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NANOPARTICULATE DRUG DELIVERY SYSTEM IN CANCER MEDICINE WITH SPECIAL EMPHASIS ON THE RECENT ADVANCES IN NANOPARTICLES

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ABSTRACT

Chemotherapy and Nanoparticle drug delivery are the two areas that have shown significant promise in cancer treatment. Nanoparticle drug delivery, on the other hand enhances therapeutic effectiveness and reduces side effects of the drug payloads by improving their pharmacokinetics. These two active research fields have been recently merged to further improve the efficacy of cancer therapeutics. Conventional anticancer drugs display significant shortcomings which limit their use in cancer therapy. For this reason, important progress has been achieved in the field of nanotechnology to solve these problems and offer a promising and effective alternative for cancer treatment. Nanoparticle drug delivery systems exploit the abnormal characteristics of tumor tissues to selectively target their payloads to cancer cells, either by passive, active or triggered targeting. More recently developed nanoparticles are demonstrating the potential sophistication of these delivery systems by incorporating multifunctional capabilities and targeting strategies in an effort to increase the efficacy of these systems against the most difficult cancer challenges, including drug resistance and metastatic disease. This review focuses on the potential of nanoparticle drug delivery system in cancer treatment and the current advances achieved. It summarizes the recent efforts in developing nanoparticle platforms to concurrently deliver multiple types of drug for cancer treatment. Apart from this it also highlight the challenges and design specifications that need to be considered in optimizing nanoparticulate based-cancer therapy.

KEYWORDS: Chemotherapy, Pharmacokinetics, Cancer Therapy, Drug targeting, Nanoparticulate drug delivery.

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INTRODUCTION

Cancer is one of the most serious fatal diseases in today's world that kills millions of people every year. It is one of the major health concerns of the 21st century which does not have any boundary and can affect any organ of people from any place[1.] Cancer, the uncontrolled proliferation of cells where apoptosis was greatly disappeared, requires very complex process of treatment. Because of complexity in genetic and phenotypic levels, it shows clinical diversity and therapeutic resistance. A variety of approaches are being practiced for the treatment of cancer each of which has some significant limitations and side effects[2.] Cancer treatment includes surgical removal, chemotherapy, radiation, and hormone therapy. Chemotherapy, a very common treatment, delivers anticancer drugs systemically to patients for quenching the uncontrolled proliferation of cancerous cells[3]. Unfortunately, due to nonspecific targeting by anticancer agents, many side effects occur and poor drug delivery of those agents cannot bring out the desired outcome in most of the cases. Cancer drug development involves a very complex procedure which is associated with advanced polymer chemistry and electronic engineering. The main challenge of cancer therapeutics is to differentiate the cancerous cells and the normal body cells. That is why the main objective becomes engineering the drug in such a way as it can identify the cancer cells to diminish their growth and proliferation. Conventional chemotherapy fails to target the cancerous cells selectively without interacting with the normal body cells. Thus they cause serious side effects including organ damage resulting in impaired treatment with lower dose and ultimately low survival rates[4]. The emergence of nanotechnology has made a significant impact on clinical therapeutics in the last two decades. Advances in biocompatible nanoscale drug carriers such as liposome's and polymeric nanoparticles have enabled more efficient and safer delivery of a myriad of drugs. Advantages in nanoparticulate drug delivery, particularly at the systemic level, include longer circulation half lives; improved pharmacokinetics and reduced side effects. Nanoparticle drug delivery is use of particles with nanoscale size to carry and transport pharmaceutical agents for benefit of improving therapeutic efficacy,drug safety and patience compliance. It is very promising both in cancer diagnosis and treatment since it can enter the tissues at molecular level. Cancer nanotechnology is being enthusiastically evaluated and implemented in cancer treatment indicating a major advance in detection, diagnosis, and treatment of the disease. Various researches are being carried out in order to discover more accurate nanotechnology based cancer treatment minimizing the side effects of the conventional ones. In this review properties and synthesis of several nanoscale drug carriers including Liposome's, Polymeric nanoparticles, Dendrimers, and Silica nanoparticles are discussed with an emphasis on mechanism through which multi-drug co-encapsulation can be achieved. Current nanotechnology based drug delivery systems for cancer treatment, which are already marketed and under research and evaluation, include liposomes, polymeric micelles, dendrimers, nanospheres, nanocapsules, and nanotubes. Nanotechnology based formulations that have already been marketed are DOXIL (liposomal doxorubicin) and Abraxane (albumin bound paclitaxel)[5].

NANOTECHNOLOGY AND TARGETED DRUG DELIVERY SYSTEM

The greatest immediate impact of nanotechnologies in cancer therapy is in drug delivery. The therapeutic index of nearly all drugs currently being used can be improved if they are more efficiently delivered to their biological targets through appropriate application of nanotechnologies. Some drugs that have previously failed clinical trials might also be re examined using Nano technological approaches. A number of obstacles may be overcome with various novel applications of Nano drug delivery. For example, many drugs are not very soluble, making it difficult to administer therapeutic doses. These compounds can be "solubilized" by formulating them into crystalline Nano suspensions that are stabilized by surfactants or by combining them with organic or lipid nanoparticles that keep them in circulation for longer periods. If an efficacious compound has a short half-life in the circulation, its stability can be increased tremendously by encasing it within nanosized liposomes as a drug carrier. In the case of central nervous system cancers, many drugs have difficulty in crossing the blood-brain barrier to attack the tumor. Drug-loaded nanoparticles are able to penetrate this barrier, and have been shown to greatly increase therapeutic concentrations of anticancer drugs in brain tumors. The best way to increase the efficacy and reduce the toxicity of a cancer drug is to direct the drug to its target and maintain its concentration at the site for a sufficient time for therapeutic action to take effect. For example, lipid cationic nanoparticles coupled to an integrin-targeting ligand were shown to deliver genes selectively to angiogenic blood vessels in tumor-bearing mice. As the therapeutic part of the nanocomplex, a mutant RAF gene was coupled to the particle for transfection and expression in the tumor cells; expression of this mutant gene was shown to block angiogenesis in this model. The directed nanoparticle caused apoptosis in the tumors and a sustained regression of established primary and metastatic tumors. The efficiency of drug delivery to various parts of the body is directly affected by particle size. Nanostructure-mediated drug delivery, a key technology for the realization of nanomedicine, has the potential to enhance drug bioavailability, improve the timed release of drug molecules, and enable precision drug targeting[6]. Nanoscale drug delivery systems can be implemented within pulmonary therapies(7), and also as a gene delivery vectors[8], and in stabilization of

