Molecular glues: enhanced protein-protein interactions and cell proteome editing

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Abstract
The druggable genome is limited by structural features that can be targeted by small molecules in disease-relevant proteins. While orthosteric and allosteric protein modulators have been well studied, they are limited to antagonistic/agonistic functions. This approach to protein modulation leaves many disease-relevant proteins as undruggable targets. Recently, protein-protein interaction modulation has emerged as a promising therapeutic field for previously undruggable protein targets. Molecular glues and heterobifunctional degraders such as PROTACs can facilitate protein interactions and bring the proteasome into proximity to induce targeted protein degradation. In this review, we discuss the function and rational design of molecular glues, heterobifunctional degraders, and hydrophobic tag degraders. We also review historic and novel molecular glues and targets and discuss the challenges and opportunities in this new therapeutic field.

Keywords Molecular glues · PROTACs · Targeted degradation · Protein modulation

Introduction

Every major cellular process relies on a complex and dynamic network of protein-protein interactions (PPIs). The dysregulation of these PPIs often leads to disease. For example, in cancer, abnormally expressed proteins interacting with their protein-binding partners can create a network of signaling pathways, driven by molecular signatures, that promote tumorigenesis, proliferation, invasion, and metastasis [1]. As such, the disruption or modulation of these cancer PPIs has emerged as a novel and promising therapeutic field.

The “druggable genome” or the proportion of the genome that can be targeted by small molecule drugs, is limited to disease-relevant proteins that have structural features that can be targeted by small molecules [2]. For decades, research has been focused on finding, designing, and optimizing small molecules that antagonize/agonize protein function. Under this approach, most protein inhibitors are small molecules that directly bind to the interaction surface of a protein, often a hydrophobic binding pocket or enzyme active site, sterically preventing binding to its substrates or interaction partner(s). Some protein targeted drugs bind to a surface region of a protein partner outside of the protein interaction interface itself, and antagonize protein function in an allosteric fashion [3]. However, many disease-relevant signaling mechanisms are carried out by interactions between proteins.

Modulating interactions between proteins can be difficult. For example, the contact surfaces involved in PPIs are large (~1500–3000 Å2) compared to those involved in protein-small molecule interactions (~300–1000 Å2). Additionally, the contact surfaces of PPIs are often flat and lack deep pockets or grooves present at the surfaces of proteins that typically bind to small molecules. Other challenges are the presence of noncontiguous amino acid binding sites, intrinsically disordered domains, and a general lack of natural ligands [4, 5]. For these reasons, some proteins have been deemed “undruggable” by small molecules. This umbrella of “undruggable” targets includes membrane-tethered scaffold proteins, transcription factors, splicing factors, non-enzyme proteins, steroid receptors, and cancer driver genes such as the RAS protein family, MYC, Hippo/YAP, STAT3, PAX3-FOXO, etc [6–8].

The challenge of tackling the undruggable proteome has inspired alternative technologies to modulate PPIs by inducing protein-protein stabilization and regulating the
abundance of disease-inducing proteins by targeting protein degradation via induced proximity with a ubiquitin ligase [9]. In other words, this new approach allows for the stabilization of PPIs which may lead to deactivation or activation of protein activity, or to protein degradation instead of inhibition. Given these innovative approaches, proteins that were once deemed “undruggable” may be druggable after all.

Targeted protein degradation focuses on the development of small molecule degraders, including molecular glues and proteolysis-targeting chimeras (PROTACs). In this review, we will highlight the role of molecular glues in PPI stabilization, modulation, and protein degradation as well as heterobifunctional degraders and their role in protein degradation.

The ubiquitin-proteasome system (UPS)

Protein homeostasis, also known as proteostasis, is a protein quality control process by which the cell balances the expression of newly synthesized proteins and the degradation of damaged or misfolded proteins that are beyond repair [10]. The ubiquitin-proteasome system (UPS) is a proteostasis mechanism designed to degrade polyubiquitinated proteins via the proteasome.

The to-be-degraded protein is targeted for proteolysis by ubiquitination, a process mediated by the E1-E2-E3 enzymatic cascade. Ubiquitin is a 76 amino acid protein that is covalently linked to lysine residues in protein substrates by an enzymatic reaction requiring ubiquitin activating (E1), ubiquitin conjugating (E2), and ubiquitin ligating (E3) enzymes acting sequentially [11]. The protein substrate becomes polyubiquitinated with at least four ubiquitin units and is then degraded by the 26S proteasome in eukaryotic cells [12]. The 26S proteasome complex is composed of a 20S catalytic subunit with 19S regulatory subunits on each end. The 20S catalytic subunit includes four ring structures and three proteolytic proteases [13]. Once a polyubiquitinated protein goes through proteolysis in the proteasome, it is cleaved into 3–25 amino acid peptides and free ubiquitin units [12, 14].

Targeted protein degradation by heterobifunctional small molecules is a strategy where the heterobifunctional molecule binds to a target protein and an E3 ligase simultaneously [15]. The induced spatial proximity can trigger a ubiquitin transfer from the E3 ligase to lysine residues on the target protein. Unlike typical small molecule inhibitors, which are controlled by occupancy for both kinetics of protein inhibition and duration of pharmacodynamics and efficacy, a heterobifunctional degrader allows for irreversible and catalytic protein degradation and oftentimes requires much lower concentrations than typical small molecule inhibitors [10].

Small molecule degraders

Molecular glues

Molecular glues are small molecule compounds (in the range of 500 Da or lower) that facilitate the interaction of proteins by bringing proteins into proximity. By inducing or “gluing” these interactions, molecular glues can stabilize and modulate PPIs [16]. In some cases, the protein-ligand-protein complexes serve to inhibit or activate the function of one or both proteins, while in others the complex stimulates degradation of one or both proteins [2]. For example, molecular glue degraders can facilitate or induce interactions between an E3 ubiquitin ligase and a target protein. Robust and compact interactions between protein-ligand and protein-protein interfaces result in the ubiquitination and subsequent degradation of the recruited protein [16]. Molecular glues can also restore or repair interactions that have become weak due to mutations or induce interactions between two proteins that are unlikely to interact on their own [17, 18]. Molecular glues, thus, can change the protein interactome by stabilizing protein interactions, repairing or restoring interactions, and inducing neo-protein interactions (Fig. 1) [19].

