



Review Article

Prodrug-Based Nanoparticles in Precision Oncology: Design Strategies, Tumor Targeting Mechanisms, and Clinical TranslationVENKATESH AN^{1*}, PRIYA P¹, SIVANANDHAN R¹, SURENTHIRAN M¹, LOGESH P², ANITHA P³¹Department of Pharmaceutics, The Erode College of Pharmacy, Erode - 638 112, Tamil Nadu, India.²Department of Pharmaceutical Analysis, The Erode College of Pharmacy, Erode - 638 112, Tamil Nadu, India.³Department of Pharmacology, The Erode College of Pharmacy, Erode - 638 112, Tamil Nadu, India**ARTICLE DETAILS***Article history:*

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Conventional chemotherapy has drug resistance and systemic toxicity and low tumor selectivity. Drug resistance, systemic toxicity, and low tumor selectivity are the problems that remain with conventional chemotherapy. In the past few years, a novel technique that integrates logical prodrug design and the development of sophisticated nanoscale delivery systems has been developed, namely the prodrug-based nanoparticles (PNPs). This review is a comprehensive summary of the principles, classification and therapeutic applications of nanoparticles in precision oncology via prodrug approach. These systems can be used to make active drugs inactive or less active as prodrugs, and can be engineered to circulate in blood for longer after administration, to be activated at the tumour site and to target the tumour. Particular attention is given to PNPs sensitive to external stimuli or to tumor specific stimuli like acidic pH, redox imbalance, overexpression of enzymes, hypoxic condition, etc., which enable the drug release in the tumor site. The review also covers various kinds of nanoarchitecture: polymer-drug conjugates, self-assembling prodrug nanoassemblies based on small molecules, encapsulated prodrug systems, as well as combination therapy platforms. Cancers like breast cancer, lung cancer, brain cancers, pancreatic cancers, colorectal cancers, leukemia, and ovarian cancers are also given attention with regard to preclinical and developing clinical studies as examples. Finally, there are some aspects about mass production, safety, translational and future perspectives of artificial intelligence and personalized nanomedicine that need to be mentioned. In summary, the development of nanoparticle-based prodrugs is an exciting and multifunctional nanotechnology solution to cancer treatment.

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INTRODUCTION

Cancer is a disease of uncontrolled proliferation of abnormal cells, perpetuated by evolutionary selection. Cancer cells also undergo continuous proliferation and acquire genetic and epigenetic changes that enable them to become malignant [1].

Genetic mutations and epigenetic modifications disrupt normal cell processes such as DNA repair, programmed cell death (apoptosis), and the control of cell growth (the cell cycle). These changes could be affected by many factors including lifestyle choices (diet, smoking, etc.),

environmental factors (processed foods, toxins, etc.), random events, and genetic susceptibility. Cancer is not a single disease; it is a collection of many different types of cancer including lung cancer, breast cancer, colorectal cancer, liver cancer, and pancreatic cancer, which have unique biological properties and treatments. Almost 90% of cancer related deaths are attributed to metastasis which is a series of events involving local invasion, intravasation, extravasation and secondary tumour growth in distant sites [2]. Thus, knowledge of the biology and progression of cancer is critical to the development of more effective therapies. The study highlights the significance of addressing challenges such as side effects and drug resistance and the need to leverage multidimensional data to inform future innovations in oncology [3]. Researchers are

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interested in smart drug delivery system (DDS) to improve cancer therapy by targeting cancer cells more effectively. There are three main types of such systems, namely: targeted, non-targeted delivery, and stimulus-responsive targeting. These developments in nanotechnology not only increase the efficacy of drugs, but make it possible to overcome the usual problems of multidrug resistance and systemic toxicity of conventional drugs [4]. Significant strides have been made in the field of nanotechnology in drug delivery systems, especially for cancer treatment. Traditional dosage forms are subjected to various issues (low bioavailability, limited targeting and inefficiencies in uptake by tumor cells). On the other hand, anticancer medications can better accumulate in tumor tissues thanks to the use of the increased permeability and retention (EPR) effect. Prodrug-based Nano-DDS integrates the benefits of prodrugs with nanotechnology, resulting in more efficient delivery of anticancer agents. The integration of nanotechnology and prodrug strategies represents a promising direction for improving cancer treatment efficacy compared to conventional dosage forms [5]. In this review, we are going to see about prodrug-based strategies in cancer therapy, types of prodrug-based nanoparticles, mechanism of tumor targeting by prodrug-based nanoparticles, synthesis of prodrug-based nanoparticles, therapeutic applications, challenges and limitations, recent advances & future perspectives.

Nanoparticles

Usually ranging from 1 to 100 nanometers (nm), nanoparticles are tiny particles having all exterior dimensions in the nanoscale. For an object to be considered a nanoparticle, the International Organization for Standardization (ISO) states that there must be a significant difference in the lengths of its longest and shortest axes. Terms such as nanofibers and nanoplates are more appropriate when there is significant variation in size. Be it amorphous or crystalline, nanoparticles can adopt various forms and morphologies including irregular, spherical, and cylindrical. Nanoparticles are the most promising field of study with regards to the application in cancer therapy since they provide novel drug delivery mechanisms with minimal side effects. Nanoparticles leverage their high surface-to-volume ratio and sub-micron size to penetrate tissues more effectively. Nanoparticles can accumulate in tumor locations due to the increased permeability and retention effect. By

decreasing immune clearance, surface alterations can increase their bioavailability even more [7].

Classification of Nanoparticles

Nanoparticles (NPs) can be classified based on various criteria, including their composition, dimensionality, and carrier type. Below is a comprehensive classification along with examples. Nanoparticles can be classified based on composition, dimensionality, and carrier type, as illustrated in Fig. 1.

Prodrug

Drug substances that are inactive in their intended pharmacological activities and require metabolic or physicochemical modification to become pharmacologically active agents are known as prodrugs. Prodrugs can be purposefully created during medication research, or they can exist naturally, such as in specific phytochemicals. L-DOPA, aspirin, and codeine are a few examples of prodrugs. They frequently aim to solve problems such as low active medication stability, absorption, or bioavailability. Prodrugs are primarily developed to overcome specific limitations associated with active drugs [9].

Limitations of Prodrug

Poor Bioavailability: Some drugs lack adequate solubility or absorption, thus limiting their effective utilization by the body (for example, corticosteroids). **High First Pass Effect:** The application of prodrugs is beneficial in cases where a drug undergoes high first pass effect before entering the bloodstream (for instance, propranolol). **Instability:** Some drugs might be unstable or possess a low half-life; hence the need for a prodrug that turns to the active drug at the right time (for example, dopamine) [10].

Classifications of Prodrugs

Prodrugs can be classified using several criteria, each highlighting different aspects of their design and function. Here are the primary categories:

1. Based on Therapeutic Categories:

Prodrugs Against Cancer: Specifically designed to target cancer cells only.

Prodrugs Against Viruses: Intended to target particular types of viruses.

Prodrugs Against Bacteria: Designed to target particular bacteria.

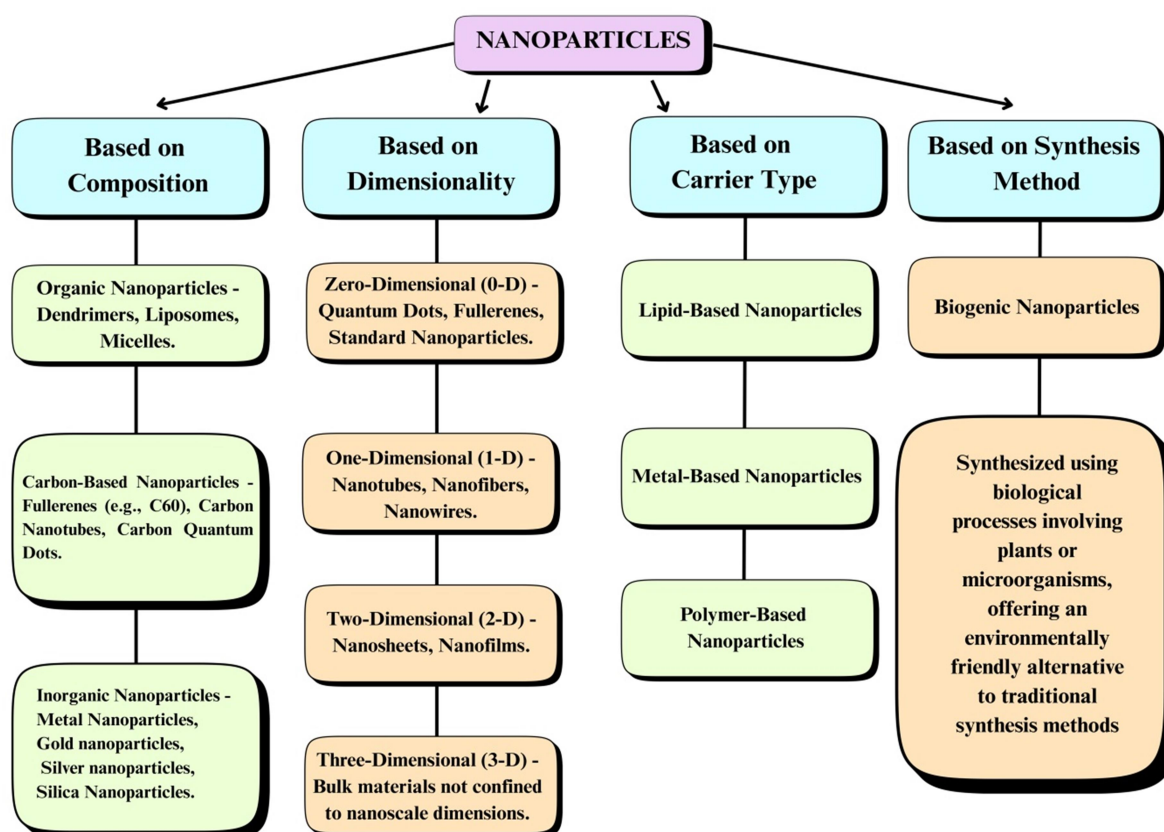


Figure 1: Nanoparticle Classification

Prodrugs for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Designed to improve their absorption and decrease gastrointestinal side effects.

Cardiovascular Prodrugs: Designed to target heart problems. [11].

2. Based on Chemical Linkages:

Esteric Prodrugs: Involve ester bonds.

Glycosidic Prodrugs: Utilize glycosidic bonds.

Bipartite and Tripartite Prodrugs: Consist of multiple components that release the active drug upon metabolic conversion.

Antibody, Gene, Virus-directed Enzyme Prodrugs: Target specific cells or tissues for activation [11].

3. Based on Functional Categories:

Prodrugs for Improving Site Specificity: Enhance targeting to specific tissues or cells.

Prodrugs to Bypass High First-Pass Metabolism: Designed to reduce metabolism in the liver before systemic circulation.

Prodrugs for Improving Absorption: Address issues related to poor solubility or permeability.

Prodrugs for Reducing Adverse Effects: Minimize side effects associated with the active drug [11].

Prodrugs can be broadly classified into two main categories:

Carrier-Linked Prodrugs

An inert transporter or carrier is covalently bound to these prodrugs. Usually, they have ester or amide bonds that bio-transform to release the active component. Carrier-linked prodrugs, designed to be non-toxic and to mask unwanted side effects, alter the physicochemical properties of the active drug [12].

Subcategories of Carrier-Linked Prodrugs:

Pro-prodrug: A prodrug that is derivatized to allow enzyme-mediated conversion before releasing the active drug (e.g., Cefpodoxime proxetil).

Macromolecular Prodrug: Uses large molecular weight compounds as carriers, such as polysaccharides or polymers (e.g., Naproxen-2-glyceride).

Site Specific Prodrug: Targets the release of the active drug at a specific site (e.g., sulfasalazine, which releases 5-aminosalicylic acid in the colon).

Mutual Prodrug: Combines two pharmacologically active drugs to mask side

effects and achieve synergistic action (e.g., Estramustine) [12].

Bio Precursors

In this classification, the parent drug is produced through redox transformations via enzymes. Bio precursors generally do not alter the lipophilicity of the parent drug and are formed by chemical modifications (e.g., phenylbutazone is a metabolic precursor of oxyphenbutazone) [12].

4. Mechanism of Prodrug in Tumor Cells

Prodrugs use peptide linkers cleavable by tumor-associated proteases to release cytotoxic drugs selectively in tumors. Many enzymes are aberrantly upregulated in cancer cells, such as proteases that contribute to aggressive tumor characteristics. Prodrugs can be designed with specific substrates that target these enzymes. Common targets include lysosomal proteases like cathepsins and matrix metalloproteases (MMPs) found in the extracellular matrix. For instance, prostate-specific antigen (PSA) is a

tissue-specific protease targeted in prostate cancer treatments [13]. Activation by cancer-specific enzymes enables antibody- or gene-directed enzyme prodrug therapy, minimizing systemic toxicity [13]. Tumor microenvironment factors such as low pH and hypoxia trigger prodrug activation selectively. Prodrugs can be activated through various mechanisms that exploit the unique biochemical environment of tumor cells. This includes utilizing the altered pH and hypoxic conditions often found in tumors, as well as the overexpression of specific surface receptors. These factors enable the delivery or bioactivation of prodrugs efficiently within the tumor microenvironment. Novel prodrug designs overcoming multidrug resistance utilize mitochondrial targeting and stimuli-responsive release [14]. Nanoparticulate prodrugs and ligand conjugates enhance selective delivery and controlled activation [14]. Table 1 explains Mechanisms of prodrug activation and examples used in cancer therapy.

