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Review paper

Beyond Inhibition: Proteolysis Targeting Chimeras and the Rise of Targeted Protein Degradation

Farooq Ahmad Mir [a] *

[a] *Associate Professor, Department of Chemistry, Higher Education, UT of J&K, India*

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***Corresponding author**
Farooq Ahmad Mir
✉ **Email**
mirfarooq219@gmail.com

ABSTRACT

For decades, small-molecule drug discovery has been organized around a single operating principle: a ligand binds a target protein and occupies its active site for long enough to block function. Proteolysis-targeting chimeras (PROTACs) and related targeted protein degradation (TPD) technologies represent a fundamental departure from this occupancy-driven paradigm, instead hijacking the cell's own ubiquitin-proteasome system to mark disease-causing proteins for destruction. Because degraders act catalytically and need only engage a target transiently to trigger its removal, they can address proteins long considered undruggable, including transcription factors, scaffolding proteins, and mutant oncoproteins lacking conventional binding pockets. This review traces the molecular architecture and mechanism of PROTAC-mediated degradation, surveys the expanding clinical pipeline spanning oncology, autoimmune disease, and neurodegeneration, and examines complementary modalities such as molecular glues. We further discuss the principal engineering challenges that continue to shape the field, including the hook effect, limited oral bioavailability associated with high molecular weight, and the restricted repertoire of validated E3 ligases currently exploited for degrader design. We conclude by considering how TPD is likely to mature from a novel modality into a mainstream pillar of medicinal chemistry over the coming decade.

1. Introduction

Traditional small molecule pharmacology operates through occupancy driven inhibition: a drug binds a functional pocket on a target protein and remains bound with sufficient residence time to suppress the protein's activity for as long as therapeutically meaningful drug concentrations persist. This model has produced the overwhelming majority of approved medicines, but it carries an important structural limitation. An estimated 80 percent of the human proteome, including many transcription factors, scaffolding proteins, and mutant oncoproteins implicated in disease, lacks a well-defined, druggable binding pocket amenable to conventional small-molecule inhibition (Sincere et al., 2023).

Targeted protein degradation reframes the therapeutic objective. Rather than asking how to inhibit a protein's function, TPD asks how to eliminate the protein altogether by co-opting the cell's endogenous quality-control machinery. Proteolysis-targeting chimeras, the most clinically advanced class of degrader, are heterobifunctional small molecules composed of a ligand for the protein of interest (POI), a ligand for an E3 ubiquitin ligase, and a chemical linker connecting the two (Sincere et al., 2023). By simultaneously engaging both proteins, a PROTAC induces the formation of a ternary complex that

brings the POI into proximity with the ubiquitination machinery, tagging it for degradation by the 26S proteasome.

First conceived at the turn of the millennium as cell impermeable peptide based constructs, PROTACs have since evolved into orally bioavailable, small molecule drugs, several of which have advanced through late phase clinical trials (Zhong et al., 2024). This review summarizes the mechanistic basis of PROTAC-mediated degradation, the current clinical landscape, and the engineering challenges that remain before the modality achieves its first regulatory approval.

2. Mechanism of PROTAC-Mediated Degradation

The ubiquitin proteasome system (UPS) is the cell's principal pathway for regulated intracellular protein turnover. Proteins destined for degradation are covalently tagged with chains of ubiquitin, a small regulatory protein, through the sequential action of E1 activating enzymes, E2 conjugating enzymes, and E3 ligases, the latter of which confer substrate specificity by directly recognizing the target protein. Once polyubiquitinated, the tagged protein is recognized and unfolded by the 26S proteasome and degraded into short peptide fragments (Zhong et al., 2024).

A PROTAC exploits this pathway by acting as a molecular bridge: one end of the molecule binds the protein of interest, while the other engages an E3 ligase, most commonly cereblon (CRBN) or von Hippel-Lindau (VHL) protein. Formation of a stable ternary complex among the PROTAC, the POI, and the E3 ligase positions the POI for polyubiquitination even though the PROTAC itself makes no direct contact with the ubiquitination machinery. Critically, because the PROTAC is released unaltered once the POI has been ubiquitinated and degraded, a single PROTAC molecule can cycle through multiple rounds of target engagement, conferring catalytic, sub-stoichiometric activity that distinguishes degraders from conventional stoichiometric inhibitors (Sincere et al., 2023).

This catalytic mechanism has two important pharmacological consequences. First, because only transient target engagement is required to trigger the degradation cascade, PROTACs can achieve therapeutic effect at lower systemic exposures than would be required for sustained inhibitor occupancy. Second, because the entire protein, not merely one functional domain, is removed, PROTACs can, in principle, silence both catalytic and non-catalytic (scaffolding) functions of a target simultaneously, a property with particular relevance for proteins whose pathogenic role extends beyond enzymatic activity.

