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REVIEW ARTICLE

Tau degradation in Alzheimer's disease: Mechanisms and therapeutic opportunities

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Abstract

In Alzheimer's disease (AD), tau undergoes abnormal post-translational modifications and aggregations. Impaired intracellular degradation pathways further exacerbate the accumulation of pathological tau. A new strategy – targeted protein degradation – recently emerged as a modality in drug discovery where bifunctional molecules bring the target protein close to the degradation machinery to promote clearance. Since 2016, this strategy has been applied to tau pathologies and attracted broad interest in academia and the pharmaceutical industry. However, a systematic review of recent studies on tau degradation mechanisms is lacking. Here we review tau degradation mechanisms (the ubiquitin–proteasome system and the autophagy–lysosome pathway), their dysfunction in AD, and tau-targeted degraders, such as proteolysis-targeting chimeras and autophagy-targeting chimeras. We emphasize the need for a continuous exploration of tau degradation mechanisms and provide a future perspective for developing tau-targeted degraders, encouraging researchers to work on new treatment options for AD patients.

KEYWORDS
Alzheimer's disease, autophagy, autophagy-targeting chimeras (AUTOTACs), degradation, proteolysis-targeting chimeras (PROTACs), targeted protein degradation, tau, ubiquitin–proteasome system

Highlights

- Post-translational modifications, aggregation, and mutations affect tau degradation.
- A vicious circle exists between impaired degradation pathways and tau pathologies.
- Ubiquitin plays an important role in complex degradation pathways.
- Tau-targeted degraders provide promising strategies for novel AD treatment.

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is accountable for around two-thirds of dementia cases in elderly people.[1] The prevalence of AD is increasing dramatically with aging populations worldwide.[2] The intracellular neurofibrillary tangle (NFT) of tau is one of the main neuropathological hallmarks in AD.[3–5] Tau is a microtubule-associated protein that plays an important role in

physiology, including stabilizing microtubules, regulating axonal transport, and maintaining the integrity of genomic DNA.[6] In AD, tau undergoes abnormal post-translational modifications and forms aggregates, which impairs its normal functions and induces neurotoxicity.[7–11] In addition, the lowered efficiency of degradation pathways in AD further exacerbates the accumulation of pathological tau. Multiple strategies have been applied to ameliorate tau pathology in AD, such as inhibiting tau expression, modulating tau post-translational modifications, inhibiting tau aggregation, and promoting tau degradation.[12,13] Most of the tau-targeting therapies in clinical trials are immunotherapies,[13,14] but tau antibodies have limited effect intracellularly, where most of the pathological tau accumulates.[15] An alternative strategy for increasing tau clearance is targeted protein degradation,[16] which promotes the ubiquitin–proteasome system (UPS) and the autophagy–lysosome pathway (ALP) for tau degradation. To guide the development of targeted protein degradation of tau, we need to understand the mechanisms of tau degradation under normal and pathological conditions and find suitable target proteins involved in intracellular degradation pathways. Therefore, in this review we summarize the main intracellular tau degradation pathways, UPS and ALP, their mechanisms, crosstalk, key proteins involved in these pathways, and their dysfunction in AD. We discuss all reported small-molecule- and peptide-based tau-targeted degraders, such as proteolysis-targeting chimeras (PROTACs) and autophagy-targeting chimeras (AUTOTACs). Finally, we emphasize the need for the continuous exploration of tau degradation mechanisms and provide a future perspective for the development of tau-targeted degraders in AD.

2 | TAU DEGRADATION MECHANISMS AND THEIR DYSFUNCTION IN AD

Protein degradation is an important cellular mechanism for protein homeostasis and essential for cell survival but is disrupted in neurodegenerative diseases such as AD.[17] Two major pathways – UPS and ALP – mediate intracellular tau degradation, and their dysregulation has been increasingly associated with tau pathology in AD.

2.1 | Ubiquitin–proteasome system

UPS is a highly conserved intracellular mechanism that maintains protein homeostasis and eliminates damaged, misfolded, and mutated proteins in both the cytoplasm and the nucleus.[18,19] UPS involves two steps: covalent attachment of multiple ubiquitin molecules to the protein substrate and subsequent degradation of the ubiquitinated protein by the proteasome complex. In the first step, the 76-amino-acid-long protein ubiquitin is activated by a ubiquitin-activating enzyme (E1) and then transferred to a ubiquitin-conjugating enzyme (E2). Subsequently, the ubiquitin–E2 conjugate interacts with the ubiquitin ligase (E3), which recognizes the protein substrate and mediates the transfer of ubiquitin from E2 to the protein substrate.[20] In the second step, ubiquitinated proteins are transported to the 26S proteasome for proteolysis into short peptides.[21] The 26S proteasome is a multicatalytic ATP-dependent protease complex (2.6 MDa) consisting of a cylindrically shaped 20S core particle and one or two 19S regulatory particles that cap the 20S core particle at either one end or both ends. The ubiquitinated proteins can be recognized by intrinsic ubiquitin receptors of the proteasome or shuttle factors, such as p62/SQSTM1, that contain both a ubiquitin-associated domain and a domain that binds to the proteasome.[22]

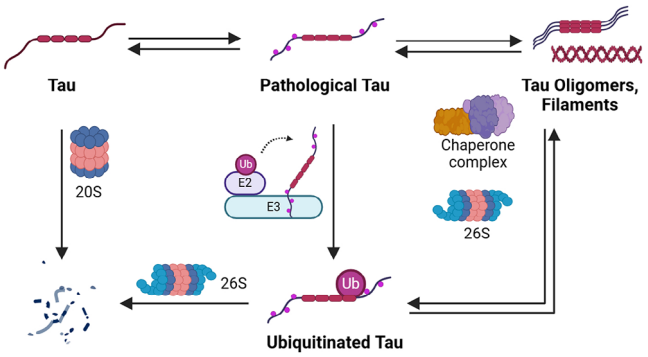

FIGURE 1 Tau degradation by ubiquitin proteasome system (UPS). Under normal conditions, tau is degraded by the 20S proteasome. After certain post-translational modifications (PTMs), tau is ubiquitinated by series E1/E2/E3 ubiquitin (Ub) transfer processes and delivered to the 26S proteasome for proteolysis into short peptides. Tau oligomers and filamentous aggregates can be disaggregated by the chaperone complex (Hsp70-Hsp110-JDPs) to monomeric tau. The 26S proteasome can also fragment filamentous aggregates and remove soluble oligomers, which is independent of its peptidase activity. Created with BioRender.com.

2.1.1 | Tau degradation by UPS

Tau, as a natively unfolded protein, is degraded by the ATP/ubiquitin-independent 20S proteasome under normal cell conditions[23,24] (Figure 1). When tau undergoes pathological modifications, such as hyperphosphorylation and truncation, it is degraded by the 26S proteasome instead of the 20S proteasome.[25] Hyperphosphorylated tau is ubiquitinated by the E3 ubiquitin ligase CHIP (carboxyl terminus of the Hsc70-interacting protein) together with the E2 ubiquitin-conjugating enzyme UbcH5, followed by UPS degradation via the 26S proteasome.[26,27] Tau fragments cleaved by caspase-2 at residues D65 and D421 are preferentially ubiquitinated by CHIP for degradation.[28] TauC3, the product of caspase cleavage at D421 in tau, is known to be a substrate of CHIP, and phosphorylation of TauC3 at a single residue (S416) is sufficient to weaken its interaction with CHIP.[29] Deletion of CHIP in mice leads to the accumulation of hyperphosphorylated tau and caspase-3-cleaved tau species,[30] and overexpression of CHIP promotes the degradation of phosphorylated tau (p-tau).[31,32] A recent study also showed that CHIP recognized a phosphorylation-dependent degron on tau,[33] although a former study revealed a multidomain dynamic interaction between CHIP and unmodified tau.[34] In addition, tau is a ubiquitinated substrate of other E3 ligases, for instance,

TABLE 1 Dysfunction of tau-targeting E3 ubiquitin ligases and deubiquitinases in AD patients.

