RESEARCH PAPER | Biotechnology | Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

Nanomedicines Targeting Cancer: Current Status and Future Prospects of the Therapeutic and Diagnostic Approaches

KEYWORDS: Cancer, Drug delivery, Nanomedicine, Nanoparticles, Tumor imaging

Foram Shukla
Department of Medical Biotechnology, Shree P. M. Patel Institute of Integrated M.Sc. in Biotechnology, Anand 388120, India

Shivang Parikh
Department of Nanobiotechnology, Life Science Foundation India, Morigeri - 583220 (PO), Bellary (District), Karnataka, India.

ABSTRACT *Nanotechnology provides a variety of nanoscale tools for medicine. Applications of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems has been referred to as nanomedicine by the National Institutes of Health. Research into the rational delivery and targeting of pharmaceutical, therapeutic, and diagnostic agents is at the forefront of projects in nanomedicine. Cancer nanotherapeutics are rapidly progressing and are being implemented to solve several limitations of conventional drug delivery systems such as nonspecific biodistribution and targeting, lack of water solubility, poor oral bioavailability, and low therapeutic indices. Current progress in nanotechnology and nanomedicine has exploited the possibility of designing tumor-targeted nanocarriers able to deliver conjugates in a selective manner to improve the efficacy and safety of cancer imaging and therapy. Nanoparticles for cancer have been designed for optimal size and surface characteristics to increase their circulation time in the bloodstream to improve the biodistribution of drugs which are carried in their loaded active form to cancer cells by selectively using the unique pathophysiology of tumors, such as their enhanced permeability and retention effect and the tumor microenvironment. Nanoparticles have the ability to accumulate in cells without being recognized by P-glycoprotein, one of the main mediators of multidrug resistance, resulting in the increased intracellular concentration of drugs. Ultimately, integrated nanotherapeutic systems may prove essential to address the challenges of tumor heterogeneity and adaptive resistance to achieve efficacious treatment of cancer. Today, nanotechnology and nanoscience approaches to particle design and formulation are beginning to expand the market for many drugs and are forming the basis for a highly profitable niche within the healthcare. The review article will highlight the rational therapeutic and diagnostic approaches of nanoscale vehicles and entities involved for site-specific drug delivery and medical imaging for tumor affected cells.*

INTRODUCTION

The development of a wide spectrum of nanoscale technologies is beginning to change the foundations of disease diagnosis, treatment, and prevention. One of the most exciting aspects of healthcare research is the increasing concurrence between biological and the physical sciences. The emerging field of nanomedicine exemplifies this trend since it seeks to bring current advances in chemistry, physics and materials science to bear on the diagnosis and therapy for wide range of diseases. These technological innovations, referred to as nanomedicines by the National Institutes of Health (Bethesda, MD, USA), have the potential to turn molecular discoveries arising from genomics and proteomics into widespread benefit for patients (Moghimi *et al.*, 2005). Nanomedicine is a large area of application, where devices such as nanoparticles, nanomachines, nanofibers and optical and mechanical nanosensors (Arciola et al., 2003) could bring fundamental benefits (Moghimi et al., 2005). The unusual mechanical, optical, electrical and chemical behaviors of nanometer materials can facilitate many new strategies for more precise and safer imaging of diseased tissues, and for novel forms of therapeutics with précised sensitivity. These intriguing opportunities have evoked much discussion about the presumed revolutionary impact of nanotechnology on medicine (Juliano, 2012).

There are two broad themes regarding the impact of nanotechnology on medicine. One is in the realm of therapeutics and the other in diagnosis. In the therapeutics area much of the interest has focused on the use of nanoparticles to more effectively deliver drugs to the sites within cells and tissues where the drugs will act in diseases like cancer where n numbers of targets are available. Nanoscale drug devices are currently being developed to deliver anticancer therapeutics specifically to tumors. Nanoparticles and liposomes are the "first generation" of these devices. Some of them have already reached the clinical practice, such as liposomal doxorubicin used to treat specific forms of cancer, or liposomal amphotericin B used to treat fungal infections often associated with aggressive anticancer treatment (Barratt G 2003). Commonly, nanoparticles will target certain tissues strictly because of their size and/or their physico-chemical properties; but new types of intelligent nanoparticles that respond to an externally applied field, be magnetic, focused heat, or light, in ways that might make them ideal therapeutics or therapeutic delivery vehicles, are under examination.

Conventional chemotherapeutic agents are distributed non-specifically in the body where they affect both cancerous and normal cells, thereby limiting the dose achievable within the tumor and also resulting in suboptimal treatment due to excessive toxicities. Molecularly targeted therapy has emerged as one approach to overcome the lack of specificity of conventional chemotherapeutic agents (Ross et al., 2004). However, the development of cancer cell resistance can evade the cytotoxicity not only of conventional chemotherapeutics but also of the newer molecularly targeted therapeutics (Morgillo et al., 2005).

