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REVIEW ARTICLE

Emerging Trends of Nanotechnology in Cancer Therapy

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ABSTRACT

Cancer is a malignant disease caused by damage of genes that control growth and division of cells and it is complex as it entails multiple cellular physiologic systems such as cell signaling and apoptosis .it is being missed at its earliest stages because of detection methods that are not directed at cellular changes of carcinogenesis .Non specific systemic distribution , inadequate drug concentrations reaching tumor , inability to monitor therapeutic responses continue to plague the area of clinical oncology . Nanotechnology has the potential to offer solution to these current obstacles in cancer therapy because of its unique size (1-100nm) and large surface-to-volume ratios .The versatility of the nanotechnology platform could allow cellular tracking using single or multimodal imaging modalities. Nanoparticles are being used to detect biomarkers which may help researchers with molecular imaging of malignant lesions and allow physicians to see cells and molecules undetectable through conventional imaging. Additionally photo luminescent nanoparticles may allow oncologists to discriminate cancerous and healthy cells. Clinical investigations suggest that therapeutic nanoparticles can improve patient care and quality of life by reducing off-target toxicities by more selectively directing drug molecules to intracellular targets of cancer cells.

KEYWORDS:

Cell signaling, Apoptosis, Multimodal imaging, Biomarkers, Photo luminescent nanoparticles.

INTRODUCTION:

Cancer is a complex disease caused by genetic instability and accumulation of multiple molecular alterations [1]. It is complex because it involves many cellular physiological systems like cell signaling and apoptosis. Survival of cancer patient largely depends on early detection followed by effective therapy. Nanotechnology deals with particles ranging in size of 1-100nm which are emerging as a class of therapeutics in cancer treatment. Very sensitively designed devices constructed from nanoscale components such as nano cantilevers, quantum dotes, nano tubes, fullerene's, and nano shells offer high potential to detect even the smallest molecular signals associated with malignancy [2]. These nanotechnological tools help in designing early imaging agents and diagnostics that will allow clinicians to detect cancer in earliest, most easily treatable, presymptomatic stage. Multifunctional targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents at high local concentrations with physiologically appropriate timing directly to cancer cells .nanotechnology also enables the technology of developing research tools that will enable investigators to quickly identify new targets for clinical development and predict drug resistance[3]. Nanoparticles offer the potential to overcome drug resistance, since nanoparticles can bypass the P-glycoprotein efflux pump, one of the main drug resistance mechanisms, leading to greater intracellular accumulation.

CANCER DETECTION:

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CONVENTIONAL:

Conventional detection of cancer is done by observing physical growth or changes in organ by X-rays or CT scans and is confirmed by biopsy through cell culture .These methods are not sensitive and are time taking process as detection is possible only after substantial growth of cancerous cells.

NANOTECHNOLOGY BASED:

Exquisitely sensitive devices designed on nanoscale components such as nano cantilevers, nano wires and nano channels offer the potential for detecting even the rarest molecular signals associated with malignancy. Collecting these signals foe analysis can be done by nanoscale harvesters. Detecting mutations and genome instability *in-situ is* another focused area. Investigators already have developed novel nanoscale in-vitro techniques that can analyse genomic variations across different tumor types and distinguish normal from malignant cells. Nanopores are finding use as real-time DNA sequencers, and nanotubes are showing promise in detecting mutations using a scanning electron microscope. Nanoscale technologies capable of determining protein expression patterns directly from tissue using mass spectroscopy. This technique has already shown that it can identify different types of cancer and provide data that correlate with clinical prognosis [4]. Nanotechnology offers the potential for developing highly sensitive imaging agents and *ex-vivo* diagnostics that can determine whether a therapeutic agent is reaching its intended target and whether that agent is stopping (killing) malignant or support cells such as growing blood vessels.

