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Review Article

Nanotechnology-Enabled Targeted Delivery of Protacs for Cancer Therapy

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ABSTRACT

Proteolysis targeting chimeras (PROTACs) is novel drug delivery use primarily in the treatments of various disease as cancer, neurodegenerative disorder, Autoimmune and inflammatory diseases. PROTACs is next generation therapeutic strategy that use nanotechnology to treat disease by selectively degrading disease causing protein, PROTACs are special molecules that can remove unwanted or disease-causing proteins from the body. They work very well and are considered a new and powerful treatment method, especially for cancer. Proteolysis Targeting Chimeras (PROTACs) are a new and promising type of cancer treatment. Instead of only blocking harmful proteins, PROTACs remove (degrade) disease-causing proteins from cancer cells. Because of this unique action, PROTACs have attracted great attention in cancer research. However, despite their strong potential, several challenges limit their successful use in clinical treatment. However PROTACs also have some problems, Limitations of Conventional PROTACs, Although PROTACs are effective, they face some important problems. One major challenge is off-target effects, where PROTACs may accidentally degrade proteins other than the intended target, which can cause side effects. Another limitation is poor cell permeability. Many PROTAC molecules are large and complex, making it difficult for them to easily enter cancer cells. In addition, PROTACs can show a hook effect. This happens when PROTACs are used at very high concentrations. Instead of working better, they become less effective because proper interaction between the target protein, PROTAC, and E3 ligase is disrupted. Nanotechnology as a Solution: Nanotechnology offers a promising solution to overcome these limitations. By loading PROTACs into very small carriers called nanoparticles, scientists have developed Nano-PROTACs. These nanoparticle-based systems help PROTACs reach tumour tissues more accurately, which reduces unwanted effects on healthy tissues. Nanoparticles also improve the ability of PROTACs to enter cancer cells more efficiently. Moreover, Nano carriers allow controlled and sustained release of PROTACs, ensuring that the drug

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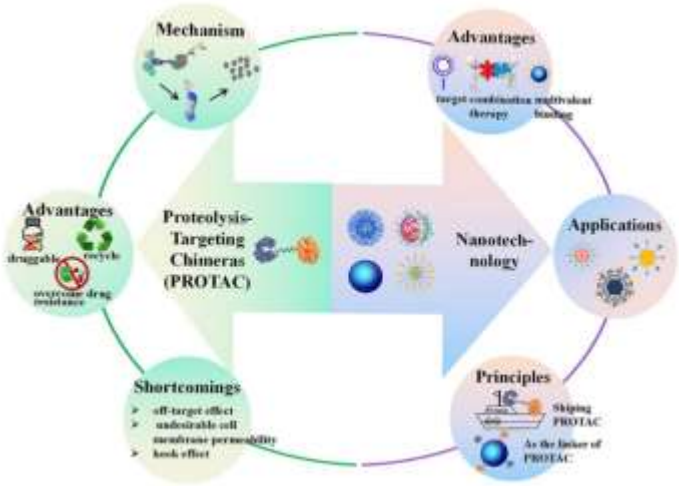
remains active for a longer time at the target site. As a result, nano-PROTACs show better protein degradation efficiency and improved safety compared to conventional PROTACs. They can also be combined with other cancer treatments, such as chemotherapy or immunotherapy, to produce stronger and more effective therapeutic outcomes.

INTRODUCTION

Cancer treatment is very important for improving human health. In recent years, targeted cancer therapies, such as small-molecule drugs and monoclonal antibodies, have been widely used to treat cancer. These therapies are designed to attack cancer cells specifically. However, they still have several problems. Many of these drugs can bind to multiple targets in the body, including proteins on the cell surface and inside the cell. This lack of selectivity can lead to side effects and toxicity, limiting their clinical use.

