Nano-targeted protein degradation: Ushering in a new era of protein degradation therapeutics

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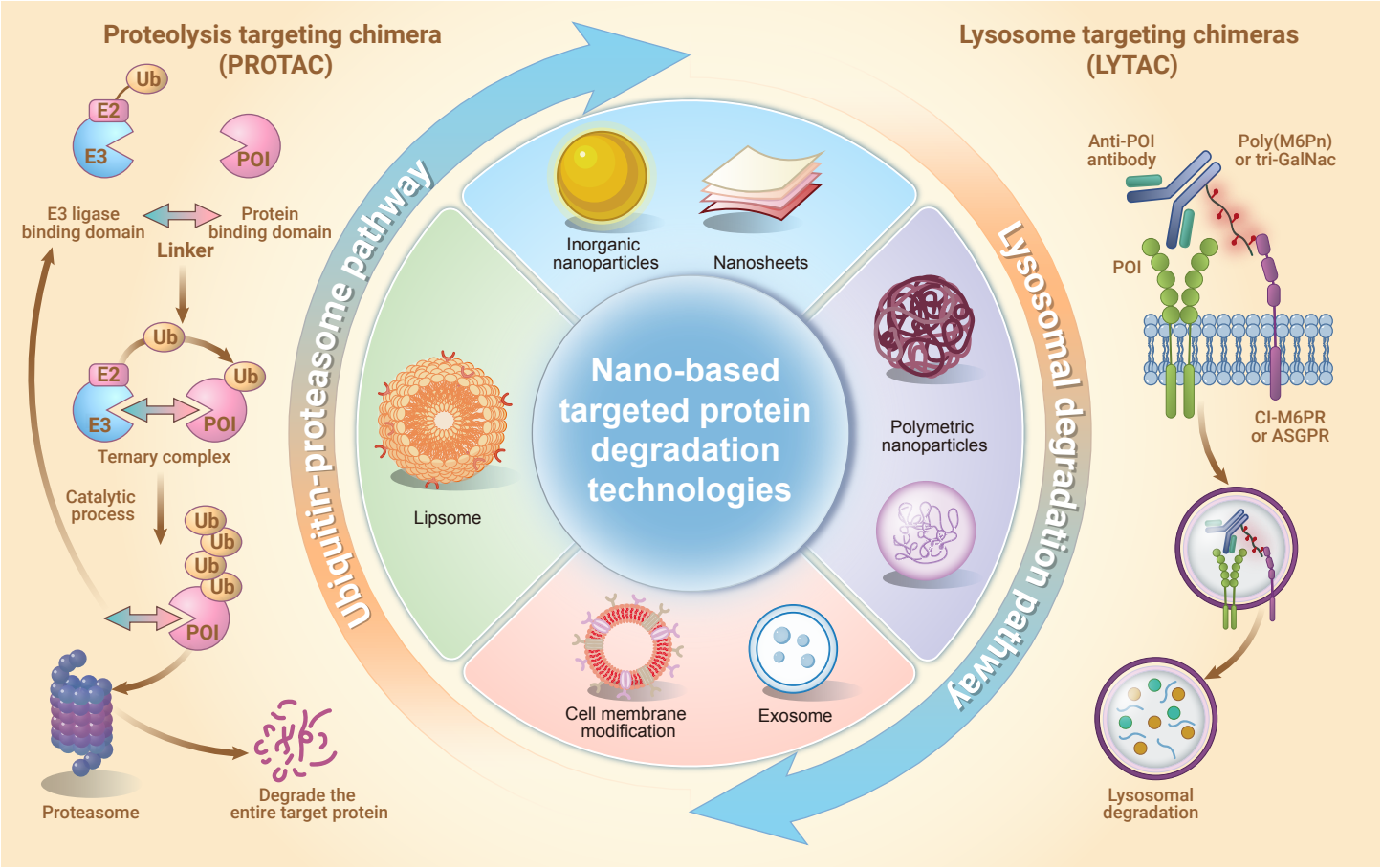
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Targeted protein degradation (TPD) has emerged as a transformative therapeutic strategy.
- This review provides a comprehensive overview of Nano-TPD.
- Nano-TPD is a next-generation therapeutic strategy with broad applicability.

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Precision Medicine REVIEW

The Innovation Drug Discovery

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Targeted protein degradation (TPD) has emerged as a transformative therapeutic strategy that overcomes the limitations of conventional small-molecule inhibitors (SMIs) by harnessing the degradation machinery, including the ubiquitin-proteasome system (UPS) and lysosomal pathway. However, traditional TPD agents face substantial challenges in clinical translation, such as poor solubility, low bioavailability, insufficient targeting specificity, and limited tissue penetration. To address these limitations, the integration of nanotechnology has given rise to Nano-TPD as a new generation therapeutic platform that revolutionizes TPD delivery. We first summarize the recent advances in TPD technology for the treatment of common clinical diseases, highlighting key molecular targets and representative degraders. Then, we focus on the design of Nano-TPD platforms, including lipid-based, polymeric, inorganic, and biomimetic nanocarriers, as well as innovative strategies. The core mechanisms of Nano-TPD, encompassing targeted delivery, intracellular trafficking, stimuli-triggered release, and enhanced protein degradation via UPS or lysosomal pathways, are systematically elaborated. Furthermore, we discuss the challenges and future perspectives of Nano-TPD. This review provides a comprehensive overview of Nano-TPD, emphasizing its role in advancing TPD toward clinical utility and expanding its therapeutic scope across various diseases.

INTRODUCTION

Proteins serve as fundamental building blocks of life and are indispensable for human growth, development, and maintaining normal physiological functions.[1] Cellular homeostasis relies on the precise coordination of protein synthesis, folding, and degradation.[2] However, genetic mutations, cellular stress, and metabolic dysregulation can lead to protein misfolding and subsequent aggregation, processes implicated in the pathogenesis of various diseases, including cancers and neurodegenerative diseases.[2-4] Conventional therapeutic strategies have largely focused on SMIs, which function primarily by occupying the active sites of target proteins to impede disease progression.[5,6] This occupancy-driven approach, however, faces significant limitations: many potential target proteins lack well-defined ligand-binding sites, rendering them "undruggable" by traditional inhibitors and thereby constraining therapeutic efficacy.[7]

In recent years, TPD has emerged as a transformative therapeutic strategy capable of overcoming these constraints. TPD technologies facilitate the selective depletion of target proteins by harnessing the cell's intrinsic degradation machinery. Current platforms primarily engage two pathways: the UPS, represented by proteolysis-targeting chimeras (PROTACs) and molecular glue degraders, and the lysosomal degradation pathway, leveraged by lysosome-targeting chimeras (LYTACs) and autophagy-targeting chimeras (AUTACs).[8,9] This innovative strategy offers a promising approach to surmounting the limitations associated with conventional therapeutic modalities. The core advantage of TPD lies in its ability to target "undruggable" proteins, which lack well-defined active sites, achieving more durable therapeutic effects via the physical elimination of proteins of interest (POI).[10]

Among various TPD technologies, PROTACs have been the most extensively studied since their initial report in 2001.[11,12] These heterobifunctional molecules consist of a ligand for a POI and a ligand for an E3 ubiquitin ligase, connected by a chemical linker. By recruiting an E3 ligase to the POI to form a ternary complex, PROTACs induce polyubiquitination and subsequent proteasomal degradation of the target.[13] Despite their promise, this strategy suffers from several drawbacks, such as poor pharmacokinetic properties, limited solubility, and suboptimal cell membrane permeability.[14] Molecular glues degraders, typically possessing smaller molecular weights and improved cellular uptake and bioavailability, offer an alternative for degrading intracellular pathogenic proteins in cancer and metabolic diseases.[8,15] Meanwhile, lysosome-based degradation strategies such as LYTACs have expanded the TPD landscape to include extracellular or membrane-associated proteins via the endolysosomal pathway.[16] These strategies are more applicable for treating neurodegenerative diseases and membrane protein-related cancers, but are also plagued by problems such as the risk of non-specific degradation of off-target substrates and challenges in delivery and stability.[13]

