International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 3, 2024

Review Article

A REVIEW OF NANOPARTICLE INNOVATIONS IN CANCER THERAPY: IMPLICATIONS, TARGETING MECHANISMS AND CLINICAL PROSPECTS

LOKESHVAR R., RAMAIYAN VELMURUGAN*

Department of Pharmacology, Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences (SIMATS), Thandalam, Saveetha Nagar, Chennai-602105, India

***Corresponding author: Ramaiyan Velmurugan; *Email: velmuruganr.scop@saveetha.com**

Received: 26 Aug 2023, Revised and Accepted: 01 Mar 2024

ABSTRACT

The main reason for morbidity and death globally is cancer, which has a complex pathophysiology. There are several traditional treatments for cancer, including chemotherapy, radiation therapy, targeted therapies, and immunotherapies. Multiple drug resistance, cytotoxicity, and lack of specificity pose significant challenges to cancer treatments. Molecular diagnostics and cancer treatment have been transformed by nanotechnology. For cancer treatment, nanoparticles (1–100 nm) are ideal because they are biocompatible, have low toxicity, excellent stability, high permeability, are precise and stable, and can deliver clear and accurate results. There are several main categories of nanoparticles. When it comes to the delivery of nanoparticle drugs, tumour characteristics and the tumour environment are considered. As well as providing advantages over conventional cancer treatments, nanoparticles prevent multidrug resistance, further overcoming their limitations. As new mechanisms are unravelled in studying multidrug resistance, nanoparticles are becoming more critical. Nano formulations have gained a new perspective on cancer treatment due to their many therapeutic applications. The number of approved nanodrugs has not increased significantly despite most research being conducted *in vivo* and *in vitro*. A review of nanoparticle oncological implications, targeting mechanisms, and approved nanotherapeutics is presented here. A current perspective on clinical translation is also provided, highlighting its advantages and challenges.

Keywords: Cancer treatment, Pathophysiology, Nanoparticles, Nanotherapeutics

DOI: https://dx.doi.org/10.22159/ijap.2024v16i3.49358 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The selections of articles for the current review were searched from specialized databases (Range of years: 1997-2021) such as Elsevier, PubMed, and Cambridge using the keywords cancer treatment, Pathophysiology, Nanoparticles, Nanotherapeutics. Other selections include articles from Springer, information from Internet sources, and online published articles from The Lancet Respiratory Medicine, Medscape, and Statpearls.

World cancers have complex pathophysiology's that contribute to death and morbidity. Chemotherapy, radiotherapy, targeted therapies, and immunotherapy are some of the traditional cancer treatments. There are several challenges associated with cancer treatments, including multiple drug resistance, cytotoxicity, and low specificity. The application of nanotechnology to cancer diagnostics and treatment has transformed both fields. The advantages of nanoparticles (1-100 nm) for cancer treatment include their biocompatibility, low toxicity, excellent stability, high permeability, precision and stability, and capacity to deliver precise and accurate results. Several main types of nanoparticles can be classified into [1, 2]. The tumour's characteristics and environment are considered for nanoparticle drug delivery. Nanoparticles have the advantage of overcoming the limitations of conventional cancer treatments, as well as preventing medical resistance to multiple drugs. Nanoparticles are also being studied as new mechanisms are unravelled in multidrug opposition. As a result of Nano formulations' many therapeutic applications, cancer treatment has taken on a whole new perspective. Despite most research being conducted *in vitro* and *in vivo*, the amount of approved Nano drugs hasn't increased significantly [3]. In this article, we discuss the oncological implications, targeting mechanisms, and approved applications of nanoparticles in oncology. In addition, the benefits and challenges of clinical translation are discussed.

Cancer is a significant public health concern, which is the 2nd leading reason for death globally. According to the American Cancer Society, 1.9 million new cancer cases will be in 2021. Surgery, chemotherapy, immunotherapy, radiation therapy, targeted therapy, and hormone therapy are common therapeutic approaches used in conventional cancer treatments [4, 5]. Cytostasis and cytotoxicity can be caused by chemotherapy and radiation [6], but the treatments have severe adverse effects and are often related to higher recurrence rates. There are also many other negative effects associated with this drug, including neuropathies, gastrointestinal disorders, hair loss, and fatigue. Cardio toxicity and pulmonary toxicity can also be caused by anthracyclines and bleomycin [7].

Precision therapy has become increasingly popular with the advent of targeted therapy [8]. Although they are still effective, drugs still have a large number of inherent adverse effects, including multi-drug resistance. Immunotherapeutic agents reduce recurrence rates, prevent distant metastases, and treat primary cancer [9]. As a result of immunotherapy, however, autoimmune diseases can develop. The effectiveness of immunotherapy against solid tumours is lower than that against lymphomas, according to several studies [10]. It is difficult for immune cells to penetrate the Extracellular Matrix (ECM) these cancers create [11]. These new targeted therapies and immunotherapies impair the epidermis and dermis' normal homeostatic functions by blocking key signalling pathways. Dermatologic Adverse Events (dAEs) result from this [12]. It has become increasingly important to find precise cancer treatments in recent years. Nanoparticles have recently been suggested to overcome the limitations of current therapeutic approaches. The disease affects the bone marrow, the digestive and skin systems, and the hair. There are also a few drug-specific adverse effects like cardio toxicity and pulmonary toxicity caused by anthracyclines and bleomycin. Precision therapy has grown as a result of targeted therapy [8]. While multiple-drug resistance has been found to limit therapeutic efficacy, there are still many inevitable adverse effects [7]. Immunotherapeutic agents have shown promise in treating primary cancers, preventing distant metastasis, and reducing recurrence rates [9]. Immunotherapy can, however, cause autoimmune diseases. The effectiveness of immunotherapy against solid tumours may differ from that against lymphomas [10]. A cancer cell-derived Extracellular Matrix (ECM) prevents immune cells from infiltrating the tissue [11]. Dermatologic Adverse Events (dAEs) can result from the development of immunotherapy and targeted therapy that interferes with signalling pathways important for malignant behaviour and maintenance of epidermal and dermal homeostasis [12]. As cancer treatments become more precise, new

approaches are becoming more popular. Various new therapeutic approaches have been developed using nanoparticles to overcome existing limitations. Several studies demonstrate good pharmacokinetics, precise targeting, a low incidence of side effects, and decreased drug resistance when nanoparticle-based drug delivery systems are used to treat or manage cancer [13, 14].

There have been several commercialised Nano therapeutic drugs due to the development of nanotechnology. Clinical trials have been conducted on several Nano therapeutic medicines since 2010. As for anti-tumour Multi Drug Resonance (MDR), Nano therapeutic drugs provide the potential to improve drug delivery and inhibit mechanisms of drug resistance [15]. ETH Zurich (Eidgenössische Technische Hochschule Zürich) pioneered medical nanotechnology in the 1960s [16]. This combination has led to several diagnostic devices and better therapies. Nano therapeutics are discussed in this review, including their basic principles, challenges, and prospects.

Nanoparticles

A nanoparticle is a small, highly specialised material with unique properties that distinguish it from bulk samples [17]. In terms of their overall shape, nanoparticles can be classified into four different categories: 0D, 1D, 2D, and 3D [18]. A Nanoparticle is made up of a core and surface, and the shell is made up of layers [19]. They have earned vast attention in several multidisciplinary fields because of their exceptional characteristics, such as high surface-to-volume ratios, dissimilarities, and submicron sizes. In addition to improving Enhanced Permeability and Retention (EPR), nanoparticles penetrate deeply into tissues. Consequently, the drug's surface characteristics directly affect the bioavailability and half-life of the drug since they facilitate penetration of epithelial fenestration into the cell [20]. It has been shown that Polyethylene Glycol (PEG)-coated nanoparticles are less likely to opsonise and circumvent immune clearance [21]. Drugs or active molecules can be released more rapidly by manipulating the polymer properties of particle polymers. Nanoparticles have distinct properties regulating their therapeutic effects in treating and managing cancer.

Synthesis of nanoparticles

Finding nanoparticles in various shapes, sizes, and structures is possible. Different synthesis methods are employed to achieve this goal. Procedures can generally be classified into 1) bottom-up and 2) top-down. It is possible to further sub-classify these approaches based on operating and reaction conditions.

bottom-up approach

In this case, the material is constructed from atoms, clusters, and nanoparticles, referred to as the constructive method [22]. As examples of standard procedures, spinning, biosynthesis, plasma or flame spraying, solvent vapour deposition and laser pyrolysis are common techniques.

Top-down approach

A destructive method also synthesises Nanoparticles by reducing bulk materials or substances. Nanoparticles are formed by breaking down larger molecules into smaller units [23]. Among the techniques used in this process are laser ablation, sputtering, micro-explosion, thermal decomposition, mechanical milling, Chemical etching and nanolithography. By altering reaction conditions and other synthesis parameters, morphological parameters, such as shape, charge, and size, can be changed [24]. Nanoparticles' chemical properties are also determined by their growth mechanism. Thus, synthesising Nanoparticles requires an understanding of the growth mechanism.

Mechanisms of cellular targeting

A drug or gene delivery system that targets cancer cells while sparing healthy cells is essential to treat cancer effectively. Normal cells are protected from cytotoxicity because it enhances therapeutic efficacy. Targeted cancer cells are indirectly targeted through the proper delivery of nanoparticles into Tumour Micro Environment (TME). Nano-formulations must overcome a wide range of physiological and biological barriers. Several layers and layers of cells from these barriers (epithelium, endothelium, and cellular membranes) and enzymes that play an essential role. Nanoparticles must meet specifications for size, biocompatibility, and surface chemistry to prevent unspecific targeting. Nanoparticle drugs can't reach their sub-cellular targets due to cytosolic internalisation. Engineering and optimisation are required to target cells or nuclei. The development of Nanoparticle-based drug-targeting designs has been the subject of several studies, and more are in progress. To be effective, these Nano carriers must generally possess several fundamental characteristics, such as: 1) stay stable in the blood system when reaching their targets, Tumour Micro Environment (TME), 2) escape Reticulo Endothelial System (RES), 3) escape mononuclear phagocyte clearance, 4) accumulate in the Tumour Micro Environment (TME) via the tumour vasculature, 5) withstand high-pressure penetration into tumour fluid, and 6) interact only with tumour cells [25]. It depends on numerous parameters, such as patho physiological properties, surface functionalization, and physicochemical properties, to control the nanoparticle drug targeting process.

For cancer treatments, nanoparticles with diameters of 10 to 100 nm are usually accounted for appropriately. For Nanoparticle carriers to interact and crosstalk with cancer cells, targeting mechanisms must be studied. Active targeting and passive targeting are the two main types of targeting tools.

Passive targeting

In the early 1980s, researchers discovered that cancer cells accumulate specific macromolecules preferentially. According to a study [26], there is evidence that poly (styrene-co-maleic acid)-neocarzino statin gets within tumours. As a result of damaged tumour blood vessels with fenestrations and poor lymphatic drainage, this preferential distribution was attributed to enhanced permeation and retention.

The endothelium layer becomes more permeable in a hypoxic or inflamed environment [27]. It is common for rapidly growing tumour cells to engulf or expand existing blood vessels in hypoxia. Neovascularisation refers to this process. In contrast to normal blood vessels, these new vessels have large pores, resulting in poor perm-selectivity [28, 29]. Large pores or fenestrations are available in different cancer types, Tumour Micro Environments (TMEs), and sites of the cancer [30]. In cancer cells, nanoparticles can diffuse out of vessels that have experienced rapid or defective angiogenesis and accumulate due to the lack of resistance to extravasation.

Extracellular Fluid (ECF) draining into lymphatic vessels in normal tissues typically flows at 0.1–2 m/s on average [31]. When a tumour forms, the lymphatic function is hindered, resulting in minimal fluid uptake [32]. This quality causes Nanoparticles to remain in the tumour interstitium since they cannot be cleared. This process enhances retention as part of the Enhanced Permeability and Retention (EPR) effect. Short circulation times and rapid removal from cancer cells are not features of molecular molecules with short circulation times. Nano-sized carriers thus play an essential role in enhancing the pharmacokinetics of small molecules, making tumour selectivity possible, and reducing the incidence of side effects with the delivery of small molecules [33].

Passive targeting is more sensitive to Tumour Micro Environment (TME) effects than Enhanced Permeability and Retention (EPR) effects. Glycolysis is one of the metabolic characteristics of proliferating tumour cells. Aside from providing energy for cell division, it helps acidify the environment around it [34]. A Tumour Micro Environment (TME) with lowered pH can be exploited to release drugs when pH is low using pH-sensitive nanoparticles [35].

Cancer carriers are heavily considered when passive cancer targeting is conducted, in addition to their size, vascularity, and leakiness. This type of tumour-targeting does not target specific types of tumour cells. Invasion of the perivascular tumour by lymph angiogenesis, Enhanced Permeability and Retention (EPR) is affected by intra-tumour pressure, lymph angiogenesis, and angiogenesis. Nanoparticle drug delivery efficiency is affected by these factors and their physicochemical characteristics.

