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*Review Article*

# Different Aspects of Nano-material and Biodegradable Polymers for Cancer Diagnosis and Treatment: A Review

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**Abstract:** Cancer, one of the most prevalent causes of death and disease, has a convoluted pathophysiology. Chemotherapy, immunotherapy and radiation therapy are examples of traditional cancer treatments. However, lack of selectivity, restrictions such cytotoxicity, and Drug resistance is a significant barrier to successful cancer treatment. With the development of nanotechnology, the study of cancer treatment has undergone a revolution. For treatment of cancer Nanoparticles can be used because of their special advantages, less toxicity, more good stability, stronger permeability, and exact placement. There are several varieties of nanoparticles. The innovative nanoparticle based drug delivery system makes advantage of characteristics of the tumour and its surroundings. Nanoparticles overcomes the disadvantages of conventional treatment of cancer in addition to avoiding multiple drug resistance. As additional multidrug resistance mechanisms are found and examined, nanoparticle research is also being pursued actively. The therapy includes consequences of Nano formulation have provided fresh perspectives on cancer treatment. The biggest chunk of studies, however, is restricted to in vivo and in vitro experiments, and the number of authorized Nano drugs has not increased significantly over time. This study covers a wide range of nanoparticle kinds, targeting strategies, and authorized Nanotherapy includes use in the cancer treatment. We also provide a summary of the pros, disadvantages, and present state of clinical translation.

**Keywords: Cellular targeting, Chemotherapy, Cryosurgery, Multidrug resistance, Nanoparticles**

## 1. INTRODUCTION

A group of disorders known collectively as cancer are characterized by uncontrolled, haphazard cell development and invasiveness. The identification of numerous cancer risk factors has been the focus of intensive research over a number of years. Numerous environmental factors, such as radiation and pollution, have been firmly related to the development of numerous types of cancer. Tobacco use, stress, smoking, and a sedentary lifestyle, among other harmful habits, have a significant influence on cancer risk assessment. It has been

difficult to determine the extent to which tumour suppressor gene expression patterns, DNA repair genes, and mutations in proto-oncogenes have contributed to cancer, despite the fact that these external variables are widely acknowledged as primary drivers of the disease. Only 5 to 20% of cancer cases are genetically inherited.

The second-leading cause of mortality worldwide is cancer, one of the major issues with public health. By the end of 2021, the American Cancer Society predicts that there will have been 1.9 million additional cases. Surgery, radiation therapy, targeted therapy, chemotherapy, and immunotherapy are some of the traditional therapeutic modalities utilized in the treatment of cancer. Despite having the capacity for cytostatic and cytotoxicity, radiation treatment and chemotherapy are usually linked to a high risk of recurrence. Bone marrow suppression, gastrointestinal, Neuropathies, and hair loss, skin disorders, and fatigue are among the most typical adverse responses brought on by. In addition, there are other side effects that are medication-specific, such as the cardiotoxicity and pulmonary toxicity of bleomycin and anthracyclines.

Precision therapy has expanded as a result of the development of targeted therapy. However, there are still a lot of unavoidable negative effects, such multi-drug resistance, that restrict the effectiveness of therapy. In addition to treating primary cancer, immunotherapeutic drugs have shown promise in preventing distant metastasis and decreasing the risk of recurrence. However, one important adverse impact of immunotherapy is autoimmune disease. Furthermore, research and circumstantial evidence point to immunotherapy's inferior efficacy against solid tumours to lymphoma. Extracellular matrix (ECM) produced by these tumours is peculiar, making it difficult for immune cells to invade. Dermatological adverse events (dAEs) are caused by these recently developed targeted treatments and immunotherapies because they disrupt signaling pathways that are important for both normal homeostatic processes of the epidermis and dermis as well as malignant tendencies.

In light of all of these facts, the need for the development of fresh approaches for pursuing targeted cancer therapy has grown in recent years. Recently, efforts have been made to use nanoparticles to overcome the shortcomings of current medicinal techniques. By displaying good pharmacokinetics, accurate targeting, decreased side effects, reduced drug resistance, nanoparticle-based drug delivery systems have shown advantages in the treatment and management.

Following the development of nanotechnology, some Nano therapeutic medications have been extensively marketed, commercialized, and many more have since 2010 entered the clinical stage. By inhibiting drug resistance mechanisms and enabling medication combination therapy, Nano therapeutic medicines have advanced the fields of drug delivery methods and anti-tumor multidrug resistance (MDR). In the 1960s, ETH Zurich launched the initial attempt to use nanotechnology in medical. This merger has shown to be a more efficient one for developing a variety of diagnostic tools and enhanced therapies. This study primarily focuses on fundamental ideas behind the use of Nano therapeutics, as well as on present issues and future directions for research.

## 2. LITERATURE SURVEY

### 2.1 Nanoparticles

Technically speaking, nanoparticles (NPs) are described as particles having a diameter less than 100 nm and special characteristics that are often absent from bulk samples of the same substance [1]. These can be categorized as 0D, 1D, 2D, or 3D depending on how the nanoparticle is shaped overall [2]. The fundamental composition of nanoparticles, which is extremely complex, is made up of three layers: the core, surface layer and the shell layer which is effectively the centre section of the NP and is sometimes referred to as the NP itself [3]. These materials' outstanding features, such as their high surface to volume ratio, sub-micron size, dissimilarity, and improved targeting mechanism, have made them particularly essential in a range of various fields.

Deep tissue penetration of NPs is reported to boost the increased retention and permeability (EPR) impact. By overcoming epithelial fenestration, the surface characteristics also affect bioavailability and half-life [4]. For instance, PEG-coated nanoparticles (NPs) diminish opsonization and escape immune system clearance [5]. By adjusting the particle polymer properties, it is also feasible to maximize the release rate of medications or active moieties. Together, the unique characteristics of NPs control their therapeutic impact in the prevention and treatment of cancer.

### 2.2 Cellular targeting mechanism

Effective cancer therapy requires the creation or manufacture of a drug or gene delivery system with exceptional ability to target tumour cells while protecting the normal healthy cells. It improves therapeutic efficiency while preventing cytotoxicity in healthy cells. It can be done by strategically delivering NPs to the tumour microenvironment (TME) and then indirectly targeting the cancer cells. These Nano formulations ought to be able to

cross several biological and physical barriers. These barriers are intricate systems made up of several membranes and layers, including endothelium, epithelium, and cellular membranes (mechanical and physicochemical barriers and enzymatic barriers). These facts limit the biocompatibility and surface chemistry of NPs in order to prevent non-specific targeting. However, merely internalizing an NP drug molecule in the cytosol does not guarantee that it has reached its subcellular target. To allow cellular or nuclear targeting, precise engineering and optimization are required.

