REVIEW PAPER

Targeted Protein Degradation: PROTACs, Molecular Glues, and the Future of Drug Discovery

Kanchan Choudhary[1], Chanchal Sahu[2], B. Sibani Patra[3], Leena Verma[4], Mausami Sahu[5], Devorat Singh[6], Khilendra Kumar Thakur[7*]

[1]Shri Rawatpura Sarkar Institute of Pharmacy, Kumhari, Durg, Chhattisgarh 490042.
[2]Prism College of Pharmacy, Utai, Bhilai, Chhattisgarh 491107.
[3]Prism College of Pharmacy, Utai, Bhilai, Chhattisgarh 491107.
[4]Yugantar Institute of Pharmacy, Thekwa, Rajnandgaon, Chhattisgarh 491443.
[5]Shri Rawatpura Sarkar Institute of Pharmacy, Kumhari, Durg, Chhattisgarh 490042.
[6]Rungta College of Pharmaceutical Sciences and Research, Kurud Road, Kohka, Bhilai, Chhattisgarh- 490024.
[7*]Prism College of Pharmacy, Utai, Bhilai, Chhattisgarh 491107.

Abstract
The ability to selectively eliminate pathogenic proteins rather than merely inhibit their activity has redefined contemporary drug discovery, positioning targeted protein degradation (TPD) as one of the most significant advances in chemical biology and precision therapeutics. By harnessing endogenous protein quality-control machinery, TPD offers a catalytic and event-driven pharmacological strategy capable of addressing limitations associated with conventional occupancy-driven inhibitors, including poor target selectivity, transient target engagement, acquired resistance, and the inaccessibility of many disease-relevant proteins. Among the expanding repertoire of degrader technologies, proteolysis-targeting chimeras (PROTACs) and molecular glues have emerged as the most mature and clinically advanced platforms, each employing distinct mechanisms to recruit E3 ubiquitin ligases and direct selective protein degradation. Their rapid evolution has been driven by breakthroughs in structural biology, medicinal chemistry, computational modeling, and artificial intelligence, enabling the rational design of degraders with enhanced potency, selectivity, and pharmacokinetic performance. Beyond oncology, these technologies are increasingly being explored for neurological, inflammatory, infectious, and rare genetic disorders, underscoring their broad therapeutic potential. Nevertheless, challenges related to E3 ligase diversity, tissue specificity, resistance mechanisms, safety, and clinical translation continue to influence their successful implementation. This review critically examines the molecular foundations, design principles, therapeutic applications, and clinical progress of PROTACs and molecular glues while integrating emerging targeted degradation platforms and technological innovations. Furthermore, it discusses the opportunities and unresolved challenges that will shape the next generation of degrader therapeutics and their transformative role in the future of precision drug discovery.

Keywords: Targeted protein degradation, PROTACs, Molecular glues, Precision medicine, Drug discovery

How to cite this article: Choudhary K, Sahu C, Patra BS, Verma L, Sahu M, Singh D, Thakur KK. Targeted Protein Degradation: PROTACs, Molecular Glues, and the Future of Drug Discovery. Int J Drug Deliv Technol. 2026;16(70s): 1178-1189. DOI: 10.25258/ijddt.16.70s.124

1.Introduction

Therapeutic strategies that provide greater precision, durability and clinical efficacy than conventional pharmacological strategies are needed due to the increasing prevalence of chronic and progressive diseases. In spite of decades of advancements in the development of new drugs, cancer, neurodegeneration, autoimmune diseases and several rare genetic diseases remain to put high burden on healthcare and society worldwide. Proteins are the main targets of therapy for these disorders, as the disorders are often complex, resulting from mis-expressed or mis-functioning proteins. As chronic disease continues to be a growing burden, however, it has also demonstrated the weaknesses of traditional approaches to treating disease and the need for a more innovative paradigm that would meet previously unmet clinical needs (Hacker, 2024). The discovery of therapeutic agents for many decades has mostly been based on the principle of pharmacology that drug action occurs by means of persistent binding to functional domains of target proteins, the principle of occupancy. This approach has led to the discovery of a number of successful drugs, but for many disease-relevant proteins, it has proved impossible to develop a suitable ligand-binding site or to find proteins with structural features that make them suitable for inhibition. Furthermore, inadequate target suppression, dose-dependent toxicity and acquired resistance are common obstacles to long-term therapeutic success. All these challenges have fostered a paradigm change towards alternative therapeutic concepts that are able to expand the druggable proteome beyond small-molecule inhibition (Team, 2020).

Protein folding, trafficking and degradation are tightly coupled to protein synthesis for the proper functioning of the cells. Ensuring the proper function of this proteostatic

network is crucial to maintain protein quality and to avoid the buildup of damaged, misfolded and aberrantly activated proteins. In many human diseases, disruption of protein degradation pathways directly affects signaling pathways and the balance of cellular functions, thus playing a direct role in the pathogenesis of these diseases. As a result, the endogenous system, which regulates protein turnover, has been identified as a novel target for molecular selective intervention in therapeutics (Hanna et al., 2019). More than just a housekeeping function, controlled protein degradation is a key factor in determining cellular health and disease (Clausen et al., 2019). Targeted protein degradation (TPD) has become one of the most revolutionary developments in modern chemical biology, which uses the natural protein quality-control systems to selectively remove pathogenic proteins, instead of merely inhibiting their functions. This is a pharmacological approach that can be used for the catalytic degradation of the target proteins, providing long-lasting biological effects without long-term drug exposure. This enables the possibility to overcome numerous constraints of occupancy-based therapeutics and pharmacological interventions for previously undruggable proteins (Samarasinghe & Crews, 2021). Proteolysis-targeting chimeras (PROTACs) and molecular glues are the most developed and clinically advanced degrader technologies in the growing family of degrader technologies available. Both have shown great versatility in the vast range of therapeutic targets they have targeted, despite the different mechanisms used to recruit the E3 ubiquitin ligases and to promote selective proteasomal degradation. Their development from experimental concepts to promising candidates is aided by rapid advances in structural biology, medicinal chemistry, computational modeling and translational research that are being used to study a variety of diseases (Zhong et al., 2024). Overall, the development of induced-proximity therapeutic modalities highlights a paradigm shift in the drug discovery process, whereby the mechanism of action of a drug is now the direct result of induced molecular interactions, which are being used to manipulate biological systems with a higher level of precision than current inhibitors can. (King et al., 2026).

