Targeted protein degradation: A novel therapeutic strategy for neurodegenerative diseases

Introduction

Neurodegenerative diseases are a heterogenous group of disorders that involve impaired brain function and dysfunction and loss of neurons.[1,2] Despite being an active area of research, developing treatments for neurodegenerative diseases has been challenging. For example, the low permeability of the blood-brain barrier can restrict or block access of therapeutics to the central nervous system and target site. And, even if drugs can reach the correct site, target proteins associated with neurodegenerative diseases can have limited druggability.[3] These challenges have led to high failure rates in neurodegenerative disease drug development, with no disease-modifying treatments currently available.[4,5] With aging populations, the number of people affected by neurodegenerative diseases is predicted to keep growing (Figure 1), emphasizing the urgent need to find new and effective strategies to treat neurodegenerative diseases.[6]

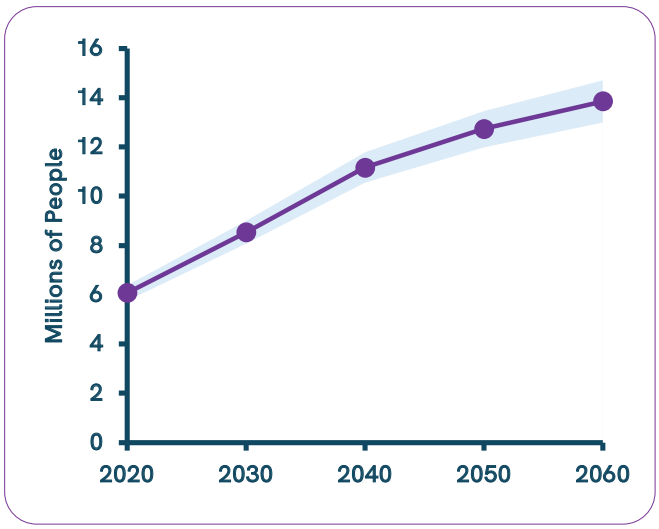

Figure 1. Graph showing increasing estimates of people affected by Alzheimer's disease each year, from 2020 to 2060.[7] Source: https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12362.

While neurodegenerative diseases are a heterogenous group of disorders, a common characteristic is the accumulation of misfolded or aggregated proteins, such as in:[2,8]

- Alzheimer's disease – Alzheimer's disease is linked with multiple protein abnormalities in the brain, such as accumulation of amyloid-β peptides (forming plaques) and hyperphosphorylation and accumulation of tau proteins (forming neurofibrillary tangles or NFTs). People affected by Alzheimer's disease can display a range of symptoms, including cognitive dysfunction and psychiatric and behavioral symptoms—such as aphasia and hallucinations.[9-11]
- Parkinson's disease – Parkinson's disease is linked with neurons accumulating misfolded and aggregated α-synuclein (which can form Lewy bodies and Lewy neurites).[12,13] Parkinson's disease involves a loss of neurons and affected individuals can display a range of motor and non-motor symptoms, such as bradykinesia, rigidity, pain, and depression.[14]
- Huntington's disease – Huntington's disease involves abnormal and aggregated forms of the huntingtin protein in brain cells. Huntington's disease is an autosomal

dominant inherited condition caused by expanded cytosine-guanine-adenine (CAG) repeats in exon 1 of the huntingtin gene. The increased number of CAG repeats in the huntingtin gene leads to an extended polyglutamine (polyQ) tract, causing the protein to misfold and accumulate in the nucleus and cytoplasm of neurons. This aggregation and accumulation of mutated huntingtin protein leads to neuronal loss, with affected individuals displaying impaired motor and cognitive function, as well as psychiatric symptoms.[15-18]

A promising and innovative therapeutic approach to neurodegenerative disease is targeted protein degradation (TPD), which recruits cell degradation machinery to selectivity degrade a target protein—such as misfolded, aggregated, or abnormal forms of tau, α-synuclein, or huntingtin. TPD offers advantages for treating neurodegenerative disease over traditional methods, such as small molecule inhibitors. For example, TPD is able to act on protein targets that were traditionally undruggable – such as α-synuclein and tau and aggregate forms of proteins – broadening the protein targets that can be acted on.[19] TPD agents (or degraders) destroy the protein, blocking all functions of the protein—unlike inhibitors, where proteins can still perform functions/interactions outside the inhibited site.[20] And, unlike gene therapy approaches, TPD can also act on proteins that are linked to disease through abnormal post-translational modifications. Here, we explore TPD as a neurodegenerative disease therapeutic, including its applications and limitations.

