Review

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Emerging Strategies in Smart Nano-PROTAC for Stimuli-Responsive Protein Degradation and Precision Cancer Therapy

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Abstract

Proteolysis-targeting chimeras (PROTACs) have emerged as a promising therapeutic strategy for targeted protein degradation. They offer several advantages over traditional small-molecule inhibitors, including catalytic efficiency, high specificity, and the ability to degrade previously undruggable targets. To date, the most advanced therapeutics of PROTAC, ARV-471, and CC-94676 have progressed into Phase III clinical trials, marking a significant milestone in the clinical translation of targeted protein degradation strategies. However, despite their success in clinical trials, current PROTACs face challenges such as poor cell permeability, systemic off-target effects, and the "hook effect", which hinder broader clinical translation. To address these limitations, stimulus-responsive nanoparticle-based PROTACs (nano-PROTACs) have been developed to enable spatiotemporally controlled protein degradation. These advances exploit endogenous or exogenous stimuli (such as redox status, enzymes, light, and ultrasound) to achieve precise activation, thereby enhancing therapeutic efficacy while minimizing systemic toxicity. This review highlights recent advances in stimulus-responsive nano-PROTACs, with particular emphasis on the design of novel ligands and linkers. These emerging smart nano-PROTAC strategies enhance specificity and controllability, paving the way for next-generation degraders with improved pharmacological properties.

Keywords: proteolysis-targeting chimera (PROTAC); nano-PROTAC; stimulus-responsive; precision cancer therapy; smart drug delivery system

Introduction

Proteolysis-targeting chimeras (PROTACs) represent a paradigm shift in targeted drug discovery. Unlike small molecule inhibitors that suppress protein activity by occupying the active site or binding pocket, PROTACs catalytically eliminate the protein of interest (POI) in an event-driven manner [1]. Introduced by Deshaies et al. in 2001 [2], PROTACs are heterobifunctional molecules that utilize the ubiquitin-proteasome system (UPS) to degrade specific target proteins. PROTACs consist of three key components: a target binding ligand, an E3 ligase ligand, and a linker, which form the ternary complex.

PROTACs bring the POI into proximity with an E3 ligase, inducing polyubiquitination. The ubiquitinated protein is subsequently recognized and degraded by the proteasome. This catalytic mechanism enables sustained protein degradation with transient PROTAC binding.

PROTACs have made significant progress in clinical trials, with several candidates entering Phase I and II trials in cancer and neurodegenerative diseases. Currently, the most advanced PROTAC therapeutics, ARV-471 and CC94676, have advanced into Phase III clinical trials, marking a significant milestone in the clinical translation of targeted protein degradation strategies [3, 4]. However, despite their promise, current PROTACs face several challenges, including poor solubility, low cellular permeability, systemic toxicity, and the "hook effect", which hinder their broader clinical translation (Fig. 1) [5, 6].

To address these limitations, the integration of nanotechnology with PROTACs has led to the development of nanoparticle-based PROTACs (nano-PROTACs), which utilize nanoscale systems for controlled release, improved pharmacokinetics, and targeted delivery [7, 8]. Recent advances in nano-PROTACs have focused on the development of carriers, including polymeric nanoparticles, liposomes, and micelles, to enhance PROTAC delivery and minimize off-target effects. For example, Ping et al. demonstrated the use of polymeric nanoparticles encapsulating BRD4-targeted PROTACs, achieving efficient intracellular delivery and sustained protein degradation [9]. Similarly, Xu et al. used lipid nanoparticles to deliver BET inhibitors, improving tumor penetration and therapeutic efficacy [10]. Most existing PROTAC delivery strategies fail to adequately address the complexity of the physiological environment, resulting in limitations such as suboptimal efficacy and increased toxicity. These approaches often overlook the heterogeneity of the tumor microenvironment and fail to exploit specific physiological features for targeted delivery. Therefore, the development of smart delivery systems that respond to tumor-specific stimuli (such as light, hypoxia, or enzymatic activity) is crucial to enhancing the therapeutic efficacy of PROTACs while minimizing side effects [11–15]. Stimuli-responsive smart nano-PROTACs have been engineered to release the active PROTAC molecule under specific conditions, such as pH-sensitive

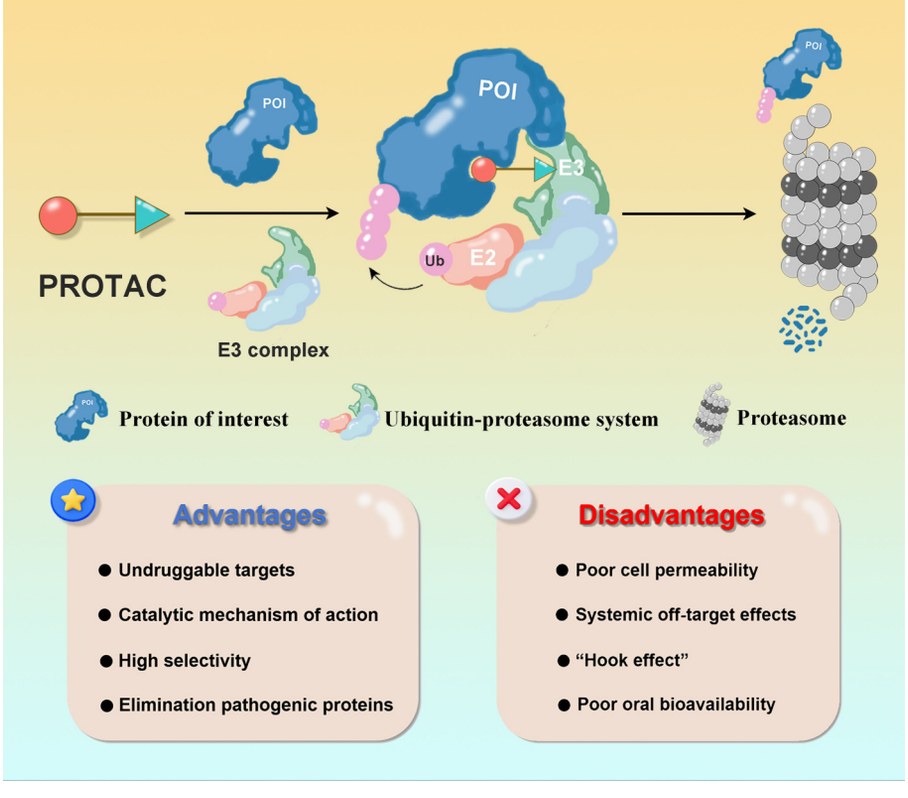

Fig. 1 Schematic diagram of the PROTAC mechanism.

carriers that respond to acidic tumor environments [16] and enzyme-responsive systems for site-specific release [17]. By enabling precise spatiotemporal control of protein degradation, these systems enhance therapeutic efficacy while minimizing systemic toxicity [18].

This review highlights recent advances in smart nano-PROTACs and the design of novel ligands and linkers of nano-PROTACs. By enhancing specificity and controllability, these emerging strategies contribute to the development of next-generation degraders with superior pharmacological properties. In addition, we explore the clinical prospects of these innovative technologies, emphasizing their potential to overcome current limitations and transform targeted protein degradation therapeutics.

Progress in Clinical Development of Heterobifunctional PROTACs in Cancer Therapy

The androgen receptor (AR) and the estrogen receptor (ER) play pivotal roles in the pathogenesis and progression of prostate and breast cancer, respectively, positioning them as critical therapeutic targets. In recent years, these receptors have received considerable attention in the development of targeted protein degraders, with efforts focused on selectively modulating their expression and activity to enhance therapeutic efficacy in hormone-driven malignancies.

Several AR-targeting PROTACs have entered clinical development, with ARV-110 and CC-94676 being the most studied. ARV-110 demonstrated significant efficacy in Phase I/II trials, particularly in patients with AR T878X/H875Y mutations (median radiographic progression-free survival (rPFS: 11.1 months; PSA reduction more than 50% in 54% of patients), while its effectiveness in AR L702H mutants was limited (NCT03888612). CC-94676, the first AR-targeting PROTAC to reach Phase III, showed dose-dependent PSA reduction in Phase I trails, among 60 patients receiving twice-daily treatment doses ranging from 400 to 900 mg, 32% (19/60) achieved a more than 50% reduction in prostate-specific antigen levels (PSA50). Notably, 10 responders were from the 900 mg cohort. The median rPFS was 6.3 months overall, with the 900 mg group exhibiting prolonged median rPFS of 8.3 months (NCT04428788). Other AR-PROTACs, such as GT-20029, AC176 and HP-518, are also in clinical trials. These results underscore the importance of mutation-specific strategies, where ARV-110 excells against T878X/H875Y mutations, while CC-94676 shows broader therapeutic potential.

