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PROTACs – A Novel and Rapidly Developing Field of Targeted Protein Degradation

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PROTACs – A Novel and Rapidly Developing Field of Targeted Protein Degradation

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

By

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Abbreviations

α-syn – α-synuclein

ABC – Activated B-cell

AbTAC – Antibody-based PROTAC

AD – Alzheimer's disease

ALK – Anaplastic lymphoma kinase

ALL – Acute lymphoblastic leukemia

ALS – Amyotrophic lateral sclerosis

AML – Acute monocytic leukemia

AMPK – AMP-activated protein kinase

APC – Aptamer-PROTAC conjugate

AR – Androgen receptor

AS – Ankylosing spondylitis

ATRA – All-trans retinoic acid

AUTAC – Autophagy-targeting chimera

BBB – Blood brain barrier

BC – Breast cancer

BCL-2 – B-cell lymphoma 2

BCL-X$_L$ – B-cell lymphoma extra-large

BCR – B-cell receptor

BET – Bromodomain & extraterminal domain

bFGF – Basic fibroblast growth factor

BK$_{Ca}$ – Large-conductance Ca^{2+}-activated K$^+$ channel

BRD2/3/4/7/9 – Bromodomain-containing protein 2/3/4/7/9

BTK – Bruton's tyrosine kinase

CD147 – Cluster of differentiation 147

cdc – Cell division control

CDK – Cyclin-dependent kinase

CHIP – C-terminal Hsc70-interacting protein

c-IAP1/2 – Cellular inhibitor of apoptosis protein 1/2

CK2 – Casein kinase II

CML - Chronic myeloid leukemia

CNS – Central nervous system

COPD – Chronic obstructive pulmonary disease

CPP – Cell-penetrating protein

CRABP1/2 – Cellular retinoic acid-binding protein 1/2

CRBN – Cereblon

CRL – Cullin-RING E3 ubiquitin ligase

C-TPD-43 - C-terminal TPD-43

Da - Dalton

DBP – DNA-binding protein

dCas9HT7 – dCas9-Halotag7 fusion protein

DLBCL – Diffuse large b-cell lymphoma

DR – Death receptor

E1 – Ubiquitin-activating enzyme

E2 – Ubiquitin-conjugating enzyme

E_2 - 17β-estradiol hormone

E3 – Ubiquitin ligase

EC – Endothelial cell

eEF2K – Eukaryotic elongation factor 2 kinase

EGFR – Epidermal growth factor receptor

EMT – Epithelial-to-mesenchymal transition

ERα – Estrogen receptor alpha

ERRα – Estrogen receptor-related receptor alpha

FAK/PTK2 – Focal adhesion kinase

FOXM1 – Forkhead box protein M1

GS – Glutamine synthetase

GSK-3β – Glycogen synthase kinase 3

HA – Hemagglutinin

HBV/HCV – Hepatitis B/C virus

HCMV – Human cytomegalovirus

HD – Huntington's disease

HDAC - Histone deacetylases

HDACi – HDAC inhibitor

HCC – Hepatocellular carcinoma

HIF-1α – Hypoxia-inducible factor 1-alpha

HIV – Human immunodeficiency virus

HMG-CoA - 3-Hydroxy-3-methylglutaryl coenzyme A

HMGCR – HMG-CoA reductase

H-PGD – Hematopoietic prostaglandin D synthase

HPK-1 - Hematopoietic progenitor kinase 1

IAP – Inhibitor of apoptosis

IBD – Inflammatory bowel disease

ILF2 – Interleukin enhancer-binding factor 2

IMID – Immune-mediated inflammatory disease

IMiD – Immunomodulatory imide drug

INM – Indomethacin

ITK – IL2-inducible T-cell kinase

JAK-STAT - Janus kinase-Signal transducer and activator of transcription

LDL – Low-density lipoprotein

LYTAC – Lysosome-targeting chimera

M1 protein – Matrix gene segment

mAbs – Monoclonal antibodies

MAPK – Mitogen-activated protein kinase

MCL-1 – Myeloid cell leukemia-1

mCRPC – Metastatic castration-resistant prostate cancer

MDCK.2 – Madin-Darby canine kidney cells

MDM2 – Human murine / mouse double minute 2

MeBS – Methyl bestatin

MetAP-2 – Methionine aminopeptidase-2

MM – Multiple myeloma

MOA – Mechanism of action

MOMP - Mitochondrial outer membrane permeabilization

MS – Multiple sclerosis

mHtt – Mutant huntingtin protein

MW – Molecular weight

NA – Neuraminidase

NF-κB – Nuclear factor κB

NSCLC – Non-Small cell lung cancer

NS3 – Nonstructural protein 3

NSP7 – Non-structural protein

PARP1 – Poly (ADP-ribose) polymerase-1

PBMC – Peripheral blood mononuclear cells

PCAF/GCNS – P300/CBP-associated factor / general control nonderepressible 5

PD – Parkinson's disease

PEG – Polyethylene glycol

PNS – Peripheral nervous system

PPI – Protein-protein interaction

POI – Protein of interest

PRC2 – Polycomb repressive complex 2

Pre-let-7 – Let-7 precursor

PROTAC – Proteolysis targeting chimera

p-PROTAC – Peptide-based PROTAC

PTGES-2 – Prostaglandin E synthase type-2

PSA – Prostate-specific antigen

PsA - Psoriatic arthritis

RA - Rheumatoid arthritis

Ras/Raf/MEK/ERK – Ras/Raf/mitogen-activated protein kinase/ERK kinase/extracellular-signal-regulated kinase

RAR – Retinoic acid receptor

RBP – RNA-binding protein

RIBOTAC – Ribonuclease-targeting chimera

RIPK2 – Receptor-interacting serine/threonine protein kinase 2

RNAi – RNA interface

RNP – Ribonucleoprotein particle

RTK – Receptor kinase domain

SARM – Selective androgen receptor modulator

SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2

SCF – Skp1-Cullin-F box complex

SERD - Selective estrogen receptor degraders

SMI – Small molecule inhibitor

SMPI – Small-molecule proteolysis inducer

SNIPER – Specific & nongenetic IAP-dependent protein eraser

SREBP – Sterol regulatory element-binding protein

STAT3 – Signal transducer & activator of transcription 3

T-ALL - T-cell acute lymphoblastic leukemia

TCR – T-cell receptor

TEV$_{CS}$ – Tobacco etch virus cleavage site

TEV$_P$ – TEV protease

TF – Transcription factor

TME – Tumor microenvironment

TNBC – Triple negative breast cancer

TPD – Targeted protein degradation

TRAFTAC – Transcription factor targeting chimera

UPS – Ubiquitin-proteasome system

VEGF – Vascular endothelial growth factor

VEGFR – Vascular endothelial growth factor receptor

VHL – von Hippel-Lindau

XIAP – X-linked inhibitor of apoptosis

Abstract

There is a continued need for new technology and strategies for tackling cancer and other diseases, and within the current century a novel therapeutic strategy has emerged in the realm of targeted protein degradation called Proteolysis-Targeting Chimeras (PROTACs). This technology specifically targets and degrades disease-causing proteins via the ubiquitin-proteasome system, and has seen an explosion of research and intrigue in both academia and industry over the past two decades. The diversity of PROTAC classes based on the E3 ligase recruiting ligand and the target protein allows for a universal molecular structure that can be customized for a specific target and disease. While it is primarily heavily focused in the realm of cancer therapeutics, PROTACs have expanded into other diseases such as cardiovascular, neurodegenerative, and virus-caused diseases. The discovery of novel PROTAC designs also allows for the field to overcome its own shortcomings and develop into new directions. Overall, the intrigue of PROTAC technology's ability to degrade 'undruggable' targets has driven the field of research to expand rapidly in the short time since its initial discovery and continued intense efforts will help further shape the field to transition into the clinical setting to benefit the world.

1. Introduction

Proteins are crucial to the vitality of all living cells and are responsible for a myriad of cellular functions. Misfolded proteins that are not degraded within the cell can develop further into malignant tumors or other diseases that can be detrimental to human health[1]. Over the past few decades multiple new therapeutic strategies have emerged in order to try and address these major issues. These strategies include utilizing RNA interference (RNAi) or CRISPR/Cas9 technologies to either correct or degrade protein-encoding genes, as well as utilizing monoclonal antibodies (mAbs) or small molecule inhibitors (SMIs) to bind to and subsequently inhibit proteins. Despite their therapeutic potential, these technologies suffer from several faults that limit their efficacy such as drug resistance and unwanted off-target effects[2-4]. A novel therapeutic strategy which is gaining immense intrigue is targeted protein degradation (TPD), which specifically targets and degrades disease-causing proteins. Two common TPD drug types currently utilized in oncology clinical trials are immunomodulatory imide drugs (ImiDs) and selective estrogen receptor degraders (SERDs). While both of these TPD classes are effective in degrading their specific targets, they still suffer from poor pharmacokinetics, drug toxicity, and observed side effects in patients[5]. One strategy of TPD that has seen a rapid development and rising interest since its initial discovery is the utilization of PRoteolysis TArgeting Chimeras (PROTACs) due to its event-driven mechanism of action (MOA) and potential for degrading "undruggable" targets[6].

PROTACs are heterobifunctional small molecule compounds composed of three elements. First is the ligand that binds to the protein of interest (POI) called the POI ligand, the ligand that binds to the E3 ubiquitin ligase called the E3 ligand, and the linker that connects the two ligands together[7]. The first reported proof of concept for a PROTAC occurred in 2001 when Deshaies laboratory developed Protac-1 to successfully induce MetAP-2 degradation via ubiquitin-dependent proteolysis[8]. Several more papers were published afterwards utilizing peptide-based PROTACs that targeted disease-promoting proteins for degradation before the first small molecule-based PROTAC utilizing a human murine/mouse double minute 2 (MDM2) E3 ligase recruiting ligand was developed and reported in 2008[9]. The field of PROTACs underwent a transformation in the mid-2010s with the discovery and exploitation of several other small molecule-based PROTACs such as the Cereblon complex (CRBN), Von Hippel–Lindau-containing complex (VHL), and inhibitor of apoptosis protein (IAP)[2, 10]. The development of numerous new PROTAC technologies and the transition into clinical trials within the past five years have caused an explosion of research interest within both academia and industry, with a PubMed search of PROTACs producing 480 resulting publications in 2022 alone. This paper will highlight PROTAC mechanism, classification, and current applications to the realm of cancer and other diseases. Newer PROTAC technologies will be addressed, along with current and future clinical trials. Finally, the advantages and limitations of PROTACs will be discussed, concluding with considerations for improvements and future research directions both *in vitro* and *in vivo*.

2. PROTACs and Ubiquitin-Proteasome System

There are two major pathways within eukaryotic cells that control and mediate protein degradation. The first is the lysosomal proteolysis pathway, which utilizes lysosomes for the uptake and degradation of proteins[11]. The second is the ubiquitin-proteasome system (UPS), which utilizes the 76-amino-acid polypeptide ubiquitin and the 26S proteasome for protein degradation (Figure 1a). Ubiquitin is tagged onto the target protein through a cascade of enzymes, beginning with the ubiquitin-activating enzyme (E1) before being transferred to the ubiquitin-conjugating enzyme (E2) and then finally the ubiquitin-ligase (E3). E3 previously underwent substrate recognition with the target protein, and its subsequent attachment with E2 allows for the transfer of ubiquitin onto the target protein via its lysine residue. Repeated ubiquitination leads to the formation of a polyubiquitin chain on the target protein, which then directs it to the 26S proteasome for ATP-dependent degradation[12-15]. This mechanism for degrading both normal and misfolded proteins is highly conversed within eukaryotic cells and is crucial in maintaining intracellular homeostasis, regulating numerous important biological processes including proliferation, cell cycle control, and apoptosis. Dysregulation of the UPS causes the loss of protein quality control within the cell, thus resulting in malignancy development and tumorigenesis[16, 17].

A.
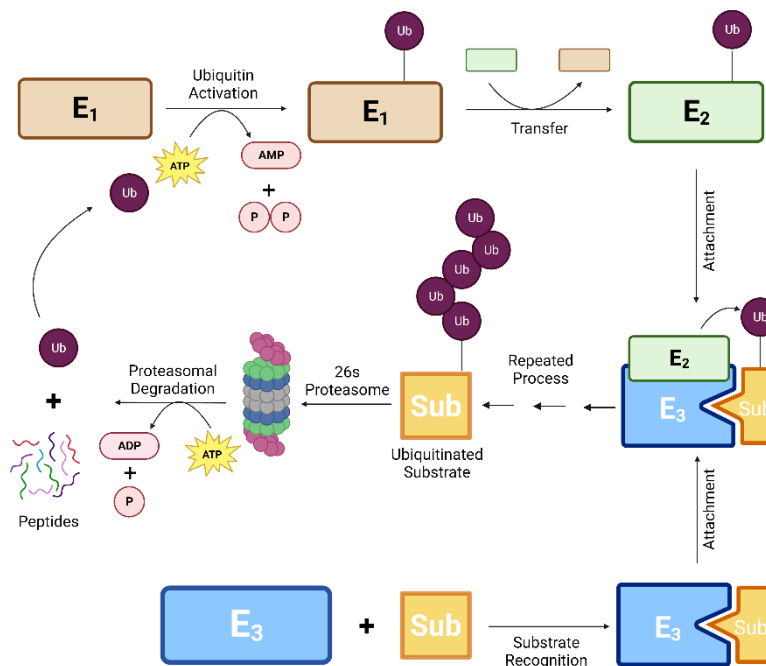
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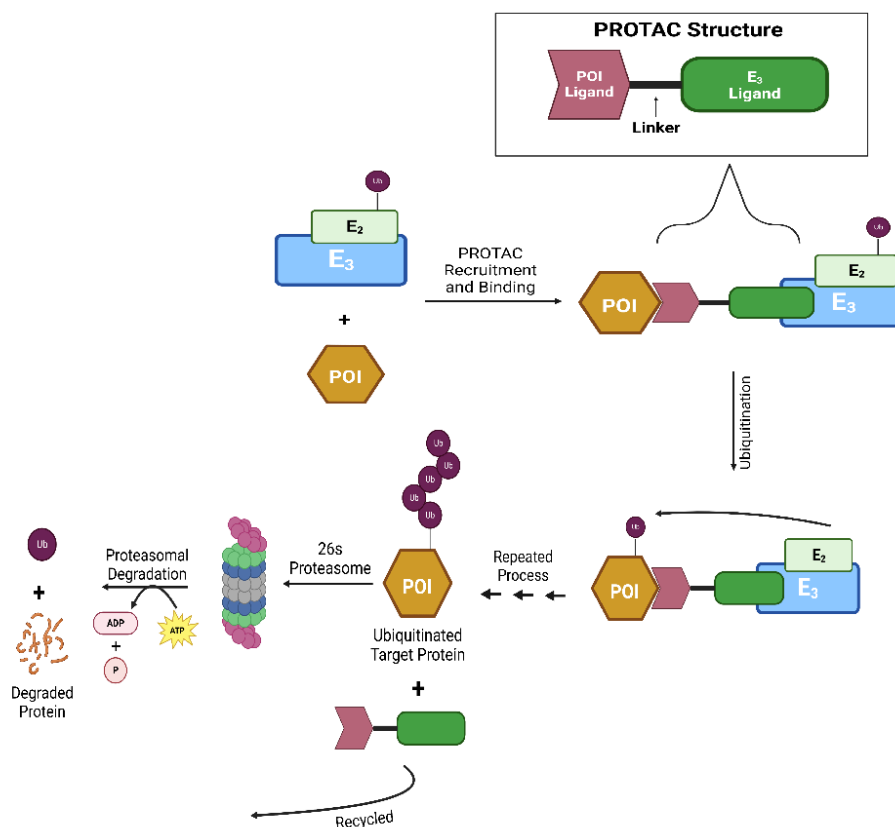
Figure 1) Mechanism of a) Ubiquitin-Proteasome System and b) PROTAC. Created using BioRender.com.

PROTACs have been designed to hijack the UPS in order to degrade target proteins (Figure 1b). Within the human proteasome, there are two E1s, roughly forty E2s, and over six hundred E3s. PROTACs simultaneously recruit and bind to the POI and E3 ligase, forming the "E3-PROTAC-POI" ternary complex. This allows for the ubiquitination of the POI and its subsequent degradation via the 26S proteasome[18-20]. The PROTAC is then recycled, targeting another copy of the POI to repeat the ubiquitination process once more. As such, a single PROTAC molecule can lead to a sub-stoichiometric protein knockdown, inducing more back-to-back protein degradation[21, 22]. While there has been significant investigation into the lipophilicity of PROTACs in order for them to interact with the UPS for degradation, there is currently no reports of the subsequent degradation and removal of PROTACs from both the cells and the body. Sub-stoichiometric activity would suggest that after a certain number of protein degradations the PROTAC will eventually lose functionality, but it is uncertain whether or not the PROTAC would be broken down into its individual components to then be degraded or exit

the cells as a whole molecule and then subsequently removed from the body. More research should be conducted into this area in order to answer this question.

3. Classification of PROTACs

The categorization of PROTACs begins with the variations of the POI ligand, whose chemical structure allows for PROTACs to be divided into three distinct groups. First are peptide-based PROTACs (p-PROTACs), then small molecule-based PROTACs, and finally the most recently contrived nucleotide-based PROTACs. These groups can then be further classified depending on the chemical structure of the E3 ligand.

3.a. Peptide-based PROTACs

p-PROTACs use peptidic POI ligands that simulate natural binding protein sequences, giving them a larger surface area contact for regulating protein-protein interaction (PPI) in comparison to small molecule PROTACs[23]. The very first PROTAC utilized IκBα phosphopeptide as the E3 ligand which recognized a ubiquitin ligase complex Skp1-Cullin-F box complex (SCF), binding to the protein β-TRCP. The POI ligand, ovalicin, was selected as the other PROTAC domain to target methionine aminopeptidase-2 (MetAP-2) due to the compound's ability to inhibit MetAP-2 activity. Because MetAP-2 is not known to have any correlation to the SCF complex, Protac-1 was synthesized to artificially recruit MetAP-2 to the $SCF^{\beta\text{-}TRCP}$ and was successful in MetAP-2 recruitment, ubiquitination, and degradation[8]. Two years later the concept of $SCF^{\beta\text{-}TRCP}$ recruitment was further expanded to develop p-PROTACs that targeted estrogen receptor alpha (Erα) and androgen receptor (AR) for degradation, successfully showing proof of concept for PROTACs to artificially target other disease-promoting proteins to the UPS[24]. Despite their potential in clinical use, these early p-PROTACs had too high of a molecular weight and needed to be microinjected, along with the potential for the phosphopeptides to be susceptible to intracellular phosphatases. This challenge was overcome with the development of cell-permeable p-PROTACs that utilized von Hippel-Lindau protein (VHL) as the E3 ligand, with the first VHL-linked p-PROTACs successfully targeting and degrading PI3K and FRS2α within various cancer cell types[25, 26].

Over the past two decades, several p-PROTACs have been successfully developed and demonstrated to target specific POIs within a myriad of cancers and neurodegenerative diseases (Table 1). p-PROTACs also benefit from the utilization of cell-penetrating peptides (CPPs), which are short peptides composed of less than 40 amino acids that can cross across the cell membrane through numerous mechanisms, namely endocytosis, direct penetration, and transitory structure translocation[27]. These peptides, such as poly-D-arginine and HIV-1 TAT, can deliver a myriad of bioactive cargo (peptides, proteins, oligonucleotides, drug molecules) into a cell via covalent or noncovalent interactions, making it an effective intracellular delivery technique[23, 28, 29].

