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Review

Nanomedicine: The role of newer drug delivery technologies in cancer

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ABSTRACT

Nanotechnology has slowly but steadily revolutionized the diagnosis, imaging and treatment of cancer. Detecting cancer at earliest stages, locating the tumor at different areas in the body and specific delivery of the drugs to malignant cells including surgically inaccessible tumors are the core areas of medical and pharmaceutical research across the world. In this endeavour, Nanodevices have emerged as the most important drug delivery devices in the treatment of cancer. Nanoscale devices smaller than 50 nm, can easily enter most cells, while those smaller than 20 nm can transit out of blood vessels. Such small sizes are capable of carrying large number of small molecules in the form of a drug or a contrast agent. These devices can readily interact with biomolecules on both the cell surface and within the cell. The ability of such devices to deliver the therapeutic agents to target cells or within specific organelles is of immense potential in cancer treatment. The major areas in nanomedicine developed in cancer include:

•Prevention and control - developing nanodevices to deliver the therapeutic agents and design of vaccines.

•Early detection and proteomics- developing new platforms for analysis of cancer-associated markers.

•Improved Diagnostics-detection of molecular changes occurring in limited number of cells with high sensitivity is another useful feature of these devices. This ensures early detection of cancer which is the most crucial step in arresting the malignant cell growth.

•Imaging diagnostics- designing targeted contrast agents that improve the resolution of cancer to a single cell.

•Multifunctional Therapeutics-creating therapeutic devices that can control the release of anti cancer agents and control their release in order to deliver to the targeted site only.

Keywords: *Barium Nanomedicine; Cancer; Nanoparticles; Quantum dots; Nanodevices*

INTRODUCTION

Nanomedicine is a subfield of nanotechnology. It is often defined as the repair construction and control of human biological systems using devices built upon nanotechnology standards. Nanosized materials have been investigated as potential medicines for several decades. Nanomaterials, which measure 1–1000 nm, allow unique interaction with biological systems at the molecular level. The sort of materials that could be called nanomedicines can include proteins, polymers, dendrimers, micelles, liposomes, emulsions, nanoparticles and nanocapsules. Nanomaterials are also used in diagnostics, e.g. colloids for radio pharmacy and as contrast agents in magnetic resonance imaging. New developments in nanomaterials are now producing small and ultra-small paramagnetic iron oxide particles (USPIOs) and investigating quantum dots for this field. Nanotechnology is used to provide more accurate and timely medical information for diagnosing the disease, and manufacturing miniature devices that can administer automated and targeted treatment. This technology is currently being explored worldwide in the treatment of diabetes, respiratory diseases, Cancer etc. like precarious diseases [1].

Cancer is a complex disease which originates from mutations and alterations to normal cellular regulatory and metabolic pathways at molecular level. It is a generic term for a group of more than 100 diseases that can affect any part of the body [2]. Accurate and sensitive diagnosis is still a constraint due to the lack of biosensors and molecular probes that are capable of rapidly recognizing the distinct molecular features of these diseases. The ability of nanomaterials and nanopatterned devices to directly interact with biologically significant molecules and to convert those interactions into directly transduced or significantly amplified electrical or electromagnetic signals, has enabled a new generation of early-stage diagnostic techniques. At present, the nanomaterials level is the most advanced in scientific knowledge as well as in commercial applications. They can facilitate important advances in detection, diagnosis, and treatment of human cancers and have led to a new discipline of nano-oncology [3, 4].

STATISTICS ON CANCER

Cancer is a leading cause of death worldwide. Cancer is the second biggest cause of death in India, growing at 11 per cent annually. From a total of 58 million deaths worldwide in 2005, cancer accounts for 7.6 million (or 13%) of all deaths. Deaths from cancer in the world are projected to continue rising, with an estimated 9 million people dying from cancer in 2015 and 11.4 million dying in 2030[5]. The burden of cancer doubled globally between 1975 and 2000. It is estimated that it will double again by 2020 and nearly triple by 2030. The projected numbers for the year 2030 are 20-26 million new diagnoses and 13-17 million deaths. There are 2.5 million cancer cases and four lakh deaths a year in India. Based on the GLOBOCAN 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008. Of these 56% of the cases and 64% of the deaths occurred in the economically developing world. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths. Lung cancer is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths [6].

