Review

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# Nanotechnology-based delivery systems to overcome drug resistance in cancer

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**Abstract:** Cancer nanomedicine is defined as the application of nanotechnology and nanomaterials for the formulation of cancer therapeutics that can overcome the impediments and restrictions of traditional chemotherapeutics. Multidrug resistance (MDR) in cancer cells can be defined as a decrease or abrogation in the efficacy of anticancer drugs that have different molecular structures and mechanisms of action and is one of the primary causes of therapeutic failure. There have been successes in the development of cancer nanomedicine to overcome MDR; however, relatively few of these formulations have been approved by the United States Food and Drug Administration for the treatment of cancer. This is primarily due to the paucity of knowledge about nanotechnology and the fundamental biology of cancer cells. Here, we discuss the advances, types of nanomedicines, and the challenges regarding the translation of *in vitro* to *in vivo* results and their relevance to effective therapies.

**Keywords:** nanotechnology; multidrug resistance; drug delivery systems; nanoformulations; enhanced permeability and retention effect

## Introduction

"There's plenty of room at the bottom", a statement by Dr. Richard P. Feynman in 1959, revealed a new range of possibilities in almost all the realms of science [1]. Prof. Norio Taniguchi, in 1974, coined the term, "nanotechnology", which is now defined as an area of technology that involves dimensions less than 100 nm, with a primary emphasis on the manipulation of individual atoms and molecules [2]. Nanomedicine involves the combination of nanotechnology with pharmaceutical and medical sciences [3, 4]. The major aims of nanomedicine are the development of drugs with higher efficacies, lower toxicities, and the efficacy to overcome multidrug resistance (MDR) [5]. Nanoparticles (NPs) have high surface-to-volume ratios compared to bulk materials and have varying physical, chemical, and biological properties [5–11]. By definition, nanomedicines are drugs or biologics that incorporate NPs (usually <100 nm) to a greater magnitude than their bulk counterparts *in vivo* [12]. Nanomedicines are primarily used to treat cancerous tumors because these NP-drug conjugates act by passive targeting, characterized by their significant accumulation in the tumor [13]. NPs have been reported to have increased permeability through blood vessels and lower lymphatic drainage. This property is known as the enhanced permeability and retention (EPR) effect, and it ultimately causes significant accumulation of the drug in the tumor microenvironment (TME) [5, 11, 12].

MDR, which causes a decrease or abolition of the efficacy of anticancer drugs that differ in their structure and mechanism of action in cancer cells, plays a major role in treatment failure, thereby increasing the risk of relapse and mortality [14]. Thus, novel drugs and techniques must be developed to surmount MDR in cancer. The delivery of anticancer drugs can be achieved by various routes of administration. The choice of the route of administration by a clinician depends on various factors, including but not limited to, the drug, type of cancer, efficacy, location of the tumor in the body, and toxicity of the drug, among others [15–18]. Furthermore, certain anticancer drugs can be administered directly into the

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tumor [19]. Over the last 3 decades, there have been numerous innovations and developments in cancer drug delivery systems [16, 20, 21]. Furthermore, the majority of these developments have some specific applications in drug delivery, such as: (1) anti-angiogenic drugs, which decrease angiogenesis in tumors; (2) biological therapies, such as gene therapy and viral oncolysis; (3) combinations of novel therapies with conventional chemotherapy and radiation therapy; (4) development of immune therapy, e.g., cancer vaccines, cytokine modulators, monoclonal antibodies and (5) nanobiotechnology for cancer therapy (targeted drug delivery systems) [16]. Chemotherapy remains the most commonly used systemic treatment to inhibit the growth and proliferation of cancer cells, progression of the disease, and metastasis [22, 23].

Despite the significant increase in research in nanobiotechnology and cancer nanomedicine, there is still a large disparity between scientific advancements and the use of these applications in the treatment of cancer patients. Figure 1 provides examples of advances in nanotechnology, with an emphasis on cancer nanomedicine. Nanomedicine has provided the concept of theranostics, defined as the simultaneous diagnosis and treatment of a disease [24, 25]. Furthermore, researchers have developed targeted drug delivery, which produces a lower frequency of adverse effects, greater efficacy, decreased immunogenicity, and a decrease in surgical intervention [21, 26]. Nanoformulations have a number of advantages compared to the non-nanoformulated parent drug, such as carrying a large amount and multiple drugs, maintaining therapeutic drug concentrations for a longer time, and permeating into cells by endocytosis, which bypasses certain resistance mechanisms [4]. However, numerous obstacles make it difficult to develop nanoformulations that can be used in humans, including biological barriers, safety profiling, and scaling-up processes [27].

In this review, we will discuss the types of nanoformulations and the challenges in drug delivery and clinical translation. We will categorize and discuss the nanoformulations as metallic NPs, NPs from natural products, albumin NPs, polymeric micelles, liposomes, and polyphenolic compounds.

## Challenges in drug delivery and the clinical translation of nanomedicine (Figure 2)

Despite the availability of non-invasive drug delivery platforms, most cancer nanomedicines use the intravenous route of administration for the transport of drug to the tumors [29, 30]. The infrastructure of NP delivery to solid tumors is based on the EPR effect [5, 11, 12]; however, there are significant differences in the EPR effect between patients and the types of tumors. For example, tumor microenvironment (TME) properties, including extravasation, diffusivity, hemodynamic regulation, heterogeneity, etc., can have adverse effects, such as uncertainty of the concentration of NPs in the tumor vasculature [13]. Furthermore, lymphatic drainage is non-uniform throughout the tumor mass and there is a greater mechanical stress and a higher degree of functional loss in the bulkier regions of tumor, compared to the

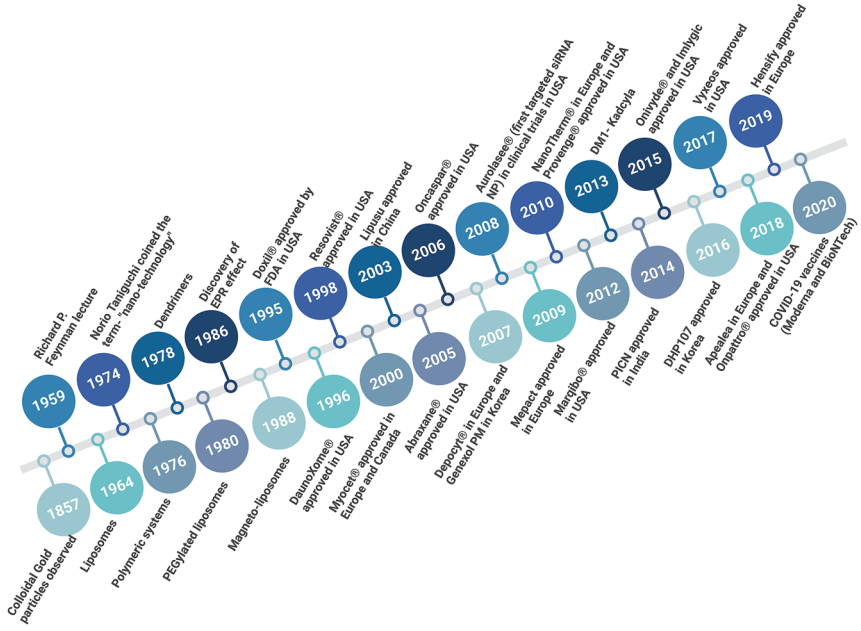


**Figure 1:** Timeline of the history of the developments in nanotechnology in the field of medicine. The figure was adapted and revised from Salvioni et al. [14], Li et al. [17], and Shi et al. [28].

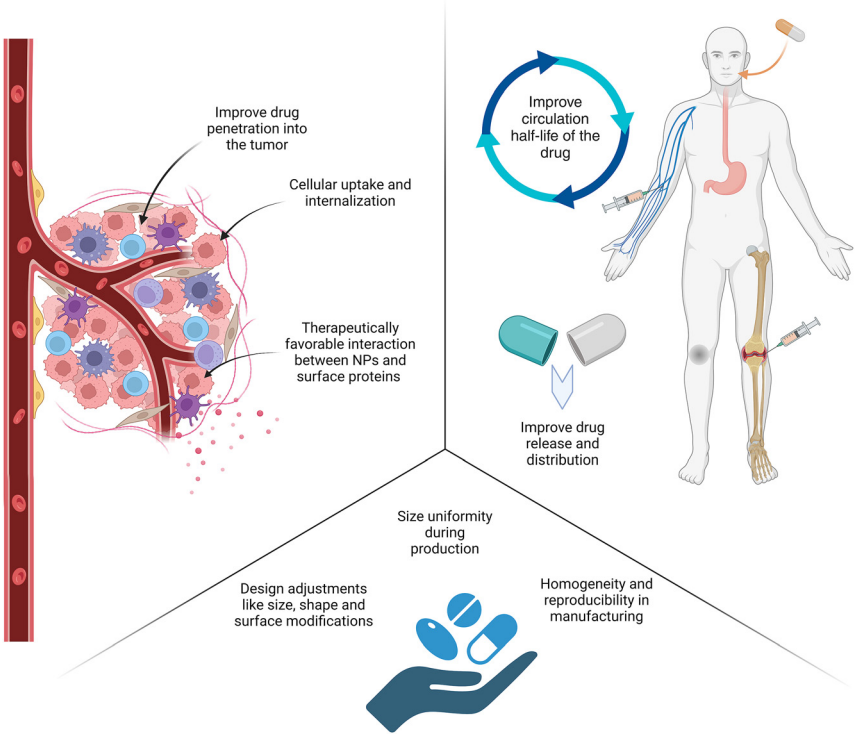


**Figure 2:** Rationale for developing cancer nanomedicines.

margins [31]. This factor must be considered in combination with other factors, such as extravasation and diffusivity, which affect the equilibrium of the NPs that accumulate inside the tumor mass [32]. Furthermore, tumor-associated factors affecting drug delivery depends on the type of material, its compatibility with tissue components, and the architecture of the tumor itself [16]. It has been reported NP accumulation increases in the interstitium of the tumor in the presence of a high number of phagocytic and dendritic cells [33]. Tumor-associated macrophages (TAMs) have been shown to significantly accumulate and retain nanoformulations and they can be gradually released in close proximity to tumor cells [34–37].

