Global Journal of Research in
Biology and Pharmacy
Journal homepage: https://gsjournals.com/gjrbp/
ISSN: 2980-4221 (Online)

(REVIEW ARTICLE)

Check for updates

PROTACS AND MOLECULAR GLUES: TARGETED PROTEIN DEGRADATION AS A NEXT-GENERATION PHARMACOLOGICAL STRATEGY

Dipti Suresh K. *

B. Pharmacy Student, R.P. Rajputana College of Pharmacy, Bangalore.
* Corresponding Author

Global Journal of Research in Biology and Pharmacy, 2024, 03(03), 001–005

Publication history: Received on 14 May 2024; revised on 24 July 2024; accepted on 27 July 2024

Article DOI: https://doi.org/10.58175/gjrbp.2024.3.3.0093

ABSTRACT

Targeted protein degradation has emerged as a transformative pharmacological approach that exploits the ubiquitin-proteasome system to eliminate disease-relevant proteins rather than merely inhibiting their function. Two principal classes of degraders have advanced rapidly: proteolysis-targeting chimeras (PROTACs) and molecular glues. PROTACs are heterobifunctional molecules that simultaneously bind a target protein and an E3 ubiquitin ligase, inducing proximity-dependent ubiquitination and subsequent proteasomal degradation. Molecular glues, by contrast, are small molecules that modify the surface of an E3 ligase or target protein to promote or enhance protein–protein interactions leading to degradation. This review critically examines the design, mechanism, and clinical progress of PROTACs and molecular glues through early 2024. Key PROTAC programs targeting the estrogen receptor, androgen receptor, Bruton's tyrosine kinase, and other oncogenic drivers have entered clinical trials, with early data demonstrating degradation and preliminary efficacy. Molecular glues, exemplified by the immunomodulatory imide drugs thalidomide, lenalidomide, and pomalidomide, have validated the clinical potential of induced proximity, and next-generation glues targeting additional ligases and substrates are in development. Challenges include oral bioavailability, permeability, selectivity, acquired resistance, and the need for robust biomarkers of target engagement and degradation. Future directions include expanding the repertoire of E3 ligases, improving tissue selectivity, and applying degradation to previously undruggable proteins. Overall, targeted protein degradation represents a paradigm shift in drug discovery, with the potential to address therapeutic targets beyond the reach of conventional inhibitors.

Keywords: PROTAC; Molecular Glue; Targeted Protein Degradation; Ubiquitin-Proteasome System; E3 Ligase; Undruggable Proteins

1 INTRODUCTION

Traditional small-molecule drugs and monoclonal antibodies typically function by binding to a target protein and inhibiting its activity. However, many disease-relevant proteins, including transcription factors, scaffolding proteins, and proteins with multiple functions, lack suitable binding pockets or are not amenable to inhibition alone. Targeted protein degradation offers an alternative approach by redirecting the ubiquitin-proteasome system to selectively eliminate a protein of interest. This strategy can remove the entire protein, including its scaffolding and enzymatic functions, potentially yielding more profound and sustained biological effects than inhibition.

Proteolysis-targeting chimeras (PROTACs) are heterobifunctional molecules composed of a target-binding ligand, an E3 ligase ligand, and a linker. By bringing the target protein into proximity with an E3 ligase, PROTACs facilitate the transfer of ubiquitin to the target, marking it for proteasomal degradation. The first PROTACs were reported in 2001, but it was not until the development of small-molecule E3 ligase ligands, such as those for von Hippel-Lindau and cereblon, that the field accelerated. Molecular glues, in contrast, are monovalent small molecules that stabilize or induce interactions between an E3 ligase and a target protein. The thalidomide analogs lenalidomide and pomalidomide are the best-known molecular glues, redirecting cereblon to degrade transcription factors IKZF1 and IKZF3, which accounts for their efficacy in multiple myeloma.

This review examines the current state of PROTACs and molecular glues, focusing on design principles, mechanisms, clinical progress through early 2024, and the challenges that must be addressed for broader therapeutic application.

2 THE UBIQUITIN-PROTEASOME SYSTEM AND INDUCED PROXIMITY

The ubiquitin-proteasome system is the primary pathway for selective protein degradation in eukaryotic cells. Proteins destined for degradation are tagged with polyubiquitin chains, which are recognized by the 26S proteasome. Ubiquitination involves three enzymes: E1 (ubiquitin-activating), E2 (ubiquitin-conjugating), and E3 (ubiquitin ligase). E3 ligases confer substrate specificity by binding both the E2-ubiquitin complex and the substrate. There are over 600 E3 ligases in humans, but only a handful have been exploited for targeted protein degradation, including cereblon, von Hippel-Lindau, MDM2, and IAPs.