Table 1: Classification of Prodrug

Mechanism	Description	Example
Enzymatic cleavage	Tumor-overexpressed enzymes cleave prodrug linkers to release active drug	(Matrix metalloproteases) MMP-cleavable peptides releasing doxorubicin [13].
Tumor microenvironment triggers	Hypoxia and acidic pH activate prodrugs via reduction or chemical changes	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	ADEPT with antibody-enzyme conjugates [15].
Nanoparticle targeted delivery	Prodrugs encapsulated or conjugated for tumor-specific uptake and intracellular release.	Folate-receptor targeted MMAE (Monomethyl auristatin E) prodrugs [14].
Mitochondrial targeting	Prodrugs accumulate in mitochondria, releasing the active drug, overcoming resistance.	Triphenylphosphonium (TPP) linked DOX prodrug [14].

Prodrug-Based Nanoparticles

Prodrug-based nanoparticles are self-assembling nanostructures formed by chemically modifying therapeutic agents into pharmacologically inactive or less active prodrugs that can transform into active drugs *in vivo*. This strategy combines both delivery and therapeutics into one molecule, leading to better drug solubility, circulation time, drug-targeting, drug-release control, and absence of the requirement for any additional carriers. Prodrug design, which includes the selection of linker and pro-drug moiety, determines the properties of nanoparticles, such as their stability, shape and

drug release pattern, making it possible to develop stimuli-responsive and targeted drug delivery system with high drug-loading capacity and low systemic toxicity [16].

In the past, the prodrug strategy has been adopted as a remedy for undesirable PK/PD properties, toxicity, poor bioavailability or efficacy issues that limited drug development efforts [17]. But the current perspective on prodrugs is more positive in that prodrugs are seen as valuable means for designing rationally drugs. Through chemical modification of the active pharmaceutical ingredient (API) in a

prodrug, properties such as solubility, permeability, stability, and release profile of drugs can be optimized for better therapeutic benefits. Such an approach has led to increased usage of prodrugs at earlier stages of drug development and is evident from the increase in the number of prodrugs being approved; almost 10% of all approved drugs are prodrugs, and almost 20% of recently approved small molecule drugs are prodrugs. Currently, prodrugs are used for optimizing properties such as formulation properties, for example, aqueous solubility for alternate modes of administration, adjusting PK

profiles, for example, extended half-lives, targeting delivery, optimizing PD response, minimizing toxicity, and even creating new intellectual properties. Overall, prodrug strategies present a versatile solution to multiple drug development challenges by enabling greater control over the pharmacological profile of therapeutic agents [17]. Prodrug-based nanoparticles are designed to enhance drug solubility, stability, and tumor targeting efficiency. These systems allow encapsulation and self-assemble shown in Fig. 2.

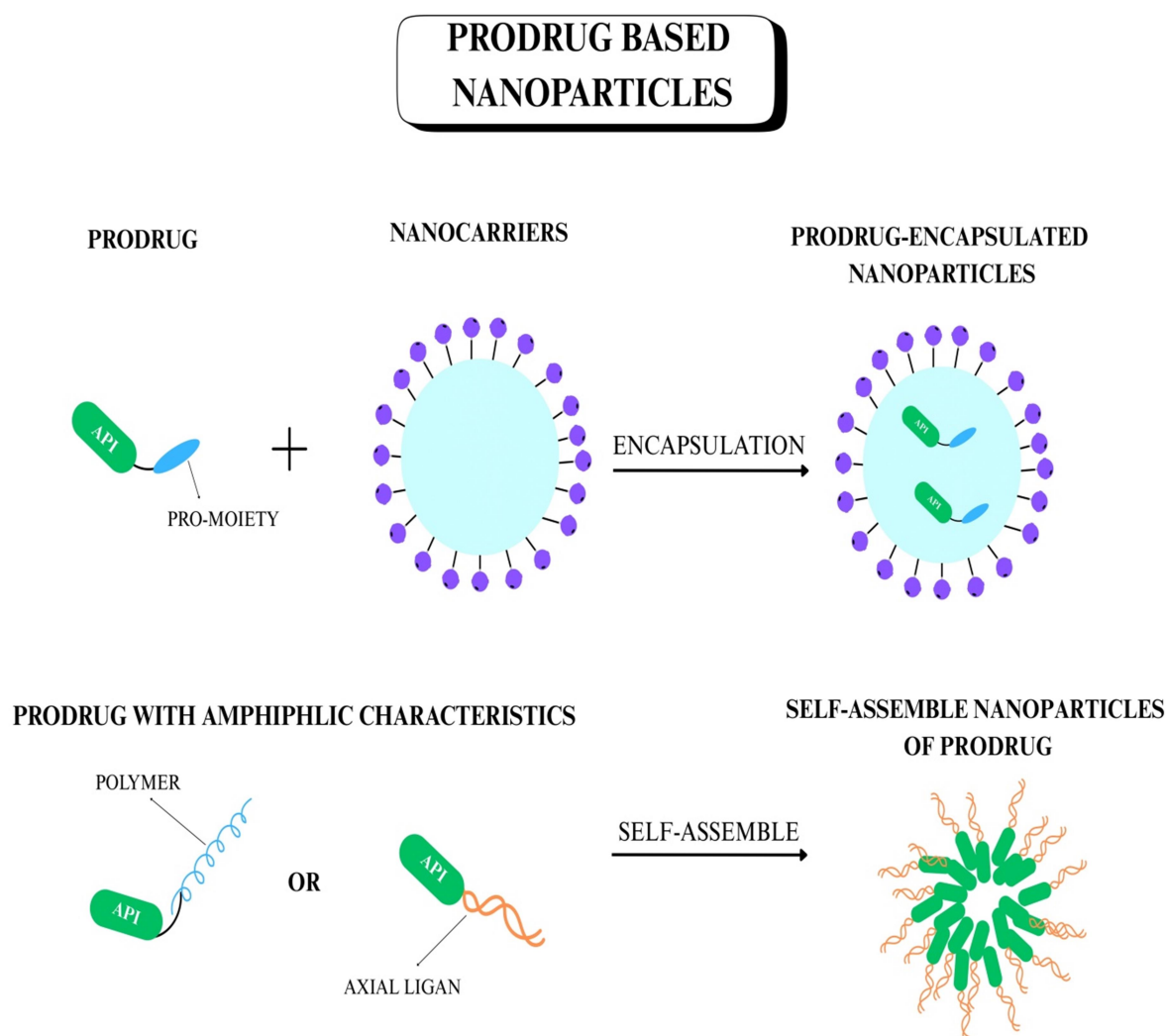


Figure 2: Pro-drug Based Nanoparticles.

Classifications of Prodrug-Based Nanoparticles

1. Polymer-Drug Conjugates (PDCs)

The polymer-drug conjugates (PDC) are one category of drug delivery systems in which drug molecules are covalently attached to polymeric vehicles by the use of bio-responsive linkers. Such attachment provides stabilization, increased solubility, and improved

pharmacokinetics to the drug, together with a controlled and specific release at diseased tissues, especially at tumors. Polymer vehicles (synthetic such as PEG, PCL, TPGS; natural such as HA), increase the circulation times and help the tumor accumulation due to EPR effect. Peptide or antibody-based targeting ligands are used for improving drug delivery selectivity, decreasing toxicity, and increasing efficacy. To

overcome multi-drug resistance, improve drug solubility and minimize side effects, PDCs have been extensively studied in cancer therapy. [18]. Examples of polymer–drug conjugates in cancer therapy include:

- (i) PEGylated Doxorubicin, which improves tumor targeting and reduces cardiotoxicity compared to free doxorubicin.
- (ii) Paclitaxel–polymer conjugates, designed with enzyme-sensitive linkers to enable drug release in the tumor microenvironment, enhancing antitumor activity [18].

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

Small molecule prodrug self-assembled nanoparticles (SMP-NAs) are nano-delivery vehicles that are assembled spontaneously through the chemical modification of small molecule drugs (prodrugs) without the requirement of carriers. The amphiphilic nature of prodrugs, i.e., their ability to have both hydrophilic and hydrophobic moieties allows self-assembly into nanoparticles in aqueous media. Such an approach has its inherent benefits including ultra-high loading capacity, decreased toxicity due to absence of excipients and easy methods of preparation. The stimuli responsive linkers employed in the design of SMP-NAs respond to triggers of tumor microenvironment such as pH, enzymes, or redox environments; thus, improving antitumor efficiency while lowering the systemic toxicity of drugs along with facilitating controlled release. Moreover, SMP-NAs allow combination therapies such as chemotherapy/phototherapy and immunotherapy [19].

Examples of small-molecule prodrug self-assembling nanoparticles include:

- (i) Cabazitaxel, a new-generation taxane chemotherapy agent, it works by binding to β -tubulin subunits, promoting microtubule stabilization. The cabazitaxel prodrug nanoassemblies are activated by reactive oxygen species (ROS) and intracellular esterase to release the active drug specifically in tumor cells [20].
- (ii) Irinotecan-based amphiphilic prodrugs: Modified with quinone propionate to self-assemble into multifunctional nano-prodrugs that enable chemo-

phototherapy via enzyme-responsive triggered drug release in non-small-cell lung cancer models [21].

- (iii) Cabazitaxel homodimeric prodrugs tethered with polyunsaturated fatty acids: Self-assemble into nanoparticles independently of carriers and reduce systemic toxicity while retaining antitumor efficacy [22].
- (iv) Hybrid homodimeric prodrug nanoassemblies: Combine chemotherapeutic taxane prodrugs with photosensitizers to enable synergistic chemo-photodynamic therapy with tumor-restricted activation triggered by reactive oxygen species [23].

3. Prodrug-Encapsulated Nanoparticles

Prodrug encapsulated nanoparticles are drug delivery systems in which a prodrug—an inactive, chemically modified form of a drug that is converted to its active form in the body—is physically encapsulated within a nanocarrier such as a liposome, polymeric nanoparticle, or solid lipid nanoparticle. This approach combines the benefits of prodrug chemistry (e.g., improved stability, reduced toxicity, and controlled release) with those of nanoparticle delivery (e.g., enhanced tumor accumulation through the enhanced permeability and retention [EPR] effect, prolonged circulation, and targeted delivery) [24]. The nanocarrier protects the prodrug during transit, enhances its solubility, and facilitates its accumulation at the disease site, where the prodrug is released and subsequently activated by local stimuli (e.g., pH, enzymes, or redox conditions) to exert its therapeutic effect [25].

Example Drugs and Systems:

- (i) SN-38–Incorporating Polymeric Micelles (NK012): SN-38, the active metabolite of irinotecan, is delivered via polymeric micelles to improve solubility and tumor targeting, showing potent antitumor activity in preclinical models [26].
- (ii) Vitamin E TPGS–Cisplatin Prodrug Nanoparticles: These nanoparticles co-deliver cisplatin (as a prodrug) and docetaxel, along with the targeting agent Herceptin, for multimodal cancer therapy [26].

- (iii) **pH-Sensitive PEG-DOX-Cur Prodrug Nanoparticles:** This system encapsulates a doxorubicin-curcumin prodrug within PEG-based nanoparticles, enabling pH-triggered release and enhanced antitumor activity in liver and cervical cancer models [27].
- (iv) **Photoactivatable Pt (IV) Prodrug-Backboned Polymeric Nanoparticles:** These nanoparticles co-deliver a platinum prodrug and siRNA, with light-controlled activation for synergistic chemotherapy and gene therapy in platinum-resistant ovarian cancer [28].

4. **Stimuli-Responsive Prodrug-Based Nanoparticles**

Stimuli-responsive nanoparticle prodrugs represent advanced drug delivery systems that are designed to deliver their therapeutic payload in response to certain stimuli found within the tumor microenvironment. The internal or external stimuli such as pH, temperature, enzymes, redox potential, light, among others, are chosen to activate the system and trigger its drug release. In turn, this approach helps avoid any adverse side effects by localizing the drug delivery process to the point of interest. The prodrug that is an inactive form of pharmacologically active molecule undergoes chemical modification adding the cleavable linker that responds to the selected stimulus. Under the effect of the chosen stimuli, the prodrug is activated and delivers the therapeutic payload [29, 30].

Example Drugs and Systems:

- (i) **Doxorubicin (DOX):** Redox-responsive DOX prodrugs conjugated to polymers via disulfide linkers self-assemble into micelles that rapidly release DOX in the reductive intracellular environment, overcoming multidrug resistance in cancer cells.
- (ii) **Camptothecin (CPT):** Stimuli-responsive CPT nano-prodrugs use various activatable linkers (pH-, enzyme-, or redox-sensitive) to achieve tumor-specific release, addressing CPT's poor solubility and toxicity [29].

