

REVIEW

ApoE-calypse tau: ApoE-tau synergy in Alzheimer's disease

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Alzheimer's disease (AD), the most common cause of dementia, is characterized by the accumulation of amyloid- β (A β) in senile plaques and abnormally hyperphosphorylated tau proteins in neurofibrillary tangles. While much of the research has focused on A β , tau-mediated neurodegeneration is more closely associated with synaptic loss and cognitive decline in AD, emphasizing the need for a deeper understanding of tau pathology. In this context, the interaction between tau and APOE, particularly the main genetic risk factor for AD APOE ϵ 4, remains underexplored. APOE encodes apolipoprotein E (apoE), a protein important in lipid metabolism. In addition to promoting A β deposition, emerging evidence suggests that APOE ϵ 4 exacerbates tau-mediated neurodegeneration and tau-related pathology. This review consolidates current knowledge on the interplay between apoE and tau, highlighting its potential as a key factor in disease progression. Targeting the apoE-tau axis may offer promising therapeutic strategies to address the molecular mechanisms driving AD and primary tauopathies.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder marked by progressive memory loss and cognitive decline that exceeds normal aging. AD is the leading cause of dementia, contributing to ~60–80% of cases, and affects over 50 million people globally. The likelihood of developing AD rises with age, impacting up to 33.4% of those over 85 (Alzheimer's Association, 2024). The disease also presents a significant economic burden, which has grown considerably in recent years (Wong, 2020).

AD can be classified into early-onset autosomal dominant AD (ADAD), early-onset non-ADAD, and late-onset AD (LOAD). ADAD is a rare hereditary form of AD linked to mutations in the APP, PSEN1, or PSEN2 genes, typically affecting individuals under 60. LOAD, accounting for more than 95% of cases, is influenced by both environmental and genetic factors, including TREM2 (Guerreiro et al., 2013; Jonsson et al., 2013), SORL1 (Pottier et al., 2012), PLD3, and CLU (Karch and Goate, 2015), with the APOE gene being the most influential genetic risk factor (Corder et al., 1993; Belloy et al., 2023).

AD pathophysiological changes occur years before symptoms appear (Perrin et al., 2009; Jack et al., 2010). The disease is characterized by two main pathological hallmarks that develop at different timepoints throughout AD (Musiek and Holtzman, 2012): extracellular neuritic amyloid plaques (senile plaques [SPs]) primarily composed of amyloid- β (A β) and intracellular neurofibrillary tangles (NFTs) comprised of hyperphosphorylated tau (p-tau) (Musiek and Holtzman, 2012). NFT accumulation correlates with neuronal loss (Gómez-Isla et al., 1997), suggesting

that tau pathology is closely linked to memory and cognitive decline (Gallardo and Holtzman, 2019; La Joie et al., 2020). The specific distribution of these hallmarks, particularly tau, is unique to humans (Ferrer, 2023), and the distribution of tau helps in assessing the severity of AD using the Braak staging system (Braak and Braak, 1991).

SPs and NFTs are considered central to AD progression, as reviewed recently (Knopman et al., 2021; Ferrer, 2023). While amyloid pathology appears to initiate AD, followed by tau pathology and neurodegeneration, the exact sequence and mechanisms remain unclear. Nonetheless, most treatments have targeted amyloid pathology reviewed in Karran and De Strooper (2022). Recent anti-amyloid antibodies have shown modest success in slowing cognitive decline in very mild dementia caused by AD (Cummings et al., 2024), likely because the treatment is administered too late. Even in trials targeting mild cognitive decline to prevent AD (Huang et al., 2020), or trials with ADAD patients that are treated sooner (Levin et al., 2022), the treatment is started too late. This is due to the fact that mild and very mild dementia due to AD are already a relatively advanced pathological state, as the clinical manifestations are already driven by tau pathology and other factors such as inflammation (Self and Holtzman, 2023). Therefore, further understanding the impact of tau and other important variables, such as the main genetic risk factor APOE, on AD progression is of great importance.

The $\varepsilon 4$ allele of *APOE* increases the risk of LOAD (Corder et al., 1993), likely due to its very strong effect in influencing the onset

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of amyloid deposition in the brain, with the effect of *APOE* being both isoform (\$\pmathrm{\

Tau

Tau is a microtubule-associated protein predominantly found in neuronal axons and oligodendrocytes, comprising 352-441 amino acids with a molecular weight of ~45-65 kDa due to different tau isoforms and posttranslational modifications. It participates in the preservation of the structural integrity and proper functioning of the microtubule cytoskeleton, which is essential for neuronal morphology, synaptic plasticity, and axonal transport of organelles (Robbins et al., 2021), and its functions extend to neuroplasticity and neuropathology (Sotiropoulos et al., 2017). Tau is an intrinsically disordered protein known for its high solubility that comprises four functional domains: the acidic N-terminal or projection domain, which presents three potential isoform configurations—exon 2 (1N), exons 2 and 3 (2N), or lack of inserted exons (0N); the proline-rich domain, situated in the central region of the protein and containing a binding site for SH3 proteins, which remains conserved across all isoforms; alongside the C-terminal region (C); and lastly, the basic repeat domain, which encompasses three to four pseudo-repeats (3R or 4R), each ~30 amino acids long (Mandelkow and Mandelkow, 2012). These repeats are crucial for facilitating microtubule binding and are referred to as the microtubule-binding domain (Naseri et al., 2019) (Fig. 1).

In humans, tau is encoded by the MAPT gene on chromosome 17 (Grundke-Iqbal et al., 1989), and six distinct isoforms (Goedert et al., 1989) are formed through alternative splicing of exons 2, 3, and 10, which can occur in different combinations. The expression of these isoforms varies across brain regions and stages of development. For example, 3R isoforms predominate during fetal development (Goedert et al., 1989), while both 3R and 4R isoforms are expressed in the adult brain, albeit in differing ratios depending on the brain region (Waheed et al., 2023), ranging between 3 and 5% expression in the case of the 2N3R isoform, and up to 23-30% expression for the 1N3R isoform (Buchholz and Zempel, 2024). Different tauopathies can be distinguished through their distinct isoform composition. In AD, all the different tau 3R and 4R isoforms contribute to the aggregates forming paired helical filaments and straight filaments, as opposed to other tauopathies that are characterized by tangles containing specific isoforms (Buée and Delacourte, 1999). For example, Pick's disease is characterized by narrow, single protofilament fibrils composed mainly of 3R tau (Falcon et al., 2018), whereas corticobasal degeneration and progressive

supranuclear palsy present unique fibril architectures composed of 4R tau (Goedert et al., 2017). There are few studies regarding the contribution of specific tau isoforms to AD pathology, although the available evidence points toward an important contribution of 1N4R and 2N4R isoforms to AD pathology (Buchholz and Zempel, 2024). It is essential for future studies to decipher the role of different tau isoforms to further understand the mechanism underlying AD pathology.

Other tau forms exist, such as the so-called "Big tau", which is double the size of regular tau due to the insertion of an extra exon 4a, and has been suggested to be protective in AD (Fischer, 2023). Intriguingly, a preprint has recently suggested that Big tau expression in AD patients is higher in the cerebellum, the brain region spared from tau pathology, indicating that it could possibly confer resistance to tau pathology (Chung et al., 2024, Preprint).

The functions of tau are regulated by posttranslational modifications, including acetylation, glycosylation, and phosphorylation (Mandelkow and Mandelkow, 2012). 85 potential phosphorylation sites have been identified (Drepper et al., 2020), some of which, such as Ser202, Thr205, Thr231, and Ser422, are more prominent in AD (Arakhamia et al., 2020; Wegmann et al., 2021). A disruption of normal levels of tau phosphorylation can result in tau dysfunction, which has been implicated in various neurodegenerative diseases including AD, Pick's disease, and other primary tauopathies (Kovacs, 2017). Traditionally, physiological tau was believed to be the low-phosphorylated form, whereas p-tau was thought to be associated with pathology. However, studies indicate that phosphorylation alone, at least at certain sites, does not distinguish between health and disease, as p-tau is also found in the brain during early development and in hibernating animals without indicating pathology (Stieler et al., 2011). In fact, a recent study has suggested a crucial role of tau217 phosphorylation in early development, with plasma p-tau217 levels exceeding even those found in AD patients (Gonzalez-Ortiz et al., 2025).

Different posttranslational modifications could drive differences in tau aggregates across tauopathies (Arakhamia et al., 2020), which appear to differ in size. Cryo-electron microscopy studies have shown that tau filaments in AD appear to be substantially bigger and more complex than filaments in other tauopathies (Fitzpatrick et al., 2017), such as Pick's disease (Falcon et al., 2018) or progressive supranuclear palsy (Shi et al., 2021b). In the following section, we will focus on the characteristics of tau specifically in AD.

Tau in AD

In AD, abnormal phosphorylation of tau protein reduces its affinity for microtubules, likely leading to tau mislocalization and intracellular aggregation (Martin et al., 2011). This abnormal tau undergoes further posttranslational modifications, such as truncations and acetylation, which promote its aggregation into paired helical filaments and straight filaments, forming NFTs (Sinsky et al., 2021). Interestingly, a recent study has suggested that soluble tau oligomers, rather than NFTs, may be some of the primary toxic species, disrupting tau's normal role in stabilizing the microtubule cytoskeleton, impairing axonal transport, and



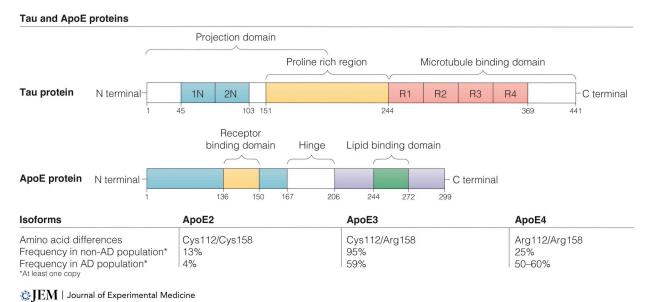


Figure 1. **Domains of tau and apoE proteins, and apoE isoform distribution.** Tau presents two domains that vary across isoforms: the projection domain (1N/2N) and the microtubule-binding region (MTBR), which can encompass either 3 or 4 repeats (3R/4R). These two domains are connected by the proline-rich region. ApoE presents three distinct regions: the N-terminal region (containing the receptor-binding domain), the C-terminal region (containing the lipid-binding domain), and a hinge region. The different apoE isoforms arise from amino acid substitutions at positions 112 and 158, where the APOE ε2 isoform (Cys112/Cys158) is the least frequent and the APOE ε3 isoform (Cys112/Arg158) is the most frequent. Within the AD population, the frequency of the risk gene, APOE ε4 (Arg112/Arg158), greatly increases.

compromising synaptic function (Zwang et al., 2024). Aggregated tau also accumulates as neuropil threads in brain areas without cell bodies (Braak and Braak, 1988) and can spread through the brain via axonal projections and synaptic circuits, propagating pathology through mechanisms such as synaptic transmission, exosomes, or tunneling nanotubes (Takeda et al., 2015; Pickett et al., 2017; Vogel et al., 2020).

Tau accumulation correlates with cognitive decline in AD (Giannakopoulos et al., 2003), impairing tau's role in maintaining synaptic functions and neuronal projections, which may underlie memory deficits in AD (Selkoe, 2002) and affect longterm potentiation (LTP) and synaptic plasticity (Shentu et al., 2018). Tau knockout (KO) mice exhibit some memory and synaptic plasticity deficits, while tau knockdown mice show minimal effects (Biundo et al., 2018). Contradictory findings indicate that tau deletion in a Drosophila model did not affect phenotype (Burnouf et al., 2016), and tau ablation in mice protected against age-related cognitive decline (Jara et al., 2020), whereas tau reduction with antisense oligonucleotides (ASOs) was seen to be highly protective (DeVos et al., 2017) and is currently being tested in human trials (Mummery et al., 2023). The discrepancies observed between mouse and Drosophila studies may be due to differences between murine and Drosophila tau, which are homologous yet not identical. It would be of interest to observe the effect of tau ablation in these animal models expressing human tau. Within murine models, the strains used both consist in tau KO; however, the strain used in Biundo et al. (2018) also involved the inclusion of GFP in the original Mapt gene, which could influence the effect of the KO and therefore account for the differences observed. It is also important to note that mice appear to splice tau differently to humans, even when human

MAPT is incorporated (Saito et al., 2019). These discrepancies highlight the need for further research on tau's normal role in development and the adult brain.

Aside from losing its physiological function in AD, tau also gains toxic functions, contributing to neurodegeneration through a plethora of mechanisms (Liang et al., 2022), such as inducing oxidative stress (Kandimalla et al., 2018), inhibiting mitochondrial transport (Briston and Hicks, 2018), and inducing the innate immune response (Mancuso et al., 2019; Shi et al., 2019). AD-associated tau oligomers reduce LTP in mouse hippocampal slices (Fá et al., 2016), and reducing tau phosphorylation can restore LTP and attenuate synapse loss in PS19 mice expressing human mutant P301S tau (Seo et al., 2017). A study using pseudo-p-tau showed that hyperphosphorylation impairs synaptic function by increasing tau dendritic localization, decreasing alpha-amino-3-hydroxy-5-methyl-4-isooxazole-propionic acid (AMPA) receptor presence, and reducing AMPA and N-methyl-D-aspartate (NMDA) receptor expression, without significant spine loss (Hoover et al., 2010). The presence of oligomeric tau presynaptically reduced excitatory postsynaptic potentials and increased short-term depression (Hill et al., 2019), whereas the presence of oligomeric tau postsynaptically impaired LTP induction (Ondrejcak et al., 2018; Hill et al., 2019). The presynaptic presence of oligomeric tau may be due to its binding to synaptic vesicles, which is mediated by the transmembrane protein synaptogyrin-3, potentially leading to vesicle clustering at presynaptic terminals (McInnes et al., 2018). As such, a reduction in synaptogyrin-3 levels rescued tau-induced pre- and postsynaptic loss and ameliorated working memory and LTP impairments (Largo-Barrientos et al., 2021). Nonetheless, it is important to note that many of these studies use extremely



high concentrations of tau that would not be found *in vivo*, which could impact the results and should be taken into consideration.

 $A\beta$ can also drive tau pathology in AD. Although tau and $A\beta$ are two independent hallmarks that have been isolated in the respective tau and amyloid hypotheses developed, various studies have demonstrated links between these elements. A β can accelerate the rate of tau hyperphosphorylation by enhancing the activity of GSK-3β and CDK-5, which phosphorylate tau at different sites (Zempel et al., 2010). The presence of amyloid pathology has also been shown to accelerate tau pathology and neurodegeneration in vivo (Lewis et al., 2001). AB also affects the aggregation of tau by potentiating tau cleavage, leading to self-aggregation and the appearance of toxic tau oligomers that damage neurons and can act as tau seeds to propagate the pathology (Zhang et al., 2021b). Tau can in turn mediate the toxicity of $A\beta$ by interacting with the Fyn kinase, the phosphorylation of which is crucial to Aβ-induced synaptic toxicity (Nygaard, 2018). Synergistic effects of AB and tau have also been described in damaging effects on mitochondria and glial cells, thus demonstrating that these proteins act together to drive AD pathology on a plethora of levels.

Given the links between tau pathology and the cognitive decline observed in AD, it is crucial to enhance our understanding of the factors underlying and driving tau pathology. In this regard, further information on the role the main genetic risk factor, APOE, plays in tau pathology could be essential to enhance our understanding of AD and potentially direct new therapeutic interventions in the future.

ApoE

ApoE is a glycoprotein composed of 299 amino acids and a molecular mass of ~34 kDa, encoded by the APOE gene. It is ubiquitously present in the body, with significant production in the brain and liver (Liu et al., 2013). In the central nervous system (CNS), apoE is primarily produced by astrocytes under physiological conditions (Boyles et al., 1985). Its transcription and secretion are regulated by liver X receptor (LXR) and retinoid X receptor (Liang et al., 2004; Hong and Tontonoz, 2014), whereas apoE production is influenced by lipids, hormones, and transcription factors (Kockx et al., 2018). It can also be produced by other cells in the CNS such as microglia, oligodendrocytes, choroidal epithelial cells, and cells surrounding the brain vasculature (Martens et al., 2022).

ApoE consists of three regions: (1) the N-terminal region (residues 1-167) containing the receptor-binding domain, (2) the C-terminal region (residues 206-299) containing the lipid-binding domain, and (3) a flexible hinge region (residues 168-205) (Chen et al., 2021). Human apoE exists predominantly in three isoforms, resulting from single amino acid substitutions at positions 112 and 158 (Martens et al., 2022) (see Fig. 1):

- ApoE2 (cysteine at both positions), which protects against AD relative to apoE3.
- ApoE3 (cysteine at 112 and arginine at 158), the most common isoform.
- ApoE4 (arginine at both positions), the AD risk-associated variant relative to apoE3.

These substitutions cause significant structural differences, such as disulfide-linked dimer formation in apoE2 and, to a lesser extent, apoE3, which is absent in apoE4 (Elliott et al., 2010), and a possible salt bridge that appears exclusively in apoE4 linking the N- and C-terminal domains, which are otherwise separated (Yu et al., 2014). As the structure of physiological forms of apoE that are present in lipoprotein particles is not completely understood at high resolution, structural differences between physiological forms of the different apoE isoforms need to be better determined to understand their implications (Strickland et al., 2024).

Physiological function of apoE

ApoE is synthesized *de novo* in the brain, given that plasma apoE does not cross the blood-brain barrier (BBB) (Liu et al., 2012; Chernick et al., 2019). ApoE is a component of high-density-like lipoproteins in the CNS, offering them stability and guiding their transport and function (Feingold, 2022), thus playing a key role in lipid transport and cholesterol metabolism. In the brain, its main function appears to be in glial cells where it plays a role in lipid export (Nugent et al., 2020), although apoE also assists in lipid clearance (Mahley, 2016) and cell membrane repair after injury (Tensaouti et al., 2020). Despite performing crucial functions in the brain, a case study of an APOE^{-/-} individual that was cognitively normal indicates that APOE may not be required for adequate brain functioning (Mak et al., 2014).

For proper functioning, apoE must be glycosylated, secreted, and lipidated. Its glycosylation varies between cerebrospinal fluid (CSF) and plasma (Flowers et al., 2020), and includes O-linked glycosylation and sialylation (Kockx et al., 2007), which modulate its lipid receptor affinity and metabolic functions (Kacperczyk et al., 2021). ApoE lipidation is regulated predominantly by ATP-binding cassette transporter A1 (ABCA1) and also ATP-binding cassette subfamily G member 1, which control cholesterol efflux to apoE (Vance and Hayashi, 2010). ApoE follows a "double-belt" model when binding discoidal lipids, as two apoE proteins wrap around the lipids in an antiparallel formation (Strickland et al., 2024). ApoE isoforms vary in lipidation and lipid-binding preferences; however, it is not yet fully understood how apoE isoforms influence lipidation, and further studies on the subject are required.

To perform its functions, apoE interacts with members of the low-density lipoprotein receptor (LDLR) family (Holtzman et al., 2012), of which LDLR itself appears to be the main apoE receptor (Fryer et al., 2005a). To bind to receptors, apoE undergoes a conformational change upon lipoprotein binding, which separates the N- and C-terminal regions and exposes the receptor-binding domain (Chen et al., 2011). ApoE dimerization could play a role in its binding to receptors (Dyer et al., 1991), either as homodimers or as heterodimers (Martens et al., 2022). ApoE isoforms exhibit different receptor affinities; apoE4 has a higher affinity for LDLR-related protein 1 (LRP1) than apoE3 (Cooper et al., 2021), while apoE2 has markedly reduced binding affinity for LDLR (Zhao et al., 2018a). These variations in affinity could potentially underlie the differential effects of apoE isoforms on AD pathology.



Role of apoE as a pathological factor in AD

Since its discovery as the primary genetic risk factor for AD, numerous studies have explored the influence of APOE on different aspects of the pathology. Carrying one copy of APOE ε4 leads to a ~4-fold risk of developing AD, whereas two copies increase the risk 12-fold relative to APOE ε3 homozygotes (Strittmatter et al., 1993; Holtzman et al., 2012; Yamazaki et al., 2019). Despite being present in around 25% of the European American population, over 50% of AD cases carry an APOE £4 allele (Alzheimer's Association, 2024). This significant association has inspired a recently proposed categorization of AD into familial AD, APOE &-related LOAD, and APOE ε 4-unrelated LOAD (Frisoni et al., 2022; Fortea et al., 2024). However, this model is highly controversial given the different impact of APOE &4 across ancestry (Belloy et al., 2023), as the allele increases the risk of AD more in East Asian populations compared with European and African American backgrounds (Vance et al., 2024). Therefore, the model has not yet been universally adopted as clear distinctions cannot be made at this time.

A strong link exists between APOE $\epsilon 4$ and amyloid pathology, with studies showing that it increases amyloid plaque load (Tiraboschi et al., 2004), A β oligomers (Hashimoto et al., 2012), amyloid seeding (Liu et al., 2017), amyloid deposition (Holtzman et al., 2000), and also alters the A β 40:A β 42 ratio (Fryer et al., 2005b) and reduces A β clearance (Castellano et al., 2011). Changes in A β concentration and clearance, which can be detected before amyloid deposition, vary according to APOE isoforms in mice: the expression of APOE ϵ 4 results in the highest levels of soluble A β in the brain interstitial fluid and the lowest clearance rate, whereas APOE ϵ 2 shows the opposite tendency (Castellano et al., 2011).

APOE $\epsilon 4$ exacerbates various properties that may influence AD risk in addition to its effects on amyloid deposition, including BBB breakdown (Montagne et al., 2020) and neuroinflammation (Cudaback et al., 2011; Parhizkar and Holtzman, 2022). ApoE may influence microglial responses via receptors like TREM2 (triggering receptor expressed on myeloid cells 2) (Gratuze et al., 2018), which has been implicated in various AD-related functions including A β and tau seeding and spreading (Leyns et al., 2019; Parhizkar et al., 2019).

Lipid dysregulation in AD may also be tied to altered apoE functions, with apoE4 being less efficient at transporting cholesterol (Zhao et al., 2017), although conflicting studies exist (Tcw et al., 2022). Mutations in transporters responsible for apoE lipidation, like ABCA1, have been linked to increased risk of AD (Nordestgaard et al., 2015), and ABCA1 deficiency in APOE ϵ 4 mice increased A β aggregation (Fitz et al., 2012).

Some studies suggest that apoE dysfunction affects synaptic maintenance and neuronal repair (Perdigão et al., 2020); APOE £4 has been associated with reduced density of synapses (Dumanis et al., 2009) and dendritic spines (Jain et al., 2013), decreased presence of pre- and postsynaptic proteins (Lin et al., 2018), decreased LTP (Trommer et al., 2004), an altered synaptic proteome and exacerbated synaptic loss (Hesse et al., 2019), and poor learning and memory (Rodriguez et al., 2013). It should be noted, however, that in humans, the presence of apoE4 is not

associated with impaired cognition in the absence of AD pathology (Knight et al., 2014).

As mentioned previously, apoE glycosylation is essential for its correct functioning, with plasma apoE glycosylation potentially being linked to amyloidosis (Lawler et al., 2023). Changes in apoE glycosylation have been associated with increased $A\beta$ levels (Chua et al., 2010), and apoE glycosylation and dimerization appear to be altered in the CSF of AD patients (Lennol et al., 2022), which could represent apoE dysfunction.

These findings highlight the multifaceted role of apoE in AD pathology, particularly the isoform-specific effects of apoE4. The role of apoE may also be influenced by epigenetic factors, in particular dietary habits, by altering APOE DNA methylation (Tulloch et al., 2018; Lozupone et al., 2023). Recent reviews have detailed the pathological roles of APOE in AD (Tzioras et al., 2019; Fernández-Calle et al., 2022; Martens et al., 2022; Parhizkar and Holtzman, 2022). This review specifically examines the impact of APOE on tau pathology, including tau spreading, seeding, and clearance, as well as direct interactions between apoE and tau, and effects mediated by microglia.

APOE and tau: A review of current knowledge

Given the direct binding between apoE and $A\beta$, much research has focused on elucidating the interactions between these proteins. Nonetheless, numerous studies have established links between APOE and tau pathology, with APOE ε4 being associated with an exacerbation of tau pathology in AD in humans (Nicoll et al., 2011). An APOE ε4-mediated exacerbation of tau pathology has also been reported in mouse studies (Brecht et al., 2004; Harris et al., 2004), although these studies were performed using the mouse model developed by the Huang laboratory, which presents a set of APOE neuronal phenotypes that have not been reported in other models. The influence of APOE $\epsilon 4$ extends beyond AD and appears to be more frequent in other tauopathies, such as chronic traumatic encephalopathy (Atherton et al., 2022) and frontotemporal dementia (FTD) (Mishra et al., 2017), in which it is linked to increased atrophy (Agosta et al., 2009) and more severe behavioral deficits (Engelborghs et al., 2006). Despite this, the extent of the contribution of APOE £4 to tau pathology in these diseases varies and is less consistently established compared with AD.

Interestingly, APOE $\epsilon 4$ is associated with decreased vulnerability to primary age-related tauopathy (PART), an Aβ-independent tauopathy with milder cognitive effects (Crary et al., 2014; Bell et al., 2019). The decreased risk of PART conflicts with the increased levels of NFTs in APOE $\epsilon 4$ AD patients (Zhao et al., 2018a), suggesting that the influence of APOE $\epsilon 4$ on tau pathology is diminished in the absence of amyloid pathology. However, this decreased vulnerability may also simply reflect an underrepresentation of APOE $\epsilon 4$ carriers in this demographic, given their drastically enhanced odds of developing AD.

The protective role of APOE $\varepsilon 2$ in primary tauopathies is also less clear, as emerging evidence suggests it may not confer the same well-documented protective effects seen in AD. Indeed, APOE $\varepsilon 2$ has been linked to an increased risk of certain tauopathies outside of AD (Zhao et al., 2018b; Robinson et al., 2020). It is unclear whether this is truly an effect of APOE $\varepsilon 2$ on



increasing risk for these diseases, or whether it simply reflects the fact that APOE $\epsilon 2$ –positive individuals are less likely to develop AD pathology and are thus more susceptible to other less common brain diseases. This divergence in the effects of APOE $\epsilon 2$ further highlights the complexity of APOE–tau interactions. The complex association between APOE and tau pathology is reviewed in the following sections, starting with the effects of APOE on tau pathology on a macroscopic level, before describing the effects on a cellular level.

Associations between tau and APOE in the CNS

APOE directs tau spreading in the human brain. In AD, intraneuronal lesions caused by misfolded and hyperphosphorylated tau protein are key to the pathology. Traditionally, the distribution and spreading of tau lesions throughout the brain were believed to follow a well-defined pattern, known as Braak stages (Braak and Braak, 1991). In Braak stages I and II, the earliest stages of the pathology, NFTs are confined to the entorhinal and transentorhinal cortex. Tau then spreads to limbic regions, including the hippocampus, in Braak stages III and IV, before spreading throughout the neocortex in stages V and VI (Braak et al., 2006). Nonetheless, despite the supposed uniform propagation of tau, different examples of tau patterns have emerged that do not fit the pre-established Braak stages, such as the limbic-predominant phenotype and a medial temporal lobesparing phenotype (Ferreira et al., 2020). The differences in tau spreading could affect AD progression and may be associated with other variables, such as APOE. In fact, studies have shown that the spread of tau is directed by APOE, and alterations in its expression levels may lead to earlier and more severe tau accumulation (Montal et al., 2022). The APOE $\varepsilon 4$ genotype leads to a more severe and Braak stage-like medial and temporal spread of tau (Baek et al., 2020; Sanchez et al., 2021), whereas APOE ε4 noncarriers more frequently present a non-Braak pattern, with increased spread in the neocortex (Mattson and Arumugam, 2018; Whitwell et al., 2018) (Fig. 2).

