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(REVIEW ARTICLE)

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Molecular erasers: Reprogramming cancer immunity through protein degradation

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Abstract

Antibody-based immunotherapies have transformed cancer treatment, but they face limitations due to pharmacokinetic challenges such as long half-lives, limited tumor penetration, the need for parenteral administration, and immunogenicity. Small molecules present a promising alternative, offering improved oral bioavailability, better tissue permeability, and the ability to target intracellular processes. A substantial advancement in this field is Targeted Protein Degradation (TPD), which utilizes the cell's natural degradation systems to eliminate disease-associated proteins, including those previously deemed "undruggable." This review highlights recent developments in TPD technologies, including proteolysis-targeting chimeras (PROTACs), molecular glues, CLIPTACs, PHOTACs, Folate-PROTACs, AUTACs, ATTECs, LYTACs, and CMA-based degraders. We also explore their applications in cancer immunotherapy, focusing on key regulators such as PD-1/PD-L1, chemokines, TGF-β, IDO1, AhR, and various epigenetic and kinase-associated pathways. Furthermore, we address current engineering challenges, including bioavailability, molecular weight, delivery strategies, and off-target effects and suggest future translational opportunities that integrate nanotechnology, computational modeling, and biomedical engineering to enhance the clinical application of TPD-based immunotherapies.

Keywords: Targeted Protein Degradation (TPD); Protacs; Cancer Immunotherapy; Tumor Microenvironment (TME); Nanotechnology-Based Delivery; Artificial Intelligence in Drug Discovery

1. Introduction

Cancer remains a major global health challenge, being a leading cause of death and illness [1]. In 2022, the World Health Organization (WHO) reported approximately 10 million cancer-related deaths and over 20 million new cases each year [2]. Despite advances in early detection and treatment, the burden is particularly high in low- and middle-income countries with limited resources [3]. Traditional treatments like chemotherapy and radiotherapy can be effective but often come with severe side effects and resistance issues [4]. Although molecularly targeted therapies are more precise, they frequently lack lasting effects due to tumor adaptations [5]. This highlights the urgent need for innovative treatment strategies that provide targeted, effective, and personalized outcomes.

Over the past decade, immunotherapy has changed the landscape of cancer treatment [6]. Unlike traditional treatments that kill cancer cells directly, immunotherapy boosts the body's immune system to identify and destroy these cells. Immune checkpoint inhibitors (ICIs), especially those targeting PD-1, PD-L1, and CTLA-4, have significantly improved patient outcomes in melanoma, lung cancer, renal cell carcinoma, and other cancers [7]. Drugs like nivolumab, pembrolizumab, and atezolizumab are now standard therapies [8]. However, immunotherapy has its limitations. Not all patients benefit, as many have either intrinsic or acquire resistance [9]. There are also immune-related adverse events (irAEs) from T cell activation, which complicate treatment [10]. The dependence on monoclonal antibodies presents

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challenges. Specifically, these antibodies have issues such as long half-lives that lead to prolonged toxicities, large sizes that limit tumor penetration, and the need for injections that affect patient compliance. They also may trigger immune responses that hinder their effectiveness and are mainly ineffective against intracellular oncogenic targets, leaving many potential treatment avenues unexplored. This has prompted interest in alternative therapeutic approaches that could provide better specificity and design flexibility.

Small molecules have emerged as effective alternatives to antibody therapies due to their low molecular weight, which allows for oral bioavailability, better tumor penetration, and the ability to cross cell membranes [11]. They pose a lower risk of immunogenicity and are cheaper to produce and transport, enhancing their accessibility in global healthcare [12]. Besides, small molecules can be engineered for short half-lives, enabling dynamic regulation of biological pathways and reducing prolonged toxicity. Their modular design facilitates high-throughput screening, computer-aided optimization, and integration with AI in drug discovery [13]. This makes small molecules valuable not only as complementary tools to immunotherapies but also as standalone therapeutic options. A notable advancement in small-molecule therapeutics is Targeted Protein Degradation (TPD). Unlike traditional small-molecule inhibitors that block enzyme activity or protein interactions, TPD completely eliminates disease-causing proteins. Techniques like proteolysis-targeting chimeras (PROTACs), molecular glues, and lysosomal-targeted degraders redirect targeted proteins to the ubiquitin–proteasome or autophagy–lysosome systems for degradation. This approach avoids the drawbacks of traditional inhibition, minimizes resistance, and expands the range of drug targets to include previously inaccessible proteins.

TPD technologies are developing a strong pipeline of candidates. PROTACs are in trials for prostate and breast cancers, while molecular glues, like thalidomide derivatives, target hematological cancers. Innovations such as PHOTACs and receptor-targeted modalities (e.g., Folate-PROTACs, LYTACs) demonstrate various strategies for enhanced precision and tumor targeting. The field is advancing with the integration of computational modeling, nanotechnology, and systems biology to improve therapeutic efficacy. This review provides a focused overview of targeted protein degradation technologies in cancer immunotherapy from engineering and biomedical sciences perspectives. Specifically, the article will

- Outline the mechanistic frameworks of major TPD platforms, including both ubiquitin–proteasome and lysosomal pathways.
- Highlight applications of TPD technologies in modulating immune checkpoints, chemokine receptors, TGF-β signaling, IDO1 metabolism, AhR pathways, and key epigenetic and kinase regulators.
- Analyze technological challenges such as bioavailability, off-target toxicity, immunogenic risks, and delivery barriers.
- Discuss engineering innovations, including nanotechnology-based carriers, rational degrader design, and AI-assisted optimization, as avenues to address these limitations.

This review highlights how TPD can transform immunotherapy by combining insights from molecular biology, biomedical engineering, and translational oncology. Merging small-molecule chemistry with protein degradation technologies offers a way to bypass the limitations of existing treatments and access a wider range of therapeutic targets. Targeted protein degradation is not just a minor improvement; it represents a significant shift toward precision cancer therapies driven by engineering.

