Int. J. Sci. R. Tech., 2026 3(4)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Degradomics-Driven Intervention: Reimagining Alzheimer's Therapy Through Targeted Protein Degradation

Debkantha Gope*[1], Sayantika Kundu[1], Sayani Debnath[2]

1. *Department pharmacy of Suresh Gyan Vihar University, Jaipur, Rajasthan with NAAC 'A+' grade accreditation, nirf ranking-39*
2. *Gitanjali College of Pharmacy, Lohapur, Birbhum, West Bengal*

ABSTRACT

The build-up of amyloid-beta proteins in the brain is one of the key problems of AD wherein the soluble oligomeric forms are believed to be the most toxic, especially for memory and learning. These soluble Aβ attacks the synapses in the hippocampus and other brain regions making synaptic loss the best morphological marker of cognitive decline. The neurophysical underpinnings of hippocampal-dependent learning and memory, known as synaptic plasticity, involves persistent changes in synaptic strength manifesting as long term potentiating (LTP) or long term depression (LTD) which was proved with the help of certain artificial Aβ oligomers. These proteins have been shown to significantly and selectively disrupt this plasticity by impairing glutamergic signaling, thereby suppressing LTP and enhancing LTD. Over time these alterations weaken synaptic connections and contribute to progressive cognitive decline.

Despite extensive research current therapeutic approaches solely targets on symptomatic relief rather on reverse or prevention of progression of disease. However the synaptotoxic effects of Aβ still remains incompletely understood .Therefore there is a critical need for novel approach that move beyond symptomatic management to directly targeting early synaptic dysfunctions and other molecular changes affected by abnormal accumulation of proteins. Such interventions could improve synaptic integrity, restore neuronal communication, and slowly or completely prevent further deterioration of AD.

Keywords: Aβ oligomers, synapses, hippocampus, synaptic plasticity.

INTRODUCTION

1. Protein Misfolding and Cellular Quality Control

In response to destabilising mutations, stress, or metabolic changes, biosynthesised proteins frequently misfold and fail to perform their biological activities. A cellular control of quality mechanism that consists of autophagy, molecular chaperones, and the proteasomal ubiquitin route (26S pathway or UPP) prevents misfolding of proteins .[1] By dissolving proteins into chains of polypeptide, these processes—often known physiological proteostasis network—avoid the build-up of harmful quantities of unfolded or improperly folded proteins. Serious neurodegenerative disorders like Alzheimer's disease (AD) [53] , Parkinson's disease (PD), prion & polyglutamine diseases, and others are brought on by any disturbance of this system, which causes an accumulation of proteins in various body areas.

2. Consequences of Proteostasis Disturbance (Neurodegenerative Disease):

At this moment one of the most well-characterised age related neurodegenerative illnesses is AD even though the potential reason is not entirely understood. Gradual loss of remembering and recognition of objects, dementia, and behavioural and linguistic abnormalities are the hallmarks of Alzheimer's disease. [2,3] This has to do with poor protein synthesis, poor membrane transport, and oxidative damage. Researchers believe that beta-amyloid (Ab) buildup is the disease's root cause. Whenever the amyloid precursor protein, also known as APP, is taken into the extracellular space and subjected to further enzymatic cleavage, amyloid beta is created.

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

[4] Ab builds up gradually as a result of overproduction or improper removal. When beta-amyloid accumulates into oligomers, it impairs proteasome function and interferes with neuronal functions. Furthermore, the Ab increases the production and buildup of hyperphosphorylated tau proteins, an exceptionally soluble microtubule-binding protein, and inhibits the proteasomal pathway. Tau usually helps axons of neuron to carry organelles, neurotransmitters, and various other cell components that actually act as trophic factors by stabilising the microtubule network in axons .[5,6] Transportation of axons and neuronal function are hampered by hyperphosphorylated tau protein, which automatically clumps forming neurofibrillary tangles (NFTs). Because of destabilising mutations, stress, or metabolic changes, biosynthesised proteins frequently misfold and fail to perform their biological roles. A cellular surveillance mechanism that consists of autophagy, molecular chaperones, and the proteasomal ubiquitin route (26S or UPP pathway) prevents the protein from misfolding.[7,6] By dissolving proteins through polypeptide chains, these processes—often recognised as an intracellular proteostasis network—avoid the building up of harmful quantities of unfolded and misfolded protein. Serious neurodegenerative illnesses are exacerbated by any disturbance of this mechanism, which causes proteins to accumulate in different body areas. [8]

CLINICAL OVERVIEW

The median temporal lobe, which comprises the areas of the entorhinal cortex & hippocampus, is the part of the brain most susceptible to neurological dysfunctionwith cell death in Alzheimer's disease.

1. Protein Aggregates associated:

Tau and Aβ are the proteins that build up in AD. [9] There are three primary stages of AD:

First, the "preclinical" stage, during which tau and Aβ start to build up before symptoms show up. Infrequent loss of memory (repeated questions, misplaced things, etc.) in the second stage of MCI is not severe enough to interfere with day-to-day activities. increasing loss of functional capacities in the third stage of dementia. Death often happens six to twelve years after the disease first manifests, and is most frequently brought on by immobilisation-related complications such as B. pneumonia and pulmonary embolism.[10,11]

