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NANOPARTICULATE PRODRUG DELIVERY SYSTEMS IN TARGETED CANCER THERAPY: FORMULATION APPROACHES, ACTIVATION MECHANISMS, AND TRANSLATIONAL PROSPECTS

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ABSTRACT

Conventional chemotherapeutic regimens continue to be hampered by inadequate tumor selectivity, systemic adverse effects, and the emergence of drug resistance. Over recent years, prodrug-incorporated nanoparticles (PNPs) have emerged as a powerful nanotechnology-driven platform to tackle these obstacles by merging rational prodrug design with sophisticated nanoscale delivery architectures. This review presents a thorough examination of the fundamental principles, structural classifications, and therapeutic prospects of prodrug-incorporated nanoparticles in targeted cancer treatment. By chemically converting active pharmaceutical ingredients into inactive or attenuated prodrug forms and incorporating them into nanoparticulate carriers, these platforms facilitate enhanced aqueous solubility, prolonged systemic circulation, programmed drug activation, and precise tumor localization. Particular focus is given to stimuli-activated PNPs that harness tumor-specific biological cues such as acidic microenvironmental pH, redox imbalances, enzyme upregulation, hypoxic states, and exogenous physical triggers to accomplish site-directed therapeutic release. The review elaborates on a variety of nanostructured architectures, encompassing polymer-drug conjugates, carrier-free self-assembling prodrug nanoassemblies, encapsulated prodrug formulations, and multidrug combination platforms. Preclinical and emerging clinical applications across principal cancer types—including breast, lung, brain, pancreatic, colorectal, ovarian cancers, and leukemia—are critically evaluated. Key barriers pertaining to large-scale fabrication, biosafety, regulatory compliance, and forward-looking directions involving artificial intelligence and individualized nanomedicine are also addressed. Collectively, prodrug-incorporated nanoparticles represent a versatile and scientifically robust nanotherapeutic strategy for realizing safer, more efficacious, and precision-guided oncological interventions.

KEYWORDS: Prodrug-incorporated nanoparticles, Nanotechnology, Targeted oncology, Stimuli-activated drug delivery, Cancer nanomedicine, Precision therapy, Prodrug nanocarrier.

1. OVERVIEW

Cancer is characterized by the unrestrained proliferation of aberrant cells, propelled by evolutionary selection pressures. Beyond unregulated growth, malignant cells accumulate genetic and epigenetic alterations that drive pathological behaviour.[1]

Core cellular processes, such as DNA damage repair, programmed cell death, and cell cycle regulation, are disrupted by genetic mutations and epigenetic reprogramming. These changes are influenced by a multitude of factors including hereditary predisposition, environmental exposures (e.g., chemical toxins and ultra-processed diets), lifestyle elements (e.g., tobacco consumption and dietary patterns), and stochastic events. Cancer is not a singular disease entity but encompasses a broad spectrum of malignancies—including pulmonary, mammary, colonic, hepatic, and pancreatic cancers—each with distinctive biological behaviours and therapeutic challenges. Nearly 90% of cancer-associated mortality is attributable to metastasis, a coordinated cascade of events encompassing local tissue invasion, vascular intravasation, extravasation at distant sites, and secondary tumor establishment.[2] A comprehensive understanding of cancer biology and disease progression is therefore indispensable for developing more effective therapeutic strategies. Contemporary research highlights the necessity of overcoming barriers such as drug-related adverse effects and treatment resistance, while leveraging multidimensional data to fuel future innovations in oncology.[3] Toward enhanced cancer treatment, investigators have directed considerable attention to intelligent drug delivery systems (DDS) capable of more precisely engaging tumor cells. These systems are broadly categorized into three functional paradigms: actively targeted delivery, passively targeted delivery, and stimulus-responsive targeting. Such nanotechnological advances not only amplify drug efficacy but also address prevalent obstacles like multidrug resistance and systemic toxicity associated with conventional treatment modalities.[4] Nanotechnology has considerably propelled the evolution of drug delivery, particularly within the oncological domain. Traditional dosage forms frequently encounter challenges including suboptimal bioavailability, limited tumor specificity, and inefficient intracellular drug uptake. Conversely, anticancer agents formulated as nanocarriers benefit from preferential tumor accumulation through the enhanced permeability and retention (EPR) effect. Prodrug-based nano-DDS integrates the inherent advantages of prodrug chemistry with those of nanoparticulate delivery, resulting in more effective and targeted anticancer agent administration. The fusion of nanotechnology with prodrug design strategies represents a highly promising avenue for advancing cancer treatment outcomes relative to conventional dosage forms.[5] In this review, we examine prodrug-based approaches in oncological therapy, classifications of prodrug nanoparticles, tumor-targeting mechanisms, synthesis methodologies, therapeutic applications, current limitations, and emerging developments and future perspectives.

2. Nanoparticles: An Overview

Nanoparticles are submicroscopic entities, generally spanning 1 to 100 nanometers (nm) in size, with all external dimensions situated within the nanoscale range. According to the International Organization for Standardization (ISO), a particle qualifies as a nanoparticle only when the difference between its longest and shortest axes is not substantially large. When dimensional disparities are more pronounced, alternative terminologies such as nanofibers or nanoplatelets are preferred. Nanoparticles may be amorphous or crystalline and exhibit diverse structural morphologies including irregular, spherical, and cylindrical geometries.[6] Nanoparticles represent an exciting frontier in oncological drug delivery, offering transformative solutions for therapeutic agent administration while constraining off-target toxicity. Their diverse typologies and tunable physicochemical properties enable personalized treatment strategies that substantially improve clinical outcomes. The elevated surface-to-volume ratio and sub-micron dimensions of nanoparticles confer enhanced tissue penetration capabilities. Selective tumor accumulation is achieved through the EPR effect, while surface engineering strategies such as PEGylation can further diminish immune-mediated clearance, extending systemic bioavailability.[7]

2.1. Classification of Nanoparticles

Nanoparticles (NPs) may be classified according to several criteria, encompassing their chemical composition, spatial dimensionality, and carrier architecture. The following section presents a systematic classification accompanied by representative examples. Nanoparticles can be organized based on composition, dimensional characteristics, and carrier type, as depicted in Figure 1.

[Insert figure 1 here]

Fig. 1. Systematic classification of nanoparticles.

2.2. Prodrugs: Conceptual Framework

Pharmacological entities that lack intrinsic activity in their administered form and necessitate metabolic biotransformation or physicochemical conversion to become pharmacologically functional are termed prodrugs. Prodrugs may be deliberately engineered during the drug discovery phase or may occur naturally, as in the case of certain phytochemical constituents. Well-known examples include L-DOPA, aspirin, and codeine. They are predominantly developed to resolve specific physicochemical or pharmacokinetic deficiencies associated with the parent active drug, such as inadequate solubility, poor absorption, or limited stability.[9]

2.3. Inherent Constraints of Prodrug Strategies

Suboptimal Bioavailability: Certain pharmacological agents exhibit insufficient aqueous solubility or gastrointestinal absorption, limiting their effective utilization by the body (e.g., corticosteroids). Pronounced Hepatic First-Pass Metabolism: Prodrug approaches may be beneficial for agents that undergo extensive presystemic hepatic metabolism before

achieving systemic exposure (e.g., propranolol). Chemical Instability: Several drugs exhibit abbreviated biological half-lives or are susceptible to degradation under physiological conditions, necessitating the development of a prodrug capable of converting to the active form at the appropriate time and site (e.g., dopamine).[10]

3. Prodrug Classification Frameworks

Prodrugs may be systematically organized using several criteria, each illuminating distinct aspects of their structural rationale and functional behavior. The principal classification categories are detailed below:

3.1. Classification According to Therapeutic Category

Anticancer Prodrugs: Engineered to selectively engage malignant cells while minimizing systemic harm. Antiviral Prodrugs: Formulated to address specific viral pathologies with a reduced adverse effect profile. Antibacterial Prodrugs: Designed to combat bacterial infections with improved targeting. Nonsteroidal Anti-inflammatory Prodrugs (NSAIDs): Developed to enhance systemic absorption and attenuate gastrointestinal adverse events. Cardiovascular Prodrugs: Specifically formulated to address cardiac conditions.[11]

