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NANOCARRIERS: AS POTENTIAL TARGETED DRUG DELIVERY SYSTEMS FOR CANCER THERAPY

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ABSTRACT

The scenario of cancer therapy has changed dramatically over the recent years. The interest in developing few formulations to target the tumor cells has gained more inquisitiveness as this is a daunting challenge to the medical fraternity and the quest to find answers to these questions is ongoing till date. There is always a dire need for a formulation which targets only the cancer cells leaving the healthy cells intact. Nanocarriers are one such formulations which allow cancer specific drug delivery by inherent passive targeting phenomena and adopted active targeting strategies. Apart from improving the stability of hydrophobic drugs, these formulations aid in increased efficacy of drugs by enhancing the biodistribution and pharmacokinetics profiles. Nanocarriers have got the potential to revolutionize cancer diagnosis and therapy. The focus of the current article is to provide an overview of various Nanocarriers such as nanoliposomes, dendrimers, michelles, magnetic, metallic nanoparticles, etc. and their applications in cancer therapy.

KEYWORDS: Cancer, Nanocarriers, active targeting, passive targeting, Nanoparticles.

INTRODUCTION

Cancer remains a leading cause of mortality worldwide, accounting for 8.2 million cancer related deaths in 2012. According to the statistics reported by World Health Organization (WHO), annual cancer cases are expected to rise from 14 million in 2012 to 22 within the next two decades.[1] More significantly, a globalization of unhealthy lifestyles, particularly cigarette smoking and the adoption of many features of the modern Western diet (high fat, low fiber content) will increase cancer incidence. Carcinogens interact with the individual's

constitution, both inherited and acquired, determining vulnerability to cancer induction. This vulnerability is based on how an individual deals with the carcinogens, ideally eliminating them in a harmless form before they do any genetic damage or being able to repair that damage. Cancer does not develop overnight, instead often evolving over many years with detectable premalignant lesions presaging the development of full-blown malignancy. Malignant tumors not only invade surrounding tissue, but are able to colonize other, often vital, organs, a process known as metastasis. Widespread metastatic disease is usually a harbinger of imminent patient death.[2]

The effectiveness of a treatment is directly related to the treatment's ability to target and to kill the cancer cells while affecting as few healthy cells as possible. The degree of change in a patient's quality of life and life expectancy is dependent to this targeting ability. A treatment with low targeting ability will cause more damage to healthy cells thus reducing a patient's quality of life and life expectancy, so more accurate methods of targeting are vital.[3] The majority of current cancer patients only get the most basic targeting which is simply the inherent tendency of the chemotherapy to affect the cancer cells more intensely than healthy cells. Sometimes the side effects of these intense drugs are so severe that the patient must discontinue therapy before the drugs can eliminate or reduce the tumor(s), and not all treatments are effective in killing the cancer before the cancer kills the patient[3]

Even though various treatment modalities, including immuno, photothermal, photodynamic, gene and hormone therapy display promising cancer eradicating potential in preclinical studies, however, surgery, radiation and chemotherapy continue to be the first line treatment option for most cancers.[4] However, these focused treatment strategies fail to control metastatic tumors that have reached in distant organs. Conventional chemotherapy, the next major strategy for cancer treatment is highly non-specific in targeting the drugs to the cancer cells causing undesirable side-effects to the healthy tissues[5] Targeted therapies have significantly changed the treatment of cancer over the past 10 years. These drugs are now a component of therapy for many common malignancies, including breast, colorectal, lung, and pancreatic cancers, as well as lymphoma, leukemia, and multiple myeloma. The mechanisms of action and toxicities of targeted therapies differ from those of traditional cytotoxic chemotherapy. Targeted therapies are generally better tolerated than traditional chemotherapy.[6] Use of nanotechnology in various biomedical applications, including drug

delivery has attracted increasing interest due to their ability to alter the drug's pharmacokinetics.[7]

Nanomedicines render improved solubility of poorly soluble drugs and reduced metabolism by dissolving them in their hydrophobic or hydrophilic compartment. Nanomedicines have prolonged plasma half-life and different biodistribution profile compared to conventional chemotherapy. Moreover, nanomedicines reach tumor tissues by evading circulation and passing through the discontinuous fenestrations in the endothelial layer in the tumor microenvironment that ranges from 300 to 4700 nm in diameter. In addition to the leaky tumor vasculature, poor lymphatic drainage is encountered in the tumors due to the dysfunctional lymph angiogenesis and compression of lymphatic vessels by proliferating cancer cells. As a result, nanomedicines get preferentially accumulated in the interstitial fluid of tumor compared to other normal tissues surrounded by endothelial cells with tight junctions and functional lymphatic drainage, which reduced the toxicity to the normal tissues. The phenomena of eventual accumulation of nanomedicines to the tumor are referred to as enhanced permeability and retention (EPR) effect.[8-10]

LIMITATIONS OF CONVENTIONAL CHEMOTHERAPY[11]

The treatment of localized and metastasized cancers with the use of chemical antineoplastic drugs, mostly administered through IV regimens, referred to as chemotherapy is the primary therapeutic approach. Although widely used in cancer treatment, chemotherapeutic drugs possess limitations as follows.

