International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Nanotechnology Advances Proteolysis Targeting Chimeras (PROTACs): Transition From Basic Research to Clinical Application

Xupeng Mu[1,*], Chongqiang Mu[2,*], Mengxue Wang[2], Chen Meng[2], Huimin Liu[2], Haibin Lu[2]

[1]Scientific Research Center, China-Japan Union Hospital of Jilin University, Changchun, Jilin Province, 130033, People's Republic of China; [2]Jilin University School of Pharmaceutical Sciences, Changchun, Jilin Province, 130021, People's Republic of China

*These authors contributed equally to this work

Correspondence: Haibin Lu, Email luhaibin@jlu.edu.cn

Abstract: Proteolysis Targeting Chimeras (PROTACs) have been extensively explored for the targeted degradation of disease-associated proteins due to their therapeutic ability to modulate proteins that are difficult to target by conventional small molecules, showing vast potential in treating refractory diseases such as cancer and neurodegenerative disorders. However, the clinical application of PROTACs is limited by their large molecular weight, low solubility, poor permeability, and the "hook effect". Fortunately, the rapid advancement of nanotechnology offers new strategies to overcome some of the key challenges faced by traditional PROTAC technologies, potentially facilitating their clinical translation. In this review, we outline the mechanisms of action of PROTACs and explore their potential clinical significance, along with the main challenges in delivering these compounds. Additionally, we comprehensively summarize recent advancements in nanotechnology for enhancing the delivery efficiency of PROTAC drugs and discuss the limitations of current strategies and future perspectives. In conclusion, this review aims to deepen researchers' understanding of this strategy, thereby advancing the clinical translation of PROTAC drugs and providing more effective strategies for treating complex, refractory diseases.

Keywords: PROTACs, nanotechnology, clinical application

Introduction

Although small molecule inhibitors (SMIs) have provided substantial benefits to many patients as valuable targeted therapeutic agents, there are still numerous significant issues that cannot be overlooked. Firstly, traditional SMIs rely on an "occupancy-driven" model, requiring high concentration and extensive systemic exposure to exert target inhibition, which poses potential off-target risks and side effects.[1] Secondly, target antagonism may trigger compensatory mechanisms, resulting in the overexpression of related proteins and significantly increasing the risk of acquired resistance.[2] Finally, the protein targets accessible to traditional small-molecule drugs are limited, with most disease-associated proteins still considered "undruggable", presenting a key challenge in current small-molecule drug development.[3,4] Over the last several years, PROTACs have gained widespread attention as an emerging drug development strategy in the field of targeted therapy. PROTAC is a heterobifunctional compound primarily composed of a particular ligand binding to the protein of interest (POI), an appropriate linker, and an E3 ubiquitin ligase substrate.[5] By taking control of the ubiquitin-proteasome system (UPS), PROTACs interact with the target protein and E3 ubiquitin ligase to form a ternary complex that ubiquitinates and degrades the target protein.[4]

In contrast to conventional small molecule inhibitors (SMIs), PROTACs operate through a catalytic mechanism, allowing for reuse after a round of degradation and achieving target protein degradation at relatively low concentrations, thus minimizing side effects.[6,7] Moreover, PROTACs function based on an "event-driven" model, which eliminates the need for direct binding to the target protein's active site, potentially acting on "undruggable" targets and overcoming

Received: 9 July 2025
Accepted: 30 September 2025
Published: 6 October 2025

resistance brought on by target protein mutation or compensatory expression.[1,7,8] The distinctive benefits of PROTACs are that they offer more effective strategies for treating challenging diseases, including cancer and neurodegenerative disorders.[9,10]

Despite the groundbreaking significance of PROTACs in the field of targeted drug development, most PROTAC molecules still face numerous obstacles and restrictions in transitioning from the research and development phase to clinical application.[11] Firstly, one significant challenge with PROTACs is their large molecular size, exceeding 700 Dalton, along with high surface polarity and numerous hydrogen bond donors. These characteristics deviate from Lipinski's "Rule of Five" (Ro5), leading to poor cell permeability, solubility, and oral bioavailability.[12–14] Secondly, while the unique dual-binding mechanism of PROTACs enhances their selectivity and specificity to some extent, the widespread expression of E3 ligases in both diseased and healthy tissues limit their ability to target specific tissues. This can lead to off-target toxicity in normal tissues, often resulting in severe side effects.[15,16] Finally, at high concentrations, PROTACs usually form non-functional binary complexes with E3 ligases or target proteins rather than the intended ternary complexes. This "hook effect" reduces the efficiency of target protein ubiquitination and degradation and can lead to unexpected off-target toxicity. These challenges complicate the design of safe dosing regimens for PROTACs.[17–19]

To date, the development of new PROTAC drugs still faces complex pharmacokinetic (PK) and pharmacodynamic (PD) issues. Consequently, researchers have attempted various strategies to overcome these limitations.[20] In recent years, the rapid development of nanotechnology, particularly in nano-drug delivery systems (nano-DDSs), has garnered significant attention. Researchers have begun exploring the combination of nanotechnology with PROTACs to improve drug solubility, stability, and intracellular delivery efficiency.[21] Additionally, nanotechnology holds the potential to improve the pharmacokinetic (PK) properties of PROTACs and achieve localized precise release, thereby reducing systemic toxicity and off-target risks.[22] In this review, we first introduce the classic structure and mechanism of action of PROTACs and summarize the latest research advancements in the application of nanotechnology in PROTACs (Figure 1). We explore how the modification of nanostructures and the introduction of nanocarriers optimize the delivery efficiency and efficacy of PROTACs and discuss the prospects and potential challenges of various nano-PROTACs in clinical applications. This review aims to enhance researchers' understanding of this field, providing valuable insights to improve the bioavailability and druggability of PROTACs, thereby promoting the transition of PROTAC drugs from basic research to clinical application.

PROTAC Mechanism of Action

A PROTAC molecule consists of three components: a ligand for the E3 ligase, a ligand specific to the target protein, and a linker that connects them. One ligand specifically binds to the target protein, while the other primarily engages the E3 ligase. This design facilitates the proximity of the target protein and the E3 ligase, leading to the ubiquitination of the target protein and marking it for degradation.[23] Ubiquitination is mediated by a three-step enzyme reaction (Figure 2). The ubiquitination process initiates when a ubiquitin-activating enzyme (E1) uses ATP to form a high-energy thioester bond between its cysteine residue and the glycine residue of ubiquitin. This activated ubiquitin is then transferred to a ubiquitin-conjugating enzyme (E2), which forms a similar high-energy bond with ubiquitin. Finally, a substrate-specific ubiquitin ligase (E3) facilitates the transfer of ubiquitin to the target substrate. This transfer can occur directly or through another high-energy thioester bond on the E3 enzyme, depending on the type of E3 ligase involved. Frequently, this process results in the formation of a polyubiquitin chain, which begins with the attachment of the initial ubiquitin molecule to the e-NH_2 group of the substrate's lysine residue. Ubiquitin moieties are interconnected via isopeptide bonds between the C-terminal Gly of one fragment and the e-NH_2 group of the internal Lys48 of the previous fragment.[24] Three different proteolytic activities are shown by the 26S proteasome: chymotrypsin-like, trypsin-like, and peptidyl-glutamyl peptide hydrolyzing activities. The deubiquitinating enzymes (DUBs) that break down the ubiquitin chain by hydrolyzing isopeptide bonds between the C-terminal glycine of ubiquitin and the amine of lysine residues in proximal ubiquitin moieties or the substrate (if it is the first ubiquitin moiety) recycle ubiquitin during protein degradation. While the protein substrate unfolds and degrades, proteasome-associated deubiquitinating enzymes (DUBs) remove and recycle the ubiquitin chains from proteins identified with polyubiquitin chains via the K48 linkage that the proteasome recognizes.[25] In theory, a PROTAC functions as a catalyst, enabling the previously described process to be repeated many times until it is broken down and eliminated.

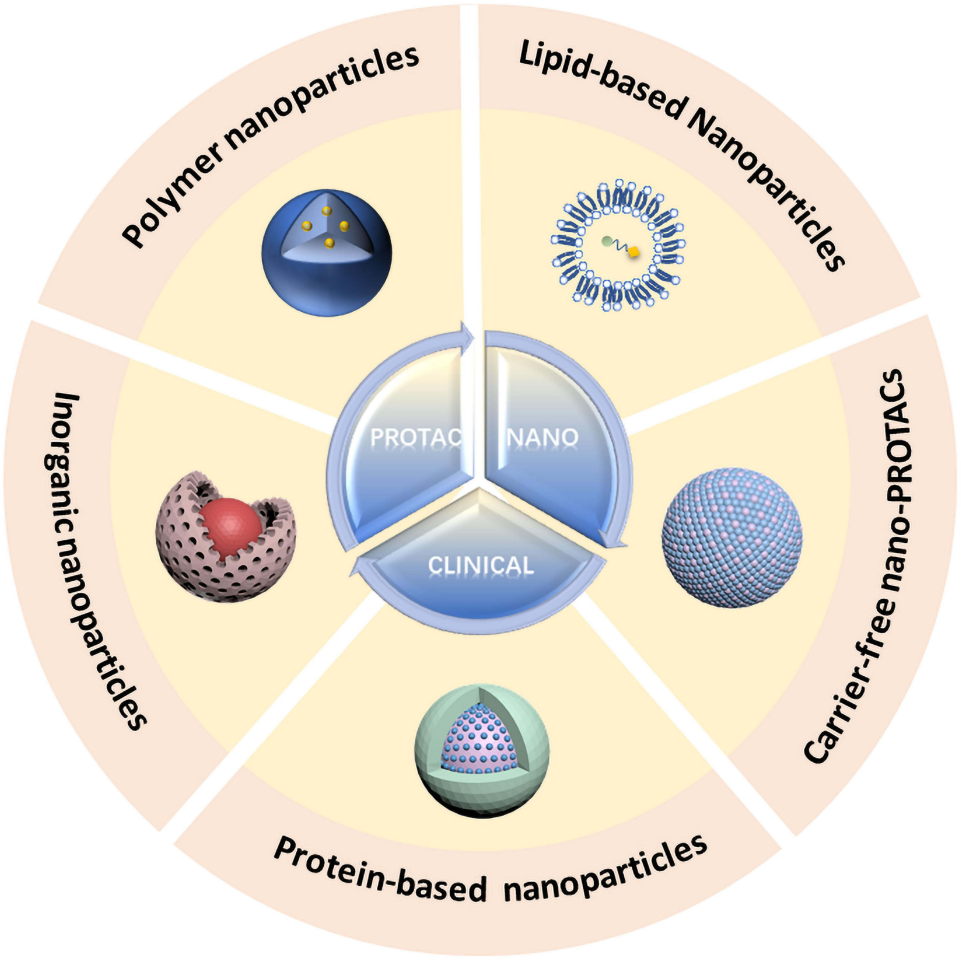

Figure 1 Schematic of the joint application of nanotechnology and PROTACs.

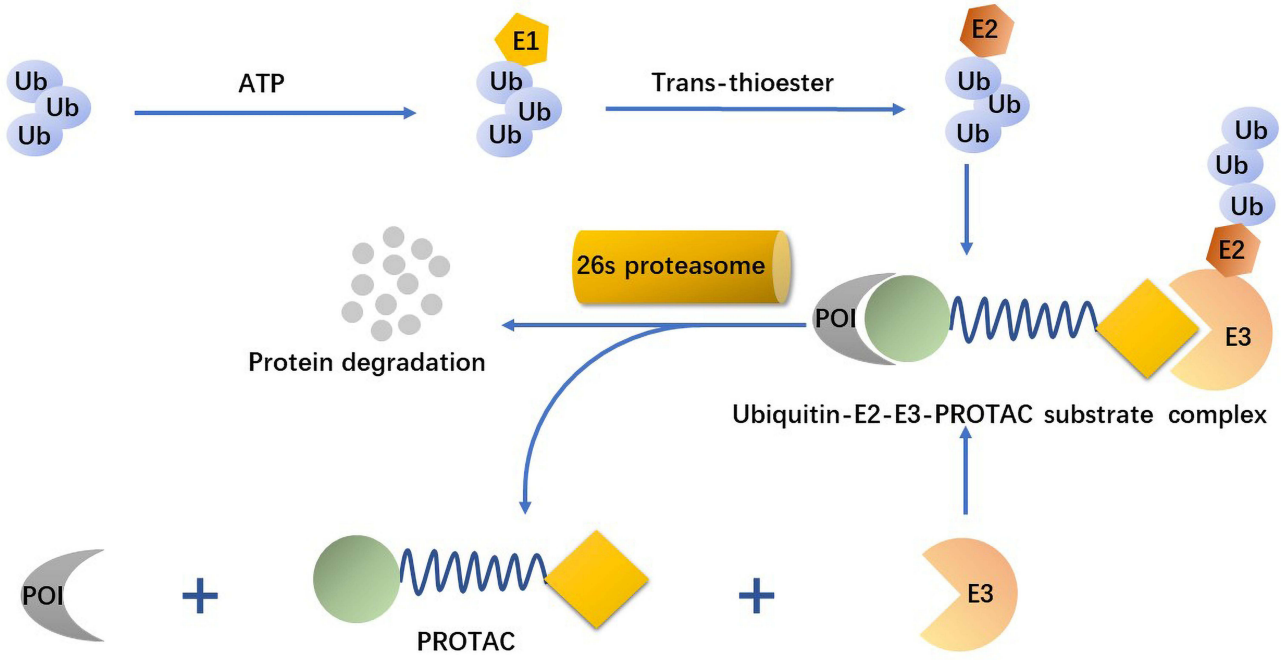

Figure 2 Schematic representation of PROTAC-mediated protein degradation.

https://doi.org/10.2147/IJN.S552644

The Application of PROTACs in the Treatment of Illness

To date, PROTACs targeting a wide range of therapeutically relevant proteins used for disease treatment have been developed. In this section, we discuss key PROTACs with promising applications for the treatment of refractory diseases to highlight their potent efficacy, broad range of action, and low drug resistance.