drug molecules that would otherwise degrade too rapidly[9, 10].Additional benefits of using targeted Nano scale drug carriers are reduced drug toxicity and more efficient drug distribution[11]. Monoclonal antibodies are good targeting vehicles for nanoparticles but other bio conjugates are being tested with varying degrees of success. Nucleic acid ligands called aptamers that mimic antibodies are potential replacements because they can be designed to bind to practically any antigen in an in vitro system. The aptamers are generated by evolutionary methods in vitro, and the molecules with high affinity are used for targeting antigens in vivo. This strategy has been applied to directing PEG-coated nanoparticles to home in on prostate-specific membrane antigen in prostate cancer cells. The aptamer conjugated particles were shown to have a 77-fold increase in binding versus the control particles, and a large increase in uptake of drug encapsulated particles. There are numerous examples of similar type targeting of nanoparticles, and this area of research promises to provide important weapons in the arsenal for developing a cure for cancer.

GOALS OF NANOTECHNOLOGY

One of the ultimate goals of nanotechnology is to create medically useful nanodevices that can function inside the body. It is envisioned that nanodevices will be hybrids of biologic molecules and synthetic polymers that can enter cells and the organelles to interact directly with DNA and proteins[12]. Additionally, nanomedicine will have an impacted on the key challenges in cancer therapy: localized drug delivery and specific targeting. Among the newly developed nanomedicine and nanodevices such as quantum dots, nanowires, nanotubes, nanocantilevers, and nanopores, nanoshells and nanoparticles are the most promising applications for various cancer treatments. The gold nanoshell-antibody complex can be used to ablate breast cancer cells. Nanoshells[13] have a core of silica and a metal outer layer. They can preferentially concentrate in cancer lesion sites through enhanced permeation retention. A near infrared laser illuminates the tissue, and the light will be absorbed by the nanoshells to generate an intense heat that destroys only the cancer cells without damaging the surrounding healthy cells[14]. Nanoparticles have already been used for targeted drug delivery, which enables much earlier detection[15] and immediate treatment of cancer. Nanoparticles attached to chemotherapeutic drugs allow them to traverse the blood-brain barrier for brain tumor treatment[16]. In January 2005, a nanoparticle-based drug called Abraxane (paclitaxel protein- bound particles, Abraxis Oncology) was approved by the Food and Drug Administration for breast cancer treatment. Abraxane uses nanoscaled particles of the natural protein albumin that can be delivered in the body without the use of solvents.

MECHANISM OF NANOPARTICULATE DRUG DELIVERY SYSTEM

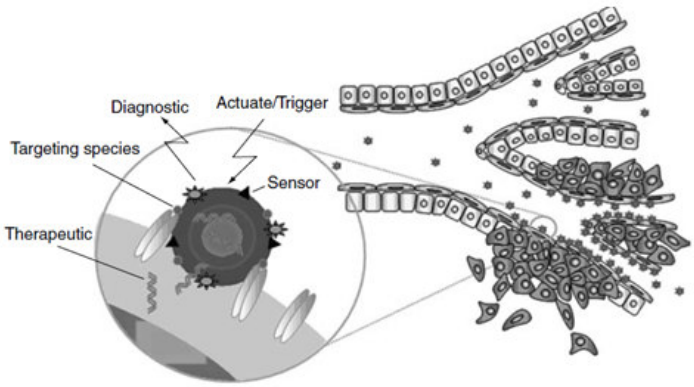

Figure 1

Schematic depiction of a multifunctional nanoparticle. A hypothetical nanoparticle targets the tumor, senses and reports molecular signatures, and delivers a therapeutic in response to an external or biological trigger.

The above figure schematically depicts a hypothetical multifunctional particle that has been engineered to include many features such as the ability to target tumors, evade uptake by the reticuloendothelial system (RES), protect therapeutics that can be released on demand, act as sensors of tumor responsiveness, and provide image contrast to visualize sites of disease and monitor disease progression. Some of these features, such as targeting, leverage biological machinery. Others are derived synthetically and enable external probing or manipulation that is otherwise not feasible in biological systems**.** One of the most widely used approaches to treat cancer is the use of radiation that helps in degenerating the cancerous tissue and prevents the of tumor cells. The use of these radiations can has many side effects on non cancerous tissues as they fail to differentiate between healthy tissues and malignant tissues Several approaches have been designed in using nanoparticles for targeting

cancerous cells during the treatment of cancer. The intratumoral heterogeneity of cancer cells stands as a hindrance in developing effective treatment agents for cancer. The drugs can be targeted to specific sites using two mechanisms[17]

- ✓ Active targeting.
- ✓ Passive targeting

Approaches using nanoparticles as targeted drug delivery systems in the treatment of cancer.

1. Aptamer based nanoparticles in targeting the specific cancerous cells[18].
2. Nanoparticles are a very challenging approach which helps in simultaneous MRI imaging of cancer cells and also treating them[19].

Thiolated chitosans nanoparticles are currently gaining great importance due to their because of their high mucoadhesiveness and extended drug release properties[20].

