Therapies for Tau-associated neurodegenerative disorders: targeting molecules, synapses, and cells

Miranda Robbins*

https://doi.org/10.4103/1673-5374.373670

Date of submission: January 5, 2023

Date of decision: February 14, 2023

Date of acceptance: March 15, 2023

Date of web publication: April 20, 2023

From the Contents

Abstract

Advances in experimental and computational technologies continue to grow rapidly to provide novel avenues for the treatment of neurodegenerative disorders. Despite this, there remain only a handful of drugs that have shown success in late-stage clinical trials for Tau-associated neurodegenerative disorders. The most commonly prescribed treatments are symptomatic treatments such as cholinesterase inhibitors and N-methyl-D-aspartate receptor blockers that were approved for use in Alzheimer's disease. As diagnostic screening can detect disorders at earlier time points, the field needs pre-symptomatic treatments that can prevent, or significantly delay the progression of these disorders (Koychev et al., 2019). These approaches may be different from late-stage treatments that may help to ameliorate symptoms and slow progression once symptoms have become more advanced should early diagnostic screening fail. This mini-review will highlight five key avenues of academic and industrial research for identifying therapeutic strategies to treat Tau-associated neurodegenerative disorders. These avenues include investigating (1) the broad class of chemicals termed "small molecules"; (2) adaptive immunity through both passive and active antibody treatments; (3) innate immunity with an emphasis on microglial modulation; (4) synaptic compartments with the view that Tau-associated neurodegenerative disorders are synaptopathies. Although this mini-review will focus on Alzheimer's disease due to its prevalence, it will also argue the need to target other tauopathies, as through understanding Alzheimer's disease as a Tau-associated neurodegenerative disorder, we may be able to generalize treatment options. For this reason, added detail linking back specifically to Tau protein as a direct therapeutic target will be added to each topic.

Key Words: Alzheimer's disease; antibody; frontotemporal dementia; immunotherapy; small molecules; synapses; tau; therapeutics

Introduction

Microtubule-associated protein Tau is linked to multiple neurodegenerative diseases where Tau inclusions are formed in the brain. Despite the diversity of their anatomical progression and symptoms, due to the commonality of Tau pathology between these disorders, they are termed "Tauopathies". Primary Tauopathies, where Tau protein deposition is the predominant feature, most commonly include frontotemporal dementia with parkinsonism-17, Pick disease, progressive supranuclear palsy, and corticobasal degeneration, with Alzheimer's disease (AD) as a "secondary tauopathy" (Spillantini et al., 2013). There are no disease-modifying therapies approved by the U.S. Food and Drug Administration for the treatment of tauopathies; all current treatments are symptomatic and therefore may reduce symptoms but do not slow disease progression (01/2023). Acetylcholinesterase inhibitors and memantine, an antagonist of N-methyl-d-aspartate receptors, are prescription drugs used for symptomatic relief of AD (O'Brien et al., 2017), with off-label use for the cognitive and behavioral symptoms in other tauopathies. Due to the high prevalence and large number of clinical trials targeted at AD treatments, this mini-review will largely focus on the current state of AD therapeutics and how this relates to the current hypotheses of disease etiology and prevention in this field. As the treatments for AD are currently used off-label for other tauopathies, breakthroughs in this field will hopefully generalize between tauopathies to offer targets for the treatment of multiple disorders. The topics have been split into investigations of (1) small molecules; (2) adaptive immunity using passive and active antibodies; (3) innate immunity with an emphasis on microglial modulation; and (4) synaptic functioning, due to the high representation of these targets among current Phase 3 clinical trials (01/2023) and their popularity as therapeutic avenues in this field. Tau will be discussed as the common thread that may act as the therapeutic target between these disorders.

Search Strategy

The reviewed literature on Tau biology and anti-tau drugs using PubMed, meeting abstracts, and Alzforum.org from inception to December 2022 for English language publications only. Literature on clinical trials was found using ClinicalTrials.gov to search "tauopathies" and selecting for Study Phase 3 and 4, and Status "not yet recruiting", "recruiting", "enrolling by invitation", and "active, not recruiting". All ClinicalTrials.gov search results are from December 2022 unless otherwise stated.

Small Molecules

Small molecules can act to upregulate neuroprotective pathways or restore homeostasis to signaling pathways that are thought to become dysregulated during disease etiology. **Table 1** shows the small molecules and their targets that are currently undergoing Phase 3 human clinical trials for Tau-based neurodegenerative disorders (ClinicalTrials.gov). These drugs appear to cluster around pathways related to glucose regulation, phosphorylation and aggregation state, and receptor activation.

Computational methods have also been employed to design small molecules with putative beneficial pharmacological actions. Small molecule drug discovery involves screening compound libraries consisting of millions of drugs. However, often the library size does not represent chemical structure diversity, which has been suggested to be a hurdle for recent therapeutic success (Galloway et al., 2010). Using ligand and structural data with artificial intelligence/computational methods, a diverse portfolio of 3-dimensional drugs can be designed that modulate key interactions with a biological target. This can hopefully improve the specificity of the ligand-target interaction and reduce the number of chemicals that need to be screened. An example of structure-based *in silico* small molecule design is provided by Seidler et al. (2022) whereby they used structural studies to find the binding position for a small molecule known to disaggregate Tau fibrils but with low blood-brain barrier penetration when used *in vivo*. They used this binding position as a pharmacophore to computationally screen thousands of similar compounds with increased blood-brain barrier permeability (Seidler et al., 2022). Deep learning methods are also being used to predetermine complex drug-drug interactions that may be beneficial or harmful when used as drug "cocktails" in human patients (Kpanou et al., 2021).