In order to increase drug delivery to a tumor, it is critical to determine the interaction between the NPs and surface proteins. A corona-like structure is formed when a NP enters an organic environment, such as interstitial fluid, the extracellular matrix or blood, and the surface of the NP is rapidly enveloped by lipoproteins or cellular receptors [5, 38–41]. This produces a series of changes in the structure, size, stability, and surface properties of the NPs [39]. In addition to the changes in the physical properties of the NPs, the adsorption will produce a biological identity for the NP, which will determine its cellular uptake, intracellular trafficking, toxicity, and pharmacokinetic (PK) profile [39, 42–45]. All of these changes will increase the efficacy of anticancer drug. Nanoparticle formulations of doxorubicin (DOX) in humans activate the complement system, producing a hypersensitivity reaction (non-immunoglobulin E (IgE) mediated) [46]. NP-protein interactions are dependent on the physicochemical properties of the NP, the source and concentration of the protein and the exposure time [47]. Studies have been conducted to predict the interaction of NPs with cells. Bigdeli et al. [48] identified a range of protein corona targets that could potentially improve the design of liposomes. Hajipour et al. [49] concluded that the type of the disease plays a critical role in determining the architecture of the corona. Walkey et al. [50] used qualitative structure-activity relationship (QSAR) to determine the interactions of NPs with biological components. A group of hyaluronan-binding proteins were identified in this study as mediators of interactions between the NPs and cells. The goal of this study was to establish a platform for building an extensive database of protein corona signatures and its biological responses for various types of NPs. Unfortunately, the majority of the studies were focused on NP-protein interactions *in vitro*. Moreover, *in vivo* corona formation and its correlation with pharmacokinetic parameters, biodistribution, and efficacy, have not been fully delineated. However, Sakulkhu et al. [51] investigated the *in vivo* protein corona interaction by using the distinct magnetic properties of supermagnetic iron oxide nanoparticles (SPIONs). They extracted NPs from rat sera after their interaction with the physiological system of rat and found differences between the types of corona formation *in vitro* and *in vivo*, such as the size of the corona, the family of proteins, surface charge and its biodistribution [51]. Similar future studies will hopefully benefit and strengthen the advancements in cancer nanomedicine.

It is well known that circulation affects the half-life of the drug. Drug molecules that need to reach poorly perfused tissues require a longer half-life than drugs that are distributed to tissues with a larger blood flow [52]. The opsonization of NPs, which causes their phagocytosis by the mononuclear phagocytic system (MPS), results from non-specific interactions between NP and certain serum proteins [52]. Therefore, the NP composition needs to be considered to decrease or avoid recognition by the immune system. For example, to prolong the time that NPs remain in circulation, polyethylene glycol (PEG) grafting is commonly used because PEGylated carriers delay absorption by the liver and the spleen [53, 54]. Alternatively, nanoformulations can be modified by adding molecules that will prevent the immune system from recognizing them as foreign antigens, such as the addition of the cluster of differentiation 47 (CD47) peptide (which decreases recognition by the MPS) [55] or by camouflaging the NP surface with a membrane derived from either red blood cells (RBCs), white blood cells (WBCs) or platelets [56, 57]. Factors, including abnormal and uneven tumor vasculature and perivascular TME, decrease extravasation of NPs from the systemic circulation to tumors [58]. This complication can be addressed by loading the nanoformulated drug into mesenchymal cells, macrophages and monocytes or by attaching NP to the membrane of these cells [58–61].

It is important to note that the size and binding affinity of the nanocarrier affects the penetration of a drug into a tumor [62]. It has been reported that higher affinity antibodies that bind to the target antigens on cancer cells, are less likely to efficiently penetrate into cancer cells, compared to lower affinity antibodies, due to internalization [62]. NPs are usually greater in size than antibodies and consequently, they have a greater probability of being trapped in the extracellular matrix of the cancer cells [63]. It has been hypothesized that the modulation of the size of the NPs may be a solution to this problem. Smaller NPs can diffuse throughout the tumor tissue but particles less than 5 nm in diameter are readily removed by renal filtration [64–66]. An *in vivo* study reported that 15 × 54 nm nanorods more rapidly penetrated into orthotopic mammary tumors, compared to nanospheres that were 35 nm in diameter [67]. Tasciotti et al. [68] developed a multistage drug delivery system, using mesoporous silica particles 3.5 μm in size as an outer shell and a 20–30 nm NP-drug conjugate as the inner core. This formulation was incubated with human umbilical vein endothelial cells and the inner core NP were released and internalized (in distinct vesicles) [68]. Another research group developed a multistage delivery system, consisting of an outer layer of 100 nm NPs enclosing a 10 nm drug conjugated quantum dot (QD) [65]. These multistage quantum dot gelatin nanoparticles (QDGelNPs) were composed of a gelatin core with amino-PEG QDs conjugated to the surface, using 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride/sulfo-N-hydroxysulfosuccinimide (EDC/sulfo-NHS) coupling chemistry. The 100 nm shell was degraded enzymatically and the 10 nm core NP was released deep into the dense collagen matrix of tumor. This formulation produced an effective delivery of drug to solid tumors.

Because most of the NPs are formulated to reach intracellular targets, their effective cellular uptake and internalization are required to produce efficacy. This can be done by placing targeted ligands on the NPs that will interact with specific receptors on the cancer cells, increasing the probability of their internalization into the cancer cells [69]. For example, the United States Food and Drug Administration (FDA)-approved drug, Abraxane®, utilizes nanoparticle albumin bound (*nab*) technology, and drug delivery was due to GP-60 receptor-mediated transcytosis through microvessel endothelial cells in the angiogenic tumor vasculature [70]. The uptake and internalization of Abraxane® in metastatic breast cancer cells was significantly greater than that of taxol or taxotere. This approach is critical for drug delivery *via* the intestinal mucosa and blood-brain barrier [71–73]. In addition to *nab* technology, it should be noted that gold nanoparticles (AuNPs) have the potential to be further modified to further increase their uptake and internalization by cancer cells [74, 75].

NP endosomal release is very important for the cytosolic delivery of the drug payload, particularly drugs that are small-interfering ribonucleic acid (siRNA)-based therapeutics, as these drugs must penetrate into cells to interact with the tumor mRNA to produce their therapeutic efficacy [76, 77]. A considerable number of siRNA-based therapeutics only have an endosomal release of 1 %–2 %, although formulations of this type have been successful in certain clinical trials [76]. The controlled release of a drug in the circulation is important in producing a constant level of drug in the blood, as it helps maintain the dosage level and dosing frequency, which can improve patient compliance. Furthermore, the controlled release of the drug decreases non-target accumulation, thus decreasing the probability of toxic effects [20]. For the controlled release of NPs, the $C_{max}$ should occur during the the infusion period; however, the concentration of the released drug will initially be lower than the $C_{max}$. Subsequently, the $C_{max}$ of the free drug administered intravenously will be significantly greater than the $C_{max}$ of the free drug administered *via* NP delivery [78]. This lower release of the drug will significantly decrease the probability of toxicity. Furthermore, the EPR produces a differential accumulation of nanoformulations in the tumor to a greater magnitude than free or conventional

drugs [79]. The same conventional drug, when released from the nanoformulation, typically accumulates to a greater extent in the tumor over a prolonged period of time [12]. Following internalization, NPs either release the loaded drug outside the cell or it is directed by the intracellular trafficking pathways and the drug is released inside the target cell [80]. Endosomal avoidance is very important for the cytosolic delivery of biomacromolecules, such as siRNA. The delivery of siRNA can be further increased by polymer-based NPs, cationic lipid, and lipid-like materials [77, 80, 81]. The majority of RNA-interference (RNAi) therapeutics is formulated in liposomes and the targeted delivery of NPs delivery can further increase the cellular uptake of siRNA molecules [82]. However, only a small fraction of the siRNA is released from cellular endosomes [76] and approximately 70 % of the internalized siRNA may undergo exocytosis by Niemann-Pick type C1 protein [83]. Thus, alternative approaches will be required to produce NP formulations that avoid sequestration by endosomes. In addition to cytosol delivery, targeting mitochondria, the Golgi apparatus, nucleus, and the endoplasmic reticulum, have been utilized [84]. However, further studies must be conducted to characterize the delivery of NPs through the membranes of organelles [84–89].

Conventional formulation techniques that are used to prepare NPs usually produce a greater magnitude of particle size heterogeneity in the mixture, compared to nanoformulations [67, 90]. Microfluidic technologies have more rapid self-assembly characteristics, with a significantly higher homogeneity and reproducibility, along with manageable physical and chemical properties [91–95], compared to sol-gel processes, molecular condensation or chemical reduction. Current approaches allow a greater control over the chemical composition, shape, size, drug loading, and surface properties [96]. However, the translation of this level of control over a larger scale of production will require the fulfillment of good manufacturing practice (GMP). The increase in complexity of the nanoformulations will also require advancements in chemistry, manufacturing, controls, and GMP challenges [28]. Advances in the scaling-up process may help in expediting the translation of these formulations from laboratory (grams) to commercial (kilograms) amounts [97, 98]. Although preclinical data suggests that NPs can increase drug delivery, a significant percentage of those studies were not translated into clinical trials. Furthermore, a study has shown that out of 94 % of successful Phase I trials, only 14 % proceeded to Phase III trials with favorable therapeutic results [99].