NANOPARTICULATE PLATFORMS FOR CANCER THERAPY

1. LIPOSOMES

Liposome's First described in 1965, the liposome is the most established drug- delivery vehicle, with many clinical products to date. The emergence of 'stealth liposomes,' or polyethyleneglycol (PEG)-coated liposomes, took liposomal drug delivery to a whole new level as they increased the in vivo circulation half life of liposomes from a few hours to approximately 45 h. currently, liposomal products used for cancer treatment include Doxil, DaunoXome® , DepoCyt® [21] and ONCO-TCS, which are liposomal formulations of doxorubicin, daunorubicin, cytarabine and vincristine, respectively. Drug encapsulation in liposomes can be achieved by two different methods. First, the drugs can be dissolved in an aqueous solution to hydrate lipid films. This process results in the formation of drug-loaded multilamellar liposomes that can then be extruded through filters with a predetermined pore size to form unilamellar liposomes. Second, unilamellar liposomes are first synthesized and subsequently incubated in an aqueous drug solution. Owing to their unique structure, liposomes can simultaneously load hydrophilic drugs in their aqueous core and hydrophobic drugs in their lipid bilayered membrane. This property makes liposomes a highly versatile platform for combination drug delivery. An early attempt to create dual drug-loaded liposomes by Agrawal et al. in 2005 highlights both the promises and challenges in combinatorial drug delivery using single nanoparticles. In the study, the authors encapsulated two antileukemia drugs, 6-mercaptopurine and daunorubicin, into a single liposome and examined their loading efficiency as well as their in vitro cytotoxicity. The two drugs have dissimilar working mechanisms as 6-mercaptopurine hinders purine biosynthesis and daunorubicin inhibits DNA topoisomerase II. The dual drug-loaded liposomes exhibited higher cytotoxicity against Jurkat and Hut 76 T-cell lymphoma as compared with monodrug-loaded liposomes containing either 6-mercaptopurine or daunorubicin, suggesting that the combination of these two mechanistically different drugs can generate higher therapeutic efficacy.[22]

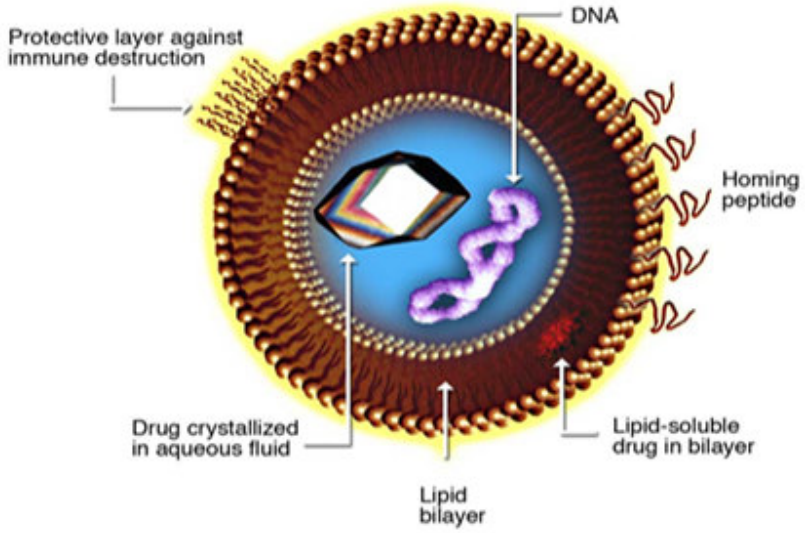

Figure 2
Liposome's for Drug delivery

2. *GOLD NANOPARTICLES*

Gold Nanoparticles (GNPs) are known for their unique optical & electronic properties. They produce vibrant colors upon interaction with visible light and thus were used by artisans in the past centuries. Gold nanoparticles have proved to be versatile for a range of applications with well characterized physical and electronic properties[23]. Moreover, their surface chemistry can be easily modified. Their large surface area to volume ratio enables surface coating with a variety of molecules including therapeutics and target agents. The optical and electronic properties of gold nanoparticles are tunable by changing the size, shape, surface chemistry, or aggregation state. One of the unique properties exhibited by GNPs is surface plasmon resonance enhanced light scattering and absorption, which can be customized by varying the size or shape of the nanoparticles for different applications. These features have made gold nanoparticles one of the most widely used nanomaterials for academic research.

3. *POLYMERIC NANOPARTICLES*

Polymeric nanoparticles are prepared from natural or synthesized polymers. Polymeric nanoparticles, the most effective nanotechnology platforms, have emerged as a versatile carrier system for targeted delivery of anticancer drugs. Polymeric nanoparticles can deliver not only small molecular weight drugs but also macromolecules such as genes and proteins[24]. A system made up of poly (D, L lactide co glycolide) nanoparticles, a potent protease inhibitor (cystatin) and cytokeratin specific monoclonal antibody, has been reported. It can neutralize the activity of excessive proteolysis in order to prevent the metastatic and invasive potential of breast tumor cells. To stabilize the surface of nanoparticle or achieve active targeting, conjugating, grafting and adsorbing hydrophilic polymers, such as polyethylene glycol (PEG), are usually used. Copolymer pegylation and folate conjugation can improve the stability of self assemblies in aqueous medium and the tumor site selectivity in vivo of ring opening metathesis polymerization based copolymers. By covalent coupling of humanized monoclonal antibodies (antiHER2) to paclitaxel loaded poly (D, L lactic acid) nanoparticles, immune nanoparticles were prepared to actively target tumor cells which overexpress HER2 receptors. PLAPEG ligand conjugate nanoparticles by a single step surface functionalizing technique were produced and found that simultaneous functionalization with biotin and folic acid induced great efficacy of paclitaxel loaded nanoparticles in a MCF7 tumor xenograft model by enhancing drug accumulation in tumors. Polymeric nanoparticles are currently the most widely investigated nanotechnology platform for cancer therapy, despite many challenging defects or drawbacks need to be resolved before clinical application. It is also considered as the most promising vehicle for site targeting anticancer drug delivery and disease diagnosis because of its good variability of chemical structures through chemical modification and the resulting flexibility of physicochemical characteristics enabling its diverse drug delivery applications. Advances in biomaterials research have led to the emergence of biocompatible and biodegradable polymeric nanoparticles for drug delivery applications. Drug encapsulation is typically achieved by mixing the drugs with the polymer solutions during particle preparation process. Many approaches have been taken to co-encapsulate multiple therapeutic agents into a single polymeric nanoparticle[25]. Presently, these approaches can be divided into three major categories, as follows:

- ✓ Directly encapsulating the multiple drugs into the hydrophobic polymeric core.
- ✓ Incorporating an additional media compartment to the nanoparticle, usually on the particle surface, to create a separate partition for drug loading.
- ✓ Covalently conjugating multiple drugs to the polymer backbone before nanoparticle synthesis.

