



Proteolysis Targeting Chimeric-Based Technology in Myeloma and Lymphoma

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ABSTRACT

Proteolysis-targeting chimeras (PROTAC) leverage the ubiquitin–proteasome system to selectively degrade oncogenic proteins, including those previously seen as undruggable. Recent preclinical studies indicate that PROTACs may represent a novel therapeutic strategy in lymphoma and myeloma. Indeed, preclinically, PROTACs have shown high efficacy and remarkable selectivity, a favorable safety profile, and lower toxicity compared with conventional therapies. Their catalytic, reusable mechanism enables drug dosing

and offers the perspective of long-term low-dose treatment. PROTACs have demonstrated their ability to overcome drug resistance by targeting and degrading overexpressed or mutant proteins that are responsible for refractory disease. This review aims to offer a comprehensive evaluation of the currently existing PROTACs that have been tested in lymphoma and myeloma to highlight the need for drug optimization and further translational research that could translate PROTACs to clinical trials.

Introduction

Proteolysis-targeting chimeras (PROTAC) are heterobifunctional molecules that induce the degradation of target proteins by harnessing the cellular ubiquitin (Ub)–proteasome system. The structure of PROTACs comprises an E3 ligase ligand and a protein of interest (POI) ligand that are joined by a linker region. After binding to the POI, PROTACs recruit E3 Ub ligase enzymes, forming an E3-PROTAC-POI ternary complex. The recruited E3 Ub ligase then catalyzes the subsequent ubiquitination of the

POI, marking it for proteasomal degradation. The Ub–proteasome system represents a protein degradation apparatus involved in maintaining cellular homeostasis by removing damaged proteins (1). The mechanism of ubiquitination involves a series of successive enzymatic processes. First, Ub is activated by the E1 enzyme in an ATP-dependent reaction, which is then transferred to E2, a Ub-conjugating enzyme. In the final step, E3 Ub ligase binds the E2-Ub complex and catalyzes the transfer of the Ub molecule to a target protein (2).

One important advantage of PROTACs is their reusability. Upon degradation of the POI, the PROTAC molecule can rebound to other proteins, leading to more POI degradation, as depicted in **Fig. 1**. This characteristic also enables PROTACs to be more efficient at low concentrations in comparison with conventional small-molecule inhibitors (SMI). Moreover, another important advantage of PROTACs is their ability to overcome mutation-induced resistance that is specific to SMIs while also requiring a shorter interaction time to induce degradation of the target protein (3–5). Targeted therapies that are currently administered in cancer, such as SMIs and monoclonal antibodies (mAb), often act by targeting proteins exhibiting enzymatic activity. A limitation of mAbs is the restriction to such antigens expressed on the surface of cells. PROTACs can overcome these challenges, as they can target intracellular proteins alike, with and without enzymatic activity, as well as transcription factors or scaffold proteins (3).

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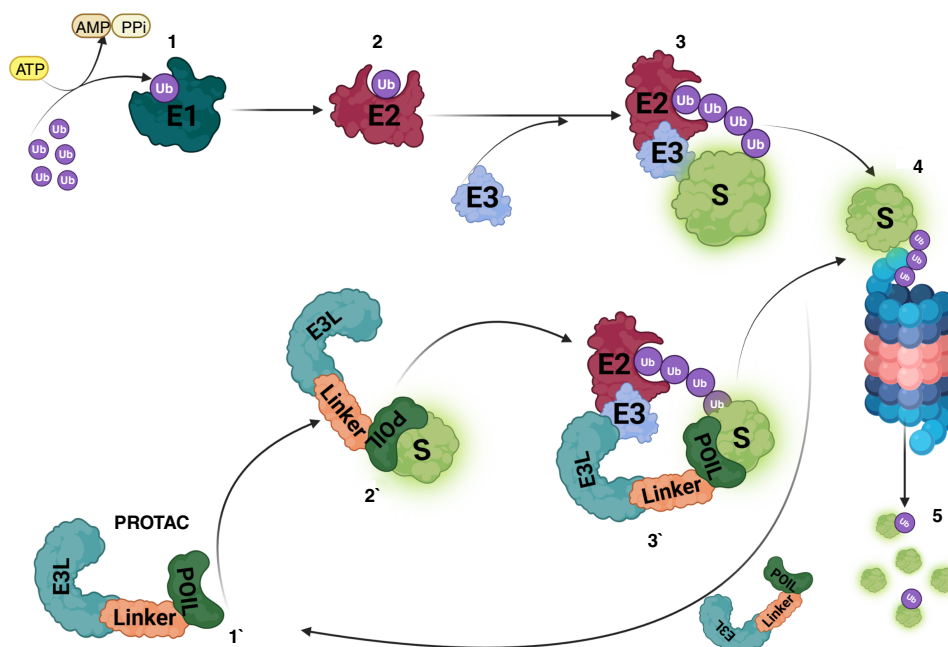
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Development of PROTACs

The development of PROTACs was pioneered by Sakamoto and colleagues in 2001. The chimeric molecule induced the degradation of methionine aminopeptidase-2 by recruiting the SCF β -TRCP E3 Ub ligase (4–7). As these early PROTACs were characterized by low cell permeability, the following studies focused on developing small-molecule PROTACs (5). The same authors introduced the first case of small-molecule PROTACs in 2008, which induced the degradation of the androgen and estrogen receptors. The PROTAC consisted of nutlin to recruit the E3 Ub ligase human homolog of mouse double molecule 2 and the selective androgen receptor modulator, which binds the androgen receptor (4–7). In the same period, another group focused on developing a PROTAC molecule

Figure 1.

Protein degradation mechanism by Ub–proteasome machinery and PROTACs. 1. Ub binds to E1 with energy consumption. 2. Ub is transferred to E2. 3. E3 binds to the POI (S) and links to E2 in which S is tagged with ubiquitin. 4. Tagged S binds to the proteasome, and degradation is initiated. 5. The protein is degraded, and its fragments can be reused. 1'. Structure of the PROTAC with E3 Ub linker (E3L), linker, and protein of interest linker (POIL). 2'. PROTAC binds the POI (S). 3'. The POI is tagged after PROTAC binds to E3. The PROTAC detaches and can be reused to target other POIs for future degradation. PPi, proton pump inhibitors. [Created in BioRender. Moldovan, R. (2025) <https://BioRender.com/fculp5f>; ref. 6].



using the cellular inhibitor of apoptosis protein 1 as an E3 ligase and bestatin esters as an E3 ligand, which were able to degrade cellular retinol and retinoic acid binding proteins. The group later named this specific class of PROTACs small and nongenetic inhibitors of apoptosis protein (IAP)–dependent protein erasers (SNIPERs). This was followed by additional IAP ligand development, leading to the production of molecules such as MV1 and LCL161. One disadvantage of SNIPERs is that they induce IAP autoubiquitination and degradation, causing a decrease in IAP E3 ligase levels. Despite representing a limitation, the autoubiquitination of IAP gives the SNIPER molecules a dual-targeting ability, which might come as an advantage in certain cases due to the oncogenic role of IAP (5–8). Of further note, Von Hippel–Lindau (VHL) is another E3 ligase that binds hydroxylated HIF-1 α . A series of studies led to the development of a VHL binding compound based on the HIF-1 α sequence. The ability of this ligand to bind VHL led to its incorporation in PROTACs, making it one of the most utilized E3 recruiting ligands in this field (8). Immunomodulatory drugs (IMiD) are a class of compounds that can modulate the function of different functions of T and NK cells by inducing the production of cytokines. Notable IMiDs are thalidomide and its analogs, lenalidomide and pomalidomide. Thalidomide targets the CRBN E3 ligase, inducing the ubiquitination and proteasomal degradation of IKZF1 and IKZF2, which are involved in hematologic malignancies such as multiple myeloma. IMiDs are used in a wide range of diseases, including multiple myeloma, myelodysplastic syndrome, mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (9). Therefore, due to its ability to target CRBN, thalidomide and other IMiDs have become widely used in PROTAC development as E3 recruiting ligands. It has been shown that CRBN can have increased neosubstrate degradation compared with VHL, but it could also lead to nonspecific degradation of the neosubstrates (8).

Advantages of PROTACs

One of the important advantages of PROTACs is their ability to induce isoform-selective degradation of the target protein. Although

SMIs do not effectively distinguish and selectively target particular isoforms of a protein, resulting in adverse effects, PROTACs that are derived from these same SMIs have demonstrated enhanced selectivity for degradation (1). Moreover, the ability of PROTACs to degrade a substrate is influenced by the ability of that specific protein to form a stable ternary complex with PROTAC and E3 ligase, whereas the binding affinity of the PROTAC for the POI turned out not to be the determining factor. Two PROTAC compounds using foretinib were developed, a c-Met tyrosine kinase inhibitor, as the POI ligand. One of the compounds was able to recruit VHL as the E3 ligase, whereas the other recruited CRBN. The results showed that despite having the same POI ligands, the binding profiles of the two PROTAC molecules were not identical. This also shows that PROTACs can turn ligands with a promiscuous targeting profile into more specific targeting molecules, based on the type of E3 ligase recruited by the PROTAC. Although foretinib alone can bind to more than 50 kinase proteins, the VHL-recruiting PROTAC degraded only 14, and the CRBN-recruiting PROTAC degraded nine (10). Histone deacetylases (HDAC) are a class of enzymes involved in histone deacetylation, modulating the epigenetic background of cells. The enzymes are classified into different classes, each consisting of certain isoforms of HDAC (11). A newly developed PROTAC construct using TMP269 (a class IIa HDAC inhibitor) as a POI ligand was able to specifically target only the HDAC7 isoform, without altering the HDAC9 isoform (12). HDAC7 is involved in regulating cell metabolism and inflammation, and its specific targeting is crucial in pathologic states associated with increased inflammation. In contrast, HDAC9 is involved in cardiac gene expression and vascular calcification, and its nonspecific targeting might lead to unwanted side effects (11, 12). The SWItch/Sucrose Non-Fermentable complexes are involved in transcriptional regulation and DNA repair. The enzymatic function of this complex is granted by the SMARCA2 and SMARCA4 proteins, which possess high sequence homology. As SMARCA4 is frequently mutated in cancer, its specific targeting has gained a lot of attention. It was found that tumors with loss-of-function mutations rely on SMARCA2 for survival, and the additional inhibition of SMARCA2 impairs cell survival through

synthetic lethality. A PROTAC construct consisting of a SMARCA2/4 ligand and a VHL recruiting moiety was able to specifically induce the degradation of SMARCA2 at picomolar concentrations, whereas SMARCA4 remained mostly unaffected (13). Additionally, as protein complexes are frequently aberrant in a series of diseases, they have emerged as viable therapeutic targets. SMIs have limitations in targeting multicomponent protein complexes, as inhibition does not lead to a complete loss of function. Therefore, PROTACs can overcome this limitation, having the ability to degrade multicomponent protein complexes (1).