To find NP-based medication targeting design, various researches has been conducted thus far, and more are under development. These nanocarriers normally need to have a few basic qualities, such as

1) The capacity to stay stable in the bloodstream until they reach the TME.

2) to avoid being cleared by the reticuloendothelial system (RES).

3. Get away from the mononuclear phagocyte system (MPS).

4) Assemble in the TME through the tumour vasculature.

5) Penetration of the tumour fluid at high pressure.

6) Arrive at the desired location and solely speak with tumour cells.

The procedure of NP drug targeting is controlled by crucial factors such surface functionalization, physicochemical features, and pathophysiological traits.

NPs that are thought to be effective for treating cancer typically range in diameter from 10 to 100 nm. It is crucial to discuss the targeting mechanisms in order to comprehend the connection and interplay between NP carriers, cancer cells, and tumour biology. The two fundamental categories into which they classified are passive and active targeting.

### 2.2.1 Passive targeting

In the late 1980s, researchers noticed a preferential buildup of a few macromolecules in cancer cells. Poly(styrene-co-maleic acid)-neocarzinostatin (SMANCS), the first macromolecule to be known to accumulate in the tumour, was discovered by Matsuura and Maeda [6]. According to additional research, the presence of fenestrations in the damaged tumour blood arteries and the inadequate lymphatic drainage, which together are known as the "increased penetration and retention effect," are the causes of this preferential distribution.

Under some conditions, such as inflammation, hypoxia, the endothelium layer of the blood vessels becomes more porous[7]. Rapidly growing tumour cells in hypoxic environments frequently engulf or activate additional blood vessels to keep up with their development. Neovascularization is the term for this action. Large holes in these new blood vessels cause them to leak, which results in poor tumour blood vessel perm-selectivity when compared to normal blood vessels [8, 9].

Extracellular fluid (ECF) draining into lymphatic capillaries regularly occurs in normal tissues with an average flow rate of 0.1-2 m/s, maintaining continual drainage and regeneration [10]. There is little interstitial fluid uptake when a tumour forms because the lymphatic system is disrupted [11]. Due to the fact that they are not removed and accumulate in the tumour interstitium, this property helps with NP retention. The improved retention component of the EPR effect is shown by this procedure. This unique property does not apply to chemicals that circulate quickly and are quickly flushed out of cancer cells. Therefore, to alleviate these circumstances, it is common practice to encapsulate these tiny compounds in nanosized drug carriers to optimize their pharmacokinetics, give tumour selectivity, and lessen adverse effects [12].

TME is a crucial component of passive targeting in comparison to the EPR effect. Glycolysis is one of the key metabolic processes in rapidly reproducing tumour cells. It makes the surroundings acidic and is the main energy source for cell division. The pH-sensitive NPs that release medicines at low pH can take advantage of the TME's decreased pH [13].

Passive tumour targeting is the name given to this method. Different tumour biology (vascularity, leakiness) and carrier properties are the key determinants of passive targeting. This form of tumor-targeting lacks a particular ligand for particular varieties of tumour cells. The core tumour biology, including 1) the level of lymphangiogenesis and angiogenesis, 2) the degree of perivascular tumour invasion or its size, and 3) intratumor pressure, heavily influences the EPR effect.

### 2.2.2 Active Targeting

Active targeting is dependent on certain ligands, such as transferrin and folate, which bind to receptors or molecules that are particularly expressed or over expressed on the particular target cells (diseased organs, cells, tissues)[14]. This is known as ligand-mediated targeting. Here, the target must be close to the NPs that have ligand with particular activities, such as retention and uptake, in order to increase affinity. This tactic increases the likelihood that NPs will connect to

cancer cells, increasing medication penetration. In 1980, when antibodies were grafted onto the surface of liposomes, the first proof of this was discovered [12], and other types of ligands such as peptides and aptamers were then used. As a result, the major strategy aims to boost crosstalk between NPs and the target without changing the overall bio distribution [15]. The target substrate receptors identification of ligands is a key component of active targeting or ligand-mediated targeting. Proteins, antibodies, peptides, carbohydrates, nucleic acids, tiny compounds like vitamins, and the like are examples of illustrative ligands [16]. Transferrin receptorand the epidermal growth factor receptor are the receptors that are most often researched (EGFR). Through receptor-mediated endocytosis, ligand-target contact causes the membrane to infold and NPs to become internalized. There are several processes via which active targeting occurs. The majority of tumour targeting is carried out by NPs targeting tumour cells in general. Cell penetration is improved by this technique. Transferrin is one of the extensively investigated receptors, as was previously mentioned. It is a particular kind of serum glycoprotein that helps get iron into cells. In most tumour cells, especially solid tumours, these receptors are known to be overexpressed, whereas in healthy cells, they are expressed less strongly. Therefore, we are able to alter the NPs that have transferrin-specific ligands linked with them. For instance, transferrin is overexpressed in A2780 ovarian cancer cells. Transferrin-modified PEG-phosphatidylethanolamine NPs that target these cells particularly employ this property. Another approach is to target cells that are nearby cancer cells that isangiogenic endothelial cells. Also in close proximity to the tumour blood arteries are these cells. Using this method, it is feasible to decrease the blood supply to the cancer cells, resulting in necrosis. Tumor tissues have been discovered to be more acidic than healthy tissues. The Warburg effect has been used extensively to explain this [17]. The multivalent nature of the NPs increases the interaction of ligand coated NPs with target cancer cells. Such NPs need difficult design since ligand-target chemistry affect the whole method's effectiveness. The effectiveness of the system is also influenced by other elements such the administration method, physicochemical characteristics like ligand density and size of NPs [8].

### 2.3 Nanoparticles in Cancer Therapy

NPs of all types, including organic, inorganic, and hybrid NPs, are widely utilized in drug delivery systems

### 2.3.1 Organic nanoparticles

Nanoparticles made of polymers

It is widely known that polymeric nanoparticles are "colloidal macromolecules" with a particular structural architecture created by various monomers [18]. To accomplish controlled drug release in the target, the drug is either bonded to NPs' exterior, generating a Nano sphere or a nanocapsule. Polyacrylamide, PMMA, and polystyrene were the non-biodegradable polymers first used to create PNPs. Due to the difficulty in getting rid of them from the system, however, the buildup of them led to toxicity. Biodegradable polymers are currently being employed because they are known to improve drug release, minimize toxicity, and improve biocompatibility. Examples include polylacticacid, chitosan, alginate, and albumin. By exploiting the polysorbates surfactant effect and coating PNPs with polysorbates, this has been demonstrated in study. The blood-brain barrier's (BBB) endothelial cell membrane interacts more favorably with NPs when they are coated on the outside [19].