To address core limitations inherent to conventional TPD agents, including poor solubility, low bioavailability, insufficient targeting ability, and limited tissue penetration, the integration of nanotechnology represents a transformative leap in enhancing TPD performance. Nanoparticle-mediated degradation systems are designed to improve the pharmacokinetic profiles, solubility, stability, and targeting specificity of TPD molecules.[17] As an innovative fusion system integrating nanotechnology with TPD, the first function of Nano-TPD is a delivery platform. It efficiently transports traditional TPD formulations (such as PROTACs) to target cells or sites without participating in protein degradation itself.[18] The core value of it lies in overcoming the bottlenecks of low bioavailability and poor tissue penetration in conventional TPD formulations. Through subsequent advancements, researchers have engineered nanoparticles capable of actively participating in protein degradation. These modified particles no longer require specialized endocytic pathways or degradation-guided structural designs. Instead, they spontaneously initiate targeted protein degradation through intrinsic structural properties (such as surface ligand modifications), directly mediating target protein recognition, internalization, and degradation.[19] Their functionality has transcended that of mere delivery vehicles, establishing them as core components of the TPD reaction. Through various formulation strategies, nanoparticles can facilitate the target delivery, tissue accumulation, membrane permeability, and controlled intracellular release. Benefiting from enhanced bioavailability, targeted delivery, and intracellular translocation of degradants, nanoparticle-based systems exhibit considerable therapeutic potential. They offer a promising platform to overcome multifaceted delivery challenges in complex diseases, positioning Nano-TPD as a next-generation therapeutic strategy with broad applicability.

TPD TECHNOLOGY FOR DISEASES

TPD technology has emerged as a transformative therapeutic paradigm for diseases driven by the pathological accumulation or dysregulation of specific proteins. By harnessing endogenous degradation pathways, primarily the UPS and the lysosomal machinery, TPD enables the selective elimination of disease-causing proteins, offering a powerful strategy against a range of conditions, including cancer, neurodegenerative disorders, and autoimmune diseases.[8] In this section, we summarize the recent advances in TPD technology across these three major therapeutic areas, focusing on key molecular targets, representative degraders, and their preclinical or clinical progress.

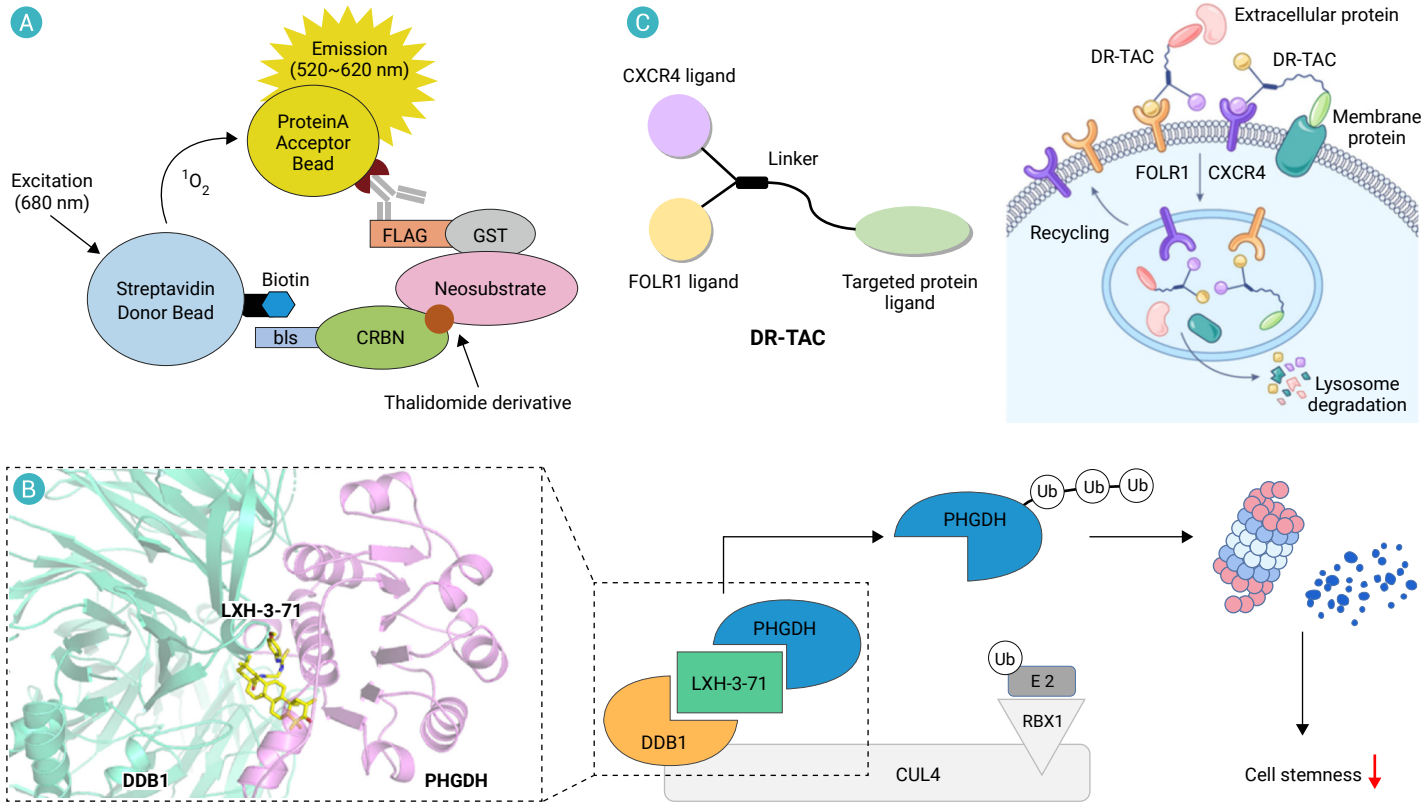

Figure 1. TPD for cancer therapy (A) Schematic diagram of the AlphaScreen (AS)-based biochemical interaction assay using recombinant proteins for detecting thalidomide-derivative-dependent complex formation between CRBN and neosubstrates.[25] (Copyright 2023, Springer Nature) (B) Mechanism of LXH-3-71 as a molecular glue. LXH-3-71 induces the interaction between PHGDH and DDB1-CUL4 ubiquitin ligase, triggering degradation of PHGDH via the ubiquitination-proteasome pathway and subsequently leading to inhibited cancer cell stemness.[26] (Copyright 2024, Elsevier) (C) Schematic illustration of the DR-TAC-mediated membrane and extracellular protein degradation.[29] (Copyright 2025, American Chemical Society)

TPD for cancer therapy

Cancer therapies have witnessed significant innovations with the advent of TPD. Among the more than 20,000 proteins in the human body, approximately 600 are closely associated with cancer.[20] However, over half of these, particularly non-enzymatic targets lacking well-defined active sites, are deemed "undruggable" by conventional SMIs.[21] TPD, which acts as a process that eliminates POI, has brought tremendous hope to the development of cancer therapy. Unlike traditional inhibitors that interfere with protein function, PROTACs mediate the degradation of pathogenic target proteins. This mechanism requires only a binding interaction with the target, bypassing the need for functional active site occupation and thereby expanding the druggable proteome to include traditionally challenging targets.

