

Targeted Protein Degradation Neurodegenerative Diseases: Emerging Therapeutic Strategies and Translational Challenges

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Received: 11-04-2026 / Revised: 18-05-2026 / Accepted: 27-06-2026

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Conflict of interest: Nil

Abstract

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis are biologically diverse disorders associated with progressive neuronal dysfunction. In several of these conditions, abnormal handling or accumulation of proteins contributes to disease pathology. Conventional small-molecule inhibitors generally reduce a protein's activity while leaving the protein itself present. Targeted protein degradation (TPD) offers a complementary approach: it aims to recruit a selected protein to cellular disposal pathways and lower its abundance. Major strategies include proteolysis-targeting chimeras (PROTACs), molecular glue degraders and autophagy-based systems such as AUTACs and ATTECs. These platforms have produced encouraging proof-of-concept results against targets relevant to neurodegeneration, including tau and mutant huntingtin, but evidence remains predominantly preclinical. Translating TPD into central nervous system (CNS) medicines requires adequate blood-brain barrier penetration, cell-specific exposure, productive target engagement, selective degradation and long-term safety. Computational tools—including structure analysis, docking, molecular dynamics, physicochemical profiling and ADMET prediction—can support early prioritisation, but they cannot establish degradation or clinical efficacy by themselves. This narrative review summarizes the biological basis of TPD, major degrader formats, selected disease applications, in silico evaluation strategies and the principal translational barriers. The central conclusion is that TPD is a promising research strategy rather than an established treatment for neurodegenerative diseases; experimental validation and careful CNS pharmacology remain essential.

Keywords: targeted protein degradation; PROTAC; molecular glue; autophagy; neurodegeneration; tau; α -synuclein; mutant huntingtin; blood-brain barrier; in silico drug discovery.

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Introduction

Neurodegenerative diseases are a group of conditions with different causes, clinical courses and affected neuronal populations. Alzheimer's disease (AD) commonly involves amyloid- β and tau pathology; Parkinson's disease (PD) is often associated with α -synuclein pathology and loss of dopaminergic neurons; Huntington's disease (HD) is caused by a CAG-repeat expansion in the HTT gene; and many cases of amyotrophic lateral sclerosis (ALS) show abnormal TDP-43 pathology, although ALS is heterogeneous [1–5]. These proteins are not interchangeable targets, and the disease mechanism must be considered before proposing a degradation strategy. Cells maintain protein homeostasis, or proteostasis, through molecular chaperones, the ubiquitin-proteasome system (UPS), and autophagy-lysosome pathways. These pathways help remove damaged, misfolded or unwanted material. When production, folding and clearance become imbalanced, abnormal protein species can accumulate and disrupt

cellular function [6,7]. The relationship between a protein and disease can be complex: a protein may have normal physiological roles, and the most harmful species may be an oligomer, modified form or specific subcellular pool rather than all forms of that protein. Traditional inhibitors usually act through occupancy-driven pharmacology: a drug binds a target and blocks one of its functions while the drug is present. TPD instead seeks to reduce the amount of the target by bringing it near a cellular degradation system. PROTACs and molecular glues commonly exploit E3 ubiquitin ligases and the UPS, while autophagy-based degraders redirect selected cargo towards lysosomal degradation [8–12]. TPD has expanded drug-discovery possibilities, but it should not be described as universally superior to inhibition. Its success depends on target biology, the availability of suitable ligands, degradation machinery, drug exposure and acceptable effects on normal proteins [8,9].

Review scope and approach

This article is a focused narrative review, not a systematic review or meta-analysis. The literature was selected to cover foundational TPD mechanisms, primary proof-of-concept studies, reviews of neurodegenerative disease applications and CNS-delivery challenges. PubMed-indexed records are linked individually in the reference list. No new laboratory, animal or patient data were generated for this review. The proposed computational workflow is a research framework and should not be interpreted as an experimentally validated protocol.

