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REVIEW ARTICLE

Smart Nanoparticles in Oncology: Redefining Drug Delivery and Clinical Outcomes

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ABSTRACT
Nanotechnology is revolutionizing oncology by enabling precise, targeted delivery of anticancer therapeutics, thereby maximizing efficacy while minimizing off-target effects. This review critically examines the design, physicochemical characteristics, and clinical potential of nanoparticle-based drug delivery systems. Key platforms—including polymeric nanoparticles, liposomes, dendrimers, quantum dots, and gold nanoparticles—are evaluated for their ability to enhance drug solubility, stability, pharmacokinetics, and tumor-selective accumulation. Nanoparticles offer controlled and sustained drug release, reduced systemic toxicity, and improved biodistribution, collectively improving treatment outcomes. Beyond therapy, multifunctional nanocarriers facilitate early tumor detection, high-resolution imaging, and seamless integration of diagnostic and therapeutic functions. Advanced strategies such as surface functionalization, stimuli-responsive responsiveness, and combination therapies further increase specificity and help overcome challenges like multidrug resistance and nonspecific tissue uptake. Recent innovations in nanoparticle engineering are accelerating the translation of these systems into personalized and precision medicine approaches. By bridging therapeutic and diagnostic capabilities, nanoparticle-based drug delivery platforms represent a transformative advancement in cancer care, offering significant promise for clinical application and improved patient outcomes.
Keywords: *Nanoparticles, Liposomes, Carbon nanotubes, Exosomes, PEGylation, EPR effect, Active targeting, Theranostics*

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INTRODUCTION

Between 377 and 460 BC, Hippocrates—often regarded as the father of medicine—first introduced the term **cancer**. Today, cancer remains one of the leading global health challenges, affecting an estimated 19.3 million people worldwide, with 18.1 million new diagnoses and nearly 10 million deaths annually. Breast cancer is the most prevalent form, while oral cancer also represents a significant burden; in 2017, the World Health Organization reported 31,910 new cases and 6,490 related deaths in the United States (1). Transitional cell carcinoma (TCC) of the bladder is the sixth most common cancer in the United States. Although most bladder cancers are detected at an early stage, they carry a substantial risk of recurrence and progression (2). Historically, Hippocrates attributed breast cancer to humoral imbalance, and by the late 1800s, William Halsted's radical mastectomy became the standard treatment. In the 21st century, the focus has shifted toward targeted therapy, immunotherapy, and personalized medicine, supported by advances in early diagnosis and cancer biology (3). Projections indicate that by 2030, cancer-related deaths could reach 30 million annually, underscoring the urgent need for more effective therapeutic strategies. Early detection remains a decisive factor in reducing mortality; for instance, patients diagnosed with metastatic disease have an estimated 5-year survival rate of only 27%, whereas those with localized breast cancer achieve a 5-year relative survival rate approaching 90% (4). Projections indicate that by 2030, cancer-related deaths could reach 30 million annually, underscoring

the urgent need for more effective therapeutic strategies. Early detection remains a decisive factor in reducing mortality; for instance, patients diagnosed with metastatic disease have an estimated 5-year survival rate of only 27%, whereas those with localized breast cancer achieve a 5-year relative survival rate approaching 90% (5). Hematopoietic malignancies (HMs) arise from the hematopoietic system and include leukemia, lymphoma, multiple myeloma (MM), and myelodysplastic syndromes (MDS). Despite therapeutic advances, the overall 5-year survival rate for HMs remains low, imposing both financial and emotional burdens on patients and families (6). Cancer continues to pose a major global public health challenge, with a profound societal and economic impact. In 2016, the United States alone reported approximately 1,685,210 new cancer cases and 595,690 cancer-related deaths. Oral cancer ranks as the sixth most common cancer worldwide, with a 5-year survival rate of about 50% (1). On a global scale, cancer accounts for an estimated 19.3 million new diagnoses and 10 million deaths annually, highlighting its status as a critical health crisis. Despite advances, conventional chemotherapy faces persistent limitations, including a lack of tumor specificity, systemic cytotoxic side effects, short plasma half-life, poor solubility under physiological conditions, multidrug resistance (MDR), and the persistence of stem-like cancer cells (7). Colorectal cancer (CRC) further illustrates this burden: in 2022, CRC accounted for over 10% of all new cancer cases and cancer-related deaths worldwide**,** with more than 1.9 million new diagnoses and approximately 904,000 fatalities. Globally, colorectal cancer ranks second in cancer-related mortality and third in incidence (8).

Nanotechnology focuses on the design and use of materials within the 1–100 nm scale, allowing precise interaction with and penetration into cellular structures. In oncology, these nanoscale systems provide key benefits for early cancer detection and targeted drug delivery by enhancing cellular uptake and improving therapeutic accuracy. Nanodevices sized 1–25 nm can efficiently enter most cell types, supporting their use in precision drug delivery. Prominent platforms with therapeutic potential include liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanocrystals, dendrimers, and inorganic systems such as magnetic nanoparticles, gold nanoparticles, and exosomes (9). For early-stage skin cancer, common treatments include excision surgery, Mohs micrographic surgery, radiation therapy, curettage, electrodesiccation, cryotherapy, and photodynamic therapy. In more advanced stages, when surgery and radiation are no longer feasible, therapeutic strategies generally involve immunotherapy, targeted therapy, and chemotherapy (10). Artificial intelligence (AI) is emerging as a critical enabler for the rational design and optimization of nanoparticle (NP)-based therapeutics. By integrating large datasets on material properties, pharmacokinetics, and tumor biology, AI-driven models can predict optimal NP size, shape, surface chemistry, and ligand configurations for improved drug loading, stability, and release kinetics. These computational tools accelerate formulation development, reduce experimental burden, and enable the design of highly tunable carriers tailored to tumor-specific microenvironments. Equally important, AI facilitates patient stratification for nanomedicine by analyzing imaging, genomic, and clinical data to identify individuals most likely to benefit from NP-based therapies. This predictive capacity helps overcome interpatient variability in phenomena such as the enhanced permeability and retention (EPR) effect and immune response. Together, AI-guided NP engineering and patient selection improve the translational efficiency of nanomedicine, enabling more precise and effective application in oncology (11). In hematological and solid malignancies, the effectiveness of conventional treatments is frequently constrained by systemic toxicity, multidrug resistance, and variable patient responses (12). From a diagnostic perspective, nanoparticles facilitate the detection of cancer biomarkers such as circulating tumor cells. Cancer-associated proteins and circulating tumor DNA (6). This nanoparticle-enabled biomarker capture improves sensitivity and enables early detection, supporting precise monitoring of therapeutic outcomes (4). In invasive breast cancer, systemic chemotherapy administered in neoadjuvant or adjuvant settings remains a mainstay of treatment, while imaging techniques such as MRI are increasingly used to evaluate therapeutic response and guide clinical decisions (13).

Table 1: Timing-Based Classification of Chemotherapy.

Type	Timing	Purpose
Neo adjuvant	Before surgery	Shrink tumor, improve surgical outcomes.
Adjuvant	After Surgery	Kill remaining cancer cells, prevent recurrence.
Palliative	At the stage (often late)	Relieve symptoms, not intended to cure.

Immunostimulants act as pathogen-associated molecular patterns (PAMPs), which the immune system recognizes as danger signals. Pattern recognition receptors (PRRs) play a central role in the development of immunostimulants designed to stimulate cytokine production. Small-molecule agonists, both

nucleotide-based and non-nucleotide-based, function as immunostimulants by activating the cGAS–STING signaling pathway. The nucleotide-based class primarily includes natural ligand molecules derived from cyclic dinucleotides. Significant progress in prostate cancer therapy has been achieved using mRNA-based cancer vaccines, including CureVac's CV9103 vaccine specifically targeting prostate cancer (14). In the field of nanotechnology, considerable attention is directed toward the development of nanomotors (NMs), particularly tubular nanomotors (TNMs). SBA-15 mesoporous silica has been functionalized with copper and iron oxide nanoparticles to produce catalytic TNMs. These nanomotors have been extensively characterized using techniques such as BET analysis, high-resolution transmission electron microscopy (HR-TEM), scanning electron microscopy with energy-dispersive spectroscopy (SEM-EDS), X-ray photoelectron spectroscopy (XPS), and X-ray diffraction (XRD). Among the various nanomotor formulations tested, high–metal oxide–loaded variants containing CuO alone or in combination with other components have shown notable potential for inducing apoptotic cell death in lung cancer treatment (15). Photodynamic therapy (PDT) utilizes photosensitizers, oxygen, and light to eliminate tumors by inducing inflammation, disrupting tumor microvasculature, and directly triggering tumor cell death. Hepatocellular carcinoma (HCC) remains one of the deadliest cancers worldwide, with only a limited fraction of patients eligible for curative surgical interventions. Preclinical studies have shown that antibody-targeted photodynamic immune nanoparticles rapidly accumulate at tumor sites, with significant localization observed within 60 minutes following administration in animal models undergoing photodynamic immunotherapy (16). Additionally, curcumin assemblies formulated with *K-cyclodextrin, poly(β-cyclodextrin),* and polymer nanoparticles have been reported to enhance curcumin stability by six- to eightfold. Representative biocompatible and biodegradable polymer micelles capable of forming hydrophobic cores include poly(ethylene-co-propylene-co-ethylene oxide) (PEO-b-PPO), poly(ethylene-co-propylene oxide) (PEO-b-PPO), poly(lactic acid) (PLA), poly(DL-lactic acid) (PDLLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(hydroxybutyrate) (PHB), and poly(β-benzyl L-aspartate) (17). Carotenoids are lipophilic compounds with a polyisoprenoid backbone, most of which contain conjugated double bonds that make them susceptible to oxidative degradation and cis–trans isomerization. Due to limited fat content in the diet, along with interactions with dietary fibers and other carotenoids, intestinal absorption of dietary lycopene is estimated at only 10–20%. Studies comparing non-encapsulated and encapsulated quercetin have demonstrated that the encapsulated form exhibits enhanced antioxidant activity. Similarly, resveratrol encapsulated in poly(lactic-co-glycolic acid) (PLGA) showed reduced effectiveness when combined with chitosan (32%) or alginate (23%). In vitro human digestion studies revealed that PLGA achieved higher encapsulation efficiency for freeze-dried aloe vera gel (86.3%) and liquid aloe vera extract (67%), with zeta potential values of –28 mV and –21.9 mV, respectively. The encapsulated forms consistently displayed superior antioxidant properties compared to their non-encapsulated counterparts (18).