3.2. Classification Based on Chemical Bond Linkages

Esteric Prodrugs: Employ ester bonds as the bioactivatable linkage. Glycosidic Prodrugs: Utilize glycosidic bond chemistry. Bipartite and Tripartite Prodrugs: Comprise multiple molecular components that liberate the active drug upon metabolic processing. Antibody-, Gene-, and Virus-Directed Enzyme Prodrugs: Engineered to achieve activation within specific cellular or tissue compartments.[11]

3.3. Classification Based on Functional Objectives

Prodrugs for Enhanced Site Specificity: Engineered to improve tissue or cellular targeting. Prodrugs to Circumvent Extensive First-Pass Hepatic Metabolism: Designed to reduce presystemic liver-mediated biotransformation. Prodrugs for Improved Absorption Profiles: Developed to address poor aqueous solubility or membrane permeability. Prodrugs for Mitigation of Adverse Effects: Formulated to minimize the undesirable effects associated with the active drug.[11]

Prodrugs can also be broadly subdivided into two overarching categories:

3.4. Carrier-Linked Prodrugs

In this category, a pharmacologically inert transport moiety or carrier is covalently tethered to the active drug. These compounds typically feature ester or amide linkages that undergo in vivo biotransformation to liberate the active component. Carrier-linked prodrugs are engineered to be non-toxic and to attenuate undesirable pharmacological effects, while simultaneously modifying the physicochemical attributes of the parent drug.[12]

3.4.1. Subcategories of Carrier-Linked Prodrugs

Pro-prodrug: A prodrug that is further derivatized to allow enzyme-catalyzed conversion prior to active drug release (e.g., Cefpodoxime proxetil). Macromolecular Prodrug: Employs high molecular weight polymeric or polysaccharide carriers (e.g., Naproxen-2-glyceride). Site-Directed Prodrug: Programmed to release the active drug at a defined anatomical or cellular locus (e.g., sulfasalazine, which releases 5-aminosalicylic acid within the colon). Mutual Prodrug: Combines two pharmacologically active agents to suppress adverse effects while achieving synergistic therapeutic benefit (e.g., Estramustine).[12]

3.5. Bioprecursor Prodrugs

In this classification, the parent drug is regenerated through enzymatic redox transformations. Bioprecursors generally do not alter the lipophilicity of the parent molecule and are generated via chemical modifications (e.g., phenylbutazone serving as a metabolic precursor of oxyphenbutazone).[12]

4. Mechanisms of Prodrug Activation Within Tumor Cells

Prodrugs exploit tumor-associated protease-cleavable peptide linkers to selectively liberate cytotoxic agents within the tumor environment. Numerous enzymatic proteins are aberrantly upregulated in malignant cells, including proteases that confer aggressive tumor characteristics. Prodrugs may be engineered with specific enzyme substrates to capitalize on this overexpression. Commonly targeted enzymes include lysosomal cathepsins and extracellular matrix-resident matrix metalloproteases (MMPs). For example, prostate-specific antigen (PSA) represents a tissue-restricted protease exploited in prostate cancer prodrug strategies.[13] Enzyme-mediated activation underlies antibody- and gene-directed enzyme prodrug therapy, substantially reducing systemic toxicity.[13] Tumor microenvironmental cues including acidic pH and hypoxia provide additional stimuli for selective prodrug activation. These activation mechanisms exploit the aberrant biochemistry of tumor cells, encompassing altered intracellular pH, hypoxic niches, and the overexpression of specific membrane receptors. Such characteristics enable efficient prodrug delivery and bioactivation within the tumor microenvironment. Emerging prodrug architectures that circumvent multidrug resistance incorporate mitochondria-directed targeting and stimuli-responsive drug release mechanisms.[14] Nanoparticulate prodrug formulations and targeted ligand conjugates further enhance selective delivery and controlled bioactivation.[14] Table 1 delineates the mechanisms of prodrug activation with representative examples relevant to cancer therapy.

Table 1: Classification of prodrug activation mechanisms in cancer therapy.
[insert table 1 here]

Mechanism	Description	Example
Enzymatic Cleavage	Enzymes overexpressed in tumors cleave prodrug linkers, liberating the active therapeutic agent	MMP-cleavable peptides releasing doxorubicin.[13]
Tumor Microenvironment Triggers	Hypoxic conditions and acidic pH activate prodrugs via reduction or chemical transformations	Hypoxia-activated prodrugs.[13]
ADEPT and GDEPT (Antibody-directed enzyme prodrug and Gene-directed enzyme prodrug therapy)	Delivery of activating enzymes via antibodies or gene therapy strategies	ADEPT with antibody-enzyme conjugates.[15]
Nanoparticle-Guided Delivery	Prodrugs encapsulated or conjugated for tumor-specific internalization and intracellular activation	Folate-receptor targeted MMAE (Monomethyl auristatin E) prodrugs.[14]
Mitochondria-Directed Targeting	Prodrugs accumulate selectively in mitochondria, releasing the active compound and overcoming resistance	Triphenylphosphonium (TPP) linked DOX prodrug.[14]

5. Prodrug-Incorporated Nanoparticles: Conceptual Foundation

Prodrug-incorporated nanoparticles are self-assembling nanostructured systems formed by the chemical conversion of therapeutic agents into pharmacologically inactive or attenuated prodrugs capable of in vivo bioactivation to their active forms. This design paradigm integrates the drug delivery vehicle and the therapeutic payload within a single chemical entity, thereby enhancing drug solubility, systemic circulation longevity, targeting specificity, and release programmability while eliminating reliance on external carrier materials. The chemical architecture of the prodrug—including linker chemistry and pro-moiety composition—governs nanoparticle stability, morphological characteristics, and drug release kinetics, facilitating stimuli-responsive and targeted therapeutic delivery with elevated drug-loading capacity and diminished systemic toxicity. This approach provides a streamlined and adaptable nanomedicine platform with superior pharmacokinetic and therapeutic profiles relative to conventional nanocarrier systems.[16]

Historically, prodrugs were considered a salvage strategy for addressing unfavorable pharmacokinetic (PK) or pharmacodynamic (PD) characteristics, toxicity, suboptimal bioavailability, or insufficient therapeutic activity that impeded drug candidates in clinical development.[17] Contemporary perspectives, however, regard prodrugs not merely as rescue interventions but as powerful instruments for rational drug design. Through deliberate chemical modification of an active pharmaceutical ingredient (API) into a prodrug, scientists can precisely modulate critical attributes including solubility, membrane permeability, physicochemical stability, and release kinetics, ultimately yielding improved clinical benefit. This paradigm shift has driven increasing adoption of prodrug strategies early in the drug development pipeline, as evidenced by the rising number of clinically approved prodrugs; approximately 10% of all commercially available drugs are prodrugs, with around 20% of recent small-molecule drug approvals belonging to this category. Prodrug strategies are currently employed to enhance formulation characteristics (e.g., aqueous solubility for alternative administration routes), customize PK parameters (e.g., half-life prolongation, targeted tissue delivery), optimize PD profiles, reduce systemic toxicity, and even generate new intellectual property. Overall, prodrug strategies provide a multifaceted solution to a broad array of drug development challenges by enabling precise control over the pharmacological profile of therapeutic agents.[17] Prodrug-incorporated nanoparticles are engineered to improve drug solubility, physicochemical stability, and tumor targeting efficiency, accommodating both encapsulation and self-assembly processes as illustrated in Figure 2.

[Insert figure 2 here]
Fig. 2. Schematic representation of prodrug-incorporated nanoparticles.