- The lack of specificity toward neoplastic tissues causes significant damage to non-cancerous cells leading to severe surplus side effects such as mucositis, suppression of bone marrow activity (immuno and myelosuppression), nausea, secondary neoplasms and infertility. In addition, the high distribution volume of chemotherapeutics makes the drug delivery non-specific to tumors resulting in an abnormal concentration of the antineoplastic drugs in healthy tissues.

- The lack of selectivity in mechanism of action is prominent drawback in conventional chemotherapy. Most chemotherapeutic drugs do not act on intracellular mechanisms unique to malignant cells but on common pathways shared by both neoplastic and normal cells. Thus, cytotoxic and cytostatic mechanisms induced by these drugs hit healthy non-cancerous tissues as well. Epirubicin (EPI), an Anthracycline derivative, used for

Hepatocellular carcinoma (HCC) causes DNA damage by disrupting the cleavage-religation equilibrium and increasing the concentration of DNA topoisomerase II covalent complexes. As a result, apoptosis mediated by p53 DNA-damage sensor and activated caspases (proteases) occurs. However, long-term clinical use of EPI is limited due to serious non-specific toxicity to normal tissues, particularly cardiac toxicity associated to intramyocardial production of reactive oxygen species (ROS). The rate of rapid clearance by the reticuloendothelial system (RES) reduces the extravasation of EPI into tumor site and thus weakens drug efficacy. Thus, there is an unmet need to develop non-toxic and more efficacious therapeutic approach for hepatocellular carcinoma (HCC).

- Chemotherapeutic agents induce cytotoxicity due to high pharmacokinetic volume of distribution for low molecular weight drugs. Chemicals of low molecular weight are excreted quickly. For this reason, a higher concentration is required to achieve a therapeutic effect that leads to toxicity. The low therapeutic index of chemotherapeutic drugs implies that the needed concentration for the effective treatment is often high leading to systemic dose-dependent side effects.

- Formulating chemotherapeutic drugs is challenging due to their poor aqueous solubility. The low solubility makes preparation of drugs difficult. Due to high hydrophobicity and poor solubility in water (50.5 mg/L), the chemotherapeutic application of paclitaxel has been limited. Other chemotherapeutic agents have poor solubility due to the inclusion of lipophilic groups that show affinity toward the target receptor. In addition, high degradation susceptibility mostly at the reticuloendothelial system allows avoiding the use of the formulation for oral drug administration and implies administration regimens, not in compliance with the patients such as IV, transdermal and intraperitoneal. Thus, the modification could be done in routes of administration of available chemotherapeutic agents by optimizing drug delivery systems. The poorly soluble drugs may cause embolization of blood vessels upon intravenous injection due to aggregation of the insoluble drugs, and often cause local toxicity as a result of high drug concentrations at the site of deposition. The currently available formulation paclitaxel comprises of Cremophor EL (polyethoxylated castor oil) and dehydrated ethanol. Though, Cremophor EL is known to be toxic and causes serious side effects, including hypersensitivity reactions, nephrotoxicity and cardiotoxicity. Alternatively, surfactants may be employed in the formulation to solubilize the drug, but this may cause the drug to precipitate in

vivo, because their critical micelle concentrations in physiological fluids are too low to hold micellar structures capable of maintaining the drugs in solubilized state. Currently, thermodynamically stable polymeric micelles composed of a hydrophobic core surrounded by a hydrophilic shell have been investigated and tested as an effective delivery system for poorly soluble drugs.

- Chemotherapy experience limited efficacy of anticancer drugs due to strong innate or acquired chemoresistance mechanisms. The interstitium of a tumor tissue is characterized by high hydrostatic pressure, leading to an outward convective interstitial flow that can remove the drug away from the tumor unlike from normal tissues. Moreover, even if the drug is successfully delivered to the tumoral interstitium, its efficacy may be limited if the cancer cells have acquired multidrug resistance (MDR). The characteristic feature of MDR is over-expression of the plasma membrane P-glycoprotein (P-gp), which is capable of keeping drugs away from the cell. Several strategies have been proposed to avoid P-gp-mediated MDR, including the encapsulation of anticancer drugs in nanoparticles (NPs) and the coadministration of P-gp inhibitors. Efflux of many lipophilic drugs via drug efflux transporters leading to suboptimal therapeutic drug concentration at the site of action is considered to be one of the barriers behind the success of chemotherapy.

- Conventional chemotherapy encounters challenge during transport of the drugs to the tumor. Physicochemical properties of the drug, including size, surface composition, charge plays major role in the transport. Further hurdles consist in the pathophysiological tumor heterogeneity, which inhibit a uniform drug delivery into the whole tumoral mass. In addition, acidic tumor microenvironment causes degradation of the acid-sensitive drugs.