Surgical intervention remains one of the most invasive local treatment options for cancer, often associated with significant physical trauma. Radiation therapy and chemotherapy can also produce adverse effects, including nausea, vomiting, and bone marrow suppression. In recent years, substantial progress has been made in the management of advanced lung cancer. Key advancements include second-generation EGFR-TKIs such as afatinib and dacomitinib, third-generation EGFR-TKIs including osimertinib and olmutinib, and ALK inhibitors such as crizotinib, ceritinib, and lorlatinib. Immunotherapeutic agents, particularly pembrolizumab and nivolumab, have also become important components of treatment strategies(19). Within the tumor microenvironment (TME), tumor-associated macrophages (TAMs) are abundant, representing roughly 30–50% of the stromal cell population. TAMs are commonly classified under a binary polarization framework as either M1-like or M2-like subtypes (20). In studies using the aggressive MDA-MB-231 breast cancer cell line, which lacks human estrogen receptor-alpha (ER-α), treatment with curcumin significantly reduced cellular invasiveness and induced apoptosis in vitro. This effect was associated with inhibition of the NF-κB survival pathway and downregulation of inflammatory cytokines, including CXCL1, CXCL2, CXCR4, and matrix metalloproteinases (MMPs) (21). Compared with unformulated curcumin, nanocurcumin showed improved cellular uptake and enhanced anti-proliferative effects. In human cervical cancer (HeLa) cells, nanocurcumin displayed greater cytotoxicity, reduced clonogenic potential, and increased apoptosis. Additionally, it modulated the expression of apoptosis-related genes such as p53, Bcl-2, and various caspases, while influencing key signaling pathways including PI3K/Akt, JAK/STAT3, and NF-κB (22). Recent progress in cancer immunotherapy has been driven largely by antibodies targeting immune checkpoints, significantly improving treatment outcomes. In parallel, nucleic acid-based strategies, including gene regulation, adoptive T-cell therapies, and cancer vaccines, are increasingly applied to enhance antitumor immune responses (23). In photodynamic therapy (PDT), photosensitizers, when

combined with a light source and oxygen, play a pivotal role by absorbing light at specific wavelengths to trigger photochemical or photophysical reactions. The efficacy of PDT in inducing tumor cell death depends on the type and concentration of photosensitizers as well as the characteristics of target cells (8). Considerable research has focused on modifying metal complexes using a variety of techniques, including the incorporation of polymers, liposomes, micelles, enzyme-mimicking metal oxide nanomaterials, functionalized inorganic nanoparticles, and combinations with conventional anticancer drugs. Recent research has explored the use of nanoparticle platforms to improve PDT and chemotherapy outcomes. Metal complexes have been modified through incorporation into polymers, liposomes, micelles, enzyme-mimicking metal oxide nanomaterials, and functionalized inorganic nanoparticles. These approaches, often combined with conventional anticancer drugs, enhance delivery efficiency, selectivity, and therapeutic potency while minimizing systemic toxicity (24). Alginate is an important polymer due to its broad applications, low cost, mild gelation behavior, biocompatibility, ease of handling, non-toxic nature, and derivation from renewable sources. Alginate is a versatile polymer widely used in nanocarrier design due to its low cost, mild gelation properties, biocompatibility, ease of handling, non-toxicity, and renewable origin. Cancer cell targeting with nanocarriers primarily relies on two strategies: passive targeting, which takes advantage of tumor-specific characteristics such as leaky vasculature to enhance accumulation in the tumor microenvironment, and active targeting, which depends on ligand receptor interactions (25). In Stage IV cancers, characterized by metastasis to distant organs such as the liver or lungs, treatment often involves multimodal strategies combining surgery, chemotherapy, targeted therapy, and immunotherapy (10). Nanoparticle-based vaccines are designed to strengthen the adaptive immune response, promoting robust and long-lasting antitumor immunity. Various cell types, including mucosal and oral epithelial cells as well as antigen-presenting cells (APCs), express pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), which serve as targets for NP-mediated immune activation (26). Antibody–drug conjugates (ADCs) aim to selectively bind receptors overexpressed on cancer cells, enhancing tumor-specific delivery. A prominent example is the HER2 receptor tyrosine kinase (ErbB2), part of the epidermal growth factor receptor (EGFR) family, which also includes HER3 and HER4. These receptors are frequently overexpressed in gastric, ovarian, and breast cancers, making HER2 a common target for maytansine-based ADCs (27). Cytokines such as interleukin-12 (IL-12) hold strong immunotherapeutic potential but are limited by systemic toxicity. Nanocarrier design has addressed this challenge by making the delivery vehicle the key determinant of efficacy and safety. For example, PLE–IL-12 nanoparticles engineered via layer-by-layer (LBL) assembly enable high cytokine loading, sustained release, and tumor-selective delivery. In C57BL/6 mouse models, these carriers minimized systemic toxicity while enhancing tumor-infiltrating lymphocyte activation and slowing colon cancer progression (28). For difficult-to-treat cancers, such as those affecting the brain and liver, strategies including prodrug design, macromolecular matrix systems, and biodegradable polymers can enhance therapeutic delivery. Magnetic nanoparticles, in particular, have shown versatile applications in cancer diagnosis and therapy, with minimal reported toxicity (18). In niosomal drug formulations, factors such as surfactant type and cholesterol or lipid concentration critically influence encapsulation efficiency (EE) and particle size, as these parameters modify the hydrophilic–lipophilic balance (HLB) of the vesicle system. An optimal nanoparticle delivery platform should be compact, achieve high encapsulation efficiency, deliver therapeutically relevant doses to the target site, penetrate tumor tissue effectively, and provide controlled drug release (29). Although the clinical application of nanotechnology remains relatively limited, it is poised to bring transformative changes to healthcare. Some researchers and clinicians, however, maintain a cautious stance, adopting a wait-and-see approach. The optimism surrounding this field is largely driven by recent innovations demonstrating the integration of nanotechnology with biological systems (30). Interleukin-10 (IL-10) is a cytokine with potent anti-inflammatory properties that contributes to immunosuppression within the tumor microenvironment (TME), allowing malignant cells to evade immune surveillance. Nanoparticle-based strategies targeting IL-10 can reprogram the TME toward a pro-inflammatory state, either by delivering inhibitory molecules or through gene-silencing approaches (31). Nanoparticles can localize to tumors via passive or active targeting mechanisms. Passive targeting exploits the enhanced permeability and retention (EPR) effect, whereby nanoparticles accumulate in tumor tissue due to characteristics of solid tumors such as high vascular permeability and limited lymphatic drainage. Currently, at least 15 nanoformulations in clinical use utilize EPR-based passive targeting, forming the basis of FDA-approved products like Doxil and Apealea (32). However, the magnitude of the EPR effect shows considerable variability among human patients, which can influence therapeutic outcomes. Advances in nanocarrier engineering have improved the pharmacokinetic and pharmacological profiles of anticancer nanomedicines, reducing off-target effects and enabling precise delivery through either passive or ligand-mediated active targeting (33).

Traditional chemotherapeutic drugs are often limited by poor efficacy, drug resistance, nonspecific distribution, low bioavailability, and toxicity to healthy tissues, which can reduce patient tolerance (34). In contrast, nanomedicine offers several advantages. By exploiting the EPR effect in the TME, nanocarriers deliver therapeutics directly to malignant cells with high specificity. The leaky vasculature and poor lymphatic clearance of tumors enable nanoparticles to preferentially accumulate in tumor tissue, achieving higher drug concentrations at the target site while minimizing harm to healthy cells, thereby improving therapeutic outcomes. In active targeting, nanocarriers functionalized with ligands such as antibodies against HER2 not only enhance selective binding but can also promote internalization into cancer cells, increasing therapeutic efficacy beyond surface attachment (35).