2. Targeted Protein Degradation Technologies

Figure 1 compares five UPS-based TPD strategies: PROTAC, Molecular Glue, CLIPTAC, PHOTAC, and Folate-PROTAC. It highlights their distinct mechanisms for recruiting E3 ligases to promote ubiquitination and proteasomal degradation. Each panel details a stepwise degradation process, contrasting molecular complexity, targeting approaches, and activation methods (such as light for PHOTAC and receptor-mediated uptake for Folate-PROTAC). PROTACs and molecular glues use standard recruitment models, while CLIPTAC and PHOTAC provide more precise control, and Folate-PROTACs are designed for tumor-specific targeting. This figure illustrates the diversity in TPD technologies and their potential for enhanced specificity, controllability, and therapeutic effectiveness in cancer treatment.

2.1. Ubiquitin–Proteasome System (UPS) Based

The ubiquitin-proteasome system (UPS) is the primary intracellular pathway responsible for protein degradation and maintaining protein homeostasis. This pathway relies on a three-enzyme cascade, which includes E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases. In this process, ubiquitin molecules are sequentially attached to a substrate protein, which is then recognized and degraded by the 26S proteasome. TPD

approaches leverage this pathway by designing small molecules that bring E3 ligases in close proximity to target proteins, promoting their ubiquitination and subsequent degradation. PROTACs (proteolysis-targeting chimeras) are the most established UPS-based degraders. These bifunctional molecules consist of a ligand for the protein of interest, a ligand for an E3 ligase, and a linker connecting the two. This structure enables the formation of a ternary complex that facilitates proteasomal degradation. Clinical trials have seen encouraging candidates, such as ARV-110 (an androgen receptor degrader) and ARV-471 (an estrogen receptor degrader). However, the relatively large molecular weight of PROTACs presents challenges in terms of cell permeability and oral bioavailability, while systemic delivery raises concerns about non-selective targeting of normal tissues. An overview of the principal TPD technologies, their potential applications, and current challenges is summarized in Table 1.

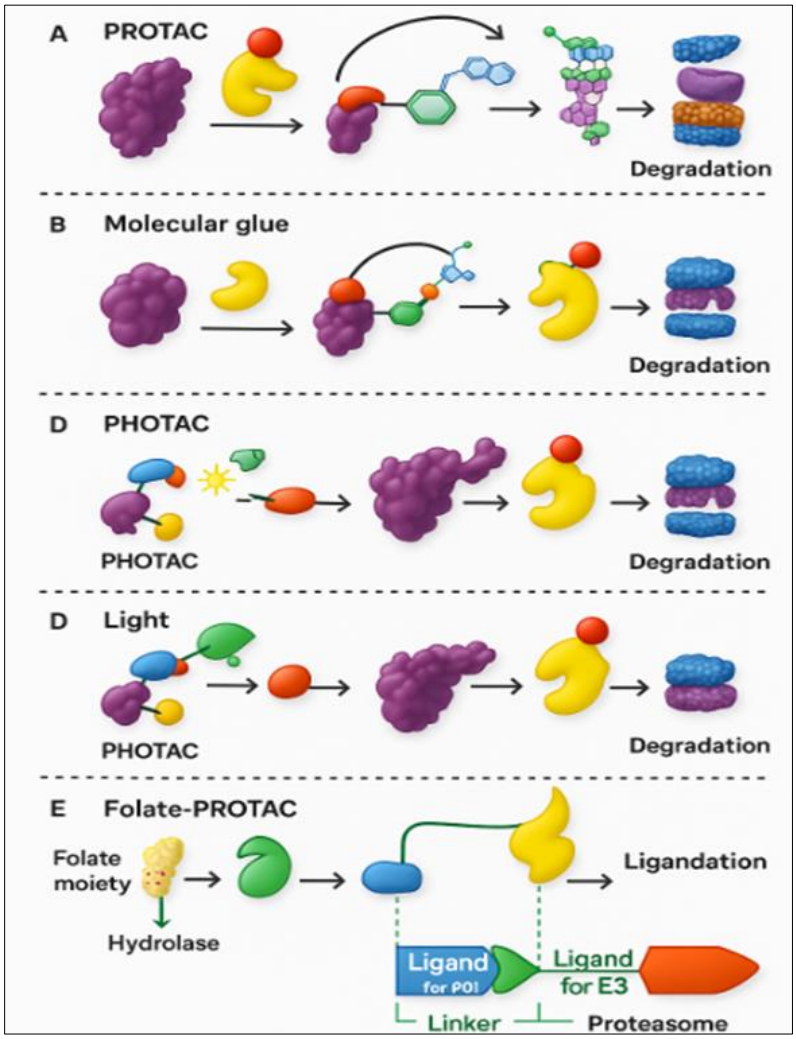

Figure 1 Mechanistic overview of UPS-based targeted protein degradation approaches: (A) PROTAC, (B) Molecular glue, (C) CLIPTAC, (D) PHOTAC, and (E) Folate-PROTAC

