REVIEW

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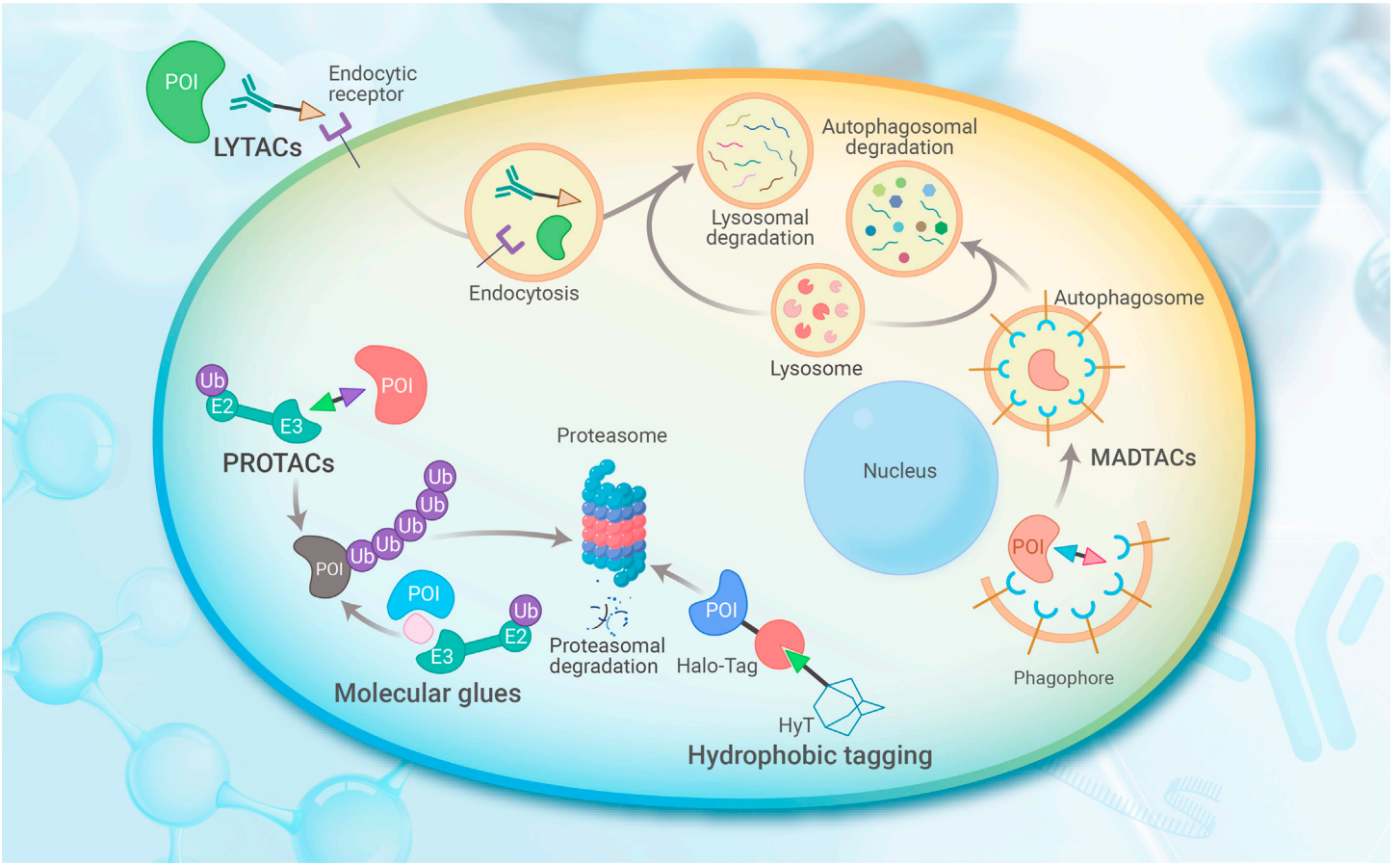
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Targeted protein degradation provides new opportunities for cancer therapy.
- Proteolysis-targeting chimeras (PROTACs) can target “undruggable” proteins.
- PROTAC drugs have entered the clinic and have the potential to become “best in class”.

REVIEW

Targeted protein degradation in cancers: Orthodox PROTACs and beyond

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Targeted protein degradation (TPD) is emerging as a strategy to overcome the limitations of traditional small-molecule inhibitors. Proteolysis-targeting chimera (PROTAC) technology can be used to target proteins by hijacking the ubiquitin-proteasome system. Conceptually, PROTAC aims to target the "undruggable" majority of proteins in the human proteome. Through constant exploration and optimization of PROTACs and the exploitation of other TPD strategies over two decades, TPD has expanded from theoretical studies to clinical strategies, with practical applications in oncological, immunological, and other diseases. In this review, we introduce the mechanisms, features, and molecular targets of orthodox PROTACs and summarize the PROTAC drugs under study as cancer therapeutics in clinical trials. We also discuss PROTAC derivatives and other TPD strategies, such as lysosome-targeting chimeras, autophagy-targeting chimeras, and molecular glue strategies. Collectively, the studies summarized herein support the full potential of TPD in the biomedical industry.

INTRODUCTION

Proteins play essential roles in processes that control the health and survival of cells. Accordingly, any abnormality in a protein can affect its constitution, functionality, homeostasis, and/or other properties, leading to various diseases.[1] Studies have shown that proteins comprise the most important class of drug targets.[2] In the past 20 years, efforts to inhibit or disrupt the biological functions of target proteins have led to several targeted cancer therapies, such as antibodies and small-molecule inhibitors (SMIs).[3,4] Antibodies have been widely used in cancer treatment because of their biological specificity.[5] However, antibodies have a high molecular weight and low permeativity and, thus, primarily target membrane-associated proteins, which has limited their clinical application.[6,7] According to the US Food and Drug Administration (FDA) database, 52 SMIs targeting protein kinases have been identified via large-scale screening and optimization efforts. These SMIs inhibit the biological activity of their target proteins by binding to the active sites of the proteins.[8,9] Compared with antibodies, SMIs have much lower molecular weights and are more suitable for targeting intracellular, membrane-associated, and extracellular proteins. However, SMI therapy faces a significant disadvantage: long-term administration of these drugs increases the risk of developing resistance via mutations in the protein targets.[10]

Approximately 16,000 proteins with no targeted active sites have been identified, accounting for 85% of the human proteome. These proteins, which include pseudokinases, transcription factors, and scaffolding proteins or adaptors, have long been known as undruggable targets.[11–14] Gene knockdown techniques, such as RNA interference and the CRISPR-Cas9 system, have been used to expand the range of druggable targets. However, the nucleic acid-based molecules used in these approaches face significant challenges, such as instability, poor cell permeativity, and inefficiency due to enzyme-catalyzed hydrolysis.[15–17] To overcome these problems, attention has increasingly been directed toward novel strategies that exploit the physiological protein degradation machinery, including the ubiquitin-proteasome system (UPS)-mediated proteolysis-targeting chimera (PROTAC),[18,19] autophagy-lysosome pathway-mediated autophagy-targeting chimera (AUTAC),[20] and endosome-lysosome pathway-mediated lysosome-targeting chimera (LYTAC);[21] molecular glue; and other PROTAC derivatives.[22–24]

In this review, we discuss the development and derivatives of PROTACs. In addition, we review the drug-discovery applications of PROTACs and other targeted protein degradation (TPD) strategies in academia and industry.

THE DEVELOPMENT OF PROTACs

The ubiquitin-proteasome system

In eukaryotic cells, the UPS is one of the primary pathways through which intracellular proteins are degraded to maintain cell homeostasis.[25,26] The UPS consists of ubiquitin (Ub), enzymes, the proteasome, and specified substrates that play crucial roles in various cellular metabolic processes, such as the regulation of cell signaling and transcription and protein turnover.[27,28] Ubiquitin, a highly evolutionarily conserved protein, is a 76-amino-acid polypeptide that is used to mark target proteins for proteolysis in the UPS. Protein ubiquitination is carried out via a reversibly ubiquitinating enzymatic cascade comprising the E1 ubiquitin-activating enzyme (E1), E2 ubiquitin-conjugating enzyme (E2), and ubiquitin (E3) ligase. E1 activates ubiquitin for conjugation and transfers it to an E2. Through catalysis by E3 ligase, ubiquitin is transferred directly from E2 to a substrate protein via the ε-amino group on a lysine residue or the N terminus. Ubiquitin comprises seven lysine residues and an N-terminal methionine residue, which allow further ubiquitination to form a polyubiquitin chain via E3 ligase.[29] A polyubiquitinated protein can be recognized by the 26S proteasome, transported to the 20S proteasome, and hydrolyzed into oligopeptides via various enzymes, which are eventually released from the proteasome (Figure 1A).[30,31]

The mechanism of action of PROTACs

PROTACs have attracted considerable attention owing to their great potential for use in cancer treatment.[32] In this strategy, the PROTAC, a heterobifunctional molecule, contains a "warhead" specific for a protein of interest (POI) and a ligand for an E3 ligase, which are joined by an intermediate linker. The PROTAC can simultaneously engage an E3 ubiquitin ligase and a POI in an event-driven manner (Figure 1B). This spatial proximity allows for the ubiquitination and subsequent proteasomal degradation of the POI. Rather than being directly degraded, PROTAC molecules are recycled to target other proteins.[33,34] The PROTAC system has opened up a new and promising drug-development pathway, leading to remarkable achievements, such as the reversal of drug resistance,[35,36] targeting of "undruggable" proteins,[37,38] and enhancement of drug selectivity and specificity.[39,40]

Structural analysis of PROTACs

The formation of a stable, high-affinity ternary complex (POI-PROTAC-E3 ligase) is a key step in the mechanism of action (MOA) of PROTAC. Ciulli and colleagues were the first to solve the crystal structure of a ternary complex comprising $BRD4^{BD2}$ (BRD4, a member of the bromo- and extraterminal [BET] family proteins; $BRD4^{BD2}$, the second bromodomain [BD] of BRD4), MZ1, and VCB (VHL [von Hippel-Lindau protein], ElonginC, and ElonginB) at a 2.7-Å resolution (PDB: 5T35).[41] MZ1, which consists of the BET inhibitor JQ1, VHL ligand VH032, and a polyethylene glycol (PEG) linker, is bound within a bowl-shaped interface formed by extensive protein-protein interactions (PPIs) between $BRD4^{BD2}$ and VHL.[42] The bowl-shaped interface is formed mainly from hydrophobic and electrostatic contacts between proteins and ligands and PPIs, including (1) the formation of a WPF shelf (W374, P375, F376) and an extended PWPF (P71, W374, P375, F376) shelf via the interaction of $BRD4^{BD2}$ with VHL, (2) the

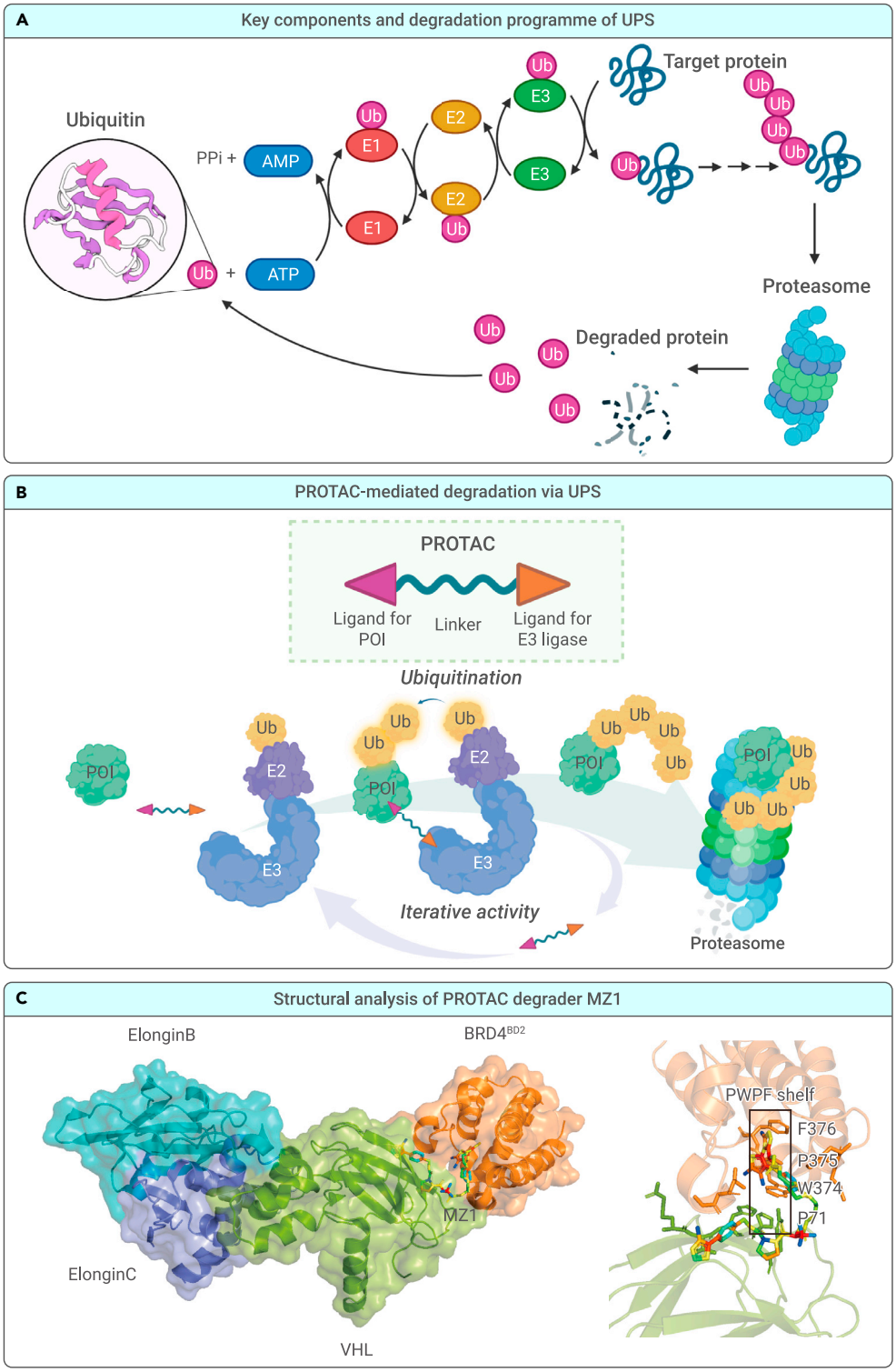

Figure 1. Background information on PROTACs

interaction between the helical turn of $BRD4^{BD2}$ and the hydrophobic side chains of VHL, (3) the embedding of JQ1 in the acetyl-lysine binding pocket of $BRD4^{BD2}$ and binding of VHL032 to the hydroxyproline binding site of VHL, and (4) van der Waals interactions and a hydrogen bond due to an interaction with the PEG linker. With this system, stabilized and selective target degradation is attributed to the extensive burial of the ternary complex surface area (from 1,933 to 2,621 $Å^2$) and the formation of new PPIs (Figure 1C).[41]

A few other examples of the X-ray crystal structures of ternary complexes are available. Fischer and colleagues solved multiple X-ray structures of BRD4-PROTAC-$CRL4^{CRBN}$ (CRBN, cereblon) complexes and showed that plasticity results in several distinct low-energy binding conformations selectively bound by ligands (PDB: 5FQD).[43] The ternary complex crystal structures of ACBI1, a potent and cooperative PROTAC of SMARCA2/4 and PBRM1, have also been solved by the Ciulli team, who optimized the structures rationally using biophysical data (PDB: 6HAY).[44]

Characteristics of PROTACs

Crews and Deshaie's group pioneered the concept of PROTACs in 2001 with PROTAC-1. PROTAC-1 was shown to simultaneously bind methionine aminopeptidase-2 (MetAP2) and the E3 ligase Skp1-Cullin-F $box^{\beta\text{-TrCP}}$ ($SCF^{\beta\text{-TrCP}}$) to induce degradation of MetAP2 in a crude cell extract.[45] However, peptide-based PROTACs have poor chemical stability and cellular permeativity, which limits their clinical applications.[46] Small-molecule-based PROTACs take advantage of small molecules to engage E3 ligases, thus advancing the development of PROTAC technology. Some small-molecule ligands of common E3 ligases, including mouse double minute 2 homolog (MDM2), inhibitors of apoptosis (IAPs), VHL, and CRBN, have been reported.[47–50]

Given its unique MOA, a PROTAC does not need to bind within the target of a functionally bioactive site to achieve degradation of the POI. PROTACs have been verified as a feasible option for targeting proteins with scaffolding functions[51,52] or mutations,[53,54] as well as those that are overexpressed,[55,56] aggregated, or present in different isoforms,[57–60] and thus can overcome the limitation of traditional SMIs, which are not capable of effective and selective employment. Most orthodox PROTACs are used in the field of oncology (Table S1), and this use is described and discussed in detail in later sections. In addition to PROTACs that target various cancer-related proteins, PROTACs relevant to hematology, immunology, neurology, and antiviral treatment have been the focus of active research in academia and industry,[37,61–63] but are not introduced in this review.