2. Role of Tau Accumulation

As significant just like microtubule-associated proteins (MAPs), tau proteins are found in large quantities in neurones andtheycontribute to the integrity of microtubules in axons. Synaptic dysfunction, whereby tau localisation is perversely moved beyond axons towards the somato-dendritic compartment, is linked to the accumulation of aggregated tau. Alzheimer's disease (AD) individuals develop intra-cellular tau clumps which is known as neurofibrillary tangles. Tau proteins combine into neurofibrillary tangles when they become too phosphorylated. Additionally, atypical Parkinsonian disorders can result in tauropathies, which are neurodegenerative illnesses marked by the production of hyperphosphorylated tau neurofibrils.**β-Amyloid** Beta-amyloid (Aβ) buildup is a hallmark of AD, the most prevalent neurodegenerative disease [11,19]. Memories, execution of tasks, language, as well as object and person identification are all affected by this degenerative illness. Two kinds of protein aggregates are responsible for the disease: (i) internal Tau MAP clumps and (ii) external aggregates known as neuritic plaques, which are made up of the Aβ peptide produced by the amyloid precursor protein's proteolytic process [12]. Although the process of aggregation is not fully understood, these clumps are known to be harmful to brain cells. Morbific proteins combine into decipherable poisonous oligomers before producing unsolvable fibrils. Oligomers destroy the phospholipid bilayer by exposing hydrophobic surfaces. [12,13]

3. Inherited Predispositions:

Early-onset of autosomal dominant AD has been linked to alterations in three genes: PSEN1 and PSEN2, which encode presenilins 1 & 2, respectively, and APP, which encrypts the Aβ ancestor protein.[14,16] The synthesis of Aβ peptides involves all three genes. Two enzymes, β-secretase & γ-secretase, sequentially cleave amyloid precursor protein to synthesise Aβ; their catalytic core of γ-secretase is composed of presenilins. The theory that amyloid plays a role in the pathophysiology of AD is supported by genetic data, the accumulation of Aβ in the cerebral cortex within the form of amyloid

oligomers and plaques, and the fact that Aβ is lethal when administered to neurones.[15,16] Numerous genes with alleles that raise the risk underlying Alzheimer's disease have been found. APOE, which codes for the lipid transporter protein ApoE, is the most significant of them. The risk of Alzheimer's disease is three times higher for those who inherited the APOE ε4 allele. More over half of the total AD cases occur in these individuals, while making up fewer than 25% of the population. [16]

PATHOPHYSIOLOGY

It has been seen that Within the cell neurofibrillary tangles, that are made of the microtubule-related protein tau, and amyloid plaques, those are outside the cell of Aβ, are the pathological hallmarks underlying AD.

1. Disease onset sequence:

In a way that is more directly linked to the onset of cognitive impairment, amyloid plaques grow earlier and the load of confusion rises over time. Aβ builds up after mutations that cause overproduction in autosomal dominant AD. [17] Aggregation of Aβ plays a significant role in the pathophysiology of AD. Even while highly structured Aβ fibrils make up plaques, soluble Aβ oligomers—possibly as tiny as dimers—seem to be more harmful.Additionally, tau forms neurofibrillary tangles by aggregating into paired helical filaments. Tau's propensity to aggregate is increased through post-translational alterations such as phosphorylation, proteolysis, besides additional alterations. Excitotoxicity, oxidative stress, neuroinflammation, and direct disruption of synaptic transmission including plasticity are among of the methods by which tau and A cause neuronal dysfunction and death.[18,19]

2. Neurotransmitter Science:

ACh deficit is the most evident neurochemical anomaly in AD. The atrophy and degradation of subcortical cholinergic neurones is the anatomical foundation of cholinergic insufficiency.[20] The "cholinergic hypothesis," which holds that ACh shortage is the mainreason of Alzheimer's disease, was sparked by the discovery that central cholinergic antagonists, such as atropine, may cause similar confusional state in AD and the selective ACh deficiency in AD. Illness persists. AD symptoms.[19,20] Nevertheless, Alzheimer's disease is complicated and includes several neurotransmitter systems, such as glutamate, 5HT, and neuropeptides. As a result, cholinergic neurones as well as target locations in the hippocampus and cerebral cortex that receive cholinergic inputs are destroyed.[20,21]

3. Commonly used cholinesterase inhibitors used for AD [22,23,24]

Properties	Donepezil	Rivastigmine	Galantamine
Enzymes involved	AchE	AchE, BuchE	AchE
Typical dose	10 mg once daily	9.5mg/24 h (transdermal) 3-6 mg twice daily(oral)	16-24 mg/day 8-12 mg /day twice daily.
FDA approval for use	Mild to severe AD	Mild to moderate AD	Mild to moderate PDD
Metabolism	CYP2D6	CYP3A4	CYP3A4

Table 2 : BuChE is a hepatic and serum cholinesterase that is increased in AD brain, while AChE is the primary cholinesterase in the brain. b. Starting dosages are usually administered for the first months of therapy and are half of the ongoing dose. c CYP2D6 and CYP3A4-metabolizing medications might cause elevated blood levels when used with medications that block these enzymes, such paroxetine and ketoconazole.

PROTEIN DEGRADATION SYSTEM IN CELLS

1. The Ubiquitin-Proteasomal System

The main part within the ubiquitin-proteasomal system (UPS) (Fig 1), the proteasome, catalyses the selective process of intracellular protein breakdown in eukaryotic cells. The key proteolytic mechanism of both usual and aberrant synaptic proteins is the proteasomal destruction of ubiquitin.

1.1 Processes of UPS (Activation, Conjugation, Recognition, Ubiquitin Elimination, Substrate Degradation):

Five procedures make up UPS: activation, conjugation, recognition, ubiquitin elimination by certain deubiquitinating enzymes (DUBs), and proteasome-mediated substrate destruction. The UPS controls protein activity through numerous forms of ubiquitination and controls protein breakdown through proteasome-mediated proteolysis.Over 80% of both normal and aberrant intracellular proteins are broken down by the UPS.[25,26] The UPP breaks down most of the intracellular proteins in tissues, whereas lysosomes endocytose and break down extracellular and certain cell surface proteins. Numerous biological functions, including the cell cycle, the transcription of DNA including repair, apoptosis, and quality control, are regulated by the UPP. Additionally, it prevents protein folding errors and agglomeration and preserves proteostasis throughout ageing and illness. [26,27]