NANOTECHNOLOGY PLATFORMS IN CANCER TREATMENT

The development of novel nanotechnologies for improving cancer mortality defined the path of opportunities in six areas including: (i) detection of molecular changes responsible for disease pathogenesis; (ii) disease diagnosis and imaging; (iii) drug delivery and therapy; (iv) multifunctional systems for combined therapeutic and diagnostic applications; (v) vehicles to report the in vivo efficacy of a therapeutic agent; (vi) and nanoscale enabling technologies, The most common examples of these nanoscale delivery vehicles (also referred to as nanocarriers) include polymeric nanoparticles[NP], dendrimers, nanoshells, liposomes, nucleic acid based nanoparticles, magnetic nanoparticles, and virus nanoparticles[7] . Nanotechnology can be used to create therapeutic agents that target specific cells and deliver toxins to

kill them. The NP will circulate through the body, detect cancer associated molecular changes, assist with imaging, release a therapeutic agent and then monitor the effectiveness of the intervention. Nanotechnology has the potential to offer solutions to these current obstacles in cancer therapies, because of its unique size (1-100nm) and large surface to-volume ratios [8, 9]. Nanotechnologies may have properties of self-assembly, stability, specificity, drug encapsulation and biocompatibility as a result of their material composition [10].

Detection and diagnostics

Nanotechnology-based detection includes cancer detection, biomarkers, and diagnostics. Nanoscale cantilevers, constructed as part of a larger diagnostic device, can provide rapid and sensitive detection of cancer-related molecules. These can be coated with molecules capable of binding specific substrates for instance DNA complementary to a specific gene sequence. DNA-coated gold nanoparticles (NPs) using larger magnetic microparticles (MMPs) are used to detect attomolar (10-18) concentrations of serum proteins. In this case, a monoclonal antibody to prostate specific antigen (PSA) is attached to the MMP, creating a reagent to capture free PSA. A second antibody to PSA, attached to the NPs, is then added, creating a "sandwich" of the captured protein and two particles that is easily separated using a magnetic field.

An example of method of detection is Photodynamic therapy (PDT) (Hopper et al., 2004) performed on head and neck tumour offers the potential for treatment and involves three key components, a photosensitizer, light and oxygen. 5-Aminolaevulinic acid (ALA) is an endogenous cellular component that is metabolized within the haem biosynthetic pathway to produce protoporphyrin IX (PpIX), a potent endogenous photosensitizer. Following exogenous administration of 5-ALA, PpIX is generated intra cellularly, and can then activated by visible light for PDT treatment [11]. The second example of cancer detection is Rapid Detection of Single Nucleotide Polymorphism (SNP), an emerging technology in the field of biomarkers using a Nano Magnetic Device. Here DNA microarrays labeled with gold nanoparticles (Au-np) are used to make the detection of SNPs, known to be associated with hereditary conditions and cancers more efficient and less time consuming [12].

The low-molecular-weight (LMW) region of the blood proteome appears to contain important biomarkers for the detection, diagnosis, and prognosis of cancers. These LMW proteins are usually in very low abundance and difficult to detect even by mass spectrometry. However, new micro or nanofabrication methods may allow the production of nanoparticles that can be used as nanoharvesters to collect and concentrate LMW proteins so that they may be easily analyzed by sensitive mass spectrometric techniques [13, 14].

Early cancer detection

Early detection will greatly increase survival rates with the reasonable assumption that an in situ tumor will be easier to eradicate than one that has metastasized. Implantable Stable molecular sensors for detection of cancer-associated biomarkers are developed. RNA or DNA markers from exfoliated tumor cells in circulation can be analyzed by polymerase chain reaction (PCR) or other amplification technologies, but tumor protein markers may be more informative. Some of the nanoscale systems used in the early detection are discussed below.

- **Carbon nanotubes**

Carbon nanotubes are a distinct molecular form of carbon atoms and in the area of cancer therapeutics, carbon nanotubes have primarily been used for transporting DNA cargoes into the cell and for thermal ablation therapy [15]. Kam et al have shown that single-walled carbon nanotubes 1 to 2 nm in diameter and carrying a cargo of 15-mer DNA adsorbed onto their surfaces can be internalized by cells and accumulate in the cytoplasm without causing cytotoxicity. In thermal ablation therapy continuous irradiation with NIR (808-nm laser at 1.4 w/cm^2) for 2 minutes will heat up a 25 mg/L solution of single-walled carbon nanotubes to 708ºC and lead to boiling of the solution with longer exposures [16].