Name	Target	E3 Ligase	Linker	POI Ligand	CPP	Cancer(s)/ Disease	Reference(s)
ErbB2PP_{PI3K}	PI3K	VHL	PEG	ErbB2 phosphorylation site	Polyarginine	BC, OC	25, 26
TrkAPP _{FRS2α}	FRS2α	VHL	Ahx	TrkA trans-autophosphorylation site	Polyarginine	Pheos	25, 26
PROTAC-X-protein	X-protein	VHL	NL	Oligomerization peptide	Polyarginine	HBV-induced HCC	30
PROTAC-Akt	Akt	VHL	PEG	tri_a	TAT	OC	31
NL	Tau-protein	VHL	GSGS	Tau recognition peptide (TH006)	Polyarginine	AD	32
TD-PROTAC	ERα	VHL	Ahx	TD-PERM	NL	BC	33
NL	Tau-protein	Keap1	GSGS	Tau recognition peptide	Polyarginine	BMC, NB, Pheos	34
Compound I-6	ERα	VHL	Ahx	Lactam cyclic peptide	NL	BC	35
PRTC	CREPT	VHL	Ahx	CREPT Ligand	Pentapeptide	PaC	36
xStAx-VHLL	Wnt/B-catenin	VHL	Ahx	xStAx	NA	CRC, HEK293T cells	37
FOXM1-PROTAC	FOXM1	Pomalidomide	PEG	F-1 peptide	TAT	Liver Cancer	38
Au-AR pep-PROTAC	AR DBD	MDM2	GGSGG	AR DBD targeting peptide	Au-peptide	CRPC	39

Table 1) Representative peptide-based PROTACs, arranged by publication date. (AD – alzheimer's disease, Ahx – aminohexanoic acid, BC – breast cancer, BMC – bone marrow cancer, CRC – colorectal cancer, CRPC – castration resistant prostate cancer, DBD – DNA binding domain, HBV-induced HCC – hepatitis b virus-induced hepatocellular carcinoma, LC – lung cancer NA – not applicable, NB – Neuroblastoma, NL – not listed in publication, OC – ovarian cancer, PaC – pancreatic cancer, PEG – polyethylene glycol, Pheos - Pheochromocytoma)

3.b. Small molecule-based PROTACs

Small molecule-based PROTACs utilize small molecules – particularly FDA approved drugs – as the POI ligand, allowing for increased cell permeability and digestion resistance[18]. The discovery of these small molecule-based PROTACs rapidly evolved and shaped the field, expanding the number of disease-promoting proteins that can be targeted. One of the major advancements with small molecule-based PROTACs is that it has more E3 ligands exploited and available for use in comparison to p-PROTACs. There are currently four major E3 ligases reportedly targeted for all small molecule-based PROTACs: MDM2, IAP, small-molecule VHL, and CRBN (Figure 2)[2].

A.
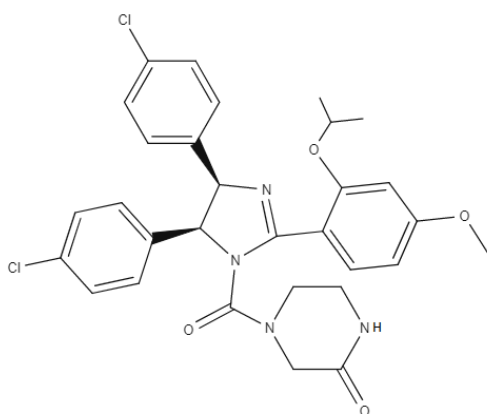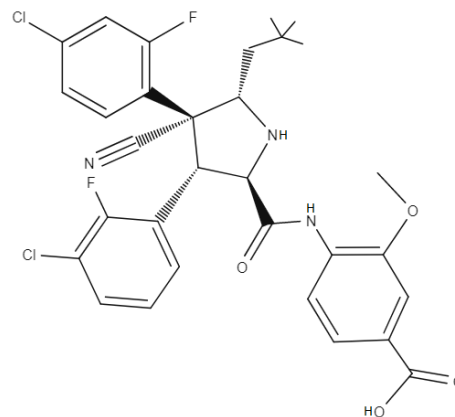
Nutlin-3   **Idasanutlin (RG7388)**

B.
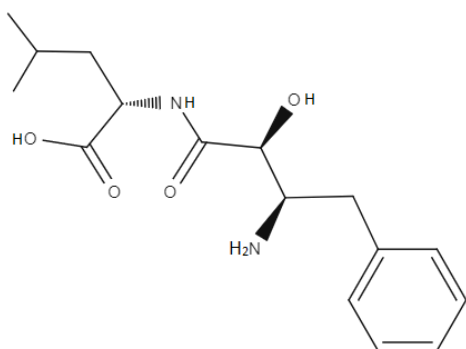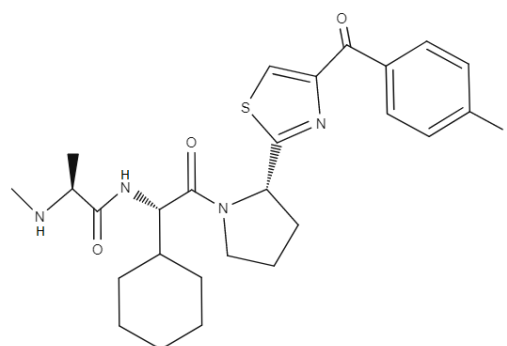
Bestatin   **LCL161**

C.
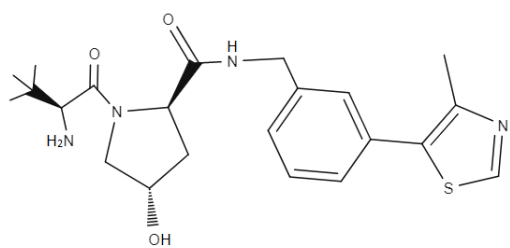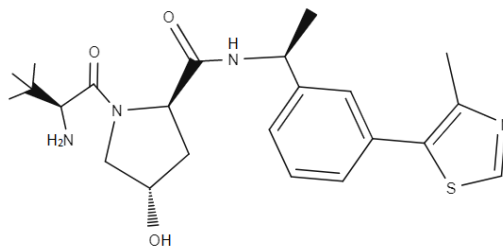
VHL-L 107 (VHL 1)   **VHL-L 122 (VHL 2)**

D.
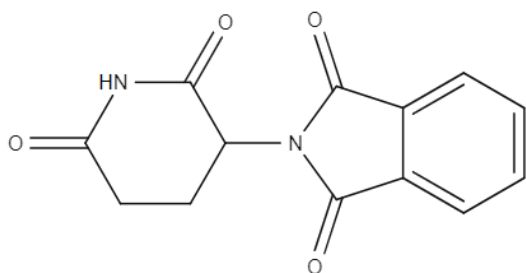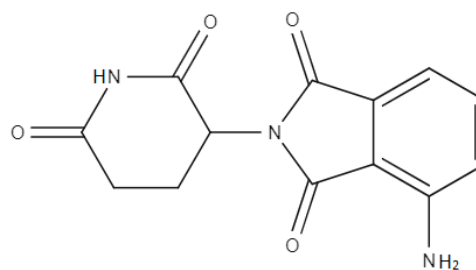
Thalidomide   **Pomalidomide**
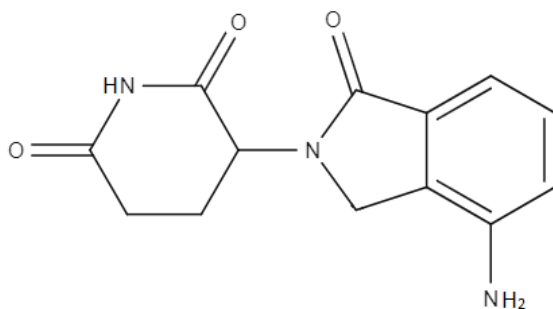
Lenalidomide

Figure 2) Structures of most reported E3 ligands for a) MDM2, b) IAP, c) small molecule VHL, and d) CRBN used for targeted protein degradation.

3.b.1. MDM2

Within normal cells, the tumor suppressor p53 protein is a crucial transcription factor (TF) in cancer prevention, either inducing growth arrest for DNA damage repair or apoptosis for unrepairable cell degradation. This "guardian of the genome" can experience a loss of function via point mutation or gene deletion, allowing for the damaged DNA to undergo unrestrained proliferation and result in cancer and other disease development. Therefore, focus on restoring p53 within cancer cells has been one of the goals for cancer therapeutic research[40-44]. MDM2 is a well-known negative regulator of the p53 tumor suppressor, able to inhibit the protein and regulate its homeostasis through three general techniques[45, 46]. First, it can directly bind to the transactivation domain and subsequently inhibit p53. Second, it contains a nuclear export signal sequence, inducing p53 nuclear export once bound together and preventing p53 from being able to bind to its target DNAs. Third, and the most efficient, it is an E3 ubiquitin ligase which stimulates p53 ubiquitylation and subsequent degradation[47-49]. The MDM2-p53 interaction is uncoupled via numerous mechanisms upon exposure to different stress signals within the cell, resulting in activation of the p53 pathway[50]. Research targeting and disrupting the MDM2-p53 interaction to result in rehabilitation of p53 function has been explored in the field of cancer therapeutics, with two current variations of MDM2-related PROTAC degraders being utilized for TPD. The first recruits an MDM2 inhibitor as the POI ligand to degrade the MDM2, and the second recruits MDM2 as the E3 ligand to degrade other POIs for degradation (Figure 2a)[46].

The first MDM2-based – and first ever small molecule-based – PROTAC utilized Nutlin-3, a powerful MDM2 inhibitor, as the E3 ligand and a non-steroidal selective androgen receptor modulator (SARM) as the POI ligand, with a PEG-based linker connecting the two domains. This SARM-nutlin PROTAC successfully recruited AR for ubiquitylation and subsequent degradation within HeLa cells[9]. Nutlin-3 (including variations 3a and 3b) is the primary E3 ligand utilized for MDM2-based PROTACs, along with RG7388 inhibitor (idasanutlin) which was discovered in 2013 as a second generation nutlin capable of MDM2-p53 interaction inhibition[51, 52]. MDM2-based PROTACs have also successfully targeted bromodomain-containing protein 4 (BRD4), Poly (ADP-ribose) polymerase-I (PARP1), and epidermal growth factor receptor (EGFR) mutants[53-55]. There has also been a recent study where a series of potent MDM2 degrading PROTACs have been synthesized, with the most promising compound MD-224 as the POI ligand and CRBN E3 ligand resulting in MDM2 degradation within human leukemia cells[56]. MG-277, an analogue of MD-224, showed that modifying the simple structure resulted in the first example of conversion of a *bona fide* MDM2 PROTAC degrader into a "molecular glue", inducing GSPT1 degradation[57]. Despite the therapeutic potential MDM2 portrays due to its dual-mode MOA, further inquiries had lagged as a result of interest directed towards other small molecule E3 ligands.

3.b.2. IAP

IAP family proteins are a class of negative regulators for apoptosis, inhibiting caspases in order to suppress apoptotic cell death. Along with their ability to inhibit apoptosis, IAP proteins can also have functions in a variety of other biological functions, such as mediating inflammatory signaling and mitogenic kinase signaling[58-61]. The IAP family consists of eight members, with

the most well-known being cellular inhibitor of apoptosis protein 1 (c-IAP1), cellular inhibitor of apoptosis protein 2 (c-IAP2), and X-linked inhibitor of apoptosis (XIAP)[62-64]. IAPs are often overexpressed in cancers and other diseases, making them a target of interest for cancer therapeutics. One of the most prominent functions of IAP is that they are an E3 ubiquitin ligase that can promote degradation of NIK, a key kinase in the noncanonical nuclear factor κB (NF-κB) signaling pathway[65]. As such, IAP-based PROTACs, also known as specific and nongenetic IAP-dependent protein erasers (SNIPERs), have been synthesized with IAP inhibitors and their derivatives as the E3 ligand (Figure 2b)[66].

The first IAP-based PROTACs utilized methyl bestatin (MeBS), which binds to and promotes cIAP1 auto-ubiquitylation and subsequent degradation, as the E3 ligand and *all-trans* retinoic acid (ATRA) as the POI ligand, connected via a linker. This PROTAC targeted and successfully degraded cellular retinoic acid-binding proteins I and II (CRABP1/CRABP2) in acute lymphoblastic leukemia (ALL) and fibrosarcoma cells[67]. Despite the successful degradation of the target protein, this PROTAC also induced auto-ubiquitylation and degradation of cIAP1, though this was overcome with a following study that redesigned the PROTAC by switching the ester group at the MeBS linker attachment with an amide group, allowing for only CRABP2 degradation[68]. IAP-based PROTACs have also successfully degraded a myriad of POIs across various cancers and diseases, including AR, BCR-ABL, BRD4, ERα, EGFR, mutant huntingtin protein (mHtt), and retinoic acid receptors (RARs)[65, 69-71]. These PROTACs have great therapeutic potential due to their parallel degrading pathways, though fewer reports of their utilization limit the target scope knowledge.

3.b.3. Small molecule VHL

The VHL protein functions as a substrate-recognizing subunit of the Cullin-RING E3 ligase complex (VHL-EloBC-Rbx1-Cul2 complex / CRL2^{VHL} complex), where it is associated with the Cullin2 central scaffold subunit, ElonginB and ElonginC adaptor subunits, and Rbx1 RING subunit. Under normoxic conditions, VHL specifically binds to hydroxylated hypoxia-inducible factor 1-alpha (HIF-1α), an oxygen-dependent TF with roles in tumor angiogenesis, resulting in its ubiquitylation and subsequent degradation[72-75]. This tumor suppressor protein acts as a negative regulator of HIF-1α, playing a role in gene regulation and cell division control, thus making it a formidable drug target for cancer therapy[76]. VHL-linked p-PROTACs were designed to target the HIF-1α peptide fragment, but had several drawbacks typically seen within p-PROTACs such as cell permeability difficulties. To overcome these limitations, VHL-based small molecule PROTACs were developed utilizing VHL ligands that focused on small molecule inhibitors as replacements for these fragments (Figure 2c)[77-79].

After the discovery of the VHL ligands, the first VHL-based small molecule PROTACs were reported, successfully targeting and degrading the estrogen receptor-related receptor α (ERRα) and receptor-interacting serine/threonine protein kinase 2 (RIPK2) in breast cancer (BC) and acute monocytic leukemia (AML)[21]. This E3 ligand is one of the most reported variations of small molecule-based PROTACs published, with over 50 POIs reported over numerous cancers and other diseases including (but not limited to) the bromodomain and extraterminal domain (BET) family, BCR-ABL, anaplastic lymphoma kinase (ALK), and TRIM24[80-84]. One of the

main intrigues of VHL-based small molecule PROTACs is that they have a high target-specificity, making them have high potency and thus are one of the two major PROTACs seen reported to date[85].

3.b.4. CRBN

The CRBN protein has several diverse roles within the body, ranging from cell metabolism and proliferation to apoptosis and pathogenesis. It acts as the substrate recognizing subunit of the CRL4^{CRBN} E3 ubiquitin ligase complex, which includes damaged DNA binding protein 1 (DDB1), Cullin-4A (Cul4A), and regulators of cullins 1 (ROC1)[86]. This complex results in the ubiquitylation and subsequent degradation of multiple POIs, including interleukin enhancer-binding factor 2 (ILF2), glutamine synthetase (GS), and Ikaros family zinc finger proteins (IFZF1/IFZF3)[87-89]. CRBN also plays a role in ion transport regulation, being responsible for targeting large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels for ubiquitylation, as well as acting as a metabolic regulator of the AMP-activated protein kinase (AMPK) signaling pathway[86, 90-93]. Defects to this cytoplasmic protein can lead to intellectual disabilities, cardiovascular disease, and varying types of cancer, thus making it a target of interest for therapeutic drug research[94-96]. CRBN is reported to be a primary target for IMiDs thalidomide, lenalidomide, and pomalidomide, these drugs being able to directly bind to the protein and mediate their anti-tumor and teratogenic activities[97, 98]. As such, many CRBN-based PROTACs have been developed utilizing these IMiDs as the E3 ligand, allowing for a rapid expansion of the PROTAC research field (Figure 2d)[10, 80].

The first CRBN-based PROTACs utilized IMiD thalidomide as the E3 ligand and inhibitor of BET bromodomains (JQ1) as the POI ligand, connected via a linker. This PROTAC, named dBET1, successfully targeted and degraded BET proteins BRD2, BRD3, and BRD4 in AML cells. They also developed another PROTAC with a similar strategy that successfully targeted and degraded FK506 binding protein 12 (FKBP12), showing the easy expansion of CRBN-based PROTAC application to other POIs[99]. Another study from the same year reported the successful degradation of BRD4 in Burkitt's lymphoma cells with CRBN-based PROTAC ARV-825[100]. Several CRBN-based PROTACs have also been reported that have successfully targeted ALK, Bruton's tyrosine kinase (BTK), cyclin-dependent kinases (CDKs), epigenetic erasers Sirt2 and HDACs, and signal transducer and activator of transcription 3 (STAT3)[101-110]. CRBN-based PROTACs potentially have a larger binding surface allowing for a broader range of target proteins in comparison to VHL-based small molecule PROTACs, along with having a lower molecular weight that makes them more desirable for oral bioavailable PROTAC development[10].

3.c. Nucleotide-based PROTACs

Nucleotide-based PROTACs (RNA-PROTACs, TF-PROTACs) utilize oligonucleotides for their POI ligands, which can include DNA-binding proteins (DBPs), specifically TFs, and RNA-binding proteins (RBPs). DBPs directly bind to and interact with single- or double-stranded DNA and are vital for many DNA-centric processes, ranging from transcription and translation to packaging and repair[111]. TFs in particular are proteins vital for DNA transcription, able to bind directly to DNA-regulatory sequences while also possessing domains that interact with RNA

polymerase II or other TFs in order to control the rate of transcription within the cell[112, 113]. RBPs directly bind to RNA to form ribonucleoprotein particles (RNPs) and are vital for regulating all RNA-related aspects, such as transcription and translation, splicing and modifying, and RNA decay[114]. Several DBPs (ex. STAT3, SOX2, NF-κB) and RBPs (ex. HuR, IGF2BPs, AUF1) have been shown to be overexpressed within cancer, with genetic mutations promoting tumor development and treatment resistance[115-119]. There has been a challenge for discovering drugs that can target these proteins due to their lack of targetable binding proteins, thus the development of nucleotide-based PROTACs can overcome this challenge.

This is a very recently contrived field of PROTACs, with the first proof of concept reported in 2021. This RNA-PROTAC utilized let-7 precursor (pre-let-7) derived oligonucleotides able to bind to the RBP Lin28 as the POI ligand and LA[Hyp]YI – a shortened VHL-recruiting peptide – as the E3 ligand, resulting in the successful ubiquitylation and subsequent degradation of Lin28 in leukemia cells. They also created a second RNA-PROTAC that successfully targeted RBFOX1 for degradation, demonstrating that RNA-PROTACs can be developed to target other RBPs using their binding elements as the POI ligand[120]. In the same year, another study was conducted that reported a DNA-based PROTAC called transcription factor targeting chimera (TRAFTAC) which utilized dsDNA to bind to the POI while also being covalently linked to a CRISPR/Cas9 binding RNA, which binds to dCas9-Halotag7 fusion protein (dCas9HT7). In the presence of a HaloPROTAC that recruits small molecule VHL E3 ligase to the proximity of the POI, TRAFTAC successfully resulted in the ubiquitination and degradation of the target NF-κB[121]. There have also been PROTACs developed utilizing Aptamers – which are short, highly selective oligonucleotide segments (either DNA or RNA) – called aptamer-PROTACs or aptamer-PROTAC conjugates (APCs), which have been proven effective in targeting RBP nucleolin and BET, respectively[122-124]. This new concept of nucleotide-based PROTACs expanded the field of PROTAC research with the potential for new cancer treatment strategies.