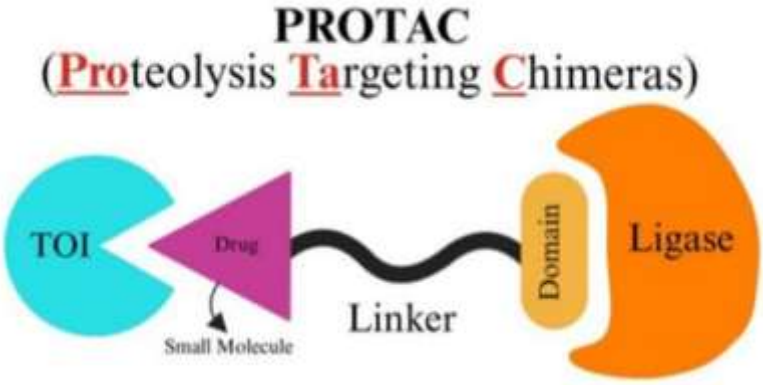


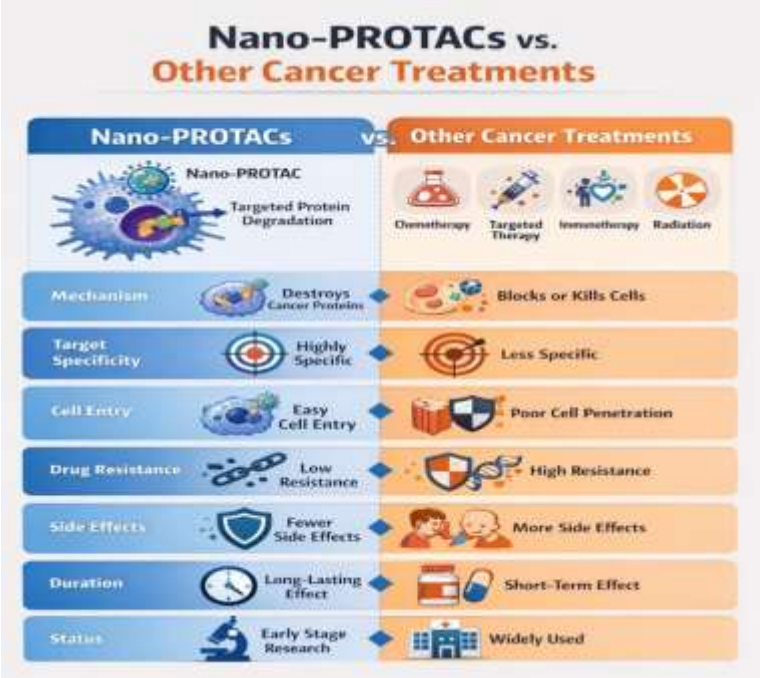
PROTACs (Proteolysis Targeting Chimeras) are a new and innovative technology for cancer treatment. Unlike traditional drugs that only block protein activity, PROTACs remove harmful proteins completely. They work by maintaining a balance between protein production and protein degradation. A PROTAC molecule has two active parts connected by a linker—one part binds to the target protein and the other binds to the cell's protein-degrading system. This leads to the destruction of unwanted proteins, such as kinases, structural proteins, and regulatory proteins.

PROTACs are very small molecules (about 10 nanometres) and can target proteins that were previously considered "undruggable." These include proteins involved in protein–protein interactions, which have large and flat surfaces that traditional drugs cannot bind effectively. About 85% of human proteins fall into this category, showing the huge potential of PROTACs in drug development. Peptide-based PROTACs have already shown successful protein degradation in laboratory studies, including targets such as MetAP-2, FKBP12F36V, oestrogen receptors, and androgen receptors.

Despite these advantages, PROTACs face challenges such as poor solubility, low stability, and limited ability to enter cells. To overcome these problems, nanodrug delivery systems (NDDS) play a very important role. NDDS help improve PROTAC delivery by increasing solubility, enhancing cell uptake, reducing side effects, and delivering drugs directly to tumours through mechanisms like the enhanced permeability and retention (EPR) effect. Various nanocarriers, such as lipid nanoparticles, polymeric nanoparticles, and inorganic

nanoparticles, are used. Review studies report strategies like drug encapsulation, chemical conjugation, and smart stimuli-responsive systems to improve tumour targeting and treatment effectiveness in cancers such as prostate, breast, and gastrointestinal cancers.





Key Design Considerations for Nano-PROTAC Systems:-

The therapeutic efficacy of nano-PROTACs is strongly influenced by their physicochemical properties, particularly particle size and surface charge, which control biodistribution, cellular uptake, and intracellular activity.

Particle Size

Particle size is a critical factor affecting circulation time and tumour accumulation. Very small nanoparticles (<5–10 nm) are rapidly cleared by the kidneys, resulting in poor therapeutic efficacy. In contrast, excessively large nanocarriers may hinder the formation of the ternary complex between the PROTAC, target protein, and E3 ligase, thereby reducing protein degradation efficiency. Nanoparticles with sizes around 100–200 nm are generally optimal for cancer therapy, as they exhibit prolonged circulation and preferential tumour accumulation through the enhanced permeability and retention (EPR) effect.

Surface Charge and Endosomal Escape

Surface charge plays a major role in cellular internalization and intracellular trafficking. Nano-PROTACs are commonly taken up by cells via endocytosis and may become trapped in endosomes and lysosomes. Cationic nanocarriers can promote endosomal escape and enhance cytoplasmic delivery of PROTACs. However, excessive positive charge can cause protein corona formation in the bloodstream, reducing targeting specificity and altering biodistribution. Therefore, careful optimization of surface charge is essential to balance efficient cellular uptake with minimal systemic side effects.

Nano-PROTAC Delivery Strategies

Recent studies highlight that successful nano-PROTAC systems require a balanced design to improve solubility, stability, tumour targeting, and mitigation of the hook effect. Current delivery approaches include physical encapsulation, chemical conjugation, carrier-free self-assembly, and smart hybrid platforms, each requiring precise control over particle size and surface charge for optimal therapeutic performance.

MECHANISM OF ACTION:

Nano-PROTACs work by using nanoparticles to deliver protein-degrading molecules to cancer cells, where the molecules then hijack the cell's natural waste disposal system to destroy specific cancer-causing protein

PROTACs (Proteolysis Targeting Chimeras) is made more efficient and targeted through the use of nanotechnology:

The mechanism involves two main stages: delivery (nanoparticle function) and degradation (PROTAC function).

1. **Nanoparticle-Enabled Delivery:**

Nanoparticles (NPs) act as a vehicle to safely transport the PROTAC molecules to the tumour site and into the cancer cells.

Tumor Accumulation: Nanoparticles circulate in the bloodstream and preferentially accumulate in tumour tissues due to the Enhanced Permeability and Retention (EPR) effect, a phenomenon where tumour blood vessels are leaky and allow nanoparticles to pass through into the tumour microenvironment.