6. Classification of Prodrug-Incorporated Nanoparticles

6.1. Polymer-Drug Conjugates (PDCs)

Polymer-drug conjugates constitute a class of drug delivery systems wherein active therapeutic molecules are covalently attached to polymeric carriers through bioresponsive chemical linkages. This conjugation

strategy enhances drug stability, aqueous solubility, and pharmacokinetic performance, while enabling controlled and targeted therapeutic release at disease sites, particularly within tumors. The polymer carrier—which may be synthetic (e.g., polyethylene glycol [PEG], polycaprolactone [PCL], D-α-tocopheryl polyethylene glycol succinate [TPGS]) or of natural origin (e.g., hyaluronic acid [HA])—extends systemic circulation and promotes tumor accumulation via the EPR effect. Targeting moieties such as peptides or antibodies can be conjugated to further augment tumor selectivity, diminish systemic toxicity, and boost therapeutic efficacy. PDCs have been extensively investigated in cancer therapeutics for the purpose of overcoming multidrug resistance, improving drug solubility, and reducing adverse effects.[18]

Representative examples of polymer-drug conjugates in oncology include: (i) PEGylated Doxorubicin, which enhances tumor targeting and reduces cardiotoxicity relative to free doxorubicin formulations. (ii) Paclitaxel-polymer conjugates, engineered with enzyme-sensitive linkers to facilitate drug liberation within the tumor microenvironment, augmenting antitumor activity.[18]

6.2. Small-Molecule Prodrug Self-Assembling Nanoparticles (SMP-NAs)

Small-molecule prodrug self-assembling nanoparticles are nanoscale delivery constructs formed through the spontaneous molecular self-organization of chemically engineered small-molecule prodrugs, negating the requirement for supplementary carrier materials. These amphiphilic prodrug molecules integrate hydrophilic and hydrophobic structural segments, enabling spontaneous nanoparticle formation in aqueous media. This strategy confers notable advantages including ultrahigh drug loading capacity, minimized excipient-derived toxicity, and simplified preparation methodologies. SMP-NAs frequently incorporate stimuli-responsive linkers sensitive to tumor microenvironmental triggers such as pH fluctuations, enzymatic activity, or redox gradients, enhancing antitumor efficacy and reducing systemic adverse effects while permitting controlled, spatially restricted drug release. Additionally, SMP-NAs provide avenues for combination therapeutic strategies (e.g., chemo-phototherapy, immunotherapy) by co-delivering multiple pharmacological agents or photosensitizers, thereby addressing tumor heterogeneity and drug resistance challenges.[19]

Representative examples include: (i) Cabazitaxel, a next-generation taxane chemotherapeutic agent that operates by binding to beta-tubulin subunits, stabilizing microtubular structures. Cabazitaxel prodrug nanoassemblies are activated by reactive oxygen species (ROS) and intracellular esterase activity, releasing the active compound selectively within tumor cells.[20] (ii) Irinotecan-based amphiphilic prodrugs: Modified with quinone propionate to self-assemble into multifunctional nano-prodrugs enabling chemo-phototherapy via enzyme-responsive triggered drug release in non-small-cell lung cancer experimental models.[21] (iii) Cabazitaxel homodimeric prodrugs conjugated with polyunsaturated fatty acids: These self-assemble into carrier-free nanoparticles and reduce systemic toxicity while preserving antitumor activity.[22] (iv) Hybrid homodimeric prodrug nanoassemblies: Incorporate chemotherapeutic taxane prodrugs alongside photosensitizers to enable synergistic chemo-photodynamic therapy with tumor-restricted activation mediated by reactive oxygen species.[23]

6.3. Prodrug-Encapsulated Nanoparticle Systems

Prodrug-encapsulated nanoparticles are drug delivery constructs in which a prodrug—an inactive, chemically modified derivative of an active drug that undergoes in vivo conversion to its pharmacologically active form—is physically encapsulated within a nanocarrier such as a liposome, polymeric nanoparticle, or solid lipid nanoparticle. This formulation strategy synergistically integrates the benefits of prodrug chemistry (e.g., enhanced physicochemical stability, attenuated toxicity, and programmed release) with those of nanoparticulate delivery (e.g., tumor accumulation via the EPR effect, extended circulatory half-life, and targeted delivery).[24] The nanocarrier provides protective shielding for the prodrug during systemic transit, augments its solubility, and facilitates preferential accumulation at the pathological site, where the prodrug is released and subsequently activated by local stimuli (e.g., pH changes, enzymatic activity, or redox conditions) to exert its therapeutic function.[25]

Representative systems include: (i) SN-38-Incorporating Polymeric Micelles (NK012): SN-38, the active metabolite of irinotecan, is encapsulated within polymeric micelles to improve solubility and tumor targeting, demonstrating potent antitumor activity in preclinical investigations.[26] (ii) Vitamin E TPGS-Cisplatin Prodrug Nanoparticles: These co-deliver cisplatin (in prodrug form) and docetaxel alongside the targeting agent Herceptin for multimodal cancer therapy.[26] (iii) pH-Sensitive PEG-DOX-Cur Prodrug Nanoparticles: This construct encapsulates a doxorubicin-curcumin prodrug within PEG-based nanoparticles, enabling pH-triggered release and amplified antitumor activity in hepatocellular and cervical cancer models.[27] (iv) Photoactivatable Pt(IV) Prodrug-Backboned Polymeric Nanoparticles: These nanoparticles co-deliver a platinum prodrug alongside siRNA, with light-mediated activation enabling synergistic chemotherapy and gene therapy in platinum-resistant ovarian cancer models.[28]

6.4. Stimuli-Responsive Prodrug Nanoparticle Systems

Stimuli-responsive prodrug nanoparticles represent advanced drug delivery architectures engineered to liberate active therapeutic agents in response to specific endogenous (e.g., pH, enzymatic activity, redox

potential) or exogenous (e.g., light, heat) triggers characteristic of the tumor microenvironment. This precision activation paradigm minimizes off-target effects, enhances drug accumulation at tumor loci, and improves therapeutic outcomes while reducing systemic toxicity. The prodrug—a pharmacologically inactive chemical derivative—is engineered to incorporate a cleavable linker sensitive to the designated stimulus. Upon exposure to the triggering stimulus, linker cleavage occurs, releasing the active drug precisely at the intended site. Such platforms can be designed to respond to single or multiple stimuli, enabling sophisticated control over drug release kinetics and spatial distribution.[29,30]

Representative systems include: (i) Doxorubicin (DOX): Redox-responsive DOX prodrugs conjugated to polymers via disulfide linkages self-assemble into micellar nanostructures that rapidly release DOX in the reductive intracellular milieu, overcoming multidrug resistance in cancer cells. (ii) Camptothecin (CPT): Stimuli-responsive CPT nano-prodrugs employ diverse activatable linker chemistries (pH-, enzyme-, or redox-sensitive) to achieve tumor-selective drug release, addressing CPT's inherent poor solubility and systemic toxicity concerns.[29]

6.5. Multi-Agent Combination Therapeutic Platforms

Combination therapeutic strategies in oncological treatment involve the concurrent or sequential administration of two or more therapeutic agents with distinct mechanisms of action, with the objective of reducing systemic toxicity, improving treatment efficacy, and circumventing drug resistance.[31] The underlying rationale is to simultaneously engage multiple tumorigenic pathways, thereby increasing the probability of eradicating malignant cells and delaying or preventing the emergence of drug-resistant clones. Nanoparticle (NP)-mediated combination therapy is particularly compelling as it facilitates the co-delivery of agents with disparate physicochemical properties within a single carrier platform, maintaining an optimized molar ratio and ensuring synchronized drug delivery to tumor cells.[32,33]

Representative drug combinations include: (i) Doxorubicin + Mitomycin C: Co-encapsulated within hybrid polymer-lipid nanoparticles, this pairing demonstrated superior antitumor activity against drug-resistant breast cancer cells compared with single-agent nanoparticles or free drug combinations.[32] (ii) Paclitaxel (Abraxane®) + Doxorubicin (Doxil®): These nanoparticulate formulations are frequently combined with complementary agents or deployed in sequential therapeutic regimens for breast cancer management.[32] (iii) Photosensitizers + Chemotherapeutics: Integrating photodynamic therapy agents with conventional chemotherapeutics in a unified nanoparticle platform enables dual-mode tumor cytotoxicity.[34]

7. Tumor-Targeting and Drug Activation Mechanisms

7.1. The Enhanced Permeability and Retention (EPR) Effect

The EPR effect describes the preferential accumulation of nanoparticles and high molecular weight drug molecules within tumor tissues compared to normal tissues. This phenomenon arises from the structural anomalies of tumor vasculature—characterized by fenestrated endothelium, deficient pericyte support, and vascular leakiness—combined with impaired lymphatic drainage within tumors. These properties permit nanoformulated drugs to reside within tumor tissue for extended durations relative to conventional small-molecule agents, which are rapidly cleared from circulation. However, delivery efficiency is not absolute, as elevated interstitial fluid pressure, dense extracellular matrix architecture, and heterogeneous tumor blood flow within neoplastic tissue present significant impediments to deep drug penetration. To enhance drug penetration, investigators have explored the use of vasodilatory agents (such as nitroglycerin, angiotensin II, and ACE inhibitors) to augment intratumoral blood flow, and enzymatic agents (such as collagenase and hyaluronidase) to degrade the dense stromal matrix. A novel approach designated Near Infrared Photoimmunotherapy (NIR-PIT) can dramatically amplify drug delivery by ablating perivascular tumor cells, generating a 'SUPR effect' capable of delivering up to 24-fold more nanoparticles than conventional EPR-mediated passive targeting. Notwithstanding these advances, challenges including tumor heterogeneity and the complexity of manufacturing clinically safe nanomedicines continue to impede widespread clinical adoption.[35,36] Nanoparticle-based tumor targeting operates via both passive and active mechanisms, as illustrated in Figure 3.