Category	Protein name	Dysfunction in AD
E3 ubiquitin ligases	CHIP	Colocalized with tau lesions.[27] Increased protein levels in AD temporal cortices.[47] Decreased protein levels in AD hippocampus (Braak III and VI).[48] No significant change in mRNA levels.[48]
	TRAF6	Colocalized with tau and ubiquitin-associating protein sequestosome1/p62 in inclusion bodies isolated from AD hippocampus (Braak VI).[35]
	Axotrophin/ MARCH7	Colocalized with NFTs in AD hippocampus (Braak II–VI).[36] Decreased protein levels in cytoplasmic and nuclear fractions obtained from AD temporal cortex (Braak II–VI).[36]
	HRD1	Colocalized with p-tau and its expression levels correlate negatively with p-tau accumulation in hippocampal neurons of AD.[37,49] Increased ratio of hHrd1-positive neurons/astrocytes to total neurons/astrocytes in AD hippocampus CA1.[49] Decreased protein levels in soluble fraction, but increased levels in insoluble fraction of cerebral cortex of AD patients.[50] Increased tendency of mRNA levels in AD.[50]
	CUL5	None reported.
	TRIAD3A	Colocalized with tau amyloid in multiple histological forms in frontal cortex (Braak V–VI).[51] Decreased protein levels in medial frontal and temporal cortex (Braak V–VI).[51]
Deubiquitinases	OTUB1	None reported.
	USP9	Decreased expression of gonosomal gene *USP9Y* (Y-chromosomal form) in male late-onset AD patients as compared to unaffected male subjects.[40]
	USP10	Colocalized with p-tau in cell body of neurons in AD brain lesions.[52] Increased protein levels in AD hippocampus (Braak IV–VI).[41] Increased gene expression levels in AD hippocampus (selected samples from GSE5281 dataset).[41]
	USP11	Increased protein levels in AD frontal gyrus cortex (Braak IV–VI).[42] More strongly associated with tau pathology in women than in men.[42]
	USP13	Increased protein levels in AD hippocampus.[43]
	USP14	Decreased gene expression level in AD and negatively correlated with aging.[53]
	UCH-L1	Colocalized with p-tau in NFTs.[54] Higher oxidatively modified in AD brain.[55] Increased protein levels in AD hippocampus.[56] Decreased protein levels in AD frontal cortex.[55] Decreased protein levels in cerebral cortex (superior frontal gyrus) of patients with late-onset sporadic AD.[57] Decreased soluble protein levels but an increasing trend of insoluble protein levels in AD frontal cortex.[58] Soluble UCH-L1 proteins are inversely proportional to NFTs numbers in AD frontal cortex.[55]

tumor necrosis factor receptor-associated factor 6 (TRAF6),[35] axotrophin/MARCH7,[36] HRD1 (endoplasmic reticulum-associated degradation)-associated ubiquitin ligase,[37] and Cullin-RING ligase CUL5 (which binds tau via adaptor protein SOCS4)[38] (Table 1). Meanwhile, ubiquitin molecules from ubiquitinated tau can be removed by deubiquitinating enzymes known as deubiquitinases (DUBs), such as ovarian-tumor domain cysteine protease DUB (OTUB1),[39] ubiquitin-specific protease (USP) 9,[40] USP10,[41] USP11,[42] USP13,[43] USP14,[44,45] and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1)[46] (Table 1).

Interestingly, Ye et al. performed in vitro assays showing that the 26S proteasome can remove soluble oligomers assembled from the monoubiquitinated tau aggregation domain (Tau^{K18}) primarily by enabling their dissociation independent of its peptidase activity.[59] They also showed that full-length tau filamentous aggregates (up to ~20 μm in length) are substrates of the 26S proteasome, which fragments them into small aggregates depending on proteasomal ATPase – but not proteolytic – activity.[60] These results amend the former view of proteasomes that can only target non-aggregated proteins.[61] Other indirect evidence comes from the development of PROTACs (summarized in Section 3), which are hetero-bifunctional molecules that bring the E3 ligase close to the protein of interest for ubiquitination. Silva et al. showed that their PROTACs (eg, QC-01-175) could reduce soluble and insoluble tau species in a UPS-dependent manner.[62,63] An intermediate step might be involved before the 26S proteasome degradation of tau aggregates as follows: disaggregation of ubiquitinated tau aggregates by chaperone Hsp70-Hsp110-JDPs (J domain proteins) complex.[64] However, this disaggregation step has not been investigated in their reported research. Taken together, the exact mechanism of tau degradation by UPS is still uncertain and requires further comprehensive investigations.

2.1.2 | UPS dysfunction in AD

In human AD brains, there is a global increase of tau ubiquitylation. A total of 28 ubiquitylation sites have been identified for tau in AD brains, mainly located on its proline-rich domain and microtubule-binding region.[65,66] K6-, K11-, K48-, and K63-linked as well as linear (head-to-tail) polyubiquitin chains have been verified in paired helical filaments (PHFs) or NFTs.[67,68] In AD, tau-targeting E3 ligases and DUBs have been reported to be either upregulated[41,47,49] or downregulated,[48,50,55] and some of them are reported to colocalize with AD tau pathology (Table 1). For example, CHIP colocalizes with tau lesions in human patients with tauopathy, including AD.[27] Sahara et al. reported increased CHIP levels in the temporal cortices of human AD brains, and CHIP protein expression levels were inversely proportional to sarkosyl-insoluble PHF-tau levels. They suggested that increases in CHIP may protect against NFT formation at the early stage of AD.[47] Later, Ravalin et al. observed a striking loss in CHIP expression in the hippocampus of human AD tissue at Braak stages III and VI, representing AD middle and late stages, respectively. They also analyzed RNA sequencing data from the Allen Brain Atlas revealing that CHIP mRNA did not significantly change, suggesting that the observed loss of CHIP occurs post-transcriptionally.[48] Another E3 ligase, HRD1, colocalizes with p-tau, and its expression levels correlate negatively with p-tau accumulation in the hippocampal neurons of AD.[37,49] The ratio of hHrd1-positive neurons/astrocytes to total neurons/astrocytes is increased in the CA1 subfield in AD hippocampus compared with the age-matched controls.[49] In the cerebral cortex of AD patients, HRD1 protein levels in the 1% NP-40 detergent-soluble fraction were significantly decreased,[50] whereas they were increased in the insoluble fraction.[69] In addition, HRD1 mRNA showed a tendency to increase in AD compared with controls.[50] The DUB UCH-L1 colocalizes with hyperphosphorylated tau in NFTs[54] and is oxidatively modified in the AD brain.[55] UCH-L1 protein levels are significantly increased in the human AD hippocampus (1.31-fold)[56] but decreased in AD frontal cortex.[55] Specifically, there is a significant decrease in soluble UCH-L1 protein levels but an increasing trend of insoluble UCH-L1 levels in AD frontal cortex,[58] and soluble UCH-L1 protein levels are inversely proportional to NFTs numbers in AD frontal cortex.[55] A recent study also reported that UCH-L1 protein levels decreased in the cerebral cortex (superior frontal gyrus) of patients with late-onset sporadic AD.[57] Therefore, in different brain regions and stages of AD, the regulation of UPS might be different, and it is crucial to investigate whether these changes are due to gene expression, protein degradation, or aggregation.

In addition, proteasome activity is significantly impaired in human AD brains (Braak stage VI), especially in the hippocampus and parahippocampal gyrus,[70] and straight gyrus.[71] However, this loss of proteasome activity is not associated with a decrease in proteasome protein expression, which suggests that the proteasome may be inhibited in AD by a post-translational modification.[70] Importantly, PHF isolated from AD brains and tau oligomers can inhibit proteasome activity.[71,72] In summary, UPS dysfunction leads to abnormal accumulation of tau, while pathological tau impairs UPS, forming a vicious circle for disease progression.

2.2 | Autophagy–lysosome pathway

ALP is another important degradation mechanism that mediates the delivery of intracellular cytosolic components to lysosomes for degradation and recycling. It includes three major types, as follows: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA).[73] Macroautophagy is the most prevalent form, and during this process the cell forms a double-membrane sequestering compartment termed the phagophore, which matures into an autophagosome with intracellular material (eg, proteins and organelles) inside, and is then delivered to lysosomes for degradation.[74] Macroautophagy is inhibited by the mammalian target of rapamycin (mTOR) and triggered by activation of adenosine monophosphate-activated protein kinase (AMPK).[75] In microautophagy, cytoplasmic material is directly taken up by lysosomes and late endosomes by membrane protrusion and invagination.[76] In CMA, lysine-phenylalanine-glutamate-arginine-glutamine (KFERQ)-like motif-bearing proteins in complex with the chaperone heat shock cognate protein of 70 kDa (HSC 70) and co-chaperones are delivered to the lysosome surface and internalized into the lysosome through a multimeric complex of lysosome-associated membrane protein 2A (LAMP2A) for degradation.[77]

2.2.1 | Tau degradation by ALP

Tau can be degraded by all three types of ALP (Figure 2). Selective macroautophagy can recognize protein aggregates and mediate their degradation, which is called "aggrephagy."[78] In aggrephagy, ubiquitinated tau is recognized by autophagy cargo receptors, such as p62/SQSTM1 (sequestosome1),[79,80] OPTN (optineurin),[80,81] NDP52/CALCOCO2 (nuclear domain 10 protein 52, calcium binding and coiled-coil domain 2),[82] NBR1 (neighbor of breast cancer 1 gene),[83] CCDC50 (coiled-coil domain containing 50),[84] and TAX1BP1 (trans-activating transcriptional regulatory protein of HTLV-1 [TAX1] binding protein 1).[85] These receptors contain not only a ubiquitin-associated domain to recognize ubiquitin chains on protein aggregates, but also an LC3-interacting region allowing for the binding of LC3 on the phagophore membrane, thereby allowing the recruitment of these protein aggregates to phagophores, eventually leading to degradation by the lysosome. Specifically, these autophagy cargo receptors target different forms of tau species in different conditions. The knocking out of p62/SQSTM1 in P301S mutant tau transgenic mice (line PS19) causes a significant accumulation of tau oligomers, suggesting the requirement of p62 to eliminate disease-related oligomeric tau species.[79] However, another study reported that p62/SQSTM1 predominantly degraded insoluble, but not soluble, mutant tau (P301L) in a seeding-based cellular assay and that overexpression of