Molecular glues offer an alternative mechanism for protein degradation. Unlike PROTACs, these small monovalent compounds do not require a linker; instead, they stabilize the interaction between the protein of interest and an E3 ligase. Thalidomide derivatives serve as classical examples, as they reprogram the cereblon (CRBN) ligase to degrade transcription factors like IKZF1 and IKZF3 [14], [15], [16]. Molecular glues are generally smaller and more drug-like compared to PROTACs, providing better cell permeability and oral bioavailability. However, many of these compounds were discovered serendipitously, and the lack of rational design principles remains a significant barrier to their broader application. CLIPTACs (click-formed PROTACs) were developed to address the poor permeability of conventional PROTACs. This approach involves creating two cell-permeable precursors that undergo a bioorthogonal click chemistry reaction inside the cell, assembling into an active degrader. This strategy enhances intracellular uptake and confines the formation of the active PROTAC to target cells, potentially reducing systemic side effects. Despite these advantages, challenges persist in optimizing reaction efficiency and minimizing toxicity from by-products of the click chemistry reaction [17]. PHOTACs (photochemically targeted chimeras) incorporate light-sensitive switches into PROTAC

scaffolds. When exposed to specific wavelengths of light, these photoswitches can activate or deactivate degrader activity, allowing for precise control over protein degradation [18], [19], [20]. This targeted approach is especially promising for localized cancers, such as skin or ocular tumors. However, clinical translation is currently limited by the penetration depth of ultraviolet light and the potential for DNA damage. Future designs utilizing near-infrared responsive systems may help overcome these challenges.

Table 1 Mechanisms, therapeutic benefits, and limitations of major TPD platforms

TPD Platform	Mechanism of Action	Therapeutic Potential	Key Limitations
PROTAC	Dual ligands linked together to recruit an E3 ligase and a protein of interest	Strong activity in preclinical studies; several candidates under clinical evaluation	Poor solubility, limited penetration into cells, possible non-specific degradation
Molecular Glue	Small molecules that stabilize direct contact between target protein and E3 ligase	Better membrane permeability and oral availability; some agents already in clinical use	Mechanisms are often discovered by chance, limited knowledge of design principles
CLIPTAC	Two small precursors assemble via intracellular click chemistry to form PROTAC	Higher intracellular uptake; can reduce unintended off-target degradation	Requires optimization of reaction efficiency; potential toxicity of by-products
PHOTAC	Light-sensitive degrader activated by specific wavelengths	Allows highly localized and time-controlled protein degradation	Limited tissue penetration of UV light; possible genotoxic effects
Folate-PROTAC	Folate conjugation ensures uptake in tumor cells expressing folate receptor	Targeted accumulation in cancer cells; improved specificity	Large molecular weight; incomplete pharmacokinetic profiling
AUTAC	Exploits autophagy through K63-linked ubiquitination for selective degradation	Can remove proteins and damaged organelles (e.g., mitochondria); wide therapeutic spectrum	Mechanisms not fully understood; may interfere with normal autophagy processes
ATTEC	Links target protein directly with LC3, directing it to autophagosomes	Independence of ubiquitination; efficient in degrading selected disease proteins	Safety concerns due to direct manipulation of autophagy; still early in validation
LYTAC	Connects extracellular or membrane proteins to lysosomal trafficking receptors	Expands degradation to non-cytosolic proteins; offers unique immunotherapy opportunities	High molecular weight; delivery challenges; risk of immune reactions
CMA Degrader	Utilizes chaperone-mediated autophagy via Hsc70/LAMP2A recognition motifs	Enables targeted elimination of both soluble and membrane-associated proteins	Need for accurate motif identification; potential competition with natural substrates

Folate-PROTACs represent another innovative strategy aimed at enhancing cancer specificity. These molecules take advantage of the overexpression of the folate receptor alpha (FOLR1) in cancers, including ovarian, breast, and lung tumors. By conjugating folate to PROTAC molecules, selective uptake is achieved through receptor-mediated endocytosis. Once inside the tumor cell, the PROTAC component is released to trigger degradation. This receptor-targeted strategy holds promise for improving selectivity, but it faces challenges, including high molecular weight, limited pharmacokinetic data, and a lack of extensive in vivo validation.

2.2. Lysosomal System Based

The lysosomal system is crucial for degrading extracellular proteins, membrane receptors, and aggregated proteins that the UPS cannot access. It operates through endocytosis, phagocytosis, and autophagy. In cancer immunotherapy, lysosome-based degradation expands treatment options by targeting non-cytosolic proteins and affecting the tumor microenvironment. Various lysosome-directed degraders have been developed, each with unique mechanisms. AUTACs (Autophagy-targeting chimeras) induce K63-linked polyubiquitination, signaling for degradation via the autophagy

receptor p62/SQSTM1. Unlike UPS-dependent PROTACs, AUTACs utilize the autophagy-lysosome pathway and can degrade proteins as well as organelles like mitochondria through mitophagy. This versatility increases their potential uses, but their mechanisms are not yet fully understood, with most studies conducted in vitro.

ATTECs (Autophagosome-tethering compounds) bypass the need for ubiquitination by directly binding both the protein of interest and LC3, a key autophagy protein. This tethering ensures efficient delivery of the cargo to autophagosomes for lysosomal clearance. Initially developed for neurodegenerative diseases, ATTECs have also been applied to cancer-related proteins like NAMPT and EGFR [21], [22]. While they show promise, manipulating autophagy may risk disrupting essential cellular processes, and in vivo safety evaluations are still required. LYTACs (Lysosome-targeting chimeras) extend TPD to extracellular and membrane proteins that are inaccessible to PROTACs and AUTACs. LYTACs bind both a surface-exposed target protein and a lysosome-shuttling receptor, such as CI-M6PR or ASGPR. This binding induces receptor-mediated endocytosis and subsequent lysosomal degradation of the target protein [23], [24]. This approach is particularly valuable for degrading immunomodulatory proteins, such as PD-L1. Figure 2 illustrates the core mechanisms of lysosomal-based TPD strategies, including AUTAC, ATTEC, LYTAC, and CMA-based degraders.

