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EMERGING TRENDS OF NANODRUG DELIVERY IN CANCER THERAPY

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ABSTRACT

For cancer treatment,nanotechnology has been extensively studied and exploited and in a drug delivery system it plays a significant role.To treat various cancers nanotechnology has been actively integrated as drug carriers. Nanotechnology is considered to be an emerging, disruptive technology that will retain a crucial impact in all industrial sectors. The investigation is recently started on the role of nanoparticles in immunotherapy which plays a most important role in cancer treatment. So nanocarriers have been increasingly used in drug delivery. By using nanoparticles, the off-target effects of such drugs can be improved, and also the cancer patients may have new hope. Utilizing nanoparticles to improve the therapeutic effect of chemotherapeutic drugs for enhancing the specificity and prolonging the circulation of life of drugs. By administrating nanoparticles, they show increasing in proliferation in tumour tissues near the blood vessels, enhancing both anticancer drug permeability and tumour retention. Compared to conventional drugs and nanoparticles-based drug delivery has certain benefits such as improved stability and biocompatibility, enhanced permeability, and retention effect. Nanoparticles applied to drug delivery systems include organic nanoparticles, inorganic nanoparticles, and hybrid nanoparticles. For cancer therapies, several nanocarriers are approved for clinical use and many novel formulations are in the later stages of clinical trials. The preclinical and clinical trials are evaluated for several nano-drug

delivery systems designed for tumour targeting and they show reasonable outcomes in cancer tumour clinical management.

Keywords: nanotechnology, drug delivery, drug resistance, hybrid nanoparticles

INTRODUCTION

Cancer includes a variety of diseases that result in abnormal cell growth and the spread of malignant cells. According to the World Health Organization, it is the most destructive disease, with more than 10 million new cases every year. Cancer-related mortality has reduced in the past last two years due to improved diagnostic devices, treatment, and molecular knowledge of cancer cell biology. To treat cancer there are several methods and it is an individualized treatment that greatly improves the therapeutic efficacy of some malignant tumours. The potential use and efficacy of various nano-drug carriers are much higher than conventional drugs. Chemotherapy is a conventional and widely used cancer treatment method but it has poor cell selectivity serious side effects and drug resistance. Drug resistance is increased due to chemotherapy drugs. Cancer therapy typically includes surgical intervention, chemotherapy, and radiation, which often also kill healthy cells and cause toxicity. By killing healthy cells and tumour cells, which causes serious side effects containing bone marrow suppression, gastrointestinal reaction, hair loss, nausea, vomiting, fatigue, and cause some toxicity **[1]**. Healthy cells are protected by the targeting systems from the cytotoxicity of drugs. To improve the drug delivery system of chemotherapeutics to the tumour site were tumour biology combined with the advancement in the development of versatile material. Over the last few decades, nanotechnology had the capability to uprising cancer diagnosis, therapy, and tumour targeting more safely and effectively by increasing its use in medicine. Nanocarriers can improve stability, drug efficacy, biocompatibility, and selectivity through enhanced permeability and retention time and precise targeting. Nanocarrier drug delivery system has multiple benefits like improved biodistribution and increased plasma half-life. On the surface of the nanocarriers, anti-neoplastics can be entrapped **[2]**. Drugs that are present inside the nanocarriers play a significant role in cytotoxic and gene therapy. The size, surface area to volume ratio, shape, charge, and composition of drug carriers are primarily related to chemotherapeutic drugs in cancer treatment. According to tumours, nanocarriers are used in drug delivery systems are designed based on their size and characteristics. Certain sized drug-loading particles manage to accumulate in

tumour tissues. Nanosize of nanoparticles are accumulated inside the tumour through enhanced permeability and retention effect **[3]**. Nanoparticles and large molecules enter easily by having high permeability of the tumour vasculature, and at the same time tumour tissues generally lack effective lymphatic drainage. Nanoparticles are encapsulated and deliver the drug into circulation when the solubility of the drug is poor. The drawbacks of chemotherapy drugs can be overcome to some extent by nanotechnology-based novel drug delivery systems mainly based on two mechanisms: passive and active targeting. By enhancing permeability and retention effect, the passive targeting exploits the characteristic features of tumour biology that allow nanocarriers to accumulate in the tumour. The efficiency of passive targeting delivery is very low and accordingly, it is insufficient so the active targeting can be attained by conjugation of nanoparticles with targeting ligand **[4]**. Active approaches achieve by molecules that bind to antigens or receptors on the target cells by conjugating nanocarriers containing chemotherapeutics. Nanoparticle-based therapy has been reported to have potential in overcoming multidrug resistance in several types of cancers like lung cancer, breast cancer, liver cancer, pancreas cancer, ovarian cancer, prostate cancer, cervical cancer, and colon cancer. Nanocarriers are sensitive to a variety of physiological stimuli such as abnormal pH, temperature, redox status, and cell enzymes, and the overexpression of certain biological molecules. Stimuli from outside the body such as light, ultrasound, and microwaves can also respond to the nanoparticles systems. Particularly on long-term cancer treatment nanocarriers show certain drawbacks like poor bio-degradation, tissue distribution, toxicity, and bioavailability thus causing safety. There are only a few clinically approved nanocarriers that incorporate molecules to selectively bind and the target cancer cells and some of the others in advanced stages of clinical development. Phase1 clinical trials are used by the nanoparticle-based system and the small interfering RNA is delivered in patients with solid cancer was conducted in 2010. The application and development of hybrid nanoparticles have more progress in the arena of nanoparticle-based drug delivery systems, which integrates the combined properties of various nanoparticles and related this type of drug carrier system to the next level **[5]**. Nanocarriers have some properties such as quantum effects, the ability to carry therapeutic active compounds to targeted sites, and a high ratio of surface to volume due to their nano size. Types of nano carrier-based drug delivery systems are liposomes, dendrimers, magnetic

nanoparticles, carbon nanotubes, quantum dots, and micelles. Nanoparticles have some advantages that inhibit the function of some mechanisms of cancer drug resistance include overexpression of drug efflux transporters, defective apoptotic pathways, and a hypoxic environment.