OVERCOMING LIMITATIONS OF CONVENTIONAL CHEMOTHERAPY AND ADVANTAGES OF NANOTECHNOLOGICAL DRUG DELIVERY SYSTEMS.[11,12]

Lack of solubility is one of the major limitations of most chemotherapeutic agents. Nanoparticles can effectively solve the solubility problem. Hydrophobic drugs can be encapsulated in micelles to increase their solubility. Dendrimers contain many binding sites with which both hydrophobic and hydrophilic molecules can bind. Liposomes also allow encapsulating hydrophobic drugs and transporting them to the desired area soon after administration. Several approaches have been taken to overcome P-glycoprotein mediated

drug resistance. P-glycoprotein locates drugs which are localized in the plasma membrane only. One strategy is to use the inhibiting agents such as verapamil or cyclosporine when concurrently administered with a cytotoxic drug can restrain P-glycoprotein. Thus both chemotherapeutic agent and inhibiting agent are incorporated into the nanoparticles to overcome the problem associated with P-glycoprotein. A new strategy was developed for inhibition of the P-glycoprotein-mediated efflux of vincristine where vincristine-loaded lipid nanoparticles, conjugated to an anti-P-glycoprotein monoclonal antibody (MRK-16), showed greater cytotoxicity in resistant human myelogenous leukaemia cell lines than nontargeted particles. Danson et al. developed SP1049C, a nonionic block copolymer composed of a hydrophobic core and hydrophilic tail that contains doxorubicin, which was able to circumvent P-glycoprotein mediated drug resistance in a mouse model of leukaemia and is now under clinical evaluation. In another study, folic acid, attached to polyethylenelglycol derivatized distearoyl-phosphatidylethanolamine, was used to target in vitro doxorubicin loaded liposomes to folate receptor overexpressing tumor cells. Folate receptor mediated cell uptake of targeted liposomal doxorubicin into a multidrug resistant subline of M109-HiFR cells (M109RHiFR) was clearly unaffected by P-glycoprotein-mediated drug efflux, in sharp contrast to uptake of free doxorubicin.

Nanotechnology is an emerging therapeutic platform that uses nanoparticles (NPs) for the diagnosis and treatment of cancer. NPs are utilized in cancer therapy due to their unique size, i.e. in general 1–1000 nm, or preferably in the range of 5–200 nm suitable for drug delivery applications. The nanoranged size, large surface-to-volume ratios and the ability for surface functionalization play a crucial role in its biodistribution in vivo. The most common examples of nanocarriers for the delivery of chemotherapeutics include liposomes, polymeric nanoparticles, dendrimers, nano-shells, inorganic, nucleic acid based and magnetic nanoparticles. Nanoparticular drug delivery systems offer distinct advantages for cancer therapy over free drug administration since NPs:

- Improve the therapeutic index of the loaded chemotherapeutic agents compared to the drugs delivered via conventional dosage forms.
- Increase drug efficacy by achieving steady state therapeutic levels of drugs over an extended period.
- Lower drug toxicity due to controlled drug release and improve drug’s pharmacokinetics by increasing drug’s solubility and stability.

Improvement in drug's pharmacokinetic parameters by the development of nanotechnology based formulations allows resuming investigation of potentially productive new chemical entities that have been hindered during the pre-clinical or clinical development due to their suboptimal pharmacokinetic or biochemical properties. In addition, targeted delivery of the chemotherapeutic agent can be achieved by developing multifunctional nanocarrier systems. The engineered nanocarriers offer various other advantages compared to free drug administration, such as (i) nanometer size range suitable for tumor targeting via EPR effect, (ii) protective insulation of drug molecules to enhance their stability and minimize their systemic clearance, (iii) ability for surface functionalization, (iv) possibility of multiple drug delivery to achieve synergistic therapeutic response, (v) opportunity for the application of combination therapy by utilizing chemotherapeutic and photothermal effects, or creating magnetic nanostructures making delivery of NPs easier with the application of an external magnetic field. The parameters such as size, conformation, non-covalent interactions and surface adsorption would have remarkable effects and variations on the interaction between the nanocarrier and the biological environment. For example, size of the NPs is critical for their renal and liver excretion: kidney filters particles smaller than 10 nm (about 70 kDa) and the liver can capture particles of diameter larger than 50 nm. For this reason, the size of an ideal nanocarrier must be in the range of 10–50 nm. In addition, surface characteristics of NPs influence their uptake and clearance in vivo. NP clearance occurs mainly via opsonization and phagocytosis by macrophages following the mechanism of receptor-mediated endocytosis. To delay degradation, surface of the NPs has been decorated using a biocompatible and non-immunogenic hydrophilic polymer, poly(ethylene glycol) (PEG) that reduces nanoparticle binding to opsonins, avoiding reticuloendothelial degradation . Furthermore, nanoparticles incorporating anticancer agents can minimize chemoresistance to drug action, increasing the selectivity of drugs toward cancer cells and reducing their toxicity toward normal cells. In addition, the selectivity of nanocarriers toward cancer cells increases by functionalizing their surface with specific antibodies or Ab-fragments, which recognize specific epitopes of tumor-associated antigens (TAA) and tumor-specific antigens (TSA). After eventual accumulation to the tumor tissues, nanocarriers are retained into the tumor interstitium due to their compromised lymphatic clearance at the tumor site. Drug release into the tumoral interstitium can be controlled by modulating the nanoparticulate structure, e.g. polymer used and the thickness of polymer wall coating the nanoparticle.