Molecular glues rely on the formation of ternary complexes to stabilize/induce interactions between proteins. A molecular glue-induced ternary complex usually refers to a protein complex composed of an E3 ubiquitin ligase, the small molecule degrader, and the target protein [20]. For a protein to be successfully polyubiquitinated, the ternary complex formation must be productive. This means that the ternary complex must serve as a scaffold between the target protein and a ubiquitin-conjugating enzyme (E2) for it to transfer ubiquitin to a surface lysine at the target protein. Predicting productive ternary complex formation remains a challenge when designing molecular glues [21].

Molecular glues are particularly attractive for drug discovery due to their lower molecular weight and more drug-like properties compared to large molecular entities such as PROTACs [19, 22]. An advantage in using molecular glues is that they have a unique mechanism of action that can either induce degradation of the target protein or stabilize PPIs [19]. Despite their desirable drug-like properties, molecular glues remain difficult to identify and even harder to design in a rational manner. In fact, most molecular glues have been found serendipitously [9].

General principles of rational discovery

Historically, small molecule drug discovery screening programs have relied upon initial biochemical assays to assess activity and rank order compounds. However, this has been a challenge for molecular glues because their activity results
in stabilized PPIs or targeted protein degradation, which is dependent on the productive assembly of ternary complexes that can trigger a cascade of cellular events [16]. Currently, the availability to screen technologies to monitor PPIs or target protein degradation in rational and a high-throughput fashion in the context of the cellular environment is still lacking. A comprehensive review about multi-omics approaches to identify molecular glues was recently published by the Georg Winter lab [23]. Here, we present examples of successful molecular glue discovery through a variety of methods (Table 1).

**Library and high-throughput screening**

Recently, novel methods have been developed to identify molecular glues using library screening. For example, Li et al. developed a screening microarray for the discovery of molecular glues that trigger degradation via the autophagosome. Lie et al. screened 3375 small molecules and found four small molecules that facilitated interactions between the autophagosome LC3 protein (microtubule-associated protein A1/1B light chain 3) and the mutated form of the huntingtin protein (HTT), which causes Huntington’s disease. The four molecular glues interacted with both the wild type and mutant HTT protein. Upon further design, the optimized molecular glues were able to selectively degrade mutant HTT via the autophagosome at nanomolar concentrations in vitro and at 0.5 mg kg\(^{-1}\) in vivo in a Huntington’s Disease mouse model. The molecular glues did not increase the number of autophagosomes or alter autophagosome-lysosome fusion [24].

Another example of library screen for molecular glues involves a yeast two-hybrid approach. Andrea Chini described a chemogenomic screen method using yeast two-hybrid to identify molecular glues that modulate plant hormone receptor complexes [25]. Jasmonic acid (JA) and derivatives, also known as jasmonates, are hormones that modulate plant immunity and development such as root growth and male and female fertility [26]. The JA signaling pathway has three major molecular components involved in JA-responses: the coronatine insensitive 1 protein (COI1), the transcriptional repressor jasmonate-ZIM domain (JAZ) family, and transcription factors that regulate expression of JA-responsive genes. COI1 is an F-box protein that forms a functional E3 ligase that targets and ubiquitinates JAZ proteins. Once transcriptional repressor JAZ proteins have been degraded, JA-responsive genes are transcribed [26–28]. In order to screen compounds to disrupt this process, the plant hormonal perception complex COI1-JAZ9-JA-Ile was reconstructed in yeast to identify novel compounds with JA-Ile (a conjugate form of JA) agonist or antagonist activities. This method was applied to screen three chemical libraries

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Fig. 1 Molecular glues and molecular glue degraders and their mechanism of action. Molecular glues can A enhance and stabilize protein interactions, B repair protein interactions weakened by mutations or C induce de novo protein interactions. D Molecular glue degraders induce the interaction of an E3 ubiquitin ligase with a protein target. This triggers polyubiquitination of the target protein, which is degraded via the proteasome. E Molecular glues can also modulate protein function, with PKM2 an example. PKM2 is a pyruvate kinase relevant to cancer that is less active in a homodimer form. A molecular glue can stabilize the dimer and “glue” two dimers together forming a PKM2 homotetramer, which increases enzymatic activity.
containing ~22,500 molecules total. The goal was to identify compounds that could interfere with COI1 interactions with JAZ proteins [29]. To identify JA-Ile agonist compounds, yeast cells co-transformed with pGBK-COI1/pGAD-JAZ9 were grown on minimal yeast media in the presence of compounds from three chemical libraries. In theory, compounds that promote COI1-JAZ9 interactions are identified due to enhanced yeast growth and compounds that interfere with COI1-JAZ interactions inhibit yeast growth in the presence of coronatine. When they screened the libraries, they did not find any agonist hit compounds but found five hit antagonist compounds. Additionally, the antagonist hit compound were confirmed by secondary screening in an in planta assay where 35S-JAZI-GUS seeds were germinated for a few days to allow for root growth and then exposed to JA and candidate antagonist compounds. A true antagonist hit compound would prevent seed root decay in the presence of JA [25, 28]. Through this secondary screening, they confirmed that the five compounds screened through yeast two-hybrid disrupted COI1-JAZ9 interactions [29]. Although this method is meant to be used in plants, it can be used in other applications in screening for compounds that facilitate interactions involving receptor complexes, if a suitable yeast two-hybrid library is available. A limitation to this assay is that yeast two-hybrid is notorious for generating false positives so a second orthogonal assay in planta or in vitro and pull-down confirmation assays are required.

### Multicovalent natural products

A rational design to identify molecular glues from electrophilic natural products was proposed by Isobe et al. [30]. Based on previous data describing natural products as a robust source of many known molecular glue interactions such as rapamycin, auxin, and brefeldin A, Isobe et al. explored electrophilic natural products since they represent an underexplored subset of natural products where molecular glues could be found. One of the unique