Nanocarriers in cancer therapy

Nanocarriers are nanosizedmaterials being used as transport modules for another substance,such as drugs and also, they can carry multiple drugs,and/or imaging agents.The nanoparticles used in medical treatmentusually have three aspects and they are sizes, shapes, and surface characteristics and these aspectshave amajor influence on the efficacy of nano-drug delivery and thus control therapeutic efficacy.In cancer therapy, nanoparticles with a diameter range of 10 to 100nm are generally suitable, as they can effectively deliver drugs and achieve enhanced permeability and retention effect. Particles that are smaller than 1 to 2nm can easily leak from the normal vasculature to damage normal cells and can easily filter by kidneys,while particles that are higher than under 100nm are likely to be cleared from circulation by phagocytes. Moreover, bioavailability and half-life are influenced by the surface characteristics of nanoparticles.Nanoparticles that are coated with hydrophilic materials such as polyethylene glycol(PEG) will avoid clearance by the immune system.The time period of drugs in circulation is increased and enhanced the permission and accumulation in tumours by modifying the nanoparticle to become hydrophilic **[6]**. Local drug concentration is increased by using nanocarrier.The efficacy of nanocarriers is extremely influenced by physical and chemical properties.Synthetic polymers, proteins,lipids, and inorganic particles, have been developed from nanoscale compounds **[7]**. Toxic side effects are reduced and pharmacokinetics is improved by the culmination of these benefits in several drug delivery vehicles, which differ according to surface physicochemical properties and size **[8]**. As a drug delivery vector, typically we use natural and synthetic polymers and lipids.Different types of nanocarriers applied to drug delivery systems include organic nanoparticles, inorganic nanoparticles, and hybrid nanoparticles (**Figure 1**).

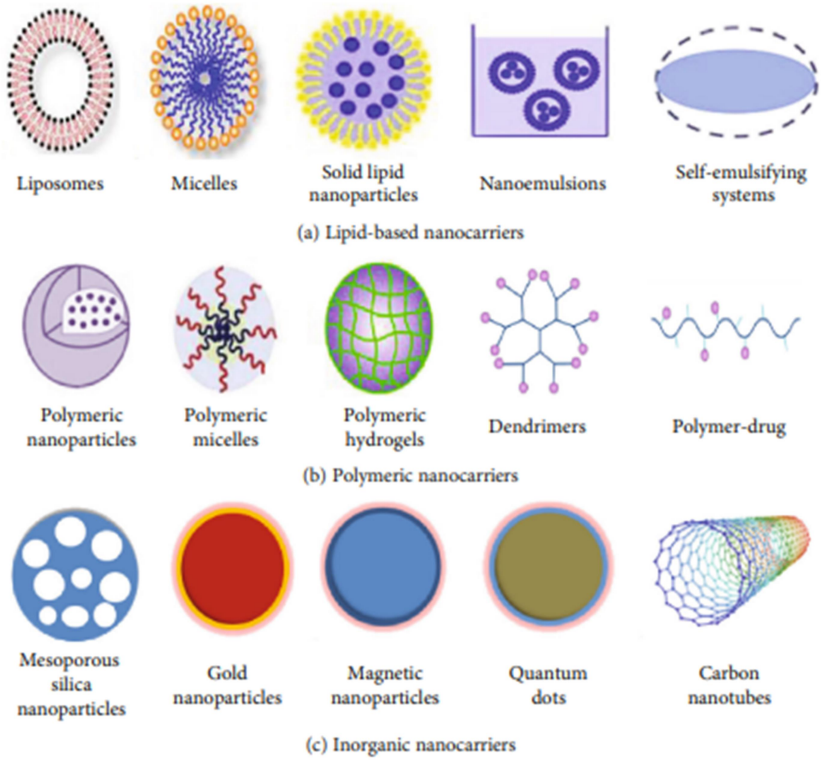

Figure 1: Different types of nanocarriers for drug delivery in cancer therapy

Organic nanoparticles

Organic nanoparticles are widely investigated for decades and include many types of materials.The organic nanoparticles include lipid-based nanoparticles and polymer-based nanoparticles.Among lipid-based nanoparticles, liposomes and solid lipid nanoparticles are common. Among polymer-based nanoparticles, polymeric nanoparticles and polymeric micelles are common.

Lipid-based nanoparticles:

Among all nanocarriers, lipid-based nanocarriers have made great progress and are useful to treat cancers.Liposome systems and solid lipid nanoparticles are different types of lipid-based formulations and among these liposomes were initially designed in 1965 **[9]**. Among other drug delivery systems such as polymer nanoparticles, the lipid-based systems manage to be less toxic because of their biocompatibility and biodegradability.The ability to entrap both hydrophilic and hydrophobic drugs and the general biocompatibility and biodegradability, isolation of drugs from the surrounding environment is the attractive biological properties of lipid-based carriers.A class of amphiphile-based particles represents liposomes, polymersomes, and micelles.The properties of lipid-based carriers such as their size, charge, and

surface functionality can easily be modified by the alteration of surface chemistry and through the addition of agents to the lipid membrane.In lipid-based carriers with polymer therapeutics, there are still no clinically improved techniques that use active cellular targeting.

i. Liposomes

Among organic nanocarriers, a self-forming phospholipid bilayer surrounds by an aqueous internal cavity is a composition of liposomes and these are spherical lipid vesicles. Liposomes are one or several concentric lipid bilayers with inner aqueous phases are constructed by self-closed structures surrounding a hollow core into which chemotherapeutic drugs can be loaded for delivery to the tumour site **[10]**. Liposomes are approved for clinical applications and the core entrapping either hydrophobic or hydrophilic drug and consists of an outer lipid layer. Liposomes are excellent drug delivery systems due to their easy degradation inside the body and additionally their property to encapsulate hydrophilic agents inside the aqueous environment and lipophilic agents in the outer lipid layers. The highest drug concentrations within the tumour cells and reduce the pooling of the drug in other tissues are limited by liposomal drug delivery. Polyethene glycol is coated on the surface of liposomes to enhance the stability of liposomes. Both water-soluble and poorly soluble drugs can be carried by liposomes to a target site. Liposomes maintain low immunogenicity, drug protection, and low toxicity. To the surface of liposomes, biocompatible and inert polymers such as polyethene glycol are added to increase circulation time. By adding inert polymers such as polyethene glycol to the surface of liposomes it forms a protective layer, which prevents the clearance of the reticuloendothelial system. By modifying the lipid layer structures, liposomes can carry out many functions. This includes imitating the biophysical characteristics of living cells which can help to obtain more effective therapeutic drugdelivery. Cholesterol, phosphate-dylserine, phosphatidylcholine, phosphatidylethanolamineare commercially available lipids for liposomes nanoparticles. Liposomes are similar to polymersomes, but polymersomes are composed of synthetic polymer amphiphiles including PLA-based copolymers. For in vivo delivery liposomes provide a good platform in cancer therapy such as doxorubicin and paclitaxel. The first nano-based therapeutic approved by FDA was the liposomal nanoparticles doxorubicin doxil® a chemotherapeutic mainly assigned for breast cancer, bladder cancer, and acute lymphocytic leukemia treatment, and this liposomal formulation results in the enhanced anticancer activity of the drug due

