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Review Article

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Engineered Nanoparticles for the Delivery of Anticancer Therapeutics

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Abstract

Therapeutic agents in cancer treatment are aimed at rapidly dividing cells, limiting their multiplication, and promoting apoptosis. Lack of selectivity of these conventional methods resulted in needless damage to normal cells leading to severe adverse effects. Nanotechnology in medicine gratify the constraint in conventional treatment by delivering conventional drugs to the targeted tissue or organ and plays an important role in targeting the delivery, thereby avoiding systemic toxicity and increasing the bioavailability and therapeutic index of the drug. The advantage of using nanoparticles as drug carriers is in their binding competence and reversing multidrug resistance. Using active and passive targeting strategies, nanoparticles enhance intracellular drug concentrations. The present review focuses the on the basic pathophysiology of cancer and the various types of nanoparticulate drug delivery systems that have been explored so far, taking advantage of the tumour vasculature and other molecular mechanisms which differentiates cancer cells from normal ones, for the delivery of anticancer therapeutics for effective management of cancer. The article also aims to focus on the various surface engineered nanoparticles for targeted delivery of cancer.

Keywords

Nanoparticles; Anticancer therapeutics; Targeted drug delivery; EPR effect; Polymeric nanoparticles; Dendrimer

Introduction

Cancer, the most shattering disease, claims more than 6 million lives every year worldwide [1,2] with increasing numbers each year. Therapeutic agents in cancer treatment are aimed at rapidly dividing cells, limiting their multiplication, and promoting apoptosis [3]. Surgery, Radiotherapy, Chemotherapy including hormonal therapy, Immunotherapy and Combined modality therapy are the standardized approaches for cancer treatment [4]. Lack of selectivity of these conventional methods resulted in needless damage to normal cells, alopecia, drug resistance, myelosupression, gastrointestinal damage, high tumor interstitial fluid pressure, making the treatment less efficacious [5-8]. With advances in cancer molecular biology and the pathways involved in cell transformation [5], the second half of the 20th century hallmarked new approaches in anticancer therapy with claimed targeted accomplishment [1,8], that not only supplemented the conventional treatment measures but also intended to overcome the challenges in conventional treatment, by involving new concepts of drug delivery, "The Targeted Therapy" [5,8]. Targeted therapy inhibits cancer cell proliferation by impeding with molecules required for growth and development of tumor, encompassing direct (by targeting tumor antigens by monoclonal antibodies or small molecule inhibitors, to alter their signalling) and indirect approaches (by relying on tumor antigens expressed on cell surface) [6,7]. Nevertheless targeted therapy has its own limitations owing to different side effects, not limited to folliculitis, nail feebleness, xerosis, diarrhoea, interstitial lung disease, cardiac toxicity, anorexia, hypertension, gastrointestinal perforation [9]. To overcome the systemic toxicity and the adverse events associated with the targeted therapy, novel methods of directing the drug to the target tissues, using nanodevices were developed [10]. Nanotechnology in medicine gratify the constraint in conventional treatment by delivering conventional drugs to the targeted tissue or organ and plays an important role in targeting the delivery, thereby avoiding systemic toxicity and increasing the bioavailability and therapeutic index of the drug [3,11]. The added advantage is in their ability to be unrecognized by P-glycoprotein, resulting in overcoming drug resistance and increased intracellular drug concentrations [11].

Physiology of Cancer

Cancer or neoplasm or tumor is a large group of diseases with the basic characteristics property of "abnormal growth" [12]. Normal growth of cells is a controlled and regulated process, whereas cancer growth is highly uncontrolled process [12]. Cancer progress is a multistep process involving progressive or rapid acquirement of genetic changes, caused by epigenetic mechanisms such as gene amplification or inactivation, leading to inception of malignancy [12,13], the crucial in understanding the molecular origins of cancer. The nature of cell transformation and the bases of tumor development and progression can be understood from the knowledge of molecular origins of cancer [14]. Cancer research has exposed that cancer is a disease involving vibrant alterations in the genome [12,13].

The gain of function of the proto-oncogenes, which provide transformation and invasive properties to the cell and loss of function of tumor suppressor genes which restrain cell division have been the basis of these genetic changes [13,14]. The basic morphological and physiological difference between normal tissue and tumor tissue is the size and shape, and vasculature [15] respectively. Tumor cells are characterized by self-reliance in growth signals, insensitivity to anti-growth signals, avoiding apoptosis, uncontrolled replication, continuous angiogenesis, tissue invasion and metastasis [15-19].

Self-reliance in growth signals

Normal cells cannot proliferate in the absence of growth signals [13]. Tumor cells on the other hand generate their own growth signals reducing their dependence on normal tissue microenvironment, leading to disruption of the homeostatic mechanism. This autocrine secretion of growth signals and responding to their own is an important concept in linking oncogene and growth factor research

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[13, 20]. Over expression of cell surface receptors may facilitate hyper responsiveness to the ambient levels of growth factor and may elicit ligand-independent signalling [13]. Cancer cells transducer signals to the extracellular matrix through the extracellular matrix receptors, Integrins, influencing cell behaviour and foyer into active cell cycle [13]. These signals convey alterations in the components of the downstream cytoplasmic track causing the deregulation in signalling pathways [13]. Also the cell-cell communications, heterotypic signalling, where the tumor cells induce the normal cells to release growth signals explains the tumor cell proliferation potential [13].

Insensitivity to anti-growth signals

Proliferation of normal cells is controlled by the signals received by transmembrane cell surface receptors coupled to intracellular signalling circuits. These signals include soluble growth inhibitors and inhibitors present on the extracellular matrix and the cell surface [13,21]. These signals inhibit proliferation by forcing the actively dividing cells into quiescent phase and/or cells nay be induced into post-mitotic phase [13,21]. Mutations in tumor suppressor genes, which inhibit cell division result in increased cell division. Retinoblastoma (Rb) protein, p53 gene, Tumor growth factor β (TGFβ) are some of the extensively studies examples of tumor suppressor proteins [13,21]. In normal cells growth and development is stimulated by transcription factor c-Myc in association with another factor, Max. Differentiation in normal cells occurs when Max complexes with Mad transcription factors. c-Myc oncoprotein is over expressed in many tumors, which favours Myc-Max complexes, inhibiting differentiation and promotes growth [13,21].

Avoiding apoptosis

Acquiring resistance to apoptosis is a trait in almost all cancer types [13,22,23]. Apoptosis is programmed cell death mediated by sensors and effectors. The apoptotic program is triggered by an over expressed oncogene and removal of such cells bearing over activated oncogene represent the way by which mutant cells are selected from body tissues [13]. Disrupting the balance between anti-apoptotic and pro-apoptotic. Proteins, impaired death receptor signalling and reduced caspase function are the mechanisms by which tumor cells evade apoptosis [13,23]. These evidences provide a rationale for the resistance to apoptosis in tumor development.

Uncontrolled replication

By basic definition, cancer cells are capacitated to divide uncontrollably. Unlike normal cells which tend to terminate division after few cell cycles, a condition termed senescence; cancer cells have triumphed over this condition and are in ever replicating stage [13,21]. The chromosome length in normal cells is maintained by the chromosomal ends, telomeres, which maintain constant length, prevent end-to-end fusion of the chromosomes and protect the DNA from degradation by nucleases. On repeated cell cycles a short segment of the telomere is lost, 'end replication problem', progressively shortening the length of DNA, chromosomal end-end fusions, array and ultimate death of the cell. Cancer cells up regulate the expression of telomerase enzyme, which adds the hexanucleotide repeat units to the ends of the chromosome, thus maintain the length of telomeres above threshold, preventing erosion and allowing unlimited replicative potential [13,21].

Continuous angiogenesis

A continuous supply of oxygen and nutrients are required for the growth, survival and functioning of the living cells. The process of formation of primary vascular plexus is called Vasculogenesis and the differentiation of the plexus is termed Angiogenesis [18]. Angiogenesis in normal cells and tissues is a controlled process and also occurs under pathological conditions such as wound repair, rheumatoid arthritis, diabetic retinopathy and tumor [24]. The main difference between normal cells and tumor cells is the vasculature [15]. As the tumor cells grow in number and size, they are limited in supply of oxygen and nutrients. Thus there develops a state of hypoxia where the cells strive for survival [18]. The ultimate success of the tumors lies in their ability to generate new blood vessels [17]. The angiogenesis initiation is facilitated by signals from platelet derived growth factor receptors, vascular endothelial growth factors, fibroblast growth factors [13,15,17]. However the newly formed blood vessels are defective structurally and physiologically, which is the hallmark of the tumor vasculature [15]. This property has been exploited in the development of anti-cancer therapeutics to target tumors in angiogenesis, drug accumulation in the tumor microenvironment, radiation, gene therapy, overcoming drug resistance [13,15,17,18].

Tissue invasion and metastasis

Tumor metastasis is a multistage process where malignant cells invade local host tissue, extravagate and colonize in the distant organs [13,25-27]. Metastasis is systemic in nature and resistant to therapeutic agents, explaining the cause of mortality in cancers [25,26]. Genetic variations lead to uncontrolled proliferation and provide survival advantage to support metastasis [25-27]. Cancer cells because of the overgrowth of the tumor leave the primary tumor through the newly formed blood vessels and invade the local host tissue. From there they enter the systemic circulation and reach distant organs, where they extravasate and form new colony of tumor [13,25-27]. Inhibition of natural proteinases and up regulation of tumor metastasis suppressor genes can suppress invasion and metastasis [25].