Small molecules can directly target Tau during aggregation, post-translational modification modulation, and degradation pathways. Molecules can bind to inhibit misfolded, pathological structures of Tau from forming, while other common molecules can act as kinase inhibitors or phosphatase activators to prevent hyperphosphorylation of Tau (For a review on small molecules for tauopathy in AD see Wang et al., 2021). Of the drugs in Phase 3 Clinical

MRC Laboratory of Molecular Biology, Cambridge Biomedical Campus, Francis Crick Ave, Trumpington, Cambridge, UK; University of Cambridge, Department of Zoology, Cambridge, UK

***Correspondence to:** Miranda Robbins, PhD, mrobbins@mrc-lmb.cam.ac.uk.

https://orcid.org/0000-0002-6576-5763 (Miranda Robbins)

Funding: *This work was supported by the MRC Laboratory of Molecular Biology (to MR).*

How to cite this article: *Robbins M (2023) Therapies for Tau-associated neurodegenerative disorders: targeting molecules, synapses, and cells. Neural Regen Res 18(12):2633-2637.*

Table 1 | **The small molecules undergoing Phase 3 clinical trials for Tau-associated neurodegenerative conditions (12/2022; ClinicalTrials.gov)**

Name	Role	Clinical trial registration
AR1001	PDE 5 inhibitor; increases messenger cGMP in NO/cGMP/PKG/CREB signaling pathway; anti-inflammatory and neuroprotection (Zuccarello et al., 2020).	Phase 3, recruiting (NCT05531526)
NE3107	Anti-inflammatory, insulin-sensitizing through ERK1/2 (Reading et al., 2021).	Phase 3, recruiting (NCT04669028)
Metformin	Antihyperglycemic medication, AMPK activator (Zhou et al., 2001).	Phase 3, recruiting (NCT04098666)
Semagludtide	Glucagon-like peptide-1 receptor activator, stimulates insulin release (Knudsen and Lau, 2019).	Phase 3, recruiting (NCT04777396)
ATH-1017	Growth factor stimulation through HGF pathway.	Phase 3, recruiting (NCT04488419)
Hydralazine	Autophagy and Nrf2 pathway. Free radical scavenger.	Phase 3, recruiting (NCT04842552)
Simufilam	Binds to filamin to stabilize actin.	Phase 3, recruiting (NCT05026177)
Nilotinib	Tyrosine Kinase Inhibitor, induces autophagy (Salomoni and Calabretta, 2009).	Phase 3, not yet recruiting (NCT05143528)
Masitinib	Tyrosine kinase inhibitor. Inhibitor of mast cell-glia axis.	Phase 3, not yet recruiting (NCT05564169)
TRx0237	Tau aggregation inhibitor. Methylene blue derivative (Wischik et al., 1996).	Phase 3, active (NCT03446001)
ALZ-801	$A\beta_{42}$ aggregation inhibitor (Gervais et al., 2007).	Phase 3, active (NCT04770220)
BPDO-1603	Undefined.	Phase 3, recruiting (NCT04229927)
Rivastigmine	Acetylcholinesterase and butyrylcholinesterase inhibitor for PSP	Phase 3, active (NCT02839642)
Lithium	Multiple, unknown. IMP inhibitor, up-regulates autophagy (Sarkar et al., 2005) GSK-3β inhibitor.	Phase 4, active (NCT03185208)
Caffeine	Adenosine receptor antagonist. Antioxidant effects. Anti-inflammatory. RyR agonist and PDE inhibitor at high dose (Zampelas et al., 2004; Kolahdouzan and Hamadeh, 2017).	Phase 3, recruiting (NCT04570085)
Piromelatine	Agonist of MT1/MT2/MT3 and 5-HT1A and 5-HT1D receptors, low-affinity antagonist of 5-HT2B, P2X3, and TRPV1 receptors. Improves insulin sensitivity (Laudon et al., 2012; She et al., 2014)	Phase 3, not yet recruiting (NCT05267535)
ANAVEX2-73	Sigma-1 and muscarinic receptor agonist; may block Tau hyperphosphorylation by GSK-3β and protect mitochondria (Lahmy et al., 2013).	Phase 3, recruiting (NCT04314934)
Guanfacine	Activates synaptic α2A noradrenergic receptors. Inhibits cAMP opening of potassium channels (Arnsten, 2020).	Phase 3, recruiting (NCT03116126)
AGB101	Inhibition of the synaptic protein SV2A. Anti-convulsant.	Phase 3, not yet recruiting (NCT03486938)

5-HT: 5-Hydroxytryptamine; AGB101: AgeneBio, Inc.; ALZ-801: Alzheon Inc.; AMPK: AMP-activated protein kinase; ANAVEX2-73: Anavex Life Science Corp.; AR1001: Aribio Co., Ltd.; ATH-1017; Athira Pharma.; Aβ42: amyloid beta 42; BPDO-1603: Hyundai Pharmaceutical Co.; cGMP: cyclic guanosine monophosphate; CREB: cAMP response element-binding protein; ERK: extracellular signal-regulated kinase; GSK-3β: glycogen synthase kinase-3 beta; HGF: hepatocyte growth factor; IMP: inositol monophosphatase; MT: melatonin receptors; NE3107: BioVie Pharma; NO: nitric oxide; Nrf2: nuclear factor erythroid 2-related factor 2; P2X : ATP-gated P2X receptor cation channel family; PDE: phosphodiesterase; PKG: cGMP-dependent protein kinase; PSP: progressive supranuclear palsy; RyR: ryanodine receptor; SV2A: synaptic vesicle glycoprotein 2A; TRPV: transient receptor potential vanilloid; TRx0237: TauRx Therapeutics Ltd.

Trials, lithium and ANAVEX2-73 influence the glycogen synthase kinase-3 beta (GSK-3β) pathway, known to be a pathway in the hyperphosphorylation of Tau. An increased concentration of Tau is known to promote aggregation (Myers et al., 2006; Hu et al., 2017). Novel small molecules such as antisense oligonucleotides (ASOs) aim to reduce Tau expression by binding to, and preventing the translation, of Tau mRNA. The ASO, IONIS-$MAPT_{Rx}$, also known as BIIB080, is currently undergoing clinical trials to lower Tau concentration in tauopathies (Crooke et al., 2019). Alternatively, proteolysis-targeted chimeras help to increase Tau degradation. Proteolysis-targeted chimeras target a protein of interest to an E3 ligase to promote degradation by the ubiquitin-proteasome system (Toure and Crews, 2016). The clinical benefits from Tau concentration-reducing drugs such as ASOs and proteolysis-targeted chimeras are not yet known, though the reduction in CSF Tau by semorinemab showed no clinical benefits. The ability to target intracellular Tau at earlier time points may have a very different effect from the use of extracellular antibodies late in the disease.

Adaptive Immunity: Antibodies

The role of adaptive immunity-based therapeutics cannot be overlooked since the report of a clinical trial of the antibody lecanemab which recently showed a minor reduction in cognitive decline over 18 months in early AD through its specificity for amyloid-beta (Aβ) soluble protofilaments, compared to monomers (van Dyck et al., 2022). Aducanumab is the first Food and Drug Administration-approved therapy to directly target pathology in AD via binding Aβ aggregates, however, its approval has been controversial (Walsh et al., 2021).

