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Review

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Exploiting targeted degradation of cyclins and cyclin-dependent kinases for cancer therapeutics: a review

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Abstract: Cancer is characterized by abnormal cell proliferation. Cyclins and cyclin-dependent kinases (CDKs) have been recognized as essential regulators of the intricate cell cycle, orchestrating DNA replication and transcription, RNA splicing, and protein synthesis. Dysregulation of the CDK pathway is prevalent in the development and progression of human cancers, rendering cyclins and CDKs attractive therapeutic targets. Several CDK4/6 inhibitors have demonstrated promising anti-cancer efficacy and have been successfully translated into clinical use, fueling the development of CDK-targeted therapies. With this enthusiasm for finding novel CDK-targeting anti-cancer agents, there have also been exciting advances in the field of targeted protein degradation through innovative strategies, such as using proteolysis-targeting chimera, heat shock protein 90 (HSP90)-mediated targeting chimera, hydrophobic tag-based protein degradation, and molecular glue. With a focus on the translational potential of cyclin- and CDK-targeting strategies in cancer, this review presents the fundamental roles of cyclins and CDKs in cancer. Furthermore, it summarizes current strategies for the proteasome-dependent targeted degradation of cyclins and CDKs, detailing the underlying mechanisms of action for each approach. A comprehensive overview of the structure and activity of existing CDK degraders is also provided. By examining the structure–activity relationships, target profiles, and biological effects of reported cyclin/CDK degraders, this review provides a valuable reference for both CDK pathway-targeted biomedical research and cancer therapeutics.

Key words: Cyclin-dependent kinase (CDK); Cyclin; Protein degrader; Targeted protein degradation

1 Introduction

Cancer is characterized by uncontrolled cell expansion, during which cell cycle control is inevitably reconfigured. Cell cycle progression is a sophisticated process governed by mitotic signals and cell cycle machineries that involve cyclins and cyclin-dependent kinases (CDKs). Human CDKs are a family of 21 serine/threonine protein kinases that usually dimerize with partner subunits known as cyclins to phosphorylate downstream substrates (Satyanarayana and Kaldis, 2009; Wood and Endicott, 2018). In the human genome,

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over 30 cyclins have been reported based on the presence of cyclin box domains (CBDs), which are critical for CDK binding and share a high homology in sequence, including a conservative Lys–Glu pair (Quandt et al., 2020). Accumulating evidence indicates that cyclins and CDKs also play diverse roles in cell cycle/proliferation, transcription, RNA processing, DNA replication, DNA repair, transcription, RNA splicing, RNA polyadenylation, and signal transduction (Hydbring et al., 2016; Chou et al., 2020; Parua and Fisher, 2020; Petroni et al., 2020; Kciuk et al., 2022). Indeed, CDKs and cyclins are frequently dysregulated in human cancer. High-throughput genetic screening assays have also suggested that most CDKs and cyclins are functional prerequisites of cell viability in cancer. Therefore, targeting CDKs and cyclins for cancer treatment has been a long-standing strategy in pharmaceutical development (Vervoort et al., 2022).

Thus far, tremendous efforts have been made to develop CDK-targeted agents, with numerous CDK inhibitors reported to date. The first breakthrough of CDK-targeted drugs stems from the investigation of palbociclib, a dual inhibitor of CDK4 and CDK6, in treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. Following palbociclib, additional CDK4/6 inhibitors, including ribociclib, abemaciclib, and trilaciclib, have been approved for targeted cancer therapy (Morrison et al., 2024). In contrast, the clinical translation of early generations of CDK inhibitors, such as flavopiridol, roscovitine, dinaciclib, and SNS-032, was hindered by treatment-associated toxicities and the lack of selectivity. Nevertheless, the success of CDK4/6 inhibitors has stimulated further research into other CDK-targeted agents with improved specificity.

Along with the pursuit of innovative CDK-targeted agents, several technical routes have been attempted, including competitive inhibitors, allosteric inhibitors, covalent inhibitors, and chemically induced protein degradation via proteolysis-targeting chimeras (PROTACs), heat shock protein 90 (HSP90)-mediated targeting chimeras (HEMTACs), hydrophobic tag (HyT) degraders, as well as molecular glues. In parallel to small molecule inhibitors, the chemical degradation of CDKs or cyclins emerges as an active area and a promising direction for developing new-modality anti-cancer drugs (Yu et al., 2022; Wang LG et al., 2023). This article reviews the latest progress in CDK degraders and their efficacy to provide a state-of-the-art understanding of this field.

2 Function of cyclins and CDKs in cancer

CDKs can be generally divided into three major classes (Table S1): cell cycle-regulatory CDKs (including CDK1, CDK2, CDK3, CDK4, and CDK6), transcription-associated CDKs (CDK7, CDK8, CDK9, CDK10, CDK11, CDK12, CDK13, and CDK19), and atypical CDKs (CDK5, CDK14, CDK15, CDK16, CDK17, CDK18, and CDK20). Cyclins can be grouped in a similar fashion: canonical (cell cycle-regulatory) cyclins, transcription-associated cyclins, and atypical cyclins (Quandt et al., 2020; Wang LG et al., 2023). Although such a classification scheme may be oversimplified, it highlights the key cellular functions of CDKs and their associated cyclins. In fact, cyclins and CDKs are widely involved in DNA replication, transcription, RNA processing, signaling transduction, and immune modulation (Chou et al., 2020; Kciuk et al., 2022; Pluta et al., 2024). The functions of nearly half of CDKs, especially atypical CDKs, remain to be further characterized. Several cyclins (namely, Cyclin G2, Cyclin-J-Like, Cyclin O, Cyclin P, Cyclin Pas1, and Cyclin N-terminal domain-containing 1) remain orphans, as their interactive CDKs have not been well established.

Cell cycle-regulatory cyclins and CDKs orchestrate the temporal order of cell cycle events, especially DNA replication and mitotic progression. Among cell cycle-regulatory cyclins and CDKs, CDK4, CDK6, and D-type cyclins are hyperactivated across a wide spectrum of human cancers via amplification, mutation, and translocation. CDK4 and CDK6, which share similar structures and functions, are key regulators of the restriction point (also known as R point) in the G1 phase. The CDK4/Cyclin D and CDK6/Cyclin D complexes phosphorylate pocket proteins (i.e., pRb, p107, and p130) and subsequently prevent them from binding with E2F transcription factors. The CDK6/Cyclin I complex was recently identified to also negatively regulate pRb (Quandt et al., 2023). The release of E2F proteins allows the transcription of E-type cyclins, DNA replication factors, and many other targets required for the initiation of DNA synthesis and entry into the S phase. Beyond the R point, the loss of CDK4/6 activity in the later stages of interphase also causes cell cycle exit due to compromised CDK2 activity and pRb phosphorylation (Cornwell et al., 2023). Similarly, the inhibitory phosphorylation of CDK1 and CDK4/6 by stress-activated protein kinases during the G2 phase triggers the exit of the cell cycle after DNA replication (McKenney et al., 2024). However, when recovering from stress, some cells can restart cell cycle, initiate a second round of DNA replication, and progress through mitotic cell division, producing daughter cells with a doubled genome. CDK6 maintains the status of normal mesenchymal stem cells, hematopoietic stem cells, and leukemic stem cells (Scheicher et al., 2015; Li et al., 2021; Hu AJ et al., 2023). As a result of CDK4/6 inhibition, the cell cycle can be arrested, and cancer cells can switch their fate to apoptosis, quiescence, or senescence. Importantly, recent studies have revealed various immune modulatory effects of CDK4/6 blockade (Goel et al., 2017; Schaer et al., 2018; Scirocchi et al., 2022; Bai et al., 2023; Fan et al., 2023; Nayyar et al., 2024). On the one hand, the inhibition of CDK4/6 increased DNA damage and the expression of endogenous retroviral elements as well as immune regulators, including intercellular adhesion molecule-1 (ICAM1) and genes related to the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS)-stimulator of interferon genes 1 (STING1) signaling pathway, interferon response, tumor antigen presentation, and immune cell interaction. On the other hand, blockade of CDK4/6 supported the maintenance and infiltration of cluster of differentiation 8-positive ($CD8^+$) T cells at the expense of regulatory T cells, thereby inducing a T-cell-inflamed tumor microenvironment that favors cytotoxic T-cell-mediated clearance of cancer cells and boosts the anti-cancer efficacy of immune checkpoint inhibitors. Of note, the successful development of CDK4/6 inhibitors such as palbociclib further validates the significance of these kinases in cancer biology (Morrison et al., 2024).

Transcription-associated CDKs regulate gene transcription and transcription-coupled RNA processing by phosphorylating the hepta-repeat YSPTSPS within the carboxy-terminal domain (CTD) of the DNA-directed RNA polymerase II (Pol II) subunit Rpb1 (Asghar et al., 2015; Zaborowska et al., 2016; Parua and Fisher, 2020; Dieci, 2021). CDK7, CDK9, CDK12, and CDK13 represent a subset of members with prominent activities in transcriptional regulation, attracting much interest in drug development. The excessive expression of CDK7 has been reported in many cancer types, including triple-negative breast cancer, lung cancer, and MYCN-driven neuroblastoma (Chipumuro et al., 2014; Christensen et al., 2014; Wang et al., 2015, 2020). CDK7 functions in a complex with Cyclin H and methionine adenosyltransferase 1 (MAT1) to form a CDK-activating kinase (CAK) that activates other cell cycle CDKs (e.g., CDK1, CDK2, CDK4, and CDK6) via T-loop phosphorylation (Glover-Cutter et al., 2009; Schachter and Fisher, 2013; Goel et al., 2022). CDK7/Cyclin H is part of the transcription factor IIH (TFIIH) module within the RNA Pol II holoenzyme and phosphorylates Rpb1 CTD at Ser5 and Ser7 sites during transcriptional initiation. Upon pause release, CDK7/Cyclin H phosphorylates CDK9 to promote transcription elongation. Moreover, CDK7 maintains the cancer-biased transcriptional output of super-enhancer targets that are often associated with cell identity, metabolism, pathobiology, and oncogenic factors (Yao et al., 2023). The inhibition of CDK7 induces transcription dysregulation and genome instability and helps trigger anti-tumor immunity and overcome drug resistance (Rusan et al., 2018; Zhang et al., 2020). Currently, CDK7-selective inhibitors are under active investigation in clinical trials; the progress regarding SY-5609 and samuraciclib is encouraging (Marineau et al., 2022). CDK9 and Cyclin T form a heterodimeric kinase complex termed positive-transcription elongation factor b (P-TEFb), where Cyclin T serves as a regulatory subunit for CDK9 (Baumli et al., 2008). P-TEFb activity is restricted by the 7SK small nuclear ribonucleoprotein (snRNP) complex, which includes 7SK RNA, hexamethylene bis-acetamide-inducible protein 1/2 (HEXIM1/2), La-related protein 7 (LARP7), methylphosphate capping enzyme (MEPCE), and other regulatory proteins. Activation of P-TEFb requires the dissociation of 7SK snRNP and the phosphorylation of CDK9 at the Thr186 residue of its activation loop (T-loop) (e.g., by the CAK) complex (Mbonye et al., 2013). The subsequent interaction of P-TEFb with either bromodomain-containing protein 4 (BRD4) or AF4/FMR2 family member 1/4 (AFF1/4) protein directs the complex to permissive gene promoters and phosphorylates Rpb1 CTD at Ser2 and other transcription factors (e.g., androgen receptor at Ser81) (Gordon et al., 2010; Zhou et al., 2022). Eventually, P-TEFb facilitates the pause release of RNA Pol II, promoting the transcription machinery for productive elongation (Filippakopoulos et al., 2012). Interfering with CDK9 activity not only induces defective transcription elongation but also impairs the process of RNA splicing and epigenetic silencing of endogenous retrovirus genes (Zhang et al., 2018; Xiao et al., 2023). Hence, CDK9 emerges as a hot therapeutic target in cancer. The clinical evaluation of CDK9-specific inhibitors (e.g., BAY1251152, GFH009, KB-0742, and Zortiraciclib) is ongoing. Zortiraciclib has been granted Orphan Drug Designation for the treatment of glioblastoma by the U.S. Food and Drug Administration (FDA) (Wu J et al., 2021). Of note, the *CDK9*$^{\text{L156F}}$ mutant confers resistance to various CDK9-targeted agents (Hu C et al., 2023). CDK12 and CDK13, both partnering with Cyclin K, are crucial for proper transcriptional elongation and RNA processing. Both of them phosphorylate Rpb1 CTD at the Ser2 residue, which is implicated in the transition from transcription initiation to elongation and the subsequent recruitment of RNA-processing factors. Alternatively, CDK12 was recently identified as a bona fide kinase of left open reading frame 1 (LEO1) (Ser608), which is a subunit of the polymerase-associated factor 1 complex (PAF1C) for processive transcription elongation (Qiu et al., 2023). Other known substrates of CDK12 and CDK13 include splicing factors and components of the spliceosome, as well as the cleavage and polyadenylation specificity factor complex. CDK12 and CDK13 share some overlapping functions in RNA Pol II processivity and transcription elongation (Fan et al., 2020). The single inhibition of either CDK12 or CDK13 elicits transcriptional programs associated with the DNA damage response (DDR) and genome stability (Bösken et al., 2014; Tien et al., 2017), but has limited impacts on cell viability. On the contrary, dual inhibition is barely tolerated by cells as a result of defective transcriptional homeostasis, especially in the aspect of alternative polyadenylation, intragenic premature termination, and aberrant co-transcriptional splicing (Fan et al., 2020; Cheng et al., 2022; Magnuson et al., 2022). Dysregulation of CDK12 results in compromised homologous recombination (HR) repair, rendering cells more susceptible to DNA-damaging agents and genomically unstable (Dubbury et al., 2018; Iniguez et al., 2018; Krajewska et al., 2019; Quereda et al., 2019). The *CDK12* gene is recurrently mutated and dysregulated in several types of cancers, especially high-grade ovarian adenocarcinoma (Cancer Genome Atlas Research Network, 2011). CDK12-deficient cancers often exhibit a breast cancer (BRCA) gene 1/2-like (BRCAness) phenotype, demonstrating increased responsiveness to poly(ADP-ribose)polymerase (PARP) inhibitors and immune therapy (Choi et al., 2020; Schweizer et al., 2020). Similarly, CDK12/13 inhibitors were shown to elicit a BRCAness phenotype and synergize with PARP inhibitors (Quereda et al., 2019). Agents targeting either CDK12/13 or Cyclin K are under active development and are marching toward early-phase clinical trials (e.g., CT7439 and CTX-439), providing a new strategy for cancer treatment.

As exemplified by the abovementioned CDKs and cyclins, the current understanding of CDKs and cyclins highlights their importance in diverse aspects of cancer biology. Targeting cyclins and CDKs is likely to have broad impacts on the cell cycle, transcription, DNA replication, RNA processing, signaling transduction, and immune response.

3 Proteasome-dependent targeted protein degradation technologies for cyclins and CDKs

Targeting CDKs and cyclins represents a promising and feasible strategy for cancer treatment. The majority of efforts have been made to develop CDK inhibitors (Huang et al., 2024). However, due to the high sequence homology and conserved adenosine triphosphate (ATP)-binding pockets, the design of a conventional inhibitor of a specific CDK has proven challenging. Recent advances in chemically induced protein degradation inspire and stimulate a new direction of drug design. To this end, we summarize the progress of CDK degraders that employ mainly proteasome-dependent techniques, such as PROTACs, HEMTACs, HyTs, and molecular glues (Figs. 1 and 2; Tables 1 and S2).

