Acta Pharmaceutica Sinica B 2026;16(8):4854−4875

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

REVIEW

A destination-driven framework for nanoparticle-enabled targeted protein degradation

Yazhen Wang[a,b,c,†], Xue Xia[b,†], Shengwei Xie[a,c], Fan Tong[b], Wen Liu[a,c,*], Huile Gao[b,*]

[a]*State Key Laboratory of Vaccines for Infectious Diseases, Xiang An Biomedicine Laboratory, School of Pharmaceutical Sciences, Xiamen University, Xiamen 361102, China*
[b]*Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry and Sichuan Province, West China School of Pharmacy, Sichuan University, Chengdu 610041, China*
[c]*Fujian Provincial Key Laboratory of Innovative Drug Target Research, School of Pharmaceutical Sciences, Xiamen University, Xiamen 361102, China*

Received 10 January 2026; received in revised form 27 February 2026; accepted 13 March 2026

KEY WORDS

Drug delivery system;
Nanoplatform;
Targeted protein degradation (TPD);
Proteostasis;
Lysosomal degradation;
Proteasomal degradation;
Intracellular protein degradation;
Extracellular protein degradation

Abstract Targeted protein degradation (TPD) offers a revolutionary paradigm to eliminate disease-driving proteins. Given the distinct technical requirements and challenges associated with degrading intracellular *versus* extracellular proteins, we classify existing TPD strategies based on subcellular localization into two categories: intracellular TPD (iTPD), which targets proteins within the cytoplasm and nucleus, and extracellular TPD (eTPD), which focuses on membrane-bound and secreted proteins. This destination-based framework facilitates precise technology selection and rational design by aligning methods with the biological context of their targets. However, the clinical translation of TPD remains constrained by a significant "delivery gap". Current nanotechnological approaches are often discussed monolithically, despite the fundamentally distinct delivery requirements between iTPD and eTPD. For iTPD, the primary nanocarrier role is to confer fundamental drug-like properties to overcome systemic pharmacokinetic hurdles. Conversely, for eTPD, the nanoplatform's chief function is to engineer cellular engagement, enhance internalization, and orchestrate correct intracellular trafficking to the lysosome. This review will dissect the distinct challenges inherent to each "geographic" space and detail the tailored

*Corresponding authors.
E-mail addresses: w2liu@xmu.edu.cn (Wen Liu), gaohuile@scu.edu.cn, gaohuilescu@163.com (Huile Gao).
[†]These authors made equal contributions to this work.
Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2026.05.009

nano-playbooks being developed to address them. We will further explore the convergence of these two worlds and the emergence of nanoparticles as intrinsic degraders. Ultimately, we argue that a location-aware design philosophy is essential for unlocking the full therapeutic potential of TPD.

1. Introduction

The precise regulation of protein synthesis and degradation is crucial for maintaining the proper functioning of organism[1−5]. When protein overexpression or hyperactivation occurs within the organism, various diseases ensue. The selective inhibition or degradation of pathogenic proteins will contribute to the disease treatment. Traditional small-molecule inhibitors and antibodies function by specifically binding to the active sites of target proteins, thereby preventing substrates from accessing the catalytic/active sites and inhibiting protein activity[6−11]. However, this "occupancy-driven" pharmacological paradigm between small-molecule inhibitors or antibodies and their target proteins typically requires sustained high drug concentrations to maintain efficacy. This not only elevates the risk of drug-induced mutations at the target site but may also contribute to reduced selectivity, resulting in off-target adverse effects[12−18]. Additionally, the majority of pathogenic proteins (80%−85%) lack well-defined pockets, making it difficult for small molecules or antibody drugs to bind and exert their effects. Therefore, there is an urgent need for new technologies to address the challenges faced by small-molecules and antibodies.

Targeted Protein Degradation (TPD) is an emerging therapeutic technology that has rapidly developed in recent years for modulating protein function. By leveraging the protein degradation systems of the cell self, such as the ubiquitin−proteasome system (UPS) and lysosomal degradation pathways, TPD efficiently degrades pathogenic proteins, demonstrating significant potential for application in disease treatment[19,20]. TPD compounds typically consist of three core structural domains: a ligand that recognizes the protein of interest (POI), an effector molecule that recruits the degradation machinery (such as the proteasome or lysosome), and a linker that connects the aforementioned two components. This structural design enables the effective tagging or delivery of the POI to the degradation pathway, thereby facilitating its efficient and selective elimination. In contrast to the "occupancy-driven" mode of small-molecule inhibitors, the "event-driven" mode of targeted protein degraders requires only transient binding to POI to guide it into the lysosome or proteasome for degradation[21]. This mode effectively overcomes the limitations of traditional "undruggable targets", thereby expanding the target options for the treatment of diverse diseases[22]. The proteolysis-targeting chimeras (PROTACs), which leverages the UPS to achieve TPD, represents the pioneering concept in this field[23,24]. In parallel, several lysosomal pathway-based degradation strategies have recently been developed. These include approaches that exploit the endo-lysosomal pathway-such as including lysosome-targeting chimeras (LYTACs)[25], antibody-based PROTACs (AbTACs)[26], and cytokine-targeting chimeras (KineTACs)[27]as well as those that operate through the autophagosome−lysosome pathway, including AUtophagy-TArgeting Chimeras (AUTACs)[28], AUTOphagy-TArgeting Chimeras (AUTOTACs)[29], and autophagosome-tethering compounds (ATTECs)[30−32]. Crucially, given that the subcellular localization of a target protein critically influences the selection of an appropriate degradative pathway and the design of the corresponding technology, these strategies are logically classified into two categories: intracellular TPD (iTPD) for targets within the cytoplasm and nucleus, and extracellular TPD (eTPD) for membrane-bound and secreted proteins. This framework, elaborated in subsequent sections, underscores the tailored approach required for different protein locales. Overall, these advancements have significantly enriched the toolkit for protein degradation research and provided innovative approaches for developing highly effective and safe therapeutic strategies.

The transition from target inhibition-based strategies to target degradation and disruption-based approaches, while demonstrating significant potential in disease treatment, is accompanied by numerous unknown risks and challenges. The molecular architecture required for this function—typically a large, polar, and flexible structure—introduces a cascade of formidable drug development hurdles[33]. These molecules almost universally exhibit poor ADME properties, including low solubility and membrane permeability. Mechanistically, their reliance on forming a ternary complex gives rise to the concentration-dependent hook effect, while their dependence on effector proteins, which may not be disease-specific, creates a substantial risk of off-target toxicity. Furthermore, each class of degrader faces unique trafficking challenges: iTPDs such as PROTACs require efficient escape from the endosome to reach the cytosol, while eTPDs such as LYTACs must overcome the avidity imperative and navigate the endo-lysosomal network to ensure lysosomal delivery. Confronting this multi-layered problem space requires a solution that moves beyond medicinal chemistry. Nano-drug delivery systems (NDDSs) have emerged as a particularly powerful and versatile strategy to overcome these intrinsic liabilities. By encapsulating the TPD molecule[34,35], a nanocarrier can immediately rectify its poor pharmacokinetic profile, shielding it from degradation and improving its solubility. The nanoparticle surface acts as a programmable interface that can be decorated with targeting ligands to enhance tissue specificity or engineered with responsive moieties that trigger payload release only in the presence of pathological cues like pH or redox potential. Furthermore, the physical properties of the nanocarrier itself can be leveraged to solve mechanism-specific challenges. The capacity for controlled, sustained release provides a direct antidote to the hook effect. For eTPDs, the engineered multivalency of a nano-scaffold can overcome avidity limitations, while the nanoparticle's own intrinsic endocytic properties can be exploited to drive internalization and lysosomal trafficking. Therefore, the rational design of NDDSs represents a highly promising and multifaceted strategy, offering a means not only to solve the fundamental delivery problems of TPDs but also to master their unique mechanistic hurdles, ultimately enhancing both their safety and efficacy.

In this review, we summarize the novel TPD strategies and recent advancements that have emerged in recent years. These developments offer a diverse range of targeted degradation strategies for disease treatment, providing new therapeutic opportunities for conditions that were previously challenging to address. Additionally, we highlight the progress and future prospects of nano-TPD delivery systems in addressing the inherent limitations of TPD-based drugs. Finally, we delineate ongoing challenges and opportunities for clinical translation and provide our insights into the future trajectory of TPD in disease treatment.

2. Targeted protein degradation strategies

The homeostasis of protein balance, characterized by the precise regulation of protein synthesis and degradation, is essential for maintaining the normal physiological functions of cells and organisms[36−38]. In eukaryotic cells, damaged proteins or organelles can be cleared through proteasomal and the lysosomal pathways[39]. The lysosomal pathway further consists of two distinct but complementary mechanisms—the autophagy−lysosomal pathway and the endosomal−lysosomal pathway. These two pathways operate independently yet are functionally interconnected, working synergistically maintain intracellular homeostasis.

Generally, the UPS serves as a major intracellular pathway for the degradation of short-lived and misfolded proteins[40]. The ubiquitination cascade involves ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin ligase (E3). Initially, E1 activates ubiquitin in the formation of an ATP-dependent manner, forming a thioester bond at its C-terminal glycine. The activated ubiquitin is then transferred to E2 *via* a thioester exchange reaction. Subsequently, the E2−ubiquitin complex associates with E3, which acts as a substrate-specific recognition factor. E3 specifically identifies the POI and forms a ternary complex (E3−E2−ubiquitin−POI), precisely guiding the transfer of ubiquitin from E2 to a specific lysine residue on the substrate protein (Fig. 1). Through the cascade of polyubiquitination, the substrate protein is marked by a K48-linked ubiquitin chain, which is subsequently recognized by the 26S proteasome, leading to the ATP-dependent hydrolysis of the substrate protein.

In contrast, the lysosomal system constitutes a versatile intracellular degradation machinery capable of processing not only intracellular proteins but also extracellular and membrane-associated proteins. This pathway mediates the clearance of long-lived proteins, insoluble aggregates, organelles, macromolecular complexes, and pathogens through three primary mechanisms: endocytosis, phagocytosis, and autophagy[41,42]. Endocytosis facilitates the internalization and degradation of extracellular and membrane proteins[43], while phagocytosis, a specialized form of endocytosis predominantly performed by immune cells, engulfs large particulates such as microbes, apoptotic cells, and foreign debris[44]. Both mechanisms are critical for the turnover of extracellular and membrane-bound proteins. Autophagy, on the other hand, targets intracellular components for lysosomal degradation. Cytoplasmic cargoes such as protein aggregates, damaged organelles, and intracellular pathogens are sequestered into autophagosomes, which subsequently fuse with lysosomes for hydrolytic breakdown[45]. Thus, the lysosomal pathway serves a dual role: it eliminates extracellular and membrane proteins through endocytic and phagocytic routes, while concurrently degrading intracellular substrates *via* autophagy (Fig. 1). These degradation mechanisms are not only essential for sustaining normal metabolic activities and structural integrity of the cell but also play a critical role in cellular stress responses, anti-pathogen defense, and the regulation of cellular homeostasis.

In recent years, advances in our understanding of the ubiquitin−proteasome and lysosomal degradation pathways have spurred the development of various TPD technologies, demonstrating considerable therapeutic potential in areas such as oncology[46−50], neurodegenerative diseases[51], and autoimmune disorders[52]. Given that the subcellular localization of a target protein dictates the choice of degradative pathway (*e.g.*, proteasome *vs.* lysosome) and the requisite technology design, it is both rational and practical to categorize TPD strategies into two classes: iTPD, which targets proteins within the cell, and eTPD, which focuses on membrane-bound and extracellular proteins. iTPD strategies primarily leverage the UPS or the autophagy−lysosomal pathway, with representative examples including PROTACs, molecular glues, and AUTACs. In contrast, eTPD strategies predominantly operate through the endosomal−lysosomal pathway. This route can engage both soluble and membrane-bound targets, typically by recognizing their extracellular domains or the surface of extracellular soluble protein. Antibodies, peptide ligands or

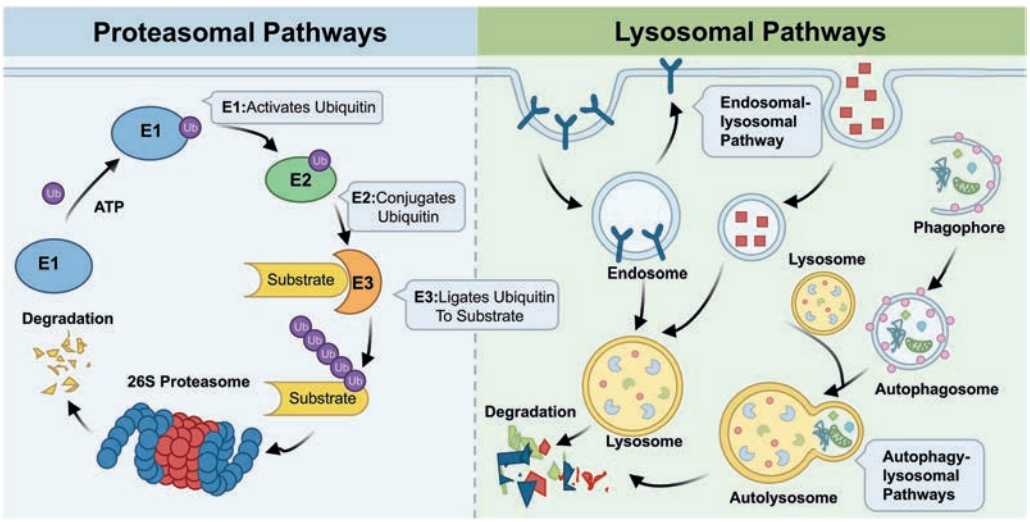

Figure 1 The process of protein degradation by the proteasomal pathways and lysosomal pathways.

small molecules that bind these accessible regions therefore serve as targeting moieties in eTPD systems, as illustrated by LYTACs. To clarify the mechanisms and subcellular specificity of each degradation strategy, the following sections will elaborate on three major pathways: iTPD mediated by the proteasomal pathway, iTPD mediated by the autophagy−lysosomal pathway, and eTPD mediated by the endosomal−lysosomal pathway. Thus, by elucidating the distinct mechanisms of action, this strategic categorization enables a systematic expansion of the druggable proteome, from intracellular oncoproteins to extracellular aggregates, thereby propelling the development of new treatments for various diseases.

2.1. *iTPD mediated by the proteasomal pathway*

Under the framework of iTPD, UPS plays a central role in degrading intracellular soluble proteins—such as kinases, nuclear receptors, and transcription factors. Among the various strategies developed to harness this pathway, PROTACs and molecular glues represent the most mature and extensively studied approaches, and will form the core focus of our discussion (Fig. 2).

2.1.1. *PROTACs*

As a pioneering and the most established technology in the field of TPD, PROTACs also represents the most mature platform within the category of iTPD. PROTACs are heterobifunctional molecule degraders composed of three components: a ligand for the POI, a ligand for an E3 ubiquitin ligase, and a linker that connects the two ligands. Through this structural design, PROTACs facilitate the proximity of the target protein and the E3 ubiquitin ligase, leading to the formation of a ternary complex (POI−PROTAC−E3). This complex induces polyubiquitination of the POI, followed by its degradation *via* the proteasome-mediated pathway. Notably, PROTACs function in a sub-stoichiometric and catalytic manner: upon the completion of each degradation cycle, the PROTACs are released from the ubiquitinated target protein and remains free to initiate subsequent rounds of degradation, thereby enabling efficient, reusable target elimination while minimizing potential off-target effects and reducing toxicity risks.

In 2001, Crews et al.[23] pioneered the design of a bifunctional molecule by linking a peptide targeting the E3 ubiquitin ligase β-transducin repeat-containing protein (β-TRCP) with a peptide targeting methionine aminopeptidase-2 (MetAp-2). This innovative approach successfully facilitated the degradation of MetAp-2 *via* the UPS, thereby demonstrating the feasibility of the concept. However, due to the poor cell permeability of peptides, this strategy remained confined to foundational research and was not further developed for broader applications. Till 2008, they continue reported the first small molecule PROTAC. They designed a PROTAC molecule consisting of nutlin-3a and an enzalutamide derivative connected by a polyethylene glycol (PEG) linker. Nutlin-3a targeted murine double minute 2

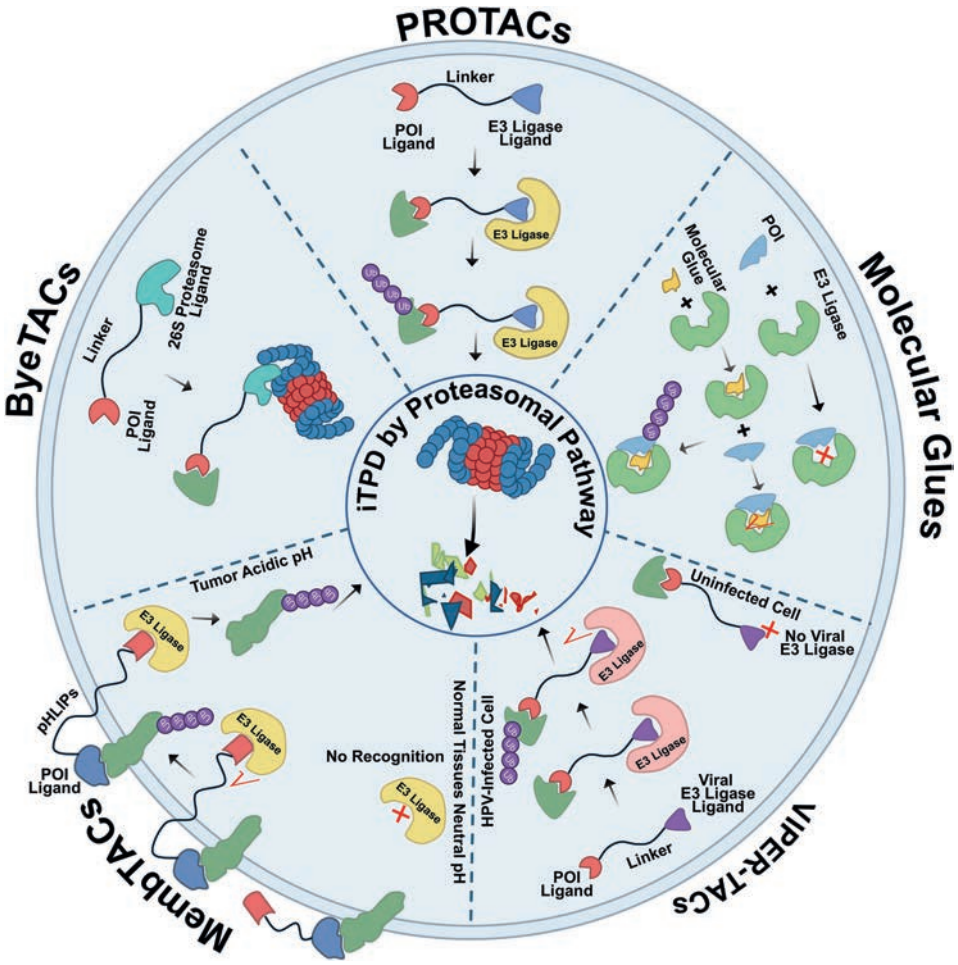

Figure 2 Various strategies for iTPDs mediated by the proteasomal pathway.