Advantages of Nanocarriers.[13]

Polymeric NPs which are made from natural and synthetic polymers were generated to achieve controlled drug release and targeting. Hydrophobic and biodegradable polymeric NPs can act as a local drug depot by providing encapsulated continuous drug release at the target site which are related by the surface make-up of the carrier system. These systems offer the opportunity to improve bioavailability, sustain the release of drugs, provide targeted delivery and solubilise drugs for systemic delivery. They also offer the opportunity to decrease the toxicity of existing drugs and overcome multidrug resistance of cancer cells.

Drug solubility can be increased by nanocarrier systems. A study with water-insoluble drug simvastatin showed that simvastatin-loaded HMC (highly ordered mesoporous carbon) samples, which were synthesized by the nanocasting technique, provided a much faster dissolution rate. Simvastatin-loaded SHMC (spherical HMC nanomatrix) provided significantly shorter tmax and higher Cmax and larger AUC0–24 h when compared with Zocor[R] which is the marketed conventional tablet. Nanotechnology can be used to improve oral absorption. The efficacy of highly lipophilic drugs is much lower than the desirable level, and to enhance their pharmacological effects, their key issues must be solved such as their poor solubility and reduced systemic exposure. Probucol is one of these lipophilic drugs. Zhang reported that the blood concentration of probucol was considerably enhanced with the nanodelivery system loaded with probucol than free probucol suspension. Also, cellular uptake of probucol in Caco-2 cell monolayers increased when the nanodelivery system was administered. Nanosystems can be used for reducing toxicity. There are some anticancer drugs which contain platinum, but there are some disadvantages of platinum such as nephrotoxicity and neurotoxicity. Also, they caused developing drug resistance limiting their uses. But nanocarrier-based delivery of platinum complexes offer the opportunity to reduce non-target toxicity. Also, in some cases nanocarriers prevent to develop drug resistance againist platinium. Additionally, these drug delivery systems can be used for multidrug resistant cancer treatment. Paclitaxel loaded NPs were eight times more efficient than Taxol plus XR9576.

TARGETING STRATEGIES.[14,15]

Two basic requirements should be realized in the design of nanocarriers to achieve effective drug delivery (Fig. 1). First, drugs should be able to reach the desired tumor sites after administration with minimal loss to their volume and activity in blood circulation. Second,

drugs should only kill tumor cells without harmful effects to healthy tissue. These requirements may be enabled using two strategies: passive and active targeting of drugs.

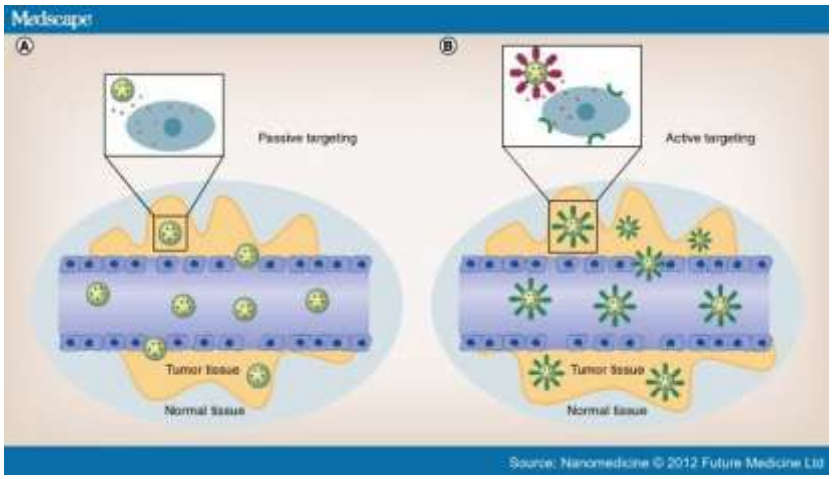

Fig. 1: Passive and Active targeting.

By the enhanced permeability and retention effect, nanoparticles can be passively extravasated through leaky vascularization, allowing their accumulation at the tumor region (A). In this case, drugs may be released in the extracellular matrix and then diffuse through the tissue. Active targeting (B) can enhance the therapeutic efficacy of drugs by the increased accumulation and cellular uptake of nanoparticles through receptor-mediated endocytosis. Nanoparticles can be engineered to incorporate ligands that bind to endothelial cell surface receptors. In this case, the enhanced permeability and retention effect does not pertain, and the presence of leaky vasculature is not required.