Targeted nanoscale devices may also enable surgeons to more readily detect margins of tumor before resection or to detect micromatastases in lymph nodes or tissues distant from the primary tumor. The greatest potential in this area would focus on detecting apoptosis following cancer therapy. Such systems could be constructed using nanoparticles containing an imaging contrast agent and a targeting molecule that recognizes a biochemical signal seen only when cells undergo apoptosis. Using the molecule annexin V as the targeting ligand attached to nanoscale iron oxide particles, which act as a powerful MRI contrast agent, investigators have shown that they can detect apoptosis in isolated cells and in tumor-bearing mice undergoing successful chemotherapy.

MULTIFUNCTIONAL THERAPEUTICS

Nanoscale devices can contain both targeting agents and therapeutic payloads at levels that can produce high local levels of a given anticancer drug, particularly in areas of body which are difficult to access because of variety of biological barriers, including those developed by tumours. Multifunctional nanodevices also offer the opportunity to utilize new approaches to therapy such as localized heating or reactive oxygen generation and to combine a diagnostic or imaging agent with a therapeutic or even a reporter of therapeutic efficacy of the package.

"Smart "nanotherapeutics provide clinicians the opportunity to time the release of anticancer drug or deliver multiple drugs sequentially in a timed manner or at several locations in the body. Smart nanotherapeutics can be effectively utilized in sustained therapy where the cancers are to be treated chronically or to control quality-of-life symptoms resulting from cancers that cannot be treated successfully. This multifunctional nanotherapeutics can also act as house to "engineered cellular factories" that would make and secrete multiple proteins and other antigrowth factors that would impact both the tumour and its immediate environment.

With the tools like proteomics the list of multifunctional nanoscale therapeutics grows as each newly discovered targeting ligand has its specific function like imaging or targeting. Nanoscale devices containing a given therapeutic agent can be decorated with a given targeting agent be it a monoclonal antibody or F fragments to a tumour surface molecule, a ligand for a tumour-associated receptor, or other tumour-specific marker. In most cases, such nanotherapeutics could double as imaging agents. In some instances, nanoscale particles will target certain tissue strictly because of their size. Nanoscale dendrimers and iron oxide particles of a specific size will target lymph nodes without any molecular targeting. Liver specific delivery can be enhanced by designing the nanoparticles such that the potent chemotherapeutic agent can be taken up by cells of reticulo-endothelial system (RES).nanoscale devices are also used in creating immunoprotected cellular factories capable of synthesizing and secreting multiple therapeutic compounds [5]. The extensive research and concerted effort on cellular factories is developing a hope of making it a powerful multivalent therapeutic agent capable of responding to local conditions in a physiologically relevant manner.

Most of the nanoparticles will respond to an externally applied field, be it magnetic, focused,

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or light, in ways that might make them ideal therapeutics or therapeutic delivery vehicles. For example, nanoparticulate hydrogels can be targeted to sites of angiogenesis, and once they have bound to vessels undergoing angiogenesis, it should be possible to apply localized heat to melt the hydrogel and release an anti-angiogenic drug. Similarly iron oxide nanoparticles, which can serve as the foundation for targeted MRI contrast agents, can be heated to temperatures lethal to cancer cell merely by increasing the magnetic field at the very location where these nanoparticles are bound to tumour cells.

NANOPARTICLES FOR CANCER TARGETING AND DELIVERY:

NANOVECTORS:

Nanovectors act as carriers for the therapeutic and imaging payloads, or their constituent materials might also possess image-enhancement properties, such as in case for iron oxide for MRI, and semi-conductor or nanocrystals or quantum dots for optical imaging. . A typical nanovector consists of a nanoparticle core coated with a targeting agent specific to the target cells and a biomolecule with designated functionality. The nanovector must be detectable by at least one characterization technique to validate its location in vivo and to evaluate its therapeutic effects in a time course. The nanovector specifically targets cancer cells and thus imposes minimal side effects to healthy tissue. For therapeutic payload delivery, a mechanism must be established to release the drug from the nanovector after entry to the target cell to induce cellular apoptosis or inhibit cell migration or proliferation. The molecular targeting of nanovectors containing active agents might be attained by the conjugation of active recognition moieties to the surface of nanovector. Specificity is then increased, at the expense of added complexity in the nanoparticle preparation, increased particle size and the risk of biological adverse reactions to the targeting agent [6]. Molecularly targeted nanovectors have several advantages like, providing selectivity enhancement, carry multiple and potentially different targeting agents, delivery of much higher therapeutic payloads per target misrecognition etc. The delivery of multiple agents results in targeted combination therapy. Nanovector modules like nanocantilever,nanowire and nanotube enable the transition from single-biomarker to multiple-biomarker cancer diagnostic,prognostics and treatment selection.nanoparticles,each with one of many different colours might be conjugated with antibodies to different molecular targets.when irradiated with a light beam of single wavelength,a precise map of the distribution of many molecular markers in a single cell,cell population or tissue is generated.this offers the potential advantage to readily identify conjugate markers and yeilding specific information on their tissue distribution.this also introduces new protocols which include cell surface,endocellular and microenvironmental antigens in the same test.

