, When, Where, Why, and How

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Abstract

The focus on amyloid plaques and neurofibrillary tangles has yielded no Alzheimer's disease (AD) modifying treatments in the past several decades, despite successful studies in preclinical mouse models. This inconsistency has caused a renewed focus on improving the fidelity and reliability of AD mouse models, with disparate views on how this can be accomplished. However, the interactive effects of the universal biological variables of AD that include age, *APOE* genotype, and sex are often overlooked. Age is the greatest risk factor for AD, while the $\epsilon 4$ allele of the human *APOE* gene, encoding apolipoprotein E, is the greatest genetic risk factor. Sex is the final universal biological variable of AD, as females develop AD at almost twice the rate of males and, importantly, female sex exacerbates the effects of *APOE4* on AD risk and rate of cognitive decline. Therefore, this review evaluates the importance of context for understanding the role of *APOE* in preclinical mouse models. Specifically, we detail how human AD pathology is mirrored in current transgenic mouse models ("What") and describe the critical need for introducing human *APOE* into these mouse models ("Who"). We next outline different methods for introducing human *APOE* into mice ("How") and highlight efforts to develop temporally defined and location-specific human apoE expression models ("When" and "Where"). We conclude with the importance of choosing the human *APOE* mouse model relevant to the question being addressed, using the selection of transgenic models for testing apoE-targeted therapeutics as an example ("Why").

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Declaration of competing interests

The authors have no conflicting interests to disclose.

Keywords

Alzheimer's Disease (AD); familial AD transgenic mice (FAD-Tg); apolipoprotein E; sex and AD risk; *APOE4* and AD risk; EFAD-Tg mouse model; *APOE*-TR mouse model; apoE as a therapeutic target

I. The “What” of *APOE* Transgenic AD Mouse Models: The Development of AD Pathology and the Effect of Universal Biological Variables

Alzheimer's Disease (AD) is a complex, uniquely human condition that has eluded understanding and effective treatment for over a century. Nevertheless, dozens of transgenic (Tg) mouse models that recapitulate specific aspects of AD pathogenesis enable mechanistic interrogation and hypothesis testing impossible to achieve in human patients. In this first section, we describe the major pathological hallmarks of AD, review Tg mouse models that reproduce AD-like pathology, and introduce the universal biological variables of AD, specifically age, *APOE* and sex. These three variables are considered universal in that all people age, and all people have a biological sex and two *APOE* alleles, as compared to rare risk-enhancing mutations or to modifiable risk factors that impact only a certain proportion of the population.

Pathological Hallmarks of AD

Amyloid is a common quaternary protein structure consisting of parallel β -pleated sheets, providing the most condensed storage form for overabundant proteins (Chiti and Dobson, 2017). Unlike other quaternary structures, there is no amino acid sequence that defines amyloidogenic proteins; rather, it is the most condensed storage for any overproduced protein. In AD, these two overproduced proteins are amyloid- β (A β) peptide and microtubule associated protein tau (MAPT) that aggregate into amyloid structures termed amyloid plaques and neurofibrillary tangles (NFT). These two structures are the pathological hallmarks required for a definitive postmortem diagnosis of AD (Serrano-Pozo et al., 2011).

Because amyloid plaques are observed before NFT in humans, early hypotheses described amyloid plaques as precipitants to tangle formation, which then produce the progressive synaptic loss, neuronal atrophy, and cognitive decline that characterize the disease (Bloom, 2014, Selkoe and Hardy, 2016, Beyreuther and Masters, 1991). Evidence has largely disproven this “amyloid hypothesis,” with two major findings contradicting a direct connection between plaque load and cognitive deficits. First, dozens of trials with amyloid-targeting therapeutic agents have failed to produce any clinical benefit, despite pronounced reductions in amyloid pathology (recent conflicting Phase 3 results with aducanumab notwithstanding) (Liu et al., 2019, Mehta et al., 2017). Second, a significant subset of the elderly displays extensive amyloid plaque deposition yet age without signs of cognitive impairment (Bennett et al., 2006). Conversely, familial AD (FAD) is caused exclusively by mutations that enhance proteolytic processing of amyloid precursor protein (APP) to amyloid- β (A β), primarily the A β 42 isoform, indicating a critical role for the A β peptide in the disease process (as reviewed by Van Cauwenberghe et al., 2016). The key research focus now resides on the soluble oligomeric A β (oA β) species – the formation, toxicity, and

persistence of which is influenced by numerous other pathologic factors beyond the scope of this review (e.g. inflammation, metabolic perturbation, and lipid homeostasis).

With NFT comprising the other pathological hallmark of AD, the role of tau has also been investigated extensively in preclinical studies. *MAPT* is a large, 134kb gene that may contain up to 16 exons in its mature RNA (Caillet-Boudin et al., 2015, Sergeant et al., 2005). Alternative splicing and other modifications result in the expression of 6 unique tau isoforms, which differ in that they possess either three or four copies of a C-terminus repeated region (3R or 4R) and anywhere from zero to two N-terminal inserts (N0, N1, N2) (Buee et al., 2000). These isoforms may be abnormally phosphorylated under various pathogenic conditions, thereby increasing the propensity of the protein to aggregate. Tau aggregates have numerous toxic effects on axonal transport, synaptic function, and neuronal survival, which may occur in both an amyloid-dependent and -independent manner (Ittner and Gotz, 2011, Chong et al., 2018).

Investigations into the aggregation cascades of A β and hyperphosphorylated tau have identified two distinct pathways (Figure 1) (Crespo et al., 2016, Powers and Powers, 2008, Necula et al., 2007, Ehrnhoefer et al., 2008, Perez et al., 2019, Uversky, 2010, Kjaergaard et al., 2018). In the “on pathway,” the given protein monomers aggregate to form oligomers, followed by continually larger structures (protofibrils, fibrils, and coiled coils for A β ; paired helical filaments for tau), ultimately culminating in the stacking of β -pleated sheets in parallel to form the final amyloid structure (plaques or tangles). Although illustrated as discrete events, this pathway may more accurately be considered a series of transient intermediates. Alternatively, in the “off pathway,” the protein monomers combine to form soluble oligomers as the stable end-product. Ongoing research continues to debate the details (and existence) of these two pathways; however, this framework provides an explanation for amyloid-positive, cognitively normal individuals. The formation of persistent A β and tau oligomers through the “off” pathway – versus their transient, intermediate nature in the “on” pathway – also better explains the critical pathogenic role and marked toxicity of both oA β and tau oligomers, which have been the subject of countless studies reviewed multiple times elsewhere (Cline et al., 2018, Sakono and Zako, 2010, Benilova et al., 2012, Lasagna-Reeves et al., 2011, Shafiei et al., 2017). While beyond the scope of this review, this framework has also been increasingly applied to other neurodegenerative conditions characterized by abnormal protein misfolding and accumulation, such as α -synuclein in Parkinson’s disease, in which the soluble oligomeric form may actually be the proximal neurotoxin (Bengoa-Vergniory et al., 2017).

Amyloid/A β Models—The critical role of A β in AD led to the development of Tg mice carrying FAD mutations (FAD-Tg) that increase the proteolytic processing of APP to A β 42 or increase the A β 42/A β 40 ratio. Under neuron-specific promoters, mutations in human (h-) genes encoding APP, presenilin-1 or presenilin-2 genes (*APP*, *PS1*, and *PS2*, respectively) result in AD-like amyloid pathology in FAD-Tg mice (Oakley et al., 2006, Games et al., 1995, Duff et al., 1996, Holcomb et al., 1998, Hsiao et al., 1996, Radde et al., 2006, Mucke et al., 2000, Jankowsky et al., 2001). These mice are a powerful tool for the study of specific features of AD pathology and as preclinical AD models. A comparison of the regional development of A β pathology in brain of FAD-Tg mice and human AD patients is provided

in Figure 2A. To aid in orientation, four particular regions (frontal cortex, hippocampus, cerebellum, and brain stem) common to both species, plus mouse olfactory bulb as an obvious difference, are labeled in the leftmost panel. A β deposition in human AD patients begins in frontal and temporal cortex before progressing to hippocampus and occipital cortex. In the final stages, amyloid deposition is saturated in the frontal and temporal cortices (Masters et al, 2015). Similarly, FAD-Tg mice exhibit plaque deposition beginning in the subiculum and deep layers of the frontal cortex, followed by a spread of deposits throughout the cortex, and into the hippocampus, and thalamus (Oakley et al., 2006, Tai et al., 2017, Youmans et al., 2012). Comparable to human AD, the most severe pathology is in the frontal cortex and subiculum. FAD-Tg models do sacrifice physiological relevance by overexpressing multiple mutant transgenes via heterologous promoters, resulting in A β accumulation occurring in early or mid-adulthood, compromising the impact of aging.

More recent models have been engineered as humanized *APP* targeted replacement (TR) mice, in which the (mutated or normal) human A β coding domain is introduced and controlled by the mouse promoter and enhancer regions. In these mice, more physiologically relevant expression levels of *APP* mutants are still sufficient to induce AD-like pathology and cognitive deficits, with a modest worsening of pathology, but not cognition, with female sex (Saito et al., 2014, Masuda et al., 2016, Sakakibara et al., 2018, Pervolaraki et al., 2019). Given their relatively recent development, these *APP*-TR mice require further analysis to ensure they consistently recapitulate various features of amyloid pathology – such as age of onset, regional progression, and morphology – that have been extensively characterized in FAD-Tg mice.