For targeting Tau in Tau-associated neurodegenerative disorders, the paratope of the antibody can be selected based on its affinity for a specific epitope of Tau, such as its aggregation-prone microtubule-binding region in monomers (Fitzpatrick et al., 2017), or specific structural conformations, or regions exposed during aggregation in oligomers or filaments. However, previous clinical trials with anti-Tau antibodies such as semorinemab, which binds the N-terminus of both monomeric and oligomeric Tau, have shown only limited effectiveness (Lee et al., 2016). In 2021, it was announced that semorinemab showed a 43.6% slowing of decline on the ADAS-Cog11 co-primary, but there were no other positive cognitive or functional outcomes. The limited benefits of this, and other N-terminus antibodies, may be linked to their inability to prevent tangle formation (No author listed, 2022a). An antibody targeting the microtubule-binding region of Tau is currently under Phase 3 trial (NCT05269394) and may provide insight into how this epitope compares to the N-terminus of Tau. Antibodies from humans resistant to diseases such as frontotemporal dementia, amyotrophic lateral sclerosis, and AD can be used either as therapeutic markers or as a therapeutic avenue. An ongoing antigen-driven immune response against Tau has been shown in healthy individuals (Pascual et al., 2017; Hromadkova and Ovsepian, 2019). In these individuals, B cell receptor sequences can be sequenced and then expressed recombinantly as an antibody.

An alternative approach is a vaccine that uses active immunity through T helper cells activating B cells to produce antibodies against Tau. Two such vaccines are candidates for clinical trials. The first vaccine contains a phospho-tau peptide anchored to a liposomal bilayer that also contains additional peptides to elicit an immune response by signaling to helper T cells (No author listed, 2022b). The second vaccine generates antibodies to target the phosphatase-activating domain of Tau in monomers, small fragments, and aggregated forms of Tau in AD patients' brain extracts (Hovakimyan et al., 2022). Results from these possible clinical trials may enable understanding of the contribution of the Tau epitope targeted, and any requirement of active versus passive immunity for long-term efficacy of the treatment (**Table 2**).

Table 2 | **Therapeutic antibodies undergoing phase 3 clinical trials for Tau-associated neurodegenerative conditions (December 2022; ClinicalTrials.gov)**

Name	Role	Clinical trial registration
Donanemab	Aβ Monoclonal Antibody	Phase 3, recruiting (NCT05508789)
E2814 *vs*. Lecanemab	Anti-microtubule-binding region (MTBR) tau antibody *vs*. Aβ Monoclonal Antibody	Phase 3, recruiting (NCT05269394)
Remternetug	Aβ Monoclonal Antibody	Phase 3, recruiting (NCT05463731)
Aducanumab	Aβ Monoclonal Antibody	Phase 3, recruiting (NCT05310071)
Gantenerumab	Aβ fibril Monoclonal Antibody	Phase 3, active (NCT05256134)

Following the apparent success of Lecanemab (van Dyck et al., 2022), many of these antibodies target the Aβ cascade, however, E2814, an antibody against the microtubule-binding region of Tau, is also being compared to lecanemab in a clinical trial (NCT05269394).

Combinations, or a "cocktail", of antibodies, could potentially be used to slow disease progression through multiple targets. In one trial (NCT05269394), the potential benefits of an anti-tau antibody (E2814) will be tested while an anti-amyloid antibody (lecanemab) is given as a background therapy. The use of E2814 with lecanemab is in part an ethical decision to change amyloid disease pathology whilst the effects of E2814 are unknown.

Modern experimental and computational methods have epitope-directed antibody selection through 'smart-design' antibodies (Chen et al., 2020; Aguilar Rangel et al., 2022). In addition, modernized high-throughput methods can be used to characterize the binding affinity of Tau antibodies for different Tau binding regions and conformations (Younger et al., 2017). Purely computational deep-learning techniques can use unobserved patterns from amino acid sequences that associate with their structure and function (Rives et al., 2021). Deep sequencing of bulk BCR repertoires provides large datasets from which antibody-specific language models can be trained for understanding antibody and B cell receptor structure and function including

DeepAb, AntiBERTa, and Sapiens (Leem et al., 2022; Prihoda et al., 2022; Ruffolo et al., 2022).

Innate Immunity: Microglia

The innate immune system is being targeted as a therapeutic intervention due to its hypothesized role in the progression of AD and the spread of pathological Tau species (Perea et al., 2018; Ennerfelt and Lukens, 2020). These therapeutics may help to control microglial activation, metabolism, and response to CNS insult to act as an early-stage intervention (Schwabe et al., 2020). The tyrosine kinase inhibitor, masitinib, met its primary goal in Phase 2 trials (Dubreuil et al., 2009) and its effects were suggested to be through modulating mast cell and microglial activation.

Novel targets are also being identified based on transcriptomic studies in microglia from human postmortem tissue in an attempt to prevent dysfunctional microglial states thought to contribute to disease progression. Progranulin and Trem2 are commonly mentioned as antagonistic targets against the innate immune system in FTD or AD whereby decreased progranulin increases microglial activity, whereas decreased Trem2 causes impaired microglial activation (Mazaheri et al., 2017; Götzl et al., 2019; **Table 3**). Stimulating Trem2 to activate microglia is a suggested therapeutic to slow AD progression (Lewcock et al., 2020), Trem2 knockout (KO) can reduce microglial hyperactivation from progranulin deficits in a progranulin KO/Trem2 KO mouse model (Reifschneider et al., 2022). An antibody against the progranulin binding protein sortilin (AL001/AL101), a genetic risk factor for AD (Rogaeva et al., 2007), which increases the level of progranulin is currently entering Phase 3 clinical trials as it has been shown to slow disease progression in FTD (AL001; NCT04374136). However, progranulin has consistently been found to be a poor biomarker of mild cognitive impairment, AD, sporadic FTD, dementia with Lewy bodies, corticobasal syndrome, or progressive supranuclear palsy (Gass et al., 2012; Morenas-Rodríguez et al., 2016; Wang et al., 2020). Due to the appearance of both hypoactivation and hyperactivation of microglia in different disorders (Kwon and Koh, 2020), alongside the inability of restoring microglial activity to ameliorate glucose uptake, lysosomal dysfunction, and lipid metabolism, it seems possible that innate immunity alone will not provide a therapeutic solution (Reifschneider et al., 2022). Co-therapies against the innate immune system could be used pre-symptomatically as preventative measures to target systemic inflammation, the gut microbiome, or traumatic brain injury to prevent aberrant activation of the innate immune system (Hickman et al., 2018). Another interesting outcome of restoring the microglial activation state in progranulin KO/Trem2 KO mice was the exacerbation of synaptic loss, suggesting a possible role for synaptic therapeutic targets (Reifschneider et al., 2022).

