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NANOTECHNOLOGY FOR CANCER TREATMENT

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Abstract

NanoTechnology has the potential to increase the selectivity and potency of chemical, physical and biological approaches for eliciting cancer cell death while minimising Collateral toxicity to nonmalignant cells. Nanotechnology is more effective in cancer treatment.

This review summarises several of the most innovative Technologies that have been reported in recent years and that hold promise for improving outcomes for cancer patients.

Keywords: Cancer; drug delivery; nanotechnology

Introduction:

The need for advanced technology to play an important role for cancer treatment. Cancer is one of the leading causes of deaths worldwide with an estimated 7.6 million individuals lost each year and accounting for 13% of all deaths.

Cancer related mortality is expected to rise to 13.1 million by 2030. Cancer is not a single disease but a multitude of diseases with each organ or system developing a distinct set of disease.

What is cancer??

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.

Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form New cells as the body needs them. When cells grow old or become damaged, they die & new cells take their place.

Sometimes this orderly process breaks down and is abnormal for damaged cells to grow and multiply when they should not.

These cells may form tumors, which are lump of tissue. Tumors can be cancerous or not cancerous (Benign). Cancerous tumors spread into nearby tissues and can travel to distant places in the body to form new tumors (a process called metastasis). Cancerous tumors may also be called malignant tumors. Many cancers form solid tumors, but cancers of the blood, such as leukaemia, generally do not. Benign tumors do not spread into nearby tissues. When removed benign tumors usually don't grow back, whereas cancerous tumors sometimes do. Some can cause serious symptoms or be life threatening, such as benign tumors in the brain.

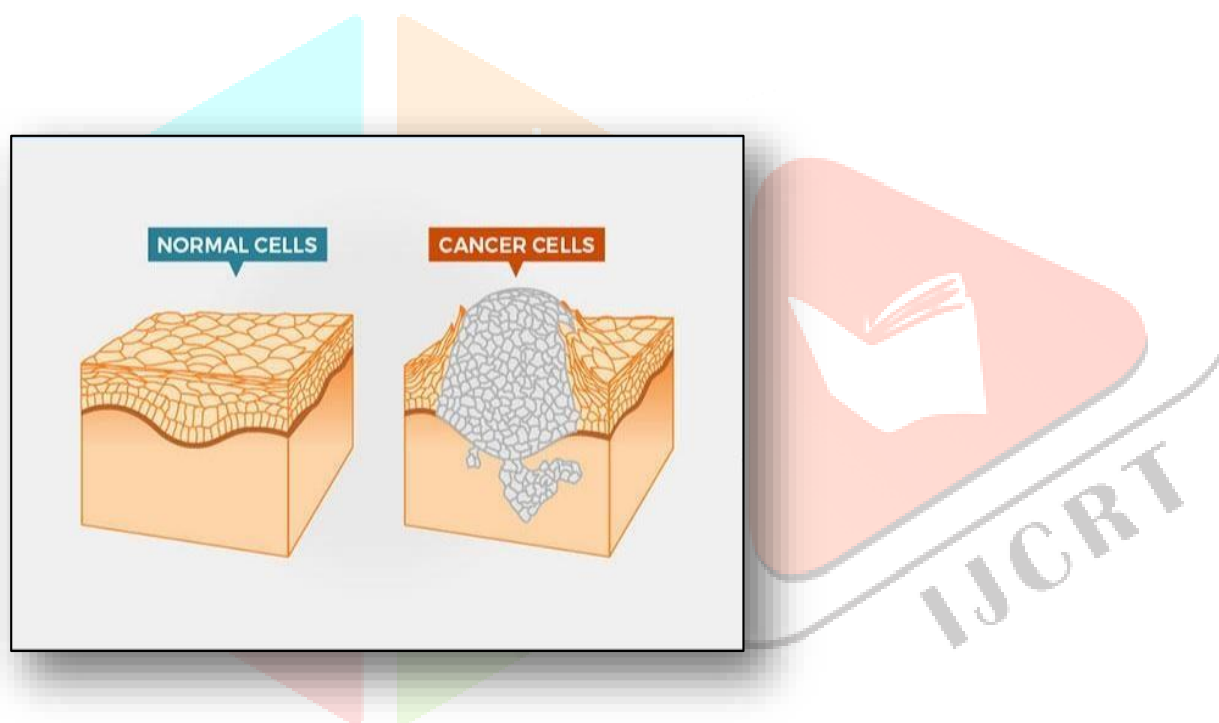


Fig. No.1.1 Normal Cell & Cancer Cell

Types of genes that causes Cancer

Three main types of geans that causes Cancer

1. Proto -oncogenes
2. Tumor suppressor genes
3. DNA repair genes

Proto- oncogenes are involved in normal cell growth and division. When these genes are altered in certain ways or are more active than normal, they may become cancer causing genes, allowing cells to grow and survive when they should not.