TARGETING VARIOUS MOLECULES USING ORTHODOX PROTACs

Targeting receptor tyrosine kinases (RTKs)

RTKs, a subgroup of tyrosine kinases, are embedded in cell membranes and mediate intercellular communication. Dysregulation of RTKs has been correlated with many diseases, especially cancer. Chromosomal rearrangements, gain-of-function mutations, overexpression, and genomic amplification are the main factors contributing to the oncogenic activation of RTKs and leading to resistance to pharmaceutical inhibitors.[64] To date, most PROTAC warheads have been inhibitors that act as ligands to recruit POIs. Viable PROTAC strategies to degrade RTKs, such as anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor 2 (VEGFR-2), and tropomyosin receptor kinase (TRK) family members, have been validated (Figure 2; Table S1). Alectinib-based degrader 17 was shown to exhibit potent ALK-binding affinity and antiproliferative activity in an ALK-dependent cell line, but not in exclusively ALK fusion-negative cells.[65] The ability of compounds 2/10 to induce EGFR degradation, with respect to the half-maximal degradation concentration (DC_{50}) values of 45.2 and 34.8 nM, and induce apoptosis in a cell line lacking *EGFR* exon 19 has been

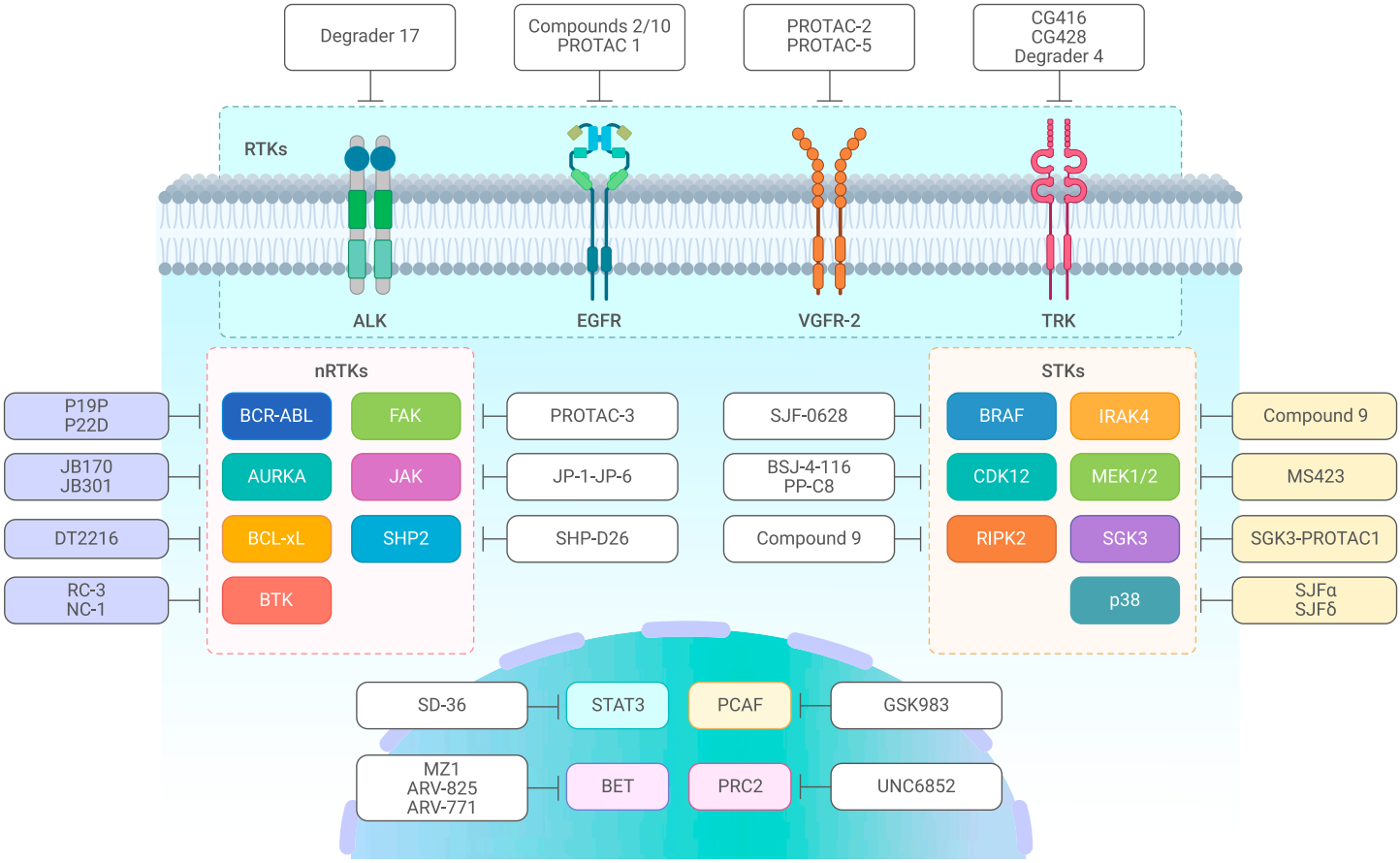

Figure 2. PROTACs of different POIs

validated.[66] Binding of a lapatinib-based PROTAC-1 to a VHL ligand effectively induces the degradation of wild-type and FLAG-labeled exon-20-mutated EGFR.[67] A series of selective $EGFR^{L858R/T790M}$ degraders exclusively target mutated EGFR, with nanomolar DC_{50} values, but do not degrade wild-type EGFR.[67–69] PROTACs based on the antiangiogenesis agents S7 and ABT-869, especially PROTAC-2 and PROTAC-5, have been shown to induce a specific decrease in VEGFR-2 levels and exhibit considerable antiproliferative activity against human umbilical vein endothelial cells.[70] Compounds 5 (CG416) and 6 (CG428) induce the selective degradation of the TPM3-TrkA fusion protein.[71] CRBN-based degrader 4 was shown to induce TrkC degradation in breast cancer cells, with an estimated DC_{50} value of 0.1–1.0 μM.[72] PROTACs that target other RTKs are listed in Table S1.

Targeting non-receptor tyrosine kinases (nRTKs)

Another subgroup of tyrosine kinases, nRTKs, includes cytosolic enzymes involved in signal transduction in activated T and B lymphocytes, the dysregulation of which can lead to hematological malignancies, such as lymphomas, leukemias, and myelomas. Point mutations resulting in oncogene formation and chromosomal translocation caused by gene fusion can cause the aberrant activation of nRTKs.[73] VHL-, CRBN-, or IAP-based PROTACs can degrade various nRTKs, including the BCR-ABL fusion gene, aurora kinase A (AURKA), B cell lymphoma 2 (BCL-2) and BCL-extra large (BCL-xL), induced myeloid leukemia cell differentiation protein (MCL-1), Bruton's tyrosine kinase (BTK), focal adhesion kinase (FAK), Janus kinase (JAK), and Src homology 2 (SH2) domain-containing phosphatase 2 (SHP2), and these PROTACs have been shown to induce cytotoxicity in multiple types of hematological tumor cells (Figure 2; Table S1). Ponatinib- and dasatinib-based PROTACs P19P and P22D have been developed to degrade the mutant protein ABL^{T315I} and thus overcome resistance to dasatinib and asciminib.[74] The thalidomide-based degraders JB170 and JB301 induce highly specific AURKA degradation at a nanomolar scale, causing profound toxicity in MV4-11 cells.[75,76] The PROTAC DT2216, which is currently being studied in a clinical trial, links the relative inhibitor ABT263, which binds BCL-2 and BCL-xL, to a VHL ligand. DT2216 has been shown to specifically target BCL-xL and exhibit increased antitumor activity and reduced platelet toxicity compared with ABT263, the BCL-xL inhibitor.[77,78] The reversible non-covalent PROTAC NC-1 has been reported to be a potent degrader that induces the depletion of wild-type and some mutated forms of BTK in chronic lymphocytic leukemia (CLL) cells from patients *in vitro*.[79] Compared with NC-1, the reversible covalent PROTAC RC-3 displays enhanced selectivity toward BTK.[80] The defactinib-based PROTAC-3 effectively degraded FAK and suppressed its activity (autophosphorylation of Y397) in the PC-3 cell line. PROTAC-3 has been shown to reduce the invasiveness of MDA-MB-231 cells by ~65%, whereas no obvious effect was observed with defactinib treatment.[81] The inhibitors pyrimidine 1 and quinoxaline 2 have been chosen as warheads that selectively bind JAKs.[82] The PROTACs JP-1 to JP-6, which bear IAP ligands, have been validated as efficient inducers of JAK1 and JAK2 degradation.[83] VHL-based SHP2-D26 mediates the depletion of SHP2, leading to a decrease in the level of the downstream protein pERK, with half-maximal inhibitory concentration (IC_{50}) values of 0.66 μM and 9.9 nM in the KYSE-520 and MV4-11 cell lines, respectively.[82] PROTACs that target other nRTKs are listed in Table S1.

Targeting serine/threonine protein kinases (STKs)

STKs are characterized by their ability to phosphorylate serine or threonine residues, and they play roles in cell proliferation, differentiation, programmed cell death, and embryonic development. For example, $BRAF^{V600E}$, an oncogenic mutant of BRAF that monomerically transmits a signal in the absence of activated RAS, is selectively degraded by SJF-0628, a vemurafenib-based PROTAC that does not affect the wild-type form or other RAF family members, such as ARAF and CRAF.[84] PROTACs that target cyclin-dependent kinase 12 (CDK12), such as BSJ-4-116 and PP-C8, have been reported to degrade functional mutants of CDK12.[85,86] However, two CDK12 mutations have exhibited resistance to BSJ-4-116, demonstrating a potential mechanism by which tumor cells can evade TPD.[85] Compound 9, a conjugate of interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitor 1, which binds to IRAK4, and pomalidomide, which binds to

CRBN, induces substantial degradation of IRAK4 in the ABC-diffuse large B cell lymphoma (DLBCL) cell lines OCI-LY10 and TMD8.[87] PROTAC_RIPK2 was shown to degrade receptor-interacting serine/threonine protein kinase 2 (RIPK2) in a highly specific manner, and at nanomolar concentrations, it leads to a decrease in the level of downstream mitogen-activated protein kinase (MAPK) in a VHL-dependent manner.[88] Degrader 23 (MS423), which is composed of PD0325901 and a VHL ligand, inhibits mitogen-activated protein kinase kinases 1/2 (MEK1/2) kinase activity *in vitro* and degrades target proteins in colorectal cancer (CRC) and melanoma cell lines, leading to decreases in the levels of p-MEK and p-ERK and inhibition of the proliferation of CRC and melanoma cell lines.[89] PROTACs SJFα and SJFδ have been shown to degrade the p38 MAPK family isoforms p38α and p38δ, respectively.[90] SJFδ has been shown to target both wild-type and mutant $p38\delta^{K220E/T221E}$. SGK3-PROTAC1 mediates the selective degradation of serum/glucocorticoid regulated kinase family member 3 (SGK3), but not SGK1/2, at a DC_{50} of <100 nM.[91] Combination therapy with PI3K inhibitors and SGK3-PROTAC1 at a micromolar concentration has been shown to outperform the effects of a conventional PI3K inhibitor (GDC0941) in the CAMA-1 breast cancer cell line (Figure 2).[91] PROTACs that target other STKs are listed in Table S1.

Targeting proteins in transcriptional regulation

Transcription factors (TFs) work alone or with other proteins in complexes to regulate gene transcription and thus contribute to cell-fate determination. Historically, TFs have been classified as undruggable targets due to their smooth surface structure and lack of a pocket resulting from protein-DNA interactions or PPIs.[92] Nuclear hormone receptors, such as estrogen receptor (ER), androgen receptor (AR), retinoic acid receptor (RAR), and cellular retinoic acid-binding protein (CRABP), have been reported as targets of PROTACs.[47,56,93,94] SD-36, a conjugate of the signal transducer and activator of transcription 3 (STAT3) inhibitor SI-109 and a CRBN ligand, is the first reported selective degrader of STAT3 protein. It has been shown to achieve complete and continuous tumor suppression in a Molm-16 mouse xenograft model at well-tolerated dose schedules.[95] In addition to targeting TFs, PROTECs are designed to target epigenetic-related proteins, such as BET family members (BRD2/3/4/7/9), P300/CBP-associated factor (PCAF), histone deacetylases (HDACs), and Polycomb repressive complex 2 (PRC2), as dysregulation of these proteins and, subsequently, the epigenome promotes cancer onset and progression (Table S1).[96] For example, SMIs (JQ1 and I-BET726) and typical PROTACs (MZ1, ARV-825, and ARV-771) have been shown to target BET family members and inhibit downstream oncogene expression.[41,57,58,97–99] The PROTAC GSK983 mediates the degradation of PCAF and its homologous protein general control non-derepressible 5 (GCN5) in a concentration-dependent manner in both macrophages and monocyte-derived dendritic cells, leading to a reduction in inflammatory cytokine production.[100] UNC6852, which selectively degrades PRC2, has been shown to reduce the levels of EZH2, EED, and SUZ12, leading to a decrease in the level of trimethylation of lysine 27 on histone H3 (H3K27me3). UNC6852 inhibits the proliferation of DB and Pfeiffer cells (DLBCL-related cell lines bearing mutated EZH2) (Figure 2).[101] PROTACs that target other proteins involved in transcriptional regulation are listed in Table S1.

CLINICAL PROOF OF CONCEPT FOR ORTHODOX PROTACs

AR-PROTACs

Bavdegalutamide (ARV-110; Arvinas) is a first-in-class PROTAC that has been shown to degrade wild-type AR and several forms of mutant AR (T878A, T878S, H875Y, F877L, and M895V), leading to a prostate-specific antigen level decline ≥50% (PSA_{50}) rate in 46% of patients. Patients receiving ARV-110 treatment have achieved tumor reductions, suggesting that this PROTAC may be useful as a form of precision medicine for metastatic castration-resistant prostate cancer (mCRPC). However, bavdegalutamide cannot penetrate the blood-brain barrier (BBB). Furthermore, it does not degrade AR^{L702H}, a form of AR containing a point mutation that is present in 3%–10% of patients with mCRPC, or AR-V7, a splice variant that lacks the ligand binding domain of AR.[102] AC0176 (Accutar Biotech) potently degrades both wild-type AR and the prevalent AR mutants (e.g., L702H, T878A, H875Y, W742, and C247) associated with drug resistance to current AR-targeted therapies. CC-94676 (AR-LDD; Bristol Myers Squibb) is another AR-PROTAC with preclinical activity similar to that of ARV-110 in terms of its favorable pharmacokinetic properties, ability to effectively degrade AR, and ability to induce continuous tumor regression in a VCaP mouse model (sources: public data from the companies) (Table 1).

ER-PROTACs

ARV-471 (Arvinas) is believed to be the only trial of an ER-targeting therapy requiring prior CDK4/6 treatment for all patients. ARV-471 is well tolerated at doses ranging from 30 to 700 mg, but the dose-limiting toxicity (DLT) and maximal tolerated dose (MTD) have not yet been determined. Recently, ARV-471 was shown to yield a clinical benefit rate of 38% in evaluable patients and it has continued to show a favorable tolerability profile in its phase II expansion trial.[103] AC0682 (Accutar Biotech) has been shown to potently and selectively degrade both wild-type and mutant forms of ERα. AC0682 has favorable pharmacological properties, can penetrate the BBB, and may offer a new form of breast cancer treatment with an MOA distinct from that of fulvestrant (sources: public data from the companies) (Table 1).