Zhang et al have demonstrated that carbon nanotubes carrying short (or small) interfering RNA (siRNA) can rapidly enter tumor cells, then release the siRNA to exert RNA interference on target gene expression . They have shown that the delivery of siRNA via carbon nanotubes into tumor cells not only silenced the target gene (i.e., reduced

both its mRNA and protein levels), but also inhibited the proliferation of cancer cells in vitro and suppressed tumor growth in mouse models upon intralesional injection of siRNA-conjugated carbon nanotubes. The use of carbon nanotubes as a vehicle for delivery of siRNA presents a great promise [17].

- **Nanowires**

Nanowires have been used to create extremely sensitive, realtime, electrically based sensors for the quantitative detection of biological species. The sensitivity of field-effect transistor (FETs) whose active areas are comprised of nanowires is greatly enhanced over conventional bulk semiconductor FETs because of their small diameters, between 10 and 20 nm, and high surface area to volume ratios, which allow the binding of a target molecule to cause accumulation or depletion of carriers throughout a much larger percentage of the channel cross-section [18]. An SiNWs (silicon nanowires) device has been developed using peptide nucleic acids as baits for the direct recognition of unlabelled, target miRNAs. Resistance change measured before and after hybridization correlates directly to the concentrations of hybridized target miRNA. This technique enables the identification of fully matched versus mismatched miRNA sequences with sensitivity as low as 1 fM in total RNA extracted from cancer cells. This approach is a promising example of label-free, early detection of miRNA as a biomarker in cancer diagnostics with very high sensitivity and good specificity [19, 20]. Recent results suggest the possibility of incorporating significant numbers of nanowire FETs into large-scale arrays with complex hierarchical structure for high-density biosensor, electronic, and optoelectronic applications [21]. Barcoded metal nanowires combined with Molecular beacons (MBs), the hairpin-shaped oligonucleotides that act like switches allow for multiplexed detection of nucleic acids [22].

- **Nanoparticle based biobarcodes**

One of the more promising recent developments with the potential for multiplexed, sensitive, low volume biomarker analysis is the bio-barcode. An aluminum oxide film is used as a stencil to create metallic bars, nanometers in diameter and microns in length, with alternating submicron bands of metals with varying optical reflectance. These bars are then coated with a targeting element that is bound to their targets by affinity capture. This system allows for multiplexed analysis, because the array of metallic bands could be arbitrarily controlled, and is therefore not limited by the range of available fluorophores. A limited amount of sample is required as the analysis can be performed directly in the sample with no further processing. In 2003, Chad Mirkins group at Northwestern University developed a different barcode system based on the use of magnetic microparticles and gold nanoparticles [23]. Nanoparticle-based bio-bar codes allows for the ultrasensitive detection of any protein where appropriate antibodies are available, and the difficulty of protein analysis as there are a few tumor-specific molecules in plasma at early stages of cancer. The sensitivity of this methodology exceeds that of ELISA by up to 106, yielding the possibility for the use of low abundance biomarkers in diagnosis [24].

Cancer diagnostics

A wide variety of nanoscale particles are developed to serve as diagnostic platform devices. For example, DNA-labeled magnetic nanobeads have the potential to serve as a versatile foundation for detecting virtually any protein or nucleic acid with far more sensitivity than conventional methods now in use. If this proves to be a general property of such systems, nanoparticle-based diagnostics could provide the means of turning even the rarest biomarkers into useful diagnostic or prognostic indicators. Quantum Dots (QDs), coated with a polyacrylate cap and covalently linked to antibodies, have been used for immunofluorescence labeling of the breast cancer marker Her-2[25]. Development of gene chips, Microarray analysis, used for gene expression profiling offers diagnostic and prognostic approach. Proteomic studies to determine the structure and function of each protein and the complexities of protein–protein interactions will be important for developing accurate, effective, and timely diagnostic and therapeutic modalities.

- **Gold nanoparticles**

Colloidal gold nanoparticles are another attractive platform for cancer diagnosis and therapy [26]. They have an incredible potential to be developed for imaging and drug delivery applications such as in vivo sensors, semiconductive photoactive agents for optical imaging, contrast enhancers for CT imaging, X-ray absorbers at tumor sites, and carriers of free-radical-generating chemicals to tumor sites [27]. Sokolov et al. successfully used gold nanoparticles conjugated to EGFR antibodies to label cervical biopsies for identification of precancerous lesions [28]. Photoacoustic tomography has been used to image gold nanoparticles to a depth of 6 cm in experiments using gelatin phantoms [29]. Based on this property, photoacoustic tomography may be useful for in vivo imaging of gold nanoparticles. In a subcutaneous model of colon cancer, it was demonstrated that systemically delivered gold nanoparticles (size, approximately 33 nm) conjugated to tumor necrosis factor (TNF) accumulated in tumors. AuNPs not only are highly stable but also toxic. The development of non-toxic AuNP vectors is very important for advancements in nanomedicine.