Novel Drug Delivery Systems in Cancer Therapeutics

Nanotechnology in cancer is an interdisciplinary branch of therapeutics that combines the expertise of Science and Engineering integrated with Medicine, implementing the bio-medical application of designing, production, and characterization through application of structures, devices and systems of nano-size, to provide targeted drug delivery, molecular diagnosis, molecular imaging, tissue regeneration, biosensors, cell culture, and other areas in molecular biology [2,28-30]. Nanoparticles with a size range of 1-100 nm [28,29] charm scientists owing to the opportunity to design the backbone structure, size, shape, surface area and attachments [31]. Nanoparticles are submicronic colloidal systems made of polymers, lipids, viruses, organometallic compounds [11], to which the drugs are either incorporated during polymerization or adsorbed [32]. The advantage of using nanoparticles as drug carriers is in their binding competence and reversing multidrug resistance [32]. Using active and passive targeting strategies, nanoparticles enhance intracellular drug concentrations [11], thereby providing an alternative to oral delivery of chemotherapeutics which have limitations of solubility, stability and permeability [33]. First pass metabolism by cytochrome P450 liver enzymes [33] and degradation by reticuloendothelial systems of liver and spleen [11], the limiting factors for drug bioavailability were overcome by designing the nanoparticles using an appropriate carrier matrix such as polymers in a size which prevents them from leaking

into blood capillaries and capture by macrophages. Anticancer drug resistance mediated by P-glycoprotein can be stunned by surface coating of the nanoparticles using bio-adhesive materials, which also improves adhesion and absorption [11,33] leading to higher intracellular concentration of the drug. Conventional methods of drug delivery have potential drawbacks such as low water solubility, nonspecific bio-distribution, poor pharmacokinetics, requirement of large drug doses, all resulting in harmful effects on healthy tissues [11,34]. Drugs loaded in suitable carrier (liposomes- lipid matrix, polymeric nanoparticles – polymer matrix, viral nanoparticles – viral matrix, nanotubes– organometallic compounds) [11] known as drug-carrier complex circumvent some of these obstacles. HPMA-Doxorubicin complex was the first to enter clinical trials [34]. But, to reduce the systemic toxicity (due to lack of specificity) and increase the systemic availability at the site of action, the drug should be directly targeted. This is achieved by conjugating the drug-carrier. Complex with a suitable ligand [3] (or simply bioconjugate) such as antibody, antigen, homing peptide [34]. Studies by Acharya et al have showed that the epidermal growth factor receptor conjugated rapamycin loaded poly (lactide-co-glycolide) nanoparticles have superior anti-proliferative activity compared to native rapamycin and unconjugated rapamycin [3]. Similar work by Alexis et al. proved the increased binding affinity of the drug encapsulated nanoparticles conjugated with poly-(D, L-lactic acid)-poly (ethylene glycol)-maleimide copolymer, targeting the HER-2 protein [35]. It is important for the increased therapeutic efficacy that the drug remains stable and for a long time at the site of action. Liposomes have high biocompatibility, encouraging pharmacokinetic outline and ease of surface modification, with limitations to insufficient drug loading, instability and fast release of hydrophobic drugs. Polymeric nanoparticles on the other hand dominate by having high permeability, small size, controlled drug release, encapsulate poorly soluble drugs and long systemic half-life, and yet are less biocompatible. Thus fabricating liposomes and polymeric nanoparticles yield lipid-polymer hybrid carriers which are biocompatible, efficacious with controlled and targeted delivery [32]. Paclitaxel loaded Poly (D, L-lactide-co-glycolide) (PLGA), a biodegradable polymer with good bioavailability, hybridized with 1,2-dilauroyl-*sn*-glycero-3-phosphatidylcholine (DLPC) having high stability resulted in improved drug encapsulation, enhanced absorption and reduced phagocytosis. Quantum dots loaded in biodegradable polymers were successfully used in imaging and targeting tumors by Pan et al. by using folate-decorated nanoparticles conjugating them with vitamin-E TPGS-carboxyl (TPGS-COOH) [36].

Types of nanoparticles

The classification of nanoparticles may be done based on the source of production and/or dimension [31,37] (Figure 1). Table 1 represents the classification of nanoparticles. Based on source of production, nanoparticles are classified as Organic nanoparticles and Inorganic nanoparticles. Organic nanoparticles are produced from organic materials, such as lipids, dendrimers, carbon, polymers, protein aggregates, milk emulsions, viruses, and so on. As these nanoparticles are organic in nature, they offer simple routes of encapsulation and fabrication, added with their ability of biocompatibility and biodegradability making them most appealing drug delivery systems. On the other hand Inorganic nanoparticles are produced from inorganic compounds such as alumina, silica, metals, metal oxides and metal sulphides [31]. The inorganic nanoparticles are highly stable and can be functionally optimized for diagnosis and treatment, using attachments such as biocompatible coatings, targeting sequences, biologically active molecules, imaging devices. Nanoparticles are classified based on the dimension as one dimensional, two dimensional and three dimensional nanoparticles [29,37]. Thin films, monolayers and manufactured surfaces with a size of 1-10 nm find their use in chemical and biosensors, optical devices [37]. Two dimensional nanoparticles range from <1 nm in diameter to about 100 nm in length. Nanowires, carbon nanotubes, nanofibres and nanopolymers come under this category. Dendrimers, fullerenes, quantum dots are classified under three dimensional nanoparticles.

Polymers: Macromolecular drugs designed using polymers have the advantage of pliability to chemical modifications, where the drug can be physically caught in or covalently bound to the polymer matrix, rendering them particularly suitable for applications in nanomaterial drug delivery systems [11,31,38]. The polymeric matrix thwarts drug degradation and allows precise control over its release kinetics from nanoparticles [3].

Polymeric nanoparticles: Polymeric nanoparticles are capsule shaped [11,31]. Based on the source of polymer, these drug carriers are classified as synthetic polymers, natural polymers, pseudosynthetic polymers [11,38]. Polymers of synthetic origin include polyethylene glycol (PEG), N-(2-hydroxypropyl) methacrylamide copolymer (HPMA), poly (lactide-co-glycolide) (PLGA), polystyrene-maleic anhydride polymer, poly (vinylpyrrolidone), poly-L-glutamic acid (PGA), poly (ethyleneimine), linear polyamidoamines (PAMAM). PLA and PLGA are biocompatible and biodegradable carriers, approved by the United States Food and Drug Administration (USFDA) for human use owing to their extremely small size and surface coating that plans their escape from hepatic degradation by P450 enzymes and capture by P-glycoprotein, thereby providing sustained and targeted drug delivery with better efficiency and fewer side effects [3,31,33]. Dextran, dextrin, albumin, alginate, gelatin, chitosan, heparin, hyaluronic acid are natural polymers [11,31,38,39] used to deliver molecules such as oligonucleotides, DNA, proteins and drugs [11]. Pseudosynthetic polymers are man made polymers and these include poly (L-lysine), poly (L-glutamic acid), poly (aspartamides), poly (malic acid) [31,38].

Polymeric micelles: Polymeric micelles have amphiphilic core or shell structures of 10 to 1000 nm [11,31]. The polymeric micelle structure consists of an external hydrophilic shell and an inner hydrophobic core [11, 39-41], suggesting the amphiphilic property of the micelles in aqueous medium. The hydrophobic core serves as a reservoir for hydrophobic and amphiphilic drugs, while the hydrophilic shell stabilizes the hydrophobic core making them water soluble and increasing the circulation time in blood and accumulation in tumoral tissues [11,39] and also protects them from enzymatic degradation, hydrolysis and elimination by reticuloendothelial system [41]. Drug loading is done by either drug conjugation and/or drug encapsulation [11,40]. Hydrophobic drugs are conjugated to the hydrophilic backbone using biodegradable chemical linkers. In drug encapsulation the drugs are physically entrapped in the hydrophobic core of the micelles [40]. Polymeric micelles constitute excellent delivery vehicles owing to their tuneable size and morphology, surface functionality, brilliant stability and high monodispersity [40,41], thus being employed for sustained targeted intracellular drug delivery and make them appropriate candidate for parenteral delivery [11,39].