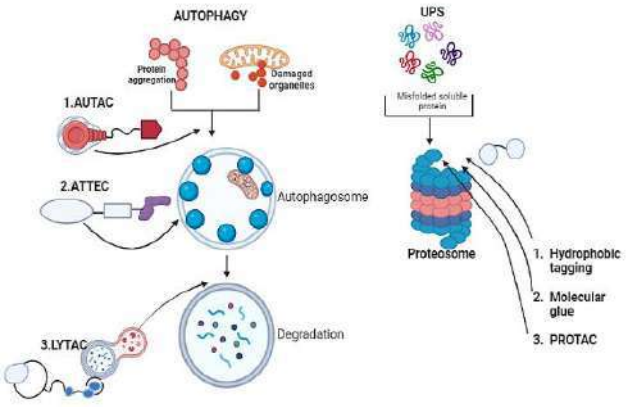


Figure 1: Techniques for chemically induced targeted degradation of proteins as well as processes for cellular protein degradation. UPS, ubiquitin-proteasome system; Ub, ubiqusers; AUTAC, car chimaeras that attack Agy; ATTEC, an autophagosome binding compounds; LYTAC, lysosome- invaded chimaeras; LC3, microtubule-related proteins, light chains 3B 1A/1B; Cl-M6PR, mannose-6-phosphate receptor that is not dependent on cations; protein of interest, or POI; E3 Chimaera; PROTAC; E3 Ubiquitin Ligase

1.2 Ubiquitination and deubiquitination

Ubiquitin Topology and the E1-E2-E3 Ligase Cascade:

All tissues contain ubiquitin, a protein which have a molecular mass of 8.5 kD and 76 amino acids that can be found free or covalently conjugated. Ubiquitin activation (E1), conjugation (E2), & ligation (E3) all contribute to the reversible process of ubiquitination, which is the covalent addon of the glycine residue of ubiquitin to the lysine residue of the intended protein via an isopeptide bond. Enzymes. Recently, the E4 enzyme's action was characterised. For conjugation, ubiquitin is produced by the enzymes E1 & E2. A particular substrate is recognised by E3 enzymes, which then catalyse the transfer of active ubiquitin to the substrates.[28]

1.3 Polyubiquitin Chain Formation and Linkages:

To create a polyubiquitin chain, E4 enzymes catalyse the coupling of extra ubiquitin monomers, often through lysine-48 (K48) linkages (Figure 1). Four additional ubiquitin proteins targeting a single substrate make up the polyubiquitin chain during 26S proteasome breakdown. E3 ligases come in two varieties: the RING finger/adapter and HECT (C-terminal homolog of E6-related protein). When faulty proteins undergo polyubiquitination

(the binding of ubiquitin to the substrate), individual the HECT region E3 ligase establishes a covalent connection with ubiquitin through a thioester intermediate. Ubiquitin is transferred directly from its attached substrate E2 enzyme by the RING finger E3 ligase.[29] The kind of ubiquitin connections (K48, K63, K6, K11, K27, K29, and K33) determines the fate of transformed proteins.While K63-linked synthetic polyubiquitinated proteins are broken down by the lysosomal pathway, K48-linked polyubiquitinated peptides are often broken down by the proteasomal system. K6 is linked to DNA repair,

K11 to protein breakdown and cell cycle regulation related to the endoplasmic reticulum (ER), K27 to ubiquitin combination and destruction, K29 to lysosomal degradation, as well as K33 to kinase alteration," according to the various forms of ubiquitin associations.

1.4 Deubiquitinating Enzymes (DUBs): Regulators of Ubiquitin Homeostasis:

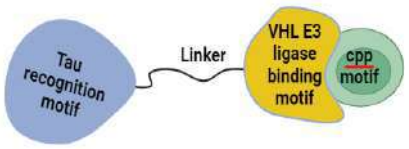
DUBs deubiquitinate it polyubiquitin chains at various UPP levels after the proteasome identifies a polyubiquitinated substrate.[30]. Deubiquitination may take place prior to or following DUB's recognition of the 26S proteasome substrate . The catalytic core breaks down the substrate during substrate identification, and DUBs process ubiquity while holding onto monoubiquitin to continue ubiquitination . When freshly translated ubiquitin attaches to the C-terminal amino acids or is broken down by terminal ubiquitin amino acid hydrolase 1 (UCHL1), deubiquitination is necessary. About 100 DUBs are found in eukaryotic cells . Seven of these are found in the protein synthesis system , and 27 are found in the neurological system (Fig. 2).[31]

Five kinds of deubiquitinating enzyme protein are distinguished. [14, 28] (i) ubiquitin C-terminal hydrolases (UCHs), such as UCHL1, UCHL3, as well as UCHL5/UCH37; (ii) ubiquitin-specific proteases (USPs), such as USP7, USP9x, and USP14; (iii) Machado-Joseph disease-causing protease, such as ataxin-3; (iv) otubain proteases (OTUs), such as otubain 1 and otubain 2 (v) metallo-enzymes (JAMMs), such as PSMD14/Rpn11 &JAB1/MPN/Mov34. Protease degradation is either facilitated or inhibited by ubiquitin chain cleavage. In order to control proteasomal breakdown and cure AD, the enzymes engaged in this process—in particular, DUB—may be useful therapeutic targets.[30,31]

TARGETED PROTEIN DEGRADATION FOR NEURODEGENERATIVE DISEASES

Tau is a key pathogenic protein in Alzheimer's disease, great attempts have been undertaken to either eradicate it or prevent its formation.

1. Peptide-Based PROTACs Targeting Tau Protein



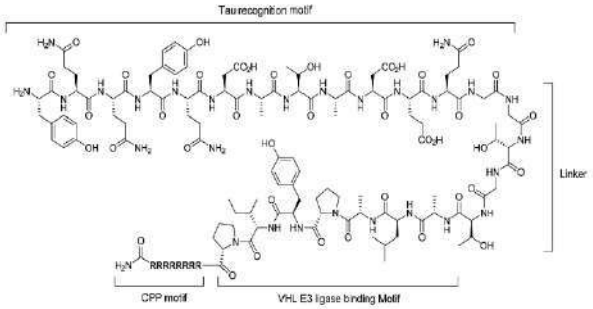


Figure 2. Structure of a peptide-based PROTAC targeting tau protein.