PROTACs in Tumor

To date, more than 50 protein-targeting PROTACs have been successfully developed, with these targets being clinically validated and used in clinical trials for cancer treatment. Moving on to a particular illustration, the STAT family comprises STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. These proteins are involved in intracellular signal transduction and gene expression manipulation.[26] STAT proteins, especially STAT3 and STAT5, control the transcriptional and epigenetic regulation of many genes in cancer while transducing signals from growth factors, overexpressed cytokines, their receptors, and other molecules in tumor cells. These genes contribute to chemoresistance, tumor cell proliferation, apoptosis inhibition, and tumor cell stemness.[27,28] PROTACs, such as AK-2992, have been created to target other STAT family members and have demonstrated encouraging results in the therapy of cancer, especially chronic myeloid leukemia. The STAT3 pathway can be efficiently inhibited by SD-36, a CRBN-based STAT3 degrader, which has selective anticancer efficacy and low toxicity.[29]

Preclinical data show that ARV-110 is an effective androgen receptor (AR) degrader, capable of reducing protein levels in relevant prostate cancer cells and inhibiting cell proliferation at low nanomolar concentrations. It further demonstrates the ability to reduce AR levels and the key prostate tumor biomarker, PSA, in plasma.[30] Arvinas and Pfizer are now working together to develop ARV-471, which will be used as a monotherapy to treat patients with ER+/HER2- locally advanced or metastatic breast cancer. It can cause the degradation of both wild-type and mutant estrogen receptors (ER). In endocrine-sensitive and resistant xenograft models, ARV-471 exhibits superior target degradation and antitumor activity compared to Fulvestrant.[6]

Bruton tyrosine kinase (BTK) is a non-receptor tyrosine kinase that is mostly expressed in hematopoietic cells. BTK is closely associated with the survival and proliferation of B-cell tumors through B-cell receptor (BCR) signaling.[31] NX-2127 achieves the interruption of cancer cell proliferation induced by BCR signaling by mediating BTK degradation through the proteasome.[32] NX-5948, developed by the American biotechnology company Nurix Therapeutics, is a novel, oral, highly selective BTK degrader. It has shown clinically significant effectiveness and tolerability in patients with relapsed or refractory B-cell malignancies.

PROTACs in Neurodegenerative Diseases

Neurodegenerative diseases (NDD) are major illnesses after cancer and cardiovascular diseases, and they represent a danger to human health and longevity. To date, the treatment of neurodegenerative diseases faces urgent and unmet clinical needs; however, these diseases have multiple potential pathogenic mechanisms, complicating their diagnosis and treatment.[33] Against this background, PROTACs have become a promising therapeutic approach, achieving therapeutic effects by targeting and degrading abnormal proteins associated with NDD. The etiology of NDD involves highly complex mechanisms, with many potential targets during treatment, such as the accumulation and aggregation of amyloid proteins in the brain, which have been associated with the progression of NDD.[34] Specific targets related to NDD pathology include tau protein in Alzheimer's disease and GSK-3β, among others.[35,36]

Neurodegeneration and the death of brain neurons can result from aberrant tau protein phosphorylation. Alzheimer's disease (AD) onset is tightly linked to tau protein misfolding and aggregation brought on by neurodegeneration. Aβ deposition and hyperphosphorylated tau protein buildup are significant pathogenic indicators in AD patients' brains.[37] By targeting tau protein, PROTAC molecules lower aberrant tau protein levels in brain cells, thereby decreasing the progression of Alzheimer's disease. Through in vitro and in vivo experiments, Wang et al confirmed that their tau protein-targeting PROTAC (C004019) may effectively increase tau clearance via the ubiquitin-proteasome pathway in a variety of tau overexpression cell lines. Additionally, intracerebral and subcutaneous administration significantly

reduced tau levels in wild-type, human tau (hTau) transgenic, and 3xTg-AD mouse models while improving synaptic and cognitive functions.[38]

PROTACs in Metabolic Syndrome

The metabolic syndrome is a complicated collection of metabolic diseases that include adipose tissue accumulation, insulin resistance, diabetes mellitus, hyperinsulinemia, hypertension, and dyslipidemia. It is typified by elevated levels of triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C).[39] Targeted regulation of particular protein for the management of metabolic syndrome may be a promising intervention, considering the important role that proteins play in metabolic disorders.

Moving to a specific example, atherosclerotic dyslipidemia is a major cause of cardiovascular diseases (CVD), characterized by elevated cholesterol levels.[40] 3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) is an acknowledged lipid-lowering drug target located on the endoplasmic reticulum. It is the rate-limiting enzyme of the mevalonate pathway, catalyzing the transformation of HMG-CoA to mevalonate, an essential precursor of cholesterol.[41] Luo et al synthesized a potent HMGCR-targeting PROTAC (21c), which includes a VHL ligand conjugated with lovastatin acid. It effectively breaks down HMGCR in Insig-silenced HepG2 cells (DC_{50}≈120 nM) and creates a stable ternary complex.[42] This study further confirmed that inducing HMGCR degradation via PROTAC technology can significantly reduce cholesterol levels, providing a novel strategy for the prevention of cardiovascular diseases. This discovery not only expands the application prospects of PROTACs in metabolic diseases but also lays the foundation for developing new lipid-lowering drugs.

PROTACs in Infectious Diseases

Viral infectious diseases have the characteristics of fast transmission speed, wide impact range, and high mortality rate.[43] At present, vaccination and combination therapy are the main means of preventing and treating viral infections. The growing number of drug-resistant strains poses a challenge to the currently available antiviral treatment strategies. However, existing antiviral drugs are facing problems such as the increase of drug-resistant strains, and vaccine inoculation usually cannot resist mutations or new viruses.[44] Therefore, exploring new antiviral strategies is crucial, and PROTAC technology is one of them. Based on the characteristics of the virus and its reproductive process after entering host cells, some of its proteins can be used as target proteins for PROTACs. The Nef gene of human immunodeficiency virus type 1 (HIV-1) encodes a unique membrane related protein, which plays a key role in virus replication, persistence and the progress of acquired immune deficiency syndrome (AIDS).[45] The existing Nef inhibitors can only bind to the Nef protein, blocking some of its functions, but cannot destroy its crucial role in HIV infection. Therefore, after stopping taking Nef inhibitor antiviral drugs, virus cells will reactivate and produce new viruses again. Smithgall et al coupled Nef binding compounds with E3 ubiquitin ligase ligands to prepare a PROTAC system targeting Nef protein, which can degrade Nef in cells, inhibit HIV-1 replication, and effectively rescue Nef mediated down-regulation of MHC-I and CD4 in T cells.[46] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that caused the global coronavirus disease 2019 (COVID-19) pandemic. The main protease (M^{pro}) of SARS-CoV-2 is crucial for viral infection and is one of the main therapeutic targets for COVID-19.[47] Huang et al coupled the target protein ligand H117 with the E3 ligase CRBN ligand pomalidomide via a linker to obtain a heterodimeric small molecule HP211206. HP211206 can induce the degradation of SARS-CoV-2 M^{pro} resistant mutants in cells, providing a new solution for the development of novel coronavirus drugs.[48] A synopsis of the therapeutic applications of PROTACs for various diseases is given in Table 1.

The Challenges in the Clinical Implementation of PROTACs

PROTAC technology, as an emerging drug development technique, exerts therapeutic effects by reducing protein levels rather than inhibiting their function. It has significant advantages in overcoming drug resistance and degrading non drug targets, and is expected to revolutionize drug development and meet the differentiated needs of clinical medication. However, although there are currently over 50 PROTAC candidate drugs being evaluated in clinical trials, no PROTAC based drugs have been launched yet. These investigational drugs can target multiple proteins, including androgen

Table 1 The Therapeutic Uses of PROTACs for a Range of Illnesses

Degrader	Target	E3 ligase	Indications	Ref.
ARV-110	AR	CRBN	Prostate cancer	[49]
ARV-471	ER	CRBN	Breast cancer	[49]
ARV-766	AR	Undisclosed	Prostate cancer	[50]
CFT-1946	BRAF	CRBN	Non-small cell lung cancer	[51]
AC-682	ER	CRBN	Breast cancer	[52]
CFT8634	BRD9	CRBN	Synovial sarcoma	[51]
CFT8919	EGFR-L858R	CRBN	Non-small cell lung cancer	[30]
CC-94676	AR	CRBN	Prostate cancer	[53]
DT-2216	BCL-X_L	VHL	Liquid and solid cancers	[54]
CG001419	TRK	CRBN	Cancer and other indications	[30]
GT-20029	AR	Undisclosed	Androgenic alopecia	[55]
HSK-40118	EGFR	Undisclosed	Non-small cell lung cancer	[51]
HSK-29116	BTK	Undisclosed	B-cell lymphoma	[56]
HP-518	AR	Undisclosed	Metastatic castration resistant prostate cancer	[51]
FHD-609	BRD9	Undisclosed	Synovial sarcoma	[57]
KT-474	IRAK4	Undisclosed	Autoimmune diseases	[30]
KT-413	IRAK4	CRBN	Diffuse large B cell lymphoma	[30]
KT-333	STAT3	Undisclosed	Liquid and solid tumours	[58]
NX-2127	BTK	CRBN	B cell malignancies	[59]
NX-5948	BTK	CRBN	B cell malignancies and autoimmune diseases	[51]

receptor (AR), estrogen receptor (ER), Bruton tyrosine kinase (BTK), and interleukin-1 receptor associated kinase 4 (IRAK4). Its potential applications cover various diseases, such as hematological malignancies, solid tumors, and autoimmune diseases. However, despite the promising prospects of PROTAC drugs, their development also faces significant challenges. Many PROTAC molecules have a high molecular weight, are difficult to crystallize, have poor solubility, and poor permeability.[12–14] In addition, the oral bioavailability of some candidate drugs is still low, which poses further obstacles to clinical translation and commercial success. With the development of nanotechnology, nano assembly strategies have gradually attracted widespread attention.

Nano-Proteolysis Targeting Chimeras (Nano-PROTACs)

Nanotechnology refers to the engineering and manufacturing of materials on the atomic and molecular levels. In recent decades, nanotechnology has continuously garnered extensive attention in the medical field and has been widely applied in drug carriers, cancer treatment, gene therapy, regenerative medicine, medical diagnostics, and more.[60–62] Nano-drug delivery systems (nano-DDSs), as a crucial component of nanomedicine, have become an important tool in medical research and clinical treatment due to their excellent loading capacity, efficient drug delivery efficiency, and controllable release rates.[63] Nanoplatforms for drug delivery can be designed in various forms, including liposomes, polymer nanoparticles, inorganic nanoparticles, nano micelles, and nanogels, where drugs can be loaded into the core or surface of nanocarriers through chemical conjugation, physical encapsulation, or electrostatic adsorption.[64,65] Nanocarriers can improve the stability, solubility, membrane permeability, and circulation time of drugs. By modifying their surface structure, size, and composition, it is possible to achieve stimulus-responsive drug release and targeted delivery to diseased tissues. This approach enables precise drug administration, enhances therapeutic efficacy, and minimizes toxicity to healthy tissues.[66–68] Additionally, nanocarriers have the capability to transport multiple drugs simultaneously, facilitating the delivery of various therapeutic agents within a single system for enhanced treatment of complex diseases.[69] Each type of nanocarrier offers unique drug loading and release characteristics, allowing researchers to tailor and engineer them to meet the specific needs and challenges of different diseases.[70] In this section, we will focus on the nanocarriers most commonly used for delivering PROTACs.

Lipid-Based Nanoparticles

Lipid-based nanoparticles offer several advantages for PROTAC delivery, including simple formulation, ideal drug loading capacity, good biocompatibility, biodegradability, and the ability to modify surfaces flexibly.[71,72] These nanoparticles use amphiphilic lipid molecules, such as phospholipids and steroids, for encapsulating and delivering PROTACs. This approach enhances cellular permeability, as these compounds mimic the cell membrane and facilitate cellular uptake.[73] Lipid-based nanoparticles commonly used to deliver PROTAC can be divided into three categories: liposome nanoparticles, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and cell membrane-coated nanoparticles.[67]

Liposome Nanoparticles (LNP)

Liposomes are supramolecular aggregates formed by amphiphilic lipid molecules dispersed in a solution,[74] initially discovered by Dr. A. D. Bangham and Dr. R.W. Horne in 1964.[75] These liposomes are primarily composed of hydrophilic head groups and hydrophobic tails, forming a bilayer structure similar cell membrane. Liposomes have an aqueous core, granting them a core-shell structure where hydrophilic drugs can be loaded into the aqueous core and lipophilic drugs into the lipid membranes.[74,76] Liposome nanoparticles exhibit non-toxicity, high biocompatibility, biodegradability, low immunogenicity, and protect drugs from degradation. Additionally, nanoliposomes can enhance drug solubility, bioavailability and alter biodistribution, and be surface-modified to achieve targeted and controlled drug release.[76,77] Therefore, nanoliposomes are considered to have enormous potential in delivering PROTACs.

In order to improve the targeting capabilities of PROTACs and decrease their off-target negative effects, Saraswat et al designed an asialoglycoprotein receptor (ASGPR)-targeted nanoliposome loaded with a novel BRD4-targeting PROTAC (ARV-825), named GALARV, which showed great potential in treating hepatocellular carcinoma (HCC).[78] The average particle size of GALARV and non-targeted liposome LARV was 93.83±10.05 nm, which can enhance selective tumor accumulation and retention through the EPR effect. By introducing PEG chains on the liposome surface, the spatial stability of GALARV was enhanced, its circulation time was extended, and accumulation at target sites was improved, while potential toxic side effects were reduced. Furthermore, GALARV used galactosylceramide (GC) as the ASGPR targeting ligand, further enhancing targeting and cellular uptake in HCC. Compared to LARV (without the targeting ligand GC) and free ARV, GALARV increased intracellular ARV concentration by approximately 3-fold and 4.5-fold respectively. GALARV has strong anti-HCC activity, and delivering PROTACs to degrade BRD4 via targeted nanomedicine may be a novel therapeutic strategy for treating and managing HCC.