With the increasing sophistication of PROTAC design and synthesis technologies, a growing number of novel PROTAC configurations have been developed, such as CLIPTACs, physically activatable PROTACs, and bioactivatable PROTACs, yielding diverse outcomes for various tumor treatments.[13,21] For instance, Sellmyer et al. developed a light-controlled trimethoprim PROTAC molecule targeting an engineered *E. coli* dihydrofolate reductase (eDHFR) protein tag. This approach enabled precise spatiotemporal regulation of CAR-T cell activity, confining CAR-T cell function exclusively to tumor sites.[22] As an oral PROTAC protein degrader currently in phase III clinical trials, ARV-471 can directly bind to the E3 ubiquitin ligase and estrogen receptor (ER), triggering ER ubiquitination and subsequent proteasomal degradation, and has demonstrated favorable safety profiles and anti-tumor activity in breast cancer therapy.[23] Additionally, Xie et al. found that PROTAC technology has not yet been applied to immune proteins. Using the Phase III clinical IDO1 inhibitor Epacadostat (Epa) as the target protein ligand and lenalidomide/ lenalidomide as the E3 ligase ligands. This PROTAC molecule mediates sustained degradation of IDO1, as a key cancer immune escape target, via the UPS and moderately enhances tumor-killing activity of HER2 CAR-T cells, offering a novel perspective for applying PROTAC technology to tumor-immune-related proteins. [24]

Molecular glues represent an alternative TPD strategy, often featuring more favorable drug-like properties due to their smaller size and simpler structure. These compounds induce proximity between an E3 ligase and a neosubstrate, leading to target degradation. Classic examples include thalidomide and its analogs (IMiDs), which redirect the $CRL4^{CRBN}$ ligase to degrade transcription factors such as IKZF1/3 or oncoproteins such as CK1α, providing effective treatment for multiple myeloma (Figure 1A).[25] Similarly, Yang et al. discovered that the molecular glue LXH-3-71 can induce the degradation of phosphoglycerate dehydrogenase (PHGDH), then suppressing the proliferation and self-renewal capacities of colorectal cancer stem cells (Figure 1B).[26] Currently, a molecular glue degrader called CC-220 has entered phase III clinical trials for the treatment of multiple myeloma.[23]

Lysosome-targeting strategies, exemplified by LYTACs, further broaden the scope of TPD to extracellular and membrane-associated proteins. LYTAC technology was first reported in 2020, which achieves lysosomal degradation of target proteins by conjugating them to lysosome-targeting receptors.[15,27] LYTACs have shown remarkable performance in reprogramming the tumor immunosuppressive microenvironment. In a study by Zhou et al., they developed a genetically encoded modular LYTAC platform that can degrade membrane-associated proteins through the recruitment of transferrin receptors (TfR) and target proteins, significantly inhibiting tumor growth in vivo.[28] However, single-receptor LYTACs suffer from limitations such as low degradation efficiency and poor selectivity. To address these obstacles, Wang et al. designed a dual-receptor LYTAC that simultaneously targets CXCR4 and FOLR1—two receptors highly expressed on the surface of various cancer cells. Through synergistic effects, this dual-receptor LYTAC significantly enhanced protein degradation efficiency and exhibited promising therapeutic potential in mouse models of lung cancer (Figure 1C).[29]

TPD for neurodegenerative diseases

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), represent a growing public health challenge, exac-

erbated by global demographic aging.[30] Currently, the treatment of these diseases mainly relies on pharmacological intervention and symptomatic management, but none of these approaches can prevent the rapid progression of the diseases.[31] A core pathological feature of neurodegenerative diseases is the abnormal accumulation of aggregated proteins represented by α-synuclein (α-Syn) and tau protein.[32,33] TPD strategies offer a promising avenue for the selective clearance of these pathogenic protein species.

Several innovative TPD technologies have also been reported recently. For instance, Pang et al. developed a bifunctional PROTAC degrader with a warhead, which can degrade neurodegeneration-related α-Syn and tau proteins at the same time through the UPS and exhibited favorable therapeutic effects in MPTP-induced PD mouse models.[34] Xie et al. designed and synthesized a series of small-molecule degraders based on PROTAC technology. These compounds utilize quinoline derivatives containing thiophene rings as tau-binding ligands, thalidomide as E3 ligase ligands, and hydrophobic long-chain alkyl groups as linkers. By degrading tau protein via the UPS, they offer a highly promising therapeutic strategy for AD and related neurodegenerative disorders.[35] While UPS holds potential, its efficacy against large protein aggregates or extracellular pathologies can be limited. In contrast, the lysosomal degradation pathway provides a complementary strategy due to its capacity to process a broader range of substrates.[36] Bertozzi et al. demonstrated that LYTAC targets and degrades apolipoprotein E4 (ApoE4), which is an extracellular protein associated with AD.[16] It is anticipated that more TPD agents for neurodegenerative diseases will be developed in the future, with enhanced blood-brain barrier (BBB) penetration, reduced off-target effects, and the ability to degrade multiple protein aggregates.

TPD for autoimmune diseases

The treatment of autoimmune diseases faces significant challenges, including dysregulated immune responses and the broad, often toxic, immunosuppressive effects of conventional therapies.[37] TPD offers a strategy for the precise ablation of key signaling proteins driving inflammation. From the perspective of preclinical research based on TPD technologies, IRAK4 is a serine-threonine kinase that acts as a core kinase in the innate immune signaling pathway, driving the production of proinflammatory cytokines.[38] Targeting IRAK4, PROTACs can selectively degrade IRAK4 to inhibit its function and cut the downstream inflammatory cascade.[39] Moreover, KT474, the first class of PROTAC drugs to enter clinical trials for immuno-inflammatory skin diseases, achieves profound degradation of IRAK4 in human skin lesions, verifying the therapeutic feasibility and advantages of IRAK4 in blocking inflammatory pathways.[23,40] Beyond IRAK4, Bruton's tyrosine kinase (BTK) is a tyrosine kinase and a key regulator of the B-cell receptor (BCR) signaling pathway, whose dysfunction is closely associated with autoimmune diseases.[41] Liu et al. designed L18I as a BTK-targeting PROTAC degrader, which exerts a potent therapeutic effect on systemic lupus erythematosus and its severe complication, diffuse alveolar hemorrhage.[42] TPD provides a novel strategy for the selective inhibition of pathologically active proteins in regulating inflammation in autoimmune diseases, which may evolve into a more effective and less toxic therapeutic regimen in the future.

In summary, TPD technology has become a revolutionary therapeutic tool in combating cancer, neurodegenerative diseases, and autoimmune diseases, effectively addressing "undruggable" targets through diverse strategies. These approaches exhibit distinct advantages by selectively eliminating pathogenic proteins, with multiple degraders advancing to clinical trials and showing promising therapeutic potential.

NANOPLATFORMS DESIGN FOR TPD

Despite the significant breakthroughs of traditional TPD technologies, their clinical translation faces substantial challenges due to inherent limitations, which include poor solubility, low bioavailability, insufficient targeting ability, and limited tissue penetration.[43-45] To overcome these bottlenecks, nanotechnology has been extensively explored to develop advanced Nano-TPD platforms that integrate the benefits of nanomaterials with protein degradation mechanisms.[46,47] From its initial role as a delivery platform that efficiently encapsulates, protects, and transports traditional TPD molecules to enhance their drug properties, to its ability to actively guide target proteins into degradation pathways, the nanoplatform fully demonstrates its unique physicochemical properties, which enable it to maximize therapeutic efficacy while minimizing systemic toxicity.