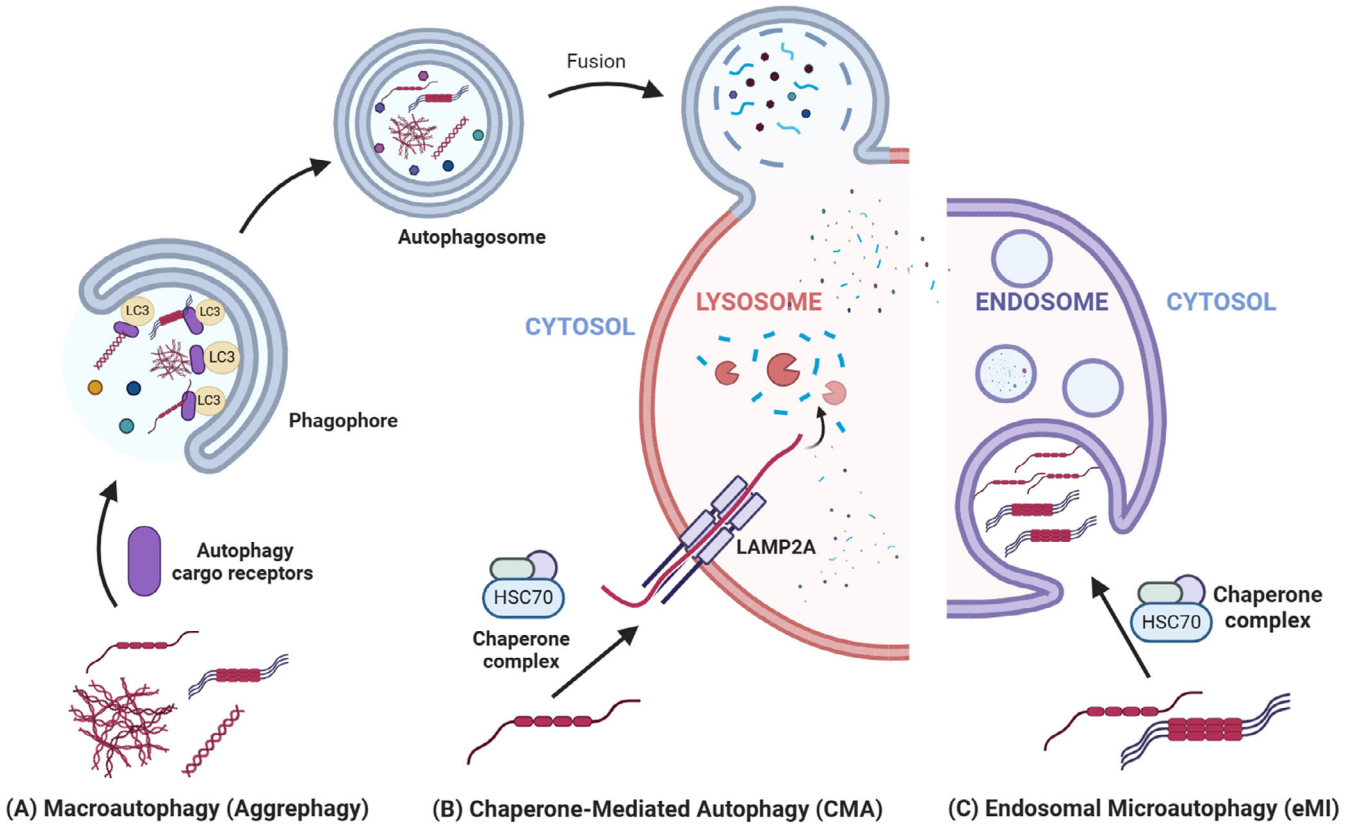

FIGURE 2 Tau degradation by the autophagy-lysosomal pathway (ALP). ALP includes three major types: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy. (A) In one of the selective macroautophagy pathways (aggrephagy), ubiquitinated tau is recognized by autophagy cargo receptors, which can bind to LC3 on the phagophore membrane. This leads to the recruitment of tau to phagophores, followed by degradation in the lysosome. (B) In CMA, KFERQ-like motifs of tau are recognized by the HSC70 chaperone complex, delivered to the lysosomal surface, and internalized into the lysosome through a multimeric complex of lysosome-associated membrane protein 2A (LAMP2A) for degradation. (C) In selective endosomal microautophagy (eMI), KFERQ-like motifs of tau are recognized by the HSC70 chaperone complex, which can bind to the endosomal membrane via electrostatic interactions. The late endosomal membrane invaginates and sequesters tau into small microvesicles. Late endosomes can degrade tau directly in the endosomal lumen or upon fusion with autophagosomes/lysosomes. Created with BioRender.com.

p62/SQSTM1 significantly reduced insoluble tau pathology in rTg4510 mice (Tau P301L).[80] OPTN primarily targets soluble endogenous WT tau expressed in physiological conditions, and OPTN expression can eliminate soluble and insoluble fractions of mutant tau (P301L) in cells[80] and reduce p-tau levels and improve learning and memory in mutant tau (P301L) expressing mice.[81] NDP52/CALCOCO2 overexpression facilitates the clearance of endogenous p-tau (Ser262/Ser356 and Ser396/Ser404) in primary cortical neurons.[82] A recent study revealed that the specificity of autophagy cargo receptors in targeting different tau species can be regulated: co-chaperone BAG3 promotes p62/SQSTM1 binding to oligomeric tau and inhibits its binding to monomeric tau, while BAG3 promotes NBR1 binding with the monomeric form of tau, which is disrupted in the absence of BAG3.[83] In the presence of p62/SQSTM1 and NBR1, TAX1BP can be recruited to monomeric ubiquitylated K63-enriched tau but not efficiently recruited to tau fibrils extracted from AD brains.[85] This lack of recruitment is due to the saturation of ubiquitin marks on fibrillar tau by p62/SQSTM1 and NBR1. In addition, there also exist other kinds of autophagy cargo receptors, such as CCT2 (chaperonin-containing TCP1 subunit 2), that promote autophagosome incorporation and clearance of mutant Tau P301L aggregates by interacting with both LC3 and tau, independent of tau ubiquitination.[86]

Tau is also a substrate of CMA and selective endosomal microautophagy (eMI), both of which require a KFERQ-like motif recognized by the HSC70 chaperone. Tau contains two such motifs in its C-terminal region: ^{336}QVEVK^{340} and ^{347}KDRVQ^{351}.[87] CMA and eMI efficiently degrade WT-unmodified tau monomer (hTau40), but tau mutations (A152T or P301L) or phosphorylation can reduce the degradation by CMA and eMI.[88] Under certain conditions, tau degradation can be rerouted from one type of autophagy to another. For example, tau mutation A152T blocks the degradation of tau by eMI, favors its rerouting toward macroautophagy degradation, and has a mild inhibitory effect on its degradation by CMA.[88] Tau acetylation has an inhibitory effect on CMA activity and reroutes tau degradation from CMA to macroautophagy and eMI.[89] Experimental CMA blockage favors rerouting of monomer and oligomers of acetylated tau toward late endosomes/multivesicular bodies by eMI, which could lead to extracellular release and cell-to-cell propagation of tau.[89]

TABLE 2 Dysfunction of tau-targeting autophagy cargo receptors in AD patients.

Protein name	Dysfunction in AD
p62/SQSTM1	Colocalized with NFTs in AD parietal cortex (Braak stages V and VI).[101] Colocalized with p-tau and Aβ in AD temporal cortex.[102] Decreased protein levels in AD frontal cortex (Braak stages IV and VI).[103] Increased protein levels in AD temporal cortex.[102,104,105]
OPTN	Not colocalized with tau inclusions.[106] A decreasing trend of protein levels in AD temporal lobe cortex.[106] Progressively increased accumulation in aggresomes in AD hippocampus (from Braak III/IV to Braak VI).[107]
NDP52/CALCOCO2	Associate with p-tau (Ser262/Ser356 [12E8] or a Ser396/Ser404 [PHF1]) in the AD cerebral cortex.[82] Inversely proportional to p-tau in insoluble fractions.[82]
NBR1	No changes in total brain homogenates from AD.[108] Reduced protein levels in neurons and microglia, but increased protein levels in astrocytes in AD hippocampus (Braak III and IV).[108]
CCDC50	None reported.
TAX1BP1	No immunoreactivity for TAX1BP1 in NFTs in AD hippocampus by immunohistochemistry.[85]
CCT2	Decreased gene expression levels in AD prefrontal cortex (GSE33000 database).[109]

2.2.2 | ALP dysfunction in AD

Accumulating evidence shows that ALP is impaired in AD.[90,91] Autophagosomes and other prelysosomal autophagic vacuoles are massively accumulated in neocortical biopsies from human AD brains as observed by electron microscopy.[92] This accumulation in AD is due to transcriptional upregulation of autophagy and impaired clearance of autophagic vacuoles.[93–95] In neurons, autophagosomes are continuously generated at the distal ends of axons and dendrites and need to be transported retrogradely long distances to fuse with lysosomes near the cell body for degradation. In AD, the maturation of autophagolysosomes and their retrograde transport are impeded, which also leads to massive accumulation of autophagic vacuoles within impaired neurites.[96] CMA downregulation was revealed by analysis of a single-nucleus RNA sequencing dataset in the prefrontal cortex of AD patients.[97] This CMA inhibition starts early in AD, becomes more severe at later disease stages, and is cell-type specific: It only appears in excitatory and inhibitory neurons, not in astrocytes, microglia, and oligodendrocytes.[97] In addition, there are several gene mutations involved in the impairment of autophagy and lysosome function in both early-onset familial AD and late-onset AD, such as presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and phosphatidylinositol binding clathrin assembly protein (*PICALM*) (summarized in Zhang et al.[98]). Tau pathology is also closely related to this impairment of ALP in AD. Pathological tau causes dysfunction of autophagy and lysosomes,[98,99] while dysfunction of ALP results in the formation of tau oligomers and insoluble aggregates,[100] which exacerbates disease progression.

