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Recent Advances and Development of Nanotechnology in the Treatment of Cancer –An Overview

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ABSTRACT
Rapid growth in nanotechnology toward the development of nanomedicine agents grips massive promise to improve therapeutic approaches against cancer.Nanomedicine products represent an opportunity to achieve sophisticated targeting strategies and multifunctionality.Nanotechnology has provided the opportunity to get direct access of the cancerous cells selectively with increased drug localization and cellular uptake. Nanoparticles can be programmed for recognizing the cancerous cells and giving selective and accurate drug delivery avoiding interaction with the healthy cells. Nanoparticles are rapidly being developed and trialed to overcome several limitations of traditional drug delivery systems and are coming up as a distinct therapeutics for cancer treatment.Conventional chemotherapeutics possess some serious side effects including damage of the immune system and other organs with rapidly proliferating cells due to nonspecific targeting, lack of solubility, and inability to enter the core of the tumors resulting in impaired treatment with reduced dose and with low survival rate.The Nano devices are being investigated for the capture of blood borne biomarkers, including cancer-associated proteins circulating tumour cells, circulating tumour DNA, and tumour-shed exosomes.In the recent years, NPs have repetitively been reported to play a significant role in modern medicine. They have been analyzed for different clinical applications, such as drug carriers, gene delivery to tumors, and contrast agents in imaging. A wide range of nanomaterials based on organic, inorganic, lipid or glycan compounds, as well as on synthetic polymers has been utilized for the development and improvement of new cancer therapeutics.This review focuses on new trends and advances in the nanotechnology for the treatment of cancer from previous anticancer therapies.

Keywords: Nanotechnology, cancer, conventional chemotherapeutics, gene therapy, etc.

I. INTRODUCTION

1.1 Cancer introduction

Cancer is one of the most serious fatal diseases in today's world that kills millions of people every year. It is one of the major health concerns of the 21st century which does not have any boundary and can affect any organ of people from any place [1]. Cancer, the uncontrolled proliferation of cells where apoptosis is greatly disappeared, requires very complex process of treatment. Because of complexity in genetic and phenotypic levels, it shows clinical diversity and therapeutic resistance. A variety of approaches are being practiced for the treatment of cancer each of which has some significant limitations and side effects [2].

Cancer treatment includes surgical removal, chemotherapy, radiation, and hormone therapy. Chemotherapy, a very common treatment, delivers anticancer drugs systemically to patients for quenching the uncontrolled proliferation of cancerous cells [3]. Unfortunately, due to nonspecific targeting by anticancer agents, many side effects occur and poor drug delivery of those agents cannot bring out the desired outcome in most of the cases. Cancer drug development involves a very complex procedure which is associated with advanced polymer chemistry and electronic engineering.

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The main challenge of cancer therapeutics is to differentiate the cancerous cells and the normal body cells. That is why the main objective becomes engineering the drug in such a way as it can identify the cancer cells to diminish their growth and proliferation. Conventional chemotherapy fails to target the cancerous cells selectively without interacting with the normal body cells. Thus they cause serious side effects including organ damage resulting in impaired treatment with lower dose and ultimately low survival rates [4].

Nanotechnology is the science that usually deals with the size range from a few nanometers (nm) to several hundred nm, depending on their intended use [5]. It has been the area of interest over the last decade for developing precise drug delivery systems as it offers numerous benefits to overcome the limitations of conventional formulations [6, 7]. It is very promising both in cancer diagnosis and treatment since it can enter the tissues at molecular level. Cancer nanotechnology is being enthusiastically evaluated and implemented in cancer treatment indicating a major advance in detection, diagnosis,and treatment of the disease.

Various researches are being carried out in order to discover more accurate nanotechnology based cancer treatment minimizing the side effects of the conventional ones [5]. Nanoparticles are now being designed to assist therapeutic agents to pass through biologic barriers, to mediate molecular interactions, and to identify molecular changes. They have larger surface area with modifiable optical, electronic, magnetic, and biologic properties compared to macroparticles. Current nanotechnology based drug delivery systems for cancer treatment, which are already marketed and under research and evaluation, include liposomes, polymeric micelles, dendrimers, nanospheres, nanocapsules, and nanotubes [8, 9]. Nanotechnology based formulations that have already been marketed are DOXIL (liposomal doxorubicin) and Abraxane (albumin bound paclitaxel) [10].

