**Supplemental Material**

**Light-controllable PROTACs for temporospatial control of protein degradation**

Jing Liu1, \*, Yunhua Peng1, \*, Wenyi Wei 1, #

1Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

\* Jing Liu and Yunhua Peng contributed equally to this work.

#: To whom correspondence should be addressed:

Dr. Wenyi Wei, [wwei2@bidmc.harvard.edu](mailto:wwei2@bidmc.harvard.edu)

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| **Supplemental Table 1. Representative PROTACs and their biological functions.** | | | |
| POI | PROTAC | Ligand, E3 and Cellular Functions | Ref. |
| ALK | TD-004 | * ceritinib; VHL. * induces the degradation of the NPM-ALK and the EML4-ALK fusion proteins; * inhibits the proliferation of SU-DHL-1 and H3122 cells; * reduces the tumor growth in H3122 xenograft model. | [[1](#_ENREF_1)] |
| ALK | Compd. 9 and 11 | * TAE684 or LDK378; pomalidomide; CRBN. * induces the degradation of NPM-ALK and EML4-ALK; * inhibits the proliferation of H3122, Karpas 229 and SU-DHL-1 cells. | [[2](#_ENREF_2)] |
| ALK | SIAIS117 | * Brigatinib; VHL-1; VHL. * induces the degradation of NPM-ALK, EML4-ALK and the ALK-G1202R mutant; * inhibits the proliferation of SR and H2228 cells, as well as 293T cells expressing ALK-G1202R-resistant proteins. | [[3](#_ENREF_3)] |
| AR | ARV-110 | * pomalidomide; CRBN. * completely degrades AR and various AR mutants; * inhibits AR-dependent cell proliferation and induces potent apoptosis in VCaP cells; * reduces AR protein abundance in xenograft VCaP tumor model. | [[4](#_ENREF_4)] |
| AR | ARCC-4 | * enzalutamide; VHL. * degrades wild type AR and clinically relevant mutant forms of AR; * inhibits the proliferation of PRCA cells; * retains anti-proliferative effect in a high androgen environment. | [[5](#_ENREF_5)] |
| AR | ARD-69 | * enzalutamide; VHL. * induces the degradation of AR; * inhibits the proliferation of AR+ PRCA cells (LNCaP, VCaP and 22Rv1); * reduces AR protein abundance in VCaP xenograft tumor tissue (IP injection). | [[6](#_ENREF_6)] |
| AKT1/2/3 | INY-03-041 | * GDC-0068; lenalidomide; CRBN. * induces the degradation of AKT1/2/3; * inhibits the proliferation of MOLT4, LNCaP and BRCA cells (ZR-75-1, T47D, MCF-7, MDA-MB-468 and HCC1937). | [[7](#_ENREF_7)] |
| AURORA-A | JB170 | * alisertib, thalidomide; CRBN. * induces rapid, durable and highly specific degradation of AURORA-A; * causes an S-phase defect, which is not observed upon kinase inhibition; * induces rampant apoptosis in cancer cell lines. | [[8](#_ENREF_8)] |
| BCL2/MCL-1 | C3, C5 | * S1-6 or Nap-1; Pomalidomide; CRBN. * induces the degradation of Mcl-1 and Bcl-2; * induces lethality in H23 cells. | [[9](#_ENREF_9)] |
| BCL6 | Compd. 15 | * pomalidomide; CRBN. * induces the degradation of BCL6; * weak anti-proliferative response in DLBCL OCI-Ly1 cells. | [[10](#_ENREF_10)] |
| BCL-XL | XZ739 | * ABT-263; pomalidomide; CRBN. * induce the degradation of BCL-XL; * inhibits the proliferation MOLT-4 cells more potent than ABT-263; * less toxic to human platelets than ABT-263; * induces apoptosis of MOLT-4 cells. | [[11](#_ENREF_11)] |
| BCL-XL | PZ15227 (PZ) | * ABT-263; pomalidomide; CRBN. * induces the degradation of BCL-XL; * less toxic to platelets, but equally or slightly more potent against senescent cells; * effectively clears senescent cells and rejuvenates tissue stem and progenitor cells in naturally aged mice without causing severe thrombocytopenia. | [[12](#_ENREF_12)] |
