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Nanotechnology Used in Cancer Disease

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ABSTRACT: Cancer is a leading cause of death and poor quality of life globally. Although many strategies have been devised to reduce mortality, alleviate chronic pain, and improve quality of life, the adequacy of these cancer treatments remains lacking. Early detection of cancer cells and using drugs with high specificity to reduce toxicity are among the key steps to ensure optimal cancer treatment. Due to increased systemic toxicity and refractoriness with traditional cancer diagnostic and therapeutic tools, other strategies, including nanotechnology, are being used to improve diagnosis and reduce disease severity. Nanotechnology has the potential to increase the selectivity and potency of chemical, physical, and biological approaches to abrogate cancer cell death while minimizing collateral toxicity to non-malignant cells. In the fight against cancer, early detection is a key factor for successful treatment. However, the detection of cancer in the early stage has been hindered by the intrinsic limits of conventional cancer diagnostic methods. Nanotechnology provides high sensitivity, specificity, and multiplexed measurement capacity and has therefore been investigated for the detection of extracellular cancer biomarkers and cancer cells, as well as for in vivo imaging. This review summarizes the latest developments in nanotechnology applications for cancer diagnosis. In addition, the challenges in the translation of nanotechnology-based diagnostic methods into clinical applications are discussed.

KEYWORDS: Nanotechnology, nanoparticle, drug, cancer

I. INTRODUCTION:

The word ‘nanotechnology’ was coined by Tokyo science university professor Norio Taniguchi, in 1974, and since then it is been used. Basic definition of nanotechnology includes – any technology which deals at nanoscale is called nanotechnology. Nano size refers to 10-9 of a particular unit thus nanometer is 10-9 of a meter. Nanotechnology is a multidisciplinary field covering areas like electronics, molecular biology, biophysics, physics, engineering, medical and pharmaceuticals. This study includes controlling of atom in an atomic or molecular scale. The properties of material/particle at nanoscale are different than that of macro scale, and this nano scale particles are called as nanoparticles. Nanoparticles are of 10-1000 nm range as particulate dispersions or solid particles. In relation to pharmaceuticals; nanoparticles, nanospheres, or nano capsules can be obtained depending on its method of preparation. The drug can be dissolved, trapped, encapsulated or attached to a matrix of nanoparticles. Less expensive and much quicker treatments can be developed by use of nanotechnology in pharmaceutical field. Precise drug delivery can be achieved with the help of nanotechnology. Therefore, nanotechnology is playing an important role in development of pharmaceutical field.

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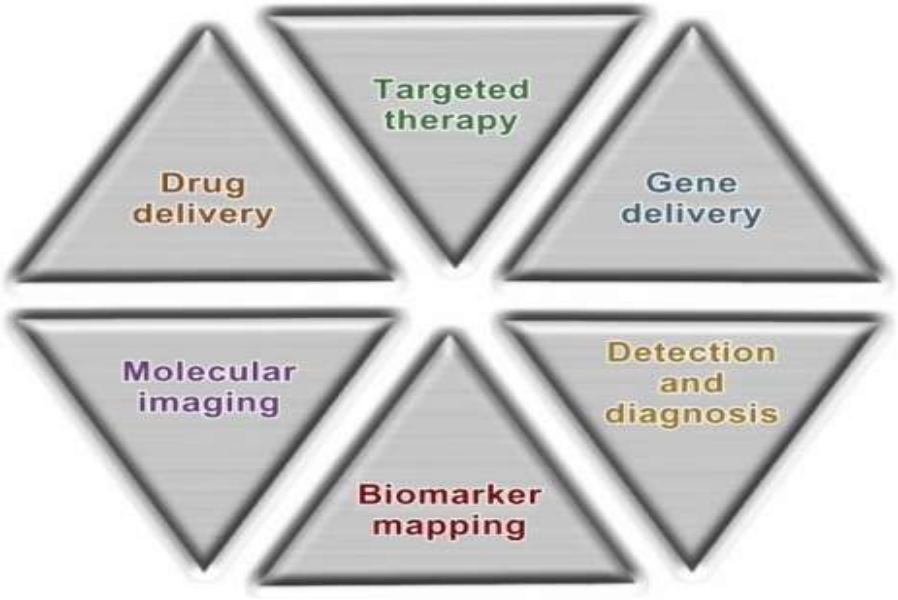

Figure 1: Biomedical applications of nano-therapeutics.