5. **Combination Therapy Strategies**

Combination therapy strategies in cancer treatment involve the simultaneous or sequential

use of two or more therapeutic agents with various modes of action to decrease toxicity, improve efficacy, and overcome drug resistance [31]. Rationale is to target multiple pathways involved in tumor growth and survival, thereby increasing the likelihood of eradicating cancer cells and delaying or preventing the emergence of resistance. Nanoparticle (NP)-mediated combination therapy is particularly promising because it allows for the co-delivery of drugs with distinct physicochemical properties in a single carrier, maintaining an optimized drug ratio and ensuring synchronized delivery to tumor cells [32, 33].

Example Drug Combinations:

- (i) **Doxorubicin + Mitomycin C:** Co-encapsulated in hybrid polymer-lipid nanoparticles, this combination showed superior efficacy against resistant breast cancer cells compared to single-agent nanoparticles or free drug combinations [32].
- (ii) **Paclitaxel (Abraxane®) + Doxorubicin (Doxil®):** These nanoparticle formulations are often used in combination with other agents or as part of sequential therapy regimens for breast cancer [32].
- (iii) **Photosensitizers + Chemotherapeutics:** Combining photodynamic therapy agents with traditional chemotherapeutics in a single nanoparticle platform enables dual-mode tumor killing [34].

Mode of Action

1. **The Enhanced Permeability and Retention (EPR) Effect**

The EPR effect is when nanoparticles and large drug molecules gather more in tumors than in healthy tissues. This happens because tumor blood vessels are abnormal; they have gaps (fenestrations), weak support, and leakiness, plus tumors have poor lymphatic drainage. This allows nano-drugs to stay longer inside tumor tissue compared to normal drugs, which wash out quickly. However, delivery isn't perfect because tumors also have high internal fluid pressure, a dense extracellular matrix, and uneven blood flow, which block deep drug penetration. This is achieved through the use of vasodilators (such as nitroglycerin, angiotensin II, and ACE inhibitors), which help to enhance the blood flow, and enzymes (such as

collagenase and hyaluronidase), which work to degrade the dense tissue. The Near Infrared Photoimmunotherapy (NIR-PIT) method helps to increase the drug delivery by up to 24 times by eliminating the cancer cells adjacent to blood vessels, leading to the “SUPR effect.” Nevertheless, issues such as tumor heterogeneity and difficulties in the development of nanomedicine limit the clinical application of the techniques [35, 36]. There are various tumor targeting mechanisms for nanoparticles, some of which include the enhanced permeability and retention (EPR) effect and ligand-mediated targeting (Fig. 3).

Examples of drugs utilizing this strategy include:

- (i) Doxil® (liposomal doxorubicin): A PEGylated liposomal formulation that accumulates in tumors via the EPR effect, exemplifying the clinical translation of EPR-based passive targeting for improved drug delivery [36].
- (ii) HPMA copolymer-pirarubicin: A macromolecular prodrug conjugate that has demonstrated significant antitumor activity in advanced prostate cancer by leveraging the EPR effect for tumor-selective delivery [37].

2. Stimuli-Responsive Activation Mechanisms

Activation processes of stimuli-responsive systems in drug delivery involve drug release that is activated by certain environmental stimuli, thus allowing precise location and timing of drug action. Such drug release systems are usually designed through material components, which change in a physical or chemical way (disintegrate, swell, or undergo bond cleavage) upon activation by the stimulus. The stimuli can be endogenous (internal to the body, such as pH, enzymes, redox potential, reactive oxygen species [ROS], or hypoxia unique to diseased tissues) or exogenous (externally applied, such as temperature, light, magnetic or electric fields, or ultrasound) (Shown in Fig. 3) [38, 39].

3. Tumor Environmental Triggered Release

Tumor environmental-triggered release refers to the use of the unique physicochemical features of the tumor microenvironment (TME)—such as hypoxia, acidic pH, elevated levels of reactive oxygen species (ROS), high glutathione (GSH), and overexpressed enzymes—to activate drug release precisely at the tumor site. These triggers are exploited to design nanocarriers and prodrug-based nanoparticles that remain stable in circulation but rapidly release their encapsulated or conjugated drugs only when exposed to the tumor-specific conditions, thereby reducing systemic toxicity and improving therapeutic efficacy (Shown in Fig. 4.) [39, 40].

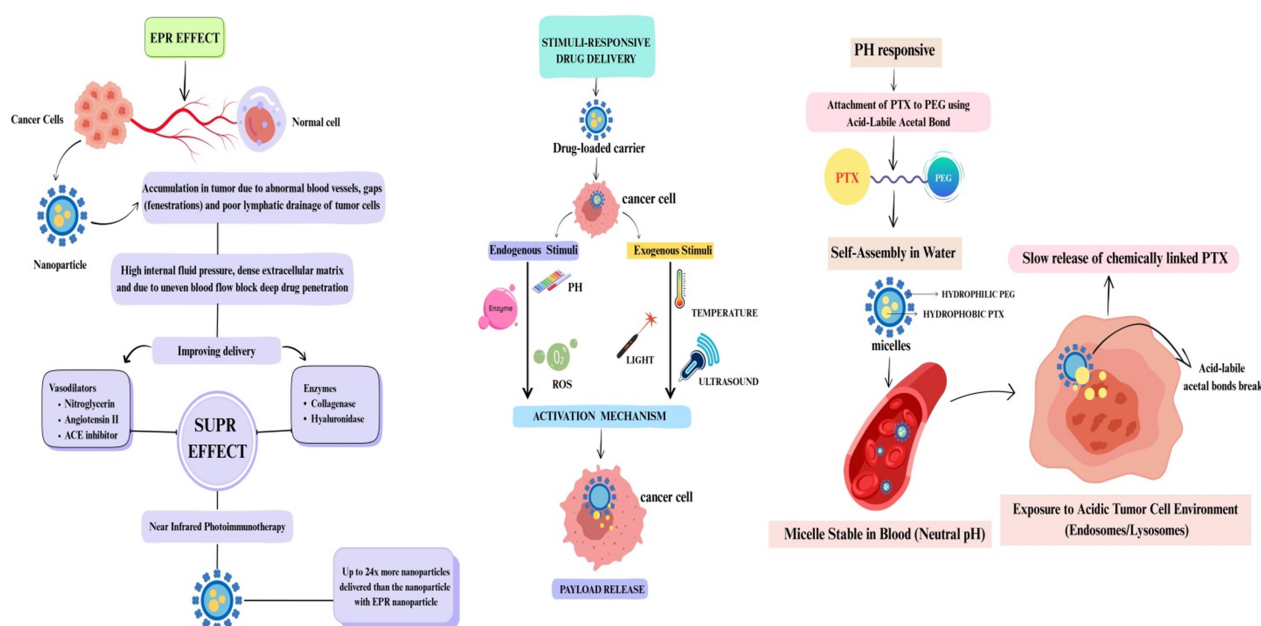


Figure 3: EPR effect, Stimuli responsive drug delivery, PH responsive.

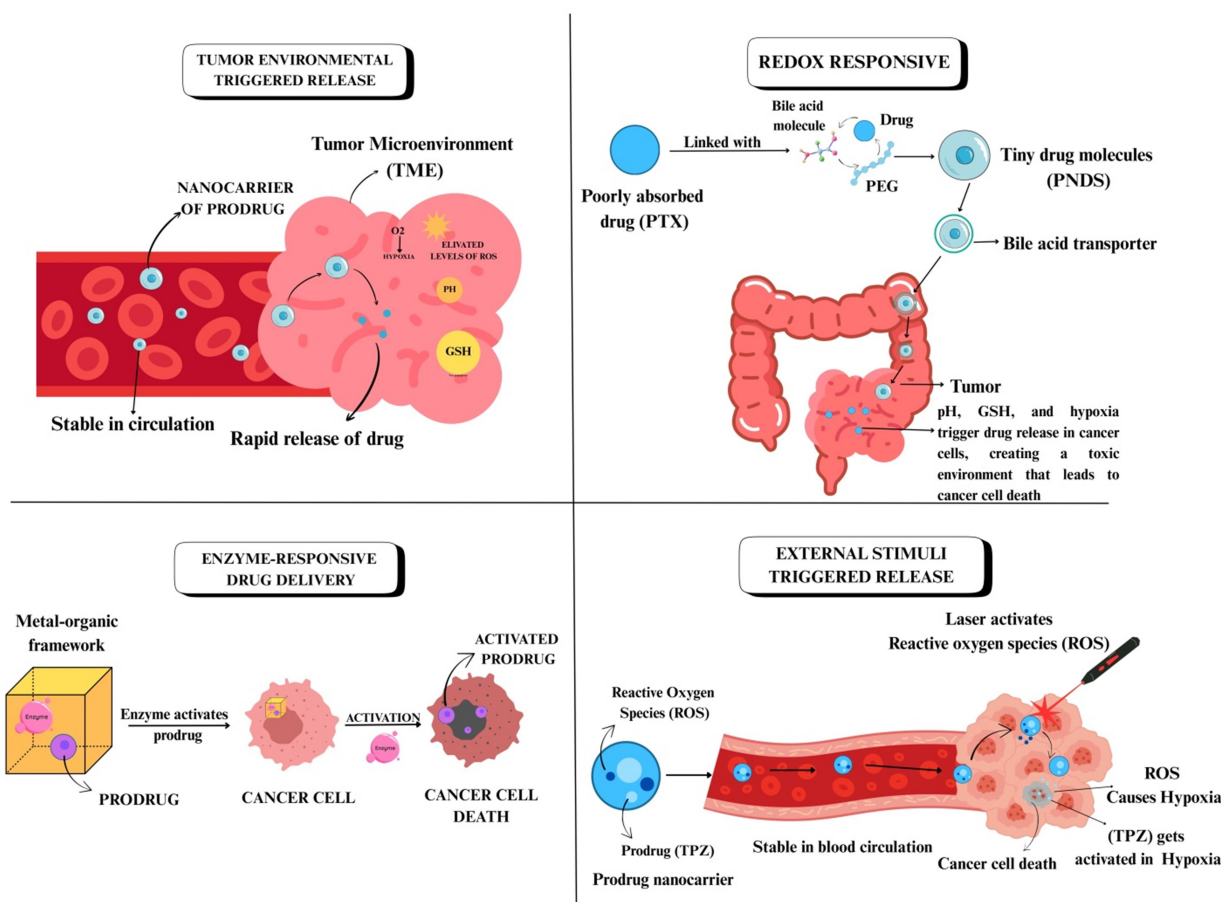


Figure 4: Tumor environmental triggered release

4. pH Responsive

Researchers have designed pH-responsive polymeric nanoparticles to deliver the chemotherapy drug paclitaxel (PTX) more effectively. They first attach PTX to polyethylene glycol (PEG) using an acid-sensitive (acid-labile) acetal bond, creating an amphiphilic prodrug molecule with both water-loving (hydrophilic) and water-fearing (hydrophobic) parts. Underwater conditions, these molecules spontaneously form micelles, which consist of hydrophilic shells made of PEG with hydrophobic cores, which contain paclitaxel. Free PTX may also be incorporated into the core to achieve increased drug loading. Under neutral pH conditions, such as in blood, the micelles remain stable and no drug release takes place. However, under acidic pH conditions (e.g., within the lumen of endosomes/lysosomes of tumor cells), the acetal linkages are cleaved, and therefore micelles disassemble. Free PTX is released instantly while chemically bound PTX is released gradually, providing biphasic and programmed drug release. It will ensure higher levels of drugs in tumor cells and thus improve their antitumor activity while lowering toxicity in normal tissue (Explained in Fig. 3) [41].

5. Enzyme Responsive

Researchers developed porous nanoparticles known as metal-organic frameworks (MOFs), which could hold both, an enzyme and a nontoxic drug-like substance, prodrug. The enzyme and prodrug were held in compartments of different sizes in order to avoid the premature reaction of these substances. It is possible for such particles to penetrate into cancer cells, where both an enzyme and a prodrug are released. After the penetration into cancer cells, the enzyme acts on the prodrug and changes its structure making it toxic and capable of killing cancer cells. Thus, the toxic drug appears inside cancer cells, which reduces negative side effects in other parts of the organism. Such MOF particles play an important role in protecting the enzyme and prodrug during transportation, as well as facilitating their action on cancer cells (Explained in Fig. 4) [42].

6. Redox Responsive

In this study, researchers have come up with a novel strategy for oral delivery of the anti-cancer agent paclitaxel (PTX), which was known to be highly challenging due to its poor solubility in water and limited intestinal absorption. Researchers modified PTX by attaching to it bile

acid and a PEG spacer, which resulted in formation of nanoparticles dissolving easily in the intestinal environment and capable of taking advantage of the unique transport protein (bile acid transporter) in the intestine. After entering the bloodstream, the modified drug passes into a tumor, where it detects high concentration of glutathione, which triggers decomposition of the molecule and release of the effective anti-cancer drug right in the spot of its action. This strategy increases absorption of PTX from the intestine and enhances tumor accumulation [43].

