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Molecular Glue Degraders: From Serendipity to Hunting and Design

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3.1 Introduction

The use of small-molecule drugs to modulate disease-relevant proteins continues to be the backbone of pharmacopeia. Classical efforts in drug development have followed an inhibitor-centric paradigm based on the occupancy of accessible pockets to block specific protein functions. Despite decades of outstanding progress, more than 80% of all human proteins remain beyond the reach of traditional inhibitors [1–3]. Novel approaches are required to target transcription factors, scaffolding proteins and other proteins central to diseases that typically lack catalytic activity and have remained recalcitrant to drug development [4]. New biological modalities, such as antibodies, have addressed some of these challenging targets. However, biologicals are hampered by issues such as poor cell permeability, chemical instability, lack of oral availability, and limited affordability for healthcare systems.

Recent innovations around targeted protein degradation (TPD) embody a fascinating new modality in pharmacotherapeutics. In this regard, the chemical ablation of proteins has emerged as an excellent alternative and complementation to occupancy-based strategies. This method builds on the (long considered impossible) concept of drug-induced proximity between proteins. To date, most work and progress on TPD has focused on hijacking the ubiquitin-proteasome system (UPS). However, additional approaches that involve other protein homeostasis machineries have been described, such as lysosome-targeting chimeras (LYTACs) [5], autophagosome-tethering compounds (ATTECs) [6, 7], autophagy-targeting chimeras (AUTACs) [8], and bacterial protease-targeting chimeras (BacPROTACs) [9]. Beyond protein degradation, further proximity-inducing small molecules that endow other neofunctions and outcomes to proteins are emerging [10–13].

The field of UPS-mediated TPD has experienced tremendous progress in recent years. This strategy is based on small molecules typically referred to as *degraders*.

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These pharmacological agents induce proximity between an E3 ubiquitin ligase and a target protein of interest (sometimes referred to as "neosubstrate"). The formation of an E3:degrader:target ternary complex results in polyubiquitination and subsequent proteasomal degradation of the target. Degraders modulate protein abundance, hence affecting both enzymatic and non-enzymatic activities. Moreover, most degraders have a catalytic mechanism of action because of their successful dissociation after promoting target polyubiquitination and are thus typically efficacious at very low doses. On the contrary, the classical inhibitor process is a competitive- and occupancy-driven event [14, 15].

Degraders can be classified on the basis of various criteria. We here divide them into multivalent or monovalent depending on the number of targeting moieties in the compound (Figure 3.1). In the multivalent category, heterobifunctional molecules known as proteolysis targeting chimeras (PROTACs) have paved the way. In 2001, pioneering work with peptidic ligands by C. M. Crews and R. J. Deshaies showed that an E3 could be redirected to ubiquitinate a protein of interest, and the term PROTAC was coined [16]. Interest in these bivalent molecules grew when they progressed to fully synthetic compounds that simultaneously bind target and E3 with dedicated warheads connected by a linker [17–22]. Recently, trivalent PROTACs have also been described [23]. Due to their modular architecture, multivalent degraders can be adapted to a spectrum of targets by exchanging the targeting warhead. This versatility renders PROTACs of particular interest for pharmaceutical development. However, this modularity also poses potential challenges for the clinical use of PROTACs as they often have high molecular weights, ranging from 700 to 1200 Da, and poor permeability (PROTACs have been extensively reviewed elsewhere [14, 15, 24]).

Monovalent degraders are single linker-less scaffolds that induce the degradation of target proteins by (a) gluing them to E3 ubiquitin ligases (*molecular glue degraders*) or by (b) promoting a vulnerable protein state (*destabilizers*) (Figure 3.1):

(a) *Molecular glue degraders* strengthen or induce de novo E3–target interactions that are often highly cooperative. This mode of action is exemplified by the clinically approved thalidomide and its analogs (the immunomodulatory imide drugs – IMiDs). Molecular glue degraders offer an exciting path for therapeutic innovations and will be the focus of this chapter.
(b) *Destabilizers* induce indirect E3–target dimerization. With this term, we refer to a diverse group of drugs that drive the target protein to a susceptible state, which is then recognized by an E3, prompting subsequent degradation. Upon target binding, destabilizers induce a variety of phenomena (e.g. revealing a degron, increasing surface hydrophobicity, inducing polymerization, and preventing protective interactions, among others). Examples are the clinically approved fulvestrant, which induces degradation of the estrogen receptor (ERα), or some kinase inhibitors that also induce target destabilization [25–27].

Whereas multivalent degraders follow a rational generalizable design, the discovery of monovalent degraders has been driven mostly by serendipity. In the following sections, we discuss the "molecular glue" concept and we review known

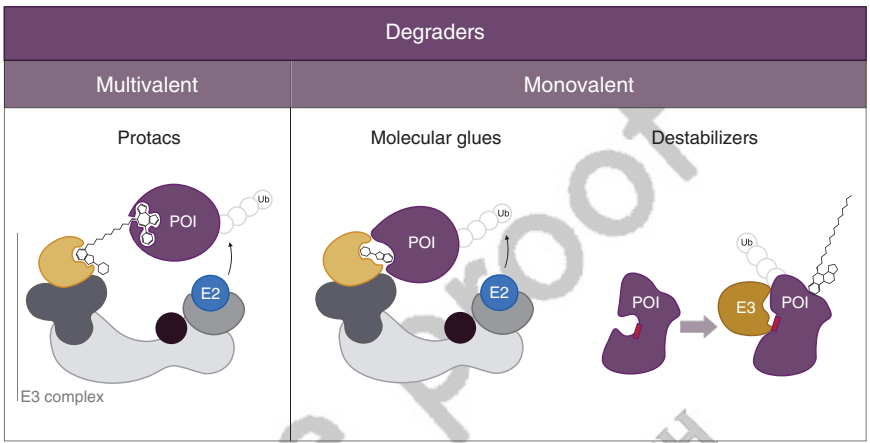


Figure 3.1 Types of degraders. Multivalent degraders (left, only bivalent PROTACs are depicted) bind E3 and target with dedicated warheads that are connected by a linker. Monovalent degraders (right) are small drug-like compounds and comprise: molecular glue degraders and destabilizers. Molecular glue degraders induce or stabilize direct protein–protein interactions between E3 and target. Destabilizers drive the target protein to a susceptible state via different phenomena (the exposure of a degron upon drug binding is shown). This susceptible state is then recognized by the degradation machinery (e.g. E3s). E3 schematics in PROTACs and molecular glue degraders represent an E3 of the cullin RING ligase (CLR) family. POI: protein of interest.