Lipid-based nanoplatforms

Lipid-based nanoplatforms, including liposomes and lipid nanoparticles (LNPs), represent one of the most clinically advanced nanocarrier classes for TPD delivery. Their widespread adoption is attributed to excellent biocompatibility, high drug loading capacity, and well-established manufacturing protocols that facilitate clinical translation.

LNPs are composed of ionizable lipids, phospholipids, cholesterol, and PEGylated lipids. They are particularly well-suited for encapsulating hydrophobic PROTAC molecules. Their unique endosomal escape mechanism relies on ionizable lipids that destabilize endosomal membranes at acidic pH, thereby enabling efficient cytosolic delivery of protein degraders. This feature is critical for accessing intracellular targets. Liposomes offer remarkable versatility as multifunctional delivery platforms. Their aqueous core and lipid bilayer permit simultaneous encapsulation of hydrophilic and hydrophobic cargo. This capability allows co-delivery of PROTACs with complementary therapeutic agents such as photosensitizers or chemotherapeutics for synergistic combination therapy.[48] Surface modification with polyethylene glycol extends circulation half-life by evading clearance by the reticuloendothelial system. In addition, conjugation of targeting ligands, including peptides, antibodies, or aptamers, confers active targeting capability to specific cell types or tissues.[49] Liposomes can also encapsulate bioorthogonal reaction precursors for in situ PROTAC assembly at disease sites, thereby minimizing systemic exposure to active degraders.[50]

The modular nature of lipid-based platforms enables precise tuning of physicochemical properties, including particle size, surface charge, lipid composition, and ligand density.[51] Such tunability facilitates optimization of pharmacokinetics, biodistribution, and cellular uptake. Collectively, these attributes position lipid-based nanoplatforms as versatile and clinically translatable vehicles for advancing Nano-TPD therapeutics.

Inorganic nanoparticles

Inorganic nanoparticles typically refer to nanoparticles composed of inorganic materials such as metals, carbon-based materials, and others.[52] It provides distinct physicochemical advantages for TPD. Gold-based nanostructures are widely explored. For instance, ultra-small gold nanoclusters[53] and gold nanoparticles conjugated with multi-headed PROTACs[54] effectively degrade membrane and intracellular proteins, respectively. Liu et al. employed polyethylene glycol-modified gold nanoparticles (PEG@GNP) as the core carrier, simultaneously conjugating anaplastic lymphoma kinase (ALK) inhibitor and pomalidomide to the PEG@GNP surface to achieve targeted degradation of ALK.[54] Gold nanoparticles also serve as versatile cores for constructing aptamer-based degraders[55] and mitophagy inducers.[56]

Other inorganic materials offer complementary functions. Carbon dots (CDs) have been engineered into PROTACs for membrane protein degradation.[57] 2D nanomaterials, such as $TaTe_2$ nanosheets, can be integrated with photothermal therapy.[58] Mesoporous silica nanocarriers (MSNs) have also been explored. Yu et al. developed near-infrared (NIR)-activated PROTAC nanocages (UMSNs@phoBET1) using MSNs to provide a "light-controlled switch" precision strategy for antitumor therapy.[59] Moreover, inorganic-organic hybrid systems like mineralized metal-organic framework nanoparticles demonstrate precise organelle targeting and pH-responsive release.[60]

The exceptional stability and multifunctional capacity of inorganic nanoparticles enable applications beyond the reach of organic carriers, particularly in imaging-guided therapy and combinatorial treatment.[61] However, concerns regarding long-term biosafety, including potential accumulation in vital organs and unclear degradation pathways, remain significant barriers to clinical translation.[62,63] Their non-biodegradable nature necessitates rigorous long-term toxicity studies before regulatory approval can be considered.

Polymeric nanocarriers

Polymeric nanocarriers offer exceptional versatility. PLGA-based nanopar-

ticles functionalized with antibodies enable targeted degradation.[64,65] Semiconducting polymers and polydopamine-based nanoparticles serve as effective nano-LYTACs.[66,67] Peptide self-assembly forms modular degraders,[68,69] and sophisticated designs combining p53-targeting peptides with autophagy enhancers achieve selective mutant protein clearance.[70] Other strategies include RAGE-targeting systems[71] and modular platforms like MONOTAB for extracellular protein degradation.[72]

To achieve precise spatiotemporal control over degradation activity, advanced polymeric platforms are increasingly designed as prodrug systems (pro-Nano-TPD) that are activated by pathological cues. They typically employ cleavable linkers responsive to acidic pH, elevated enzymes, high GSH, or ROS in disease microenvironments. Responsiveness to the acidic tumor microenvironment (TME) is a common strategy. For example, pH-sensitive nano-formulations such as ARV@PEG-ICG disassemble to release PROTACs,[73] and supramolecular assemblies like GM NPs for pH-sensitive drug release,[74] while more sophisticated systems like PSRNs dissociate at low pH for enhanced penetration and subsequently release cargo via cathepsin B (CatB) cleavage (Figure 2A).[18]

Enzyme-activatable designs are prominent, with platforms like SPNCOX, SPNpro, and LPNs employing CatB-cleavable linkers to conjugate PROTACs to polymer backbones for controlled release.[75-77] This approach extends to LYTACs and nano-ATTECs using pH-triggered charge switching or PEG detachment.[78,79] A lysosome-targeting nanoparticle (LYS-NP) exhibits pH-sensitive degradation in the acidic lysosomal environment, enabling controlled release of perforin and granzyme B upon T cell activation.[60]

The high intracellular GSH level is another key trigger. Simple disulfide-containing nanoparticles (ARV@PDSA Nano-PROTACs) degrade to release PROTACs,[80] while innovative designs like Nano-MP@PSI use GSH to disassemble gold-thiol nanocomplexes.[81] More complex GSH-responsive platforms, such as those developed by Wang et al. (Nano-PROTACs)[82] and Yuan et al. (Cle-NP),[83] trigger the in situ self-assembly of active degraders or the release of molecular glues. Moreover, Zhang et al. developed a versatile nano-PROTAC (CREATE) by encapsulating dBET6 within a pH/GSH-responsive DS-PLGA polymer, followed by coating with CRV-engineered lung cancer cell membranes (Figure 2B).[84]

Light provides precise external control. NIR-light-activatable nano-PROTACs (NAP) utilize ROS-cleavable linkers,[85] while other systems exploit apoptosis-specific enzymes. For instance, checkpoint nano-PROTACs are activated by caspase-3, creating a self-amplifying therapeutic cycle.[86]

The field is further enriched by innovative self-assembling systems. These include self-delivery nano-PROTACs (DdLD NPs), which eliminate the need for an exogenous carrier,[87] and programmable peptide assemblies (SM-PROTACs) that simplify PROTAC design.[88] Other frontiers involve engineered protein chimeras (GlueTAC) for covalent targeting,[89] and specialized compounds (LD-ATTECs) designed for the degradation of non-protein biomolecules like lipid droplets.[90]

Despite their excellent spatiotemporal control, these polymeric platforms face inherent limitations. The reliance on specific trigger thresholds may lead to heterogeneous activation within tumors due to microenvironmental variability.[91] Furthermore, the incorporation of cleavable linkers and responsive materials increases synthetic complexity and may compromise drug loading capacity. Nevertheless, these systems represent one of the most clinically translatable approaches among Nano-TPD platforms, as their design principles align with established prodrug and stimuli-responsive drug delivery paradigms. Collectively, these diverse polymeric nanocarriers demonstrate the remarkable adaptability and powerful potential of the Nano-TPD platform.

