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RESEARCH ARTICLE

MOLECULAR GLUES FOR TARGETED PROTEIN DEGRADATION: A NEW PARADIGM BEYOND CONVENTIONAL PROTACS

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ABSTRACT

Targeted protein degradation (TPD) represents a transformative therapeutic modality that exploits the intracellular ubiquitin-proteasome system (UPS) to selectively eliminate disease-causing proteins. Within the TPD landscape, two distinct mechanistic classes have emerged: Proteolysis-Targeting Chimeras (PROTACs), bifunctional heterodimeric molecules that bridge a protein of interest (POI) with an E3 ubiquitin ligase via a chemical linker; and molecular glues, typically monofunctional small molecules that stabilize neo-substrate recruitment on the surface of an E3 ligase through induced protein-protein interaction interfaces. While PROTACs offer unparalleled modularity and rational design accessibility, molecular glues, exemplified by the immunomodulatory drug (IMiD) class and next-generation cereblon E3 ligase modulators (CELMoDs), have accumulated the most robust clinical validation in the field, including multiple FDA and EMA approvals for hematological malignancies. This review provides a comprehensive and critical comparative analysis of both paradigms, covering mechanism of action at atomic resolution, structural basis of E3 ligase recruitment, pharmacological properties, resistance mechanisms, and clinical development status. This review position as a compelling and clinically superior paradigm for targeted protein degradation, while acknowledging the complementary strengths that both classes offer to the broader TPD therapeutic landscape.

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INTRODUCTION

The dominant paradigm of small-molecule drug discovery, rooted in occupancy-based inhibition of enzymatically active protein targets, faces fundamental and increasingly recognized limitations (1). Conventional inhibitors must maintain continuous, stoichiometric target engagement for efficacy; are susceptible to resistance from target mutations that diminish drug binding (2). The~75% of the proteome — encompassing transcription factors, scaffolding proteins, proteins with flat or disordered interaction surfaces, and proteins that function through protein-protein interactions (PPIs) — constitutes the 'undruggable' proteome, representing an enormous reservoir of high-value therapeutic targets that have been inaccessible to conventional drug discovery (3). Targeted protein degradation (TPD) redefines this paradigm by co-opting the cell's endogenous protein quality control machinery — the ubiquitin-proteasome system (UPS) — to achieve complete, catalytic elimination of disease-driving proteins(4). This 'event-driven' pharmacology confers three fundamental advantages over occupancy-based inhibition: first, catalytic substoichiometric dosing (one degrader molecule can eliminate many copies of the target before recycling); second, simultaneous ablation of all protein functions (kinase, scaffolding, and PPI roles); and third, a distinct resistance profile that allows degradation of mutant proteins that have escaped conventional inhibitors (5). Two mechanistically distinct classes of TPD agents have emerged as the leading approaches: PROTACs, first reported by Sakamoto *et al*. in 2001 and formally conceptualized by the Crews (6)and Deshaies laboratories, are bifunctional molecules comprising a target-binding warhead and an E3 ligase ligand connected by a chemical linker; and molecular glues, a term applied to small molecules that stabilize or induce protein-protein interactions between an E3 ligase and a neo-substrate, often without covalently linking the interacting partners (7). The IMiD (immunomodulatory drug) class — thalidomide, lenalidomide, and pomalidomide — represents the most clinically mature molecular glue degraders, with their mechanism of action involving CRBN-mediated ubiquitination of IKZF1, IKZF3, and CK1α revealed through landmark structural studies in 2014(8). This review provides an integrated and comprehensive analysis of both platforms, with particular emphasis on the unique features of molecular glues that position them as a compelling and potentially superior paradigm for TPD drug discovery. We cover structural mechanisms, approved therapeutics, active clinical trials, resistance biology, and emerging rational design strategies, providing an authoritative reference for researchers and

clinicians engaged in the rapidly expanding targeted protein degradation field.