Mechanisms of targeted protein degradation

TPD degrades target proteins by exploiting cell degradation systems, such as through proteasomal or lysosomal degradation. Proteasomal degradation involves the ubiquitin–proteasome system (or UPS), where ubiquitin is attached to a lysine residue on a target protein through sequential action of three enzymes: E1 ubiquitin-activating (E1) enzymes; E2 ubiquitin-conjugating (E2) enzymes; and E3 ubiquitin (E3) ligases (see Figure 2).[22-24] TPD degraders often recruit or interact with E3 ligases, with the two most targeted E3 ligases being cereblon and von Hippel-Lindau (VHL).[25-27]

As ubiquitin also contains lysine (K) residues accessible for ubiquitination, multiple ubiquitin molecules can be linked together to create ubiquitin chains (polyubiquitination). The diversity in ubiquitin chain structures or 'tags' can signal for different cellular processes, such as degradation by the proteasome (K48-linked polyubiquitination) or the lysosome (K63-linked polyubiquitination).[28]

Autophagy–lysosome pathway

The autophagy–lysosome system (or ALS) is another major cellular degradation system that can handle longer-lived proteins, as well as larger structures (such as aggregated proteins and organelles).[29] The autophagy–lysosome system relies on material being delivered to the lysosome

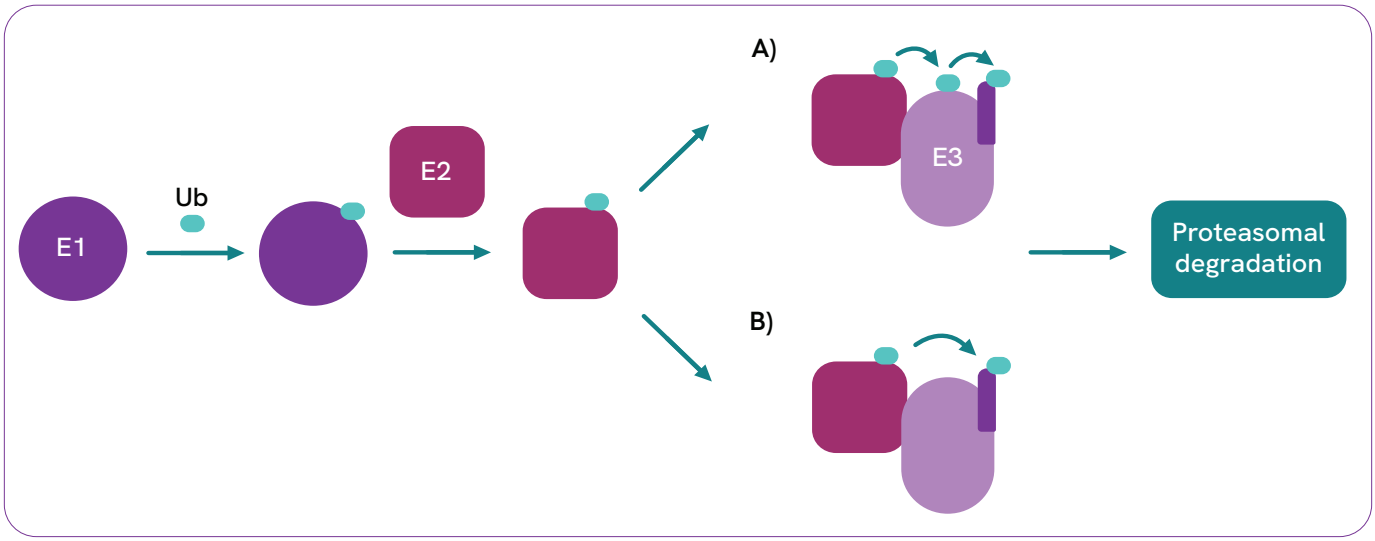

Figure 2. Overview of protein ubiquitination in ubiquitin–proteasome system. E1 enzymes recruit and activate ubiquitin, where ubiquitin is transferred to E2 enzymes. Ubiquitin is then attached to lysine residues on target proteins via E3 ligases either by direct transfer, where an E3 ligase recruits the target protein and E2 ligase allowing direct transfer of the ubiquitin to the protein; or by indirect transfer, where ubiquitin is transferred from E2 to the to the active site of the E3 ligase, before then being conjugated to the target protein.[24]

for degradation and can be split into three major forms[13]: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy involves material being enclosed by a double-membraned vesicle (autophagosome), which fuses with the lysosome for degradation (Figure 3).[29] Macroautophagy relies on a variety of proteins, such as:

- ULK1 — a serine/threonine kinase that – through a ULK1 complex (ULK1/ATG13/FIP200/ATG101) – initiates autophagy, promoting phagophore formation.[30,31]
- LC3 — a protein that can be conjugated to a lipid found on autophagasome membranes (phosphatidylethanolamine), forming LC3-II.[32]
- p62/SQTM1 — an autophagy receptor that can bind to ubiquitinated proteins and LC3-II, helping recruit degradation material to the autophagasome.[33]

The lysosome can also receive material for degradation from other routes, such as the endosome–lysosome pathway, where extracellular, cell surface, or membrane material can be endocytosed and delivered to the lysosome via a series of endosomes.[34]

Key technologies

A wide variety of degraders have been developed that trigger proteasomal or lysosomal degradation of target proteins (Figure 4). PROTACs (proteolysis targeting chimeras) are heterobifunctional compounds that have a target protein-binding domain and an E3 ligase-binding domain. PROTACs bind to both the target protein and the E3 ligase, bringing the E3 ligase within close enough contact to ubiquitinate the target protein, signaling for degradation of the target protein via the proteasome.[35] Molecular glues are another group of TPD agents being explored. Molecular glues bind to and modify the surface of a protein (such as the E3 ligase or target protein), allowing new interactions between the two proteins to occur—which can stabilize or strengthen binding between these proteins.[36] Molecular glues can form complexes between an E3 ligase and target protein to allow ubiquitination of the target protein and – consequently – degradation by the proteasome.[20]

In addition, TPD technologies that act through lysosomal degradation are also gaining traction and may be a promising approach for treating neurodegenerative diseases—particularly as the lysosome can degrade aggregated and extracellular proteins.[37] For example, ATTECs (autophagosome-tethering compounds) involve a domain that binds to the target protein and a domain that binds to LC3 (found on the phagophore and autophagosome membranes). Consequently, ATTECs link the target protein to the phagophore via LC3, allowing the target protein to be degraded through the autophagy–lysosome system.[38] In addition, AUTACs (autophagy-targeting chimeras) also act through the autophagy–lysosome system and involve a structure that binds to the target protein and a structure – or 'degradation tag' – that recruits autophagy machinery. The degradation tag leads to K68-linked polyubiquitination of the target protein, which signals for transport to the autophagosome and degradation of the target protein via the autophagy–lysosome system.[35,39]

Techniques have also been developed to act on the endosome–lysosome pathway, such as LYTACs (lysosome-

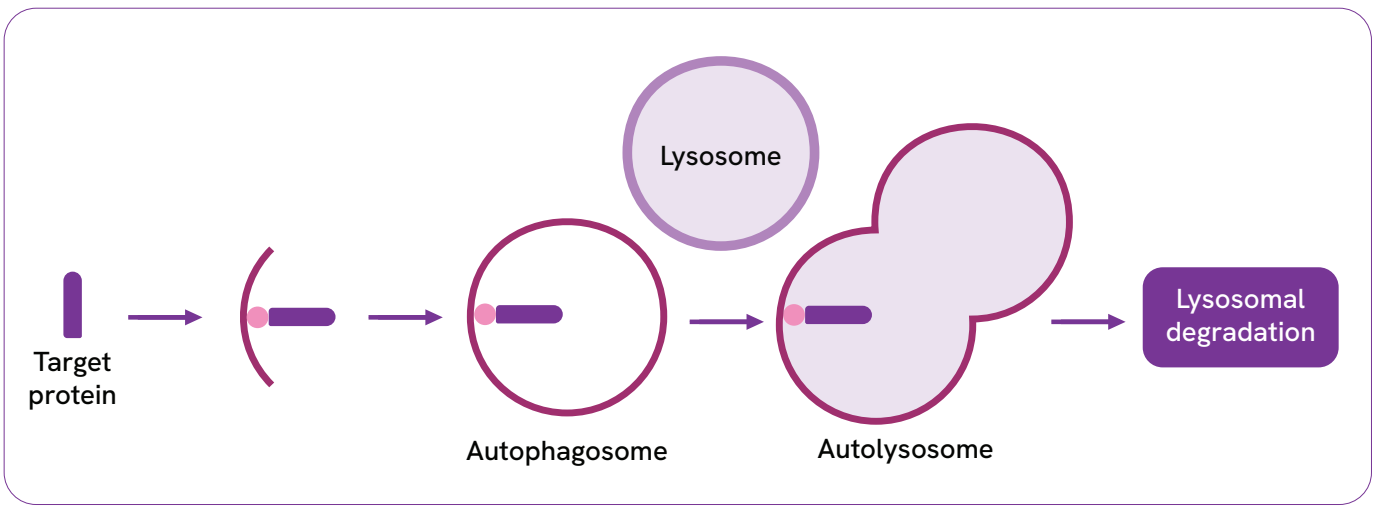

Figure 3. Overview of macroautophagy.