The scope of pharmaceutical nanotechnology is very wide and some of them are listed below

1. Tissue engineering
2. Nano medicines
3. Nano robots
4. Biosensors
5. Biomarkers
6. Intelligent tools for delivery of drugs.
7. Image enhancement device
8. Bioactive surfaces
9. Implant technology
10. Tools for and diagnostics
11. Artificial RBC

II. NANOTECHNOLOGY USED IN CANCER :

Human cancer is a complex disease caused by genetic instability and accumulation of multiple molecular alterations. Current diagnostic and prognostic classifications do not reflect the whole clinical heterogeneity of tumors and are insufficient to make predictions for successful treatment and patient outcome. Most current anticancer agents do not greatly differentiate between cancerous and normal cells, leading to systemic toxicity and adverse effects. In addition, cancer is often diagnosed and treated too late, when the cancer cells have already invaded and metastasized into other parts of the body. At the time of clinical presentation, for example, more than 60% of patients with breast, lung, colon, prostate, and ovarian cancer have hidden or overt metastatic colonies. At this stage, therapeutic modalities are limited in their effectiveness. Due to these problems, cancer has overtaken heart disease as the leading cause of death for adults in the United State.

Current problems and unmet needs in translational oncology include:

a) advanced technologies for tumor imaging and early detection,
b) new methods for accurate diagnosis and prognosis,
c) strategies to overcome the toxicity and adverse side effects of chemotherapy drugs, and
d) Basic discovery in cancer biology leading to new knowledge for treating aggressive and lethal cancer phenotypes such as bone metastasis. Advances in these areas will form the major cornerstones for a future medical practice of personalized oncology in which cancer detection, diagnosis, and therapy are tailored to each individual's tumor molecular profile and also for predictive oncology in which genetic/molecular markers are used to predict disease development, progression, and clinical outcomes.

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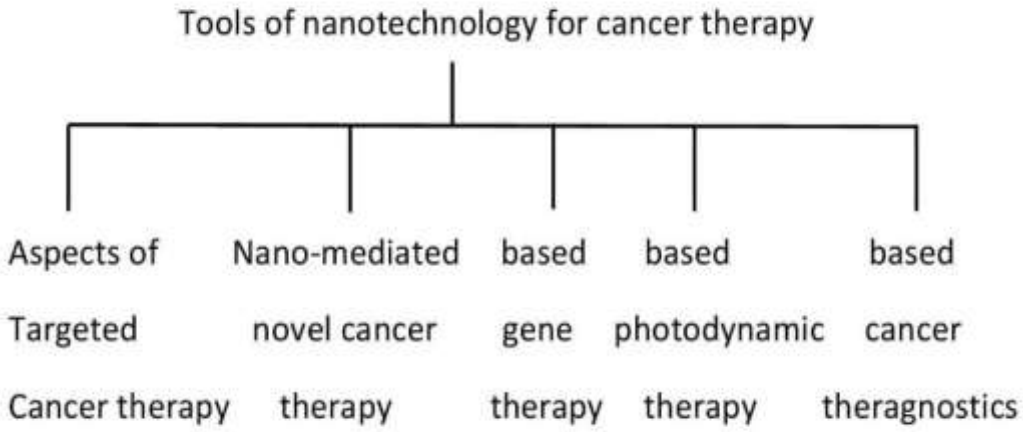

Aspects of targeted cancer therapy:

Ideally, for anticancer drugs to be effective in cancer treatment, they should first (after administration) be able to reach the desired tumor tissues through the penetration of barriers in the body with minimal loss of volume or activity in the blood circulation. Second, after reaching the tumor tissue, drugs should have the ability to selectively kill tumor cells without affecting normal cells with a controlled release mechanism of the active form. These two basic strategies are also associated with improvements in patient survival and quality of life, by simultaneously increasing the intracellular concentration of drugs and reducing dose-limiting toxicities.

Nanotechnology-mediated novel cancer therapy:

In the treatment of cancer, targeted treatment – in which only cancer cells are killed and normal cells are not harmed – has become increasingly desirable. The introduction of nanotechnology has brought new materials and pathways for the targeted treatment of cancer. Engineered properties of nanoparticles are opening the door to new, non-invasive strategies for cancer therapy that were not previously possible, including nanotechnology-based advance cancer therapy strategies such as photodynamic therapy (PDT), radiotherapy and radiofrequency therapy, and theragnostics

Nanotechnology-based gene therapy:

Gene therapy is based on the concept that specific exogenous genes can be incorporated into the tumor cell genome to produce a tumoricidal effect. It represents one of the most rapidly developing areas in preclinical and clinical cancer research. Although viral vectors have traditionally been the primary agents used to deliver genes to target cells, they carry the risk of serious immune and inflammatory responses in the host. The problem associated with the viral vector is the toxicity, immune and inflammatory responses, gene control and targeting issue; in addition, there is always a fear of the virus recovering and causing disease.