Representative examples include: (i) Doxil® (liposomal doxorubicin): A PEGylated liposomal formulation that achieves tumor accumulation via the EPR effect, representing the prototype clinical translation of EPR-based passive targeting for enhanced drug delivery.[36] (ii) HPMA copolymer-pirarubicin: A macromolecular prodrug conjugate that has exhibited significant antitumor activity in advanced prostate cancer by exploiting the EPR effect for tumor-selective delivery.[37]

7.2. Stimuli-Activated Release Mechanisms

Stimuli-activated release mechanisms in drug delivery refer to strategies whereby active drug liberation is triggered by specific environmental conditions, enabling precise temporal and spatial regulation of therapeutic action. These systems are typically constructed using responsive materials—including polymers, liposomes, or nanoparticles—that undergo physical or chemical transformations (e.g., structural disintegration, volumetric swelling, or covalent bond cleavage) in response to a triggering stimulus, thereby releasing the encapsulated therapeutic payload. The stimuli may be

endogenous (intrinsic to the body, including pH shifts, enzymatic activity, redox potential, reactive oxygen species [ROS], or hypoxia within diseased tissue) or exogenous (externally applied, such as thermal energy, light irradiation, magnetic or electric fields, or ultrasonic waves).[38,39] Depicted in Figure 3.

7.3. Tumor Microenvironment-Triggered Drug Liberation

Tumor microenvironment-triggered drug release harnesses the distinctive physicochemical features of the tumor microenvironment (TME)—including hypoxia, acidic pH, elevated reactive oxygen species (ROS) concentrations, high intracellular glutathione (GSH) levels, and upregulated enzymatic activity—to facilitate precision drug release at the tumor site. These characteristics are exploited to engineer nanocarriers and prodrug-incorporated nanoparticles that maintain physicochemical stability during systemic circulation but rapidly release their encapsulated or conjugated payloads upon exposure to tumor-specific conditions, thereby minimizing systemic adverse effects and optimizing therapeutic benefit.[39,40] Illustrated in Figure 4.

[figure 3 here]

Fig. 3. EPR effect, stimuli-responsive drug delivery, and pH-responsive mechanisms.

7.4. pH-Activated Drug Release

Investigators have engineered pH-responsive polymeric nanoparticles to deliver the chemotherapeutic agent paclitaxel (PTX) with enhanced precision. PTX is first chemically coupled to polyethylene glycol (PEG) via an acid-labile acetal linkage, generating an amphiphilic prodrug molecule bearing both hydrophilic and hydrophobic structural components. In aqueous media, these amphiphilic molecules undergo spontaneous self-assembly into micellar nanostructures featuring a hydrophilic PEG corona and a hydrophobic interior compartment that accommodates the paclitaxel payload. Additional free PTX may also be loaded within the hydrophobic core to increase drug loading efficiency. Under physiologically neutral conditions such as those in the bloodstream, the micellar structures maintain integrity and prevent premature drug efflux. However, upon encountering acidic microenvironments—such as those within endosomal or lysosomal compartments of tumor cells—the acetal linkages undergo hydrolytic cleavage, triggering micellar destabilization. This results in rapid liberation of unbound PTX, while chemically conjugated PTX is released in a more gradual, sustained manner, generating a biphasic, programmed release profile. This strategy sustains elevated drug concentrations within tumor cells for prolonged durations, potentially augmenting cytotoxic efficacy while reducing off-target toxicity to healthy tissues.[41] Detailed in Figure 3.

7.5. Enzyme-Responsive Drug Activation

Scientists have fabricated porous nanoscale carriers designated metal-organic frameworks (MOFs) capable of simultaneously loading both a catalytic enzyme and an inert prodrug molecule within the same nanostructured platform. The enzyme and prodrug are compartmentalized within distinct nanopore spaces within the MOF matrix to prevent premature activation. These nanocarriers can be internalized by cancer cells, enabling gradual intracellular release of both the enzyme and the prodrug over time. Upon intracellular liberation, the enzyme catalytically converts the prodrug into its cytotoxic active form, selectively killing the tumor cells. This approach restricts generation of the toxic agent to within the cancer cell, substantially reducing systemic toxicity. The MOF nanocarriers safeguard the enzyme and prodrug during systemic delivery, facilitate endosomal escape to prevent lysosomal degradation of the enzyme, and augment the cytotoxic efficacy of the activated drug.[42] Detailed in Figure 4.

7.6. Redox-Responsive Drug Release

This study describes a novel oral delivery strategy for the anticancer agent paclitaxel (PTX), a drug that is intrinsically challenging to administer orally due to its poor aqueous solubility and limited gastrointestinal absorption. Investigators attached a bile acid moiety and a protective PEG linker to PTX, enabling the drug to form readily dissolving particles in the gastrointestinal environment that can engage the intestinal bile acid transporter for efficient systemic absorption. Once systemically absorbed, the prodrug circulates safely in the bloodstream until it reaches the tumor site, where elevated intracellular glutathione concentrations trigger bond cleavage and release of the active anticancer agent precisely at the target site. This approach markedly improves oral PTX bioavailability, enhances intratumoral drug accumulation, and reduces adverse effects in normal tissues.[43]

7.7. Externally Triggered Drug Release Mechanisms

This delivery system employs specialized nanoparticles engineered to combat malignant cells in both well-oxygenated (perivascular) and poorly oxygenated (hypoxic core) tumor regions. The nanoparticles are surface-engineered to maintain stability in the bloodstream but become selectively activated under the mildly acidic conditions of the tumor microenvironment, augmenting cellular binding and internalization efficiency. Following intratumoral uptake, laser irradiation activates a photosensitizer incorporated within the particles, generating cytotoxic reactive oxygen species that kill proximal tumor cells while simultaneously depleting local oxygen, thereby intensifying regional hypoxia. This induced hypoxia triggers structural disassembly of the nanoparticles, releasing a secondary therapeutic payload (e.g., Tirapazamine—TPZ) that becomes selectively toxic under low-oxygen conditions, enabling elimination of hypoxic cells deep within the tumor core. The system

therefore delivers two sequential therapeutic modalities: laser-activated photodynamic therapy targeting well-oxygenated cells, followed by hypoxia-activated chemotherapy targeting oxygen-deprived cells, collectively achieving more comprehensive tumor eradication.[44]

[Figure 4 here]

Fig. 4. Tumor microenvironment-triggered drug release mechanisms.