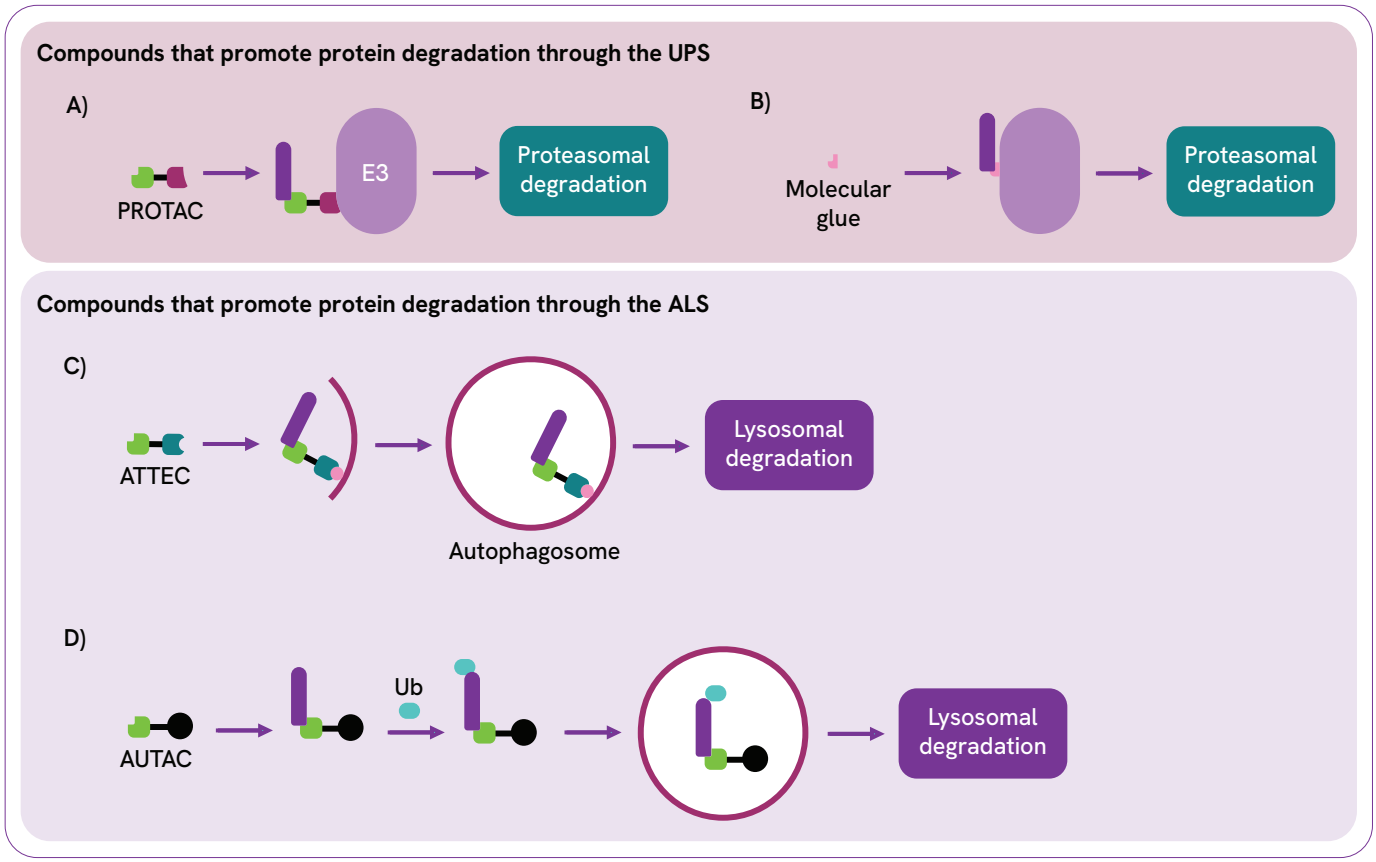

Figure 4. Overview of example degraders that facilitate degradation of target proteins through the UPS or the ALS, such as A) PROTACs; B) molecular glues; C) ATTECs; and D) AUTACs.

targeting chimaeras). LYTACs have a structure that binds to a target membrane or extracellular protein and a structure that binds to lysosome-targeting receptor.[36,37] By forming a complex with the target protein and lysosome-targeting receptor, LYTACs allow target proteins to be delivered to the lysosome for degradation through endocytosis.[37]

Applications in neurodegenerative diseases

TPD had been investigated as a method of destroying disease-linked proteins (Figure 5) in a range of preclinical and clinical studies for neurodegenerative diseases, with approaches facilitating proteasomal or lysosomal degradation.[40] Below we explore TPD approaches under investigation in the literature, focusing largely on Alzheimer's disease, Parkinson's disease, and Huntington's disease.

