INSIGHTS INTO MOLECULAR GLUE DEGRADERS: A REVIEW

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ABSTRACT

Researchers in drug discovery are continually investigating new approaches to develop potential anticancer agents that are effective, safe, tolerable, and exhibit reduced resistance. Targeted protein degraders (TPD) represent a progressive paradigm in drug discovery. Conventional small molecules are generally designed to inhibit specific targets, whereas molecular glues function to recruit critical problematic proteins to the ubiquitin-proteasome system (UPS), resulting in the degradation of disease-causing proteins through proteolysis. This study highlights the critical functions of TPD, particularly molecular glue degraders, in combating cancer and their implications for anticancer strategies. We aim to summarize recent advancements and offer insights into the development of medications associated with TPD technologies.

Keywords: anti-tumor, targeted protein degraders, molecular glues, molecular prosthetics, PROTACs, HyTs

Introduction

Targeted protein degraders (TPDs) are transforming the way we think about discovering novel treatments in the dynamic drug discovery field. TPDs have opened the door for developing novel and innovative classes of therapeutic agents, which can effectively address pathogenic proteins that are typically challenging for traditional small compounds to target with "featureless targets". In addition, TPD-technologies have played a significant role in addressing the challenges of drug resistance (Lai and Crews 2017). Furthermore, TPDs exist in various forms, such as molecular glues, proteolysis targeting chimeras (PROTACs), lysosomal targeting chimeras (LYTACs), hydrophobic tags (HyTs), autophagy-targeting chimeras (AUTACs). These were developed based on three strategies used in drug design and medicinal chemistry: linking, merging, and ligand-growing strategies. In this context, we will outline and emphasize molecular glue degraders, which have been released by serendipitous discovery (Schreiber 2021). These molecules, aptly named for their ability to induce neo-protein-protein interactions (neo-PPIs), display a novel strategy for addressing complex diseases, like cancer and immune disorders through targeting key misregulated proteins, as depicted in (**Fig. 1**). Herein, we explored the targeted protein degradation concept, PROTACs, molecular glues, molecular prosthetics, and HyTs technologies and investigated several examples that clarify their higher potentiality in revolutionizing cancer era of research.

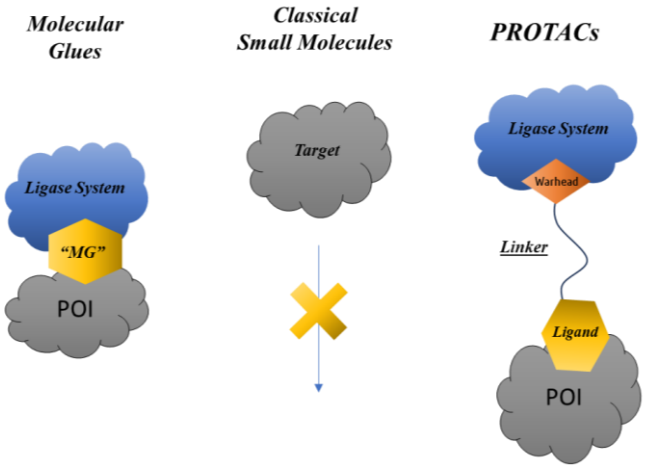


Fig. 1. Schematic comparison of traditional inhibitors, molecular glues, and PROTACs. This Figure illustrates the mechanisms of action for each type of therapeutic agent: traditional inhibitors block target proteins directly, molecular glues facilitate the interaction between proteins, and PROTACs induce targeted protein degradation.

1. PROTACs

Molecular glues and PROTACs both leverage the ubiquitin-proteasome system to modulate protein function, but they differ in their mechanisms. Molecular glues facilitate the interaction between two proteins, leading to their degradation, while PROTACs are bifunctional molecules that recruit an E3 ligase to induce targeted protein degradation. While both strategies hold great therapeutic potential, PROTACs generally offer more versatility in targeting a wider range of proteins, whereas molecular glues may be more selective in their action."It may be helpful to point out, at a glance, that the key difference between molecular glues and PROTACs lies in their peculiar mechanism and structure, as highlighted in (Table 1). Proteolysis targeting chimeras (PROTACs) are bivalent (heterobifunctional) compounds designed with dual binding sites: one end attaches to the protein of interest (POI), wherease the other end (warhead or bait) harnesses E3 ubiquitin ligases via an optimized linker (**Fig. 2**). In the presence of two covalently bridged ligands, one of which leverages an E3 ubiquitin ligase (the cellular waste disposal system) while the other binds a targeted protein. PROTACs tag undesirable proteins for polyubiquitination and subsequent degradation. As illustrated in (**Fig. 3**), PROTAC-technology is a rapidly expanding approach to TPD and is available in several versions (Henning, Boike *et al*. 2022, Salama, Trkulja *et al*. 2022).

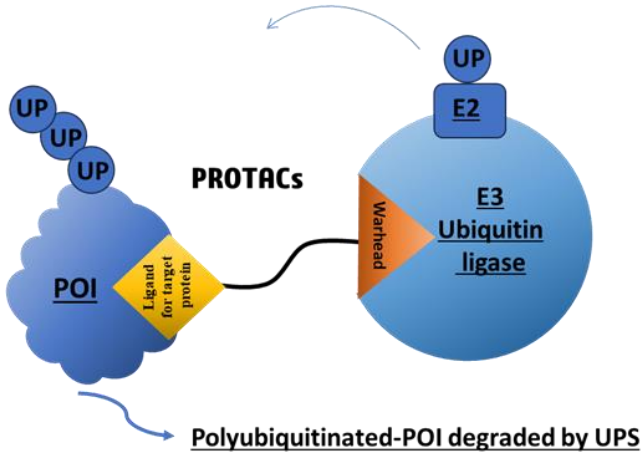


Fig. 2. Anatomical sketch of POI-PROTAC-E3 ligase polynary complex

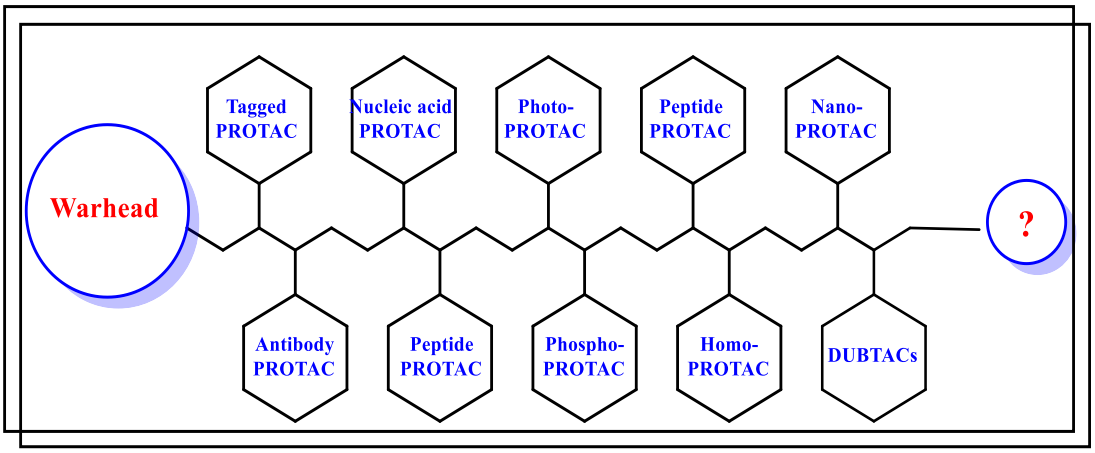


Fig. 3. Schematic overview of different versions of PROTACs

Table 1. Comparison between Molecular glues and PROTACs

Item	**Molecular glues**	**PROTACs**
Feature	Monovalent	Bivalent (heterobifunctional)
Linker	Linker-less	Have a linker
Binding pocket	Not required	Required
MW	<500 Da	700-1000 Da
Role of Pfizer (Lipinski's rule)	Obey	Challenge
Target affinity	Weak “stick-to”	Strong
Limitations	Mainly based on serendipitous discovery	High molecular weight, high surface area
Clinical progression	Straightforward	Challenging
First-in-class	Lenalidomide	ARV-110

2. Hydrophobic tag (HyT) technology

Hydrophobic tag tethering degrader (HyTTD) approach is parallel to PROTACs, as it involves bifunctional molecules combining a small molecule (ligand) specific to the POI and a lipophilic moiety (tags). This building complex can mimic deteriorated or misfolded proteins, triggering the protein quality control (PQC) system, subsequently, the cell consider them as unstable or foreign and targets them for degradation via the proteasome, bypassing the demand for E3 ligases or ubiquitination, as shown pictorially in (**Fig. 4**) (Kubota 2009). The ubiquitin proteasome system (UPS) and lysosomal autophagy are the core mechanisms involved in PQC, which is essential for retaining cellular homeostasis (Li, Li *et al.* 2022).

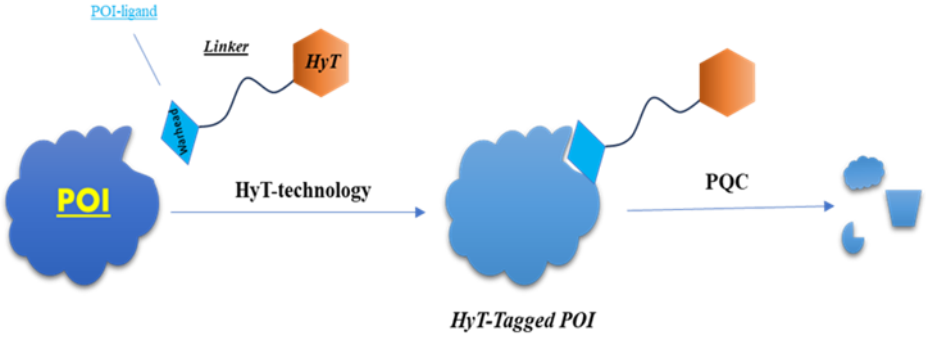


Fig. 4. Schematic illustration of targeted protein degradations (TPD) induced by HyT-technology

Tags aid the interaction with biological membranes and cellular structures, enhancing cellular penetration, increasing solubility, improving metabolic stability, optimizing physicochemical parameters (ADME) and enabling targeted drug delivery. Strikingly, selective estrogen receptor degrader (SERD) fulvestrant, developed by grafting a pentafluoropentylsulfane-arm into the estradiol scaffold, can thus transfer the concept of HyTs from complexity to simplicity (Osborne, Wakeling *et al*. 2004).