Biological basis and major TPD platforms

Ubiquitin–proteasome system

Ubiquitination is a regulated process involving ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin-ligating (E3) enzymes. E3 ligases help determine which proteins are recognized. When an appropriate ubiquitin signal is assembled, the substrate may be recognized and degraded by the proteasome. The UPS is central to protein turnover and is the principal pathway used by many conventional PROTACs [6,8]. A degrader must do more than bind the target: the target–degrader–E3 complex must have productive geometry, the target must be ubiquitinated at accessible sites, and the cellular machinery must process it.

PROTACs

A typical PROTAC is a heterobifunctional molecule containing a ligand for the protein of interest, a ligand for an E3 ligase and a chemical linker connecting the two. By binding both partners, it can promote formation of a ternary complex, enable target ubiquitination and facilitate proteasomal degradation [8,10–13]. Early PROTAC work established the concept of chemically directing proteins to ubiquitination machinery, and subsequent studies demonstrated catalytic protein knockdown in cells and in vivo models [13,14]. However, catalytic turnover is context-dependent; it is not guaranteed for every degrader. PROTAC activity depends on more than the affinity of each individual ligand. Linker length and flexibility, ternary-complex cooperativity, target lysine accessibility, E3 expression, permeability, solubility and intracellular exposure can all influence degradation. A compound with strong binary binding may still show weak degradation if it forms a non-productive ternary complex [8,13,14].

Target protein + PROTAC + E3 ligase → productive ternary complex → target ubiquitination → proteasomal degradation → reduced target abundance.

Molecular glue degraders

Molecular glue degraders are generally smaller, monovalent compounds that stabilize or induce an interaction between a target protein and another protein, often an E3-ligase substrate receptor. Unlike a

conventional PROTAC, a glue does not usually contain two separate binding ligands joined by a linker. Some molecular glues were discovered serendipitously, and newer research seeks systematic methods to identify or design them [8,14]. Their compact size can be advantageous for drug-like properties, but discovery and prediction are difficult because the relevant protein–protein interface may be unexpected and highly context-dependent.

Autophagy- and lysosome-directed degraders

The autophagy–lysosome system can handle long-lived proteins, aggregates and cellular components that may not be readily processed by the proteasome. AUTACs were developed to direct selected cargo into selective autophagy [15,17–19]. ATTECs use compounds that connect a target such as mutant huntingtin with LC3, a protein associated with autophagosome membranes. A landmark study reported compounds that lowered mutant huntingtin in an allele-selective manner and improved disease-relevant phenotypes in cellular and animal models [16]. AUTOTACs represent another approach to promote autophagy–lysosome-mediated degradation [20]. LYTACs were designed primarily to route extracellular or membrane-associated proteins to lysosomes through cell-surface trafficking receptors; their relevance differs from intracellular neuronal targets [21]. These technologies should not be grouped as if they use the same machinery. PROTACs and many molecular glues commonly rely on the UPS, whereas AUTACs, ATTECs and AUTOTACs are associated with autophagy-related pathways. LYTACs primarily exploit endosomal–lysosomal trafficking. The target's location and physical state therefore influence which platform is plausible [1,7,17,20,21].

Key limitation

- PROTAC Target ligand + linker + E3-ligase UPS / proteasome Often large and flexible; productive ligand ternary complex is essential
- Molecular glue Small molecule promotes a new or Often UPS / Hard to predict and discover rationally stabilised protein interaction proteasome
- AUTAC / Cargo recognition plus autophagy Autophagy–lysosome Mechanistic and selectivity questions AUTOTAC recruitment or activation remain
- ATTEC Links target to LC3-associated Autophagy–lysosome Target-specific evidence and delivery are autophagosome machinery needed
- LYTAC Binds extracellular or membrane Endosome–lysosome Not a direct substitute for intracellular target and trafficking receptor neuronal degraders

Opportunities in neurodegenerative diseases

Alzheimer's disease

AD involves multiple interacting processes, including amyloid- β biology, tau abnormalities, synaptic dysfunction, inflammation and neuronal loss [2]. Tau is an intracellular protein and a candidate for degradation because pathological tau species can misfold and aggregate. A preclinical study described a Keap1-dependent peptide PROTAC approach that promoted tau ubiquitination and proteasomal degradation [22]. Reviews have discussed PROTAC strategies for AD, but these concepts have not established a clinically approved TPD treatment for AD [23]. For tau, a central challenge is to lower disease-associated species without unnecessarily depleting normal tau, which contributes to microtubule biology and neuronal function. The target species, brain exposure, cell type, degradation duration and recovery after drug withdrawal should be assessed. Amyloid- β raises additional complexity because it exists in different forms and compartments, including extracellular deposits; an intracellular UPS degrader may not directly clear all extracellular material. The proposed mechanism must match the target's location and biology [1,23].