The concept of induced proximity underpins both PROTACs and molecular glues. PROTACs simultaneously engage the target and an E3 ligase, forming a ternary complex. This complex is stabilized by favorable protein–protein interactions, and the target is ubiquitinated on surface lysines. Because PROTACs act catalytically—releasing the target after ubiquitination and engaging another molecule—they can achieve degradation at substoichiometric concentrations. The efficiency of degradation depends on the cooperativity of ternary complex formation, the surface lysine availability, and the orientation of the ubiquitin transfer.

Molecular glues bind to a single protein, often the E3 ligase, and create a new surface that recruits a neosubstrate. They do not require a binding pocket on the target and can degrade proteins considered undruggable by conventional occupancy-based inhibitors. The immunomodulatory imide drugs bind to cereblon and induce degradation of IKZF1 and IKZF3, which are transcription factors without enzymatic activity. This mechanism was discovered retrospectively after lenalidomide's clinical use.

3 PROTAC DESIGN AND OPTIMIZATION

3.1 Components of PROTACs

A PROTAC consists of three parts: a ligand for the target protein, a ligand for an E3 ligase, and a linker. Target ligands are often derived from known inhibitors, but they need not be potent inhibitors—only binders—since degradation rather than inhibition is the goal. E3 ligase ligands include small molecules for von Hippel-Lindau (VHL), cereblon (thalidomide analogs), MDM2 (nutlin derivatives), and IAP (smac mimetics). The linker connects the two ligands and must be optimized for length, rigidity, and chemical composition to maximize ternary complex formation and minimize steric clashes.

3.2 Properties and Challenges

Early PROTACs were large (molecular weight > 1000 Da) and had poor cell permeability and oral bioavailability, limiting their drug-likeness. The development of smaller, more rigid linkers and the use of cereblon-based ligands (which are more drug-like) have improved properties. However, PROTACs still often violate Lipinski's rules and face challenges in achieving systemic exposure after oral administration. Medicinal chemists have made progress by optimizing linker composition (e.g., incorporating piperazine, triazole, or macrocyclic elements) and by using structure-based design informed by ternary complex crystal structures.

3.3 Selectivity and Off-Target Degradation

Because PROTACs can degrade proteins that are not the intended target if they form stable ternary complexes, selectivity must be carefully characterized. Proteomics approaches, such as mass spectrometry-based degradation profiling, are used to identify unintended degradation events. The choice of target ligand and linker can influence selectivity, and the development of covalent or mutant-selective PROTACs is an active area.

4 MOLECULAR GLUES: MECHANISMS AND DESIGN

4.1 Cereblon Modulators

Cereblon is a component of the CRL4^CRBN E3 ubiquitin ligase complex. Thalidomide, lenalidomide, and pomalidomide bind to cereblon and alter its substrate specificity, leading to degradation of IKZF1 and IKZF3. This accounts for their anti-myeloma and immunomodulatory activity. Structural studies revealed that these drugs occupy a shallow pocket in cereblon and create a new binding surface that recruits the zinc finger transcription factors. This discovery has inspired the search for novel cereblon modulators with different neosubstrate profiles.

4.2 Beyond Cereblon: Other E3 Ligases

Molecular glues that recruit other E3 ligases are being developed. Examples include aryl sulfonamides that stabilize the interaction between DCAF15 and the splicing factor RBM39, leading to RBM39 degradation, and compounds that target DCAF11 or DDB1. The discovery of new molecular glues often relies on phenotypic screening followed by target deconvolution, as rational design is challenging due to the subtle nature of induced interactions. Advances in chemical proteomics and high-throughput screening have accelerated the identification of novel glues.

4.3 Advantages and Limitations

Molecular glues are generally smaller and more drug-like than PROTACs, with better oral bioavailability and pharmacokinetic properties. They can degrade proteins lacking conventional ligand-binding pockets. However, rational design is difficult because the interactions are often low-affinity and context-dependent. The discovery of new glues has been largely serendipitous, and predicting neosubstrates remains a major challenge.

5 CLINICAL PROGRESS OF PROTACS

5.1 Androgen Receptor Degraders

ARV-110 (bavdegalutamide) is an oral PROTAC targeting the androgen receptor. It was the first PROTAC to enter clinical trials. Phase 1/2 data in metastatic castration-resistant prostate cancer showed declines in prostate-specific antigen and evidence of androgen receptor degradation. However, responses were modest, and the program was discontinued in 2023 due to strategic prioritization. ARV-766, a next-generation androgen receptor PROTAC, is being evaluated with promising early results. These programs provide important proof of concept for oral PROTAC delivery and clinical degradation.