Other innovative nanoplatform forms

Nano-TPD is expanding into non-traditional forms that leverage unique biological interactions, programmable chemistry, or physical modalities. Programmable DNA nanostructures, such as tetrahedron-based DbTACs, enable precise spatial control over ligand placement for optimized degradation.[92] Biomimetic platforms harness biological components for enhanced targeting, including genetically engineered lysosome-targeting exosomes,[93] red blood cell membrane-fused hybrid nanoparticles,[94] and engineered conjugates such as GalNAc-LYTACs for liver-specific targeting and human serum albumin nanoparticles.[95] Other innovative covalent strategies, such as DNA-based systems,[96] enhance on-target engagement. Programmable nanomaterials, such as pH-switchable DNA origami LYTACs, allow ligand reconfiguration.[97] A DNA nanodevice (LALTD) requires concurrent GSH and UV light to activate lysosomal targeting.[98] For localized delivery, physical forms such as effervescent microneedle patches[99] and nanocomposite hydrogels[100] can overcome anatomical barriers. These diverse platforms significantly expand the versatility of Nano-TPD.

These Nano-TPD strategies represent a paradigm shift from passive delivery to active, context-dependent therapeutic intervention.[101,102] By harnessing disease-specific signals, diverse Nano-TPD systems progressively achieve superior protein degradation efficacy, thereby minimizing off-target effects and broadening therapeutic windows. It demonstrates the exceptional adaptability of Nano-TPD across diverse disease scenarios and establishes Nano-TPD as a multifunctional strategy in precision medicine.

NANO-TPD FOR DISEASES

The clinical application of conventional TPD strategies faces distinct biological barriers across different disease contexts. In this section, we re-summarized and categorized the construction strategies of TPD from the perspective of different diseases based on the characteristics of advanced Nano-TPD platforms summarized above. These innovative systems address critical limitations of conventional protein degraders through sophisticated targeting strategies, stimuli-responsive activation mechanisms, and multifunctional architectures that collectively enhance therapeutic precision while minimizing off-target effects in complex disease microenvironments.

Cancer therapy

The primary clinical challenge of conventional TPD in cancer therapy lies in achieving therapeutic precision, severely limiting its efficacy against solid tumors. To address these limitations, Nano-TPD platforms are engineered with sophisticated targeting and responsive mechanisms. The construction strategies focus on enhancing tumor targeting and penetration, active remodeling of the TME, and overcoming specific resistance mechanisms, often through synergistic combination therapies.[103]

Enhancing tumor targeting and deep tissue penetration. A cornerstone of nano-cancer therapy is leveraging the enhanced permeability and retention (EPR) effect for passive tumor accumulation.[104] Numerous platforms rely on this effect for initial tumor localization. Beyond passive accumulation, active targeting significantly improves specificity. Gao et al. engineered tumor-targeting copolymers to achieve combined delivery of DOX and the BRD4 PROTAC degrader ARV-825 (ARV-DOX/cRGD-P), thereby promoting tumor apoptosis and inhibiting tumor proliferation and angiogenesis.[105] Ligands such as cyclic RGD peptides enable tumor-selective delivery of liposomal PROTACs,[50] while cancer cell membrane coatings confer homotypic targeting capabilities.[84] Receptor-specific targeting is exemplified by GalNAc-LYTACs, which hijack the hepatocyte-specific asialoglycoprotein receptor (ASGPR) for precise liver cancer therapy.[95] To overcome the dense stromal barrier, smart size-switching strategies have been developed. PSRNs transform from large nanoparticles to small unimers in the acidic TME, facilitating deeper penetration before releasing CDK4/6-targeting PROTACs intracellularly.[18]

Reprogramming the immunosuppressive tumor microenvironment. A key advantage of Nano-TPD is the direct degradation of proteins that sustain an immunosuppressive TME, moving beyond mere inhibition. A major focus is on the degradation of immune checkpoints. Monofunctional nanoparticles like Covalent LYTAC, MONOTAB, and NanoTACPD-L1 effectively shuttle PD-L1 to lysosomes, enhancing antitumor immunity (Figure 3A).[65,72,96] Covalent strategies like GlueTAC ensure irreversible PD-L1 removal, eliciting durable immune responses.[89] Biomimetic platforms, such as genetically engineered exosomes (LYTEXs), offer enhanced tumor accumulation and dual-targeting for checkpoint degradation.[93] Biomimetic DNA nanostructures (IMTACs) and logic-gate devices (LALTD) offer spatiotemporally controlled, dual-target degradation of PD-L1 and other checkpoints (Figure 3B).[97,98] Simultaneously, Nano-TPD platforms target immunosuppressive metabolites and signaling pathways. Degradation of indoleamine 2,3-dioxygenase (IDO) depletes kynurenine, reversing T-cell suppression.[74,76] Similarly, degrading cyclooxygenase (COX-1/2) reduces prostaglandin E2 levels.[77] Notably, nano-LYTACs