Tau Models—Given the toxic effects of tau and following failures of A β -targeting therapies tested in FAD-Tg mouse models, mouse models of tau pathology have become more widespread as an alternative or complementary approach. Mouse (m-) tau is predominantly expressed as the three 4R isoforms and does not naturally aggregate into stable NFTs (Janke et al., 1999, Kampers et al., 1999). To account for these features, Tg mice that incorporate h-*MAPT* (*MAPT*-Tg) have been developed. Because h-tau expression is complex, *MAPT*-Tg mice have utilized different isoforms of h-tau with or without various *MAPT* mutations to induce tau protein aggregation and NFT formation, including P301S, P301L and K280 (Roberson, 2012, Mocanu et al., 2008, Ramsden et al., 2005, Yoshiyama et al., 2007; as summarized in Koss et al., 2016, Jankowsky and Zheng, 2017). This extensive variation means that a diverse library of *MAPT*-Tg mouse models, which develop tau pathology to varying degrees over unique time courses, is available to study tau-mediated neurodegeneration. However, the complexity of h-tau makes standardization and comparison of *MAPT*-Tg mouse models challenging.

Importantly, while mutations in *APP* or *PS1* cause FAD in humans, mutations in *MAPT* cause various forms of frontotemporal dementia (FTD) (Poorkaj et al., 1998, Spillantini and Goedert, 1998, Hutton et al., 1998, Irwin, 2016). Notably, FTD demonstrates a pattern of tauopathy distinct from the Braak staging characteristic of tauopathy in AD (Figure 2B). While tauopathy associated with AD in humans begins in the entorhinal cortex and midbrain (Braak and Braak, 1991, Hyman et al., 2012), FTD, as its name suggests, first impacts the frontal and temporal cortices with the entorhinal cortex only affected later in the disease

(Irwin, 2016). As reviewed recently, *MAPT*-Tg mice more closely recapitulate a human FTD pattern than an AD pattern with pathology concentrated in the frontal cortex (Jankowsky and Zheng, 2017). Compared to even the most aggressive FAD-Tg models (e.g. 5xFAD), mutated h-*MAPT* drives massive neuronal loss in *MAPT*-Tg mice, resulting in significant enlargement of the ventricles and extensive atrophy of the frontal cortex (Ramsden et al., 2005, Yoshiyama et al., 2007, Jawhar et al., 2012). These unique features and limitations of *MAPT*-Tg mice should be considered in designing preclinical studies.

Amyloid/A β + Tau Models—Given the toxic and poorly understood interaction between tau and amyloid observed in AD, mouse models that combine both pathologies have also been studied (Oddo et al., 2003b, Oddo et al., 2003a, Jackson et al., 2016, Jankowsky and Zheng, 2017, Lippi et al., 2018, Saito et al., 2019). The most well-characterized of these models is the 3xTg mouse, which incorporates h-*APP*, *PS1*, and *MAPT* mutations (Billings et al., 2005, Oddo et al., 2003b, Oddo et al., 2003a). However, in these mice, cognitive deficits appear before any appreciable amyloid or tau pathology, which is the reverse of human AD. Numerous other mice that develop both tau and A β pathology via overexpressed FAD- or FTD-causing mutants have been reported (summarized in Lippi et al., 2018). An alternative strategy to insert non-mutated human *APP* and/or *MAPT* genes into mouse genome through targeted replacement “humanizes” the mice and provides a more physiologically relevant expression profile of APP or tau proteins, but these mice show mild pathology even at old age (Saito et al., 2019, Andorfer et al., 2003, Yetman et al., 2016). Moreover, despite important advances made in our ability to replicate the pathological hallmarks of AD with these mice, the models referenced in this section fail to adequately consider the universal biological variables of AD, which limits their translatability to human patients. Acting as a “decision guide” for choosing an *APOE*-Tg mouse model, the following sections of this review detail the progress made in incorporating the h-*APOE* gene into mouse models of AD and explore the enhanced physiological relevance of these models over their m-*APOE*-expressing counterparts (Table 1).

Universal Biological Variables

The universal biological variables of AD are age, *APOE* genotype, and sex. Age is the greatest risk factor for AD, with *APOE4* the greatest genetic risk factor. The human *APOE* gene encodes apolipoprotein E (apoE), with three isoforms: apoE2, apoE3 and apoE4. Sex is the other universal biological variable of AD, as females exhibit an almost two-fold greater lifetime AD risk and greater dementia burden compared to males (Barnes et al., 2005, Andersen et al., 1999, Oveisgharan et al., 2018, Vest and Pike, 2013). Underappreciated until relatively recently was the interaction between *APOE4* and sex, with female *APOE4* carriers possessing an increased AD risk compared to male *APOE4* carriers (Ungar et al., 2014, Altmann et al., 2014, Fleisher et al., 2005, Breitner et al., 1999, Farrer et al., 1997, Martinez et al., 1998, Andersen et al., 1999, Bretsky et al., 1999, Molero et al., 2001, Corder et al., 2004). Few studies with FAD- and/or *MAPT*-Tg mice have stratified results by sex, but results are consistent with female sex exacerbating the development of AD-like pathology in these mice (Wang et al., 2003, Masuda et al., 2016, Gimenez-Llort et al., 2008, Bhattacharya et al., 2014). However, Tg mouse models that lack *APOE4*, or studies that use

only male mice, produce results that cannot be fully interpreted either by sex, *APOE*, or the critical interaction found in female *APOE4* carriers.

II. The “Who” of *APOE* Transgenic AD Mouse Models: The Role of Human *APOE* in AD Pathology

Proper consideration of *APOE* as a universal biological variable of AD in preclinical mouse studies requires recognition of the significant protein differences between m- and h-apoE. ApoE variation observed across humans is unique to our species, which makes modeling its significant impact on AD risk and pathogenesis challenging. In this section, we first discuss important distinctions between m- and h-apoE. Then, we review the various mouse models that incorporate h-*APOE*, either on its own in an otherwise normal mouse, or in combination with other Tg mutations or exogenous insults that produce AD-like pathology.

Notably, we do not describe in detail Tg mice that combine h-*APOE* expression with other late-onset AD risk-enhancing mutations. These models, such as the *APOE4/TREM2^{R47H}* mouse, are in early stages of development with limited data reported to date (Sasner, 2019). Moreover, these secondary mutations are quite rare, ranging from allele frequencies of 0.12–0.26% for *TREM2^{R47H}* in Caucasian populations to non-existent in Chinese or African-American populations (Guerreiro et al., 2013, Jonsson et al., 2013, Mehrjoo et al., 2015, Jay et al., 2017, Miyashita et al., 2014, Ma et al., 2014, Wang, 2018b, Guo et al., 2018, Jin et al., 2015). Thus, both the reliability and translatability of results gathered in these models are limited. Rather, in this section we discuss better characterized and more informative *APOE*-Tg mouse models that guide interpretation of AD-like pathology through the universal biological variables of AD.

APOE Transgenic Mice

Mouse vs. Human *APOE*—Differences between mouse and human apoE are numerous and significant. The human apoE protein exists in three main isoforms, while mice express only one form of apoE. These three human isoforms vary at only two of the 299 amino acids within the protein secondary structure (apoE2: Cys¹¹²/Cys¹⁵⁸, apoE3: Cys¹¹²/Arg¹⁵⁸, apoE4: Arg¹¹²/Arg¹⁵⁸). Importantly, the homology between m- and h-apoE amino acid sequences is only 70% (Rajavashisth et al., 1985). Although m-apoE includes the equivalent of Arg¹¹²/Arg¹⁵⁸ residues found in h-apoE4, the extent of the coding sequence variation between the two species produces substantial downstream consequences in the tertiary structure, as m-apoE functions as a single-domain protein, while h-apoE forms two distinct N- and C-terminus domains (Nguyen et al., 2014). Numerous studies comparing m- and h-apoE have identified significant differences, ranging from their basic function in lipid binding and transport to their effects on AD pathology (Weisgraber, 1994, Nguyen et al., 2014, Liao et al., 2015, Hudry et al., 2013, Fagan et al., 2002, Fagan et al., 1999). With regard to AD pathology, in spite of the negative consequences associated with the *APOE4* allele, replacement of m-apoE with h-apoE critically delays AD pathology and decline in memory performance, while also introducing an isoform-specificity that mirrors human AD patients (*APOE4* earlier and more severe; *APOE2* later and more mild) in FAD-Tg mouse

models (Balu et al., 2019, Bales et al., 1997, Bales et al., 2009, Youmans et al., 2012, Tai et al., 2011, Tai et al., 2017).

