MOLECULAR GLUES: A NEW APPROACH TO TARGETED PROTEIN DEGRADATION

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Abstract

Targeted protein degradation (TPD) is an emerging strategy in drug discovery that aims to eliminate disease-associated proteins rather than simply inhibit their biological activity. Molecular glue degraders are small molecules that promote or stabilize interactions between two proteins, commonly an E3 ubiquitin ligase and a target protein. This interaction can lead to ubiquitination of the target protein and its subsequent degradation by the ubiquitin–proteasome system. Unlike conventional inhibitors, molecular glues may act on proteins that lack suitable binding pockets, thereby expanding the range of potential therapeutic targets. Important examples include immunomodulatory drugs such as thalidomide, lenalidomide and pomalidomide, which recruit neosubstrates to cereblon (CRBN), and anticancer sulfonamides such as indisulam, which promote the interaction of DCAF15 with the splicing factor RBM39. Advances in structural biology, chemical biology, computational modelling and high-throughput screening have improved the understanding of molecular glue mechanisms and their discovery. Despite these advances, challenges remain in predicting target selectivity, identifying suitable molecular scaffolds, understanding resistance mechanisms and minimizing unwanted protein degradation. This review discusses the mechanism of action, classification, major examples, therapeutic applications, advantages, limitations and future prospects of molecular glue degraders in modern drug discovery.

Keywords: Molecular glues, targeted protein degradation, E3 ubiquitin ligase, cereblon, ubiquitin–proteasome system, drug discovery, protein degradation, molecular pharmacology.

1. Introduction

Proteins regulate nearly every important biological process, including cell growth, metabolism, signal transduction, gene expression and immune responses. Abnormal protein expression or activity can contribute to several diseases, particularly cancer, inflammatory disorders and certain genetic conditions. Conventional drug discovery has mainly focused on small molecules that bind to functional sites of proteins and inhibit their activity. However, some disease-associated proteins lack suitable binding pockets, making them difficult to target using conventional approaches. These proteins are often described as *undruggable targets* [1,2].

Targeted protein degradation has emerged as an alternative approach that aims to remove specific proteins from cells. Instead of continuously blocking a protein's function, this strategy uses the cell's natural protein degradation machinery to eliminate the target. Two important approaches in this field are proteolysis-targeting chimeras (PROTACs) and molecular glue degraders [1,3].

Molecular glues are generally small, monovalent compounds that promote or stabilize interactions between proteins that would otherwise interact weakly or not efficiently. In targeted

degradation, they can bring an E3 ubiquitin ligase into proximity with a target protein, resulting in ubiquitination and proteasomal degradation [2,4]. This approach has gained considerable attention because it can expand the range of proteins accessible to drug discovery and may offer advantages in molecular size and drug-like properties.

The discovery of the interaction between thalidomide-related drugs, cereblon and specific target proteins has been particularly important in establishing the therapeutic potential of molecular glue degraders. Further studies involving anticancer sulfonamides have demonstrated that different chemical classes can induce selective protein degradation through distinct E3 ubiquitin ligases [5–8].

2. Aim and Objectives

2.1 Aim

To review the mechanism, development, therapeutic applications, advantages and limitations of molecular glues as an emerging approach to targeted protein degradation.

2.2 Objectives

1. To explain the basic principles of molecular glue-mediated protein degradation.
2. To describe the role of E3 ubiquitin ligases and the ubiquitin–proteasome system.
3. To discuss established examples of molecular glue degraders.
4. To evaluate their potential applications in cancer and other diseases.
5. To examine current challenges and future opportunities in molecular glue drug discovery.

3. Overview of Targeted Protein Degradation

Targeted protein degradation is a therapeutic strategy that exploits endogenous cellular systems to remove selected proteins. In the ubiquitin–proteasome pathway, proteins are marked for degradation through the attachment of ubiquitin molecules. This process involves three main enzyme classes: E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes and E3 ubiquitin ligases.