Color Fig. 3.1

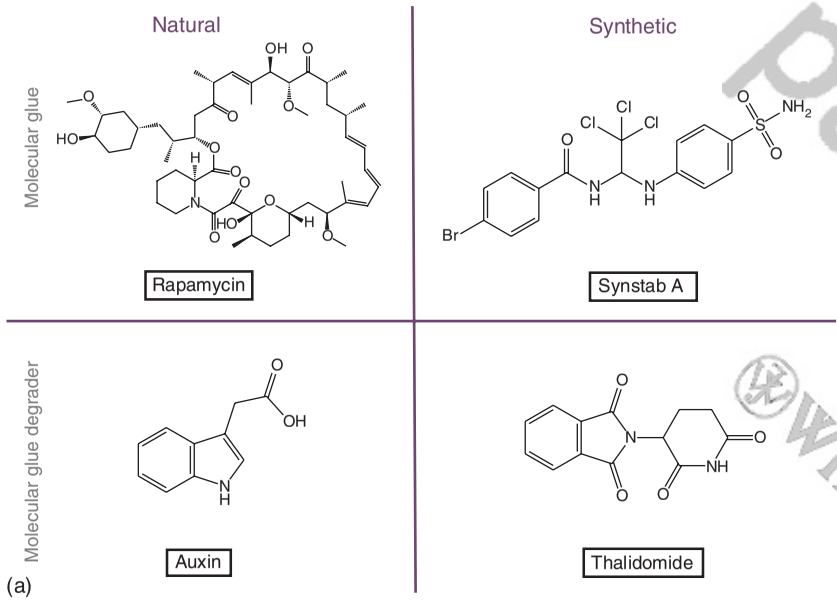
molecular glue degraders, with a special focus on (i) their accidental discovery and (ii) the progression toward more prospective strategies to identify and/or design them.

3.2 "Molecular Glue" Concept

3.2.1 Natural Compounds

3.2.1.1 Molecular Glues

Given that an estimated ~300 000 protein–protein interactions (PPIs) occur in human cells [28] and are involved in every physiological process, PPIs are an interesting, but arguably underexplored, target class. PPIs have recently become a major focus of investigation in drug discovery as the dysregulation of a number of PPIs has been linked to disease. Targeting PPI interfaces is challenging but not infeasible [29, 30]; however, inducing PPIs was long considered almost impossible. This view changed over the years with the discovery of a pool of natural compounds that cause protein associations and provide us with a wealth of inspiration and examples [31–34]. In particular, this capacity is well established for structurally complex natural products [35–40]. The concept of "molecular glue" was used in the early 1990s to describe the mechanism of action of the microbial macrolides FK506 and rapamycin (Figure 3.2a) and the cyclic peptide cyclosporin A. The former two bind to FKPB12, inducing neointeractions with calcineurin and mTOR, respectively



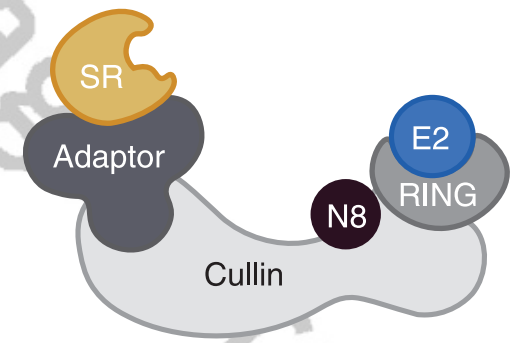


Figure 3.2 The "molecular glue" concept. (a) Selected natural and synthetic molecular glues and molecular glue degraders. (b) Schematic representation of the components of an E3 of the cullin-RING ligase (CRL) family. SR: substrate receptor. (c) Chemical properties of molecular glue degraders vs. bivalent PROTACs. Molecular weight, estimated topological polar surface area (TPSA), number of rotatable bonds, and octanol–water partition coefficient (logP) are shown. Molecular glue degraders: IMiDs (n = 13), aryl sulfonamides (n = 5) and cyclin K molecular glue degraders (n = 20). Bivalent degraders: VHL-based PROTACs (n = 21) and CRBN-based PROTACs (n = 20). Representative PROTACs were selected for the analysis (the 20 most cited PROTACs against the most common targets as reported in the open-access database PROTAC-DB) [41]. Chemical properties were either obtained from ChEMBL or calculated using ChemDraw v.20.1.0.112.