To date, various liposome-based formulations have been successfully implemented in the clinical field, such as Doxil® (the first), DepoCyt®, Ambisome®, Exparel®, and Visudyne®.[76] Additionally, two liposome nanoparticle-based COVID-19 vaccines have been successfully approved, indicating that liposome nanoparticle-based PROTAC delivery technology has broad prospects and is anticipated to encourage the clinical translation of PROTAC.[73] Although liposome nanoparticles have unique advantages in delivering PROTACs, there are still some potential issues that need attention. One challenge with using liposome nanoparticles for PROTAC delivery is that many PROTAC compounds are poorly soluble in water. As a result, they can only be incorporated into the hydrophobic bilayer, rather than the larger aqueous core, limiting the drug-loading capacity. Additionally, drug leakage from liposome nanoparticles can occur, impacting both their usage and storage stability.[65] However, these challenges can be addressed through technological advancements. By modifying the chemical structure of PROTACs or adjusting the composition of liposome nanocarriers, it is possible to enhance their stability and effectiveness, thereby facilitating progress in PROTAC clinical research.

Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)

SLNs are spherical nanoparticles composed of solid fats (such as monoglycerides and fatty acids) and surfactants, featuring a solid lipid core and a monolayer shell.[79] Compared to LNPs, their rigid solid lipid core instead of an aqueous core enhances the encapsulation efficiency and storage stability of hydrophobic drugs, beneficial for loading poorly

water-soluble PROTAC molecules.[73,80] Nanostructured lipid carriers (NLC) consist of a non-structured lipid interior and a monolayer surfactant exterior. The core is formed by a mixture of solid and liquid lipids, creating an imperfect crystalline interior. Compared to the solid crystalline lattice of SLNs, the imperfect crystalline structure and liquid phase in NLCs increase drug loading and prevent drug leakage.[80] Therefore, the combination of SLN and NLC with PROTAC is expected to overcome the potential limitations of LNPs, such as drug loading capacity and leakage, thereby improving therapeutic efficacy.

For instance, Vartak et al developed a polyethylene glycol-modified nanostructured lipid carrier (AP-NLC) for delivering ARV-825 to treat non-small cell lung cancer (NSCLC).[81] The AP-NLC utilized Precirol®ATO5 and Captex®300EP/NF as solid and liquid lipids, respectively, to enhance the stability and drug-loading capacity of ARV-825 (Figure 3). This was further improved by hydrophobic ion pairing with medium-chain fatty acids. In vitro experiments demonstrated that ARV-825 delivered via AP-NLC exhibits strong anticancer efficacy against NSCLC cells. Moreover, it highlighted the potential of PROTACs to treat NSCLC effectively at nanomolar concentrations, potentially avoiding the "hook effect". This study underscores the promising role of nanotechnology in delivering hydrophobic PROTACs for cancer treatment.

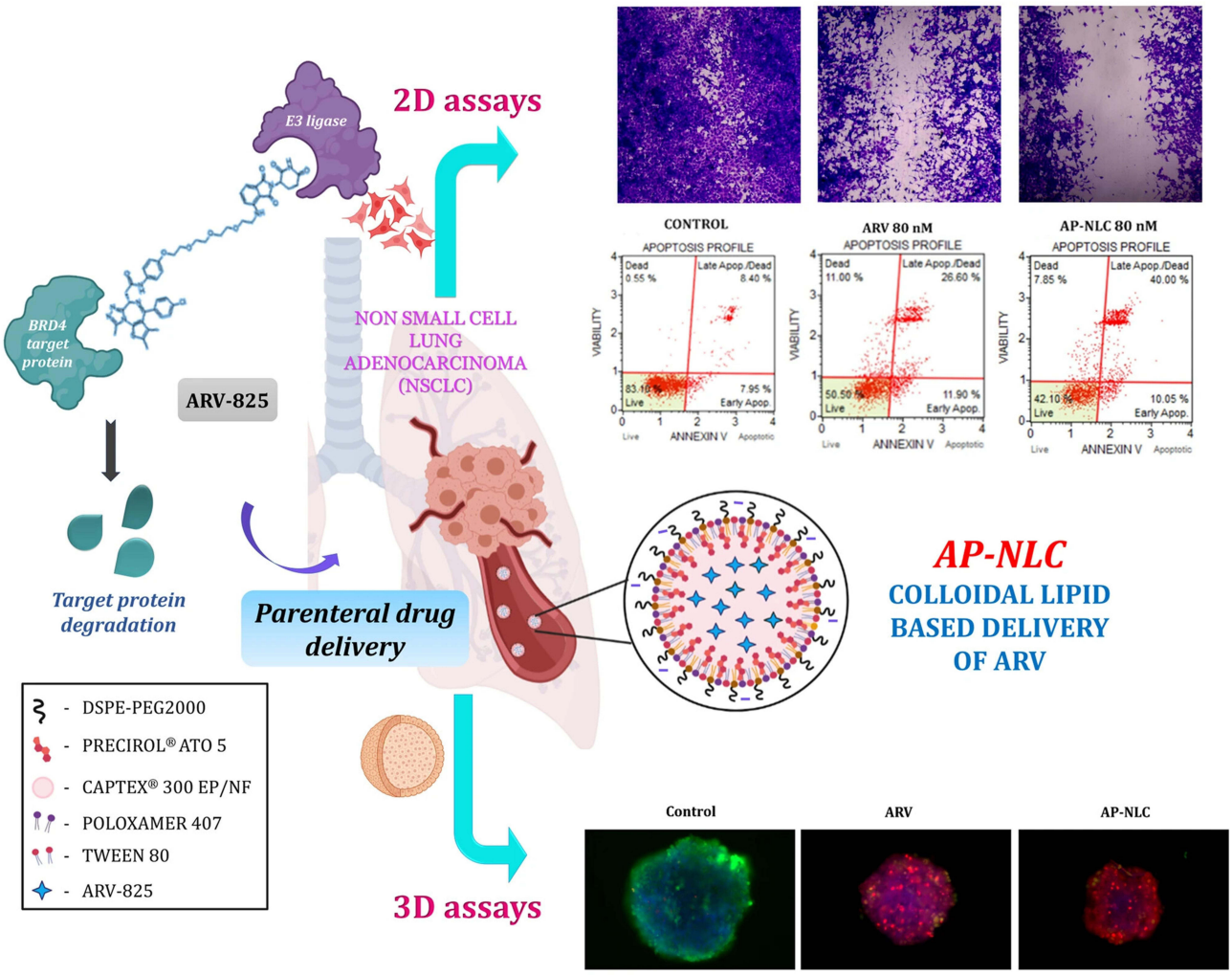

Figure 3 Schematic representation of ARV-825 loaded nanostructured lipid carrier for targeting NSCLC. Adapted from Vartak R, Saraswat A, Yang Y et al. Susceptibility of lung carcinoma cells to nanostructured lipid carrier of ARV-825, a BRD4 degrading proteolysis targeting chimera. *Pharm Res*. 2022;39(11):2745–2759. Copyright 2022, with permission from Springer Nature.[81]

Cell Membrane-Coated Nanoparticles (CNPs)

Compared to traditional lipid-based nanocarriers, drug delivery systems based on cell membrane-coated nanoparticles (CNPs) demonstrate significant application prospects in cancer therapy. Depending on the type of cell membrane used, biomimetic membrane-coated nanomedicines exhibit properties similar to their source cell membranes, significantly enhancing biocompatibility, immune evasion, and tumor targeting.[82] For instance, Zhang et al used biomimetic lung cancer cell membranes to camouflage BRD4-targeting PROTACs, enabling concurrent targeting of lung cancer cells and tumor-associated macrophages (TAMs), enhancing the internalization of PROTAC nanoparticles, and remodeling the tumor microenvironment, demonstrating efficient tumor inhibition.[83] Additionally, for different application purposes, the source of cell membrane materials (including red blood cells, platelets, immune cells, cancer cells, stem cells, or bacteria) determines the function of the nanoparticles.[84] Huang et al employed macrophage membranes coated on PROTAC-loaded PLGA nanoparticles for treating atherosclerosis. Mouse model experiments showed that this PROTAC-loaded biomimetic nanomedicine effectively improved the accumulation in atherosclerotic plaques and alleviated the progression of atherosclerosis, offering a successful method for treating targeted atherosclerosis (Figure 4).[85] Thus, the combination of PROTAC and CNPs effectively improves the targeting specificity of PROTACs and enhances their pharmacokinetic properties. With continuous technological advancements, this emerging technology shows considerable potential for clinical applications.

Polymer Nanoparticles

Polymer nanoparticles are self-assembled from amphiphilic macromolecules, typically consisting of diblock or triblock copolymers with hydrophilic and hydrophobic segments.[86] This unique structure allows polymer NPs to adeptly deliver various hydrophobic and hydrophilic drugs and is widely used for encapsulating unstable proteins and gene drugs.[87] Polymer nanoparticles are usually synthesized from highly biocompatible and biodegradable polymer materials, such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), chitosan, or polycaprolactone (PCL), with PLGA being the most commonly used and extensively studied as a drug carrier.[88,89] Polymer nanoparticles can prolong drug circulation in the bloodstream and control drug release by incorporating PEG modifications and adjusting the type of polymers and the balance of hydrophilic and hydrophobic segments.[87] To treat pancreatic cancer, Saraswat et al created PLGA-PEG polymer nanoparticles loaded with a novel BRD4 protein degrader (ARV-825) using nanoprecipitation (ARV-NP).[90] Through the increased permeability and retention (EPR) effect, the particle size of ARV-NP (<200 nm) is appropriate for passively targeting solid tumors. Additionally, the PEG-rich surface helps to circumvent the reticuloendothelial system, hence prolonging the duration of drug circulation. ARV-NP is compatible with red blood cells, improves the half-life of ARV-825, and demonstrates excellent physical stability and negligible hemolysis. In vitro cell experiments show that ARV-NP exhibits significant inhibitory effects on human pancreatic cancer cell models, with notable cytotoxicity, apoptosis, and anti-clonogenic effects.

Moreover, small-molecule modification of the polymer nanoparticle surface can confer specific targeting or other diverse functionalities, further enhancing the targeting specificity of PROTACs and addressing pharmacokinetic issues.[91] For example, Cimas et al prepared trastuzumab-conjugated polymer nanoparticles (MZI-ACNPs) loaded with BRD4-targeting MZI PROTAC for the treatment of breast cancer.[92] Compared to free MZI PROTAC, MZI-ACNP exhibits pronounced toxicity against breast cancer cell lines due to active targeting mediated by trastuzumab (an antibody targeting HER2+ breast cancer) conjugation. In another study, He et al created a polymer nanoparticle modified with cRGD ($\alpha_v\beta_3$ integrin-targeting peptide) to deliver doxorubicin (DOX) and the BRD4 PROTAC degrader ARV-825 simultaneously, aiming to achieve synergistic therapy and enhanced efficacy (Figure 5).[93] Experimental results show that cRGD-modified polymer nanoparticles enhance the cellular uptake and targeting properties of both drugs, overcoming DOX-induced acquired resistance and enhancing anticancer effects.

Compared to liposome nanoparticles and other conventional nano delivery systems, polymer nanoparticles offer several advantages. They are made from relatively inexpensive raw materials, can be produced through various methods such as emulsification, nanoprecipitation, and ionotropic gelation, and provide enhanced stability. PROTAC molecules can be flexibly loaded into the hydrophobic core of polymer nanoparticles, onto the particle surface, encapsulated within

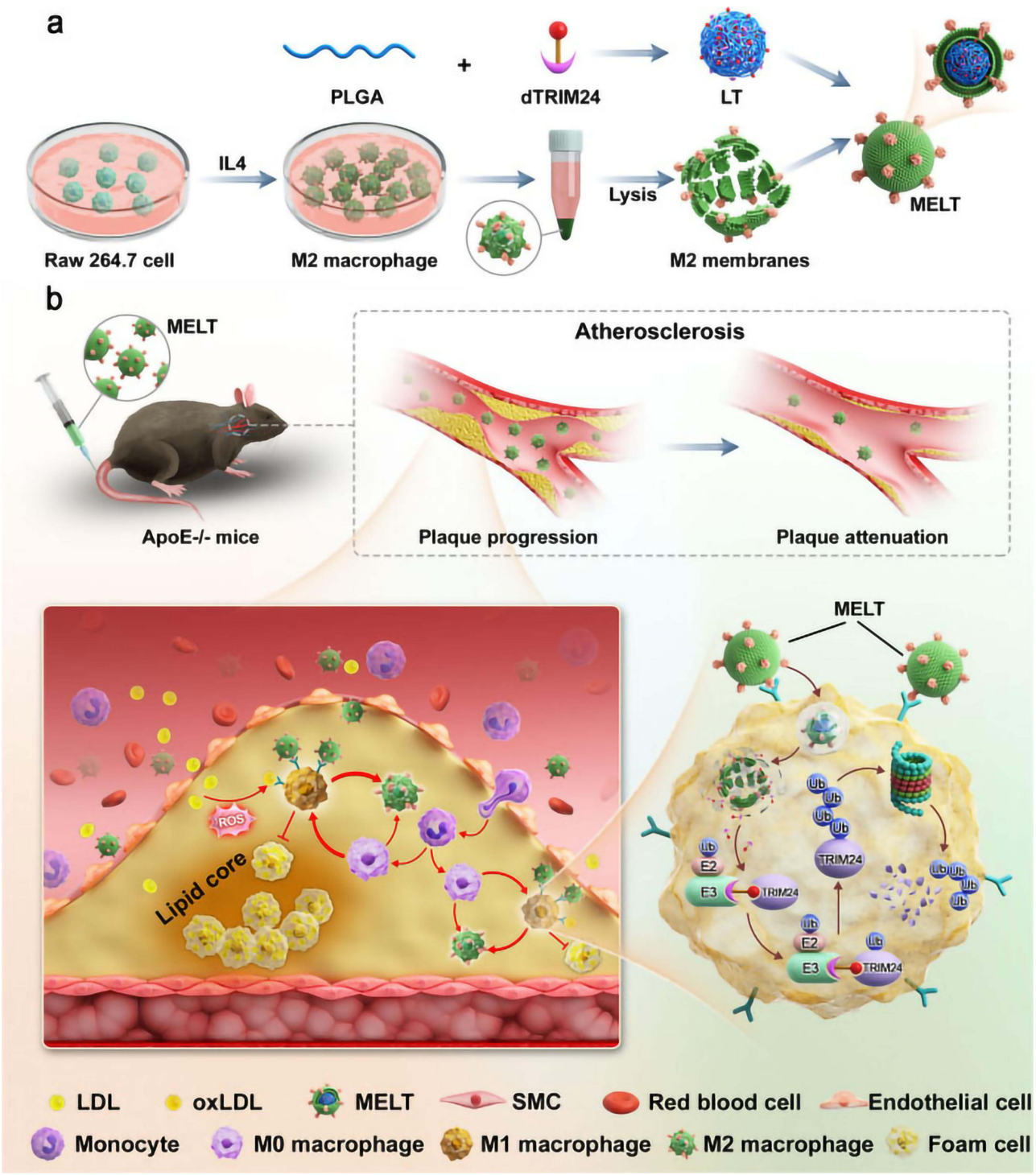

Figure 4 (**a**) The preparation procedure of membranes derived from M2 macrophages/PLGA/dTRIM24 (MELT). (**b**) The PROTAC-induced macrophage fate determination of MELT on the atherosclerotic plaque by eliminating TRIM24 and polarizing macrophages to the M2 subtype in vivo. Adapted from Huang JH, Huang CJ, Yu LN et al. Bioinspired PROTAC-induced macrophage fate determination alleviates atherosclerosis. *Acta Pharmacol Sin*. 2023;44(10):1962–1976. Copyright 2023, with permission from Springer Nature.[85]