7.8. Multi-Stimuli Responsive Drug Delivery

This therapeutic delivery architecture employs nanoparticles loaded with the anticancer agent SN38 (7-ethyl-10-hydroxycamptothecin), engineered to maintain stability during systemic circulation and release their payload exclusively upon entry into malignant cells. The nanoparticles are assembled using chemical linkages—specifically disulfide and ester bonds—that remain intact under normal physiological conditions but are selectively cleaved within the unique intracellular tumor environment, characterized by elevated glutathione concentrations (a reducing agent), specific esterase enzymes, and heightened hydrogen peroxide levels. When internalized by tumor cells, these concurrent intracellular triggers cooperatively cleave the chemical linkers, releasing the active therapeutic precisely at the intended site. This multi-stimuli responsive design concept ensures maximal drug delivery to tumor cells while preserving healthy tissues from adverse effects.[45]

7.9. Receptor-Mediated Active Targeting via Ligand Conjugation

In this formulation strategy, nanoparticles are functionalized with folic acid, which functions as a molecular 'recognition key' (ligand) designed to interact with specific 'receptor locks' called folate receptors expressed on the surface of certain malignant cells and tumor-associated macrophages (TAMs). When these folic acid-decorated nanoparticles reach the tumor site, the folic acid moieties bind to folate receptors (FOLR1 expressed on tumor cells and FOLR2 expressed on TAMs), analogous to a key engaging its complementary lock. This specific binding interaction promotes nanoparticle attachment and receptor-mediated endocytic uptake by target cells, enabling direct intracellular delivery of the encapsulated anticancer agents. This receptor-targeted delivery approach substantially increases therapeutic efficacy while reducing off-target effects on healthy tissues.[46]

7.10. Synergistic Combination Therapy Mechanisms

Combination therapy employing prodrugs and nanocarriers functions by co-loading two or more anticancer agents—frequently in inactive prodrug forms—within nanoparticles engineered to deliver their payload directly to tumor sites. These nanocarrier systems protect the therapeutic agents during systemic circulation, enhancing tumor accumulation and diminishing off-target adverse effects. Upon reaching the tumor microenvironment, the prodrugs undergo controlled bioactivation—typically driven by the specific biochemical milieu within or proximal to malignant cells—enabling site-directed release of the active therapeutic agents. This strategy enables multiple drugs to engage distinct oncological targets concurrently, amplifying treatment effectiveness, helping to overcome drug resistance mechanisms, and mitigating adverse effects compared to administration of individual agents as standalone therapies.[47]

7.11. Immunomodulatory Approaches and Tumor Microenvironment Reprogramming

Combined immunotherapy with tumor microenvironment modulation functions by simultaneously activating the host immune system to mount an anti-tumor response and restructuring the immunosuppressive tumor microenvironment to be more permissive to immune-mediated tumor eradication. In this approach, rationally designed nanoparticles deliver immunomodulatory therapeutic agents to the tumor site, where they reactivate immune cells—including dendritic cells and cytotoxic T lymphocytes—enabling recognition and elimination of malignant cells. Simultaneously, these nanoparticles reprogram the tumor microenvironment by counteracting factors such as hypoxia, suppressing immunosuppressive cellular populations (e.g., regulatory T cells and tolerogenic macrophage phenotypes), and fostering immune-permissive conditions. This dual-action strategy enhances immunotherapeutic efficacy by enabling immune cells to more effectively infiltrate and attack tumors within a more receptive and less immunosuppressive microenvironment.[48]

[Figure 5 here]

Fig. 5. Multi-stimuli responsiveness, combination therapy mechanisms, active receptor-mediated targeting, and immunotherapy with microenvironment modulation.

8. Cancer Burden and Epidemiological Context

8.1. Breast Cancer

Breast cancer exhibits distinct epidemiological patterns and substantial heterogeneity, continuing to rank among the leading contributors to cancer-related mortality in women.[49] In the context of global public health, breast cancer remains a formidable challenge, with its multifactorial etiology and broad spectrum of clinical presentations creating substantial barriers to effective prevention and treatment.[50,51] The carcinogenesis of breast cancer is influenced by a diverse range of factors, and research continues to illuminate the intricate interplay between genetic, environmental, and lifestyle determinants.[52,53] Breast cancer accounts for approximately one-third of all female malignancies globally, with a case fatality rate of approximately 15% among all diagnosed cases.[54,55] Hereditary susceptibility to breast cancer arises from germline mutations in moderate- to high-penetrance susceptibility genes (e.g., BRCA1/2, CHEK2, PALB2, and TP53), and inactivation

of the tumor suppressor gene second allele represents an early carcinogenic event. Hormonal factors also contribute significantly to breast cancer risk.[56] Breast cancer susceptibility is influenced by hormonal factors including prolonged estrogen exposure and reproductive history modulated by variables such as elective termination, earlier age at menarche, and late onset of menopause. Prodrug-incorporated nanoparticles represent a significant therapeutic approach in this context.[57,58]

8.2. Lung Cancer

Lung cancer and chronic obstructive pulmonary disease (COPD) constitute two major intersecting public health challenges. In 2020, lung cancer was responsible for 1.8 million fatalities globally, representing 18% of all cancer-related deaths and ranking as the malignancy with the highest case fatality rate.[59] The global prevalence of COPD continues to escalate, with projections indicating it will become the third leading cause of death worldwide. By 2060, COPD is predicted to claim the lives of approximately 5.4 million individuals annually.[60] Approximately 40 to 70% of lung cancer patients concurrently have COPD, and the majority of lung cancer cases occur in elderly individuals with a history of tobacco use.[61] Prolonged tobacco smoking remains the predominant risk factor. Significant advances in understanding molecular alterations—particularly in adenocarcinoma—have enabled targeted therapies employing tyrosine kinase inhibitors for EGFR mutations and ALK or ROS1 translocations in advanced-stage disease. Although mutation profiling is not yet standard practice in squamous cell carcinoma, ongoing research continues to identify novel therapeutic targets including ROS, MET, FGFR, DDR-2, and RET, offering optimism that continued progress in detection and therapeutic innovation will improve patient prognoses.[62]

8.3. Brain Cancer

Central nervous system (CNS) malignancies rank among the most lethal cancers due to the extreme difficulty of achieving adequate drug concentrations across the blood-brain barrier at tumor sites. As a result, therapeutic advances have been incremental, and mortality rates have remained largely unchanged for decades. Supramolecular nanomedicines present compelling alternatives that enhance drug distribution and treatment outcomes by improving systemic bioavailability, facilitating augmented BBB and blood-brain tumor barrier (BBTB) penetration, and enabling precise drug release at the tumor site. The clinical translation of these nanomedicine-based strategies is being actively pursued, with current research addressing key technical challenges to increase the probability of achieving curative outcomes for these devastating malignancies.[63]

8.4. Pancreatic Cancer

Pancreatic cancer represents one of the foremost contributors to cancer-associated mortality, with the majority of patients presenting at advanced, unresectable, or metastatic stages. Improved surgical safety standards and the adoption of minimally invasive operative techniques have enhanced outcomes for patients with localized disease, particularly when integrated within multidisciplinary treatment frameworks. Advances in systemic chemotherapy—including its deployment as neoadjuvant therapy prior to surgical resection and in combination with radiation—have begun to influence survival outcomes. Genomic profiling for metastatic disease has facilitated the development of targeted interventions, including PARP inhibitors and immune checkpoint inhibitors, which demonstrate promising activity in defined patient subgroups. Prodrug-incorporated nanoparticles represent a significant emerging component of pancreatic cancer treatment strategies.[64]

8.5. Colorectal Cancer

With approximately 1.85 million new cases and 850,000 annual deaths, colorectal cancer (CRC) ranks as the third most prevalent cause of cancer-related mortality globally. Approximately 20% of CRC patients are diagnosed with metastatic disease at presentation, while an additional 25% of those with initially localized disease subsequently develop metastases. Systemic therapeutic modalities—including immunotherapy, targeted biological agents, conventional chemotherapy, or combination regimens—constitute the primary treatment approach for incurable metastatic colorectal cancer. Evidence from recent clinical trials demonstrates that individualized treatment based on molecular and pathological tumor profiling improves survival, and genomic characterization aids in identifying effective therapeutic options. In combination with chemotherapy, the anti-EGFR monoclonal antibodies cetuximab and panitumumab can extend median survival by two to four months in patients with metastatic CRC harboring KRAS/NRAS/BRAF wild-type tumor profiles.[65] Three principal molecular pathways—chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP)—underpin the pathogenesis of colorectal cancer. CIN is characterized by loss of key tumor suppressor genes including APC and p53, alongside chromosomal copy number alterations. DNA mismatch repair gene defects drive MSI and elevated mutational burden. CIMP operates through aberrant epigenetic silencing of tumor suppressor genes via DNA methylation. Oncogenic driver mutations, including KRAS, disrupt critical intracellular signaling cascades to promote tumor expansion. Non-coding RNA species, including microRNAs, also contribute to CRC development. Elucidating these molecular mechanisms is essential for understanding the transformation of normal colonic epithelium into malignant cells.[66]

