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Newer Developments in the Nanoparticles for Cancer Treatment.

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Review Article

ABSTRACT

The surgery, radiation therapy and chemo therapy are the conventional treatments of cancers which have own limitations. Certain Nano Particles (NP) can be designed to absorb preferentially certain wave length of radiation if they enter in the cancerous cells then they will burn them. The NP will circulate through the body, detect cancer associated molecular changes, assist with imaging, release a therapeutic agent and then monitor the effectiveness of the intervention. Recent advancement in nanoparticles have been done with more emphasis on targeting of nanoparticle to the tumour cells which can decrease the side effects to the normal cells. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Over the last two decades, a large number of nanoparticle delivery systems have been developed for cancer therapy some of them are liposomal, polymer–drug conjugates, and micellar formulations and an even greater number of nanoparticle platforms are currently in the preclinical stages of development. In this review, we discuss the various nanoparticle drug delivery platforms, the important concepts involved in nanoparticle drug delivery and basis fundamentals behind targeting of nanoparticles. We have also reviewed the clinical data on the approved nanoparticle therapeutics as well as the nanotherapeutics under clinical investigation.

INTRODUCTION

The most lethal diseases in the world are cancer and each year number of new cases increases with decreases the life quality of patients. The total survival rate form cancer is not enhanced importantly since last 30 years even though quick advances in the diagnostic procedures and treatments. There is a need for tailored medicines which can give the accurate detection of early stage of cancer and targeted deliveries of drugs to the tumour sites [1]. Conventional chemotherapeutic drugs circulated non-specifically in the body so they affect both tumour and non-cancerous cells producing dose related side effects. There may be other serious problems of non-specific drug delivery system like insufficient drug concentration reaching to the tumour site and existence of resistance problem which can decreases the effectiveness of cancer treatment. These problems can be solved using targeting of nanoparticles to the tumour cells which can increases the drug concentration at the site of action and minimizing the toxic effects to the normal cells. The strategies for increasing the drug concentration to the tumour cells may be done with active and passive targeting which restrict the undesirable toxicity to healthy tissue [2, 3].

The ability of nanoparticles to accumulate in the tumour cells is due to its enhanced permeability and retention (EPR) effect [4]. Naoparticles are generally <100 nm in size and have capacity to transport and deliver drugs to disease sites because they can bypass the P-glycoprotein efflux pump and so ability to overcome drug resistance. There are noteworthy efforts have been made to develop more efficient

nanoparticles which can deliver the anticancer drug to the target sites and minimize its toxic effects to the tumour cells. Many developed innovative nanotechnology platforms, such as polymeric nanoparticles, liposomes, dendrimers, nanoshells, carbon nanotubes, superparamagnetic nanoparticles, and nucleic acid based nanoparticles [DNA, RNA interference (RNAi), and antisense oligonucleotide (ASO)], have been applied to the delivery of specific anticancer drugs, including small molecular weight drugs and macromolecules (proteins, peptides or genes). There are also ligand targeted therapeutics approaches like immunotoxins, radioimmunotherapeutics and drug immunoconjugates which can increases the specificity of conventional anticancer drugs. There are also certain limitations of these conjugated agents even though they have capable effectiveness compared with conventional chemotherapy drugs [5]. The nanotechnology platforms may act as tailored made medicine and serve as customizable, targeted drug delivery vehicles to carry large dose of anticancer drugs to tumour cells because their physical and chemical properties like composition, particle size, surface charge, surface functionalization with hydrophilic polymers, and inclusion of tissue recognition ligands, will conduct their bio distribution and pharmacokinetics. This article overviewed current nanotechnologies for cancer therapy, recent advancement in the current technologies, basis for targeting, and nanotechnologies for combination therapeutic strategies. We examine the fundamentals behind targeting of nanomedicines to tumors and cancer cells. The purpose of this review article is to summarize the results of the use of therapeutic nanoparticles in the clinic and discuss the opportunities and challenges faced by therapeutic nanoparticles.

TARGETED DRUG DELIVERY

Targeted drug delivery brings the therapeutics to the target site and should accumulate the required amount of drug within target zone irrespective of method and route of drug administration. There must be two basic properties which should have with nanoparticles to improve the patient quality of life and their survival. The first property is they must reach to the desired target site with minimal loss of their activity in the blood circulation for an effective cancer treatment and second is after reaching to the target site they must release the drug in controlled manner to kill the tumour cells [6]. They can have reduced dose-limiting toxicities also. Increasingly, nanoparticles seem to have the potential to satisfy both of these requirements for effective drug carrier systems. Targeted therapy or targeted medicine means specific interaction between a drug and its receptor at the molecular level [7, 8].

Enhanced Permeability and Retention Effect (EPR)

The certain sizes of molecules like nanoparticles, liposomes, niosomes, and macromolecular drugs have capacities to accumulate more in tumour cells compared to normal cells because of the enhanced permeability and retention (EPR) effect [9, 10]. The normal normal vasculature present in tumour vicinity is not sufficient to provide all the oxygen supply required for its further proliferation when a solid tumour reaches a maximum size, so the normal cells starts to die and they secrete the growth factors which can trigger the budding of new blood vessels from the nearby capillaries. These phenomena known as angiogenesis which promotes the rapid formation of new, uneven blood vessels that shows an irregular epithelium and absence of basal membrane of normal vascular structures. This may results in increase in the size of capillaries from 200 to 2000 nm. When blood components reach the irregular, broken vascular bed, this situation may offer little resistance to extravasation to the tumour interstitium. This denotes the enhanced permeation portion of the EPR effect. Many pathophysiological factors involved in enhancement of the extravasation of macromolecules in solid tumor tissues like bradykinin, nitric oxide, prostaglandins, vascular endothelial growth factor (VEGF), and tumour necrosis factor may enhances the EPR effect. The EPR effect of tumour cells helps to carry the nanoparticles and accumulated in the cancer cells so it is important for nanoparticles and liposomal drug delivery to cancer tissues.

Basics of passive targeting and active targeting

There are basically two types of Drug targeting "passive" and "active." The EPR effect is responsible for improving drug bioavability and its accumulation in the tumour cells of Non-targeted nanoparticles circulating in the blood. (Fig. 1). The pathological abnormalities in the tumour vasculature generated due to EPR effect is responsible for passive targeting of nanoparticles to tumours. Poor lymphatic drainage in tumours may also increase the accumulation of nanoparticles. The accumulation of anticancer drugs from nanoparticles at the tumour sites may be possible because of passive targeting effect. The enhanced tumour cytotoxicity has been observed due to diffusion of hydrophobic drug extracellular and taken up by tumour cells. Nanoparticle biodistribution and circulation time in the tumour cells are critical factors for cancer therapy because cancer cell populations, antigen expression, cell

density, microenvironment, and vasculature density are expressively different across different cancers and also within primary and secondary metastatic sites [11]. Nanoparticles must be engineered with ideal size and long circulation to take advantage of EPR effect, [12 - 14]. For passive targeting, nanoparticles must circulate in vessels to meet a leaky vessel of tumour and go through them to reach the tumour site [15].

