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Review Article

Advances in molecular glue degraders for targeted protein degradation: Focus on NEK7, WEE1, CDK2, GSPT1 and VAV1

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ABSTRACT

Molecular glues (MGs), a class of small-molecule degraders, exhibit drug-like properties that generally conform to Lipinski's rule of five, while uniquely mediating the stabilization or induction of protein-protein interactions. By altering the surface properties of either target proteins or E3 ligases, MGs promote the formation of a ternary complex comprising the MG, an E3 ligase, and a target protein. This interaction facilitates the polyubiquitination and subsequent degradation of the target protein via the ubiquitin-proteasome system. Owing to its distinctive mechanism of action and broad therapeutic potential, MG is offering novel approaches to disease treatment. This review summarizes recent advances in MGs targeting NEK7, WEE1, CDK2, GSPT1 and VAV1, emphasizing the rational design, benefits, and potential limitations, highlighting rational design principles, advantages, and current limitations including challenges in achieving selectivity and rational design that provide critical insights for enhancing MG efficacy. These developments are crucial for advancing the application and optimization of molecular glues targeting NEK7, WEE1, CDK2, GSPT1 and VAV1.

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1. Introduction

Targeted Protein Degradation (TPD) has emerged as a promising strategy in disease treatment. This strategy focuses on selectively degrading specific proteins within cells, which significantly impacts various disease-related processes [1–3]. Many degraders function by inducing proximity between intracellular ubiquitin ligases and a protein of interest (POI) [4,5], leading to POI polyubiquitination and proteasomal degradation. Bivalent proximity inducers such as proteolysis-targeting chimeras (PROTACs) recruit POI and E3 ligases by using high-affinity ligands to engage their respective pockets, which are connected by a linker [6,7]. In contrast, molecular Glues (MGs) stabilize protein-protein interactions (PPI) by modifying the interaction surface without relying on strong binary affinity. PROTACs can be utilized in the rational design of degraders by leveraging potent and highly selective chemical ligands. These ligands can target both the target proteins and the ubiquitination-related machinery. However, the comparatively large size of PROTACs often leads to suboptimal physicochemical and pharmacokinetic properties, including poor solubility and permeability [8,9].

1.1. *MGs vs PROTACs*

MGs exhibit lower molecular weights than PROTACs and typically comply with Lipinski's rule of five, which contributes to their generally more favorable pharmacokinetic profiles compared to PROTACs [10–13]. The growing complexity of human diseases, combined with the limitations of conventional small-molecule inhibitors and biologic therapies, has spurred the development of innovative strategies targeting previously undruggable proteins. MGs represent a transformative class of degraders that address critical gaps in therapeutic development. Unlike traditional inhibitors, which depend on preexisting binding pockets, MGs harness endogenous PPI networks to bring E3 ubiquitin ligases into proximity with disease-relevant targets, promoting their ubiquitination and degradation. This mechanism is particularly relevant in polypharmacy and multi-target treatment paradigms, where MGs offer three major benefits: (1) Targeting plasticity: MGs enable degradation of structurally flat or disordered protein regions inaccessible to conventional inhibitors; (2) Signal pathway modulation: simultaneous degradation of non-enzymatic scaffold proteins can disrupt entire oncogenic signaling cascades; (3) Resistance mitigation: by eliminating target proteins rather than inhibiting them, MGs reduce the risk of mutation-driven resistance commonly associated with kinase inhibitors. Although some MGs have been discovered serendipitously, de novo rational design of MG degraders remains challenging [11–14]. Fig. 1**A** illustrates the mechanism of MG-induced protein degradation via the ubiquitin-proteasome system (UPS). MGs function by binding to cellular proteins, such as CRBN E3 ligases, and inducing conformational changes that enable these proteins to interact with disease-causing targets typically inaccessible to conventional drugs. This results in the formation of a ternary complex (glue-effector-target), which either marks the target protein for degradation via the cellular protein degradation machinery or modulates its activity. By targeting undruggable proteins like GSPT1, MGs overcome limitations of traditional inhibitors and offer a versatile strategy to modulate cancer signaling pathways through degradation or controlled activation [15].

1.2. *Cereblon as a key E3 ligase*

Cereblon (CRBN), a key substrate receptor within the CUL4-RBX1-DDB1-CRBN (CRL4-CRBN) ubiquitin E3 ligase complex, is targeted by glutarimide-containing MGs (Fig. 1**B**). Notably, glutarimide-containing MGs target CRBN to degrade neosubstrates [12,13]. These glutarimide-containing ligands have a prominent role in binding to CRBN [11,16,17] and chemical modification of this scaffold is a well-established strategy for expanding the target spectrum of CRBN MGs [18,19]. Upon binding CRBN, these degraders induce ternary complex formation with neosubstrate proteins [20–22]. As a result, the neosubstrate proteins undergo polyubiquitination and subsequent degradation [23,24]. Typically, the phthalimide and isoindolinone cores of these degraders are structured to occupy the cytosol-exposed tritryptophan pocket of CRBN [25] providing a structural basis for further derivatization [19,26]. Previous research has shown that chemical modifications of CRBN ligands can significantly enhance their binding promiscuity, thereby expanding the repertoire of potential neosubstrates and having greater potential for therapeutic applications [19,27–29]. For example, numerous MGs have advanced to clinical trials, exhibiting notable target diversity and improved specificity (Fig. 2). These advances have significantly propelled the TPD field forward [30–32].

MGs represent a rapidly evolving area in modern drug discovery, offering substantial therapeutic promise alongside considerable scientific and technical challenges. This untapped clinical potential, combined with their unique mechanism, has established MG-based drug discovery as a dynamic field attracting growing scientific and investment interest. This review focuses on recent progress in MGs targeting NEK7, WEE1, CDK2, GSPT1, and VAV1 within oncology and inflammation research, emphasizing rational design, therapeutic benefits, and limitations, as discussed in the following sections.

2. Development strategy of selective MGs targeting NEK7

NEK7 is a serine/threonine kinase and the smallest member of the mammalian NEK kinase family. NEK7 regulates mitotic spindle formation, cytokinesis, and NLRP3 inflammasome activation [33,34]. Under normal conditions, NEK7 is in a low-activity state [35]; however, under pathological conditions such as cancer or inflammatory disorders, it is aberrantly expressed and contributes to the progression of various tumors and chronic inflammatory diseases [36]. NEK7 has been identified as a critical regulator in the activation of inflammasomes, particularly serving as an essential mediator in the assembly and activation of the NLRP3 inflammasome complex (Fig. 3) [37]. After receiving

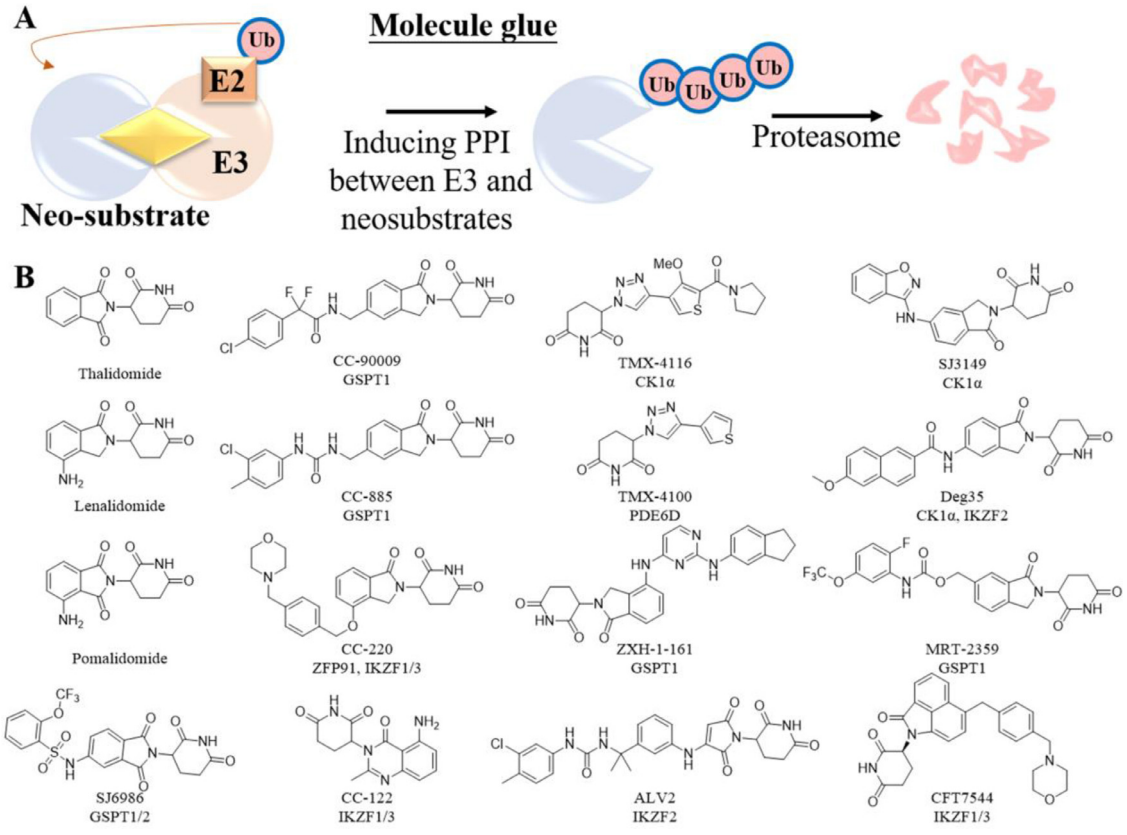


Fig. 1 – (A) Mechanism of MGs causing neosubstrate degradation through the UPS pathway; (B) Reported CRBN MG degraders and their primary targets.