Dendrimers: Dendrimers are polymer based, monodisperse,

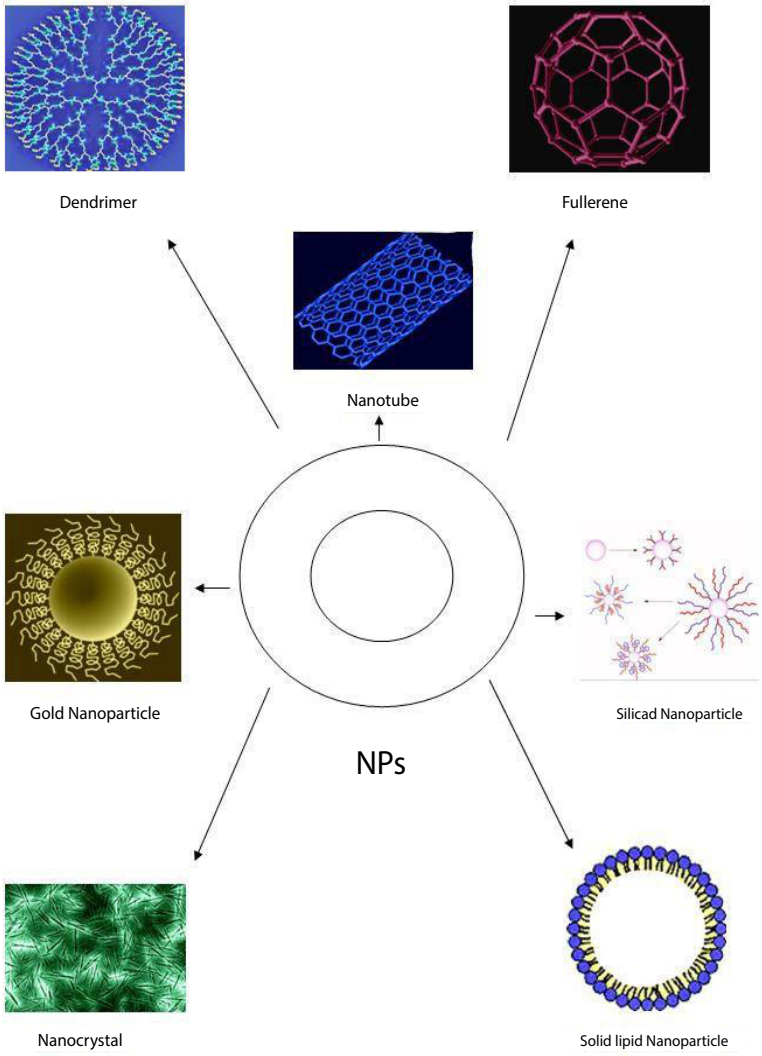


Figure 1: Types of nanoparticles.

Table 1: Classification of nanoparticles.

Classification of Nanoparticles	
Based on production source	
Organic Polymeric nanoparticles, Liposomes,Dendrimers, Carbon nanotubes	*Inorganic* Gold nanoparticles, Nanorods, Nanoshells, Quantum, dots Nanowires, Paramagnetic nanoparticles, Solid lipid nanoparticles, Fullerenes
Based on dimension	
One dimensional, Two dimensional, Three dimensional	Thin films, monolayers, Carbon nanotubes,Fullerenes, Dendrimers, Quantum dots

highly branched macromolecules with symmetric architecture [11,29,30,31,37-39,41,42]. Their structural units are monomeric or oligomeric units and consist of a central core, branching units and terminal functional groups [31,41]. They have a symmetrical structure and the core shell architecture grows linearly in diameter and exponentially with respect to the surface groups [31,38]. The core determines the environment of the nanocavities and chemical behaviour while external groups determine the chemical behaviour and the solubility. The globular structure and the presence of internal cavities enable encapsulation of drugs and modification of the degree of branching may allow for more [31,39]. Drugs can be physically entrapped or chemically attached. With a size of about 10 nm, they are considered to be basic elements for the synthesis of 1 to 100 nm organic and inorganic nanostructures [29,37,39]. They also can

be functionalized with hydrophilic end groups making them water soluble, and designed with internal hydrophobicity for incorporation of hydrophobic drugs. Functionalizing the terminal groups with amino group renders positive charge enabling interaction with negatively charged phosphate group of nucleic acids [29,31,37]. Monodisperse size, ease of preparation, modifiable structure, functionality, water solubility, availability of internal cavity, multivalency to display multiple copies of surface groups make them attractive candidates for chemotherapeutic drug delivery, imaging, targeting ligands [11,29,30,31,37-39,41,42]. However, toxicity is of main concern in the use of dendrimers as carriers along with stability and capture by mononuclear phagocytes, which can be overcome by surface functionalization with PEG chains [30,38,41].

Metal nanoparticles

Gold nanoparticles: Gold nanoparticles (GNPs) were applied in the field of medical sciences since the past decade [43]. They are produced and characterized by a variety of methods, and functionalized biocompatible gold nanoparticles demonstrate encouraging optical and chemical properties used in diagnosis, imaging and therapy [2,30,31,39,42,43]. GNPs accumulate in the tumor site via the EPR effect and are engulfed into the cell via non-specific receptor mediated endocytosis. Functionalization of the GNPs with PEG, folate, and thiamine prevents their destruction by the reticuloendothelial cells and render increased circulation times, internalization [39,43]. Nanoshells, nanocages, nanospheres, nanorods, nanogold, Surface enhanced Raman scattering (SERS) nanoparticles are the different types of gold nanoparticles [2,30,42,44]. Large surface are of GNPs facilitate more drug loading, but the toxicity issues need to be considered [39,43,45].

Nanoshells are synthesised using growing silica cores with gold, and gold and copper, gold and silver find their application in photothermal ablation and in imaging respectively [2,30,42]. Nanoshells are also used in diagnostics by coupling them with antibodies in whole blood immunoassays [30]. Gold nanospheres range from 2 to 100 nm in diameter and with their fast penetration ability they find their use in phototherapy and diagnostics [43,45]. Colloidal gold particles or nanogold44 are used in immunotargeting owing to their ease of bioconjugation [45]. GNPs targeting epidermal growth factor receptor are used in the treatment of breast cancer, pancreatic cancer [43]. They also enhance the apoptosis and antiproliferation of human hepatoma cells [2].

Iron oxide and super paramagnetic iron oxide nanoparticles: Iron oxide nanoparticles have been extensively used as imaging agents, owing to their magnetic make up and biocompatibility [30,39]. Targeting these nanoparticles enables evaluation of tumor location as well as the stage of the disease. Conjugation with antibodies to HER-2, luteinizing hormone release hormone facilitates detection of breast cancers [30]. Circulation time of these nanoparticles can be increased by covalently linking with chemicals and internalization by treating with drugs like lovastatin [30]. Owing to their miniscule size, large surface area and magnetic properties, these NPs serve as excellent drug carriers to the desired tumor location [39]. Flavin mononucleotide coated fluorescent nanoparticles are used in targeting and labelling of endothelial cells and active cancer cells by targeting riboflavin carrier protein [46].

Silica nanoparticles: Silica nanoparticles are generally prepared by sol-gel methods [31]. They have uniform pore size and high surface area, making them ideal drug carriers, where the drugs are physically adsorbed [40]. Treated cells showed reduced viability [42]. Ease of synthesis and functionalization with amino-hexyl-amino-propyltrimethoxysilane, decrease the toxic effects and enable as ideal drug carriers [31,42].

Calcium phosphate nanoparticles: Calcium phosphate nanoparticles are efficient carriers of DNA for the targeted delivery of genes in anticancer therapy [47,48]. The calcium ions form ionic complexes with DNA and impart stability to DNA [44]. Single shell and multi shell calcium phosphate functionalized with DNA, siRNA are carried across the cell membrane through endocytosis mediated by ion channels [47,48]. These nanoparticles are also used for the delivery of vaccines across the skin [49].

Carbon nanoparticles: Carbon nanoparticles include carbon nanotubes and fullerenes. Carbon nanotubes are long cylindrical structures in a hexagonal network of carbon atoms, ranging approximately 1.5 nm in diameter and 100 nm in length [11,29,30,38,42]. These nanotubes are either single walled or multi walled [29-31,37,42]. They are composed of either polymer or silica or carbon or metal [38]. Carbon nanotubes are insoluble and render toxicity issues [11]. Chemical modification causes them to be water soluble and functionalized to be linked to peptides, proteins, nucleic acids, therapeutic agents [11]. They are nontoxic, highly biocompatible, and chemically stable with high surface area, low leakage of the drug [30,37,39]. Nanotubes can be conjugated with fluorescent or radiolabelled ligands and can be used in imaging and targeting [30]. Fullerenes, also known as bucky balls are carbon allotropes made of more than 60 carbon atoms and are spherical in shape [29,30,39]. They find their use in the delivery of anticancer drugs, biomolecules across cell membrane and to stimulate the host immune responses [30,39]. Endohedral, exohedral and heterofullerenes are the different types of Fullerenes [30].

Quantum dots: Quantum dots are assorted, colloidal, semiconductor, luminescent, nanocrystals extending from 1 to 10 nm in diameter [29-31,37,42]. They are synthesised from semiconductor materials using methods like colloidal synthesis and/or electrochemistry [37]. Their structure consists of an inorganic core, inorganic shell and aqueous organic coating [30,31]. The size of these nanoparticles determines the luminescence colour and colour coded quantum dots are used in DNA testing [30,37]. Quantum dots are used in diagnostics, drug delivery, imaging, tissue engineering, owing to their large surface area [30,31,37]. Toxicity is a major constraint in the use of quantum dots which can be overcome by surface modification with N-acetylcystine [42]. PEGylation of quantum dots increase the biocompatibility and stability [31]. Cadmium selenide, cadmium telluride, indium phosphide and indium arsenide are the commonly used quantum dots [37].