Imaging

Imaging plays an increasingly important role in disease detection and planning of therapy and surgery. The nanoscale systems regularly used in the treatment of cancer contain contrast agents and radiopharmaceuticals for imaging. In vivo, imaging of these nanoscale systems can be carried out by using various types of imaging techniques, including single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), fluorescence microscopy, computed tomography, and ultrasound[30]. Some of the various nanoscale systems used for imaging are given below.

- **Liposomes for imaging**

Liposomes are defined as vesicles in which an aqueous volume is entirely surrounded by a phospholipid membrane .The size can vary from 30 nm to several micrometers, and can be uni- or multilamellar. The properties have been extensively investigated and can vary substantially with desired size, lipid composition, surface charge, and method of preparation. Liposomes have to be smaller than the vascular pore cutoff (380 to 780 nm) to extravasate and reach solid tumors.They were extensively studied as potential vectors for gene therapy. Liposomes have been developed as carriers for a variety of contrast agents and radiopharmaceuticals. Studies have shown that over- expressed VIP receptors exist homogeneously in surgically resected human breast cancer and biopsies. Some *in vivo* imaging studies showed that sterically stabilized liposomes (SSLs) encapsulating 99mTc-HMPAO with and without covalently attached VIP ligand accumulated more significantly in breast cancer than normal breast tissues[31,32]. Paramagnetic liposomes loaded with gadolinium (Gd) exhibited a 3-fold increase in relaxivity compared to the conventional paramagnetic complexes gadoterate meglumine (Gd- DOTA) and gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA) and there was good contrast enhancement in the tumor even 20 hours after injection [33].

- **Quantum dots for imaging**

Quantum dots are frequently referred to as nanocrystals. QD have a future in imaging because their size range (2 to 8 nm) confers unique optical and electronic properties such as tunable fluorescent emission by varying particle size or composition. They are made of semiconductors, the most common being cadmium selenide capped by zinc sulfide (CdSe/ZnS). Quantum dots are composed of 10–50 atoms, and they confine electron-hole pairs to a discrete quantized energy level. When excited with ultraviolet light, they fluoresce in different neon colors depending on their size, which determines the energy level of the quantum dot. Larger particles emit light in the red end of the visible spectrum, whereas smaller particles emit in the blue range. They can be linked to antibodies for the detection of cancer markers such as human epidermal growth factor receptor-2 and other antigens on the cell surface [34]. Tumor cells labeled with quantum dots can be used to track metastasis to specific tissues and organs [35].
The greatest advantage of using quantum dots over radioactive tags or organic fluorophores such as fluorescein or cyanine dyes is that quantum dots can fluoresce for several months in a living animal,

they do not degrade or bleed through, and they are much more resistant to photobleaching [36].

Akerman et al modified ZnS-capped CdSe QD to render them water soluble and coated them with targeting peptide sequences (GFE, F3, and LyP-1). QD coated with GFE, F^3, and LyP-1 peptides that preferentially binded to lung, blood vessels, and lymphatics in tumors, respectively were directed accordingly when administered intravenously to mice. Adding PEG to the quantum dot coating reduced MPS uptake [37]. Most recent advances have attempted to use quantum dots as carriers for siRNA. In a study by Tan et al, siRNA targeting the gene encoding human epidermal growth factor receptor-2 was conjugated to quantum dots, which not only functioned as the carrier but also permitted monitoring of the transfection efficiency. Human epidermal growth factor receptor-2 antibodies attached to the quantum dots permitted targeted delivery of the siRNA–quantum dots to breast cancer cells over expressing this receptor, and subsequent receptor-mediated endocytosis of the quantum dot conjugates [38].