A peptide-based molecule called PROTAC , which has four motifs—one tau recognition motif, a linker, an E3 ligase attachment motif, and a cell penetration peptide (CPP) motif—was used by Chu et al. in 2016 to describe the initial targeted tau degradation system.[32,38] Three known peptides were assessed in order to determine the finest peptide for tau recognition, and the peptide that corresponded with the sequence YQQYQDATADEQG was determined to be the best in their investigation. The binding peptide structures DRHDS(p)GLDS(p)M and ALAPYIP were used to test two E3 ligases: von Hippel-Lindau tumour suppresser protein (VHL) and Skp1-cullin F-box ligase (SCF).The findings demonstrated that VHL outperforms SCF. The most active molecule, PROTAC TH006, which comprises an arrangement of 32 acidic amines, was discovered by use of the short linker sequences (GSGS) that links the tau binding structure, the ligase E3 interaction motif, and the poly arginine CPP (Figure 2).[33,34] It has been demonstrated that TH006 effectively penetrates cells and causes tau protein breakdown by boosting VHL E3 ligase polyubiquitination (Fig 2). Additionally, using an AD transgenic mice model, that was demonstrated to decrease tau levels of proteins via TU005 to lessen Aβ neurotoxicity.[34,38]

2. HyT-Tau-CPP Degrader:

It has been demonstrated that HyT an another technology effectively breaks down tau protein. The

collapse of tau protein by the tagged accepting hydrophobic degrader HyT was reported by Gao et al. in 2017. By affixing a taubin binding motif to a poly-D-arginine CPP motif and an N-terminal hydrophobic amino acid tag, they created a tau protein degrader. The linker was not taken into account in this HyT-Tau-CPP combination (Figure 3), and motif was chosen as the Tau protein's binding sequence.[35] The scientists treated Neuro cells expressing tau-EGFP with HyT-Tau-CPP (Fig 3) at varying doses and for varying lengths of time in order to examine the cellular breakdown of tau protein by the chemical.HyT-Tau-CPP decreased tau protein in a dosage- and time-dependent manner, according to tau protein Western blot analysis and flow cytometry assay results.[36] Furthermore, a co-treatment investigation with the proteasome antagonist MG132 was conducted to show if tau breakdown by HyT-Tau-CPP is controlled by the UPS. Since the target protein was not destroyed in the data, it is likely that HyT-Tau-CPP (Fig 3) broke down the tau protein by the UPS.[36,37]

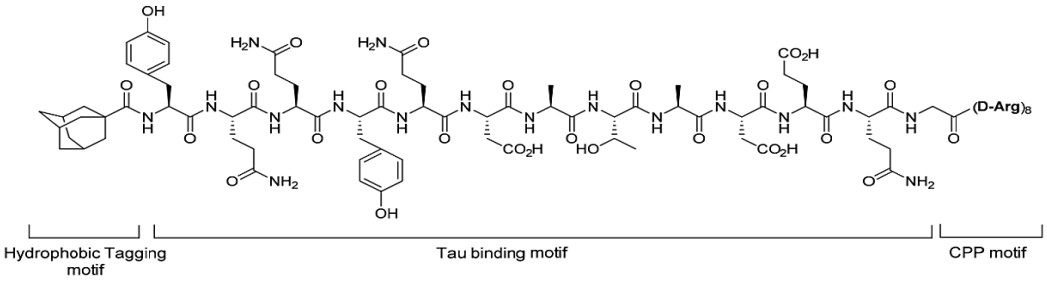


Figure 3. Structure of HyT-Tau-CPP

A peptide-based PROTAC that targets the protein tau as the POI and adopts a Keap1 E3 ligase (Figure 4) interaction motif was described by Lu et al. in 2018 . One of the connecter amino acids in the Cul3-RING Ubiquity ligase complex, Keap1 (Kelch-like ECH-associated protein 1) is well-known due to the cell-protective properties of the Keap1-Nrf2 pathway against a variety of xenobiotic and oxidative stressors that cause cancer and neurodegenerative diseases.[39,40]

