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TARGETED PROTEIN DEGRADATION (PROTACs & MOLECULAR GLUES): A NEW PHARMACOLOGICAL ERA---WHY? CONSIDERED THE NEXT REVOLUTION IN PHARMACOLOGY AFTER BIOLOGICS.

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ABSTRACT Targeted protein degradation (TPD) represents a major paradigm shift in pharmacology by enabling selective elimination of disease-causing proteins rather than transient functional inhibition. Proteolysis-targeting chimeras (PROTACs) and molecular glues are the most advanced TPD modalities, exploiting the ubiquitin–proteasome system to induce catalytic, event-driven protein degradation with sustained biological effects at lower drug exposure. This approach expands the druggable proteome to include transcription factors, scaffolding proteins, and regulatory complexes previously considered undruggable. PROTACs are bifunctional molecules that recruit E3 ubiquitin ligases to target proteins, promoting proximity-induced ubiquitination and proteasomal degradation, while molecular glues are monovalent small molecules that stabilize novel protein–protein interactions with improved physicochemical and pharmacokinetic properties. The clinical success of thalidomide-derived molecular glues, such as lenalidomide and pomalidomide in multiple myeloma, has validated TPD as a therapeutic strategy. A rapidly expanding clinical pipeline now includes degraders targeting estrogen and androgen receptors, Bruton's tyrosine kinase, STAT3, and BCL-XL across oncology, immunology, and emerging neurodegenerative indications. Despite significant progress, challenges related to molecular size, oral bioavailability, E3 ligase diversity, selectivity, and translational predictability remain. Ongoing advances in medicinal chemistry, artificial intelligence-guided design, proteomics-based safety profiling, and novel delivery platforms are accelerating clinical translation. Collectively, TPD represents a post-biologics revolution with broad implications for precision therapeutics and future drug discovery.

KEYWORDS : Targeted protein degradation, PROTACs, molecular glues, ubiquitin-proteasome system, chemical biology, clinical translation, pharmacokinetics

INTRODUCTION

Conventional drug discovery has predominantly relied on small molecules and biologics that regulate protein function through direct inhibition or activation of enzymes or receptors. This classical occupancy-driven pharmacological model requires sustained target engagement to maintain therapeutic efficacy. While successful for proteins with well-defined binding pockets, this approach fails to address a substantial proportion of disease-associated proteins, including transcription factors, scaffolding proteins, and intrinsically disordered proteins, which lack suitable ligand-binding sites and are therefore considered "undruggable" by traditional strategies **[1,2]**.

Targeted protein degradation (TPD) has emerged as a transformative pharmacological paradigm that overcomes these limitations by inducing selective elimination of pathogenic proteins rather than transient functional suppression. TPD primarily exploits endogenous cellular protein quality-control mechanisms, most notably the ubiquitin–proteasome system (UPS), which governs regulated intracellular protein turnover **[3–5]**. By redirecting this machinery toward disease-causing proteins, TPD enables event-driven pharmacology, wherein brief target engagement is sufficient to trigger sustained biological effects through catalytic protein removal **[9]**.

Among TPD approaches, proteolysis-targeting chimeras (PROTACs) and molecular glues represent the most advanced and clinically validated modalities. PROTACs are heterobifunctional molecules that simultaneously bind a protein of interest and an E3 ubiquitin ligase, promoting proximity-induced ubiquitination and proteasomal degradation **[8,9]**. In contrast, molecular glues are typically monovalent small molecules that stabilize novel interactions between target proteins and E3 ligases, often exhibiting favorable physicochemical and pharmacokinetic properties **[12]**.

Clinical validation of this strategy has been firmly established by thalidomide-derived molecular glues such as lenalidomide and pomalidomide, which selectively degrade IKZF1 and IKZF3 transcription factors in multiple myeloma **[13,14]**. Building on this success, recent advances have expanded degrader pipelines across oncology, immunology, and emerging neurodegenerative indications, with multiple PROTACs and molecular glues advancing through early- and late-phase clinical trials **[18,21]**. Despite ongoing challenges related to E3 ligase diversity, pharmacokinetics, and translational predictability, continued innovations in medicinal chemistry, artificial intelligence-guided design, and delivery strategies are accelerating the clinical impact of TPD technologies **[19,20]**.

Background

Protein Homeostasis and Degradation

Maintenance of protein homeostasis (proteostasis) is essential for cellular function and survival. Cells employ highly regulated degradation systems to remove misfolded, damaged, or excess proteins, thereby preventing toxic accumulation and ensuring dynamic control of signaling pathways.

Ubiquitin–Proteasome System (UPS)

The ubiquitin–proteasome system (UPS) is the primary pathway for selective degradation of short-lived and intracellular regulatory proteins. This process involves a coordinated enzymatic cascade comprising ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3), which confer substrate specificity. Polyubiquitinated proteins are subsequently recognized and degraded by the 26S proteasome into short peptides **[3,4]**. Dysregulation of the UPS has been implicated in cancer, neurodegenerative disorders, and immune dysregulation, making it an attractive therapeutic target **[5]**.