The *in vitro* assessment of NP formulations is essential to determine the biocompatibility with the targets and candidates before progressing to *in vivo* studies. Despite generating a large amount of information, *in vitro* studies lack the complexities of biological tissues and may not have the complex interactions of NPs with the physiological barriers [100]. Consequently, further developments are needed in the field of biomimetic devices [100–102]. However, animal models continue to provide critical information regarding the pharmacokinetics, efficacy, biodistribution, and toxicity, of the drugs being tested. It is imperative to note that PK scaling varies widely across species for different nanoformulations [103–106]. Furthermore, human cancers are not always recapitulated *in vivo* and a single model cannot possibly contain all the biological characteristics of the disease. For example, EPR is more erratic in cancer patients than in animal models [13].

The TME play a significant role in cancer progression and metastasis and thus, it has become a target for cancer treatment [107–109]. Certain *in vivo* studies in mice models have shown that blocking angiogenesis causes tumor suppression and a decrease in metastasis [110, 111]. The targeting of TAMs and fibroblasts can be utilized for cancer treatment. Cellax (docetaxel-conjugate nanoparticles)-treated mice had a significant decrease in α-smooth muscle actin (α-SMA)-expressing fibroblasts, which, in turn, significantly decreased the tumor extracellular matrix (ECM) and interstitial fluid pressure (IFP), increased the vascular permeability and decreased the metastasis of breast cancer [112]. Thus, there is a direct relationship between ECM and IFP and drug penetration and subsequently, the metastatic potential of cancer cells.

# Various classes of nanomedicines

## Metallic NPs

Nanotechnology is used in medical and pharmaceutical applications, e.g., the delivery of biological materials, vaccines, and drugs [113]. NPs, particularly metallic NPs, have unique electrical, optical, magnetic, catalytic, and favorable biological characteristics [114]. Metallic NPs are a type of inorganic nanomaterials that are composed of titanium, silver, gold, ruthenium, zinc, selenium, iron, copper, gadolinium or hafnium, have been used for cancer treatment [115]. The characteristics and advantages of using metallic nanomaterials will be discussed in this section.

Because of its applications in many areas, metallic NPs, such as titanium dioxide ($TiO_2$NPs), silver (AgNPs), gold (AuNPs), and ruthenium (ruthenium nanoparticles, RuNPs), represent useful and versatile molecules [116, 117]. $TiO_2$NPs have a high capacity for the absorption of short-wavelength light, which has been widely utilized in various cosmetics and sunscreens [118]. Due to the innate antioxidant and

antimicrobial efficacies of silver (which is slowly released from AgNPs as $Ag^+$ ions), AgNPs have been used as biocidal compounds, treatment of multidrug resistant microbes, preservatives for food packing, and decontamination of water [119, 120]. Indeed, AgNPs have been used to inhibit microorganism proliferation, as they have broad antibacterial [114], antifungal, and antiviral efficacy [121]. Finally, there are *in vitro* data indicating that AgNPs induced the death of breast and colorectal cancer cells [122].

AuNPs have received increasing interest because of their stability, biocompatibility, tunable surface, facile synthesis, optical properties, and ease of chemical modifications, as AuNPs can be attached to hundreds of different molecules [116, 123]. AuNPs have been shown to be useful as diagnostic and therapeutic molecules [124]. Furthermore, AuNPs can be synthesized as solid spheres, nanospheres, nanorods, nanocages, nanoclusters, and nanostars, among others, thereby making AuNPs well-suited for various biomedical purposes (Figure 3) [125]. Consequently, AuNPs have the potential to be used for the diagnosis, treatment, and prevention of certain types of cancer [126]. AuNPs can be used for the early diagnosis of a thrombus by detecting biomarkers for direct imaging [116]. Recently, clinical trials have been conducted with AuNPs. In 2021, the clinical trial (NCT04907422) proposed a novel diagnostic and prognostic approach for the prompt and timely discovery of cancer stem cells in salivary gland tumors, using AuNPs conjugated to CD24. CD24 is used as a conjugate as it regulates the epithelial-mesenchymal transition in cancer cells [127]. The validation in this trial was done by real-time quantitative polymerase chain reaction (RT-qPCR). AuNPs have been reported to increase the efficiency of proton therapy, as the insertion of AuNPs increases the absorbed radiation dose in tumors [127]. A novel nucleotide-carrying AuNP formulation, known as NU-0129, is undergoing early Phase I clinical trials for patients with relapsing glioblastoma or gliosarcoma [128]. DOX tethered with AuNPs were synthesized for drug release into the acidic microenvironment of the cells, resulting in a reversal of adenosine triphosphate (ATP)-binding cassette (ABC) transporter activity and higher nuclear localization in MCF-7/ADR cells [129]. This represents an excellent example of mitigating MDR in cancer using nanomedicine. Luo et al. developed a prostate cancer (PCa)-targeted gold nanocluster radiosensitizer, coupled with monomethyl auristatin E (a potent cytotoxin), for radiotherapy and chemotherapy. This approach produced a greater nanocluster uptake by prostate-specific membrane antigen (PSMA)-positive cancer cells and it produced an increased efficacy of radiotherapy *in vitro* and *in vivo* [130]. RuNPs have been investigated as antibacterial molecules, catalysts, and pharmaceuticals, due to their biotoxicity, high surface-to-volume ratio, large optical properties, and high photothermal conversion rate [131]. Similar to AuNPs, RuNPs also have good biocompatibility [132, 133]. RuNPs target cancer by DNA damage-induced apoptosis, topoisomerase-II inhibition, inhibition of the mitogen-activated protein kinase (MAPK) signaling pathway, activation of the p53-dependent caspase-3 mediated signaling, upregulation of adenomatous polyposis coli (APC) and *p53* genes, inhibition of proteasome activity, p53-independent activity, inhibition of the hypoxia-inducible factor-1 (HIF-1) pathway, anti-metastasis activity and the induction of dysfunction in lysosomal activity [134]. RuNPs

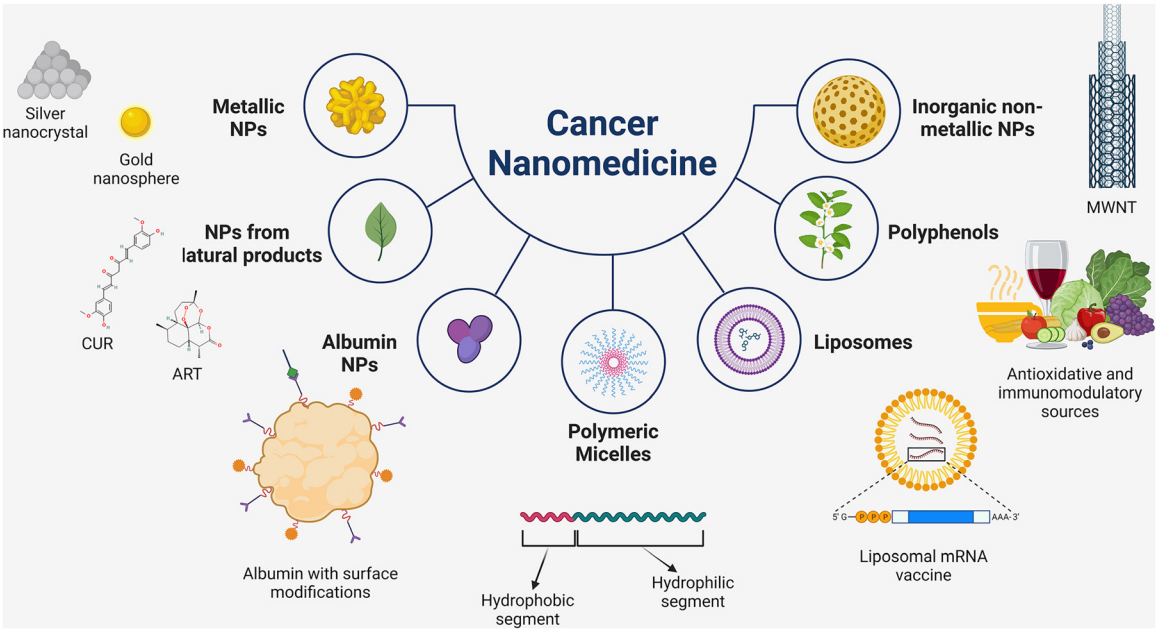


**Figure 3:** Various classes of cancer nanomedicines.

are being developed as a nanoparticle drug delivery system for the photothermal treatment of cancer, as they have efficient near-infrared (NIR) efficacy in colorectal HIEC-6, Caco-2, SW480, HCT116, and CT26 WT cancer cells [132, 133]. Li et al. [135] reported that RuZ (ruthenium [II] complex), at a maximum concentration of 30 mg/mL, self-assembles in the cell culture media and had high penetration in SW620/Ad300, KB-C2, KB-ATO, H460/MX20, BEL-7404/CP20, BIU-87/DDP, and MDA-MB-231/Adr MDR cancer cell lines, with half maximal inhibitory concentration ($IC_{50}$) values of 1.75, 2.64, 1.58, 0.70, 1.34, 1.26 and 1.96 µmol/L, respectively [135]. Lakshmi et al. [136] synthesized ruthenium (II)-curcumin liposome NPs and it produced cytotoxicity and nuclear damage in HeLa cells [IC50 value=99 µg/mL].