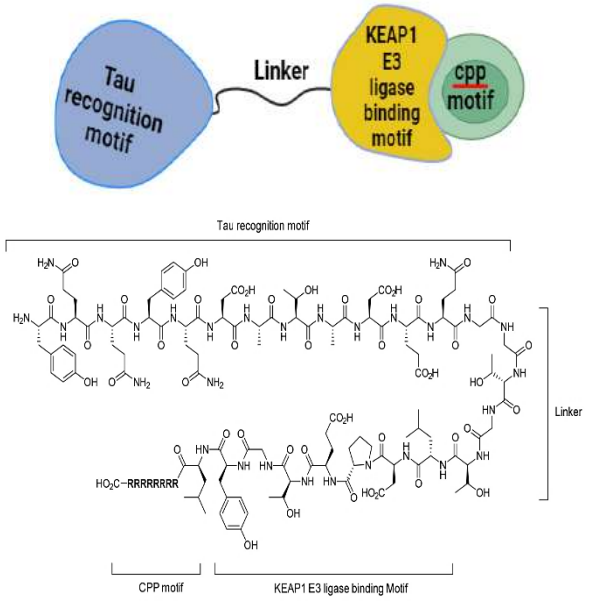


Figure 4. Structure of Tau-Keap1-CPP PROTAC as a degrader

3. VHL E3 Ligase:

The authors of this work tried to demonstrate the potential uses of the Keap1 E3 ligase by using it as a PROTAC (Fig 4) technologies platform. TauKeap1-CPP PROTAC's general structure is comparable to that which was previously described in 2016, where the VHL E3 ligase-obligatory motif was used. The sole distinction was the substitution of the Keap1-binding motif (LDPETGEYL) with the VHL E3 ligase-binding motif. By using the isothermal titration calorimetry experiment, the Kd values of the Tau-Keap1-CPP PROTAC protein and Keap1 were determined to be 22.8 and 763 nM, respectively.[40,41] It was demonstrated that the produced PROTAC molecules degraded cellular tau in a way that was dependent on both time and dosage. Degradation through the UPS was also demonstrated in a co-treatment experiment involving the proteasome antagonist MG132 and Keap1 siRNA knockdown. This work is significant since it extended the PROTAC technology and showed that Keap1 ligands contain peptides by demonstrating the utilisation of the Keap1 E3ligase in PROTAC technology. [52]

According to the "Patent Highlight" article by R.B., the first extremely tiny molecule PROTAC was released in 2019 as a tau degrader (Fig 5). Kargbo

(Fig. 5, n denotes number of reeating ethylene glycol unit in linker). "Compounds for degrading tau proteins" was the title of the initial report . Six significant PROTACs that target tau have been chosen for this article, and their molecular makeup are shown. The two fragments were joined utilising polyethylene glycol (PEG)-based links after the introduction of a pyridoindole moiety as the tau binding motif and the minor molecule linkers Cereblon (CRBN) and VHL. The new method successfully eliminated total and hyperphosphorylated Tau proteins in a depletion trial using human Tau P301L and Tau A152T neurones.[42]

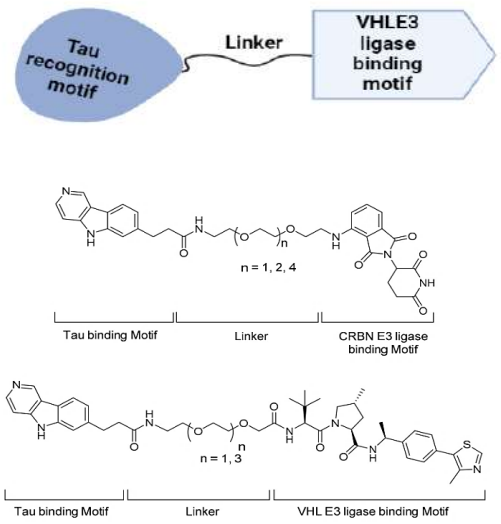


Figure 5.Structures of small-molecule Tau degrader

CLINICAL SIGNIFICANCE & ETIOLOGICAL CHANGES:

1. Precision Targeting and Disease Specificity:

Targeted Degradation versus Inhibition: Differentiating the "event-based" characteristics of TPD (catalytic elimination) from the "occupancy-based" nature of conventional small-molecule inhibitors (transient blocking). Selectivity for Pathogenic Conformations; The capacity of TPD agents to selectively identify and dismantle hazardous, misfolded protein variants (e.g; hyperphosphorylated Tau or Aβ oligomers) while preserving functioning native proteins. [43] Dose Response Efficacy.The possibility of sub-stoichiometric dosage resulting from the catalytic mechanism, which provides enhanced therapeutic indices and less overall drug exposure relative to inhibitors.

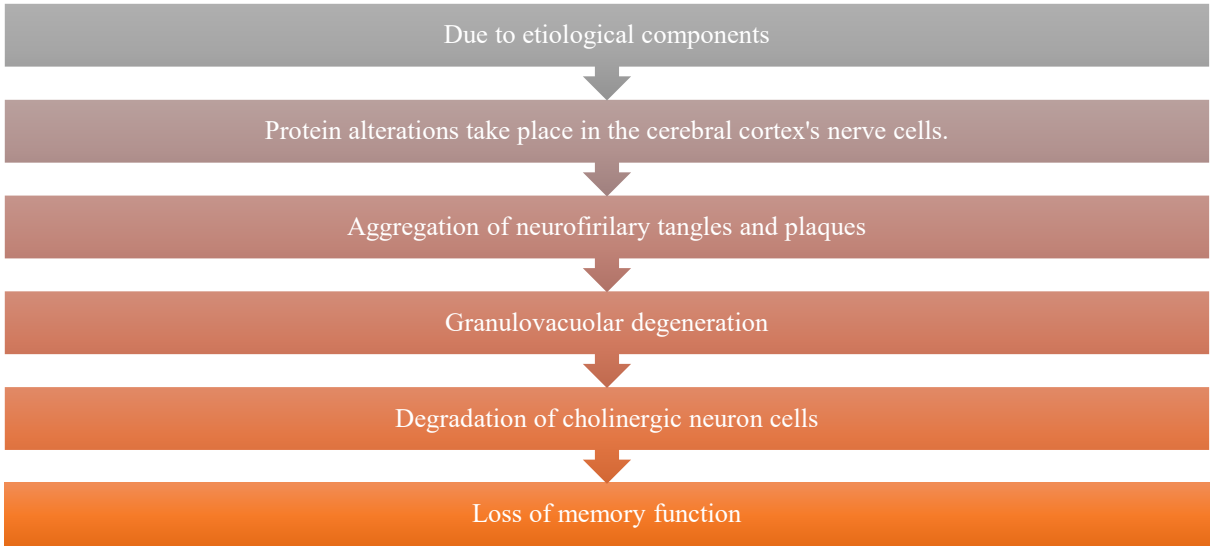
2. Disease Modification and Therapeutic Potential:

Reversal of synaptotoxicity: Clinical potential to restore memory function and Long-Term Potentiation (LTP) by stopping or reversing Aβ oligomer-induced synaptic damage.Clearance of Aggregates; TPD's molecular benefit is that it eliminates protein aggregates, the cause of pathology, instead of just reducing its consequences downstream;Addressing Drug Resistance: TPD's ability to target proteins that were previously thought to be "undruggable" by traditional binding inhibitors increases the number of potential therapeutic targets.