| Compound | Target protein | Molecular glue function | Ligase | References |
|----------|----------------|-------------------------|--------|------------|
| Asukamycin | UBR7 | Stabilization of TP53 | UBR7 | [30] |
| Indisulam | RBM39 | Degradation of RBM39 | DCAF15-CUL4-CRL | [39, 40] |
| CR8 | CDK12 | Degradation of Cyclin K | DDB1-CUL4 | [41] |
| dCeMM1 | CDK12 | Degradation of RBM39 | CRL4-DCAF15 | [42] |
| dCeMM2 | CDK12 | Degradation of CRL4-DCAF15 | CRL4-DCAF15 | [42] |
| dCeMM3 | CDK12 | Degradation of Cyclin K | CRL4-DCAF15 | [42] |
| dCeMM4 | CDK12 | Degradation of Cyclin K | CRL4-DCAF15 | [42] |
| HQ-461 | CDK12 | Degradation of Cyclin K | DDB1-CUL4-RRX1 | [43] |
| NCT02 | CDK12 | Degradation of Cyclin K | DDB1 | [44] |
| Thalidomide | CRBN | Degradation of IKZF1, IKZF3 | DDB1-CUL4A | [108, 109] |
| Arylsulfonamides | DCAF15 | Degradation of RBM39 | CRL4-DCAF15 | [39, 111] |
| TP-1454 | PMK2 | Stabilization of PKM2 tetramer | N/A | [123, 129] |
| Mitapivat | PKR | Stabilization of PKR tetramer | N/A | [132, 135] |
| FT-4202 | PKR | Stabilization of PKR tetramer | N/A | [136] |
| Fusicoccin A | PMA/14-3-3 | Stabilization of 14-3-3 binary complex | N/A | [153] |
| Cotylenin A | PMA/14-3-3 | Stabilization of 14-3-3 binary complex | N/A | [152] |
| Fusicoccin THF | PMA/14-3-3 | Stabilization of 14-3-3 binary complex | N/A | [152] |
| ISIR-005 | PMA/14-3-3 | Stabilization of 14-3-3 binary complex | N/A | [152] |
| Epibestatin | PMA/14-3-3 | Stabilization of 14-3-3 binary complex | N/A | [155] |
| Pyrrolidone1 | PMA/14-3-3 | Stabilization of 14-3-3 binary complex | N/A | [155] |
| Compounds 1-16 | SLP76/14-3-3 | Stabilization of SLP76/14-3-3 complex | N/A | [157] |
characteristics about electrophilic natural products is their potential for covalent bond formation due to their multiple reactive sites that could produce ternary complexes for PPIs and protein degradation. Two fungal polyketide natural products were explored: asukamycin and manumycin A, which exhibit antibiotic and antiproliferative properties. Both natural products possess three potentially electrophilic functional groups with the additional possibility of regioisomeric nucleophilic attack (Fig. 2A). Targets of the covalent ligand asukamycin were explored in 231MPF cells by isotopic tandem orthogonal proteolysis activity-based protein profiling. Briefly, vehicle or asukamycin-treated samples were labeled with either IA-alkyne or N-hex-5-yny-2-iodoacetamide. Samples were then sequentially digested with trypsin and TEV and prepared for liquid chromatography-mass spectrometry. The validated method can be found here [31, 32]. Amino acid C374 of UBR7, a putative E3 ubiquitin ligase, was identified as the primary target of asukamycin and was validated by gel based ABPP. The UBR7-asukamycin interaction led to a gain of function as opposed to simple inhibition. Using proteomic analysis of pull-down eluates of UBR7-expressing 231MPF cells, 13 interacting proteins were identified, including DNA protein kinase (PRKDC) and TP53. Furthermore, the UBR7-asukamycin complex thermodynamically stabilized TP53 and increased its transcriptional activity resulting in antiproliferative effects in 231MPF cells [30, 33]. However, the authors were not able to identify the binding mode of UBR7-asukamycin to TP53 and proposed this could be clarified by solving the crystal structure of the ternary of UBR7-asukamycin-TP53 complex. This method could be used to explore new molecular glues from natural products with multiple, distal electrophilic sites such as isariotins and abikoviromycin [34–36]. Given their multicovalent nature, screening similar natural products could lead to the discovery of multiple molecular glue targets.

Chemogenomic screening

Chemogenomics is the study of gene products using small molecule pharmacological modulators [37]. Chemogenomic libraries, comprised of selective annotated small molecules, are used in phenotypic screens, where target deconvolution is driven by the known pharmacological targets of the hits. Chemogenomic screens have demonstrated a significant impact in uncovering new biology. However, further experiments to validate the target modulation and mechanism of action are almost always necessary [38].

One recent example of successful chemogenomic screening is the target identification of molecular glue indisulam, RBM39. Indisulam facilitates the interaction of RBM39 with the DCAF15-CUL4-CRL E3 complex, which causes RBM39 polyubiquitination and subsequent degradation [39, 40]. The increased understanding of E3 ligase biology through the story of indisulam inspired chemogenomic screening for previously undruggable targets. For example, Simonetta et al. conducted a screen aimed at identifying small molecules with glue activity that could enhance the interaction between β-catenin and the natural E3 ligase β-TrCP, subsequently mediating the degradation of mutant β-catenin present in cancers [17].

Another example are the multiple chemogenomic screening approaches to discover cyclin K molecular glue degraders Slabicki et al. used a systemic data mining screening approach analyzing the correlations between an antitumor drug sensitivity database of 4518 compounds against 578 cancer cell lines and the mRNA expression level of 499 E3 ligase compounds [41]. From this screening, they discovered that the mRNA level of DDB1, a CUL4 adapter protein, correlated with the cytotoxicity of the CDK inhibitor (R)-CR8 (Fig. 3). Subsequent quantitative proteome-wide mass spectrometry to evaluate protein abundance after treating cells with (R)-CR8 showed that (R)-CR8 had targeted degradation activity toward cyclin K. The crystal structure revealed that CR8 binds to the ATP pocket site of CDK12 inducing an interaction between CDK12 and DDB1 through its phenylpyridine group. The ternary DDB1-(R)-CR8-CDK12 complex acts as a recruiter of cyclin K to DDB1, which leads to its polyubiquitination and degradation [41].

Mayor-Ruiz et al. used a scalable strategy toward glue degrader discovery by comparative chemical screening in hyponeddylated cellular models with broadly abrogated ligase activity [42]. They based this approach on the knowledge that cullin-RING ligase activity is dependent on the reversible attachment of the ubiquitin-like protein NEDD8 to the respective cullin scaffold, a process that is managed by NAE (an E1 enzyme), UBE2M and UBE2F (E2 enzymes), and several E3 enzymes. Their hypothesis was that comparing the chemical profiles in hyponeddylated vs. neddylation-proficient cells would allow to screen for small molecules that are functionally linked to cullin-RING ligases. They screened a library of ~2000 small molecules in wild type and UB2M mutant cells that yielded four
chemical scaffolds dCeMM1, dCeMM2, dCeMM3, and dCeMM4 that were functionally dependent on uninterrupted neddylation levels (Fig. 3). They identified dCeMM1 as a new molecular glue that rewired CRL4 DCAF15 ligase, capable of degrading RBM39. dCeMM2, dCeMM3, and dCeMM4 were found to be cyclin K degraders and mild CDK13 and CDK13 degraders mediated by the CRL4B ligase complex [42]. The authors did not address the therapeutic value of these compounds or their pharmacological activities.