Alzheimer's disease

A variety of preclinical studies have investigated TPD strategies to target and clear multiple disease-linked proteins in Alzheimer's disease, such as tau, amyloid-β, and GSK-3β proteins. For example, Chu et al. designed a series of PROTAC degraders that targeted tau protein and recruited either the VHL (von Hippel-Lindau tumor suppressor protein) or SCF (Skp1-cullin-F box) E3 ligases, promoting ubiquitination and proteasomal degradation of tau proteins. The most effective tau-degrading compound was TH006, which reduced intracellular tau levels *in vitro* and *in vivo* (in an Alzheimer's disease mouse model). These reduced Tau levels were found to lower the cytotoxicity effects of amyloid-β.[41] Wang et al. also designed a PROTAC (C004019) that recruits the VHL E3 ligase for proteasomal degradation of tau proteins. C004019 was found to effectively degrade tau proteins *in vitro* and in mouse models, reducing cytotoxicity triggered by amyloid-β and improving "synaptic and cognitive functioning".[42] GSK-3β – a serine/threonine protein kinase that can increase phosphorylation of tau and amyloid-β levels – has also been targeted by TPD. For example, Guardigni et al. developed PROTACs that recruit cereblon (CBRN) E3 ligase for ubiquitination and proteasomal degradation of GSK-3β. One of the compounds (compound 1) – a potent and selective inhibitor of GSK3-β linked to pomalidomide – was able to

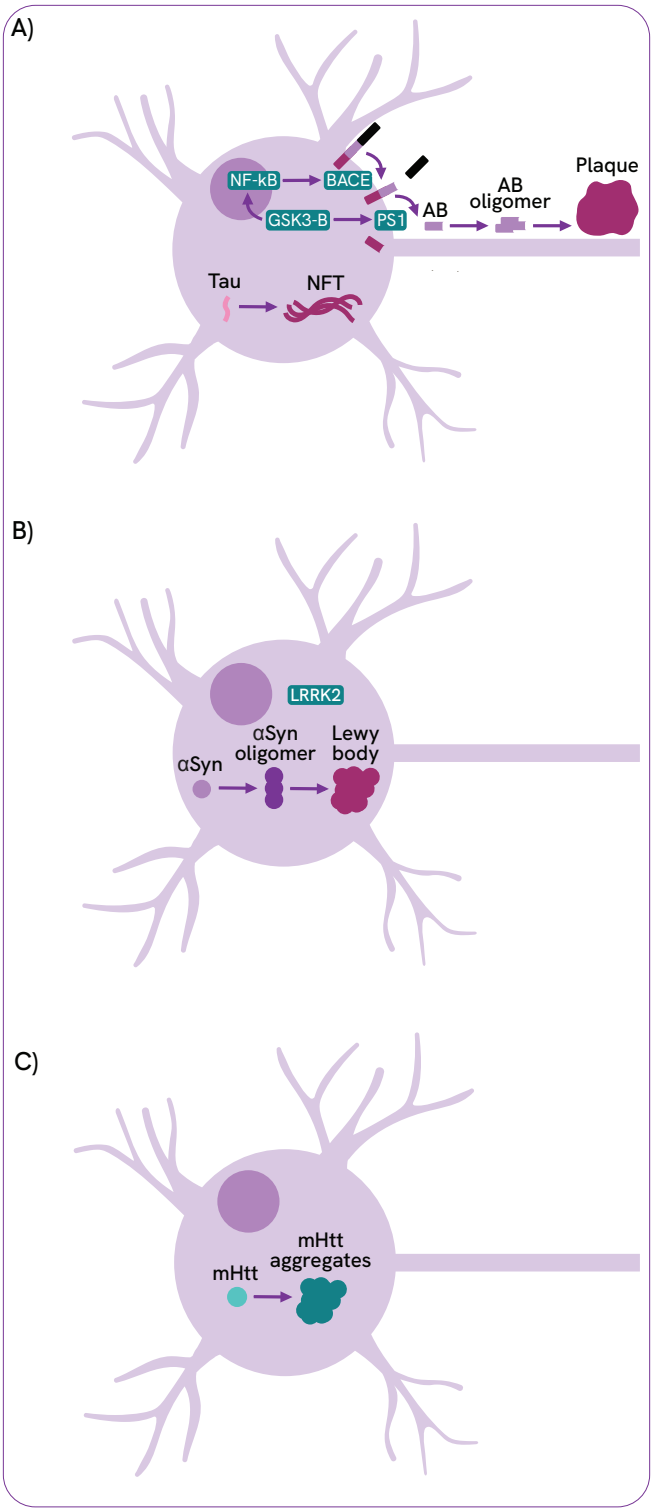

Figure 5. Overview of example proteins targeted in TPD research for A) Alzheimer's disease; B) Parkinson's disease; and C) Huntington's disease.