4. PROTAC Application in Targeted Cancer Therapeutics

Cancer is the second highest cause of death worldwide, and it is projected that in 2023 roughly 2 million people will be diagnosed with cancer and around 610,000 people will have cancer-related deaths within the United States alone[125]. Despite the fact that there are over 200 varying types of cancer, each with their unique location within the body and resulting symptoms, all cancers have the same set of underlying principles that allow for vindicating these neoplastic diseases complexities. These 'hallmarks of cancer' characterize cancer induction and progression as causing angiogenesis, resisting apoptosis, avoiding growth suppressors, initiating metastasis, supporting proliferative signaling, and permitting replicative immortality. There have also been additions to these core six hallmarks over the years, such as nonmutational epigenetic reprogramming, avoiding immune destruction, senescent cells, and unlocking phenotypic plasticity (Figure 3)[126]. Some proteins that are overexpressed or inactivated within cancer cell have been shown to play vital roles in tumorigenesis, thus understanding their functionalities can

allow them to become potential therapeutic targets. PROTACs are synthesized and used to target specific proteins, thus there have been a wide application of this novel technology within targeted cancer therapeutic research.
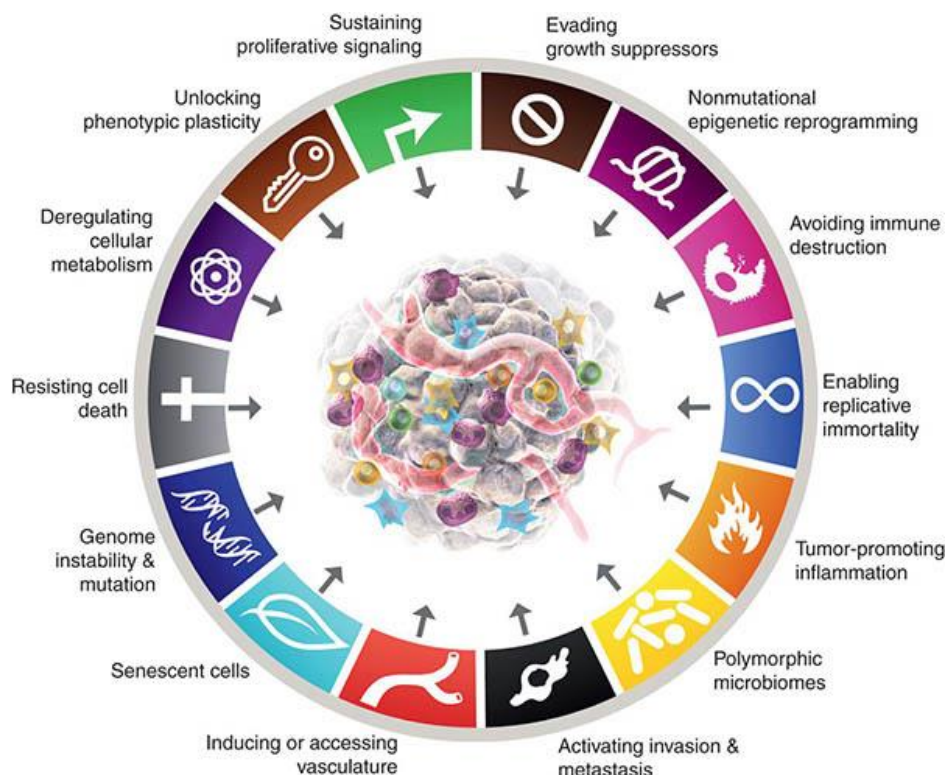
Figure 3) Updated Hallmarks of Cancer graphic as of 2022. Reused with the permission from Hanahan, D. (2022). Hallmarks of cancer: new dimensions. Cancer Discovery, 12(1), 31-46.

4.a. Targeting angiogenesis induction

Angiogenesis, the growth of new blood vessels from the pre-existing vasculature, is a crucial process within the human body as it functions during both normal development and restoration of wounds. However, this process is critical for tumorigenesis as well, since neovasculature allows for the tumors to receive the nutrients and oxygen needed to survive and metastasize. Angiogenesis is regulated by both pro-angiogenic activators such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiogenin, transforming growth factor alpha and beta, and tumor necrosis factor alpha, along with anti-angiogenic inhibitors including angiostatin, endostatin, and interferon. An improper regulation of these two factors plus

activation of multiple growth factors via hypoxia triggers angiogenesis and induces neovasculature, making it crucial for exploring novel anti-angiogenesis therapeutic options (Table 2)[127-129].

Name	Target	E3 Ligase	Linker	POI Ligand	Name of Disease / Cell Line	Reference(s)
E$_2$-octa	ER	p-VHL	CL	Estradiol	BC	130
E$_2$-penta	ER	p-VHL	CL	Estradiol	HUVECs	131
Compound D	PI3K	CRBN	CL	ZSTK474	Liver Cancer	132
INY-03-041	pan-Akt	CRBN	CL	GDC-0068	TNBC	133
PROTAC 23a	eIF4E	CRBN	CL	Sulfamate-containing Bn^{7}GMP	TNBC, CML	134
SGK3-PROTAC1	SGK3	VHL	PEG	Sanofi 308-R	BC	135
PROTAC-2, PROTAC-5	VEGFR-2	VHL	PEG	S7	EA.hy926, HEK293 cells	136
dCBP-1	CBP/p300	CRBN	PEG	GNE-781	MM	137
d4E-4, d4E-6	eIF4E	CRBN	CL	i4EG-BiP	HEK293T cells	138
MS98	Akt	VHL	PEG	GDC-0068	BC, PC, TNBC	139
MS170	Akt	CRBN	PEG	GDC-0068	BC, PC, TNBC	139
PROTAC-1	VEGFR-2, BRAF	VHL	PEG	S5	EA.hy926, NSCLC, TNBC, HEK293 cells	140

Table 2) Representative PROTACs targeting cancer angiogenesis, arranged by publication date. (CL – alkyl linker, CML – chronic myeloid leukemia, EA.hy926 – HUVEC / A549/8 fusion cell, HUVEC – human umbilical vein endothelial cell, PEG – polyethylene glycol, PC – prostate cancer, p-VHL – peptide VHL, S5/S7 – potent angiogenic inhibitors)

17β-estradiol (E$_2$) is a potent endogenous estrogen hormone that promotes angiogenesis through a multitude of processes. It can induce the proliferation and migration of vascular endothelial cells (ECs) as well as promote VEGF, VEGF receptor (VEGFR), and bFGF upregulation, thus making it a potential target for anti-angiogenesis treatment[141, 142]. One of the earlier studies in the field of PROTACs showed the development of a cell-permeable small-molecule proteolysis inducer (SMPI) that successfully targeted ER for degradation in *in vivo* lung cancer cells[130]. This technology was further improved upon in a later study where the refined p-PROTAC was able to function at a lower dose concentration in the examined cell line, suggesting the potential EC-targeting activity of the PROTAC in a variety of angiogenic diseases[131].

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/ mammalian target of rapamycin (mTOR) signaling pathway helps regulate several functions within the cell such as cell proliferation and apoptosis. It also contributes to regulating angiogenesis due to it increasing HIF-1α levels, which ultimately increases VEGF expression[143, 144]. Several PROTACs have been synthesized and reported to target various proteins within this pathway. One such report showed the development of a series of PROTACs targeting PI3K by utilizing PI3K inhibitor ZSTK474 as the POI ligand. Not only did a few of the synthesized PROTACs result in PI3K degradation and subsequent downregulation for other proteins (Akt, S6K and GSK-3β), but compound D also induced autophagy instead of apoptosis or cell cycle arrest[132]. Another study reported the synthesis of a PROTAC targeting Akt utilizing the Akt inhibitor GDC-0068 as the POI ligand. This PROTAC, called INY-03-041, demonstrated to be not only more efficient at degrading Akt than GDC-0068 by itself, but it also was able to induce sustained AKT degradation and downstream signaling inhibition for up to 96 hours even after compound washout[133]. The following year another study reported two Akt-targeting PROTACs, one with a VHL-recruiting E3 ligand called MS98 and one with a CRBN-recruiting E3 ligand called MS170. Both PROTACs were able to degrade Akt in breast cancer cells, along with demonstrate inhibitory activity in both breast cancer and prostate cancer cells[139].Other proteins of the PI3K/Akt/mTOR signaling pathway that have had PROTACs developed targeting them include eukaryotic translation initiation factor 4E (eIF4E), enhancer factors CREB-binding protein and p300 (CBP/p300), and serum- and glucocorticoid-inducible kinase 3 (SGK3)[134, 135, 137, 138].

Within the VEGF system, the series of signaling pathways that result in vascular EC proliferation and angiogenesis are specifically moderated by the VEGFA/VEGFR-2 system. Within this system is the VEGFR-2, a receptor crucial for mediating several key signaling pathways which has become a prominent target for cancer therapy research[145-147]. In 2020 a study developed a series of PROTACs designed to specifically target and degrade VEGFR-2. Two of these PROTACs not only successfully degraded the protein and exhibited anti-proliferation activity but also had low cytotoxicity in HEK293 cells, displaying the PROTACs' safety to human cells that are VEGFR-2 negative[136]. A very recent study synthesized several PROTACs and examined them against both VEGFR-2 and BRAF, once again showing degradation for both proteins while also retaining low cytotoxicity in the HEK293 cells[140].

4.b. Targeting apoptosis resistance

Apoptosis, also referred to as programmed cell death, is the natural cellular process of removing aged cells from the body via recognition of cellular stress, DNA damage or compromised cellular health and immunity. It is a crucial process responsible for maintaining tissue homeostasis and overall organism development. Several signaling pathways and proteins are critical for apoptosis, including intrinsic cell death resulting from mitochondrial outer membrane permeabilization (MOMP) with cytochrome c release and extrinsic cell death resulting from external pro-death signals interacting with death receptors (DR) such as Fas, TNF1/2, and TRAIL. Loss of apoptotic control can result in malignant cancer cells to evade cell death and undergo uncontrolled proliferation, making apoptosis reduction/resistance crucial for tumorigenesis. Multiple mechanisms contribute to cancer cell apoptosis evasion, including anti-apoptotic protein upregulation (BCL-2, BCL-X$_L$, MCL-1, etc.), pro-apoptotic protein downregulation (Puma, BAX, BAK), DR signaling impairment, and caspase function reduction[148-152]. Apoptosis is one of the most targeted cellular functions for cancer therapeutics, and a multitude of PROTACs have been developed to target these affected proteins (Table 3).

Name	Target	E3 Ligase	Linker	POI Ligand	Name of Disease / Cell Line	Reference(s)
Compound 4b	CRABP1/2	IAP	PEG	ATRA	NB	67
Compound 6	c-IAP, CRABP2	IAP	PEG	ATRA	FS	153
DAS-6-2-2-6-CRBN	BCR-ABL	CRBN	NL	Dasatinib	CML	81
SNIPER(ABL)-38	BCR-ABL	IAP	PEG	Dasatinib	CML	154
MD-224	MDM2	CRBN	CL + alkyne group	MI-1061	ALL, AML	56
dMCL1-2	MCL-1	CRBN	PEG	A-1210477	MM	155
GMB-475	BCR-ABL	VHL	Aryl ether	GNF-5	CML	156
WB156	MDM2	CRBN	CL + alkyne group	Nutlin	ALL	157
C3	MCL-1	CRBN	CL	Nap-1	CC, CML, NSCLC	158
C5	BCL-2	CRBN	PEG	Nap-1	CC, CML, NSCLC	158

SIAIS178	BCR-ABL	VHL	CL	Dasatinib	CML	159
DT2216	BCL-X$_L$	VHL	CL	ABT-263	T-ALL	160
XZ424	BCL-X$_L$	VHL	NL	A-1155463	T-ALL	161
B-NF-ATRA	CRABP1/2	AhR	PEG	ATRA	BC, NB	162
iRucaparib-AP6	PARP-1	CRBN	PEG	Rucaparib	CC, RCC, BC, PC	163
XZ739	BCL-X$_L$	CRBN	PEG	ABT-263	T-ALL	164
PROTAC 4 (JPS004)	HDAC1/2/3	VHL	CL	CI-994	CRC	165
PZ15527	BCL-X$_L$	CRBN	NL	ABT-263	WI38 NS cells	166
GMB-805	BCR-ABL	VHL	Aryl ether	ABL001	CML	167
BT1	BCR-ABL	RNF114	PEG	Dasatinib	CML	168
PROTAC 8a	BCL-X$_L$	IAP	Alkane	ABT-263	CTCL, LC, TNBC, CRC, MM, and CHL-1 cells	169
PROTAC 6	BCL-X$_L$	VHL	PEG	A-1155463	AML	170
TM-P4-Thal	Sirt2	CRBN	PEG	TM	BC	171
SK-575	PARP-1	CRBN	CL	Olaparib	BC, CRC, PC, PaC	172
Compound 111	eEF2K	CRBN	PEG	A484954	BC	173
Degrader 7o	BCR-ABL	CRBN	CL	GZD824	CML	174
Compound 2	PARP-1	CRBN	CL	Olaparib	CRC	175
1B	MDM2	CRBN	PEG	Ursolic acid	Huh7 cells, LC, NSCLC	176
WB214	MDM2	CRBN	CL + alkyne group	Ugi ligand	ALL, AML, AML FAB M5, T-ALL	177
PZ703b	BCL-X$_L$/BCL-2	VHL	CL	ABT-263	ALL	178

SIAIS056	BCR-ABL	CRBN	Sulfur-substituted CL	Dasatinib	CML	179
753b	BCL-X_L/BCL-2	VHL	CL	ABT-263	HEK293T cells, AML	180
JPS014, JPS016	HDAC1/2/3	VHL	CL + 1 or 2 oxygen atoms	CI-994	CRC	181
BMM4	BCL-X_L	MDM2	CL	ABT-263	AML FAB M5, GBM, NSCLC	182
PZ18753b	BCL-X_L/BCL-2	VHL	NL	ABT-263	OSU-CLL	183

Table 3) Representative PROTACs targeting cancer apoptosis, arranged by publication date. (AML FAB M5 – AML biphenotypic b-myelomonocytic leukemia, CC – cervical cancer, CL – alkyl linker, OSU-CLL – chronic lymphocytic leukemia, CRC – colorectal cancer, CTCL – cutaneous T-cell lymphoma, FS – fibrosarcoma, GBM – glioblastoma, LC – lung cancer, MM – malignant melanoma, NL – not listed in publication, NS – non-senescent, NB – neuroblastoma, NSCLC – non-small cell lung cancer, PaC – pancreatic cancer, PEG – polyethylene glycol, PC – prostate cancer, RCC – renal cell carcinoma)

One of the members of the B-cell lymphoma 2 (BCL-2) family is the B-cell lymphoma extra-large (BCL-X_L) protein, an anti-apoptotic protein that prevents MOMP to encourage cell survival. This protein is commonly overexpressed in cancer cells and inhibitors such as ABT-263 and A-1155463 have been developed and profusely studied for cancer therapeutic research[184-186]. Despite their success for some hematological malignancies, these inhibitors are limited by low target engagement and dose-limiting thrombocytopenia, thus prompting the synthesis of several BCL-X_L-targeting PROTACs in an attempt to develop safer and more effective cancer therapeutic options[187, 188]. The first BCL-X_L-targeting PROTAC was reported in 2019, composed of ABT-263 as the POI ligand and a VHL E3 ligand. The resulting PROTAC DT2216 effectively degraded BCL-X_L in T-cell acute lymphoblastic leukemia (T-ALL) cells, as well as inhibit xenograft tumor growth without significant thrombocytopenia due to low VHL expression in platelets[160]. A following study took the design concept of DT2216 and swapped the VHL E3 ligand for a CRBN one, resulting in the PROTAC XZ739 effectively degrading BCL-X_L and demonstrating good antiproliferative activity in T-ALL cells[164]. A similar PROTAC named PZ15527 was designed with the same ligands as XZ739 and was found to not only effectively degrade BCL-X_L in non-senescent W138 cells but also clear senescent cells and revitalize tissue stem and progenitor cells in aged mice without causing significant thrombocytopenia[166]. While VHL and CRBN are the most commonly used E3 ligases, there have been BCL-X_L-targeting PROTACs designed with IAP and MDM2 E3 ligases, both effectively degrading BCL-X_L in their

respective cancer cell lines[169, 182]. PROTACs have also been developed utilizing the potent BCL-X_L inhibitor A-1155463 as the POI ligand, demonstrating selectively-induced protein degradation in both a time- and dose-dependent manner[161, 170]. Finally, some PROTACs have been developed from prior BCL-X_L-targeting PROTAC technology to develop BCL-X_L/BCL-2 dual degrading PROTACs, which demonstrated both great degradation and growth inhibiting activity[178, 180, 183]. All of these PROTACs show that this technology has great cancer therapeutic potential and should be further investigated with the possibility of eventually transitioning into clinical settings.

BCR-ABL is an oncogenic fusion protein that activates BCL-2 which in turn prevents MOMP to halt apoptosis, and it is the key driving factor for chronic myelogenous leukemia (CML). Three generations of BCR-ABL (Imatinib, Nilotinib, Dasatinib, Bosutinib, Ponatinib, etc.) have been clinically approved for treating CML, yet these inhibitors are suspectable to severe side effects and drug resistance[189-191]. There is a big need for new drug treatment options targeting BCR-ABL, and PROTAC technology has been extensively researched into degradation of this fusion protein. Although the first reported BCR-ABL-targeting PROTAC containing Dasatinib and CRBN was able to show potent protein degradation, it could not overcome simple drug-resistant mutants such as T315I mutant[81]. CRBN, along with other E3 ligases such as VHL, IAP, and RNF114 which is recruited by the natural product Nimbolide have been utilized for PROTACs that use Dasatinib inhibitor as the POI ligand to show effective BCR-ABL degradation[154, 159, 168, 179]. Other inhibitors have been selected for PROTAC design, such as one report synthesizing a series of BCR-ABL-targeting PROTACs utilizing inhibitor GNF-5. The best PROTAC named GMB-475 not only induced rapid protein degradation and downstream biomarker inhibition but also inhibited cell proliferation of drug-resistant mutants (T312I and G250E) better than the Imatinib inhibitor by itself[156]. A follow-up study from the same group employed a scaffold hopping approach, where a novel core scaffold is obtained by changing a known active compound's core structure, to enhance GMB-475 into a new PROTAC. This new PROTAC, called GMB-805, utilized ABL001, a more potent allosteric BCR-ABL ligand, as the POI ligand and exhibited an over ten-fold ability to induce BCR-ABL protein degradation along with improved *in vivo* activity in comparison to GMB-475[167]. Finally, a series of PROTACs were developed based on GZD824, a BCR-ABL^{T315I} inhibitor. Degrader 7o was found to have the most potent degradation of the mutant protein as well as show significant tumor regression *in vivo*[174]. These myriad of PROTACs show the potential of this technology in selective anticancer treatment for those affected with CML.