Lv et al. also discovered a molecular glue, HQ-461 (Fig. 3), that binds to CDK12’s kinase domain, creating a modified CDK12 version that becomes a substrate specific receptor for DDB1-CUL4-RBX1 E3 ubiquitin ligase and triggers polyubiquitination of cyclin K via the proteasome [43]. HQ-461 was discovered by phenotype-based high-throughput screening of small molecules looking for NRF2 activity suppression but its role as molecular glue was elucidated by chemical genetics and biochemical reconstitution [43]. For the chemical genetics approach, a gain of function screening was performed in HCT-116 cells, which are defective in mismatch repair and therefore have a high rate of random point mutation. HQ-461 resistant HCT-116 cells were generated and whole-exon sequencing in both the HQ-461 sensitive and resistant HCT-116 cells identified a variant G731E CDK12 gene in the resistant cell line. Further experiments confirmed CDK12 as the target of HQ-461 [43].

Phenotypic screens and chemical proteomics

Another CDK12 molecular glue was recently discovered by phenotypic screening in 3D patient-derived tumor models [44]. The authors cultured patient-derived colorectal cancer tumor spheroids and performed high-throughput screening of a ~80,000 non-characterized small molecule compound library. From the library hits, compounds of interest were narrowed to those that showed inhibitory activity in only a subset of patient-derived tumor spheroid cultures to minimize the risk of non-specific toxicity. From that criterion and due to a pronounced activity in tumor spheroid cultures and no activity in primary fibroblasts, NCT02 was selected (Fig. 3). NCT02 induced apoptosis and arrested the cell cycle in tumor spheroid cultures. To identify a potential target of NCT02, the authors performed thermal proteome profiling, which revealed CDK12 had the strongest and most significant shift in thermal stability. NCT02 destabilized the CDK12-cyclin K complex and mass spectrometry showed that cyclin K was only identified in cells treated with inactive NCT02 or DMSO but not NCT02. Further chemical proteomic analysis showed that NCT02 triggers degradation of both cyclin K and CDK12 via the proteasome and that CDK12 degradation occurs after cyclin K degradation. To test whether NCT02 acted as a molecular glue, co-immunoprecipitation experiments were performed with DDB1 in the presence of cyclin K, the kinase domain of CDK12, and multiple CDK12 inhibitors such as THZ-531 (non-degrading), SR-485 (cyclin K degrading), CR8 (molecular glue to CDK12 and cyclin K degrader), and NCT02 acted in a similar way to CR8. Structure-based docking revealed that NCT02 acts a molecular glue by mediating the interaction between cyclin K and DDB1 [44].

**Heterobifunctional degraders**

**PROTACs**

Proteolysis-targeting chimeras or PROTACs are heterobifunctional small molecules whereby one end of the molecule recruits an E3 ubiquitin ligase while the other end engages the target protein (Fig. 4A). These molecules were developed under different names and are sometimes referred as Specific and Non-genetic inhibitors of apoptosis protein [IAP]-dependent Protein Erasers or SNIPERs [45]. A PROTAC consists of three elements: an E3 ubiquitin ligase ligand, a protein of interest (POI) ligand, and a linker [8]. The E3 ubiquitin ligase ligand recruits a E3 ubiquitin ligase, the POI ligand targets and hijacks the POI, and the linker conjugates these two ligands. Once a stable ternary
complex forms between the POI and the E3 ubiquitin ligase, ubiquitin-mediated proteolysis is triggered, where the E3 ligase recognizes the POI and covalently attaches ubiquitin onto it, leading to subsequent degradation by the proteasome [46]. In contrast to inhibitor-based pharmacology, PROTACs require only transient drug-target binding to rewire the ubiquitin-proteasome pathway to induce ubiquitination and degradation of target proteins [47]. As such, PROTACs have emerged as a novel therapeutic approach to the challenging multidomain proteins or “undruggable” proteins.

Crews and Deshaies reported the first PROTAC in 2001. This PROTAC was peptide based and recruited MetAP2 to SCF, a ubiquitin ligase complex [48]. In 2008, Schneekloth et al. reported the first small molecule PROTAC in 2008, which degraded the androgen receptor through the recruitment of the E3 ligase MDM2 [49]. Recently, PROTACs have been optimized for lower molecular weights to increase cell permeability. Some PROTACs have been designed to degrade undruggable targets such as estrogen-related receptor alpha, androgen receptor, cellular retinoic acid binding proteins, bromodomain proteins and multiple tyrosine kinases [50–55]. Currently there are three clinical trials in phase 1 or 1/2 involving PROTACs targeting the androgen receptor (drug ARV-110, NCT03888612), the estrogen receptor (drug ARV-471, NCT04072952), and Bruton Tyrosine Kinase (BGB-16673, NCT05006716).

Advantages to using PROTACs vs. traditional small molecule inhibitors are the ability to target undruggable targets, avoid drug resistance by point mutations in the POI, gain target specificity, increased potency through the catalytic MOA, remove all functions of the target protein through degradation, and prolonged pharmacodynamic effects [56]. Some limitations of PROTACs are higher molecular weights that can restrict cellular permeability, the need for a stable ternary complex formation, and the “hook effect” that can inhibit ternary complex formation at high concentrations.

**Rational design of PROTACs**

Unlike molecular glues, PROTACs are, in theory, much easier to design rationally due to their modular structure. Theoretically, a new PROTAC can be developed by...
replacing its “warhead” or target ligand domain [16, 45]. Since the target ligand does not need to be a potent inhibitor of the target protein, a nonselective or promiscuous ligand can have the potential to be converted to a potent degrader when incorporated into a PROTAC [57, 58]. Bondeson et al. found proof of concept of this by designing CRBN- and VHL-recruiting PROTACs using a promiscuous kinase inhibitor with the potential to degrade over 100 substrate proteins. They found that the warhead affinity to the target ligand did not necessarily predict successful degradation. The factor that best correlated with degradation potency was the ability of that protein to induce a stable ternary complex with the PROTAC and the E3 ligase [59].