1.1 Limitations of Conventional Chemotherapy

Conventional chemotherapeutic agents work by destroying rapidly dividing cells, which is the main property of neoplastic cells. This is why chemotherapy also damages normal healthy cells that divide rapidly such as cells in the bone marrow, macrophages, digestive tract, and hair follicles [2]. The main drawback of conventional chemotherapy is that it cannot give selective action only to the cancerous cells. This results in common side effects of most chemotherapeutic agents which include myelosuppression (decreased production of white blood cells causing immunosuppression), mucositis (inflammation of the lining of the digestive tract), alopecia (hair loss), organ dysfunction, and even anemia or thrombocytopenia. These side effects sometimes impose dose reduction, treatment delay, or discontinuance of the given therapy [11, 12].

In case of solid tumors cell division may be effectively ceased near the center, making chemotherapeutic agents insensitive to chemotherapy. Furthermore, chemotherapeutic agents often cannot penetrate and reach the core of solid tumors, failing to kill the cancerous cells [13]. Traditional chemotherapeutic agents often get washed out from the circulation being engulfed by macrophages. Thus they remain in the circulation for a very short time and cannot interact with the cancerous cells making the chemotherapy completely ineffective. The poor solubility of the drugs is also a major problem in conventional chemotherapy making them unable to penetrate the biological membranes [4]. Another problem is associated with Pglycoprotein, a multidrug resistance protein that is overexpressed on the surface of the cancerous cells, which prevents drug accumulation inside the tumor, acting as the efflux pump, and often mediates the development of resistance to anticancer drugs. Thus the administered drugs remain unsuccessful or cannot bring the desired output [14–17].

1.3 Cancer Diagnostics

More lives could be saved by early detection of cancer than by any form of treatment at advanced stages. Circulating tumor cells (CTCs), which are viable cells derived from tumors, are hypothesized to represent the origin of metastatic disease.

Nanotechnology can be used to develop devices that indicate when those markers appear in the body and that deliver agents to reverse premalignant changes or to kill those cells that have the potential to become malignant.

For instance, a quick and simple blood test to detect early-stage cancer relies on the discovery of cancer biomarker molecules from the 'protein corona' formed on the gold nanoparticles upon adsorption of blood serum proteins to the nanoparticle surface With increasing accuracy, liquid biopsies – where CTCs are isolated from

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blood samples – are becoming a viable complement or even alternative to invasive biopsies of metastatic tumors. CTCs are of great interest for evaluating cancer dissemination, predicting patient prognosis, and also for the evaluation of therapeutic treatments, representing a reliable potential alternative to invasive biopsies and subsequent proteomic and functional genetic analysis.

Two examples of nanotechnology in this area: rather than using magnetic and microfluidic methods for the isolation of CTCs, researchers have demonstrated a carbon nanotube chip that captures and analyzes circulating tumor cells in blood. Others have used a nanosilicon platform to capture and release circulating tumor cells.

Quantum dots in particular have finally taken the step from pure demonstration experiments to real applications in imaging. In recent years, scientists have discovered that these nanocrystals can enable researchers to study cell processes at the level of a single molecule. This may significantly improve nanotechnology cancer diagnostics and treatment. Fluorescent semiconductor quantum dots are proving to be extremely beneficial for medical applications, such as high-resolution cellular imaging.

1.4 Cancer screening

Diagnosing cancer at its earliest stages often provides the best chance for a cure. With this in mind, talk with your doctor about what types of cancer screening may be appropriate for you.

For a few cancers, studies show screening tests can save lives by diagnosing cancer early. For other cancers, screening tests are recommended only for people with increased risk.A variety of medical organizations and patient-advocacy groups have recommendations and guidelines for cancer screening. Review the various guidelines with your doctor and together you can determine what's best for you based on your own risk factors for cancer.