7. External Stimuli Triggered Release

This system incorporates specially engineered nanoparticles that are able to better target cancer cells because they can attack both oxygen-rich and oxygen-poor tumor cells. The nanoparticles are coated to stay stable in the bloodstream, but become activated in the slightly acidic environment of tumors, which makes them better at sticking to and getting inside cancer cells. Once inside the tumor, a laser is used to activate a photosensitizer in the particles, creating toxic reactive oxygen species that kill nearby tumor cells and eat up oxygen, making the area even more hypoxic (low in oxygen). This hypoxia causes the nanoparticles to break apart, releasing a second drug (e.g., Tirapazamine "TPZ") that becomes toxic specifically in low oxygen, allowing it to destroy hard-to-reach tumor cells deeper inside the tumor. Two therapies are delivered to these particles in a sequential manner: the laser-induced therapy is administered to cells that have more oxygen content, and the hypoxic-induced therapy is delivered to the cells having low oxygen content [44].

8. Multi-Stimuli Responsive

The delivery technology involves using unique nanoparticles that have been loaded with a cancer-fighting drug called SN38-7-ethyl-10-hydroxycamptothecin. The nanoparticles will only be stable in the bloodstream, and the drug will only be released when the particles get into the cancer cells. In this case, the nanoparticles are synthesized using unique chemical bonds like disulfide bonds and ester bonds. These bonds will remain intact under ordinary conditions but will be broken down when exposed to conditions in the tumor environment that are rich in glutathione (reducing agents), certain enzymes (esterase), and higher concentration of hydrogen peroxide. In this way, the internal conditions act as stimuli to the nanoparticles and cause the

breakdown of bonds leading to the release of the drug [45].

9. Active Targeting by Ligand

Here, the nanoparticles have a layer of folic acid coating, which works as the "key" or ligand that fits into specific "locks" or receptors known as folate receptors that exist on the surface of some cancer cells and special immune cells known as tumor-associated macrophages (TAMs). These folic acid-coated nanoparticles, when they arrive at the tumor site, interact with folate receptors (FOLR1 in case of tumor cells and FOLR2 in case of TAMs) through an interaction that is just like that of a key and its lock. Through this interaction, the nanoparticles get bound to these cells and can deliver cancer drugs present in their lumen to the desired cells [46].

10. Combination Therapy Mechanism

Prodrugs and nanocarriers combination therapy is based on the encapsulation of several drugs for killing cancer cells in the form of prodrugs into small nanoparticles that will transport them specifically to the target area of the disease development. Nanoparticles will be able to protect the loaded drugs while circulating in the bloodstream, thus increasing the delivery rate and decreasing the side effects caused by the treatment. After reaching the target site, the prodrugs will be converted back to the active form of the drugs due to the unique properties of the chemical environment inside or in the vicinity of the cancer cells [47].

11. Immunotherapy & Microenvironment Modulation

The concept of immune therapy in combination with the modification of tumor microenvironment is characterized by activation of the immune system in order to stimulate an attack on cancer cells along with changing the tumor microenvironment in order to make it more favorable for immune attack. In this case, special nanoparticles can deliver treatment to the tumor itself. The nanoparticles will contribute to the process of "awakening" immune cells, like dendritic cells and T-cells, in order to initiate an attack on cancer cells. At the same time, these nanoparticles are able to contribute to the modification of the tumor microenvironment through decreasing hypoxia and reducing the number of negative factors that can hinder immune attack on the tumor, like regulatory T cells and certain macrophages [48].

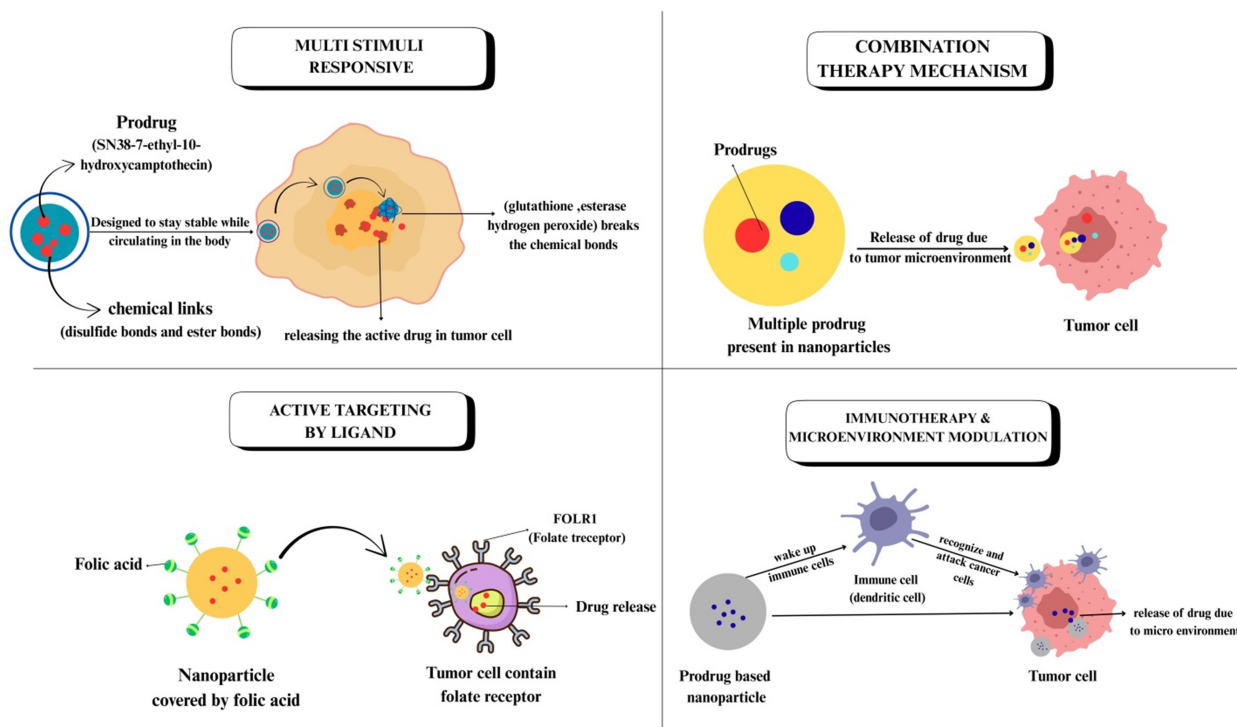


Figure 5: Multi stimuli responsive, Combination therapy mechanism, Active targeting, Immunotherapy & microenvironment modulation.

Morbidity State

1. Breast Cancer

Breast cancer is a cancer type that is characterized by certain epidemiology and a lot of variations and still remains one of the leading types causing deaths from cancer in women [49]. Within the scope of global health problems, breast cancer remains a strong opponent because of its complicated origin and various ways of manifestation that make it hard to prevent and treat effectively [50, 51]. The process of breast cancer development depends on many different factors and the interaction of various genetic, environmental, and lifestyle factors has been studied [52, 53]. Breast cancer constitutes about one-third of all women cancers around the world and causes the deaths of 15% of all diagnosed cases of this disease [54, 55]. A mutation in a single allele of a susceptibility gene with moderate to high penetrance (for example, BRCA1/2, CHEK2, PALB2, and TP53) is the basis of hereditary susceptibility to breast cancer. Tumor suppressor gene second allele deactivation would be an early step in this carcinogenic process. Hormonal factors [56]. Breast cancer susceptibility is linked to hormonal factors, including long-term intake of estrogen and reproductive history influenced by factors like abortion, absence of early periods for each year younger at menarche, and late

menopause. One of the main causes of breast cancer is prodrug-based nanoparticles [57, 58].

2. Lung Cancer

Two significant public health issues and concerns are lung cancer and chronic obstructive pulmonary disease (COPD). In 2020, lung cancer killed 1.8 million people globally, making up 18% of all cancer deaths, making it the cancer with the highest fatality rate [59]. The prevalence of COPD will continue to increase, making it the third most common cause of death globally. By 2060, COPD is predicted to claim the lives of almost 5.4 million people [60]. About 40–70% of patients with lung cancer also have COPD, and the majority of lung cancer patients are elderly and have a history of tobacco use [61]. Long-term smoking remains the main risk factor. Tyrosine kinase inhibitors for EGFR mutations and ALK or ROS1 translocations in advanced disease are now possible due to important discoveries in molecular changes in recent years, particularly in adenocarcinoma. Even though mutation testing for squamous cell carcinoma is not currently common practice, research is still being done to identify new therapeutic targets, including as ROS, MET, FGFR, DDR-2, and RET. This gives optimism that future patient prognoses may be improved by ongoing advancements in detection and therapy [62].

3. Brain Cancer

Because it is difficult to get adequate drug concentrations across the blood-brain barrier to tumor locations, central nervous system (CNS) malignancies are among the deadliest cancers. As a result, treatment advancements have been modest, and fatality rates have remained stable for decades. By improving drug bioavailability, facilitating increased BBB and BBTB penetration, and releasing medications precisely at tumor locations, supramolecular nanomedicines present promising alternatives that improve distribution and treatment outcomes. The clinical translation of these nanomedicine-based strategies is being actively investigated, with current research tackling important problems to increase the likelihood of curing these deadly tumors [63].

4. Pancreatic Cancer

The majority of individuals with pancreatic cancer appear at advanced, incurable, or metastatic stages, making it one of the top causes of cancer-related deaths. Improved surgical safety and the use of minimally invasive procedures have improved results for patients with localized disease, particularly when paired with multidisciplinary therapy. Improvements in systemic chemotherapy, such as its use as a neoadjuvant prior to surgery and in conjunction with radiation therapy, have begun to affect survival rates. Targeted medicines like PARP inhibitors and immune checkpoint inhibitors, which show encouraging results in a small number of patients, have been made possible by genomic testing for metastatic cases, which has also enhanced our understanding of tumor biology. A significant factor in pancreatic cancer is prodrug-based nanoparticles [64].

5. Colorectal Cancer

With approximately 1.85 million new instance and 850,000 deaths per year, colorectal cancer (CRC) is the third most common cause of cancer-related deaths globally. About 20% of CRC patients are diagnosed with metastatic disease, and another 25% who have localized disease eventually develop metastases. Systemic therapy, which may include immunotherapy, biologic treatments, chemotherapy, or combinations of these, is the primary treatment for metastatic colorectal cancer that cannot be cured. According to recent clinical trials, survival is increased when treatment is customized according to the molecular and pathological characteristics of the tumor, and genomic profiling aids in the

discovery of successful treatments. When used in conjunction with chemotherapy, the monoclonal antibodies cetuximab and panitumumab that target EGFR can increase median survival for patients with metastatic colorectal cancer (CRC) who have KRAS/NRAS/BRAF wild-type tumors by two to four months [65]. Three genetic pathways—chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP)—are the primary causes of colorectal cancer (CRC). APC, p53, and other important tumor suppressor genes are lost in CIN, along with alterations in the number of chromosomes. Defects in DNA mismatch repair genes cause genetic mutations and MSI. CIMP silences tumor suppressor genes by aberrant DNA methylation. Tumor growth is aided by epigenetic modifications and mutations in oncogenes like Kirsten rat sarcoma virus (KRAS) that interfere with critical cellular processes. The development of CRC is also influenced by non-coding RNAs, such as microRNAs. Knowing these processes makes it easier to understand how healthy colon cells can develop into cancer [66].

6. Ovarian Cancer

Despite being the third most prevalent gynecologic malignancy, ovarian cancer has the highest death rate. A multidisciplinary strategy combining radiologists, pathologists, medical oncologists, and gynecologic oncologists is necessary for effective care. Chemotherapy continues to be the primary treatment once all visible tumors are surgically removed (cytoreduction to R0). For women with epithelial ovarian cancer, genetic testing is routinely performed to direct treatment. Treatment is complicated because most patients recur, however maintenance therapy including bevacizumab, PARP inhibitors, and medications that target homologous recombination deficit improve results. Another promising treatment approach is immunotherapy [67].

With some now in clinical usage and others showing promising trial results, new cancer treatments like personalized medicine, immunotherapy, and nanomedicine are displaying a lot of promise. Immunotherapy, particularly immune checkpoint inhibitors, has demonstrated efficacy in tumor reduction and the treatment of resistant colorectal cancer, frequently competing with conventional therapies. Future colorectal cancer treatment is anticipated to significantly improve with the combination of immunotherapy and targeted medicines [68].

Ovarian cancer has at least five distinct histological subtypes, each with its own genetic profile, clinical features, cells of origin, risk factors, and available treatments. These main subtypes include endometrioid and mucinous carcinoma, clear cell carcinoma, low grade serous carcinoma, and high grade serous carcinoma. Worldwide, ovarian cancer is typically discovered at a late stage and is not well screened for. The usual course of treatment consists of platinum-based chemotherapy after cytoreductive surgery [69]. Since there are now no trustworthy screening techniques for ovarian cancer, effective early identification is still difficult. Preventive surgery, such as bilateral salpingo-oophorectomy, can lower the risk for high-risk patients, such as those with BRCA1/2 mutations. Transvaginal ultrasonography and the biomarker CA125 are the main screening tools for average-risk women. While they can identify early-stage malignancies, they haven't yet demonstrated a discernible improvement in mortality rates. Although they need more testing, emerging technologies like liquid biopsies, radiomics, and artificial intelligence have the potential to increase the accuracy of early detection [70, 71]. Platinum analogues (cisplatin or carboplatin) combined with a taxane (paclitaxel or docetaxel) are the most effective treatment agents for newly diagnosed ovarian cancer [72, 73].