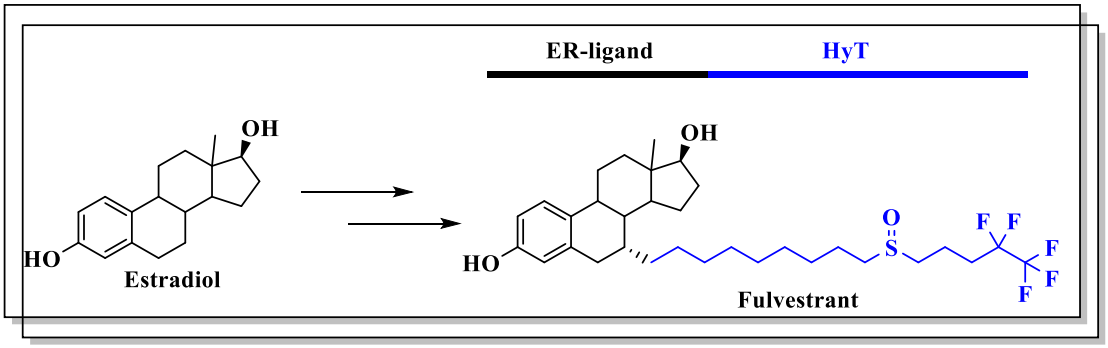


Fig. 5. Striking illustrative example of HyT-technology

Small lipophilic moieties act as effective hydrophobic tags that improve the lipophilicity of pharmacophores, thereby aiding in the absorption, distribution, metabolism, and

excretion (ADME) parameters when conjugated together. Several examples (**Fig. 6**) of these tags include polycyclic aromatic and aliphatic hydrocarbons, such as adamantane, ß-naphthoflavone (ß-NF), Boc3Arg (B3A), fluorene, norbornene, pyrene, and carborane (Shi, Long *et al.* 2016, Li, Ban *et al.* 2018, Ohoka, Tsuji *et al.* 2019, Shoda, Ohoka *et al.* 2020, Wassel, Ammar *et al.* 2021, Xie, Zhan *et al.* 2023). Aside from the carcinogenic risks of polycyclic aromatic hydrocarbons, the HyT- technology faces certain challenges, such as off-target affinity, some sort of toxicity, and optimal tag design (Iwano, Nukaya *et al.* 2005, Straif, Baan *et al.* 2005). Remarkably, adamantyl moieties (**Fig. 7**) are documented as privileged motifs in medicinal chemistry due to their expanded applications in formulations and drug delivery systems (Wanka, Iqbal *et al.* 2013, Ali, Mohamed *et al.* 2017, Štimac, Šekutor *et al.* 2017). In addition, the regulatory point of view for including HyT into drug candidates should be taken into consideration. However, this technology augments pharmacokinetics (PKs) and has the potential to unlock new innovative therapeutic applications.

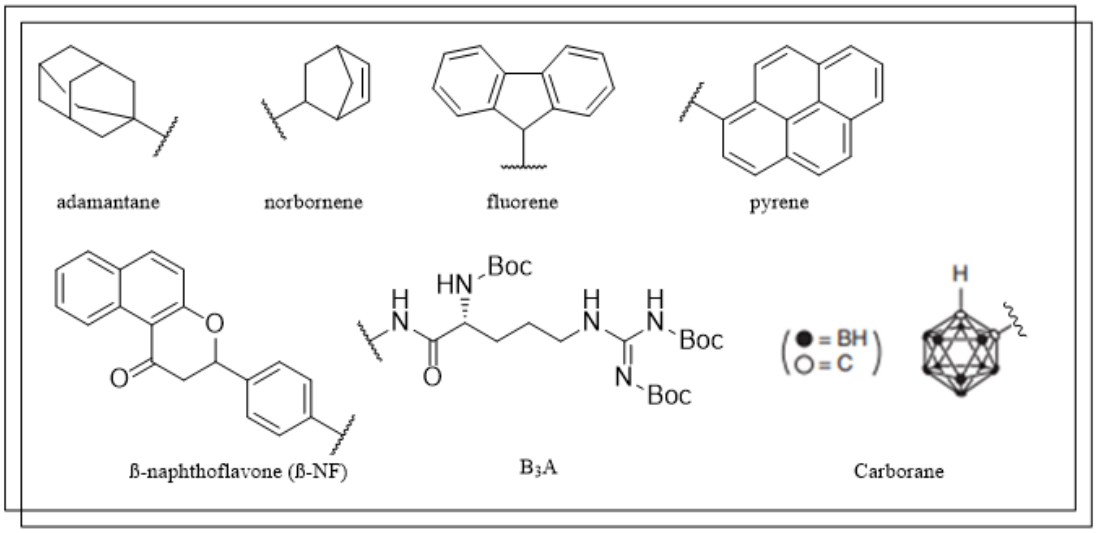


Fig. 6. Representation of common HyT-moieties

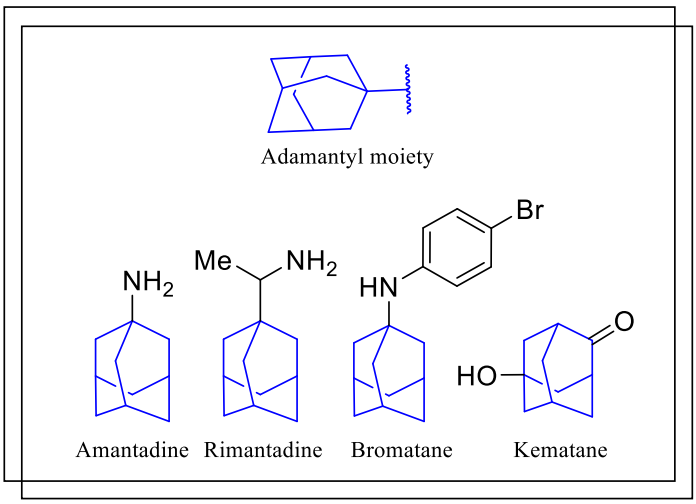


Fig. 7. Illustration of some biologically active adamantane derivatives

3. The profile of molecular glues

3.1. The perplexing role of molecular glues

Another vital strategy that leverages the ubiquitin-proteasome system (UPS) is molecular glues (MGs). Unlike traditional small molecules, which primarily inhibit or block their specific targets, molecular glues act by glueing problematic POIs to ubiquitin ligases (the cell's proteolytic machinery), leading to polyubiquitination followed by degradation, as illustrated in (**Fig. 8**). Molecular glues appear to reshape protein surfaces (neosurfaces). Neosurfaces are synthetic or engineered interfaces designed to interact with biological systems in specific ways. These surfaces are often used in the development of new materials or therapeutic strategies, providing enhanced functionality or specific interactions with cells or proteins. Various essential biological processes, including cell signaling, chromatin remodeling, protein folding, localization, and degradation, are orchestrated by such neo-protein interactions)Schreiber 2024(. A molecular glue can reprogramme (or hijack) ubiquitin ligases to ubiquitinate the recruited POIs after forming higher-order assemblies (ternary or polynary complexes). As a result, molecular glues act as proximity-inducing agents (PIAs). The molecular glue drugs contribute to therapeutic effects by shaping the assembly and stability of protein complexes in a cellular environment (Liu and Ciulli 2023).

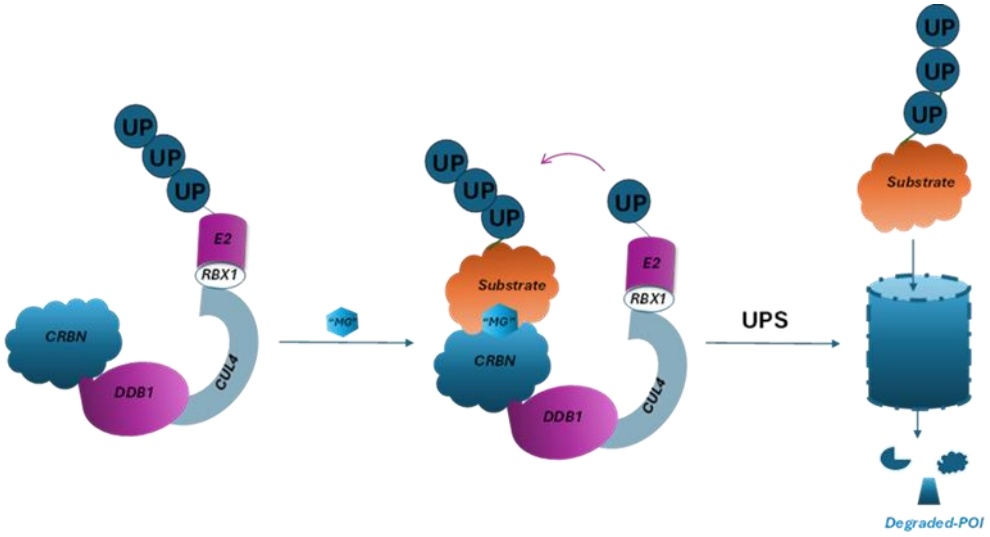
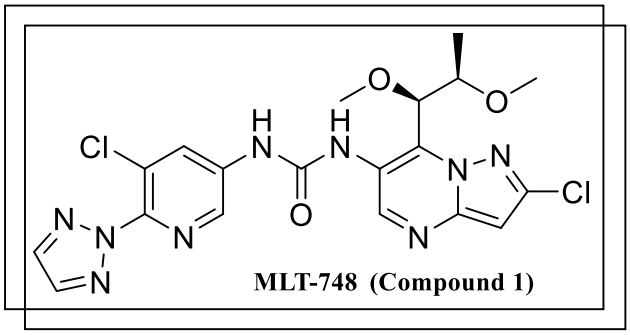


Fig. 8. Conceptual diagram of molecular glue degraders

3.2. Small, molecular prosthetics (correctors)

Molecular glue offers novel therapeutic approaches for various disorders by mimicking or fufilling the role of deficient or dysregulated key biomolecules that contribute to disease, thereby restoring or augmenting normal physiological function. As a result, molecular glue serves as molecular prosthetics (synthetic substitutes). An illustrative example in the context of immunomodultory anticancer era of research is MLT-748 (Compound 1), discovered by Novartis researchers as a prosthetic molecule capable of filling the mutated pocket of MALT1, which lacks an indole side chain (due

to the Trp580-to-serine mutation), thus correcting the disease phenotype (Quancard, Klein *et al*. 2019).



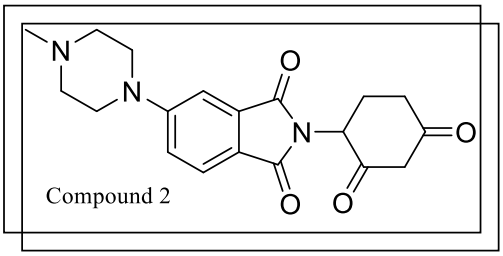
3.3. Molecular glues: Drugging the undruggable targets

Molecular glue discloses a peculiar mode of action, by driving featureless proteins that have been stigmatized as "undruggable" to develop a druggable interface, particularly for crucial targets that lack small-molecule-binding pockets (hard-to-reach targets)(Fan, Boyle *et al.* 2023). The human proteome is classified as undruggable to a degree of approximately 85% (Neklesa, Winkler *et al.* 2017).