Tumor suppressor genes are also involved in controlling cell growth and division. Cells with certain alteration in tumor suppressor genes may divide in an uncontrolled manner.

DNA repair genes are involved in fixing damaged DNA. Cells with mutations in these genes tend to develop additional mutations in other genes and changes in their chromosome, such as duplications and deletion of chromosome parts. Together this mutation may cause the cells to become cancerous.

❖ Symptoms-

● Abnormal periods or pelvic pain

Most women have their irregular period or cramps, constant pain, or changes in your cycle can be a sign of cervical, uterine or ovarian cancer.

● Changes in bathroom habits

Significant changes in body functions can indicate colon, prostate or bladder cancer. Other signs are black or red blood in your stool; black, tarry stools; more frequent urination; and blood in urine.

● Bloating

All feel bloated now and then. But bloating for more than two weeks can be a sign of ovarian cancer as well as different gastrointestinal cancer.

● Breast changes

These include a new lump, dimpling, discolouring, changes around the nipple or unusual discharge that you didn't have before. Most breast cancer occurs in women, men can develop it too.

● Chronic coughing

A cough that persists for more than 2 weeks, a dry cough sign of lung cancer. ● **Difficulty**

swallowing

Difficulty with swallowing for more than 2 weeks particularly when eating meat, bread or raw vegetables, this can be a sign of throat, lung or stomach cancer.

● Excessive bruising

People with leukaemia are more likely to bruise because their bodies don't make enough platelets to plug bleeding blood vessels. They may show up on unusual areas of your body, such as the back.

● Frequent fever or infections

Fever is rarely an early symptom of cancer, but it may be if a person has a blood cancer, such as leukaemia or lymphoma.

● Oral changes

People who smoke or drink heavily, can indicate various oral cancers. Oral cancer which includes cancer of the lips, tongue, cheek, floor of the mouth, hard and soft palate. ● **Skin changes**

Sign of skin cancer to look for:

1. Asymmetry: One part of the mole or birthmark doesn't match the other.
2. Border: The edges are irregular, ragged, notched or blurred.

3. Colour: The colour is not the same all over and may include shades of brown or black, sometimes with patches of pink, red, white or blue.
4. Diameter: It's larger than the size of a pencil eraser.
5. Evolving: This refers to any mole that grows, bleeds or otherwise changes over time.

- **Pain that lasts**

Persistent pain anywhere in your body that has no clear cause and doesn't respond to standard treatments should be estimated.

- **Persistent fatigue**

A sudden, lasting change in your energy level, no matter how much sleep you have been getting can be a sign of leukaemia or lymphoma.

- **Postmenopausal bleeding**

Postmenopausal bleeding is due to benign (non cancerous) gynaecological condition such as endometrial polyps. But for about 10% of women, bleeding after menopause is a sign of uterine cancer. Postmenopausal bleeding is a common symptom of endometrial cancer but it also can be caused by cervical and vulvar of cancer.

- **Stomach pain or nausea**

Unusual discomfort that lasts more than two weeks can be a sign of liver, pancreatic or different digestive system cancer.

- **Unexplained weight loss**

Weight loss is common among people with cancer. Unexplained weight loss is the first noticeable symptom of Cancer of the oesophagus, pancreas, stomach and lungs.

Need For Study

Nanotechnology is a rapidly developing field, so there is need to develop nanotechnology. The field of nanotechnology relates to the study & micromanipulation of nanostructure properties at dimensions between 1 & 100nm.

Nanotechnology increasing therapeutic indices & safety profiles of new therapeutics activity
This technology is on the many innovative advances.