Cellular Internalization and Release: Once at the tumour, the nanoparticles are internalized by cancer cells. Many advanced nano-PROTAC systems are stimuli-responsive (e.g., pH, enzyme, or light-responsive), meaning they release the active PROTAC payload only when triggered by specific conditions within the tumour environment, minimizing side effects in healthy tissues.

2. **PROTAC-Induced Protein Degradation**

Inside the cancer cell, the PROTAC molecule performs its primary function:

Ternary Complex Formation: A PROTAC molecule is a bivalent small molecule with two "ends" connected by a linker.

One end binds to the target protein that is driving cancer cell growth (e.g., BRD4).

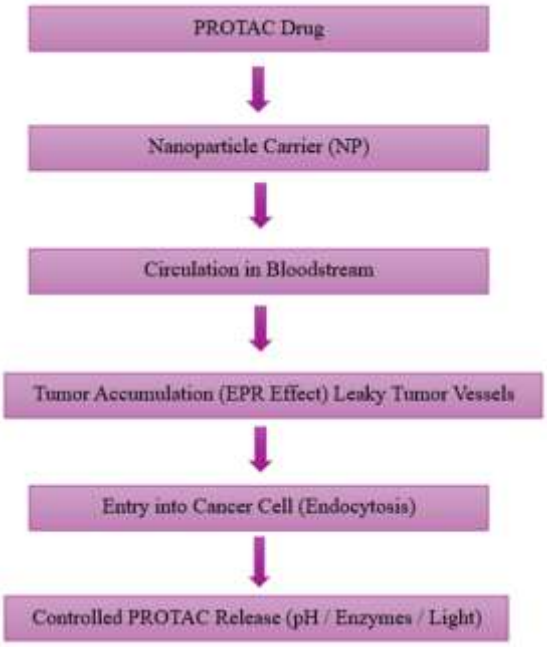
The other end recruits a specific E3 ubiquitin ligase enzyme, a key component of the cell's natural waste disposal system (the ubiquitin-proteasome system).

Ubiquitination: The E3 ligase, now in close proximity to the target protein, attaches a chain of ubiquitin tags to the target protein.

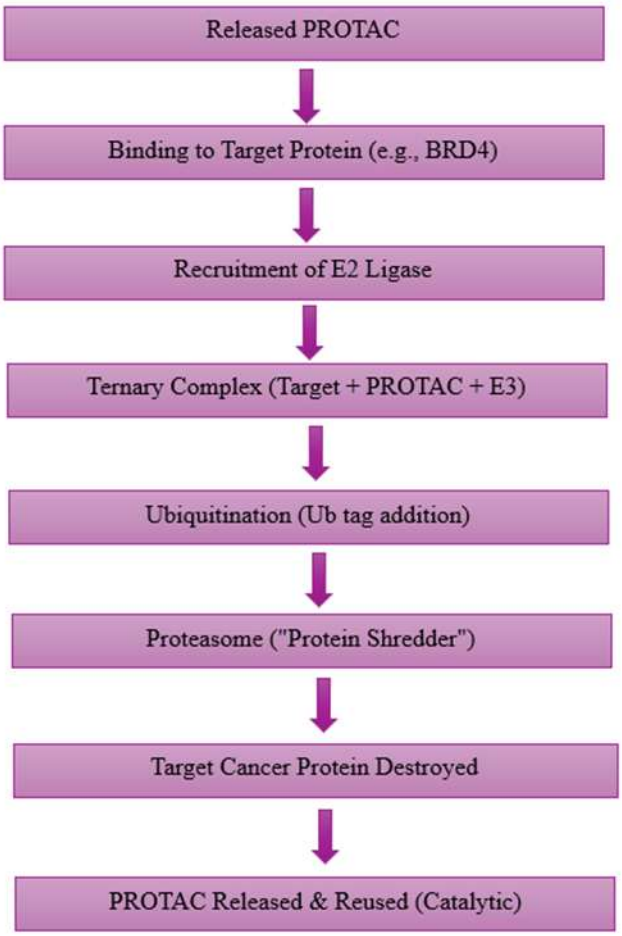
Proteasomal Degradation: These ubiquitin tags act as a signal, marking the target protein for destruction by the proteasome, the cell's "protein shredder".

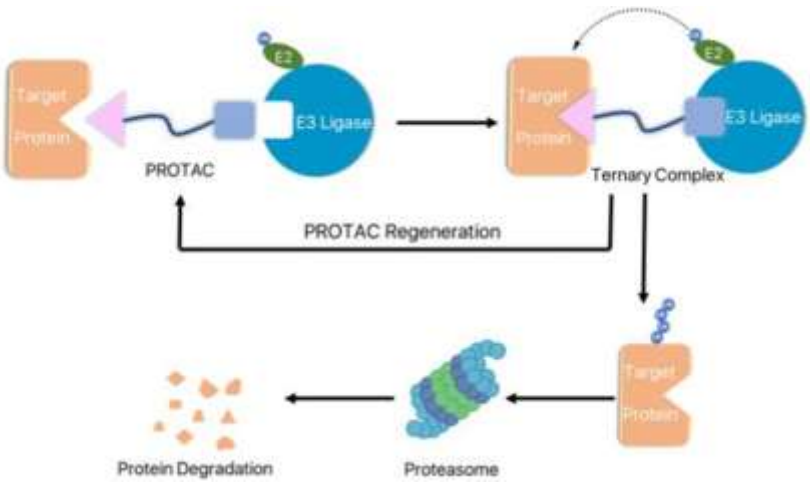
Catalytic Cycle: The PROTAC molecule then detaches and is free to bind to other target proteins, initiating multiple degradation cycles. This catalytic nature means lower doses can achieve significant therapeutic effects compared to traditional inhibitor.