8.6. Ovarian Cancer

Despite ranking as the third most prevalent gynecologic malignancy, ovarian cancer carries the highest mortality rate among gynecological cancers. Effective

management necessitates a coordinated multidisciplinary team encompassing radiologists, pathologists, medical oncologists, and gynecologic oncologists. Chemotherapy remains the foundational treatment modality following maximal surgical cytoreduction (to R0 status). Genetic testing is routinely performed in women with epithelial ovarian cancer to guide therapeutic decision-making. Treatment is further complicated by the high recurrence rate; however, maintenance therapeutic regimens incorporating bevacizumab, PARP inhibitors, and agents targeting homologous recombination deficiency improve clinical outcomes. Immunotherapeutic approaches also represent a promising treatment paradigm.[67]

Contemporary advances in oncological management—including precision medicine, immunotherapy, and nanomedicine—are demonstrating considerable promise, with some modalities now in routine clinical use and others showing favorable results in ongoing trials. Immunotherapy, particularly immune checkpoint inhibitor-based strategies, has shown efficacy in tumor regression and the treatment of chemorefractory colorectal cancer, frequently rivaling conventional therapeutic approaches. Combination regimens integrating immunotherapy with molecularly targeted agents are anticipated to substantially advance colorectal cancer treatment outcomes in the future.[68]

Ovarian cancer comprises at least five histologically and molecularly distinct subtypes, each with a characteristic genetic profile, clinical presentation, putative cell of origin, risk factor landscape, and treatment algorithm. These principal subtypes encompass endometrioid carcinoma, mucinous carcinoma, clear cell carcinoma, low-grade serous carcinoma, and high-grade serous carcinoma. Globally, ovarian cancer is typically diagnosed at an advanced stage and lacks an effective screening program. Standard treatment consists of platinum-based chemotherapy following cytoreductive surgery.[69] Given the absence of reliable screening methodologies, effective early detection of ovarian cancer remains an elusive goal. Risk-reducing surgical procedures, such as bilateral salpingo-oophorectomy, can substantially lower risk in high-risk individuals, including those carrying BRCA1/2 pathogenic variants. For average-risk women, transvaginal ultrasonography and the serum biomarker CA125 serve as the principal screening tools. Although they can identify early-stage malignancies, these modalities have not yet demonstrated a meaningful reduction in ovarian cancer mortality. Emerging technologies including liquid biopsy, radiomics, and artificial intelligence hold promise for improving early detection accuracy but require further clinical validation.[70,71] Platinum analogues (cisplatin or carboplatin) combined with a taxane compound (paclitaxel or docetaxel) constitute the most efficacious treatment regimen for newly diagnosed ovarian cancer.[72,73]

8.7. Leukemia

Leukemia is classified by the World Health Organization (WHO) according to the lineage of the involved blood cells and the tempo of disease progression. The 2016 WHO classification revision restructured leukemias into acute and chronic categories, further delineated by myeloid and lymphoid lineage derivation. Principal leukemia subtypes include acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia. The revised classification incorporated pivotal advances from next-generation sequencing-based genetic and molecular profiling, substantially refining diagnostic criteria and therapeutic approaches for myeloid neoplasms and acute leukemias.[74]

9. Therapeutic Applications of Prodrug-Incorporated Nanoparticles in Oncology

9.1. Prodrug-Incorporated Nanoparticles in Breast Cancer

A novel hyaluronic acid-coated glutathione (GSH)-responsive chitosan (CS)-derived nano-prodrug exhibiting aggregation-induced emission (AIE) characteristics was developed for paclitaxel (PTX) delivery in breast cancer treatment. These prodrug nanoparticles, with a drug loading efficiency of 29.32% and a mean particle diameter of 105 nm, exhibited excellent fluorescence stability and uniform spherical morphology. They selectively target tumor cells with high CD44 surface expression and undergo disassembly in response to elevated intracellular glutathione concentrations. In vitro, they demonstrate significant cytotoxicity against 4T1 breast cancer cells and enable real-time intracellular tracking owing to their AIE characteristics. In vivo experiments confirmed superior antitumor efficacy. Overall, these nanoparticles possess excellent bio-imaging capability and represent a promising nanomedicine platform for PTX delivery in breast cancer therapy.[75]

A docetaxel prodrug nanoparticle co-delivering ROR1 siRNA was engineered for synergistic treatment of triple-negative breast cancer (TNBC). The BBRM nanocarrier was effectively internalized by tumor cells, facilitating endosomal escape and concurrent release of DTX and siRNA, downregulating ROR1 protein expression, inhibiting tumor proliferation and metastatic dissemination, and reversing the immunosuppressive tumor microenvironment. In 4T1 tumor-bearing mice, BBRM demonstrated selective targeting of both lung tissues and tumor, with high biosafety, achieving a 74.1% tumor inhibition rate and suppressing lung metastasis. This pioneering nanodevice integrates chemotherapy with RNA interference to augment TNBC therapeutic efficacy and offers a promising strategy for clinical translation.[76]

9.2. Prodrug-Incorporated Nanoparticles in Lung Cancer

Paclitaxel (PTX) prodrug-based, dual-drug-loaded, redox-sensitive lipid-polymer nanoparticles conjugated with arginylglycylaspartic acid (RGD) peptide were fabricated for targeted lung cancer treatment. With IC50 values of 26.7 and 75.3 μg/mL for nanoparticle formulations and free drug combinations respectively, these nanoparticles (approximately 190 nm; zeta potential -35 mV) demonstrated markedly superior anticancer activity relative to free drug formulations. In vivo, nanoparticles exhibited reduced systemic toxicity compared with free drug and significantly suppressed tumor growth in mice, reducing tumor volume from 1486 mm^3 to 263 mm^3. This approach demonstrates promising synergistic combination therapy potential and targeted nanomedicine utility for lung cancer treatment.[77]

Redox-sensitive pullulan/PTX-based prodrug nanoparticles surface-modified with transferrin (TF) were developed to enhance paclitaxel (PTX) delivery for lung cancer therapy. These prodrug NPs (>37% drug loading content, 134-163 nm) underwent rapid disassembly under reducing conditions for triggered drug release, demonstrating excellent colloidal stability, intracellular uptake efficiency, and selective cytotoxicity. In murine models of melanoma lung metastasis and transferrin receptor-overexpressing Lewis lung carcinoma, these nanoparticles demonstrated enhanced tumor suppression and targeting efficiency relative to control formulations and Taxol, with diminished systemic toxicity. This TF-modified prodrug NP system holds significant potential for intracellular PTX delivery in metastatic lung cancer.[78]

An aptamer-coated lipid-polymer hybrid nanoparticle system was developed for co-delivery of cisplatin (DDP) and docetaxel prodrug (DTXp) for combined treatment of non-small cell lung cancer. These nanoparticles (size 213.5 ± 5.3 nm; zeta potential 15.9 ± 1.9 mV) demonstrated profound tumor inhibition (81.4% tumor inhibition ratio), a synergistic antitumor effect (combination index 0.62), and substantially augmented cytotoxicity (IC50 0.71 ± 0.09 μg/mL) compared with non-aptamer counterparts and single-agent formulations. This approach demonstrates considerable promise in suppressing the development of lung carcinoma cells in vivo.[79]

9.3. Prodrug-Incorporated Nanoparticles in Brain Cancer

Hydrogel-based nanoparticles demonstrate promising therapeutic potential as innovative drug delivery systems for brain tumor therapy by providing extended systemic circulation and tumor-directed delivery, thereby improving survival outcomes. These nanoparticles are engineered with optimized physicochemical properties to effectively traverse the blood-brain barrier, enabling direct drug delivery to the tumor site, enhancing therapeutic outcomes, and minimizing systemic adverse effects. Characterization, visualization, and surface modification strategies, alongside prevailing challenges and research opportunities, are actively being explored. Future studies are encouraged to investigate tailored hydrogel formulations, hybrid platform systems, computational modeling, gene therapy integration, and immunotherapy combination approaches. Addressing challenges related to synthesis reproducibility, long-term stability, manufacturing scalability, and cost-effectiveness is critical to advancing the clinical applicability of hydrogel-based nanoparticles in brain tumor treatment.[80]