The mechanism of action of PROTACs involves the degradation of the target protein, which functionally culminates in a complete loss of function. This is particularly useful in the case of proteins that harbor both enzymatic and scaffolding functions, as is the case for certain receptor tyrosine kinases (RTK). SMIs that block the enzymatic activity of such multifunctional proteins fall short of inhibiting the specific pathway as, in certain cases, the scaffolding roles of the RTKs can induce pathway reactivation. PROTACs overcome this limitation by completely removing the target protein, eliminating both catalytic and scaffolding functions (1). The ability of PROTAC molecules to eliminate the activity of multifunctional proteins was shown in a series of studies. A PROTAC construct derived from the VS6063 FAK inhibitor was able to completely deplete the FAK protein in ovarian cancer cell lines, leading to the loss of both its kinase-dependent and kinase-independent activity (14). BCR::ABL is a tyrosine kinase with constitutive activity that is derived from the Philadelphia chromosome and is a driving factor in chronic myeloid leukemia (15). Besides its tyrosine kinase activity, this protein has been shown to be involved in kinase-independent roles, such as protein scaffolding (16). The efficiency of PROTACs in eliminating this protein was demonstrated in a study that used a chimeric molecule derived from BCR::ABL inhibitors conjugated to a VHL ligand (17).

Despite having many advantages, the implementation of PROTACs in cancer treatment still faces a series of challenges. One of the most important disadvantages of PROTACs is the hook effect, in which higher concentrations of the compound do not lead to an increased effect. This is caused by the formation of inactive dimers such as E3 ligase:PROTAC or POI:PROTAC, instead of the active E3 ligase:PROTAC:POI trimers (8, 18). Similar to SMIs or mAbs, PROTACs can induce off-target effects, leading to unwanted side effects. The binding of an E3 ligase could influence the binding of its endogenous substrates, leading to the ubiquitination and degradation of undesired neosubstrates. In addition, POIs can also be present in normal tissue, in which their degradation can be detrimental (18). Furthermore, due to their high molecular weight and polar nature, PROTAC molecules can often exhibit decreased membrane permeability and reduced bioavailability (19).

The unique potential of PROTACs to degrade mutant oncoproteins and targets that were considered undruggable positions them as a promising therapeutic strategy distinct from conventional SMIs. This therapeutic potential is particularly relevant in hematologic malignancies such as lymphoma and myeloma, in which dysregulation of protein homeostasis and resistance to standard therapies remain critical clinical challenges. PROTAC molecules can often exhibit decreased membrane permeability and reduced bioavailability. In parallel, cellular immunotherapy strategies are also being developed to target the undruggable intracellular space. For example, Cheng and colleagues (20) engineered costimulatory signal-armed alpha (α) chain and a beta (β) chain of T cell receptor

(abTCR) T cells to target the Epstein Barr Virus (EBV) latency antigen LMP2, highlighting how both PROTAC degraders and engineered T cells are converging on the challenge of intracellular oncogenic drivers. Recent advances have demonstrated that PROTACs can selectively target and degrade key oncogenic drivers involved in the pathogenesis and progression of these malignancies, including proteins involved in resistance to therapy, apoptosis, or cell-cycle regulation. Below, we aim to present that several PROTACs show high potential as therapeutic agents in lymphoma and myeloma, debating the outcomes and perspectives.

Translational Limitations and Challenges in PROTACs Technology

PROTACs have opened new chapters for the development of novel drugs, offering unprecedented opportunities in medicine to overcome drug resistance, degrade targets considered undruggable, and bring hope for better management of oncologic patients. However, as a new technology, the use of PROTACs faces many challenges and has limitations that need to be addressed. The main translational limitations include bioavailability issues, tumor selectivity and off-target toxicity, delivery challenges, resistance to therapy, substrate degradation and selectivity, and compound stability (21, 22). Usually, PROTACs are large, heterobifunctional molecules with low oral bioavailability and poor membrane permeability, features that limit their systemic exposure and tumor penetration, particularly in bone marrow and lymphatic tissues (23, 24).

Off-target toxicity is a constant risk in PROTAC approaches, as they recruit ubiquitously expressed E3 ligases such as CRBN or VHL, with the risk of degrading target proteins in normal cells. The lack of tumor-specific E3 ligases remains a major barrier to selective degradation in malignant cells. Besides the off-target toxicity, the delivery challenges are critical, as efficient intracellular delivery is hampered by their high molecular weight and hydrophobicity. Thus, the use of nanomedicine and cell-penetrating peptides could improve drug delivery in future studies (24, 25).

PROTAC efficacy can be compromised when tumor cells develop resistance through downregulation or mutation of E3 ligases, altered expression of target proteins, or changes in the Ub-proteasome system. IMiD-based PROTACs can induce degradation of neosubstrates that have critical roles in normal cellular functions, embryonic development, disease progression, or other cellular processes, leading to adverse effects; thus, achieving selective neosubstrate targeting remains a significant challenge (26, 27).

All these challenges are responsible for the translational limitations of the current PROTACs. Furthermore, in the case of myeloma and lymphoma, PROTACs have been reported to induce hematologic toxicities like neutropenia, lymphopenia, and thrombocytopenia; off-target protein degradation; and gastrointestinal symptoms such as diarrhea and nausea. These effects occur due to the mechanism of action, which involves the Ub-proteasome system and the use of E3 ligase recruiters, such as CRBN, which are effective against oncogenic targets but also affect normal cells (26–28).

The pharmacokinetic and bioavailability issues related to PROTACs in myeloma and lymphoma include low oral bioavailability, poor aqueous solubility, limited cell membrane permeability, and rapid clearance from the body. Typically, these therapeutic agents are complicated, large, heterobifunctional molecules that have high molecular weight and complicated structures, which limit passive diffusion through cell membranes and decrease absorption after oral

administration. Thus, most of the agents require parenteral delivery, and even in these systems, the distribution to bone marrow and lymphatic tissues is poor. Furthermore, these therapeutics usually show poor metabolic stability and undergo rapid degradation and clearance from the blood, which decreases the therapeutic window, requiring frequent dosing or special delivery systems to be employed. One such complication associated with dosing strategies is the “hook effect,” which is a concentration-dependent phenomenon in which high levels of PROTAC, paradoxically, decrease target degradation. Novel approaches in formulation, such as lipid-based nanoparticles and polymeric micelles, are being investigated to improve bioavailability, tumor targeting, and systemic exposure (29–31).

Another critical barrier is the tumor microenvironment (TME). In multiple myeloma, the bone marrow microenvironment is characterized by high cellular density, a robust extracellular matrix, and altered vasculature, all of which inhibit the transport and distribution of drugs to malignant plasma cells. Moreover, both stromal cells and immune cells produce soluble factors, including cytokines and chemokines, which generate physical and biochemical barriers that limit access to PROTACs at their intracellular sites of action. Hypoxia, as well as altered metabolic pathways within TMEs, may also lead to decreased cellular uptake and altered drug metabolism, thus decreasing the efficacy of PROTACs. In addition, cell adhesion-mediated drug resistance, due to myeloma cell–stromal cell and microenvironment-to-myeloid cell interactions, limits the intracellular delivery of drugs and promotes survival signals, reducing the efficacy of this therapy. In lymphoma, relatively similar interstitial pressure, a network of stromal cells, and immune-suppressive niches are present in lymphoid tissues, which limit the diffusion and cellular uptake of PROTACs. In addition, the high molecular weight and low permeability of most PROTACs reduce their efficacy, and an increased focus on developing novel delivery systems, including nanoparticles and membrane carriers to mimic tumor biology or enzyme-activated prodrugs, is essential to improve the tumor localization and penetration of these molecules (31–33).

Molecular stability is a significant issue as PROTACs are subject to rapid metabolic degradation and hydrolysis owing to their large size, flexible nature, and heterobifunctional properties. Rapid degradation and low drug concentrations will limit the effectiveness of the therapy. Chemical modifications of linker stabilities, as well as improving the metabolic stability of E3 ligase ligands, could offer a better perspective in terms of drug availability and efficacy. The presence of a dense extracellular matrix, abnormal vasculature, and excessive interstitial tissue pressure in the marrow and lymphoid tissues presents further challenges to effective translation by slowing down the penetration and distribution of PROTACs. In an effort to overcome these limitations, nanotechnology-based delivery vehicles, such as lipid nanoparticles, polymeric micelles, or stimuli-responsive carriers, are being developed to protect PROTACs from premature metabolic degradation, promote tumor-specific codelivery, and allow for the controlled release of the PROTAC in the presence of environmental stimuli such as pH and enzymes (29, 31, 34).

PROTACs can synergistically enhance the efficacy of bispecific antibodies or chimeric antigen receptor (CAR) T-cell therapy; they can increase the abundance of tumor antigen–derived peptides presented to MHC class I molecules. Thus, T-cell activation can be improved, cytokine secretion can be enhanced, and tumor killing can be more effective (35). PROTAC mechanisms of action can enhance immunotherapy in various types of cancer, enhancing

immune response and inhibiting immune suppression (36). Other therapies are facing difficulties in implementation due to biological barriers, and one notable example is the engineered costimulatory signal-armed abTCR T cells designed to target the EBV latency antigen LMP2, which underwent multiple testing and molecular adjustments to obtain augmented T-cell proliferation and antitumor efficacy (20).

For a better clinical translation, PROTAC design should consider structures that can offer stability, high efficacy, better delivery rates, and low off-target toxicities.

Lymphoma

Lymphomas represent a heterogeneous group of malignancies of lymphoid origin that are characterized by complex and varied genetic landscapes, different cells of origin, and treatments. Depending on their origin, lymphoid neoplasms are divided into lymphomas originating in precursor lymphoid cells and lymphomas originating in mature lymphoid cells. Mature lymphoid neoplasms are subclassified depending on T- or B-cell origin. Additionally, mature lymphomas are categorized as non-Hodgkin lymphomas (NHL) and Hodgkin lymphomas (37).

