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MOLECULAR GLUES IN CANCER THERAPY: FROM SERENDIPITY TO RATIONAL DRUG DESIGN

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ABSTRACT

Molecular glues modulate protein function by inducing or stabilizing interactions between proteins. Their most clinically established oncological application is targeted protein degradation, in which a compound redirects a ubiquitin ligase towards a therapeutically relevant neosubstrate. The elucidation of cereblon-dependent degradation by thalidomide analogues transformed a longstanding clinical observation into a mechanistic framework for drug discovery. Subsequent discoveries involving DCAF15, DDB1, BCL6 polymerization and conformationally induced BRD4 recruitment revealed that productive proximity can arise through several distinct architectures. Structural biology, genetic perturbation and quantitative proteomics now permit increasingly deliberate optimization of these mechanisms, although general prediction of a successful glue for an arbitrary protein pair remains unresolved. This narrative review examines the transition from phenotypic discovery to rational design, emphasizing the difference between explaining a mechanism, optimizing an established interface and prospectively selecting a new target–partner interaction. It also assesses clinical evidence in multiple myeloma, including the 2026 accelerated approval of an iberdomide-containing regimen and randomized evidence for mezigdomide, while distinguishing these developments from preclinical advances in solid tumors. Emerging HuR degraders and charged glues illustrate opportunities to expand both target and ligase repertoires. Future progress will depend on integrating interface design with productive ubiquitination, cellular selectivity, resistance mapping and pharmacokinetic–pharmacodynamic analysis. Molecular glues are becoming a tractable therapeutic strategy, but their successful design requires control of biological context as well as molecular recognition.

Keywords: Molecular glue; Targeted protein degradation; Cereblon; Induced proximity; Cancer therapy; Ternary complex; Rational drug design.

1 INTRODUCTION

Cancer drug discovery has traditionally sought compounds that occupy a defined binding pocket and inhibit a protein's catalytic or signaling activity. This strategy has produced effective therapies, but it is less straightforward for transcription factors, RNA-binding proteins and scaffolding proteins whose oncogenic functions depend on distributed interaction surfaces. Molecular glues offer another route: a small molecule changes how proteins recognize one another, thereby creating a pharmacological function that neither protein possesses in the untreated state. In oncology, the best-established implementation recruits disease-associated proteins to the ubiquitin–proteasome system. The discovery that lenalidomide promotes degradation of IKZF1 and IKZF3 provided direct evidence that an apparently difficult protein class could be targeted through induced recognition rather than conventional active-site inhibition [1–4].

The appeal of this approach should not obscure its complexity. A compound can stabilize a protein complex without causing degradation, and degradation can occur without selective cancer-cell killing. Conversely, some glues suppress oncogenic signaling without recruiting a ubiquitin ligase. Mechanistic categories therefore matter when comparing compounds, interpreting biomarkers or claiming that a platform has solved a druggability problem. A productive review must connect three levels of evidence: molecular recognition, cellular consequences and patient outcomes.

The central argument of this article is that rational molecular-glue design is best understood as a progression in experimental control. Retrospective structural explanation, prospective optimization of a known mechanism and de novo design of a predefined interaction are distinct achievements. Studies of DCAF15, cyclin K and BRD4 have advanced this progression, but none establishes a universal recipe applicable to any oncogenic protein [5–11]. The clinically relevant question is consequently broader than whether a compound can glue two purified proteins together: can it generate the desired biological event at tolerable exposures in a tumor with a defined vulnerability?

1.1 Scope and evidence selection

This article is a focused narrative review, not a systematic review or meta-analysis. Sources were identified through targeted web searches of PubMed-indexed publications, primary journal pages and official regulatory materials, with an evidence cut-off of 12 October 2026. Searches addressed molecular-glue degradation, CRBN, DCAF15, cyclin K, BCL6, BRD4, HuR, induced-proximity RAS inhibition, resistance and clinical cereblon modulators. Primary mechanistic studies were prioritized for causal claims; clinical trial reports and FDA documentation were prioritized for clinical and regulatory statements. Landmark earlier publications were retained where necessary to explain the field's development.

The selection is intended to support a mechanistic and translational argument rather than provide an exhaustive compound catalogue. No pooled efficacy estimates, formal risk-of-bias scoring or claims of comprehensive retrieval are made. Computational predictions, cellular observations, animal efficacy and clinical evidence are treated as separate evidence levels. Regulatory statements refer specifically to the United States unless another jurisdiction is named.

2 WHAT DEFINES A MOLECULAR GLUE

2.1 Induced recognition rather than a chemical size category

A molecular glue induces or strengthens an interaction by modifying the recognition surface or conformation of one or both protein partners. In many classical degraders, the compound binds an E3 ligase receptor, and the resulting composite surface recruits a neosubstrate. The neosubstrate is not necessarily a physiological client of that ligase. Structural studies of CRBN and DCAF15 show how a relatively small chemical contribution can work together with extensive protein–protein contacts to create selective recognition [4,6,12].