ARV-471 is the first orally administered ER-targeting PROTAC to advance into Phase III clinical trials for the treatment of ER-positive/HER2-negative breast cancer, marks a milestone in targeted protein degradation therapy. Phase III clinical trial results indicate that in patients with ESR1 mutations, ARV-471 monotherapy significantly prolonged PFS versus fulvestrant, reducing the risk of disease progression or death by more than 40% (hazard ratio <0.60), meeting the predefined endpoint. However, in the intent-to-treat (ITT) population, the improvement in PFS was not statistically significant. While OS data remain immature, these findings represent the first Phase III validation of PROTAC technology, underscoring its clinical potential and advancing the field of targeted protein degradation (NCT05654623). In addition to ARV-471, other ER-targeting PROTACs, such as HRS-1358 and AC699, are in Phase I clinical trials. Building on prior research, these compounds have been further optimized for enhanced ER degradation efficiency and pharmacokinetic properties, aiming to overcome resistance to the conventional endocrine therapies and improve their clinical applicability.

Bruton's tyrosine kinase (BTK), a key regulator of B-cell receptor (BCR) signaling (BCR), plays a central role in the pathogenesis of B-cell malignancies. NX-2127, the first BTK degrader in clinical trials, effectively targets both wild-type and C481S-mutant BTK, exhibits enhanced robust, sustained BTK degradation along with immune modulation and antitumor activity in relapsed/refractory CLL (NCT04830137). NX-5948, a second-generation BTK PROTAC, enhances selectivity and CNS penetration, showing promise for CNS B-cell malignancies and resistance to ibrutinib (NCT05131022). BGB-16673 achieved a response rate higher than 70% in early-phase trials, including in patients resistant to prior BTK inhibitors, with remissions lasting up to 60 weeks (NCT05006716). These BTK-targeting PROTACs offer new therapeutic strategies for treatment-resistant B-cell malignancies, with ongoing trials expected to further validate their clinical utility.

The BRAF V600E mutation drives oncogenesis in

multiple malignancies and contributes to resistance against conventional therapies. While BRAF inhibitors like vemurafenib and dabrafenib have been developed, their efficacy is often limited by acquired resistance. CFT1946, the first BRAF V600E-targeting degrader in clinical trials, selectively degrades mutant BRAF, effectively inhibiting the MAPK pathway. Early clinical data demonstrate favorable tolerability, with minimal high-grade adverse events, and dose-dependent drug exposure (NCT05668585). Biopsy analyses confirm consistent BRAF V600E degradation, and preliminary antitumor activity has been observed in patients with prior BRAF inhibitor resistance. Notably, partial responses were reported in melanoma and pancreatic cancer cases. These findings highlight CFT1946's potential as a novel therapeutic strategy and enlighten the future studies that explore its role in combination therapies and broader clinical applications.

ARV-393 and BMS-986458 are two BCL6-targeting PROTACs with promising preclinical efficacy. ARV-393 effectively degrades BCL6 and inhibits tumor growth in xenograft models, while BMS-986458 demonstrates potent BCL6 degradation in 80% of BCL6-expressing NHL cell lines and all tested patient-derived xenograft models (NCT06393738). Notably, BMS-986458 upregulates CD20 expression, potentially synergizing with anti-CD20 therapies like rituximab. Both compounds are in Phase I trials for relapsed/refractory NHL (NCT06090539). Some early data already confirmed the robust BCL6-degradating and antitumor activity in ARV-393, while BMS-986458 is still under assessment for its safety, pharmacokinetics, and combination potential. These findings highlight BCL6-targeting PROTACs as a promising strategy for B-cell lymphomas.

Up to now, PROTAC technology has made significant progress in oncology, with several PROTAC-based therapeutics successfully progressing through late-stage clinical trials, exhibiting notable protein degradation efficiency and antitumor activity in multiple malignancies (Table 1 and Fig. 2). In addition, a subset of PROTAC drugs in clinical trials are being investigated for applications in conditions such as androgenic alopecia, autoimmune and neurodegenerative diseases. However, despite advantages like high specificity in targeted protein degradation and the potential to overcome resistance to conventional small-molecule inhibitors, challenges remain in their clinical application. For instance, the pharmacokinetic properties of orally administered PROTACs require further optimization, due to their high molecular weight and poor membrane permeability, which impede *in vivo* stability and bioavailability. Moreover, resistance to certain target proteins may constrain the long-term therapeutic efficacy of PROTACs. Additionally, enhancing tissue-specific delivery while minimizing off-target effects and potential toxicity remains a key focus of ongoing research.

Emerging Strategies in Smart Nano-PROTAC

The integration of nanotechnology with PROTACs offers a powerful synergistic approach to address the inherent limitations of traditional PROTACs [1, 19–21]. One major obstacle to clinical translation of PROTACs is their unfavorable pharmacokinetic properties, including poor solubility, rapid clearance, low bioavailability and "hook effect". Nanocarrier systems, such as liposomes, polymers, and inorganic nanoparticles, can encapsulate PROTAC molecules, enhancing their stability, solubility, and circulation half-time *in vivo* [22]. This nanocarrier-based strategy facilitates more efficient delivery of PROTACs to target sites, thereby improving therapeutic efficacy. Furthermore, the design of stimuli-responsive smart nano-PROTACs, novel E3 ligase ligands, and eptimized linkers enales spatiotemporal control of drug release, fine-tuning PROTAC pharmacology (Fig. 3). By exploiting disease-specific microenvironments for controlled release, responsive systems enhance the targeted action of PROTACs, reducing off-target effects and improving their therapeutic profile. This strategy not only enhances the specificity of PROTACs, but also expands their applicability in complex physiological settings, positioning them as a promising therapeutic modality.

Stimulus-Responsive Smart Nano-PROTACs

Photocaged nano-PROTACs

Photocaged nano-PROTACs represent an innovative strategy for spatiotemporally controlled protein degradation, offering precise spatial and temporal regulation of therapeutic interventions. While

Table 1 PROTACs in clinical trials.

Target protein	PROTAC name	E3 ligase	Indications	Clinical phase	NCT number	R&D institution
AR	ARV-110	CRBN	Prostate cancer	II/III	NCT03888612	Arvinas
	CC-94676	CRBN	Prostate cancer	III	NCT04428788	Bristol-Myers Squibb
	ARV-766	CRBN	Prostate cancer	II	NCT05067140	Arvinas
	GT-20029	—	Androgenic alopecia and acne	II	NCT06468579	Kintor
	AC176	—	Prostate cancer	I	NCT05241613	Accutar Biotechnology
	HP-518	—	Metastatic castration resistant prostate cancer	I	NCT05252364	Hinova
	HRS-5041	—	Metastatic castration resistant prostate cancer	I	NCT05942001	Jiangsu HengRui
BCL-xL	DT2216	VHL	Hematological malignancies	I	NCT04886622	Dialectic Therapeutics
BCL6	ARV-393	CRBN	B-Cell malignancies	I	NCT06393738	Arvinas
	BMS-986458	—	Unspecified/diffuse large B-cell lymphomas	I	NCT06090539	Bristol-Myers Squibb
BRAF V600E	CFT1946	CRBN	Melanoma colorectal cancer	I/II	NCT05668585	C4 Therapeutics
BRD4	RNK-05047	—	Diffuse large B cell lymphoma	I/II	NCT05487170	RANOK Therapeutics
BRD9	FHD-609	CRBN	Synovial sarcoma	I	NCT04965753	Foghorn Therapeutics
BTK	BGB-16673	CRBN	B cell lymphoma	I/II	NCT05006716	Beigene
	NX-5948	CRBN	B cell malignancies	I	NCT05131022	Nurix Therapeutics
	NX-2127	CRBN	Relapsed/refractory B cell malignancies	I	NCT04830137	Nurix Therapeutics
	AC676	—	Hematology oncology indications	I	NCT05780034	Accutar Biotechnology
	HSK29116	—	B cell lymphoma	I	NCT04861779	Haisco
	ABBV-101	—	B cell malignancies	I	NCT05753501	Abbvie
EGFR	HSK40118	—	Non-small cell lung cancer	I	NCT06050980	Haisco
EGFR L858R	CFT8919	CRBN	Non-small cell lung cancer	I	NCT06641609	C4 Therapeutics
ER	ARV-471	CRBN	ER+/HER2-breast cancer	III	NCT05654623	Arvinas
	AC699	—	Breast cancer	I	NCT05654532	Accutar Biotechnology
	HRS-1358	—	Breast cancer	I	NCT05628870	Jiangsu HengRui
IRAK4	KT-474	CRBN	Hidradenitis suppurativa	II	NCT04772885	Kymera Therapeutics
	BGB-45035	—	Autoimmune dermatological diseases	I	NCT06342713	Beigene
MDM2	KT-253	CRBN	Acute myeloid/lymphoblastic leukemia	I	NCT05775406	Kymera Therapeutics
STAT3	KT-333	VHL	Hematological malignancies and solid tumors	I	NCT05225584	Kymera Therapeutics
KRAS G12D	ASP3082	VHL	Pancreatic ductal adenocarcinoma	I	NCT05382559	Astellas
SMARCA2	PRT3789	VHL	Non-small cell lung cancer	I	NCT05639751	Prelude Therapeutics
	QLH12016	—	Adensocarcinoma of prostate	I	NCT05973149	Oilu Pharmaceutical