- **Magnetic nanoparticles for imaging**

Super paramagnetic nanoparticles refer to iron oxide particles or magnetite (Fe_3O_4) particles that are less than 10 nm in diameter. Many groups have explored the use of magnetic fields to localize magnetic nanoparticles to targeted sites, a system known as magnetic drug targeting. Iron oxide nanoparticles can be water-solubilized with hydrophilic polymer coatings, such as dextran or PEG to sterically preventing opsonization of nanoparticles in the serum and reducing their uptake by the reticuloendothelial system Colloidal iron oxide formulations with dextran are also used as MRI contrast agents[39] .This effectively enhances biocompatibility and increases the circulation time of nanoparticles and therefore used for imaging.Iron oxide nanoparticles can also be made hydrophobic by coating with aliphatic surfactants or liposomes (resulting in magnetoliposomes)[40] . Magnetic nanoparticles can be activated using electromagnetic fields, and they can also be used to thermally treat cancers [41].Under the influence of an alternating field, super paramagnetic nanoparticles undergo Brownian relaxation, in which heat is generated by the rotation of particles in the field. Multiple crystals of iron oxide have been embedded in nanoparticle matrices such as polyacrylamide with surface PEG and solid lipid nanoparticles. Iron oxide in such polyacrylamide nanoparticles when injected into rats bearing orthotopic 9L gliomas had significant increase in relaxivity and circulation half-life up to 3-fold[42]. Most recently, super paramagnetic nanoparticles have been used in the clinical thermotherapy of locally recurrent prostate cancer [43].

- **Dendrimer nanocomposites for imaging**

Dendrimers are spherical polymers that are normally less than 5 nm in diameter. Their key useful feature is the polymer branches that provide vast amounts of surface area to which therapeutic agents and targeting molecules could be attached. Smaller dendrimer-based MRI contrast agents have been developed to overcome the prolonged retention times and toxicity of larger dendrimer and albumin MRI products. In early 2006, Majoros et al synthesized and characterized a multifunctional dendrimer conjugated with fluorescein isothiocyanate (for imaging), folic acid (for targeting cancer cells over expressing folate receptors), and paclitaxel (chemotherapeutic drug)[44]. The first study to demonstrate successful in vivo– targeted drug delivery to cancer cells by intravenously administered nanoparticles involved methotrexate-carrying dendrimers that could recognize cells expressing folate receptors. Targeted delivery of methotrexate via dendrimers was shown to be markedly more effective at delaying the growth of epithelial cancer xenografts in mice than the drug given alone [45]. In addition to methotrexate and folic acid, these dendrimers also carried fluorescein to permit tracking of their location in the bloodstream. These smaller dendrimer-based MRI agents were more quickly excreted by the kidneys and were able to make good visualization of vascular structures due to less extravasation [46].

Targeting in cancer

Passive targeting occurs due to extravasation of the nanoparticles at the diseased site where the microvasculature is leaky. Examples of such diseases where passive targeting of nanocarriers

can be achieved are tumor and inflamed tissues. There are now several nanocarrier-based drugs on the market, which rely on passive targeting through a process known as "enhanced permeability and retention." Because of their size and surface properties, certain nanoparticles can escape through blood vessel walls into tissues. In addition, tumors tend to have leaky blood vessels and defective lymphatic drainage, causing nanoparticles to accumulate in them, thereby concentrating the attached cytotoxic drug where needed, protecting healthy tissue and greatly reducing adverse side effects. Nanoparticles will actively target drugs to cancerous cells, based on the molecules that they express on their cell surface. Molecules that bind particular cellular receptors can be attached to a nanoparticle to actively target cells expressing the receptor. Active targeting can even be used to bring drugs into the cancerous cell, by inducing the cell to absorb the nanocarrier. Active targeting can be combined with passive targeting to further reduce the interaction of carried drugs with healthy tissue. Nanotechnology-enabled active and passive targeting can also increase the efficacy of a chemotherapeutic, achieving greater tumor reduction with lower doses of the drug.

- **Antibodies or antibody fragments**

Antibodies are the first macromolecular ligands used for targeted delivery [47]. The use of monoclonal antibodies (mAb) became widespread after the discovery of hybridoma technology. Due to their inherent immunogenicity, murine monoclonal antibodies were not suitable for clinical applications. Engineering antibody technologies led to the development of chimeric humanized and fully humanized antibodies. Several methods have been developed to produce human immunoglobulins from transgenic mice to select human antibodies against specific cell types or antigens. This process can be designed to improve the properties of the ligand such as stability, affinity, selectivity and internalization [48]. This approach was also used to isolate cancer targeting antibodies using live cancer patients [49]. Antibody molecules show good stability but are limited by their large hydrodynamic diameter (20 nm; MW 150 kDa) to diffuse into tumor tissues [50, 51]. Recent advances have led to the development of single chain antibodies, antibody fragments (Fab or scFv) and dibodies [52]. There are several examples of FDA approved antibodies in clinical practice today, including Rituxan—a chimeric anti-CD20 antibody effective against CD20_ B-cell non- Hodgkin's lymphomas. Other examples include anti- HER2 Herceptin, anti-EGFR Erbitux, and anti-VEGF Avastin.