3. Therapeutic Potential: TPD offers a promising avenue for the development of disease-modifying therapies for AD. By harnessing the body's own protein degradation machinery, TPD compounds have the capacity to slow or halt disease progression, providing hope for patients and their families. [44,45]

4. Combination Therapies: To effectively address several facets of AD pathogenesis, TPD can be used in conjunction with already available therapeutic methods like immunotherapies or tiny-molecule inhibitors. The range of patients who might benefit from treatment may be expanded by this multimodal strategy, which may also increase therapeutic efficacy. [45,46] Even though TPD remains in its infancy, it has really interesting promise for treating AD. The potential of TPD to target different proteins implicated in AD is being intensively studied by researchers. To evaluate its efficacy and safety in people, clinical studies are being conducted. TPD is a significant advancement in the ongoing search for a treatment for Alzheimer's disease.

Millions of people with AD may have a better future with this novel techniques if research based on these approaches continues with efficacy.[47,48]



FUTURE DIRECTIONS AND LIMITATIONS:

1. Expanding TPD Targets: While current TPD approaches have successfully targeted Tau protein, future research must focus on developing potent PROTACs or other degraders [50] that effectively target highly toxic Aβ oligomers and the enzymes responsible for their generation.

2. CNS Drug delivery Optimization: The primary challenge for any neurodegenerative therapy is CNS bioavailability. Future work must prioritize optimizing the physicochemical properties and cross-linkers of TPD molecules to enhance their blood-brain barrier penetration and reduce off-target effects.[50]

3. Advancing Other Degradation Modalities: Further exploration of other non UPS pathways such as AUTAC, ATTEC, and LYTAC (which utilize the autophagy-lysosomal route), is needed to address aggregated or extracellular proteins that are less amenable to UPS-based degradation. [51]

4. Combination Therapies: Creating plans to combine targeted protein degradation with current treatments, including immunotherapies or small-molecule inhibitors, may result in a multimodal strategy that simultaneously treats several aspects of AD pathogenesis, boosting overall therapeutic success.[49]

5. Clinical Translation: In order to assess the safety and effectiveness of highly effective TPD agents in human AD patients, the field must quickly translate them into clinical trials.

LIMITATIONS:

Off-Target Degradation Risk: As TPD relies on hijacking endogenous E3 ligases, there is an inherent risk off-target protein degradation, which could led to unforeseen toxicity or side-effects; **Large Molecular Size:** Drug development is hampered by the comparatively large peptide-based molecules seen in many first-generation PROTACs (e.g; TH006, HyT-Tau-CPP), which often lead to poor cell permeability and low oral bioavailability. It is necessary to expedite the switch to small-molecule PROTACs (such as those that use VHL or CRBN linkers); **Catalytic Mechanism Difficulties**: In contrast to occupancy-based inhibitors, TPD's catalytic nature in which a single degrader molecule can eliminate several target proteins might make dose-response relationships and pharmacokinetic/pharmacodynamic modeling more difficult.[54]

CONCLUSION

A paradigm shift in treatment approach is required due to the increasing prevalence of neurodegenerative illness which are essentially protienopathies caused by the build-up of toxic and misfolded protein aggregates. Because then only momentarily impede protein activity and frequently miss many "undruggable" targets, traditional small molecule inhibitors and "occupancy based" pharmacology are intrinsically limited and cannot stop the underlying illness development. Target protein degradation is a method that employs small and medium sized molecules to intentionally and selectively dismantle intracellular target proteins. This represents a

revolutionary therapeutic strategy that significantly diverges from antiquated small-molecule pharmaceuticals. The utilization of certain populations as therapeutic agents constitutes the basis of conventional drug development. The target protein becomes non-functional upon the application of small molecule inhibitors. However, the lack of additional, non-specific binding sites restricts the effectiveness of traditional "occupational" pharmacotherapy. These restraints are overcome by targeted protein degradation, a modality that demonstrates how a transient binding interaction can induce the functional inactivation of a protein through its selective removal from the cell. In this study, the introduction of Targeted Protein Degradation (TPD) as a powerful and innovative therapeutic approach that addresses the drawbacks of traditional medication is highlighted.