The choice of which E3 ligase to recruit matters in PROTAC design. There are hundreds of E3 ligases in cells but only a handful have been used for targeted protein degradation [45]. Many groups have shown that using a different E3 ligase to the same target protein results in different degradation potencies [54, 59–63]. This again suggests that stability of the ternary complex is important for targeted degradation. Exploring E3 ligases for recruitment may be worthwhile for a variety of reasons. For example, some E3 ligases are tissue specific or tumor specific [64–67] which could restrict degradation of target proteins to a tissue type or a tumor site and increase selective toxicity. Moreover, resistance to PROTAC induced targeted degradation has been recently reported [68]. The resistance mechanism lies in an alteration of the UPS pathway rather than the target proteins. Recruiting novel E3 ligases could restore degradation of the target proteins [68].

The PROTAC linker length and attachment point can also affect stability of the ternary complex formation and selectivity and degradation profiles can be affected [69]. In 2017, the structure solution of the BET bromodomain degrader MZ1 in complex with BRD4BD2 and VBC (VHL: ElonginB:ElonginC) showed that the linker coiled around itself, aiding in the formation of PPIs that resulted in a stable ternary complex [57]. Another study demonstrated that PROTACs with the same protein ligand and E3 recruiting ligand offer different selectivity profiles depending on the linker chemistry. Furthermore, an increase in linker length of 3 atoms changed the degradation profile of a lapatinib-based PROTAC from targeting both EGFR and HER2 into one that only degrades EGFR [70].

Screening for PROTAC mediated degradation in a high-throughput fashion has been a challenge. Traditional approaches for quantifying protein level changes, such as Western blots, are typically low throughput with limited quantification. Recently, several approaches for high-throughput screening of PROTACs have been published that are noteworthy. For example, the utilization of native mass spectrometry to study ternary structures. Sternicki et al. used native mass spectrometry at high resolution to measure ternary complex formation as a function of PROTAC concentration using the PROTAC GNE-987 between Brd4 bromodomains 1 and 2 and VHL [71]. This method was used to measure complex stability and affinity in both the ternary complex and other intermediate protein species in a high-throughput fashion [71]. Beveridge et al. also utilized native mass spectrometry to study binary and ternary complex formation that specifically revealed preferentially formed E3-PROTAC-protein of interest (POI) combinations and this method could also be used for high-throughput screening for the development of PROTACs [72]. Simard et al. recently published a review of high-throughput screening of PROTACs that included high-throughput flow cytometry, in-cell based Western blotting, AlphaLISA, TR-FRET assays, and Nano-Glo HiBiT technology, all of which are promising to speed up the development and optimization of PROTACs [73].

Designing PROTACs with desirable pharmacokinetics remains a big challenge. Additionally, PROTACs often do not conform to Lipinski’s “rule of five” due to their high molecular weight, which restricts their cellular absorbance and other drug-like properties [74]. For these reasons, many doubted that PROTACs could ever be anything other than tool compounds. Against the odds, in 2019, ARV-110 and ARV-471, PROTACs targeting the androgen and estrogen receptor, respectively, were the first PROTACs to enter clinical trials (NCT03888612, NCT04072952). Both PROTACs are now in phase II clinical trials. Since then, multiple other PROTACs have entered the clinic for multiple indications (NCT04886622, NCT04830137, NCT05006716, NCT04772885, NCT04428788). Moreover, a database with the aim to promote PROTAC rational design is now available with open source structural and experimental data related to warheads, linkers, and E3 ligands, along with their biological activity and physiochemical properties [74].

**LYTAC**

Lysosome targeting chimeras (LYTACs) are bifunctional degraders that carry an oligoglycopeptide on one end, an antibody or small molecule on the other end, with both regions joined by a chemical linker (Fig. 4B) [75, 76]. The purpose of a LYTAC is to deliver a target protein to the lysosome, where it will be degraded, while the LYTAC is recycled. Unlike the ubiquitin-proteasomal pathway, the lysosomal pathway for protein degradation is not limited to proteins with intracellular domains, therefore, LYTACs can induce degradation of secreted, extracellular, and membrane-bound proteins [77].

Banik et al. reported the first LYTAC in 2020 with an oligoglycopeptide group that binds to the cell surface
receptor CI-M6PR and an antibody that binds to a transmembrane or extracellular protein. The resulting complex is engulfed by the cell membrane forming a transport vesicle that carries the complex to the lysosome. The protein is then degraded, and the receptor is recycled. The authors could not determine if the LYTC was also degraded [78].

**AUTAC**

Autophagy-targeting chimeras (AUTACs) are small molecule protein degraders that induce autophagy. Autophagy is an important cellular process that can degrade not only proteins but dysfunctional organelles and intracellular pathogens [79]. AUTACs are designed to link a specific ligand to a guanine tag (Fig. 4C). This event signals for selective autophagy of the substrate. AUTACs have a therapeutic component in the sense that they can degrade both cytosolic and membrane-bound proteins, which can mediate clearance of disease-related proteins and debris. In 2019, Takahashi et al. described AUTACs as cargo-specific degraders that used autophagy as the degradation pathway. The authors found that S-guanylation of a protein was sufficient to designate it for autophagy. Furthermore, AUTACs can degrade fragmented mitochondria and promote mitochondria turnover, which is beneficial as it enhances mitochondria quality [80].

**ATTECs**

ATTECs, autophagy-tethering compounds, are a novel class of bifunctional molecules that can hijack the autophagosomal pathway for the potential degradation of other cellular components in addition to proteins. The mechanism of action of ATTECs is to recruit LC3, a lipitated protein found on the membranes of autophagosomes, and direct a target of interest for autophagy without a guanine tag, like with AUTACs (Fig. 4D) [81]. Although ATTECs seem an attractive technology for targeted degradation, ATTECs are limited in the breadth of targets and are selective only for proteins with polyarginine groups. Multiple biophysical/structural studies would be required to establish the LC3-binding moiety to create ATTECs that induce degradation of other proteins [79].

Fu et al. developed a proof-of-concept molecule from ATTECs called LD-ATTECs, designed to clear lipid droplets (LD), which could be helpful in fighting chronic diseases such as obesity, cardiovascular disease, cancer, etc. This is one of the few examples of targeted degradation of non-protein targets [82]. LD-ATTECs were designed by linking LC3-binding molecules with LD detection probes and tested in mouse embryonic fibroblasts, where near complete clearance of oleic acid was observed. Degradation of large LD was also observed in differentiated adipocytes treated with LD-ATTECs. In mouse models, treatment with LD-ATTECs reduced whole-body weight, body fat:lean ratio, liver weight, liver LDs, and serum TAG and cholesterol levels [82]. Further studies are warranted to confirm the potential therapeutic benefits of these degraders.