Autophagy cargo receptors are involved in tau pathology in AD (Table 2). For example, p62/SQSTM1 has been found to colocalize with NFTs in the parietal cortex of AD patients (Braak stages V and VI)[101] and with p-tau and amyloid β-peptide (Aβ) in the temporal cortex of human AD brain.[102] In the middle and late stages of AD individuals (Braak stages IV and VI), the expression of p62 was decreased in the frontal cortex relative to age-matched controls and correlated with increased oxidative damage to p62 DNA promoter.[103] In the temporal cortex, increased p62 protein levels are found in AD compared to controls.[102,104,105] In AD brains, OPTN-positive neuronal and glial cytoplasmic inclusions appear in areas severely affected by AD-type tau pathology. However, double immunofluorescence labeling did not show colocalization of the rare OPTN inclusions with the more frequent tau inclusions.[106] In *post mortem* hippocampal tissues, the accumulation of OPTN in histone deacetylase 6-positive aggresomes progressively increases from AD Braak stages III/IV to Braak stage VI.[107] Co-immunoprecipitation studies show that NDP52 associates with p-tau (Ser262/Ser356 [12E8] or a Ser396/Ser404 [PHF1]) from AD cerebral cortical samples, and the amount of p-tau in sarkosyl-insoluble fractions is inversely proportional to that of NDP52.[82] The NBR1 protein and mRNA expressions are not altered in total brain homogenates from AD human patients compared to healthy controls.[108] However, NBR1 protein levels are significantly reduced in neurons and microglia, particularly in regions with intense Aβ deposition, but increased in astrocytes in the hippocampus of AD brains (Braak stages III and IV).[108] Therefore, in human AD brains, the dysregulation of autophagy cargo receptors may differ between brain regions and even between different cell types in the same area. Still, further comprehensive studies are needed to provide a clear understanding of AD pathology related to autophagy.

2.3 | Crosstalk between UPS and ALP

Multiple lines of evidence show that crosstalk exists between UPS and ALP. The initial observation of their connection was the compensatory balance between the activities of UPS and ALP.[110] For instance, inhibition of the UPS by proteasome inhibitors results in compensatory activation of the ALP in cultured primary neurons, with a subsequent increase in tau degradation.[111,112] Underlying their crosstalk for tau

degradation, ubiquitin plays an important role in the molecular mechanism: Both systems target ubiquitinated tau and share a common ubiquitin receptor for delivery.

Ubiquitinated tau can be degraded by either the 26S proteasome or aggrephagy, an important selective variant of macroautophagy, depending on which type of ubiquitin chain linkage occurs. The ubiquitin sequence contains seven lysine residues (at positions 6, 11, 27, 29, 33, 48, and 63), and polyubiquitin chain assembly can occur by covalent bonds between the C-terminus of one ubiquitin and any one of the seven lysine residues or the N-terminus of the adjacent ubiquitin.[113] The predominant polyubiquitin conjugation is K48-linked chains, which target proteins to the proteasome for degradation.[114] Another common polyubiquitin conjugation is K63-linked chains, which regulate proteasome-independent pathways, such as ALP.[115] In addition to polyubiquitination, monoubiquitination, conjugation of a single ubiquitin molecule to the substrate's protein amino group or multiple amino groups, is another important signal for proteasomal degradation.[116] Tan et al. showed that K48- and K63-linked polyubiquitination, as well as monoubiquitin modification, contributed to the biogenesis of tau inclusions, but only K63 ubiquitin-modified tau inclusions were preferentially cleared by autophagy.[117] K63-linked ubiquitination is also associated with enhanced seeding activity and propagation of pathological tau.[118] The E3 ligase CHIP can ubiquitinate tau by forming K48- and K63-linked ubiquitin chains.[27] The ability of CHIP to form different ubiquitin linkages depends on its E2 partners: CHIP forms specific K63-linked chains using Ubc13-Uev1a as its E2, but when CHIP is paired with E2 UbcH5a, it forms either K63- or K48-linked chains.[119] Tau is also a K63-polyubiquitinated substrate of TRAF6, another E3 ligase targeting tau.[35] Interestingly, a recent study revealed that E3 ligase TRIAD3A catalyzes mixed K11/K63 polyubiquitin chains and self-assembles into liquid–liquid phase separated droplets.[51] Tau is ubiquitinated and converted into fibrillar aggregates within TRIAD3A droplets, which interact with LC3 to deliver the complex to autophagosomes for autophagic degradation. Regarding tau monoubiquitylation, E3 ligase axotrophin/MARCH7 monoubiquitinates tau at multiple sites including the microtubule-binding domain,[36] and E2 UBE2W monoubiquitinates the N-terminus of Tau^{K18}.[59] Therefore, under various circumstances, tau can be ubiquitinated by different enzymes, forming distinct ubiquitin linkages that encode the degradation pathway.

The most studied ubiquitin receptor is p62/SQSTM1, which is not only the shuttle factor for UPS but also the autophagy cargo receptor for ALP. p62/SQSTM1 can bind to ubiquitinated proteins via its C-terminal ubiquitin-associated domain, to the proteasome via its N-terminal Phox-BEM1 domain, and to autophagic membranes via its LC3-interacting region.[22] Studies show that the UPS/ALP choice is determined by the oligomeric state of ubiquitin receptors, rather than their ubiquitin-binding properties.[120] The p62/SQSTM1 dimers recognize ubiquitinated proteins and shuttle them to the proteasome for UPS degradation, whereas higher-order oligomers of p62/SQSTM1 take up ubiquitinated proteins in the form of p62/SQSTM1 bodies that subsequently recruit autophagic membranes for ALP (reviewed in Pohl and Dikic[121]). Regarding tau degradation, Babu et al.[35] found that polyubiquitinated tau interacts with the ubiquitin-associated domain of p62/SQSTM1 and that tau fails to interact with the proteasome in brain lysates of p62/SQSTM1 knockout mice, indicating a requirement for p62/SQSTM1 shuttling of tau to the proteasome. Falcon et al. showed that p62/SQSTM1 targeted seeded tau aggregates for ALP degradation in cells overexpressing Tau P301S treated with DyLight-labeled aggregated Tau P301S.[122] In animal models, genetic inactivation of p62/SQSTM1 leads to the accumulation of hyperphosphorylated tau,[79,123] and overexpression of p62/SQSTM1 in tau transgenic mouse (rTg4510) brains ameliorates tau pathology.[80] In the brains of AD patients, p62/SQSTM1 is colocalized with pathological tau (Table 2). However, detailed molecular roles of p62/SQSTM1 in tau degradation by UPS or ALP are lacking. This needs to be investigated to reveal, for instance, which oligomeric state of p62/SQSTM1 is involved in which tau degradation pathway.

3 | TARGETING DEGRADATION PATHWAYS FOR TAU CLEARANCE

There are multiple strategies to promote the clearance of pathological tau for AD treatment, such as proteasome activators and autophagy modulators.[12] However, proteasome activators have tumorigenesis potential and show unspecific effects on other proteolytic pathways,[124] and autophagy modulators exhibit low pharmacological specificity for their targets in the autophagy process.[125] A new strategy – targeted protein degradation – recently emerged as a modality in drug discovery where bifunctional molecules bring the target protein to the degradation machinery. In this way, targeted protein degraders can promote the degradation of tau, an "undruggable" protein, with high specificity.[16] Moreover, targeted protein degraders are event-driven with catalytic activity, requiring only a transient binding event for activity, which significantly lowers the effective concentrations and expands the therapeutic window.[126]

3.1 | Small-molecule-based PROTACs for targeting tau

Currently, most of the targeted protein degraders for tau are PROTACs (Table 3). PROTACs are bifunctional molecules that induce selective degradation of specific proteins by harnessing a cell's UPS. By linking a ligand that binds to tau with an E3 ligase ligand, PROTACs can promote the ubiquitination and subsequent degradation of tau, offering a new avenue for therapeutic development[127] (Figures 3 and 4).

3.1.1 | PROTAC C8

The PROTAC C8 was designed using thalidomide as an E3 ligase binder, a long-chain alkyl group was used as a linker, and quinoxaline attached a thiophene ring as tau binder.[129] This quinoxaline derivative tau binder has high affinity and selectivity for tau aggregates,

TABLE 3 Summary of tau-targeting PROTACs.