"Active targeting" is used to describe specific interactions between drug/drug carrier and the target cells, usually through specific ligand– receptor interactions. The mechanism behind active targeting is extremely specific interaction between the targeting ligand and cell surface antigens which can increase the cellular uptake and retention. Ligand–receptor interactions are possible only when the two components are in close proximity (≥0.5 nm). The term "active targeting" has been able to guide a drug/ drug carrier to a target site. Existing drug delivery systems, however, do not have the ability to guide themselves to a target site [16, 17]. They have a capacity to reach the target area only as a result of blood circulation and extravasation followed by intra tumoral retention and distribution [18]. The active targeting involves surface modification of drug carriers by conjugating ligands including proteins, glycolipids, peptides, polysaccharides, glycoproteins, aptamers and monoclonal antibodies which specifically attach to receptors exist at the target site [19]. The term "active targeting" simply means a specific "ligand–receptor type interaction" for intracellular localization which occurs only after blood circulation and extravasation. To control the amount of targeting ligands on the surface of the nanoparticles, conjugation approach has been developed. In the case of weak binding ligands, multivalent functionalization on the surface of the nanoparticles provides sufficient avidity. Small molecule ligands such as peptides, sugars, and small molecules have higher stability, purity, simple production and non-immunogenicity compared to antibodies so they are more attractive. There are two methods for receptor-mediated targeting. The first approach is to target the tumor cells, together with the extracellular matrix or surface receptors on tumour blood vessel endothelial cells (Fig. 2). This may be most efficient for the delivery of immune stimulation or antiangiogenesis molecules. The Second approach is to target the tumour cell surface receptors for intracellular delivery (Fig. 3) of cytotoxic agents.
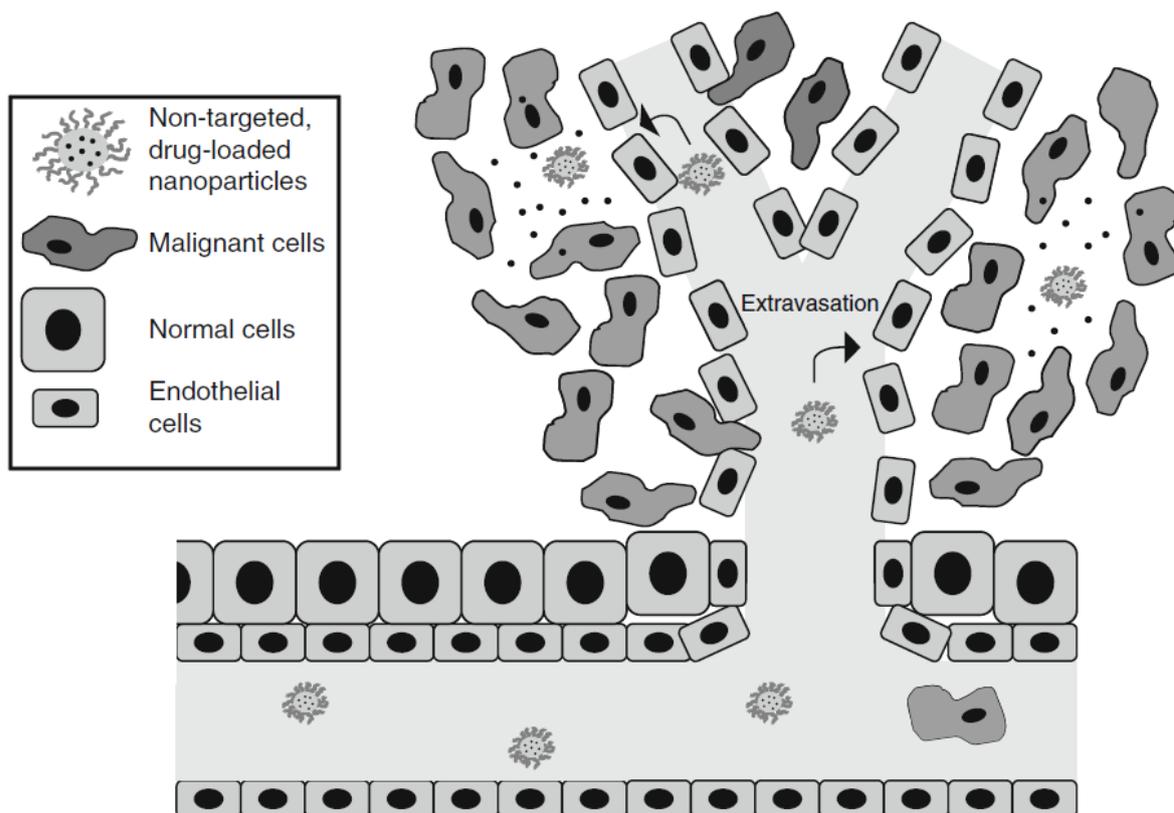

Figure 1: Schematic of "passive targeting" via enhanced permeability and retention effect (EPR).The small size of nanoparticles allows them to circulate for a long period of time, extravasate, and accumulate into tumor tissues through leaky tumor vasculature
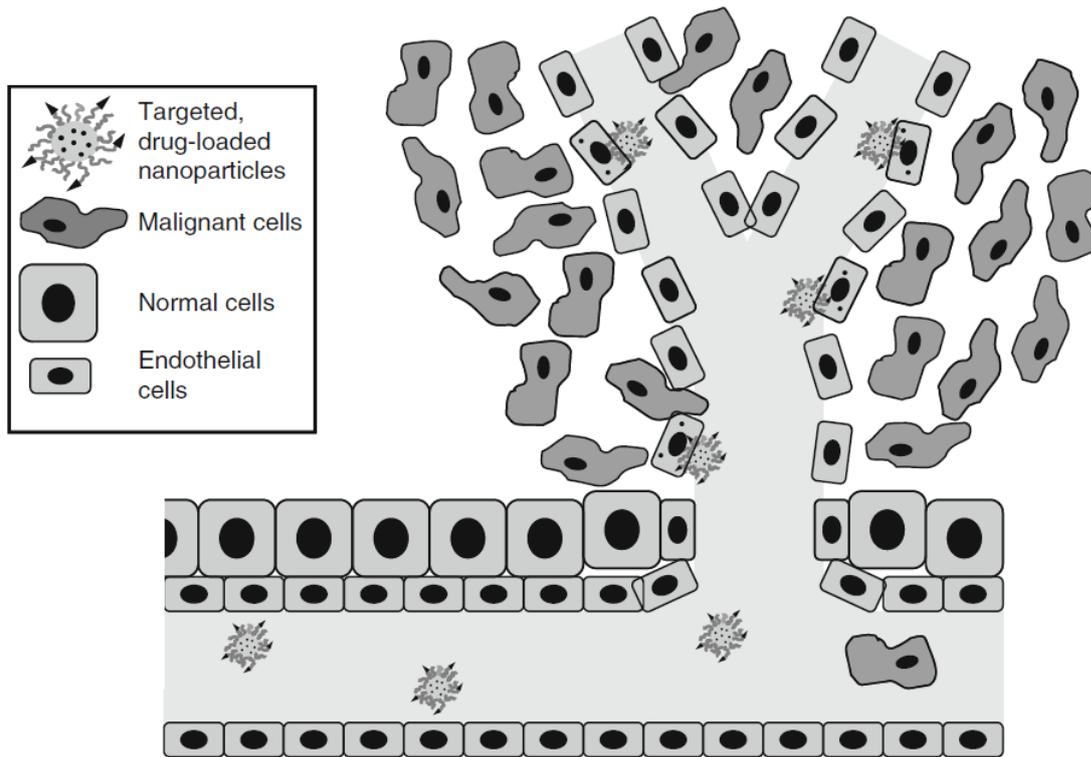
Figure 2: Schematic of "active targeting" of functionalized nanoparticles to cancer cells. Targeting ligands on the surface of nanoparticles are able to bind to receptors on malignant cells, causing local drug delivery or uptake through receptor-mediated endocytosis
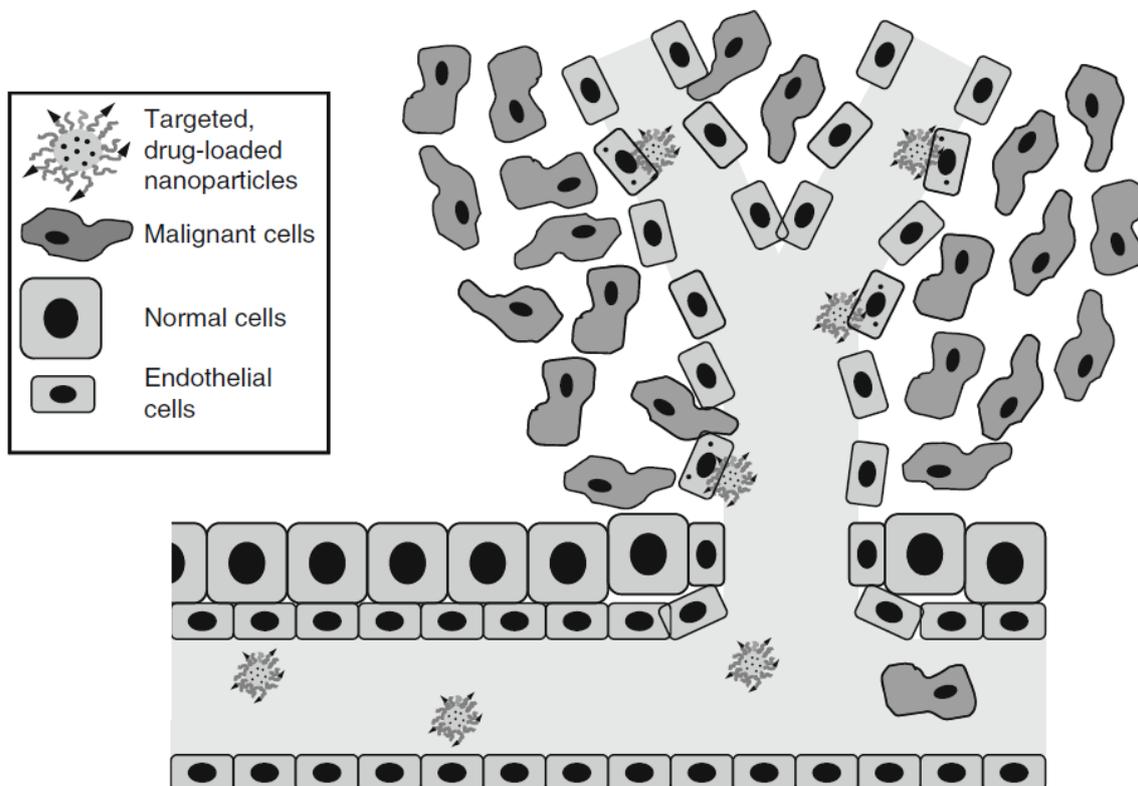