E3 ubiquitin ligases play a particularly important role because they help recognize substrates and facilitate the transfer of ubiquitin. When a target protein receives an appropriate ubiquitin signal, it may be recognized and degraded by the 26S proteasome [1,3].

Molecular glue degraders modify this process by promoting an interaction between an E3 ligase complex and a target protein. The target may then become a neosubstrate, meaning a protein recruited for recognition and degradation through the action of the compound.

An important distinction is that not every molecular glue causes degradation. Some stabilize protein–protein interactions without inducing ubiquitination or proteasomal breakdown. Therefore, molecular glue-mediated targeted degradation represents a specific functional category within the broader molecular glue concept [2,4].

4. Mechanism of Action of Molecular Glue Degraders

The mechanism of molecular glue degraders can be divided into the following steps.

4.1 Binding to the protein complex

The molecular glue binds to one protein, commonly a component of an E3 ubiquitin ligase complex. In some systems, the compound interacts with a target protein or a composite surface formed by two proteins.

4.2 Formation of a productive protein–protein interaction

The compound promotes or stabilizes the interaction between the E3 ligase and the target protein. The resulting complex brings the two proteins into a suitable spatial arrangement.

4.3 Ubiquitination of the target protein

The E3 ligase complex facilitates the attachment of ubiquitin molecules to the target protein. The nature and extent of ubiquitination influence whether the protein is directed toward degradation.

4.4 Proteasomal degradation

The ubiquitinated target is recognized by the cellular proteasome and broken down into smaller peptides. This reduces the abundance of the target protein inside the cell.

4.5 Biological response

The loss of the target protein changes downstream cellular processes. Depending on the target, this may reduce cancer cell survival, alter gene expression or modify immune-cell function [1,3,5].

Mechanism summary:

Molecular glue → productive E3 ligase–target interaction → target ubiquitination → proteasomal degradation → biological response.

The selectivity of this process depends on the chemical structure of the glue, the interaction surface, the availability of the E3 ligase and target protein, and the cellular context [4,9].

5. Classification of Molecular Glues

Molecular glues can be classified according to their biological mechanism and the proteins involved.

5.1 E3 ubiquitin ligase-dependent molecular glue degraders

These compounds promote the interaction of a target protein with an E3 ubiquitin ligase, leading to ubiquitination and proteasomal degradation. They represent the most established class of molecular glue degraders.

Examples include:

- Thalidomide and its analogues, which act through cereblon (CRBN).
- Indisulam and related sulfonamides, which promote DCAF15-dependent degradation of splicing factors.
- CR8, which can promote the recruitment of cyclin K to the DDB1-associated ubiquitin ligase machinery [5–8,10].

5.2 Molecular glues that stabilize protein–protein interactions without degradation

Some molecular glues strengthen interactions between proteins to produce a biological effect without necessarily directing either protein for destruction. Such compounds are relevant to chemical biology and therapeutic research but should not automatically be classified as protein degraders [2,4].

5.3 Naturally occurring and synthetic molecular glues

Some molecular glue effects were identified through the study of naturally occurring compounds or existing drugs. Other compounds are developed or optimized synthetically to improve potency, selectivity and pharmacological properties.

The distinction between naturally discovered and rationally designed glues is important because many early examples were identified through unexpected biological effects rather than through a fully predictive design process [9,11].

6. Important Examples of Molecular Glue Degraders

6.1 Thalidomide and its analogues

Thalidomide is one of the best-studied examples of a compound with molecular glue activity. Research established cereblon as a direct target of thalidomide, linking the compound to a previously unrecognized mechanism of protein regulation [5].

Its analogues, lenalidomide and pomalidomide, are used in the treatment of selected haematological malignancies. These drugs bind to CRBN, a substrate receptor within the CRL4–CRBN E3 ubiquitin ligase complex. This interaction changes substrate recognition and promotes the degradation of proteins including IKZF1 (Ikaros) and IKZF3 (Aiolos) [6,7].

The degradation of these transcription factors alters gene-expression programmes that support the survival and proliferation of malignant plasma cells. This mechanism helps explain important aspects of the therapeutic activity of immunomodulatory drugs in multiple myeloma.