Liposomes: Liposomes are lipid based drug carriers, composed of a lipid bilayer with a surrounded phospholipid membrane and contains a central aqueous core [11,30,31,39,41]. They may also be unilamellar or multilamellar [30]. The phospholipids include phosphatidylglycerine, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine [39]. The drugs can be loaded either in the aqueous compartment or in the lipid membrane [30]. Polar drugs are generally loaded in the aqueous interior, while the amphiphillic

and lipophilic drugs are solubilized in the phospholipid bilayer [41]. Ease of modification, high biocompatibility, targeted drug delivery, preventing drug degradation, amphiphillic nature, less side effects make them ideal drug carriers [11,30,31,39,41]. However, poor storage capacities, low encapsulation efficiency, rapid leakage of the drug are the limitations, yet to be overcome [39]. Surface modification with PEG improves the circulation time of the liposomes in blood, while conjugating them with antibodies, ligands render targeted delivery and stability [31,39]. Niosomes, marinosomes, ethosomes, transferosomes are the different types of liposomes in use for drug delivery [39].

Viral nanoparticles: Viral nanoparticles (VNPs) are naturally occurring bionanomaterials derived from plants, insects and bacteria which are not only biocompatible and biodegradable, but also non-infectious and non-hazardous to humans. Virus-like nanoparticles (VLNPs) are a subtype of VNPs that are devoid of genetic material [50]. VNPs are well-characterised, structurally uniform with high loading capacity, safe, and easy to produce in bulk and engineer [50,51]. The first VNPs produced were from plant cowpea mosaic virus, which showed increased delivery to cancer cells due to the ease of binding of the drug encapsulated nanoparticles to the virus cells. The protein coating of VNPs can be conjugated or encapsulated with specific ligands and antibodies for targeted delivery [11,50]. VNPs can thus be used in delivery of vaccines, imaging using iron oxide, gene delivery and targeted delivery of chemotherapeutic drugs [11,50,51].

Solid lipid nanoparticles (SLN): Solid lipid nanoparticles are submicron colloidal lipid carriers, made of biodegradabale solid lipids like cetylpalmitate, glycerol tripalmitate, glyceryl behenate, having a size range of 10 to 1000 nm and added advantage over lipid emulsions and polymeric nanoparticles [31,39,40,52]. They possess solid, rigid core matrix consisting of hydrophobic lipids surrounded by a monolayer of phospholipids [19]. These NPs are stabilised by inclusion of high levels of surfactants to solubilize lipophilic molecules [40]. They are easily biodegradable, less toxic with high physical stability, high drug loading capacity, controlled drug release and can be produced on large scale [31,39,40,52]. They also show good tolerability, site specific targeting and controlled release of drugs [39,40]. Nanostructured lipid carriers (NLC) composed of solid and liquid lipids were designed to overcome the limitations of solid lipid nanoparticles. NLCs have high drug loading capacity and increased stability over solid lipid nanoparticles. Lipid drug conjugates take the advantage of incorporating both lipophilic and hydrophilic drugs. These nanoparticles can be used to deliver drugs orally, topically and via inhalation [31,39,40]

Nanocrystals: Nanocrystals are aggregates of crystalline form of drugs surrounded by a surfactant coating [31] and have emerged as an alternative form of drug delivery for poorly soluble drugs [53]. Nanocrystals have been formulated for hydrophobic drugs with a thin hydrophilic coating [31,54], and can be prepared by top-down method or bottom-up method [53,55]. The hydrophilic layer determines the biological reactions, and benefits in biodistribution and bioavailability, preventing aggregation [31]. The drugs loading capacity of these nanocrystals is about 100% and are most stable [55]. These formulations can be delivered intravenously and does not require prior solubilisation of the drug and hence are safer in terms of cellular toxicity [53,55]. The advantages of nanocrystals are in their ease of drug-loading, formulating poorly soluble drugs, excellent antitumor activity, easy scale-up for manufacture, cost effective, dose escalation and less toxicity [31,53-55].

Characteristics of nanoparticles

The asset of using nanoparticles in therapeutics lies in their modifiability with regards to their physicochemical properties and biological activity for desired biodistribution, establishing sustained-release drug profiles and providing an intracellular haven to protect them from degradation [31,56]. Characterization of nanoparticles involves evaluation of the physicochemical properties, assessment of pyrogenicity, toxicity, sterility, and biodistribution tailored to individual therapeutics and dosage regimen [31,56], as these assess the safety and toxicity of the nanoparticles [56].

Physicochemical characterization: This involves particle size, size distribution, surface chemistry, porosity, solubility, purity, stability, aggregation/agglomeration state, all of which determine/influence the *in vivo* distribution, targeting ability, drug loading ability and release pattern, safety, stability, toxicity, efficacy of the nanoparticle and provide a basis for understanding the structure and activity relationship [3,11,29,37,56,57]. Simple molecules can be adequately characterized by their molecular weight and spectral properties to determine purity and functionality. However for nanoparticles which are multipart and multifunctional, thorough assessment individual parts, chemical stability, physicochemical properties along with *in vitro* and *in vivo* evaluation needs to be performed [56].

Size, size distribution and surface properties: Particle size affects the drug release, as smaller particles have large surface area [37]. Surface properties influence the adsorption of proteins, fugacity from phagocytes and fate of bioavailability. These parameters, which are often complicated, are determined by the following techniques. Particle size, size distribution and polydispersity index (PDI) can be determined by Scanning Electron Microscopy (SEM), Atomic force microscopy (AFM) and Photon-correlation spectroscopy (PCS) {also known as Dynamic Light Scattering (DLS)} [56,57]. Transmission electron microscopy (TEM) is used to determine the core size of the particles along with the homogeneity [57]. The hydrodynamic size at physiological pH and temperature in an isotonic solution, which influence the degree of agglomeration, can be measured by DLS, Quasi elastic light scattering (QELS) and Analytical Ultracentrifugation (AU) [56,57]. Mercury porositometry, Laser defractrometry, Rose bangle (dye) binding, X-ray photoelectron spectroscopy are also techniques used to determine the particle size [29,58,59].

Surface charge and hydrophobicity: Surface charge determines the electrostatic interaction of nanoparticles with bioactive compounds. This is evaluated through Zeta potential of the nanoparticles, which provides information about surface hydrophobicity, storage stability, and nature of the material encapsulated [37]. Surface hydrophobicity can also be determined by contact angle measurements, biphasic partitioning, hydrophobic interaction chromatography, while specific chemical groups attached to the surface can be identified by X-ray photon correlation spectroscopy [37].

Purity, composition and functional characterization: The structure, purity and functionality can be characterized by Nuclear Magnetic Resonance (NMR) spectroscopy [57,60-62]. Purity of the particles can be determined by UV-Visible detectors and fluorescence detectors. CHN analysis ascertains the purity and elemental composition of the nanoparticles. Composition can also be determined by Atomic absorption (AA) and Atomic emission

(AE) [57]. Surface Plasmon resonance (SPR) characterizes functional components like quantity, activity, orientation and distribution.

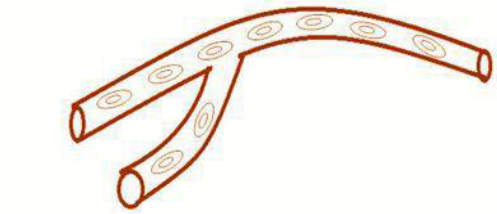
Stability, molecular weight and other characteristics: Stability of the nanoparticles under physiological and non physiological conditions deems essential for their biological activity, storage, light and thermal exposure, lyophilisation, ultra filtration, pH variation [57]. Molecular weight can be determined by Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy, along with presence of impurities [57]. The structural, magnetic, thermal and electronic properties can be considered using scanning tunnelling microscopy (STM), magnetic field microscopy (MFM), scanning thermal microscopy and electric field gradient microscopy (EFM) [57]. Quantification of nanoparticles can be performed by Enzyme-linked immunosorbent assay (ELISA) or bicinchoninic acid (BCA), UV spectroscopy or High performance liquid chromatography [37,57].

Drug loading and drug release: Drug loading and subsequent release are the two major factors which determine the amount of drug reaching the tumor site. The process of incorporation of a drug in a nano carrier is known as drug loading/encapsulation, and the reverse process of drug liberation is known as drug release, both depend on the type of nanoparticle [63]. Drugs can be loaded during the preparation of nanoparticles and /or after the preparation [63]. There are 3 methods of drug loading, viz., physical entrapment, chemical conjugation and poly ionic complexation [64]. Different techniques for analysing the mechanisms of drug loading are UV spectroscopy, ultra filtration, gel filtration, NMR, Fourier transform infrared spectroscopy (FTIR) [63], while X-ray photoelectron spectroscopy (XPS) and electron spectroscopy for chemical analysis (ESCA) investigate the surface chemistry [63]. As the drug reached the targeted site, its release is governed by drug solubility, desorption of the surface adsorbed drug, nanoparticle matrix degradation, drug diffusion through nanoparticle matrix and combination of erosion/diffusion processes [37]. Dialysis bag diffusion method, reverse dialysis bag method, agitation followed by ultracentrifugation, side-by-side diffusion cells, centrifugal ultracentrifugation methods, analyse the time period for the release of drugs [37]. An important parameter in the development of successful formulations is the efficient release of the nanoparticle encapsulated drug [3].