**HaloPROTAC**

HaloPROTAC are PROTACs molecules designed to degrade HaloTag fusion proteins [83]. HaloTag is a modified bacterial dehalogenase that reacts covalently with hexyl chloride tags. HaloTag fusion proteins have been used to bioorthogonally label proteins in vivo. HaloPROTACs have two motifs and a linker: one motif binds to the to the HaloTag fusion protein and the other motif binds to an E3 ligase such as VHL or cIAP1 (Fig. 4E) [83, 84]. The linker length is crucial for the HaloPROTAC to be able to induce degradation, and it was reporter that lack of long peptidic chains in linker lengths deem HaloPROTACs more effective [83]. This provides a higher advantage for the usage of HaloPROTACs because in general they are smaller in size and possess drug-like properties. A potential limitation of HaloPROTACs is that stoichiometric occupancy of the tagged protein is needed to achieve full degradation of the target protein [85].

**AbTACs**

AbTACs are fully recombinant bispecific antibodies that recruit membrane-bound E3 ligases for the degradation of cell-surface proteins [86]. Bispecific antibodies refer to a family of immunoglobulins that bind to different epitopes co-localizing their proteins [87]. By designing one of the binding-epitopes to be one of a protein of interest and the other to be a membrane-bound E3 ligase, an AbTAC could target protein degradation for membrane-bound proteins (Fig. 4F) [88].

Proof of concept for AbTACs was recently reported by the Wells lab in the development of an AbTAC with bifunctionality for PD-L1 (atezolizumab) and RNF43 (transmembrane E3 ligase) [86]. The AbTAC, AC-1, induced PD-L1 degradation in MDA-MB-24 cells via the lysosome, although the endocytosis mechanism is unclear. AC-1 demonstrated partial degradation of PD-L1 in cell lines derived from clinically relevant indications for atezolizumab [86].

**Hydrophobic tag-mediated degraders**

Hydrophobic tagging is another approach for targeted protein degradation. Hydrophobic tag-mediated degraders link
a protein of interest ligand with a highly lipophilic moiety that triggers the unfolded protein response, a cellular stress response that is activated by high levels of misfolded or unfolded proteins in the endoplasmic reticulum. This response will then trigger degradation of the protein of interest [22].

This concept of hydrophobic tagging was first grasped with fulvestrant, also known as Faslodex, 7α-alkylsulphinyl analog of 17β-estradiol (Fig. 5A) [89]. Fulvestrant binds to the ER in a conformation that exposes the hydrophobic tag region. This conformation inhibits receptor dimerization, blocks nuclear localization, and renders the receptor inactive. Moreover, the fulvestrant-ER complex is unstable, which triggers the unfolded protein response and subsequent degradation via the proteasome [90]. This results in full anti-estrogen effects due to halting all transcriptional ER activity (Fig. 5B) [91]. Fulvestrant is currently approved for use alone and in combination with palbociclib, ribociclib, and abemaciclib to treat hormone receptor positive advanced breast cancer and is undergoing additional clinical trials to be used in combination with other drugs for breast cancer treatment [92–96].

**Historical examples of molecular glues**

**Molecular glue origins**

The field of molecular glues began when a series of natural products were found to have immunosuppressive and cell growth inhibitory effects and yet an unknown mechanism of action. This was the case for cyclosporin A and FK506, also known as tacrolimus. Both drugs are macrocyclic molecules used in the clinic for their ability to prevent rejection following organ transplant by inhibiting T cell activation [97]. Schreiber and Crabtree described their unknown mechanism of action in 1992, where they pointed out that cyclosporin A and FK506 bound to endogenous intracellular receptors, a termed they coined as “the immunophilins”, and the resulting complex targets the protein phosphatase, calcineurin, to exert an immunosuppressive effect [98]. In other words, these “molecular glues” simultaneously bind two proteins and inhibit the function of one of the proteins.

Another example this mechanism of action was demonstrated with another macrolide called rapamycin, which was shown to have potent immunosuppressive activity in IL-2 stimulated T cells by cell cycle arrest. Rapamycin binds to immunophilin FKBP12 forming a unique effector molecular complex, which then interacts with mammalian target of rapamycin or mTOR [99, 100]. The downstream effects of this interaction include inhibition of translational pathways and ribosomal biogenesis, which leads to overall translation blockade and cell cycle arrest [101]. Later it was discovered that mTOR was a kinase involved in many cellular pathways such as immune cell differentiation, apoptosis, autophagy, and tumor metabolism [102]. As such, rapamycin and derivatives, acting as molecular glues, modulate mTOR’s multiple functions.

One of the first biological indications that molecular glues could induce protein degradation came from plant...
hormones. Auxin and methyl jasmonate, both phyto-
hormones, were found to bind the plant F-box CRL
receptors (RIR1 and COI1, respectively) and facilitate
interaction and degradation of two transcription factors [16].
Auxin-RIP1 and methyl jasmonate-COI1 crystal structures
revealed that these phytohormones facilitate nanomolar
target-ligase interactions through a small protein-ligand
interface [17, 103].

**Thalidomide and analogs (IMiDs)**

In 1957, thalidomide was introduced to the West German
market as a completely non-toxic sedative that could be
used safely, even during pregnancy. After many babies
were born with phocomelia or abnormally short limb out-
growth, thalidomide was withdrawn from market in 1962 [104].
Not long after its market withdrawal, a single case
report was published describing thalidomide’s anti-
inflammatory properties in which a patient suffering from
Hansen’s disease, commonly known as leprosy, had com-
plete resolution of their inflammatory skin lesions [105].
Since then, and through a series of unexpected discoveries,
thalidomide and derivatives lenalidomide and pomalido-
mide have been repurposed for treating multiple myeloma
and myelodysplastic syndrome (Fig. 6A) [106]. They also
show promise in the treatment of autoimmune disorders
such as systemic lupus erythematosus and inflammatory
bowel disease [107].