Despite its potential, concerns remain regarding tissue-specific delivery, high molecular weight, and the possibility of immunogenicity caused by glycopeptide ligands. CMA-based degraders leverage chaperone-mediated autophagy (CMA), a process regulated by the chaperone Hsc70 and the lysosomal receptor LAMP2A. These degraders are designed with a ligand for the protein of interest and a CMA-targeting motif, allowing for selective delivery to lysosomes. Recent advancements include HSP90-conjugated degraders that effectively target oncogenic proteins in cancer models. Although CMA-based degraders offer high specificity, challenges include the need for precise identification of targeting motifs and the potential competition with endogenous substrates for the CMA machinery.

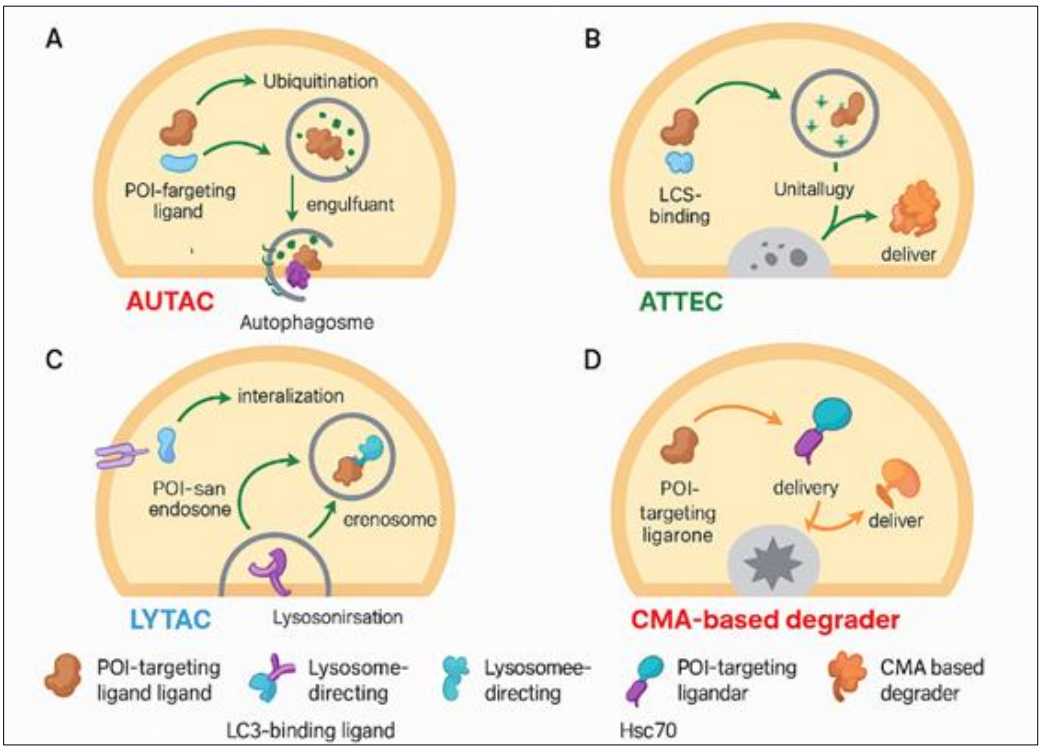

Figure 2 lysosomal-based targeted protein degradation mechanisms: (A) AUTAC, (B) ATTEC, (C) LYTAC, and (D) CMA-based degraders.

3. Applications of Small Molecule Degraders in Cancer Immunotherapy

Small-molecule degraders are emerging as effective tools in cancer immunotherapy. They can eliminate proteins that control immune checkpoints, metabolic pathways, transcription, and apoptosis. By promoting permanent protein removal rather than temporary inhibition, these degraders can reshape the tumor microenvironment, reactivate T-cells, and help overcome resistance to standard treatments. Their use can be categorized into four key areas, each targeting important challenges in immuno-oncology [25], [26]. Figure 3 illustrates the PD-1/PD-L1 interaction between T cells

and tumor cells, along with the chemical structures of representative small-molecule degraders targeting this immune checkpoint axis.

3.1. Targeting Immune Checkpoints (PD-1/PD-L1 and TGF-β)

The PD-1/PD-L1 axis is one of the most established therapeutic checkpoints in cancer immunotherapy. Tumors utilize PD-L1 expression to inhibit the function of cytotoxic T cells, which allows them to evade the immune system. Although antibody therapies like pembrolizumab have shown significant success, issues such as limited tissue penetration, resistance, and variable patient responses emphasize the need for alternative approaches. Small-molecule degraders can address these challenges by targeting and eliminating PD-L1 itself rather than merely blocking its interaction with PD-1. PROTACs and lysosome-directed molecules have proven effective in degrading PD-L1 in preclinical models, resulting in greater infiltration of CD8+ T cells and enhanced secretion of interferon-γ. Innovative strategies like integrin-facilitated lysosomal degradation (IFLD) further enhance specificity by utilizing integrin-mediated internalization, offering a new pathway for targeted checkpoint inhibition.