A study by Vogel et al. (2021) described four spatiotemporal subtypes of AD: limbic-predominant, medial temporal lobesparing, posterior occipitotemporal, and temporoparietal. Individuals with the limbic subtype were more likely to carry the APOE £4 allele and exhibited relatively better performance in global cognition but worse memory scores, despite having a lower tau tangle burden compared with other subtypes. In contrast, APOE ε4 noncarriers can exhibit the medial temporal lobe-sparing subtype, associated with a higher neocortical tau burden, suggesting that APOE may play a role in guiding tau spreading throughout the brain of AD patients. Other studies have shown that APOE &4 carriers present increased medial temporal neurodegeneration, with increased vulnerability to atrophy (Donix et al., 2010), and enhanced tau pathology in the entorhinal cortex and hippocampus, independent of AB (Therriault et al., 2020; Singh et al., 2023). Sex may also be important in the association between tau and APOE E4, with stronger interactions being described in women (Ramanan et al., 2019; Wang et al., 2021); however, an opposite effect of APOE ε4 dosage on brain region-specific tau deposition exclusively in men has been reported (Yan et al., 2021).

It is worth noting that the precise mechanism through which APOE influences tau spreading in the brain is unclear. Some studies suggest it could be mediated by the amyloid burden and through microglial and astrocytic responses affecting neuroinflammation, which could facilitate the spread of tau throughout certain brain areas, such as the entorhinal cortex. Other studies suggest that carrying the APOE $\epsilon 4$ gene increases the vulnerability of the medial temporal lobes to hypometabolism (Lehmann et al., 2014) and atrophy (Donix et al., 2010), which could lead to an increase in tau spreading. It is therefore plausible that APOE $\epsilon 4$ enhances the vulnerability of specific brain areas to tau pathology, which can then spread to other areas in the presence of A β .

The study of tau aggregates spreading throughout the brain in vivo using positron emission tomography (PET) and the tau-PET tracer ¹⁸F-AV-1451 (¹⁸F-flortaucipir) has high diagnostic potential, as it allows one to observe pathology progression in vivo. The topography of tau-PET binding correlates with cognitive deficits (Ossenkoppele et al., 2016; Aschenbrenner et al., 2018), including memory loss (Young et al., 2023), and predicts the rate of atrophy (La Joie et al., 2020). Studies implementing this tau tracer have shown conflicting results, with some showing associations between medial temporal tau and APOE ε4 (Weigand et al., 2021), whereas others show no association (Salvadó et al., 2021). It is worth noting that the field of tau imaging is relatively young, as such it is still imperfect. For example, off-target binding to monoamine oxidase-B in the basal ganglia can complicate interpretation of results with some tau tracers (Leuzy et al., 2019), which is likely responsible for some of the discrepancies observed. Nevertheless, novel imaging techniques and the refinement of tau-PET tracers will help in the diagnosis of AD. Studying large cohorts of individuals with AD pathology at various stages of clinical disease and healthy individuals while controlling for factors such as APOE will contribute to our knowledge of variables that guide tau propagation and assist in predicting AD progression.

Associations between tau and apoE in the CSF. In recent years, the field of biomarkers in the diagnosis of AD has sparked a lot of interest, given the difficulties in achieving an early AD diagnosis. In this regard, CSF biomarkers present a potential advantage over blood biomarkers due to the proximity to the brain parenchyma, allowing easier detection of certain brain-derived proteins (Blennow et al., 2010). Both A β and tau are found in the CSF, and alterations in their levels contribute to the diagnosis of AD (Blennow and Zetterberg, 2018).

Both total tau (T-tau) and forms of p-tau can be detected in the CSF. T-tau levels correlate with the intensity of neuro-degeneration in the brain (Blennow and Hampel, 2003), which appears to be increased in AD (Olsson et al., 2016), and higher levels are indicative of stronger disease progression (Buchhave et al., 2012). T-tau levels increase following acute brain damage (Zetterberg et al., 2006), and this lack of specificity limits its diagnostic utility in distinguishing AD from other disorders. P-tau levels, in contrast, are associated with tau phosphorylation, and certain p-tau forms are more characteristic of AD (Wallin et al., 2010), as they remain unaltered following acute brain damage or in individuals lacking NFTs (Skillbäck et al.,



2014). Although p-tau forms are also present in other tauopathies, they are usually present with distinct patterns. As such, the measurement of CSF p-tau levels is included in the diagnostic evaluation procedure of AD (Self and Holtzman, 2023). In particular, levels of p-tau 181 and p-tau 217 are especially good markers of amyloid deposition in the brain, while the levels of MTBR-243 are a very good marker for tau tangle burden (Barthélemy et al., 2020; Horie et al., 2022, 2023).

The concordance between tau CSF and PET studies assessing tau is low (Gordon et al., 2016) and may depend on factors such as disease state (Wolters et al., 2020). This discrepancy is likely because these techniques reflect distinct pathological processes, as CSF biomarkers measure soluble forms of tau, whereas PET imaging detects aggregated, misfolded tau; and also due to the timing of these changes, as CSF p-tau becomes elevated before tau-PET binding occurs (Groot et al., 2023). In this regard, T-tau and p-tau in the CSF represent neurodegeneration and tau phosphorylation, respectively, at several sites related to amyloid deposition and correlate with early markers of AD, whereas ¹⁸F-flortaucipir tags tau misfolding, with PET scans correlating more closely with cerebral atrophy and cognitive deficits (Ossenkoppele et al., 2021).

Other AD-related proteins can be detected in the CSF, including apoE. ApoE alterations have been described in the CSF, affecting the glycosylation and dimerization of the protein (Lennol et al., 2022), and an imbalance of isoforms in heterozygous subjects has been reported (Minta et al., 2020). Studies quantifying CSF apoE levels have produced inconclusive findings, with APOE ε4 carriers presenting the lowest in some studies (Riddell et al., 2008), and the highest in others (Darreh-Shori et al., 2011). These discrepancies could be due to the experimental approach, as lower apoE levels were detected in the CSF of human APOE-targeted replacement mice, whereas higher levels were found in the CSF of APOE ε4 AD patients. The simplified mouse model may therefore not recapitulate all aspects of AD pathology, and apoE4 could be subjected to degradation that does not occur during AD due to complex factors that are not accounted for in mice. It is of utmost importance to determine which mechanisms differ between human patients and the mouse models used to further comprehend why discrepancies occur and how these differences could be impacting AD.

Associations have been found between apoE and levels of T-tau and p-tau (Martínez-Morillo et al., 2014), particularly in APOE ε4 carriers (Deming et al., 2017; Wattmo et al., 2020), who present higher tau CSF levels (Toledo et al., 2015; Dincer et al., 2022) (Fig. 2). These associations are likely modulated by amyloid pathology (Jack et al., 2017), as APOE &4 carriers present higher levels of T-tau and p-tau even before tau pathology has been developed (Lim et al., 2023), which is very likely caused by elevations in tau species due to amyloid deposition (Maia et al., 2013; Barthélemy et al., 2020). In APOE ε4 carriers, tau levels seem to correlate with cognitive decline, whereas p-tau181 and p-tau217 correlate with amyloid pathology (Koch et al., 2017). Interestingly, the protective effect of APOE ε2 on AD pathology is not reflected in tau CSF levels, although most APOE ε2 carriers have no elevation of p-tau in CSF due to a delayed amyloid deposition (Grothe et al., 2017).

The effect of APOE on tau CSF levels may be mediated by factors such as ancestry (Morris et al., 2019; Xu et al., 2024) or sex. Female APOE ε4 carriers reportedly have higher T-tau and p-tau levels (Altmann et al., 2014) and accelerated rates of longitudinal CSF p-tau accumulation (Buckley et al., 2019), leading to a stronger association between APOE and tau in women (Hohman et al., 2018). The influence of sex may be dependent on disease state, as the differences that are exacerbated in early stages of the pathology in APOE ε4 carriers diminish in the latter stages (Babapour Mofrad et al., 2020). Intriguingly, other factors, such as sleep deprivation, can alter the CSF levels of tau (Holth et al., 2019). Therefore, different factors should be considered when assessing associations between CSF levels of apoE and tau.

The development of plasma biomarkers, which are more accessible than the CSF, is promising, and may serve to screen for potential neurological damage or injuries, such as neurofilament light chain (Mattsson et al., 2019). In addition, plasma p-tau 217 is an excellent indicator of amyloid deposition (Barthélemy et al., 2024). A recent study correlating APOE ε4 with proteins involved in oxidative stress and mitochondrial function in the CSF demonstrated the same correlation when assessing plasma samples, thus showing the potential of using plasma samples (Dammer et al., 2024). Future studies should take place across different AD stages to determine which biomarkers are most useful at different time points, and when possible in the environment of primary care in order to account for the diverse populations and the possible interference of medical comorbidities (Ossenkoppele et al., 2022). For more information regarding recent advances in AD diagnostics, see Self and Holtzman (2023).

Transcriptomic links between APOE and tau. RNA sequencing (RNA-seq) allows the study of the transcriptomic profiles of different cell types in human AD brains, which could enhance our understanding of the different roles particular cells are playing in the disease. Studies have shown there are diverse microglial phenotypes in AD, with distinct profiles associated with Aβ and tau pathologies (Gerrits et al., 2021). Tau pathology has also been correlated with upregulated APOE expression in microglia, but not in astrocytes (Smith et al., 2022), which has been supported by a study identifying cell subtype-specific genetic variants that only affect microglial expression of APOE (Fujita et al., 2024). Regarding microglia, a TREM2-APOE pathway has also been shown to regulate microglial activation in neurodegenerative diseases (Krasemann et al., 2017). Astrocytic transcriptional changes have also been assessed (Sadick et al., 2022), and studies show that APOE follows an opposite trend and appears to be downregulated in astrocytes in AD (Grubman et al., 2019; Mathys et al., 2019).

Despite the promise surrounding RNA-seq, the approach presents certain limitations, such as the difficulty in performing high-throughput RNA profiling due to high costs and technical variability (Zhang et al., 2014; Stark et al., 2019), the loss of microglial signatures upon extraction (Thrupp et al., 2020), or the enrichment of certain cell types (Oh et al., 2022). Additional studies have also shown that the cellular isolation technique can lead to important biases when assessing microglial activation



(Kang et al., 2018a; Haimon et al., 2018). Furthermore, RNA-seq alone is unable to determine whether transcriptomic changes occur near SPs and NFTs, or whether they occur diffusely throughout the brain. As such, spatial transcriptomic methods have been developed (Zeng et al., 2023). Das et al. assessed transcriptomic changes in areas surrounding NFTs obtained via laser capture microdissection and showed that APOE £4/£4 was linked to the upregulation of proinflammatory, phagocytosis, cell death, protein translation, extracellular matrix, and cholesterol metabolism-associated genes, and the downregulation of neurotransmission and synaptic pathway-associated genes (Das et al., 2024) (Fig. 2). Single-nucleus RNA-seq offers an alternative approach and allows for the characterization of transcriptomic profiles of individual cells from postmortem human brain tissue (Hodge et al., 2019), and has been used to analyze the transcriptomic cellular heterogeneity in AD brains (Del-Aguila et al., 2019; Lau et al., 2020; Leng et al., 2021; Mathys et al., 2023; Sun et al., 2023). Nonetheless, the postmortem interval may be of crucial importance, as a recent study showed a postmortem interval of around 3 h significantly diminished the number of differentially expressed genes between WT and PS19 mice expressing human tau with the P301S mutation (Olney et al., 2025).

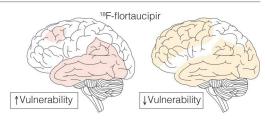
When assessing the field of RNA-seq in AD, it is also important to note that the results of studies in humans tend to vary significantly to those found in AD mouse models, given the heterogeneity of certain cell types across species (Zhou et al., 2020). Notwithstanding, various studies in murine models have described intriguing links between APOE and tau on a transcriptional level. A study in adeno-associated virus (AAV)mediated P301L mice, a mouse model of tau pathology, showed that APOE upregulation leads to the activation of a microglial APOE-driven network that contributes to AD pathology (Kang et al., 2018a). In PS19 tau transgenic mice expressing human APOE ε4, a unique innate and adaptive immune response was found in mice with tauopathy, but not with amyloid deposition (Chen et al., 2023). Another study in THY-Tau22 mice, a different mouse model of tau pathology, found that, although tau pathology did not affect microglial gene expression to the same extent as Aβ, APOE was still upregulated (Sierksma et al., 2020). Importantly, some of the research models used (THY-Tau22 mice and AAV-mediated P301L) show little neurodegeneration, which could explain the discrepancy in the results observed.

Further studies are required to determine a common transcriptomic and proteomic background in AD. Furthermore, direct comparisons between transcriptomic and proteomic alterations across different *APOE* genotypes are necessary, as many studies assess individuals of a specific genotype to reduce variability, thus making the comparison difficult. Performing these studies in the brains of patients from different time points of AD could shed some light on the progression of the pathology.

Effects of APOE on tau pathology at a cellular level

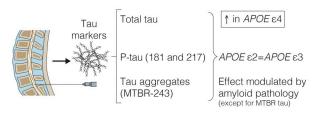
Animal models to study AD. Various different mouse models have been developed to study AD, expressing different mutations that lead to amyloid and/or tau pathology. These models present an important level of heterogeneity, which is essential to

Human PET studies

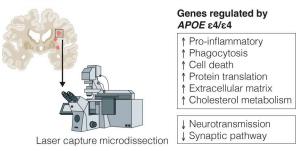


| | APOE ε4 | Non-APOE ε4 |
|------------------|-----------------|------------------|
| Tau accumulation | Medial temporal | More neocortical |
| Tau burden | Severe | Mild |
| Braak profile | Braak-like | Non-Braak like |

Cerebrospinal fluid studies



RNA-sequencing studies



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Figure 2. **APOE** and tau in AD: Key findings from human studies. A series of studies in humans have demonstrated that APOE ϵ 4 is linked to exacerbated tau pathology. In PET studies, APOE ϵ 4 has been linked to a more severe and Braak-like medial temporal accumulation of tau, whereas non-APOE ϵ 4 individuals tend to present a more neocortical and mild tau burden. In the CSF, studies have shown that the levels of all tau markers (T-tau, p-tau, and tau aggregates) tend to increase in APOE ϵ 4 individuals, an effect that appears to be modulated by sex and amyloid pathology (except for MTBR tau). Within the CSF, the tau biomarker levels do not appear to differ significantly between APOE ϵ 2 and APOE ϵ 3 individuals, despite the protective role of APOE ϵ 2. RNA-seq studies have found that APOE ϵ 4 appears to upregulate a series of genes, including genes associated with phagocytosis, cell death, and proinflammatory genes, whereas it downregulates neurotransmission and synaptic pathway genes.

take into consideration when interpreting the results obtained across studies. One of the most common models is the 5xFAD mouse model, which expresses human APP and PSENI transgenes, two crucial genes that can cause ADAD when they present mutations. In this model, five total mutations are present: the Swedish, Florida, and London mutations in APP, and the M146L and L286V mutations in PSENI, leading to the rapid development of severe amyloid pathology (Oakley et al., 2006). It is important to note that the 5xFAD model also presents



artifactual intraneuronal $\ensuremath{A\beta}$ accumulation that is not present in AD or in most other models.

Other models that will be mentioned frequently in the subsequent sections focus on tau pathology, usually in the absence of amyloid pathology. It should be noted that although the following models express human mutant tau, endogenous mouse tau is also produced, leading to tau pathology in brain areas that are less relevant in AD (Sanchez-Varo et al., 2022). One such example is PS19 mice, which overexpress 1N4R human tau with the P301S mutation approximately fivefold under the control of the PrP promoter (Yoshiyama et al., 2007). The P301S mutation in humans causes early-onset FTD, and appears to lower the threshold for the protein to enter an aggregate-prone conformation. PS19 mice develop NFTs, LTP/LTD deficits, and cognitive impairment at 6 months, followed by neuronal loss at 9 months of age. Other variants of P301S mutant tau mice exist, such as the Thy1-driven P301S (Thy1-hTau.P301S) mice expressing P301S under the murine Thy1 promoter (Allen et al., 2002), or the THY-Tau22 model, which displays cognitive impairment at 10 months without motor deficits (Schindowski et al., 2006). Nonetheless, the tau pathology present in PS19 mice is more robust, given that the expression levels of human mutant tau are higher under the PrP promoter. The use of different promoters also influences the regions in which tau pathology occurs: in PS19 mice, the pathology mainly affects the hippocampus and spreads to the neocortex (Yoshiyama et al., 2007), whereas in Thyl-driven P301S, the pathology appears mostly in the spinal cord (Xu et al., 2014).

Other tau models incorporate the P301L mutation, which also causes FTD and mainly affects the hippocampus and neocortex (Mirra et al., 1999). PS19 mice show NFTs earlier than P301L mice, and synaptic loss is present from an early age. It is worth noting, however, that the median life expectancy of these animals is significantly lower and that amyloid pathology is absent in both models, thus only partially recapitulating AD-like pathology. It has been reported that the P301S mutation may cause the inability of microtubule assembly, whereas the P301L mutation could interfere with the rate of paired helical filament formation in vitro (Myers and McGonigle, 2019), although both leucine and serine substitutions at P301 have been shown to destabilize the local structure of tau and facilitate aggregation (Mirbaha et al., 2018). Importantly, both models lack tau ubiquitination and acetylation, which are relevant for late-stage AD, thus limiting their use (Wenger et al., 2023).

The background of these models is also of relevance, as earlier PS19 mice expressing the P301S mutation were originally bred on a mixed background and have now been backcrossed with C57BL/6J to generate a congenic line. Both lines exhibit tau inclusions and neuronal loss, although neuronal loss is observed later in the congenic model (Maruyama et al., 2013). Therefore, the specific mutations and promoters used, and the background of the specific strain of mice are of great importance and can contribute significantly to the results observed in studies. As mentioned, many models inducing tauopathy lack amyloid pathology, and thus, extrapolating these results to human AD is complex, and the relevance of the conclusions could be limited. Although double tau-amyloid models exist that likely recapitulate

more aspects of AD, such as the 3xTg-AD model combining *MAPT*, *APP*, and *PSI* mutations, in this review, we will focus mainly on pure tauopathy models.

Potential mechanisms underlying APOE influence on tau pathology. Aside from the effects that APOE has on tau throughout the CNS, various early studies already demonstrated direct physical interactions between these proteins. ApoE has been detected in the damaged neurons of neurodegenerative disease patients (Farrer et al., 1995), and has been suggested to interact directly with tau (Strittmatter et al., 1994; Fleming et al., 1996) and to colocalize in NFTs (Namba et al., 1991), also in the form of apoE fragments (Huang et al., 2001; Rohn et al., 2012).

When assessing the impact apoE has on tau at a cellular level, it is important to reiterate that apoE is a secreted protein, whereas tau is present within the cytoplasm of neurons and axonal regions. Although some studies have reported that tau is also present in the extracellular space (Yamada et al., 2011), the direct interaction between the proteins in the extracellular space has yet to be definitively reported and remains controversial. Further studies using more sensitive methods, such as nuclear magnetic resonance spectroscopy, surface plasmon resonance, and/or size-exclusion chromatography coupled with multiangle light scattering would be essential to confirm the direct physical interaction between tau and apoE. An indirect interaction may also take place through apoE receptors such as LRP1, which has been shown to bind tau and is present in both neurons and glial cells (Rauch et al., 2020).

Astrocytes can take up tau that is released from neurons (Narasimhan et al., 2017; Perea et al., 2019), which may be neuroprotective (Kovacs, 2020), an effect that could be influenced by APOE (Steele et al., 2022) (Fig. 3). As apoE is responsible for interacting with lipids released from neurons, it may also interact with extracellular pathophysiological forms of tau. Soluble oligomeric tau may be highly toxic (Maté de Gérando et al., 2021); therefore, excessive levels could result in damage to astrocytes (Sidoryk-Wegrzynowicz et al., 2017), which can cause a switch to a neurotoxic phenotype (Ezerskiy et al., 2022; Eltom et al., 2024), ultimately leading to damage to surrounding neurons (Wang and Ye, 2021). Intriguingly, a recent study from Eisenbaum and colleagues showed that astrocytic tau internalization is APOE isoform-specific, where APOE ε4 astrocytes appear to have the lowest rate of tau uptake (Eisenbaum et al., 2024). Although a reduced rate of tau internalization may be seen as beneficial for the reasons mentioned previously, the enhanced presence of tau in the extracellular space could facilitate its propagation or reuptake by neurons, as the rate of tau internalization is concentration-dependent (Evans et al., 2018). Furthermore, Eisenbaum et al. also demonstrated that APOE ε4 astrocytes presented the lowest rate of tau clearance due to an impairment in the endosomal-exosomal pathway, the mechanism through which astrocytes appear to clear tau (Chiarini et al., 2017), leading to an increased accumulation of tau within the cell. Moreover, these astrocytes presented lower resilience to neurodegenerative conditions and impacted mitochondrial homeostasis due to the lack of a compensatory response observed in APOE ε2 and APOE ε3 astrocytes. In this manner, the APOE ε4 genotype would be associated with both a



Tau uptake, seeding and clearance

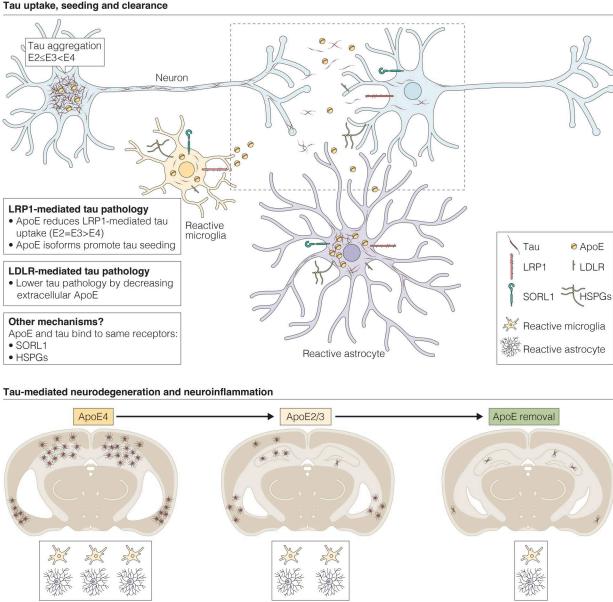


Figure 3. Effects of APOE on tau propagation and tau-mediated neurodegeneration. Despite the lack of definitive evidence suggesting direct interactions between apoE and tau, a series of studies have shown that APOE can modulate tau pathology. Tau aggregation varies across APOE genotypes, with ε4 cases presenting the highest levels and ε2 the lowest. Tau propagation and subsequent seeding could be mediated through apoE receptors capable of internalizing tau, such as LRP1, HSPGs, and SORL1. LDLR overexpression has also been seen to protect against tau-mediated neurodegeneration by reducing extracellular apoE levels. With regard to tau-mediated neurodegeneration and neuroinflammation, both appear to be exacerbated in APOE ε4 brains compared with APOE ε2 or APOE ε3, whereas APOE removal results in a decrease in both.

toxic accumulation of tau within astrocytes, exacerbating the pathology due to their increased sensitivity, and the accumulation of tau in the extracellular space due to a decreased rate of uptake and clearance through astrocytes.

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Effects of APOE on the cell-to-cell propagation of tau. As mentioned, tau pathology propagates throughout cells in the CNS. For tau spreading to occur, tau species must be released from neurons to then enter recipient cells and induce tau aggregation (Kanmert et al., 2015). This cell-to-cell propagation can occur with tau monomers, oligomers, and aggregates (Zhang

et al., 2021a) and occurs in a prion-like manner (Jucker and Walker, 2013). Different mechanisms leading to tau spreading exist, as tau oligomers can be internalized through the endolysosomal pathway (Wu et al., 2013), although tau can also spread following interaction with specialized receptors, such as heparan sulfate proteoglycans (HSPGs) or LRP1, which are also expressed in astrocytes and microglia. Astrocytes can internalize fibrillar and monomeric tau, whereas microglia phagocytose secreted tau, which can then be spread via exosomes to neurons (Asai et al., 2015), although this microglial function can be



abolished in the presence of amyloid pathology as demonstrated in studies using 5xFAD mice (Gratuze et al., 2021). The glial uptake of tau could therefore also significantly contribute to the propagation of tau.

APOE could play a role in the seeding and propagation of tau (Fig. 3), potentially through neuron communication pathways (Wegmann et al., 2019; Franzmeier et al., 2020), as human APOE has been seen to lead to an exacerbated response to tau pathology in PS19 mice (Williams et al., 2022). Interestingly, some studies have shown that APOE $\epsilon 3$ is associated with a more intense prion-like propagation of tau (Williams et al., 2022), whereas others have shown more Aβ-associated tau spread in APOE ε4 mice in the presence of sleep deprivation (Wang et al., 2023), supporting an APOE-dependent propagation of tau pathology, as observed in patients (Sabbagh et al., 2013; Zhao et al., 2018b; Therriault et al., 2021). Nonetheless, other studies failed to detect any influence of APOE on tau propagation (Koller et al., 2020; Davies et al., 2023). It is plausible that microglia might regulate this process, where apoE isoforms could play a crucial role (Shi et al., 2019; van der Kant et al., 2020; Chen et al., 2024), or that Aβ pathology is required for tau propagation to be exacerbated (Pooler et al., 2015). Furthermore, an indirect effect on tau propagation could be mediated by a loss-of-function alteration in apoE leading to cholesterol dysregulation, which is a key feature in AD (Tuck et al., 2022). Therefore, no clear consensus regarding the effect of the APOE genotype on tau spreading has been accomplished (Tzioras et al., 2019). These incongruences highlight the need for further studies regarding the interactions between tau and apoE, while taking into consideration crucial variables such as apoE lipidation and receptor binding, A\beta pathology, and microglial reactivity, among others.

Potential roles of apoE receptors in tau pathology. The effects of apoE internalization by certain cells through LDLR and other apoE receptors may be damaging, as suggested in a recent study (Guo et al., 2025). Lipidated apoE2 was seen to present significantly less binding to LDLR compared with lipidated apoE3 and apoE4, thus resulting in a reduced lipid burden. Furthermore, the internalization of apoE resulted in the redistribution of cell surface LDLR, which suppressed lipoprotein uptake, thus impacting lipid homeostasis and ultimately leading to enhanced lipid burden and consequent inflammatory responses, particularly in apoE4-treated cells (Guo et al., 2025). Finally, apoE also leads to the lysosomal deposition of lipofuscin, which is linked to vulnerability in the AD brain. PS19 mice expressing APOE ε4 accumulated even more lipofuscin in their neurons. Similarly, in induced pluripotent stem cell (iPSC)-derived neurons, adding tau seeds alongside apoE lipoprotein particles revealed that higher lipofuscin formation correlated with increased tau fibril internalization, with cells accumulating more fibrils under conditions promoting lipofuscin (Guo et al., 2025).