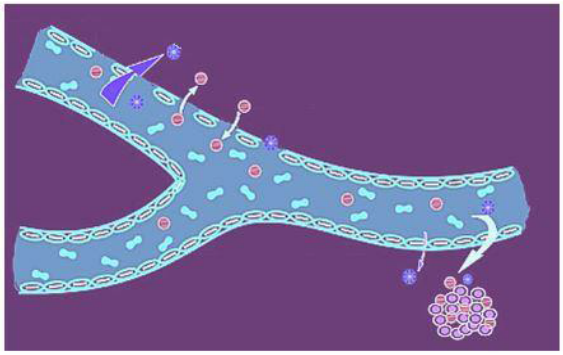
***In vitro* and *in vivo* characterization:** *In vitro* characterization of nanoparticles performed frequently with *in vivo* studies assesses the pharmacokinetics, efficacy, physiological and biochemical mechanisms, providing information about the biodistribution and toxicity profiles [56,57] of nanoparticles. *In vitro* studies offer a preliminary assessment concerning therapeutic nanoparticles, establishing the strategy of investigations required for *in vivo* trials [56]. *In vitro* characterization includes binding and pharmacology, cellular uptake and distribution, contact with blood, sterility and pyrogenicity [56,57,65]. The toxicological end points include protein synthesis inhibition and microtubule injury, which provide information of the potential cell death mechanisms and identify the compounds that cause these toxicities via mechanisms like apoptosis, oxidative stress, and mitochondrial dysfunction [57]. Target organ toxicity assessments are carried out on liver and kidneys, as these are the principle sites of accumulation, processing and clearance of nanoparticles [57]. Trypan blue exclusion assay and lactate dehydrogenase (LDH) leakage assay measure the membrane integrity. Metabolic activity can be measured by 3-(4, 5-dimethyl-2-thiazolyl) 2,5-diphenyl-2H-tetrazolium bromide (MTT) reduction assay. Monolayer adherence can be investigated by Sulforhodamine B total protein staining assay [56,57]. Cell cycle analysis, Cell binding and pharmacology can be elucidated by Flow Cytometry, ELISA, Surface Plasmon Resonance (SPR), Liquid scintillation counter (LSC) [37,57,65,66]. Biodistribution and Pharmacokinetics which are indexed by localization of the nanoparticle in the tissues can be identified by Energy dispersive x-ray (EDX) [56]. Blood contact is determined by Chromatography, High Performance Liquid Chromatography and Gel Electrophoresis. Cellular uptake is determined by Fluoresence Microscopy, Scanning Electron Miscroscopy, and Electrophoresis. Reactive oxygen species generation by nanoparticles is vowed to the unique surface chemistry, large surface area and catalytic contaminants of nanoparticles, which can be assessed by fluorescent dichlorohydroflourescein (DCFH) assay [57]. Phagocytosis can be assayed by EM, chemiluminescence [56]. Sterility and pyrogenicity of the nanoparticles is determined by lumulus amebocye lysate (LAL)-based assay and rabbit pyrogen test [56]. *In vivo* characterization involves the examination of effects on internal organs and immune system, evaluating the hematology, pathology, clinical chemistry, histology [56], the primary goal of which is to evaluate the pharmacokinetics, safety and efficacy [57].

Exploiting tumor properties

Lack of selectivity, systemic toxicity and rapid renal clearance are the major constraints of delivering drugs to solid tumors [67-



Normal Blood vessel



Tumor leaky blood vessel

Figure 2: Normal *vs* tumor vasculature.

70]. Nanoparticles exploit the advantage of tumor vasculature characteristics such as the disorganised tumor vessels, the enlarged gap junctions between the vascular endothelial cells and compromised lymphatic drainage, and are passively targeted to the tumor site, thereby limiting systemic toxicity and bypassing elimination (Figure 2). Selective targeting is achieved by taking advantage of the aberrant vascular construction, hypervascularization, thereby enhancing the permeability of the drug to the tumor site, while lack of lymphatic drainage and tight endothelial junctions prevent their escape leading to increased retention in plasma. This effect known as "Enhanced Permeability and Retention" (EPR) effect [7,11,67 80] is a medal standard for novel drug design. Macromolecular drugs easily are spilled through the gaps in the vascular endothelial cells and are cleared from tumor tissue at a much slower rate than from normal inflammatory tissue [73,75]. This permeability has become an important phenomenon for the targeted delivery of drugs and imaging using Magnetic resonance imaging (MRI), Positron emitting tomography (PET), fluorescent imaging [73]. The vascular permeability and the EPR effect are generally enhanced by mediators such as bradykinins, angiotensin converting enzyme inhibitors, oxygen radicals, nitric oxide [69,70,73,75,81]. Also, the tumor tissue has derailed autoregulatory homeostatic blood flow control, allowing elevated blood pressure and flow. This property can be made use to deliver specific drugs to the tumor [75]. Impaired lymphatic drainage due to tissue destruction and increased interstitial pressure is another attribute permitting selective accumulation/retention of the drug for longer time in the tumor interstitium [7,11,69,70,73,75,82,83]. Cancer cells are hyper proliferative and hyper metabolic [84]. The circulating enzymes metabolise the nutrients providing energy and tumor cells obtain extra energy *via* glycolysis [11,69,70,77,85], creating tumor acidic environment [7,11,67,69,70]. This acidic microenvironment is yet another imperative feature for selective release of pH sensitive slow release drugs. All these features added together can be used in tumor specific drug delivery.

Passive and active targeting

The conclusive objective of cancer therapeutics is to potentially target tumor cells alone, limit the drug dose and dosage, and avoid systemic toxicity and side effects. Nanoparticle technology offers a rousing stand for drug delivery and to perform more intricate and targeting functions by engineering them [28,70]. The phenomenon by which nanoparticles escape from the tumor vasculature and get aggregated in the interstitia by EPR effect is called Passive targeting [11,28,34,40,69,70,86,87,88], taking the advantage of vascular permeability. For the nanoparticle to reach the target site, the systemic circulation time should be increased, which can be achieved by coupling the chemotherapeutic agent to a suitable molecular carrier [34,40]. Very high concentrations of the nanoparticles can be achieved in the tumor site and the basis for this is the differential accumulation of nanoparticles, which in turn depends on the interstitial fluid pressure [69,86,87]. For passive targeting to be effective three properties should be carefully considered. (1) Nanoparticles should be effectively sized to escape the capture of liver and filtration by kidneys, ideally between 10 nm to 100 nm. (2) The nanoparticles should be of neutral or anionic charge for evading renal elimination and (3) Nanoparticles should escape destruction by reticulo-endothelial system [28,69,87]. Drugs coupled to certain molecular carrier via degradable linker effectively increase the concentration in tumor site [28,34]. As the tumor microenvironment is acidic in nature, many drugs are conjugated to tumor specific molecules/delivery systems and administered, where the nanoparticle is degraded to release the active drug [11,34]. The delivery systems include liposomes, nanocrystals, inorganic nanoparticles, micelles, etc and molecules include PEG, polyvinyl alcohol, chitosan, dextran, etc [40,87]. Successful passive targeting is limited by the extravasation of the nanoparticle, as being tumor specific and high interstitial fluid pressure [11,69]. To overcome these obstacles, the nanoparticles have to be actively targeted. Active targeting involves conjugation of targeting ligands on the surface of the nano carrier with receptors that are over expressed on the target tumor site, evading drug efflux pump, to increase tumor cellular take and retention [3,11,28,34,40,69,86,87,88]. One approach to achieve this is to target the tumor microenvironment including the extracellular matrix and alternatively to target the tumor surface receptors [88]. Peptides, antibodies, growth factors, transferrins, cytokines, nucleic acids, glycoproteins, polysaccharides, folate, small molecules are expansively engaged as targeting moieties [3,34,40,69,87]. Nevertheless large hydrodynamic size limits their intratumoral uptake, and distribution in tumor. On the top, conjugation of antibody to multifunctional nanoparticle adds further complexity in the scale-up production [35].