(MDM2), an E3 ligase, while the enzalutamide derivative targeted the androgen receptor (AR). Experimental results demonstrated that this molecule not only successfully degraded AR but also significantly inhibited the growth of prostate cancer cells[24]. Compared to peptide PROTACs, small molecule PROTACs exhibited superior cellular permeability and enhanced drug-like properties, rendering them more suitable for therapeutic development[53]. As a result, PROTACs entered a period of rapid progress. On one hand, a variety of other E3 ligases, including the von Hippel-Lindau tumor suppressor (VHL), Cereblon (CRBN), and inhibitor of apoptosis proteins (IAPs), were incorporated into PROTAC development, significantly enhancing its flexibility. The availability of diverse ligand structures also provided a broader range of options for structural optimization. On the other hand, PROTAC molecules successfully targeted and degraded multiple therapeutic proteins, including epidermal growth factor receptor (EGFR), Bruton's tyrosine kinase (BTK), bromodomain-containing protein 4 (BRD4), signal transducer and activator of transcription 6 (STAT6), and microtubule-associated protein tau (Tau), demonstrating substantial potential in cancer therapy, neurodegenerative diseases[54], and autoimmune disorders. In 2019, the PROTAC molecules ARV-471, targeting the ER, and ARV-110, targeting the AR, advanced into clinical trials, marking a significant milestone in the transition of PROTAC technology from laboratory research to clinical application[55,56]. And in 2025, ARV-471 formally submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for the treatment of patients with ESR1-mutated, $ER^+/HER2^-$ advanced or metastatic breast cancer. These advancements not only further validated the feasibility and efficacy of PROTACs in drug development but also laid a solid foundation for the future development of additional PROTACs-based therapeutics.

2.1.2. *Molecular glues*

Molecular glues are monovalent molecules capable of inducing protein−protein interactions between the POI and the E3 ubiquitin ligase, thereby facilitating the formation of a ternary complex. And this interaction triggers the polyubiquitination of the POI, leading to its efficient degradation *via* the proteasome pathway. The concept of molecular glues was first proposed in 1990, with the immunosuppressants cyclosporine A (CsA) and tacrolimus (FK506) being the earliest identified examples[57]. Although CsA and FK506 bound to distinct primary receptors, cyclophilin and FK506-binding protein (FKBP), respectively, they both formed ternary complexes with calcineurin. Specifically, CsA bound to cyclophilin to form the cyclophilin−CsA−calcineurin complex, while FK506 bound to FKBP to form the FKBP−FK506−calcineurin complex. These complexes mediated the immunosuppressive effects, whereas free cyclophilin and FKBP cannot interact with calcineurin[57]. Subsequent structural biology studies elucidated the detailed mechanisms of these molecular glues, confirming their ability to directly mediate protein−protein interactions, form ternary complexes, and inhibited the function of target proteins[58,59]. Since the identification of the first molecular glue in 2010, research in this filed had made significant breakthroughs in recent years. Thalidomide, lenalidomide, and pomalidomide functioned by inducing the formation of ternary complexes between the E3 ligase CRBN and target proteins, including transcription factor substrates such as IKZF1, IKZF3, and CD1α[60−62]. This interaction triggered polyubiquitination and subsequent degradation of the target proteins, demonstrating remarkable therapeutic efficacy in various hematologic malignancies, and had been approved by the U.S. FDA for the treatment of multiple myeloma. And anticancer arylsulfonamide compounds, including indisulam and E7820, bound to the E3 ubiquitin ligase DCAF15, inducing its interaction with the RNA-binding protein RBM39[63,64]. This led to the ubiquitination and degradation of RBM39, thereby exerting antitumor activity. Additionally, newly identified targets such as GSPT1[65−67], BRD4[68], and CDK12/13[69] are gradually demonstrating significant therapeutic potential in areas including solid tumors and autoimmune diseases.

Compared to the heterobifunctional degraders of PROTACs, molecular glues offer a series of unique advantages. First, molecular glues have a lower molecular weight, which means better cell permeability. Second, the chemical structure of molecular glues is simpler, which not only reduces the complexity of synthesis but also enhances their stability both *in vitro* and *in vivo*, facilitating drug development. Thirdly, molecular glues exhibit higher druggability, making them easier to formulate into various drug forms such as oral or injectable, which highlights their significant clinical advantages in disease treatment[70]. Despite the numerous advantages of molecular glues, their discovery process currently lacks systematic and rational design strategies, which significantly limits the development efficiency and clinical application breadth of novel molecular glue degraders. Additionally, traditional drug discovery methods often struggle to systematically screen and design molecular glues that effectively induce protein−protein interactions, further constraining the development of these drugs. With the advancement of future design strategies, it is anticipated that molecular glues will garner increased attention from both academia and the pharmaceutical industry.

2.1.3. *Others*

In addition to PROTACs and molecular glues, several novel TPD strategies harnessing the UPS have emerged, such as Viral E3 Pan-Essential Removing TACs (VIPER-TACs) technology[71], Bypassing E-Ligase-Targeting Chimeras (ByeTACs) technology[72] and membrane-bounded intracellular E3 ubiquitin ligase-targeting chimeras (MembTACs)[73]. Mangano et al.[71] developed the VIPER-TACs technology, which leveraged the viral E3 ligase vE3 (also known as E6) from human papillomavirus (HPV) to achieve selective protein degradation. The VIPER-TAC molecule consists of three components: a small-molecule ligand for vE3, a linker, and a ligand for the target protein. In uninfected cells, VIPER-TAC can bind to the target protein but cannot initiate degradation due to the absence of vE3. However, in HPV-infected cells, vE3 is expressed, enabling VIPER-TAC to form a ternary complex comprising the viral enzyme, the target protein, and the degradation molecule, thereby triggering the ubiquitination process. Ultimately, the critical protein is degraded by the proteasome, leading to the death of infected cells due to the loss of essential functions. The key advantage of VIPER-TACs lies in their exceptional selectivity, as degradation is initiated only in virus-infected cells, making them particularly suitable for treating HPV-positive cancers, such as certain cervical and head-and-neck cancers. Compared to chemotherapy or targeted inhibitors, VIPER-TACs enable precise elimination of virus-infected cells, minimize damage to normal tissues, and effectively suppress tumor core dependency proteins, significantly enhancing antitumor efficacy. In addition, the ByeTACs technology enables the direct delivery of target proteins into the proteasome for degradation[72]. This technology consists of three components: a small-

molecule ligand that binds to Rpn13, a recognition subunit of the 26S proteasome; a linker; and a small-molecule ligand that binds to POI. Upon the formation of the ternary complex, the target protein is "pulled" into the proteasome and degraded without the need for ubiquitin tagging. The unique advantages of the ByeTAC platform lie in its independence from E3 ligases, which simplifies molecular design, and its ability to achieve faster, more direct, and potentially more efficient protein degradation without ubiquitin labeling. Furthermore, this technology is particularly suitable for disease contexts characterized by E3 ligase deficiency, such as cancer and neurodegenerative disorders. Its compact structure and strong druggability, with smaller and more stable molecules, not only facilitate oral administration but also enhance tissue penetration, demonstrating broad therapeutic potential. And MembTACs utilize pH-low insertion peptides (pHLIPs) to recruit intracellular E3 ubiquitin ligases, such as CRBN, to the inner cell membrane within the acidic tumor microenvironment[73]. Simultaneously, the N-terminal recognition domain binds to target membrane proteins, enabling their targeted degradation. This approach offers several advantages, including low cost, straightforward synthesis, and broad applicability. Notably, MembTACs do not rely on cellular permeability, thereby circumventing issues related to endocytosis efficiency. These features highlight the potential of MembTACs as a versatile and efficient tool for membrane protein degradation in diverse biological contexts. Overall, these emerging technologies not only expand the application scope of protein degradation therapies but also provide innovative solutions to the limitations of traditional approaches, such as insufficient selectivity and dependence on E3 ligases, demonstrating broad prospects for clinical application.

2.2. *iTPD mediated by the autophagy−lysosomal pathway*

Under the framework of iTPD mediated by the autophagy−lysosomal pathway, the autophagy−lysosome system serves as a critical mechanism for degrading a broad range of intracellular targets—including aggregated proteins, lipid droplets, and damaged organelles. Among the key strategies leveraging this pathway, ATTECs, AUTACs, AUTOTACs, and chaperone-mediated autophagy (CMA)-based degrader have emerged as promising approaches capable of targeting such structurally diverse and pathologically relevant biomolecules, and will form the core focus of our discussion (Fig. 3)[74,75].

2.2.1. *AUTACs*

AUTACs stands as the first-in-class compound specifically engineered to mediate iTPD through the autophagy−lysosome pathway. It is based on the innate autophagic clearance organism of group A streptococcus (GAS)[76,77]. The structure of AUTACs consist of three main components: a ligand targeting POI, a linker, and a guanine derivative (GD) degradation tag. In the degradation process, the POI ligand binds specifically to the POI, while the GD component triggers *S*-guanosylation modification. This modification leads to K63-linked polyubiquitination, which recruits autophagosomes for subsequent lysosomal degradation. Arimoto et al.[28] pioneered the conjugation of GD tag to target protein-binding moieties, successfully degrading a range of proteins, including methionine aminopeptidase 2, FK506-binding protein, and bromodomain and extra-terminal domain (BET) family proteins. Moreover, AUTACs can degrade larger organelles, such as mitochondria. Takahashi et al.[78] developed AUTAC4, which utilizes a 2-phenylindole derivative as a mitochondria-targeting ligand. This derivative specifically binds to the translocase of the outer mitochondrial membrane, enabling precise organelle localization. Experimental results revealed that AUTAC4 treatment reduces the number of fragmented and damaged mitochondria, mitigates carbonyl cyanide *m*-chlorophenylhydrazone (CCCP)-induced mitochondrial apoptosis and loss of mitochondrial membrane potential, and maintains cellular ATP levels. These results highlight the versatile potential of AUTACs, paving the way for its application in diverse areas, including the degradation of protein aggregates.

2.2.2. *AUTOTACs*

AUTOTACs represent another major class of iTPD molecules, designed to specifically eliminate misfolded proteins *via* the autophagy−lysosomal pathway[29]. AUTOTAC is also a heterobifunctional molecule, consisting of a p62 ligand, a POI ligand, and a linker connecting these two components. The p62 protein contains domains that recognize and bind polyubiquitin chains and can interact with LC3 on the autophagosome membrane[79,80], serving as a bridge between polyubiquitinated proteins and autophagosomes. During autophagy, p62 recognizes and binds ubiquitinated proteins, delivering them to LC3 on the autophagosome membrane. This process facilitates the encapsulation of these proteins into autophagosomes, ultimately leading to their transport to lysosomes for degradation. By linking a p62 ligand to AR or ER, Ji et al.[29] achieved the degradation of AR and ER *via* the autophagy pathway, effectively suppressing their downstream signaling pathways. This strategy demonstrates significant potential in treating hormone-dependent cancers, such as prostate and breast cancer. Additionally, AUTOTAC has been shown to mediate the targeted degradation of tau protein aggregates, further expanding its therapeutic potential for various diseases[29]. Importantly, since AUTOTAC induces degradation through the direct interaction between p62 and LC3, it does not rely on specific linker lengths or the ubiquitination process of target proteins. This feature enhances its flexibility and broad applicability in disease treatment.

2.2.3. *ATTECs*

In 2019, the ATTECs was developed as a pioneering iTPD strategy, enabling selective elimination of pathogenic proteins through the autophagy−lysosome pathway[30,81]. During autophagy initiation, the LC3 protein plays a critical role by facilitating the formation of autophagic vesicles, which encapsulate POIs to form autophagosomes[81]. These autophagosomes are then transported to lysosomes, where they fuse to form autolysosomes, ultimately leading to protein degradation. Given the close association between autophagy and the LC3 protein, Li et al.[30] designed a compound capable of simultaneously recognizing the POI and LC3. Specifically, through high-throughput screening, they identified an ATTEC that specifically binds to LC3 and the pathogenic protein mHTT, which is implicated in Huntington's disease, then inducing the pathogenic protein into autophagosomes for degradation. By bypassing the ubiquitination process, ATTECs functions more like a molecular glue, directly binding to both POI and the essential autophagosome protein LC3, thereby triggering the degradation of the target protein. Additionally, it exhibits several advantages, including low molecular weight, a direct targeted degradation mechanism, and efficacy even at low concentrations. These features enable it to degrade not only cytoplasmic aggregate proteins but also non-protein cargoes such as lipid droplets[30],

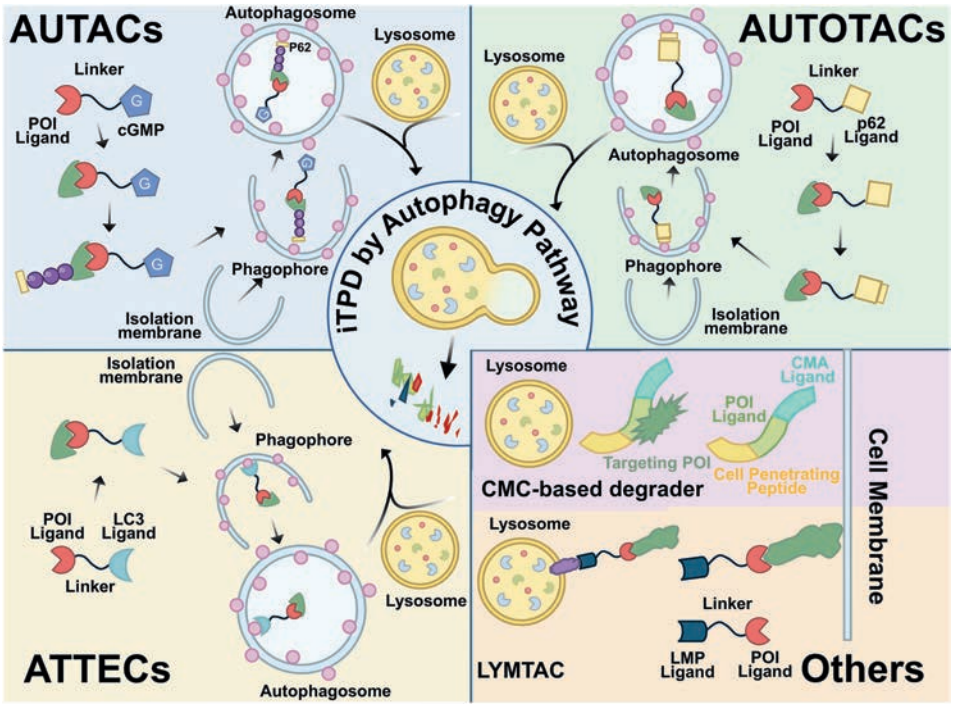

Figure 3 Various strategies for iTPDs mediated by the autophagy−lysosomal pathway.

offering new possibilities for the targeted degradation of diseased-related proteins.

2.2.4. *CMA-based degraders*

CMA is also a mechanism for the selective degradation of iTPD *via* the autophagy−lysosome pathway. Firstly, heat shock cognate protein 70 (HSC70) recognizes the KFERQ motif on soluble protein substrates[82], and forms a complex. This complex then interacts with lysosome-associated membrane protein 2A (LAMP2A) on the lysosomal membrane, facilitating the translocation of the substrate protein into the lysosome for degradation[83]. It should be noted that CMA-mediated degradation does not involve autophagosome formation. CMA-based degraders typically consist of three functional domains: a cell-penetrating sequence, a POI-binding sequence, and a CMA-targeting motif[82]. This strategy has been demonstrated to effectively reduce levels of mutant huntingtin protein, rat postsynaptic density protein-95, death-associated protein kinase 1, and α-synuclein, highlighting its significant potential for treating a variety of diseases[84,85].

2.3. *eTPD mediated by the endosome−lysosomal pathway*

While iTPD strategies such as PROTACs have revolutionized drug discovery by targeting internal proteins, a complementary frontier has emerged focusing on the extracellular space and cell surface: eTPD. A primary mechanism for eTPD is hijacking the endosome−lysosome pathway, a natural cellular process for internalizing and degrading extracellular cargo. The pioneering technology in this field, LYTACs, demonstrated the feasibility of this approach. Subsequently, a range of innovative technologies have been developed to further expand this strategy, including AbTACs and KineTACs, which employ distinct mechanisms to direct specific targets toward lysosomal degradation. These advances continue to broaden the scope of degradable targets and enhance the toolbox for precision medicine (Fig. 4).