"Active targeting" is used to describe specific interactions between drug/drug carrier and the target cells, usually through specific ligand– receptor interaction. The term "active targeting" simply means a specific "ligand–receptor type interaction" for intracellular localization which occurs only after blood circulation and extravasation. This is why increasing blood circulation time by PEGylation (i.e., modifying the surface of nanoparticles with poly(ethylene glycol)) and/or improving the EPR effect is expected to enhance delivery to the tumor site. 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. 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.[16]

"Passive targeting" is based on drug accumulation in the areas around the tumors with leaky vasculature; commonly referred to as the enhanced permeation and retention (EPR) effect. Passive targeting happens to almost all drug carriers whether such distribution is intended or not. While the EPR effect may be in effect for I.V. administered nanoparticles, the majority (N95%) of administered nanoparticles are known to accumulate in other organs, in particular the liver, spleen, and lungs. Nanoparticles can easily accumulate selectively by enhanced permeability and retention effect and then diffuse into the cells.

COMMON NANOPARTICLES AS TARGETING AGENTS IN CANCER THERAPY

Nanocarriers are used as targeting agents for cancer therapy comprising anticancer drugs, targeting moieties, and polymers. There are a variety of nanocarriers such as liposomes, dendrimers, micelles, polymer-drug conjugates, protein-drug conjugates, metallic nanoparticles and so forth. Therapeutic agents can be entrapped, covalently bound, encapsulated, or adsorbed to the nanoparticles.

Nanoliposomes.[17-27]

The term nanoliposome has recently been introduced to exclusively refer to nanoscale lipid vesicles while liposome refers to a lipid vesicle with diameter range from around 20 nm to several micrometers. Nanoliposomes possess the same physical, structural, thermodynamic properties manufacturing and mechanism of formation as the liposomes. The underlying mechanism for the formation of liposomes and nanoliposomes is basically the hydrophilic–hydrophobic interaction between phospholipids and water molecules. Liposomes and particularly nanoliposomes are one of the most used delivery systems for small molecules, peptides, small and long nucleic acids, and proteins. Liposomes were the first nanoparticle platform applied in medicine since Bangham described them in 1961. Nanoliposomes are nanometric (30–100 nm) versions of liposomes formed by expontaneous self-organization of phospholipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol and phosphatidylserine, and other molecules such as cholesterol. Importantly, many of the lipids used for liposome preparation are major components of naturally occurring bilayers. The key common characteristic of bilayer-forming molecules is their defined polar and nonpolar regions that allow hydrophobic drugs to be embedded in the lipid bilayer, or be encapsulated in the central aqueous cavity when the molecule is hydrophilic. Nanoliposomes have been used in medicine, biology, biochemistry, and in food and cosmetics industries. Liposomes for therapeutic purposes are commonly manufactured using lipids, cholesterol and

drug in a specific ratio. Functional groups are generally covalently bound to PEG which is normally 5% mol/mol of the total lipid. To ensure a homogenous mixture of the liposome formulation, chloroform or chloroform: methanol are used as solvents. However, for therapeutic purposes, the use of chloroform is objectionable and tertiary butanol or cyclohexanes are used as alternatives. After freezing completely, the frozen lipid cake is placed on a vacuum pump and lyophilized until dry. Dry lipid films or cakes are then hydrated to obtain onion-like multilamellar vesicles (MLV). Small unilamelar vesicles (30–100 nm) are obtained by sonication or extrusion of MLV. As drug carriers, nanoliposomes are able to increase the in vivo drug stability and bioavailability, by preventing interactions of the transported drug with unwanted molecules, and reducing toxic side effects. Nanoliposomes offer the extra advantages of low toxicity, ability to modify size and surface, biocompatibility, and biodegradability. In order to reduce the recognition of liposomes by macrophages, liposomes can be coated with biocompatible polymers like polyethylene glycol (PEG) (known as PEGylated or stealth liposomes). This strategy has greatly increased the liposomal stability and circulation half-time. A liposome is a vesicle composed of a lipid bilayer. Liposomes are made of phospholipids and small amounts of other molecules as cholesterol and/or PEG (PEGylated or stealth liposomes). Functional groups (targeted liposomes) improve the specificity of the nanoparticle. Functional groups are generally covalently bound to PEG. SiRNA, miRNA inhibitors (antagomiRs) and miRNA mimics are encapsulated in the nanoliposome. Currently, around fifteen liposomal-drug formulations for different conditions are in clinical use. Currently, liposomal products used for cancer treatment include Doxil, DaunoXome®, DepoCyt® and ONCO-TCS, which are liposomal formulations of doxorubicin, daunorubicin, cytarabine and vincristine, respectively. Nab-paclitaxel (Abraxane) represents one of the new strategies to overcome the solvent-related problems of paclitaxel, and was recently approved by the US Food and Drug Administration (FDA) for pretreated metastatic breast cancer patients. Additionally, several liposomal formulations are in different clinical trial phases. Other liposomal drug formulations include, SPI-077 (liposomal cisplatin for solid tumors), CPX-351 (cytarabine: daunorubicin for acute myeloid leukemia), Lipoplatin (cisplatin for non-small cell lung cancer), ThermoDox (a thermosensitive doxorubicin for hepatocellularcarcinoma, and other advanced cancers), and Stimulax (an anti-MUC1 cancer vaccine for non-small cell lung cancer). In addition, Yakult Honsha Co., Ltd. developed IHL-305, a PEGylated liposome containing irinotecan.