Mature lymphomas of T-cell origin are referred to as peripheral T-cell lymphomas and represent 10% to 15% of NHL. Anaplastic large-cell lymphoma (ALCL) is a mature T-cell neoplasm originating in T cells expressing the CD30 lymphocyte activation marker. ALK-positive ALCL is a lymphoma subset presenting chromosomal rearrangements of the *ALK* gene, with most cases carrying the t(2;5)(p23;q25) translocation and expressing nucleophosmin-ALK fusion proteins. This leads to the constitutive activation of ALK that sends downstream signals related to survival and cell growth. Other chromosomal aberrations found in ALCL include *TP63* and *DUSP22* rearrangements. T-cell lymphomas of T follicular helper (TFH) origin are characterized by the expression of TFH markers such as CD10, CD279, CXCL13, B-cell lymphoma 6 (BCL6), CD40L, and NFATC1. Other common genetic alterations present in T-cell lymphomas of TFH origin include somatic mutations in *TET2*, *THOA*, *IDH2*, *CD28*, *DNMT3A*, and fusions of *ITK-SYK* or *CD28-CTLA4* (37). Yet other cases of T-cell lymphoma fall into the category of peripheral T-cell lymphoma, not otherwise specified, or PTCL-NOS. Although this category shows a high level of heterogeneity between phenotypes, different studies have identified that PTCL-NOS is associated with genetic alterations like *GATA3* and *TBX21* overexpression or mutations of certain genes such as epigenetic mediators [*KMT2D* (*MLL2*), *TET2*, *KDM6A*, *ARID1B*, *DNMT3A*, *CREBBP*, *MLL*, and *ARID2*], tumor suppressor genes (*TP53*, *FOXO1*, *BCORL1*, and *ATM*), or genes involved in signaling pathways (*TNFAIP3*, *APC*, *CHD8*, *ZAP70*, *NF1*, *TNFRSF14*, and *TRAF3*). Cytotoxic T-cell and NK cell lymphomas and leukemias are another group of diseases characterized by heterogeneous prognosis and clinical behavior. Most of these neoplastic diseases present extranodal disease, involving the liver, spleen, and bone marrow. Studies have found that many T-cell and NK cell malignancies are characterized by mutations in the JAK/signal transducer and activator of transcription (STAT) pathway, more specifically in the *STAT3* and *STAT5B* genes (38).

Lymphomas deriving from B cells account for 85% to 90% of non-Hodgkin neoplasms, their main origin being in the germinal centers. Physiologic processes such as somatic hypermutation and class switch recombination that are present during the germinal

center reaction can support lymphomagenesis due to their proneness to errors that can cause DNA damage. Aside from these cases, there are neoplasms derived from post-germinal center cells, including marginal zone lymphoma (MZL) and lymphomas derived from B cells that have not entered the germinal center, such as MCL (39). Burkitt lymphoma is an aggressive subtype of germinal center B-cell lymphoma, expressing CD45, CD20, CD79a, CD10, and BCL6, while being BCL2-negative. The cells are highly proliferative, having an almost ubiquitous Ki-67 expression index. This disease is associated with genetic alterations spanning mutations in *TCF3*, *ID3*, *CCND3*, *TP53*, or *CDKN2A*. Moreover, MYC has a constitutive activity caused by the t(8;14) chromosomal translocation (38, 39). Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin B-cell lymphoma, representing up to 40% of cases. Typical genetic alterations found in this B-cell neoplasm are rearrangements in the MYC, BCL2, and BCL6 genes. DLBCL is associated with mutations in several genes, such as *MYD88*, *CD79B*, *NOTCH1/2*, *EZH2*, *PI3K*, *CREBBP*, *TP53*, *CDKN2A*, *JAK/STAT*, and *BRAF/MEK1*. MCL represents 5% to 7% of non-Hodgkin B-cell neoplasms. It is characterized by an unmutated IGHV due to the absence of germinal center reaction and an overexpression of SOX11. MCL is associated with cell-cycle dysregulation at the G₁-S-phase due to cyclin D1 overexpression caused by the t(11;14)(q13;q32) chromosomal translocation. In addition, MCL has recurrent somatic mutations in a number of genes such as *ATM*, *TP53*, *CDKN2A*, *NSD2*, *KMT2D*, *MEF2B*, *KMT2C*, *SMARCA4*, *CCND1*, *BIRC3*, *TRAF2*, and *NOTCH1/2* (39). MZL is derived from post-germinal center B cells and accounts for 5% to 15% of all NHLs of B-cell origin (39). MZL is divided into three subtypes, which differ in clinical representation and behavior: splenic MZL, extranodal MZL, and primary nodal MZL (NMZL). Splenic MZL cells possess a nonspecific phenotype, usually lacking the expression of annexin A1, CD5, CD10, CD23, CD25, CD43, cyclin D1, LEF1, and CD103. The most common chromosomal abnormality, found in approximately a third of the cases, is the deletion of the 7q chromosome. Extranodal MZL presents a phenotype that is negative for CD5, CD10, CD23, LEF1, cyclin D1, and SOX11, with some rare cases that are CD5- or CD10-positive. Frequent chromosomal aberrations are represented by the *BIRC::MALT1*, *IGH::MALT1*, and *FOX-P1::IGH* translocations, whereas mutations with the highest incidence occur in *NOTCH1*, *TNFAIP3*, *TBL1XR1*, *KMT2D*, *TET2*, *TNFRSF14*, *PICK3CD*, *NF1*, *TRAF3*, and *SPEN*, depending on the subtype of extranodal MZL (40). NMZL cells have a phenotype similar to extranodal MZL cells. The cells are positive for CD19, CD20, CD79a, Oct2, Pax5, BCL2, and CD43 and negative for CD5, CD10, CD23, and cyclin D1. In terms of cytogenetics, NMZL cells have a nonspecific profile that includes chromosomal abnormalities found in other types of MZL, such as trisomy 3, trisomy 18, trisomy 7, and trisomy 8. Molecular features specific to NMZL are represented by the absence of the 7q losses (splenic MZL), the inactivation of the *A20* gene, and specific expression patterns of *MNDA*, *CHIT1*, *TAC1*, *TGFβ*, miR-221, and miR-223 (41).

Hodgkin lymphoma accounts for approximately 10% of lymphoma cases, and it is characterized by the presence of pathognomonic multinucleate giant cells or large mononuclear cells called Hodgkin or Reed-Sternberg (HRS) cells, surrounded by lymphocytes, eosinophils, neutrophils, histiocytes, and plasma cells, to form an inflammatory milieu (42). Hodgkin lymphoma is divided into two subtypes: classical Hodgkin lymphoma (CHL), accounting for 85% of all Hodgkin cases, and nodular lymphocyte predominant (LP) Hodgkin lymphoma (NLPHL). CHL HRS cells usually possess

a repressed B-cell program and have defective immunoglobulin expression. CHL is characterized by the expression of CD30 and CD15 in most cases, with a more frequent expression of CD30. Frequent chromosomal alterations found in CHL HRS cells include chromosome material gains in 2p, 9p, 17q, 19q, and 20q and losses in 6q and 13q. These chromosomal alterations lead to differential expression patterns of several genes involved in signaling pathways, such as *JAK2*, *PDL1*, *PDL2*, *REL*, *RELB*, *CD40*, and *MAP3K14*. A clinically important modification is the amplification of *PDL1/PDL2* caused by gains in 9p24.1 and by amplification of *JAK2*. Genetic analyses found recurrent mutations in JAK-STAT pathway genes: *STAT6*, *GNA13*, *XPO1*, and *ITPKB* (43). The characteristic cells of NLPHL are the LP cells. These cells possess a phenotype that indicates a germinal center B-cell origin, due to the expression of B-cell markers such as CD19, CD20, and CD79 and germinal center B cell-associated molecules including BCL6, HGAL, and AICD. The number of known genetic alterations present in LP cells is lower than that found in HRS cells. The most common mutations are found in BCL6, SOCS1, SGK1, JUNB, DUSP2, and REL (44).

PROTACs in lymphoma

PROTACs are heterobifunctional small molecules that are designed to induce selective degradation of specific proteins, harnessing the Ub-proteasome system. PROTACs are not part of the standard of care in lymphoma, as ongoing studies evaluate their potential efficacy and toxicity and optimize tumor selectivity. In the context of lymphoma, several PROTACs are being developed and tested, targeting BCL-xL, STAT3/JAK, Bruton's tyrosine kinase (BTK), BET, IRAK4, IL2-inducible kinase (ITK), HDAC7, Bax inhibitor-1 (BI-1), BCL6, maternal embryonic leucine zipper kinase (MELK), Polycomb repressive complex 2 (PRC2), and ALK, summarized in Fig. 2.

PROTACs targeting BCL-xL

BCL-xL is an antiapoptotic protein that is part of the BCL2 family of proteins. The role of the BCL2 family of proteins is to regulate apoptosis through competitive fluxes of anti- and proapoptotic proteins. BCL-xL possesses two distinct mechanisms of regulating apoptosis. First, it can bind the BH3 domain of proapoptotic regulators, leading to an inhibition of apoptosis. Additionally, it can bind cytosolic p53, blocking the activation of BAX/BAK and leading to an inhibition of apoptosis (45). It was shown that BCL-xL is frequently overexpressed in Hodgkin lymphomas and in more than 80% of NHL cases, as well as in multiple myeloma, making it an important target (46).

DT2216 is a BCL-xL-targeting PROTAC. The construct was based on navitoclax, a BCL2/BCL-xL inhibitor, targeting and inducing the degradation of BCL-xL by recruiting the VHL E3 ligase. DT2216 was able to kill T-cell lymphoma cell lines by selectively degrading BCL-xL in a dose- and time-dependent manner. These findings revealed that the PROTAC construct is more potent against lymphoma cell lines and has reduced toxicity compared with navitoclax (47). Similar findings were reported with an IAP E3 ligase recruiting a PROTAC targeting BCL-xL. The compound was able to potentially degrade BCL-xL in a T-cell lymphoma cell line while also exhibiting improved efficiency and lower toxicity compared with the parent compound, navitoclax (ABT-263; ref. 48). The efficiency of BCL-xL targeting PROTACs was reported in other studies using different experimental models, including acute myeloid leukemia (AML) cell lines and colon cancer cell lines (49, 50).