PROTACs are chemical degraders that consist of a ligand that binds to a protein of interest (POI), a ligand that recruits an E3 ubiquitin ligase, and a linker that connects the two ligands (Sakamoto et al., 2001). PROTAC induces the formation of a POI-PROTAC-E3 ternary complex, facilitating ubiquitin conjugation to lysine residues on the surface of the POI and subsequent proteasome-dependent degradation (Fig. 1a) (Deshaies, 2015). Bridged PROTAC is a variant of

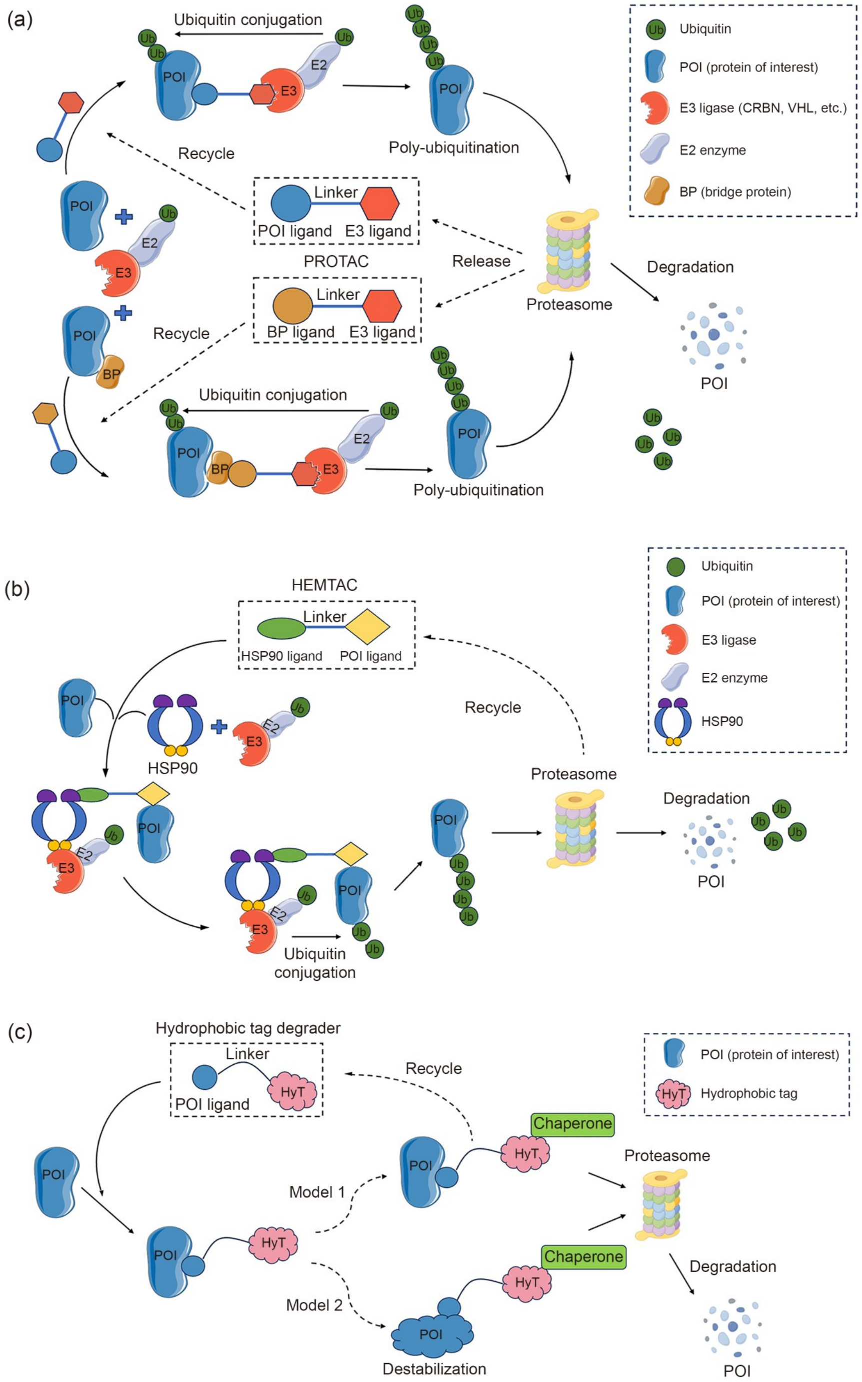


Fig. 1 Working mechanisms of proteolysis-targeting chimera (PROTAC), heat shock protein 90 (HSP90)-mediated targeting chimera (HEMTAC), and hydrophobic tag (HyT). (a) PROTAC induces proteasome-dependent degradation of the protein of interest (POI) via the formation of the POI-PROTAC-E3 ternary complex, while bridged PROTAC recruits POI indirectly via a POI-interacting protein (bridge protein, BP) and degrades POI via the formation of a POI-BP-PROTAC-E3 complex. (b) HEMTAC recruits various E3 ubiquitin ligases via the adaptor protein HSP90 and subsequently forms the POI-HEMTAC-HSP90-E3 complex to induce targeted protein degradation. (c) HyT binds to POI and mimics the partially denatured state or misfolding state by exposing the hydrophobic moiety to the protein surface (Model 1). Alternatively, HyT may destabilize POI by direct interference with protein folding (Model 2). Subsequently, either signal mimicking the abnormal protein folding or failure of chaperones in protein folding activates the protein quality control machinery to target POI for proteasomal degradation. CRBN: cereblon; E2: ubiquitin-conjugating enzyme; E3: ubiquitin ligase; VHL: von Hippel-Lindau. Partially created by Figdraw.

Table 1 Comparison among inhibitors and various proteasome-dependent chemical degraders

Inhibitor/degrader	Molecular feature	Reaction process	Active binding site	Mechanism of action	Potency	Druggable targets
Inhibitors	Monovalent; smaller molecular weight (usually <500 Da)	Stoichiometric	Required in most cases	Reversible, irreversible, or competitive inhibition of target activity	Variable	Enzymes and proteins containing suitable active sites
PROTAC	Bivalent/heterobifunctional; large molecular weight (usually >800 Da)	Catalytic	Not necessary; expanded to druggable spaces beyond active sites	Proximity-induced target degradation through the ubiquitin proteasome system after formation of the POI-PROTAC-E3 ligase ternary complex	Variable; potential to possess enhanced potency over parental inhibitors	Can be proteins with or without active sites (e.g., non-catalytic regulatory subunits and scaffolding proteins); contain lysine residues susceptible to ubiquitination by specific E3 ligases
HEMTAC	Bivalent/heterobifunctional; large molecular weight	Catalytic	Not necessary; expanded to druggable spaces beyond active sites	Proximity-induced target degradation through the ubiquitin proteasome system after formation of a POI-HEMTAC-HSP90-E3 ternary complex	Moderate; lower than PROTACs	Can be proteins with or without active sites; contain lysine residues susceptible to ubiquitination after formation of the ternary complex; contain lysine residues susceptible to ubiquitination by HSP90-associaeted E3 ligases
Hydrophobic tag	Bivalent/heterobifunctional; medium molecular weight (variable)	Sometimes catalytic	Not necessary; expanded to druggable spaces beyond active sites	Recruiting the protein quality control machinery to target POI for proteasomal or lysosomal degradation by mimicking the partially denatured state or misfolding of POI	Moderate; lower than PROTACs	Can be proteins with or without active sites; contain lysine residues susceptible to ubiquitination by protein quality control machinery
Molecular glue	Monovalent; smaller molecular weight (usually <500 Da)	Catalytic	Involved in some cases; expanded to druggable spaces beyond active sites	Proximity-induced neo-substrate degradation through the ubiquitin proteasome system after formation of the POI-molecular glue-E3 ligase ternary complex	Variable	Can be proteins with or without active sites; contain lysine residues susceptible to ubiquitination by specific CRL E3 ligase complexes

Inhibitor/degrader	Fate of target proteins	Permissive CDK/cyclin in the literature	Isoform selectivity	Drug-like properties (bioavailability, hydrophobicity)	Developmental status
Inhibitors	Impaired function, protein stabilization (in many cases), or destabilization	Most CDKs	Generally challenging due to high homology among ATP-binding pockets of CDKs; achievable in very limited cases	Relatively good	Several CDK4/6 inhibitors have been successfully translated into clinics; many other inhibitors are under active preclinical and early phase clinical development
PROTAC	Degradation	CDK1/2/4/5/6/7/8/9/12/13/17/19, Cyclin C, Cyclin D1, Cyclin D3, Cyclin E, Cyclin K	Potential to enhance target selectivity after optimization; achievable for several CDKs	Hardly meet the Rule of Five; generally low in oral bioavailability	Under preclinical development
HEMTAC	Degradation	CDK4/6		Similar to PROTACs; limited information of bioavailability	Under preclinical development
Hydrophobic tag	Degradation	CDK9, Cyclin T1		Simpler in chemical structure with fewer hydrogen bond donors/acceptors; more favorable bioavailability than PROTACs	Under preclinical development
Molecular glue	Degradation	CDK12/13, Cyclin K	Reported to have variability in target engagement	Relatively good	Most are under preclinical development; some are in early phase clinical development

ATP: adenosine triphosphate; CDK: cyclin-dependent kinase; CRL: Cullin-RING ubiquitin ligase; HSP90: heat shock protein 90; HEMTAC: HSP90-mediated targeting chimera; PROTAC: proteolysis-targeting chimera.

PROTAC that indirectly recruits POI via a bridge protein (BP). Compared with conventional inhibitors that rely on "occupancy-driven" effects (i.e., high affinity and high concentration in vivo), PROTACs are based on an "event-driven" mode (Dogan et al., 2012; Leiser et al., 2014). PROTACs possess catalytic activity where one molecule can induce multiple rounds of POI degradation (Ishida and Ciulli, 2021). Moreover, PROTACs have an advantageous capability, which means abolishing both the enzymatic and scaffolding functions of POI via induced protein degradation (Huang and Dixit, 2016; Moon and Lee, 2018). Remarkably, PROTACs targeting androgen receptors (ARV-110 and ARV-766), estrogen receptor (ARV-471), and Bruton's tyrosine kinase (BTK) (NX-2127) have entered clinical trials and show promise in treating cancers of interest (Békés et al., 2022; Chirnomas et al., 2023). The preclinical development of CDK-targeted PROTACs is advancing rapidly.

HSP90, a well-established molecular chaperone, has been shown to interact with many E3 ligases and is able to recognize misfolded proteins to accelerate their clearance through the ubiquitin-proteasome pathway. In contrast to the engagement of a selective E3 ligase by PTOTACs, HEMTACs hijack HSP90 together with various E3 ubiquitin ligases (the HSP90-E3 complex) and form a POI-HEMTAC-HSP90-E3 ternary complex to induce targeted protein degradation (Fig. 1b). The structure of a HEMTAC resembles that of a PROTAC except for the HSP90-E3-binding moiety. Such a strategy has been applied successfully to degrade BRD4 and CDK4/6 in pre-clinical studies (Kargbo, 2021; Li et al., 2023).

Apart from PROTACs and HEMTACs, HyTs are heterobifunctional molecules that consist of a ligand with binding affinity to a POI, a lipophilic moiety, and a small-molecule linker (Neklesa et al., 2011). HyTs bind to the POI and expose the hydrophobic moiety to the surface of a protein, mimicking the partially denatured state or misfolding of the protein. They then recruit the protein quality control machinery to target the POI for proteasomal degradation (Fig. 1c). Compared with PROTACs, HyTs may be applicable to a broader array of proteins by circumventing the limitations of amenable E3 ligases (Xie et al., 2023).

Molecular glue degraders are small molecules that induce proximity between two intracellular proteins and further the proximity-induced protein degradation (Fig. 2). They typically alter protein–protein interaction surfaces to either create or enhance the interaction affinity. Representative examples include thalidomide, lenalidomide, pomalidomide, and other immunomodulatory drugs (IMiDs), which are indicated for multiple myeloma. IMiDs induce interactions between the E3 ligase cereblon (CRBN) and neo-substrates, including IKAROS family zinc finger 1/3 (IKZF1/3) and casein kinase 1α (CK1α), and subsequently target them for degradation. Molecular glues are generally smaller in molecular weight and have more favorable physicochemical properties. Until now, the strategy of using molecular glues to target CDK12 and Cyclin K has been explored.

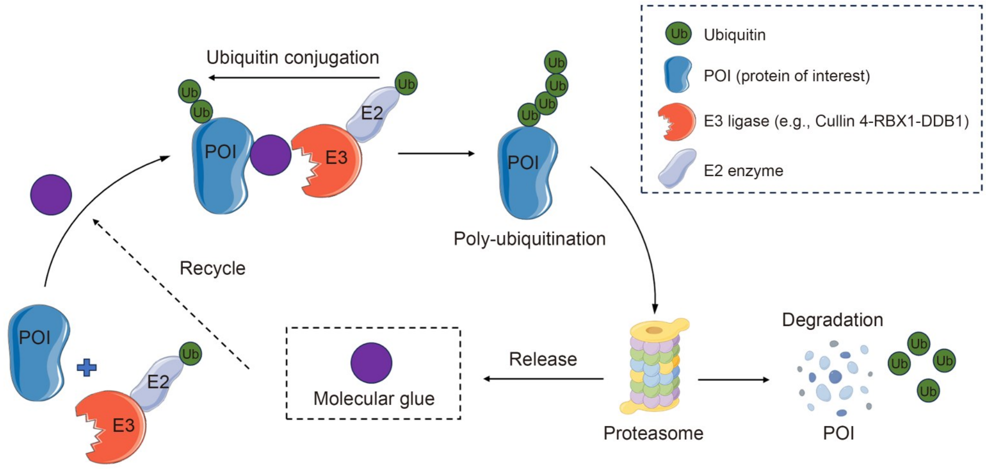


Fig. 2 Working mechanisms of molecular glue degraders. Molecular glue alters protein–protein interaction surfaces between an E3 ligase complex and a protein of interest (POI) or a complex containing POI, thereby either creating or enhancing the interaction affinity to trigger proximity-induced protein degradation. E2: ubiquitin-conjugating enzyme; E3: ubiquitin ligase. Partially created by Figdraw.

4 Advances in small-molecule degraders of cyclins and CDKs

4.1 CDK2 degradation via PROTACs

PROTACs represent a primary approach for targeted CDK2 degradation (Fig. 3), utilizing CDK2 inhibitors (AT7519, AT7519-7, AZD5438, FN-1501, PF-069736, JNJ-7706621/J2, TMX-2039, and TAE684) conjugated to either CRBN- or von Hippel-Lindau (VHL)-targeting ligands to recruit E3 ubiquitin ligases (Zhou et al., 2020; Hati et al., 2021; Wu et al., 2024).

Zhou et al. (2020) designed a series of CRBN-dependent PROTACs that connect pomalidomide or 3-hydroxy thalidomide to CDK2 inhibitors AT7519 and FN-1501. In general, FN-1501-based compounds are more potent and effective in inducing the degradation of CDK2 than AT7519-based ones. Of note, CDK9 was identified frequently as another target that was co-depleted with CDK2 by these FN-1501-based PROTACs. Molecule **1** (F3) is one of the leading candidates with desirable activities in human prostate cancer PC-3 cells, where its half-maximal inhibitory concentration (IC_{50}) against cell viability, half-maximal degradation concentration (DC_{50}) against CDK2, and DC_{50} against CDK9 are 120, 62, and 33 nmol/L, respectively. Mirroring the effect of FN-1501, Molecule **1** impairs cell proliferation and arrests the cell cycle in the G2/M phase. Kumarasamy et al. (2023) reported another pomalidomide and FN-1501 chimera Molecule **2** (FN-pom) that simultaneously depletes CDK2 and Cyclin E1. Through the hybrid design of a pan-CDK inhibitor TMX-2039 and CRBN binder, Teng et al. (2020) developed Molecule **3** (TMX-1160), a PROTAC that turned out to exhibit cell type-dependent target profiles, acting as a multi degrader

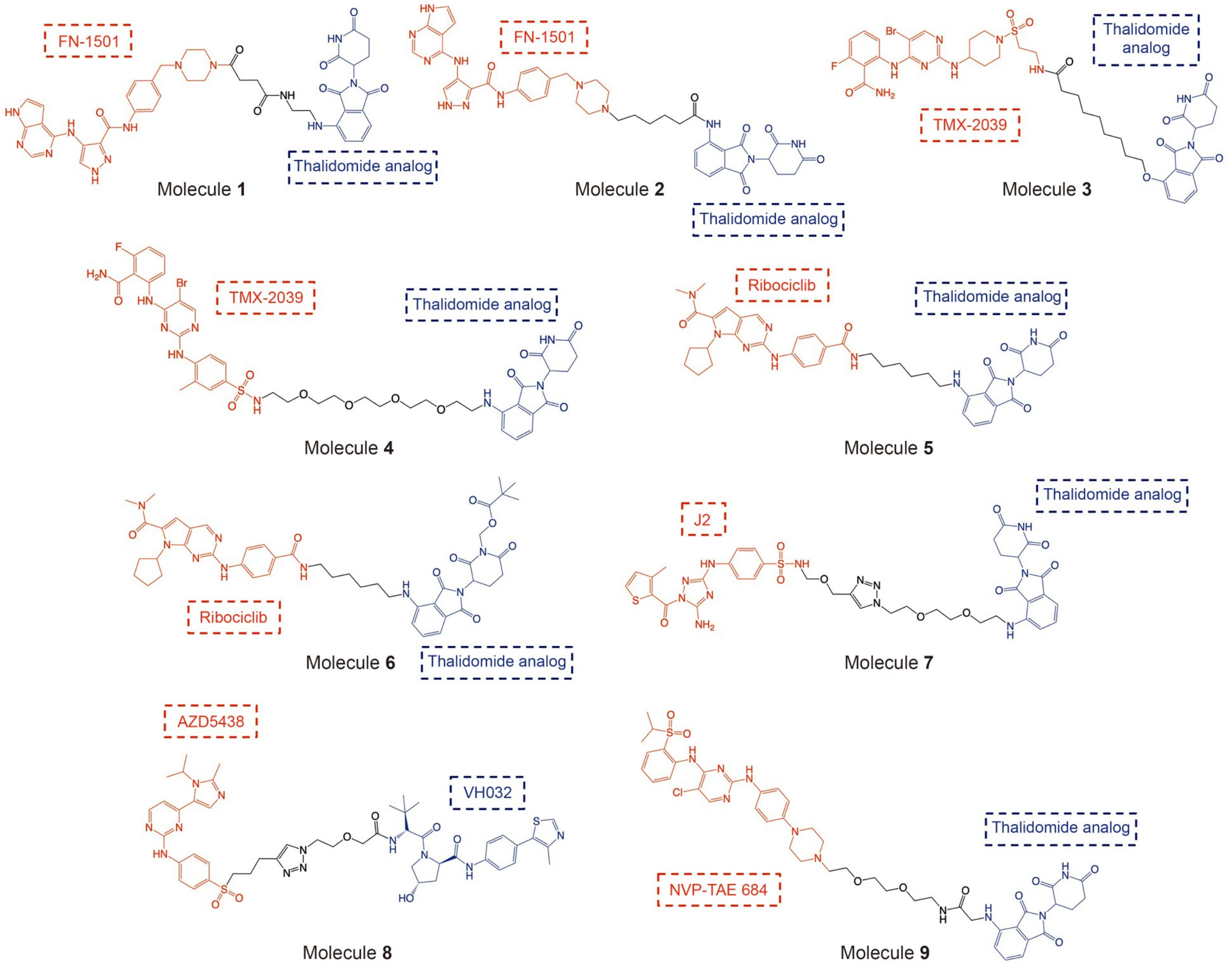


Fig. 3 Molecular structures of selective proteolysis-targeting chimeras (PROTACs) that target cyclin-dependent kinase 2 (CDK2). Molecule 8 is a von Hippel-Lindau (VHL)-dependent PROTAC, while the rest are cereblon (CRBN)-dependent.

