Dean&Francis
ISSN 2959-409X

Mechanisms of Molecular Glue Degraders and Their Applications in Hematological Malignancies

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Abstract:

Molecular glue degraders (MGDs) belong to a category of small-molecule compounds that bring E3 ubiquitin ligases and target proteins close to each other, thereby initiating the ubiquitination process and the subsequent breakdown of the target proteins. In the past few years, these substances have shown considerable therapeutic potential in the treatment of hematological malignancies. This review comprehensively summarizes the action mechanisms of MGDs, sorts out their preclinical and clinical advances in hematological cancers, and explores the existing challenges as well as future development directions. MGDs offer a new approach for cancer treatment, yet further research is needed to clarify their resistance mechanisms and improve the precision of target selection.

Keywords: Molecular glue degraders, E3 ubiquitin ligase, Hematological malignancies, Targeted protein degradation, Resistance mechanisms

1. Introduction

1.1 Evolution of Drug Discovery: From Inhibition to Degradation

Traditional drug discovery strategies primarily focus on inhibiting the active sites of disease-related proteins to exert therapeutic effects[1].Although this approach has achieved considerable success, its inherent limitations have become increasingly apparent, including the problem of drug resistance and the difficulty in targeting proteins that cannot be bound by conventional means[1,2].To solve these problems, targeted protein degradation (TPD) has emerged as a new drug development mode. TPD makes full use of the cell's inherent protein clearance mechanism, especially the ubiquitin–proteasome system, to specifically break down all pathogenic proteins involved[1,3].

The shift from inhibition to degradation represents a fundamental transformation in pharmacological strategy.This is not merely an incremental improvement but a conceptual leap, as degradation offers a catalytic mechanism whereby a single degrader molecule can eliminate multiple copies of a target protein. This catalytic efficiency, combined with the ability to abolish all functions of a protein, provides enhanced therapeutic efficacy and addresses drug resistance. Consequently, it significantly expands the druggable proteome and opens new avenues for treating previ-

ISSN 2959-409X

ously intractable diseases[2,3].

1.2 Definition of Molecular Glue Degraders (MGDs)

Molecular glue degraders function as small compounds that promote or stabilize new protein–protein contacts between E3 ubiquitin ligases and desired substrates, resulting in ubiquitination and later proteasomal breakdown of the targeted protein[1].In contrast to bifunctional PROTACs, which link two binding moieties through a chemical bridge, MGDs usually act as single-site small molecules that reshape the surface of E3 ligases to support novel binding events[1,4]. This structural feature often provides MGDs with more favorable druglike traits, including enhanced oral absorption, cellular membrane crossing ability, and tissue distribution capacity[1].The phrase "molecular glue" was first applied to natural compounds such as cyclosporin A and FK506, which mediate the association of protein pairs[4].

The mechanism of molecular glues extends beyond simple binding and involves active remodeling of E3 ligase surfaces to promote novel interactions.This fundamentally distinguishes them from classical inhibitors, enabling E3 ligases to recognize and ubiquitinate non-native substrates.This proximity-induced effect represents a dynamic "induced fit" model mediated by small molecules[5,6].

2. Mechanisms of Molecular Glue Degraders

2.1 The Ubiquitin–Proteasome System as the Core Mechanism

The Ubiquitin-Proteasome System (UPS) serves as the primary intracellular route for targeted protein breakdown and is vital for sustaining cellular protein homeostasis[1]. This system relies on a sequential cascade of enzymatic reactions, namely E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases [1,3].Among these enzyme groups, E3 ligases play a pivotal part in identifying substrate proteins and mediating the transfer of ubiquitin to target proteins[1].Once a target protein is marked by polyubiquitination, it will be recognized and degraded by the 26S proteasome[1].

The efficacy of MGDs arises from their catalytic induction of ubiquitination.Unlike stoichiometric inhibitors, MGDs can dissociate after promoting polyubiquitination, allowing a single molecule to degrade multiple targets[1].This catalytic property is key to sustained target depletion and overcoming resistance[7].

2.2 Key E3 Ligases Utilized by MGDs

Although over 600 E3 ligases are encoded in the human genome, only a few have been successfully harnessed for MGD-mediated degradation[1,3].

2.2.1 Cereblon (CRBN): A Pioneer Ligase

CRBN is part of the CRL4CRBN E3 ligase complex and is the most well-characterized and clinically validated MGD target[1,6].Thalidomide and its analogs bind CRBN, alter its conformation, and recruit neosubstrates such as IKZF1/3 and CK1α for degradation[1,8].Structural studies have elucidated ligand-induced binding pockets and conformational changes in CRBN[5,6].