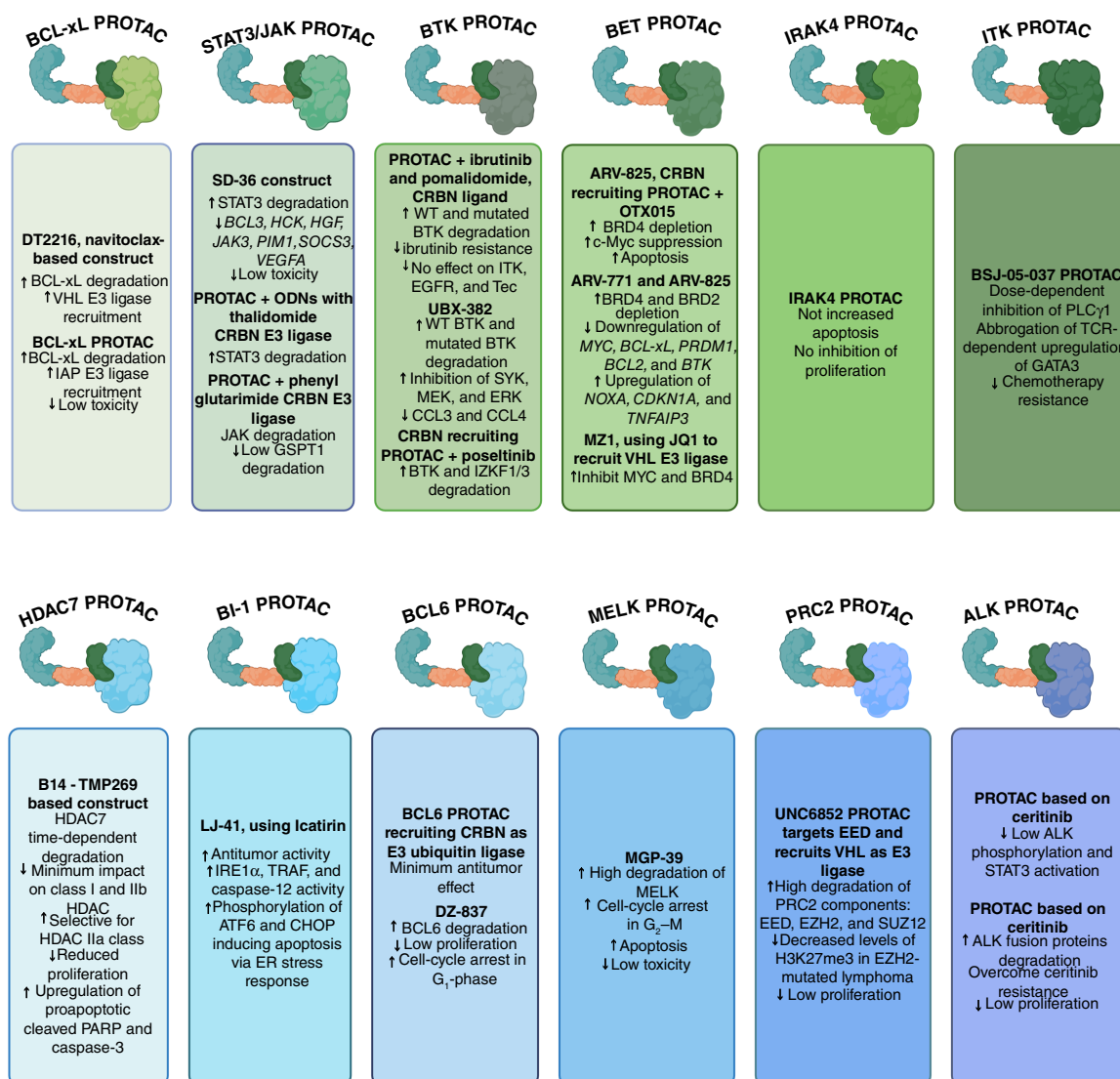


Figure 2.

Downstream effect of PROTACs in lymphoma. PROTACs specific to BCL-xL, STAT3/JAK, BTK, BET, IRAK4, ITK, HDAC7, BI-1, BCL6, MELK, PRC2, and ALK. Different PROTACs designed for targeting specific proteins in lymphoma, aiming to reduce proliferation, induce cell-cycle arrest, reduce resistance to therapy, and induce programmed cell death. PROTACs could modulate gene expression and histone acetylation for favorable outcomes and antitumor effects. The cumulative effect of PROTACs leads to target degradation via the Ub-proteasome machinery with high specificity and low off-target effects. ODN, oligodeoxynucleotides. [Created in BioRender. Moldovan, R. (2025) <https://BioRender.com/ywwcwu3>].

PROTACs targeting JAK/STAT

The JAK/STAT signaling pathway is one of the most important pathways involved in cell function, encompassing numerous signaling molecules such as growth factors and cytokines (51). The JAK/STAT pathway has a variety of roles in immune function, hematopoiesis, inflammation, and apoptosis (52). JAK represents a family of non-RTKs, having a total of four members: JAK1, JAK2, JAK3, and TYK2. They are associated with cytokine or growth factor receptors via specific motifs, and upon the binding of the signal molecule and receptor activation, JAK proteins phosphorylate specific tyrosine residues on the intracellular side of the receptor, which then act as binding sites for the STAT proteins (52). The STAT protein family represents a group of transcription factors

sharing a similar structure. The members of the STAT family are STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. After STAT phosphorylation by JAK kinases, they dimerize and translocate to the nucleus in which they induce the transcription of various genes. STAT3 is involved in cell survival, proliferation, differentiation, and angiogenesis. In normal cells, its activity is tightly regulated by different suppressors and protein phosphatases. In contrast, STAT3 can become hyperactivated in cancers, leading to tumor formation, metastasis, and drug resistance (53). The role of the JAK/STAT pathway in hematologic malignancies, including lymphoma, was shown by a series of studies. The JAK/STAT pathway has increased activity in T-cell lymphoma, with frequent mutations in JAK1, JAK2, JAK3, STAT3, and STAT5b (54). The

JAK/STAT pathway was found to regulate the expression of CD38 on myeloma cells in the bone marrow microenvironment (55). JAK inhibitors are classified into reversible and irreversible inhibitors. Reversible inhibitors bind to JAK via hydrogen bonds and hydrophobic interactions. This category includes ATP-competitive inhibitors such as filgotinib and fedratinib, which are type I inhibitors, and NVP-BBT594 and NVP-CHZ868, which are type II. Type I inhibitors bind to the active conformation of JAK, whereas type II inhibitors bind to the inactive conformation. These molecules bind to the ATP binding site of JAK proteins, blocking the binding of ATP. Another category of JAK reversible inhibitors are allosteric inhibitors, which bind to different sites than the ATP binding pocket. Examples include deucravacitinib and LS104. Irreversible JAK inhibitors, represented by ritlecitinib, form a covalent bond to the C909 residue in JAK3 (56). With respect to JAK inhibitor resistance, it was found that cells harboring JAK2 mutations p.Y931C, p.L983F, or p.G993A become resistant to multiple type I JAK inhibitors (57). Numerous STAT inhibitors have been developed for cancer treatment with various structures and mechanisms of action. Stattic was the first SMI of STAT3 to be discovered. It blocked STAT3 dimerization and could bind to STAT3 with high selectivity in comparison with other STAT molecules. Decoy oligonucleotides are a form of nucleotide-based inhibitor of STAT. They consist of transfecting synthetically derived cis-elements into cells. These sequences bind to the DNA binding domain of STAT, preventing its interaction with the DNA response element and reducing STAT-induced gene expression. An extensive list of STAT inhibitors can be found elsewhere (58).

SD-36 is a PROTAC molecule specifically targeting STAT3. This construct potentially induced the degradation of STAT3 in human leukemia and lymphoma cell lines, as well as in murine ones. Additionally, transcriptome analyses revealed that SD-36 treatment induced downregulation of STAT3 target genes such as *BCL3*, *HCK*, *HGF*, *JAK3*, *PIM1*, *SOCS3*, and *VEGFA*. It was also demonstrated that the compound exhibited a high specificity for STAT3, demonstrating more than 100-fold selectivity for the degradation of STAT3 over other STAT proteins. Besides its *in vitro* efficiency, SD-36 was able to deplete STAT3 levels *in vivo*, leading to long-lasting tumor regression in murine models while also exhibiting low toxicity (59, 60). Another study focused on developing a STAT3-degrading PROTAC by conjugating decoy oligodeoxynucleotides with thalidomide, a CRBN E3 ligase ligand, highlighting the induced STAT3 degradation in B-cell lymphoma cell lines while also inhibiting the growth of human B-cell xenotransplants in mice (61). In another study, it was found that a JAK-targeting PROTAC using phenyl glutarimide as a CRBN-recruiting ligand managed to efficiently reduce the levels of JAK2 and JAK3 in B-cell lymphoma cell lines, displaying cytotoxic effects. Moreover, it was found that the compound had a high selective degradation of JAK2 and JAK3, minimizing the degradation of GSPT1, a common off-target neosubstrate of IMiD-based PROTACs (62).

PROTACs targeting BTK

BTK is a protein from the Tec family of kinases, primarily found in B cells. The protein can be activated by a series of surface receptors such as B-cell, Toll-like, chemokine, and Fc receptors (63). Upon activation, BTK binds to PIP3 and is then phosphorylated by SYK. BTK then undergoes autophosphorylation in the SH3 domain, leading to the release of secondary messengers like IP3 and DAG, which induce the activation of NFAT and NF- κ B transcription

factors. Moreover, BTK activation can lead to the activation of the Akt pathway. Therefore, BTK is involved in processes such as B-cell development, differentiation, activation, maturation, and migration (64). Due to its crucial role in B-cell development, BTK is involved in many B-cell malignancies, including chronic lymphocytic leukemia, MCL, and MZL, which has led to the development of BTK inhibitors for the management of these diseases (65). BTK inhibitors can be further classified as covalent or noncovalent. Covalent inhibitors irreversibly bind with the C481 residue in the ATP binding pocket of BTK. Important examples are ibrutinib, acalabrutinib, zanubrutinib, and tirabrutinib. Ibrutinib was the first BTK inhibitor approved by the FDA for the treatment of lymphomas such as MCL, MZL, and Waldenström's macroglobulinemia. The efficacy of ibrutinib against DLBCL was shown in clinical studies. When added to standard R-CHOP treatment, ibrutinib improved patient outcomes and overall survival rates; however, it led to serious side effects in more than 50% of patients. Noncovalent BTK inhibitors function without binding to C481, which implies potential for activity blockade of both wild-type (WT) and mutated forms of BTK. Important examples are pirtobrutinib, nemtabrutinib, and vecabrutinib (66). The most common mutation accounting for ibrutinib resistance is C481S (substitution of a cytosine with serine at position 481), which blocks the binding of ibrutinib and other second-generation BTK inhibitors while maintaining BTK function (65). Moreover, mutations outside of BTK have been found to be responsible for acquired BTK resistance. The S707Y, R665W, and L845F mutations in *PLCY2* could allow B-cell receptor-mediated activation that is independent of BTK (67).