Biological Basis: The Ubiquitin-Proteasome System

The ubiquitin-proteasome system represents the principal intracellular regulated proteolysis and protein quality control machinery in eukaryotes, responsible for the turnover of approximately 70–80% of all cellular proteins(9). Ubiquitin, a 76-amino acid protein with >96% sequence conservation from yeast to humans, is conjugated to substrate proteins through an enzymatic cascade: E1 ubiquitin-activating enzymes (two in humans) form a thioester-linked ubiquitin intermediate; E2 ubiquitin-conjugating enzymes (~30 human E2s) receive ubiquitin from E1 and serve as donors to E3 ubiquitin ligases; and E3 ubiquitin ligases (>600 human E3s) catalyze the final transfer of ubiquitin to specific lysine residues on substrate proteins, providing the substrate specificity of the entire cascade (10). E3 ligases are organized into three major structural classes: RING (Really Interesting New Gene)-type E3s, which constitute ~90% of human E3 ligases and catalyze direct ubiquitin transfer from the E2 without forming a covalent E3-ubiquitin intermediate; HECT (Homologous to E6AP Carboxyl Terminus)-type E3s, which form a thioester-linked intermediate with ubiquitin before transfer; and the hybrid RBR (RING-Between-RING) family(11). The RING-type Cullin-RING Ligases (CRLs) — comprising Cullin scaffold proteins (CUL1-5, CUL7), adaptor proteins (e.g., DDB1, Elongin B/C), substrate receptor proteins (e.g., CRBN, VHL, FBXW7), and the RING-box protein RBX1 — represent the largest and most therapeutically important subfamily, with substrate specificity determined by the exchangeable substrate receptor component (12). For TPD, the CRL4A-CRBN complex is the dominant therapeutic target, recruited by IMiDs, CELMoDs, and the majority of CRBN-based PROTACs(13). Substrate recognition requires post-translational modification of Cullin by NEDD8 (neddylation), which activates the E3 complex and enables productive E2-ubiquitin positioning(14). This neddylation dependency is therapeutically exploitable: the NEDD8-activating enzyme inhibitor MLN4924 (pevonedistat) blocks all CRL activity and can be used to validate CRL-dependency of TPD mechanisms, or combined with PROTACs at sub-maximal doses to enhance efficacy (15).

PROTACs: Mechanism, Advantages, and Pharmacological Challenges

Structural Architecture and Ternary Complex Formation: PROTACs are heterobifunctional molecules comprising three covalently connected pharmacophoric elements: a warhead that engages the POI at a ligandable surface (active site, allosteric site, or binding groove); an E3 ligase-recruiting ligand; and a linker of variable length, rigidity, and chemical composition that positions the two binding elements for productive ternary complex geometry(17, 18). The warhead and E3 ligand are typically derived from known target-binding compounds (often inhibitors) and E3-recruiting ligands (pomalidomide/lenalidomide for CRBN, VH032 and related derivatives for VHL, nutlin-3 derivatives for MDM2)(19). The linker chemistry — ranging from flexible PEG chains to rigid alkyl chains to heterocyclic spacers — critically determines the conformational landscape of the ternary complex and thereby the efficiency of ubiquitin transfer(20, 21).The formation of a productive ternary complex — in which the POI and E3 ligase are bridged by the PROTAC and the E2-ubiquitin thioester is positioned within transfer distance of a surface-exposed POI lysine — is the key rate-limiting step in PROTAC efficacy and constitutes the most challenging aspect of PROTAC design(4, 22).

Clinical Advances and Landmark Achievements: Clinical translation of PROTACs has been remarkable given the recency of the technology. ARV-110 (Bavdegalutamide)(23), targeting the androgen receptor (AR) via CRBN, was the first PROTAC to enter human clinical trials and demonstrated pharmacodynamic evidence of AR degradation in circulating tumor cells in Phase I/II. ARV-471 (vepdegestrant)(24), co-developed by Arvinas and Pfizer, progressed to Phase III clinical trials for ER+/HER2- metastatic breast cancer — the first PROTAC to achieve this milestone — following Phase I data demonstrating >90% ERα degradation and clinical activity including in ESR1-mutant disease.The spectrum of indications being addressed by PROTAC clinical trials has rapidly expanded beyond hematological malignancies and breast/prostate cancer to include inflammatory disease (KT-474 for IRAK4 in atopic dermatitis)(25), pediatric solid tumors (CFT8634 for BRD9 in synovial sarcoma)(26), and B-cell malignancies (NX-2127 targeting both BTK and IKZF1/3 simultaneously — a dual-degradation concept unique to PROTACs) (27).