While significant advances have been made, there are significant challenges that still need to be overcome to enable the widespread clinical use of targeted protein degradation. The lack of access to a variety of E3 ubiquitin ligases, problems with tissue specificity, pharmacokinetic modifications, resistance and long-term safety are important challenges. In addition, there are many reviews that individually cover PROTACs, molecular glues or emerging degrader technologies, but few that offer a comprehensive and critical overview that ties together the various aspects of their use, the principles of rational design, therapeutic uses, clinical advances, enabling technologies and future prospects for the whole field of precision drug discovery. The rising number of studies to develop alternative treatments to traditional types of therapy further highlights the need for such a comprehensive evaluation (Hoda, 2021).

This review critically evaluates the molecular mechanisms and design principles of PROTACs and molecular glues, their therapeutic applications, clinical development, enabling technologies, limitations, and future opportunities.

2. Review Methodology

A structured literature-based review was performed to synthesize the current evidence on targeted protein degradation in this comprehensive review. Systematic searches with keywords on targeted protein degradation, PROTACs, molecular glues, ubiquitin-proteasome system, E3 ubiquitin ligases, induced proximity, therapeutic applications, clinical development, and precision medicine led to the identification of relevant peer-reviewed publications. English-Language articles authored by researchers of original research articles, clinical investigations and authoritative review papers were considered. Greater emphasis was placed on recent studies, while landmark publications establishing the conceptual and mechanistic foundations of the field were also included. Literature retrieved was critically screened for scientific relevance, methodological quality and relevance to the objectives of this review. The selected studies were then grouped by theme, with a section on molecular mechanisms, a section on degrader design, a section on technological advances, a section on therapeutic applications, a section on clinical progress, a section on current challenges and a section on emerging future directions to give a comprehensive and balanced overview of the field.

3. Molecular Basis of Targeted Protein Degradation

The principle behind targeted protein degradation (TPD) is to make use of the protein quality-control systems already present in cells to specifically degrade disease-causing proteins and not just inhibit their activity. Unlike traditional therapeutics based on occupancy, TPD would follow an event-driven mechanism whereby irreversible protein degradation would occur once the degrader molecule is transiently bound to its target. This catalytic mechanism of action allows for degradation to be repeated multiple times and expands the therapeutic potential to proteins that were previously regarded as undruggable, making TPD a significant step forward in current drug discovery (Cromm & Crews, 2017). This approach will rely on maintaining the integrity of cellular proteostasis, which involves a dynamic network of protein synthesis, folding, trafficking, quality control and degradation. These are interdependent processes, which maintain the normal function of cells and cope with the cell's physiological and environmental stress by preventing the accumulation of damaged and misfolded proteins. The loss of protein homeostasis can result in pathologies like cancer, neurodegenerative disorders and many other chronic diseases, underscoring the biological basis of proteostasis as the foundation for targeted protein degradation drug development (Hoppe & Cohen, 2020). The proteostasis network consists of modules with molecular chaperones, folding machinery, degradation systems, and pathways for the responses to stress that help ensure protein integrity during the lifetime of the cell (Jayaraj et al., 2020).

The ubiquitin–proteasome system (UPS) is the major pathway for degradation inside cells that is currently used by current technologies of degradation. In this pathway, proteins that are to be destroyed are sequentially tagged by ubiquitin by a series of ubiquitin-activating (E1) enzymes, ubiquitin-conjugating (E2) enzymes, and ubiquitin ligase (E3) proteins. Polyubiquitinated substrates are then recognized by the 26S proteasome, which then unfolds the substrate and processes it into small peptides, releasing ubiquitin molecules for reutilization. Its precision and efficiency have led to the UPS being a promising therapeutic target, especially in diseases caused by misfolded proteins or dysregulated signaling (Park et al., 2020). Two additional layers of quality control are provided by an interplay between the UPS and autophagy systems, enabling cells to respond to proteotoxic stress by utilizing alternative mechanisms of degradation that are suited to the type of protein damage and the cell's needs (Li et al., 2022).

The specificity-determining element in the UPS is the E3 ubiquitin ligases, which bind to proteins to be broken down and promote the transfer of ubiquitin. In humans, over 600 E3 ligases have been identified, and the catalytic mechanism and structure of these enzymes can be broadly categorised into the RING, HECT and RBR families. Due to their extraordinary diversity, they enable highly accurate control of protein turnover in various tissues, developmental stages and physiological situations, and are essential molecular mediators for specifically degrading proteins (Yang et al., 2021). Structural studies have also shed light on the mechanism of substrate recognition, catalytic activity, and ligand activation of ligases, which have led to rational degrader design and target specificity (Zheng & Shabek, 2017). Such endogenous mechanisms of protein degradation are currently exploited by TPD platforms such as PROTACs and molecular glues, which promote the proximity of a target protein to an appropriate E3 ligase, resulting in the ubiquitination of the target protein and its subsequent degradation by the proteasome. Target elimination is accompanied by the release of degrader molecules which act catalytically, meaning that they can catalyse more target elimination events. Over the years, the design of the degrader has continued to evolve, adding new methods for temporal control of protein degradation, such as controllable ligation strategies and scavenging strategies that enable on-demand degradation to ensure therapeutic safety and precision (Jin et al., 2023). Together, these mechanistic principles create the molecular landscape of targeted protein degradation and the growing use of this technology in precision medicine and the development of next-generation drugs (Zhao et al., 2022). The mechanism of targeted protein degradation via the ubiquitin–proteasome system is shown in Figure 1.

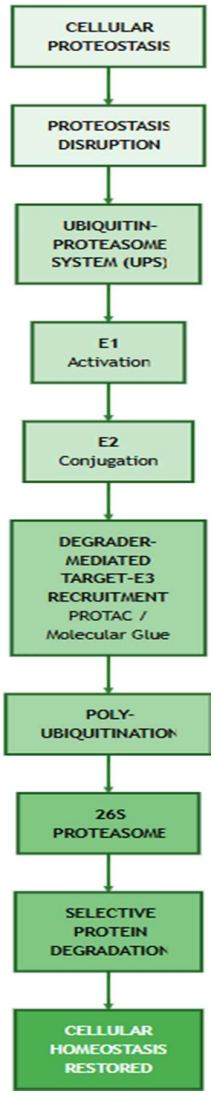

Figure 1. Molecular basis of targeted protein degradation through the ubiquitin–proteasome system

Thus, targeted protein degradation is best seen as an application of the endogenous proteostasis system instead of a concept in its own right. The effectiveness of targeted protein degradation is critically dependent on coordinated protein quality-control pathways, selective E3 ligase recruitment, and catalytic degradation mechanisms.