Classical proteolysis-targeting chimeras, or PROTACs, usually contain distinct ligands for a target and a ligase connected by a linker. Many canonical glues do not require two independently optimized ligands. However, molecular size or the number of binding groups is not a sufficient mechanistic definition. Intramolecular bivalent glues can engage two domains within the target and thereby expose a ligase-compatible surface, rather than bridge target and ligase with separate binding modules [9]. Thus, chemical architecture must be interpreted alongside experimentally demonstrated mechanism.

2.2 Complex formation and protein degradation are different events

For a degradative glue, recruitment must be followed by productive ubiquitin transfer and proteasomal processing. A tightly bound complex may still present the target in an unfavorable orientation for ubiquitination. The CR8 system provides an instructive example: the compound binds CDK12, promotes association with DDB1 and causes depletion of

the associated cyclin K. The protein engaged by the compound, the recruited recognition partner and the degraded component therefore need not be identical [7].

This distinction affects assay design. Binary binding measurements describe engagement of an isolated component; ternary assays describe partner recruitment; degradation assays describe a downstream cellular event. Their concentration–response values are not interchangeable. Half-maximal degradation concentration, maximal depletion, onset and recovery after washout should be reported together with assay duration and cellular background. A single endpoint cannot establish whether improved activity reflects stronger recruitment, more productive ubiquitination, altered exposure or slower protein replacement. These are methodological implications of the different recruitment and degradation architectures, rather than properties established uniformly for every glue [7,9–12].

2.3 Advantages are conditional

Removal of a protein can suppress both catalytic and noncatalytic functions, and recovery may depend on new protein synthesis. Reversible degraders can, in principle, participate in multiple degradation events. However, catalytic recycling should not be assumed for every chemical architecture, especially when covalent attachment changes the fate of the compound or recruiting protein. Similarly, many glues are compact and amenable to oral administration, but this is not guaranteed by their classification. Covalent handles and intracellularly activated charged glues introduce their own exposure and selectivity constraints [10,11,13].

Some glues avoid the high-concentration loss of productive assembly associated with a PROTAC hook effect, as demonstrated for particular charged-glue systems [13]. This should not be converted into a universal claim that molecular glues never show nonmonotonic pharmacology. Across modalities, the relevant benchmark is clinically achievable target modulation with an acceptable therapeutic index, rather than chemical simplicity alone.

3 FROM CLINICAL OBSERVATION TO MECHANISTIC UNDERSTANDING

3.1 Thalidomide and the cereblon framework

The identification of CRBN as a thalidomide-binding protein in 2010 connected the drug to a ubiquitin ligase complex [1]. In 2014, independent studies demonstrated that lenalidomide redirects CRBN to the lymphoid transcription factors IKZF1 and IKZF3, linking their loss to antimyeloma activity [2,3]. Structural analysis then established how thalidomide analogues bind the CRBN substrate receptor [4]. These findings changed the interpretation of drug action: the compounds alter substrate recognition rather than simply inhibiting an enzyme.

The sequence also illustrates the limits of retrospective knowledge. Clinical activity preceded molecular explanation, and the identification of a binding protein did not by itself reveal the therapeutically important neosubstrates. Only the integration of degradation measurements and genetic experiments established a causal mechanism. The practical lesson is that target engagement must be connected to the phenotype, rather than treated as sufficient proof of therapeutic action.

3.2 Neosubstrate choice links chemistry to tumor vulnerability

Lenalidomide-induced CK1α degradation in del(5q) myelodysplastic syndrome showed that the same recruiting system can operate through a different disease-relevant substrate. CSNK1A1 lies within the commonly deleted region, and reduced CK1α gene dosage sensitizes del(5q) cells to further depletion [14]. Structural work explained recruitment of CK1α to the lenalidomide-bound CRBN complex [12]. This example is valuable because it connects degradation to a genetically defined therapeutic window, rather than implying that protein depletion is intrinsically tumor selective.

CC-885 extended the CRBN platform to GSPT1, a translation-termination factor, demonstrating that chemical elaboration could redirect the neosubstrate repertoire [15]. CC-90009 subsequently provided a GSPT1-selective cereblon modulator with activity against acute myeloid leukemia blasts and leukemia stem cells in preclinical systems [16]. These results support a strategy of designing recognition surfaces around a ligase-binding core. They do not establish that inhibition of an essential translation process will be safe in patients or that preclinical leukemia activity predicts efficacy across solid tumors.