traditional PROTACs have demonstrated immense potential in modulating undruggable proteins via the ubiquitin-proteasome system, their constitutive activity often leads to off-target degradation and systemic toxicity. To address these challenges, a variety of photocaging moieties groups [23, 24], including ortho-nitrobenzyl, para-hydroxyphenacyl, and coumarin, have been engineered and incorporated into PROTAC prodrugs (Fig. 4(a)). These photocaging moieties conjugate with PROTAC molecules, facilitating cellular delivery via nanocarriers while sterically blocking target protein engagement. Upon light irradiation, the protecting groups undergo photolysis, triggering the release of the active PROTAC, thereby restoring its therapeutic function.

In 2019, Pan and colleagues pioneered the development of a photocaged PROTAC (pc-PROTAC) by incorporating the photocaged DMNB group (4,5-dimethoxy-2-nitrobenzyl) into the BRD4-

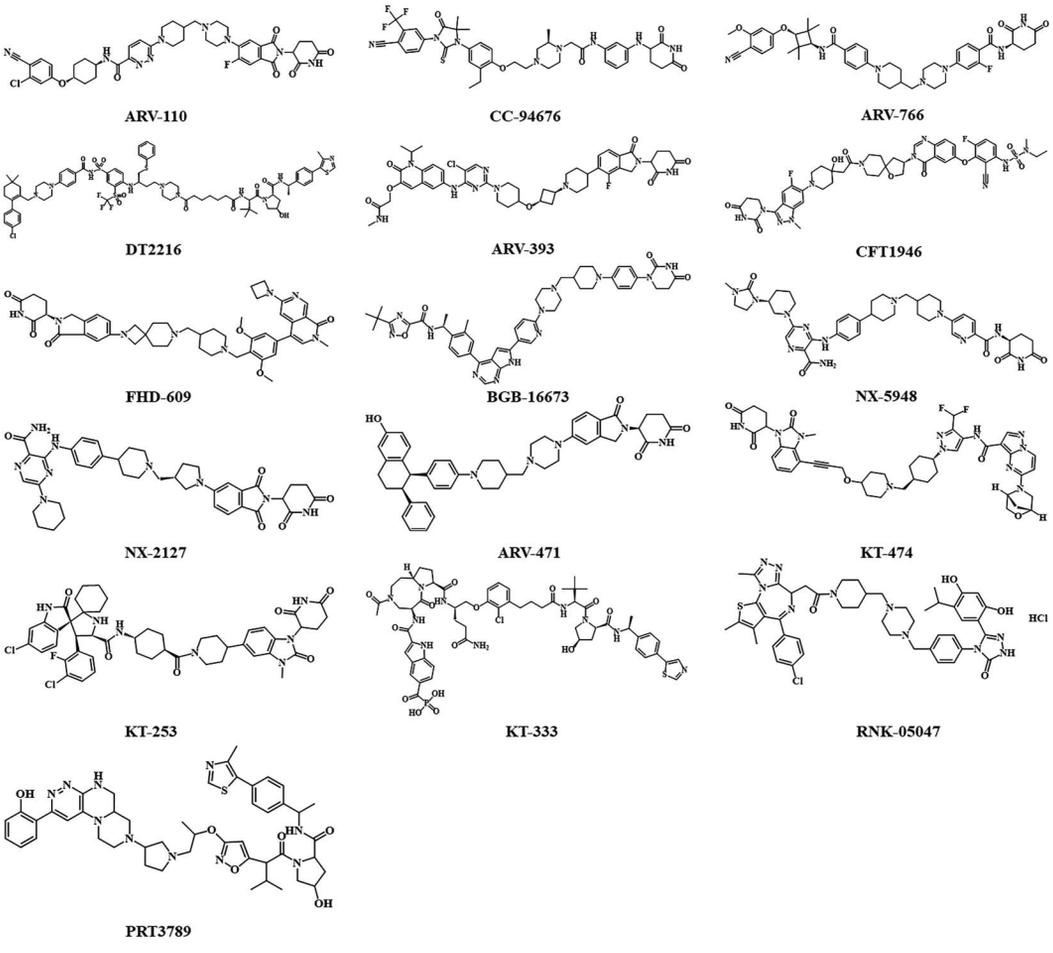

Fig. 2 The molecular structures of PROTACs that have entered clinical trials.

targeting PROTAC molecule dBET1 [25]. dBET1, a heterobifunctional degrader consisting of thalidomide (a CRBN E3 ligase ligand) linked to JQ-1 (a BRD4 ligand), was modified to generate two photocaged variants: pc-PROTAC 1 (Fig. 4(b)), in which a DMNB group was installed on the amide nitrogen of JQ1, and pc-PROTAC 2, where DMNB was conjugated to the imide nitrogen of thalidomide. Upon ultraviolet (UV) irradiation (365 nm, 3 mW/cm²), pc-PROTAC 1 underwent photolysis, yielding approximately 50% of active dBET1. In contrast, pc-PROTAC 2 failed to generate a detectable amount of dBET1, indicating that the positioning of the photocaged group can significantly impact PROTAC binding and degradation efficiency. Extending the photocaged PROTAC toolbox, Deiters et al. developed a broadly applicable strategy for optically controlled protein degradation [26], by conjugating diethylamino coumarin and 6-nitropiperonyloxymethyl photocaging groups to ligands that recruit the von Hippel-Lindau (VHL) and CRBN E3 ubiquitin ligases, respectively (Figs. 4(c) and 4(d)). This strategy provides a versatile and generalizable platform for the spatiotemporal control of targeted protein degradation. In a complementary

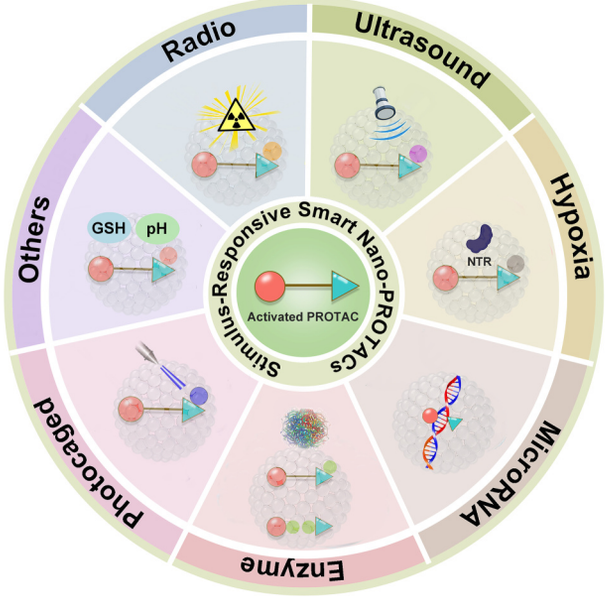

Fig. 3 Schematic diagram of the factors that induce the activation of smart nano-PROTACs.

