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Targeted protein degradation in CNS disorders: a promising route to novel therapeutics?

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Targeted protein degradation (TPD) is a rapidly expanding field, with various PROTACs (proteolysis-targeting chimeras) in clinical trials and molecular glues such as immunomodulatory imide drugs (IMiDs) already well established in the treatment of certain blood cancers. Many current approaches are focused on oncology targets, leaving numerous potential applications underexplored. Targeting proteins for degradation offers a novel therapeutic route for targets whose inhibition remains challenging, such as protein aggregates in neurodegenerative diseases. This mini review focuses on the prospect of utilizing TPD for neurodegenerative disease targets, particularly PROTAC and molecular glue formats and opportunities for novel CNS E3 ligases. Some key challenges of utilizing such modalities including molecular design of degrader molecules, drug delivery and blood brain barrier penetrance will be discussed.

KEYWORDS

CNS degraders, TPD, PROTAC, molecular glue, UPS, E3 ligase

Introduction

Targeted protein degradation (TPD) is a new modality with potential to drug poorly tractable targets. PROTAC (proteolysis-targeting chimera) or molecular glue (MG)-driven ternary complex formation with an E3 ligase utilizes cells' ubiquitin-proteasome system (UPS) to degrade targets. Several such molecules have entered clinical development (Kong and Jones, 2023). Two E3 ligases, Von Hippel-Lindau (VHL) and Cereblon (CRBN), are regularly harnessed for therapeutic TPD approaches; both belong to the Cullin-RING E3 Ligase (CRL) family (Bondeson et al., 2015; Zengerle et al., 2015). Most current activity is in oncology, with indications including central nervous system (CNS)-associated pathologies less explored. Therapeutic development for CNS diseases is challenging due to blood brain barrier (BBB) permeability constraints, and in the druggability of protein aggregates which often characterize neurodegenerative pathologies. Commonly used degrader approaches have the potential to target proteins or aggregated complexes for degradation by the ubiquitin-proteasome (UPS) system (Bekes et al., 2022; Zhu et al., 2024) or autophagy-lysosome machinery (Pei et al., 2021; Ji et al., 2022). Targeted protein degraders act through event-driven pharmacology via non-reversible removal of functional components, and their potency is boosted by a catalytic mode of action (MOA), enabling sub-stoichiometric dosing regimens (Bekes et al., 2022). An extended pharmacokinetic (PK)- pharmacodynamic (PD) disconnect (Mares et al., 2020), can afford a reduction in off-target toxicity. These represent advantages over occupancy driven pharmacology often displayed by small molecule inhibitors. Further, degradation can be driven by ternary complex stability (Bondeson et al., 2018), for which protein-protein

interaction (PPI) driven cooperativity is a key factor. As such, ligand-binding site affinity can be lower, potentially useful in targeting proteins without functional sites, such as the protein aggregates observed in neurodegenerative disease (Figure 1).