of CDK2/4/5/6 in Jurkat cells and a dual degrader of CDK2 and CDK5 in OVCAR8 cells. Further optimization of the linker and CDK-binding moiety yielded Molecule **4** (TMX-2172), exhibiting enhanced selectivity and degradation efficacy against CDK2/CDK5 in both Jurkat and OVCAR8 cells. Similarly, through the hybrid design of the CDK2/4/6 inhibitor PF-069736-based PROTACs, Wei MM et al. (2021) developed a CDK2/4/6 degrader, Molecule **5**, and subsequently converted it into a prodrug, Molecule **6**, with good oral pharmacokinetic profiles (rat: bioavailability 68%) and anti-melanoma activities in vivo. Remarkably, Molecule **7** (CPS2) and Molecule **8** (PROTAC-8) represent two CDK2-selective degraders (Zhou et al., 2020; Wei MM et al., 2021). Molecule **7** is a heterobifunctional degrader based on pomalidomide and a JNJ-7706621 derivative J2, and has impressive selectivity for CDK2 over other CDKs. Although Molecule **7** degrades Aurora kinase A (AURKA) as an unintentional target, biological studies have suggested that it induces the differentiation of acute myeloid leukemia (AML) cells and human hematopoietic stem cells without inducing cytotoxicity primarily through CDK2 depletion. Different from Molecule **7**, Molecule **8** was developed from the linkage of the VHL binder VH032 and the CDK2 inhibitor AZD5438 (Hati et al., 2021). Despite good selectivity, Molecule **8** only induces partial degradation of CDK2.

Interestingly, Huang et al. (2018) studied the CRBN-dependent multi-kinase degrader Molecule **9** (TL12-186), which was later shown to exhibit cell cycle phase-specific activity for protein degradation (Riching et al., 2021; Wang et al., 2021). Molecule **9** is able to degrade 16 CDKs, including CDK2. While it retains good binding affinity for CDK2 throughout the cell cycle, it only induces efficient degradation of CDK2 in G1 or unsynchronized cells. One possible explanation for the reduced efficacy of Molecule **9** in CDK2 degradation in the S and G2/M phases is its inability to form a ternary complex with CRBN. It would be interesting to examine whether the pattern of cell cycle-dependent degradation holds true for other CDK degraders.

To date, PROTACs appear as the predominant strategy for achieving targeted proteasomal degradation of CDK2. Notably, a few CDK2-directed PROTACs have demonstrated the ability to degrade CDK2-associated cyclins (e.g., Cyclin E) (Kumarasamy et al., 2023). While CRBN-recruiting CDK2 PROTACs exhibit potent on-target degradation, they frequently deplete unintended kinases (CDK4/5/6/9 and AURKA). In contrast, VHL-based CDK2 PROTACs show improved selectivity but reduced maximal degradation efficiency.

4.2 CDK4/6 degradation via PROTACs and HEMTACs

PROTACs (including bridged PROTACs) and HEMTACs achieve proteasome-dependent CDK4/6 degradation through bifunctional designs coupling CDK4/6 inhibitors with E3 ligase-recruiting ligands (Fig. 4). HEMTACs substitute specific E3 ligands with HSP90-recruiting ligands, leveraging chaperone-mediated degradation pathways for selective CDK4/6 degradation.

Many research groups have independently explored strategies for CRBN-dependent degradation of CDK4/6 via conjugating a CRBN binder to CDK4/6 inhibitors, including palbociclib, ribociclib, abemaciclib, and YY173 (Jiang et al., 2019; Zhao and Burgess, 2019; He et al., 2024). Zhao and Burgess (2019) connected pomalidomide to either palbociclib or ribociclib to develop dual degraders of CDK4/6, including Molecule **10** (pal-pom) and rib-pom. The assembly of Molecule **10** with the photosensitizer Chlorin e6 into nanoparticles potentiated the development of photodynamic combination therapy (Wang TY et al., 2023). Jiang et al. (2019) also reported a series of CDK4/6 degraders derived from palbociclib, ribociclib, and abemaciclib. Among those, abemaciclib-based Molecule **11** (BSJ-01-184) demonstrated dual degradation activities toward CDK6 and CDK4, while palbociclib-based Molecule **12** (BSJ-02-162) and ribociclib-based Molecule **13** (BSJ-01-152) showed a CDK6-biased and CDK4-biased activity, respectively. Using a similar strategy, Rana et al. (2019) also found a series of PROTACs that degrade CDK6 preferentially in pancreatic cancer cells via phthalimide conjugation to palbociclib. Molecule **14** (PROTAC 6) with a longer linker exhibited the strongest CDK6-proteolytic efficacy. Similarly, palbociclib/thalidomide-based CDK6 degrader Molecule **15** (YX-2-107) showed good antitumor effects on Philadelphia-positive acute lymphoblastic leukemia (de Dominici et al., 2020). Wu XW et al. (2021) developed a CDK4/6 degrader, Molecule **16** (MS140), which is a palbociclib/pomalidomide

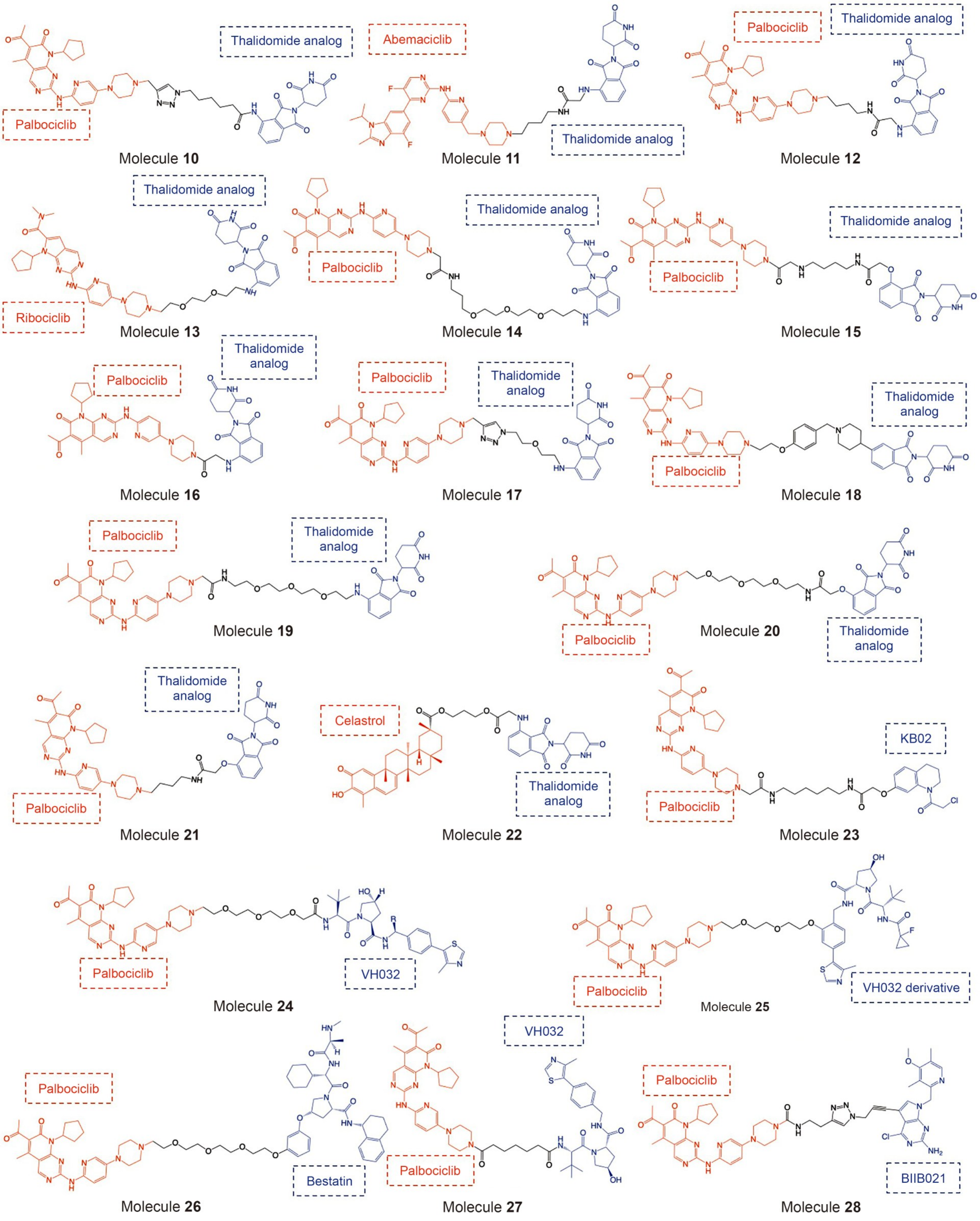


Fig. 4 Molecular structures of selective proteolysis-targeting chimeras (PROTACs) and heat shock protein 90 (HSP90)-mediated targeting chimeras (HEMTACs) that target cyclin-dependent kinase 4/6 (CDK4/6). Cereblon (CRBN) is frequently hijacked by CDK4/6 PROTACs for protein degradation, while DDB1- and CUL4-associated factor 16 (DCAF16) (Molecule 23), von Hippel-Lindau (VHL) (Molecules 24, 25, and 27), and cellular inhibitor of apoptosis protein 1 (cIAP1) (Molecule 26) prove amenable for the design of CDK4/6 PROTACs. Molecule 28 is a HEMTAC targeting CDK4/6.

chimera with a short linker. Molecule **16** suppressed the pRb-E2F pathway and limited the E2F output and cell growth in sensitive cells. Su et al. (2019) compared the applicability of various E3 ligase moieties (i.e., pomalidomide for CRBN, VH032 for VHL, Nutlin-3b for mouse double minute 2 (MDM2), and bestatin for cellular inhibitor of apoptosis protein 1 (cIAP1)) for CDK4/6 degraders. PROTACs based on CRBN were able to degrade CDK6 with high efficiency; among those, Molecule **17** (CP-10) exerted potent and selective activity against CDK6, with a DC_{50} of 2.1 nmol/L. Of note, IKZF1 and IKZF3 are targets of IMiDs and the abovementioned IMiD-based PROTACs (Lu et al., 2014). Since DKY709 is an alternative IMiD that targets IKZF2 instead of IKZF1/3, palbociclib-DKY709 chimeras, such as Molecule **18** (ALV-07-082-03), have been developed as potent CDK4/CDK6/IKZF2 triple degraders (Verano et al., 2022). The co-depletion of CDK4/6 and IKZF not only conferred enhanced anti-proliferative activity against cancer cells (e.g., mantle cell lymphoma cells) but also caused unwanted side effects in normal cells. Through optimization of the linker design, Brand et al. (2019) converted a palbociclib/phthalimide-based CDK6 and IKZF1/3 dual degrader Molecule **19** (YKL-06-102) into Molecule **20** (BSJ-03-123), which achieved the potent, fast, and selective degradation of CDK6 while leaving IKZF1/3 unaffected. Similarly, Molecule **21** (BSJ-03-204) was identified as a palbociclib/phthalimide-based CDK4/6 dual degrader without IKZF1/3 activity (Jiang et al., 2019). It seems that palbociclib-based CRBN-dependent PROTACs exhibit preferential CDK6 degradation selectivity over CDK4 (Anderson et al., 2020). In addition to the use of known CDK4/6 inhibitors as substrate-recruiting moieties, Gan et al. (2024) developed Molecule **22** (6a) with CDK1, CDK4, and glucose-regulated protein 94 (GRP94) degradation activities through the hybrid design of thalidomide and the natural, promiscuous compound celastrol.

Alternative E3 ligases have been tested for the induced degradation of CDK4/6. Failed attempts have been reported to develop MDM2-based CDK4/6. However, encouraging findings were obtained from CDK4/6 PROTACs dependent on DDB1- and CUL4-associated factor 16 (DCAF16), VHL, and cIAP1. Recently, Pu et al. (2023) designed a series of DCAF16-based CDK4/6 degraders that combine palbociclib and DCAF16 E3 ligase ligand KB02 with various linkers. Despite the relatively high DC_{50} values (CDK4: 6.5 μmol/L; CDK6: 8.0 μmol/L), Molecule **23** (A4) represents a leading DCAF16-dependent CDK4/6 PROTAC with anti-breast cancer activities both in vitro and in vivo. Steinebach et al. (2020) showed that VHL- and cIAP1-based targeted degradation of CDK4/6 is indeed feasible in cancer. Representative VHL-based selective CDK6 degraders include Molecules **24** and **25**. cIAP1-based Molecule **26** caused the concurrent degradation of CDK4/6 and IAPs at a concentration of 1 μmol/L, yielding a synergistic anti-proliferative effect on cancer cells. Of note, several palbociclib-based VHL-dependent PROTACs, including Molecule **27** (MS28), effectively degrade Cyclin D1 prior to CDK4/6 (Wang TY et al., 2023), mitigating the pRb-E2F pathway and the proliferation and clonogenicity of non-small cell lung cancer cells. Molecule **27** represents the first-in-class degrader of Cyclin D1 working through the formation of the Cyclin D1-CDK6-PROTAC-VHL quaternary complex. Further investigation revealed that Molecule **27** simultaneously degrades Cyclin D3 but not Cyclin D2 or other cyclins. As inspired by MS28, "bridged PROTAC" emerges as a new strategy to degrade protein binding partners (Fig. 1a).

The potential mechanisms of resistance to CDK4/6 inhibitors have been thoroughly reviewed (Steinebach et al., 2020). Retinoblastoma 1 (RB1) loss and hyper-activation of CDK2, Cyclin E, and inhibitor of CDK4 (INK4) proteins have been associated with CDK4/6 inhibitor resistance (Condorelli et al., 2018; Wander et al., 2020; Xu et al., 2021; Li Q et al., 2022). The application of a CDK2/Cyclin E PROTAC Molecule **2** synergized with CDK4/6 PROTACs against p16/INK4A-proficient cancer cells (Kumarasamy et al., 2023). The recent development of YY173/pomalidomide-based CDK2/4/6 PROTAC may be beneficial to overcome resistance to CDK4/6 inhibitors (He et al., 2024). Wu XW et al. (2021) also reported that CDK6 is a thermostable, weak HSP90-client, with lower affinity for either inhibitors or degraders of CDK4/6 in cells resistant to CDK4/6-targeted agents. In line with the relevance of HSP90's affinity to drug response, a new approach termed HEMTACs was devised by connecting palbociclib with the HSP90 ligand BIIB021 via a flexible linker (Li et al., 2023). In the presence of HEMTACs, HSP90-E3, HEMTAC, and CDK4/6 form ternary complexes that prime ubiquitin transfer and proteasomal degradation of CDK4/6. Molecule **28** (HEMTAC 26) was showcased as a good example, exhibiting desirable degradation efficiency and anti-tumor activity. Hence, HEMTACs provide a valuable strategy to cause the degradation of weak- or non-HSP90 client proteins.

PROTAC and HEMTAC studies have evaluated a number of E3 ligases for degrading CDK4/6. Remarkably, "bridged PROTAC" represents a promising strategy for developing cyclin degraders. Thus far, the effective degradation of CDK4/6 has been achieved using CRBN, VHL, cIAP1, DCAF16, and HEMTACs, whereas MDM2-based approaches remain unsuccessful. Notably, CRBN-recruiting PROTACs frequently cause the co-depletion of IKZF proteins, which constitute the major source of toxicity in normal cells. While CDK4/6 share functional redundancy, lineage-associated dependency on each isoform has been recognized. For example, HER2$^+$ breast cancer and prostate cancer exhibit CDK4 dependence (Zhang ZW et al., 2022), whereas hematopoietic cells rely primarily on CDK6 (Maurer et al., 2021). Although CDK4-selective agents may offer a path to circumvent the hematologic toxicity associated with dual CDK4/6 inhibitors (Palmer et al., 2025), achieving selective inhibition remains very challenging because of the highly homologous ATP-binding pockets of CDK4 and CDK6. Encouragingly, through PROTAC optimization, researchers have developed degraders achieving CDK4-specific, CDK6-specific, or dual-targeted degradation. These isoform-selective degraders represent valuable tools for dissecting CDK4/6 biology and advancing precision cancer therapy.