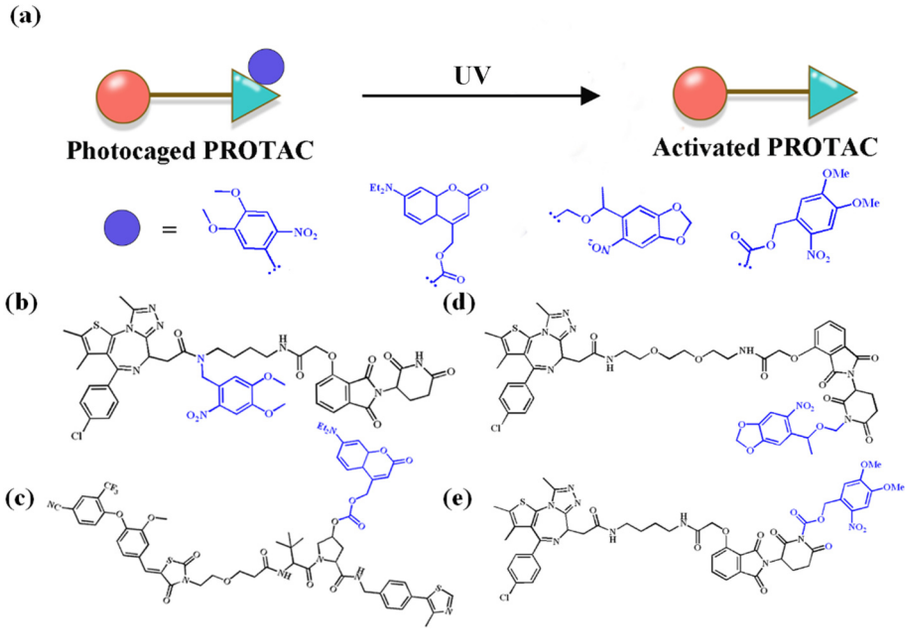

Fig. 4 (a) Schematic diagram of the release of activated PROTAC by photocaged PROTAC upon exposure to UV light. **(b)** Structure of NPOM-caged BRD4 pc-PROTAC1. **(c)** Structure of DEACM-caged ERRa PROTAC2. **(d)** Structure of NPOM-caged BRD4 PROTAC. **(e)** Structure of nitroveratryloxycarbonyl-caged opto-dBET1.

approach, Wei et al. took an alternative approach by introducing a nitroveratryloxycarbonyl photocaging group onto pomalidomide as a precursor scaffold [27]. Using this strategy, they synthesized two pomalidomide-based opto-PROTACs (opto-dBET1 and opto-dALK, Fig. 4(e)). Upon UV irradiation, opto-dBET1, and opto-dALK efficiently underwent photolysis *in vitro*, resulting in the targeted degradation of BRD4 and EML4-ALK, respectively. Subsequent biochemical and cellular validation demonstrated the feasibility of this platform to precisely control intracellular protein degradation in a highly specific and spatiotemporally regulated manner, establishing a versatile framework for light-induced targeted protein modulation.

Building on advances in photocaged PROTAC prodrugs, UV light has been widely used to activate PROTACs, but its limited tissue penetration remains a significant challenge. To overcome this limitation, Yu et al. developed a photocaged pro-PROTAC (phoBET1) by functionalizing the thalidomide ligand of dBET1 with an N-(2-aminoethyl)-2-(4-(1-ethoxyethyl)-2-methoxy-5-nitrophenoxy)-acetamide photocaged group (Fig. 5(a)) [28]. To enable near-infrared (NIR) activation, phoBET1 was encapsulated in upconversion nanoparticle (UCNP)-based mesoporous silica nanoparticles (UMSNs), forming a NIR-responsive PROTAC nanocage (UMSNs@

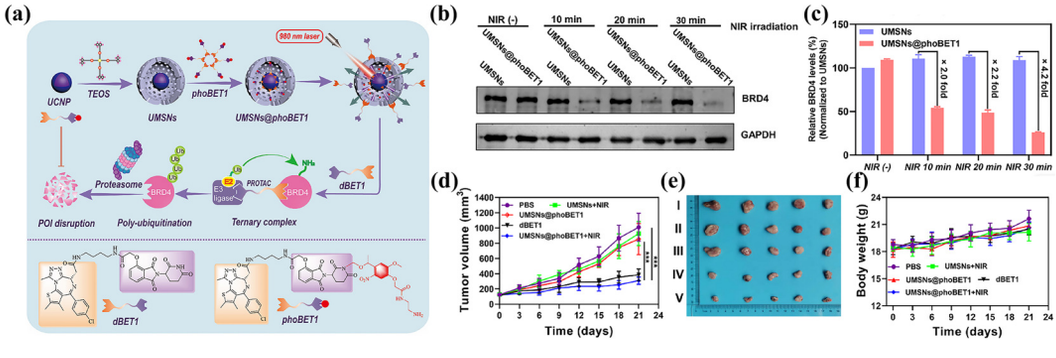

Fig. 5 (a) Schematic illustration of the NIR light-activatable UMSNs@phoBET1 and its mechanism for BRD4 degradation. **(b)** and **(c)** Western blot analysis of BRD4 expression levels after different treatments. **(d)** Curves of average tumor volume change after administration of different formulations during the 21 days treatment period. **(e)** Tumors after various treatments. **(f)** Changes in body weight of tumor-bearing mice during the treatment period. Reproduced with permission from Ref. [28] © 2023 American Chemical Society.

phoBET1) for spatiotemporally controlled BRD4 degradation. Upon 980 nm NIR irradiation, UCNPs converted NIR light into UV emissions, triggering photocage cleavage and release of active PROTAC molecules. As expected, NIR laser irradiation induced significant BRD4 degradation in a time-dependent manner, with relative BRD4 expression levels decreasing to 54.2%, 48.5%, and 25.9% after 10, 20, and 30 min of activation, respectively (Figs. 5(b) and 5(c)). *In vivo*, UMSNs@phoBET1 combined with NIR treatment showed significant tumor growth inhibition (tumor growth inhibition = 58.7%), significantly outperforming controls (Figs. 5(d) and 5(e)). Furthermore, treated mice maintained steady weight gain, indicating a favorable biocompatibility. This study overcomes the tissue penetration limitation of UV light and establishes a NIR-activatable nano-PROTAC platform for precise *in vivo* protein degradation.

Current photocaging groups still face challenges such as suboptimal photoactivation efficiency and background hydrolysis, which limit their broader applicability [29]. As a result, nano-photocaged PROTACs remain an emerging field with relatively few studies to date. However, with ongoing advances in photo-responsive strategies and nanomedicine-based drug delivery, this approach holds great promise for precision cancer therapy and spatiotemporally controlled intracellular protein degradation.

Enzyme-triggered nano-PROTACs

Tumor-specific enzymes, a class of pathognomonic biomarkers, exhibit several functions that are critical for mediating biochemical reactions in tumors. These over-expressed enzymes can be strategically employed to regulate PROTAC structures, enabling the tumor-selective protein degradation pathways [30, 31]. By harnessing enzyme-triggered activation, this approach not only minimizes off-target toxicity and improves drug safety profiles, but also overcomes the limitations of traditional PROTACs, such as poor bioavailability and *in vivo* limited stability.

For instance, Pu et al. developed a cathepsin B (CatB)-responsive smart nano-PROTAC, SPN_{COX}, consisting of a semiconductor polymer backbone conjugated to a COX-1/2-targeting PROTAC peptide via a CatB-cleavable linker (Fig. 6(a)) [32]. Following accumulation in the tumor site, CatB-mediated linker cleavage, releasing the active PROTAC peptide that incorporates an indomethacin moiety and a VHL-targeting sequence (GSGSALAPYIP). This design facilitates the recruitment of the VHL E3 ligase to promote degradation of COX-1/2. *In vitro* studies using 4T1 cells, SPN_{COX} treatment resulted in an 82.5% or 92.0% reduction in COX-1 levels and an 85.9% or 89.1% reduction in COX-2 levels (Figs. 6(b) and 6(c)). When combined with photodynamic therapy (PDT), SPN_{COX} reprogrammed the immunosuppressive tumor microenvironment and restored immune responses, demonstrating potent synergistic anti-tumor effects *in vitro*.

Another enzyme-triggered system was developed by Gao et al., who constructed a multifunctional nanoplatform, dBET6@CFMPD, for BRD4 degradation and PDT-based treatment of breast cancer and its metastases [33]. This system employed a PEG-DSPE backbone modified with a matrix metalloproteinase-2 (MMP-2)-responsive peptide, self-assembled with the small-molecule PROTAC dBET6 and conjugated with the photosensitizer chlorin e6 (Ce6). It enabled tumor-specific activation and synergistic therapy. Results showed that dBET6@CFMPD significantly enhanced BRD4 degradation and c-Myc downregulation, while also inhibiting the upregulation of PD-L1 typically induced by PDT, thus augmenting immune therapeutic efficacy (Figs. 6(d) and 6(e)).

Additionally, Chen et al. proposed a novel Supra-PROTAC strategy, which relies on sulfatase-mediated peptide assembly to induce in situ nanofiber formation within cancer cells [17]. This is achieved through intracellular sulfatase-responsive assembly of sulfated peptides, which co-assemble with ligands targeting ubiquitin ligase VHL and Bcl-xL. The resulting pro-Supra-PROTACs undergo enzyme-responsive assembly into nanofibrous structures inside cancer cells that overexpress sulfatase. This assembly triggers the degradation of Bcl-xL and activates caspase-dependent apoptosis, selectively killing cancer cells. Rational optimization of ligand ratios improves the bioactivity of the pro-Supra-PROTACs, thereby improving their therapeutic efficacy. *In vivo* studies demonstrate that this approach enhances tumor accumulation, retention, and overall tumor growth inhibition, with excellent biosafety when co-administered with chemodrugs.