Pharmacological Limitations: Despite clinical progress, PROTACs face well-characterized pharmacological challenges that distinguish them from conventional small molecules and molecular glues(28, 29). Their large molecular weight (700–1100 Da), high number of rotatable bonds (15–30), and multiple hydrogen bond donors/acceptors place them firmly beyond Lipinski's Rule of Five (Ro5) space, resulting in generally poor aqueous solubility, limited membrane permeability, susceptibility to P-glycoprotein efflux (ABCB1), and poor oral bioavailability in unformulated settings. The 'beyond Ro5' (bRo5) chemical space presents formulation challenges that have required the development of amorphous solid dispersions, nanoparticle formulations, and prodrug strategies to achieve therapeutically relevant systemic exposures following oral administration.The 'hook effect' — the paradoxical reduction in degradation activity at high PROTAC concentrations — arises when excess PROTAC molecules saturate either the POI or the E3 ligase independently, forming non-productive binary complexes that compete with the productive ternary complex(30, 31). This creates a bell-shaped concentration-response relationship that can be mistaken for cellular toxicity and complicates the identification of optimal clinical dosing. The hook effect is absent in molecular glue systems operating through monovalent binding, representing a meaningful pharmacodynamic advantage for glue-based degraders.

Molecular Glues: Mechanism, Classification, and Clinical Superiority

Atomic-Resolution Mechanism: The mechanistic basis of molecular glue activity has been most completely elucidated for the CRBN-IMiD-IKZF1/3 system through a series of landmark structural studies. Crystal structures of CRBN bound

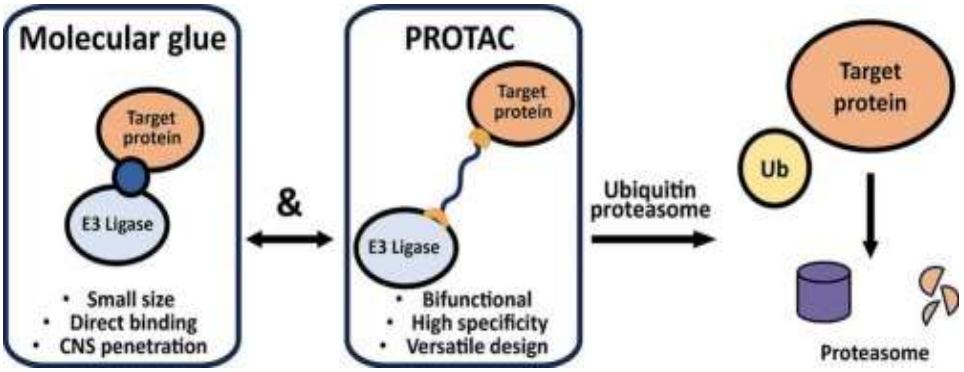

Figure 1. Molecular glues and PROTACs in targeted protein degradation (TPD) Figure adapted from Eladl, 2025 (16)

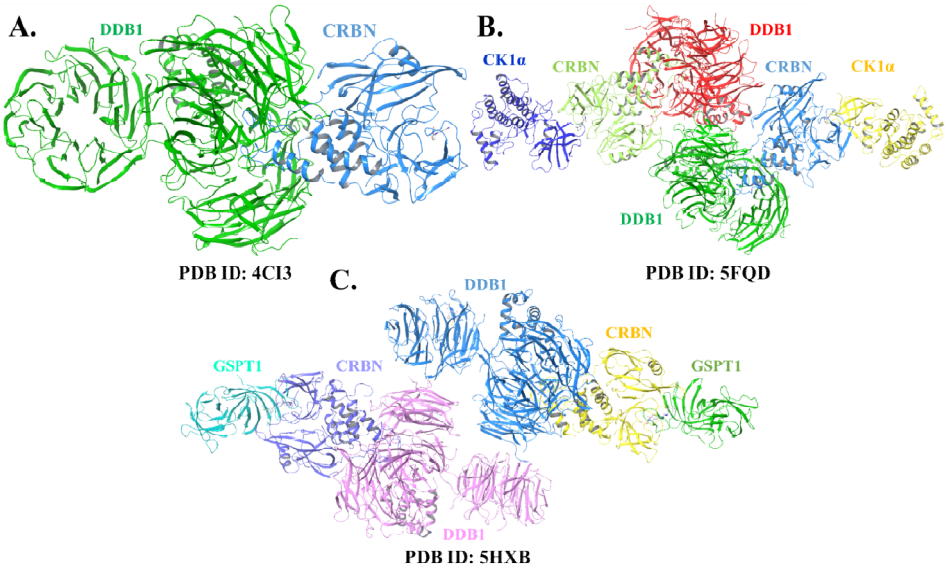

Figure 2. Reported crystallography structures of PROTACs (A)DDB1-CRBN E3 ubiquitin ligase bound to Pomalidomide; (B) Lenalidomide induced CK1a degradation by the crl4crbn ubiquitin ligase; (C) Cereblon in complex with DDB1, CC-885, and GSPT1