3.3 DCAF15 establishes a second recognition system

Indisulam and related anticancer sulfonamides were mechanistically reinterpreted when studies showed DCAF15-dependent ubiquitination and degradation of the splicing factor RBM39, also known as CAPERα [5,17]. Recruitment-disrupting RBM39 mutations conferred resistance, providing evidence that this interaction drives the cytotoxic response [5]. The discovery expanded the field beyond CRBN and demonstrated that an existing phenotypic compound collection could contain unrecognized glues.

Structural analysis of E7820-mediated recruitment showed a shallow DCAF15 pocket and extensive contacts with RBM39, with DDA1 contributing to ligase-complex organization [6]. Strong isolated ligand affinity was not required to obtain productive recruitment because the assembled interface contributed substantial recognition energy. For discovery, this means a weak binary interaction can still be useful. For translation, it means that predicting sensitivity from compound–ligase affinity alone is inadequate; ligase availability, substrate compatibility and dependency on RNA processing must also be examined.

4 MECHANISTIC DIVERSITY EXPANDS THE DESIGN SPACE

4.1 Cyclin K degradation through DDB1 recruitment

CR8 was identified as a glue through systematic comparison of compound sensitivity with expression of E3-ligase components across cancer cell lines [7]. Structural and biochemical experiments revealed that CDK12-bound CR8 creates an interface for DDB1 recruitment and subsequent cyclin K degradation. This architecture bypasses the usual requirement for a dedicated substrate receptor to recognize the drug-engaged target complex. Its importance is therefore mechanistic as well as pharmacological: an inhibitor scaffold can acquire a proximity-dependent function through features presented at the protein surface.

4.2 Polymerization precedes degradation in the BCL6 system

BI-3802 binds the BCL6 BTB domain and induces ordered polymerization, followed by recruitment of the ubiquitin ligase SIAH1 and degradation [18]. Here, the glue initially promotes target–target association rather than directly joining an E3 receptor to a soluble neosubstrate. Polymerization changes the substrate state that the degradation machinery recognizes. This mechanism also cautions against treating all intracellular protein assemblies as nonspecific aggregation: ordered, structurally defined association can be a causal pharmacological intermediate. Nevertheless, localization or visible foci alone do not demonstrate productive degradation or selective antitumor activity.

4.3 Conformational and covalent routes to BRD4 recruitment

Intramolecular bivalent glues connect adjacent bromodomains in BRD4 or BRD2 and induce a conformation favorable for recruitment by DCAF16 or DCAF11 [9]. The original compound's PROTAC-like appearance did not predict its actual ligase dependency. Structure-guided optimization generated derivatives with improved degradation potency. This is a clear example of rational improvement after mechanism discovery, and it shows why ligand composition cannot substitute for genetic validation of the recruiting machinery.

Other BRD4 degraders operate through template-assisted covalent modification. In the TMX1 system, existing complementarity between BRD4 BD2 and DCAF16 helps orient an electrophile for reaction with DCAF16 Cys58 [10]. A separate DCAF16 covalent-handle strategy demonstrated that appending suitable chemical functionality to target-binding ligands can induce degradation of several protein classes [11]. Such results make target-first campaigns more feasible, while leaving important questions about reactive selectivity, target dependence and transferability between proteins. Covalency should be assessed as part of the recruitment mechanism, not used as an explanation for potency without identifying the modified protein and residue.

4.4 Beyond direct degradation of a single recruited protein

The UM171 system illustrates recruitment within a multiprotein complex. Structural studies showed that UM171 enables asymmetric recognition of HDAC1/2 by dimeric KBTBD4 and promotes degradation of CoREST corepressor components [19]. Companion work demonstrated convergence between the compound-induced interface and neomorphic KBTBD4 mutations found in medulloblastoma [20]. Chemical and genetic changes can therefore create similar recognition surfaces.

This convergence offers a useful source of design hypotheses, but it is not an automatic therapeutic endorsement. The mutations themselves can support oncogenic biology, and UM171's hematopoietic stem-cell expansion context differs from direct cancer treatment. The translational objective must be defined before selecting an interaction to mimic. Inducing a biologically powerful interface can be beneficial, neutral or harmful depending on cell type and disease state.

