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Nanotechnology: A novel approach towards cancer treatment

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Abstract: Nanotechnology deals with the study of any material substance having size in the range of 1-100 nm. It is a cutting edge technology having extensive scope in the fields of food and environmental science, chemistry, physics, biology, and many other fields with unprecedented applications. Nanoparticles are the building blocks of nanotechnology offering diverse applications in almost every field at the atomic scale. Nanoparticles exhibit novel characteristics like optical, electrical conductance, mechanical, thermal and magnetic properties which are different from properties of the same material exhibiting at the bulk scale. Nanotechnology is the most prominent technology in the field of medical science for the treatment and prevention of severe and incurable fatal diseases like cancer. Nanoparticles and nano devices enable cancer detection, treatment and prevention faster than conventional therapies. This review article explains cancer and causes, factors responsible for cancer occurrence and finally, nanotechnology based therapies for cancer detection and treatment.

Keywords: Cancer, Cantilevers, Quantum Dots, Nanoshells, Nanotechnology

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Cancer is an abnormal growth of cells. Cancer cells rapidly reproduce and divide uncontrollably and their growth rate is not restricted by space, nutrients etc. Cancer cells are usually different in shapes as compared to healthy cells, which do not perform biological functions properly, and they can spread into many areas of the body. The study of cancer and tumors is called Oncology. The term cancer is used when a tumor is of malignant type, having potential to cause death (Hanahan et al. 2000). Tumors can be of two types *(1) Benign (noncancerous):* These tumors tend to grow slowly and do not spread and *(2) Malignant (cancerous):* These tumors can grow rapidly, invade and destroy nearby normal tissues, and spread throughout the body. Cancer is malignant because it can be locally invasive and metastatic. Locally invasive - the tumor can invade the tissues surrounding it by sending out fingers of cancerous cells into the normal tissue (Hanahan et al. 2000). Metastatic - the tumor can spread cells into other tissues inside the body, which may be distant from the original tumor (Hahn et al. 2002).

Cancer is generally classified either according to the kind of fluid or tissue from which is being originated, or according to the location in the body where it was first developed (Hahn et al. 2002). The following five broad categories indicating the classifications of cancer: Carcinoma- When cancer is found covering epithelial layer, surface of organs, glands or body structures; this is recognized as carcinoma. The most glaring example of cancer is stomach lining. Carcinoma adversely affects glands secretion like breast that produce milk. Carcinomas account for 80 to 90 percent of all cancer cases. Sarcoma- it is a malignant tumor growing from connective tissues, such as cartilage, fat, muscle, tendons, and bones. Lymphoma – it refers to a cancer that originates in the nodes or glands of the lymphatic system - Lymphomas are classified into two categories: Hodgkin's lymphoma and non-Hodgkin's lymphoma. Leukemia – it's a cancer of blood cells called leucocytes. It starts in the bone marrow, producing abnormal white blood cells and grows faster than normal cells. Sometimes, it spreads to

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lymph nodes also. It is of two types: acute and chronic. Acute is fast progressive cancer and chronic is slow. It may be myelogenous or lymphocytic. Myelogenous leukemia affects white blood cells called myelocytes. Myeloma – it grows in the plasma cells of bone marrow. In some cases, myeloma cells get deposited or accumulated in one bone and form a single tumor, called a plasmacytoma. However, in other cases, myeloma cells get accumulated in several bones, forming many bone tumors. This is called multiple myeloma.

Cancer cells can vary in how fast they grow and how they spread in the body. The stage is based on the size of the tumor and on how much the cancer has spread. Stage I - Primary tumor only; Stage II - Primary tumor, but larger than stage I; Stage III - Primary tumor and metastasis to lymph nodes only and Stage IV - Primary tumor and distant metastasis

CANCER RISK FACTORS

Lifestyle factors

Cigarette smoking, alcohol consumption, obesity, low fruits and vegetable intake, lack of physical activity, environmental pollution and working with toxic chemicals are some examples of lifestyle choices that may be risk factors for some adult cancers. Hereditary and genetic factors also play crucial role in some childhood cancers development like retinoblastoma (Peto, 2001).

Some genetic disorders

For example, Wiskott-Aldrich and Beckwith-Wiedemann syndrome are known to alter the immune system. The immune system is a complex system which protects us from various infections and diseases. The bone marrow produces cells that later mature and function as part of the immune system. One theory suggests that the cells in the bone marrow, the stem cells, become damaged or defective, so when they reproduce to make more cells, they make abnormal cells or cancer cells. The cause of the defect in the stem cells could be related to an inherited genetic defect or exposure to a virus or toxin (Vogelstein et al. 2004).

Exposures to certain viruses

Epstein-Barr virus and HIV have been associated with an increased risk of childhood malignancies like Hodgkin and non-Hodgkin lymphoma. Probably, the virus alters a cell in some way and that altered cell then reproduces an altered cell and eventually, these alterations leads to cancerous cells (Palefsky et al. 2003).

Environmental exposures

Pesticides, fertilizers, and power lines have been researched for a direct link to childhood cancers. There have been evidences of cancer occurring among nonrelated children in certain neighborhoods and/or cities. It is still an unknown fact that whether prenatal or infant exposure to these agents causes cancer, or whether it is a coincidence (Kaul et al. 1997).

High dose chemotherapy and radiation

Secondary malignancies are cancers caused by treatment with radiation or chemotherapy. Some treatments increase the risk of developing a secondary cancer, such as the chemotherapy drugs etoposide. These anticancer agents can also alter immune system. Some lymphomas and childhood leukemia occurs in secondary cancers, are more frequent in patients which are exposed to radiation and chemotherapy together compared to either treatment alone (Ron, 2003; Preston et al. 2002).