the polymer matrix, or chemically bonded to the polymer structure.[7] Additionally, targeted or stimulus-responsive polymer nanoparticles can effectively improve the targeting specificity of PROTACs, enhance the bioavailability, reduce side effects, and potentially avoid the "hook effect" by controlling the release. However, the potential toxicity and high immunogenicity of polymer nanoparticle components are key challenges for their clinical translation. Moreover, it is yet

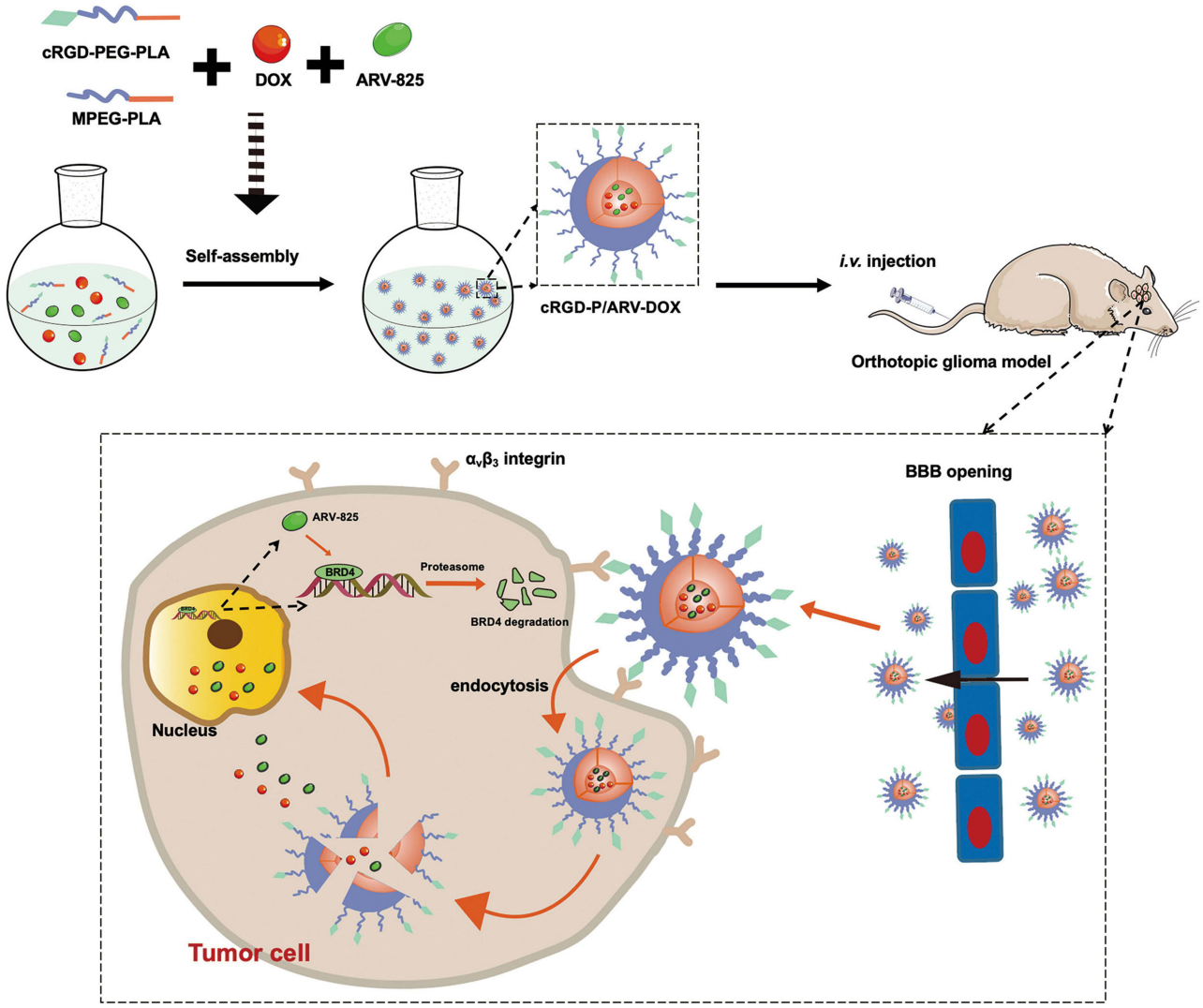

Figure 5 Schematic representation of the structure model about co-loading DOX and ARV-825 by cRGD-decorated nanoparticles (cRGD-PEG-PLA), and the processes of drug delivery in orthotopic glioma model. Adapted from He Y, Zan X, Miao J et al. Enhanced anti-glioma efficacy of doxorubicin with BRD4 PROTAC degrader using targeted nanoparticles. *Mater Today Bio.* 2022;16:100423. Copyright 2022, with permission from Elsevier.[93]

unclear how polymer nanoparticles circulate, distribute, and metabolize in vivo. Therefore, although some polymer nanomedicines are in clinical trial stages, only a few have received FDA approval and are used clinically.

Inorganic Nanoparticles

Inorganic nanoparticles (INPs) possess distinct physicochemical properties and structural features that enable precise control over the size, structure, and geometry of drugs. This control improves pharmacokinetics (PK), making INPs an ideal choice for PROTAC delivery systems.[70,94] Additionally, the rigid structure of INPs can minimize the possibility of drug leakage to non-target locations while in circulation.[95] Mesoporous silica nanoparticles (MSN), gold nanoparticles (GNP), iron oxide nanoparticles, and quantum dots are considered ideal INPs for delivering PROTACs.[96] Among them, gold nanoparticles are regarded as the most promising drug carriers due to their biocompatibility, low toxicity, tunable size, high drug loading capacity, compatibility with surface plasmon resonance, multifunctionality, and ease of synthesis.[97,98]

Typically, thiol-modified polyethylene glycol (PEG) can be used as a spacer, enhancing the connection between drug molecules and GNPs through gold-sulfur (Au-S) interactions, thereby improving solubility and stability.[99] Therefore, Wang et al designed polyethylene glycolated GNPs (Cer/Pom-PEG@GNPs) loaded with ceritinib and pomalidomide

https://doi.org/10.2147/IJN.S552644

molecules for delivering novel multi-headed PROTACs to target anaplastic lymphoma kinase (ALK) for treating non-small cell lung cancer.[98] Cer/Pom-PEG@GNPs demonstrate excellent stability, with surface-bound ceritinib and pomalidomide molecules effectively targeting ALK and connecting with E3 ligase ligands in confined spaces. This approach eliminates the need for complex structural optimization of PROTACs and enhances the likelihood of forming ternary complexes. Experimental results indicate that Cer/Pom-PEG@GNPs effectively degrade intracellular ALK fusion proteins, showing promise for use in patients who are resistant to ALK inhibitors. In another study, to lessen the off-target toxicity often connected to systemic administration of PROTACs, He et al prepared UCNP-based mesoporous silica nanoparticles (UMSNs) to load photo-caged PROTAC (phoBET1) for controllable targeted protein degradation (Figure 6).[100] Under alternating "on-off" NIR light irradiation, the release of active PROTAC (dBET1) can be regulated to achieve on-demand dosing and adjust the required drug dose. In vivo, experiments show that UMSNs@phoBET1 nanocages efficiently suppress tumor growth by degrading BRD4 in response to NIR light in tumor tissues. This may open new possibilities for PROTAC-photothermal combination therapy.

Inorganic nanoparticles mostly have good biocompatibility and stability, meeting characteristic requirements that organic nanoparticles cannot achieve.[101] Although the high drug-loading capacity and multifunctionality of inorganic nanoparticles hold great potential for improving the pharmacokinetics (PK) and drug-likeness of PROTACs, potential long-term toxicity and limited biodegradability are obstacles to sustainable translation.[102,103] Inspired by the work of

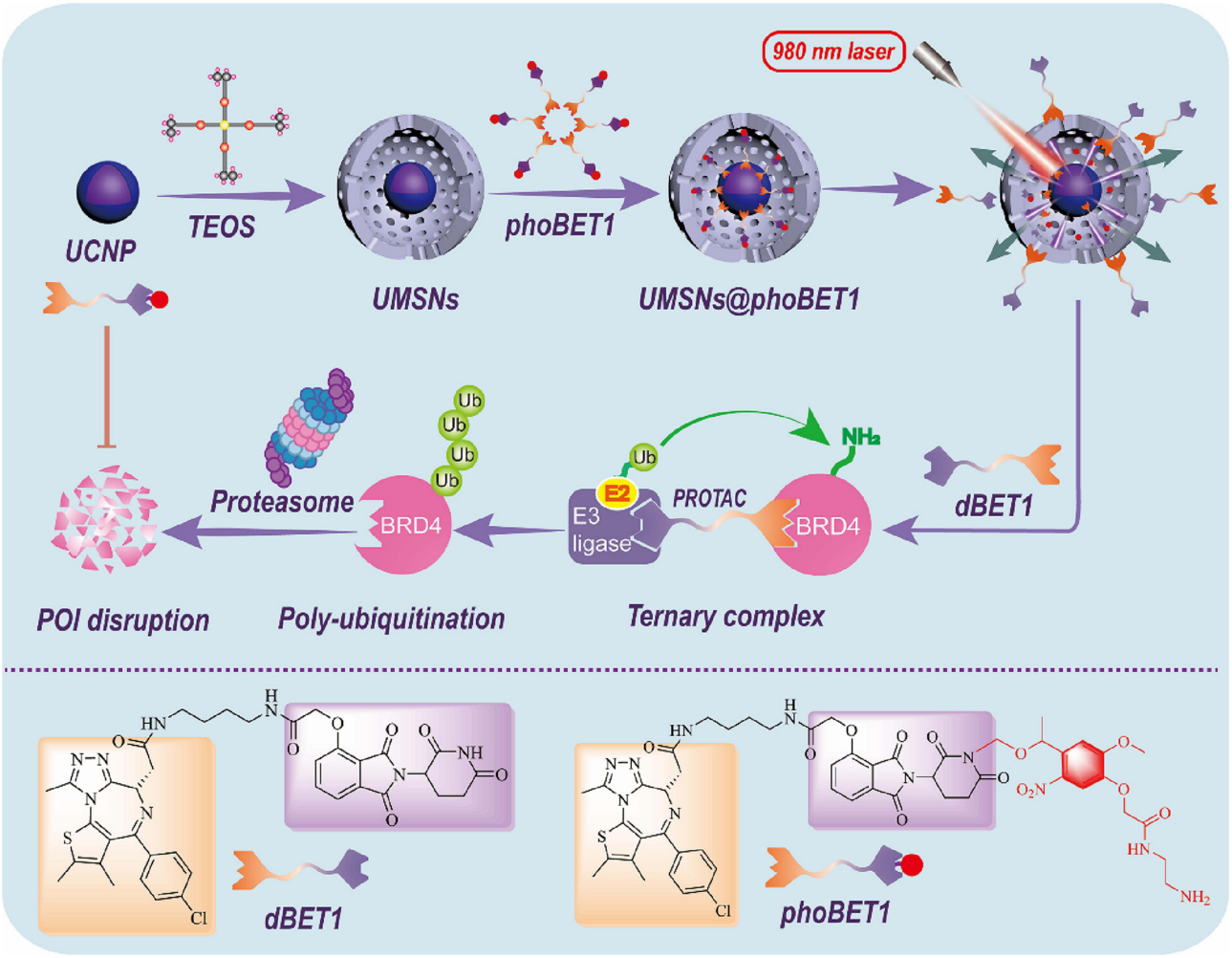

Figure 6 Schematic diagram for designing the NIR light-activatable PROTAC nanocage and its working mode for degrading the protein of interest (POI). Adapted from He Q, Zhou L, Yu D et al. Near-infrared-activatable PROTAC nanocages for controllable target protein degradation and on-demand antitumor therapy. *J Med Chem*. 2023; 66(15):10,458–10472. Copyright 2023, with permission from American Chemical Society.[100]

Khandekar et al, coating inorganic NPs with biodegradable and non-toxic polymers can overcome potential toxicity issues, potentially promoting the clinical application of inorganic NPs.[104]

Protein-Based Nanoparticles

Proteins are ideal nanoscale drug carriers with biocompatibility, biodegradability, and low toxicity.[105] They possess various functional groups that can effectively bind and carry more drugs through diverse intermolecular forces.[106,107] Proteins such as albumin, protein cages, soy protein, and whey protein can be engineered or self-assembled to serve as nanocarriers for drug encapsulation, providing new functions like selective targeting or tracking.[108,109] Among them, albumin is the most commonly used protein for nanoparticle preparation to achieve drug delivery, because of its high structural stability and long half-life (19 days), and is anticipated to play a crucial role in improving the pharmacokinetic properties of PROTAC molecules and achieving targeted delivery.[109,110] The extended retention of albumin, which is aggressively absorbed by cancer cells under stress and converted into amino acids as nutrition, is caused by the high permeability of blood arteries and the absence of lymphatic outflow in the tumor microenvironment.[111] Benefiting from this, Cho et al utilized albumin to load an esterase-cleavable maleimide linker (ECMal) BRD4-degrading PROTAC, achieving tumor-specific accumulation and cellular uptake of the PROTAC (Figure 7).[112] After Alb-ECMal-PROTAC is internalized by tumor cells, the esterase cleaves the maleimide linker to release the free PROTAC, enabling selective degradation of BRD4 protein. Compared to the free PROTAC, this method increases antitumor efficacy by 5.3 times without causing any significant systemic toxicity. Additionally, the binding of ECMal-PROTAC to albumin effectively improves the hydrophobicity and low water solubility of PROTAC molecules, significantly extending circulation time and half-life. In summary, albumin-bound ECMal-PROTAC represents a highly promising strategy that could be applicable to other types of PROTACs, improving pharmacokinetic properties and enhancing therapeutic efficacy.