5.2 Estrogen Receptor Degraders

ARV-471 (vepdegestrant) is an oral PROTAC targeting the estrogen receptor. Phase 1/2 trials in heavily pretreated ER+/HER2− breast cancer demonstrated degradation of the estrogen receptor and clinical benefit, including partial responses. A phase 3 trial comparing vepdegestrant to fulvestrant was initiated, and combinations with CDK4/6 inhibitors are being explored. This program represents the most advanced PROTAC in clinical development.

5.3 Bruton's Tyrosine Kinase Degraders

PROTACs targeting BTK, such as NX-2127 and BGB-16673, are being evaluated in B-cell malignancies, including chronic lymphocytic leukemia and mantle cell lymphoma. BTK degraders may overcome resistance mutations (e.g., C481S) that limit covalent BTK inhibitors. Early clinical data have shown degradation of BTK and clinical responses, including in patients with prior BTK inhibitor therapy.

5.4 Other Targets

Additional PROTACs in early clinical trials target IRAK4, STAT3, BRD9, and mutant KRAS. These programs are exploring degradation of transcription factors and other challenging targets. While most are phase 1, they demonstrate the broadening scope of degradation-based therapies.

6 CLINICAL PROGRESS OF MOLECULAR GLUES

The immunomodulatory imide drugs lenalidomide, pomalidomide, and thalidomide are approved for multiple myeloma, myelodysplastic syndromes, and other conditions. Their mechanism as molecular glues was recognized after approval. Next-generation cereblon modulators with distinct neosubstrate profiles are in clinical development, including iberdomide and mezigdomide, which are more potent degraders of IKZF1/IKZF3 and are being evaluated in

relapsed or refractory multiple myeloma. These agents may overcome resistance to lenalidomide and provide deeper responses.

Beyond cereblon, molecular glues targeting other E3 ligases are in early clinical testing. For example, RMC-4630, a SHP2 inhibitor, is not a glue, but compounds like indisulam (an aryl sulfonamide) that degrade RBM39 via DCAF15 have been studied clinically, although development has been challenging. Newer glues are emerging from screening platforms.

7 CHALLENGES AND LIMITATIONS

7.1 Oral Bioavailability and Permeability

PROTACs are typically larger and more polar than conventional small molecules, leading to poor oral absorption and limited brain penetration. Optimization of physicochemical properties is essential. Some PROTACs have achieved sufficient oral exposure, but this remains a hurdle for many targets.

7.2 Selectivity and Off-Target Effects

Both PROTACs and molecular glues can induce unintended protein degradation. Cereblon modulators can degrade multiple neosubstrates, leading to pleiotropic effects. Rigorous proteomic profiling is required to assess selectivity. Tissue-specific E3 ligases may improve targeting, but most current ligases are ubiquitously expressed.

7.3 Resistance

Resistance to degraders can occur through mutations in the target protein that reduce ternary complex formation, upregulation of drug efflux pumps, or alterations in the ubiquitin-proteasome system. In multiple myeloma, resistance to lenalidomide involves cereblon mutations, target downregulation, or pathways bypassing IKZF degradation. Combination strategies and next-generation degraders may overcome resistance.

7.4 Safety and Toxicities

Degradation of essential proteins or off-target degradation can cause toxicities. For example, cereblon modulators can cause neutropenia and teratogenicity. On-target degradation of proteins with critical functions in normal tissues requires careful therapeutic windows. Long-term safety data are needed.

7.5 Biomarkers and Pharmacodynamics

Assessing target engagement and degradation in patients is challenging. Peripheral blood mononuclear cells or tumor biopsies are used, but tissue-specific degradation may not be reflected. Development of positron emission tomography tracers or mass spectrometry-based assays will aid dose selection and response prediction.

8 FUTURE PERSPECTIVES

The field of targeted protein degradation is expanding rapidly. Future directions include:

- Expanding the E3 ligase repertoire: Only a handful of the >600 human E3 ligases have been exploited. New ligands for tissue-specific or disease-specific ligases could improve selectivity.
- Tissue-selective degradation: Engineering PROTACs with targeting moieties (e.g., antibody-PROTAC conjugates) to deliver degraders to specific cells.
- Degrading “undruggable” targets: Transcription factors, scaffolding proteins, and aggregated proteins (e.g., tau, alpha-synuclein) are attractive targets.
- Combination therapies: Combining degraders with inhibitors, immunotherapies, or other modalities may enhance efficacy and overcome resistance.
- Covalent and reversible PROTACs: Covalent target engagement may improve degradation of challenging proteins.
- Clinical translation: More phase 2/3 data are needed to establish the therapeutic index and determine where degraders fit in treatment algorithms.

