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Review Article

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PROTACs for Targeted Protein Degradation: Mechanisms, Design, and Controllable Delivery Strategies

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ABSTRACT

Proteolysis-targeting chimeras (PROTACs) are an emerging class of bifunctional small molecules that induce targeted protein degradation by hijacking the cell's ubiquitin–proteasome system. A PROTAC simultaneously binds a protein of interest (POI) and an E3 ubiquitin ligase, forming a ternary complex that leads to ubiquitination and proteasomal destruction of the target protein. Here, we present a concise review of PROTAC technology aimed at synthesizing recent advances in mechanism, molecular components, and rational design. Relevant literature was identified through searches of PubMed, Scopus, and Web of Science up to August 2025. Articles were thematically analyzed to highlight mechanistic principles, structure–activity relationships, and delivery innovations. Evidence consistently shows that efficient degradation depends more on productive ternary-complex formation and cooperativity than on binary binding affinities, that linker geometry and E3 ligase choice are decisive factors for selectivity, and that new approaches such as photoswitchable PROTACs, pro-drug designs, and antibody or aptamer conjugates offer spatiotemporal control. The review concludes that standardization of cooperativity metrics, expansion to new E3 ligases, and integration with clinically validated targeting vectors are key priorities for future development.

Key Words: Linker design, Protein degradation, Cancer, Ligands, Clinical trial, Ubiquitin–proteasome system

INTRODUCTION

In the past two decades, PROTACs have emerged as a revolutionary modality in targeted protein degradation, offering a new approach to tackle diseases driven by pathogenic proteins that are difficult to inhibit with conventional drugs. The PROTAC concept was first introduced in the early 2000s. Early PROTACs were peptide-based and proved that induced protein degradation was feasible, but they suffered from poor cell permeability and stability due to their large size and peptidic nature.[1, 2, 3, 4]

The field advanced in 2008 when the first all-small-molecule PROTAC was reported by Schneekloth et al. This PROTAC, composed of an androgen receptor ligand (a SARM) linked to the MDM2-binding nutlin, demonstrated degradation of the androgen receptor, heralding a new generation of drug-like PROTACs.[5]

Since then, PROTAC design has rapidly evolved, with key milestones including the development of VHL (von Hippel–Lindau) recruiting PROTACs around 2012 and cereblon (CRBN) recruiting PROTACs in 2015. These leveraged the first small-molecule ligands for the E3 ubiquitin ligases VHL and CRBN, dramatically broadening PROTAC applicability.

Notably, in 2015, two landmark studies demonstrated potent degradation of BRD4 using VHL and CRBN ligands, respectively.[6,7] By bringing targets into proximity with an E3 ligase, PROTACs achieve what conventional inhibitors often cannot: they eliminate the target protein rather than simply inhibiting it, which can provide more durable therapeutic effects and overcome adaptive resistance mechanisms. PROTACs operate catalytically, meaning one PROTAC molecule can trigger the destruction of multiple protein molecules in a cycle, distinguishing them from occupancy-driven inhibitors.[8] The promise of PROTACs has translated into vigorous efforts to develop them as therapeutics.

The first PROTACs entered clinical trials in 2019, with ARV-110 (targeting androgen receptor) and ARV-471 (targeting estrogen receptor) showing initial evidence of clinical activity against prostate and breast cancers.[6,9,10]

As of today, numerous PROTAC candidates have progressed into clinical development for cancer and other diseases.

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Despite this progress, challenges remain that prevent many PROTACs from advancing beyond preclinical stages.[11] Chief among these are issues of on-target toxicity in normal tissues, suboptimal pharmacokinetic properties (e.g. large size leading to poor permeability and bioavailability), and the so-called "hook effect" where excessive PROTAC can reduce degradation efficiency.[12] To address these challenges, current research is intensely focused on refining PROTAC molecular design and developing innovative strategies for controllable or selective activity.[13]

METHODOLOGY

Relevant literature was identified through comprehensive searches of three major electronic databases: PubMed, Scopus, and Web of Science. The search was limited to English-language peer-reviewed articles published up to August 2025. Search terms included combinations of the following keywords: "PROTAC," "proteolysis-targeting chimera," "targeted protein degradation," "ternary complex," "linker design," "E3 ligase," and "controllable delivery." Reference lists of key articles were also manually screened to identify additional relevant studies.

Inclusion criteria comprised original research articles, reviews, and clinical studies that addressed the chemical structure, mechanism of action, optimization, delivery innovations, or therapeutic development of PROTACs. Exclusion criteria encompassed non-English publications, editorials, conference abstracts, and reports not primarily focused on PROTAC technologies.