Table 1: Mechanistic architectures of representative molecular glues

Compound or class	Recognition architecture	Primary consequence	Evidence
Lenalidomide	CRBN composite surface recruits IKZF1/3 or CK1α	Degradation linked to myeloma or del(5q) biology	Mechanistic and clinical [2–4,12,14]
CC-885 / CC-90009	CRBN recruits GSPT1	Translation-factor depletion	Preclinical [15,16]
Indisulam / E7820	DCAF15 recruits RBM39	Splicing-factor degradation	Mechanistic [5,6,17]
CR8	CDK12-bound ligand recruits DDB1	Associated cyclin K degradation	Preclinical [7]
BI-3802	BCL6 polymerization enables SIAH1 recognition	BCL6 degradation	Preclinical [18]
BRD4 intramolecular bivalent glues	Two target domains are joined in cis	DCAF16/11-dependent depletion	Preclinical [9]
TMX1	Target-templated DCAF16 covalent modification	BRD4 depletion	Preclinical [10]
UM171	Dimeric KBTBD4 recruits HDAC1/2-containing complex	CoREST-component degradation	Mechanistic [19,20]
dHuR	CRBN recruits HuR G-loop degron	HuR loss and altered BRAF processing	Preclinical [21]
Charged BET glues	Activated compound recruits YPEL5–CTLH	BET protein degradation	Preclinical [13]

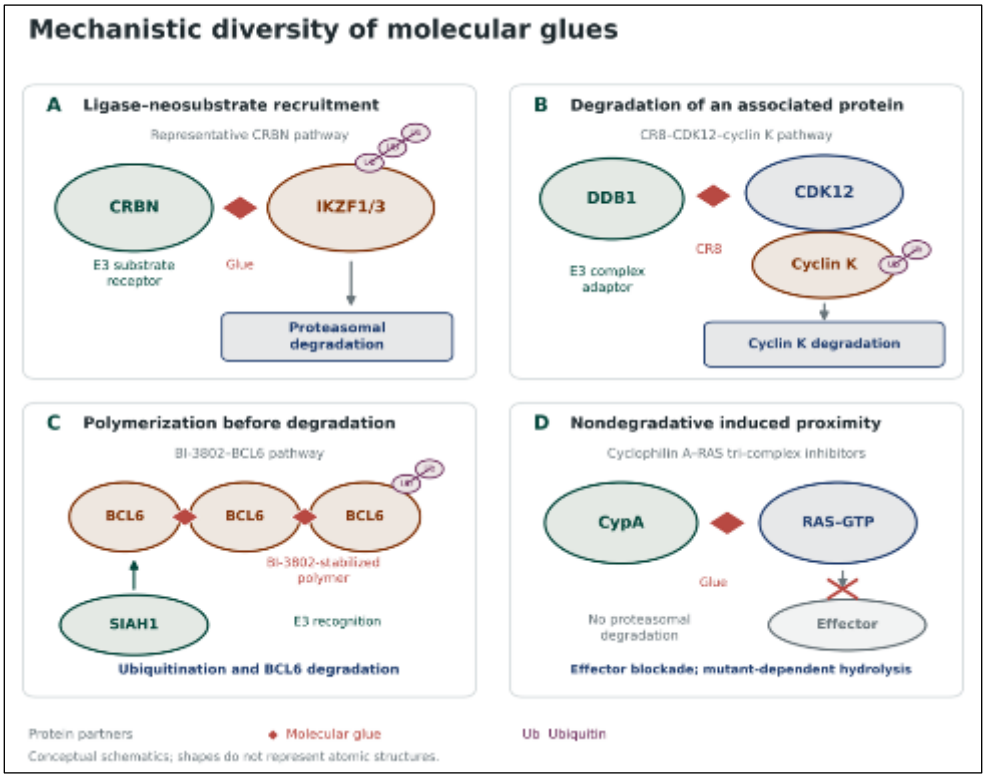

Figure 1: Mechanistic diversity of molecular glues. A, CRBN-mediated recruitment and degradation of IKZF1/3. B, CR8 recruits DDB1 to a CDK12–cyclin K complex, enabling degradation of the associated cyclin K. C, BI-3802 induces BCL6 polymerization, followed by SIAH1-dependent ubiquitination and degradation. D, cyclophilin A–RAS tri-complex inhibitors act without proteasomal degradation; enhanced GTP hydrolysis depends on the RAS mutant and inhibitor. Conceptual schematic based on [2–4,7,18,28,29].

5 WHAT RATIONAL DESIGN NOW MEANS

5.1 Three levels of rationality

Retrospective rationalization explains why an active compound works. It is indispensable for choosing assays and interpreting structure–activity relationships, but it does not demonstrate prospective discovery. Rational optimization begins with an established glue mechanism and modifies chemistry to improve recruitment, degradation, selectivity or exposure. De novo design starts with a desired target–partner pair and seeks a compound that generates a productive interaction. These levels require different evidence and should not be merged into a single claim of rational discovery [6–11,22].

The strongest demonstration of prospective design includes a documented hypothesis, compounds selected before testing, appropriate negative controls and experimental confirmation of the intended mechanism. Successful optimization of a single known scaffold is meaningful, but provides narrower evidence than reproducible discovery across unrelated targets. This distinction is particularly important when evaluating computational or platform-based claims.