Aim: To study Nanotechnology For Cancer Treatment

Objective:

1. To determine the particle size, size distribution, molecular weight density, surface area
2. To target chemotherapies directly and selectively to cancerous cells & neoplasm.
3. To provide rapid & sensitive detection of cancer- related molecules.
4. To generate novel & highly effective therapeutic agent
5. To develop nanoscale devices that may lead to detection of the earliest stages of cancer

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DNA repair genes are involved in fixing damaged DNA. Cells with mutations in these genes tend to develop additional mutations in other genes and changes in their chromosome, such as duplications and deletion of chromosome parts. Together this mutation may cause the cells to become cancerous. **When cancer spreads**

In metastasis, cancer cells break away from where they first formed, travel through the blood or lymph system, and form new tumors in other parts of the body. The metastatic tumor is the same type of cancer as the primary tumor .

Cancer that has spread from the place where it first formed to another place in the body is called metastasis cancer. The process by which cancer cells spread to other parts of the body is called metastasis.

Metastasis cancer has the same name and same type of cancer cells as the original or primary cancer. For example breast cancer that forms a metastasis tumor in the lung is metastatic breast cancer, or not lung cancer.

Diagnosis:

Genetic mutation can cause changes in the synthesis of certain molecules leading to uncontrolled cell proliferation and ultimately cancerous tissues. Cancer diagnostic and therapeutic strategies are targeted at early detection and inhibition of cancerous cell growth and their spread. The early Diagnostic tools for cancer are the use of Positron emission tomography(PET), Magnetic resonance imaging(MRI), Computed tomography(CT), and ultrasound.

These imaging systems are limited by their inadequate provision of relevant clinical information about different cancer types and the stage. So it makes it difficult to obtain a full evaluation of the disease state based on which an optimum therapy can be provided.

Nanotechnology tools used in in Cancer diagnosis:

Nanotechnology can validate cancer imaging at the tissue cells and molecular levels. This is achieved through the capacity of nanotechnology applications to explore the tumor's environment, For instance, pH- response to fluorescent nanoprobes can help detect fibroblast activated proteina on the cell membrane of tumor-associated fibroblasts.

Nanotechnology-based spatial and temporal techniques that can help accurately track living cells and monitor dynamic cellular events in tumors.

1. Near Infrared (NIR) Quantum Dots

The lack of ability to penetrate objects limits the use of visible spectral imaging. Quantum dots that emit fluorescence in the near-infrared spectrum (700-1000 nanometers) have been designed to overcome this problem, making them more suitable for imaging colorectal cancer, liver cancer, pancreatic cancer, and lymphoma. A second near-infrared (NIR) window (NIR-ii, 900-1700 nm) with higher tissue penetration depth, higher spatial and temporal resolution has also been developed to aid cancer imaging. Also, the development of silver-rich Ag₂Te quantum dots (QDs) containing a sulfur source has been reported to allow visualization of better spatial resolution images over a wide infrared range.

2. Nanoshells

Another commonly used nanotechnology application is the nanoshells. Nanoshells are dielectric cores between 10 and 300 nanometers in size, usually made of silicon and coated with a thin metal shell (usually gold). These nanoshells work by converting plasma-mediated electrical energy into light energy and can be flexibly tuned optically through UV-infrared emission/absorption arrays. Nanoshells are desirable because their imaging is devoid of the heavy metal toxicity even though their uses are limited by their large sizes.

Gold nanoshells (AuNSs) are currently being investigated as nanocarriers for drug delivery systems & have both diagnostic & therapeutic application. [6]

3. Colloidal Gold Nanoparticles

Gold nanoparticles (AuNPs) are a good contrast agent because of their small size, good biocompatibility, and high atomic number. Several advantages of colloidal gold nanoparticles are safer, eco-friendly, simple, fast, energy efficient, low cost & less toxic. [5]

Research shows that AuNPs work in both active and passive ways to target cells. The principle of passive targeting is governed by a gathering of the gold nanoparticles to enhance imaging because of the permeability tension effect (EPR) in tumor tissues. Active targeting, on the other hand, is mediated by the coupling of AuNPs with tumor-specific targeted drugs, such as EGFR monoclonal antibodies, to achieve AuNP active targeting of tumor cells.

When the energy exceeds 80 keV, the mass attenuation rate of gold becomes higher than alternative elements like iodine, indicating a greater prospect of gold nanoparticles. These findings have important implications for early diagnosis, with the technique allowing tumors as small as a few millimeters in diameter to be detected in the body.

Treatment

Cancer therapies are currently limited to surgery, radiation and chemotherapy. All three methods risk damage to normal tissue of the cancer. Nanotechnology the engineering and manufacturing of materials using atomic and molecular components is expected to benefit all branches of medicine. Nanotechnology offers the means to target chemotherapies directly and selectively to cancerous cells and neoplasm, guides in surgical resection of tumors, and improves the therapeutic efficacy of radiation based and other current treatment techniques. All of this can add up to a decreased risk to the patient and an increased chance of survival.