Articles meeting these criteria were thematically analyzed using an inductive synthesis approach. Extracted data were grouped into three principal domains reflecting the scope of the review: mechanistic principles (e.g., ternary complex dynamics, ubiquitination), structural design considerations (e.g., linker chemistry, E3 ligase selection), and strategies for controllable or targeted delivery (e.g., photoactivatable, antibody-conjugated, or prodrug systems). This thematic categorization enabled an integrative synthesis of advances and challenges in PROTAC development.

MECHANISM OF ACTION OF PROTACS

A PROTAC operates by orchestrating a proximity-induced interaction between a target protein and an E3 ubiquitin ligase, leading to the target's ubiquitination and subsequent destruction by the 26S proteasome (Figure 1).[1] The PROTAC molecule contains two ligands connected by an appropriate linker: one end (the "warhead") binds the protein of interest (POI), and the other binds an E3 ligase. When a PROTAC bridges its target and an E3 enzyme, it forms a transient ternary complex (Target–PROTAC–E3). This proximity allows the E3's associated ubiquitin-conjugating enzyme (E2) to transfer multiple ubiquitin molecules to lysine residues on the target protein's surface.[14,15] Polyubiquitination tags the protein for recognition by the proteasome.[16] The proteasome then unfolds and degrades the target protein, thereby eliminating it from the cell. Importantly, the PROTAC itself is not consumed in this process; after the target is degraded, the PROTAC can be released and potentially engage another POI/E3 pair. This mechanism contrasts with traditional inhibitors that require continuous occupancy of the target and do not remove the protein. As a result, PROTACs can achieve prolonged effects even after the compound has been cleared.[17]

Because PROTACs function by inducing protein-protein proximity rather than simply binding and blocking an active site, their pharmacology has unique features. They do not require tight or long-lived binding to the target protein to be effective; even transient binding can suffice to recruit an E3 and label the target for destruction.[18] Furthermore, PROTAC-induced ternary complex formation can exhibit cooperativity as in some cases, the simultaneous binding of target and E3 can enhance the affinity of each interaction (positive cooperativity), resulting in a more stable ternary complex than the binary interactions alone. Such positive cooperativity can translate to efficient target degradation and even enable a PROTAC to discriminate between closely related proteins. For example, a modestly selective inhibitor can be converted into a highly selective degrader if the geometry of ternary complex formation favors one substrate over another.[19] On the other hand, at high concentrations, PROTACs may saturate the target or E3 individually, forming non-productive binary complexes; this is known as the "hook effect" and can reduce degradation efficiency at excessive dose.[20]

KEY COMPONENTS AND DESIGN STRATEGIES

A PROTAC molecule comprises three components: (1) a target-binding ligand (also called the warhead), which recognizes and binds the protein of interest; (2) an E3 ligase ligand, which recruits a specific ubiquitin E3 ligase; and (3) a flexible linker that bridges the two ligands. Each component plays a critical role in dictating the PROTAC's potency, selectivity, and pharmacokinetic properties.[22] Rational PROTAC design involves optimizing each part and the interplay between them to promote protein degradation.

Target-Binding Ligands (Warheads)

Much of early PROTAC development relied on repurposing existing inhibitors as POI ligands. For example, the first small-molecule PROTAC used a non-steroidal antiandrogen

(SARM – selective androgen receptor modulator) as the androgen receptor (AR) ligand [23], BET family PROTACs have used BET bromodomain inhibitors (e.g. JQ1) as warheads. Using a high-affinity inhibitor as the warhead ensures that the PROTAC can efficiently seek out and bind the target protein inside cells.[1]

However, a unique advantage of PROTACs is that extremely high affinity is not always required as even a ligand with moderate affinity can induce potent degradation if the overall ternary complex is stabilized by cooperative interactions. This means PROTAC warheads can, in principle, bind to sites other than the active site or even to protein–protein interaction interfaces on the target. This broadens the scope of ligands that can be used. For previously "undruggable" targets that lack obvious active-site pockets, researchers have identified shallow grooves or secondary pockets where small molecules or even fragment-like ligands can bind and leverage those as warheads for PROTAC design.[24,25]