Another member of the BCL-2 family is myeloid cell leukemia-1 (MCL-1), an anti-apoptotic protein that prevents MOMP. This protein is often overexpressed in many types of solid tumors and hematological malignancies but it is a difficult drug target due to the competitive PPI binding in shallow binding regions[192-194]. Due to its status as a 'undruggable target', PROTAC technology could potentially be an effective therapeutic option due to its lack of specific binding region requirement. The first report of MCL-1-targeting PROTAC utilized MCL-1 inhibitor A-1210477 as the POI ligand and CRBN for the E3 ligase. This PROTAC, named dMCL1-2, was able to successfully induce MCL-1 degradation at nanomolar concentration, subsequently activating cellular apoptosis[155]. A study published in the same year developed a series of

PROTACs utilizing either S1-6 or Nap-1, both of which are MCL-1/BCL-2 dual inhibitors, as the POI ligand. The resulting PROTACs C3 and C5 successfully induced potent, selective, and reversible MCL-1 and BCL-2 degradation respectively, thus potentially supplying a new toolbox for selective therapeutic strategies for BCL-2 family protein[158].

PARP-1 is a nuclear protein that plays a crucial role in repairing damaged DNA in order to maintain cellular genomic stability. It is also a well-known substrate of caspases, as its activation of caspases 3 and 7 via intrinsic cellular apoptosis results in the loss of PARP-1 and thus suppressing DNA repair. PARP-1 is often overexpressed in cancer and other diseases, making it a major target of interest for anticancer drug treatment. Currently several PARP-1 inhibitors (ex. Olaparib, Rucaparib, Niraparib, Talazoparib) have been clinically approved for cancer treatment, but these inhibitors still face challenges of drug resistance and PARP-1 trapping causing cytotoxicity[195-197]. In 2019 a series of PROTACs were synthesized utilizing various PARP-1 inhibitors for the POI ligand. The best PROTAC was iRucaparib-AP6, which used inhibitor Rucaparib, as it was able to not only induce significant PARP-1 degradation but also blocked PARP-1 catalytic and scaffolding functions without causing PARP-1 trapping, resulting in low cytotoxicity[163]. Two studies the following year developed PARP-1-targeting PROTACs utilizing Olaparib inhibitor as the POI ligand and was able to successfully induce PARP-1 degradation across multiple cancer cell lines[172, 175].

There are multiple other PROTACs developed to target proteins with key regulatory roles in apoptosis. The extrinsic cell death signaling pathway has multiple targets in its cascade that have been discovered to be overexpressed in cancer cells. c-IAP is one of the adaptors attached to the DR TNF1/2 and is responsible for activating pro-caspases and ASK1, and a PROTAC was developed that dual degraded c-IAP and CRABP2 and prevented cancer cell proliferation[153]. Progressing further down the extrinsic cell death pathway is p53 that, when activated, promotes cell death. P53 can be regulated by MDM2 and Sirt2 and several PROTACs have been synthesized to degrade these proteins[56, 157, 171, 176, 177]. Other general proteins of apoptosis that have PROTACs developed targeting them include CRABP1/2, eukaryotic elongation factor 2 kinase (eEF2K), and histone deacetylases 1/2/3 (HDAC1/2/3)[67, 162, 165, 173, 181].

4.c. Targeting inflammation and immune evasion induction

From initial tumorigenesis to eventual metastasis, cancer cells are reliant on strategies to evade detection and destruction from both the cell and body's immune system. Two ways cancer cells can achieve this is by inducing inflammation and immune evasion through multiple different processes. Inflammation can be the result of either an extrinsic factor (bacterial/viral infection, autoimmune diseases, obesity, etc.) or an intrinsic factor (cancer-initiating mutations), both of which contributes to malignant progression. Inflammation can also cause immune evasion by mutating the tumor microenvironment (TME), thus affecting immune cell crosstalk and preventing tumor detection. Several of the TMEs that can be affected include the B-cell receptor (BCR), T-cell receptor (TCR), and Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathways[198-203]. There has been effort in immunotherapy research to develop immune-checkpoint inhibitors and anti-inflammatory drugs as potential treatment options. While several developed treatments have been clinically approved for treating various

cancers and diseases, drug resistance and unwanted effects limit their effectiveness[204-206]. As such, PROTACs have been developed targeting a myriad of proteins relating to cancer inflammation and immunity evasion (Table 4).

Name	Target	E3 Ligase	Linker	POI Ligand	Name of Disease / Cell Line	Reference(s)
dFKBP-1	FKBP12	CRBN	CL	SLF	AML	99
SNIPER(PDE4)-9	PDE4	IAP	PEG	PDE4 binding ligand	FS	154
dTAG-13	FKBP12	CRBN	CL	FKBP12^{F36V} selective ligand	AML	207
DD-04-015	BTK	CRBN	PEG	RN486	DLBCL	208
TL12-186	ITK	CRBN	PEG	TAE648	AML, T-ALL	208
PROTAC 3i	TBK1	VHL	PEG	Compound 1a	NSCLC	209
CCT367766	Pirin	CRBN	PEG	CCT251236	OC	210
MT-802	BTK	CRBN	PEG	Ibrutinib	CLL	102
PROTAC 1o	BTK	CRBN	PEG	BTK binding scaffold	BL, AML	211
FLT-3 PROTAC	FLT-3	VHL	PEG	Quizartinib	AML	212
DD-03-171	BTK	CRBN	CL	CGI1746	DLBCL, MCL	213
L18I	BTK	CRBN	PEG	Ibrutinib	ABC DLBCL, DLCBL, MCL	214
SD-36	STAT3	CRBN	CL + alkyne group	SI-109 (gem-difluoride)	AML, ALCL	109, 110
WL-40	Rpn13	CRBN	PEG	RA190	MM	215
SJF620	BTK	CRBN	PEG	MT-802	BL	103
KB02-SLF	FKBP12	KB02	PEG	SLF	HEK293T cells, TNBC	216

PROTAC 1	PCR2	VHL	CL	EED ligand compound	DLBCL	217
UNC6852	PCR2	VHL	CL	EED ligand	CC, DLBCL	218
SPB5208	BTK	CRBN	PEG	Ibrutinib	MCL	219
MS1943	PRC2	AM41-44A	CL	C24	TNBC	220
JP-6	JAK	IAP	CL	Quinoxaline 2	AML	221
PROTAC 3	PDEδ	CRBN	CL	Deltazinone 1	CC, PaC, T-ALL	222
RC-3	BTK	CRBN	PEG + cyano-acrylamide	Ibrutinib	BL, CLL, MCL	223
Compound 17f	PDEδ	CRBN	CL	Deltazinone	CRC	224
SHP2-D26	SHP2	VHL	CL	SHP inhibitor 5	AML, EC	225
P22	PD-L1	CRBN	CL	BMS-8	M, NSCLC, TNBC	226
RC-1	BTK	CRBN	CL + cyano-acrylamide	Ibrutinib + reversible covalent (RC)	AML, MCL	227
MS4332	PRMT5	VHL	PEG	EPZO15666	BC	228
SS44, SS47	HPK1	CRBN	CL	ZYF0033	BL, CAR-T cells, CML, MM	229
Compound 6a	CD147	CRBN	CL + nitrogen hinge	Pseudolaric acid B	M	230
PROTAC 7	BTK	VHL	PEG	Ibrutinib	BL, CML	231
ORN3P1	Lin28	VHL	CL	Pre-let-7	CML	119
BCP5	BTK	IAP	PEG	BTK ligand	AML	232
BCPyr	BTK	IAP	PEG + pyrazine	BTK ligand	AML	232
E7	PRC2	CRBN	CL	EPZ6438	DLBCL, OC, PC	233
SD-91	STAT3	CRBN	CL + alkyne group	SI-109 (ketone)	AML, ALCL	234
GW3965-PEG5-VHL032	LXR-β	VHLa	PEG	Gw3965	Huh7 cells	235

Compound 21a	PD-L1	CRBN	CL + alkyne group	BMS-37	CRC	236
YM181, YM281	PRC2	VHL	PEG	EPZ6438	DLBCL	237
MD13	MIF	CRBN	CL	MIF tautomerase inhibitor	LC	238
PROTAC 1 & 2	FLT3	CRBN	CL	Dovitinib	AML	239
PROTAC 6e	BTK	CRBN	PEG	ARQ531	DLBCL	240
Compounds 5, 6, 7, 8	JAK	CRBN	CL	Barictinib & Ruxptonib	Precursor B-ALL, T-ALL	241

Table 4) Representative PROTACs targeting cancer inflammation or immune evasion, arranged by publication date. (ABC DLBCL – activated b cell-line DLBCL, ALCL – anaplastic large cell lymphoma, BL – Burkitt's lymphoma, CC – cervical cancer, CL – alkyl linker, CLL – chronic lymphocytic leukemia, CRC – colorectal cancer, DLBCL – diffuse large b-cell lymphoma, EC – esophageal cancer, FS – fibrosarcoma, GBM – glioblastoma, LC – lung cancer, M – melanoma, MCL – mantle cell lymphoma, NL – not listed in publication, NS – non-senescent, NB – neuroblastoma, NSCLC – non-small cell lung cancer, OC – ovarian cancer, PaC – pancreatic cancer, PEG – polyethylene glycol, PC – prostate cancer)

BTK, a non-receptor cytoplasmic tyrosine kinase, is a key regulator of the BCR signaling pathway which is crucial for B-cell development, survival, and antibody production. This protein also plays a critical role in leukemia cell survival for multiple B cell malignancies, making it a key target for anticancer drug research. Several BTK inhibitors such as Ibrutinib and Zanubrutinib have been shown to treat multiple leukemias and lymphomas via BCR signal blocking. However, many patients treated with these inhibitors have shown drug resistance as a result of a missense mutation of the Ibrutinib binding site C4818, prompting PROTAC development to overcome this mutation and promote BTK degradation[242, 243]. Ibrutinib is the most commonly used BTK inhibitor utilized for BTK-targeting PROTACs, as PROTACs SPB5208 and MT-802 linked Ibrutinib with a CRBN recruiting E3 ligand to successfully induce BTK degradation in MCL and CLL cancer cells, respectively[102, 219]. Another study further improved upon the MT-802 PROTAC as it was also reported to have poor pharmacokinetic properties. By modifying the linker and E3 ligand, the resulting PROTAC SJF620 was found to exhibit both potent BTK degradation and better pharmacokinetic properties[103]. Despite Ibrutinib being an irreversible covalent inhibitor, the majority of BTK-targeting PROTACs used noncovalent binding, thus efforts for synthesizing covalent PROTACs have been made over the past few years. Two studies worked to develop irreversible covalent BTK-targeting PROTACs

with a Ibrutinib POI ligand, resulting in PROTAC 7 and L18I which recruited either VHL or CRBN E3 ligase respectively. Despite both PROTACs being shown to induce BTK degradation across multiple leukemia and lymphoma cell lines, they do not display the event driven MOA typically seen with PROTAC technology, thus lowering their potency[214, 231]. This issue was resolved in two later studies that developed reversible covalent BTK-targeting PROTACs RC-3 and RC-1 that utilized cyano-acrylamide moiety to enhance binding affinity without sacrificing sub-stoichiometric activity[223, 227]. Besides Ibrutinib, other non-covalent BTK inhibitors such as ARQ531, CGI1746, and RN486 have been utilized to form PROTACs with potent BTK degradation across multiple leukemia and lymphoma cell lines[208, 213, 240]. Other BTK-targeting PROTACs have been reported, indicating the interest in utilizing PROTAC technology for treating BTK-mutated cancers and potentially beginning the transition of these PROTACs into clinical setting[211, 232].

The TCR signaling pathway is another member of the TME that can result in chronic inflammation and immune evasion. Two proteins that play a critical role in the regulation of the TCR are the IL2-inducible T-cell kinase (ITK) and the hematopoietic progenitor kinase 1 (HPK-1). ITK is the predominate Tec family that is a key regulator of the antigen receptor signaling in lymphocytes while HPK-1 negatively regulates the TCR by reducing the persistence of signaling microclusters[244, 245]. A study set out to create a potential multi-kinase degrader, developing an ITK-targeting PROTAC with ALK inhibitor as the POI ligand since it has been proven to bind to other kinase targets. This PROTAC, named TL12-186, not only was found to induce ITK degradation but was also found to degrade 14 other identified proteins in MOLM-14 cells, 12 of which were kinases[208]. A different study sought to synthesize a HPK-1-targeting PROTAC, utilizing inhibitor ZYF0033 as the POI ligand and CRBN as the E3 ligase. The resulting PROTAC SS44 showed induced HPK-1 degradation across multiple cancer cell lines as well as optimized linker PROTAC SS47 demonstrating HPK-1 degradation in *ex vivo* CAR-T cells[229].

The JAK-STAT signaling pathway is a fundamental regulator of multiple cellular function such as haematopoiesis and inflammatory response, functioning through various cytokines, growth factors, interleukins, and kinases along with the cell receptor IL-6. Overexpression of several of these components can result in inflammatory and immune evasion, marking this pathway as one of the cornerstones of cancer progression[246, 247]. JAK is a non-receptor tyrosine kinase family which has interest in drug development research as by blocking the kinase results in the entire signaling pathway being blocked. The first JAK-targeting PROTACs utilized the JAK inhibitor Quinoxaline as the POI ligand and examined various E3 ligands for optimal degradation. Several PROTACs were developed with JP-6 in particular showing significantly JAK1/2 degradation, also demonstrating that PROTACs with IAP recruiting E3 ligands worked while those with CRBN or VHL recruiting E3 ligands did not[221]. Another study developed a series of JAK-targeting PROTACs utilizing either Ruxotinib or Barictinib inhibitors as the POI ligand. Several of the resulting PROTACs induced JAK1/2/3 degradation as well as have good degradation activity of GSPT1/IKZF1[241]. STAT3 is a member of the STAT family that helps to transmit external signals to the nucleus and its overexpression can inhibit immune response. The first study to develop a STAT3-targeting PROTAC utilized a *gem*-difluoride SI-109 inhibitor as the POI ligand. The resulting PROTAC SD-36 selectively degraded STAT3, inhibited leukemia and

lymphoma cell proliferation, and was able to induce tumor regression in *in vivo* xenograft models[109, 110]. A following study further improved upon SD-36 by converting the *gem*-difluoride into a ketone. SD-91 was found to be more potent in STAT3 degradation in comparison to SD-36, as well as achieved whole, long-lasting tumor regression in *in vivo* xenograft models[234]. There have been several more published reports of PROTACs designed to target other JAK-STAT pathway proteins, including FLT3, PD-L1, and SHP2[212, 225, 226, 236, 239].

There are many other PROTACs that have been reported to target proteins involved in cancer cell inflammation and immune evasion. One such target is the polycomb repressive complex 2 (PRC2), an epigenetic transcription modulator with four subunits that catalyzes H3K27 methylation. H3K27 hyper-trimethylation can be found in several tumors and while a couple inhibitors have been designed there is still a need for other PRC2 cancer therapeutic options[248, 249]. Two PROTACs have been designed to target PRC2 with EHZ2 inhibitor EPZ6438 as the POI ligand and another with inhibitor C24, which were able to degrade PRC2 across multiple cancer cell lines[220, 233, 237]. Two more PRC2-targeting PROTACs have been reported with VHL recruiting E3 ligase and EED ligand[217, 218]. Cluster of differentiation 147 (CD147) is a transmembrane glycoprotein that is part of the immunoglobulin superfamily that plays a crucial role in inflammation and tumor development. Compound 6a was a PROTAC developed utilizing pseudolaric acid B, a natural product that antagonizes CD147, as the POI ligand and was reported to successfully induce CD147 degradation in melanoma cells both *in vitro* and *in vivo*[230]. Other inflammation and immune evasion targets with PROTACs include FKBP12, Lin28, LXR-β, MIF, PDE4, PDEδ, Pirin, PRMT5, Rpn13, and TBK1[99, 119, 154, 207, 209, 210, 215, 216, 222, 224, 228, 235, 238].

4.d. Targeting cancer cell metastasis

Metastasis is one of the key hallmarks of cancer as the initial tumor cells extravasate and disperse throughout the body via circulatory systems in order to colonize distant organs and form new secondary tumors, making it responsible for the most cancer-related deaths worldwide. One key process during metastasis is epithelial-to-mesenchymal transition (EMT), where epithelial cells convert to acquire mesenchymal features, as it allows for solid tumors to become more malignant. This process can be activated via multiple upstream cellular signaling pathways such as the integrin/FAK/PI3K/Akt axis[250-254]. Due to the slow process of discovering effective cancer therapeutic options to combat metastasis, PROTAC technology has been employed to target EMT-related proteins (Table 5).

Name	Target	E3 Ligase	Linker	POI Ligand	Name of Disease / Cell Line	Reference(s)
PROTAC-Smad3	Smad3	VHL	CL	EN300-72284	RCC	255
PROTAC 1	p38	VHL	PEG	Foretinib	BC, CC	256

PROTAC-3	FAK	VHL	PEG	Defactinib	PC, TNBC	257
SJFα, SJFδ	p38	VHL	PEG	Foretinib	BC, CC	258
BI-0319	FAK	VHL	PEG	BI-4464	HCC	259
BI-3663	FAK	CRBN	PEG	BI-4464	HCC	259
ARV771	TCF4	VHL	PEG	BET inhibitor	ABC DLBCL	260
DT-6	TGF-β1	CRBN	CL	P144	BC, HCC, NSCLC	261
CPR3, CPR4	IGF-1R, SRC	CRBN	PEG	Compound C	BC, NSCLC	262
xStAx-VHLL	Wnt/β-catenin	VHL	Ahx	xStAx peptide	CRC, HEK293T cells	37
ND1-YL2	SRC	UBR box	NL	VL2	TNBC	263
GSK215	FAK	VHL	CL	VS-4718	LC, TNBC	264
Compound 17d	FOXM1	CRBN	PEG	FDI-6	TNBC	265
FOXM1-PROTAC	FOXM1	Pomalidomide	PEG	FIP-1	Liver Cancer	38
TEP PROTAC	c-Myc	CRBN	E Box DNA	TNA aptamer	TNBC	266

Table 5) Representative PROTACs targeting cancer metastasis, arranged by publication date. (ABC DLBCL – activated b cell-line DLBCL, Ahx – aminohexanoic acid, CC – cervical cancer, CL – alkyl linker, FIP-1 – F-1 peptide + TAT CPP, HCC – hepatocellular carcinoma, NL – not listed in publication, NSCLC – non-small cell lung cancer, PEG – polyethylene glycol, RCC – renal cell carcinoma)

Focal adhesion kinase (FAK/PTK2), a cytoplasmic non-receptor protein tyrosine kinase, is one of the most outstanding agents of integrin signaling that regulates multiple signaling pathways like PI3K/Akt and RAS/MAPK. As such, overexpression of FAK can result in cell invasion and metastasis via exertion of both kinase-dependent enzyme function and kinase-independent scaffold function. While multiple FAK inhibitors have been developed, the scaffolding function is unable to be affected by these current inhibitors, thus giving the opportunity for applying

PROTAC technology to examine these non-enzymatic functions[267-269]. The first report of a FAK-targeting PROTAC was published in 2018 and utilized FAK inhibitor Defactinib as the POI ligand with a VHL recruiting E3 ligand. PROTAC-3 was found to induce selective and potent FAK degradation, as well as suppress cancer cell migration and invasion[257]. Another study utilized the FAK inhibitor BI-4464 and developed two PROTACs (BI-0319, BI-3663) with VHL or CRBN recruiting E3 ligand respectively. Both PROTACs successfully induced FAK degradation in hepatocellular carcinoma (HCC) cell lines[259]. In addition, FAK inhibitor VS-4718 has been utilized as the POI ligand to develop PROTAC GSK-215, which was able to both induce FAK degradation and prevent cell proliferation in various cancer cell lines[264].