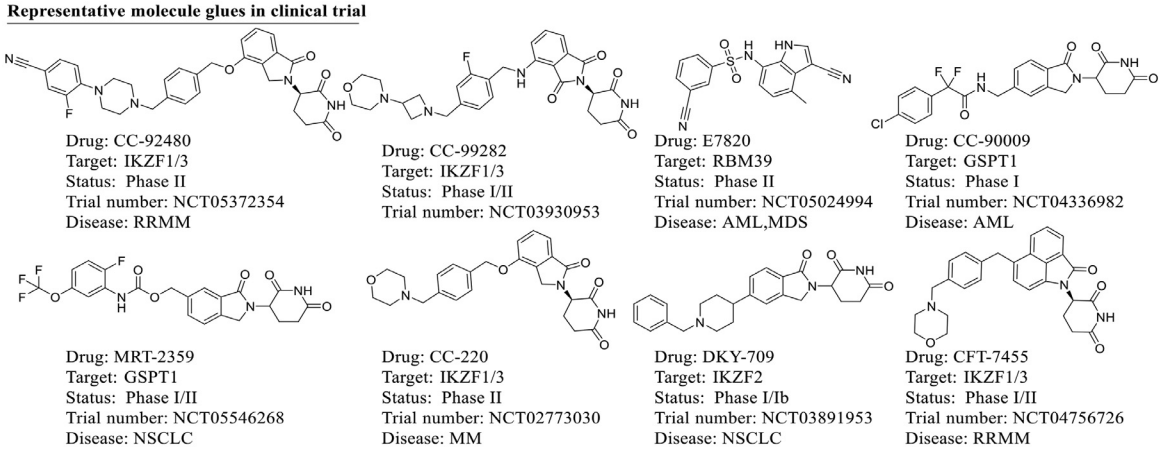


Fig. 2 – Representative MGs in clinical trials.

appropriate cellular stress signals, NEK7 interacts with NLRP3 [38]. This interaction is a critical step in the assembly and activation process of the NLRP3 inflammasome [39]. In this process, NEK7 assists in maintaining the correct folding and stability of NLRP3, but also promotes its aggregation with the adaptor protein ASC (apoptosis-associated speck-like protein containing CARD), further triggering the activation of caspase-1. This cascade induces the production and release of inflammatory cytokines, driving the inflammatory response [40]. Therefore, NEK7 has become a potential target for chronic inflammatory diseases [41–43].

Currently, numerous small-molecule inhibitors targeting NEK7 have been discovered through structure-based drug design and high-throughput screening, including Berberine, Dacomitinib, and Entrectinib (Fig. 4) [40,42,45]. These compounds suppress inflammasome assembly and activation by engaging NEK7, thereby attenuating immune

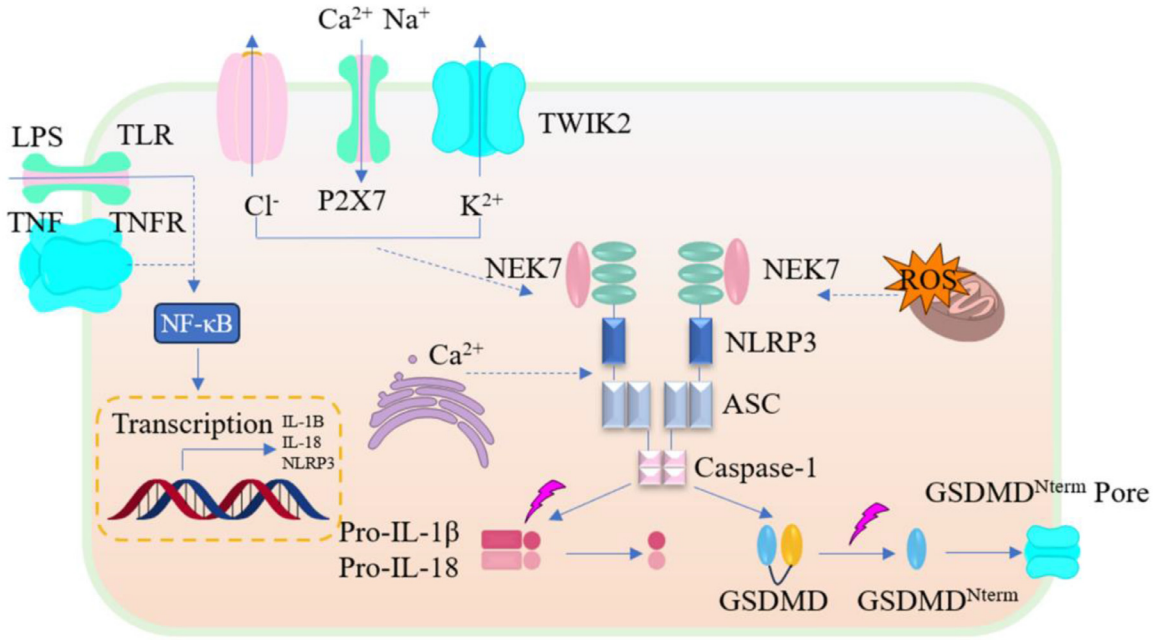


Fig. 3 – Mechanism of NEK7 in regulating the activity of NLRP3 inflammasome. Reprinted (adapted) with permission from [44], Copyright© 2024 John Wiley & Sons A/S.

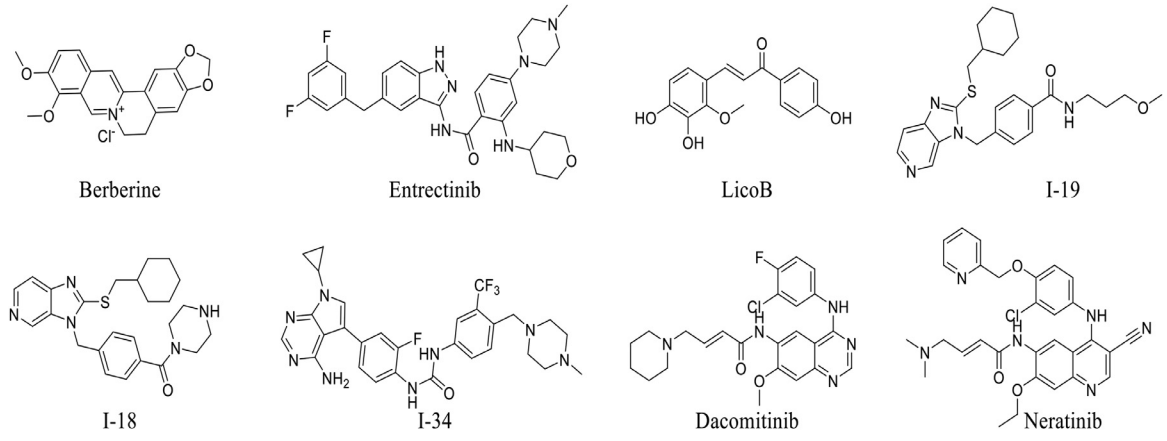


Fig. 4 – Representative NLRP3-NEK7 blockers and NEK7 inhibitors.

response and relieving inflammatory diseases. Additionally, HT-6184, an allosteric NEK7 inhibitor developed by Halia Therapeutics, is currently in a phase II clinical study for the treatment of myelodysplastic syndrome/pain (NCT05447546). However, indicates that inflammasome activation does not rely solely on NEK7's kinase activity; its scaffolding function also plays an essential role [33,46,47]. Consequently, inhibiting NEK7's catalytic activity alone may be insufficient to fully abrogate inflammatory responses. Furthermore, the high degree of homology between NEK7 and other family members such as NEK6 poses a considerable challenge to the development of selective NEK7 inhibitors [48,49]. Traditional kinase inhibitors frequently exhibit limited specificity in distinguishing between NEK7 and its closely related homolog NEK6, thereby compromising their therapeutic selectivity and clinical applicability [49,50]. In contrast, the emerging strategy of developing NEK7 degraders offers distinct advantages: (1) MGs completely eliminate both catalytic and scaffolding functions of NEK7, and (2) MGs offer enhanced specificity over traditional inhibitors. These characteristics position NEK7 degraders as a highly promising therapeutic modality with considerable clinical potential.

LC-03-052, a novel MG degrader targeting NEK7, was identified via high-throughput screening using CRISPR/Cas9-edited MOLT-4 cells featuring endogenously HiBiT-tagged NEK7 model (Fig. 5**A**) [51]. Importantly, LC-03-052 exhibited encouraging NEK7-degrading activities with a DC_{50} of 26 nM and a D_{max} of 75% after compound treatment for 6 h in biological triplicate. Mechanism of action studies showed that the degradation of LC-03-052 was reversed by pretreatment with bortezomib (a proteasome inhibitor) and MLN4924 (a ubiquitin ligase inhibitor), supporting a UPS-dependent

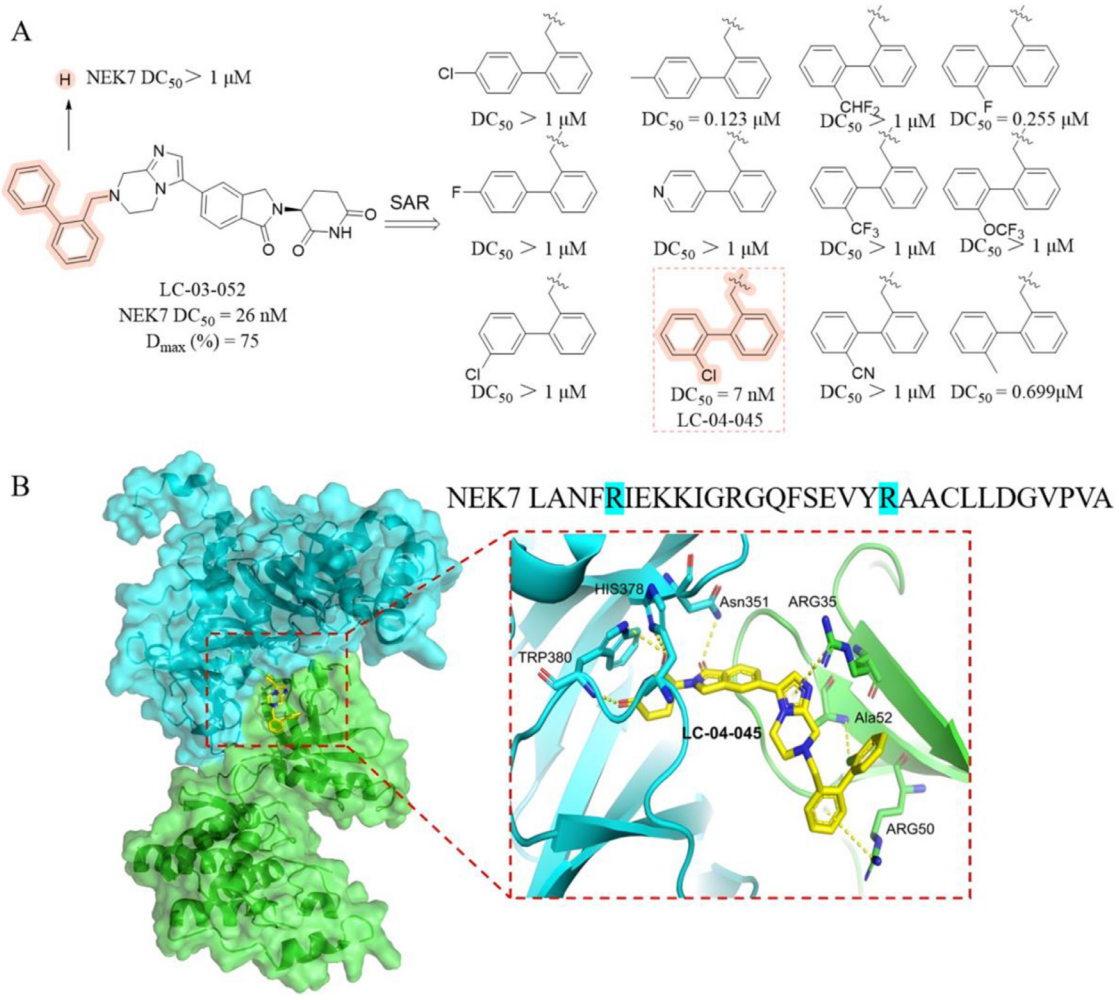


Fig. 5 – (A) Discovery of selective and potent MG degraders for NEK7; (B) Computational model CRBN-LC-04-045-NEK7 complex. Reprinted (adapted) with permission from [51], Copyright© 2025 Wiley-VCH GmbH.