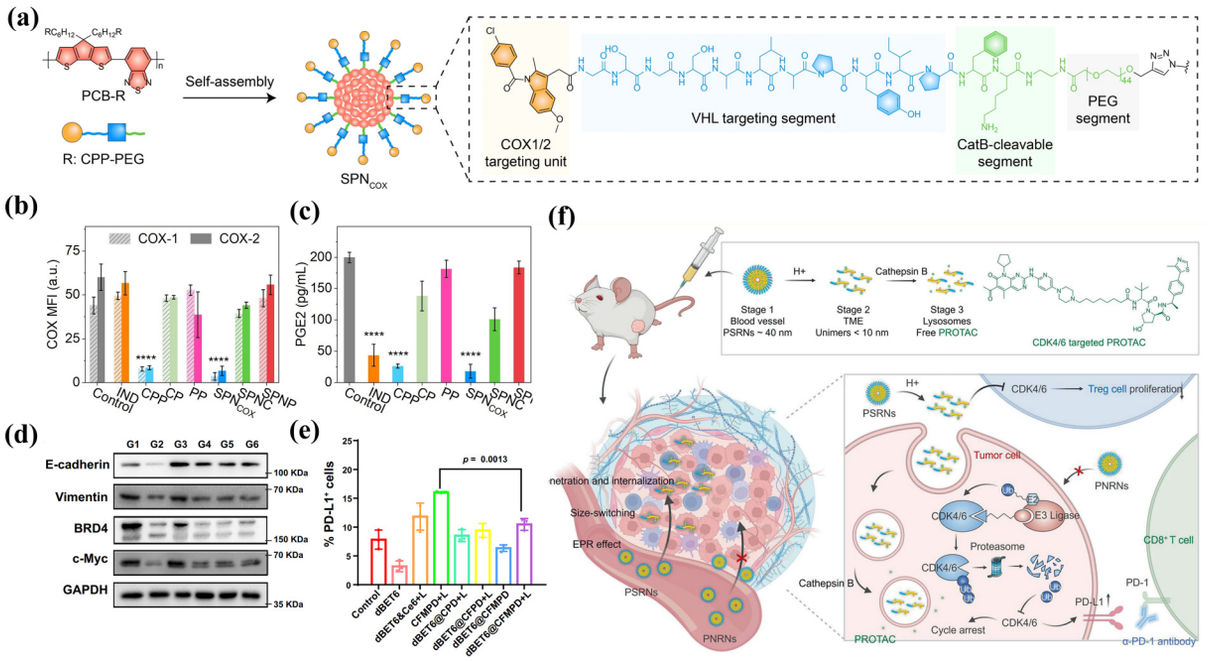

Fig. 6 (a) Synthesis and structure of SPN_{COX}. **(b)** Mean fluorescence intensity of 4T1 cells after incubation with different formulations. **(c)** The concentrtion of PGE2 in the supernatants of 4T1 treated with different formulations. Reproduced with permission from Ref. [32] © 2021 Wiley-VCH GmbH. **(d)** Western blot analysis of BRD4 inhibition and downregulation of endothelial-mesenchymal transition in 4T1 cells. **(e)** PD-L1 expression of 4T1 cells treated with different formulations. Reproduced from Ref. [33] © 2024 Tong, et al. **(f)** The structure of CDK4/6-targeted PROTAC and schematic illustration of the sequential responsive process of PSRNs after intravenous administration. Reproduced from Ref. [16] © 2024 Yang, et al.

Radio-triggered nano-PROTACs

X-rays can induce specific chemical reactions, such as the cleavage of diselenide bonds or other radiation-sensitive linkages, thereby enabling the controlled release of PROTACs [34, 35]. Compared to conventional chemical or enzymatic activation mechanisms, X-ray-triggered smart nano-PROTAC strategies offer superior spatiotemporal precision, ensuring that protein degradation occurs exclusively at the desired time and location. This characteristic is particularly advantageous for deep-seated tumors, as X-rays can penetrate tissues, allowing for precise modulation of drug activation within the tumor microenvironment.

Despite the potential advantages of radiation-triggered drug release, its application in PROTAC-based targeted protein degradation remains in its early stages. Li et al. pioneered the first radiotherapy-triggered PROTAC prodrug (RT-PROTAC), demonstrating precise control over protein degradation both *in vitro* and *in vivo* [34]. In this study, a radiation-responsive phenyl azide caging group was incorporated into the VHL ligand, rendering the molecule inactive under physiological conditions. Upon X-ray irradiation, the caging group was removed, resulting in the release of the active PROTAC. Experimental results confirmed that RT-PROTAC effectively promoted the degradation of BRD4 and BRD2, with Western blot analysis showing a D_{max} of 77.47%. *In vivo* studies further demonstrated that RT-PROTAC significantly inhibited tumor growth and exerted a synergistic antitumor effect when combined with radiotherapy.

While RT-PROTAC represents a breakthrough in radiation-triggered protein degradation, challenges remain, particularly concerning the stability of small-molecule PROTACs in circulation, which may lead to premature degradation. To address this issue, Sun et al. developed X-ray-responsive PROTAC nanomicelles (RCNprotac), leveraging self-assembled nanocarriers to enhance PROTAC stability and controlled release [35]. In this approach, the small-molecule PROTAC (MZ1) was covalently conjugated to hydrophilic PEG via a diselenide-containing carbon linker, resulting in the self-assembly of nanomicelles with an average diameter of (141.80 ± 5.66) nm. These nanomicelles remained inactive in circulation due to the masking of the hydroxyl group on the VHL ligand, thereby preventing premature target degradation. Upon X-ray irradiation, the diselenide bonds were cleaved, triggering the precise

release of MZ1, which subsequently induced BRD4 degradation, a key regulatory protein in tumor progression. *In vivo* studies confirmed that RCNprotac significantly enhanced radiosensitization and reduced tumor resistance to radiation therapy, highlighting its potential for precise tumor-targeted therapy.

Ultrasound-triggered nano-PROTACs

Ultrasound, a non-invasive and clinically established modality, offers unique advantages as an external trigger for controlled drug activation. Its deep-tissue penetration, precise spatial targeting, and minimal side effects make it an ideal candidate for activating therapeutic agents in a highly localized manner. Recent advancements in ultrasound-mediated drug delivery have paved the way for the development of ultrasound-activated smart nano-PROTACs, which exploit the precision of ultrasound for site-specific protein degradation [36–38]. By incorporating ultrasound-responsive elements into PROTAC designs, researchers can achieve targeted activation, minimizing systemic toxicity and enhancing therapeutic efficacy.

One notable example of this is the work by Li et al., who introduced a dual-programmable semiconducting polymer nano-PROTAC (SPN_{FeP}) for deep-tissue tumor therapy [39]. To achieve the dual programmable activation of PROTAC molecules in response to reactive oxygen species (ROS) generated by sonodynamic therapy (SDT) and the Fenton reaction, SPN_{FeP} was engineered. This system was constructed via nanoprecipitation of a semiconductor polymer, a nicotinamide phosphoribosyl transferase (NAMPT)-targeting PROTAC molecule, ferrocene, and a ROS-cleavable DSPE-thioketal (TK)-PEG conjugate. Upon ultrasound irradiation, the system generates singlet oxygen ($^1O_2$), while the ferroptosis inducer reacts with intratumoral hydrogen peroxide (H_2O_2) to produce hydroxyl radicals (·OH), effectively triggering ferroptosis and immunogenic cell death (ICD). This approach enables on-demand activation of PROTAC molecules, facilitating the targeted degradation of NAMPT to suppress the infiltration of myeloid-derived suppressor cells and enhance antitumor immunity. In preclinical mouse models, SPN_{FeP} demonstrated significant tumor inhibition in both subcutaneous and deep-tissue tumors (up to 2 cm). Yuan et al. presented an innovative ultrasound-activated PROTAC prodrug ($NP_{Ce6+PRO}$), which integrates Ce6-mediated SDT with the targeted degradation of BRD4 [40]. Upon ultrasound activation, this system generates ROS, inducing ICD and cleaving the TK linker to release active PROTAC molecules. This targeted degradation of BRD4 not only suppresses tumor growth but also mitigates the upregulation of PD-L1, commonly seen in SDT treatments, thus enhancing antitumor immune responses. In orthotopic pancreatic cancer mouse models, $NP_{Ce6+PRO}$ showed robust tumor inhibition and provided a spatiotemporally controlled therapeutic strategy with minimized off-target toxicity.