2.3.1. *LYTACs*

LYTACs, a pioneering eTPD technology, operates by harnessing the endosome−lysosome pathway to mediate the degradation of extracellular and membrane-associated proteins[86]. In 2020, the first LYTAC molecules, aimed to degrade extracellular and membrane proteins *via* the endosome−lysosome pathway, were reported, offering a novel targeted degradation strategy for disease treatment[25]. The molecular structure of LYTACs consists of three key components: a ligand that recognizes POI in extracellular or membrane, a linker, and a ligand that binds to lysosome-targeting receptors (LTRs) on the cell surface. LYTACs simultaneously bind to POI and LTRs, forming a POI−LYTAC−LTR ternary complex, which triggers endocytosis and the formation of endosomes. Subsequently, the endosomes mature through intracellular transport mechanisms and eventually fuse with lysosomes, enabling the efficient degradation of extracellular and membrane proteins[25]. Given the critical roles of numerous extracellular and membrane proteins in the pathogenesis and progression of neurodegenerative diseases, autoimmune disorders, and cancers, LYTACs has emerged as a novel targeted degradation tool.

The advancement of LYTACs depend strongly on the development of LTRs. Cation-independent mannose-6-phosphate receptor (CI-M6PR) was the first LTR utilized in LYTACs degradation system[25]. The ubiquity of the receptor across human tissues and its ability to internalize ligands for lysosomal degradation make it an attractive target for LYTACs. And mannose-6-phosphate (M6Pn) is commonly employed as CI-M6PR ligand. By conjugating M6Pn with antibodies targeting various proteins, such as apolipoprotein E4 (ApoE4), EGFR, cluster of differentiation 71 (CD71), and programmed death-ligand 1 (PD-L1), the constructed LYTACs molecules efficiently mediate the endocytosis and lysosomal degradation of target proteins, significantly

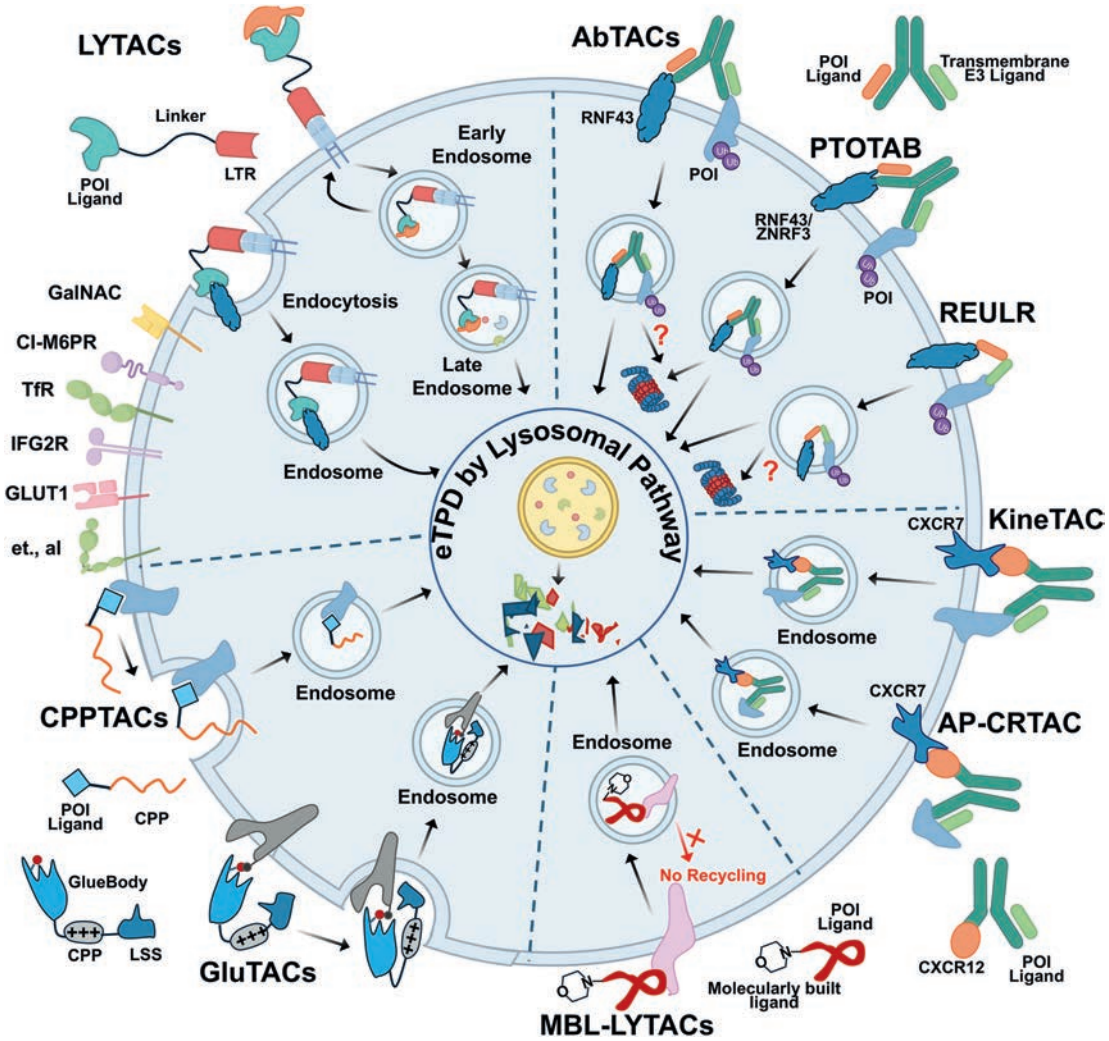

Figure 4 Various strategies for eTPDs mediated by the endosome−lysosomal pathway.

reducing their levels. ASGPR represents another classical LTR. It is primarily expressed on the surface of hepatocytes and functions as a liver-specific receptor. *N*-Acetylgalactosamine (GalNAc) serves as the ligand for ASGPR, enabling the specific delivery of POIs, such as EGFR and integrins, to lysosomes within hepatocytes for degradation[87]. Meanwhile, other LTRs, such as transferrin receptor (TfR)[88], insulin-like growth factor 2 receptor (IGF2R)[89], glucose transporter 1 (GLUT1)[90], scavenger receptor class A (SR-A)[91], folate receptor α (FRα)[92], Her2[93], sortilin[94] and low-density lipoprotein receptor-related protein 1 (LRP-1)[95], are being actively explored. These developments hold promise for further expanding the application scope of LYTACs-based degraders in the future.

Notably, LYTACs bypasses the need for intracellular components, such as E3 ligases. By leveraging LTRs, LYTACs offers increased modularity and flexibility in the design of degraders. These features not only expand the range of POIs but also enhance the ability to modulate disease-specific mechanisms. With continuous progress in the study of LTRs and the development of novel ligands, the LYTACs holds substantial promise as a next-generation platform for advancing targeted therapies.

2.3.2. Transmembrane E3 ubiquitin ligases-based degraders

Transmembrane E3 ubiquitin ligases-based degraders represent a key eTPD strategy that mediates the degradation of membrane proteins *via* the endosome−lysosome pathway[96]. Representative strategies include AbTACs[26,97] and Protein Targeting Antibody (PROTAB)[98], both of which are essentially recombinant bispecific antibodies. These antibodies specifically recognize cell surface target proteins on one end and bind to transmembrane E3 ligases on the other. For example, RNF43, a single-pass transmembrane E3 ligase, contains an extracellular domain, a transmembrane domain, and an intracellular RING domain[99]. It has the potential to facilitate the internalization of ternary complexes and their subsequent degradation in the lysosome. In 2021, Wells's group[26] reported AbTACs, a form of bispecific antibodies that specifically recognize PD-L1 and the transmembrane E3 ligase RNF43, effectively inducing lysosomal degradation of PD-L1 by recruiting RNF43. Subsequently, Melo's group[98] reported a similar technology in Nature, called PROTAB. This bispecific antibody binds to insulin-like growth factor 1 receptor (IGF1R) on one end and recognizes the N-terminal glycoprotein D (gD) of either RNF43 or zinc and ring finger 3 (ZNRF3), another membrane-bound E3 ligase, on the other. Results demonstrated that PROTAB effectively degraded cell surface IGF1R in cells expressing RNF43 or ZNRF3. Further studies confirmed that this platform exhibits significant degradation efficacy against multiple cell surface targets, such as HER2 and PD-L1. Notably, PROTAB can engage both the proteasome and lysosome pathways for degradation.

Overall, AbTACs and PROTAB technologies, as transmembrane E3 ligase-based TPD strategies, enable the specific degradation of cell surface proteins through fully recombinant biomacromolecules, significantly reducing the immunogenicity associated with traditional chimera molecules. However, they currently face certain limitations, such as a strong dependence on the expression levels and availability of cell surface E3 ubiquitin ligases. This reliance introduces variability and restricts their generalizability across diverse cellular environments.

Furthermore, the nanobody-based targeted degradation platform, Receptor Elimination by E3 Ubiquitin Ligase Recruitment (REULR), has also seen significant advancements[100]. REULR molecules consist of bispecific VHH domains that specifically recruit E3 ubiquitin ligases and induce the degradation of target receptors. Specifically, researchers designed corresponding nanobodies targeting five transmembrane E3 ligases (RNF128, RNF130, RNF167, RNF43, and ZNRF3) and constructed bifunctional REULR molecules. Experiments demonstrated that these molecules efficiently clear disease-related target receptors (including EGFR, EPOR, and PD-1) at various levels by inducing proximity interactions between transmembrane E3 ligases and the target receptors. Compared to traditional antibodies, REULR molecules have a smaller size, which provides potential advantages in tumor tissue penetration. However, their smaller size also makes them more susceptible to rapid renal clearance, which limits their *in vivo* stability and half-life to some extent.

2.3.3. KineTACs

KineTACs effectively induce the degradation of extracellular and membrane proteins through the endosome−lysosome pathway. The underlying principle of KineTACs is that various cytokines and interleukins can be internalized *via* their receptors and subsequently degraded in the lysosome. Wells et al.[27] developed a bispecific Fc fusion protein composed of two functional domains: one specifically binds to target proteins, while the other is a cytokine that interacts with cell surface cytokine receptors, rather than traditional membrane-bound E3 ligases. Validated cytokines include CXCL12 (targeting the membrane receptor CXCR7), CXCR7 (targeting the membrane ligands CXCL11 and vMIPII), and interleukin-2 (targeting the membrane IL-2 receptor). Through cytokine receptor-mediated internalization, target proteins (such as membrane proteins PD-L1 and EGFR, as well as soluble extracellular proteins VEGF and TNF-α) are endocytosed and transported to the lysosome for degradation. In a parallel approach, Wu et al.[101] developed an alternative strategy centered on an engineered mutant of CXCL12. This peptide exhibits high-affinity binding to CXCR7 and strongly promotes its internalization and lysosomal delivery. The core peptide was further functionalized *via* click chemistry conjugation to nucleic acid-based binders, such as DNA, RNA, or bispecific aptamers, yielding a modular construct termed AP-CRTAC. This system enables not only degradation of CXCR7 itself but also, through programmable nucleic acid adaptors, the selective degradation of one or multiple target proteins, including pathogenic mutants. Although nomenclature differs, both platforms fundamentally exploit cytokine-receptor internalization mechanisms for TPD. Thus, KineTACs-in a broader functional definition-represent a versatile, modular, and highly selective eTPD strategy capable of facilitating lysosomal degradation of diverse extracellular and membrane-bound targets.

2.3.4. Cell-penetrating peptides (CPPs)-based degraders

Utilizing the endocytosis mechanism mediated by CPPs, two new membrane protein-targeting degradation technologies, GlueTACs[102] and CPPTACs[103], have been developed in recent years. Since CPPs-mediated endocytosis facilitates cargo entry *via* the endosomal pathway, these platforms also represent an emerging strategy within the eTPD landscape. The GlueTACs consists of two main components: a nanobody (Gluebody) modified with unnatural amino acids, which specifically binds to the target (such as PD-L1) and forms covalent bonds, and a CPP coupled with a LTS, which collectively facilitate nanobody internalization and lysosomal targeting, ultimately constructing an efficient membrane protein-targeting degradation chimera[102]. With a molecular weight of only 15 kDa, the nanobody's compact size and high penetration capability confer significant advantages in targeted degradation technologies. The CPPTACs molecule involves a CPP conjugated to a POI ligand, enabling the endocytosis of membrane and extracellular POIs (including PD-L1, CAIX, and CB2R, among other disease-related membrane proteins) driven by various CPPs, followed by their transport to the lysosome for efficient degradation[103]. Further mechanistic studies revealed that CPPTACs rely on electrostatic interactions between their positive charges and the negative charges of proteoglycans on the cell membrane, rather than a single lysosomal trafficking receptor. This mechanism overcomes the dependency of traditional methods like LYTACs and AbTACs on intracellular LTRs or specific E3 ligase expression levels, achieving highly specific and efficient degradation of membrane proteins with advantages such as structural simplicity, a broad therapeutic window, and wide applicability.

2.3.5. MBL-LYTACs

In parallel, several non-canonical lysosomal degradation strategies have emerged, such as molecular-based lysosome-targeting chimeras (MBL-LYTACs), representing a distinct eTPD strategy[104]. These constructs enable efficient, broad-spectrum, and lysosomal shuttle receptor-independent degradation of membrane proteins through minimal chemical modification. The mechanism begins with specific binding to cell surface receptors, followed by receptor-mediated endocytosis that directs the complex into the endosomal−lysosomal trafficking route. Within the acidic lysosomal compartment, weakly basic lipophilic functional groups—such as morpholine and dimethylamino moieties—become protonated, while low-polymerization-degree mPEG forms stable associations with hydronium ions. This markedly enhances molecular hydrophilicity, leading to entrapment of the entire assembly within the lysosome by inhibiting retrotranslocation across the membrane. As a result, the accumulated cargo undergoes thorough lysosomal degradation, establishing a robust and adaptable platform for targeting oncogenic membrane receptors. This system provides a promising new therapeutic framework based on TPD, with particular relevance for cancer therapy.

3. Emerging challenges and the rationale for nanoparticle-enabled TPD

3.1. Universal and mechanism-specific bottlenecks in TPD development

The expanding universe of TPD technologies—from the proteasome-recruiting PROTACs and molecular glues, to the autophagy-engaging AUTACs and ATTECs, to the extracellular-targeting LYTACs—collectively represents a paradigm shift in pharmacology. However, despite their diverse mechanisms, a common theme of "molecular difficulty" unites them, creating a formidable gap between conceptual elegance and clinical

translation. This gap arises from the intrinsic structural conflict between the complex architectures required for bifunctional degradation and strict physiological barriers. It manifests as a dual failure in spatial control: the high molecular weight restricts passive access to the intracellular, while indiscriminate biodistribution leads to uncontrolled systemic exposure and off-tissue toxicity.

Beyond these shared hurdles, each class of degrader faces its own unique, mechanism-derived bottlenecks. iTPDs like PROTACs are famously susceptible to the hook effect, a concentration-dependent loss of efficacy. Autophagy-based degraders like AUTACs are tethered to the variable and complex efficiency of the cellular autophagy flux. And eTPDs like LYTACs are constrained by the Avidity Imperative, the necessity of multivalent ligand engagement to trigger receptor clustering and internalization, at the cell surface and the subsequent, intricate challenge of ensuring productive lysosomal trafficking. This multi-layered problem space—defined by universal physicochemical liabilities on one hand, and distinct, mechanism-specific hurdles on the other—cannot be solved by medicinal chemistry alone. It necessitates a paradigm shift towards external engineering. It is here that nanotechnology emerges, not as a singular solution, but as a versatile and programmable toolkit capable of providing tailored strategies to overcome these diverse and deeply-rooted challenges.

3.2. The core rational dichotomy: nanoparticles as delivery carriers and intrinsic degraders

Before delineating specific therapeutic modalities, it is essential to establish the fundamental architectural dichotomy that currently governs the integration of nanotechnology with TPD. The field has been classified into two distinct design philosophies: the conventional "nanocarrier-based" strategy and the emerging "nanoparticle as an intrinsic degrader" strategy. Delineating the divergence in their design principles and mechanisms is a prerequisite for rational engineering.

The nanocarrier-based strategy operates on a "delivery-and-release" principle, utilizing the nanoparticle strictly as a protective vehicle. In this paradigm, the primary objective is to mask the suboptimal physicochemical profile of iTPD payloads during systemic circulation, orchestrating spatiotemporally controlled release at the target site. Crucially, this approach ensures that once released, the iTPD molecules function independently of the carrier matrix, retaining the conformational flexibility required for intracellular targets. In stark contrast, the intrinsic degrader paradigm reimagines the nanoparticle not as a passive vessel, but as the active structural scaffold itself, wherein targeting ligands and degradation effectors are co-displayed directly on the surface. This design leverages the "multivalency effect" to dramatically enhance binding avidity and facilitate modular surface engineering. Furthermore, the inherent propensity of NPs for endocytosis and lysosomal sorting renders them an ideal platform for engaging and transporting extracellular or membrane-associated POIs for lysosomal degradation.

Recognizing this critical mechanistic dichotomy deeply informs the strategic nano-platform designs discussed in the following sections: serving as intelligent nanocarriers to orchestrate drug delivery for iTPDs, while acting as integral, polyvalent functional scaffolds to unleash unparalleled endocytotic power for robust eTPDs (Fig. 5).