Cancer symptoms (Calle et al. 2004)

- Any sore that does not heal
- Thickening or lump in the body
- Obvious change in a wart or mole
- Unexplained bleeding or discharge
- Changes in bowel or bladder habits
- Cough or hoarseness that does not go away
- Unusual upset stomach or difficulty in swallowing

Recently, many functional nanoparticles have been developed, covalently linked to biological molecules such as peptides, proteins, nucleic acids, or small molecule ligands (Leserman et al. 1980). Super paramagnetic iron oxide nanoparticles are employed as a contrast agent for lymph node prostate cancer detection (Ganta et al. 2008) and polymeric nanoparticles (poly-lactic acid and poly glycolic acid) are deployed for targeted gene delivery to tumors (Allen et al. 2004). Therapeutic nanoparticles technologies have enough potential to revolutionize the drug development process and change the landscape of the pharmaceutical industry (Cai et al. 2007). Due to unique physicochemical properties, nanoparticles have shown potential in delivering a range of molecules to desired sites inside the body. Nanotechnology improves the therapeutic index of drugs by enhancing their efficacy or increasing their tolerability inside the body. Nanoparticles could also improve the bioavailability of water insoluble drugs, carry large payloads, protect the therapeutic agents from physiological barriers, as well as enable the development of novel classes of bioactive macromolecules (DNA and siRNA). Additionally, incorporation of imaging contrast agents within nanoparticles can allow us to visualize the site of drug delivery or monitor the *in vivo* efficacy of the therapeutic agent (Gao, 2005). In order to develop safe and effective therapeutic nanoparticles, researchers have developed multifunctional nanoparticles platforms for cell and tissue specific targeting, enabling sustained or triggered drug delivery and co delivery of synergistic drug combinations (Shi et al. 2010; Kukowska - Latallo, 2005).

STRATEGIES FOR THE TREATMENT OF CANCER

It can be achieved mainly by deploying two therapies, one of which is conventional therapy involving surgery, radiation, chemotherapy, biological and hormone treatment and other is nano technology based therapy involving nanocantilever, nanoshells, nanopores, brachySil and nanowires. The details about these therapies are mentioned below:

Conventional approaches for cancer treatment

These are mainly four cancer treatment therapies including surgery, chemotherapy, radiation therapy and biological therapy. Clinical trials may be an option for some exceptional cases where cancer treatment meets required study criteria.

Surgery

Surgery is the most commonly used therapy in cancer treatment. It involves the removal of cancer affected body part for the diagnosis and treatment. This therapy remove tumors or cancerous tissue which is possible to prevent, treat and for the diagnosis of cancer. It is oftenly investigated in combination with chemotherapy or radiation therapy. When cancer is in extreme stage then the palliative surgery is the only option and which does not cure or treat cancer but provides some relief from the cancer discomfort.

Chemotherapy

Chemotherapy is one of mostly used therapy for cancer treatment involving drugs to treat cancerous cells. Chemotherapy can also damage normal cells as they are harmful for the genes located in the cell nucleus. Some of the genes get damaged at the time of splitting and while some get damaged at the time of replication. Sometimes, a combination of chemotherapy drugs are given, which causes the destruction of abnormal cells effectively, so combination of drugs is more favorable. During chemotherapy, chances of destruction of normal body cells (e.g., hair follicle cells and cells lining stomach) are very less. That is why; chemotherapy can also cause several side effects like hair loss and stomach related problems. Chemotherapy can be operated by pill or intravenously, or some other route likes surgery. Chemotherapy can be prescribed alone or in combination with radiation or biological therapy.

Radiation therapy

Radiation therapy involves high energy radiation beams on the cancer affected body part. In this therapy, gamma rays, x-rays and charged particles are applied for cancer treatment. It is also of two types involving internal and external beam radiation therapy. Internal beam radiation therapy (brachytherapy) radiation treatment from a radioactive material placed in the body part near cancer cells. External beam radiation therapy is oftenly directed by a machine on the diseased part. Radiation therapy works by destroying cancer cell's DNA, making it unable to multiply, as cancer cells are extremely sensitive to radiations and massively get destroyed on radiations treatment. Radiation therapy may be given alone or in combination with chemotherapy or with surgery.

Biological therapy

Biological therapy is also known as immunotherapy/ biotherapy/biological response modifier therapy. This is a new therapy for cancer treatment employing chemotherapy, surgery and radiation treatment also. This therapy involves body's immune system; by either direct or indirect way to fight against cancer, parallel to reduce the side effects caused by some other cancer therapies. This therapy generally employs interferon, monoclonal antibodies, vaccines, gene therapy, interleukins and colony stimulating factors for the destruction of cancer infected cells.

Limitations of conventional cancer therapy:

- Lack of early disease detection
- Inadequate drug concentrations targeting to tumors
- Non specific systemic anticancer drug distribution
- The side effects of this therapy are nausea, vomiting, fatigue, anemia, due to current chemotherapeutic agents, which are highly cytotoxic, and destroy not only cancerous cells but also affect a number of healthy cells in the process and finally affecting patient's quality of life.

NANOTECHNOLOGY

It is the advanced field of science involving the design and synthesis of materials, devices and structures in the range of 1-100nm. In the medical science/health sector, it provides sensitive and rapid detection of cancer, and other diseases progression at very early stages.

Application of Nanotechnology in cancer treatment

Nanotechnology is laying down the new foundations in cancer diagnosis, treatment and prevention as illustrated in figure 1.