5.2 Phenotypic discovery can be made mechanistically selective

Systematic profiling does not require full knowledge of the final interface before screening. Mayor-Ruiz and colleagues used differences in compound response under reduced cullin neddylation, followed by genetic and proteomic analyses, to identify degradation-dependent activities [8]. Combined with the expression–sensitivity strategy used for CR8 [7], this work shows how phenotype-first discovery can be guided towards a mechanistic class rather than left to chance.

Such approaches have a defined sampling bias. A screen centered on cullin-dependent activity is suited to cullin–RING ligases, but may miss mechanisms that use other E3 systems. The 2026 discovery of charged glues recruiting YPEL5 within the CTLH ligase complex provides an example of degradation outside the conventional CRL-centered framework [13]. In practical terms, the choice of screening perturbation partly determines which mechanisms a campaign can discover.

5.3 The assembled interface is the medicinal chemistry objective

In an inhibitor campaign, optimizing affinity for one protein can be a useful central objective. For a glue, optimization must consider the whole assembly: ligand placement, interprotein contacts, conformational compatibility and presentation to the downstream machinery. The DCAF15 and CRBN structures show that substrate selectivity resides in the composite interface [6,12]. BRD4 studies further show that changing target conformation or the position of a reactive group can be decisive [9,10].

This creates an unusual structure–activity landscape. A small chemical change may preserve ligase engagement yet switch recruitment between substrates. Conversely, stronger binding to an isolated partner need not improve cellular depletion. A useful experimental cycle therefore measures engagement, recruitment, depletion and proteome-level selectivity in parallel. The hypothesis being tested should identify which of these steps is expected to improve; otherwise, medicinal chemistry risks optimizing a convenient assay rather than the desired biological event.

5.4 Target-first discovery is gaining experimental support

An earlier target-oriented route was demonstrated by Toriki and colleagues, who appended a compact covalent chemical handle to protein-binding ligands and used chemoproteomics to identify recruitment involving RNF126 and other RING-family ligases [23]. The study provided proof of concept for converting established ligands into monovalent degraders without constructing a conventional two-ligand PROTAC. Its generality remained limited by compound potency, selectivity and the dependence of activity on the target and recruiting machinery. Together with subsequent DCAF16 work, this strategy makes the protein-binding ligand a starting point for discovery while preserving the need to identify which ligase actually drives depletion [11,23].

In 2026, a rationally designed CRBN-oriented chemical library combined with proteomic screening yielded dHuR, a degrader of the RNA-binding protein HuR [21]. The compound generates a CRBN composite surface that recognizes a HuR β-hairpin G-loop degron. HuR depletion altered BRAF RNA processing, including exon 18 skipping, and suppressed BRAF-mutant colorectal cancer models, including models with resistance to BRAF inhibitors. This links a designed recognition surface to a tumor-relevant downstream effect.

The findings are preclinical. They do not establish a validated patient-selection biomarker, a clinically safe exposure range or benefit over current treatment in patients. Their design significance is nevertheless substantial: productive

recruitment can be discovered by combining planned chemical diversity with broad measurement of protein depletion, without relying solely on conventional target inhibition.

Charged-glue discovery adds a complementary chemical strategy. Zhuang and colleagues identified intracellularly activated compounds whose sulfinic-acid-containing products engage a basic pocket on YPEL5 and promote BET protein recruitment to CTLH [13]. This work expands the interaction chemistry available for glues and uses prodrug activation to address membrane permeability. Whether differential activation can generate a useful cancer-selective therapeutic window remains a question for further investigation.

5.5 Computation is a prioritization tool

Structure prediction, docking and interface analysis can reduce the number of protein combinations and compounds taken into experiments. GlueFinder uses structural bioinformatics to identify ligand-binding pockets near protein interfaces and propose candidate assemblies, including configurations involving EGFR, HER2 and KRAS [22]. Its role is to generate experimentally testable hypotheses rather than establish degradation from a docking score.

This limitation is fundamental. A predicted complex does not demonstrate sufficient intracellular concentration, competition with endogenous partners, productive ubiquitination or selective killing. Evaluation of a design method should separate predicted contacts, measured complex formation, cellular depletion and antitumor activity. Prospective benchmarks should also avoid overrepresenting familiar CRBN chemotypes, because apparent accuracy within a well-characterized family may not translate to unfamiliar ligases or protein surfaces.