4. iTPD loaded nanoplatform with the cytosolic destination: engineering the "great escape"

The vast majority of TPD modalities developed to date are designed to function within the intricate environment of the cytoplasm. As outlined in previous sections, these iTPDs can be broadly divided by the machinery they hijack: UPS-utilizing agents like PROTACs and molecular glues, and autophagy–lysosome pathway-recruiting molecules such as AUTACs and ATTECs. Despite their different terminal degradation sites—the proteasome for the former, the lysosome for the latter after autophagosome fusion—all iTPDs share a single, non-negotiable prerequisite: they must achieve productive entry into the cytosol to initiate their mechanistic cascade.

For these modalities, successful cell permeability is synonymous with achieving a sufficient concentration at their intracellular site of action. Once there, they can form the crucial ternary complexes with E3 ligases and target proteins or engage autophagy adaptors like p62/SQSTM1. Failure to reach this cytosolic threshold directly aborts the degradation event before it can even begin. While molecular glues, often discovered serendipitously, possess simpler structures, the majority of rationally designed iTPDs (PROTACs, AUTACs, etc.) are built on a common scaffold with three chemical elements: two binding ligands, one specific to a target protein and the other for the E3 ubiquitin ligase, along with a linker connecting these two ligands[105]. This design axiom frequently places them in the challenging bRo5 chemical space. Characterized by high molecular weight (MW $>$ 500 Da), extensive polar surface area (PSA), and significant flexibility, these molecules inherently present a formidable challenge to drug developers. Their bRo5 properties often translate directly into poor aqueous solubility, low passive membrane permeability, and complex ADME (absorption, distribution, metabolism, and excretion) profiles[106]. While tremendous medicinal chemistry efforts are underway to optimize these intrinsic properties, this section focuses on the transformative potential of nanotechnology to address these universal hurdles externally. By viewing PROTACs as the archetypal bRo5 degrader, we can establish nano-engineering principles that provide invaluable insights for the entire class of iTPD drugs.

4.1. The multi-stage obstacle course for cytosolic iTPD payloads and nano-engineering principles

Irrespective of their therapeutic potential, the successful navigation of an iTPD payload from systemic circulation to the cytosol of a target cell is imperative, yet it constitutes a multi-stage obstacle course rooted in the very molecular architecture of these degraders.

4.1.1. The "molecular obesity" obstacle

The majority of classical PROTACs, as the quintessential iTPD, tend to fall into the bRo5 chemical space. To be effective, both ends of the molecule must bind with high affinity to their respective protein partners—the target and the E3 ligase. The moieties that achieve this are often carbon-rich, aromatic systems, which, while optimal for binding, are inherently lipophilic. This leads to a "molecular obesity" that paradoxically limits clinical efficacy. These molecules are characterized by a high molecular weight (often approaching 1000 Da), a large polar surface area (PSA $>$200 Å), and numerous hydrogen bond donors and acceptors. This bRo5 profile gives rise to a cascade of daunting ADME challenges. Poor aqueous solubility is a primary hurdle, not only compromising absorption in the gastrointestinal tract but also leading to compound precipitation and inaccurate concentration assessments in critical *in vitro* assays. Compounding this, their lipophilicity often leads to rapid hepatic uptake and metabolic clearance, making them more susceptible to oxidative metabolism than their smaller, more polar drug counterparts. The real-world consequences of these suboptimal properties are stark. For instance, an early attempt to generate PROTACs targeting the pirin protein failed to induce

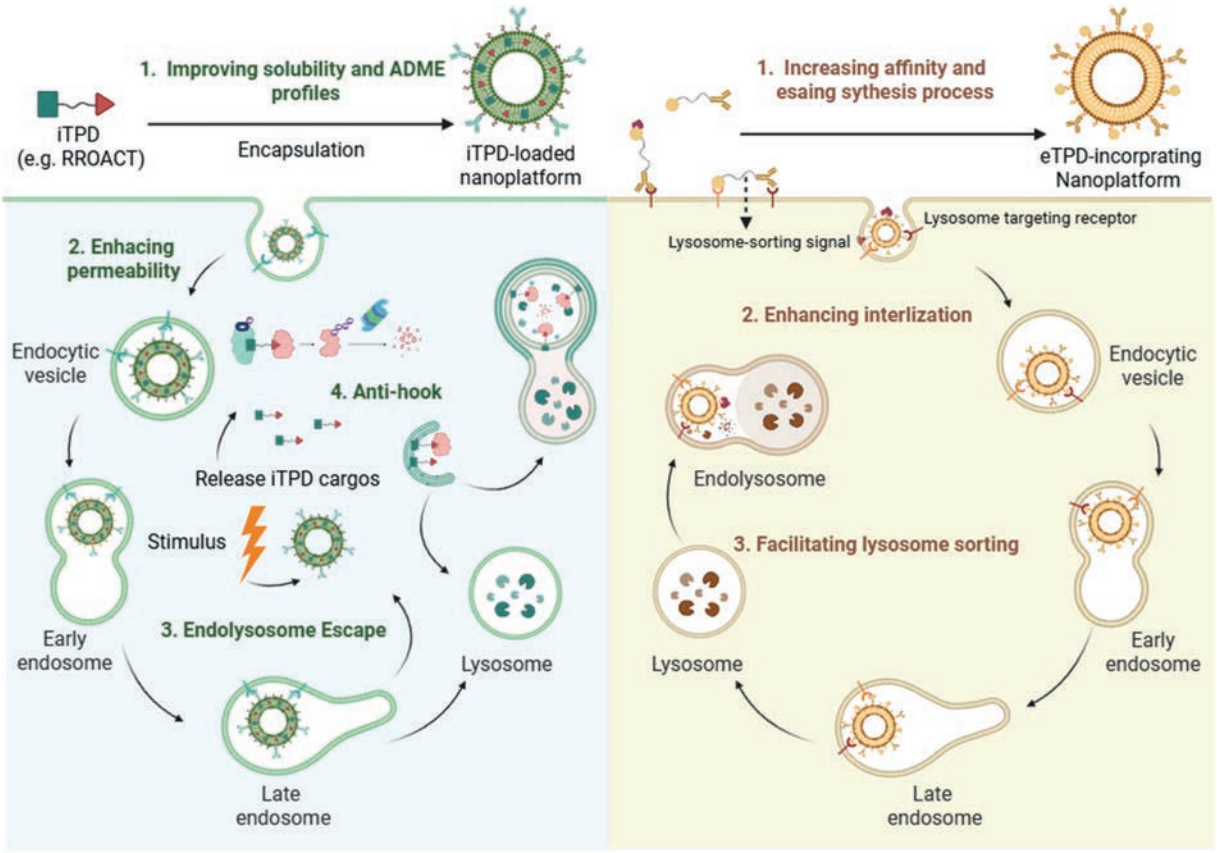

Figure 5 Schematic illustration of nano-platform to address challenges facing TPDs.

degradation, a lack of success attributed not to poor design of the binding moieties, but directly to the unfavorable physicochemical properties of the molecules themselves.

4.1.2. The "poor permeability" obstacle

In an effort to circumvent the challenges of small-molecule degraders, alternative scaffolds such as bioPROTACs—based on peptides[107], proteins[108], antibodies[109], or aptamers[110]—have been explored[111]. While these biomolecules often solve the solubility issue, they trade one set of problems for another. They tend to be highly polar and negatively charged, which severely hinders their ability to passively cross the cell membrane. Furthermore, their biological nature makes them acutely vulnerable to degradation by ubiquitous enzymes in circulation, such as peptidases and nucleases. Thus, a universal dilemma emerges: iTPDs are either too lipophilic or too polar, creating a formidable delivery barrier regardless of their chemical composition.

4.1.3. iTPD loaded nanoplatform as solutions

While medicinal chemistry efforts to refine these properties through iterative structural modification remain an active and vital area of research, such strategies often involve a delicate balancing act that can compromise binding affinity or introduce new liabilities[106,112−114]. These efforts are now being dramatically accelerated by computational and machine learning models, which leverage deep reinforcement learning to rationally design novel PROTACs with predicted optimal pharmacokinetics de novo[115,116]. However, even these powerful *in silico* approaches ultimately navigate the same fundamental chemical trade-offs. Optimizing for ADME properties can still inadvertently weaken the high-affinity protein−protein interactions essential for potent degradation, and the vast chemical space means that many promising degraders will inevitably fall into the bRo5 category. Thus, a parallel and highly pragmatic strategy has emerged: instead of solely re-engineering the molecule, we can re-engineer its "package" and delivery system[117]. Compared to structural design modifications, nano-system-based solution delivery systems to enhance PROTAC drug-like possibility focuses more on carrier selection, which is less stringent on the PROTAC molecule itself. Over the past few decades, nanotechnology have been extensively studied and exploited due to their ability to improve the PK profiles of therapeutic agents[118]. Nano-based systems offer a powerful and versatile toolkit to overcome these fundamental physicochemical challenges externally. By encapsulating the iTPD, a nanocarrier can effectively mask its intrinsic properties, significantly improving its solubility, metabolic stability, cell permeability, and pharmacokinetic profile[119−121]. This external management of ADME allows the iTPD molecule to be optimized for its primary biological function: potent and specific protein degradation.

4.1.4. Nano-scaffolds for iTPD: feasibility and geometric constraints

Beyond serving as passive vehicles, a more ambitious strategy reimagines the nanoparticle itself as the degrader's active scaffold. In these "NanoTAC" architectures, the nanoparticle core replaces the flexible linker of a conventional degrader. A prime example is the "split-and-mix" platform, which uses a self-assembling peptide core to display various target and E3 ligands, boasting advantages like modular screening and improved solubility[122].

However, for intracellular applications, this elegant design faces two fundamental hurdles. First is subcellular trafficking: without an explicit endosomal escape mechanism, there is no guarantee these constructs can reach the cytosol. They may simply be doomed to lysosomal destruction, rendering them inert. The second, more profound question concerns geometric feasibility. The very mechanism of a PROTAC is predicated on a proximity-inducing effect that operates within a critical distance, typically estimated to be less than 10 nm between the ligase's active site and a target lysine[123−125]. A rigid nanoscale scaffold, while achieving co-localization, may fail to mimic a flexible linker's ability to satisfy these stringent geometric constraints. This reveals a crucial distinction: mere co-localization is not productive ubiquitination. The risk is that the nanoparticle becomes a high-avidity inhibitor of degradation, locking its targets in a "binding-competent but catalytically-incompetent" state. Addressing these dual challenges of subcellular trafficking and biophysical geometry is paramount if NanoTACs are to evolve from intriguing concepts into viable therapeutic strategies.

Given these profound geometric and trafficking challenges, a more pragmatic and arguably more powerful paradigm has emerged: decoupling the delivery platform from the degradation mechanism. This iTPD-loaded nanocarrier strategy, which focuses on encapsulating the degrader, presents as a more logical and rational approach to combat the hurdles facing iTPD clinical translation. By sequestering iTPD molecules through various physical interactions, a nanocarrier can effectively shield their suboptimal physicochemical properties.

4.2. Enhancing the pharmacokinetic properties of PROTAC molecules

Liposomes, with their unique structure of a lipid bilayer surrounding an aqueous core, function as powerful nanocarriers that fundamentally reshape how drugs behave in the body, offering a versatile toolkit to dramatically improve their pharmacokinetic profiles. A compelling demonstration of this principle was provided by Kou et al.[126] in their work with insoluble BRM-targeting PROTACs (GNE-01 and GNE-02). They engineered two distinct liposomal platforms: a conventional design with the PROTAC loaded into the lipid bilayer, and an advanced system where a PROTAC−cyclodextrin complex was housed within the liposome's aqueous core. Both platforms successfully rendered the insoluble PROTACs suitable for intravenous administration and markedly improved their pharmacokinetic profiles, evidenced by increased systemic exposure and reduced clearance. These findings powerfully suggest that such formulation strategies could be broadly applied to remedy the ADME liabilities of many bRo5 compounds.

Serum albumin, a natural transporter of endogenous molecules, also offers a compelling path for optimizing PROTAC delivery[127]. Its ability to improve biocompatibility, stability, solubility and half-life can be harnessed to ameliorate the poor pharmacokinetic profiles of PROTACs. In one illustrative case, Hu et al.[128] addressed the aqueous insolubility of a PROTAC-Cy molecule—built from a pomalidomide E3 ligase ligand, an MCL-1 inhibitor, and a cyanine-based linker—by encapsulating it within bovine serum albumin (BSA) nanoparticles. This formulation not only conferred water solubility and plasma stability but also modulated excretion kinetics, leading to more sustained exposure and improved therapeutic efficacy. A related, yet distinct, strategy involves the *in situ* recruitment of serum albumin through covalent modification. This was demonstrated by the development of an esterase-cleavable maleimide linker conjugated to the BRD4-degrading PROTAC ARV-771, creating ECMal-PROTAC. The conjugate exploits albumin's long circulatory half-life, enhancing the parent molecule's solubility, prolonging systemic exposure, and reducing rates of metabolism and excretion[129].

4.3. Enhancing the cellular permeability and further promoting endo-lysosome escape of iTPD

However, solving the systemic pharmacokinetic puzzle is only the first stage of the obstacle course. As the Kou et al.[126] study critically revealed, enhanced tumor accumulation does not guarantee therapeutic efficacy if the payload remains entrapped. This highlights the next, and arguably challenges: ensuring productive cellular uptake.

Nanoparticles have emerged as a versatile solution to overcome the permeability challenges associated with PROTACs due to their favorable properties. Their tunable size and customizable surface characteristics facilitate enhanced interactions with cellular membranes, promoting efficient endocytosis. Building on the versatility of nanoparticle platforms, Li's group[130] engineered a self-delivery nano-PROTAC system termed DdLD NPs. This was achieved through the co-assembly of the chemotherapeutic doxorubicin (DOX) and the BET-degrading PROTAC dBET57, facilitated by the lipid DSPE-PEG2000. The resulting nanoparticles enhanced the stability and intracellular delivery of both cargoes, ultimately amplifying the therapeutic outcome. In a separate approach to overcome cellular entry barriers, the PROTAC molecule LC-2 was formulated into liposomes whose surface was precisely functionalized with the cell-penetrating peptide R8. This rational design yielded R8-LC-2 liposomes, which, as anticipated, significantly boosted cellular permeability and targeting efficacy compared to the unmodified PROTAC[131].

Then it comes subsequent endosomal escape. A nanocarrier that cannot efficiently ferry its cargo across the cell membrane and then liberate it from the endo-lysosomal pathway is ultimately a failed delivery system. Therefore, the rational design of iTPD-loaded platforms has evolved to incorporate sophisticated modules engineered specifically to master this intracellular journey. To surmount these barriers, a key strategy has emerged: the use of pH-responsive nanoparticles that leverage the acidic endosomal environment as a specific trigger for release. This principle is perhaps best exemplified by the clinical success of ionizable lipid nanoparticles (LNPs)—the cornerstone of the first FDA-approved siRNA therapeutic, Patisiran[132], and the recent COVID-19 mRNA vaccines[133]. This clinically-validated technology has been masterfully repurposed for the delivery of challenging iTPD modalities. For instance, peptide-based PROTACs (PepTACs), while promising for targeting oncoproteins, are notoriously poor at penetrating cells and are vulnerable to serum degradation[134]. Ghosal et al.[134] demonstrated that by formulating a PepTAC against the oncotarget CREPT within an optimized LNP, these limitations could be overcome. The resulting PepTAC-LNP was rapidly internalized, and the ionizable lipids facilitated endosomal escape, enabling potent, targeted degradation of CREPT at sub-nanomolar doses—an efficacy rivaling traditional small-molecule PROTACs. This principle extends across iTPD classes. Chan et al.[108] al successfully delivered larger protein-based PROTACs using a screened LNP library, while Zhu's group[5] engineered aptamer-based PROTACs (APTACs) to self-assemble with a protonatable poly(β-amino ester), forming micelles that

destabilize upon endosomal acidification. Likewise, Qi's group[135] integrated a tertiary-amine motif into amphiphilic conjugates, which co-assemble into nano-PROTACs and realize optimized endosomal escape for protein degradation. A common thread unites these successful examples: their rational design consciously incorporates a mechanism for endosomal escape, acknowledging that adequate cytosolic exposure is a non-negotiable prerequisite for any iTPD that recruits the UPS or autophagy machinery.

4.4. Optimizing the releasing profile of iTPD

Crucially, however, liberation of the iTPD-loaded nanoparticle from the endosome is not synonymous with the liberation of the iTPD molecule from its carrier. It is plausible that the payload could remain tightly associated with or encapsulated within its nanocarrier in the cytosol. This sequestration would severely hinder its ability to freely form a ternary complex with its target protein and the requisite degradation machinery. Therefore, the ultimate challenge in iTPD delivery lies in engineering a delicate balance: the nanocarrier must be stable enough to protect its cargo in circulation, yet labile enough to release it upon reaching the target compartment. Mastering this final payload release profile—transforming the nanocarrier from a mere container into an intelligent responsive delivery system (IRDS)—is the next frontier in nano-iTPD design.

The design philosophy for such systems is to embed a "logic gate" into the nanoparticle, rendering it responsive to specific triggers. One elegant strategy is to harness endogenous cues found within the unique biochemical landscape of the pathological microenvironment. For instance, the intracellular concentration of glutathione (GSH) in tumor cells can be up to a thousand-fold higher than in the extracellular milieu, providing a robust and widely exploited differential. This was leveraged by Liu et al.[136], who developed a redox-responsive nanocarrier from a poly(-disulfide amide) (PDSA) polymer whose disulfide backbone is rapidly cleaved by high GSH levels, triggering nanoparticle disassembly and releasing the encapsulated BRD4 degrader. Similarly, the aberrant expression of enzymes like cathepsins or esterases offers another avenue for specific activation. This was powerfully demonstrated by Cho and colleagues[129], who engineered an esterase-cleavable moiety into a BRD4-targeting PROTAC, allowing intracellular esterases to liberate the active drug only after successful cellular delivery.