***APOE* Targeted Replacement**—Mice expressing h-apoE isoforms have become a critical tool to study AD pathogenesis. Even without any additional FAD mutations, these mice exhibit isoform-specific differences in lipid physiology and synaptic function – both critical aspects of AD pathology. *APOE*-TR mice, in which the m-*APOE* coding sequence is replaced by that of a h-*APOE* allele, display alterations in synaptic number and structure, network connectivity, and behavior based on the specific apoE isoform expressed (Zhu et al., 2012, Sun et al., 2017, Neustadtl et al., 2017, Dumanis et al., 2013, Gillespie et al., 2016, Dumanis et al., 2009, Ji et al., 2003, Wang et al., 2005, Bour et al., 2008, Grootendorst et al., 2005, Koutseff et al., 2014). Some of these studies have also observed interaction between *APOE* genotype, sex, and aging, showing the ability of *APOE*-TR mice to reproduce the critical interaction of the universal biological variables of AD (Andrews-Zwilling et al., 2010, Leung et al., 2012). At a more fundamental level, the apoE4 protein is found at lower concentrations than apoE3 in these mice, and, in apoE3/E4 heterozygotes, the apoE4 isoform contributes to reduced apoE levels (Ramaswamy et al., 2005, Riddell et al., 2008a). This reduced presence of apoE4 may be due to its relative lack of structural stability and a greater propensity to undergo proteolytic degradation compared to apoE3 (Tamboli et al., 2014, Rohn, 2013). Functionally, apoE4 exhibits decreased affinity for lipids such as cholesterol compared to apoE3, with numerous studies demonstrating that apoE4-containing lipoproteins in the brain are smaller compared to apoE3-containing lipoproteins (Huang and Mahley, 2014, Weisgraber, 1994, Tai et al., 2014b, Hu et al., 2015, Heinsinger et al., 2016, Samieri et al., 2013). Reduced protein levels combined with hypolipidation of apoE4 contribute to the many pathological interactions described in the following sections and form the basis of several therapeutic strategies detailed at the end of this review. As a result, incorporating h-*APOE* into mouse models is critical for studying AD. However, one major limitation is that, although *APOE2* is considered neuroprotective in humans, 100% of homozygous *APOE2* mice have type III hyperlipoproteinemia, compared to only 10% of humans homozygous for *APOE2* (Sullivan et al., 1998, Mahley et al., 1999, Koopal et al., 2017, Corsetti et al., 2018). Thus, *APOE2*-TR mice should be used with caution when compared with *APOE3*- or *APOE4*-TR mice, as the consequences of this condition, which is characterized by significantly increased plasma levels of chylomicron and VLDL remnants, for AD remain unknown.

Amyloid/A β Pathology and *APOE*

Given its wide-ranging toxic effects, reliable replication of oA β pathophysiology is a necessary feature of preclinical AD models. This reproduction requires consideration of the differential effects of apoE isoforms on the formation and clearance of soluble oA β . Across studies, A β deposition, soluble oA β levels, and amyloid plaque pathology are consistently elevated in human AD brain samples in the presence of apoE4 compared to other isoforms (Tai et al., 2013, Hashimoto et al., 2012, Koffie et al., 2012, Hoggund et al., 2017). Also, oA β efflux was diminished across engineered human vessels with apoE4 compared to apoE3 (Robert et al., 2017). The presence of any h-apoE isoform accelerates proteolytic

degradation of soluble A β by microglia, but this effect is weaker with apoE4-containing particles compared to apoE3 and apoE2 (Jiang et al., 2008).

H-apoE-expressing FAD mouse models (FAD/*APOE*-Tg) reproduce this apoE isoform-dependent variation in A β pathology. In Tg2576, APP/PS1, PDAPP, and 5xFAD mice, genetic replacement of m-*APOE* with one of the three human alleles introduced a delayed isoform-specific effect on oA β levels, A β deposition, and amyloid plaque pathology in the brain, with levels highest in apoE4-expressing mice (Bales et al., 2009, Pankiewicz et al., 2014, Youmans et al., 2012, Tai et al., 2013, Castellano et al., 2011, Pankiewicz et al., 2017, Kim et al., 2011, Fryer et al., 2005, Holtzman et al., 2000, Tai et al., 2017). Viral-mediated expression of human apoE in PDAPP, APP/PS1, and Tg2576 mice also induced an isoform-dependent effect on A β pathology, again highest in apoE4-expressing mice (Hudry et al., 2013, Dodart et al., 2005). Importantly, studies in EFAD mice, which overexpress A β via 5xFAD mutations and express h-apoE3 (E3FAD) or h-apoE4 (E4FAD), reproduce the interactive effects of *APOE4* and female sex on AD pathology. These interactive effects include increased A β pathology, greater cognitive deficits, decreased microglial interaction with plaques and lower microglial *TREM2* expression, and increased cerebrovascular pathology in female *APOE4* carriers compared to male *APOE4* carriers (Tai et al., 2017, Stephen et al., 2019, Thomas et al., 2016, Balu et al., 2019). Moreover, with EFAD mice, the interactive effects of age, *APOE* genotype, and sex on survival rates were examined with female E4FADs exhibiting the shortest lifespan and male E3FADs the longest, with male E4FADs and female E3FADs in between (Balu et al., 2019). These findings demonstrate the importance of FAD/*APOE*Tg mice in modeling the apoE/A β interaction, which cannot be achieved with mice expressing their natural apoE protein.

Tau Pathology and *APOE*

Compared to the *APOE4*/A β interaction, the correlation between tau pathology and *APOE4* is relatively poorly established in human patients. One recent study showed that apoE4 reduced the age of onset for FTD patients, independent of A β pathology (Koriath et al., 2019), while data from Rush University's longitudinal human cohorts suggest that apoE isoforms only modulate tau pathology in the presence of A β pathology (Farfel et al., 2016). Neither of these studies stratified participants by sex; thus, these conflicting results may be the product of our limited understanding of the effects of the universal biological variables of AD on tau pathology.

In attempts to further elucidate the relationship between *APOE* genotype and tau pathology, *MAPT*-Tg mouse models that express h-*APOE* (*MAPT/APOE*-Tg) have been developed. In a key study, the Holtzman group demonstrated that, compared to P301STg mice crossed with *APOE3*- or *APOE2*-TR mice, P301S/*APOE4*-TR mice demonstrated increased tau levels, inflammation, and brain atrophy (Shi et al., 2017). However, a follow-up report from the Bu group employing viral-mediated P301L *MAPT* expression in *APOE*-TR mice found no exacerbation of tau pathology, inflammation, or cognitive deficits with apoE4 (Zhao et al., 2018). In fact, this second study observed exacerbation of this pathology in the presence of apoE2. However, the complete penetrance of Type III hyperlipoproteinemia in *APOE2*-TR mice as detailed above represents an important caveat for interpreting results from this

model. Moreover, these two studies utilized different *MAPT* mutants (P301S vs P301L) and different expression methods (Tg vs. viral). Further study of *MAPT/APOE*-Tg mice is certainly warranted in order to better define the relationship between h-apoE isoforms and tau pathology, especially given the observations that late-stage AD may become increasingly amyloid-independent in spite of continued accumulation of pathology (Hyman, 2011). As noted in Section I, investigators must pay particular attention to whether the *MAPT*-Tg mutation employed more closely models human AD or FTD, although the clinical data described at the beginning of this subsection (Koriath et al., 2019, Farfel et al., 2016) suggest that the relationship of both pathologies with *APOE* status is worthy of further investigation.

Amyloid/A β + Tau Pathology and *APOE*

Recent work suggests that the presence of amyloid plaques and phosphorylated tau synergistically promote neurodegeneration in AD patients (Pascoal et al., 2017a, Pascoal et al., 2017b, Fortea et al., 2014, Desikan et al., 2012). However, information on the interaction between the two proteins is severely limited in the context of *APOE* genotype and sex. Although human cohorts are in majority *APOE4* carriers and females, many studies do not stratify their human populations by *APOE* genotype and sex. Therefore, models expressing h-apoE in combination with A β and tau pathologies provide greater insight into their interactions.

To study the effects of h-apoE on the interaction between A β and tau pathology, a cross between *APOE4*-TR and 3xTg mice was developed (3xTg/*APOE*-TR) (Oddo et al., 2009). This initial study noted that h-apoE4 delayed both A β and tau pathology compared to m-apoE. Further studies observed that female 3xTg/*APOE4*-TR exhibited greater A β pathology compared to male 3xTg/*APOE4*-TR and female 3xTg, demonstrating a synergistic interaction between *APOE4* genotype and female sex (Hou et al., 2015). While analysis of sex differences was an important inclusion, the comparison of h-apoE4 to m-apoE (rather than to other h-apoE isoforms) was a major limitation of these studies. When a full h-apoE isoform comparison was performed, greater tau pathology was observed in 3xTg/*APOE4*-TR compared to 3xTg/*APOE3*-TR or 3xTg/*APOE2*-TR mice (Bennett et al., 2013). However, because the majority of that study focused on acute effects of traumatic brain injury, a longitudinal analysis of 3xTg/*APOE*-TR mice on a wider range of AD pathological markers is still needed to further characterize this model.

Modifiable Risk Factors and *APOE*

Amyloid plaques and NFTs together constitute the classic AD pathology, but the vast majority of patients with dementia, including those with a clinical AD diagnosis, do not develop these pathological hallmarks on an otherwise healthy background. This so-called “mixed pathology” is actually the most commonly observed phenotype in demented patients, and, in particular, cerebrovascular disease has been identified as a major contributor to dementia (Bennett, 2017, Matthews et al., 2009). Another study estimated that roughly 30% of the AD burden could be attributed to modifiable risk factors, including hypertension, diabetes mellitus, smoking, obesity, and physical inactivity (Norton et al., 2014). *APOE4* allele increases the risk for cardiovascular disease and diabetes and correlates with increased

plasma low-density lipoprotein cholesterol levels (Bennet et al., 2007, Xu et al., 2016, El-Lebedy et al., 2016). Synergistic effects have also been observed between *APOE4* and these modifiable factors in AD risk (Peila et al., 2002). Therefore, apoE4 could be considered to act as a “first hit” primer for the central nervous system (CNS) to be further compromised by a “second hit” (e.g. traumatic brain injury (TBI), diabetes, vascular disease, etc.), such that apoE4 exacerbates the effects of the modifiable risk factor on brain pathology (Mahley et al., 2006).

