



WISELEAF SCIENTIFIC VENTURES

NANOPARTICLE MEDIATED DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Chapter 11: Toxicological and Regulatory Consideration

Ms. Sakshi S. Kohakade¹, Mr. Sushant M. Ahire², Ms. Prerana S. Pawar³

¹Department of Pharmaceutics Tssm's Jayawant Institute of Pharmaceutical Sciences & Research, Bavdhan, Pune-41103

²Assistant Professor, Department of Pharmaceutical Chemistry, Divine College of Pharmacy, Satana

³Assistant Professor, Department of Pharmaceutics, Divine College of Pharmacy, Satana

Abstract

Nanoparticle-based drug delivery systems (NDDS) have become a major advancement in cancer treatment, providing several benefits compared to traditional methods. This review looks at the various ways nanoparticles are used in cancer therapy and explains how they help in delivering drugs more effectively, reduce harmful effects on the body, and deal with issues like drug resistance and differences among tumors. Different types of nanoparticles, such as liposomes, polymeric nanoparticles, metallic nanoparticles, and newer ones like carbon nanotubes, dendrimers, and exosomes, are designed to deliver drugs directly to cancer cells. These nanoparticles improve how well drugs work in the body and help them accumulate at the tumor site through mechanisms like the enhanced permeability and retention (EPR) effect and by using ligands for active targeting. Nanoparticles are also important in combination therapies and targeting cancer stem cells (CSCs). Recent developments in “smart” nanoparticles that react to changes in their environment, such as pH or temperature, as well as their use with RNA-based therapies and artificial intelligence (AI) for personalized treatment, show the direction of future cancer nanomedicine. Although there has been progress, challenges like regulatory issues, safety concerns, and producing these systems on a large scale still need to be solved. This review gives an overview of the current state, challenges, and future possibilities of NDDS in cancer treatment, focusing on their potential to improve patient





WISELEAF SCIENTIFIC VENTURES

outcomes and change how cancer is treated. Nanoparticle-based drug delivery systems are used in various treatments such as chemotherapy, immunotherapy, targeted therapy, gene therapy, and combination therapy. However, issues such as toxicity, translating these systems into clinical use, and unintended effects on healthy cells must be addressed.

Keywords: Nanoparticles, Cancer therapy, Drug delivery, Multidrug resistance, Combination therapy, Personalized medicine, Immunotherapy, chemotherapy.

Introduction: Cancer is a condition where cells in the body undergo structural changes due to genetic mutations. It is one of the leading causes of death worldwide [1]. Cancer remains one of the most significant health challenges globally, with millions of new cases being diagnosed every year. Although there has been considerable progress in the field of oncology, traditional treatment methods such as chemotherapy, radiotherapy, and surgery still play a major role in clinical practice [2]. In 2018, the United States alone was projected to experience about 610,000 cancer-related deaths and approximately 1.7 million new cancer diagnoses. Conventional first-line cancer treatments involve radiation, chemotherapy, surgery, or a combination of these. However, these treatments have limitations in severe cases, and relapses can significantly reduce the five-year survival rate by more than 50%. When cancer is in its early stages, before it spreads, tumour removal is most effective. [3] Globally, cancer is considered a major public health issue in the 21st century. [4] Cancer is an abnormal condition caused by changes in the cell's structure. The three primary treatment approaches for cancer are surgical removal, chemotherapy, and radiation. Immunotherapy is now emerging as a promising new treatment for cancer. The development of immunotherapeutic treatments and combination therapies has been greatly advanced by drug delivery systems (DDSs). The use of nano, micro, and macro-scale DDSs to deliver various immune stimulatory agents to reprogram the immune system in order to combat cancer is the focus of this comprehensive review. Next-generation cancer immunotherapy based on drug delivery systems. [5] The complex relationship between cancer and the immune system, which Daniel S. Chen and Ira Mellman described as the "famous cancer-immunity cycle" in 2013, is crucial to understanding cancer immunotherapy. The role of T-cell immunity in fighting cancer is now widely acknowledged. The initiation of an anti-cancer T-cell immune response usually follows a sequence of steps. [6] (Fig.1)





WISELEAF SCIENTIFIC VENTURES

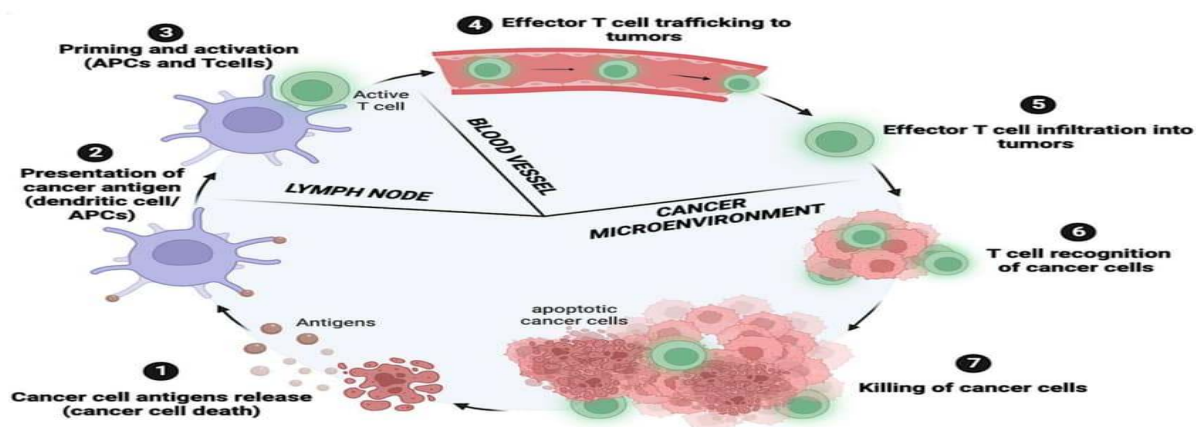


Figure 1: A schematic diagram of the cancer-immunity cycle.