Table 2 Representative PROTAC molecules in clinical trials for cancer therapy

Compound	Main Target	Trial Stage	Cancer Indications	Clinical Trial ID(s)
ARV-471	Estrogen receptor (ER)	Phase III	Advanced or metastatic breast cancers	NCT05654623; NCT05909397
ARV-110	Androgen receptor (AR)	Phase II	Castration-resistant prostate cancer	NCT03888612
ARV-766	Androgen receptor (AR)	Phase I/II	Metastatic castration-resistant prostate cancer	NCT05067140
DT2216	Bcl-xL	Phase I/II	Childhood fibrolamellar carcinoma, recurrent fibrolamellar carcinoma	NCT06620302
CFT8634	BRD9	Phase I/II	Advanced or metastatic SMARCB1-deficient cancers	NCT05355753
CFT1946b	BRAF^V600X	Phase I/II	Solid tumors including melanoma	NCT05668585
CC-94676	Androgen receptor (AR)	Phase I	Castration-resistant prostate cancer	NCT04428788
HP518	Androgen receptor (AR)	Phase I	Castration-resistant prostate cancer	NCT05252364
FHD-609b	BRD9	Phase I	Synovial sarcoma, SMARCB1-loss tumors	NCT04965753
NX-2127	BTK/IKZF3	Phase I	Chronic lymphocytic leukemia, small lymphocytic lymphoma	NCT04830137
NX-5948	BTK	Phase I	Chronic lymphocytic leukemia, small lymphocytic lymphoma	NCT05131022
BGB-16673	BTK	Phase I	B-cell malignancies, non-Hodgkin lymphoma	NCT05006716
HSK29116	BTK	Phase I	Relapsed or refractory B-cell cancers	NCT04861779
KT-413	IRAK4	Phase I	Non-Hodgkin lymphoma, diffuse large B-cell lymphoma	NCT05233033
ASP3082	KRAS G12D	Phase I	Pancreatic and colorectal cancers	NCT05382559
KT-333	STAT3	Phase I	Non-Hodgkin lymphoma, peripheral T-cell lymphoma	NCT05225584
LNK01002	Ras GTPase	Phase I	Acute myeloid leukemia	NCT04896112

At the same time, transforming growth factor-beta (TGF-β) is another key immunosuppressive pathway present in the tumor microenvironment (TME). Elevated levels of TGF-β not only promote epithelial-to-mesenchymal transition and

tumor invasion but also suppress the activity of effector T cells while recruiting regulatory T cells and myeloid-derived suppressor cells. Traditional inhibitors of TGF-β signaling have faced challenges due to systemic toxicity and insufficient suppression. However, targeted degraders can dismantle TGF-β or its downstream effectors, thereby reshaping the TME and restoring immune surveillance. Preliminary studies show that PROTAC-based degraders can inhibit epithelial-to-mesenchymal transition and enhance responses to checkpoint blockades, suggesting a synergistic effect when used in combination with PD-1/PD-L1 degradation. Together, these degraders targeting PD-1/PD-L1 and TGF-β provide complementary strategies for reactivating T-cell function and dismantling tumor-driven immunosuppression.

Table 2 shows the rapid clinical advancement of PROTAC-based therapeutics, with several agents targeting androgen receptors, BTK, and Bcl-xL moving into early- and late-stage trials. Their application across various cancers, including prostate, breast, leukemia, and lymphoma, highlights the versatility of this platform. However, most candidates are still in Phase I or Phase I/II trials, indicating that the field is still in its early stages and that there are unresolved issues concerning pharmacokinetics, safety, and tumor-specific delivery. While ARV-471 progressing to Phase III suggests clinical potential, the predominance of hematologic and hormone-driven malignancies indicates limited application thus far in solid tumors, revealing a significant translational gap.

3.2. Modulating Tumor Microenvironment and Immune Infiltration (Chemokines, IDO1, AhR)

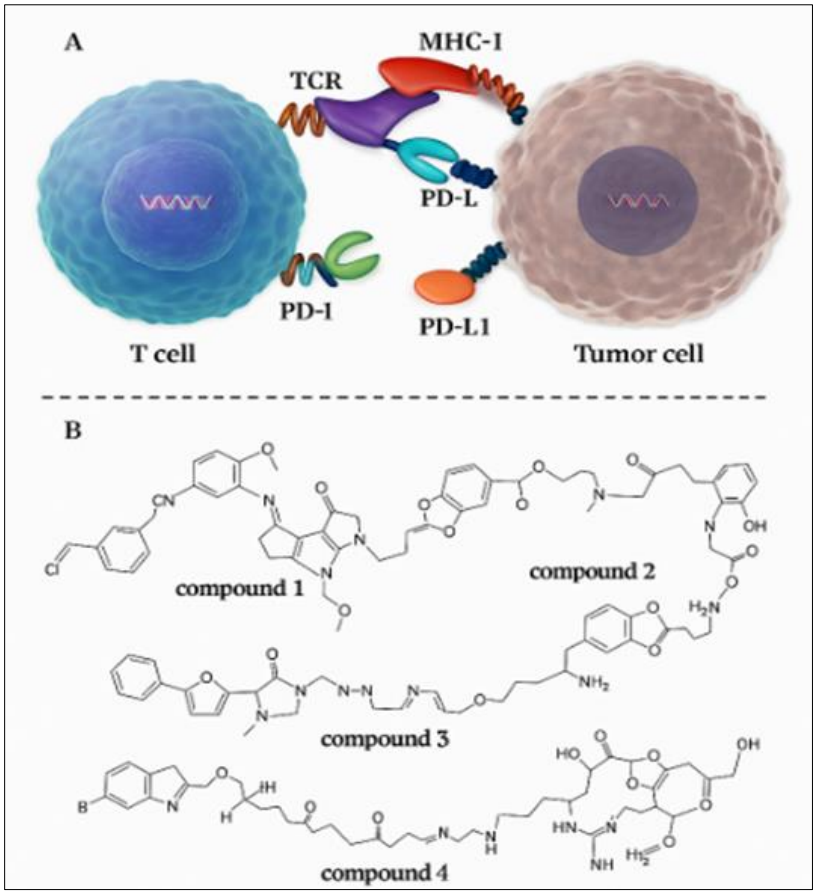

Figure 3 PD-1/PD-L1 checkpoint mechanism between immune and tumor cells, alongside chemical structures of representative small-molecule degraders designed to disrupt this interaction

The TME is influenced by chemokine signaling, metabolic suppression, and T-cell state control. Chemokines like CXCL12 promote tumor invasiveness and hinder immune cell infiltration, while CXCL10 aids T-cell recruitment. Targeting chemokine pathways with inhibitors has been challenging due to redundancy and receptor recycling. However, small-molecule degraders can remove chemokine receptors from the cell surface, blocking both signaling and recycling. For instance, PROTACs against CCR9 effectively suppress tumor-promoting signals, enhancing immune infiltration. Metabolic enzymes also contribute to immunosuppression. Indoleamine 2,3-dioxygenase 1 (IDO1) depletes tryptophan, causing T-cell anergy. Although IDO1 inhibitors like epacadostat showed initial promise, they ultimately failed due to incomplete inhibition. IDO1 degraders eliminate the enzyme entirely, overcoming resistance. Some IDO1 PROTACs can even penetrate the blood-brain barrier, offering potential for treating brain tumors.