A BTK-targeting PROTAC, created by conjugating ibrutinib and pomalidomide, a CRBN ligand, was previously developed. The construct could potentially degrade BTK in a human diffuse B-cell lymphoma cell line, culminating in cytotoxicity. This chimeric molecule could overcome ibrutinib resistance due to its ability to degrade the C481S mutant BTK. It further had increased selectivity for BTK, with almost no effect on ITK, EGFR, or other Tec family kinases, which are known off-targets of ibrutinib (68). The ability of a BTK-binding PROTAC to effectively overcome drug resistance in BTK mutant lymphoma could subsequently be demonstrated. Here, UBX-382 could strongly degrade WT BTK in various B-cell lymphoma cell lines, as well as mutated versions such as E41K, T474I, C481S, C481R, C481T, C481Y, C481F, and L528W *in vitro* and *in vivo*. UBX-382 had a more potent effect than ibrutinib and ARQ-531, presenting high cytotoxicity in lymphoma cell lines and leading to complete tumor regression *in vivo*. Additionally, UBX-382 inhibited SYK, MEK, and ERK and decreased the production of CCL3 and CCL4 (69, 70). A CRBN-recruiting reversible covalent PROTAC used poseltinib as the targeting ligand. Besides being a potent BTK degrader, the molecule also managed to target and degrade IZKF1/3, leading to decreased cell growth in different B-cell lymphoma cell lines (71). Therefore, BTK-degrading PROTACs seem to be a highly efficient way of managing BTK-driven hematologic malignancies, especially due to their ability to overcome acquired BTK inhibitor resistance, as shown in other similar studies (72, 73).

PROTACs targeting BET

The bromodomains are amino acid sequences that recognize and bind acetylated lysine residues in a series of proteins such as histones. Proteins from the BET family can also interact with transcription factors and transcription elongation complexes in a lysine acetylation-dependent or lysine acetylation-independent

manner (73). The BET family consists of four distinct subtypes: bromodomain-containing protein 2 (BRD2), BRD3, BRD4, and BRDT, a testis-specific form. The roles of BETs are multiple. First, proteins containing BET domains act as epigenetic regulators, being found in helicases, transcriptional coactivators, methyltransferases, and nuclear scaffolding proteins. In addition, BRD4 has been found to regulate the expression of the MYC proto-oncogene. Common signaling pathways associated with BETs are the NF- κ B, PI3K/AKT, and JAK/STAT pathways (74). MYC has been found to be associated with different types of lymphomas, being involved in lymphomagenesis. MYC plays an important role in hematologic malignancies such as large B-cell lymphoma or DLBCL and is involved in the pathogenesis of multiple myeloma (75, 76). Additionally, epigenetic dysregulations have been found to play an important role in T-cell as well as B-cell lymphomas (77, 78). Therefore, the influence of BET proteins on MYC and epigenetic regulators, as well as different signaling pathways, has led to the development of a series of BET inhibitors for cancer management. JQ1 is an inhibitor of BET proteins, its main target being BRD4. JQ1 acts by competitively binding to the acetyllysine-binding bromodomains of BRD4, inhibiting further protein-protein interactions (79). JQ1 is a potent BET inhibitor, and its efficacy against lymphoma has been shown in a series of studies. JQ1 treatment led to senescence and apoptosis in cutaneous T-cell lymphoma cell lines, as well as a downregulation of c-Myc, CD30, and CCR4 expression (80). Moreover, JQ1 was able to induce p53-independent apoptosis in an aggressive BCL cell line by upregulating proapoptotic proteins and downregulating antiapoptotic BCL2 family members (81). OTX015 is another BET inhibitor with better oral bioavailability than JQ1. The compound can inhibit BRD2, BRD3, and BRD4 and exhibit good antitumoral activity in B-cell lymphoma. Multiple ways of achieving BET inhibitor resistance have been reported. In AML, the response to BET inhibitor therapy was found to be reduced by compensatory MYC upregulation via the WNT pathway. In colorectal cancer, IL6/8-Janus kinase 2 signaling promotes BRD4 phosphorylation, decreasing the binding affinity of BET inhibitors (82).

ARV-825 is a CRBN-recruiting PROTAC that uses OTX015 as the targeting ligand. ARV-825 treatment led to almost complete BRD4 depletion and increased c-Myc suppression compared with cells treated with JQ1 or OTX015. ARV-825 further induced a more pronounced inhibition of proliferation and apoptosis in different B-cell lymphoma cell lines compared with regular BET inhibitors such as JQ1 and OTX015 (83). Similar results were obtained elsewhere (84). BRD4-targeting PROTACs, ARV-771 and ARV-825, were also tested in the context of MCL. These PROTAC constructs could efficiently deplete BRD4 and BRD2 levels and induce apoptosis in different MCL cell lines *in vitro* while also improving the median overall survival of NSG mice with MCL xenografts. Moreover, ARV-771 and ARV-825 were more efficient at depleting BRD4 than conventional BETi like JQ1 or OTX015, which induced incomplete inhibition and led to the accumulation of BRD4. The BET-PROTAC treatment also downregulated the expression of certain genes, including MYC, BCL-xL, PRDM1, BCL2, and BTK, whereas NOXA, CDKN1A, and TNFAIP3 were upregulated (85). In another study, the efficiency of ARV-771 was probed in a PDX model of Richter-transformed (RT) DLBCL. ARV-771 treatment led to the depletion of BRD4 and BRD2 and reduced cell viability. Cotreatment of ARV-771 and the BCL-xL inhibitor, venetoclax, acted synergistically, leading to increased lethality in RT-DLBCL

cells. Combined treatment had beneficial effects *in vivo* as well, leading to prolonged survival and tumor reduction in NSG mice engrafted with DLBCL cells (86). MZ1 is another BET PROTAC that uses JQ1 as the targeting warhead and recruits VHL as the E3 Ub ligase. The molecule was found to be more effective at inhibiting MYC and BRD4 than the BET inhibitor birabresib, leading to increased cytotoxic effects in a series of DLBCL cell lines. Besides its *in vitro* effects, MZ1 exhibited *in vivo* efficacy as well, inhibiting tumor growth in mice (87).

PROTACs targeting IRAK4

IRAK4 is a member of the IL1 receptor-associated kinases (IRAK) protein family, which is involved in the signal transduction of Toll-IL1 receptor (TIR) family members. TIRs are involved in immunity, having a large series of functions such as pathogen or proinflammatory cytokine recognition and the transition between innate and adaptive immunity. IRAK proteins are recruited by TIRs via MyD88, leading to their activation and rapid phosphorylation. IRAK then leaves the receptor complex and interacts with TRAF6. The IRAK/TRAF6 complex is involved in the formation of the signalosome complex, which activates different downstream signaling pathways such as IKKs, p38, and JNKs, activating NF- κ B and AP-1 transcription factors (88). MyD88-IRAK tonic signaling caused by MYD88 activating mutations is found in many cases of lymphomas, including Waldenström macroglobulinemia and DLBCL, as well as other B-cell malignancies. The implications of IRAK1/4 in lymphoma pathogenesis led to the development of a series of inhibitors that target these kinases at clinical and pre-clinical levels. In a clinical study in patients with NHL, CA-4948 had a favorable safety profile and reduced tumor burden in 20% of patients. In another study, the same compound reduced bone marrow blasts in 10 of 12 patients. Other IRAK4 degraders studied in the context of lymphoma are BAY1830839 and KT-474 (89).

An IRAK4 degrader induced a potent reduction of IRAK4 and an inhibition of p-IRAK4, p-IKK α/β , and p-NF- κ B in a DLBCL cell line, compared with a regular IRAK4 inhibitor. Moreover, the compound could reduce the proliferation of the lymphoma cell line compared with the IRAK4 inhibitor. The IRAK4 degrader removed the kinase and scaffolding functions of the protein, leading to a complete inhibition of NF- κ B signaling, halting the proliferation of cells (90). On the other hand, an IRAK4 PROTAC did not lead to increased apoptosis or inhibition of proliferation compared with IRAK4 inhibition, suggesting that IRAK4 has a redundant role in DLBCL survival (91).

PROTACs targeting ITK

ITK is a protein involved in T-cell receptor signaling. Upon TCR activation, ITK is recruited to the TCR in which it interacts with LAT and SLP76, which then activates PLC γ 1, leading to increases in intracellular calcium levels and activation of ERK, JNK, NFAT, and AP-1. ITK also forms a complex with LAT, SLP76, Vav, Rac, and Cdc-42, which induces actin polymerization and cell migration (92, 93). ITK has been associated with T-cell lymphoma, especially through a translocation that leads to the formation of the ITK-SYK fusion protein (94).

BSJ-05-037 is an ITK PROTAC, which could effectively target and degrade ITK in T-cell lymphoma cell lines. In addition, the PROTAC led to a dose-dependent inhibition of PLC γ 1 and abrogated the TCR-dependent upregulation of GATA3, which induces chemotherapy resistance. Therefore, the administration of BSJ-05-037

could alleviate chemotherapy resistance *in vitro*, with similar effects observed *in vivo* as well (95). Several ITK inhibitors have been developed in recent years, which were extensively reviewed elsewhere (96, 97).

PROTACs targeting HDAC7

HDAC7 is an HDAC enzyme from the HDAC family. It can deacetylate histones or nonhistones and regulates a series of functions through its deacetylating activity, such as immunity, angiogenesis, embryonic development, and energy metabolism. HDAC7 also regulates signaling pathways, causing the deacetylation of STAT3 and β -catenin. Upon deacetylation by HDAC7, the phosphorylation of β -catenin is inhibited, and it accumulates in the nucleus, in which it binds to TCF/LEF, inducing the expression of certain genes. HDAC7 can induce PI3K/AKT activation by upregulating PI3K and AKT and downregulating PTEN. HDAC7 further plays a role in inhibiting the JAK/STAT pathway. HDAC7 inhibits the phosphorylation of STAT3 by deacetylation and downregulates the expression of JAK1 (98). HDAC7 is involved in the pathology of different types of lymphomas, with its overexpression being associated with DLBCL (99). Examples of HDAC inhibitors approved by the FDA for the treatment of lymphoma are vorinostat and romidepsin. Despite their efficacy in hematologic malignancies, these inhibitors lack antitumoral activity in solid tumors and have been associated with cardiotoxicity (100).

HDAC7-degrading PROTAC based on the HDAC class IIa inhibitor TMP269 recruited CRBN as the E3 ligase, named B14. This compound induced HDAC7 degradation in a time- and concentration-dependent manner in DLBCL and AML cell lines. The compound exhibited increased selectivity for class IIa HDACs, having minimal impact on class I HDACs like HDAC1, HDAC2, or HDAC3 and on class IIb HDACs like HDAC6 and HDAC10. It also had limited influence on the degradation of neosubstrates such as SALL4, IKZF1/3, and GSPT1. Treatment with compound B14 reduced proliferation and induced apoptosis in both DLBCL and AML cell lines by upregulating the proapoptotic cleaved PARP and cleaved Cas3. In addition, the compound induced cell-cycle arrest in the G₀-phase more efficiently than TMP269. B14 exhibited antitumoral effects *in vivo* as well, being able to degrade HDAC7 and reduce tumor growth in mice with xenografted DLBCL cells (101).