PROTACs in CNS disease

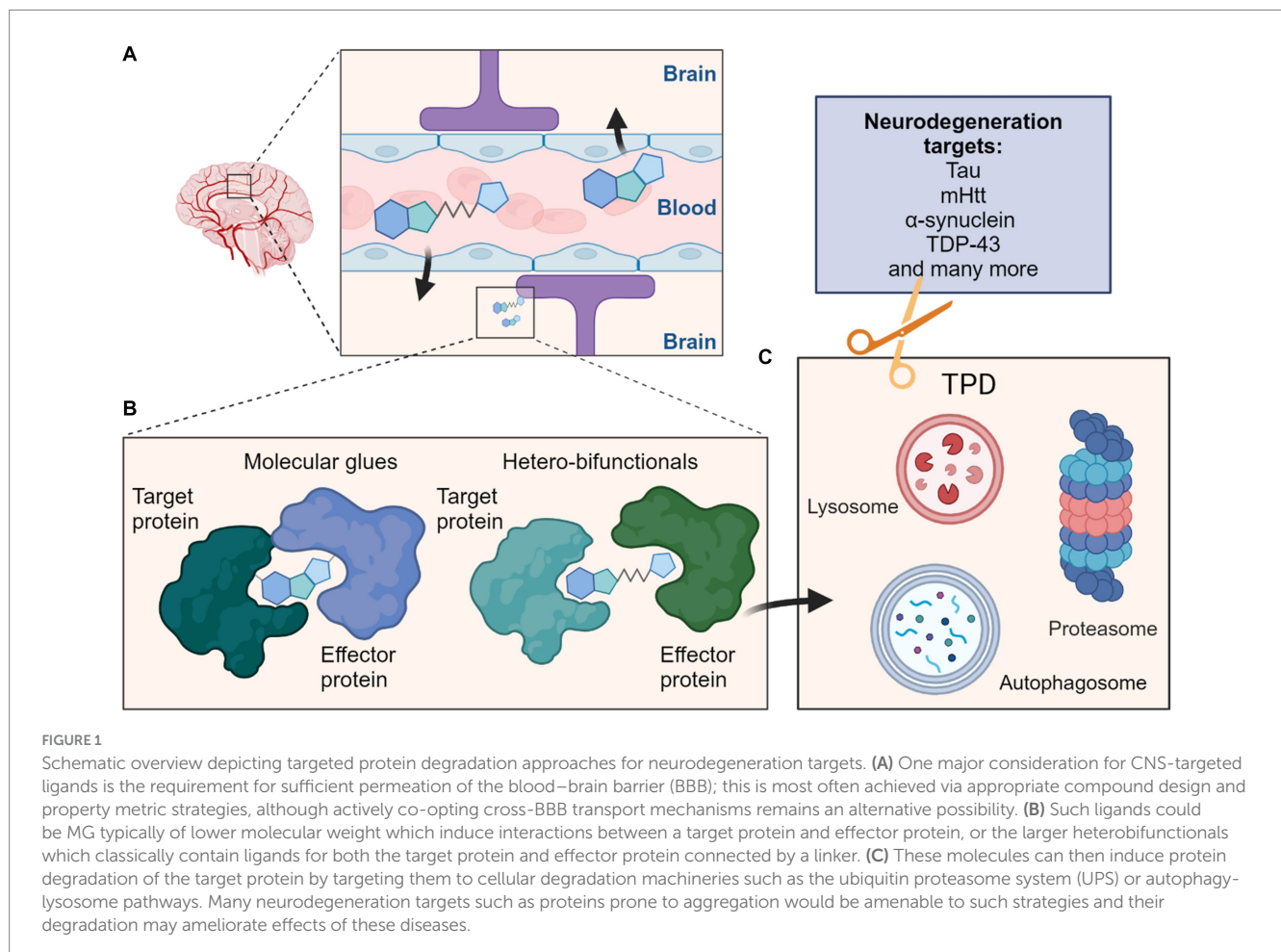
Degradation approaches have been examined in proof-of-concept studies for neurodegenerative diseases (Thomas et al., 2023). Conceptually, protein or aggregates can be degraded if a selective small molecule binder is available. Utilizing degron tagging to induce proximity between a given target and an E3 ligase of interest may validate the approach (Ottis et al., 2017).

Many neurodegenerative disorders feature accumulation of aggregated proteins. Examples include Tauopathies, described in frontotemporal dementia (FTD) and Alzheimer's disease (AD), and characterized by accumulation of aberrant Tau proteins (Morris et al., 2011; Gotz et al., 2013; Wang et al., 2014). Post-translational modifications of Tau lead to misfolding, mislocalization and oligomerization, resulting in neuronal toxicity (Gotz et al., 2013; Medina, 2018; Congdon et al., 2023). Studies utilizing a KEAP1-dependent peptide PROTAC showed degradation of intracellular Tau (Lu et al., 2018), providing evidence that Tau can be degraded by TPD approaches. Several studies report ternary complex formation and

degradation of toxic forms of Tau using PROTACs to recruit the E3 ligases VHL or CRBN (Silva et al., 2019; Wang et al., 2021; Silva et al., 2022). A Tau-selective degrader QC-01-175, showed preferential degradation of aberrant Tau in FTD patient-derived neuronal cell models compared to healthy controls (Silva et al., 2019). A follow-up study optimized the linkers and demonstrated improved degradation of insoluble protein (Silva et al., 2022).