effectively degrade GSK-3β in SH-SY5Y cells and reduce cytotoxicity effects induced by amyloid-β and Cu^{2+}.[43]

Lysosomal degradation-based TPD approaches have also been explored for Alzheimer's disease. For example, Liu et al. designed an innovative multicomponent LYTAC-based structure (KPLY) that targets extracellular amyloid-β aggregates for lysosomal degradation. Once KPLY reaches an Alzheimer disease lesion area, the degrader (cli-LYTAC) is generated in situ—as inactive precursors are activated by Cu that gathers in amyloid-β plaques. Cli-LYTACs then deliver extracellular amyloid-β aggregates to the lysosomal shuttling receptor: CD206, where the amyloid-β aggregates are internalized through endocytosis and delivered to the lysosome for degradation. Cli-LYTACs were found to selectively degrade amyloid-β aggregates. In addition, KPLY had anti-oxidative properties which can help trigger microglia to transition into an M2-like phenotype, increasing lysosome targeting receptor levels—which enhances amyloid-β lysosomal degradation.[44]

Parkinson's disease

With misfolded and aggregated forms of α-synuclein playing a role in Parkinson's disease, a variety of TPD approaches have been investigated to target α-synuclein. For example, Jin et al. developed a peptide-based degrader (Tat-α syn-degron) that triggers proteasomal degradation of α-synuclein. The degrader involves Tat, which helps the structure pass through the blood–brain barrier and cell membranes; a beta-synuclein derivative, which binds to α-synuclein; and degron, which signals for proteasomal degradation.[45,46] Tat-αsyn-degron was found to reduce α-synuclein levels *in vitro* and *in vivo* (in two Parkinson's disease mice models)—with a reduction in spread between cells.[45]

Degraders that recruit lysosomal degradation may be advantageous as lysosomal degradation can handle oligomeric and aggregated forms of α-synuclein, which are linked with Parkinson's disease pathology.[47] Lee et al. developed an α-synuclein AUTOTAC degrader (ATC161), which relies on macroautophagy for degradation of alpha-synuclein. ATC161 involves a structure that binds α-synuclein and a structure that binds the autophagic receptor p62/SQSTM1/Sequestosome-1, leading to degradation of α-synuclein via the autophagy–lysosome system. ATC161 was found to effectively degrade α-synuclein aggregates *in vitro* and *in vivo* (using a Parkinson's disease mouse model). ATC161 also reduced spread of alpha-synuclein aggregates between cells, the glial cell immune response, and motor symptoms in mice.[47]

Other protein targets are also being investigated in Parkinson's disease TPD research, such as leucine-

rich repeat kinase 2 (LRRK2)—which is a protein linked to Parkinson's disease and other disorders, such as progressive supranuclear palsy.[48] Liu et al. designed an LRKK2 PROTAC degrader (XL01126), which binds LRKK2 and VHL, triggering ubiquitination and degradation of LRKK2 via the proteasome. XL01126 effectively degraded LRKK2 in multiple cell lines and was found to be an orally-available structure that can cross the blood-brain barrier in mice—providing promising findings that warrant further *in vivo* investigation (which the authors note is ongoing).[49] The potential of LRKK2 as a target for TPD in Parkinson's disease has been further highlighted by Arvinas, who have recently begun a phase I clinical trial for their LRKK2 PROTAC degrader (ARV-102). The phase I clinical trial will assess the safety profile of ARV-102 in healthy individuals.[50]

Huntington's disease

Both proteasomal- and lysosomal-based TPD approaches have been explored in Huntington's disease. For example, Tomoshige et al. developed two inhibitors of apoptosis-based PROTACS – also known as SNIPERs (specific and nongenetic IAP-dependent protein erasers) – to target mutant huntingtin protein for proteasomal degradation. The two SNIPERs involved a structure that binds to the cellular inhibitor of apoptosis protein 1 (cIAP1) E3 ligase (bestatin) linked to a structure that binds to mutant huntingtin-binding domain (involving BE04 attached to BTA for compound 1 or PDP for compound 2). Both compounds were able to effectively degrade mutant huntingtin in patient fibroblasts, with compound 1 also capable of handling mutant huntingtin proteins that had long polyQ repeats and aggregates of huntingtin with long polyQ repeats.[51] In addition, both Arvinas and Origami Therapeutics are developing mutant huntingtin PROTAC degraders.[52,53]