| BCR-ABL | SIAIS178 | * dasatinib; VHL 1; VHL. * induces the degradation of BCR-ABL and several clinically relevant resistance-conferring mutant forms of BCR-ABL; * achieves significant growth inhibition of BCR-ABL+ leukemic cells *in vitro;* * induces substantial tumor regression against K562 xenograft tumors *in vivo.* | [[13](#_ENREF_13)] |
| BCR-ABL | GMB-475 | * VHL. * induces rapid degradation of BCR-ABL and inhibition of downstream biomarkers, such as STAT5 in CML K562 cells and murine Ba/F3 cells expressing BCR-ABL1; * inhibits the proliferation of certain clinically relevant BCR-ABL1 kinase domain point mutants and further sensitizes Ba/F3 BCR-ABL1 cells to inhibition by imatinib, while demonstrating no toxicity toward Ba/F3 parental cells; * reduces the viability and increases apoptosis of primary CML CD34+ cells, with no effect on healthy CD34+ cells; * degrades BCR-ABL1 and reduces cell viability in primary CML stem cells. | [[14](#_ENREF_14)] |
| BCR-ABL | DAS-6-2-2-6-CRBN | * dasatinib or bosutinib; pomalidomide; CRBN. * induces the degradation of ABL and ABL/BCR; * inhibits the proliferation of ABL/BCR-expressing K562 cells. | [[15](#_ENREF_15)] |
| BRAF | Compd. 2 | * RGS; pomalidomide; CRBN. * induces the degradation of BRAF; * induces apoptosis of MCF-7 cells. | [[16](#_ENREF_16)] |
| BRAF | Compd. 12 and 23 | * vemurafenib or BI882370; thalidomide; CRBN. * induces selective degradation of BRAF-V600E, but not wild-type BRAF; * inhibits the proliferation of A375 and HT-29 cells. | [[17](#_ENREF_17)] |
| BRD4 | dBET1 | * JQ1; pomalidomide; CRBN. * induces the degradation of BRD4; * inhibits the proliferation of MV4-11 cells. | [[18](#_ENREF_18)] |
| BRD4 | ARV-825 | * JQ1; pomalidomide; CRBN. * induces the degradation of BRD4 in Burkitt's lymphoma (BL) cells; * inhibits the proliferation and induces apoptosis in BL cells. | [[19](#_ENREF_19)] |
| BRD4 | dBET6 | * JQ1; pomalidomide; CRBN. * induces the degradation of BRD4; * inhibits the proliferation of T-ALL cells; * prompts a collapse of global elongation that phenocopies CDK9 inhibition. | [[20](#_ENREF_20)] |
| BRD4 | MZ1 | * JQ1, VHL. * induces reversible, long-lasting and unexpectedly selective removal of BRD4 over BRD2 and BRD3. | [[21](#_ENREF_21)] |
| BRD7/9 | VZ185 | * VHL. * degrades BRD7 and BRD9; * inhibits the proliferation of EOL-1 and A-204 cancer cells. | [[22](#_ENREF_22)] |
| BTK | Compd. 10 | * pomalidomide; CRBN. * induces the degradation of BTK in Ramos cells and in Rat’s spleen. | [[23](#_ENREF_23)] |
| BTK and BTK-C481S | P13I | * ibrutinib; pomalidomide; CRBN. * induces BTK degradation in human ABC-DLBCL, HBL-1 cells and other NHL cell lines including MCL (Mino cells) and MM cell lines; * inhibits the proliferation of HBL-1 cells expressing BTK-C481S. | [[24](#_ENREF_24)] |
| BTK-C481S | L18I | * ibrutinib; lenalidomide; CRBN. * induces the degradation of BTK-C481S and other C481 mutates; * inhibits the growth of DLBCL and MCL cells; * induces rapid tumor regression of C481S BTK HBL-1 xenograft tumors. | [[25](#_ENREF_25)] |
| BTK | CJH-005-067 and DD-04-015 | * bosutinib or RN486; pomalidomide; CRBN. * induces the degradation of BTK; * inhibits the proliferation of TMD8 DLBCL cell. | [[26](#_ENREF_26)] |
| CDC20 | CP5V | * Apcin; VHL. * degrades Cdc20 in MCF7 and MDA-MB-231 BRCA cells; * leads to significant inhibition of BRCA cell proliferation and re-sensitization of Taxol-resistant cell lines; * suppresses breast tumor progression in 4T1 xenograft mouse model. | [[27](#_ENREF_27)] |
| CDK2 | CPS1/2/3 | * JNJ-7706621; pomalidomide; CRBN. * promotes rapid and potent degradation of CDK2, but not other CDKs; * induces remarkable differentiation of AML cell lines and primary patient cells. | [[28](#_ENREF_28)] |