1.5 Cancer diagnosis

Your doctor may use one or more approaches to diagnose cancer:

- **Physical exam.** Your doctor may feel areas of your body for lumps that may indicate a tumor. During a physical exam, he or she may look for abnormalities, such as changes in skin color or enlargement of an organ that may indicate the presence of cancer.
- **Laboratory tests.** Laboratory tests, such as urine and blood tests, may help your doctor identify abnormalities that can be caused by cancer. For instance, in people with leukemia, a common blood test called complete blood count may reveal an unusual number or type of white blood cells.
- **Imaging tests.** Imaging tests allow your doctor to examine your bones and internal organs in a noninvasive way. Imaging tests used in diagnosing cancer may include a computerized tomography (CT) scan, bone scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, ultrasound and X-ray, among others.
- **Biopsy.** During a biopsy, your doctor collects a sample of cells for testing in the laboratory. There are several ways of collecting a sample. Which biopsy procedure is right for you depends on your type of cancer and its location. In most cases, a biopsy is the only way to definitively diagnose cancer.

In the laboratory, doctors look at cell samples under the microscope. Normal cells look uniform, with similar sizes and orderly organization. Cancer cells look less orderly, with varying sizes and without apparent organization.

1.6 Cancer stages

Once cancer is diagnosed, your doctor will work to determine the extent (stage) of your cancer. Your doctor uses your cancer's stage to determine your treatment options and your chances for a cure. Staging tests and procedures may include imaging tests, such as bone scans or X-rays, to see if cancer has spread to other parts of the body.

Cancer stages are generally indicated by Roman numerals — I through IV, with higher numerals indicating more advanced cancer. In some cases, cancer stage is indicated using letters or words.

1.7 Duration of Therapy

The final aspect unique to chemoprevention is the expected duration of treatment. Experimental work with both in vitro cell culture systems and animal studies have shown that most chemoprevention agents with antipromotional activity must be continuously present for efficacy. If the agent is removed from the culture system or discontinued in the animal, the cancer incidence returns to the pretreatment rate. This suggests that chemoprevention agents will be given for prolonged periods. An issue usually not addressed in phase I/II/III studies of cytotoxic drugs is the incidence of long term side

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effects. In chemoprevention, where the majority of participants will live a normal life span and not develop cancer, determining the incidence of long term side effects is critical. The planning of phase I, II, and III trials must consider this aspect of chemoprevention; these agents will likely be administered for life.

1.8 Cancer Therapy

In therapy, nanotechnology to kill cancer cells is at the forefront of both targeted drug delivery and intrinsic therapies. For instance, nanoparticles can be used as tumor-destroying hyperthermia agents that are injected into the tumor and then be activated to produce heat and destroy cancer cells locally either by magnetic fields, X-Rays or light.

Sneaking existing chemotherapy drugs or genes into tumor cells via nanomaterials allows much more localized delivery both reducing significantly the quantity of drugs absorbed by the patient for equal impact and the side effects on healthy tissues in the body.

Coupling both modes of action has also been achieved with gold nanorods carrying chemotherapy drugs and locally excited in the tumor by infrared light. The induced heat both releases the encapsulated drug and helps destroying the cancer cells, resulting in a combined effect of enhanced delivery and intrinsic therapy.

Smart cancer theranostics – a combination of the words therapeutics and diagnostics – describes a treatment platform that combines a diagnostic test with targeted therapy based on the test results, i.e. a step towards personalized medicine.

1.9 Cancer Theranostics

Theranostics – a combination of the words therapeutics and diagnostics – describes a treatment platform that combines a nanotechnology cancer diagnostics test with targeted therapy based on the test results, i.e. a step towards personalized medicine. Making use of nanotechnology materials and applications, theranostic nanomedicine can be understood as an integrated nanotherapeutic system, which can diagnose, deliver targeted therapy and monitor the response to therapy.
Theranostic nanomedicine has the potential for simultaneous and real time monitoring of drug delivery, trafficking of drug and therapeutic responses.

1.10 Cancer Immunotherapy

Immunotherapy has become an important part of treating some types of cancer. It uses certain parts of a person's immune system to fight the cancer. Usually this is done by administering immune system components, such as man-made immune system proteins. Tumors evade the immune system by suppressing its ability to recognize and kill cancer cells. The goal of immunotherapy is to normalize and harness the body's immune system so that it can more effectively fight the tumors.

In recent years, nanomedicine has played an increasingly important role in pursuing efficient vaccine delivery in cancer immunotherapy. For instance, a proof-of-principle study ("Nanoparticles reprogram immune cells to fight cancer") has shown that nanoparticle-programmed immune cells, known as T cells, can rapidly clear or slow the progression of leukemia in a mouse model. In another study, researchers had initial success in mice using nanodiscs to deliver a customized therapeutic vaccine for the treatment of colon and melanoma cancer tumors ("Nanodiscs deliver personalized cancer therapy to immune system").