A glutathione (GSH)-responsive, actively targeted nano-prodrug delivery system incorporating a cyclic Arginine-Glycine-Aspartic acid copolymer covalently linked to doxorubicin and curcumin within nanoparticles (cRGD/PSDOX-Cur@NPs) was engineered for glioma treatment. The system features a disulfide bond-bridged DOX prodrug (PEG-SS-DOX) that releases selectively within the high-glutathione tumor environment, reducing DOX-related cardiotoxicity. Curcumin serves as a P-glycoprotein inhibitor to elevate intracellular DOX concentrations and overcome drug resistance. cRGD/PSDOX-Cur@NPs demonstrated the ability to treat both subcutaneous and orthotopic glioma models while addressing resistance mechanisms and systemic toxicity, exhibiting synergistic antitumor activity in vitro and superior BBB penetration and brain-targeting efficacy in vivo.[81]

9.4. Prodrug-Incorporated Nanoparticles in Pancreatic Cancer

For photoimmunotherapy of pancreatic cancer, a supramolecular prodrug nanoplatform was engineered to co-deliver a photosensitizer alongside the JQ-1 prodrug containing a bromodomain protein 4 inhibitor (BRD4i). The nanoparticles, synthesized by host-guest complexation of cyclodextrin-grafted hyaluronic acid and adamantine-conjugated pyropheophorbide a (PPa)-JQ1 heterodimers, achieve tumor-directed delivery via HA binding to CD44 surface receptors. PPa-mediated photodynamic therapy enhances tumor immunogenicity and facilitates T cell infiltration, while JQ-1 inhibits c-Myc and PD-L1 expression to counteract immune evasion and tumor metabolic reprogramming. This integrated strategy enhances photoimmunotherapy outcomes by activating T cell responses and overcoming adaptive immune resistance in pancreatic cancer models.[82]

A nano-prodrug system was developed to enhance chemotherapy in pancreatic cancer (PC) by simultaneously delivering three therapeutic agents: gemcitabine (GEM), all-trans retinoic acid (ATRA), and nitric oxide (NO) donors. The nano-prodrug was engineered to selectively target PC tumors and respond to the tumor microenvironment by releasing ATRA, which attenuates the activation of pancreatic stellate cells, thereby reducing the dense desmoplastic stroma.

Concurrently, it generates NO to promote vasodilation and produce a 'nanomotor' effect that enhances intratumoral drug penetration. This multimodal approach significantly increases drug delivery efficiency and therapeutic efficacy, demonstrating substantial tumor growth inhibition in murine PDAC models.[83]

9.5. Prodrug-Incorporated Nanoparticles in Colorectal Cancer

Fluoropyrimidine agents serve as cornerstone components of combination chemotherapy regimens for colorectal cancer (CRC) and have improved patient survival through optimized dosing and delivery strategies. To further advance treatment outcomes, novel prodrug formulations and nano-delivery systems for fluoropyrimidine agents are under active development. This area of research highlights recent progress in nano-delivery approaches for fluoropyrimidine agents that demonstrate therapeutic promise. It covers established fluoropyrimidine prodrug strategies, such as capecitabine, which harnesses tumor-specific enzymatic conversion for improved cancer-selective therapy. Fluoropyrimidine DNA-based polymeric platforms for delivery of activated fluoropyrimidine nucleotides have also demonstrated success in preclinical studies with potential for clinical translation. Diverse nano-delivery platforms—including albumin-based formulations, mesoporous silica nanoparticles, emulsion-based nanoparticles, metallic nanoparticles, hydrogels, liposomes, and lipid nanoparticles—show promise for colorectal cancer treatment. Fluoropyrimidine nano-delivery systems are expected to meaningfully advance colorectal cancer management and improve patient survival outcomes in the near future.[84]

To overcome colorectal cancer chemoresistance (CRC) and prevent tumor recurrence, a targeted polymeric prodrug nanoplatform was designed to suppress cancer cell stemness. The platform incorporates hyaluronic acid (HA) for tumor-targeted delivery, alpha-cyano-4-hydroxycinnamic acid (CHC) for inhibition of monocarboxylic acid transporter 1 (MCT-1), and hydroxychloroquine sulphate (HCQ) for autophagy inhibition, all conjugated through pH-responsive ester linkages. A chitosan-derived conjugate co-assembled with the mitochondria-targeting photosensitizer IR820 (T820) to generate CHH-T/NPs, which perturb cellular metabolic homeostasis and inhibit lactate export, culminating in mitochondrial dysfunction and suppression of stemness phenotypes. HCQ-mediated autophagy inhibition disrupts the self-protective mechanisms of CRC cells. CHH-T/NPs effectively suppressed chemoresistance and tumor recurrence in CRC experimental models, offering a promising therapeutic strategy against drug-resistant and relapsing CRC.[85]

9.6. Prodrug-Incorporated Nanoparticles in Leukemia

Investigators developed nanoparticle constructs designated SXP-NPs. These nanoparticles are surface-decorated with two distinct leukemia-specific aptamers (short nucleic acid molecules with high-affinity binding to specific molecular targets): Sgc8c and XQ-2d. The nanoparticles also carry a chemically modified form of the anticancer compound podophyllotoxin (POD) attached via a reduction-responsive linkage that liberates the active drug exclusively upon internalization into cells with elevated intracellular reducing agent concentrations. The nanoparticles additionally incorporate 1,2-Distearoyl-sn-glycero-3- phosphoethanolamine-polyethylene glycol-2000 (DSPE-PEG2000) to impart stability and biocompatibility. The XQ-2d aptamer targets the CD71 receptor, while the Sgc8c aptamer engages the PTK7 (Protein Tyrosine Kinase 7) receptor. Both receptors are differentially overexpressed across distinct leukemia subtypes. By incorporating dual aptamers, SXP-NPs can recognize and bind to multiple leukemia subtypes following systemic administration. Upon internalization by leukemic cells, the reductive intracellular environment triggers prodrug activation and release of podophyllotoxin, inducing selective cytotoxicity in the malignant cells.[86]

9.7. Prodrug-Incorporated Nanoparticles in Ovarian Cancer

Maleimide-functionalized platinum(IV) [Pt(IV)] prodrug-loaded biodegradable polymeric nanoparticles were developed for ovarian cancer treatment. These nanoparticles enhance tumor targeting and intratumoral drug accumulation in ovarian cancer models, improving therapeutic efficacy and reducing toxicity relative to conventional cisplatin formulations. Drug release is triggered by elevated intracellular glutathione (GSH) concentrations within tumor cells, facilitating the circumvention of drug resistance mechanisms and reduction of cisplatin-associated toxicity, resulting in significantly improved survival in ovarian cancer murine models with peritoneal metastases.[87]

Cathepsin B-specific doxorubicin prodrug nanoparticles were evaluated for intraperitoneal chemotherapy of ovarian cancer. These doxorubicin prodrug nanoparticles undergo enzymatic activation in ovarian cancer cells with high cathepsin B expression, enabling targeted intracellular drug release. Intraperitoneal administration demonstrated effective tumor suppression with minimal local and systemic adverse effects in ovarian cancer models with peritoneal carcinomatosis.[88]

A hyaluronic acid-functionalized polymeric prodrug nanoparticle system was developed for paclitaxel delivery to ovarian cancer. A novel HA-coated paclitaxel prodrug nanoparticle selectively targets CD44-expressing ovarian cancer cells, enhancing cytotoxic potency, reducing tumor cell proliferation, and augmenting apoptotic tumor cell death in experimental

models. In vivo studies demonstrated superior therapeutic efficacy compared to conventional paclitaxel formulations, offering a targeted delivery paradigm for ovarian cancer management.[89]