In general, professional antigen-presenting cells, such as dendritic cells, identify and take in tumor antigens, then process them. During this process, dendritic cells mature and present fragments of the antigen to T-cells, initiating T-cell immunity. Effector T-cells migrate to the tumor site and kill cancer cells. However, immune checkpoints and regulatory T-cells can suppress this antitumor response. Chemotherapy side effects are a major concern because traditional chemotherapeutic agents, such as small anticancer drugs, have non-specific cytotoxic effects. These side effects can include severe systemic toxicity, low drug uptake, and the development of multidrug resistance (MDR). MDR is the main way many cancers become resistant to chemotherapy drugs. These unsatisfactory outcomes can also be caused by specific properties of anticancer drugs, such as poor solubility, low stability, and rapid metabolism. To address these issues, drug delivery systems (DDSs) have been developed to transport chemotherapeutic molecules directly to the tumor site, thereby improving therapeutic effectiveness. (Fig.2) Since new technological platforms have shown better outcomes in cancer treatment, nanotechnology is playing an increasing role in the development of DDSs. Another approach to improve cancer treatment involves using multiple therapeutic agents, including combinations of drugs with each other, drugs with genes, and genes with each other. [7]

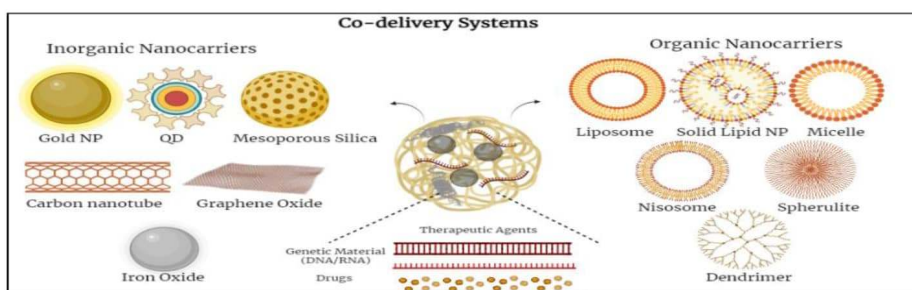


Figure 2: A schematic illustration of different inorganic, polymeric, and lipid-based nanoparticles and possible co-delivery approaches.





WISELEAF SCIENTIFIC VENTURES

2. Nanoparticle-based drug delivery systems (NPDDS) for cancer therapy

Nanoparticles, which are tiny particles with sizes ranging from 1 to 100 nanometers, are considered one of the most important areas in medical material research. These particles exhibit special physical, chemical, and biological properties such as the small-size effect, surface effect, and quantum size effect. Their small size and unique properties make them highly adaptable for various applications. Nanoparticles can be designed with different shapes and structures to enhance their targeting abilities and biocompatibility. Their ability to be used in various medical treatments is due to their versatility. The scalability and functional qualities of these materials have demonstrated significant potential in enhancing drug delivery, creating improved diagnostic techniques, and achieving accurate disease detection. Because of this potential, they are being employed to develop more targeted and effective medical treatments. The primary types of nanoparticles used in cancer therapy are liposomes, polymeric nanoparticles, metallic nanoparticles, dendrimers, carbon nanotubes, and exosomes. [8]

2.1. Liposomes: Liposomes are spherical structures made of one or more layers of phospholipids, which can carry a variety of drugs, both water-soluble and fat-soluble. They are commonly used in cancer treatment because they are biocompatible, can carry multiple types of drugs, and can target tumors through the enhanced permeability and retention (EPR) effect. The surface of liposomes can be modified with polyethylene glycol (PEG) to prolong their presence in the bloodstream or with specific molecules to direct them to cancer cells.⁹ One of the earliest FDA-approved liposomal formulations is Doxil, which uses PEGylated liposomes containing doxorubicin. This formulation has been used to treat various types of cancer, including ovarian cancer and Kaposi's sarcoma. The PEG coating on liposomes helps prevent them from being recognized and destroyed by the immune system, allowing more of the drug to reach the cancer site. [8,10]

2.2. Polymeric Nanoparticles: Polymeric nanoparticles are made from biodegradable materials such as poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and chitosan. These nanoparticles can be designed to release drugs over long periods, which helps maintain a steady concentration of the drug in the body. They are flexible in design and can carry a wide variety of substances, including drugs, proteins, and nucleic acids. Their surfaces can also be modified for targeted delivery.^{8,9} PLGA-based nanoparticles have been widely studied because they can effectively deliver chemotherapy drugs and provide a controlled release. For example, PLGA nanoparticles loaded with paclitaxel have been developed to improve the effectiveness of the drug while reducing its side effects. [9,10]

2.3. Metallic Nanoparticles: Metallic nanoparticles, such as gold, silver, and iron oxide nanoparticles, have unique properties that make them useful in cancer therapy. Gold





WISELEAF SCIENTIFIC VENTURES

nanoparticles (AuNPs) are particularly valuable because they are biocompatible and can absorb and scatter light, making them suitable for photothermal therapy (PTT) and imaging. Gold nanoparticles can be used to enhance the effectiveness of radiation therapy or combined with other agents to cause localized heating and destroy cancer cells. Iron oxide nanoparticles are primarily used in magnetic hyperthermia and as contrast agents for magnetic resonance imaging (MRI), helping both in the diagnosis and treatment of cancer. [8,9]

2.4. Dendrimers: Dendrimers are highly branched, tree-like synthetic polymers that are useful for delivering drugs. They have a well-defined structure with multiple layers, allowing them to carry a variety of therapeutic agents, including drugs, genes, and imaging agents. Their surface can be modified with targeting molecules and their size can be precisely controlled, making them effective for targeted delivery. Dendrimer-based systems have been used to deliver chemotherapeutic agents like doxorubicin with improved targeting and reduced side effects. Additionally, dendrimers can deliver multiple types of drugs and genes together, offering the potential for combination therapies that target multiple aspects of cancer. [8,10]

2.5. Carbon Nanotubes (CNTs): Carbon nanotubes (CNTs) are cylindrical nanostructures formed by rolling graphene sheets into a tube. They have unique mechanical, electrical, and thermal properties, making them suitable for drug delivery, imaging, and photothermal therapy. CNTs can be modified with targeting molecules and used to deliver chemotherapy drugs directly to cancer cells. They also play a role in cancer imaging and treatment through photothermal therapy, where they absorb near-infrared light and convert it to heat, which helps destroy cancer cells. Their ability to deliver drugs while generating heat has made them a promising option for combination therapies in cancer treatment. [8,10]

2.6. Exosomes: Exosomes are naturally occurring vesicles, ranging from about 30 to 150 nanometers in size, that are secreted by various cells. They have the ability to carry proteins, lipids, and nucleic acids, and they play an important role in cell communication. In recent years, exosomes have gained attention as drug delivery systems due to their biocompatibility, ability to cross biological barriers, and low immunogenicity. In cancer therapy, exosomes can be engineered to transport chemotherapeutic agents, nucleic acids like siRNA or miRNA, and immunomodulatory molecules. Exosome-based drug delivery systems are still in early development, but they hold promise for delivering personalized cancer treatments because of their natural targeting ability. [10,11]