3.4. Molecular glues: Towards less resistant therapeutic molecules

Drug resistance is highly expected and could happen after a few doses or after a couple of months. Chemotherapeutic agents face two challenges: drugs induce adverse events and drug resistance (Szakács, Paterson *et al.* 2006). The pharmacological anti-myloma activities of IMiDs (pomalidomide and lenalidomide) is CRBN dependant (Zhu, Braggio *et al.* 2011). By triggering missense mutations in the CRBN-binding region of IMiDs, tumor cells can escape the degradation of essential E3 ubiquitin ligase neosubstrates induced by thalidomide analogs. IMiDs resistance may originate from interface mutations of CRBN-neosubstrates, decreased CRBN expression, or competition from alternative neosubstrates (Jan, Sperling *et al.* 2021). Minor changes in chemical structure may lead to dramatic change in activity, as amino group at C4 of Phthaloyl moiety of IMiDs is crucial for maximizing the potency by approximately 100 fold of pomalidomide over thalidomide, as it lacks phthalimido C4-amino group which interferes with water mediated hydrogen bonding with glutamine side chain, therefore a mutation in this glutamine can disrupt the superiority of pomalidomide and lenalidomide over thalidomide (Gertz 2013). The side chain of IKZF1 Q146 (IKZF3 Q147) aligns with the phthalimido moiety of pomalidomide, and lenalidomide forming a water-mediated hydrogen bond, a feature not observed with thalidomide, as it lacks the key C4 amino group. Mutating IKZF1 Q146 (IKZF3 Q147) from glutamine to isoleucine disrupts this hydrogen bond, thereby altering the binding affinity of theIMiDs to the IKZF1 ZF2-ZF3 domains of CRBN (Toriki, Papatzimas *et al.* 2023). Only humans and rabbits exhibit thalidomide's teratogenic effects; rodents do not, due to distinctions in SALL4 degradation; because of sequence variations. Individuals with mutations in the SALL4 gene often display severe deformities, such as phocomelia or amelia, which are linked to the teratogenicity of thalidomide and its metabolite 5-hydroxythalidomide (5-HT), as represented in (**Table 2**) (Matyskiela, Couto *et al.*

2018). Promisingly, an analog of "Bumped" IMiD (compound 2) emerged as selective degraders of the mutant IKZF3, in contrast to pomalidomide can degrade endogenous IKZF1\3 (Brennan, Saunders *et al.* 2024).



3.5. Simplicity in design and synthesis, as they pertain to small molecules

3.5.1. Scaffold-hopping and Scaffold-morphing concept

In an effort to identify molecular glue degraders, a great deal of research has been conducted across multiple laboratories and companies. Thalidomide is an "iconic drug" in the pharmaceutical drug discovery field, currently and historically. From what the molecule needs to be a lead compound point of view; thalidomide has emerged as an intriguing prototype with many significant criteria for further optimization. Post translational modifications (PTMs) cycloheximide (Aspartimide and Glutarimide) have paved the way for molecular glue degraders (natural inspiration), as shown in **(Fig. 9)** (Ichikawa, Flaxman *et al.* 2022).

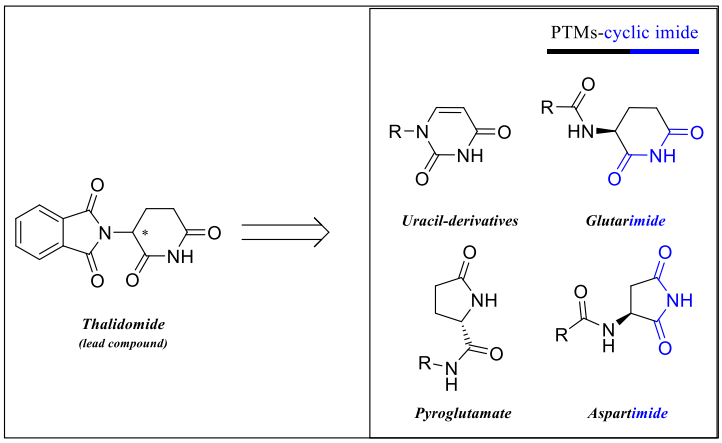


Fig. 9. A reassessment of thalidomide development

Thalidomide offers a good starting point in molecular glues development, characterized by two distinct moieties: the phthalimido and glutarimido rings. By fine-tunning its structure-activity relationship and structure-affinity relationship, researchers have synthesized more potent derivatives, specifically, pomalidomide and lenalidomide. Thalidomide derivatives display most molecules in this class of medicine, with many others under clinical investigation. Roughly, through derivatization at the phthalimido C-5 position, selectivity is broadly oriented toward GSPT subtypes rather than IKZF1/2, as observed with phthalimido C-4 derivatives. In addition, as shown with lenalidomide,

SJ3149, and SJ0040, eliminating one of the two phthalimido carbonyl groups shifts selectivity toward CK1α. Furthemore, switching the five-membered phthalimido ring to six-membered analogs restores selectivity for IKZF1 and IKZF3, as displayed with avadomide (quinazolinone) and TD-106 (benzimidazolone). Finally, replacing the phthalimido moiety with triazolo derivatives redirects selectivity toward CK1α and PDE6D, while reducing affinity for IKZF subtypes. A selected list of molecular glues and their POIs is provided below (**Table 2**), starting with thalidomide, the IMiD prototype, and its pharmacophoric features, as depicted in (**Fig. 10**).

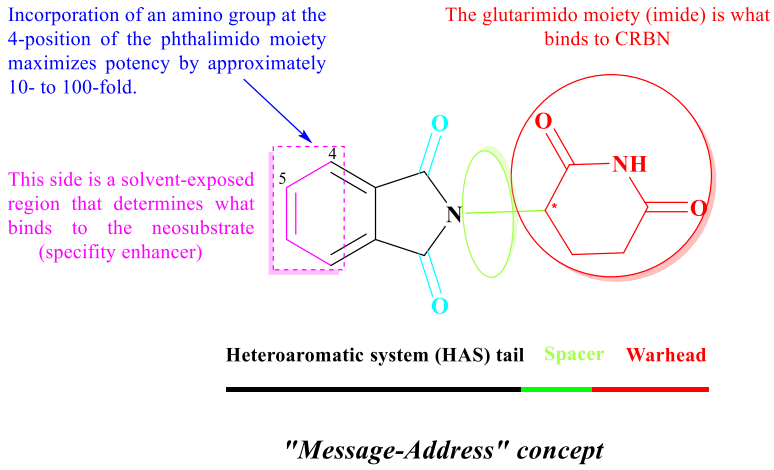
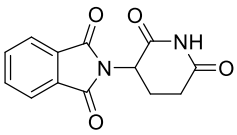
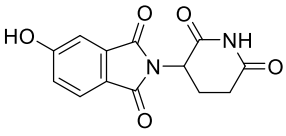
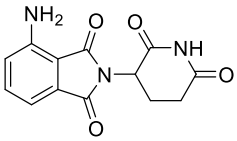
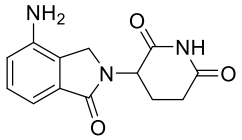
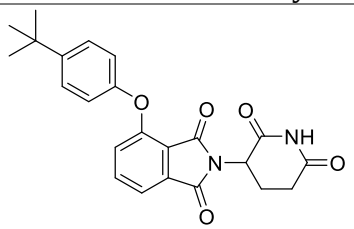
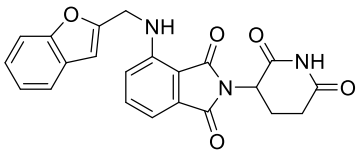
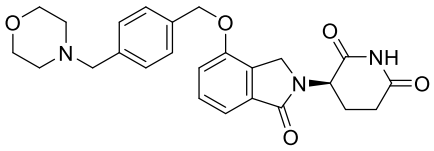
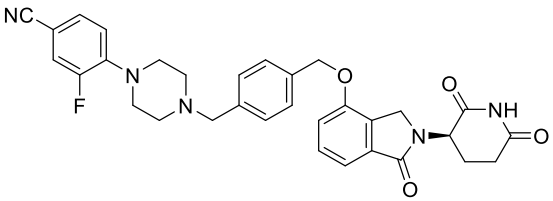
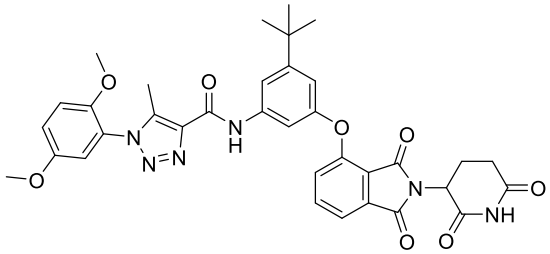
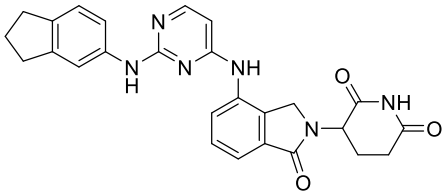
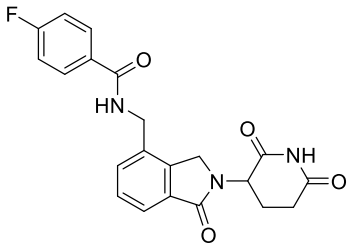
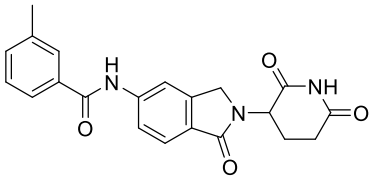
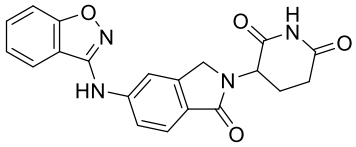
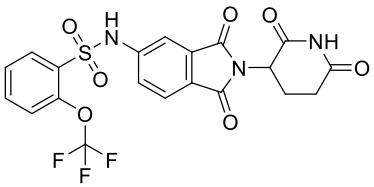
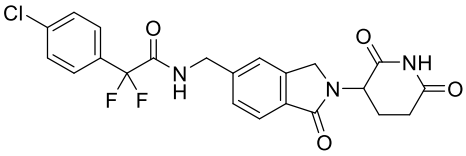
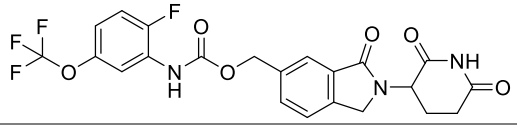
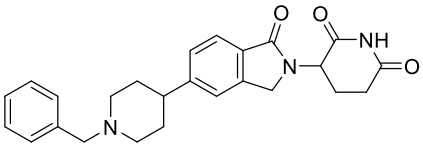
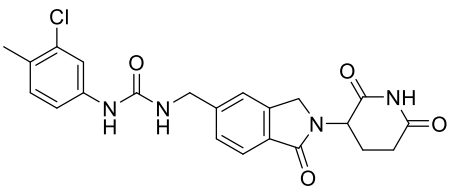


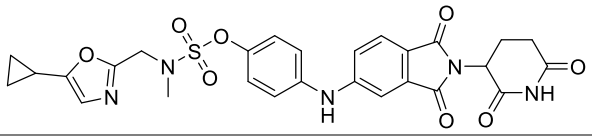
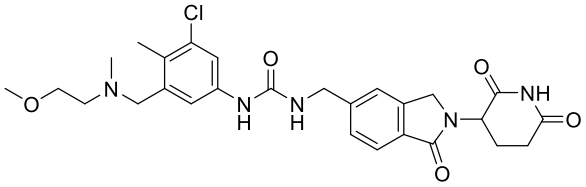
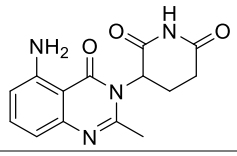
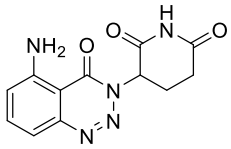
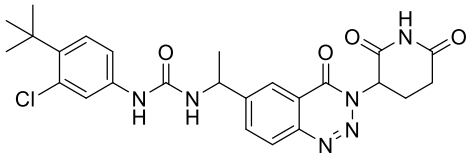
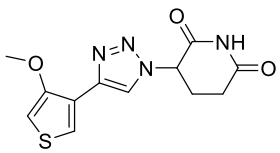
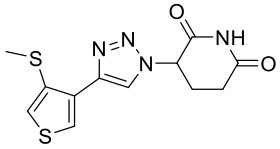
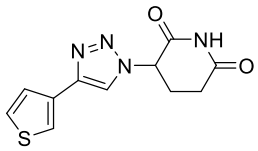
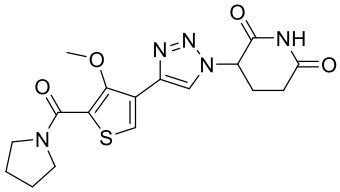
Fig.10. Anatomical sketch of the prototype thalidomide pharmacophoric features