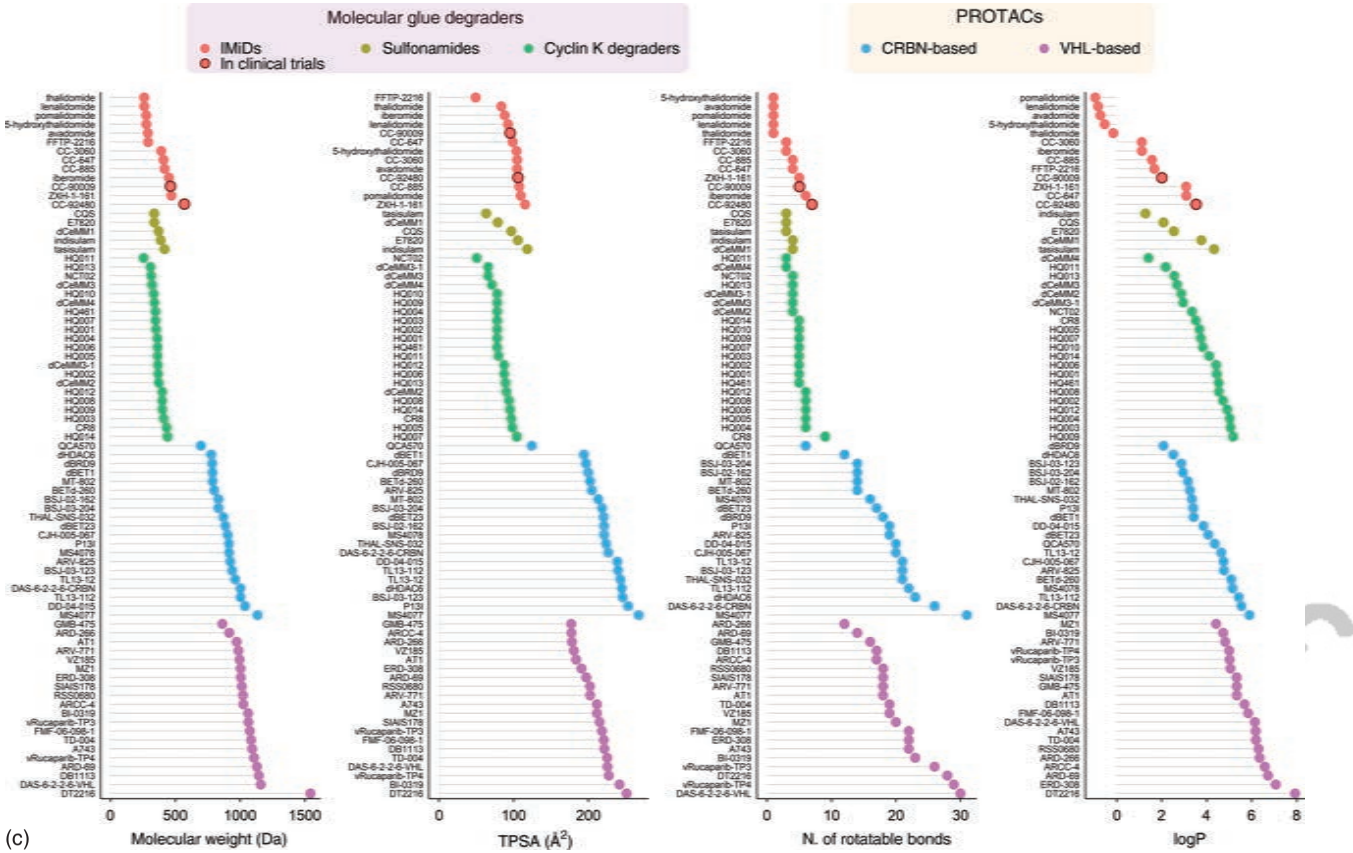


Figure 3.2 (continued)

[37, 38]. Cyclosporin A induces dimerization between calcineurin and cyclophilin [36, 42]. These findings paved the way for the discovery of additional compounds with similar proximity-inducing properties. One example is sanglifehrin A, found to induce PPIs between cyclophilin and IMP [43]. The molecular glue-type mechanism is not a privilege of highly complex chemical structures [44]. The fungal metabolite brefeldin A, arguably simpler, is a macrocyclic lactone that selectively stabilizes the interaction of the complex formed by ARF–GDP and the guanine exchange factor ARNO, thereby preventing guanine release [45, 46]. In this case, brefeldin A is a PPI stabilizer rather than an inducer as it binds only to a site formed in the complex.

In plant biology, we also find examples of structurally simple molecules that induce the dimerization of proteins. Brassinosteroids are plant hormones that function as molecular glues to bring the membrane receptor kinase BRI1 and its co-receptors together [47, 48].

3.2.1.2 Molecular Glue Degraders

The concept of *molecular glue degrader* is used for molecules that, like the phytohormone auxin (Figure 3.2a), induce proximity to an E3 ubiquitin ligase. Auxin binds TIR1 (part of the E3 ligase SCF^{TIR1}) and facilitates its interaction with the transcriptional repressors AUX/IAA, resulting in their proteasomal degradation [49, 50]. Another example of a natural molecular glue degrader is methyl jasmonate, a phytohormone that recruits the E3 ligase SCF^{COI1} via binding to COI1 to trigger the degradation of JAZ repressor proteins [51]. Beyond plant biology, hijacking E3 ligases is used by many viruses to defend themselves against the host's response [52, 53]. Recently, the polyketide natural products asukamycin and manumycin A have been proposed to function as covalent molecular glue degraders [54].

We consider that the most compelling argument in favor of small-molecule modulation of PPIs stems from all the aforementioned natural products, which convey their physiological activity using this mode of action. Some of these molecules have been used for many years as therapeutic agents, such as the immunosuppressants FK506 (e.g. Prograf), rapamycin (Rapamune), and cyclosporin A (e.g. Sandimmun). Others, like auxin, are widely used tools in research.

As discussed in the next section, it was the discovery that simple synthetic compounds can also function as molecular glues (or molecular glue degraders) that drove greater interest in this seemly rare type of small molecules.

3.2.2 Synthetic Compounds

3.2.2.1 Molecular Glues

In 2000, synstab A (Figure 3.2a), a simple synthetic compound functioning as a molecular glue that promoted microtubule formation, was discovered [55] and followed by many other notable examples [56]. Of note, simple synthetic compounds can also function as intramolecular molecular glues, as exemplified by DT-061 [57] or ET070 [58]. The former alters the interaction subunits of PP2A, thereby

modifying substrate selectivity [57] while the latter corrects the hyperactivation of mutant SHP2 [58]. All these synthetic molecular glues provided a proof of concept that simple, non-natural compounds can also induce PPIs.

3.2.2.2 Molecular Glue Degraders

The same pattern of events was true for molecular glue degraders. Episodic discoveries identified structurally simple synthetic compounds with anticancer activities and which were then shown to act as glue degraders. Prime examples are thalidomide (Figure 3.2a) and its analogs (IMiDs). Seminal studies uncovered that IMiD binding to the E3 $CRL4^{CRBN}$ leads to the recruitment and induced degradation of several targets (e.g. IZKF1/3) [59–62]. Similarly, aryl sulfonamides, such as indisulam or E7820, hijack $CRL4^{DCAF15}$ to degrade the splicing factor RBM39 and the paralog RBM23 [63, 64]. Importantly, all these molecular glue degraders, whether natural or synthetic, share a common feature, namely, their capacity to induce the degradation of target proteins considered *undruggable* according to conventional classifications (e.g. transcription factors). In addition, the E3 ubiquitin ligases hijacked belong to the cullin RING ligase (CRL) family. There are around 250 CRLs, which make up the largest family of E3s and account for almost 20% of all cellular UPS-dependent protein degradation. CRLs are modular assemblies formed by a cullin scaffold (in mammals Cul1, Cul2, Cul3, Cul4A/B, Cul5, Cul7, and Cul9), an adaptor protein, a substrate receptor that engages specific substrate proteins, and a RING protein subunit (RBX1 or RBX2) that recruits ubiquitin-loaded E2s to enable ubiquitin transfer onto the substrate (Figure 3.2b) [65, 66]. The E3 activity is tightly regulated, including activation by Nedd8 attachment, inhibition and substrate receptor exchange by Cand1, and inactivation with Nedd8 removal by the COP9 signalosome, among other regulatory layers. The substrate receptor governs endogenous substrate specificity and is typically the CRL component that is hijacked by molecular glue degraders. Most PROTACs also hijack the substrate receptors of CRLs, although additional E3s belonging to other families have also been utilized successfully (e.g. IAPs [67], MDM2 [68–70], RNF4 [71], and RNF114 [72]).

All the aforementioned discoveries have illustrated the great potential of molecular glue degraders. While these molecules share key features with PROTACs (e.g. modulation of protein abundance), they also have important advantages. For example, molecular glue degraders have favorable drug-like properties (e.g. molecular weight < 500 Da; Figure 3.2c). In addition, they have proven capacity to induce the degradation of seemingly unligandable proteins by strengthening and/or inducing de novo PPIs that are highly cooperative. Conversely, PROTACs are typically not designed to capitalize on cooperative interfaces, although there are examples that also prompt large PPIs [73–75]. In addition, molecular glue degraders have already provided clinical validation for the therapeutic concept of TPD [76–87]. A significant disadvantage of the glue degraders available is that most of them have been discovered unintentionally. In the following sections, we review known synthetic molecular glue degraders divided into two categories: serendipitous discoveries and the first examples of intentional findings.