to long-circulating properties **[11]**. The application of liposomes has been commonly increased in the field of breast and prostate cancer. Expensive preparation methods, rapid disintegration in the human body before achieving the therapeutic effect, low drug-loading capacity, and stability are the major disadvantages. The tumour microenvironment is uploaded by its payload due to its responsiveness to a temperature above 40°c that leads to an increase in efficacy of anticancer of its loaded drug.

ii. Solid lipid nanoparticles

Solid lipid nanoparticles are spherical and nano-sized (10 to 100nm) lipid-based colloidal carrier systems. The colloidal carriers of natural or synthetic lipid-based drug delivery systems, combine the advantages of colloidal counterparts such as polymeric nanoparticles, liposomes, and nano-emulsions. Better than their counterparts, solid lipid nanoparticles perform better in some areas like economical large-scale production, long-term stability, and control drug release. To improve the oral bioavailability of water-soluble drugs the solid lipid nanoparticles are the most common method. When compared to polymeric or inorganic nanoparticles, solid lipid nanoparticles have less toxicity profile and are biocompatible. The solid core of the lipid matrix is carried by solid lipid nanoparticles. The term lipid usually includes triglycerides, partial glycerides, PEGylated lipids, fatty acids, steroids, and waxes. By using surfactants lipid core is balanced. Depending on the route of administration the amount of emulsifier is used and for parenteral administration, it is more limited **[12]**. Lipid core, surfactants, and drugs are present in this drug delivery system, the appropriate ratios show some unbeatable properties that make them superior across other existing drug carriers. Some unique characteristics are present in solid lipid nanoparticles-based preparations, the unique characteristics include increased drug stability and high drug loading. For intravascular administration, the solid lipid nanoparticles are frequently used as nanoparticles and it contains a hydrophobic lipid core into which they can be dissolved allowing high drug-loading efficiencies. Solid lipid nanoparticles can improve the efficiency of pharmaceuticals, nutraceuticals, and other materials. Solid lipid nanoparticles have superior cellular uptake when compared to traditional colloidal carriers and they can also improve the solubility and bioavailability of drugs.

iii. Micelles

Micelles are self-assembling closed lipid monolayers that have been successfully used as pharmaceutical carriers for water-insoluble drugs.Micelles are constructed with amphiphilic colloids that

spontaneously aggregate in water into spherical vessels.Micelles belong to a group of amphiphilic colloids that can be formed spontaneously under certain concentrations and temperatures and their well-designed properties are based on the nature of copolymers.Micelles have nano-sized core or shells and the outer shell forms hydrophilic heads and the interior forms a hydrophobic tail that can protect hydrophobic drugs from the external environment. Particularly by improving the bioavailability of low water-soluble drugs, micelles have attracted attention as a drug delivery system.The inner hydrophobic cavity act as a reservoir for lipophilic drug molecules and the hydrophilic outer shell help the micelle stability in an aqueous environment and micelles are suitable for intravenous administration because of these properties.Micelles can be improved with drug molecules by using two methods, physical encapsulation methods, and chemical covalent attachment methods.NK911 is a block copolymer of PEG and poly (aspartic acid) and it is an example of polymeric micelles under clinical evaluation.Another carrier is NK105 the pancreatic, colonic, and gastric tumour treatment was evaluated by micelle containing paclitaxel **[13]**.

Polymer-based nanoparticles:

For the preparation of nanocarriers, the various types of polymers are being used and the active therapeutic agents are either physically involved with polymeric matrix or bounded covalently with polymers.For the development of nanocarriers, both natural and synthetic polymers are used. These polymers are broken down in the body which are further eliminated via metabolic pathways, and the polymers are broken down in the body in the form of oligomers and monomers.The popularity of nanocarrier fabrication is gained by polymers such as polylactic acid (PLA) esters and their copolymers with glycolic acid, and polyglutamic acid, and recently the nanoparticles are based on biocompatible and biodegradable **[14]**.

i. Dendrimers

Dendrimers are highly symmetric spherical with a diameter of 1 to 10 nm and are chemically synthetic, branched macromolecules that form tree-like structures.The dendrimers are constructed by branched monomers that protect externally starting from the central core.Dueto modifiable surface, monodisperse size, multivalences, and hydrophilic internal cavities, dendrimer-based drug delivery systems have a lot of unique properties. From natural or synthetic ingredients dendrimers are produced, and the natural or synthetic ingredients include sugars, amino acids, and nucleotides. By hydrogen bonds, electrostatic (or) hydrophobic interaction the drugs can be

entrapped in the dendrimer core and can also be covalently linked to the surface of dendrimers.The enhanced solubilization of the drugs, the effective concentration of drugs at the target site, and the controlled release of the drugs are the results when the drug is attached to many peripheral groups of dendrimers **[15]**. Usually, the structures of low-generation dendrimers are flexible and open, and the high-generation dendrimer is dense and globular. Dendritic polymers are easy to be functionalized and make them an attractive drug delivery carrier by decreasing immunogenicity and antigenicity and it is having some unique advantages like stability water solubility.

ii. Polymeric micelles

Polymeric micelles are composed of phospholipids, and polymers that spontaneously form in an aqueous solution and they are also in another form of lipid-based nanoparticles having a size less than 100 nm **[16]**. Polymeric micelles contain a hydrophobic core and hydrophilic shell and the hydrophobic core can include large amounts of hydrophobic drugs at higher concentrations.Polymeric micelles are self-assembled core-shell constructs in selective solvents.The shell not only provides stability of nanostructured micelles but also facilitates their functionalization and allows the drugs to deliver to the target site by controlling pH, temperature, and ultrasound.The polymeric micelles are characterized by long drug retention time in blood, increased drug permeability, high drug encapsulation rate, and strong tumour penetration.The drugs which are having poor water solubility due to their amphiphilic characteristics this type of carriers are suitable.