STAGE 1: DELIVERY (Nanoparticle Function):-



STAGE 2: DEGRADATION (PROTAC Function):-





HISTORY OF PROTACS:-

Year	Development	What Happen
2001	First PROTAC was developed	Scientists made first PROTAC molecule-it helps remove bad proteins from cells.
2003	Targeted nuclear receptors (AR, ER)	They tested PROTACs on important cell proteins.
2007	Targeted transcription factors	PROTACs could now control genes by removing "gene control" proteins.
2008	MDM2-based small molecule PROTAC	Created a new , smaller PROTACs -easier to use
2013	First in vivo (in living body) PROTACs	PROTACs demonstrated activity inside animals.
2018	First VHL- and CRBN-based PROTACs	New type of PROTAC that can remove protein inside living bodies.
2019	ARV-110 (bavdegalutamide) entered Phase I clinical trials	the first PROTAC tested in humans
2020	ARV-110 entered Phase II trials	PROTAC showed good result, move to next stage of testing
2022	First nano-PROTACs develop	Used nanoparticles to target lung cancer Improved delivery and effectiveness
2023	First PROTACs targeting BRD4 protein	Shown to be better than traditional drugs
2024	Very effective PROTACs discovered Successfully destroyed CBP proteins	Strong cancer result Reduced cancer growth significantly
2025	The first PROTAC drug candidate, vepdegestrant (ARV-471)	Demonstrated positive Phase III results in a specific patient population and the New Drug Application (NDA) was submitted to the FDA.

LIMITATIONS OF PROTACS:-

While PROTACs are highly effective in principle, they often have limitations☹large molecular size, poor solubility, low cell membrane permeability, off-target toxicity, poor PK, chemical and metabolic instability, limited tumour selectively, dose limiting toxicity, resistance mechanism, suboptimal intracellular trafficking, Challenges in Targeting "Undruggable" Tissue, Complex Structure–Activity Relationship (SAR), that make their clinical use challenging).

Large Molecular Size: PROTACs are inherently large molecules due to their hetero bifunctional design, which incorporates a target-binding ligand, an E3 ligase ligand, and a connecting linker. This results in a high molecular weight, often exceeding the limits defined by Lipinski's "rule of five." The large size of PROTACs negatively impacts their drug-like properties, contributing to poor pharmacokinetics, limited tissue penetration, and reduced cellular uptake. Moreover, steric bulk can hinder efficient diffusion across biological barriers, thereby restricting access to intracellular targets.

Poor Aqueous Solubility: The structural complexity and hydrophobic nature of many PROTAC components frequently lead to poor aqueous solubility. Low solubility poses significant challenges for formulation, systemic administration, and dose optimization. Inadequate solubility can also result in inconsistent drug exposure and reduced bioavailability in vivo, ultimately limiting therapeutic efficacy. Poor solubility further complicates oral delivery and often necessitates the use of high doses or specialized formulation strategies.

Low Cell Membrane Permeability: Effective PROTAC function requires sufficient intracellular

concentrations to enable simultaneous binding of the target protein and the E3 ligase. However, due to their large molecular size, high polarity, and multiple hydrogen bond donors and acceptors, PROTACs generally exhibit low passive diffusion across cell membranes. This limited membrane permeability significantly reduces intracellular target engagement and protein degradation efficiency. Additionally, PROTACs may be subject to efflux by membrane transporters or sequestration in endosomal compartments, further diminishing their cytosolic availability.

Poor Pharmacokinetic (PK) Properties: PROTACs often exhibit unfavorable pharmacokinetics, including rapid systemic clearance, low oral bioavailability, and limited tissue distribution, which restrict their therapeutic effectiveness in vivo. Due to their complex structures and linker regions, PROTACs can be prone to chemical degradation and metabolic breakdown, reducing their half-life in biological systems.

Limited Tumour Selectivity: Many PROTACs rely on ubiquitously expressed E3 ligases, which can result in non-selective protein degradation in healthy tissues, increasing the risk of systemic toxicity

Dose-Limiting Toxicity: Excessive or prolonged protein degradation may lead to unintended cellular stress, proteasome overload, or degradation of essential proteins, thereby limiting the maximum tolerable dose.

Resistance Mechanisms: Cancer cells may develop resistance to PROTACs through mutations or down regulation of E3 ligases, altered target protein expression, or changes in the ubiquitin–proteasome system.

Suboptimal Intracellular Trafficking: Even after cellular uptake, PROTACs may become trapped in endosomes or lysosomes, preventing efficient engagement with target proteins and E3 ligases in the cytosol or nucleus.

Challenges in Targeting "Undruggable" Tissues: Although PROTACs expand the druggable proteome, delivering them effectively to certain tissues (e.g., brain tumours due to the blood–brain barrier) remains difficult.

Complex Structure–Activity Relationship (SAR): Small changes in linker length, flexibility, or orientation can dramatically affect PROTAC efficacy, making rational design and optimization challenging and time-consuming.