2.7. Mesoporous Silica Nanoparticles (MSNs): Mesoporous silica nanoparticles (MSNs) are a type of inorganic nanoparticle characterized by their high surface area, large pore volume, and adjustable pore size. They can encapsulate a range of drugs and release them in response to stimuli such as pH or temperature. Their surfaces can be modified with targeting molecules to improve the accuracy of drug delivery. 9,10 MSNs have been studied for delivering





WISELEAF SCIENTIFIC VENTURES

chemotherapy drugs like doxorubicin, paclitaxel, and cisplatin. They have shown the potential to deliver a controlled release of drugs, enhance therapy effectiveness, and reduce side effects in cancer treatment. [8,11]

3.Types of Cancer

3.1 Breast Cancer: Breast cancer is the most common type of cancer in the USA, according to the American Cancer Society. In 2023, it is estimated that about 298,000 women and 3,000 men were diagnosed with invasive breast cancer, leading to approximately 43,700 deaths.¹² Factors such as weight gain after the age of 18, lack of physical activity, and hormone therapy during menopause have contributed to an increase in breast cancer cases by 0.5% since 2020. Risk factors for developing breast cancer include a history of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS), high breast tissue density, inherited genetic mutations like BRCA1 or BRCA2, and exposure to high doses of radiation to the chest before the age of 30.¹³

3.2 Prostate Cancer: These cancers are the most common cause of cancer-related deaths among men worldwide. Although photodynamic therapy (PDT) shows promise as a treatment for prostate cancer, it is still considered an experimental or investigational therapy. Research and clinical trials are ongoing to evaluate its effectiveness and safety. Typically, prostate cancer is treated with surgery or radiotherapy. [13]

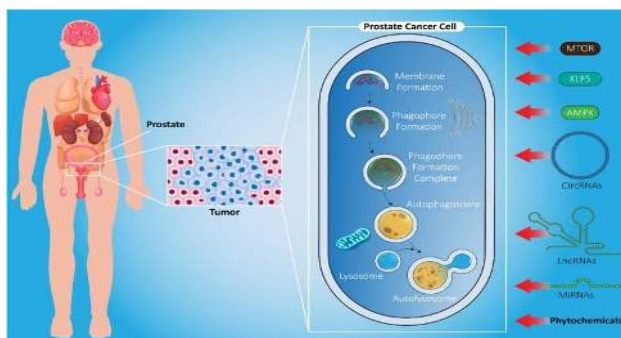


Figure 5: Diagrammatic representation of prostate cancer.

3.3 Skin Cancer: According to WHO estimates, around 132,000 cases of melanoma and between 2 to 3 million cases of non-melanoma skin cancers are diagnosed worldwide each year. Melanoma is the deadliest form of skin cancer. If not detected and treated early, it can spread to other parts of the body. In 2023, the American Cancer Society reported approximately 106,110 new cases of melanoma and 7,180 deaths from the disease in the U.S. [13]





WISELEAF SCIENTIFIC VENTURES

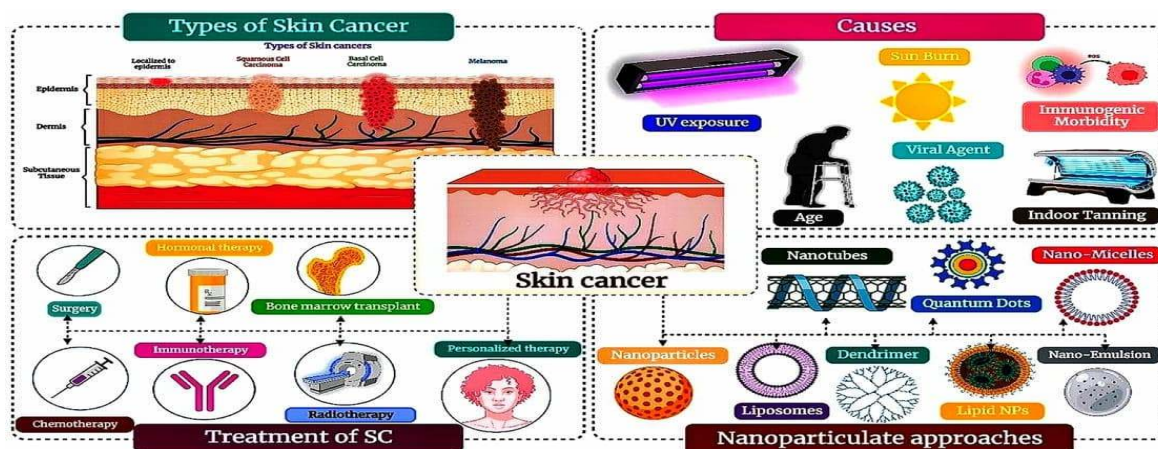


Figure 5: Diagrammatic representation of skin cancer.

3.4 Gynecological Cancers: Uterine corpus cancer is one of the most commonly diagnosed gynecological cancers. Human papillomavirus (HPV) infection is linked to this type of cancer, which is sixth in prevalence among cancers affecting women. This virus can affect the cervix, vulva, vagina, perineum, and anus of women. [13]

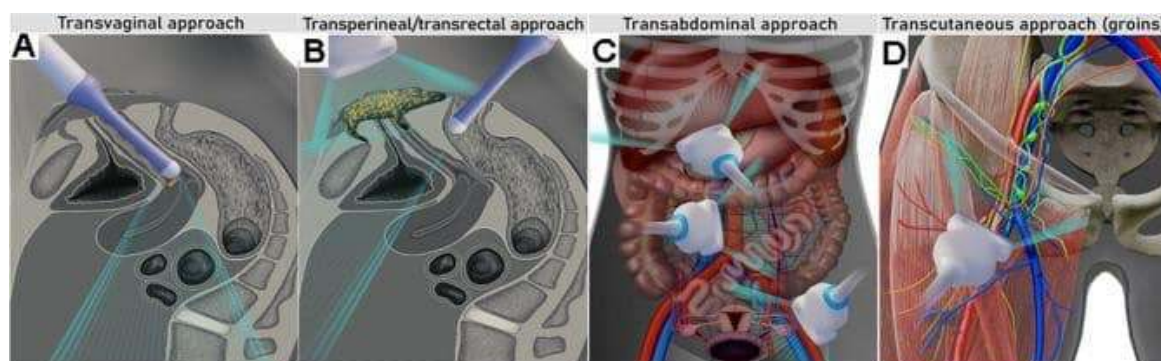


Figure 6: Ultrasound methods for staging gynecological cancers: transvaginal (A) and transperineal combined with transrectal (B) approaches for local staging; transabdominal approach using a convex array probe for evaluating abdominal infiltrated visceral and retroperitoneal lymph nodes, peritoneal, or parenchymal metastases (C); transcutaneous approach with a linear array probe for evaluating inguinofemoral lymph nodes (D).