PROTAC name	Target	Tau binder	Target E3 ligase	DC_{50}	Cell models	Animal models	BBB permeability	Reference
C8	Total tau and p-tau (S202, T205, S262, S396, and S404)	QNN-3b (modified quinoxaline)[128]	CRBN	0.05 μM	HEK293-hTau, SH-SY5Y (p-tau induced using okadaic acid)	C57BL/6 mice overexpressing hTau	Yes, in BALB/C nude mice, maximum fluorescence intensity of C8 was observed at 1 h after i.v. at 3 mg/kg dose	[129]
T3	α-syn, p α-syn (S129), total tau, and Tau-S404	BTA[130,131]	CRBN	1.57 μM (α-Syn), 4.09 μM (tau)	Tau preformed fibril-seeding HEK293T, SH-SY5Y overexpressing α-syn	MPTP-induced C57BL/6 mice model	Yes, in vitro: bEnd3 cells transwell assay with SH-SY5Y cells seeded at the bottom well In vivo: In male C57BL/6 mice, the maximal brain concentration of T3 was 1.73 μM at 0.25 h, after i.v. at 8 mg/kg	[132]
C004019	Total tau, p-tau (S202, T205, S214, S262, S396, S404), and tau oligomers (T22)	ID220149[133,134]	VHL	0.00785 μM in HEK293-hTau cell model. Subcutaneous 3 mg/kg for 24 h in mouse model	HEK293-hTau and SH-SY5Y	hTau-transgenic and 3×Tg-AD mouse models	Yes. In male C57BL/6 mice, maximal brain concentration of C004019 was 10.8 ng/mL at 0.167 h, after s.c. at 3 mg/kg	[135]
QC-01-175	Total tau and p-tau (S396, S202, and T205)	T807 core scaffold [136]	CRBN	0.1 μM	Human neuronal cell models derived from a PSP patient carrier of Tau-A152T risk variant and one derived from a FTD patient carrier of Tau P301L	Not reported	Yes. In male CD-I mice, maximum brain concentration of QC-01-175 was 56.4 ng/mL at 0.5 h, after i.p. at 30 mg/kg (patent: WO2019014429A1[137])	[62]
I3	Total tau	THK5105[138]	CRBN	50 μM	PC12 cells and PC12 transfected with GFT-tau plasmid	Not reported	Yes, in ICR male nude mice, the maximum brain concentration of I3 was 29.10 ng/mL at 0.25 h, after intragastric (po) administration at 30 mg/kg	[139]
Peptide 2	Total tau	YQQYQDATADEQG (β-tubulin sequence)[140,141]	VHL	~50 μM	N2a cells	Not reported	Not reported	[142]
TH006	Total tau	YQQYQDATADEQG (β-tubulin sequence)[140,141]	VHL	50 μM	Tau-EGFP-overexpressed N2a cells, tau-overexpressed SH-SY5Y cells, 3×Tg-AD mouse primary neuron cells	3×Tg-AD mouse model	Not reported	[143]
Keap1-dependent Peptide 1	Total tau and p-tau (T205)	YQQYQDATADEQG (β-tubulin sequence)[140,141]	Keap1	20 μM	Tau overexpressed cell lines (SH-SY5Y, N2a and PC-12)	3×Tg-AD mouse model	Yes, when loaded within neurotransmitter-derived lipidoid nanoparticle delivery system[144]	[144,145]

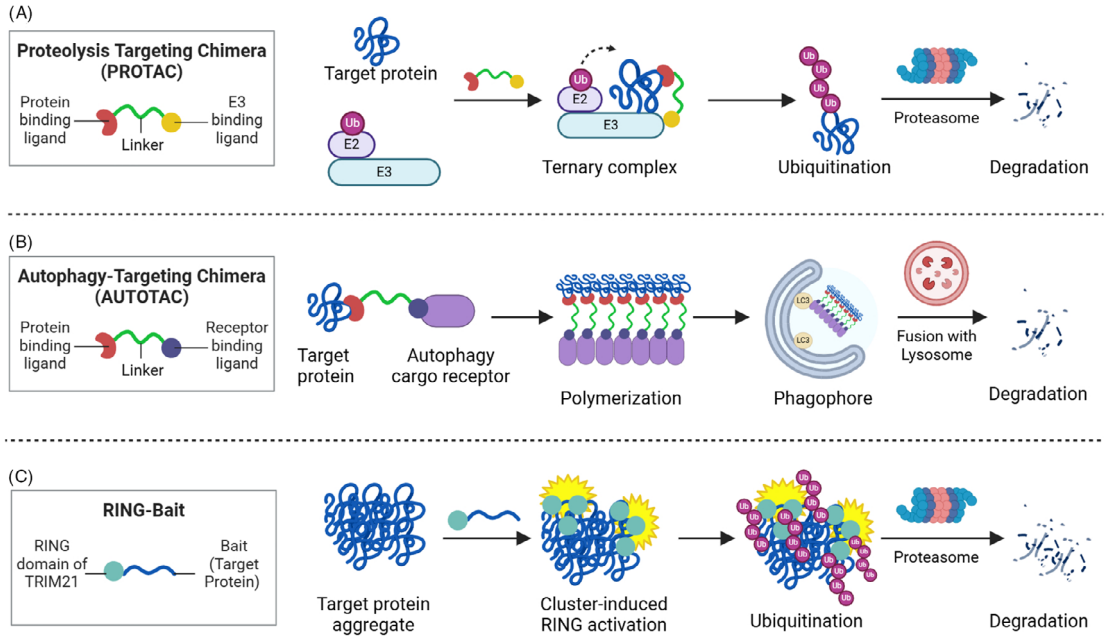

FIGURE 3 Schematic of proteolysis-targeting chimeras (PROTACs), autophagy-targeting chimeras (AUTOTACs), and RING-Bait technology. (A) PROTACs bring the target protein close to the E3 ligase, which results in protein ubiquitination, followed by proteasomal degradation. (B) AUTOTACs simultaneously interact with the target protein and the autophagy cargo receptor (eg, p62/SQSTM1), which facilitates p62/SQSTM1 self-polymerization in complex with target proteins. Then the complex is delivered to the phagophore by binding to LC3, followed by autophagosome formation and lysosomal degradation. (C) RING-Bait contains a RING domain of the E3 ligase tripartite motif-containing protein 21 (TRIM21) and a bait, such as the target protein. During the target protein aggregation, RING-Baits are recruited into the aggregates. This clustering dimerizes the RING domain and activates its E3 function, leading to subsequent proteasomal degradation. Created with BioRender.com.

which enables the detection of tau aggregates in the brain through fluorescence imaging.[128] C8 effectively decreased total tau and p-tau levels in HEK293 cells stably expressing WT full-length human tau (referred to as HEK293-hTau). Tau clearance induced by C8 in the HEK293-hTau cell model is through the UPS but not the ALP, as shown by using proteasome inhibitor MG132 and autophagy inhibitor bafilomycin A1.[129] C8 showed good blood-brain barrier (BBB) permeability in BALB/C nude mice by in vivo imaging after intravenous injection (3.0 mg/kg). Purified pAAV-hSyn-hTau-mCHERRY-3×FLAG virus was injected bilaterally into the hippocampus CA1 region of male C57BL/6 mice (8 weeks old) to induce hTau-overexpressed mouse model. In this mouse model, C8 treatment (10 mg/kg, i.p., 3 times/week for 1 month) ameliorated cognitive dysfunction in novel object recognition and Morris water maze and reduced total tau and p-tau levels in the hippocampus.[129]

3.1.2 | PROTAC T3: Degradation of alpha-synuclein and tau

In several neurodegenerative illnesses, tau and alpha-synuclein (α-Syn) play key roles in the manifestation of pathology.[146–148] Under pathological conditions, partially unfolded proteins like tau and α-Syn can form aberrant cellular aggregates and toxic oligomers. Genome-wide association studies of tau and α-Syn support their clinical relationship and the co-occurrence of their fibrillar aggregates in many illnesses.[149,150] In neurodegenerative diseases, multitarget treatment may hold significant promise for improving efficacy. Zhu et al. devised an innovative approach to targeting both tau and α-Syn: a dual PROTAC T3.[132] This PROTAC was developed by using 2-[49-(Methylamino)phenyl]-6-methylbenzothiazole (BTA) as tau and α-Syn target warhead and pomalidomide as E3 ligase cereblon (CRBN) binder. BTA, an analog of thioflavin-T, can be used as a warhead to degrade protein aggregates due to its high brain penetration and ability to bind to aggregates and oligomers.[130,131] A label-free fluorescence polarization assay demonstrated that BTA had a strong ability to bind to preformed fibrils from tau and α-Syn; the K_D values were 2.55 ± 0.72 and 0.32 ± 0.17 μM, respectively. To increase the likelihood that the target protein would associate with the ubiquitin ligase complex, conformational flexible polyethylene glycol (PEG)-based chains were used.[151] The PEG_4-derived linkers exhibited higher degradation efficiency compared to other types of linkers. A preformed tau fibril-seeding HEK293T cellular model and an α-Syn overexpression preformed fibril-seeding model in HEK293T cells were created to evaluate the degrading effects of T3. T3 induced a concentration-dependent decrease in total tau and p-tau levels following a 24-h treatment. T3 demonstrated the highest degradation rate (D_{max}) of 61% and a half degradation concentration (DC_{50}) of 4.09 ± 0.90 μM against tau. Additionally, there was a notable decrease in the p-tau (S404) protein level. It is interesting to note that after 24 h of T3 therapy, p-tau was more effectively degraded than total tau. For α-Syn, T3 showed the greater degradation rate (D_{max}) of 78% and the half degradation concentra-