### Dendrimers

Spherical polymeric macromolecules known as dendrimers have a well-defined hyper branched topology. Dendrimers are characterized by their highly branching architectures. Typically, an ammonia core and acrylic acid are reacted to begin the production of dendrimers. After additional interaction with ethylene diamine to produce "tri-amine," a GO product, this process produces a "tri-acid" molecule. This item further combines with acrylic acid to create hexa-acid, which then creates "hexa-amine" and so on [20]. The dendrimers typically have sizes between 1 and 10 nm. The size, however, might be as small as 15 nm. These are utilized to target nucleic acids because of their unique structure, which includes specified bioavailability, modifiable branching, molecular weight, and charge. Poly(ethyleneglycol), polyamidoamine (PAMAM), polypropylenimine (PPI), and triethanolamine (TEA) are a few dendrimers that are often utilized [21].

Initially, a PAMAM dendrimer was intended to control MDR. PAMAM dendrimers made of DNA have received considerable description. The development of epithelial cancer xenografts was markedly slowed down by the synthetic dendrimers as compared to mice given single-agent treatment.

### mAb Nanoparticles

Due to their unique targeting capabilities, monoclonal antibodies are frequently utilized in the therapy of cancer. NPs are now added to these mAb to create antibody-drug conjugates. These have been shown to be more powerful and precise than cytotoxic medications or mAb by alone. In the control of HER2 positive breast epithelial cells, for example, compared to single-agent paclitaxel or trastuzumab, an antibody-drug NP with a paclitaxel

core demonstrated greater anti-tumor efficacy and reduced toxicity [22].

**Extracellular Vesicles**

Extracellular vesicles (EVs), which range in size from 50 to 1000 nm, are double-layered phosphor-lipid vesicles [23]. Different cell types continually release EVs, which vary in size, origin, and content. Three categories are used to classify EVs: Exosomes, microvesicles, and apoptotic bodies are the first three. Because they include lipid and chemicals that are highly comparable to those of origin cells, NPs mixed with exosomes are commonly employed. Additionally, they bypass immune monitoring and internalize the cancer cells extremely fast. By transporting cytotoxic medications and other anti-tumor medications to the target locations, they serve as natural delivery systems.The finest example is exosomes that have been loaded with doxorubicin (exoDOX). Breast cancer is treated with exoDOXand has demonstrated excellent outcomes when compared to doxorubicin-based conservative therapy [24]. This is because it increases cytotoxicity while minimizing cardiotoxicity. Compared to manufactured NPs, exosome NPs offer inherent biocompatibility characteristics, enhanced chemical stability and intracellular communications. But there are issues that must be resolved, such as the lack of standardized conditions for exosomal separation and purification [25].

**Liposomes**

These spherical vesicles, which may be unilamellar or multilamellar and include phospholipids, are used to encapsulate pharmacological molecules [26]. Because they have properties like little immunogenicity, low intrinsic toxicity, and liposomes biological inertness, are exceptional. The first nanoscale medication, liposomes, received approval in 1965 [27]. "Hydrophobic phospholipid bilayer" and a "hydrophilic core" make up the usual liposome structure. They can efficiently preserve the entrapped medication from degradation of the environment in circulation thanks to their special design, this enables them to entrap drugs that are both hydrophilic and hydrophobic.

Doxorubicin, paclitaxel, and nucleic acid may all be delivered via liposomes, which also have improved anti-tumor activity and increased bioavailability. Daunorubicin liposome-based formulations for the treatment of MBC include Doxil® and Myocet® [28, 29]. The use of liposome-based NPs is constrained by drawbacks such reduced encapsulation effectiveness, rapid MP removal, cell adsorption.

**Solid Lipid Nanoparticles (SLN)**

The colloidal nanocarriers (1-100 nm) comprised of water, an emulsifier, and a monolayer of phospholipids [30]. These are referred to as nanomaterials with zero dimensions. Triglycerides, fatty acids, steroids and PEGylated lipids are some examples of the lipid component. SLNs, in contrast to traditional liposomes, feature a "micelle-like structure" that houses the medication in a non-aqueous core. One example is mitoxantrone-loaded SLN, which has demonstrated improved absorption and decreased toxicity. Positive results have been obtained when Idarubin and doxorubinare incorporated by SLN into "P388/ADR leukaemia cells" and the "murine leukaemia mice model" [31].

**Nanoemulsions**

Colloidal Nanoparticles with oil droplet heterogeneous mixtures in aqueous media that range in size from 10 to 1000 nm are known as nanoemulsions. Oil-in-water systems, water-in-oil systems, and bi-continuous are three common forms of nanoemulsions. Research on membrane-modified nanoemulsions is substantial. For example, nanoemulsions containing paclitaxel and spirulina demonstrated better anti-tumor activity by controlling immunity via TLR4/NF-kB signaling pathways [32]. Advanced melanoma has been successfully treated with bevacizumab, rapamycin, and temozolomidenanoemulsion. Liposomes are distinct from nanoemulsions, which unquestionably have superior qualities such stability and biodegradability [33]. However, there are difficulties in using these nanoemulsions in clinical settings since they require costly homogenizers and microfluidizers as well as high temperatures and pressures.

**CyclodextrinNanosponges**

In order to enhance the drug loading capability of NPs, cyclodextrins are frequently utilised as stabilizers. Small, mesh-like structures are known as nanosponges. In the culture of the MCF-7 cell line loaded with paclitaxel demonstrated reliable cytotoxic effects. Similar improvements in solubility and stability were seen for camptothecin when it was combined using cyclodextrin-based nanosponges [34].

**2.3.2 Inorganic Nanoparticles**

**Carbon Nanoparticles**

As the name implies, carbon serves as the basis for carbon nanoparticles. Because of their mechanical, optical, and electrical qualities as well as their biocompatibility, they have been widely used in the medical field. Carbon nanoparticles (NPs) can encapsulate pharmaceuticals by - stacking because they are inherently hydrophobic [35]. Graphene, carbon nanohorns, fullerenes, carbon nanotubes, and graphene are further categories for carbon nanoparticles (NPs). Although they are all carbon-

based, each of them has a different structure, morphology, and set of characteristics.

With sp2-hybridized carbon sheet, "graphene" is a 2D crystal that possesses exceptional electrochemical, mechanical, and high drug loading capabilities. Graphene may also be classified into the following groups based on its characteristics, composition, and composition: There are four types of graphene: single-layer, reduced graphene oxide (rGO), graphene oxide (GO), and multilayer. Due to their capacity to target hypoxia and irregular angiogenesis in TME [36], GO and rGOs are often employed. According to studies, GO-doxorubicin is more effective against breast cancer in cellular models.