4. PROTACs and Molecular Glues: Mechanisms, Design, and Comparative Perspectives

Over the past few years, two major classes of protein degraders have been developed: proteolysis-targeting chimeras (PROTACs) and molecular glues. Both technologies take advantage of the ubiquitin–proteasome system to degrade disease-associated proteins but differ in molecular architecture, engagement and the mechanisms of E3 ligase recruitment. These modalities have combined to revolutionize degrader-based drug discovery, allowing for specific proteins to be degraded with catalytic efficiency and expanding therapeutic possibilities beyond those of traditional inhibitors (Eladl, 2025). The PROTACs consist of three components – a ligand for the protein under study, an E3 ubiquitin ligase ligand, and a chemical linker that links the two. Their mode of action is that the target protein must bind to an E3 ligase simultaneously to form a productive ternary complex to allow ubiquitination and proteasomal degradation. After degradation, the PROTAC releases itself and is free to catalyze more degradation cycles, but is not involved on a stoichiometric basis. The event-triggered pharmacology sets PROTACs apart from conventional inhibitors and plays a role in their sustained biological activity even if the target is only bound for a short period of time (Neklesa et al., 2017). Each structural part in the PROTAC molecule is required to be carefully optimized to achieve high degradation efficiency along with desirable pharmacokinetic properties. The ternary complex stability, cellular permeability and degradation potency are influenced by target ligand affinity, E3 ligase selection, linker length, flexibility, and physicochemical properties. The rational design of PROTACs has been greatly enhanced by developments in medicinal chemistry and structural biology, which have allowed the selective

degradation of proteins that play a role in cancer, inflammation, neurodegeneration, and other diseases. The evolution of PROTACs has hastened the transition of PROTAC proof-of-concept molecules to clinically evaluated therapeutic candidates (Sun et al., 2019). Optimization principles have also been followed to overcome the challenges of molecular size, oral bioavailability and tissue distribution, making PROTACs an attractive drug discovery paradigm (Liu et al., 2022).

Compared to the PROTACs, molecular glues generally are small, monovalent molecules that generate/connect protein–protein interactions without the need for a bifunctional structure. Unlike a physical linkage of two proteins by specific binding domains, molecular glues modify protein interaction interfaces so that an E3 ligase can interact with a substrate and promote its ubiquitination when it would otherwise not be targeted for degradation. It provides several benefits such as lower molecular weight, enhanced drug-like properties and simplified chemical structures, without sacrificing the catalytic activity of the targeted protein degradation (Schreiber, 2021). Over the past few years, molecular glues have been discovered by a variety of serendipitous and progressively rational and structure-guided methods. New developments in chemoproteomics, high-throughput screening, structural biology and computational modelling have broadened the range of protein interactions that can be induced by the glue and speeded up the discovery of novel degraders. These technologies have greatly expanded the range of targets that are accessible and also enhanced the understanding and mechanistic efficiency of induced proximity and selectivity for degradation (Dewey et al., 2023). Recently, molecular glues have also been shown to selectively stabilise hitherto unrecognised protein–protein interactions, opening up new avenues to control biological pathways that could not be controlled with small molecules previously (Konstantinidou & Arkin, 2024).

Both PROTACs and molecular glues are based on the same degradation machinery, but are complementary rather than competing. While PROTACs offer modularity and rational programmability relying on diversity of target and ligase ligands, molecular glues degrade proteins by being structurally simple and directly remodelling surfaces of protein-protein interactions. The choice of these platforms will depend on the biology being targeted, structural accessibility, whether or not the targeted biology is compatible with an E3 ligase, and the desired pharmacological properties. The convergence of these two has also helped advance the general idea of induced-proximity therapeutics in which engineered molecular interactions are harnessed to control a variety of cellular functions outside of protein degradation (Robinson & Banik, 2024). The growing clinical landscape shows the clinical promise of both platforms in several disease areas. In oncology, both PROTACs and molecular glues have shown promising preclinical and early clinical activity against cyclin-dependent kinases, hormone receptors, and oncogenic transcription factors, which show themselves to be good complements for combating resistance to classical targeted drugs (Marei et al., 2025). Concurrently, next-generation degrader technologies (NGDs) have diversified, with the degrader field being extended from classical PROTACs to a larger family of targeting chimeras (TACs) that are able to target various intracellular pathways by inducing proximity (Hollingsworth et al., 2023). The major differences between PROTACs and molecular glues are summarized in Table 1.

Table 1. Comparison between PROTACs and Molecular Glues

Feature	PROTACs	Molecular Glues	References
Structure	Bifunctional molecule	Small monovalent molecule	Neklesa et al. (2017); Schreiber (2021)
Mechanism	Bridges target and E3 ligase	Stabilizes protein–protein interaction	Eladl (2025)
Design	Rational and modular	Mostly structure-/screening-guided	Sun et al. (2019); Dewey et al. (2023)
Advantages	Broad target scope; programmable	Better drug-like properties	Liu et al. (2022); Konstantinidou & Arkin (2024)
Current status	Multiple clinical candidates	Rapidly expanding pipeline	Marei et al. (2025); Hollingsworth et al. (2023)

The ongoing development of PROTACs and molecular glues illustrates that a single molecular approach is not the only way to achieve targeted protein degradation, but is a flexible therapeutic paradigm. Advances in complementary mechanisms, along with rational design and induced proximity engineering, are expected to increase the number of targets that can be targeted by drugs and thus increase the next generation of precision therapeutics.