BRD9-PROTACs

CFT8634 (C4 Therapeutics) is a highly selective BRD9-PROTAC currently being investigated in a phase I clinical trial. It has been shown to specifically inhibit the growth of SMARCB1-perturbed (SMARCB1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1) cells and to be robustly effective in a clinically relevant patient-derived synovial sarcoma (SS) xenograft model.[104] FHD-609 (Foghorn Therapeutics) is an intravenous BRD9-PROTAC under investigation to determine the primary (DLT and adverse events) and secondary outcome measures (pharmacokinetics [PK], objective response rate, duration of response, time to response, progression-free survival, and overall survival) (sources: public data from the companies) (Table 1).

IRAK4-PROTACs

KT-474 (Kymera/Sanofi) selectively degrades IRAK4. It has been shown to reduce IRAK4 expression levels in peripheral blood mononuclear cells (PBMCs) and block cytokine induction at considerably lower doses than those required for toll-like receptor (TLR) agonists. At day 14, KT-474 shows consistent degradation of 92% at the lowest dose level (25 mg) and 96%–98% at the two highest dose levels (100 and 200 mg). KT-474, delivered in multiple doses, has been shown to be well tolerated in blood and skin for at least 14–21 days. KT-413 (Kymera) is a CRBN-based IRAK4 degrader that is being investigated in a phase I clinical trial to determine its safety, PK/pharmacodynamics (PD), and preliminary efficacy in DLBCL and to explore its target knockdown and downstream effects in PBMCs and tumors (sources: public data from the companies) (Table 1).

Other PROTACs

KT-333 (Kymera) degrades STAT3 and is expected to receive investigational new drug (IND) clearance for evaluation of its metrics in liquid (e.g., peripheral T cell lymphoma, cutaneous T cell lymphoma, large granular lymphocytic leukemia) and solid tumors. KT-253 (Kymera) is an MDM2 degrader that stabilizes p53, as wild-type p53 exists in approximately 50% of tumor cells. KT-253 shows antitumor activity at picomolar concentrations, with a potency >200-fold greater than that of clinically active MDM2 SMIs. It achieves its effects by blocking the feedback loop, which upregulates MDM2 production and drives tumor cells to undergo rapid apoptosis. CFT1946 (C4 Therapeutics) is an on-mechanism, CRBN-based PROTAC that selectively degrades $BRAF^{V600X}$; it was shown to potently inhibit MAPK signaling and promote tumor regression in a $BRAF^{V600E}$ A375 xenograft mouse model. CFT1946 also acts against $BRAF^{V600E}$/$NRAS^{Q61K}$, a model of clinical resistance to BRAF inhibitors, and has exhibited potential efficacy as a TPD-based therapy in non-V600X-mutated BRAF-driven cancers. CFT7455 (C4 Therapeutics) is a potent small molecule that degrades IKZF1/3. It has been shown to exhibit enhanced catalytic activity, resulting in a >1,000-fold improvement in potency compared with pomalidomide, and has been shown to be efficacious in a model of systemic multiple myeloma. NX-2127 (Nurix Therapeutics) is a heterobifunctional, orally administered, CRBN-based BTK degrader that has been shown to catalyze the neo-substrate degradation of IKZF1/3 in DLBCL cell lines, including cells harboring the ibrutinib-resistance mutation BTKC481S, and in the cynomolgus monkey.[105] NX-5948 (Nurix

Table 1. Ongoing clinical trials of bifunctional degraders (PROTACs)

Clinical trial NCT no.	Highest phase	Degrader	ROA	POI	E3 ligase	Indications	Sponsor
NCT03888612	II	ARV-110	oral	AR	CRBN	PC	Arvinas
NCT05067140	I	ARV-766	oral	AR	undisclosed	PC	Arvinas
NCT05241613	I	AC0176	oral	AR	undisclosed	PC	Accutar Biotech
NCT04428788	I	CC-94676	oral	AR	CRBN	PC	Bristol Myers Squibb
NCT05252364	I	HP518	oral	AR	undisclosed	PC	Hinova
NCT05428449	I	GT20029	topical	AR	undisclosed	acne vulgaris, androgenetic alopecia	Kintor
NCT04072952	II	ARV-471	oral	ER	CRBN	BC	Arvinas/Pfizer
NCT05080842	I	AC0682	oral	ER	CRBN	BC	Accutar Biotech
NCT05487170	II	RNK05047	i.v.	BRD4	chaperone	DLBCL	Ranok
	IND-e	CFT8634	oral	BRD9	CRBN	SS, SMARCB1-null solid tumors	C4 Therapeutics
NCT04965753	I	FHD-609	i.v.	BRD9	undisclosed	SS	Foghorn Therapeutics
NCT04772885	I	KT-474	oral	IRAK4	undisclosed	multiple immunoinflammatory diseases: HS, AD, RA, others	Kymera/Sanofi
NCT05233033	I	KT-413	i.v.	IRAK4	CRBN	MYD88-mutant DLBCL	Kymera
NCT04830137	I	NX-2127	oral	BTK	CRBN	B cell malignancies	Nurix Therapeutics
NCT05131022	I	NX-5948	oral	BTK	CRBN	B cell malignancies and autoimmune diseases	Nurix Therapeutics
NCT04861779	I	HSK29116	oral	BTK	undisclosed	B cell malignancies	HAISCO
NCT05006716	I	BGB-16673	oral	BTK	undisclosed	B cell malignancies	BeiGene
NCT05225584	I	KT-333	i.v.	STAT3	undisclosed	liquid and solid tumors	Kymera
NCT04886622	I	DT2216	i.v.	BCL-xL	VHL	liquid and solid tumors	Dialectic Therapeutics
	IND-e	CFT8919	oral	$EGFR^{L858R}$	CRBN	NSCLC	C4 Therapeutics
CTR20222742	II	CG001419	oral	TRK	CRBN	cancer and other indications	Cullgen
	IND-e	CFT1946	oral	$BRAF^{V600X}$	undisclosed	melanoma, CRC, NSCLC	C4 Therapeutics
	IND-e	KT-253	undisclosed	MDM2	undisclosed	liquid and solid tumors	Kymera

AD, atopic dermatitis; AR, androgen receptor; BC, breast cancer; BCL-xL, B cell lymphoma-extra large; BRD9, bromodomain-containing protein 9; BTK, Bruton's tyrosine kinase; CRBN, cereblon; CRC, colorectal cancer; DLBCL, diffuse large B cell lymphoma; EGFR, epidermal growth factor receptor; ER, estrogen receptor; HS, hidradenitis suppurativa; IND-e, in IND-enabling preclinical studies; IRAK4, interleukin-1 receptor-associated kinase 4; i.v., intravenous; MDM2, mouse double minute 2 homolog; NSCLC, non-small-cell lung cancer; PC, prostate cancer; PROTAC, proteolysis-targeting chimera; RA, rheumatoid arthritis; ROA, route of administration; SS, synovial sarcoma; STAT3, signal transducer and activator of transcription 3; TRK, tropomyosin receptor kinase; VHL, von Hippel-Lindau.

Therapeutics) degrades BTK and has been shown to penetrate the BBB in preclinical models to degrade BTK in both microglia and CNS-resident lymphoma cells and to exert antilymphoma activity in a primary model of CNS lymphoma. CFT8919 (C4 Therapeutics) specifically induces $EGFR^{L858R}$ degradation at low (nanomolar) concentrations without affecting wild-type EGFR, and its activity is equivalent to that of EGFR inhibitors. CF8919 has been shown to have antitumor activity in multiple tumor models, including NCI-H1975 $EGFR^{L858R/T790M}$ xenograft, BaF3 allograft, and H1975-LUC ($EGFR^{L858R/T790M}$) brain metastasis models (sources: public data from the companies) (Table 1).

MAJOR CONCERNS OF PROTAC

The "hook effect"

A PROTAC forms a cooperative ternary complex to degrade its target. At concentrations above a certain threshold, however, PROTACs tend to form ineffective binary complexes (e.g., PROTAC-POI or PROTAC-E3 ligase) (Figure 3). The competition between these binary and active ternary complexes (e.g., POI-PROTAC-E3 ligase) is described as the "hook effect" and it reduces the degradation efficiency of the PROTAC.[90,106] The hook effect reduces the potency of the PROTAC, and it typically occurs at micromolar concentrations and is difficult to evade.[83,99,107] Unfortunately, *in vivo* data on the hook effect are scarce, and the MTDs identified from preclinical profiles in animal studies indicate that the PROTAC concentration threshold may be too high to enable adequate degradation of POIs.[108,109] To confirm the most appropriate doses, PROTACs should be tested over a wide concentration gradient *in vitro* and *in vivo*. Intriguingly, the study of ligand-bound structures can promote the design of next-generation PROTACs. By modifying some components, PROTACs can be used to form new ligand-induced PPIs, yielding PROTAC catalytic activity via a principle similar to enzyme-substrate convergence.[110] AT1, a structure-designed compound, was developed by updating the BET degrader MZ1 and it possesses a more stable ternary complex (POI-PROTAC-E3 ligase) and a higher hook effect threshold.[41]

Low tissue/cell permeativity

PROTACs are iterative (Figure 3) and, unlike SMIs, degrade POIs in an event-driven, rather than occupancy-driven, manner. Most known orthodox PROTACs are beyond Lipinski's rule of five, which helps distinguish the druggability of molecular determinants with undesirably high molecular weights (1,000–2,000 Da). PROTACs have high molecular weights, and the resulting low permeativity and solubility contribute to their lack of ideal cellular uptake and target degradation, as well as a high rate of active transporter-mediated efflux (Figure 3).[111] The

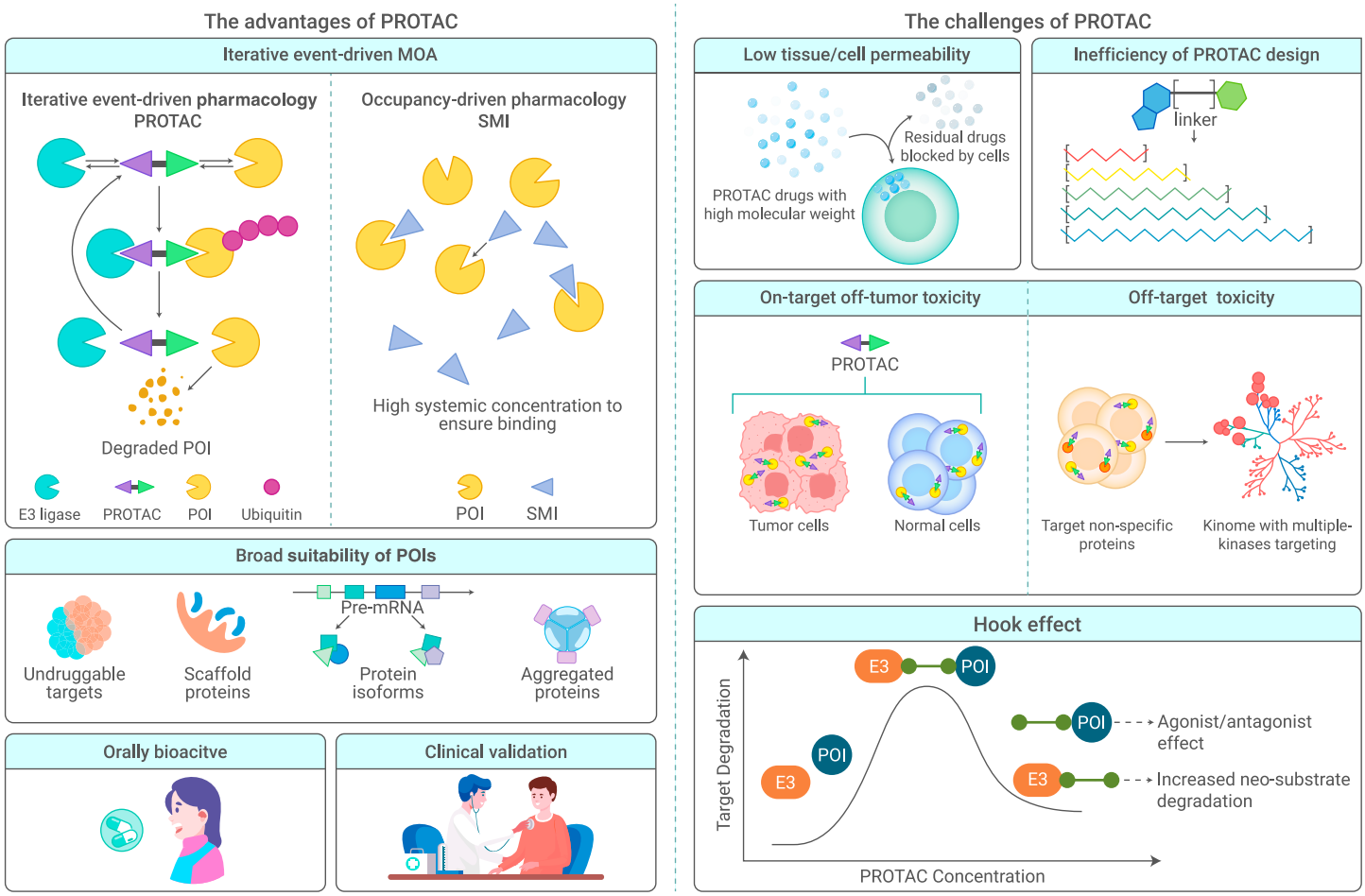

Figure 3. The advantages and challenges of PROTACs

highly polar surface of a PROTAC limits its ability to cross physiological barriers and cell membranes. In clinical settings, CRBN is strongly preferred over other E3 ligases due to its lower molecular weight, fewer hydrogen bond donors, and smaller number of rotatable bonds, even though VHL-based PROTACs are more likely than other PROTACs to form functional ternary structures.[112] Various properties of PROTAC-delivery agents (e.g., prodrugs, nanoparticles, and protein- or nucleic acid-based formulations), such as their ability to improve solubility, intracellular accumulation, and site-specific distribution and minimal side effects, have been summarized.[113] The problem of cell permeativity has been addressed by attaching cell-permeative peptides (e.g., poly-D-arginine sequences) to E3 ligands.[46] Furthermore, an in-cell click-formed proteolysis-targeting chimera (CLIPTAC) contains two individual precursors—one each is bound to POI and E3 ligase—that form a heterobifunctional molecule intracellularly via a bio-orthogonal "click" reaction (Figure 4). Upon entering cells, a tetrazine-tagged thalidomide derivative (Tz-thalidomide) and TCO-tagged inhibitor of POI can self-assemble to recruit CRBN to the POI, thus triggering its ubiquitination and degradation.[114] Compared with a high-molecular-weight compound, it is easier for two compounds with lower molecular weights to enter a cell. In addition to the direct modification of PROTACs, nanoparticles can be used to improve the action of PROTACs. The encapsulation of PROTACs with different modified nanoparticles was shown to increase tumor permeability via the enhanced permeability and retention (EPR) effect controlled by delivering high concentrations of PROTACs. The improved cell permeability relies on the MOA of nanoparticles via endocytosis with reduced PROTAC metabolism.[115]

Inefficiency of PROTAC design

Traditionally, PROTAC design has required extensive experiments and trials, and the generation of linkers has played a crucial role in the physiochemical properties and degradation activities of PROTACs.[55,116] As the development of POI warheads and E3 is fundamentally identical to that of other small molecules, *de novo* linker design methods, such as a graph-based deep generator (DeLinker) and a language model (SyntaLinker), are emphasized and exploited to fill the gap in linker generation.[117,118] However, the open-source database of PROTACs is small (~2,300 PROTACs),[119] and thus, linkers designed using these *de novo* methods are not practical for developing druggable PROTACs. Hence, it is difficult to train a model capable of designing PROTACs with ideal properties and activity both *in vitro* and *in vivo*. PROTAC-RL, a novel deep generative model for rational PROTAC design, combines an augmented transformer architecture with memory-assisted reinforcement learning (RL). As a proof of concept, 5,000 PROTACs were generated to target BRD4 during a 49-day discovery period, and one exclusive candidate was validated to have antiproliferative activity *in vivo*.[120] The biotech company Differentiated Therapeutics built Auto/dx, a unique platform that integrates proprietary protein interaction dynamics, AI, and synthetic biology methodologies for molecular simulation. The company announced the completion of a $5 million seed financing round. The combination of drug discovery and cutting-edge computational tools is likely to be essential for advancing the development of TPD strategies (Figure 3).