Large carbon-cage molecules known as fullerenes come in a variety of conformations, including spherical, ellipsoid, and tube. Due to their characteristic physical, chemical, structural, and electrical features, they are the most extensively investigated nano carriers. These are utilized in photodynamic treatment because to their triple yield, capacity to absorb light, prolonged - conjugation, and generation of oxygen species. On tumour cells, PEG-modified fullerenes shown potential photodynamic effects [37].

The cylinder-shaped carbon nanotubes (CNTs), which are sometimes thought of as rolls of graphene, were first identified in the late 1980s. One category includes single-walled CNTs, and the other includes multi-walled CNTs. Since they are carbon-based, they can interact with immune cells to elicit an immunological response, which will suppress the development of the tumour. They have previously been employed for thermal ablation treatment and as DNA delivery vectors. For instance, colon cancer cells are targeted using fluorescent single-walled CNTs with mAb encapsulating doxorubicin. Doxorubicin is released intracellularly when such CNTs are successfully absorbed by cancer cells, but the CNTs themselves are kept in the cytoplasm [38].

**Metallic Nanoparticles**

In "biological imaging" and targeted DDS, metallic nanoparticles are frequently investigated because of their exceptional optical, magnetic, and photothermal characteristics. Gold, silver and copper nanoparticles are some of the most widely utilized metallic NPs. The size and surface features of gold NPs may be easily manipulated; they are utilized as intracellular targeting drug carriers [39]. Furthermore, it is feasible to follow NP trajectories inside the cells thanks to their visible light extinction behavior. It has been demonstrated that "Anti-HER2 functionalized gold-on-silica nanoshells" target breast cancer cells that are HER2 positive. For the purpose of identifying nodal metastases, an iron oxide NP formulation, is now undergoing late-stage clinical testing. Feraheme®, an iron oxide NP formulation with ferumoxytol, is used to treat iron-deficiency anemia. This was approved by the FDA in June 2009 and is also utilized to treat testicular and prostate cancer nodal metastases [40].

**Magnetic Nanoparticles**

Drug delivery often uses magnetic nanoparticles (NPs) and metal or metal oxides. They are typically coated with organic compounds, such as polymers and fatty acids, to improve stability and biocompatibility. LHRH-conjugated superparamagnetic iron oxide NPs can be utilized to efficiently target and photograph breast malignancy. In order to heat kill cancer cells, magnetic nanoparticles are also used in magnetic hyperthermia. Two magnetic NPs for colon cancer and liver metastases are available on the market or in clinical trials: Resovist® and Feridex® [41].

**Calcium Phosphate Nanoparticles**

Calcium phosphate nanoparticles (NPs) are biocompatible, biodegradable, and have little side effects. As a result, they serve as a vehicle for the transfer of antibiotics, growth hormones, insulin, and contraceptives. They are also employed in the delivery of plasmid DNA and oligonucleotides. Cellular gene transfer has successfully employed calcium phosphate nanoparticles in combination with either viral or non-viral vectors as delivery vectors. Reduced toxicity and improved transfection properties have been demonstrated using a "liposomal nanolipoplex formulation" of calcium [42].

**Drug Resistance Overcoming Mechanism of NPs**

One of the main issues in treating and managing cancer is drug resistance. It holds true for every form of cancer and every treatment option. Diseases can develop a tolerance to pharmacological treatments, which can lead to a condition known as drug resistance. Two forms of drug resistance can be distinguished: 1) Natural and 2) Learned [43]. The majority of the time, innate resistance is the product of pre-existing mutations in the genes responsible for cell proliferation or death. The term "acquired resistance" refers to the kind of resistance that emerges following a specific anti-tumor therapy and may be brought on by the occurrence of novel mutations or changes in the TME during therapy. Nanoparticles can be employed to overcome cancer-related treatment resistance because of their exceptional capacity to co-encapsulate several therapeutic substances.

**Targeting Efflux Transporters**

The family of "ATP-binding cassette (ABC) transporters" includes efflux transporters. These play a crucial part in MDR. These transporters'

main job is to remove medicines from cells and lower their concentration. One such efflux solute carrier that is abundantly expressed by cancer cells that are resistant to treatment is "P-glycoprotein (P-gp)"[44]

Overexpression of P-glycoprotein has been associated with poor therapeutic response, particularly in breast and ovarian cancer. NPs are effective against efflux pumps. NPs can avoid the efflux pumps because they internalize the cell by "endocytosis" rather than diffusion and release the medication in the "perinuclear location," which is far from the active efflux pumps. Additionally, NPs can successfully avoid efflux pumps by altering the regulation of drug releases, for as by using low pH levels and redox as triggers [45].

Combination treatment is a further strategy for overcoming MDR. A single drug carrier can contain many medicines packaged into NPs. Another strategy would be to prevent the expression of efflux transporters as opposed to merely avoiding them. This can be done by creating NPs that can entrap both chemotherapeutic drugs and efflux pump inhibitors. According to a recent study, employing NPs that simultaneously transport doxorubicin and COX-2 inhibitors can successfully reverse MDR in breast cancer cells. Similar to this, employing silica NP that contains doxorubicin and miRNA-495 has been successful in breaking down drug resistance in lung cancer cells [46].

**Targeting Hypoxia**

Another factor supporting MDR is hypoxia. Some tumour cells are frequently in a hypoxic state as a result of the aberrant blood arteries around the tumour and the rising oxygen demand caused by the tumor's fast growth. The chemotherapy medications frequently fail to reach the portion of the tumour that is hypoxic. By intensifying tumour heterogeneity and causing an oxygen ramp inside the tumour, hypoxia promotes a more aggressive phenotype. Additionally, it has been demonstrated that the hypoxic state promotes the expression level of efflux proteins. Hypoxia-inducible factor 1 (HIF-1), the main protein, plays a significant function. In order to overcome medication resistance, HIF-1 can be targeted or its gene silenced.Drug resistance brought on by hypoxia can be decreased by using NPs that carry HIF-1 siRNA. HIF-1 signaling can be indirectly inhibited as an alternative to direct targeting. For instance, it is known that the "PI3K/Akt/mTOR pathway" regulates the production of HIF-1. The expression of HIF-1 is efficiently down-regulated by this pathway inhibition, increasing the susceptibility of MDR cells to cancer therapy. Effective uses may be made of NPs like PLGA-PEG, PEGylated and non-PEGylated liposomes. Furthermore, HIF-1's transcriptional activity and inhibition, which decrease HIF-1 production, depend on "heat shock protein 90 (HSP90)".The MDR for the treatment of bladder cancer has been significantly enhanced by the HSP90 inhibitor in "17AAG loaded NPs".