Table 3 | **The anti-progranulin antibody AL001/AL101 targets innate immunity for its therapeutic function**

Name	Role	Clinical trial registration
AL001/AL101	Antibody against the progranulin binding protein sortilin	NCT04374136

Synaptic Targets

Synaptic dysfunction is known to precede any gross structural changes, and the currently approved therapeutics modulate synaptic function (Lleó et al., 2019). It has previously been suggested that the synaptic vesicle cycle may be an effective early-stage treatment avenue and that the binding partners of Tau may play a role in synaptopathy in AD and frontotemporal dementia (Robbins et al., 2021; Robbins and Clayton, 2023; **Table 4**).

Table 4 | **The therapies in phase 3 clinical trials targeting synaptic compartments are small molecules**

Name	Role	Clinical trial registration
AGB101	Binding to the synaptic vesicle (SV) protein SV2A	NCT03486938
Mastinib	Inhibitor of tyrosine kinase, Lyn and Fyn kinase	NCT05564169
Simufilam	Binds to filamin to stabilize actin	NCT05026177

AGB101: AgeneBio, Inc.; SV2A: Synaptic vesicle glycoprotein 2A. Other therapeutic targets may still have benefits to synapses by targeting pathways required for synaptic function.

To target the pre-synaptic compartment, the small molecule AGB101, which is currently approved by the Food and Drug Administration as an anti-convulsant through its mechanism of binding to the synaptic vesicle (SV) protein SV2A, is currently undergoing Phase 3 clinical trials to test whether it can delay mild cognitive decline in AD (NCT03486938). SV2A was suggested to regulate AD-related proteins through inverse expression of Tau for Tau-mediated inhibition of SV release; or promoting the production of Aβ by stabilizing amyloid precursor protein on the cell surface for cleavage, and by the inverse expression of BACE1. SV2A may additionally play a role in the PI3K pathway and promote insulin growth factor secretion (Kong et al., 2021). SV protein synaptogyrin-3 has also been suggested as a therapeutic target for tauopathies, as reducing its expression rescues synaptic dysfunction in tauopathy mouse models (Zhou et al., 2017; McInnes et al., 2018; Largo-Barrientos et al., 2021a). The reduction of synaptogyrin-3 expression in neurons expressing FTD mutant P301S Tau ameliorates synaptic plasticity defects, synaptic loss, and decline in working memory, whilst having no effect on microglial reactivity. This was taken to suggest that Tau-induced synaptic dysfunction can be rescued independently of the microglial state (Largo-Barrientos et al., 2021b).

Two small molecules, AZD0530 and simufilam, act at the intersection of Tau and Aβ pathology at post-synaptic receptors through the targets Fyn kinase or filamin, respectively. The drug AZD0530 is an Src family, including fyn kinase, an inhibitor that was tested in Phase 2 clinical trials but was not shown to be effective based on the study criteria (Van Dyck et al., 2019). Mastinib, a tyrosine kinase inhibitor undergoing Phase 3 clinical trials (NCT05564169) has listed effects including mast cell and migroglial modulation but also inhibiting Lyn and Fyn kinase (Dubreuil et al., 2009). The outcome of this clinical trial and through which mechanisms the small molecule is found to exert its effects in the phase 2 trial will be of interest (Piette et al., 2011; No author listed, 2020). Simufilam is another small molecule with post-synaptic therapeutic mechanisms acting via the scaffolding and actin-regulating protein filamin (Wang et al., 2017). Overexpression of filamin has been shown to promote Tau aggregation in progressive supranuclear palsy (Tsujikawa et al., 2022). Simufilam is reported to normalize signaling through the α7, NDMA, and insulin receptors by preventing or reversing the high-affinity binding of $A\beta_{42}$ and the α7 nicotinic acetylcholine receptor that is stabilized by filamin. This is an important property as the $A\beta_{42}$-α7 interaction may cause tau phosphorylation and synaptic dysfunction (Wang et al., 2003, 2017).

More alternative synaptic therapeutics are also coming into sight, such as an mRNA vaccine to increase ATP to target synaptic hypometabolism that occurs before cognitive loss (Fessel, 2021). A synthetic synaptic protein that co-interacts with presynaptic neurexins and postsynaptic AMPA-type glutamate receptors was found to restore synaptic function, motor coordination, spatial and contextual memories, as well as locomotion in mouse models for cerebellar ataxia, AD, and spinal cord injury, respectively (Suzuki and Kimura, 2017). This is an example of a 'structure-guided' design and application that may help to design therapeutics that are specifically able to target synaptic impairment at the earliest stages of disease progression. In addition, by better understanding the diversity between different synapse types, we may be able to understand what makes some synapses vulnerable or resilient to pathology (Griffiths and Grant, 2023).

Discussion

The diversity of research aimed at developing a treatment against Tau-based neurodegenerative diseases offers great hope to this currently limited field. Other therapies undergoing Phase 3 trials (Dec 2022) include 3 dietary supplement, 2 omega-3-based (NCT03691519; NCT02719327), and a glucose alternative (Tricaprilin; NCT04187547), a neuroprotective agent against oxidative and Aβ-induced stress (GV1001; NCT05303701), and a behavioral treatment based on computerized cognitive training (NCT03848312). Alongside these, the use of stem cells and extracellular vesicles, and deep brain stimulation, which have shown some success in Parkinson's disease, are also being further investigated (Mondragón-Rodríguez et al., 2017; Gonçalves et al., 2023). Whilst further therapeutic avenues are being investigated, a "healthy lifestyle" remains one of the best methods for a longer lifespan with later disease onset (Dhana et al., 2022).

It is also important to consider the limitations of the classes of therapeutics. Small molecules often suffer from limited specificity, leading to adverse effects and drug resistance. The tyrosine kinase inhibitors are an example of limited specificity and resistance, such as nilotinib, whereby cells showed drug resistance through upregulated expression of five kinase targets (Kim et al., 2011). Antibodies have poor blood-brain barrier penetration which therefore often requires high doses of intravenous infusion or subcutaneous injection on a regular basis. This may limit cocktail combinations until higher doses of a single antibody are achieved. In addition, there has been much publicity of amyloid-related imaging abnormalities, which results in swelling and/or bleeding in the brain in 21.3% of patients compared with 9% of placebo control patients (The Lancet, 2022; van Dyck et al., 2022). As we have seen, although a drug may ameliorate behavioral function in one domain, it does not always translate between cognitive tasks and therefore multiple therapeutic avenues may be required.