Examples of passive targeting

Many people are familiar with the fact that taxanes are very successful cancer treatments. The drug paclitaxel has been proven to be ineffective against a wide variety of cancers. In terms of histology, lung cancer (non-small and small cells), ovarian cancer and breast cancer are most commonly treated with taxanes. By preventing the depolymerisation of microtubules, Abraxane® stabilises them. As a result, microtubules are assembled from tubulin dimers when the drug promotes their assembly. This stabilisation is believed to inhibit microtubule reorganisation during interphase and mitotic functions. In cell cycle and mitosis, the well-known taxane paclitaxel causes multiple asters and unusual microtubule arrays. Xenograft mouse models of pancreatic cancer have been shown to reduce the pancreatic stroma when abraxane® is taken alone or in combination with gemcitabine [36].

In addition to its micellar form, Genexol PM® is a nanoformulation, or polymeric structure, of paclitaxel without Cremophor EL (CrEL). There was a three-fold increase in the maximum tolerated dose of Genexol PM® in nude mice compared to those in male mice when using Genexol PM®. As well as cancer cells, the bio distribution of this drug was found to be 2-to 3-fold higher in the lung, liver, kidney, spleen, and liver, respectively. The South Korean government has approved the treatment of Metastatic Breast Cancer (MBC). Currently [37], the drug is being studied for the treatment of pancreatic cancer in the United States of America (USA) [38].

Gilead Science/Diatos manufacture the anticancer drug DaunoXome® (liposomal daunorubicin). It contains a substance called daunorubicin. The liposome-based daunorubicin formulation treats Kaposi's sarcoma (affecting the intestine, lungs and skin). The United States Food and Drug Administration (US-FDA) approved this in 1996 [39].

As angiogenesis and neovascularisation increase, Nanoparticle diffusion is inhibited, but Nanoparticle accumulation is enhanced as interstitial pressure increases. Furthermore, tumour cells multiply irregularly because of heterogeneous blood supply, resulting in hypoxic or necrotic areas close to blood vessels-deficiencies in drug delivery and accumulation, high interstitial pressure and slow neovascularization [33]. Chemically or mechanically, controlling the Enhanced Permeability and Retention (EPR) effect is possible. The process involves many other agents, including peroxynitrite, nitric oxide, hyperthermia, ultrasound, bradykinin, radiation, etc. Contraindications and limitations apply, however.

Active targeting

Transferrin and folate are active targeting ligands that bind to receptors on target cells that are specifically expressed or over-expressed (diseased cells, tissues, organs or subcellular domains) [40]. The process of ligand-mediated targeting is known as ligand-driven targeting [41]. A greater affinity can be achieved by placing Nanoparticles with ligands with specific functions near the target to increase retention and uptake. Nanoparticles are more likely to bind to cancer cells using this strategy, enhancing their penetration. Initially, antibodies were grafted on liposome surfaces in 1980 [33], followed by other ligands such as aptamers and peptides. The main objective of this technique is to increase Nanoparticle-target crosstalk without changing the total bio distribution [42]. Identifying the ligand by the target substrate receptor makes active or ligand-mediated targeting possible. Ligands include nucleic acids, antibodies, peptides, sugars, proteins, and small molecules such as vitamins [43].

In addition to the Epidermal Growth Factor Receptor (EGFR), transferrin receptors and folate receptors are commonly studied receptors. As a result of ligand-target interactions, the membrane is folded, and Nanoparticles are internalised by receptor-mediated endocytosis. Active targeting occurs through various mechanisms. Nanoparticles are mainly responsible for tumour-targeting because they target tumour cells in general. This process improves cell penetration. It is well known that transferrin is a widely studied receptor. Iron is transported into cells by this type of serum glycoprotein. Almost all tumour cells, substantial tumours, overexpress these receptors, whereas healthy cells express them in lower amounts. Consequently, they can be modified with ligands targeting transferrin [44]. A2780 overexpresses transferrin in ovarian carcinoma cells. Transferrin-modified poly (ethylene glycol)-phosphatidylethanolamine Nanoparticles that target such cells specifically use this feature to adjust Poly Ethylene Glycol (PEG)-phosphatidylethanolamine [45]. Angiogenic endothelial cells can also be targeted as an alternative to cancer cells. A close relationship exists between these cells and the blood vessels of the tumour. As a result of this strategy, cancer cells are left hypoxic and necrotic, which results in hypoxia and necrosis. The acidity of tumour tissues is higher than that of normal tissues. Warburg's effect has been extensively discussed [46]. Lactic acid is formed when cancer cells undergo glycolysis instead of aerobic metabolism. A cell dies when lactic acid accumulates. A better solution to this dilemma would be to over-express proton pumps, which are responsible for pumping excess lactic acid from the cells into the extracellular pH, thus causing the pH levels in the extracellular environment to increase. It is therefore being investigated whether liposomes can be used to deliver drugs in a pH-sensitive manner.

As a result of their multivalent nature, ligand-coated nanoparticles have improved crosstalk with cancer cells. Designing such nanoparticles is complex due to the complex interaction between nanoparticles' architecture and ligand-target chemistry [47]. Other factors contribute to the system's success, such as the ligand density, size of Nanoparticles and route of administration.

Examples of active targeting

Different types of cancer, particularly squamous cell carcinoma, overexpress Epidermal Growth Factor Receptors (EGFR), a tyrosine kinase receptor. There has been a demonstration of the use of gold nanoparticles combined with Immunoglobulin G–Poly Ethylene Glycol (PEG)-Gold nanoparticles or anti-anti-Epidermal Growth Factor Receptor (EGFR)–Poly Ethylene Glycol (PEG)-Gold nanoparticles to treat human Squamous Cell Carcinoma (SCC) [48].

It is known that breast cancer cells over express Human Epidermal Growth Factor Receptor-2 (HER2). Herceptin® targets this receptor. It has been developed to reduce cardio toxicity caused by anthracyclines with Human Epidermal Growth Factor Receptor-2 (Her2) targeting Poly Ethylene Glycol (PEG) related liposomal doxorubicin [49].

During angiogenesis, Vascular Cell Adhesion Molecule-1 (VCAM-1) is expressed on the surface of the tumour endothelium. Vascular Cell Adhesion Molecule-1 (VCAM-1) may play a role in breast cancer, according to a study that identified Nanoparticles that target Vascular Cell Adhesion Molecule-1 (VCAM-1) [50]. Vitamin B9, or folic acid, is essential to nucleotide synthesis. Cells internalise folate through the folate receptor. However, tumour cells over-express Folate Receptor-α (alpha isoform of folate receptor), while Folate Receptor β is over-expressed in liquid cancer cells [51].

Nanoparticles in cancer therapy

A variety of nanoparticles are employed in drug delivery systems, including inorganic, hybrid and organic nanoparticles [52, 53]

Organic nanoparticle

Polymeric nanoparticle

According to physicists, polymeric nanoparticles are colloidal macromolecules derived from different monomers but have a specific structure that differentiates them [54]. A controlled drug release is achieved by entrapping or attaching drugs to the exterior of nanoparticles [55]. The original polymeric nanoparticles were manufactured with polyacrylamide, Poly Methyl Methacrylate (PMMA), and polystyrene, all non-biodegradable materials [56]. These compounds were toxic because they were difficult to eliminate from the body. These materials have been demonstrated to lessen toxicity, enhance drug release, and improve biocompatibility when developed as biodegradable polymers like polylactic acid, alginate, chitosan, albumin and poly (amino acids) [57]. Researchers have demonstrated that polysorbates can coat polymeric nanoparticles because they have surfactant properties. Nanoparticles are covered on the outside to increase their interaction with endothelial cells in the Blood-Brain Barrier (BBB) [58].

An indomethacin-loaded Nano capsule model of xenograft glioma in rats showed significantly reduced tumour size and improved survival [59]. More than ten polymeric nanoparticles are currently containing anticancer drugs in clinical development. Additionally N-(2-Hydroxy Propyl) Meth Acrylamide (HPMA) copolymer-paclitaxel (PNU166945), N-(2-Hydroxy Propyl) Meth Acrylamide (HPMA) copolymer-platinate (AP 5280), N-(2-Hydroxy Propyl) Meth Acrylamide (HPMA) copolymer-doxorubicin galactosamine and N-(2-Hydroxy Propyl) Meth Acrylamide (HPMA) copolymer-dACH-platinate (AP5346) are examples in addition to poliglumex, paclitaxel, and modified dextran-camptothecin (DE 310) [60].

Dendrimers

A dendrimer is a spherical polymeric macromolecule with a defined hyper-branched structure. Highly branched structures characterise dendrimers. An ammonia core typically reacts with acrylic acid to form dendrimers. Graphene oxide products are created by reacting ethylene diamine with tri-acid molecules to form tri-amines. The result of this reaction is hexa-acid, which then gives rise to "hexa-amine" (Generation 1) and so forth [61]. Dendrimers typically range from 1–10 nm in size. Sizes of up to 15 nm have been reported [62]. The specific structure of these molecules, such as their defined molecular weight, flexible branches, bioavailability, and charges, makes them ideal for targeting nucleic acids. Polyamido amine, Poly Ethylene Glycol (PEG), polypropylene imine, and triethanolamine are some of the dendrimers that are commonly used [63].

It was initially designed to manage Multi-Drug Resistance (MDRs) with a Polyamidoamine dendrimer. The DNA assembly of Polyamidoamine dendrimers has been extensively discussed. The effects of synthetic dendrimers on epithelial cancer xenografts were significantly delayed compared with single-agent chemotherapy [64].

Monoclonal antibodies nanoparticles

The particular targeting abilities of monoclonal antibodies make them widely used in cancer treatment [65]. Combining these monoclonal antibodies with nanoparticles creates antibody-drug conjugates. Compared to cytotoxic drugs or Monoclonal antibodies alone, these are highly specific and compelling. A nanoparticle containing paclitaxel in the core and trastuzumab on the surface demonstrated better antitumor efficacy and less toxicity in Human Epidermal Growth Factor Receptor (HER2)-positive breast epithelial cells [66].

Extracellular vesicle

A phosphor-lipid vesicle is an extracellular vesicle, typically between 50 and 1000 nanometres in size [67]. Different types of cells secrete Extracellular vesicles, and their origin, size, and composition vary greatly. Three categories of extracellular vesicles have been identified, including exosomes, micro vesicles, and apoptotic bodies [68]. The lipids and molecules in Nanoparticles and exosomes are identical to those in the origin cells, so they are widely used. The cancer cells are also exposed to them, escaping immune surveillance and quickly internalising them. By using these natural vehicles, cytotoxic drugs and other antitumor drugs are delivered to the target sites. There is no better example than exosomes that carry doxorubicin. Breast cancer patients treated with doxorubicin experience enhanced cytotoxicity and avoid cardio toxicity when compared to conventional treatment with doxorubicin [69]. Exosome nanoparticles' intrinsic biocompatibility and advanced chemical stability allow them to communicate intra-cellularly with other cells more effectively than synthetic nanoparticles. Despite this, there are still drawbacks, such as the lack of standard conditions for the isolation and purification of exosomes [70, 71].

Liposomes

Spherical vesicles encapsulating drug molecules comprise uni lamellar or multi-lamellar phospholipids. It is unique that liposomes are low in intrinsic toxicity, immunogenic, and biologically inert [72]. The Food and Drug Administration (FDA) approved the first Nano scale drug using liposomes in 1965 [73]. This unique architecture allows liposomes to encapsulate both hydrophobic and hydrophilic drugs effectively, protecting the drugs entrapped in circulation against degradation [74]. Liposomes typically contain a "hydrophobic phospholipid bilayer" and "hydrophilic core."

Because liposomes deliver medications with improved bioavailability and anti-tumour efficacy, many drugs, like nucleic acids, doxorubicin and paclitaxel, are considered excellent delivery systems [75]. In addition to Daunorubicin liposome-based formulations like Myocet® and Doxil®, the treatment for Metastatic Breast Cancer (MBC) has been approved by the Food and Drug Administration (FDA) [76, 77]. While liposome-based nanoparticles offer convenience and effectiveness, they have several drawbacks, including reduced encapsulation efficiency and quick cell adsorption.

Solid lipid nanoparticles

Water and phospholipid monolayers are present in colloidal nanocarriers (1-100 nm) [78]. Nanomaterials of this type are known as zero-dimensional nanomaterials. The composition of lipids ranges from triglycerides to Poly Ethylene Glycol (PEG) related lipids, steroids, fatty acids and waxes [79]. In Solid Lipid Nanoparticles, the drug is encapsulated in a non-aqueous core similar to a liposome [80]. It has been shown that Solid Lipid Nanoparticles loaded with mitoxantrone have superior bioavailability and reduced toxicity [81]. The Solid Lipid Nanoparticles incorporated doxorubicin and idarubicin into P388/ADR and murine leukaemia mouse models [82].