Lysosomal Pathways

In contrast, lysosomal degradation pathways primarily regulate long-

lived proteins, protein aggregates, membrane proteins, and entire organelles. These pathways include macroautophagy, microautophagy, chaperone-mediated autophagy, and receptor-mediated endocytosis. Lysosomal systems play a central role in maintaining cellular quality control and are increasingly exploited for therapeutic protein degradation strategies, particularly for extracellular and membrane-bound targets **[6,7]**.

Emergence of Targeted Protein Degradation (TPD) Modalities

Targeted protein degradation technologies have evolved to harness both proteasomal and lysosomal pathways. PROTACs and molecular glues primarily exploit the UPS to induce selective degradation of intracellular proteins. In contrast, emerging lysosome-based approaches such as lysosome-targeting chimeras (LYTACs) and antibody-based TPDs (AbTACs) extend degradative strategies to membrane and extracellular proteins, thereby broadening the therapeutic scope of TPD beyond intracellular targets **[16,17]**.

Mechanistic Insights

PROTACs

Proteolysis-targeting chimeras (PROTACs) are heterobifunctional small molecules consisting of a ligand for the protein of interest (POI), a ligand for an E3 ubiquitin ligase, and a chemical linker connecting the two. By simultaneously binding the POI and E3 ligase, PROTACs induce formation of a ternary complex, leading to ubiquitination and proteasomal degradation of the target protein in a catalytic and programmable manner **[9]**. Clinically advanced examples include ARV-471, an estrogen receptor degrader for breast cancer, and ARV-110, an androgen receptor degrader for prostate cancer, both demonstrating proof-of-concept for PROTAC-based therapeutics in humans **[18]**.

Molecular Glues

Molecular glues are monovalent, linker-free small molecules that stabilize or induce novel interactions between an E3 ubiquitin ligase and a target protein. This mechanism expands the druggable proteome without the structural complexity of bifunctional degraders **[12]**. The most prominent examples are thalidomide and its derivatives, which act as molecular bridges between the CRBN E3 ligase and transcription factors such as IKZF1 (Ikaros) and IKZF3 (Aiolos), leading to their selective degradation **[13]**.

Thalidomide derivatives, including lenalidomide and pomalidomide, have revolutionized the treatment of multiple myeloma and are widely approved by regulatory authorities. These agents exert their therapeutic effects by degrading IKZF1/3, key transcriptional regulators essential for myeloma cell survival and proliferation **[14]**. Newer, next-generation immunomodulatory drugs (IMiDs) such as iberdomide and mezigdomide exhibit enhanced cereblon binding, improved potency, and broader substrate degradation profiles, and are currently demonstrating promising efficacy in clinical trials for hematological malignancies **[15,25]**.

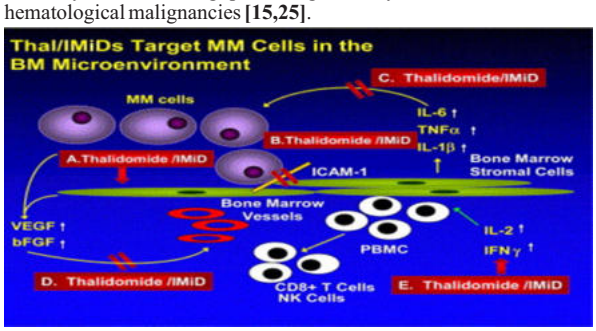

Fig 1: Thalidomide/IMiDs Effects On MM In The Bone Marrow Microenvironment

Comparative Analysis: PROTACs vs Molecular Glues

Comparative analysis of PROTACs vs Molecular Glues for targeted protein degradation strategies

Advantages: Higher oral bioavailability, easier CNS penetration, and potential for Targeting protein interactions beyond simple inhibition.

Table 1: Key Differences Between PROTACs And Molecular Glues

Feature	PROTACs	Molecular Glues
Structure	Heterobifunctional	Monovalent
Linker	Required	None
Typical MW	700–1200 Da	<500 Da
Oral Bioavailability	Challenging	Generally improved
BBB Penetration	Difficult	Favorable

Table 2: PROTACs And Molecular Glues: Disease Indications And Targets

Indication	Selected Agents	Targets
Oncology	ARV-471, ARV-110	ER, AR, BTK, STAT3, MDM2, BCL-XL
Neurodegeneration	Custom PROTACs	tau, α-synuclein, mHtt, LRRK2
Immunology	IRAK4-PROTACs, thalidomide-derived glues	Cyclooxygenases, IRAK4, IKZF1/3

Current Clinical and Translational Applications

Beyond early clinical proof-of-concept studies, targeted protein degradation has entered late-stage clinical evaluation. ARV-471 (vepdegestrant) is currently undergoing Phase III trials in estrogen receptor–positive, HER2-negative advanced breast cancer and has demonstrated superior estrogen receptor degradation and improved progression-free survival compared with standard endocrine therapies, particularly in ESR1-mutant tumors **[22,23]**.