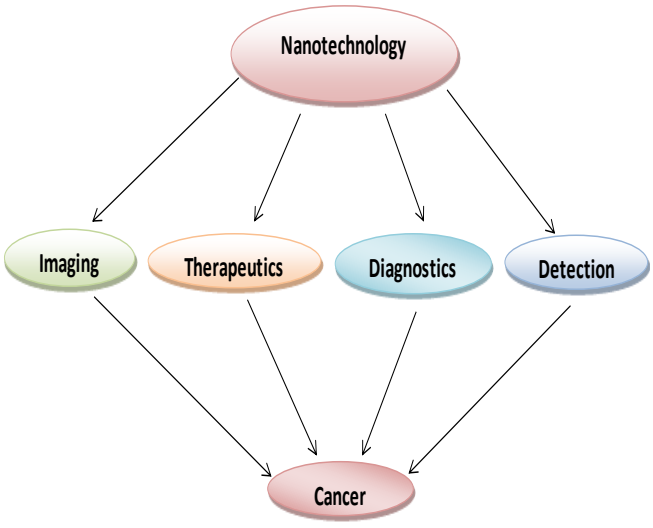

Figure 1 Nanotechnology applications in cancer

Advantages of nanotechnology in cancer treatment

1) Capable of detecting cancer at very early stages and delivering anticancer drugs specifically to malignant cells.
2) Protect drugs from being degraded inside the body before they reach their target.
3) Prevent drugs from interacting with normal cells, thus avoiding side effects.
4) Allow for better control over the timing and distribution of drugs to the tissue, making it easier for oncologists to assess how well they work.

OPTIMAL DESIGN OF NANOPARTICLES FOR CANCER THERAPY

The most important considerable factor for the successful development of therapeutic nanoparticles is quick clearance from the living system when deployed for systemic delivery. Whenever, nanoparticles enter into bloodstream, their surface may experience nonspecific adsorption, making them more visible to phagocytic cells (Ostuni et al. 2001). After opsonisation, nanoparticles could be rapidly cleared from the bloodstream through phagocytosis by mononuclear phagocyte system (MPS) in the liver and by spleen filtration (Alexis et al. 2008). So, in order to maintain timely clearance and bio distribution of nanoparticles within the living systems, physico-chemical properties and targeting ligand functionalization (Petros et al. 2010), should be carefully considered and applied during optimal design of therapeutic nanoparticles to reduce the nanoparticles toxicity in the living cells, tissues and vital organs (Nagayama et al. 2007).

Size

Nanoparticles size is very crucial during circulation and bio-distribution inside living system. Nanoparticles having size less than 10 nm can be easily cleared from kidneys or through extravasation, while larger nanoparticles have higher tendency to be cleared by cells of reticuloendothelial system (RES) (Yuan, 1995). For example, *in-vivo* bio-distribution of polystyrene nanoparticles with regular composition and varying particle size from 50 to 500 nm have shown greater agglomeration rate of nanoparticles inside the liver (Kong et al. 2000).

It has been observed that nanoparticles having size less than 100 nm have a higher potential to circulate inside the blood for longer periods of time and causes reduction in hepatic filtration activity. Nanoparticles size also play an important role in tumor accumulation sites due to enhanced permeation retention effect. For example, sterically stabilized liposomes having size 100–600 nm have been investigated for transvascular transport application, and the cut off size of the pores was found to be in the range of 400–600 nm in diameter (Roser et al. 1998). In some studies, the pore cut off size was found to be in between 7 and 100 nm at 34°C and was increased to greater than 400 nm at 42°C, allowing nanoparticles to be delivered successfully to the tumor sites up to certain extent (Schwendener et al. 1984).

Surface charge

It has been found that the surface charge of nanoparticles affect their uptake by the MPS cells (Alexis et al. 2008). Neutrally charged nanoparticles have shown much lower opsonisation rate as compared to charged particles (Davis, 2009). It was also found that positively charged nanoparticles generate a higher immune response as compared to neutral or negatively charged nanoparticles (Knop et al. 2010). Nanoparticles with a primary amine at the surface promote higher rates of phagocytic uptake when compared to other nanoparticles having sulphate, hydroxyl, and carboxyl group at the surface (Moghimi et al. 2003). It has been found that optimal range of nanoparticles surface charge should be between -30 and +30 mV for reduced phagocytic activity and minimized nonspecific interactions of nanoparticles with biological molecules (Gref, 2000).

PEGylation

Nanoparticles surface modification employing polyethylene glycol (PEG) exhibits favourable intrinsic physico-chemical properties like high flexibility and hydrophilicity, low toxicity and immunogenicity, resulted in less nanoparticles accumulation in organs like liver and spleen (Owens et al. 2006). PEG coated nanoparticles leads to prolonged circulation time inside living system as compared to non PEGylated nanoparticles, exhibited half circulation time (Vonarbourg et al. 2006). The length, shape, and density of PEG chains on the nanoparticles surface largely affect its surface hydrophilicity and phagocytic activity. When PEG has low surface density, then PEG chains and nanoparticles will be closer to each other, resulting in a mushroom configuration and on increasing PEG surface density, most of the chains are unmitigated away from the surface brush configuration which decides the thickness of the PEG shell on the nanoparticles corona (Takae, 2005). It has been found that brush configuration exhibits more effective blocking or repulsion of opsonins than the mushroom configuration (Allen, 2002).

Ligand functionalization

Targeting ligands conjugation on PEGylated nanoparticles surface has also been found to affect their bio-distribution inside the living system (Torchilin, 2008). Although targeting ligands could improve the cell and tissue specific delivery of nanoparticles, they may compromise the particle surface properties by masking the effect of PEG layer and adversely affecting the nanoparticles anti-bio fouling properties in *in-vivo*. Thus, the successful development of targeted nanoparticles system for efficient drug delivery strongly depends on maintaining a balance between cellular targeting and immune evasion.

Targeting ligands

Successful development of targeted nanoparticles for drug delivery solely depends upon the choice of targeting ligands. Several variables must be

considered during targeted nanoparticles formulation is ligand biocompatibility, cell specificity, binding affinity, and ligand purity (Gabizon, 2001). Size and charge of the ligand molecule and their ease of modification and conjugation with nanoparticles is also a crucial consideration for successful in-vivo investigation. Ligand selection from a practical point of view is also dependent on production cost, scalability, and stability (organic solvent and high temperature stability) in mass production.