2.2.2 DCAF15

DCAF15 is another E3 adaptor protein that can be hijacked by sulfonamide molecular glues to degrade RBM39[9,10].

2.2.3 β-TrCP

β-TrCP belongs to the F-box family within the SCF E3 ligase assembly, and took part in early proofofconcept investigations of targeted protein degradation.[3].

2.2.4 SIAH1

SIAH1 is an E3 ligase targeted by molecular glues to degrade the oncogenic transcription factor BCL6 in lymphoma[11].

Although the human genome contains more than 600 distinct E3 ubiquitin ligase proteins, only a small number (such as CRBN, DCAF15, β-TrCP, and SIAH1) have been successfully employed in molecular glue-mediated protein degradation.The limited utilization of E3 ligases highlights significant untapped potential for future MGD discovery[1,3].

Expanding the E3 ligase repertoire is essential for targeting a broader range of undruggable proteins and achieving tissue-specific degradation[12].

2.3 Mechanistic Classification of MGDs

MGDs can be broadly classified based on how they modulate protein–protein interactions[4].

Type I (Occluding): These trigger non-native interactions, which in turn physically hinder the inherent activity of endogenous proteins[4].

Type II (Redirecting): These compounds bind existing interactions and redirect their conformation or dynamics[4].

Type III (Neomorphic): These induce novel interactions that generate new activities such as ubiquitination[4].

This classification highlights that molecular glues represent a broader concept beyond targeted degradation.They encompass small molecules that induce or stabilize protein

interactions to achieve diverse functional outcomes[4,6].

3. Applications of MGDs in Hematological Malignancies

3.1 Multiple Myeloma (MM)

Multiple myeloma is a plasma cell malignancy with significantly improved outcomes due to novel therapies[12].

3.1.1 Approved IMiDs

The molecular glue mode of action of thalidomide and its related compounds was clarified long after these agents were first identified.[1,6].Lenalidomide exhibits greater potency and improved safety compared to thalidomide[1]. Pomalidomide further enhances efficacy and overcomes resistance[1,13].

3.1.2 Next-Generation CELMoDs

Mezigdomide (CC-92480) serves as a new type of CELMoD that regulates CRBN E3 ligase, engineered to boost the breakdown of IKZF1/3. It shows strong growth-inhibiting and tumor-killing effects in MM cell lines resistant to lenalidomide or pomalidomide [14]. This drug is now being tested in Phase III trials for relapsed and refractory multiple myeloma [14].

Iberdomide (CC-220) represents an additional CELMoD compound, which binds CRBN more strongly and degrades IKZF1/3 more effectively than lenalidomide and pomalidomide [1,15]. It is now under Phase I/II/III clinical evaluation for the treatment of MM and non-Hodgkin lymphoma [15].

CFT-7455 is an advanced degrader that acts on IKZF1/3 via the CRBN E3 ligase. Preclinical research has confirmed its excellent physical and chemical traits, pharmacokinetic features, and oral absorption ability [1]. This candidate is presently being assessed in Phase I/II trials for MM and NHL [1].

The development of next-generation CELMoD agents (e.g., mezigdomide and iberdomide) directly addresses the challenge of IMiD resistance by delivering enhanced potency and improved degradation properties [13,14]. This reflects an ongoing evolutionary cycle in drug development, in which insights into resistance mechanisms (e.g., CRBN mutations or reduced target protein binding affinity) directly guide the design of more effective compounds [13,16].

3.2 Acute Myeloid Leukemia (AML) and Myelodysplastic Syndromes (MDS)

MGDs are also being explored in aggressive malignancies such as AML and MDS[12,17].

3.2.1 CC-90009 (GSPT1 Degrader)

CC-90009 is a CRBN-based molecular glue degrader (MGD) that selectively targets GSPT1 and induces apoptosis in AML cells [1]. Nevertheless, the clinical trial (NCT02848001) targeting relapsed or refractory AML/MDS was halted because of limited therapeutic effect in acute short-term treatment [18].

Although molecular glue degraders hold great promise as a therapeutic modality, the termination of the CC-90009 clinical trial owing to inadequate short-term efficacy highlights that not all molecular glue degraders can be successfully translated into clinical agents, even with strong preclinical rationale. This underscores the complexities of in vivo drug activity, pharmacokinetics, and patient heterogeneity, indicating that target validation and clinical trial design remain critical hurdles despite innovative mechanisms of action [18].

3.2.2 E7820 (RBM39 Degrader)

E7820, a sulfonamide-derived small molecular glue, facilitates the breakdown of splicing factor RBM39 through DCAF15 [9,10]. A Phase II clinical trial (NCT05024994) targeting splicing factor-mutated myeloid malignancies has been completed [9].