5. Technological Advances Driving Next-Generation Degrader Discovery

Technological advances have revolutionized the discovery of degraders from trial and error to a rational and multidisciplinary approach, which has contributed to the swift progress of targeted protein degradation. Advances in structural biology, medicinal chemistry, computational sciences, artificial intelligence, and, in particular, high-throughput proteomics have significantly increased the knowledge of the mechanisms of degradation and increased the identification and optimization of clinically relevant degrader candidates. These complementary technologies have facilitated the precise characterization of target proteins, E3 ligases and ternary complexes, which have helped to improve the efficiency of the design

of next-generation degraders (Chamberlain & Hamann, 2019). Structural biology has been a major factor in unraveling the molecular structure of degradation complexes. The near-atomic resolution images of large macromolecular assemblies achieved by advances in cryo-electron microscopy (cryo-EM) have opened new windows of opportunity for understanding conformational changes in proteins that were not possible with traditional structural methods. This has made it so much easier to study the mechanistic aspects of protein-protein interactions with degraders and has inspired structure-based drug design (Shoemaker & Ando, 2018). In addition, complementary biophysical techniques, such as nuclear magnetic resonance spectroscopy, X-ray crystallography and biophysical binding assays, remain useful for elucidating protein stability, protein-ligand interactions and conformational changes that underlie rational degrader development (Dobson, 2019).

Structure-based medicinal chemistry has also optimized the degrader by incorporating structure-based information in the design of ligands/linkers that favor ternary complex formation. Rational design of molecular geometry, flexibility of the linker and binding orientation has led to enhanced degradation efficiency, overcoming the limitations of the molecular size, selectivity, and pharmacokinetic properties. The successful discovery of macrocyclic PROTACs is a good example of the use of structure to increase conformational stability and target specificity, thereby broadening the chemical space for degrader discovery (Testa et al., 2020). In addition to small molecules, other tools of recognition, including aptamer-based degraders, have been developed that target proteins with high affinity, thus providing more flexibility in terms of potentially targeting more proteins that can be degraded (Liu et al., 2023). Computational modeling is an indispensable tool to uncover new protein-protein interactions, ligand binding sites or ternary complex stabilities prior to experimental efforts, and has become a crucial element of degrader discovery in the modern era. The rational prioritization of degrader candidates is done by molecular docking, molecular dynamics simulation and free-energy calculation to shorten development time and reduce resources. Such computational methods are also especially useful for understanding the cooperativity of the ternary complexes, which is crucial for the efficiency of degradation and target specificity (Ward et al., 2023). The ability to integrate artificial intelligence and multiomics datasets has expanded the identification of targets and the optimization of degraders, as well as the interpretation of mechanisms, by uncovering complex relationships between biological changes that go beyond structure-based target identification and optimization (Duran-Frigola et al., 2023). The machine learning algorithms are being widely used to predict degrader activity, design linkers, and find novel molecular glue candidates, and therefore, data-driven methodologies are now becoming another cornerstone of targeted protein degradation research (Lin et al., 2025).

Degrader performance evaluation and understanding of the biological response on a systems level has become equally important with proteomics. Mass spectrometry-based proteomics allows for a comprehensive evaluation of abundance, selective degradation, off-target effects and pathway modulation, thus offering critical proof of efficacy and safety during drug development. These technologies have been incorporated into today's drug discovery process because they are a way to characterize the response of the whole proteome after degrader treatment, without bias (Meissner et al., 2022). The identification of degradation substrates, E3 ligase interaction, and resistance mechanism have been further advanced by quantitative proteomics and chemoproteomics, which provide an in-depth understanding of the mechanisms for the rational optimisation of targeted degradation strategies (Sathe & Sapkota, 2023). These technological advances are complemented by the use of biomarker discovery platforms, which are also becoming more common in the field. The potential of proteomic biomarker analysis to identify disease-related molecular signatures, track response to therapy and contribute to precision medicine approaches in complex diseases is quite significant. Originally designed for neurodegenerative diseases, these analytical approaches are growing applicable for degrader therapeutics, where selection of patients based on biomarkers could enhance clinical benefits and contribute to decision-making processes for individual patients (Hedl et al., 2019).

The structural biology, medicinal chemistry, computational modeling, artificial intelligence and proteomics fields have revolutionized degrader discovery. All these technologies can be used to better design, conduct in-depth biological studies, and translate emerging PROTACs, molecular glues and degradation platforms for clinical use, which increases the speed of next-generation precision therapeutics. Table 2 outlines the key technologies that will enable the discovery of next-generation degraders.

Table 2. Technologies accelerating targeted protein degrader discovery

Technology	Major contribution	Application	References
Structural biology	Resolves degrader complexes	Structure-guided design	Shoemaker & Ando (2018); Dobson (2019)
Medicinal chemistry	Optimizes degrader structure	Potency and PK improvement	Chamberlain & Hamann (2019); Testa et al. (2020)
AI & computational modeling	Predicts degrader performance	Candidate prioritization	Ward et al. (2023); Lin et al. (2025)
Proteomics	Measures degradation selectivity	Target validation	Meissner et al. (2022); Sathe & Sapkota (2023)

Multiomics & novel platforms	Biomarkers and new degraders	Precision medicine	Duran-Frigola et al. (2023); Liu et al. (2023); Hedl et al. (2019)

6. Therapeutic Applications and Clinical Development

Transforming targeted protein degradation (TPD) from a conceptual strategy to a clinically relevant platform with therapeutic potential has grown rapidly, covering a wide range of different disease mechanisms. Degrader technologies have the potential to provide long-lasting pharmacological activity, overcome resistance related to conventional inhibitors, and open up an unexplored space of previously undruggable targets. The benefits of PROTACs and molecular glues have contributed to their translation into various therapeutic areas, with oncology the most advanced of these areas, where applications have been developed, but also other therapeutic areas such as neurological, inflammatory, autoimmune, infectious and rare genetic diseases are becoming increasingly common (Chirnomas et al., 2023). In oncology, targeted protein degradation is the most prominent clinically relevant use case, as most cancers are either triggered by abnormal expression of proteins or by disrupted signaling pathways, or have resistance to available targeted therapies. However, degraders targeting androgen receptors, estrogen receptors, Bruton's tyrosine kinase, cyclin-dependent kinases, and other oncogenic proteins have had promising preclinical activity and are now making their way up the clinical pipeline. The catalytic mechanism also provides the potential to exploit resistance mutations that are seen with conventional inhibitors to achieve continued suppression of oncogenic signaling, making protein degradation a promising therapeutic approach in precision oncology (Salama et al., 2022).