These compounds demonstrate that molecular glue activity can be therapeutically useful and that changes in a small molecule's chemical structure can influence which proteins are recruited for degradation [6,7,9].

6.2 Indisulam and related anticancer sulfonamides

Indisulam is an anticancer sulfonamide that has been investigated for its effects on cellular protein regulation. Studies showed that indisulam and related compounds promote the

interaction of the splicing factor RBM39 with DCAF15, a substrate receptor of a CUL4-based E3 ubiquitin ligase complex [8].

This interaction results in RBM39 ubiquitination and degradation. RBM39 is involved in RNA processing and pre-mRNA splicing; its depletion disrupts normal splicing programmes and can impair cancer-cell survival.

The discovery of this mechanism was significant because it demonstrated that molecular glue-mediated degradation is not restricted to CRBN. It also showed that proteins involved in RNA processing may be targeted through induced protein–protein interactions [8].

6.3 CR8 and cyclin K degradation

CR8 is a cyclin-dependent kinase inhibitor that has also been identified as a molecular glue-like degrader. It promotes the interaction of cyclin K with DDB1, a component of the CUL4–DDB1 ubiquitin ligase machinery, leading to cyclin K degradation [10].

This example illustrates that a compound originally studied for its enzyme-inhibitory activity can also produce an additional biological effect through protein degradation. Such findings have encouraged researchers to investigate existing chemical libraries for unexpected molecular glue activity.

6.4 Other emerging molecular glue degraders

Research has expanded beyond the best-known CRBN- and DCAF15-dependent examples. Investigational compounds are being studied against targets involved in transcription, cell-cycle regulation and other disease-related pathways. These include degraders directed toward proteins that are difficult to inhibit through conventional active-site binding [2,9,11].

However, the developmental status of individual compounds varies. Evidence from biochemical experiments or preclinical models does not establish clinical efficacy, and investigational molecular glues should not be described as approved medicines unless their regulatory status has been independently verified.

7. Therapeutic Applications

7.1 Cancer treatment

Cancer is one of the most developed areas for molecular glue research. Cancer cells often depend on specific transcription factors, signalling proteins and regulatory pathways for their growth and survival. Some of these proteins have proven difficult to inhibit directly.

Molecular glue degraders may provide an alternative by reducing the abundance of such proteins. The clinical use of lenalidomide and pomalidomide in selected haematological malignancies demonstrates the importance of this mechanism in cancer pharmacology [6,7].

Other compounds targeting proteins such as RBM39 and cyclin K have helped establish additional strategies for exploiting protein degradation in oncology [8,10].

7.2 Haematological malignancies

Multiple myeloma and certain other blood cancers are important indications for immunomodulatory drugs. The degradation of IKZF1 and IKZF3 contributes to their pharmacological effects, although their overall activity also depends on broader cellular and immunological mechanisms.

These medicines provide a clinically relevant example of how selective changes in protein stability can translate into therapeutic benefit [6,7].

7.3 Inflammatory and immune-related disorders

The regulation of transcription factors and immune-cell signalling proteins offers potential opportunities for molecular glue development in inflammatory and autoimmune conditions. However, the biological effects of a degrader depend on its target and tissue distribution. Selective protein removal may be beneficial in one cellular context but harmful in another.

Consequently, further research is required to establish the safety, selectivity and clinical utility of new molecular glue candidates in these diseases [2,9].

7.4 Potential applications beyond oncology

Molecular glue research may also contribute to the development of therapies for neurological disorders, infectious diseases and other conditions involving proteins that are difficult to target conventionally. These areas remain active fields of investigation, and their clinical potential will depend on identifying suitable targets, achieving adequate tissue exposure and demonstrating acceptable safety [2,11].

8. Advantages of Molecular Glue Degraders

Molecular glue degraders offer several potential advantages over conventional inhibitors and some other targeted degradation strategies.

1. **Access to difficult targets:** They may enable the degradation of proteins that lack suitable active-site binding pockets.