The mechanism of action of thalidomide was discovered
by the Handa laboratory where they identified cereblon
(CRBN) as a thalidomide-binding protein [108]. They also
showed CRBN forms an E3 ubiquitin ligase complex with
damage-specific DNA binding protein 1 (DDB1) and
CUL4A, inhibiting its autoubiquitination activity. Later
research suggested thalidomide and its derivatives IMiDs
(Immunomodulatory imide Drug derivatives) acted as
molecular glue by stabilizing CRBN and recruited several
neosubstrates for ubiquitination leading to the proteasomal
degradation of the transcription factors (IKZF1) and Aiolos
(IKZF3) (Fig. 6B) [109]. The direct outcome of IKZF1 and
IKZF3 is the downregulation of the IRF4/MYC pathway
immunomodulating the function of T cells and B cells,
which leads to the observed cytotoxicity in multiple mye-
loblastoma cells [110].

This new mechanism of action in which small molecules
could stabilize PPIs and selectively target proteins for ubi-
quitination and further degradation presented a novel class
of therapeutics for certain proteins that were thought to be
undruggable. A recent example of this was the development
of arylsulfonamides, which bind and stabilize DCAF15, the
substrate receptor for the CRL4-DCAF15 E3 ubiquitin
ligase and promote targeted protein degradation of mRNA
splicing factor RBM39 [39, 111]. This in turn inhibits cell
cycle progression and has potential use as an anticancer
therapeutic.

**Novel molecular glue compounds and targets**

**PKM2 molecular glues**

Pyruvate kinase is an enzyme involved in the final and rate-
limiting step of glycolysis: the conversion of phospho-
enoxypyruvate (PEP) to pyruvate. As such, pyruvate kinase
plays an important role in regulating cell metabolism. In
mammals, pyruvate kinase has four isomeric, tissue specific
forms: PKL, PKR, PKM1, and PKM2 [112]. PKL is mainly
found in kidney, liver, and red blood cells; PKR is found in
red blood cells; PKM1 is found in myocardium, skeletal
muscle, and brain tissues; PKM2 is found in brain and liver
tissues [113, 114].

PKM1 and PKM2 are formed by alternative splicing
from a single PKM mRNA transcript [115]. PKM1 and
PKM2 differ by 22 amino acids and have distinct regulatory
properties. PKM1 is a constitutively active enzyme that
shows increased affinity for its substrate PEP, and thus,
PKM1 expression is predominantly found in differentiated
adult tissues with high ATP requirements. PKM2 enzyme
activity is dependent on allosteric regulation by fructose-
1,6-bisphosphate (FBP) and posttranslational modifications
[116]. PKM2 is usually expressed during fetal development.

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**Fig. 6 A** Thalidomide and selected IMiD thalidomide
analogs. These IMiDs recruit Cerebrion, an E3 ligase, for
targeted protein degradation. **B** Rendition of thalidomide
acting as a molecular glue between Ikaros or Aiolos and
Cerebrion, triggering the ubiquitination of Ikaros
or Aiolos.
and upregulated in all cancers and cancer cell lines, suggesting that PKM2 has a role in tumorigenesis and tumor growth [117]. Due to increased metabolic requirements in tumorigenesis, we observe cancer cells favor glycolysis over oxidative phosphorylation for their energy production, a phenomenon known as the Warburg effect. One would think that during cancer formation, there would be a switch from PKM1 to PKM2 isoform expression. However, the data suggests that there is no exchange in PKM1 to PKM2 isoform expression during cancer formation. Additionally, PKM2 is not specific to proliferating tissue and PKM1 is not specific for non-proliferation tissue [118].

PKM2 has high and low-activity oligomers. PKM2’s high activity oligomer is its tetrameric conformation. PKM2 is activated in this conformation by binding to FBP, which causes PKM2 to adopt a stable, active conformation similar to that of PKM1. PKM2 tetramer activation by FBP can be overridden by interaction of PKM2 with tyrosine-phosphorylated proteins in response to growth factor signaling, by post translational modifications, and by interactions with other metabolites, such as serine, rendering PKM2 into a dimeric conformation. The low-activity dimer PKM2 has low affinity for its substrate (PEP) and regulates the rate-limiting step of glycolysis that shifts the glucose metabolism from the normal respiratory chain to lactate production in tumor cells, thus allowing proliferating cells to accumulate glycolytic intermediates needed for biosynthesis [119]. Additionally, the dimeric form of PKM2 has been shown to translocate to the nucleus in response to epidermal growth factor receptor (EGFR) signaling, where it can regulate gene transcription by acting as a protein kinase [120]. From here, PKM2 can promote EMT and stemness in cancer cells [121]. Multiple studies have shown that activating PKM2 (tetramer conformation) correlates with reduced tumorigenicity in both in vitro and in vivo studies [122–125].

In the last 10 years, academic groups and pharmaceutical companies have been working on developing small molecule PKM2 activators [113, 122, 124, 126]. A recently published article by the Kumar lab offers a comprehensive review on PKM2 activators [127]. Well-known PKM2 activators such as Michelolide (MCL), DASA-58, and TEPP-46 (Fig. 7A) act by allosterically binding to PKM2 (Fig. 7B). Tolero Pharmaceuticals, now known as Sumitomo Dainippon Pharma Oncology, recently developed a small molecule PKM2 activator: TP-1454. TP-1454 was derived from SGI-9380, compounds designed by Astex Pharmaceuticals in 2013 [128]. One of the main differences between SGI-9380 and other PKM2 activators is that each SGI-9380 molecule makes contact with at least one residue in a second PKM2 monomer. This in turns bridges two PKM2 monomer forming a homodimer. The newly formed homodimer then binds to another homodimer forming a tetramer containing four SGI-9380 molecules (Fig. 7B). TP-1454, optimized from SGI-9380 for improved metabolic activity and pharmacokinetics, is thought to bind in a similar fashion at the dimer-dimer interface of PKM2, acting as a glue between each monomer of PKM2, which then form a tetramer with four bound TP-1454 molecules.

TP-1454 has shown success at modulating cellular metabolism and enhancing response to checkpoint inhibitors in preclinical solid tumor models [123]. Additionally, TP-1454 is a potent PKM2 activator in biochemical assays (AC50 = 10 nM) and cellular assays (AC < 50 nM). It is
also reported to have low toxicity and be well tolerated in mice, rats, and dogs, even in repeat doses as high as 1000 mg/kg/day [129]. In 2020, TP-1454 entered human clinical trials as the first oral PKM2 activator for the treatment of advanced solid tumors alone and in combination with ipilimumab and nivolumab (NCT04328740).