In addition to albumin, researchers have shown significant interest in abundant and cost-effective plant proteins. These proteins can form stable nanoparticles without the need for chemical linkers and offer long-term sustained drug-release properties.[109,113,114] Additionally, protein nanocages, with their defined and reproducible geometric hollow structures, offer strong stability, a long half-life, and uniform cage size, making them promising candidates for future production of ideal nanocarriers for PROTAC delivery.[115,116]

PROTAC medications may also be delivered by a few more delivery systems in addition to the previously stated nanocarriers. For instance, hydrogel-based PROTAC delivery systems can load multiple drugs simultaneously, thereby enhancing therapeutic effects through synergistic treatment. Wu et al developed an injectable PLGA-PEG-PLGA nanocomposite hydrogel capable of co-delivering mesoporous silica nanoparticles (PepM@PacC) coated with cancer cell membranes (CCM) loaded with PROTAC and paclitaxel (Pac) and $CaCO_3$ nanoparticles (RC) loaded with R837 (Figure 8).[117] When this nanocomposite hydrogel is injected, it gels in situ and breaks down over time in the immunosuppressive tumor microenvironment (TME), releasing RC and PepM@PacC nanoparticles for chemotherapy and immunotherapy that work in concert to effectively stop the growth and metastasis of head and neck squamous cell carcinoma (HNSCC).

In summary, nano-DDSs have garnered wide attention due to their inherent nanoscale advantages and drug-loading capabilities. Despite some unavoidable limitations, such as poor degradability, immunogenicity, limited drug-loading capacity, and toxicity from additional excipients or chemical modifications, their unique functions and characteristics help overcome the key challenges currently faced by PROTACs.[118–120] Overall, Nano-drug delivery systems (nano-DDSs) offer a promising strategy for treating refractory diseases and advancing the clinical translation of PROTACs. Based on these advancements and limitations, the nanocarriers that are frequently employed to load PROTAC are systematically described in Table 2 to support clinical translation through future logical design and enhancement of PROTAC delivery systems.

Carrier-Free Nano-PROTACs

In recent years, emerging carrier-free delivery systems based on the self-assembly of active drug molecules have demonstrated significant promise in delivering PROTACs, as they can overcome some limitations of nano-drug delivery systems.[123] Therefore, to block the DNA damage repair mechanism degraded by BRD4 and enhance the inhibitory effect of photodynamic therapy (PDT) on tumor cell proliferation, Zhao et al constructed a carrier-free nano-PROTAC

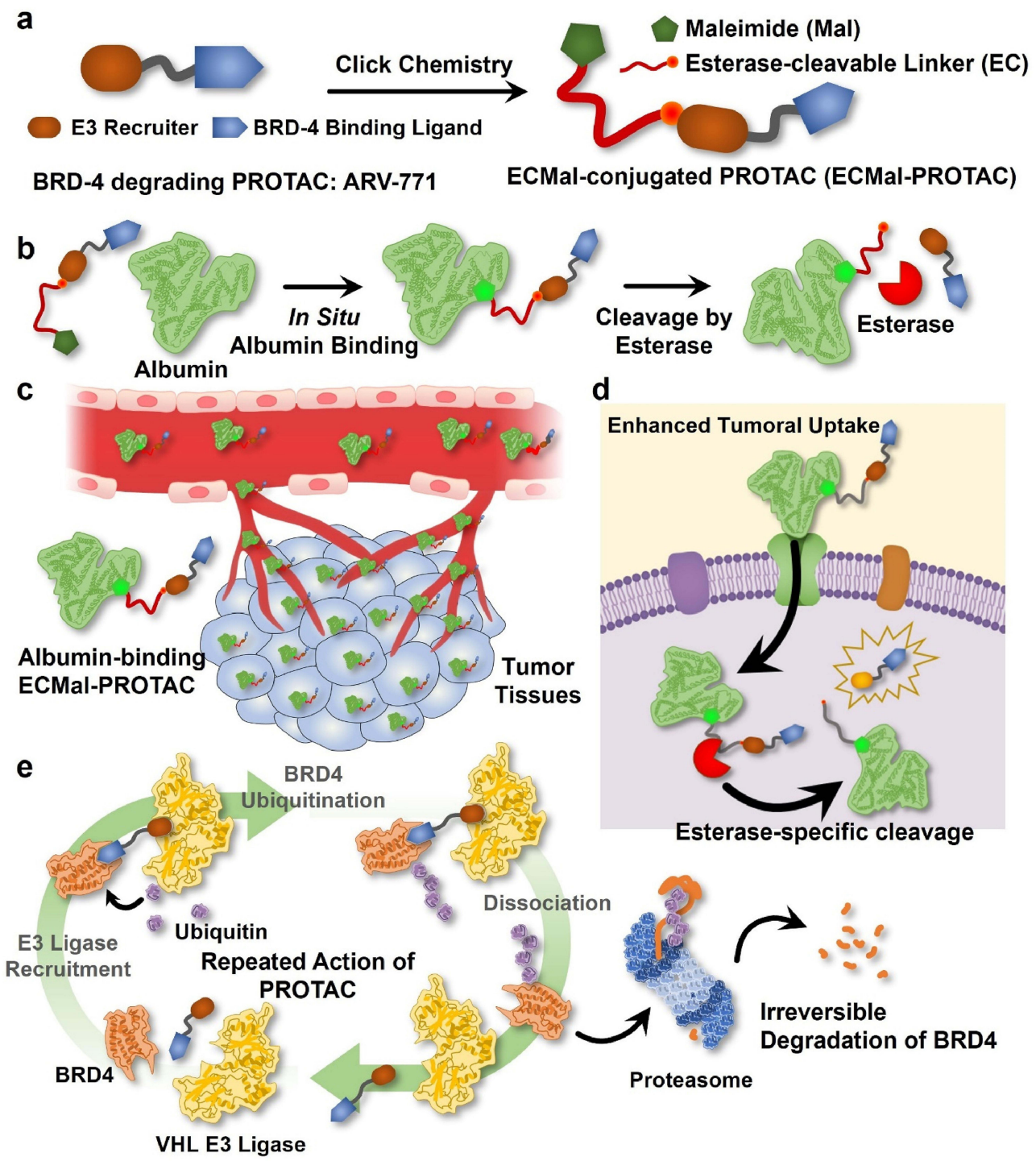

Figure 7 Schematic diagram for the MOA of ECMal-PROTAC. (**a**) In situ albumin-binding esterase-cleavable BRD4-degrading PROTAC (ECMal-PROTAC) was developed by conjugating the ECMal linkers to ARV-771 molecules. (**b**) ECMal-PROTACs administered in blood vessels spontaneously bind to plasma albumins via site-specific Thiol-Mal reaction, and the maleimide linkers in ECMal-PROTACs are cleaved by esterase to recover the free ARV-771s after they are internalized. (**c**) Through the in situ albumin binding, ECMal-PROTACs can be improved with their blood half-lives and selectively accumulated in tumor tissues. (**d**) The albumin-bound ECMal-PROTACs are actively internalized to cancer cells and cleaved to recover free ARV-771s. (**e**) The ARV-771s concurrently bind both BRD4 and VHL E3 ligase, inducing the polyubiquitination of BRD4. Afterward, the BRD4/ARV-771/E3 ligase complexes are dissociated and the polyubiquitinated BRD4 is degraded into oligopeptides as it is recognized by the proteasome. The dissociated ARV-771s are recycled to participate in the degradation of another BRD4. Adapted from Cho H, Jeon SI, Shim MK et al. In situ albumin-binding and esterase-specifically cleaved BRD4-degrading PROTAC for targeted cancer therapy. *Biomaterials*. 2023;295:122038. Copyright 2023, with permission from Elsevier.[112]

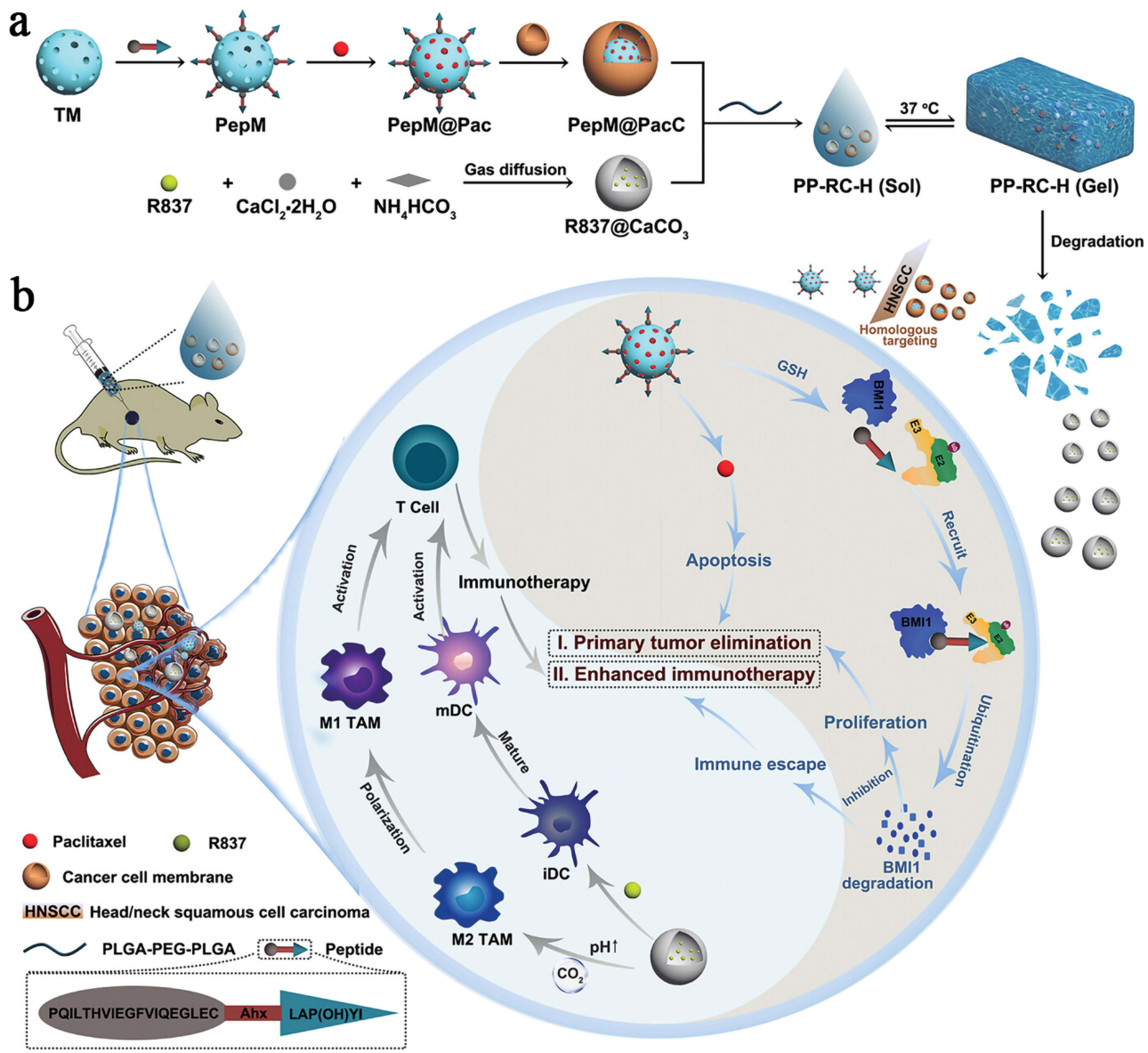

Figure 8 An antitumor nanocomposite hydrogel for the treatment of primary and metastatic HNSCC. (**a** and **b**) The peptide-based BMI1 PROTAC drug is linked via disulfide bonds to MSNs, into the pores of which paclitaxel has been loaded ("PepM@Pac"). The PepM@Pac NPs are then wrapped with a CCM to form "PepM@PacC" NPs. The imiquimod (also known as R837) is encapsulated with $CaCO_3$ to form R837@$CaCO_3$ ("RC") NPs. The PepM@PacC and RC NPs are co-dispersed within a PLGA-PEG-PLGA-based hydrogel to make up the injectable thermosensitive nanocomposite hydrogel. The nanocomposite hydrogel inhibits primary and metastatic HNSCC tumors via intratumoral injection. Adapted from Wu Y, Chang X, Yang G et al. A physiologically responsive nanocomposite hydrogel for treatment of head and neck squamous cell carcinoma via proteolysis-targeting chimeras enhanced immunotherapy. *Adv Mater.* 2023;35(12):e2210787. Copyright 2023, with permission from Wiley-VCH GmbH.[117]

(SDNpros) through the non-covalent self-assembly of photosensitizer chlorin e6 (Ce6) and BRD4 degrader (dBET57) PROTAC.[121] SDNpros possess a uniform nanoscale size distribution, good dispersibility, and stability, which enhance the delivery efficiency of Ce6 and dBET57, increasing cellular internalization and tumor-targeted accumulation. Importantly, SDNpros generate abundant reactive oxygen species (ROS) under light irradiation to induce oxidative DNA damage. Concurrently, by releasing dBET57 to continuously degrade BRD4, SDNpros interrupt the DNA repair pathway, thereby exacerbating oxidative DNA damage and enhancing the effectiveness of PDT in inhibiting tumor growth.