Antibodies and Antibody fragments

Antibodies and antibody fragments form an important class of targeting ligands with high degree of specificity for cellular receptors and a wide range of binding affinities and have been extensively investigated in targeted drug delivery (Wang, 2008). Over the past two decades, the feasibility of antibody based tissue targeting has been clinically investigated with several different monoclonal antibodies (mAbs) (Carter, 2001). The recent advancements in hybridoma technology have led to the development of chimeric, humanized, and fully human mAbs to reduce their immunogenicity. The ability of engineered mAbs to target disease processes has been demonstrated by the success of several monoclonal antibody therapeutics, including cetuximab rituximab, trastuzumab, and bevacizumab. mAbs have also been employed for nanoparticles carrier agent for site specific delivery applications. For example, mAbs conjugated PLA nanoparticles exhibited a sixfold increase in the particle uptake rate compared with non targeted particles. Nevertheless, mAbs conjugated nanoparticles encounter considerable challenges and limitations for drug delivery, since mAbs are generally complex and large (~150 kDa) molecules and require significant engineering at the molecular level for efficacy enhancement. Compared to mAbs, antibody fragments have demonstrated higher potential for targeted nanoparticles engineering, as they are smaller in size and lack the complement activation region of mAbs, while retaining the antigen binding specificity (Arap, 2002). Some pioneering examples of antibody fragment targeted liposomes delivery (immunoliposomes) are in clinical trials include MCC-465 uses F (ab ¢) 2 for the targeted delivery of doxorubicin and SGT-53 uses scFv to deliver tumor suppressor gene, p53 (Lam et al. 1997).

Peptide

Peptide ligands have demonstrated significant targeting potential due to small size, high stability and relative ease of large scale synthesis with excellent quality control. Peptide conjugated nanoparticles have been widely deployed for targeting cancer cells and tumor vasculature (Lee et al. 2007). For example, peptide (SP5-52) can recognize only tumor vasculature, while avoiding normal blood vessels (Chang et al. 2009). The SP5-52 peptide conjugated liposome has exhibited enhancement in the therapeutic potential of doxorubicin and thereby reducing the growth rate of tumor blood vessels, and enabling high survival rates among human lung and oral cancer bearing mice xenograft (Ohannesian, 1995). Recently, this system has been used to target non small cell lung cancer (NSCLC) cells and demonstrated increased drug accumulation at tumor tissues by 5.7 folds as compared to free drugs (Zubieta, 2006).

Sugars

Specific sugar molecules (*e.g.*, lactose, galactose, and mannose) can recognize lectins that are over expressed on the surface of numerous cancer cells (Davis et al. 2008). Sugar molecules are also helpful in specific targeting of nanoparticles against cancer cells (Managit et al. 2003). For example, galactose can identify the asialoglycoprotein receptor, expressed on hepatocytes, and its high expression is retained on primary liver cancer cells. The galactosamine conjugate N - (2-hydroxypropyl) methacrylamide copolymers (HPMA) (PK2) is currently under clinical investigation for the treatment of primary liver cancer (Ross et al. 1994). However, to compensate for the weak binding affinity of carbohydrates, multiple or multivalent molecules can be easily conjugated to the nanoparticles surface in order to achieve multivalent interactions. It was also found that when galactosylated liposome acts as a carrier, then the targeting efficacy depends mainly on the galactose ligand density (Stella, 2000).

Small Molecules

Small molecules have also attracted considerable attention as potential targeting ligand due to low molecular weight, low production cost, and ease of conjugation with nanoparticles. Small size of targeting ligand allows the easier functionalization of compound ligands molecules on several nanoparticles. Folic acid is essential in metabolic processes for cell survival, has exhibited high specificity in recognizing folate receptors which are generally over expressed in many tumor cells (Park et al. 2005). There are several examples of folate conjugated nanoparticles employed for drug delivery applications (Kukowska-Latallo et al. 2005) such as liposomes, polymeric nanoparticles, and dendrimers (Low et al. 2007). Folate conjugated nanoparticles are effective in treatment of ovary, breast, lung, renal, and colon cancer (Zhao et al. 2008). However, immunochemistry research studies have shown over expression of folate receptors in normal tissues such as placenta and kidney as well, raising some concerns for the translation of folate targeted nanoparticles from bench to bedside (Weissleder et al. 2005). One strategy to improve the targeting of small molecule conjugated nanoparticles is through multivalent binding effects, by conjugating multiple ligands on the nanoparticles surface. Another strategy is the selection of small molecules with high affinity and specificity by using high throughput screening approach (Wang et al. 2004). Using fluorescent magnetic nanoparticles, recently screened several small molecular ligands from a library of 146 small molecules (£ 500 Da), which can

specifically bind to endothelial cells, activated human macrophages, and pancreatic cancer cells, respectively (Brigger et al. 2002).

Aptamers

Aptamers are small oligonucleotides, such as ribonucleic acid (RNA) and single stranded deoxyribonucleic acid (ssDNA) or peptide molecules that can bind to their targets with high affinity and specificity due to their highly specific three dimensional structures. Though RNA and ssDNA aptamers bind to same target entity differing from each other in folding and sequence patterns (Song et al. 2012). They offer many advantages than monoclonal antibodies. They can be synthesized exponentially via chemical route, which is more cost effective than antibodies production. They can withstand high temperature, and thermal denaturation of aptamers is reversible (Han et al. 2010). Aptamer targeted nanoparticles proved to be highly effective in targeting prostate cancer cells and thereby decreasing tumor size (Farokhzad et al. 2006). Multimodal nanoparticle conjugated with aptamer AS1411 is used to detect nucleolin, a protein expressed commonly on the surface of cancer cells membrane, making it possible to image and detect the presence of cancer. Aptamer conjugated nanoparticles (ACNPs) can be used to detect accurately biomarkers and cancer cells even at very low concentrations (Chang et al. 2013).