α -Synucleinopathies in Parkinson's disease (PD) are also a potential degrader target. Abnormal accumulation in neurons leads to the formation of Lewy bodies and neurites, hallmarks of PD (Spillantini et al., 1997, 1998), and α -synuclein may disrupt normal lysosomal function (Bourdenx et al., 2014), suggesting degradation via the UPS as a possible approach. Utilizing an α -synuclein peptide and proteasome-targeting motif resulted in ubiquitination and degradation, attenuating neuronal toxicity (Qu et al., 2020). PROTACs based on three E3 ligase binders and α -synuclein aggregation inhibitor sery384, which binds oligomeric α -synuclein (Wagner et al., 2013; Pena-Diaz et al., 2023), induced degradation of aggregated α -synuclein in an overexpression system using preformed fibrils (Wen et al., 2023). The efficacy of these molecules was low and PROTAC MOA experiments are required to determine the value of this approach.

Mutant huntingtin (mHTT) aggregation is thought to cause neuronal injury and apoptosis in Huntington's disease (Fiorillo et al., 2021). One approach to targeting mHTT for degradation linked amyloid binding imaging agents (Olsen et al., 2010; Matsumura et al.,



2012) to IAP binders and showed degradation of HTT and mHTT in cells (Tomoshige et al., 2017, 2018).

Amyotrophic Lateral Sclerosis (ALS) and FTD show formation of cytoplasmic TAR DNA-binding protein (TDP-43) aggregates (Jo et al., 2020). In healthy cells, TDP-43 is predominantly nuclear and involved in transcriptional and post-transcriptional regulation and pre-mRNA splicing (Jo et al., 2020). A proportion of TDP-43 shuttles between the cytoplasm and nucleus as part of cellular stress responses. In ALS pathology, TDP-43 is found in insoluble cytoplasmic aggregates where it is often hyperphosphorylated, ubiquitinated and fragmented (Neumann et al., 2006; Hasegawa et al., 2008). Loss of nuclear TDP-43 into cytoplasmic aggregates could be a driver of ALS pathology (Ling et al., 2013). PROTACs linking aggregate binders, benzothiazole-aniline derivatives (BTA), to Pomalidomide, degraded overexpressed truncated c-terminal TDP-43, attenuating the reduction in cell viability (Tseng et al., 2023). Both varying expression and subcellular localization of target proteins would offer opportunities for selectivity, giving spatiotemporal control of therapeutic activity.

PROTAC molecular design constraints

Constraining small molecule property design space within thresholds improves toxicity and PKPD outcomes in later development (Lipinski et al., 2001; Wager et al., 2010; Shultz, 2019). CNS-targeted PROTACs are large molecules which also require BBB penetration, and as such occupy several restrictive and complex design spaces. Property considerations are stricter for CNS-targeted ligands requiring passive BBB permeation (Wager et al., 2016). A detailed analysis of CNS metrics is beyond the scope of this review, but consideration of the widely used Pfizer CNS MPO metric (Wager et al., 2010, 2016) favors chemotypes of moderate size and limited polarity (total polar surface area, TPSA, LogD, hydrogen bond donors, HBD), a pattern reproduced in the B3DB compound database with annotated BBB permeation characteristics (Meng et al., 2021).