PROTACs targeting BI-1

BI-1 is a protein that suppresses apoptosis by inhibiting the translocation of proapoptotic Bax to the mitochondria. BI-1 is highly conserved among plants and animals, and it is mainly localized to the endoplasmic reticulum (ER) membranes. It was found that BI-1 inhibits apoptosis signaling linked to ER stress by blocking calcium release from the ER. Overexpression thereof protects cells from apoptosis induced by a series of ER stress agents. Additionally, BI-1 interferes with cell death signaling between the ER and mitochondria, reducing caspase processing and activation, Bax activation, depolarization of the mitochondrial membrane, and mitochondrial ultrastructural changes (102). Other studies revealed that BI-1 can enhance the sensitivity of cancer cells to Fas-induced cell death, especially in cells cultured in high glucose media, through a mechanism mediated by the inhibition of NHE activity (103). Icaritin is a compound of plant origin that possesses a large series of biological and pharmacologic activities, such as immunomodulation, improvement of hematopoietic function, and differentiation of cardiomyocytes. It also has significant

antitumoral activity, being able to inhibit various hematologic cancer cells, including lymphoma cells (104).

Interestingly, a PROTAC construct named LJ-41 used icaritin as the targeting warhead and recruited CRBN as the E3 ligase. The compound was tested on the Burkitt lymphoma cell line, and it exhibited great antitumoral activity. After further analyses, BI-1 was revealed as a direct target of LJ-41, and the compound induced apoptosis in Burkitt lymphoma cells by activating IRE1 α , TRAF, and caspase-12. Phosphorylated ATF6 and CHOP were also induced, which indicates that the apoptosis was induced via the ER stress response (105).

PROTACs targeting BCL6

BCL6 is a protein that acts as a multifunctional regulator and is involved in immune cell development. The main function of BCL6 is the transcriptional repression of its target genes by deacetylating and/or demethylating histones in their vicinity (106). In the humoral immune system, BCL6 contributes to the formation of germinal centers by suppressing the transcription of hundreds of genes, including *ATR*, *CHECK1*, *TP53*, *ARF*, *CDKN1A*, *CDKN1B*, *PTEN*, *IRF4*, and *PRDM1* (107). At the same time, BCL6 can also induce the transcription and expression of a series of genes involved in proliferation, immune avoidance, antiapoptosis, cell-cycle arrest, and cell differentiation (108). BCL6 is associated with various B-cell lymphomas, in which the protein is constitutively expressed due to different chromosomal translocations or the disruption of regulatory regions of the same BCL6 gene (109). Several BCL6 inhibitors were developed for the treatment of hematologic malignancies, including FX1, WK369, WK499, GSK137, WK500B, and RI-BPI, which were found to be effective preclinically against DLBCL cells (109).

A BCL6 PROTAC recruited CRBN as the E3 Ub ligase. Despite a high degree of BCL6 degradation, the compound did not manage to completely remove BCL6 from a series of DLBCL cell lines. Antitumoral effects were minimal, comparable with the effects of BCL6 inhibitors. A possible explanation for the lack of activity was the presence of small residual BCL6 populations, represented by chromatin-bound BCL6, in the cells treated with the BCL6 PROTAC. This led to the hypothesis that chromatin-bound BCL6 might be more difficult to target and degrade, and additional studies on the residual BCL6 population might provide useful information about the function of this protein in DLBCL (110). Contrary findings were found with the BCL6 degrader, DZ-837, being able to effectively degrade BCL6 and inhibit proliferation in different DLBCL cell lines *in vitro* and to inhibit tumor growth *in vivo*. This compound induced cell-cycle arrest in the G₁-phase and exhibited synergistic effects in combination with ibrutinib on various DLBCL cell lines (111). Similar results were obtained in another study, in which BI-3802, a BCL6 degrader, effectively reduced BCL6 levels in DLBCL cell lines. Moreover, the compound upregulated a series of BCL6 target genes such as *ATM*, *PRDM1*, *PTPN6*, *CD69*, *IRF4*, and *DUSP5*. The compound was able to induce slow-onset cell growth arrest in the tested cell lines, but it failed to induce apoptosis (112).

PROTACs targeting MELK

MELK, also known as MPK38, is a serine-threonine kinase involved in a series of cellular roles. MELK was found to regulate different signaling pathways, being involved in physiologic processes like cell proliferation, cell-cycle progression, metabolism, and apoptosis. MELK can directly activate ASK1, leading to increased ASK1-mediated signaling to JNK and p38, and it can also induce H₂

O₂-mediated apoptosis via increased ASK1 activity. Furthermore, MELK was found to stimulate TGFβ-mediated signaling. MELK phosphorylates different Smad proteins, a vital step for the stimulation of TGFβ-mediated apoptosis and cell-cycle arrest. MELK also regulates p53 by phosphorylation, this interaction leading to p53 nuclear translocation and cell-cycle arrest and apoptosis (113). The involvement of MELK in cancer is controversial, as numerous studies have had opposing findings. Overexpression of MELK is found in various types of cancer, correlating with high-grade tumors, increased aggressiveness, poor patient outcomes, and resistance to radiotherapy. Similarly, overexpression of MELK was associated with the upregulation of genes involved in cell-cycle progression, such as *CDK1*, *CCNB1/2*, *TOP2A*, *AURKB*, *PLK1*, and *BUB1*. In contrast, MELK-deficient cancer cells could still proliferate normally, leading to the hypothesis that its involvement in cancer progression might be minimal (114). In the context of hematologic malignancies, MELK was found to be associated with DLBCL and MCL, exhibiting upregulated expression and being correlated with increased tumor aggressiveness and poor survival. Treatment with MELK inhibitors reduces the viability of lymphoma cell lines and induces caspase-mediated apoptosis (115). Several MELK inhibitors have been developed for the treatment of different types of cancer, which were reviewed elsewhere (116). OTSSP167 is a MELK inhibitor that was found to possess antitumoral activity against two DLBCL cell lines, inducing apoptosis and cell-cycle arrest (117).

MGP-39, an MELK PROTAC, achieved a high grade of MELK degradation in a Burkitt lymphoma cell line. The compound induced G₂-M cell-cycle arrest and apoptosis. In addition, MGP-39 exhibited higher efficiency and lower toxicity than MELK inhibitors (118).

PROTACs targeting PRCs

The Polycomb group of proteins is a family of chromatin-modifying enzymes that act as repressors of genes involved in developmental regulation. These proteins are part of two classes of multiprotein complexes, divided into PRC1 and PRC2 (119). PRC2 consists of SUZ1, EED, EZH2, or EZH1, and the complex associates with histone-binding proteins like RBBP4 or RBBP7. PRC2 functions by catalyzing mono-, di-, and trimethylation on lysine 27 on histone H3 via the EZH1 or EZH2 methyltransferases (120). The PRC2-methylated lysine plays an important role in gene silencing, being involved in chromatin compaction and transcriptional repression (119). PRC2 mutations have been associated with hematologic diseases, with EZH2 mutations frequently occurring in lymphoma. These mutations lead to aberrant histone H3 methylation and altered epigenetic landscapes (121). The list of inhibitors targeting PRC2 component proteins in various types of cancer is vast and has been reviewed elsewhere (122). EL1 is an EZH2 inhibitor that could reduce the proliferation of DLBCL cells by reducing the levels of aberrantly methylated histone H3 (H3K27Me3). Besides targeting WT EZH2, the compound could also target mutated Y641F EZH2. Other examples of EZH2 inhibitors with efficacy in different lymphoma cell lines are GSK126, CPI-169, EH22-IN-3, EBI-2511, and UNC1999. All these compounds exhibited good antitumoral activity in different lymphoma cell lines *in vitro*, as well as in the context of *in vivo* models. A-395 is an EED inhibitor that could inhibit the activation of the PRC2 complex in two DLBCL cell lines. Astemizole is an FDA-approved drug that inhibits the interaction between EZH2 and EED, leading to an inhibition of the PRC2 complex. The compound had good antitumoral effects, reducing the viability of DLBCL cells (122).

Despite their antitumoral activity, the prolonged exposure of cancer cells to EZH2/PRC2 inhibitors ultimately leads to acquired resistance to these compounds. Mutations involved in this acquired resistance are Y111L and Y661D (123). Moreover, it was found that the activation of the IGF-1R, PI3K, and MAPK pathways could induce resistance to GSK126 in a DLBCL cell line (124).

UNC6852 is a PRC2 PROTAC that targets EED and recruits VHL as the E3 ligase and was able to effectively induce degradation of PRC2 components like EED, EZH2, and SUZ12 in a DLBCL cell line. The compound managed to decrease the levels of the H3K27me3 in the EZH2-mutated DLBCL cells, and it led to reduced cell proliferation and increased cytotoxic effects (125). EZH2 degraders displayed high levels of EZH2, EED, and SUZ12 degradation and led to a decrease in H3K27me3 in a series of lymphoma cell lines. Moreover, degraders had antitumoral activity that was more potent than EZH2 inhibitors, reducing cell viability and inducing cell-cycle arrest and apoptosis. Anticancer effects also translated to *in vivo* settings, with EZH2 degraders having the ability to reduce tumor growth in murine models and to reduce the growth of cells from patients with primary lymphoma (126). Similar results were obtained in other studies, further highlighting the potential of targeting PRC2 using PROTAC technology (127, 128).

PROTACs targeting anaplastic lymphoma kinase

Anaplastic lymphoma kinase (ALK) is a RTK that was first discovered in ALCL cell lines, in which it formed fusion proteins. ALK activation can lead to the activation of different signaling pathways, such as RAS/MAPK, JAK/STAT, PI3K/Akt, and the PLC pathway (129). ALK fusions are frequently present in hematologic malignancies, including ALCL and DLBCL. ALCL is associated with NPM-ALK, TPM3-ALK, TGF-ALK, ATIC-ALK, and CLTC1-ALK fusions, whereas DLBCL is more commonly characterized by the presence of CLTC-ALK and rare SEC31A-ALK and SQSTM1-ALK rearrangements (130). Crizotinib is a small-molecule oral tyrosine kinase inhibitor that represented the first generation of ALK inhibitors to be approved by the FDA. The compound demonstrated increased efficacy in comparison with standard chemotherapy, leading to improved survival rates in a series of clinical studies. Ceritinib represents a next generation of ALK inhibitors that is 20 times more potent than crizotinib. The compound is characterized by increased efficiency, leading to increased survival in patients with crizotinib resistance (131). Despite its efficiency, most patients usually develop resistance to these inhibitors. Studies found that crizotinib resistance commonly develops within 1 to 2 years of treatment, the most common mutations being L1196M and G1269A in the tyrosine kinase domain of ALK. In addition, acquired ceritinib resistance is commonly caused by the mutations G1202R and F1174C/L (132).