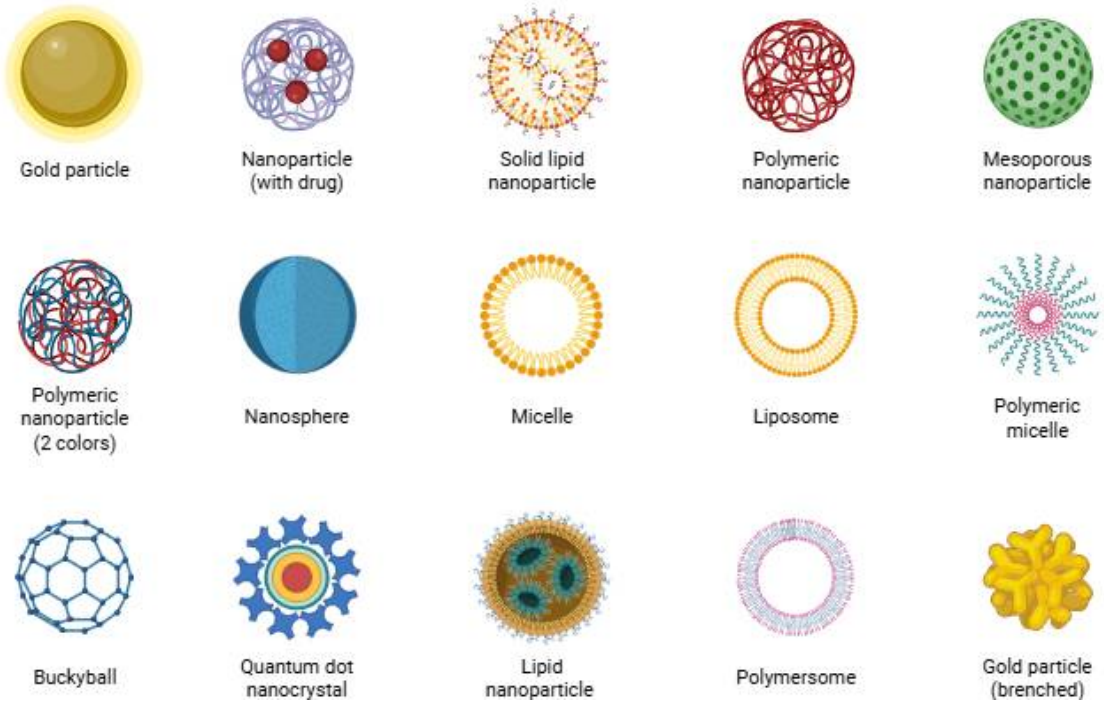

Figure 1: Representative smart nanoparticle types enabling targeted cancer drug delivery and enhanced clinical outcomes

CLASSES OF BIOACTIVE COMPOUND

A wide range of physical, chemical, and biological methods can be employed to produce nanomaterials and nanostructures with functionalities at the nanoscale. These approaches enable the conversion of both inorganic and organic substances into nanosized systems that display unique physicochemical properties and specialized applications. The remarkable adaptability of nanomaterials is evident from the diversity of materials that can be engineered at this scale, ranging from inorganic types such as silicon, metallic nanoparticles, and quantum dots to organic systems like micelles, liposomes, polymeric nanoparticles, and dendrimers. Physical fabrication techniques typically rely on top-down processes, in which bulk materials are reduced to nanoscale dimensions using methods such as milling, grinding, and lithography. In contrast, chemical synthesis methods generally follow bottom-up strategies, where nanomaterials are generated via controlled chemical reactions (36).

Overview of Nanoparticle-Based System in Oncology

Liposomes:- Liposomes are spherical vesicular nanocarriers primarily composed of cholesterol and phospholipids, which self-assemble into one or more lipid bilayers surrounding an aqueous core. This bilayer arrangement enables the simultaneous encapsulation of both hydrophilic and hydrophobic therapeutic agents—hydrophilic molecules partition into the aqueous compartment, whereas hydrophobic drugs integrate within the lipid bilayer. First described by Alec D. Bangham in the early 1960s during studies on phospholipid bilayer structures, liposomes have since become one of the most widely investigated nanocarrier systems for biomedical applications, including drug delivery, gene therapy, and diagnostic imaging. They address critical limitations of conventional chemotherapy, such as short plasma half-life, multidrug resistance (MDR), poor solubility, systemic toxicity, and lack of tumor specificity. A notable clinical milestone is the approval of PEGylated doxorubicin (Doxil®/Caelyx®),

which is used in indications such as ovarian cancer, Kaposi's sarcoma, and multiple myeloma, and has demonstrated prolonged circulation time and reduced cardiotoxicity compared to free doxorubicin. However, repeated administration of PEGylated liposomes may induce the accelerated blood clearance (ABC) phenomenon, which can compromise therapeutic efficacy and remains a recognized limitation of this platform (10,37,38).

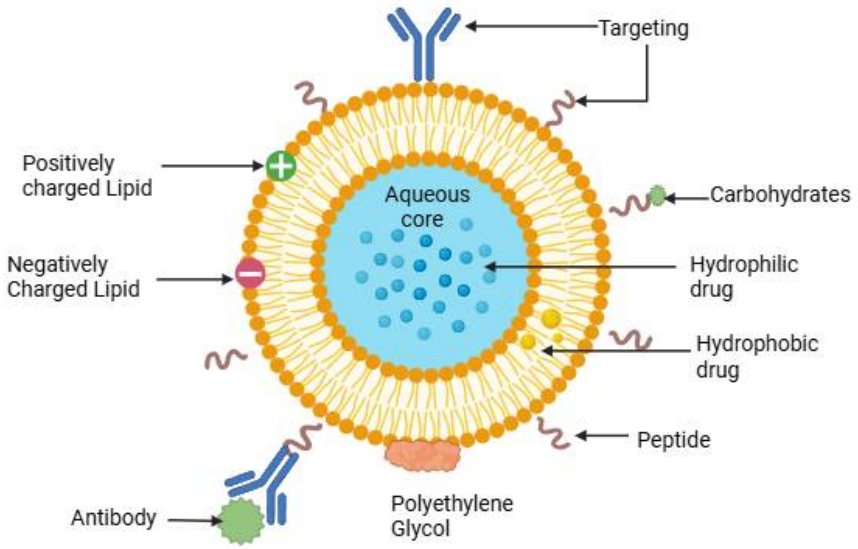

Figure 2: Schematic representation of a multifunctional liposome showing surface functionalization with antibodies, peptides, and carbohydrates for targeted drug delivery.

Methods of liposome formulation:

Liposomes can be prepared by several methods, such as thin-film hydration, reverse-phase evaporation, ethanol injection, and detergent dialysis. In thin-film hydration, lipids form a dry film that is later hydrated a with drug solution, while reverse-phase evaporation uses organic solvents to create vesicles. Ethanol injection is a rapid mixing method where lipids in ethanol are injected into water, and detergent dialysis relies on gradual detergent removal. Although useful in research, these methods face challenges in large-scale production and long-term stability. To overcome this, proliposomes were developed as dry, stable particles that form liposomes upon hydration, making them more suitable for industrial applications (39).

Silver Nanoparticles:

Silver nanoparticles (AgNPs) have attracted considerable attention in oncology due to their distinctive physicochemical characteristics, including nanoscale dimensions, high surface area-to-volume ratio, excellent electrical conductivity, chemical stability, and unique surface plasmon resonance (SPR) properties. SPR is particularly valuable in photothermal therapy, where localized heating induced by SPR selectively damages tumor tissue. The therapeutic potential of AgNPs is largely attributed to the release of silver ions (Ag^+), which exert cytotoxic effects on cancer cells through multiple mechanisms, including oxidative stress induction, disruption of cellular redox balance, and modulation of immune responses. Nanoparticles with diameters below 100 nm can exploit the enhanced permeability and retention (EPR) effect, promoting preferential accumulation in tumors due to leaky vasculature. Once localized in the tumor microenvironment, AgNPs suppress tumor proliferation by inducing apoptotic and necrotic cell death, while enhancing cytotoxic immune cell activity. Experimental evidence demonstrated that AgNP treatment increases infiltration and activation of $CD8^+$ cytotoxic T lymphocytes. Flow cytometry analyses revealed a significant rise in tumor-infiltrating $GZMB^+$ (granzyme B-positive) and IFN-γ^+ $CD8^+$ T cells, indicating a robust antitumor immune response. Immunofluorescence imaging further confirmed elevated $CD8^+GZMB^+$ T cells within tumor regions following AgNP administration (10,26). Beyond anticancer activity, AgNPs possess potent antimicrobial properties, effectively targeting bacteria, viruses, and pathogenic eukaryotes (40). Their synthesis can be achieved through both chemical and green methods, with the seeded growth technique offering precise control over particle size and monodispersity. In a typical seeded growth procedure, seeds are produced by reacting 0.01 M silver

perchlorate (250 μL, 0.0025 mmol) with 0.1 M cetyltrimethylammonium bromide (CTAB; 7.5 mL, 0.75 mmol) and freshly prepared ice-cold 0.01 M sodium borohydride ($NaBH_4$; 600 μL, 0.006 mmol). The mixture is rapidly inverted for two minutes to ensure uniform nucleation, then allowed to stabilize for one hour at room temperature. The growth solution is prepared by combining 0.1 M CTAB (6.4 mL, 0.64 mmol), 0.01 M $AgClO_4$ (800 μL, 0.008 mmol), and 0.1 M ascorbic acid (3.8 mL, 0.38 mmol) in 32 mL deionized water, after which the seed solution is diluted tenfold before addition (41). For biomedical applications, precise control over nanoparticle size, morphology, and surface chemistry is critical for optimal therapeutic outcomes. Functional coatings such as polyethylene glycol (PEG) extend systemic circulation time, while antibodies, peptides, or aptamers provide active tumor targeting. Surface engineering enhances stability, biocompatibility, and selective tumor accumulation. Drug molecules—including chemotherapeutics, proteins, or nucleic acids—can be incorporated via adsorption, covalent conjugation, or encapsulation. Drug release at the tumor site can be triggered by environmental stimuli (pH changes, enzymatic activity) or external energy sources (e.g., light in photothermal therapy), maximizing efficacy while minimizing off-target toxicity (42).

Chimeric antigen receptor (CAR) T-cell therapy is an advanced immunotherapeutic approach that utilizes a patient's own T lymphocytes, which are genetically engineered to identify and destroy malignant cells. These modified lymphocytes, known as CAR T cells, are equipped with synthetic receptors that specifically bind to tumor-associated antigens present on cancer cell membranes. Upon antigen recognition, CAR T cells undergo rapid proliferation, secrete pro-inflammatory cytokines, and release cytotoxic granules, thereby inducing targeted tumor cell death (43).

Paraptosis represents a unique programmed cell death mechanism that is morphologically and biochemically distinct from apoptosis and necrosis. It is characterized by extensive cytoplasmic vacuolization, mitochondrial swelling, and endoplasmic reticulum dilation, without the DNA fragmentation typical of apoptosis. Emerging evidence indicates that therapeutic strategies combining paraptosis-inducing agents with conventional chemotherapy can significantly potentiate anticancer efficacy. For instance, the co-administration of afatinib with celastrol has demonstrated synergistic antitumor effects in non-small cell lung cancer models (44).