PROTACs are also large molecules which extend into challenging non-traditional, “beyond rule of 5” (bRo5) property space (Matsson et al., 2016; Volak et al., 2023). There are additional resulting challenges: (i) larger molecules can behave differently especially regarding permeability and transport (Guimaraes et al., 2012; Doak et al., 2014; Matsson et al., 2016; Matsson and Kihlberg, 2017; Pye et al., 2017; Linker et al., 2023); (ii) available chemical space is larger; (iii) large molecules are often more conformationally complex (Rossi Sebastiano et al., 2018; Mobitz, 2023); (iv) fewer molecules from bRo5 space have been studied; (v) those studied molecules cluster in niches (e.g., macrocycles) and represent a less even distribution (Doak et al., 2014). Metric-based approaches nonetheless exist (Degeoey et al., 2018; Poongavanam et al., 2018; Mobitz, 2023). Broadly, these suggest that higher LogP values are tolerated; greater ligand complexity could compensate for lipophilicity driven promiscuity (Hann et al., 2001; Doak et al., 2016; Matsson et al., 2016; Egbert et al., 2019). This may compensate for size associated permeability challenges (Pye et al., 2017; Pike et al., 2020). With increasing size, TPSA becomes less representative of ligand polarity, and conformational changes which modulate exposed polarity in response to environment (chameleonic behavior) become accessible (Rossi Sebastiano et al., 2018; Ono et al., 2021; Garcia Jimenez et al., 2023). While the extent to which this behavior is observed in bRo5 chemical matter is debated (Mobitz,

2023), accessible conformations of significantly lower polarity than suggested by TPSA values may be required (Whitty et al., 2016; Mobitz, 2023). Tight restrictions on hydrogen bonding are suggested (Doak et al., 2014; Matsson et al., 2016; Whitty et al., 2016; Mobitz, 2023; Volak et al., 2023).

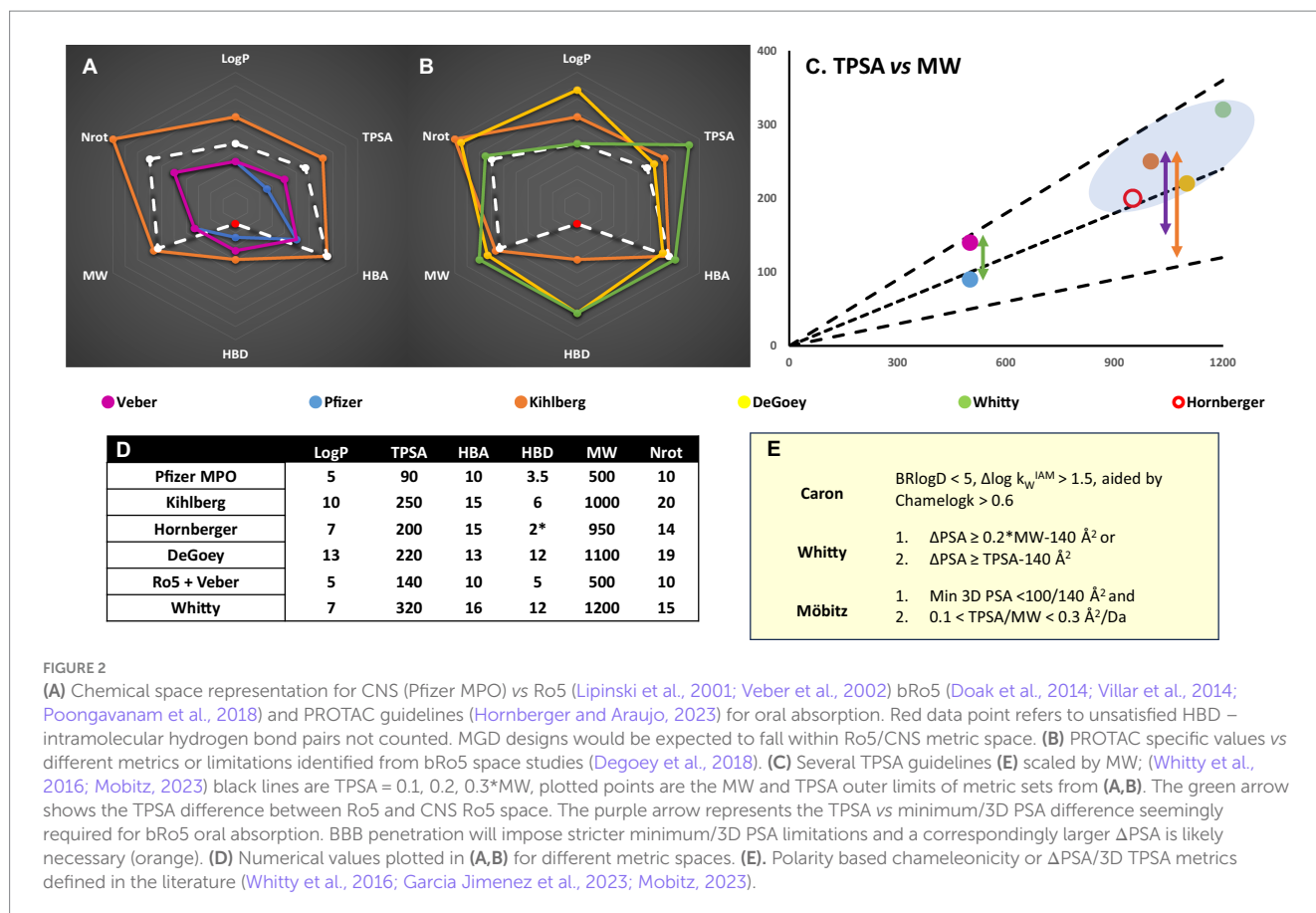
Analysis of PROTAC chemotypes shows these molecules broadly comply with bRo5 paradigms (Edmondson et al., 2019), although stricter limits on HBD were observed in rat absorption data (Hornberger and Araujo, 2023). A CNS penetrant PROTAC must balance sufficient polarity to provide specific target engagement and solubility while crossing the BBB (Doak et al., 2014). Additionally, increased efflux is common in bRo5 (Doak et al., 2014; Matsson et al., 2016; Cantrill et al., 2020; Cox et al., 2023) and PROTAC development space (Klein et al., 2021). Beyond CNS considerations, the combination of differentiated property space (in particular lipophilicity) and pharmacology results in additional considerations around absorption, distribution, metabolism, and excretion (ADME) testing (Cantrill et al., 2020; Pike et al., 2020; Apprato et al., 2023; Hornberger and Araujo, 2023; Volak et al., 2023).