Gold nanostars are synthesized from $HAuCl_4$ as precursors and hydroxylamine as a reductant above pH 11 [137]. Gold nanorods and nanospheres are some of the simplest nano-preparations in metallic NPs, with sizes of 60 nm and 20–40 nm, respectively [138]. Gold nanocages and nanoclusters are approximately 7–20 nm in size and they have positive and negative charges [139, 140]. Silver nanocrystals range in size from 1 to 100 nm and are used for diagnosis, drug delivery, treatment, and personal health care [121]. Liposomal ruthenium (II)-curcumin nanoformulation is a hybrid preparation that was developed to overcome the hydrophobicity of curcumin [136].

There are several physical and chemical methods that can be used to synthesize and stabilize metallic NPs [120, 141]. Currently, environmentally friendly methods (known as green chemistry) of nanoparticle synthesis have received increasing interest [131, 142–148]. In physical processes, metallic NPs are produced using evaporation/condensation techniques [149]. Conventionally, certain NPs materials, such as silver (Ag), gold (Au) and lead (II) sulfide (PbS), were synthesized using a tube furnace at atmospheric pressure [150]. Chemical reduction, using organic and inorganic reducing compounds, such as sodium citrate, ascorbate, and the Tollens reagent, is the most widely used chemical method to synthesize metallic NPs [151]. Since conventional methods of NP production involves using chemical compounds that produce environmental toxicity, green syntheses have been widely studied, which used eco-friendly and biocompatible procedures [151, 152]. The green-synthesis of $TiO_2$NPs can be accomplished using extracts of clove (*Syzygium aromaticum*), black pepper (*Piper nigrum*), and coriander (*Coriandrum sativum*) [142]. AuNPs and AgNPs were first synthesized using a leaf extract from *Perilla frutescens* [141]. Bark [143, 153] and plant water extracts [146] may be a good source of reducing compounds for the synthesis of metallic NPs. Biological green synthesis has been reported using fungi, bacteria, and other microorganisms [144]. The biological AuNPs (conjugated with proteins, lipids, DNA or antibodies), and AgNPs (*Trichoderma* spp.-AgNP-T or *Sclerotinia* sp.-AgNP-S), which had antifungal efficacy in pathogenic fungi, were synthesized using the fungus, *Trichoderma longibrachiatum* [145, 148].

Metallic NPs have been of significant interest to researchers due to their extensive medical applications, such as targeted delivery, enhancement of anticancer efficacy, and increased contrast for imaging tumors [150, 154, 155]. Therapeutically, metallic NPs are considered a useful treatment due to their multifunctional physical, optical, and magnetic properties, which results in increased penetration and detection in the body [156]. Numerous studies have reported that metallic NPs have efficacy in liver, breast, colon, prostate, and human leukemic monocyte cancer cells [157–160]. Metallic NPs are usually coupled with a targeting compound or molecule and are loaded with chemotherapeutic drug to increase therapeutic efficacy [161]. AuNPs have been utilized to a greater extent than other NPs because they are relatively easy to synthesize and have a tolerable safety profile [162]. AuNPs capped with bovine serum albumin (BSA) are effective carriers of methotrexate (MTX, an anticancer drug) to MCF-7 breast cancer cells, thereby increasing the drug efficacy, compared to conventional formulations [163]. Similarly, Majoumouo et al. reported that AuNPs had efficacy in MCF-7 and Caco-2 cancer cells [147]. NPs can penetrate the blood-brain barrier (BBB) due to their diminutive size, and surface properties, such as high interactivity and plasmon resonance [164–166]. AuNPs were developed as an alternative delivery platform to the central nervous system with modified ligands, using targeting moieties, such as transferrin (Tf) [167]. As nanocarriers, AuNPs provide a platform to attach biomolecules, such as oligonucleotides, proteins and peptides, and exosomes [154]. Zhang et al. [168] generated exosomes combined with AuNPs, which was used as the vehicle for the chemotherapeutic drug, DOX, for the treatment of melanoma. They used C57BL/6 mice and used the B16F10 tumor-bearing model to determine the *in vivo* biodistribution of EVdox@AuNP at a dose of 2.5 mg/kg *via* intravenous infusion. The results indicated that the AuNP formulation accumulated to a greater extent in the tumors, compared to unconjugated AuNPs. Following drug accumulation in the tumors, a laser beam was used to irradiate the tumors for 5 min. There was a slight increase in temperature (to 38.1 °C) in areas without NP accumulation, however, the areas that accumulated AuNPs had a rapid increase in temperature (to 46.1 °C) in just 1 min. These results suggest that the EVdox@AuNPs photothermal transformation, internalization, and retention in the tumor region [168]. Chen et al. [169] used DOX to prepare a thermo-responsive drug release formulation to determine its efficacy in KB-3-1 cancer cells. Their results indicated that the novel fragmented polymer nanotubes had favorable biocompatibility and were cytotoxic in KB-3-1 cancer cells ($IC_{50}$=1.4 µmol/L).

These specific types of polymer nanotubes have the potential to be used as efficient delivery systems for anti-cancer drugs because of their thermo-responsive gating system [169].

Metallic NPs have been evaluated as diagnostic and therapeutic molecules. Currently, however, only a few technologies based on metallic NPs have been approved by the FDA for diagnostic and therapeutic use [15]. For example, the nanodrug, Aurimune (CYT-6091), was produced by linking AuNPs to recombinant human tumor necrosis factor-α (rhTNF-α) and PEG [170]. The results of a Phase I clinical trial indicated that CYT-6091 was significantly more efficacious than rhTNF-α in patients with advanced solid tumors, compared to conventionally formulated treatment. Patents based on NPs, can be used to develop more precisely targeted therapeutics in support of the respective inventions. Chauhan et al. disclosed their invention (Patent No. US10456363B2), which is composed of modified cyclodextrin-coated magnetite NPs as a targeted nanocarrier for hydrophobic drugs [171]. The patent (WO 2013/176468 Al) reported the development of a liver-targeted drug delivery systems, using AuNPs [172]. Another patent (WO 2014/047318) for drug delivery, invented by Kaittanis et al. [15] is based on iron oxide NPs [173]. In breast cancer patients, superparamagnetic iron oxide nanoparticles (SPION) accumulate in the sentinel lymph nodes (SLN). In a Phase I clinical trial (NCT05359783), SPION was used as neoadjuvant therapy and a biopsy was done by minimal invasion to the tissue, resulting in a de-escalated, less complex surgery [174]. Bort et al. showed that the activation and guiding of irradiation by X-ray (AGuIX® NP) had improved accumulation and retention in tumors *via* an EPR effect [175]. A novel nanoradiosensitizer for the radiotherapy of cancers, NBTXR3, is a hafnium-based theranostic tool [176]. Additional research with metallic NPs should provide important data about the properties of metallic NPs that can be studied to provide efficacious cancer treatments (Table 1).

## Nanoformulations of natural products

Natural products and their numerous derivatives are valuable sources of compounds with anticancer efficacy, including extracts from animals, plants, and microorganisms, among others [183, 184]. Due to their effects on multiple cellular signaling pathways and their acceptable safety profile, more than half of all clinically used chemotherapeutic drugs are natural products [185, 186]. For anticancer therapy, various nanoformulations have been designed to: (1) decrease or abrogate MDR and/or the adverse and toxic effects produced by anticancer therapeutics and (2) improve targeted drug delivery and bioavailability [187]. In this section, we will discuss the anticancer efficacy of natural product nanoformulations.

Certain nanoformulations (i.e., dendrimers, polymers, liposomes, nano-emulsions, and micelles) can decrease particle sizes and have been used to increase bioavailability and minimize the adverse effects produced by the ligand(s) they deliver to the tumor site(s) [188]. The nanoformulations generally have a size range from 10 to 100 nm and can be classified as nanocarriers, no-carrier-added nanosuspensions and polymer-drug conjugates [189]. During the formulation of nano-drugs, investigators need to consider whether the drug is dissolved, entrapped, encapsulated or adhered to the drug carrier [28]. The formulation should target the tumor site and release the drug during the delivery process [4]. Various methods used to synthesize nanoformulations are selected based on the different nanoformulations (i.e., dendrimers, polymers, liposomes, nano-emulsions, and micelles) [190]. It is vital to indicate that certain natural products alone have off-target toxicity, low solubility, and low cell permeability, which can limit their anti-cancer efficacy [191]. Therefore, a drug delivery system, based on nanoformulation methods, represents an alternative strategy to significantly increase the chemopreventive and chemotherapeutic efficacy of natural products [183]. Nanopreparation techniques can be used to successfully deliver the natural products to the target site [157]. In this section, we discuss relevant nanoformulations of natural products that have the potential to be used as anticancer drugs.