3.5 Head and Neck Cancer: Approximately 4% of all new cancer cases are head and neck malignancies, making it the sixth most common type of cancer worldwide. To treat head and neck cancer comprehensively, PDT is often used in combination with other treatments such as chemotherapy, radiation therapy, or surgery. It can be used in early stages of the disease or as a palliative treatment in advanced cases to help relieve symptoms.[14]





WISELEAF SCIENTIFIC VENTURES

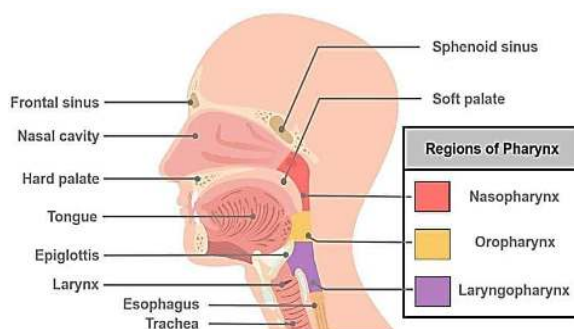


Figure 7: Schematic diagram showing major sites of head and neck cancers.

4. Mechanisms of Nanoparticle-Based Drug Delivery in Cancer Therapy

Nanoparticles (NPs) offer multiple methods for drug delivery, which help improve the effectiveness of anticancer drugs by increasing targeting accuracy, reducing unwanted effects on healthy tissues, and ensuring controlled release of medication. These methods typically involve passive and active targeting strategies that utilize the unique characteristics of tumors or involve modifying the surface of nanoparticles for more precise delivery. [15,16]

4.1. Passive Targeting via the Enhanced Permeability and Retention (EPR) Effect: One of the main ways nanoparticles deliver drugs is through passive targeting, which uses the enhanced permeability and retention (EPR) effect. Tumors, especially solid tumors, have abnormal and leaky blood vessels due to rapid and irregular growth, leading to increased permeability. Additionally, poor lymphatic drainage allows nanoparticles to accumulate and stay in the tumor area for a longer time. [15,17] Nanoparticles in the size range of 10–100 nm can take advantage of the EPR effect to enter the tumor through leaky vessels and remain due to poor drainage. This passive targeting increases the concentration of the drug at the tumor site while reducing exposure to healthy tissues, thus minimizing side effects. However, the EPR effect may vary between tumor types and individuals due to differences in their vascular structure. To enhance passive targeting, researchers are developing stimulus-responsive nanoparticles that release their contents in response to the tumor's specific environment, such as pH levels, low oxygen conditions, or certain enzymes. [8,15]

4.2. Active Targeting via Ligand-Modified Nanoparticles: While passive targeting relies on the unique physiological features of tumors, active targeting adds a more specific level of precision. In active targeting, nanoparticles are modified with ligands, peptides, or antibodies that have a high affinity for receptors that are often overexpressed on cancer cells. This not only increases the selectivity of the drug delivery system but also ensures that the therapeutic agents are delivered more effectively to the cancer cells, increasing the possibility of internalization and improving treatment outcomes by reducing unwanted effects on healthy tissues. [8,17,18]





WISELEAF SCIENTIFIC VENTURES

4.3. Commonly Used Ligands for Active Targeting Include:

Antibodies or antibody fragments: Monoclonal antibodies that target specific tumor-related antigens, such as HER2 in breast cancer, can be attached to nanoparticles, improving their ability to bind to cancer cells.

Peptides: Short sequences of amino acids, such as RGD peptides that target integrins, can be attached to nanoparticles to direct the drug to proteins that are overexpressed in tumors.

Folate: Folate receptors are commonly overexpressed in various cancers.

Nanoparticles conjugated with folic acid or its derivatives can selectively target these cancers.

Aptamers: These are small, single-stranded DNA or RNA molecules that can bind to specific proteins with high affinity. Nanoparticles modified with aptamers can be used to target specific tumor markers.

Active targeting allows for more precise delivery of drugs to cancer cells, thereby improving therapeutic effectiveness and minimizing side effects. [15,18]

4.4. Controlled Drug Release: One of the main benefits of using nanoparticles for drug delivery is their ability to control when and how the drug is released. Controlled release means the nanoparticles can gradually release their medication over time, maintaining a steady level of the drug at the cancer site. This controlled release can be done through several methods, such as: **pH-Sensitive Nanoparticles:** Tumors often have a more acidic environment than healthy tissues. These nanoparticles are designed to remain stable in the normal blood pH but release their drug when they reach the acidic tumor environment. This helps deliver the drug more effectively to cancer cells and reduces side effects on healthy tissues. [8,18]

Thermo-Responsive Nanoparticles: These nanoparticles are designed to release their drug payload when exposed to higher temperatures, such as those created by external heat treatments. By heating the tumor area, these nanoparticles can be triggered to release the drug. [15,16]

Redox-Sensitive Nanoparticles: Cancer cells typically have a higher level of reactive oxygen species (ROS) and a more reducing environment than normal cells. Redox-sensitive nanoparticles can break down and release their drug in response to the high redox activity of cancer cells. [15]

4.5. Cellular Uptake of Nanoparticles: Once nanoparticles reach the tumor, they must be absorbed by cancer cells to release the medication. Nanoparticles can enter cells via various pathways, including clathrin-mediated endocytosis and caveolae-mediated endocytosis,





WISELEAF SCIENTIFIC VENTURES

caveolae-mediated endocytosis, and macropinocytosis. The method of entry depends on the nanoparticle's size, shape, electrical charge, and composition. [9,18] After being taken into the cell, nanoparticles typically move to the endo-lysosomal pathway, where acidic conditions or enzyme activity can cause the drug to be released. To ensure the drug reaches its target inside the cell, researchers have designed nanoparticles that can escape from endosomes before they are broken down. This process, known as endosomal escape, is important for successful drug delivery inside the cell. [15,16]