mechanism. Subsequent structural optimization based on LC-03-052 revealed that the introduction of a chlorine or fluorine at the para-position of the 1′-phenyl group reduced the degradation activity against NEK7, while the introduction of a methyl group restored the potency against NEK7, although lower than that of LC-03-052. Replacement of the 1′-phenyl group with a 4′-pyridyl moiety completely abolished degradation activity. Further, at the ortho position of the 1′-phenyl group of LC-03-052, through the introduction of different halogens, electron-withdrawing substituents such as -CF_3, and electron-donating substituents such as methyl groups for SAR studies, a potent degrader LC-04-045 was discovered. *In vitro*, LC-04-045 showed highly efficient NEK7 degradation activity in MOLT-4 cells (DC_{50} = 7 nM, D_{max} = 90%) in a concentration- and time-dependent manner. confirmed that LC-04-045 was highly specific for NEK7, with minimal off-target effects. As shown in Fig. 5**B**, the ternary complex model of CRBN-LC-04-045-NEK7 shows that LC-04-045 can form hydrogen bonds with ARG35 and ARG50 of the NEK7 protein. Furthermore, in the MOLT-4 cell models overexpressing HiBiT-$NEK7^{R35A}$ and HiBiT-$NEK7^{R50A}$, LC-04-045 loses its degradation activity against NEK7. These results indicate that the ARG35 and ARG50 amino acid residues of the degron motif serve as a vital factor in determining the potency and selectivity of the NEK7 MG. Further pharmacological evaluation demonstrated that LC-04-045 effectively inhibits secretion of the downstream cytokines IL-1β and IL-18 in LPS-stimulated human monocyte-derived macrophages (hMDMs). Its efficacy is comparable to that of the NLRP3 inhibitor MCC950, suggesting therapeutic potential in inflammatory conditions such as rheumatoid arthritis or sepsis.

A cell-based split enzyme recruitment assay was employed to screen an in-house library of 2500 CRBN-binding molecules for their ability to recruit NEK7 to CRBN. One hit compound, NK7-288, was discovered with weak NEK7 degradation activity [52]. By replacing the isoindolinone of NK7-288 with phthalimide, NK7-147 with improved potency was obtained. Further optimization of the tail structure led to the discovery of NK7-902, which exhibited a DC_{50} of 0.2 nM and a D_{max} > 95% for NEK7 (Fig. 6**A**). The selectivity profile of NK7-902 was systematically evaluated using quantitative proteomic analysis in human primary monocytes treated with 1 μM compound for 18 h. NEK7 was identified as the most

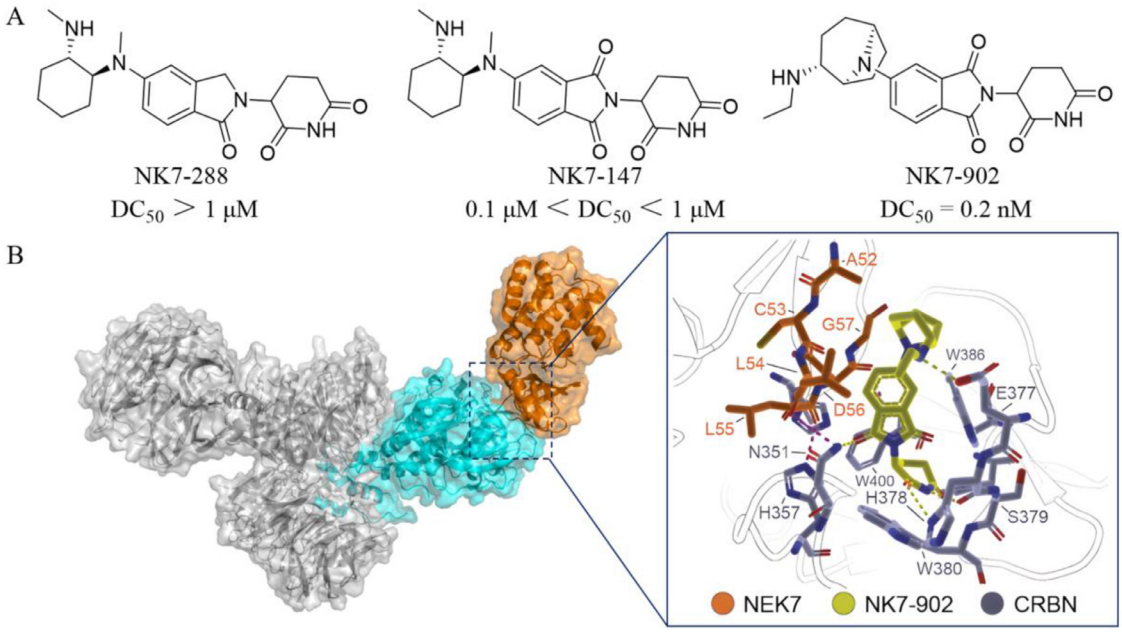


Fig. 6 – (A) Identification of NK7-902, a CRBN glue degrader of NEK7; (B) Modeled interactions of the ternary complex of CRBN-DDB1-NK7-902-NEK7. Reprinted (adapted) with permission from [52], Copyright© 2025 Elsevier Ltd.

significantly depleted protein, underscoring the compound's high degradation specificity. Notably, NEK6, sharing 86% catalytic domain homology with NEK7, remained unaffected by NK7-902 treatment. This discrimination correlates with the absence of the β-hairpin structural motif in NEK6, a critical determinant for CRBN-dependent proteasomal targeting, thereby validating the structure-activity relationship (SAR) underlying MG-mediated degradation. Point mutation studies and CRBN knockout experiments confirmed that NK7-902 engages CRBN via the β-hairpin domain of NEK7. Cryo-EM and molecular modeling analyses revealed a stable ternary complex involving NEK7, NK7-902, and CRBN–DDB1, in which NK7-902 forms hydrogen bonds with His378 and Asn351. Additionally, the secondary amine of NK7-902 interacts with the side chain of Glu377, while residues within the NEK7 β-hairpin establish hydrogen bonds with both CRBN and NK7-902 (Fig. 6**B**). In a mouse acute peritonitis model, NK7-902 degraded NEK7 in a dose-dependent manner and inhibited the release of IL-1β after *in vivo* LPS plus ATP-activated NLRP3 inflammasome. Additionally, NK7-902 effectively degraded NEK7 in a mouse CAPS model and inhibited the release of IL-1β in the blood, with levels close to the complete inhibition observed with the NLRP3 inhibitor. NEK7 is a multi-functional protein kinase of great significance in mitosis and NLRP3 inflammasome activation. As research progresses, next-generation NEK7 degraders are anticipated to offer novel therapeutic avenues for inflammatory diseases.

3. MGs targeting WEE1 and CDK2 for regulating cell cycle progression

Cell cycle regulation involves a complex network of critical regulatory proteins and kinases such as WEE1 and CDK2, which collectively ensure cells undergo mitosis only after successful DNA repair (Fig. 7) [53–55]. WEE1, a serine/threonine kinase, phosphorylates and inhibits cyclin-dependent kinase 1 (CDK1) at the G_2/M checkpoint, thereby preventing mitotic entry [56,57]. In response to DNA damage during S and G2 phases, WEE1 activity increases to facilitate DNA repair [58]. If DNA damage persists without being repaired, WEE1 will cause cell cycle arrest, providing time for DNA repair before mitotic entry and preventing cells with damaged DNA from entering mitosis [59,60]. CDK2 [61], a cyclin-dependent kinase, binds to cyclin E and cyclin A, playing a crucial role in the G1/S transition and the S phase [62]. Specifically, the activity of CDK2 is necessary for cells to enter the S phase by phosphorylating key substrates like Rb from the G1 phase and maintaining the cells' proliferative state in the S and G2 phases [63]. Moreover, the activity of CDK2 tightly controlled by checkpoint mechanisms to ensure orderly cell cycle progression [64–66]. Therefore, WEE1 and CDK2 function as integral components of a coordinated regulatory network that responds to internal and external cues, including DNA damage.

In oncology, WEE1 and CDK2 are attractive therapeutic targets due to their central roles in tumor cell proliferation and survival. Inhibiting the activity of WEE1 can cause cell-cycle arrest, thereby preventing the division and growth of tumor cells. Meanwhile, CDK2 inhibitors disrupts DNA replication and G1/S transition, thereby suppressing tumor growth. WEE1 and CDK2 cooperate in cell-cycle regulation to ensure that cells safely enter mitosis after DNA damage repair via opposing roles at G2/M and G1/S checkpoints, respectively. Their dysfunctions may lead to abnormal cell cycle, which in turn affects cell growth and division. Currently, numerous WEE1 inhibitors have entered clinical trials for cancer treatment, such as AZD1775 (Fig. 8**A**) [67,68]. However,

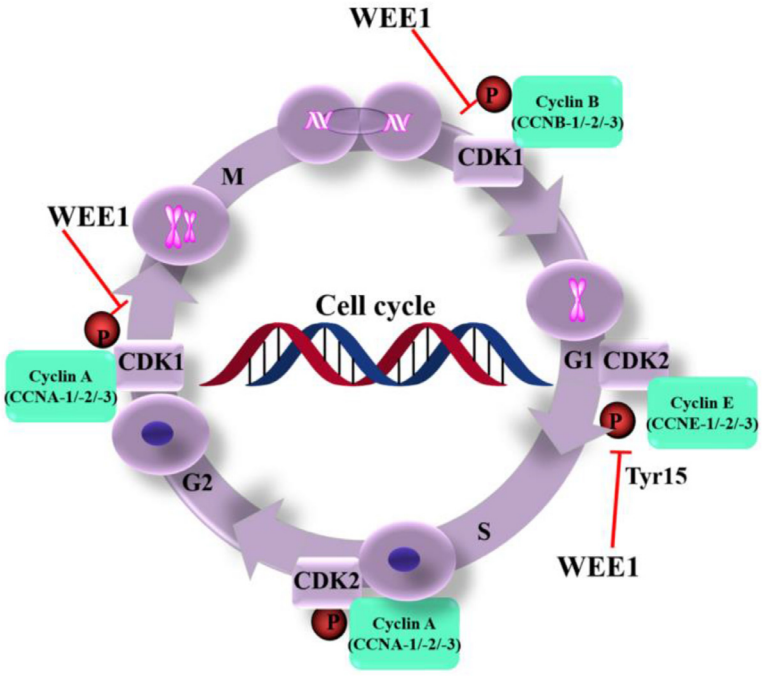


Fig. 7 – Biological functions of WEE1 and CDK2 in cell cycle.

clinical research has revealed that AZD1775 treatment is associated with adverse effects including myelosuppression, neutropenia, and thrombocytopenia have been reported, likely due to off-target inhibition of polo-like kinase 1 (PLK1) [69,70]. To address these limitations, a new PROTAC strategy was implemented by conjugating AZD1775 with the VHL ligand VH032 or the CRBN ligand pomalidomide through different linkers to achieve selective degradation of WEE1. For example, WEE1 PROTAC degraders 1–3 (Fig. 8**A**) can potently induce the degradation of WEE1 via the proteasome pathway [71]. Moreover, these molecules can selectively degrade WEE1 without affecting other related proteins such as PLK1/2/3, thus reducing the off-target clinical toxicity of WEE1 inhibitors.