7. Leukemia

According to the type of blood cells involved and the rate at which the disease progresses, leukemia is categorized by the World Health Organization (WHO). By separating leukemias into acute and chronic forms, as well as myeloid and lymphoid lineages, the 2016 WHO revision revised the categorization. Important subtypes of leukemia include acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia. Advanced genetic and molecular discoveries from next-generation sequencing were included into the update, improving myeloid neoplasm and acute leukemia diagnostic and treatment approaches [74].

Therapeutic Applications of Prodrug-Based Nanoparticles for Disease Management

1. Prodrug Based Nanoparticle in Breastcancer

A novel hyaluronic acidcoated glutathione (GSH) sensitive chitosan (CS)-derived nano-prodrug with aggregation-induced emission effects (AIE)

was created for the delivery of paclitaxel (PTX) in breast cancer treatment. These prodrug nanoparticles, with 29.32% drug loading and 105 nm size, exhibit excellent fluorescence stability and regular sphericity. They target tumor cells with high CD44 expression and decompose in the presence of high glutathione concentrations. *In vitro*, they show significant cytotoxicity against 4T1 cells and enable intracellular tracking due to their AIE properties. *In vivo* experiments demonstrated superior anti-tumor efficacy. Overall, Nanoparticles possess excellent bio-imaging capability and have potential as a nanomedicine to deliver PTX to treat breast cancer [75].

A docetaxel prodrug nanoparticle delivering ROR1 siRNA was constructed for synergistic therapy of triple-negative breast cancer (TNBC). BBRM effectively internalized by tumor cells facilitated endosomal escape to release DTX and siRNA, down regulating ROR1 protein expression, inhibiting tumor proliferation and metastasis, and reversing the immunosuppressive tumor microenvironment. In 4T1 tumor-bearing mice, BBRM targeted the lung tissues as well as tumor with high biosafety, attaining a 74.1% tumor inhibition rate and suppressing lung metastasis. This pioneering nanodevice integrates chemotherapy and RNA interference to improve TNBC therapeutic efficacy and offers a promising strategy for clinical translation [76].

2. Prodrug based Nanoparticle in Lung Cancer

Paclitaxel (PTX) prodrug-based, dual-drug-loaded, redox-sensitive lipid-polymer nanoparticles modified with the arginylglycylaspartic acid (RGD) peptide were created for targeted lung cancer treatment. With IC₅₀ values of 26.7 and 75.3 µg/mL for LPNs and free drug combinations, respectively, these nanoparticles, which are around 190 nm in size and have a zeta potential of -35 mV, demonstrated noticeably more anticancer activity than free pharmaceuticals. Nanoparticles were found to be less toxic systemically than the drugs themselves and reduced tumor sizes from 1486 mm³ to 263 mm³ in mice. In treating lung cancer, this method seems promising in terms of combined synergistic therapy [77].

Redox-sensitive pullulan/PTX-based prodrug nanoparticles surface-decorated with transferrin (TF) were developed to improve paclitaxel (PTX) therapy for lung cancer. These prodrug NPs

(>37% drug content, 134-163 nm) rapidly disassemble under reducing conditions for triggered drug release, showing excellent colloidal stability, cellular uptake, and selective cytotoxicity. In mouse models of melanoma lung metastasis and transferrin receptor-overexpressing Lewis lung carcinoma, these nanoparticles demonstrated enhanced tumor suppression and targeting efficiency compared to controls and Taxol, with reduced systemic toxicity. There is potential for intracellular PTX delivery toward metastatic lung cancer using this TF-engineered prodrug NP system [78].

A lipid-polymer hybrid nanoparticle coated with an aptamer was created to deliver cisplatin (DDP) and docetaxel prodrug (DTXp) in order to treat non-small cell lung cancers simultaneously. In comparison to their non-aptamer and single drug-loaded counterparts, these nanoparticles, which had a zeta potential of 15.9 ± 1.9 mV and a size of 213.5 ± 5.3 nm, demonstrated profound tumor inhibition (81.4% tumor inhibition ratio), a synergistic antitumor effect (combination index 0.62), and significantly increased cytotoxicity (IC₅₀ of 0.71 ± 0.09 µg/mL). This technique shows tremendous promise in preventing the development of lung carcinoma cells *in vivo* [79].

3. Prodrug based Nanoparticle in Brain Cancer

Hydrogel-based nanoparticles offer promise as new drug delivery systems for brain tumor therapy due to their prolonged blood circulation and targeted administration, which enhance survival rates. The blood-brain barrier can be successfully crossed by these nanoparticles because of their excellent physicochemical characteristics, delivering drugs directly to the tumor site, enhancing therapeutic outcomes, and minimizing side effects. The characterization, visualization, and modification techniques, along with current challenges and research opportunities. Future studies are encouraged to explore tailored hydrogels, hybrid systems, computational modelling, gene therapy, and immunotherapy integration. Addressing synthesis, stability, scalability, and cost issues is crucial to advancing clinical application of hydrogel-based nanoparticles in brain tumor treatment [80].

A Glutathione (GSH)-responsive and actively targeted nano prodrug delivery system, a **cyclic Arginine-Glycine-Aspartic acid** copolymer linked to doxorubicin and curcumin in nanoparticle (cRGD/PSDOX-Cur@NPs) was

developed for glioma treatment. It features a disulfide bond-bridged DOX prodrug (PEG-SS-DOX) that releases specifically in the high glutathione tumor environment, reducing DOX cardiotoxicity. Curcumin acts as a P-glycoprotein inhibitor to increase cellular DOX concentration and overcome resistance. (cRGD/PSDOX-Cur@NPs) shown the ability to treat subcutaneous and orthotopic gliomas while addressing resistance with systemic toxicity and exhibited synergistic anti-tumor actions *in vitro* as well as better BBB penetration and brain-targeting *in vivo* [81].

4. Prodrug based Nanoparticle in Pancreatic Cancer

For combined photoimmunotherapy of pancreatic cancer, a supramolecular prodrug nanopatform was created that co-delivers a photosensitizer and the prodrug JQ-1, which contains a protein 4 inhibitor (BRD4i). The host guest complexation of cyclodextrin-grafted hyaluronic acid and adamantine-conjugated pyropheophorbide a (PPa)-JQ1 heterodimers produced the nanoparticles, target tumors via HA binding to CD44. PPa-mediated photodynamic therapy enhances tumor immunogenicity and T cell infiltration, while JQ-1 inhibits c-Myc and PD-L1 expression to counteract immune evasion and glycolysis. This strategy enhances photoimmunotherapy by activating T cells and overcoming adaptive immune resistance in pancreatic cancer [82].

A nano-prodrug was developed to improve chemotherapy in pancreatic cancer (PC) by delivering three agents together: gemcitabine (GEM), all-trans retinoic acid (ATRA), and nitric oxide (NO) donors. The nano-prodrug is designed to target PC tumors and respond to the tumor environment by releasing ATRA, which calms activated pancreatic stellate cells to reduce dense tumor tissue (desmoplasia). At the same time, it produces (NO) to widen blood vessels and generate a "nanomotor" effect, enhancing drug penetration. This combined approach increases drug delivery and effectiveness, significantly inhibiting tumor growth in mouse PDAC models [83].

5. Prodrug based Nanoparticle in Colorectal Cancer

Fluoropyrimidine drugs are key parts of combination chemotherapy for colorectal cancer (CRC) and have improved survival by optimizing dose and delivery. To further increase effectiveness, new prodrugs and nano delivery

systems for Fluoropyrimidine drugs are being developed. This review highlights recent advancements in nano delivery approaches for Fluoropyrimidine drugs that show therapeutic potential. It covers established Fluoropyrimidine prodrug strategies like capecitabine, which use tumor-specific enzymes for better cancer treatment. It also discusses Fluoropyrimidine DNA-based polymers for delivering activated Fluoropyrimidine nucleotides, which have shown success in preclinical studies and potential for clinical use. Various nano delivery systems, including albumin-based delivery, mesoporous silica, emulsion nanoparticles, metal nanoparticles, hydrogels, liposomes, and lipid nanoparticles, show promise for colorectal cancer treatment. It is possible that fluoropyrimidine nano-delivery will soon enhance the treatment of colorectal cancer and patient survival [84].

By preventing cancer cell stemness, a targeted polymer prodrug nanoplatfrom was created to combat colorectal cancer chemoresistance (CRC) and recurrence. The platform uses hyaluronic acid (HA) for tumor targeting, α -cyan hydroxycinnamic acid (CHC) to inhibit monocarboxylic acid transporter 1 (MCT-1), and hydroxychloroquine sulphate (HCQ) to inhibit autophagy, all linked by pH-responsive ester bonds. Chitosan-derived conjugate self-assembled with mitochondria-targeting IR820 (T820) to form (CHH-T/NPs), which disrupt cellular metabolism and inhibit lactate transport, leading to mitochondrial dysfunction and stemness inhibition. HCQ blocks autophagy, disrupting CRC cells' self-protection. CHH-T/NPs successfully suppressed chemoresistance and tumor recurrence in CRC models, offering a promising strategy against CRC resistance and relapse [85].

6. Prodrug Based Nanoparticle in Leukemia

Researchers developed nanoparticles called SXP-NPs. These nanoparticles are decorated with two different leukemia-specific aptamers (which are short DNA or RNA molecules that can bind to specific targets). The two aptamers used are Sgc8c and XQ-2d. The nanoparticles also carry a special form of the anti-cancer drug podophyllotoxin (POD) that is linked in a way that it only releases the active drug inside cells that have a high concentration of reducing agents (this is called reduction-responsive). The nanoparticles also contain a molecule called 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-

polyethylene glycol -2000 (DSPE-PEG2000), which helps make them stable and biocompatible. The XQ-2d aptamer targets a receptor called CD71, and the Sgc8c aptamer targets a receptor called PTK7 (Protein Tyrosine Kinase 7). These receptors are found in higher amounts on different leukemia subtypes. So, by having both aptamers, the SXP-NPs can recognize and bind to many subtypes of leukemia cells after being injected into the bloodstream. Once inside the leukemia cells, the high-reduction environment triggers the release of the podophyllotoxin drug, which kills the cancer cells [86].

7. Prodrug based Nanoparticle in Ovarian Cancer

Maleimide-modified platinum (IV) [Pt(IV)] prodrug-loaded biodegradable polymeric nanoparticles. These nanoparticles enhance tumor targeting and accumulation in ovarian cancer models, improving therapeutic efficiency and reducing side effects compared to traditional cisplatin. They release the drug in response to high glutathione (GSH) levels inside tumor cells, helping overcome drug resistance and reduce toxicity, leading to significantly improved survival in ovarian cancer mouse models with peritoneal metastasis [87].

Cathepsin B-specific doxorubicin prodrug nanoparticles for intraperitoneal chemotherapy. These doxorubicin prodrug nanoparticles are activated enzymatically in ovarian cancer cells with high cathepsin B expression, allowing targeted drug release. Intraperitoneal administration showed effective tumor inhibition with minimal local and systemic toxicity in ovarian cancer with peritoneal carcinomatosis [88].

Hyaluronic acid-coated polymeric prodrug nanoparticles for paclitaxel delivery, a novel hyaluronic acid (HA) coated paclitaxel prodrug nanoparticle selectively targets CD44-expressing ovarian cancer cells, improving cytotoxicity, reducing cell proliferation, and increasing tumor apoptosis in models. It showed better efficacy than conventional paclitaxel formulations *in vivo*, offering a targeted delivery approach to ovarian cancer [89].

Platinum (IV) prodrug-loaded phase-transitional nanoparticles with ultrasound responsiveness, these nanoparticles combine platinum (IV) prodrugs with ultrasound-triggered drug release

and tumor targeting to increase efficacy and reduce toxicity in ovarian cancer treatment. They induce mitochondrial apoptosis by enhancing reactive oxygen species (ROS) levels and show promise in precise theranostics against ovarian cancer [90].

Development and Scalability Challenges

The main drawback to the clinical translation of prodrug-based nanoparticles is that they are difficult to manufacture at an industrial scale due to the multistep chemical synthesis, strict control over reaction conditions, and advanced purification processes required for these systems; batch-to-batch reproducibility can be a significant challenge especially with self-assembled systems where slight variations in conditions can have dramatic effects on particle size, drug-loading, and stability [91]. The successful scale-up of mRNA lipid nanoparticle vaccines during the (COVID-19) pandemic, shows that the pharmaceutical industry has made great strides in tackling these issues. This experience has shown that, with the right investment in process development and quality control systems, complex nanoparticle systems can be produced on a global scale [92].

Current Limitations

Despite their potential, prodrug-based nanoparticles have several significant issues that must be fixed before they can be applied extensively in therapeutic settings. High development and production costs arise due to the complexity of the manufacturing process which requires specialist knowledge, high-level facilities, and quality control measures [93]. The complexities and high cost of the manufacturing process which involve the use of exact chemical synthesis and quality control processes are some of the current limitations of nanoparticles using prodrugs. Drugs that are released early before reaching the desired destination are less effective and can cause systemic effects. These nanoparticles are also unable to penetrate into the fibrotic and dense tumor tissue effectively. The use of the new nanoparticle materials can bring about immune response especially after multiple doses. Over time, certain non-biodegradable substances may build up in the body and present safety hazards. Finally, clinical development can be delayed and costs can rise due to unclear and changing regulatory pathways. In order to make prodrug-based nanoparticles practical and efficient for wider

therapeutic applications, these issues must be resolved [94].