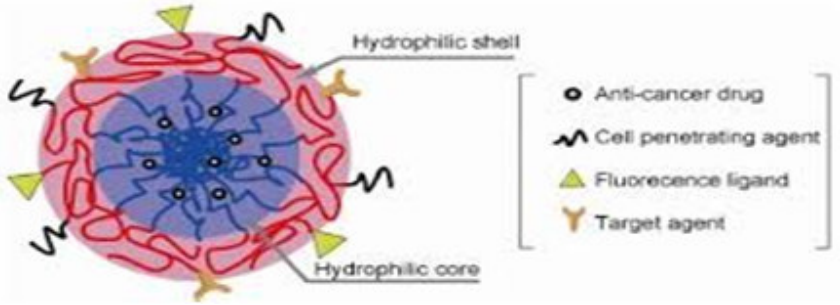

Figure 4
Polymeric Nanoparticles

4. *POLYMER –DRUG CONJUGATE NANOPARTICLES*

Polymer–drug conjugates are one of the most investigated types of nanocarriers and is currently in clinical trials as advanced as phase III. Polymer–drug conjugates were formed through side-chain grafting of drugs to polymer chains, allowing them to deliver high doses of chemotherapeutic drugs, the size of polymer–drug conjugates is generally below 20 nm. HPMA-doxorubicin[26] (N-(2-hydroxypropyl) methacrylamide) copolymer (PK1) was the first synthetic polymer–anticancer drug conjugate to enter clinical trials more than a decade ago. Overall, polymer–drug conjugates are considered simple nanocarrier systems, but tuning the optimal formulation might require extensive development. For example, small changes in the polymer–drug conjugation efficiency may significantly modify the pharmacokinetic parameters and tissue biodistribution. The resulting formulation could also be considered a new chemical entity, complicating regulatory approval.

Table 1

Polymeric nanoparticles and polymer – drug conjugates for cancer therapy

Formulation	Drugs	Indication
HPMA – Gem – Dox	Gemicitabine and doxorubicin	Prostate cancer and various cancer types.
Poly(ethylene glycol) – poly(aspartate hydrazice) block copolymers – Dox – WOR	Doxorubicin and Phospatidylinositol – 3 kinase inhibitor (Wor)	Breast cancer and various cancer types.
Combretastatin – doxorubicin nanocell	Combretastatin and doxorubicin	Lung carcinoma, melanoma and various cancer types.
Cationic core-shell nanoparticles.	Paclitaxel and Bcl – 2- targeted siRNA	Breast cancer.
Nanoparticle-aptamer biconjugates	Doxorubicin and Docetaxel	Prostate cancer and various cancer types.
Polyalkylcyanoacrylate nanoparticles co-encapsulating doxorubicin and cyclosporine A	Doxorubicin and Cyclosporin A	Various cancer types.

5. *DENDRIMERS*

Dendrimers are the novel class of nanoparticles that are emerging as a drug-delivery vehicle for cancer therapeutics. They are highly branched globular macromolecules that are synthesized in a step wise and iterative fashion. The structure of the dendrimers can be defined by an initiator core, layers of branched repeating units and functional end groups on the outermost layer[27]. The unique properties of dendrimers make them a desirable platform for concurrent delivery of water. Soluble and insoluble drugs. For instance, the hydrophobic core contains a cavity that can encapsulate hydrophobic drugs. The multivalent surface, on the other hand, can be conjugated with the hydrophilic drugs. Even though dendrimers have not attracted as much attention as liposomes and polymeric nanoparticles, several attempts have been made to deliver multiple therapeutic drugs simultaneously using a dendritic platform. As highly branched artificial macromolecules with tree like structures, dendrimers are monodisperse three dimensional molecules which have defined molecular weights and entrapment properties. With the size ranging from 1 to 10 nm, dendrimers with different chemical structures and functional groups can be synthesized. Through a series of repeating chemical synthesis on the core, the size and shape of the dendrimers are determined by the generation. The key useful character of the dendrimers is the branches which can provide vast amounts of surface area for drugs and targeting molecules. Meanwhile, the surface functionalities, the interior branching and chemical composition of the core play a significant role in reactivating the macromolecule. Dendrimer is one of the most elegant nanotechnology platforms for the targeted drug delivery. Conjugated with biotin as the targeting moiety, the in vitro targeting ability of partially acetylated generation 5 poly amidoamine (PAMAM) dendrimer (AcG5) in HeLa cells was assessed. The multifunctional conjugate AcG5 biotin FITC (fluorescein isothiocyanate) showed much higher cellular uptake than the conjugate with biotin. The energy dependent uptake process can be blocked effectively by biotin polymer conjugates, exhibiting an expected dose response curve.

Table 2

Dendrimers and other nanoparticles for cancer treatment.