Associations between modifiable risk factors and *APOE* genotype are reproduced in *APOE*-TR mice. *APOE4*-TR mice that are genetically obese or placed on a high-fat diet (HFD) – two models of diabetes/dyslipidemia – show greater disturbances in glucose and lipid metabolism (Arbones-Mainar et al., 2016, Johnson et al., 2017, Arbones-Mainar et al., 2008). *APOE4*-TR mice on HFD performed worse in Morris water maze testing and had less cerebral blood flow than *APOE3*-TR mice. Moreover, EFAD mice on HFD exhibited greater signs of AD pathology and glial activation in apoE4- than apoE3-expressing mice (Johnson et al., 2017, Johnson et al., 2019, Moser and Pike, 2017, Nam et al., 2018). In a separate study of EFAD mice, apoE4 exacerbated cerebrovascular pathology and cognitive deficits following exposure to the bacterial endotoxin lipopolysaccharide (LPS), a model of chronic, low-grade peripheral inflammation characteristic of comorbid conditions such as diabetes (Marottoli et al., 2017). *APOE4* carriage also exacerbated pathology following TBI in multiple studies in *APOE*-TR, FAD/*APOE*-Tg, and 3xTg/*APOE*-TR mouse models (Laskowitz et al., 2010, Bennett et al., 2013, Cao et al., 2017). These findings that connect apoE4 to exacerbated AD and vascular pathology following metabolic and/or inflammatory insults underscore the importance of incorporating h-*APOE* in modeling modifiable risk factors for AD. The contribution of these modifiable risk factors to AD burden also suggests that future studies should incorporate measures of metabolism, inflammation, and vascular function as efficacy readouts along with A β and tau pathology to enhance translatability to human disease.

III. The “How” of *APOE* Transgenic AD Mouse Models: Transgenic Strategies for Incorporating Human *APOE*

After the *APOE4* allele was identified as the greatest genetic risk factor for AD, the demand for mouse models expressing h-*APOE* grew rapidly. As research technologies have advanced, several different strategies to introduce h-*APOE* into mice have emerged. In this portion of the review, we provide an overview of these strategies and comment on their contributions to AD research over the past three decades.

Multi-Gene Cluster

An initial method of introducing h-*APOE* consisted of recombining the entire ~58 kilobase locus of human chromosome 19 that encodes *APOE* and two members of the apolipoprotein C family (*APOC1* and *APOC2*) into a large artificial chromosome, such as the P1 bacteriophage-derived or yeast artificial chromosome (PAC or YAC, respectively) (Simonet et al., 1993, Allan et al., 1995, Loring et al., 1996). Transfer of the entire multi-gene cluster provided valuable information on many distal regulatory elements. However, transfecting

these large strands of DNA resulted in the overexpression of apoE in irrelevant tissues, with no expression in the brain, reducing their relevance to AD (Simonet et al., 1993, Allan et al., 1995).

Heterologous Promoters

A common method of introducing *APOE* is with heterologous promoter constructs, ensuring expression in CNS cell types. As reviewed previously by our group, heterologous promoters, including Thy1, GFAP, PGK, PDGF, transferrin, and NSE, drive the expression of apoE in either neurons or astrocytes in various brain regions (Tai et al., 2011, Bowman et al., 1995, Smith et al., 1998, Sun et al., 1998, Buttini et al., 1999, Tesseur et al., 2000b, Tesseur et al., 2000a, Huber et al., 2000). With these models, cell- and region-specific effects of h-apoE isoforms were elucidated (discussed in greater detail in Section IV below). However, the use of heterologous promoters introduced two major challenges. First, as these mice were developed in an *APOE*^{-/-} background, only promoter-specific cells produced apoE. Second, the cells that produced apoE generally expressed it at higher than physiological levels and outside of the endogenous regulatory mechanisms. Thus, while useful for studying certain aspects of apoE biology, heterologous promoters are insufficient to accurately model h-*APOE* expression in mice.

Endogenous Promoters

The *APOE*-TR model is the predominant method to express h-*APOE* in mice. These mice were engineered through homologous recombination to contain the h-*APOE* coding sequences in place of the m-*APOE* coding sequences, but with intact mouse regulatory sequences (Sullivan et al., 1997). As described in the preceding sections of this review, *APOE*-TR mice exhibit isoform-specific phenotypes that mirror human patients, ranging from reduced apoE4 protein levels in the brain (compared to apoE3 or apoE2) to memory/cognitive deficits in *APOE4* carriers, particularly females (Koutseff et al., 2014, Zhu et al., 2012, Dumanis et al., 2009, Bour et al., 2008, Riddell et al., 2008a). *APOE*-TR mice provide a more patient-relevant baseline to explore the cognitive and pathologic effects of various insults that are modulated by apoE isoforms (e.g. TBI, high-fat diet, etc.), and the crosses with other Tg models of AD detailed above in Section II are critical for modeling the interaction of h-apoE with amyloid and tau pathology.

IV. The “When” and “Where” of *APOE* Transgenic AD Mouse Models: Location- and Time-specific Effects of ApoE on AD Pathology

Development of pathology and cognitive decline in AD patients occurs over the course of decades and involves numerous interactions between the brain and peripheral tissues. In the next section of this review, we will discuss recent advances in the temporal- and regional-specificity of apoE expression. These studies represent preliminary efforts to better understand how the isoform-specific impact of apoE varies over the lifespan or with the location of apoE expression.

Temporal Specificity

Having described numerous interactions between apoE and AD pathology in the above sections of this review, we must also recognize that AD pathogenesis is characterized by a long prodromal period before onset of clinical symptoms. A β aggregation, tau accumulation, synaptic loss, and even neuronal death occur years to decades before any appreciable cognitive deficit in patients (Sperling et al., 2011, Jack et al., 2010, Gomez-Isla et al., 1996). Because each copy of the *APOE4* allele accelerates age of onset by approximately eight years, apoE4 likely produces detrimental effects at a young age (Liu et al., 2013). Determining the precise time course of apoE isoform-specific effects on AD pathogenesis will eventually facilitate optimal treatment strategies for patients.

Two recent studies controlled temporal expression of h-apoE in mice to further define the timeline of apoE4-related AD pathology. In APP/PS1 mice engineered to express h-apoE in astrocytes by an inducible promoter, the critical window for the effect of apoE4 in promoting A β aggregation was early in life (<6M) (Liu et al., 2017a). In that study, apoE4 had no effect during the rapid phase of insoluble amyloid (e.g. fibrils and plaques) deposition later in life (>6M). Conversely, induction of apoE3 at any age did not exacerbate amyloid pathology and, in fact, reduced A β -associated gliosis and increased PSD-95, suggesting that both the temporal window and the specific apoE isoform are critical for modulating AD pathology. In a complementary study, anti-sense oligonucleotides (ASOs) were used to knock down h-apoE expression in APP/PS1 mice at various time points. When apoE (either apoE3 or apoE4) was reduced at birth, A β aggregation and deposition were also significantly reduced, but when apoE was not knocked down until 6 weeks of age (after A β aggregation had begun), no change in overall amyloid burden was noted at 4M (Huynh et al., 2017). Both of these studies demonstrated increased pathology with apoE4 vs. apoE3 and indicated that apoE isoform effects are restricted to the initial seeding and oligomerization of A β 42. However, a key limitation of these studies was that they did not stratify for sex and, for the ASO study in particular, only analyzed amyloid aggregation, without evaluating the other AD pathological factors that, as mentioned above, become more prominent later in disease progression. Utilizing these time-limited *APOE* expression models in broader studies will enhance our understanding of the time course over which apoE isoforms differentially modulate AD pathology development.

Cell and Region Specificity

In addition to the varying effects of apoE on AD pathogenesis with time, the location of apoE expression also plays an important role in disease progression. Regional analysis of *APOE-TR* mice reveals that apoE protein levels are highest in cerebellum and lowest in hippocampus and frontal cortex (Sullivan et al., 2004). In the EFAD mice, apoE levels, regardless of isoform, are cerebellum > cortex > hippocampus (Youmans et al., 2012). This regional variation may provide some explanation as to why AD pathology preferentially affects the hippocampal regions first, as lower apoE levels could provide less protection against early A β aggregation. Importantly, we must note that certain observations, such as delayed amyloid pathology in mice expressing any h-apoE isoform compared to *APOE* knockout (KO) mice described in Section II, support the hypothesis that apoE4 is a loss of positive function; conversely, other observations, such as reduced amyloid pathology

following early reductions in apoE reviewed here in Section IV, might conversely suggest a gain of toxic function. Two explanations may help resolve this apparent conflict. First, the specific apoE isoform exerts a critical impact on A β pathology, such that apoE3 provides greater protection than apoE4. Moreover, study results depend on the particular form of amyloid being quantified. As shown in Figure 1, the “on” vs. “off” pathways of A β aggregation allow for increased oA β to occur simultaneously with decreased plaques, and vice versa. Thus, particular attention should be paid in future studies into the apoE/A β interaction to sensitively and specifically detecting these various aggregated species. The ability of *APOE*-TR and *FAD/APOE*-Tg mice to recapitulate human regional brain expression patterns in the context of the three apoE isoforms make them a useful tool for these studies and for other mechanistic investigations into the influence of apoE on other AD-relevant pathology.