Optimizing nanoparticles by computing and engineering

Nanoparticles have significantly influenced the medical domain with imprints in diagnosis, treatment, prevention. The effectiveness of the nanoparticles can be enhanced by understanding their behaviour *in vivo* using computational methods, allowing classification of nanomaterials, analysis of data derived from biomedical application, and simulation of nanoparticles interaction with biological environment [89]. Identification of specific biomarkers or drug targets minimizes adverse effects of the drug molecule, while it simultaneously maximizes the therapeutic efficiency. This computer modelling is done at different levels based on timescale and length scale, viz., electronic scale, atmositic level, mesoscale level and continuum level [90,91]. Strategies to bypass the physiological barriers, like use of targeting agents, employment of materials that promote intracellular trafficking and enable controlled drug release, to maximize blood half-life and facilitate the navigation in the body have been facilitated by tuning the overall size and surface chemistry of the nanoparticles. Surface modification of nanoparticles is done by physical and chemical methods [92,93]. Chemically, organic and inorganic compounds are used or polymeric grafting is done. This way hydrophilic nanoparticles are made hydrophobic which ultimately increases the interface interactions [92]. Surfactants or macromolecules are adsorbed on the surface of nanoparticles in physical methods [92], which decrease the particle-particle interactions, deteriorating agglomerate development. Natural or synthetic polymer nanoparticles can be engineered, because of their stability and ease of surface modification, to achieve controlled drug release and localization at the disease site. Mahmoudi et al., have architecture the surface of superparamagnetic iron oxide nanopartciles by surface coating with polymers, polyethylene glycol, polyethylene glycol fumarate, polyvinyl alcohol, polysaccharide-based coatings, acrylate-based coatings, alginate, chitosan and polyethylenimine, and inorganically with iron silica to achieve nanoparticles with hydrophilic surface without deterioration of magnetic properties to have high colloidal stability and dispersibility [94]. Liposomes, dendrimers, micelles which are macromolecules with globular structure can encapsulate or entrap the therapeutic and/or diagnostic

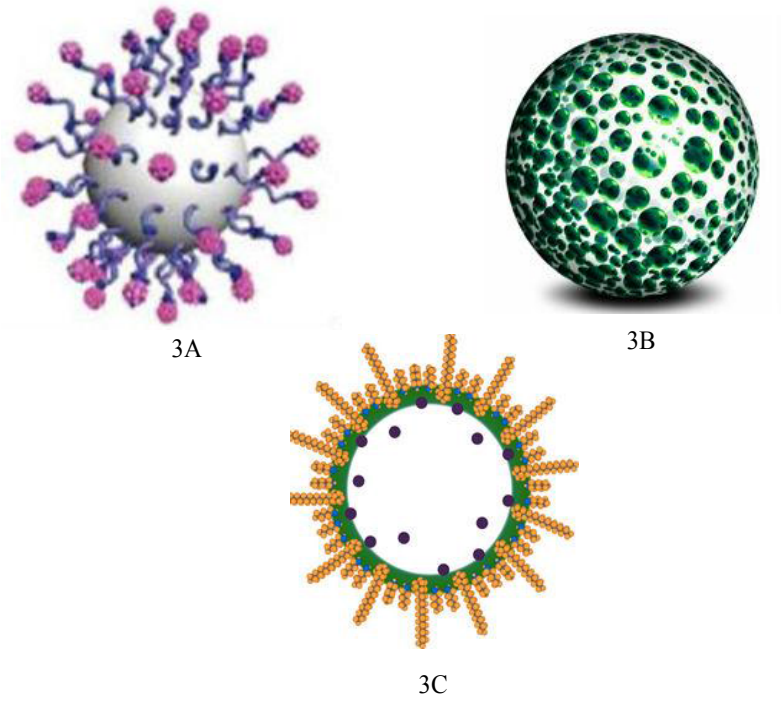


Figure 3: Surface modified nanoparticles (A) nanoparticle coated with synthetic polymers, (B) surface modified liposomes (C) surface modified polymeric micelles.

agent(s) improving solubility and systemic circulation period while protecting them from biodegradation and/or elimination [95]. For maximum effectiveness the surface of the nanoparticles are modified with hydrophilic agents such as polyethylele glycol, and conjugated with homing devices such as antibodies or aptamers and imaging devices such as quantum dots and gold nanoparticles (Figure 3).

Applications in cancer therapeutics

In gene therapy:

Tumor growth and metastasis are dependent on angiogenesis and this has led to the development of a new therapeutic modality to target the tumor vasculature where gene therapy a novel approach holds promising clinical applications in this regards [5,67,96-99]. The use of gene therapy yields sustained expression, while lack of safety and efficient delivery systems, and efficacy are the setbacks [67,96-98]. Two types of vectors find their use in gene therapy – viral and non-viral vectors [97,98,100,101]. Despite their high transfection efficiency of viral vectors, their toxic and immunogenic apprehensions encumber their usage, making non-viral vectors a better choice [30,67,97,98,100,101]. Non-viral vectors are safer and easy to produce with low immunogenicity, have long term gene expression, can incorporate large DNA molecules targeting specific genomic sites with no detrimental consequences [67,101]. Gene therapy entails the delivery of antisense oligonucleotides, specific to oncogene targets which can inhibit or alter the gene expression in target cell or tissue [32,67]. Nanoparticles in gene delivery are of two types: cationic and anionic nanoparticles, which overcome the hindrance in intracellular penetration, degradation and cytotoxicity by using an appropriate bioconjugated vehicle [32,67,100].

Drug delivery to brain, ovaries, breast, skin, and lung: Tumors of the brain represent the most challenging and difficult areas of medical treatment, due to the lack of effective drug delivery methods to the brain and blood-brain barrier (BBB), blood-brain tumor barrier (BBTB) limiting the uptake of neurotherapeutics and neuroimaging contrast agents [5,31,45,79,103-106]. Novel nano-drug delivery systems targeting brain tumors have been researched successfully over the past years with decreased toxicity and improved pharmacological profile 104]. Though the exact mechanism of delivery of nanoparticles to the brain is not elucidated [105] nanoparticle targeting to brain relies on the presence of specific receptor-mediated transport systems in the BBB and the interaction of the nanoparticles with them [45,79,104]. Physical adhesion of the drug to the nanoparticle is necessary and uptake of anionic nanoparticles was superior to neutral and cationic nanoparticles at lower concentrations [45]. Targeting low-density lipoprotein receptors (LDLR) offers the potential of therapeutic selectivity in chemotherapeutic drug delivery to treat Glioblastoma multiforme, a most lethal and devastating neoplasm [31]. Poly (alkylcyanoacrylate), polyacetate, polysaccharide nanoparticles were able to deliver dalagrin, doxorubicin and other agents successfully into the brain [45,79,104]. Biodegradable polymers greatly expand the spectrum of drugs available for the treatment of malignant brain tumors [5,103,105]. Other routes to bypass the BBB would be olfactory and trigeminal nerve endings, by conjugating nanoparticles with bioactive ligands-lectins to the surface of poly (ethylene glycol)-poly (lactic acid) (PEG-PLGA) [45]. Therapeutic agent loaded nanoparticles using mesenchymal cells as carriers injected intracranially, show increased therapeutic activity [107].

The fifth leading cause of cancer deaths, ovarian cancer, is associated with high morbidity and mortality among women [108]. Con-

ventional treatment measures such as surgery, chemotherapy with paclitaxel and intraperitoneal delivery of therapeutic DNA increased survival rate, nevertheless relapse due to multidrug resistance could not be deprived of [108-110]. Nanoparticles, liposomes, polymers, micelles, conjugated peptides are of use in ovarian cancer therapy recently [108]. Use of nanoparticle targeted therapy results in the overall increased survival rate with efficous outcomes. With the advancements in cancer therapy, there have been reduced mortality rates in women with breast cancer [111,112]. Well established treatment measures of breast cancer include surgery, hormonal therapy, radiation and chemotherapy [24]. Treatment with alkaloids, alkylating agents, anthracyclines, antimetabolites, topoisomerase inhibitors focused on suppression of cell division and inhibition of proliferation of cancer cells [24], but led to serious side-effects [24,112]. Understanding the pathophysiology of breast cancer paved way to therapy by molecular targeting [112,113]. Targeting therapies in breast cancer involve targeting the hormonal and nonhormonal receptors, which regulate cell differentiation, and growth, movement, cell-cell communications, and other complex interactions between cancer and tumor cells, respectively [113]. Liposomes, dendrimers, micelles, nucleic acids are the different carriers used in the novel treatment strategies against breast cancer [24,113]. The most common targets of these carriers include HER-2 receptor, which is over expressed in about 20-30% breast cancers [6,7,113,114], folate receptors, estrogen receptors [112], epidermal growth factor receptors [114-116]. Application of these treatment measures increased the survival rate and reduced the overall side effects of the conventional therapy [113]. Skin serves as a physical biological barrier for the penetration of microbes, chemicals, ultraviolet (UV) and infrared (IR) radiation and some drugs, thereby protecting the body form the callous eternal environment [117-119]. Skin cancers are mainly of two types: Melanoma skin cancers and Non-melanoma skin cancers [117,118]. Melanoma skin cancer originates from melanocytes, the cells which produce melanin, the pigment that gives the skin its characteristic colour or tan, and is malignant in nature [118]. Non-melanoma skin cancer is of two types: Basal cell carcinoma and Squamous cell carcinoma, and are the most common of the skin cancers in humans [117,118]. Though the under etiology is not completely understood, interactions between the skin and environmental factors, such as UV radiation might explain the pathogenesis [117,118]. Conventional surgical treatment measures include surgery, curettage and nonsurgical methods involve chemotherapy, radiation [118]. However, owing to the non-specific targeting and side effects such as pain, inflammation, scars these healing techniques are limited [117,118]. Nanoparticulate systems have been successful in increasing skin drug absorption and release time, achieved by the use of liposomes as nanoemulsions, biodegradable polymers, solid lipid nanoparticles, magnetic nanoparticles, which improve the drug adhesion to the skin and create hydration [117,118]. Titanium dioxide, zinc oxide, 5-fluorouracil, imiquimod are some of the chemotherapeutic agents frequently formulated with naoparticles for use in skin cancers [117]. Lung cancer is the leading cause of cancer transience globally [120-122], amongst all types of cancers. Small cell lung carcinoma and non-small cell lung carcinoma are the two types of lung cancers widely classified [120-122], the causative being the use of tobacco and nicotine products. Adenocarcinoma is another type of lung cancer associated with radiation, asbestos, and other environmental toxins [120]. Conventional treatment involves surgery, chemotherapy with Cisplatin and Carboplatin, radiation therapy, gene therapy [120-122]. However these methods have limitations such as poor targeting, systemic toxicity, intolerability, which can be overcome by the use of nanoparticles mediated drug delivery [120-122]. Carbon nanoparticles, polymeric nanoparticles, metal nanoparticles, liposomes, viral nanoparticles just to name a few are commonly used novel treatment measures [120-123].