3.2.3 BMS-986397 (CK1α Degrader)

BMS-986397 is a novel CRBN-recruiting CELMoD capable of degrading CK1α, leading to p53 stabilization and apoptosis in TP53 wild-type AML/MDS cells [19]. This agent exhibits potent antiproliferative activity in preclinical models [19].

3.3 Lymphoma

Molecular glue degraders are also being explored in various lymphoma subtypes, including non-Hodgkin lymphoma (NHL) and diffuse large B-cell lymphoma (DLBCL) [12,17].

3.3.1 CC-122 (Avadomide) and CC-99282 (Golcadomide)

CC-122 (Avadomide) and CC-99282 (Golcadomide) are CRBN-based molecular glue degraders (MGDs) that triggering the breakdown of IKZF1/3 and ZFP91, and demonstrate antitumor activity in NHL and multiple myeloma (MM) [1]. Golcadomide in combination with R-CHOP exhibits potent antitumor activity in aggressive B-cell lymphomas [20].

3.3.2 BCL6 Degraders (e.g., BI-3802)

Molecular glue degraders target BCL6, a key oncogenic transcription factor in lymphomas, by inducing BCL6 polymerization and subsequent degradation mediated by the SIAH1 E3 ligase [11]. Preclinical studies have shown

ISSN 2959-409X

promising results in lymphoma cells [11].

The success of molecular glue degraders in lymphoma therapy highlights the great potential of targeting transcription factors, which are often regarded as "undruggable" with traditional inhibitors, as they lack clearly defined functional binding regions [2,17]. Through promoting new protein–protein associations, such degraders make these essential regulatory proteins accessible to pharmacological intervention [11].

3.4 Combination Therapies of MGDs

Molecular glue degraders (MGDs) are now frequently studied alongside other conventional therapeutic drugs, such as proteasome inhibitors, anti-CD38 antibodies, and chemotherapeutic drugs, to enhance efficacy and overcome drug resistance [12,17]. Examples include the combination of mezigdomide with bortezomib/carfilzomib and dexamethasone in multiple myeloma (MM) [14], pairing iberdomide with daratumumab/bortezomib and dexamethasone for MM management [15], and golcadomide with RCHOP in lymphomas [20].

The trend of combining molecular glue degraders with other standard treatment regimens suggests synergistic effects between their unique protein degradation mechanism and existing therapies [12]. This strategy aims to target vulnerable points in cancer cells through distinct pathways of action, thereby improving response rates, achieving deeper and more durable remissions (e.g., minimal residual disease negativity in multiple myeloma), and potentially overcoming or delaying the emergence of resistance to monotherapy [15,20].

Table 1 Major Molecular Glue Degraders in Clinical Trials for Hematologic Malignancies

Drug Name	Target Protein(s)	Recruited E3 Ligase	Indication (Hematologic Malignancy-Related)	Current Clinical Stage	Key Findings/Status
Mezigdomide (CC-92480)	IKZF1/3	CRBN	Relapsed/Refractory Multiple Myeloma (RRMM)	Phase III	Exhibits enhanced activity in IMiD-resistant MM cell lines; early clinical trial data demonstrates significant activity and manageable safety profile in heavily pretreated patients [14].
Iberdomide (CC-220)	IKZF1/3	CRBN	Multiple Myeloma (MM), Non-Hodgkin Lymphoma (NHL)	Phases I/II/III	Possesses higher CRBN binding affinity and more potent IKZF1/3 degradation efficacy compared with lenalidomide and pomalidomide [1,15].
CC-90009	GSPT1	CRBN	Acute Myeloid Leukemia (AML), Myelodysplastic Syndromes (MDS)	Phase II (Discontinued)	Clinical trial terminated due to insufficient efficacy in the short-term acute setting [18].
E7820	RBM39	DCAF15	Splicing factor-mutated myeloid malignancies (AML, MDS, CMML)	Phase II (Completed)	Induces RBM39 degradation in preclinical models and shows favorable tolerability in clinical trials [9].
CFT-7455	IKZF1/3	CRBN	MM, NHL	Phases I/II	Demonstrates favorable physicochemical and pharmacokinetic properties in preclinical studies; currently under evaluation in clinical trials for MM and NHL [1].
Golcadomide (CC-99282)	IKZF1/3, ZFP91	CRBN	NHL, MM	Phases I/II	Shows potent antitumor activity in combination with R-CHOP in aggressive B-cell lymphomas [20].
BMS-986397	CK1α	CRBN	TP53 wild-type AML, High-risk MDS	Preclinical	Exhibits strong antiproliferative activity in preclinical models; induces p53 stabilization and apoptosis via CK1α degradation [19].
BI-3802	BCL6	SIAH1	Lymphoma	Preclinical	Induces BCL6 polymerization and degradation, showing promising results in preclinical studies [11].