An ALK PROTAC construct based on ceritinib as the targeting ligand potently degraded ALK and ALK fusion proteins in a DLBCL lymphoma cell line. The compound inhibited ALK autophosphorylation and downstream STAT3 activation. In addition, the compound reduced proliferation and viability of DLBCL cells *in vitro* while also exhibiting good bioavailability *in vivo* (133). Comparable results were obtained in other similar studies (134). Furthermore, an ALK PROTAC based on ceritinib could degrade ALK fusion proteins and have antiproliferative activity in a T-cell lymphoma cell line. The compound had the potential to overcome ceritinib resistance by exhibiting reduced antiproliferative activity in ceritinib resistant cells (135).

Myeloma

Multiple myeloma is a hematologic neoplasm consisting of clonal plasma cells with post-germinal lymphoid B-cell lineage (136). The primary characteristic of multiple myeloma is the accumulation of clonal, malignant plasma cells in the bone marrow. The underlying causes of multiple myeloma are unknown, but possible factors include radiation, exposure to industrial toxins, or viruses (137). In general, multiple myeloma evolves from monoclonal gammopathy of undetermined significance (MGUS), which represents an asymptomatic premalignant stage of clonal plasma cell proliferation and is present in more than 3% of the population above the age of 50. In other cases, multiple myeloma evolves from smoldering multiple myeloma, which is a more advanced, intermediate asymptomatic premalignant stage (138). Multiple myeloma debuts in the bone marrow and leads to bone marrow failure, lytic bone disease, renal failure, immunodeficiency, and early death. Multiple myeloma is characterized by recurrent primary chromosomal alterations that are present in up to 90% of patients at diagnosis. During its progression, the disease accumulates secondary chromosomal alterations that lead to tumor progression. Primary chromosomal alterations are present from the MGUS stage and establish the dominant clone of the neoplasm. These alterations consist of numerical alterations, such as hyperdiploidy and hypodiploidy, and structural alterations. Hyperdiploidy is present in 50% to 60% of patients at diagnosis, and it leads to trisomies in odd-numbered chromosomes, usually 3, 5, 7, 9, 11, 15, 19, and 21, and a karyotype of 48 to 75 chromosomes. Hypodiploidy is characterized by a karyotype of less than 44 chromosomes. This abnormality is far less common than hyperdiploidy but is associated with reduced overall survival. The most common structural aberrations present in multiple myeloma are chromosomal translocations involving the IGH locus, which are present in up to 50% of patients with multiple myeloma. These translocations occur in mature B cells during class switch recombination in the germinal center but can also arise via other molecular mechanisms. The most common fusion proteins resulting from chromosomal translocations are the following: IGH::CCND1, IGH::FGFR3/MMSET, IGH::MAF, IGH::CCND3, and IGH::MAFB (139). Besides chromosomal aberrations, multiple myeloma is characterized by altered signaling pathways, leading to cell proliferation, migration, survival, and drug resistance. Important signaling pathways that are involved in multiple myeloma pathogenesis are the PI3K/AKT/mTOR, RAS/MAPK, JAK/STAT, Wnt/ β -catenin, and NF- κ B pathways. These pathways can become activated by different mutations or by stimulating factors from the bone marrow TME (140).

PROTACs in multiple myeloma

In multiple myeloma, PROTACs represent a novel therapeutic strategy, aiming to degrade oncogenic proteins that drive disease progression and confer drug resistance. Several PROTACs are being tested for their efficacy in multiple myeloma, showing potential selectivity compared with conventional therapies. A summary of PROTACs designed for multiple myeloma is depicted in **Fig. 3**.

PROTACs represent a novel therapeutic approach in multiple myeloma by inducing selective degradation of oncogenic proteins through the Ub-proteasome system, including targets that were unapproachable before by conventional therapy. Preclinical efficacy was demonstrated in multiple myeloma cell lines and animal models, notably by degrading the BRD4-like proteins, downregulating MYC, and promoting apoptosis. Furthermore, combining the PROTAC

(ARV825) with SMIs demonstrated synergistic activity, improving the apoptosis rate and mice survival (26).

The use of a combined therapy of PROTACs with proteasome inhibitors may not be feasible in all cases, as the two therapies have antagonistic effects, and PROTACs need the proteasome to function. However, PROTACs could be used to overcome resistance to proteasome inhibitors, like bortezomib, in patients with multiple myeloma. Resistance to bortezomib can be caused by modifications in the protein degradation pathway, mutations in the proteasome subunits, or upregulation of proteasome assembly. The results showed that the PROTAC designed to degrade the 20S subunit β 5 had superior outcomes compared with conventional therapies and exhibited antitumor properties, having the potential to overcome resistance to bortezomib in multiple myeloma-resistant cells (141).

The use of dual therapy, including IMiDs or chemotherapy with PROTACs, is a promising strategy for multiple myeloma. IMiDs such as lenalidomide and pomalidomide act via CRBN, which is an E3 ligase exploited by many PROTACs for substrate recruitment. Thus, PROTACs built on IMiD scaffolds can enhance neosubstrate selectivity and antimyeloma activity, with preclinical data suggesting that synergy may occur in these combinations (27). Chemotherapy could also contribute to PROTACs' efficacy, leveraging complementary mechanisms of cytotoxicity and protein degradation. Currently, no combination of chemotherapy and PROTACs is used in clinical practice, nor in preclinical setups, as the use of IMiDs or targeted therapies is a better and safer option (26, 142).

PROTACs targeting BCL-xL

DT2216, a BCL-xL PROTAC, was tested in the context of multiple hematologic and solid tumor cell lines, including multiple myeloma, and potently reduces the levels of BCL-xL in two multiple myeloma cell lines. The compound could reduce the viability of BCL-xL-dependent cell lines but showed limited effects on the multiple myeloma cell lines, which are dependent on BCL2 and myeloid cell leukemia 1 (MCL-1) for survival. However, the combined administration of an MCL-1 inhibitor and DT2216 exhibited synergistic effects, greatly reducing the cell viability of the multiple myeloma cells in comparison with individual compounds (143). Similarly, DT2216 degraded up to 80% of BCL-xL present in multiple myeloma cell lines. The compound induced apoptosis in venetoclax-resistant multiple myeloma cell lines that expressed high levels of BCL-xL while having minimal effects in cells expressing low levels of BCL-xL and high levels of BCL2 and/or MCL-1 (144).

PROTACs targeting BET

ARV-825 and ARV-763, BRD4 PROTACs, demonstrated that the PROTACs could induce BRD4 degradation, leading to reduced proliferation, cell-cycle arrest, and apoptosis in all multiple myeloma cell lines tested. PROTACs exhibited greater antitumoral effects than the BRD4 inhibitors JQ1 and OTX015. PROTAC treatment led to the downregulation of various genes, including *MYC*, *HNF4A*, *E2F*, *PLK1*, *CHEK1*, and cyclins B1 and E1, and it managed to suppress the Akt/mTOR signaling pathway. In addition, PROTACs could overcome drug resistance, possessing antitumoral activity in multiple myeloma cell lines resistant to various chemotherapeutic drugs like dexamethasone, doxorubicin, bortezomib, carfilzomib, lenalidomide, and pomalidomide (145). Similar results were obtained in other studies, further showcasing the potential of ARV-825 and ARV-763 in the treatment of multiple myeloma. In addition to antitumoral effects on immortalized multiple myeloma

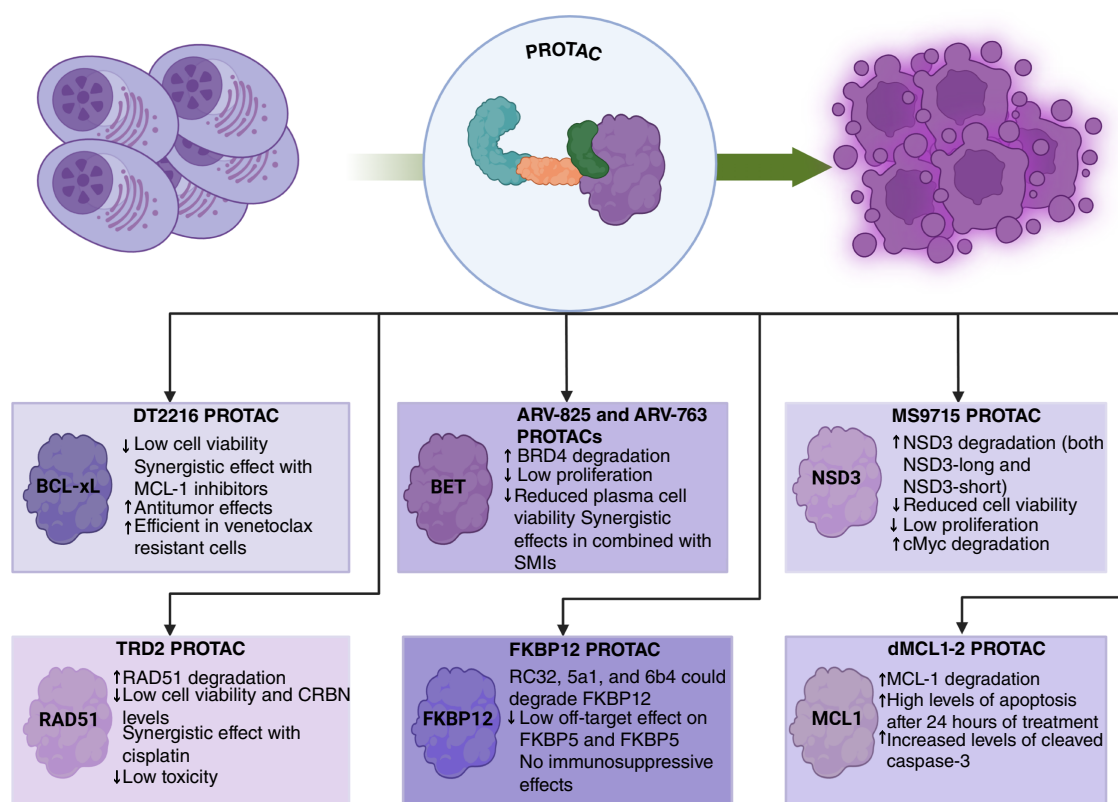


Figure 3.