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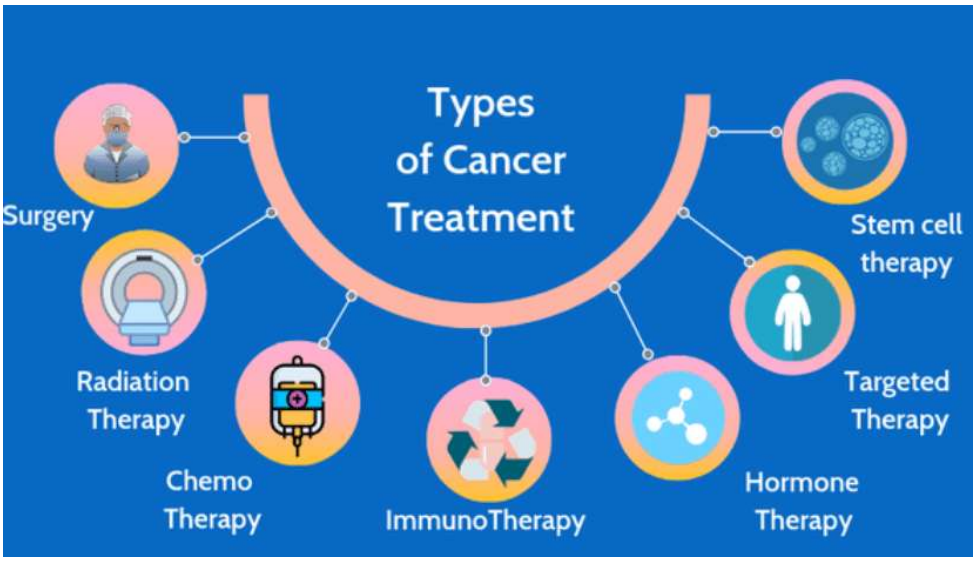

Fig no: 1 Types of cancer treatment

Biological processes, including ones necessary for life and those that lead to cancer, occur at the nanoscale. Thus, in fact, we are composed of a multitude of biological nano-machines. Nanotechnology provides researchers with the opportunity to study and manipulate macromolecules in real time and during the earliest stages of cancer progression. Nanotechnology can provide rapid and sensitive detection of cancer-related molecules, enabling scientists to detect molecular changes even when they occur only in a small percentage of cells. Nanotechnology also has the potential to generate entirely novel and highly effective therapeutic agents.

Ultimately and uniquely, the use of nanoscale materials for cancer, comes down to its ability to be readily functionalized and easily tuned; its ability to deliver and / or act as the therapeutic, diagnostic, or both; and its ability to passively accumulate at the tumor site, to be actively targeted to cancer cells, and to be delivered across traditional biological barriers in the body such as dense stromal tissue of the pancreas or the blood-brain barrier that highly regulates delivery of biomolecules to / from, our central nervous system.

1.11 Nanotechnology

History

Titanium exposed to air forms an active biological field due to oxidation that promotes ingrowth of living tissues. Discovery of this phenomenon in 1950'slead to the development of nanotechnology and a tremendous leap in bone implant applications in medical technology.

1.12 The concept of nanotechnology

At nanoscopic size, the materials acquire altered physical and chemical properties. They have unique and advantageous surface characteristics compared to their original size. Nanoparticles are between 1 and 100 nm in size with a surrounding interfacial layer. Nanotechnology enables exploitation and organization of nanomaterials of one dimension below 100 nm. High surface area to volume ratio is responsible for the infinite property achieved by their smaller size. Mechanical, optical, magnetic, and chemical characteristic of nanoparticles achieved due to its particle size which enable them as ideal choice for wide applications in the fields of science, electronics, defense cosmetics and medicine. It has developed into a multibillion-dollar industry.

Nanotechnology is science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers.Nanoscience and nanotechnology are the study and application of extremely small things and can be used across all the other science fields, such as chemistry, biology, physics, materials science, and engineering.