Through screening of glutarimide derivatives in CRBN wild-type and knockout MOLT-4 cells, several MG degraders of WEE1 (compounds 4–8) were identified [72]. Specifically, compound 4 exhibited DC_{50} values of 1.1 nM and 3.1 nM for WEE1 and CK1α, respectively, and had a D_{max} of >90% (Fig. 8**A**). Western blot analysis confirmed that compound 4 mediated the degradation of WEE1 and CK1α via a CRBN-dependent ubiquitination mechanism without affecting known CRBN neosubstrates such as IKZF1, IKZF2 or GSPT1. Further optimization yielded compound 10, which demonstrated sub-2 nM DC_{50} values for both WEE1 and CK1α. TR-FRET experiments proved that WEE1, CRBN, and compound 10 can form a stable ternary complex. Unlike WEE1 PROTACs, compound 10 showed no apparent hook effect, indicating a cooperative binding mechanism in the ternary complex. Furthermore, structural analysis of the WEE1–compound 10–CRBN complex highlighted the importance of the G-loop in WEE1, particularly Gly322, in mediating MG binding (Fig. 8**B**). The point-mutation experiment further confirmed that mutating Gly322 to Asn completely prevented compound 10 from degrading WEE1, indicating that this glycine is the core site for molecular-glue binding. WEE1 PROTAC degraders usually have a hook effect at high concentrations. As a result, the formation of trimers is prevented, which in turn inhibits the degradation of WEE1. In contrast, the WEE1 MG does not exhibit this phenomenon. Additionally, compared with PROTACs, WEE1 MGs may have better druggability due to their smaller sizes.

CDK2, a cyclin-dependent kinase, binds to cyclin E (CCNE1) and regulates progression of the G1/S and S phases in the cell cycle. Increased CDK2 activity is recognized as a key mechanism underlying resistance to CDK4 and CDK6 inhibitors. Therefore, CDK2 has important research and application values as a drug target. So far, a large number of CDK2 inhibitors have been developed, with several advancing into clinical trials (Fig. 9) [66]. For example, tagtociclib (PF-07104091), the most advanced selective CDK2 inhibitor, is currently in Phase II clinical trials for the treatment of advanced breast cancer. However, prolonged CDK2 inhibitor treatment can induce resistance, primarily through a negative feedback loop that drives transcriptional upregulation of CCNE1 and elevates cyclin E protein levels, thereby restoring CDK2 activity [73].

Unlike the CDK2 inhibitors, CDK2-directed PROTACs mediate full protein degradation, disrupting both enzymatic and non-enzymatic functions, including transcriptional activity [74]. This mechanism offers a potential strategy to overcome resistance associated with conventional small molecules. Consequently, several PROTAC degraders targeting CDK2 have been developed (Fig. 9). For example, compound CPS2 can selectively and dose-dependently degrade CDK2

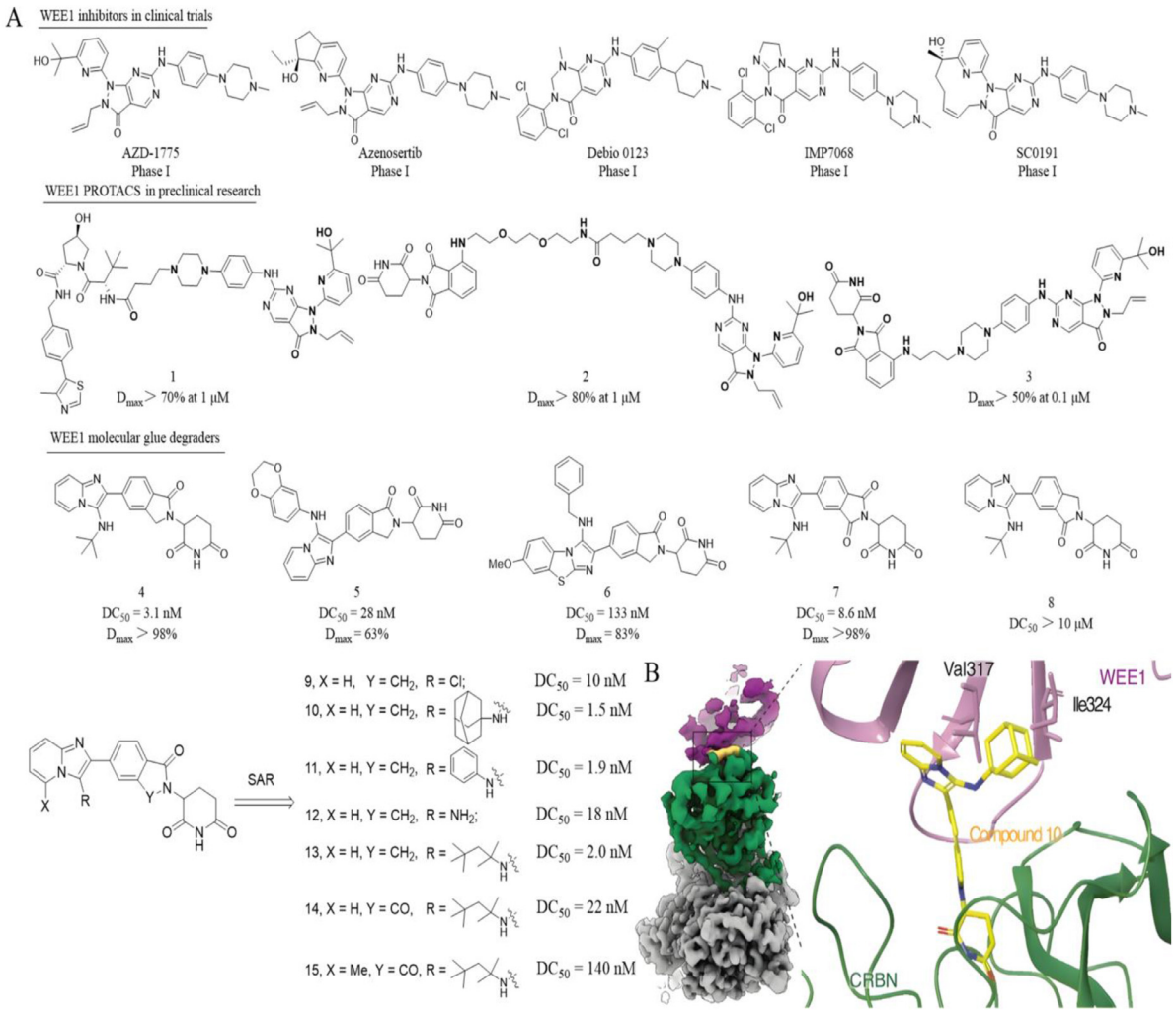


Fig. 8 – (A) Representative WEE1 inhibitors, PROTACs, and MGs; (B) Docking models for compound 10 into the WEE1-CRBN interface derived from the Cryo-EM structure. Reprinted (adapted) with permission from [72], copyright © 2024 American Chemical Society.

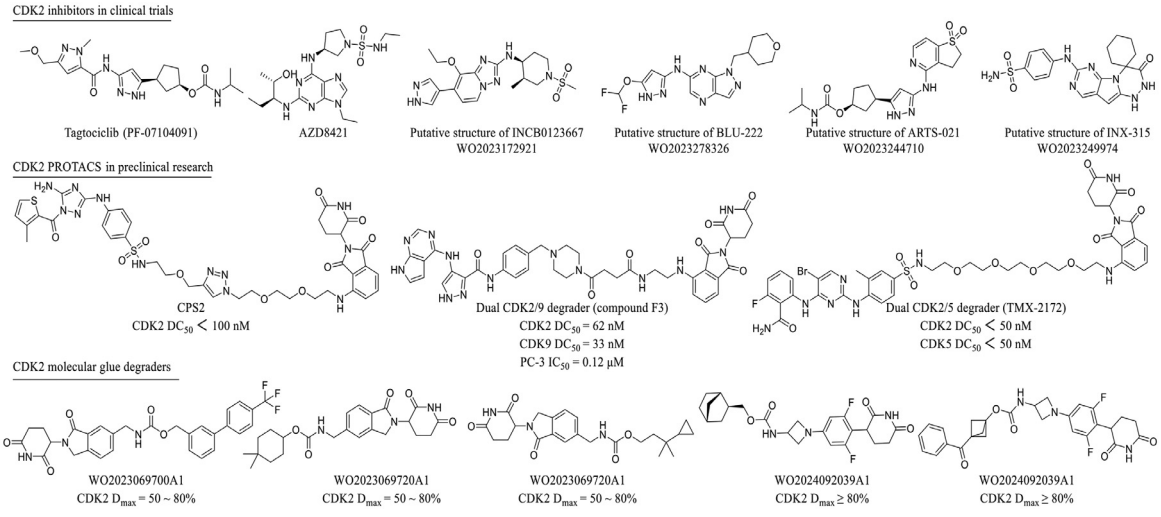


Fig. 9 – Characterization of CDK2-targeted inhibitors, PROTAC degraders and MGs.

with a DC_{50} < 100 nM in Ramos cells [75]. Further research shows that CPS2 can induce the differentiation of AML primary cells and hematopoietic stem cells by decreasing CDK2, providing a new method for the treatment of AML and CDK2-related diseases. Compound F3 acts as a CDK2/9 dual-degrader, which potently induces the degradation of both CDK2 (DC_{50} = 62 nM) and CDK9 (DC_{50} = 33 nM) [76]. In PC-3 human prostate cancer cells, F3 inhibits proliferation by inducing cell cycle in the S and G2/M phases. TMX-2172, a heterobifunctional CDK2 degrader, can selectively degrade CDK2 (DC_{50} < 50 nM) and CDK5 (DC_{50} < 50 nM), yet it has almost no effect on CDK1, CDK4, CDK6, CDK7 and CDK9. In OVCAR8 cells, TMX-2172 exhibits a remarkable growth-inhibitory effect (IC_{50} = 33.1 nM). As a G-loop target, CDK2 is easily degraded by CRBN [77]. Currently, several CDK2-targeted MGs have been discovered (Fig. 9). Unlike CDK2 inhibitors, these MGs do not induce CCNE1 upregulation or p-Rb rebound, mechanisms often responsible for inhibitor resistance. Moreover, MGs possess improved drug-like properties compared to PROTACs and greater selectivity and resistance mitigation potential than conventional inhibitors, highlighting their clinical promise.