Research on nanotechnology cancer therapy extends beyond Drug Delivery into the creation of new therapeutic available only through use of nanomaterial properties. While small compared to cells, nanoparticles are large enough to encapsulate many small molecule compounds, which can be of multiple types.

Simultaneously, the relatively large surface area of nanoparticles can be functionalized with ligands, including small molecules, DNA or RNA strands, peptides or antibodies. These ligands can be used for therapeutic

effect. The physical properties of nanoparticles such as energy absorption and re-radiation, can also be used to disrupt disease tissue, as in laser removal and hyperthermia application.

Nanotechnology refers to structure roughly in the 1- 200nm size in at least one dimension. Nanomaterials have large surface area to volume ratio and their physico-chemical properties, such as friction and interaction with other molecules.

The most common examples of the nanoscale delivery vehicles include polymeric nanoparticles, dendrimers, Nanoshells, liposomes, nucleic acid based nanoparticles, magnetic nanoparticles and Virus nanoparticles.

Nanocarriers have the potential to improve the therapeutic index, drug solubility and drug stability. The traditional use of Nanotechnology in Cancer therapeutics has been to improve the pharmacokinetics and decrease the systemic toxicity of chemotherapies through the selective targeting & delivery of these anticancer drugs to tumor tissues.

The benefits of nano-sized Carriers is that they can increase the delivered drugs over all therapeutic index through nanoformulations in which chemotherapeutics are either encapsulated to the surface of the nanoparticle. This capability is largely due to their co-ordinate size and surface properties. Size is an important factor in the delivery of nanotechnology-based therapeutics to tumor tissues.

Delivery of nanotherapeutics platform depends on the passive targeting of tumors through the increased permeability and retention effect. This phenomenon depends on defects specific to the tumor microenvironment such as defects in lymphatic drainage, along with increased tumor vascular permeability, to allow Nanoparticles(<200nm) to collect in the tumor microenvironment.

Also the timing for site of drug release can be controlled by triggered events, such as ultrasound, PH, heat or by material composition.

Developing nanomaterial based delivery platforms that will reduce the toxicity of chemotherapeutics and increase their overall effectiveness.

Nanotechnologies are also being investigated to deliver immunotherapy. This includes use of nanoparticles for delivery of immunostimulatory for immunomodulatory molecules in combination with chemo or radiotherapy.

Standalone nanoparticles vaccines are also being designed to raise sufficient T cells response to remove tumors, through co-delivery of antigen and adjuvant, the inclusion of multiple antigens to stimulate multiple dendritic cell targets, and continuous release of antigens for prolonged immune stimulation.

Molecular blockers of immune-suppressive factors produced can also be co-encapsulated in nanoparticle vaccines to alter the immune context of tumors and improve response.

Nanotechnology for immunotherapy includes immune depots placed in or near tumors for in situ vaccination and artificial antigen presenting cells. These and other approaches will advance and be refined as our understanding of cancer immunotherapy deepens.

The value of nanomaterial-based delivery has become apparent for new types of therapeutics such as those using nucleic acids, which are highly unstable in systemic circulation and sensitive to degradation.

These include DNA and RNA based on genetic therapy such as small interfering RNAs & microRNAs. The increased stability of genetic therapies delivered by nanocarriers, and often combined with controlled release, has been shown to prolong their effects. Nanotechnology-based delivery of nucleic acid as effective treatment Strategies for a variety of cancer.

Nanotechnology has been applied in the development of Nanomaterials such as gold nanoparticles and Quantum dots, which are used for cancer diagnosis at the molecular level. Molecular diagnostics based on nanotechnology, such as the development of biomarkers, can accurately and quickly detect the cancers. Nanotechnology treatment, such as the development of nanoscale drug delivery, can ensure precise cancerous tissue targeting with minimal side effects. Due to its biological nature, nanomaterials can easily cross barriers. Nanomaterials have been used in the treatment of tumors, due to their active and passive targeting. Although many drugs can be used to treat cancers, the sensitivity of the drugs generally leads to inadequate results and can have various side effects, as well as damage to the healthy cells.

Different forms of Nanomaterials such as liposomes, polymers, molecules and antibodies.