3.3 Synthetic Molecular Glue Degraders: Serendipitous Discoveries

3.3.1 Molecular Glue Degraders Hijacking $CRL4^{CRBN}$ (IMiDs): Broad Target Accommodation

Thalidomide was used in the late 1950s to treat morning sickness in pregnant women but was withdrawn from the market soon after due to terrible teratogenic effects [79, 88]. Further studies revealed important therapeutic activities that led to the approval of thalidomide for the treatment of erythema nodosum leprosum (in 1998) and multiple myeloma (in 1999) [89]. This spurred the development of chemically similar analogs (IMiDs), first lenalidomide and then pomalidomide. The immunomodulatory and antiangiogenic properties of these analogs warranted clinical approval in 2006 for the treatment of relapsed or refractory myelomas [90]. Of note, IMiDs were approved before the elucidation of their mode of action. In 2010, over fifty years after thalidomide was first used in humans, Hiroshi Handa and colleagues found that this drug directly binds to the protein cereblon (CRBN), the substrate receptor of the E3 ligase $CLR4^{CRBN}$ [59]. By binding to CRBN, thalidomide was first thought to inhibit the activity of $CLR4^{CRBN}$, thus contributing to its teratogenicity. However, it was then shown that CRBN is necessary for the therapeutic effects of lenalidomide and pomalidomide [91, 92]. Soon after, several groups discovered that IMiDs do not inhibit the enzymatic activity of $CRL4^{CRBN}$ but instead confer neofunctions to this E3 ligase. In this regard, IMiDs induce CRBN-dependent proteasomal degradation of the C2H2-type zing-finger (ZF) transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) [60–62]. Shortly after, lenalidomide was shown to also induce the degradation of the kinase CK1α, while the structurally similar thalidomide and pomalidomide do not [93]. This discovery reflected that small differences in the chemical structure could drive substantial differences in the specific set of proteins targeted for degradation. A plethora of additional targets of IMiDs have been identified since then [94].

These discoveries were key catalyzers in the field of TPD. In addition, decades of clinical experience have established thalidomide and its analogs as frontline agents in the treatment of some hematological malignancies, thus providing evidence that the induction of protein degradation via a glue-like mechanism can be an efficacious therapeutic strategy. Currently, thalidomide, lenalidomide, and pomalidomide are used in a variety of clinical settings, including the treatment of multiple myeloma, non-Hodgkin lymphoma, and myelodysplastic syndrome, as well as Kaposi sarcoma [79].

In 2014, the first crystal structures of IMiDs bound to CRBN in complex with the CRL adaptor DDB1 were published [95, 96]. They revealed that (i) the conserved glutarimide ring interacts with a hydrophobic pocket of CRBN made up of three tryptophan residues with a phenylalanine side chain as the base and (ii) the variable part of IMiDs (phthalimide or isoindolinone groups) was solvent exposed. ZF transcription factors are the biggest structural class of IMiD-induced targets. However, the first structures of ternary complexes, confirming that IMiDs are indeed molecular glue degraders, came in 2016 and involved two non-ZF targets: (i) CRBN in

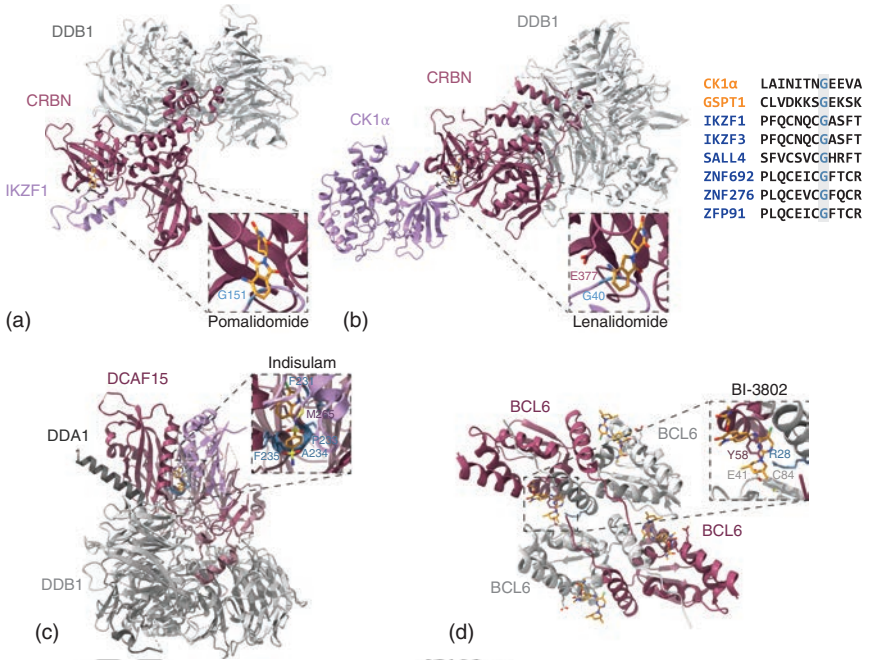


Figure 3.3 Overview of molecular glue degrader-induced protein–protein interfaces. (a) Selected IMIDs: DDB1–CRBN–lenalidomide–CK1α X-ray structure (PDB: 5FQD, left) [97] and DDB1–CRBN–pomalidomide–IKZF1 X-ray structure (PDB: 6H0F, right) [98]. (b) Sequence alignment of ZF targets of IMiDs (blue) and non-ZF targets (yellow). The key glycine of the β-hairpin loop is highlighted in blue (as in panel A). (c) Aryl sulfonamide example: DDB1–DDA1–DDCAF15–indisulam–RBM39 complex (PDB: 6Q0W). *Source:* Adapted from Faust et al. [99]. (d) BCL6–BI3802–BCL6 oligomers (PDB: 6XMX). *Source:* Adapted from Słabicki et al. [100].

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complex with CK1α and lenalidomide (Figure 3.3a) [97] and (ii) CRBN in complex with the glue degrader CC-885 and the translation termination factor GSPT1 [101]. Subsequent studies showed IMiD-induced ternary complexes of CRBN and various ZF factors, namely, IKZF1 (Figure 3.3a) [98], ZNF692 [98], and SALL4 [102, 103]. These studies revealed common features in the degron of all these ZF targets. They all share a β-hairpin loop structure in one ZF domain, with a key glycine residue. The new IMiD derivatives CC-3060 and CC-647 target the ZF transcription factor ZBTB16 for degradation by primarily engaging distinct structural degrons on different ZF domains [104]. Similar structural features in proteins without ZF domains can also serve as IMiD degrons, as exemplified by GSPT1. This degron has little sequence homology to the known ZF targets of IMiDs but shares a β-hairpin loop containing a key glycine residue (Figure 3.3b) [97].