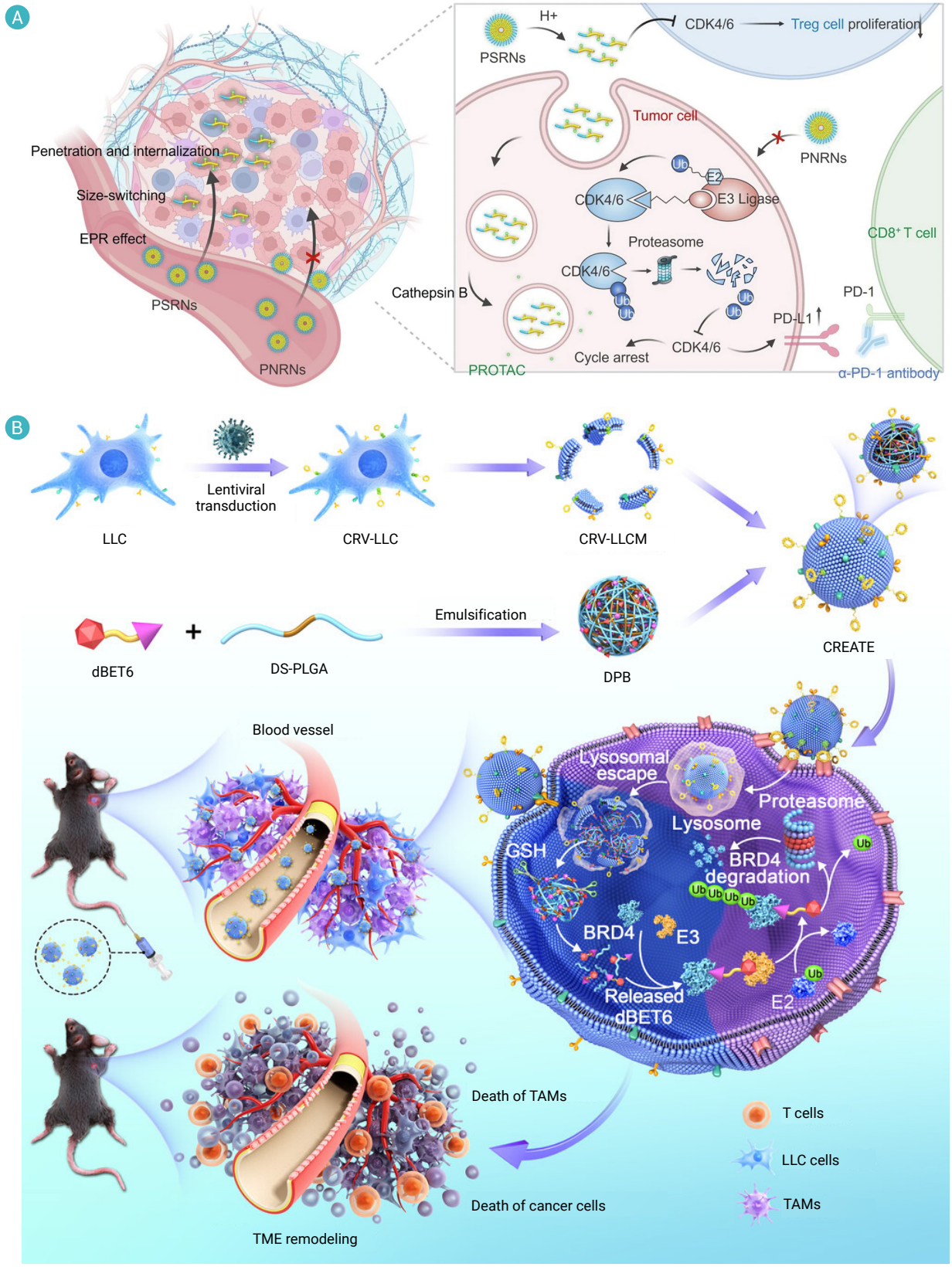

Figure 2. Polymeric nanocarriers (A) The schematic illustration of the sequential responsive process of PSRNs after intravenous administration. The proposed behavior of protein degradation and immunoregulation post PSRNs and ICBs combination therapy in the tumor-bearing mice.[18] (Copyright 2024, Springer Nature) (B) The CREATEs were constructed by the use of a pH/GSH responsive polymer to load dBET6, followed by the camouflage with CRV-engineered Lewis lung carcinoma (LLC) cell membranes (CRV-LLCM). The pH/GSH-responsiveness significantly facilitated the release of dBET6 from the nanoparticles within the cells, which led to the efficient degradation of BRD4.[84] (Copyright 2022, John Wiley and Sons)

such as SPNly are designed to selectively degrade the IL-4 receptor on M2-type tumor-associated macrophages, repolarizing them to a tumoricidal phenotype and synergizing with sonodynamic therapy.[66] Furthermore, inorganic-organic hybrid nanoparticles (LYS-NPs) can reprogram CD8$^+$ T cells by

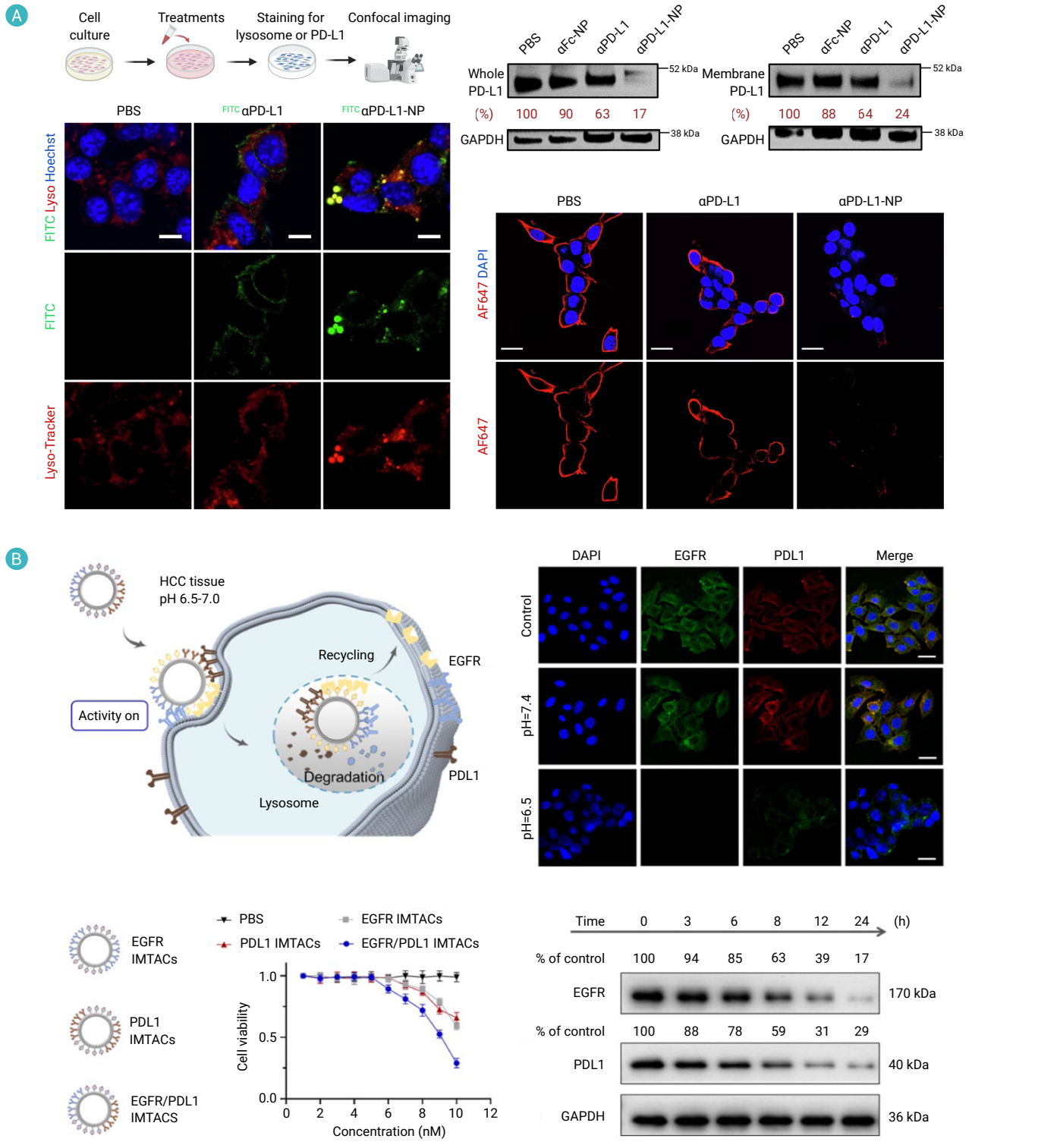

Figure 3. Reprogramming the immunosuppressive tumor microenvironment (A) MONOTAB-mediated degradation of membrane-associated protein PD-L1.[72] (Copyright 2024, Springer Nature) (B) The EGFR/PDL1 IMTACs enable accurate localization and delivery into tumor tissues, where the acidic tumor microenvironment triggers degradation switch activation, multivalent binding, and efficient degradation of EGFR and PD-L1.[97] (Copyright 2023, John Wiley and Sons)

enhancing their lysosomal storage and release of cytotoxic granules, directly boosting cellular immunity.[60]

Overcoming drug resistance and the "hook effect". Nano-TPD provides innovative solutions to classic challenges in targeted therapy. Multidrug resistance (MDR), often mediated by efflux pumps like ABCG2, can be circumvented by degrading the pump itself. Aptamer-functionalized gold nanoparticles (AuNP-APTACs) induce lysosomal degradation of ABCG2, re-sensitizing resistant cancer cells to chemotherapy,[55] or by employing metabolic potentiation strategies like fasting-mimicking diets to enhance nanocarrier uptake and proteasome activity.[49,57] For intracellular oncoproteins, overcoming the "hook effect" is critical. Self-assembling peptide platforms (Nano-PROTACs) form multivalent fibrous networks inside cells, which enhance cooperative binding and eliminate the hook effect, leading to dose-dependent degradation of targets like EGFR.[82] Similarly, pre-fusing PROTACs with E3 ligases and delivering them via lipid nanoparticles creates a more efficient binary degradation system.[106] Expanding the scope of degradation,