Passive and active targeting strategies for Nanoparticles can enhance the intracellular concentration of drugs in cancer cells while avoiding toxicity in normal cells (Maeda, 2001 and Allen, 2002). Furthermore, when nanoparticles bind to specific receptors and then enter the cell, they are usually enveloped by endosomes via receptor-mediated endocytosis, thereby bypassing the recognition of P-glycoprotein, one of the main drug resistance mechanisms (Larsen et al., 2000). However nanoparticles offer many advantages as drug carrier systems but still there are many limitations to be solved such as poor oral bioavailability, instability in circulation, inadequate tissue distribution, and toxicity.

THE DISTINCTIVE CHARACTERISTICS OF NANOPARTICLES

Materials at the nanometer scale having numerous engineered constructs, assemblies, architectures and particu-

Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

late systems often have different physical and biochemical properties that make nanostructures attractive for diagnostic and therapy applications. For example, the electronic, optical, and chemical properties of nanoparticles may be very different from those of each component in the bulk. At the nanoscale, materials behave very differently compared to larger scales and it is still very difficult to predict the physical and chemical properties of particles of such a very small size. Since the size of the nanoparticles is significantly smaller than a cell, they can deliver a large payload of drugs (Anticancer Drugs), contrast agents or fluorescent probe onto the surface or interior of the cell (Cancerous tissue), without disrupting the normal cell homeostasis (Conti, 2006). Conventional surface non-modified nanoparticles are usually entangled in the reticuloendothelial circulation, such as the liver and the spleen, depending on their size and surface characteristics (Moghimi, 2001). The above botheration of injected nanoparticles can be controlled by adjusting their size and surface characteristics which are the principal parameters of nanoparticles as shown in (Table 1).

Nanoparticles can be encountered as aerosols (solids or liquids in air), suspensions (solids in liquids) or as emulsions (liquids in liquids). In the presence of certain chemicals, properties of nanoparticles may be modified. Nanoparticles are able to deeply penetrate tissues, going through the aperture of the small blood-vessel epithelial tissue. They can enter the systemic blood circulation without forming blood platelet aggregates. The reduced particle size provides high surface area and hence used for faster drug release. Drug delivery rates and particle integrity can be controlled by engineering entities which can activate by changing in the environmental pH, chemical stimuli in the form of rapidly oscillating magnetic field or by external heat source (Drummond, 2000; Panyam, 2002 and Clark, 1999).

PRINCIPAL CHARACTERISTICS OF NANOPARTICLES	
Size Characteristics • Size is tunable • Size of nanoparticles large enough to prevent their rapid leakage into blood capillaries but small enough to escape capture by fixed macrophages that are lodged in the reticuloendothelial system • Preferred size of the Nanoparticles is kept up to 100 nm to reach tumor affected cells and surpass sinusoid in the spleen and fenestra of the Kuffer cells in the liver (150 to 200 nm) (Wisse, 1996) and the size of gap junction between endothelial cells of the leaky tumor vasculature (100 to 600 nm) (Yuan, 1995)	Surface Characteristics • To determine the life span and fate of nanoparticles during circulation relating to their capture by macrophages • Nanoparticles ideally have a hydrophilic surface to escape macrophage capture • Coating the surface of nanoparticles with a hydrophilic polymer such as PEG protects them from opsonization by repelling plasma proteins • Nanoparticles can be formed from block copolymers with hydrophilic and hydrophobic domains

Table1: - size and surface characteristics of nanoparticles

RANGE OF NANOCARRIERS FOR ANTI-CANCER DIAGNOSTIC AND THERAPEUTIC APPROACHES

Nanocarriers are nanosized materials with numerous engineered constructs, assemblies, architecture systems of diameter ranging 1–100 nm that can carry multiple drugs or imaging agents. It is possible to achieve high ligand density on the surface for targeting purposes owing to their high surface-area-to-volume ratio (Langer, 2007). Materials at the nanometer scale often have different physical and biochemical properties that make nanostructures attractive for diagnostic and therapy applications. The family of nanocarriers includes polymer based nanoparticles (Polymeric Nanoparticles, Polymeric micelles and Dendrimers) , lipid-based carriers (liposomes), carbon nanotubes, gold nanoparticles (GNPs), Carbon Tubes, Magnetic Nanoparticles, Quantum dots, Ceramic based Nanoparticles and carbohydrate-ceramic nanoparticles (Aquasomes). These nanocarriers have been explored for a variety of applications such as drug delivery, imaging, photo thermal ablation of tumors, radiation sensitizers and detection of apoptosis as shown in (Table 2).

Nanoparticles	Characteristics	Applications	References
Gold Nanoparticles (GNPs)	- Easy Preparation - Have low toxicity - Attached easily to the molecules of biological interest (E.g. Proteins and Drugs) -Accumulate easily at tumor sites	- Gold nanoparticles are emerging as promising agents for cancer therapy and are being investigated as drug carriers, photo thermal agents, contrast agents and radiosensitisers -This technology might enable tracking of a single molecule of a drug in a cell or other biological samples - As a vector for tumor directed drug delivery	(Farrer et al., 2005 and Paciotti et al., 2004)
Quantum dots (QDs)	- Nano-scale crystalline structures made from a variety of different compounds, such as cadmium selenide that can transform the color of light - Quantum dots absorb white light and then re-emit it a couple of nanoseconds later at a specific wavelength - Greater flexibility	-These structures offer new capabilities for multicolor optical coding in gene expression studies, high throughput screening, and *in vivo* imaging of Cancerous tissues and cells	(Moghimi et al., 2005)

Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

Dendrimers	- 3-D nanoscale core-shell structures - Highly branched macromolecules	- Conjugated with antibodies that act as recognition sites to kill cancer cells - Targeted delivery of small molecular drugs, proteins/peptides and genes	(Choi Y 2005, Kukowska-Latallo et al., 2005 and Yang et al., 2006)
Polymeric micelles	- usually below 50 nm in diameter - Generally arranged in a spheroid structure with hydrophobic cores shielded from the water by a mantle of hydrophilic groups	- Drugs or contrast agents may be trapped physically within the hydrophobic cores or can be linked covalently to component molecules of the micelle	(Moghimi et al., 2005)
Magnetic-Fluorescent Nanoparticles	- Magnetic and fluorescent	- In vivo imaging rapid screening - Loco regional delivery of Chemotherapeutic particles	(Weissleder et al., 2005, Jordan et al., 2006 and Alexiou et al., 2006)
Lipoparticles	- Enable integral membrane proteins to be solubilized but retain their intact structural conformation	- To improve selective drug delivery by targeting tumor vasculature - As a potential carrier to deliver a lipophilic antitumor drug into hepatoma cells - Passive tumor targeting	(Schmitt-Sody et al., 2003 and Lou 2005)
Nano bodies	- The smallest available intact antigen-binding fragments harboring the full antigen-binding capacity of the naturally occurring heavy-chain antibodies	- Potential of a new generation of antibody-based therapeutics in addition to diagnostics for diseases such as cancer	(Revets et al., 2005)

Table 2: Types of Nanoparticles for diagnostic and therapeutic applications

Polymer-based drug carriers
Polymers are the most commonly explored materials for constructing nanoparticle-based drug carriers. One of the earliest reports was described by Couvreur et al. in 1979 where the use for cancer therapy included the adsorption of anticancer drugs to polyalkylcyanoacrylate nanoparticles.

Polymeric nanoparticles (polymer-drug conjugates)
Polymers such as albumin, chitosan, and heparin occur naturally and have been a material of choice for the delivery of oligonucleotides, DNA, protein as well as drugs. Another studies conducted by Gradishar et al., 2005 revealed that nanoparticle formulation of paclitaxel in which serum albumin was included as a carrier to synthesize nanometer-sized albumin bound paclitaxel (Abraxane] which has been applied in the clinic for the treatment of metastatic breast cancer. Abraxane has also been evaluated in clinical trials involving many other cancers including non–small-cell lung cancer and advanced non-hematologic malignancies (Green et al., 2006 and Nyman et al., 2005). Among synthetic polymers such as N-(2-hydroxypropyl) - methacrylamide copolymer (HPMA), polystyrene-maleic anhydride copolymer, polyethylene glycol (PEG), and poly-L-glutamic acid (PGA), PGA was the first biodegradable polymer to be used for conjugate synthesis (Li C, 2002).

Polymeric micelles
Micelles are formed in solution as aggregates in which the component molecules (e.g., amphiphilic AB-type or ABA-type block copolymers where A and B are hydrophobic and hydrophilic components. They are generally arranged in a spheroidal structure with hydrophobic cores shielded from the water by a mantle of hydrophilic groups. These dynamic systems are usually below 50 nm in diameter and are used for the systemic delivery of water-insoluble drugs. Anticancer Drugs or contrast agents may be trapped physically encapsulated within the hydrophobic cores or can be linked covalently to component molecules of the micelle (Sahoo and Labhasetwar 2003 and Moghimi et al., 2005). The first polymeric micelle formulation of paclitaxel, Genexol-PM (PEG-poly (D, L-lactide)-paclitaxel), is a cremophor- free polymeric micelle-formulated paclitaxel (Kim, 2004).

Dendrimers
A dendrimer is a synthetic polymeric macromolecule of nanometer dimensions, composed of multiple highly branched monomers that emerge radially from the central core molecule and growth occurs in an outward direction by a series of polymerisation reactions. Hence, precise control over size can be achieved by the extent of polymerisation, starting from a few nanometers. Cavities in the core structure and folding of the branches create cages and channels. Monodisperse size, modifiable surface functionality, multivalency, water solubility and available internal cavity make them attractive for anticancer drug delivery. Polyamidoamine dendrimer, the dendrimer most widely used as a scaffold, was conjugated with cisplatin, a chemotherapeutic drug (Malik, 1999).

Lipid-based drug carriers
Lipid-based carriers have attractive biological properties including general biocompatibility, biodegradability, isolation of drugs from the surrounding environment and the ability to entrap both hydrophilic and hydrophobic drugs. The properties of lipid-based carriers such as their size, charge and surface functionality can easily be modified by surface chemistry (Langer, 2007).