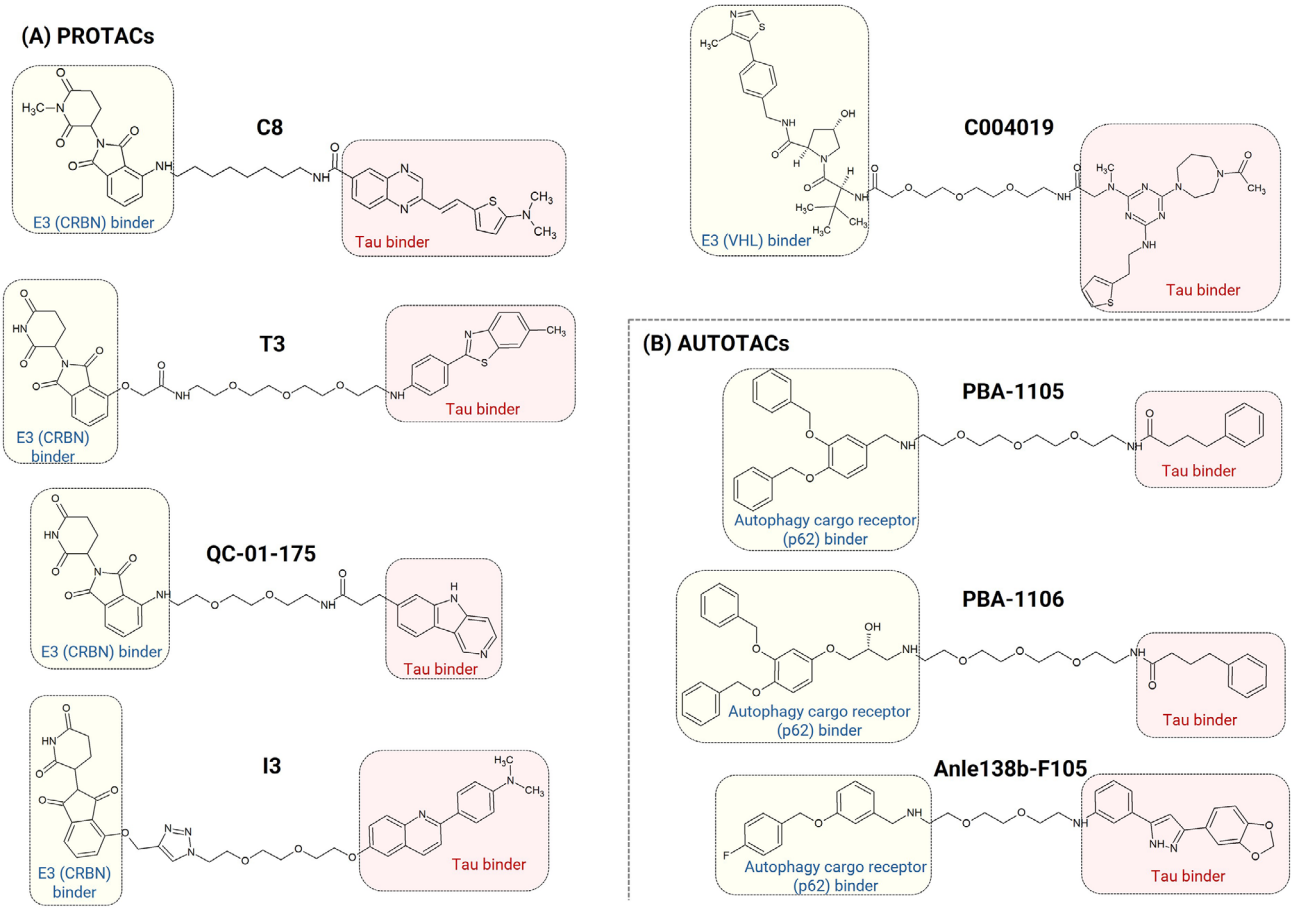

FIGURE 4 Chemical structures of small-molecule proteolysis-targeting chimeras (PROTACs) and autophagy-targeting chimeras (AUTOTACs) for tau degradation. (A) C8, T3, QC-01-175, and I3 are PROTACs with ligands binding to tau and E3 ligase cereblon (CRBN). C004019 is the PROTAC with ligands binding to tau and E3 ligase von Hippel-Lindau protein (VHL). (B) PBA-1105, PBA-1106, and Anle138b-F105 are AUTOTACs with ligands binding to tau and the autophagy cargo receptor (p62/SQSTM1).

tion (DC_{50}) of 1.57 ± 0.55 μM. Following a 48-h T3 therapy, there was a substantial drop in the protein level of p-αSyn (S129). T3 also reduced α-Syn aggregate-induced toxicity in the SH-SY5Y cell model stably overexpressing α-Syn treated with liposome-packaged preformed fibrils. Under mechanistic evaluation, T3 enhanced the interaction between ubiquitination and α-Syn in co-immunoprecipitation analysis, and T3-mediated clearance of tau and α-Syn was through UPS, proved by using proteasome inhibitor MG132 and NEDDylation inhibitor MLN4924. T3 showed good BBB permeability not only in a monolayer cell model but also in a mouse model, as visualized by fluorescence imaging and a pharmacokinetic study. In vivo effects of T3 were evaluated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model. T3 treatment (8 mg/kg/day, i.v., 7 days) reduced total tau and p-tau (S404) in the midbrain and hippocampus and reduced α-Syn and p-αSyn (S129) in the midbrain and substantia nigra pars compacta. Preliminary safety testing showed that T3 had no significant side effects up to 80 mg/kg/day for 2 days. Even though T3 efficiently reduces aggregation, the binding to other potential targets or cellular receptors at micromolar concentrations limits the application of this molecule in clinical studies.[132]

3.1.3 | PROTAC C004019

The small-molecule PROTAC C004019 has been shown to selectively promote tau clearance through ubiquitination-proteasome-dependent pathways.[135] C004019 was designed using a von Hippel–Lindau (VHL) binder conjugated with tau binder ID220149, which has been shown to interact with tau[133] and can inhibit tau aggregation.[134] C004019 induced a concentration-dependent clearance of total tau and p-tau in cell models, including HEK293-hTau, HEK293 cells with transient expression of human tau (HEK293-3xFlag-hTau or HEK293-EGFP-hTau), and SH-SY5Y cells. C004019 promoted tau ubiquitination by inducing the association between tau and E3 ligase VHL, and proteasome inhibitor MG132 abolished C004019-induced tau clearance in HEK293-hTau cells. In vivo study showed that C004019 crossed the BBB in C57BL/6 mice after subcutaneous administration. C004019 effectively reduced total tau and p-tau levels in hippocampus and cortex of the human tau (hTau) transgenic mice (*Mapt*$^{tm1(EGFP)Klt}$ Tg(MAPT)8cPdav/J) and 3×Tg-AD mice, leading to improved synaptic and cognitive functions.[135] One concern is that C004019 can induce a sustained total-tau reduction in the brain of WT mice (4 months

old) by a single-dose subcutaneous injection (3 mg/kg). Its effects on physiological tau might induce toxicity by impairing the physiological functions of tau.

3.1.4 | PROTAC QC-01-175: targeting tau in frontotemporal dementia

The positron emission tomography (PET) tracer 18^{F}-T807 exhibits a conformation-dependent binding of p-tau, demonstrating maximal efficacy in carriers of MAPT mutations that result in AD-like PHF pathophysiology.[152] The design of QC-01-175, utilizing a T807 PET tracer core scaffold and pomalidomide as an E3 ligase binder, marks a significant step forward in targeting tau in frontotemporal dementia (FTD).[62] In the biolayer interferometry assay, T807 and QC-01-175 displayed a significantly lower affinity for immobilized, soluble tau than the reported affinity of T807 for native aggregated tau filaments.[62] QC-01-175 was tested in two tauopathy neuronal cell models, one derived from a progressive supranuclear palsy patient carrier of the Tau-A152T risk variant and one derived from a behavioral-variant FTD patient carrier of the Tau P301L autosomal-dominant mutation.[62] Dermal fibroblasts were reprogrammed into patient-induced pluripotent stem cells (iPSCs), which were subsequently converted into cortical-enriched neural progenitor cells and differentiated into neuronal cells (Tau-A152T and Tau P301L neurons). QC-01-175 treatment showed an efficient concentration-dependent reduction of total tau and p-tau (S396) levels in A152T and P301L neurons, leading on average to more than 70% and 60% clearance, respectively. The PROTAC selectively targeted tau in FTD neurons (mutant variants A152T and P301L) with minimal impact on tau in healthy control neurons, suggesting the potential to develop therapies that specifically degrade disease-associated tau in FTD-affected neurons while sparing normal tau protein. Further investigations showed that QC-01-175-mediated tau degradation was dependent on E3 ligase CRBN and tau binding, NEDDylation (E3 ligase function, using MLN4924), and proteasome function (using irreversible proteasome inhibitor carfilzomib), but not autophagy (using autophagy inhibitor bafilomycin A1). They also proved the ternary complex formation between tau, degrader, and $CRL4^{CRBN}$, followed by increased tau ubiquitination upon QC-01-175 treatment. Moreover, QC-01-175 rescued viability loss caused by $A\beta_{1\text{-}42}$ in A152T neurons and had minimal off-target activity as determined by mass spectrometry proteomics. A pharmacokinetic study proved that QC-01-175 entered the brain after administration in mice.[137]

Further, this group established a structure–activity relationship for QC-01-175 and optimized the PROTAC for better efficiency.[63] The study indicated that CRBN-targeting PROTACs are more effective in promoting tau degradation in human neurons compared to PROTACs targeting the E3 ligase VHL. These CRBN-targeting PROTACs have a more pronounced effect on insoluble tau in FTD neurons. Even though they have low to modest cellular permeability, they can exhibit prolonged effects on tau reduction up to 8 days following compound washout. The application of such a highly potent PROTAC in iPSC models underscores the potential of this approach in precision medicine, where targeted therapies can be tailored to specific disease subtypes and patient populations.