In hematological malignancies, next-generation cereblon modulators such as mezigdomide (CC-92480) have progressed into Phase III trials for relapsed or refractory multiple myeloma, exhibiting enhanced IKZF1/3 degradation and improved clinical responses in IMiD-resistant disease **[25]**. In parallel, BCL-XL–targeting PROTACs have entered advanced translational development to reduce thrombocytopenia associated with conventional BCL-XL inhibitors **[24]**. Additionally, IRAK4-targeting degraders are advancing toward late-phase trials in autoimmune and inflammatory diseases, highlighting expansion beyond oncology **[26]**.

Challenges And Gaps

- Pharmacokinetics: PROTACs' high molecular mass (700–1200 Da) impairs cell permeability and oral bioavailability.
- Selectivity and Toxicity: Both approaches face the challenge of off-target effects and the risk of disrupting entire regulatory pathways.
- Design Complexity: Rational design of effective PROTACs and identification of new E3 ligase–target pairs remains non-trivial. While AI and big data approaches are accelerating discovery, much is left to optimize.

Ongoing Research & Clinical Pipeline

Large-scale databases such as PROTAC-DB 3.0 now catalogue over 6,000 PROTAC molecules with associated structural and pharmacokinetic data, enabling AI-assisted degrader optimization **[19]**. Concurrently, agents such as ARV-471, ARV-110, KT-253, and DT2216 are progressing across clinical phases, while next-generation molecular glues continue to expand indications in solid tumors, CNS disorders, and immunology **[18,21]**. Artificial intelligence and deep learning approaches are increasingly integrated into TPD discovery to predict ternary complex formation, degradation efficiency, and translational success **[20]**.

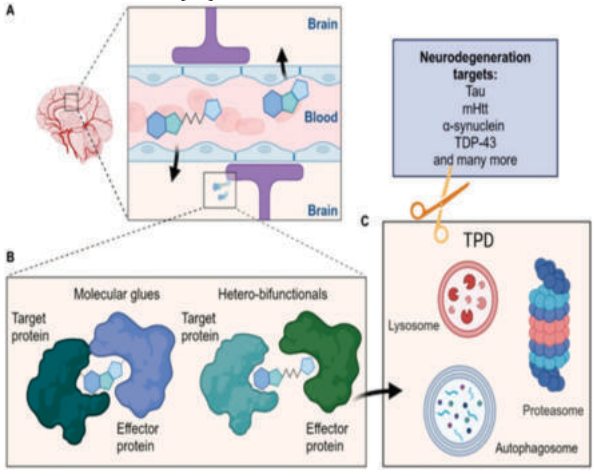

Fig 2: Targeted Protein Degradation Strategies for Neurodegenerative Diseases

Table 3: Selected PROTAC & Targeted Protein Degrader Therapies in Clinical Development

Compound	Target	Indication	Clinical Phase	Key Reference
ARV-471 (Vepdegestrant)	Estrogen receptor (ER)	ER-positive, HER2-negative breast cancer	Phase III	Bardia et al., 2024 [22]
ARV-110	Androgen receptor (AR)	Metastatic castration-resistant prostate cancer	Phase II/III	Hamilton et al., 2024 [23]
KT-253	MDM2 / p53 pathway	Solid tumors (TP53 wild-type)	Phase I	Mullard, 2021 [18]
DT2216	BCL-XL	Hematologic malignancies	Phase II	Khan et al., 2024 [24]
Lenalidomide	IKZF1/IKZF3 (via CRBN)	Multiple myeloma	Approved	Krönke et al., 2014 [14]
Pomalidomide	IKZF1/IKZF3 (via CRBN)	Multiple myeloma	Approved	Krönke et al., 2014 [14]
Iberdomide (CC-220)	IKZF1/IKZF3	Multiple myeloma	Phase III	Matyskiela et al., 2020 [15]
Mezigdomide (CC-92480)	IKZF1/IKZF3	Relapsed/refractory multiple myeloma	Phase III	Richardson et al., 2025 [25]
IRAK4 PROTACs	IRAK4 kinase	Autoimmune and inflammatory diseases	Phase II/III	Werth et al., 2025 [26]

Gaps & Future Needs

- Enhanced oral bioavailability and CNS penetration, especially for large-molecule PROTACs.
- Expanding the repertoire of E3 ligases.
- Improved high-throughput phenotypic screening for molecular glue discovery.
- Better proteomic-based safety profiling and rational structure-guided design with AI integration.

Integration With Nanomedicine And Next-Gen Delivery

- Nanoparticle-based, stimuli-responsive "Nano-PROTAC" systems are in early clinical translation, improving targeting and bioavailability.
- Antibody-drug conjugates and smart delivery vehicles expand the therapeutic index and tissue selectivity of TPD agents.

Future Directions

- Focus on non-oncological and rare-disease expansion.
- Synergy with gene therapy, smart nanotechnology, and AI-driven structure-based design.
- Improved regulatory, manufacturing, and patient selection frameworks as therapy classes mature.

CONCLUSION

Targeted protein degradation represents a paradigm shift in pharmacology by enabling programmable elimination of disease-causing proteins. Although challenges related to pharmacokinetics, selectivity, and translational predictability persist, rapid advances in chemistry, computational biology, and drug delivery systems are positioning TPD as a post-biologics therapeutic revolution with broad clinical impact **[21]**.

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