In diagnostics and imaging: Enhanced cancer treatment is aimed at identifying the cancer signatures, monitoring drug delivery and assessing the drug-induced effects using noninvasive methods [123]. Cancer nanotechnology this is a multidisciplinary, problem-driven approach with the aim of bringing advances in cancer detection, diagnosis, imaging and treatment [44,124]. In order to diagnose, treat and monitor responses to therapy, single integrated nanoparaticles termed Theranostic nanoparticles were developed, with a hope of reducing the manufacturing cost and toxicity, while promoting the targeted delivery of chemotherapeutic agents [40,77]. Multifunctional magneto-polymeric nanohybrids, supramagnetic iron oxide nanoparticles (SPION), polyacrylamide-based hydrogel nanoparticles are some of the potential theranostic agents extensively studied [40,77]. For personalised therapy, the theranostic agent has to be modified to produce required physical and chemical changes in the body based on the response by activating them. This holds the advantage of restricting the amount and the duration of drug release, thereby closely monitoring the treatment efficacy [40]. Radio labelled nanoparticles tagged with appropriate fluorescent moieties conjugated with functional molecules serve as new diagnostic tools in cancer therapy [44]. Also the fluorescent nanoparticles such as Quantum dots can be used as subtle and highly specific probes for high-throughput screening, cellular biology and cell imaging [123]. Conventional imaging techniques such as MRI, PET, Ultrasound, Single photon emission computed tomography (SPECT), etc. are able to detect cancer only once the tumor or lumps are visible, while noninvasive molecular cancer imaging permits early detection of cancer at molecular level, even before the onset of phenotypic changes [40,77]. Lipid-based nanoparticles, quantum dots, multimodal imaging theranostic nanoparticles have growing importance in cancer imaging [28,29,124]. Carbon nanotubes, and gold nanoparticles are extensively studied for optical and acoustic imaging [77]. These imaging functionalized nanoparticles have the capability to allow focused and targeted therapy monitoring [77]. Polymeric nanoparticles loaded with docetaxel and superparamagnetic iron oxide nanocrystals are used in cancer therapy and imaging [125].

Targeted delivery

Antibody – targeted therapy and targeted delivery by small molecules: With the advent of therapies that target critical molecular pathways of tumors, finest treatment at low doses has become possible, as these offer better tolerance with fewer side effects [6]. Targeted therapy interferes with specific molecules that are required for growth and development of tumor, thereby inhibiting the tumor cell proliferation [6]. Antibodies were the earliest targeted therapies, and have emerged as important therapeutic agents for several malignancies [6,7] and their ability to target tumors enabled improved selectivity, which is influenced by multiple antigen recognition sites, effector domains, altered size [7]. Also, cytotoxic drugs can be selectively delivered using tumor-specific antigens as targeting moieties, reducing toxic side effects [3]. Vascular epithelial growth factors (VEGF), epidermal growth factor (EGF/HER1), HER2/neu are some of the pathways often targeted [6,7]. Two antibody-targeted therapies [6]-Monoclonal antibodies target extracellular components such as

ligands and receptor binding domains and small molecule inhibitors enter cell and block receptor signalling and interfere downstream intracellular molecules are actively under research and development, the differences of which are depicted in Table 2. The fragment antigen binding (Fab) site of the monoclonal antibody recognises and binds to the antigen with high specificity [6]. Monoclonal antibodies serve as carriers in immunoconjugate therapy by conjugating monoclonal antibodies to drugs, toxins, radioisotopes to enable enhanced killing of tumor cells [126]. Choice of target tumor antigen, ability to penetrate solid tumors, immunogenicity, half-life and immune effector functions of the antibodies are consideration factors for designing the appropriate monoclonal antibodies [7,126,127]. The development of antibodies in linked to the understanding of *in vivo* antibody properties, cancer serology, mechanisms of resistance, protein-engineering techniques and the assessment of the functional effects on cancer cells [127,128]. Based on the mechanism of action, i.e., engagement of antibodies with cell surface receptors, or to activate complement-dependent cytotoxicity (CDC), or antibody-dependent cell-mediated cytotoxicity (ADCC) the antigen-monoclonal antibody complex should not be internalized, allowing maximum availability of Fc region to complement proteins and immune effector cells [127,128]. Antibodies that function by downstream regulation of cell surface receptors and by delivering toxins into cancer cells require internalization [127,128]. These antibodies are administered intravenously to avoid gastrointestinal degradation and hepatic metabolism [6]. Identification of antigens and receptors specifically overexpressed on tumor cells are under active research and utilize data from serological, proteomic, genomic and bioinformatic branches [128]. Therapeutically loaded nanoparticles with surface bound specific recognition ligands such as antibodies open a new era in the diagnosis, imaging and treatment of neoplasms [129,130]. Nanoparticle-antibody conjugates can be used both as targeting agent for the drug loaded nanoparticle and a therapeutic agent. Some of the nanoparticle-antibody conjugates are exemplified in Table 3. Size of the nanoparticle and the surface ligand density are the critical features to be optimized in the development of NP-Ab conjugates for better clinical applications [130]. Small molecule inhibitors on the other hand interrupt cellular processes by interfering with intracellular signalling of tyrosine kinases, which plays a key role in cell growth and proliferation, migration, angiogenesis [6]. Phosphorylation of proteins regulates most cellular activities and abnormality leads to flawed proliferation, anti-apoptosis and angiogenesis [7]. The delivery of small molecules by nanoparticles bypasses limitations such as poor water solubility, nonspecific biodistribution and targeting, and drug resistance thereby enhancing solubilized drug delivery, increased systemic circulation time, enhanced accumulation in tumor cells and reduced drug resistance [78]. Several small molecule chemotherapeutic agents [78] are encapsulated in nanoparticles with

Table 2: Difference between monoclonal antibodies and small molecule.

Attribute	Monoclonal antibodies	Small molecule inhibitors	Reference
Administration	Intravenous	Oral	6
Preparation	Bio-engineering	Chemical methods	
Targeting	Specific targeting	Less specific targeting	
Metabolism	Not metabolized	Metabolized by P450	
Drug interactions	Not significant	Significant	
Half life	Long (days to weeks)	Short (few hours)	
Dosage	Weekly	Daily	

Table 3: Nanoparticle-antibody conjugates..

Antibody	Nanoparticle	Target	Indication	Reference
Rituximab		CD20	Non-Hodgkin's lymphoma	7, 125, 126
Trastuzumab	PLGA	HER-2	Metastatic breast cancer	6,7, 125-128
Bevacizumab		VEGF	Metastatic colorectal cancer	6, 7, 125-127
Anti-nectin -2		Nectin-2	Breast and ovarian cancers	130
Gemtuzumab		CD33	Acute myeloid leukemia	127, 131
Alemtuzumab	Gold	CD52/ VEGF	Chronic lymphotic leukemia	125-127, 131
Cetuximab	Gold	EGFR	Colorectal cancer	6, 125-128
Panitumumab	Gold	EGFR	Colorectal cancer	6, 125-128
Herceptin	Polymeric	HER-2	Breast cancer	122

Table 4: Small molecule inhibitors. (CML: Chronic myeloid leukaemia, Ph +ALL: Pheladelphia chromosome-positive acute lymphoblastic leukaemia)..

Drug	Nanoparticle	Targeted Ligand	Target organ/tissue	References
Rapamycin	PLGA	EGFR	Breast cancer	1
Paclitaxel	PLGA	N-acetylglucosamine, sialic acid	Colon cancer	134
Cisplatin	PLGA-mPEG		Multiple cancers	76
Paclitaxel	SLNPs	Folate receptor	Solid tumors	49
Doxorubicin	Human serum albumin	DR4, DR5	Multiple tumors	135

Table 5: Ligand targeted nanoparticles.

Small molecule	Target	Indication	Reference
Gefitinib	EGFR	Small cell lung cancer	6, 7
Imatinib	Tyrosine kinase	Chronic myeloid leukemia	6
Dasatinib	Tyrosine kinase	CML, Ph + ALL	6
Sorafenib	Protein kinases	Hepatocellular and renal cell carcinoma	6
Sunitinib	Tyrosine kinase	Renal cell carcinoma	6
Doxorubicin	DNA	Metastatic breast cancer	75

wide and approved treatment of several cancers, some of them are listed in Table 4.

Ligand-targeted therapy: The delivery of ligand-targeted nanoparticles involves active targeting, which is based on molecular recognition of biomarkers overexpressed on tumor cells, through specific molecules conjugated to their surface and aims to increase specific cell uptake reducing systemic toxicity [7,133,134]. Ligands such as monoclonal antibodies, peptides, lectins, aptamers, and folate are coupled to nanoparticles so that the ligand can interact with the specific receptor at the target site, portrayed in Table 5.

Paclitaxel loaded heparin carrier target folate receptors in head and neck tumor [11].