In contrast to the natural expression patterns produced in *APOE*-TR mice, heterologous promoter constructs (introduced in Section III above) drive h-*APOE* expression toward specific cell types or regions within the brain. Using Thy1 and PDGF promoters resulted in apoE expression in hippocampal and cortical neurons, while the PGK promoter directed neuronal expression throughout the entire mouse brain (Tesseur et al., 2000b). Use of these promoter constructs demonstrated that neuronal expression of h-apoE4 contributed to tau hyperphosphorylation, which, in follow-up experiments, caused significant axonal dysfunction and degeneration (Tesseur et al., 2000a). Subsequent studies using either Thy1 or NSE promoter constructs combined neuron-specific apoE expression with additional insults, such as crossing with h-*APP* mice or administering the excitotoxin kainic acid, to reveal increased A β pathology and neurodegeneration, respectively, in the presence of apoE4 compared to apoE3 (Buttini et al., 1999, Brecht et al., 2004, Van Dooren et al., 2006). NSE promoter-driven apoE expression also revealed apoE4-mediated deficits in cognitive behavioral tasks that was worse in female mice, which may be explained by particular toxicity of apoE4 fragments to GABAergic interneuron populations (Raber et al., 1998, Andrews-Zwilling et al., 2010, Knoferle et al., 2014). The other major cell-specific apoE expression model utilizes the GFAP promoter to restrict h-apoE expression to astrocytes, which are the major cell type that produces apoE protein in the brain. Mice transfected with GFAP-apoE demonstrate isoform-specific worsening in neuronal morphology, microvascular pathology, motor function, and cognitive performance (Smith et al., 1998, Sun et al., 1998, Tang et al., 2009, Meng et al., 2015, Chaudhari et al., 2016, Ji et al., 2003, Hartman et al., 2001, van Meer et al., 2007).

Because the heterologous promoter strategy results in overexpression of apoE significantly above normal protein levels, these mice have not received widespread use. Instead, *APOE*-TR mice, which express h-apoE at normal physiological levels, are more prevalent given their greater accuracy and translatability. However, models of neuron- and astrocyte-specific expression still fill an important niche for mechanistic investigation of the isoform-specific effects of apoE.

Central vs. Peripheral *APOE* Expression

In recent years, appreciation of the interactions between peripheral and CNS apoE on AD pathology has grown. The apoE protein does not cross the blood-brain barrier, meaning that peripheral apoE (expressed primarily by hepatocytes) and CNS apoE (expressed primarily by astrocytes) form two distinct “pools” (reviewed recently in (Chernick et al., 2019)). While the contributions of peripheral apoE to AD modifiable risk factors and comorbid pathologies (high cholesterol, type 2 diabetes, cardiovascular disease) are described above, the development of new *APOE*-Tg models that spatially restrict the expression of apoE has illuminated the direct role of peripheral versus CNS apoE on AD pathology as well. Knocking out m-*APOE* in the brain did not result in cognitive deficits, whereas full *APOE*-KO mice did exhibit cognitive deficits (Lane-Donovan and Herz, 2016). However, this study utilized m-*APOE*, which limits translatability to h-*APOE* and AD.

To build on those findings, researchers from the Bu and Nielsen groups recently presented data from mice expressing h-apoE isoforms specifically in either vascular mural cells or hepatocytes, with apoE4 worsening vascular and neuropathology as compared to apoE3 or apoE2 in both cases (Yamazaki et al., 2018, Patra et al., 2018). When crossed with APP/PS1 mice, liver-specific apoE4 expression worsened A β pathology while liver-derived apoE3 was protective (Alzforum, 2018). Notably, in these studies, region-specific apoE isoform expression occurred on an *APOE*-KO background, which complicates the interpretation of their findings. In a separate article, the Holtzman group recently reported that specific reduction of h-apoE expression in the livers of APP/PS1/*APOE*-TR mice did not affect brain A β plaque deposition (Huynh et al., 2019). As only the Holtzman results have been peer-reviewed and published, further study on the role of peripheral apoE in modulating brain pathology is necessary. Moreover, because these studies used the APP/PS1 model, analysis naturally focused on amyloid pathology, but the effect of central vs. peripheral apoE expression on other pathological factors is also worthy of exploration. These cell-type or region-specific inducible models will be critical tools for the next phase of AD research, particularly with the heightened focus recently on the brain-periphery connection.

V. The “Why” of *APOE* Transgenic AD Mouse Models: Preclinical Testing of Therapeutic Strategies Targeting ApoE

The above-reviewed *APOE*-Tg preclinical mouse models highlight the critical role of h-apoE isoforms in modulating AD pathology and the importance of *APOE4* in unmasking the increased risk in females. Another consequence of the pleiotropic effects of apoE in the brain is that a drug acting through improving positive functions or reducing toxic gain of functions of apoE at a foundational level could provide wide-ranging therapeutic benefit. AD mouse models can be used to refine a hypothesis, dissect a signaling mechanism or, as in our example, test a therapeutic targeting apoE. The choice of a mouse model requires not simply choosing a mouse that develops the relevant pathology, but fully understanding the strengths and limitations of the model. In this final section, we evaluate six major categories of therapeutic compounds in development that target apoE and discuss the importance of choosing the specific *APOE*-Tg mouse model relevant to the hypothesized mechanism of action of each candidate. Based on the universal biological variables of AD, we assume the

importance of h-*APOE* and the use of male and female cohorts. In addition, while a particular model of pathology may be indicated as the primary model, examination in models that mimic other pathological mechanisms is also suggested as the role of *APOE* in AD pathology is multifaceted.

ApoE2 Overexpression (Figure 3.1)

While *APOE4* constitutes the most important genetic risk factor for AD, the *APOE2* allele induces a significant protective effect, lowering AD risk two- to four-fold for one or two copies, respectively, compared to *APOE3* carriers (Bertram et al., 2007, Corder et al., 1994). Thus, overexpression of apoE2 has been postulated as a potential therapeutic strategy to correct apoE4-associated deficits. Indeed, intracerebroventricular injection of lentiviral *APOE2* reduced hippocampal A β load in PDAPP mice (Dodart et al., 2005). More recently, a single thalamic injection of an adeno-associated virus (AAV)rh.10h vector engineered to contain the *APOE2* coding sequence significantly decreased brain A β levels in APP/PS1/*APOE4* mice (Zhao et al., 2016). An open label Phase 1 clinical trial (NCT03634007) to determine maximum tolerated dose and assess brain apoE2 expression levels with this vector in 15 *APOE4* homozygous MCI/AD patients was scheduled to begin in October 2019.

Despite positive results, numerous challenges remain in the development of this virus-based therapeutic. Along with ensuring intracisternal injection safety in human patients, potential adverse effects of apoE2 overexpression and detrimental interactions of the new apoE2 protein with endogenous apoE4 must both be identified. Additionally, the use of an *APOE*-Tg model to test this strategy should include both A β and tau pathology (only A β has been utilized to date), with careful attention paid to readouts that assess inflammation as well, given the diverse effects of apoE on AD pathology.

More generally, we lack a full understanding of the *APOE2* protective mechanism. ApoE2 may be in a functional continuum with apoE3 and apoE4 (Table 2), based on relative apoE protein levels and lipid binding affinities observed in both *APOE*-TR mice and human cortical samples (Conejero-Goldberg et al., 2014, Riddell et al., 2008b, Tai et al., 2014a). Other observations, including significantly reduced binding to low-density lipoprotein receptors (LDLRs), suggest apoE2 may have a unique function compared to apoE3 and apoE4 (Mahley et al., 2006). Further complicating an apoE isoform functional continuum is the recent identification of the *APOE3* Christchurch (R136S) mutation, which delayed symptom onset in a familial AD patient for several decades (Arboleda-Velasquez et al., 2019). However, the *APOE3* Christchurch mutation is an exceedingly rare mutation that requires homozygosity to delay FAD. Moreover, case reports describing carriers of this mutation suggest it confers an even greater risk for type III hyperlipoproteinemia than the apoE2 allele (Wardell et al., 1987). Additional study is critical before comparison can be made between the *APOE3* Christchurch mutation and common *APOE* genotypes.

With the known limitation of type III hyperlipoproteinemia in *APOE2*-TR mice, the AAV delivery strategy offers an alternative for studying these allelic differences and, more generally, the effects of apoE2 *in vivo*. Virus-mediated expression of apoE2 on an *APOE3*- or *APOE4*-TR background will facilitate identification of physiologic differences and help probe continual vs. discrete functions of the isoforms. Future research efforts such as these

will provide valuable insight into the protective mechanism of apoE2 and, potentially, illuminate new routes to harness this protection for a therapeutic purpose.

ApoE Lipidation Inducers (Figure 3.2)

Reduced lipidation of apoE4, observed both *in vitro* and *in vivo*, is a structural deficit that has been implicated in several pathological deficits, and, thus, is a hypothesized therapeutic target for AD (Wahrle et al., 2004, Fitz et al., 2012, Wahrle et al., 2008, Rebeck, 2017, Wahrle et al., 2005). Nascent apoE particles secreted by glial cells are lipidated primarily by cholesterol transport proteins ABCA1 and ABCG1, leading to the hypothesis that increasing expression of these transporters will reverse apoE4 lipidation deficits. The primary molecular target for increasing ABCA1/G1 is the liver X receptor (LXR), a nuclear receptor that serves as the primary transcription factor controlling ABCA1/G1 expression (Qiu et al., 2001, Costet et al., 2000). LXR agonists TO901317 and GW3965 decrease A β pathological burden and improve memory performance in various FAD-Tg mouse models (Riddell et al., 2007, Fitz et al., 2010, Cui et al., 2011, Koldamova et al., 2005, Vanmierlo et al., 2011, Burns et al., 2006, Terwel et al., 2011, Donkin et al., 2010). However, LXR α -stimulated production of triglycerides in the liver leads to adverse effects, precluding clinical development of these agents (Schultz et al., 2000, Quinet et al., 2006). Newer, selective LXR β agonists have been synthesized and characterized (reviewed in El-Gendy et al., 2018), with compounds from both Bristol-Myers Squibb and Wyeth entering Phase 1 trials. However, BMS-852927 (NCT01651273) decreased circulating neutrophil levels, while LXR-623 (Wyeth, NCT00366522) produced CNS-related adverse effects (Katz et al., 2009, Kirchgessner et al., 2016). From these two trials, it is difficult to determine whether the side effects were due to LXR agonism or were unique to the individual drug candidates being tested.