The p38 mitogen-activated protein kinase (MAPK) family are serine/threonine-specific protein kinases composed of four p38 isoforms: p38α (MAPK14), p38β (MAPK11), p38γ (MAPK12), and p38δ (MAPK13). p38α is the most common isoform seen across a myriad of cell types, its functionality varying based on the cell type and environment. It not only can regulate upstream cancer-causing TFs, but also act as a downstream target for TFs via various signaling pathways, making it a target of interest for cancer therapeutic research[270-272]. One study sought out to develop a PROTAC that could effectively bind to and subsequently degrade multiple kinases, utilizing c-Met tyrosine kinase inhibitor Foretinib. They were surprised to see p38α was effectively degraded with the VHL PROTAC 1 despite it having a lower binding affinity in comparison to kinases with higher affinities that were not degraded such as SLK and Axl[256]. Another study developed two PROTACs targeting p38α and p38δ, the latter which does not have any current therapeutic options available. Both PROTACs were able to degrade their targeted isoform despite having the same E3 ligase and POI ligand (Foretinib), suggesting the importance of the ternary complex formed in order to induce degradation in cancer cells[258].

There are several other PROTACs reportedly targeting proteins involved in cancer cell metastasis. One pathway that plays a critical role in normal cell development and migration is the Wnt/β-catenin pathway, therefore mutations in this pathway can lead to carcinogenesis and eventual metastasis[273]. A study developed a p-PROTAC targeting β-catenin with stapled peptides xStAx as the POI ligand due to its ability to impair Wnt/β-catenin. Despite the clinical limitations typically seen with p-PROTACs, xStAx-VHLL was reported to effectively induce long-term β-catenin degradation as well as significantly inhibit the signaling pathway in cancer cells[37]. PROTACs have also been developed to target forkhead box protein M1 (FOXM1), which is a downstream component of several signaling pathways. One study synthesized a p-PROTAC that successfully degraded FOXM1 in liver cancer cells[38]. Another study utilized FOXM1 inhibitor FDI-6 with a CRBN recruiting E3 ligand to form a series of PROTACs, with the best PROTACs being compound 17d which successfully induced FOXM1 degradation in TNBC cells[265]. Other metastasis targets with PROTACs include c-Myc, IGF-1R, Smad3, Src, TCF4, and TGF-β1[255, 260-263, 266].

4.e. Targeting cancer cell proliferation

One of the most fundamental hallmarks of cancer is its ability to stimulate hyperactive cell proliferation, allowing for mutated DNA to replicate and the cancer cell to undergo the necessary cell cycle steps needed to divide and multiply. This process is encouraged by the overexpression

of growth-promoting and tumorigenic signals and proteins directly involved with or influencing cell cycle regulation, such as the Ras/Raf/mitogen-activated protein kinase/ERK kinase/extracellular-signal-regulated kinase (Ras/Raf/MEK/ERK) signaling pathway[274-277]. Several drugs have been developed targeting the cell cycle, with many also entering clinical trials including drug inhibitors for BET proteins and CDKs. However, many of these drugs have been unsuccessful as a result of severe off-target effects and low response rates[278-281]. Due to its importance for tumorigenesis, there is a continued need for novel and improved cell cycle inhibiting drugs. PROTAC technology has been utilized to target several targets of cell proliferation, making several breakthroughs in the field of cancer therapeutic research (Table 6).

Name	Target	E3 Ligase	Linker	POI Ligand	Name of Disease / Cell Line	Reference(s)
PROTAC 14	AR	MDM2	PEG	SARM	CC	9
SNIPER-9	Rar	IAP	PEG	Ch55	FS	282
SNIPER-11	ER	IAP	PEG	Estrone	BC	282
SNIPER-13	AR	IAP	PEG	DHT	BC	282
SNIPER(ER)-3	ERα	CRBN	CL	4-OHT	BC, FS, HeLa cells	283
SNIPER(TACC3)-1	TACC3	IAP	PEG	KHS108	BC, CRC, FS, OS, PC	284
ARV-825	BRD4	CRBN	PEG	OTX015	BL	285
dBET1	BRD4	CRBN	CL	JQ1	AML	286
MZ1	BRD	VHL	PEG	JQ1	CC	287
ARV-771	BRD4	VHL	PEG	JQ1	CRPC	84
SNIPER(ER)-87	ERα	IAP	PEG	4-OHT	BC	154
SNIPER(BRD4)-1	BRD4	IAP	PEG	JQ1	BC	288
BETd-246	BRD4	CRBN	PEG	BETi-211	TNBC	289

dBRD9	BRD9	CRBN	PEG	BI7273	AML	290
AT1	BRD4	VHL	CL	JQ1	HeLa cells	22
MZ1	BRD4	VHL	PEG	JQ1	CC	22
PROTAC 3	CDK9	CRBN	CL	Aminopyrazole analog	CRC	291
dBET6	BRD4	CRBN	CL	JQ1	T-ALL	285
Probe 10	DHODH	VHL	PEG	Brequinar	PaC	292
TD-PROTAC	ERα	p-VHL	Ahx	TD-PERM	BC	33
Compound 1	EGFR, HER2	VHL	PEG	Lapatinib	CC, OC	293
Compound 7	c-Met	VHL	PEG	Foretinib	GC, TNBC	293
BETd-260/ ZBC260	BRD4	CRBN	CL	HJB97	ALL, AML	294
MZP-54	BRD4	VHL	PEG	I-BET726	AML, APL, HeLa cells	295
SNIPER(AR)-51	AR	IAP	PEG	AR ligand	PC	296
THAL-SNS-032	CDK9	CRBN	PEG	SNS-032	T-ALL	104
JH-XI-10-02	CDK8	CRBN	PEG	JH-VIII-49	T-ALL	297
SNIPER(ER)-110	ERα	IAP	PEG	4-OHT	BC	298
MS4077	ALK	CRBN	PEG	Ceritinib	ALCL, NSCLC	101
TL13-12	ALK	CRBN	PEG	TAE684	ALCL, NB, NSCLC	299
ZXH-326	BRD4	CRBN	CL	JQ1	MM	300
ARCC-4	AR	VHL	CL	Enzalutamide	PC	301
TD-004	ALK	VHL	CL	Ceritinib	ALCL, NSCLC	83
A1874	BRD4	MDM2	PEG	JQ1	AML, BL, CRC LC, M, OS	53

Name	Target	E3	Linker	Ligand	Cell/Cancer	Ref
ARD-69	AR	VHL	S/RL	ARI-16	PC	302
VZ185	BRD4	VHL	CL	BI7273	HEK293T cells, HeLa cells	303
ERD-308	ER	VHL	PEG	Raloxifene	BC	304
BSJ-03-123	CDK4/6	CRBN	PEG	Palbociclib	AML	106
TD-428	BRD4	TD-106	PEG	JQ1	PC	305
BSJ-02-162	CDK4/6	CRBN	CL	Palbociclib	MCL	306
BSJ-04-132	CDK4/6	CRBN	CL	Ribociclib	T-ALL	306
Compound 2	BRAF^{V600E}	CRBN	CL	RGS	Liver cancer, M, TNBC	307
KB02-JQ1	BRD4	KB02	PEG	JQ1	HEK293T cells	216
PROTAC 1, ACBI1	SMARCA2/4	VHL	PEG	BD ligand	AML FAB M5	308
XH2	BRD4	RNF114	CL	JQ1	CML, HEK293 cells, TNBC	309
CP5V	cdc20	VHL	PEG	apcin-A	BC, TNBC	310
PAP508	AR	CRBN	CL	RU-59063	PC	311
MS432	MEK1/2	VHL	CL	PD0325901	CRC, MM	312
ARD-266	AR	VHL	S/RL	ARI-16	PC	313
Compound 15	BRD2/4	CRBN	CL	Compound 6	AML, M, TNBC	314
Compound 3	MEK1/2	VHL	PEG	Refametinib	M	315
PROTAC 7	BLK	VHL	PEG	Ibrutinib	CML	231
XY-4-88	KRAS^{G12C}	CRBN	CL	ARS-1620	NSCLC, PaC	316
ZNL-02-096	Wee1	CRBN	CL	AZD1775	OC, T-ALL	317
macroPROTAC	BRD4	VHL	2 cyclized PEG	JQ1	AML, PC	318

HBL-4	BRD4, PLK1	CRBN	PEG	BI2536	AML	319
Compound A9	CDK2	CRBN	PEG	AT-7519	BC, CRC, PC	320
Compound F3	CDK2/9	CRBN	PEG	FN-1501	BC, CRC, PC	320
Compound I-6	ERα	p-VHL	Ahx	Lactam cyclic peptide	BC	35
MS39	EGFR	VHL	CL	Gefitinib	LC	321
MS154	EGFR	CRBN	CL	Gefitinib	LC	321
ARD-61	AR	VHL	S/RL	ARI-16	PC	322
Compound 2	EGFR	CRBN	CL	EGFR-TK	NSCLC	323
Compound 10	EGFR	VHL	CL	EGFR-TKI	NSCLC	323
Compound 34	CDK2/4/6	VHL	PEG	Palbociclib	ALL, AML, MM, TNBC	324
Compound 14o	EGFR	VHL	CL	XTF-262	NSCLC	55
Compound 12	BRAF^{V600E}	CRBN	CL	Vermurafenib	CRC, M	325
Compound 23	BRAF^{V600E}	CRBN	CL	BI 882370	CRC, M	325
YX-2-107	CDK2/4/6	CRBN	CL	Palbociclib	ALL	326
ERD-148	ERα	VHL	CL	Raloxifene	BC, TNBC	327
SIAIS117	ALK	VHL	CL	Brigatinib	ALCL, NSCLC	328
PROTAC 15	AR	CRBN	PEG	Enzalutamide	PC	329
Compound 16c	EGFR	CRBN	PEG	Osimertinib	NSCLC	330
d9A-2	SLC9A1	CRBN	PEG	W9a	CML	331
AM-A3	ER	VHL	CL	Raloxifene	BC	332
DP1	BRD4	E7820	PEG	JQ1	DLBCL	333

TMX-2172	CDK2/5	CRBN	PEG	TMX-3010	OC	334
DDC-01-163	EGFR	CRBN	PEG	EA1001	LC	335
LC-2	KRAS^{G12C}	VHL	PEG	MRTX849	NSCLC	336
ARD-61	AR	VHL	S/RL	ARI-16	PC, TNBC	337
JB170	AURORA-a	CRBN	PEG	Alisertib	AML, HCC, NB, OS	338
P4B	BRAF^{V600E}	CRBN	PEG	BI 882370	CRC, M	339
CG416	TRKA/C	CRBN	CL	GNF-8625	AML, CRC	340, 341
CG428	TRKA/C	CRBN	PEG	GNF-8625	AML, CRC	340, 341
dAURK-4	AURORA-a	CRBN	PEG	Alisertib	GC, HEK293T cells, MCL, MM, NB, OS, T-ALL	342
Compound P3	EGFR	VHL	CL	Compound F	NSCLC	343
TD-802	AR	CRBN	RL	TD-106	PC	344
MS928, MS934	MEK1/2	VHL	CL	PD0325901	CRC, MM	345
MS910	MEK1/2	CRBN	PEG	PD0325901	CRC, MM	345
Compound 11	CDK2/4/6	CRBN	CL	Ribociclib	M	346
Compound 45	CDK9	CRBN	PEG	BAY-1143572	AML	347
SJF-0628, SJF-0661	BRAF^{V600E}	VHL	RL	Vemurafenib	LC, M, NSCLC	348
B3	ALK	CRBN	PEG	Ceritinib	NSCLC	280
UI-EP002	ER	VHL	PEG	E2	BC, TNBC	349
MTX-23	AR	VHL	CL	AR ligand	CRPC, PC	350
21-ARL	AR	DACF11	PEG	ARI-16	PC	351

A031	AR	VHL	PEG	AR-1	PC	352
Compound 13b	AR	CRBN	PEG	Bicalutamide	HEK293T cells, PC	353
SIAIS001	ALK	CRBN	CL + alkyne group	Alectinib	ALCL, NSCLC	354
SIAIS091	ALK	CRBN	CL	Alectinib	ALCL, NSCLC	354
PROTAC-D	AURORA-a	CRBN	PEG	Alisertib	HeLa cells, OS	355
NL	EGFR	VHL	PEG	Gefitinib	NSCLC	356
SIAIS125, SIAIS126	EGFR	CRBN	CL	Canertinib	NSCLC	357
BSJ-4-116	CDK12	CRBN	CL	THZ531 fragment 5	T-ALL	358
PROTAC 2	CDK9	CRBN	CL	Aminopyrazole analog	HEK293 cells, Pac	359
Compound 17	ALK	CRBN	CL	Alectinib	ALCL, NSCLC	360
DGY-09-192	FGFR1/2	VHL	CL	BGJ398	CCC, GC	361
SIAIS164018	ALK	CRBN	CL	Brigatinib	NSCLC, TNBC	362
ARD-2128	AR	CRBN	RL	ARI-16	PC	363
ARD-2585	AR	CRBN	RL	Compound 10	PC	364
Compound 45	CDK9	CRBN	CL	CDK9 ligand	BC, TNBC	365
Compound 15	BRD4	CRBN	CL	ABBV-075	ALL, AML	366
PROTAC-O4I2	SF3B1	CRBN	CL	O4I	CML, HCC, HEK-OCT4 cells, HeLa cells	367
SM1	BRD2/4	VHL	Branched VHL	Bi-BET	AML, HEK293 cells, LC, PC	368
SJ995973	BRD4	CRBN	CL	JQ1	AML	369
KP-14	KRAS^{G12C}	CRBN	CL	KRas G12C-IN-3	NSCLC	370
PP-C8	CDK12	CRBN	CL	SR-4835	TNBC	371

Compound 6	AR	VHL	CL	VPC-14228	CRPC	372
WWL0245	BRD4, PLK1	CRBN	CL	WNY0824	PC	373
BP3	HSP90	CRBN	CL	BIIB021	TNBC	374
AU-15330	SMARCA2/4	VHL	CL	BD ligand	HEK293 cells, HeLa cells	375
YF135	KRAS^{G12C}	VHL	PEG	MRTX849	NSCLC	376
MDEG-541	MYC	CRBN	CL	10058-F4 derivative 28RH	GIC	377
dAurA383	AURORA-a	CRBN	PEG	MLN8054	AML, APL, HEK293T cells, NHL	378
dAurA425	AURORA-a	VHL	PEG	MLN8054	AML, APL, HEK293T cells, NHL	378
dAurA450	AURORA-a	IAP	PEG	MLN8054	AML, APL, HEK293T cells, NHL	378
JB301	AURORA-a	CRBN	PEG	MK-5108	AML	379

Table 6) Representative PROTACs targeting cancer proliferation, arranged by publication date. (Ahx – aminohexanoic acid, ALCL – anaplastic large cell lymphoma, AML FAB M5 – AML biphenotypic b-myelomonocytic leukemia, APL – acute promyelocytic leukemia, BD – bromodomain, BL – burkitt's lymphoma, CC – cervical cancer, CCC – cholangiocarcinoma cancer, CL – alkyl linker, CRC – colorectal cancer, CRPC – castrate resistant prostate cancer, FS – fibrosarcoma, GC – gastric cancer, GIC – gastrointestinal cancer, HCC – hepatocellular carcinoma, M – melanoma, MCL – mantle cell lymphoma, NB – neuroblastoma, NHL – non-hodgkin's lymphoma, NL – not listed in publication, NSCLC – non-small cell lung cancer, OC – ovarian cancer, OS – osteosarcoma, PaC – pancreatic cancer, PEG – polyethylene glycol, p-VHL – peptide VHL, RL – rigid linker, S/RL – soluble/rigid linker, T-ALL – t-cell acute lymphoblastic leukemia)

The Ras/Raf/MEK/ERK signaling pathway is one of the most crucial pathways in cell biology, assisting in cell growth and differentiation regulation. Overexpression of this pathway promotes mutated proliferative gene expression and replication and is reported in over 40% of cancer cases[276, 380]. Multiple PROTACs have been synthesized targeting several components of this pathway, starting from the receptor tyrosine kinases (RTKs) embedded in the cell membrane that receive extracellular signals, down the signaling cascade, and eventually to the cell division

control (cdc) proteins to affect the cell cycle. One important RTK is EGFR, which has inhibitors (gefitinib, lapatinib, afatinib) approved for use but suffers from severe drug resistance from drug-induced mutations[381]. One study developed a series of EGFR-targeting PROTACs utilizing the inhibitor Gefitinib as the POI and different E3 ligases, resulting in the most significant degraders as MS39 and MS154 with an E3 ligand recruiting VHL and CRBN respectively. These two PROTACs not only effectively degraded mutant EGFR proteins but also were unable to degrade the EGFR in WT cells, indicating that they are selective against mutant-type EGFR[321]. Another study published the same year created an EGFR-targeting PROTAC utilizing another inhibitor, Osimertinib, as the POI ligand and was reported to induce EGFR mutation degradation in non-small cell lung cancer (NSCLC) cells. It was also reported that the PROTAC was able to significantly induce apoptosis and G0/G1 phase arrest in the NSCLC cell line[330]. Several other PROTACs have been synthesized to target EGFR and HER2, another member of the same RTK family[55, 293, 323, 335, 343, 356, 357]. Progressing down from the RTKs there are PROTACs developed to target Ras and Raf, specifically mutants $KRAS^{G12C}$ and $BRAF^{V600E}$ respectively[307, 316, 325, 336, 339, 348, 370, 376, 382]. Next in the signaling cascade is MEK1/2, with one study that developed a PROTAC that utilized the non-ATP competitive inhibitor PD0325901 as the POI ligand. The resulting PROTAC, named MS432, showed effective degradation without being selective for MEK1/2 as well as ERK phosphorylation blockage in cancer cells[312]. There are a couple more reports for MEK1/2-targeting PROTACs, as well as one ERK1/2 PROTAC that is discussed later in this paper[315, 345].

AURORA kinases are serine/threonine protein kinases crucial for mitosis initiation, particularly AURORA-a which promotes G2/M phase change via centrosome maturation mitotic spindle regulation. If overexpressed AURORA-a will be unable to halt G2/M transition to induce apoptosis, promoting tumorigenesis[383]. The first reported selective PROTAC targeting AURORA-a utilized the AURORA-a inhibitor Alisertib as the POI ligand and the resulting PROTAC, JB170, had strong kinase binding and degradation. It is important to note JB170 only caused cell accumulation in the S phase instead of the G2/M arrest phase, suggesting that it regulated AURORA-a's non-enzymatic activity[338]. Another study wanted to create a series of novel AURORA-a-targeting PROTACs with different E3 ligases but all utilizing the same inhibitor MLN8054 as the POI ligand. The end result showed that three major PROTACs with CRBN, VHL, or IAP as the E3 ligase were able to induce AURORA-a degradation across multiple cancer cell lines[378]. A few more PROTAC studies have been published in recent years with AURORA-a as the POI, further suggesting the kinase's importance in cell cycle regulation[342, 355, 379].