4. MGs targeting GSPT1

GSPT1 (G1 to S phase transition 1, also known as eRF3a) was crucial for translation termination and mRNA quality control via eRF1 coordination in the translation termination process of protein synthesis [78,79]. It works in coordination with the eRF1 protein to recognize the stop codons on the messenger RNA (mRNA), facilitating the release of the nascent polypeptide from the ribosome and thus terminating protein translation [80]. Besides translation termination, GSPT1 participates in nonsense-mediated mRNA decay (NMD) and other cellular processes critical for mRNA surveillance [81–84]. The degradation of GSPT1 leads to the accumulation of truncated proteins and cellular stress, ultimately impairing tumor cell proliferation and survival (Fig. 10**A**) [85].

Based on large-scale chemical screening and subsequent mass spectrometry analysis, CC-885 was identified as a potent GSPT1 degrader (DC_{50} < 1 nM, D_{max} > 90%). Nevertheless, due to the significant off-target effects of CC-885 on IKAROS family zinc finger protein 1 (IKZF1), IKZF3 and casein kinase 1α (CK1α), as well as its high toxicity to normal PBMC cells (IC_{50} = 1.1 nM) and THLE-2 cells (IC_{50} = 11 nM), the further development of CC-885 was halted (Fig. 10**B**) [86,87]. Structural modification of CC-885, that is, replacing the urea group with a difluoromethylene moiety, yielded CC-90009, which retained broad anti-AML activity (IC_{50} = 3.22–78.1 nM) while exhibiting improved selectivity for cancer cells over THLE-2 and PBMC cells, and preferential degradation of GSPT1 over IKZF1/3, indicating a better safety profile (Fig. 10**B**) [88,89]. Besides CC-885 and CC-90009, a great number of MGs targeting GSPT1 have been discovered through the scaffold-hopping strategy, and all of these compounds exhibit potent GSPT1-degrading activities (Fig. 10**B**) [90–97]. Additionally, several bifunctional degraders combining MG and PROTAC mechanisms have been found (Fig. 10**C**). For example, YB-3–17 can efficiently and selectively inhibit mTOR (IC_{50} = 0.22 nM) and degrade GSPT1 (DC_{50} = 5 nM) [98] functions as a dual-mechanism degrader, operating as a PROTAC against BTK (DC_{50} = 37 nM) and as a MG for GSPT1 (DC_{50} = 26 nM) [99]. DP-15, as a bifunctional GSPT1 & BRD4 degrader, has DC_{50} values of 0.48 nM for BRD4 and 5.25 nM for GSPT1 [100]. ORM-5029, an antibody-degrader conjugate (ADeC), selectively targets and degrades GSPT1 to minimize off-target toxicity and is currently in a phase I clinical trial for HER2-positive cancers (NCT05511844) [85]. The structure of ORM-5029 consists of three parts: the HER2 antibody pertuzumab, the payload SMol006 (a GSPT1 degrader), and the linker Val-Cit PABc (Fig. 10**D**). In the MV4-11 tumor-bearing model, ORM-6151 demonstrates superior efficacy and safety profiles compared to CC-90009. Administration of a single 3 mg/kg dose of ORM-5029 resulted in complete tumor regression, achieving complete remission (CR) in all nine subjects (9/9 CR). PROTACs usually face problems such as poor cell uptake and off-target toxicity. Compared with PROTACs, ADeC can deliver PROTACs into specific cells through the targeting ability of antibodies. This dual-specificity approach markedly diminishes off-target effects, which can widen the therapeutic window and has better prospects for clinical application.

5. MGs targeting VAV1

VAV1 acts as a guanine nucleotide exchange factor (GEF) and a scaffold protein in immune signaling that can serve as a guanine nucleotide exchange factor (GEF) [101,102]. Its GEF activity catalyzes GDP/GTP exchange in Rac/Rho family GTPases, leading to their activation [103]. Once activated, VAV1 modulates cytoskeleton rearrangement, cell migration, and immunological synapse formation. In addition, in its role as a scaffold protein, VAV1 facilitates the assembly of TCR and BCR signaling complexes and modulates pathway activation through interactions with diverse signal molecules [104]. As shown in Fig. 11, VAV1 has multiple roles in immune cell activation, migration, and inflammatory response. It not only regulates GTPases such as Rac1 via its GEF domain, that is, impacting cytoskeletal dynamics and synapse formation, but also contributes critically to cell migration and the synthesis of inflammatory mediators through Rac1 activation [105,106]. Thus, VAV1 is regarded as a potential therapeutic target in autoimmune and chronic inflammatory diseases. Targeting VAV1 may enable simultaneous modulation of multiple inflammatory processes, offering a novel strategy for managing complex immune diseases.

As previously noted, VAV1 may serve as a potential target in autoimmune and chronic inflammatory diseases, as several VAV1-targeted MGs have been discovered. VAV1-targeted MGs (e.g., compounds 16–19, Fig. 12**A**) exhibit potent VAV1-degrading activity (DC_{50} = 4.4–7 nM), and can significantly attenuate inflammatory responses and ameliorate tissue damage in models of arthritis and colitis. Structurally, VAV1 MGs are composed of three parts, including glutarimide, a chlorobenzene moiety (Part A), and an end-aryl ring (Part B). The glutarimide moiety can interact with the CRBN protein, which enables the recruitment and degradation of the target protein. The chlorobenzene ring enhances lipophilicity and may improve membrane

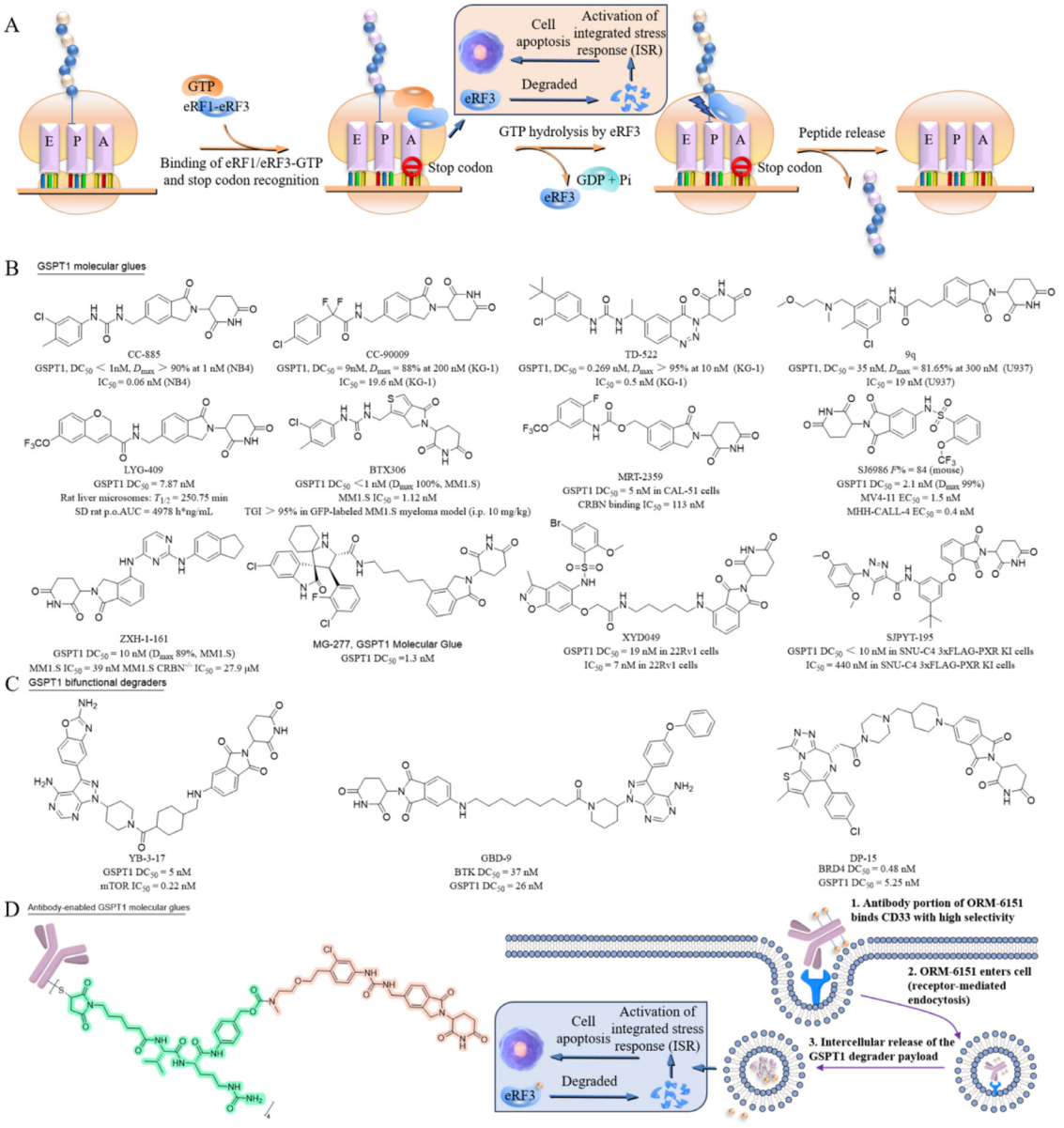


Fig. 10 – (A) Mechanism of cell-integrated stress response induced by degradation of GSPT1; (B) GSPT1 MGs; (C) Bifunctional GSPT1 degraders; (D) Antibody-enabled GSPT1 MGs.

permeability. Chlorine substitution augments the electron-withdrawing character of the ring, strengthening target binding affinity. Part B moiety is mainly a lipophilic benzene ring with a substituent of certain polarity. This part can tolerate multiple substitution patterns, providing enough space for the structural optimization of the compound. Modifications at the R1 position can refine the compound's potency, selectivity, and pharmacokinetic profile. Based on this framework, novel VAV1-directed MGs may be developed by replacing the chlorobenzene group with heterocycles or incorporating fused ring systems in Parts A and B, further optimizing physicochemical properties (Fig. 12B). VAV1 is mainly expressed in hematopoietic cells, including T cells and B cells. Thus, VAV1-targeted MGs can inhibit the immune response more effectively and reduce damage to other organs and tissues. Moreover, as a bifunctional protein possessing both GEF and scaffolding activities, degradation of VAV1 via MGs concurrently disrupts its GEF activity and scaffold function, thereby comprehensively inhibiting key signaling pathways in T and B cells and providing a broader immunosuppressive effect. All in all, as a new type of targeted therapeutic agents, VAV1 MGs may offer a novel therapeutic approach in treating autoimmune diseases and chronic inflammatory diseases.