Because abnormal protein aggregation and impaired proteostasis are crucial components in disease progression, neurodegenerative diseases represent another promising targeted protein degradation therapeutic opportunity. Conditions like Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis involve the buildup of abnormal proteins that interfere with the way the neurons function and eventually lead to the degeneration of the neurons. Selective targeting of pathogenic proteins for degradation thus became a rational treatment strategy that might allow the treatment of underlying disease mechanisms and not just symptom relief (Höhn et al., 2020). Furthermore, the increasing knowledge about ubiquitin-based signaling pathways in neuronal survival and protein quality control, in light of these new opportunities, opens the door for the development of degrader-based therapies for neurodegenerative diseases by selectively modulating disease-associated proteins (Schmidt et al., 2021). Targeted protein degradation is also gaining momentum in the field of immune-mediated diseases outside the realm of oncology and neurology. Chronic inflammatory signaling pathways and aberrant immune regulators are common characteristics of autoimmune diseases and are resistant to current immunosuppressive agents. Disease-driving protein (DPP) degradation provides the opportunity to precisely modulate immune responses without systemic immunosuppression, which is the reason for its increasing use in autoimmune diseases (Song et al., 2025). Protein degraders are emerging as anti-inflammatory therapeutics, and the protein degradation strategy may also yield long-lasting therapeutic effects with greater selectivity than conventional anti-inflammatory drugs (Gudjonsson et al., 2024).

Targeted protein degradation has also been applied to infectious diseases, with the idea of selectively degrading host or pathogen proteins required for the replication of the microbes. Degrader technologies can take advantage of host–pathogen interactions to inhibit infection, but they can also help to prevent the emergence of antimicrobial resistance, unlike current antimicrobial agents, which directly inhibit the enzymes of the virus or bacteria. The broad applicability of targeted degradation beyond chronic noncommunicable diseases (NCDs) is clearly demonstrated in this growing area, and it has significant promise for addressing new and emerging infectious disease threats (Espinoza-Chávez et al., 2022). Another promising frontier is rare genetic disorders, with many inherited diseases being caused by aberrations in protein expression, toxic gain-of-function mutations and defective protein quality-control pathways. Amyotrophic lateral sclerosis and frontotemporal dementia are examples of genetically complex diseases in which pathogenic proteins can act directly on the dysfunction of neurons, making the selective degradation of proteins an attractive therapeutic approach. The use of degrader technologies has the potential to become more personalized to treat previously intractable diseases, as genetic and molecular characterization of these disorders continues to grow (Nguyen et al., 2018). A summary of the current therapeutic landscape of targeted protein degradation in major disease areas is shown in Table 3.

Table 3. Therapeutic applications of targeted protein degradation

Disease area	Major application	Current status	Key References

Oncology	Elimination of oncogenic proteins	Clinical trials	Chirnomas et al. (2023); Salama et al. (2022)
Neurodegenerative diseases	Clearance of toxic protein aggregates	Active preclinical development	Höhn et al. (2020); Schmidt et al. (2021)
Autoimmune diseases	Modulation of immune regulators	Emerging therapeutic area	Song et al. (2025); Gudjonsson et al. (2024)
Infectious diseases	Targeting pathogen/host proteins	Early-stage research	Espinoza-Chávez et al. (2022)
Rare genetic diseases	Removal of mutant proteins	Precision medicine potential	Nguyen et al. (2018)

The medicinal chemistry, structural biology, and use of biomarkers to select patients are driving the rapid clinical progress of targeted protein degraders in a range of therapeutic areas. While oncology is currently the most prominent clinical pipeline player, increasing mechanistic understanding and enhanced degrader design will expand therapeutic applications to many diseases with aberrant protein function, further validating targeted protein degradation as a key element of precision medicine. Targeted protein degradation is not only in a proof-of-concept phase, but is also developing as a broadly applicable therapeutic platform with significant clinical potential. As it continues to expand its reach into new disease indications, along with ongoing clinical testing, it also has the capacity to transform precision therapeutics by selectively stripping proteins that drive disease at the protein level, rather than just the function.

7. Challenges and Limitations in Targeted Protein Degradation

Although targeted protein degradation (TPD) has made tremendous progress, there are still a number of scientific and translational hurdles to widespread clinical use. While PROTACs and molecular glues have been shown to be useful for the targeted degradation of disease-associated proteins, each has its own drawbacks that must be addressed for use, such as degrader design, accessibility of the target protein, drug pharmacokinetics, tissue specificity, resistance, safety, and translation. A major challenge for the technology to advance and move beyond the current therapeutic applications of degraders is to overcome these limitations (Ming et al., 2023). The first problem is the fact that there is not so much diversity in the degradation pathways and E3 ubiquitin ligases that can be exploited. The clinically advanced degraders are based on just a fraction of the over 600 human E3 ligases, and mainly on cereblon (CRBN) and von Hippel–Lindau (VHL) to limit tissue selectivity and target compatibility. Thus, efforts have taken a major thrust toward expanding the number of ligases and alternative degradation systems that are available for recruitment. These limitations can be overcome by novel degradation platforms, such as emerging technologies such as receptor elimination by E3 ubiquitin ligase recruitment (REULR), that expand the set of accessible targets and cellular compartments (Siepe et al., 2023).

The other significant challenge is the drug-like properties, especially heterobifunctional degraders like PROTACS. They are often very polar, have a large molecular size and are quite high in molecular weight, which can lead to low membrane permeability, low oral bioavailability, low metabolic stability and low overall pharmacokinetic properties. The properties make formulation development difficult and restrict bioavailability upon oral administration. In view of a lack of clinical utility, optimization of absorption, distribution, metabolism and excretion (ADME) properties has become a key part of degrader medicinal chemistry to enhance its clinical utility (Pike et al., 2020). Tissue- and cell-type specificity is also difficult to obtain, as many of the intracellular degraders require the ubiquitin-proteasome system which is tissue-specific. Degradation of unwanted non-target cells can have potential therapeutic selectivity issues and toxicity. In response to such worries, other strategies for the degradation of extracellular or membrane-associated proteins have been devised. For instance, lysosome-targeting chimeras (LYTACs) take advantage of the receptor-mediated lysosomal trafficking to selectively degrade extracellular proteins and membrane receptors that would otherwise not be degraded, thus enriching the degradable proteome and at the same time providing opportunities for better tissue-selective targeting (Ahn et al., 2021).