Utilization of nanotechnology in PROTACs to solve limitations of PROTACs

The Role of Nanotechnology

Nanotechnology addresses these limitations by:

Enhanced Solubility & Stability: Encapsulating PROTACs in nanocarriers improves their solubility and protects them from degradation, a common issue with these large molecules.

Enhancing Delivery: Encapsulating PROTACs in nanocarriers (such as liposomes or polymeric nanoparticles) improves their solubility, stability, and ability to enter cells.

Targeted Accumulation: Nanoparticles can be engineered with targeting ligands (e.g., antibodies, peptides) to accumulate specifically in diseased tissues, like tumours, minimizing harm to healthy cells (reducing off-target effects).

Controlled Release: Nano-PROTAC systems can be designed to release the active drug in response to specific triggers present in the disease

microenvironment (e.g., abnormal pH or enzyme levels), allowing for spatially and temporally controlled protein degradation.

Precise Intracellular Release: Nanocarriers can be designed to release PROTACs only inside cancer cells or at specific intracellular sites (e.g., in response to tumour pH or enzymes).

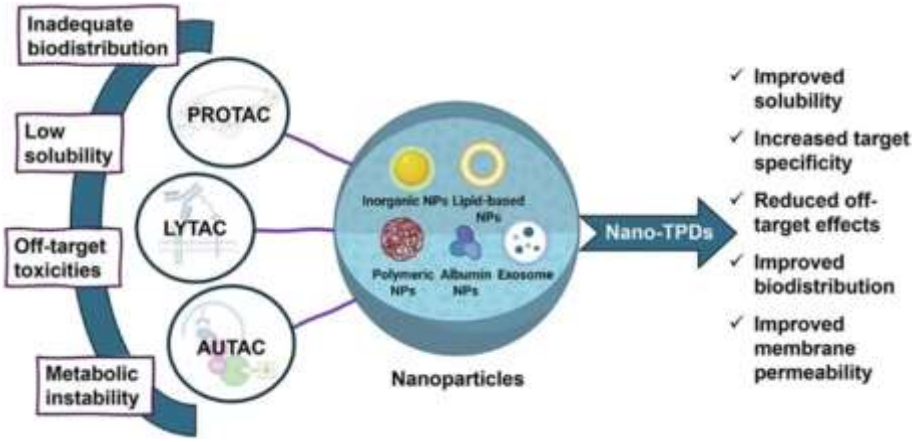
Overcoming the "Hook Effect": By controlling PROTAC concentration, nano carriers prevent the "hook effect," where excess PROTACs bind to target proteins without degrading them, ensuring efficient degradation.

Combination Therapy: Nano platforms offer space to carry multiple drugs (e.g., PROTACs + immunotherapy), creating synergistic treatments in one delivery system.

Stimuli-Responsive Release: "Smart" nanoparticles can release PROTACs triggered by external stimuli (light, heat) or internal tumour cues (pH, redox), allowing precise spatial and temporal control.

Reduced Systemic Toxicity: Precise targeting and controlled release minimize exposure to healthy tissues, tackling off-target effects and improving safety.

The core mechanism of selective protein degradation is inherent to PROTAC molecules, and nanotechnology is a powerful and promising tool used to deliver and optimize these molecules for effective and safe clinical application.



PROTAC Delivery Strategies via NanoDDSs

Nano drug delivery systems (NanoDDSs) possess unique physicochemical characteristics and multifunctional design capabilities that effectively address key delivery challenges associated with PROTACs, including poor aqueous solubility, unfavorable pharmacokinetics (PK), limited cellular permeability, and insufficient tissue targeting, thereby significantly enhancing their bioavailability and therapeutic potential. Structurally engineered nanocarriers—such as polymeric and lipid-based nanoparticles, inorganic nanomaterials, and biomimetic carriers—utilize nanoscale dimensions and self-assembly properties to improve PROTAC solubility, protect labile molecules, and prolong systemic circulation time.

In addition, surface functionalization of nanocarriers with targeting ligands, including antibodies, peptides, or small-molecule moieties, enables active and tissue-specific delivery of nano-PROTACs. This strategy promotes preferential

accumulation at disease sites while minimizing off-target protein degradation and systemic toxicity. NanoDDSs further facilitate enhanced cellular uptake and intracellular trafficking of PROTACs through endocytosis-mediated pathways, thereby overcoming intrinsic membrane permeability barriers.

Advanced stimuli-responsive nanoDDSs—designed to respond to endogenous (pH, enzymes, redox potential) or exogenous (light, heat) triggers—enable spatiotemporally controlled PROTAC release within the tumor microenvironment or diseased tissues, resulting in amplified therapeutic efficacy and reduced adverse effects. Building upon these foundational advantages, nano-PROTAC delivery platforms have been extensively explored in recent years. Currently, the principal strategies for nano-PROTAC formulation include physical encapsulation of PROTACs within nanocarriers, chemical conjugation of PROTAC molecules to carrier matrices, and carrier-free nanodrug delivery systems based on the self-assembly of PROTACs themselves.

Notably, owing to the bifunctional architecture of PROTACs and their unique mechanism of action—mediating proximity-induced interactions between E3 ubiquitin ligases and proteins of interest (POIs)—an emerging and significant design strategy involves the construction of NanoDDSs with active carrier participation. These systems are engineered to spatially organize or co-localize E3 ligases and target proteins, thereby facilitating efficient ternary complex formation and enhancing targeted protein degradation. Such proximity-inducing nano-PROTAC platforms represent a promising direction for next-generation targeted degradation therapies.