Nanovectors used for anticancer drug delivery can be made from a variety of materials, including polymers, liposomes, carbon nanotubes, gold and iron oxide nanoparticles, dendrimers etc. Most of the nanoparticles delivery systems that have been approved by FDA or that are in clinical trails are based on polymers or liposome technologies.

POLYMERIC NANOPARTICLES:

Generally the polymeric material that is used for nanoparticles preparation falls under two major categories.

1. **NATURAL POLYMERS**

Eg: dextran, heparin, chitosan, alginates, gelatin, collagen have been investigated.

2. **SYNTHETIC POLYMERS**

Eg: Polyethylene glycols (PEG), polycarprolactone (PCL), polylactic acid (PLA), N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA) have been exploited.

Generally the polymer contains two parts a hydrophobic core which serves as container for anticancer drug and a hydrophilic shell which stabilizes the nanoparticles in aqueous environments.

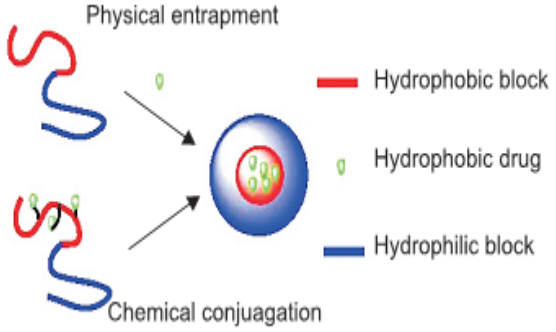

Figure: 1 Polymer based nanoparticles.

A hydrophobic interaction between the core of polymeric nanoparticle and the drug molecule allow the drug to be entrapped in the nanoparticles core .A proper linker is very much important to drug-polymer conjugate as the stability of linker affects the release of nanoparticles. If linker is too stable the drug release is delayed while if the linker is too unstable, drug may be released before the nanoparticles reaches the tumor a variety of pH-sensitive linkers have been developed such as hydrozone and cis aconity [7].

LIPOSOMES: Structurally, liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids (Figure: 2). the molecular geometry and liposome formation can be ascertained by israelachili hypothesis.

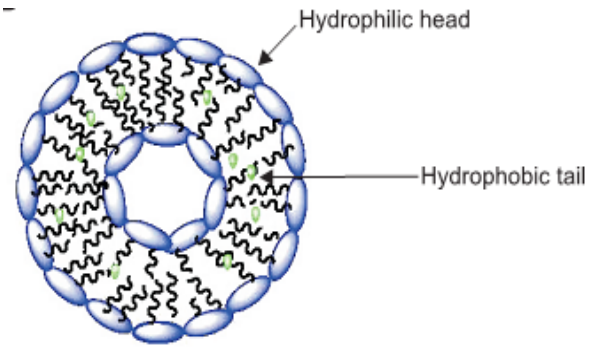

Figure: 2. Liposome based Nano-Particles.

Liposomes can be produced by wide variety of methods. Their nomenclature depends thus on the method of preparation, structural parameters or special functions assigned to them.

Based on structural parameters: MLV, UV, OLV, and SUV.

Based on method of preparation: REV, SPLV, and FATMLV.