To recap on the therapeutic targets in this review, growth factor stimulation, insulin signaling, and promoting synaptic function offer great hope for the future of pre-symptomatic treatments, either as monotherapy or as a "cocktail" combination with therapies reducing protein aggregation. An interesting intersection of growth factor stimulation, insulin signaling, and synaptic function is through the activation state of GSK-3β (see lithium; ANAVEX2-73) and thereby both protein and polyglucan synthesis, as well as Tau phosphorylation state (Sperbera et al., 1995). GSK-3β can be inhibited by insulin (see semagludtide, piromelatine) and several growth factors, hormones, and AMPK (see metformin) downstream of caloric restriction. Increased GSK-3β increases Tau hyperphosphorylation, promotes inflammation, prevents synaptic vesicle exocytosis, and can activate Fyn

kinase to cause nuclear export of Nrf2 (see hydralazine) (Eldar-Finkelman, 2002; Jain and Jaiswal, 2007; Jope et al., 2007; Zhu et al., 2010). Tau is also required for transient anchoring of GSK-3B in the postsynaptic compartment where it can phosphorylate Tau to induce long-term depression (Kimura et al., 2013). Tau deletion can promote brain insulin resistance which could further feedback to influence the GSK-3β signaling pathway (Marciniak et al., 2017). Of the disease-modifying therapies in Phase 3 clinical trials in January 2022, 29% targeted amyloid pathology, 19% targeted synaptic plasticity, and only 5% targeted Tau (Cummings et al., 2022). Many drugs against Aβ target Tau indirectly on the principle that Tau pathology is downstream of Aβ-pathology and therefore would be abolished if Aβ-pathology was prevented in the first instance (Bloom, 2014). However, it is also known that Tau is required for Aβ-induced pathology (Rapoport et al., 2002). In fact, as we have seen, Fyn (AZD0530, mastinib) is translocated by Tau to dendrites to phosphorylate NMDA receptors thereby allowing their stabilization by PSD95. This can lead to the excitotoxicity that increases Aβ-toxicity on neurons (Haass and Mandelkow, 2010). One of the currently prescribed AD treatments, memantine, is an NMDAR blocker, which also inhibits and reverses the protein phosphatase 2A inhibition-induced pathological hyperphosphorylation and accumulation of tau *in vitro* (Li et al., 2004). Memantine hints at the effectiveness of a synaptic target known to be influenced by Tau pathology. In addition, in primary tauopathies, Tau is the initial driving factor of disease pathology, and therefore directly targeting and preventing this pathology may allow generalized therapies between Tau-associated neurodegenerative disorders.

Acknowledgments: *The author would like to acknowledge Jayson Squires (MRC Laboratory of Molecular Biology, UK) for his technical contribution to the review paper.*
Author contributions: *MR wrote the manuscript, searched, collected, analyzed data, and approved the final version of the manuscript.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Data availability statement: *The data are available from the corresponding author on reasonable request.*

Open peer reviewer: *Eliana C B Toscano, Universidade Federal de Juiz de Fora Faculdade de Medicina, Brazil.*
Additional file: *Open peer review report 1.*

References

Aguilar Rangel M, Bedwell A, Costanzi E, Taylor RJ, Russo R, Bernardes GJL, Ricagno S, Frydman J, Vendruscolo M, Sormanni P (2022) Fragment-based computational design of antibodies targeting structured epitopes. Sci Adv 8:eabp9540.

Arnsten AFT (2020) Guanfacine's mechanism of action in treating prefrontal cortical disorders: Successful translation across species. Neurobiol Learn Mem 176:107327.

Bloom GS (2014) Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol 71:505-508.

Chen L, Zhu C, Guo H, Li R, Zhang L, Xing Z, Song Y, Zhang Z, Wang F, Liu X, Zhang Y, Ma RZ, Wang F (2020) Epitope-directed antibody selection by site-specific photocrosslinking. Sci Adv 6:eaaz7825.

Crooke ST, Witztum JL, Bennett CF, Baker BF (2019) RNA-targeted therapeutics. Cell Metab 29:501.

Cummings J, Lee G, Nahed P, Kambar MEZN, Zhong K, Fonseca J, Taghva K (2022) Alzheimer's disease drug development pipeline: 2022. Alzheimers Dement 8:e12295.

Dubreuil P, Letard S, Ciufolini M, Gros L, Humbert M, Castéran N, Borge L, Hajem B, Lermet A, Sippl W, Voisset E, Arock M, Auclair C, Leventhal PS, Mansfield CD, Moussy A, Hermine O (2009) Masitinib (AB1010), a potent and selective tyrosine kinase inhibitor targeting KIT. PLoS One 4:e7258.

Eldar-Finkelman H (2002) Glycogen synthase kinase 3: an emerging therapeutic target. Trends Mol Med 8:126-132.

Ennerfelt HE, Lukens JR (2020) The role of innate immunity in Alzheimer's disease. Immunol Rev 297:225-246.

Fessel J (2021) A vaccine to prevent initial loss of cognition and eventual Alzheimer's disease in elderly persons. Alzheimers Dement 7:e12126.

Fitzpatrick AWP, Falcon B, He S, Murzin AG, Murshudov G, Garringer HJ, Crowther RA, Ghetti B, Goedert M, Scheres SHW (2017) Cryo-EM structures of tau filaments from Alzheimer's disease. Nature 547:185.

Galloway WR, Isidro-Llobet A, Spring DR (2010) Diversity-oriented synthesis as a tool for the discovery of novel biologically active small molecules. Nat Commun 2010 1:80.

Gass J, Prudencio M, Stetler C, Petrucelli L (2012) Progranulin: an emerging target for FTLD therapies. Brain Res 1462:118-128.

Gervais F, Paquette J, Morissette C, Krzywkowski P, Yu M, Azzi M, Lacombe D, Kong X, Aman A, Laurin J, Szarek WA, Tremblay P (2007) Targeting soluble Abeta peptide with Tramiprosate for the treatment of brain amyloidosis. Neurobiol Aging 28:537-547.

Gonçalves RdJ, Vasques J, da Silva-Junior A, Gubert F, Mendez-Otero R (2023) Mesenchymal stem cell- and extracellular vesicle-based therapies for Alzheimer's disease: progress, advantages, and challenges. Neural Regen Res 18:1645-1651.