Another point of interest in the long-term use of degrader therapy is the development of resistance. Reduced degradation efficiency or altered expression of E3 ligases, mutations in the binding site for the degraders, defective ubiquitination and the adaptive response of the cells to the signals can lead to a decreased response to therapy. As with resistance seen with traditional targeted therapies, these mechanisms emphasize the need for multiple degrader platforms, combination therapy, and alternate degradation pathways that may be able to remain effective in the presence of selective therapeutic pressure (Ming et al., 2023). Safety concerns are additionally pertinent for the reason that targeted degradation causes complete protein elimination rather than temporary functional inhibition. Adverse events that do not occur with conventional inhibitors may be related to excess degradation, unwanted substrate specificity, long-lasting pharmacodynamic effects and a disruption of normal physiological protein networks. Therefore, it is critical to evaluate degradation selectivity, optimize dose, and assess long-term toxic effects prior to the general use of degrader therapeutics (Moreau et al., 2020). Manufacturing complexity and a changing regulatory landscape also play

a role in clinical translation. High-quality control and complex synthetic methods are necessary to allow reproducibility and stability of many degrader molecules during development. As the field continues to evolve, regulatory guidelines need to be modified to fit targeted degraders' specific pharmacological profile and ensure product consistency, safety and therapeutic efficacy. Other issues such as stability, formulation and regulatory compliance that span the whole class of advanced protein- and peptide-based therapeutics give helpful guidance for future development and commercialization of degrader-based medicines (Patel et al., 2025). In Figure 2, some of the main scientific and translational obstacles to the clinical translation of TPD are shown.

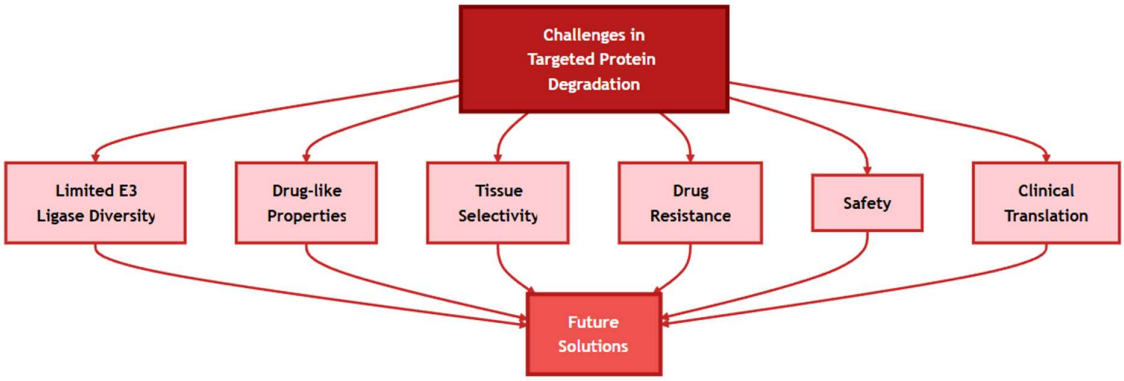

Figure 2. Major challenges limiting the clinical translation of targeted protein degradation

Future development of targeted protein degradation will rely on the ability to combine developments in degrader chemistry, delivery methods, systems biology and regulatory science. The solutions to these challenges will lead to better safety and clinical activity for current PROTACs and molecular glues and pave the way for the creation of more versatile, tissue-selective, and clinically relevant degradation platforms.

8. Emerging Directions and Future Perspectives

Research avenues in targeted protein degradation are evolving and going far beyond the original concept of a PROTAC and molecular glue into ever more sophisticated, targeted, programmable and disease-specific therapeutic platforms. There have been some recent advancements, such as next-generation degradation technologies, nano-enabled delivery systems and molecules with higher tissue selectivity and with controlled protein elimination (Hou et al., 2025). Meanwhile, chemical biology has made substantial progress in achieving spatiotemporal control over the degradation of proteins via stimulus-responsive degraders, conditionally activated systems and engineered E3 ligase recruitment strategies, enhancing therapeutic selectivity and minimizing off-target effects (He et al., 2025). As clinical experience of using degrader-type therapeutics has grown, it has become apparent that patient selection, substrate specificity, and resistance profiling are all critical elements of the rational design of future degrader molecules, offering valuable lessons for the design of future molecules of this type (Jan et al., 2021). Moreover, synthetic lethality is opening up novel opportunities for exploiting molecular vulnerabilities in disease, such as oncology, with targeted protein degradation that could also lead to reduced toxicity (Huang et al., 2020). The major technological and therapeutic trends foreseen to affect the next generation of targeted protein degradation are highlighted in Figure 3.

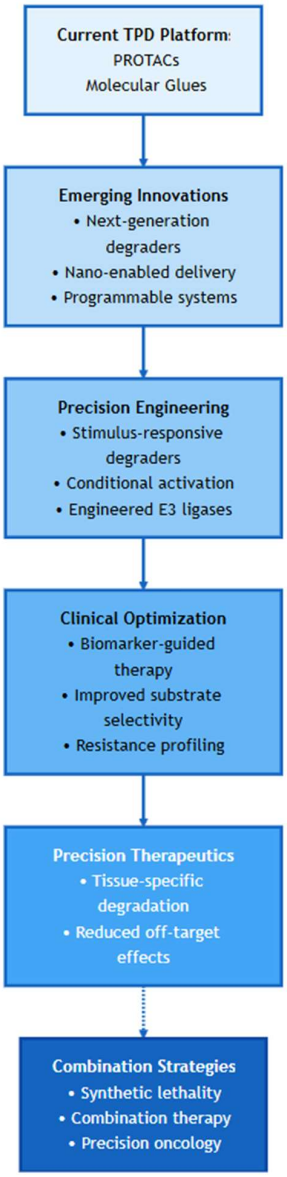

Figure 3. Emerging directions shaping next-generation targeted protein degradation

Targeted protein degradation is poised to become an essential precision-medicine component over the coming years as it moves from an emerging therapy to a core precision-medicine tool. Advancements in the E3 ligase repertoire, tissue-specific and programmable degraders, and the combination of artificial intelligence and multiomics-based target discovery will significantly expand the druggable proteome. Future work should also focus on enhancing pharmacokinetic parameters, safety for long-term use and clinical translatability, and optimization of the strategies for degradation according to the nature of the disease and the clinical molecular profile of the patients. With the development of targeted protein degradation, new innovative pharmaceutical solutions are emerging for diseases that have not been sufficiently targeted by the current one-protein-one-target paradigm in drug discovery. As such, targeted protein degradation has the potential to completely change the course of drug discovery, providing highly selective, long-lasting and adaptable therapeutic solutions.