2. **Small-molecule design:** Many molecular glues are relatively compact compounds, which can be advantageous for physicochemical properties and drug development.

3. **Use of endogenous machinery:** They exploit cellular ubiquitination and degradation pathways rather than requiring an entirely new protein-removal system.

4. **Potentially prolonged effects:** Biological activity may persist until the target protein is resynthesized, although the duration depends on the compound, target and cellular context.

5. **Distinct mechanism of action:** Protein removal may provide an alternative when conventional inhibition is insufficient.

6. **Potential for improved selectivity:** Carefully designed compounds may recruit particular target proteins through specific molecular recognition surfaces [1,3,9].

These advantages are not guaranteed for every compound. Molecular size, cell permeability, selectivity and duration of action must be evaluated experimentally during drug development.

9. Limitations and Challenges

9.1 Difficulty in rational design

Many molecular glues have been discovered serendipitously. Predicting which small molecules will create a productive protein–protein interaction remains difficult because the process depends on complex structural and energetic relationships [9,11].

9.2 Limited understanding of target selectivity

A molecular glue may recruit more than one protein or produce unintended degradation events. Such off-target effects may lead to toxicity or reduce the therapeutic window. Detailed proteomic and mechanistic studies are therefore important.

9.3 Dependence on cellular protein machinery

The degradation process requires functional components of the relevant ubiquitin ligase system and proteasome. Variations in the expression or activity of these components may influence drug response.

9.4 Drug resistance

Resistance may arise through changes in the target protein, alterations in E3 ligase components, changes in drug transport or changes in downstream cellular pathways. These mechanisms may reduce the effectiveness of a molecular glue and require alternative treatment strategies.

9.5 Pharmacokinetic and safety considerations

A candidate must reach the relevant tissue at an effective concentration while maintaining acceptable stability, absorption, distribution, metabolism and excretion. Unintended protein degradation can also affect normal cellular functions, making safety evaluation essential.

9.6 Limited predictive screening methods

Traditional screening approaches may fail to identify molecular glues if the resulting activity is not detected by standard enzyme-inhibition assays. Integrated methods that assess protein interactions, degradation, cellular activity and selectivity are needed to improve discovery [9,11].

10. Emerging Strategies for Molecular Glue Discovery

Recent research is moving from accidental discovery toward more systematic identification and optimization.

10.1 Structure-based drug design

Structural biology can reveal the interaction surfaces formed by a molecular glue, an E3 ligase and a target protein. Structural information may help researchers identify chemical modifications that improve interaction strength and selectivity.

10.2 High-throughput screening

Large chemical libraries can be screened for compounds that induce protein degradation or alter protein–protein interactions. Follow-up studies are necessary to determine whether the observed effect is selective and dependent on the intended degradation machinery.

10.3 Chemical proteomics

Proteomic techniques can measure changes in protein abundance across the cell. These approaches help identify degraded targets, detect off-target effects and investigate the mechanisms responsible for a compound's biological activity.

10.4 Computational methods and artificial intelligence

Molecular modelling, docking, machine learning and other computational approaches may help prioritize compounds and predict suitable interaction surfaces. However, computational predictions must be validated through biochemical and cellular experiments.

10.5 Rational chemical optimization

Structure–activity relationship studies can identify how changes in a compound's chemical structure affect binding, degradation potency and selectivity. This is particularly important when a compound recruits multiple potential substrates [9,11,12].

11. Future Perspectives

The future of molecular glue research will depend on improving the predictability of compound discovery and understanding the biological factors that determine selective degradation. Better structural information, more comprehensive proteomic analysis and improved computational models may help researchers discover new molecular glues more efficiently.

An important goal is to expand the range of proteins that can be targeted. Current examples demonstrate that molecular glues can recruit transcription factors and RNA-processing proteins for degradation. Identifying new E3 ligases and understanding their substrate-recognition properties may create additional opportunities for drug development.