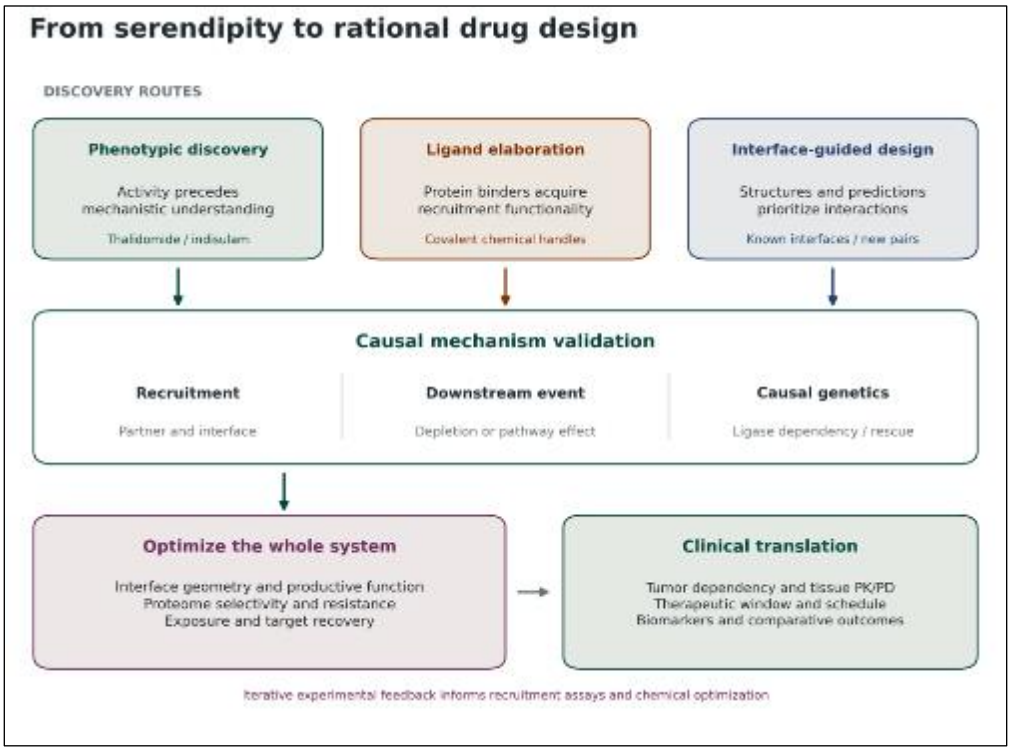

Figure 2: A framework for molecular glue discovery and development. Complementary discovery routes feed into causal validation, followed by iterative optimization and clinical translation. Computation prioritizes hypotheses that require experimental testing. PK/PD, pharmacokinetics/pharmacodynamics. Author synthesis based on [6–13,21–23,30–33].

6 CLINICAL TRANSLATION IN HEMATOLOGICAL MALIGNANCIES

6.1 Early trials established activity beyond older immunomodulatory drugs

Iberdomide and mezigdomide extend the CRBN-modulator strategy within multiple myeloma. In the phase 1/2 CC-220-MM-001 study, iberdomide plus dexamethasone produced responses in 28 of 107 patients in the dose-expansion cohort, an overall response rate of 26% (95% confidence interval, 18–36). These patients had heavily pretreated, triple-class-refractory disease. Grade 3 or worse neutropenia occurred in 45% and infection in 27% [24]. The results established clinical activity, but the single-arm design did not determine comparative benefit.

The phase 1/2 mezigdomide study evaluated 101 patients in the dose-expansion cohort, all with triple-class-refractory myeloma. Mezigdomide plus dexamethasone produced a 41% response rate (95% confidence interval, 31–51); median progression-free survival was 4.4 months, and neutropenia and infection were prominent adverse events [25]. These observations justified further study while showing that more potent degradation does not remove the constraints imposed by marrow toxicity and infectious risk. Numerical comparison between these two trials is inappropriate because populations, schedules and study contexts differ.

6.2 Randomized evidence for mezigdomide

The 2026 SUCCESSOR-2 report compared mezigdomide–carfilzomib–dexamethasone with carfilzomib–dexamethasone. In the prespecified analysis of 479 patients, median progression-free survival was 18.0 versus 8.3 months at a median follow-up of 10.6 months; the hazard ratio was 0.48 (95% confidence interval, 0.36–0.63). Grade 3 or 4 adverse events occurred in 84% versus 56%, with neutropenia in 61% versus 9% and infections in 34% versus 16% [26].

These findings move the evidence beyond uncontrolled response rates. They support the efficacy of a specific mezigdomide-containing regimen in the studied relapsed or refractory population, while quantifying a substantial toxicity burden. They do not isolate the clinical contribution of a particular molecular design feature, establish general efficacy for other glues or prove an overall-survival advantage. Longer follow-up and treatment-sequencing data remain important for judging the regimen's place in care.