Based on composition and applications: conventional liposomes, fusogenic liposomes, pH sensitive liposomes, immune liposomes etc.

Techniques like passive loading and active loading can be effectively used to load the drug material into the liposomes. It has been demonstrated that small and stable liposomes can passively target several different tumours because they can circulate for prolonged times and extravasate in tissues with enhanced vascular permeability, which is often the case with tumours. Their envisioned use is for the *in vivo*, non-invasive visualization of molecular markers of early stages of disease. Liposomes use the over expression of fenestrations in cancer neovasculature to increase drug concentration at tumour sites. Liposomes continue to be refined and applied to more cancer indications. They play a major part in ever-growing number of nanovectors under development for novel and efficacious drug-delivery modalities. Recent trends in research often frequently opt for specially engineered long-circulatory liposomes (stealth liposomes) for long circulation times and increased probability. Liposomes based imaging agents have already been successfully used fir gamma-, MR, CT, US imaging of tumours.

NANOSHELLS: A nano particle composed of a gold shell surrounding a semi-conductor. When nanoshells reach their target they can be irradiated to make the nanoshell hot and the heat kills the cancer cell (Figure: 3). A two particle DNA-detection technology was developed by chad mirkin and colleagues. Dubbed 'bio-barcode' it involves oligonucleotide-modified gold nanoparticles and magnetic particles that carry a predetermined nucleotide sequence acting as an identification label. This system has demonstrated 500zeptomolar(zepto =10-21) sensitivity, and is therefore competitive with PCR because it doesn't require enzymatic amplification and is applicable to proteins, as well as DNA.gold-nanoparticle-modified probes have been used in conjunction with microcantilevers to develop a DNA assay with single mismatch discrimination and to transducer molecular binding into readily detectable micrometer-scale deflections

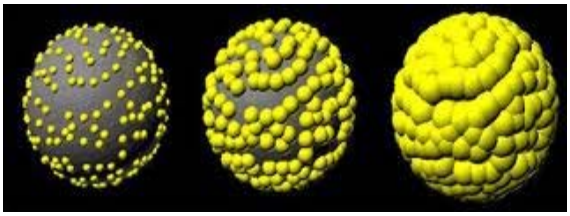

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Figure: 3 Nanoshells.

Blood vessels surrounding tumors are leakier than those in healthy tissue, so the gold plated glass nano shells injected into the bloodstream tend to accumulate at tumor sites. These particles 'glow' when subjected to low intensity infra-red radiation, which allows the tumor area to be found by 'optical coherence tomography [8]. This involves shining low power, infrared light onto the tissue and then measuring where the scattered light bounces back from the nanoparticles. Then a higher-power infrared laser is applied to each tumor site for 3 minutes to heat the tissue.

NANOWIRES: These are the nanosized sensing wires that can be coated with molecules such as antibodies to bind to proteins of interest and transmit their information through electrodes to computers [9]. Researchers have developed coated nanowires that bind to certain proteins that can indicate the presence of prostate cancer before conventional tests can. Other potential applications for nanowires include the early sensing of breast and ovarian malignancies. Nanowires are so small that doctors could one day implant them into the body as permanent health detectives that continuously monitor molecular levels. Nanowires are available in metallic, semi-conductor, magnetic, oxide, and polymer

compositions and are promising as ultra small chemical and biological sensors.