Platinum(IV) prodrug-loaded phase-transitional nanoparticles with ultrasound-responsive drug release capability were developed for ovarian cancer treatment. These nanoparticles integrate platinum(IV) prodrug chemistry with ultrasound-triggered drug activation and tumor-directed targeting to enhance antitumor efficacy and reduce dose-limiting toxicity in ovarian cancer models. They promote mitochondrial apoptosis by elevating intracellular reactive oxygen species (ROS) levels and demonstrate significant potential in precision theranostic applications against ovarian cancer.[90]

10. Manufacturing and Scalability Challenges

The principal impediment to clinical translation of prodrug-incorporated nanoparticles lies in the challenges associated with industrial-scale manufacturing. Multistep chemical synthesis, stringent reaction condition control, and sophisticated purification processes are prerequisites for these systems, and achieving batch-to-batch manufacturing reproducibility represents a formidable challenge, particularly for self-assembled systems where minor process parameter variations can exert dramatic effects on particle size distribution, drug loading efficiency, and physicochemical stability.[91] The successful scale-up of mRNA lipid nanoparticle vaccine production during the COVID-19 pandemic demonstrates that the pharmaceutical industry has made substantial progress in addressing these challenges. This experience established that, given appropriate investment in process development and quality assurance infrastructure, complex nanoparticulate systems can indeed be manufactured at global scale.[92]

11. Current Limitations and Technical Barriers

Despite their considerable therapeutic potential, prodrug-incorporated nanoparticles face several significant obstacles that must be overcome before widespread clinical implementation can be realized. Substantial development and manufacturing costs arise from the requirement for complex production processes demanding specialized expertise, advanced manufacturing facilities, and rigorous quality control protocols.[93] The principal current limitations of prodrug-incorporated nanoparticles include complex and cost-intensive manufacturing procedures requiring precise chemical synthesis and stringent quality management. Premature drug release prior to reaching the intended target site reduces therapeutic efficacy and may produce systemic adverse effects. Additionally, these nanoparticles encounter difficulties in achieving deep penetration into fibrotic and densely packed tumor stroma, restricting their therapeutic reach and efficacy. Furthermore, the introduction of novel nanoparticulate materials may provoke immunological reactions, particularly upon repeated dosing. Certain non-biodegradable constituent materials may accumulate within biological compartments over time, presenting potential long-term safety concerns. Finally, unclear and evolving regulatory frameworks can impede clinical development timelines and escalate development costs. Addressing these multifaceted challenges is essential for transforming prodrug-incorporated nanoparticles into practically viable and clinically effective therapeutic platforms.[94]

12. Current Clinical Achievements

The field of antibody-drug conjugates (ADCs) has yielded the most clinically impactful applications of prodrug-based systems, with several FDA-approved products demonstrating notable therapeutic benefit. Gemtuzumab ozogamicin, the inaugural approved ADC, demonstrated a 30% response rate in patients with relapsed acute myeloid leukemia, despite being withdrawn from the market due to safety concerns and subsequently reapproved with refined indications. More recent regulatory approvals of brentuximab vedotin (54% response rate), inotuzumab ozogamicin (57% response rate), and enfortumab vedotin (44% response rate) have firmly established ADCs as a major therapeutic modality in oncology.[95,96,97,98]

13. Future Directions and Emerging Technological Trends

13.1. Integration of Artificial Intelligence and Machine Learning

The integration of artificial intelligence and machine learning technologies accelerates the development of prodrug nanoparticle systems by enabling the identification of promising drug-linker structural combinations, predicting optimal prodrug molecular designs, and optimizing nanoparticle physicochemical properties for specific therapeutic applications. Machine learning algorithms interrogate extensive databases of chemical structural information and biological activity data to identify patterns and design principles that are challenging to discern through conventional experimental approaches. This results in improved nanoparticle stability, targeting precision, controlled release performance, and therapeutic personalization, ultimately enhancing therapeutic efficiency and substantially reducing development timelines.[99]

13.2. Precision Medicine and Personalized Therapeutic Approaches

Given their inherent modularity and physicochemical tunability, prodrug nanoparticle systems represent ideal platforms for precision medicine strategies wherein patient-specific parameters—including individual pharmacokinetic profiles, genetic biomarkers, and tumor enzyme expression signatures—can be leveraged to select optimal prodrug designs for each individual patient. Nanotheranostics, which integrate diagnostic and therapeutic functions within a single nanotechnology-based platform, hold exceptional promise for personalized oncological medicine. Given that effective

cancer treatment must be tailored to the unique molecular and biological characteristics of individual patients, nanotheranostics platforms facilitate noninvasive biomarker identification and biomarker-guided precision therapy delivery. Although still in developmental phases, such approaches hold substantial potential to revolutionize cancer diagnosis, treatment administration, and therapeutic monitoring within a personalized medicine framework.[100]

14. Infrastructure Development for Nanotechnology-Based Medicine

Clinical application of nanoparticles (NPs) as therapeutic delivery vehicles is constrained by their inherent limitations including suboptimal biocompatibility, poor physiological stability, rapid systemic clearance, and nonspecific biodistribution. Biofilm-mediated biomimetic nanodrug delivery systems (BNDDS) represent an intriguing strategy to overcome these constraints. BNDDS employs bionanotechnology to encapsulate synthetic NPs within biomimetic membranes derived from biological membranes. This approach combines the adaptive flexibility and functional versatility of the nanocarrier with the inherent biocompatibility, effective tumor targeting, low intrinsic toxicity, and minimal immunogenicity of biologically-derived membrane systems.[101] By augmenting tumor targeting efficiency and drug delivery effectiveness, BNDDS demonstrates promising applications in precision tumor therapy. Recent advances in BNDDS continue to optimize drug delivery performance and aim to develop safe, efficacious therapeutic platforms to improve tumor therapy outcomes.[101] The integration of living therapeutic systems, such as cell-based delivery vehicles or engineered bacterial carriers, with the controlled release properties of prodrug chemistry may provide even greater precision over prodrug activation and intratumoral drug distribution.[102]

15. Concluding Remarks

Prodrug-incorporated nanoparticles represent a scientifically robust and therapeutically versatile strategy for advancing the precision, efficacy, and safety profile of cancer therapeutics. By integrating the controlled bioactivation capabilities of prodrug chemistry with the tumor-targeting functionalities of nanocarrier systems, these platforms can overcome many of the intrinsic limitations of conventional chemotherapy, including poor aqueous solubility, inadequate tumor selectivity, dose-limiting systemic toxicity, and drug resistance mechanisms. Through exploitation of tumor-specific biological triggers—including enzymatic activity, acidic pH, hypoxic conditions, or external physical stimuli—drug release can be precisely controlled in both time and space, minimizing adverse effects and optimizing therapeutic outcomes. Recent advances in nanoscale engineering have expanded the design possibilities, enabling the creation of multi-stimuli-responsive systems, multifunctional platforms for combination therapeutic strategies, and nanocarriers capable of modulating the tumor microenvironment to potentiate immunotherapy. Despite these remarkable advances, significant challenges remain, particularly in the domains of large-scale manufacturing reproducibility, long-term biosafety evaluation, tumor penetration in heterogeneous and fibrotic tumors, and navigation of complex regulatory approval pathways. Overcoming these barriers through interdisciplinary collaboration, optimized formulation engineering, and robust quality control frameworks will be essential for successful clinical translation. Collectively, the convergence of prodrug chemistry and nanotechnology holds extraordinary potential to transform cancer treatment paradigms. Continued innovation—supported by advances in materials science, bioengineering, and precision medicine—may ultimately lead to the development of next-generation therapeutics capable of selectively eradicating tumors while preserving patient quality of life, thereby establishing the pathway toward less toxic, more individualized, and more effective cancer treatment strategies.

Author Contributions

Venkatesh Aditiyaa narayanaa and Priya Palanisamy contributed to the conceptual design and overall structure of the study. A.N. Venkatesh performed the comprehensive literature survey, data compilation, and preparation of the initial manuscript draft. Priya Palanisamy contributed to data interpretation, manuscript revision, and formatting. All authors reviewed, critically evaluated, and approved the final version of the manuscript. The authors declare that no paper mill services were employed and that all data and materials presented in this work were independently generated and prepared by the authors.

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Declarations

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