Current Clinical Successes

Prodrug-based approaches are most successful clinically in the area of antibody-drug conjugates (ADCs), with some FDA-approved drugs displaying clear advantages for treatment. Although it was pulled from the market because of safety issues and later reintroduced with better indications, gemtuzumab ozogamicin, the first-ever FDA-approved ADC, demonstrated a 30% response rate in patients suffering from relapsed acute myeloid leukemia. ADCs have become a significant choice for treatment in oncology since the approval of such ADCs as brentuximab vedotin (response rate of 54%), inotuzumab ozogamicin (response rate of 57%), and enfortumab vedotin (response rate of 44%). [95-98].

Future Perspectives and Emerging Trends

1. Artificial Intelligence (AI) and Machine Learning (ML) Applications

The combination of AI and machine learning accelerates prodrug nanoparticle development by enabling the identification of promising drug-linker combinations, predicting optimal prodrug structures, and optimizing nanoparticle properties for specific therapeutic applications. In order to identify patterns and design principles that are difficult to locate using conventional approaches, machine learning algorithms examine enormous databases of chemical structures and biological activity. This leads to improved stability, targeting accuracy, controlled release, and personalization in drug delivery, ultimately enhancing therapeutic efficiency and reducing development time [99].

2. Personalized Medicine Applications

Prodrug nanoparticle technology is well suited for personalized medicine approach owing to its modularity and tunability, which enables the consideration of patient-specific variables like pharmacokinetics, gene signature, and tumor enzymes profile during the selection of appropriate prodrugs for the individual patients. The nanotheranostics approach is a combination of diagnosis and treatment in a single nanotechnology system that makes it very attractive for personalized medicine. Since cancer treatment must be tailored to individual patients' specific biomolecules, nanotheranostics help identify biomarkers noninvasively and deliver targeted therapy based on these

biomarkers. While still developing, such approaches hold great potential to improve diagnosis, treatment, and monitoring in personalized cancer care [100].

Developing Infrastructure for Nanotechnology

Clinical application is limited by the drawbacks of nanoparticles (NPs) as drug delivery vehicles, including their low biocompatibility, poor physiological stability, quick elimination, and nonspecific targeting. One intriguing method to get around this is the biofilm-mediated biomimetic nanodrug delivery system (BNDDS). BNDDS uses bionanotechnology to encapsulate synthetic NPs within biomimetic membranes derived from biofilms. The adaptability and versatility of the nanocarrier are combined with the biofilm's excellent biocompatibility, effective tumor targeting, low toxicity, and minimal immunogenicity [101]. By increasing tumor targeting and drug delivery effectiveness, BNDDS demonstrates prospective uses in precision tumor therapy. Recent progress in BNDDS optimizes drug delivery and aims to design safe, effective therapeutic approaches to enhance the results of tumor therapy¹⁰¹. Therapeutic living systems, including the use of cell delivery vectors or genetically engineered bacteria, can further enhance control of prodrug activation and administration by combining the specificity of biological systems with controlled release features of prodrug chemistry [102].

CONCLUSION

Nanoparticle-based delivery of prodrugs offers an innovative and versatile strategy to improve the accuracy and efficiency of anticancer drugs. The use of the prodrug activation process combined with the targeted delivery of nanotechnology systems enables overcoming many limitations of classical chemotherapy treatments, such as poor solubility, lack of tumor selectivity, side effects and multidrug resistance. Tumor-selective stimuli, including enzymes, pH level, hypoxia, and external stimulus, allow regulating the drug release according to both time and space principles. Modern progress in nanotechnology has widened the possibilities of developing multifunctional and multidrug-delivery systems, multimodal approaches and nanoparticles able to modulate the tumor microenvironment to improve immunotherapy outcomes. Despite the great success of such developments, there are still major difficulties associated with mass production, long-term

safety, heterogeneity of tumors in terms of tissue penetration, and regulatory issues. These difficulties can be addressed through interdisciplinary research and appropriate formulation design. In general, the merging of prodrugs and nanotechnology can offer significant opportunities for cancer therapy. Further innovations, driven by material science and bioengineering advances, could result in novel drugs that will be able to target cancer cells and kill them, but not harm other parts of patients' bodies, which means improved patient quality of life and new, more effective cancer therapy techniques.

REFERENCES

- [1] Brown JS, Amend SR, Austin RH, Gatenby RA, Hammarlund EU, Pienta KJ. Updating the Definition of Cancer. *Mol Cancer Res.* 2023 Nov 1;21(11):1142-1147. doi: 10.1158/1541-7786.MCR-23-0411. PMID: 37409952; PMCID: PMC10618731.
- [2] Piña-Sánchez P, Chávez-González A, Ruiz-Tachiquín M, Vadillo E, Monroy-García A, Montesinos JJ, Grajales R, Gutiérrez de la Barrera M, Mayani H. Cancer Biology, Epidemiology, and Treatment in the 21st Century: Current Status and Future Challenges From a Biomedical Perspective. *Cancer Control.* 2021 Jan-Dec; 28:10732748211038735. doi: 10.1177/10732748211038735. PMID: 34565215; PMCID: PMC8481752.
- [3] Spagnolo F, Brugiapaglia S, Perin M, Intonti S, Curcio C. Anti-Cancer Drugs: Trends and Insights from PubMed Records. *Pharmaceutics.* 2025 May 4;17(5):610. doi: 10.3390/pharmaceutics17050610. PMID: 40430901; PMCID: PMC12115157.
- [4] Morales-Cruz M, Delgado Y, Castillo B, Figueroa CM, Molina AM, Torres A, Milián M, Griebenow K. Smart Targeting To Improve Cancer Therapeutics. *Drug Des Devel Ther.* 2019 Oct 30;13:3753-3772. doi: 10.2147/DDDT.S219489. PMID: 31802849; PMCID: PMC6826196.
- [5] Abujamous L, Soltani A, Al-Thawadi H, Agouni A. Advances in nanotechnology-enabled drug delivery for combining PARP inhibitors and immunotherapy in advanced ovarian cancer. *Biomol Biomed.* 2024 Mar 11;24(2):230-237. doi: 10.17305/bb.2023.9757. PMID: 38231530; PMCID: PMC10950340.
- [6] Wang B, Hu S, Teng Y, Chen J, Wang H, Xu Y, Wang K, Xu J, Cheng Y, Gao X. Current

- advance of nanotechnology in diagnosis and treatment for malignant tumors. *Signal Transduct Target Ther.* 2024 Aug 12;9(1):200. doi: 10.1038/s41392-024-01889-y. PMID: 39128942; PMCID: PMC11323968.
- [7] Gavas S, Quazi S, Karpiński TM. Nanoparticles for Cancer Therapy: Current Progress and Challenges. *Nanoscale Res Lett.* 2021 Dec 5;16(1):173. doi: 10.1186/s11671-021-03628-6. PMID: 34866166; PMCID: PMC8645667.
- [8] Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. *J Nanobiotechnology.* 2022 Jun 7;20(1):262. doi: 10.1186/s12951-022-01477-8. PMID: 35672712; PMCID: PMC9171489.
- [9] Giang I, Boland EL, Poon GM. Prodrug applications for targeted cancer therapy. *AAPS J.* 2014 Sep;16(5):899-913. doi: 10.1208/s12248-014-9638-z. Epub 2014 Jul 9. PMID: 25004822; PMCID: PMC4147050.
- [10] Wang W, Fan J, Zhu G, Wang J, Qian Y, Li H, Ju J, Shan L. Targeted Prodrug-Based Self-Assembled Nanoparticles for Cancer Therapy. *Int J Nanomedicine.* 2020 Apr 24;15:2921-2933. doi: 10.2147/IJN.S247443. PMID: 32425524; PMCID: PMC7187935.
- [11] Wu KM. A New Classification of Prodrugs: Regulatory Perspectives. *Pharmaceuticals (Basel).* 2009 Oct 14;2(3):77-81. doi: 10.3390/ph2030077. PMID: 27713225; PMCID: PMC3978533.
- [12] Shah K, Gupta JK, Chauhan NS, Upmanyu N, Shrivastava SK, Mishra P. Prodrugs of NSAIDs: A Review. *Open Med Chem J.* 2017 Nov 30;11:146-195. doi: 10.2174/1874104501711010146. PMID: 29387273; PMCID: PMC5748882.
- [13] Markovic M, Ben-Shabat S, Dahan A. Prodrugs for Improved Drug Delivery: Lessons Learned from Recently Developed and Marketed Products. *Pharmaceutics.* 2020 Oct 29;12(11):1031. doi: 10.3390/pharmaceutics12111031. PMID: 33137942; PMCID: PMC7692606.
- [14] Tu Y, Gong J, Mou J, Jiang H, Zhao H, Gao J. Strategies for the development of stimuli-responsive small molecule prodrugs for cancer treatment. *Front Pharmacol.* 2024 Jul 31;15:1434137. doi: 10.3389/fphar.2024.1434137. PMID: 39144632; PMCID: PMC11322083.
- [15] Mahato R, Tai W, Cheng K. Prodrugs for improving tumor targetability and efficiency. *Adv Drug Deliv Rev.* 2011 Jul 18;63(8):659-70. doi: 10.1016/j.addr.2011.02.002. Epub 2011 Feb 17. PMID: 21333700; PMCID: PMC3132824.
- [16] Wang H, Monroe M, Leslie F, Flexner C, Cui H. Supramolecular nanomedicines through rational design of self-assembling prodrugs. *Trends Pharmacol Sci.* 2022 Jun;43(6):510-521. doi: 10.1016/j.tips.2022.03.003. Epub 2022 Apr 19. PMID: 35459589; PMCID: PMC9106924.
- [17] Chen KJ, Plaunt AJ, Leifer FG, Kang JY, Cipolla D. Recent advances in prodrug-based nanoparticle therapeutics. *Eur J Pharm Biopharm.* 2021 Aug;165:219-243. doi: 10.1016/j.ejpb.2021.04.025. Epub 2021 May 9. PMID: 33979661.
- [18] Junyaprasert VB, Thummarati P. Innovative Design of Targeted Nanoparticles: Polymer-Drug Conjugates for Enhanced Cancer Therapy. *Pharmaceutics.* 2023 Aug 27;15(9):2216. doi: 10.3390/pharmaceutics15092216. PMID: 37765185; PMCID: PMC10537251.
- [19] Li G, Sun B, Li Y, Luo C, He Z, Sun J. Small-Molecule Prodrug Nanoassemblies: An Emerging Nanoplatfrom for Anticancer Drug Delivery. *Small.* 2021 Dec;17(52):e2101460. doi: 10.1002/sml.202101460. Epub 2021 Aug 3. PMID: 34342126.
- [20] Wang J, Xu P, Zhang Y, Han S, Wang G, Wang H, Song H, Li S. Dynamic nanoassemblies derived from small-molecule homodimeric prodrugs for *in situ* drug activation and safe osteosarcoma treatment. *iScience.* 2023 Jul 17;26(8):107409. doi: 10.1016/j.isci.2023.107409. PMID: 37554455; PMCID: PMC10404730.
- [21] Liu P, Huang Y, Zhan C, Zhang F, Deng C, Jia Y, Wan T, Wang S, Li B. Tumor-overexpressed enzyme responsive amphiphiles small molecular self-assembly nano-prodrug for the chemo-phototherapy against non-small-cell lung cancer. *Mater Today Bio.* 2023 Jul 4;21:100722. doi: 10.1016/j.mtbio.2023.100722. PMID: 37545562; PMCID: PMC10401344.