Niosomes:- Niosomes are self-assembled, bilayered nanocarriers composed of cholesterol and nonionic surfactants, designed to encapsulate both hydrophilic and lipophilic drugs. Their nonionic surfactant composition confers low inherent toxicity, making them suitable for biomedical use. Critical parameters—such as biocompatibility, encapsulation efficiency, release kinetics, and polydispersity index (PDI)—play decisive roles in determining therapeutic performance (25). Among innovative formulations, melittin-loaded niosomes have shown remarkable potential in breast cancer therapy due to their enhanced cellular uptake, targeted delivery, and controlled release properties. In vitro studies revealed that treatment with melittin-loaded niosomes significantly increased the expression of pro-apoptotic genes (Bax, Caspase-3, Caspase-9) while downregulating anti-apoptotic and metastasis-associated genes (Bcl-2, MMP2, MMP9), thereby amplifying cytotoxic effects on cancer cells (45).

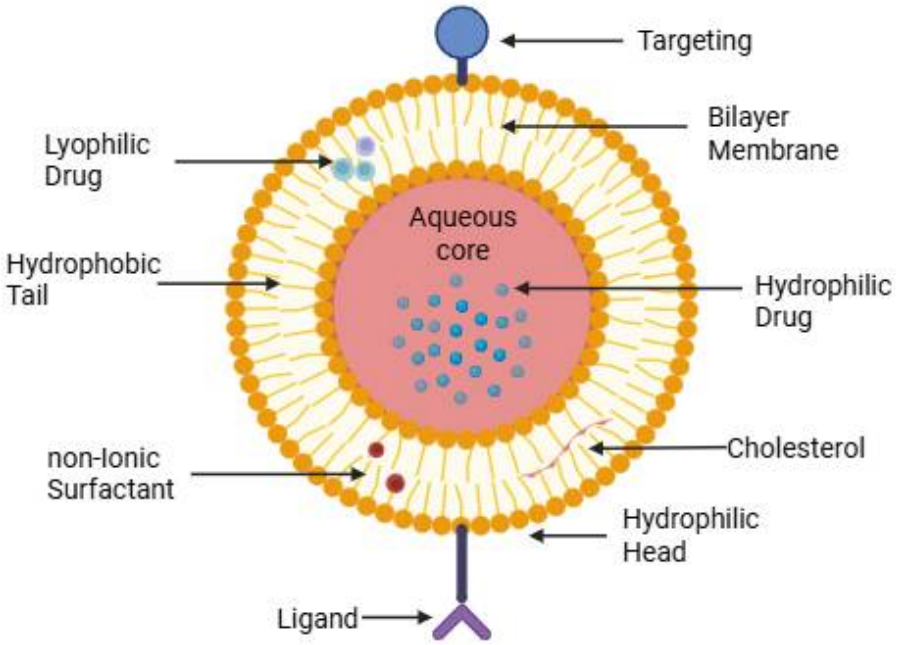

Figure 3: Schematic representation of a niosomal nanocarrier illustrating its bilayer structure, encapsulation of hydrophilic and hydrophobic drugs, and ligand-mediated targeting.

Curcumin: Curcumin, a naturally occurring polyphenolic compound extracted from the rhizome of ***Curcuma longa***, has attracted substantial interest in cancer research due to its broad-spectrum anticancer activities, which include chemopreventive, chemosensitizing, and radiosensitizing effects. Extensive in vitro and in vivo studies have demonstrated that curcumin modulates multiple cellular processes, such as inhibition of proliferation, induction of apoptosis, suppression of angiogenesis, and reduction of metastatic potential. Mechanistically, it regulates diverse signaling pathways, including NF-κB, STAT3, PI3K/Akt, and MAPK, while downregulating oncogenic and anti-apoptotic proteins such as Bcl-2, Cyclin D1, and survivin. In experimental tumor models, such as chemically induced skin carcinogenesis, topical or systemic administration of curcumin has been shown to reduce tumor initiation and progression, whereas in breast and colorectal cancer models, it enhances radiosensitivity and potentiates the cytotoxicity of conventional chemotherapeutics like paclitaxel and doxorubicin (21). Importantly, nanocarrier-mediated curcumin delivery has shown superior therapeutic outcomes compared with free curcumin. In combination therapy, curcumin-loaded nanoparticles synergize with chemotherapy by reversing multidrug resistance, modulating efflux transporters such as P-glycoprotein, and sensitizing tumor cells to apoptosis. Similarly, in radiotherapy settings, curcumin-loaded nanocarriers improve radiosensitization by suppressing ROS-induced DNA repair pathways and promoting tumor cell apoptosis, thereby reducing tumor burden and improving survival in preclinical cancer models. These findings highlight the potential of nanocarrier-based curcumin formulations as effective adjuvant strategies that integrate with conventional cancer therapies for enhanced clinical outcomes. Despite its therapeutic promise, curcumin suffers from critical pharmacokinetic limitations, including poor aqueous solubility, instability under physiological conditions, extensive metabolism, and rapid systemic clearance, all of which contribute to its extremely low oral bioavailability (<1%). These challenges have significantly hindered its clinical translation, as high doses are often required to achieve pharmacologically relevant plasma concentrations, which may not be feasible for long-term therapy (37).

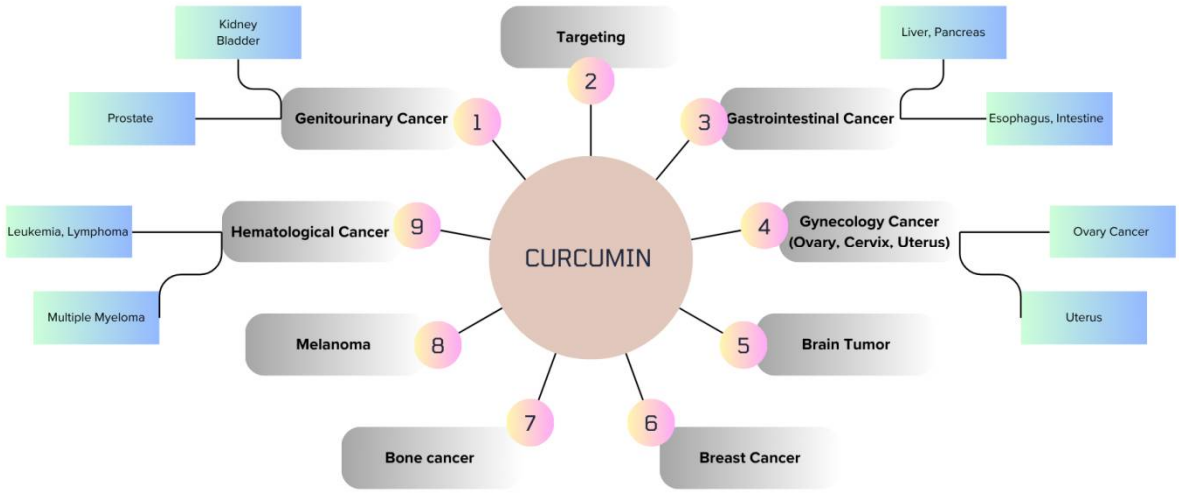

Figure 4: "Curcumin: A Multi-Targeted Approach in Cancer Therapy"

To address these barriers, a wide range of nanotechnology-based delivery strategies have been explored. Polymeric nanoparticles, liposomes, solid lipid nanoparticles, dendrimers, micelles, and inorganic nanocarriers have all been employed to improve curcumin stability, enhance solubility, and prolong systemic circulation. For example, chitosan-conjugated nanoparticles have demonstrated improved intestinal absorption and tumor uptake, while pluronic-stabilized iron oxide nanoparticles have enabled targeted delivery in HER2-positive breast cancer models. Polymeric micelles and lipid-based carriers have further provided controlled release and enhanced curcumin accumulation in tumor tissues through the enhanced permeability and retention (EPR) effect (20).

RuPoP@CM: Ruthenium-based polypyridyl complexes (RuPOP) have attracted significant interest in cancer nanomedicine due to their unique photophysical properties, ability to interact with DNA, and potential to circumvent drug resistance. A novel strategy to enhance their therapeutic selectivity involves coating these complexes with cancer cell membranes (CMs), which impart biomimetic characteristics such as homologous targeting and immune evasion.

Two primary mechanisms underlie the in vitro antitumor effects of CM-coated RuPOP nanoplatforms:

1. Induction of programmed cell death through apoptosis activation pathways.
2. Disruption of the cell cycle to prevent uncontrolled proliferation.

Experimental findings using flow cytometry analysis demonstrated that both RuPOP@MCM (RuPOP coated with MDA-MB-231 cell membranes) and RuPOP@KCM (RuPOP coated with K562 cell membranes) significantly increased apoptotic cell populations while simultaneously causing marked cell cycle arrest. Specifically, RuPOP@MCM showed high potency against triple-negative breast cancer (MDA-MB-231) cells, whereas RuPOP@KCM was highly effective against chronic myelogenous leukemia (K562) cells, confirming the advantage of homologous membrane coating in enhancing targeted cancer cell recognition and cytotoxicity (24).

Carbon Nanotubes: (CNTs) are nanoscale, cylindrical allotropes of carbon formed by rolling graphene sheets into seamless tubes. They were first described in 1991 by Japanese physicist Sumio Iijima (10). (CNTs) are nanoscale, cylindrical allotropes of carbon formed by rolling graphene sheets into seamless tubes. They were first described in 1991 by Japanese physicist Sumio Iijima (46). The distinctive physicochemical properties of CNTs, particularly their high aspect ratio, large surface area, and ability to traverse biological membranes via a needle-like piercing mechanism, make them promising nanocarriers for anticancer drug delivery. Their surface can be chemically functionalized to enhance solubility, biocompatibility, and targeted delivery efficiency. Recent studies have demonstrated their therapeutic potential. For instance, SWCNTs conjugated with paclitaxel exhibited superior tumor growth inhibition

compared to paclitaxel alone in in vitro cancer models, highlighting the advantages of CNT-mediated delivery in improving drug bioavailability and tumor-specific targeting (38).