(1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, also known as curcumin (CUR), a natural bioactive compound, which has antioxidant and anticancer efficacy, belongs to the curcuminoid subgroup of polyphenols (Figure 3) [192, 193]. Due to its poor bioavailability, certain nanotechnology strategies are utilized to improve the pharmacokinetic properties of CUR, thereby increasing the probability of significant therapeutic efficacy. One of these strategies is to deliver CUR to the target site, using various stimuli, such as light, pH, magnetic field, solubility, and chemical modifications [194]. A nanosystem was developed by encapsulating CUR into pH-responsive poly D,L-lactic-co-glycolic acid (PLGA) microspheres, which delivered hydrophobic drugs to the triple negative breast cancer cell lines, MCF-7, MDA-MB-231 and MDA-MB-468, that overexpress folate receptors [195]. Lai et al. [196] developed a pH-reactive hyaluronic acid-based NPs for targeted CUR delivery to increase its anticancer efficacy biosafety profile. Numerous researchers used photoresponsive nanoformulations to increase the stability and solubility of CUR. Alvi et al. [197] entrapped Au-liposome NPs as an adjuvant for photothermal therapy (PTT). NIR light exposure (780 nm for 5 min) in B16 melanoma cells activated the release of CUR nanocrystals,

**Table 1:** Various novel nanoparticles in clinical trials.

| NCT identifiers and phase | Topics | Drugs | Formulations | References |
|---|---|---|---|---|
| NCT04789486 (Phase I/II) | Nano-SMART: nanoparticles with MR guided SBRT in centrally located lung tumors and pancreatic cancer | AGuIX | Metallic NPs | [175] |
| NCT04881032 (Phase I/II) | AGuIX nanoparticles with radiotherapy plus concomitant temozolomide in the treatment of newly diagnosed glioblastoma (NANO-GBM) | AGuIX | Metallic NPs | – |
| NCT04899908 (Phase II) | Stereotactic brain-directed radiation with or without aguix gadolinium-based nanoparticles in brain metastases | AGuIX | Metallic NPs | [175, 177] |
| NCT05039632 (Phase I/II) | Phase I/II randomized study of NBTXR3 activated by abscopal or RadScopal radiation in combination with immunotherapy (anti-PD-1/L-1) for patients with advanced solid malignancies | Hafnium oxide-containing nanoparticles NBTXR3 | Metallic NPs | – |
| NCT04505267 (Phase I) | NBTXR3 and radiation therapy for the treatment of inoperable recurrent non-small cell lung cancer | Hafnium oxide-containing nanoparticles NBTXR3 | Metallic NPs | [176] |
| NCT05359783 (Phase I/II) | Sentinel node localization and staging with low dose superparamagnetic iron oxide (MAGSNOW) | Superparamagnetic iron oxide | Metallic NPs | [174] |
| NCT03020017 (Phase I) | NU-0129 in treating patients with recurrent glioblastoma or gliosarcoma undergoing surgery | NU-019 SNA consists of nucleic acids arranged on the surface of a small spherical gold nanoparticle | Metallic NPs | [128] |
| NCT02837094 (Phase I) | Enhanced epidermal antigen specific immunotherapy trial-1 (EE-ASI-1) | C19-A3 GNP | Metallic NPs | – |
| NCT05359783 (Phase II) | Sentinel node localization and staging with low dose superparamagnetic iron oxide | Superparamagnetic iron oxide | Metallic NPs | [174] |
| NCT05456022 (Phase II) | Therapeutic efficacy of quercetin vs. its encapsulated nanoparticle on tongue squamous cell carcinoma cell line | Quercetin-encapsulated PLGA-PEG nanoparticles (Nano-QUT) | Polymeric micelles | [178] |
| NCT04640480 (Phase I) | Dose-finding study to evaluate the safety, tolerability, and pharmacokinetics of SNB-101 (SN-38) in patients with tumors | SNB-101 | Polymeric micelles | [179] |
| NCT05893888 (Phase I/II) | Safety and efficacy study of PRV211 in subjects with oral squamous cell carcinoma | PRV211 (intraoperative cisplatin system) | Polymeric micelles | – |
| NCT04751786 (Phase I) | Dose escalation study of immunomodulatory nanoparticles (PRECIOUS-01) | PRECIOUS-01 | Polymeric micelles | [180] |
| NCT05340725 (Phase II/III) | Rectal dexmedetomidine niosomes for postoperative analgesia in pediatric cancer patients (DEX-NANO). | Dexmedetomidine niosomes | Liposomes | [181] |
| NCT05700955 (Phase I) | Neoadjuvant chemoimmunotherapy in recurrent glioblastoma | Pembrolizumab and temozolomide | Liposomes | – |
| NCT04675996 (Phase I) | First-in-human study of INT-1B3 in patients with advanced solid tumors | INT-1B3 | Liposomes | [182] |
| NCT05969041 (Phase I) | Study of MT-302 in adults with advanced or metastatic epithelial tumors (MYE symphony) | MT-302 | Liposomes | – |
| NCT05497453 (Phase I/II) | A Phase 1/2 study to evaluate OTX-2002 in patients with hepatocellular carcinoma and other solid tumor types known for association with the MYC oncogene (MYCHELANGELO I) | OTX-2002 | Liposomes | – |
| NCT05001282 (Phase I/II) | A study to evaluate ELU001 in patients with solid tumors that overexpress folate receptor alpha (FRα) | ELU001 | CDC | – |
| NCT02439580 (Phase I) | Effect of *Annona muricata* leaves on colorectal cancer patients and colorectal cancer cells | *Annona muricata* extract, placebo | Polyphenols | – |

NPs, nanoparticles; NCT, national clinical trial; CDC, C'Dot drug conjugate.

which coalesced to form CUR microcrystals for the continuous release of the active compound [197]. Studies have been conducted to increase the solubility, bioavailability, and stability of CUR [198, 199]. A self-assembling acylated ovalbumin nanogel for CUR was synthesized that had a relatively uniform size distribution and higher stability under high ionic strength and different pH [198]. Due to the poor water solubility of CUR (11 μg/L) [200], researchers have synthesized nanoformulations of CUR to surmount this problem. Mangalathillam et al. [201] developed curcumin-loaded chitin nanogels using biocompatible and biodegradable chitin. The formulation was cytotoxic to A375 melanoma cells, at concentrations from 0.1 to 1.0 mg/mL. Gou et al. [202] developed curcumin encapsulated with monomethoxy poly(ethylene glycol)-poly(ε-caprolactone) (MPEG-PCL) micelles, using a nano-precipitation method. This formulation decreased the viability ($IC_{50}$=5.78 μg/mL) of C-26 colon cancer cells. CUR or Cur/MPEG-PCL micelles (curcumin, 100 mg/kg) were intravenously injected in rats and blood collection was performed at different intervals of time. For Cur/MPEG-PCL micelles, the following PK data was obtained: $t_{max}$=5 min, $t_{1/2}$=34.2 min, area under the curve $(AUC)_{(0\rightarrow t)}$=47,642.1 μg/L/min, $AUC_{(0\rightarrow\infty)}$=47,864.6 μg/L/min, and $C_{max}$=430.5 μg/mL. These values were significantly higher than those for free curcumin and indicated that the encapsulation increased the $t_{1/2}$, $AUC_{(0\rightarrow t)}$, $AUC_{(0\rightarrow\infty)}$, and $C_{max}$ *in vivo*. Furthermore, a transgenic zebrafish model was used to ascertain the anti-angiogenic efficacy of Cur/MPEG-PCL micelles. Zebrafish were exposed to free CUR (5 μg/mL) or Cur/MPEG-PCL micelles (5 μg/mL) for 72 h. The results indicated that both free CUR and Cur/MPEG-PCL micelles inhibited angiogenesis by different magnitudes (significantly greater in micellar CUR), resulting in the abnormal formation or absence of intersegmental vessels in the Zebrafish.

The compound (3R,5aS,6R,8aS,9R,12S,12aR)-octahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10(3H)-one, also known as artemisinin (ART), is present in the plant *Artemisia annua* [203]. *In vitro* and *in vivo* studies have reported that ART has antitumor, antifungal, anti-malarial, and anti-ulcer efficacy [204]. However, ART has a lower solubility in water, a shorter half-life and an increased first-passage metabolism, which limits its therapeutic efficacy [205]. The synthesis of ART-containing NPs improve the pharmacokinetic profile of ART and increase the *in vivo* efficacy of ART. Zhang et al. [206] synthesized hollow mesoporous manganese trioxide NPs for the *in vivo* delivery of ART. They synthesized a drug delivery system, TKD@RBCm-$Mn_2O_3$-ART, that specifically releases and produces a uniform dispersion of chemotherapeutic drugs in tumors. ART was loaded into $Mn_2O_3$ to facilitate the co-delivery of $Mn^{2+}$ with ART. *In vitro* experiments indicated that the cumulative drug release reached a maximum of 97.5 % in the presence of glutathione. TKD@RBCm-$Mn_2O_3$-ART released $Mn^{2+}$ and ART simultaneously, which produced high levels of reactive oxygen species (ROS) and DNA damage. *In vivo* results indicated that TKD@RBCm-$Mn_2O_3$/ART penetrated deep into solid tumors and produced a definitive diagnosis and treatment of breast cancer. Yu et al. [207] modified ART-loaded liposomes with activatable cell-penetrating peptides. This formulation was composed of Tf-coated, dihydroartemisinin (DHA), L-buthionine-sulfoximine (BSO), and CellROX-loaded liposomal nanoparticles (Tf-DBC NPs). ART was integrated into acidic pH-responsive liposomes that significantly decreased the proliferation of HepG2 cancer cells ($IC_{50}$=2.5 μmol/L) and avoided oxidative stress to normal cells, as indicated by a fluorescence response of CellROX in HepG2 and normal cells. Tf-coated liposomal NPs encapsulating Cyanine7 (Tf-Cy7 NPs) were prepared to provide data about the circulation profile of the nanoformulation in tumor-bearing female BALB/c nude mice (that were subcutaneously injected with HepG2 cancer cells to create a HepG2 tumor model). After injecting 0.9 mg/kg *via* intravenous infusion, the circulation half-life ($t_{1/2}$) was 4.81 h, which indicated the presence of Tf-Cy7 NPs in the bloodstream, thus indicating that the formulation was stable *in vivo*. *In vivo* and *ex vivo* analysis showed that fluorescence occurred only in tumorous areas after the intravenous injection of Tf-DBC NPs, indicating that the normal cells were not affected by the oxidative stress induced by the nanoformulation. Halevas et al. [208] designed a dendritic-linear-dendritic hybrid copolymer to encapsulate ART, using linear PEG chains and hyperbranched 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) and this preparation was hydrophilic. The $IC_{50}$ value of Art-loaded bis-MPA PEG6k-OH, pseudo-generation 4 (G4-PEG6k-OH) hyperbranched dendritic scaffolds (AHDS) in MCF-7 after 72 h of incubation was 30.5 μmol/L. The results indicated that the formulation maintained the anticancer efficacy of ART but was not toxic in normal 3T3 fibroblasts cells.