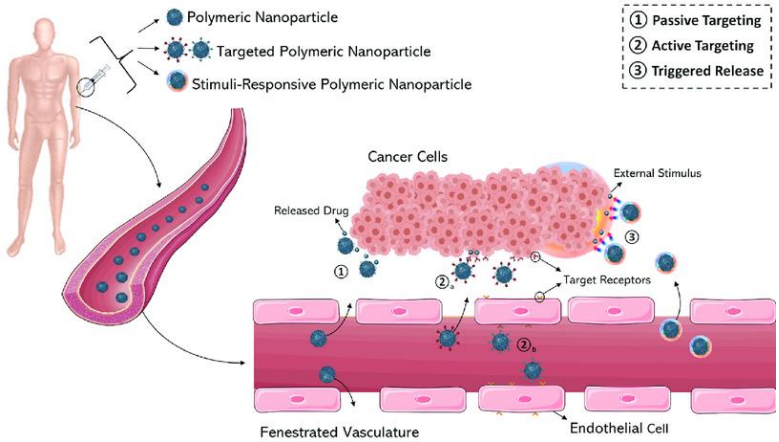

Fig. 1: Schematic representation of various drug-targeting approaches

Nano emulsions

A colloidal Nano emulsion is a heterogeneous mixture of oil droplets in an aqueous medium having a size range of 10 to 1000 nm [83]. In addition to water-in-oil Nano emulsions, there are three types: oil-in-water aerosols, oil-in-oil aerosols, and bicontinuous aerosols. Much research has been conducted in the field of membrane-modified Nano emulsions. Evidence, for instance, suggests that

spirulina and paclitaxel Nano emulsions could increase the antitumor activity of TLR4/NF-kB signalling pathways through which immunity is regulated [84]. Rapamycin, bevacizumab, and temozolomide Nano emulsions have shown positive results in melanoma patients [85]. Nano emulsions have higher optical clarity, stability, and biodegradability than liposomes [86]. High temperatures, pressures, and costly instruments such as homogenisers and micro fluidisers can make Nano emulsion applications challenging. The use of ligands directed at specific targets is one way to target drugs, while the use of the unique pathophysiology of a tumour tissue is another (fig. 1).

Cyclodextrin nanosponges

Nanoparticles can be stabilised by adding cyclodextrins to increase their drug-loading capacity by adding cyclodextrins to Nanoparticles [87]. Some nanosponges resemble meshes. B-cyclodextrin nano-sponges loaded with paclitaxel have demonstrated cytotoxic effects in MCF-7 cell line culture [88]. A cyclodextrin-based nano-sponge formulation improved camptothecin's solubility and stability [89].

Inorganic nanoparticle

Carbon nanoparticles

Carbon nanoparticles, as their name implies, are derived from carbon. Optical, mechanical, and electrical properties make them suitable for various medical applications [90]. The hydrophobic nature of carbon Nanoparticles makes them ideal for encapsulating drugs by stacking. In addition to carbon nanohorns, carbon nanotubes and graphene, there are additional categories of carbon nanoparticles. Carbon-based materials' morphology, structure, and physical characteristics vary despite their carbon composition [91].

The 2D graphene crystals also have sp2-hybridized carbon sheets with exceptional mechanical and electrochemical properties. Aside from its composition, graphene is also classified according to its properties and design: a) graphene oxide, b) reduced graphene oxide, c) multilayer grapheme and d) single-layer graphene [92]. Because they can target hypoxia [93] and irregular angiogenesis, graphene oxide and reduced graphene oxide are widely used in Tumour Micro Environment (TME) [94]. The anticancer activity of graphene oxide-doxorubicin was greater than that of conventional doxorubicin in cellular models of breast cancer [95].

Molecular spheres, ellipsoids, and tubes are all types of fullerenes, which are large carbon-cage molecules. Nano carriers are known for their typical chemical, electrical, physical, and structural properties [96]. Despite their triple yield and ability to absorb light, these compounds are used primarily in photodynamic therapy due to their ability to generate oxygen species [97]. The photo-dynamic effects of fullerenes modified with Polyethylene glycol l(PEG) are promising on tumour cells [98].

Since the late 1980s, graphene nanotubes have been observed to contain carbon nanotubes. One type of carbon nanotubes, single-walled carbon nanotubes, and another, multi-walled carbon nanotubes, can be divided into two categories. Having carbon-based structures, their ability to interact with immune cells suppresses tumour growth through an immune response. Deoxy Ribonucleic Acid (DNA) has traditionally been delivered through these vectors, and tumours have been diminished with them. Using fluorescent carbon nanotubes encapsulated with monoclonal antibodies, doxorubicin is targeted at colon cancer cells. The carbon nanotubes remain in the cytoplasm while cancer cells engulf them, releasing the doxorubicin intra cellularly [99].

Quantum dots

A biological imaging device is possible with molecular dots, a nanometer-scale semiconductor with broad absorption and narrow emission bands, and high photo stability [100]. Quantum dots made from carbon are classified into three categories: Nano diamond quantum dots, carbon quantum dots and graphene quantum dots. The use of quantum dots for cancer treatment is being investigated in addition to biological imaging. Biocompatibility and rapid excretion are the most essential characteristics of graphene quantum dots. In this category are quantum dots and aptamers conjugated to doxorubicin [101]. Nevertheless, a lack of optimisation of processes remains a significant obstacle to producing quantum dots.

Metallic nanoparticle

Nanoparticles of metallic materials are used in biological imaging and targeted drug delivery because of their excellent optical, magnetic, and photo thermal properties. Several types of metal nanoparticles are commonly used, including silver [102], copper, iron and gold nanoparticles. In intracellular drug delivery, gold nanoparticles are used due to their size and surface properties [103]. It is possible to track Nanoparticle trajectories within cells due to the extinction of visible light by these particles. The anti-Human Epidermal Growth Factor Receptor (HER2) function of gold-on-silica nanoshells has been demonstrated to target breast cancer cells that express the Human Epidermal Growth Factor Receptor (HER2) Gene [104]. In clinical trials, Combidex® is being tested to detect nodal metastases with iron oxide nanoparticles [105]. Feraheme® is a Nanoparticle formulation containing ferumoxytol used to treat iron-deficiency anaemia. Nodal metastasis in prostate cancer and testicular cancer are treated in the same way by the Food and Drug Administration (FDA) [106, 107].

Magnetic nanoparticle

Metal oxides and metals generally deliver drugs, while magnetic nanoparticles are commonly used in Magnetic Resonance Imaging (MRI). A polymer or fatty acid coating is often applied to enhance stability and biocompatibility [108]. A new type of super paramagnetic iron oxide nanoparticle can be used to target and image breast cancer effectively using the LHRH-conjugated iron oxide nanoparticles [109]. Furthermore, magnetic nanoparticles can also ablate cancer cells by using magnetic hyperthermia [110, 111]. In addition to Resovist® and Feridex®, magnetic nanoparticles for colon cancer and liver metastasis are currently being evaluated in clinical trials [112].

Calcium phosphate nanoparticles

Biocompatible and biodegradable, Calcium phosphate nanoparticles have no harsh adverse effects. The use of them for insulin delivery, growth factors, antibiotics, and contraception is thereby widespread [113]. Additionally, oligo nucleotides and plasmid Deoxy Ribonucleic Acid (DNA) can be delivered using these techniques [114]. Cellular gene transfer has been positively facilitated using calcium phosphate nanoparticles combined with viral or non-viral vectors. Calcium and glycerol in a "liposome nanolipoplex formulation" have enhanced transfection properties and reduced toxicity [115, 116].

Silica nanoparticles

It has only been recently discovered that silica has biological properties despite its presence in many natural materials. To deliver genes to silica nanoparticle surfaces, amino silicanes are commonly used [117]. Commercially available N-(6-aminohexyl)-3-aminopropyl-trimethoxysilane functionalised silica nanoparticles have shown excellent transfection efficiency and minimal toxicity in Cos-1 cells [118]. The best drug carriers are mesoporous silica nanoparticles because of their superior pharmacokinetic properties. Immunotherapy has been extensively used them. In a study, mesoporous silica nanoparticles loaded with camptothecin successfully absorbed colorectal cancer cells.

Overcoming drug resistance-NPs mechanism

Cancer therapy and management are plagued by drug resistance. Cancers of all types and treatment modalities are affected by it. The emergence of drug resistance is caused by diseases that become tolerant to pharmaceutical treatments. The two types of drug resistance are acquired and innate [119]. Mutations in the cell growth and apoptosis genes typically cause natural resistance. As a result of new modifications or alterations in the Tumour Micro Environment (TME), acquired resistance can occur following a specific anti-tumour treatment. The ability of nanoparticles to encapsulate multiple therapeutic agents simultaneously makes them ideal for overcoming cancer drug resistance.

Targeting efflux transporters

Efflux transporters are primarily affected by Multi Drug Resistance (MDR), classified under the Adenosine Tri Phosphate (ATP)-binding cassette transporter family. Transporters are mainly responsible for pumping drugs out of cells and reducing their concentration. A drug-resistant cancer cell over-expresses P-glycoprotein, a transporter involved in efflux [120, 121].

P-glycoprotein over expression is associated with insufficient treatment responses in ovarian and breast cancer [122, 123]. The efflux pumps can be targeted with Nanoparticles. Through endocytosis rather than diffusion, Nanoparticles bypass efflux pumps and release drugs distant from active efflux pumps [124]. Aside from forgetting efflux pumps, Nanoparticles can also trigger drug release by modifying pH levels or using redox as a trigger to trigger drug release [125, 126].

Another method of overcoming Multi Drug Resistance (MDR) is combination therapy. A single drug carrier can contain multiple drugs [127]. Inhibiting efflux trans-porter expression would be another viable option instead of avoiding them. The Nanoparticles should be designed so that efflux pump inhibitors and chemotherapy agents can be entrapped together [128]. Nanoparticles co-deliver Cyclooxygenase 2inhibitors and doxorubicin to breast cancer cells, reverse magnetic resonance in the breast [129]. Researchers have also shown that silica nanoparticles encapsulating microRNA-495 and doxorubicin can overcome drug resistance in lung cancer cells [130]. Nanoparticles targeting Kinase Insert Domain Receptors (KDR) in the tumour neo-vasculature were found to have more excellent anti-tumor activity than P-glyco protein inhibitors alone in another interesting study. Depleting Adenosine Tri Phosphate (ATP), essential for Adenosine Tri Phosphate (ATP)-binding cassette transporters to function, is another way to overcome drug resistance. To achieve this, mitochondria can be targeted, which results in a decrease in Adenosine Tri Phosphate (ATP) production.

Targeting an apoptotic pathway

Because of faulty apoptotic machinery, cancer cells proliferate and survive longer, leading to drug resistance [131]. It is believed that “deregulation of Bcl-2" and “nuclear factor kappa B” activates the faulty apoptotic pathway. These proteins are considered the most widely studied anti-apoptotic proteins and can potentially be used to reverse drug resistance. Using nanoparticles can overcome Multi-Drug Resistance (MDR) by co-delivering chemotherapeutics and Bcl-2 siRNA [132]. Combining nuclear factor kappa B (NF-B) inhibitors with pyrrolidine dithio carbamate and curcumin has been tested [133, 134]. Another method to fight "apoptosis pathway-mediated drug resistance" is to activate pro-apoptotic factors. Ceramide and paclitaxel are examples [135]. The ceramide molecule regulates alternative pre-mRNA splicing to restore the expression of p53, a major tumor suppressor. It is feasible to correct p53 missense mutations by delivering ceramide via nanoparticles [136]. Due to their potential, Ceramide and paclitaxel have demonstrated significant therapeutic efficacy against cancer drug resistance. It has been reported that cationic solid lipid nanoparticles can transfect the p53 gene in lung cancer cases [137]. Additionally, Apoptosis was induced, and tumour growth was inhibited by transfecting the p53 gene with Poly (Lactic-Co-Glycolic Acid) (PLGA) in breast cancer cell models [138].

Targeting hypoxia

Multi-Drug Resistance (MDR) is also supported by hypoxia [139]. Some tumour cells undergo repeated hypoxia due to oxygen deficiency due to their rapid growth and abnormal blood vessels nearby. As a result of being in an anoxic state, hypoxic tumours often escape chemotherapy drugs because they are hypoxic. The oxygen ramp inside the tumour promotes an aggressive phenotype by increasing tumour heterogeneity. Hypoxia has also been shown to promote the overexpression of efflux proteins in cells [140]. Instead of directly targeting HIF-1α, indirect inhibition of HIF-1α signalling can be used. PEGylated and non-PEGylated liposomes and Poly (Lactic-Co-Glycolic Acid) (PLGA)-Polyethylene Glycol (PEG) can be used effectively as Nano particles. The transcription of HIF-1 is also controlled by heat shock protein 90 (HSP90). HSP90 inhibits HIF-1 expression and inhibits HSP90 [141]. Multi-Drug Resistance (MDR) has been significantly improved in bladder cancer treatment with 17AAG-loaded nanoparticles [142].