Expansion of the E3 ligase landscape

Peptide-based E3 ligands are used to recruit β-TrCP and VHL, but their use is restricted due to poor cell permeativity. Although more than 600 human-genome-encoded E3 ligases have been identified, the lack of specific high-affinity ligands has limited the scope of application of PROTAC technology.[121] Further exploration of E3 ligases is needed to address the following challenges: (1) in tumor cells, drug resistance inactivates degraders; (2) resistance to components of immunomodulatory imide drugs (IMiDs), such as pomalidomide, lenalidomide, and thalidomide, cause genomic alterations that affect neo-substrates (IKZF1/IKZF3)[122]; and (3) there is a lack of effective E3 ligases known to be exclusive to tumor cells. Beyond the ligases initially used in PROTAC technology (CRBN,

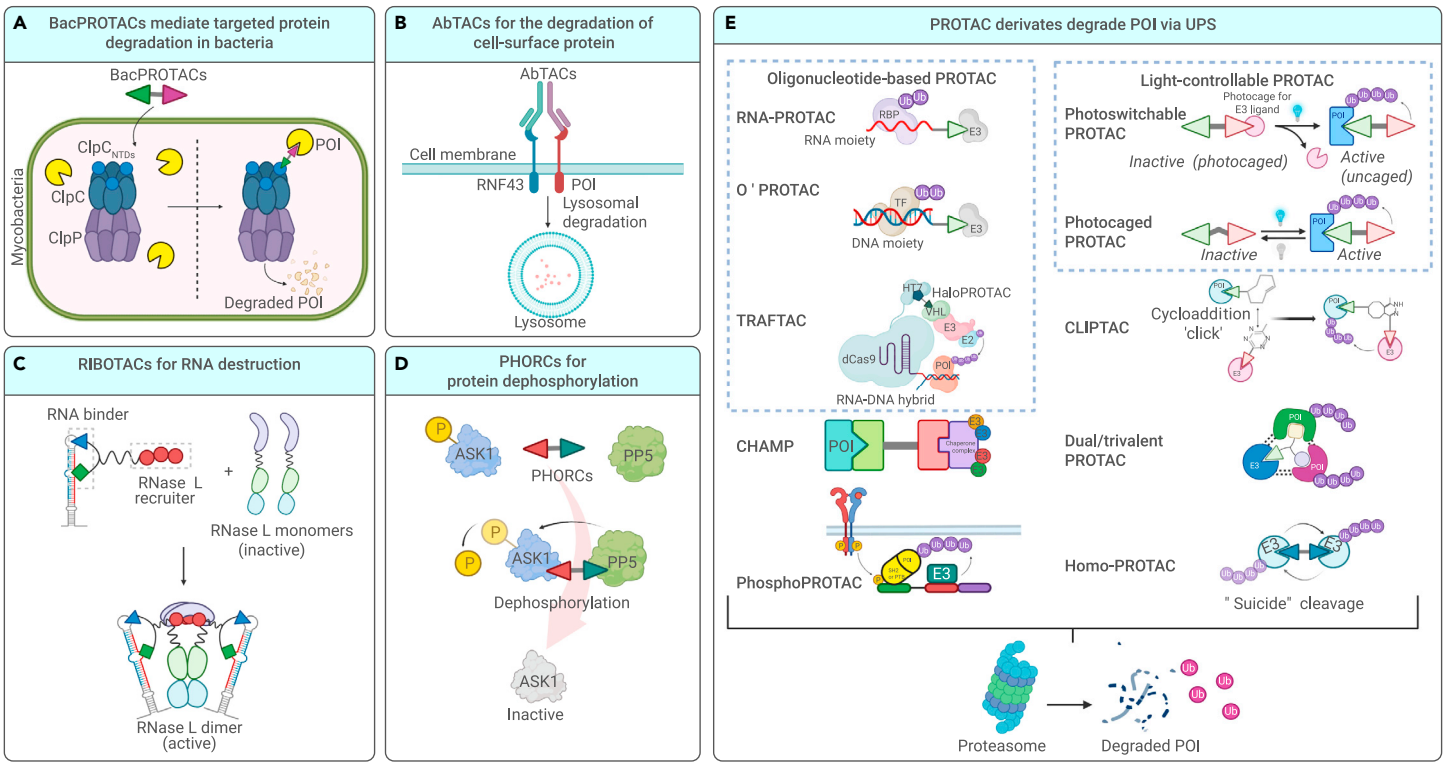

Figure 4. Derivates from orthodox PROTACs

VHL, MDM2, and IAP), other E3 ligases may be useful in PROTAC development and other TPD strategies. These include damage-specific DNA binding protein 1 (DDB1)-CUL4-associated factor 16 (DCAF16), DCAF15, ring-finger protein 4 (RNF4), RNF114, Kelch-like ECH-associated protein 1 (KEAP1), fem-1 homolog B (FEM1B), and the aryl hydrocarbon receptor (AhR) (Table 2).

On-target off-tumor toxicity

On-target toxicity commonly results from interactions of the drug with its intended target. In the context of this review, a PROTAC degrades its POI in both tumor and normal cells, meaning that the therapeutic and toxic targets are the same (Figure 3). Accordingly, prolonged TPD eliminates entire proteins, including enzymatic and scaffolding subunits. If the POI is essential for normal cellular functions, TPD may cause intolerance and significant adverse effects.[81,95,136] For example, the phase II trial of ARV-110 revealed that treatment-related adverse events (TRAEs) such as nausea, fatigue, vomiting, weight loss, and anemia are common in treated patients. Hence, the future development of PROTACs is challenged by the need to exclusively target tumor cells or the tumor microenvironment to avoid on-target toxicity.

PROTACs with additional agents that target specific cell membrane receptors (e.g., nucleolin [NCL], c-type lectin-like molecule-1 [CLL1], human EGFR 2 [HER2], and folate receptor α [FORL1]) have been introduced to improve off-tumor toxicity and further expand the practical applicability of PROTAC technology. For example, AS1411 is a 26-base, guanine-rich, single-stranded DNA aptamer that binds to NCL with high affinity and specificity. NCL is typically overexpressed on the plasma membrane of tumor cells relative to normal cells. As AS1411 can be internalized into cells by NCL-dependent micropinocytosis, it provides both suitable tumor targeting and antitumor activity. Aptamer-PROTAC conjugates (APCs) that use AS1411 as the aptamer have been designed to target tumors specifically. The BET degrader APR has been shown to degrade BRD2/3/4 and exhibit effective tumor-targeting and antitumor activity.[137] Folate has a strong affinity for FOLR1, which is highly expressed in many tumor cells. Hence, the development of PROTACs conjugated with folate represents a strategy for delivering PROTACs into specific tumor cells for on-target degradation by targeting FOLR1. The degradation of POIs (e.g., BRD, MEK, ALK, and IKZF1/3) via folate-PROTACs or molecular glues has been validated.[138,139] Given the outstanding successes of antibody-drug conjugates (ADCs) in the field of anticancer therapeutics,[140] antibody-PROTAC conjugates have also been brought forward as a concept for achieving tissue-specific degradation. For example, PROTACs that target the cell membrane proteins CLL1 and HER2 have been used to degrade BRD4 in a specific target-positive manner.[22,141–143]

Off-target toxicity

Drugs that target non-POI proteins, such as receptors or enzymes, may have severe downstream effects.[37,144] Theoretically, PROTACs are more selective than traditional SMIs because of the strictness and ingenuity of forming a viable ternary complex that enables polyubiquitination and degradation via the UPS. Compared with the occupancy-driven MOA of SMIs, PROTACs frequently induce new PPIs that alter the selectivity of the parent compounds.[145] For instance, foretinib, a multikinase inhibitor that targets more than 130 kinases, has been used to generate PROTACs with different E3 ligands (VHL and CRBN). The formation of bifunctional degraders reduces the target binding selectivity of VHL- and CRBN-PROTACs to 52 and 62 kinases, respectively, and the stricter condition of degradation selectivity reduces the numbers of targets to only 9 and 14 kinases, respectively.[146] Many similar reductions in the number of targeted kinases have been reported, suggesting that the selective degradation of POIs is not dependent solely on target ligand binding selectivity or affinity.[147–150] In addition, the match between the E3 ligase and the POI is one of the most crucial factors in the formation of ternary complexes with preferred PROTACs and optimal E3 ligases. Degradation selectivity is largely associated with E3 ligase preference. Pairings of different E3 ligases with a given POI can alter the degradation selectivity and efficiency, as demonstrated by the CDK4/6 selectivity of a VHL-based palbociclib degrader[151] and the weak HDAC6 selectivity of an IAP-based degrader.[152] There is one exception regarding unexpected neo-substrates for IMiDs, such as IKZF1/3 for CRBN. It remains uncertain whether E3 ligases can recruit nonspecific substrates in an IMiD-like manner.[153] NX-2127, a CRBN-based BTK degrader from Nurix Therapeutics, has been shown to catalyze the neo-substrate degradation of IKZF1/3 in DLBCL cell lines (Figure 3).

PROTAC DERIVATES

BacPROTACs

BacPROTACs, which are small-molecule degraders, hijack bacterial ClpC:ClpP (ClpCP) proteases to extend inducible protein-targeted degradation techniques that interfere with microbial infection. Phosphorylated arginine residue

Table 2. List of E3 ligases and related POIs

E3 ligase	Complex	POI	Reference
CRBN	CUL4-RBX1-DDB1-CRBN	POIs involved in cancers, immune diseases, neology, and HCV	de Wispelaere et al.,[62] Bassi et al.,[100] Sun et al.,[123] Silva et al.[124]
VHL	CUL2-RBX1-ElonginB-ElonginC-VHL	KRAS, EGFR, BCR-ABL, etc.	Bond et al.,[53] Zhao et al.,[68] Khan et al.,[77] Sun et al.,[123]
MDM2		BTK, PARP1	Sun et al.,[125] Zhao et al.[126]
IAP		RAR	Itoh et al.[47]
DCAF16	CUL4-RBX1-DDB1-DCAF16	BRD4, FKBP12	Zhang et al.[127]
DCAF15	CUL4-RBX1-DDB1-DCAF15	RBM39, BRD4	Li et al.,[128] Han et al.,[129] Bussiere et al.[130]
RNF4		BRD4	Ward et al.[131]
RNF114		BRD4	Spradlin et al.[132]
KEAP1	KEAP1-CUL3	BRD4	Tong et al.[133]
FEM1B		BRD4	Henning et al.[134]
AhR	CUL4-RBX1-DDB1-AhR	CRABP1	Ohoka et al.[135]

(pArg)-containing BacPROTACs consist of a POI ligand, chemical linker, and pArg bound to the $ClpC_{NTD}$ domain to induce its reassembly and activation. BacPROTAC targets $ClpC_{NTD}$ and activates ClpC, transforming the resting unfoldase into its functional state. The successful use of a BacPROTAC for degradation in mycobacteria has provided new ideas for the development of antimicrobial compounds (Figure 4A).[154]

Antibody-based PROTACs (AbTACs)

AbTACs are recombinant bispecific antibodies used to tether cell-surface E3 ligases to transmembrane proteins to induce target degradation *in vitro* and *in vivo*. AC-1, a fully recombinant bispecific IgG, was developed to target programmed death-ligand 1 (PD-L1), a membrane protein not targeted by orthodox PROTACs. AC-1 recruits ring-finger protein 43 (RNF43), an E3 ligase on the cell surface, to degrade PD-L1 via internalization and lysosome-mediated degradation (Figure 4B).[22] The abilities of multiple Wnt-responsive ligases (e.g., RNF43 and zinc- and ring-finger 3) to induce cancer-specific degradation in an "on-demand" manner have been validated,[155] and these findings have partially addressed the issues of poor permeativity and difficulties in targeting membrane-associated proteins.

Ribonuclease-targeting chimeras (RIBOTACs)

Since various TPD strategies have been shown to successfully degrade target proteins, decaying RNA by related nucleases is considered a prospective mimicry. More than 80% of the human genome is transcribed into RNA, of which less than 2% comprises mRNAs that are translated into proteins. Non-coding RNAs can regulate gene expression and, thus, are potential drug targets. RIBOTACs consist of an RNA binder, a small molecule (2′-5′-linked tetra-adenylate) that recruits and activates a local latent ribonuclease (RNase L), and a linker that binds these two components. RIBOTACs thus recruit monomeric RNase L and dimerize it to form an active structure (Figure 4C). The first RIBOTAC molecule was shown to selectively cleave the precursor of microRNA 96 (*miR-96*), and the subsequent silencing of *miR-96* derepressed a proapoptotic TF, leading to the selective apoptosis of breast cancer cells.[156] The compound TGP-210-RL has been shown to selectively degrade pre-*miR-210* and thus block the formation of *miR-210*, which is essential for cancer cell survival in a hypoxic microenvironment.[157] DNA-encoded libraries have been screened to identify new binders that can recruit RNase L. The RTK inhibitor dovitinib and a binder have been incorporated into the design of a next-generation RIBOTAC intended to target the *miRNA-21* precursor.[158] The potential use of RIBOTACs for selective RNA degradation has broadened the prospect of targeting vulnerabilities in RNA-based diseases.

Phosphatase-recruitment chimeras (PHORCs)

Disease onset is frequently caused by the dysregulation of signal transduction, especially the hyperphosphorylation, of oncoproteins. PHORCs have been designed to reduce the phosphorylation of target proteins via proximity to a relevant phosphatase. DDO3711, the first PHORC, comprises an activator of protein phosphatase 5 (PP5; a serine/threonine phosphatase), an SMI of apoptosis signal-regulated kinase 1 (ASK1), and a chemical linker. Overexpression of ASK1 has been linked to the progression of multiple cancers. PP5 is characterized by its explicit reversal of ASK1 Thr838 autophosphorylation (p-$ASK1^{T838}$); however, PP5 is autoinhibited in some cancer types, leading to an excessive level of p-$ASK1^{T838}$. Activation of PP5 and colocalization of PP5 with its substrate ASK1 are expected to accelerate the specific dephosphorylation of p-$ASK1^{T838}$ (Figure 4D). DDO3711 has shown desirable antiproliferative activity (IC_{50} 0.5 μM) against cancer cells, whereas the individual components (ASK1, SMI, and PP5 activator) have shown no effects in cancer cells.[159]

Oligonucleotide-based PROTACs

Some oligonucleotide-based PROTACs, including RNA-PROTACs, programmable oligonucleotide PROTACs (O'PROTACs), and TF-targeting chimeras (TRAFTACs), have been developed according to the characteristic abilities of RNA-binding proteins (RBPs) and TFs to bind RNA and dsDNA consensus sequences, respectively (Figure 4E). Such constructs have been demonstrated to degrade Lin-28 homolog A (LIN28A) and the TFs, including ETS TF (ERG), lymphoid enhancer-binding factor 1 (LEF1), NF-κB, and brachyury.[24,160–164] The PROTAC ZL216 comprises AS1411 as the warhead and a VHL ligand to enable the selective internalization and degradation of NCL, and it has been shown to exert antiproliferative activity against breast cancer cells *in vitro* and *in vivo*.[165]

Phospho-dependent PROTACs (phosphoPROTACs)

Phosphorylation, a post-translational modification, is a crucial step in the activation of proteins, especially kinases, and their downstream signaling pathways. PhosphoPROTACs represent an update of orthodox PROTACs, wherein PROTAC-mediated protein degradation is coupled with the activation state of a particular signaling pathway.[30] RTKs are activated by autophosphorylation, and their downstream signaling cascades are amplified by recruiting and phosphorylating molecules with phosphotyrosine-binding (PTB) and SH2 domains. A phosphoPROTAC contains a warhead with a common RTK phosphorylation sequence that can be phosphorylated by activated RTKs, and an E3 ligand is a residue of HIF-1α binding to VHL. Poly-D-Arg is linked to the E3 ligand to improve cell permeativity. Under specific situations involving RTK activation, the controllable phosphoPROTAC can be phosphorylated, which is followed by the recruitment of target proteins with PTB and SH2 domains. These target proteins are ubiquitinated and consequently degraded via the VHL-mediated ubiquitin-proteasome pathway. The phosphoPROTACs $^{TrkA}PP_{FRS2\alpha}$ and $^{ErbB2}PP_{PI3K}$ (FRS2α and PI3K are the downstream proteins of TrkA and ErbB2, respectively) have been shown to inactivate the TrkA- and ErbB2/ErbB3-regulated signaling pathways, respectively, in breast cancer cell lines (Figure 4E).[166]