REFERENCES

1. Tseng CS, Chao YW, Liu YH, Huang YS, Chao HW. Dysregulated proteostasis network in neuronal diseases. Vol. 11, Frontiers in Cell and Developmental Biology. Frontiers Media S.A.; 2023.
2. Kocaturk NM, Gozuacik D. Crosstalk between mammalian autophagy and the ubiquitin-proteasome system. Vol. 6, Frontiers in Cell and Developmental Biology. Frontiers Media S.A.; 2018.
3. Ashraf GM, Greig NH, Khan TA, Hassan I, Tabrez S, Shakil S, et al. Protein misfolding and aggregation in Alzheimer's disease and Type 2 Diabetes Mellitus HHS Public Access. Vol. 13, CNS NeurolDisord Drug Targets. 2014.
4. Murphy MP, Levine H. Alzheimer's disease and the amyloid-β peptide. Vol. 19, Journal of Alzheimer's Disease. IOS Press; 2010. p. 311–23.
5. Tseng BP, Green KN, Chan JL, Blurton-Jones M, LaFerla FM. Aβ inhibits the proteasome and enhances amyloid and tau accumulation. Neurobiology of Aging. 2008 Nov;29(11):1607–18.
6. Sadigh-Eteghad S, Sabermarouf B, Majdi A, Talebi M, Farhoudi M, Mahmoudi J. Amyloid-beta: A crucial factor in Alzheimer's disease. Vol. 24, Medical Principles and Practice. S. Karger AG; 2015. p. 1–10.
7. Cario A, Berger CL. Tau, microtubule dynamics, and axonal transport: New paradigms for neurodegenerative disease. BioEssays. 2023 Aug 1;45(8).
8. Zhang Y, Chen H, Li R, Sterling K, Song W. Amyloid β-based therapy for Alzheimer's disease: challenges, successes and future. Vol. 8, Signal Transduction and Targeted Therapy. Springer Nature; 2023.
9. Rao YL, Ganaraja B, Murlimanju B v., Joy T, Krishnamurthy A, Agrawal A. Hippocampus and its involvement in Alzheimer's disease: a review. Vol. 12, 3 Biotech. Springer Science and Business Media Deutschland GmbH; 2022.
10. Mark RE, Brehmer Y. Preclinical Alzheimer's dementia: a useful concept or another dead end? Vol. 19, European Journal of Ageing. Springer Science and Business Media B.V.; 2022. p. 997–1004.
11. Hrybouski S, Das SR, Xie L, Wisse LEM, Kelley M, Lane J, et al. Aging and Alzheimer's disease have dissociable effects on local and regional medial temporal lobe connectivity. Brain Communications. 2023;5(5).
12. Mandelkow EM, Mandelkow E. Biochemistry and cell biology of Tau protein in neurofibrillary degeneration. Vol. 3, Cold Spring Harbor Perspectives in Biology. 2011. p. 1–25.
13. Ghetti B, Oblak AL, Boeve BF, Johnson KA, Dickerson BC, Goedert M. Invited review: Frontotemporal dementia caused by microtubule-associated protein tau gene (MAPT) mutations: A chameleon for neuropathology and neuroimaging. Vol. 41, Neuropathology and Applied Neurobiology. 2015. p. 24–46.
14. Yamazaki Y, Painter MM, Bu G, Kanekiyo T. Apolipoprotein E as a Therapeutic Target in Alzheimer's Disease: A Review of Basic Research and Clinical Evidence. CNS Drugs. 2016 Sep 1;30(9):773–89.
15. Pires M, Rego AC. Apoe4 and Alzheimer's Disease Pathogenesis—Mitochondrial Deregulation and Targeted Therapeutic Strategies. Vol. 24, International Journal of Molecular Sciences. MDPI; 2023.
16. Dai MH, Zheng H, Zeng LD, Zhang Y. The genes associated with early-onset Alzheimer's disease. Vol. 9, Oncotarget. Impact Journals LLC; 2018. p. 15132–43.

17. Dominguez-Gortaire J, Ruiz A, Porto-Pazos AB, Rodriguez-Yanez S, Cedron F. Alzheimer's Disease: Exploring Pathophysiological Hypotheses and the Role of Machine Learning in Drug Discovery. Vol. 26, International Journal of Molecular Sciences. Multidisciplinary Digital Publishing Institute (MDPI); 2025.
18. Zhang H, Wei W, Zhao M, Ma L, Jiang X, Pei H, et al. Review interaction between aβ and tau in the pathogenesis of alzheimer's disease. International Journal of Biological Sciences. 2021;17(9):2181–92.
19. Hong X, Huang L, Lei F, Li T, Luo Y, Zeng M, et al. The Role and Pathogenesis of Tau Protein in Alzheimer's Disease. Vol. 15, Biomolecules. Multidisciplinary Digital Publishing Institute (MDPI); 2025.
20. Chen ZR, Huang JB, Yang SL, Hong FF. Role of Cholinergic Signaling in Alzheimer's Disease. Vol. 27, Molecules. MDPI; 2022.
21. Binvignat O, Olloquequi J. Excitotoxicity as a Target Against Neurodegenerative Processes. Current Pharmaceutical Design. 2020 Jan 14;26(12):1251–62.
22. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Effi cacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: A systematic review and meta-analysis [Internet]. Vol. 3, Clinical Interventions in Aging. 2008. Available from: www.clinicaltrials.
23. Sharma K. Cholinesterase inhibitors as Alzheimer's therapeutics (Review). Vol. 20, Molecular Medicine Reports. Spandidos Publications; 2019. p. 1479–87.
24. Grossberg GT. Cholinesterase inhibitors for the treatment of Alzheimer's disease: Getting on and staying on. Vol. 64, Current Therapeutic Research - Clinical and Experimental. Excerpta Medica Inc.; 2003. p. 216–35.
25. Çetin G, Klafack S, Studencka-Turski M, Krüger E, Ebstein F. The ubiquitin–proteasome system in immune cells. Vol. 11, Biomolecules. MDPI AG; 2021. p. 1–23.
26. Dantuma NP, Bott LC. The ubiquitin-proteasome system in neurodegenerative diseases: Precipitating factor, yet part of the solution. Vol. 7, Frontiers in Molecular Neuroscience. Frontiers Research Foundation; 2014.
27. Kang D, Baek Y, Lee JS. Mechanisms of RNA and Protein Quality Control and Their Roles in Cellular Senescence and Age-Related Diseases. Vol. 11, Cells. MDPI; 2022.
28. Csizmadia T, Lőw P. The role of deubiquitinating enzymes in the various forms of autophagy. Vol. 21, International Journal of Molecular Sciences. MDPI AG; 2020. p. 1–16.
29. Tong Z, Wu X, Cai H, Wu S, Zhang T, Deng Z, et al. Structural basis for E4 enzyme Ufd2-catalyzed K48/K29 branched ubiquitin chains [Internet]. Available from: https://www.nature.com/articles/s41589-025-01985-2
30. Weber J, Polo S, Maspero E. HECT E3 ligases: A tale with multiple facets. Vol. 10, Frontiers in Physiology. Frontiers Media S.A.; 2019.
31. Akutsu M, Dikic I, Bremm A. Ubiquitin chain diversity at a glance. Journal of Cell Science. 2016;129(5):875–80.
32. Sandhof CA, Murray HFB, Silva MC, Haggarty SJ. Targeted protein degradation with bifunctional molecules as a novel therapeutic modality for Alzheimer's disease & beyond. Vol. 22, Neurotherapeutics. Elsevier B.V.; 2025.
33. Guedeney N, Cornu M, Schwalen F, Kieffer C, Sophie Voisin-Chiret A. PROTAC technology: a new drug design modality for chemical biology with many challenges in drug discovery [Internet]. 2022. Available from: https://www.elsevier.com/open-access/userlicense/1.0/
34. Zhong G, Chang X, Xie W, Zhou X. Targeted protein degradation: advances in drug discovery and clinical practice. Vol. 9, Signal Transduction and Targeted Therapy. Springer Nature; 2024.
35. Kubryń N, Fijałkowski Ł, Nowaczyk J, Jamil A, Nowaczyk A. PROTAC Technology as a New Tool for Modern Pharmacotherapy. Vol. 30, Molecules. Multidisciplinary Digital Publishing Institute (MDPI); 2025.
36. Zhou QQ, Xiao HT, Yang F, Wang YD, Li P, Zheng ZG. Advancing targeted protein degradation for metabolic diseases therapy. Vol. 188, Pharmacological Research. Academic Press; 2023.
37. Wang X, Shuai W, Yang P, Liu Y, Zhang Y, Wang G. Targeted protein degradation: expanding the technology to facilitate the