In another study, Wang et al self-assembled CDK4/6 PROTAC with Ce6 into carrier-free nanoparticles to achieve co-delivery of the two drugs, thereby enhancing tumor accumulation and reprogramming the immunosuppressive tumor microenvironment for antitumor immunity (Figure 9).[122]

Table 2 Nanocarriers and Carrier-Free Nano-PROTACs Commonly Used for Loading and Delivery of PROTCAs

Type	Example	Improvement	Limitation	Ref.
Lipid-based nanoparticles	Liposome	Endocytosis-mediated internalization; prolonged circulation; EPReffect	Volume and stability of drug loads affected	[78]
Cell membrane-coated nanoparticles	Bionic lung cancer CNP	Targeting effect; increased permeability	Production process complexity; poor stability	[85]
Polymeric nanoparticles	Micelle	Endocytosis-mediated internalization; prolonged circulation; EPR effect; improved pharmacokinetics	Potential aggregation and immunogenicity-related toxicity	[92,93]
Inorganic nanoparticles	Gold nanoparticles	Endocytosis-mediated internalization; EPR effect; improved stability and PK; prolonged circulation	Potential long-term toxicity and limited biodegradability	[98,100]
Protein-based nanoparticles	Albumin	Targeting effect; prolonged circulation; improved pharmacokinetics	Compromised in vivo stability	[112]
Gels	Hydrogel	Combinational therapy; on-demand release; increased lesion accumulation	Limited application to the superficial lesion and post-surgery treatments	[117]
Carrier-free nano-PROTACs	SDNpros	Combinational therapy; excellent drug loading efficiency; improved pharmacokinetics; on-demand release	Restricted self-assembly of different drug molecules; Compromised in vivo stability	[121,122]

Since the self-assembled carrier-free nano-PROTACs are made completely of active pharmaceutical ingredients (APIs) without any additional excipients, they exhibit excellent drug-loading efficiency (close to 100%) and avoid potential toxicity issues associated with inert carriers. Additionally, surface modification of carrier-free nano-PROTACs can enhance their targeting ability while improving pharmacokinetic characteristics. Importantly, with further research

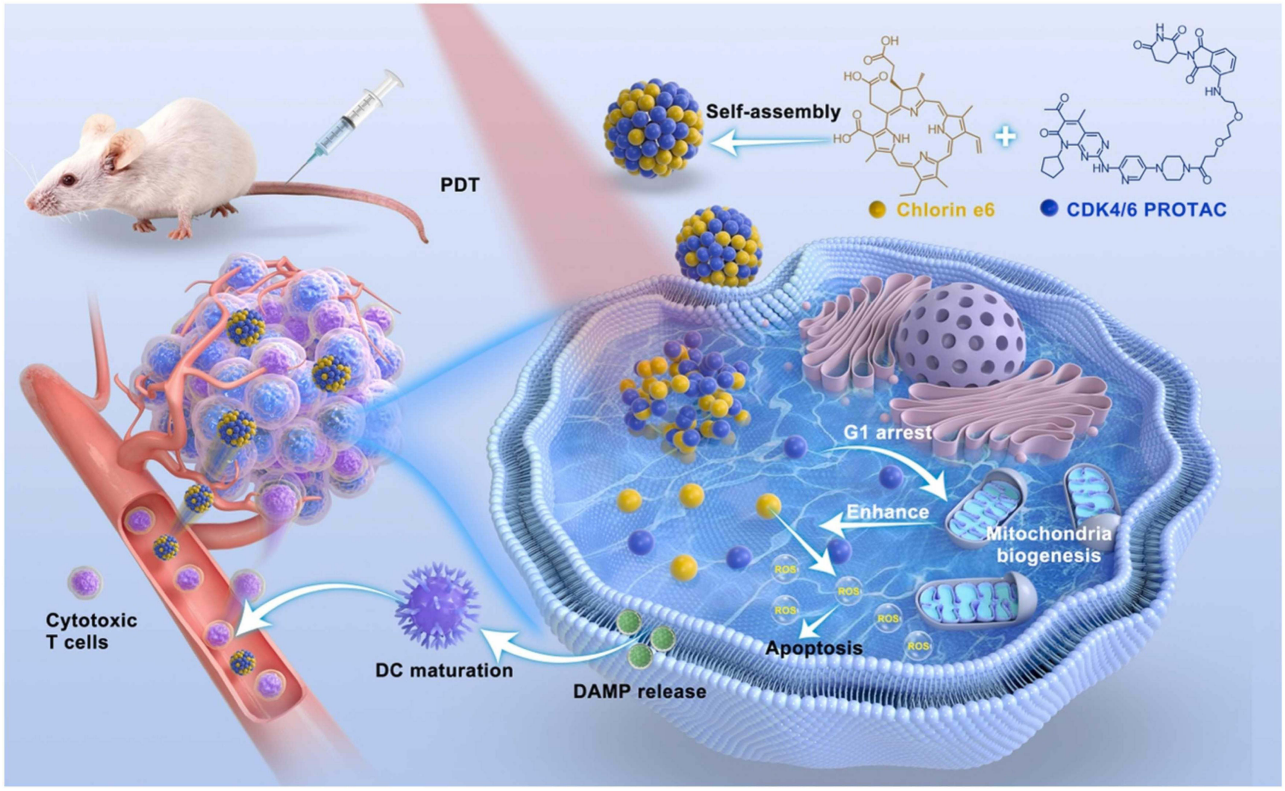

Figure 9 Schematic illustration of synergistic anti-tumor photodynamic therapy and immunotherapy based on CDK4/6 Nano PROTAC. Adapted from Wang T, Zhang Y, Chen K et al. CDK4/6 nano-PROTAC enhances mitochondria-dependent photodynamic therapy and anti-tumor immunity. *Nano Today.* 2023; 50:101890. Copyright 2023, with permission from American Chemical Elsevier.[122]

into self-assembled, carrier-free nanomedicines, it is expected that PROTACs can be co-assembled with other drug molecules (photosensitizers, photothermal agents, immunoreagents, and gene drugs) to achieve synergistic therapy and enhance therapeutic effects. However, despite the unique advantages of carrier-free PROTACs, varying solubility, and pharmacokinetic properties make the co-assembly of different drug molecules extremely challenging, hindering synergistic effects, which is a primary concern in constructing carrier-free nano-PROTACs.[124]

Conclusion and Perspectives

Overall, the combination of nanotechnology and PROTACs is ushering in a new era in the field of targeted protein degradation. Due to their nanoscale size, drug delivery properties, and controlled drug release, nanocarriers effectively increase the solubility, stability, and intracellular delivery efficiency of PROTACs, improving their pharmacokinetic properties and druggability. Simultaneously, different responsive nano formulations are constantly being developed and preliminarily applied in disease diagnosis and treatment,[125,126] the use of stimuli-responsive nanocarrier may be a promising way to improve delivery of PROTACs. By introducing targeting ligands and stimulus-responsive functional groups onto the surface of nanocarriers, controlled targeted release of PROTACs and modulation of systemic biodistribution can be achieved, potentially addressing the safe dosing challenges posed by the hook effect and minimizing the toxic side effects associated with non-target tissue accumulation. Chen et al encapsulated BRD4 PROTAC (ARV-825) in PEG modified with pH responsive ligands and phototherapy agent ICG. The nano-PROTAC can degrade and release BRD4 PROTAC in the acidic tumor microenvironment, thereby reducing the toxic side effects on normal tissues.[127] Additionally, benefiting from the excellent drug-loading capacity of various nanoparticle-PROTACs and carrier-free nano-PROTACs based on drug molecule self-assembly, PROTACs can be co-delivered with other drugs to synergistically enhance therapeutic efficacy.

However, despite nanotechnology offering a promising path for advancing the clinical translation of PROTACs, there are still new challenges that hinder their clinical translation or approval. The biocompatibility and biodegradability of nanocarriers remain primary concerns, as they may induce carrier-related adverse reactions and immune responses. Furthermore, polymers and inorganic nanocarriers with slow or inefficient biodegradation may accumulate in organs and tissues, posing challenges for dose regulation and quality control in the clinical application of nano-PROTACs. Although multifunctional components can be used to modify nanocarriers to mitigate these adverse risks, complex synthetic design strategies introduce additional barriers and manufacturing costs for batch synthesis, quality control, and clinical translation. Therefore, future research should focus on exploring new non-toxic, degradable materials and continually optimizing delivery technology designs while conducting comprehensive safety assessments of nanocarriers and their excipients to adapt to new PROTAC production and discovery technologies. Additionally, the complexity of nanocarriers presents challenges in production and quality control, necessitating the establishment of standardized production and quality control processes to ensure batch stability and reliability of nanocarriers. Finally, although most current nano-PROTACs have demonstrated promising pharmacological activity in cell and animal models. However, drug resistance, clinical application heterogeneity, and complicated pathological microenvironments all affect the clinical use of nano-PROTACs, making it difficult to predict how consistently effective bioactivity will be demonstrated in clinical trials. Therefore, future research needs to elucidate the mechanisms affecting the efficacy of nano-PROTACs in the human body and establish new models that better represent human pathological conditions.

In summary, nanotechnology provides a bridge for the development of PROTACs from basic research to clinical application. With synergistic innovations in fields such as nanotechnology, medicinal chemistry, materials science, biology, industrial production technology, and clinical medicine, emerging nanotechnologies are expected to address current technical bottlenecks and challenges, thus facilitating the transformation of PROTACs into clinical drugs for treating various refractory diseases, offering patients safer and more effective therapeutic options.

Abbreviations

PROTACs, Proteolysis Targeting Chimeras; SMIs, small molecule inhibitors; POI, protein of interest; UPS, ubiquitin-proteasome system; Ro5, Rule of Five; PK, pharmacokinetics; PD, pharmacodynamic; nano-DDSs, nano-drug delivery systems; AR, androgen receptor; ER, estrogen receptors; CRBN, cereblon; BTK, bruton tyrosine kinase; VHL, von

Hippel-Lindau; BCR, B-cell receptor; IRAK4, interleukin-1 receptor-associated kinase-4; EGFR, epidermal growth factor receptor; NDD, neurodegenerative diseases; AD, alzheimer's disease; HIV-1, human immunodeficiency virus type 1; AIDS, acquired immune deficiency syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; M^{pro}, main protease; EPR, enhanced permeability and retention effect; HDL-C, high-density lipoprotein cholesterol; CVD, cardiovascular diseases; HMGCR, 3-Hydroxy-3-methylglutaryl-coenzyme a reductase; SLN, solid lipid nanoparticles; ASGPR, asialoglycoprotein receptor; HCC, hepatocellular carcinoma; GC, galactosylceramide; NSCLC, non-small cell lung cancer; CNPs, cell membrane-coated nanoparticles; TAMs, tumor-associated macrophages; PLGA, poly(lactic-co-glycolic acid); INPs, Inorganic nanoparticles; MSN, Mesoporous silica nanoparticles; PEG, polyethylene glycol; ALK, anaplastic lymphoma kinase; TME, tumor microenvironment; PDT, photodynamic therapy; ROS, reactive oxygen species; APIs, active pharmaceutical ingredients.