Another important area is the development of compounds with improved selectivity and reduced toxicity. This will require careful assessment of target engagement, degradation efficiency, cellular responses and off-target protein loss. Biomarkers may also help identify patients who are more likely to respond to a particular degrader.

Finally, future studies should distinguish clearly between preclinical promise and proven clinical benefit. Although established immunomodulatory drugs provide strong clinical evidence for the therapeutic value of molecular glue mechanisms, many newer candidates still require extensive clinical evaluation [1,9,11].

12. Conclusion

Molecular glue degraders represent an important development in targeted protein degradation and modern drug discovery. By promoting productive interactions between proteins, these small molecules can redirect selected cellular proteins toward ubiquitination and proteasomal

degradation. This mechanism differs from conventional inhibition and provides opportunities to target proteins that are difficult to address using traditional drug-discovery methods.

The clinical success of immunomodulatory drugs and the discovery of DCAF15-dependent degraders have demonstrated the biological and therapeutic relevance of molecular glue mechanisms. Nevertheless, challenges involving rational design, target selectivity, resistance and safety remain. Continued progress in structural biology, chemical proteomics, computational modelling and medicinal chemistry may support the development of more selective and effective molecular glue degraders. Overall, this approach represents a promising, but still evolving, area of pharmaceutical research.

References

1. Tsai JM, Nowak RP, Ebert BL, Fischer ES. Targeted protein degradation: from mechanisms to clinic. *Nature Reviews Molecular Cell Biology*. 2024;25:740–757. doi:10.1038/s41580-024-00729-9.

2. Lemaitre T, Cornu M, Schwalen F, Since M, Kieffer C, Voisin-Chiret AS. Molecular glue degraders: exciting opportunities for novel drug discovery. *Expert Opinion on Drug Discovery*. 2024;19(4):433–449. doi:10.1080/17460441.2024.2306845.

3. Sakamoto KM, Kim KB, Kumagai A, Mercurio F, Crews CM, Deshaies RJ. Protacs: chimeric molecules that target proteins to the Skp1–Cullin–F box complex for ubiquitination and degradation. *Proceedings of the National Academy of Sciences of the United States of America*. 2001;98(15):8554–8559. doi:10.1073/pnas.141230798.

4. Słabicki M, Kozicka Z, Petzold G, et al. The CDK inhibitor CR8 acts as a molecular glue degrader that depletes cyclin K. *Nature*. 2020;585:293–297. doi:10.1038/s41586-020-2374-x.

5. Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. *Science*. 2010;327(5971):1345–1350. doi:10.1126/science.1177319.

6. 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. doi:10.1126/science.1244851.

7. 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. doi:10.1126/science.1244917.

8. Han T, Goralski M, Gaskill N, et al. Anticancer sulfonamides target splicing by inducing RBM39 degradation via recruitment to DCAF15. *Science*. 2017;356(6336). doi:10.1126/science.aal3755.

9. Oleinikovas V, Gainza P, Ryckmans T, Fasching B, Thomä NH. From thalidomide to rational molecular glue design for targeted protein degradation. *Annual Review of Pharmacology and Toxicology*. 2024;64:291–312. doi:10.1146/annurev-pharmtox-022123-104147.

10. Uehara T, Minoshima Y, Sagane K, et al. Selective degradation of splicing factor CAPERα by anticancer sulfonamides. *Nature Chemical Biology*. 2017;13:675–680. doi:10.1038/nchembio.2363.

11. Kumar SH, Venkatachalapathy M, Sistla R, Poongavanam V. Advances in molecular glues: exploring chemical space and design principles for targeted protein degradation. *Drug Discovery Today*. 2024;29(11):104205. doi:10.1016/j.drudis.2024.104205.

12. Liu Y, Bai J, Li D, Cang Y. Routes to molecular glue degrader discovery. *Trends in Biochemical Sciences*. 2025. doi:10.1016/j.tibs.2024.12.006.

13. Molecular glue-mediated targeted protein degradation: a novel strategy in small-molecule drug development. *iScience*. 2024;27(9):110712. doi:10.1016/j.isci.2024.110712.

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