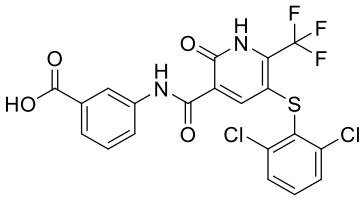
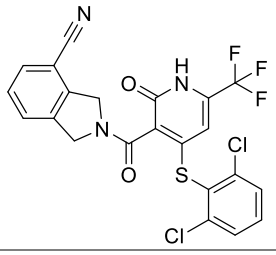
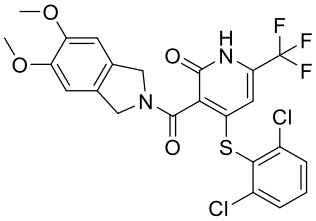
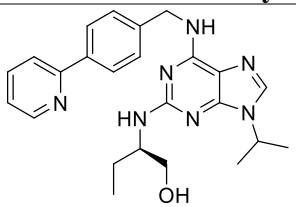
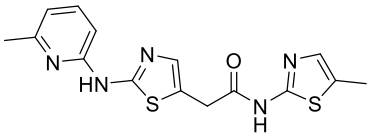
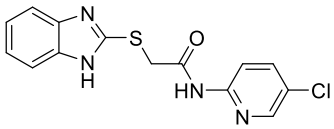
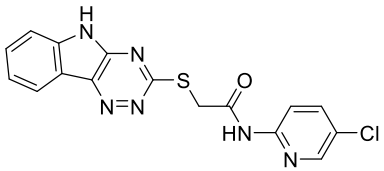
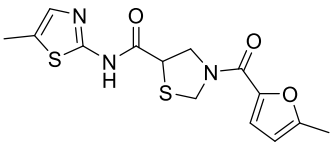
***Table 2. Selected list of anti-cancer small, molecular glue compounds and their corresponding POI**

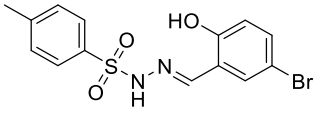
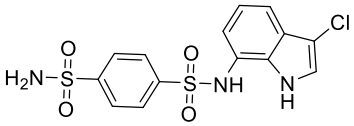
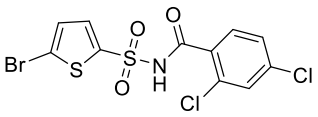
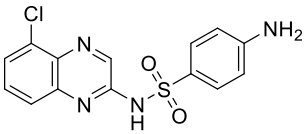
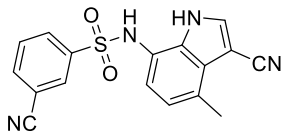
Small molecule	Chemical structure	Target protein	Discovery strategy	Refs.
"Cycloheximide and congeners-based degraders"				
Thalidomide		IKZF1, IKZF3, SALL4, RNF166, ZBTB16, FAM83F, p63, ZNF692, ZNF276	Serendipitous discovery	(Donovan, An *et al.* 2018, Sievers, Petzold *et al.* 2018, Asatsuma-Okumura, Ando *et al.* 2019, Yamanaka, Murai *et al.* 2020)
5HT		SALL4, ZBTB16	…	(Donovan, An *et al.* 2018, Asatsuma-Okumura, Ando *et al.* 2019, Furihata, Yamanaka *et al.* 2020, Yamanaka, Murai *et al.* 2020)
Pomalidomide		IKZF1, IKZF3, SALL4, ZFP91, ZBTB39, ZNF98, ZFP692, ZNF276, ZNF653,	Serendipitous discovery	(Krönke, Udeshi *et al.* 2014, Lu, Middleton *et al.* 2014, An, Ponthier *et al.* 2017, Donovan, An *et al.*

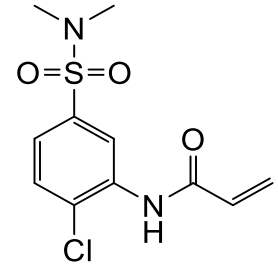
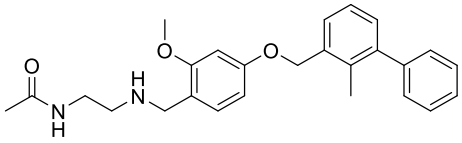
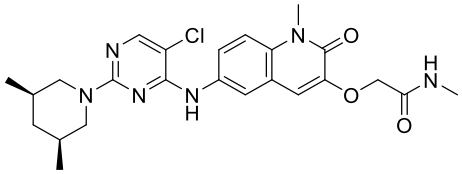
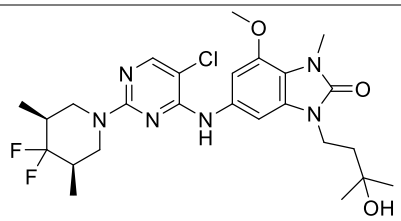
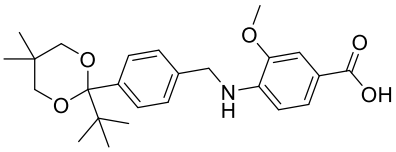
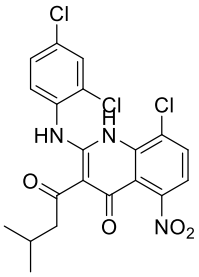
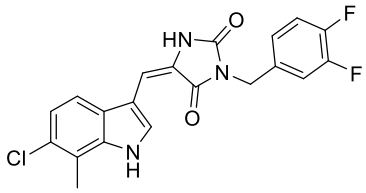
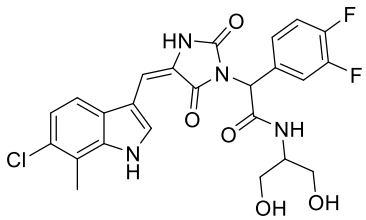
		ZNF827, ZBTB16, FAM83F, RNF166, GZF1, WIZ1, RAB28, DTWD1		2018, Sievers, Petzold *et* al. 2018, Yu, Reitsma *et al.* 2019, Matyskiela, Zhu *et al*. 2020)
Lenalidomide		IKZF1, IKZF3, ZNF276,ZNF653, ZFP91,ZFP692, ZNF827,SALL4, WIZ1,RNF166, CK1a, RAB28, FAM83F	Serendipitous discovery	(Krönke, Udeshi *et al.* 2014, Lu, Middleton *et al.* 2014, Krönke, Fink *et al.* 2015, Donovan, An *et al.* 2018, Sievers, Petzold *et al.* 2018, Yu, Reitsma *et al.* 2019)
"Phthaloyl C-4 based derivatives"				
CC-647		ZBTB16	Serendipitous discovery	(Matyskiela, Zhu *et al.* 2020)
CC-3060		ZBTB16, IKZF1, ZFP91, ZNF276	Serendipitous discovery	(Matyskiela, Zhu *et al.* 2020)
Iberdomide (CC-220)		IKZF1, IKZF3, ZFP91, ZNF98	Rational design	(Donovan, An *et al.* 2018, Matyskiela, Zhang *et al.* 2018)
Mezigdomide (CC-92480)		IKZF1, IKZF3	Phenotypic screening, SAR-exploration	(Lopez-Girona, Havens *et al.* 2019, Hansen, Correa *et al.* 2020)
SJPYT-195		GSPT1	Serendipitous discovery	(Huber, Li *et al.* 2022)

ZXH-1-161		GSPT1, GSPT2	Chemical screening	(Powell, Du *et al*. 2020)
SJ7095		CK1α, IKZF1, IKZF3	Chemical screening	(Nishiguchi, Mascibroda *et al*. 2024)
"Phthaloyl C-5 based derivatives"				
SJ0040		CK1α	Chemical screening	(Nishiguchi, Mascibroda *et al.* 2024)
SJ3149		CK1α	Chemical screening	(Nishiguchi, Mascibroda *et al*. 2024)
SJ6986		GSPT1, GSPT2	Rational design	(Chang, Keramatnia *et al*. 2023)
Eragidomide (CC-90009)		GSPT1	Rational design	(Surka, Jin *et al.* 2021)
MRT-2359		GSPT1	Chemical screening	(Gavory, Ghandi *et al.* 2023)
NVP-DKY709		IKZF2	SAR-analysis, rational design	(Bonazzi, d'Hennezel *et al.* 2023)
CC-885		IKZF1, IKZF3, GSPT1, CK1a, PLK1, HBS1L	Rational design	(Matyskiela, Lu *et al.* 2016, Li, Xue *et al.* 2020, Surka, Jin *et al.* 2021)

FL2-14		GSPT2	Isogenic morphological profiling	(Ng, Offensperger *et al.* 2023)
9q		GSPT1	Rational design	(Wei, Xu *et al.* 2023)
"Six membered congeners"				
Avadomide (CC-122)		IKZF1, IKZF3, ZFP91	Rational design	(Hagner, Man *et al.* 2015)
TD-106		IKZF1, IKZF3	Rational design	(Kim, Go *et al.* 2019)
TD-522		GSPT1	SAR-analysis, rational design	(Takwale, Kim *et al.* 2022)
"Five membered congeners"				
FPFT-2216		IKZF1, IKZF3, CK1α, PDE6D	Rational design	(Gemechu, Millrine *et al.* 2018, Teng, Lu *et al.* 2021)
TMX-4113		CK1α, PDE6D	Rational design	(Teng, Lu *et al.* 2021)
TMX-4100		PDE6D	Rational design	(Teng, Lu *et al.* 2021)
TMX-4116		CK1α	Rational design	(Teng, Lu *et al.* 2021)

"β-catenin degraders"				
NRX-103094		β-catenin	HTS & Rational design	(Simonetta, Taygerly *et al*. 2019)
NRX-252114		β-catenin	HTS & Rational design	(Simonetta, Taygerly *et al*. 2019)
NRX-252262		β-catenin	HTS & Rational design	(Simonetta, Taygerly *et al*. 2019)
"Cyclin K degraders"				
(*R*)-CR8		cyclin K	Data mining	(Słabicki, Kozicka *et al.* 2020)
HQ461		cyclin K	HTS	(Lv, Chen *et al.* 2020)
dCeMM3		cyclin K	Chemical screening	(Mayor-Ruiz, Bauer *et al.* 2020)
dCeMM2		cyclin K	Chemical screening	(Mayor-Ruiz, Bauer *et al*. 2020)
dCeMM4		cyclin K	Chemical screening	(Mayor-Ruiz, Bauer *et al.* 2020)