6. Discussion and perspective

MG is an emerging area of research in drug discovery, as it can promote or induce PPI of target proteins by changing

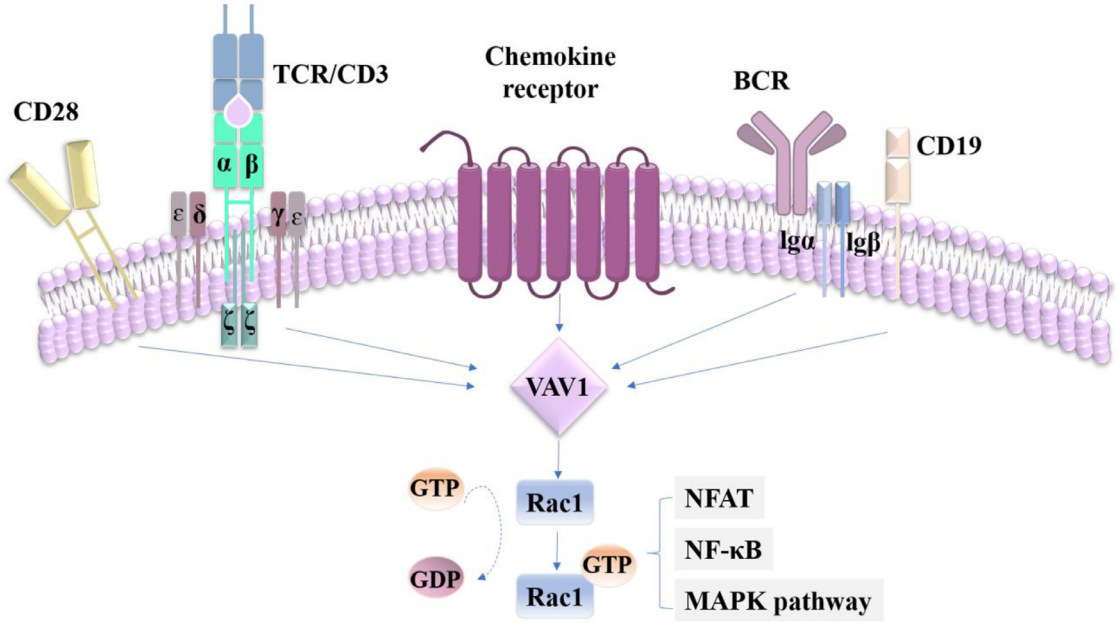


Fig. 11 – Core guanine nucleotide exchange factor (GEF)-dependent functions of VAV1. Reprinted (adapted) with permission from [102], Copyright© 2024 The Authors.

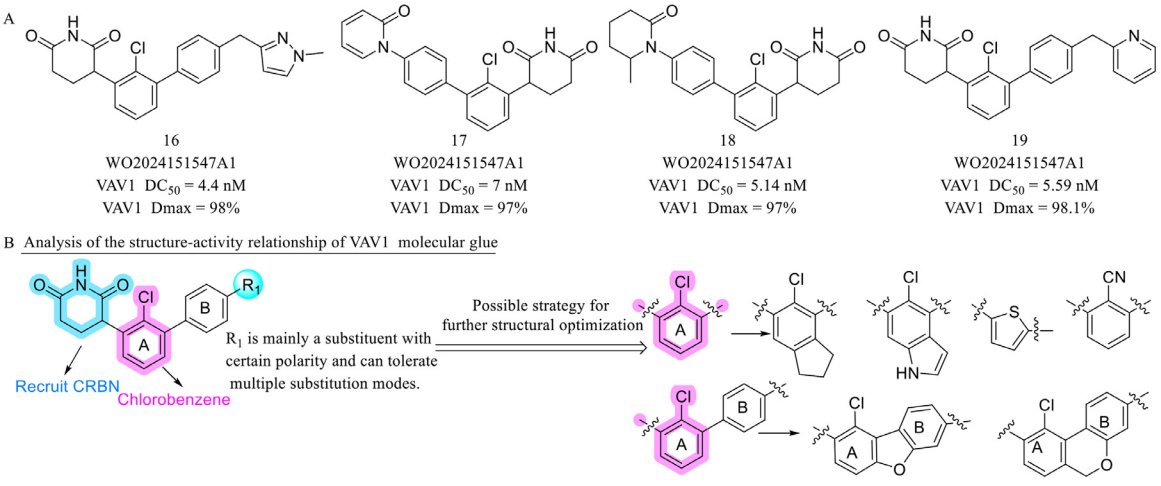


Fig. 12 – (A) Representative VAV1 MGs; (B) Proposed design strategy of novel VAV1 MGs via scaffold hopping strategy.

their surface characteristics. Through PPI induction, MGs can elicit specific biological outcomes such as TPD. Compared to PROTACs, MGs often exhibit improved physicochemical properties including enhanced solubility and stability absence of a Hook effect, and reduced affinity requirements. These advantages endow MG-based drugs with great clinical application potential. However, unlike PROTACs, which are amenable to rational design, the development of MGs remains largely empirical. Current discovery approaches rely on serendipitous findings, high-throughput screening, informatics-driven methods, and medicinal chemistry optimization. Although there are already quite a few positive examples, such as GSPT1 MGs, the discovery of MGs still faces many challenges. Since MGs operate through induced PPIs, which often involve conformational rearrangements, high-throughput screening campaigns typically yield low hit rates (~1%–2%), complicating SAR analysis and structure-based design. Faced with this series of challenges, the current mainstream strategy is to achieve the discovery of lead compounds through large-scale screening, including DNA encoded library screening (DEL), affinity screen mass spectrometry (ASMS), and high throughput screening (HTS).

Currently, most newly discovered MGs are structurally derived from thalidomide, such as NEK7, WEE1 and CDK2 MGs. However, the thalidomide structure is prone to racemization, reducing efficacy due to keto-enol tautomerism under physiological conditions, and this process occurs very frequently under physiological conditions. A recent strategy involves eliminating the chiral center by replacing the glutarimide carbon with nitrogen, thereby preventing

racemization. Additionally, poor solubility often impedes the development of thalidomide-based MGs, resulting in limited bioavailability, high clearance rates, and absorption-limited pharmacokinetics. One promising solution is the prodrug strategy, wherein the imide nitrogen of CRBN-binding glutarimide is conjugated to amino acid esters to markedly enhance solubility and bioavailability.

MGs, as a novel class of therapeutic agents, encounter numerous challenges but also present distinct advantages and substantial market potential, positioning them as a pivotal focus in future pharmaceutical development. For instance, NEK7-targeting MGs demonstrate exceptional selectivity, as evidenced by the specific degradation of NEK7 without impacting its homolog NEK6 in human primary monocytes. This specificity is governed by a β-hairpin motif that mediates topological complementarity between NEK7 and the CRBN–E3 ligase complex, providing a structural rationale for kinase-selective degradation. Such findings exemplify a shift from conventional catalytic inhibition to structure-guided degradation, underscoring the therapeutic potential of MGs in targeting undruggable kinases.

Future research should aim to diversify MG scaffolds beyond thalidomide derivatives to harness alternative E3 ligases such as DCAF15 or RNF114, thereby expanding the range of actionable targets. Advanced structural characterization techniques, including cryo-EM and hydrogen-deuterium exchange mass spectrometry, could elucidate dynamic interactions between glues, E3 ligases, and target proteins across tissue-specific contexts. Moreover, rational design of β-hairpin-mimetic pharmacophores may enable selective degradation of structurally analogous yet functionally divergent proteins within kinase families. Collectively, these efforts will accelerate the transition of MGs from fortuitous discoveries to precision therapeutic tools. With advancing technologies and growing interdisciplinary collaboration, MGs are poised to offer new hope for patients with diverse conditions.

Conflicts of interest

The authors declare that there is no conflicts of interest.

CRediT authorship contribution statement

Binbin Cheng: Writing – original draft, Conceptualization. **Yaping Wang:** Software, Data curation. **Yimeng Hong:** Software. **Yingxing Zhou:** Supervision, Resources, Methodology. **Xiaopeng Peng:** Writing – review & editing. **Jianjun Chen:** Writing – review & editing. **Chunlai Zeng:** Supervision, Resources, Conceptualization.

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References

[1] Bekes M, Langley DR, Crews CM. PROTAC targeted protein degraders: the past is prologue. Nat Rev Drug Discov 2022;21(3):181–200.
[2] Hsia O, Hinterndorfer M, Cowan AD, Iso K, Ishida T, Sundaramoorthy R, et al. Targeted protein degradation via intramolecular bivalent glues. Nature 2024;627(8002):204–11.
[3] Zhao L, Zhao J, Zhong K, Tong A, Jia D. Targeted protein degradation: mechanisms, strategies and application. Signal Transduct Target Ther 2022;7(1):113.
[4] Dong G, Ding Y, He S, Sheng C. Molecular glues for targeted protein degradation: from serendipity to rational discovery. J Med Chem 2021;64(15):10606–20.
[5] Song J, Hu M, Zhou J, Xie S, Li T, Li Y, et al. Targeted protein degradation in drug development: recent advances and future challenges. Eur J Med Chem 2023;261:115839.
[6] Kim J, Byun I, Kim DY, Joh H, Kim HJ, Lee MJ, et al. Targeted protein degradation directly engaging lysosomes or proteasomes. Chem Soc Rev 2024;53(7):3253–72.
[7] Samarasinghe KTG, Crews CM. Targeted protein degradation: a promise for undruggable proteins. Cell Chem Biol 2021;28(7):934–51.
[8] Kong NR, Jones LH. Clinical translation of targeted protein degraders. Clin Pharmacol Ther 2023;114(3):558–68.
[9] Stockley ML, Ferdinand A, Benedetti G, Blencowe P, Boyd SM, Calder M, et al. Discovery, characterization, and structure-based optimization of small-molecule in vitro and in vivo probes for human DNA polymerase theta. J Med Chem 2022;65(20):13879–91.
[10] Mayor-Ruiz C, Bauer S, Brand M, Kozicka Z, Siklos M, Imrichova H, et al. Rational discovery of molecular glue degraders via scalable chemical profiling. Nat Chem Biol 2020;16(11):1199–207.
[11] Lemaitre T, Cornu M, Schwalen F, Since M, Kieffer C, Voisin-Chiret AS, et al. Molecular glue degraders: exciting opportunities for novel drug discovery. Expert Opin Drug Discov 2024;19(5):433–49.
[12] Oleinikovas V, Gainza P, Ryckmans T, Fasching B, Thoma NH. From thalidomide to rational molecular glue design for targeted protein degradation. Annu Rev Pharmacol Toxicol 2024;64:291–312.
[13] Domostegui A, Nieto-Barrado L, Perez-Lopez C, Mayor-Ruiz C. Chasing molecular glue degraders: screening approaches. Chem Soc Rev 2022;51(13):5498–517.
[14] Cao S. Lessons from natural molecular glue degraders. Biochem Soc Trans 2024;52(3):1191–7.
[15] Cheng B, Li H, Peng X, Chen J, Shao C, Kong Z, et al. Recent advances in developing targeted protein degraders. Eur J Med Chem 2025;284:117212.
[16] Kuchta R, Heim C, Herrmann A, Maiwald S, Ng YLD, Sosic I, et al. Accessing three-branched high-affinity cereblon ligands for molecular glue and protein degrader design. RSC Chem Biol 2023;4(3):229–34.
[17] Watson ER, Novick S, Matyskiela ME, Chamberlain PP, de la Peña A A, Zhu J, et al. Molecular glue CELMoD compounds are regulators of cereblon conformation. Science 2022;378(6619):549–53.