Lastly, heterobifunctional molecules display behaviors not attributable to a single component, including different target specificity to their POI ligands, whose affinity does not predict ternary complex stability or productivity (Bondeson et al., 2018). Cooperative binding behavior can arise from induced PPI (Song et al., 2021). Given the limitations implied by the combination of CNS permeation, bRo5 space and efflux liabilities, the ‘budget’ of polar contacts and hydrogen bonds available for the POI binder alone is limited (Hughes et al., 2021; Hornberger and Araujo, 2023). The interactions induced in ternary complex formation can generate contact areas equivalent to those in other bRo5 modalities (Doak and Kihlberg, 2017; Bondeson et al., 2018). Considered alongside the importance of conformational masking of polarity in bRo5 space, property-based linker design and rigidification (Troup et al., 2020; Klein et al., 2021; Poongavanam et al., 2022), and holistic consideration of molecular properties will prove vital. The combination of CNS and PROTAC constraints will require greater chameleonicity and cooperativity (Figure 2), and each component to adopt multiple roles to achieve sufficient permeability and binding specificity.

Several CNS penetrant PROTACs have been reported, utilizing VHL (Wang et al., 2021; Liu et al., 2022) and CRBN binders (Mihalic, 2023); oral exposure was demonstrated for each (Liu et al., 2022; Mihalic, 2023). All display low $K_{p,uu}$ values (Loryan et al., 2022), but nonetheless several demonstrate *in vivo* activity (Wang et al., 2021; Mihalic, 2023). These observations may reflect exposure requirements depending on potency and event vs occupancy driven pharmacology (Volak et al., 2023). Notably the clinical candidate NX-5948 minimizes size and hydrogen bonding consistent with earlier considerations (Mihalic, 2023). Though development of PROTACs for neurodegenerative diseases will have to meet the challenges of BBB and brain penetration, there is considerable commercial activity in employing this therapeutic strategy (Kargbo, 2020).