The BET family, and BRD4 in particular, are epigenetic histone readers that trigger pro-proliferative gene transcription. A huge number of inhibitors targeting BET family proteins have been reported though they require a high dosage amount, resulting in the desire for more effective therapeutic options[384-386]. The majority of BRD4-targeting PROTACs utilize the inhibitor JQ1 as the POI ligand [22, 53, 84, 216, 287, 288, 300, 305, 309, 318, 333, 369]. One study developed PROTAC dBET1 which induced not only BRD4 and c-Myc degradation both *in vitro* and *in vivo*, but also BRD2 and BRD3 as JQ1 is a nonselective inhibitor[286]. A follow-up study focused on optimizing the PROTAC, the resulting dBET6 demonstrating improved potency and global

productive transcription elongation disruption in T-ALL cells[285]. Other BET inhibitors such as BETi-211 and OTX015 have been employed as POI ligands for PROTACs[289, 294, 295, 314, 366, 368, 387]. PROTACs have also been utilized for dual degradation, targeting both BRD4 and PLK1[319, 373]. In addition to BRD2/3/4, there are also two important non-BET BRDs called BRD7 and BRD9 that are epigenetic histone readers and, if overexpressed, promote tumorigenesis. Two studies have developed PROTACs targeting BRD7/9 with the inhibitor BI7273 as the POI ligand. The two PROTACS – dBRD9 and VZ185 – successfully induced degradation across multiple cancer cell lines[290, 303].

CDKs are serine/threonine kinases that are key regulators of cell cycle progression and division. CDK2/4/6 in particular regulate G1/S phase transition and have several inhibitors such as Palbociclib and Ribociclib [388-390]. PROTAC technology has been employed to target CDKs for degradation, such as one study that formed PROTAC YX-2-107 with Palbociclib as the POI ligand which effectively induced CDK2/4/6 degradation in ALL cells and inhibited S phase cells[326]. Another study developed two PROTACs either with Palbociclib and Ribociclib as the POI ligand and synthesized BSJ-02-162 and BSJ-04-132, respectively[306]. Along with Palbociclib and Ribociclib, other inhibitors such as FN-1501 and TMX-3010 have been used for CDK2/4/6-targeting PROTAC development[106, 320, 324, 334, 346]. While CDK2/4/6 is a major target of interest for PROTAC technology research, PROTACs have also been made targeting CDK8, CDK9, and CDK12[104, 291, 297, 347, 358, 359, 365, 371]. There are several other PROTACs reported targeting proteins involved in cancer cell proliferation including ALK, AR, BLK, cdc20, c-Met, DHODH, ER/Erα, FGFR1/2, HSP90, MYC, Rar, SF3B1, SLC9A1, SMARCA2/4, TACC3, TRKA/C, and Wee-1[9, 33, 35, 83, 101, 154, 282, 283, 292, 293, 296, 298, 299, 301, 302, 304, 308, 310, 311, 313, 317, 322, 327-329, 331, 332, 337, 340, 341, 344, 349-354, 360-364, 367, 372, 374, 375, 377, 391-393].

5. PROTAC Application in Other Diseases

Cancer is the second highest cause of death both in the US and worldwide. While it is incredibly crucial for continued effort in the field of cancer therapeutics, other diseases are prevalent and demand the same rigorous research into treatment options[394]. While the majority of PROTAC research is concentrated on cancer therapeutics, there are other fields of diseases that the technology has been applied to. Because of the conception and design of PROTACs, they can be tailored to target specific proteins that are affected within a multitude of diseases, making it a universally customizable therapeutic option. PROTAC research has been seen to expand into the realm of cardiovascular, immune-mediated, neurodegenerative, and viral diseases, showing several proofs of concept of the technology's capability to target and degrade disease-promoting proteins (Table 7).

Name	Target	E3 Ligase	Linker	POI Ligand	Name of Disease / Cell Line	Reference(s)
PROTAC-RIPK2	RIPK2	VHL	PEG	Vandetanib	BC, AML, THP-1 cells	21
Compound 1	mHtt	cIAP1	PEG	BTA	HD	70
Compound 2	mHtt	cIAP1	PEG	PDB	HD	70
Compound 7	mHtt	cIAP1	PEG	PDB	HD	395
GSK983	PCAF/ GCN5	CRBN	NL	GSK4027	LPS-stimulated macrophages and dendritic cells	396
QC-01-175	Tau protein	CRBN	NL	PET tracer T807	AD	397
Compound 3	IRAK4	VHL	HPHO all-carbon chain	PF-06650833	PBMC and human dermal fibroblasts	398
Degrader 12d	HDAC6	CRBN	CL	Nex A	MM	399
DGY-08-097	NS3	CRBN	NL	VX-950	Hepatitis C	400
NP8	HDAC6	CRBN	NL	Nex A	MM	401
Compound 3j	HDAC6	VHL	NL	Nex A	MM1S cells	402
PROTAC 2	RIPK2	IAP	PEG	RIPK2 inhibitor	THP-1 cells	403
PROTAC 3	RIPK2	CRBN	PEG	RIPK2 inhibitor	THP-1 cells	403
P22A	HMGCR	CRBN	Via click chemistry	Atorvastatin	SRD-15 cells Huh7 cells	404
Compound 4	α-syn	VHL	NL	α-syn binder	AD & PD	405
PROTAC 23	IIRAK3	CRBN	NL	Pyrrolotriazines	THP-1 cells Primary macrophages	406
XZ9002	HDAC3	VHL	PEG	SR-3558	MDA-MB-468 cells T47D cells	407
Degrader 2c	IDO1	CRBN	PEG	Epacadostat	CAR-T cells HeLa cells	408
Compound 9	IRAK4	CRBN	PEG	IRAK4 inhibitor 1	DLBCL	409

HD-TAC7	HDAC3	CRBN	PEG	CI-994	LPS/IFNγ-stimulated RAW 264.7 macrophages	410
Degrader 5	IRAK4	CRBN	CL	Compound 1	ABC DLBCL	411
PROTAC(H-PCDS)-1	H-PGDs	CRBN	PEG	TFC-007	KU812 cells	412
PG21	GSK-3β	CRBN	PEG	Pyridine thiazole-based inhibitor	AD	413
C004019	Tau protein	VHL	NL	Tau binder	AD	414
Compound 21b	HMGCR	VHL	CL	Lovastatin acid	MFD-induced mouse model with hypercholesterolemia	415
Compound 21c	HMGCR	VHL	CL	Lovastatin acid	HepG2	415
THAL-SNS032	CDK9	CRBN	NL	PKI SNS032	HCMV	416
Compound 14a	HDAC6	CRBN	NL	Indirubin derivatives	K562 cells THP-1 cells	417
Compound 3	PTGES-2	VHL	6-methylene units	INM	SARS-CoV-2	418
Compound 5	PTGES-2	VHL	Piperazine-based	INM	SARS-CoV-2	418
Compound 8e	NA	VHL	NL	Oseltamivir	Influenza type B	419
JMF4560	C-TPD-43	CRBN	PEG	BTA	ALS	420

Table 7) Representative PROTACs for Cardiovascular, IMID, Neurodegenerative, and Viral Diseases, arranged by publication date. (ABC DLBCL – activated b-cell-like diffuse large b-cell lymphoma, BTA – benzothiazole-aniline derivative, CAR-T – chimeric antigen receptor-modified t, CL – alkyl chain, HPHO – hydrophobic, LPS/IFNγ – lipopolysaccharide/gamma interferon, MFD – medium fat diet, MM – multiple myeloma, NA – neuraminidase, Nex A – Nexturastat A, NL – not listed in publication, PDB – phenyldiazenyl benzothiazole derivative, PKI – protein kinase inhibitor)

5.a. Cardiovascular diseases

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (HMGCR) is the rate-limiting enzyme for cholesterol biosynthesis, catalyzing conversion of HMG-CoA into mevalonate.

HMGCR acts as the target for cholesterol-lowering drugs called statins, which are typically prescribed to patients to prevent or treat cardiovascular diseases[421, 422]. While they are extremely efficient in lowering plasma low-density lipoprotein (LDL) cholesterol levels, statins can provoke compensatory HMGCR protein upregulation, thus limiting the drug's maximal effectiveness[423-425]. There was a study published in 2020 that reported the synthesis of a CRBN-based PROTAC with atorvastatin – a class of statins – as the POI ligand. This PROTAC, called P22A, was successful in not only degrading HMGCR levels, but also activating the sterol regulatory element-binding protein (SREBP) pathway to block cholesterol synthesis[404]. In the same year, another study reported two VHL-based small molecule PROTACs utilizing lovastatin acid as the HMGCR-targeting POI ligand. One compound (21c) was effective in degrading HMGCR in Insig-silenced HepG2 cells, while the second compound (21b) induced HMGCR degradation and cholesterol reduction during *in vivo* studies[415]. Recently the Heart Research Institute in Australia announced a research project with the aims of developing Akt-isoform-specific PROTACs and examining their therapeutic possibility in thrombosis, a major complication of cardiovascular disease[426].

5.b. Immune-mediated inflammatory diseases

Immune-mediated inflammatory diseases (IMIDs) are a broad collection of multifactorial diseases with systemic inflammation and a severely dysregulated immune system. IMIDs include ankylosing spondylitis (AS), asthma, autoimmune diseases, inflammatory bowel disease (IBD), multiple sclerosis (MS), psoriasis, psoriatic arthritis (PsA), rheumatoid arthritis (RA), uveitis, and several more. These common diseases lower an individual's quality of life significantly with severe morbidity and potential premature death, thus research for drug therapeutic options against these diseases is constantly ongoing[427-429]. PROTAC technology has begun to emerge in the field of IMID treatment research, having been successfully applied against a myriad of IMID targets.

HDACs are a group of enzymes that regulate gene expression via deacetylating acetylated histones, as well as targeting non-histone proteins such as NF-κB, a crucial regulator for numerous inflammatory genes. Among the 18 members of this protease family are HDAC3, which can directly repress or indirectly activate gene expression, and HDAC6, which helps regulate gene expression and is crucial for the assembly and activation of NLRP3 inflammasome. These two proteins have been reported to affect several IMIDs such as asthma, chronic obstructive pulmonary disease (COPD), IBD, and RA, making them targets of interest for treatment research[430-434]. A study in 2020 synthesized a HDAC3-targeting PROTAC composed of a HDAC inhibitor (HDACi) CI-994 as the POI ligand connected to the CRBN ligand via a linker. The HD-TAC7 had little impact on the LPS/IFNγ-stimulated RAW 264.7 macrophage gene expression but was able to selectively reduce HDAC3 levels in comparison to siRNA. The most likely reason for the low effect was due to the consequential downregulation of the NF-κB subunit p65, which is a known pomalidomide treatment side effect[410]. In the same year another group reported a HDAC3-targeting PROTAC composed of a HDACi SR-3558 as the POI ligand connected to the VHL ligand via a linker. This PROTAC, called XZ9002, was able to induce and selectively degrade HDAC3, potentially due to its catalytic MOA and

isoenzyme selectivity[407]. Several reports have been published displaying PROTAC technology targeting HDAC6, with the first being in 2018 utilizing previous reported pan-HDACi[435]. This PROTAC was later refined with different E3 ligands and a more selective HDAC6i, thus resulting in improved PROTAC activity[399, 402, 436]. Concurrently, another group published about two PROTACs that were also successful in degrading HDAC6 in different cell lines[108, 401]. Finally, in 2021 a study reported the development of a HDAC6-targeting PROTAC using a HDACi from a natural product called indirubin. A downregulation of NLRP3 levels, along with downregulation of related cytokines, were reported in the THP-1 cells that constructed the NLRP3 inflammasome activation model[417].

The IRAK family are a group of Ser/Thr kinases that play a central role in inflammatory responses due to regulating multiple inflammatory genes. In particular, both IRAK3 and IRAK4 are crucial to mediating TLR/IL-1R signaling pathways, and mutations of these two kinases have been seen in several IMIDs such as autoimmune diseases, IBD, RA, and sepsis[437-440]. As such, both IRAK3 and IRAK4 have potential as targets for therapeutic research against IMIDs. In 2020 the first PROTACs targeting IRAK3 were synthesized, with PROTAC 23 resulting in more than 98% of IRAK degradation in both THP1 cells and primary macrophages[406]. The first IRAK4-targeting PROTACs was reported in 2019, where several PROTACs were synthesized but specifically compound 3 was able to successfully degrade IRAK4 in peripheral blood mononuclear cells (PBMC) and human dermal fibroblasts[398]. A following report from the same group found another PROTAC that successfully degraded more than 90% of the IRAK4 in HEK293T cells 24 hours after treatment, along with hindering the NF-κB signaling pathway in activated B-cell-like (ABC) diffuse large B-cell lymphomas (DLBCLs)[411]. Finally, another study screened a PROTAC capable of inducing IRAK4 degradation in DLBCL cells[409]. These reports highlight the potential for PROTAC technology to target IRAK3/4 in IMIDs.

Other IMID targets have also been utilized for PROTAC development. RIPK2 plays an important role in inflammation and innate immunity by releasing several inflammatory cytokines when activated. Dysregulation in this pathway is associated with several IMIDs such as autoimmune diseases and IBD[441, 442]. In 2015 a PROTAC was announced to effectively degrade more than 95% of RIPK2 at nanomolar concentration[21]. Five years later another study synthesized two PROTACs that, when compared to the previous study's PROTAC, was not as effective in degrading RIPK2 in the THP-1 cells. However, the two PROTACs had a stronger binding ability to RIPK2[403]. Other IMID targets with PROTACs reported include hematopoietic prostaglandin D synthases (H-PGDs), IDO1, and P300/CBP-associated factor / general control nonderepressible 5 (PCAF/GCN5)[396, 408, 412].

5.c. Neurodegenerative diseases

The central nervous system (CNS) is made up of the brain and spinal cord and has ultimate control over all bodily functions. More than 600 known diseases affect the CNS, ranging across a broad spectrum of neurological, neurodegenerative, and neurodevelopmental disorders. This system poses several unique challenges that has made drug development widely unsuccessful, from poor understanding of the disease as a whole and its underlying pathophysiology to malfunctioning proteins expressed in both the CNS and peripheral nervous system (PNS) that

make CNS-specific treatment targeting more difficult[443, 444]. PROTAC technology could be a potential new strategy to targeting CNS disorders for therapeutic treatment, with several published reports examining their utilization against common neurodegenerative diseases.

Alzheimer's Disease (AD) is one of the most common neurodegenerative disorders worldwide, characterized by a slow progression of deteriorating cognition, memory, and other mental functions[445]. There have been several hypotheses made towards understanding the complex and widely unknown pathophysiology of AD, one of which being caused by presence of abnormally regulated tau proteins. Tau proteins are microtubule-associated proteins profusely expressed in neurons responsible for microtubule stabilization and axonal transport and are associated with a myriad of neurodegenerative diseases, making it a major target of interest for drug therapeutic research[446]. Several reports have shown the development and success of tau-targeting PROTACs over the past several years, with two papers published in 2016 and 2018 showing the first proofs of concept with p-PROTACs that used VHL and Keap1 E3 ligands, respectively[32, 33]. The following year the first small molecule PROTACs targeting tau was reported, with the patent stating six PROTACs were developed with either CRBN or VHL ligands. These PROTACs were able to successfully degrade tau in both tau-p301L and tau-a152T, along with many other favorable pharmacokinetic parameters being met[447]. Another study the same year synthesized numerous tau-targeting PROTACs with PET tracer T807 as the POI ligand and CRBN for the E3 ligand. One of the PROTACs, called QC-01-175, effectively degraded WT and mutant tau, as well as preferentially degrading frontotemporal dementia FTD neuron tau protein in comparison to normal cells[397]. There has also been reported preclinical evidence from Arvinas for a PROTAC that successfully targeted pathological tau. This PROTAC was able to cross the blood-brain barrier (BBB) degrade the pathological tau while avoiding the WT tau in the mouse models 24 hours after treatment[414]. Finally, glycogen synthase kinase 3 (GSK-3β) is a serine/threonine protein kinase capable of boosting tau phosphorylation as well as amyloid-β peptide production to induce AD development[448]. In 2021 there was the first report of GSK-3β-targeting PROTACs capable of accomplishing kinase degradation at a nanomolar level. Specifically, the PROTAC PG21 was also able to prevent mouse hippocampal neuron HT-22 cells from dying after being induced by glutamate[413]. All these reports give evidence showing that PROTAC technology can be beneficial in treating tricky neurodegenerative disorders such as AD.

Amyotrophic Lateral Sclerosis (ALS) is a multisystem neurodegenerative disorder consisting of onset focal muscle weakening and decay which eventually spread throughout the body by the disease progression. While more than 20 genes have been linked to ALS, two of the most common neuropathological signatures are the aggregation of cytoplasmic TDP-43 protein, and the aggregation of mutant SOD1 protein[449]. A study in 2018 discovered and utilized a unique E3 ligase Zfn179 which has autoubiquitination features to specifically target and degrade TDP-43 as well as regulate the protein aggregate clearance[450]. Another study published in 2023 synthesized a PROTAC targeting C-terminal TPD-43 (C-TPD-43) which successfully degraded the aggregated protein and reduced its compactness and oligomer population[420]. For mutant SOD1 protein one study developed a Dorfin-CHIP PROTAC where the two components are an E3 protein Dorfin that binds to the mutant protein and the U-box domain for C-terminal Hsc70-interacting protein (CHIP) which also exhibits strong E3 ligase activity. This PROTAC was able

to successfully target and degrade the mutant SOD1 and cause decrease aggregation formation while not affecting the WT SOD1[451]. While more research is needed, these beginning studies show potential for PROTAC technology in ALS therapeutic research.

An autosomal dominant neurodegenerative disorder called Huntington's disease (HD) is caused by an excessive expansion of a CAG trinucleotide repeat in the HTT gene's exon 1 that results in mHtt aggregating in nerve cells[452]. A study in 2017 designed two PROTACs targeting mHtt, successfully reducing mHtt levels in the fibroblasts of HD patient primary cells and mHtt-transfected HeLa cells. These PROTACs were able to reduce the mHtt levels via protein degradation without knowing the specific POI ligand that was targeted, showing that this technology can successfully target neurodegenerative disease-causing aggregate-prone proteins even when the specific POI ligand is unknown[70]. A year later the same group synthesized a new PROTAC which used IAP inhibitor MV1 which was found to have stronger affinity for the E3 ligase in comparison to the previous PROTACs. Additionally, this PROTAC was able to degrade mHtt in HD-affected fibroblasts in both time- and dose-dependent manner[395]. Despite the success of these PROTACs to effectively degrade mHtt, all of the compounds struggled to differentiate between the WT Htt and mHtt and ultimately resulted in decreased WT Htt levels[453]. As a result, the potential for PROTAC-mediated HD treatment needs to be further investigated.

Parkinson's disease (PD) is a progressive neurodegenerative disorder that severely affects the individual's motor system and is the second most common neurodegenerative disease after AD. Its main characteristic is the accumulation of aggregated α-synuclein proteins (α-syn), which leads to the aggregation of Lewy bodies and eventual neuronal degeneration[454]. In 2020 a study developed six PROTACs targeting α-syn for PD and AD treatment. Four of the PROTACs were able to significantly lower α-syn levels *in vitro*, degrading more than 65% of the total α-syn while the other two PROTACs degraded 30-65%[405]. Another study synthesized a cell-permeable p-PROTAC for α-syn proteasomal degradation, combining a CPP domain, α-syn protein binding domain and a proteasome-targeting motif. The p-PROTAC was able to successfully target and degrade α-syn in primary neurons and neuroblastoma cells, thus decreasing the cytotoxicity and mitochondrial dysfunction[455].