3.1.5 | PROTAC I3

The PROTAC I3 is designed using PET tracer moiety THK5105 (2-arylquinoline derivatives) as tau binder and modified thalidomide as E3 ligase recruiter and PEG as linker.[139] Molecule I3 has been evaluated for its ability to degrade tau in PC12 cell lines. The degradation of tau by I3 was found to be time-dependent, with maximum activity observed at 36 h after treatment. Mechanistic studies indicate that I3 promoted tau degradation via UPS, and not ALP, proved by using proteasome inhibitor MG132 and autophagy inhibitor bafilomycin A1, respectively. I3 treatment improved the uneven distribution of mitochondria induced by tau overexpression and reduced the toxicity induced by $A\beta_{1\text{-}42}$ in PC12 cells. Pharmacokinetic profiling for I3 was done in ICR male nude mice at a dose of 30 mg/kg. The brain to plasma concentration distribution of I3 was >1.6, suggesting the compound favors brain penetration. Though it was shown that I3 degraded total tau at 50 kDa in Western blot, it is unclear whether I3 is selective and can distinguish between healthy tau and pathological tau.

3.1.6 | Pharmacokinetic challenges and strategies for CNS-targeted small-molecule PROTACs

Small-molecule PROTACs have a molecular weight exceeding 700 Da, poor solubility, and low permeability, making them challenging to formulate for oral delivery and limiting their ability to penetrate the BBB, a crucial factor for central nervous system (CNS)-targeted therapies.[153] Optimizing the pharmacokinetic properties of PROTACs, particularly for CNS applications, presents distinct challenges due to their structural complexity and physicochemical characteristics. The size and molecular complexity of PROTACs frequently violate traditional drug development guidelines, such as Lipinski's so-called Rule of Five, that emphasize the importance of parameters like molecular weight, lipophilicity, and hydrogen bonding for oral bioavailability. Moreover, during optimization, small structural modifications can affect the oral bioavailability, indicating that properties such as solubility/permeability can be affected not only by lipophilicity but shape, flexibility/rigidity, and pKa.[154]

Achieving the optimal balance of lipophilicity in PROTACs is another major challenge. Adequate lipophilicity can facilitate membrane permeability and support BBB penetration, but excessive lipophilicity can lead to increased non-specific interactions, poor solubility, and off-target effects. Hence, tuning the lipophilic properties of PROTACs is essential to maintain a balance between efficacy and safety. The modular design of PROTACs – comprising a ligand for the protein of interest, a linker, and an E3 ligase binder – offers multiple avenues for optimization.

CNS-targeted drugs specifically benefit from having fewer hydrogen bond donors (HBDs) and a low polar surface area (PSA), typically below 90 $Å^2$, to effectively cross the BBB.[155] However, PROTACs often

have high PSA values and multiple HBDs due to their bifunctional nature, necessitating design modifications to reduce these features while retaining sufficient activity to induce protein degradation.

Linker design plays a pivotal role in the pharmacokinetic profile of PROTACs. Incorporating rigid, cyclic structures within the linker can constrain the conformational flexibility of the molecule, leading to enhanced metabolic stability and improved BBB permeability. Reducing the number of rotatable bonds in the linker can also decrease the entropic penalty during target binding, making the overall molecule more drug-like. In recent studies, PROTACs that demonstrated "chameleonic" properties, where they adapted their conformation based on environmental factors, showed promise in achieving better passive permeability.[156] These chameleonic behaviors often involve reversible intramolecular hydrogen bonds that stabilize compact, non-polar conformations in non-aqueous environments, aiding in BBB penetration while maintaining biological activity in target-rich aqueous conditions.

Experimental and computational approaches to optimizing PROTAC pharmacokinetics face inherent challenges due to the unique properties of these molecules. Standard in vitro assays for assessing parameters like permeability and protein binding, originally designed for small molecules, often yield unreliable or inconsistent results with PROTACs. This discrepancy is attributed to their size, lipophilicity, and tendency to adhere to labware or biological membranes, which can distort assay outcomes. Consequently, there is a pressing need for assay adaptations and new methodologies tailored to PROTAC evaluation.[157] Computational modeling of PROTAC dynamics is similarly complicated. The flexibility and size of PROTACs create a multitude of potential conformations, complicating the prediction of how these molecules form the ternary complexes required for effective target degradation. Advances in molecular dynamic simulations and NMR spectroscopy are providing critical insights into the conformational states of PROTACs, but the predictive accuracy for CNS-targeting remains limited.

To address these challenges, researchers are trying novel approaches, such as designing PROTACs with conformationally constrained linkers, which reduces flexibility while maintaining high affinity for the target and E3 ligase. Additionally, the development of high-throughput screening methods, including direct-to-biology approaches, enables rapid assessment of large libraries of PROTAC variants. These screening techniques allow researchers to bypass some of the synthetic bottlenecks and directly evaluate PROTAC efficacy in cell-based systems, accelerating the optimization process. Furthermore, property-based guidelines specific to CNS-targeted PROTACs are being established, with particular emphasis on minimizing HBDs, managing PSA, and ensuring that lipophilicity remains within a suitable range for both oral bioavailability and CNS penetration.[158]

3.2 | Peptide-based PROTACs for targeting tau

3.2.1 | Peptide 2

Peptide-based PROTACs are bifunctional molecules with a target protein binding sequence and a specific amino acid degradation sequence (degron) that binds to an E3 ligase for proteasomal degradation.[159] Peptide therapeutics typically have advantages over small molecules because of their larger protein–protein interaction interface but have historically been limited by their instability and membrane impermeability.[160] One such example is a peptide PROTAC, Peptide 2, incorporating a β-hairpin sequence motif, which significantly increases intracellular stability and cell permeability.[142] Peptide 2 was synthesized by combining a β-hairpin sequence RWVRVpGRWIRQ and tau binding sequence YQQYQDATADEQG. It significantly reduced total tau levels at concentrations above 100 μM in N2a cells.[142] This tau-reducing effect is dependent on both the E1 enzyme and proteasome activity, which was confirmed by using E1 ubiquitin-activating enzyme inhibitor PYR-41 and proteasome inhibitor MG-132, respectively. To characterize the ability of Peptide 2 to penetrate cells, a fluorescent version of the peptide was synthesized by labeling it with 5(6)-carboxyfluorescein. Peptide 2 showed time-dependent uptake into N2a cells by live-cell fluorescence imaging. However, this study lacks testing in suitable animal models with tau pathology and further in vivo investigation on pharmacokinetics and BBB permeability properties.

3.2.2 | TH006

TH006, a peptide-based PROTAC, was designed with a tau-binding sequence (YQQYQDATADEQG), an E3 ligase binder (ALAPYIP), a GSGS linker, and an octa D-arginine cell-penetrating peptide.[143] TH006 labeled by 5(6)-carboxyfluorescein showed tau binding affinity in a fluorescence polarization assay and good cell permeability by flow cytometry and confocal microscopy. TH006 can reduce total tau levels in tau-EGFP-overexpressed N2a cells, SH-SY5Y cells transfected with pEGFP-tau vector, and primary neurons derived from 3×Tg-AD mouse. Mechanism investigations showed that TH006 promoted K48-linked polyubiquitination of tau and interacted with E3 ligase VHL. The addition of proteasome inhibitor MG132 or autophagy inhibitor bafilomycin A1 can counteract its tau clearance effect, suggesting that both UPS and ALP are involved in its tau degradation. In addition, TH006 can rescue the uneven distribution of mitochondria in tau-overexpressing cells and reduce the toxicity of $A\beta_{1\text{-}42}$. An in vivo study showed that TH006 treatment (intranasal administration combined with i.v. for 10 days) could reduce total tau levels in the cerebral cortex region of 3×Tg-AD mice.[143]