The success of ARV-471, BTK degraders, and next-generation cereblon modulators will be pivotal. If favorable, these could validate the approach and catalyze investment in additional programs.

9 CONCLUSION

PROTACs and molecular glues represent a new pharmacological paradigm that leverages the cell's own degradation machinery to eliminate disease-relevant proteins. PROTACs have entered clinical trials with promising early data, particularly for estrogen receptor and BTK, demonstrating that oral, systemic protein degradation is feasible. Molecular glues, exemplified by immunomodulatory imide drugs, have already transformed multiple myeloma therapy and continue to evolve. Challenges in drug-like properties, selectivity, resistance, and safety remain, but the potential to address previously undruggable targets is substantial. Continued research into E3 ligase biology, ternary complex structure, and clinical pharmacodynamics will be critical. Targeted protein degradation is poised to become a cornerstone of modern drug discovery.

REFERENCES

[1] Sakamoto KM, Kim KB, Kumagai A, et al. Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation. Proc Natl Acad Sci U S A. 2001;98(15):8554–8559.

[2] Winter GE, Buckley DL, Paulk J, et al. Phthalimide conjugation as a strategy for in vivo target protein degradation. Science. 2015;348(6241):1376–1381.

[3] Bondeson DP, Mares A, Smith IE, et al. Catalytic in vivo protein knockdown by small-molecule PROTACs. Nat Chem Biol. 2015;11(8):611–617.

[4] Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. Science. 2010;327(5971):1345–1350.

[5] Krönke J, Udeshi ND, Narla A, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. Science. 2014;343(6168):301–305.

[6] Lu G, Middleton RE, Sun H, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. Science. 2014;343(6168):305–309.

[7] Burslem GM, Crews CM. Proteolysis-targeting chimeras as therapeutics and tools for biological discovery. Cell. 2020;181(1):102–114.

[8] Mullard A. Targeted protein degraders crowd into the clinic. Nat Rev Drug Discov. 2021;20(4):247–250.

[9] Flanagan JJ, Neklesa TK. Targeting nuclear receptors with PROTAC therapeutics. Mol Cell Endocrinol. 2019;493:110452.

[10] Snyder LB, Neklesa TK, Chen X, et al. Discovery of ARV-110, a first-in-class androgen receptor degrading PROTAC for the treatment of men with metastatic castration resistant prostate cancer. Cancer Res. 2021;81(13_Suppl):43.

[11] Lin X, Xiang H, Luo G. Targeting estrogen receptor α for degradation with PROTACs: A promising approach to overcome endocrine resistance. Eur J Med Chem. 2020;206:112689.

[12] Brand M, Jiang B, Bauer S, et al. Homolog-selective degradation as a strategy to probe the function of CDK6 in AML. Cell Chem Biol. 2019;26(2):300–306.e9.

[13] Słabicki M, Kozicka Z, Petzold G, et al. The CDK inhibitor CR8 acts as a molecular glue degrader that depletes cyclin K. Nature. 2020;585(7825):293–297.

[14] Mayor-Ruiz C, Bauer S, Brand M, et al. Rational discovery of molecular glue degraders via scalable chemical profiling. Nat Chem Biol. 2020;16(11):1199–1207.

[15] Schreiber SL. The rise of molecular glues. Cell. 2021;184(1):3–9.

[16] Bekes M, Langley DR, Crews CM. PROTAC targeted protein degraders: the past is prologue. Nat Rev Drug Discov. 2022;21(3):181–200.

[17] Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet. 2021;397(10292):2361–2371. (Note: This is a multiple myeloma trial, not directly a glue, but relevant to cereblon modulators; could replace with more specific reference if needed.)

[18] Matyskiela ME, Lu G, Ito T, et al. A novel cereblon modulator recruits GSPT1 to the CRL4(CRBN) ubiquitin ligase. Nature. 2016;535(7611):252–257.

[19] Neklesa TK, Winkler JD, Crews CM. Targeted protein degradation by PROTACs. Pharmacol Ther. 2017;174:138–144.

[20] Zengerle M, Chan KH, Ciulli A. Selective small molecule induced degradation of the BET bromodomain protein BRD4. ACS Chem Biol. 2015;10(8):1770–1777.