Degraders recruiting autophagic systems have also been investigated for Huntington's disease. Lin et al. developed four mutant huntingtin ATTEC degraders, which are structures that contain a mutant huntingtin-binding domain and an LC3-binding domain. Consequently, the ATTEC recruits mutant huntingtin to the phagophore (via binding to LC3), allowing degradation of mutant huntingtin through macroautophagy. These mutant huntingtin ATTEC degraders were found to effectively degrade mutant huntingtin levels *in vitro*, with no effect on wild type huntingtin—an important aspect of Huntington's disease therapeutics as wildtype huntingtin is needed for a variety of cellular processes. The degraders were also capable of reducing mutant huntingtin levels in animal models (fly and mouse) *in vivo*, with treatment providing benefits to animals, such as reducing apoptosis of neuronal cells and improving motor symptoms.[54] In addition, Bauer et al. designed a degrader that triggered degradation of mutant huntingtin via chaperone-mediated autophagy. The multicomponent degrader involved two copies of a structure that bound to mutant huntingtin (polyglutamine binding peptide 1 or QBP1) and copies of two different structures that bound to the chaperone protein: heat shock cognate protein 70 (HSC70). The degrader (QBP1-HSC70bm) effectively degraded mutant huntingtin without affecting wild type huntingtin levels *in vitro* and *in vivo* (using a Huntington's disease mouse model)—the degrader was delivered *in vivo* using viral particles. *In vivo* experiments showed that degrader treatment provided benefits in mice, such as reducing mutant huntingtin aggregation and improving motor symptoms.[55]

Other neurodegenerative disorders:

Other neurodegenerative disorders, such as amyotrophic lateral sclerosis and frontotemporal dementia, are also associated with misfolded or aggregated proteins, which has led researchers to target these diseases using TPD. For example, Tseng et al. developed a PROTAC degrader to target TDP-43 (TAR DNA Binding Protein 43 kDa) in amyotrophic lateral sclerosis. TDP-43 is a hallmark of amyotrophic lateral sclerosis, with TDP-43 found in cytosolic aggregates in most ALS cases—and nearly half (around 45%) of frontotemporal dementia cases.[56] Tseng et al. designed four PROTAC degraders (termed PROTAC1–4) to target C-terminal TDP-43 oligomers and aggregates. PROTAC2 was found to effectively degrade C-terminal TDP-43 aggregates *in vitro* and *in vivo* (using transgenic *C. elegans*), showing selectivity for misfolded TDP-43. This *in vivo* reduction of C-terminal TDP-43 aggregates was also found to improve motility in *C. elegans*.[57]

Aggregates of hyper-phosphorylated tau are associated with frontotemporal dementia (as well as Alzheimer's disease and progressive supranuclear palsy). Silva et al. designed a tau PROTAC degrader (QC-01-175) that had a tau-binding domain (based on the positron emission tomography tracer: T807) linked to a cereblon-binding domain (pomalidomide) to trigger proteasomal degradation of phosphorylated tau proteins. The degrader reduced aggregates in *in vitro* neuronal cell models (cells derived from frontotemporal dementia patients) and had no effect on tau in healthy controls.[58]

TPD challenges, limitations, and outlook

While TPD has huge potential as an effective neurodegenerative disease treatment approach, TPD can face a number of challenges and limitations. Depending on the degrader system, these challenges can span selectivity, stability, off-target effects, and delivery.

Delivery and stability

The wide selection of degrader systems and structures holds promise for finding new treatment strategies for neurodegenerative diseases. However, these new structures can be complex and have unknown, unfamiliar, or undesirable drug profiles.[59] For example, complex and high molecular weight degraders can have poor solubility and stability, as well as poor penetrance across cell membranes and the blood–brain barrier.[60] The blood–brain barrier – with its tightly packed cells and efflux systems – restricts access of compounds to the central nervous system and is a major hurdle facing successful delivery of drugs in neurodegenerative diseases.[61] And the high molecular weight and polar nature of some degraders can lead to these structures having poor permeability across the blood–brain barrier.[59] This poor bioavailability and stability can lower efficacy of a degrader as the degrader can be cleared from the body too quickly or not reach the target region in sufficient quantities. However, as well as ensuring adequate delivery and sufficient levels to the target site, degraders such as PROTACs must be optimized for dosing levels. If degrader levels are too high, degrader–target protein or degrader–E3 ligase complexes can form, reducing degradation efficacy.[60]