Table 1. Comprehensive Comparative Properties of PROTACs and Molecular Glue Degraders

Property	PROTACs	Molecular Glues
Molecular Weight	700–1100 Da (bifunctional scaffold)	200–600 Da (monofunctional entity)
Mechanism	Ternary complex: warhead + linker + E3 ligand bridges POI and E3	Stabilizes neo-substrate recruitment on reshaped E3 surface
E3 Engagement	Chemical E3 ligand (CRBN, VHL, MDM2, IAP, DCAF16)	Direct binding to E3 substrate receptor, induces conformational change
Target Scope	Any protein with accessible ligandable pocket or proximity-capable surface	Proteins bearing compatible degron (C2H2 ZF, RRM, WD40 domain)
Oral Bioavailability	Challenging — multiple Ro5 violations, formulation required	Generally favorable; approaches drug-likeness space
Cell Permeability	Limited; P-gp efflux substrate; requires efflux-evading design	Good; complies with or approaches Lipinski parameters
Hook Effect	Significant at supratherapeutic concentrations — bell-shaped curve	Minimal; monovalent binding eliminates competitive unproductive complex
Catalytic Mechanism	Yes — PROTAC recycled after POI ubiquitination	Yes — glue dissociates after neo-substrate ubiquitination
Selectivity	Engineered via warhead selectivity and linker geometry	Intrinsic; determined by degron surface complementarity
Discovery Approach	Rational, modular — well-defined design rules and SAR guidelines	Historical: phenotypic/serendipitous; Emerging: rational structure-guided
Key Resistance	E3 mutation, target mutation, MDR/P-gp efflux, degron loss	CRBN mutation, IKZF isoform switching, CRL4 inactivation, DUB upregulation
CNS Penetration	Poor — large MW and P-gp efflux limits brain exposure	Potential advantage — smaller molecules may penetrate BBB
Synthesis Complexity	High — multi-step conjugation, linker optimization, 3-part assembly	Lower — single chemical entity, fewer synthetic steps
Clinical Status	Phase I–III (ARV-471 in Phase III); >30 active trials	FDA/EMA approved (IMiDs) + CELMoDs in Phase I–III
Leading Examples	ARV-471, ARV-110, DT2216, CFT8634, KT-474, NX-2127	Lenalidomide, Pomalidomide, Iberdomide, Mezigdomide, CC-90009