Table 1 Structural Components of a Proteolysis-Targeting Chimera (PROTAC)

Component	Function	Common Examples
POI-binding warhead	Engages the protein of interest, often derived from an existing inhibitor scaffold	Kinase inhibitor fragments; hormone receptor ligands
Linker	Connects the two ligands; governs ternary complex geometry, stability, and cooperativity	Alkyl, PEG, or rigid aromatic linkers of varying length
E3 ligase ligand	Recruits an E3 ubiquitin ligase to enable ternary complex formation	Cereblon (CRBN) binders (e.g., thalidomide analogs); VHL ligands
Resulting ternary complex	Positions POI for polyubiquitination and proteasomal degradation	POI-PROTAC-E3 ligase assembly

3. Clinical Development Landscape

The clinical translation of PROTACs has accelerated markedly since the first degrader entered human trials in 2019. Oncology remains the dominant application area, particularly for targets where resistance to conventional inhibitors is common or where the protein of interest has scaffolding functions that inhibitors cannot address (Zhong et al., 2024). Androgen receptor and estrogen receptor degraders have been among the most clinically advanced programs, reflecting the long-established validation of hormone receptor signaling as a druggable pathway in prostate and breast cancer, respectively.

Degraders targeting Bruton's tyrosine kinase (BTK) have generated particular interest because they can retain activity against BTK mutations that confer resistance to covalent small-molecule BTK inhibitors, a clinically significant problem in B-cell malignancies. Multiple BTK-targeting PROTACs have progressed to clinical trials, with early data presented at major hematology conferences showing encouraging response rates in relapsed or refractory disease (Zhong et al., 2024). Beyond hematologic malignancies, degraders directed against BRD9, a chromatin-remodeling protein exploited by certain sarcomas through a synthetic lethal mechanism, and against BCL-xL, an anti-apoptotic protein relevant to both solid and hematologic tumors, illustrate the expanding diversity of targets now considered tractable through degradation.

Table 2 Selected PROTAC Degraders in Clinical Development

Target	Representative Degrader(s)	Indication	Development Status	Reference
Estrogen receptor (ER)	ARV-471 (vepdegestrant)	ER-positive breast cancer	Phase II/III	Zhong et al., 2024
BTK	NX-2127, BGB-16673	B-cell malignancies	Phase I/II; ~67% ORR reported in R/R disease	Zhong et al., 2024
BCL-xL	DT2216	Hematologic and solid tumors	Phase I	Zhong et al., 2024
BRD9	CFT8634, FHD-609	Advanced/metastatic synovial sarcoma	Phase I (enrollment complications reported for FHD-609)	PROTAC clinical update review
Androgen receptor (AR)	ARV-110 and related CRBN-based degraders	Metastatic castration-resistant prostate cancer	Phase I/II	Sincere et al., 2023

4. Molecular Glues and Complementary Degradation Modalities

Molecular glues represent a mechanistically related but structurally distinct class of degrader. Unlike PROTACs, which are heterobifunctional and rationally designed to bridge two proteins via a linker, molecular glues are typically smaller, monovalent compounds that induce or stabilize a protein-protein interaction between an E3 ligase and a neosubstrate that would not otherwise be recognized, without requiring an explicit linker architecture (Zhong et al., 2024). Historically, molecular glue activity was discovered largely by serendipity, as exemplified by the immunomodulatory drugs derived from thalidomide, which act by redirecting the CRBN E3 ligase toward novel substrates. More recent efforts have sought to rationalize and systematize molecular glue discovery through structural and computational approaches, narrowing the gap between glue discovery and the more deliberate design processes historically associated with PROTACs.

Beyond ubiquitin-proteasome-based approaches, complementary TPD modalities exploit alternative cellular degradation pathways. Lysosome-targeting chimeras and related approaches route extracellular or membrane-bound proteins to the lysosome rather than the proteasome, expanding the substrate scope of targeted degradation to proteins not accessible to UPS-based mechanisms (Zhong et al., 2024). Collectively, these complementary modalities illustrate that targeted protein degradation is best understood not as a single technology but as a broader therapeutic strategy encompassing multiple mechanistically distinct approaches to achieving selective protein elimination.

5. Engineering Challenges

5.1 Molecular Size and Oral Bioavailability

PROTACs are substantially larger than typical small-molecule drugs, commonly falling in the 700-1000 Dalton range compared with the 300-500 Dalton range characteristic of conventional oral therapeutics (Sincere et al., 2023). This increased size, driven by the need to accommodate two distinct binding ligands and a connecting linker, poses challenges for oral absorption, membrane permeability, and metabolic stability. While intravenous, intraperitoneal, or subcutaneous administration circumvents some of these limitations, achieving reliable oral bioavailability, a key driver of patient convenience and commercial viability, remains an active area of medicinal chemistry optimization, including efforts to design more compact linkers and to exploit prodrug strategies that improve permeability without compromising degradation potency (Sun et al., 2023).

5.2 The Hook Effect

A distinctive pharmacological feature of bifunctional degraders is the hook effect, in which degradation efficiency paradoxically declines at very high compound concentrations. This occurs because excess PROTAC saturates the POI and E3 ligase binding sites independently, favoring the formation of unproductive binary complexes over the productive ternary complex required for degradation. Careful dose-finding and formulation strategies are therefore essential to ensure that PROTACs are administered within the concentration window that maximizes ternary complex formation and degradation efficiency.