Light-controllable PROTACs

Light-controllable PROTACs can be divided into two main groups, namely photoswitchable PROTACs and photocaged PROTACs, which are characterized by reversible or irreversible light control, respectively, at a high spatiotemporal resolution. Photoswitchable PROTACs induce reversible TPD via an optically controlled moiety on the linker or E3 ligand. Exposure to light at a specific wavelength induces an "inactive-active" transition in the PROTAC that enables the formation of a stable ternary complex (Figure 4E).[167–169] The incorporation of azobenzene photoswitches into PROTACs has led to a series of BET and FKBP12 degraders whose precise ability to regulate activation and inactivation is regulated under two conditions: blue-violet light (380–440 nM) and darkness.[169]

Photocaged PROTACs are characterized by the binding of a photolabile blocking group to the E3 ligand, which blocks the interaction between the PROTAC and the E3 ligase. Upon light stimulation, the PROTAC is released from the photocaging group, enabling the active conformation of the ternary complex (Figure 4E).[170–173] The degraders dBET1 and dALK, along with a photolabile caging group (nitroveratryloxy-carbonyl group), have been conjugated to the E3 ligand pomalidomide, and photolysis has been shown to be induced by ultraviolet A irradiation. The substrates of pomalidomide, dBET, and dALK (including IKZF1/3, BRD2/3/4, and ALK) were shown to be degraded in a light-controllable manner.[173]

Dual/trivalent PROTACs

Inspired by dual-targeting drugs,[174] especially bispecific antibodies, Li and colleagues first presented the concept of a dual PROTAC that could degrade two distinct POIs (EGFR and PARP).[175] The EGFR inhibitor gefitinib, the PARP inhibitor olaparib, and a CRBN/VHL ligand were linked with a star-type core linker of trifunctional amino acids. The dual PROTACs DP-C-1 and DP-V-4 have demonstrated potent ability to degrade both EGFR and PARP in a dose- and time-dependent manner. However, DP-V-4 was shown to possess a weaker antiproliferative activity (IC_{50} 19.92 ± 1.08 μM) than its parent inhibitors in H1299 cells, potentially because its high molecular weight led to low solubility and poor cell permeativity.[175]

To address incomplete target degradation and the hook effect due to unproductive high concentrations of ternary complexes, a trivalent PROTAC SIM1 was developed to degrade the BET domain family members BRD2, BRD3, and BRD4. A trivalent PROTAC comprises bivalent POI ligands and a moiety for recruiting E3 ligase, tethered by a branched linker. As the most potent trivalent PROTAC, SIM1 can degrade target proteins over a wide range of concentrations (10 pM–30 μM), thus eliminating the hook effect.[176] This avidity- and cooperativity-enhanced ternary complex outperforms the BET degraders MZ1 and MT1 by forming a 1:1:1 complex with VHL and the tandem bromodomain BD1–BD2 with conformational change. Moreover, SIM1 has been shown to degrade its targets rapidly and at a lower concentration than that reported for the BET degraders ARV-771 and MZ1, and it has been shown to have a higher residence time rate and longer half-life *in vivo*.[176] In principle, trivalent PROTACs use the same MOA as the above-mentioned dual PROTACs (Figure 4E).

Chaperone-mediated protein degradation (CHAMP)

CHAMP, another important PROTAC derivative, directly hijacks the chaperone molecule HSP90, instead of E3 ligase, to achieve target degradation. The compound BRD4-CHAMP, which comprises a BRD4:CHAMP:HSP90 ternary complex, has been shown to selectively degrade BRD4 and exert antitumor activity *in vitro* and *in vivo*.[177] First, the CHAMP compound RNK05047 (CHAMP-1) is being explored in a clinical trial as a potential DLBCL treatment (Figure 4E).

Homo-PROTACs

Homo-PROTACs have been designed and validated to mediate the self-destruction of E3 ligases, such as VHL, MDM2, and CRBN (Figure 4E).[178–180] For example, CM11, a homo-PROTAC, has been shown to induce the selective depletion of a VHL isoform (pVHL30) at a nanomolar concentration. However, this exclusive and highly isoform-selective degradation of pVHL30 was unexpected because CM11 does not differentiate between pVHL19 and pVHL30 in ternary complexes.[180]

BioPROTACs

A bioPROTAC was exploited at an early stage after the first PROTAC debut. This hybrid molecule comprises a small-molecule warhead and a phosphopeptide. BioPROTAC activity against some clinically relevant cancer targets, such as HER2, MYC, and KRAS, has been validated in human cancer cell lines and mouse xenograft tumor models.[181–184] However, bioPROTACs cannot be administered orally due to the high molecular weights of their peptide components, and a suitable drug-delivery system needs to be chosen.

OTHER TPD THERAPIES

Macroautophagy degradation-targeting chimeras (MADTACs) AUTACs/ATTECs/AUTOTACs

Macroautophagy is another degradation pathway in cells, wherein lysosomes engulf and degrade cytoplasmic substrates.[185] Many studies of TPD technologies that engage lysosomal pathways through different mechanisms have been summarized.[186] Because many intracellular proteins are not targeted by the UPS for degradation, AUTACs have been designed to degrade proteins and dysfunctional mitochondria via autophagy.[187] AUTACs consist of three parts: a warhead that specifically targets the proteins to be degraded, a tag for selective autophagic degradation, and a linker connecting the other two parts. In addition to their target proteins, AUTACs can degrade disease-related debris, such as fragmented mitochondria. Compared with earlier PROTACs, AUTACs can potentially degrade a broader range of disease-related organelles and intracellular pathogens.[188] Once macroautophagy is initiated, the area of cytoplasm containing the cargo to be degraded is elongated and isolated.[189] The cytoplasmic membrane subsequently closes around the contents and matures to form an autophagosome, which then fuses with a lysosome to degrade the cargo.[190] S-Guanylation (cysteine conjugation of 8-nitro-cGMP) is a post-translational modification important for K63 ubiquitination that is used to clear intracellular bacterial pathogens.[191] S-guanylate may be an ideal tag for substrate targeting. The pairing of a degradation tag (e.g., guanine derivatives such as FBnG) and a ligand for the target can be characterized by the induction of K63-polyubiquitination to mediate substrate S-guanylation for selective autophagy. AUTAC platforms have been proven effective against MetAP2, FKBP12, BRD4, and mitochondria.

ATTECs have been shown to provide a more direct approach, interacting with both the mutant huntingtin protein (mHTT) with an expanded polyglutamine (polyQ) tract, which causes Huntington disease, and the autophagosome protein microtube-associated protein 1A/1B light chain 3 (LC3), but not with wild-type HTT.[192] Using small-molecule-microarray-based screening technology, compounds that can conjugate LC3 and mHTT have been exploited to degrade mHTT rather than wild-type HTT, with high specificity. As these compounds recognize polyQ tracts in their targets, they might be useful for degrading other disease-related polyQ-containing proteins.[193] In addition to polyQ as the LC3 ligand, GW5074 and ispinesib have been used to design ATTECs that have been verified to effectively degrade the oncoproteins BRD4 and nicotinamide phosphoribosyltransferase (NAMPT).[194,195] Furthermore, non-proteinaceous targets, such as lipid droplets (LDs), cannot be degraded using orthodox PROTAC technology but are potential targets for ATTECs because they are known to be degraded via autophagy. ATTEC degraders are able to clear LDs almost completely and rescue LD-related phenotypes *in vitro* and *in vivo*, thus expanding the scope of TPD platform applications.[196]

AUTOTAC is generated by connecting a POI ligand to a p62-binding autophagy-targeting ligand via an intermediate linker. AUTOTACs recruit POIs in tandem with the binding ZZ domain of the otherwise dormant autophagy receptor p62/Sequestosome-1/SQSTM1.[197] This interaction stimulates self-polymerization in complex with the cargo and the macroautophagy induction cascade in a p62-dependent manner. AUTOTACs have been designed and verified to mediate the degradation of various oncoproteins (e.g., ERβ, AR, and MetAP2) and degradation-resistant misfolded protein aggregates associated with neurodegeneration *in vitro* and *in vivo*.[197]

Lysosome-targeting chimeras

Although the first AbTAC was able to target the cell-surface protein PD-L1 with a ligandable intracellular domain,[22] most extracellular and membrane-associated proteins still cannot be targeted by PROTACs. Approximately 40% of the proteins in the human proteome are secreted or membrane proteins, and this proportion

Table 3. Ongoing clinical trials of bifunctional degraders (molecular glues)

Clinical trial NCT no.	Highest phase	Degrader	POI	E3 ligase	Indications	Sponsor
NCT02773030	II	CC-220	IKZF1/3	CRBN	MM	Bristol Myers Squibb
NCT03989414	II	CC-92480	IKZF1/3	CRBN	MM	Bristol Myers Squibb
NCT02848001/NCT04336982	II	CC-90009	GSPT1	CRBN	AML	Bristol Myers Squibb
NCT01421524	I	CC-122	IKZF1/3	CRBN	MM	Bristol Myers Squibb
NCT05144334	I	BTX-1188	IKZF1/3	CRBN	AML and solid tumor	Biotheryx
NCT04434196/NCT03930953	I	CC-99282	IKZF1/3	CRBN	CML and NHL	Bristol Myers Squibb
NCT04756726	I	CFT7455	IKZF1/3	CRBN	MM and lymphoma	C4 Therapeutics
NCT04283097	I	KPG-818	IKZF1/3	CRBN	Hematological malignancies and SLE	Kangpu
NCT03569280	I	KPG-121	IKZF1/3	CRBN	CRPC	Kangpu
	IND-e	ICP-490	IKZF1/3	CRBN	MM and NHL	InnoCare
NCT03891953	I	DKY709	IKZF2	CRBN	NSCLC	Novartis

AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell lung cancer; SLE, systemic lupus erythematosus.

is even higher in the pancreas, salivary gland, and liver.[198] Therefore, LYTACs have been designed to target extracellular and membrane-associated proteins, using conjugates that bind to both a cell-surface lysosome-targeting receptor (LTR) and the extracellular domain of the target protein.[21] A LYTAC is a heterobifunctional molecule comprising a warhead that binds to the protein targeted for degradation and a tail containing chemically synthesized glycopeptide ligands that can hijack the cation-independent mannose-6-phosphate receptor (CI-M6PR), a prototypical LTR. When the POI is linked to CI-M6PR by M6Pn-LYTAC molecules, TPD is triggered, and the POI is transported to the lysosome and degraded. The ability of M6Pn-LYTACs to effectively degrade clusters of targets, such as the extracellular protein apolipoprotein E4 (APOE4) and membrane proteins (e.g., EGFR, PD-L1, and CD71), has been validated, thus expanding the scope of the TPD platform.[21]

Drawing on experiences from the first generation of systemically non-specific LYTACs, another tissue-specific LTR has been chosen to develop a localized-targeting LYTAC. N-acetylgalactosamine (tri-GalNAc), a ligand of the liver-specific LTR asialoglycoprotein receptor (ASGPR) that can be internalized via clathrin-mediated endocytosis, was selected as the LYTAC warhead.[199] Antibody-based GalNAc-LYTACs have been shown to successfully degrade membrane-associated proteins (EGFR, HER2, and integrins) in the hepatocellular carcinoma cell line HepG2.[200,201] In addition, molecular degraders of extracellular proteins through ASGPR (MoDE-As) have been generated as the first non-proteinogenic synthetic tri-GalNAc conjugates, and their ability to effectively degrade extracellular proteins in lysosomes has been validated both *in vitro* and *in vivo*.[202]

Taken together, these studies have shown the potential use and feasibility of the LYTAC platform for lysosomal degradation of extracellular and membrane-associated proteins; accordingly, LYTAC is a powerful solution to the drawbacks of PROTACs.

Hydrophobic tagging

In hydrophobic tagging (HyT) technology, bifunctional small molecules bind to a bacterial dehalogenase (the HaloTag protein) and present a hydrophobic group on the surface of the POI. Two possible MOAs of HyT-mediated degradation have been proposed as follows. First, the hydrophobic tag destabilizes the POI irreversibly, enabling the recruitment of endogenous chaperones and the shuttling of the POI to the proteasome for degradation. Second, chaperones recognize the hydrophobic tag directly and mediate proteasomal degradation of the tagged protein.[203,204] Hydrophobic tags can be divided into three types: typical adamantane,[23,205] *tert*-butyl carbamate-protected arginine,[206,207] and carborane.[208] HyT molecules, which target POIs such as HER3, Tau, and PDEδ, have validated degradation efficacy and antiproliferation activity in human cancer cell lines and mouse xenograft tumor models.[61,205,209,210] Selective ER degraders (SERDs; e.g., fulvestrant, RU 58668) for the treatment of estrogen-responsive cancers and the selective AR degrader (SARD) (e.g., SARD279) used to treat prostate cancer have similar functions: a hydrophobic chain is exposed on the surface of a POI to mimic a misfolded protein state and, thus, induce degradation.[211,212]

Molecular glues

Molecular glues are commonly used to induce proteolysis of a target and have an MOA similar to that of PROTACs. Unlike PROTACs, however, a molecular glue contacts and is optimized for both the target protein and the E3 ligase via insertion into a naturally occurring PPI interface. Molecular glues have the obvious advantages of a low molecular weight and good druggability. Due to a limited understanding of the controlling factors, however, molecular glue design remains challenging, and few successful cases have been reported.