**Nanoparticles and Proteomics**

Protein corona (PC), a structure known as cellular and serum proteins, surrounds NPs when they are exposed to the biological system. These proteins are divided into the hard corona and the soft corona depending on how much they interact with the NPs. "Hard corona" is produced when these proteins have a strong affinity for the NPs. When these proteins are weakly attached to the NPS, "soft corona" is created. It is known that proteins with greater affinities would gradually replace the majority of proteins that first form a PC. The V Roman effect is what causes this. Therefore, it is crucial to create the technology necessary to produce NPs with the needed qualities. There are several proteomic techniques in use, including MS, SDS-PAGE, LC-MS, etc. PC influences how NP interacts with the biological environment, which in turn controls how it is applied and used in the medical profession.

Cancer proteomics examines the quantity of proteins in cancer cells, supporting the discovery of biomarkers and hunting proteins that facilitate cancer diagnosis, prognosis, and therapy. Additionally, it aids in the study of drug resistance mechanisms and cancer development. PTMs (post-translational modifications) are crucial for metastasis, recurrence, and incidence. Novel medicines including mRNA, siRNA, and gene editing are key treatments employed with NPs in addition to chemotherapy and kinase inhibitors.

**Nanotechnology for the Delivery of Small Interfering RNA (siRNA)**

Small ds RNA molecules called siRNAs, which are around 21 nucleotides long, suppress gene expression in the target. RNA interference is the name given to this process. Atu027, a liposomal siRNA that specifically targets kinase N3 and TKM-ApoB, which inhibits the production of ApoB, and ALN-TTR01, It aims to cure transthyretin-mediated amyloidosis by targeting the transthyretin gene, are a few siRNA-based NPs that are currently being explored in the clinic.

**Tumor microRNA Profiling and Delivery Using Nanotechnology**

MicroRNAs are a kind of naturally occurring "single-stranded non-coding RNA" molecules that regulate post-transcriptional gene expression by preventing the target mRNA from being translated or by suppressing the creation of proteins by destabilizing the target mRNA. These are becoming important biomarkers that are a key focus for the detection and treatment of cancer. The

fundamental building block of the nanotechnology-based miRNA profiling approaches is nucleic acid's base priming property. Several profiling methods combine molecular biology enzymatic operations with biosensors or surface plasmon resonance imaging methods. MicroRNAs can be delivered via nanotechnology. For instance, the modulation of polyamine metabolism demonstrated encouraging findings for biodegradable polycationic prodrugs.Single-chain antibody fragments loaded with microRNA have demonstrated gradual down-regulation of "survivin expression" in murine B16F10 melanoma lung metastatic carcinoma load.

**Cancer Therapy Using DNA Nanotechnology**

Numerous DNA-based nanostructures have been developed, such as scaffolding for arranging organic, inorganic, and biological molecules into different morphologies of molecular transporters, nucleic acid sensors, gold nanoparticles coated with DNA for lead detection, and drug delivery systems.

## 3. THE BENEFITS OF NANOPARTICLES IN CANCER THERAPY

The application of nanotechnology to cancer diagnosis, monitoring, and therapy has ushered in a new age. NPs increase the intracellular concentration of medications while minimizing toxicity in healthy tissue by actively or passively targeting. To begin and regulate medicine release, the targeted NPs can be created and modified to be pH-sensitive or temperature-sensitive. The pH-sensitive drug delivery method allows for the administration of pharmaceuticals to the acidic TME. Temperature-sensitive NPs also release medications in the target region in response to temperature variations caused by sources such as magnetic fields and sonic waves. A considerable role in the targeted drug delivery system is also played by the "physicochemical properties" of NPs, such as size, shape, molecular mass, and surface chemistry. Additionally, NPs can be altered for a specific target and applied to focus on a certain moiety.

Because of unequal distribution and cytotoxicity, conventional radiation and chemotherapy have a number of drawbacks in terms of effectiveness and adverse effects. In order to successfully eliminate cancer cells without causing too much harm, judicious dosage is necessary. Before the medication can reach the intended location, it must pass through several defenses. Given physiological circumstances, the drug must successfully pass through the RES, TME, BBB, and renal infiltrate. In response to the medications, MPS in the liver or lungs activate "macrophages or leukocytes," which quickly eliminate the drug. As a result, the drug's half-life is reduced. To get around this, NPs with "surface modification," like PEG, extend the "drug half-life" and get around this process. In addition, the kidney's role in the human body is vital. Thus, effective renal infiltration reduces the toxicity brought on by NPs.

The brain-blood barrier is a unique defense mechanism designed to shield the central nervous system (CNS) from poisonous and damaging substances. The "brain capillary endothelial cells" are organized to form a wall that feeds the brain with vital nutrients. Since the BBB's main purpose is to prevent hazardous substances from entering the brain, the only effective chemotherapeutic treatments for brain cancer at the moment are intraventricular or intracerebral infusions. But NPs have been known to cross the BBB. Currently, NPs are delivered by a variety of methods, including transcytosis, the EPR effect, targeted ultrasound, and peptide-modified endocytosis. Methotrexate absorption in rats was enhanced by glutathione PEGylated liposomes that were encapsulated with the drug. Due to their ability to carry medications that cause apoptosis, Au-NPs are frequently employed.

Since NPs are transporters, they also stop the encapsulated payload from deteriorating, enhancing the stability of the medicine. Additionally, a significant quantity of medications may be contained without causing a chemical reaction. Dry solid dosage formulations are more stable than nanoliquid substances. To improve stability, stabilizers can be utilized. The use of porous NPs is yet another method for enhancing stability.

The pathophysiology of tumours is distinct, with abnormal lymphatic drainage, excessive angiogenesis, and faulty vascular architecture. These characteristics enable the NPs to target tumour tissue. NPs are efficiently maintained because tumour tissue has a decreased venous return and a weak lymphatic clearance. EPR is the name of these phenomena. Similar to this, tumor-targeting is possible by focusing on the nearby tissues.

NPs can be delivered in a number of ways, including orally, nasally, parenterally, intraocularly, etc. NPs are readily absorbed into cells and have a high surface-to-volume ratio. According to studies, NPs are superior to microparticles as drug carriers.