6.3 Regulatory advancement of iberdomide

On 13 August 2026, the FDA granted accelerated approval to iberdomide with daratumumab and hyaluronidase-fihj and dexamethasone for adults with multiple myeloma after at least one prior line including a proteasome inhibitor and an immunomodulatory agent [27]. The supporting EXCALIBER-RRMM primary efficacy population comprised 420 patients. MRD-negative complete response at any time occurred in 41% with the iberdomide regimen versus 21% with daratumumab–bortezomib–dexamethasone.

The regulatory route and endpoint are essential to interpretation. MRD-negative complete response measures depth of disease clearance; it is not itself a demonstration of longer overall survival. The FDA notification also identifies embryo-fetal toxicity and serious thromboembolism in the boxed warning, with additional concerns including neutropenia and infection [27]. The approval is a concrete clinical milestone for newer CRBN degraders, but should not be represented as unrestricted approval of the molecular-glue platform.

Table 2: Selected clinical evidence for newer CRBN modulators

Study or decision	Population or analysis	Key result	Interpretation
Iberdomide phase 1/2 [24]	107 patients in expansion cohort; triple-class-refractory myeloma	Response rate 26%	Single-arm evidence; cytopenias and infection
Mezigdomide phase 1/2 [25]	101 patients in expansion cohort; triple-class-refractory myeloma	Response rate 41%; median PFS 4.4 months	Single-arm evidence; no cross-trial comparison
SUCCESSOR-2 [26]	479 patients in prespecified randomized analysis	Median PFS 18.0 vs 8.3 months; HR 0.48	Regimen-specific PFS benefit; more grade 3/4 toxicity
FDA iberdomide decision [27]	420 patients in primary EXCALIBER-RRMM efficacy population	MRD-negative CR 41% vs 21%	Accelerated approval; survival benefit not established by this endpoint

CR, complete response; HR, hazard ratio; MRD, minimal residual disease; PFS, progression-free survival. Each result refers to its stated regimen and population.

7 SOLID TUMORS AND NONDEGRADATIVE INDUCED PROXIMITY

7.1 Biological dependency must accompany a degradable target

Solid-tumor translation requires more than demonstrating that a protein can be depleted in a cell line. Tumor exposure, heterogeneous ligase expression, dependency on the depleted protein and effects on normal tissues all influence the

therapeutic window. HuR degradation provides a recent example in which an RNA-binding target was connected to a defined downstream BRAF-processing phenotype [21]. GSPT1 work provides a different model, in which depletion of a translation factor can create vulnerabilities but also raises concerns about effects on normal proliferating cells [15,16].

A target-expression biomarker is therefore insufficient on its own. A useful biomarker strategy would assess target dependency, the availability of competent recruiting machinery and the degree of depletion required to alter tumor biology. These are proposed translational criteria, not clinically validated universal biomarkers. Functional measurements from tumor tissue may ultimately be more informative than expression alone, but their clinical utility must be established for each compound and disease.

7.2 RAS tri-complex inhibitors broaden the therapeutic concept

RMC-6236 illustrates induced proximity without proteasomal degradation. The compound forms a complex with cyclophilin A that engages active RAS, preventing productive signaling interactions. Translational characterization connected this architecture to activity in RAS-driven cancer models and initial clinical observations [28]. The mechanism should not be grouped with E3-recruiting degraders merely because both involve a compound-stabilized protein complex.

Subsequent work showed that drug-bound cyclophilin A can enhance GTP hydrolysis by particular mutant RAS proteins, with mutation-dependent effects on the catalytic machinery [29]. Thus, induced proximity can alter enzymatic behavior as well as obstruct effector binding. The breadth of this mechanism underscores why molecular-glue terminology should retain a functional distinction between degradation, interaction blockade and catalytic modulation. A clinical pipeline inventory is outside this review's scope; the RAS example is included to explain the mechanistic boundary, not to claim a current regulatory status for RMC-6236.

8 RESISTANCE AND SAFETY MUST INFORM DESIGN

8.1 Resistance can occur at several stages

Molecular glues are not resistance-proof. CRISPR suppressor scanning of GSPT1 and RBM39 identified neosubstrate mutations that interfere with glue action [30]. Such mutations can preserve a protein's essential function while changing the surface recognized by the recruiting complex. Clinical myeloma analyses also identified CRBN mutations, copy-number or structural changes and altered transcripts associated with resistance after successive immunomodulatory-drug exposures [31].

The implications differ by mechanism. A neosubstrate-interface change may be overcome by alternative chemistry or a different recruitment surface. Loss of the recruiting machinery may affect several compounds that share that machinery, making ligand optimization alone insufficient. Downstream adaptation can also separate degradation from cell death, so retained target depletion does not necessarily exclude biological resistance. A rational resistance program should measure compound exposure, recruitment competence, protein depletion and pathway consequences separately rather than label every resistant phenotype as loss of binding.