Most molecular glues induce protein degradation via E3 ligases, including iMIDs (thalidomide, lenalidomide, and pomalidomide) via CRBN binding,[153,213–217] aryl sulfonamide via engagement with DCAF15,[218] and other small molecules that adhere to the adaptor proteins DDB1,[219–221] SIAH1,[222] UBR7,[223] or $SCF^{\beta\text{-}TrCP}$.[223] Molecular glues for TPD, such as the neo-substrates (IKZF1/3 and CK1α) of iMIDs and POIs (RBM39,[129,224,225] BCL6,[222] and CDK[220]) for some SMIs, were discovered serendipitously. Other molecular glues have been shown to induce TPD via an autophagy-mediated degradation pathway, wherein LC3 is hijacked to degrade mHTT via the compounds AN1, AN2, 1005, and 8F20 derived from microarray-based high-throughput screening. The mechanisms of these autophagic degraders remain to be clarified.[193]

Clinical trials of the IKZF1/3 degraders iberdomide (CC-220),[226,227] CC-92480, CC-99282, and CFT7455 for hematologic malignancies, including multiple myeloma, acute myeloid leukemia, chronic myeloid leukemia, and non-Hodgkin's lymphoma, are beginning. CC-90009 is a CRBN-based GSPT1 degrader with antileukemic activity and is currently in a dose-escalation phase and combination trial. DKY709, a degrader of IKZF2, is being used as a monotherapy and combination therapy with PDR001, a ligand-blocking IgG4 monoclonal antibody specific for PD-1. GBD-9 combines PROTAC and molecular glue strategies to yield a dual-mechanism inhibitor that effectively degrades BTK and GSPT1 and inhibits cancer cell growth by recruiting the E3 ligase CRBN (Table 3).[228]

CONCLUSIONS

Since the debut of PROTAC technology in 2001, TPD has expanded through two decades of development. The clinical proof of concept of PROTACs has been completed, and a series of TPD spin-offs have emerged consecutively, allowing the potential applications of this technology to be continuously tapped for biomedicine. The entry of the first PROTAC drug into the clinic has validated the potential of this technology to become the best in class. The characteristics of clinical practicability and an orally bioactive medication have promoted the transition of PROTACs from academia to industry. However, the on-target/off-tumor toxicity, potentially off-target effects, and other challenges associated with PROTACs will continue to hinder future developmental efforts. The

development and application of an expanded toolbox of E3 ligases for PROTACs should be another focal point. Some tissue-specific E3 ligases are expected to serve as passive targeting carriers.[110,229] In this review, we comprehensively list various target proteins of PROTACs, including kinases and transcription regulators, and provide verification of the effectiveness of these treatments for cancers, autoimmune diseases, and other pathologies. In the clinic, PROTAC drugs mainly target the AR, ER BRD9, and BTK proteins, and progress in the treatment of mCRPC, ER^{+}/HER^{-} breast cancer, SS, and liquid tumors has been gratifying. PROTAC derivatives have expanded the spectrum of POIs of various forms that can be inactivated. Other TPD strategies, such as AUTACs, ATTECs, and LYTACs, have expanded the platforms for degrading target proteins to the autophagy and lysosomal degradation pathways, which can target proteins in different locations, including cytosolic, intramembrane, and extracellular proteins.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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Supplemental Information

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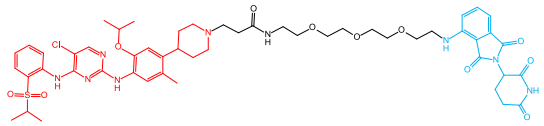
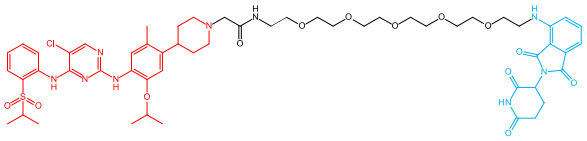
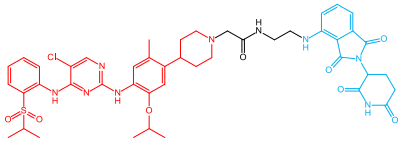
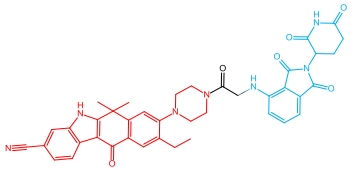
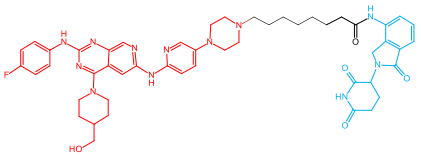
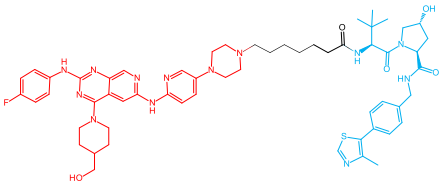
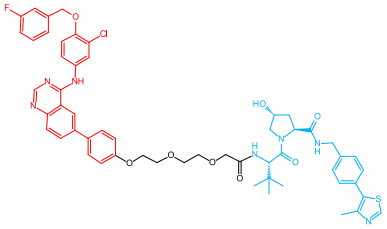
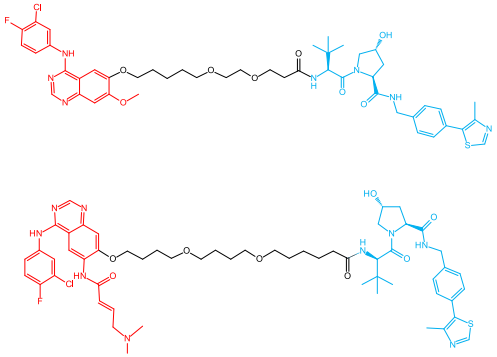
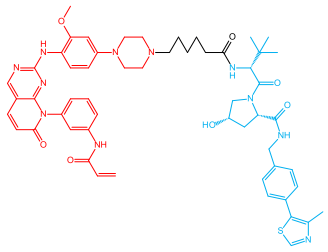
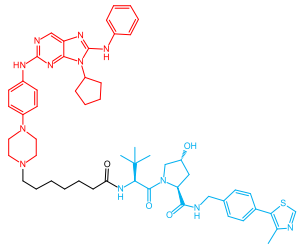
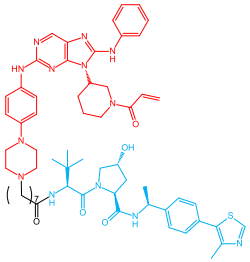
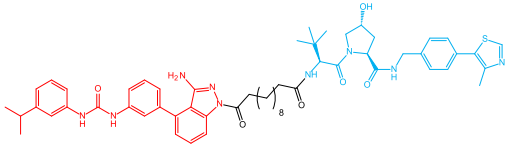
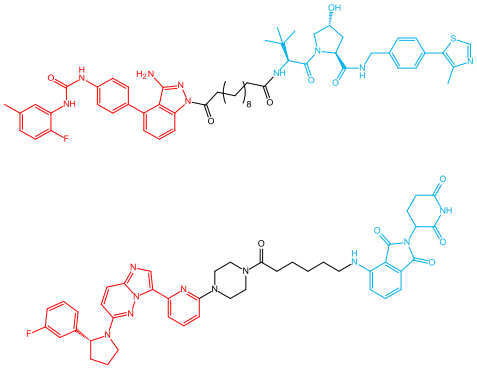
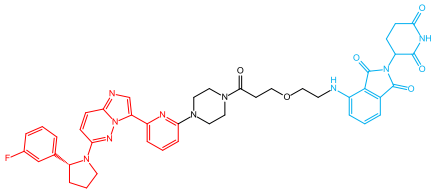
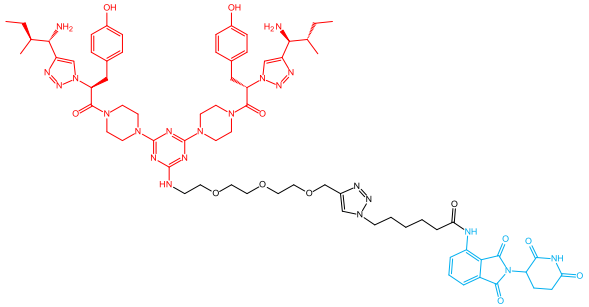
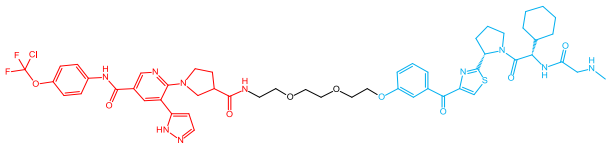
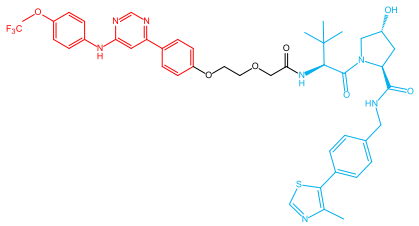
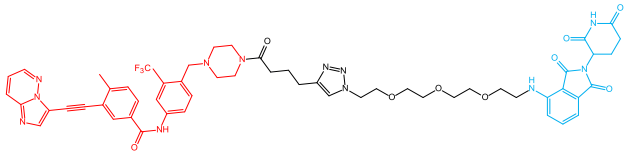
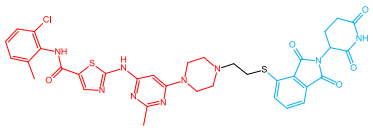
Table S1. PROTACs and Related Diseases in Academia

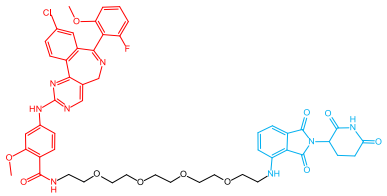
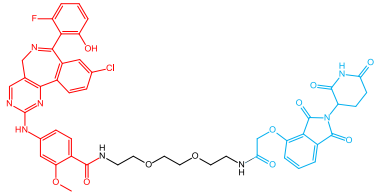
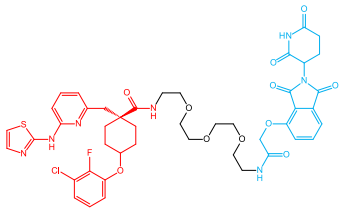
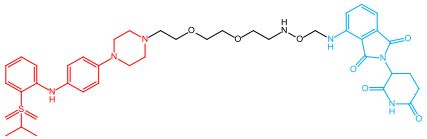
Name	Structure	POI	E3 Ligase	Disease (Related Cell Line)	Reference
Compound B3		ALK	CRBN	NSCLC (H3122)	1
MS4077		ALK	CRBN	NHL (SU-DHL-1), NSCLC (NCI-H2228)	2
MS4078		ALK	CRBN	NHL (SU-DHL-1), NSCLC (NCI-H2228)	2
Degrader 17		ALK	CRBN	NSCLC (A549), Human Fetal Lung Fibroblast (HFL-1)	3

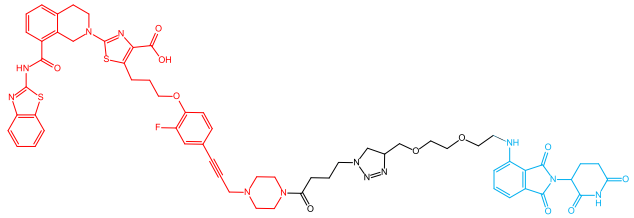
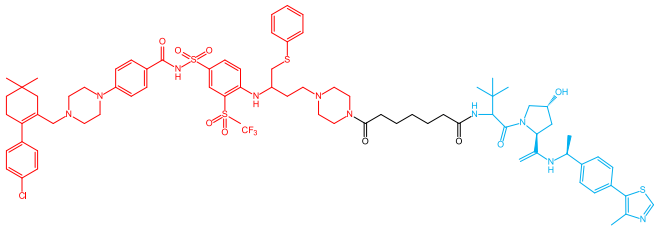
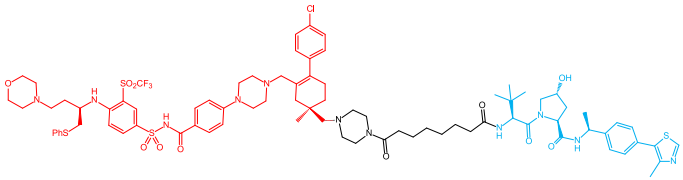
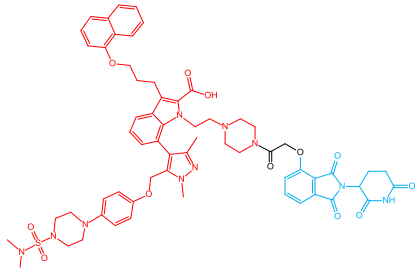
Compound 2		$EGFR^{Del19}$	CRBN	NSCLC (HCC827)	4
Compound 10		$EGFR^{Del19}$	VHL	NSCLC (HCC827)	4
PROTAC 1		$EGFR^{Ex20Ins}$	VHL	Human Ovarian Carcinoma (OVAR8), Cervical Cancer (HeLa)	5
PROTACs 3/4		$EGFR^{Del19}$, $EGFR^{L858R/T790M}$	VHL	NSCLC (HCC827, H1975)	5

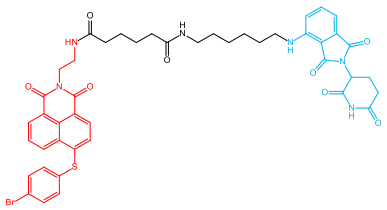
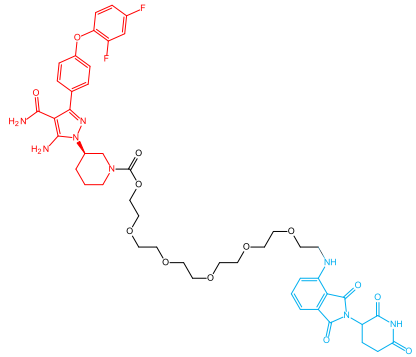
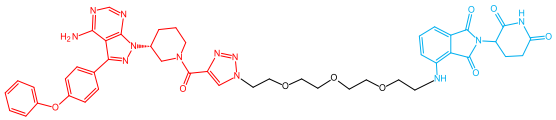
14o		EGFR L858R/T790M	VHL	NSCLC (H1975)	6
Compound P3		$EGFR^{Del19}$, EGFR $^{L858R/T790M}$	VHL	NSCLC (HCC827, H1975)	7
CP17		$EGFR^{Del19}$, EGFR $^{L858R/T790M}$	VHL	NSCLC (HCC827, H1975)	8
PROTACs-2/5		VEGFR-2	VHL	HUVEC (EA.hy926)	9

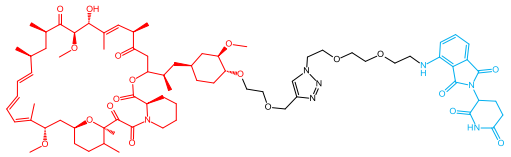
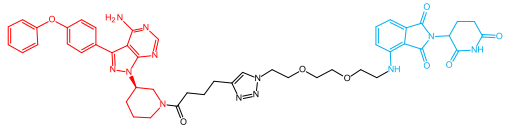
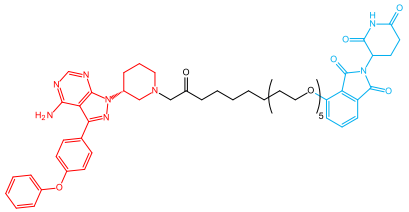
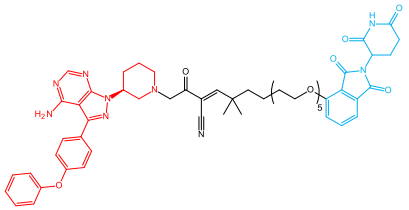
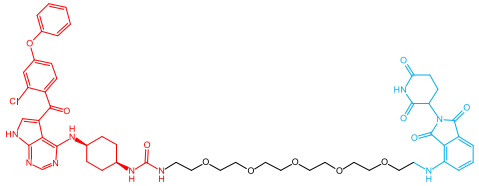
CG416		TPM3-TrkA Fusion Protein, Wild Type TRKA	CRBN	CRC (KM12)	10
CG428		TPM3-TrkA fusion protein, Wild Type TrkA	CRBN	CRC (KM12)	10
Degrader 4		TrkC	CRBN	BC (Hs578t and MDA-MB-231)	11

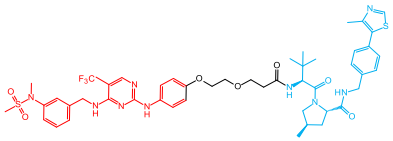
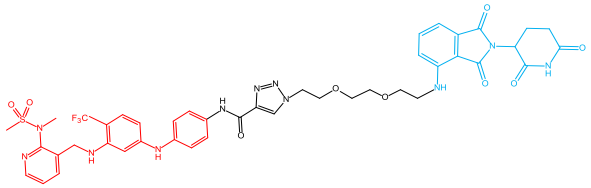
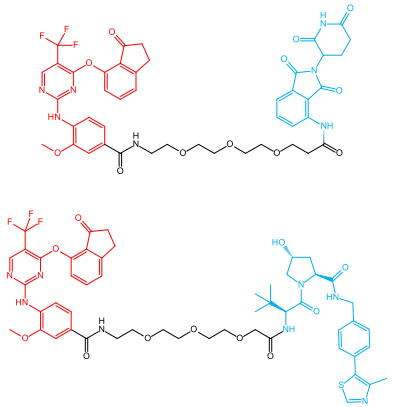
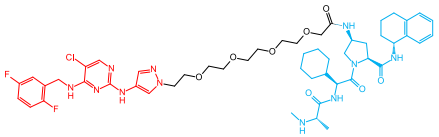
SNIPER(ABL)-62		BCR-ABL	cIAP1	CML (K562)	12
GMB-475		BCR-ABL	VHL	CML (K562)	13
P19P and P22D		BCR-ABL	CRBN	CML (K562)	14
Degrader 17		BCR-ABL	CRBN	CML (K562)	15