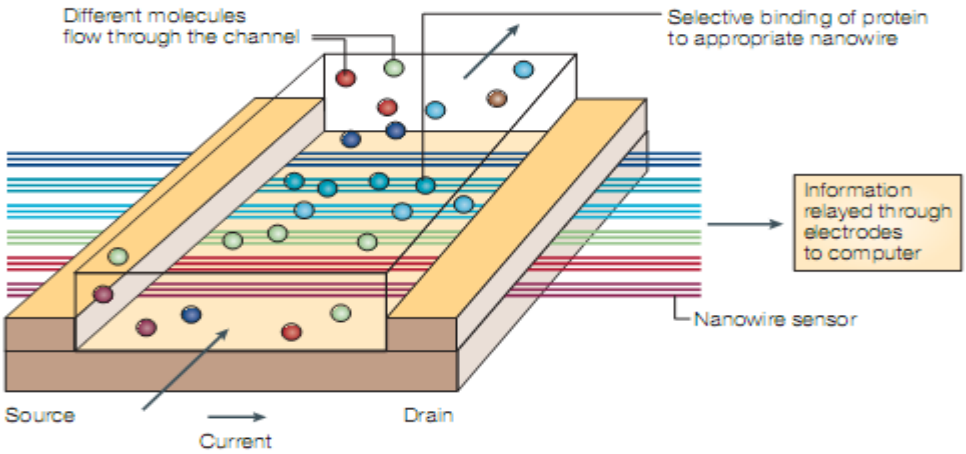

Fig 4: Nanowires deployed within a micro fluidic system. Different colours indicate that different molecules (coloured circles) adsorb or affinity-bind to different nanowire sensors. The binding causes a change in conductance of the wires, which can be electronically and quantitatively detected in real time. The working principle is that of a (biologically gated) transistor and is illustrated in the insert. The charges of the binding protein disrupt electrical conduction in the underlying nanowire. The 'nano' size of the wire is required to attain high signal-to-noise ratios

NANOCANTILEVERS: These are the flexible beams, resembling a row of dividing boards that can be coated with molecules capable of binding to cancer biomarkers. Cantilevers are beams anchored at only one end [10,11]. In the nanotechnology, they function as sensors ideal for detecting the presence of extremely small molecules in biological fluids.

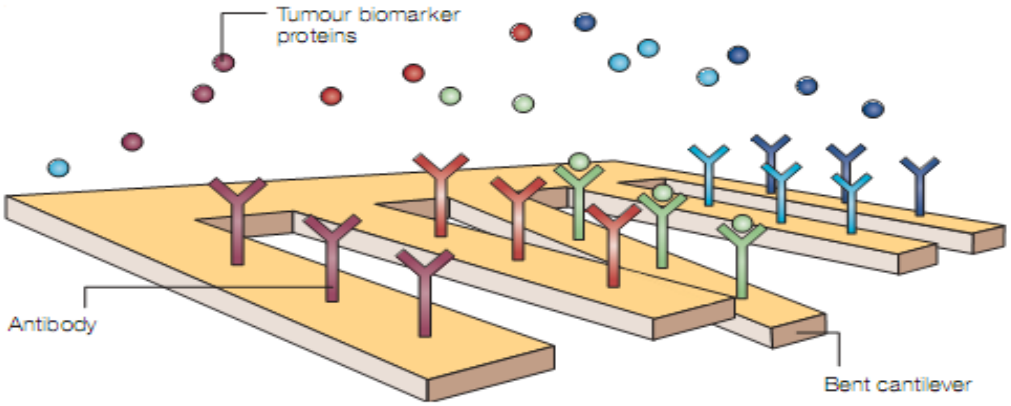

Fig5: Nanocantilever array. The biomarker proteins are affinity-bound to the cantilevers and cause them to deflect. The deflections can be directly observed with lasers. Alternatively, the shift in resonant frequencies caused by the binding can be electronically detected. As for nanowire sensors, the breakthrough potential in nanocantilever technology is the ability to sense a large number of different proteins at the same time, in real time.

NANOTUBES: A cylinder likes assemblies of carbon atoms, with cross sectional diameters in the nanometer range and lengths that can extend over thousand times its diameters (Figure: 6). Nano tubes and carbon rods about half the diameter of DNA will also help identify DNA changes associated with cancer [12]. It helps to exactly pinpoint location of changes. Cancer cells can be destroyed from within, by injecting them with nanotubes and then zapping the tubes with radio-frequency waves [13]. Radio waves turn injected carbon into heat bombs against tumours. One way to do this is to find a material that reacts to a frequency of radiation that leaves the rest of the body alone. If this material is embedded in cancerous cells, then only the cancerous cells would be targeted. Carbon nanotubes have been used before because, unusually, they can absorb

near-infrared radiation, which penetrates human tissue without causing damage.