Formulation	Drugs	Indication
Generation – 3 poly (L-lysine) octa (3-aminopropyl) silsequioxane dendrimer	Doxorubicin and siRNA	Glioblastoma
Generation – 5 poly (propyleneimine) dendrimer with ethylenediamine core	Methotrexate and *all-trans* retinoic acid	Leukemia
Oil nanoemulsion coencapsulating paclitaxel and curcumin	Paclitaxel and curcumin	Ovarian cancer
Mesoporous silica nanoparticles	Doxorubicin and Bcl2 – targeted siRNA	Ovarian cancer

6. *NANOSHELLS*

As layer by layer assembly of the nanoparticles, polymeric nanoshells (2060 nm) of diblock copolymers can be made by self assembly of oppositely charged polymers forming a core/shell structure. With a biodegradable polymer core and mixed lipid monolayer shell, a system of folic acid conjugated nanoparticle was developed for targeted delivery for targeted delivery of Docetaxel. Gold nanoshells (10 to 300 nm) are optically tunable nanoparticles comprising a dielectric core with a thin gold shell surrounded. In order to achieving maximal penetration of light through tissue over a near infrared gold nanoshell can be designed by adjusting the core radius and the shell thickness[28]. Laser activated gold nanoshells thermal ablation is a selective and effective technique for the ablation of prostate cancer in an ectopic tumor model.

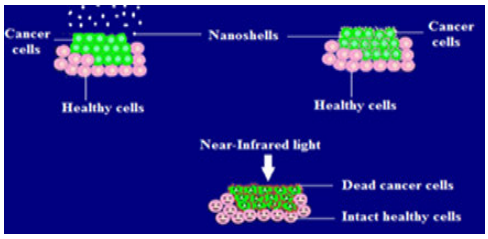

Figure 5
Nanoshells in Cancer Therapy

7. *CARBON NANOTUBES*

As a distinct molecular form of carbon atoms which bond with each other via sp2 bonds and present a hexagonal arrangement, carbon nanotubes were first discovered in the late 1980s. Conceptually, Carbon nanotubes are described as well ordered, hollow nanotubes formed when single or multiple graphene sheets are rolled into a cylinder.

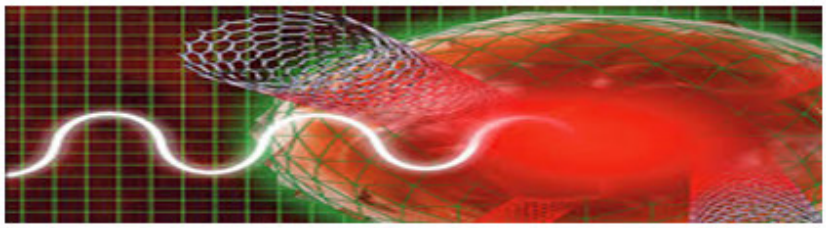

Figure 6
Carbon Nanotubes

The two forms of carbon nanotubes are single and multiwalled carbon nanotubes. In the family of nanotechnology platforms, carbon nanotubes have been identified as anovel tool for anticancer drug delivery. Apart from that, carbon nanotubes can immobilize molecules, such as antibodies, DNA and drugs, in order to penetrate cellmembranes. *Heisters have* used an oxidized single walled carbon nanotube, consisting of a fluorescent marker and a monoclonal antibody at non competing binding sites, to deliver anticancer drug Doxorubicin. However, because of the needle like fiber shape, the safety of the carbon nanotubes is concerned. Recently, the biological impacts (cytotoxicity, DNA damage and inflammation) induced by different sized multi walled and single walled carbon nanotubes, have been studied.[29]

8. *SUPER PARAMAGNETIC NANOPARTICLES*

Super paramagnetic nanoparticles, iron oxide magnetic nanoparticles with particle sizes of about 20 nm, are composed of Fe_2O_3 or Fe_3O_4 and do not keep any magnetism after removal of the magnetic field hence, may be used in vivo. Super paramagnetic nanoparticles can be used as contrast agents for magnetic resonance imaging (MRI) can be used for cancer thermal therapy, and can concentrate in target sites through an external magnetic field. Functionalized with recombinant single chain Fv antibody fragments (scFv), super paramagnetic iron oxide nanoparticles (SPIONS) could be used to target and image cancer cells. Conjugated to luteinizing hormone releasing hormone (LHRH), SPIONS not only achieve breast cancer cell targeting but also play the role as contrast agents in the MRI of breast cancer Xenografts. The postmortem neuropathologic studies of the glioblastoma multiforme (GBM) patients treated by thermotherapy using magnetic nanoparticles were reported[30]. Magnetic nanoparticles were injected into the tumor and then heated in an alternating magnetic field. The instillation of magnetic nanoparticles in GBM patients induced the uptake of nanoparticles in macrophages to a major extent, and the uptake was further promoted by magnetic fluid hyperthermia.

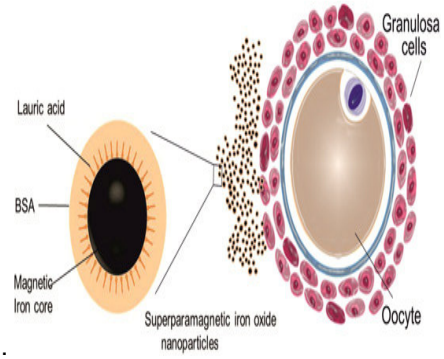

Figure 7
Super paramagnetic Nanoparticles

9. NUCLEIC ACID BASED NANOPARTICLES

Gene therapy refers to the direct transfer and expression of DNA into the diseased cells for the therapeutic applications. *Veiseh* had developed a ligand mediated nanovector by binding the chlorotoxin (CTX) peptide and pegylation of DNA complexing polyethylenimine (PE) in nanoparticles which functionalized with an Alexa Fluor 647 near infrared fluorophore.