In addition to employing TK as a release-control mechanism, Li et al. combined PROTAC with ultrasound-targeted microbubble (MB) destruction technology and proposed an ultrasound-activated BRD4 nano-PROTAC [41]. PROTAC (ARV-825)-encapsulated microbubbles (ARV-MBs) ensured the initial silencing of the proteolytic activity of PROTAC. Following systemic administration, ARV-MBs preferentially accumulated in tumor tissues, where ultrasound irradiation triggered microbubble disruption, resulting in the localized release and enrichment of the PROTAC, thereby enhancing its therapeutic precision and efficacy. Both *in vitro* and *in vivo* experiments showed that ultrasound-triggered ARV-MBs promoted the ubiquitination and degradation of BRD4, effectively inhibiting tumor growth. This approach also enhanced tumor-specific accumulation of the PROTAC, while minimizing systemic toxicity.

MicroRNA-triggered nano-PROTACs

The development of nucleic acid-responsive smart nano-PROTACs has emerged as a cutting-edge approach in the field of targeted protein degradation, offering precise spatiotemporal control over protein degradation by exploiting nucleic acid triggers. This strategy aims to enhance therapeutic specificity and efficacy by utilizing nucleic acid-based regulatory elements.

Zhang et al. explored the application of dynamic DNA nanotechnology, specifically the hybridization chain reaction (HCR), in the design of nucleic acid-responsive nano-PROTACs [42]. They developed a DNA-encoded precursor PROTAC, termed miRiaTAC, which is selectively activated in response to specific microRNAs (miRNAs), enabling precise

regulation of target protein degradation. Upon recognition of target miRNA sequences, the HCR cascade is initiated, resulting in the assembly of the functional PROTAC molecule. A multifunctional NIR light-responsive nano-delivery system was developed by coating UCNPs with a mesoporous silica shell, followed by the efficient loading of the photosensitizer hypocrellin A (HA) into the mesoporous structure. Additionally, miaTAC was electrostatically adsorbed onto the surface. Upon 980 nm NIR irradiation, the UCNPs converted NIR light into blue light, activating HA to generate ROS. The ROS disrupted endo/lysosomal membranes, facilitating lysosomal escape and enhancing intracellular drug bioavailability.

Multi-stimuli-triggered nano-PROTACs

To further improve smart nano-PROTAC stability, tissue penetration, and controlled release in complex tumor microenvironments, researchers have developed multi-stimuli-triggered smart nano-PROTAC systems. These systems are engineered to respond to various tumor-specific hallmarks, such as acidic pH, redox gradients, ROS, and hypoxia, thus broadening their applicability and enhancing therapeutic synergy.

Zhang et al. developed a sequentially responsive CDK4/6-targeted nano-PROTAC system (PSRNs) designed for the precision treatment of colorectal cancer (Fig. 6(f)) [16]. This innovative platform uses a dual-responsive polymer-PROTAC conjugate, PEG-B-P (EPA-r-PROTAC), to achieve controlled drug release and efficient degradation of CDK4/6. The system integrates a pH-sensitive monomer and a CatB-cleavable monomer, enabling precise activation in the tumor microenvironment. By exploiting these dual stimuli, the platform enhances intracellular uptake and protein degradation efficiency, addressing key challenges in PROTAC delivery. In both *in vitro* and *in vivo* studies, PSRNs demonstrated superior tumor penetration and robust immunomodulatory effects, further highlighting their potential to improve therapeutic outcomes in colorectal cancer therapy.

Building further on multi-responsive strategies, Yu et al. designed POLY-PROTAC, an enzyme-, acid-, and reduction-sensitive nanoparticle constructed by covalently linking small-molecule PROTACs to an amphiphilic block copolymer backbone via bioorthogonal chemistry [43]. This nanoplatform is responsive to extracellular MMP-2, as well as intracellular acidic pH and reductive environments, enabling controlled release and enhanced tumor selectivity. *In vivo* studies using an MDA-MB-231 breast cancer model revealed a ~50% reduction in tumor volume and prolonged survival, with effective targeting of both tumor cells and cancer stem cells.

Xu et al. recently further introduced a regionally-restricted PROTAC nanoplatform that integrates both ROS-responsive and hypoxia-responsive prodrugs to precisely modulate BRD4 expression, thereby achieving comprehensive tumor suppression [44]. To develop a ROS-responsive PROTAC prodrug, ARV771-TK was synthesized by introducing a TK linker. The prodrug was subsequently copolymerized with an acid-responsive 2-(diisopropylamino)ethyl methacrylate (DPA) monomer via reversible addition-fragmentation chain transfer polymerization. Additionally, a separate polymer incorporating the photosensitizer pyropheophorbide a and DPA monomers was synthesized. Upon intravenous administration, the self-assembled smart nano-PROTAC nanoparticles exhibited selective tumor accumulation via the enhanced permeability and retention effect, offering a promising platform for stimuli-responsive cancer therapy. This platform can respond to multiple stimuli existing in the tumor microenvironment, including MMP-2, NTR, pH, and ROS, to significantly inhibit the progression of breast cancer and head and neck cancers.

Novel Ligand Design for Smart Nano-PROTAC

Nucleic acid-based ligands

As ligands, nucleic acids, such as aptamers, offer high specificity and strong affinity toward target proteins, making them ideal candidates for PROTAC development (Fig. 7). Compared to traditional small-molecule ligands, nucleic acid ligands provide the advantages of programmability, structural flexibility, and minimal off-target effects, thus enhancing therapeutic precision and reducing systemic toxicity.

Tang et al. reported a series of miRNA-based Lin28A-miRNA proteolysis-targeting chimeras (Lin28A-miRNA-PROTACs) designed to effciently degrade Lin28A through the UPS mechanism, resulting in upregulation of the demonstrated an

effective miRNA-based PROTAC strategy mature lethal-7 (let-7) family [45]. The linker length and type have a significant impact on Lin28A degradation efficiency. When pomalidomide was used as the E3 ubiquitin ligase ligand, most Lin28A-miRNA-PROTACs with carbon-based linkers exhibited higher efficiency in inducing Lin28A degradation. Additionally, the PEG linker demonstrated optimal suitability for targeting the full-length Lin28A protein. This study demonstrated an effective miRNA-based PROTAC strategy that degraded Lin28A and suppressed tumor growth, providing a highly promising therapeutic approach for miRNA-mediated cancer treatment. Liu et al. developed artificial long non-coding RNAs (alncRNAs) for targeted protein degradation by integrating RNA aptamers with sequences from the lncRNA HOTAIR to induce ubiquitination and degradation of oncogenic factors, such as c-MYC and EGFR [46]. This approach reduces malignant phenotypes, and shows high efficiency and adaptability. Guan et al. developed a threose nucleic acid (TNA)-DNA-based PROTAC targeting c-Myc for triple-negative breast cancer (TNBC) [47]. The TNA-E box-pomalidomide conjugate selectively degrades c-Myc/Max, inhibits TNBC cell proliferation and enhances tumor suppression when combined with palbociclib.

Zhao et al. further expanded the field with ProMyc, an aptamer-nano-PROTAC conjugate specifically designed to degrade the undruggable oncogene c-Myc [48]. Using the SELEX-derived aptamer MA9C1, conjugated to pomalidomide, ProMyc achieved potent c-Myc degradation and downstream transcriptional inhibition. A cyclized version, circPA1-ProMyc, incorporating an anti-PD-L1 aptamer, enhanced tumor targeting and therapeutic efficacy *in vivo*, providing a promising approach for targeting challenging oncogenic transcription factors.

Besides, G-quadruplexes and Z-DNA also exhibit distinctive binding properties that enable the selective degradation of target proteins. For example, a Z-DNA-based PROTAC (Z-PROTAC) was introduced by Wei et al. to degrade the RNA-editing enzyme ADAR1, a protein implicated in immune evasion in cancer [49]. By exploiting the unique binding affinity of Z-DNA to ADAR1, the system facilitated its recruitment to the VHL E3 ligase, resulting in efficient degradation. Z-PROTAC effectively suppressed tumor cell proliferation and migration in both *in vitro* and *in vivo* models while exhibiting minimal toxicity toward normal cells, underscoring the potential of DNA structural elements in PROTAC design. Another intriguing study reported by Peng et al. describes the development of a G-quadruplex RNA-based smart nano-PROTAC designed to degrade fragile X mental retardation protein (FMRP), a key regulator of mRNA stability and translation in cancer [50]. The G-quadruplex RNA structure enabled high-affinity binding to FMRP, facilitating its degradation via the VHL E3 ligase pathway. This approach modulated tumor immune responses by altering cytokine secretion and extracellular vesicle profiles, demonstrating synergistic effects when combined with immune checkpoint inhibitors *in vivo*.