“Aryl sulfonamide-based degraders”				
dCeMM1		RBM39	Serendipitous discovery	(Mayor-Ruiz, Bauer *et al*. 2020)
Indisulam **(E7070)**		RBM39, RBM23	Serendipitous discovery	(Han, Goralski *et al.* , Uehara, Minoshima *et al*. 2017, Ting, Goralski *et al.* 2019)
Tasisulam		RBM39, RBM23	Serendipitous discovery	(Han, Goralski *et al.* , Ting, Goralski *et al*. 2019)
CQS		RBM39, RBM23	Serendipitous discovery	(Han, Goralski *et al.* , Uehara, Minoshima *et al*. 2017, Ting, Goralski *et al.* 2019)
E7820		RBM39, RBM23	Serendipitous discovery	(Uehara, Minoshima *et al.* 2017, Ting, Goralsk***i*** *et al.* 2019, Faust, Yoon *et al.* 2020)

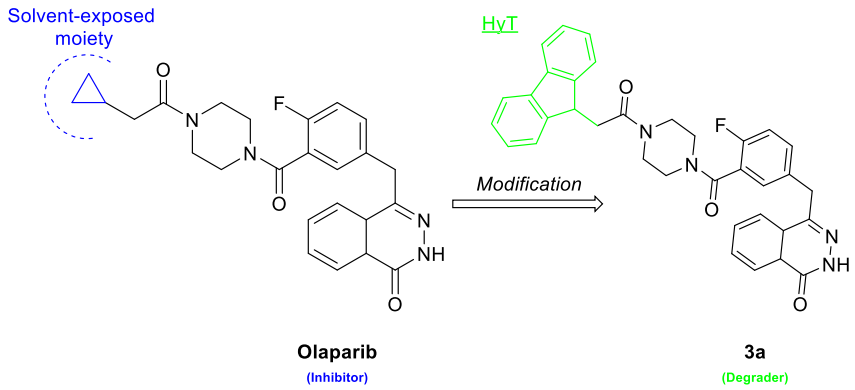
EN450		NFKB1	Serendipitous discovery	(King, Cho *et al*. 2023)
	"Miscellaneous"			
BMS-202		PD-L1	Serendipitous discovery	(Zak, Grudnik *et al*. 2016)
BI-3802		BCL6	Serendipitous discovery	(Słabicki, Yoon *et al*. 2020)
CCT369260		BCL6	Serendipitous discovery	(Słabicki, Yoon *et al.* 2020)
NVS-STG2		STING	Chemical screening	(Słabicki, Yoon *et al.* 2020)
JH-RE-06		REV1	Serendipitous discovery	(Wojtaszek, Chatterjee *et al*. 2019)
RO-2443		MDMX	Serendipitous discovery	(Graves, Thompson *et al.* 2012)
RO-5986		MDMX	Serendipitous discovery	(Graves, Thompson *et al.* 2012)

3.6. Progression toward molecular glues and targeted protein degradation approaches: Shifting from inhibitors to degraders

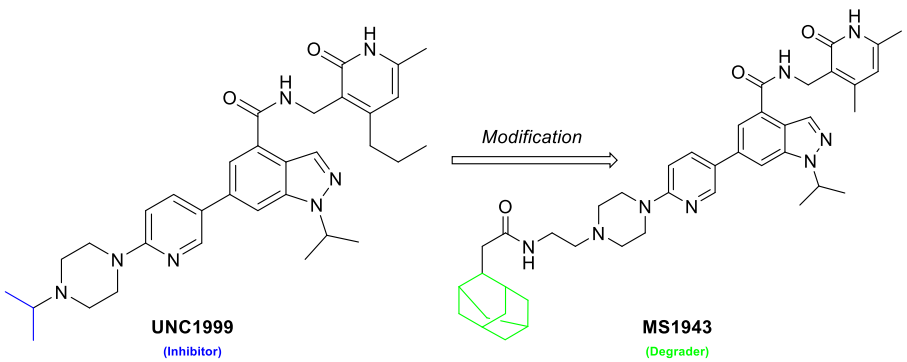
Analogous to traditional inhibitors, MGs are also small molecules that have unique mechanisms of action. However, the big challenge is how we integrate the insights required to develop such glues, which are between serendipitous discovery, screening-based discovery, and rational designing. From adrug design perspective, solvent-exposed region (solvent-filled pocket) serve as a key point for substantial modifications (Jiang, Yu *et al.* 2019, Geiger, Schäfer *et al*. 2022). The following examples demonstrate how adding solvent-filling small chemical moieties (degradation tail) to inhibitors can result in degraders, like molecular glues.

3.6.1. Olaparib and 3a.

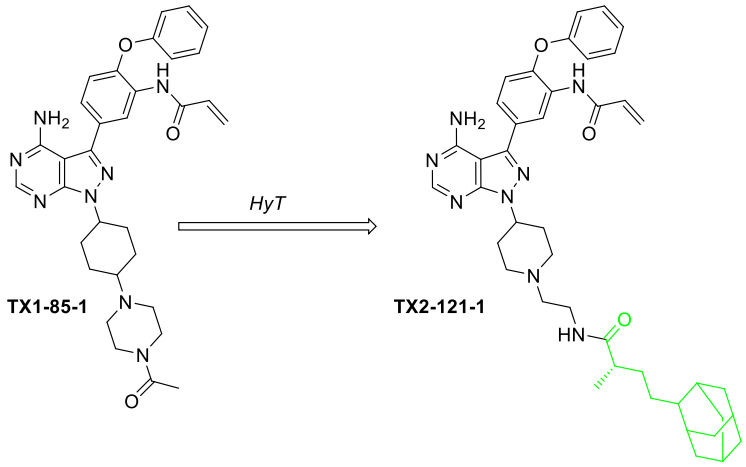
Olaparib, an inhibitor of poly (ADP-ribose) polymerase (PARP), has been approved for the treatment of breast and/or ovarian cancer. By shifting the terminal, solvent exposed cyclopropyl group to a rigid planar fluorene moiety (HyT) enabling development of degrader (Go, Jang *et al.* 2020).



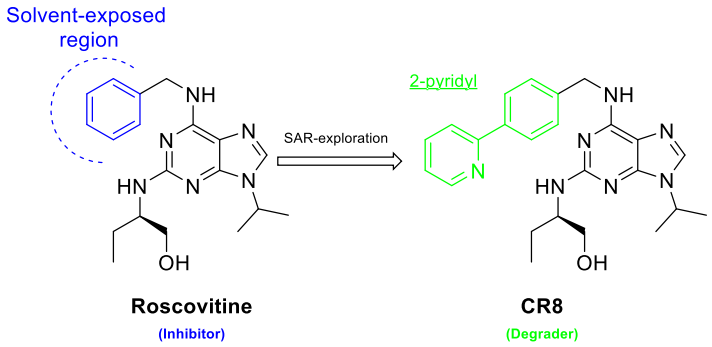
3.6.2. EZH2 selective degrader MS1943 is a first-in-class, orally bioavailable treatment for triple-negative breast cancer (TNBC), was obtained by inserting adamantane HyT into UNC1999 (Yang, Li *et al*. 2016, Hansen, Correa *et al.* 2020).



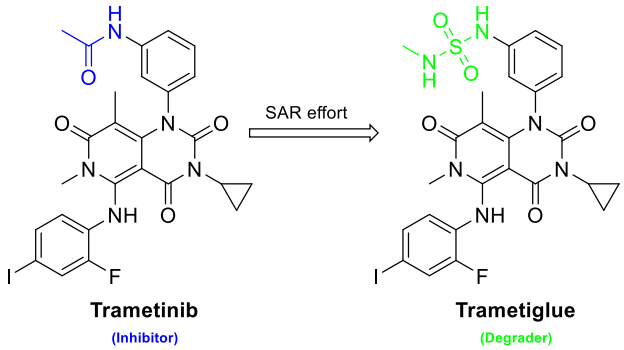
3.6.3. By adding a hydrophobic adamantyl moiety to TX1-85-1, a selective Her3 inhibitor, TX2-121-1 was developed. Interestingly, TX2-121-1 boosted the inhibitory effect of Her3-dependent signaling and led to the death of Her3-dependent cell lines (Xie, Lim *et al.* 2014) .



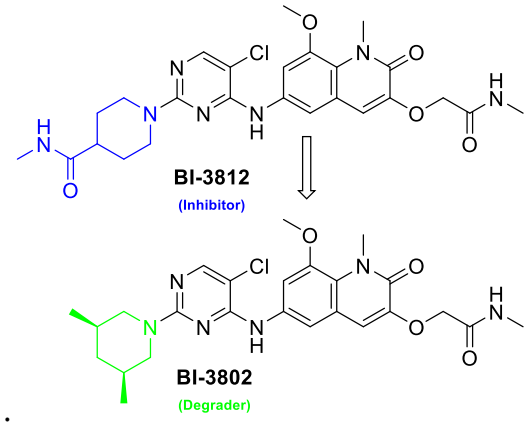
3.6.4. A new molecular glue degrader called CR8 , a pan-CDK inhibitor, was developed by incorporating a 2-pyridyl group to the solvent exposed site of CDK12 inhibitor (R)-roscovitine, as CR8 exhibit acceptable cytotoxicity in cell lines with elevated E3 ligase expression (Słabicki, Kozicka *et al.* 2020).



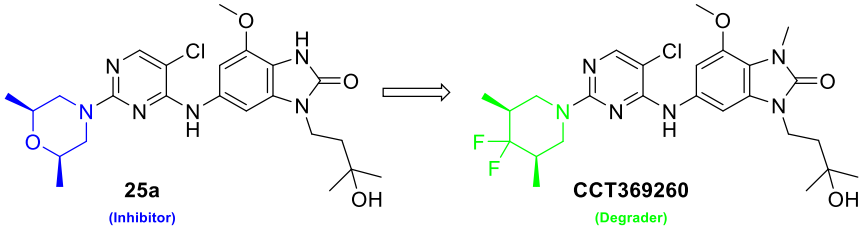
3.6.5. Trametinib is an orally active MEK inhibitor that inhibits MEK1\2, while trametiglue degrade both KSR-MEK and RAF-MEK, in which replace acetamide moiety of trametinib by key sulfamide moiety (good hydrogen bond donor\acceptor) of trametiglue (Khan, Real *et al.* 2020).



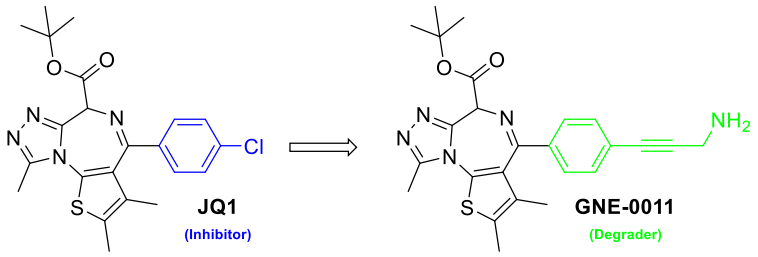
3.6.6. More than 1.5 million compounds were screened for molecular glue degraders by fluorescence polarization (FP). BI-3802, a degrader reflects distinct similarity matched with B-cell lymphoma 6 (BCL6) inhibitor BI-3812, emerged as promising candidates (Słabicki, Yoon *et al.* 2020).