Figure: 6 Schematic Diagram showing Nanotubes(Source: National Cancer Institute (USA))

NANODUMBBELLS: these are the recently developed nanoparticles that function like 'guided missiles' in the targeted destruction of breast cancer cells. The approach could reduce side effects associated with anti-cancer drugs and has the potential to be adapted for different types of cancer, as well as a wide range of other diseases(Figure:7). A research was carried utilising gold and iron oxide nanoparticles together to make dumbbell-shaped drug delivery vessels [14,15]. On the gold side they anchored cisplatin - a powerful anticancer agent, and to the iron oxide they attached a targeting molecule called Herceptin. Herceptin is an antibody that recognises molecules unique to breast cancer cells, allowing the complex to home in on them.

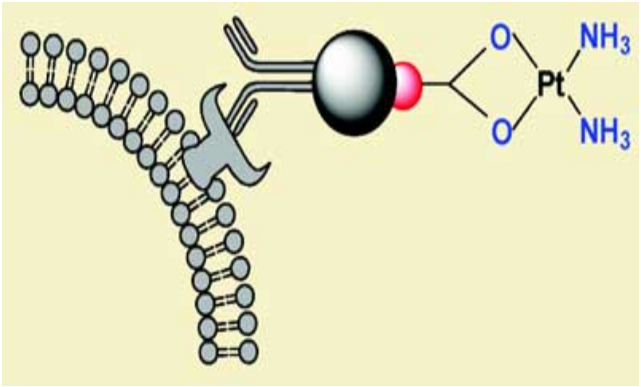

Fig 7: The platin-Au-Fe3O4-Herceptin nano particles acting as target-specific nanocarriers

This approach not only enable the researchers to pinpoint diseased cells, it also incorporates a safety catch which prevents the drug from being released until it enters the cell - at which point, a drop in pH triggers decoupling of cisplatin from the gold particles. After the drug enters the cellular system, it can be hydrolysed, becoming smaller species which then attack nuclear regions and interact with the DNA.

FULLERENE: A nanoscale structure composed of carbon atoms arranged in a specific soccer-ball-like architecture [16,17]. These crystalline particles are a form of carbon atom whose molecular architecture is arranged in a soccer ball-like structure (figure: 8). Also known as buckyballs, they were discovered in 1985 among the detritus of laser-vaporized graphite. Unlike other molecules that have applications as cancer drug delivery vehicles, fullerenes don't break down in the body and are excreted intact. This trait gives an approach where fullerene drug delivery particles that contain radioactive atoms would allow for the complete removal of radiation from the body following treatment [18].

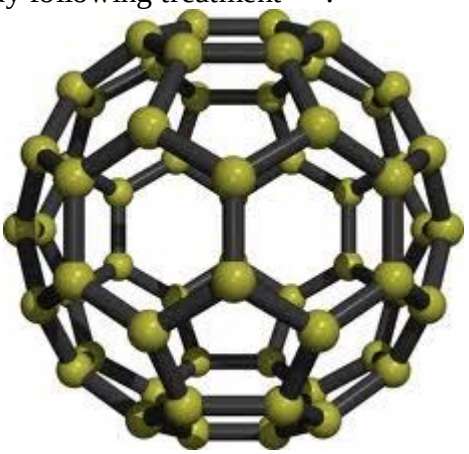

Figure: 8. Schematic Diagram of fullerene

DENDRIMERS:

The dendrimers,poly(amidoamine),are highly branched, monodispersed and macromolecules with well-defined architecture making them an ideal platform to covalently link molecules of interestThis fascinating particle holds significant promise for cancer treatment. Its many branches allow other molecules to easily attach to its surface (Figure: 9). These are self asembling synthetic polymers with exquisitely tunable nanoscale dimensions,which were recently used for MRi of lymphatic drainage in mouse model of breast cancer.thus dendrimer-based contrast agents might be used to non-invasively detect cancer cells in lymph nodes in patients,to provide early signals of disease,or information about patterns of metastatic spread.a triplex-forming growth-inhibitory oligonucleotide was effectively delivered by dendrimers to breast,ovarian [19,20] and prostate cell lines.several antigens have been used to preferentially direct nanoparticles to

angiogenic vessels.