9. Conclusion

The concept of targeted protein degradation has given rise to a new paradigm in drug discovery and development that goes beyond the paradigm of protein inhibition and into the realm of catalytic protein degradation. The current state of the art includes PROTACs and molecular glues that are complementary in their mechanisms of recruiting E3 ubiquitin ligases and in their ability to reach previously untargeted proteins. Advances in structural biology, medicinal chemistry, proteomics, computational modeling, and artificial intelligence have driven their development to accelerate the ability to control their potency, selectivity, and degrader performance in a more rational fashion. TPD's therapeutic applications are also expanding to rare genetic diseases, oncological,

neurological, autoimmune, inflammatory and infectious diseases. However, clinical translation is still limited due to limited usage of E3 ligases, suboptimal pharmacokinetics, tissue-selective delivery, resistance, safety concerns and manufacturing complexity. Programmable systems to degrade the proteins, biomarker selection, better delivery methods and combination approaches like synthetic lethality will be needed to overcome these barriers. TPD is becoming more than an experimental concept and has the potential to become a precision-medicine platform that changes the way disease-driving proteins are therapeutically targeted.

References

1. Ahn, G., Banik, S. M., Miller, C. L., Riley, N. M., Cochran, J. R., & Bertozzi, C. R. (2021). LYTACs that engage the asialoglycoprotein receptor for targeted protein degradation. Nature Chemical Biology, 17(9), 937-946.
2. Chamberlain, P. P., & Hamann, L. G. (2019). Development of targeted protein degradation therapeutics. Nature chemical biology, 15(10), 937-944.
3. Chirnomas, D., Hornberger, K. R., & Crews, C. M. (2023). Protein degraders enter the clinic—a new approach to cancer therapy. Nature reviews Clinical oncology, 20(4), 265-278.
4. Clausen, L., Abildgaard, A. B., Gersing, S. K., Stein, A., Lindorff-Larsen, K., & Hartmann-Petersen, R. (2019). Protein stability and degradation in health and disease. Advances in protein chemistry and structural biology, 114, 61-83.
5. Cromm, P. M., & Crews, C. M. (2017). Targeted protein degradation: from chemical biology to drug discovery. Cell chemical biology, 24(9), 1181-1190.
6. Dewey, J. A., Delalande, C., Azizi, S. A., Lu, V., Antonopoulos, D., & Babnigg, G. (2023). Molecular glue discovery: current and future approaches. Journal of Medicinal Chemistry, 66(14), 9278-9296.
7. Dobson, C. M. (2019). Biophysical techniques in structural biology. Annual review of biochemistry, 88(1), 25-33.
8. Duran-Frigola, M., Cigler, M., & Winter, G. E. (2023). Advancing targeted protein degradation via multiomics profiling and artificial intelligence. Journal of the American Chemical Society, 145(5), 2711-2732.
9. Eladl, O. (2025). Molecular glues and PROTACs in targeted protein degradation: mechanisms, advances, and therapeutic potential. Biochemical Pharmacology, 117297.
10. Espinoza-Chávez, R. M., Salerno, A., Liuzzi, A., Ilari, A., Milelli, A., Uliassi, E., & Bolognesi, M. L. (2022). Targeted protein degradation for infectious diseases: from basic biology to drug discovery. ACS bio & med chem Au, 3(1), 32-45.
11. Gudjonsson, J. E., Weidinger, S., & Kabashima, K. (2024). The coming of age of protein degraders as anti-inflammatory therapeutics. Journal of Allergy and Clinical Immunology, 154(1), 76-78.
12. Hacker, K. (2024). The burden of chronic disease. Mayo Clinic Proceedings: Innovations, Quality & Outcomes, 8(1), 112-119.
13. Hanna, J., Guerra-Moreno, A., Ang, J., & Micoogullari, Y. (2019). Protein degradation and the pathologic basis of disease. The American journal of pathology, 189(1), 94-103.
14. He, S., Dong, G., & Sheng, C. (2025). Strategies for precise modulation of protein degradation. Accounts of Chemical Research, 58(8), 1236-1248.
15. Hedl, T. J., San Gil, R., Cheng, F., Rayner, S. L., Davidson, J. M., De Luca, A., ... & Lee, A. (2019). Proteomics approaches for biomarker and drug target discovery in ALS and FTD. Frontiers in Neuroscience, 13, 548.
16. Hoda, M. (2021). Potential alternatives to conventional cancer therapeutic approaches: the way forward. Current Pharmaceutical Biotechnology, 22(9), 1141-1148.
17. Höhn, A., Tramutola, A., & Cascella, R. (2020). Proteostasis failure in neurodegenerative diseases: focus on oxidative stress. Oxidative medicine and cellular longevity, 2020(1), 5497046.
18. Hollingsworth, S., Johnson, S., Khakbaz, P., Meng, Y., Mouchlis, V., Pierce, O., ... & Shanmugasundaram, V. (2023). The rise of targeting chimeras (TACs): next-generation medicines that preempt cellular events. Medicinal Chemistry Research, 32(7), 1294-1314.
19. Hoppe, T., & Cohen, E. (2020). Organismal protein homeostasis mechanisms. Genetics, 215(4), 889-901.
20. Hou, M., Zhao, R., Wang, S., Jiang, B., & Yan, X. (2025). Targeted protein degradation technologies: Emerging mechanisms and nano-based innovations. Nano Research, 18(10), 94907983.
21. Huang, A., Garraway, L. A., Ashworth, A., & Weber, B. (2020). Synthetic lethality as an engine for cancer drug target discovery. Nature reviews Drug discovery, 19(1), 23-38.
22. Jan, M., Sperling, A. S., & Ebert, B. L. (2021). Cancer therapies based on targeted protein degradation—lessons learned with lenalidomide. Nature Reviews Clinical Oncology, 18(7), 401-417.
23. Jayaraj, G. G., Hipp, M. S., & Hartl, F. U. (2020). Functional modules of the proteostasis network. Cold Spring Harbor Perspectives in Biology, 12(1), a033951.
24. Jin, Y., Fan, J., Wang, R., Wang, X., Li, N., You, Q., & Jiang, Z. (2023). Ligation to scavenging strategy enables on-demand termination of targeted protein