New thalidomide derivatives aiming to increase the selectivity and potency and that circumvent resistance to approved IMiDs have been developed, and some of them are approaching the clinic [105]. These next-generation CRBN modulators are based on modifications that alter the target–CRBN binding interface. These agents

include the IKZF1/3 molecular glue degraders avadomide (CC-122) [106], iberdomide (CC-220) [107, 108], CC-92480 [109], CC-99282 [110], and CFT7455 [111, 112], among others.

Other chemical substituents have *altered the recruitment of targets*. Some of these pharmacologic agents are currently in clinical trials: CC-90009 (GSPT1 glue degrader) [113] and DKY709 (Helios degrader; NCT03891953).

Why are pharmaceutical companies investing so heavily in the development of thalidomide analogs? The prospect of having next-generation IMiD derivatives that might overcome therapeutic resistance or that, by altering the targets recruited to CRBN, have activity in new disease indications are highly appealing. With regard to potential revenue, lenalidomide was ranked the third top drug by global sales and the best-selling small-molecule drug worldwide both in 2019 [114] and in 2020 [115].

The downside of the broad target repertoire exhibited by IMiDs is the risk of toxicity, such as the tragic teratogenicity that occurred with thalidomide in the 1960s. Of note, the teratogenicity shown by thalidomide has recently been related to the degradation of SALL4 [102, 107, 116], PLZF [117], and p63 [118]. The potential of IMiDs other than thalidomide itself showing teratogenic effects has not been assessed (or reported).

Of note, IMiDs have also had a remarkable impact on the progression of PROTACs in recent years. The realization that IMiDs bind to CRBN fueled interest in heterobifunctional degraders (PROTACs) by showing that IMiD-like molecules could be turned into CRBN-recruiting warheads. In 2015, Winter et al. reported the first *in vivo* compatible PROTAC (dBET1) by conjugation of an IMiD-like phthalimide moiety to the BET-bromodomain inhibitor JQ1 [20]. dBET1 induced fast and potent degradation of BRD2/3/4 both in cell lines and in xenograft models. The same year, Lu et al. reported IMiD-based PROTACs [119]. $CRL4^{CRBN}$, together with $CRL2^{VHL}$, have proven to be versatile E3 ligases that are ideally suited for PROTAC design. CRBN and VHL warheads are currently the most common moieties used in PROTACs. Of note, current VHL-based PROTACs did not evolve from molecular glue binders but initially relied on peptidic VHL ligands based on the natural substrate HIF1α. The subsequent design of small-molecule mimetics of the HIF1α peptide as VHL binders culminated in the first fully synthetic VHL-based PROTACs [21, 22].

While CRBN has shown broad IMiD-induced target accommodation, not all E3-based systems can be expected to exhibit similar flexibility. An example is DCAF15, which is hijacked by aryl sulfonamides and has a much more limited target spectrum, as discussed in the next section.

3.3.2 Molecular Glue Degraders Hijacking $CRL4^{DCAF15}$ (Aryl Sulfonamides): High Shape Complementarity

Anticancer aryl sulfonamides are the second class of synthetic molecular glue degraders described. A representative example is indisulam (E7070), initially

identified in a phenotypic screen for small molecules with anticancer activity [120]. Its cytotoxic activity promotes G1-phase arrest and the death of human cancer cell lines [120, 121]. More than a decade later, the mechanism of action of indisulam and the related sulfonamides tasisulam, chloroquinoxaline sulfonamide (CQS), and E7820 was deciphered [63, 64]. They were found to promote the recruitment of the splicing factor RBM39 to the substrate receptor DCAF15 (part of the E3 ligase $CRL4^{DCAF15}$), leading to RBM39 polyubiquitination and proteasomal degradation. In addition to RBM39, subsequent studies identified the paralog RBM23 as an additional destabilized target [122]. Interestingly, the recently discovered aryl sulfonamide dCeMM1 displays exquisite selectivity for RBM39 degradation but not for RBM23 [123]. The pre-mRNA splicing factor PRPF39 [124] and HIF1-β [125] are additional targets of some aryl sulfonamides. The crystal structures of some ternary complexes have revealed that indisulam (Figure 3.3c) and E7820 interact with DCAF15 through the aryl sulfonamide moiety, which functionalizes a shallow, non-conserved cavity on DCAF15 [99, 126, 127]. This cavity establishes hydrophobic interactions with an α-helical degron motif on the RRM2 domain of RMB39, leading to its selective recruitment to DCAF15. RBM39 interacts both with DCAF15 and with the adaptor DDB1. The binding of DDB1 to an additional factor, DDA1, stabilizes the overall assembly (Figure 3.3c). Interestingly, IMiDs and sulfonamides show completely different binary binding affinities to the corresponding E3 substrate receptors. IMiDs display a strong nanomolar affinity for CRBN and their binding reshapes the E3 surface, promoting the recruitment of targets. In contrast, aryl sulfonamides present much lower binding affinities to DCAF15 alone. The low binary affinity is compensated by a large interaction surface between DCAF15 and RBM39, which almost doubles the area of CRBN–target interactions mediated by IMiDs. The large sulfonamide-dependent surface appears to be critical for overcoming an entropically unfavorable scenario: only when all three entities (DCAF15, aryl sulfonamide, and RBM39) come together does ternary complex formation occur. CRBN-bound IMiDs recruit a conserved β-hairpin loop, whereas DCAF15-bound sulfonamides recruit particular side chains from a helical scaffold.

While IMiDs are already a clinical reality, no aryl sulfonamide has merited approval to date. Earlier phase II clinical trials with indisulam and E7820 focused on patients with advanced-stage solid tumors but showed limited efficacy [128–135]. Current efforts to elucidate their mechanism of action may establish the bases for improved patient stratification.

Sulfonamide-based PROTAC design is not as straightforward as IMiD- or VHL ligand-based approaches [136]. The buried nature of aryl sulfonamides and the extensive DCAF15:RBM39 surface interface suggest a hard transition from a glue mechanism to a DCAF15-based PROTAC. Nevertheless, a novel DCAF15-based PROTAC against BRD4, named DP1, has recently been reported [137]. Conceptually, the sulfonamide-like mode of action suggests that non-ligandable E3s are also valuable for drug development campaigns, given that molecular glue degraders do not necessarily depend on high-affinity binding to the E3 in isolation.