3.2.3 | Keap1-dependent Peptide 1

Kelch-like ECH-associated protein-1 (Keap1) functions as a substrate adaptor protein for Cullin 3/Ring-Box1-dependent E3 ubiquitin ligase complex.[161] A PROTAC was designed by joining Keap1 binding peptide (LDPETGEYL) and tau binder (YQQYQDATADEQG) with a short stretch of linker peptide (GSGS) (Peptide 1). To enhance cell uptake of the designed construct an octa D-arginine stretch (rrrrrrrr) was joined at the C-terminal side of the construct.[145] Keap1-dependent Peptide 1 showed strong binding ability to Keap1 or tau in

the isothermal titration calorimetry assay and promoted interactions between Keap1 and tau in SH-SY5Y cells in co-immunoprecipitation analysis. TAMRA-Peptide 1 was used to prove its cell permeability by flow cytometry and fluorescence imaging. Keap1-dependent Peptide 1 reduced total tau levels in different tau-overexpressed cell lines (SH-SY5Y, N2a, and PC-12), with no changes in Keap1 levels. The mechanistic studies revealed that the tau clearance was mediated through Keap1-dependent ubiquitination and proteasome-mediated pathways, confirmed by the application of Keap1 siRNA silencing and the proteasome inhibitor MG132. This study proved that Keap1 could also be a promising E3 ligase adaptor for the design of tau-targeting PROTACs.[145]

Most peptides have poor stability in vivo due to the presence of proteases and low membrane penetration ability. To overcome these limitations, one study generated a neurotransmitter-derived lipidoid nanoparticle delivery system.[144] Keap1-dependent Peptide 1 was loaded onto these positively charged nanoparticles using DNA-intercalation technology, known as Neurotransmitter-Derived Lipidoids-PROTACs-DNA Nanocomplex. The nanocomplex had good cell permeability and crossed BBB efficiently, not only in a two-dimensional cell model but also in an in vivo mouse model. Compared to Peptide 1 only, the nanocomplex showed increased clearance efficiency for total tau and p-tau (T205) in N2a cells and induced the association between tau and Keap1 successfully. In 3×Tg-AD mice, the nanocomplex also demonstrated a superior clearance of total tau and p-tau (T205) in the hippocampal and cortical regions of the brain and a superior therapeutic efficacy on cognitive function in Morris water maze. Moreover, the nanocomplex displayed good safety profiles in N2a cells and a 3×Tg-AD mouse model, providing support for its further clinical development.

3.3 | AUTOTACs: an emerging strategy for tau degradation

In addition to PROTACs, a new class of bifunctional molecules known as AUTOTACs has emerged (Figures 3 and 4). AUTOTACs differ from PROTACs in that they target proteins for degradation via the ALP rather than the UPS. AUTOTACs are composed of a target-binding ligand, a linker, and an autophagy-targeting domain. They can promote interactions between target protein and autophagy cargo receptors, leading to the activation of autophagy and the subsequent degradation of the target protein in the lysosome.

Ji et al. developed several ligands binding to the ZZ domain of p62/SQSTM1, which is one of the important autophagy cargo receptors for selective autophagy.[162,163] Then they used these p62/SQSTM1-ZZ-binding ligands to synthesize AUTOTACs, linking to different target-binding ligands via a repeating PEG moiety. The oligomeric modulator anle138b ([3-(1,3-benzodioxol-5-yl)-5-(3-bromophenyl)-1H-pyrazole])[164] and the chemical chaperone 4-phenylbutiryl acid (PBA) were selected as the two target-binding warheads for misfolded protein aggregates. PBA-1105, PBA-1106, PBA-1105b, and Anle138b-F105 are examples of their designed AUTOTACs. These AUTOTACs exhibited excellent degradative potency against aggregation-prone P301L mutant tau and its aggregates and Q97 mutant huntingtin in cell models. An in vivo study showed that PBA-1105 treatment (20 or 50 mg/kg, i.p., 3 times/week, 4 weeks) induced marked clearance of detergent-insoluble Tau P301L in the brain in a dosage-dependent manner, but with no effects on WT murine tau levels. The use of AUTOTACs for targeted protein degradation represents a novel therapeutic approach, particularly for diseases where proteasome function may be compromised or where autophagy plays a critical role in disease pathology.

3.4 | RING-Bait technology

RING-Bait technology, a selective degradation method for tau aggregates, has shown promise in treating AD. In this approach, the RING domain of the E3 ligase tripartite motif-containing protein 21 (TRIM21) is fused to the "Bait," tau[165] (Figure 3). When the RING-tau is recruited into tau aggregates, the clustering dimerizes the RING domain and activates its E3 function, leading to subsequent degradation of tau aggregates.[165,166] In HEK293 cell models, RING-tau (P301S, 0N4R) prevented seeded tau (induced by heparin) aggregation and removed existing aggregates, with no significant effects on soluble endogenous tau levels. RING-tau (WT, 0N3R) and RING-tau (WT, 0N4R) prevented seeded tau aggregation induced by AD and PSP *post mortem* brain extracts, respectively. Similar effects were also observed in primary neurons from transgenic mice (Tau P301S). Mechanism investigation showed that E1 ubiquitin-activating enzyme inhibitor TAK-243, VCP inhibitor NMS-873, or proteasome inhibitor MG-132 was able to reverse the aggregate removal effects, indicating that RING-tau was dependent on the UPS to degrade tau aggregates. An in vivo study showed that RING-tau treatment (packaged in AAV 9P31, i.v.) significantly and selectively reduced the burden of tau aggregates and improved motor functions in Tg2541 (Tau P301S) mice. A similar kind of approach based on the TRIM21 RING domain was devised by Benn et al.[167] In this approach, the RING domain of TRIM21 is fused with anti-tau C-terminal nanobody F8-2[168] and delivered to cells. RING-nanobody degraders prevented or reversed tau aggregation in cell and animal models, with minimal impact on monomeric tau. Though this technology can selectively clear tau aggregates, introducing a sufficient amount of RING-Bait degraders into the human brain is challenging. Both approaches used AAV gene delivery vehicles in animal studies; however, host immune responses remain a principal barrier for successful AAV gene therapy in humans.[169] Combining strategies to overcome AAV immune responses or apply alternative delivery methods for administration will increase the potential of RING-Bait technology in clinical study.

4 | CONCLUSIONS AND PERSPECTIVES

In summary, tau degradation mechanisms are complicated, and many factors determine which route is taken, such as tau post-translational

modifications, aggregation, and mutations. In AD, both UPS and ALP are impaired, and their lower efficiency has detrimental effects on tau turnover, potentially enhancing tau accumulation and pathology. Moreover, pathological tau further impairs degradative pathways, forming a vicious circle for AD progression. Several key factors targeting tau degradation, such as E3 ligases, DUBs, and autophagy cargo receptors, have been summarized, and their dysfunction in AD varies considerably depending on different brain regions and disease stages. The human genome encodes over 600 E3 ligases[170] and nearly 100 DUBs.[171] Only a few of them have been reported to relate to tau degradation. More investigations are needed to determine whether other important E3 ligases or DUBs mediate tau degradation, especially distributed only in the brain and neurons, which can provide novel specific therapeutic targets. Importantly, UPS and ALP are coordinated, and ubiquitin plays an important role in most of their communications.[121] A deep understanding of their crosstalk can provide more specific controls for tau turnover by enabling the choice of the optimal pathway for degradation.

An emerging strategy to increase tau clearance is to target protein degradation by promoting UPS or ALP functions. Currently, most of the targeted protein degraders for tau are PROTACs. Almost all of these tau-targeting PROTACs are designed to recruit E3 ligase VHL or CRBN, which are expressed in the whole body and attach K48-linked ubiquitin chains to the target protein for proteasome degradation.[172] Choosing other E3 ligases with brain-, neuron-, or disease-specific expression profiles will significantly improve the specificity of PROTACs. Designing PROTACs to recruit E3 ligases able to form specific ubiquitin chains for aggrephagy could promote tau degradation via ALP, which is especially important for the clearance of tau-insoluble aggregates. Until now, only one publication reported the development of tau-targeting AUTOTACs, bringing tau close to p62/SQSTM1 to promote ALP degradation.[162] Other autophagy cargo receptors can also be applied for the design of tau-targeting AUTOTACs. In addition, many other strategies, such as autophagy-targeting chimera, autophagosome-tethering compounds, and lysosome-targeting chimera, can be applied to tau degradation via lysosomes.[173] The recent development of dephosphorylation-targeting chimaera provides an alternative strategy to promote tau degradation by recruiting phosphatases to tau for reducing tau hyperphosphorylation.[174–176] In most small-molecule-targeted tau degraders, the structures of tau-binding ligands are from tau PET tracers, tau aggregation inhibitors, and fluorescence probes for tau aggregates. Investigation into new ligands that selectively bind to more toxic forms of tau, such as hyperphosphorylated tau and tau oligomers,[177,178] might provide more efficient targeted protein degraders to cure tau pathologies. With more advanced biomarkers to help with staging AD,[179] it is crucial to apply these targeted tau degraders at the early stage, since both degradation pathways are impaired during disease progress.

With encouragement from PROTAC ARV-471, which degrades the estrogen receptor in breast tumors, in the clinical phase III stage,[180] we believe that targeted tau degraders will offer new treatment options for patients with AD or other diseases with tau pathologies.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All human subjects provided informed consent or their consent was unnecessary. The informed consent of human subjects is not applicable to this review.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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