Nanoparticles and proteomics

Coronas formed by proteins in the biological system occurs when nanoparticles are surrounded by cellular or serum proteins [143]. Nanoparticles and proteins interact with each other in a variety of ways, leading to different types of coronas. These proteins must bind to nanoparticles with high affinity to form a "hard corona." A nanoparticle produces a "soft corona" when these proteins are loosely tied. Eventually, proteins with higher affinity will replace most proteins, forming proteomics first. This phenomenon is referred to as the Roman effect [144]. The development of this technology is essential for manufacturing nanoparticles with desired properties. Sodium Dodecyl-Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE), isothermal micro calorimetry, Mass Spectroscopy, Liquid Chromatography–Mass Spectrometry (LC-MS), etc., have all been developed for proteomic analyses [145]. The role of proteomics in medicine is to influence crosstalk between nanoparticles and biological settings, thereby determining how nanoparticles and natural environments are integrated.

Biomarkers and hunting proteins in cancer cells and serum may be helpful in diagnosing, treating, and prognosing cancer based on cancer proteomics [146]. It also helps understand how drugs resist certain medicines and cancer pathogenesis. Metastasis, recurrence, and cancer occurrence depend on Post-Translational Modifications (PTMs). With nanoparticles, novel agents such as mRNA, siRNA and gene editing are used in addition to chemotherapy and kinase inhibitors.

Nanotechnology for small interfering rna (siRNA) delivery

A siRNA molecule (around 21 nucleotides long) suppresses gene activity. A few siRNA-based Nano particles targeting the transthyretin gene are currently under clinical investigation for treating transthyretin-mediated amyloidosis. Transthyretin-mediated amyloidosis can be treated with ALN-TTR01. As a result of targeting protein kinase N3 and TKM-ApoB, Atu027 inhibits the expression of ApoB [147, 148].

Nanotechnology for tumor microrna profiling and delivery

MicroRNA blocks translation or destabilises mRNA after transcription to regulate gene expression by either blocking or destabilising it [149]. These biomarkers are becoming increasingly important as cancer diagnostic, therapy, and treatment targets. Nanotechnology uses miRNA profiling techniques based on the base priming nature of nucleic acids [150-152]. Combining molecular biology enzyme reactions with biosensors and surface Plasmon resonance imaging techniques are several profiling techniques. Nanotechnology can be used to deliver microRNAs. The polyamine metabolism was regulated by biodegradable polycationic pro drugs, for example [153]. The expression of "survivin" in murine B16F10 melanoma lung metastases is progressive when single-chain antibodies containing microRNA are used.

DNA nanotechnology for cancer therapy

For the detection of nucleic acids, DNA-based nanostructures have been synthesised, gold nanoparticles coated with DNA-zyme for lead sensing, scaffolds for organising organics, inorganics, and bio molecules into drug delivery and distinct morphology molecular transporters.

Nanoparticles in cancer therapy-advantages

Cancer diagnosis, treatment, and management have been transformed by nanotechnology. Through passive or active targeting, nanoparticles augment intracellular drug concentrations while avoiding toxicity in healthy tissues. Drug release can be established and regulated by designing and altering targeted nanoparticles to be pH-sensitive or temperature-sensitive. PH-sensitive drug delivery systems can treat acidic Tumour Micro Environments (TMEs). Temperature-sensitive nanoparticles release drugs in the targeted area when magnetic fields or ultrasound waves change temperature. Aside from shape, size, surface chemistry and

molecular mass, Nanoparticles can deliver drugs selectively. In addition, Nanoparticles can be modified to target particular moieties according to their target.

The uneven dispersion and cytotoxicity of radiation treatment and conventional chemotherapy have several disadvantages when it comes to efficacy and side effects. To effectively kill cancer cells, a cautious dose must be administered without causing significant toxicity. Several fortifications are required for the drug to reach the target site. The metabolism of drugs is a very complex process. It is necessary for a cure to pass through the Tumor Micro Environment (TME), Reticulo Endothelial System (RES), Brain-Blood Barrier (BBB), and kidney infiltration under physiological conditions. Three types of immune cells contribute to the Reticulo Endothelial System (RES): macrophages, blood monocytes and other immune cells [154]. Drugs are dealt with by Micro Physiological Systems (MPS) in the liver, spleen, or lungs that activate "macrophages" or leukocytes to remove them quickly. As a result, the drug has a short half-life [155]. As kidney infiltration is one of the essential functions of the human body, nanoparticles that have surface modifications, such as Poly Ethylene Glycol (PEG), bypass this mechanism and prolong drug half-lives. Thus, properly infiltrating the kidneys results in less toxic nanoparticles.

A specialised protection structure, The Brain-Blood Barrier (BBB), protects the central nervous system from toxic and harmful agents-a layer of endothelial cells lines capillaries in the brain, which supply oxygen and nutrients. Chemotherapy for brain cancer is currently restricted to intra-ventricular or intra cerebral administration due to the Brain-Blood Barrier (BBB) role in blocking toxic agents from entering the brain [156]. There is evidence, however, that Nanoparticles can cross the Brain-Blood Barrier (BBB). The Enhanced Permeability and Retention (EPR) effect, focused ultrasound, phosphate-modified endocytosis, and transcytosis are all used today to deliver nanoparticles. Using glutathione PEGylated liposomes, rats took up methotrexate more readily [157]. Induced apoptosis can be achieved with the help of gold nanoparticles. Also, Nanoparticles protect the cargo encapsulated in them from degradation, which increases their stability. The encapsulation process doesn't require any chemical reaction to encapsulate a large volume of drugs. Nano liquid products are less stable than dry solid dosage forms [158]. Stabilisers can be used to enhance stability. Porous nanoparticles can also increase strength.

A tumour's pathophysiology is characterised by extensive angiogenesis, flaws in its vascular structure, and defects in lymph drainage. These features enable nanoparticles to target tumour tissue. Nanoparticles are effectively retained in tumour tissues since venous return is reduced and lymphatic clearance is limited. Enhanced Permeability and Retention (EPR) refers to this phenomenon. Targeting the adjacent tissues can also achieve tumour-targeting [158].

There are several ways to administer nanoparticles, including oral, nasal, parenteral, intraocular, etc. As a result of their high surface-to-volume ratio and intracellular uptake, nanoparticles are highly effective. In studies, nanoparticles are more effective drug carriers than micro particles [159].

Nanoparticles in immunotherapy

Cancer cells develop and are established primarily through the immune system. Advances in immunotherapy have transformed cancer therapy. Along with aiding chemotherapy delivery, nanoparticles can also help with immunotherapy. Several immunotherapy approaches can activate the immune system against cancerous cells [160-162], including immune checkpoint blockade therapies, cancer vaccines, and Chimeric Antigen Receptor Therapies (CAR-T). As far as nano vaccines go, Artificial Antigen-Presenting Cells (aAPCs) are available, and immune-suppressed Tumour Micro Environment (TME) can be targeted using nanoparticle-based immunotherapy.

Dendritic cells deliver tumor-associated antigens and adjuvants in Nano vaccines [163]. Furthermore, they play an essential role in enhancing “Antigen-Presenting Cells (APC) antigen presentation" and activating cytotoxic T cells with antitumor functions [164, 165]. Researchers have found that liposomes, polylactide nanoparticles, and gold nanoparticles can all deliver Tumour-Associated Adipocytes (TAAs) into the dendritic cell cytoplasm [166]. It is possible to provide Tumour-Associated Adipocytes (TAAs) into dendritic cell cytoplasm using liposomes, Poly (Lactic-Co-Glycolic Acid) (PLGA) nanoparticles, and gold nanoparticles [167]. Mesoporous silica, for example, has been found to stimulate immune responses as an adjuvant [168]. Major Histocompatibility Complex (MHC) antigen complexes bind directly to T cells when Artificial Antigen-Presenting Cells (aAPCs) interact with them. Additionally, they bind to co-stimulatory molecules, which stimulate T cells to activate [168]. In addition to targeting immune-suppressed Tumour Micro Environment (TME), Nanoparticles can also be used in immunotherapy. A specific method of achieving this objective utilises Myeloid-Derived Suppressor Cells (MDSCs), regulatory T cells, and macrophages associated with tumours.

Chemotherapy combined with immunotherapy is an effective cancer treatment. Researchers found that ACETYLATED DEXTRAN nanoparticles co-loaded with Granulocyte Macrophage Colony–Stimulating Factor (GM-CSF) and Nutlin-3a increased CD8 (+) T cell proliferation and stimulated immune responses in a study. PD ligand 1 activates programmed cell death protein 1 (PD-1) and acts as an immune checkpoint [169]. Nanoparticles are commonly used to target immune checkpoints. A study found that PD-L1/PD-1 immune checkpoint inhibitors had inconsistent responses. There is a more extraordinary ability for immune checkpoint inhibitors to bind to poly (amidoamine) dendrimers than conventional dendrimers. PD-L1 blocking agents were combined with dendrimers to improve drug accumulation at tumour sites [170].

Cryosurgery with nanoparticles

Through cryosurgery, cancerous tissue is destroyed by freezing. Despite its advantages, such as low invasiveness and fewer complications during surgery and postoperatively, the procedure has some disadvantages, such as insufficient freezing capacity and damage to adjacent cells [171]. As nanotechnology has advanced, cryosurgery has become possible.

Nano cryosurgery involves introducing Nanoparticles that have specific properties into cancer cells and freezing them [172]. The cells are damaged due to the formation of ice within them during this process. It is a necessary process that can be efficiently carried out with the help of nanoparticles. Nanoparticles have high thermal conductivity, so they can freeze and damage tumour tissue [173]. Aside from that, they cool quickly, and the "direction of the ice ball" and “growth direction" can be controlled.

Cryosurgery may be infeasible due to the tumour's location or if other nearby organs are at risk of being damaged by the freezing. It has recently been discovered that Phase Change Materials (PCMs) made up of nanoparticles are used during cryosurgery to protect the adjacent healthy normal tissue during the procedure [178]. Liposome-based microencapsulated phase change nanoparticles have been demonstrated to effectively preserve healthy tissue around them [174]. These nanoparticles' low thermal conductivity and sizeable latent heat make them ideal for cryosurgery.

Nanoparticles in clinical practice: challenges and opportunities

With nanotechnology flourishing, nanoparticle knowledge and research have dramatically increased. Clinical trials are only conducted on a small number of these therapies. It is common for them to stop at either the *in vivo* or the *in vitro* stage. In terms of biology, technology, and study design, different Nan formulations face different challenges in clinical translation.

Several biological challenges include the lack of administration routes, the tempered distribution of nanoparticles and the ability to cross physical barriers, decay, and toxicity [175]. Due to their intravenous injection, nanoparticles are injected directly into the bloodstream, which transports them away from the targeted area, preventing them from interacting with the target site. It may not be adequate to use a high-concentration drug because the therapeutic effect may not be achieved [176]. It has been demonstrated in several *in vivo* and *in vitro* studies that 3D magnetic fields can be used to control the movements

of nanoparticles against blood flow. Magnetic fields need to be investigated, as well as the effects of nanoparticles, crosstalk, and the results of magnetic fields on humans.

Nanoparticles are challenging to control biologically. It is possible that lung, liver, and kidney damage may be caused by nanoparticles containing bio-safety materials and modifying retention times and half-lives. Toxicity is affected by factors such as agglomeration, particle size, surface area, shape and solubility [177]. Nanoparticles accumulate in the lungs causing inflammation, oxidative damage, and cytotoxicity [178]. In many cases, nanoparticles produce free radicals that damage healthy cells [179]. Nanoparticles disintegrating after near-infrared light irradiation are possible solutions using biocompatible materials such as chitosan.

In biological fluids, nanoparticles adsorb proteins, resulting in peptides, which are then taken up by the Multinuclear Phagocytic System (MPS). The protein corona cannot form on nanoparticles because they have been coated with a material. The results, however, have not been significant. This issue could be solved by developing new drug vehicles that target macrophages. At the moment, it is commonly used strategies such as to prevent macrophage recruitment, deplete and reprogram Tumor-Associated Macrophages (TAMs), and to obstruct the "Pathway CD47-HIPPA" to prevent macrophage recruitment [180].

One of the technological challenges of nanoparticles is scaling up syntheses, optimizing equally, and predicting performance. For nanoparticles to be successful in the clinic, they must adhere to these requirements. Because of instrumentation and other factors, some nanoparticles used *in vivo* and *in vitro* studies cannot always be scaled up to enormous quantities. A clinical candidate that proves successful in animal models is not systematically optimized. Through selective iterations, we can test multiple Nano formulations and select the most optimal formulation through specific methods [181-183]. Because nanoparticle efficacy and performance cannot be predicted, and *in vivo* results cannot be reproduced, it is not a good idea to introduce such hits directly into human trials. In order to produce physiological tissue and its surrounding environment, computational or theoretical modelling can be combined with experimental results. Nanoparticle prediction can be improved, for example, by organs-on-chips.