**Immunotherapy using Nanoparticles**

An essential role for the creation and growth of cancer cells is played by the immune system. The development of immunotherapy has transformed cancer treatment. It has been discovered that NPs may be employed in conjunction with immunotherapy in addition to aiding in the targeted administration of chemotherapy. Immune checkpoint blockade treatment, CAR-T cell therapy, cancer vaccine therapy, and immune

system modulator therapy are some of the immunotherapy strategies that attempt to activate the immune system's response to cancer cells. "Nanovaccines," "aAPCs (artificial antigen-presenting cells)," and "immunosuppressed TME targeting" are all components of NP-based immunotherapy.

Dendritic cells (DCs), which present antigens, are a target for "tumor-associated antigens" and "adjuvants" delivered by Nano vaccines. Additionally, they can be used as adjuvants to improve "APC antigen presentation" and to encourage DC maturation, which in turn stimulates cytotoxic T cells with anti-tumor activity. TAAs are reported to be capable of being delivered into DCs in the cytoplasm via liposomes, PLGA NPs, and gold NPs. The most popular inorganic NP, mesoporous silica, has demonstrated an adjuvant function that stimulates immunological response. Artificial APCs engage in direct interactions with MHC-antigen complexes that attach to T lymphocytes. They also engage in interactions with co-stimulatory molecules, which interact with co-stimulatory receptors and activate T cells. Another way to use NPs in immunotherapies is to target the immunosuppressed TME. This is accomplished by focusing on crucial TME cell types as "myeloid-derived suppressor cells (MDSCs)," "tumor-associated macrophages (TAMs)," and regulatory T cells.

Some of the crucial immunological checkpoints are "programmed cell death protein 1 (PD-1)" and "programmed cell death ligand 1 (PD-L1)". Therefore, they are targeted utilizing NPs and immune checkpoint inhibitors. A research found that PD-L1/PD-1 conventional immune checkpoint drugs produced erratic results. Multivalent poly (amidoamine) dendrimers were utilized to increase the likelihood of immune checkpoint inhibitors and joining. Utilizing these dendrimers demonstrated better drug accumulation at the tumour location in addition to greater PD-L1 inhibition.

**Cryosurgery using Nanoparticles**

Cryosurgery is a sophisticated method of freezing and removing cancerous tissue. Although less intrusive, it causes intraoperative hemorrhagingand postoperative complications, there are several downsides that need to be addressed, such as insufficient freezing capability and harm to neighboring cells. The use of NPs in cryosurgery has been made possible by the growth of nanotechnology.

Nano cryosurgery's main method of action is the introduction of NPs with specific characteristics into cancer cells, which results in freezing. Ice is created inside the cells during this process, which harms them. NPs can be used successfully to carry out this crucial activity. The thermal conductivity of NPs can be used to promote tumour damage by dramatically freezing the tumour tissue. Additionally, they cool down quickly, making it possible to control the "ice ball's direction of development" and "growth direction".

There are substantial odds that the freezing might harm healthy tissue when the tumor's position makes cryosurgery impractical or when other nearby organs are at risk. Recently, phase change materials (PMs) composed of NPs have been employed in cryosurgery to shield the nearby healthy, normal tissue. An excellent example is the preservation of nearby healthy tissue via liposome-based microencapsulated phase change NPs. These NPs are regarded to be appropriate for cryosurgery because they have a low thermal conductivity and a high latent heat capacity.

## 4. SIGNIFICANT OBSTACLES IN NANOPARTICLE CLINICAL APPLICATIONS

As nanotechnology has growing, there has been a steep increase in the quantity of information and study done on nanoparticles. However, only a small number of them actually advance to clinical trials. The majority of them only stop during the in vivo and in vitro stages. The clinical translation of each unique Nano formulation has unique problems, however the majority of NPs deal with common issues that may be categorized as biological, technical, and study-design-related.

NPs are often administered by intravenous injections into the circulation, which removes NPs and makes it difficult for NPs to remain at and interact with the target location. In order to avoid this, a medicine with a high concentration is utilized, which may not have the intended therapeutic benefits. The effects of magnetic fields on the human body and the interactions of many NPs with magnetic fields, however, still need more research.

It is challenging and requires a lot of concentration to control the biological destiny of NPs. Even when NPs are made of biosafety materials and are adequately controlled to extend the retention, there is a danger of kidney, liver, and lung damage. Surface area, solubility, particle size and shape, and agglomeration are a few variables that affect toxicity. Greater lung deposition of NPs with inflammatory, cytotoxic, and oxidative effects has been observed. Studies show that free radicals produced by NPs frequently damage healthy cells. Making NPs from biocompatible compounds such as chitosan and molecules that degrade when subjected to near infrared radiation might be feasible solutions.

Avoiding the "mononuclear phagocytic system (MPS)" is another difficult task. NPs adsorb proteins in bodily fluids to create PC, which then assaults MPS to absorb NPs. To avoid this, NPs contain coatings made of substances that stop the protein corona from forming. They haven't, however, produced any notable effects.

Scale-up synthesis, performance, and equal optimization projections are NPs' technological hurdles. These are extremely important in ensuring NPs' clinical success. Most NPs utilized in in vivo and in vitro experiments are typically manufactured in small amounts, and scaling up for large numbers is frequently impractical due to equipment and other considerations. Not always are the best lead clinical prospects in animal models carefully developed and refined. This may be avoided by using certain methods that analyze a range of Nano compositions and select one ideal formulation through meticulous iteration. Such impacts, meanwhile, shouldn't be added immediately to human testing. It is challenging to predict the effectiveness and performance of nanoparticles, and it is impossible to reproduce in vivo findings in human trials. Experimental data and theoretical or computational modelling can be used to create an environment and tissue that mimic physiological conditions. For instance, organs-on-chips are a topic of ongoing research and can enhance NP performance and efficacy estimates.

Clinical trials are substantially impacted by study-design issues such research size, purpose, and scheduling of NP treatments during the therapy. The majority of research use "cell and animal models," which might not produce clear outcomes in human trials. Therefore, it is difficult to replicate genuine bodily processes using only one model. Additionally, as metastasis is one of the important characteristics of cancer, "models of cancer metastasis" should be actively explored. Furthermore, if we concentrate on individualized therapy, N = 1 clinical investigation will be necessary. Numerous factors, including genetic, environmental, and previous medical histories, must be taken into account.

## 5. CONCLUSION

Nanotechnology has demonstrated the promise for a new age in cancer treatment by supplying tiny molecules for cancer diagnostics, therapy, and detection. Cancer medications based on the unique properties of Nano particles are used to treat a various cancer types. NP-based DDS has better biocompatibility, pharmacokinetics and stability compared to conventional structured medicines. In addition, NPs provide a strong foundation for integration therapy, which helps to overcome MDR. As a result of expanding research, many NP types, along with polymeric, metallic, and hybrid NPs have demonstrated increased drug-delivery efficiency. Researchers need to carefully examine the similarities and differences between the properties of the suggested Nanoplatforms and those of medicinal medicines. There are certain disadvantages, such as the lack of in vitro models that adequately reflect the in vivo stage, as well as long-term toxicity, immune toxicity, and neurotoxicity.