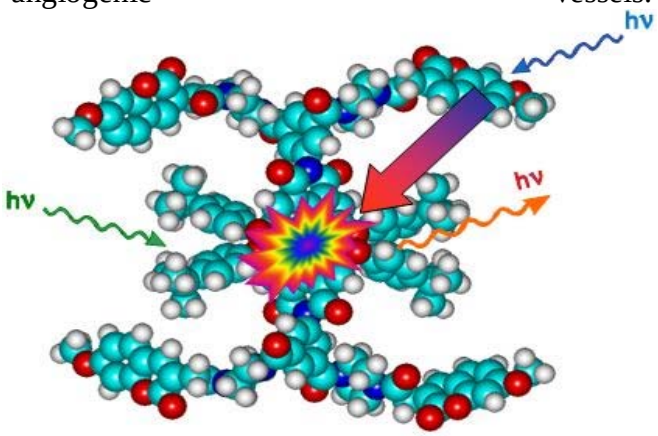

Figure:9 Schematic Diagram of Dendrimer

QUANTUM DOTES: Quantum dots are miniscule semiconductor particles that can serve as signposts of certain types of cells or molecules in the body [21,22]. these are tiny crystals that glow when these are stimulated by ultraviolet light.the latex beads filled with these crystals when stimulated by light, the colours they emit act as dyes that light up the sequence of interest(figure:10) .By combining different sized quantum dotes within a single bead, probes can be created that release a distinct spectrum of various colours and intensities of lights,serving as sort of spectral bar code.

Fig: 10 Semiconductor quantum dots with quantum confinement and size-tunable optical properties.this image shows ten distinguishable emission colors of ZnS-capped cdse quantum dots excited with a near-UV lamp.from left to right(blue to red), the emission maxima are located at 443,473,481,500,518,543,565,610 and 655 nm.

Quantum dotes emit different wavelengths of light depending on the type of cadmium used cadmium sulfide for ultraviolet to blue, cadmium selenide for most of the visible spectrum, and cadmium telluride for the far red and near-infrared. A polymer coating enables researchers to attach molecules such as antibodies that will seek out and attach to tumors and other targeted cells. The coating also shields nearby cells from the cadmium's toxicity. nanoparticles like quantum dotes have advantages of stability and tunability over conventional staining methods.for instance,quantum dots do not lose their signal intensity over time that is they do not 'photobleach'. The different colors of quantum dots provide a powerful tool for labeling and monitoring multiple cells and molecules simultaneously.

Reduction of multi drug resistance: drug resistance remains one of the major concerns in cancer therapy. Several mechanisms of drug resistance have been described. drug resistance can be caused by physiological barriers(non-cellular based mechanisms) or alterations in biology and bio-chemistry of cancer cells(cellular mechanisms).non-cellular based drug resistance can be caused by poorly vascularised tumour regions and/or physiological barriers that greatly reduce the drug access to tumour tissues, thus protecting cancerous cells from drug induced cytotoxicity. Cellular drug resistance can be due to over expressed drug export pumps such as P-glycoprotein (P-gp) and other drug resistance proteins, increased DNA repair capacity and reduced apoptosis regulation. Among these the drug efflux pumps have been extensively investigated. P-gp a product of MDR1 gene is a 160 kD transmembrane glycoprotein that functions as an efflux pump to remove drug from cells. Several specific P-gp inhibitors have been investigated to overcome drug resistance but disappointing results were obtained. The emerging nanoparticle system allows selective drug accumulation in tumour tissues, tumour cells, or even compartments of tumour cells. With the aid of targeting moiety nanoparticles enter cells through endocytosis, it is expected that they can bypass the P-gp efflux pump, leading to their greater intra cellular accumulation. Many nanoparticles have been used to overcome or minimize drug resistance in preclinical studies and the results are very promising.