For an even greater degree of spatiotemporal precision, payload release can be orchestrated by exogenous signals that can be applied non-invasively[137]. Light offers unparalleled control, and while many strategies involve re-engineering the PROTAC itself with photocages, nanotechnology enables the use of tissue-penetrant near-infrared (NIR) light for deep-tissue activation[138]. In a landmark example, He et al.[138] prepared UCNPs-based mesoporous silica nanoparticles (UMSNs) and then loaded the well-designed photocaged-PROTAC of BRD4 to construct a NIR light-activatable PROTAC nanocage (UMSNs@phoBET1). Upon 980 nm laser irradiation, the upconverted UV emission from UCNP cores in UMSNs@phoBET1 could photolyze phoBET1 and release active PROTAC for controllable BRD4 degradation. Offering even deeper tissue penetration, ultrasound represents another powerful external trigger. A highly sophisticated example is the dual-programmable nanoPROTAC, termed SPNFeP, developed by Li and colleagues[139], which co-encapsulated a novel PROTAC against nicotinamide phosphoribosyl transferase (NAMPT) within a nanoparticle built from a ROS-cleavable amphiphilic polymer. Crucially, the nanoparticle was also loaded with two pro-oxidative agents: a semiconducting polymer (SP) that generates singlet oxygen ($^1O_2$) under ultrasound irradiation for sonodynamic therapy (SDT), and ferrocene to catalyze hydroxyl radical ($\cdot$OH) generation *via* the Fenton reaction. This elegant design creates a self-amplifying feedback loop, where the ROS generated by both SDT and ferroptosis triggers the cleavage of the nanoparticle scaffold, ensuring the specific and effective release of the PROTAC payload directly within the oxidatively-stressed target environment.

The strategic value of these responsive systems is therefore twofold. First, they ensure the intracellular bioavailability required for target engagement. Second, by being gated to specific pathological cues or external triggers, they impose a powerful layer of selectivity, confining the drug's activity to the diseased tissue. This principle of enhancing selectivity is powerfully complemented by active targeting, a parallel strategy where the nanoparticle surface is decorated with ligands (*e.g.*, antibodies, aptamers, peptides) to act as a "molecular GPS". By guiding the nanocarrier to receptors overexpressed on pathological cells, active targeting dramatically increases local drug concentration and further mitigates the risk of systemic, off-target effects.

Beyond strategies aimed at enhancing precision and selectivity, nanotechnology offers a platform to expand the very functionality of the therapy itself. The most prominent example is combination therapy, where a single nanoparticle is co-loaded with an iTPD and one or more synergistic agents, and exert function in combination with chemotherapy, immunotherapy, photothermal therapy, and other modalities[35]. This approach provides a powerful method to attack disease pathways from multiple angles, overcome acquired drug resistance, and achieve therapeutic effects greater than the sum of the individual agents.

Given that both active targeting and nano-based combination therapy represent vast and well-established fields in their own right, with each being the subject of extensive reviews, a detailed discussion is beyond the scope of this chapter. Nevertheless, the core principles discussed herein—from engineering systemic stability and endosomal escape to mastering responsive payload liberation—form the essential playbook for surmounting the fundamental delivery challenges of iTPD molecules. By successfully navigating this multi-stage obstacle course, nanotechnology does not merely improve the properties of these powerful degraders; it unlocks their full therapeutic potential, transforming them from promising chemical tools into viable clinical candidates.

4.5. Mitigating the hook effect: from stoichiometric revolution to concentration control

Beyond delivery, nanotechnology offers a unique toolkit to address intrinsic, concentration-dependent limitations of the PROTAC molecule itself. Perhaps the most vexing of these is the Hook effect, a pharmacological phenomenon arising directly from the trimolecular nature of PROTAC-induced degradation. While effective degradation requires a productive ternary complex (POI−PROTAC−E3), excessively high PROTAC concentrations saturate the available binding partners, leading preferentially to the formation of inert binary complexes (PROTAC−POI or PROTAC−E3). This paradox, where efficacy diminishes at supraphysiological doses, severely narrows the therapeutic window. Overcoming this liability has inspired several conceptually distinct nano-engineering strategies, each with its own level of

complexity and translational feasibility. The most radical of these approaches attempt to fundamentally re-engineer the system's stoichiometry or intracellular organization.

One such strategy aims to pre-organize the components from a three-component system into a two-component one[140]. This "pre-fused PROTAC" concept involves incubating the PROTAC molecule with its partner E3 ligase protein *ex vivo* to form a stable binary conjugate, which is then encapsulated within LNP. While theoretically elegant in its direct circumvention of the non-productive binary interactions, this approach introduces significant manufacturing complexity and faces the substantial hurdle of ensuring the high-fidelity cytosolic delivery of a large, intact protein-drug conjugate.

An even more sophisticated strategy leverages *in situ* self-assembly to create multivalent degradation hubs[137]. In this "bottom-up" approach, independent peptide precursors are programmed to undergo an intracellular, trigger-induced click reaction and self-assemble into an ordered nanofiber. This "Artificial Topological Nanostructure" (ATN) then acts as a multivalent scaffold, recruiting multiple POIs and E3 ligases into a "polynary degradation hub." By harnessing the power of avidity, this design thermodynamically favors the formation of productive complexes. However, this frontier strategy, while conceptually brilliant, depends on the precise control of complex intracellular reaction kinetics and assembly processes, presenting its own set of practical challenges.

In contrast to these stoichiometric revolutions, a more pragmatic and perhaps more universally applicable strategy has emerged, one that does not alter the fundamental mechanism but instead masters the local concentration of the PROTAC itself. By encapsulating the PROTAC within a nanocarrier engineered for sustained or stimuli-responsive release, the nanoparticle acts as a local drug depot. This design elegantly sidesteps the high initial concentration spike from bolus administration that drives the Hook effect, maintaining the cytosolic PROTAC concentration within its optimal, highly productive range over an extended period. This approach represents a powerful convergence of simplicity and efficacy: it leverages the core strength of nanocarriers—controlled release—to solve one of the most stubborn mechanistic problems in the TPD field. Thus, while stoichiometric engineering represents an exciting frontier, it is the precise, temporal control over payload concentration that may offer the most direct and translatable path to widening the therapeutic window for potent degraders.

4.6. Expanding the playbook: nano-enabled strategies for autophagy-based iTPD

While PROTACs represent the most mature class of iTPD, the fundamental principles of nano-delivery are readily adaptable to other emerging modalities, particularly those that leverage the autophagy−lysosome pathway. These strategies, while promising, often face the same "bRo5" delivery challenges, creating a fertile ground for nano-engineering.

One prominent strategy is the use of ATTECs, which directly recruit the autophagy protein LC3 to a target. To overcome the poor uptake and lack of specificity of small-molecule ATTECs, a "nano-ATTEC" platform was developed by self-assembling three distinct block copolymers. This system was engineered to be inert at physiological pH but became activated in the acidic tumor microenvironment, triggering enhanced cellular uptake specifically in tumor cells. This intelligent design provided a crucial layer of targeting for the autophagy-based degrader[141].

Beyond simply acting as a delivery vehicle, a recurring and powerful theme in these nano-autophagy platforms is their ability to simultaneously enhance autophagy flux, creating a positive feedback loop that potentiates degradation. This was elegantly demonstrated by a second approach using biomimetic nanoreceptors to clear aggregates of mutant p53 (mutp53), an oncogene poorly handled by the proteasome. Researchers designed nanoparticles functionalized with a mutp53-binding peptide, but critically, they incorporated the cationic lipid DOTAP into the nanoparticle core. In this design, the nanoparticle acted as a synthetic, mutp53-specific autophagy receptor: the peptide bound the target, while the DOTAP component simultaneously acted as a potent autophagy inducer, dramatically increasing the efficiency of sequestration and destruction[142].

This principle of synergistic co-delivery was further highlighted in a strategy for an AUTACs designed against the immunosuppressive enzyme IDO. Here, researchers discovered that the AUTAC's guanine-derivative tag could drive the co-assembly of the degrader with the chemotherapeutic drug methotrexate (MTX) into "Nano-AUTAC" nanoparticles. This platform provided a trifecta of synergistic benefits: (1) it solved the AUTAC's delivery problem; (2) the MTX provided a direct cytotoxic effect; and, crucially, (3) MTX itself was found to be an autophagy inducer. The nanoparticle therefore not only delivered the "degrader" but also delivered an "accelerant" for the very pathway the degrader relies upon[143].

Together, these examples illustrate the remarkable sophistication of nanotechnology. For autophagy-based degraders, the nano-platform is evolving from a simple delivery shuttle into a multi-functional effector that can provide targeting, enhance delivery, and actively potentiate the biological machinery required for its payload's function.

5. Nano-scaffolds as eTPD mimics: engineering the lysosomal trafficking pathway

While the cytosol is the primary arena for many TPD strategies, a vast landscape of pathogenic proteins resides on the cell surface or in the extracellular space. To address these targets, a distinct technological platform has emerged: eTPD. This strategy fundamentally inverts the engineering challenge of its intracellular counterparts. Instead of engineering an escape from the endosome, the goal is to orchestrate a direct and efficient trafficking route to the lysosome for final degradation. While this mechanism liberates eTPD design from the constraints of membrane permeability and endosomal escape, its efficacy becomes exquisitely sensitive to two core requirements: (1) high-avidity engagement with the POI to form a stable complex, and (2) efficient, effector-mediated internalization and lysosomal sorting. The monovalent nature and fragile stoichiometry of first-generation eTPDs often fail to meet these demands. Nanotechnology, by reimagining the eTPD as a programmable nano-scaffold, provides a rational toolkit to overcome these challenges.

The first-generation nano-scaffolds operate as LYTAC mimics, designed to solve the avidity imperative. The fragile 1:1:1 stoichiometry of a monovalent degrader often fails to stabilize the tripartite complex on the dynamic cell membrane. By creating a nanoparticle decorated with multiple copies of both a POI ligand and a cell-surface effector ligand, one can leverage multivalency to dramatically increase functional binding strength, robustly driving complex formation and subsequent internalization[144].

These principles have been powerfully demonstrated through two distinct, yet complementary, design philosophies. The first is a "bottom-up" approach based on *in situ* self-assembly. The Lysosome-Targeting Co-assembly (LYTACA) strategy, developed by Dong's group, exemplifies this concept[91]. They designed two distinct peptide ligands—one binding the POI and the other an effector receptor—and modified each with hydrophobic aromatic motifs. Upon mixing, these components co-assemble into bispecific nanoparticles that present a multivalent display of both ligands, effectively driving endocytosis and lysosomal degradation of the target. The profound modularity of this platform was showcased by its rapid adaptation to degrade different targets, such as IL-17A or PD-L1, and to engage different effectors, like the scavenger receptor SR-A or the liver-specific ASGPR, simply by swapping the constituent peptide modules.

The second philosophy is a "top-down" approach, which leverages pre-synthesized, multi-functional polymers as the nano-scaffold. This is masterfully illustrated by a semiconducting polymer nano-LYTAC (SPNly) designed for cancer immunotherapy[145]. In this architecture, a semiconducting polymer backbone was covalently conjugated with both an IL-4R targeting peptide and a lysosome-sorting peptide. This created a discrete, multivalent nano-scaffold that efficiently directed the degradation of the IL-4R on tumor-promoting M2 macrophages, effectively reprogramming them. Crucially, this "top-down" design allowed for the integration of an additional, pre-engineered function: the polymer backbone itself acted as a sonosensitizer. Under ultrasound irradiation, the SPNly generated singlet oxygen to directly kill cancer cells, thus combining TPD strategies with sonodynamic therapy in a single, precisely engineered entity that achieved complete tumor suppression in mouse models[145].

While the nano-scaffold strategies effectively enhance the conventional eTPD mechanism, the LTR-dependency, which replyied on the engagement of an endogenous LTR as the "effector" introduces fundamental liabilities. Therapeutic efficacy becomes tethered to the expression level and tissue specificity of the chosen LTR, which are often suboptimal[146]. Furthermore, competition with abundant endogenous ligands can limit degrader access, and hijacking key physiological players like TfR or GLP-1R raises safety concerns about interfering with their normal biological functions[147,148].This challenge has inspired a more advanced and versatile strategy: bypassing the LTR altogether. Nanotechnology provides a particularly elegant solution by leveraging a nanoparticle's intrinsic ability to be endocytosed. Unlike small molecules or antibodies, nanoparticles are readily internalized by cells through various receptor-independent pathways (*e.g.*, macropinocytosis) and are naturally trafficked through the endo-lysosomal network. This inherent property allows a nano-scaffold functionalized with only a POI-targeting ligand to act as its own effector. A clear demonstration of this principle was provided by Shi and colleagues[149], who developed a general strategy for degrading extracellular proteins using clinically-approved components. They showed that by simply conjugating a targeting antibody (*e.g.*, anti-EGFR) to the surface of a poly (lactic-*co*-glycolic acid) (PLGA) nanoparticle, they could induce the degradation of EGFR without recruiting a LTR. The nanoparticle itself mediated the internalization and subsequent lysosomal trafficking of the bound protein. They further proved the versatility of this "TPD-NP" strategy by extending it to other targets like Her2 and PD-L1, and demonstrated that it was platform-agnostic, working efficiently with various nanocarriers including liposomes, LNPs and lipopolyplexes. Building on this effector-independent principle, Shen's group[150] developed a highly modular, "plug-and-play" platform termed MONOTAB (Modified Nanoparticles with Targeting Binders). By using streptavidin-coated nanoparticles as a universal chassis, they could rapidly and facilely assemble functional degraders simply by attaching corresponding biotinylated targeting antibodies. This modularity elegantly demonstrated the platform's versatility, enabling the degradation of diverse targets ranging from membrane proteins like PD-L1 and extracellular enzymes like MMP2, to even complex, non-protein entities such as extracellular vesicles (EVs). This concept of using the nanoparticle as a multifunctional chassis was further advanced by Gao's group[151] with their development of an endoTAC platform targeting the pathological receptor RAGE, implicated in Alzheimer's disease. The endoTAC itself leveraged the nanoparticle's intrinsic lysosomal tropism, enhanced by multivalent binding, to efficiently degrade RAGE. What's more, the platform's power was also revealed in its capacity for combination therapy. By encapsulating simvastatin within the nanoparticle core (termed SV@endoTAC), the system could simultaneously upregulate LRP1 to promote the clearance of amyloid-beta (Aβ). This single, precisely engineered nanoplatform was therefore able to both degrade a key pathological receptor and modulate a separate, complementary pathway, showcasing the immense potential of nano-scaffolds to serve not just as degraders, but as integrated, multi-modal therapeutic systems[151].

A parallel strategy to achieve effector-independence, drawn from molecular engineering, seeks to directly co-opt the cell's own intracellular trafficking code. The cytosolic domains of LTRs contain specific peptide motifs (*e.g.*, tyrosine- or dileucine-based signals) that are recognized by the cellular sorting machinery, such as clathrin coats, to ensure lysosomal delivery[152,153]. Inspired by this, Cai's group[154] developed SignalTACs, a platform that bypasses the need for an external effector receptor entirely. They engineered a chimera by fusing a membrane-protein binder directly to a canonical lysosome-sorting signal. This elegant design effectively "writes" a lysosomal delivery instruction onto the target protein, instructing the cell to internalize and degrade it. The power of this approach was demonstrated by the successful degradation of multiple key targets, including EGFR, HER2, and PD-L1[154]. This concept of integrating sorting signals can be powerfully combined with nano-scaffold design. The SPNly platform, for instance, exemplifies this strategic convergence by incorporating a lysosome-sorting peptide directly onto its semiconducting polymer backbone, thus using both multivalency and an explicit trafficking signal to guarantee efficient lysosomal delivery[145].

While effector-independent nanoparticle strategies elegantly bypass the requirement for internal effectors to drive lysosomal trafficking, they simultaneously shift the entire burden of target specificity onto the POI-binding moiety. Consequently, if the target protein is ubiquitously expressed across healthy tissues, these broadly applicable platforms risk inducing severe off-target degradation-essentially trading the constraint of LTR dependency for the critical translational hurdle of systemic toxicity. To surmount this barrier, a secondary layer of spatial specificity must be introduced to restrict the formulation's *in vivo* biodistribution. Nanoparticle platforms offer a modular technological solution to this *via* active tissue targeting. Their unique surface functionalization capacity enables researchers to co-display multivalent, tissue-specific targeting ligands (such as peptides or antibodies) alongside the POI binder on a single nanoscaffold. This multitasking architectural design creates a highly localized "AND" logic gate, ensuring that degradation predominantly occurs only within microenvironments where the spatial anchor is highly

expressed, thereby successfully circumventing broad, POI-related off-target risks.

Theoretically, any tissue-restricted surface moiety can serve as this spatial anchor to govern macroscopic biodistribution[155]. Interestingly, however, many rationally selected active targeting receptors serendipitously overlap with well-characterized, canonical LTRs. Notable examples include the TfR for penetrating the blood−brain barrier (BBB) and tumor solid tissues[156], integrins and the folate receptor for localizing selectively to neoplastic niches, and the ASGPR for robust hepatic tropism. In the context of NP-mediated TPD, these functionally overlapping receptors exert a powerful synergistic dual-function: their primary organismal role dictates macroscopic pharmacokinetics to restrict off-target distribution, while their intrinsic endolysosomal propensity cumulatively enhances intracellular degradation efficiency.