[18] Asatsuma-Okumura T, Ito T, Handa H. Molecular mechanisms of cereblon-based drugs. Pharmacol Ther 2019;202:132–9.
[19] Ito T, Yamaguchi Y, Handa H. Exploiting ubiquitin ligase cereblon as a target for small-molecule compounds in medicine and chemical biology. Cell Chem Biol 2021;28(7):987–99.
[20] Zhou Y, Garrigues SL, Villemure E, Ishisoko N, Nguyen HQ, Hamidi NK, et al. Heteroaryl glutarimides and dihydrouracils as cereblon ligand scaffolds for molecular glue degrader discovery. ACS Med Chem Lett 2024;15(12):2158–63.
[21] Merino-Cacho L, Barroso-Gomila O, Pozo-Rodriguez M, Muratore V, Guinea-Perez C, Serrano A, et al. Cullin-RING ligase BioE3 reveals molecular-glue-induced neosubstrates and rewiring of the endogenous cereblon ubiquitome. Cell Commun Signal 2025;23:101.
[22] Bailey HJ, Eisert J, Kazi R, Gerhartz J, Pienkowska DE, Dressel I, et al. An engineered cereblon optimized for high-throughput screening and molecular glue discovery. Cell Chem Biol 2025;32(3):363–76.
[23] Ito T. Protein degraders - from thalidomide to new PROTACs. J Biochem 2024;175(6):507–19.
[24] Liu Y, Bai J, Li D, Cang Y. Routes to molecular glue degrader discovery. Trends Biochem Sci 2025;50(2):134–42.
[25] Hemant Kumar S, Venkatachalapathy M, Sistla R, Poongavanam V. Advances in molecular glues: exploring chemical space and design principles for targeted protein degradation. Drug Discov Today 2024;29(3):104205.
[26] Meyers M, Cismoski S, Panidapu A, Chie-Leon B, Nomura DK. Targeted protein degradation through recruitment of the CUL4 complex adaptor protein DDB1. ACS Chem Biol 2024;19(1):58–68.
[27] Sasso JM, Tenchov R, Wang D, Johnson LS, Wang X, Zhou QA, et al. Molecular glues: the adhesive connecting targeted protein degradation to the clinic. Biochemistry 2023;62(3):601–23.
[28] Yan J, Zheng Z. Discovery of highly potent CRBN ligands and insight into their binding mode through molecular docking and molecular dynamics simulations. ChemMedChem 2023;18(5):e202200573.
[29] Krasavin M, Adamchik M, Bubyrev A, Heim C, Maiwald S, Zhukovsky D, et al. Synthesis of novel glutarimide ligands for the E3 ligase substrate receptor cereblon (CRBN): investigation of their binding mode and antiproliferative effects against myeloma cell lines. Eur J Med Chem 2023;246:114990.
[30] Fang Y, He Q, Cao J. Targeted protein degradation and regulation with molecular glue: past and recent discoveries. Curr Med Chem 2022;29(15):2490–503.
[31] Chen S, Cui J, Chen H, Yu B, Long S. Recent progress in degradation of membrane proteins by PROTACs and alternative targeted protein degradation techniques. Eur J Med Chem 2023;262:115911.
[32] Dai XJ, Ji SK, Fu MJ, Liu GZ, Liu HM, Wang SP, et al. Degraders in epigenetic therapy: PROTACs and beyond. Theranostics 2024;14(4):1464–99.
[33] Sharif H, Wang L, Wang WL, Magupalli VG, Andreeva L, Qiao Q, et al. Structural mechanism for NEK7-licensed activation of NLRP3 inflammasome. Nature 2019;570(7761):338–43.
[34] Zheng S, Que X, Wang S, Zhou Q, Xing X, Chen L, et al. ZDHHC5-mediated NLRP3 palmitoylation promotes NLRP3-NEK7 interaction and inflammasome activation. Mol Cell 2023;83(24):4570–85.
[35] Chen X, Liu G, Yuan Y, Wu G, Wang S, Yuan L. NEK7 interacts with NLRP3 to modulate the pyroptosis in inflammatory bowel disease via NF-kappaB signaling. Cell Death Dis 2019;10(12):906.
[36] Wang J, Chen S, Liu M, Zhang M, Jia X. NEK7: a new target for the treatment of multiple tumors and chronic inflammatory diseases. Inflammopharmacology 2022;30(4):1179–87.
[37] Shi H, Wang Y, Li X, Zhan X, Tang M, Fina M, et al. NLRP3 activation and mitosis are mutually exclusive events coordinated by NEK7, a new inflammasome component. Nat Immunol 2016;17(3):250–8.
[38] Li YK, Zhu XR, Zhan Y, Yuan WZ, Jin WL. NEK7 promotes gastric cancer progression as a cell proliferation regulator. Cancer Cell Int 2021;21(1):438.
[39] Xiao L, Magupalli VG, Wu H. Cryo-EM structures of the active NLRP3 inflammasome disc. Nature 2023;613(7944):595–600.
[40] Zhao N, Li CC, Di B, Xu LL. Recent advances in the NEK7-licensed NLRP3 inflammasome activation: mechanisms, role in diseases and related inhibitors. J Autoimmun 2020;113:102515.
[41] Wen L, Quan Z, Guan C, Zheng J, Li Y, Zeng S, et al. Targeted inhibition of NEK7 preventing sepsis-induced cardiomyopathy by inhibiting NLRP3 inflammasome. Int Immunopharmacol 2025;151:114245.
[42] Jin X, Yang Y, Liu D, Zhou X, Huang Y. Identification of a covalent NEK7 inhibitor to alleviate NLRP3 inflammasome-driven metainflammation. Cell Commun Signal 2024;22(1):565.
[43] Liu H, Gu C, Liu M, Liu G, Wang Y. NEK7 mediated assembly and activation of NLRP3 inflammasome downstream of potassium efflux in ventilator-induced lung injury. Biochem Pharmacol 2020;177:113998.
[44] Gupta S, Cassel SL, Sutterwala FS, Dagvadorj J. Regulation of the NLRP3 inflammasome by autophagy and mitophagy. Immunol Rev 2025;329(1):8–19.
[45] Wang L, Zhu K, Tian Z, Wang H, Jia Y, Feng C, et al. Discovery of novel biaryl urea derivatives against IL-1beta release with low toxicity based on NEK7 inhibitor. Eur J Med Chem 2025;283:117125.
[46] Coll RC, Schroder K. Inflammasome components as new therapeutic targets in inflammatory disease. Nat Rev Immunol 2025;25(1):22–41.
[47] Vande Walle L, Lamkanfi M. Drugging the NLRP3 inflammasome: from signalling mechanisms to therapeutic targets. Nat Rev Drug Discov 2024;23(1):43–66.
[48] Panchal NK, Evan Prince S. The NEK family of serine/threonine kinases as a biomarker for cancer. Clin Exp Med 2023;23(1):17–30.
[49] Jeltema D, Wang J, Cai J, Kelley N, Yang Z, He Y. A single amino acid residue defines the difference in NLRP3 inflammasome activation between NEK7 and NEK6. J Immunol 2022;208(9):2029–36.
[50] Moraes EC, Meirelles GV, Honorato RV, de Souza Tde A, de Souza EE, Murakami MT, et al. Kinase inhibitor profile for human nek1, nek6, and nek7 and analysis of the structural basis for inhibitor specificity. Molecules 2015;20(1):1176–91.
[51] Chen L, Huang L, Wen W, Zeng P, Wu Y, Han Q, et al. Selective and potent molecular glue degraders for NIMA-related kinase 7. Angew Chem Int Ed Engl 2025;64(12):e202500169.
[52] Sylvain A, Stoehr N, Ma F, Cernijenko A, Schroder M, Khoshouei M, et al. A cereblon-based glue degrader of NEK7 regulates NLRP3 inflammasome in a context-dependent manner. Cell Chem Biol 2025;32(6):955–68.
[53] Elbaek CR, Petrosius V, Sorensen CS. WEE1 kinase limits CDK activities to safeguard DNA replication and mitotic entry. Mutat Res 2020;819-820:111694.
[54] Elbaek CR, Petrosius V, Benada J, Erichsen L, Damgaard RB, Sorensen CS. WEE1 kinase protects the stability of stalled DNA replication forks by limiting CDK2 activity. Cell Rep 2022;38(3):110261.
[55] Smith HL, Southgate H, Tweddle DA, Curtin NJ. DNA damage checkpoint kinases in cancer. Expert Rev Mol Med 2020;22:e2.