APTAMERS APPLICATIONS

Blockade of angiogenesis and cancer

Angiogenesis generally occurs during the body growth and wound healing which is vital in various disease states, like cancer and diabetic retinopathy. It has been found that whenever aptamers are ligated with vascular endothelial growth factor (VEGF) have successfully inhibited VEGF binding to its receptors molecules and inhibited *in vivo* growth of blood vessel or angiogenesis and tumors growth (Hasegawa et al. 2008). Plasminogen is the key serine protease in the fibrinolytic system and also involved in tumor invasion and metastasis activities. Introduction of vectors expressing aptamers against plasminogen and plasmin into cancerous cells have been resulted in successful destruction of metastasis in mice (Lupold et al. 2002; Zhai et al. 2001). According to the recent research, the first cancer therapeutic aptamer is introduced as aptamera (AS1411), currently in phase I trials in human beings (Ireson et al. 2006). This particular aptamer forms an intracellular complex with nuclear factor known as κB (NF-κB) essential modulator and nucleolin and hence inhibits activation of NF-κB factor (Girvan et al. 2006). Successful therapeutic potential of aptamera in cancer will definitely bring some more new aptamers based therapeutic molecules in the medical science.

Aptamers and thrombosis treatment

Thrombin is the important enzyme involved in the thrombosis and haemostasis regulation. Current anticoagulant and antithrombotic therapies work on the basis of low molecular weight heparin and coumarin (Nobile, 1998). Both therapies demands extensive monitoring of the patients during drug administration to prevent sudden side effects like systemic hemorrhage. These therapies are not suitable and applicable for long term disease treatment and in case of severe symptoms, it is impossible to cope up with the severe situations. Recently, a number of aptamers have been developed which acts as antithrombotic agents. These molecules bind specifically with thrombin enzyme, prevents its activity. Highly specific action of aptamers has been successful in inhibiting clotting without any side effects. The potential of aptamers as therapeutic agents are the best substitute against present therapies (Haung et al. 2001). Recently, it has been found that RNA aptamer deployed in targeting of von willebrand factor (VWF) has been resulted in successful inhibition of VWF mediated platelet adhesion and aggregation. By successful targeting of VWF mediated platelet adhesion, it has been demonstrated that the aptamer molecules can also prevent platelet aggregation in ristocetin induced platelet aggregation assays.

AIDS gene therapy

Among the recent treatment therapies, aptamers have also been employed in gene therapy of AIDS. Aptamer mediated gene therapy basically involves vectors which express aptamers against the human immunodeficiency virus-1 (HIV-1) proteins, mainly integrase, reverse transcriptase and nucleocapsid proteins (e.g. NCp7) (Symensma, 1996; Jing, 1997). It was also observed that the aptamers such as rev-decoys have the potential in preventing virus expression successfully. Aptamer mediated gene therapy against HIV reverse transcriptase resulted in more than 75% deduction in viral replication (Jing, 1997). It has been observed that application of these vectors *in vivo* may be resulted as a potential therapy for the HIV infection.

Aptamers as nanoprobe

Aptamers can be deployed easily against any target molecule. Their target molecules involve simple ions, small molecules and peptides to complex proteins, organelles, viruses and even an entire cell (Murphy et al. 2003; But et al. 2001; Shangguan et al. 2008). Aptamers can also identify various kinds of chemical targets covering organic, inorganic compounds and all kinds of biomolecules such as saccharides, glycosides, antibiotics, vitamins, dopamine, cocaine and adenosine (Mannironi, 1997; Baker et al. 2006; Zayats et al. 2006). Aptamers against any target molecule can be synthesized through a series of *in vitro* selection tests known as selective expansion of ligands by exponential enrichment, SELEX. This method has the potential applications in exact identification of aptamers which bind with high affinity and specificity with their target molecules (Golden et al.

2000; Shamah et al. 2008). In this process, aptamers are firstly isolated from an extremely large collection of random nucleic acid such as RNA or DNA sequences, generated from sequential randomized solid phase synthesis of oligonucleotides. Affinity chromatography is applied for nucleic acid isolation with specific and selective binding properties to the target molecules. The molecules of interest (targets or ligands) are first immobilized on sepharose or synthetic beads and then treated with a solution containing random nucleic acids. Bound nucleic acids (aptamers) are then isolated, purified and characterized (e.g., sequencing). The selection procedure has now been converted to an automated *in vitro* process, which helps in the high throughput selection against infinite target molecules (Ellington et al. 2006). Isolated aptamers can be easily modified chemically by routine process, or can be amplified indirectly by cloning into an appropriate vector or directly using PCR or RT-PCR (Kaur, 1997).

DIVERSE NANOTECHNOLOGY THERAPIES AND CANCER TREATMENT

BrachySil

It is a tiny structure approximately one millionth of a meter in size and consisted of modified particles of silicon impregnated with the radioactive isotope of phosphorus 32^P. Unlike other radiation treatments, it involves highly focused radiation beams at the tumours site. BrachySil is injected directly at the cancer site using a fine gauge needle. By using 32^P, the radiation is limited to a range of just 8 millimetres, resulting in the destructions of only tumour cells rather than healthy cells. For several years, doctors have been using a similar technique known as brachytherapy, which involves the injection of radioisotopes directly at the tumour sites.