4. Resistance Mechanisms of Molecular Glue Degraders

4.1 CRBN-Mediated Resistance

Loss or mutation of CRBN represents a common mechanism underlying resistance to IMiDs and next-generation CELMoD agents [13,16]. In particular, specific CRBN mutations (such as exon 10 deletions) can lead to reduced drug-binding capacity or altered substrate specificity [16]. The identification of CRBN mutations as a major driver of resistance underscores the importance of genomic profiling in patient selection and therapeutic stratification. Knowledge of the CRBN mutational status in individual patients enables the prediction of response to IMiD-based therapies. This allows clinicians to avoid ineffective regimens and direct patients toward next-generation CELMoDs specifically designed to overcome these distinct resistance mechanisms [13,16]. Such molecular insights directly inform clinical decision-making, thereby facilitating precision medicine.

4.2 Target Protein Alterations

Mutations within the degradation-competent regions of target proteins (e.g., IKZF3) can prevent their recognition by the E3 ligase–MGD complex, resulting in drug resistance [8,13]. Furthermore, overexpression of target proteins may saturate the degradation machinery and attenuate therapeutic efficacy.

4.3 Efflux Pump- and Pharmacokinetics-Mediated Resistance

Drug efflux pumps (such as P-glycoprotein/MDR1) with elevated expression levels lower the intracellular drug content, which in turn leads to the development of drug resistance [7]. This represents a well-established mechanism of multidrug resistance in cancer.

5. Future Directions and Challenges

5.1 Rational Design and Discovery of Novel MGDs

The discovery of early molecular glue degraders was largely serendipitous, but the field is gradually shifting toward more rational design strategies [4,5]. These include ligand-based, structure-based, and fragment-based drug design approaches, as well as computational modeling. A crucial direction for future molecular glue discovery is expanding the range of E3 ligases used, moving beyond the currently dominant CRBN [1,3].

The sector is evolving from accidental discovery to the intentional, methodical design of molecular glue degraders. This shift, enabled by a deeper understanding of ternary complex formation and E3 ligase biology, is expected to accelerate the identification of novel molecular glue degraders and improve their specificity, potency, and pharmacokinetic profiles [5,6].

5.2 Safety and Off-Target Effects

The development of molecular glue degraders faces safety challenges, particularly the historical teratogenicity of thalidomide, which is closely linked to its CRBN-binding mechanism [6]. In addition, potential off-target degradation and nonspecific binding to E3 ligases remain issues to be addressed to enhance drug selectivity and minimize adverse reactions [1,3].

5.3 Expansion of Therapeutic Scope Beyond Hematologic Malignancies

Molecular glue degraders also show broad therapeutic potential beyond hematologic malignancies, including solid tumors, neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease), and infectious diseases [2,17].

6. Conclusion

Molecular glue degraders (MGDs) have brought about a profound shift in the landscape of drug discovery, introducing a transformative new approach. Their distinct catalytic mode of action grants them unparalleled potential in the targeted breakdown of specific proteins. In the treatment of hematologic malignancies, MGDs have made notable advances; particularly, thalidomide and its derivatives have been successfully used to treat multiple myeloma, while next-generation CELMoD agents have also shown promising clinical results. By modifying the surface of E3 ubiquitin ligases, these compounds exert their antitumor effects, enabling the selective degradation of target proteins—many of which are transcription factors once considered "undruggable" with conventional therapeutic methods.

Despite the considerable advantages of MGDs, resistance mechanisms (such as CRBN mutations, target protein alterations, and upregulation of drug efflux pumps), along with off-target effects and safety concerns, remain key challenges in the field [7,13]. Nevertheless, fueled by deeper mechanistic insights and advances in rational design strategies, researchers are actively developing MGDs with improved specificity, potency, and safety profiles [4,5]. Furthermore, combination regimens pairing MGDs

ISSN 2959-409X

with standard therapies are expected to enhance efficacy via synergistic interactions, overcome drug resistance, and achieve deeper disease remissions [15,20].

Looking ahead, the therapeutic potential of molecular glue degraders extends far beyond hematologic malignancies. Their ongoing investigation in solid tumors, neurodegenerative diseases, and infectious disorders underscores significant potential in tackling numerous unmet clinical demands [2,17]. Through continued scientific research and technological innovation, MGDs are poised to further expand the druggable proteome and deliver additional breakthrough therapeutic options for human health.

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