As mentioned previously, apoE receptors could mediate an indirect interaction between apoE and tau and could play a key part in apoE-mediated tau internalization and seeding, such as LRP1 (Rauch et al., 2020) (Fig. 3). LRP1 influences tau internalization in an apoE-dependent manner, with apoE4 presenting the highest receptor affinity and, intriguingly, the lowest levels of tau seeding, an effect that was absent in cells lacking LRP1

(Cooper et al., 2021). As such, LRP1 has been proposed as a potential regulator of tau spreading.

LDLR overexpression has been seen to protect against tau pathology and tau-associated neurodegeneration, likely by reducing the levels of extracellular apoE in PS19 mice (Shi et al., 2021a). Other apoE receptors could also be involved in the uptake of tau, such as HSPGs (Holmes and Diamond, 2014), which have been shown to internalize monomeric and oligomeric tau, but not tau fibrils (Rauch et al., 2018), and could be important for tau uptake and neuron-to-neuron transmission (Holmes et al., 2013). SORL1 is another candidate, as it has recently been shown to facilitate the internalization of monomeric and high molecular weight tau species, and to mediate tau seeding, therefore potentially playing an important role in modulating tau trafficking (Cooper et al., 2024). LRP1 has also been shown to be a receptor for monomeric and aggregated tau (Rauch et al., 2020; Chen et al., 2024). Other lesser known LDLR family members, such as LRP3 (Cuchillo-Ibañez et al., 2021), could also contribute to this process, although they have not been shown to internalize tau to date. Further studies are required to understand the importance of apoE receptors in the propagation of tau pathology.

APOE-mediated exacerbation of tau-linked neurodegeneration. Shi and colleagues studied the impact of human APOE and APOE KO in the PS19 tau mouse model (Shi et al., 2017). They found that APOE knock-in (KI) leads to significant amounts of brain atrophy in an APOE-dependent manner ($\varepsilon 4 > \varepsilon 2/\varepsilon 3 > \varepsilon KO$), with significant atrophy in the hippocampus, amygdala, and piriform and entorhinal cortex, as well as ventricular enlargement, whereas APOE KO largely protected against these effects (Fig. 3). These results were supported by in vitro data with high levels of neuronal cell death in P301S tauexpressing neurons cocultured with APOE ε4 KI glial cells. Neuronal loss was also observed in neuronal cultures treated with apoE directly, with an exacerbated effect in apoE4treated cells, suggesting a direct role of apoE in mediating neurotoxicity. ApoE thus appears to affect tau pathology, particularly tau-related neurodegeneration, independently of Aβ. Intriguingly, these results suggest that in the context of tau pathology, APOE ε2 appears to act in the same manner as APOE E3, rather than presenting a protective effect, which may indicate that the influence of apoE on tau is complex and may be modulated by characteristics such as lipid preference. In fact, a conflicting study by Zhao et al. showed that APOE ε2 is associated with increased tau pathology in progressive supranuclear palsy, another tauopathy (Zhao et al., 2018b). The same study demonstrated enhanced tau pathology in an AAV-mediated P301L model (Cook et al., 2015) expressing APOE ε2, with increased accumulation of p-tau, thioflavin Spositive tau aggregates, and tau-related astrogliosis, whereas APOE £4 showed no effect on tau pathology (Zhao et al., 2018b). Nonetheless, it is important to note that neurodegeneration was not present in this AAV model. The discrepancies in the effects of APOE ε2 and APOE ε4 on tau pathology could be accounted for by the approaches used, as they differ significantly in various aspects, including the levels of tau expression, the tau mutation used, the age of the animals, and the lack of neurodegeneration in the AAV approach of Zhao et al. (2018b). It is therefore



plausible that both the detrimental effects of APOE $\epsilon 4$ and the protective effects of APOE $\epsilon 2$ are triggered by neurodegeneration or some aspect of tau pathology that is not present in every model, thus highlighting the need for further consensus and understanding of the models used.

APOE $\epsilon4$ has also been seen to exacerbate tau pathology in AD iPSC-derived organoids, with enhanced levels of p-tau (Lin et al., 2018), an effect that can be attenuated by converting APOE $\epsilon4$ to APOE $\epsilon3$ (Zhao et al., 2020). iPSC-derived neurons expressing APOE $\epsilon4$ had decreased neurite branching, higher levels of p-tau, enhanced sensitivity to calcium dysregulation, and more cell death compared with cells corrected to APOE $\epsilon3$, and these effects appear to be independent of A β pathology (Wadhwani et al., 2019).

As mentioned, APOE ϵ 2 has been largely seen as protective against AD; however, the studies presented here show that it appears to act in a similar fashion to APOE ϵ 3 in animal models with tau pathology, as it does not exert a protective effect in the context of tauopathy. As such, the role apoE plays in propagating tau pathology likely occurs through common mechanisms between apoE2 and apoE3, such as their shared lipid preference or dimerization capacity, rather than specific gains of function that may be present in other aspects. The influence of apoE on tau propagation may also be influenced by apoE receptors; however, apoE2 and apoE3 appear to lead to similar levels of LRP1-mediated tau internalization (Cooper et al., 2021). Therefore, further knowledge regarding the protective effect of APOE ϵ 2 in AD is required, which may be associated mostly with A β pathology.

Effects of cell type-specific APOE removal. The impact of astrocyte-derived apoE removal has been studied in the PS19 model, and an attenuation in the brain atrophy described previously (Shi et al., 2017) in APOE ε4 mice was observed, as well as significantly reduced p-tau levels, particularly in female mice (Wang et al., 2021) (Fig. 3). Removal of astrocytic APOE ε4 also protected against a reduction in the transcriptional levels of neuronal populations, and leads to an increased proportion of homeostatic astrocytes and microglia-dependent phagocytosis of synapses, but only when APOE ε4 was removed (Wang et al., 2021). No comparable effects were observed in these studies when removing APOE ε3, thus highlighting the specific impact of this deleterious isoform on AD pathology.

Neuronal APOE £4 removal reduced NFTs, p-tau levels, tau propagation, and gliosis, while also preventing tau-induced neurodegeneration and neuronal hyperexcitability (Koutsodendris et al., 2023). Transcriptomic changes following neuronal APOE £4 removal showed reduced disease-associated neuronal, astrocytic, and microglial profiles, consistent with findings that link neuronal APOE to exacerbated tau pathology and neuro-degeneration (Zalocusky et al., 2021). Interestingly, these protective effects of neuronal APOE removal were observed across all genotypes, suggesting that neuronal apoE may generally play a harmful role in tauopathies. It is worth noting, however, that other studies have shown that neuron-specific overexpression of APOE £4 is not sufficient to affect tau pathology (Koller et al., 2020). This discrepancy could be due to the model used, as the studies performed by

Koutsodendris et al. and Zalocusky et al. used the Huang APOE £4 model, which, as mentioned previously, presents a neuronal APOE phenotype that has not been replicated in other APOE knock-in or conditional KO models. As the apoE that may be expressed by neurons could be a compensatory mechanism that ultimately proves to be harmful to neurons, further studies are required to confirm whether apoE is secreted from neurons, and what role this species plays in AD. Furthermore, it is important to note that no single-cell RNA-seq studies have provided definitive evidence of APOE expression in neurons of AD patients, and the effects may be due to the research model used or other factors. Therefore, although the role of neuronal apoE could be an exciting field of research, further information is required.

An important aspect to be studied is the characteristics of apoE produced by astrocytes (and other cell types) under the stress conditions induced by AD. As the levels of apoE production increase, potentially to cope with the increase in lipids in the extracellular space due to neuronal death, this apoE may be functionally or structurally different to apoE produced under physiological conditions, such as through poor glycosylation. ApoE produced from reactive astrocytes may present gain-of-function effects, in which it participates in the clearance of different proteins. Although this process may be beneficial at first, the long-term consequences may exacerbate AD through the propagation of the pathology, and could explain why certain phenomena, such as the presence of tau in astrocytes or the presence of intraneuronal apoE, occur in AD.

The role of microglia in APOE and tau interplay

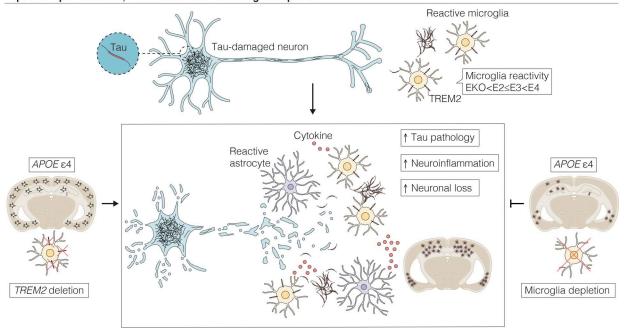
Recent research indicates that *APOE* affects AD progression partly by modulating the immune response through its influence on microglial reactivity (Fig. 4). This immunomodulatory role of *APOE* is likely linked to its indirect interactions with TREM2, a receptor primarily expressed by microglia in the CNS.

Microglia, the innate immune cells of the CNS, are crucial for maintaining brain homeostasis by monitoring and responding to threats and cellular damage (Kreutzberg, 1996; Colonna and Butovsky, 2017). In AD, microgliosis manifests and leads to changes in microglial morphology and function (Butovsky and Weiner, 2018). Key microglial states, such as disease-associated microglia (DAM) (Keren-Shaul et al., 2017; Krasemann et al., 2017) and lipid droplet-accumulating microglia (LDAM) (Haney et al., 2024), have been identified, with DAM showing increased proinflammatory and phagocytosis-related genes, and LDAM exhibiting elevated lipid processing genes.

To elucidate the role of microglia in tau propagation, pathology, and consequent neurodegeneration, studies involving microglial ablation have been conducted using AD models presenting A β and tau pathologies (Table 1). In a model combining 5xFAD mice for amyloid pathology and PS19 mice for tau pathology (5xFAD/P301S), microglial depletion reduced tau propagation following the injection of pre-aggregated tau (Lodder et al., 2021). Additionally, in the amyloid model of humanized APP mutant knock-in mice expressing P301L in the medial entorhinal cortex, p-tau propagation decreased, while plaque burden increased when microglia were depleted (Clayton et al.,



Impact of ApoE isoforms, TREM2 deletion and microglial depletion



Loss of microglial ApoE modulates reactivity and Tau-driven neurodegeneration in an isoform-specific manner

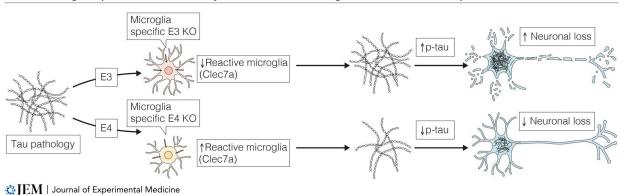


Figure 4. **Microglial contributions to the effects of APOE on tau-linked pathologies.** APOE ε4 is linked with harmful microglial states that exacerbate tau pathology. Tau-induced microglial reactivity is modulated by the APOE genotype, with ε4 conferring the highest microglial reactivity and ε2 the lowest, whereas microglia in an APOE KO context present even lower reactivity. APOE ε4 is linked to higher tau pathology, neuronal loss, and neuroinflammation, an effect that is exacerbated following depletion of TREM2, a crucial regulator of the microglial response. On the other hand, microglial depletion has an opposite effect and dampens the influence of APOE ε4 on tau pathology. In the context of tau pathology, the loss of microglial APOE has opposing effects according to the specific isoform. Loss of microglial apoE3 leads to a reduced number of reactive microglia, resulting in enhanced levels of p-tau and subsequent neuronal loss. In contrast, removal of microglial apoE4 enhances the level of reactive microglia, reducing the levels of p-tau and neuronal loss, thus demonstrating the negative influence of apoE4 on tau pathology. https://BioRender.com/u31n304.

2021). On the other hand, in 5xFAD mice injected with AD brainderived tau, microglial depletion strongly exacerbated Aβ-associated p-tau seeds, whereas plaque burden remained unchanged (Gratuze et al., 2021). Despite these variations, both models showed an increase in plaque-associated p-tau+ dystrophic neurites. Decreased DAM gene expression was linked to elevated tau seeding due to inefficient clearance, despite repopulated microglial clustering around Aβ plaques (Gratuze et al., 2021). Early microglial depletion in 5xFAD mice injected with AD brain-derived tau decreased cortical plaque-associated microglia, Aβ plaque burden, and cortical APP-

positive dystrophic processes, as well as tau pathology (Delizannis et al., 2021).

TREM2, a cell surface receptor predominantly expressed in myeloid cells and involved in key immune pathways, is crucial in regulating the microglial response (Ulrich et al., 2017). Studies examining TREM2 deficiency in various A β mouse models, including those co-expressing tau or injected with tau aggregates, have demonstrated increased A β -associated tau propagation (Leyns et al., 2019; Gratuze et al., 2021), elevated levels of p-tau, enhanced neuritic dystrophy, and reduced microglial responses (Leyns et al., 2019; Gratuze et al., 2021; Lee et al., 2021). Similar



 $\mathsf{Table}\ 1.$ Summary of microglia and TREM2 effects on tau-linked pathologies in animal models

| Condition | | Model | Age | Tau propagation and Neurodegeneration tau pathology | Neurodegeneration | Glial reactivity | Аβ | Reference |
|----------------------|---------------|--|-----------|--|--|---|--------------------------------|--------------------------|
| Microglial depletion | Aβ models | 5xFAD × P301S + injection of recombinant tau seeds | 7 mo | ↓AT8 area (CX, HC) | ↓ Neurodegeneration (CX, HC) | Remaining microglia exhibit DAM phenotype | No difference | Lodder et al. (2021) |
| | | App ^{WL-G-F} + AAV-P301L-tau injection | 6 mo | ↓AT8 propagation ↑AT8 plaque area | · | ↓ MGnD+ total and plaque area (Clec7a) | ↑SP N ↑SP areas ↑SP size | Clayton et al. (2021) |
| | | 5xFAD + injection of AD brain- derived tau | 9.5 mo | ↑ AT8 seeding and propagation ↑ AT8 area (CX, HC) | | No difference in microglial reactivity (CD68) No difference in astrocyte clustering around plaques ↑ GFAP RNA expression | No difference | Gratuze et al. (2021) |
| | | 5xFAD + injection of AD brain- derived tau | е то | ↓ AT8 signal (CX) | | | ↓ SP load ↓ SP size | Delizannis et al. (2021) |
| | Tau models | P301S | 4 mo | ↓AT8 ↓ globular tau oligomers ↓ NFTs No difference in AT8 or T-tau (ELISA) | ↓ Neurodegeneration | ↓ Expression of proinflammatory cytokines | , | Mancuso et al. (2019) |
| | | P301S × APOE4 KI or apoE KO | ош 6 | ↓ AT8 area (HC) ↓ HJ14.5 (pSer396) levels (CX) | ↓ Neurodegeneration (entorhinal/piriform CX, HC) | Remaining microglia exhibit reactive state (CD68) | 1 | Shi et al. (2019) |
| | | C57BL/6 + injection of AAV-GFP/tau 4.5 mo | 4.5 mo | ↓tau propagation (?) ↓AT8⁺ cells (EC and DG) | | , | 1 | Asai et al. (2015) |
| | | Tg4510 | 15 mo | No differences | No difference | Microglia exhibit DAM phenotype (e.g., apoE, CD68) No change in astrocyte reactivity (GFAP) | | Bennett et al. (2018) |

Table 1. Summary of microglia and TREM2 effects on tau-linked pathologies in animal models (Continued)

| Condition | | Model | Age | Tau propagation and tau pathology | Neurodegeneration | Glial reactivity | Аβ | Reference |
|------------------------------------|---------------|--|-----------|--|---|---|---------------------------------|-------------------------------|
| TREM2 depletion or R47H expression | Aβ models | APPSI-21 × TREM2 KO Or TREM2 R47H + injection of AD brain- derived tau | 8.5 mo | ↑ AT8 seeding and propagation ↑ AT8 area (CX) ↑ AT8 signal near plaques | | ↓ Microglial reactivity (lba1) | ↑ Aβ42 in and around SP (CX) | Leyns et al. (2019) |
| | | 5xFAD + injection of AD brain- derived tau | 9 то | ↑AT8 seeding and propagation ↑AT8 area (CX, HC) | | ↓ Microglial reactivity (lba1) ↓ Astrocytic reactivity (GFAP) | ↑ SP coverage (CX, HC) | Gratuze et al. (2021) |
| l · - | Tau models | P301S + TREM2 shRNA injection | 7 mo | ↑ AT8, AT100, and AT180 | ↑ Neurodegeneration (CX, HC) | ↑ Expression of proinflammatory cytokines | - | Jiang et al. (2015) |
| | | htau × TREM2 KO | е шо | ↑ AT8 (CX, HC) ↑ AT180, PHF-1 (CX) | | | 1 | Bemiller et al. (2017) |
| | | P301S × TREM2 KO or TREM2 haploinsufficient mice | 8–9 mo | ↑AT8 area (CX of haploinsufficient mice) ↑MC1 area (HC of haploinsufficient mice) No difference in TREM2 KO mice | ↓ Neurodegeneration (ventricle area) | ↑ Microglial reactivity (based on morphology in haploinsufficient mice) TREM2 KO microglial morphology similar to WT | | Sayed et al. (2018) |
| | | THY-Tau22 × TREM2 KO | 12 mo | ↑ AT8 (HC) ↑ N° of AT100⁺ and Gallyas⁺ neurons | ↓ Neurodegeneration (surface CA1) No difference in pyramidal nucleus layer thickness | ↓Microglial reactivity (e.g., CD68, IL- 1β) No difference in astrocyte reactivity (GFAP) | | Vautheny et al. (2021) |
| | | AAV-P301L tau injection | 5 то | ↑tau spreading | · | ↑ Microglial reactivity (e.g., CD68, Clec7a, CD9 in DG) ↑ Microglial reactivity in MEC (CD9) | | Zhu et al. (2022) |
| | | P301S x R47H | 9 mo | ↓ AT8 and PG5 area (HC) ↓ AT180 area (piriform CX) | ↓ Neurodegeneration (HC, entorhinal, piriform CX, pyramidal and DG layer thickness, ventricle volume) | ↓ Microglial reactivity (lba1, CD68)↓ DAM gene expression↓ Proinflammatory cytokines | | Gratuze et al. (2020) |
| | | TREM2 KO + injection of AD brainderived tau | 9 то | ↓AT8 area No difference in HC | | ↓ Microglial reactivity (lba1) ↓ Neuroinflammatory response No change in astrocyte reactivity (GFAP) | | Lee-Gosselin et al. (2023) |
| | | P301S × TREM2 KO | 9 то | No difference | ↓ Neurodegeneration (entorhinal, piriform CX, ventricle volume) | ↓ Microglial reactivity (lba1) ↓ Inflammatory markers Reduced astrocytic reactivity (GFAP) | 1 | Leyns et al. (2017) |
| | | TREM2 ^{R47H} /TYROBP (<i>Drosophila</i> melanogaster) | p | No difference | No difference | ↓ Inflammatory response | 1 | Sekiya et al. (2018) |
| TREM2 overexpression | | P301S + lentiviral-mediated TREM2 overexpression | 7 mo | ↓ AT8 and AT180 (CX, HC) | ↓ Neurodegeneration (CX, HC) | ↓ Proinflammatory cytokines ↑ Anti-inflammatory markers | | Jiang et al. (2016) |

CX: cortex; HC: hippocampus; GFAP: Glial Fibrillary Acidic Protein; SP: senile plaque; EC: entorhinal cortex; DG: dentate gyrus.

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findings were observed in mice carrying the TREM2 loss-of-function R47H mutation (Leyns et al., 2019), a well-known risk factor for AD (Guerreiro et al., 2013; Jonsson et al., 2013). Additionally, TREM2 deletion in the presence of A β was linked to increased neuronal loss (Lee et al., 2021). Taken together, these findings indicate that in the absence of TREM2, tau accumulation and propagation are increased, thereby accelerating brain atrophy.

In the absence of A β pathology, microglial depletion with a CSF1R inhibitor has been shown to strikingly protect against taumediated neurodegeneration in mice overexpressing P301S tau protein under the murine Thy-1 promoter (Mancuso et al., 2019) and in PS19 mice expressing human APOE ϵ 4 (Shi et al., 2019; Chen et al., 2023). Similar protective effects have been shown on tau propagation and neurotoxicity in AAV-GFP/tau-injected mice (Asai et al., 2015). Microglial depletion in 12-month-old Tg4510 mice, a tauopathy mouse model, resulted in only mild microglial depletion and had no impact on tau burden, cortical atrophy, or astrocytic activation despite exacerbating some DAM gene expression (Bennett et al., 2018).

TREM2 ablation or the presence of the R47H mutation has been reported to reduce microgliosis (Fig. 4). The impact of TREM2 on tau pathology is inconsistent across studies: some report exacerbation (Jiang et al., 2015; Bemiller et al., 2017; Sayed et al., 2018; Vautheny et al., 2021; Zhu et al., 2022), others report reduction (Gratuze et al., 2020; Lee-Gosselin et al., 2023), whereas some observe no effect (Lee et al., 2021; Leyns et al., 2017; Sekiya et al., 2018) in TREM2 KO or haploinsufficient mice, or those carrying the R47H mutation. Not surprisingly, the effects of TREM2 loss of function on tau-mediated neurodegeneration and astrogliosis are similarly mixed (Jiang et al., 2015, 2016; Leyns et al., 2017; Sayed et al., 2018; Sekiya et al., 2018; Gratuze et al., 2020; Vautheny et al., 2021; Lee-Gosselin et al., 2023). Additionally, synaptic and memory impairments were noted in TREM2-deficient animals (Jiang et al., 2015, 2016; Zhu et al., 2022); however, mice with the R47H mutation showed reduced synaptic loss (Gratuze et al., 2020). The conflicting results across studies likely arise from variations in experimental conditions, genetic backgrounds, mouse models, and methodologies. Some of these discrepancies could also be caused by side products of some of the TREM2 KO lines, such as an artifactual ~350-fold overexpression of TREML1 due to the lack of UbC-neo cassette removal (Kang et al., 2018b). Therefore, differences in how TREM2 is removed, the specific models used, the variation in disease progression, and the timing of assessments can all contribute to the incongruent findings.

Recent studies propose that TREM2 and apoE are functionally connected, acting as key regulators of microglial responses to neurodegenerative challenges in AD. At the microglial level, APOE expression was reduced in TREM2-deficient mice (Leyns et al., 2017), and in vitro studies have identified apoE as a possible ligand of TREM2, hinting at a potential partnership and modulatory effect on TREM2 activity (Atagi et al., 2015; Bailey et al., 2015; Yeh et al., 2016; Jendresen et al., 2017). However, there is no direct evidence that apoE acts as a TREM2 ligand in vivo. ApoE appears to function downstream of TREM2 activation, modulating phagocytosis of apoptotic neurons, and regulating genes

associated with neurodegeneration (Krasemann et al., 2017). The interaction between TREM2 and apoE appears to be equal across all APOE isoforms (Atagi et al., 2015; Bailey et al., 2015; Jendresen et al., 2017; Yeh et al., 2017), and apoE appears to regulate microglial reactivity in both TREM2-dependent and TREM2independent manners (Keren-Shaul et al., 2017; Krasemann et al., 2017). However, in the context of tau-related neurodegeneration, TREM2-independent microglial reactivity seems to be sufficient to drive tau-linked pathologies when APOE $\epsilon 4$ is present (Gratuze et al., 2023). In PS19 mice carrying an APOE ε4 knock-in, neurodegeneration increased in the absence of TREM2, accompanied by elevated levels of phosphorylated and pathologically aggregated tau, despite a decrease in TREM2dependent microgliosis. Interestingly, synaptic loss was predominantly influenced by the presence of APOE ε4 in PS19 mice and remained unaltered by TREM2 deficiency (Gratuze et al., 2023). These results were further supported by comparable observations in AD patients carrying the R47H and R62H TREM2

The complex relationship between APOE and microglial activity is a key factor in regulating neuroinflammation and tau pathology. LDAM, which are characterized by significant lipid accumulation (Marschallinger et al., 2020; Victor et al., 2022; Haney et al., 2024), are especially common in AD patients with APOE $\varepsilon 4$ (Haney et al., 2024). Recent findings suggest that an LDAM-associated impairment in lipid metabolism is associated with increased neuronal p-tau accumulation and subsequent neurotoxicity (Haney et al., 2024).

APOE is upregulated in DAM (Keren-Shaul et al., 2017), and its impact on DAM activation has generated conflicting results. In PS19 mice, APOE ε4 led to an increase in neuroinflammation (Shi et al., 2017) and tau-mediated neurodegeneration (Shi et al., 2017; Shi et al., 2019). APOE ε4 reduced the expression of homeostatic microglial genes, whereas the absence of APOE prevented tau-induced neurodegeneration and the increase in DAM (Shi et al., 2017). Likewise, a transcriptional study in microglia lacking APOE revealed that APOE modulates Microglial Neurodegenerative phenotype (MGnD), as its deletion resulted in the reduction of microglial homeostatic factors, alongside the activation of an inflammatory transcriptional program (Krasemann et al., 2017). APOE also appears to regulate the transcriptional profile of MGnD, as APOE &4 impedes the transition into the MGnD phenotype upon neurodegeneration in PS19 mice, whereas microglial APOE ε4 removal restored the MGnD phenotype linked with neuroprotection, thereby reducing tau hyperphosphorylation and ameliorating neuronal survival (Yin et al., 2023). Selective microglial deletion of APOE ε3 decreased the MGnD marker CLEC7A to levels comparable to APOE ε4 knock-in mice, suggesting that the microglial expression of APOE £3 is crucial for triggering the MGnD response, and its absence accelerates neurodegeneration. Another study demonstrated that eliminating microglia or deleting APOE in PS19 mice provided marked protection against the worsening effect of APOE ε4 on tau-induced neurodegeneration (Shi et al., 2019). Interestingly, in contrast to Yin et al., they noted reduced levels of CD68+-reactive microglia, a marker for MGnD, in mice lacking APOE compared with those expressing APOE ε4. This



discrepancy may be because they explored the complete KO of APOE, whereas Yin et al. investigated the targeted removal of microglial APOE ϵ 4. Intriguingly, the influence of APOE on tau pathology and immunoreactivity was abolished in the absence of microglia, indicating that microglia-mediated damage significantly contributes to the neurotoxic effects of pathological tau and is a strong driver of neurodegeneration in the presence of APOE ϵ 4 in PS19 mice (Shi et al., 2019).

Taken together, APOE $\varepsilon 4$ is associated with harmful microglial states that exacerbate tau accumulation and neurotoxicity, potentially leading to accelerated disease progression (Fig. 4). In contrast, the absence or selective removal of APOE from microglia, similar to microglia depletion, can abolish these effects, suggesting a crucial role of microglia in apoE-mediated neuro-degeneration. Further research is needed to determine whether these findings are specific to APOE $\varepsilon 4$.