Nanotechnology-based photodynamic therapy:

PDT is an alternative to current adjuvant therapy that carries little local or systemic treatment-associated morbidity and is not susceptible to the development of resistance. It involves the administration of a photosensitizing drug. PDT relies on activation of a photosensitizer, which – when activated by a specific wavelength of light – induces the release of reactive oxygen species that can kill tumor cells directly, as well as the tumor-associated vasculature, leading to tumor infraction.

Nanotechnology-based cancer theragnostics:

Combining diagnosis and therapy in one process is an emerging biomedical method referred to as theragnostics. The primary goal of theragnostics is to selectively target-specific (diseased) tissues or cells to increase diagnostic and therapeutic accuracy. With the help of theragnostics, we can bring together key stages of a

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medical treatment, such as diagnosis and therapy, and make a treatment shorter, safer and more efficient. Several theragnostic methods have employed nanoparticles as the carriers of diagnostic agents and drugs. Biocompatible nanoparticles are currently under development as cancer theragnostic agents that would enable non-invasive diagnosis and precise cancer therapy.

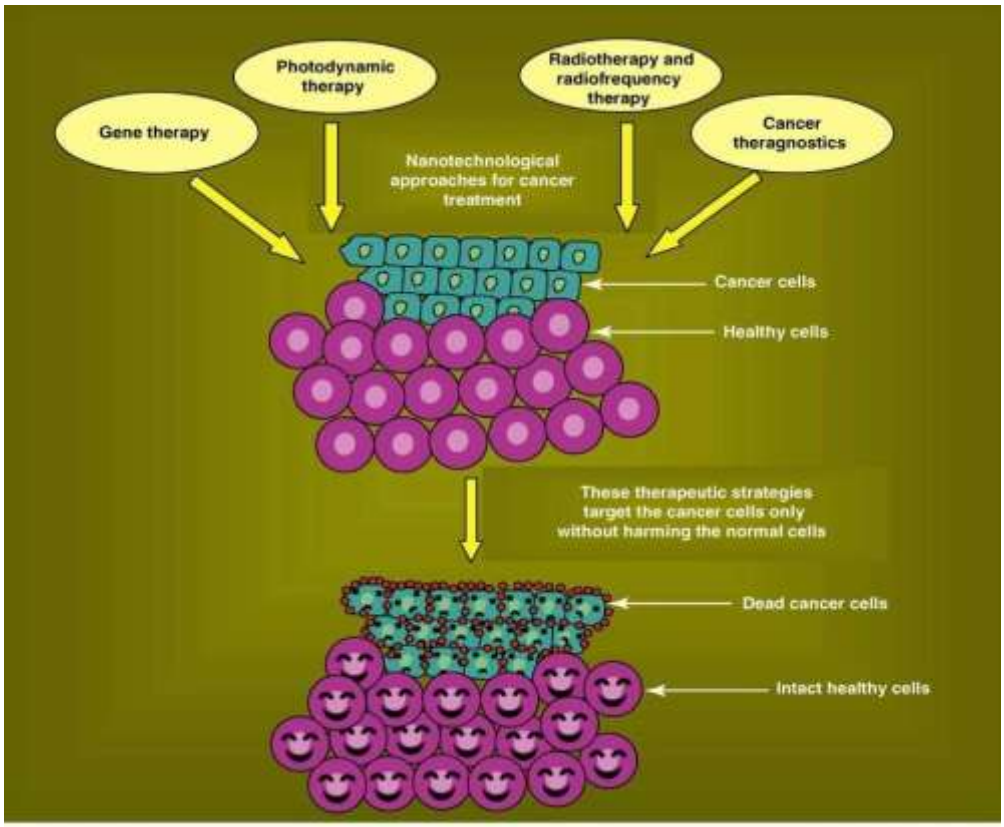

Figure 2: Tools of Nanotechnology

III. TYPES OF NANOTECHNOLOGY TO TREAT CANCER :(11 BOLD)

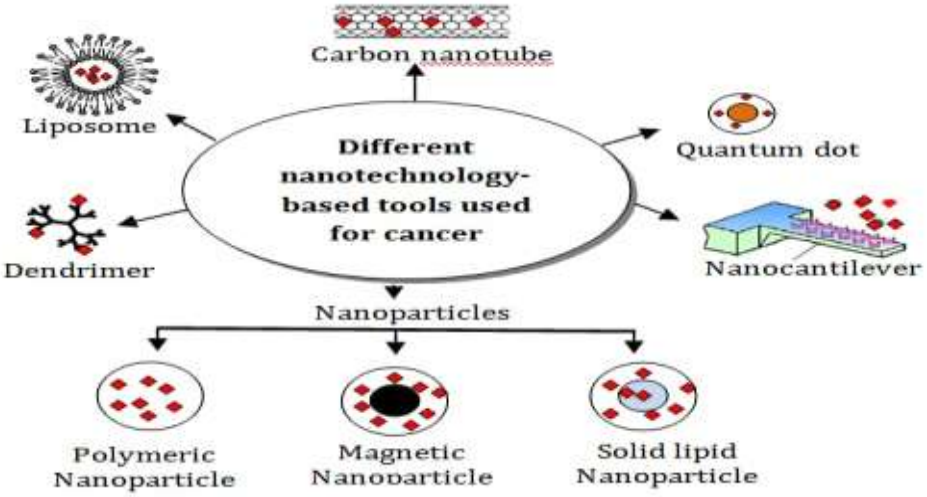

Figure 3: Types of Nanotechnology

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1. Liposome: Liposomes have become very versatile tools in biology, biochemistry and medicine because of their enormous diversity of structure and compositions. Examples of liposome-mediated drug delivery are doxorubicin (Doxil) and daunorubicin (Daunoxome), which are currently being marketed as liposome delivery systems. Polyethylene glycol (PEG) ylated liposomal doxorubicin (Doxil1, Caelyx1; Alza Pharmaceuticals, San Bruno, CA, USA) has achieved the most prolonged circulation to date, with a terminal half-life of 55 hours in humans. These PEGylated (also referred to as sterically stabilized, or 'Stealth') liposomes display inhibited interaction with plasma