3.3.3 BCL6 Degraders: Induction of Polymerization

Screens for novel BCL6 inhibitors by two independent groups led to the discovery of small molecules that, unexpectedly, induce the proteasomal degradation of BCL6, a transcriptional repressor and known oncogenic driver for lymphoma development [138, 139]. A recent study addressed the mechanism of action of one of these compounds: BI-3802 [100]. The authors revealed that BCL6 destabilization was elicited via compound-induced polymerization, with BI-3802 acting as a molecular glue between BCL6 proteins (Figure 3.3d). These filaments led to the enhanced ubiquitination by SIAH1, an E3 ligase of the RING family, and subsequent proteasomal degradation. To be precise, this mechanism of action is at the interface of both monovalent degrader subcategories (molecular glue degrader and destabilizer, Figure 3.1). BI-3802 does not directly glue an E3 to BCL6 and thus could be classified as a destabilizer. However, the glue-like mechanism prompting BCL6 polymerization and subsequent E3-dependent degradation supports the consideration of BI-3802 as a peculiar molecular glue degrader. Interestingly, and in contrast to all the aforementioned glue degraders, the E3 SIAH1 mediates the degradation of both endogenous and compound-dependent aggregated BCL6, the latter strongly facilitating SIAH1 ubiquitination and degradation. The concept of polymerization-dependent degradation induced by monovalent degraders offers interesting new opportunities for TPD. This mechanism of action may be shared with other monovalent degraders reported in the literature whose exact functioning has yet to be elucidated.

3.4 Synthetic Molecular Glue Degraders: Intentional Developments

The discovery of molecular glue degraders has been driven by fortuity, as outlined in the previous section, and strategies for their systematic development or identification are still lacking. Recently, we and others have challenged the "non-rational discovery" notion around this seemingly rare class of degraders. In this section, we discuss the first examples of rational strategies to develop molecular glue degraders, falling into binary combinations of the following categories: target agnostic, ligase agnostic, target driven, and ligase driven (Figure 3.4a).

3.4.1 β-Catenin Molecular Glue Degraders

In 2019, a target-driven and ligase-driven drug discovery effort by Simonetta et al. identified small molecules that enhanced the interaction between $CRL1^{\beta\text{-}TrCP}$ and mutant β-catenin [143]. They provided the first example of the intentional design of molecular glue degraders. Moreover, this was the first example of glue degraders that reinforce a native E3 ligase: substrate pair altered in cancer. β-catenin is often mutated at a phosphodegron recognized by $CRL1^{\beta\text{-}TrCP}$, leading to the stabilization of β-catenin with subsequent oncogenic consequences. A high-throughput biochemical screen based on fluorescence polarization was then coupled to

structure-based lead optimization to identify several compounds, such as NRX-1532 or NRX-103094, able to re-enhance the binding and ubiquitination of mutant β-catenin (Figure 3.4b) [143]. This elegant study provides a blueprint for similar future endeavors toward the intentional development of molecular glue degraders.

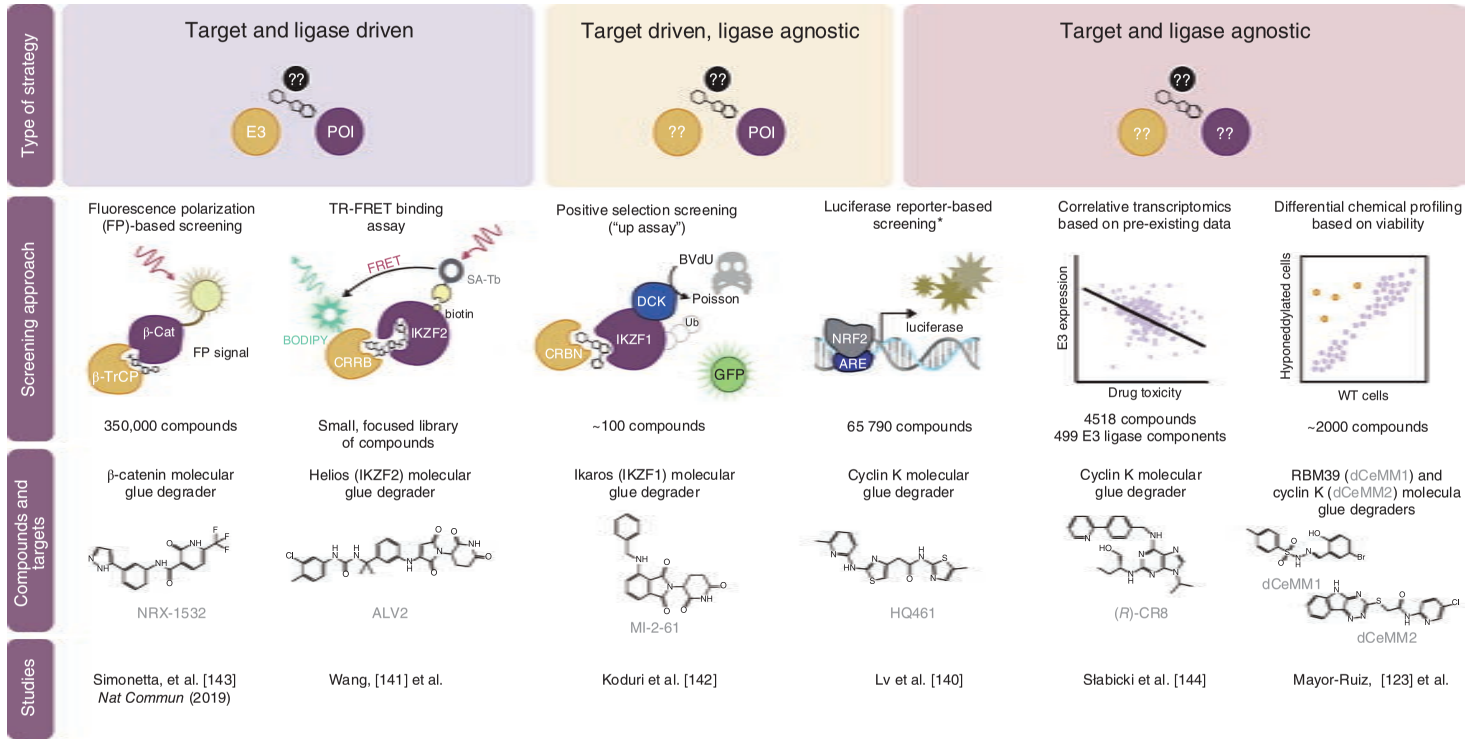
3.4.2 Cyclin K Molecular Glue Degraders

In 2020, three groups reported the discovery of structurally divergent cyclin K (CycK) molecular glue degraders. Although all the studies converged on the identification of compounds with the same mechanism of action, they used distinct strategies as a starting point. Słabicki et al. and Mayor-Ruiz et al. developed target- and E3-agnostic approaches [123, 144]. Lv et al. executed a target-driven approach looking for NRF2 inhibitors, which then led to the identification of a molecular glue degrader against a different target (CycK) [140].