Acknowledgments

This work was supported by the Science and Technology Development Plan Projects of Jilin Province (Grant No. YDZJ202401466ZYTS).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Toure M, Crews CM. Small-molecule PROTACS: new approaches to protein degradation. *Angew Chem Int Ed*. 2016;55(6):1966–1973. doi:10.1002/anie.201507978
2. Logue JS, Morrison DK. Complexity in the signaling network: insights from the use of targeted inhibitors in cancer therapy. *Genes Dev*. 2012;26(7):641–650. doi:10.1101/gad.186965.112
3. Hopkins AL, Groom CR. The druggable genome. *Nat Rev Drug Discov*. 2002;1(9):727–730. doi:10.1038/nrd892
4. Dale B, Cheng M, Park KS, Kaniskan HU, Xiong Y, Jin J. Advancing targeted protein degradation for cancer therapy. *Nat Rev Cancer*. 2021;21(10):638–654. doi:10.1038/s41568-021-00365-x
5. Liang Y, Nandakumar KS, Cheng K. Design and pharmaceutical applications of proteolysis-targeting chimeric molecules. *Biochem Pharmacol*. 2020;182:114211. doi:10.1016/j.bcp.2020.114211
6. Bondeson DP, Mares A, Smith IE, et al. Catalytic in vivo protein knockdown by small-molecule PROTACs. *Nat Chem Biol*. 2015;11(8):611–617. doi:10.1038/nchembio.1858
7. Chen Y, Tandon I, Heelan W, Wang Y, Tang W, Hu Q. Proteolysis-targeting chimera (PROTAC) delivery system: advancing protein degraders towards clinical translation. *Chem Soc Rev*. 2022;51(13):5330–5350. doi:10.1039/d1cs00762a
8. Zhao L, Zhao J, Zhong K, Tong A, Jia D. Targeted protein degradation: mechanisms, strategies and application. *Signal Transduct Target Ther*. 2022;7(1):113. doi:10.1038/s41392-022-00966-4
9. Li R, Liu M, Yang Z, Li J, Gao Y, Tan R. Proteolysis-targeting chimeras (PROTACs) in cancer therapy: present and future. *Molecules*. 2022;27(24):8828. doi:10.3390/molecules27248828
10. Tomoshige S, Ishikawa M. PROTACs and other chemical protein degradation technologies for the treatment of neurodegenerative disorders. *Angew Chem Int Ed*. 2021;60(7):3346–3354. doi:10.1002/anie.202004746
11. Garber K. The PROTAC gold rush. *Nat Biotechnol*. 2022;40(1):12–16. doi:10.1038/s41587-021-01173-2
12. Poongavanam V, Doak BC, Kihlberg J. Opportunities and guidelines for discovery of orally absorbed drugs in beyond rule of 5 space. *Curr Opin Chem Biol*. 2018;44:23–29. doi:10.1016/j.cbpa.2018.05.010
13. Edmondson SD, Yang B, Fallan C. Proteolysis targeting chimeras (PROTACs) in 'beyond rule-of-five' chemical space: recent progress and future challenges. *Bioorg Med Chem Lett*. 2019;29(13):1555–1564. doi:10.1016/j.bmcl.2019.04.030
14. Chen C, Yang Y, Wang Z, Li H, Dong C, Zhang X. Recent advances in Pro-PROTAC development to address on-target off-tumor toxicity. *J Med Chem*. 2023;66(13):8428–8440. doi:10.1021/acs.jmedchem.3c00302
15. Liu J, Chen H, Ma L, et al. Light-induced control of protein destruction by opto-PROTAC. *Sci Adv*. 2020;6(8):eaay5154. doi:10.1126/sciadv.aay5154
16. Gao J, Yang L, Lei S, et al. Stimuli-activatable PROTACs for precise protein degradation and cancer therapy. *Sci Bull*. 2023;68(10):1069–1085. doi:10.1016/j.scib.2023.04.028
17. Douglass EF Jr, Miller CJ, Sparer G, Shapiro H, Spiegel DA. A comprehensive mathematical model for three-body binding equilibria. *J Am Chem Soc*. 2013;135(16):6092–6099. doi:10.1021/ja311795d
18. Klein VG, Bond AG, Craigon C, Lokey RS, Ciulli A. Amide-to-ester substitution as a strategy for optimizing PROTAC permeability and cellular activity. *J Med Chem*. 2021;64(24):18082–18101. doi:10.1021/acs.jmedchem.1c01496
19. Moreau K, Coen M, Zhang AX, et al. Proteolysis-targeting chimeras in drug development: a safety perspective. *Br J Pharmacol*. 2020;177(8):1709–1718. doi:10.1111/bph.15014
20. Zhang X, Song Z, Zhang X, et al. Unconventional PROTACs for targeted protein degradation in cancer therapy. *Angew Chem Int Ed Engl*. 2025;64(31):e202507702. doi:10.1002/anie.202507702

21. Zhong J, Zhao R, Wang Y, Su YX, Lan X. Nano-PROTACs: state of the art and perspectives. *Nanoscale*. 2024;16(9):4378–4391. doi:10.1039/d3nr06059d
22. Lin JY, Liu HJ, Wu Y, et al. Targeted protein degradation technology and nanomedicine: powerful allies against cancer. *Small*. 2023;19(18):e2207778. doi:10.1002/smll.202207778
23. Raina K, Crews CM. Chemical inducers of targeted protein degradation. *J Biol Chem*. 2010;285(15):11057–11060. doi:10.1074/jbc.R109.078105
24. Burslem GM, Crews CM. Proteolysis-targeting chimeras as therapeutics and tools for biological discovery. *Cell*. 2020;181(1):102–114. doi:10.1016/j.cell.2019.11.031
25. Grice GL, Nathan JA. The recognition of ubiquitinated proteins by the proteasome. *Cell Mol Life Sci*. 2016;73(18):3497–3506. doi:10.1007/s00018-016-2255-5
26. Li Y-J, Zhang C, Martincuks A, Herrmann A, Yu H. STAT proteins in cancer: orchestration of metabolism. *Nat Rev Cancer*. 2023;23(3):115–134. doi:10.1038/s41568-022-00537-3
27. Schepers H, Wierenga ATJ, Vellenga E, Schuringa JJ. STAT5-mediated self-renewal of normal hematopoietic and leukemic stem cells. *Jak-Stat*. 2012;1(1):13–22. doi:10.4161/jkst.19316
28. Yu H, Jove R. The STATs of cancer-new molecular targets come of age. *Nat Rev Cancer*. 2004;4(2):97–105. doi:10.1038/nrc1275
29. Zou S, Tong Q, Liu B, Huang W, Tian Y, Fu X. Targeting STAT3 in cancer immunotherapy. *Mol Cancer*. 2020;19(1):145. doi:10.1186/s12943-020-01258-7
30. Bekes M, Langley DR, Crews CM. PROTAC targeted protein degraders: the past is prologue. *Nat Rev Drug Discov*. 2022;21(3):181–200. doi:10.1038/s41573-021-00371-6
31. Young RM, Shaffer AL, Phelan JD, Staudt LM. B-cell receptor signaling in diffuse large B-cell lymphoma. *Semin Hematol*. 2015;52(2):77–85. doi:10.1053/j.seminhematol.2015.01.008
32. Montoya S, Bourcier J, Noviski M, et al. Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127. *Science*. 2024;383(6682):eadi5798. doi:10.1126/science.adi5798
33. Erkkinen MG, Kim M-O, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. *Cold Spring Harbor Perspect Biol*. 2018;10(4):a033118. doi:10.1101/cshperspect.a033118
34. Soto C, Pritzkow S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. *Nat Neurosci*. 2018;21(10):1332–1340. doi:10.1038/s41593-018-0235-9
35. Yuan A, Nixon RA. Posttranscriptional regulation of neurofilament proteins and tau in health and disease. *Brain Res Bull*. 2023;192:115–127. doi:10.1016/j.brainresbull.2022.10.017
36. Zhang Y, Huang N-Q, Yan F, et al. Diabetes mellitus and Alzheimer's disease: GSK-3β as a potential link. *Behav Brain Res*. 2018;339:57–65. doi:10.1016/j.bbr.2017.11.015
37. Hu Z, Chen P-H, Li W, et al. Targeted dephosphorylation of Tau by phosphorylation targeting chimeras (PhosTACs) as a therapeutic modality. *J Am Chem Soc*. 2023;145(7):4045–4055. doi:10.1021/jacs.2c11706
38. Wang W, Zhou Q, Jiang T, et al. A novel small-molecule PROTAC selectively promotes tau clearance to improve cognitive functions in Alzheimer-like models. *Theranostics*. 2021;11(11):5279–5295. doi:10.7150/thno.55680
39. Zhou -Q-Q, Xiao H-T, Yang F, Wang Y-D, Li P, Zheng Z-G. Advancing targeted protein degradation for metabolic diseases therapy. *Pharmacol Res*. 2023;188:106627. doi:10.1016/j.phrs.2022.106627
40. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American heart association. *Circulation*. 2020;141(9):e139–e596. doi:10.1161/cir.0000000000000757
41. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science*. 2001;292(5519):1160–1164. doi:10.1126/science.1059344
42. Luo G, Li Z, Lin X, et al. Discovery of an orally active VHL-recruiting PROTAC that achieves robust HMGCR degradation and potent hypolipidemic activity in vivo. *Acta Pharm Sin B*. 2021;11(5):1300–1314. doi:10.1016/j.apsb.2020.11.001
43. Choi YK. Emerging and re-emerging fatal viral diseases. *Exp Mol Med*. 2021;53(5):711–712. doi:10.1038/s12276-021-00608-9
44. He Y, Zhou J, Gao H, Liu C, Zhan P, Liu X. Broad-spectrum antiviral strategy: host-targeting antivirals against emerging and re-emerging viruses. *Eur J Med Chem*. 2024;265:116069. doi:10.1016/j.ejmech.2023.116069
45. Buffalo CZ, Iwamoto Y, Hurley JH, Ren X. How HIV Nef proteins hijack membrane traffic to promote infection. *J Virol*. 2019;93(24):e01322–19. doi:10.1128/JVI.01322-19
46. Emert-Sedlak LA, Tice CM, Shi H, et al. PROTAC-mediated degradation of HIV-1 Nef efficiently restores cell-surface CD4 and MHC-I expression and blocks HIV-1 replication. *Cell Chem Biol*. 2024;31(4):658–668.e14. doi:10.1016/j.chembiol.2024.02.004
47. Jin Z, Du X, Xu Y, et al. Structure of M^{pro} from SARS-CoV-2 and discovery of its inhibitors. *Nature*. 2020;582(7811):289–293. doi:10.1038/s41586-020-2223-y
48. Sang X, Wang J, Zhou J, et al. A chemical strategy for the degradation of the main protease of SARS-CoV-2 in cells. *J Am Chem Soc*. 2023;145(50):27248–27253. doi:10.1021/jacs.3c12678
49. Qi SM, Dong J, Xu ZY, et al. PROTAC: an effective targeted protein degradation strategy for cancer therapy. *Front Pharmacol*. 2021;12:692574. doi:10.3389/fphar.2021.692574
50. Petrylak DP, McKean M, Lang JM, et al. ARV-766, a proteolysis targeting chimera (PROTAC) androgen receptor (AR) degrader, in metastatic castration-resistant prostate cancer (mCRPC): initial results of a Phase 1/2 study. *J Clin Oncol*. 2024;42(16_suppl):5011. doi:10.1200/JCO.2024.42.16_suppl.5011
51. Vetma V, O'Connor S, Ciulli A. Development of PROTAC degrader drugs for cancer. *Ann Rev Cancer Biol*. 2025;9(1):119–140. doi:10.1146/annurev-cancerbio-061824-105806
52. Campone M, De Laurentiis M, Jhaveri K, et al. Vepdegestrant, a PROTAC estrogen receptor degrader, in advanced breast cancer. *N Engl J Med*. 2025;393(6):556–568. doi:10.1056/NEJMoa2505725
53. Rathkopf DE, Patel MR, Choudhury AD, et al. Safety and clinical activity of BMS-986365 (CC-94676), a dual androgen receptor ligand-directed degrader and antagonist, in heavily pretreated patients with metastatic castration-resistant prostate cancer. *Ann Oncol*. 2025;36(1):76–88. doi:10.1016/j.annonc.2024.09.005