Figure 3: Schematic of "active targeting" of functionalized nanoparticles to endothelial wall. Targeting ligands on the surface of nanoparticles are able to bind to receptors on endothelial cells or basement membrane matrix, causing local drug delivery on the endothelial wall for antiangiogenesis therapy
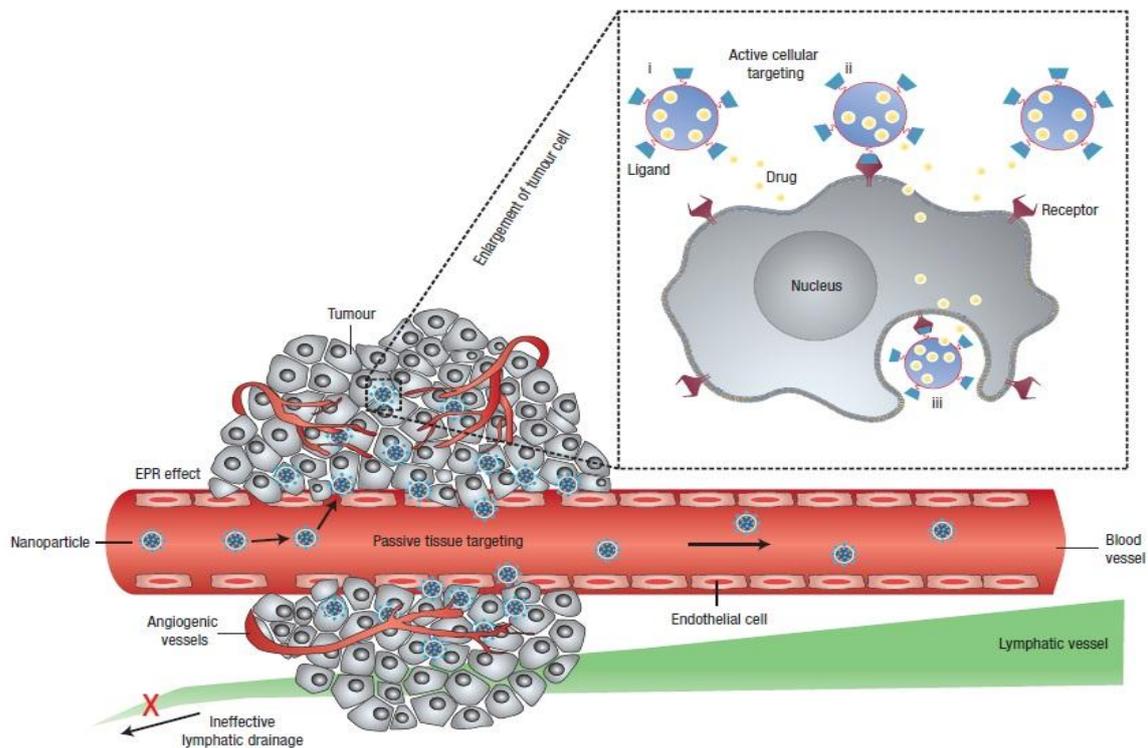
Figure 4: Schematic representation of different mechanisms by which nanocarriers can deliver drugs to tumours. Polymeric nanoparticles are shown as representative nanocarriers (circles). Passive tissue targeting is achieved by extravasation of nanoparticles through increased permeability of the tumour vasculature and ineffective lymphatic drainage (EPR effect). Active cellular targeting (inset) can be achieved by functionalizing the surface of nanoparticles with ligands that promote cell-specific recognition and binding. The nanoparticles can (i) release their contents in close proximity to the target cells; (ii) attach to the membrane of the cell and act as an extracellular sustained-release drug depot; or (iii) internalize into the cell.
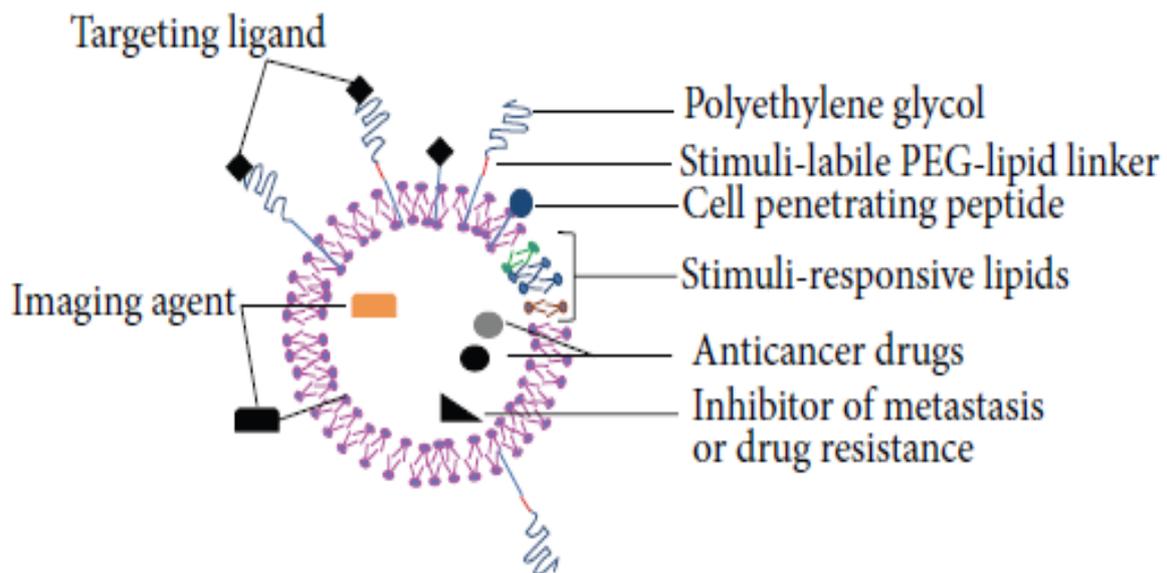

Figure 5: Schematic picture of a multifunctional liposomal Nano carrier.

Figure 6: Passive targeting, the EPR effect. Tumor tissues are known to have leaky vasculature and results in a passive accumulation of nanoparticles and this phenomenon is referred to as EPR.

Figure 7: Schematic diagram of nanoparticle accumulation in tumor tissue through EPR effect. Normal tissue vasculatures are lined by tight endothelial cells, thereby preventing nanoparticle drugs from escaping, whereas tumor tissue vasculatures are leaky and hyperpermeable allowing preferential accumulation of nanoparticles in the tumor interstitial space (passive targeting)

Figure 8: Active targeting. Nanoparticles with ligands or molecules attached to their surface can target tumor cells preferentially over healthy cells.

Figure 9: Internalization of nanoparticles via receptor-mediated endocytosis. Tumor-specific ligands/antibodies on the nanoparticles bind to cell through an endosome-dependent mechanism. Drug loaded nanoparticles bypass the drug efflux pump not being recognized when the drug enters cells, leading to high intracellular concentration.