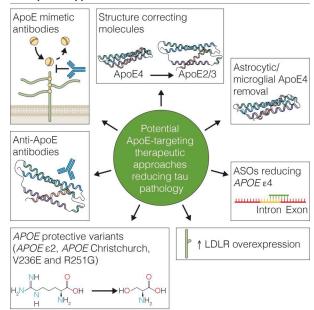
Tau pathology treatment: apoE as a mediator

Therapies targeting A β pathology have been the focus of attention, and although the progress made has been substantial, there is a need for complementary therapeutic targets. The efficacy of anti-amyloid antibody treatments may be influenced by APOE $\epsilon 4$, as this allele has been linked to increased risks of amyloid-related imaging abnormalities (ARIA) during A β immunotherapy (Cummings et al., 2022; Filippi et al., 2022; Cummings et al., 2023). ARIA-E (edema) and ARIA-H (microhemorrhages) can occur in treated individuals, especially among APOE $\epsilon 4$ carriers. While severe symptomatic complications are rare—occurring in about 1% of treated patients—the high prevalence of ARIA in trials requires careful consideration. Notably, around 70% of patients participating in these trials present at least one copy of APOE $\epsilon 4$.

While tau pathology is a potential therapeutic target given its correlation to AD progression, no effective treatments are currently available (Imbimbo et al., 2022). Tau antibody approaches have failed to target toxic intracellular forms of tau, and to date only affect tau found in the extracellular space (Teng et al., 2022; Florian et al., 2023). ASOs successfully reversed tau pathology in PS19 mice (DeVos et al., 2017), and reduced aggregated tau as detected by tau-PET scans in humans (Mummery et al., 2023). While promising, these trials are in the experimental stages, and their long-term efficacy and safety remain to be determined.

ApoE is a focus for novel therapeutic approaches, particularly APOE $\epsilon 4$ (Vance et al., 2024) (Fig. 5). Removal of astrocytic (Wang et al., 2021), microglial (Butovsky and Weiner, 2018; Yin et al., 2023), and neuronal apoE4 (Koutsodendris et al., 2023) all protect against tau-mediated neuronal loss. Whether lowering apoE in the brain has any detrimental effects needs to be monitored, although the case study by Mak et al. (2014) indicates that humans may present normal brain function even in the absence of APOE. Strategies to reduce apoE4 levels, such as using ASOs (Litvinchuk et al., 2021) or LDLR overexpression (Shi et al., 2021a), show promise in preclinical models, mitigating tau pathology and neurodegeneration. An anti-apoE antibody binding to nonlipidated apoE that is bound to amyloid plaques reduces brain apoE and A β levels, as well as A β -mediated tau seeding and spreading (Liao et al., 2018; Xiong et al., 2021; Gratuze et al.,

Therapeutic approaches



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Figure 5. Targeting the apoE-tau interplay for therapeutic interventions. Given the evidence of the effects APOE has on tau pathology and tau-mediated neurodegeneration, a series of therapeutic approaches targeting tau through apoE have been proposed. Specific removal of astrocytic or microglial apoE has proven beneficial with regard to tau-mediated neuronal loss. The reduction of apoE levels through ASOs or LDLR overexpression has shown preclinical promise in reducing tau pathology. Anti-apoE antibodies targeting nonlipidated amyloid-bound apoE reduce A β -mediated tau seeding and spreading. To mitigate the risks of apoE depletion, apoE mimetic antibodies that compete particularly with apoE4 for binding at receptors are a potential approach. Finally, molecules correcting the structure of apoE4 to that of apoE2 or apoE3 have been shown to recover the functionality of apoE.

2022). Given the risks of depleting apoE, especially peripherally, novel approaches could be promising, like apoE mimetic antibodies that compete with apoE4 for receptor binding, such as HSPGs (Marino et al., 2023), small interfering RNAs (Zhang et al., 2021c), or ASOs (Litvinchuk et al., 2021). Structure-correcting molecules can restore the functionality of apoE4 to that of apoE3 or apoE2 (Chen et al., 2012), an effect replicated in iPSC-derived neurons (Wang et al., 2018). Interestingly, expressing APOE ϵ 2 in APP/PS1/APOE ϵ 4 mice can protect against further A β deposition and cognitive decline, without the necessity of removing APOE ϵ 4 (Jackson et al., 2024).

Augmenting glial lipid export function with an LXR agonist has recently been seen to attenuate tau pathology and neuro-degeneration in the PS19 model expressing APOE $\epsilon 4$, by increasing lipid efflux and reducing astrocytic and microglial reactivity (Litvinchuk et al., 2024).

Recent findings could lead to additional therapeutic advances, such as the discovery of the Christchurch mutation in APOE $\epsilon 3$ (APOEch) (Arboleda-Velasquez et al., 2019), which replaces arginine with serine at position 136 within the receptor-binding domain and heparin sulfate-binding domain (Mahley et al., 1999). The homozygous presence of the APOEch mutation reduced tau pathology and protected against neurodegeneration



and cognitive decline in an individual with a *PSEN1* mutation despite high levels of brain amyloid.

In PS19 mice expressing APOE $\epsilon 4$ and human iPSCs, the Christchurch mutation protected against APOE $\epsilon 4$ -driven tau pathology and lipid accumulation (Nelson et al., 2023). In one study, the Christchurch variant has also been seen to strongly bind tau and reduce its uptake into neurons and microglia in PS19 mice, thus reducing neurotoxicity (Chen et al., 2025). In the PSEN1 carrier with the APOE ε3^{Ch} variant, there was reduced microgliosis (Sepulveda-Falla et al., 2022). Interestingly, in PS19 mice the variant protected against synaptic loss by suppressing the microglial and astrocytic response to tau-damaged neurons, whereas it enhanced the DAM microglial profile in 5xFAD mice, thus reducing plaque load (Tran et al., 2025). The variant therefore appears to have distinct modulatory effects on glial cells by enhancing DAM reactivity when faced with amyloid pathology, yet reducing neuroinflammation when in the context of tau pathology (Tran et al., 2025). Importantly, in a mouse model of amyloidosis, the APOE ε3^{Ch} variant reduced Aβ-induced tau seeding by enhancing the clustering of microglia around plaques and elevating microglial phagolysosomal activity (Chen et al., 2024). The phenotype seen in this model is similar to what was seen in the PSEN1 carrier homozygous for the APOE ε3^{Ch} variant (Arboleda-Velasquez et al., 2019). Furthermore, recent studies have shown that APOE E3Ch shows impaired receptor binding, leading to reduced binding to HSPGs and decreased LDLR-dependent uptake of lipids and apoE similar to apoE2, which could be responsible for its protective effects in AD (Guo et al., 2025).

Heterozygous carriers of the mutation were recently shown to present delayed onset of AD pathology (Quiroz et al., 2024), although a conflicting study showed earlier AD onset and increased A β deposition in brain vessels, suggesting a potential deleterious effect (Hernandez et al., 2021). Other APOE variants like the V236E (or Jacksonville variant) in APOE ϵ 3 and the R251G variant in APOE ϵ 4 also protect against AD (Le Guen et al., 2022). For a detailed review of apoE-directed therapeutic approaches, see Serrano-Pozo et al. (2021).

Daily life habits can significantly impact AD development and progression, for example, through changes in gut microbiota (Seo et al., 2023) and sleep patterns. Sleep disturbances are common in AD and correlate with poor cognitive performance (Lucey et al., 2021) and tau pathology (Holth et al., 2017; Wang and Holtzman, 2020), as sleep deprivation increases interstitial fluid levels of $A\beta$ and tau (Holth et al., 2019). Sleep deprivation affects microglial reactivity in a TREM2-dependent manner, which may also be influenced by apoE (as discussed above in the Microglia section) (Parhizkar et al., 2023). APOE ε4 may exacerbate AD progression associated with sleep deprivation by reducing AB clearance, increasing dystrophic neurites around plaques (Sadleir and Vassar, 2023), and decreasing microglial clustering (Wang et al., 2023). These findings highlight the complex interplay between APOE, tau, and AD progression influenced by various factors.

Conclusions

While also influenced by other factors such as $A\beta$ and neuro-inflammation, the development of tau pathology highly

correlates with synaptic loss and cognitive deficits present in AD, pointing out its importance in the disease. The role of APOE, especially the risk-enhancing $\varepsilon 4$ allele, has been well documented, but studies exploring interactions between tau and APOE are limited. These studies show important connections and emphasize the need for further research on their interactions in AD.

Current A β -targeted therapies are promising as they appear to mitigate AD symptoms; nonetheless, combinatory therapies are likely necessary to yield more positive results, highlighting the need to explore new targets like tau and apoE. Targeting the interplay between apoE and tau could be crucial for developing effective interventions. Furthermore, clarity regarding the characteristics of the apoE produced under physiological and pathological conditions would also be beneficial, as would clear conclusions regarding the differences derived from the source of apoE (e.g., neuronal vs. glial vs. other cells).

A clear consensus regarding the research models used is required. Mouse models are an invaluable tool in AD research, as they can model the progression of different aspects of pathology in a stable and reproducible manner. Nonetheless, many models incorporate A β or tau pathology alone, and do not control other important variables such as *APOE*. The inclusion of human *APOE* is crucial, given the differences between human and mouse apoE, and the functions they perform. Coherence in the models used would reduce the incongruences between studies and allow for more reproducible data. Importantly, the interpretation of *APOE* effects should always consider the limitations of experimental models, which may not fully replicate the complexity of human pathology.

In conclusion, apoE and tau appear to be two factors contributing to AD not only independently, but also through complex intrinsic relationships. Future studies are required to clarify how these proteins interact, directly, indirectly, or both. In a similar manner, other yet undiscovered protein interactions could be playing important roles in the multifaceted pathology that is AD, and therefore, a shift in the focus away from just the key candidates to other potential players could lead to new and important breakthroughs in the field.

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Holtzman had a patent to Antibodies to APOE licensed "Next-Cure." No other disclosures were reported.

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References

- Agosta, F., K.A. Vossel, B.L. Miller, R. Migliaccio, S.J. Bonasera, M. Filippi, A.L. Boxer, A. Karydas, K.L. Possin, and M.L. Gorno-Tempini. 2009. Apolipoprotein E epsilon4 is associated with disease-specific effects on brain atrophy in Alzheimer's disease and frontotemporal dementia. Proc. Natl. Acad. Sci. USA. 106:2018–2022. https://doi.org/10.1073/pnas.0812697106
- Allen, B., E. Ingram, M. Takao, M.J. Smith, R. Jakes, K. Virdee, H. Yoshida, M. Holzer, M. Craxton, P.C. Emson, et al. 2002. Abundant tau filaments and nonapoptotic neurodegeneration in transgenic mice expressing human P301S tau protein. J. Neurosci. 22:9340–9351. https://doi.org/10.1523/JNEUROSCI.22-21-09340.2002
- Altmann, A., L. Tian, V.W. Henderson, M.D. Greicius, and Alzheimer's Disease Neuroimaging Initiative Investigators. 2014. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann. Neurol.* 75: 563–573. https://doi.org/10.1002/ana.24135
- Alzheimer's Association. 2024. 2024 Alzheimer's disease facts and figures. Alzheimer's Dement. 20:3708–3821. https://doi.org/10.1002/alz.13809
- Arakhamia, T., C.E. Lee, Y. Carlomagno, D.M. Duong, S.R. Kundinger, K. Wang, D. Williams, M. DeTure, D.W. Dickson, C.N. Cook, et al. 2020. Posttranslational modifications mediate the structural diversity of tauopathy strains. Cell. 180:633–644.e12. https://doi.org/10.1016/j.cell.2020.01.027
- Arboleda-Velasquez, J.F., F. Lopera, M. O'Hare, S. Delgado-Tirado, C. Marino, N. Chmielewska, K.L. Saez-Torres, D. Amarnani, A.P. Schultz, R.A. Sperling, et al. 2019. Resistance to autosomal dominant alzheimer's disease in an APOE3 christchurch homozygote: A case report. Nat. Med. 25:1680-1683. https://doi.org/10.1038/s41591-019-0611-3
- Asai, H., S. Ikezu, S. Tsunoda, M. Medalla, J. Luebke, T. Haydar, B. Wolozin, O. Butovsky, S. Kügler, and T. Ikezu. 2015. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. *Nat. Neurosci.* 18: 1584–1593. https://doi.org/10.1038/nn.4132
- Aschenbrenner, A.J., B.A. Gordon, T.L.S. Benzinger, J.C. Morris, and J.J. Hassenstab. 2018. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. *Neurology*. 91:e859–e866. https://doi.org/10.1212/WNL.00000000000006075
- Atagi, Y., C.-C. Liu, M.M. Painter, X.-F. Chen, C. Verbeeck, H. Zheng, X. Li, R. Rademakers, S.S. Kang, H. Xu, et al. 2015. Apolipoprotein E is a ligand for triggering receptor expressed on myeloid cells 2 (TREM2). J. Biol. Chem. 290:26043–26050. https://doi.org/10.1074/jbc.M115.679043
- Atherton, K., X. Han, J. Chung, J.D. Cherry, Z. Baucom, N. Saltiel, E. Nair, B. Abdolmohammadi, M. Uretsky, M.M. Khan, et al. 2022. Association of APOE genotypes and chronic traumatic encephalopathy. *JAMA Neurol.* 79:787–796. https://doi.org/10.1001/jamaneurol.2022.1634
- Babapour Mofrad, R., B.M. Tijms, P. Scheltens, F. Barkhof, W.M. van der Flier, S.A.M. Sikkes, and C.E. Teunissen. 2020. Sex differences in CSF biomarkers vary by Alzheimer disease stage and APOE ε4 genotype. *Neurology*. 95: e2378–e2388. https://doi.org/10.1212/WNL.0000000000010629
- Baek, M.S., H. Cho, H.S. Lee, J.H. Lee, Y.H. Ryu, and C.H. Lyoo. 2020. Effect of APOE ε4 genotype on amyloid-β and tau accumulation in Alzheimer's disease. Alzheimer's Res. Ther. 12:140. https://doi.org/10.1186/s13195-020-00710-6
- Bailey, C.C., L.B. DeVaux, and M. Farzan. 2015. The triggering receptor expressed on myeloid Cells 2 binds apolipoprotein E. J. Biol. Chem. 290: 26033–26042. https://doi.org/10.1074/jbc.M115.677286
- Barthélemy, N.R., Y. Li, N. Joseph-Mathurin, B.A. Gordon, J. Hassenstab, T.L.S. Benzinger, V. Buckles, A.M. Fagan, R.J. Perrin, A.M. Goate, et al. 2020. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. *Nat. Med.* 26:398–407. https://doi.org/10.1038/s41591-020-0781-z
- Barthélemy, N.R., G. Salvadó, S.E. Schindler, Y. He, S. Janelidze, L.E. Collij, B. Saef, R.L. Henson, C.D. Chen, B.A. Gordon, et al. 2024. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat. Med.* 30:1085–1095. https://doi.org/10.1038/s41591-024-02869-z

- Bell, W.R., Y. An, Y. Kageyama, C. English, G.L. Rudow, O. Pletnikova, M. Thambisetty, R. O'Brien, A.R. Moghekar, M.S. Albert, et al. 2019. Neuropathologic, genetic, and longitudinal cognitive profiles in primary age-related tauopathy (PART) and Alzheimer's disease. Alzheimer's Dement. 15:8-16. https://doi.org/10.1016/j.jalz.2018.07.215
- Belloy, M.E., S.J. Andrews, Y. Le Guen, M. Cuccaro, L.A. Farrer, V. Napolioni, and M.D. Greicius. 2023. APOE genotype and alzheimer disease risk across age, sex, and population ancestry. JAMA Neurol. 80:1284–1294. https://doi.org/10.1001/jamaneurol.2023.3599
- Bemiller, S.M., T.J. McCray, K. Allan, S.V. Formica, G. Xu, G. Wilson, O.N. Kokiko-Cochran, S.D. Crish, C.A. Lasagna-Reeves, R.M. Ransohoff, et al. 2017. TREM2 deficiency exacerbates tau pathology through dysregulated kinase signaling in a mouse model of tauopathy. Mol. Neurodegener. 12:74. https://doi.org/10.1186/s13024-017-0216-6
- Bennett, R.E., A. Bryant, M. Hu, A.B. Robbins, S.C. Hopp, and B.T. Hyman. 2018. Partial reduction of microglia does not affect tau pathology in aged mice. *J. Neuroinflammation*. 15:311. https://doi.org/10.1186/s12974-018-1348-5
- Biundo, F., D. Del Prete, H. Zhang, O. Arancio, and L. D'Adamio. 2018. A role for tau in learning, memory and synaptic plasticity. Sci. Rep. 8:3184. https://doi.org/10.1038/s41598-018-21596-3
- Blennow, K., and H. Hampel. 2003. CSF markers for incipient Alzheimer's disease. Lancet Neurol. 2:605-613. https://doi.org/10.1016/s1474-4422(03)00530-1
- Blennow, K., and H. Zetterberg. 2018. Biomarkers for alzheimer's disease: Current status and prospects for the future. *J. Intern. Med.* 284:643–663. https://doi.org/10.1111/joim.12816
- Blennow, K., H. Hampel, M. Weiner, and H. Zetterberg. 2010. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat. Rev. Neurol. 6: 131-144. https://doi.org/10.1038/nrneurol.2010.4
- Boyles, J.K., R.E. Pitas, E. Wilson, R.W. Mahley, and J.M. Taylor. 1985. Apolipoprotein E associated with astrocytic glia of the central nervous system and with nonmyelinating glia of the peripheral nervous system. J. Clin. Invest. 76:1501–1513. https://doi.org/10.1172/JCI112130
- Braak, H., and E. Braak. 1988. Neuropil threads occur in dendrites of tanglebearing nerve cells. *Neuropathol. Appl. Neurobiol.* 14:39–44. https://doi .org/10.1111/j.1365-2990.1988.tb00864.x
- Braak, H., and E. Braak. 1991. Neuropathological stageing of Alzheimerrelated changes. Acta Neuropathol. (Berl.). 82:239–259. https://doi.org/ 10.1007/BF00308809
- Braak, H., I. Alafuzoff, T. Arzberger, H. Kretzschmar, and K. Del Tredici. 2006. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol. 112:389-404. https://doi.org/10.1007/s00401-006-0127-z
- Brecht, W.J., F.M. Harris, S. Chang, I. Tesseur, G.-Q. Yu, Q. Xu, J. Dee Fish, T. Wyss-Coray, M. Buttini, L. Mucke, et al. 2004. Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. J. Neurosci. 24:2527–2534. https://doi.org/10.1523/JNEUROSCI.4315-03.2004
- Briston, T., and A.R. Hicks. 2018. Mitochondrial dysfunction and neurodegenerative proteinopathies: Mechanisms and prospects for therapeutic intervention. Biochem. Soc. Trans. 46:829-842. https://doi.org/10.1042/ BST20180025
- Buchhave, P., L. Minthon, H. Zetterberg, A.K. Wallin, K. Blennow, and O. Hansson. 2012. Cerebrospinal fluid levels of β-amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. *Arch. Gen. Psychiatry*. 69:98–106. https://doi.org/10.1001/archgenpsychiatry.2011.155
- Buchholz, S., and H. Zempel. 2024. The six brain-specific TAU isoforms and their role in Alzheimer's disease and related neurodegenerative dementia syndromes. Alzheimer's Dement. 20:3606-3628. https://doi.org/ 10.1002/alz.13784
- Buckley, R.F., E.C. Mormino, J. Chhatwal, A.P. Schultz, J.S. Rabin, D.M. Rentz, D. Acar, M.J. Properzi, J. Dumurgier, H. Jacobs, et al. 2019. Associations between baseline amyloid, sex, and APOE on subsequent tau accumulation in cerebrospinal fluid. Neurobiol. Aging. 78:178–185. https://doi .org/10.1016/j.neurobiolaging.2019.02.019
- Buée, L., and A. Delacourte. 1999. Comparative biochemistry of tau in progressive supranuclear palsy, corticobasal degeneration, FTDP-17 and Pick's disease. Brain Pathol. 9:681-693. https://doi.org/10.1111/j.1750-3639.1999.tb00550.x
- Burnouf, S., S. Grönke, H. Augustin, J. Dols, M.K. Gorsky, J. Werner, F. Kerr, N. Alic, P. Martinez, and L. Partridge. 2016. Deletion of endogenous Tau proteins is not detrimental in Drosophila. Sci. Rep. 6:23102. https://doi.org/10.1038/srep23102



- Butovsky, O., and H.L. Weiner. 2018. Microglial signatures and their role in health and disease. *Nat. Rev. Neurosci.* 19:622–635. https://doi.org/10.1038/s41583-018-0057-5
- Castellano, J.M., J. Kim, F.R. Stewart, H. Jiang, R.B. DeMattos, B.W. Patterson, A.M. Fagan, J.C. Morris, K.G. Mawuenyega, C. Cruchaga, et al. 2011. Human apoE isoforms differentially regulate brain amyloid-β peptide clearance. Sci. Transl. Med. 3:89ra57. https://doi.org/10.1126/scitranslmed.3002156
- Chen, J., Q. Li, and J. Wang. 2011. Topology of human apolipoprotein E3 uniquely regulates its diverse biological functions. *Proc. Natl. Acad. Sci. USA*. 108:14813-14818. https://doi.org/10.1073/pnas.1106420108
- Chen, H.-K., Z. Liu, A. Meyer-Franke, J. Brodbeck, R.D. Miranda, J.G. McGuire, M.A. Pleiss, Z.-S. Ji, M.E. Balestra, D.W. Walker, et al. 2012. Small molecule structure correctors abolish detrimental effects of apolipoprotein E4 in cultured neurons. J. Biol. Chem. 287:5253-5266. https://doi.org/10.1074/jbc.M111.276162
- Chen, Y., M.R. Strickland, A. Soranno, and D.M. Holtzman. 2021. Apolipoprotein E: Structural insights and links to Alzheimer disease pathogenesis. *Neuron.* 109:205–221. https://doi.org/10.1016/j.neuron.2020.10
- Chen, X., M. Firulyova, M. Manis, J. Herz, I. Smirnov, E. Aladyeva, C. Wang, X. Bao, M.B. Finn, H. Hu, et al. 2023. Microglia-mediated T cell infiltration drives neurodegeneration in tauopathy. *Nature*. 615:668–677. https://doi.org/10.1038/s41586-023-05788-0
- Chen, Y., S. Song, S. Parhizkar, J. Lord, Y. Zhu, M.R. Strickland, C. Wang, J. Park, G.T. Tabor, H. Jiang, et al. 2024. APOE3ch alters microglial response and suppresses Aβ-induced tau seeding and spread. Cell. 187: 428-445.e20. https://doi.org/10.1016/j.cell.2023.11.029
- Chen, G., M. Wang, Z. Zhang, D.K. Hong, E.H. Ahn, X. Liu, S.S. Kang, and K. Ye. 2025. ApoE3 R136S binds to Tau and blocks its propagation, suppressing neurodegeneration in mice with Alzheimer's disease. *Neuron*. 113:719–736.e5. https://doi.org/10.1016/j.neuron.2024.12.015
- Chernick, D., S. Ortiz-Valle, A. Jeong, W. Qu, and L. Li. 2019. Peripheral versus central nervous system APOE in Alzheimer's disease: Interplay across the blood-brain barrier. *Neurosci. Lett.* 708:134306. https://doi.org/10.1016/j.neulet.2019.134306
- Chiarini, A., U. Armato, E. Gardenal, L. Gui, and I. Dal Prà. 2017. Amyloid β-exposed human astrocytes overproduce Phospho-Tau and overrelease it within exosomes, effects suppressed by calcilytic NPS 2143further implications for alzheimer's therapy. Front. Neurosci. 11:217. https://doi.org/10.3389/fnins.2017.00217
- Chua, C.-C., M.-L. Lim, and B.-S. Wong. 2010. Altered apolipoprotein E glycosylation is associated with Abeta(42) accumulation in an animal model of Niemann-Pick Type C disease. *J. Neurochem.* 112:1619–1626. https://doi.org/10.1111/j.1471-4159.2010.06586.x
- Chung, D.-E.C., X. Deng, H.K. Yalamanchili, J.-P. Revelli, A.L. Han, B. Tadros, R. Richman, M. Dias, F.A. Naini, S. Boeynaems, et al. 2024. The big tau splice isoform resists Alzheimer's-related pathological changes. bioRxiv. https://doi.org/10.1101/2024.07.30.605685 ((Preprint posted July 31, 2024).
- Clayton, K., J.C. Delpech, S. Herron, N. Iwahara, M. Ericsson, T. Saito, T.C. Saido, S. Ikezu, and T. Ikezu. 2021. Plaque associated microglia hypersecrete extracellular vesicles and accelerate tau propagation in a humanized APP mouse model. *Mol. Neurodegener*. 16:18. https://doi.org/10.1186/s13024-021-00440-9
- Colonna, M., and O. Butovsky. 2017. Microglia function in the central nervous system during health and neurodegeneration. *Annu. Rev. Immunol.* 35: 441–468. https://doi.org/10.1146/annurev-immunol-051116-052358
- Cook, C., S.S. Kang, Y. Carlomagno, W.-L. Lin, M. Yue, A. Kurti, M. Shinohara, K. Jansen-West, E. Perkerson, M. Castanedes-Casey, et al. 2015. Tau deposition drives neuropathological, inflammatory and behavioral abnormalities independently of neuronal loss in a novel mouse model. Hum. Mol. Genet. 24:6198–6212. https://doi.org/10.1093/hmg/ddv336
- Cooper, J.M., A. Lathuiliere, M. Migliorini, A.L. Arai, M.M. Wani, S. Dujardin, S.C. Muratoglu, B.T. Hyman, and D.K. Strickland. 2021. Regulation of tau internalization, degradation, and seeding by LRP1 reveals multiple pathways for tau catabolism. J. Biol. Chem. 296:100715. https://doi.org/ 10.1016/j.jbc.2021.100715
- Cooper, J.M., A. Lathuiliere, E.J. Su, Y. Song, D. Torrente, Y. Jo, N. Weinrich, J.D. Sales, M. Migliorini, T.H. Sisson, et al. 2024. SORL1 is a receptor for tau that promotes tau seeding. J. Biol. Chem. 300:107313. https://doi.org/ 10.1016/j.jbc.2024.107313
- Corder, E.H., A.M. Saunders, W.J. Strittmatter, D.E. Schmechel, P.C. Gaskell, G.W. Small, A.D. Roses, J.L. Haines, and M.A. Pericak-Vance. 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease

- in late onset families. *Science*. 261:921–923. https://doi.org/10.1126/science.8346443
- Crary, J.F., J.Q. Trojanowski, J.A. Schneider, J.F. Abisambra, E.L. Abner, I. Alafuzoff, S.E. Arnold, J. Attems, T.G. Beach, E.H. Bigio, et al. 2014. Primary age-related tauopathy (PART): A common pathology associated with human aging. *Acta Neuropathol.* 128:755–766. https://doi.org/10.1007/s00401-014-1349-0
- Cuchillo-Ibañez, I., M.P. Lennol, S. Escamilla, T. Mata-Balaguer, L. Valverde-Vozmediano, I. Lopez-Font, I. Ferrer, and J. Sáez-Valero. 2021. The apolipoprotein receptor LRP3 compromises APP levels. Alzheimer's Res. Ther. 13:181. https://doi.org/10.1186/s13195-021-00921-5
- Cudaback, E., X. Li, K.S. Montine, T.J. Montine, and C.D. Keene. 2011. Apolipoprotein E isoform-dependent microglia migration. FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 25:2082–2091. https://doi.org/10.1096/fj.10-176891
- Cummings, J., G.D. Rabinovici, A. Atri, P. Aisen, L.G. Apostolova, S. Hendrix, M. Sabbagh, D. Selkoe, M. Weiner, and S. Salloway. 2022. Aducanumab: Appropriate use recommendations update. J. Prev. Alzheimer's Dis. 9: 221–230. https://doi.org/10.14283/jpad.2022.34
- Cummings, J., L. Apostolova, G.D. Rabinovici, A. Atri, P. Aisen, S. Greenberg, S. Hendrix, D. Selkoe, M. Weiner, R.C. Petersen, et al. 2023. Lecanemab: Appropriate use recommendations. J. Prev. Alzheimer's Dis. 10:362–377. https://doi.org/10.14283/jpad.2023.30
- Cummings, J., A.M.L. Osse, D. Cammann, J. Powell, and J. Chen. 2024. Antiamyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 38:5–22. https://doi.org/10.1007/s40259-023-00633-2
- Dammer, E.B., A. Shantaraman, L. Ping, D.M. Duong, E.S. Gerasimov, S.P. Ravindran, V. Gudmundsdottir, E.A. Frick, G.T. Gomez, K.A. Walker, et al. 2024. Proteomic analysis of Alzheimer's disease cerebrospinal fluid reveals alterations associated with APOE ε4 and atomoxetine treatment. *Sci. Transl. Med.* 16:eadn3504. https://doi.org/10.1126/scitranslmed.adn3504
- Darreh-Shori, T., A. Forsberg, N. Modiri, N. Andreasen, K. Blennow, C. Kamil, H. Ahmed, O. Almkvist, B. Långström, and A. Nordberg. 2011. Differential levels of apolipoprotein E and butyrylcholinesterase show strong association with pathological signs of Alzheimer's disease in the brain in vivo. Neurobiol. Aging. 32:2320.e15-2320.e2.32E32. https://doi.org/10 .1016/j.neurobiolaging.2010.04.028
- Das, S., Z. Li, A. Wachter, S. Alla, A. Noori, A. Abdourahman, J.A. Tamm, M.E. Woodbury, R.V. Talanian, K. Biber, et al. 2024. Distinct transcriptomic responses to Aβ plaques, neurofibrillary tangles, and APOE in Alzheimer's disease. Alzheimer's Dement. 20:74–90. https://doi.org/10 .1002/alz.13387
- Davies, C., J. Tulloch, E. Yip, L. Currie, M. Colom-Cadena, S. Wegmann, B.T. Hyman, L. Wilkins, M. Hooley, M. Tzioras, and T.L. Spires-Jones. 2023. Apolipoprotein E isoform does not influence trans-synaptic spread of tau pathology in a mouse model. *Brain Neurosci. Adv.* 7:23982128231191046. https://doi.org/10.1177/23982128231191046
- Del-Aguila, J.L., Z. Li, U. Dube, K.A. Mihindukulasuriya, J.P. Budde, M.V. Fernandez, L. Ibanez, J. Bradley, F. Wang, K. Bergmann, et al. 2019. A single-nuclei RNA sequencing study of Mendelian and sporadic AD in the human brain. Alzheimer's Res. Ther. 11:71. https://doi.org/10.1186/s13195-019-0524-x
- Delizannis, A.T., A. Nonneman, W. Tsering, A. De Bondt, I. Van den Wyngaert, B. Zhang, E. Meymand, M.F. Olufemi, P. Koivula, S. Maimaiti, et al. 2021. Effects of microglial depletion and TREM2 deficiency on Aβ plaque burden and neuritic plaque tau pathology in 5XFAD mice. Acta Neuropathol. Commun. 9:150. https://doi.org/10.1186/s40478-021-01251
- DeMattos, R.B. 2004. Apolipoprotein E dose-dependent modulation of betaamyloid deposition in a transgenic mouse model of Alzheimer's disease. J. Mol. Neurosci. 23:255-262. https://doi.org/10.1385/JMN:23:3:255
- Deming, Y., Z. Li, M. Kapoor, O. Harari, J.L. Del-Aguila, K. Black, D. Carrell, Y. Cai, M.V. Fernandez, J. Budde, et al. 2017. Genome-wide association study identifies four novel loci associated with Alzheimer's endophenotypes and disease modifiers. Acta Neuropathol. 133:839–856. https://doi.org/10.1007/s00401-017-1685-y
- DeVos, S.L., R.L. Miller, K.M. Schoch, B.B. Holmes, C.S. Kebodeaux, A.J. Wegener, G. Chen, T. Shen, H. Tran, B. Nichols, et al. 2017. Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy. Sci. Transl. Med. 9:eaag0481. https://doi.org/10.1126/scitranslmed.aag0481
- Dincer, A., C.D. Chen, N.S. McKay, L.N. Koenig, A. McCullough, S. Flores, S.J. Keefe, S.A. Schultz, R.L. Feldman, N. Joseph-Mathurin, et al. 2022. APOE ε4 genotype, amyloid-β, and sex interact to predict tau in regions



- of high APOE mRNA expression. Sci. Transl. Med. 14:eabl7646. https://doi.org/10.1126/scitranslmed.abl7646
- Donix, M., A.C. Burggren, N.A. Suthana, P. Siddarth, A.D. Ekstrom, A.K. Krupa, M. Jones, A. Rao, L. Martin-Harris, L.M. Ercoli, et al. 2010. Longitudinal changes in medial temporal cortical thickness in normal subjects with the APOE-4 polymorphism. *NeuroImage*. 53:37–43. https://doi.org/10.1016/j.neuroimage.2010.06.009
- Drepper, F., J. Biernat, S. Kaniyappan, H.E. Meyer, E.M. Mandelkow, B. Warscheid, and E. Mandelkow. 2020. A combinatorial native MS and LC-MS/MS approach reveals high intrinsic phosphorylation of human Tau but minimal levels of other key modifications. J. Biol. Chem. 295: 18213-18225. https://doi.org/10.1074/jbc.RA120.015882
- Dumanis, S.B., J.A. Tesoriero, L.W. Babus, M.T. Nguyen, J.H. Trotter, M.J. Ladu, E.J. Weeber, R.S. Turner, B. Xu, G.W. Rebeck, and H.-S. Hoe. 2009. ApoE4 decreases spine density and dendritic complexity in cortical neurons in vivo. J. Neurosci. 29:15317–15322. https://doi.org/10.1523/JNEUROSCI.4026-09.2009
- Dyer, C.A., R.S. Smith, and L.K. Curtiss. 1991. Only multimers of a synthetic peptide of human apolipoprotein E are biologically active. J. Biol. Chem. 266:15009-15015.
- Eisenbaum, M., A. Pearson, C. Ortiz, M. Mullan, F. Crawford, J. Ojo, and C. Bachmeier. 2024. ApoE4 expression disrupts tau uptake, trafficking, and clearance in astrocytes. *Glia*. 72:184–205. https://doi.org/10.1002/glia.24469
- Elliott, D.A., G.M. Halliday, and B. Garner. 2010. Apolipoprotein-E forms dimers in human frontal cortex and hippocampus. *BMC Neurosci.* 11:23. https://doi.org/10.1186/1471-2202-11-23
- Eltom, K., T. Mothes, S. Libard, M. Ingelsson, and A. Erlandsson. 2024. Astrocytic accumulation of tau fibrils isolated from Alzheimer's disease brains induces inflammation, cell-to-cell propagation and neuronal impairment. Acta Neuropathol. Commun. 12:34. https://doi.org/10.1186/s40478-024-01745-8
- Engelborghs, S., B. Dermaut, P. Mariën, A. Symons, E. Vloeberghs, K. Maertens, N. Somers, J. Goeman, R. Rademakers, M. Van den Broeck, et al. 2006. Dose dependent effect of APOE epsilon4 on behavioral symptoms in frontal lobe dementia. Neurobiol. Aging. 27:285–292. https://doi.org/10.1016/j.neurobiolaging.2005.02.005
- Evans, L.D., T. Wassmer, G. Fraser, J. Smith, M. Perkinton, A. Billinton, and F.J. Livesey. 2018. Extracellular monomeric and aggregated tau efficiently enter human neurons through overlapping but distinct pathways. Cell Rep. 22:3612–3624. https://doi.org/10.1016/j.celrep.2018.03 .021
- Ezerskiy, L.A., K.M. Schoch, C. Sato, M. Beltcheva, K. Horie, F. Rigo, R. Martynowicz, C.M. Karch, R.J. Bateman, and T.M. Miller. 2022. Astrocytic 4R tau expression drives astrocyte reactivity and dysfunction. JCI Insight. 7:e152012. https://doi.org/10.1172/jci.insight.152012
- Fá, M., D. Puzzo, R. Piacentini, A. Staniszewski, H. Zhang, M.A. Baltrons, D.D. Li Puma, I. Chatterjee, J. Li, F. Saeed, et al. 2016. Extracellular Tau oligomers produce an Immediate impairment of LTP and memory. Sci. Rep. 6:19393. https://doi.org/10.1038/srep19393
- Fagan, A.M., M. Watson, M. Parsadanian, K.R. Bales, S.M. Paul, and D.M. Holtzman. 2002. Human and murine ApoE markedly alters A beta metabolism before and after plaque formation in a mouse model of Alzheimer's disease. Neurobiol. Dis. 9:305–318. https://doi.org/10.1006/nbdi.2002.0483
- Falcon, B., W. Zhang, A.G. Murzin, G. Murshudov, H.J. Garringer, R. Vidal, R.A. Crowther, B. Ghetti, S.H.W. Scheres, and M. Goedert. 2018. Structures of filaments from Pick's disease reveal a novel tau protein fold. Nature. 561:137–140. https://doi.org/10.1038/s41586-018-0454-y
- Farrer, L.A., C.R. Abraham, L. Volicer, E.J. Foley, N.W. Kowall, A.C. McKee, and J.M. Wells. 1995. Allele epsilon 4 of apolipoprotein E shows a dose effect on age at onset of Pick disease. Exp. Neurol. 136:162–170. https://doi.org/10.1006/exnr.1995.1093
- Feingold, K.R. 2022. Lipid and lipoprotein metabolism. Endocrinol. Metab. Clin. North Am. 51:437–458. https://doi.org/10.1016/j.ecl.2022.02.008
- Fernández-Calle, R., S.C. Konings, J. Frontiñán-Rubio, J. García-Revilla, L. Camprubí-Ferrer, M. Svensson, I. Martinson, A. Boza-Serrano, J.L. Venero, H.M. Nielsen, et al. 2022. APOE in the bullseye of neurodegenerative diseases: Impact of the APOE genotype in alzheimer's disease pathology and brain diseases. Mol. Neurodegener. 17:62. https://doi.org/10.1186/s13024-022-00566-4
- Ferrari-Souza, J.P., B. Bellaver, P.C.L. Ferreira, A.L. Benedet, G. Povala, F.Z. Lussier, D.T. Leffa, J. Therriault, C. Tissot, C. Soares, et al. 2023. APOE ϵ 4 potentiates amyloid β effects on longitudinal tau pathology. *Nat. Aging*. 3:1210–1218. https://doi.org/10.1038/s43587-023-00490-2

- Ferreira, D., A. Nordberg, and E. Westman. 2020. Biological subtypes of alzheimer disease: A systematic review and meta-analysis. *Neurology*. 94:436-448. https://doi.org/10.1212/WNL.000000000009058
- Ferrer, I. 2023. Hypothesis review: Alzheimer's overture guidelines. Brain Pathol. 33:e13122. https://doi.org/10.1111/bpa.13122
- Filippi, M., G. Cecchetti, E.G. Spinelli, P. Vezzulli, A. Falini, and F. Agosta. 2022. Amyloid-related imaging abnormalities and β-Amyloid-targeting antibodies: A systematic review. JAMA Neurol. 79:291–304. https://doi.org/10.1001/jamaneurol.2021.5205
- Fischer, I. 2023. Big tau: What we know, and we need to know. eNeuro. 10: ENEURO.0052-23.2023. https://doi.org/10.1523/ENEURO.0052-23.2023
- Fitz, N.F., A.A. Cronican, M. Saleem, A.H. Fauq, R. Chapman, I. Lefterov, and R. Koldamova. 2012. Abca1 deficiency affects Alzheimer's disease-like phenotype in human ApoE4 but Not in ApoE3-targeted replacement mice. J. Neurosci. 32:13125–13136. https://doi.org/10.1523/JNEUROSCI .1937-12.2012
- Fitzpatrick, A.W.P., B. Falcon, S. He, A.G. Murzin, G. Murshudov, H.J. Garringer, R.A. Crowther, B. Ghetti, M. Goedert, and S.H.W. Scheres. 2017. Cryo-EM structures of tau filaments from Alzheimer's disease. *Nature*. 547:185–190. https://doi.org/10.1038/nature23002
- Fleming, L.M., K.H. Weisgraber, W.J. Strittmatter, J.C. Troncoso, and G.V. Johnson. 1996. Differential binding of apolipoprotein E isoforms to tau and other cytoskeletal proteins. Exp. Neurol. 138:252-260. https://doi.org/10.1006/exnr.1996.0064
- Florian, H., D. Wang, S.E. Arnold, M. Boada, Q. Guo, Z. Jin, H. Zheng, N. Fisseha, H.V. Kalluri, B. Rendenbach-Mueller, et al. 2023. Tilavonemab in early alzheimer's disease: Results from a phase 2, randomized, double-blind study. Brain. 146:2275-2284. https://doi.org/10.1093/brain/awad024
- Flowers, S.A., O.C. Grant, R.J. Woods, and G.W. Rebeck. 2020. O-glycosylation on cerebrospinal fluid and plasma apolipoprotein E differs in the lipid-binding domain. *Glycobiology*. 30:74–85. https://doi.org/10.1093/glycob/cwz084
- Fortea, J., J. Pegueroles, D. Alcolea, O. Belbin, O. Dols-Icardo, L. Vaqué-Alcázar, L. Videla, J.D. Gispert, M. Suárez-Calvet, S.C. Johnson, et al. 2024. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. *Nat. Med.* 30:1284–1291. https://doi.org/10.1038/s41591-024-02931-w
- Franzmeier, N., J. Neitzel, A. Rubinski, R. Smith, O. Strandberg, R. Ossenkoppele, O. Hansson, M. Ewers, and Alzheimer's Disease Neuroimaging Initiative (adni). 2020. Functional brain architecture is associated with the rate of tau accumulation in Alzheimer's disease. *Nat. Commun.* 11: 347. https://doi.org/10.1038/s41467-019-14159-1
- Frisoni, G.B., D. Altomare, D.R. Thal, F. Ribaldi, R. van der Kant, R. Ossenkoppele, K. Blennow, J. Cummings, C. van Duijn, P.M. Nilsson, et al. 2022. The probabilistic model of alzheimer disease: The amyloid hypothesis revised. Nat. Rev. Neurosci. 23:53-66. https://doi.org/10.1038/s41583-021-00533-w
- Fryer, J.D., R.B. Demattos, L.M. McCormick, M.A. O'Dell, M.L. Spinner, K.R. Bales, S.M. Paul, P.M. Sullivan, M. Parsadanian, G. Bu, and D.M. Holtzman. 2005a. The low density lipoprotein receptor regulates the level of central nervous system human and murine apolipoprotein E but does not modify amyloid plaque pathology in PDAPP mice. J. Biol. Chem. 280:25754–25759. https://doi.org/10.1074/jbc.M502143200
- Fryer, J.D., K. Simmons, M. Parsadanian, K.R. Bales, S.M. Paul, P.M. Sullivan, and D.M. Holtzman. 2005b. Human apolipoprotein E4 alters the amyloid-beta 40:42 ratio and promotes the formation of cerebral amyloid angiopathy in an amyloid precursor protein transgenic model. J. Neurosci. 25:2803-2810. https://doi.org/10.1523/JNEUROSCI.5170-04.2005
- Fujita, M., Z. Gao, L. Zeng, C. McCabe, C.C. White, B. Ng, G.S. Green, O. Rozenblatt-Rosen, D. Phillips, L. Amir-Zilberstein, et al. 2024. Cell subtype-specific effects of genetic variation in the Alzheimer's disease brain. Nat. Genet. 56:605–614. https://doi.org/10.1038/s41588-024-01685-y
- Gallardo, G., and D.M. Holtzman. 2019. Amyloid-β and Tau at the crossroads of Alzheimer's disease. Adv. Exp. Med. Biol. 1184:187–203. https://doi.org/10.1007/978-981-32-9358-8_16
- Gerrits, E., N. Brouwer, S.M. Kooistra, M.E. Woodbury, Y. Vermeiren, M. Lambourne, J. Mulder, M. Kummer, T. Möller, K. Biber, et al. 2021. Distinct amyloid-β and tau-associated microglia profiles in Alzheimer's disease. Acta Neuropathol. (Berl.). 141:681-696. https://doi.org/10.1007/s00401-021-02263-w
- Giannakopoulos, P., F.R. Herrmann, T. Bussière, C. Bouras, E. Kövari, D.P. Perl, J.H. Morrison, G. Gold, and P.R. Hof. 2003. Tangle and neuron



- numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. *Neurology*. 60:1495–1500. https://doi.org/10.1212/01.wnl .0000063311.58879.01
- Goedert, M., M.G. Spillantini, R. Jakes, D. Rutherford, and R.A. Crowther. 1989. Multiple isoforms of human microtubule-associated protein tau: Sequences and localization in neurofibrillary tangles of alzheimer's disease. *Neuron.* 3:519–526. https://doi.org/10.1016/0896-6273(89)90210-9
- Goedert, M., D.S. Eisenberg, and R.A. Crowther. 2017. Propagation of Tau aggregates and neurodegeneration. Annu. Rev. Neurosci. 40:189-210. https://doi.org/10.1146/annurev-neuro-072116-031153
- Gómez-Isla, T., R. Hollister, H. West, S. Mui, J.H. Growdon, R.C. Petersen, J.E. Parisi, and B.T. Hyman. 1997. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann. Neurol.* 41:17–24. https://doi.org/10.1002/ana.410410106
- Gonzalez-Ortiz, F., J. Vávra, E. Payne, B.E. Kirsebom, U. Sjöbom, C. Santos, J. Júlvez, K. Kramer, D. Zalcberg, L. Montoliu-Gaya, et al. 2025. The potential dual role of tau phosphorylation: Plasma phosphorylated-tau217 in newborns and alzheimer's disease. *Brain Commun.* 7:fcaf221. https://doi.org/10.1093/braincomms/fcaf221
- Gordon, B.A., K. Friedrichsen, M. Brier, T. Blazey, Y. Su, J. Christensen, P. Aldea, J. McConathy, D.M. Holtzman, N.J. Cairns, et al. 2016. The relationship between cerebrospinal fluid markers of Alzheimer pathology and positron emission tomography tau imaging. *Brain.* 139:2249–2260. https://doi.org/10.1093/brain/aww139
- Gratuze, M., C.E.G. Leyns, and D.M. Holtzman. 2018. New insights into the role of TREM2 in Alzheimer's disease. *Mol. Neurodegener.* 13:66. https://doi.org/10.1186/s13024-018-0298-9
- Gratuze, M., C.E. Leyns, A.D. Sauerbeck, M.-K. St-Pierre, M. Xiong, N. Kim, J.R. Serrano, M.È. Tremblay, T.T. Kummer, M. Colonna, et al. 2020. Impact of TREM2R47H variant on tau pathology-induced gliosis and neurodegeneration. J. Clin. Invest. 130:4954–4968. https://doi.org/10.1172/JCI138179
- Gratuze, M., Y. Chen, S. Parhizkar, N. Jain, M.R. Strickland, J.R. Serrano, M. Colonna, J.D. Ulrich, and D.M. Holtzman. 2021. Activated microglia mitigate Aβ-associated tau seeding and spreading. J. Exp. Med. 218: e20210542. https://doi.org/10.1084/jem.20210542
- Gratuze, M., H. Jiang, C. Wang, M. Xiong, X. Bao, and D.M. Holtzman. 2022.

 APOE antibody inhibits Aβ-associated Tau seeding and spreading in a mouse model. *Ann. Neurol.* 91:847–852. https://doi.org/10.1002/ana
- Gratuze, M., J.C.M. Schlachetzki, R. D'Oliveira Albanus, N. Jain, B. Novotny, L. Brase, L. Rodriguez, C. Mansel, M. Kipnis, S. O'Brien, et al. 2023. TREM2-independent microgliosis promotes tau-mediated neuro-degeneration in the presence of ApoE4. Neuron. 111:202–219.e7. https://doi.org/10.1016/j.neuron.2022.10.022
- Groot, C., R. Smith, E. Stomrud, A.P. Binette, A. Leuzy, A. Wuestefeld, L.E.M. Wisse, S. Palmqvist, N. Mattsson-Carlgren, S. Janelidze, et al. 2023. Phospho-tau with subthreshold tau-PET predicts increased tau accumulation rates in amyloid-positive individuals. *Brain.* 146:1580–1591. https://doi.org/10.1093/brain/awac329
- Grothe, M.J., S. Villeneuve, M. Dyrba, D. Bartrés-Faz, M. Wirth, and Alzheimer's Disease Neuroimaging Initiative. 2017. Multimodal characterization of older APOE2 carriers reveals selective reduction of amyloid load. *Neurology*. 88:569–576. https://doi.org/10.1212/WNL.00000000000003585
- Grubman, A., G. Chew, J.F. Ouyang, G. Sun, X.Y. Choo, C. McLean, R.K. Simmons, S. Buckberry, D.B. Vargas-Landin, D. Poppe, et al. 2019. A single-cell atlas of entorhinal cortex from individuals with Alzheimer's disease reveals cell-type-specific gene expression regulation. *Nat. Neurosci.* 22:2087–2097. https://doi.org/10.1038/s41593-019-0539-4
- Grundke-Iqbal, I., K. Iqbal, L. George, Y.C. Tung, K.S. Kim, and H.M. Wisniewski. 1989. Amyloid protein and neurofibrillary tangles coexist in the same neuron in Alzheimer disease. *Proc. Natl. Acad. Sci. USA*. 86: 2853–2857. https://doi.org/10.1073/pnas.86.8.2853
- Guerreiro, R., A. Wojtas, J. Bras, M. Carrasquillo, E. Rogaeva, E. Majounie, C. Cruchaga, C. Sassi, J.S.K. Kauwe, S. Younkin, et al. 2013. TREM2 variants in Alzheimer's disease. N. Engl. J. Med. 368:117–127. https://doi.org/10.1056/NEJMoa1211851
- Guo, J.L., D. Braun, G.A. Fitzgerald, Y.-T. Hsieh, L. Rougé, A. Litvinchuk, M. Steffek, N.E. Propson, C.M. Heffner, C. Discenza, et al. 2025. Decreased lipidated ApoE-receptor interactions confer protection against pathogenicity of ApoE and its lipid cargoes in lysosomes. *Cell.* 188: 187–206.e26. https://doi.org/10.1016/j.cell.2024.10.027
- Haimon, Z., A. Volaski, J. Orthgiess, S. Boura-Halfon, D. Varol, A. Shemer, S. Yona, B. Zuckerman, E. David, L. Chappell-Maor, et al. 2018. Re-

- evaluating microglia expression profiles using ribotag and cell isolation strategies. *Nat. Immunol.* 19:636-644. https://doi.org/10.1038/s41590-018-0110-6
- Haney, M.S., R. Pálovics, C.N. Munson, C. Long, P.K. Johansson, O. Yip, W. Dong, E. Rawat, E. West, J.C.M. Schlachetzki, et al. 2024. APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia. Nature. 628:154–161. https://doi.org/10.1038/s41586-024-07185-7
- Harris, F.M., W.J. Brecht, Q. Xu, R.W. Mahley, and Y. Huang. 2004. Increased tau phosphorylation in apolipoprotein E4 transgenic mice is associated with activation of extracellular signal-regulated kinase: Modulation by zinc. J. Biol. Chem. 279:44795-44801. https://doi.org/10.1074/jbc .M408127200
- Hashimoto, T., A. Serrano-Pozo, Y. Hori, K.W. Adams, S. Takeda, A.O. Banerji, A. Mitani, D. Joyner, D.H. Thyssen, B.J. Bacskai, et al. 2012. Apolipoprotein E, especially apolipoprotein E4, increases the oligomerization of amyloid β peptide. J. Neurosci. 32:15181-15192. https://doi.org/10.1523/ JNEUROSCI.1542-12.2012
- Hernandez, I., E. Gelpi, L. Molina-Porcel, S. Bernal, B. Rodríguez-Santiago, O. Dols-Icardo, A. Ruiz, D. Alcolea, M. Boada, A. Lleó, and J. Clarimón. 2021. Heterozygous APOE Christchurch in familial Alzheimer's disease without mutations in other Mendelian genes. Neuropathol. Appl. Neurobiol. 47:579–582. https://doi.org/10.1111/nan.12670
- Hesse, R., M.L. Hurtado, R.J. Jackson, S.L. Eaton, A.G. Herrmann, M. Colom-Cadena, M. Tzioras, D. King, J. Rose, J. Tulloch, et al. 2019. Comparative profiling of the synaptic proteome from Alzheimer's disease patients with focus on the APOE genotype. Acta Neuropathol. Commun. 7:214. https://doi.org/10.1186/s40478-019-0847-7
- Hill, E., T.K. Karikari, K.G. Moffat, M.J.E. Richardson, and M.J. Wall. 2019. Introduction of Tau oligomers into cortical neurons alters action potential dynamics and disrupts synaptic transmission and plasticity. eNeuro. 6:ENEURO.0166-19.2019. https://doi.org/10.1523/ENEURO.0166-19.2019
- Hodge, R.D., T.E. Bakken, J.A. Miller, K.A. Smith, E.R. Barkan, L.T. Graybuck, J.L. Close, B. Long, N. Johansen, O. Penn, et al. 2019. Conserved cell types with divergent features in human versus mouse cortex. *Nature*. 573: 61–68. https://doi.org/10.1038/s41586-019-1506-7
- Hohman, T.J., L. Dumitrescu, L.L. Barnes, M. Thambisetty, G. Beecham, B. Kunkle, K.A. Gifford, W.S. Bush, L.B. Chibnik, S. Mukherjee, et al. 2018. Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of Tau. JAMA Neurol. 75:989–998. https://doi.org/10.1001/jamaneurol.2018.0821
- Holmes, B.B., and M.I. Diamond. 2014. Prion-like properties of tau protein: The importance of extracellular tau as a therapeutic target. *J. Biol. Chem.* 289:19855–19861. https://doi.org/10.1074/jbc.R114.549295
- Holmes, B.B., S.L. DeVos, N. Kfoury, M. Li, R. Jacks, K. Yanamandra, M.O. Ouidja, F.M. Brodsky, J. Marasa, D.P. Bagchi, et al. 2013. Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. Proc. Natl. Acad. Sci. USA. 110:E3138–E3147. https://doi.org/10.1073/pnas.1301440110
- Holth, J., T. Patel, and D.M. Holtzman. 2017. Sleep in alzheimer's disease beyond amyloid. Neurobiol. Sleep Circadian Rhythms. 2:4-14. https://doi .org/10.1016/j.nbscr.2016.08.002
- Holth, J.K., S.K. Fritschi, C. Wang, N.P. Pedersen, J.R. Cirrito, T.E. Mahan, M.B. Finn, M. Manis, J.C. Geerling, P.M. Fuller, et al. 2019. The sleepwake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. Science. 363:880-884. https://doi.org/10.1126/science.aav2546
- Holtzman, D.M., K.R. Bales, T. Tenkova, A.M. Fagan, M. Parsadanian, L.J. Sartorius, B. Mackey, J. Olney, D. McKeel, D. Wozniak, and S.M. Paul. 2000. Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. Proc. Natl. Acad. Sci. USA. 97:2892–2897. https://doi.org/10.1073/pnas.050004797
- Holtzman, D.M., J. Herz, and G. Bu. 2012. Apolipoprotein E and apolipoprotein E receptors: Normal biology and roles in Alzheimer disease. Cold Spring Harb. Perspect. Med. 2:a006312. https://doi.org/10.1101/cshperspect .a006312
- Hong, C., and P. Tontonoz. 2014. Liver X receptors in lipid metabolism: Opportunities for drug discovery. Nat. Rev. Drug Discov. 13:433–444. https://doi.org/10.1038/nrd4280
- Hoover, B.R., M.N. Reed, J. Su, R.D. Penrod, L.A. Kotilinek, M.K. Grant, R. Pitstick, G.A. Carlson, L.M. Lanier, L.-L. Yuan, et al. 2010. Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. *Neuron*. 68:1067–1081. https://doi.org/10.1016/j.neuron.2010.11.030
- Horie, K., N.R. Barthélemy, S. Spina, L. VandeVrede, Y. He, R.W. Paterson, B.A. Wright, G.S. Day, A.A. Davis, C.M. Karch, et al. 2022. CSF tau