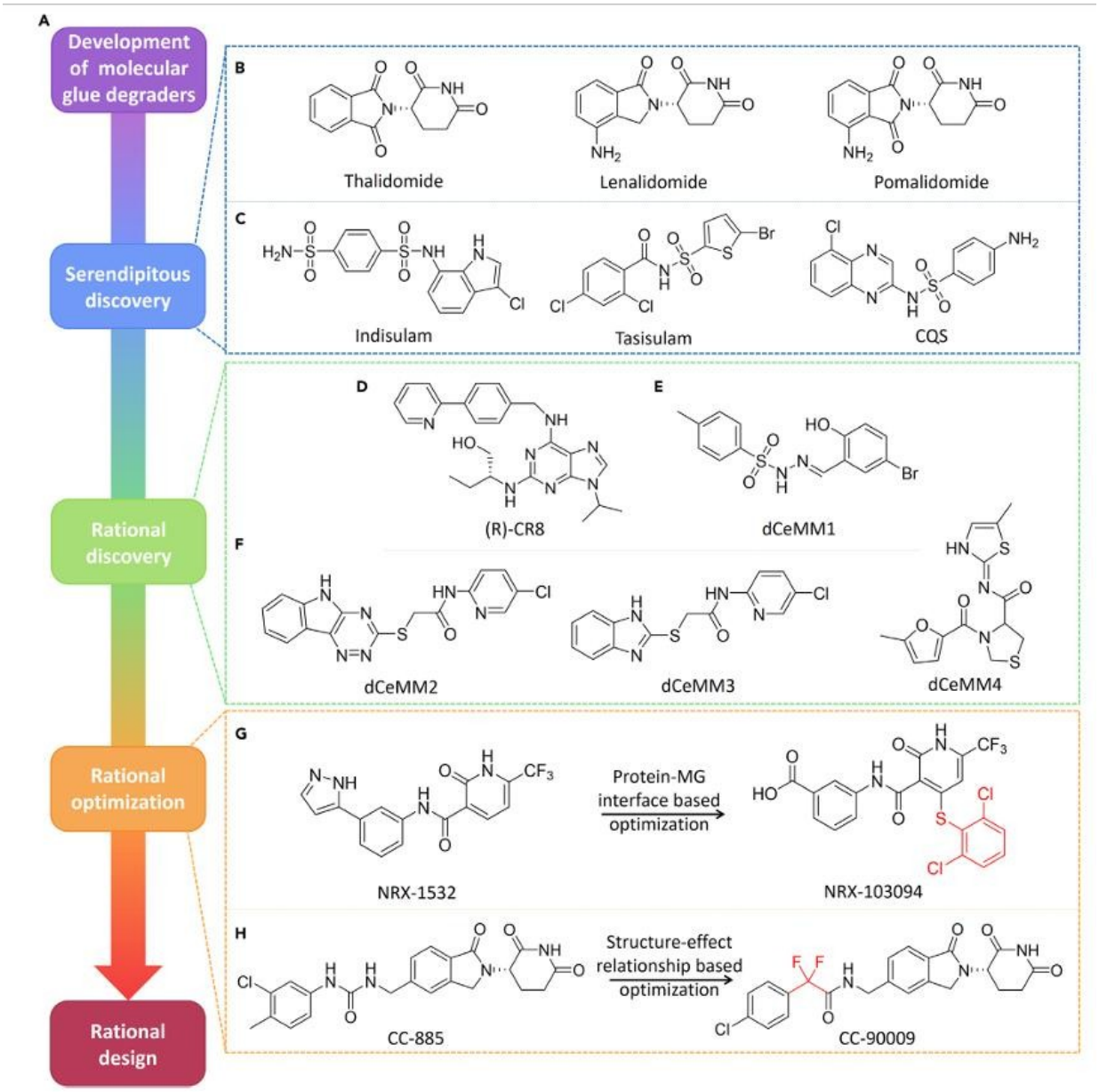

Figure 3. General classification of Molecular glue process with their notable examples, Figure adapted from Tan et al. 2024 under CC-BY 4.0 authorization (41)

Table 2. FDA/EMA-Approved and Investigational Molecular Glue Degraders (2024–2025)

Compound	Class	Target(s) Degraded	E3 Ligase	Indication	Status
Thalidomide	1st Gen IMiD	IKZF1, IKZF3, CK1α	CRL4-CRBN	MM, ENL	FDA Approved (2006)
Lenalidomide	2nd Gen IMiD	IKZF1, IKZF3, CK1α, GSPT1	CRL4-CRBN	MM, MDS del(5q), MCL	FDA Approved (2005/2006)
Pomalidomide	3rd Gen IMiD	IKZF1, IKZF3	CRL4-CRBN	RRMM, Kaposi Sarcoma	FDA Approved (2013)
Iberdomide (CC-220)	CELMoD	IKZF1/3 (enhanced; 10-30x vs Len)	CRL4-CRBN	RRMM, SLE, Lupus	EU Conditional Approval 2024; Phase III
Mezigdomide (CC-92480)	CELMoD	IKZF1/3 (pM potency, Dmax>95%)	CRL4-CRBN	Penta-refractory RRMM	Phase III SUCCESSOR (NCT05519968)
CC-90009	CELMoD	GSPT1 (eRF3a)	CRL4-CRBN	r/r AML	Phase I/II (NCT02848001)
BMS-986325	CELMoD	IKZF1/3, GSPT1	CRL4-CRBN	AML, NHL	Phase I (NCT05016167)
GT-919	MG Degrader	GSPT1	CRL4-CRBN	r/r AML	Phase I (NCT05546125)
CFT1946	Rational MG	BRAF-V600E (selective vs WT)	CRL4-CRBN	Melanoma, CRC, Thyroid Ca	Phase I (NCT05668585)
RO7589831	Rational MG	KRAS-G12C	CRL4-CRBN	NSCLC, CRC	Phase I (initiated 2024)
Indisulam	Aryl sulfonamide	RBM39, RBM23	CRL4-DCAF15	AML, solid tumors	Phase I/II (multiple trials)