How PROTACs Are Different from other Cancer Treatments:

Nanocarrier Systems for PROTAC Delivery:-

Nanocarriers possess the capability to simultaneously transport multiple therapeutic agents, enabling combination therapy within a single delivery platform and improving treatment outcomes for complex diseases. Different nanocarrier systems exhibit distinct drug-loading capacities and release behaviors, allowing precise engineering to address disease-specific challenges. This section summarizes the nanocarriers most commonly employed for the delivery of proteolysis-targeting chimeras (PROTACs).

1. Lipid-Based Nanoparticles

Lipid-based nanoparticles represent one of the most widely investigated platforms for PROTAC delivery due to their excellent biocompatibility and ability to enhance cellular uptake. These systems are typically composed of amphiphilic lipid molecules, including phospholipids and steroids, which facilitate efficient encapsulation of PROTACs. By mimicking the structure of biological membranes, lipid-based nanoparticles improve membrane permeability and promote intracellular delivery.

Lipid-based nanocarriers for PROTAC delivery can be broadly classified into liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and cell membrane-coated nanoparticles.

1.1 Liposomes and Nanoliposomes

Liposomes are supramolecular vesicles formed by the self-assembly of amphiphilic lipid molecules in aqueous environments. Nanoliposomes offer several advantages, including improved drug solubility, enhanced bioavailability, and altered biodistribution. In addition, their surfaces can be functionalized with targeting ligands, enabling controlled and site-specific drug release. Owing to these features, nanoliposomes are considered highly promising carriers for PROTAC delivery.

1.2 Solid Lipid Nanoparticles (SLNs)

SLNs are spherical nanoparticles composed of solid lipids, such as monoglycerides and fatty acids, stabilized by surfactants. They possess a solid lipid core surrounded by a monolayer shell, providing improved stability and sustained drug release. SLNs offer protection of PROTACs from premature degradation but may exhibit limited drug-loading capacity.

1.3 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers consist of a partially disordered lipid core combined with a monolayer

surfactant shell. Compared with SLNs, NLCs exhibit enhanced drug-loading capacity and reduced drug expulsion during storage, making them more suitable for accommodating large or complex PROTAC molecules.

1.4 Cell Membrane-Coated Nanoparticles (CNPs)

Cell membrane-coated nanoparticles represent an emerging lipid-based delivery strategy in which synthetic nanoparticles are cloaked with natural cell membranes. The combination of PROTACs with CNPs significantly enhances targeting specificity, prolongs circulation time, and improves pharmacokinetic profiles. With ongoing technological advancements, CNP-based PROTAC delivery systems show strong potential for future clinical applications.

2. Polymer Nanoparticles

Polymer nanoparticles are typically formed through the self-assembly of amphiphilic macromolecules and offer high structural versatility. These systems can be engineered to be ligand-targeted or stimulus-responsive, enabling controlled PROTAC release in response to tumor-specific conditions such as pH or enzymatic activity. Polymer nanoparticles can improve bioavailability, reduce systemic toxicity, and potentially mitigate the “hook effect” associated with PROTAC overdose. However, concerns related to polymer-induced toxicity and immunogenicity remain major challenges for their clinical translation.

3. Inorganic Nanoparticles

Inorganic nanoparticles (INPs) possess unique physicochemical and structural properties that allow precise control over particle size, geometry, and surface characteristics. Such control enhances pharmacokinetics and biodistribution, making INPs attractive carriers for PROTAC delivery. The rigid structure of INPs also minimizes premature drug leakage during systemic circulation. Common inorganic nanocarriers investigated for PROTAC delivery include mesoporous silica nanoparticles (MSNs), gold nanoparticles (GNPs), iron oxide nanoparticles, and quantum dots.

4. Protein-Based Nanoparticles

Protein-based nanoparticles utilize naturally occurring proteins as drug carriers and are characterized by excellent biocompatibility, biodegradability, and low toxicity. These properties make protein nanoparticles attractive platforms for safe and efficient PROTAC delivery, particularly in applications requiring minimal immunogenicity.

5. Carrier-Free Nano-PROTACs

Recently, carrier-free nano-PROTAC systems based on the self-assembly of active PROTAC molecules have emerged as a promising alternative to traditional nanocarriers. These systems eliminate the need for additional carrier materials, thereby reducing potential toxicity and simplifying formulation. Carrier-free nano-PROTACs offer a novel strategy to overcome limitations associated with conventional nano-drug delivery systems.

This work aims to provide theoretical foundations and practical guidance for developing next-generation targeted protein degradation therapies based on nanoplatforms.