proteins and mononuclear phagocytes and, consequently, display greatly prolonged circulation time. A similar approach was utilized by packaging therapeutic molecules inside a liposome and decorating the surface of liposome using molecular 'Trojan Horse' technology. Zhang et al. prepared OX-26-transferrin-targeted PEGylated immunoliposomes carrying expression plasmids of gene encoding tyrosine hydroxylase, and promising results were obtained in a rat model for Parkinson's disease. Leamon et al. have recently evaluated the in vitro and in vivo status of the delivery of oligonucleotides encapsulated in folate-coated liposomes. Moreover, folate-receptor-targeted liposomes have proven effective in delivering doxorubicin in vivo and have been found to bypass multidrug resistance in cultured tumor cells.

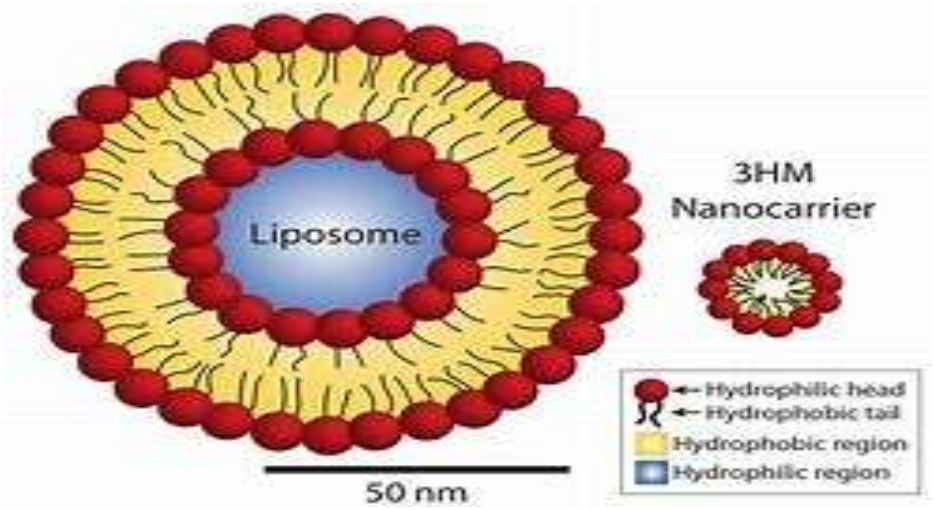

Figure 4: Structure of Liposome

2. Nanoparticles: These are submicron-sized colloidal particles with a therapeutic agent of interest encapsulated within their polymeric matrix or adsorbed or conjugated onto the surface. Nanoparticles are targeted to specific sites by surface modifications, which provide specific biochemical interactions with the receptors expressed on target cells. Another important function of nanoparticles is their ability to deliver drugs to the target site, crossing several biological barriers such as the blood–brain barrier. By coating the nanoparticles with polysorbates, the drug-loaded nanoparticles can be transported across the blood–brain barrier, enabling brain targeting after an intravenous injection. Recently, our group has developed several different potential Nano carrier systems for the treatment of cancer. Acharya et al. have designed epithelial growth factor antibody-conjugated rapamycin-loaded nanoparticles and showed the enhanced efficacy of these formulated immunonanoparticles in MCF 7 breast cancer-cell line. Misra et al. have improved the therapeutic efficacy of the potent anticancer drug doxorubicin by directly targeting the drug to the nucleus of breast cancer cells by conjugating a nuclear localization sequence to the surface of the nanoparticles. Mohanty and Sahoo have formulated a Nano particulate delivery system through the use of glycerol monooleate and