- **Peptides**

Peptides are small, synthetic molecules that can be manufactured in large quantities with excellent quality control. Peptides are more stable than antibodies and unlikely to be immunogenic. The discovery of new peptide targeting domains has been successful due to the development of peptide library screening methods (e.g., phage display). A large number of high affinity peptides with potential for targeting application have been isolated against a variety of cell surface antigens. Peptides that contain RGD (Arg-Gly-Asp) domains can preferentially bind cells in tumor microvasculature that express the (V) 3 integrin. Functional, single-domain heavy chain antibodies also known as nanobodies have been raised against cancer targets, which either antagonize receptor function or deliver an enzyme for prodrug activation both for therapeutic benefit [53,54]. Another important strategy employing phage display technology used a 58 residue -helical domain of staphylococcal protein A as a platform to develop polypeptide targeting ligands named affibodies against a variety of cancer-related targets [55].

- **Small molecule targeting**

Small molecules are very attractive as targeting ligands due to their low cost and ease to conjugate with drugs such as imaging probes (quantum dots, etc.) and nanoparticles. The small size of the targeting ligand allows functionalization of multiple molecules on single nanoparticles. Folic acid and sugar molecules have been extensively used. Folic acid is required for cell survival and folate receptors are homogeneously over-expressed in many cancer cells. Folic acid receptors (FR) interact with high affinity [56, 57]. Folic acid conjugates are transported via receptor mediated endocytosis. Folate targeted nanoparticles have shown to be effective in a number of tumors using liposomes or polyplexed nanosystems [58, 59]. Recently, Weissleder et al. have demonstrated that

small molecules can change the biological affinity of nanoparticles used for imaging specific tissues. Using a high-throughput screening based on surface chemistry, 146 different small molecules (500 Da) were conjugated to nanoparticles and the results showed that very small molecules can drastically affect the binding of nanoparticles to different cell lines and pancreatic tumor xenografts [60].

- **Aptamers**

Nucleic acid aptamers are single stranded DNA, RNA or unnatural oligonucleotides that fold into unique structures capable of binding to specific targets with high affinity and specificity [61]. Nucleic acid aptamers are a novel class of ligands that are small (10–20 kDa), non-immunogenic, easy to isolate, and exhibit high specificity and affinity for their target antigen at best in the picomolar scale [62]. Aptamers are synthetic molecules that can be easily modified and scaled up for synthesis. The unique antigen-aptamer binding mechanism has led to the isolation of ligands with high binding affinity. It was shown that aptamer-antigen interaction occurs by a complex mechanism involving the folding of the aptamer on its antigen like a "paper clip"[63]. There was an efficacy study done which shows that a single intratumoral injection of aptamer targeted nanoparticles loaded with docetaxel allowed all the treated mice to survive more than three months in contrast to other controls [64]. More recently, a study reported a novel strategy for targeted doxorubicin delivery to cancer cells using an aptamer-Dox physical conjugate. Other strategies involving aptamers in cancer therapy have included targeting the growth factors PDGF[65,66] and VEGF for delivery of therapeutic or diagnostic agents, discovering new cancer-associated antigens using cell-SELEX ,and delivering toxins or siRNA[67,68,69].

Multifunctional therapeutics

Multifunctional nanoparticles share common approaches, of different types of nanoparticles. In addition to these platform nanoparticles, there are a large variety of nanoparticles constructed of other types of materials. They all involve encapsulation, covalent conjugation, or noncovalent adsorption of various moieties (e.g., chemicals, drugs, DNA, small interfering RNAs, peptides, aptamers, ligands, stealth molecules, homing molecules, and other cell targeting molecules) to allow the nanoparticles to recognize and locate the tumor, deliver a load or kill the tumor cells, and permit visualization and imaging . Different peptides that can act together synergistically could be strategically attached in combination, and the nanoparticles could also be loaded with multidrug regimens. Engineering these smart nanoparticles could involve even more complex schemes for targeted drug release or nanoparticle activation, by using heat-labile or protease susceptible tethers. The heat-labile linkers could be a variety of molecules, including DNA with heat labile hydrogen bonding between complementary strands. Substrates for tumor-specific or tumor environment–specific enzymes could be chosen to serve as the protease susceptible linkers. Harris et al have developed a strategy for superparamagnetic nanoparticle self assembly by designing biotin and neutravidin-coated iron oxide nanoparticles that are inhibited from self-assembly by PEG chains and anchored to the nanoparticles via matrix MMP-2–cleavable peptide substrates. Only upon proteolytic removal of surface PEG through MMP-2cleavage of the peptides, the nanoparticles get self-assembled through unhindered biotin-neutravidin interactions. MMP-2 is a tumor-specific protease correlated with cancer invasion and metastasis, and this assembly and clustering of nanoparticles permits MRI detection of tumor-derived cells that are producing the protease and enhanced image contrast of tumor invasion in the body [70]. Such multifunctional nanodevices, sometimes referred to as nanoclinics, may also enable new types of therapeutic approaches or broader application of existing approaches to kill malignant cells. Such multifunctional nanodevices hold out the possibility of radically changing the practice of oncology, perhaps providing the means to survey the body for the first signs of cancer and deliver effective therapeutics during the earliest stages of the disease.