The difficulty faced in this particular technique is that the injected material would not remain longer at the cancer site, but over the period of time, it could be carried to other parts of the body. The main advantage of employing brachySil is its silicon structure, preventing the leakage of radioisotope material which enable the efficient focusing of radiation doses at the tumour sites. The silicon eventually breaks down and is excreted. 32^P, half life of 14 days, eventually decomposes into stable isotopes or is excreted. As, brachySil therapy is highly localized and side effects encountered are very less than other forms of brachytherapy. None of the side effects have been observed to date in deploying brachySil in cancer treatment. BrachySil is basically consisted of very tiny pockets made up of silicon micro particles. The pores or holes in the silicon pocket are the size of about 10 atoms. Radioactive phosphorus is bombarded at the cancer sites. Focused bombardment of radiation doses enables cancer treatment to a broader range than the other forms of brachytherapy, which is currently limited to prostate and liver cancer treatment (Weissleder et al. 2005).

Nanowires

Nanowires by nature have incredible properties of selectivity and specificity. Nanowires can be engineered to sense and pick up molecular markers of cancer cells (Fig. 2). Laying down the nanowires across a micro fluidic channels and allowing cells or particles to flow through it and then nanowires detect the presence of genes or biomarkers associated with cancer and relay the information via electrical connections to doctors and researchers.

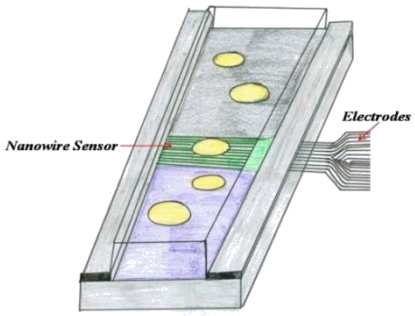

Figure 2 Nanowire detects biomarkers of cancer (adapted from Singh and Nehru, 2008).

Nanowires help in pinpointing the changes associated with the cancer genetics. Nanowires can be coated with a probe such as an antibody which can bind specifically with a target protein. Whenever, proteins bind with antibody, change the nanowires electrical conductance and can be further measured by a detector. Recently, Jim Heath, a nanotechnology researcher at California Institute of Technology has designed a nanowire detector. Each nanowire bears a different antibody or oligonucleotide, used for recognition of specific RNA sequences. They have started testing of biochip for detection of proteins secreted by cancer cells (Wang et al. 2004).

Carbon nanotube (CNT)

Nanotubes are smaller than nano pores. Nanotubes and carbon rods, about half the diameter of a DNA molecule, helps in the identification of changes in DNA molecule associated with cancer. It helps to exactly pin point location of the molecular changes associated with cancer. Mutated regions associated with cancer are first tagged with bulky molecules. Using a carbon nanotube tip, resembling the needle in a record player, the physical shape of the DNA molecule can be traced. A computer translates this information into topographical map. The bulky molecules identify the regions on the map where mutations are present. Since the mutations location can influence the effects they have on a cell, this particular technique will be beneficial in predicting and detecting diseases in the living entities (Zhang et al. 2009).

Cantilevers

These are the tiny bars anchored at one end, can be engineered to bind to molecules associated with cancer. These molecules may bind to altered DNA

proteins, present only in certain types of cancer (Fig. 3). This will change the surface tension and cause the cantilevers to bend (Weinberg, 2005). By monitoring the bending of cantilevers, it would be easier in detection of molecules associated with cancer and hence will enable us to detect earlier molecular events in cancer development.

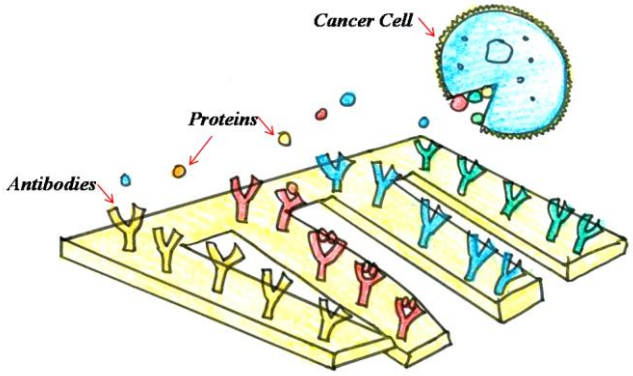

Figure 3 Cantilevers detect biomarkers of cancer (adapted from Singh and Nehru, 2008).

Nanopores

Nanopores allow DNA to pass through one strand at a time and hence DNA sequencing can be made more efficient. Thus, the shape and electrical properties of each base on the DNA strand can be monitored easily (Zubieta, 2006). As these properties are unique for each of the four bases making up the genetic code, the passage of DNA through a nanopore can be used to decipher the encoded information, including errors in the code known to be associated with cancer.

Quantum Dots (QD)

These are tiny semiconductor crystals, glow when are stimulated by ultraviolet light (Manna et al. 2002). The latex beads filled with these crystals when stimulated by light, the color they emit act as dyes that light up the sequence of interest (Fig. 4). By combining different sized quantum dots within a single bead, probes can be created which emit a distinct spectrum of various colours and intensity of light, serving as sort of spectral bar code (Hines et al.1996).

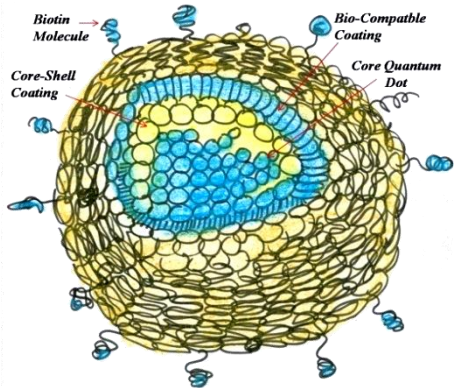

Figure 4 Sample quantum dot with bio-coating (adapted from Torchilin, 2008).

QUANTUM DOTS APPLICATIONS

Fixed cells and tissue imaging

The application of quantum dots for antigen detection in fixed cellular monolayers was first demonstrated in 1998 (Bruchez et al. 1998). The simultaneous detection of the two spatially distinct intracellular antigens such as nuclear antigen and F-actin filaments have been achieved successfully by labelling of target antigens with green silica coated CdSe/ZnS quantum dots and red quantum dots in fixed mouse fibroblasts. For cellular labelling investigations, quantum dots enable in achieving the desirable results as these are approximately 20 times brighter and more photo stable over many weeks after injection than organic fluorophores (Chan et al. 1998). Recently, it has also been investigated that specific genomic sequences and antigens in tissue sections have been labeled using quantum dots (Sukhanova, 2004).