54. He Y, Koch R, Budamagunta V, et al. DT2216-a Bcl-xL-specific degrader is highly active against Bcl-xL-dependent T cell lymphomas. *J Hematol Oncol*. 2020;13(1):95. doi:10.1186/s13045-020-00928-9
55. Ha S, Luo G, Xiang H. A comprehensive overview of small-molecule androgen receptor degraders: recent progress and future perspectives. *J Med Chem*. 2022;65(24):16128–16154. doi:10.1021/acs.jmedchem.2c01487
56. Li J, Xu W, Yan P, et al. Abstract CT128: phase 1 study of HSK29116, a Bruton tyrosine kinase (BTK) proteolysis-targeting chimera (PROTAC) agent, in patients with relapsed or refractory B-cell malignancies. *Cancer Res*. 2023;83(8_Supplement):CT128–CT128. doi:10.1158/1538-7445.AM2023-CT128
57. Livingston JA, Blay JY, Trent J, et al. A Phase I study of FHD-609, a heterobifunctional degrader of bromodomain-containing protein 9, in patients with advanced synovial sarcoma or SMARCB1-deficient tumors. *Clin Cancer Res*. 2025;31(4):628–638. doi:10.1158/1078-0432.Ccr-24-2583
58. Shastri A, Feldman EJ, Starodub AN, et al. Preliminary safety, pharmacokinetics, pharmacodynamics and clinical activity of KT-333, a targeted protein degrader of STAT3, in patients with relapsed or refractory lymphomas, large granular lymphocytic leukemia, and solid tumors. *Blood*. 2023;142:3081. doi:10.1182/blood-2023-181130
59. Danilov A, Tees MT, Patel K, et al. A first-in-human phase 1 trial of NX-2127, a first-in-class bruton's tyrosine kinase (BTK) dual-targeted protein degrader with immunomodulatory activity, in patients with relapsed/Refractory B cell malignancies. *Blood*. 2023;142:4463. doi:10.1182/blood-2023-179872
60. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The history of nanoscience and nanotechnology: from chemical-physical applications to nanomedicine. *Molecules*. 2019;25(1):112. doi:10.3390/molecules25010112
61. Dessale M, Mengistu G, Mengist HM. Nanotechnology: a promising approach for cancer diagnosis, therapeutics and theragnosis. *Int J Nanomed*. 2022;17:3735–3749. doi:10.2147/IJN.S378074
62. Ferdows BE, Patel DN, Chen W, Huang X, Kong N, Tao W. RNA cancer nanomedicine: nanotechnology-mediated RNA therapy. *Nanoscale*. 2022;14(12):4448–4455. doi:10.1039/d1nr06991h
63. Wang J, Ni Q, Wang Y, et al. Nanoscale drug delivery systems for controllable drug behaviors by multi-stage barrier penetration. *J Control Release*. 2021;331:282–295. doi:10.1016/j.jconrel.2020.08.045
64. Song Y, Dong QQ, Ni YK, Xu XL, Chen CX, Chen W. Nano-proteolysis targeting chimeras (Nano-PROTACs) in cancer therapy. *Int J Nanomed*. 2024;19:5739–5761. doi:10.2147/IJN.S448684
65. Wang W, Lu KJ, Yu CH, Huang QL, Du YZ. Nano-drug delivery systems in wound treatment and skin regeneration. *J Nanobiotechnol*. 2019;17(1):82. doi:10.1186/s12951-019-0514-y
66. Etter EL, Mei KC, Nguyen J. Delivering more for less: nanosized, minimal-carrier and pharmacoactive drug delivery systems. *Adv Drug Deliv Rev*. 2021;179:113994. doi:10.1016/j.addr.2021.113994
67. Prakash S. Nano-based drug delivery system for therapeutics: a comprehensive review. *Biomed Phys Eng Express*. 2023;9(5):052002. doi:10.1088/2057-1976/acedb2
68. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS Nano*. 2009;3(1):16–20. doi:10.1021/nn900002m
69. Gao F, Wu Y, Wang R, et al. Precise nano-system-based drug delivery and synergistic therapy against androgen receptor-positive triple-negative breast cancer. *Acta Pharm Sin B*. 2024;14(6):2685–2697. doi:10.1016/j.apsb.2024.03.012
70. Xie H, Zhang C. Potential of the nanoplatform and PROTAC interface to achieve targeted protein degradation through the Ubiquitin-Proteasome system. *Eur J Med Chem*. 2024;267:116168. doi:10.1016/j.ejmech.2024.116168
71. Yonezawa S, Koide H, Asai T. Recent advances in siRNA delivery mediated by lipid-based nanoparticles. *Adv Drug Deliv Rev*. 2020;154-155:64–78. doi:10.1016/j.addr.2020.07.022
72. Fonseca-Santos B, Gremiao MP, Chorilli M. Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease. *Int J Nanomed*. 2015;10:4981–5003. doi:10.2147/IJN.S87148
73. Thi TTH, Suys EJA, Lee JS, Nguyen DH, Park KD, Truong NP. Lipid-based nanoparticles in the clinic and clinical trials: from cancer nanomedicine to COVID-19 vaccines. *Vaccines*. 2021;9(4):359. doi:10.3390/vaccines9040359
74. De Leo V, Maurelli AM, Giotta L, Catucci L. Liposomes containing nanoparticles: preparation and applications. *Colloid Surf B-Biointerfaces*. 2022;218:112737. doi:10.1016/j.colsurfb.2022.112737
75. Bangham AD, Home RW. Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. *J Mol Biol*. 1964;85:660. doi:10.1016/s0022-2836(64)80115-7
76. Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: structure, composition, types, and clinical applications. *Heliyon*. 2022;8(5):e09394. doi:10.1016/j.heliyon.2022.e09394
77. Shah S, Dhawan V, Holm R, et al. Liposomes: advancements and innovation in the manufacturing process. *Adv Drug Deliv Rev*. 2020;154-155:102–122. doi:10.1016/j.addr.2020.07.002
78. Saraswat A, Vemana HP, Dukhande VV, Patel K. Galactose-decorated liver tumor-specific nanoliposomes incorporating selective BRD4-targeted PROTAC for hepatocellular carcinoma therapy. *Heliyon*. 2022;8(1):e08702. doi:10.1016/j.heliyon.2021.e08702
79. Salah E, Abouelfetouh MM, Pan Y, et al. Solid lipid nanoparticles for enhanced oral absorption: a review. *Colloid Surf B-Biointerfaces*. 2020;196:111305. doi:10.1016/j.colsurfb.2020.111305
80. Laffleur F, Keckeis V. Advances in drug delivery systems: work in progress still needed? *Int J Pharm*. 2020;590:119912. doi:10.1016/j.ijpharm.2020.119912
81. Vartak R, Saraswat A, Yang Y, et al. Susceptibility of lung carcinoma cells to nanostructured lipid carrier of ARV-825, a BRD4 degrading proteolysis targeting chimera. *Pharm Res*. 2022;39(11):2745–2759. doi:10.1007/s11095-022-03184-3
82. Fang RH, Gao W, Zhang L. Targeting drugs to tumours using cell membrane-coated nanoparticles. *Nat Rev Clin Oncol*. 2023;20(1):33–48. doi:10.1038/s41571-022-00699-x
83. Zhang HT, Peng R, Chen S, et al. Versatile nano-PROTAC-induced epigenetic reader degradation for efficient lung cancer therapy. *Adv Sci*. 2022;9(29):e2202039. doi:10.1002/advs.202202039
84. Fang RH, Kroll AV, Gao W, Zhang L. Cell membrane coating nanotechnology. *Adv Mater*. 2018;30(23). doi:10.1002/adma.201706759
85. Huang JH, Huang CJ, Yu LN, et al. Bioinspired PROTAC-induced macrophage fate determination alleviates atherosclerosis. *Acta Pharmacol Sin*. 2023;44(10):1962–1976. doi:10.1038/s41401-023-01088-5

86. Qin X, Yu C, Wei J, et al. Rational design of nanocarriers for intracellular protein delivery. *Adv Mater*. 2019;31(46):e1902791. doi:10.1002/adma.201902791
87. Xiao X, Teng F, Shi C, et al. Polymeric nanoparticles-Promising carriers for cancer therapy. *Front Bioeng Biotechnol*. 2022;10:1024143. doi:10.3389/fbioe.2022.1024143
88. Mandal M, Banerjee I, Mandal M. Nanoparticle-mediated gene therapy as a novel strategy for the treatment of retinoblastoma. *Colloid Surf B-Biointerfaces*. 2022;220:112899. doi:10.1016/j.colsurfb.2022.112899
89. Zhao K, Li D, Shi C, et al. Biodegradable polymeric nanoparticles as the delivery carrier for drug. *Curr Drug Deliv*. 2016;13(4):494–499. doi:10.2174/1567201813041605210046O9
90. Saraswat A, Patki M, Fu Y, et al. Nanoformulation of PROteolysis targeting chimera targeting 'undruggable' C-Myc for The treatment of pancreatic cancer. *Nanomedicine*. 2020;15(18):1761–1777. doi:10.2217/nnm-2020-0156
91. Sun Y, Li B, Cao Q, et al. Targeting cancer stem cells with polymer nanoparticles for gastrointestinal cancer treatment. *Stem Cell Res Ther*. 2022;13(1):489. doi:10.1186/s13287-022-03180-9
92. Cimas FJ, Niza E, Juan A, et al. Controlled delivery of BET-PROTACs: in vitro evaluation of MZ1-loaded polymeric antibody conjugated nanoparticles in breast cancer. *Pharmaceutics*. 2020;12(10):986. doi:10.3390/pharmaceutics12100986
93. He Y, Zan X, Miao J, et al. Enhanced anti-glioma efficacy of doxorubicin with BRD4 PROTAC degrader using targeted nanoparticles. *Mater Today Bio*. 2022;16:100423. doi:10.1016/j.mtbio.2022.100423
94. Luther DC, Huang R, Jeon T, et al. Delivery of drugs, proteins, and nucleic acids using inorganic nanoparticles. *Adv Drug Deliv Rev*. 2020;156:188–213. doi:10.1016/j.addr.2020.06.020
95. Ariga K, Ji Q, McShane MJ, et al. Inorganic nanoarchitectonics for biological applications. *Chem Mat*. 2012;24(5):728–737. doi:10.1021/cm202281m
96. Moon Y, Jeon SI, Shim MK, Kim K. Cancer-specific delivery of proteolysis-targeting chimeras (PROTACs) and their application to cancer immunotherapy. *Pharmaceutics*. 2023;15(2):411. doi:10.3390/pharmaceutics15020411
97. Ding Y, Jiang Z, Saha K, et al. Gold nanoparticles for nucleic acid delivery. *Mol Ther*. 2014;22(6):1075–1083. doi:10.1038/mt.2014.30
98. Wang Y, Han L, Liu F, et al. Targeted degradation of anaplastic lymphoma kinase by gold nanoparticle-based multi-headed proteolysis targeting chimeras. *Colloid Surf B-Biointerfaces*. 2020;188:110795. doi:10.1016/j.colsurfb.2020.110795
99. Gibson JD, Khanal BP, Zubarev ER. Paclitaxel-functionalized gold nanoparticles. *J Am Chem Soc*. 2007;129(37):11653–11661. doi:10.1021/ja075181k
100. He Q, Zhou L, Yu D, et al. Near-infrared-activatable PROTAC nanocages for controllable target protein degradation and on-demand antitumor therapy. *J Med Chem*. 2023;66(15):10458–10472. doi:10.1021/acs.jmedchem.3c00587
101. Mitchell MJ, Billingsley MM, Haley RM, et al. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov*. 2021;20(2):101–124. doi:10.1038/s41573-020-0090-8
102. Pugazhendhi A, Edison T, Karuppusamy I, Kathirvel B. Inorganic nanoparticles: a potential cancer therapy for human welfare. *Int J Pharm*. 2018;539(1–2):104–111. doi:10.1016/j.ijpharm.2018.01.034
103. Fadeel B, Garcia-Bennett AE. Better safe than sorry: understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical applications. *Adv Drug Deliv Rev*. 2010;62(3):362–374. doi:10.1016/j.addr.2009.11.008
104. Khandekar SV, Kulkarni MG, Devarajan PV. Polyaspartic acid functionalized gold nanoparticles for tumor targeted doxorubicin delivery. *J Biomed Nanotechnol*. 2014;10(1):143–153. doi:10.1166/jbn.2014.1772
105. Cano-Garrido O, Serna N, Unzueta U, et al. Protein scaffolds in human clinics. *Biotechnol Adv*. 2022;61:108032. doi:10.1016/j.biotechadv.2022.108032
106. Xiao W, Gao H. The impact of protein Corona on the behavior and targeting capability of nanoparticle-based delivery system. *Int J Pharm*. 2018;552(1–2):328–339. doi:10.1016/j.ijpharm.2018.10.011
107. Schöttler S, Becker G, Winzen S, et al. Protein adsorption is required for stealth effect of poly(ethylene glycol)- and poly(phosphoester)-coated nanocarriers. *Nat Nanotechnol*. 2016;11(4):372–377. doi:10.1038/nnano.2015.330
108. Aljabali AA, Rezigue M, Alsharedeh RH, et al. Protein-based drug delivery nanomedicine platforms: recent developments. *Pharm Nanotechnol*. 2022;10(4):257–267. doi:10.2174/2211738510666220817120307
109. Kianfar E. Protein nanoparticles in drug delivery: animal protein, plant proteins and protein cages, albumin nanoparticles. *J Nanobiotechnol*. 2021;19(1):159. doi:10.1186/s12951-021-00896-3
110. Elzoghby AO. Gelatin-based nanoparticles as drug and gene delivery systems: reviewing three decades of research. *J Control Release*. 2013;172(3):1075–1091. doi:10.1016/j.jconrel.2013.09.019
111. Davidson SM, Jonas O, Keibler MA, et al. Direct evidence for cancer-cell-autonomous extracellular protein catabolism in pancreatic tumors. *Nat Med*. 2017;23(2):235–241. doi:10.1038/nm.4256
112. Cho H, Jeon SI, Shim MK, Ahn C-H, Kim K. In situ albumin-binding and esterase-specifically cleaved BRD4-degrading PROTAC for targeted cancer therapy. *Biomaterials*. 2023;295:122038. doi:10.1016/j.biomaterials.2023.122038
113. Wan S, Kelly PM, Mahon E, et al. The "sweet" side of the protein Corona: effects of glycosylation on nanoparticle-cell interactions. *ACS Nano*. 2015;9(2):2157–2166. doi:10.1021/nn506060q
114. Röcker C, Pötzl M, Zhang F, et al. A quantitative fluorescence study of protein monolayer formation on colloidal nanoparticles. *Nat Nanotechnol*. 2009;4(9):577–580. doi:10.1038/nnano.2009.195
115. Maham A, Tang Z, Wu H, Wang J, Lin Y. Protein-based nanomedicine platforms for drug delivery. *Small*. 2009;5(15):1706–1721. doi:10.1002/smll.200801602
116. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. *Nat Rev Mater*. 2016;1(5):16014. doi:10.1038/natrevmats.2016.14
117. Wu Y, Chang X, Yang G, et al. A physiologically responsive nanocomposite hydrogel for treatment of head and neck squamous cell carcinoma via proteolysis-targeting chimeras enhanced immunotherapy. *Adv Mater*. 2023;35(12):e2210787. doi:10.1002/adma.202210787
118. Zhang J, Li S, An FF, et al. Self-carried curcumin nanoparticles for in vitro and in vivo cancer therapy with real-time monitoring of drug release. *Nanoscale*. 2015;7(32):13503–13510. doi:10.1039/c5nr03259h

119. Zolnik BS, González-Fernández Á, Sadrieh N, Dobrovolskaia MA. Minireview: nanoparticles and the immune system. *Endocrinology*. 2010;151(2):458–465. doi:10.1210/en.2009-1082
120. Qin SY, Zhang AQ, Cheng SX, Rong L, Zhang XZ. Drug self-delivery systems for cancer therapy. *Biomaterials*. 2017;112:234–247. doi:10.1016/j.biomaterials.2016.10.016
121. Zhao LP, Rao XN, Zheng RR, et al. Carrier-free nano-PROTACs to amplify photodynamic therapy induced DNA damage through BRD4 degradation. *Nano Lett*. 2023;23(13):6193–6201. doi:10.1021/acs.nanolett.3c01812
122. Wang T, Zhang Y, Chen K, et al. CDK4/6 nano-PROTAC enhances mitochondria-dependent photodynamic therapy and anti-tumor immunity. *Nano Today*. 2023;50:101890. doi:10.1016/j.nantod.2023.101890
123. Huang L, Zhao S, Fang F, et al. Advances and perspectives in carrier-free nanodrugs for cancer chemo-monotherapy and combination therapy. *Biomaterials*. 2021;268:120557. doi:10.1016/j.biomaterials.2020.120557
124. Zhao LP, Zheng RR, Chen HQ, et al. Self-delivery nanomedicine for O_2-economized photodynamic tumor therapy. *Nano Lett*. 2020;20(3):2062–2071. doi:10.1021/acs.nanolett.0c00047
125. Cheng G, Zong W, Guo H, et al. Programmed size-changeable nanotheranostic agents for enhanced imaging-guided chemo/photodynamic combination therapy and fast elimination. *Adv Mater*. 2021;33(21):e2100398. doi:10.1002/adma.202100398
126. Wang S, Yu G, Yang W, et al. Photodynamic-chemodynamic cascade reactions for efficient drug delivery and enhanced combination therapy. *Adv Sci*. 2021;8(10):2002927. doi:10.1002/advs.202002927
127. Li Z, Ren G, Wang X, et al. Tumor microenvironment responsive nano-PROTAC for BRD4 degradation enhanced cancer photo-immunotherapy. *Biomaterials*. 2025;322:123387. doi:10.1016/j.biomaterials.2025.123387