Selectivity and off-target effects

Degraders may act on non-target proteins, which can damage normal cell functioning and create off-target effects. In addition, only a small selection of the ca. 600 E3 ligases in humans are commonly targeted in TPD research. With E3 ligase expression varying in the body and degradation efficiency/capability dependent on successful E3 ligase–target protein–degrader complexes forming, using only a small selection of the E3 ligase pool can limit the application of where a degrader can act effectively and what disease it can treat. For example, levels of a commonly used E3 ligase, cereblon, can vary across different regions of the brain, impacting selectivity of the degrader.[61]

Outlook

Advances in technology to better characterize degraders and their interactions may aid development and identification of effective degraders that have good drug profiles and can reach target sites in desired levels. For example, Zhang et al. developed a proteomic platform to reveal off-target protein interactions with systems such as PROTACs, which could help better identify off-target interactions.[62] Studies are also ongoing to find ligands to recruit unused or underexplored E3 ligases, which will hopefully help expand the use of TPD in neurodegenerative disease. In addition, variable E3 ligase expression may offer an advantage in terms of selectivity and side effects. By identifying E3 ligases that are specific or highly expressed in target cells/diseased areas, researchers could improve the selectivity by designing degraders that act in a specific location or cell type.[59] For example, RNF182 levels were found to be higher in the brain tissue of Alzheimer disease patients.[63]

Exploring alternative delivery routes may help overcome the limitations of some degraders in removing bioavailability limitations and the hurdle of crossing the blood–brain barrier.[59] In addition, solubility of degraders could be improved by considering the design of the degrader—such as developing effective linkers that help balance lipophilicity (for membrane permeability) and hydrophilicity (for solubility).[61,64]

Advancing neurodegenerative disease research with no-wash immunoassays

Revvity provides a comprehensive range of HTRF and AlphaLISA cell-based detection assays (Table 1), empowering neurodegenerative disease research. Our solutions enable precise quantification of target proteins, facilitating the identification of targeted protein degraders in research samples.

Table 1: HTRF and AlphaLISA cell-based detection assays.

	AlphaLISA™ or AlphaLISA™ *SureFire® Ultra™* *	HTRF™*
Tau, Total	ALSU-TTAU-A500	64NTAUPEG
Tau Aggregation		6FTAUPEG
Amyloid β 1-40 (Human)	AL373C	62B40PEG
Amyloid β 1-42 (Human)	AL203C	62B42PEG
LRRK2, Total	ALSU-TLRRK2-A500	64LRRKTPEG
α-Synuclein, Total	ALSU-TASYN-A500	6FNSYPEG
α-Synuclein Aggregation	ALSU-AASYN-A500	6FASYPEG
HTT, Total		64HTTTPEG
HTT, Mutant		64HTTMPEG
TDP43, Total	ALSU-TTDP43-A500	64TDPTPEG
TDP43, Total aggregated	ALSU-ATDP43-A500	62TDP43PEG
LC3B-II		64LC3B2PEG
p62/STSQM1, Phospho-Ser351	ALSU-PSQSTM-A500	
p62/STSQM1, Phospho-Ser403	ALSU-PSQSTM-B500	64P62S4PEG
p62/STSQM1, Total	ALSU-TSQSTM-A500	64N62PEG
ULK1, Phospho	ALSU-PULK1-A500	64ULKPEG
GSK3β, Total	ALSU-TGS3B-A500	64GTAPEG

*This list is non-exhaustive. For a complete selection of our kits, please visit our website.

Conclusion

TPD offers huge potential as an approach to treat neurodegenerative diseases—as emphasized by the array of promising preclinical studies in a range of neurodegenerative diseases and Arvinas' ARV-102 PROTAC that has recently begun phase I clinical trial investigation. TPD also improves on conventional treatments, such as being able to act on "undruggable" proteins and ablating all functions of a protein. Notably, TPD degraders that use lysosomal degradation can address aggregated proteins, which are common in various neurodegenerative diseases. Advances in technology and degrader design hope to overcome some of the challenges and limitations facing current degrader development, such as better identifying off-target effects through proteomic platforms and improving drug profile by incorporating linkers that can improve solubility and cell membrane/blood-brain barrier permeability. A better understanding of the underlying mechanisms that cause disease and cell death would also improve development of therapies.[58]

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