3.6.7. Researchers hypothesized that a molecular glue akin to BI-3802 could be developed via modification on the solvent-exposed region, after several BCL6 inhibitors with structural similarities were disclosed. Among these is CCT369260, an oral active B-cell lymphoma 6 (BCL6) molecular glue that was discoverd to produce BCL6 polymers that SIAH1 can recognize and degrade (Bellenie, Cheung *et al*. 2020).



3.6.8. It has been reported that GNE-0011, a derivative of the inhibitor JQ1 bearing a key propargyl amine, exhibits a new class of monovalent BRD4 degrader, using a tail of degradation approach (Blake 2019).



3.6.9. Designing a tailed chemical handle for ligands that target key POIs in order to obtain molecular glue degraders was the aim of a promising design strategy developed by Nomura *et al.* (Toriki, Papatzimas *et al.* 2023). The handle recognized as a degradation tail, was then grafted onto various ligands of interest, resulting in the degradation of various oncoproteins, as shown in (**Fig. 11**).

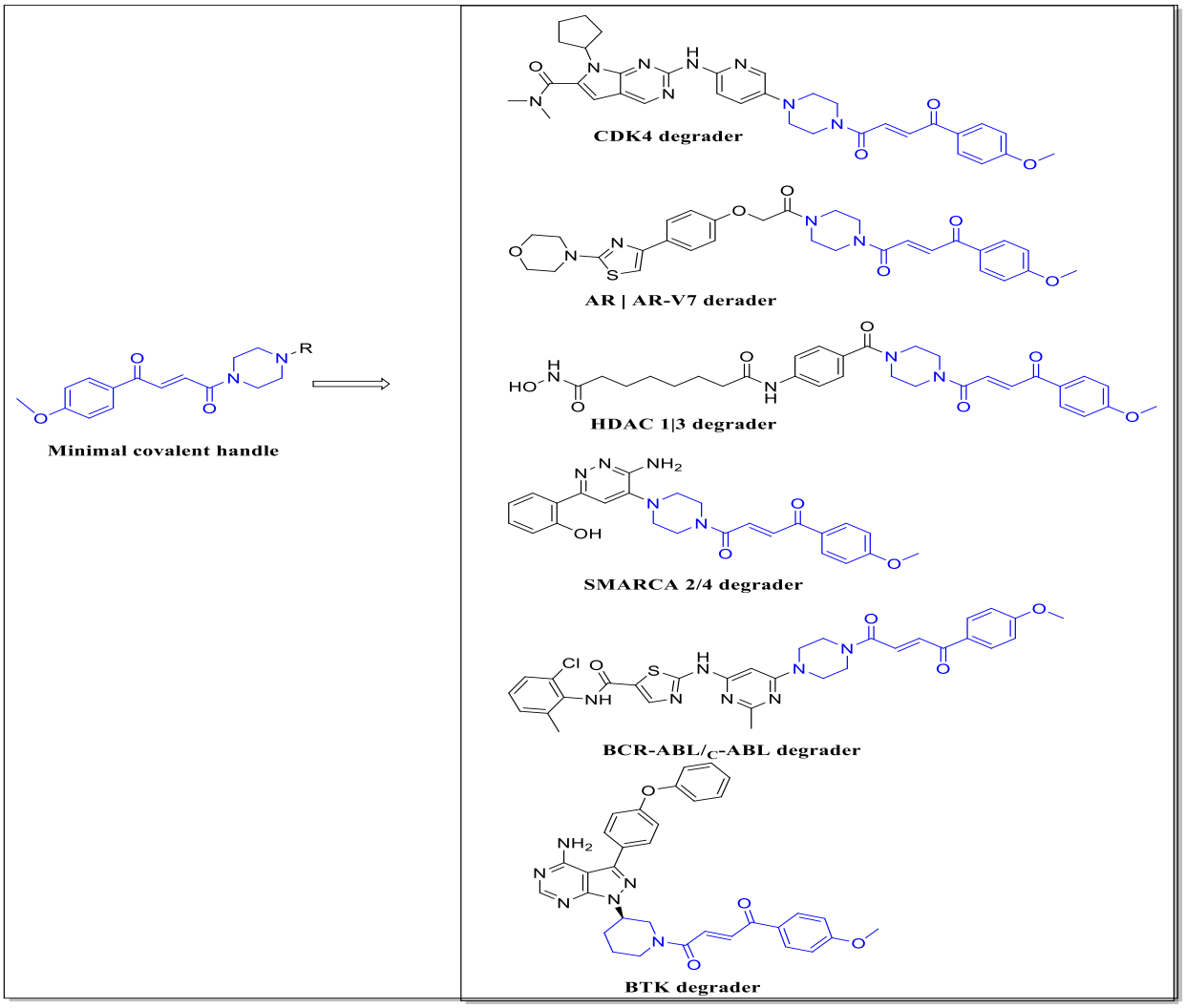


Fig. 11. Representation of a chemical handle as a degradation tail

3.6.10. A recent promising modality, termed intramolecular bivalent glues (IBGs) has emerged. Distinct from monovalent MGs and bivalent PROTACs, IBGs act as novel bifunctional degraders for BRD2 and BRD4. IBG1 is a JQ1 tethered to E7820. Unlike PROTACs, which link the two flanking domains of the POI in trans, IBGs connect them

in cis, as demonstrated in (**Fig. 12**) (Hsia, Hinterndorfer *et al*. 2024). Interestingly, this might blur the distinction between PROTACs and molecular glues.

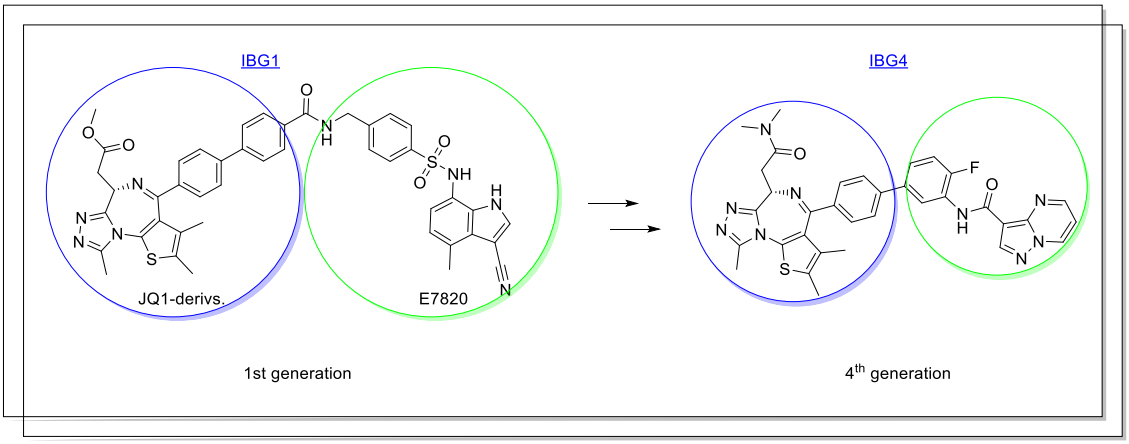


Fig. 12. Depiction of IBG technology

Concluding remarks

To summarize, designing and developing of anti-tumor drugs with novel mechanisms is both pressing, and challenging. Proximity-induced chemistry and the modality of protein degraders is the dynamite behind revolutionary class of therapeutics. In the following years, TPDs are expected to become more tailored, focused, and hold huge promise drug discovery strategy, offering powerful classes of medicines for unligandable proteins, intriguingly, through molecular glues. Moreover, TPDs will provide valuable insights into the intricate drug discovery process. Innovative approaches to targeting undruggable targets, which extend beyond the proteasomal pathway, offer exciting potential to advance new treatments that traditional modalities cannot achieve.

REFERENCES

Ali, A. G., M. F. Mohamed, A. O. Abdelhamid and M. S. Mohamed (2017). "A novel adamantane thiadiazole derivative induces mitochondria-mediated apoptosis in lung carcinoma cell line." Bioorganic & Medicinal Chemistry **25**(1): 241-253.

An, J., C. M. Ponthier, R. Sack, J. Seebacher, M. B. Stadler, K. A. Donovan and E. S. Fischer (2017). "pSILAC mass spectrometry reveals ZFP91 as IMiD-dependent substrate of the CRL4CRBN ubiquitin ligase." Nature communications **8**(1): 15398.

Asatsuma-Okumura, T., H. Ando, M. De Simone, J. Yamamoto, T. Sato, N. Shimizu, K. Asakawa, Y. Yamaguchi, T. Ito and L. Guerrini (2019). "p63 is a cereblon substrate involved in thalidomide teratogenicity." Nature chemical biology **15**(11): 1077-1084.

Bellenie, B. R., K.-M. J. Cheung, A. Varela, O. A. Pierrat, G. W. Collie, G. M. Box, M. D. Bright, S. Gowan, A. Hayes and M. J. Rodrigues (2020). "Achieving in vivo target depletion through the discovery and optimization of benzimidazolone BCL6 degraders." Journal of Medicinal Chemistry **63**(8): 4047-4068.

Blake, R. A. (2019). "GNE-0011, a novel monovalent BRD4 degrader." Cancer Research **79**(13_Supplement): 4452-4452.

Bonazzi, S., E. d'Hennezel, R. E. Beckwith, L. Xu, A. Fazal, A. Magracheva, R. Ramesh, A. Cernijenko, B. Antonakos and C. B. Hyo-eun (2023). "Discovery and characterization of a selective IKZF2 glue degrader for cancer immunotherapy." Cell Chemical Biology **30**(3): 235-247. e212.

Brennan, P. J., R. E. Saunders, M. Spanou, M. Serafini, L. Sun, G. P. Heger, A. Konopacka, R. D. Beveridge, L. Gordon and S. B. Bunally (2024). "Orthogonal IMiD-Degron Pairs Induce Selective Protein Degradation in Cells." bioRxiv.

Chang, Y., F. Keramatnia, P. S. Ghate, G. Nishiguchi, Q. Gao, I. Iacobucci, L. Yang, D. Chepyala, A. Mishra and A. A. High (2023). "The orally bioavailable GSPT1/2 degrader SJ6986 exhibits in vivo efficacy in acute lymphoblastic leukemia." Blood **142**(7): 629-642.

Donovan, K. A., J. An, R. P. Nowak, J. C. Yuan, E. C. Fink, B. C. Berry, B. L. Ebert and E. S. Fischer (2018). "Thalidomide promotes degradation of SALL4, a transcription factor implicated in Duane Radial Ray syndrome." elife **7**: e38430.

Fan, A. T., B. T. Boyle and F. M. Ferguson (2023). "A new avenue for molecular glues: Rapid discovery of a NFKB1 degrader." Cell Chemical Biology **30**(4): 340-342.

Faust, T. B., H. Yoon, R. P. Nowak, K. A. Donovan, Z. Li, Q. Cai, N. A. Eleuteri, T. Zhang, N. S. Gray and E. S. Fischer (2020). "Structural complementarity facilitates E7820-mediated degradation of RBM39 by DCAF15." Nature chemical biology **16**(1): 7-14.