5.d. Viral infections

Diseases caused by viral infections have resulted in some of the highest mortality pandemics seen across human history, affecting hundreds of millions of people worldwide and acting as a serious threat to public health and safety. These include mostly eradicated diseases such as smallpox and polio to devastating diseases still prevalent today such as human immunodeficiency virus (HIV) and hepatitis B/C virus (HBV/HCV). The most recent addition to this list was the outbreak of COVID-19 via the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in 2020, having since been labeled as one of the deadliest pandemics within the last century[456-458]. Current prevention and treatment options against these diseases rely on a combination of vaccines and drugs, either administered at birth, during age milestones, or at/after viral infection. Nevertheless, developing drug-resistant viral strains and failure of vaccines against altered and novel viruses provide extreme challenges against the currently available antiviral therapeutic options, making it crucial to discover new cutting-edge antiviral

strategies[459-461]. PROTAC technology has begun to be implemented into the field of antiviral therapeutic research, targeting various viral targets such as surface proteins, proteases, host proteins, and CDKs[462].

A virus is surrounded by a lipid bilayer which is embedded with several glycoproteins, such as hemagglutinin (HA) and neuraminidase (NA). These surface proteins help the virus attach to and penetrate the host cell via attachment to specific cell receptors, along with allowing for the release of newly created virion particles. Due to their unique composition that separates them from the host cell's receptors, these surface proteins have become new targets of interest for antiviral therapeutic research[463, 464]. Oseltamivir is a type of NA inhibitor that prevents the exit of the new virion particles and has been widely utilized in treating influenza A and B virus infections[465]. A PROTAC has been developed utilizing oseltamivir as the POI against NA for the influenza A virus, which connected to a VHL ligand via a linker. This oseltamivir-based PROTAC tended to have two functions by first connecting to and inhibiting NA and then degrading the surface protein via the UPS, subsequently preventing newly synthesized virion particles from leaving the host cell. Further investigation found that the PROTAC was also effective against oseltamivir-resistant virus strains as well[419].

Hepatitis C is caused by HCV infection and is one of the main causes for liver diseases such as chronic hepatitis, hepatocellular carcinoma (HCC), and liver cirrhosis. The HCV nonstructural protein 3 (NS3) plays several crucial roles in the virus's infection cycle, making the NS3/4A serine protease a target for drug treatment[466, 467]. One such drug called Telaprevir (VX-950) has been approved for treatment of HCV, though patients run the risk of developing drug resistance, resulting in the need for new treatment options[468]. A study in 2019 developed a PROTAC targeting NS3 with VX-950 as the protease-binding ligand and CRBN as the E3 ligand connected via a linker. This PROTAC called DGY-08-097 was able to effectively degrade NS3 in human hepatoma-derived Huh7.5 cells, as well as degrade A156S and V55A mutant NS3[400].

Vaccines are biological preparations of disease-causing microorganisms able to induce an immune response upon detection of foreign entities, thus helping to develop the body's humoral immunity. The current most common vaccine types are either inactivated (killed disease-causing microorganism) or live attenuated (weakened disease-causing microorganism), with the live attenuated vaccines being the most conventional technology used against influenza viral infections. While this technology can potentially induce robust and broad immune responses, it also is limited by insignificant immunogenicity, time-consuming manufacturing procedures, and overall safety concerns[469, 470]. A study in 2022 utilized PROTAC technology to create an attenuated influenza PROTAC virus strain which would target and degrade influenza viral proteins via the host cell's UPS, thus dramatically decreasing viral replication. Synthesis of the attenuated influenza PROTAC virus linked the proteasome targeting domain (PTD), which acted as the E3 ligand due to it containing a peptide region recognized by VHL, with a matrix gene segment (M1 protein) via a tobacco etch virus cleavage site (TEVcs) linker. This linker can be specifically cleaved by TEV protease (TEVp) to separate M1 protein from PTD and prevent its degradation, allowing for normal influenza virus replication in stable TEVp-expressed cells which can produce viral particles crucial for vaccine production. The study reported that M1-

PTD successfully controlled M1 protein degradation, along with effective PROTAC virus replication occurring within TEVp-expressing Madin-Darby canine kidney (MDCK.2) cells in comparison to a WT virus. In vivo, it was able to cause robust and broad immunity (humoral, mucosal, cellular) against both homologous and heterologous virus challenges[471]. Overall, PROTAC viruses have a lot of potential for vaccine manufacturing, not only against influenza but also other pathogens, though further investigation into PROTAC vaccine safety is needed[472, 473].

Several other PROTACs have emerged in recent years against various other viral infections. Indomethacin (INM) is a drug that was designed to inhibit the SARS-CoV-2 replication cycle by targeting and inhibiting the host cell's prostaglandin E synthase type-2 (PTGES-2), which interacts with non-structural protein (NSP7), one of the NSPs involved in viral RNA replication[474]. INM-based PROTACs were developed by conjugating INM as the POI ligand with VHL via either an aliphatic or polyethylene glycol linkers, successfully targeting the host protein PTGES-2 and provide proof of concept for PROTAC-based pan-CoV antiviral treatments[418]. The X-protein for HBV, a disease that affects more than 1/3 of the human population and runs a major risk for developing HCC, is crucial in maintaining viral infection and productivity[475]. A p-PROTAC was developed that targeted and successfully degraded the X-protein, allowing for not only the therapeutic treatment of HBV but also in preventing HCC[30]. CDKs are well known for playing important roles in virus life cycles and act as potential targets against multiple viruses such as HIV, Human cytomegalovirus (HCMV), and SARS-CoV-2[476]. THAL-SNS032 is a commercially available PROTAC developed coupling CRBN ligand and CDK inhibitor SNS032 as the POI ligand. This PROTAC not only successfully degraded CDK9 but also CDK1/2/7 as well as targeting HCMV-encoded ortholog pUL97, showing that THAL-SNS032 was significantly sensitive to the HCMV virus[416].

6. PROTAC Transition into Clinical Setting

As the research of PROTACs progress in the laboratory both *in vivo* and *in vitro*, there becomes a need to begin implementing this technology into clinical settings. Bench-to-bedside research is a crucial transition for medicinal research as it allows for the application of laboratory results in the clinic to observe their effectiveness in human patients. If the novel treatment is effective enough to progress through all clinical trial phases, then it will transition into general practice for treating the targeted cancer or disease[477]. Since 2013, several companies such as Arvinas and C4 Therapeutics have been established focusing on the development of PROTACs and other TPD technologies. Several pharmaceutical giants such as Pfizer, Genentech, and Merck have also branched into this field, pushing the industry to begin implementing this technology into clinical settings[478]. However, there were four key questions remaining that needed to be answered for PROTACs: 1) Were they safe for humans? 2) Would they have drug-like properties? 3) Would they accurately work for their target protein? 4) Are they therapeutically effective? In 2019 the first two PROTACs entered phase I clinical trials and their results reported the following year

positively answered all four of these questions, allowing them to progress to phase II clinical testing. These positive clinical proof-of-concepts also paved the way for more PROTACs to enter the clinical setting, resulting in at least 15 PROTACs from various biotechnology and pharmaceutical companies currently undergoing clinical trials (Table 8)[479].

PROTAC Name	Target	E3 Ligand	Cancer(s)/ Disease	Current Trial Phase	Current Trial Start Date	ROA	Company	Clinical Trial No.
AC682	ER	CRBN	Locally Advanced or Metastatic ER+/HER- Breast Cancer	Phase I	2021	Oral	Accutar Biotech	NCT05080842
ARV-110	AR	CRBN	mCRPC	Phase II	2020	Oral	Arvinas	NCT03888612
ARV-471	ER	CRBN	Advanced Breast Cancer	Phase III	2023	Oral	Arvinas / Pfizer	NCT04072952
ARV-766	AR	NL	mCRPC	Phase I/II	2021	Oral	Arvinas	NCT05067140
CC-94676	ARB	CRBN	mCRPC	Phase I	2020	Oral	Bristol Myers Squibb	NCT04428788
CG001419	TRK	CRBN	Cancer and Other Indications	IND-e	2021	Oral	Cullgen	NL
CFT8634	BRD9	CRBN	Synovial Sarcoma, Soft Tissue Sarcoma	Phase I/II	2022	Oral	C4 Therapeutics	NCT05355753
CFT8919	EGFR-L858R	CRBN	NSCLC	IND-e	2021	Oral	C4 Therapeutics	NL
DT2216	BCL-X_L	VHL	Solid Tumors & Hematologic Malignancy	Phase I	2021	IV	Dialectic Therapeutics	NCT04886622
FHD-609	BRD9	NL	Advanced Synovial Sarcoma	Phase I	2021	IV	Foghorn Therapeutics	NCT04965753
KT- 333	STAT3	NL	Solid Tumors, CTCL, LGL-L, NHL, PTCL	Phase I	2022	NL	Kymera	NCT05225584
KT-413	IRAK4	CRBN	DLBCL	Phase I	2022	IV	Kymera	NCT05233033
KT-474	IRAK4	NL	Autoimmune Diseases (AD/HS)	Phase I	2021	Oral	Kymera / Sanofi	NCT04772885
NX-2127	BTK	CRBN	B Cell Malignancies	Phase I	2021	Oral	Nurix Therapeutics	NCT04830137
NX-5948	BTK	CRBN	B Cell Malignancies	Phase I	2022	Oral	Nurix Therapeutics	NCT05131022

Table 8) PROTACs currently in clinical application or in clinical development, arranged by PROTAC name. (AD – atopic dermatitis, CTCL – cutaneous T-cell lymphoma, DLBCL – diffuse large B cell lymphoma, HS – hidradenitis suppurativa, IND-e – in IND-enabling preclinical studies, IV – intravenous, LGL-L – large granular lymphocytic leukemia, mCRPC – metastatic castration-resistant prostate cancer, NHL – non hodgkin lymphoma, NL – not listed in publication, NSCLC – non-small cell lung cancer, PTCL – peripheral T-cell lymphoma, ROA – route of administration)

One of the first PROTACs to enter clinical trials in 2019 was Vepdegestrant (ARV-471), a CRBN-based PROTAC co-developed by Arvinas and Pfizer targeting ER in patients with locally advanced or metastatic ER+/HER- breast cancer that have previously received CDK4/6 inhibitors (Figure 4a). In preclinical trials ARV-471 exhibited tumor growth suppression in breast cancer models, as well as significant tumor reduction when combined with palbociclib in comparison to fulvestrant treatment[480]. The clinical trials for ARV-471 is a Phase 1/2 dose escalation and cohort expansion study that has previously presented data showing that PROTAC monotherapy in a heavily pretreated population demonstrated a 42% clinical benefit rate. It was also seen that ARV-471 was well tolerated at all dose levels (30 mg – 700 mg) with no reported dose-limiting toxicities, as well as robust ER degradation (up to 89%) reported at all doses daily in paired biopsy samples[481]. The phase II clinical trial is still ongoing, examining the combination of ARV-471 with palbociclib (NCT04072952). Additionally, recruitment for a Phase III trial began in March 2023, with the aim to randomly assign half the patients ARV-471 and the other half fulvestrant in order to examine the safety and efficiency of ARV-471 in comparison to fulvestrant in patients with advanced breast cancer (NCT05654623).

A.

B.

Figure 4) Structures of clinical trial PROTAC drugs a) ARV-471 and b) ARV-110. Chemical structures created using MolView.

The other PROTAC to enter clinical trials in 2019 was Bavdegalutamide (ARV-110), a CRBN-based PROTAC developed by Arvinas targeting AR in heavily pretreated patients with metastatic castration-resistant prostate cancer (mCRPC) (Figure 4b). These patients were recruited due to their severely limited therapeutic options as a result of the mainstream method of antiandrogen therapy being ineffective[482]. The clinical trials for ARV-110 is a Phase 1/2 dose escalation study with initial trial data reporting the PROTAC to have an acceptable safety profile, being well tolerated with doses ranging between 35 mg and 420 mg. ARV-110 also demonstrated degradation of AR within tumors as 46% of patients with AR T878A/S and/or H875Y mutations showed a prostate-specific antigen (PSA) decline of over 50%, giving early signs of antitumor activity[483]. Phase II initiated in 2020 with a dosage of 420 mg and is currently ongoing (NCT03888612).
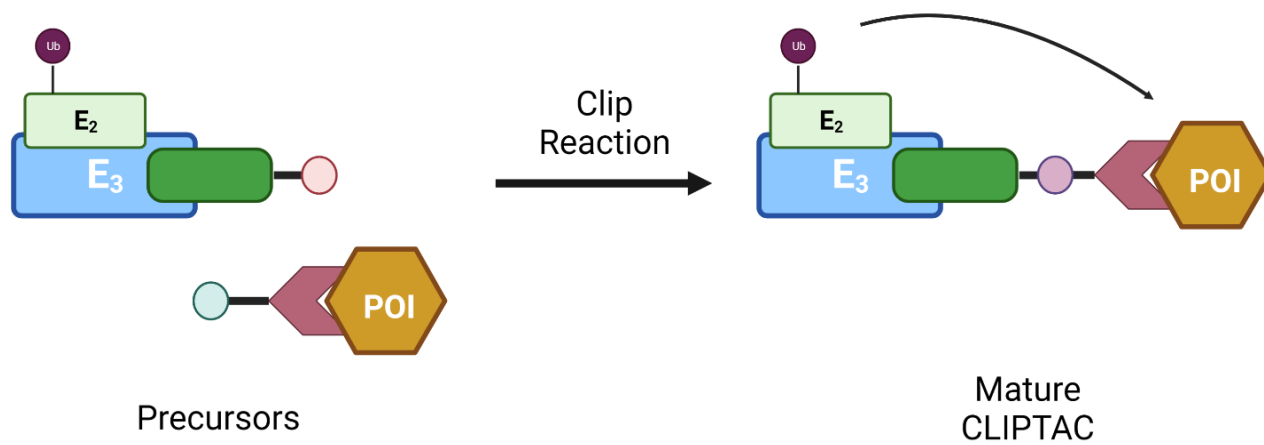
Beyond the initial two PROTACs there are other PROTACs that are currently in clinical settings. AC682 is a CRBN-based PROTAC developed by Accutar Biotech targeting ER in patients with locally advanced or metastatic ER+/HER- breast cancer. Preclinical data reported robust reduction of ER levels and anti-tumor efficacy within ER+ breast cancer cell models, including those with ESR1 mutation[484, 485]. The phase I for AC682 began in 2021 and is currently ongoing (NCT05080842). DT2216, designed by Dialectic Therapeutics, is unique as it is a VHL-based small molecule PROTAC in comparison to other PROTACs undergoing clinical trials that are CRBN-based. It targets $BCL-X_L$ in multiple solid and hematologic tumors and successfully demonstrated antitumor activity both *in vitro* and *in vivo*[160, 486]. Phase I for DT2216 began in 2021 and is currently ongoing (NCT04886622). KT-474 is a PROTAC co-developed by Kymera and Sanofi targeting IRAK4 in patients with autoimmune diseases Atopic Dermatitis or Hidradenitis Suppurativa. The phase I trial began in 2021 and finished the following year with KT-474 showing an acceptable safety and tolerability profile, with more than 95% IRAK4 degradation after a single dose (NCT04772885).

7. Novel PROTAC Technologies

As there have been rapid developments in the discovery of proteins that can be targeted, there have also been developments of the PROTAC technology as a whole. These newer technologies help to address certain limitations that the general PROTAC structures (p-PROTACs, small molecule-based, nucleotide-based) currently face. Based on previously reported research demonstrating the effectiveness of these techniques within other fields of science, many laboratories have synthesized PROTACs with similar concepts that have shown high success. These technologies include CLIPTACs, Homo-PROTACs, PhotoPROTACs, and Tag-based PROTACs (Figure 5)

A.

Precursors   Mature
                              CLIPTAC

B.

Homo-PROTAC

C.

Inactive   Active

D.

Caged
(Inactive)

Uncaged
(Active)

E.

Universal
PROTAC
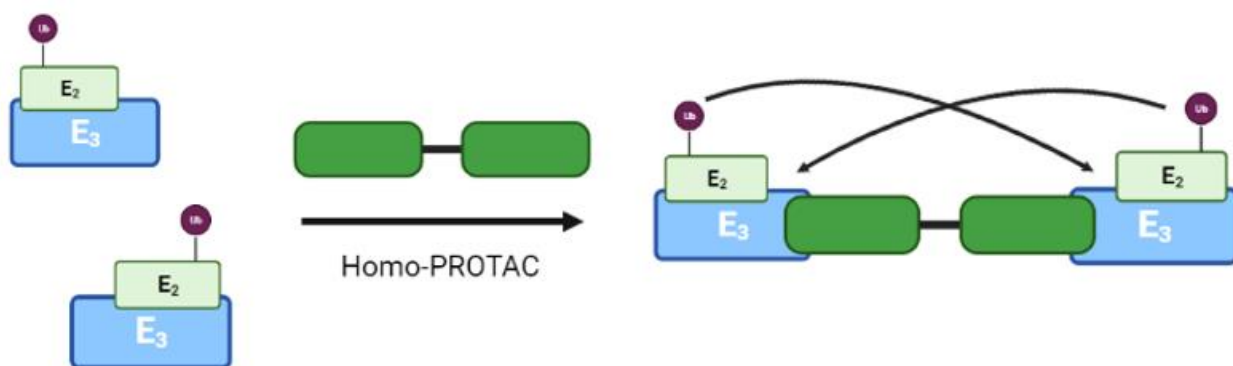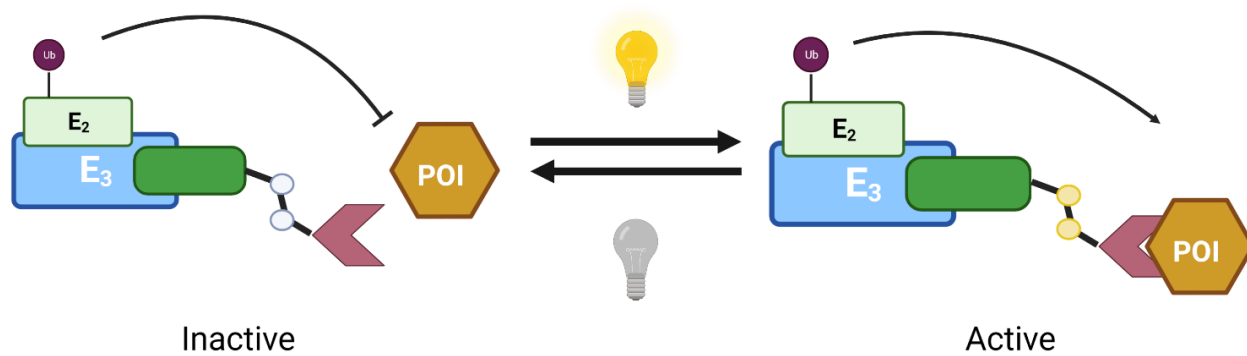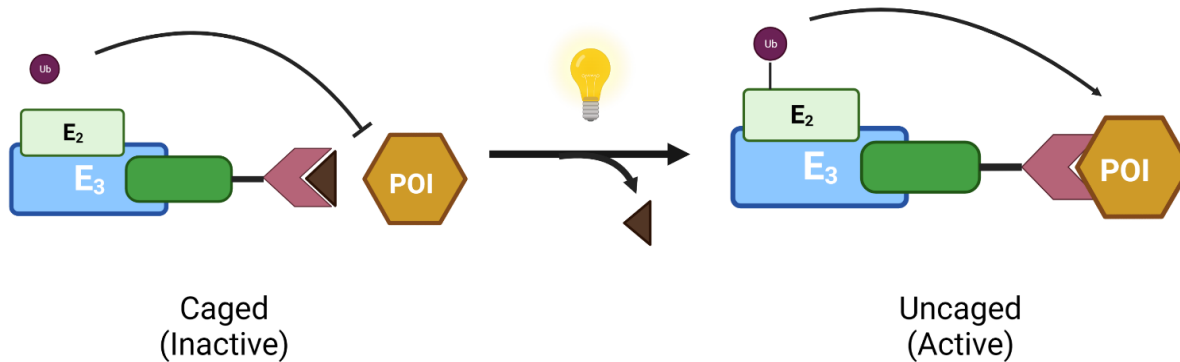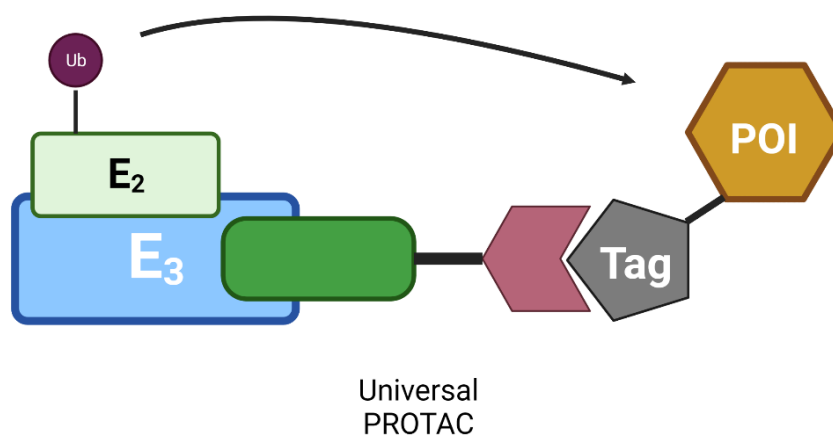
Figure 5) Mechanism of novel PROTAC technologies a) CLIPTACs, b) Homo-PROTACs, c) Photoswitchable PhotoPROTACs, d) Photocaged PhotoPROTACs, and e) Tag-based PROTACs. Created using BioRender, adapted from Li., X. (2022). Proteolysis-targeting chimeras (PROTACs) in cancer therapy. Molecular Cancer, 21(1), 99.