Nano-TPD enables organelle-targeted clearance. Biomimetic nanoparticles (NanoTAC^{Org}) cluster and degrade entire mitochondria in cancer cells, disrupting metabolism and synergizing with glycolysis inhibitors.[64] Ultrasmall gold nanoparticles (mitoNIDs) also induce selective mitophagy, enhancing tumor immunogenicity and the efficacy of adoptive T-cell therapies.[56]

Synergistic combination therapies. The integration of TPD with other treatment modalities within a single nanoplatform achieves potent synergy. Phototherapy combinations are particularly effective. Platforms like ARV@PEG-ICG and NAP co-deliver PROTACs with photosensitizers, where therapy induces immunogenic cell death (ICD) while protein degradation further sensitizes tumors.[73,75,85] Checkpoint nano-PROTACs are uniquely activated by caspase-3, upregulated during phototherapy, creating a self-amplifying cycle of apoptosis and immune checkpoint degradation.[86] Chemotherapy combinations are also powerful. DdLD NPs combine a BRD4 degrader with doxorubicin to simultaneously induce ICD and downregulate PD-L1.[87] Similarly, NLTC-BMS/CAT-PDA nanoparticles combine PD-L1 degradation with catalase-mediated oxygen generation to alleviate tumor hypoxia.[79] Localized and sustained delivery strategies further enhance the therapeutic index. Injectable nanocomposite hydrogels provide a depot for the controlled release of PROTAC-loaded nanoparticles and immunomodulators, enabling potent local therapy with minimal systemic exposure.[100]

Collectively, these case studies demonstrate that Nano-TPD transforms the limitations of conventional degraders into therapeutic opportunities. By integrating precise targeting, intelligent responsiveness, and multimodal actions, these platforms achieve enhanced tumor-specific protein degradation, effective TME reprogramming, and potent synergy with established therapies. The progression from targeting single proteins to dismantling entire resistance pathways and organelles marks a significant evolution in the application of TPD for cancer treatment, offering a more robust and versatile arsenal against malignant diseases.

Neurodegenerative diseases

The application of TPD in neurodegenerative diseases is primarily hindered by the BBB, which severely restricts the delivery of macromolecular degraders to the central nervous system. Nano-TPD platforms are engineered to overcome this fundamental challenge through BBB-penetrating targeting strategies and to address multifactorial pathology via multi-mechanism interventions.[107]

A key strategy involves leveraging receptor-mediated transcytosis (RMT) at the BBB. For instance, the KPLYs platform utilizes the Receptor for Advanced Glycation End Products (RAGE), which is upregulated in the inflamed BBB of AD, to facilitate brain entry.[67] Once in the brain parenchyma, these nanoparticles can be further activated by the pathological microenvironment to release functional degraders that promote the clearance of toxic protein aggregates like Aβ. Building on RAGE targeting, a more sophisticated dual-mechanism approach is exemplified by the SV@endoTAC system.[71] This platform not only employs multivalent RAP-RAGE interactions for enhanced BBB crossing and subsequent degradation of pathogenic RAGE but also co-delivers simvastatin to upregulate the lipoprotein receptor LRP1, thereby promoting Aβ clearance and restoring BBB integrity. This degrade-and-repair strategy highlights the capacity of Nano-TPD to perform combinatorial interventions addressing both proteinopathy and vascular dysfunction. Yin et al. developed an innovative neurotransmitter-derived lipidoid (NT-lipidoid) nanocomplex (NPD) for delivering peptide-based PROTACs against tau protein in Alzheimer's disease. NPD could efficiently deliver tau-targeting PROTACs to the brain. Following systemic administration, NPD facilitated significant accumulation of PROTACs in the brains of AD model mice, leading to potent degradation of both total and pathologically phosphorylated tau (p-tau) via the ubiquitin-proteasome system.[108]

Inflammatory and metabolic diseases

In inflammatory diseases, Nano-TPD strategies focus on degrading key immune mediators with spatial control. For psoriasis, the LYTAC platform utilizes self-assembled nanoparticles to achieve multivalent binding and degradation of the pivotal cytokine IL-17A via scavenger receptor-mediated uptake, offering a superior alternative to linker-optimized LYTACs (Figure 4).[68] For myocardial injury, a biomimetic nanodegrader (aRLP) hijacks neutrophils to deliver its payload to inflamed cardiac tissue, where it specifically degrades the macrophage "don't-eat-me" signal SIRPα to promote repair, demonstrating precise site-specific immunomodulation without broad immunosuppression.[95] Wang et.al. proposed "supramolecular targeted chimeras" (SupTAC), which self-assemble into supramolecular nanoparticles (SNP) complexes through host-guest interactions between adamantane-modified metal-organic cages (Ada-MOC) and β-cyclodextrin-polyethyleneimine (β-CD-PEI). This approach enables spatiotemporally resolved protein degradation in vivo, effectively alleviating ferroptosis and pulmonary inflammation in acute lung injury models.[109]

For metabolic disorders, Nano-TPD enables targeting of dysfunctional tissues and organelles. In obesity, chitosan-based nanoparticles (COA NPs) selectively accumulate in adipose tissue via electrostatic targeting, where they synergize with photothermal therapy to induce lipophagy and "browning" of white fat.[99] Expanding beyond proteins, chimeric compounds like LD-ATTECs directly tether lipid droplets (LDs) to autophagosomes, inducing selective lipophagy to ameliorate hepatic steatosis—a strategy that overcomes the inherent limitation of conventional PROTACs in degrading non-protein targets.[90]

Collectively, these examples illustrate the transformative potential of Nano-TPD in treating complex chronic diseases. By achieving precise cellular and tissue targeting, degrading diverse pathogenic entities, and integrating with complementary therapies, Nano-TPD platforms offer a powerful and versatile toolkit for managing inflammation and metabolic dysregulation.

In summary, Nano-TPD offers a revolutionary solution for treating complex diseases involving core biological barriers by deeply integrating nanotechnology's precision delivery and spatiotemporal control advantages with TPD's targeted degradation properties. This approach provides a novel pathway for improving treatment outcomes in refractory diseases.

CURRENT CHALLENGES AND FUTURE PERSPECTIVES

The integration of TPD with nanotechnology has forged a promising path to overcome the inherent limitations of conventional degraders and broaden their therapeutic applications. Nano-TPD strategies can achieve protein clearance via novel pathways by leveraging diverse materials, degradation mechanisms, and conjugation strategies. Nonetheless, significant challenges accompany these opportunities, impeding the clinical translation of Nano-TPD platforms. Key hurdles include suboptimal delivery efficiency, the formation of protein coronas, and unresolved biocompatibility concerns.[17]