4.3 CDK8/19 degradation via PROTACs

CDK8 and CDK19 are closely related CDKs that function as key regulatory components within the Mediator complex. PROTAC technology has demonstrated feasibility in transforming CDK8/19 inhibitors into either CDK8-selective degraders or CDK8/19/Cyclin C triple degraders (Fig. 5).

Hatcher et al. (2018) developed JH-VIII-49, a CDK8/19 inhibitor analogous to Cortistatin A. The conjugation of JH-VIII-49 and pomalidomide via a polyethylene glycol (PEG) linker further yielded the CDK8-selective PROTAC Molecule **29** (JH-XI-10-02). Another CDK8-selective degrader, Molecule **30** (YKL-06-101), was synthesized by linking the mechanistic target of rapamycin (mTOR)/CDK8 inhibitor THZ4-55 with thalidomide (Menzl et al., 2019). While retaining the function to inhibit mTOR, Molecule **30** acts as a CDK8 degrader without altering the levels of CDK19, Cyclin C, Mediator complex subunit 12 (MED12), and MED13. Interestingly, CDK8-dependent transcriptional changes impaired the mTOR pathway in Philadelphia-positive acute lymphoblastic leukemia cells, whereas CDK8 kinase inhibitors showed minimal effects. In this scenario, simultaneous CDK8 depletion and mTOR inhibition by Molecule **30** induced the apoptosis of leukemic cells. Chen et al. (2023) developed a CDK8/19 PROTAC named Molecule **31** (SNX7886) on the basis of the hybridization of pomalidomide and the CDK8/19 inhibitor BI1347. Molecule **31** degraded CDK8 by up to 90% and CDK19 by up to 80% at 30 nmol/L, with concurrent depletion of Cyclin C.

Collectively, the abovementioned findings for CDK8/19 PROTACs suggest the feasibility of developing CRBN-based CDK8 degraders and CDK8/19/Cyclin C degraders. However, CDK19-selective degraders remain unavailable to date. Besides, information on anti-cancer activities that can be attributed to on-targeted effects of CDK8/19 PROTACs remains limited.

4.4 CDK7 degradation via PROTACs

CDK7-targeting PROTACs have been developed via the conjugation of CDK7 inhibitors (i.e., YKL-5-167 and A86) to either VHL- or CRBN-targeting ligands. Ji et al. (2024) recently reported a series of CDK7 PROTACs that connect the selective CDK7 inhibitor YKL-5-167 analog to either VHL or CRBN recruiter (Fig. 5). The VHL-based CDK7 PROTAC Molecule **32** (JWZ-5-13) induced the near-complete degradation of CDK7 with low nanomolar efficacy in various cancer cell lines. Of note, the CDK7-interacting partners Cyclin H and MAT1, which form the CAK complex, could be depleted simultaneously, while other CDKs were barely affected. Molecule **32** exhibited an improved anti-proliferative capability over the CDK7 inhibitor YKL-5-167. Moreover, it was well tolerated by the mice and exhibited half-lives ($T_{1/2}$) of 3.76 and 2.82 h via intravenous and intraperitoneal injection, respectively. However, CRBN-based compounds were not able to induce the complete degradation of CDK7,

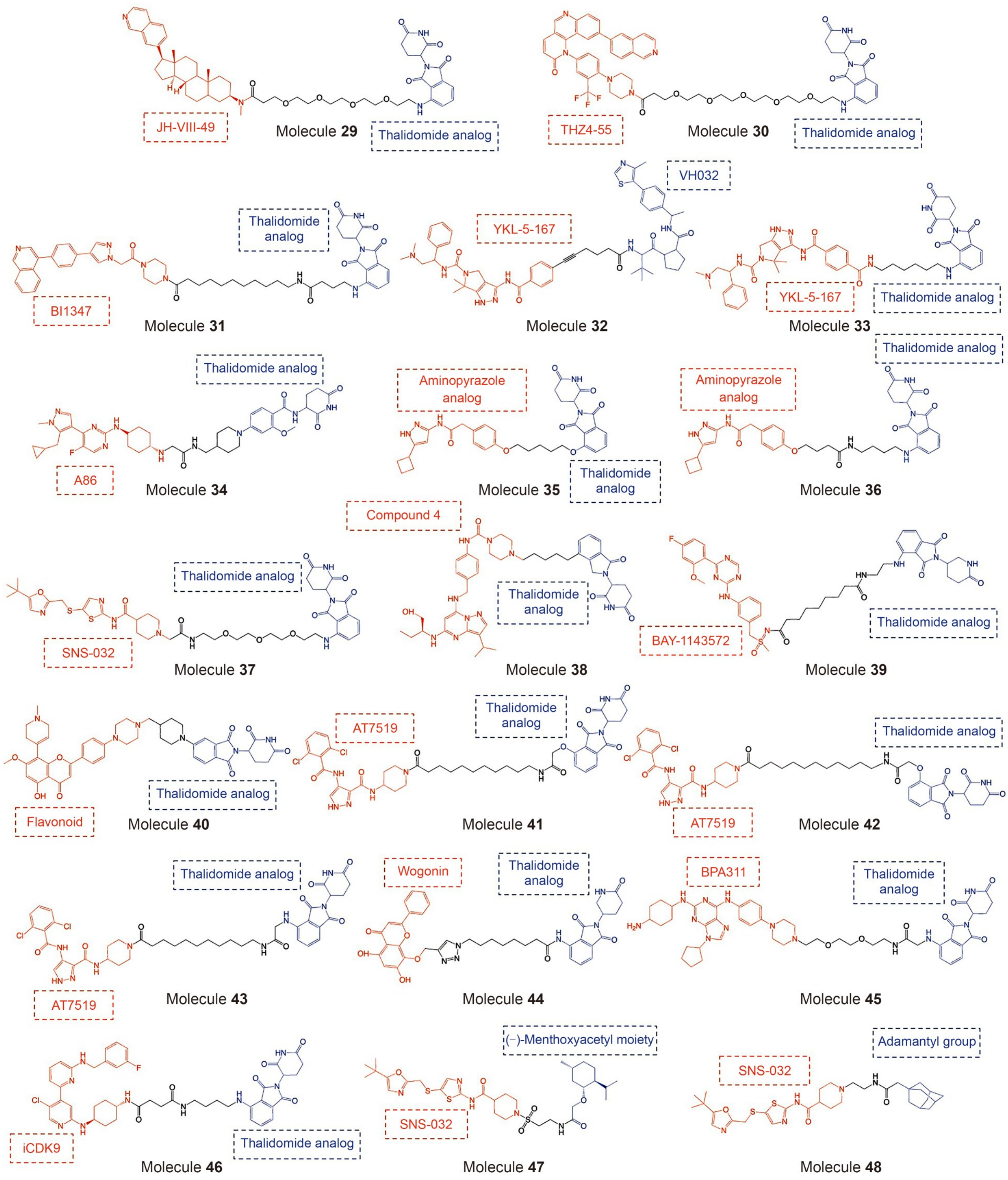


Fig. 5 Molecular structures of selective degraders against cyclin-dependent kinase 8/19 (CDK8/19), CDK7, and CDK9/Cyclin T. Molecules 29–31 are cereblon (CRBN)-dependent proteolysis-targeting chimeras (PROTACs) against CDK8/19. Molecules 32 and 33 are von Hippel-Lindau (VHL)-dependent and CRBN-dependent PROTACs against CDK7, respectively. Molecule 34 is a CRBN-dependent PROTAC of casein kinase 1α (CK1α), CDK7, and CDK9. Molecules 35–46 are CRBN-dependent CDK9 PROTACs. Molecules 47 and 48 are hydrophobic tags (HyTs) against CDK9/Cyclin T1 heterodimer.

as Molecule **33**, which exhibited the best activity, only achieved a nearly 50% reduction. These data suggest that induced degradation of CDK7 may be more permissive to VHL than CRBN. Nevertheless, Wang et al.

(2024) developed a CRBN-based multiple-target degrader, Molecule **34** (PROTAC 13i), which elicited efficient degradation of CK1α, CDK7, and CDK9. It also induced p53 and exerted anti-AML potentials at the expense of the transcriptional downregulation of survival genes (e.g., *MDM2*, *MYC*, B-cell lymphoma 2 (*BCL2*), and myeloid cell leukemia 1 (*MCL1*)) and cytokine genes. Altogether, CDK7-targeting PROTACs have the potential to deplete the CAK complex, thereby indirectly regulating downstream CDK activity. Unlike most CDKs, which are generally more vulnerable to CRBN-based degraders, CDK7 displays preferential degradation via VHL-recruiting PROTAC. This ligase-selective vulnerability presents a compelling model for probing structural determinants governing productive E3 ligase engagement.

4.5 CDK9 degradation via PROTACs and HyTs

The widespread dysregulation and critical roles of CDK9 in oncogenic transcription stimulate the development of CDK9 degraders. To date, a number of structurally diverse PROTACs and HyTs with CDK9-related proteolytic activities have been developed (Fig. 5). These CDK9 degraders exhibit robust target degradation and potent anti-proliferative activities across a wide spectrum of cancers.

The first CDK9 PROTAC, Molecule **35**, was reported by connecting an aminopyrazole analog to thalidomide in 2017 and showed low micromolar activity (Robb et al., 2017). Another aminopyrazole-based Molecule **36** (PROTAC 2) improved CDK9 degradation efficiency, with a DC_{50} value of approximately 150 nmol/L, where a shortened linker length had a negative impact on CDK9 degradation (King et al., 2021). In 2018, Olson et al. (2018) reported a CDK9 PROTAC Molecule **37** (THAL-SNS-032) through the chimeric design of a CDK inhibitor SNS-032 and thalidomide. Affinity competition assay showed that Molecule **37** degraded CDK9 in a catalytic, sub-stoichiometric fashion. Molecule **37** caused an efficient and selective depletion of CDK9 at 250 nmol/L within 2 h and subsequently induced the loss of Ser2 phosphorylation at the Rpb1 CTD and substantial perturbation of global messenger RNA (mRNA) biogenesis. As a result, the cancer-associated core regulatory circuitry was disrupted and apoptosis was induced in leukemic cells upon treatment with Molecule **37** (Boyer et al., 2005; Sanda et al., 2012; Olson et al., 2018). Wei D et al. (2021) developed a highly potent and selective CDK9 degrader, Molecule **38**, which showed IC_{50} of <20 nmol/L and strong anti-tumor effects in triple-negative breast cancer models. It had an on-target DC_{50} of <100 nmol/L, while it showed minimal effects on G1 to S phase transition 1 (GSPT1) and other CDK proteins, including CDK1, CDK2, CDK4, CDK5, CDK6, and CDK7, at doses up to 500 nmol/L in breast cancer cells. The CDK9 inhibitor BAY-1143572 was also converted successfully into a series of CDK9 PROTACs, among which Molecule **39** (B03) showed an enhanced anti-proliferative effect in AML cells (Qiu et al., 2021). Flavonoid-based CDK9 PROTAC Molecule **40** (CP-07) had a CDK9 DC_{50} of 43 nmol/L in 22RV1 prostate cancer cells and was able to reduce the expression of MCL1 and MYC, cell viability, and clonogenicity (Wu et al., 2023). AT7519-based CDK9 PROTACs with aminoalkanoic acid linkers, such as Molecules **41**–**43**, displayed impressive potency in CDK9 degradation and cytotoxicity against AML cells (Tokarski et al., 2023). Among those AT7519-based CDK9 PROTACs, compounds with PEG linker were generally less effective. Further exploration of linker length indicated that longer-chain compounds performed better than their shorter-chain analogs.

CRBN-dependent PROTACs with dual activity to degrade CDK9 and other kinases are available from the literature. For example, a wogonin (natural flavone compound)-based Molecule **44** (PROTAC 11c) could target both CDK9 and CDK7; BPA311-based Molecule **45** (PROTAC 13) could selectively degrade CDK9 and FMS-like tyrosine kinase 3 (FLT3) in leukemic cells with FLT3-internal tandem duplications (ITDs) (Řezníčková et al., 2022); and Molecule **46** (PROTAC CD-5) exhibited a degradation efficacy against CDK9, CDK1, and KAT6A (Ao et al., 2023).

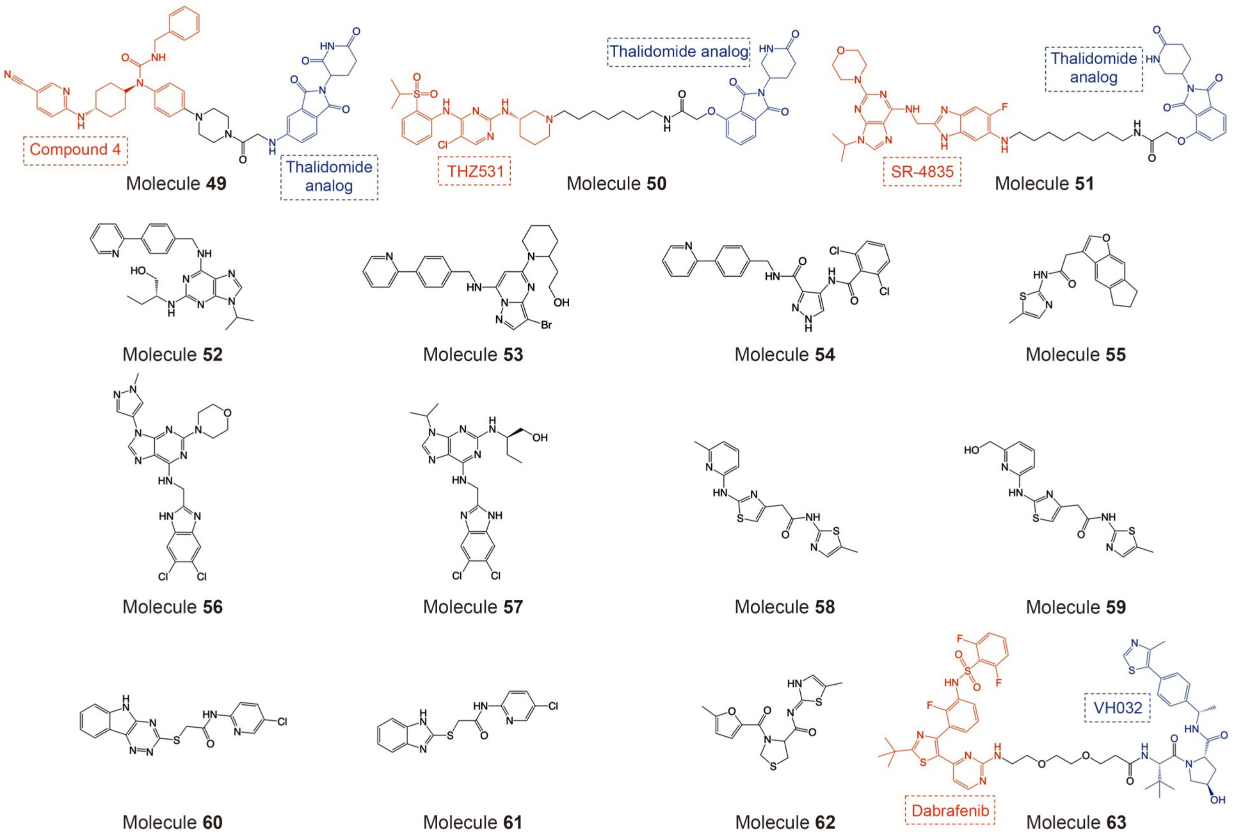
In parallel with PROTACs, HyT-based small-molecule degraders have been developed by tagging a (−)-methoxyacetyl degron to SNS-032. Molecule **47** (LL-K9-3) and Molecule **48** (LL-CDK9-12) were showcased as two potent CDK9/Cyclin T1-targeted HyTs that could selectively degrade the CDK9/Cyclin T1 heterodimer without affecting other CDKs (Li JC et al., 2022; Lin et al., 2023). While Molecule **47** had off-target effects, including glycogen synthase kinase 3α (GSK3α), Molecule **48** possessed a more efficient and selective degradation capability, with DC_{50} values of 0.36 and 0.68 μmol/L against CDK9 and Cyclin T1, respectively. Both CDK9 HyTs exerted stronger inhibitory effects than SNS-032 on oncogenic transcription programs driven by MYC and androgen receptor in prostate cancer cells (Niu et al., 2022; Yang et al., 2022).