Table 3. Active Clinical Trials: PROTAC-Based Targeted Protein Degraders

Drug	Developer	Target	E3 Ligase	Indication	NCT No.	Phase
ARV-471 (Vepdegestrant)	Arvinas/Pfizer	ERα (ESR1)	VHL	ER+/HER2- MBC	NCT04072952	III
ARV-110 (Bavdegalutamide)	Arvinas	AR	CRBN	mCRPC	NCT03888612	II
DT2216	Dialectic Biosciences	BCL-XL	VHL	Heme malignancy, solid tumors	NCT04886622	I
CFT8634	C4 Therapeutics	BRD9	CRBN	Synovial sarcoma, SMARCB1-null	NCT05355753	I/II
NX-2127	Nurix Therapeutics	BTK + IKZF1/3	CRBN	B-cell malignancies, CLL	NCT04830137	I
KT-474	Kymera Therapeutics	IRAK4	CRBN	Atopic dermatitis, HS	NCT04772885	I/II
KT-413	Kymera Therapeutics	IRAK4	CRBN	DLBCL, MYD88-mutant NHL	NCT04986319	I
BGB-16673	BeiGene	BTK (WT+C481S)	CRBN	CLL, MCL, WM	NCT04546607	I/II
BI-3802	Boehringer Ingelheim	BCL6	SIAH1	DLBCL, GCB lymphoma	NCT04972695	I
AC682	Accutar Biotech	ERα	CRBN	ER+ Breast Cancer	NCT05383196	I/II
CFT7455	C4 Therapeutics	IKZF1/3 (CELMoD-type)	CRBN	MM, NHL	NCT04756726	I/II

to thalidomide (PDB ID: 4CI3)(32), lenalidomide-CRBN-IKZF1 (PDB ID: 5FQD)(33), and pomalidomide-CRBN-IKZF3 (PDB ID: 5HXB)(34) reveal that IMiDs occupy the tri-tryptophan (Trp380, Trp386, Trp400) hydrophobic pocket within the CRBN beta-propeller thalidomide-binding domain (TBD). This binding is mediated primarily by pi-pi stacking interactions between the IMiD phthalimide ring and the tryptophan indole rings, and is supplemented by hydrogen bonding between the IMi Dglutarimide carbonyl groups and the Asn351 and His378 residues of CRBN. Critically, the glutarimide ring of IMiDs projects out of the CRBN pocket and exposes a molecular surface — particularly the carbonyl oxygen at positions 2/6 and the NH group — that acts as a hydrogen bond donor/acceptor complement for the beta-hairpin loop of C2H2 zinc-finger proteins(35). The ZF-degron of IKZF1 and IKZF3 contains a conserved Gln-X-X-Cys motif in the beta-hairpin tip that makes two backbone hydrogen bonds with the IMiD carbonyl/NH groups, effectively inserting the ZF-degron into the composite CRBN-IMiD surface(36). This composite interface buries approximately 800-1000 A^2 of surface area and achieves dissociation constants of 1–100 nM for the ternary complex — sufficient for efficient ubiquitination.

Molecular Glue Classification: Molecular glues can be classified based on their E3 ligase target system, the nature of the neo-substrate degron, and their discovery provenance. The IMiD/CELMoD class — Thalidomide, Lenalidomide, Pomalidomide, Iberdomide, Mezigdomide — targets CRL4-CRBN and recruits C2H2 zinc-finger neo-substrates via glutarimide-mediated TBD engagement(37, 38). This class contains the only FDA/EMA-approved molecular glue degraders and has the largest clinical dataset. The aryl sulfonamide class — Indisulam, E7820, Chloroquinoxaline sulfonamide, Tasisulam — targets CRL4-DCAF15 to degrade RNA splicing factors RBM39 and RBM23, utilizing a mechanistically distinct 'molecular pin' insertion into the DCAF15-RBM39 interface(39). The third class encompasses rationally designed and fragment-based molecular glues targeting novel E3 ligases (RNF114, DCAF16, TRIM24, AhR) or reprogramming CRBN for novel non-zinc-finger neo-substrates (40).