Liposomes
Liposomes are spherical, self-closed structures formed by one or several concentric lipid bilayers with inner aqueous phases. Liposomes are classified into three basic types based on their size and number of bilayers including Multilamellar vesicles (MUVs) that consist of several lipid bilayers separated from one another by aqueous spaces. On the other hand both small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) consist of a single bilayer surrounding the entrapped aqueous space (Moghimi et al., 2005). Currently, several kinds of cancer drugs have been applied to this lipid-based system using a variety of preparation methods. Among them liposomal formulations of the anthracyclines doxorubicin (Doxil, Myocet) and daunorubicin (DaunoXome) are approved for the treatment of metastatic breast cancer

Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

and AIDS-related Kaposi's sarcoma (Markman, 2006; Rivera, 2003 and Rosenthal, 2002).

Carbon Nanotubes

Carbon nanotubes are carbon cylinders composed of benzene rings acting as sensors for detecting DNA and protein, diagnostic devices for the discrimination of different proteins from serum samples and carriers to deliver vaccine or protein (Bianco et al., 2005 and Kwangjae, 2008). The diameter and the length of single-walled nanotubes may vary between 0.5–3.0 nm and 20–1000 nm, respectively. Carbon nanotubes can be made water soluble by surface functionalization. Molecular and ionic migration through carbon naotubes can occur, thus offering opportunities for fabrication of molecular sensors and electronic nucleic acid sequencing. Carbon nanotubes can cross the cell membrane as 'nanoneedles' without perturbing or disrupting the membrane and localize into cytosol and mitochondria (Moghimi, 2005).

The multiple covalent functionalizations on the sidewall or tips of carbon nanotubes allow them to carry several molecules at once, and this strategy provides a fundamental advantage in the treatment of cancer. For an example, the anticancer drug (methotrexate) has been covalently linked to carbon nanotubes with a fluorescent agent FITC (Bianco et al., 2005).

Magnetic-drug targeting

Magnetic drug targeting offers a unique opportunity to treat malignant tumors loco-regionally. In 2006 Alexiou et al. have treated squamous cell carcinoma in vivo with the injection of magnetic nanoparticles called ferrofluids bound to mitoxantrone, as a chemotherapeutic agent which was locally induced to concentrate by means of a magnetic field. The intra-tumoral accumulation of the magnetic particles can be additionally be visualized by means of MRI (Alexiou et al., 2006 and Conti, 2006).

Ceramic-based nanoparticles

Ceramic based nanocarriers posses extensive potential and applications in photodynamic cancer therapy (PCT) in the field of Oncology. PCT is based on the principal that light-sensitive species can be preferentially localized in tumor tissues upon systemic administration. In 2003 in vitro studies by Roy et al. shown that silica based nanoparticles carrying the water-insoluble photosensitizing anticancer drug-dye, 2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide (HPPH), were taken up by the tumor infected cells and the resulting light irradiation results in significant cell death (Roy, 2003). Aquasomes also called the carbohydrate-ceramic nanoparticles are spherical 60–300 nm particles used for anticancer drug and antigen delivery. The particle core is composed of nanocrystalline calcium phosphate or ceramic diamond and is covered by a polyhydroxyl oligomeric film. Anticancer Drugs and antigens are then adsorbed on to the surface of these particles (Kossovsky, 1996).

NANOPARTICLES FOR TUMOR IMAGING

There are many approaches which are generally used for labeling or encapsulating radionuclides on nanocarriers including labeling nanocarriers by encapsulation, nanocarrier surface labeling, nanocarrier surface labeling of bioconjugates, Incorporation into the lipid bilayer, after-loading of the aqueous phase of the nanocarriers (Ting G et al., 2009). The main concept behind the after-loading methods is that it provides higher labeling efficiencies (>90%) and the greatest in vivo stability for radionuclides used for nuclear imaging (Mitra et al., 2006 and Hamoudeh et al., 2008). Liposomes are spherical bilayers of small phospholipid vesicles which spontaneously form when water is added to a dried lipid mixture. The ability to modify the surface of nanocarriers permits improvement in the pharmacokinetics, bioavailability, toxicity and customization of nanocarrier formulations for particular tumor imaging agents (Huwyler, 2008).

Delivery of ^{99m}Tc, ^{111}In, ^{67}Ga radionuclides is done by liposomes for gamma-imaging for Multitude diagnostics of tumor, infection, inflammation, and lymphoscintigraphy (Phillips, 1999 and Kleiter, 2006). Liposome labeled with radionuclide ^{111}In for gamma/SPECT imaging used for Clinical biodistribution, PK and imaging, studies of breast, head and neck, glioma and lung cancer patients (Harrington, 2001). The other form of liposome known as Immunoliposome was labeled with ^{111}In for gamma imaging was applied for the ^{111}In-liposome-2C5 (mAb) nucleosome-specific monoclonal 2C5 targeting delivery vehicles for tumor visualization of murine lewis lung carcinoma and human HT-29 tumors (Elbayoumi et al., 2006 and Erdogan et al., 2006). Perfluorocarbon nanoparticles are labeled with ^{111}In for active targeting and gamma imaging of targeted tumor angiogenesis of αvα3-integrin in Vx-2 rabbit tumors (Hu et al., 2007). On the other hand the Carbon Nanotubes are labeled with ^{111}In for Active targeting and gamma or SPECT imaging for Multifunctional targeted delivery with functionalized and bioconjugated 111In-DOTA-CNT-Rituximab nanoconstructs (McDevitt et al., 2007). Quantum dot Nanoparticles are labeled with ^{64}Cu for active targeting and bifunctional PET/NIRF imaging applied for tumor angiogenesis PET/NIRF imaging for dual-functional targeted delivery with amine functionalized 64Cu-DOTA-QD-VEGF (Chen et al., 2008).