- microtubule-binding region identifies pathological changes in primary tauopathies. *Nat. Med.* 28:2547–2554. https://doi.org/10.1038/s41591-022-02075-9
- Horie, K., G. Salvadó, N.R. Barthélemy, S. Janelidze, Y. Li, Y. He, B. Saef, C.D. Chen, H. Jiang, O. Strandberg, et al. 2023. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. *Nat. Med.* 29: 1954–1963. https://doi.org/10.1038/s41591-023-02443-z
- Huang, Y., X.Q. Liu, T. Wyss-Coray, W.J. Brecht, D.A. Sanan, and R.W. Mahley. 2001. Apolipoprotein E fragments present in Alzheimer's disease brains induce neurofibrillary tangle-like intracellular inclusions in neurons. Proc. Natl. Acad. Sci. USA. 98:8838–8843. https://doi.org/10.1073/pnas.151254698
- Huang, L.-K., S.-P. Chao, and C.-J. Hu. 2020. Clinical trials of new drugs for Alzheimer disease. J. Biomed. Sci. 27:18. https://doi.org/10.1186/s12929
- Imbimbo, B.P., S. Ippati, M. Watling, and C. Balducci. 2022. A critical appraisal of tau-targeting therapies for primary and secondary tauopathies. Alzheimer's Dement. 18:1008–1037. https://doi.org/10.1002/alz.12453
- Jack, C.R., D.S. Knopman, W.J. Jagust, L.M. Shaw, P.S. Aisen, M.W. Weiner, R.C. Petersen, and J.Q. Trojanowski. 2010. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 9:119–128. https://doi.org/10.1016/S1474-4422(09)70299-6
- Jack, C.R., H.J. Wiste, S.D. Weigand, T.M. Therneau, D.S. Knopman, V. Lowe, P. Vemuri, M.M. Mielke, R.O. Roberts, M.M. Machulda, et al. 2017. Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: A cross-sectional study. *Lancet Neurol*. 16:435–444. https://doi.org/10.1016/S1474-4422(17)30077-7
- Jackson, R.J., M.S. Keiser, J.C. Meltzer, D.P. Fykstra, S.E. Dierksmeier, S. Hajizadeh, J. Kreuzer, R. Morris, A. Melloni, T. Nakajima, et al. 2024. APOE2 gene therapy reduces amyloid deposition, and improves markers of neuroinflammation and neurodegeneration in a mouse model of Alzheimer disease. Mol. Ther. 32:1373-1386. https://doi.org/10.1016/j.vmthe.2024.03.024
- Jain, S., S.Y. Yoon, L. Leung, J. Knoferle, and Y. Huang. 2013. Cellular source-specific effects of apolipoprotein (apo) E4 on dendrite arborization and dendritic spine development. PLoS One. 8:e59478. https://doi.org/10.1371/journal.pone.0059478
- Jara, C., W. Cerpa, C. Tapia-Rojas, and R.A. Quintanilla. 2020. Tau Deletion prevents cognitive impairment and mitochondrial dysfunction age associated by a mechanism dependent on cyclophilin-D. Front. Neurosci. 14:586710. https://doi.org/10.3389/fnins.2020.586710
- Jendresen, C., V. Arskog, M.R. Daws, and L.N.G. Nilsson. 2017. The Alzheimer's disease risk factors apolipoprotein E and TREM2 are linked in a receptor signaling pathway. J. Neuroinflammation. 14:59. https://doi.org/10.1186/s12974-017-0835-4
- Jiang, T., L. Tan, X.-C. Zhu, J.-S. Zhou, L. Cao, M.-S. Tan, H.-F. Wang, Q. Chen, Y.-D. Zhang, and J.-T. Yu. 2015. Silencing of TREM2 exacerbates tau pathology, neurodegenerative changes, and spatial learning deficits in P301S tau transgenic mice. *Neurobiol. Aging*. 36:3176–3186. https://doi.org/10.1016/j.neurobiolaging.2015.08.019
- Jiang, T., Y.-D. Zhang, Q. Chen, Q. Gao, X.-C. Zhu, J.-S. Zhou, J.-Q. Shi, H. Lu, L. Tan, and J.-T. Yu. 2016. TREM2 modifies microglial phenotype and provides neuroprotection in P301S tau transgenic mice. Neuropharmacology. 105:196–206. https://doi.org/10.1016/j.neuropharm.2016.01.028
- Jonsson, T., H. Stefansson, S. Steinberg, I. Jonsdottir, P.V. Jonsson, J. Snaedal, S. Bjornsson, J. Huttenlocher, A.I. Levey, J.J. Lah, et al. 2013. Variant of TREM2 associated with the risk of Alzheimer's disease. N. Engl. J. Med. 368:107-116. https://doi.org/10.1056/NEJMoa1211103
- Jucker, M., and L.C. Walker. 2013. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. *Nature*. 501:45-51. https://doi.org/10.1038/nature12481
- Kacperczyk, M., A. Kmieciak, and E.M. Kratz. 2021. The role of ApoE expression and variability of its glycosylation in human reproductive health in the light of current information. *Int. J. Mol. Sci.* 22:7197. https://doi.org/10.3390/ijms22137197
- Kandimalla, R., M. Manczak, X. Yin, R. Wang, and P.H. Reddy. 2018. Hippocampal phosphorylated tau induced cognitive decline, dendritic spine loss and mitochondrial abnormalities in a mouse model of Alzheimer's disease. Hum. Mol. Genet. 27:30–40. https://doi.org/10.1093/hmg/ddx381
- Kang, S.S., M.T.W. Ebbert, K.E. Baker, C. Cook, X. Wang, J.P. Sens, J.-P. Kocher, L. Petrucelli, and J.D. Fryer. 2018a. Microglial translational profiling reveals a convergent APOE pathway from aging, amyloid,

- and tau. J. Exp. Med. 215:2235-2245. https://doi.org/10.1084/jem.20180653
- Kang, S.S., A. Kurti, K.E. Baker, C.-C. Liu, M. Colonna, J.D. Ulrich, D.M. Holtzman, G. Bu, and J.D. Fryer. 2018b. Behavioral and transcriptomic analysis of Trem2-null mice: Not all knockout mice are created equal. Hum. Mol. Genet. 27:211–223. https://doi.org/10.1093/hmg/ddx366
- Kanmert, D., A. Cantlon, C.R. Muratore, M. Jin, T.T. O'Malley, G. Lee, T.L. Young-Pearse, D.J. Selkoe, and D.M. Walsh. 2015. C-terminally truncated forms of Tau, but not full-length Tau or its C-terminal fragments, are released from neurons independently of cell death. J. Neurosci. 35: 10851-10865. https://doi.org/10.1523/JNEUROSCI.0387-15.2015
- Karch, C.M., and A.M. Goate. 2015. Alzheimer's disease risk genes and mechanisms of disease pathogenesis. *Biol. Psychiatry*. 77:43–51. https://doi.org/10.1016/j.biopsych.2014.05.006
- Karran, E., and B. De Strooper. 2022. The amyloid hypothesis in Alzheimer disease: New insights from new therapeutics. Nat. Rev. Drug Discov. 21: 306-318. https://doi.org/10.1038/s41573-022-00391-w
- Keren-Shaul, H., A. Spinrad, A. Weiner, O. Matcovitch-Natan, R. Dvir-Szternfeld, T.K. Ulland, E. David, K. Baruch, D. Lara-Astaiso, B. Toth, et al. 2017. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell.* 169:1276–1290.e17. https://doi.org/10.1016/j.cell.2017.05.018
- Knight, R.G., H.S.L. Tsui, W.C. Abraham, C.M. Skeaff, J.A. McMahon, and N.J. Cutfield. 2014. Lack of effect of the apolipoprotein E ε4 genotype on cognition during healthy aging. J. Clin. Exp. Neuropsychol. 36:742–750. https://doi.org/10.1080/13803395.2014.935706
- Knopman, D.S., H. Amieva, R.C. Petersen, G. Chételat, D.M. Holtzman, B.T. Hyman, R.A. Nixon, and D.T. Jones. 2021. Alzheimer disease. Nat. Rev. Dis. Primers. 7:33. https://doi.org/10.1038/s41572-021-00269-y
- Koch, G., F. Di Lorenzo, S. Loizzo, C. Motta, S. Travaglione, M. Baiula, R. Rimondini, V. Ponzo, S. Bonnì, S. Toniolo, et al. 2017. CSF tau is associated with impaired cortical plasticity, cognitive decline and astrocyte survival only in APOE4-positive Alzheimer's disease. Sci. Rep. 7:13728. https://doi.org/10.1038/s41598-017-14204-3
- Kockx, M., D.L. Guo, T. Huby, P. Lesnik, J. Kay, T. Sabaretnam, E. Jary, M. Hill, K. Gaus, J. Chapman, et al. 2007. Secretion of apolipoprotein E from macrophages occurs via a protein kinase A and calcium-dependent pathway along the microtubule network. Circ. Res. 101:607–616. https://doi.org/10.1161/CIRCRESAHA.107.157198
- Kockx, M., M. Traini, and L. Kritharides. 2018. Cell-specific production, secretion, and function of apolipoprotein E. J. Mol. Med. 96:361–371. https://doi.org/10.1007/s00109-018-1632-y
- Koller, E.J., E. Gonzalez De La Cruz, M. Weinrich, T. Williams, P.E. Cruz, D. Ryu, T.E. Golde, P.M. Sullivan, J. Lewis, D.R. Borchelt, and P. Chakrabarty. 2020. Intracerebral expression of AAV-APOE4 is not sufficient to alter tau burden in two distinct models of tauopathy. Mol. Neurobiol. 57: 1986–2001. https://doi.org/10.1007/s12035-019-01859-4
- Koutsodendris, N., J. Blumenfeld, A. Agrawal, M. Traglia, B. Grone, M. Zilberter, O. Yip, A. Rao, M.R. Nelson, Y. Hao, et al. 2023. Neuronal APOE4 removal protects against tau-mediated gliosis, neurodegeneration and myelin deficits. Nat. Aging. 3:275–296. https://doi.org/10.1038/s43587-023-00368-3
- Kovacs, G.G. 2017. Tauopathies. Handb. Clin. Neurol. 145:355–368. https://doi.org/10.1016/B978-0-12-802395-2.00025-0
- Kovacs, G.G. 2020. Astroglia and tau: New perspectives. Front. Aging Neurosci. 12:96. https://doi.org/10.3389/fnagi.2020.00096
- Krasemann, S., C. Madore, R. Cialic, C. Baufeld, N. Calcagno, R. El Fatimy, L. Beckers, E. O'Loughlin, Y. Xu, Z. Fanek, et al. 2017. The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. *Immunity*. 47:566–581.e9. https://doi.org/10.1016/j.immuni.2017.08.008
- Kreutzberg, G.W. 1996. Microglia: A sensor for pathological events in the CNS. Trends Neurosci. 19:312–318. https://doi.org/10.1016/0166-2236(96)10049-7
- La Joie, R., A.V. Visani, S.L. Baker, J.A. Brown, V. Bourakova, J. Cha, K. Chaudhary, L. Edwards, L. Iaccarino, M. Janabi, et al. 2020. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. Sci. Transl. Med. 12:eaau5732. https://doi.org/10.1126/scitranslmed.aau5732
- Largo-Barrientos, P., N. Apóstolo, E. Creemers, Z. Callaerts-Vegh, J. Swerts, C. Davies, J. McInnes, K. Wierda, B. De Strooper, T. Spires-Jones, et al. 2021. Lowering Synaptogyrin-3 expression rescues Tau-induced memory defects and synaptic loss in the presence of microglial activation. *Neuron*. 109:767–777.e5. https://doi.org/10.1016/j.neuron.2020.12.016
- Lau, S.-F., H. Cao, A.K.Y. Fu, and N.Y. Ip. 2020. Single-nucleus transcriptome analysis reveals dysregulation of angiogenic endothelial cells and



- neuroprotective glia in Alzheimer's disease. *Proc. Natl. Acad. Sci. USA*. 117:25800–25809. https://doi.org/10.1073/pnas.2008762117
- Lawler, P.E., J.G. Bollinger, S.E. Schindler, C.R. Hodge, N.J. Iglesias, V. Krishnan, J.B. Coulton, Y. Li, D.M. Holtzman, and R.J. Bateman. 2023. Apolipoprotein E O-glycosylation is associated with amyloid plaques and APOE genotype. *Anal. Biochem.* 672:115156. https://doi.org/10.1016/j.ab.2023.115156
- Le Guen, Y., M.E. Belloy, B. Grenier-Boley, I. de Rojas, A. Castillo-Morales, I. Jansen, A. Nicolas, C. Bellenguez, C. Dalmasso, F. Küçükali, et al. 2022. Association of rare APOE Missense variants V236E and R251G with risk of alzheimer disease. *JAMA Neurol.* 79:652–663. https://doi.org/10.1001/jamaneurol.2022.1166
- Lee, S.-H., W.J. Meilandt, L. Xie, V.D. Gandham, H. Ngu, K.H. Barck, M.G. Rezzonico, J. Imperio, G. Lalehzadeh, M.A. Huntley, et al. 2021. Trem2 restrains the enhancement of tau accumulation and neurodegeneration by β -amyloid pathology. *Neuron*. 109:1283–1301.e6. https://doi.org/10.1016/j.neuron.2021.02.010
- Lee-Gosselin, A., N. Jury-Garfe, Y. You, L. Dabin, D. Soni, S. Dutta, J.-C. Rochet, J. Kim, A.L. Oblak, and C.A. Lasagna-Reeves. 2023. TREM2-deficient microglia attenuate tau spreading in vivo. Cells. 12:1597. https://doi.org/10.3390/cells12121597
- Lehmann, M., P.M. Ghosh, C. Madison, A. Karydas, G. Coppola, J.P. O'Neil, Y. Huang, B.L. Miller, W.J. Jagust, and G.D. Rabinovici. 2014. Greater medial temporal hypometabolism and lower cortical amyloid burden in ApoE4-positive AD patients. J. Neurol. Neurosurg. Psychiatry. 85:266–273. https://doi.org/10.1136/jnnp-2013-305858
- Leng, K., E. Li, R. Eser, A. Piergies, R. Sit, M. Tan, N. Neff, S.H. Li, R.D. Rodriguez, C.K. Suemoto, et al. 2021. Molecular characterization of selectively vulnerable neurons in Alzheimer's disease. *Nat. Neurosci.* 24: 276–287. https://doi.org/10.1038/s41593-020-00764-7
- Lennol, M.P., I. Sánchez-Domínguez, I. Cuchillo-Ibañez, E. Camporesi, G. Brinkmalm, D. Alcolea, J. Fortea, A. Lleó, G. Soria, F. Aguado, et al. 2022. Apolipoprotein E imbalance in the cerebrospinal fluid of Alzheimer's disease patients. Alzheimer's Res. Ther. 14:161. https://doi.org/10.1186/s13195-022-01108-2
- Leuzy, A., K. Chiotis, L. Lemoine, P.G. Gillberg, O. Almkvist, E. Rodriguez-Vieitez, and A. Nordberg. 2019. Tau PET imaging in neurodegenerative tauopathies-still a challenge. *Mol. Psychiatry*. 24:1112–1134. https://doi.org/10.1038/s41380-018-0342-8
- Levin, J., J. Vöglein, Y.T. Quiroz, R.J. Bateman, V. Ghisays, F. Lopera, E. McDade, E. Reiman, P.N. Tariot, and J.C. Morris. 2022. Testing the amyloid cascade hypothesis: Prevention trials in autosomal dominant Alzheimer disease. Alzheimer's Dement. 18:2687–2698. https://doi.org/10.1002/alz.12624
- Lewis, J., D.W. Dickson, W.L. Lin, L. Chisholm, A. Corral, G. Jones, S.H. Yen, N. Sahara, L. Skipper, D. Yager, et al. 2001. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science. 293:1487–1491. https://doi.org/10.1126/science.1058189
- Leyns, C.E.G., J.D. Ulrich, M.B. Finn, F.R. Stewart, L.J. Koscal, J. Remolina Serrano, G.O. Robinson, E. Anderson, M. Colonna, and D.M. Holtzman. 2017. TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy. Proc. Natl. Acad. Sci. USA. 114:11524-11529. https://doi.org/10.1073/ pnas.1710311114
- Leyns, C.E.G., M. Gratuze, S. Narasimhan, N. Jain, L.J. Koscal, H. Jiang, M. Manis, M. Colonna, V.M.Y. Lee, J.D. Ulrich, and D.M. Holtzman. 2019. TREM2 function impedes tau seeding in neuritic plaques. *Nat. Neurosci.* 22:1217-1222. https://doi.org/10.1038/s41593-019-0433-0
- Liang, Y., S. Lin, T.P. Beyer, Y. Zhang, X. Wu, K.R. Bales, R.B. DeMattos, P.C. May, S.D. Li, X.-C. Jiang, et al. 2004. A liver X receptor and retinoid X receptor heterodimer mediates apolipoprotein E expression, secretion and cholesterol homeostasis in astrocytes. *J. Neurochem.* 88:623–634. https://doi.org/10.1111/j.1471-4159.2004.02183.x
- Liang, S.-Y., Z.-T. Wang, L. Tan, and J.-T. Yu. 2022. Tau toxicity in neuro-degeneration. Mol. Neurobiol. 59:3617–3634. https://doi.org/10.1007/s12035-022-02809-3
- Liao, F., A. Li, M. Xiong, N. Bien-Ly, H. Jiang, Y. Zhang, M.B. Finn, R. Hoyle, J. Keyser, K.B. Lefton, et al. 2018. Targeting of nonlipidated, aggregated apoE with antibodies inhibits amyloid accumulation. J. Clin. Invest. 128: 2144–2155. https://doi.org/10.1172/JC196429
- Lim, Y.Y., N. Yassi, L. Bransby, S. Ayton, R.F. Buckley, D. Eratne, D. Velakoulis, Q.-X. Li, C. Fowler, C.L. Masters, and P. Maruff. 2023. CSF Aβ42 and tau biomarkers in cognitively unimpaired Aβ- middle-aged and older APOE ε4 carriers. *Neurobiol. Aging*. 129:209–218. https://doi.org/10 .1016/j.neurobiolaging.2023.05.009

- Lin, Y.-T., J. Seo, F. Gao, H.M. Feldman, H.-L. Wen, J. Penney, H.P. Cam, E. Gjoneska, W.K. Raja, J. Cheng, et al. 2018. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. *Neuron.* 98: 1141–1154.e7. https://doi.org/10.1016/j.neuron.2018.05.008
- Litvinchuk, A., T.-P.V. Huynh, Y. Shi, R.J. Jackson, M.B. Finn, M. Manis, C.M. Francis, A.C. Tran, P.M. Sullivan, J.D. Ulrich, et al. 2021. Apolipoprotein E4 reduction with antisense oligonucleotides decreases neuro-degeneration in a tauopathy model. *Ann. Neurol.* 89:952–966. https://doi.org/10.1002/ana.26043
- Litvinchuk, A., J.H. Suh, J.L. Guo, K. Lin, S.S. Davis, N. Bien-Ly, E. Tycksen, G.T. Tabor, J. Remolina Serrano, M. Manis, et al. 2024. Amelioration of Tau and ApoE4-linked glial lipid accumulation and neurodegeneration with an LXR agonist. *Neuron*. 112:384–403.e8. https://doi.org/10.1016/j.neuron.2023.10.023
- Liu, M., D.G. Kuhel, L. Shen, D.Y. Hui, and S.C. Woods. 2012. Apolipoprotein E does not cross the blood-cerebrospinal fluid barrier, as revealed by an improved technique for sampling CSF from mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 303:R903-R908. https://doi.org/10.1152/ajpregu.00219.2012.
- Liu, C.-C., C.C. Liu, T. Kanekiyo, H. Xu, and G. Bu. 2013. Apolipoprotein E and Alzheimer disease: Risk, mechanisms, and therapy. Nat. Rev. Neurol. 9: 106–118. https://doi.org/10.1038/nrneurol.2012.263
- Liu, C.-C., N. Zhao, Y. Fu, N. Wang, C. Linares, C.-W. Tsai, and G. Bu. 2017. ApoE4 accelerates early seeding of amyloid pathology. *Neuron*. 96: 1024–1032.e3. https://doi.org/10.1016/j.neuron.2017.11.013
- Lodder, C., I. Scheyltjens, I.C. Stancu, P. Botella Lucena, M. Gutiérrez de Ravé, S. Vanherle, T. Vanmierlo, N. Cremers, H. Vanrusselt, B. Brône, et al. 2021. CSF1R inhibition rescues tau pathology and neurodegeneration in an A/T/N model with combined AD pathologies, while preserving plaque associated microglia. Acta Neuropathol. Commun. 9:108. https:// doi.org/10.1186/s40478-021-01204-8
- Lozupone, M., V. Dibello, R. Sardone, F. Castellana, R. Zupo, L. Lampignano, I. Bortone, A. Daniele, A. Bellomo, V. Solfrizzi, and F. Panza. 2023. The impact of apolipoprotein E (APOE) epigenetics on aging and sporadic alzheimer's disease. *Biology*. 12:1529. https://doi.org/10.3390/biology12121529
- Lucey, B.P., J. Wisch, A.H. Boerwinkle, E.C. Landsness, C.D. Toedebusch, J.S. McLeland, O.H. Butt, J. Hassenstab, J.C. Morris, B.M. Ances, and D.M. Holtzman. 2021. Sleep and longitudinal cognitive performance in preclinical and early symptomatic Alzheimer's disease. *Brain*. 144: 2852–2862. https://doi.org/10.1093/brain/awab272
- Mahley, R.W. 2016. Central nervous system lipoproteins: ApoE and regulation of cholesterol metabolism. Arterioscler. Thromb. Vasc. Biol. 36:1305–1315. https://doi.org/10.1161/ATVBAHA.116.307023
- Mahley, R.W., Y. Huang, and S.C. Rall. 1999. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. J. Lipid Res. 40:1933–1949.
- Maia, L.F., S.A. Kaeser, J. Reichwald, M. Hruscha, P. Martus, M. Staufenbiel, and M. Jucker. 2013. Changes in amyloid-β and Tau in the cerebrospinal fluid of transgenic mice overexpressing amyloid precursor protein. *Sci. Transl. Med.* 5:194re2. https://doi.org/10.1126/scitranslmed.3006446
- Mak, A.C.Y., C.R. Pullinger, L.F. Tang, J.S. Wong, R.C. Deo, J.-M. Schwarz, A. Gugliucci, I. Movsesyan, B.Y. Ishida, C. Chu, et al. 2014. Effects of the absence of apolipoprotein e on lipoproteins, neurocognitive function, and retinal function. JAMA Neurol. 71:1228–1236. https://doi.org/10.1001/jamaneurol.2014.2011
- Mancuso, R., G. Fryatt, M. Cleal, J. Obst, E. Pipi, J. Monzón-Sandoval, E. Ribe, L. Winchester, C. Webber, A. Nevado, et al. 2019. CSF1R inhibitor JNJ-40346527 attenuates microglial proliferation and neurodegeneration in P301S mice. *Brain*. 142:3243-3264. https://doi.org/10.1093/brain/awz241
- Mandelkow, E.-M., and E. Mandelkow. 2012. Biochemistry and cell biology of tau protein in neurofibrillary degeneration. Cold Spring Harb. Perspect. Med. 2:a006247. https://doi.org/10.1101/cshperspect.a006247
- Marino, C., P. Perez-Corredor, M. O'Hare, A. Heuer, N. Chmielewska, H. Gordon, A.S. Chandrahas, L. Gonzalez-Buendia, S. Delgado-Tirado, T.H. Doan, et al. 2023. APOE Christchurch-mimetic therapeutic antibody reduces APOE-mediated toxicity and tau phosphorylation. Alzheimer's Dement. 20:819–836. https://doi.org/10.1002/alz.13436
- Marschallinger, J., T. Iram, M. Zardeneta, S.E. Lee, B. Lehallier, M.S. Haney, J.V. Pluvinage, V. Mathur, O. Hahn, D.W. Morgens, et al. 2020. Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. Nat. Neurosci. 23:194–208. https://doi.org/10.1038/s41593-019-0566-1