4.6. Nanoparticles in Tumor Penetration: For effective cancer treatment, the drug needs to reach all parts of the tumor. However, the dense extracellular matrix (ECM) and poor blood flow in tumors make it challenging for drugs to penetrate deeply. Nanoparticles can be engineered to improve this penetration in the following ways:

Multistage Nanoparticles: These nanoparticles are designed to change their size or surface characteristics once they reach the tumor. For example, they can shrink from large to smaller sizes inside the tumor, which helps them move more easily through the ECM. [16,17]

Enzyme-Responsive Nanoparticles: Certain nanoparticles are developed to release enzymes like collagenase that can break down the ECM, allowing the drug to reach the center of the tumor more effectively. [16,18]

5. Regulatory Perspectives and Clinical Translation of Nanoparticle-Based Drug Delivery Systems: Moving nanoparticle-based drug delivery systems from research to real-world use requires careful navigation through complex regulatory processes to ensure safety, effectiveness, and quality. Understanding the regulatory landscape is important for researchers, developers, and healthcare professionals who aim to bring new nanoparticle-based treatments to the market. [19,20]

5.1. Regulatory Frameworks for Nanomedicine: Regulatory agencies such as the U. S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other global bodies have created guidelines to assess the safety and effectiveness of nanoparticle-based drug delivery systems. These standards address challenges related to the unique properties of nanomaterials, including their size, structure, and how they interact with the body. [21,22]

5.2. Risk Assessment and Safety Evaluation: Safety evaluation for nanoparticle-based drugs involves assessing potential toxicity, immune responses, and environmental effects. Regulatory agencies require thorough preclinical testing, including in vitro and in vivo studies of the nanoparticles' safety profile, how they spread in the body (biodistribution), their breakdown in the body (pharmacokinetics), and possible side effects. These assessments should also consider long-term exposure and accumulation in tissues. [22,23]





WISELEAF SCIENTIFIC VENTURES

5.3. Quality Control and Manufacturing Standards: Maintaining consistent quality and performance of nanoparticles across different batches is essential. Regulatory guidelines focus on standardizing processes for making, purifying, and analyzing nanoparticles. Important factors such as size, surface charge, drug loading, and stability must be carefully checked to ensure reliable results in clinical settings. [22,23]

5.4. Clinical Trials and Approval Pathways: The approval process for nanoparticle-based therapies generally follows a staged clinical trial approach, similar to traditional drug development. It includes preclinical studies followed by Phase I, II, and III trials to examine safety, effectiveness, and optimal dosage. The complexity of nanoparticle formulations brings additional challenges, making it necessary for regulatory agencies to carefully evaluate drug release mechanisms, which can impact the overall treatment outcome and side effects. [24]

5.5. Phased Clinical Trials: Clinical trials for nanoparticle-based therapies typically include three phases:

Phase I: Focuses on testing the safety, tolerability, and how the nanoparticles move through the body (pharmacokinetics) in a small group of patients.

Phase II: Evaluates the effectiveness and determines the best dosage in a larger group of patients with specific types of cancer.

Phase III: Compares the nanoparticle therapy with standard treatments in a large, randomized, controlled study to confirm its effectiveness and safety. [25]

5.6. Adaptive Trial Designs: Because responses to nanoparticle-based therapies can vary among patients, adaptive trial designs are increasingly used. These designs allow for changes in the trial plan based on early results, making the testing process more efficient and tailored. Adaptive designs help identify effective treatments more quickly and reduce the exposure of patients to therapies that are not working. [26]

5.7. Post-Market Surveillance and Real-World Evidence: After approval, ongoing monitoring of nanoparticle-based therapies through post-market surveillance is critical to ensure long-term safety and effectiveness. Collecting real-world evidence can provide insights into how these therapies perform in different patient groups and under various clinical conditions. [27]

5.8. Real-World Evidence Generation: Real-world evidence, gathered from electronic health records, patient databases, and observational studies, can supplement clinical trial data. It offers insights into treatment outcomes, adverse effects, and patient experiences, helping to shape clinical guidelines and improve future nanoparticle-based therapies. [28]





WISELEAF SCIENTIFIC VENTURES

5.9. Pharmacovigilance and Risk Management: Regulatory bodies require continuous monitoring of the safety of approved nanomedicines after they are approved. Risk management plans must be in place to deal with possible side effects and ensure the safety of patients. Systems for reporting adverse events related to nanoparticle-based therapies should be strong and open, allowing for quick action when safety issues arise. [29]

6. Application of Npdds In Cancer Therapy: Nanotechnology has demonstrated previously unheard-of potential in the field of cancer diagnostics as medical technology develops, particularly in the early detection and precise diagnosis of colorectal cancer. Blood tests (such as the CEA test), digital rectal examination, computed tomography (CT), magnetic resonance imaging (MRI), colonoscopy, and other conventional techniques are currently used for screening, identifying, and diagnosing colorectal cancer (CRC).

1. Capturing antigens shed from tumors following radiotherapy.
2. Designing nanoparticle-based vaccines to raise T cell responses.
3. In situ vaccination with artificial antigen presenting cells or immune depots placed near tumors. By increasing sensitivity, specificity, and the ability to detect many markers at once, nanoparticles can be used to create highly sensitive and specific biomarker detection platforms. [12]

6.1. Chemotherapy: A few decades ago, the first chemotherapeutic medication to be clinically approved for melanoma was dacarbazine (DTIC; 1970s), an alkylating agent with cytostatic action. Since temozolomide, an analogue of DTIC that is approved for glioblastoma multiforme, is taken orally, enters the central nervous system, and has a favourable toxicity profile, it is frequently utilized in patients with advanced melanoma. However, because they are not selective to tumour sites and melanoma cells frequently develop resistance to alkylating agents, these drugs do not demonstrate significant therapeutic benefits and instead cause side effects. [30]

6.2. Cancer Immunotherapy: By encouraging the immune system to attack and destroy cancer cells, cancer immunotherapy might prevent the disease from spreading or coming back. One of the most crucial ways this works is through the Cancer Immunity Cycle (CI cycle). Anti-PD-1 immune checkpoint drugs are also used to treat cancers, helping to strengthen the immune system's ability to fight against genetic mutations or viral gene activity. Even with major advancements in immunotherapy techniques, many patients do not benefit from these treatments.³¹ T cells then recognize antigens on Major Histocompatibility Complex I (MHC I) and MHC II molecules produced by dendritic cells, which initiates and activates effector T cells for a specific immune reaction against new antigens. [32]