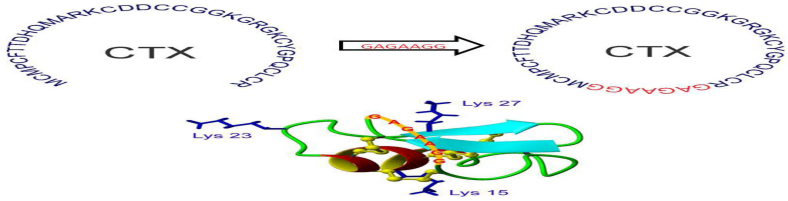

Figure 8
Nucleic Acid Based Nanoparticles

10.*MICELLE NANOPARTICLES*

Micelles are composed of lipids or other amphiphilic molecules, such as polymers or polyamino acids, and self-assemble into small nanoparticles composed of a hydrophobic core. Micelles have been developed as drug delivery carriers for hydrophobic drugs. There are multiple examples of micellar formulations under investigation or in clinical trials, such as Genexol-PM. Genexol-PM is the first nontargeted polymeric micellar formulation approved for cancer therapy. It was approved in Korea in 2006 as a first-line therapy for metastatic breast and NSCL cancer.

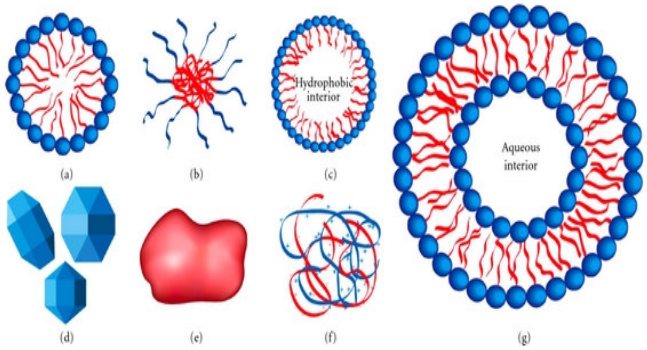

Figure 9

Various nanoparticles that may be used in ultrasound-enhanced drug and gene delivery. (a) Micelle (nonpolymeric) composed of amphiphilic surfactants. (b) Polymeric micelle composed of amphiphilic block copolymers. (c) Nanoemulsion consisting of a hydrophobic liquid core stabilized by surfactant. (d) Crystalline nanoparticles. (e) Amorphous polymeric nanoparticle. (f) Condensed ionic oligomers, such as DNA condensed with PEI or cationic lipids. (g) Single-walled liposome consisting of an amphiphilic bilayer surrounding an aqueous core.

11.*POLYSOME NANOPARTICLES*

Polymersomes have a structure similar to liposomes, but are composed of synthetic polymer/polypeptide amphiphiles and self-assemble to form polymer shell vesicles (~100 nm) when hydrated and extruded. The hydrophilicity/hydrophobicity ratio is used to control the morphology of the nanoparticle, which can range from spherical to cylindrical. The membrane core thickness can be controlled by the molecular weight of the diblock copolymer.

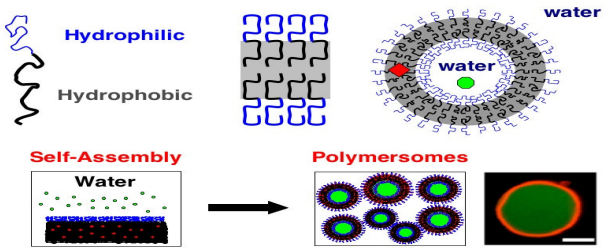

Figure 10
Polymersomes self assembled Nanoparticles

Polymersomes show higher stability and lateral fluidity than liposomes and the release is triggered by the degradation of the polymer chain and destabilization of the shell layer. Incubation of polymersomes in the blood showed adherence and uptake by white blood cells within 10 h. In vivo results using a breast cancer tumor xenograft model showed therapeutic efficacy after a single i.v. injection using polymersomes loaded with paclitaxel and doxorubicin at the maximum tolerated dose (2.5 mg kg1 for each drug).

12.*PROTEIN NANOPARTICLES*

Protein-based drug delivery systems have recently made a big impact with albuminbound drug nanoparticles (~130 nm). The recent approval of albumin-bound paclitaxel (Abraxane, ABI-008, January 2005) by the Food and Drug Administration (FDA) for metastatic breast cancer therapy, as well as multiple clinical trials currently in progress for other types of cancer, has now opened the possibility of using protein-based nanoparticles for delivery of therapeutic agents (Gradishar 2006).

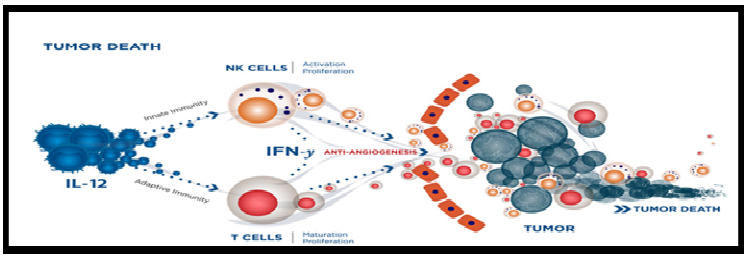

Figure 11
Protein Nanoparticles

Given the limiting pharmacokinetic properties and numerous side effects of Taxol (hypersensitivity), the albumin-bound paclitaxel allows the formulation of the hydrophobic drug in a solvent-free solution. Albumin is a natural noncovalent physiological transporter of molecules across endothelial barriers through a 66 F. Abraxane is currently being tested as a first-line therapy or in combination with other drugs (rapamycin, verinostat, etc.) for metastatic breast cancer and other cancers that have been shown to be sensitive to taxane drugs, such as ovarian and prostate. In addition, albumin is now being tested as a platform for delivery of other molecules that have reduced water solubility, such as rapamycin (~2.5 mg ml–1).

13.BIOLOGICAL NANOPARTICLES

Biological nanoparticles such as bacteria are unicellular microorganisms with different shapes and sizes that encapsulate essential components of the cytoplasm as well as hydrophobic and hydrophilic molecules. One example of biological nanoparticles being evaluated for cancer therapy is a drug delivery system developed by EnGeneIC Pty Ltd called a “nanocell”, which consists of anucleate globular bacteria (~400 nm). The absence of DNA prevents endogenous mutations and replication originally reported in 1967 (Adler et al. 1967). It has been demonstrated that a nanocell can be efficiently loaded with molecules of different solubility and charge, such as doxorubicin, paclitaxel, and siRNA, through drug diffusion into the bacteria within a few hours (MacDiarmid et al. 2007). No signs of toxicity have been reported in large animals such as pigs and monkeys with repeated dosages at high titers, although there is the potential for an immunological response to the carrier due to the presence of lipopolysaccharide.