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pluronic F-127 that can solubilize curcumin in aqueous media at clinically relevant concentrations, protect it from hydrolytic degradation and in vivo biotransformation, and deliver curcumin in a controlled manner. It is well recognized that the development of novel approaches for early cancer detection and effective therapy will contribute notably to improving patient survival. New synthetic methods have been developed to control precisely the size and shape of nanoparticles as a means to tune absorption and emission properties. The development of nanoparticles as imaging contrast agents also makes possible the production of multifunctional nanoparticles with a capacity for targeted tumor imaging and delivery of therapeutic agents.

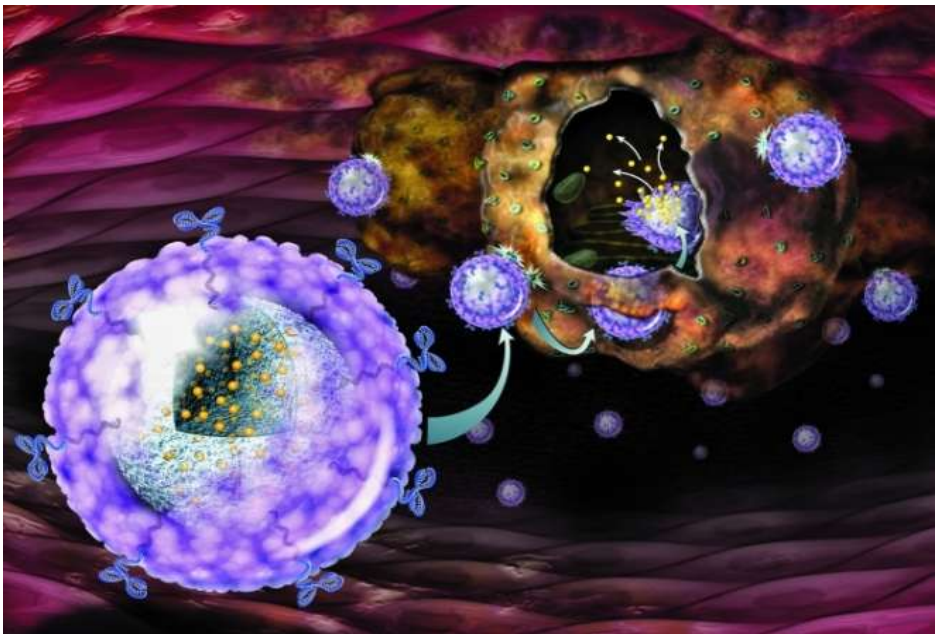

Figure 5: Structure of Nanoparticles

3. Polymeric micelles: A micelle is defined as a collection of amphiphilic surfactant molecules; micelles are turning out to be a keystone in the future of therapeutics. The first polymeric micelle formulation of paclitaxel, Genexol-PM (PEG-poly (D,L-lactide)-paclitaxel), is a cremophor-EL-free polymeric micelle-formulated paclitaxel. A phase I and pharmacokinetic study has been conducted in patients with advanced refractory malignancies. Several polymeric PEG-micelle formulations have entered clinical trials; for example, doxorubicin-loaded polymeric micelle has gone through a phase I clinical trial for solid tumors and shown encouraging results in treating restenosis by encouraging accumulation in vascular lesions. Torchilin et al. have formulated antitumor antibody-conjugated polymeric micelles (immunomicelles), encapsulating the water-insoluble drug Taxol, that effectively recognize and bind to various cancer cells in vitro. Mohanty et al. have developed curcumin-loaded methoxy poly ethylene glycol/poly-e-caprolactone diblock copolymeric micelles and have shown the improved efficacy of the micellar system over the native drug using pancreatic cell lines.