Table 1: Examples of non-targeted nanoparticles in clinical development

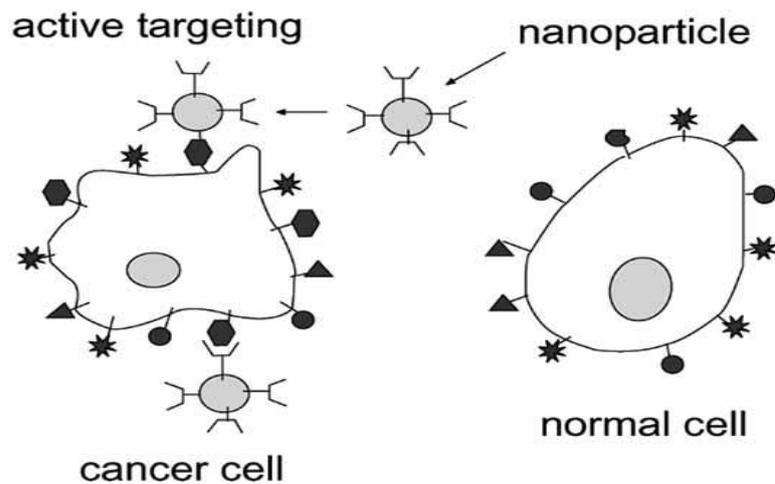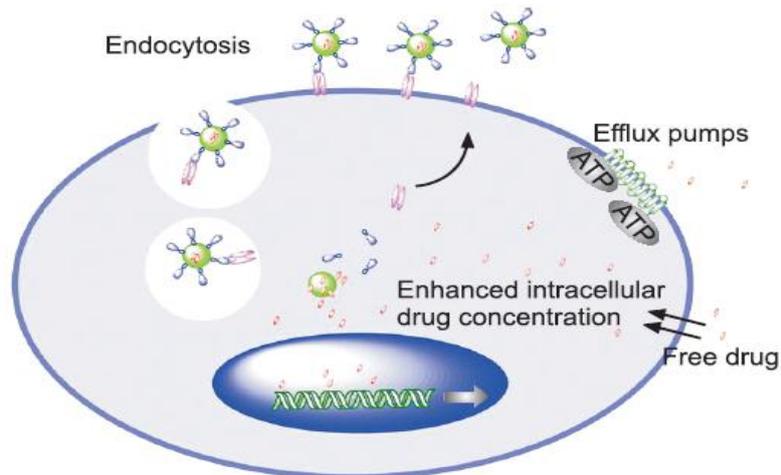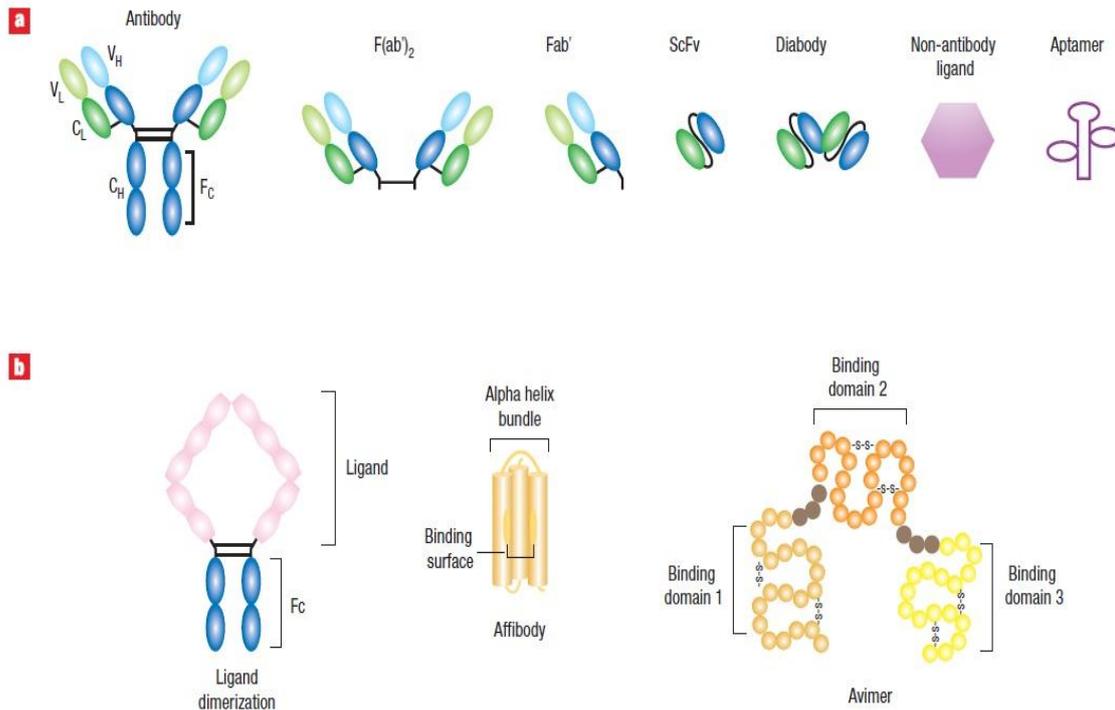| Type of Nanoparticle	Name	Therapeutic agent	Status
Liposomes	Daunoxome®	DXO	Approved
	Doxil® /Caelyx®	Dox	Approved
	Myocet®	Dox	Approved (Europe)
	SPI-077	Cisplatin	Phase II
	Oncolipin	Interleukin 2	Phase II
	OSI-7904L	Thymidylate Synthase inhibitor	Phase II
	LEP ETU	Paclitaxel	Phase I/II
	LE-SN38	SN-38	Phase I/II
	OSI-211	lurtotecan	Phase II
	Aroplatin	Oxaliplatin	Phase II
Polymeric micelles	Genexol-PM	Paclitaxel	Approved (South Korea)
	NK911	Dox	Phase I
	SP1049C	Dox	Phase I
	NC-6004	Cisplatin	Phase I
	NK012	SN-38	Phase I
	NK105	Paclitaxel	Phase I
Polymer-drug conjugate-based nanoparticles	CT-2103, Xyotax ™	Paclitaxel	Phase I
	PK1; FCE28068	Dox	Phase II
	PK2; FCE28069	Dox	Phase I/II
	PNU166945	Paclitaxel	Phase I
	MAG-CPT	Camptothecin	Phase I
	AP5280	Platinate	Phase I/II
	AP5346	Platinum	Phase II
	AD-70, DOX-OXD	Dox	Phase I
	DE-310	Camptothecin	Phase I/II
	Prothecan	Camptothecin	Phase II
	EZN-2208	SN-38	Phase I
	IT-101	Camptothecin	Phase II
	NKTR-102	Irinotecan	Phase II
Albumin-based nanoparticles	Abraxane	Paclitaxel	Approved

Figure 10: Common targeting agents and ways to improve their affinity and selectivity.

a, The panel shows a variety of targeting molecules such as a monoclonal antibody or antibodies' fragments, non-antibody ligands, and aptamers. The antibody fragments F(ab')2 and Fab' are generated by enzymatic cleavage whereas the Fab', scFv, and bivalent scFv (diabody) fragments are created by molecular biology techniques. VH: variable heavy chain; VL: variable light chain; CH: constant heavy chain; CL: constant light chain. Non-antibody ligands include vitamins, carbohydrates, peptides, and other proteins. Aptamers can be composed of either DNA or RNA. b, Affinity and selectivity can be increased through ligand dimerization or by screening for conformational-sensitive targeting agents such as affibodies, avimers and nanobodies, as well as intact antibodies and their fragments.

Table 2: Examples of targeted nanoparticles in preclinical and clinical development

Name	Targeting agent	Therapeutic agent	Status
FCE28069	Galactose	DXO	Phase I (Stopped)
MCC-465	F(ab')2 fragment of human antibody GAH	DOX	Phase I
MBP-426	Transferrin	Oxaliplatin	Phase I
SGT-53	Transferrin Receptor antibody fragment	Plasmid DNA with p53 gene	Phase I
CALAA-01	Transferrin	Small interfering RNA	Phase I
DOX-PEG-FOL	Folate receptor	DOX	Pre-clinic
cRGD-Functionalized Dox micelle	cRGD peptide	DOX	Pre-clinic
Dtxl-NP-Apt	RNA aptamer	DOX	Pre-clinic
2C5 -Immunomicelles	mAntibody 2C5	Paclitaxel	Pre-clinic
ASGPR-paclitaxel	Galactosel	Paclitaxe	Pre-clinic
Pt-NP-Apt	PSMA targeting aptamer	Cisplatin	Pre-clinic

Nanoparticles for tumour targeting and delivery

Nanoparticles are particulate dispersions or solid particles with a size in the range of 10-1000 nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. They can be made using a variety of materials including polymers (polymeric nanoparticles, micelles, or dendrimers), lipids (liposomes), viruses (viral nanoparticles), and even organometallic compound (nanotubes) (Table 1). They recognize and bind to the target cells through ligand–receptor interactions, and bound carriers released the drug inside the cell (Fig. 4) [20].

Table 3: Nanoparticle therapeutics undergoing clinical investigation

Agent	Formulation	Company	Indication	Status
Nontargeted nanoparticle therapeutics				
S-CKD602	Pegylated liposomal CKD602 (topoisomerase inhibitor)	Alza Corporation	Various cancers	Phase I/II
CRLX101	Polymeric nanoparticle (cyclodextrin) formulation of camptothecin	Cerulean Pharma	Various cancers	Phase II
CPX-1	Liposomal irinotecan	Celator Pharmaceuticals	Colorectal cancer	Phase II
LE-SN38	Liposomal SN38	NeoPharm	Colorectal cancer	Phase II
NC-6004	Polymeric nanoparticle (PEG-poly amino acid) formulation of cisplatin	NanoCarrier Co.	Various cancers	Phase I
NK105	Polymeric nanoparticle (PEG-poly aspartate) formulation of paclitaxel	Nippon Kayaku Co., Ltd.	Various cancers	Phase II
NK911	Polymeric nanoparticle (PEG-poly aspartate) formulation of doxorubicin	Nippon Kayaku Co., Ltd.	Various cancers	Phase I
SP1049C	Glycoprotein micelle of doxorubicin	Supratek Pharma Inc.	Various cancers	Phase II
SPI-077	Pegylated liposomal cisplatin	Alza Corporation	Head and neck cancer, lung cancer	Phase II
NK012	Polymeric micelle SN-38	Nippon Kayaku Co., Ltd.	Various cancers	Phase II
ALN-VSP	Lipid nanoparticle formulation of siRNA against vascular endothelial growth factor and kinesin spindle protein	Alnylam Pharmaceuticals	Liver cancer	Phase I
CPX-351	Liposomal cytarabine and daunorubicin(5:1)	Celator Pharmaceuticals	Acute myeloid leukemia	Phase I
OSI-7904L	Liposomal thymidylate synthase inhibitor	OSI Pharmaceuticals	Various cancers	Phase II
OSI-211	Liposomal lurtotecan	OSI Pharmaceuticals	Various cancers	Phase II
Molecular targeted nanoparticle therapeutics				
BIND-014	Polymeric nanoparticle (PEG-PLGA)[a] formulation of docetaxel	BIND Bioscience	Various cancers	Phase I
MCC-465	Human antibody fragment (GAH) targeted liposomal doxorubicin	National Cancer Center, Japan	Gastric cancer	Phase I (not continued)
MBP-426	Transferrin targeted liposomal oxaliplatin	Mebiopharm Co., Ltd.	Various cancers	Phase II
CALAA-01	Transferrin targeted polymeric nanoparticle (cyclodextrin) formulation of siRNA	Calando Pharmaceuticals	Solid tumors	Phase I
SGT53-01	Transferrin targeted liposome with p53 gene	SynerGene Therapeutics	Solid tumors	Phase I

[a] PLGA: poly(lactic-co-glycolic acid).