FUTURE DIRECTIONS:

Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutic drugs, and have shown a bright future as a new generation of cancer therapeutics. Furthermore, the development of multifunctional nanotechnology may eventually render nanoparticles able to detect and kill cancer

cells simultaneously. Although there are certain critical questions and many challenges remaining for the clinical development of nanotechnology, as more clinical data are available, further understanding in nanotechnology will certainly lead to the more rational design of optimized nanoparticles with improved selectivity, efficacy, and safety.

REFERENCES:

1. Mauro Ferrari, Nature review paper, cancer nanotechnology opportunities and challenges, March 2005, 161-171 volume-5.
2. Nanotechnology and cancer treatment, by Om palsingh and R.M.Nehru. Asian j.exp.sci, vol22, no. 2, 2008, 45-5
3. Jain, K.K.drug delivery in cancer, Jain pharmabiotech publications, basel (2005).
4. Beeta ehdaie, application of nanotechnology in cancer research, review article Int.j.biol.sci.2007, 3(2):108-110.
5. Qiu LY, Bae YH.Polymer architecture and drug delivery. Harm Res.2006; 23:1-30.
6. Tong R, cheng JJ.Anticancer polymeric nanomedicines.polym Rev.2007; 47:345-81.
7. Cho K, Wang X, Nie S, chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer.clin cancer Res. 2008;14:1310-6.
8. Peppas, N.A., Intelligent Therapeutics: Biomimetic Systems and Nanotechnology in Drug Delivery, Advanced Drug Delivery Reviews, 2004; 56(11), pp.1529-1531.
9. Joon Won Park et.al, Nanotechnology for Early Cancer Detection review article, sensors 2010, 10, 428-455;doi:10.3390/s,100100428.
10. Gao XH, Cui YY, Levenson RM, Chung LWK, Nie SM. *In vivo* cancer targeting and imaging with semiconductor quantum dots. *nat.biotechnol*2004, .22:969-76.
11. McCarthy J.R., et al, "polymeric Nanoparticle Preaparation that Eradicates Tumors," Nano Lett, 2005, (12), pp.2552-2556.
12. Govindan S.V., Griffiths G.L., Hansen, H.J., et.al.Cancer therapy with Radiolabelled and Drug/toxin-conjugated Antibodies.TCRT, 2005; 4,375-392.
13. Clinical developments in nanotechnology for cancer therapy, Heidel JD, Davis ME. Calando Pharmaceuticals, Pasadena, California, USA.
14. Bloch, S. H., Wan, M., Dayton, P. A. & Ferrara, K. W. Optical observation of lipid- and polymer-shelled ultrasound microbubble contrast agents. Appl. Phys. Lett. 2004;84, 631–633
15. Bruckbauer, A. & Klenerman, D. An addressable antibody nanoarray produced on a nanostructured surface. J. Am. Chem. Soc. 2004;126, 6508–6509.
16. Sinek, J., Frieboes, H., Zheng, X. & Cristini, V. Two dimensional chemotherapy simulations demonstrate fundamental transport and tumor response limitations involving nanoparticles. Biomed. Microdevices ,2005;7, 71–79.
17. Strategic workshops on cancer nanotechnology, nagahara LA, Lee JS, center for strategic scientific initiatives, National Cancer Institute, Bethesda, Maryland 20892, USA.
18. Allen, T.M. Ligand –targeted therapeutics in anticancer therapy. Nature Rev.Drug Discov. 2002;2, 750-763.
19. Jain, R.K. The next frontier of molecular medicine: delivery of therapeutics.Nature Med. 1998,4, 655-657.
20. Srinivas, P.R., Barker, P .srivastava, S. nanotechnology in early detection of cancer. Lab.Invest 2002; 82, 657-662.
21. Alivisatos, p.semiconductor clusters, nanocrystals, and quantum dots. Science, 1996; 271, 933-937.
22. Rosenblatt,k.p.etal.Serumproteomicsincancer diagnosisandmanagement.Annu.Rev.Med. 2004;55, 97-112.