A significant interest in the development of nano-drugs has resulted in more inventions related to preparation methods and applications [209]. Nano-curcumin and its derivatives, such as isovanillin curcumin, ferulic acid curcumin, 3,5-di-tert-butyl-4-hydroxybenzaldehyde curcumin, syringaldehyde curcumin, and 4-methoxy-1-naphthaldehyde curcumin, have been the most common compounds evaluated for pharmacological efficacy in cancer cells. Xiao et al. [210] (patent no. WO2020088702A1) invented a method of making nanocrystals that increased the bioavailability of certain curcuminoids and camptothecin. The patent (WO2020249383A1) reported the invention of an active substance delivery system

for curcumin to be used for the treatment of peritoneal metastases in numerous cancers [211]. Although the nanoparticle formulations of natural products have garnered increased attention, challenges, and problems, such as nanotoxicity, must be determined.

## Albumin NPs

Albumin is the most abundant protein in the plasma that is involved in many physiological processes, such as maintenance of osmotic pressure, transport of hormones, ligands, drugs, and neutralization of free radicals, among others [212]. It is a multifunctional protein that is highly stable, biodegradable, biocompatible and non-immunogenic [213]. Albumin has numerous high-affinity hydrophobic binding sites that can bind a number of ligands and drugs [214]. Thus, based on these aforementioned properties, albumin is commonly used as a nanocarrier [213]. Albumin NPs can be formulated in combination with other nanocarriers, such as polymeric micelles, liposomes, metallic NPs, silica, and nanosheets, among others, to improve cellular uptake efficiency and minimize the immunogenicity of the parent drug [215–220]. Albumin has a number of properties that make it a highly suited nanocarrier. Albumin has an isoelectric point of 4.25 at physiological pH [221] and thus, it has dense negatively charged areas that will induce a strong repulsive force towards negatively charged proteins, such as hemopexin, haptoglobin and transferrin, which increases its stability and half-life in the circulation [222–224]. Multiple functional groups in albumin, such as amino and carboxyl groups, facilitate the binding with ligands by forming covalent or non-covalent bonds [225]. The most commonly used albumin for nanoformulations is derived from BSA or human serum albumin (HSA), although ovalbumin can also be used [226]. HSA is a protein (molecular weight [MW]=133 kDa, 5.2 × 5.3 × 11.7 nm in dimensions) that consists of three homologous α-helical domains that are composed of ten antiparallel helices that form a heart-shaped, asymmetric structure [227]. BSA NPs offer biocompatibility, non-toxicity, biodegradability, non-immunogenicity and a higher drug-binding capacity [228]. BSA (MW=69 kDa) is an acidic, globular, single polypeptide chain protein that is found abundantly in some mammals, with a half-life of 19 days [228]. Anti-cancer drug binding with albumin can be done *via* covalent and/or non-covalent conjugation [229]. Since albumin NPs are very versatile molecules, this conjugation can be manipulated as required.

The majority of albumin nanoformulations are prepared by desolvation, which involves: (1) the precipitation of NPs by depleting the solvation layer, using a dehydrating agent, such as ethanol; (2) densification and stabilization by chemical crosslinking; (3) additional purification to remove redundant solvents and crosslinking molecules [230]. Desolvation is a simple and inexpensive process that can be completed in approximately 3 h [231]. In addition, thermal gelation, emulsification (used for hydrophobic drugs) and electrostatic interactions (used for positively charged drugs), are used when desolvation is not achievable [226]. For other proteins, nanoformulations, such as gelatin NPs, collagen NPs, milk proteins, casein NPs, silk fibroin NPs, elastin NPs, and various other plant-based protein NPs have been used. Methods such as, pH variation [232], nano-spray drying [233], sonochemical method [18], phase separation [234], rapid laminar jet [235], milling [236], and polymer chain collapse [237], are the most commonly used preparatory methods [18, 233, 238, 239]. However, there is no perfect approach and each method has its advantages and disadvantages. Abraxane® (FDA approved) is one of the well-known nanoformulations that are based on albumin NPs [70, 240]. Other examples include DOX-loaded in BSA-dextran-chitosan NPs prepared by thermal gelation [241], poorly soluble 10-hydroxycamptothecin-loaded in BSA NPs *via* emulsification [242], and paclitaxel-loaded BSA NPs, using desolvation [243].

Albumin NPs target the cancer cells *via* active or passive targeting [228]. Active targeting includes binding of the NPs to the surface receptors entering the cell *via* internalization. In contrast, there is an EPR effect in passive targeting. Cancer cells usually express a high level of certain glycoproteins, such as Gp18, Gp30, and Gp60, secreted protein acidic rich in cysteine (SPARC) receptors, which are important binding sites for albumin NPs [228]. The accumulation of albumin-based NPs in solid tumors can be affected by the angiogenesis, leaky vasculature, and defective lymphatic drainage [213]. PEGylation increases the circulation half-life by >50-fold, decreases immunogenicity, and increases the accumulation of BSA nanoformulation of 5-fluorouracil in tumors due to the EPR effect [244]. HSA NPs represent a viable approach for targeted drug delivery by increasing drug bioavailability and distribution, decreasing drug toxicity and immunogenicity [70, 240]. Despite having several advantages, albumin NPs have certain drawbacks. For example, manipulation of particle size, shape, distribution, and stability poses major challenges. Furthermore, the factors affecting the toxicity of albumin NPs, such as the composition and surface properties must be precisely controlled. There is also batch-to-batch quality variation, which can impede the scaling-up process. A compelling approach to overcome this challenge is recombinant protein technology, where mono-dispersity and predefined characteristics of polymers along with the predictable arrangement of crosslinking groups, binding moieties at specific sites or their programmable degradation rates, makes them

suitable and convenient for drug delivery and tissue engineering systems [226]. Moreover, there are limited publications about the immunogenicity of proteins, although there are no published reports about the antigenicity of albumin NPs, even after intravenous (IV) injections [245–248].

## Polymeric micelles

Polymeric micelles are composed of various amphiphilic polymers that preferentially self-assemble in an aqueous medium [249]. Each unit of polymeric micelles comprises a hydrophilic and a hydrophobic segment (Figure 3). These amphiphilic polymers are synthesized using various polymeric blocks, which can be customized, as needed, depending on the size, capacity, hydrophobicity, micellization capacity, and stability in blood [249]. Similar to the albumin NPs, the nanosize of the micelles facilitates penetration through the leaky vasculature and retention due to defective lymphatic drainage in tumors [250]. The outer layer of micellar encapsulation is typically hydrophilic and therefore, it evades detection by the reticulo-endothelial system [251]. Polymeric micelles can be modulated or adjusted by the addition of ligands on the surface that are involved in active targeting [250]. Various building blocks of polymers, such as PEG coupled with either phosphatidylethanolamine (PE), polypropylene oxide (PPO) triblock polymer (PEG-PPO-PEG), PEG-amino acids or PEG-carbonates, can be used individually or in combination. PEG-PE was one of the first lipid-based amphiphilic polymers to be used to integrate in the liposomal lipid bilayer to sterically stabilize liposomes [252]. In the next step of PEG-PE preparation by self-assembly, drugs are added and this process is primarily based on the physicochemical characteristics of the drug and the method of preparation [253]. PEG-PE self assembles at a low micellar concentration, allowing for the encapsulation of hydrophobic drugs [254, 255]. PEG-PE, coupled with vitamin-E micelles, has been used to formulate camptothecin, DOX and paclitaxel, with sizes ranging from 15 to 100 nm [256]. PEG-PPO-PEG triblock polymers, also known as pluronics or poloxamers, have core shell structures of pluronics, 10–100 nm in diameter and the preparation and formation process is temperature- and concentration-dependent [249]. These polymers, such as Pluronic® P85 carrying DOX and Pluronic® P123/F127 block copolymers carrying rhodamine-123, rhodamine-G, DOX and paclitaxel, have been reported to inhibit the ABC transporters, P-glycoprotein (P-gp), multidrug resistance-associated protein-1 (MRP1) and breast cancer resistance protein (BCRP), thereby effectively decreasing MDR [257–259]. Anti-cancer drugs, either individually or in combination with adjuvants or other anticancer drugs, can be loaded onto pluronics [260–264]. Du et al. [265] used α-tocopherol polyethylene glycol 2000 succinate ($TPGS_{2k}$) to modify PEG NPs and the NPs were co-loaded with simvastatin and DOX [265]. The resulting formulation significantly decreased lipid raft formation (>80 %) in SW620/AD300 (colon cancer cells resistant to DOX) cells. In the presence of 20 μg/mL of free simvastatin (SV) or DOX, SW620 cell viability following incubation with SV@$TPGS_{2k}$-PLGA NPs, DOX@$TPGS_{2k}$-PLGA NPs and SV/DOX@$TPGS_{2k}$-PLGA NPs was 28.1 , 25.9 and 13.2 %, respectively and the viability of SW620/AD300 cells was 27.2 , 24.1, and 11.3 %, respectively. The preparation of PEG-amino acids has only been recently reported in the scientific literature. Polypeptide chains can be linked to PEG and amino acids, based on the type of formulation desired, are used. For example, the amino acids, L-lysine, L-glutamate, and L-aspartate are used for hydrophilic preparations [266]. DOX [267, 268] and cisplatin [269] can be loaded to produce PEG-amino acids.