Polymeric Nanoparticles

Polymeric nanoparticles which are engineered from biocompatible and biodegradable polymers have been widely investigated as therapeutic carriers [21].They are formulated through a self-assembly process using block-copolymers containing two or more polymer chains and these copolymers instinctively accumulate into a core-shell structure in an aqueous environment [22]. The hydrophobic blocks form the core is minimize their exposure to aqueous environments and the hydrophilic blocks form the shell is stabilize the core which results in a structure that is well suitable for drug delivery. Polymeric nanoparticles have been formulated to encapsulate either hydrophilic or hydrophobic small drug molecules, or also macromolecules such as proteins and nucleic acids. Polymers that are used for preparation of nanoparticles fall into two major groups: natural polymers and synthetic polymers. A polymer used in controlled or sustained drug delivery formulations, must be chemically inert, non-toxic and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable. Gums (Ex. Acacia, Guar, etc.), Chitosan, Gelatin, Sodium alginate, Albumin, heparin, dextran, and collagen are the examples of Natural polymers. Some of the synthetic polymeric materials are Cellulosics, Poly(2-hydroxy ethyl methacrylate), Poly(N-vinyl pyrrolidone), Poly(methyl methacrylate), Poly(vinyl alcohol), Poly(acrylic acid), Polyacrylamide, Poly(ethylene-co-vinyl acetate),

Poly(ethylene glycol), Poly(methacrylic acid). The newer polymers for tailored made release of bioactive agents has been also investigated and they are designed to degrade within the body, most popular ones are; Polylactides (PLA), Polyglycolides (PGA), Poly(lactide-co-glycolides)(PLGA), Polyanhydrides, Polyorthoesters, Polycyanoacrylates, Polycaprolactone, polycarprolactone (PCL) and N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA). They are biocompatible, biodegradable and their capacity to be functionalized [23]. There are two methods to load the drug into polymeric nanoparticles: by physical entrapment or by chemical conjugation. A type of hydrophobic interaction between the nanoparticle and drug decided the entrapment of drug into nanoparticle. When the drug molecule is covalently conjugated onto the polymer, the chemical properties of the linker between the drug and polymer are critical and if it is too stable, drug should not release, while if the linker is too unstable, drug may be released before the nanoparticle reaches the tumor. So, a proper linker is very important to the drug-polymer conjugate. A various pH-sensitive linkers have been developed like hydrozone, cis-aconityl, disulfide etc. These chemical bonds are stable in the blood circulation system (pH=7), but quickly decompose and release drug molecules inside the tumor where pH values typically drop below 5.5. Disulfide bonds are very attractive because they can be cleaved by glutathione and the intracellular level of glutathione is much higher than its extracellular level, so, the disulfide linker is relatively stable in blood circulation and becomes unstable and releases the drug molecules once it is suppressed by cells [24, 25].

Tao et al., 2013 has demonstrated a novel copolymer docetaxel-loaded M-PLGA-TPGS NPs, (modified nanoprecipitation method), which were observed to be near-spherical shape with narrow size distribution. The author reported that the uptake level of M-PLGA-TPGS NPs observed higher than that of PLGA NPs and PLGA-TPGS NPs in MCF-7 breast cancer cells. Also a significantly higher level of cytotoxicity found with docetaxel-loaded M-PLGA TPGS NPs. The in vivo experiment animal model data revealed docetaxel-loaded M-PLGA-TPGS NPs has the highest anti-tumor efficacy in treating breast cancer [26].

Paul et al., 2013 has demonstrated the encapsulation of chelidonine in biodegradable (PLGA) polymers and evaluated nano-chelidonine's (NCs) anti-cancer efficacy vis-a-vis free chelidonine (FC) against HepG2 cells and demonstrated its bioavailability in experimental mice model. Nano-chelidonine's exhibited rapid cellular uptake and stronger apoptotic effect than FC, blocking HepG2 cells at G2/M phase p53, cyclin-D1, Bax, Bcl-2, cytochrome c, Apaf-1, caspase-9 and caspase-3 expressions also corroborated well to recommend greater anti-cancer potentials of NC. The author further reported that NC to have greater bioavailability with better tissue distribution with toxicity. Therefore the authors reported that NCs could be a better anti-cancer agent [27]. Wang et al., 2013 shown PLGA NPs modified with chitosan reported an initial burst release followed by a moderate and sustained release. PLGA NPs modified by chitosan reveal versatility of surface and a possible improvement in the efficacy of current PLGA-based drug delivery system [28].

Liposomal nanoparticles

Liposomes, one of the first nanoparticle platforms to be applied in medicine are self-assembling spherical particles with a membrane composed of phospholipid bilayers and their size can range from 25 nm to 10μm depending on the preparation method [29]. They contain a single or multiple bilayer membrane structure composed of natural or synthetic lipids like Phosphatidylethanolamine and phosphatidylcholine. Today, there are more than 12 formulations approved for clinical use, with many more in clinical and preclinical development. Commercial liposomes have already gained approval from US Food and Drug Administration (FDA). The typical example is doxorubicin encapsulated liposomes (Doxil), which has strong antitumor activity against a wide range of cancers.

Their unique ability to encapsulate hydrophilic agents in their aqueous core and hydrophobic agents within their lamellae as well as their biocompatible and biodegradable composition makes them excellent therapeutic carriers for anticancer drugs. Drug delivery systems based on unmodified liposomes are limited by their short blood circulation time. This is mainly due to the fast clearance of liposomes by macrophages of the reticuloendothelial system (RES) [30]. The unmodified phospholipid surface of liposomes can attract plasma proteins and thus recognition by the mononuclear phagocytic system (MPS), resulting in their rapid clearance from the circulation. This property obstructs the distribution of liposome-associated drugs to solid tumors. Surface-modified (stealth) liposomes have solved the problem of fast clearance from the circulation, yielding liposomes with a significantly increased half-life in the blood. This can be avoided by the second generation of polymer-coated liposomes, which can dramatically increase blood circulation times from several minutes up to 3 days. Liposomes can be also coated with polymers like polyethylene glycol (PEG) to improve their stability and circulation half-life. Sterically stabilized liposomes, ones modified at the surface with hydrophilic polymers (PEG), have proven to reduce in vivo

recognition and phagocytic uptake, resulting in prolonged circulation and localization in tumors as well as other sites of pathology. It may improve the pharmacokinetics and biodistribution of a drug. For example, pegylated liposomal doxorubicin reduces the volume of distribution of doxorubicin from ~1,000 liters/m^2 in the free drug form to 2.8 liters/m^2 by restricting the distribution within the plasma. Furthermore, it can achieve higher drug concentrations within tumor while reducing drug concentration in normal tissues, such as heart [31]. Liposomes must be of small size and have long circulation to reach the tumour and increases the accumulation of drug into cancer cells. A targeting ligand must distinguish between cancer cells and supportive cells, and a suppressing carrier for intracellular delivery. The ligand must be accessible to the target for identification and surface should be coated with PEG for long blood circulation. (Fig. 5) [32]. The presentation of the ligand at the distal end of PEG allows better ligand recognition in addition to protection from steric hindrance and multivalent binding thanks to the flexibility of PEG. Such a combination allowed ultimately superior therapeutic activity compared to PEGylated drug-loaded liposomes without ligand. The rationale of targeting plus PEGylation for antitumor efficacy has been well demonstrated by Yamada et al. using folate-linked PEGylated liposomal doxorubicin. They compared the in vitro cytotoxicity and in vivo anti-tumor efficacy of untargeted PEGylated doxorubicin-loaded liposomes, non-PEGylated liposomes harboring folate, and PEGylated liposomes with folate exposure at the liposomal surface. While the non-PEGylated folate-modified liposomes showed the highest toxicity in vitro, the highest antitumor efficacy was reported with PEGylated, folate-modified doxorubicin-loaded liposomes.