Słabicki et al. employed bioinformatic correlations of the transcriptional expression of E3 ligase components in cancer cell lines with pre-existing drug sensitivity data [144]. This exercise identified that DCAF15 expression correlated with aryl sulfonamide toxicity. In addition, the cytotoxicity of (*R*)-CR8, a known CDK inhibitor, correlated with the expression of the CRL adaptor DDB1. They showed that (*R*)-CR8 induces selective degradation of CycK in a DDB1-dependent manner. Mayor-Ruiz et al. developed a scalable chemical profiling strategy based on hyponeddylated models (UBE2M mutant cancer cells [145]) with widely impaired CRL function. The strategy was validated with the discovery of a novel RBM39 molecular degrader (dCeMM1) that hijacks $CRL4^{DCAF15}$. In addition, three small-molecule drugs, dCeMM2/3/4, identified as dependent on functional CRLs to exert their toxicity, proved to be CycK molecular glue degraders [123]. Finally, Lv et al. used a luciferase-based high-throughput screen in principle designed to identify NRF2 inhibitors, leading to the identification of yet another CycK molecular glue degrader, namely, HQ461 [140].

Deciphering the mechanisms of action of (*R*)-CR8, dCeMM2/3/4, and HQ461 was enabled by multi-omics campaigns to identify and validate the target and E3 involved. Importantly, all the studies converged on a unifying and unprecedented mechanism of action: drug binding to the active site of the usual CycK partner CDK12 (and, presumably, the paralog CDK13) strengthened the dimerization between CDK12:CycK and the CRL adaptor DDB1 in the absence of a dedicated substrate receptor. CDK12/13 act as non-native substrate receptors that position CycK in the ubiquitination zone accessible to the E2 loaded in the partial CRL4 complex. Extensive profiling, including a 3.5 Å structure solved by Słabicki et al., confirmed the DDB1–CR8–CDK12 complex formation and revealed a substantial protein–protein interface (Figure 3.4c). Of note, another group reported in 2021 the serendipitous discovery of yet another chemically distinct CycK glue degrader: NCT02. They conducted a screen for inhibitory compounds of colorectal cancer spheroids [146].

All these findings provided evidence of a novel mechanism in which a molecular glue degrader induces target degradation by a distant PPI rather than by directly reprogramming the target–E3 interface. In addition, these glue degraders showed that it is indeed possible to rewire a CRL adaptor instead of the substrate receptor as



(a)

Figure 3.4 Prospective discovery of molecular glue degraders. (a) Strategies to intentionally discover molecular glue degraders. *The identification of the CycK degrader HQ461 is not categorized as a fully target-driven strategy as it was initially designed to identify NRF2 inhibitors. Source: Adapted from Lv et al. [140]. POI: protein of interest. **β**-Cat: **β**-catenin. CycK: Cyclin K. TR-FRET: Time-resolved fluorescence energy transfer. (b) Crystal structure of NRX-103094 bound to SKP1–**β**TrCP in complex with monophosphorylated Ser33 **β**-catenin (residues 16–48) (PDB: 6M91) [143]. (c) DDB1–CR8–CDK12:CycK (PDB: 6TD3). *Source:* Adapted from Słabicki et al. [144].

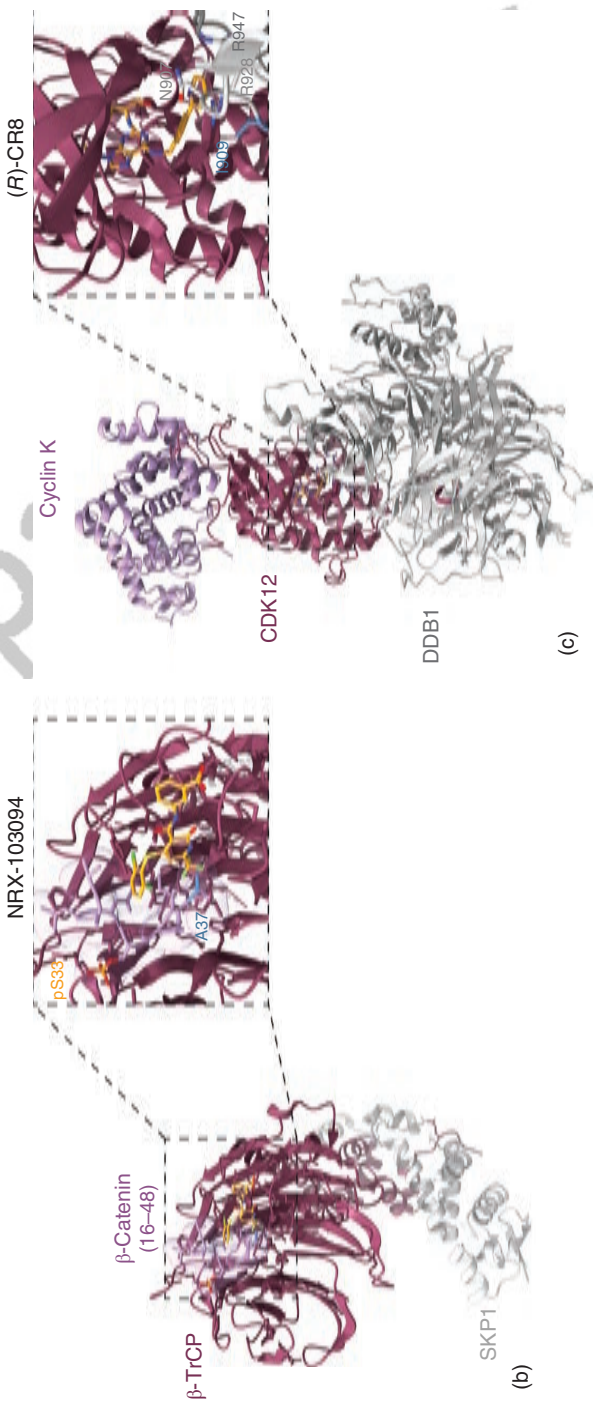


Figure 3.4 (continued)

IMiDs and aryl sulfonamides do. As aryl sulfonamides showed with DCAF15, the CycK glue degraders recruit an E3 component (DDB1) considered unligandable. How the remarkable chemical diversity of CR8, dCeMM2/3/4, and HQ461 converges in the induced degradation of CycK remains unclear.