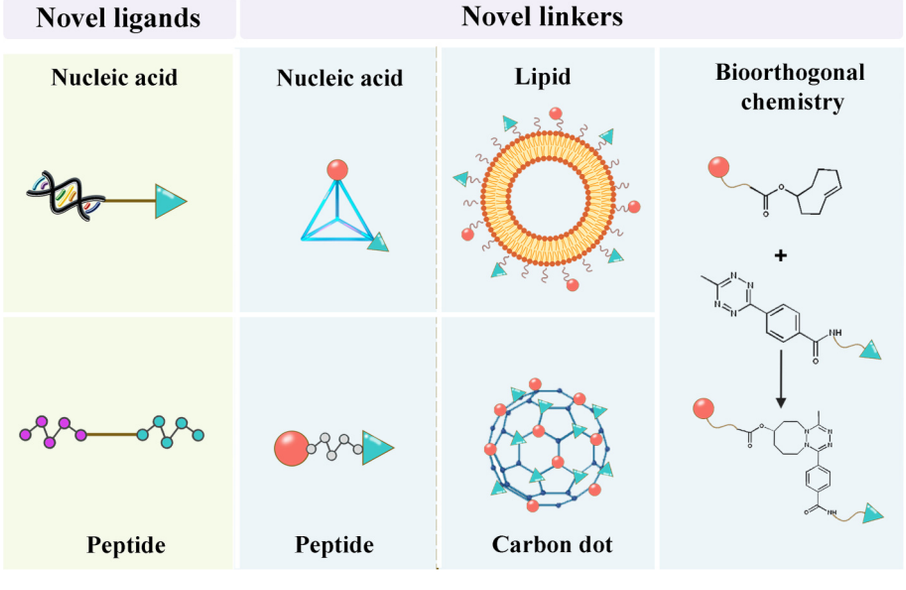

Fig. 7 Schematic diagram of the design of novel ligands and linker for smart nano-PROTACs.

Another pivotal development is a PROTAC based on chemically modified nucleic acids, reported by Wei et al. They designed a methyl-nucleotide-based PROTAC targeting MeCP2, an epigenetic regulator implicated in cancer progression [51]. By exploiting the high affinity of methylated cytosine for MeCP2, the study achieved effective degradation and modulation of apoptotic pathways, resulting in significant tumor suppression in preclinical models with minimal toxicity to normal tissues.

Peptide-based ligands

Peptide-based PROTACs offer a unique advantage in targeting protein surfaces that are traditionally considered undruggable by small molecules. Through strategic structural optimization, these peptide conjugates achieve enhanced cellular uptake and improved stability, extending the therapeutic potential of PROTAC technology. Their versatility enables applications across diverse fields, including oncology, neurodegenerative disorders, and immunotherapy, positioning peptide-based PROTACs as a promising avenue for next-generation targeted protein degradation strategies.

Building on the potential of self-assembled systems, Kim et al. introduced peptide-derived self-assembled smart nano-PROTAC (PT-NPs) for tumor-specific and sustained degradation of PD-L1 (Fig. 8(a)) [52]. PT-NPs, with an average size of 211.8 nm, effectively entered tumor cells via receptor-mediated endocytosis, facilitating PD-L1 degradation through the lysosomal and ubiquitin-proteasome pathways. In wild-type CT26 cells treated with PT-NP, PD-L1 expression levels continued to decline over 48 h, reaching a reduction of up to 95% (Fig. 8(b)). In colorectal tumor models, PT-NPs exhibited potent tumor suppression and elicited strong antitumor immune responses while maintaining favorable biocompatibility and low toxicity.

Novel Linker Design for Smart Nano-PROTAC

Nucleic acid-based linkers

In addition to serving as ligands, nucleic acids also play a crucial role in the design of linkers for PROTAC delivery [53]. DNA- and RNA-based nanostructures, including DNA origami and RNA nanoparticles, offer a highly programmable and structurally robust platform for precise PROTAC delivery and target protein degradation.

Ma et al. introduced a covalent DNA framework-based PROTAC (DbTAC) strategy, exploiting the programmability and structural rigidity of DNA tetrahedra to achieve precise spatial control over protein degradation (Fig. 9(a)) [54]. By employing DNA tetrahedra as templates, the study enabled the precise positioning of both the POI and the E3 ligase ligand, with tunable inter-ligand distances ranging from 8 Å to 57 Å. The results demonstrated that DbTACs with optimal linker lengths exhibited superior degradation efficiency and binding affinity, while the development of bispecific DbTACs (bis-DbTACs) enabled the simultaneous degradation of multiple targets with high subtype selectivity. Furthermore, DbTACs exhibited robust degradation

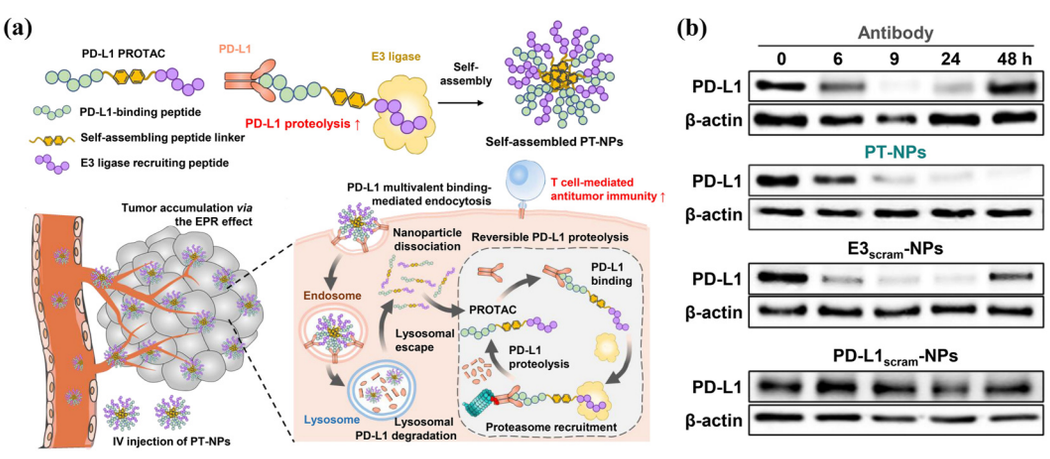

Fig. 8 (a) Schematic illustration of durable PD-L1 degradation by self-assembled peptide-derived PROTAC nanoparticles. **(b)** PD-L1 expression levels after treatment with different formulations in wild-type CT26 cells. Reproduced with permission from Ref. [52] © 2024 Wiley-VCH GmbH.

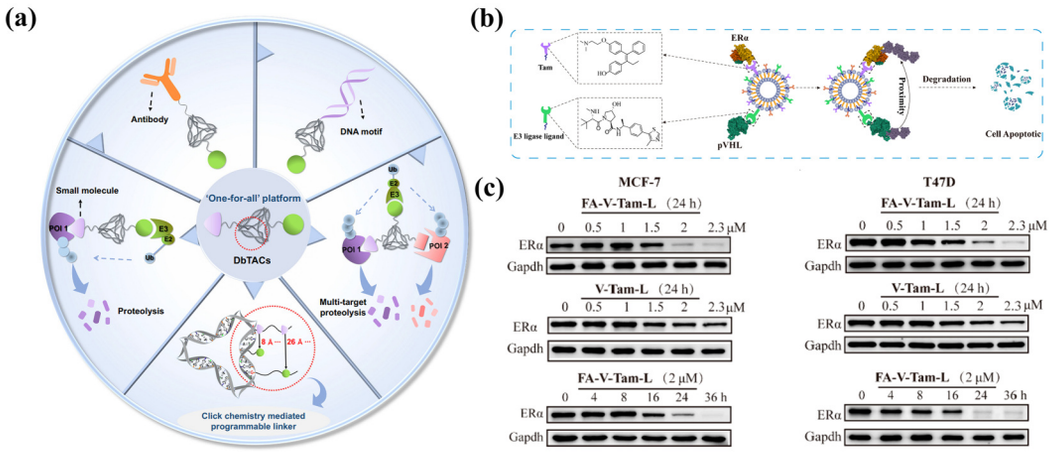

Fig. 9 (a) Schematic diagram of the DbTACs platform. Reproduced with permission from Ref. [54] © 2023 Zhou, et al. **(b)** Schematic diagram of LipoSM-PROTAC-mediated ERα degradation via the proteasome. **(c)** Western blot analysis of Erα degradation in MCF-7 cells treated with different formulations. Reproduced with permission from Ref. [56] © 2023 American Chemical Society.

capabilities across different cellular compartments, targeting both protein kinases and transcription factors, thereby offering a novel strategy for drug discovery and therapeutic intervention.