Clinical trials are significantly impacted by nanoparticle therapies because of their size, purpose, and timing. Most studies use cell models and animals, which might not yield comprehensible results when applied to humans. Using a solitary model, therefore, it is impossible to simulate natural body reactions. It is essential to investigate "models of cancer metastasis" since this is one of the critical characteristics of cancer. In addition, if we are interested in personalized medicine, we must conduct N = 1 clinical studies. In addition to genetics, environment, and past medical history, other factors need to be taken into account [184]. In addition, Nanoparticles are a major challenge when used as first-line therapies. When disease progression is observed, Nano formulations are generally saved for future use when they are approved for use in clinical trials. Multiple treatment lines have either been tried or patients have become resistant to treatments. In these situations, Nanoparticle treatments have a lower likelihood of benefiting those who can still be treated, which can cause clinical trial results to be skewed.

Future perspective

The development of immune modulatory factor-loaded nanoparticles may enhance vaccine efficacy. A growing number of Nano Particle-based drugs will be exploited in this emerging field thanks to proteomics research on cancer origin, Multi Drug Resistance (MDR), and occurrence. Most Nanoparticle-based drugs are still in the exploratory stages of their development, and only a few are in clinical trials. An in-depth understanding of Nanoparticle-based drug delivery, cellular and physiological factors influencing Nanoparticle-based drug delivery, and Enhanced Permeability and Retention (EPR) mechanisms in the human body is necessary for rational nanotechnology design. According to the evidence cited above, clinical translation of Nanoparticle-based cancer therapies will be revolutionised.

CONCLUSION

The delivery of small molecules for the detection, diagnosis, and treatment of cancer is made possible by nanotechnology. Nanoparticles have exceptional characteristics that make them helpful in treating a wide range of cancer types. When compared with conventional drugs, Drug delivery system based on nanoparticles has improved pharmacokinetics, biocompatibility, and tumour-targeting characteristics. A significant benefit of nanoparticles is their ability to combine therapies to help lower the likelihood of Multi Drug Resistance (MDR), the delivery of drugs has improved dramatically with the use of polymeric nanoparticles, metallic nanoparticles, and hybrid nanoparticles in recent years. The properties of therapeutic agents and the properties of Nano platforms should be taken into consideration by researchers. *In vitro* models are not always perfect replicas of *in vivo* stages, immune toxicity is a problem, and long-term toxicity is a concern. Despite "Nano vaccines" and " Artificial Antigen Presenting Cells (aAPCs)" being more effective than conventional immunotherapy, their clinical efficacy is substandard. These new methods should be tested for safety and tolerance.

ACKNOWLEDGEMENT

The author acknowledges the Principal of Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, for all support.

FUNDING

Nil

ABBREVIATIONS

Tumour Micro Environment (TME), Dermatologic Adverse Events (dAEs), Reticulo Endothelial System (RES), Extracellular Fluid (ECF), Extracellular Matrix (ECM), Enhanced Permeability and Retention (EPR), Cremophor EL (CrEL), Metastatic Breast Cancer (MBC), Epidermal Growth Factor Receptor (EGFR), Polyethylene Glycol (PEG), Squamous Cell Carcinoma (SCC), Vascular Cell Adhesion Molecule-1 (VCAM-1), Poly Methyl Methacrylate (PMMA), Multi Drug Resonance (MDR), Adenosine Tri Phosphate(ATP), Blood-Brain Barrier (BBB), N-(2-Hydroxy Propyl) Meth Acrylamide (HPMA), Human Epidermal Growth Factor Receptor (HER2), The Food and Drug Administration (FDA), Magnetic Resonance Imaging (MRI), Deoxy Ribonucleic Acid (DNA), Kinase Insert Domain Receptors (KDR), Poly (Lactic-Co-Glycolic Acid) (PLGA), Sodium Dodecyl-Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE), Liquid Chromatography–Mass Spectrometry (LC-MS), Post-Translational Modifications (PTMs), Micro Physiological Systems (MPS), Chimeric Antigen Receptor Therapies (CAR-T), Artificial Antigen-Presenting Cells (aAPCs), Antigen-Presenting Cells (APC), Tumor-Associated Adipocytes (TAAs), Major Histocompatibility Complex (MHC), Myeloid-Derived Suppressor Cells (MDSCs), Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), Phase Change Materials (PCMs), Multinuclear Phagocytic System (MPS), Tumor-Associated Macrophages (TAMs)

AUTHORS CONTRIBUTIONS

R Lokeshvar: Conceptualization, Writing–Original draft, R Velmurugan: Data Curation, Writing–Review and Editing, Supervision.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in this article

REFERENCES

1. Wu S, Zhu W, Thompson P, Hannun YA. Evaluating intrinsic and non-intrinsic cancer risk factors. Nat Commun. 2018;9(1):3490. doi: 10.1038/s41467-018-05467-z, PMID 30154431.
2. Quazi S. Telomerase gene therapy: a remission toward cancer. Med Oncol. 2022;39(6):105. doi: 10.1007/s12032-022-01702-2, PMID 35429243.
3. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res. 2008;25(9):2097-116. doi: 10.1007/s11095-008-9661-9, PMID 18626751.

4. Park W, Heo YJ, Han DK. New opportunities for nanoparticles in cancer immunotherapy. Biomater Res. 2018;22:24. doi: 10.1186/s40824-018-0133-y, PMID 30275967.
5. Jovcevska I, Muyldermans S. The therapeutic potential of nanobodies. BioDrugs. 2020;34(1):11-26. doi: 10.1007/s40259-019-00392-z, PMID 31686399.
6. Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. Nat Rev Immunol. 2008;8(1):59-73. doi: 10.1038/nri2216, PMID 18097448.
7. Chan HK, Ismail S. Side effects of chemotherapy among cancer patients in a Malaysian general hospital: experiences, perceptions and informational needs from clinical pharmacists. Asian Pac J Cancer Prev. 2014;15(13):5305-9. doi: 10.7314/apjcp.2014.15.13.5305, PMID 25040993.
8. Quazi S. Artificial intelligence and machine learning in precision and genomic medicine. Med Oncol. 2022;39(8):120. doi: 10.1007/s12032-022-01711-1, PMID 35704152.
9. Mahapatro A, Singh DK. Biodegradable nanoparticles are excellent vehicle for site-directed *in vivo* delivery of drugs and vaccines. J Nanobiotechnology. 2011;9:55. doi: 10.1186/1477-3155-9-55, PMID 22123084.
10. Kroemer G, Zitvogel L. Cancer immunotherapy in 2017: the breakthrough of the microbiota. Nat Rev Immunol. 2018;18(2):87-8. doi: 10.1038/nri.2018.4, PMID 29379189.
11. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat Rev Cancer. 2008;8(4):299-308. doi: 10.1038/nrc2355, PMID 18354418.
12. Melero I, Rouzaut A, Motz GT, Coukos G. T-cell and NK-cell infiltration into solid tumors: a key limiting factor for efficacious cancer immunotherapy. Cancer Discov. 2014;4(5):522-6. doi: 10.1158/2159-8290.CD-13-0985, PMID 24795012.
13. Lacouture M, Sibaud V. Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. Am J Clin Dermatol. 2018;19Suppl 1:31-9. doi: 10.1007/s40257-018-0384-3, PMID 30374901.
14. Dadwal A, Baldi A, Kumar Narang R. Nanoparticles as carriers for drug delivery in cancer. Artif Cells Nanomed Biotechnol. 2018;46Suppl2:295-305. doi: 10.1080/21691401.2018.1457039, PMID 30043651.
15. Palazzolo S, Bayda S, Hadla M, Caligiuri I, Corona G, Toffoli G. The clinical translation of organic nanomaterials for cancer therapy: a focus on polymeric nanoparticles, micelles, liposomes and exosomes. Curr Med Chem. 2018;25(34):4224-68. doi: 10.2174/0929867324666170830113755, PMID 28875844.
16. Li W, Zhang H, Assaraf YG, Zhao K, Xu X, Xie J. Overcoming ABC transporter-mediated multidrug resistance: molecular mechanisms and novel therapeutic drug strategies. Drug Resist Updat. 2016;27:14-29. doi: 10.1016/j.drup.2016.05.001, PMID 27449595.
17. Boisseau P, Loubaton B. Nanomedicine, nanotechnology in medicine. C R Phys. 2011;12(7):620-36. doi: 10.1016/j.crhy.2011.06.001.
18. Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L. Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. Chem Rev. 2008;108(6):2064-110. doi: 10.1021/cr068445e, PMID 18543879.
19. Tiwari JN, Tiwari RN, Kim KS. Zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructured materials for advanced electrochemical energy devices. Prog Mater Sci. 2012;57(4):724-803. doi: 10.1016/j.pmatsci.2011.08.003.
20. Shin WK, Cho J, Kannan AG, Lee YS, Kim DW. Cross-linked composite gel polymer electrolyte using mesoporous methacrylate-functionalized SiO2 nanoparticles for lithium-ion polymer batteries. Sci Rep. 2016;6:26332. doi: 10.1038/srep26332, PMID 27189842.
21. Prokop A, Davidson JM. Nanovehicular intracellular delivery systems. J Pharm Sci. 2008;97(9):3518-90. doi: 10.1002/jps.21270, PMID 18200527.
22. Yang Q, Jones SW, Parker CL, Zamboni WC, Bear JE, Lai SK. Evading immune cell uptake and clearance requires PEG grafting at densities substantially exceeding the minimum for brush conformation. Mol Pharm. 2014;11(4):1250-8. doi: 10.1021/mp400703d, PMID 24521246.
23. El SAM. Green synthesis of metal and metal oxide nanoparticles from plant leaf extracts and their applications: a review. Green Process Synth; 2020.
24. Lassalle V, Ferreira ML. PLA nano and microparticles for drug delivery: an overview of the methods of preparation. Macromol Biosci. 2007;7(6):767-83. doi: 10.1002/mabi.200700022, PMID 17541922.
25. Omidi Y, Barar J. Targeting tumor microenvironment: crossing tumor interstitial fluid by multifunctional nanomedicines. BioImpacts. 2014;4(2):55-67. doi: 10.5681/bi.2014.021, PMID 25035848.
26. Barar J, Omidi Y. Dysregulated pH in tumor microenvironment checkmates cancer therapy. BioImpacts. 2013;3(4):149-62. doi: 10.5681/bi.2013.036, PMID 24455478.
27. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res. 1986;46:6387-92. PMID 2946403.
28. Torchilin V. Tumor delivery of macromolecular drugs based on the EPR effect. Adv Drug Deliv Rev. 2011;63(3):131-5. doi: 10.1016/j.addr.2010.03.011, PMID 20304019.
29. Bates DO, Hillman NJ, Williams B, Neal CR, Pocock TM. Regulation of microvascular permeability by vascular endothelial growth factors. J Anat. 2002;200(6):581-97. doi: 10.1046/j.1469-7580.2002.00066.x, PMID 12162726.
30. Jain RK. The next frontier of molecular medicine: delivery of therapeutics. Nat Med. 1998;4(6):655-7. doi: 10.1038/nm0698-655, PMID 9623964.
31. Hobbs SK, Monsky WL, Yuan F, Roberts WG, Griffith L, Torchilin VP. Regulation of transport pathways in tumor vessels: role of tumor type and microenvironment. Proc Natl Acad Sci USA. 1998;95(8):4607-12. doi: 10.1073/pnas.95.8.4607, PMID 9539785.
32. Swartz MA, Fleury ME. Interstitial flow and its effects in soft tissues. Annu Rev Biomed Eng. 2007;9:229-56. doi: 10.1146/annurev.bioeng.9.060906.151850, PMID 17459001.
33. 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, PMID 14973470.
34. Attia MF, Anton N, Wallyn J, Omran Z, Vandamme TF. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. J Pharm Pharmacol. 2019;71(8):1185-98. doi: 10.1111/jphp.13098, PMID 31049986.
35. Pelicano H, Martin DS, Xu RH, Huang P. Glycolysis inhibition for anticancer treatment. Oncogene. 2006;25(34):4633-46. doi: 10.1038/sj.onc.1209597, PMID 16892078.
36. Lim EK, Chung BH, Chung SJ. Recent advances in pH-sensitive polymeric nanoparticles for smart drug delivery in cancer therapy. Curr Drug Targets. 2018;19(4):300-17. doi: 10.2174/1389450117666160602202339, PMID 27262486.
37. Karthikhaeyan TR, Periasamy AK, Sharma A. Correlation of CA 15.3 levels with metastasis in breast cancer. Asian J Pharm Clin Res. 2023;16(9):42-4. doi: 10.22159/ajpcr.2023v16i9.49016.
38. Miele E, Spinelli GP, Miele E, Tomao F, Tomao S. Albumin-bound formulation of paclitaxel (Abraxane ABI-007) in the treatment of breast cancer. Int J Nanomedicine. 2009;4:99-105. doi: 10.2147/ijn.s3061, PMID 19516888.
39. Kim DW, Kim SY, Kim HK, Kim SW, Shin SW, Kim JS. Multicenter phase II trial of genexol-PM, a novel cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. Ann Oncol. 2007;18(12):2009-14. doi: 10.1093/annonc/mdm374, PMID 17785767.
40. Mukwaya G, Forssen EA, Schmidt P. DaunoXome® (liposomal daunorubicin) for first-line treatment of advanced, HIV-related Kaposi's sarcoma. Long circulating liposomes. Old Drugs, New Therapeutics; 1998.
41. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol. 2007;2(12):751-60. doi: 10.1038/nnano.2007.387, PMID 18654426.