Polymer-drug conjugates.[28]

While the use of both liposomes and micelles as drug delivery systems for chemotherapeutics have received much attention in cancer therapy, there are numerous other polymer-based nanocarriers that have experienced similar clinical success. For example, Zoladex and Lupron Depot are composed of either small polymer rods or polymer microparticles respectively, and both entrap Luteinizing hormone-releasing hormone (LHRH) analogues in order to treat prostate cancer. Both Oncaspar and PEG intron are PEGylated drugs used to treat acute lymphoblastic leukemia and various types of cancers respectively. Zinostatin (Stimamler) is a polymer-protein conjugate, which is composed of the anti-tumor protein neocarzinostatin covalently linked to two styrene maleic anhydride polymer chains, and is used to treat hepatocellular carcinoma . As far as promising new polymerdrug conjugates, PK1 is a nanocarrier-based system composed of N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer which is in Phase-II/III stages of clinical trials for the treatment of breast cancer.

Protein-drug conjugates.[28]

Another group of notable nanocarriers successfully used in cancer therapy involve protein-drug conjugates in which the protein used can act as the nanocarrier. For example, Abraxane which is classified as an antimicrotubule agent is composed of albumin bound to paclitaxel and is currently used to treat metastatic breast cancer. A distinctive additional advantage associated with the use of some proteindrug conjugates is the ability to actively bind cancer cells, as is the case with the drug Ontak. It is a protein-drug conjugate in which a fusion protein is generated by combining sequences from IL-2 (specific for the CD25 component of the IL-2 receptor) with sequences from diphtheria, and is currently used to treat cutaneous T-cell lymphoma. Also, both Zevalin and Bexxar function in a similar manner, and are used to treat patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. It should be noted however, that while Ontak undergoes cellular internalization, both Zevalin and Bexxar do not as their target is the non-internalizing receptor CD20 antigen.

Micelles.[29]

Micelles are colloidal particles with a size usually within a range of 5–100 nm. Micelles consist of amphiphiles or surface-active agents (surfactants), which exist of two distinct regions: mostly a hydrophilic head-group and a hydrophobic tail.

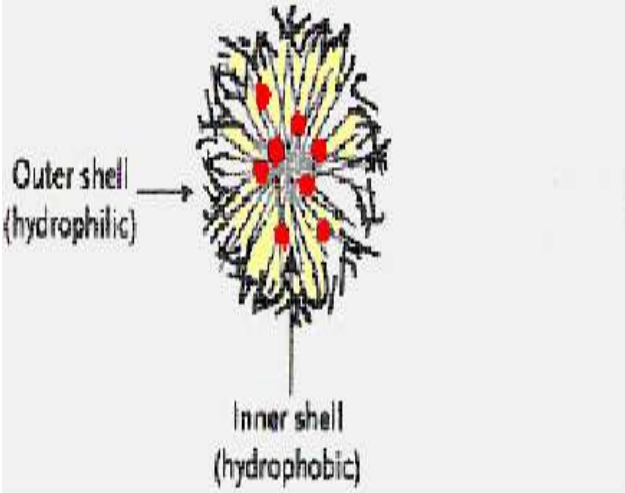

Fig. 2: Cross Section of polymeric micelles

At low concentrations in an aqueous medium, such amphiphilic molecules exist separately, however, as their concentration is increased, aggregation takes place within a rather narrow concentration interval. The concentration of a monomeric amphiphile at which micelles appear is called the critical micelle concentration (CMC), while the temperature, below which amphiphilic molecules exist as unimers and above as aggregates, is called the critical micellization temperature (CMT). The studies on the application of polymer micelles in drug delivery have mostly focused on the following areas that are considered below:

1. Delivery of anticancer agents to treat tumors;
2. Drug delivery to the brain to treat neurodegenerative diseases;
3. Delivery of antifungal agents
4. Stimuli-responsive nanocarriers for drug and gene delivery.
5. Ocular drug delivery.