WISELEAF SCIENTIFIC VENTURES

6.3. Targeted Therapy: As the pharmaceutical industry grew, targeted medicines became a promising field of study. For instance, all mammalian cells grow, multiply, differentiate, move, and survive through the mitogen activated protein kinase/extracellular signal-related kinase (MAPK/ERK) signaling pathway. [31] Medicines are delivered to target cells using nanodelivery systems, which are tiny particles, reducing harm to healthy cells and improving the medicine's effectiveness. [33]

6.4. Gene Therapy: This section includes gene therapy, mechanical stability devices, and tissue engineering methods that use autologous or allogeneic grafts and substitutes along with mesenchymal stem cells.³⁴ According to animal studies, mice treated with PEDF-PLGA nanoparticles showed more apoptotic CT26 cells compared to those treated with normal saline (NS). Using the PEDF gene and PLGA nanoparticles for treating primary colorectal cancer is considered both safe and efficient for gene delivery.³⁵

6.5. Combination Therapy: Although human trials based on mesoporous silica nanoparticles (MSN) have begun, there is still a long way to go before effective treatment becomes possible. To enhance and evaluate the benefits of combination therapy, more fundamental research on MSN-immune cell interactions is needed to create new delivery systems and actively manage the immune response. [31]

7. Challenges and Limitations of Npdds in Cancer Therapy

Although epigenetic drugs show promise in cancer therapy due to their ability to change gene expression, safety and off-target effects remain issues. Various diseases and functions can be affected by mitochondrial dysfunction. Some of these disorders have been linked to mutations or deletions in mitochondrial DNA (mt-DNA).³⁶ These drugs, including EZH2 inhibitors (like tazemetostat), HDAC inhibitors (like vorinostat and romidepsin), and DNA methylation inhibitors (like azacitidine, decitabine), might unintentionally affect non-target genes or pathways, leading to negative effects. Off-target effects can alter gene expression and disrupt normal cell functions. Risks to consider include haematologic toxicity (like cytoplasmic), gastrointestinal toxicity (like nausea and vomiting), neurological toxicity (like peripheral neuropathy), cardiovascular toxicity (like hypertension), and impacts on the immune system (like immune-related adverse effects). Mitigation methods include careful dosing and monitoring, supportive care to reduce side effects, ongoing research to find biomarkers and improve drug design, and combination techniques to boost treatment effectiveness. [37]

7.1. Toxicity: Since nanoparticles are used in tissue repair, drug delivery, food packaging, and related fields, toxicity is a key concern. The toxicity depends on the base material and is similar to the application area. A nanoparticle's toxicity is influenced by its administration concentration, stability, bioavailability, and tendency to accumulate in a tissue or organ. The





WISELEAF SCIENTIFIC VENTURES

material and type of nanoparticle, as well as its size and surface properties, affect all these factors. Reactive oxygen species (ROS) production can make nanoparticles harmful regardless of the substance.³⁸ Despite their many advantages, very little is known about the short- and long-term health effects of nanoparticles on living organisms and the environment. Safety concerns have been raised due to the known toxicity and potential risks of nanomaterials. [39]

7.2 Clinical Translation: Only a few treatments are currently approved for reducing cancer risk due to major challenges that have slowed development. One of the biggest obstacles to successful clinical translation of potential preventive medicines is the lack of pharmacodynamic biomarkers to provide early signs of biological activity in humans and adjust dosages for large-scale randomized clinical trials.⁴⁰ It must be noted that only a small number of new products have progressed to human use, despite the potential for significant clinical benefits and ongoing research into oral drug delivery systems based on nanotechnology. Additionally, all oral nanomedicines used in clinical therapy today are SDNs, and their goal is to increase the rate at which poorly soluble drugs dissolve. [41]

7.3 Future Direction: Even with major progress in cancer treatment, most cancers still do not respond to standard treatment methods. Compared to alternative drug delivery methods, the use of nanoparticles as anti-cancer agents and drug resistance modulators has several advantages. [42] Experiments on a B16F10 lung metastasis tumor model showed promising and notable synergistic effects of the combination, opening the door for potential future clinical use. [43] Combining small molecule inhibitors like Enhancer of Zeste Homolog 2 (EZH2) or Histone Deacetylase (HDAC) inhibitors with advances in clustered regularly interspaced short palindromic repeat (CRISPR) and its associated protein (Cas9)-based epigenetic editing allows for precise gene and epigenetic regulation, potentially leading to treatments for genetic disorders and cancer. [31] Small drugs typically target specific molecular targets crucial for angiogenesis, metastasis, and the growth of cancer cells. [44] Focusing on Pancreatic Ductal Adenocarcinoma (PDAC), this review aims to provide a thorough examination of current methods and potential future directions in the use of therapeutic radiopharmaceuticals for pancreatic cancer treatment. It also explores the evolving field of radio pharmaceutical therapy, emphasizing its potential benefits, drawbacks, and new developments. [45]

8. Advance Therapeutic Approaches

8.1. Combination Therapies: The growth of cancer and its ability to avoid immune detection and anti-tumor responses are heavily influenced by immune checkpoint proteins. Immune checkpoint inhibitors (ICIs), such as pembrolizumab and nivolumab, have transformed cancer treatment. [46]





WISELEAF SCIENTIFIC VENTURES

8.2. Targeting Cells: Targeted therapy involves using drugs that specifically target certain parts of cancer cells through biological, physical, or chemical methods to destroy cancer cells while keeping healthy cells unaffected. This approach has become the main treatment for leukemia. In leukemia treatment, multiple drugs are often used together to create a stronger effect and improve treatment success. [47] The development of nano-vehicles that can safely transport various genetic materials to the intended target is driven by the challenge of delivering genetic material effectively. [7] The liver and kidneys also act as barriers by removing nanoparticles from the bloodstream, making drug delivery to the target area more difficult in systemic nanomedicine applications for skin cancer treatment. [31]