A quintessential example of this paradigm is the recently developed modular platform based on human heavy-chain ferritin (HFn) nanocages (HFn-LYTAC)[156]. Functionalized *via* the SpyTag-SpyCatcher system, these self-assembling NPs were decorated with affibodies targeting therapeutically relevant, yet broadly expressed, membrane proteins (EGFR, HER2, and PD-L1). Because the HFn scaffold inherently exhibits robust multivalent binding to TfR1-a receptor highly overexpressed in tumor microenvironments and uniquely enriched at the BBB-it functions distinctly as a macroscopic spatial anchor. By exploiting this spatial gating, the HFn system selectively restricted its biodistribution to tumor xenografts and demonstrated a remarkable capacity to cross the BBB for glioblastoma localization, actively circumventing systemic toxicity. Crucially, mechanistic investigations elaborated on HFn's dual role: operating primarily as a tissue-selective homing ligand to correct macroscopic distribution, while synergistically engaging classical TfR1-dependent mechanisms to facilitate potent lysosomal trafficking. Similarly, structural functionalization of poly (glutamic acid) NPs with both POI-targeting PD-L1 antibodies and the integrin-binding RGD peptide successfully confined degradative activity to the tumor site, yielding significantly improved tumor-specific protein clearance[157]. Another particularly elegant demonstration of this principle is the Supra-LYTAC platform, which targets the tumor-associated enzyme carbonic anhydrase IX (CAIX)[158]. This system utilizes two distinct, self-assembling peptides: one bearing a CAIX-targeting ligand (acetazolamide) and the other a POI-binding moiety. These peptides are designed to co-assemble into functional, bifunctional nanofibers only upon engaging with CAIX on the cancer cell membrane. This targeted self-assembly creates a multivalent degradation hub directly at the site of disease, which is then internalized *via* the endocytic activity of CAIX itself, ensuring tumor-selective degradation of the chosen POI.

An alternative, and perhaps more versatile, approach to achieving tumor specificity is to create a "smart" nano-scaffold that responds not to a specific receptor, but to the unique physicochemical properties of the tumor microenvironment (TME). This was masterfully illustrated by Liu and colleagues with their innovative NLTC (Nanoscale LYTAC) platform[159]. They designed a core LYTAC nanoparticle capable of binding both a POI (PD-L1) and a ubiquitous LTR (CI-M6PR), but shielded its surface with a pH-sensitive PEG layer. During systemic circulation in neutral pH blood, the NLTC remains inert and "stealthed". However, upon extravasation into the acidic TME, the PEG layer is shed, exposing the active degrader functionalities precisely at the site of the tumor. This TME-gated activation allows the use of a broadly expressed LTR for efficient degradation, while still achieving exceptional tumor selectivity by ensuring the degrader is only "armed" in the immediate vicinity of the cancer cells.

Together, these strategies showcase the sophisticated logic that can be engineered into nano-scaffolds: one achieves specificity by targeting a disease-specific protein, while the other does so by responding to a disease-specific environment. Both represent a significant leap towards safer and more effective eTPD therapeutics. Beyond the currently explored paradigms, the broader landscape of precision nanomedicine offers a vast arsenal of established off-target-mitigating strategies that could also serve as blueprints for the next generation of NP based TPD platforms[160]. For example, the incorporation of exogenous physical triggers, such as photo- or ultrasound-cleavable crosslinkers, could afford absolute macroscopic spatiotemporal control over localized degradation. Complementing these synthetic architectures, EVs are emerging as a transformative, bio-inspired solution for targeting[161]. Distinguished by their intrinsic ability to navigate the circulatory system with minimal immunogenicity. By biologically displaying targeting ligands and degradation effectors on the vesicle surface, this strategy enables the precise modulate multiple pathogenic mediators[162]. Ultimately, the convergence of these advanced nanotechnological modalities with the structural modularity of degraders represents a fertile, underexplored frontier for achieving high-precision therapeutic protein degradation. Integrating these advanced nanotechnological modalities with the inherent modularity of effector-independent degraders undoubtedly outlines a fertile, yet underexplored, frontier for achieving "reduced-off-target" therapeutic protein degradation.

6. Conclusions

TPD is creating a paradigm shift in drug development, moving beyond the limitations of classical, occupancy-driven pharmacology. In addition to classical iTPD strategies based on the UPS, recent advances have seen growing emphasis on autophagy−lysosome system-based iTPD and endosome−lysosome-mediated eTPD, significantly expanding the scope of degradable targets from intracellular proteins to extracellular and membrane-associated ones. This diversification opens new therapeutic possibilities and enhances intervention flexibility. However, several critical challenges remain. Firstly, many degraders exhibit unfavorable physicochemical properties—typically large, complex structures that fall into the bRo5 category, resulting in poor solubility, limited stability, and suboptimal pharmacokinetics. Secondly, concerns around off-target and on-target, off-tissue effects persist, representing a common hurdle for highly potent therapeutics. Moreover, class-specific limitations must be addressed. iTPDs face obstacles such as the hook effect in PROTACs, where efficacy diminishes at high concentrations, and the reliance of autophagy-dependent degraders (*e.g.*, AUTACs) on variable autophagic activity. Meanwhile, eTPDs (*e.g.*, LYTACs) are challenged by the avidity imperative for effective cell surface engagement and the complexities of ensuring efficient lysosomal trafficking.

The convergence of TPD and nanotechnology represents another transformative advance in pharmaceutical research. As we have dissected, nanotechnology is not a monolithic solution but a versatile and programmable toolkit that can be rationally tailored to the distinct biological challenges posed by different TPD strategies. The "Destination-Driven Framework" proposed herein provides a clear logic for this tailoring. For iTPD, where the target is the cytosol, the nano-platform serves as the ultimate "delivery vehicle", engineered with a sophisticated playbook to chaperone a

poorly drug-like molecule through a multi-stage obstacle course culminating in the "escape from the endosome". Conversely, for eTPD, where the destination is the lysosome, the nanoparticle transforms into a "programmable nano-scaffold", designed to master the intricate choreography of cell-surface engagement, internalization, and lysosomal trafficking.

While the preclinical proof-of-concept for NanoTPD is compelling, translating academic innovation into clinical reality demands a clear-eyed assessment of the biological barriers. A critical lesson from the broader field of nanomedicine is that the nanoparticle is never a truly "passive" entity. The future of NanoTPD lies in transcending the "carrier-centric" mindset—where the vehicle is viewed merely as an inert shuttle—toward a "bio-integrated" paradigm, where the complex interactions at the nano-bio interface are not only understood but actively exploited to drive therapeutic efficacy.

Central to this challenge is the protein corona, the spontaneous acquisition of a "biological identity" upon contact with physiological fluids. Upon systemic administration, the engineered surface of any nanoparticle is instantly coated by a complex layer of plasma proteins. For Nanoparticle-Enabled TPD, this interaction dictates *in vivo* fate through distinct, yet equally critical, mechanisms:

First, for iTPD-loaded nanocarriers, the corona challenges structural integrity. Recent bibliometric analyses highlight that "soft" carriers, such as predominantly LNPs, are highly susceptible to interactions with biological fluids. The competitive adsorption and insertion of blood proteins can trigger lipid rearrangement and structural remodeling. This leads to the premature leakage of hydrophobic payloads (such as PROTACs) before they reach the target tissue, effectively uncoupling the nanocarrier's biodistribution from the payload's pharmacodynamics. Second, for rigid carriers and nanoparticles acting as intrinsic degraders, the corona imposes functional masking and misrouting. Even if structural integrity is maintained, the adsorbed protein layer can sterically obscure surface ligands, resulting in "ligand masking" and thus less-effective tissue targeting. For nanoparticles as intrinsic degraders, this is catastrophic as it diminishes the binding affinity to LTRs or POIs, thereby aborting the formation of the ternary complex required for degradation. More fundamentally, at the cellular level, the target cell does not directly recognize the engineered nanoparticle surface, but rather the topological arrangement of the corona[163]. Although substantial effort has been devoted to understanding protein corona formation in the extracellular milieu and its influence on nanoparticle uptake, far less attention has been paid to the intracellular fate of the corona once internalization occurs. Accumulating evidence indicates that corona composition not only dictates the kinetics and pathway of endocytosis, but also exerts a profound influence on downstream cellular processing[164]. A corona enriched in denatured proteins or opsonins, for instance, may function as a molecular "danger" signature, preferentially engaging scavenger receptors and routing nanoparticles toward lysosomal sequestration. For iTPD payloads, which require cytosolic access to co-opt the ubiquitin—proteasome system, such lysosomal confinement constitutes a functional dead end, effectively precluding productive degradation.

Another layer of biological interaction that fundamentally shapes degradation efficiency lies in the capacity of nanoparticles to modulate the basal autophagic state of host cells. Nanomaterials are seldom biologically inert; rather, their physicochemical attributes can actively reprogram intracellular homeostasis. Positively charged lipids such as 1,2-dioleoyl-3-trimethylammoniumpropane (DOTAP), for example can act as bioactive stimuli to elevate basal autophagy, thereby reshaping the intracellular proteostatic landscape[142]. Elucidating the fundamental nano—bio interface is therefore not a purely academic endeavour, but a prerequisite for the rational development of next-generation NanoTPD platforms with enhanced efficiency and predictability. Achieving this objective will require the deployment of increasingly sophisticated and quantitative methodologies. Live-cell, high-resolution imaging approaches are needed to resolve nanoparticle trafficking and payload release dynamics in real time. Complementary genetic perturbation strategies, including CRISPR-based screens, can systematically delineate the repertoire of surface receptors and endocytic machinery governing nanoparticle entry. At the systems level, quantitative profiling of ubiquitination landscapes and autophagic flux will be essential to define how nano-induced perturbations reshape cellular proteostasis. Together, such integrated analyses will enable a mechanistically informed framework for engineering more precise and controllable degradation platforms.

While the mechanistic potential of Nanoparticle-Enabled TPD strategy is vast, bridging the "bench-to-bedside" chasm demands confronting the persistent hurdles of nanomedicine. The first barrier is Chemistry, Manufacturing, and Controls, primarily rooted in the intricate physicochemical processes required for their supramolecular assembly. Unlike conventional therapeutics, the formulation of nanocarriers, whether through nanoprecipitation, emulsification, or microfluidic self-assembly, operates within exceedingly narrow thermodynamic and kinetic windows, demonstrating extreme sensitivity to processing parameters such as temperature, pH, and shear forces. Consequently, transitioning from meticulously controlled laboratory-scale synthesis to commercial bioreactors frequently induces profound batch-to-batch heterogeneity in critical quality attributes, including particle size distribution, zeta potential, and encapsulation efficiency. This scalability hurdle is further exacerbated by a pervasive lack of high-resolution, standardized analytical methodologies, which renders the precise characterization of surface properties and the separation of structurally analogous impurities exceptionally difficult. Moreover, the inherent physical instability of these nanostructures presents a dual paradox during downstream processing and storage; rigorous purification to eliminate residual organic solvents and unencapsulated payloads often compromises carrier integrity, leading to premature drug leakage, particle aggregation, and severely diminished yields. Ultimately, this intricate nexus of manufacturing fragility and analytical limitations, coupled with an exorbitant reliance on cost-prohibitive raw materials (*e.g.*, highly purified functional lipids) and specialized Good Manufacturing Practice infrastructure, imposes a stringent techno-economic barrier that severely restricts the commercial viability of emerging nanotherapeutics.

Inextricably intertwined with these manufacturing inconsistencies is the profound uncertainty surrounding the biological fate and safety profiles of nanotherapeutics, where even minor physicochemical variations can precipitate drastic shifts in pharmacokinetics and toxicity[165]. Unlike conventional small molecules, once administered, these complex nanomedicines often evade traditional clearance mechanisms, leading to unmonitored accumulation in the reticuloendothelial system (RES), cardiovascular, and central nervous systems, potentially triggering oxidative stress-mediated mitochondrial dysfunction, inflammatory cascades, and DNA damage. This risk is compounded by the non-linear relationship between formulation attributes and biological response; for instance, subtle structural differences in LNPs, as evidenced by the distinct pH gradients and core structures of COVID-19 mRNA vaccines compared to liposomal doxorubicin, dictate their specific *in vivo* behavior and efficacy[166].

What's more, the regulatory landscape represents one of the most formidable bottlenecks in the clinical translation of nanoformulations, primarily because regulatory frameworks have

lagged significantly behind the rapid evolution of nanotechnology. Currently, major regulatory bodies such as the FDA and EMA lack standalone, globally harmonized guidelines specifically tailored for complex nanomedicines. Instead, authorities often rely on an ambiguous "case-by-case" assessment approach or attempt to fit these highly advanced therapeutics into conventional small-molecule approval pathways. This fundamental regulatory gap directly exacerbates the engineering challenges of manufacturing and scalability. Without universally defined Critical Quality Attributes for nanoscale structures, developers face immense difficulties in establishing standardized Quality by Design parameters. Consequently, maintaining batch-to-batch consistency, particularly regarding particle size distribution, drug loading, and surface modifications, during industrial scale-up becomes exceptionally challenging and costly[167]. Furthermore, the absence of a distinct and streamlined regulatory pathway adds significant commercial and legal uncertainty for long-term clinical application.

Confronting these immense challenges directly informs a necessary strategic pivot towards "engineered simplicity" and "problem-driven pragmatism". We must concede that the classical EPR effect has proven to be an unreliable predictor of clinical success, forcing a paradigm shift in our approach. A more pragmatic and promising path forward is to first target diseases in organs of natural nanoparticle accumulation—the liver, spleen, and immune cells—where the certainty of delivery is far greater. The definitive success of Onpattro® is the ultimate validation of this strategy. This focus on pragmatism extends to design philosophy itself; instead of building a multi-functional "Swiss Army knife," we should design a "scalpel" that solves one critical bottleneck with minimal necessary complexity, as functional simplicity is often the most direct path to stability and control. This new mindset even allows us to re-examine biological interactions once seen as obstacles, turning foes into friends. We can, for example, actively engineer the protein corona to recruit specific plasma proteins that "chaperone" the nanoparticle to its target, or leverage the unique pH of the endosome not as a barrier, but as a precise trigger to activate the payload.

In conclusion, the future of NanoTPD will not be defined by how complex we can make a nanoparticle, but by how we apply the smartest and simplest design to solve a significant clinical problem that is otherwise intractable. By embracing the nanoparticle as an active, designable "biological entity"—not a passive "delivery truck"—we can finally begin to rationally engineer platforms that are not only effective, but truly transformative. Thus, the fusion of nanotechnology with TPD is creating a therapeutic paradigm of unprecedented power and versatility. It offers a tangible path to drugging the "undruggable" and programming therapeutic outcomes with increasing precision. The journey from the laboratory bench to the patient's bedside is formidable, paved with significant challenges in mechanistic understanding, engineering complexity, and clinical translation. However, by learning the hard-won lessons from the broader fields of nanomedicine and proximity-induced biology, and by fostering a deeply interdisciplinary approach, the scientific community is poised to transform these innovative concepts into a powerful new class of medicines that can truly redefine the future of therapy.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

This study used AI-4.0 in the preparation of this assignment specifically for translating source material from Chinese to English, and for improving the grammatical structure of my writing. The core arguments, analysis, and references are entirely our own original work.

Acknowledgments

The work was supported by National Natural Science Foundation of China (Nos. 82373801, U25A20125, 82125028, and U22A20320), Research Funds of Sichuan Science and Technology Department (2025JDRC0029, China), Shenzhen Science and Technology Program (JCYJ20230807091159001 and JCYJ20250604122924032, China), and the Fundamental of Research Funds for the Central Universities.

Author contributions

Yazhen Wang and Xue Xia contributed equally for this manuscript. Both Yazhen Wang and Xue Xia conceived the review topic, designed the structure and wrote the original draft. Shengwei Xie and Fan Tong provided critical revisions for the content and edited the manuscript. Huile Gao and Wen Liu reviewed and provided final approval of the version to be published. All authors reviewed and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Sun R, Xu Z, Zhu C, Chen T, Munoz LE, Dai L, et al. Alpha-1 antitrypsin in autoimmune diseases: roles and therapeutic prospects. *Int Immunopharmacol* 2022;**110**:109001.
2. Li X, Xu Z. Applications of matrix metalloproteinase-9-related nanomedicines in tumors and vascular diseases. *Pharmaceutics* 2025. Available from: https://doi.org/10.3390/pharmaceutics17040479.
3. Luo B, Ma Y, Zhou Y, Zhang N, Luo Y. Human ClpP protease, a promising therapy target for diseases of mitochondrial dysfunction. *Drug Discov Today* 2021;**26**:968−81.
4. Ju Y, An Q, Zhang Y, Sun K, Bai L, Luo Y. Recent advances in Clp protease modulation to address virulence, resistance and persistence of MRSA infection. *Drug Discov Today* 2021;**26**:2190−7.
5. Xiang X, Bao R, Wu Y, Luo Y. Targeting mitochondrial proteases for therapy of acute myeloid leukaemia. *Br J Pharmacol* 2022;**179**: 3268−82.
6. Javed SA, Najmi A, Ahsan W, Zoghebi K. Targeting PD-1/PD-L-1 immune checkpoint inhibition for cancer immunotherapy: success and challenges. *Front Immunol* 2024;**15**:1383456.
7. Xu J, Kong Y, Zhu P, Du M, Liang X, Tong Y, et al. Progress in small-molecule inhibitors targeting PD-L1. *RSC Med Chem* 2024;**15**: 1161−75.
8. Redman JM, Hill EM, AlDeghaither D, Weiner LM. Mechanisms of action of therapeutic antibodies for cancer. *Mol Immunol* 2015;**67**: 28−45.
9. Deng H, Zhang Q, Lei Q, Yang N, Yang K, Jiang J, et al. Discovering monoacylglycerol lipase inhibitors by a combination of fluorogenic substrate assay and activity-based protein profiling. *Front Pharmacol* 2022;**13**:941522.
10. Xu X, Zhang L, Yang T, Qiu Z, Bai L, Luo Y. Targeting caseinolytic protease P and its AAA1 chaperone for tuberculosis treatment. *Drug Discov Today* 2023;**28**:103508.
11. Wan G, Li S, Tang Q, Qiu H, Zhang Q, Yu L. An updated patent review of EZH2 inhibitors (2024−present). *Expert Opin Ther Pat* 2025;**35**:597−610.