PKR Glues

PKR is the constitutively expressed pyruvate kinase isoform found in red blood cells with an important role in erythropoiesis. Mutations in PKR cause autosomal recessive enzymopathy that leads to deficiencies in pyruvate kinase activity in red blood cells [130]. These deficiencies result in compromised red-cell membrane homeostasis and hemolysis, which causes hemolytic anemia. In addition, pyruvate kinase deficiencies in red blood cells are associated with gallstones, pulmonary hypertension, extramedullary hematopoiesis, and iron overload [131]. Studies in mouse models genetically lacking PKR have shown extramedullary erythropoiesis associated with ineffective erythropoiesis, further supporting the role of PKR in erythropoiesis maturation [132].

Mitapivat (AG-348) (Fig. 7F) is a PKR activator that functions as a molecular glue, currently in clinical trials and developed by Agios. Mitapivat specifically binds to a PKR allosteric pocket to stabilize/glu the active tetrameric form and enhance its affinity for its substrate, PEP, successfully modulating PKR activity [133, 134]. A phase 2 clinical trial of mitapivat in adult patients with pyruvate kinase deficiency who were not receiving regular transfusions showed that the molecule elicited a rapid and sustained increase in hemoglobin levels in ~50% of treated patients. Mitapivat was well tolerated, with a few transient adverse effects [135].

Another molecular glue that stabilizes the tetrameric form of PKR similarly to mitapivat is FT-4202, a compound developed by FORMA Therapeutics. FT-4202 works as an allosteric activator of PKR that also stabilizes the tetrameric form of PKR (both wild type and R510Q mutant), thereby lowering the Michaelis-Menten constant for PEP [136]. FT-4202 is also in clinical trials (NCT03815695) showing that the molecule library, two compounds were found to stabilize the 14-3-3/PMA2 complex in different ways to each other and to fusicoccin A. Crystal structures revealed that pyrrolidone1 shares most of its protein contact surface with 14-3-3 (288.2 Å from a total of 349.7 Å) and has limited contact with PMA2. In contrast, epibestatin is trapped between 14-3-3 and PMA2 and has a roughly equal contact surface with 14-3-3 (164.4 Å) and PMA2 (135.5 Å) [155]. The structure of pyrrolidone1 was further optimized by converting the pyrrolineone scaffold into a pyrazole, adding a tetrazole moiety to the phenyl ring that contacts PMA2, and introducing a bromine to the phenyl ring that exclusively contacts the 14-3-3 protein. This optimization rendered the compound with a threefold increase in stabilization of the 14-3-3/PMA2 complex [156].

Recently, a molecular glue to the SLP76/14-3-3 was reported to increase degradation of SLP76 [157]. Under
normal conditions, 14-3-3 interacts with Ser376 of SLP76, mediating the proteasomal degradation of SLP76. SLP76 is an adapter protein that regulates the downstream signaling of TCRs helping to modulate the immune response. SLP76 is phosphorylated on Ser376 by the kinase HPK1 (hematopoietic progenitor kinase 1), resulting in a negative feedback mechanism. Enhanced degradation of SLP76 could negatively regulate TCR signaling, which could be beneficial in the context of autoimmune or T cell mediated inflammatory conditions [158]. Through high-throughput screening of the “Diversity Set” small molecule library (20,000 compounds), HTRF dose–response and dose-ratio assays, there were 16 compounds that showed increased stabilization of the 14-3-3/SLP76 complex, and thus the degradation of SLP76. Moreover, 13 of the 16 compounds were orthogonally confirmed by SPR to stabilize the 14-3-3/SLP76 interaction [157].

**Conclusion**

PPIs are crucial for functional cellular processes. In the field of therapeutics, we aim at developing drugs that can modulate these PPIs when PPIs are dysregulated and lead to disease. Most conventional drug development has been focused on protein inhibitory functions. However, a substantial portion of the genome has remained undruggable by this approach. Molecular glues and heterobifunctional degrader technology have made the undruggable genome more amicable to modulation.

Molecular glues can strengthen and stabilize PPIs, repair PPIs, and facilitate de novo PPIs [16]. By doing so, they can modulate protein function by inhibition or activation of one or both protein partners or by recruiting an E3 ubiquitin ligase that targets the protein complex for degradation. Likewise, PROTACs and other heterobifunctional degraders such as LYTACs, AUTACs, ATTECs, HaloPROTACs, AbTACs, and hydrophobic mediated degraders can facilitate the interactions between macromolecules and degradation machinery such as an E3 ligase or the lysosome or the autophagosome.

Designing molecular glues in a rational fashion has been and continues to be a challenge. Most molecular glues and their mechanism of action has been found serendipitously. Several approaches for high-throughput screening of molecular glues have involved screening small molecule libraries in the hope of finding needles in a haystack. Moving forward, it is crucial to understand and study protein-protein interfaces and functional ternary structures to better (semi) rationally design molecular glues in a high-throughput manner [16].

Heterobifunctional degraders are in theory, easier to design due to their modular nature. However, their degradation functionality depends on productive ternary complex formation. Recently, two groups have independently published native mass spectrometry as a method to study and predict functional ternary complexes and intermediaries, which can be a great tool to screen to rationally design PROTACs and their functionality in a high-throughput fashion [71, 72].

Against all odds, molecular glues have been found, optimized, and brought to the clinic. Of note is TP-1454, a molecular glue that stabilizes PMK2 and activates the kinase, the first of its kind to make it to clinical trials in oncology. Other molecular glues such as Mitapivat and FT-4202, both stabilizing PKR, are also success stories. Newly

**Fig. 8** Select 14-3-3 molecular glues. **A** Fusicoxcin A and analogs that stabilize 14-3-3 by inducing dimerization. **B** Epibestatin structure that binds 14-3-3 and PMA2, stabilizing the complex.

**C** Pyrrolidone1 structure that binds mostly to 14-3-3 but creates a stable ternary complex between 14-3-3 and PMA2.
discovered CDK12 molecular glues that degrade cyclin K show promise as new cancer therapeutics [41–44]. Likewise, PROTACs have also been designed and brought to the clinic targeting androgen and estrogen receptor, BTK, BCL-XL, IRAK4, etc. and other targets show promising results. All in all, molecular glues and heterobifunctional degraders have the potential for enhanced PPIs or cell proteome editing and can have a significant impact on how we treat diseases in the future.

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Compliance with ethical standards

Conflict of interest EGW, JMF, ASJ, and SLW are employed by Sumitomo Dainippon Pharma Oncology.

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