8.2 Selectivity includes unanticipated neosubstrates

The same composite surface that enables a desired target can recognize other proteins with compatible structural motifs. Mapping of the human zinc-finger degrome demonstrated that thalidomide analogues can engage a wider substrate repertoire than IKZF1 and IKZF3 alone [32]. Whole-proteome profiling is therefore necessary, but its sensitivity depends on cell type, protein abundance, treatment concentration and sampling time. Absence of a detectable change in one experiment cannot establish universal selectivity.

Thalidomide-associated SALL4 degradation provides a particularly consequential example. SALL4 is a developmental transcription factor, and its drug-induced loss offers a mechanistic link to characteristic embryonic defects. The response also differs between species [33]. Accordingly, apparently reassuring results in a conventional animal model may not capture human neosubstrate liability. Human developmental and relevant normal-tissue systems should complement animal studies when the recruiting scaffold or predicted substrate motifs raise such concerns.

8.3 Exposure and schedule are part of the mechanism

Target depletion is a time-dependent process, so conventional plasma exposure measurements should be linked to protein loss and recovery in the relevant tissue. For an essential target, intermittent treatment may permit normal-tissue recovery, but this possibility must be tested rather than assumed. The cytopenias and infections reported with newer myeloma regimens demonstrate why target potency alone is an inadequate measure of success [24–27].

Combination therapy adds another layer. Proteasome inhibition can block degradation in a short mechanistic experiment, yet proteasome inhibitors are effective partners for CRBN modulators in clinical regimens [26]. Different schedules, exposure patterns and complementary antitumor actions make the clinical situation more complex than an isolated rescue assay. Mechanistic experiments establish causal dependence; they do not, by themselves, predict whether a combination will be useful or antagonistic in patients.

9 A PRACTICAL FRAMEWORK FOR PROSPECTIVE DEVELOPMENT

The available evidence supports a staged development framework rather than one universal chemical recipe. A campaign should begin with a disease dependency and a proposed biological event, then establish whether the chosen target surface and recruiting partner can support that event. Candidate compounds should advance on the basis of concordant recruitment, downstream modulation, causal genetics and achievable exposure. Table 3 summarizes this proposed framework, derived from the mechanistic and translational examples discussed above [5–13,21,22,24–27,30–32].

Table 3: Proposed framework for prospective molecular glue development

Development step	Core evidence	Decision supported
Select the disease dependency	Genetic or functional evidence in relevant tumor and normal models	A plausible therapeutic window
Verify recruitment	Orthogonal complex assays and interface perturbation	The intended protein interaction occurs
Establish the downstream event	Time-resolved depletion, ubiquitination or pathway modulation	Recruitment produces the desired function
Connect mechanism to phenotype	Ligase perturbation and rescue by resistant target variants	Antitumor activity depends on the mechanism
Assess selectivity and escape	Proteomics across contexts and resistance mapping	Manageable liabilities and rational alternatives
Translate exposure to tissue response	PK/PD, target recovery and schedule studies	Clinically feasible modulation and biomarker testing

Three priorities follow from this framework. First, ligase diversification should be driven by a demonstrated advantage, such as a new target repertoire or a different resistance profile, rather than by novelty alone. Second, proteomic and genetic measurements should enter early medicinal chemistry, before potency improvements lock a project into an unfavorable substrate spectrum. Third, clinical development should connect tissue pharmacodynamics to a prospectively defined biological hypothesis. An association between a biomarker and response is a starting point; a reliable patient-selection tool requires validation.

There are also important limits to what current platforms can promise. Structural methods describe selected stable assemblies, whereas cellular recruitment occurs among competing partners and changing conformational states. Computational libraries sample the structures and chemistries available to them. Phenotypic screens enrich for mechanisms detectable in the chosen model. Rationality consists in recognizing these boundaries and using complementary experiments to reduce uncertainty, not in removing experimentation from discovery.

10 CONCLUSION

Molecular glues have developed from clinically useful compounds with poorly understood mechanisms into an increasingly designable form of pharmacology. CRBN established neosubstrate recruitment as a therapeutic principle; DCAF15, cyclin K, BCL6 and BRD4 showed that productive proximity can arise through several architectures. Recent HuR and charged-glue studies extend the available target surfaces and recruiting systems, while newer myeloma trials demonstrate that mechanistic advances can translate into clinically meaningful regimens.

The transition to rational design remains incomplete. Prospective optimization of an established interface is now achievable in multiple systems, whereas reliable de novo construction of arbitrary target–partner interactions remains difficult. The next decisive advances will connect molecular recognition to selective cellular consequences and a sustainable therapeutic window. For cancer therapy, the value of a molecular glue ultimately resides in the biological event it produces in the appropriate patient, rather than in the ternary complex alone.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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