Parkinson's disease

PD is associated with progressive loss of dopaminergic neurons and, in many cases, α -synuclein-containing Lewy pathology [3]. TPD is being explored as a way to reduce disease-associated proteins rather than merely block a single activity. Reviews of TPD in PD describe PROTAC and other degradation concepts, but the evidence base remains early and largely preclinical [24]. α -Synuclein also has physiological roles in synaptic function; therefore, indiscriminate depletion could create risks. Studies should distinguish soluble, aggregated and modified species where possible and evaluate brain-region exposure, neuronal function and off-target degradation.

Huntington's disease

HD is caused by an expanded CAG repeat in HTT, leading to production of mutant huntingtin (mHTT) [4,25]. Reducing mHTT is an attractive strategy because it is directly linked to disease causation, but wild-type huntingtin also has important biological functions. ATTEC research has demonstrated the concept of lowering mutant huntingtin through autophagosome recruitment, including allele-selective effects in preclinical models [16]. This is a valuable proof of concept, not proof of clinical benefit in humans. Key questions include selectivity for mutant versus normal protein, long-term safety, distribution throughout the brain and whether molecular changes translate into functional improvement.

Amyotrophic lateral sclerosis

ALS is a heterogeneous disease with multiple genetic and pathological subtypes. TDP-43 pathology is common in many cases, while SOD1 variants define a subset of disease; other mechanisms also contribute [5,26]. A single degrader strategy is therefore unlikely to suit every patient. Candidate selection should be tied to a defined molecular subtype and supported by evidence that lowering the target is beneficial. Because TDP-43 and other candidate proteins have normal cellular functions, target depletion must be titrated carefully, with attention to cell-type distribution and long-term effects.

Disease Candidate protein / Potential rationale essential caution pathology-

- Alzheimer's Pathological tau; selected Reduce a pathological Preserve normal tau; match mechanism to disease amyloid-related targets protein burden intracellular or extracellular location
- Parkinson's α -Synuclein Reduce disease-associated Avoid harmful depletion of physiological disease α -synuclein species synaptic protein
- Huntington's Mutant huntingtin Lower a genetically causal Preserve wild-type huntingtin where disease protein possible
- ALS Subtype-specific targets such Address a defined disease ALS heterogeneity; target proteins may be as SOD1; TDP-43-related mechanism essential in healthy cells pathology

Pharmacological and in silico evaluation

Target selection and degradation metrics

A computational project should begin with a defensible biological question: which protein, which pathological form, which disease subtype and why would reducing its abundance plausibly help? Protein accumulation alone is not sufficient evidence that degradation will improve disease. A target may be a consequence rather than a driver, and excessive depletion may disrupt normal biology [1,8,23].

Two commonly used metrics are DC50, the concentration associated with 50% of the maximal degradation response under a defined assay, and Dmax, the maximum degradation observed under the tested conditions. These are assay-dependent and should be interpreted with time-course data, exposure, selectivity and protein recovery after compound removal. Binding affinity, target engagement and degradation are related but distinct measurements; docking scores alone cannot demonstrate a degrader's pharmacological activity [8,9].

Useful computational methods and their limits

Structure inspection can identify binding pockets and assess whether a proposed ligand is compatible with the target structure. Molecular docking can suggest plausible binding poses for a target ligand or

E3 ligand, while molecular dynamics can explore stability and conformational behaviour. For a PROTAC, modelling the ternary complex and linker geometry is more relevant than docking only the target-binding end. Nevertheless, predicted structures and energies do not prove that a productive complex forms in cells or that ubiquitination occurs [8,9,15,16]. Physicochemical descriptors and ADMET prediction can flag possible issues such as poor aqueous solubility, high polarity, metabolic instability, transporter-mediated efflux or low likelihood of CNS exposure. These predictions are especially uncertain for large, flexible degraders. BBB prediction should therefore be reported as a prioritisation estimate, not evidence that a compound reaches the human brain. Experimental permeability, unbound brain exposure, cellular uptake and degradation assays remain necessary [27–30].