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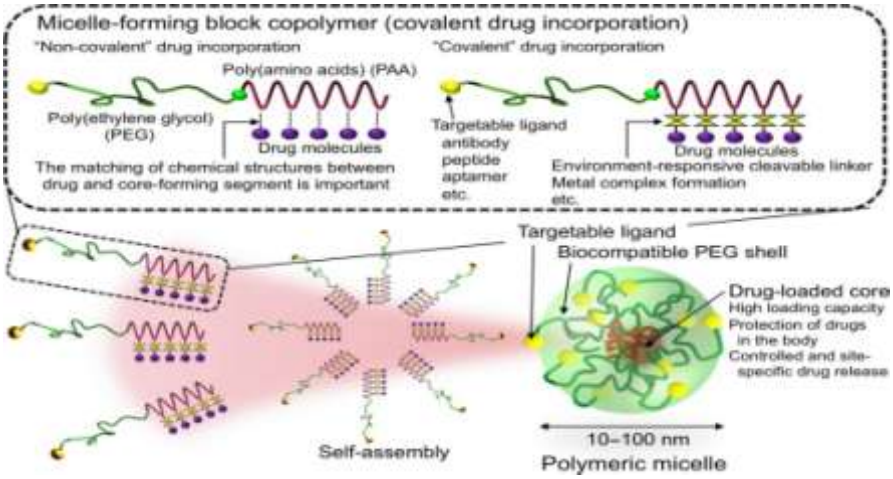

Figure 6: Structure of Polymeric Micelles

4. Dendrimers: Dendrimers are macromolecular compounds that comprise a series of branches around an inner core, the size and shape of which can be altered as desired, and hence serve as an attractive modality for drug delivery. In a recent work by Choi et al. DNA assembled polyamidoamine dendrimer clusters were prepared for cancer-cell-specific targeting. They have prepared dendrimer-5FU conjugates by acetylation, which – upon hydrolysis – release free 5FU, thus minimizing the toxicity of 5FU. The unique architecture of dendrimers enables for multivalent attachment of imaging probes, as well as targeting moieties; thus, it can be also used as a highly efficient diagnostic tool for cancer imaging. Gadolinium-based magnetic resonance imaging contrast agents can operate at an approximately 100-fold less concentration than iodine atoms required for computed tomography imaging. They can be targeted to a single site, which improves the sensitivity of imaging. Phase I clinical trials of Starpharma's dendrimerbased microbicide (VivaGel) are also the first human dendrimer pharmaceutical clinical trials.