Exosomes:- Exosomes have attracted growing attention as natural nanocarriers capable of delivering drugs or bioactive molecules with high specificity. A particularly appealing feature is their inherent ability to cross the blood–brain barrier (47). a property that synthetic nanocarriers often struggle to replicate. However, despite this promise, translation into the clinic is hampered by several critical barriers. Exosomes are inherently heterogeneous in size and composition, which complicates quality control. In addition, their drug-loading efficiency remains relatively low, and large-scale isolation and purification techniques are still underdeveloped. These challenges raise concerns regarding reproducibility, therapeutic consistency, and scalability, all of which are essential for clinical adoption. To address some of these limitations, polymeric nanocarriers have emerged as a versatile alternative. Built from biocompatible polymers with high purity and well-defined physicochemical characteristics, they enable efficient encapsulation of therapeutic agents, offer controlled release profiles, and are amenable to large-scale manufacturing processes (48).

Palladium Nanoparticles: Palladium Nanoparticles have garnered significant attention in oncology for both diagnostic and therapeutic applications. Their primary advantage lies in palladium's remarkable electrocatalytic activity, particularly in reactions involving hydrogen peroxide (H_2O_2)—a key metabolite generated in the tumor microenvironment. Elevated levels of H_2O_2 are associated with tumor progression, metastasis, and aging processes in multiple tissues.

When Palladium Nanoparticles act as catalysts, they promote the decomposition of H_2O_2 into water (H_2O) and oxygen (O_2). This catalytic conversion alleviates tumor hypoxia, a condition that often reduces the effectiveness of cancer treatments. By enhancing local oxygen availability, Palladium Nanoparticles can significantly improve the therapeutic efficiency of reactive oxygen species (ROS)-dependent modalities such as photodynamic therapy (PDT) and photothermal therapy (PTT)**.** Consequently, palladium-based nanomaterials not only contribute to tumor microenvironment modulation but also serve as versatile platforms for integrating detection and treatment strategies (49).

Magnetic Nanoparticles: (MN), typically ranging from 10 nm to 50 nm, have strong binding capabilities and display several advantageous properties (18). They are produced from metal salts and oxides, with common examples including iron (Fe), copper (Cu), platinum (Pt), silver (Ag), and gold (Au), all known for their high thermodynamic stability (50). Temperature-controlled drug release can be achieved by heating iron oxide nanoparticles through alternating magnetic fields. For example, NanoTherm, an aminosilane-coated iron oxide nanoparticle, has been approved for the treatment of prostate cancer and glioblastoma (51). Various forms of magnetism exist in nature, including diamagnetism, ferromagnetism, antiferromagnetism, ferrimagnetism, and paramagnetism. For biomedical use of magnetic nanoparticles (MNPs), superparamagnetism is particularly valuable. This property emerges in particles smaller than 30 nm, where thermal fluctuations cause their magnetic moments to flip randomly. As a result, in the absence of an external field, the overall magnetization averages out to zero (52).

Synthesis of SPIONs: SPIONs can be synthesized by physical, biological, or chemical methods, with chemical routes being the most common due to better control over size and shape. Co-precipitation is simple and scalable but gives variable particle sizes, while thermal decomposition ensures uniformity with the help of surface modifications. Hydrothermal and solution combustion methods are eco-friendly, producing crystalline nanoparticles under high temperature and pressure or rapid self-sustaining reactions. Emerging microwave and sonochemical techniques further improve speed and uniformity (39).

Chemotherapy in Cancer Treatment

Chemotherapy works by stopping the growth, division, and spread of cancer cells. It is usually given in cycles, which allows time for healthy cells to recover after damage from the treatment (53). However, both radiotherapy (RT) and chemotherapy (CT) are associated with toxicity to normal tissues, making it necessary to develop new strategies. Nanoparticle (NP) carriers offer a promising approach by enabling targeted delivery of radiosensitizers to tumors and controlled release of chemotherapeutic agents directly to cancer cells, thereby improving treatment effectiveness and reducing side effects (54).

Extracellular Vesicles: EV Purification and Isolation

During large-scale production, large volumes of conditioned media are separated from extracellular vesicles (EVs). Major contaminants include other vesicles, EV aggregates, products of cell necrosis, DNA, cellular debris, organelles, free proteins, and protein aggregates. Preventing microbial contamination—such as mycoplasma, fungi, and bacteria—is essential. In research applications, EVs are often isolated from small quantities of highly complex biological samples, which can vary greatly in composition. Non-EV nanoparticles, primarily lipoproteins, ribonucleoproteins, and protein aggregates, are the main sources of contamination. Commonly used purity indicators include the particle-to-protein ratio and the

protein-to-lipid ratio (55). A variety of tumors, such as colorectal cancer, metastatic breast cancer, and metastatic melanoma, can be effectively eliminated by extracellular vehicles (EVs) (56). Mesoporous silica nanoparticles (MSNs) can be synthesized with particle sizes ranging from 50 nm to 300 nm, promoting efficient cellular uptake through phagocytosis, pinocytosis, endocytosis, and both caveolin- and clathrin-mediated pathways, while minimizing cellular toxicity (7).

Two-Dimensional Nanomaterials (2D NMs): Dimensional Nanomaterials are a unique class of nanomaterials with a pronounced arrangement of atoms or molecules in one dimension (thickness) and minimal extension in the other two dimensions. This structural distinction imparts exceptional physical, chemical, and electronic properties, enabling wide applications in nanotechnology, electronics, materials science, and biomedicine.

- Enhanced surface area allows for greater drug-loading capacity and improved combined therapeutic outcomes.

Surface-exposed atoms, most of which are located on the surface, provide distinctive physicochemical characteristics and enable precise chemical functionalization (57).

Table 2: Comparison of nanoparticles used in cancer treatment

Nanoparticle Types	Structure	Application	Advantages	Example	Typical size	Limitation	Approaches	Release Controls
Liposomes	Phospholipid bilayer Vesicles with aqueous core	Drug Delivery (e.g., Doxil)	Biocompatible, encapsulation of both hydrophilic &hydrophobic drugs, FDA-Approved	Doxil® (pegylated liposomal doxorubicin)	50–200 nm	Stability issues, RES clearance without PEGylation	Passive encapsulation, active loading (pH gradient, ion gradient)	Diffusion, lipid bilayer destabilization
Dendrimers	Highly Branched Tree-like Polymer	Gene and drug delivery, imaging	High loading capacity, Multivalency, tunable Surface	PAMAM dendrimers (experimental)	5–20 nm	Surface toxicity, Expensive synthesis	Covalent conjugation, encapsulation in cavities	Diffusion, pH-triggered release, surface erosion
Polymeric Nanoparticles	Solid Colloidal Particles Made From Biodegradable Polymer (Eg. PLGA, PEGylation)	Controlled drug release tumor targeting	Biodegradable, customizable drug release, approved in clinical trials	PLGA, PLA nanoparticles	50–300 nm	Low drug loading complex Formulation	Emulsion/solvent evaporation, nanoprecipitation	Diffusion, polymer degradation /erosion
Gold nanoparticles	Inorganic gold core, Often Surface functionalized	Photothermal therapy, drug delivery, and imaging	Easy to modify, good biocompatibility	AuNPs, nanoshells	10-100nm	Long-term toxicity Concern, potential Accumulation	Surface adsorption, thiol/PEG conjugation	Stimuli-responsive (light, heat)
Quantum Dots	Semiconductor Nanocrystals With Fluorescent Properties	Cancer imaging diagnostics	High brightness, photostability, tunable emission	CdSe/ZnS QDs	2-10nm	Heavy Metal content, toxicity risks	Surface adsorption, ligand exchange, polymer coating	Diffusion, photo-triggered release
Carbon Nanotubes	Cylindrical carbon molecule	Drug/Gene delivery photothermal therapy	High surface area, cell penetration ability	SWCNT, MWCNT	1–50 nm (diameter)	Non-biodegradable potential immunogenicity	π–π stacking, covalent conjugation	Diffusion, NIR-triggered release

Magnetic Nanoparticles	Typically, iron oxide cores (Fe_2O_3), surface–coated	MRI contract agents, magnetic targeting	Magnetic + therapy (theranostics)	Fe3O4, γ-Fe2O3	10-30nm	Oxidation, possible cytotoxicity	Surface adsorption, covalent conjugation, and co-precipitation	Magnetic field-responsive, diffusion
Silica Nanoparticles	Porous or non-porous silica–based particles	Drug/gene delivery, Imaging	High stability, Tunable pore Size, Easy Surface modification	Mesoporous silica nanoparticles (MSNs)	50-200nm	Non-biodegradable, potential for long-term retention	Pore loading, surface functionalization	Stimuli-responsive, controlled release