Gold and iron oxide nanoparticles

Gold nanoparticles (GNPs) are small and can penetrate throughout the body, specially accumulating at tumour sites because of EPR effects. They are biocompatible and can bind with proteins and drugs which are actively targeted to cancer cells. These properties of GNPs can make them attractive for use in cancer therapy. GNPs have a high atomic number, which leads to superior absorption of kilo voltage X-rays and delivers better contrast than standard agents. When they exposed to the light of specific energies produce the heat which may be used for tumour-selective photo thermal therapy. Targeted GNPs need to exit tumour vasculature, cross the tumour interstitial, enter cells and potentially exit lysosomes to be effective *in vivo.* Recently, several novel nanotechnology concepts have been applied to the development of a new generation of anti-cancer drug delivery systems. Gold nanoparticles can be synthesized through the reduction of HAlCl$_4$ with a very narrow polydispersity [33] and gold is inert under physiological environments but the long term toxicity of gold nanoparticles remains an unanswered question. The gold concentrations are naturally low in animal bodies, which are attractive properties of GNPs which allows the convenient use of them for in vivo pharmacokinetic and biodistribution studies. A gold nanorod formulation is shows very capable potential as a photothermal therapy agent as they can generate heat when it is radiated by a near infra-red (IR) laser (wavelength > 650 nm). At this range, the laser is comparatively nontoxic to the tissue and organs. Once the gold nanorod has accumulated inside the tumor through passive/active targeting, it can be heated locally up to 43°C by radiation with a near IR laser to destroy the tumor without causing damage to surrounding healthy tissues [34]. Iron oxide nanoparticles have been clinically used as imaging agents for MRI and recently a number of researchers have been investigated them as drug carriers while retaining their imaging functions. By applying an external magnetic field, iron oxide NPs delivers a drug to the target area. The Properties of Magnetic iron oxide (IO) nanoparticles are long blood retention time, biodegradability and low toxicity and these may use for biomedical applications in vitro and in vivo. IO nanoparticles have a large surface area and can be engineered to provide a large number of functional groups for cross-linking to tumor-targeting ligands such as monoclonal antibodies, peptides, or small molecules for diagnostic imaging or delivery of therapeutic agents.

Dendrimers

Dendrimer is one of the most graceful nanotechnology platforms for targeted drug delivery of anticancer drugs. Dendrimers are monodisperse, three dimensional molecules with defined molecular weights and host-guest entrapment properties and highly branch artificial macromolecules with treelike structures. They are able to improve the therapeutic index of cytotoxic drugs because they can directly target the nanoparticle therapeutics to the cancer cells. They can bypass p-glycoprotein pumps which would export the drug and not allowed to diffuse them into cells. So, this approach may avoid drug resistance in tumour cells. Additional toxicological studies and GMP synthesis of this material is on-going to allow the beginning of clinical trials. , The in vitro targeting ability of partially acetylated generation 5 polyamidoamine (PAMAM) dendrimer (Ac-G5) in HeLa cells was assessed by its conjugation with biotin as the targeting moiety. The multifunctional conjugate Ac-G5-biotin-FITC (fluoresceinisothiocyanate) showed

much higher cellular uptake than the conjugate without biotin [35]. The energy-dependent uptake process can be blocked effectively by biotin polymer conjugates, exhibiting an expected dose response curve.

Jan et al. 2014 describes the formulation of arginine conjugated 3.0G Poly (propylene) imine (PPI) dendrimers, mimicking the surface structure of an endogenous angiogenesis-inhibitor endostatin; for tumor specific delivery of a model anticancer drug, doxorubicin hydrochloride (Dox). The system exhibited the initial rapid release followed by sustained release of Dox with significant antiangiogenic activity in the CAM assay. Further, the arginine conjugated dendrimers was found to inhibit growth of cancer cells in ex vivo studies with MCF-7 cell lines. Cell uptake studies suggested that in comparison to free drug the formulation was preferably taken up by the tumor cells [36]. The branches of dendrimers which have vast amounts of surface area for drugs and targeting molecules and the surface functionalities, interior branching, and chemical composition of the core are useful key characters in reactivating the macromolecule [37].

Nanoshell

A type of spherical nanoparticle consisting of a dielectric core which is covered by a thin metallic shell (usually gold) is known as nanoshell, or rather a nanoshell plasmon. Plasmon, a quasiparticle of nanoashell is a collective excitation or plasma oscillation where the electrons simultaneously oscillate with respect to all the ions. Nanoshells are optically tunable core/shell nanoparticles that can be fabricated to strongly absorb in the near-infrared (NIR) region where light transmits deeply into tissue. These particles have capacity to accumulate in the tumor cells due to the enhanced permeability and retention (EPR) effect when injected systematically and encourage photothermal ablation of the tumor when irradiated with an NIR laser. Their tumour specificity can be increased via functionalizing the nanoshell surface with tumor-targeting moieties. They can also scatter the light and therefore can be used in various imaging modalities such as dark-field microscopy and optical coherence tomography (OCT) [38].

Carbon nanotubes

Carbon nanotubes (CNTs) are tubular materials with nanometer-sized diameters and have axial symmetry, which give them exceptional properties that can be exploited in the diagnosis and treatment of cancer, thermal ablation, and drug delivery in cancer. They have the potential to deliver drugs directly to targeted cells and tissues.   Ringel et al. suggest that carbon nanomaterials can act as antitumor agents themselves by increasing the efficiency of cytotoxic agents when applied in combination. Carbon nanofibers (CNFs) and multi-walled carbon nanotubes (CNTs) were investigated regarding their impact on cellular function, cellular uptake and ability to sensitize cancer cells of urological origin to the conventional chemotherapeutics cisplatin and carboplatin. CNFs and CNTs (1-200 microg/ml) showed a low to moderate impairment of cellular function with CNFs being more deleterious than CNTs. In fact, CNFs enhanced the cellular accumulation of carboplatin by 28% as compared to the single treatment with carboplatin. Carbon nanomaterial-based applications could present a new strategy to overcome chemoresistance by sensitizing cancer cells to conventional chemotherapeutics [39].

Passive targeting

The characteristic of solid tumors such as the enhanced permeability and retention (EPR) effect and several distinctive features such as hyper vasculature, faulty vascular architecture and a lacking lymphatic drainage are exploited by Nanoparticulate delivery systems which can lead macromolecules and particulates to be gathered specially and to be retained for a longer time in tumors (Fig. 6) [40]. The pathophysiologic characteristics of tumour blood vessels are responsible for accumulation of nanoparticles in tumours. Delivery of nutrients to an actively growing tumor becomes diffusion-limited so new blood vessel formation is required to supply nutrients and oxygen. The leaky vessels with enlarged gap junctions of 100 nm to 2 μm generated due to incomplete tumour vasculature so macromolecules easily access the tumour interstitium. Doxil®, a poly (ethylene glycol)-coated (PEGylated) liposomal system for doxorubicin (Dox) delivery, and Abraxane®, albumin-bound paclitaxel nanoparticles for the treatment of metastatic breast cancer, are illustrative examples of US food and Drug Administration (FDA)-approved nanocarrier-based drugs for cancer therapy. These agents circulate in the body with a half-life about 100 times longer than that of free anticancer drugs while simultaneously reducing systemic toxicity. Table **2** lists nanoparticles that have been used in the clinic and utilize passive targeting to achieve their selective delivery to tumors. The inherent size of nanoparticles and the unique properties of tumor vasculature are the responsible for passive targeting. The formation of new blood vessels in the tumor cells is known as angiogenesis because as the tumour grows, they require more oxygen and nutrients also they release

cytokines and other signalling molecules. Angiogenic blood vessels in tumor tissues have gaps as large as 600 to 800 nm between adjacent endothelial cells [41]. This type of defect in vascular architecture coupled with poor lymphatic drainage induces an enhanced permeability and retention effect (EPR) [42, 43]. Nanoparticles can selectively accumulate into the tumor interstitium through these gaps. (Fig. **7**) [44]. Several factors including the size, surface characteristics, and circulation half-life of the nanoparticles and the degree of angiogenesis of the tumour are responsible for accumulation of nanoparticles in tumor tissues. Nanoparticles with a size between 10 and 100 nm will be best for tumor accumulation. For example, smaller polymeric micelles (20 nm) have been shown to accumulate more readily in tumors than larger liposomes (100 nm) [45]. Proper surface characteristics and longer circulation times of nanoparticles can also improve tumor uptake. Dramatically reduced clearance rates have also been obtained with other nanoparticles such as Abraxane, [46] Xyotax [47] and IT-101 [48]. Tumor vascularization also affects nanoparticle accumulation; usually nanoparticles accumulate poorly in poorly vascularized tumors, small preangiogenic tumors, or large necrotic tumors. As drug delivery systems, nanoparticles have shown an ability to improve pharmacokinetics, pharmacodynamics, efficacy, and to reduce the toxicity of associated drugs. For example, Abraxane (ABI-007), an albumin-bound nanoparticle of paclitaxel (Taxol) which has been approved for the treatment of metastatic breast cancer, showed significant greater efficacy than free paclitaxel in a phase III clinic trial [49]. Other nanoparticles currently used in the clinic or undergoing clinic trials also showed an improved pharmacokinetic profile compared with the respective free drugs, such as Doxil, a PEG-liposome loaded with doxorubicin (DOX), [50] SP1049C, a pluronic micelle loaded with DOX, NK911, a PEG-Asp micelle loaded with DOX, and Xyotax, a polyglutamic acid nanoparticle carrying paclitaxel.