Further, the aryl hydrocarbon receptor (AhR) promotes regulatory T cell differentiation and T-cell exhaustion, hindering effective antitumor responses. AhR inhibitors have had limited success, but degraders like Api-Protac-II can directly target and eliminate AhR, reversing T-cell dysfunction in preclinical models. Overall, degraders that target chemokines, IDO1, and AhR provide a comprehensive approach to remodeling the TME, improving immune infiltration, and reversing immune tolerance.

3.3. Reprogramming Epigenetic and Transcriptional Networks (BRD4, NAMPT, FOXM1)

Epigenetic and transcriptional regulators play critical roles in tumor progression and immune evasion. However, many of these proteins are considered "undruggable" by conventional inhibitors. Recently, proteolysis-targeting chimeras (degraders) have emerged as a promising approach to tackle these challenging targets by dismantling proteins that drive oncogenic transcription and metabolic adaptation [27], [28], [29], [30], [31]. One prominent example is BRD4, which promotes the transcription of oncogenes and upregulates PD-L1. Degraders like MZ1 have shown potent effectiveness in eliminating BRD4, leading to a reduction in PD-L1 expression and enhanced T-cell responses in tumor models. This dual action of directly suppressing tumors while modulating the immune response highlights the versatility of degraders in cancer treatment.

Another important target is BRD4, which supports tumor survival and suppresses antitumor immunity by promoting the expansion of myeloid-derived suppressor cells. NAMPT degraders not only inhibit its metabolic function but also lower extracellular NAMPT levels, thereby alleviating immunosuppression and restoring immune surveillance [32], [33]. Besides, Forkhead box protein M1 (FOXM1)—a transcription factor involved in cell proliferation and PD-L1 expression has been effectively targeted using peptide-based PROTACs. These degraders suppress FOXM1-driven oncogenic pathways, inhibit tumor metabolism, and enhance the visibility of tumors to cytotoxic T cells. Overall, the degraders targeting BRD4, NAMPT, and FOXM1 illustrate how epigenetic and transcriptional reprogramming can be utilized to enhance cancer immunotherapy. Figure 4 depicts the immunomodulatory roles of CCR9 and TGF-β in the tumor microenvironment, along with representative chemical structures of their corresponding small-molecule degraders.

3.4. Kinase and Apoptosis Regulators (BTK and Bcl-2/ Bcl-xL)

Kinases and apoptosis regulators play a crucial role in cancer progression and immune modulation. For instance, Bruton's tyrosine kinase (BTK) is essential for B-cell receptor signaling and the regulation of the innate immune system. Although inhibitors like ibrutinib have revolutionized the treatment of hematological malignancies, resistance mutations often emerge. BTK degraders, such as NX-2127, address this issue by degrading both wild-type and mutant BTK. Additionally, they eliminate immunomodulatory proteins like IKZF1 and IKZF3, which enhances T-cell activity. This dual mechanism makes BTK degraders superior to conventional inhibitors in terms of both tumor suppression and immune modulation.

Apoptosis regulators in the Bcl-2 family also represent important therapeutic targets. Venetoclax, a Bcl-2 inhibitor, has been approved for the treatment of leukemia; however, its clinical use is constrained by toxicity and the development of resistance. Bcl-xL is another important target but inhibiting it can lead to severe thrombocytopenia due to its role in platelet survival. Selective PROTAC degraders, such as DT2216, resolve this problem by selectively degrading Bcl-xL in tumor cells while sparing platelets, thereby reducing toxicity and improving the therapeutic index. These degraders not only promote apoptosis in tumor cells but also enhance immune responses by removing immunosuppressive survival signals. Together, BTK and Bcl-xL degraders demonstrate how TPD can effectively bridge tumor cell biology and immune regulation, highlighting its potential in next-generation immunotherapy.