Altogether, CDK9 represents a highly tractable degradation target for many CDK-targeting PROTACs. CRBN-recruiting warheads are commonly utilized in the CDK9 PROTAC design, where optimizing linker length critically influences degradation efficiency. To date, the known CDK9-selective PROTACs remain limited; however, appending HyTs to CDK9 inhibitors enables the selective degradation of the CDK9/Cyclin T1 complex. Since *CDK9* is a common essential gene for cancer and normal cells, enhancing cancer selectivity is critical for the clinical translation of CDK9-targeting degraders.

4.6 CDK12/13/Cyclin K degradation via PROTACs and molecular glues

CDK12 and CDK13 share a high degree of sequence and functional similarity. Both of them interact with Cyclin K. A number of PROTACs successfully degrade CDK12/13, while molecular glues predominantly deplete Cyclin K (Fig. 6). Structurally diverse degraders now enable distinct degradation profiles: CDK12-only, CDK12/13-dual, CDK12/Cyclin K-complex, Cyclin K-only, or CDK12/13/Cyclin K-triple depletion.

Yang et al. (2022) reported a CRBN-dependent dual CDK12/13 degrader, Molecule **49**, which degraded CDK12 (DC_{50}: 2.2 nmol/L), CDK13 (DC_{50}: 2.1 nmol/L), and Cyclin K in MDA-MB-231 breast cancer cells (Yang et al., 2022). In line with the deleterious effect of dual kinase inhibition on cells, Molecule **49** reduced the viability of multiple triple-negative breast cancer cell lines, along with a marked inhibition of *DDR* gene transcription. Selective CDK12 PROTACs include Molecule **50** (BSJ-4-116) and Molecule **51** (PP-C8) (Niu et al., 2022; Liu et al., 2023). Molecule **50** was the first selective CDK12 degrader developed using a fragment of a dual CDK12/13 covalent inhibitor



Molecule **49** Molecule **50** Molecule **51**
Molecule **52** Molecule **53** Molecule **54** Molecule **55**
Molecule **56** Molecule **57** Molecule **58** Molecule **59**
Molecule **60** Molecule **61** Molecule **62** Molecule **63**

Fig. 6 Molecular structures of the selective molecular glue degraders of Cyclin K and proteolysis-targeting chimeras (PROTACs) that target either cyclin-dependent kinase 12/13 (CDK12/13) or CDK17. Molecules 49–51 are cereblon (CRBN)-dependent PROTACs against CDK12 and/or CDK13, while molecules 52–62 are molecular glue degraders of Cyclin K. Molecule 63 is a von Hippel-Lindau (VHL)-dependent PROTAC against CDK17.

THZ531 as a CDK12 binder. It depletes CDK12 in a dose- and time-dependent manner with any trivial effect on CDK13. In cellular assays, Molecule **50** treatment not only significantly downregulated *DDR* genes but also overcame resistance to covalent CDK12/13 inhibitors. However, upon chronic exposure, mutations in *CDK12* (i.e., I733V and G739S), which impair degrader binding, conferred the acquired resistance to Molecule **50**. Molecule **51** is another PROTAC with the capability to dually degrade both CDK12 (DC_{50}: 416 nmol/L) and Cyclin K (DC_{50}: 412 nmol/L). Both Molecule **50** and Molecule **51** showed a profound synthetic lethality with respect to PARP inhibition in preclinical anti-cancer studies.

Molecular glues are best explored in the targeted degradation of Cyclin K, the dimerization partner of CDK12/13. Representative compounds include CR8, DS17/30, compound 21195, SR-4835, HQ461, NCT02, and dCeMM2/3/4 (Lv et al., 2020; Mayor-Ruiz et al., 2020; Słabicki et al., 2020; Dieter et al., 2021; Houles et al., 2023; Kozicka et al., 2024), all of which act through the engagement of CDK12/13 active sites and DDB1/CUL4/RBX1 E3 ubiquitin ligases. Słabicki et al. (2020) identified Molecule **52** (CR8) as a small-molecule glue that bridges the interaction between CDK12/Cyclin K and DDB1, promoting Cyclin K for ubiquitination and proteasomal degradation. This discovery emerged from correlating drug sensitivity data for 4518 clinical/preclinical small molecules with the mRNA levels of 499 E3 ligase components across hundreds of human cancer cell lines. The surface-exposed 2-pyridyl moiety of CR8 confers it gluing function. Subsequent structural, biophysical, and cellular studies of Molecule **52** derivatives and other Cyclin K molecular glues revealed that simultaneous binding to CDK12 and engagement of DDB1 interfacial residues (in particular, Arg928) are essential for glue activity (Kozicka et al., 2024). Through the exploration of Molecule **52** analogs in Cyclin K degradation, Thomas et al. (2024) demonstrated that a wide range of modifications to the degradation-inducing group are tolerable as long as the solvent-exposed groups are sufficient for the interaction between CDK12 and DDB1. The addition of solvent-exposed groups such as pyridine and furan to the core of pan-CDK inhibitors dinaciclib and AT7519 converted them to Cyclin K degraders. Molecule **53** in the dinaciclib series was found to be both an effective CDK12 inhibitor and a Cyclin K degrader, while AT7519-based Molecule **54** was a strong Cyclin K degrader but with approximately 500-fold weaker CDK12 affinity. Dieter et al. (2021) also identified Molecule **55** (NCT02) as a molecular glue degrader of Cyclin K, CDK12, and CDK13. Upon treatment with Molecule **55** in colorectal cancer cells, degradation of Cyclin K occurred before that of CDK12. In line with the preferential growth dependency of TP53-defective colorectal cancer cells on Cyclin K and CDK12, targeted CDK12/Cyclin K degradation by Molecule **55** decreased the corresponding cell expansion both in vitro and in vivo. Molecule **55** further sensitized patient-derived colorectal cancer spheroids to chemotherapy agents, including oxaliplatin and irinotecan. Molecule **56** (SR-4835) and Molecule **57** (DS17) are representatives of CDK12/13-selective inhibitors with concurrent glue activities as Cyclin K degraders. Alterations in the benzimidazole side chain of Molecule **56** decreased cyclin K degradation and cytotoxicity (Houles et al., 2023). Molecule **58** (HQ461) was shown to be a relatively weak glue degrader of Cyclin K with lower inhibitory activities against CDKs (Lv et al., 2020). Structure–activity relationship analysis unveiled a 5-methylthiazol-2-amine moiety as the important pharmacophore of Molecule **58** and further guided the development of Molecule **59** (HQ005) with an improved potency (Cyclin K DC_{50}: 41 nmol/L). *CDK12* mutations in G731R/E and *CDK13* mutations in G709R/E conferred resistance to Molecule **57**. Through screening a library of approximately 2000 cytostatic/cytotoxic small molecules against wild-type and *UBE2M*-mutated near-haploid KBM7 cells, Mayor-Ruiz et al. (2020) identified a series of chemical scaffolds that exhibited functional dependence on intact neddylation pathways. Subsequent quantitative proteomics analysis indicated that Molecules **60**–**62** (dCeMM2/3/4) profoundly downregulate Cyclin K, whereas they have a milder effect on CDK12/CDK13. On the basis of the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) screening assay using a Cullin-RING ubiquitin ligase (CRL)-focused single-guide RNA (sgRNA) library, a number of genes, including *DDB1*, *CUL4B*, *UBE2M*, *UBE2G1*, *UBE2Z*, and *UBA6*, were identified to confer cellular sensitivity to Molecules **60**–**62**. These glues also exhibited selective dependence on CUL4B over CUL4A, suggestive of the CRL4B ligase complex-dependent degradation of Cyclin K. Moreover, the engagement of CDK12/13 active site was required for drug-induced degradation of Cyclin K via the CRL4B-DDB1 complex, albeit the cellular efficacy of Molecules **60**–**62** appeared to be independent of their weak inhibitory activity against CDK12/13. Acquired resistance to Molecules **60**–**62** emerged from mutations in *DDB1*, *CUL4B*, *CDK12*, and *CDK13*. A *CDK13* (P1043H) mutation outside the kinase domain blunted Cyclin K degradation following treatment with Molecules **60**–**62**. Of note, in spite of the common effect on Cyclin K degradation, Cyclin K molecular glues had distinct target profiles beyond Cyclin K. Through rational design, the independent optimization of CDK inhibition and Cyclin K degradation activity seems feasible, leading to compounds with different target profiles and biological activities (Thomas et al., 2024).

To sum up, chemically induced degradation of CDK12/13 strongly disrupts *DDR* gene expression, potentiating synthetic lethality with PARP inhibition. In contrast, Cyclin K molecular glues trigger diverse transcriptomic responses that are different from the selective degradation or inhibition of CDK12/13. This variability in target engagement profiles necessitates rigorous characterization and, in turn, may be beneficial to the development of diverse drugs. Furthermore, developing a CDK13-selective degrader may be helpful for delineating the isoform-specific function between CDK12 and CDK13.

4.7 CDK17 degradation via PROTACs

CDK17 is a poorly studied kinase with the highest expression in brain tissue. Although its function remains a mystery, CDK17 was shown to be a degradable protein by PROTACs. By employing a chemoproteomics approach, Donovan et al. (2020) found that CDK17 was degraded by 15 different compounds, including two potent and two selective PROTACs for CDK17. Molecule **63** (DD-03-156; Fig. 6) is the chimeric design of the VHL binder and dabrafenib (an inhibitor of *BRAF*$^{\mathrm{V600E}}$ mutant). Interestingly, instead of V-raf murine sarcoma viral oncogene homolog B1 (BRAF), Molecule **63** induced the potent and selective degradation of CDK17 and LIM domain kinase 2 (LIMK2), suggesting that turning an inhibitor with prominent targets into a PROTAC may generate novel, potent, and selective degradation events distinct from a warhead inhibitor's primary targets. Meanwhile, the impact of CDK17 degraders on cellular phenotypes remains unclear.

5 Conclusions and future perspectives

As summarized above, cyclins and CDKs are reliable drivers and thus attractive targets in human cancer. The inhibition of cyclins and CDKs impairs diverse oncogenic pathways, not limited to the cell cycle, transcription, DNA replication, RNA processing, signaling transduction, and immune response. In recent years, encouraging progress has been made in developing CDK and/or cyclin degraders via PROTAC, HEMTAC, HyT, and molecular glue techniques. Chemically induced protein degradation emerges as an innovative and promising strategy to target cyclins and CDKs.

5.1 Unfilled gaps in CDK and cyclin biology

Many biological aspects of cyclins and CDKs remain unexplored. For example, functional redundancy and cooperation among CDKs with high homology have not been well addressed. Such situations apply to but are not limited to CDK11A versus CDK11B, CDK4 versus CDK6, CDK8 versus CDK19, CDK12 versus CDK13, as well as CDK7 versus CDK20. Protein degraders, especially PROTACs, usually trigger highly efficient depletion of CDKs or cyclins within hours. Leveraging this advantage, protein degraders with high selectivity serve as valuable tools to elucidate the phase-specific roles of CDK/cyclin complexes during cell cycle progression (Fig. 7).

While the non-canonical functions and kinase-independent scaffolding roles of several CDKs have been recognized, their mechanistic underpinnings and biological consequences remain inadequately characterized. This knowledge gap impedes both fundamental understanding and therapeutic exploitation. Furthermore, the functional relevance of cyclins and CDKs to various cancer hallmarks beyond cell cycle biology awaits thorough investigations, especially in the context of cancer signaling transduction, metabolism, epigenetics, immunity, and the microenvironment. It should also be emphasized that CDK/cyclin-targeted cancer therapy simultaneously influences both cancer cells and non-cancer compartments. The roles of cyclins and CDKs in immune cells and stromal cells are still elusive.

5.2 Advantages of targeted protein degradation over conventional protein inhibition

Rapid advances in targeted protein degradation technologies have yielded diverse therapeutic modalities,

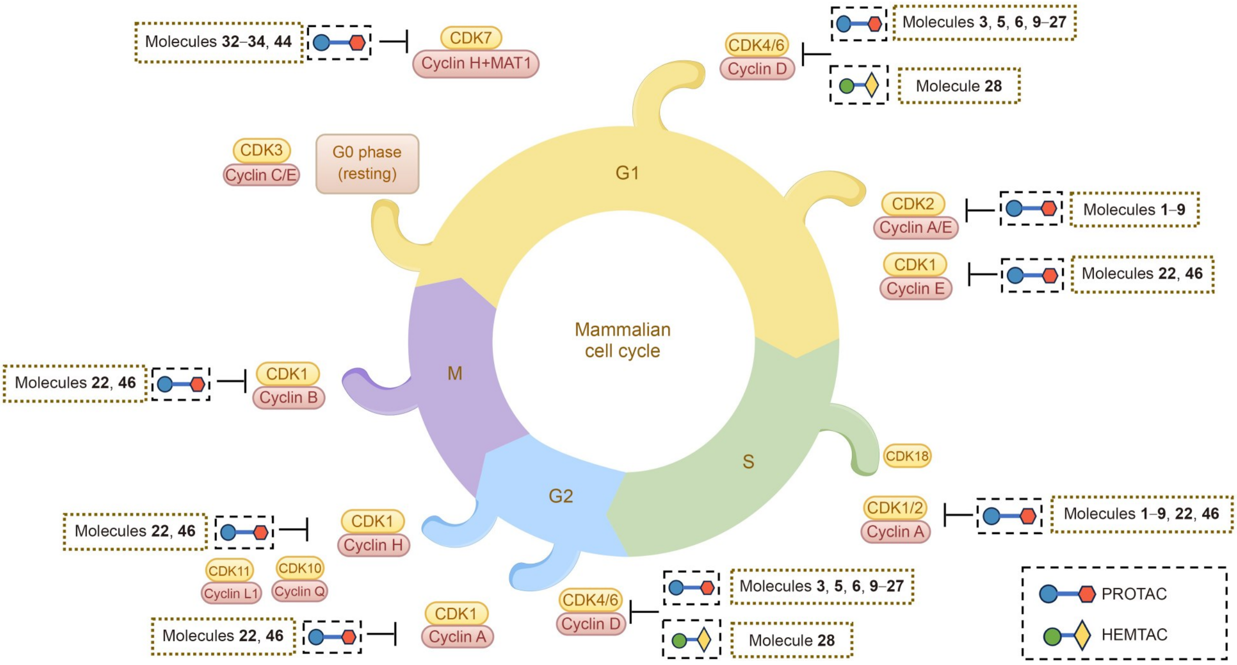


Fig. 7 Cell cycle regulatory cyclin-dependent kinase (CDK)/cyclin complexes and their reported degraders. HEMTAC: heat shock protein 90 (HSP90)-mediated targeting chimera; MAT1: methionine adenosyltransferase 1; PROTAC: proteolysis-targeting chimera. Partially created by Figdraw.

including PROTACs, HEMTACs, HyTs, and molecular glues, all of which hijack the cellular degradation machinery (e.g., the ubiquitin-proteasome system) to eliminate POI. As extensively documented in the literature, targeted protein degradation offers strategic advantages over conventional inhibition through expanded target druggability, catalytic mechanism of action, disruption of scaffolding functions, and reduced susceptibility to resistance (Table 1).

Conventional small-molecule drug design relies on binding to a specific catalytic or allosteric site on a target protein, triggering the so-called occupancy-driven inhibition. However, this occupancy-driven pharmacology usually becomes ineffective in case of proteins either lacking well-defined catalytic pockets (e.g., cyclins and other CDK partners) or exhibiting highly homologous binding sites (e.g., kinase domains within CDKs). In these scenarios, targeted protein degradation can overcome limitations by utilizing accessible spaces beyond the active sites and an expanded layer of selectivity regulation through substrate permissibility, providing novel chemical tools and therapeutic strategies for protein-based therapy targeting an undruggable or difficult-to-target proteome.

Most proteasome-dependent protein degraders behave catalytically, enabling the ubiquitination of super-stoichiometric target protein pools without occupancy-based equilibrium constraints. The catalytic cycle of PROTACs/molecular glues, operated through dynamic assembly and disassembly of the POI-degrader-E3 complex, permits a single degrader molecule to facilitate multiple rounds of target ubiquitination (Wu XW et al., 2021).

By inducing protein elimination, degraders uniquely abolish all functions of target proteins, including non-catalytic scaffolding roles, while traditional inhibitors usually block specific activities (e.g., enzymatic sites). Evidence from non-CDK/cyclin-targeting PROTACs has demonstrated their superior efficacy over parental inhibitors and their ability to overcome acquired resistance (Xu et al., 2018). CDK-targeting PROTACs have also shown potential to overcome therapy resistance to CDK inhibitors. For example, CDK2/Cyclin E-targeting PROTACs have demonstrated the ability to overcome resistance to CDK4/6 inhibition (Kumarasamy et al., 2023). Similarly, treatment with the CDK12 degrader Molecule **50** achieved robust protein depletion and bypassed cellular resistance to covalent CDK12/13 inhibitors. By degrading entire target proteins, PROTACs can eliminate mutant isoforms or overexpressed proteins that evade occupancy-based inhibition, including clinically relevant variants (e.g., *BTK*^{C481S}, *BRAF*^{V600E}, and *KRAS*^{G12V}), establishing a new paradigm for precision oncology. Furthermore, some CDK/cyclin-targeting degraders achieve dual or triple depletion of complex subunits. For instance, Molecule **32** induces the degradation of CAK complex components, while Molecules **47** and **48** are able to deplete both CDK9 and Cyclin T1. This co-depletion of CDK/cyclin complexes likely raises the genetic barrier for cells to develop resistance-conferring mutations, as the simultaneous acquisition of secondary mutations in both protein subunits (two or more hits) is considered a low-possibility genetic event.