PROTACs in multiple myeloma. PROTACs designed to target BCL-xL, BET, NSD3, RAD51, FKBP12, and MCL1. Different designs of PROTACs showed high selectivity for BCL-xL, BET, NSD3, RAD51, FKBP12, and MCL1. PROTACs induced high rates of degradation of their targets leading to a low proliferation rate of plasma cells, reduced viability, and displayed low toxicity. TRD2 PROTAC has a synergistic effect with platinum compounds, DT2216 has synergistic potential with MCL-1 inhibitors, and ARV-825/ARV-763 has a synergistic effect with SMIs. [Created in BioRender. Moldovan, R. (2025) <https://BioRender.com/pqp5wmm>].

cell lines, the studies found that the PROTACs could also reduce the viability of plasma cells derived from patients with multiple myeloma. These studies highlighted that the combined treatment of CRBN-recruiting ARV-825 and IMiDs like lenalidomide and pomalidomide presented antagonistic effects. In contrast, the administration of proteasome inhibitors such as bortezomib and carfilzomib inhibited the activity of both the CRBN- and VHL-recruiting PROTACs (26, 146). In addition, ARV-825 seems to act synergistically with different SMIs on various multiple myeloma cell lines. Such SMIs include cediranib, crenolanib, GSK 1904529A, motesanib, LY3023414, selinexor, gilteritinib, LY333531, IGC003, and ruxolitinib. Besides the observed *in vitro* effects, ARV-825 could inhibit multiple myeloma growth *in vivo*, improving the overall survival of SCID beige mice with multiple myeloma xenografts (26). ARV-825 was found to act synergistically with the CDK9 inhibitor AZD 4573 in different multiple myeloma cell lines, both *in vitro* and *in vivo*. The combination of the compounds (ARV-825 and AZD 4573) reduced the expression of BRD2, BRD4, MYC, and phosphorylated RNA polymerase II, inducing apoptosis and decreasing cell proliferation (142).

PROTACs targeting NSD3

The nuclear receptor-binding SET domain (NSD) family of proteins comprises histone lysine methyltransferases that are involved in regulating chromatin integrity and gene expression

by carrying out mono- or dimethylation reactions at lysine 36 in histone H3, generating H3K36me1 and H3K36me2. The three members of the NSD family are NSD1, NSD2, and NSD3 (147). NSD family members are multidomain proteins, the SET domain being involved in catalytic activity. Besides the SET domain, NSD proteins possess two PWWP (Pro-Trp-Trp-Pro) domains, which have been shown to bind methylated H3K36 to stabilize NSD2 and NSD1 at the level of chromatin. NSD3 exists in three different isoforms: NSD3-long, NSD3-short, and NSD3-WHIS-TLE. NSD3-short was found to interact with BRD4, a protein involved in oncogene expression. Besides histone methylation, NSD3 has been shown to methylate EGFR and p65, an NF- κ B subunit, leading to their activation (148). The NSD family was found to be associated with myeloma, which led to the development of SET domain inhibitors, like sinefungin, MCTP-39, BI-9321, and MS9715. KTX-1001, an NSD2 inhibitor, progressed into phase I clinical trials for the treatment of refractory multiple myeloma (149).

MS9715 is an NSD3-targeting PROTAC using BI-9321 as a targeting ligand that was shown to potently degrade NSD3 in hematologic cancer cells, including multiple myeloma cells. The compound managed to degrade both NSD3-long and NSD3-short in the multiple myeloma cell line. In contrast, BI-3921 and MS9715 (an analog incapable of binding VHL) did not reduce

NSD3 levels. MS9715 could reduce cell proliferation and cell viability in a multiple myeloma cell line, leading to increased apoptosis in comparison with controls. In addition, the compound induced c-Myc degradation, leading to a repressed expression of c-Myc-related gene sets (150).

PROTACs targeting RAD51

RAD51 is a recombinase that is vital to the homologous recombination mechanism for repairing double-strand breaks (DSB) in DNA. RAD51 is involved in three DSB repair pathways: gene conversion, synthesis-dependent strand annealing, and RAD51-dependent break-induced replication, all sharing initial steps. First, the MRE11-RAD50-NBS1 complex with CtIP recognizes and binds DSBs, enabling short- and long-range resection, which exposes 3' single-stranded DNA (ssDNA) overhangs. The ssDNA is then coated by replication protein A (RPA) to prevent the formation of ssDNA secondary structures and degradation. Then, RAD51 displaces RPA, assembling nucleoprotein filaments with the three ssDNA ends. The assembly of these filaments is stimulated by a series of RAD51 mediators, including the RAD51 loader, BRCA2, and RAD51 paralogs (RAD51B, RAD51C, RAD51D, XRCC2, XRCC3, and SWSAP1; ref. 151). In contrast to its roles in protecting DNA stability, the overexpression of RAD51 was found to be associated with many solid and hematologic tumors. The overexpression of RAD51 can lead to improper hyper-recombination, leading to genomic instability. RAD51 was found to be associated with drug resistance in leukemia, epithelial-to-mesenchymal transition-associated drug resistance, drug resistance of cancer stem cells, and hypoxia chemoresistance in cancer cells (152). It was found that homologous recombination mediated by RAD51 is highly elevated in multiple myeloma, and this process leads to the acquisition of genetic alterations in multiple myeloma cells (153). Therefore, the targeted degradation of RAD51 might be an efficient way of dealing with multiple myeloma.

TRD2, a RAD51 PROTAC, was tested in the context of IMiD-resistant multiple myeloma. The compound had the ability to degrade RAD51 via proteasomal degradation in IMiD-sensitive and IMiD-resistant multiple myeloma cells, reducing cell viability. While exhibiting antiproliferative effects in both the sensitive and resistant multiple myeloma cells, IMiD-resistant cells required a higher concentration of TRD2 for reduction in cell viability due to decreased levels of CRBN. Combined treatment of TRD2 and the chemotherapeutic drug cisplatin was found to act in a synergistic manner, leading to reduced cell viability in the sensitive and resistant multiple myeloma cells compared with the individual compounds. Moreover, the combination of TRD2 and cisplatin was tested *in vivo* by using BALB/c nude mice xenografted with lenalidomide-resistant multiple myeloma cells. The results revealed that the combination of TRD2 and cisplatin led to decreased tumor growth *in vivo* compared with the individual compounds, while exhibiting reduced toxicity (154).

PROTACs targeting FKBP12

FKBP12 represents an immunophilin that acts as the cytoplasmic receptor for FK506 and rapamycin, mediating the immunosuppressive functions of these drugs. FKBP12 was found to catalyze cis-trans isomerization of the proline amide in a tetrapeptide substrate, being involved in immunomodulatory processes. Binding of FK506 or rapamycin inhibits this function, leading to immunosuppressive effects. FK506/FKBP12 inhibits transcriptional activation of IL2, preventing antigen receptor-induced activation of T lymphocytes. This complex

interacts with calcineurin, inhibiting its activity and preventing activation of NFAT, leading to inhibited IL2 transcription. FKBP12 was found to be an important regulator of the TGF β family type I receptors, being able to inhibit BMP-mediated signaling (155). Upon BPN binding, receptors become active and phosphorylate SMAD1, SMAD5, and SMAD8, rendering them active and increasing their association with SMAD4 (156). With respect to multiple myeloma, it was found that BMP-induced signaling can induce apoptosis via activation of SMAD1/5/8, causing downregulation of c-Myc and BCL-xL. Therefore, targeting FKBP12 could potentiate the activation of SMAD1/5/8, leading to increased apoptosis in multiple myeloma cells (157).

Different FKBP12 PROTACs were tested in the context of multiple myeloma. The compounds (RC32, 5a1, and 6b4) could potentially degrade FKBP12 levels in multiple myeloma cells *in vitro*, with the most efficient being 5a1. 5a1 had increased specificity, with minimal degradation effects on other FKBP proteins like FKBP4 and FKBP5. The combination of 5a1 and BMP6 could significantly increase apoptosis via SMAD1/5 activation in multiple myeloma cells compared with BMP6 alone, highlighting that FKBP12 degradation potentiates BMP-induced apoptosis in multiple myeloma. 5a1 caused no calcineurin and NFAT inhibition in a T-cell line, suggesting that FKBP12 PROTACs do not have the same immunosuppressive effects as the FKBP12 inhibitor, FK506 (158).

PROTACs targeting MCL-1

MCL-1 is an antiapoptotic protein from the BCL2 family of proteins. The protein was found to contain three putative BH domains and to inhibit apoptosis by binding and sequestering the proapoptotic Bak and Bax proteins, preventing the formation of pores in the mitochondrial membrane. MCL-1 can also bind and sequester a subset of the BH3-only proapoptotic BCL2 family members involved in the polymerization of Bak and Bax. MCL-1 was found to be required for the development and maintenance of T and B cells and neural development, while also being crucial for mouse embryogenesis. Expression of MCL-1 is growth factor-dependent; a series of trophic factors like ILs, EGF, and VEGF can induce its transcriptional upregulation (159). MCL-1 was found to have a pivotal role in multiple myeloma, being the main antiapoptotic BCL2 member that protects multiple myeloma cells against apoptosis and promotes their survival. In addition, it was observed that IL6 secreted by bone marrow stroma cells from the TME of multiple myeloma cells leads to the activation of JAK/STAT signaling, promoting MCL-1 expression (160).

The AMCL-1 PROTAC construct is based on the MCL-1 inhibitor A-1210477. The compound, named dMCL1-2, induced significant degradation of MCL-1 in a multiple myeloma cell line via proteasomal degradation. Moreover, the compound could induce apoptosis after 24 hours of treatment in multiple myeloma cells by increasing cleaved caspase-3 levels (161).

Conclusion

Recent advances in the development of PROTACs have positioned these therapeutic agents as a promising strategy for lymphoma and myeloma. As PROTACs leverage the Ub-proteasome system to degrade in a selective manner oncogenic proteins, including those that were considered “undruggable” or resistant to current therapy, multiple studies have evaluated the efficacy of PROTACs. Early data from current studies presented in this review highlight the potential benefits of using PROTACs as a therapeutic strategy in lymphoma and myeloma. PROTACs have shown the

ability to overcome drug resistance by degrading mutant or over-expressed proteins that drive the disease to a refractory state. PROTACs exhibit low toxicity and less side effects due to their high affinity for the targeted proteins. Additionally, the reusability of PROTACs could facilitate repeated cycles of therapy without the need for additional therapy, offering the prospect of low-dose therapy with high efficacy. Furthermore, several features of PROTACs can be exploited to synergistically enhance the efficacy of bispecific antibodies or CAR T cells in different malignancies, as they increase the abundance of tumor antigen-derived peptides presented to MHC class I molecules, enhance T-cell activation, and stimulate cytokine secretion, thereby enhancing the immune response. PROTACs deserve attention from the scientific community, as continued translational research on their efficacy, toxicity, and pharmacodynamics could lead to clinical trials that may highlight the full potential of PROTACs in lymphoma and myeloma.

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