iii. Polymeric nanoparticles

Polymeric nanoparticles are organic polymer compounds that are in the form of nanospheres and nanocapsules.Polymeric nanoparticles are composed of natural polymers and synthetic polymers.Synthetic polymers including poly (lactic acid) (PLA) and poly (lactic-co-glycolic acid)or from natural polymers such as chitosan, cellulose, corn starch, and collagen can be made by polymeric nanoparticles and they may be used to encapsulate drugs without chemical modification.Polymers are the most commonly investigated materials for constructing nanoparticles-based drug carriers.Only four drugs and four polymers have been repeatedly used to develop polymer-drug conjugates.The four drugs are doxorubicin, camptothecin, paclitaxel, and platinate and the four polymers are (N-(2-hydroxypropyl) methacrylamide(HPMA) copolymer, poly-L-glutamic acid, poly(ethylene glycol)(PEG), and dextran.The encapsulation of hydrophobic drugs controls drug release, and the extents circulation time is facilitated by the core-shell structures of polymeric

nanosystems.To achieve high biodegradability, high content of drug loads, and target tumour locations the physicochemical characteristics of the polymers (e.g.-size, shape, surface charge, flexibility, and length of the main carbon chain) can also be easily arranged [17].Difficulty in large-scale industrial production, residual organic solvents in the preparation process, and polymer cytotoxicity are the major disadvantages of polymer nanoparticles.12 polymer-drug conjugates have entered phase I and phase II clinical trials and are especially useful for targeting blood vessels in tumours.

Inorganic nanoparticles

Inorganic nanoparticles are mainly metal-based and have the potential to be produced with near monodispersity and which related to nanocarriers synthesized by metal and semi-metal materials that have attained increasing interest in the recent past. Magnetic resonance imaging and high-resolution superconducting quantum interference devices are extensively studied by inorganic materials **[18]**. Due to easily scalable synthesis, simplified modification of targeting molecules, high stability, controlled release of the drugs, and ability to stimulate targeted drug delivery with imaging possibilities, inorganic nanomedicines have been studied to find out a nanocarrier for delivering chemotherapeutic drugs.Among various inorganic nanoparticles carbon nanotubes, quantum dots, magnetic nanoparticles, mesoporous silica nanoparticles, and gold nano-particles. Gold nanoparticles and nanoshells are recently developed inorganic nanoparticles.

i. Carbon Nanotubes

The carbon nanotubes are tube-shaped materials made up of carbon with diameters typically measured on a nanometer scale. The walls formed by one-atom-thick sheets of carbon are known as graphene. Carbon nanotubes are formed by rolling up a single graphene sheet or by rolling up multiple graphene sheets. However, by the chemical modification and attaching some functional groups, they can be transformed into water-soluble nanocarriers to improve their biocompatibility and to reduce toxicity. Carbon nanotubes are a type of tubular material that has unique biological, physical, and chemical properties, as the hollow monolithic structure that can accommodate high payload and the ability to add any functional groups **[19]**. By incorporating an antifungal agent and by combining the antitumor agents the most interesting delivery systems have been developed. Compare to free drug molecules, the internalization of drug molecules shows more effectiveness by drugs attaching to nanotubes. In breast cancer cells the drug delivery is improved inside the cells up to 80%. Carbon

nanotubes can also be used for targeted thermal ablation therapy and produce heat when they are exposed to near-infrared radiation. Carbon nanotube will carry short interfering (RNA) and (siRNA) was coupled to single-walled carbon nanotubes. siRNA can rapidly enter tumour cells, then release the siRNA to exert RNA interference on target gene expression, not only silencing the target gene but also inhibiting the proliferation of cancer cells in vitro and suppressing tumour growth in mouse models, upon intralesional injection of siRNA-conjugated carbon nanotubes.

ii. Quantum Dots

Quantum dots are nanosized inorganic semiconductor nanocrystals with a diameter of 1 to 10nm which are used in the treatment of different types of cancer. By Surface modification, water solubility and biocompatibility of quantum dots are improved. Quantum dots are used as fluorescent probes with targeting molecules **[20]**. The strong absorption spectra and unique optical and chemical properties are the exceptional features that are maintained by quantum dot nanocarriers. Quantum dots will show resilience to chemical degradation, pH changes and have high thermal stability. Quantum dots can be used as photosensitizers and act as a radiosensitizer by being an absorber of high-energy photons (X-ray and gamma rays). The general structure of quantum dots is made up of core and shell, the core includes various metal complexes for example like semiconductors and magnetic transition metals and it is coated with the shell. To change its physical and chemical properties and to improve solubility a semiconductor core is coated with the shell. Group III-V sequences quantum dots contain indium arsenate (InAs), indium phosphate (InP), gallium arsenate (GaAs), and gallium nitride (GaN) metalloid cores. Group II-IV sequences Quantum dots involves has cadmium- selenium (CdSe), Zinc sulfide (ZnS), Zinc-selenium (ZnSe), and cadmium-tellurium (CdTe) cores. The major component of the quantum dot is cadmium containing semiconductors and however, cadmium is probably harmful. They have attracted much attention in tumour research and become an ideal material for targeted drug delivery due to their unique surface chemistry available for modification. However, the main disadvantage of quantum dots is their toxicity studies and excretion pathway, and the toxicity of the cadmium including quantum dots in human living cells is completely not evaluated yet.