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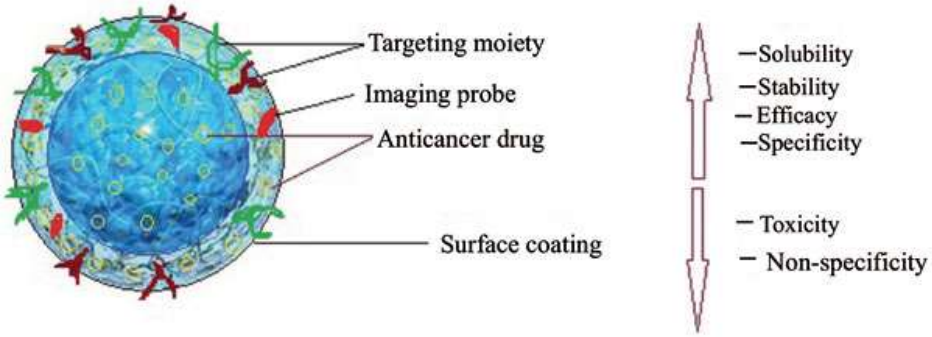

Fig no: 2 Nanoparticle drug targeting

The ideas and concepts behind nanoscience and nanotechnology started with a talk entitled "There's Plenty of Room at the Bottom" by physicist Richard Feynman at an American Physical Society meeting at the California Institute of Technology (CalTech) on December 29, 1959, long before the term nanotechnology was used. In his talk, Feynman described a process in which scientists would be able to manipulate and control individual atoms and molecules. Over a decade later, in his explorations of ultraprecision machining, Professor Norio Taniguchi coined the term nanotechnology. It wasn't until 1981, with the development of the scanning tunneling microscope that could "see" individual atoms that modern nanotechnology began.

1.13 Fundamental Concepts in Nanoscience and Nanotechnology

It's hard to imagine just how small nanotechnology is. One nanometer is a billionth of a meter, or 10-9 of a meter. Here are a few illustrative examples:

Fig no: 3 Medieval stained glass windows are an example of how nanotechnology was used in the pre-modern era. There are 25,400,000 nanometers in an inch .A sheet of newspaper is about 100,000 nanometers thick. On a comparative scale, if a marble were a nanometer, then one meter would be the size of the Earth.

Nanoscience and nanotechnology involve the ability to see and to control individual atoms and molecules. Everything on Earth is made up of atoms—the food we eat, the clothes we wear, the buildings and houses we live in, and our own bodies. But something as small as an atom is impossible to see with the naked eye. In fact, it's impossible to see with the microscopes typically used in a high school science classes. The microscopes needed to see things at the nanoscale were invented in the early 1980s.Once scientists had the right tools, such as the scanning tunneling microscope (STM) and the atomic force microscope (AFM), the age of nanotechnology was born.

Although modern nanoscience and nanotechnology are quite new, nanoscale materials were used for centuries. Alternate-sized gold and

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silver particles created colors in the stained glass windows of medieval churches hundreds of years ago. The artists back then just didn't know that the process they used to create these beautiful works of art actually led to changes in the composition of the materials they were working with.

Today's scientists and engineers are finding a wide variety of ways to deliberately make materials at the nanoscale to take advantage of their enhanced properties such as higher strength, lighter weight, increased control of light spectrum, and greater chemical reactivity than their larger-scale counterparts.

1.14 Advantages of nanoparticles technologies in cancer therapy

Various studies show that Nanoparticles have ability to target to cancer cells without damaging healthy cells. So now a day Nanoparticles technologies are considered as superior drug delivery system in cancer therapy than other conventional dosage form. Target and enter into selective tissue at molecular level.

- Increase cellular uptake and drug localization.
- Accurate and selective drug delivery to cancerous cell without interaction with healthy cells
- Providing large surface area
- Providing high absorption rate
- Less amount of dose required.
- Decrease drug resistance.
- Decrease toxicity.
- To improve the uptake of poorly soluble drugs
- Nanoparticles can better deliver drugs to tiny areas within the body.
- Nanoparticles overcome the resistance offered by the physiological barriers in the bod

1.15 Factors affecting the selection of material for nanoparticles preparation are

- Need of Nanoparticles size.
- Drug properties such as stability and aqueous solubility
- Desired drug release profile
- Required surface charge of Nanoparticles
- Biocompatibility and biodegradability
- Toxicity and antigenicity of product

Cancer is one of the most common problems and serious health issue in this world. Human body contains millions of tiny cells; these tiny cells are living units of the body. Cancer is a complex disorder that results from multiple genetic changes and cellular abnormalities. Genetic changes that cause cancer can be, Inherited from our parents, Person's lifetime and Environmental exposures such as chemicals in tobacco, smoke, radiation, ultraviolet rays from the sun.