5.3 Potential of PROTACs to improve selectivity for CDK targets

Lack of selectivity is considered a critical issue associated with therapeutic toxicity, hindering the clinical translation of many CDK-targeting agents. Due to high sequence homology across CDKs, particularly within conserved ATP-binding pockets, developing isoform-specific CDK inhibitors remains challenging. Indeed, most conventional CDK inhibitors exhibit multi-target activity. For example, SNS-032 inhibits CDK2, CDK7, and CDK9; AT7519 inhibits CDK1, CDK2, CDK4, CDK6, and CDK9; and dinaciclib inhibits CDK1, CDK2, CDK4, and CDK9. In contrast to conventional CDK inhibitors, PROTACs operate via an event-driven catalytic mechanism rather than occupancy-driven inhibition. While warhead selectivity influences target engagement, simply repurposing promiscuous CDK inhibitors for PROTAC design often yields non-selective degraders. Notably, a number of CDK PROTACs showing exceptional isoform selectivity have been successfully developed: CDK2-selective CPS2 and PROTAC-8, CDK4-selective BSJ-04-132, CDK6-selective BSJ-03-123 and CP-10, CDK7-selective JWZ-5-13, CDK8-selective JH-XI-10-02, CDK9-selective THAL-SNS-032 and compound C3, and CDK12-selective BSJ-4-116. When compared to inhibitors, PROTACs confer at least three key advantages: (1) access to expanded druggable spaces beyond the active sites; (2) utilization of warheads with moderate affinity but higher intrinsic specificity; and (3) exploitation of the ternary complex (POI-PROTAC-E3) conformation-driven substrate permissibility. Accumulating evidence supports that linker length/properties and the spatial positioning of vulnerable lysines for ubiquitination are key factors determining substrate permissibility in the ternary complex. To sum up, the abovementioned mechanisms of PROTACs (i.e., expanded druggable spaces, versatile warhead selection, and the emerging paradigm of substrate permissibility) collectively potentiate the development of degraders with enhanced target selectivity.

5.4 Strategies and challenges in heterobifunctional CDK degrader design

The current development of cyclin/CDK degraders is still in its early stages of initial discovery and preclinical investigation. Undoubtedly, improving efficiency and specificity is worthy of further attention. The activity of degraders is greatly influenced by target affinity, warhead physicochemical properties, attachment sites, and linker composition/length. More insights are required to elucidate the principles of structure–activity relationships, target engagement, bioavailability, and biological effects of cyclin/CDK degraders.

In terms of the selection of substrate warheads, the majority of heterobifunctional CDK degraders, including PROTACs, HEMTACs, and HyTs, were designed based on corresponding inhibitors. Interestingly, reports of CDK PROTACs based on wogonin and celastrol may stimulate the research to expand the pool of warheads to natural products. When it comes to the E3 warheads, in particular for PROTACs, limited choices for E3 ligases and E3 ligase binders appear to be the bottleneck. In fact, CRBN and VHL are employed preferentially by CDK PROTACs. To a lesser extent, cIAP1 and DCAF16 are amenable, while MDM2 has been found to be inefficient in inducing CDK degradation. Therefore, expanding the choices of E3 ligases and new E3 ligase binders would be valuable for PROTAC design.

With regard to designing de novo warheads, fragment-based screening may be used. When high-resolution crystal structures are available, solvent-exposed positions identified from the substrate and E3 ligase can serve as candidate attachment sites for new warheads. Insights from explainable artificial intelligence and molecular dynamics simulations may guide the selection of optimal attachment points. Apart from warheads, linkers play a critical role in determining the physicochemical properties and degradation efficacy of PROTACs. While identifying both substrate and E3 warheads follows established small-molecule discovery principles, linker design presents a unique challenge in PROTAC design due to the structural complexity and dynamic assembly of the POI-PROTAC-E3 ternary complex. The linker length and flexibility dictate the formation of ternary complexes and the subsequent efficiency of POI degradation. The simulation of the binding and dissociation dynamics of VHL-based BRD4 PROTAC MZ1 suggested that an appropriate linker orientation is essential for exposing lysine on the surface of the target protein (Tang et al., 2023). So far, commonly used PROTAC linkers include PEG and linear alkanes, which are typically synthesized via amidation, esterification, or click chemistry. To improve overall molecular performance, subsequent linker optimization strategies involve adjusting length, enhancing hydrophobicity/rigidity (e.g., incorporating aryl groups), and reducing molecular twisting (e.g., adding conformation-restricting chains). In fact, early and conventional methods rely on inefficient trial-and-error for PROTAC design. Remarkably, recent efforts in computational approaches (e.g., generative pre-trained transformer and reinforcement learning) demonstrated the potential to aid in linker design. For instance, a recently developed ProLinker-Generator supports rational PROTAC linker design featuring the increased structural diversity and improved control of molecular properties (Luo et al., 2025). After putting warheads and linker together, a functional PROTAC hinges critically on the dynamic assembly and disassembly of the induced POI-PROTAC-E3 ternary complex, posing a challenge given the absence of natural target-E3 interactions. Consequently, developing computational tools to predict the ternary complex structure and stability is very helpful for rational PROTAC design. Advances in molecular docking and simulation, deep learning, protein structure prediction, and artificial intelligence now enable a more precise prediction of ternary complex conformations and expedite PROTAC design (Weng et al., 2021; Li FL et al., 2022; Zheng et al., 2022; Chou et al., 2024; Ugurlu et al., 2025). Representative tools include DeepPROTACs (a predictive model for PROTAC degradation capability) (Li FL et al., 2022), PROTAC-RL (a deep reinforcement learning-driven generative model for de novo PROTAC design) (Zheng et al., 2022), and PROTAC-Model (a computational method combining the FRODOCK-based protocol and RosettaDock-based refinement for predicting ternary complex modeling) (Weng et al., 2021). Encouragingly, these tools have also demonstrated the potential to address key limitations, including linker design, target selectivity, and bioavailability, although they have not been tested for CDK PROTACs. The generalizability of these approaches to the rational design of CDK PROTACs merits further investigation.

5.5 Bioavailability challenges for protein degraders

Bioavailability remains a critical challenge for most protein degraders (especially heterobifunctional compounds), limiting their therapeutic potential. Hence, technical advances in medicinal chemistry are in great demand to guide optimization and further translation of these classes of degraders into orally bioavailable forms. Drug-like properties of heterobifunctional compounds, including most PROTACs, HEMTACs, and HyTs, do not comply with Lipinski's "Rule of Five." In contrast, molecular glues are advantageous because of their smaller molecular weight and more drug-like properties. Since most molecular glues were discovered serendipitously, the rational design of molecular glues would be considered more challenging than that of other entities of protein degraders. Nevertheless, recent practices in the design of Cyclin K glue degraders provide good examples for the development and optimization of compounds with gluing activities.

5.6 Underdeveloped fields for degraders targeting CDKs and cyclins

Based on the literature, heterobifunctional degraders mainly target CDKs, while molecular glues predominantly degrade Cyclin K. Unlike conventional small-molecule drugs that modulate predefined binding pockets on target proteins, molecular glues function by rewiring protein–protein interactions through specifically inducing novel ternary complexes between an E3 ligase complex and a neo-substrate. CRL4, which comprises the CUL4 scaffold protein, E2 enzyme linker protein (e.g., RBX1), substrate adapter protein (e.g., DDB1), and diverse substrate receptors (e.g., DCAF15), is frequently hijacked by molecular glues. With regard to reported Cyclin K glues, most of them contact DDB1 Arg928, a residue essential for complex formation (Kozicka et al., 2024). The central challenge in molecular glue discovery lies in identifying neo-substrates that become susceptible to degradation only upon induced proximity to the hijacked CRL4 complex. Once a neo-substrate is implicated, further optimization of molecular glues may be focused on inducing and stabilizing the novel ternary complex between an E3 ligase, a neo-substrate, and the molecular glue itself. Until now, few degraders are available for other cyclins and a number of CDKs, including CDK1, CDK3, CDK5, CDK10, CDK11, CDK14, CDK15, CDK16, CDK18, and CDK20, while future studies are expected to fill in the blanks. Alternatively, the targeted degradation of other proteins with CDK/cyclin regulatory potential may be an alternative strategy for cancer therapy. Early successes have been achieved for VHL-dependent CDC20 PROTAC CP5V and WEE1 PROTAC MA055 (Chi et al., 2019; Aublette et al., 2022), as well as CRBN-dependent polo-like kinase 4 (PLK4) PROTAC SP27 (Sun et al., 2023) and AURKA PROTACs (e.g., JB170, dAurA383, and SK2188) (Adhikari et al., 2020; Liu et al., 2022; Rishfi et al., 2023).

Apart from proteasome-dependent targeted protein degradation techniques, several lysosome-dependent protein degraders, such as *S*-indacene-dependent autophagy-targeting chimeras (Zhong et al., 2025), CDK9/Cyclin T1-targeting autophagosome-tethering compounds (ATTECs) (Zeng et al., 2025), and a peptide-based lysosomal degrader of CDK5 (Zhou et al., 2019), demonstrate feasibility and encouraging efficacy in targeting CDKs and cyclins. For example, AZ-9 was recently developed as a HyT-based autophagy-targeting chimera degrading both CDK9 and Cyclin T1 (Maurer et al., 2021). Through conjugating the pan-CDK inhibitor AT7519 to *S*-indacene, AZ-9 recruited ATG101, a component of the autophagy-initiating Unc-51-like kinase (ULK) complex, and activated the autophagy-lysosome pathway. Notably, despite utilizing a multi-CDK inhibitor AT7519 as its "warhead," AZ-9 exhibited a degradation selectivity profile favoring CDK9/Cyclin T1 over other CDKs. In addition, an anti-cancer drug homoharringtonine was shown to disrupt the interaction between CDK2 and Cyclin A and trigger tripartite motif-containing protein 21 (TRIM21)-dependent autophagic degradation of CDK2 in cancer cells (Zhang JW et al., 2022). It is interesting to note that lysosome-dependent protein degraders preferentially induce the co-depletion of the CDK/cyclin complex. Compared to PROTACs and molecular glues, lysosome-dependent CDK/cyclin degraders operate through a distinct pathway and thus may offer unique opportunities for combination therapy. To date, the development of lysosome-dependent CDK/cyclin degraders is still in its infancy, underscoring the need for further research.

In summary, cyclins and CDKs play critical roles in cancer. A better understanding of their mechanism and function will therefore provide important insights for the development of targeted anti-cancer therapy. Cyclin and CDK degraders not only provide novel tools for biomedical research but also represent a bright future in pharmaceutical development.

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Author contributions

Suya ZHENG: methodology, visualization, writing – original draft, and writing – review & editing. Ye CHEN: conceptualization, methodology, visualization, writing – original draft, writing – review & editing, supervision, and funding acquisition. Zhipeng ZHU and Chunyu HE: methodology, visualization, validation, and writing – review & editing. Nan LI: visualization, validation, and writing – review & editing. H. Phillip KOEFFLER: writing – review & editing and supervision. Xin HAN: visualization, validation, writing – review & editing, and funding acquisition. Qichun WEI: writing – review & editing, funding acquisition, and supervision. Liang XU: conceptualization, methodology, writing – original draft, writing – review & editing, supervision, and funding acquisition. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Suya ZHENG, Ye CHEN, Zhipeng ZHU, Nan LI, Chunyu HE, H. Phillip KOEFFLER, Xin HAN, Qichun WEI, and Liang XU declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

References

Adhikari B, Bozilovic J, Diebold M, et al., 2020. PROTAC-mediated degradation reveals a non-catalytic function of AURORA-A kinase. *Nat Chem Biol*, 16(11):1179-1188. https://doi.org/10.1038/s41589-020-00652-y

Anderson NA, Cryan J, Ahmed A, et al., 2020. Selective CDK6 degradation mediated by cereblon, VHL, and novel IAP-recruiting PROTACs. *Bioorg Med Chem Lett*, 30(9): 127106. https://doi.org/10.1016/j.bmcl.2020.127106

Ao MT, Wu J, Cao Y, et al., 2023. The synthesis of PROTAC molecule and new target KAT6A identification of CDK9 inhibitor iCDK9. *Chin Chem Lett*, 34(4):107741. https://doi.org/10.1016/j.cclet.2022.107741

Asghar U, Witkiewicz AK, Turner NC, et al., 2015. The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nat Revi Drug Discov*, 14(2):130-146. https://doi.org/10.1038/nrd4504

Aublette MC, Harrison TA, Thorpe EJ, et al., 2022. Selective Wee1 degradation by PROTAC degraders recruiting VHL and CRBN E3 ubiquitin ligases. *Bioorg Med Chem Lett*, 64:128636. https://doi.org/10.1016/j.bmcl.2022.128636

Bai X, Guo ZQ, Zhang YP, et al., 2023. CDK4/6 inhibition triggers ICAM1-driven immune response and sensitizes *LKB1* mutant lung cancer to immunotherapy. *Nat Commun*, 14:1247. https://doi.org/10.1038/s41467-023-36892-4

Baumli S, Lolli G, Lowe ED, et al., 2008. The structure of P-TEFb (CDK9/cyclin T1), its complex with flavopiridol and regulation by phosphorylation. *EMBO J*, 27(13): 1907-1918. https://doi.org/10.1038/emboj.2008.121

Békés M, Langley DR, Crews CM, 2022. PROTAC targeted protein degraders: the past is prologue. *Nate Rev Drug Discov*, 21(3):181-200. https://doi.org/10.1038/s41573-021-00371-6

Bösken CA, Farnung L, Hintermair C, et al., 2014. The structure and substrate specificity of human Cdk12/Cyclin K. *Nat Commun*, 5:3505. https://doi.org/10.1038/ncomms4505

Boyer LA, Lee TI, Cole MF, et al., 2005. Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell*, 122(6):947-956. https://doi.org/10.1016/j.cell.2005.08.020

Brand M, Jiang BS, Bauer S, et al., 2019. Homolog-selective degradation as a strategy to probe the function of CDK6 in AML. *Cell Chem Biol*, 26(2):300-306.e9. https://doi.org/10.1016/j.chembiol.2018.11.006

Cancer Genome Atlas Research Network, 2011. Integrated genomic analyses of ovarian carcinoma. *Nature*, 474(7353): 609-615. https://doi.org/10.1038/nature10166

Chen MQ, Li J, Zhang L, et al., 2023. CDK8 and CDK19: positive regulators of signal-induced transcription and negative regulators of Mediator complex proteins. *Nucleic Acids Res*, 51(14):7288-7313. https://doi.org/10.1093/nar/gkad538

Cheng L, Zhou SC, Zhou SQ, et al., 2022. Dual inhibition of CDK12/CDK13 targets both tumor and immune cells in ovarian cancer. *Cancer Res*, 82(19):3588-3602. https://doi.org/10.1158/0008-5472.CAN-22-0222

Chi J, Li HC, Zhou Z, et al., 2019. A novel strategy to block mitotic progression for targeted therapy. *eBioMedicine*, 49: 40-54. https://doi.org/10.1016/j.ebiom.2019.10.013

Chipumuro E, Marco E, Christensen CL, et al., 2014. CDK7 inhibition suppresses super-enhancer-linked oncogenic transcription in MYCN-driven cancer. *Cell*, 159(5):1126-1139. https://doi.org/10.1016/j.cell.2014.10.024

Chirnomas D, Hornberger KR, Crews CM, 2023. Protein degraders enter the clinic—a new approach to cancer therapy. *Nat Rev Clin Oncol*, 20(4):265-278. https://doi.org/10.1038/s41571-023-00736-3

Choi SH, Kim S, Jones KA, 2020. Gene expression regulation by CDK12: a versatile kinase in cancer with functions beyond CTD phosphorylation. *Exp Mol Med*, 52(5): 762-771. https://doi.org/10.1038/s12276-020-0442-9

Chou CL, Lin CT, Kao CT, et al., 2024. A novel rational PROTACs design and validation via AI-driven drug design approach. *ACS Omega*, 9(37):38371-38384. https://doi.org/10.1021/acsomega.3c10183

Chou J, Quigley DA, Robinson TM, et al., 2020. Transcription-associated cyclin-dependent kinases as targets and biomarkers for cancer therapy. *Cancer Discov*, 10(3):351-370. https://doi.org/10.1158/2159-8290.CD-19-0528

Christensen CL, Kwiatkowski N, Abraham BJ, et al., 2014. Targeting transcriptional addictions in small cell lung cancer with a covalent CDK7 inhibitor. *Cancer Cell*, 26(6): 909-922. https://doi.org/10.1016/j.ccell.2014.10.019

Condorelli R, Spring L, O'Shaughnessy J, et al., 2018. Polyclonal RB1 mutations and acquired resistance to CDK 4/6 inhibitors in patients with metastatic breast cancer. *Ann Oncol*, 29(3):640-645. https://doi.org/10.1093/annonc/mdx784