E3 Ligase Ligands

On the opposite end of the PROTAC is the E3 ligase-recruiting ligand. Selecting an appropriate E3 ligase and ligand is crucial for achieving efficient degradation, cell permeability, and tissue specificity. Humans have over 600 E3 ligases, but to date only a handful have been "hijacked" by small-molecule ligands for use in PROTACs. The most commonly used E3s in PROTAC design are CRBN (cereblon) and VHL (von Hippel–Lindau), followed by IAPs (inhibitor of apoptosis proteins such as XIAP) and MDM2.These four E3 systems (CRBN, VHL, IAP, MDM2) account for virtually all small-molecule PROTACs, and they remain the workhorses of the field.[1]

Cereblon (CRBN) is part of the CUL4 E3 ligase complex and was famously discovered as the target of thalidomide which is an immunomodulatory *imide* drug (IMiD). Small molecules like thalidomide, lenalidomide, and pomalidomide bind to CRBN and act as glue-like recruiters – they have been widely adopted as CRBN-binding PROTAC ligands. These have favorable drug-like properties and, importantly, CRBN is ubiquitously expressed in cells, making CRBN-recruiting PROTACs broadly effective. CRBN-based PROTACs have shown potency against many targets including kinases, transcription factors, and epigenetic proteins. One consideration is that IMiD-based PROTACs can also induce degradation of neosubstrates (like IKZF1/3) that bind to CRBN when the IMiD is present. This on-target side effect (transcription factor degradation) needs to be weighed, though in cancer contexts it can be beneficial.[26–29]

VHL (Von Hippel–Lindau) is another E3 ligase commonly co-opted for PROTACs. VHL's endogenous role is to ubiquitinate HIF1α; small-molecule VHL ligands were developed through fragment-based design and structural biology in 2012–2015, enabling the first non-peptidic VHL-recruiting PROTACs.[30,31] VHL-based PROTACs have achieved excellent potency and selectivity for many targets and often display high stability of the ternary complex due to favorable protein–PROTAC–protein interfaces. VHL ligands tend to be polar but cell-permeable enough when optimized with proper capping groups.[2]

IAP ligases (XIAP, cIAP1) were employed in early PROTACs termed "SNIPERs" (Specific and Non-genetic IAP-Dependent Protein Erasers).[1] IAPs have small-molecule binders such as LCL161 (an IAP antagonist) and bestatin derivatives that recruit them.[32] IAP-based PROTACs have been used to target proteins like BCL-xL, where using VHL or CRBN led to undesired degradation in platelets (causing toxicity), whereas IAP is less active in platelets, providing a safer alternative.[33]

MDM2 is the E3 ligase that naturally ubiquitinates p53. Nutlin-class compounds bind MDM2 and were used in the first small-molecule PROTAC.[23] One recent strategy is to exploit cancers that overexpress MDM2: PROTACs leveraging overexpressed MDM2 can achieve tumor-selective degradation by requiring MDM2 for activity. For example, an MDM2-recruiting PROTAC was shown to degrade oncogenic BRD4 in cancer cells while simultaneously freeing p53 from MDM2, yielding a dual tumoricidal effect.[34]

Beyond these, several other E3 ligases are under investigation to expand the toolkit. For instance, DCAF15 (targeted by ligands like indisulam) induces degradation of RBM39 and has been co-opted for selective degradation of splicing factors. More recently, covalent recruiters to E3s such as RNF114 (with zinc-chelating compounds) and DCAF16 have been identified.[34] The discovery of novel E3 ligands is a hot area of research, as each new ligase could enable targeting specific tissues or subcellular contexts.[35]

Linker Design and Optimization

The linker influences the relative orientation and distance between the target protein and the E3 ligase when bound, essentially governing the geometry of the ternary complex. A well-optimized linker allows the PROTAC to adopt a conformation that brings the target and E3 into close proximity with minimal steric clash, promoting ubiquitin transfer. In contrast, a suboptimal linker might be too short to permit ternary complex formation or too long/flexible, leading to floppy complexes that do not ubiquitinate efficiently.[15,36] Flexible linkers (like PEG chains or alkyl chains) can confer entropy cost but allow the molecule to search conformational space for a productive complex, whereas more rigid linkers (incorporating aryl rings or alkynes) can pre-organize the orientation but might fit only certain targets.[37] In practice, PROTAC development involves synthesizing a library of variants altering the linker length and composition. It is not uncommon

that only a subset of these show robust degradation, highlighting the empirical nature of linker optimization.[38–40]