- Martens, Y.A., N. Zhao, C.-C. Liu, T. Kanekiyo, A.J. Yang, A.M. Goate, D.M. Holtzman, and G. Bu. 2022. ApoE Cascade Hypothesis in the pathogenesis of Alzheimer's disease and related dementias. *Neuron*. 110: 1304–1317. https://doi.org/10.1016/j.neuron.2022.03.004
- Martin, L., X. Latypova, and F. Terro. 2011. Post-translational modifications of tau protein: Implications for alzheimer's disease. Neurochem. Int. 58: 458-471. https://doi.org/10.1016/j.neuint.2010.12.023
- Martínez-Morillo, E., O. Hansson, Y. Atagi, G. Bu, L. Minthon, E.P. Diamandis, and H.M. Nielsen. 2014. Total apolipoprotein E levels and specific isoform composition in cerebrospinal fluid and plasma from Alzheimer's disease patients and controls. *Acta Neuropathol. (Berl.)*. 127:633–643. https://doi.org/10.1007/s00401-014-1266-2
- Maruyama, M., H. Shimada, T. Suhara, H. Shinotoh, B. Ji, J. Maeda, M.-R. Zhang, J.Q. Trojanowski, V.M.-Y. Lee, M. Ono, et al. 2013. Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron*. 79:1094-1108. https://doi.org/10.1016/j.neuron.2013.07.037
- Maté de Gérando, A., M. d'Orange, E. Augustin, C. Joséphine, G. Aurégan, M. Gaudin-Guérif, M. Guillermier, A.-S. Hérard, L. Stimmer, F. Petit, et al. 2021. Neuronal tau species transfer to astrocytes and induce their loss according to tau aggregation state. *Brain J. Neurol.* 144:1167–1182. https://doi.org/10.1093/brain/awab011
- Mathys, H., J. Davila-Velderrain, Z. Peng, F. Gao, S. Mohammadi, J.Z. Young, M. Menon, L. He, F. Abdurrob, X. Jiang, et al. 2019. Single-cell transcriptomic analysis of Alzheimer's disease. *Nature*. 570:332–337. https://doi.org/10.1038/s41586-019-1195-2
- Mathys, H., Z. Peng, C.A. Boix, M.B. Victor, N. Leary, S. Babu, G. Abdelhady, X. Jiang, A.P. Ng, K. Ghafari, et al. 2023. Single-cell atlas reveals correlates of high cognitive function, dementia, and resilience to Alzheimer's disease pathology. Cell. 186:4365–4385.e27. https://doi.org/10.1016/j.cell.2023.08.039
- Mattson, M.P., and T.V. Arumugam. 2018. Hallmarks of brain aging: Adaptive and pathological modification by metabolic states. *Cell Metab.* 27: 1176–1199. https://doi.org/10.1016/j.cmet.2018.05.011
- Mattsson, N., N.C. Cullen, U. Andreasson, H. Zetterberg, and K. Blennow. 2019. Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. *JAMA Neurol.* 76: 791–799. https://doi.org/10.1001/jamaneurol.2019.0765
- McInnes, J., K. Wierda, A. Snellinx, L. Bounti, Y.-C. Wang, I.-C. Stancu, N. Apóstolo, K. Gevaert, I. Dewachter, T.L. Spires-Jones, et al. 2018. Synaptogyrin-3 mediates presynaptic dysfunction induced by tau. Neuron. 97:823–835.e8. https://doi.org/10.1016/j.neuron.2018.01.022
- Minta, K., G. Brinkmalm, S. Janelidze, S. Sjödin, E. Portelius, E. Stomrud, H. Zetterberg, K. Blennow, O. Hansson, and U. Andreasson. 2020. Quantification of total apolipoprotein E and its isoforms in cerebrospinal fluid from patients with neurodegenerative diseases. Alzheimer's Res. Ther. 12:19. https://doi.org/10.1186/s13195-020-00585-7
- Mirbaha, H., D. Chen, O.A. Morazova, K.M. Ruff, A.M. Sharma, X. Liu, M. Goodarzi, R.V. Pappu, D.W. Colby, H. Mirzaei, et al. 2018. Inert and seed-competent tau monomers suggest structural origins of aggregation. Elife. 7:e36584. https://doi.org/10.7554/eLife.36584
- Mirra, S.S., J.R. Murrell, M. Gearing, M.G. Spillantini, M. Goedert, R.A. Crowther, A.I. Levey, R. Jones, J. Green, J.M. Shoffner, et al. 1999. Tau pathology in a family with dementia and a P301L mutation in tau. J. Neuropathol. Exp. Neurol. 58:335–345. https://doi.org/10.1097/00005072-199904000-00004
- Mishra, A., R. Ferrari, P. Heutink, J. Hardy, Y. Pijnenburg, D. Posthuma, and International ftd-Genomics Consortium. 2017. Gene-based association studies report genetic links for clinical subtypes of frontotemporal dementia. Brain. 140:1437-1446. https://doi.org/10.1093/brain/awx066
- Montagne, A., D.A. Nation, A.P. Sagare, G. Barisano, M.D. Sweeney, A. Chakhoyan, M. Pachicano, E. Joe, A.R. Nelson, L.M. D'Orazio, et al. 2020. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. Nature. 581:71–76. https://doi.org/10.1038/s41586-020-2247-3
- Montal, V., I. Diez, C.-M. Kim, W. Orwig, E. Bueichekú, R. Gutiérrez-Zúñiga, A. Bejanin, J. Pegueroles, O. Dols-Icardo, P. Vannini, et al. 2022. Network Tau spreading is vulnerable to the expression gradients of APOE and glutamatergic-related genes. Sci. Transl. Med. 14:eabn7273. https:// doi.org/10.1126/scitranslmed.abn7273
- Morris, J.C., S.E. Schindler, L.M. McCue, K.L. Moulder, T.L.S. Benzinger, C. Cruchaga, A.M. Fagan, E. Grant, B.A. Gordon, D.M. Holtzman, and C. Xiong. 2019. Assessment of racial disparities in biomarkers for Alzheimer disease. JAMA Neurol. 76:264–273. https://doi.org/10.1001/jamaneurol.2018.4249
- Mummery, C.J., A. Börjesson-Hanson, D.J. Blackburn, E.G.B. Vijverberg, P.P. De Deyn, S. Ducharme, M. Jonsson, A. Schneider, J.O. Rinne, A.C.

- Ludolph, et al. 2023. Tau-targeting antisense oligonucleotide MAPTRx in mild alzheimer's disease: A phase 1b, randomized, placebo-controlled trial. *Nat. Med.* 29:1437–1447. https://doi.org/10.1038/s41591-023-02326
- Musiek, E.S., and D.M. Holtzman. 2012. Origins of Alzheimer's disease: Reconciling cerebrospinal fluid biomarker and neuropathology data regarding the temporal sequence of amyloid-beta and tau involvement. Curr. Opin. Neurol. 25:715-720. https://doi.org/10.1097/WCO .0b013e32835a30f4
- Myers, A., and P. McGonigle. 2019. Overview of transgenic mouse models for alzheimer's disease. *Curr. Protoc. Neurosci.* 89:e81. https://doi.org/10.1002/cpns.81
- Namba, Y., M. Tomonaga, H. Kawasaki, E. Otomo, and K. Ikeda. 1991. Apolioprotein E immunoreactivity in cerebral amyloid deposits and neurofibrillary tangles in Alzheimer's disease and kuru plaque amyloid in Creutzfeldt-Jakob disease. Brain Res. 541:163–166. https://doi.org/10.1016/0006-8993(91)91092-f
- Narasimhan, S., J.L. Guo, L. Changolkar, A. Stieber, J.D. McBride, L.V. Silva, Z. He, B. Zhang, R.J. Gathagan, J.Q. Trojanowski, and V.M.Y. Lee. 2017. Pathological tau strains from human brains recapitulate the diversity of tauopathies in nontransgenic mouse brain. J. Neurosci. 37:11406–11423. https://doi.org/10.1523/JNEUROSCI.1230-17.2017
- Naseri, N.N., H. Wang, J. Guo, M. Sharma, and W. Luo. 2019. The complexity of tau in Alzheimer's disease. Neurosci. Lett. 705:183–194. https://doi .org/10.1016/j.neulet.2019.04.022
- Nelson, M.R., P. Liu, A. Agrawal, O. Yip, J. Blumenfeld, M. Traglia, M.J. Kim, N. Koutsodendris, A. Rao, B. Grone, et al. 2023. The APOE-R136S mutation protects against APOE4-driven Tau pathology, neuro-degeneration and neuroinflammation. Nat. Neurosci. 26:2104–2121. https://doi.org/10.1038/s41593-023-01480-8
- Nicoll, J.a. R., G.M. Savva, J. Stewart, F.E. Matthews, C. Brayne, P. Ince, and Medical Research Council Cognitive Function and Ageing Study. 2011. Association between APOE genotype, neuropathology and dementia in the older population of England and Wales. Neuropathol. Appl. Neurobiol. 37:285-294. https://doi.org/10.1111/j.1365-2990.2010.01130.x
- Nordestgaard, L.T., A. Tybjærg-Hansen, B.G. Nordestgaard, and R. Frikke-Schmidt. 2015. Loss-of-function mutation in ABCA1 and risk of Alzheimer's disease and cerebrovascular disease. Alzheimer's Dement. J. Alzheimer's Assoc. 11:1430-1438. https://doi.org/10.1016/j.jalz.2015.04.006
- Nugent, A.A., K. Lin, B. van Lengerich, S. Lianoglou, L. Przybyla, S.S. Davis, C. Llapashtica, J. Wang, D.J. Kim, D. Xia, et al. 2020. TREM2 regulates microglial cholesterol metabolism upon chronic phagocytic challenge. Neuron. 105:837–854.e9. https://doi.org/10.1016/j.neuron.2019.12.007
- Nygaard, H.B. 2018. Targeting fyn kinase in Alzheimer's disease. Biol. Psychiatry. 83:369–376. https://doi.org/10.1016/j.biopsych.2017.06.004
- Oakley, H., S.L. Cole, S. Logan, E. Maus, P. Shao, J. Craft, A. Guillozet-Bongaarts, M. Ohno, J. Disterhoft, L. Van Eldik, et al. 2006. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial alzheimer's disease mutations: Potential factors in amyloid plaque formation. *J. Neurosci.* 26:10129–10140. https://doi.org/10.1523/JNEUROSCI.1202-06.2006
- Oh, J.-M., M. An, D.-S. Son, J. Choi, Y.B. Cho, C.E. Yoo, and W.-Y. Park. 2022. Comparison of cell type distribution between single-cell and single-nucleus RNA sequencing: Enrichment of adherent cell types in single-nucleus RNA sequencing. Exp. Mol. Med. 54:2128–2134. https://doi.org/10.1038/s12276-022-00892-z
- Olney, K.C., K.A. Gibson, M.P. Cadiz, N. Rahimzadeh, V. Swarup, and J.D. Fryer. 2025. Postmortem interval leads to loss of disease-specific signatures in brain tissue. *eNeuro*. 12:ENEURO.0505-24.2025. https://doi.org/10.1523/ENEURO.0505-24.2025
- Olsson, B., R. Lautner, U. Andreasson, A. Öhrfelt, E. Portelius, M. Bjerke, M. Hölttä, C. Rosén, C. Olsson, G. Strobel, et al. 2016. CSF and blood biomarkers for the diagnosis of alzheimer's disease: A systematic review and meta-analysis. *Lancet Neurol*. 15:673–684. https://doi.org/10.1016/S1474-4422(16)00070-3
- Ondrejcak, T., I. Klyubin, G.T. Corbett, G. Fraser, W. Hong, A.J. Mably, M. Gardener, J. Hammersley, M.S. Perkinton, A. Billinton, et al. 2018. Cellular prion protein mediates the disruption of hippocampal synaptic plasticity by soluble tau in vivo. *J. Neurosci.* 38:10595–10606. https://doi.org/10.1523/JNEUROSCI.1700-18.2018
- Ossenkoppele, R., D.R. Schonhaut, M. Schöll, S.N. Lockhart, N. Ayakta, S.L. Baker, J.P. O'Neil, M. Janabi, A. Lazaris, A. Cantwell, et al. 2016. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain*. 139:1551–1567. https://doi.org/10.1093/brain/aww027



- Ossenkoppele, R., J. Reimand, R. Smith, A. Leuzy, O. Strandberg, S. Palmqvist, E. Stomrud, H. Zetterberg, Alzheimer's Disease Neuroimaging Initiative, P. Scheltens, et al. 2021. Tau PET correlates with different Alzheimer's disease-related features compared to CSF and plasma p-tau biomarkers. EMBO Mol. Med. 13:e14398. https://doi.org/10.15252/emmm.202114398
- Ossenkoppele, R., R. van der Kant, and O. Hansson. 2022. Tau biomarkers in Alzheimer's disease: Towards implementation in clinical practice and trials. Lancet Neurol. 21:726–734. https://doi.org/10.1016/S1474-4422(22)00168-5
- Parhizkar, S., and D.M. Holtzman. 2022. APOE mediated neuroinflammation and neurodegeneration in Alzheimer's disease. Semin. Immunol. 59: 101594. https://doi.org/10.1016/j.smim.2022.101594
- Parhizkar, S., T. Arzberger, M. Brendel, G. Kleinberger, M. Deussing, C. Focke, B. Nuscher, M. Xiong, A. Ghasemigharagoz, N. Katzmarski, et al. 2019. Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. Nat. Neurosci. 22:191–204. https://doi.org/10.1038/s41593-018-0296-9
- Parhizkar, S., G. Gent, Y. Chen, N. Rensing, M. Gratuze, G. Strout, S. Sviben, E. Tycksen, Q. Zhang, P.E. Gilmore, et al. 2023. Sleep deprivation exacerbates microglial reactivity and A β deposition in a TREM2-dependent manner in mice. *Sci. Transl. Med.* 15:eade6285. https://doi.org/10.1126/scitranslmed.ade6285
- Perdigão, C., M.A. Barata, M.N. Araújo, F.S. Mirfakhar, J. Castanheira, and C. Guimas Almeida. 2020. Intracellular trafficking mechanisms of synaptic dysfunction in Alzheimer's disease. Front. Cell. Neurosci. 14:72. https://doi.org/10.3389/fncel.2020.00072
- Perea, J.R., E. López, J.C. Díez-Ballesteros, J. Ávila, F. Hernández, and M. Bolós. 2019. Extracellular monomeric tau is internalized by astrocytes. Front. Neurosci. 13:442. https://doi.org/10.3389/fnins.2019.00442
- Perrin, R.J., A.M. Fagan, and D.M. Holtzman. 2009. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature*. 461:916–922. https://doi.org/10.1038/nature08538
- Pickett, E.K., C.M. Henstridge, E. Allison, R. Pitstick, A. Pooler, S. Wegmann, G. Carlson, B.T. Hyman, and T.L. Spires-Jones. 2017. Spread of tau down neural circuits precedes synapse and neuronal loss in the rTgTauEC mouse model of early Alzheimer's disease. Synapse. 71:e21965. https://doi.org/10.1002/syn.21965
- Pooler, A.M., M. Polydoro, E.A. Maury, S.B. Nicholls, S.M. Reddy, S. Wegmann, C. William, L. Saqran, O. Cagsal-Getkin, R. Pitstick, et al. 2015. Amyloid accelerates tau propagation and toxicity in a model of early Alzheimer's disease. Acta Neuropathol. Commun. 3:14. https://doi.org/10.1186/s40478-015-0199-x
- Pottier, C., D. Hannequin, S. Coutant, A. Rovelet-Lecrux, D. Wallon, S. Rousseau, S. Legallic, C. Paquet, S. Bombois, J. Pariente, et al. 2012. High frequency of potentially pathogenic SORL1 mutations in autosomal dominant early-onset Alzheimer disease. *Mol. Psychiatry*. 17:875–879. https://doi.org/10.1038/mp.2012.15
- Quiroz, Y.T., D. Aguillon, D.C. Aguirre-Acevedo, D. Vasquez, Y. Zuluaga, A.Y. Baena, L. Madrigal, L. Hincapié, J.S. Sanchez, S. Langella, et al. 2024. APOE3 christchurch heterozygosity and autosomal dominant Alzheimer's disease. N. Engl. J. Med. 390:2156-2164. https://doi.org/10.1056/NEJMoa2308583
- Ramanan, V.K., A.M. Castillo, D.S. Knopman, J. Graff-Radford, V.J. Lowe, R.C. Petersen, C.R. Jack, M.M. Mielke, and P. Vemuri. 2019. Association of apolipoprotein Ε ε4, educational level, and sex with tau deposition and tau-mediated metabolic dysfunction in older adults. *JAMA Netw. Open.* 2: e1913909. https://doi.org/10.1001/jamanetworkopen.2019.13909
- Rauch, J.N., J.J. Chen, A.W. Sorum, G.M. Miller, T. Sharf, S.K. See, L.C. Hsieh-Wilson, M. Kampmann, and K.S. Kosik. 2018. Tau internalization is regulated by 6-O sulfation on heparan sulfate proteoglycans (HSPGs). Sci. Rep. 8:6382. https://doi.org/10.1038/s41598-018-24904-z
- Rauch, J.N., G. Luna, E. Guzman, M. Audouard, C. Challis, Y.E. Sibih, C. Leshuk, I. Hernandez, S. Wegmann, B.T. Hyman, et al. 2020. LRP1 is a master regulator of tau uptake and spread. *Nature*. 580:381–385. https://doi.org/10.1038/s41586-020-2156-5
- Raulin, A.-C., S.V. Doss, Z.A. Trottier, T.C. Ikezu, G. Bu, and C.-C. Liu. 2022. ApoE in Alzheimer's disease: Pathophysiology and therapeutic strategies. *Mol. Neurodegener*. 17:72. https://doi.org/10.1186/s13024-022-00574-4
- Riddell, D.R., H. Zhou, K. Atchison, H.K. Warwick, P.J. Atkinson, J. Jefferson, L. Xu, S. Aschmies, Y. Kirksey, Y. Hu, et al. 2008. Impact of apolipoprotein E (ApoE) polymorphism on brain ApoE levels. J. Neurosci. 28: 11445–11453. https://doi.org/10.1523/JNEUROSCI.1972-08.2008
- Robbins, M., E. Clayton, and G.S. Kaminski Schierle. 2021. Synaptic tau: A pathological or physiological phenomenon? *Acta Neuropathol. Commun.* 9:149. https://doi.org/10.1186/s40478-021-01246-y

- Robinson, A.C., Y.S. Davidson, F. Roncaroli, J. Minshull, P. Tinkler, M.A. Horan, A. Payton, N. Pendleton, and D.M.A. Mann. 2020. Influence of APOE genotype in primary age-related tauopathy. Acta Neuropathol. Commun. 8:215. https://doi.org/10.1186/s40478-020-01095-1
- Rodriguez, G.A., M.P. Burns, E.J. Weeber, and G.W. Rebeck. 2013. Young APOE4 targeted replacement mice exhibit poor spatial learning and memory, with reduced dendritic spine density in the medial entorhinal cortex. *Learn. Mem.* 20:256–266. https://doi.org/10.1101/lm.030031.112
- Rohn, T.T., L.W. Catlin, K.G. Coonse, and J.W. Habig. 2012. Identification of an amino-terminal fragment of apolipoprotein E4 that localizes to neurofibrillary tangles of the Alzheimer's disease brain. *Brain Res.* 1475: 106-115. https://doi.org/10.1016/j.brainres.2012.08.003
- Sabbagh, M.N., M. Malek-Ahmadi, B.N. Dugger, K. Lee, L.I. Sue, G. Serrano, D.G. Walker, K. Davis, S.A. Jacobson, and T.G. Beach. 2013. The influence of Apolipoprotein E genotype on regional pathology in Alzheimer's disease. *BMC Neurol*. 13:44. https://doi.org/10.1186/1471-2377-13-44
- Sadick, J.S., M.R. O'Dea, P. Hasel, T. Dykstra, A. Faustin, and S.A. Liddelow. 2022. Astrocytes and oligodendrocytes undergo subtype-specific transcriptional changes in Alzheimer's disease. *Neuron*. 110:1788–1805.e10. https://doi.org/10.1016/j.neuron.2022.03.008
- Sadleir, K.R., and R. Vassar. 2023. Connections between ApoE, sleep, and Aβ and tau pathologies in Alzheimer's disease. *J. Clin. Invest.* 133:e171838. https://doi.org/10.1172/JCII71838
- Saito, T., N. Mihira, Y. Matsuba, H. Sasaguri, S. Hashimoto, S. Narasimhan, B. Zhang, S. Murayama, M. Higuchi, V.M.Y. Lee, et al. 2019. Humanization of the entire murine Mapt gene provides a murine model of pathological human tau propagation. J. Biol. Chem. 294:12754–12765. https://doi.org/10.1074/jbc.RA119.009487
- Salvadó, G., M.J. Grothe, C. Groot, A. Moscoso, M. Schöll, J.D. Gispert, R. Ossenkoppele, and Alzheimer's Disease Neuroimaging Initiative. 2021. Differential associations of APOE-ε2 and APOE-ε4 alleles with PET-measured amyloid-β and tau deposition in older individuals without dementia. Eur. J. Nucl. Med. Mol. Imaging. 48:2212–2224. https://doi.org/10.1007/s00259-021-05192-8
- Sanchez, J.S., J.A. Becker, H.I.L. Jacobs, B.J. Hanseeuw, S. Jiang, A.P. Schultz, M.J. Properzi, S.R. Katz, A. Beiser, C.L. Satizabal, et al. 2021. The cortical origin and initial spread of medial temporal tauopathy in Alzheimer's disease assessed with positron emission tomography. Sci. Transl. Med. 13:eabc0655. https://doi.org/10.1126/scitranslmed.abc0655
- Sanchez-Varo, R., M. Mejias-Ortega, J.J. Fernandez-Valenzuela, C. Nuñez-Diaz, L. Caceres-Palomo, L. Vegas-Gomez, E. Sanchez-Mejias, L. Tru-jillo-Estrada, J.A. Garcia-Leon, I. Moreno-Gonzalez, et al. 2022. Transgenic mouse models of Alzheimer's disease: An integrative analysis. *Int. J. Mol. Sci.* 23:5404. https://doi.org/10.3390/ijms23105404
- Sayed, F.A., M. Telpoukhovskaia, L. Kodama, Y. Li, Y. Zhou, D. Le, A. Hauduc, C. Ludwig, F. Gao, C. Clelland, et al. 2018. Differential effects of partial and complete loss of TREM2 on microglial injury response and tauopathy. Proc. Natl. Acad. Sci. USA. 115:10172–10177. https://doi.org/10.1073/pnas.1811411115
- Schindowski, K., A. Bretteville, K. Leroy, S. Bégard, J.-P. Brion, M. Hamdane, and L. Buée. 2006. Alzheimer's disease-like tau neuropathology leads to memory deficits and loss of functional synapses in a novel mutated tau transgenic mouse without any motor deficits. Am. J. Pathol. 169:599–616. https://doi.org/10.2353/ajpath.2006.060002
- Sekiya, M., M. Wang, N. Fujisaki, Y. Sakakibara, X. Quan, M.E. Ehrlich, P.L. De Jager, D.A. Bennett, E.E. Schadt, S. Gandy, et al. 2018. Integrated biology approach reveals molecular and pathological interactions among Alzheimer's Aβ42, Tau, TREM2, and TYROBP in Drosophila models. Genome Med. 10:26. https://doi.org/10.1186/s13073-018-0530-9
- Self, W.K., and D.M. Holtzman. 2023. Emerging diagnostics and therapeutics for Alzheimer disease. Nat. Med. 29:2187–2199. https://doi.org/10.1038/ s41591-023-02505-2
- Selkoe, D.J. 2002. Alzheimer's disease is a synaptic failure. Science. 298: 789-791. https://doi.org/10.1126/science.1074069
- Seo, J., O. Kritskiy, L.A. Watson, S.J. Barker, D. Dey, W.K. Raja, Y.-T. Lin, T. Ko, S. Cho, J. Penney, et al. 2017. Inhibition of p25/Cdk5 attenuates tauopathy in mouse and iPSC models of frontotemporal dementia. *J. Neurosci.* 37:9917–9924. https://doi.org/10.1523/JNEUROSCI.0621-17.2017
- Seo, D.-O., D. O'Donnell, N. Jain, J.D. Ulrich, J. Herz, Y. Li, M. Lemieux, J. Cheng, H. Hu, J.R. Serrano, et al. 2023. ApoE isoform- and microbiota-dependent progression of neurodegeneration in a mouse model of tauopathy. Science. 379:eadd1236. https://doi.org/10.1126/science.add1236
- Sepulveda-Falla, D., J.S. Sanchez, M.C. Almeida, D. Boassa, J. Acosta-Uribe, C. Vila-Castelar, L. Ramirez-Gomez, A. Baena, D. Aguillon, N.D. Villalba-



- Moreno, et al. 2022. Distinct tau neuropathology and cellular profiles of an APOE3 Christchurch homozygote protected against autosomal dominant Alzheimer's dementia. *Acta Neuropathol.* (Berl.). 144:589–601. https://doi.org/10.1007/s00401-022-02467-8
- Serrano-Pozo, A., S. Das, and B.T. Hyman. 2021. APOE and Alzheimer's disease: Advances in genetics, pathophysiology, and therapeutic approaches. *Lancet Neurol.* 20:68-80. https://doi.org/10.1016/S1474-4422(20)30412-9
- Shentu, Y.-P., Y. Huo, X.-L. Feng, J. Gilbert, Q. Zhang, Z.-Y. Liuyang, X.-L. Wang, G. Wang, H. Zhou, X.-C. Wang, et al. 2018. CIP2A Causes Tau/APP phosphorylation, synaptopathy, and memory deficits in Alzheimer's disease. Cell Rep. 24:713-723. https://doi.org/10.1016/j.celrep.2018.06.009
- Shi, Y., K. Yamada, S.A. Liddelow, S.T. Smith, L. Zhao, W. Luo, R.M. Tsai, S. Spina, L.T. Grinberg, J.C. Rojas, et al. 2017. ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature*. 549:523–527. https://doi.org/10.1038/nature24016
- Shi, Y., M. Manis, J. Long, K. Wang, P.M. Sullivan, J. Remolina Serrano, R. Hoyle, and D.M. Holtzman. 2019. Microglia drive APOE-dependent neurodegeneration in a tauopathy mouse model. J. Exp. Med. 216: 2546–2561. https://doi.org/10.1084/jem.20190980
- Shi, Y., P.S. Andhey, C. Ising, K. Wang, L.L. Snipes, K. Boyer, S. Lawson, K. Yamada, W. Qin, M. Manis, et al. 2021a. Overexpressing low-density lipoprotein receptor reduces tau-associated neurodegeneration in relation to apoE-linked mechanisms. *Neuron.* 109:2413–2426.e7. https://doi.org/10.1016/j.neuron.2021.05.034
- Shi, Y., W. Zhang, Y. Yang, A.G. Murzin, B. Falcon, A. Kotecha, M. van Beers, A. Tarutani, F. Kametani, H.J. Garringer, et al. 2021b. Structure-based classification of tauopathies. *Nature*. 598:359–363. https://doi.org/10 .1038/s41586-021-03911-7
- Sidoryk-Wegrzynowicz, M., Y.N. Gerber, M. Ries, M. Sastre, A.M. Tolkovsky, and M.G. Spillantini. 2017. Astrocytes in mouse models of tauopathies acquire early deficits and lose neurosupportive functions. Acta Neuropathol. Commun. 5:89. https://doi.org/10.1186/s40478-017-0478-9
- Sierksma, A., A. Lu, R. Mancuso, N. Fattorelli, N. Thrupp, E. Salta, J. Zoco, D. Blum, L. Buée, B. De Strooper, and M. Fiers. 2020. Novel Alzheimer risk genes determine the microglia response to amyloid-β but not to TAU pathology. EMBO Mol. Med. 12:e10606. https://doi.org/10.15252/emmm.201910606
- Singh, N.A., N. Tosakulwong, J. Graff-Radford, M.M. Machulda, N.T.T. Pham, I. Sintini, S.D. Weigand, C.G. Schwarz, M.L. Senjem, M.M. Carrasquillo, et al. 2023. APOE ε4 influences medial temporal atrophy and tau deposition in atypical Alzheimer's disease. *Alzheimer's Dement*. 19:784–796. https://doi.org/10.1002/alz.12711
- Sinsky, J., K. Pichlerova, and J. Hanes. 2021. Tau protein interaction partners and their roles in Alzheimer's disease and other tauopathies. *Int. J. Mol. Sci.* 22:9207. https://doi.org/10.3390/ijms22179207
- Skillbäck, T., C. Rosén, F. Asztely, N. Mattsson, K. Blennow, and H. Zetterberg. 2014. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: Results from the Swedish Mortality Registry. JAMA Neurol. 71:476–483. https://doi.org/10.1001/jamaneurol.2013.6455
- Smith, A.M., K. Davey, S. Tsartsalis, C. Khozoie, N. Fancy, S.S. Tang, E. Liaptsi, M. Weinert, A. McGarry, R.C.J. Muirhead, et al. 2022. Diverse human astrocyte and microglial transcriptional responses to Alzheimer's pathology. Acta Neuropathol. 143:75–91. https://doi.org/10.1007/s00401-021-02372-6
- Sotiropoulos, I., M.-C. Galas, J.M. Silva, E. Skoulakis, S. Wegmann, M.B. Maina, D. Blum, C.L. Sayas, E.-M. Mandelkow, E. Mandelkow, et al. 2017. Atypical, non-standard functions of the microtubule associated Tau protein. Acta Neuropathol. Commun. 5:91. https://doi.org/10.1186/s40478-017-0489-6
- Stark, R., M. Grzelak, and J. Hadfield. 2019. RNA sequencing: The teenage years. Nat. Rev. Genet. 20:631-656. https://doi.org/10.1038/s41576-019 -0150-2
- Steele, O.G., A.C. Stuart, L. Minkley, K. Shaw, O. Bonnar, S. Anderle, A.C. Penn, J. Rusted, L. Serpell, C. Hall, and S. King. 2022. A multi-hit hypothesis for an APOE4-dependent pathophysiological state. Eur. J. Neurosci. 56:5476–5515. https://doi.org/10.1111/ejn.15685
- Stieler, J.T., T. Bullmann, F. Kohl, Ø. Tøien, M.K. Brückner, W. Härtig, B.M. Barnes, and T. Arendt. 2011. The physiological link between metabolic rate depression and tau phosphorylation in mammalian hibernation. *PLoS ONE*. 6:e14530. https://doi.org/10.1371/journal.pone.0014530
- Strickland, M.R., M.J. Rau, B. Summers, K. Basore, J. Wulf, H. Jiang, Y. Chen, J.D. Ulrich, G.J. Randolph, R. Zhang, et al. 2024. Apolipoprotein E