Nanotechnology in Cancer therapy

Tools of Nanotechnology for cancer therapy

The development of Nanotechnology is based on the usage of small molecular structures and particles as tools for delivering drugs. Nano-carriers such as liposomes, micelles, dendritic macromolecules, Quantum dots and carbon nanotubes have been widely used in cancer treatment.

1. Liposomes

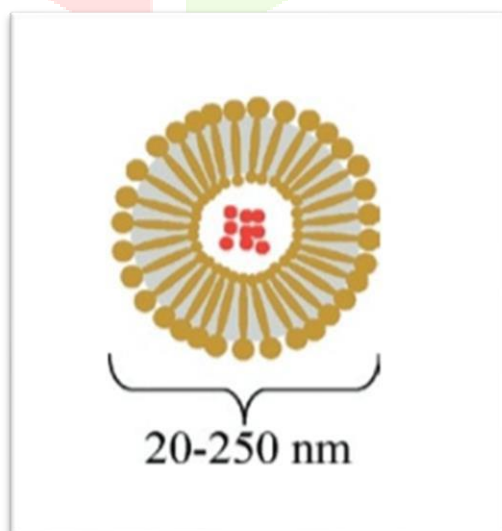


Fig.No.4.1 Structure of Liposome

Liposomes is one of the most successful drug delivery systems applying nanotechnology to potentiate the therapeutic efficacy and reduce toxicities of conventional medicines. [8]

Liposomes are one of the most studied nanomaterials, which are nanoscale spheres composed of natural or synthesized phospholipid bilayer membrane and water phase nuclei. Because of the amphiphilicity of phospholipids, liposomes form spontaneously, allowing hydrophilic drugs to preferentially stay in the monolayer liposome while hydrophobic ones form before the multilayer liposome. Some drugs could be incorporated into liposomes by exchanging them from the acidic buffer to the neutral buffer. Neutral drugs can be transported in liposomes also, but due to a poor avidity for acidic environments, they are not readily released from the inside of the liposomes. Other mechanisms of drug delivery are the combination of saturated drugs with organic solvents to form liposomes. In tumors they can fuse with cells, are internalized by endocytosis, and release drugs in the intracellular space. In the case of the appropriate pH, redox potential, ultrasonic and under the electromagnetic field, the liposome can also release the drug through passive or active ligand-mediated activity. The targeted therapy has an advantage in the vascular system, micrometastases, and blood cancers.

It has been shown that the half-life of liposomes is affected by size. The liposome up to 100 nanometers easily penetrate the tumor and stay longer, while the half-life of the bigger liposome is shorter because they are easily recognized and cleared by the mononuclear phagocyte system.

Liposome-bound antibodies target tumorspecific antigens to ensure active targeting and then transport drugs to the tumor.

Some liposomal drugs are approved for clinical therapy.

2. Carbon Nanotubes

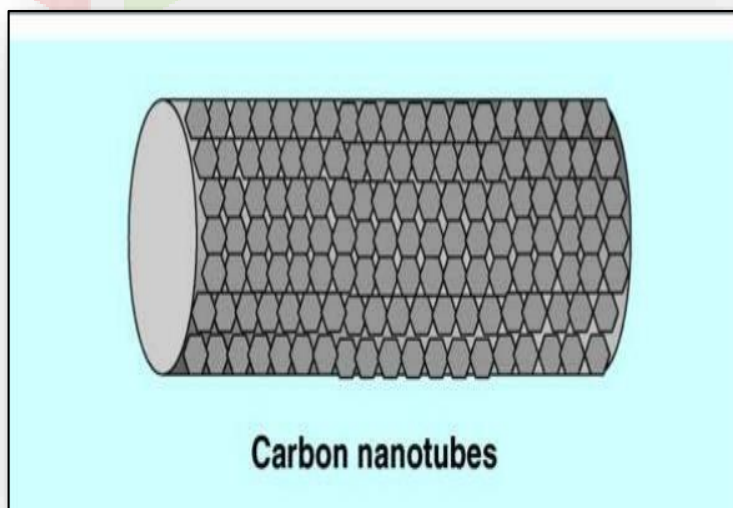


Fig.4.2 Structure of Carbon nanotubes

Based on the structure and the diameter, Carbon nanotubes (CNTs) can be categorized into two kinds, the single-walled CNTs (SWNTs) and the multiwalled CNTs (MWNTs). The SWNTs are composed of monolithic cylindrical graphene, and the MWNTs are composed of concentric graphene. Because of the physical and chemical properties of carbon nanotubes, that include surface area, mechanical strength, metal properties, electrical and thermal conductivity.