Extending upon this concept, Yang et al. developed multivalent DNA tetrahedron-based PROTACs (ASTD2-PRO) to enhance protein degradation efficiency and tumor-targeting specificity [55]. Using signal transducer and activator of transcription 3 (STAT3) as a model protein, ASTD2-PRO incorporated multiple functional modules within the DNA framework to achieve high-efficiency STAT3 degradation. Compared with conventional bivalent PROTACs, ASTD2-PRO exhibited significantly improved degradation efficiency and antitumor activity both *in vitro* and *in vivo*. In addition, ASTD2-PRO effectively suppressed tumor proliferation and migration by downregulating key downstream genes of STAT3, including VEGF, c-Myc, cyclin D1, and BCL-2, thereby inducing cell cycle arrest and apoptosis.

Lipid-based and carbon dot-based linkers

Lipid-based nanocarriers, in addition to DNA tetrahedra, have emerged as promising alternatives for PROTAC delivery, offering enhanced biocompatibility, membrane permeability, and controllable release properties. However, few studies have explored their potential as linkers for PROTACs. Recently, Yin et al. developed a liposome-based split-mix PROTAC system (LipoSM-PROTAC) for the targeted degradation of estrogen receptor α (ERα) (Fig. 9(b)) [56]. Functionalization of liposomal surfaces with folic acid enhanced tumor cell targeting, significantly improving drug efficacy and specificity compared to conventional peptide-based SM-PROTACs. Following treatment with FA-V-Tam-L, a dose-dependent degradation of ERα was observed, with nearly complete degradation at a concentration of 2 μmol/L (Fig. 9(c)). In contrast, the V-Tam-L group did not exhibit such significant degradation. This effect is likely attributable to the selective uptake of FA-V-Tam-L particles by FR(+) cells. Consistently, western blot analysis confirmed that ERα degradation in MCF-7 and T47D cells was time-dependent, reaching its maximum at 36 h.

Beyond liposomal systems, recent advances have explored the use of carbon dot (CD)-based platforms, which offer additional benefits such as superior stability, tunable surface chemistry, and enhanced intracellular trafficking. A CD-based PROTAC system, termed CDTACs, was introduced for the targeted degradation of PD-L1 in tumor cells by Wang et al., aiming to potentiate immunotherapy through activation of the STING signaling pathway [57]. By conjugating a PD-L1-targeting ligand and an E3 ubiquitin ligase ligand onto CDs, the system achieved enhanced PD-L1 degradation compared to conventional small-molecule PROTACs, exhibiting superior membrane protein degradation efficiency, tumor selectivity, and immune activation. Notably, the study revealed that fasting-mimicking diets further augmented cellular uptake of CDTACs and enhanced proteasomal activity, resulting in improved PD-L1 degradation. CDTACs exhibited potent antitumor activity in both CT26 and B16-F10 tumor

models, highlighting their potential as a promising platform for combination cancer immunotherapy.

Peptide-based linkers

Xu et al. reported the development of peptide nanofiber-based PROTACs utilizing β-sheet self-assembly and click chemistry to create multivalent complexes capable of recruiting multiple target proteins and E3 ligases [58]. Upon activation by elevated intracellular glutathione (GSH) levels, these assemblies exhibit enhanced binding affinity and form stable polynary complexes. The smart nano-PROTACs achieve potent and durable degradation of EGFR and AR *in vitro*, with efficiencies exceeding 95%. *In vivo*, the system demonstrates tumour-specific accumulation, robust antitumour efficacy, and minimal systemic toxicity in xenograft models. This platform offers a broadly applicable strategy to improve the therapeutic index of PROTACs by mitigating the "hook effect" and facilitating tumor-selective delivery via nanostructural precision.

Bioorthogonal chemistry-based linkers

Xu et al. introduced a novel strategy termed Nano-Click-formed PROTACs (Nano-CLIPTACs) for precise tumor-targeted protein degradation *in vivo* [59]. This approach exploits an inverse electron-demand Diels–Alder reaction between a trans-cyclooctene-tagged POI ligand (POI-TCO) and a tetrazine-modified pomalidomide derivative to assemble PROTACs in situ. To ensure tumor-specific localization, bioorthogonal CLIPTAC components were individually encapsulated within integrin $\alpha_v\beta_3$-engineered nanomaterials, enabling their spatiotemporal enrichment at the tumor site. These tumor-targeting nanomaterials synergize with the CLIPTAC system to establish the Nano-CLIPTAC platform, facilitating precise and efficient ALK degradation. Moreover, this in situ self-assembly PROTAC technology mitigates the intrinsic "hook effect" commonly associated with PROTACs, broadening its applicability across diverse biological settings.

Li et al. developed a ClickRNA-PROTAC system that enables selective and efficient degradation of POI within tumor cells [60]. This approach exploits mRNA transfection to express a fusion protein containing a covalent tag and an E3 ubiquitin ligase within live cells. The fusion protein is then functionalized through a dibenzylcyclooctyne-modified ligand, which facilitates its bioorthogonal conjugation with an azide-linked POI ligand, ultimately triggering POI ubiquitination and degradation. Furthermore, by integrating a tumor-specific mRNA-responsive translation regulation strategy based on A-to-I base editing at UAG stop codons, ClickRNA-PROTAC enables selective degradation of POI specifically within tumor cells, offering a precise and programmable approach to targeted protein degradation. This strategy enables efficient POI degradation while offering key advantages such as independence from endogenous E3 ligases, tumor-specific action, and molecular programmability. These features provide a promising new avenue for cancer therapy, allowing for precise and adaptable therapeutic interventions.

Conclusions

In the clinical settings, several PROTACs targeting proteins, such as AR, ER, BTK, BRAF V600E, and BCL6, have shown promising results in Phase I/II/III trials, highlighting their potential in the treatment of various cancers and neurodegenerative diseases. The ongoing research in this field continues to push the boundaries of targeted protein degradation, with a focus on improving specificity, controllability, and pharmacological properties. The development of smart nano-PROTACs has emerged as a transformative approach in targeted protein degradation, addressing key limitations of traditional PROTACs such as poor cell permeability, systemic toxicity, and off-target effects. By integrating nanotechnology and stimuli-responsive elements, these advanced systems enable precise spatiotemporal control of protein degradation, using endogenous or exogenous triggers, including light, enzymes, ultrasound, hypoxia, and microRNAs. Recent advances have demonstrated the potential of various stimulus-responsive smart nano-PROTACs, including photocaged, enzyme-triggered, ultrasound-activated, hypoxia-responsive, and microRNA-triggered systems. These innovations not only enhance the pharmacokinetic properties of PROTACs, but also offer new ways to overcome resistance mechanisms and enhance antitumor immunity. Additionally, the development of novel ligands and linkers, such as nucleic acid-based aptamers, peptides, and antibody conjugates, has expanded the scope of PROTAC applications, enabling the degradation of previously undruggable targets and improving tumor selectivity.

Stimuli-responsive smart nano-PROTACs

represent a next-generation strategy for precision-targeted protein degradation. Despite their therapeutic promise, several translational hurdles remain. Limited tissue penetration and heterogeneous intratumoral distribution hinder effective delivery, while the variability and limited depth of endogenous or exogenous triggers pose challenges for on-demand activation. Concerns about the long-term toxicity, immunogenicity, and metabolic fate of synthetic nanomaterials further complicate their clinical development [61]. The future development of smart nano-PROTACs is expected to further enhance their precision and efficacy by addressing key challenges such as tissue penetration, systemic toxicity, and resistance mechanisms. Ongoing innovations in nanotechnology and smart drug design are likely to lead to the development of multi-stimuli-responsive systems that can adapt to complex physiological environments, thereby maximizing therapeutic outcomes while minimizing side effects. Additionally, the integration of advanced imaging techniques will provide real-time monitoring of drug release and therapeutic efficacy, facilitating more informed clinical decision-making [62–64].

The combination of smart nano-PROTACs with other therapeutic modalities, such as immunotherapy, photodynamic therapy, and radiotherapy, holds great promise for overcoming the limitations of monotherapy and improving patient outcomes. This multimodal approach is expected to yield synergistic effects, enhancing antitumor immunity and overcoming resistance mechanisms [65]. Furthermore, the exploration of novel ligands and linkers, as well as the optimization of existing designs, will continue to drive the evolution of next-generation PROTACs, making them more versatile and effective in treating a broader range of diseases.

In conclusion, the field of smart nano-PROTACs is poised for significant breakthroughs, with the potential to revolutionize targeted protein degradation and transform the landscape of cancer treatment. As research progresses, continued collaboration between academia, industry, and clinical practice will be critical to translating these innovative strategies into effective therapies for patients in need.

CRediT Author Statement

Zhimin Weng: conceptualization, writing original manuscript, and editing; **Jiaojiao Yu, Yuanrong Liao, and Yuanyuan Zhang**: writing–review and editing. **Changmai Chen and Wei Chen**: conceptualization, investigation, project administration, supervision, writing–review, and editing.

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Conflict of Interests

The authors have no conflicts of interest to declare.

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