[56] Du X, Li J, Luo X, Li R, Li F, Zhang Y, et al. Structure-activity relationships of Wee1 inhibitors: a review. Eur J Med Chem 2020;203:112524.
[57] Kong A, Mehanna H. WEE1 inhibitor: clinical development. Curr Oncol Rep 2021;23(9):107.
[58] Alli VJ, Yadav P, Suresh V, Jadav SS. Synthetic and medicinal chemistry approaches toward WEE1 kinase inhibitors and its degraders. ACS Omega 2023;8(23):20196–233.
[59] Yan J, Zhuang L, Wang Y, Jiang Y, Tu Z, Dong C, et al. Inhibitors of cell cycle checkpoint target Wee1 kinase—a patent review (2003-2022). Expert Opin Ther Pat 2022;32(11):1217–44.
[60] Sidaway P. WEE1 kinase inhibitor shows promise. Nat Rev Clin Oncol 2019;16(10):593.
[61] Tadesse S, Anshabo AT, Portman N, Lim E, Tilley W, Caldon CE, et al. Targeting CDK2 in cancer: challenges and opportunities for therapy. Drug Discov Today 2020;25(2):406–13.
[62] Fagundes R, Teixeira LK. Cyclin E/CDK2: DNA replication, replication stress and genomic instability. Front Cell Dev Biol 2021;9:774845.
[63] Zhang J, Gan Y, Li H, Yin J, He X, Lin L, et al. Inhibition of the CDK2 and cyclin A complex leads to autophagic degradation of CDK2 in cancer cells. Nat Commun 2022;13(1):2835.
[64] Liu Q, Gao J, Zhao C, Guo Y, Wang S, Shen F, et al. To control or to be controlled? Dual roles of CDK2 in DNA damage and DNA damage response. DNA Repair (Amst) 2020;85:102702.
[65] Tadesse S, Caldon EC, Tilley W, Wang S. Cyclin-dependent kinase 2 inhibitors in cancer therapy: an update. J Med Chem 2019;62(9):4233–51.
[66] Said MA, Abdelrahman MA, Abourehab MAS, Fares M, Eldehna WM. A patent review of anticancer CDK2 inhibitors (2017-present). Expert Opin Ther Pat 2022;32(9):885–98.
[67] Cheng B, Pan W, Xing Y, Xiao Y, Chen J, Xu Z. Recent advances in DDR (DNA damage response) inhibitors for cancer therapy. Eur J Med Chem 2022;230:114109.
[68] Yu D, Zeng L, Wang Y, Cheng B, Li D. Protein arginine methyltransferase 7 modulators in disease therapy: current progress and emerged opportunity. Bioorg Chem 2025;154:108094.
[69] Li Z, Pinch BJ, Olson CM, Donovan KA, Nowak RP, Mills CE, et al. Development and characterization of a Wee1 kinase degrader. Cell Chem Biol 2020;27(1):57–65.
[70] Guler S, DiPoto MC, Crespo A, Caldwell R, Doerfel B, Grossmann N, et al. Selective Wee1 inhibitors led to antitumor activity in vitro and correlated with myelosuppression. ACS Med Chem Lett 2023;14(5):566–76.
[71] Razumkov H, Jiang Z, Baek K, You I, Geng Q, Donovan KA, et al. Discovery of CRBN-dependent WEE1 molecular glue degraders from a multicomponent combinatorial library. J Am Chem Soc 2024;146:31433–43.
[72] Razumkov H, Jiang Z, Baek K, You I, Geng Q, Donovan KA, et al. Discovery of CRBN-dependent WEE1 molecular glue degraders from a multicomponent combinatorial library. J Am Chem Soc 2024;146(46):31433–43.
[73] Brown VE, Moore SL, Chen M, House N, Ramsden P, Wu HJ, et al. CDK2 regulates collapsed replication fork repair in CCNE1-amplified ovarian cancer cells via homologous recombination. NAR Cancer 2023;5(2):zcad039.
[74] Zeng Y, Ren X, Jin P, Fan Z, Liu M, Zhang Y, et al. Inhibitors and PROTACs of CDK2: challenges and opportunities. Expert Opin Drug Discov 2024;19(9):1125–48.
[75] Wang L, Shao X, Zhong T, Wu Y, Xu A, Sun X, et al. Discovery of a first-in-class CDK2 selective degrader for AML differentiation therapy. Nat Chem Biol 2021;17(5):567–75.
[76] Zhou F, Chen L, Cao C, Yu J, Luo X, Zhou P, et al. Development of selective mono or dual PROTAC degrader probe of CDK isoforms. Eur J Med Chem 2020;187:111952.
[77] Teng M, Jiang J, He Z, Kwiatkowski NP, Donovan KA, Mills CE, et al. Development of CDK2 and CDK5 dual degrader TMX-2172. Angew Chem Int Ed Engl 2020;59(32):13865–70.
[78] Sasayama T, Hamada T, Tanaka K, Nagashima H, Yamanishi S, Ueyama T. Potential of GSPT1 as a novel target for glioblastoma therapy. Cell Death Dis 2024;15(7):572.
[79] Sellar RS, Sperling AS, Slabicki M, Gasser JA, McConkey ME, Donovan KA, et al. Degradation of GSPT1 causes TP53-independent cell death in leukemia while sparing normal hematopoietic stem cells. J Clin Invest 2022;132(8):e153514.
[80] Zhang D, Lin P, Lin J. Molecular glues targeting GSPT1 in cancers: a potent therapy. Bioorg Chem 2024;143:107000.
[81] Jackson RJ, Hellen CU, Pestova TV. The mechanism of eukaryotic translation initiation and principles of its regulation. Nat Rev Mol Cell Biol 2010;11(2):113–27.
[82] Hinnebusch AG. The scanning mechanism of eukaryotic translation initiation. Annu Rev Biochem 2014;83:779–812.
[83] Le Roy F, Salehzada T, Bisbal C, Dougherty JP, Peltz SW. A newly discovered function for RNase L in regulating translation termination. Nat Struct Mol Biol 2005;12(6):505–12.
[84] Kozlov G, Gehring K. Molecular basis of eRF3 recognition by the MLLE domain of poly(A)-binding protein. PLoS One 2010;5(4):e10169.
[85] Chang X, Qu F, Li C, Zhang J, Zhang Y, Xie Y, et al. Development and therapeutic potential of GSPT1 molecular glue degraders: a medicinal chemistry perspective. Med Res Rev 2024;44(4):1727–67.
[86] Fuchs O. Targeting cereblon in hematologic malignancies. Blood Rev 2023;57:100994.
[87] Matyskiela ME, Lu G, Ito T, Pagarigan B, Lu CC, Miller K, et al. A novel cereblon modulator recruits GSPT1 to the CRL4(CRBN) ubiquitin ligase. Nature 2016;535(7611):252–7.
[88] Surka C, Jin L, Mbong N, Lu CC, Jang IS, Rychak E, et al. CC-90009, a novel cereblon E3 ligase modulator, targets acute myeloid leukemia blasts and leukemia stem cells. Blood 2021;137(5):661–77.
[89] Hansen JD, Correa M, Alexander M, Nagy M, Huang D, Sapienza J, et al. CC-90009: a cereblon E3 ligase modulating drug that promotes selective degradation of GSPT1 for the treatment of acute myeloid leukemia. J Med Chem 2021;64(4):1835–43.
[90] Huber AD, Li Y, Lin W, Galbraith AN, Mishra A, Porter SN, et al. SJPYT-195: a designed nuclear receptor degrader that functions as a molecular glue degrader of GSPT1. ACS Med Chem Lett 2022;13(8):1311–20.
[91] Shen H, Xu H, Jin W, Wu T, Hu J, Zhang C, et al. Discovery of a potent and selective GSPT1 molecular glue degrader for the treatment of castration-resistant prostate cancer. J Med Chem 2025;68(3):1553–71.
[92] Chang Y, Keramatnia F, Ghate PS, Nishiguchi G, Gao Q, Iacobucci I, et al. The orally bioavailable GSPT1/2 degrader SJ6986 exhibits in vivo efficacy in acute lymphoblastic leukemia. Blood 2023;142(7):629–42.
[93] Nishiguchi G, Keramatnia F, Min J, Chang Y, Jonchere B, Das S, et al. Identification of potent, selective, and orally bioavailable small-molecule GSPT1/2 degraders from a focused library of cereblon modulators. J Med Chem 2021;64(11):7296–311.
[94] Powell CE, Du G, Che J, He Z, Donovan KA, Yue H, et al. Selective degradation of GSPT1 by cereblon modulators identified via a focused combinatorial library. ACS Chem Biol 2020;15(10):2722–30.
[95] Zhang S, Nie S, Ma G, Shen M, Kong L, Zuo Z, et al. Identification of novel GSPT1 degraders by virtual screening and bioassay. Eur J Med Chem 2024;273:116524.
[96] Zhang Y, Liu W, Tong C, Wang X, Chang X, Qu F, et al. Design and discovery of preclinical candidate LYG-409 as a highly

potent and selective GSPT1 molecular glue degraders. J Med Chem 2025;68(4):2608–38.
[97] Wei Y, Xu X, Jiang M, Wang Y, Zhou Y, Wang Z, et al. Discovery of new lenalidomide derivatives as potent and selective GSPT1 degraders. Eur J Med Chem 2023;258:115580.
[98] Liu Y, Sun X, Liu Q, Han C, Rao Y. A dual-target and dual-mechanism design strategy by combining inhibition and degradation together. J Am Chem Soc 2025;147(7):3110–3118.
[99] Yang Z, Sun Y, Ni Z, Yang C, Tong Y, Liu Y, et al. Merging PROTAC and molecular glue for degrading BTK and GSPT1 proteins concurrently. Cell Res 2021;31(12):1315–18.
[100] Xu Y, Yang H, Li Y, Qi Y, Zhao F, Hong Y, et al. Discovery of highly potent dual GSPT1/BRD4 degraders with anti-AML activity. Eur J Med Chem 2025;288:117381.
[101] Shalom B, Salaymeh Y, Risling M, Katzav S. Unraveling the oncogenic potential of VAV1 in human cancer: lessons from mouse models. Cells 2023;12(9):1276.
[102] Neurath MF, Berg LJ. VAV1 as a putative therapeutic target in autoimmune and chronic inflammatory diseases. Trends Immunol 2024;45(7):580–96.
[103] Tybulewicz VL, Ardouin L, Prisco A, Reynolds LF. Vav1: a key signal transducer downstream of the TCR. Immunol Rev 2003;192:42–52.
[104] Pawlik A, Malinowski D, Paradowska-Gorycka A, Safranow K, Dziedziejko V. VAV1 gene polymorphisms in patients with rheumatoid arthritis. Int J Environ Res Public Health 2020;17(9):3214.
[105] Qiu J, Guo J, Liu L, Liu X, Sun X, Chen H. Vav1 promotes inflammation and neuronal apoptosis in cerebral ischemia/reperfusion injury by upregulating microglial and NLRP3 inflammasome activation. Neural Regen Res 2023;18(11):2436–42.
[106] Wang Q, Gong L, Mao S, Yao C, Liu M, Wang Y, et al. Klf2-Vav1-Rac1 axis promotes axon regeneration after peripheral nerve injury. Exp Neurol 2021;343:113788.