Götzl JK, Brendel M, Werner G, Parhizkar S, Sebastian Monasor L, Kleinberger G, Colombo AV, Deussing M, Wagner M, Winkelmann J, Diehl-Schmid J, Levin J, Fellerer K, Reifschneider A, Bultmann S, Bartenstein P, Rominger A, Tahirovic S, Smith ST, Madore C, et al. (2019) Opposite microglial activation stages upon loss of PGRN or TREM2 result in reduced cerebral glucose metabolism. EMBO Mol Med 11:e9711.

Griffiths J, Grant SGN (2023) Synapse pathology in Alzheimer's disease. Semin Cell Dev Biol 139:13-23.

Haass C, Mandelkow E (2010) Fyn-Tau-amyloid: a toxic triad. Cell 142:356-358.

Hickman S, Izzy S, Sen P, Morsett L, El Khoury J (2018) Microglia in neurodegeneration. Nat Neurosci 21:1359-1369.

Hovakimyan A, Zagorski K, Chailyan G, Antonyan T, Melikyan L, Petrushina I, Batt DG, King O, Ghazaryan M, Donthi A, Foose C, Petrovsky N, Cribbs DH, Agadjanyan MG, Ghochikyan A (2022) Immunogenicity of MultiTEP platform technology-based Tau vaccine in non-human primates. NPJ Vaccines 7:117.

Hromadkova L, Ovsepian SV (2019) Tau-reactive endogenous antibodies: origin, functionality, and implications for the pathophysiology of Alzheimer's disease. J Immunol Res 2019:7406810.

Hu W, Wu F, Zhang Y, Gong CX, Iqbal K, Liu F (2017) Expression of tau pathology-related proteins in different brain regions: a molecular basis of tau pathogenesis. Front Aging Neurosci 9:311.

Jain AK, Jaiswal AK (2007) GSK-3beta acts upstream of Fyn kinase in regulation of nuclear export and degradation of NF-E2 related factor 2. J Biol Chem 282:16502-16510.

Jope RS, Yuskaitis CJ, Beurel E (2007) Glycogen synthase kinase-3 (GSK3): inflammation, diseases, and therapeutics. Neurochem Res 32:577-577.

Kim TM, Ha SA, Kim HK, Yoo J, Kim S, Yim SH, Jung SH, Kim DW, Chung YJ, Kim JW (2011) Gene expression signatures associated with the in vitro resistance to two tyrosine kinase inhibitors, nilotinib and imatinib. Blood Cancer J 1:e32.

Kimura T, Whitcomb DJ, Jo J, Regan P, Piers T, Heo S, Brown C, Hashikawa T, Murayama M, Seok H, Sotiropoulos I, Kim E, Collingridge GL, Takashima A, Cho K (2013) Microtubule-associated protein tau is essential for long-term depression in the hippocampus. Philos Trans R Soc Lond B Biol Sci 369:20130144.

Knudsen LB, Lau J (2019) The discovery and development of liraglutide and semaglutide. Front Endocrinol 10:155.

Kolahdouzan M, Hamadeh MJ (2017) The neuroprotective effects of caffeine in neurodegenerative diseases. CNS Neurosci Ther 23:272-290.

Kong Y, Huang L, Li W, Liu X, Zhou Y, Liu C, Zhang S, Xie F, Zhang Z, Jiang D, Zhou W, Ni R, Zhang C, Sun B, Wang J, Guan Y (2021) The synaptic vesicle protein 2A interacts with key pathogenic factors in Alzheimer's disease: implications for treatment. Front Cell Dev Biol 9:1555-1555.

Koychev I, Lawson J, Chessell T, Mackay C, Gunn R, Sahakian B, Rowe JB, Thomas AJ, Rochester L, Chan D, Tom B, Malhotra P, Ballard C, Chessell I, Ritchie CW, Raymont V, Leroi I, Lengyel I, Murray M, Thomas DL, et al. (2019) Deep and frequent phenotyping study protocol: an observational study in prodromal Alzheimer's disease. BMJ Open 9:e024498.

Kpanou R, Osseni MA, Tossou P, Laviolette F, Corbeil J (2021) On the robustness of generalization of drug–drug interaction models. BMC Bioinformatics 22:1-21.

Kwon HS, Koh SH (2020) Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl Neurodegener 2020 9:42.

Lahmy V, Meunier J, Malmström S, Naert G, Givalois L, Kim SH, Villard V, Vamvakides A, Maurice T (2013) Blockade of Tau hyperphosphorylation and $A\beta_{1-42}$ generation by the aminotetrahydrofuran derivative ANAVEX2-73, a mixed muscarinic and σ_1 receptor agonist, in a nontransgenic mouse model of Alzheimer's disease. Neuropsychopharmacology 38:1706-1723.

Largo-Barrientos P, Uyterhoeven V, de Wit J, De Strooper B, Verstreken P (2021a) Synaptic tau and synaptogyrin-3 are promising targets to tackle tauopathies. Alzheimers Dement 17:e054187.

Largo-Barrientos P, Apóstolo N, Creemers E, Callaerts-Vegh Z, Swerts J, Davies C, McInnes J, Wierda K, De Strooper B, Spires-Jones T, de Wit J, Uyterhoeven V, Verstreken P (2021b) Lowering Synaptogyrin-3 expression rescues Tau-induced memory defects and synaptic loss in the presence of microglial activation. Neuron 109:767-777.

Laudon M, Katz A, Metzger D, Staner L, Pross N, Cornette F, Guichard N, Nir T, Zisapel N (2012) Tolerability, pharmacokinetic and pharmacodynamic evaluation of multiple ascending doses of Neu-P11 in insomnia patients. Westchester: Amer Acad Sleep Medicine One Westbrook Corporate Ctr.

Lee SH, Le Pichon CE, Adolfsson O, Gafner V, Pihlgren M, Lin H, Solanoy H, Brendza R, Ngu H, Foreman O, Chan R, Ernst JA, DiCara D, Hotzel I, Srinivasan K, Hansen DV, Atwal J, Lu Y, Bumbaca D, Pfeifer A, et al. (2016) Antibody-mediated targeting of tau in vivo does not require effector function and microglial engagement. Cell Rep 16:1690-1700.

Leem J, Mitchell LS, Farmery JHR, Barton J, Galson JD (2022) Deciphering the language of antibodies using self-supervised learning. Patterns 3:100513.

Lewcock JW, Schlepckow K, Di Paolo G, Tahirovic S, Monroe KM, Haass C (2020) Emerging microglia biology defines novel therapeutic approaches for Alzheimer's disease. Neuron 108:801-821.

Li L, Sengupta A, Haque N, Grundke-Iqbal I, Iqbal K (2004) Memantine inhibits and reverses the Alzheimer type abnormal hyperphosphorylation of tau and associated neurodegeneration. FEBS Lett 566:261-269.