Proteomics findings on the "mechanism of cancer genesis, MDR, incidence" continues to rise, more NP-based drugs will be able to benefit from this developing area. In contrast to the vast amount of research, only a small number of NP-based drugs are now in use, a smaller number are in clinical trials, and the most are still in the experimental stage. More work has to be put into "understanding toxicity, cellular and physiological parameters that influence NP-based medication delivery, EPR, and PC mechanism" in the human body for logical nanotechnology design. Based on the evidence presented above, we believe that nanotechnology and cancer therapy development will usher in a clinical translation for NP-based cancer therapy.

## REFERENCES


[1] Boisseau P, Loubaton B (2011) Nanomedicine, nanotechnology in medicine. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S1631070511001538

[2] Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L, Muller R (2008) Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. 10.1021/Cr068445e. https://www.academia.edu/1082933/Magnetic_iron_oxide_nanoparticles_synthesis_stabilization_vectorization_physicochemical_characterizations_and_biological_applications [PubMed]

[3] Tiwari JN (2011) Zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructured materials for advanced electrochemical energy devices. https://www.academia.edu/32389141/Zero_dimensional_one_dimensional_two_dimensional_and_three_dimensional_nanostructured_materials_for_advanced_electrochemical_energy_devices

[4] Shin WK, Cho J, Kannan A, et al. Cross-linked composite gel polymer electrolyte using mesoporous methacrylate-functionalized $SiO_2$ nanoparticles for lithium-ion polymer batteries. *Sci Rep.* 2016;**6**:26332. doi: 10.1038/srep26332. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[5] Prokop A, Davidson JM. Nanovehicular intracellular delivery systems. *J Pharm Sci.* 2008;**97**(9):3518–3590. doi: 10.1002/jps.21270. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[6] Barar J, Omidi Y. Dysregulated pH in tumor microenvironment checkmates cancer therapy. Bioimpacts. 2013;3(4):149–162. doi: 10.5681/bi.2013.036. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[7] Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs a new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropicaccum. Cancer Res. 1987;46:6387–6392. [PubMed] [Google Scholar]
[8] Torchilin V. Tumor delivery of macromolecular drugs based on the EPR effect. Adv Drug Deliv Rev. 2011;63(3):131–135. doi: 10.1016/j.addr.2010.03.011.
[9] Bates DO, Hillman NJ, Williams B, Neal CR, Pocock TM. Regulation of microvascular permeability by vascular endothelial growth factors. J Anat. 2002;200(6):581–597. doi: 10.1046/j.1469-7580.2002.00066.x.
[10] Hobbs SK, Monsky WL, Yuan F, Roberts WG, Griffith L, Torchilin VP, Jain RK. Regulation of transport pathways in tumor vessels: role of tumor type and microenvironment. Proc Natl AcadSci USA. 1998;95(8):4607–4612. doi: 10.1073/pnas.95.8.4607.
[11] Melody A. Swartz and Mark E. FleuryInstitute of Bioengineering (2007) Interstitial flow and its effects in soft tissues. Retrieved July 29, 2021, from 10.1146/annurev.bioeng.9.060906.151850
[12] Padera TP, Stoll BR, Tooredman JB, Capen D, di Tomaso E, Jain RK. Pathology: cancer cells compress intratumour vessels. Nature. 2004;427(6976):695. doi: 10.1038/427695a. [PubMed] [CrossRef] [Google Scholar]
[13] Pelicano H, Martin DS, Xu RH, Huang P. Glycolysis inhibition for anticancer treatment. Oncogene. 2006;25(34):4633–4646. doi: 10.1038/sj.onc.1209597.
[14] Mukwaya G, Forssen EA, Schmidt P, Ross M (1998) DaunoXome® (Liposomal Daunorubicin) for first-line treatment of advanced, HIV-related Kaposi's Sarcoma. In: Woodle MC, Storm G (eds) Long circulating liposomes: old drugs, new therapeutics. biotechnology intelligence unit. Springer, Berlin, Heidelberg. 10.1007/978-3-662-22115-0_10
[15] Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Farokhzad OC. Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. ChemSoc Rev. 2012;41(7):2971–3010. doi: 10.1039/c2cs15344k. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[16] Byrne JD, Betancourt T, Brannon-Peppas L. Active targeting schemes for nanoparticle systems in cancer therapeutics. Adv Drug Deliv Rev. 2008;60(15):1615–1626. doi: 10.1016/j.addr.2008.08.005.
[17] Santi M, Maccari G, Mereghetti P, Voliani V, Rocchiccioli S, Ucciferri N, Luin S, Signore G. Rational design of a transferrin-binding peptide sequence tailored to targeted nanoparticle internalization. Bioconjug Chem. 2017;28(2):471–480. doi: 10.1021/acs.bioconjchem.6b00611. [PubMed] [CrossRef] [Google Scholar]
[18] Samadian H, Hosseini-Nami S, Kamrava SK, Ghaznavi H, Shakeri-Zadeh A. Folate-conjugated gold nanoparticle as a new nanoplatform for targeted cancer therapy. J Cancer Res ClinOncol. 2016;142(11):2217–2229. doi: 10.1007/s00432-016-2179-3. [PubMed] [CrossRef] [Google Scholar]
[19] Elsabahy M, Wooley KL. Design of polymeric nanoparticles for biomedical delivery applications. ChemSoc Rev. 2012;41(7):2545–2561. doi: 10.1039/c2cs15327k.
[20] Wang X, Yang L, Chen ZG, Shin DM (2008) Application of nanotechnology in cancer therapy and imaging. CA 58(2):97–110. 10.3322/CA.2007.0003 [PubMed]
[21] Lim J, Kostiainen M, Maly J, da Costa VC, Annunziata O, Pavan GM, Simanek EE. Synthesis of large dendrimers with the dimensions of small viruses. J Am Chem Soc. 2013;135(12):4660–4663. doi: 10.1021/ja400432e. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[22] Sievers EL, Senter PD. Antibody-drug conjugates in cancer therapy. Annu Rev Med. 2013;64:15–29. doi: 10.1146/annurev-med-050311-201823. [PubMed] [CrossRef] [Google Scholar]
[23] Abedin MR, Powers K, Aiardo R, Barua D, Barua S. Antibody-drug nanoparticle induces synergistic treatment efficacies in HER2 positive breast cancer cells. Sci Rep. 2021;11(1):7347. doi: 10.1038/s41598-021-86762-6. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[24] Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 2013;200(4):373–383. doi: 10.1083/jcb.201211138. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[25] Hadla M, Palazzolo S, Corona G, Caligiuri I, Canzonieri V, Toffoli G, Rizzolio F. Exosomes increase the therapeutic index of doxorubicin in breast and ovarian cancer mouse models. Nanomedicine (Lond) 2016;11(18):2431–2441. doi: 10.2217/nnm-2016-0154.
[26] 26. Michiel Pegtel1 D, Stephen J, Gould21Amsterdam UMC. (2019) Exosomes. Retrieved July 29, 2021, from 10.1146/annurev-biochem-013118-111902
[27] Visht S, Awasthi R, Rai R, Srivastav P. Development of dehydration-rehydration liposomal system using film hydration technique followed by sonication. Curr Drug Deliv. 2014;11(6):763–770. doi: 10.2174/1567201811666140910122945. [PubMed] [CrossRef] [Google Scholar]
[28] Wang X, Liu X, Li Y, Wang P, Feng X, Liu Q, Yan F, Zheng H. Sensitivity to antitubulin chemotherapeutics is potentiated by a photoactivablenanoliposome. Biomaterials. 2017;141:50–62. doi: 10.1016/j.biomaterials.2017.06.034. [PubMed] [CrossRef] [Google Scholar]