Live cell bio imaging

Live cell imaging is a highly complex task as compared to fixed cells and tissues due to the care that must be taken to keep cells alive and due to the challenge of delivering probes across the plasma membrane for investigating intracellular targets. Quantum dots have been extensively employed for in vivo labelling of cell surface antigens (Chan et al. 1998). It has been found that covalently conjugated mercaptoacetic acid coated CdSe/ZnS quantum dots to the transferrin protein, quantum dots were spontaneously endocytosed by cancer cells and retained their bright fluorescence, indicating that quantum dots can be applied as intracellular labels. For intracellular staining of cells, poly (ethylene glycol)-coated CdSe/ZnS quantum dots with green emission were injected into single cells of a xenopus laevis embryo (Dubertret et al. 2002). Microscopic fluorescence imaging enables real time monitoring of cell lineage and differentiation. Even though, most of the embryos exhibited normal development, and there was no evidence of toxicity, even with the injection of more than one thousand million quantum dot particles per cell. Recently, the advantages of quantum dots for live cell imaging have been demonstrated by labelling plasma membrane receptors, such as glycine receptors (Dahan et al. 2003) and erbB/HER receptors (Lidke, 2004) enabling real time tracking of biomarkers and imaging single molecules. Targeting of quantum dots to specific cytoplasmic or nuclear locations for monitoring biological events is a very difficult task as the plasma membrane barrier and the entrapment of quantum dots in the endocytic pathway has to be circumvented. Different mechanisms have been investigated for quantum dots delivery into the cells including microinjection (Dubertret et al. 2002), non specific uptake of quantum dots through endocytosis (Jaiswal et al. 2003), quantum dots conjugation to translocating proteins (Chan et al. 1998) or cationic peptides, or specific membrane

receptors (Lidke, 2004). All these techniques have been investigated for successful delivery of quantum dots into cells.

Immunoassays

The applications of quantum dots in immunology especially in immunoassays have been extensively investigated. Harma et al. (2001) has developed a fluoro immunoassay for the detection of prostate specific antigen (PSA). This assay was performed incorporating streptavidin coated QDs having size of 107 nm consisting of β-diketones entrapping N 30,000 europium molecules. This assay demonstrated a detection limit of 0.38 ng/L for biotinylated PSA and employed a time resolved fluorometer for signal detection. PSA detection was performed in both solid and liquid phases, and visualization of individual PSA molecules was also possible with fluorescence microscope. Goldman et al. (2004) has also performed another multiplex immunoassay for the detection of cholera toxin, ricin, shiga like toxin, and staphylococcal enterotoxin B incorporating the relevant antibodies conjugated to QDs of different sizes. QDs excitation was achieved using a single wavelength and toxin concentration of 30 ng/mL and 1000 ng/mL were investigated, and the signals were detected simultaneously. These quantum dots based immunoassays are significantly simpler and efficient as compared to the studies performed using different organic fluorophores.

Drug delivery

Surface functionalized QDs have potantial in targeting of specific sub cellular targets (Alivisatos et al. 2005; Hoshino et al. 2004). Peptide coated QDs can be internalized after cell surface binding and therefore will be vital carrier for drug delivery (Akerman et al. 2002; Rozenzhak et al. 2005) QDs can also be employed for controlled drug delivery applications deploying their surface modifications (Alivisatos et al. 2005). This kind of work has already been demonstrated by Lai et al. (2003) which has used surface modified CdS QDs as chemically removable caps to retain drug molecules and neuro transmitters inside mesoporous silica nanospheres. The CdS cap confirms the drug is inside the system until released by disulfide bond reducing reagents. The QDs also inhibit the leakage of pharmaceutical molecules of a defined size outside the spheres prematurely (Alivisatos et al. 2005; Lai et al. 2003).

Nanoshells (NS)

These are another recent invention. NS are miniscule beads coated with gold (Oldenburg et al. 1999). By manipulating the thickness of the layers making up the NS, the beads can be designed in such a fashion so that these can absorb specific wavelength of light. The most useful nanoshells are those which absorb near infrared light and can be easily penetrate several centimetres inside human tissues. Absorption of light by nanoshells create an intense heat which is lethal for cancer cells (Bradbury, 2003). Nanoshells can be linked to antibodies that recognize cancer cells. In laboratory culture experiments, it has been investigated that the heat generated by the light absorbing nanoshells has successfully destroyed tumor cells while leaving neighbouring cells intact without any harm (Brongersma, 2003).

Dendrimer

In the current scenario, various nanoparticle facilitate drug delivery are being developed. One such molecule having potential to link treatment with detection and diagnostic is known as dendrimer (Fig. 5 a and b). Dendrimers are highly branched structures which provide them large surface area to volume ratio by which high payloads of therapeutic agents or biologically active molecules can be attached with them. A single dendrimer can carry therapeutic agent to kill those cells and a molecule that recognizes the cell death signals (Cheng et al. 2008). It is hoped that dendrimers can be manipulated to release their contents only in the presence of certain trigger molecules associated with cancer. Following drug release, dendrimers may also report back whether they are successfully destroying their targets. The technologies mentioned above are still in the various stages of discovery and development. Some of the technologies like quantum dots, nano pores and other nanodevices might be available for detection and diagnosis and for clinical uses within next ten years (LaVan, 2003).