| CDK2 and CDK5 | TMX-2172 | * TMX-2039; pomalidomide; CRBN. * induces the degradation of CDK2 and CDK5; * inhibits the proliferation of OVCAR8 cells. | [[29](#_ENREF_29)] |
| CDK2 and CDK9 | Compd. F3 | * FN-1501; pomalidomide; CRBN. * induces the degradation of CDK2 and CDK9; * inhibits the proliferation of PC-3 cells. | [[30](#_ENREF_30)] |
| CDK4 | BSJ-03-132 | * abemaciclib; pomalidomide; CRBN. * induces the degradation of CDK4. | [[31](#_ENREF_31)] |
| CDK4 and CDK6 | BSJ-02-162; BSJ-03-204 | * palbociclib; pomalidomide ; CRBN. * induces the degradation of CDK4 and CDK6; * inhibits the proliferation of MCL cell lines. | [[31](#_ENREF_31)] |
| CDK4 and CDK6 | pal-pom | * palbociclib; pomalidomide ; CRBN. * degrades CDK4 and CDK6. | [[32](#_ENREF_32)] |
| CDK6 | Degrader 6 | * palbociclib; pomalidomide ; CRBN. * induces the degradation of CDK6, but not CDK4 or other CDKs. | [[33](#_ENREF_33)] |
| CDK6 | YX-2-107 | * palbociclib; thalidomide; CRBN. * promotes the degradation of CDK6 over CDK4 in Ph+ ALL cells; * suppresses S-phase cells; * suppresses leukemia burden in mice injected with primary Ph+ ALL cells. | [[34](#_ENREF_34)] |
| CDK6 | BSJ-03-123 | * palbociclib; pomalidomide; CRBN. * induces the degradation of CDK6; * inhibits the proliferation of AML cell lines. | [[35](#_ENREF_35)] |
| CDK6 | CP-10 | * palbociclib; pomalidomide; CRBN. * inhibits the proliferation of cancer cells (MM.1S, Mino, HL-60, JeKo-1); * induces the degradation of CDK6-WT, D163G and S178P mutants. | [[36](#_ENREF_36)] |
| CDK9 | Compd. 3 | * aminopyrazole; thalidomide; CRBN. * induces the degradation of CDK9 in HCT116 cells. | [[37](#_ENREF_37)] |
| CDK9 | 11c | * flavopiridol; pomalidomide; CRBN. * selectively degrades CDK9; * inhibits the proliferation of CDK9-overexpressed cancer cells. | [[38](#_ENREF_38)] |
| EGFR | PROTAC 2 | * lenalidomide; CRBN. * induces degradation of EGFR in HCC827 cells; * induces the apoptosis of HCC827 cells and arrest the cells in G1 phase. | [[39](#_ENREF_39)] |
| EGFR | PROTAC 10 | * VHL ligand; VHL. * induces the degradation of EGFR in HCC827 cells; * induces the apoptosis of HCC827 cells and arrest the cells in G1 phase. | [[40](#_ENREF_40)] |
| EGFR | MS39 | * gefitinib; VHL ligand; VHL. * induces the degradation of mutant, but not wild-type EGFR; * suppresses the growth of lung cancer cells (HCC-827 with EGFR-e19d and H3255 cells with EGFR-L858R mutant). | [[41](#_ENREF_41)] |
| EGFR mutant | 14o | * XTF262; VHL. * effectively and selectively degraded EGFRL858R/T790M, but not wild-type EGFR. | [[42](#_ENREF_42)] |
| EGFR mutant | MS154 | * gefitinib; pomalidomide; CRBN. * induces the degradation of mutant, but not wild-type EGFR; * suppresses the growth of lung cancer cells (HCC-827 with EGFR-e19d and H3255 cells with EGFR-L858R mutant). | [[41](#_ENREF_41)] |
| EGFR mutant | DDC-01-163 | * pomalidomide; CRBN. * allosteric EGFR degrader; * selective degrades clinically relevant EGFR mutants; * selectively inhibits the proliferation of L858R/T790M (L/T) mutant Ba/F3 cells but not wildtype EGFR Ba/F3 cells; * inhibits the proliferation of osimertinib-resistant cells with L/T/C797S and L/T/L718Q EGFR mutations. | [[39](#_ENREF_39)] |
| ER | ERD-308 | * tamoxifen; VHL. * degrades ER in MCF-7 and T47D ER+ BRCA cell lines; * more effective in inhibition of cell proliferation than fulvestrant in MCF-7 cells. | [[43](#_ENREF_43)] |