Common strategies for constructing nano-PROTAC delivery systems:-

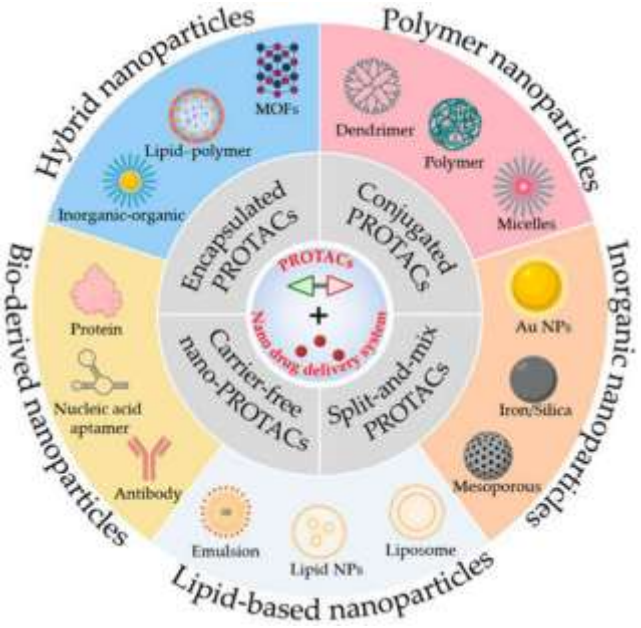


Figure .Common strategies and delivery carrier classifications for constructing nano-PROTAC delivery systems. This figure includes a portion generated from BioRender.

Advantages of PROTACs:

- Helping overcome drug resistance:-Cancer cells often become resistant to traditional drugs because the target proteins change, increase in number, or become overactive. This can cause cancer to return after treatment. PROTACs work differently. Instead of just blocking these proteins, they remove and destroy them, even if they are mutated or resistant to other drugs. For example, ARV-110 can break down mutated androgen receptors in prostate cancer patients who no longer respond to standard treatments.

- Work like catalysts (need less drug):- Traditional drugs must stay attached to their target all the time to work, so high doses are often needed. PROTACs act more efficiently. One PROTAC molecule can destroy many copies of a target protein. Because of this "reusable" action, PROTACs can work at lower doses, last longer, and may cause fewer side effects.

- Can target "undruggable" proteins:-Some important cancer-causing proteins, such as transcription factors and RAS proteins, are very hard to block PROTACs solve this problem by marking these proteins for destruction instead of trying to block them. For example, new PROTACs like MP-16 and MP-17 can degrade c-MYC, a protein involved in many cancers that was previously very difficult to target.

- High selectivity (more precise action):- PROTACs are highly selective because they must bind both the target protein and an E3 ligase at the same time. This double requirement reduces unwanted effects on other proteins. Studies have shown that some PROTACs can specifically destroy one protein (like BRD4) while leaving very similar proteins untouched, leading to better and safer treatments.

- Can also help the immune system fight cancer:-PROTACs do more than just kill cancer-driving proteins. They can also

improve the immune response against tumours. For example: PROTACs targeting STAT3 can slow tumour growth and reduce immune suppression. PROTACs degrading IRAK4 are being tested for certain blood cancers.NX-2127 not only degrades BTK (a cancer-related protein) but also boosts immune activity. This means PROTACs may work both as direct cancer fighters and immune system helpers.

Disadvantages of PROTACs:

- Difficulty entering cells:-PROTACs are large and complex molecules, which makes it hard for them to pass through the cell membrane. Because of this, they may not reach their target proteins inside the cell efficiently. Their structure includes two binding parts joined by a linker, which further increases their size. This also makes it difficult to improve important drug properties such as solubility, stability, and absorption in the body.

- High manufacturing cost:-Making PROTACs is expensive and time-consuming. Scientists must carefully design and connect two different ligands—one for the target protein and one for the E3 ligase. This complex design requires advanced technology, special facilities, and strict quality control, which increases production costs and slows down development. Large-scale manufacturing is therefore a major challenge.

- Dependence on E3 ligases:-PROTACs only work if the required E3 ligase is present and active in the target cells. However, the level of E3 ligases can vary between different tissues and cancer types.If a cell has low or no expression of the needed E3 ligase, the PROTAC may not work well.In addition, cancer cells may change or reduce E3 ligase expression, leading to resistance. To overcome this, researchers are trying to discover and use more types of E3 ligases.

- Possible off-target effects:-Even though PROTACs are designed to be selective, they can still sometimes affect the wrong proteins. Unwanted interactions involving the linker or E3 ligase-binding part may cause the destruction of proteins that were not meant to be targeted. This can lead to side effects or toxicity. To reduce this risk, scientists focus on improving linker design and increasing the specificity of binding molecules.

Recent Research Advances in Nano-PROTAC Delivery Systems:-

We Building upon the successful clinical and preclinical application of Nano platforms for small-molecule drugs, nucleic acid therapeutics, and protein-based pharmaceuticals, Nano carrier technologies have been progressively integrated into PROTAC delivery strategies. The implementation of these nanoplatforms using smart and functional materials significantly facilitates the clinical translation of nano-PROTACs by addressing critical challenges related to molecular stability, biodistribution, pharmacokinetics, and degradation efficiency.

Importantly, increasing evidence suggests that certain nanomaterials exhibit intrinsic synergistic effects with PROTACs. For instance, specific metal ions or metal-oxide–based nanomaterials can modulate the tumour microenvironment, thereby enhancing ubiquitin–proteasome system activity and amplifying PROTAC-mediated protein degradation. In parallel, natural polymers and biomimetic membrane-coated nanostructures have demonstrated improved immune evasion, enhanced blood stability, and prolonged systemic

circulation, ultimately extending the in vivo half-life and therapeutic window of PROTACs.