Cornwell JA, Crncec A, Afifi MM, et al., 2023. Loss of CDK4/6 activity in S/G2 phase leads to cell cycle reversal. *Nature*, 619(7969):363-370. https://doi.org/10.1038/s41586-023-06274-3

de Dominici M, Porazzi P, Xiao YC, et al., 2020. Selective inhibition of Ph-positive ALL cell growth through kinase-dependent and -independent effects by CDK6-specific PROTACs. *Blood*, 135(18):1560-1573. https://doi.org/10.1182/blood.2019003604

Deshaies RJ, 2015. Prime time for PROTACs. *Nat Chem Biol*, 11(9):634-635. https://doi.org/10.1038/nchembio.1887

Dieci G, 2021. Removing quote marks from the RNA polymerase II CTD 'code'. *Biosystems*, 207:104468. https://doi.org/10.1016/j.biosystems.2021.104468

Dieter SM, Siegl C, Codó PL, et al., 2021. Degradation of

CCNK/CDK12 is a druggable vulnerability of colorectal cancer. *Cell Rep*, 36(3):109394.
https://doi.org/10.1016/j.celrep.2021.109394

Dogan S, Shen RL, Ang DC, et al., 2012. Molecular epidemiology of *EGFR* and *KRAS* mutations in 3026 lung adenocarcinomas: higher susceptibility of women to smoking-related *KRAS*-mutant cancers. *Clin Cancer Res*, 18(22): 6169-6177.
https://doi.org/10.1158/1078-0432.CCR-11-3265

Donovan KA, Ferguson FM, Bushman JW, et al., 2020. Mapping the degradable kinome provides a resource for expedited degrader development. *Cell*, 183(6):1714-1731.e10.
https://doi.org/10.1016/j.cell.2020.10.038

Dubbury SJ, Boutz PL, Sharp PA, 2018. CDK12 regulates DNA repair genes by suppressing intronic polyadenylation. *Nature*, 564(7734):141-145.
https://doi.org/10.1038/s41586-018-0758-y

Fan HM, Liu WC, Zeng YQ, et al., 2023. DNA damage induced by CDK4 and CDK6 blockade triggers anti-tumor immune responses through cGAS-STING pathway. *Commun Biol*, 6:1041.
https://doi.org/10.1038/s42003-023-05412-x

Fan Z, Devlin JR, Hogg SJ, et al., 2020. CDK13 cooperates with CDK12 to control global RNA polymerase II processivity. *Sci Adv*, 6(18):eaaz5041.
https://doi.org/10.1126/sciadv.aaz5041

Filippakopoulos P, Picaud S, Mangos M, et al., 2012. Histone recognition and large-scale structural analysis of the human bromodomain family. *Cell*, 149(1):214-231.
https://doi.org/10.1016/j.cell.2012.02.013

Gan XL, Wang F, Luo JG, et al., 2024. Proteolysis Targeting Chimeras (PROTACs) based on celastrol induce multiple protein degradation for triple-negative breast cancer treatment. *Eur J Pharm Sci*, 192:106624.
https://doi.org/10.1016/j.ejps.2023.106624

Glover-Cutter K, Larochelle S, Erickson B, et al., 2009. TFIIH-associated Cdk7 kinase functions in phosphorylation of C-terminal domain Ser7 residues, promoter-proximal pausing, and termination by RNA polymerase II. *Mol Cell Biol*, 29(20):5455-5464.
https://doi.org/10.1128/MCB.00637-09

Goel S, DeCristo MJ, Watt AC, et al., 2017. CDK4/6 inhibition triggers anti-tumour immunity. *Nature*, 548(7668): 471-475.
https://doi.org/10.1038/nature23465

Goel S, Bergholz JS, Zhao JJ, 2022. Targeting CDK4 and CDK6 in cancer. *Nat Rev Cancer*, 22(6):356-372.
https://doi.org/10.1038/s41568-022-00456-3

Gordon V, Bhadel S, Wunderlich W, et al., 2010. CDK9 regulates AR promoter selectivity and cell growth through serine 81 phosphorylation. *Mol Endocrinol*, 24(12):2267-2280.
https://doi.org/10.1210/me.2010-0238

Hatcher JM, Wang ES, Johannessen L, et al., 2018. Development of highly potent and selective steroidal inhibitors and degraders of CDK8. *ACS Med Chem Lett*, 9(6):540-545.
https://doi.org/10.1021/acsmedchemlett.8b00011

Hati S, Zallocchi M, Hazlitt R, et al., 2021. AZD5438-PROTAC: a selective CDK2 degrader that protects against cisplatin- and noise-induced hearing loss. *Eur J Med Chem*, 226: 113849.
https://doi.org/10.1016/j.ejmech.2021.113849

He H, Zhang XS, Wang J, et al., 2024. Development of degraders of cyclin-dependent kinases 4 and 6 based on rational drug design. *J Med Chem*, 67(13):11354-11364.
https://doi.org/10.1021/acs.jmedchem.4c00965

Houles T, Boucher J, Lavoie G, et al., 2023. The CDK12 inhibitor SR-4835 functions as a molecular glue that promotes cyclin K degradation in melanoma. *Cell Death Discov*, 9:459.
https://doi.org/10.1038/s41420-023-01754-x

Hu AJ, Li W, Pathak A, et al., 2023. CDK6 is essential for mesenchymal stem cell proliferation and adipocyte differentiation. *Front Mol Biosci*, 10:1146047.
https://doi.org/10.3389/fmolb.2023.1146047

Hu C, Shen LJ, Zou FM, et al., 2023. Predicting and overcoming resistance to CDK9 inhibitors for cancer therapy. *Acta Pharm Sin B*, 13(9):3694-3707.
https://doi.org/10.1016/j.apsb.2023.05.026

Huang HT, Dobrovolsky D, Paulk J, et al., 2018. A chemoproteomic approach to query the degradable kinome using a multi-kinase degrader. *Cell Chem Biol*, 25(1):88-99.e6.
https://doi.org/10.1016/j.chembiol.2017.10.005

Huang XD, Dixit VM, 2016. Drugging the undruggables: exploring the ubiquitin system for drug development. *Cell Res*, 26(4):484-498.
https://doi.org/10.1038/cr.2016.31

Huang YG, Liu WW, Zhao CH, et al., 2024. Targeting cyclin-dependent kinases: from pocket specificity to drug selectivity. *Eur J Med Chem*, 275:116547.
https://doi.org/10.1016/j.ejmech.2024.116547

Hydbring P, Malumbres M, Sicinski P, 2016. Non-canonical functions of cell cycle cyclins and cyclin-dependent kinases. *Nat Rev Mol Cell Biol*, 17(5):280-292.
https://doi.org/10.1038/nrm.2016.27

Iniguez AB, Stolte B, Wang EJ, et al., 2018. EWS/FLI confers tumor cell synthetic lethality to CDK12 inhibition in Ewing sarcoma. *Cancer Cell*, 33(2):202-216.e6.
https://doi.org/10.1016/j.ccell.2017.12.009

Ishida T, Ciulli A, 2021. E3 ligase ligands for PROTACs: how they were found and how to discover new ones. *SLAS Discov*, 26(4):484-502.
https://doi.org/10.1177/2472555220965528

Ji WZ, Du GY, Jiang J, et al., 2024. Discovery of bivalent small molecule degraders of cyclin-dependent kinase 7 (CDK7). *Eur J Med Chem*, 276:116613.
https://doi.org/10.1016/j.ejmech.2024.116613

Jiang BS, Wang ES, Donovan KA, et al., 2019. Development of dual and selective degraders of cyclin-dependent kinases 4 and 6. *Angew Chem Int Ed*, 58(19):6321-6326.
https://doi.org/10.1002/anie.201901336

Kargbo RB, 2021. Tumor-targeted bivalent protein degradation for application in cancer therapy. *ACS Med Chem Lett*,

12(3):326-327.
https://doi.org/10.1021/acsmedchemlett.1c00084

Kciuk M, Gielecińska A, Mujwar S, et al., 2022. Cyclin-dependent kinases in DNA damage response. *Biochim Biophys Acta Rev Cancer*, 1877(3):188716.
https://doi.org/10.1016/j.bbcan.2022.188716

King HM, Rana S, Kubica SP, et al., 2021. Aminopyrazole based CDK9 PROTAC sensitizes pancreatic cancer cells to venetoclax. *Bioorg Med Chem Lett*, 43:128061.
https://doi.org/10.1016/j.bmcl.2021.128061

Kozicka Z, Suchyta DJ, Focht V, et al., 2024. Design principles for cyclin K molecular glue degraders. *Nat Chem Biol*, 20(1):93-102.
https://doi.org/10.1038/s41589-023-01409-z

Krajewska M, Dries R, Grassetti AV, et al., 2019. CDK12 loss in cancer cells affects DNA damage response genes through premature cleavage and polyadenylation. *Nat Commun*, 10:1757.
https://doi.org/10.1038/s41467-019-09703-y

Kumarasamy V, Gao Z, Zhao BS, et al., 2023. PROTAC-mediated CDK degradation differentially impacts cancer cell cycles due to heterogeneity in kinase dependencies. *Br J Cancer*, 129(8):1238-1250.
https://doi.org/10.1038/s41416-023-02399-4

Leiser D, Pochon B, Blank-Liss W, et al., 2014. Targeting of the MET receptor tyrosine kinase by small molecule inhibitors leads to MET accumulation by impairing the receptor downregulation. *FEBS Lett*, 588(5):653-658.
https://doi.org/10.1016/j.febslet.2013.12.025

Li FL, Hu QY, Zhang XL, et al., 2022. DeepPROTACs is a deep learning-based targeted degradation predictor for PROTACs. *Nat Commun*, 13:7133.
https://doi.org/10.1038/s41467-022-34807-3

Li JC, Liu T, Song YL, et al., 2022. Discovery of small-molecule degraders of the CDK9-cyclin T1 complex for targeting transcriptional addiction in prostate cancer. *J Med Chem*, 65(16):11034-11057.
https://doi.org/10.1021/acs.jmedchem.2c00257

Li Q, Jiang BS, Guo JY, et al., 2022. INK4 tumor suppressor proteins mediate resistance to CDK4/6 kinase inhibitors. *Cancer Discov*, 12(2):356-371.
https://doi.org/10.1158/2159-8290.CD-20-1726

Li Z, Wang FC, Tian XX, et al., 2021. HCK maintains the self-renewal of leukaemia stem cells via CDK6 in AML. *J Exp Clin Cancer Res*, 40:210.
https://doi.org/10.1186/s13046-021-02007-4

Li ZZ, Ma SY, Zhang L, et al., 2023. Targeted protein degradation induced by HEMTACs based on HSP90. *J Med Chem*, 66(1):733-751.
https://doi.org/10.1021/acs.jmedchem.2c01648

Lin RK, Yang J, Liu T, et al., 2023. Discovery of HyT-based degraders of CDK9-cyclin T1 complex. *Chem Biodivers*, 20(8):e202300769.
https://doi.org/10.1002/cbdv.202300769

Liu F, Wang X, Duan JL, et al., 2022. A temporal PROTAC cocktail-mediated sequential degradation of AURKA abrogates acute myeloid leukemia stem cells. *Adv Sci*, 9(22):e2104823.
https://doi.org/10.1002/advs.202104823

Liu Y, Yang JW, Wang TL, et al., 2023. Expanding PROTACtable genome universe of E3 ligases. *Nat Commun*, 1:6509.
https://doi.org/10.1038/s41467-023-42233-2

Lu G, Middleton RE, Sun HH, et al., 2014. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science*, 343(6168):305-309.
https://doi.org/10.1126/science.1244917

Luo YL, Song DY, Zhang CW, et al., 2025. ProLinker–generator: design of a PROTAC linker base on a generation model using transfer and reinforcement learning. *Appl Sci*, 15(10):5616.
https://doi.org/10.3390/app15105616

Lv L, Chen PH, Cao LZ, et al., 2020. Discovery of a molecular glue promoting CDK12-DDB1 interaction to trigger cyclin K degradation. *eLife*, 9:e59994.
https://doi.org/10.7554/eLife.59994

Magnuson B, Bedi K, Narayanan IV, et al., 2022. CDK12 regulates co-transcriptional splicing and RNA turnover in human cells. *iScience*, 25(9):105030.
https://doi.org/10.1016/j.isci.2022.105030

Marineau JJ, Hamman KB, Hu SH, et al., 2022. Discovery of SY-5609: a selective, noncovalent inhibitor of CDK7. *J Med Chem*, 65(2):1458-1480.
https://doi.org/10.1021/acs.jmedchem.1c01171

Maurer B, Brandstoetter T, Kollmann S, et al., 2021. Inducible deletion of CDK4 and CDK6 – deciphering CDK4/6 inhibitor effects in the hematopoietic system. *Haematologica*, 106(10):2624-2632.
https://doi.org/10.3324/haematol.2020.256313

Mayor-Ruiz C, Bauer S, Brand M, et al., 2020. Rational discovery of molecular glue degraders via scalable chemical profiling. *Nat Chem Biol*, 16(11):1199-1207.
https://doi.org/10.1038/s41589-020-0594-x

Mbonye UR, Gokulrangan G, Datt M, et al., 2013. Phosphorylation of CDK9 at Ser175 enhances HIV transcription and is a marker of activated P-TEFb in $CD4^+$ T lymphocytes. *PLoS Pathogens*, 9(5):e1003338.
https://doi.org/10.1371/journal.ppat.1003338

McKenney C, Lendner Y, Guerrero Zuniga A, et al., 2024. CDK4/6 activity is required during G_2 arrest to prevent stress-induced endoreplication. *Science*, 384(6695):eadi2421.
https://doi.org/10.1126/science.adi2421

Menzl I, Zhang TH, Berger-Becvar A, et al., 2019. A kinase-independent role for CDK8 in BCR-$ABL1^+$ leukemia. *Nat Commun*, 10:4741.
https://doi.org/10.1038/s41467-019-12656-x

Moon S, Lee BH, 2018. Chemically induced cellular proteolysis: an emerging therapeutic strategy for undruggable targets. *Mol Cells*, 41(11):933-942.
https://doi.org/10.14348/molcells.2018.0372

Morrison L, Loibl S, Turner NC, 2024. The CDK4/6 inhibitor revolution – a game-changing era for breast cancer treatment. *Nat Rev Clin Oncol*, 21(2):89-105.
https://doi.org/10.1038/s41571-023-00840-4

Nayyar N, de Sauvage MA, Chuprin J, et al., 2024. CDK4/6 inhibition sensitizes intracranial tumors to PD-1 blockade in preclinical models of brain metastasis. *Clin Cancer Res*, 30(2):420-435.
https://doi.org/10.1158/1078-0432.CCR-23-0433

Neklesa TK, Tae HS, Schneekloth AR, et al., 2011. Small-molecule hydrophobic tagging-induced degradation of HaloTag fusion proteins. *Nat Chem Biol*, 7(8):538-543.
https://doi.org/10.1038/nchembio.597

Niu T, Li KL, Jiang L, et al., 2022. Noncovalent CDK12/13 dual inhibitors-based PROTACs degrade CDK12-Cyclin K complex and induce synthetic lethality with PARP inhibitor. *Eur J Med Chem*, 228:114012.
https://doi.org/10.1016/j.ejmech.2021.114012

Olson CM, Jiang BS, Erb MA, et al., 2018. Pharmacological perturbation of CDK9 using selective CDK9 inhibition or degradation. *Nat Chem Biol*, 14(2):163-170.
https://doi.org/10.1038/nchembio.2538

Palmer CL, Boras B, Pascual B, et al., 2025. CDK4 selective inhibition improves preclinical anti-tumor efficacy and safety. *Cancer Cell*, 43(3):464-481.e14.
https://doi.org/10.1016/j.ccell.2025.02.006

Parua PK, Fisher RP, 2020. Dissecting the Pol II transcription cycle and derailing cancer with CDK inhibitors. *Nat Chem Biol*, 16(7):716-724.
https://doi.org/10.1038/s41589-020-0563-4

Petroni G, Formenti SC, Chen-Kiang S, et al., 2020. Immunomodulation by anticancer cell cycle inhibitors. *Nat Rev Immunol*, 20(11):669-679.
https://doi.org/10.1038/s41577-020-0300-y

Pluta AJ, Studniarek C, Murphy S, et al., 2024. Cyclin-dependent kinases: masters of the eukaryotic universe. *WIREs RNA*, 15(1):e1816.
https://doi.org/10.1002/wrna.1816

Pu CL, Liu YY, Deng R, et al., 2023. Development of PROTAC degrader probe of CDK4/6 based on DCAF16. *Bioorg Chem*, 138:106637.
https://doi.org/10.1016/j.bioorg.2023.106637

Qiu M, Yin ZN, Wang HH, et al., 2023. CDK12 and Integrator-PP2A complex modulates LEO1 phosphorylation for processive transcription elongation. *Sci Adv*, 9(20):eadf8698.
https://doi.org/10.1126/sciadv.adf8698