8.3. Immune Checkpoint Inhibition: Even though many drugs have been approved by the FDA and are undergoing clinical trials, several challenges remain in the battle against cancer. One major challenge is the immunosuppressive tumour microenvironment (TME), which hinders cancer immunity. Antigen-presenting cells (APCs), such as dendritic cells, engulf, process, and present cancer antigens via the major histocompatibility complex. These APCs travel to lymph nodes, where T cells detect the antigens through their T-cell receptors and begin the activation process. [48] It is intriguing to explore the use of immune checkpoint inhibitors (ICIs) for treating upper tract urothelial carcinoma (UTUC). In reality, UTUC remains a challenging cancer to treat for several reasons. Immune checkpoints are pathways on T-cells that suppress their activation, playing a key role in immune responses. If these checkpoints are activated, they inhibit immune cells. Cancer cells often activate these checkpoints to avoid being attacked by the immune system. Preventing cancer cells from activating immune checkpoints could allow the immune system to function normally and effectively fight cancer cells.[49]

9. Conclusion

Nanoparticle-based drug delivery systems (NPDDS) have shown great potential in cancer treatment by delivering therapeutic agents in a targeted and efficient manner. Different types of nanoparticles, including liposomes, polymeric nanoparticles, metal nanoparticles, dendrimers, and micelles, have shown promise in enhancing treatment results. The design and development of NPDDS involve strategies to target specific areas, functionalize nanoparticles, and modify them to improve effectiveness and reduce unwanted effects. Despite challenges like toxicity and difficulties in moving these systems into clinical use, ongoing research and progress in NPDDS are expected to address these issues.





WISELEAF SCIENTIFIC VENTURES

References

1. Hatwar PR, Bakal RL, Dumare AA, Dere MD, Hage PD. Targeted drug delivery system for the treatment of cancer. *World J Pharm Res.* 2023;12(12):808-816.
2. Kunjalwar R, Keerti A, Chaudhari A, Sahoo K, Meshram S. Microbial therapeutics in oncology: a comprehensive review of bacterial role in cancer treatment. *Cureus.* 2024;16(10). doi:10.7759/cureus.70920.
3. Batty CJ, Tiet P, Bachelder EM, Ainslie KM. Drug delivery for cancer immunotherapy and vaccines. *Pharm Nanotechnol.* 2018;6(4):232-244. doi:10.2174/2211738506666180918122337.
4. Ameer SF, Mohamed MY, Elzubair QA, Sharif EAM, Ibrahim WN. Curcumin as a novel therapeutic candidate for cancer: can this natural compound revolutionize cancer treatment? *Front Oncol.* 2024;14:1438040. doi:10.3389/fonc.2024.1438040.
5. Huang P, Wang X, Liang X, Yang J, Zhang C, Kong D, et al. Nano-, micro-, and macroscale drug delivery systems for cancer immunotherapy. *Acta Biomater.* 2019;85:1-26. doi:10.1016/j.actbio.2018.12.028.
6. Carvalho BG, Vit FF, Carvalho HF, Han SW, de la Torre LG. Recent advances in co-delivery nanosystems for synergistic action in cancer treatment. *J Mater Chem B.* 2021;9(5):1208-1237. doi:10.1039/D0TB02168G.
7. Zhao Y, Zeng Y, Li Y. Lipid-coated polymeric nanoparticles for cancer drug delivery. *Biomater Sci.* 2014;2(5):690-702.
8. Vangijzegem T, Stanicki D, Laurent S. Magnetic nanoparticle-based hyperthermia for cancer therapy. *Prog Nanomed.* 2020;37(3):71-82.
9. Barenholz Y. Doxil®—the first FDA-approved nano-drug: lessons learned. *J Control Release.* 2012;160(2):117-134.
10. Wang X, Zhang H, Chen X. Drug resistance and combating drug resistance in cancer. *Cancer Drug Resist.* 2019;2(2):141-160.
11. Pawar SP, Ahire MS, Shewale VV, Jadhav S, Mahajan KS, Sonawane DD. Silver nanoparticles: A comprehensive review on synthesis, properties and applications.





WISELEAF SCIENTIFIC VENTURES

- Research Journal of Pharmaceutical Dosage Forms and Technology. 2025;17(4):279-85.
12. Ashkbar A, Rezaei F, Attari F, Ashkevarian S. Treatment of breast cancer in vivo by dual photodynamic and photothermal approaches with the aid of curcumin photosensitizer and magnetic nanoparticles. *Sci Rep*. 2020;10(1):21206. doi:10.1038/s41598-020-78241-1.
 13. Jadhav SP, Ahire SM, Shewale VV, Patil CD, Pagar RY, Sonawane DD, Mahajan SK. Formulation of Tablet of Nifedipine co-crystal for enhancement of solubility and other physical properties. *Biotech Res Asia*. 2025 Mar 25;22(1):191-200.
 14. Danhier F, Feron O, Préat V. To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. *J Control Release*. 2010;148(2):135-146.
 15. Ahire SM, Pawar PS, Jadhav SP, Mahajan SK. Herbal Nutraceuticals and Functional Applications of *Celosia argentea* and Allied Botanicals.
 16. Chen Q, Xu L, Liu Z. Nanoparticle-mediated targeted drug delivery systems for precision cancer therapy. *Signal Transduct Target Ther*. 2020;5:193.
 17. Sharma T, Jain A, Kaur R, Saini S, Katare O, Singh B. Supersaturated LFCS type III self-emulsifying delivery systems of sorafenib tosylate with improved biopharmaceutical performance: QbD-enabled development and evaluation. *Drug Deliv Transl Res*. 2020;10(3):839-861.
 18. Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J. The big picture on nanomedicine: the state of investigational and approved nanomedicine products. *Nanomedicine (Lond)*. 2013;9(1):1-14.
 19. Lim M, Park J, Shin SW, Lee W, Moon JH. Regulatory considerations and challenges in nanomedicine. *J Pharm Sci*. 2018;107(5):1247-1254.
 20. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. *Pharm Res*. 2016;33(10):2373-2387.