Emerging Strategies and Future Directions

Rational Molecular Glue Design: The historical perception of molecular glues as undruggable-by-design — arising from their serendipitous discovery history and the complexity of induced PPI formation — is being rapidly overturned by advances in computational chemistry, structural biology, and machine learning. Cryo-EM structures of E3: glue: neo-substrate ternary complexes at <3 Å resolution now provide atomic blueprints for medicinal chemistry, enabling quantitative SAR development around glue-E3 and glue-neo-substrate interactions simultaneously. AlphaFold2 multimer predictions of candidate glue-induced ternary complexes, validated against experimental co-crystallography data, are enabling prospective computational screening of glue scaffolds against databases of potential neo-substrates. Fragment-based molecular glue discovery (FBMG) exploits the principle that small, weak-binding fragments that stabilize E3: substrate complexes can be identified by biophysical screening methods (SPR, NMR, thermal shift) and then grown into potent molecular glues through structure-guided elaboration(42). The CRBN TBD has been particularly amenable to FBMG approaches, with novel fragment-derived glue scaffolds (distinct from the glutarimide pharmacophore) now entering preclinical development. Machine learning models trained on quantitative ternary complex stability (AlphaScreen, TR-FRET) and cellular degradation data (quantitative TMT proteomics) are beginning to enable predictive models of molecular glue activity from chemical structure, potentially enabling high-throughput in silico glue screening(43).

Conditional and Cell-Type-Selective Degradation: A critical frontier in TPD is the achievement of cell-type-selective or conditional degradation to improve therapeutic windows and enable previously impossible applications. Photoswitchable PROTACs and molecular glues employing azobenzene or diarylethene switches enable light-activated degradation in accessible tissues, with demonstrated applications in dermatological disease, retinal disorders, and surgically accessible solid tumors (44).

Hypoxia-activated prodrug PROTACs employ nitro-aromatic or quinone-based bioreductive triggers that undergo single-electron reduction in the hypoxic tumor microenvironment, generating active degraders exclusively in tumor cells while remaining inactive in normoxic normal tissues(45).Antibody-PROTAC conjugates (AbPROTACs, or PROTAC-based ADCs) exploit tumor-specific surface antigens for targeted delivery of PROTACs to tumor cells through receptor-mediated endocytosis and lysosomal release.

This approach overcomes the poor tumor penetration of large molecular weight PROTACs and enables selective tumor cell exposure while sparing normal tissues. Analogous antibody-molecular glue conjugates are under development for tumors expressing unique surface antigens, particularly for CNS tumors where blood-brain barrier penetration is limiting.

CONCLUSION

The field of targeted protein degradation has undergone a remarkable transformation over the past decade, from a largely academic concept to a clinically validated therapeutic modality with multiple approved drugs and an extensive active clinical pipeline. Molecular glues, through the IMiD/CELMoD lineage, represent the most clinically proven TPD strategy in human medicine, with lenalidomide alone among the highest-revenue oncology drugs in history. The retrospective elucidation of the IMiD molecular glue mechanism in 2014 provided the structural foundation for rational CELMoD design, yielding next-generation compounds including iberdomide and mezigdomide with dramatically enhanced potency, activity against IMiD-resistant disease, and ongoing Phase III clinical trials that may establish new standards of care in relapsed/refractory myeloma.PROTACs, with their modular architecture, expansive target scope, and rapidly growing clinical trial portfolio, have achieved a complementary position in the TPD landscape. The advancement of ARV-471 (vepdegestrant) to Phase III represents a watershed moment for the entire PROTAC field and will determine whether PROTAC-mediated ERα degradation offers a clinically meaningful advantage over conventional endocrine therapies in metastatic breast cancer. The expanding PROTAC clinical pipeline — encompassing AR, BTK, BCL-XL, BRD9, IRAK4, and ERα — demonstrates the versatility of the bifunctional degrader approach across diverse oncological and inflammatory indications.Emerging rationally designed molecular glues targeting KRAS-G12C, BRAF-V600E, GSPT1, and CDK12 represent the vanguard of the next generation of glue therapeutics — compounds where the power of structural biology, computational chemistry, and medicinal chemistry optimization are being applied prospectively to create glue interfaces for the most clinically significant undruggable targets. The convergence of cryo-EM structural biology, AlphaFold-enabled interface prediction, machine learning-guided hit identification, and fragment-based glue discovery is transforming molecular glue development from an art into a science.

Authors Contribution: A.K.: Written original manuscript, curated information, literature; A.K.K: Project administrator, supervised, reviewed and submitted full manuscript; R.K.G.: formal analysis and review manuscript; S.P.S.: formal analysis and review manuscript.

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