12. Marine JC, Dawson SJ, Dawson MA. Non-genetic mechanisms of therapeutic resistance in cancer. *Nat Rev Cancer* 2020;**20**: 743−56.
13. Ward RA, Fawell S, Floc'h N, Flemington V, McKerrecher D, Smith PD. Challenges and opportunities in cancer drug resistance. *Chem Rev* 2021;**121**:3297−351.
14. Yang QE, Ma X, Li M, Zhao M, Zeng L, He M, et al. Evolution of triclosan resistance modulates bacterial permissiveness to multidrug resistance plasmids and phages. *Nat Commun* 2024;**15**:3654.
15. Bedard PL, Hyman DM, Davids MS, Siu LL. Small molecules, big impact: 20 years of targeted therapy in oncology. *Lancet* 2020;**395**: 1078−88.
16. Zhong L, Li Y, Xiong L, Wang W, Wu M, Yuan T, et al. Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. *Signal Transduct Target Ther* 2021;**6**:201.
17. Guo J, Zheng Q, Peng Y. BET proteins: biological functions and therapeutic interventions. *Pharmacol Ther* 2023;**243**:108354.
18. Zhang Q, Yang H, Feng Q, Cao J, Zhang Y, Li L, et al. Focus on the classical and non-classical functions of EZH2: guide the development of inhibitors and degraders. *Pharmacol Res* 2022;**178**:106159.
19. Mullard A. Targeted protein degraders crowd into the clinic. *Nat Rev Drug Discov* 2021;**20**:247−50.
20. Zhao L, Zhao J, Zhong K, Tong A, Jia D. Targeted protein degradation: mechanisms, strategies and application. *Signal Transduct Target Ther* 2022;**7**:113.
21. Campos MA, Riha IA, Zhang C, Mozes C, Scheidt KA, Zhang X. Discovery of DCAF16 binders for targeted protein degradation. *ACS Chem Biol* 2025;**20**:479−88.
22. Samarasinghe KTG, Crews CM. Targeted protein degradation: a promise for undruggable proteins. *Cell Chem Biol* 2021;**28**:934−51.
23. Sakamoto KM, Kim KB, Kumagai A, Mercurio F, Crews CM, Deshaies RJ. Protacs: chimeric molecules that target proteins to the Skp1−Cullin−F box complex for ubiquitination and degradation. *Proc Natl Acad Sci U S A* 2001;**98**:8554−9.
24. Schneekloth AR, Pucheault M, Tae HS, Crews CM. Targeted intracellular protein degradation induced by a small molecule: en route to chemical proteomics. *Bioorg Med Chem Lett* 2008;**18**:5904−8.
25. Banik SM, Pedram K, Wisnovsky S, Ahn G, Riley NM, Bertozzi CR. Lysosome-targeting chimaeras for degradation of extracellular proteins. *Nature* 2020;**584**:291−7.
26. Cotton AD, Nguyen DP, Gramespacher JA, Seiple IB, Wells JA. Development of antibody-based PROTACs for the degradation of the cell-surface immune checkpoint protein PD-L1. *J Am Chem Soc* 2021;**143**:593−8.
27. Pance K, Gramespacher JA, Byrnes JR, Salangsang F, Serrano JC, Cotton AD, et al. Modular cytokine receptor-targeting chimeras for targeted degradation of cell surface and extracellular proteins. *Nat Biotechnol* 2023;**41**:273−81.
28. Takahashi D, Moriyama J, Nakamura T, Miki E, Takahashi E, Sato A, et al. AUTACs: cargo-specific degraders using selective autophagy. *Mol Cell* 2019;**76**:797−810.e10.
29. Ji CH, Kim HY, Lee MJ, Heo AJ, Park DY, Lim S, et al. The AUTOTAC chemical biology platform for targeted protein degradation *via* the autophagy−lysosome system. *Nat Commun* 2022;**13**:904.
30. Li Z, Zhu C, Ding Y, Fei Y, Lu B. ATTEC: a potential new approach to target proteinopathies. *Autophagy* 2020;**16**:185−7.
31. Fu Y, Lu B. Targeting lipid droplets for autophagic degradation by ATTEC. *Autophagy* 2021;**17**:4486−8.
32. Tan S, Wang D, Fu Y, Zheng H, Liu Y, Lu B. Targeted clearance of mitochondria by an autophagy-tethering compound (ATTEC) and its potential therapeutic effects. *Sci Bull (Beijing)* 2023;**68**:3013−26.
33. Yao J, Tao Y, Hu Z, Li J, Xue Z, Zhang Y, et al. Optimization of small molecule degraders and antagonists for targeting estrogen receptor based on breast cancer: current status and future. *Front Pharmacol* 2023;**14**:1225951.
34. He Y, Ju Y, Hu Y, Wang B, Che S, Jian Y, et al. Brd4 proteolysis-targeting chimera nanoparticles sensitized colorectal cancer chemotherapy. *J Control Release* 2023;**354**:155−66.
35. Wu X, Shu Y, Zheng Y, Zhang P, Cong H, Zou Y, et al. Recent advances in nanomedicine: cutting-edge research on nano-PROTAC delivery systems for cancer therapy. *Pharmaceutics* 2025;**17**:1037.
36. Dissmeyer N, Coux O, Rodriguez MS, Barrio R. Core Group Members of P. PROTEOSTASIS: a european network to break barriers and integrate science on protein homeostasis. *Trends Biochem Sci* 2019;**44**:383−7.
37. Muller JB, Geyer PE, Colaco AR, Treit PV, Strauss MT, Oroshi M, et al. The proteome landscape of the kingdoms of life. *Nature* 2020; **582**:592−6.
38. Kuzu OF, Granerud LJT, Saatcioglu F. Navigating the landscape of protein folding and proteostasis: from molecular chaperones to therapeutic innovations. *Signal Transduct Target Ther* 2025;**10**:358.
39. Dikic I. Proteasomal and autophagic degradation systems. *Annu Rev Biochem* 2017;**86**:193−224.
40. Pohl C, Dikic I. Cellular quality control by the ubiquitin−proteasome system and autophagy. *Science* 2019;**366**:818−22.
41. Ohtake F, Saeki Y, Ishido S, Kanno J, Tanaka K. The k48−k63 branched ubiquitin chain regulates NF-kappaB signaling. *Mol Cell* 2016;**64**:251−66.
42. Luzio JP, Pryor PR, Bright NA. Lysosomes: fusion and function. *Nat Rev Mol Cell Biol* 2007;**8**:622−32.
43. Doherty GJ, McMahon HT. Mechanisms of endocytosis. *Annu Rev Biochem* 2009;**78**:857−902.
44. Lancaster CE, Ho CY, Hipolito VEB, Botelho RJ, Terebiznik MR. Phagocytosis: what's on the menu?. *Biochem Cell Biol* 2019;**97**:21−9.
45. Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. *Cell* 2011;**147**:728−41.
46. Hu M, Zhou W, Wang Y, Yao D, Ye T, Yao Y, et al. Discovery of the first potent proteolysis targeting chimera (PROTAC) degrader of indoleamine 2,3-dioxygenase 1. *Acta Pharm Sin B* 2020;**10**: 1943−53.
47. Wang L, Cai X, Kong Y, Wu Q, Hu W, Wang Y. Evaluation of anti-leukemic activity and underlying mechanisms of the novel GSPT1 degrader AB138 in acute myeloid leukemia. *Invest New Drugs* 2025;**43**:646−55.
48. Xue J, Zhu Y, Bai S, He C, Du G, Zhang Y, et al. Nanoparticles with rough surface improve the therapeutic effect of photothermal immunotherapy against melanoma. *Acta Pharm Sin B* 2022;**12**: 2934−49.
49. Yang T, Hu Y, Miao J, Chen J, Liu J, Cheng Y, et al. A BRD4 PROTAC nanodrug for glioma therapy *via* the intervention of tumor cells proliferation, apoptosis and M2 macrophages polarization. *Acta Pharm Sin B* 2022;**12**:2658−71.
50. Ye W, Wu X, Wang X, Wei X, Tang Y, Ouyang X, et al. The proteolysis targeting chimera GMB-475 combined with dasatinib for the treatment of chronic myeloid leukemia with BCR::ABL1 mutants. *Front Pharmacol* 2022;**13**:931772.
51. Yao D, Li T, Yu L, Hu M, He Y, Zhang R, et al. Selective degradation of hyperphosphorylated tau by proteolysis-targeting chimeras ameliorates cognitive function in Alzheimer's disease model mice. *Front Pharmacol* 2024;**15**:1351792.
52. Zhu C, Yang Z, Zhang Y, Li Z, Li G, Yang B, et al. PROTAC for Bruton's tyrosine kinase degradation alleviates inflammation in autoimmune diseases. *Cell Discov* 2024;**10**:82.
53. Toure M, Crews CM. Small-molecule PROTACS: new approaches to protein degradation. *Angew Chem Int Ed Engl* 2016;**55**: 1966−73.
54. Fu Y, Zhang J, Qin R, Ren Y, Zhou T, Han B, et al. Activating autophagy to eliminate toxic protein aggregates with small molecules in neurodegenerative diseases. *Pharmacol Rev* 2025;**77**:100053.
55. Lin X, Xiang H, Luo G. Targeting estrogen receptor alpha for degradation with PROTACs: a promising approach to overcome endocrine resistance. *Eur J Med Chem* 2020;**206**:112689.
56. Snyder LB, Flanagan JJ, Qian Y, Gough SM, Andreoli M, Bookbinder M, et al. The discovery of ARV-471, an orally bioavailable estrogen receptor degrading PROTAC for the treatment of patients with breast cancer. *Cancer Res* 2021;**81**:44.

57. Liu J, Farmer Jr JD, Lane WS, Friedman J, Weissman I, Schreiber SL. Calcineurin is a common target of cyclophilin−cyclosporin A and FKBP−FK506 complexes. *Cell* 1991;**66**:807−15.
58. Griffith JP, Kim JL, Kim EE, Sintchak MD, Thomson JA, Fitzgibbon MJ, et al. X-Ray structure of calcineurin inhibited by the immunophilin-immunosuppressant FKBP12−FK506 complex. *Cell* 1995;**82**:507−22.
59. Kissinger CR, Parge HE, Knighton DR, Lewis CT, Pelletier LA, Tempczyk A, et al. Crystal structures of human calcineurin and the human FKBP12−FK506−calcineurin complex. *Nature* 1995;**378**: 641−4.
60. Chamberlain PP, Cathers BE. Cereblon modulators: low molecular weight inducers of protein degradation. *Drug Discov Today Technol* 2019;**31**:29−34.
61. Kronke J, Fink EC, Hollenbach PW, MacBeth KJ, Hurst SN, Udeshi ND, et al. Lenalidomide induces ubiquitination and degradation of CK1alpha in del(5q) MDS. *Nature* 2015;**523**:183−8.
62. Guo H. Bumped pomalidomide-based PROTACs. *Commun Chem* 2024;**7**:41.
63. Han T, Goralski M, Gaskill N, Capota E, Kim J, Ting TC, et al. Anticancer sulfonamides target splicing by inducing RBM39 degradation *via* recruitment to DCAF15. *Science* 2017;**356**:eaal3755.
64. Du X, Volkov OA, Czerwinski RM, Tan H, Huerta C, Morton ER, et al. Structural basis and kinetic pathway of RBM39 recruitment to DCAF15 by a mulfonamide molecular glue E7820. *Structure* 2019; **27**:1625-33.e3.
65. Hansen JD, Correa M, Alexander M, Nagy M, Huang D, Sapienza J, et al. CC-90009: a cereblon E3 ligase modulating drug that promotes selective degradation of GSPT1 for the treatment of acute myeloid leukemia. *J Med Chem* 2021;**64**:1835−43.
66. Sellar RS, Sperling AS, Slabicki M, Gasser JA, McConkey ME, Donovan KA, et al. Degradation of GSPT1 causes TP53-independent cell death in leukemia while sparing normal hematopoietic stem cells. *J Clin Investig* 2022;**132**:e153514.
67. Zhang Y, Liu W, Tong C, Wang X, Chang X, Qu F, et al. Design and discovery of preclinical candidate LYG-409 as a highly potent and selective GSPT1 molecular glue degraders. *J Med Chem* 2025;**68**: 2608−38.
68. Li YD, Ma MW, Hassan MM, Hunkeler M, Teng M, Puvar K, et al. Template-assisted covalent modification underlies activity of covalent molecular glues. *Nat Chem Biol* 2024;**20**:1640−9.
69. Zhuang Z, Byun WS, Kozicka Z, Donovan KA, Dwyer BG, Thornhill AM, et al. Rational design of CDK12/13 and BRD4 molecular glue degraders. *Angew Chem Int Ed Engl* 2025;**64**: e202508427.
70. Dong G, Ding Y, He S, Sheng C. Molecular glues for targeted protein degradation: from serendipity to rational discovery. *J Med Chem* 2021;**64**:10606−20.
71. Mangano K, Guenette RG, Hill S, Li S, Liu JJ, Nadel CM, et al. VIPER-TACs leverage viral E3 ligases for disease-specific targeted protein degradation. *Cell Chem Biol* 2025;**32**:423-33.e9.
72. Loy CA, Ali EMH, Seabrook LJ, Harris Jr TJ, Kragness KA, Albrecht L, et al. ByeTAC: bypassing E-ligase-targeting chimeras for direct proteasome degradation. *J Med Chem* 2025;**68**:9694−705.
73. Mo M, Wang F, Zhang H, Zhang Y, Yang C, Shang J, et al. Membrane-bounded intracellular E3 ubiquitin ligase-targeting chimeras (MembTACs) for targeted membrane protein degradation. *Angew Chem Int Ed Engl* 2025;**64**:e202501857.
74. Li X, Liu Q, Xie X, Peng C, Pang Q, Liu B, et al. Application of novel degraders employing autophagy for expediting medicinal research. *J Med Chem* 2023;**66**:1700−11.
75. Cassidy K, Zhao H. Redefining the scope of targeted protein degradation: translational opportunities in hijacking the autophagy−lysosome pathway. *Biochemistry* 2023;**62**:580−7.
76. Sawa T, Zaki MH, Okamoto T, Akuta T, Tokutomi Y, Kim-Mitsuyama S, et al. Protein *S*-guanylation by the biological signal 8-nitroguanosine 3′,5′-cyclic monophosphate. *Nat Chem Biol* 2007;**3**:727−35.
77. Ito C, Saito Y, Nozawa T, Fujii S, Sawa T, Inoue H, et al. Endogenous nitrated nucleotide is a key mediator of autophagy and innate defense against bacteria. *Mol Cell* 2013;**52**:794−804.
78. Takahashi D, Arimoto H. Targeting selective autophagy by AUTAC degraders. *Autophagy* 2020;**16**:765−6.
79. Anding AL, Baehrecke EH. Cleaning house: selective autophagy of organelles. *Dev Cell* 2017;**41**:10−22.
80. Runwal G, Stamatakou E, Siddiqi FH, Puri C, Zhu Y, Rubinsztein DC. LC3-positive structures are prominent in autophagy-deficient cells. *Sci Rep* 2019;**9**:10147.
81. Li Z, Wang C, Wang Z, Zhu C, Li J, Sha T, et al. Allele-selective lowering of mutant HTT protein by HTT-LC3 linker compounds. *Nature* 2019;**575**:203−9.
82. Bourdenx M, Martin-Segura A, Scrivo A, Rodriguez-Navarro JA, Kaushik S, Tasset I, et al. Chaperone-mediated autophagy prevents collapse of the neuronal metastable proteome. *Cell* 2021;**184**:2696-714.e25.
83. Gough NR, Hatem CL, Fambrough DM. The family of LAMP-2 proteins arises by alternative splicing from a single gene: characterization of the avian LAMP-2 gene and identification of mammalian homologs of LAMP-2b and LAMP-2c. *DNA Cell Biol* 1995;**14**: 863−7.
84. Fan X, Jin WY, Lu J, Wang J, Wang YT. Rapid and reversible knockdown of endogenous proteins by peptide-directed lysosomal degradation. *Nat Neurosci* 2014;**17**:471−80.
85. Bauer PO, Goswami A, Wong HK, Okuno M, Kurosawa M, Yamada M, et al. Harnessing chaperone-mediated autophagy for the selective degradation of mutant huntingtin protein. *Nat Biotechnol* 2010;**28**:256−63.
86. Li YY, Yang Y, Zhang RS, Ge RX, Xie SB. Targeted degradation of membrane and extracellular proteins with LYTACs. *Acta Pharmacol Sin* 2025;**46**:1−7.
87. Ahn G, Banik SM, Miller CL, Riley NM, Cochran JR, Bertozzi CR. LYTACs that engage the asialoglycoprotein receptor for targeted protein degradation. *Nat Chem Biol* 2021;**17**:937−46.
88. Zhang D, Duque-Jimenez J, Facchinetti F, Brixi G, Rhee K, Feng WW, et al. Transferrin receptor targeting chimeras for membrane protein degradation. *Nature* 2025;**638**:787−95.
89. Zhang B, Brahma RK, Zhu L, Feng J, Hu S, Qian L, et al. Insulin-like growth factor 2 (IGF2)-fused lysosomal targeting chimeras for degradation of extracellular and membrane proteins. *J Am Chem Soc* 2023;**145**:24272−83.
90. Luo J, Gao Q, Tan K, Zhang S, Shi W, Luo L, et al. Lysosome targeting chimeras for glut1-facilitated targeted protein degradation. *J Am Chem Soc* 2024;**146**:17728−37.
91. Wang Q, Yang X, Yuan R, Shen A, Wang P, Li H, et al. A co-assembly platform engaging macrophage scavenger receptor A for lysosome-targeting protein degradation. *Nat Commun* 2024;**15**: 1663.
92. Xiao D, Dong J, Xie F, Feng X, Wang J, Xu X, et al. Polyvalent folate receptor-targeting chimeras for degradation of membrane proteins. *Nat Chem Biol* 2025;**21**:1731−41.
93. He S, Huang W, Zhu Y, Gao F, Fang Y, Zhu J, et al. HerTACs enable tumor-selective lysosomal degradation of membrane and extracellular proteins *via* HER2 trafficking. *Angew Chem Int Ed Engl* 2025; **64**:e202511467.
94. Chang X, Qiu X, Tong X, Gan S, Yi W, Xie S, et al. Sortilin-mediated rapid, precise and sustained degradation of membrane proteins *via* mRNA-encoded lysosome-targeting chimera. *Adv Sci (Weinh)* 2025;**12**:e2501222.
95. Loppinet E, Besser HA, Lee CE, Zhang W, Cui B, Khosla C. Targeted lysosomal degradation of secreted and cell surface proteins through the LRP-1 pathway. *J Am Chem Soc* 2023;**145**:18705−10.
96. Till NA, Ramanathan M, Bertozzi CR. Induced proximity at the cell surface. *Nat Biotechnol* 2025;**43**:702−11.
97. Gramespacher JA, Cotton AD, Burroughs PWW, Seiple IB, Wells JA. Roadmap for optimizing and broadening antibody-based PROTACs