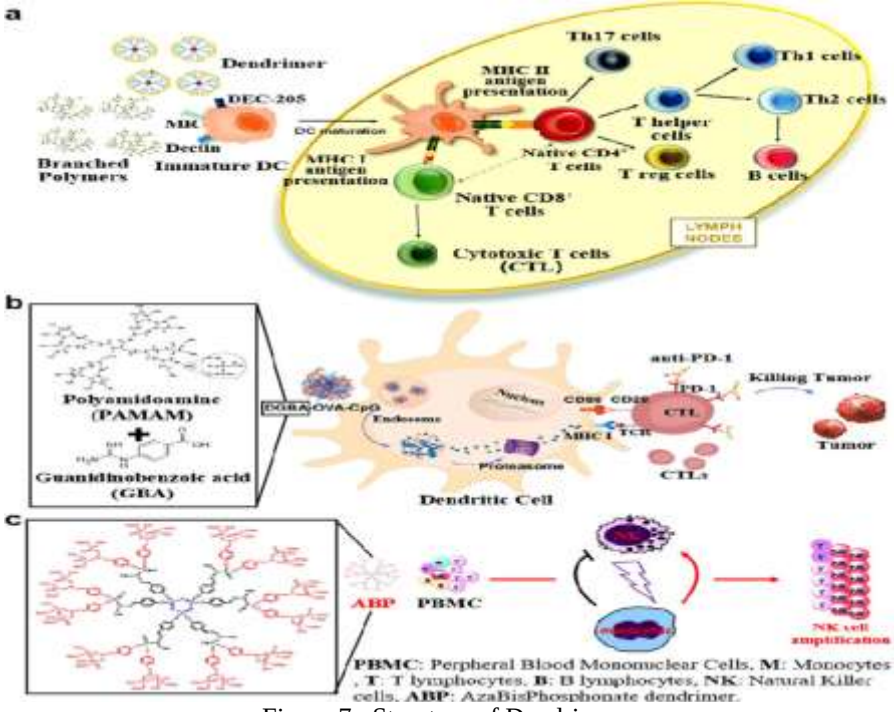

Figure 7: Structure of Dendrimers

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5. Nanocantilever: Microarray methods employing the detection of specific biomolecular interactions are now an indispensable tool for disease diagnosis, genome research and drug discovery. Tiny bars anchored at one end can be engineered to bind to molecules associated with cancer. These molecules can bind to altered DNA proteins that are present in certain types of cancer. During detection procedures, when biospecific interactions occur between a receptor immobilized on one side of a cantilever and a ligand in solution, the cantilever bends; if detected optically, it is possible to tell whether cancer molecules are present and, hence, detect early molecular events in the development of cancer. The deflection of silicon beams depends on the amount of DNA or protein bound to the cantilever surface. The deflection can be observed directly, using laser light, or by measurement of perturbations in their resonant vibration frequency. Arun Majumdar and colleagues used microcantilevers to detect single-nucleotide polymorphisms in a 10-mer DNA target oligonucleotide without the use of extrinsic fluorescent or radioactive labeling. They also demonstrated the applicability of microcantilevers for the quantitation of PSA at clinically considerable concentrations. The breakthrough potential afforded by nanocantilevers resides in their extraordinary multiplexing capability.

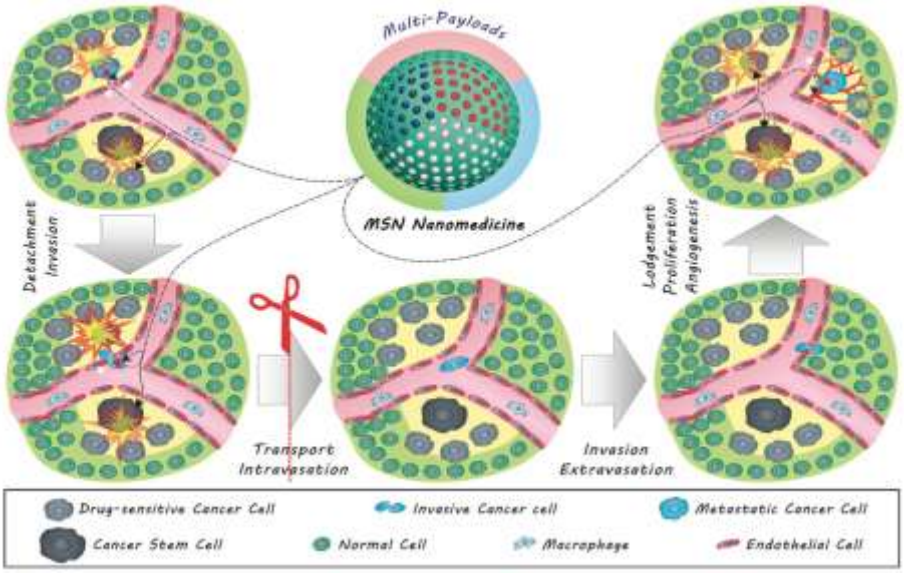

Figure 8: Structure of Nanocantilever

6. Carbon nanotubes: Another type of nanodevice for biomarker detection is the carbon nanotube. Carbon nanotubes are carbon cylinders composed of benzene rings that have been applied in biology as sensors for detecting DNA and protein, as diagnostic devices for the discrimination of different proteins from serum samples and as carriers to deliver drug, vaccine or protein. An emerging field in nanotechnology is the exploration of interesting structural, mechanical, electrical and optical properties of single-walled carbon nanotubes (SWNTs) for biological applications including biosensors, molecular transporters for drug delivery and potential new therapies. The high optical absorbance of SWNTs in the near-infrared regime causes heating under laser irradiation, which is useful for destroying cancer cells that are selectively internalized with nanotubes. Current trends in biomedical imaging have focused on the Near Infrared fluorescence properties of SWNTs and on surface functionalization. NIR fluorescence lies in the biologically transparent region (700–1300 nm) where autofluorescence, absorption and scattering by blood and tissue are minimized. Surface-functionalized multiwalled carbon nanotubes have also been used successfully for bioimaging purposes. In an in vitro study, drugs bound to carbon nanotubes were shown to be more effectively internalized into cells than free drug alone.

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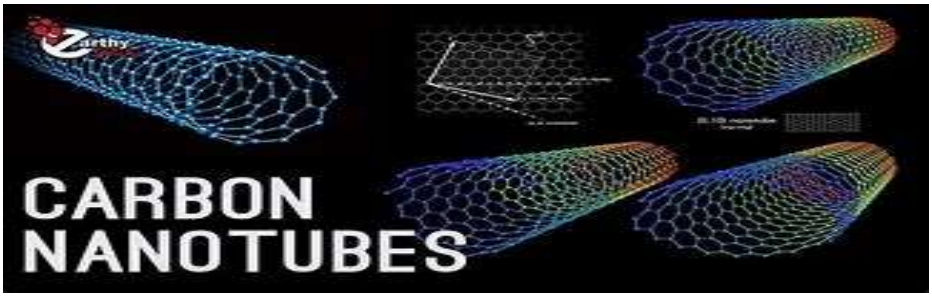