Cisplatin loaded PEG-PLGA nanoparticles conjugated with aptamers are used to target angiogenic blood vessels in cancer tumor and endothelial cells.

Stem cell therapy: Researchers have confirmed the presence of two types of cells in a tumor: small, unusual, dormant, transformed cells known as Cancer stem cells (CSCs) or tumor initiating cells (TICs) and rapidly proliferating cells [74-76]. CSCs have the ability to retain their genetic program and thus can self-renew, regenerating the tumor and offer self-protection. Moreover these cells are resistant to conventional therapies, leading to relapse and formation of metastases [77,137,138]. CSCs have been identified in numerous tumors such as cancer of breast, lung, brain, colon, liver, bladder, prostrate, pancreas, head and neck, kidney, melanoma [137,138]. Normal stem cells have their application in the replenishment of blood and immune systems that were injured in cancer treatments. They also subsidize as delivery vehicles and in tissue regeneration in cancer [139]. Self-renewal, ability to produce wide spectrum of progeny, utilization of common signalling pathways, expression of specific surface markers and oncogenes are some traits commonly shared by both normal and cancer stem cells. One character that differentiates these cells is that CSCs have tumorigenic ability, and that these cells do not have the control on their cell number, a trait which is thought to be obtained through multiple mutations in the genomic level resulting in their genetic instability or oncogene-induced plasticity [138,139]. Ligand targeted nanoparticles with impounded chemotherapeutic agents overcome the risk of drug resistance increasing the selectivity and internalization [137]. Examples of nanoparticles targeting CSCs have been depicted in the Table 6. New treatment models targeting CSCs are under research with several of these nanomedicines under clinical trials, with a focus on the elimination of cancer initiating cells [137,138].

In vaccines: Immunotherapy is a new cancer treatment modality where Nanoparticles as cancer vaccine carriers increase tumor-associated antigen delivery efficiency to the target immune cells, and prevent the degradation of vaccine, thereby increasing the immune responses against tumor cells [39,67,144-146]. The benefit of this approach lies in the ability to systemically stimulate the anti-tumor immune response in the host body inducing tumor cell killing specificity while resulting in immunological memory to provide long term protection against relapse [146]. Tumor associated antigens (TAAs) are proteins that are specifically expressed on tumor cells and nanocariers loaded with TAAs can be specifically targeted to the Antigen-presenting cells (APCs) or dendritic cells (DCs), to successfully deliver tumor specific antigens and enhance immune response for cytotoxic T cells [143,146]. Moreover the potential of the nanocarriers to control or sustain the release of antigens at tumor site results in site-specific accumulation for long term antigenic memory [144,146]. The advantage of nanoparticles is that they can encapsulate various antigens simultaneously demonstrating inhibition of tumor growth and metastasis, while boosting the immunity and relapse prevention [143,145]. Surface fabrication is one more attribute to functionalize the nanoparticles, for example, in dimensions resembling pathogens to orient surface active nanoparticles to attract and engulf more nanoparticles [144,146]. Antigen loaded polymeric nanoparticles hold noteworthy potential as vaccine delivery systems [147].

Challenges involved with nanoparticles

In manufacturing, research and development, and regulatory: Production of nanoparticles using the conventional trials and safety procedures may not be apt [147]. The testing procedures for assessing the safety of nanoparticles are deemed inadequate [9,29-31,37, 39,41,42,148] and extra measures and assays are under investigation to call off the toxicities associated with the use of nanoparticles. For the nanoparticle to penetrate the deeper tissues, they should be nanosized. The smaller is the size, the greater is the surface area and some nanoparticles with large surface area show increased toxicity [29,37,39]. Any drug, device or biologic product meant for human and/or animal intervention has to be approved by certain regulatory authorities, complying with the good clinical practice (GCP) and good manufacturing practices (GMP) guidelines [30,148]. Nanoparticles have to triumph the stringent assessment criteria to be approved for human use. This calls for investors and manufacturers to invest time and capital [30,148]. More over the data and statistics generated from animal and *in vitro* studies cannot be completely co-related with use in humans, which demands further research and tests obsessed by the applications and risk involved [30,42,148]. Producing nanoparticles of desired size, using the correct choice of carrier, drug entrapment, biocompatibility, biodegradability, to permit enhanced retention and controlled release of the encapsulated drug sustain as major challenges in the research and development and manufacturing [29-31,39,41]. Modifying the characterization of the nanoparticles,

Table 6: Nanoparticles in stem cell therapy.

Nanoparticle	Conjugated/ encapsulated with	Target	Reference
Curcimin loaded NP	Polymer	Brain tumor	136, 139
Gold NP	Doxorubicin	Breast	140
Mesoporous silica NP	Folate	Notch signalling	136, 141
Paclitaxel loaded NP	Anti-CD133 antibody	Liver cancer	142

conjugation with appropriate ligands, are some of the ways to tackle the scenario [39]. However large scale up production poses the risk of low concentration of nanomaterial, improper encapsulation of the drug, agglomeration, cost of material and time involved in production. These challenges are still to be addressed, standards to be designed to characterize and measure the benefits and risks [39].

In drug delivery: Nanoparticles are designed and optimised to overcome the barriers in drug delivery, by improving the bioavailability, stability, solubility, sustained release of drug at the tumor site, and ease of access to the targeted location, and to by-pass the systemic toxicity and macrophage uptake [1,10,11,28,34,41,67-70,148]. Of all the routes of drug administration peroral route is still extensively investigated owing to the advantage of convenience and low manufacturing cost [41]. However the barriers of acid and enzymatic degradation are still live. Pulmonary delivery has the risk of drug accumulation in the alveoli and blood capillaries. Inhalation and sublingual routes have the shortcoming of ocular and delivery to internal tissues. Transdermal delivery avoids gastrointestinal discomfort and first pass metabolism, but cannot dodge slow penetration, lack of dose precision [41]. One more deficiency is the lack of understanding of the *in vivo* behaviour of the nanoparticles, in terms of distribution, accumulation and elimination [31,42], which is currently under investigation.

Toxicity, hazards and ethics: Regardless of the potential benefits of nanoparticles, there are certain detriments that were not considered until recently [29,42,148]. Cytotoxicity, by-products, inflammation, accumulation in the body tissues are some of the major problems associated with the use of nanoparticles that are beyond those caused with traditional drug delivery systems [39,41,42,148]. Pathologies of gastrointestinal system, cardiovascular and respiratory systems are not exhaustive [30]. Size of the nanoparticle, surface area and characteristics including shape, may play a role in determining the toxicity potential [29,42]. Carbon nanotubes are cytotoxic, while metals, metal oxides are inflammatory and cytotoxic [30,148]. It is thus palpable that the composition of nanoparticles determines their interaction with cells and tissues, and the potential toxicity [42]. The suspicion arises from the fact that ultrafine particles produced in nature as products of combustion or fuel exhaust have the same adverse effects compared to those caused by engineered nanoparticles [37,42]. Toxicity data of the nanoparticle is not merely sufficient to evaluate the safety and risk, but the data of each and every component involved [42]. Inflammation and tumor in lungs [29-31,37,42], skin toxicity [9], gastrointestinal toxicity [9,30,31,37], embolism, stroke, myocardial infarction, other cardiovascular diseases [9,30,31,148], platelet aggregation [42], central nervous disorders [30,31] are just a few serious adverse effects to add. Co-ordinated efforts of scientists in pharmaceutical industries and academia can help better to understand the underlying causes of the toxicity of nanoparticles and the data obtained from in vitro studies should be extrapolated with *in vivo* studies [9,30,42]. Also, the challenges like chances of developing lung cancer, systemic breakdown or conglomeration, accumulation and correlation of animal test results with human trails are the ethical issues that need to be responded to.

Future Prospects

Despite the technological advances in the fields of cell and molecular biology, pharmacology, engineering, proteomics, bioinformatics just to name a few, the longevity of survival of mankind is still at stake, owing to the increasing number of diseases, less effective treatment regimen, acquired drug resistance and toxicity, and cancer occupies the first position. Novel therapeutic agents and methods have been developed which tend to increase the treatment efficiency and survival rate. However, this set of advancement has its own limitations not limited to systemic toxicity, drug resistance, bulk drug doses, targeting inefficiency, side effects and high treatment costs. The advances in molecular biology and understanding of the critical pathways involved in cell transformation has escorted to the development of targeted drug delivery using nanoparticles, which have overcome most of the limitation of the conventional healing course. Biocompatible and biodegradable nanoparticles, with high drug loading and release capacity have been developed in the recent years and stand as the active tools of clinical research. Nevertheless, nanotechnology in cancer has the cons of large scale manufacturability, high cost, unexpected toxicity, intervention with normal biological processes, which when overcome might direct the medical sciences to prosperity.

Conclusion

Cancer nanotechnology unlocks opportunities for personalised diagnosis and treatment by the use of multifunctional nanoparticles for sensing cancer specific biomarkers, imaging tumors and functional delivery of therapeutic agent with real time progress monitoring. Extensive research is going on all over the world for exploring engineered nanoparticles for the delivery of anticancer therapeutics. While some such formulations are already in the market, the regulatory agencies are still sceptical about the safety, efficacy, scalability and stability of these formulations.

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