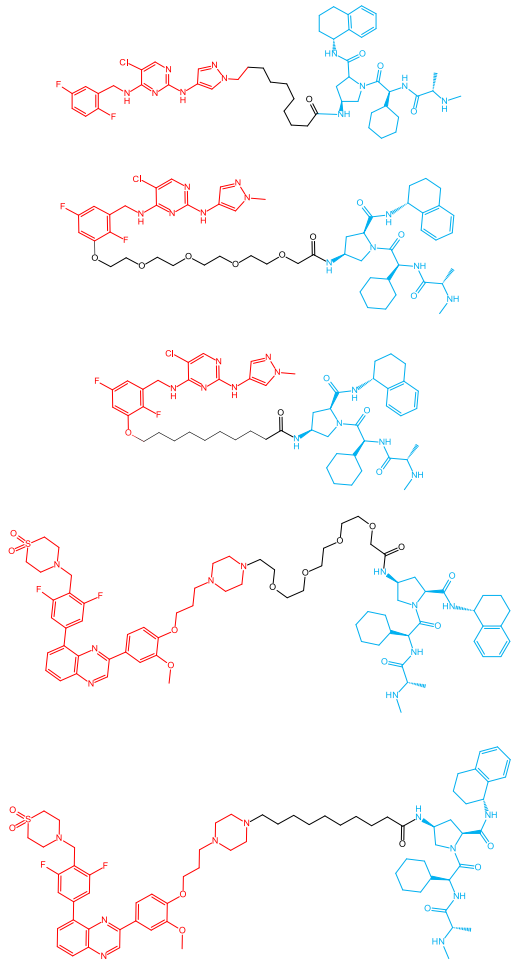
PROTAC-D		AURKA	CRBN	Osteosarcoma (U2OS)	16
JB170		AURKA	CRBN	AML(MV4;11)	17
JB301		AURKA	CRBN	AML(MV4;11)	18
TL12-186		AURKA and Other Proteins	CRBN	AML(MOLM14) and ALL(MOLT-4)	19

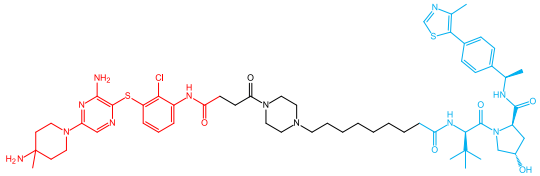
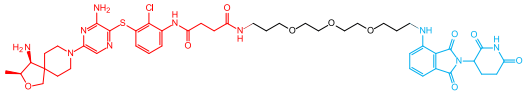
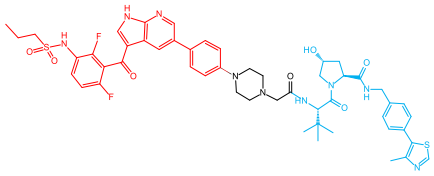
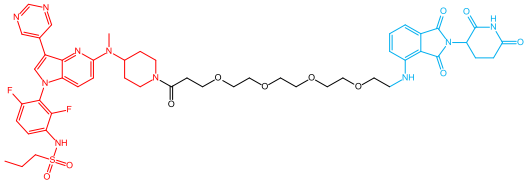
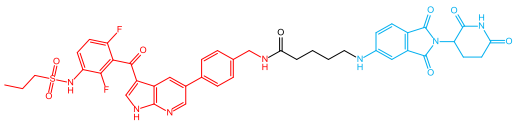
XZ424		BCL-xL	VHL	ALL(MOLT-4)	20
DT2216		BCL-xL	VHL	ALL(MOLT-4)	21,22
753b		BCL-2/BCL-xL	VHL	AML (Kasumi-1)	23
dMCL 1-2		MCL-1	CRBN	MM (OPM2)	24

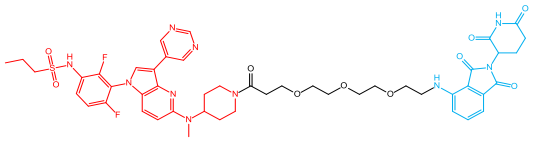
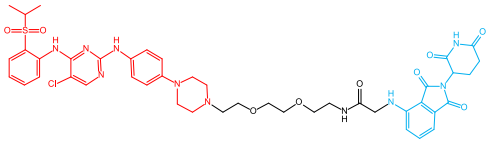
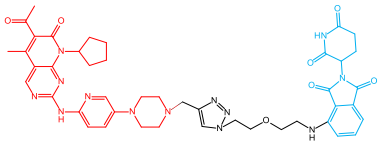
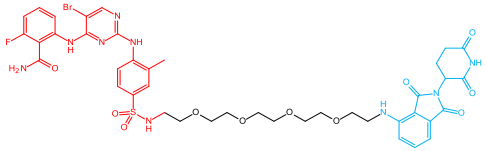
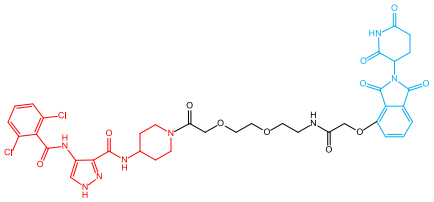
C3/5		MCL-1/BCL-2	CRBN	NSCLC (H23)	25
PROTAC (10)		BTK	CRBN	NHL (Ramos)	26
P13I		BTK	CRBN	NHL (Ramos)	27

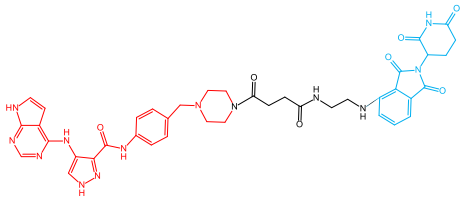
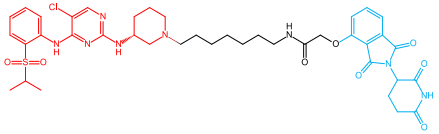
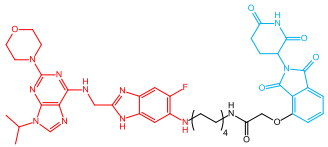
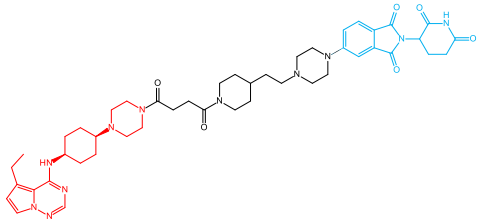
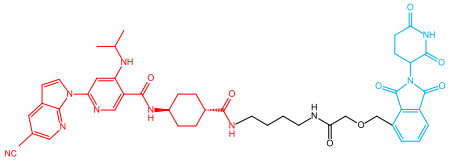
RC32		FKBP12	CRBN		28
P13IS		BTK	CRBN		28
NC-1		Wild Type BTK and BTK$^{C481S/Y}$	CRBN	MCL (Mino), Osteosarcoma (U2OS), CLL (Samples from patients)	29
RC-3		Wild Type BTK and BTK^{C481S}	CRBN	MCL (Mino), Osteosarcoma (U2OS), CLL (Samples from patients)	30
6e		BTK	CRBN	MCL(JeKo-1), DLBCL (TMD8)	31

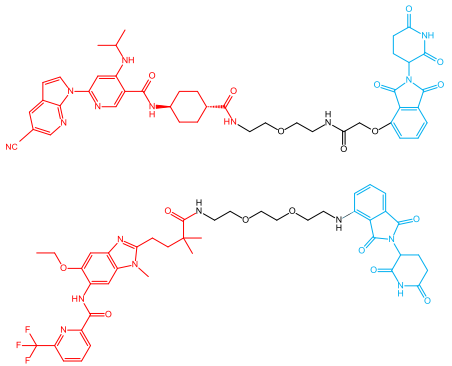
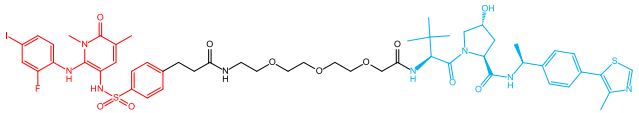
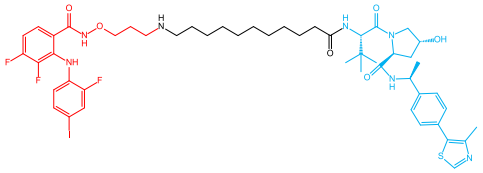
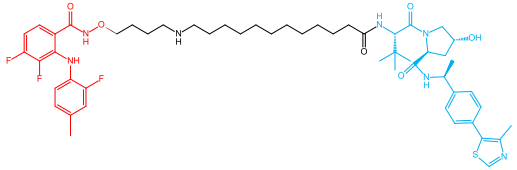
PROTAC-3		FAK	VHL	PC (PC-3) and BC (MDA-MB-231)	32
FC-11		FAK	CRBN	Leydig Cells (TM3), Primary Sertoli/Germ Cells	33
PROTAC 6/8		FAK	VHL or CRBN	NSCLC (A549)	34
JP-1 – JP-6		JAK	IAP	AML (THP-1)	35

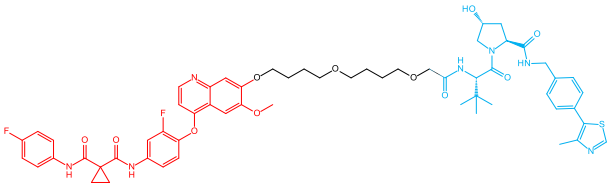
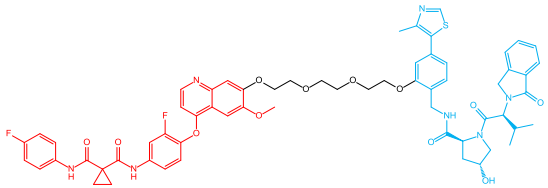
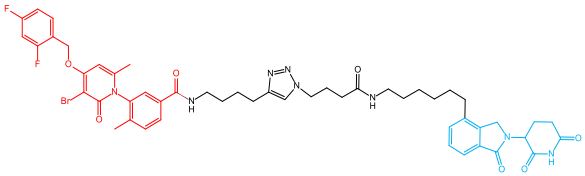
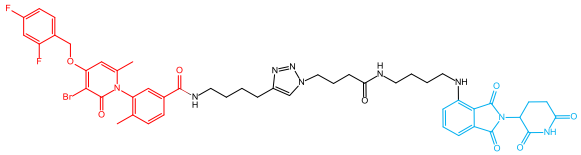
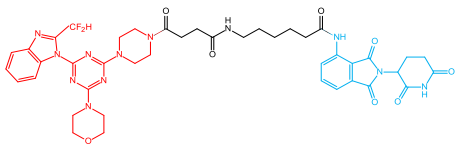


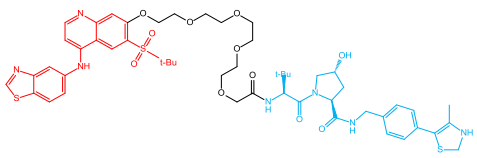
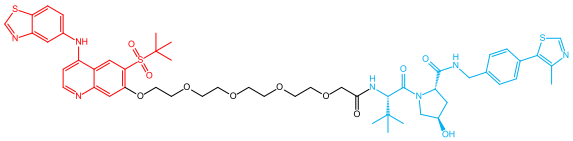
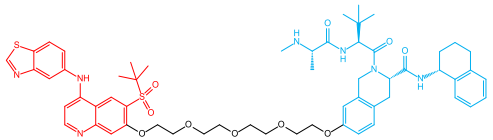
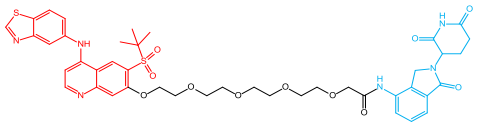
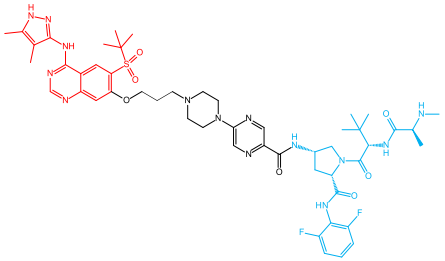
SHP2-D26		SHP2	VHL	ESCC (KYSE-520), AML(MV4;11)	36
ZB-S-29		SHP2	CRBN	AML(MV4;11)	37
SJF-0628		BRAF mutations	VHL	Various Cancers	38
P4B		$BRAF^{V600E}$	CRBN	MM (A375)	39
Compounds 12/23		$BRAF^{V600E}$	CRBN	MM (A375)	40

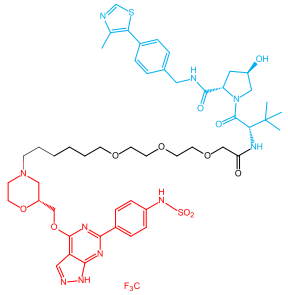
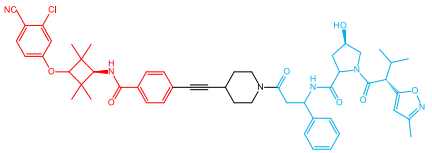
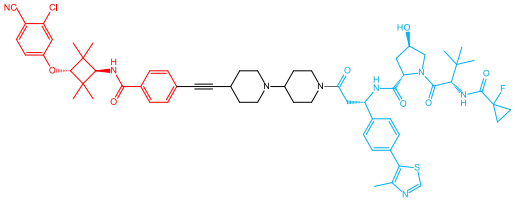
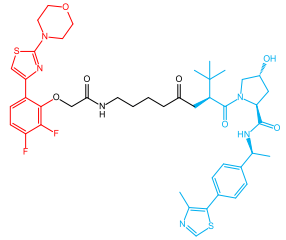
TL12-186		CDK	CRBN	HEK293	[41]
Pal-pom		CDK4/6	CRBN	BC (MDA-MB-231)	[42]
CP-10		Wild Type and mutated CDK6	CRBN	MM (MM.1S)	[43]
TMX-2172		CDK2/4/5/6/7/9	CRBN	Human Ovarian Carcinoma (OVAR8)	[44]
A9		CDK2	CRBN	PC (PC-3)	[45]

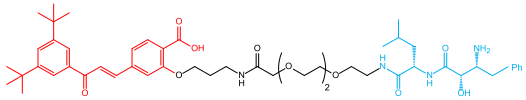
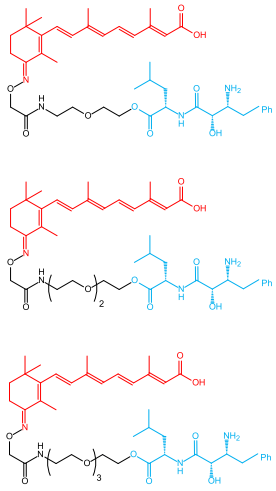
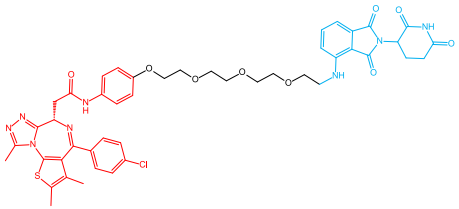
F3		CDK2/9	CRBN	PC (PC-3)	[45]
BSJ-4-116		CDK12	CRBN	ALL (Jurkat, MOLT-4)	[46]
PP-C8		CDK12	CRBN	BC (MDA-MB-231), HCC (Bel-7402)	[47]
PROTAC 23		IRAK3	CRBN	AML (THP-1)	[48]
Degraders 3/5		IRAK4	CRBN	AML (THP-1)	[49]

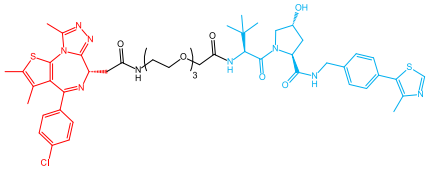
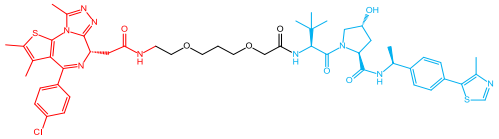
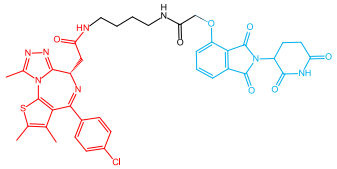
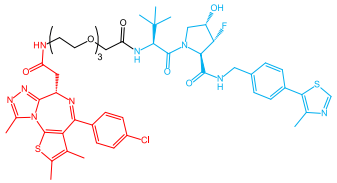
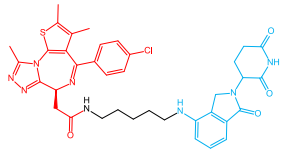
Compound 9		IRAK4	CRBN	ABC-DLBCL (OCI-LY10, TMD8)	50
Compound 3		MEK	VHK	MM (A375)	51
MS423		MEK	VHL	CRC(HT29) and MM(SK-MEL-28)	52
MS934		MEK	CRBN	CRC(HT29) and MM(SK-MEL-28)	53