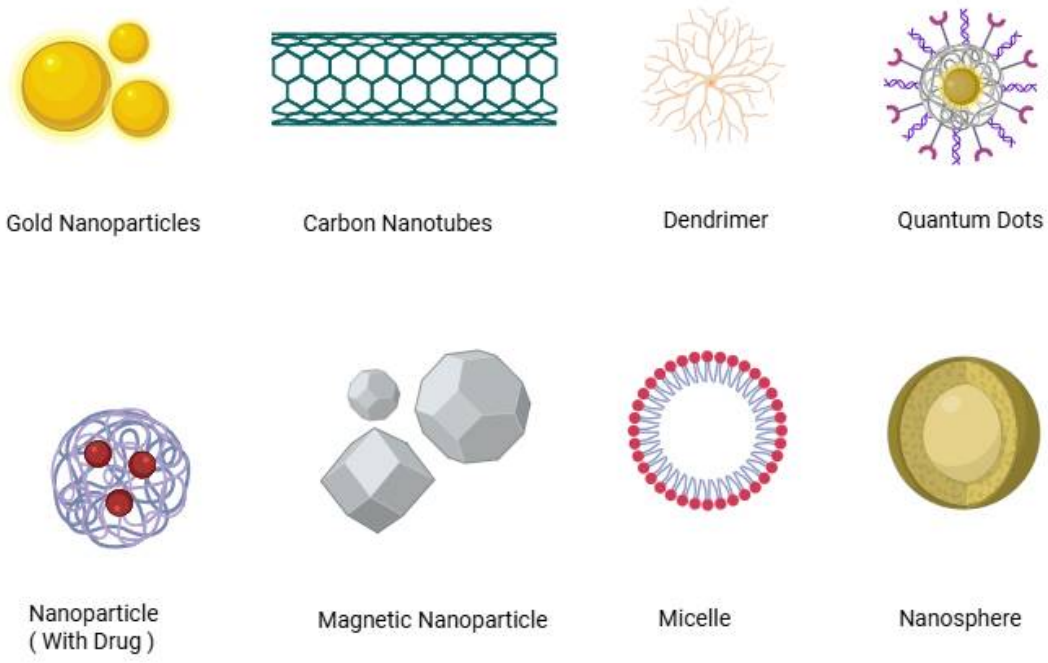

Figure 5: Various smart nanoparticle types, including gold nanoparticles, carbon nanotubes, dendrimers, quantum dots, magnetic nanoparticles, and micelles, are highlighted in their roles in targeted cancer drug delivery

Types of cancer in the body:

Oral Cancer: Oral Cancer develops through a complex, multi-stage progression. Several oral potentially malignant disorders (OPMDs) are known for their high risk of malignant transformation, including oral leukoplakia, oral erythroplakia, oral lichen planus, oral submucous fibrosis, actinic keratosis, and discoid lupus erythematosus (1).

Ovarian Cancer (OC): Ovarian cancer, often termed a "silent killer," has seen advancements in recent years with the development of new drugs aimed at reducing side effects and introducing novel therapeutic approaches. These strategies focus on minimizing damage to healthy cells while specifically targeting cancer cells for potential cure (58). Transitional cell carcinoma (TCC) of the bladder is the sixth most prevalent cancer in the United States. While the majority of bladder cancer cases are detected in their early stages, there remains a significant risk of recurrence and progression to more advanced disease (2). Roughly 80% of cancers originate from epithelial cells, which are typically located in close proximity to each other. Germ cell tumors represent about 5–10% of cases in the US, sex cord stromal tumors account for 7–8%, and other types occur less frequently (53).

Gastric Cancer: Gastric cancer is a common malignant tumor of the digestive tract and poses a serious threat to human health.

The primary surgical treatments for gastric cancer in clinical practice include:

- Laparoscopic procedures: total gastrectomy, distal gastrectomy, subtotal gastrectomy, and colectomy.
- Robot-assisted surgeries: gastrectomy, laparoscopic gastrectomy, and laparoscopic colectomy.
- Other surgical approaches: transanal local excision, transanal endoscopic microsurgery, total mesorectal excision, low anterior resection, and abdominoperineal resection.

For soft tissue imaging, photoacoustic imaging (PAI) is emerging as an alternative diagnostic technique that provides deep tissue penetration, high spatial resolution, and strong imaging contrast. Intercellular mitochondrial transfer has emerged as a critical process in the regulation of cancer progression. Evidence suggests that astrocyte-derived mitochondria promote glioblastoma development, whereas mitochondria transferred from endothelial cells facilitate tumor proliferation and contribute to resistance against chemotherapy. Interestingly, an opposite role is observed with osteocytes, where mitochondrial donation to malignant cells suppresses tumor growth (8,59). The financial strain on the healthcare system and cancer patients is significant due to the initial health complications caused by gastrointestinal cancer. Each individual's outlook for gastrointestinal diseases varies based on the stage of the illness at the time of diagnosis (40).

Lung Cancer: Lung cancer cells express a range of surface proteins, including EGFR family, ALK, ROS1, MET, RET, and NTRK**.** Nanotechnology-based approaches have been explored for targeted therapy. PD-L1 antibody-conjugated liposome-polymer nanoparticles, encapsulating doxorubicin and an infrared dye**,** demonstrated the ability to inhibit tumor growth and induce cancer cell death**.** Another study in mice assessed lipid nanoparticles containing calcium phosphate and lumefantrine (LF-CaP-Ls)**,** which significantly delayed tumor progression (5). Additionally**,** Gracilaria lemaneiformis polysaccharide (GLP) has been used as a surface modifier to stabilize selenium nanoparticles (SeNPs) and control their size. These GLP-SeNPs showed high cancer cell selectivity**,** efficient cellular uptake, and notable anticancer effects (60). Lung cancer originates from the mucosa or bronchial glands and remains the leading cause of cancer**-**related deaths worldwide. In 2022, approximately 2.48 million new cases were reported, accounting for 12.4% of all global cancer diagnoses. Pathologically, it manifests as small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC)**,** with NSCLC comprising 80–85% of cases (61).

The results from the experiments showed that following PDT treatment, HY-CH-NP significantly lowered the viability of A549 human lung cancer cells to 56%, increased ROS production by 1.6 times, and resulted in a cell death rate of 40%; additionally, the heightened release of lactate dehydrogenase indicated an increase in necrosis (8).

Intestinal Cancer: Al_2O_3 nanoparticles have been shown to enhance the spread of antibiotic resistance by increasing the expression of the bacterial membrane-binding gene RP4**.** The integration of nanoparticles significantly improves the mechanical properties of hydrogels**.** Nanofiber composites**,** known for their high crystallinity and needle-like structure**,** usually measure several hundred nanometers in length and 10–20 nanometers in width**.** They combine flexibility, stiffness, tensile strength**,** and a high surface area-to-volume ratio (62).

Breast Cancer: Breast cancer is the most common cancer among women in Iran**,** representing 24.4% of all cancer cases and causing 3.3% of cancer-related deaths per 1,000 individuals**.** Aptamers, which may be single-stranded DNA (ssDNA)**,** RNA molecules**,** or peptides, show high specificity and can bind effectively to targets such as small molecules, proteins, or cells**.** They hold promise for the diagnosis and treatment of diseases, including cancer. While RNA aptamers provide greater flexibility**,** DNA aptamers are more stable (63). This approach led to the creation of spherical Janus nanoparticles (JNPs) consisting of polyacrylic acid (Au/PAA) and gold. To improve biocompatibility and enable targeted delivery, the nanoparticles were engineered with 5-aminolevulinic acid (5-ALA) for photodynamic therapy (PDT) on one side, and selectively modified with folic acid (FA) and thiol PEG amine (SH-PEG-NH_2) on the opposite side. In in vitro PDT experiments, the FA-Au/PAA-ALA JNPs displayed strong cytotoxic activity against MCF-7 breast cancer cells, highlighting their potential in cancer treatment (8). When utilized either on its own or in conjunction with other therapies, erlotinib, an EGFR inhibitor, plays a crucial role in the management of breast cancer (64).Genetic susceptibility, in combination with microbial exposure and dietary habits, plays a key role in the development of gastric cancer (GC). In addition to modifying the gut microbiome, poor eating patterns such as diets rich in fat or salt contribute to localized and systemic inflammation. When ***Helicobacter pylori*** infection causes long-term inflammation, it disrupts the tumor microenvironment and facilitates the formation of new tumors (65). Any modification in the type or formation of chemical constituents directly affects the hydrophilic–lipophilic balance (HLB) of a niosomal formulation. Both the selection of surfactants and the proportion of cholesterol (lipid) within the composition play a critical role in determining the encapsulation efficiency (EE) and the overall size of the niosomes. For an ideal drug delivery system, the vesicles should be small in size, display high encapsulation efficiency, and be capable of carrying a large quantity of therapeutic agents, enabling them to reach the target tissue and release the drug precisely at that site (66). Changes in the chemical composition or structure can markedly influence the hydrophilic–lipophilic balance (HLB) of a niosomal system. Both the type of surfactant used and the concentration of cholesterol (lipid) incorporated into the formulation strongly determine the encapsulation efficiency (EE) as well as the vesicle size. An optimal

drug delivery system should possess a small particle size, demonstrate high encapsulation efficiency, and be capable of carrying a large drug load, effectively reaching the target tissue and releasing the therapeutic molecules at the desired site (67). Ferroptosis in breast cancer is associated with four major subtypes: Luminal A, Luminal B, HER2-positive, and triple-negative breast cancer (also known as basal-like). Each of these subtypes requires distinct therapeutic approaches. The Luminal A subtype is defined by tumors that are positive for estrogen receptors (ER) and progesterone receptors (PR) but negative for human epidermal growth factor receptor 2 (HER2). This form of breast cancer generally responds well to hormonal therapy and chemotherapy. Breast cancer metastasis to bone occurs through multiple complex steps, including invasion, migration, adhesion, and the survival of tumor cells at the metastatic site. The well-known "seed and soil" hypothesis, first proposed in 1889, suggests that the spread of cancer results from the interaction between the “seed” (tumor cells) and the “soil” (the microenvironment of the potential metastatic site) (37). Liposome-based formulations containing C6 ceramide have been shown to markedly suppress cell growth and trigger cell death in highly aggressive metastatic breast cancer cells (68).

In assessing biosafety for medical use, the hemocompatibility of metal complexes is a key factor. The biosafety of RuPOP@CM was examined in mice, with particular focus on red blood cells. Red blood cells treated with RuPOP exhibited visible alterations, including small pores and structural damage. In contrast, exposure to RuPOP@CM did not produce notable morphological changes, indicating improved compatibility (24). Surgical intervention continues to be the mainstay of treatment for breast cancer. Alongside this, targeted chemotherapeutic agents like letrozole (Let) are frequently administered to reduce the risk of tumor recurrence effectively (25).