5.3 E3 Ligase Repertoire and Tissue Selectivity

Although the human genome encodes more than 600 E3 ligases, current PROTAC design draws overwhelmingly on a small number of well-characterized ligases, principally CRBN and VHL. This narrow reliance limits the ability to achieve tissue-selective degradation and may constrain the range of accessible protein conformations for ternary complex formation. Expanding the validated toolbox of E3 ligases, including ligases with tissue-restricted or disease-selective expression patterns, is viewed as a priority for reducing on-target, off-tissue toxicity and

improving the therapeutic index of next-generation degraders (Yim et al., 2024; Sun et al., 2023).

6. Future Directions

- Rational expansion of the validated E3 ligase toolbox to improve tissue selectivity and reduce off-target toxicity.
- Development of stimuli-responsive and conditionally activated degraders that restrict activity to diseased tissue or specific cellular contexts.
- Continued optimization of linker chemistry and prodrug strategies to improve oral bioavailability without sacrificing degradation potency.
- Systematic, structure-guided discovery of molecular glues to complement and potentially simplify heterobifunctional PROTAC design.
- Extension of TPD approaches beyond oncology into autoimmune disease, viral infection, and neurodegenerative disorders, where pathogenic proteins with scaffolding or aggregation-prone properties may be particularly well suited to a degradation-based strategy.

7. PROTACs in Context: Comparing Degradation to Inhibition

Placing targeted protein degradation alongside conventional inhibition clarifies both its distinctive advantages and the trade-offs medicinal chemists must weigh when selecting a modality for a given target. Occupancy-driven inhibitors generally benefit from decades of accumulated design experience, well-established structure-activity relationships, and, in many cases, more favorable oral pharmacokinetics owing to their smaller size. Degraders, by contrast, offer catalytic efficiency, the potential to silence non-enzymatic scaffolding functions, and a route to targets that lack a druggable active site altogether, but do so at the cost of increased molecular complexity, more demanding synthetic routes, and, in many current-generation molecules, a continued reliance on parenteral or carefully engineered oral formulations (Sincere et al., 2023; Zhong et al., 2024).

These trade-offs suggest that degradation and inhibition are best viewed as complementary rather than competing strategies. For targets with well-defined, ligandable active sites and no known resistance liabilities, conventional inhibition may remain the more pragmatic first choice. For targets characterized by scaffolding dependent pathology, acquired resistance to existing inhibitors, or the absence of a tractable binding pocket, degradation offers a mechanistically distinct route that inhibition cannot replicate. Selecting between these strategies, or pursuing both in parallel, is increasingly treated as an early and consequential decision point in target to lead programs (Zheng et al., 2023).

Table 3 Comparison of Occupancy-Driven Inhibition and Targeted Protein Degradation

Dimension	Occupancy-Driven Inhibition	Targeted Protein Degradation (PROTACs/Glues)
Mechanism	Sustained binding blocks protein function	Catalytic recruitment of E3 ligase triggers proteasomal destruction
Target requirements	Requires a well-defined, ligandable binding pocket	Requires only a ligandable surface; can address scaffolding proteins
Dosing implications	Requires sustained target occupancy and exposure	Sub-stoichiometric activity; effect can persist after compound clearance
Molecular size / oral delivery	Generally favorable (300-500 Da typical)	Larger (700-1000 Da for PROTACs); oral delivery more challenging
Resistance liability	Vulnerable to binding-site mutations	Can retain activity against certain resistance mutations affecting inhibitor binding

8. Conclusion

Targeted protein degradation has evolved, within roughly two decades, from a conceptually elegant but practically limited peptide-based strategy into a clinically validated therapeutic modality with a rapidly expanding pipeline spanning oncology and beyond. By exploiting the cell's own proteolytic machinery, PROTACs and molecular glues offer a route to previously undruggable targets and a catalytic mechanism of action distinct from conventional inhibition. Persistent engineering challenges, including molecular size, the hook effect, and a still-narrow E3 ligase toolbox, continue to shape the medicinal chemistry agenda for this modality. As these challenges are addressed, targeted protein degradation is well positioned to take its place alongside occupancy-driven inhibition as a mainstream strategy for converting biological insight into medicine.

9. Manufacturing and Intellectual Property Considerations

The heterobifunctional architecture of PROTACs also carries practical consequences for manufacturing and intellectual property strategy that distinguish the modality from conventional small-molecule development. Synthesis of a degrader typically requires independent optimization of the POI-binding

warhead, the E3 ligase ligand, and the linker, followed by convergent coupling steps that can introduce additional purification and quality-control complexity relative to a single-fragment small molecule. From an intellectual property perspective, because POI-binding warheads and E3 ligase ligands are often derived from previously disclosed inhibitor or ligand scaffolds, companies developing degraders must carefully map the freedom to operate landscape across both starting fragments as well as the specific ternary complex geometry the assembled molecule occupies, an analysis that is often more layered than for single fragment inhibitors (Zheng et al., 2023). These considerations have contributed to a licensing and partnership landscape in which specialized degrader focused biotechnology companies frequently collaborate with larger pharmaceutical partners who supply warhead chemistry or clinical development capacity.

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