From the delivery perspective, numerous biological barriers in vivo pose successive obstacles to nanoparticle delivery,[110] among which the BBB is the most difficult to penetrate. While modulating nanoparticle size and shape can enhance circulation time and stability, it often leads to unintended sequestration by the reticuloendothelial system (RES) and rapid clearance.[111] Generally, nanoparticles smaller than 8 nm may undergo rapid renal filtration, while larger nanoparticles often accumulate in the liver and are quickly cleared from the circulation, impairing the protein degradation efficacy.[112] Related reports also indicate that mucus within the human body can significantly impede the uptake of nanocarriers by epithelial cells, making experiments to overcome the mucus barrier increasingly noteworthy. Therefore, appropriately adjusting the hydrophilicity and hydrophobicity or surface charge of nanocarriers may better meet the multifaceted demands of systemic delivery in the future.[113] What's more, insufficient targeting of nanoparticles may lead to off-target protein degradation. Additionally, poor encapsulation can cause drug leakage into healthy tissues, not only damaging normal cells and causing toxicity but also compromising the body's natural immune defenses.[114] Furthermore, nanoparticles in the biological environment tend to form a protein corona due to their surface charge, causing plasma proteins and other biomolecules to adsorb onto their surfaces, which alters their structural and functional properties and affects their stability.[115,116] The most common mechanism is that the protein corona impedes the binding of target ligands to target cell receptors. For example, Mahdieh et al. demonstrated that the formation of a protein corona significantly suppresses the targeting properties of folate-modified chitosan nanoparticles and impedes their uptake by tumor cells.[117] As exogenous materials, nanoparticles may trigger systemic non-specific immune activation, leading to immune-related toxicity.[118] Lysosomes are vital organelles responsible for the degradation of macro-

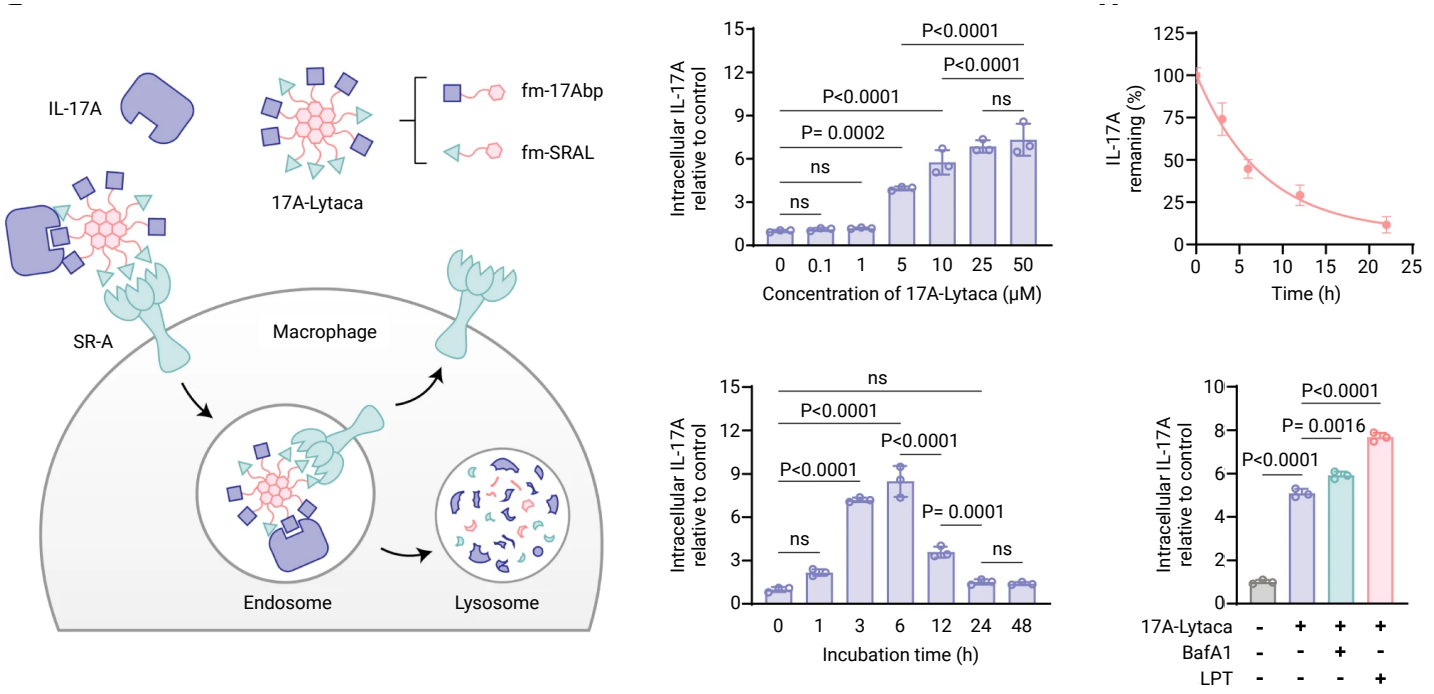

Figure 4. Inflammatory diseases 17A-Lytaca induced the lysosomal degradation of IL-17A.[68] (Copyright 2024, Springer Nature)

molecules within cells, playing a crucial role in maintaining cellular homeostasis and participating in key biological processes.[119] Lysosomal sequestration presents another intractable challenge, as it restricts the availability of TPD molecules and nanoparticles. Studies estimate that less than 2% of nanoparticles, regardless of their shape and size, can successfully escape into the cytoplasm after administration.[120] For instance, encapsulation of TPD degraders within nanoparticles has a high probability of resulting in their direct delivery to lysosomes, where the acidic microenvironment and hydrolases induce their complete degradation and ultimately impair their therapeutic efficacy. Enhancing lysosomal escape efficiency is therefore a paramount objective for improving therapeutic outcomes. Subsequently, it is worth noting that lysosomal overload, massive intracellular accumulation of nanoparticles may impair lysosomal function causing lysosomal overload, thereby affecting cellular homeostasis.[121]

Beyond these delivery and safety-related challenges, the clinical translation of Nano-TPD is also hindered by multiple key barriers in regulation, manufacturing, and safety assessment. Among the strategies discussed, lipid-based and stimuli-responsive polymeric nanoparticles are the most likely candidates for near-term translation, given their alignment with established manufacturing protocols and regulatory precedents for nanomedicines. However, key challenges persist across all platforms. Scalable production under good manufacturing practice conditions remains difficult, particularly for complex systems requiring precise ligand conjugation or multi-component assembly. Regulatory pathways for these combination products are still evolving, necessitating comprehensive physicochemical characterization and standardized safety assessment frameworks. Long-term biocompatibility concerns, especially for non-biodegradable inorganic nanoparticles, demand rigorous toxicological evaluation. Addressing these translational hurdles through interdisciplinary collaboration will be essential to bridge the gap between proof-of-concept innovation and clinical adoption.

Despite these challenges, Nano-TPD still has broad development prospects. Future advancements may involve: (1) screening and engineering novel, biocompatible nanocarrier materials with improved targeting and stealth properties; (2) integrating stimuli-responsive mechanisms (e.g., pH, ROS, or enzyme-sensitive linkers) for spatiotemporally controlled release of TPD agents; (3) combining Nano-TPD with adjuvants like photothermal therapy to disrupt endolysosomal membranes and facilitate escape; and (4) leveraging artificial intelligence (AI) to accelerate the design of both TPD molecules and their nanocarriers, enabling predictive modeling of target engagement, degradation efficiency, and pharmacokinetics.

In conclusion, while Nano-TPD delivery strategies are still in a nascent stage and their clinical translation requires overcoming multifaceted technical and biological barriers, focused research on intelligent, multifunctional nanocarriers holds the key to unlocking their full potential across a wider spectrum of diseases.

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M.L., J.M., and C.H. were responsible for the literature collection, writing of the initial draft, and figure preparation. R.W., J.Z., and Q.C. supervised the overall structure and focus of the review, provided critical revisions, and are responsible for correspondence during submission and revision stages. M.L., J.M., C.H., Q.Z., J.L., and H.Y. contributed to language polishing, content revision, and final proofreading. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.