iii. Magnetic Nanoparticles

Magnetic nanoparticles are nanostructures with a diameter of 1 to 100 nm used for drug delivery and it usually contains metal or metal-oxide nanoparticles.Magnetic nanoparticles are developed by pure metals

such as iron, nickel, cobalt, and manganese.Magnetic nanoparticles are mostly used in biomedical applications and it is a class of nanoscale carriers containing iron oxide nanoparticles. Paramagnetic, ferromagnetic, diamagnetic, anti-ferromagnetic, and super-paramagnetic materials are classified from nanoparticles, based on magnetic characteristics **[21]**. Diamagnetic materials are repelled on the external magnetic field thus due to the absence of an external magnetic field; it results in zero magnetic moments.However, paramagnetic materials do not retain their magnetic properties in the absence of a magnetic field, and then it forms a weak magnetic moment. Even when the external magnetic field is absent due to unpaired electrons, the ferromagnetic materials will remain magnetized and their areas line up in the magnetic field direction resulting in a massive magnetic moment.Due to magnetic moments having opposite moments and equal magnitude, the anti-ferromagnetic material will result in zero magnetization. In the presence of a magnetic field the super-paramagnetism acts as paramagnet.To enhance stability and bio-compatibility under the physiological environment the magnetic nanoparticles consist of an inorganic material including polymers and fatty acids.It indicates high efficacy in gene therapy and chemotherapy for cancer treatment.The bio-compatibility (or) toxicity of magnetic nanoparticles is mainly influenced by various magnetic nanoparticle features like coating, size, and type of core material. Due to acid erosion and oxidation, the nickel and cobalt magnetic nanoparticles are susceptible and also, they are considered toxic.To improve the efficacy of magnetic nanoparticles various novel techniques of coating and functionalization are needed to avoid phagocytosis by RES.

iv. Mesoporous Silica Nanoparticles

Among nonlipid-based nanoparticles, due to their facile synthesis mesoporous materials hold promise, highly ordered structures, biocompatibility, and large pores sizes, typically prepared from assemblies of inorganic components such as silica **[22]**. The maximum numbers of anticancer drugs are encapsulated in the large internal pores, and the supramolecular components act as a cap, allowing the capture and release of drugs.Their pharmacological potential in terms of drug adsorption, drug release, and loading capacity is influenced by the pore size of mesoporous silica nanoparticles **[22]**. Pore diameters differ from 2 to 50 nm by stimulating the production of nanoparticles that bind to small drug molecules or macromolecules.Controlled drug-release kinetics enacts the stability of the pore.Silica nanoparticles are considered as one of the best vehicles for drug delivery due to their better pharmacokinetics, and

treatment efficacy. Temperature, pH, enzymes, magnetic field, irradiation, and ultrasounds are characterized by mesoporous silica nanoparticles (MSNs).

v. Gold Nanoparticles

Gold Nanoparticles are the most widely studied inorganic nanoparticles and mixed monolayer-protected clusters based on gold core and the gold core is inert and nontoxic,and surface functionalized **[23]**. Gold nanoparticles are attractive challenges in cancer therapy; maintain unique properties including ease of production and functionalization and high biocompatibility. The gold nanoparticle can be constructed to generate heat in response to near-infrared radiation light and thus may also be useful in hyperthermia-based therapeutics.Gold nanoparticles have been verified to improve drug accumulation in tumours as well as to overcome drug resistance.In multimodal cancer treatment including gene therapy,photothermal therapy,and immunotherapy,the gold nanoparticles are thought to be involved.

Hybrid Nanoparticles

Inorganic and Organic ingredients are the mixture of hybrid nanomedicines that facilitates the need for hybrid and nanomaterial formulation and allow the system to change to attain the desired results. By combining both Inorganic and Organic nanoparticles into a single hybrid drug delivery system enriches the multifunctional carrier with biological properties that can improve treatment efficacy as well as reduce drug resistance **[24]**.

i. Lipid-Polymer Hybrid Nanoparticles

Polymer-lipid hybrid nanoparticles (PLNs), are characterized by particle sizes less than 100nm in diameter. Polymer-drug complex is a core of polymer-lipid hybrid nanoparticles and the increasing number of bio-polymers offers several opportunities for drug conjugation. Polymer lipid hybrid nanoparticles of an inner polymeric core, and have been indicated to be a promising drug delivery platform in the treatment of pancreatic cancer, breast cancer **[25]**, and metastatic prostate cancer. Lipids that contribute to their high biological compatibility are composed has an outer shell of polymer-lipid hybrid nanoparticles. Polymer lipid hybrid nanoparticles combine the biomimetic properties of liposomes with a large number of biodegradable polymers, which display high structural integrity, controllable drug release, and the possibility of binding to the targeted delivery factor.

ii. Metal-Organic Frameworks

Metal-organic frameworks include a class of porous nanoparticles with modifying hybrid structures that contains an organic linker and a metal ion. Due to large surface area and tunable pore size, metal-organic frameworks (MOFs) show promise for

controlled drug release. For the utility as in vivo anticancer drug carriers, the metal-organic frameworks must be scaled down to the nanoscale level and the nano metal-organic frameworks have particular utility in pharmaceutical applications **[26]**. Higher amounts of drugs are incorporated in nano metal-organic frameworks when compared to conventional porous materials. The pH, redox-based, ATP, magnetic fields, temperature, pressure, irradiation, and humidity have been developed by responding to metal-organic framework-based stimuli-responsive systems.

iii. Liposomes-Silica Hybrid

In NP design, the combination of Organic and Inorganic hybrid nanomaterials is a common method. For example, liposome-silica hybrid (LSH) nanoparticles consist of a silica core and a surrounding lipid bilayer, and to kill prostate and breast cancer cells it has been synthesized and shown to be valid in delivering drugs. The synergistic delivery of gemcitabine and Paclitaxel to Pancreatic cancer in a mouse model of the disease is a platform that is offered by liposome silica nanoparticles **[27]**.

iv. Cell Membrane Coated Nanoparticles

In Nanoparticle design, the hybridization of natural biomaterial with organic or inorganic nanoparticles is another method. For example, cell membrane coating nanotechnology is developing and has increasingly attained more attention. This technology manages to give the nanoparticles biological characteristics directly by coating nanoparticles with naturally derived cell membrane which enhances the potency and safety of conventional nanoparticles.

- Leukocytes, red blood cells, cancer cells, platelet, and even bacteria are derived from the coatings included cell membrane.
- The stability and targeting ability of nanocarriers are improved and some studies have utilized cancer cell membrane-coated mesoporous silica nanoparticles for cancer treatment **[28]**.
- The function of nanoparticles enhances by the further development of dual-membrane coated nanoparticles.
- For example, erythrocyte-platelet hybrid and erythrocyte-cancer hybrid membrane-coated nanoparticles were substantiated to give better stability and longer circulation life.