Colorectal Cancer: Globally, colon cancer is the second leading cause of cancer-related deaths and the third most commonly diagnosed malignancy. To investigate new therapeutic options, a physician synthesized and characterized AlClPcTS41, a novel aluminum phthalocyanine derivative, as a potential photosensitizer. Further, AlClPcTS41 was combined with polyethylene glycol-coated copper–gold bimetallic nanoparticles (PEG-CuAuNPs) to develop AlCLPcTS41-PEG-CuAuNPs (8). A phase-II clinical trial was conducted in which 38 patients with metastatic colorectal cancer received a daily oral dose of 150 mg erlotinib. The treatment produced common adverse effects, such as skin rash in 34 patients and diarrhea in 23, but overall was well tolerated. Correlative analysis after one week of therapy revealed a significant decline in phosphorylated EGFR ($p = 0.008$) and phosphorylated extracellular signal-regulated kinase ($p = 0.008$). Additionally, one-third of the participants achieved stable disease for at least eight weeks (64).

Prostate Cancer: Prostate cancer is the second most common cancer worldwide and is especially prevalent among men, with incidence rates increasing markedly in those over 60 years of age. In 2022, an estimated 1.5 million new cases were reported globally, resulting in approximately 397,000 deaths. To overcome certain limitations of photodynamic therapy (PDT), a novel nanocarrier termed RB-M has been developed and evaluated for enhancing the delivery of rose bengal (RB) as a photosensitizer. This system enables controlled release of RB and its diffusion into the cytoplasm, where PDT activation is initiated using a light-emitting diode (LED) device. Experimental findings demonstrated that prostate cancer cells treated with RB-M achieved strong PDT effects when subjected to continuous irradiation within the 405–580 nm wavelength range. These outcomes were observed in both two-dimensional cultures and three-dimensional tumor spheroids. This innovative nanocarrier design addresses the challenge of limited light penetration in PDT and presents a potential therapeutic approach, particularly for patients unsuitable for chemotherapy (8).

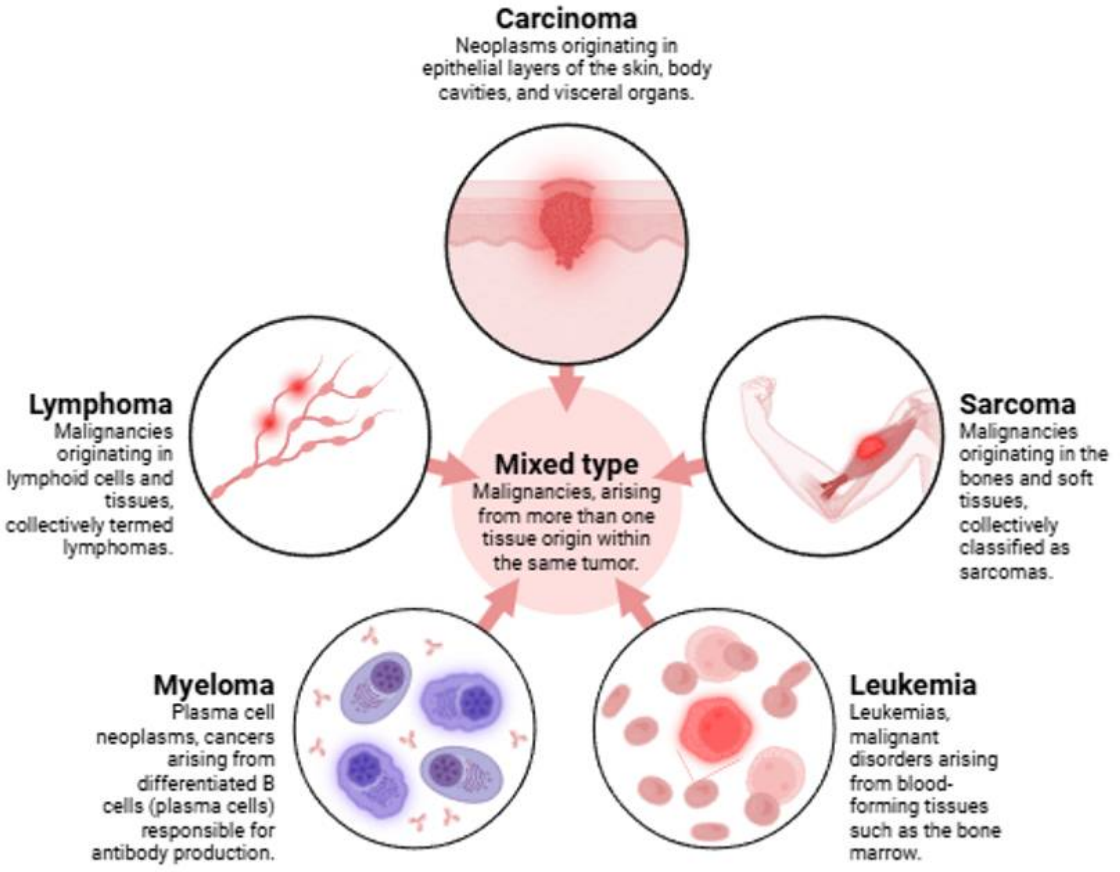

Figure 6: Types of Cancer Origin

Types of Cancer Detection:

Magnetic resonance imaging: Magnetic Resonance Imaging (MRI) is widely used for detecting cancer cells and for accurately determining tumor margins during surgical interventions. A common example of an MRI contrast agent is the Gd^{3+} ion complexed with diethylenetriamine pentaacetic acid (Gd-DTPA) (1). MET-RADS-P is a standardized reporting framework designed for assessing metastasis in prostate cancer. It enables the detection of both epithelial and non-epithelial tumor cells. Gadolinium-based contrast agents can further improve the diagnostic performance of whole-body MRI (WB-MRI), especially in regions such as the brain (69). Hereditary Paraganglioma-Pheochromocytoma Syndromes (HPP) are genetic disorders marked by tumors originating from neural crest cells. These syndromes are primarily linked to mutations in the SDHx gene family, along with other nuclear genes encoding different subunits of the succinate dehydrogenase (SDH) enzyme. In addition to paragangliomas and pheochromocytomas, affected individuals may also develop renal cell carcinoma (RCC), pituitary adenomas, gastrointestinal stromal tumors, and several other uncommon tumor types (70). To advance tumor diagnostic methods, researchers are combining nanotechnology with magnetic resonance (MR) imaging. Since low-magnetic nanoparticles are required, materials such as iron diselenide ($FeSe_2$) nanoparticles and selenium-based nanoparticles with a TMDC structure have been explored as potential contrast agents. Magnetic FeSe nanoparticles were synthesized and subsequently coated with polyethylene glycol (PEGylation) to create pegylated FeSe nanoparticles. These modified nanoparticles demonstrate strong suitability for MRI because of their high R2 relaxation rate and notable near-infrared (NIR) absorption properties (19). Magnetic nanoparticles, particularly Fe_3O_4 (magnetite) and Fe_2O_3 (maghemite), have recently gained attention as promising materials due to their biocompatibility and ability to interact with external magnetic fields (40).

Superparamagnetic Iron Oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles are among the most widely investigated negative contrast agents for detecting liver and spleen abnormalities, as they effectively reduce T2 and T2* relaxation times. Optical coherence tomography (OCT), often considered an optical counterpart to ultrasound, employs infrared light that

penetrates tissues up to around 2 mm in depth to generate cross-sectional images of internal structures, including basement membranes and epithelial layers. This imaging approach is particularly useful for monitoring oral dysplasia and enabling early detection of oral cancer (1).

Table 3: Whole body MRI work flow chat for cancer screening for the local population (69).

Sequence description	Characteristics
Whole body T1WGRE, Dixon technique	Axial or frontal plane
Whole body T2W, TSE Without fat-suppression	Axial or frontal plane
Whole body DWI, STIR fat suppression, contiguous slicing, multiple stations.	Axial 2 b-values
Brain: T2W FLAIR	Brain: Axial
Lung: T1 GRE short echo-time single breath hold	Lung: Axial
Whole spine T1W,TSE	Sagittal
Whole spine STIR or Fat-suppressed T2W	Sagittal

Raman spectroscopy: Raman spectroscopy is applied in cancer treatment to distinguish malignant cells from normal ones by generating chemical fingerprints based on molecular vibrations. As a vibrational spectroscopic method, it depends on the inelastic scattering that occurs when light interacts with matter. Gold nanorods are particularly effective for molecular imaging because of their high sensitivity to refractive index variations and the subtle environmental changes that result in shifts of peak wavelengths. Despite these advantages, Raman spectroscopy faces limitations such as shallow penetration depth, its near-field nature, slow spectral acquisition, and weak signal intensity, which have restricted its broader clinical application (1).

X-RAY Diffraction: Modern approaches employ X-ray diffraction (XRD) to study the molecular architecture of tissues, offering potential for detecting early signs of cancer. Nanomotors produce distinct, sharp diffraction peaks that reflect their high degree of crystallinity (15).

X-ray photoelectron spectroscopy (XPS): Using a surface-sensitive technique, the analysis examines elemental composition, chemical states, and electronic structures, while also accounting for the influence of ionizing radiation on DNA. The spectra of NM-1 and NC-4 displayed several peaks between 285.15–285.25 eV and at 289.35 eV, corresponding to carboxylate carbon and C–C (sp^3) bonds. Furthermore, the NC-4 spectrum exhibited an additional peak within the 103.51–103.83 eV range, which is attributed to the presence of SiO_2c (15).