Expanding the repertoire of E3 ligases

Two key E3 ligases have been routinely harnessed for TPD approaches. CRBN ligands dominate PROTACs and MG in clinical stages (Kong and Jones, 2023), mainly due to their size and “drug-like”



properties, although the risk of teratogenicity remains a concern (Smith and Mitchell, 2018). Two VHL-based PROTACs, namely BCL-X_L degrader DT2216 (Khan et al., 2019) and KRAS^{G12D} degrader ASP-3082 (Nagashima et al., 2022) are in clinical trials, and E7820, which glues RBM39 to the DCAF15 ligase complex (Chirnomas et al., 2023; Kong and Jones, 2023). Other E3 ligases such as RNF114 (Spradlin et al., 2019; Luo et al., 2021), KEAP1 (Wei et al., 2021; Du et al., 2022), DCAF11 (Zhang et al., 2021; Xue et al., 2023) and DCAF16 (Zhang et al., 2019) have been harnessed for TPD, but not progressed beyond pre-clinical investigations and their effectiveness in degrading a wide range of targets remains unclear. Several of these E3s are ubiquitously expressed, likely leading to target degradation in multiple tissues increasing toxicity when targeting essential proteins. The use of tissue enriched or selective E3 ligases as PROTAC or molecular glue degrader (MGD) targets has huge potential for diseases restricted to one tissue or organ such as CNS pathologies. One clinical example is DT2116, which degrades BCL-X_L. BCL-X_L inhibition causes on-target and dose-limiting thrombocytopenia (Kaefer et al., 2014); however, the PROTAC showed significantly lower toxicity due to low VHL expression in platelets (Khan et al., 2019). CNS enriched E3s may allow CNS target degradation while limiting potential toxicity in unwanted tissues. Examples include RNF182 identified as a brain-enriched E3 upregulated in AD patients (Liu et al., 2008). Several E3s of the Kelch family such as ENC1, KBTBD11, KLHL2, KLHL32, KLHL35 and KLHL4 also have preferential brain expression (Ehrlich et al., 2020), where other family members such as KEAP1 have already been utilized in PROTAC-based degraders (Wei et al., 2021). Two TRIM-family E3 Ligases (TRIM9 and TRIM67) are neuronally

enriched and regulate neuronal morphological changes (Tanji et al., 2010; Menon et al., 2015; Boyer et al., 2020). A related E3 Ligase TRIM21 shows proximity-induced degradation using the “Trim-away” technique, degrading targets through binding the Fc region of antibodies (Clift et al., 2017). Developments in specific fragment libraries (Whitehurst et al., 2023) and covalent approaches have been investigated for E3 ligand finding (Tao et al., 2022; Belcher et al., 2023; Toriki et al., 2023), but not demonstrated in CNS space. Advances in understanding which E3 ligases could be utilized for TPD purposes (Liu et al., 2023) will support efforts to discover and develop new E3 ligase ligands (Ishida and Ciulli, 2021).

Molecular glue degraders (MGDs) for CNS disease

Most MGDs facilitate degradation via induced protein–protein interactions between an E3 ligase and a target (Rui et al., 2023). Historically, the discovery of MG and their mechanism was retrospective. For example, the severe birth defects caused by thalidomide (Vargesson, 2015) are thought to be caused by degradation of the neosubstrate transcription factor SALL4 via thalidomide binding to the E3 ligase CRBN (Ito et al., 2010) The landscape of neosubstrates depends on ligand structure (Matyskiela et al., 2016; Nowak et al., 2023; Szewczyk et al., 2024), unlocking opportunities for novel target discovery. The aryl sulfonamide Indisulam blocks cell cycle progression (Owa et al., 1999) through degradation of mRNA splicing factor RBM39 mediated by recruitment

of the E3 ligase DCAF15 (Han et al., 2017). Indisulam and derivatives do not display high affinity to either target protein; ternary complex formation results in nanomolar affinities (Du et al., 2019). Linking aryl sulfonamides to the BET bromodomain inhibitor JQ1 demonstrated that BRD4 degradation was independent of DCAF15 and driven by stabilizing existing interactions of adjacent bromodomains with the E3 ligase DCAF16 (Hsia et al., 2024). These intramolecular bivalent glues highlight another mechanistic possibility, demonstrating the pharmacological scope of these approaches and the importance of evaluating off-target degradation profiles of novel degraders.