NANOROBOTS

Nanomedicine using of the nanorobots (e.g., Computational Genes), was introduced to repair or detect damages and infections in the body. Nanorobots are tiny machines used to cure diseases

in human or in any organism. A typical blood borne medical nanorobot would be between 0.5-3 micrometres in size. Carbon can be the primary element used to build these nanorobots due to the inherent strength and other characteristics of some forms of carbon (diamond/fullerene composites). Nanorobots are fabricated in desktop nano factories specialized for this purpose. Nanodevices are observed at work inside the body using MRI, especially if their components were manufactured using mostly 13C atoms rather than the natural 12C isotope of carbon, since 13C has a nonzero nuclear magnetic moment. Medical nanodevices are first injected into a human body, and which would further traverse into different organs or tissue [71].

Pharmacytes

Pharmacyte is a self-powered; computer controlled medical nanorobot system capable of digital transport timing, and targeted delivery of pharmaceutical agents to specific cellular and intracellular destinations within the human body. Pharmacytes could also tag target cells with biochemical substances capable of triggering a reaction by the body's natural defensive or scavenging systems, a strategy called "phagocytic flagging". Pharmacytes are constructed using future molecular manufacturing technologies such as diamond mechanosynthesis which are currently being investigated theoretically using quantum ab initio and density-functional computational methods. Pharmacytes have many applications in nanomedicine such as initiation of apoptosis in cancer cells and direct control of cell signaling processes [72].

NANODIAMONDS (ND)

NDs are chemically inert, and are nontoxic toward several cell lines. A new tool was designed to precisely deliver tiny doses of drug-carrying to individual cells - the Nanofountain Probe. Nan fountain Probe is used to injected tiny doses of nanodiamonds into both healthy and cancerous cells. NDs could be surface-functionalized easily with carboxyl groups and their derivatives for specific or nonspecific binding with nucleic acids and proteins and showed possible application in biomedicine. Ho.et.al worked on nanodiamonds and the results indicated that drug molecules could be adsorbed by NDs to form a drug-ND complex. Some inorganic small molecules could promote the loading of drugs on NDs, and mediated desorption of drugs from the complexes. With these approaches, water-insoluble drugs could be delivered into cells to effectively perform their biological efficacy. The main drugs used in these studies included doxorubicin hydrochloride (DOX), Purvalanol A and 4-hydroxytamoxifen (4-OHT), and insulin for diabetes therapeutics [73, 74, 75].

NANOMIDICINE IN THE TREATMENT OF DIFFERENT CANCERS

Breast cancer

Breast cancer detection involves self and clinical examination and radiography (including mammography positron emission tomography and magnetic resonance imaging) followed by invasive biopsy for the histological confirmation of invasive disease. The development of mammography has greatly increased the likelihood of early detection of breast cancer [76]. Many different types of nano-delivery systems with different materials and physico-chemical properties have been developed for application to this type of cancer. Most well studied among these are liposomes, polymer-based platforms, dendrimers, gold nanoshells, nanocrystal, carbon-60 fullerenes , silicon- and silica-based nanoparticle, and super paramagnetic nanoparticulate systems.