- [22] Wang H, Lu Z, Wang L, Guo T, Wu J, Wan J, Zhou L, Li H, Li Z, Jiang D, Song P, Xie H, Zhou L, Xu X, Zheng S. New Generation Nanomedicines Constructed from Self-Assembling Small-Molecule Prodrugs Alleviate Cancer Drug Toxicity. *Cancer Res.* 2017 Dec 15;77(24):6963-6974. doi: 10.1158/0008-5472.CAN-17-0984. Epub 2017 Oct 20. PMID: 29055017.
- [23] Xu P, Meng F, Wan J, Zhu H, Fang S, Wang H. Hybrid Homodimeric Prodrug Nanoassemblies for Low-Toxicity and Synergistic Chemophotodynamic Therapy of Melanoma. *Biomater Res.* 2024 Nov 1;28:0101. doi: 10.34133/bmr.0101. PMID: 39492977; PMCID: PMC11529783.
- [24] Linlin Shi, a Shanshan Lin, Fengping Zhou, a Hao Jianga and Jin Zhang a. Recent advances in engineering prodrug-based nanomedicines for cancer therapy. *Mater. Adv.* 2024, 5, 4634. Doi: DOI: 10.1039/d3ma01132a
- [25] Zhang Y, Cui H, Zhang R, Zhang H, Huang W. Nanoparticulation of Prodrug into Medicines for Cancer Therapy. *Adv Sci (Weinh).* 2021 Sep;8(18):e2101454. doi: 10.1002/advs.202101454. Epub 2021 Jul 29. PMID: 34323373; PMCID: PMC8456229.
- [26] Luo C, Sun J, Sun B, He Z. Prodrug-based nanoparticulate drug delivery strategies for cancer therapy. *Trends Pharmacol Sci.* 2014 Nov;35(11):556-66. doi: 10.1016/j.tips.2014.09.008. Epub 2014 Oct 16. PMID: 25441774.
- [27] Cui T, Zhang S, Sun H. Co-delivery of doxorubicin and pH-sensitive curcumin prodrug by transferrin-targeted nanoparticles for breast cancer treatment. *Oncol Rep.* 2017 Feb;37(2):1253-1260. doi: 10.3892/or.2017.5345. Epub 2017 Jan 2. PMID: 28075466.
- [28] Zhang Q, Kuang G, He S, Lu H, Cheng Y, Zhou D, Huang Y. Photoactivatable Prodrug-Backboned Polymeric Nanoparticles for Efficient Light-Controlled Gene Delivery and Synergistic Treatment of Platinum-Resistant Ovarian Cancer. *Nano Lett.* 2020 May 13;20(5):3039-3049. doi: 10.1021/acs.nanolett.9b04981. Epub 2020 Apr 9. PMID: 32250633.
- [29] Xie A, Hanif S, Ouyang J, Tang Z, Kong N, Kim NY, Qi B, Patel D, Shi B, Tao W. Stimuli-responsive prodrug-based cancer nanomedicine. *EBioMedicine.* 2020 Jun;56:102821. doi: 10.1016/j.ebiom.2020.102821. Epub 2020 Jun 7. PMID: 32505922; PMCID: PMC7280365.
- [30] Dong X, Brahma RK, Fang C, Yao SQ. Stimulus-responsive self-assembled prodrugs in cancer therapy. *Chem Sci.* 2022 Mar 18;13(15):4239-4269. doi: 10.1039/d2sc01003h. PMID: 35509461; PMCID: PMC9006903.
- [31] Gurunathan S, Kang MH, Qasim M, Kim JH. Nanoparticle-Mediated Combination Therapy: Two-in-One Approach for Cancer. *Int J Mol Sci.* 2018 Oct 20;19(10):3264. doi: 10.3390/ijms19103264. PMID: 30347840; PMCID: PMC6214025.
- [32] Zhang RX, Wong HL, Xue HY, Eoh JY, Wu XY. Nanomedicine of synergistic drug combinations for cancer therapy - Strategies and perspectives. *J Control Release.* 2016 Oct 28;240:489-503. doi: 10.1016/j.jconrel.2016.06.012. Epub 2016 Jun 8. PMID: 27287891; PMCID: PMC5064882.
- [33] Hairui Wang, Yongzhuo Huang. Combination Therapy Based on Nano Codelivery for Overcoming Cancer Drug Resistance. *March 2020 Medicine in Drug Discovery* 6:100024. DOI:10.1016/j.medidd.2020.100024.
- [34] Jadia R, Scandore C, Rai P. Nanoparticles for Effective Combination Therapy of Cancer. *Int J Nanotechnol Nanomed.* 2016; Epub 2016 Oct 30. PMID: 28540369; PMCID: PMC5439947.
- [35] Nakamura Y, Mochida A, Choyke PL, Kobayashi H. Nanodrug Delivery: Is the Enhanced Permeability and Retention Effect Sufficient for Curing Cancer? *Bioconj Chem.* 2016 Oct 19;27(10):2225-2238. doi: 10.1021/acs.bioconjchem.6b00437. Epub 2016 Sep 2. PMID: 27547843; PMCID: PMC7397928.
- [36] Maeda H, Nakamura H, Fang J. The EPR effect for macromolecular drug delivery to solid tumors: Improvement of tumor uptake, lowering of systemic toxicity, and distinct tumor imaging *in vivo*. *Adv Drug Deliv Rev.* 2013 Jan;65(1):71-9. doi: 10.1016/j.addr.2012.10.002. Epub 2012 Oct 23. PMID: 23088862.
- [37] Wu J. The Enhanced Permeability and Retention (EPR) Effect: The Significance of the Concept and Methods to Enhance Its Application. *J Pers Med.* 2021 Aug

- 6;11(8):771. doi: 10.3390/jpm11080771. PMID: 34442415; PMCID: PMC8402171.
- [38] Rahim MA, Jan N, Khan S, Shah H, Madni A, Khan A, Jabar A, Khan S, Elhissi A, Hussain Z, Aziz HC, Sohail M, Khan M, Thu HE. Recent Advancements in Stimuli Responsive Drug Delivery Platforms for Active and Passive Cancer Targeting. *Cancers (Basel)*. 2021 Feb 7;13(4):670. doi: 10.3390/cancers13040670. PMID: 33562376; PMCID: PMC7914759.
- [39] Thomas RG, Surendran SP, Jeong YY. Tumor Microenvironment-Stimuli Responsive Nanoparticles for Anticancer Therapy. *Front Mol Biosci*. 2020 Dec 18;7:610533. doi: 10.3389/fmolb.2020.610533. Erratum in: *Front Mol Biosci*. 2021 May 06;8:693909. doi: 10.3389/fmolb.2021.693909. PMID: 33392264; PMCID: PMC7775573.
- [40] Saiqa Imtiaz, Umme Tamanna Ferdous, Alexis Nizela, Anwarul Hasan. Mechanistic Study of Cancer Drug Delivery: Current Techniques, Limitations, and Future Prospects. *March 2025 European Journal of Medicinal Chemistry* 290(2):117535. DOI:10.1016/j.ejmech.2025.117535
- [41] Huang D, Zhuang Y, Shen H, Yang F, Wang X, Wu D. Acetal-linked PEGylated paclitaxel prodrugs forming free-paclitaxel-loaded pH-responsive micelles with high drug loading capacity and improved drug delivery. *Mater Sci Eng C Mater Biol Appl*. 2018 Jan 1;82:60-68. doi: 10.1016/j.msec.2017.08.063. Epub 2017 Aug 17. PMID: 29025675.
- [42] Fan Wang, Jian Yang, Yongsheng Li, Qixin Zhuang. Efficient enzyme-activated therapy based on the different location of protein and prodrug in nanoMOFs. *June 2020 Journal of Materials Chemistry B* 8(28). DOI:10.1039/D0TB01004A
- [43] Lu X, Wu H, Liang Y, Zhang Z, Lv H. Redox-responsive prodrug for improving oral bioavailability of paclitaxel through bile acid transporter-mediated pathway. *Int J Pharm*. 2021 May 1;600:120496. doi: 10.1016/j.ijpharm.2021.120496. Epub 2021 Mar 19. PMID: 33746013.
- [44] [44] Ihsanullah KM, Kumar BN, Zhao Y, Muhammad H, Liu Y, Wang L, Liu H, Jiang W. Stepwise-activatable hypoxia triggered nanocarrier-based photodynamic therapy for effective synergistic bio-reductive chemotherapy. *Biomaterials*. 2020 Jul;245:119982. doi: 10.1016/j.biomaterials.2020.119982. Epub 2020 Mar 18. PMID: 32224374.
- [45] Xun Liu, ab Qian Huang, ab Caixia Yang, abc Qianzhi Zhang, ab Wan Chen, ab Youqing Shen and Meihua Sui*ba. A multi-stimuli responsive nanoparticulate SN38 prodrug for cancer chemotherapy. *Cite this: J. Mater. Chem. B*, 2017. 5, 661. Received 2nd September 2016, Accepted 14th November 2016 DOI: 10.1039/c6tb02262f
- [46] Moharil P, Wan Z, Pardeshi A, Li J, Huang H, Luo Z, Rathod S, Zhang Z, Chen Y, Zhang B, Fernandez CA, Sun J, Li S. Engineering a folic acid-decorated ultrasmall gemcitabine nanocarrier for breast cancer therapy: Dual targeting of tumor cells and tumor-associated macrophages. *Acta Pharm Sin B*. 2022 Mar;12(3):1148-1162. doi: 10.1016/j.apsb.2021.09.024. Epub 2021 Sep 30. PMID: 35530140; PMCID: PMC9072252.
- [47] Lin MH, Hung CF, Hsu CY, Lin ZC, Fang JY. Prodrugs in combination with nanocarriers as a strategy for promoting antitumoral efficiency. *Future Med Chem*. 2019 Aug;11(16):2131-2150. doi: 10.4155/fmc-2018-0388. PMID: 31538520.
- [48] Chen B, Guo K, Zhao X, Liu Z, Xu C, Zhao N, Xu FJ. Tumor microenvironment-responsive delivery nanosystems reverse immunosuppression for enhanced CO gas/immunotherapy. *Exploration (Beijing)*. 2023 Jul 27;3(6):20220140. doi: 10.1002/EXP.20220140. PMID: 38264682; PMCID: PMC10742199.
- [49] Xiong X, Zheng LW, Ding Y, Chen YF, Cai YW, Wang LP, Huang L, Liu CC, Shao ZM, Yu KD. Breast cancer: pathogenesis and treatments. *Signal Transduct Target Ther*. 2025 Feb 19;10(1):49. doi: 10.1038/s41392-024-02108-4. PMID: 39966355; PMCID: PMC11836418.
- [50] Giaquinto, A. N. et al. Breast cancer statistics, 2022. *CA Cancer J. Clin.* 72, 524–541 (2022).
- [51] Loibl, S., Poortmans, P., Morrow, M., Denkert, C. & Curigliano, G. Breast cancer. *Lancet* 397, 1750–1769 (2021).
- [52] Hickey, M. et al. Managing menopause after cancer. *Lancet* 403, 984–996 (2024).
- [53] Hu, C. et al. A population-based study of genes previously implicated in breast cancer. *N. Engl. J. Med.* 384, 440–451 (2021).

- [54] Siegel, R. L., Giaquinto, A. N. & Jemal, A. Cancer statistics, 2024. *CA Cancer J. Clin.* 74, 12–49 (2024).
- [55] Xu, Y. et al. Global trends and forecasts of breast cancer incidence and deaths. *Sci. Data* 10, 334 (2023).
- [56] Cui, Y. et al. Associations of hormone-related factors with breast cancer risk according to hormone receptor status among white and African American women. *Clin. Breast Cancer* 14, 417–425 (2014).
- [57] Huang, Y. et al. A meta-analysis of the association between induced abortion and breast cancer risk among Chinese females. *Cancer Causes Control* 25, 227–236 (2014).
- [58] Łukasiewicz S, Czezelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. *Cancers (Basel)*. 2021 Aug 25;13(17):4287. doi: 10.3390/cancers13174287. PMID: 34503097; PMCID: PMC8428369.
- [59] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209–49.
- [60] Liang ZY, Chen RC. Revision to the guidelines for the diagnosis and management of chronic obstructive pulmonary disease (revised version 2021): process and perspective. *Zhonghua Jie He He Hu Xi Za Zhi* 2021;44:165-6.
- [61] Miao JL, Cai JJ, Qin XF, et al. Analysis of the Clinicopathological Characteristics and Risk Factors in Patients with Lung Cancer and Chronic Obstructive Pulmonary Disease. *Biomed Res Int* 2018;2018:8398156.
- [62] Smolarz B, Łukasiewicz H, Samulak D, Piekarska E, Kołaciński R, Romanowicz H. Lung Cancer-Epidemiology, Pathogenesis, Treatment and Molecular Aspect (Review of Literature). *Int J Mol Sci*. 2025 Feb 26;26(5):2049. doi: 10.3390/ijms26052049. PMID: 40076671; PMCID: PMC11900952.
- [63] Quader S, Kataoka K, Cabral H. Nanomedicine for brain cancer. *Adv Drug Deliv Rev*. 2022 Mar;182:114115. doi: 10.1016/j.addr.2022.114115. Epub 2022 Jan 22. PMID: 35077821.
- [64] Kolbeinsson HM, Chandana S, Wright GP, Chung M. Pancreatic Cancer: A Review of Current Treatment and Novel Therapies. *J Invest Surg*. 2023 Dec 31;36(1):2129884. doi: 10.1080/08941939.2022.2129884. Epub 2022 Oct 3. PMID: 36191926.
- [65] Biller LH, Schrag D. Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. *JAMA*. 2021 Feb 16;325(7):669–685. doi: 10.1001/jama.2021.0106. PMID: 33591350.
- [66] Baidoun F, Elshiwiy K, Elkerai Y, Merjaneh Z, Khoudari G, Sarmini MT, Gad M, Al-Husseini M, Saad A. Colorectal Cancer Epidemiology: Recent Trends and Impact on Outcomes. *Curr Drug Targets*. 2021;22(9):998-1009. doi: 10.2174/1389450121999201117115717. PMID: 33208072.
- [67] Kuroki L, Guntupalli SR. Treatment of epithelial ovarian cancer. *BMJ*. 2020 Nov 9;371:m3773. doi: 10.1136/bmj.m3773. PMID: 33168565.
- [68] Abedizadeh R, Majidi F, Khorasani HR, Abedi H, Sabour D. Colorectal cancer: a comprehensive review of carcinogenesis, diagnosis, and novel strategies for classified treatments. *Cancer Metastasis Rev*. 2024 Jun;43(2):729-753. doi: 10.1007/s10555-023-10158-3. Epub 2023 Dec 19. PMID: 38112903.
- [69] Matulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. *Nat Rev Dis Primers*. 2016 Aug 25;2:16061. doi: 10.1038/nrdp.2016.61. PMID: 27558151; PMCID: PMC7290868.
- [70] Menon U et al. Risk algorithm using serial biomarker measurements doubles the number of screen-detected cancers compared with a single-threshold rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. *J. Clin. Oncol* 33, 2062–2071 (2015). [PubMed: 25964255]
- [71] Jacobs IJ et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet* 387, 945–956 (2016). [PubMed: 26707054]
- [72] McGuire WP et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N. Engl. J. Med* 334, 1–6 (1996). [PubMed: 7494563] This trial was the first to demonstrate a PFS and overall survival benefit of the addition of paclitaxel to platinum therapy, thereby helping to