Mechanism of targeting

Targeting cancer cells specifically is an important characteristic of nanocarriers for drug delivery systems. Due to its vital characteristic of nanocarriers, the therapeutic efficacy is enhanced while protecting normal cells from cytotoxicity. To explore the targeting design of

nanoparticle-based drugs the several studies have been carried out. To deal with the challenges of nano-carrier system design and tumor targeting, it is critical to understand tumor biology and interactions between nanocarriers and tumor cells. Targeting mechanisms can be divided into two categories, passive targeting, and active targeting (**Figure 2**). While enroute to their target, nanocarriers encounter several barriers such as mucosal barriers and non-specific uptake. Leaky blood vessels and poor lymphatic drainage are the general features of tumours. Free drugs may diffuse non-specifically, and via leaky vessels, by the EPR effect, the nanocarriers can escape into the tumour tissues. The permeability of blood vessels in tumours is increased and this is the characteristic of rapid and defective angiogenesis (the development of new blood vessels from existing ones).

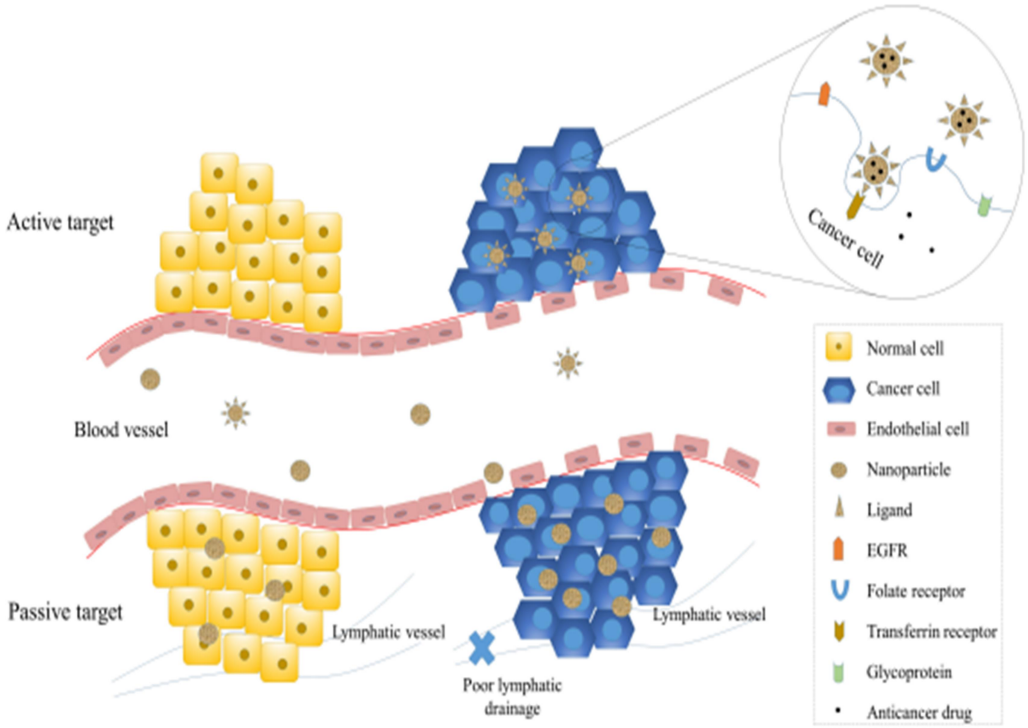

Figure 2: Passive and active targeting of nanoparticles to cancer cells

Passive Targeting

To utilize the different characteristics of the tumour and normal tissues the passive targeting is designed. In passive targeting, to play a therapeutic role the drugs are successfully delivered to the target site. To leak from blood vessels the rapid and defective angiogenesis facilitates macromolecules, including nanoparticles. That supplies tumour and increases within tumour tissue. Meanwhile, the poor lymphatic drainage associated with cancer increases the retention of nanoparticles and allows them to release drugs into the

vicinity of the tumour cells. These processes cause the EPR effect and it is one of the driving forces of passive targeting. By the size of nanoparticles, the enhanced permeability and retention effect are influenced. As many studies have indicated that smaller nanoparticles do not leak into normal vessels and have a better penetrability and larger particles are more likely to be cleared by the immune system **[29]**. Not only the EPR effect in addition to that tumour microenvironment is also an important factor of the passive targeting. Including non-specific drug distribution, non-universal existence of the EPR effect, and different permeability of blood vessels across various tumours are some limitations with passive targeting. In the mid-1980s, passively targeting nanocarriers reached clinical trials and in the mid-1990s the first products based on liposomes and polymer-protein conjugate were marketed.

Active Targeting

Through direct interaction between ligands and receptors, the active targeting particularly targets cancer cells. The ligands on the surface of nanoparticles are selected to target the molecules that bind to overexpressed antigens or receptors on the target cells which allows them to characterize targeted cells from healthy cells **[30]**. Receptor-mediated endocytosis is induced by the interactions between ligands on nanoparticles and receptors on the surface of cancer cells, which allows internalized nanoparticles to successfully release therapeutic drugs. Macromolecular drug delivery such as protein and siRNAs are particularly suitable for active targeting. Monoclonal antibodies, amino acids, vitamins, peptides, and carbohydrates are contained as types of targeting moieties. The ligands are particularly bound to receptors on targeted cells, and the transferrin receptor, glycoprotein, folate receptor, epidermal growth factor receptor (EGFR) are widely examined receptors.