42. Kamaly N, Xiao Z, Valencia PM, Radovic Moreno AF, Farokhzad OC. Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. Chem Soc Rev. 2012;41(7):2971-3010. doi: 10.1039/c2cs15344k, PMID 22388185.
43. Byrne JD, Betancourt T, Brannon Peppas L. Active targeting schemes for nanoparticle systems in cancer therapeutics. Adv Drug Deliv Rev. 2008;60(15):1615-26. doi: 10.1016/j.addr.2008.08.005, PMID 18840489.
44. Saha RN, Vasanthakumar S, Bende G, Snehalatha M. Nanoparticulate drug delivery systems for cancer chemotherapy. Mol Membr Biol. 2010;27(7):215-31. doi: 10.3109/09687688.2010.510804, PMID 20939772.
45. Amreddy N, Muralidharan R, Babu A, Mehta M, Johnson EV, Zhao YD. Tumor-targeted and pH-controlled delivery of doxorubicin using gold nanorods for lung cancer therapy. Int J Nanomedicine. 2015;10:6773-88. doi: 10.2147/IJN.S93237, PMID 26604751.
46. Santi M, Maccari G, Mereghetti P, Voliani V, Rocchiccioli S, Ucciferri N. Rational design of a transferrin-binding peptide sequence tailored to targeted nanoparticle internalization. Bioconjug Chem. 2017;28(2):471-80. doi: 10.1021/acs.bioconjchem.6b00611, PMID 27977155.
47. Warburg O. On the origin of cancer cells. Science. 1956;123(3191):309-14. doi: 10.1126/science.123.3191.309, PMID 13298683.
48. Jiang W, Kim BYS, Rutka JT, Chan WC. Nanoparticle-mediated cellular response is size-dependent. Nat Nanotechnol. 2008;3(3):145-50. doi: 10.1038/nnano.2008.30, PMID 18654486.
49. Reuveni T, Motiei M, Romman Z, Popovtzer A, Popovtzer R. Targeted gold nanoparticles enable molecular CT imaging of cancer: an *in vivo* study. Int J Nanomedicine. 2011;6:2859-64. doi: 10.2147/IJN.S25446, PMID 22131831.
50. Reynolds JG, Geretti E, Hendriks BS, Lee H, Leonard SC, Klinz SG. HER2-targeted liposomal doxorubicin displays enhanced anti-tumorigenic effects without associated cardiotoxicity. Toxicol Appl Pharmacol. 2012;262(1):1-10. doi: 10.1016/j.taap.2012.04.008, PMID 22676972.
51. Pan H, Myerson JW, Hu L, Marsh JN, Hou K, Scott MJ. Programmable nanoparticle functionalization for *in vivo* targeting. FASEB J. 2013;27(1):255-64. doi: 10.1096/fj.12-218081, PMID 23047896.
52. Low PS, Kularatne SA. Folate-targeted therapeutic and imaging agents for cancer. Curr Opin Chem Biol. 2009;13(3):256-62. doi: 10.1016/j.cbpa.2009.03.022, PMID 19419901.
53. Muralidharan R, Babu A, Amreddy N, Basalingappa K, Mehta M, Chen A. Folate receptor-targeted nanoparticle delivery of HuR-RNAi suppresses lung cancer cell proliferation and migration. J Nanobiotechnology. 2016;14(1):47. doi: 10.1186/s12951-016-0201-1, PMID 27328938.
54. Samadian H, Hosseini Nami S, Kamrava SK, Ghaznavi H, Shakeri Zadeh A. Folate-conjugated gold nanoparticle as a new nano platform for targeted cancer therapy. J Cancer Res Clin Oncol. 2016;142(11):2217-29. doi: 10.1007/s00432-016-2179-3, PMID 27209529.
55. Amreddy N, Babu A, Muralidharan R, Panneerselvam J, Srivastava A, Ahmed R. Recent advances in nanoparticle-based cancer drug and gene delivery. Adv Cancer Res. 2018;137:115-70. doi: 10.1016/bs.acr.2017.11.003, PMID 29405974.
56. Masood F. Polymeric nanoparticles for targeted drug delivery system for cancer therapy. Mater Sci Eng C Mater Biol Appl. 2016;60:569-78. doi: 10.1016/j.msec.2015.11.067, PMID 26706565.
57. Vijayan V, Reddy KR, Sakthivel S, Swetha C. Optimization and charaterization of repaglinide biodegradable polymeric nanoparticle loaded transdermal patchs: *in vitro* and *in vivo* studies. Colloids Surf B Biointerfaces. 2013;111:150-5. doi: 10.1016/j.colsurfb.2013.05.020, PMID 23792547.
58. Elsabahy M, Wooley KL. Design of polymeric nanoparticles for biomedical delivery applications. Chem Soc Rev. 2012;41(7):2545-61. doi: 10.1039/c2cs15327k, PMID 22334259.
59. Andronescu E, Grumezescu AM. Nanostructures for drug delivery. Nanostruct Drug Deliv; 2017.
60. Bernardi A, Braganhol E, Jager E, Figueiro F, Edelweiss MI, Pohlmann AR. Indomethacin-loaded nanocapsules treatment reduces *in vivo* glioblastoma growth in a rat glioma model. Cancer Lett. 2009;281(1):53-63. doi: 10.1016/j.canlet.2009.02.018, PMID 19286307.
61. Wang X, Yang L, Chen ZG, Shin DM. Application of nanotechnology in cancer therapy and imaging. CA Cancer J Clin. 2008;58(2):97-110. doi: 10.3322/CA.2007.0003, PMID 18227410.
62. Kim KY. Nanotechnology platforms and physiological challenges for cancer therapeutics. Nanomedicine. 2007;3(2):103-10. doi: 10.1016/j.nano.2006.12.002, PMID 17442621.
63. Lim J, Kostiainen M, Maly J, da Costa VC, Annunziata O, Pavan GM. Synthesis of large dendrimers with the dimensions of small viruses. J Am Chem Soc. 2013;135(12):4660-3. doi: 10.1021/ja400432e, PMID 23398590.
64. Lo ST, Kumar A, Hsieh JT, Sun X. Dendrimer nanoscaffolds for potential theranostics of prostate cancer with a focus on radiochemistry. Mol Pharm. 2013;10(3):793-812. doi: 10.1021/mp3005325, PMID 23294202.
65. Kukowska Latallo JF, Candido KA, Cao Z, Nigavekar SS, Majoros IJ, Thomas TP. Nanoparticle targeting of anticancer drug improves therapeutic response in an animal model of human epithelial cancer. Cancer Res. 2005;65(12):5317-24. doi: 10.1158/0008-5472.CAN-04-3921, PMID 15958579.
66. 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, PMID 33795712.
67. Gyorgy B, Szabo TG, Pasztoi M, Pal Z, Misjak P, Aradi B. Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles. Cell Mol Life Sci. 2011;68(16):2667-88. doi: 10.1007/s00018-011-0689-3, PMID 21560073.
68. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 2013;200(4):373-83. doi: 10.1083/jcb.201211138, PMID 23420871.
69. Hadla M, Palazzolo S, Corona G, Caligiuri I, Canzonieri V, Toffoli G. Exosomes increase the therapeutic index of doxorubicin in breast and ovarian cancer mouse models. Nanomedicine (Lond). 2016;11(18):2431-41. doi: 10.2217/nnm-2016-0154, PMID 27558906.
70. Wei W, Ao Q, Wang X, Cao Y, Liu Y, Zheng SG. Mesenchymal stem cell-derived exosomes: a promising biological tool in nanomedicine. Front Pharmacol. 2020;11:590470. doi: 10.3389/fphar.2020.590470, PMID 33716723.
71. Samad A, Sultana Y, Aqil M. Liposomal drug delivery systems: an update review. Curr Drug Deliv. 2007;4(4):297-305. doi: 10.2174/156720107782151269, PMID 17979650.
72. 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):763-70. doi: 10.2174/1567201811666140910122945, PMID 25213073.
73. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Deliv Rev. 2013;65(1):36-48. doi: 10.1016/j.addr.2012.09.037, PMID 23036225.
74. Zhang L, Gu FX, Chan JM, Wang A, Langer R, Farokhzad O. Nanoparticles in medicine: therapeutic applications and developments. Clin Pharmacol Ther. 2008;83(5):761-9. doi: 10.1038/sj.clpt.6100400.
75. Wang X, Liu X, Li Y, Wang P, Feng X, Liu Q. Sensitivity to antitubulin chemotherapeutics is potentiated by a photoactivable nanoliposome. Biomaterials. 2017;141:50-62. doi: 10.1016/j.biomaterials.2017.06.034, PMID 28667899.
76. Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer. 2005;5(3):161-71. doi: 10.1038/nrc1566, PMID 15738981.
77. 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, PMID 16027517.
78. Uner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J Nanomedicine. 2007;2(3):289-300. PMID 18019829.