- establish the standard of care of a platinum plus taxane chemotherapy regimen for newly diagnosed ovarian cancer.
- [73] Vasey PA et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J. Natl Cancer Inst* 96, 1682-1691 (2004). [PubMed: 15547181]
- [74] Chennamadhavuni A, Iyengar V, Mukkamalla SKR, Shimanovsky A. Leukemia. 2023 Jan 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. PMID: 32809325.
- [75] Weiwei Ma, *Qiufeng Zhao, Shilong Zhu, Xinyue Wang, Chuangchuang Zhang, Daming Ma, Na Li* and Yanyan Yin*, Construction of glutathione-responsive paclitaxel prodrug nanoparticles for image-guided targeted delivery and breast cancer therapy. *RSC Adv.*,2024,14,12796, DOI: 10.1039/d4ra00610k
- [76] Yin L, Fu Z, Wang M, Liu B, Sun X, Liu K, Feng X, He Z, Wang Y, Hou J, Shao X, Yang N, Zhang T, Liu Y, Huang Z, Yin Q, Xie Y, Li Y, Lang T. A prodrug nanodevice co-delivering docetaxel and ROR1 siRNA for enhanced triple negative breast cancer therapy. *Acta Biomater.* 2025 Jan 24;193:498-513. doi: 10.1016/j.actbio.2024.12.055. Epub 2024 Dec 25. PMID: 39730101.
- [77] Zhao X, Guo H, Bera H, Jiang H, Chen Y, Guo X, Tian X, Cun D, Yang M. Engineering Transferrin-Decorated Pullulan-Based Prodrug Nanoparticles for Redox Responsive Paclitaxel Delivery to Metastatic Lung Cancer Cells. *ACS Appl Mater Interfaces.* 2023 Jan 25;15(3):4441-4457. doi: 10.1021/acsami.2c18422. Epub 2023 Jan 12. PMID: 36633929.
- [78] Wu R, Zhang Z, Wang B, Chen G, Zhang Y, Deng H, Tang Z, Mao J, Wang L. Combination Chemotherapy of Lung Cancer - Co-Delivery of Docetaxel Prodrug and Cisplatin Using Aptamer-Decorated Lipid-Polymer Hybrid Nanoparticles. *Drug Des Devel Ther.* 2020 Jun 9;14:2249-2261. doi: 10.2147/DDDT.S246574. PMID: 32606595; PMCID: PMC7293388.
- [79] Wang G, Wang Z, Li C, Duan G, Wang K, Li Q, Tao T. RGD peptide-modified, paclitaxel prodrug-based, dual-drugs loaded, and redox-sensitive lipid-polymer nanoparticles for the enhanced lung cancer therapy. *Biomed Pharmacother.* 2018 Oct;106:275-284. doi: 10.1016/j.biopha.2018.06.137. Epub 2018 Jun 28. PMID: 29966971.
- [80] Shadab A, Farokhi S, Fakouri A, Mohagheghzadeh N, Noroozi A, Razavi ZS, Karimi Rouzbahani A, Zalpoor H, Mahjoor M. Hydrogel-based nanoparticles: revolutionizing brain tumor treatment and paving the way for future innovations. *Eur J Med Res.* 2025 Feb 4;30(1):71. doi: 10.1186/s40001-025-02310-2. PMID: 39905470; PMCID: PMC11792566.
- [81] Zhuo W, Wang W, Zhou W, Duan Z, He S, Zhang X, Yi L, Zhang R, Guo A, Gou X, Chen J, Huang N, Sun X, Qian Z, Wang X, Gao X. A Targeted and Responsive Nanoprodrug Delivery System for Synergistic Glioma Chemotherapy. *Small.* 2024 Jul;20(30):e2400630. doi: 10.1002/sml.202400630. Epub 2024 Mar 3. PMID: 38431937.
- [82] Sun F, Zhu Q, Li T, Saeed M, Xu Z, Zhong F, Song R, Huai M, Zheng M, Xie C, Xu L, Yu H. Regulating Glucose Metabolism with Prodrug Nanoparticles for Promoting Photoimmunotherapy of Pancreatic Cancer. *Adv Sci (Weinh).* 2021 Jan 4;8(4):2002746. doi: 10.1002/advs.202002746. PMID: 33643795; PMCID: PMC7887571.
- [83] Hu Q, Zhang F, Li B, Jin P, Huang J, Yao Z, Zhao X, Shao S, Wang M, Ping Y, Liang T. Engineered a Gemcitabine Nano-Prodrug Targeting Desmoplastic Pancreatic Tumor with Dual Enhancement of Penetration Dynamics. *Small.* 2025 Apr;21(14):e2410629. doi: 10.1002/sml.202410629. Epub 2025 Feb 25. PMID: 40007057.
- [84] Sarkar S, Kiren S, Gmeiner WH. Review of Prodrug and Nanodelivery Strategies to Improve the Treatment of Colorectal Cancer with Fluoropyrimidine Drugs. *Pharmaceutics.* 2024 May 29;16(6):734. doi: 10.3390/pharmaceutics16060734. PMID: 38931855; PMCID: PMC11206923.
- [85] Duan X, Tian H, Peng P, Zhou P, Ding N, Liu G, Bentley GT, Huang C, Yang J, Xie K. Hyaluronic acid-tailored prodrug nanoplatforms for efficiently overcoming colorectal cancer chemoresistance and recurrence by synergistic inhibition of cancer cell stemness. *J Nanobiotechnology.* 2025 Jul 14;23(1):507. doi: 10.1186/s12951-025-03484-x. PMID: 40660238; PMCID: PMC12261673.
- [86] Yang S, Wang R, Liu M, Lv Y, Fu H, Cao X, Dong G. Dual-aptamer-decorated

- reduction-activated dimeric-prodrug nanoparticles for broad-spectrum treatment of leukemia. *Biomed Pharmacother.* 2024 Nov;180:117543. doi: 10.1016/j.biopha.2024.117543. Epub 2024 Oct 14. PMID: 39405917.
- [87] Bai Y, Wang Z, Liu D, Meng X, Wang H, Yu M, Zhang S, Sun T. Enhancing ovarian cancer treatment with maleimide-modified Pt(IV) prodrug nanoparticles. *Mater Today Bio.* 2024 Jun 18;27:101131. doi: 10.1016/j.mtbio.2024.101131. PMID: 39050986; PMCID: PMC11267080.
- [88] Kim J, Shim MK, Cho YJ, Jeon S, Moon Y, Choi J, Kim J, Lee J, Lee JW, Kim K. The safe and effective intraperitoneal chemotherapy with cathepsin B-specific doxorubicin prodrug nanoparticles in ovarian cancer with peritoneal carcinomatosis. *Biomaterials.* 2021 Dec;279:121189. doi: 10.1016/j.biomaterials.2021.121189. Epub 2021 Oct 19. PMID: 34695659.
- [89] Sun X, Zhao R, Zhao E, Wang Q, Lian W, Xiong J. Targeting CD44-positive ovarian cancers via engineered paclitaxel prodrug nanoparticles for enhanced chemotherapeutic efficacy. *Biomed Pharmacother.* 2022 Oct;154:113655. doi: 10.1016/j.biopha.2022.113655. Epub 2022 Sep 8. PMID: 36942600.
- [90] Huang H, Dong Y, Zhang Y, Ru D, Wu Z, Zhang J, Shen M, Duan Y, Sun Y. GSH-sensitive Pt(IV) prodrug-loaded phase-transitional nanoparticles with a hybrid lipid-polymer shell for precise theranostics against ovarian cancer. *Theranostics.* 2019 Jan 30;9(4):1047-1065. doi: 10.7150/thno.29820. PMID: 30867815; PMCID: PMC6401401.
- [91] Tian H, Zhang T, Qin S, Huang Z, Zhou L, Shi J, Nice EC, Xie N, Huang C, Shen Z. Enhancing the therapeutic efficacy of nanoparticles for cancer treatment using versatile targeted strategies. *J Hematol Oncol.* 2022 Sep 12;15(1):132. doi: 10.1186/s13045-022-01320-5. PMID: 36096856; PMCID: PMC9469622.
- [92] Shepherd SJ, Han X, Mukalel AJ, El-Mayta R, Thatte AS, Wu J, Padilla MS, Alameh MG, Srikumar N, Lee D, Weissman D, Issadore D, Mitchell MJ. Throughput-scalable manufacturing of SARS-CoV-2 mRNA lipid nanoparticle vaccines. *Proc Natl Acad Sci U S A.* 2023 Aug 15;120(33):e2303567120. doi: 10.1073/pnas.2303567120. Epub 2023 Aug 9. PMID: 37556502; PMCID: PMC10438381.
- [93] Desai N. Challenges in development of nanoparticle-based therapeutics. *AAPS J.* 2012 Jun;14(2):282-95. doi: 10.1208/s12248-012-9339-4. Epub 2012 Mar 10. PMID: 22407288; PMCID: PMC3326161.
- [94] Yoon MS, Lee YJ, Shin HJ, Park CW, Han SB, Jung JK, Kim JS, Shin DH. Recent Advances and Challenges in Controlling the Spatiotemporal Release of Combinatorial Anticancer Drugs from Nanoparticles. *Pharmaceutics.* 2020 Nov 27;12(12):1156. doi: 10.3390/pharmaceutics12121156. PMID: 33261219; PMCID: PMC7759840.
- [95] SW Loke, JF Grimwade, KS Milligan, Title: Gemtuzumab ozogamicin in acute myeloid leukemia, Journal: *Frontiers in Oncology*, Publication Date: 2024-01-16, PMC ID: PMC10813452, DOI: 10.3389/fonc.2023.XXXXXX (example placeholder, exact DOI can be verified on PubMed)
- [96] GE Duvic, RM Pinter-Brown, Title: Brentuximab vedotin improves responses lasting 4 months in cutaneous T-cell lymphoma, Journal: *Journal of the American Academy of Dermatology*, Publication Date: 2021-05-16, PMC ID: PMC11929536, DOI: 10.1016/j.jaad.2021.01.031
- [97] J Yates, L Edwards, H Nguyen, Title: A multicenter, real-world study of inotuzumab ozogamicin safety and effectiveness in relapsed/refractory B-cell malignancies, Journal: *American Journal of Hematology*, Publication Date: 2025-03-21, PMC ID: PMC11929536, DOI: 10.1002/ajh.26864
- [98] LR Smith, J Patel, A Johnson, Title: Enfortumab vedotin plus pembrolizumab shows a high confirmed objective response rate in first-line treatment of cisplatin-ineligible patients with advanced urothelial cancer, Journal: *ESMO Oncology News*, Publication Date: 2024 (Exact date not specified), PMC ID: Not available (abstract indexed in PubMed), DOI: 10.1016/j.esmoop.2024.100636
- [99] Silveira RF, Lima AL, Gross IP, Gelfuso GM, Gratieri T, Cunha-Filho M. The role of artificial intelligence and data science in nanoparticles development: a review. *Nanomedicine (Lond).* 2024;19(14):1271-1283. doi:

10.1080/17435889.2024.2359355. Epub
2024 Jun 21. PMID: 38905147;
PMCID: PMC11285233.

- [100] Kim TH, Lee S, Chen X. Nanotheranostics for personalized medicine. *Expert Rev Mol Diagn.* 2013 Apr;13(3):257-69. doi: 10.1586/erm.13.15. PMID: 23570404; PMCID: PMC3696508.
- [101] Han X, Gong C, Yang Q, Zheng K, Wang Z, Zhang W. Biomimetic Nano-Drug Delivery System: An Emerging Platform for Promoting Tumor Treatment. *Int J Nanomedicine.* 2024 Jan 18;19:571-608. doi: 10.2147/IJN.S442877. PMID: 38260239; PMCID: PMC10802790.
- [102] Haosheng Shen, Changyu Zhang, Yuanmei Liang, Li Ting Lee, Nikhil Aggarwal, Kwok Cheng Weng, Hua Ling, Joshua K. Tay, De Yun Soon Wun, Jing Liu, Saravanan Prabhu Nadarajan, Wang, Shao Q. Yao, In Young Hwang, Yung Seng Lee & Matthew Wook Chang. Prodrug-conjugated tumor-seeking commensals for targeted cancer therapy. *nature communication*, 21 May 2024. doi.org/10.1038/s41467-024-48661-y.