Furihata, H., S. Yamanaka, T. Honda, Y. Miyauchi, A. Asano, N. Shibata, M. Tanokura, T. Sawasaki and T. Miyakawa (2020). "Structural bases of IMiD selectivity that emerges by 5-hydroxythalidomide." Nature communications **11**(1): 4578.

Gavory, G., M. Ghandi, A.-C. d'Alessandro, D. Bonenfant, M. Cabanski, L. Cantagallo, A. Chicas, Q. Chen, A. Diesslin and C. King (2023). "Development of MRT-2359, an orally bioavailable GSPT1 molecular glue

degrader, for the treatment of lung cancers with MYC-induced translational addiction." Cancer Research **83**(7_Supplement): 3449-3449.

Geiger, T. M., S. C. Schäfer, J. K. Dreizler, M. Walz and F. Hausch (2022). "Clues to molecular glues." Current Research in Chemical Biology **2**: 100018.

Gemechu, Y., D. Millrine, S. Hashimoto, J. Prakash, K. Sanchenkova, H. Metwally, P. Gyanu, S. Kang and T. Kishimoto (2018). "Humanized cereblon mice revealed two distinct therapeutic pathways of immunomodulatory drugs." Proceedings of the National Academy of Sciences **115**(46): 11802-11807.

Gertz, M. A. (2013). "Pomalidomide and myeloma meningitis." Leukemia & lymphoma **54**(4): 681-682.

Go, A., J. W. Jang, W. Lee, J. Du Ha, H. J. Kim and H. J. Nam (2020). "Augmentation of the antitumor effects of PARP inhibitors in triple-negative breast cancer via degradation by hydrophobic tagging modulation." European Journal of Medicinal Chemistry **204**: 112635.

Graves, B., T. Thompson, M. Xia, C. Janson, C. Lukacs, D. Deo, P. Di Lello, D. Fry, C. Garvie and K.-S. Huang (2012). "Activation of the p53 pathway by small-molecule-induced MDM2 and MDMX dimerization." Proceedings of the National Academy of Sciences **109**(29): 11788-11793.

Hagner, P. R., H.-W. Man, C. Fontanillo, M. Wang, S. Couto, M. Breider, C. Bjorklund, C. G. Havens, G. Lu and E. Rychak (2015). "CC-122, a pleiotropic pathway modifier, mimics an interferon response and has antitumor activity in DLBCL." Blood, The Journal of the American Society of Hematology **126**(6): 779-789.

Han, T., M. Goralski, N. Gaskill, E. Capota, J. Kim, T. C. Ting, Y. Xie, N. S. Williams and D. Nijhawan (2017). "Anticancer sulfonamides target splicing by inducing RBM39 degradation via recruitment to DCAF15." Science **356**.

Hansen, J. D., M. Correa, M. A. Nagy, M. Alexander, V. Plantevin, V. Grant, B. Whitefield, D. Huang, T. Kercher and R. Harris (2020). "Discovery of CRBN E3 ligase modulator CC-92480 for the treatment of relapsed and refractory multiple myeloma." Journal of medicinal chemistry **63**(13): 6648-6676.

Henning, N. J., L. Boike, J. N. Spradlin, C. C. Ward, G. Liu, E. Zhang, B. P. Belcher, S. M. Brittain, M. J. Hesse and D. Dovala (2022). "Deubiquitinase-targeting chimeras for targeted protein stabilization." Nature chemical biology **18**(4): 412-421.

Hsia, O., M. Hinterndorfer, A. D. Cowan, K. Iso, T. Ishida, R. Sundaramoorthy, M. A. Nakasone, H. Imrichova, C. Schätz and A. Rukavina (2024).

"Targeted protein degradation via intramolecular bivalent glues." Nature **627**(8002): 204-211.

Huber, A. D., Y. Li, W. Lin, A. N. Galbraith, A. Mishra, S. N. Porter, J. Wu, R. R. Florke Gee, W. Zhuang and S. M. Pruett-Miller (2022). "SJPYT-195: a designed nuclear receptor degrader that functions as a molecular glue degrader of GSPT1." ACS Medicinal Chemistry Letters **13**(8): 1311-1320.

Ichikawa, S., H. A. Flaxman, W. Xu, N. Vallavoju, H. C. Lloyd, B. Wang, D. Shen, M. R. Pratt and C. M. Woo (2022). "The E3 ligase adapter cereblon targets the C-terminal cyclic imide degron." Nature **610**(7933): 775-782.

Iwano, S., M. Nukaya, T. Saito, F. Asanuma and T. Kamataki (2005). "A possible mechanism for atherosclerosis induced by polycyclic aromatic hydrocarbons." Biochemical and biophysical research communications **335**(1): 220-226.

Jan, M., A. S. Sperling and B. L. Ebert (2021). "Cancer therapies based on targeted protein degradation—lessons learned with lenalidomide." Nature Reviews Clinical Oncology **18**(7): 401-417.

Jiang, X., J. Yu, Z. Zhou, J. Kongsted, Y. Song, C. Pannecouque, E. De Clercq, D. Kang, V. Poongavanam and X. Liu (2019). "Molecular design opportunities presented by solvent-exposed regions of target proteins." Medicinal Research Reviews **39**(6): 2194-2238.

Khan, Z. M., A. M. Real, W. M. Marsiglia, A. Chow, M. E. Duffy, J. R. Yerabolu, A. P. Scopton and A. C. Dar (2020). "Structural basis for the action of the drug trametinib at KSR-bound MEK." Nature **588**(7838): 509-514.

Kim, S. A., A. Go, S.-H. Jo, S. J. Park, Y. U. Jeon, J. E. Kim, H. K. Lee, C. H. Park, C.-O. Lee and S. G. Park (2019). "A novel cereblon modulator for targeted protein degradation." European Journal of Medicinal Chemistry **166**: 65-74.

King, E. A., Y. Cho, N. S. Hsu, D. Dovala, J. M. McKenna, J. A. Tallarico, M. Schirle and D. K. Nomura (2023). "Chemoproteomics-enabled discovery of a covalent molecular glue degrader targeting NF-κB." Cell chemical biology **30**(4): 394-402. e399.

Krönke, J., E. C. Fink, P. W. Hollenbach, K. J. MacBeth, S. N. Hurst, N. D. Udeshi, P. P. Chamberlain, D. Mani, H. W. Man and A. K. Gandhi (2015). "Lenalidomide induces ubiquitination and degradation of CK1α in del (5q) MDS." Nature **523**(7559): 183-188.

Krönke, J., N. D. Udeshi, A. Narla, P. Grauman, S. N. Hurst, M. McConkey, T. Svinkina, D. Heckl, E. Comer and X. Li (2014). "Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells." Science **343**(6168): 301-305.

Kubota, H. (2009). "Quality control against misfolded proteins in the cytosol: a network for cell survival." Journal of biochemistry **146**(5): 609-616.

Lai, A. C. and C. M. Crews (2017). "Induced protein degradation: an emerging drug discovery paradigm." Nature reviews Drug discovery **16**(2): 101-114.

Li, G., H. S. Ban and H. Nakamura (2018). "Design of Carborane-Based Hypoxia-Inducible Factor Inhibitors." Boron-Based Compounds: Potential and Emerging Applications in Medicine: 35-59.

Li, L., W. Xue, Z. Shen, J. Liu, M. Hu, Z. Cheng, Y. Wang, Y. Chen, H. Chang and Y. Liu (2020). "A cereblon modulator CC-885 induces CRBN-and p97-dependent PLK1 degradation and synergizes with volasertib to suppress lung cancer." Molecular Therapy-Oncolytics **18**: 215-225.

Li, Y., S. Li and H. Wu (2022). "Ubiquitination-proteasome system (UPS) and autophagy two main protein degradation machineries in response to cell stress." Cells **11**(5): 851.

Liu, X. and A. Ciulli (2023). "Proximity-based modalities for biology and medicine." ACS Central Science **9**(7): 1269-1284.

Lopez-Girona, A., C. G. Havens, G. Lu, E. Rychak, D. Mendy, B. Gaffney, C. Surka, C.-C. Lu, M. Matyskiela and G. Khambatta (2019). "CC-92480 is a novel cereblon E3 ligase modulator with enhanced tumoricidal and immunomodulatory activity against sensitive and resistant multiple myeloma cells." Blood **134**: 1812.

Lu, G., R. E. Middleton, H. Sun, M. Naniong, C. J. Ott, C. S. Mitsiades, K.-K. Wong, J. E. Bradner and W. G. Kaelin Jr (2014). "The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins." Science **343**(6168): 305-309.

Lv, L., P. Chen, L. Cao, Y. Li, Z. Zeng, Y. Cui, Q. Wu, J. Li, J.-H. Wang and M.-Q. Dong (2020). "Discovery of a molecular glue promoting CDK12-DDB1 interaction to trigger cyclin K degradation." Elife **9**: e59994.

Matyskiela, M. E., S. Couto, X. Zheng, G. Lu, J. Hui, K. Stamp, C. Drew, Y. Ren, M. Wang and A. Carpenter (2018). "SALL4 mediates teratogenicity as a thalidomide-dependent cereblon substrate." Nature chemical biology **14**(10): 981-987.

Matyskiela, M. E., G. Lu, T. Ito, B. Pagarigan, C.-C. Lu, K. Miller, W. Fang, N.-Y. Wang, D. Nguyen and J. Houston (2016). "A novel cereblon modulator recruits GSPT1 to the CRL4CRBN ubiquitin ligase." Nature **535**(7611): 252-257.

Matyskiela, M. E., W. Zhang, H.-W. Man, G. Muller, G. Khambatta, F. Baculi, M. Hickman, L. LeBrun, B. Pagarigan and G. Carmel (2018). "A cereblon modulator (CC-220) with improved degradation of Ikaros and Aiolos." Journal of medicinal chemistry **61**(2): 535-542.

Matyskiela, M. E., J. Zhu, J. M. Baughman, T. Clayton, M. Slade, H. K. Wong, K. Danga, X. Zheng, M. Labow and L. LeBrun (2020). "Cereblon modulators target ZBTB16 and its oncogenic fusion partners for degradation via distinct structural degrons." ACS chemical biology **15**(12): 3149-3158.

Mayor-Ruiz, C., S. Bauer, M. Brand, Z. Kozicka, M. Siklos, H. Imrichova, I. H. Kaltheuner, E. Hahn, K. Seiler and A. Koren (2020). "Rational discovery of molecular glue degraders via scalable chemical profiling." Nature chemical biology **16**(11): 1199-1207.

Neklesa, T. K., J. D. Winkler and C. M. Crews (2017). "Targeted protein degradation by PROTACs." Pharmacology & therapeutics **174**: 138-144.

Ng, A., F. Offensperger, J. A. Cisneros, N. S. Scholes, M. Malik, L. Villanti, A. Rukavina, E. Ferrada, J. T. Hannich and A. Koren (2023). "Discovery of molecular glue degraders via isogenic morphological profiling." ACS Chemical Biology **18**(12): 2464-2473.

Nishiguchi, G., L. G. Mascibroda, S. M. Young, E. A. Caine, S. Abdelhamed, J. J. Kooijman, D. J. Miller, S. Das, K. McGowan and A. Mayasundari (2024). "Selective CK1α degraders exert antiproliferative activity against a broad range of human cancer cell lines." Nature Communications **15**(1): 482.