Figure 9: carbon Nanotubes

7. Quantum dots: In recent years, semiconductor quantum dots (QDs) have attracted the attention of many research groups because of their scientific and technological significance in microelectronics, optoelectronics and cellular imaging. Semiconductor QDs are emerging as a new class of fluorescent labels for biology and medicine. The broad absorption and narrow emission characteristics of the QDs make it possible to perform multicolor imaging with a single excitation source. The high fluorescence quantum yield of the QDs, their resistance to photo bleaching and their unique physical, chemical and optical properties make them good candidates for fluorescent tagging for in vivo molecular and cellular imaging. QDs also provide a versatile nanoscale scaffold for designing multifunctional nanoparticles with both imaging and therapeutic functions. For in vivo and intraoperative tumor imaging, QDs hold great promise, mainly because of their intense fluorescent signals and multiplexing capabilities, which could enable a high degree of sensitivity and selectivity. QDs have been the subject of toxicological scrutiny because of their material formulations; however, several groups have reported that with biocompatible surface coatings, such as PEG-silica, QDs can be well tolerated by cells in vitro. Nie et al. first reported that it is feasible to simultaneously target and image prostate tumors in living animal models using bio conjugated, prostate membrane antigen-targeted QDs. The surface of QDs can be engineered or modified to improve QD solubility, sensitivity, specificity and visualization in target tissue.

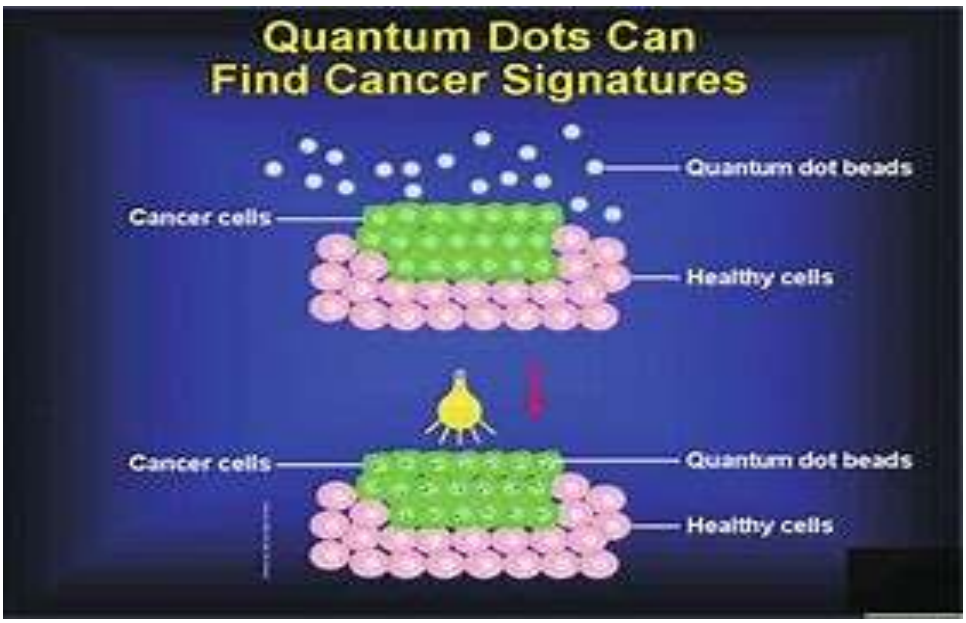

Figure 10: Structure of Quantum Dots

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IV. CONCLUSION

Nanotechnology has shown a lot of promise in cancer therapy over the years. By their improved pharmacokinetic and pharmacodynamics properties, nanomaterials have contributed to improved cancer diagnosis and treatment. Nanotechnology allows targeted drug delivery in affected organs with minimal systemic toxicities due to their specificities. However, as with other therapeutic options, nanotechnology is not completely devoid of toxicities and comes with few challenges with its use including systemic and certain organ toxicities, hence, causing setbacks with their clinical applications. Given the limitations with nanotechnology, more advancements must be done to improve drug delivery, maximize their efficacy while keeping the disadvantages to the minimum. By improving the interactions between the physicochemical properties of the nanomaterials employed, safer and more efficacious derivatives for diagnosis and treatment can be made available for cancer management. In sum, we sought to highlight the key advantages of nanotechnology and the shortfalls in their use to meet clinical needs for cancer. Adding to that, the therapeutic benefits of nanotechnology and future advancements could make them a therapeutic potential to be applied in other disease conditions. These may include ischemic stroke and rheumatoid arthritis which would require targeted delivery of a suitable pharmacologic agent at the affected site.

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