The preparation of polymeric micelles depends on the following factors and conditions: temperature, pH, micellar concentration, ionic charge, surface characteristics, interaction with organic counterparts, and kinetic stability [250]. Some of the methods used for the preparation of polymeric micelles include dissolution, dialysis, emulsion and solvent-casting, and film hydration [270–273]. The characterization of micelles is clinically important as it helps to define and predict their interactions with other molecules [274]. The thorough characterization of micelles involves the determination of critical micellar concentration (CMC), the drug payload, and its release [274–276]. Generally, this characterization is accomplished using dynamic light scattering (DLS) [277], atomic force microscopy (AFM) [274, 278], cryo-transmission electric microscopy (Cryo-TEM) [279], X-ray scattering [280–282], and Foerster resonance energy transfer (FRET) [275, 276, 283, 284]. A study involving DOX formulated with a dextran-based polymeric nanosystem reported a higher toxicity in various cancer cells *in vitro*, compared to the parent drug [285]. SNB-101 is a novel micellar nanoformulation for the anticancer drug, SN-38, that has an approved investigational new drug (IND) application for the treatment of various cancers and it is in Phase I clinical trials for tumors (NCT04640480) [179]. A drug named PRECIOUS-01 is undergoing evaluation in Phase I clinical trials for advanced solid tumors. This is a PLGA-based nanocarrier that has promising therapeutic potential [180].

It is important to note that polymeric micelles can prematurely release drugs prior to reaching the target site [286]. Drug release is an essential step in drug delivery, as an optimum drug concentration must reach the tumor site(s) to

achieve an intracellular level that is efficacious [287]. Membrane dialysis or ultracentrifugation can be used to determine the amount of a drug that is released from polymeric micelles [288–291].

## Liposomes

Dr. Alec Bangham discovered liposomes in 1964 [292], which are now some of the most commonly used nanosystems. Basically, liposomes are spherical systems that have two outer hydrophilic layers with a lipophilic layer in between [293]. Liposomes that have more than one concentric lipid bilayer are known as multilamellar vesicles (MLVs) [293]. Liposomes are typically classified into small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), MLVs, and multi-vesicular vesicles (MVV) [294]. The best route of administration for liposomal drug delivery is the parenteral route, as these formulations will circumvent: (1) first pass metabolism; (2) adverse gastrointestinal (GI) effects; (3) poor GI tract absorption [294]. Furthermore, parenteral administration results in a higher bioavailability and increased efficacy, compared to oral or rectal administration [295]. Liposomes are biodegradable, highly biocompatible, and are prepared *via* self-assembly [296]. One of the most extensively used polymers is PEG. PEGylated liposomes are considered to be a "stealth formulation", as these molecules are sterically stabilized liposomes that have a decreased propensity to aggregate, which decreases their interaction with opsonins, thereby decreasing their removal from the circulation by phagocytosis [297]. Doxil® was the first liposome-based DOX formulation and FDA approved liposome-based formulations include DaunoXome® (AIDS-related Kaposi's sarcoma), Myocet® (metastatic breast cancer), DepoCyt® (neoplastic meningitis), Marqibo® (acute lymphoblastic leukemia), Onivyde™ (metastatic adenocarcinoma of pancreas), and Mepact® (metastatic osteosarcoma) [196]. Lipid-saporin combination of NPs can serve as a novel therapeutic regimen for ABCB1/ABCG2-positive drug-resistant cancers. Patel et al. developed palmitoyl carnitine-anchored nano-liposomes for targeted delivery of gemcitabine elaidate for the treatment of pancreatic cancer [298]. This combination therapy of gemcitabine elaidate with palmitoyl DL-carnitine chloride inhibits protein kinase-C inhibitor in a nano-liposomal carrier that had increased cellular uptake, producing a decrease in angiogenesis and increasing the anticancer potential in both 2D and 3D models of pancreatic tumors *in vitro*. Dinakar et al. exploited the abundance of folate receptors in breast cancer to develop a folate and poly-I-Lysine conjugate and coated it on liposomes for targeted drug delivery [299]. Their result indicates a decrease in the $IC_{50}$ values and the induction of death in breast cancer cells *via* folate receptor-mediated internalization, followed by rapid drug release. Furthermore, they determined that luteolin formation inhibits cell migration and proliferation by regulating the expression of vascular endothelial growth factor (VEGF) and the induction of apoptosis by caspase-3 upregulation. Zhan et al. reported that liposomal dexmedetomidine could provide controlled, adjustable and on-demand local anesthesia *in vivo* [181]. INT-1B3 is a novel synthetic liposomal miR-193a-3p (tumor suppressor microRNA) mimicking NP [182]. INT-1B3 decreased target gene expression, resulting in decreased cell proliferation, increased cell cycle arrest, initiation of apoptosis, inhibition of migration, DNA damage and cell senescence *in vivo* [182]. In addition, research in the area of liposomal mRNA vaccine delivery (Figure 3) has gained an increased interest in recent years. These NPs have the unique advantages of controlled release, improved biosafety and high biocompatibility [80]. They also serve as immunotherapy adjuvants, in addition to delivering mRNA vaccines. This results in killing the cancer cells by reviving the anti-tumor immune response, maintaining the response and improving the threshold, producing prolonged survival and a better quality of life in patients with advanced tumors [300].

The laboratory manufacturing of liposomes primarily involves the dissolution of phospholipids in certain organic solvents, ethanol, isopropyl ether, diethyl ether, chloroform or methanol, either individually or in various combinations [296]. The fundamental molecular units of a liposome preparation are phospholipids and cholesterol [296]. At the CMC, typically in the nanomolar range, liposomes undergo self-assembly when exposed to an aqueous environment [301, 302]. In a method known as lipid film hydration, an organic solvent, such as trichloromethane, is used to dissolve the phospholipids [303, 304]. The lipophilic drug is subsequently added to the solvent to form a one-phase solution and the removal of the organic solvent is done under a vacuum, forming thin sheets of lipid with uniform distribution of the drug along the film [303, 304]. This procedure produces hydration of the sheets in the presence of an aqueous buffer that is above the glass transition phase (a reversible transition phase that occurs when an amorphous material is cooled or heated over a certain range of temperatures, which causes the material to become hard and brittle upon cooling and softer upon heating) of the lipid [295, 305]. If the drug is hydrophilic, it will dissolve in the aqueous buffer, leading to a particle size greater than 500 nm, with an entrapment efficiency of 10–30 %. In contrast, for lipophilic drugs, an optimum vesicle size is obtained, with an entrapment efficiency >90 % [306, 307].

Another technique, known as solvent dispersion, involves phospholipids being dissolved in a water-miscible organic solvent, usually ethanol [308–310]. If the lipophilic drug is not miscible in ethanol, other organic solvents, such as diethyl ether or ether–methanol mixture, may be

used [296]. Instead of an aqueous buffer being added to the organic solution in the previous method, the mixture (organic solvent and drug) is added to the aqueous buffer, the solvent becomes diluted and there is a spontaneous formation of MLVs, usually of size above 500 nm [294]. This technique is best suited for lipophilic drugs.

Reverse phase evaporation, yet another technique used to formulate liposomes and it is the most frequently used technique for forming liposomes with hydrophilic drugs [311]. This technique can entrap a large amount of an aqueous core during the formation, yielding high entrapment efficiency [312, 313]. In a water/oil emulsion, the hydrophilic drug is dissolved in water and the phospholipid is dissolved in a water-immiscible solvent, usually diethyl ether or isopropyl ether [314]. The removal of the organic solvent using a vacuum leads to the gradual formation of a gel [296]. A liposomal dispersion is produced when the organic solvent is further evaporated [315]. The passive drug-loading efficiency for liposomes prepared *via* reverse phase evaporation is 30–50 % and it can be increased to >90 %, using active drug-loading techniques [311, 316, 317]. The stability of the final preparation depends on the physical and chemical environment and the storage conditions. The size of the carrier, the drug payload and chemical stability, can be significantly altered by improper storage conditions [295]. Importantly, the majority of marketed liposomal formulations need to be stored at 2–8 ° C [295].

Scaling-up technologies for liposomal preparation are very limited. One of the most commonly used techniques is the rapid injection of ethanol and phospholipids into an aqueous medium, followed by extrusion of solvent, using a polycarbonate membrane. This approach ensures size reproducibility and the quality of the liposomes [308]. A typical commercial preparation involves the following sequential steps: preparation of buffer, filtration, preparation of a phospholipid solution, second filtration, lipid hydration, extrusion, diafiltration, dilution, sterile filtration, and filling [318–321].

## Polyphenols

An estimated 10,000 polyphenolic substances have a structure that includes multiple hydroxyl groups and aromatic rings [322, 323]. These compounds are present in high concentrations in various fruits and vegetables as secondary plant metabolites [323], and the most frequently occurring of these are the flavonoids (about 60 %) and phenolic acids (about 33 %) [324]. Polyphenols are primarily obtained from (1) fruits: plums, apricots, oranges, apples, tomatoes, cherries, peaches, berries, and other tropical fruits; (2) vegetables: broccoli, spinach, onions, carrots, olives, beans, capers, artichokes and cauliflowers; (3) herbs and spices: celery, rosemary, cloves, turmeric, parsley, thyme, mint, sage, dill weed, ginger, and curry and; (4) other sources: red wine, black or green tea, cocoa, coffee, fruit juices, beer, seeds, grains, and nuts [191, 322, 325–331]. Polyphenols have been reported to be efficacious in dyslipidemia, GI diseases, cardiovascular diseases, inflammatory disorders, neurological disorders and various cancers, due to their antioxidative and immunomodulatory effects [332–334]. Epigenetic modifications (primarily a result of DNA methyltransferases or histone deacetylases) also play an important role in the efficacy of dietary polyphenols. For example, the consumption of quercetin-rich food is significantly correlated with decreasing the risk of lung and gastric cancer [335–337]. *In vitro* studies indicate that resveratrol is efficacious in inhibiting the proliferation of stomach, breast, colon, prostate, lung, pancreatic, and thyroid cancer cell lines [338]. Green tea extract contains a high concentration catechins, such as epigallocatechin-3-gallate, epicatechin-3-gallate, and epigallocatechin, which inhibit cancer cell growth, metastasis, and angiogenesis *in vitro* [339–341]. An *in vitro* study has shown that epigallocatechin-3-gallate modulates the expression of regulatory proteins involved in cell cycle, activates caspases-3, caspase-8, and caspase-9 and suppresses the activation of nuclear factor-kappa B (NF-κB), resulting in the induction of apoptosis and the inhibition of cancer cell growth [342]. Cruciferous vegetables in the *Brassica* genus (e.g., cabbage, broccoli, kale) contain sulfur-rich compounds, known as glucosinates, that can decrease the risk of lung cancer and colon cancer in humans [343, 344].