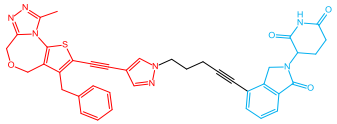
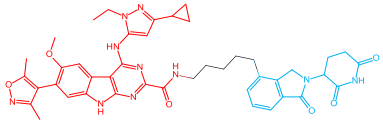
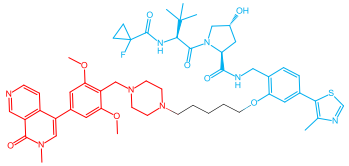
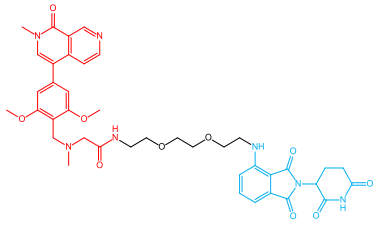
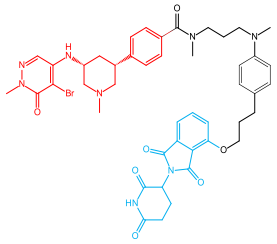
SJFα and SJFδ	 	p38α and p38δ	VHL	BC (MDA-MB-231)	54
NR-6a and NR-7h	 	p38α/β	CRBN	Various Cancers	55
Compound D		PI3K	CRBN	HCC (HepG2)	56

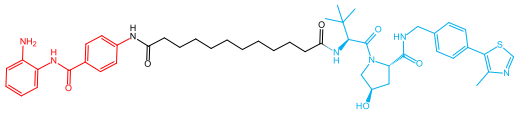
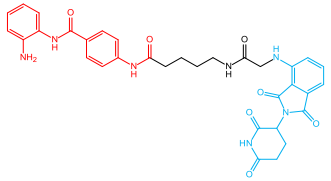
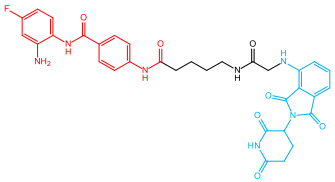
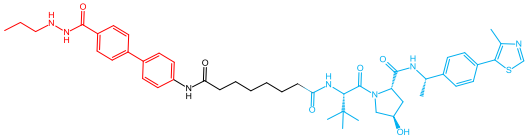
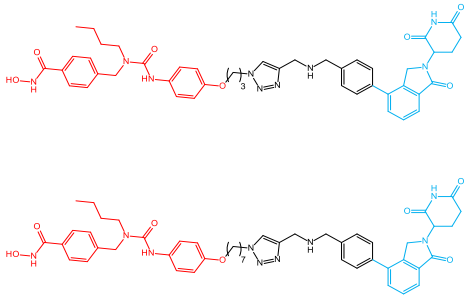
PROTAC_RIPK2		RIPK2	VHL	AML (THP-1)	57
PROTACs 1/2/3	  	RIPK2	VHL/IAP/CRBN	AML (THP-1)	58
PROTAC 6		RIPK2	IAP	AML (THP-1)	58

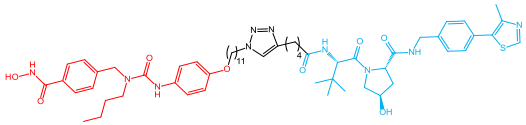
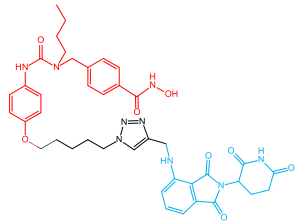
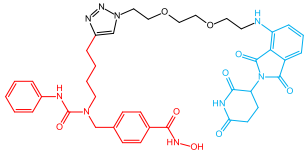
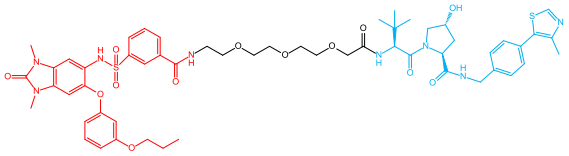
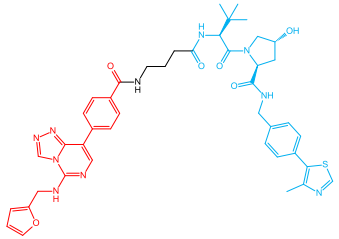
SGK3-PROTAC1		SGK3	VHL	BC (CAMA-1)	59
ARD-266		AR	VHL	mCRPC (LNCaP, VCaP, 22Rv1)	60
ARD-69		AR	VHL	mCRPC (LNCaP, VCaP, 22Rv1)	61
MTX-23		AR	VHL	mCRPC (LNCaP, VCaP, 22Rv1)	62

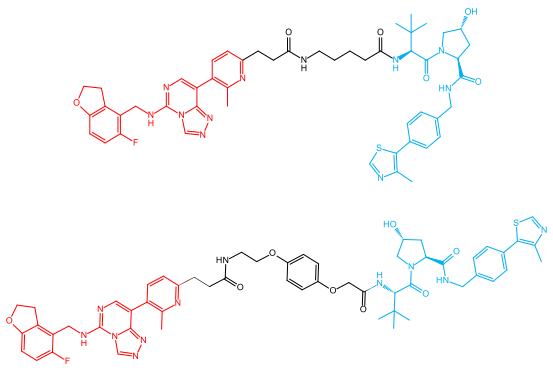
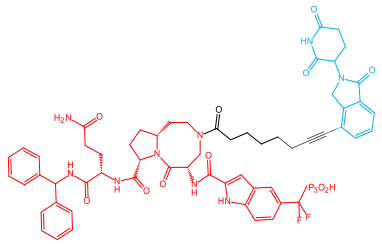
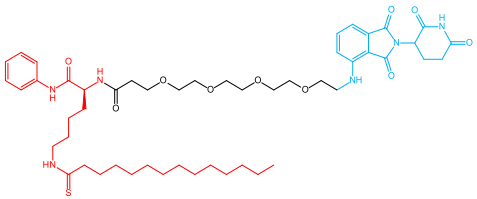
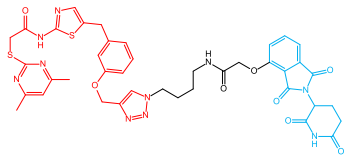
SNIPER Compound 9		PAR	cIAP1	Fibrosarcoma (HT1080)	63
Compound 4a/4b/4c		CRABP	cIAP1	ALL(MOLT-4), Fibrosarcoma (HT1080), Neuroblastoma (IMR-32)	64
ARV-825		BRD4	CRBN	BL (Namalwa), NHL (Ramos)	65

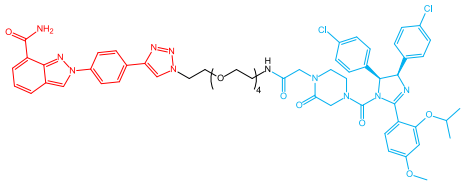
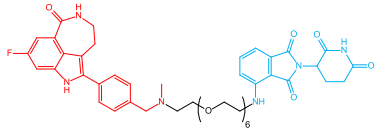
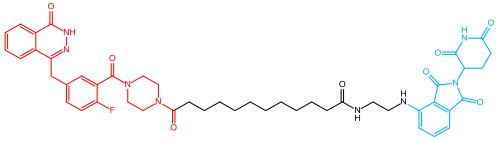
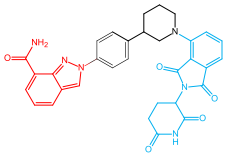
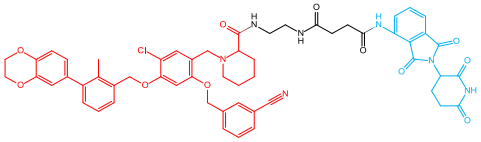
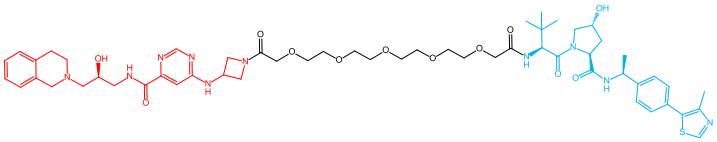
MZ1		BRD4	VHL	AML(MV4;11)	66-69
ARV-771		BRD2/3/4	VHL	mCRPC (LNCaP95, VCaP, 22Rv1)	70
dBET1		BRD4	CRBN	AML(MV4;11)	71
15a		BRD4	VHL	AML(MV4;11), NSCLC (A549)	72
SIAIS213110		BRD2/3/4	CRBN	MM (MM.1S), AML(MV4;11), TNBC (MDA-MB-468)	73

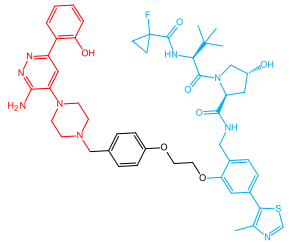
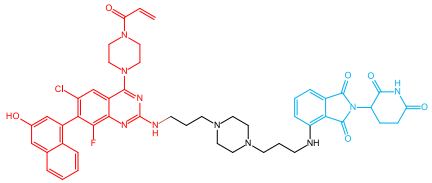
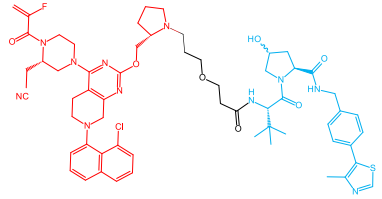
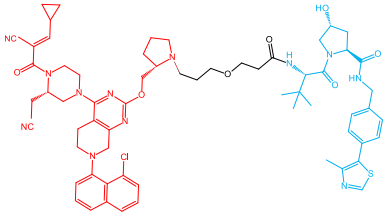
QCA570		BRD2/3/4	CRBN	ALL (RS4;11), AML(MV4;11)	74
BETd-260/ZBC260		BRD2/3/4	CRBN	ALL (RS4;11)	75
VZ185		BRD7/9	VHL	AML (EOL-1), Rhabdomyosarcoma (A-204)	76
dBRD9		BRD9	CRBN	AML (EOL-1), ALL (MOLM-13)	77
GSK983		PCAF	CRBN	AML (THP-1)	78

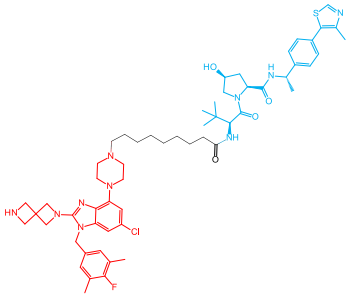
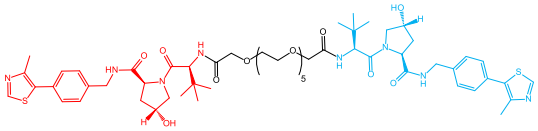
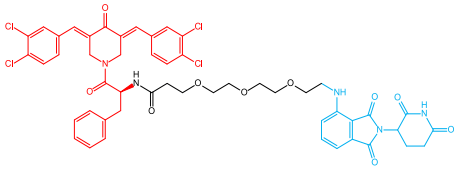
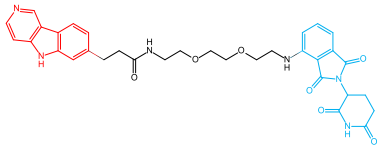
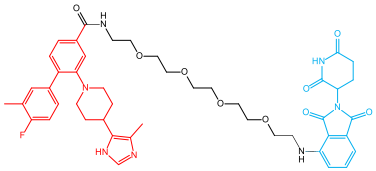
PROTAC 4		HDAC1/2/3	VHL	E14 mESCs, CRC (HCT-116)	79
HD-TAC1		HDAC3	CRBN	Macrophage (RAW 264.7)	80
HD-TAC7		HDAC3	CRBN	Macrophage (RAW 264.7)	80
XZ9002		HDAC3	VHL	TNBC (MDA-MB-468)	81
WH624, YZ268		HDAC6	CRBN	MM (MM.1S)	82

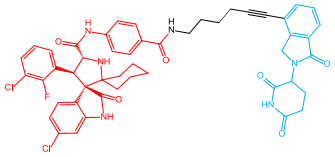
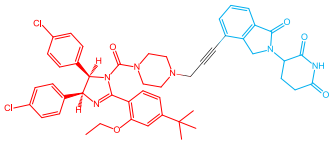
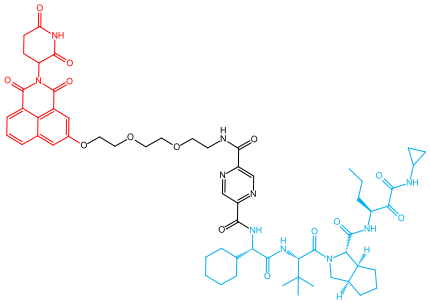
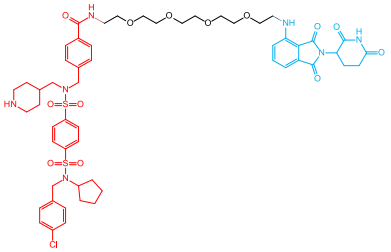
Compound 3j		HDAC6	VHL	MM (MM.1S) and Mouse 4935 Cell Line	83
12d		HDAC6	CRBN	MM (MM.1S)	84
NP8		HDAC6	CRBN	MM (MM.1S)	85
dTRIM24		TRIM24	VHL	ALL (MOLM-13)	86
UNC6852		PRC2	VHL	DLBCL (DB, Pfeiffer)	87

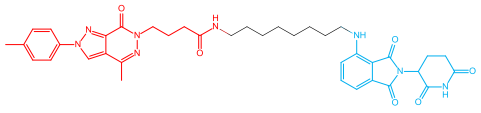
PROTAC 1/2		PRC2	VHL	NHL (Karpas-422)	88
SD-36		STAT3	CRBN	AML (MOLM-16)	89
TM-P4-Thal		SIRT2	CRBN	BC (MCF-7, BT-549)	90
Compound 12		SIRT2	CRBN	Cervical Cancer (HeLa)	91

Compound 3		PARP-1	CRBN	BC (MDA-MB-231)	92
iRucaparib-AP6		PARP-1	CRBN	Mouse C2C12 Myotubes	93
Degrader SK575		PARP-1	CRBN	CRC (SW620)	94
CN0		PARP-1	CRBN	BC (MDA-MB-231)	95
P22		PD-L1	CRBN	BC (MDA-MB-231)	96
Compound 15		PRMT5	VHL	BC (MCF-7)	97

ACBI1		SMARCA2/4, PBRM1	VHL	AML (MV4;11), NSCLC (H1568)	98
XY-4-88		KRASG12C	CRBN	Pancreatic Cancer (Paca-2), NSCLC (H358)	99
LC-2		KRASG12C	VHL	NSCLC (H2030, H23), Pancreatic Cancer (Paca-2)	100
YF135		KRAS	VHL	NSCLC (H358, A549, H23)	101

9d		SOS1	VHL	NSCLC (H358)	102
CM11		pVHL30	VHL	Cervical Cancer (HeLa), Osteosarcoma (U2OS)	103
WL40		Rpn13	CRBN	MM (MM.1S)	104
QC-01-175		Tau	CRBN	Patient-Derived Frontotemporal Dementia Neuronal Cells (A25T)	105
d9A2		SCL9	CRBN	CML (HAP1, KBM7)	106

MD-224		TP53	CRBN	ALL (RS4;11)	107
PROTAC 32		MDM2	CRBN	ALL (RS4;11)	108
DGY-08-097		NS3	CRBN	Huh7.5 Cells Infected with Wild Type HCV-Jc1	109
PROTACs 3/5		PDEδ	CRBN	ALL (Jurkat)	110

Compound 17f		PDEδ	CRBN	CRC (SW480)	[111]

ABC-DLBCL, activated B cell-like diffuse large B-cell lymphoma; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BC, breast cancer; BL, Burkitt lymphoma; mESCs, mouse embryonic stem cells; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; HUVECs, human umbilical vein endothelial cells; MCL, mantle cell lymphoma, mCRPC, metastatic castration-resistant prostate cancer; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell Lung cancer; PC, prostate cancer; TNBC, triple-negative breast cancer.

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