As a result of these advantages, nano-PROTAC systems have emerged as versatile platforms for combinatorial anticancer therapy. Beyond single-target protein degradation, nano-PROTACs have been successfully integrated with chemotherapy, immunotherapy, photothermal therapy, and other therapeutic modalities, leading to synergistic antitumor efficacy and delayed onset of drug resistance.

Based on a comprehensive analysis of recent literature, the number of reported nano-PROTAC systems has increased substantially over the past five years. Leveraging established delivery strategies—such as encapsulation, conjugation, and self-assembly- nanocarriers have evolved from simple drug carriers into multifunctional, stimuli-responsive, and proximity-inducing platforms. To clearly illustrate current technological progress and design trends, recently reported nano-PROTAC studies are systematically summarized in Table.

New Innovations in Nano-PROTAC and PROTAC Technology:-

1. Stimuli-Responsive Nano-PROTACs

Smart nanocarriers are being engineered to release PROTACs only in response to tumor-specific stimuli such as acidic pH, overexpressed enzymes (e.g., MMPs, cathepsins), redox conditions (high GSH), or external triggers (light, ultrasound, magnetic fields). This innovation significantly improves spatiotemporal control, minimizes off-target toxicity, and enhances therapeutic index.

2. Targeted Nano-PROTACs with Ligand or Antibody Functionalization

Nanoparticles surface-modified with tumour-specific ligands, antibodies, peptides, or aptamers enable active targeting of cancer cells. This approach enhances cellular uptake and intracellular accumulation of PROTACs, overcoming poor permeability and nonspecific biodistribution of conventional PROTAC molecules.

3. Organelle-Specific PROTAC Delivery

Next-generation nano-PROTACs are designed to deliver PROTACs selectively to specific subcellular compartments such as the nucleus, mitochondria, lysosome, or endoplasmic reticulum. Organelle-targeted degradation enables selective elimination of compartment-restricted oncogenic proteins and improves degradation efficiency.

4. Multi-Functional and Combination Nano-PROTACs

Innovative Nano platforms now co-deliver PROTACs with chemotherapeutics, immunomodulators, or gene-silencing agents. These systems enable synergistic anticancer effects by simultaneously degrading oncogenic proteins and modulating complementary signalling pathways.

5. PROTAC-Based Protein Degraders beyond the Proteasome

Novel degraders such as LYTACs, AUTACs, ATTECs, and MITACs expand protein degradation beyond the ubiquitin–proteasome system to include lysosomal and autophagy-mediated pathways. Nano-delivery systems further enhance their stability, tissue penetration, and in vivo applicability.

6. Nanoparticle-Enabled Delivery of "Undruggable" PROTACs

Nanotechnology allows the delivery of large, polar, or unstable PROTAC molecules that were previously unsuitable for clinical translation. Encapsulation improves solubility, protects against metabolic degradation, and extends circulation time, enabling access to challenging intracellular targets.

7. Personalized and Precision Nano-PROTAC Therapy

Advances in genomics and proteomics are driving patient-specific PROTAC design, while nanocarriers enable customizable delivery based on tumor type, protein expression, and microenvironment. This innovation supports precision oncology and individualized treatment strategies.

8. Immune-Modulating Nano-PROTACs

Emerging nano-PROTAC systems target immune checkpoints, transcription factors, or suppressive proteins within immune cells, enabling immune reprogramming. This approach shows promise in enhancing immunotherapy efficacy and overcoming resistance to checkpoint inhibitors.

9 Catalytic Amplification via Nano-PROTAC Recycling

Nanoparticle platforms are being optimized to promote efficient PROTAC recycling after target degradation, maximizing catalytic turnover. This innovation allows effective protein depletion at ultra-low doses and reduces systemic exposure.

10. AI-Assisted Nano-PROTAC Design

Artificial intelligence and machine learning are increasingly used to optimize PROTAC linker

length, E3 ligase selection, nanoparticle composition, and targeting ligands, accelerating rational design and reducing trial-and-error experimentation.

Overall Significance:-

These innovations position nano-PROTAC technology as a next-generation therapeutic platform, capable of overcoming the pharmacokinetic, selectivity, and delivery limitations of conventional PROTACs while expanding the scope of targeted protein degradation in cancer and other diseases.

CONCLUSION

This publication highlights how nano PROTACs are a new and powerful technology for treating many diseases, especially cancer. PROTACs work by removing harmful proteins from cells Instead of just blocking them. This helps stop cancer cells from growing and can also activate the immune system, making treatment more effective.

Beyond cancer, PROTACs may be useful in other diseases. They could help in viral infections by destroying viral proteins, support vaccine development, and treat atherosclerosis by controlling proteins involved in inflammation and fat metabolism. PROTACs also show promise in Huntington's disease by breaking down toxic proteins and slowing disease progression. In addition, they may help treat fatty liver disease by regulating lipid-related proteins.

The development of polymer-based nano-PROTACs represents a significant advancement in targeted cancer therapy. By addressing the challenges of tissue penetration and cellular internalization, nanotechnology offer a promising approach to enhance the delivery and efficacy of PROTACs in cancer treatment.

Overall PROTACs offer a new and promising approach for treating many complex diseases, and future improvements could greatly impact medicine.

PROTACs are a next-generation cancer treatment because they are more precise, work at lower doses, overcome drug resistance, and can target proteins that other drugs cannot. As NDDS, they represent a smarter and more effective approach than many existing cancer therapies.

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