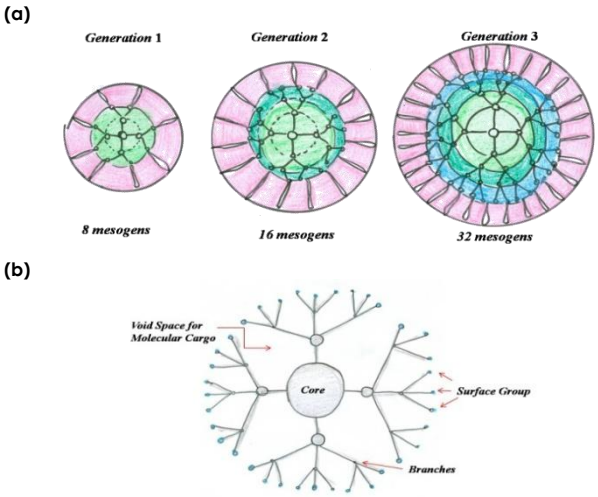

Figure 5 (a) Carbosilane LC dendrimers, (b) 2nd Generation dendrimer (adapted from Han et al. 2010)

Fullerenes

Fullerenes are quite stable molecules, making them good candidates for safe delivery of highly toxic substances to tumour sites. Fullerenes are consisted of large carbon cage molecules. Some of them are C60, C70, C76 and C84. The most common one is C60, also called as buckyball. The subscripts, of course, refer to the number of carbon atoms that can be found in the structure (Chang et al. 2013).

Magnetic Nanoparticles

Magnetic nanoparticles contain an iron oxide core particle, having size in the range of 1 to 100 nm and are generally super paramagnetic in nature (Fig. 6) (Lu et al. 2007). The iron oxide core facilitate enhanced magnetic behavior when combined with antigens that recognize and detect the tumor cell by MRI or magnetic trapping of cancer cells. Research studies have demonstrated that cobalt and iron oxide core magnetic nanoparticles conjugated with Ephrin A2, a protein, expressed at high levels on the surface of free floating ovarian cancer cells and finally Ephrin A2 positive cells are magnetically trapped and removed and hence reducing the chances of metastases (Scarberry et al. 2011).

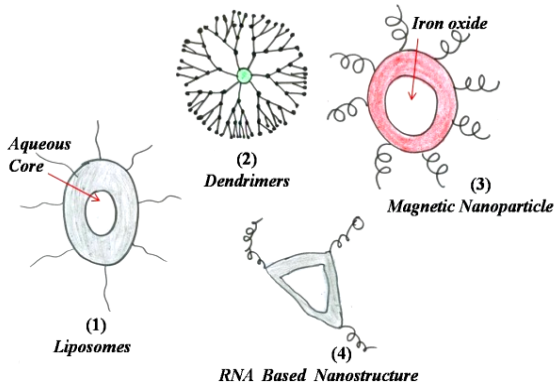

Figure 6 Some nanoscale objects application in cancer treatment (adapted from Han et al. 2010)

Pros and Cons associated with Conventional and Nanotechnology therapies

In the current scenario, there are many ways to treat cancer. Currently, cancer is being treated by deploying conventional as well as nanotechnology therapies. Both of the therapies have some advantages as well as disadvantages. The pros associated with the conventional therapy is that they are being employed since from many years and quite cheaper than modern therapies like nanodevices which are very costly and only few of the patients can afford them. Some of the conventional therapies enable successful destruction of cancer cell like surgery and chemotherapy but the disadvantages of these therapies are that they have various side effects like hair loss, upset stomach, generalized weakness, fever, vomiting, and difficulty in swallowing. Nanotechnology therapies are advanced therapeutic tool in the medical science offering better treatment with good recovery rate as well as real time monitoring of the ongoing therapy. Nanotechnology applications in cancer treatment are really having tremendous potential for the effective and efficient cancer destruction as these therapies are target specific, bio acceptable and offer rapid and prolonged circulation of therapeutic agents inside the living system. There are some disadvantages also apart from the advantages of these therapies as these are new and will take some more time for people to accept as some of the nanotechnology therapies are still in the clinical trials. These modern therapies are also costly than the conventional therapies. The major disadvantages associated with nanotechnology therapies is of toxicity concern of various nano materials deployed because it is still uncertain how much toxicity might be caused. After careful considering the pros and cons of conventional and nanotechnology therapies for cancer treatment, it is concluded that nanotechnology therapies are definitely more beneficial, effective and would definitely be favourable for the cancer patients in the upcoming time so that cancer patient would not compromise more with their money, time and more important their precious health.

Conclusion

Nano devices represent a novel and exciting frontier in cancer management. Unique properties of nano materials help medical experts to concentrate more on nano devices as these can penetrate easily through biological barriers where even small molecules cannot pass through. Nanoparticles can be modified in several ways to improve drug target localization, enhance drug efficacy and drug delivery of therapeutic agents to target cells and within specific organelles and potentially reduces chances of multi drug resistance. Nano devices are also capable in rapid cancer biomarkers detection. Hence, keeping in view the importance of the nanotechnology, we can finally conclude that nano device potential has made cancer screening as well as treatment much faster and cost effective and nanotechnology will definitely bring a positive hope among the various researchers investigating globally in this direction with fruitful results (Table 1).

Table 1 Various Conventional and Nano-technology strategies for cancer treatment

Conventional	Nanotechnology	References
Surgery	brachySil	Weissleder et al. 2005
Chemotherapy	Nanowires	Wang et al. 2004
Radiation	Carbon nanotubes	Zhang et al. 2009
Biological	Cantilever	Weinberg, 2005
Hormonal	Nanopores	Zubieta, 2006
Vaccine Therapy	Quanum dots	Sukhanova, 2004
Gene Therapy	Nanoshell	Brongersma, 2003
Bacteria Therapy	Dendrimer	Cheng et al. 2008
Curcumin Therapy	Fullerens	Chang et al. 2013
Oncolytic Virotherapy	Magnetic nanoparticles	Scarberry et al. 2011

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