Efforts are underway to rationalize the discovery of MG. One approach is the E3 ligase centric generation of compound libraries, currently focused on CRBN-binding chemotypes (Powell et al., 2020) but which will extend to other E3s upon ligand and neosubstrate discovery. Another is to engineer cell lines to overexpress, eliminate, conformationally trap or inactivate a given E3 ligase; then screen libraries for their ability to degrade targets (Mayor-Ruiz et al., 2019; Hanzl et al., 2023; Ng et al., 2023). However, CNS relevant cell types are often more difficult to manipulate than cancer cell lines. DNA-encoded library (DEL) screening has been adapted to screen for ternary complex formation (Mason et al., 2023) and in combination with disease relevant recombinant aggregates or proteins would be a definite starting point for CNS relevant MG identification. Opportunities for novel MG identification depend on an understanding of interactions between relevant proteins. Techniques such as Bio-ID/Turbo-ID can identify potential E3 ligase substrates and weak protein–protein interactions (Branon et al., 2018; Barroso-Gomila et al., 2023) in disease relevant cell types as a precursor to DEL screening for novel MG discovery. Matching an E3 ligase to a target protein through CRISPR-based degron mapping would further annotate pre-selection (Timms et al., 2023; Zhang et al., 2023) to identify CNS-enriched E3s and target pairings.

Structure-based design of MG remains an enticing but challenging prospect. Modeling or obtaining structural information on ternary complexes is difficult due to their complexity (Casement et al., 2021). Artificial Intelligence (AI) and Machine Learning (ML) approaches have driven advances in protein structure prediction, but their utility in predicting protein–protein complexes remains uncertain (Burke et al., 2023), although improvements in accuracy within classes may be realized as more structural data is acquired.

Glue molecular design considerations

A CNS-targeted MG would generally comprise a small molecule requiring BBB permeability; although differences in binding (Cao et al., 2022; Sasso et al., 2023) and the specifics of event driven pharmacology (Riching et al., 2022) may create distinctions. MG chemotype diversity (e.g., thalidomide vs rapamycin), and scaffold over-representation complicate definition of generic design constraints (Dong et al., 2021; Sasso et al., 2023) although it appears that most non-natural product MG can achieve their function within Ro5 parameter space (Dong et al., 2021; Dewey et al., 2023). Re-positioning existing chemotypes is common in glue development- (Guo et al., 2019; Geiger et al., 2022; Sasso et al., 2023; Toriki et al., 2023), so scaffold specific considerations may be widely applicable.

The most studied MGD class are immunomodulatory imide drugs (IMiD) analogues, which bind to CRBN (Cao et al., 2022) via

structures related to biological signaling motifs (Ichikawa et al., 2022) and engage a recurring POI motif represented in numerous targets, largely via hydrophobic groups (Oleinikovas et al., 2024). Recent work on parameter optimization for CRBN ligand specificity (Szewczyk et al., 2024) suggested significant target dependence, but reduction in aromatic carbocycles, introduction of heteroatoms and increased spatial complexity appear beneficial. LogP or TPSA were not determinative, while increasing HBD count was detrimental in several classes. This suggests that CRBN MGD *selectivity* optimization is not necessarily in tension with CNS property space. However, the determinative power of these MPOs was weak across much of the chemical space surveyed. The observation that CRBN ligands extend the PPI surface (Oleinikovas et al., 2024), and can cause PPI relevant conformational changes (Watson et al., 2022) is consistent with groups apparently distal from the common binding site influencing substrate selectivity (Nowak et al., 2023; Nguyen et al., 2024). In studies of CRBN binders it was observed that more proteins interact than are degraded (Sievers et al., 2018) an effect which may give rise to stronger selectivity in cells (Oleinikovas et al., 2024).