| ER | ARV-471 | * thalidomide; CRBN. * robustly degrades ER in ER-positive breast cancer cell lines; * decreases the expression of classically-regulated ER-target genes (PR, GREB1, TFF); * inhibits the proliferation of ER-dependent cell lines (MCF7, T47D); * degrades clinically-relevant ER variants (Y537S and D538G) and inhibits growth of cell lines expressing those variants; * degrades rat uterine ER in an immature rat uterotrophic model; * daily, oral-administration leads to tumor volume regression of estradiol-dependent MCF7 xenografts and tumor ER protein reduction; * inhibits the growth and reduces mutant ER protein levels in an ER-Y537S, hormone-independent patient-derived xenograft model. | [[44](#_ENREF_44)] |
| ERR | Compd. 6c | * XCT790; VHL. * capable of specifically degrading ERRα. | [[45](#_ENREF_45)] |
| FAK | FC-11 | * PF562271; thalidomide; CRBN. * induces a potent and reversible FAK degradation in reproductive tissues of male mice. | [[46](#_ENREF_46)] |
| FAK | PROTAC-3 | * defactinib; VHL. * degrades FAK; * inhibits FAK signaling; * represses FAK-mediated cell migration and invasion in MDA-MB-231 cells. | [[47](#_ENREF_47)] |
| FLT3 | TL13-117; TL13-149 | * AC220; pomalidomide; CRBN. * induces the degradation of FLT3; * inhibits the proliferation of MOLM-14 and MV4-11 cells. | [[26](#_ENREF_26)] |
| HDAC1/2/3 | Compd. 4 | * benzamide; VHL. * degrades HDAC 1/2/3; * increases histone acetylation levels; * compromises the viability of colon cancer HCT116 cells. | [[48](#_ENREF_48)] |
| HDAC6 | dHDAC6-9c | * a pan-HDAC inhibitor; pomalidomide; CRBN. * induces the degradation of HDAC6 in MCF7 and MM.1S cells. | [[49](#_ENREF_49)] |
| HDAC6 | dHDAC6-12d | * nexturastat A; pomalidomide; CRBN. * induces the degradation of HDAC6; * inhibits the proliferation of multiple myeloma cells. | [[50](#_ENREF_50)] |
| HDAC6 | NP8 | * nexturastat A; pomalidomide; CRBN. * induces the degradation of HDAC6; * inhibits the proliferation of multiple myeloma cells. | [[51](#_ENREF_51)] |
| HDAC6 | Compd. 3j | * nexturastat A; VHL. * degrades HDAC6 in human MM1S cells and mouse 4935 cells. | [[52](#_ENREF_52)] |
| HMGCR | P22A | * atorvastatin; pomalidomide; CRBN. * reduces HMGCR protein in SRD15 cells; * blocks cholesterol biosynthesis potently with less compensatory upregulation of HMGCR. | [[53](#_ENREF_53)] |
| KRAS | LC-2 | * MRTX849; VHL. * covalently binds and degrades KRAS-G12C; * leads to suppression of the MAPK signaling in both homozygous and heterozygous KRAS-G12C cell lines. | [[54](#_ENREF_54)] |
| IRAK4 | Compd. 9 | * PF06650833; VHL. * induces the degradation of IRAK4; * induces the inhibition of multiple cytokines in PBMCs, but not in IL-1β stimulated human dermal fibroblasts. | [[55](#_ENREF_55)] |
| MDM2 | PROTAC 8 | * MI-1061; lenalidomide; CRBN. * reduces MDM2 protein level; * exhibits enhanced efficacy in the RS4;11 xenograft model relative to MI-1061. | [[56](#_ENREF_56)] |
| MDM2 | MD-224 | * MI-1061; lenalidomide; CRBN. * induces rapid degradation of MDM2 at concentrations <1 nM in human leukemia cells. * inhibits the growth of RS4;11 cells and leukemia cell lines; * achieves complete and durable tumor regression *in vivo* in the RS4;11 xenograft tumor model in mice. | [[57](#_ENREF_57)] |
| MEK1/2 | Compd. 3 | * refametinib virtual analog 1; VHL ligand; VHL. * reduces MEK1 and MEK2 protein levels; * inhibits the proliferation of A375 cells. | [[58](#_ENREF_58)] |
| MEK1/2 | MS432 | * PD0325901; VHL. * induces the degradation of MEK1/2; * inhibits the proliferation of HT-29 colorectal cancer and SK-MEL-28 melanoma cell, phenocopied by MEK1/2 knockdown. | [[59](#_ENREF_59)] |
| PARP1 | iRucaparib | * rucaparib; pomalidomide; CRBN. * selectively targets PARP1 for degradation; * inhibits PARylation-mediated signaling events downstream of PARP1; * protects cells from genotoxicity-induced cell death. | [[60](#_ENREF_60)] |