Transmission electron microscopy (TEM): A highly effective strategy for examining the absorption and distribution of nanomaterials within cells is to employ a combination of complementary techniques. Iron oxide nanoparticles were found to be internalized by breast cancer cell lines (SKBR-3 and MDA-453) through the endocytic pathway in a time-dependent manner. In mixed culture assays, uptake was suppressed in the HER2-negative cells, whereas selective uptake occurred in the HER2-positive cell line (63). Bismuth nanoparticles and paramagnetic nanoparticles within the 0–10 nm size range can function as contrast agents for CT and MRI imaging, respectively. Although they display rapid pharmacokinetics and a nonspecific distribution profile, they are efficiently absorbed. Quantum particles operating at infrared wavelengths have also been applied in non-invasive in vivo tumor imaging. These quantum particles are encapsulated within triplet copolymers composed of hydrophilic poly(methacrylate) segments, two hydrophobic poly(butyl acrylate) segments, and a polyethylene acrylate unit (71). Image-guided radiotherapy (IGRT) is a treatment approach that delivers radiation while reducing exposure to surrounding healthy tissues. By incorporating imaging techniques, IGRT improves both the accuracy and precision of directing radiation to the tumor site. Commonly used imaging modalities in this method include computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), and X-ray imaging (72). When coupled with nanoparticle-based drug delivery systems, IGRT can be further enhanced by enabling simultaneous tumor visualization, precision targeting, and controlled therapeutic release, thus bridging diagnostics with therapy. Advances in nanotechnology and microfabrication have also led to the development of diverse micro/nanorobots (MNRs), including nanoswimmers, nanoengines, and bio-inspired microbats. By integrating artificial intelligence (AI) and machine learning, these nanorobots are being designed to navigate biological environments, cross the blood–brain barrier (BBB), and deliver nanoparticle-encapsulated drugs or radiosensitizers directly to tumors in a safe and non-toxic manner (73). Nature itself provides remarkable examples of nanomachines, often referred to as "bionanorobots," found within living organisms. For clinical translation, the materials used in nanorobot construction must exhibit flexibility and adaptability to ensure proper mechanical performance and

operability (74). Positron Emission Tomography (PET) is another widely used non-invasive imaging technique in clinical practice. From a molecular biology perspective, combining 18F-fluorodeoxyglucose (FDG) PET with computed tomography (18F-FDG PET/CT) enables the evaluation of cellular metabolic activity, which serves as an important marker for distinguishing normal cells from cancerous ones (75).

Future prospect:

Cancer research is approaching a paradigm shift, driven by precision medicine, advanced diagnostics, and next-generation therapeutics. The overarching aim of this transition is to deliver therapies that maximize efficacy while minimizing systemic toxicity, thereby improving both survival rates and patient quality of life. Within this context, nanomedicine has gained momentum as a promising platform for targeted cancer therapy, drug delivery, and diagnostic integration. However, its clinical translation has been hindered by persistent challenges related to biodistribution, biological interactions, patient variability, manufacturability, and cost. Addressing these issues in tandem with the application of artificial intelligence (AI)-driven optimization frameworks is essential for realizing the full potential of nanotechnology in oncology. A central barrier to clinical success lies in the biodistribution and systemic stability of nanodrugs**.** Nanocarriers must accumulate in tumors at therapeutic concentrations while limiting off-target deposition in healthy tissues. Yet, the human body presents a highly complex environment where nanoparticles encounter multiple barriers, including vascular heterogeneity, stromal density, and immune surveillance. One critical factor influencing these outcomes is the formation of a protein corona**.** Upon entering circulation, nanoparticles rapidly adsorb a layer of serum proteins, which changes their biological identity and alters pharmacokinetics. The protein corona can mask targeting ligands, promote opsonization, accelerate clearance by the mononuclear phagocyte system, and even induce immunogenic or cytotoxic responses. These phenomena often compromise delivery efficiency, highlighting the importance of engineering particle properties such as size, shape, charge, elasticity, and surface chemistry to minimize undesirable corona effects and improve tumor penetration. Another layer of complexity arises from patient-to-patient variability**.** Tumor heterogeneity, genetic polymorphisms, metabolic differences, and immune system status all shape treatment outcomes. Even within the same cancer type, variations in vascular permeability, extracellular matrix composition, and receptor expression can produce markedly different nanoparticle uptake profiles. This variability underscores the importance of developing personalized nanomedicine strategies**,** including biomarker-driven patient selection and individualized dosing regimens. Multi-omics platforms spanning genomics, proteomics, metabolomics, and transcriptomics hold promise for mapping patient-specific tumor biology and predicting responsiveness to nanodrug formulations. Integrating these datasets with computational models can enable more precise treatment planning and stratification. Beyond biological considerations, manufacturability and scalability remain significant translational hurdles. While many nanomedicines show impressive preclinical efficacy, reproducing these formulations consistently at an industrial scale is challenging. Batch-to-batch variability, complex synthesis protocols, limited stability during storage, and high-quality control requirements hinder large-scale production. Moreover, regulatory agencies demand a stringent characterization of nanoparticle physicochemical properties, adding further technical and financial burdens. These challenges are directly linked to cost, which is another critical barrier. The sophisticated equipment, raw materials, and multi-step fabrication processes often make nanodrugs prohibitively expensive, limiting accessibility for patients in low and middle-income regions. Ensuring cost-effective production methods such as microfluidics, continuous manufacturing, or green chemistry approaches will be key to enabling widespread adoption. Emerging strategies aim to overcome these hurdles by combining multiple nanomaterials or employing hybrid designs that integrate therapeutic and diagnostic functions. While promising, these approaches require systematic studies to decipher the precise mechanisms of drug release, biodistribution, and synergistic effects. Here, AI and machine learning (ML) are proving indispensable as enabling tools for delivery optimization**.** Unlike conventional trial-and-error design, AI models can rapidly analyze massive datasets to predict nanoparticle behavior in complex biological systems. Applications include predicting protein corona composition, simulating biodistribution and clearance patterns, identifying optimal particle architectures, and optimizing drug loading and release kinetics. Furthermore, adaptive AI-driven platforms can integrate clinical data to continuously refine predictions, tailoring nanoparticle formulations to individual patient physiology and tumor biology. These tools significantly accelerate the development pipeline, reduce costs, and enhance the probability of clinical success. Looking forward, the convergence of nanotechnology, multi-omics, and AI-guided optimization represents a transformative strategy for the future of oncology. By systematically addressing biodistribution barriers, protein corona formation, inter-patient variability, manufacturing scalability, and economic feasibility, the field can move beyond preclinical promise toward clinically impactful solutions. Such an integrative framework will not only refine drug design and delivery but also

enable the personalization of cancer therapy at an unprecedented scale. Ultimately, these innovations have the potential to reshape cancer treatment paradigms, offering clinicians the tools to provide safe, effective, and accessible therapies that significantly improve patient prognosis.

CONCLUSION

Nanotechnology has emerged as a transformative and interdisciplinary approach in oncology. With particle sizes typically ranging from 1 to 100 nm, nanomaterials display unique physicochemical properties that allow them to cross biological barriers, penetrate cellular and subcellular structures, and enable highly specific drug delivery. Their small dimensions not only enhance cellular uptake but also allow surface modifications, such as ligand or antibody conjugation, which facilitate targeted therapy. Among the wide variety of nanomaterials investigated, a few have already advanced into clinical use and reshaped cancer care. Liposomal formulations, such as liposomal doxorubicin (Doxil), exploit the enhanced permeability and retention (EPR) effect to improve tumor accumulation while lowering systemic toxicity. Similarly, albumin-bound paclitaxel (Abraxane) enhances the solubility and delivery of hydrophobic drugs, and nanocrystal formulations have improved the oral bioavailability of otherwise poorly soluble chemotherapeutics. Inorganic platforms like gold and magnetic nanoparticles, while still largely preclinical, add value through their dual role as carriers and diagnostic or theranostic agents, owing to optical, magnetic, and radiosensitizing properties. These examples highlight a key point: nanomedicine is no longer only a promise; it is already delivering impact in select clinical contexts. At the same time, important challenges remain before the field can be broadly transformative. A persistent issue is the variability of the EPR effect in human patients, which complicates predictions of nanoparticle accumulation and therapeutic benefit. Standardized reporting of pharmacokinetic and pharmacodynamic (PK/PD) profiles is also urgently needed to compare results across studies and translate preclinical findings into reproducible clinical outcomes. In addition, patient stratification strategies must be strengthened so that nanomedicines are directed toward individuals most likely to benefit, rather than being deployed in heterogeneous populations where efficacy is diluted. Artificial intelligence (AI) is emerging as a powerful enabler of this transition. AI-driven models can integrate material properties, PK/PD data, and tumor biology to predict optimal nanoparticle design parameters such as size, surface chemistry, and ligand density, thereby accelerating formulation development. Equally, AI-based analytics can support patient stratification by linking imaging, genomic, and clinical data to identify those in whom nanocarriers will achieve meaningful delivery. By tackling both design and patient-matching challenges, AI complements nanotechnology and helps move the field from promise toward precision. Nanomedicine's value is clearest when we focus on what is already working, approved nanoformulations that improve drug solubility, stability, and tumor targeting and remain candid about what comes next: more rigorous PK/PD reporting, reliable biomarkers for patient selection, and validated strategies to account for human variability. This pragmatic approach will not only refine the science of nanomedicine but also bring its benefits closer to patients who need better, safer, and more personalized cancer therapies.

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Abbreviation:-

AgNP- Silver nanoparticles
AuNP- Gold nanoparticles
CNT -Carbon nanotubes
CUR- Curcumin
EPR -Enhanced permeability and retention
EGFR-TKIs- Epidermal growth factor receptor–tyrosine kinase inhibitors
TEM- Transmission electron microscopy
PDT- Photodynamic therapy
NP- Nanoparticle
HER-2- human epidermal growth factor receptors 2
MRI- Magnetic resonance imaging
PEG- Polyethylene glycol
NMs- Nanomotors

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