Translational challenges

Blood–brain barrier and CNS exposure

The blood–brain barrier (BBB) is formed by specialized brain endothelial cells and supported by pericytes, astrocytes and other neurovascular components. Tight junctions, transport processes and efflux systems restrict entry of many substances into the CNS [28,29]. Many PROTACs have relatively high molecular weight, high polarity and substantial flexibility, which can make passive brain penetration difficult. Transporters such as P-glycoprotein may further reduce CNS exposure for susceptible molecules [27]. Potential strategies include careful optimisation of molecular size and polarity, reducing unnecessary flexibility, selecting suitable E3 ligases and exploring carrier-mediated or receptor-mediated transport. PROTAC delivery reviews discuss approaches such as receptor-mediated transcytosis and PROTAC–antibody conjugates, but these approaches face their own challenges, including construct complexity, release of active compound, selectivity and manufacturing [27]. Nano carriers or intranasal approaches may be investigated, but should not be presented as proven solutions without supporting data. A compound that is predicted to cross the BBB may still fail to reach the relevant neuronal population at sufficient unbound concentration.

Selectivity, target biology and safety

A degrader may affect proteins beyond the intended target if its ligands or induced protein interactions are not sufficiently selective. E3 ligases are not expressed equally in every cell type, and the abundance of the target and degradation machinery can differ by brain region and disease stage. Long-term safety is particularly important in chronic neurological disorders. Removing a disease-associated protein may be beneficial, but eliminating its normal counterpart or disturbing essential pathways may be harmful [8,9,23].

Evidence gap between models and patients

Cellular and animal models are valuable for mechanism testing, but they do not fully reproduce human neurodegeneration, ageing, comorbidities or the complexity of the BBB. A change in protein abundance is not automatically a meaningful clinical outcome. Translational studies should connect exposure, target engagement, degradation, downstream pathology, behaviour or function, and safety. At present, TPD is a rapidly advancing drug-discovery field, but the disease-specific applications reviewed here should be described as experimental unless a human clinical evidence source explicitly supports a stronger claim [1,8,23,31–36].

Future directions

Future work should prioritise disease-relevant target validation, brain-penetrant chemical design, selective E3-ligase recruitment and robust biomarkers of target degradation. More systematic comparison of degrader formats may clarify when UPS-based degradation is preferable to autophagy- or lysosome-directed approaches. For neurodegenerative diseases, selectivity for pathological protein forms and preservation of normal protein function may be as important as the absolute degree of degradation [1,7,11,17,31–37]. In silico research can make a useful contribution by comparing structures, reviewing reported ligands, exploring binding poses and ranking candidates for later experimental work. To improve reproducibility, a project should document software versions, structures, preparation steps, protonation assumptions, grid coordinates, scoring functions and all inclusion/exclusion decisions. Negative findings and prediction uncertainty should be reported. A responsible conclusion should distinguish computational predictions from observed pharmacology and avoid claims of treatment efficacy without experimental or clinical evidence.

Conclusion

Targeted protein degradation offers a different way to modulate disease-associated proteins by recruiting them to cellular disposal pathways. PROTACs and molecular glues commonly exploit the UPS, while AUTACs, ATTECs and related platforms use autophagy–lysosome biology. Preclinical studies provide encouraging examples, including tau-directed approaches and mutant-huntingtin lowering. However, CNS delivery, productive degradation, target selectivity, normal protein function and long-term safety remain major barriers. In silico methods can help prioritise candidates, but docking and ADMET predictions cannot establish degradation or therapeutic efficacy. TPD should therefore be viewed as a promising research direction for neurodegenerative diseases, not an established treatment for these conditions.

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