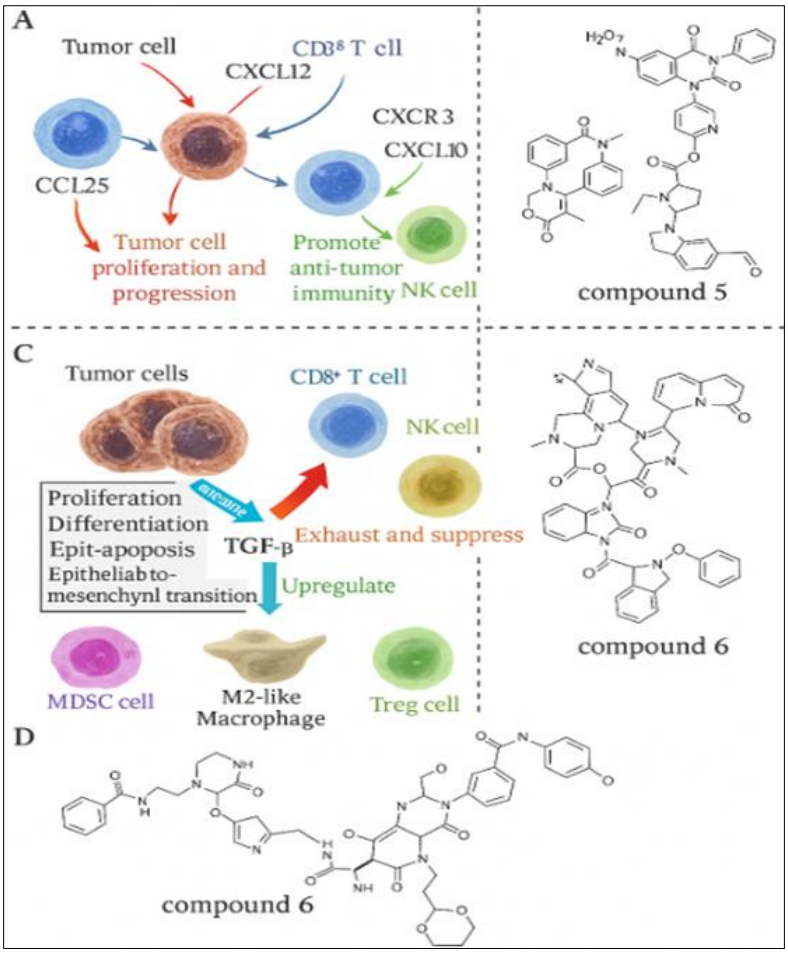

Figure 4 Multifaceted roles of chemokines (CCR9) and TGF-β in tumor progression and immunosuppression alongside representative small-molecule degraders.

4. Technological and Engineering Challenges

TPD holds great promise for advancing cancer immunotherapy, but several significant challenges must be overcome before these approaches can be widely implemented in clinical settings. These challenges stem from the complexity of degraded molecules, their interactions with biological systems, and the necessity for selective and safe therapeutic action. To overcome these obstacles, innovation is needed at the intersection of chemistry, nanotechnology, and computational biology. Table 3 outlines key molecular glues and CMA-based degraders currently undergoing clinical evaluation, demonstrating the growing diversity of targeted protein degradation strategies beyond PROTACs.

4.1. Molecular Size, Permeability, and Delivery

The relatively large size of PROTACs, often exceeding 800 to 1,000 Da, reduces their ability to penetrate cell membranes and limits their oral bioavailability. Additionally, their poor solubility and uneven distribution in the body restrict their ability to infiltrate solid tumors and immune-privileged sites, such as the brain. These factors collectively impede systemic stability and the achievement of therapeutic concentrations at tumor sites. To improve permeability and targeted delivery, researchers are exploring various strategies, including linker optimization, prodrug modification, and advanced formulations using nanocarriers such as liposomes, polymeric nanoparticles, and exosomes.

Table 3 Selected molecular glues and CMA-based degraders under clinical investigation for cancer treatment

Compound	Target	Trial Stage	Cancer Type(s)	Clinical Trial ID(s)
Thalidomide	IKZF1/3	Approved	Multiple myeloma	NCT04975997; NCT05827016
Lenalidomide	IKZF1/3	Approved	Multiple myeloma	—
Pomalidomide	IKZF1/3	Approved	Multiple myeloma	—
CC-220	IKZF1/3	Phase III	Refractory or relapsed multiple myeloma	NCT05150985; NCT05525976
CC-92480	IKZF1/3	Phase III	Refractory or relapsed multiple myeloma	NCT03340163
CC-122	IKZF1/3	Phase I/II	Lymphoma, leukemia, melanoma, hepatocellular carcinoma	NCT02406742; NCT03340163
E7070	RBM23/39	Phase I/II	Leukemia, colorectal, renal, breast, gastric, and metastatic solid tumors	NCT01659217; NCT01658540
E7820	RBM39	Phase II	AML, CMML, and colorectal cancer	NCT05024994
CC-99282	IKZF1/3	Phase I/II	Follicular lymphoma, large B-cell lymphoma	NCT03003179; NCT03340163
CC-90009	GSPT1	Phase I/II	Acute myeloid leukemia	NCT04336982
CFT7455	IKZF1/3	Phase I/II	Multiple myeloma, non-Hodgkin lymphoma	NCT04756726
MRT-2359	GSPT1	Phase I	Small cell lung cancer, neuroendocrine tumors	NCT05546268
CC-91633	CK1α	Phase I	AML	NCT04915789
DKY709	IKZF2/4	Phase I	Nasopharyngeal carcinoma and other cancers	NCT03891953
BTX-1188	IKZF1/3, GSPT1	Phase I	Advanced solid tumors, non-Hodgkin lymphoma	NCT05144334
ORM-5029	GSPT1	Phase I	HER2-positive advanced breast cancer	NCT05511844
KPG-121	IKZF1/3	Phase I	Castration-resistant prostate cancer	NCT05369280
TQB3820	IKZF1/3	Phase I	Hematologic malignancies	NCT05320639
IK-595	MEK	Phase I	Colorectal and pancreatic cancer	NCT06720082
CDDO-Me	EGFR	Phase I	Solid tumors, lymphoid cancers	NCT00529438
RNK05047b	BRD4	Phase I/II	Solid tumors and diffuse large B-cell lymphoma	NCT05487170

4.2. Off-Target Effects and Toxicity Risks

By seizing either, the ubiquitin-proteasome system or lysosomal pathways, degraders risk causing non-specific degradation of essential proteins. This could disrupt cellular balance and lead to systemic toxicity. The issue is further complicated when E3 ligases inadvertently bind to unintended substrates, resulting in widespread substrate degradation. To mitigate off-target effects while preserving therapeutic efficacy, key strategies include enhancing ligand selectivity, optimizing the formation of ternary complexes, and utilizing computational modeling and structural biology tools.