Qiu XQ, Li YQ, Yu B, et al., 2021. Discovery of selective CDK9 degraders with enhancing antiproliferative activity through PROTAC conversion. *Eur J Med Chem*, 211: 113091.
https://doi.org/10.1016/j.ejmech.2020.113091

Quandt E, Ribeiro MPC, Clotet J, 2020. Atypical cyclins: the extended family portrait. *Cell Mol Life Sci*, 77(2):231-242.
https://doi.org/10.1007/s00018-019-03262-7

Quandt E, Masip N, Hernández-Ortega S, et al., 2023. CDK6 is activated by the atypical cyclin I to promote E2F-mediated gene expression and cancer cell proliferation. *Mol Oncol*, 17(7):1228-1245.
https://doi.org/10.1002/1878-0261.13438

Quereda V, Bayle S, Vena F, et al., 2019. Therapeutic targeting of CDK12/CDK13 in triple-negative breast cancer. *Cancer Cell*, 36(5):545-558.e7.
https://doi.org/10.1016/j.ccell.2019.09.004

Rana S, Bendjennat M, Kour S, et al., 2019. Selective degradation of CDK6 by a palbociclib based PROTAC. *Bioorg Med Chem Lett*, 29(11):1375-1379.
https://doi.org/10.1016/j.bmcl.2019.03.035

Řezníčková E, Krajčovičová S, Peřina M, et al., 2022. Modulation of FLT3-ITD and CDK9 in acute myeloid leukaemia cells by novel proteolysis targeting chimera (PROTAC). *Eur J Med Chem*, 243:114792.
https://doi.org/10.1016/j.ejmech.2022.114792

Riching KM, Schwinn MK, Vasta JD, et al., 2021. CDK family PROTAC profiling reveals distinct kinetic responses and cell cycle-dependent degradation of CDK2. *SLAS Discov*, 26(4):560-569.
https://doi.org/10.1177/2472555220973602

Rishfi M, Krols S, Martens F, et al., 2023. Targeted AURKA degradation: towards new therapeutic agents for neuroblastoma. *Eur J Med Chem*, 247:115033.
https://doi.org/10.1016/j.ejmech.2022.115033

Robb CM, Contreras JI, Kour S, et al., 2017. Chemically induced degradation of CDK9 by a proteolysis targeting chimera (PROTAC). *Chem Commun*, 53(54):7577-7580.
https://doi.org/10.1039/C7CC03879H

Rusan M, Li K, Li Y, et al., 2018. Suppression of adaptive responses to targeted cancer therapy by transcriptional repression. *Cancer Discov*, 8(1):59-73.
https://doi.org/10.1158/2159-8290.CD-17-0461

Sakamoto KM, Kim KB, Kumagai A, et al., 2001. Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation. *Proc Natl Acad Sci USA*, 98(15):8554-8559.
https://doi.org/10.1073/pnas.141230798

Sanda T, Lawton LN, Barrasa MI, et al., 2012. Core transcriptional regulatory circuit controlled by the TAL1 complex in human T cell acute lymphoblastic leukemia. *Cancer Cell*, 22(2):209-221.
https://doi.org/10.1016/j.ccr.2012.06.007

Satyanarayana A, Kaldis P, 2009. Mammalian cell-cycle regulation: several Cdks, numerous cyclins and diverse compensatory mechanisms. *Oncogene*, 28(33):2925-2939.
https://doi.org/10.1038/onc.2009.170

Schachter MM, Fisher RP, 2013. The CDK-activating kinase Cdk7: taking yes for an answer. *Cell Cycle*, 12(20):3239-3240.
https://doi.org/10.4161/cc.26355

Schaer DA, Beckmann RP, Dempsey JA, et al., 2018. The CDK4/6 inhibitor abemaciclib induces a T cell inflamed tumor microenvironment and enhances the efficacy of PD-L1 checkpoint blockade. *Cell Rep*, 22(11):2978-2994.
https://doi.org/10.1016/j.celrep.2018.02.053

Scheicher R, Hoelbl-Kovacic A, Bellutti F, et al., 2015. CDK6 as a key regulator of hematopoietic and leukemic stem cell activation. *Blood*, 125(1):90-101.
https://doi.org/10.1182/blood-2014-06-584417

Schweizer MT, Ha G, Gulati R, et al., 2020. *CDK12*-mutated prostate cancer: clinical outcomes with standard therapies

and immune checkpoint blockade. *JCO Precis Oncol*, 4: 382-392.
https://doi.org/10.1200/po.19.00383

Scirocchi F, Scagnoli S, Botticelli A, et al., 2022. Immune effects of CDK4/6 inhibitors in patients with HR^+/$HER2^-$ metastatic breast cancer: relief from immunosuppression is associated with clinical response. *eBioMedicine*, 79: 104010.
https://doi.org/10.1016/j.ebiom.2022.104010

Słabicki M, Kozicka Z, Petzold G, et al., 2020. The CDK inhibitor CR8 acts as a molecular glue degrader that depletes cyclin K. *Nature*, 585(7824):293-297.
https://doi.org/10.1038/s41586-020-2374-x

Steinebach C, Ng YLD, Sosič I, et al., 2020. Systematic exploration of different E3 ubiquitin ligases: an approach towards potent and selective CDK6 degraders. *Chem Sci*, 11(13):3474-3486.
https://doi.org/10.1039/D0SC00167H

Su S, Yang ZM, Gao HY, et al., 2019. Potent and preferential degradation of CDK6 via proteolysis targeting chimera degraders. *J Med Chem*, 62(16):7575-7582.
https://doi.org/10.1021/acs.jmedchem.9b00871

Sun Y, Xue YL, Sun PK, et al., 2023. Discovery of the first potent, selective, and *in vivo* efficacious polo-like kinase 4 proteolysis targeting chimera degrader for the treatment of *TRIM37*-amplified breast cancer. *J Med Chem*, 66(12):8200-8221.
https://doi.org/10.1021/acs.jmedchem.3c00505

Tang RF, Wang Z, Xiang ST, et al., 2023. Uncovering the kinetic characteristics and degradation preference of PROTAC systems with advanced theoretical analyses. *JACS Au*, 3(6):1775-1789.
https://doi.org/10.1021/jacsau.3c00195

Teng MX, Jiang J, He ZX, et al., 2020. Development of CDK2 and CDK5 dual degrader TMX-2172. *Angew Chem Int Ed*, 59(33):13865-13870.
https://doi.org/10.1002/anie.202004087

Thomas KL, Bouguenina H, Miller DSJ, et al., 2024. Degradation by design: new cyclin K degraders from old CDK inhibitors. *ACS Chem Biol*, 19(1):173-184.
https://doi.org/10.1021/acschembio.3c00616

Tien JF, Mazloomian A, Cheng SWG, et al., 2017. CDK12 regulates alternative last exon mRNA splicing and promotes breast cancer cell invasion. *Nucleic Acids Res*, 45(11):6698-6716.
https://doi.org/10.1093/nar/gkx187

Tokarski RJ, Sharpe CM, Huntsman AC, et al., 2023. Bifunctional degraders of cyclin dependent kinase 9 (CDK9): probing the relationship between linker length, properties, and selective protein degradation. *Eur J Med Chem*, 254:115342.
https://doi.org/10.1016/j.ejmech.2023.115342

Ugurlu SY, McDonald D, Enisoglu R, et al., 2025. MEGA PROTAC, MEGA DOCK-based PROTAC mediated ternary complex formation pipeline with sequential filtering and rank aggregation. *Sci Rep*, 15:5545.
https://doi.org/10.1038/s41598-024-83558-2

Verano AL, You I, Donovan KA, et al., 2022. Redirecting the neo-substrate specificity of cereblon-targeting PROTACs to Helios. *ACS Chem Biol*, 17(9):2404-2410.
https://doi.org/10.1021/acschembio.2c00439

Vervoort SJ, Devlin JR, Kwiatkowski N, et al., 2022. Targeting transcription cycles in cancer. *Nat Rev Cancer*, 22(1): 5-24.
https://doi.org/10.1038/s41568-021-00411-8

Wander SA, Cohen O, Gong XQ, et al., 2020. The genomic landscape of intrinsic and acquired resistance to cyclin-dependent kinase 4/6 inhibitors in patients with hormone receptor-positive metastatic breast cancer. *Cancer Discov*, 10(8):1174-1193.
https://doi.org/10.1158/2159-8290.CD-19-1390

Wang J, Zhang RG, Lin ZY, et al., 2020. CDK7 inhibitor THZ1 enhances antiPD-1 therapy efficacy via the p38α/MYC/PD-L1 signaling in non-small cell lung cancer. *J Hematol Oncol*, 13:99.
https://doi.org/10.1186/s13045-020-00926-x

Wang K, Jiang MX, Liu HM, et al., 2024. Discovery of novel co-degradation CK1α and CDK7/9 PROTACs with p53 activation for treating acute myeloid leukemia. *Bioorg Chem*, 147:107319.
https://doi.org/10.1016/j.bioorg.2024.107319

Wang LG, Shao XJ, Zhong TB, et al., 2021. Discovery of a first-in-class CDK2 selective degrader for AML differentiation therapy. *Nat Chem Biol*, 17(5):567-575.
https://doi.org/10.1038/s41589-021-00742-5

Wang LG, Yang ZL, Li GC, et al., 2023. Discovery of small molecule degraders for modulating cell cycle. *Front Med*, 17(5):823-854.
https://doi.org/10.1007/s11684-023-1027-5

Wang TY, Zhang YM, Chen K, et al., 2023. CDK4/6 nano-PROTAC enhances mitochondria-dependent photodynamic therapy and anti-tumor immunity. *Nano Today*, 50: 101890.
https://doi.org/10.1016/j.nantod.2023.101890

Wang YB, Zhang TH, Kwiatkowski N, et al., 2015. CDK7-dependent transcriptional addiction in triple-negative breast cancer. *Cell*, 163(1):174-186.
https://doi.org/10.1016/j.cell.2015.08.063

Wei D, Wang HL, Zeng QH, et al., 2021. Discovery of potent and selective CDK9 degraders for targeting transcription regulation in triple-negative breast cancer. *J Med Chem*, 64(19):14822-14847.
https://doi.org/10.1021/acs.jmedchem.1c01350

Wei MM, Zhao R, Cao YT, et al., 2021. First orally bioavailable prodrug of proteolysis targeting chimera (PROTAC) degrades cyclin-dependent kinases 2/4/6 *in vivo*. *Eur J Med Chem*, 209:112903.
https://doi.org/10.1016/j.ejmech.2020.112903

Weng GQ, Li D, Kang Y, et al., 2021. Integrative modeling of PROTAC-mediated ternary complexes. *J Med Chem*, 64(21):16271-16281.
https://doi.org/10.1021/acs.jmedchem.1c01576

Wood DJ, Endicott JA, 2018. Structural insights into the functional diversity of the CDK–cyclin family. *Open Biol*,

8(9):180112.
https://doi.org/10.1098/rsob.180112

Wu J, Yuan Y, Long Priel DA, et al., 2021. Phase I study of zotiraciclib in combination with temozolomide for patients with recurrent high-grade astrocytomas. *Clin Cancer Res*, 27(12):3298-3306.
https://doi.org/10.1158/1078-0432.CCR-20-4730

Wu MF, Wang W, Mao XF, et al., 2024. Discovery of a potent CDKs/FLT3 PROTAC with enhanced differentiation and proliferation inhibition for AML. *Eur J Med Chem*, 275: 116539.
https://doi.org/10.1016/j.ejmech.2024.116539

Wu TZ, Zhang ZM, Gong GY, et al., 2023. Discovery of novel flavonoid-based CDK9 degraders for prostate cancer treatment via a PROTAC strategy. *Eur J Med Chem*, 260:115774.
https://doi.org/10.1016/j.ejmech.2023.115774

Wu XW, Yang XB, Xiong Y, et al., 2021. Distinct CDK6 complexes determine tumor cell response to CDK4/6 inhibitors and degraders. *Nat Cancer*, 2(4):429-443.
https://doi.org/10.1038/s43018-021-00174-z

Xiao LS, Liu Y, Chen H, et al., 2023. Targeting CDK9 with selective inhibitors or degraders in tumor therapy: an overview of recent developments. *Cancer Biol Ther*, 24(1): 2219470.
https://doi.org/10.1080/15384047.2023.2219470

Xie SW, Zhu JJ, Li JD, et al., 2023. Small-molecule hydrophobic tagging: a promising strategy of druglike technology for targeted protein degradation. *J Med Chem*, 66(16): 10917-10933.
https://doi.org/10.1021/acs.jmedchem.3c00736

Xu L, Chen Y, Mayakonda A, et al., 2018. Targetable BET proteins- and E2F1-dependent transcriptional program maintains the malignancy of glioblastoma. *Proc Natl Acad Sci USA*, 115(22):E5086-E5095.
https://doi.org/10.1073/pnas.1712363115

Xu XQ, Pan XH, Wang TT, et al., 2021. Intrinsic and acquired resistance to CDK4/6 inhibitors and potential overcoming strategies. *Acta Pharmacol Sin*, 42(2):171-178.
https://doi.org/10.1038/s41401-020-0416-4

Yang JZ, Chang Y, Tien JCY, et al., 2022. Discovery of a highly potent and selective dual PROTAC degrader of CDK12 and CDK13. *J Med Chem*, 65(16):11066-11083.
https://doi.org/10.1021/acs.jmedchem.2c00384

Yao Y, Ng JF, Park WD, et al., 2023. CDK7 controls E2F- and MYC-driven proliferative and metabolic vulnerabilities in multiple myeloma. *Blood*, 141(23):2841-2852.
https://doi.org/10.1182/blood.2022018885

Yu B, Du ZK, Zhang YM, et al., 2022. Small-molecule degraders of cyclin-dependent kinase protein: a review. *Future Med Chem*, 14(3):167-185.
https://doi.org/10.4155/fmc-2021-0154

Zaborowska J, Egloff S, Murphy S, 2016. The pol II CTD: new twists in the tail. *Nat Struct Mol Biol*, 23(9):771-777.
https://doi.org/10.1038/nsmb.3285

Zeng YP, Xiao J, Shi L, et al., 2025. Discovery of 2,4-quinazolinedione derivatives as LC3B recruiters in the facilitation of protein complex degradations. *Eur J Med Chem*, 287:117293.
https://doi.org/10.1016/j.ejmech.2025.117293

Zhang H, Christensen CL, Dries R, et al., 2020. CDK7 inhibition potentiates genome instability triggering anti-tumor immunity in small cell lung cancer. *Cancer Cell*, 37(1): 37-54.e9.
https://doi.org/10.1016/j.ccell.2019.11.003

Zhang HH, Pandey S, Travers M, et al., 2018. Targeting CDK9 reactivates epigenetically silenced genes in cancer. *Cell*, 175(5):1244-1258.e26.
https://doi.org/10.1016/j.cell.2018.09.051

Zhang JW, Gan YC, Li HZ, et al., 2022. Inhibition of the CDK2 and Cyclin A complex leads to autophagic degradation of CDK2 in cancer cells. *Nat Commun*, 13:2835.
https://doi.org/10.1038/s41467-022-30264-0

Zhang ZW, Golomb L, Meyerson M, 2022. Functional genomic analysis of *CDK4* and *CDK6* gene dependency across human cancer cell lines. *Cancer Res*, 82(11):2171-2184.
https://doi.org/10.1158/0008-5472.CAN-21-2428

Zhao BS, Burgess K, 2019. PROTACs suppression of CDK4/6, crucial kinases for cell cycle regulation in cancer. *Chem Commun*, 55(18):2704-2707.
https://doi.org/10.1039/C9CC00163H

Zheng SJ, Tan YH, Wang ZY, et al., 2022. Accelerated rational PROTAC design via deep learning and molecular simulations. *Nat Mach Intell*, 4(9):739-748.
https://doi.org/10.1038/s42256-022-00527-y

Zhong Y, Xu J, Cao HY, et al., 2025. First ATG101-recruiting small molecule degrader for selective CDK9 degradation via autophagy-lysosome pathway. *Acta Pharm Sin B*, 15(5): 2612-2624.
https://doi.org/10.1016/j.apsb.2025.03.047

Zhou F, Chen LY, Cao CG, et al., 2020. Development of selective mono or dual PROTAC degrader probe of CDK isoforms. *Eur J Med Chem*, 187:111952.
https://doi.org/10.1016/j.ejmech.2019.111952

Zhou K, Zhuang SK, Liu FL, et al., 2022. Disrupting the Cdk9/Cyclin T1 heterodimer of 7SK snRNP for the Brd4 and AFF1/4 guided reconstitution of active P-TEFb. *Nucleic Acids Res*, 50(2):750-762.
https://doi.org/10.1093/nar/gkab1228

Zhou YF, Wang J, Deng MF, et al., 2019. The peptide-directed lysosomal degradation of CDK5 exerts therapeutic effects against stroke. *Aging Dis*, 10(5):1140-1145.
https://doi.org/10.14336/AD.2018.1225

Supplementary information

Tables S1 and S2