Polymeric micelles possess an excellent ability to solubilize poorly water-soluble drugs and increase their bioavailability. In addition, micelles, due to their small size demonstrate a very efficient spontaneous accumulation via the enhanced permeability and retention effect in pathological areas with compromised vasculature

Currently, many drug-loaded polymeric micelles for anticancer therapy are under investigation in preclinical Studies to improve drug efficacy. Five micellar formulations have been tested in clinical trials. They are as below:

Table 1: Micellar Formulations[29]

Polymeric Micelle	Block Copolymer	Drug	Indication	Micelle Size (diameter)
Genexol PM	PEG-P(D,L-lactide	Paclitaxel	Breast cancer, Pancreatic cancer, Small cell lung cancer,	20-50 nm
SP1049C	Pluronic L61and F127	Doxorubicin	Adenocarcinoma of oesophagus	22-27 nm
NC-6004	PEG-PGL(Cisplatin)	Cisplatin	Solid tumors	30 nm
NK105	PEG-(aspartate)	Paclitaxel	Advanced stomach cancer	85 nm
NK012	PEG-PGL(SN-38)	SN-38	Breast cancer	20 nm

Polymeric micelles possess an excellent ability to solubilize poorly water-soluble drugs and increase their bioavailability. In addition, micelles, due to their small size demonstrate a very efficient spontaneous accumulation via the enhanced permeability and retention effect in pathological areas with compromised vasculature.

Dendrimers.[30,31]

Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous and monodisperse structure consisting of tree-like arms or branches. The overall shapes of dendrimers range from spheres to flattened spheroids (disks) to amoeba-like structures, especially in cases where surface charges exist and give the macromolecule a ‘‘starfish’’-like shape. Many commercial small molecule drugs with anticancer, anti-inflammatory, and antimicrobial activity have been successfully associated with dendrimers such as poly(amidoamine) (PAMAM), poly(propyleneimine) (PPI or DAB) and poly(etherhydroxylamine) (PEHAM) dendrimers.

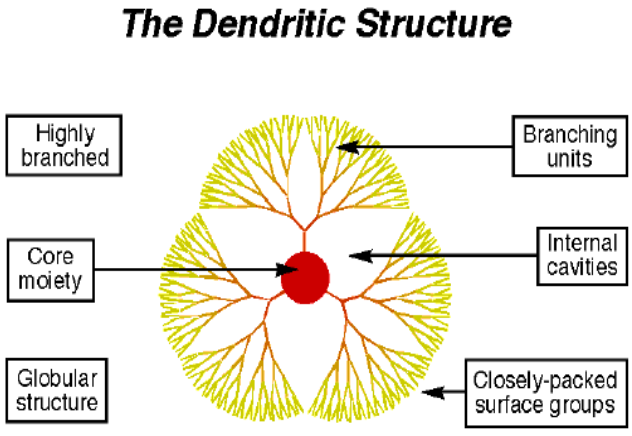

Fig. 3: The Dentritic Structure

Cancer epitomizes the challenges faced during drug delivery: an anticancer drug must be able to seek out subtle changes that distinguish a transformed cell from the other 200 or so types of healthy cells found in the body and then provide a sufficiently high dose of a toxic agent to selectively kill the cell while not harming its healthy neighbours. Therefore, dendrimers can be endowed with many favorable properties for drug delivery. They can successfully meet the formidable tasks of diagnosing and treating of malignant disease. In cancer chemotherapy, the desirable size-based features are reinforced by the enhanced permeability and retention (EPR) effect that improves the delivery of macromolecules to tumors. The EPR effect is based on unique pathophysiological features of a solid tumor, such as extensive angiogenesis resulting in hyper-vascularization, limited lymphatic drainage, and increased permeability to lipids and macromolecules. These features, which help ensure adequate nutrient supply to meet the metabolic requirements of rapidly growing tumors, can be turned to the tumor's disadvantage by the use of nano-sized therapeutic agents.

The EPR response was subsequently demonstrated for similarly-sized liposomes, thereby establishing that this effect was largely a function of particle size and did not solely depend on the chemical or biophysical properties of the macromolecule. Specifically, in one study, optimal tumor delivery occurred for liposomes having a size distribution between 70 and 200nm in diameter. An independent study showed efficacy for liposomes loaded with daunorubicin in the same size range; specifically, those with 142nm in diameter exhibited an inhibitory effect against Yoshida sarcoma whereas smaller (57–58 nm) and larger (272nm) liposomes had weaker or no effect. Over time, cautionary notes were raised that tempered initial enthusiasm for exploiting the EPR effect for cancer treatment. For example, the porosity of the vasculature in tumors can be highly variable even with a single vessel that can be leaky to one size of particle in one region but not in another. The ability to match exact and uniform sizes needed to target an individual tumor – is highly tractable with dendrimers because selection of an exactly-sized entity is possible compared with the large size distributions that plague liposome and most polymeric materials.