An excellent example that nanotechnology has already achieved in the field of medicine is liposomal drug delivery. Several different formulations of liposomal doxorubicin have successfully been used in the clinic for the treatment of breast, ovarian, and Kaposi sarcoma [77, 78]. In addition to liposomal doxorubicin, albumin-bound paclitaxel (Abraxane®) is another example of an EPR based nanovector application for breast cancer chemotherapy. Paclitaxel is highly hydrophobic and dissolved in cremophor to prevent paclitaxel precipitation [79]. A transmission electron microscopy (TEM) study was carried out to investigate the ability of magnetic nanoparticles (MNPs) to target breast cancer cells in mice. MNPs were functionalized using Luteinizing Hormone Releasing Hormone (LHRH), whose receptors are expressed in most types of breast cancer cells and found that dispersive LHRH-MNPs were

distributed in tumor cells and cells in lungs and livers. No LHRH-MNPs were observed in kidney cells. Furthermore, LHRH-MNPs tend to aggregate and form clusters in tumor cells and cells in lungs where metastases were developed. These suggest that MNPs functionalized using LHRH can be used to target both primary cancer cells and the metastatic cells [80].

Lung cancer

Lung cancer is one of the most lethal cancers and the second most common cancer in both men and women [81]. Aerosol therapy using particulate drug carrier systems is becoming a popular method to deliver therapeutic or diagnostic compounds either locally or systemically [82]. These recent developments of inhalable biodegradable nanoparticles, large porous particles and liposomal dry powders make inhalation a feasible alternative approach to deliver macromolecules such as insulin and treat lung specific diseases like tuberculosis [83,84]. There was a study where in Doxorubicin-loaded nanoparticles (NPs) were incorporated into inhalable effervescent and non-effervescent carrier particles using a spray–freeze drying technique and found that animals treated with inhalable effervescent nanoparticle powder containing 30 μg doxorubicin showed a highly significant improvement in survival compared to all other treatment groups.[85]

Prostate cancer

A novel approach to increasing the sensitivity and specificity of early prostrate cancer detection is through the application of nanotechnology, where luminescent semiconductor nanocrystals or quantum dots (QDs) are conjugated with biomolecules. QDs have unique properties that allow for the long-term immunofluorescence imaging of molecular activities inside living cells. Some studies used luminescent QDs to target several established prostate cancer biomarkers, including prostate-specific antigen (PSA), kallikrein 2 (KLK2), kallikrein 14 (KLK14), osteoprotegerin (OPG), antip53Ab, caveolin-1 (Cav-1), and interleukin-6 (IL-6). Nanowires are also used in the detection of this type of cancer by modifying with antibodies for prostrate specific antigen (PSA)[86] .This multiplexed detection of different cancer markers is achieved with a sensitivity to concentrations at the 50-100 fg/ml level and with complete selectivity. Several researchers found that biodegradable polymer nanoparticles, linked to a protein-binding nucleic acid known as an aptamer and loaded with the anticancer agent docetaxel, can target and kill prostate tumors growing in mice. These targeted nanoparticles to deliver docetaxel appear to reduce the toxic side effects associated with this drug.

Ovarian cancer

Epithelial ovarian cancer arises from the ovarian surface epithelium (OSE) and it accounts for approximately ~90% of ovarian malignancies [87]. Nanotechnology can enhance OVCA imaging by introducing new contrast agents and by targeting OVCA through specific OVCA surface markers due to the property of multiple functionalizations of nanocarriers. Ovarian cancer is known to initially spread throughout the peritoneal cavity, and current therapeutic approaches in humans include direct injection into the peritoneal space, thereby targeting the therapy to the ovaries and nearby tissues where tumors may have spread. The nanoparticles are administered by injection into the peritoneal cavity, which encases all abdominal organs including ovaries .Magnetic nanoparticles were prepared that can selectively bind to and remove ovarian tumor cells from abdominal cavity fluid which overcome the problem of shedding of malignant cells into abdominal cavity [88].

CONCLUSION

The field of nanomedicine has a bright future with the emergence of several promising approaches for delivery of therapeutic agents and imaging using the advantages of the nanoscale carriers. Novel nanoscale systems still lack sufficient safety data as far as toxicity studies are concerned. Issues related to scale-up and large-scale manufacturing need to be improved. Long-term storage stability is another requirement when considering these systems for clinical application. Nanomedicine is envisioned to participate in the development of personalized medicine by which the patients may now undergo treatment to their unique genetic makeup. Nanovectors, nanostructures, nanoplatforms, and nanoscale objects hold the potential to bring about less

invasive and more selective treatment of brain tumors. Reaching this potential will require more research and the development of nanovectors that are less toxic, more versatile, and more biodegradable than the current ones. Many groups have functionalized very stable nanoplatforms such as CNT and gold nanoparticles in order to achieve solubility. A new generation of nanovectors to incorporate multi-functional compounds, allowing multistage complex delivery of therapeutic compounds augmented cellular therapies at a reasonable cost and with patient compliance is foreseen in the arena of future cancer treatment.

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