Ternary Complex Formation and Cooperativity

While binary binding affinity of the PROTAC for its target and for the E3 are important, it is the thermodynamics of the tertiary assembly that ultimately govern the efficiency and selectivity of ubiquitination.[37,41,42] This has led to a paradigm in PROTAC development focusing on cooperativity – the extent to which the formation of the ternary complex is more (or less) favorable than the independent binary interactions. Positive cooperativity means the ternary complex is more stable than expected from the two binary affinities, often due to favorable protein–protein contacts between the target and E3 when brought together. Achieving a positively cooperative ternary complex is generally desired for potent degradation. It can dramatically amplify the effective affinity (termed avidity) with which a PROTAC binds its target in the presence of the E3. For example, if a PROTAC has moderate binary affinities for both target and E3 individually, but when all three come together the protein-protein interface contributes additional -ΔG, the functional affinity can become sub-nanomolar in the ternary state, driving very efficient ubiquitination.[43] Cooperativity can also confer selectivity advantages. If two proteins share the same warhead binding site, a conventional inhibitor hits both, but a PROTAC might degrade only the one that yields a stable ternary complex with the chosen E3. This was observed in the case of PROTACs targeting the BAF complex components BRD9 vs BRD7: the warhead (a pan-BRD7/9 ligand) bound both, but only BRD9 formed a productive complex with VHL, resulting in selective BRD9 degradation. Thus, by tuning cooperativity, PROTACs can achieve selective degradation where small-molecule inhibitors cannot, effectively turning a non-specific binder into a specific degrader.[44,45] In the design phase, measuring cooperativity is often done by a parameter called α (alpha), where $\alpha > 1$ indicates positive cooperativity, $\alpha < 1$ negative, and $\alpha = 1$ no cooperativity. Lead PROTACs frequently have $\alpha \gg 1$ for their intended target. A high-cooperativity degrader not only tends to be more potent at lower concentrations but also might better overcome the hook effect (since once ternary complex forms it preferentially goes to ubiquitination rather than dissociating). One must note that cooperativity is target-specific, so a PROTAC might form a highly cooperative ternary with one substrate and not with another, even if the warhead binds both.[46,47]

RECENT ADVANCES AND NOVEL PROTAC STRATEGIES

While first-generation PROTACs demonstrated the feasibility of targeted protein degradation, they also highlighted challenges such as off-tumor toxicity, limited cellular delivery, and lack of control once the drug is administered. To address these issues, researchers have developed a host of innovative strategies that refine when, where, and how PROTACs act.[48]

For example, researchers have created PROTACs that remain inactive until exposed to a certain wavelength of light, allowing degradation to be turned "on" only in illuminated regions.[49] Photocaged PROTACs have a photo-labile protecting group that blocks either the warhead or E3 ligand, preventing target or ligase binding. Upon UV or visible light irradiation, the cage is cleaved, releasing the active PROTAC which can then induce degradation.[50,51]

Photoswitchable PROTACs incorporate a photochromic linker (most commonly an azobenzene) that can reversibly toggle between two conformations upon illumination with different wavelengths. One conformation of the azobenzene linker produces an active PROTAC geometry, whereas the other conformation forces a geometry that cannot effectively form the ternary complex.[52] PHOTACs (photo-PROTACs) have been used to achieve optical control of degradation for targets like kinases and epigenetic proteins, even in live cells and in localized regions of organisms. A notable example is the optical control of CAMKIIα degradation in neurons, where light activation of a PHOTAC led to acute modulation of synaptic function.[53]

Another innovative strategy is to activate PROTACs via a chemical trigger that can be administered separately. One such design is a click-activated PROTAC prodrug. In this approach, the PROTAC is synthesized in an inactive, "caged" form that contains two bioorthogonal chemical handles. Only when a benign reagent carrying complementary handles is administered does it "click" the two pieces together (for example via an azide-alkyne cycloaddition or tetrazine ligation), assembling the active PROTAC inside the system.[54]

Similarly, enzyme-activated PROTACs have been made, where a PROTAC is rendered inactive by a cleavable cap that only a specific enzyme can remove. For instance, a PROTAC can be designed to be activated by the cancer-associated enzyme NQO1: a quinone-based masking group prevents activity until NQO1 (overexpressed in certain tumors) reduces it and triggers release of the active PROTAC.[55]

Another frontier in PROTAC development is hitching PROTACs onto targeting macromolecules such as antibodies or nucleic acid aptamers. These PROTAC-bioconjugates aim to combine the cell-selective targeting of biologics with the potent intracellular degradation activity of PROTACs. In essence, the PROTAC becomes a payload delivered by a larger targeting vehicle, analogous to antibody-drug conjugates (ADCs) in chemotherapy, but here delivering a protein degrader often termed a degrader-antibody conjugate (DAC).[56]