Lleó A, Núñez-Llaves R, Alcolea D, Chiva C, Balateu-Paños D, Colom-Cadena M, Gomez-Giro G, Muñoz L, Querol-Vilaseca M, Pegueroles J, Rami L, Lladó A, Molinuevo JL, Tainta M, Clarimón J, Spires-Jones T, Blesa R, Fortea J, Martínez-Lage P, Sánchez-Valle R, et al. (2019) Changes in synaptic proteins precede neurodegeneration markers in preclinical Alzheimer's disease cerebrospinal fluid. Mol Cell Proteomics 18:546-560.

Marciniak E, Leboucher A, Caron E, Ahmed T, Tailleux A, Dumont J, Issad T, Gerhardt E, Pagesy P, Vileno M, Bournonville C, Hamdane M, Bantubungi K, Lancel S, Demeyer D, Eddarkaoui S, Vallez E, Vieau D, Humez S, Faivre E, et al. (2017) Tau deletion promotes brain insulin resistance. J Exp Med 214:2257-2269.

Mazaheri F, Snaidero N, Kleinberger G, Madore C, Daria A, Werner G, Krasemann S, Capell A, Trümbach D, Wurst W, Brunner B, Bultmann S, Tahirovic S, Kerschensteiner M, Misgeld T, Butovsky O, Haass C (2017) TREM2 deficiency impairs chemotaxis and microglial responses to neuronal injury. EMBO Rep 18:1186-1198.

McInnes J, Wierda K, Snellinx A, Bounti L, Wang YC, Stancu IC, Apóstolo N, Gevaert K, Dewachter I, Spires-Jones TL, De Strooper B, De Wit J, Zhou L, Verstreken P (2018) Synaptogyrin-3 mediates presynaptic dysfunction induced by tau. Neuron 97:823-835.

Mondragón-Rodríguez S, Perry G, Pena-Ortega F, Williams S (2017) Tau, amyloid beta and deep brain stimulation: aiming to restore cognitive deficit in Alzheimer's disease. Curr Alzheimer Res 14:40-46.

Morenas-Rodríguez E, Cervera-Carles L, Vilaplana E, Alcolea D, Carmona-Iragui M, Dols-Icardo O, Ribosa-Nogué R, Muñoz-Llahuna L, Sala I, Belén Sánchez-Saudinós M, Blesa R, Clarimón J, Fortea J, Lleó A (2016) Progranulin protein levels in cerebrospinal fluid in primary neurodegenerative dementias. J Alzheimers Dis 50:539-546.

Myers AJ, Pittman AM, Zhao AS, Rohrer K, Kaleem M, Marlowe L, Lees A, Leung D, McKeith IG, Perry RH, Morris CM, Trojanowski JQ, Clark C, Karlawish J, Arnold S, Forman MS, Deerlin VV, De Silva R, Hardy J (2006) The MAPT H1c risk haplotype is associated with increased expression of tau and especially of 4 repeat containing transcripts. Neurobiol Dis 25:561-570.

No author listed (2020) Positive phase 2 results claimed for masitinib in Alzheimer's. Available at: https://www.alzforum.org/news/research-news/positive-phase-2-results-claimed-masitinib-alzheimers. Accessed March 11, 2023.

No author listed (2022a) Semorinemab. Available at: https://www.alzforum.org/therapeutics/semorinemab. Accessed March 11, 2023.

No author listed (2022b) Two new stabs at vaccinating people against pathologic tau. Available at: https://www.alzforum.org/news/conference-coverage/two-new-stabs-vaccinating-people-against-pathologic-tau. Accessed March 11, 2023.

O'Brien JT, Holmes C, Jones M, Jones R, Livingston G, McKeith I, Mittler P, Passmore P, Ritchie C, Robinson L, Sampson EL, Taylor JP, Thomas A, Burns A (2017) Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. J Psychopharmacol 31:147-168.

Pascual G, Wadia JS, Zhu X, Keogh E, Kükrer B, van Ameijde J, Inganäs H, Siregar B, Perdok G, Diefenbach O, Nahar T, Sprengers I, Koldijk MH, der Linden EC, Peferoen LA, Zhang H, Yu W, Li X, Wagner M, Moreno V, et al. (2017) Immunological memory to hyperphosphorylated tau in asymptomatic individuals. Acta Neuropathol 133:767-783.

Perea JR, Llorens-Martín M, Ávila J, Bolós M (2018) The role of microglia in the spread of Tau: Relevance for tauopathies. Front Cell Neurosci 12:172.

Piette F, Belmin J, Vincent H, Schmidt N, Pariel S, Verny M, Marquis C, Mely J, Hugonot-Diener L, Kinet JP, Dubreuil P, Moussy A, Hermine O (2011) Masitinib as an adjunct therapy for mild-to-moderate Alzheimer's disease: a randomised, placebo-controlled phase 2 trial. Alzheimers Res Ther 3:16.

Prihoda D, Maamary J, Waight A, Juan V, Fayadat-Dilman L, Svozil D, Bitton DA (2022) BioPhi: A platform for antibody design, humanization, and humanness evaluation based on natural antibody repertoires and deep learning. MAbs 14:2020203.

Rapoport M, Dawson HN, Binder LI, Vitek MP, Ferreira A (2002) Tau is essential to beta -amyloid-induced neurotoxicity. Proc Natl Acad Sci U S A 99:6364-6369.

Reading CL, Ahlem CN, Parameswaran N (2021) Rationale for an anti-inflammatory insulin sensitizer in a phase 3 Alzheimer's disease trial. Alzheimers Dement 17:e057438.

Reifschneider A, Robinson S, van Lengerich B, Gnörich J, Logan T, Heindl S, Vogt MA, Weidinger E, Riedl L, Wind K, Zatcepin A, Pesämaa I, Haberl S, Nuscher B, Kleinberger G, Klimmt J, Götzl JK, Liesz A, Bürger K, Brendel M, et al. (2022) Loss of TREM2 rescues hyperactivation of microglia, but not lysosomal deficits and neurotoxicity in models of progranulin deficiency. EMBO J 41:e109108.

Rives A, Meier J, Sercu T, Goyal S, Lin Z, Liu J, Guo D, Ott M, Zitnick CL, Ma J, Fergus R (2021) Biological structure and function emerge from scaling unsupervised learning to 250 million protein sequences. Proc Natl Acad Sci U S A 118:e2016239118.

Robbins M, Clayton E (2023) Synaptopathy in CHMP2B frontotemporal dementia highlights the synaptic vesicle cycle as a therapeutic target. Neural Regen Res 18:315-316.