Carbon nanotubes also possess a property that allows them to absorb light from the near-infrared (NIR) region, causing the nanotubes to heat up by the thermal effect, hence can target tumor cells.

3. Polymeric Micelles

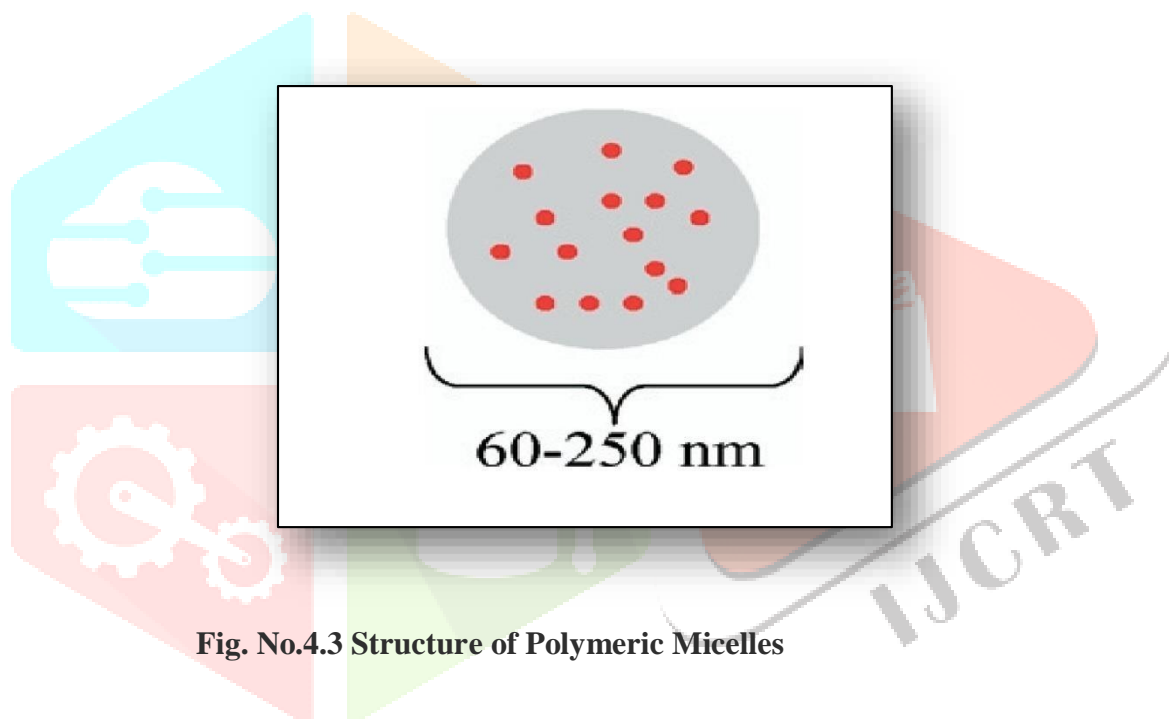


Fig. No.4.3 Structure of Polymeric Micelles

Polymeric nanoparticles (PNPs) are the inventions that relate to a solid micelle. Polymeric micelles represent an effective delivery system for poorly water-soluble anticancer drugs with particle size range of 10-100nm. [11]

PNPs are collectively known as polymer nanoparticles, nanospheres, nanocapsules or polymer micelles and they were the first polymers reported for drug delivery systems. PNPs serve as drug carriers for hydrophobic drugs and are widely used for drug discovery.

The PNPs constructed from amphiphilic polymers with a hydrophilic and hydrophobic block can perform rapid self-assembly because of the hydrophobic interactions in an aqueous solution. The PNPs can capture the hydrophobic drugs because of a covalent bond or the interaction via a hydrophobic core. Thus, to carry the hydrophilic charged molecules, such as proteins, peptides, and nucleic acids, these blocks are switched to allow interactions in the core and neutralize the charge.

The advantages of the higher thermodynamic stability and the smaller volume make the PNPs a suitable drug carrier with good endothelial cell permeability while avoiding kidney rejection. The hydrophobic macromolecules and drugs can be transferred to the center of the PNPs, hence, the injection of PNPs suspension after being separated in an aqueous solution could achieve therapeutic effect.