Active targeting

"Active targeting" is used to describe specific interactions between drug/drug carrier and the target cells, usually through specific ligand–receptor interactions [51] which are possible only when the two components are in close proximity (<0.5 nm). Current drug delivery systems do not have the ability to guide themselves to a target cells and they reach the target area as a result of blood circulation and extravasation followed by intratumoral retention and distribution. The term "active targeting" simply means a specific "ligand–receptor type interaction" for intracellular localization which occurs only after blood circulation and extravasation because increasing blood circulation time by PEGylation and/or improving the EPR effect is expected to enhance delivery to the tumor site.Previous studies have also shown that the presence of the tumor-targeting ligand does not always result in increased accumulation of the nanoparticles in tumors, [52, 53] suggesting that "active targeting" does not consider as an effective delivery to the entire tumor. Active targeting, also called ligand-mediated targeting, involves utilizing affinity ligands on the surface of NPs for specific retention and uptake by the targeted disease cells. To that end, ligands are selected to bind surface molecules or receptors overexpressed in diseased organs, tissues, cells or subcellular domains. Actively targeted material needs to be in the proximity of their target to benefit from this increased affinity. Therefore, the approach is aimed toward increasing interactions between NPs and cells and enhancing internalization of drugs without altering the overall biodistribution [54, 55]. The design of actively-targeted NP drug carriers is complex because the NP architecture, the ligand conjugation chemistry and the types of ligand available all contribute to the efficacy of the system. Other factors like the administration route or the non-specific binding of proteins during the NP's journey through the bloodstream have been shown to affect the targeting ability of NPs. Physicochemical properties like the ligand density, the size of the NPs or the choice of the targeting ligand might also possibly affect the efficacy of the active targeting strategy in vitro and, most importantly in vivo. The following section will highlight the strategies, benefits and drawbacks of combining targeting ligands with NP drug delivery systems in the targeting of solid tumors [56]. Active targeting has been performed to obtain a high degree of selectivity to specific tissues and to enhance the uptake of nanoparticles into target areas such as cancer cells and angiogenic microcapillaries growing around malignant cells (Fig. 8). Most importantly, accumulation merely within the tumor microenvironment by the EPR effect may not always correlate with therapeutic efficacy since internalization into the tumor cells is required for most anticancer drugs to exert their biological functions. To overcome these limitations, a rational approach is to incorporate a targeting moiety on the nanoparticle surface. The targeting moiety is expected to bind a tumor-associated antigen or receptor and facilitate the delivery of nanoparticles to the intracellular site of drug action, enabling a greater therapeutic effect (Fig. **9**). Recent preclinical studies have shown that targeted nanoparticles have better antitumor activity compared with nontargeted nanoparticles. Although targeted nanoparticles may not always mediate an increase in tumor drug accumulation when compared with non-targeted nanoparticles, targeted nanoparticles show greater intracellular drug delivery to cancer cells than nontargeted nanoparticles, resulting in dramatically increased antitumor efficacy. These findings suggest

that the primary role of the targeting ligands is to enhance cellular uptake into cancer cells and to minimize cellular uptake in normal cells.

Types of targeting moieties

Targeting moieties are classified as proteins (mainly antibodies and their fragments), peptides, nucleic acids (aptamers), small molecules, or others (vitamins or carbohydrates). Although monoclonal antibodies (mAbs) have been widely used as escort molecules for the targeted delivery of nanoparticles, several limitations including large size and difficulty in conjugation to nanoparticles have hampered their uses. Thus, other smaller-sized ligands including peptides have attracted greater attention these days. Common targeting agents and ways to improve their affinity and selectivity are described in (Fig. 10.) [57].

Selection of target receptor and ligand

Selection of the target receptor or antigen on cancer cells is crucial for the optimal design of targeted nanoparticles. In general, cell-surface antigens and receptors should have several properties that render them particularly suitable as tumor-specific targets. First, they should be abundantly and uniquely expressed on tumor cells, but negligibly or less expressed on normal cells. Second, they should have a high density on tumor cells. A targeting ligand should selectively and successfully transport nanoparticles into targeted cancer cells. It is believed that internalization of nanoparticles after binding to targeted tumor cells is necessary for good therapeutic responses, so whether the targeted nanoparticles can be internalized is an important issue in the selection of proper targeting ligand. Use of a ligand that can not trigger the internalization process may result in drug release outside the cell and its redistribution to the surrounding normal tissues. A variety of targeting ligands, including antibodies, antibody fragments, peptides, growth factors, and aptamers, [58] has been used to facilitate the uptake of carriers into target cells [59].

Optimal nanoparticle characteristics for cancer treatment

There has been intense interest in identifying nanoparticle characteristics that are best suited for oncology applications. Many studies have demonstrated that nanoparticle size is a major factor affecting nanoparticle distribution into tumors [60, 61]. In general, nanoparticles smaller than 100 nm are considered excellent for tumor targeting. Recently, Perrault et al. studied the effect of nanoparticle size on tumor accumulation in a murine cancer model. Their data suggested sub-20-nm particles have rapid permeation into tumors but have poor retention/accumulation [62]. Particles that are larger than 100 nm tend to have low permeation into tumors. In this study, the optimal nanoparticle sizes were approximately 60 nm to 80 nm. Nanoparticle sizes also affect the intracellular trafficking, which in turn can affect tumor accumulation [63, 64]. In addition to size, nanoparticle surface charge is also a major factor affecting tumor uptake. Although positive-charged nanoparticles are rapidly taken up by tumor cells, they also lead to significant immune reactions. Thus, neutral and negatively charged nanoparticles are preferable for clinical applications [65]. Shape is also beginning to emerge as a key variable in macrophage clearance, cell uptake, and biodistribution. Although there is currently no clear consensus on optimal characteristics for nanoparticles, more studies are addressing these issues in a systematic fashion.

Multifunctional nanoparticles for targeted imaging and therapy

Perhaps the most common form of nanocarrier multifunctionalization finds itself in the combination of imaging modalities and drug therapy into a single nanoparticle platform. Since the improvement in survival outcome of cancer patients over the last few decades can be largely attributed to improvements in both therapy as well as diagnostics, the combination of both modalities seems obvious, particularly since the tumor targeting properties of nanoparticles would benefit both therapy and imaging. A concept that is readily attainable through nanoparticles, and would be greatly beneficial to cancer patients, is the idea of "real-time" therapy, a situation whereby a clinician can visually track where in the body the administered dose disperses and how much accumulates at the tumor site, and as a result, can either predict therapeutic outcome, or even go as far as to visually monitor tumor shrinkage over time. Multifunctionalization of nanoparticles through the co-inclusion of therapeutics and imaging contrast agents will allow for such major advances.

Superparamagnetic iron oxide nanoparticles are colloidal suspensions of magnetite (Fe_3O_4) that were approved over a decade ago by the FDA for parental use as a contrast agent in MRI. Originally approved for liver imaging, the superparamagnetic nature of iron oxide nanoparticles enhances contrast of