| PARP1 | compound 3 | * VHL. * induces significant PARP1 cleavage; * induces programmed cell death in MDA-MB-231 cells. | [[61](#_ENREF_61)] |
| PCAF/GCN5 | GSK983 | * GSK4027; pomalidomide; CRBN. * degrades PCAF/GCN5; * potently modulates the expression of multiple inflammatory mediators in LPS-stimulated macrophages and dendritic cells. | [[62](#_ENREF_62)] |
| PRC2 (EED/EZH2/SUZ12) | UNC6852 | * EED226; VHL. * induces the degradation of PRC2 components, EED, EZH2, and SUZ12; * blocks the histone methyltransferase activity of EZH2, decreasing H3K27me3 levels in HeLa cells and diffuse large B cell lymphoma (DLBCL) cells containing EZH2 gain-of-function mutations; * degrades both wild-type and mutant EZH2; * displays anti-proliferative effects. | [[63](#_ENREF_63)] |
| P38 | SJFα and SJF | * foretinib; VHL. * induces the degradation of p38α or p38δ in MDA-MB-231 cells. | [[64](#_ENREF_64)] |
| PI3K | Compounds D-F | * ZSTK474; pomalidomide; CRBN. * induces remarkable PI3K degradation and down-regulation of downstream signaling (p-Akt, p-S6K and p-GSK-3β) in HepG2 cells; * inhibits the proliferation of HepG2 cells by induction of autophagy instead of apoptosis or cell cycle arrest. | [[65](#_ENREF_65)] |
| RIPK2 | PROTAC 6 | * aminobenzothiazole-quinoline; VHL ligand; VHL. * induces potent degradation of RIPK2 in human PBMCs; * inhibits cytokine release in human disease tissue; * *in vivo* degradation of endogenous RIPK2 in rats at low doses with persisted PD. | [[66](#_ENREF_66)] |
| RTK | PROTAC 1 and 7 | * lapatinib and foretinib; VHL. * PROTAC 1 degrades HER2 in SKBR3 and OVCAR8 cells; * PROTAC 7 degrades c-MET in MDA-MB-231 cells. | [[67](#_ENREF_67)] |
| SGK3 | SGK3-PROTAC1 | * 308-R; VH032; VHL. * induces the degradation of SGK3 but not SGK1 and SGK2; * suppresses the proliferation of ZR-75-1 and CAMA-1 BRCA cells treated with a PI3K inhibitor (GDC0941); * restores the sensitivity of SGK3-dependent ZR-75-1 and CAMA-1 BRCA cells to Akt (AZD5363) and PI3K (GDC0941) inhibitors. | [[68](#_ENREF_68)] |
| SHP2 | SHP2-D26 | * SHP099; VHL. * degrades SHP2 in esophageal cancer KYSE520 cells and MV4-11 AML cells; * more potent in inhibition of p-ERK and of cell growth. | [[69](#_ENREF_69)] |
| SIRT2 | Compd. 12 | * SirReals; thalidomide; CRBN. * induces isotype-selective Sirt2 degradation; * causes hyperacetylation of the microtubule network coupled with enhanced process elongation in HeLa cells. | [[70](#_ENREF_70)] |
| SMAD 3 | SMAD PROTAC | * induces the degradation of Smad3 in ACHN cells; * inhibits the upregulation of fibronectin and Collagen I induced by TGF-β1 in both renal fibroblast and mesangial cells. | [[71](#_ENREF_71)] |
| SMARCA2/4 and PBRM1 | ACBI1 | * 2-(6-aminopyridazin-3-yl)phenols; VHL. * inhibits the proliferation and induces cell death in SMARCA4 mutant cancer cells and in AML cells. | [[72](#_ENREF_72)] |
| STAT3 | SD-36 | * SI-109; thalidomide; CRBN. * induces rapid degradation of STAT3, but not other STAT proteins; * inhibits cell growth in leukemia and lymphoma cell lines with high levels of p-STAT3; * a single dose results in complete STAT3 protein degradation in xenograft tumor tissue and normal mouse tissues. | [[73](#_ENREF_73), [74](#_ENREF_74)] |
| TRIM24 | dTRIM24 | * IACS-9571; VHL. * elicits potent and selective degradation of TRIM24; * induces anti-proliferative response. | [[75](#_ENREF_75)] |
| WEE1 | ZNL-02-096 | * AZD1775; pomalidomide; CRBN. * degrades Wee1 while sparing PLK1; * induces G2/M accumulation; * synergizes with Olaparib in ovarian cancer cells (OVCAR8, COV283, and Kuramochi). | [[76](#_ENREF_76)] |

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