4.3. Spatiotemporal Control and Phototoxicity in PHOTACs

PHOTACs provide spatiotemporal precision by utilizing photoswitchable moieties to regulate degradation. However, their dependence on ultraviolet (UV) light presents two significant limitations: poor penetration into deep tissues and

the risk of DNA damage. These issues primarily restrict the use of PHOTACs to superficial tumors, such as skin or ocular cancers [34], [35], [36]. To overcome these challenges, research is currently focused on developing red- and near-infrared–responsive switches that allow for deeper tissue penetration while minimizing genotoxicity. However, further optimization is necessary for successful clinical translation.

4.4. Immunogenic Risks and Engineering Solutions

Degraders that use engineered ligands, such as LYTACs and Folate-PROTACs, may trigger immune responses, leading to neutralization or autoimmunity due to their foreign components. To reduce immunogenicity, it is essential to design ligands based on endogenous receptor motifs, humanize peptide scaffolds, and utilize computational antigenicity prediction. More broadly, addressing the challenges of TPD will require interdisciplinary solutions [37], [38], [39]. These include developing nanocarrier delivery systems to enhance bioavailability, applying Artificial Intelligence for optimizing degraders, and fostering collaboration across fields such as chemistry, biomedical engineering, and clinical science to integrate design and ensure translational validation.

5. Discussion

TPD has emerged as a promising strategy in cancer immunotherapy by removing disease-driving proteins rather than just inhibiting them. To maximize the potential of TPD, it's crucial to combine computational sciences, engineering innovations, and clinical strategies [40], [41]. Key advancements include the use of Artificial Intelligence (AI) and computational modeling, which are transforming the discovery and optimization of degraders. Traditional drug discovery often relies on trial and error, but AI techniques like structural predictions, molecular docking, and dynamics simulations offer more accurate modeling of interactions between degraders, target proteins, and E3 ligases [42], [43]. Machine learning algorithms can now predict binding affinity, stability, and degradation efficiency based on existing datasets, while computational chemistry tools help optimize linker flexibility and pharmacokinetics [44]. These advancements accelerate the identification of effective degraders, lower experimental costs, and improve chances of success in clinical applications.

Nanotechnology offers effective solutions for enhancing the delivery and bioavailability of degraders. Platforms like liposomes, polymeric nanoparticles, dendrimers, and exosomes can encapsulate these molecules, improving their solubility, stability, and accumulation in tumors [45], [46]. By incorporating targeting ligands—such as peptides, antibodies, and aptamers, these nanocarriers can be directed specifically to tumor tissues. Additionally, stimuli-responsive systems can release their cargo in conditions unique to the tumor microenvironment, like pH-sensitive nanoparticles, which enhance uptake by cancer cells while reducing systemic exposure. This enables precise delivery, improves the therapeutic index, and allows for the co-delivery of degraders with other anticancer agents [47], [48]. Combining degraders with current immunotherapies is also crucial. Immune checkpoint inhibitors have transformed oncology, but some patients either don't respond or develop resistance due to suppressive pathways in the tumor microenvironment. Degraders can dismantle these pathways and enhance checkpoint blockades [49], [50]. For example, pairing PD-L1 degraders with CTLA-4 inhibitors can boost T-cell activation, while TGF-β degraders can remodel the tumor stroma to improve PD-1 blockade. Degraders targeting metabolic regulators like IDO1 or NAMPT can also restore nutrient availability for T cells, leading to better outcomes in adoptive T-cell therapies. This multifaceted approach highlights the potential of degraders as effective partners for existing immunotherapies.

Resistance to cancer therapy poses major challenges, but degraders offer a promising solution. Resistance often arises from mutations that hinder inhibitor binding, redundant pathways, or compensatory upregulation. Degraders work by eliminating the entire protein, which minimizes issues related to mutations and compensatory signaling. For instance, BTK degraders remain effective against ibrutinib-resistant variants, and Bcl-xL degraders avoid the toxicity linked to traditional inhibitors [51]. Similarly, degraders targeting BRD4 or FOXM1 can effectively suppress challenging oncogenic programs. By addressing resistance directly, degraders enhance the potential for sustained treatment benefits. The future of TPD relies on integrating engineering, medicine, and computational sciences. Chemical engineering will optimize degrader structures for better selectivity, while biomedical engineering will improve delivery systems using nanotechnology. Computational sciences will support predictive modeling and AI-driven design. It's essential to conduct well-designed clinical trials to evaluate the effectiveness of degraders, both alone and alongside standard immunotherapies. Interdisciplinary collaboration is key to fully optimizing degraders for patient benefit.

6. Conclusion

TPD is revolutionizing cancer immunotherapy by focusing on eliminating disease-driving proteins instead of just inhibiting their activity. Unlike traditional antibodies and inhibitors, TPD can more effectively modulate immune

checkpoints, tumor microenvironment factors, metabolic enzymes, transcriptional regulators, and apoptosis-related proteins. This approach broadens the range of druggable targets, allowing for treatment of both intracellular and extracellular targets that are often inaccessible with antibody therapies. However, TPD faces several challenges in clinical applications, including issues related to molecular size, bioavailability, delivery efficiency, off-target effects, and immunogenicity. Various platforms like PROTACs, molecular glues, PHOTACs, and lysosomal-directed degraders each have specific advantages and require ongoing refinement. To overcome these challenges, interdisciplinary innovations are necessary, particularly in nanotechnology for targeted delivery, Artificial Intelligence for designing degraders, and biomedical engineering for optimizing translation to clinical settings. TPD also has the potential to enhance existing immunotherapies and counter resistance mechanisms that limit current treatment effectiveness. By dismantling immune checkpoints, reversing T-cell exhaustion, reprogramming tumor environments, and eliminating resistant oncogenic drivers, TPD could transform cancer treatment. Looking forward, the integration of engineering, medicine, and computational sciences will be key to realizing TPD's clinical potential, moving it from a promising experimental approach to a cornerstone of precision immunotherapy.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest.

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