clearance of neurotoxic proteins in neurodegenerative diseases. Vol. 102, Ageing Research Reviews. Elsevier Ireland Ltd; 2024.
38. Ma S, Ji J, Tong Y, Zhu Y, Dou J, Zhang X, et al. Non-small molecule PROTACs (NSM-PROTACs): Protein degradation kaleidoscope. Vol. 12, Acta Pharmaceutica Sinica B. Chinese Academy of Medical Sciences; 2022. p. 2990–3005.
39. Lu M, Liu T, Jiao Q, Ji J, Tao M, Liu Y, et al. Discovery of a Keap1-dependent peptide PROTAC to knockdown Tau by ubiquitination-proteasome degradation pathway. European Journal of Medicinal Chemistry. 2018 Feb 25;146:251–9.
40. Kargbo RB. Treatment of Alzheimer's by PROTAC-Tau Protein Degradation. ACS Medicinal Chemistry Letters. 2019 May 9;10(5):699–700.
41. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020–2060). Alzheimer's and Dementia. 2021 Dec 1;17(12):1966–75.
42. Gray, N.S.; Haggarty, S.J.; Cai, Q.; Telo Baptista Lima Da Silva, M.C.; Zhang, T.; Ferguson, F.M. Compounds for Tau Protein Degradation. U.S. Patent WO2019014429, 17 January 2019.
43. Cummings JL, Osse AML, Kinney JW, Cammann D, Chen J. Alzheimer's Disease: Combination Therapies and Clinical Trials for Combination Therapy Development. Vol. 38, CNS Drugs. Adis; 2024. p. 613–24.
44. Xue Y, Bolinger AA, Zhou J. Novel approaches to targeted protein degradation technologies in drug discovery. Vol. 18, Expert Opinion on Drug Discovery. Taylor and Francis Ltd.; 2023. p. 467–83.
45. Kumar D, Hassan MI. Targeted protein degraders march towards the clinic for neurodegenerative diseases. Vol. 78, Ageing Research Reviews. Elsevier Ireland Ltd; 2022.
46. Hyun S, Shin D. Chemical-mediated targeted protein degradation in neurodegenerative diseases. Vol. 11, Life. MDPI AG; 2021.
47. Silva MC, Ferguson FM, Cai Q, Donovan KA, Nandi G, Patnaik D, Zhang T, Huang HT, Lucente DE, Dickerson BC, Mitchison TJ. Targeted degradation of aberrant tau in frontotemporal dementia patient-derived neuronal cell models. elife. 2019 Mar 25;8:e45457.
48. Qi SM, Dong J, Xu ZY, Cheng XD, Zhang WD, Qin JJ. PROTAC: an effective targeted protein degradation strategy for cancer therapy. Frontiers in pharmacology. 2021 May 7;12:692574.
49. Yao D, Li T, Yu L, Hu M, He Y, Zhang R, Wu J, Li S, Kuang W, Yang X, Liu G. Selective degradation of hyperphosphorylated tau by proteolysis-targeting chimeras ameliorates cognitive function in Alzheimer's disease model mice. Frontiers in Pharmacology. 2024 Jun 11;15:1351792.
50. Hyun S, Shin D. Chemical-mediated targeted protein degradation in neurodegenerative diseases. Life. 2021 Jun 24;11(7):607.
51. Paudel RR, Lu D, Roy Chowdhury S, Monroy EY, Wang J. Targeted protein degradation via lysosomes. Biochemistry. 2022 Sep 21;62(3):564-79.
52. Hanzl A, Casement R, Imrichova H, Hughes SJ, Barone E, Testa A, Bauer S, Wright J, Brand M, Ciulli A, Winter GE. Functional E3 ligase hotspots and resistance mechanisms to small-molecule degraders. Nature chemical biology. 2023 Mar;19(3):323-33.
53. Lane CA, Hardy J, Schott JM. Alzheimer's disease. European journal of neurology. 2018 Jan;25(1):59-70.
54. Liu Z, Hu M, Yang Y, Du C, Zhou H, Liu C, Chen Y, Fan L, Ma H, Gong Y, Xie Y. An overview of PROTACs: a promising drug discovery paradigm. Molecular biomedicine. 2022 Dec 20;3(1):46.

HOW TO CITE: Debkantha Gope*[1], Sayantika Kundu[1], Sayani Debnath[2], Degradomics-Driven Intervention: Reimagining Alzheimer's Therapy Through Targeted Protein Degradation, Int. J. Sci. R. Tech., 2026, 3 (4), 1249-1259. https://doi.org/10.5281/zenodo.19925861