their area of accumulation on a T$_2$ weighted MRI image, a feat that is advantageous in the tumor detection as well. While MRI in itself is a very useful technique for detection of solid tumors, by providing clear anatomical detail and soft tissue contrast, in the past MRI has been quite insensitive for smaller events in cancer imaging, such as the detection of lymph node metastasis and therapeutic efficacy of cancer treatment. Iron oxide nanoparticles were successful in the detection of 90.5% lymph node metastasis in patients with prostate cancer as opposed to 35.4% detection using conventional MRI, a 2.5-fold greater increase in diagnostic sensitivity [66]. In a more advanced use of contrast imaging, iron oxide nanoparticles have been shown to image cellular events in vivo. Targeted iron oxide nanoparticles to anionic phospholipids present on the surface of apoptotic cells by incorporating the C2-domain of synaptotagmin I onto the surface of the nanoparticles, allowing for a real-time visualization of apoptotic activity as an indicator of chemotherapeutic efficacy. Magnetite nanoparticles formulated with PLGA have been successful in combining delivery of chemotherapeutic drugs to the tumor, while retaining enough magnetic strength for imaging contrast enhancement, a potential use for real-time tracking of therapeutic efficacy. This potential has also been demonstrated by [67] who used iron oxide nanoparticles as a tumor contrast enhancement in MRI to visualize the tumor therapeutic response of MV522 colon carcinoma xenografts to a VEGF receptor tyrosine kinase inhibitor over time. From this study, they were able to show a statistically significant decrease in relative vascular volume fraction in real-time over the duration of treatment, as measured by sequential MRI of the tumors using these iron oxide nanoparticles as a tumor-imaging enhancer. Similarly, [68] developed multifunctional polymeric micelles loaded with doxorubicin and superparamagnetic nanoparticles in the core, and surface modified by inclusion of cyclic RGD for active tumor targeting. Self-assembling dermatan sulfate based nanoparticles formulated as a superparamagnetic nanoparticle with inclusion of the chemotherapeutic drug doxorubicin, is another example of a multifunctional nanoparticle for tumor imaging and treatment [69]. Not only have these nanoparticles been shown successful in imaging AT1 tumors in vivo by MRI, surprisingly, therapeutic efficacy against MX-1 breast tumor xenografts increased significantly when doxorubicin was delivered encapsulated in these nanoparticles, versus treatment with free doxorubicin, as indicated by the drastic tumor growth delay in 60% of mice and complete tumor regression in 40% of mice treated with the nanoparticle formulation, as opposed to the lack of tumor regression and shorter tumor growth delay in mice treated with doxorubicin alone. An alternative approach to a similar multifunctional nanoparticle by [70] multifunctionalized iron oxide nanoparticles by binding methotrexate to the surface to produce a targeting construct to folate receptors; however, once internalized by the cancer cell, lysosomal pH cleaved methotrexate from the surface, allowing it to further serve as a chemotherapeutic for cancer eradication, thereby producing a multifunctional system that allows for simultaneous tumor therapy and real-time imaging of drug delivery.

Another MRI contrast agent applicable in nanotechnology is gadolinium. Gadolinium-157 is a stable (nonradioactive) nuclide that is frequently used as a contrast agent in MRI diagnostics, to enhance contrast in T1 weighted images, [71] for example, in MRI in vivo models of lymph node metastasis [72] However, an additional benefit of gadolinium nanoparticles is that upon irradiation with thermal neutrons gadolinium-157 produces cytotoxic γ-ray radiation, [73] enabling gadolinium for the additional use in neutron capture therapy (NCT) of cancer. Thus, the combined therapeutic and imaging properties of gadolinium make it an excellent candidate for multifunctional cancer treatment. As another imaging modality, gold nanoparticles and gold nanoshells (silica core nanoparticles surrounded by a layer of gold coating) are favorable to be used as contrast agents in optical coherence tomography (OCT), since variations in their size and shape allows for precise tuning of their resonance wavelength between near-ultraviolet and mid-infrared. For example, a gold nanoshell with a 20-nm shell on a 60-nm silica core will resonate at around 700–750 nm, while a nanoshell with a 5-nm shell on the same 60-nm core will resonate at around 1,000–1,050 nm. In this manner, multifunctionalized gold nanoparticles have been used for tumor imaging and drug delivery.

Finally, a more recent nanoparticle platform that emerged for cancer diagnostics, and has further allowed for the multifunctional modality of imaging and therapy is the semiconductor nanocrystal, otherwise known as the quantum dot. Quantum dots are semiconductor-based nanoparticles that function as fluorescent probes for imaging purposes [74]. Similar to gold nanoshells, quantum dots are favorable imaging agents, that is their absorption properties can be tuned from visible to infrared wavelengths, they emit highly intense signals, and they are chemically, photochemically, and thermally stable [75].

Clinically approved nanoparticles

Advances in nanomedicine have been rapidly translated into clinical practice. Today, there are six clinically approved nanoparticle-based cancer therapeutics. These include liposomal formulations of

anthracyclines, the liposomal formulation of cytarabine, the nab formulation of paclitaxel, and the polymeric nanoparticle formulation of paclitaxel (Genexol-PM). Table **3** list out the Nanoparticles undergoing clinical investigation.

Potential toxicity of nanoparticles

An important consideration in nanoparticle development is the biological behavior of carrier constituents and their potential toxicity, especially during chronic administration. Many candidate polymers have been defined with particular toxicities, such as hematotoxicity, complementactivation, carcinogenicity, teratogenicity, and immunogenicity, [76, 77] indicating the importance of choosing safe polymers for the design of nanoparticles. In addition, the biological properties of polymers are molecular weight-dependent and can be changed once the respective conjugates are prepared. Therefore, careful characterization of the potential toxicity of both the polymer and the final nanoparticle is critically important. For nonbiodegradable polymers, potential toxicity is concerning when the polymer molecular weight is greater than the renal threshold. Increased understanding of the potentially deleterious properties of polymers leads to the design of new and safer polymeric nanoparticles. Currently, most nanoparticles use nontoxic and biodegradable ingredients, so toxicities associated with the carrier molecules per se tend to be mild. However, particular nanoparticles cause increased accumulation of drugs in MPS cells in the liver, spleen, and bone marrow, with the possibility of increased toxicities to these organs. Among these organs, the liver has been identified in many studies as the primary organ responsible for reticuloendothelial capture of nanoparticles, often due to phagocytosis by Kupffer cells [78, 79]. Hepatic uptakes have been shown to be a main mechanism of hepatic clearance from the blood circulation following the intravenous injection of nanoparticles. In addition to hepatic accumulation, some nanoparticles have been reported to cause liver injury (decreased function and hepatic morphology changes) [80, 81] For example, intravenous administration of cationic PAMAM dendrimers caused liver injury when administered intravenously to mice [82]. Hepatotoxicity has also been observed in mice treated orally with nano-zinc particles [83]. Also there are safety concerns with particular nanoparticles that are able to cross the blood brain barrier. Lessons have been learned from many of the early clinical studies. For example, due to neurotoxicity, a clinical trial testing an HPMA conjugated paclitaxel was terminated. The failure of MAG camptothecin due to cumulative bladder toxicity in phase I was also reported. Attempts are being made to decrease the uptake of nanoparticles by MPS cells and to increase their accumulation in the active site, through polymer or nanoparticle surface modifications, and/or incorporating targeting ligands. With more rational design, many nanoparticles have shown an improved safety profile and enhanced antitumor efficacy compared with free drugs in preclinical and clinical studies. For example, Doxil (PEGliposome loaded with doxorubicin) showed a reduction in cardiotoxicity over that of doxorubicin in a clinical study [84, 85]. Abraxane (albumin nanoparticle loaded with paclitaxel) showed a greater therapeutic outcome compared with free paclitaxel and, taking advantage of the water solubility of the nanoparticle, successfully eliminated the side effects associated with the toxic vehicle Cremophor EL.

The near future of cancer nanomedicines

Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutic drugs, and have shown a bright future as a new generation of cancer therapeutics. Furthermore, the development of multifunctional nanoparticles may eventually render nanoparticles able to detect and kill cancer cells simultaneously. Although there are certain critical questions and many challenges remaining for the clinical development of nanoparticles, as more clinical data are available, further understanding in nanotechnology will certainly lead to the more rational design of optimized nanoparticles with improved selectivity, efficacy, and safety [86].

The unique properties of nanoparticle drug carriers make them well suited for oncology applications. Although nanomedicine is a relatively new branch of science, its translation into clinical care has been rapid. Nanoparticle chemotherapeutics are poised to impact the treatment of most cancers. However, there are still limited clinical data and a limited number of nanotherapeutics approved for clinical use. More clinical data are needed to fully understand the advantages and disadvantages of nanoparticle therapeutics. Additional clinical data can also identify the best applications for nanochemotherapeutics. Thus, it is crucial to develop and carry out well-designed clinical trials to further the development of these drugs. Clinical investigators should fully understand the particular nanoparticles they are investigating and design trials that take advantage of nanoparticle properties. The field of nanomedicine is moving at a very rapid pace [87, 88]. New and improved nanoparticle platforms are being developed; these platforms quickly enter preclinical and clinical investigation. This new generation of nanoparticle platforms holds even more promise to improve the treatment of cancer. For example, molecular targeted nanoparticles were first

developed less than a decade ago and have already entered clinical investigation. These nanocarriers combine biological targeting and nanomedicine, and they have the potential to further improve the therapeutic ratio of nanotherapeutics. More complex targeted systems, which can release therapeutics at a target site when exposed to external stimuli such as light and temperature, are also under development [89]. Another potential for improvement is the development of more nanoparticles capable of delivering combination chemotherapeutics. Such nanotherapeutic agents can take full advantage of synergistic effects of combination therapy, which in turn can significantly improve the therapeutic efficacy. CPX-351, a liposomal formulation of cytarabine and daunorubicin, showed promising results in its first human study. Last, preclinical and clinical investigators should also explore additional applications of nanotherapeutics for the treatment of cancer. These indications include utilizing nanotherapeutics as chemosensitizers and radiosensitizers.

ACKNOWLEDGMENTS

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