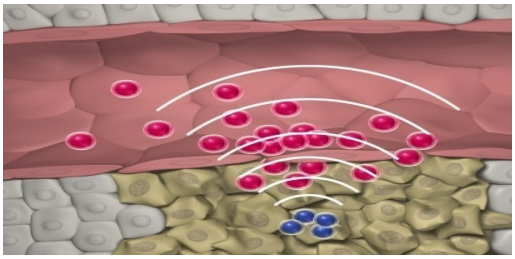

Figure 12
Biological Nanoparticle

14.HYBRID NANOPARTCLES

Hybrid nanoparticles are recently developed nanocarriers that combine advantages from existing systems with well-characterized properties to form lipid–polymer nanoparticles and solid liposomal nanoparticles. Hybrid nanoparticles are composed of at least two different materials to form the core and the corona structure. In general, metallic and polymeric materials form the core and are coated with a single or multiple lipid layers to form a protecting membrane (corona) similar to a liposome or micelle. *Sasisekharan and co-workers (Sengupta et al. 2005)* have reported PLGA-core nanoparticles coated with a bi-phospholipid layer to carry multiple drugs for cancer therapy using melanoma and Lewis lung carcinoma models. In their system, doxorubicin is conjugated to PLGA to form the core of the nanoparticle (~1% load by weight of doxorubicin, 70% encapsulation efficiency) while an anti-angiogenesis drug, combrestatin, is mixed with phospholipids and encapsulated in the lipid bi-layer during the self-assembly process to form nanoparticles (~200 nm) described as “nanocells”. The drugs were release at different rates over a period of ~3 days, with combrestatin released first to reduce vascular density in the tumor followed by the release of doxorubicin to kill the cancer cells.

APPLICATIONS OF NANOPARTICLES DRUG DELIVERY IN CANCER THERAPY

The challenge of modern drug therapy is the optimization of the pharmacological action of drug, coupled with the reduction of their toxic side effect in vivo. In cancer treatment and detection, nanoparticles serve many targeted functions in chemotherapy, thermotherapy, radiotherapy, photodynamic therapy, immunotherapy and anti angiogenesis.

1. *PHOTO THERMAL ABLATION THERAPY*

In general, thermal ablation therapy refers to hyperthermia as well as thermotherapy. Hyperthermia therapy is based on the fact that tumour cells are more sensitive to temperature increase than normal tissue cells. It involves tumour heating to temperatures between 41- 45 °C inducing almost reversible damage to cells and tissues. For thermal ablation therapy higher temperatures are applied, i.e. ranging from 50 °C to 70 °C, leading to the destruction of pathologically degenerated cells[31]. In case of successful treatment, either the tumour disappears, diminishes, or at least stops growing; Hyperthermia therapy in combination with immunotherapy could also offer feasible treatment of advanced malignancies.

I. *Photo-thermal ablation therapy using silica nanoshells*

Nanoshells can be used for photo-thermal ablation of tumor tissue as demonstrated both human breast carcinoma cells *in vitro* and in a murine model *in vivo.* The gold nanoparticles readily absorb the energy and turn it into heat resulting in an average temperature increase of ~37 °C which induces irreversible cancerous tissue damage. The heating is localised and does not affect healthy tissue adjacent to the tumor. It is also possible to attach biological markers, such as antibodies and proteins, to the nanoshells, in order to direct them to their target tissues[32]. The advantage of using smaller particles is that they can be inserted into any part of the human body to treat cancer cells in their infancy.

II.Photo-thermal ablation therapy using carbon nanotubes

Functionalised Single walled carbon nanotubes (SWCNTs) can achieve near-infrared light-triggered selective tumor cell destruction without harming normal cells in vitro. Folate-functionalised SWCNTs are internalised inside HeLa tumor cells as the surface of these cancer cells was covered with abundant folate receptors. Continuous near-infrared light radiation by a laser for 2 min causes excessive local heating and triggers cell death. Compared to the optical properties of other nanomaterials, such as gold-coated silica nanoshells, SWCNTs are favourable with lower laser power and shorter radiation times necessary for effective tumor cell destruction. It should be noted that pulsed laser radiation causes delivery of DNA-SWCNT conjugates without destroying cells. Hence, the optical and transporting properties of SWCNTs could lead to new classes of novel nanomaterials for drug delivery and cancer therapy[33].

2. MAGNETIC NANOPARICLES FOR CANCER THERAPY

Another approach uses magnetic fields in conjunction with magnetic nanoparticles, such as super paramagnetic iron oxide nanoparticles, paramagnetic copper-nickel alloy nanoparticles, or magnetite (Fe_3O_4) cationic liposomes. Once an alternating magnetic field is applied heat is generated within the nanoparticles providing selective heating to cancerous tissues loaded with the thermal agent only. The magnetic fluid consists of super paramagnetic iron oxide nanoparticles in aqueous solution administered by

stereotactic navigation-based injection into brain tumour tissue[34]. The iron oxide is covered by an aminosilane type shell. Due to the universal design of the magnetic applicator, it can be used for hyperthermia as well as thermal ablation treatment of malignancies in any part of the human body.

3. *PHOTODYNAMIC THERAPY*

Photodynamic therapy is an emerging treatment modality where a light-sensitive molecule or photosensitiser exposed to visible or near-infrared light induces cytotoxic effects in the presence of oxygen. When photosensitisers are irradiated, the excited molecules can transfer their energy to molecular oxygen. Photodynamic therapy can be used to treat a variety of oncological, cardiovascular, dermatological, ophthalmic, and immunological disorders. Compared with conventional surgery, the approach is non-invasive, enables accurate targeting, repeated administration without total-dose limitations associated with radiotherapy, and results in little or no scarring after healing[35].