degradation. Journal of the American Chemical Society, 145(13), 7218-7229.
25. King, E. A., Meyers, M., & Nomura, D. K. (2026). Induced proximity-based therapeutic modalities. Nature Reviews Drug Discovery, 25(3), 175-203.
26. Konstantinidou, M., & Arkin, M. R. (2024). Molecular glues for protein-protein interactions: Progressing toward a new dream. Cell Chemical Biology, 31(6), 1064-1088.
27. Li, Y., Li, S., & Wu, H. (2022). Ubiquitination-proteasome system (UPS) and autophagy two main protein degradation machineries in response to cell stress. Cells, 11(5), 851.
28. Lin, C. T., Shiau, Y. P., & Lin, C. C. (2025). Machine learning in targeted protein degradation drug design: a technical review of PROTACs and molecular glues. Drug Discovery Today, 104563.
29. Liu, Y., Qian, X., Ran, C., Li, L., Fu, T., Su, D., ... & Tan, W. (2023). Aptamer-based targeted protein degradation. ACS nano, 17(7), 6150-6164.
30. Liu, Z., Hu, M., Yang, Y., Du, C., Zhou, H., Liu, C., ... & Xie, Y. (2022). An overview of PROTACs: a promising drug discovery paradigm. Molecular biomedicine, 3(1), 46.
31. Marei, H. E., Bedair, K., Hasan, A., Al-Mansoori, L., Gaiba, A., Morrione, A., ... & Giordano, A. (2025). Targeting CDKs in cancer therapy: advances in PROTACs and molecular glues. NPJ Precision Oncology, 9(1), 204.
32. Meissner, F., Geddes-McAlister, J., Mann, M., & Bantscheff, M. (2022). The emerging role of mass spectrometry-based proteomics in drug discovery. Nature Reviews Drug Discovery, 21(9), 637-654.
33. Ming, H., Li, B., Jiang, J., Qin, S., Nice, E. C., He, W., ... & Huang, C. (2023). Protein degradation: expanding the toolbox to restrain cancer drug resistance. Journal of hematology & oncology, 16(1), 6.
34. Moreau, K., Coen, M., Zhang, A. X., Pachl, F., Castaldi, M. P., Dahl, G., ... & Newham, P. (2020). Proteolysis-targeting chimeras in drug development: a safety perspective. British journal of pharmacology, 177(8), 1709-1718.
35. Neklesa, T. K., Winkler, J. D., & Crews, C. M. (2017). Targeted protein degradation by PROTACs. Pharmacology & therapeutics, 174, 138-144.
36. Nguyen, H. P., Van Broeckhoven, C., & van der Zee, J. (2018). ALS genes in the genomic era and their implications for FTD. Trends in Genetics, 34(6), 404-423.
37. Park, J., Cho, J., & Song, E. J. (2020). Ubiquitin–proteasome system (UPS) as a target for anticancer treatment. Archives of pharmacal research, 43(11), 1144-1161.
38. Patel, M., Parikh, D., Parihar, A., Prajapati, B., Patel, M. B., Salave, S., ... & Khunt, D. (2025). Protein and peptide therapeutics: stability challenges, regulatory demands, and innovative formulation solutions for enhanced clinical effectiveness. Protein & Peptide Letters.
39. Pike, A., Williamson, B., Harlfinger, S., Martin, S., & McGinnity, D. F. (2020). Optimising proteolysis-targeting chimeras (PROTACs) for oral drug delivery: a drug metabolism and pharmacokinetics perspective. Drug Discovery Today, 25(10), 1793-1800.
40. Robinson, S. A., & Banik, S. M. (2024). Molecular glues and induced proximity: An evolution of tools and discovery. Cell Chemical Biology, 31(6), 1089-1100.
41. Salama, A. K., Trkulja, M. V., Casanova, E., & Uras, I. Z. (2022). Targeted protein degradation: clinical advances in the field of oncology. International Journal of Molecular Sciences, 23(23), 15440.
42. Samarasinghe, K. T., & Crews, C. M. (2021). Targeted protein degradation: A promise for undruggable proteins. Cell chemical biology, 28(7), 934-951.
43. Sathe, G., & Sapkota, G. P. (2023). Proteomic approaches advancing targeted protein degradation. Trends in pharmacological sciences, 44(11), 786-801.
44. Schmidt, M. F., Gan, Z. Y., Komander, D., & Dewson, G. (2021). Ubiquitin signalling in neurodegeneration: mechanisms and therapeutic opportunities. Cell Death & Differentiation, 28(2), 570-590.
45. Schreiber, S. L. (2021). The rise of molecular glues. Cell, 184(1), 3-9.
46. Shoemaker, S. C., & Ando, N. (2018). X-rays in the cryo-electron microscopy era: structural biology's dynamic future. Biochemistry, 57(3), 277-285.
47. Siepe, D. H., Picton, L. K., & Garcia, K. C. (2023). Receptor elimination by E3 ubiquitin ligase recruitment (REULR): a targeted protein degradation toolbox. ACS synthetic biology, 12(4), 1081-1093.
48. Song, Y., Zhou, B., Long, J., & Peng, Y. (2025). Targeted protein degradation in autoimmune diseases: from mechanisms to therapeutic breakthroughs. Journal of Autoimmunity, 156, 103475.
49. Sun, X., Gao, H., Yang, Y., He, M., Wu, Y., Song, Y., ... & Rao, Y. (2019). PROTACs: great opportunities for academia and industry. Signal transduction and targeted therapy, 4(1), 64.
50. Team, T. C. E. (2020). Embracing the landscape of therapeutics. Cell, 181(1), 1.