Nanocarrier delivery systems for cancer treatment

The treatment of tumours targeting nanoparticles has been widely studied, based on the unique physical and chemical properties of the tumour microenvironment. Generally, to attack certain molecular agents the nanomedicines are designed. The selection of nanoparticles shown in (**Figure 3**)

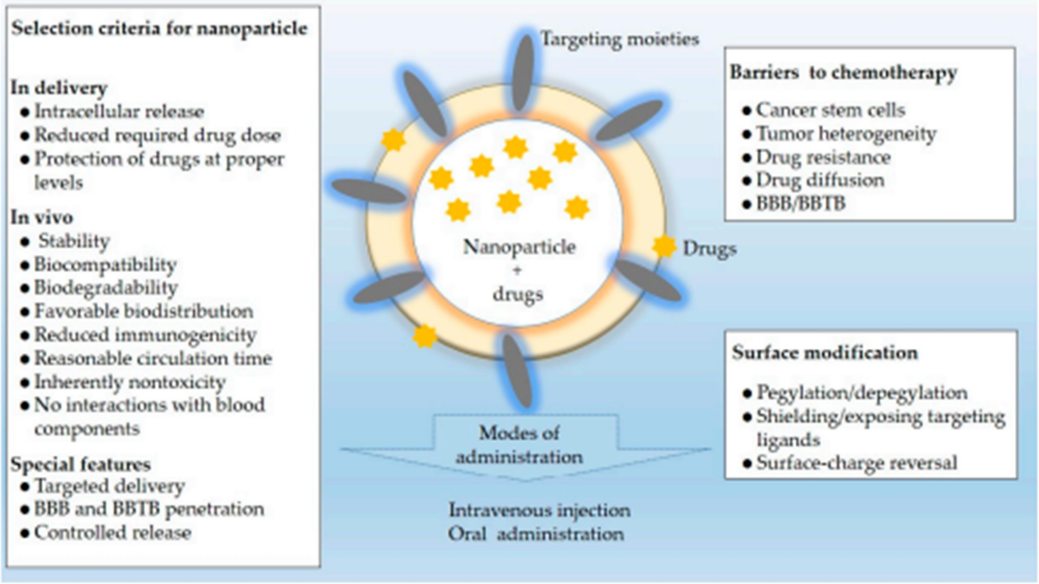

Figure 3: Selection criteria, barriers to chemotherapy, and surface modification associated with nanoparticles

Lung Cancer

Lung cancer is an aggressive type of cancer and it leads to Global cause of cancer-related deaths with the highest morbidity and mortality. Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are divided from lung cancer.Among these two lung cancers, non-small cell lung cancer is the most common.In current treatments due to poor targeting of chemotherapeutic drugs, heterogeneity, therapeutic resistance, and metastasis of cancer cells the lung cancer will have met limited success.In the treatment of lung cancer, one alternative method, active targeting via nanoparticles has shown promise.In previous studies, epidermal growth factor receptor (EGFR) up-regulation is always related to non-small cell lung cancer (NSCLC), thus to target the delivery of chemotherapy agents the epidermal growth factor receptor is used as a targeted molecule.To deliver anti-cancer drugs to tumour cells without harming normal cells they use targeted molecules.The targeted molecule we can also use are CD44, sigma, DR 4/5, transferrin, andglucose receptor. For lung cancer-initiating cells, the CD133 and CD44 are also specific markers.To deliver chemotherapeutic drugs by exosomes so many attempts have been made.More than 50 times cytotoxicity is increased in drug resistance MDCK-MDR1(Pgp+) cells by incorporating PTX into exosomes.A powerful anti-cancer effect is an LLC mouse model, which has shown that nearly complete cool localization of airway delivered exosomes with cancer cells in an LLC mouse model.According to a study report, the delivery of conventional chemotherapeutics is improved by using

quantum dots that had very low toxicity as a nanocarrier.In another study, PTX is loaded into HA-modified selenium nanoparticles and display significant, cellular update and control the release of PTX in vitro.Huang and coworkers developed CD133 and CD44 aptamer-conjugated nanomicelles to achieve the dual-target, the CD133 and CD44 aptamer-conjugated nano micelles are loaded with gefitinib (CD133/CD44 NM-Gef) that were capable of simultaneous targeting to CD44+ and CD133+ lung cancer-initiating cells.CD133/CD44-NM-Gef showed greater therapeutic efficacy against lung cancer-initiating cells.HHT is loaded into a smart PLGA system and targeted epidermal growth factor receptor has been evaluated in vitro and in vivo.It shows that the nanotherapeutic method to be safe with a better targeting effect.By using an epidermal growth factor receptor aptamer, the cancer cells are targeted and as a targeted nanomedicine, PLGA-SS-PEG is a polymeric drug carrier **[31]**. Against lung cancer, immunotherapy has become an effective additional therapeutic technique.Pulmonary surfactant, related to local inflammation and immune response, is sufficient in the lung making it different from other organs.Through van der wall forces and hydrogen bonding, the Pluronic P105 can interact with pulmonary surfactants.To form into PEG-PLA/P105/PTX micelles the PTX is encapsulated by nanocarriers, and amphiphilic polymers polyethyleneglycol-polylactic acid (PEG-PLA) and Pluronic P105 is required as nanocarriers. In preclinical studies, PEG-PLA/P105/PTX micelles are responded to the biological functions of Ax [32].That inhibits autophagy and promotes the secretion of pulmonary surfactant, thus modulating the tumour microenvironment to improve the drug transportation and cell killing sensitivity of micelles **[32]**.

Using cell membrane protein-based biomimetic a new study is carried out.DOX and icotinib were encapsulated by nanoparticles to epidermal growth factor receptor-mutant non-small cell lung cancer which improved cytotoxicity of chemotherapeutic drugs and in tumours, a high drug accumulation is achieved.In another study, PTX and ligustrazine are loaded into DQA modified micelles, and to inhibit tumour metastasis it was synthesized.The inhibitory impact of DQA modified PTX Plus ligustrazine micelles on A549 cell invasion was better than PTX plus ligustrazine micelles and it is shown in results.The strongest adhesion inhibition and the down-regulation effect on metastatic related proteins are shown by DQA modified PTX plus ligustrazine micelles.The drug accumulation in tumour tissues and

improved cellular uptake are also observed in vivo **[33]**. Recently on non-small cell lung cancer, a study was conducted using PTX and GEM-conjugated nanostructured lipid carriers.A study was conducted on the NSCLC to determine its efficacy against cancer.Sequential release of drugs is seen in vitro release studies, and first PTX (redox-triggered) and then GEM (pH-triggered) is released.

Breast Cancer

Breast cancer is the second most frequent cancer and it is a highly malignant tumour that is leading with a cause of death in women.The therapeutic agents are administered orally or intravenously and to reach the target tumours through many barriers.To treat breast tumours there are several chemotherapeutic drugs and some patients do not respond to these products.Due to high heterogeneity, cancer cells use drug delivery pumps to throw away the drugs which are inside the cells, stem cells develop resistance to chemotherapy, and metastasis that is not affected by drugs are the reasons for the failure in breast cancer treatment.