[29] Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer. 2005;5(3):161–171. doi: 10.1038/nrc1566. [PubMed] [CrossRef] [Google Scholar]
[30] Hofheinz RD, Gnad-Vogt SU, Beyer U, Hochhaus A. Liposomal encapsulated anti-cancer drugs. Anticancer Drugs. 2005;16(7):691–707. doi: 10.1097/01.cad.0000167902.53039.5a.
[31] Lu B, Xiong SB, Yang H, Yin XD, Chao RB. Solid lipid nanoparticles of mitoxantrone for local injection against breast cancer and its lymph node metastases. Eur J Pharm Sci. 2006;28(1–2):86–95. doi: 10.1016/j.ejps.2006.01.001. [PubMed] [CrossRef] [Google Scholar]
[32] Jaiswal M, Dudhe R, Sharma PK (2015) Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech 5(2):123–127. 10.1007/s13205-014-0214-0 [PMC free article] [PubMed]
[33] Dianzani C, Monge C, Miglio G, Serpe L, Martina K, Cangemi L, Battaglia L. (2020) Nanoemulsions as delivery systems for poly-chemotherapy aiming at melanoma treatment. https://www.mdpi.com/2072-6694/12/5/1198
[34] Ansari KA, Torne SJ, Vavia PR, Trotta F, Cavalli R. Paclitaxel loaded nanosponges: in-vitro characterization and cytotoxicity study on MCF-7 cell line culture. Curr Drug Deliv. 2011;8(2):194–202. doi: 10.2174/156720111794479934. [PubMed] [CrossRef] [Google Scholar]
[35] Ou L, Song B, Liang H, Liu J, Feng X, Deng B, Shao L (2016) Toxicity of graphene-family nanoparticles: a general review of the origins and mechanisms. Retrieved July 29, 2021, from 10.1186/s12989-016-0168-y [PMC free article] [PubMed]
[36] Tao Y, Zhu L, Zhao Y, Yi X, Zhu L, Ge F, Mou X, Chen L, Sun L, Yang K. Nano-graphene oxide-manganese dioxide nanocomposites for overcoming tumor hypoxia and enhancing cancer radioisotope therapy. Nanoscale. 2018;10(11):5114–5123. doi: 10.1039/c7nr08747k.
[37] Mroz P, Tegos GP, Gali H, Wharton T, Sarna T, Hamblin MR. Photodynamic therapy with fullerenes. PhotochemPhotobiol Sci. 2007;6(11):1139–1149. doi: 10.1039/b711141j.
[38] Tabata Y, Murakami Y, Ikada Y. Photodynamic effect of polyethylene glycol-modified fullerene on tumor. Jpn J Cancer Res Gann. 1997;88(11):1108–1116. doi: 10.1111/j.1349-7006.1997.tb00336.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[39] Bagalkot V, Zhang L, Levy-Nissenbaum E, Jon S, Kantoff PW, Langer R, Farokhzad OC. Quantum dot-aptamer conjugates for synchronous cancer imaging, therapy, and sensing of drug delivery based on bi-fluorescence resonance energy transfer. Nano Lett. 2007;7(10):3065–3070. doi: 10.1021/nl071546n. [PubMed] [CrossRef] [Google Scholar]
[40] Mousa SA, Bharali DJ. Nanotechnology-based detection and targeted therapy in cancer: nano-bio paradigms and applications. Cancers. 2011;3(3):2888–2903. doi: 10.3390/cancers3032888. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[41] Legge CJ, Colley HE, Lawson MA, Rawlings AE. Targeted magnetic nanoparticle hyperthermia for the treatment of oral cancer. J Oral Pathol Med. 2019;48(9):803–809. doi: 10.1111/jop.12921. .
[42] Mozafari MR, Reed CJ, Rostron C, Kocum C, Piskin E. Construction of stable anionic liposome-plasmid particles using the heating method: a preliminary investigation. Cell MolBiol Lett. 2002;7(3):923–927.
[43] Gary-Bobo M, Hocine O, Brevet D, Maynadier M, Raehm L, Richeter S, Charasson V, Loock B, Morère A, Maillard P, Garcia M, Durand JO. Cancer therapy improvement with mesoporous silica nanoparticles combining targeting, drug delivery and PDT. Int J Pharm. 2012;423(2):509–515. doi: 10.1016/j.ijpharm.2011.11.045. [PubMed] [CrossRef] [Google Scholar]
[44] Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, Sarkar S. Drug resistance in cancer: an overview. Cancers. 2014;6(3):1769–1792. doi: 10.3390/cancers6031769. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[45] Murakami M, Cabral H, Matsumoto Y, Wu S, Kano MR, Yamori T, Nishiyama N, Kataoka K (2011) Improving drug potency and efficacy by nanocarrier-mediated subcellular targeting. SciTransl Med 3(64):64ra2. 10.1126/scitranslmed.3001385 [PubMed]
[46] Zhang S, Guo N, Wan G, Zhang T, Li C, Wang Y, Wang Y, Liu Y. pH and redox dual-responsive nanoparticles based on disulfide-containing poly(β-amino ester) for combining chemotherapy and COX-2 inhibitor to overcome drug resistance in breast cancer. J Nanobiotechnol. 2019;17(1):109. doi: 10.1186/s12951-019-0540-9. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

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