Despite challenges in achieving selectivity, preclinical development of LXR agonists continues, and strategies to bypass LXR α -mediated side effects have been reported (Fan et al., 2018). Because ABCA1 deficiency has been linked to both amyloid-dependent and -independent AD-related pathology (Karasinska et al., 2009, Karasinska et al., 2013, Corona et al., 2015, Fitz et al., 2014, Castranio et al., 2018), a diverse set of preclinical *APOE*-TR models will be appropriate for future *in vivo* studies with these compounds. Specifically, *APOE*-TR mice provide a platform for evaluating target engagement with assays ranging from native gel electrophoresis for apoE-containing particle size to size exclusion chromatography techniques that evaluate shifts in lipid and lipoprotein profiles (LaDu et al., 1994, LaDu et al., 2012). FAD/*APOE*-Tg models would enable testing of amyloid-dependent effects, and combining *APOE*-TR with a second hit, such as HFD-, TBI- or LPS-induced inflammation, could be used to analyze amyloid-independent effects. Moreover, peripheral ABCA1 modulates vascular cholesterol deposition (Oram, 2002, Stukas et al., 2014), permitting a comparison between CNS vs. peripheral apoE-expressing mice, provided these Tg models become better characterized in the next several years. These testing strategies using *APOE*-Tg mice enhance translational impact that has been limited to date by the use of FAD-Tg mice expressing m-apoE (Moutinho and Landreth, 2017).

ApoE4 Structural Correctors (Figure 3.3)

Small-molecule structure correctors of apoE4 remain in an early stage of development. ApoE4 structural correctors were initially identified in 2005 from a library of small molecules that bind to apoE4 to prevent the N- to C-terminal domain interaction, “converting” it to an apoE3-like structure (Ye et al., 2005). While beneficial functional effects have been reported in N2a neuroblastoma cells and iPSC-derived neurons (Brodbeck et al., 2011, Wang et al., 2018a, Chen et al., 2012, Mahley and Huang, 2012), the lack of any reported animal studies limits the therapeutic potential of these compounds. Although structure correcting drugs have been developed for other conditions (e.g. Ivacaftor for cystic fibrosis), evidence of bioavailability, tolerability, and efficacy in animal models is necessary to establish structure correctors as therapeutic candidates for AD. In particular, *APOE-TR* mice serve as a basic model to test the hypothesis that expression levels and lipidation of apoE4 mirror those of apoE3 following treatment. As *in vitro* studies have described a reversal of apoE isoform-dependent tau pathology in neurons (Wang et al., 2018a), efficacy studies could utilize a *MAPT/APOE-Tg* model to evaluate the translation of these results from cells to animals, although such a model must be better established. A more fundamental issue is the use of neuronal cells for the production of apoE as it is widely accepted that glial cells, particularly astrocytes, are the primary apoE-expressing cell type in the brain.

ApoE Inducers (Figure 3.4)

In both human and *APOE-TR* mouse brains, apoE4 levels are lower than those of apoE3 (Riddell et al., 2008a, Martinez-Morillo et al., 2014). To address the reduced levels of apoE4 in the brain, compounds that increase apoE expression, particularly in *APOE4* carriers, have been proposed as therapeutic agents for AD. The most prominent such compound is bexarotene (Bex), a retinoid X receptor (RXR) agonist that is an FDA-approved chemotherapeutic. However, because RXR is a nuclear receptor in the same family as LXR, it is critical to keep in mind that while Bex may induce the expression of *APOE*, it also targets ABCA1/G1. Thus, Bex could also have been classified as a potential therapeutic to induce apoE lipidation (Figure 3.2). In a high-profile study, Cramer and colleagues demonstrated rapid clearance of A β and reversal of numerous functional deficits with Bex administration, though results from follow-up experiments were mixed (Veeraraghavalu et al., 2013, Tesseur et al., 2013, Price et al., 2013, Fitz et al., 2013, Cramer et al., 2012). A Phase 2 human clinical trial ([NCT01782742](#)) found no change in amyloid burden, with adverse increases in serum triglycerides (Cummings et al., 2016). Another proposed apoE-inducing therapeutic for AD is probucol, which reduces blood-brain barrier (BBB) dysfunction, cognitive deficits, and synaptic impairment in wild-type mice when paired with a diabetogenic diet or following intracerebroventricular A β peptide injections (Mamo et al., 2019, Santos et al., 2012). A Phase 1b/2a clinical trial with probucol is listed as complete nearly two years ago, though results have yet to be reported ([NCT02707458](#))

Novel analogs of Bex, along with other LXR/RXR agonists, have been developed in the past year, and new screens for apoE inducers have been performed as well (Yuan et al., 2019, Ren et al., 2019, Pollinger et al., 2019, Fan et al., 2016, Finan et al., 2016). Most of these newly-described compounds have limited (or no) *in vivo* data supporting their efficacy, thus

moving into animal models represents an important next phase of their development. Given that reduced apoE4 or apoE3 levels have been found to correlate with increased brain A β deposition in mice and humans (DeMattos, 2004, Lambert et al., 2005, Bales et al., 2009, Gupta et al., 2011), an FAD/*APOE*-Tg mouse (such as EFAD, or APP/PS1/*APOE*-TR) will be a useful model to study whether apoE inducers can reverse the development of A β pathology. Importantly, a study by our group with Bex revealed reduction in soluble A β levels in E4FAD mice, but not E3FAD mice, highlighting the clarity of analysis provided by a model that incorporates *APOE* genotype (Tai et al., 2014a, Koster et al., 2017). Studies with h-*APOE* inducible mice discussed in Section IV also emphasize a critical period of AD progression during which apoE inducers would provide the highest therapeutic impact.

ApoE-targeted Peptides (Figure 3.5)

Several peptides that target various aspects of apoE-mediated pathology via diverse mechanisms have been developed. The first peptide, CS-6253, consists of 26 amino acids from the C-terminus of the apoE protein that form an amphipathic helical structure. The peptide acts to stabilize ABCA1 in the cell membrane, thus facilitating cholesterol efflux *in vitro* and improving apoE4 lipidation in *APOE4*-TR mice (Hafiane et al., 2015, Boehm-Cagan et al., 2016). Another peptide with similar function, named 4F for its four phenylalanine residues, has been studied extensively for cardiovascular disease before it was observed to increase apoE4 lipidation *in vitro* and reduce A β pathology and cognitive deficits in APP/PS1 mice (Handattu et al., 2009, Chernick et al., 2018). Additionally, two peptides based on the receptor-binding domain of apoE (COG133, consisting of residues 133–149 of apoE, and COG1410, derived from residues 138–149) have been described as anti-inflammatory and neuroprotective following testing in FAD mice with a knockout of the nitric oxide synthase 2 gene; another similar peptide reversed pathology and cognitive deficits in 3xTg and 5xFAD mice (Lynch et al., 2005, Laskowitz et al., 2007, Christensen et al., 2011, Vitek et al., 2012, Sawmiller et al., 2019). Notably, none of the aforementioned peptides (Figure 3.5.A) has been studied in an AD model that incorporates h-*APOE* expression, a critical limitation for a drug with proposed mechanism of action mimicking or enhancing h-apoE lipidation, as the h-apoE isoforms are known to have functional and pathological differences.

Finally, a peptoid based on residues 12–28 of the A β 42 sequence has been reported to block the apoE/A β 42 interaction (Figure 3.5.B), with beneficial reductions in amyloid pathology and cognition in APP/PS1 and, with an earlier peptide version, APP/PS1/*APOE*-TR mice (Sadowski et al., 2004, Liu et al., 2017b, Liu et al., 2014). Whether blocking this interaction will ultimately prove beneficial or harmful in human AD patients remains to be determined, as the authors aim to specifically prevent the apoE/A β 42 interaction. The drug instead likely inhibits all interaction regardless of apoE isoform, potentially ameliorating any protective actions of apoE3 or apoE2 (Pankiewicz et al., 2014). Further, the possibility exists that this peptoid simply disrupts A β aggregation independent of apoE; testing in a FAD/*APOE*-KO mouse alongside the FAD/*APOE*-Tg models expressing various isoforms would rule out this possibility and show the importance of apoE – or the apoE4 isoform in particular – in the mechanism of action of this drug candidate.

ApoE-targeted Antibodies (Figure 3.6)

Monoclonal antibodies have become an attractive therapeutic option for many diseases due to their high specificity and minimal off-target effects compared to small molecules. However, poor results with A β -directed antibodies in late-stage trials may temper excitement for therapeutic antibodies targeting other AD-related proteins. Efficacy of several apoE-targeting antibodies has been reported, with one recently described that preferentially binds non-lipidated and aggregated forms of apoE3 and apoE4 to reduce A β pathology in APP/PS1/*APOE4*-TR mice (Kim et al., 2012, Liao et al., 2014, Liao et al., 2018). Continued research into apoE-directed antibodies as AD therapeutics will require a broader assessment of their effects. While published studies noted a decrease in A β plaque burden, no other changes in CNS pathological markers of AD have been reported. Moreover, no changes in apoE levels were observed, and any changes in apoE structure or function (e.g. lipidation state) were not described.