7.a. CLIPTACs

The term 'click chemistry' was first introduced in 2001 as an approach used to develop new compounds that are clearly defined and controlled via a series of 'spring-loaded' chemical reactions[487]. Through the use of heteroatom links (C-X-C) and covalent conjugation, these new compounds have the advantage of being highly reliable, selective, and able to work on a broad

scope. This technology has been seen successfully applied in multiple scientific disciplinaries, from its application among nucleic acids in biochemistry to development of prodrugs and other beneficial biotechnologies[488-490]. As such, CLIPTACs utilize the concept of click chemistry, where two small precursors are covalently built to form a conjugated biomolecule (Figure 5a). The first reported development and utilization of this concept was in 2016 when Heightman laboratory synthesized a *trans*-cyclooctene-tagged JQ1 as the POI ligand and a tetrazine-tagged thalidomide as the E3 ligand for the two precursors that formed a covalent six-membered ring moiety via a click reaction. This CLIPTAC was able to successfully degrade BRD4 and ERK1/2 in HeLa and A375 cells, respectively[491]. Two years later another CLIPTAC was created targeting casein kinase II (CK2) with CK2 inhibitor CX-4945 as the POI ligand and a CRBN recruiting E3 ligand. Of the four CLIPTACs synthesized, compound 2 was able to induce CK2 degradation in TNBC and NSCLC cells, resulting in more apoptosis in a shorter period of time[492]. In 2020 a series of BCR-ABL-targeting PROTACs were synthesized to form a global PROTAC toolbox for WT and T315I-mutated BCR-ABL degradation utilizing multiple BCR-ABL inhibitors. Three prominent PROTACs (PD22, P19A, P19P) based on Dasatinib, Asciminib, and Ponatinib respectively utilized 'click chemistry' in their linkers and all three of these PROTACs displayed effective protein degradation activity[493]. More target proteins that have PROTACs designed with a 'click chemistry' linker for their degradation include α_{1A}-AR, AR, BRD4, BTK, CDKs, CYP1B1, Erα, FAK, FKBP12, FLT3, p38, PARP-1, Sirt2, and TRKC[52, 107, 494-509]. Due to the smaller molecular weight of the precursors that will eventually link within the cell to form the full biomolecule, it makes it easier for cell permeability and thus has become a very intriguing solution for reducing PROTAC molecular weight.

7.b. Homo-PROTACs

E3 ligases are the most plentiful and specific enzymes within the UPS, having key roles in regulating protein degradation by directly interacting with and affecting protein levels within the cell. As such, deregulation of these E3 ligases can result in cancer proliferation and tumorigenesis due to the altered expression and activity of the proteins that it interacts with. E3 ligases themselves have become therapeutic targets of interest for a multitude of diseases due to their protein regulation abilities[510-514]. Homo-PROTACs are homo-bivalent PROTACs which recruit dimerized E3 ligases able to induce their own protein degradation[515]. This classifies the biomolecule as a chemical inducer of dimerization since it forms a PROTAC ternary complex where the E3 ligase is concurrently the enzyme and the POI (Figure 5b). In 2017, a Homo-PROTAC was developed to target the VHL E3 ligase with the most potent degrader across the three cell lines (HeLa, U2OS, HEK293) synthesized to be symmetric via the acetyl groups connection[516]. Similar techniques have also been used to develop Homo-PROTACs that resulted in the self-degradation of E3 ligases CRBN and MDM2[517, 518]. This concept has also been further built upon with the development of 'heterodimerizing' PROTACs, which are PROTACs that target two different E3 ligases for degradation. The premier report of this concept highlighted a PROTAC that targeted CRBN and VHL E3 ligases, successfully degrading the two in HeLa and HEK293 cells. However, it was seen that the specificity for either ligase within these heterodimerizing PROTACs was determined by their concentration, with a higher

PROTAC concentration resulting in potent CRBN degradation and lower concentration in potent VHL degradation[519].

7.c. PhotoPROTACs

There has been extensive research conducted to find and utilize different techniques of controlling biomolecular activity in either a reversible or irreversible manner. One ideal element that could be employed as an external control for intracellular manipulation is light, since it is generally noninvasive, mostly bioorthogonal, and can be precisely regulated (wavelength, intensity)[520, 521]. The field of photopharmacology has seen rapid growth over the past decade due to high spatiotemporal resolution light being used to either generate or activate small molecules. PhotoPROTACs utilize the concept that some moieties within molecules (ex. azobenzene) could undergo reversible or irreversible changes from light stimulation, thus switching on or off the PROTAC for protein degradation[522-524].

7.c.1. Photoswitchable photoPROTACs

Photoswitchable PROTACs use a photoswitchable moiety on the linker or E3 ligand to reversibly control protein degradation (Figure 5c). This PROTAC will rest in the inactive state until light exposure of a desired wavelength results in activation and subsequent PROTAC binding[525]. The first report of photoswitchable PROTACs added a light-controllable azobenzene group on the CRBN ligand that would be inactive in the dark but activate PROTAC function with blue-violet light (390 nm). Continued exposure under the desired wavelength resulted in the degradation of BRD2/4 and FKBP12 in ALL cells[526]. A later study showed a similar technique used to develop a photoswitchable PROTAC that resulted in the degradation of ABL and BCR-ABL proteins within CML[527]. An interesting observation found across multiple research papers was that at certain light exposures the photoswitchable PROTACs would revert back into its inactive state, thus ceasing protein degradation and proving the concept that a specific light exposure range is necessary for activation.

7.c.2. Photocaged photoPROTACs

In comparison to the photoswitchable PROTACs, photocaged PROTACs use photoliable blocking groups (ex. nitroveratryloxycarbonyl group, NVOC) to irreversibly control protein degradation (Figure 5d). This PROTAC will rest with a photocaging group label on the POI ligand, preventing binding until light exposure releases the photocaging group and results in activation and subsequent PROTAC binding[528, 529]. The first report of this PROTAC utilized photoliable blocker dimethoxy-2-nitrobenzyl group to the JQ1 POI ligand that activated under blue-violet light (365 nm), thus resulting in the degradation of BRD4 within live cells and zebrafish[530]. Another report developed multiple photocaged PROTACs that used the blocking group NVOC on the CRBN ligand which activated under blue-violet light (365 nm), resulting in the degradation of IKZF1/3, BRD2/3, and ALK fusion proteins across multiple cancer lines[531]. Photocage technology is not a 'one-size-fits-all' method, allowing for specificity to be incorporated into the design of the PROTACs.

<u>7.d. Tag-based PROTACs</u>

One of the challenges faced with developing new PROTACs is the tedious, multistep process required, from designing the molecular structure and establishing the chemical synthesis to evaluating its effectiveness in *in vivo* and *in vitro* models. Selecting the appropriate E3 ligase ligand is critical for PROTAC development progression, but there are hundreds of E3 ligases in the human proteasome to select from, thus making it difficult to differentiate potential POI-E3 ligase interactions that would be efficient for PROTAC structures[532, 533]. Tag-based PROTACs have been developed where the tag-POI fusion protein is expressed in the cell so then a universal PROTAC can be utilized to recruit candidate E3 ligases and the tag of the fusion protein (Figure 5e). Measuring the levels of fusion protein within the cell can allow for the determination of the candidate E3 ligase's effectiveness for degrading the targeted POI[534]. HaloPROTACs and dTAGs are the most widely used tag-based PROTACs, having been reported to successfully degrade fusions including oncogenic BRDs, ERK1, HRAS, KRAS, MEK1, and Sirt2[535-542]. While these tag-based PROTACs can be efficient in aiding researchers in examining potential E3 ligase ligands for future PROTAC development, they cannot be utilized as a disease therapeutic option.

8. PROTAC Advantages and Limitations

As the field of PROTAC continues to expand and evolve, many advantages have been declared that makes the utilization of this technology favorable in cancer and disease research. But it is important to address and understand the limitations the technology faces as well, allowing for an equal balance of pros and cons researchers must consider before deciding whether or not to use PROTAC technology.

<u>8.a. Advantages of PROTAC technology</u>

PROTACs function with catalytic MOA via event-driven mechanisms, allowing for complete degradation of the protein. The vast majority of inherited/acquired diseases are based on overexpression of proteins so current small molecule treatment strategies rely largely on occupancy-driven pharmacology. This means that inhibitors bind to the disease-causing proteins in order to block their signaling and the longer the binding occurs, the better the clinical benefits are. Despite the effectiveness of this strategy, high doses are typically required to encourage higher competitive binding activity which contributes to drug toxicity and severe side effects, plus the increased risk of the disease-causing protein mutating to resist the inhibitor treatment. Occupancy-driven MOA also suffers from its inability to work with all biological targets, especially enzymatic activity-lacking targets[543]. The utilization of event-driven MOA means that instead of simply inhibiting the protein's function, the PROTAC triggers the UPS for protein degradation, thus lowering the amount of the protein within the cell and providing overall control of abundant protein levels[543, 544]. Complete degradation of the protein means that not only is the protein's enzymatic activity knocked down but its non-enzymatic activity as well, which can

counter drug resistance[478, 545]. Occupancy-driven MOA also functions stoichiometrically, meaning that the inhibitor is used up on the disease-promoting protein in a 1:1 ratio, which is why higher doses are required in order to induce higher blockage. On the other hand, event-driven MOA PROTACs function sub-stoichiometrically, meaning that a single PROTAC can cause more protein degradation at lower dosage, which in terms lowers the potential for drug toxicity to occur[22].

Another advantage of PROTACs is that they are highly selective as a result of their ternary complex. Many protein and kinase families have several isotypes. Being able to selectively target one isotype for degradation without subsequent degradation of the other isotypes is crucial for targeted cancer and disease therapeutic research. Small molecule inhibitors are also mostly designed to be non-specific to their target protein, which can result in unwanted off-target effects[546]. PROTACs are a universal tool due to their customization ability depending on the POI ligand and E3 ligand, allowing for specificity to be considered in the design. By keeping in mind the inhibitor and E3 recruiting ligand, varying types of PROTACs can be customized for different isotypes without dramatic redesigns of the PROTAC itself, contributing to more precise therapeutic options[546, 547].

Finally, the biggest advantage that PROTAC technology benefits from is the potential for it to treat 'undruggable' targets. Majority of small molecule inhibitors require specific binding pockets on the disease-promoting protein in order to cause subsequent inhibition, meaning that a mutated or lack of that binding pocket increases drug resistance. There are several 'undruggable' targets resulting from lack of binding pockets or non-enzymatic activity, such as TFs, scaffolding proteins, and cofactors. PROTACs have the advantage of being able to, theoretically speaking, bind to any nook and cranny of the disease-promoting protein so it is not restricted to a specific enzymatic binding location, also allowing it to bind to and subsequently degrade non-enzymatic proteins and kinases[2, 3, 18, 479, 548]. The ability for PROTACs to bind to anywhere on the protein has resulted in PROTACs having extreme intrigue in the field of cancer and disease therapeutic research as it opens door to treating targets that were previously inaccessible.

8.b. Limitations of PROTAC technology

While the ternary complex is crucial for PROTAC function, there is a possibility for a 'hook effect' to occur. This means that binary complexes – either POI-PROTAC or PROTAC-E3 – will form instead of the required ternary complex due to an excessive amount of PROTAC in the cell. 'Hook effect' can also occur if the structure of the PROTAC is not appropriate, mostly as a result of a too short or too long linker chain between the two ligands[549, 550]. There is also the important factor that while there are over 600 different types of E3 ligases reported in the human genome, only less than 1% of them have been utilized for PROTAC development. The few E3 ligases that have been successfully validated and utilized have been useful so far but each have their own limitations that must be considered[551]. PROTACs, due to completely degrading the protein instead of just inhibiting the function, significantly lowers the protein levels within the cell. While this is beneficial for lowering disease-causing protein levels, complete degradation of particular proteins that have crucial function at normal levels can cause harmful results. Some PROTACs have also been reported to cause unwanted off-target effects. While this is not as

common as for small molecule inhibitors, it is still important to note that it can occur and be harmful to the cell as well[10].

One of the major limitations of PROTAC technology is that many suffer from cell permeability difficulties as a result of high molecular weight (MW) and polarity. PROTACs typically weigh between 900 to 1100 daltons (Das) and the drastic decrease of passive permeability for a molecule ranges typically between 800 and 1000 Das. This also negatively affects the PROTAC's pharmacokinetic ability, making its lower cell permeability potentially prevent its ability to enter the cell and perform its necessary functions[552-554]. Due to this high molecular weight, PROTACs are considered to lie "beyond [the] rule of five". Lipinski's rule of five (MW < 500 Das, hydrogen bond donors < 5, hydrogen bond acceptors < 10, clogP < 5) is a principle for orally delivered drug development; if a drug does not meet one of the criteria it falls 'outside the rule of five' and thus should not be used for drug treatment[555]. While some PROTACs have been developed into orally available drugs despite lying outside the rule of five, the high molecular weight of the molecule still makes it difficult for it to penetrate cells and solid tumors[556].

9. Considerations for Future Directions

As the field of PROTAC technology continues to evolve, many considerations should be taken in terms of which directions research should move. One such consideration is the improvement of the PROTAC structure as a whole, focusing on refining the individual components to vastly improve the overall product. E3 ligase and POI recruitment are crucial for PROTAC functionality, as both need to be linked simultaneously in order to induce ubiquitination and subsequent degradation. As such, the two components cannot be too far apart from one another or else the Ub will not be able to smoothly transition from the E2 to the POI for tagging. One thing that can assist in improving the E3/POI structure is improving linker structure for PROTAC use. The vast majority of linkers found in reports are either alkyl linkers or polyethylene glycol (PEG), with varying lengths of the chain and combinations chemicals. However, the process to optimize linker length and format is arduous and time-consuming, relying on the traditional 'trial-and-error' PROTAC synthesis to examine PROTACs and linkers. There is also the challenge that a linker that is not the proper size will assist in the formation of 'hook effect'. While new styles of linkers have been developed for novel PROTACs, finding technology or techniques to optimize linker examination will not only save time and money but also help to minimize the possibility of 'hook effect' occurring[557, 558].

Another improvement that is necessary for PROTAC structure is to identify new E3 ligase and E3 ligase ligands for utilization. There have been new strategies developed to help with researching potential E3 ligases for possible PROTAC usage, such as the activity-based protein profiling (ABPP), function first approach, and rational design strategy. For example, ABPP is a chemoproteomic strategy where a broad proteome spectrum profile is probed in order to provide quantitative and site-specific assessment to determine potential E3-ligand pairs[559]. Several new

E3 ligases and ligands have recently been discovered over the past few years: DCAF15, RNF4, RNF114, AhR, and DCAF16. While steps have been taken in the right direction, there are still hundreds of E3 ligases to examine and validate so new strategies of screening will be necessary in order to uncover new E3 ligases and, subsequently, new PROTACs[560].

Another crucial step for the future of PROTAC technology is to fix the problem of the high MW and polarity. There is constant research occurring in an attempt to tackle this pressing issue, taking different kinds of approaches. One approach is to add CPPs to p-PROTACs in order to help with penetration through the membrane and into the cell. Another is to break the PROTAC into two smaller MW parts with better solubility and polarity to cross the membrane and then assemble into the full PROTAC once inside via 'click chemistry'. A third technique is using solubility predictive technology in order to compute experimental trials to examine and distinguish soluble and insoluble degraders[561]. The combined forces of improving PROTAC solubility and decreasing overall MW is needed to expand PROTAC lipophilicity and increase delivery options.

Finally, as improvements are continued on PROTAC structures as a whole, another direction that can begin to be examined is researching PROTAC involvement in combinational therapy. PROTACs have successfully reported the degradation of several dozen target proteins and kinases with a wide range of functions by utilizing established inhibitors as the POI ligand, so it is possible that these effectively-proven PROTACs can work well when combined with another inhibitor or FDA-approved drug. How this could work is by, for example, treating cancer cells with PROTACs targeting a specific POI as the primary treatment, allowing for degradation to occur and significantly lowering the protein level within the cell. Next, another FDA-approved drug can be used to treat the cancer cells as the secondary treatment in order to inhibit any of remaining disease-promoting proteins and effectively stall the hyperactive signaling and proliferation. A few published studies have begun to examine this strategy of combination therapy, with one such report combining PROTAC PP-C8 and the PARP inhibitor Olaparib to significantly lower CDK12 protein levels in TNBC cell lines[371]. By combining two treatment options it can result in lower dosage required by both for the desired effect, thus lowering the chances of drug toxicity and severe side effects.

10. Conclusion

PROTACs are heterobifunctional molecules that can selectively degrade a POI via the UPS, allowing for significantly decreased levels of disease-promoting proteins within cancer or other disease cells. The field of PROTACs has rapidly evolved since its initial introduction in 2001 due to its event-driven MOA and potential for degrading 'undruggable' targets. With newer PROTACs being synthesized and limitations discovered, new techniques and technologies are being developed to address them. Some recent variations of the PROTAC technology that have since come out in the last few years include Antibody-based PROTACs (AbTACs), Lysosome-Targeting Chimeras (LYTACs), autophagy-targeting chimeras (AUTACs), and Ribonuclease-

targeting chimeras (RIBOTACs)[562-564]. PROTAC-DB 2.0 is an online database of structural and experimental PROTACs that was recently updated in 2023. This database lists the number of PROTACs, POI ligands, linkers, and E3 ligands currently published. It also has a PROTAC-Model technology to predict strong PROTAC ternary complexes as well as a E3 ligase filtering strategy, which can be incredibly beneficial in improving and validating new PROTACs for research[565]. With the continued extreme interest in TPD and the rapid development of the field over the last two decades, the realm of PROTAC technology can be projected to further expand and break into the clinical setting, ushering in a new era of therapeutic access for all.

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