Development of a bifunctional polyaspartic acid-coated nanotargeted iron oxide molecular probe for PET and magnetic resonance imaging (MRI) of tumor integrin-αvα3 expression was reported by Lee et al. and this bifunctional 64Cu-DOTA-IO-RGD nanotargeted molecular imaging approach may allow for earlier tumor detection and may provide insight into the molecular mechanisms of cancer (Lee et al., 2008).

GENERATIONS OF NANOCARRIERS

Nanocarriers encounter numerous barriers en route to their target, such as mucosal barriers and non-specific uptake (Alonso, 2004). There are three generations of nanocarriers. Firstly, the passive targeting which is rapidly trapped in the recticuloendothelial system (RES) organs (e.g. liver and/or spleen). Secondly, the second generation of pegylated nanocarriers (passive targeting), which can evade the RES of the liver and spleen and enjoys a prolonged circulation in the blood through the enhanced permeability and retention (EPR) effect in leaky tumor tissues. Lastly, the active targeting that has a bioconjugated surface modification using specific antibodies or peptides to actively targeted specific tumor or tissues (Ting et al., 2009). General features of tumors include leaky blood vessels and poor lymphatic drainage. Whereas free drugs may diffuse nonspecifically, a nanocarrier can escape into the tumor tissues via the leaky vessels by the EPR effect.

Passive Targeting by Nanoparticles

Nanoparticles that satisfy the size and surface characteristics requirements as mentioned above for escaping reticuloendothelial system capture have the ability to circulate for longer times in the bloodstream and a greater chance of reaching the targeted tumor tissues. The unique pathophysiologic characteristics of tumor vessels enable macromolecules to selectively accumulate in tumor tissues (Maeda, 2001). One of the most important characteristics of the tumor cells are fast-growth and demand the recruitment of new vessels (neovascularization) or rerouting of existing vessels near the tumor mass to supply them with oxygen and nutrients for their growth. This result in imbalance of angiogenic regulators which makes tumor vessels highly disorganized and dilated with numerous pores showing enlarged gap junctions between endothelial cells and compromised lymphatic drainage (Carmeliet, 2000). By the virtue of the above features called the enhanced permeability and retention helps to accumulate the nanoparticles with molecular weight above 50 kDa in the interstitial spaces in the tumor tissues. Fast-growing, high proliferative cancer cells show a high metabolic rate and the supply of oxygen and nutrients is usually not suf-

Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

ficient for them to maintain the homeostasis and it produces a unique microenvironment surrounding tumor cells, which is different from that of normal cells.

Active targeting by Nanoparticles

A binary conjugate drug delivery system comprises of polymer-drug conjugate that depends only on passive targeting mechanisms have intrinsic limitations to its specificity. One approach suggested to overcome these limitations is the inclusion of a targeting ligand or antibody in polymer-drug conjugates (Allen, 2002). Initially direct conjugation of an antibody to a drug was attempted but in clinical trials conducted so far reveals that such early antibody-drug conjugates have failed to show superiority as a targeted delivery tool for the treatment of cancer (Tolcher et al., 1999). The number of the anti-cancer drug molecule loaded or conjugated with the antibody is very limited to preserve its immune recognition. The recent development of liposomes and polymers as drug delivery carriers increases the potential number of drugs that can be conjugated to targeted nanoparticles without compromising their targeting affinity relative to earlier antibody-drug conjugates. Taking advantage of the technology, targeting moieties and drugs many recently developed active targeting drug conjugates use a ternary structure composed of a ligand or antibody as a targeting moiety, a polymer or lipid as a carrier, and an active chemotherapeutic drug (Kwangjae et al., 2008).

Antigens have various receptors present on the surface as particularly most suitable for tumor-specific targets (Allen, 2002). The antigen receptors should have the several properties like uniqueness, expressed homogeneously on all targeted tumor cells and the specific antigen receptors should not be circulated in the blood circulation. Internalization of the conjugated nanoparticles is by receptor-mediated endocytosis. Tumor-specific ligands or antibodies on the nanoparticles bind to cell-surface receptors which trigger internalization of the nanoparticles into the cell through endosome. As a pH value in the interior of the endosome becomes acidic, the drug is released from the nanoparticles and goes into the cytoplasm. Drug-loaded nanoparticles bypass the P-glycoprotein efflux pump not being recognized when the drug enters cells, leading to high intracellular concentration.