Dietary polyphenols are primarily present in glycosylated forms, with sugar residues linked to the aromatic ring or the hydroxyl group [326, 345], which are more efficiently absorbed by the GI tract *via* passive diffusion [345]. Gallic acid, catechins, flavanones, and quercetin glucosides have been reported to have the highest GI absorption, compared to galloylated tea catechins, proanthocyanidins, and anthocyanins, which are among the least GI-absorbed polyphenols [346]. The extraction process used to obtain polyphenols from natural sources can be done using fresh, frozen, or dried samples and before the process begins, the material is exposed to milling, grinding, drying, and homogenization [347]. The freeze-drying process produces a higher yield of phenolic compounds, compared to air drying [348]. Liquid-liquid and solid-liquid extraction are widely used methods because of their applicability, efficiency, and ease of use [347, 349]. Solvents, such as ethanol, ethyl acetate, acetone, and diethyl ether, are generally used in various ratios with water. The extraction of nonpolar compounds, such as oils, waxes, chlorophyll and sterols and the extraction from

less polar solvents, such as chloroform, benzene, dichloromethane and hexane, may be possible [347]. Solvents, such as methanol, yield a higher level of low molecular weight polyphenols, whereas acetone yields a higher level of high molecular weight flavanols [350–353]. Modern techniques, like supercritical fluid technology, have been widely used for the separation of polyphenols from their natural sources [354]. This technique prevents the oxidation and degradation of the polyphenols [354, 355]. The main advantage of supercritical fluids is that they dynamically change the solvent characteristics and yield the desired levels of the extracts from raw materials [354]. Typically, supercritical $CO_2$ is used as the solvent because of its high penetration into cellular materials or tissue explants and its solvent power [356]. Propane, argon, and sulfur hexafluoride ($SF_6$) are supercritical fluids that have been used in supercritical fluid extraction methods [356]. Certain end products of polyphenol extraction include curcuminoids, stilbenes, tannins, lignans, phenolic acids, and flavonoids, i.e., flavanones, flavanols, anthocyanidins, catechins, isoflavones, and chalcones [347].

## Discussion

Cancer is one of the leading causes of death in the world and the efficacy of anticancer drugs can be significantly decreased or abolished by MDR that occurs *via* a number of mechanisms. Furthermore, physiological factors, such as higher IFP, hypoxia, leaky tumor vasculature, low pH, and irregular drug penetration due to inaccessible location of cells, also decrease the efficacy of anti-cancer drugs (Figure 4) [28]. Unfortunately, increasing the dose of an anticancer drug, as well as drug combinations, significantly increases the probability of adverse effects and toxicity, thereby causing a decrease or absence of patient compliance, which increases cancer cell proliferation and a subsequent relapse. Studies over the past two decades suggest that certain nanomedicine formulations can overcome some of the mechanisms that produce MDR in cancer cells. There are certain advantages in using nanomedicine, compared to conventional preparations [357]. Nanoformulations effectively permeate and overcome biological barriers, such as transporters in cell membranes throughout the body. Some studies have reported that nanopreparations bypass ABC transporters and effectively kill the cancer cells. One study reported an increase in the nuclear localization of DOX in a few sets of sensitive- and drug-resistant cells when the drug was introduced with nanospheres, compared to parent drug [358]. It is important to state that cancer nanomedicine is not a "magic bullet" for the treatment of cancer. Certain factors, such as the interaction between NPs and surface proteins, i.e., protein corona formation, while maintaining the stability and half-life of the

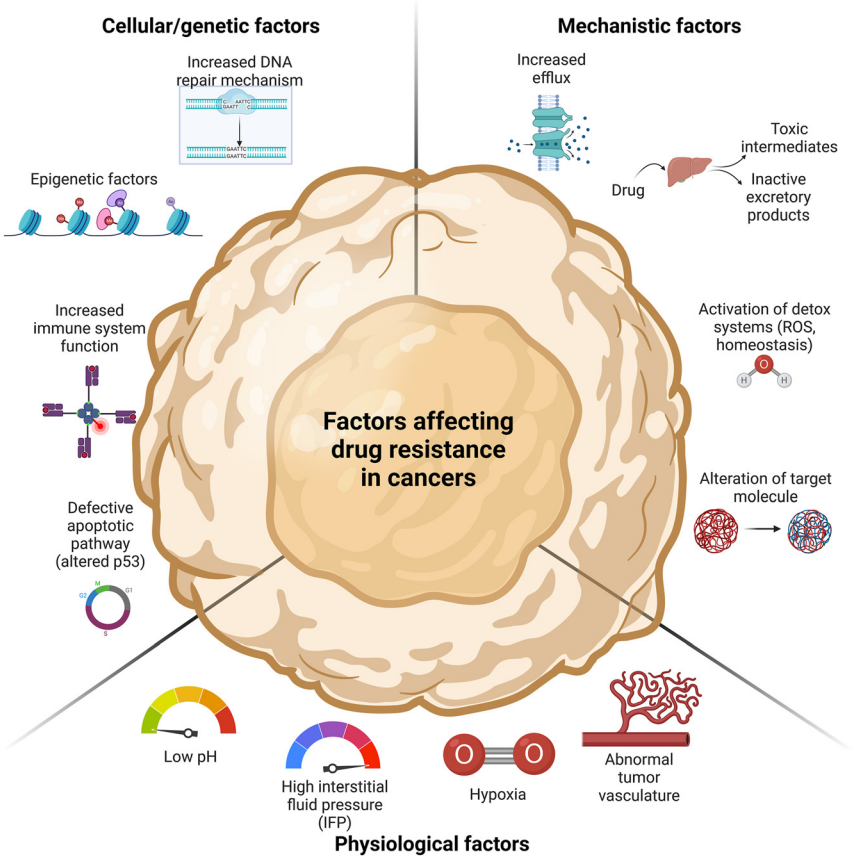


**Figure 4:** An overview of factors affecting multidrug resistance in cancer.

drug, must be taken into consideration. The size and binding affinity of NPs must be evaluated for the internalization of the therapeutic. Furthermore, the magnitude of cellular uptake is critical in determining the efficacy of nanoformulations. A drug may not enter the cell even after successful delivery near the target cell due to inadequate cellular uptake. Furthermore, NP endosomal release is crucial for successful drug delivery, especially for siRNA-based therapeutics. Although numerous researchers have studied the nanodelivery and co-delivery of NPs for the reversal of MDR, there have been ambiguous results in clinical trials [359–361]. This could have been due to a number of factors, such as a decrease in the effective release of a drug from the core [249]. Also, immune response reactivation is only seen in a small subset of patients. Finally, the absence of biomarkers to assess the efficacy of cancer nanotherapeutics is one of the main obstacles to attaining tailored immunotherapy.

As discussed in the main text, it is apparent that the field of cancer nanomedicine has great potential. Cancer nanomedicine caters unique advantages such as controlled and sustained release, better biosafety, higher biocompatibility, and lower systemic toxicity. Furthermore, certain types of NPs like liposomes and polymeric micelles serve as adjuvants in addition to delivering therapeutic payloads like mRNA vaccines. Nanoformulations can efficiently accumulate at the tumor site(s) *via* active or passive targeting or by the EPR effect. NPs have an increased circulation time and increased half-life. The interaction between NPs and biological components may improve drug delivery. Furthermore, nanomedicine can co-deliver a multi-drug or a multistage payload, which represents a promising approach to overcome MDR. Nonetheless, it will be critical to ascertain the toxicity profile of these novel therapeutics to determine if these compounds can be used to treat cancer in humans. Moreover, certain challenges, such as varied efficacy of industrial production, various side effects like pruritus, rashes, nausea, diarrhea and thyroid disorders, must be further evaluated. Consequently, *in vivo* studies must be conducted to determine the safety and efficacy of anticancer nanomedicines. Finally, researchers in academia and industry must develop scaling-up technologies without the loss of reproducibility. The gap in clinical translation of cancer nanomedicine can be further decreased by the development of humanized animal models, as there are significant structural and biochemical differences between tumors in rodents and humans. These humanized animal models must contain human-derived factors such as immune cells. EPR is vital for drug delivery; however, the uncertainty of the EPR effect in different patients leads to dubious results in clinical trials. This can possibly be solved by determining the level of the EPR effect in the patients. Although most NPs achieve active targeting, the mechanism behind this phenomenon remains unclear. However, it is firmly believed that the efficacy of cancer nanomedicine can be significantly improved by combining the advancements in cancer biology and nanotechnology.

The uniqueness of each case of cancer is a huge hurdle in the clinical translation of cancer drug research. In the past 50 years, a plethora of knowledge has been amassed, producing notable progress in the field of cancer nanomedicine. The era of personalized and customized nanomedicine has inevitably arrived that must help in overcoming unique but fundamental mechanisms of MDR.

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