4. QUANTUM DOTS AS PHOTOSENSITIZERS AND CARRIERS

Quantum dots offer several advantages as potential delivery systems for photosensitisers. The optical properties of this nanomaterial can be tuned to absorb and emit in the near-infrared region of the spectrum by changing their size and composition. Light of low intensity can be used to penetrate tissue several centimeters allowing access to deep-seated tumors. Importantly, the surface coating of quantum dots can be functionalized to make them more water soluble and biocompatible, which facilitates systemic delivery. Nevertheless, the prolonged and repetitive exposure of quantum dot-treated cells to irradiation may have the potential to mediate a high steady-state level of singlet oxygen, enough perhaps to induce apoptotic and/or necrotic cell death in the target tissue[36].

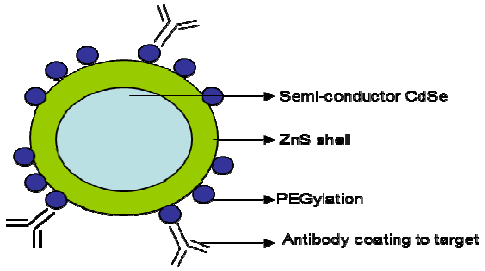

Figure 13
Quantum Dots

5. *CERAMIC BASED NANOPARTICLES AS CARRIERS FOR CANCER THERAPY*

Ceramic-based nanoparticles have the potential to act as delivery system for photosensitiser agents. For example, silica-based nanospheres doped with water-insoluble photosensitisers are efficiently taken up into the cytosol of tumor cells and generate singlet oxygen in vitro. The size of the nanosphere is important because the lifetime of $1O_2$ in aqueous media is in the microsecond domain, during which interval it can diffuse over a radial distance of at least 100 nm. Silica-based nanospheres are highly stable and are unlikely to release any embedded substances, although their porous matrix is permeable to triplet as well as singlet oxygen and subsequent light irradiation results in significant cell death. Experiments using silica-based nanospheres in tumor-model animals are in progress[37].

6. BIODEGRADABLE BASED NANOPARTICLES FOR CANCER THERAPY

Other approaches involve the incorporation/encapsulation of hydrophobic photosensitisers into size of 200 nm nanoparticles composed of biodegradable polymers, and polyacrylamide, or photosensitiser-stabilised gold Nanoparticles. The photocytotoxicity of the polymeric nanoparticles has been evaluated on mouse mammary tumour cells in vitro, rat glioma tumour cells in vitro, as well as on an in vivo chick embryo model showing inhibition of tumour cell growth more effectively than free photosensitisers and selective destruction of chick embryo vasculature of the chorioallantoic membrane while protecting surrounding tissues[38].

7. NANOPLATFORMS BASED ON NANOCOMPOSITE PARTICLES

A magnetic core of γ-Fe_2O_3 can be embedded within silica-based nanospheres functionalised with a targeting agent. Applying a DC magnetic field results in a selective magneto cytolysis of targeted cells only. DC magnetic fields can be generated by medical magnetic resonance imaging devices and require less power compared to devices generating AC magnetic fields used for thermotherapy. Recently, the synthesis of magnetic nanoparticles (γ-Fe_2O_3) and CdSe based quantum dots encapsulated in a silica shell has been reported. These materials have potential in combining targeting, bioimaging, biolabelling, and biosensing applications enabling novel platforms that are aimed at deployment for clinical applications in cancer research[39].

CHALLENGES & DESIGN SPECIFICATION

One of the biggest motivations behind nanoparticle-assisted drug delivery is the ability to unify the pharmacokinetics of different drugs by simultaneously delivering multiple therapeutic agents to the target site. This would minimize the gap between *in vitro* and *in vivo* studies and enhance the possibility of bench-to-bedside translation. The therapeutic efficacy of multiple-drug-loaded Nanoparticles would be greatly compromised if drug loading of different drugs cannot

be precisely controlled. This is especially an issue for passive drug loading in a delivery vehicle such as polymeric Nanoparticles because drug–drug and drug–polymer interactions often cause unpredictable batch-to-batch inconsistency of drug loading yields.

FUTURE PERSPECTIVE

Nanoparticle drug delivery has yielded an unprecedented level of control over the pharmacokinetics of chemotherpeutic agents. Recent development in nanoparticle-based therapy has shown several unique features that are untenable in traditional chemotherapy. Drug combinations can now be optimized and cleverly delivered in a more effective way. With a growing alliance between oncologists and pharmaceutical scientists, we envision that more therapeutic nanoparticles containing multiple drugs with precise drug dosage and release profiles will be developed to treat various types of cancer. In addition, emerging techniques in drug–polymer conjugations and nanomaterials engineering will continue to expand the nanoparticle platforms on which better therapeutic regimens can be designed.

- ✓ Identification of more precise molecules/pathways required for tumor development and growth.
- ✓ As most of the studies assessing the biological and molecular effects of targeting miRNAs have been performed in cells in culture, and in some animal models, more *in vivo* studies of the therapeutic consequences of miRNA-based therapies are required.
- ✓ Additional pharmacokinetic, pharmacodynamics, and tissue distribution studies of the nanoparticle and nanoparticle-RNAi formulations.
- ✓ Elaboration of easy administration (oral and spray) of nanoparticle RNAi formulations. These delivery methods may be advantageous in terms of cost and for patient's quality of life.

CONCLUSION

In summary, this review has shown a range of nanoparticle platforms for cancer therapy. Liposomes, polymeric nanoparticles, dendrimers and other nanoparticles have been demonstrated to carry a variety of anticancer agents including cytotoxic drugs, chemomodulators, siRNA and antiangiogenic agents. Precise control over the particle composition and preparation has enabled ratiometric drug loading and temporal drug release, both of which carry significant clinical implications in cancer treatments.

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