WISELEAF SCIENTIFIC VENTURES

21. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS Nano*. 2009;3(1):16-20.
22. Ahire SM, Pawar PS, Jadhav SP, Shewale VV, Patil CD, Mahajan SK, Vishwas S. Nanotechnology-driven antioxidants and immunomodulators for polycystic ovary syndrome (PCOS) therapy. *Nanotechnology NextGen: From Treatment to Transformation in Polycystic Ovary Syndrome (PCOS)*. 2025 Jul 15:184.
23. Akhter S, Ahmad Z, Ahmad M. Emerging applications of nanomedicines in cancer therapy. *Drug Dev Ind Pharm*. 2018;44(8):1295-1308.
24. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Mol Pharm*. 2008;5(4):505-515.
25. Amreddy N, Babu A, Muralidharan R, Munshi A, Ramesh R. Polymeric nanoparticle-mediated gene delivery for lung cancer treatment. *Mater Sci Eng C Mater Biol Appl*. 2018;89:108-119.
26. Aryal S, Hu CMJ, Zhang L. Polymeric nanoparticles with precise ratiometric control over drug loading for combination therapy. *Mol Pharm*. 2011;8(4):1401-1407.
27. Deore AD, Ahire MS, Mahajan KS. Herbal Medicine Meets Nanotechnology: A Transformative Approach. *Asian Journal of Pharmaceutical Research*. 2025;15(3):302-8.
28. Cabral H, Kataoka K. Progress of drug-loaded polymeric micelles into clinical studies. *J Control Release*. 2014;190:465-476.
29. Oliveira Pinho J, Matias M, Gaspar MM. Emergent nanotechnological strategies for systemic chemotherapy against melanoma. *Nanomaterials (Basel)*. 2019;9(10):1455. doi:10.3390/nano9101455.
30. Ahire SM, Jadhav SP, Shewale VV, Pawar PS, Kokande AM, Sonawane DP, Patil DM. A review on computer-aided drug design and discovery. *J. Reattach Therapy Dev. Diversities*. 2023;6:1573-82.
31. Gu B, Zhao Q, Ao Y. Advances in immunomodulatory mesoporous silica nanoparticles for inflammatory and cancer therapies. *Biomolecules*. 2024;14(9):1057. doi:10.3390/biom14091057.





WISELEAF SCIENTIFIC VENTURES

32. Wang L, Cai F, Li Y, Lin X, Wang Y, Liang W, et al. pH-responsive block copolymer micelles of temsirolimus: preparation, characterization and antitumor activity evaluation. *Int J Nanomedicine*. 2024;19:9821-9841. doi:10.2147/IJN.S469913.
33. Mercatali L, Vanni S, Miserocchi G, Liverani C, Spadazzi C, Cocchi C, et al. The emerging role of cancer nanotechnology in the panorama of sarcoma. *Front Bioeng Biotechnol*. 2022;10:953555. doi:10.3389/fbioe.2022.953555.
34. Sun R, Chen Y, Pei Y, Wang W, Zhu Z, Zheng Z, et al. The drug release of PLGA-based nanoparticles and their application in treatment of gastrointestinal cancers. *Heliyon*. 2024;10(18). doi:10.1016/j.heliyon.2024.e38165.
35. Yamada Y, Sato Y, Nakamura T, Harashima H. Evolution of drug delivery system from viewpoint of controlled intracellular trafficking and selective tissue targeting toward future nanomedicine. *J Control Release*. 2020;327:533-545. doi:10.1016/j.jconrel.2020.09.007.
36. Panda R, Mohan S, Vellapandian C. Harnessing epigenetic mechanisms to overcome immune evasion in cancer: the current strategies and future directions. *Cureus*. 2024;16(10). doi:10.7759/cureus.70631.
37. Eker F, Duman H, Akdaşçi E, Bolat E, Sarıtaş S, Karav S, et al. A comprehensive review of nanoparticles: from classification to application and toxicity. *Molecules*. 2024;29(15):3482. doi:10.3390/molecules29153482.
38. Mahure LD, Hatwar PR, Bakal RL, Turankar CC. Nanotechnology based approaches for acne treatment: a comprehensive review. *GSC Biol Pharm Sci*. 2025;31(1):156-162.
39. Brown K, Rufini A. New concepts and challenges in the clinical translation of cancer preventive therapies: the role of pharmacodynamic biomarkers. *Ecancermedicalscience*. 2015;9:601. doi:10.3332/ecancer.2015.601.
40. Moss DM, Curley P, Kinvig H, Hoskins C, Owen A. The biological challenges and pharmacological opportunities of orally administered nanomedicine delivery. *Expert Rev Gastroenterol Hepatol*. 2018;12(3):223-236. doi:10.1080/17474124.2018.1399794.





WISELEAF SCIENTIFIC VENTURES

41. Gupta P, Jani KA, Yang DH, Sadoqi M, Squillante E, Chen ZS. Revisiting the role of nanoparticles as modulators of drug resistance and metabolism in cancer. *Expert Opin Drug Metab Toxicol.* 2016;12(3):281-289. doi:10.1517/17425255.2016.1145655.
42. Bale S, Khurana A, Reddy AS, Singh M, Godugu C. Overview on therapeutic applications of microparticulate drug delivery systems. *Crit Rev Ther Drug Carrier Syst.* 2016;33(4):309-361. doi:10.1615/CritRevTherDrugCarrierSyst.2016015798.
43. Pakade ID, Barewar SS, Hatwar PR, Bakal RL, Shelke PG. Targeted drug therapy. *World J Pharm Pharm Sci.* 2024;13(5):1642-1656.
44. Calistri S, Ottaviano G, Ubaldini A. Radiopharmaceuticals for pancreatic cancer: a review of current approaches and future directions. *Pharmaceuticals (Basel).* 2024;17(10):1314. doi:10.3390/ph17101314.
45. Xu S, Li X, Ma W. Redefining the tumor microenvironment with emerging therapeutic strategies. *Oncol Res.* 2024;32(11):1701-1708. doi:10.32604/or.2024.055161.
46. Qian S, Zheng C, Wu Y, Huang H, Wu G, Zhang J. Targeted therapy for leukemia based on nanomaterials. *Heliyon.* 2024;10(15). doi:10.1016/j.heliyon.2024.e34951.
47. Ma GL, Lin WF. Immune checkpoint inhibition mediated with liposomal nanomedicine for cancer therapy. *Mil Med Res.* 2023;10(1):20. doi:10.1186/s40779-023-00455-x.
48. Califano G, Ouzaid I, Laine-Caroff P, Peyrottes A, Collà Ruvolo C, Pradère B, et al. Current advances in immune checkpoint inhibition and clinical genomics in upper tract urothelial carcinoma: state of the art. *Curr Oncol.* 2022;29(2):687-697. doi:10.3390/curroncol29020060.
49. Zhou L, Zou M, Xu Y, Lin P, Lei C, Xia X. Nano drug delivery system for tumor immunotherapy: next-generation therapeutics. *Front Oncol.* 2022;12:864301. doi:10.3389/fonc.2022.864301.