Over the next several years, it is likely that antibodies will be developed that preferentially target single apoE isoforms, bind to functional lipidated apoE rather than aggregated forms, and/or alter brain levels of apoE (either by targeting apoE for degradation to decrease apoE or by stabilizing lipoproteins to increase apoE). With regard to preclinical testing of these antibodies, the failure to clinically translate reduced plaques to improved cognition with A β -directed monoclonal antibodies suggests that we should explore other potential mechanisms of action aside from amyloid plaque reduction. Thus, despite positive observations with one anti-apoE antibody in APP/PS1/*APOE4*-TR mice, these antibodies could also be examined for their effects on apoE isoform-dependent tau pathology (i.e. in an *MAPT/APOE*-Tg model) or on apoE-dependent inflammation (i.e. *APOE*-TR mice injected with LPS). A more diverse preclinical profiling of apoE-targeted antibodies will answer critical questions about their desired therapeutic profile and better position them for clinical development as AD treatments.

VI. Conclusion: Choosing the Right Mouse Model

Because mouse *APP* and *MAPT* genes do not readily produce toxic A β species or NFT, modeling AD pathology in mice remains a challenge. New models are continually generated, with a recent AlzForum search yielding 179 different AD mouse models, each of which is often characterized for only a single feature of interest. Given the complexity of the disease, hundreds of additional models could be generated without ever producing one that fully recapitulates human AD or is characterized beyond a gene of interest to provide context and allow for informed conclusions. Thus, the focus of AD transgenics should be on maximizing the reliability and validity of the mouse model to answer a given research question. In order to accomplish this goal, the universal biological variables of AD must be considered. FAD- and *MAPT*-Tg mice, along with newer “humanized” *APP*-TR and *MAPT*-TR mice, recapitulate aspects of AD-like (or FTD-like) pathology but do not permit interpretation of the effects of *APOE* or sex as universal biological variables of AD. Incorporation of h-*APOE* is critical for accurate preclinical modeling of the disease and for exposing the increased risk to female *APOE4* carriers, and, in this review, we have described numerous contexts for understanding apoE isoform-dependent impact in mice. *APOE4*

exacerbates amyloid pathology in FAD-Tg mouse models, may affect tau pathology in *MAPT*-Tg mouse models, and aggravates the effects of a second insult that reproduces modifiable risk factors. An even more nuanced interrogation has occurred with Tg mice that have been engineered to express h-*APOE* only in specific cell types, in certain brain regions, in CNS vs. peripheral compartments, or at certain times throughout the lifespan. Thus, diverse AD mouse models that express h-*APOE* are available for future mechanistic studies, though it is critical that the correct models be chosen to test the hypothesis at hand. To demonstrate this point, we concluded by reviewing apoE-targeted therapeutics and, in particular, an analysis of their results in appropriate *APOE*-Tg mouse models.

Acknowledgements

The authors thank Deebika Balu and Ana Carolina Valencia-Olvera for their review of the manuscript and figures.

Funding

The LaDu lab is funded by NIH (NIA) R01 AG056472, R01 AG057008, UH2/3 NS10012, R56 AG058655, 1R44 AG060826, UIC-DPI Phase 2 POC Award, and generous philanthropic support. C.T.L. received support from NIH (NIA) T32AG57468, the American Heart Association (20PRE35150022), and the University of Illinois at Chicago Center for Clinical and Translational Science (NIH UL1TR002003).

ABBREVIATIONS

3xTg	triple-transgenic (mutated human <i>APP</i> , <i>PS1</i> , and <i>MAPT</i>) mouse
3xTg/<i>APOE</i>-TR	triple-transgenic (mutated human <i>APP</i> , <i>PS1</i> , and <i>MAPT</i>) mouse expressing human <i>APOE</i>
5xFAD	transgenic mouse harboring five familial AD mutations (three in <i>APP</i> , 2 in <i>PS1</i>)
Aβ	amyloid- β
AAV	adeno-associated virus
ABCA1	ATP-binding cassette protein A1
AD	Alzheimer's disease
ASOs	anti-sense oligonucleotides
<i>APOC</i>	apolipoprotein C gene
<i>APOE</i>	apolipoprotein E gene
ApoE	apolipoprotein E
APP	amyloid precursor protein
<i>APP</i>	amyloid precursor protein gene
APP/<i>PS1</i>	transgenic mouse expressing mutant human <i>APP</i> and <i>PS1</i>

APP/PS1/APOE-TR	APP/PS1 transgenic mouse expressing a human apoE isoform
BBB	blood-brain barrier
Bex	Bexarotene
CNS	central nervous system
EFAD	5xFAD transgenic mouse expressing a human apoE isoform
FAD	familial Alzheimer's disease
FAD/APOE-Tg	FAD transgenic mice expressing human <i>APOE</i>
FAD/APOE-KO	<i>APOE</i> -null FAD mice
FAD-Tg	FAD transgenic mice
FTD	frontotemporal dementia
FTDP-17	frontotemporal dementia and parkinsonism linked to chromosome 17
GFAP	glial fibrillary acidic protein
h-	human
HFD	high-fat diet
iPSC	induced pluripotent stem cells
KO	knock-out
LDLR	low-density lipoprotein receptor
LPS	lipopolysaccharides
LXR	liver X receptor
MAPT	microtubule-associated protein tau
MAPT-Tg	transgenic mouse with human tau
MAPT/APOE-Tg	transgenic mouse with human tau and human <i>APOE</i>
MCI	mild cognitive impairment
M	months
m-	mouse
NFT	neurofibrillary tangles
NSE	neuron-specific enolase

oAβ	oligomeric A β
PAC	phage P1-derived artificial chromosome
PDAPP	PDGF promoter-driven APP expression transgenic mouse
PDGF	platelet-derived growth factor
PGK	phosphoglycerate kinase
PP2A	protein phosphatase 2A
PS1	presenilin-1
PS1	presenilin-1 gene
RXR	retinoid X receptor
TR	targeted replacement
Tg	transgenic
Thy1	thymocyte-differentiation antigen 1
TREM2	gene encoding the triggering receptor expressed on myeloid cells 2
TBI	traumatic brain injury
YAC	yeast artificial chromosome

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HIGHLIGHTS

- What: AD is uniquely human, but molecular mechanisms can be measured in Tg-mice.
- Who: A universal biological variable of AD, *APOE* is critical for preclinical models.
- How: There are several strategies for developing an *APOE*-Tg mice.
- When/Where: Developmental and region-specific models probe *APOE*-expression patterns.
- Why: Therapeutic strategies targeting apoE can exploit the relevant mouse model(s).

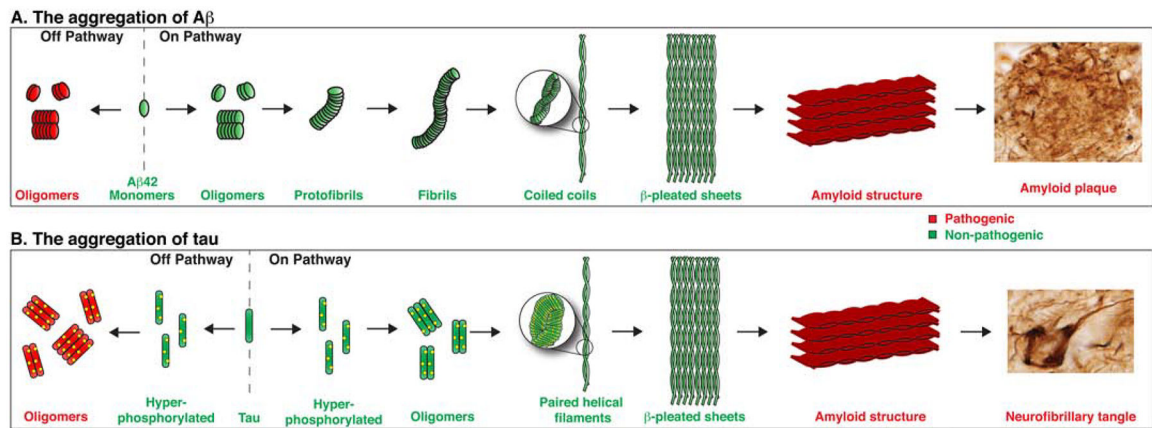


Figure 1. A β and tau aggregation.

Two pathways for A β and tau monomer aggregation. In the on pathway, protein monomers sequentially aggregate to form larger structures culminating in an amyloid structure, either amyloid plaques for A β or NFT for tau. In the off pathway, protein monomers aggregate into oligomers – a persistent, stable, and pathogenic conformation. The upper panel was adapted from Pimplikar (2009); amyloid plaque and NFT staining adapted from Winblad and colleagues (2016).

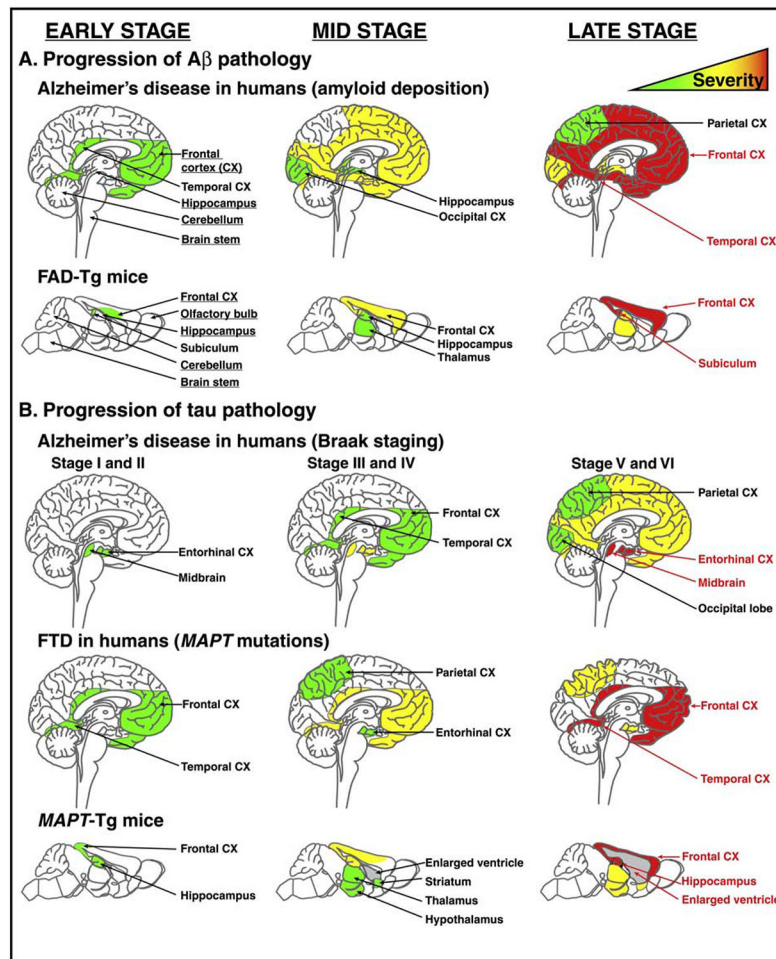


Figure 2. Progression of A β and tau pathology in humans and Tg mice.