3.4.3 Prospective Discovery of IKZF1 Molecular Glue Degraders via "Up Assays"

Koduri et al. reported a target-driven E3-agnostic positive selection assay ("up assay") to identify novel monovalent degraders of IKZF1 [142]. This strategy makes use of the enzyme DCK fused to IKZF1. DCK converts a pro-drug (the non-natural nucleoside BVdU) into a toxic compound. Hence, degradation of the fusion protein prevents the DCK-mediated conversion of BVdU into a toxin. For the screening setup, they used a small library of several uncharacterized IMiD-like molecules described in the literature and approximately 100 newly synthesized analogs of pomalidomide. Chemical screens coupled to co-treatment with the BVdU allowed them to identify novel IMiD-like molecular glue degraders of IKZF1 via the concomitant resistance (e.g. MI-2-61). Although IMiD analogs were used for the screening, we have classified this strategy as "prospective" given the foreseen potential. Indeed, using a non-IMiD-like small library of compounds enriched in metabolic inhibitors, the same authors found that the small-molecule Spautin-1 degrades IKZF1 in a CRBN-independent manner. The exact mechanism of action of the direct/indirect compound-mediated IKZF1 degradation remains to be elucidated. Overall, this study provided proof of principle of how phenotypic "up assays" based on target fusion to suicide genes can be used to identify glue degraders.

3.4.4 Structure-Guided Development of Helios (IKZF2) Molecular Glue Degraders

In 2021, Wang et al. reported the structure-guided development of molecular glue degraders that recruit CRBN to the transcription factor Helios (IKZF2) involved in immunosuppression [141]. This study exemplified a target-driven, E3-driven approach to develop glue degraders.

Within the Ikaros family of ZF transcription factors, only Ikaros (IKZF1) and Aiolos (IKZF3) are degraded by canonical IMiDs. The presence of a glutamine residue in their second ZF domain enables IMiD-induced degradation [61], while the histidine residues in Helios (IKZF2) do not. Since the IMiD analog CC-885 can induce weak dimerization between CRBN and a mutant version of IKZF1 in which glutamine 146 is a histidine [101], they hypothesized that a more flexible CRBN-binding core could accommodate a key Helios histidine residue. They screened a small, focused library of analogs through a CRBN:Helios dimerization assay based on time-resolved fluorescence energy transfer (TR-FRET). Several rounds of medicinal chemistry optimization led to ALV1 and ALV2. The former induces CRBN-dependent degradation of both Ikaros and Helios, while the latter has relative selectivity for Helios over Ikaros/Aiolos. Of note, Eos (IKZF4), another member of

the Ikaros transcription factor family, also encodes a histidine at the same position as Helios within the critical ZF domain that regulates the degradability of this family of proteins. As expected, ALV1 and ALV2 also induce Eos destabilization [141].

Although intentional, this strategy builds on the abundant structural information available for other members of the Ikaros family in complex with canonical IMiDs. Hence, it remains to be seen how similar strategies could be applied for different targets and E3 ligases. Nevertheless, similar structure-based efforts may yield molecular glue degraders for other previously unligandable targets by reprogramming E3 ligase substrate specificity.

3.4.5 Discovery of VHL-Binding Molecular Glue Degraders

VHL-focused approaches to discover molecular glue degraders, both in a target-agnostic and in a target-driven fashion, have been covered recently at several scientific events. Although not yet published, we provide a succinct description of these approaches.

Novartis (NIBR) has already disclosed a prototypical example of an E3-driven target-agnostic strategy based on *protein arrays* (unpublished). This strategy was used to screen for compound-induced interactions between the substrate receptor VHL and thousands of proteins. The small molecules "compound 4" and "compound 5" recruit VHL to CDO1, a critical regulator of cysteine metabolism, resulting in proteasomal degradation of the latter. Although the scalability of this approach is limited, it provides yet another valid avenue toward intended discoveries of molecular glue degraders.

Stuart Schreiber's lab and colleagues have developed an unpublished strategy named diversity-oriented synthesis encoded by DNA oligonucleotides (DOSEDO) to synthesize DNA-barcoded compounds. The resulting DNA-encoded libraries (DELs) are incubated with tagged target proteins to advance the discovery of protein binders that can be "decoded" using DNA sequencing. They have also applied this strategy to molecular glue discovery for preselected targets by screening for cooperative binding. Differential screening using these DELs in the absence and presence of "presenter" proteins has brought about the discovery of presenter-dependent binders. As a proof-of-principle study, in collaboration with Novartis (NIBR), they used BRD4 as a preselected target and VHL as a presenter to find the molecular glue degrader FYI979 (unpublished).

The use of both protein arrays and DELs showcase exciting new possibilities to facilitate the intentional discovery of molecular glue degraders.

3.5 Conclusions and Outlook

Progress in the TPD field has brought us to exciting times on multiple fronts: approved drugs shown to act as molecular glue degraders, PROTACs in clinical phases, and a growing repertoire of new strategies to identify and design more

of these pharmacological modalities. In this chapter, we aimed to summarize the discovery of molecular glue degraders, both by unintentional and by intentional endeavors. These examples, together with exhaustive mechanistic characterizations, have revealed that molecular glue degraders are more frequent than we anticipated, and they offer important lessons about compound-induced proximity for the development of efficient therapeutics. In addition, these molecules keep surprising us with new mechanisms of action. The pairing mechanisms by which molecular glue degraders may induce proximity between ~600 human E3 ligases (and potentially involving several core components in modular E3s) and > 20 000 protein targets seem virtually unlimited. We envisage that phenotypic screens will continue to be pivotal for the discovery of glue degraders, evolving toward more advanced and sophisticated target-driven approaches. It is also exciting to see the emergence of an increasing number of structural hypotheses on features that can determine the likelihood of a substrate being glued via this mechanism. Accordingly, structure-based drug design is also foreseen to pave the way toward more rational developments, together with in silico modeling tools and virtual screening assisted by artificial intelligence. Furthermore, critical technological progress in high-throughput proteomics will further help to accelerate drug discovery in this area. Finally, the advances made in TPD have fueled interest in other proximity-inducing pharmacological strategies, whose development will be fascinating to follow in the coming years.

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Conflict of Interest Statement

C.M-R. is part of the Scientific Advisory Board of Nostrum Biodiscovery. The remaining authors report no competing interests.

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Abstract

Many essential biological processes are regulated through protein–protein interactions. Some natural and synthetic small-molecule compounds also operate through induced protein proximity. In particular, molecular glue degraders are small drug-like compounds that prompt or strengthen the dimerization between E3 ubiquitin ligases and target proteins, prompting the target ubiquitination and subsequent proteasomal degradation. This and other pharmacological strategies of targeted protein degradation hold the promise to overcome some limitations of traditional occupancy-based therapeutic modalities. In this chapter, we summarize our current understanding of protein destabilization by molecular glue degraders, with a special focus on the following: (i) the serendipitous discoveries of some clinical and preclinical compounds and (ii) the first examples of intentional discoveries. By inducing proximity to E3 ligases, molecular glue degraders open up an exciting avenue for the development of novel therapeutics against otherwise undruggable proteins

Keywords

molecular glue degraders; targeted protein degradation; chemical biology