By the expression of estrogen, progesterone, and HER-2 the breast cancer is defined.In this disease, breast cancer cell receptors play a strong role in the treatment as it forms the basis of a targeted technique for treatment.In the active targeting of breast cancer with HER-2, some other molecular targets have been used. Epidermal growth factor receptor is an important receptor and it is overexpressed in up to half of the breast cancer cases and as a high density on the cell surface.For drug delivery, the folate receptor is a common target, folate receptor is expressed in 50-86% of metastatic triple-negative breast cancer patients who generally have a poorer prognosis.In targeted techniques, transferrin receptors, CXC chemokine receptor type 4 (CXCR-4), estrogen receptors are used.Liposomes formulations have prolonged drug action time, and they can effectively be targeted and the tumour site it is specifically identified. CD44 and CD133 receptors are included by targets of breast cancer stem cells **[34, 35]**. Not only anti-CD44 monoclonal antibodies but various nano-delivery systems have been developed to target CD44 receptors. Target CD44 receptors are developed by using different targeting moieties such as HA **[34]**. By understanding the molecular biology of breast cancer, nanotherapeutic techniques have been developed. Pegylated PTX nanocrystals (PEG-PTX-NCs) are prepared and investigated the antitumor efficacy of PEG-PTX-NCs. To the animal mice, the drug is administrated intravenously and after administration, the experiment results showed that PEG-PTX-NCs is significantly improved the antitumor effect in treating an in-situ tumour or

metastatic tumour.In another study, the cisplatin efficacy is loaded into ultra-short single-walled carbon nanotubes capsules and it was investigated *in vivo*. Results indicate that compared to free cisplatin the nano drugs will show a prolonged circulation time which enhances permeability and retention effects resulting in significantly more cisplatin accumulation in tumours. The use of plant viral nanoparticles for delivering DOX is reported in recent research.Although at lower efficacy than the free DOX the DOX-loaded viral nanoparticles were effective in MDA-MB-231 cells. The efficiency of the DOX-loaded silica nanoparticles is additionally investigated. The efficiency of cellular drug delivery exhibited high cytotoxicity and successfully inhibited the tumour growth is improved by silica nanoparticles or DOX.Researchers reported that cross-linked multifunctional polymeric nanoparticles loaded with DTX and when compared to the free DTX group *in vivo* show better inhibition of primary 4T1-Luc tumour growth and lung metastasis with little bodyweight loss **[36]**. The main cause of failure of breast cancer treatment is difficulty in eliminating cancer stem cells.Against breast cancer stem cells, the dual drugs (PTX, DOX, 5-fluorouracil (5-Fu), and dexamethasone) simultaneously loaded nanoparticles are effective.The dual drug delivery system particularly carcinogenic drugs are combined with plant or other natural source compounds will show better effects by reducing toxicity in the treatment of breast cancer. To target both HER-2-positive breast cancer stem cells and cancer cells the salinomycin-loaded PLNs anti-HER2 nanoparticles (Sali-NP-HER2) were developed.This results in the improvement of efficiency while compared with non-targeted nanoparticles or salinomycin.

To deal with drug-resistant breast cancer, arginine-glycine-aspartic (RGD) tripeptide coated, pH-sensitive solid lipid nanoparticles (RGD-DOX-SLNs) were required to load DOX. When compared to DOX solution with no apparent toxicity on cell the RGD-DOX-SLNs show area under the plasma concentration-time curve, and peak concentration **[37]**. In another study, polymeric micelles were designed for improving tumour multidrug-resistant reversal and chemotherapy efficiency in breast cancer.New polymeric micelles are composed of phenylboronic acid (PBA)-modified F127 (active-targeting group) and DOX-grafted P123 prodrugs group (FBP-CAD). The results substituted that FBP-CAD micelles are specifically accumulated at the tumour site with decreased cardiotoxicity *in vivo* and retained stronger cell-killing capacity *in vitro*. In another study, an RNA four-way Junction nanoparticles with ultra-thermodynamic

stability covalently loaded with high-density PTX (RNA-PTXResults show that RNA-PTX is inhibited tumour growth with negligible toxicity in vivo and strongly accumulated in tumour.

CONCLUSION

Due to its non-invasive nature and killing of cancerous cells chemotherapy is preferred as an effective treatment of various types of cancers. Traditional therapies, including chemotherapy, surgery, and radiotherapy are still considered acceptable, but due to their unique physicochemical properties and lack of targets selectivity, additional work is required for some advancement in cancer treatment. Nanocarriers are applied to cancer therapy due to their small size and modulated physicochemical properties, and that can be increasingly utilized in cancer therapeutics. In biomedical applications, the nano carrier-based approaches will play a dynamic role. Various types of nanocarriers include lipid-based carriers, polymeric-based nanoparticles, liposomes, micelles, carbon nanotubes, nano metal-organic frameworks, dendrimers, and quantum dots have been effectively used for targeted delivery of chemotherapeutic agents such as lung, colon, cervical, and breast cancer treatment. When compared to chemotherapy the nanoparticle-based drug delivery systems are related with enhanced pharmacokinetics, biocompatibility, tumour targeting, and stability, and it reduces systemic toxicity and overcomes drug resistance.We discuss nanocarriers, in cancer drug delivery, drug targeting, and cancer diagnosis. So based on the current review the nanocarriers will increase drug delivery at the site of action.

FUTURE PROSPECTS

The selection of an appropriate nanocarrier is not apparent and interpreting a few existing comparative studies is difficult because simultaneously several factors may affect biodistribution and targeting.For determining optimal characteristics of nanocarriers the suitable screening methodologies are developing. On a case-by-case basis, successful targeting strategies must be determined experimentally, which is complicated. In addition, nanocarriers using systemic therapies required methods that can overcome non-specific uptake by non-targeted cells and mononuclear phagocytic cells.The therapeutic efficacy of targeted nanocarriers is improved and established in multiple animal models of cancer.With several antibody-containing nanocarrier formulations currently, more than 120 clinical trials are underway.In the future, there is the ability to choose specific nanocarrier or targeted molecule combinations to reduce cost and to improve therapeutic outcomes.

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