A) Comparison of A β pathology progression between AD human patients and FAD-Tg mouse models. B) Comparison of tau pathology progression among AD human patients (Braak staging), FTD human patients, and *MAPT*-Tg mouse models. The frontal cortex, hippocampus, cerebellum, and brainstem in both human and mouse brain are labeled in leftmost panel in A) to aid in orientation, with additional labels provided to indicate regions affected by pathological progression. Human A β and Braak staging panels were adapted from Masters and colleagues (2015). Human FTD was adapted from Wszolek and colleagues (2006). *MAPT*-Tg mouse pathology was adapted from Sahara and colleagues (2013).

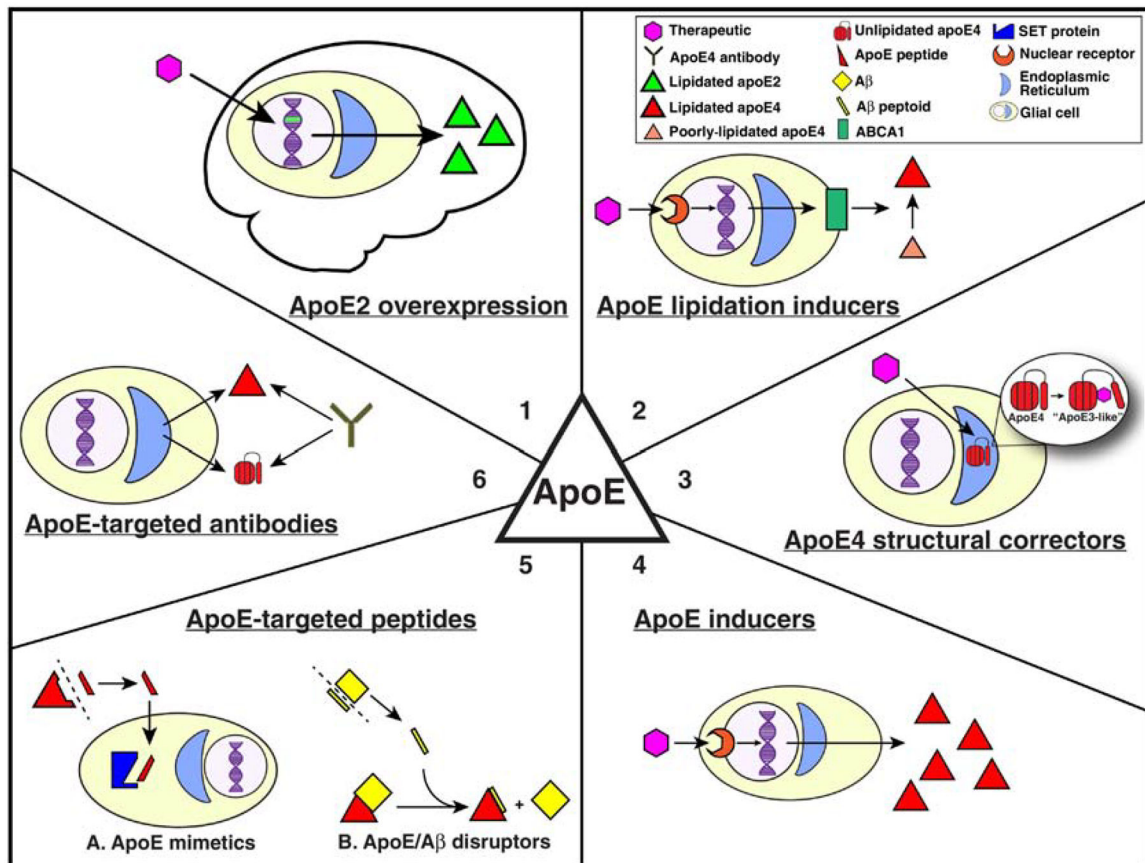


Figure 3. Therapeutic strategies to target apoE.

Six major categories of apoE-targeted therapeutic candidates in development are ideal for preclinical testing in *APOE*-Tg mouse models. These include apoE2 overexpression, apoE4 structural correctors, apoE lipidation promoters, apoE inducers, apoE-directed peptides, and antibodies that target various forms of apoE.

Table 1.

Decision guide for choosing *APOE*-Tg mouse models.

What?	Who?	How?	When/Where?	Why?
<p>I. AD pathology</p> <p>A. Progression of Aβ pathology</p> <p>B. Progression of tau pathology</p> <p>C. Models of Aβ pathology</p> <p>a. FAD-Transgenic</p> <p>b. h-<i>APP</i> Knock-in</p> <p>c. FAD Knock-in</p> <p>D. Models of tau pathology</p> <p>a. Mutant <i>MAPT</i> transgenic</p> <p>b. h-tau isoforms knock-in</p> <p>E. Models of Aβ + tau pathology</p> <p>a. FAD + <i>MAPT</i> transgenic</p> <p>b. h-<i>APP</i> knock-in + <i>MAPT</i></p> <p>II. Universal biological variables of AD</p> <p>A. Age</p> <p>B. <i>APOE</i></p> <p>C. Sex</p>	<p>I. <i>APOE</i> transgenics</p> <p>A. Mouse vs human <i>APOE</i></p> <p>B. <i>APOE</i>-TR</p> <p>C. Amyloid/Aβ + <i>APOE</i></p> <p>a. Tg2576/<i>APOE</i>-TR</p> <p>b. PDAPP x <i>APOE</i>-TR</p> <p>c. <i>APP/PS1</i>/<i>APOE</i>-TR</p> <p>d. EFAD</p> <p>e. 5xFAD/<i>APOE</i>-TR</p> <p>D. Tau + <i>APOE</i></p> <p>a. P301S/<i>APOE</i>-TR</p> <p>b. P301L/<i>APOE</i>-TR</p> <p>E. Amyloid/Aβ + Tau + <i>APOE</i></p> <p>a. 3xTG + <i>APOE</i>-TR</p> <p>F. Modifiable risk factors + <i>APOE</i></p> <p>a. High-fat diet</p> <p>b. Peripheral inflammation</p> <p>c. Traumatic brain injury</p>	<p>I. Multi-gene cluster</p> <p>II. Heterologous promoters</p> <p>A. CNS-specific</p> <p>a. Thy-1</p> <p>b. GFAP</p> <p>c. PGK</p> <p>d. PDGF</p> <p>e. Transferrin</p> <p>f. NSE</p> <p>III. Endogenous promoters</p>	<p>I. Temporal specificity</p> <p>II. Cell and region specificity</p> <p>III. CNS vs periphery</p>	<p>I. ApoE2 overexpression</p> <p>II. ApoE lipidation inducers</p> <p>III. ApoE4 structural correctors</p> <p>IV. ApoE inducers</p> <p>V. ApoE-targeted peptides</p> <p>VI. ApoE-targeted antibodies</p>
<p>The transgenic mouse models that mirror human AD pathology.</p>	<p>The introduction of human <i>APOE</i> into the transgenic mouse models.</p>	<p>The different methods of introducing human <i>APOE</i> into mouse models.</p>	<p>The development of mice with location- and time-specific apoE expression.</p>	<p>The importance of h-<i>APOE</i>-Tg mice for testing apoE-targeted therapeutics.</p>

Table 2.

Functional and pathologic differences among apoE isoforms in the periphery and central nervous system.

Readouts in Human Periphery	<i>APOE2</i>	<i>APOE3</i>	<i>APOE4</i>
Cholesterol	Low	Intermediate	High
Plasma apoE levels	High	Intermediate	Low
VLDL affinity	Low	Similar to <i>APOE2</i>	High
LDL affinity	High	Similar to <i>APOE4</i>	Low
HDL affinity	High	Similar to <i>APOE2</i>	Low
Plasma LDL levels	Low	Intermediate LDL	High
	<ul style="list-style-type: none"> Less efficient clearance of remnant particles by LDL receptor (LDLR) 		<ul style="list-style-type: none"> More efficient clearance of remnant particles
	<ul style="list-style-type: none"> Hepatic LDLR up-regulated as a result of slowed clearance 		<ul style="list-style-type: none"> Hepatic LDLR down-regulated as a result of efficient clearance
Cardiovascular risk	Low	Intermediate	High
Type III hyperlipoproteinemia risk	Develops in < 10% of <i>APOE2/2</i> (requires second genetic or environmental factor).	No risk	No risk
Readouts in Human CNS	<i>APOE2</i>	<i>APOE3</i>	<i>APOE4</i>
ApoE levels	Similar to ApoE3	High	Low
AD risk	Low	Intermediate	High