79. Ali ES, Sharker SM, Islam MT, Khan IN, Shaw S, Rahman MA. Targeting cancer cells with nanotherapeutics and nanodiagnostics: current status and future perspectives. Semin Cancer Biol. 2021;69:52-68. doi: 10.1016/j.semcancer.2020.01.011, PMID 32014609.
80. Priyanka P, Sri Rekha M, Devi AS. Review on formulation and evaluation of solid lipid nanoparticles for vaginal application. Int J Pharm Pharm Sci. 2022:1-8. doi: 10.22159/ijpps.2022v14i1.42595.
81. 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, PMID 16472996.
82. Ma P, Dong X, Swadley CL, Gupte A, Leggas M, Ledebur HC. Development of idarubicin and doxorubicin solid lipid nanoparticles to overcome Pgp-mediated multiple drug resistance in leukemia. J Biomed Nanotechnol. 2009;5(2):151-61. doi: 10.1166/jbn.2009.1021, PMID 20055093.
83. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech. 2015;5(2):123-7. doi: 10.1007/s13205-014-0214-0, PMID 28324579.
84. Du M, Yang Z, Lu W, Wang B, Wang Q, Chen Z. Design and development of spirulina polysaccharide-loaded nanoemulsions with improved the antitumor effects of paclitaxel. J Microencapsul. 2020;37(6):403-12. doi: 10.1080/02652048.2020.1767224, PMID 32401077.
85. Dianzani C, Monge C, Miglio G, Serpe L, Martina K, Cangemi L. Nanoemulsions as delivery systems for poly-chemotherapy aiming at melanoma treatment. Cancers (Basel). 2020;12(5);1198. doi: 10.3390/cancers12051198, PMID 32397484.
86. Gorain B, Choudhury H, Nair AB, Dubey SK, Kesharwani P. Theranostic application of nanoemulsions in chemotherapy. Drug Discov Today. 2020;25(7):1174-88. doi: 10.1016/j.drudis.2020.04.013, PMID 32344042.
87. Subramanian S, Singireddy A, Krishnamoorthy K. Nanosponges: a novel class of drug delivery system-review. J Pharm Pharm Sci. 2012;15(1):103-11. doi: 10.18433/J3K308.
88. Ansari AK, J Torne S, Pradeep R, Vavia P. Paclitaxel loaded nanosponges: *in vitro* characterization and cytotoxicity study on MCF-7 cell line culture. Curr Drug Deliv. 2011 Mar;8(2):194-202. doi: 10.2174/156720111794479934, PMID 21235471.
89. Swaminathan S, Pastero L, Serpe L, Trotta F, Vavia P, Aquilano D. Cyclodextrin-based nanosponges encapsulating camptothecin: physicochemical characterization, stability and cytotoxicity. Eur J Pharm Biopharm. 2010;74(2):193-201. doi: 10.1016/j.ejpb.2009.11.003, PMID 19900544.
90. Ou L, Song B, Liang H, Liu J, Feng X, Deng B. Toxicity of graphene-family nanoparticles: A general review of the origins and mechanisms. Part Fibre Toxicol. 2016;13(1):57. doi: 10.1186/s12989-016-0168-y, PMID 27799056.
91. Krishna KV, Menard Moyon C, Verma S, Bianco A. Graphene-based nanomaterials for nanobiotechnology and biomedical applications. Nanomedicine (Lond). 2013;8(10):1669-88. doi: 10.2217/nnm.13.140, PMID 24074389.
92. Liu J, Dong J, Zhang T, Peng Q. Graphene-based nanomaterials and their potentials in advanced drug delivery and cancer therapy. J Control Release. 2018;286:64-73. doi: 10.1016/j.jconrel.2018.07.034, PMID 30031155.
93. Tao Y, Zhu L, Zhao Y, Yi X, Zhu L, Ge F. Nano-graphene oxide-manganese dioxide nanocomposites for overcoming tumor hypoxia and enhancing cancer radioisotope therapy. Nanoscale. 2018;10(11):5114-23. doi: 10.1039/c7nr08747k, PMID 29487939.
94. Zhang X, Tian W, Cai X, Wang X, Dang W, Tang H. Hydrazinocurcumin encapsuled nanoparticles "re-educate" tumor-associated macrophages and exhibit anti-tumor effects on breast cancer following STAT3 suppression. PLOS ONE. 2013;8(6):e65896. doi: 10.1371/journal.pone.0065896, PMID 23825527.
95. Fiorillo M, Verre AF, Iliut M, Peiris Pages M, Ozsvari B, Gandara R. Graphene oxide selectively targets cancer stem cells, across multiple tumor types: implications for non-toxic cancer treatment, via "differentiation-based nano-therapy" Oncotarget. 2015;6(6):3553-62. doi: 10.18632/oncotarget.3348, PMID 25708684.
96. Chen Z, Mao R, Liu Y. Fullerenes for cancer diagnosis and therapy: preparation, biological and clinical perspectives. Curr Drug Metab. 2012;13(8):1035-45. doi: 10.2174/138920012802850128, PMID 22380017.
97. Mroz P, Tegos GP, Gali H, Wharton T, Sarna T, Hamblin MR. Photodynamic therapy with fullerenes. Photochem Photobiol Sci. 2007;6(11):1139-49. doi: 10.1039/b711141j, PMID 17973044.
98. Tabata Y, Murakami Y, Ikada Y. Photodynamic effect of polyethylene glycol-modified fullerene on tumor. Japan J Cancer Res. 1997;88(11):1108-16. doi: 10.1111/j.1349-7006.1997.tb00336.x, PMID 9439687.
99. Heister E, Neves V, Tîlmaciu C, Lipert K, Beltran VS, Coley HM. Triple functionalisation of single-walled carbon nanotubes with doxorubicin, a monoclonal antibody, and a fluorescent marker for targeted cancer therapy. Carbon. 2009;47(9):2152-60. doi: 10.1016/j.carbon.2009.03.057.
100. Jamieson T, Bakhshi R, Petrova D, Pocock R, Imani M, Seifalian AM. Biological applications of quantum dots. Biomaterials. 2007;28(31):4717-32. doi: 10.1016/j.biomaterials.2007.07.014, PMID 17686516.
101. Bagalkot V, Zhang L, Levy Nissenbaum E, Jon S, Kantoff PW, Langer R. 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):3065-70. doi: 10.1021/nl071546n, PMID 17854227.
102. Joshi V, Sulthana F, Ramadas D. Oral delivery of silver nanoparticles-a review. Asian J Pharm Clin Res. 2021;14(11):9-14. doi: 10.22159/ajpcr.2021.v14i11.42986.
103. Xu ZP, Zeng QH, Lu GQ. Inorganic nanoparticles as carriers for efficient cellular delivery. Chem Eng Sci. 2006;61(3):1027-40. doi; 10.1016/j.ces.2005.06.019.
104. Zhao X, Hilliard LR, Mechery SJ, Wang Y, Bagwe RP, Jin S. A rapid bioassay for single bacterial cell quantitation using bioconjugated nanoparticles. Proc Natl Acad Sci USA. 2004;101(42):15027-32. doi: 10.1073/pnas.0404806101, PMID 15477593.
105. Mousa SA, Bharali DJ. Nanotechnology-based detection and targeted therapy in cancer: nano-bio paradigms and applications. Cancers (Basel). 2011;3(3):2888-903. doi: 10.3390/cancers3032888, PMID 24212938.
106. Schroeder A, Heller DA, Winslow MM, Dahlman JE, Pratt GW, Langer R. Treating metastatic cancer with nanotechnology. Nat Rev Cancer. 2011;12(1):39-50. doi: 10.1038/nrc3180, PMID 22193407.
107. Castaneda RT, Khurana A, Khan R, Daldrup Link HE. Labeling stem cells with ferumoxytol, an FDA-approved iron oxide nanoparticle. J Vis Exp. 2011;(57):e3482. doi: 10.3791/3482, PMID 22083287.
108. Basoglu H, Goncu B, Akbas F. Magnetic nanoparticle-mediated gene therapy to induce Fas apoptosis pathway in breast cancer. Cancer Gene Ther. 2018;25(5-6):141-7. doi: 10.1038/s41417-018-0017-2, PMID 29593359.
109. Meng J, Fan J, Galiana G, Branca RT, Clasen PL, Ma S. LHRH-functionalized superparamagnetic iron oxide nanoparticles for breast cancer targeting and contrast enhancement in MRI. Mater Sci Eng C. 2009;29(4):1467-79. doi: 10.1016/j.msec.2008.09.039.
110. Hoopes PJ, Moodie KL, Petryk AA, Petryk JD, Sechrist S, Gladstone DJ. Hypo-fractionated radiation, magnetic nanoparticle hyperthermia and a viral immunotherapy treatment of spontaneous canine cancer. Proc SPIE Int Soc Opt Eng. 2017;10066. doi: 10.1117/12.2256213, PMID 29203951.
111. 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):803-9. doi: 10.1111/jop.12921, PMID 31309616.
112. Maurya A, Singh AK, Mishra G, Kumari K, Rai A, Sharma B. Strategic use of nanotechnology in drug targeting and its consequences on human health: a focused review. Interv Med Appl Sci. 2019;11(1):38-54. doi: 10.1556/1646.11.2019.04.
113. Khosravi Darani K, Mozafari MR, Rashidi L, Mohammadi M. Calcium-based non-viral gene delivery: an overview of methodology and applications. Acta Med Iran. 2010;48(3):133-41. PMID 21137647.

114. Mozafari MR, Reed CJ, Rostron C. Construction of stable anionic liposome-plasmid particles using the heating method: a preliminary investigation. Cell Mol Biol Lett. 2002;7(3):923-7. PMID 12378277.
115. Mozafari MR, Reed CJ, Rostron C. Cytotoxicity evaluation of anionic nanoliposomes and nanolipoplexes prepared by the heating method without employing volatile solvents and detergents. Pharmazie. 2007;62(3):205-9. PMID 17416197.
116. Katragadda CS, Choudhury PK, Murthy PN. Nanoparticles as nonviral gene delivery vectors. Indian J Pharm Educ Res. 2010;44(2):109-20.
117. Kneuer C, Sameti M, Bakowsky U, Schiestel T, Schirra H, Schmidt H. A nonviral DNA delivery system based on surface-modified silica-nanoparticles can efficiently transfect cells *in vitro*. Bioconjug Chem. 2000;11(6):926-32. doi: 10.1021/bc0000637, PMID 11087343.
118. Gary Bobo M, Hocine O, Brevet D, Maynadier M, Raehm L, Richeter S. Cancer therapy improvement with mesoporous silica nanoparticles combining targeting, drug delivery and PDT. Int J Pharm. 2012;423(2):509-15. doi: 10.1016/j.ijpharm.2011.11.045, PMID 22178618.
119. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N. Drug resistance in cancer: an overview. Cancers (Basel). 2014;6(3):1769-92. doi: 10.3390/cancers6031769, PMID 25198391.
120. Schneider E, Hunke S. ATP-binding-cassette (ABC) transport systems: functional and structural aspects of the ATP-hydrolyzing subunits/domains. FEMS Microbiol Rev. 1998;22(1):1-20. doi: 10.1111/j.1574-6976.1998.tb00358.x, PMID 9640644.
121. Allen JD, Brinkhuis RF, Van Deemter L, Wijnholds J, Schinkel AH. Extensive contribution of the multidrug transporters P-glycoprotein and Mrp1 to basal drug resistance. Cancer Res. 2000;60(20):5761-6. PMID 11059771.
122. Chintamani SJP, Singh JP, Mittal MK, Saxena S, Bansal A, Bhatia A. Role of p-glycoprotein expression in predicting response to neoadjuvant chemotherapy in breast cancer-a prospective clinical study. World J Surg Oncol. 2005;3:61. doi: 10.1186/1477-7819-3-61, PMID 16164742.
123. Agarwal R, Kaye SB. Ovarian cancer: strategies for overcoming resistance to chemotherapy. Nat Rev Cancer. 2003;3(7):502-16. doi: 10.1038/nrc1123, PMID 12835670.
124. Murakami M, Cabral H, Matsumoto Y, Wu S, Kano MR, Yamori T. Improving drug potency and efficacy by nanocarrier-mediated subcellular targeting. Sci Transl Med. 2011;3(64):64ra2. doi: 10.1126/scitranslmed.3001385, PMID 21209412.
125. Yu B, Song N, Hu H, Chen G, Shen Y, Cong H. A degradable triple temperature-, pH and redox-responsive drug system for cancer chemotherapy. J Biomed Mater Res A. 2018;106(12):3203-10. doi: 10.1002/jbm.a.36515, PMID 30242956.
126. Kundu M, Sadhukhan P, Ghosh N, Chatterjee S, Manna P, Das J. pH-responsive and targeted delivery of curcumin via phenylboronic acid-functionalized ZnO nanoparticles for breast cancer therapy. J Adv Res. 2019;18:161-72. doi: 10.1016/j.jare.2019.02.036, PMID 31032117.
127. Cuvier C, Roblot Treupel L, Millot JM, Lizard G, Chevillard S, Manfait M. Doxorubicin-loaded nanospheres bypass tumor cell multidrug resistance. Biochem Pharmacol. 1992;44(3):509-17. doi: 10.1016/0006-2952(92)90443-m, PMID 1354963.
128. Emilienne Soma C, Dubernet C, Bentolila D, Benita S, Couvreur P. Reversion of multidrug resistance by co-encapsulation of doxorubicin and cyclosporin a in polyalkylcyanoacrylate nanoparticles. Biomaterials. 2000;21(1):1-7. doi: 10.1016/S0142-9612(99)00125-8.
129. Zhang S, Guo N, Wan G, Zhang T, Li C, Wang 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 Nanobiotechnology. 2019;17(1):109. doi: 10.1186/s12951-019-0540-9, PMID 31623608.
130. He J, Gong C, Qin J, Li M, Huang S. Cancer cell membrane decorated silica nanoparticle loaded with miR495 and doxorubicin to overcome drug resistance for effective lung cancer therapy. Nanoscale Res Lett. 2019;14(1):339. doi: 10.1186/s11671-019-3143-3, PMID 31705398.
131. Viktorsson K, Lewensohn R, Zhivotovsky B. Apoptotic pathways and therapy resistance in human malignancies. Adv Cancer Res. 2005;94:143-96. doi: 10.1016/S0065-230X(05)94004-9, PMID 16096001.
132. Choi KY, Correa S, Min J, Li J, Roy S, Laccetti KH. Binary targeting of siRNA to hematologic cancer cells *in vivo* using layer-by-layer nanoparticles. Adv Funct Mater. 2019;29(20):1900018. doi: 10.1002/adfm.201900018, PMID 31839764.
133. Fan L, Li F, Zhang H, Wang Y, Cheng C, Li X. Co-delivery of PDTC and doxorubicin by multifunctional micellar nanoparticles to achieve active targeted drug delivery and overcome multidrug resistance. Biomaterials. 2010;31(21):5634-42. doi: 10.1016/j.biomaterials.2010.03.066, PMID 20430433.
134. Zhao MD, Li JQ, Chen FY, Dong W, Wen LJ, Fei WD. Co-delivery of curcumin and paclitaxel by "core-shell" targeting amphiphilic copolymer to reverse resistance in the treatment of ovarian cancer. Int J Nanomedicine. 2019;14:9453-67. doi: 10.2147/IJN.S224579, PMID 31819443.
135. Van Vlerken LE, Duan Z, Little SR, Seiden MV, Amiji MM. Augmentation of therapeutic efficacy in drug-resistant tumor models using ceramide coadministration in temporal-controlled polymer-blend nanoparticle delivery systems. AAPS J. 2010;12(2):171-80. doi: 10.1208/s12248-010-9174-4, PMID 20143195.
136. Khiste SK, Liu Z, Roy KR, Uddin MB, Hosain SB, Gu X. Ceramide-riboside nanomicelles, a potential therapeutic approach to target cancers carrying p53 missense mutations. Mol Cancer Ther. 2020;19(2):564-74. doi: 10.1158/1535-7163.MCT-19-0366, PMID 31645443.
137. Choi SH, Jin SE, Lee MK, Lim SJ, Park JS, Kim BG. Novel cationic solid lipid nanoparticles enhanced p53 gene transfer to lung cancer cells. Eur J Pharm Biopharm. 2008;68(3):545-54. doi: 10.1016/j.ejpb.2007.07.011, PMID 17881199.
138. Prabha S, Labhasetwar V. Nanoparticle-mediated wild-type p53 gene delivery results in sustained antiproliferative activity in breast cancer cells. Mol Pharm. 2004;1(3):211-9. doi: 10.1021/mp049970+, PMID 15981924.
139. Cheng H, Wu Z, Wu C, Wang X, Liow SS, Li Z. Overcoming STC2 mediated drug resistance through drug and gene co-delivery by PHB-PDMAEMA cationic polyester in liver cancer cells. Mater Sci Eng C Mater Biol Appl. 2018;83:210-7. doi: 10.1016/j.msec.2017.08.075, PMID 29208281.
140. Zhao Y, Huan ML, Liu M, Cheng Y, Sun Y, Cui H. Doxorubicin and resveratrol co-delivery nanoparticle to overcome doxorubicin resistance. Sci Rep. 2016;6:35267. doi: 10.1038/srep35267, PMID 27731405.
141. Singh SK, Lillard JW, Singh R. Reversal of drug resistance by planetary ball milled (PBM) nanoparticle loaded with resveratrol and docetaxel in prostate cancer. Cancer Lett. 2018;427:49-62. doi: 10.1016/j.canlet.2018.04.017, PMID 29678549.
142. Jing X, Yang F, Shao C, Wei K, Xie M, Shen H. Role of hypoxia in cancer therapy by regulating the tumor microenvironment. Mol Cancer. 2019;18(1):157. doi: 10.1186/s12943-019-1089-9, PMID 31711497.
143. Zhang J, Zhang Q, Lou Y, Fu Q, Chen Q, Wei T. Hypoxia-inducible factor-1α/interleukin-1β signaling enhances hepatoma epithelial–mesenchymal transition through macrophages in a hypoxic-inflammatory microenvironment. Hepatology. 2018;67(5):1872-89. doi: 10.1002/hep.29681, PMID 29171040.
144. Semenza GL. Evaluation of HIF-1 inhibitors as anticancer agents. Drug Discov Today. 2007;12(19-20):853-9. doi: 10.1016/j.drudis.2007.08.006, PMID 17933687.
145. Long Q, Lin T Yin, Huang Y. Image-guided photo-therapeutic nanoporphyrin synergized HSP90 inhibitor in patient-derived xenograft bladder cancer model. Nanomedicine. 2018 Apr;14(3):789-99. doi: 10.1016/j.nano.2017.12.014, PMID 29317342, PMCID PMC5898975.
146. Sebak AA, Gomaa IEO, Elmeshad AN. Distinct proteins in protein corona of nanoparticles represent a promising venue for endogenous targeting-part ii: *in vitro* and *in vivo* kinetics study. Int J Nanomedicine. 2020;15:9539-56. doi: 10.2147/IJN.S273721, PMID: 33299308.
147. Vroman L, Adams AL, Fischer GC, Munoz PC. Interaction of high molecular weight kininogen, factor XII, and fibrinogen in plasma at interfaces. Blood. 1980;55(1):156-9, PMID 7350935.