Metallic Nanoparticles.[32-34]

In recent years, theranostic metallic nanoparticles (TMNPs) have shown potential application in field of magnetic resonance imaging (MRI) and colloidal mediators for cancer magnetic hyperthermia. Nanotechnology based imaging and therapy has been investigated independently and their understanding has now evolved to a point enabling the birth of

theranostics agent. The term ‘theranostics’ was coined about a decade ago and was first used to describe diagnostic tests developed to guide personalised therapies. It may be defined as the combination of therapeutic and diagnostic agents on a single platform i.e. the development of theranostic nanoparticles (TNPs) that may simultaneously monitor and treat disease. Here diagnostic means those agents which provide enhanced visibility of specific tissues by increasing the signal to noise ratio relative to surrounding tissues and provide a quick, high fidelity snapshot of the living system. Theranostic agent enables an entirely new category of clinical solution for oncological disorders, permitting early recognition of disease through the use of contrast agents combined with existing imaging modalities followed by tailored release of therapeutic agent. Advantage with the use of metallic nanoparticle based theranostic system in cancer therapeutics includes.

- Tumor targeting ligands, that bind to a particular tumour cell and are capable of sequestering anticancer drugs exclusively within tumour, thus reducing the accumulation of the drugs in healthy tissues,
- Large surface to volume ratio, that provides opportunity for surface modification with improved cell entry,
- Protection of the therapeutic agent from the biological milieu,
- Improved bioavailability of the anticancer agent
- Additionally, MNPs can detect and attack the heterogeneous crowd of tumour cells,
- High drug loading capacity
- Delaying the drug resistance and
- Increasing therapeutic index through oncological site specific delivery.

Metallic nanoparticles (MNPs) such as gold or silver have optical and electronic properties derived from their size and composition. Among MNPs mediated oncological drug delivery, gold MNPs have emerged as promising carriers. Gold nanomaterials have been extensively studied for potential applications in the emerging and highly interdisciplinary field of nanotechnology. Gold nanoparticles have been used to deliver antitumour agents such as tumour necrosis factor (TNF) or paclitaxel at the site of the tumour by the enhanced permeability and retention (EPR) effect. Two characteristics of gold nanomaterials make them particularly suitable for therapeutic applications: 1) antibodies and other bioactive molecules can be easily conjugated to the surface of gold nanomaterials, and 2) gold nanomaterials have absorption efficiencies that are 4 to 5 times greater than conventional

photothermal dyes and are not affected by photobleaching. Besides the physical and chemical properties of gold nanoparticles, their unique optical properties make them particularly attractive tools for cancer detection and therapy. Taking advantage of their unique properties, most studies of gold nanoparticlebased cancer therapy have used photothermal therapy for the destruction of cancer cells or tumor tissue, which may be potentially useful in the clinical setting. When irradiated with focused laser pulses of suitable wavelength, targeted gold nanospheres, nanorods, nanoshells, and nanocages can kill bacteria and cancer cells. The use of a mNP platform will not only increase drug concentration in the tumour, but also reveal the tumour itself in MRI. This is a very important feature, especially at an early stage of the disease, when the cancer is not yet diagnosed, but there are grounds for suspecting a cancer

Magnetic Nanoparticles.[35]

Magnetic nanoparticles (mNPs) are the most suitable NPs in terms of rapid availability for in vivo human diagnostics and imaging of cancer. They also show the immense advantage of selectively delivering a drug to the cancer cells. Although mNPs are not the only NPs combining drug delivery and imaging, they are the most advanced in the process of research and development as therapeutic agents as well as MRI contrast labels in humans. The most widely used mNPs are magnetite Fe_3O_4 and maghemite γ-Fe_2O_3. Pure metals such as Fe, Ni and Co, ferrites of the form MeO@Fe_2O_3 (Me = Mg, Zn, Mn, Ni, Co, etc) may be also used to prepare mNPs. mNPs appear to be very appropriate for drug delivery. Indeed, they can be synthesized in different sizes and can be functionalized (surface-coated) in order to carry various molecules. A number of issues need to be considered when using mNPs as carriers including colloidal stability and biocompatibility. The use of a magnetic NP platform will not only increase drug concentration in the tumour, but also reveal the tumour itself in MRI. This is a very important feature, especially at an early stage of the disease, when the cancer is not yet diagnosed, but there are grounds for suspecting a cancer. Another advantage of these NPs is that they are nontoxic and well tolerated in vivo, independently of the administration routes. Magnetic nanoparticles technology has one more advantage; it attracts NPs near the tumour and increases gene transfer into cells. This technique is called magnetofection and uses an external magnetic field (magnet) to concentrate and retain MNPs in a specific area. However, this approach is not applicable for non-accessible tumours.

CONCLUSION

The development of nanoparticle drug delivery systems is expected to have a big impact on the clinical approaches for cancer therapy, as these systems has greatly improved the stability and therapeutic effectiveness of several anticancer agents. Various nanocarriers possess excellent ability to solubilize poorly water-soluble drugs and increase their bioavailability. Due to their, small size, nanocarriers demonstrate a very efficient spontaneous accumulation via the enhanced permeability and retention effect in pathological areas with compromised vasculature. As the future of nanotechnology is expected to grow at a blistering pace day-by- day, more and more of scientific research work can be put forth for the further development in this particular arena of pharmaceutical drug delivery systems. The application of nanotechnology holds a potential prospect to produce promising results in cancer therapy thereby eventually contributing to an optimistic drive in this life saving approach.

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