THE FUTURE OF NANOMEDICINES FOR CANCEROUS CELLS

In present day scenario, physicians must chiefly rely on the body's ability to repair it but if this fails external efforts may be useless. The component parts of human cells cannot be placed exactly where they should be and restructure them as they should be to ensure a healthy state of life. There are no such tools for working precisely and with three-dimensional control at the molecular level other than Nanotechnology. Today, nanotechnology and nanoscience approaches to particle design and formulation are beginning to expand the market for many drugs and are forming the basis for a highly profitable niche within the healthcare. As described by Robert A. Freitas Jr. one of the ultimate future nanomedicine tools is the medical Nanorobot. A robot approximately the size of a bacterium, composing of many thousands of molecule-size mechanical parts perhaps resembling macroscale gears, bearings, and ratchets, possibly composed of a strong diamond-like material. A nanorobot will need motors to make things move, and manipulator arms or mechanical legs for dexterity and mobility. It will have a power supply for energy, sensors to guide its actions, and an onboard computer to control its behavior. A nanorobot that would travel through the bloodstream must be smaller than the red cells in our blood tiny enough to squeeze through even the narrowest capillaries in the human body. Medical nanorobotics holds the greatest promise for curing cancer and extending the human health span.

One of the examples of medical nanorobot is *"microbivore"* which could act as an artificial mechanical white cell, seeking out and digesting unwanted pathogens including bacteria, viruses, or fungi in the bloodstream. Once inside, the microbe is minced and digested into amino acids, mononucleotides, simple fatty acids and sugars in just minutes. These basic molecules are then harmlessly discharged back into the bloodstream through an exhaust port at the rear of the device. A complete treatment might take a few hours.When the nanorobotic treatment is finished, the doctor broadcasts an ultrasound signal and the nanorobots exit the body through the kidneys, to be excreted with the urine in due course. Related nanorobots could be programmed to quickly recognize and digest even the tiniest aggregates of early cancer cells.

In the present state of Nanotechnology the Nanorobots is skepticism. To actually build them, a new technology is to be created called molecular manufacturing. Molecular manufacturing is the production of complex atomically precise structures using positionally controlled fabrication and assembly of nanoparts inside a nanofactory, much like cars are manufactured on an assembly line. Together with the progression of nanoscale drug delivery systems, advances in nanoscale imaging suggest the potential for the development of multifunctional nanoparticles that may facilitate the realization of individualized cancer therapy. Many aspects of the Nanomedicines are to be focused which includes successful targeting strategies, extracellular and intracellular drug release rates in different pathologies, interaction with biological milieu, such as opsonization, and other barriers to the target site like anatomical, physiological, immunological or biochemical, targeting cell specific surface markers and targeting tumor vasculature. Similar to combination drug strategies that may be personalized to optimize treatment options where in the near future may be presented which could lead to improved therapeutic outcomes and reduced costs. The future of nanomedicine will depend on rational design of nanotechnology materials and tools based around a detailed and thorough understanding of the biological processes rather than the forcing applications of some materials currently in business.

Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

REFERENCE

Alexiou C, Schmid RJ, Jurgons R et al. (2006). Targeting cancer cells: magnetic nanoparticles as drug carriers. Eur Biophys J 35: 446- 450. | Allen TM (2002). Ligand-targeted therapeutics in anticancer therapy. Nat Rev Cancer 2: 750-763. | Alonso MJ (2004). Nanomedicines for overcoming biological barriers. Biomed. Pharmacother. 58: 168–172. | Arciola CR, Bustanji Y, Conti M et al. (2003). Staphylococcus epidermidis-fibronectin binding and its inhibition by heparin. Biomaterials 24:3013-3019. | Barratt G (2003). Colloidal drug carriers: Achievements and Perspectives. Cell Mol Life Sci 60: 21-37. | Bianco A, Kostarelos K, Partidos CD, Prato M (2005). Biomedical applications of functionalised carbon nanotubes. Chem Commun 5:571-577. | Bianco A, Kostarelos K, Prato M (2005). Applications of carbon nanotubes in drug delivery. Curr Opin Chem Biol 9:674-679. | Brannon-Peppas L and Blanchette JO (2004). Nanoparticle and targeted systems for cancer therapy. Adv Drug Deliv Rev 56: 1649- 1659. | Carmeliet P and Jain RK (2000). Angiogenesis in cancer and other diseases. Nature 407:249-257. | Chan WC, Maxwell DJ, Gao X, Bailey RE, Han M and Nie S (2002). Luminescent quantum dots for multiplexed biological detection and imaging. Curr Opin Biotechnol 13: 40-46. | Chen K, Li ZB, Wang H, Cai W and Chen X (2008). Dual-modality optical and positron emission tomography imaging of vascular endothelial growth factor receptor on tumor vasculature using quantum dots. Eur J Nucl Med Mol Imaging 35: 2235-2244. | Choi Y and Baker JR Jr: (2005). Targeting cancer cells with DNA assembled dendrimers: a mix and match strategy for cancer. Cell Cycle 4: 669-671. | Clark HA, Hoyer M, Philbert MA and Kopelman R (1999). Optical nanosensors for chemical analysis inside single living cells. 1. Fabrication, characterization, and methods for intracellular delivery of PEBBLE sensors. Anal Chem 71(21): 4831-4836. | Conti M, Tazzari V, Baccini C, Pertici G, Serino LP, Ugo De Giorgi (2006). Anticancer Drug Delivery with Nanoparticles. In vivo 20: 697-702 | Couvreur P, Kante B, Roland M and Speiser P (1979). Adsorption of anti-neoplastic drugs to polyalkylcyanoacrylate nanoparticles and their release in calf serum. J. Pharm. Sci. 68: 1521–1524. | Drummond DC, Zignani M and Leroux J (2000). Current status of pHsensitive liposomes in drug delivery. Prog Lipid Res 5: 409- 460. | Elbayoumi TA and Torchilin VP (2006). Enhanced accumulation of long-circulating liposomes modified with the nucleosomespecific monoclonal antibody 2C5 in various tumours in mice: gamma-imaging studies. Eur J Nucl Med Mol Imaging 33: 1196- 1205. | Erdogan S, Roby A and Torchilin VP (2006). Enhanced tumor visualization by gamma-scintigraphy with 111In-labeled polychelating-polymer-containing immunoliposomes. Mol Pharm 3: 525-530. | Farrer RA, Butterfield FL, Chen VW and Fourkas JT (2005). Highly efficient multiphoton-absorption-induced luminescence from gold nanoparticles. Nano Lett 5: 1139-1142. | Gradishar WJ,Tjulandin S, Davidson N (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 23: 7794-7803. | Green MR, Manikhas GM, Orlov S (2006). Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced nonsmall- cell lung cancer. Ann Oncol 17:1263-1268. | Harrington KJ, Mohammadtaghi S, Uster PS, Glass D, Peters AM, Vile RG and Stewart JS (2001). Effective targeting of solid tumors in patients with locally advanced cancers by radiolabeled pegylated liposomes. Clin Cancer Res 7: 243-254. | Hamoudeh M, Kamleh MA, Diab R, Fessi H (2008). Radionuclides delivery systems for nuclear imaging and radiotherapy of cancer. Adv Drug Deliv Rev 60: 1329-1346. | Hu G, Lijowski M, Zhang H, Partlow KC, Caruthers SD, Kiefer G, Gulyas G, Athey P, Scott MJ, Wickline SA and Lanza GM (2007). Imaging of Vx-2 rabbit tumors with alpha(nu)beta3-integrintargeted 111In nanoparticles. Int J Cancer 120: 1951-1957. | Huwyler J, Drewe J and Krahenbuhl S (2008). Tumor targeting using liposomal antineoplastic drugs. Int J Nanomedicine 3: 21-29. | Jordan A, Scholz R, Maier-Hauff K et al. (2006). The effect of thermotherapy using magnetic nanoparticles on rat malignant glioma. J Neurooncol 78: 7-14. | Juliano RL (2012). The future of nanomedicine: Promises and limitations. Science and Public Policy 39: 99–104. | Kim TY, Kim DW, Chung JY (2004). Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. Clin Cancer Res 10:3708-3716. | Kleiter MM, Yu D, Mohammadian LA, Niehaus N, Spasojevic I, Sanders L, Viglianti BL, Yarmolenko PS, Hauck M, Petry NA, Wong TZ, Dewhirst MW and Thrall DE (2006). A tracer dose of technetium-99m-labeled liposomes can estimate the effect of hyperthermia on intratumoral doxil extravasation. Clin Cancer Res 12: 6800-6807. | Kossovsky N, Gelman A, Rajguru S, Nguyen R, Sponsler E, Hnatyszyn H J, Chow K, Chung A, Torres M, Zemanovich J (1996). Control of molecular polymorphisms by a structured carbohydrate/ceramic delivery vehicle – aquasomes. J. Control Release 39:383–388. | Kukowska-Latallo JF, Candido KA, Cao Z et al. (2005). Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. Cancer Res 65: 5317-5324. | Kwangjae C, Xu W, Shuming N et al. (2008). Therapeutic Nanoparticles for Drug Delivery in Cancer. Clin Cancer Res 14:1310-1316. | Langer R, Karp JM, Hong, Farokhzad OC, Margalit R and Peer D (2007). Nanocarriers as an emerging platform for cancer therapy. Nature Nanotechnology 2: 751-760. | Larsen AK, Escargueil AE, Skladanowski A. (2000). Resistance mechanisms associated with altered intracellular distribution of anticancer agents. Pharmacol Ther 85:217-229. | Lee HY, Li Z, Chen K, Hsu AR, Xu C, Xie J, Sun S and Chen X (2008). PET/MRI dual-modality tumor imaging using arginineglycine- aspartic (RGD)-conjugated radiolabeled iron oxide nanoparticles. J Nucl Med 49: 1371-1379. | Li C (2002). Poly(L-glutamic acid)-anticancer drug conjugates. Adv Drug Deliv Rev 54:695-713. | Lou B, Liao XL, Wu MP, Cheng PF, Yin CY and Fei Z. (2005). High density lipoprotein as a potential carrier for delivery of a lipophilic antitumoral drug into hepatoma cells. World J Gastroenterol 11: 954-959. | Markman M (2006). Pegylated liposomal doxorubicin in the treatment of cancers of the breast and ovary. Expert Opin Pharmacother 7:1469-1474. | Maeda H (2001). The enhanced permeability and retention (EPR) effect in tumor vasculature: The key role of tumor-selective macromolecular drug targeting. Adv Enzyme Regul 41:189-207. | Malik N, Evagorou EG, Duncan R (1999). Dendrimerplatinate: a novel approach to cancer chemotherapy. Anticancer Drugs 10:767-776. | McDevitt MR, Chattopadhyay D, Kappel BJ, Jaggi JS, Schiffman SR, Antczak C, Njardarson JT, Brentjens R and Scheinberg DA (2007). Tumor targeting with antibody-functionalized, radiolabeled carbon nanotubes. J Nucl Med 48: 1180-1189. | Michalet X, Pinaud FF, Bentolila LA et al. (2005). Quantum dots for live cells, in vivo imaging, and diagnostics. Science 307: 538-544. | Mitra A, Nan A, Line BR, Ghandehari H (2006). Nanocarriers for nuclear imaging and radiotherapy of cancer. Curr Pharm Des 12: 4729-4749. | Moghimi SM, Hunter AC, Murray JC (2001). Long-circulating and target-specific nanoparticles: theory to practice. Pharmacol Rev 53:283-318. | Moghimi SM, Hunter AC, and Murray JC (2005). Nanomedicine: current status and future prospects. The FASEB Journal 19:311-330. | Morgillo F, Lee HY. (2005¬). Resistance to epidermal growth factor receptor-targeted therapy. Drug Resist Updat 8:298-310. | Nyman DW, Campbell KJ, Hersh E (2005). Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticles formulation of paclitaxel in patients with advanced nonhematologic malignancies. J Clin Oncol 23:7785-7793. | Ozkan M (2004). Quantum dots and other nanoparticles: what can they offer to drug discovery? Drug Discov Today 9: 1065-1071. | Paciotti GF, Myer L, Weinreich D et al. (2004). Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery. Drug Deliv 11: 169-183. | Panyam J, Zhou WZ, Prabha S, Sahoo SK and Labhasetwar V (2002). Rapid endo-lysosomal escape of poly(DL-lactide-co-glycolide) nanoparticles: implications for drug and gene delivery. Faseb J 10: 1217-1226. | Phillips WT (1999). Delivery of gamma-imaging agents by liposomes. Adv Drug Deliv Rev 37: 13-32. | Revets H, De Baetselier P, Muyldermans S (2005). Nanobodies as novel agents for cancer therapy. Expert Opin Biol Ther 5: 111-124. | Rivera E (2003). Current status of liposomal anthracycline therapy in metastatic breast cancer. Clin Breast Cancer 4:576-583. | Rosenthal E, Poizot-Martin I, Saint-Marc T, Spano JP, Cacoub P, Group DNXS (2002). Phase IV study of liposomal daunorubicin (DaunoXome) in AIDS-related Kaposi sarcoma. AmJClin Oncol 25:57-59. | Ross JS, Schenkein DP, Pietrusko R, et al. (2004). Targeted therapies for cancer 2004. Am J Clin Pathol 122: 598-609. | Roy I, Ohulchanskyy TY, Pudavar HE et al. (2003). Ceramic-based nanoparticles entrapping water-insoluble photosensitizing anticancer drugs: a novel drug-carrier system for photodynamic therapy. J Am Chem Soc 125: 7860-7865. | Sahoo SK, and Labhasetwar V (2003). Nanotech approaches to drug delivery and imaging. Drug Discov. Today 8: 1112–1120. | Schmitt-Sody M, Strieth S, Krasnici S (2003). Neovascular targeting therapy: paclitaxel encapsulated in cationic liposomes improves antitumoral efficacy. Clin Cancer Res 9: 2335-2341. | Ting G, Chang CH and wang Hsin-ell (2009). Cancer Nanotargeted Radiopharmaceuticals for Tumor Imaging and Therapy. Anticancer Research 29: 4107-4118. | Tolcher AW, Sugarman S, Gelmon KA. (1999). Randomized phase II study of BR96-doxorubicin conjugate in patients with metastatic breast cancer. J Clin Oncol 17:478-484. | Weissleder R, Kelly K, Sun EY, Shtatland T and Josephson L (2005). Cell-specific targeting of nanoparticles by multivalent attachment of small molecules. Nat Biotechnol 23: 1418-1423. | Wisse E, Braet F, Luo D (1996). Structure and function of sinusoidal lining cells in the liver. Toxicol Pathol 24:100-111. | Yang YY, Wang Y, Powell R and Chan P (2006). Polymeric core-shell nanoparticles for therapeutics. Clin Exp Pharmacol Physiol 33: 557-562. | Yuan F, Dellian M, Fukumura D (1995). Vascular permeability in a human tumor xenograft: molecular size dependence and cutoff size. Cancer Res 55: 3752-375 6. | Zou Y, Fu H, Ghosh S, Farquhar D and Klostergaard J (2004). Antitumor activity of hydrophilic Paclitaxel copolymer prodrug using locoregional delivery in human orthotopic non-small cell lung cancer xenograft models. Clin Cancer Res 10: 7382-7391. |