Ohoka, N., G. Tsuji, T. Shoda, T. Fujisato, M. Kurihara, Y. Demizu and M. Naito (2019). "Development of small molecule chimeras that recruit AhR E3 ligase to target proteins." ACS chemical biology **14**(12): 2822-2832.

Osborne, C., A. Wakeling and R. Nicholson (2004). "Fulvestrant: an oestrogen receptor antagonist with a novel mechanism of action." British journal of cancer **90**(1): S2-S6.

Powell, C. E., G. Du, J. Che, Z. He, K. A. Donovan, H. Yue, E. S. Wang, R. P. Nowak, T. Zhang and E. S. Fischer (2020). "Selective degradation of GSPT1 by cereblon modulators identified via a focused combinatorial library." ACS chemical biology **15**(10): 2722-2730.

Quancard, J., T. Klein, S.-Y. Fung, M. Renatus, N. Hughes, L. Israël, J. J. Priatel, S. Kang, M. A. Blank and R. I. Viner (2019). "An allosteric MALT1 inhibitor is a molecular corrector rescuing function in an immunodeficient patient." Nature chemical biology **15**(3): 304-313.

Salama, A. K., M. V. Trkulja, E. Casanova and I. Z. Uras (2022). "Targeted protein degradation: clinical advances in the field of oncology." International Journal of Molecular Sciences **23**(23): 15440.

Schreiber, S. L. (2021). "The rise of molecular glues." Cell **184**(1): 3-9.

Schreiber, S. L. (2024). "Molecular glues and bifunctional compounds: Therapeutic modalities based on induced proximity." Cell Chemical Biology.

Shi, Y., M. J. Long, M. M. Rosenberg, S. Li, A. Kobjack, P. Lessans, R. T. Coffey and L. Hedstrom (2016). "Boc3Arg-linked ligands induce degradation by localizing target proteins to the 20S proteasome." ACS chemical biology **11**(12): 3328-3337.

Shoda, T., N. Ohoka, G. Tsuji, T. Fujisato, H. Inoue, Y. Demizu, M. Naito and M. Kurihara (2020). "Targeted protein degradation by chimeric compounds using hydrophobic E3 ligands and adamantane moiety." Pharmaceuticals **13**(3): 34.

Sievers, Q. L., G. Petzold, R. D. Bunker, A. Renneville, M. Słabicki, B. J. Liddicoat, W. Abdulrahman, T. Mikkelsen, B. L. Ebert and N. H. Thomä (2018). "Defining the human C2H2 zinc finger degrome targeted by thalidomide analogs through CRBN." Science **362**(6414): eaat0572.

Simonetta, K. R., J. Taygerly, K. Boyle, S. E. Basham, C. Padovani, Y. Lou, T. J. Cummins, S. L. Yung, S. K. von Soly and F. Kayser (2019). "Prospective discovery of small molecule enhancers of an E3 ligase-substrate interaction." Nature Communications **10**(1): 1402.

Słabicki, M., Z. Kozicka, G. Petzold, Y.-D. Li, M. Manojkumar, R. D. Bunker, K. A. Donovan, Q. L. Sievers, J. Koeppel and D. Suchyta (2020). "The CDK inhibitor CR8 acts as a molecular glue degrader that depletes cyclin K." Nature **585**(7824): 293-297.

Słabicki, M., H. Yoon, J. Koeppel, L. Nitsch, S. S. Roy Burman, C. Di Genua, K. A. Donovan, A. S. Sperling, M. Hunkeler and J. M. Tsai (2020). "Small-molecule-induced polymerization triggers degradation of BCL6." Nature **588**(7836): 164-168.

Štimac, A., M. Šekutor, K. Mlinarić-Majerski, L. Frkanec and R. Frkanec (2017). "Adamantane in drug delivery systems and surface recognition." Molecules **22**(2): 297.

Straif, K., R. Baan, Y. Grosse, B. Secretan, F. El Ghissassi and V. Cogliano (2005). "Carcinogenicity of polycyclic aromatic hydrocarbons." The lancet oncology **6**(12): 931-932.

Surka, C., L. Jin, N. Mbong, C.-C. Lu, I. S. Jang, E. Rychak, D. Mendy, T. Clayton, E. Tindall and C. Hsu (2021). "CC-90009, a novel cereblon E3

ligase modulator, targets acute myeloid leukemia blasts and leukemia stem cells." Blood, The Journal of the American Society of Hematology **137**(5): 661-677.

Szakács, G., J. K. Paterson, J. A. Ludwig, C. Booth-Genthe and M. M. Gottesman (2006). "Targeting multidrug resistance in cancer." Nature reviews Drug discovery **5**(3): 219-234.

Takwale, A. D., E. Y. Kim, Y. Jang, D. H. Lee, S. Kim, Y. Choi, J. H. Kim, Y. Kim, S. M. Lee and H. K. Lee (2022). "Structure-activity relationship analysis of novel GSPT1 degraders based on benzotriazinone scaffold and its antitumor effect on xenograft mouse model." Bioorganic chemistry **127**: 105923.

Teng, M., W. Lu, K. A. Donovan, J. Sun, N. M. Krupnick, R. P. Nowak, Y.-D. Li, A. S. Sperling, T. Zhang and B. L. Ebert (2021). "Development of PDE6D and CK1α degraders through chemical derivatization of FPFT-2216." Journal of medicinal chemistry **65**(1): 747-756.

Ting, T. C., M. Goralski, K. Klein, B. Wang, J. Kim, Y. Xie and D. Nijhawan (2019). "Aryl sulfonamides degrade RBM39 and RBM23 by recruitment to CRL4-DCAF15." Cell Reports **29**(6): 1499-1510. e1496.

Toriki, E. S., J. W. Papatzimas, K. Nishikawa, D. Dovala, A. O. Frank, M. J. Hesse, D. Dankova, J.-G. Song, M. Bruce-Smythe and H. Struble (2023). "Rational chemical design of molecular glue degraders." ACS central science **9**(5): 915-926.

Uehara, T., Y. Minoshima, K. Sagane, N. H. Sugi, K. O. Mitsuhashi, N. Yamamoto, H. Kamiyama, K. Takahashi, Y. Kotake and M. Uesugi (2017). "Selective degradation of splicing factor CAPERα by anticancer sulfonamides." Nature chemical biology **13**(6): 675-680.

Wanka, L., K. Iqbal and P. R. Schreiner (2013). "The lipophilic bullet hits the targets: medicinal chemistry of adamantane derivatives." Chemical reviews **113**(5): 3516-3604.

Wassel, M. M., Y. A. Ammar, G. A. E. Ali, A. Belal, A. B. Mehany and A. Ragab (2021). "Development of adamantane scaffold containing 1, 3, 4-thiadiazole derivatives: Design, synthesis, anti-proliferative activity and molecular docking study targeting EGFR." Bioorganic Chemistry **110**: 104794.

Wei, Y., X. Xu, M. Jiang, Y. Wang, Y. Zhou, Z. Wang, Z. Zhang, F. Zhou and K. Ding (2023). "Discovery of new Lenalidomide derivatives as potent and selective GSPT1 degraders." European Journal of Medicinal Chemistry **258**: 115580.

Wojtaszek, J. L., N. Chatterjee, J. Najeeb, A. Ramos, M. Lee, K. Bian, J. Y. Xue, B. A. Fenton, H. Park and D. Li (2019). "A small molecule targeting

mutagenic translesion synthesis improves chemotherapy." Cell **178**(1): 152-159. e111.

Xie, S., F. Zhan, J. Zhu, Y. Sun, H. Zhu, J. Liu, J. Chen, Z. Zhu, D. H. Yang and Z. S. Chen (2023). "Discovery of norbornene as a novel hydrophobic tag applied in protein degradation." Angewandte Chemie **135**(13): e202217246.

Xie, T., S. M. Lim, K. D. Westover, M. E. Dodge, D. Ercan, S. B. Ficarro, D. Udayakumar, D. Gurbani, H. S. Tae and S. M. Riddle (2014). "Pharmacological targeting of the pseudokinase Her3." Nature chemical biology **10**(12): 1006-1012.

Yamanaka, S., H. Murai, D. Saito, G. Abe, E. Tokunaga, T. Iwasaki, H. Takahashi, H. Takeda, T. Suzuki and N. Shibata (2020). "PLZF is a new substrate of CRBN with thalidomide and 5-hydroxythalidomide." BioRxiv: 2020.2002. 2028.969071.

Yang, X., F. Li, K. D. Konze, J. Meslamani, A. Ma, P. J. Brown, M.-M. Zhou, C. H. Arrowsmith, H. U. Kaniskan and M. Vedadi (2016). "Structure–activity relationship studies for enhancer of zeste homologue 2 (EZH2) and enhancer of zeste homologue 1 (EZH1) inhibitors." Journal of medicinal chemistry **59**(16): 7617-7633.

Yu, H. H., J. M. Reitsma, M. J. Sweredoski, A. Moradian, S. Hess and R. J. Deshaies (2019). "Single subunit degradation of WIZ, a lenalidomide-and pomalidomide-dependent substrate of E3 ubiquitin ligase CRL4CRBN." BioRxiv: 595389.

Zak, K. M., P. Grudnik, K. Guzik, B. J. Zieba, B. Musielak, A. Dömling, G. Dubin and T. A. Holak (2016). "Structural basis for small molecule targeting of the programmed death ligand 1 (PD-L1)." Oncotarget **7**(21): 30323.

Zhu, Y. X., E. Braggio, C.-X. Shi, L. A. Bruins, J. E. Schmidt, S. Van Wier, X.-B. Chang, C. C. Bjorklund, R. Fonseca and P. L. Bergsagel (2011). "Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide." Blood, The Journal of the American Society of Hematology **118**(18): 4771-4779.

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الملخص:

في إطار السعي لعلاج السرطان، يستكشف باحثو إكتشاف وتطوير الأدوية باستمرار سبلًا جديدة لتطوير عوامل مضادة للسرطان بحيث تكون فعّالة، أكثر أمانًا، محتملة، وأقل مقاومة. من النماذج المتقدمة في مجال تطوير وإكتشاف الأدوية هو محفزات تكسير البروتينات المستهدفة Targeted Protein Degraders (TPD). عادةً ما تُصمم الجزيئات الصغيرة التقليدية Small Molecules Traditional لحجب أو تثبيط أهدافها المحددة، بينما تُصمم محفزات الإلتصاق الجزيئي لتطويع البروتينات المحورية المُشكلة إلى نظام يوبكويتين-بروتيوزوم (UPS)، مما يؤدي إلى تكسير البروتينات المسببة للأمراض (التحلل البروتيني الخلوي). في هذا السياق، نسلط الضوء على الأدوار الحيوية والواعدة لمحفزات تكسير البروتين المستهدفة، لا سيما محفزات الإلتصاق الجزيئي، في التصدي للسرطان. وأخيرًا، نأمل في توضيح التطورات الحديثة وتقديم رؤى قيّمة في تطوير الأدوية المرتبطة بهذه التقنيات المتقدمة.

الكلمات المفتاحية: مضادات الأورام، محفزات تكسير البروتينات المستهدفة، محفزات الإلتصاق الجزيئي، الجزيئات الصناعية، البروتاكس، الهايتاكس.