Oral or parenteral administration drugs can reach the target cells in different ways, potentially providing alternative ways to lower cytotoxicity in healthy tissues compared to the cancer cells. However, the major challenges in the use of PNPs for cancer nanomedicine still exist in how to effectively deliver the drugs to the target site with limited side effects or drug resistance.

Recently, the PNPs have been used widely in nanotechnology-based cancer drug design due to their excellent potential benefits for patient care.

4. Dendrimers

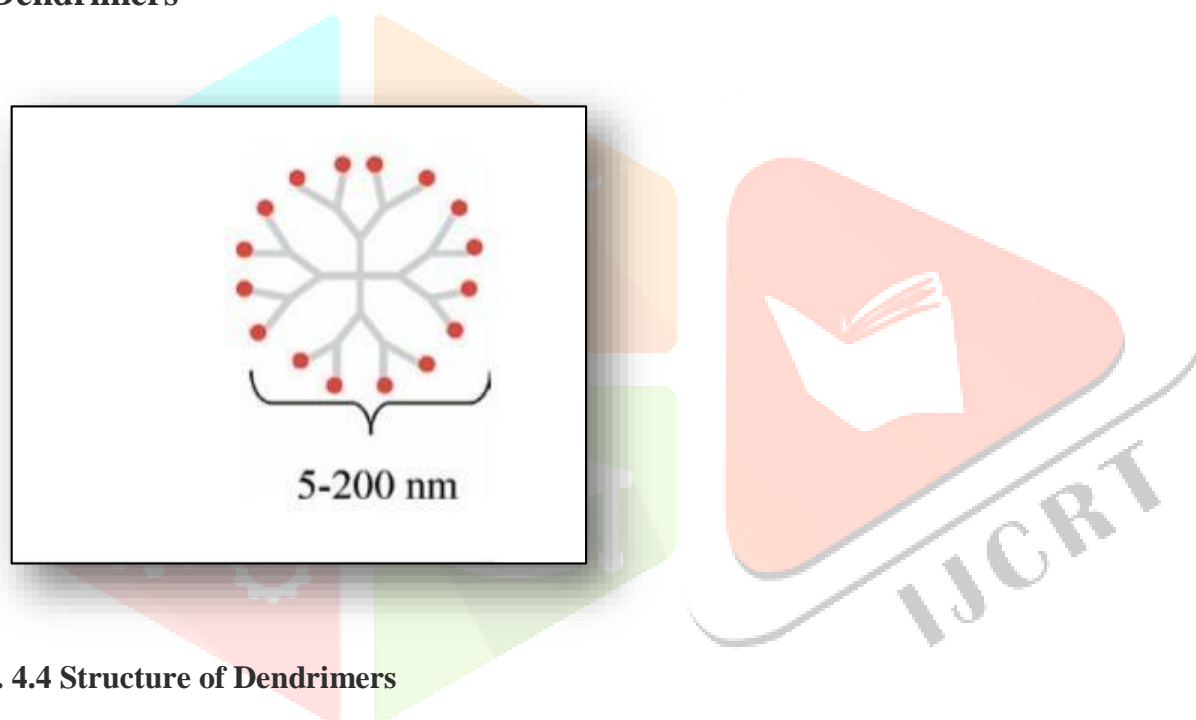


Fig. 4.4 Structure of Dendrimers

The dendrimers are highly branched polymer of nano size. These are three dimensional, monodisperse, globular macromolecules having high number of functional groups on their surface.[10]

As the dendritic macromolecule diameter increases, the tendency to tilt towards a spherical structure increases. There are usually two ways to synthesize dendrimers, a divergent method in which the dendrimers can grow outward from the central nucleus, and a convergence method, where the dendrimers grow inward from the edges and end up in the central nucleus.

Various molecules including polyacrylamide, polyglycerol-succinic acid, polylysine, polyglycerin, poly(2, 2bis (hydroxymethyl) propionic acid), and melamine are commonly used to form dendrimers. These dendritic macromolecules exhibit different chemical structures and properties, such as alkalinity, hydrogen bond

capacity and charge, which can be regulated by growing dendritic macromolecules or changing the groups on the surface of dendritic macromolecules.

The dendritic drug conjugates are formed by the covalent binding of antitumor drugs to dendritic peripheral groups. Thus, several drug molecules can attach to each dendritic molecule and the release of these therapeutic molecules is controlled in part by the nature of the attachment. The physicochemical and biological properties of the polymer including the size, charge, multi-ligand groups, lipid bilayer interactions, cytotoxicity, internalization, plasma retention time, biological distribution, and filtration of dendritic macromolecules, have made dendrimers potential nanoscale carriers.