- secreted by astrocytes forms antiparallel dimers in discoidal lip-oproteins. *Neuron*. 112:1100–1109.e5. https://doi.org/10.1016/j.neuron.2023.12.018
- Strittmatter, W.J., A.M. Saunders, D. Schmechel, M. Pericak-Vance, J. Enghild, G.S. Salvesen, and A.D. Roses. 1993. Apolipoprotein E: Highavidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial alzheimer disease. *Proc. Natl. Acad. Sci. USA*. 90:1977–1981. https://doi.org/10.1073/pnas.90.5.1977
- Strittmatter, W.J., A.M. Saunders, M. Goedert, K.H. Weisgraber, L.M. Dong, R. Jakes, D.Y. Huang, M. Pericak-Vance, D. Schmechel, and A.D. Roses. 1994. Isoform-specific interactions of apolipoprotein E with microtubule-associated protein tau: Implications for alzheimer disease. Proc. Natl. Acad. Sci. USA. 91:11183-11186. https://doi.org/10.1073/pnas.91.23.11183
- Sun, N., M.B. Victor, Y.P. Park, X. Xiong, A.N. Scannail, N. Leary, S. Prosper, S. Viswanathan, X. Luna, C.A. Boix, et al. 2023. Human microglial state dynamics in Alzheimer's disease progression. *Cell.* 186:4386–4403.e29. https://doi.org/10.1016/j.cell.2023.08.037
- Takeda, S., S. Wegmann, H. Cho, S.L. DeVos, C. Commins, A.D. Roe, S.B. Nicholls, G.A. Carlson, R. Pitstick, C.K. Nobuhara, et al. 2015. Neuronal uptake and propagation of a rare phosphorylated high-molecular-weight tau derived from Alzheimer's disease brain. Nat. Commun. 6: 8490. https://doi.org/10.1038/ncomms9490
- Tcw, J., L. Qian, N.H. Pipalia, M.J. Chao, S.A. Liang, Y. Shi, B.R. Jain, S.E. Bertelsen, M. Kapoor, E. Marcora, et al. 2022. Cholesterol and matrisome pathways dysregulated in astrocytes and microglia. Cell. 185: 2213–2233.e25. https://doi.org/10.1016/j.cell.2022.05.017
- Teng, E., P.T. Manser, K. Pickthorn, F. Brunstein, M. Blendstrup, S. Sanabria Bohorquez, K.R. Wildsmith, B. Toth, M. Dolton, V. Ramakrishnan, et al. 2022. Safety and efficacy of semorinemab in individuals with prodromal to mild alzheimer disease: A randomized clinical trial. *JAMA Neurol*. 79:758-767. https://doi.org/10.1001/jamaneurol.2022.1375
- Tensaouti, Y., T.-S. Yu, and S.G. Kernie. 2020. Apolipoprotein E regulates the maturation of injury-induced adult-born hippocampal neurons following traumatic brain injury. PLoS One. 15:e0229240. https://doi.org/ 10.1371/journal.pone.0229240
- Therriault, J., A.L. Benedet, T.A. Pascoal, S. Mathotaarachchi, M. Chamoun, M. Savard, E. Thomas, M.S. Kang, F. Lussier, C. Tissot, et al. 2020. Association of apolipoprotein E ε4 with medial temporal tau independent of amyloid-β. JAMA Neurol. 77:470-479. https://doi.org/10.1001/jamaneurol.2019.4421
- Therriault, J., A.L. Benedet, T.A. Pascoal, S. Mathotaarachchi, M. Savard, M. Chamoun, E. Thomas, M.S. Kang, F. Lussier, C. Tissot, et al. 2021. APOEε4 potentiates the relationship between amyloid-β and tau pathologies. Mol. Psychiatry. 26:5977–5988. https://doi.org/10.1038/s41380-020-0688-6
- Thrupp, N., C. Sala Frigerio, L. Wolfs, N.G. Skene, N. Fattorelli, S. Poovathingal, Y. Fourne, P.M. Matthews, T. Theys, R. Mancuso, et al. 2020. Single-nucleus RNA-Seq Is not suitable for detection of microglial activation genes in humans. Cell Rep. 32:108189. https://doi.org/10.1016/j.celrep.2020.108189
- Tiraboschi, P., L.A. Hansen, E. Masliah, M. Alford, L.J. Thal, and J. Corey-Bloom. 2004. Impact of APOE genotype on neuropathologic and neurochemical markers of Alzheimer disease. *Neurology*. 62:1977–1983. https://doi.org/10.1212/01.wnl.0000128091.92139.0f
- Toledo, J.B., H. Zetterberg, A.C. van Harten, L. Glodzik, P. Martinez-Lage, L. Bocchio-Chiavetto, L. Rami, O. Hansson, R. Sperling, S. Engelborghs, et al. 2015. Alzheimer's disease cerebrospinal fluid biomarker in cognitively normal subjects. *Brain*. 138:2701-2715. https://doi.org/10.1093/brain/awv199
- Tran, K.M., N.E. Kwang, C.A. Butler, A. Gomez-Arboledas, S. Kawauchi, C. Mar, D. Chao, R.A. Barahona, C. Da Cunha, K.I. Tsourmas, et al. 2025. APOE Christchurch enhances a disease-associated microglial response to plaque but suppresses response to tau pathology. Mol. Neurodegener. 20:9. https://doi.org/10.1186/s13024-024-00793-x
- Trommer, B.L., C. Shah, S.H. Yun, G. Gamkrelidze, E.S. Pasternak, G.L. Ye, M. Sotak, P.M. Sullivan, J.F. Pasternak, and M.J. LaDu. 2004. ApoE isoform affects LTP in human targeted replacement mice. Neuroreport. 15: 2655–2658. https://doi.org/10.1097/00001756-200412030-00020
- Tuck, B.J., L.V.C. Miller, T. Katsinelos, A.E. Smith, E.L. Wilson, S. Keeling, S. Cheng, M.J. Vaysburd, C. Knox, L. Tredgett, et al. 2022. Cholesterol determines the cytosolic entry and seeded aggregation of tau. Cell Rep. 39:110776. https://doi.org/10.1016/j.celrep.2022.110776
- Tulloch, J., L. Leong, Z. Thomson, S. Chen, E.-G. Lee, C.D. Keene, S.P. Millard, and C.-E. Yu. 2018. Glia-specific APOE epigenetic changes in the



- Alzheimer's disease brain. *Brain Res.* 1698:179–186. https://doi.org/10.1016/j.brainres.2018.08.006
- Tzioras, M., C. Davies, A. Newman, R. Jackson, and T. Spires-Jones. 2019. Invited review: APOE at the interface of inflammation, neuro-degeneration and pathological protein spread in alzheimer's disease. Neuropathol. Appl. Neurobiol. 45:327–346. https://doi.org/10.1111/nan 12529
- Ulrich, J.D., T.K. Ulland, M. Colonna, and D.M. Holtzman. 2017. Elucidating the role of TREM2 in Alzheimer's disease. *Neuron*. 94:237–248. https://doi.org/10.1016/j.neuron.2017.02.042
- van der Kant, R., L.S.B. Goldstein, and R. Ossenkoppele. 2020. Amyloid-β-independent regulators of tau pathology in Alzheimer disease. *Nat. Rev. Neurosci.* 21:21–35. https://doi.org/10.1038/s41583-019-0240-3
- Vance, J.E., and H. Hayashi. 2010. Formation and function of apolipoprotein E-containing lipoproteins in the nervous system. Biochim. Biophys. Acta. 1801:806–818. https://doi.org/10.1016/j.bbalip.2010.02.007
- Vance, J.M., L.A. Farrer, Y. Huang, C. Cruchaga, B.T. Hyman, M.A. Pericak-Vance, A.M. Goate, M.D. Greicius, A.J. Griswold, J.L. Haines, et al. 2024. Report of the APOE4 National Institute on Aging/Alzheimer disease sequencing project consortium working group: Reducing APOE4 in carriers is a therapeutic goal for Alzheimer's disease. Ann. Neurol. 95: 625-634. https://doi.org/10.1002/ana.26864
- Vautheny, A., C. Duwat, G. Aurégan, C. Joséphine, A.-S. Hérard, C. Jan, J. Mitja, P. Gipchtein, M.-C. Gaillard, L. Buée, et al. 2021. THY-Tau22 mouse model accumulates more tauopathy at late stage of the disease in response to microglia deactivation through TREM2 deficiency. Neurobiol. Dis. 155:105398. https://doi.org/10.1016/j.nbd.2021.105398
- Victor, M.B., N. Leary, X. Luna, H.S. Meharena, A.N. Scannail, P.L. Bozzelli, G. Samaan, M.H. Murdock, D. von Maydell, A.H. Effenberger, et al. 2022. Lipid accumulation induced by APOE4 impairs microglial surveillance of neuronal-network activity. *Cell Stem Cell*. 29:1197–1212.e8. https://doi.org/10.1016/j.stem.2022.07.005
- Vogel, J.W., Y. Iturria-Medina, O.T. Strandberg, R. Smith, E. Levitis, A.C. Evans, O. Hansson, Alzheimer's Disease Neuroimaging Initiative, and Swedish BioFinder Study. 2020. Spread of pathological tau proteins through communicating neurons in human Alzheimer's disease. *Nat. Commun.* 11:2612. https://doi.org/10.1038/s41467-020-15701-2
- Vogel, J.W., A.L. Young, N.P. Oxtoby, R. Smith, R. Ossenkoppele, O.T. Strandberg, R. La Joie, L.M. Aksman, M.J. Grothe, Y. Iturria-Medina, et al. 2021. Four distinct trajectories of tau deposition identified in Alzheimer's disease. Nat. Med. 27:871–881. https://doi.org/10.1038/s41591-021-01309-6
- Wadhwani, A.R., A. Affaneh, S. Van Gulden, and J.A. Kessler. 2019. Neuronal apolipoprotein E4 increases cell death and phosphorylated tau release in alzheimer disease. Ann. Neurol. 85:726-739. https://doi.org/10.1002/ana .25455
- Waheed, Z., J. Choudhary, F.H. Jatala, null Fatimah, A. Noor, I. Zerr, and S. Zafar. 2023. The role of Tau proteoforms in health and disease. Mol. Neurobiol. 60:5155–5166. https://doi.org/10.1007/s12035-023-03387-8
- Wallin, A.K., K. Blennow, H. Zetterberg, E. Londos, L. Minthon, and O. Hansson. 2010. CSF biomarkers predict a more malignant outcome in Alzheimer disease. *Neurology*. 74:1531–1537. https://doi.org/10.1212/WNL.0b013e3181dd4dd8
- Wang, C., and D.M. Holtzman. 2020. Bidirectional relationship between sleep and Alzheimer's disease: Role of amyloid, tau, and other factors. Neuropsychopharmacology. 45:104–120. https://doi.org/10.1038/s41386-019 -0478-5
- Wang, P., and Y. Ye. 2021. Filamentous recombinant human Tau activates primary astrocytes via an integrin receptor complex. *Nat. Commun.* 12: 95. https://doi.org/10.1038/s41467-020-20322-w
- Wang, C., R. Najm, Q. Xu, D.-E. Jeong, D. Walker, M.E. Balestra, S.Y. Yoon, H. Yuan, G. Li, Z.A. Miller, et al. 2018. Gain of toxic apolipoprotein E4 effects in human iPSC-derived neurons is ameliorated by a small-molecule structure corrector. Nat. Med. 24:647–657. https://doi.org/10.1038/s41591-018-0004-z
- Wang, C., M. Xiong, M. Gratuze, X. Bao, Y. Shi, P.S. Andhey, M. Manis, C. Schroeder, Z. Yin, C. Madore, et al. 2021. Selective removal of astrocytic APOE4 strongly protects against tau-mediated neurodegeneration and decreases synaptic phagocytosis by microglia. *Neuron*. 109:1657–1674.e7. https://doi.org/10.1016/j.neuron.2021.03.024
- Wang, C., A. Nambiar, M.R. Strickland, C. Lee, S. Parhizkar, A.C. Moore, E.S. Musiek, J.D. Ulrich, and D.M. Holtzman. 2023. APOE- $\epsilon 4$ synergizes with sleep disruption to accelerate A β deposition and A β -associated tau seeding and spreading. *J. Clin. Invest.* 133:e169131. https://doi.org/10.1172/JCI169131

- Wattmo, C., K. Blennow, and O. Hansson. 2020. Cerebro-spinal fluid biomarker levels: Phosphorylated tau (T) and total tau (N) as markers for rate of progression in alzheimer's disease. *BMC Neurol*. 20:10. https://doi.org/10.1186/s12883-019-1591-0
- Wegmann, S., R.E. Bennett, L. Delorme, A.B. Robbins, M. Hu, D. McKenzie, M.J. Kirk, J. Schiantarelli, N. Tunio, A.C. Amaral, et al. 2019. Experimental evidence for the age dependence of tau protein spread in the brain. Sci. Adv. 5:eaaw6404. https://doi.org/10.1126/sciadv.aaw6404
- Wegmann, S., J. Biernat, and E. Mandelkow. 2021. A current view on Tau protein phosphorylation in Alzheimer's disease. Curr. Opin. Neurobiol. 69:131-138. https://doi.org/10.1016/j.conb.2021.03.003
- Weigand, A.J., K.R. Thomas, K.J. Bangen, G.M.L. Eglit, L. Delano-Wood, P.E. Gilbert, A.M. Brickman, and M.W. Bondi; Alzheimer's Disease Neuro-imaging Initiative. 2021. APOE interacts with tau PET to influence memory independently of amyloid PET in older adults without dementia. Alzheimer's Dement. 17:61-69. https://doi.org/10.1002/alz.12173
- Wenger, K., A. Viode, C.N. Schlaffner, P. van Zalm, L. Cheng, T. Dellovade, X. Langlois, A. Bannon, R. Chang, T.R. Connors, et al. 2023. Common mouse models of tauopathy reflect early but not late human disease. Mol. Neurodegener. 18:10. https://doi.org/10.1186/s13024-023-00601-y
- Whitwell, J.L., J. Graff-Radford, N. Tosakulwong, S.D. Weigand, M. Machulda, M.L. Senjem, C.G. Schwarz, A.J. Spychalla, D.T. Jones, D.A. Drubach, et al. 2018. [18 F]AV-1451 clustering of entorhinal and cortical uptake in Alzheimer's disease. Ann. Neurol. 83:248-257. https://doi.org/10.1002/ ana 25142
- Williams, T., A.J. Ruiz, A.M. Ruiz, Q. Vo, W. Tsering, G. Xu, K. McFarland, B.I. Giasson, P. Sullivan, D.R. Borchelt, and P. Chakrabarty. 2022. Impact of APOE genotype on prion-type propagation of tauopathy. Acta Neuropathol. Commun. 10:57. https://doi.org/10.1186/s40478-022-01359-y
- Wolters, E.E., R. Ossenkoppele, S.C.J. Verfaillie, E.M. Coomans, T. Timmers, D. Visser, H. Tuncel, S.S.V. Golla, A.D. Windhorst, R. Boellaard, et al. 2020. Regional [18F]flortaucipir PET is more closely associated with disease severity than CSF p-tau in Alzheimer's disease. Eur. J. Nucl. Med. Mol. Imaging. 47:2866-2878. https://doi.org/10.1007/s00259-020-04758-2
- Wong, W. 2020. Economic burden of Alzheimer disease and managed care considerations. Am. J. Manag. Care. 26:S177–S183. https://doi.org/10 .37765/ajmc.2020.88482
- Wu, J.W., M. Herman, L. Liu, S. Simoes, C.M. Acker, H. Figueroa, J.I. Steinberg, M. Margittai, R. Kayed, C. Zurzolo, et al. 2013. Small misfolded Tau species are internalized via bulk endocytosis and anterogradely and retrogradely transported in neurons. J. Biol. Chem. 288:1856–1870. https://doi.org/10.1074/jbc.M112.394528
- Xiong, M., H. Jiang, J.R. Serrano, E.R. Gonzales, C. Wang, M. Gratuze, R. Hoyle, N. Bien-Ly, A.P. Silverman, P.M. Sullivan, et al. 2021. APOE immunotherapy reduces cerebral amyloid angiopathy and amyloid plaques while improving cerebrovascular function. Sci. Transl. Med. 13: eabd7522. https://doi.org/10.1126/scitranslmed.abd7522
- Xu, H., T.W. Rösler, T. Carlsson, A. de Andrade, J. Bruch, M. Höllerhage, W.H. Oertel, and G.U. Höglinger. 2014. Memory deficits correlate with tau and spine pathology in P301S MAPT transgenic mice. Neuropathol. Appl. Neurobiol. 40:833–843. https://doi.org/10.1111/nan.12160
- Xu, C., D. Xiao, B.B. Su, J.M. Saveron, D. Gamez, R.O. Navia, N. Wang, U. Roy, D.A. Adjeroh, K. Wang, and Alzheimer and Disease Neuroimaging Initiative. 2024. Association of APOE gene with longitudinal changes of CSF amyloid beta and tau levels in alzheimer's disease: Racial differences. Neurol. Sci. 45:1041-1050. https://doi.org/10.1007/s10072-023-07076-1
- Yamada, K., J.R. Cirrito, F.R. Stewart, H. Jiang, M.B. Finn, B.B. Holmes, L.I. Binder, E.-M. Mandelkow, M.I. Diamond, V.M.-Y. Lee, and D.M. Holtzman. 2011. In vivo microdialysis reveals age-dependent decrease of brain interstitial fluid tau levels in P301S human tau transgenic mice. J. Neurosci. 31:13110-13117. https://doi.org/10.1523/JNEUROSCI.2569-11 2011
- Yamazaki, Y., N. Zhao, T.R. Caulfield, C.-C. Liu, and G. Bu. 2019. Apolipoprotein E and alzheimer disease: Pathobiology and targeting strategies. Nat. Rev. Neurol. 15:501-518. https://doi.org/10.1038/s41582-019-0228-7
- Yan, S., C. Zheng, M.D. Paranjpe, Y. Li, W. Li, X. Wang, T.L.S. Benzinger, J. Lu, and Y. Zhou. 2021. Sex modifies APOE ε4 dose effect on brain tau deposition in cognitively impaired individuals. *Brain*. 144:3201–3211. https://doi.org/10.1093/brain/awab160
- Yeh, F.L., Y. Wang, I. Tom, L.C. Gonzalez, and M. Sheng. 2016. TREM2 binds to apolipoproteins, including APOE and CLU/APOJ, and thereby facilitates uptake of amyloid-beta by microglia. Neuron. 91:328–340. https://doi.org/10.1016/j.neuron.2016.06.015



- Yeh, F.L., D.V. Hansen, and M. Sheng. 2017. TREM2, microglia, and neuro-degenerative diseases. Trends Mol. Med. 23:512–533. https://doi.org/10.1016/j.molmed.2017.03.008
- Yin, Z., N. Rosenzweig, K.L. Kleemann, X. Zhang, W. Brandão, M.A. Margeta, C. Schroeder, K.N. Sivanathan, S. Silveira, C. Gauthier, et al. 2023. APOE4 impairs the microglial response in Alzheimer's disease by inducing TGFβ-mediated checkpoints. Nat. Immunol. 24:1839–1853. https://doi.org/10.1038/s41590-023-01627-6
- Yoshiyama, Y., M. Higuchi, B. Zhang, S.-M. Huang, N. Iwata, T.C. Saido, J. Maeda, T. Suhara, J.Q. Trojanowski, and V.M.-Y. Lee. 2007. Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron*. 53:337–351. https://doi.org/10.1016/j.neuron.2007.01.010
- Young, C.B., E.C. Mormino, K.L. Poston, K.A. Johnson, D.M. Rentz, R.A. Sperling, and K.V. Papp. 2023. Computerized cognitive practice effects in relation to amyloid and tau in preclinical Alzheimer's disease: Results from a multi-site cohort. Alzheimer's Dement. 15. e12414. https://doi.org/10.1002/dad2.12414
- Yu, J.-T., L. Tan, and J. Hardy. 2014. Apolipoprotein E in Alzheimer's disease: An update. Annu. Rev. Neurosci. 37:79–100. https://doi.org/10.1146/annurev-neuro-071013-014300
- Zalocusky, K.A., R. Najm, A.L. Taubes, Y. Hao, S.Y. Yoon, N. Koutsodendris, M.R. Nelson, A. Rao, D.A. Bennett, J. Bant, et al. 2021. Neuronal ApoE upregulates MHC-I expression to drive selective neurodegeneration in Alzheimer's disease. Nat. Neurosci. 24:786-798. https://doi.org/10.1038/ s41593-021-00851-3
- Zempel, H., E. Thies, E. Mandelkow, and E.-M. Mandelkow. 2010. Abeta oligomers cause localized Ca(2+) elevation, missorting of endogenous Tau into dendrites, Tau phosphorylation, and destruction of microtubules and spines. *J. Neurosci.* 30:11938–11950. https://doi.org/10.1523/JNEUROSCI.2357-10.2010
- Zeng, H., J. Huang, H. Zhou, W.J. Meilandt, B. Dejanovic, Y. Zhou, C.J. Bohlen, S.-H. Lee, J. Ren, A. Liu, et al. 2023. Integrative in situ mapping of single-cell transcriptional states and tissue histopathology in a mouse model of Alzheimer's disease. Nat. Neurosci. 26:430–446. https://doi.org/10.1038/s41593-022-01251-x
- Zetterberg, H., M.A. Hietala, M. Jonsson, N. Andreasen, E. Styrud, I. Karlsson, A. Edman, C. Popa, A. Rasulzada, L.-O. Wahlund, et al. 2006. Neurochemical aftermath of amateur boxing. *Arch. Neurol.* 63:1277–1280. https://doi.org/10.1001/archneur.63.9.1277
- Zhang, Y., K. Chen, S.A. Sloan, M.L. Bennett, A.R. Scholze, S. O'Keeffe, H.P. Phatnani, P. Guarnieri, C. Caneda, N. Ruderisch, et al. 2014. An RNA-

- sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J. Neurosci.* 34:11929–11947. https://doi.org/10.1523/INEUROSCI.1860-14.2014
- Zhang, H., Y. Cao, L. Ma, Y. Wei, and H. Li. 2021a. Possible mechanisms of tau spread and toxicity in Alzheimer's disease. Front. Cell Dev. Biol. 9:707268. https://doi.org/10.3389/fcell.2021.707268
- Zhang, H., W. Wei, M. Zhao, L. Ma, X. Jiang, H. Pei, Y. Cao, and H. Li. 2021b. Interaction between Aβ and Tau in the pathogenesis of Alzheimer's disease. *Int. J. Biol. Sci.* 17:2181–2192. https://doi.org/10.7150/ijbs.57078
- Zhang, M.M., R. Bahal, T.P. Rasmussen, J.E. Manautou, and X.-B. Zhong. 2021c. The growth of siRNA-based therapeutics: Updated clinical studies. Biochem. Pharmacol. 189:114432. https://doi.org/10.1016/j.bcp .2021.114432
- Zhao, J., M.D. Davis, Y.A. Martens, M. Shinohara, N.R. Graff-Radford, S.G. Younkin, Z.K. Wszolek, T. Kanekiyo, and G. Bu. 2017. APOE ε4/ε4 diminishes neurotrophic function of human iPSC-derived astrocytes. *Hum. Mol. Genet.* 26:2690–2700. https://doi.org/10.1093/hmg/ddx155
- Zhao, N., C.-C. Liu, W. Qiao, and G. Bu. 2018a. Apolipoprotein E, receptors, and modulation of Alzheimer's disease. Biol. Psychiatry. 83:347–357. https://doi.org/10.1016/j.biopsych.2017.03.003
- Zhao, N., C.-C. Liu, A.J. Van Ingelgom, C. Linares, A. Kurti, J.A. Knight, M.G. Heckman, N.N. Diehl, M. Shinohara, Y.A. Martens, et al. 2018b. APOE ε2 is associated with increased tau pathology in primary tauopathy. *Nat. Commun.* 9:4388. https://doi.org/10.1038/s41467-018-06783-0
- Zhao, J., Y. Fu, Y. Yamazaki, Y. Ren, M.D. Davis, C.-C. Liu, W. Lu, X. Wang, K. Chen, Y. Cherukuri, et al. 2020. APOE4 exacerbates synapse loss and neurodegeneration in Alzheimer's disease patient iPSC-derived cerebral organoids. *Nat. Commun.* 11:5540. https://doi.org/10.1038/s41467-020-19264-0
- Zhou, Y., W.M. Song, P.S. Andhey, A. Swain, T. Levy, K.R. Miller, P.L. Poliani, M. Cominelli, S. Grover, S. Gilfillan, et al. 2020. Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. *Nat. Med.* 26: 131–142. https://doi.org/10.1038/s41591-019-0695-9
- Zhu, B., Y. Liu, S. Hwang, K. Archuleta, H. Huang, A. Campos, R. Murad, J. Piña-Crespo, H. Xu, and T.Y. Huang. 2022. Trem2 deletion enhances tau dispersion and pathology through microglia exosomes. Mol. Neuro-degener. 17:58. https://doi.org/10.1186/s13024-022-00562-8
- Zwang, T.J., E.D. Sastre, N. Wolf, N. Ruiz-Uribe, B. Woost, Z. Hoglund, Z. Fan, J. Bailey, L. Nfor, L. Buée, et al. 2024. Neurofibrillary tangle-bearing neurons have reduced risk of cell death in mice with Alzheimer's pathology. Cell Rep. 43:114574. https://doi.org/10.1016/j.celrep.2024.114574