Among other known degrader classes, Cyclin K degraders have been shown to function throughout the Ro5 LogP and MW range, with a hydrophobic contact and ligand modification of the PPI again noted as key considerations in binding and selectivity (Kozicka et al., 2023). Indisulam analogues have less binary affinity and bind in a less conserved site but are involved in extensive interface interactions which modify the resulting PPI surfaces (Faust et al., 2020). From the limited studies to date the influence of conformational and PPI effects such as extending or remodeling surfaces and steric exclusion appear to be considerations for the efficacy and selectivity of glue interactions, which may influence the choices made in glue design (Geiger et al., 2022; Kozicka et al., 2023; Jiang et al., 2024; Oleinikovas et al., 2024).

In practical terms non-natural product MG fall mostly within chemical space for which existing ADME assays are effective. Compound efficiency metrics, however, may need to be re-defined to adequately discriminate between early stage ligands (Jia et al., 2024).

Non E3-ligase driven degradation

Strategies to target proteins or aggregates to the autophagy-lysosome machinery are less well understood than UPS-targeting degraders. For example, microarray-based screening led to the discovery of mHTT–light chain 3 (LC3) binders which induced autophagy-mediated degradation of mHTT (Li et al., 2019). The underlying MOA has since been questioned as it was found that the indolinone LC3 binders covalently bind to the E3 Ligase DCAF11, leading to UPS-driven degradation (Xue et al., 2023). α -Synuclein has been targeted to the lysosomal proteolytic machinery by peptides containing α -synuclein-binding, membrane-penetrating and chaperone-mediated autophagy-targeting motifs (Tong et al., 2023). α -Synuclein has also been degraded by macroautophagy, employing an autophagy-targeting chimera (AUTOTAC) binding both α -Synuclein aggregates and autophagy receptor p62/SQSTM1/Sequestosome-1 (Lee et al., 2023). Strategies to clear extracellular proteins or aggregates include lysosome-targeting chimeras (LYTACs), which are bifunctional molecules binding both a cell-surface

lysosome-shuttling receptor and the target of interest (Banik et al., 2020), which could be especially valuable for neurodegenerative diseases characterized by toxic insoluble extracellular aggregates. Some of these techniques may lead to the activation of autophagy having an added benefit, since mutations in genes encoding regulators of the autophagy and UPS machineries, such as p62/SQSTM1, VCP or Ubiquilin-2 are often found in FTD or ALS and are thought to cause downregulation of autophagy/proteasomal functions (Deng et al., 2017). Further, protein aggregates or oligomers may interfere with proteasomal function, resulting in lower PROTAC efficacy. One study describes allosteric impairment of the 20S proteasome substrate gate by soluble oligomers composed of either amyloid- β (A β) 1–42, α -synuclein, or mHTT, preventing substrates from entering the 19S pore (Thibaut et al., 2018). It is not known whether these oligomers inhibit the proteasome sufficiently to prevent efficient degradation.

Concluding remarks and outlook

Several proof-of-concept studies have been published on the degradation of known neurodegenerative disease targets. Key challenges remain in the discovery of selective small molecules suitable for degradation approaches and their development towards therapeutic applications in CNS space. For heterobifunctional molecules such as PROTACs, the most important aspects center on complex mechanistic and property design considerations. By contrast, MG discovery space particularly requires identification of degraders and the PPI which they enable. For both contexts, novel CNS-enriched E3 ligase enablement will drive progress in this area. Despite these challenges, the event driven pharmacology allowed by degraders may be especially suited to CNS disease targets, allowing for innovative therapeutic developments in an area of significant unmet medical need.

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Author contributions

SK: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. AC: Conceptualization, Writing – original draft, Writing – review & editing. KB: Writing – original draft, Writing – review & editing. ZY: Writing – original draft, Writing – review & editing. JL: Writing – original draft, Writing – review & editing.

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