for degradation of cell surface proteins. *ACS Chem Biol* 2022;**17**: 1259−68.
98. Marei H, Tsai WK, Kee YS, Ruiz K, He J, Cox C, et al. Antibody targeting of E3 ubiquitin ligases for receptor degradation. *Nature* 2022;**610**:182−9.
99. Koo BK, Spit M, Jordens I, Low TY, Stange DE, van de Wetering M, et al. Tumour suppressor RNF43 is a stem-cell E3 ligase that induces endocytosis of wnt receptors. *Nature* 2012;**488**:665−9.
100. Siepe DH, Picton LK, Garcia KC. Receptor elimination by E3 ubiquitin ligase recruitment (REULR): a targeted protein degradation toolbox. *ACS Synth Biol* 2023;**12**:1081−93.
101. Wu J, Gao Q, Xia Q, Wang Y, Zheng Z, He A, et al. Highly specific cytokine receptor-targeting chimeras for targeted membrane protein degradation and sensitization of osimertinib in EGFR-mutated non-small-cell lung cancer. *Adv Mater* 2025;**37**:e2504050.
102. Zhang H, Han Y, Yang Y, Lin F, Li K, Kong L, et al. Covalently engineered nanobody chimeras for targeted membrane protein egradation. *J Am Chem Soc* 2021;**143**:16377−82.
103. He WY, Chen CL, Zheng JW, Li YY, Shi HH, Zhou YM, et al. Targeted degradation of cell surface proteins through endocytosis triggered by cell-penetrating peptide-small molecule conjugates. *Nat Commun* 2025;**16**:7575.
104. Zhang D, Zhou X, Cai J, Tan W, Liu Y, Zhao Z. Molecularly built ligands degrade membrane receptors *via* enhancing their accumulation in lysosomes. *ACS Cent Sci* 2025;**11**:2460−73.
105. Saraswat AL, Vartak R, Hegazy R, Patel A, Patel K. Drug delivery challenges and formulation aspects of proteolysis targeting chimera (PROTACs). *Drug Discov Today* 2023;**28**:103387.
106. Cantrill C, Chaturvedi P, Rynn C, Petrig Schaffland J, Walter I, Wittwer MB. Fundamental aspects of DMPK optimization of targeted protein degraders. *Drug Discov Today* 2020;**25**:969−82.
107. Zhang W, Yuan L, Liu R, Jing Y, Lin S, Fang H, et al. A covalent self-reporting peptide degrader enables real-time monitoring of targeted protein degradation *in vivo*. *J Am Chem Soc* 2025;**147**: 27862−75.
108. Chan A, Haley RM, Najar MA, Gonzalez-Martinez D, Bugaj LJ, Burslem GM, et al. Lipid-mediated intracellular delivery of recombinant bioPROTACs for the rapid degradation of undruggable proteins. *Nat Commun* 2024;**15**:5808.
109. Wang Z, Li H, Gou L, Li W, Wang Y. Antibody−drug conjugates: recent advances in payloads. *Acta Pharm Sin B* 2023;**13**: 4025−59.
110. Xu J, Wang FJ, Xie M, Huang YY, Liu XL, Guo YY, et al. Modification-powered engineering of the aptamer-based proteolysis targeting chimeras for enhanced membrane protein degradation. *CCS Chem* 2026;**8**:2570−82.
111. Huang X, Wu F, Ye J, Wang L, Wang X, Li X, et al. Expanding the horizons of targeted protein degradation: a non-small molecule perspective. *Acta Pharm Sin B* 2024;**14**:2402−27.
112. Cecchini C, Tardy S, Scapozza L. Linkers as game-changers in PROTAC technology: emphasizing general trends in PROTAC pharmacokinetics for their rational design. *Chimia* 2022;**76**:341−5.
113. Dong YW, Ma TT, Xu T, Feng ZY, Li YG, Song LL, et al. Characteristic roadmap of linker governs the rational design of PROTACs. *Acta Pharm Sin B* 2024;**14**:4266−95.
114. Farouk F, Shamma R. Chemical structure modifications and nanotechnology applications for improving ADME-Tox properties, a review. *Arch Pharm (Weinheim)* 2019;**352**:e1800213.
115. Tan SY, Chen ZL, Lu RQ, Liu HX, Yao XJ. Rational proteolysis targeting chimera design driven by molecular modeling and machine learning. *WIREs Comput Mol Sci* 2025;**15**:70013.
116. Zheng SJ, Tan YH, Wang ZY, Li CT, Zhang ZQ, Sang X, et al. Accelerated rational PROTAC design *via* deep learning and molecular simulations. *Nat Mach Intell* 2022;**4**:739−48.
117. Liang J, Yang B, Zhou X, Han Q, Zou J, Cheng L. Stimuli-responsive drug delivery systems for head and neck cancer therapy. *Drug Deliv* 2021;**28**:272−84.
118. Li Z, Xiao C, Yong T, Li Z, Gan L, Yang X. Influence of nanomedicine mechanical properties on tumor targeting delivery. *Chem Soc Rev* 2020;**49**:2273−90.
119. Wang C, Zhang YJ, Chen WJ, Wu YD, Xing DM. New-generation advanced PROTACs as potential therapeutic agents in cancer therapy. *Mol Cancer* 2024;**23**:110.
120. Zhao W, Jiang Y, Li X, Wang H. Nanotechnology-enabled targeted protein degradation for cancer therapeutics. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2024;**16**:e2020.
121. Lin JY, Liu HJ, Wu Y, Jin JM, Zhou YD, Zhang H, et al. Targeted protein degradation technology and nanomedicine: powerful allies against cancer. *Small* 2023;**19**:e2207778.
122. Yang F, Luo Q, Wang Y, Liang H, Wang Y, Hou Z, et al. Targeted biomolecule regulation platform: a split-and-mix PROTAC approach. *J Am Chem Soc* 2023;**145**:7879−87.
123. Chrustowicz J, Sherpa D, Li J, Langlois CR, Papadopoulou EC, Vu DT, et al. Multisite phosphorylation dictates selective E2−E3 pairing as revealed by Ubc8/UBE2H-GID/CTLH assemblies. *Mol Cell* 2024;**84**:293−308.e14.
124. Dai ZL, Liang L, Wang WZ, Zuo P, Yu S, Liu YQ, et al. Structural insights into the ubiquitylation strategy of the oligomeric CRL2 E3 ubiquitin ligase. *EMBO J* 2024;**43**:1089−109.
125. Gadd MS, Testa A, Lucas X, Chan KH, Chen WZ, Lamont DJ, et al. Structural basis of PROTAC cooperative recognition for selective protein degradation. *Nat Chem Biol* 2017;**13**:514−21.
126. Kou P, Levy ES, Nguyen AD, Zhang D, Chen S, Cui Y, et al. Development of liposome systems for enhancing the PK properties of bivalent PROTACs. *Pharmaceutics* 2023;**15**:2098.
127. Hoogenboezem EN, Duvall CL. Harnessing albumin as a carrier for cancer therapies. *Adv Drug Deliv Rev* 2018;**130**:73−89.
128. Hu Z, Li R, Cui X, Hu C, Chen Z. Tailoring albumin-based theranostic PROTACs nanoparticles for enhanced NIR-II bioimaging and synergistic cancer chemo-phototherapy. *Chem Eng J* 2023;**469**: 143883.
129. Cho HH, Jeon SI, Shim MK, Ahn CH, Kim K. *In situ* albumin-binding and esterase-specifically cleaved BRD4-degrading PROTAC for targeted cancer therapy. *Biomaterials* 2023;**295**:122038.
130. Zhao LP, Zheng RR, Rao XN, Huang CY, Zhou HY, Yu XY, et al. Chemotherapy-enabled colorectal cancer immunotherapy of self-delivery nano-PROTACs by inhibiting tumor glycolysis and avoiding adaptive immune resistance. *Adv Sci (Weinh)* 2024;**11**:2309204.
131. Wang X, Su L, Niu C, Li X, Wang R, Li B, et al. Targeted degradation of KRAS protein in non-small cell lung cancer: therapeutic strategies using liposomal PROTACs with enhanced cellular uptake and pharmacokinetic profiles. *Drug Dev Res* 2024;**85**:e22241.
132. Akinc A, Maier MA, Manoharan M, Fitzgerald K, Jayaraman M, Barros S, et al. The Onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. *Nat Nanotechnol* 2019;**14**:1084−7.
133. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. *Nat Rev Mater* 2021;**6**:1078−94.
134. Ghosal S, Robertus C, Wang J, Chan HW, Alamgir A, Almonte J, et al. Nanoparticle-mediated delivery of peptide-based degraders enables targeted protein degradation. *bioRxiv* 2024. Available from: https://doi.org/10.1101/2024.03.17.584721.
135. Min H, Sun MC, Hu K, Zhang Y, Li J, Li Y, et al. Ionizable nano-PROTAC overcomes endosomal entrapment for enhanced LRG1 degradation and tumor suppression. *Angew Chem Int Ed Engl* 2026; **65**:e20235.
136. Liu HJ, Chen W, Wu G, Zhou J, Liu C, Tang Z, et al. Glutathione-scavenging nanoparticle-mediated PROTACs delivery for targeted protein degradation and amplified antitumor effects. *Adv Sci (Weinh)* 2023;**10**:2207439.
137. Yu YW, Hu WT, Xu YH, Xu HB, Gao JQ. Advancements in delivery systems for proteolysis-targeting chimeras (PROTACs): overcoming challenges and expanding biomedical applications. *J Control Release* 2025;**382**:113719.

138. He Q, Zhou L, Yu D, Zhu R, Chen Y, Song M, et al. Near-infrared-activatable PROTAC nanocages for controllable target protein degradation and on-demand antitumor therapy. *J Med Chem* 2023;**66**: 10458−72.
139. Wang F, Dong G, Ding M, Yu N, Sheng C, Li J. Dual-programmable semiconducting polymer nanoPROTACs for deep-tissue sonodynamic-ferroptosis activatable immunotherapy. *Small* 2024;**20**: 2306378.
140. Chen JJ, Qiu M, Ma FH, Yang L, Glass Z, Xu QB. Enhanced protein degradation by intracellular delivery of pre-fused PROTACs using lipid-like nanoparticles. *J Control Release* 2021;**330**:1244−9.
141. Xu MC, Chen JJ, Wang SY, Xu LL, Wu XH, Yu JP, et al. Autophagy-activating nanoautophagosome-tethering compounds for targeted protein degradation specifically in tumor cells. *ACS Macro Lett* 2025; **14**:250−7.
142. Huang X, Cao Z, Qian J, Ding T, Wu Y, Zhang H, et al. Nano-receptors promote mutant p53 protein degradation by mimicking selective autophagy receptors. *Nat Nanotechnol* 2024;**19**:545−53.
143. Wang YZ, Yang LY, Yan CX, Du YF, Li TH, Yang WQ, et al. Supramolecular artificial nano-AUTACs enable tumor-specific metabolism protein degradation for synergistic immunotherapy. *Sci Adv* 2024;**10**:eadn8079.
144. Divine R, Dang H, Ueda G, Fallas JA, Vulovic I, Sheffler W, et al. Designed proteins assemble antibodies into modular nanocages. *Science* 2021;**372**:eabd9994.
145. Xu MK, Hu YX, Wu JY, Liu J, Pu KY. Sonodynamic nano-LYTACs reverse tumor immunosuppressive microenvironment for cancer immunotherapy. *J Am Chem Soc* 2024;**146**:34669−80.
146. Mamun MAA, Bakunts AG, Chernorudskiy AL. Targeted degradation of extracellular proteins: state of the art and diversity of degrader designs. *J Hematol Oncol* 2025;**18**:52.
147. Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, Zhang C, et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Signal Transduct Target Ther* 2024;**9**:234.
148. Huang BW, Abedi M, Ahn G, Coventry B, Sappington I, Tang C, et al. Designed endocytosis-inducing proteins degrade targets and amplify signals. *Nature* 2025;**638**:796−804.
149. Liu Y, Liu R, Dong J, Xia X, Yang H, Wei S, et al. Targeted protein degradation *via* cellular trafficking of nanoparticles. *Nat Nanotechnol* 2025;**20**:296−302.
150. Yao S, Wang Y, Tang Q, Yin Y, Geng Y, Xu L, et al. A plug-and-play monofunctional platform for targeted degradation of extracellular proteins and vesicles. *Nat Commun* 2024;**15**:7237.
151. Wang XR, Chen SQ, Xia X, Du YF, Wei Y, Yang WQ, et al. Lysosome-targeting protein degradation through endocytosis pathway triggered by polyvalent nano-chimera for AD therapy. *Adv Mater* 2025;**37**:e2411061.
152. Saftig P, Klumperman J. Lysosome biogenesis and lysosomal membrane proteins: trafficking meets function. *Nat Rev Mol Cell Biol* 2009;**10**:623−35.
153. Braulke T, Bonifacino JS. Sorting of lysosomal proteins. *Biochim Biophys Acta* 2009;**1793**:605−14.
154. Yu J, Li H, Fang T, Yun C, Liu X, Xu J, et al. Harnessing the lysosomal sorting signals of the cation-mndependent mannose-6-phosphate receptor for targeted degradation of membrane proteins. *J Am Chem Soc* 2023;**145**:19107−19.
155. Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. *Adv Drug Deliv Rev* 2014;**66**:2−25.
156. Fan K, Zhang S, Jin Y, Hou Y, Tang G, Wang Z, et al. *Bioengineered ferritin-based LYTAC platform for tumor-targeted therapy.* 2024. Available from: https://doi.org/10.21203/rs.3.rs-5515153/v1.
157. Song Y, Cui L, Liu Z, Tang Z, Chen X. Multivalent RGD peptide-mediated nanochimera for lysosomal degradation of PDL1 protein. *Nano Lett* 2025;**25**:4078−86.
158. Kim D, Yang G, Lim C, Park G, Lee J, Sim Y, et al. Cancer specific CAIX-targeting supramolecular lysosome-targeting chimeras (supra-LYTAC) for targeted protein degradation. *Adv Sci (Weinh)* 2025;**12**: e2503134.
159. Xing Y, Li J, Wang L, Zhu Z, Yan J, Liu Y, et al. A bifunctional lysosome-targeting chimera nanoplatform for tumor-selective protein degradation and enhanced cancer immunotherapy. *Adv Mater* 2025; **37**:2417942.
160. Huang S, Ding X. Precise design strategies of nanotechnologies for controlled drug delivery. *J Funct Biomater* 2022;**13**:188.
161. Xiao Y, Zhou X, Niu X, Ye X, Chen D, Dong Q, et al. An engineered nanovesicles-based lysosome-targeting protein degradation platform (NV-TACs) for cancer immunotherapy. *J Am Chem Soc* 2026;**148**: 7008−23.
162. Tong B, Zhang X, Zhu D, Wang Y, Wei J, Ou Z, et al. Extracellular vesicle-based targeted protein degradation platform for multiple extracellular proteins. *EMBO Mol Med* 2026;**18**:759−94.
163. Hajipour MJ, Safavi-Sohi R, Sharifi S, Mahmoud N, Ashkarran AA, Voke E, et al. An overview of nanoparticle protein corona literature. *Small* 2023;**19**:e2301838.
164. Han S, da Costa Marques R, Simon J, Kaltbeitzel A, Koynov K, Landfester K, et al. Endosomal sorting results in a selective separation of the protein corona from nanoparticles. *Nat Commun* 2023;**14**:295.
165. Ramos TI, Villacis-Aguirre CA, Lopez-Aguilar KV, Santiago Padilla L, Altamirano C, Toledo JR, et al. The hitchhiker's guide to human therapeutic nanoparticle development. *Pharmaceutics* 2022;**14**:247.
166. Szebeni J, Kiss B, Bozo T, Turjeman K, Levi-Kalisman Y, Barenholz Y, et al. Insights into the structure of comirnaty covid-19 vaccine: a theory on soft, partially bilayer-covered nanoparticles with hydrogen bond-stabilized mRNA-lipid complexes. *ACS Nano* 2023; **17**:13147−57.
167. Gioria S, Caputo F, Urban P, Maguire CM, Bremer-Hoffmann S, Prina-Mello A, et al. Are existing standard methods suitable for the evaluation of nanomedicines: some case studies. *Nanomedicine (Lond)* 2018;**13**:539−54.