148. Pederzoli F, Tosi G, Vandelli MA, Belletti D, Forni F, Ruozi B. Protein corona and nanoparticles: how can we investigate on? Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2017;9(6). doi: 10.1002/wnan.1467, PMID 28296346.
149. Risha Y, Minic Z, Ghobadloo SM, Berezovski MV. The proteomic analysis of breast cell line exosomes reveals disease patterns and potential biomarkers. Sci Rep. 2020;10(1):13572. doi: 10.1038/s41598-020-70393-4, PMID 32782317.
150. Burnett JC, Rossi JJ, Tiemann K. Current progress of siRNA/shRNA therapeutics in clinical trials. Biotechnol J. 2011;6(9):1130-46. doi: 10.1002/biot.201100054, PMID 21744502.
151. Aleku M, Schulz P, Keil O, Santel A, Schaeper U, Dieckhoff B. Atu027, a liposomal small interfering RNA formulation targeting protein kinase N3, inhibits cancer progression. Cancer Res. 2008;68(23):9788-98. doi: 10.1158/0008-5472.CAN-08-2428, PMID 19047158.
152. Winter J, Jung S, Keller S, Gregory RI, Diederichs S. Many roads to maturity: microRNA biogenesis pathways and their regulation. Nat Cell Biol. 2009;11(3):228-34. doi: 10.1038/ncb0309-228, PMID 19255566.
153. Kato RB, Roy B, De Oliveira FS, Ferraz EP, De Oliveira PT, Kemper AG. Nanotopography directs mesenchymal stem cells to osteoblast lineage through regulation of microRNA-SMAD-BMP-2 circuit. J Cell Physiol. 2014;229(11):1690-6. doi: 10.1002/jcp.24614, PMID 24619927.
154. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res. 2016;33(10):2373-87. doi: 10.1007/s11095-016-1958-5, PMID 27299311.
155. Liang T, Zhang R, Liu X, Ding Q, Wu S, Li C. Recent advances in macrophage-mediated drug delivery systems. Int J Nanomedicine. 2021;16:2703-14. doi: 10.2147/IJN.S298159, PMID 33854316.
156. Tran S, DeGiovanni PJ, Piel B, Rai P. Cancer nanomedicine: a review of recent success in drug delivery. Clin Transl Med. 2017;6(1):44. doi: 10.1186/s40169-017-0175-0, PMID 29230567.
157. Hu Y, Gaillard PJ, de Lange ECM, Hammarlund Udenaes M. Targeted brain delivery of methotrexate by glutathione pegylated liposomes: how can the formulation make a difference? Eur J Pharm Biopharm. 2019;139:197-204. doi: 10.1016/j.ejpb.2019.04.004, PMID 30951819.
158. Feng Q, Shen Y, Fu Y, Muroski ME, Zhang P, Wang Q. Self-assembly of gold nanoparticles shows microenvironment-mediated dynamic switching and enhanced brain tumor targeting. Theranostics. 2017;7(7):1875-89. doi: 10.7150/thno.18985, PMID 28638474.
159. Wu L, Zhang J, Watanabe W. Physical and chemical stability of drug nanoparticles. Adv Drug Deliv Rev. 2011;63(6):456-69. doi: 10.1016/j.addr.2011.02.001, PMID 21315781.
160. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev. 2002;54(5):631-51. doi: 10.1016/s0169-409x(02)00044-3, PMID 12204596.
161. Desai MP, Labhasetwar V, Amidon GL, Levy RJ. Gastrointestinal uptake of biodegradable microparticles: effect of particle size. Pharm Res. 1996;13(12):1838-45. doi: 10.1023/a:1016085108889, PMID 8987081.
162. Zang X, Zhao X, Hu H, Qiao M, Deng Y, Chen D. Nanoparticles for tumor immunotherapy. Eur J Pharm Biopharm. 2017;115:243-56. doi: 10.1016/j.ejpb.2017.03.013, PMID 28323111.
163. Paulis LE, Mandal S, Kreutz M, Figdor CG. Dendritic cell-based nanovaccines for cancer immunotherapy. Curr Opin Immunol. 2013;25(3):389-95. doi: 10.1016/j.coi.2013.03.001, PMID 23571027.
164. Shao K, Singha S, Clemente Casares X, Tsai S, Yang Y, Santamaria P. Nanoparticle-based immunotherapy for cancer. ACS Nano. 2015;9(1):16-30. doi: 10.1021/nn5062029, PMID 25469470.
165. Yang R, Xu J, Xu L, Sun X, Chen Q, Zhao Y. Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination. ACS Nano. 2018;12(6):5121-9. doi: 10.1021/acsnano.7b09041, PMID 29771487.
166. Guo Y, Wang D, Song Q, Wu T, Zhuang X, Bao Y. Erythrocyte membrane-enveloped polymeric nanoparticles as nanovaccine for induction of antitumor immunity against melanoma. ACS Nano. 2015;9(7):6918-33. doi: 10.1021/acsnano.5b01042, PMID 26153897.
167. Fontana F, Shahbazi MA, Liu D, Zhang H, Makila E, Salonen J. Multistaged nanovaccines based on porous Silicon@Acetalated Dextran@Cancer Cell membrane for cancer immunotherapy. Adv Mater. 2017;29(7). doi: 10.1002/adma.201603239, PMID 28009461.
168. Perica K, De Leon Medero A, Durai M, Chiu YL, Bieler JG, Sibener L. Nanoscale artificial antigen presenting cells for T cell immunotherapy. Nanomedicine. 2014;10(1):119-29. doi: 10.1016/j.nano.2013.06.015, PMID 23891987.
169. Bauleth Ramos T, Shahbazi MA, Liu D, Fontana F, Correia A, Figueiredo P. Nutlin-3a and cytokine co-loaded spermine-modified acetalated dextran nanoparticles for cancer chemo-immunotherapy. Adv Funct Materials. 2017;27(42). doi: 10.1002/adfm.201703303.
170. Liu YT, Sun ZJ. Turning cold tumors into hot tumors by improving T-cell infiltration. Theranostics. 2021;11(11):5365-86. doi: 10.7150/thno.58390, PMID 33859752.
171. Hou Y, Sun Z, Rao W, Liu J. Nanoparticle-mediated cryosurgery for tumor therapy. Nanomedicine. 2018;14(2):493-506. doi: 10.1016/j.nano.2017.11.018, PMID 29197593.
172. Liu J, Deng ZS. Nano-cryosurgery: advances and challenges. J Nanosci Nanotechnol. 2009;9(8):4521-42. doi: 10.1166/jnn.2009.1264, PMID 19928115.
173. Di DR, He ZZ, Sun ZQ, Liu J. A new nano-cryosurgical modality for tumor treatment using biodegradable MgO nanoparticles. Nanomedicine. 2012;8(8):1233-41. doi: 10.1016/j.nano.2012.02.010, PMID 22406189.
174. Chua KJ, Chou SK, Ho JC. An analytical study on the thermal effects of cryosurgery on selective cell destruction. J Biomech. 2007;40(1):100-16. doi: 10.1016/j.jbiomech.2005.11.005.
175. Lv Y, Zou Y, Yang L. Uncertainty and sensitivity analysis of properties of phase change micro/nanoparticles for thermal protection during cryosurgery. Forschungim Ingenieurwesen/Engineering research. Vol. 76; 2012.
176. Ryman Rasmussen JP, Riviere JE, Monteiro Riviere NA. Penetration of intact skin by quantum dots with diverse physicochemical properties. Toxicol Sci. 2006;91(1):159-65. doi: 10.1093/toxsci/kfj122, PMID 16443688.
177. Jia G, Han Y, An Y, Ding Y, He C, Wang X. NRP-1 targeted and cargo-loaded exosomes facilitate simultaneous imaging and therapy of glioma *in vitro* and *in vivo*. Biomaterials. 2018;178:302-16. doi: 10.1016/j.biomaterials.2018.06.029, PMID 29982104.
178. Awasthi R, Pant I, T Kulkarni G, Satiko Kikuchi I, de Jesus Andreoli Pinto T, Dua K. Opportunities and challenges in nano-structure mediated drug delivery: where do we stand? CNANOM. 2016;6(2):78-104. doi: 10.2174/2468187306666160808160330.
179. Xia T, Kovochich M, Brant J, Hotze M, Sempf J, Oberley T. Comparison of the abilities of ambient and manufactured nanoparticles to induce cellular toxicity according to an oxidative stress paradigm. Nano Lett. 2006;6(8):1794-807. doi: 10.1021/nl061025k, PMID 16895376.
180. Xia Y, Rao L, Yao H, Wang Z, Ning P, Chen X. Engineering macrophages for cancer immunotherapy and drug delivery. Adv Mater. 2020;32(40):e2002054. doi: 10.1002/adma.202002054, PMID 32856350.
181. Dobrovolskaia MA, Aggarwal P, Hall JB, McNeil SE. Preclinical studies to understand nanoparticle interaction with the immune system and its potential effects on nanoparticle biodistribution. Mol Pharm. 2008;5(4):487-95. doi: 10.1021/mp800032f, PMID 18510338.
182. Akinc A, Zumbuehl A, Goldberg M, Leshchiner ES, Busini V, Hossain N. A combinatorial library of lipid-like materials for delivery of RNAi therapeutics. Nat Biotechnol. 2008;26(5):561-9. doi: 10.1038/nbt1402, PMID 18438401.
183. Love KT, Mahon KP, Levins CG, Whitehead KA, Querbes W, Dorkin JR. Lipid-like materials for low-dose, *in vivo* gene silencing. Proc Natl Acad Sci USA. 2010;107(5):1864-9. doi: 10.1073/pnas.0910603106, PMID 20080679.
184. Schork NJ. Personalized medicine: time for one-person trials. Nature. 2015;520(7549):609-11. doi: 10.1038/520609a, PMID 25925459.