Several studies have further shown that cancer cells with a high expression of folate receptors could form foils from dendritic molecules bound to folate. An added advantage of dendrimers is their ability to bind to DNA as seen with the DNA-polyamides clustering DNA-poly(amidoamine) (DNAPAMAM), making them highly effective at killing cancer cells that express the folate receptor.

4. Quantum Dots

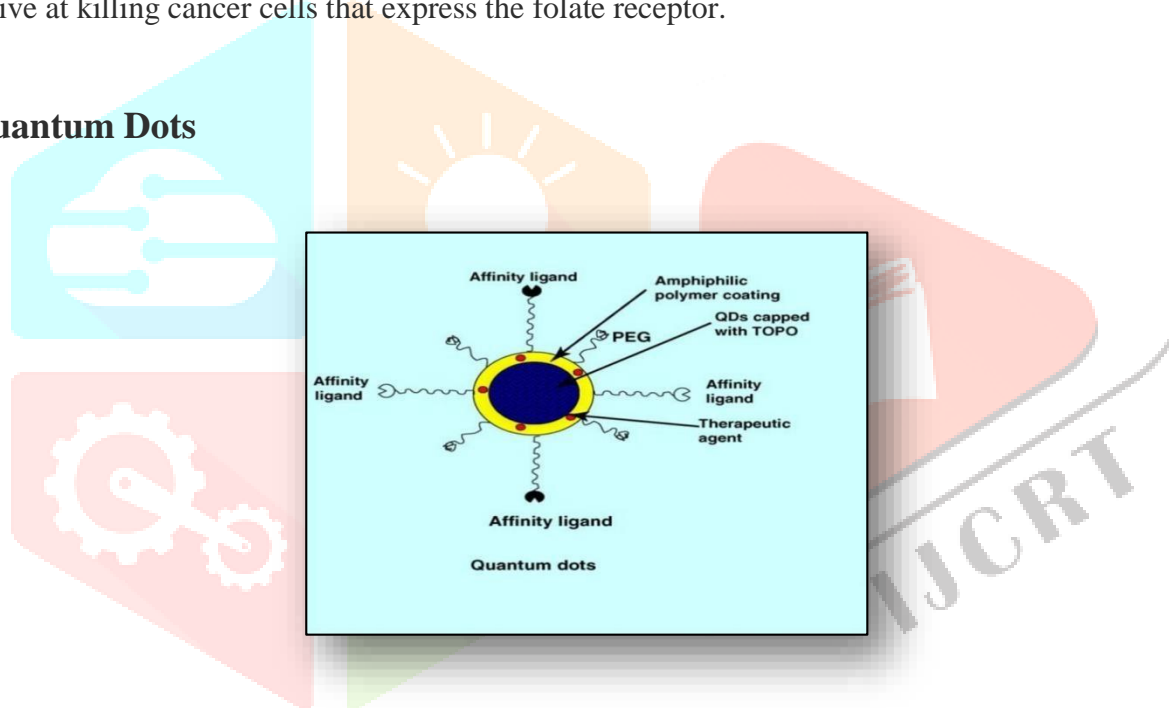


Fig.4.4 Structure of Quantum Dots

Quantum dots (QDs) are small particles or nanocrystals of semiconductor materials with a particle size of less than 10nanometer. [9]

The ratio of the height of the surface to the volume of these particles gives the QDs the intermediate electron property which is between a mass semiconductor and a discrete atom.

In cancer diagnosis, QD immunostaining is a potential tool for the detection of various tumor biomarkers, such as a cell protein or other components of a heterogeneous tumor sample. Quantum dots can gather in specific parts of the body and transfer the drugs to those parts. The ability of the QDs to concentrate in a single internal

organ makes them a potential solution against non targeted drug delivery, and possibly avoid the side effects of chemotherapy.

Conclusion:

The application of Nanotechnology in the field of cancer nanotechnology has experienced exponential growth in the past few years. Nanoparticles provide opportunities for designing & tuning properties that are not possible with other types of therapeutics drugs & have shown they have a bright future as a new generation of cancer therapeutics.

Nanoparticles system have great potentials to advance the field of biotechnology & medical research.

The multidisciplinary field of nanotechnology holds the promise of delivering a technological break through & is moving very fast from concept to reality.

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