Monoclonal antibodies can provide exquisite specificity for cell-surface markers (antigens) that distinguish cell types

(HER2 overexpressed on certain breast cancer cells, CD33 on certain leukemic cells, etc.). By attaching a PROTAC to an antibody that binds a tumor antigen, one can create an antibody–PROTAC conjugate that homes to those cells. Upon binding to the cell surface, the conjugate is usually designed to undergo receptor-mediated endocytosis, dragging the PROTAC inside the target cell. Inside the cell, the PROTAC is released and can then diffuse to find its intracellular target and recruit an E3 ligase.[57,58] A critical aspect of Ab-PROTACs is the linker between the antibody and the PROTAC. Typically, a cleavable linker is used so that once internalized, the PROTAC can be released in its active form. Common linkers include disulfides[59], protease-sensitive peptides, or acid-sensitive linkers.[35]

DISCUSSION

PROTAC efficacy is driven by productive ternary-complex assembly and cooperativity rather than binary affinity alone; residence time and dosing windows that avoid the "hook effect" are critical to sustain ubiquitination and degradation.[12,13,20,46,47] Linker length/rigidity and exit vectors frequently invert SAR, while E3 choice (e.g., CRBN vs VHL) shapes cooperativity and neosubstrate liabilities, demanding careful profiling beyond potency alone.[38,40,44,47] Next-generation control and delivery strategies are maturing. Emerging control/delivery strategies including photoswitchable/photocaged systems, enzyme/bioorthogonal pro-PROTACs, and antibody/aptamer conjugates offer spatiotemporal precision and tissue selectivity that will allow to widen the therapeutic window.[48-58]

CONCLUSION

PROTAC technology has catalyzed a paradigm shift in drug discovery, transforming the classical approach of occupancy-driven enzyme inhibition into a new modality of event-driven protein ablation. We highlighted several of these novel developments. These strategies collectively aim to sharpen the precision of PROTAC action degrading the right protein, at the right place, at the right time.

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AUTHOR'S CONTRIBUTION

The author confirms sole responsibility for the conception, literature search, analysis, drafting, and critical revision of the manuscript, and approved the final version.

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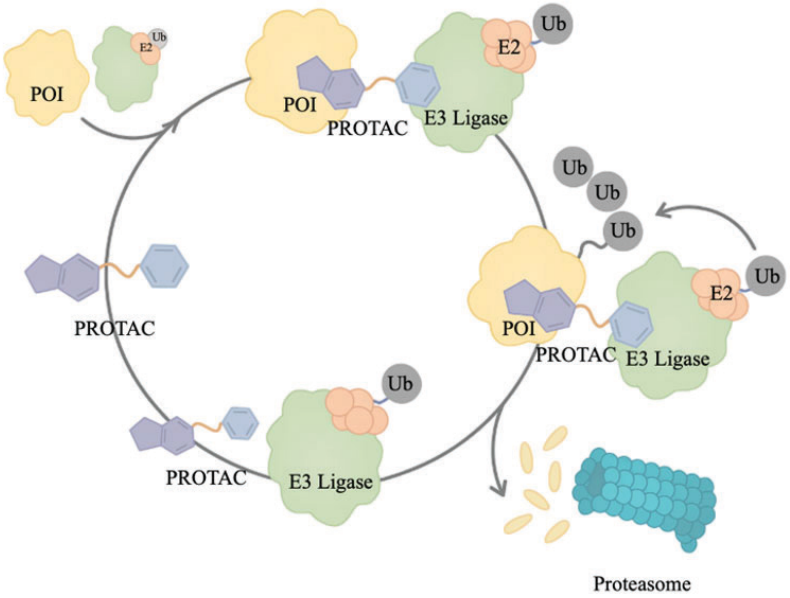

Figure 1: PROTAC-mediated targeted protein degradation. Schematic of the ubiquitin–proteasome–targeting chimera (PROTAC) cycle. A bifunctional PROTAC comprising a target-binding "warhead" linked to an E3ligase recruiter bridges the protein of interest (POI) and an E3 ligase to form a ternary complex. In the presence of an E2~Ub conjugate, ubiquitin (Ub) is transferred to lysine residues on the POI; repeated transfers build a poly-Ub chain that marks the POI for destruction. The 26S proteasome recognizes the polyubiquitinated POI and degrades it into short peptides, while the PROTAC dissociates and is recycled to catalyze additional rounds of degradation.[21]