Robbins M, Clayton E, Kaminski Schierle GS (2021) Synaptic tau: a pathological or physiological phenomenon? Acta Neuropathol Commun 2021 9:149.

Rogaeva E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, Katayama T, Baldwin CT, Cheng R, Hasegawa H, Chen F, Shibata N, Lunetta KL, Pardossi-Piquard R, Bohm C, Wakutani Y, Cupples LA, Cuenco KT, Green RC, Pinessi L, et al. (2007) The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nat Genet 39:168-177.

Ruffolo JA, Sulam J, Gray JJ (2022) Antibody structure prediction using interpretable deep learning. Patterns 3:100406.

Salomoni P, Calabretta B (2009) Targeted therapies and autophagy: new insights from chronic myeloid leukemia. Autophagy 5:1050-1051.

Sarkar S, Floto RA, Berger Z, Imarisio S, Cordenier A, Pasco M, Cook LJ, Rubinsztein DC (2005) Lithium induces autophagy by inhibiting inositol monophosphatase. J Cell Biol 170:1101-1111.

Schwabe T, Srinivasan K, Rhinn H (2020) Shifting paradigms: the central role of microglia in Alzheimer's disease. Neurobiol Dis 143:104962.

Seidler PM, Murray KA, Boyer DR, Ge P, Sawaya MR, Hu CJ, Cheng X, Abskharon R, Pan H, DeTure MA, Williams CK, Dickson DW, Vinters HV, Eisenberg DS (2022) Structure-based discovery of small molecules that disaggregate Alzheimer's disease tissue derived tau fibrils in vitro. Nat Commun 2022 13:5451.

She M, Hu X, Su Z, Zhang C, Yang S, Ding L, Laudon M, Yin W (2014) Piromelatine, a novel melatonin receptor agonist, stabilizes metabolic profiles and ameliorates insulin resistance in chronic sleep restricted rats. Eur J Pharmacol 727:60-65.

Sperbera BR, Leight S, Goedert M, Lee VMY (1995) Glycogen synthase kinase-3β phosphorylates tau protein at multiple sites in intact cells. Neurosci Lett 197:149-153.

Spillantini MG, Goedert M (2013) Tau pathology and neurodegeneration. Lancet Neurol 12:609-622.

Suzuki M, Kimura T (2017) Microtubule-associated tau contributes to intra-dendritic trafficking of AMPA receptors in multiple ways. Neurosci Lett 653:276-282.

The Lancet (2022) Lecanemab for Alzheimer's disease: tempering hype and hope. Lancet 400:1899-1899.

Toure M, Crews CM (2016) Small-molecule PROTACS: new approaches to protein degradation. Angew Chem Int Ed Engl 55:1966-1973.

Tsujikawa K, Hamanaka K, Riku Y, Hattori Y, Hara N, Iguchi Y, Ishigaki S, Hashizume A, Miyatake S, Mitsuhashi S, Miyazaki Y, Kataoka M, Jiayi L, Yasui K, Kuru S, Koike H, Kobayashi K, Sahara N, Ozaki N, Yoshida M, et al. (2022) Actin-binding protein filamin-A drives tau aggregation and contributes to progressive supranuclear palsy pathology. Sci Adv 8:eabm5029.

Van Dyck CH, Nygaard HB, Chen K, Donohue MC, Raman R, Rissman RA, Brewer JB, Koeppe RA, Chow TW, Rafii MS, Gessert D, Choi J, Turner RS, Kaye JA, Gale SA, Reiman EM, Aisen PS, Strittmatter SM (2019) Effect of AZD0530 on cerebral metabolic decline in Alzheimer disease: a randomized clinical trial. JAMA Neurol 76:1219-1229.

van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T (2022) Lecanemab in early Alzheimer's disease. N Engl J Med 388:9-21 .

Walsh S, Merrick R, Milne R, Brayne C (2021) Aducanumab for Alzheimer's disease? BMJ 374:n1682.

Wang HY, Li W, Benedetti NJ, Lee DHS (2003) Alpha 7 nicotinic acetylcholine receptors mediate beta-amyloid peptide-induced tau protein phosphorylation. J Biol Chem 278:31547-31553.

Wang HY, Lee KC, Pei Z, Khan A, Bakshi K, Burns LH (2017) PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis. Neurobiol Aging 55:99-114.

Wang L, Bharti, Kumar R, Pavlov PF, Winblad B (2021) Small molecule therapeutics for tauopathy in Alzheimer's disease: walking on the path of most resistance. Eur J Med Chem 209:112915.

Wang S, Mustafa M, Yuede CM, Salazar SV, Kong P, Long H, Ward M, Siddiqui O, Paul R, Gilfillan S, Ibrahim A, Rhinn H, Tassi I, Rosenthal A, Schwabe T, Colonna M (2020) Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. J Exp Med 217:e20200785.

Wischik CM, Edwards PC, Lai RYK, Roth M, Harrington CR (1996) Selective inhibition of Alzheimer disease-like tau aggregation by phenothiazines. Proc Natl Acad Sci U S A 93:11213-11218.

Younger D, Berger S, Baker D, Klavins E (2017) High-throughput characterization of protein–protein interactions by reprogramming yeast mating. Proc Natl Acad Sci U S A 114:12166-12171.

Zampelas A, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C (2004) Associations between coffee consumption and inflammatory markers in healthy persons: the ATTICA study. Am J Clin Nutr 80:862-867.

Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE (2001) Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 108:1167-1174.

Zhou L, McInnes J, Wierda K, Holt M, Herrmann AG, Jackson RJ, Wang YC, Swerts J, Beyens J, Miskiewicz K, Vilain S, Dewachter I, Moechars D, De Strooper B, Spires-Jones TL, De Wit J, Verstreken P (2017) Tau association with synaptic vesicles causes presynaptic dysfunction. Nat Commun 8:15295.

Zhu LQ, Liu D, Hu J, Cheng J, Wang SH, Wang Q, Wang F, Chen JG, Wang JZ (2010) GSK-3 beta inhibits presynaptic vesicle exocytosis by phosphorylating P/Q-type calcium channel and interrupting SNARE complex formation. J Neurosci 30:3624-3633.

Zuccarello E, Acquarone E, Calcagno E, Argyrousi EK, Deng SX, Landry DW, Arancio O, Fiorito J (2020) Development of novel phosphodiesterase 5 inhibitors for the therapy of Alzheimer's disease. Biochem Pharmacol 176:113818.

P-Reviewer: Toscano CB; C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y