1.16 Nanotechnology Applications in:

Medicine

Researchers are developing customized nanoparticles the size of molecules that can deliver drugs directly to diseased cells in your body. When it's perfected, this method should greatly reduce the damage treatment such as chemotherapy does to a patient's healthy cells.

Electronics

Nanotechnology holds some answers for how we might increase the capabilities of electronics devices while we reduce their weight and power consumption. Check out our Nanotechnology Applications in Electronics page to see how nanotechnology is being used in electronics.

Food

Nanotechnology is having an impact on several aspects of food science, from how food is grown to how it is packaged. Companies are developing nanomaterials that will make a difference not only in the taste of food, but also in food safety, and the health benefits that food delivers. Check out our Nanotechnology Applications in Food page for the details.

Fuel Cells

Nanotechnology is being used to reduce the cost of catalysts used in fuel cells to produce hydrogen ions from fuel such as methanol and to improve the efficiency of membranes used in fuel cells to separate hydrogen ions from other gases such as oxygen. Check out our Nanotechnology Applications in Fuel Cells page for the details.

Solar Cells

Companies have developed nanotech solar cells that can be manufactured at significantly lower cost than conventional solar cells. Check out our Nanotechnology Applications in Solar Cells page for the details.

Batteries

Companies are currently developing batteries using nanomaterials. One such battery will be a good as new after sitting on the shelf for decades. Another battery can be recharged significantly faster than conventional batteries.

Space

Nanotechnology may hold the key to making space-flight more practical. Advancements

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in nanomaterials make lightweight spacecraft and a cable for the space elevator possible. By significantly reducing the amount of rocket fuel required, these advances could lower the cost of reaching orbit and traveling in space.

Fuels

Nanotechnology can address the shortage of fossil fuels such as diesel and gasoline by making the production of fuels from low grade raw materials economical, increasing the mileage of engines, and making the production of fuels from normal raw materials more efficient.

Better Air Quality

Nanotechnology can improve the performance of catalysts used to transform vapors escaping from cars or industrial plants into harmless gasses. That's because catalysts made from nanoparticles have a greater surface area to interact with the reacting chemicals than catalysts made from larger particles. The larger surface area allows more chemicals to interact with the catalyst simultaneously, which makes the catalyst more effective. Check our Nanotechnology and Air Quality page for details.

Better Water Quality

Nanotechnology is being used to develop solutions to three very different problems in water quality. One challenge is the removal of industrial wastes, such as a cleaning solvent called TCE, from groundwater. Nanoparticles can be used to convert the contaminating chemical through a chemical reaction to make it harmless. Studies have shown that this method can be used successfully to reach contaminates dispersed in underground ponds and at much lower cost than methods which require pumping the water out of the ground for treatment. Check out our Nanotechnology and Water Quality page for details.

Chemical Sensors

Nanotechnology can enable sensors to detect very small amounts of chemical vapors. Various types of detecting elements, such as carbon nanotubes, zinc oxide nanowires or palladium nanoparticles can be used in nanotechnology-based sensors. Because of the small size of nanotubes, nanowires, or nanoparticles, a few gas molecules are sufficient to change the electrical properties of the sensing elements. This allows the detection of a very low concentration of chemical vapors. Check out our Nanotechnology Applications in Chemical Sensors page for details.

Sporting Goods

If you're a tennis or golf fan, you'll be glad to hear that even sporting goods has wandered into the nano realm. Current nanotechnology applications in the sports arena include increasing the strength of tennis racquets, filling any imperfections in club shaft materials and reducing the rate at which air leaks from tennis balls. Check out our Nanotechnology Applications in Sporting Goods page for details.

Fabric

Making composite fabric with nano-sized particles or fibers allows improvement of fabric properties without a significant increase in weight, thickness, or stiffness as might have been the case with previously-used techniques. For details see our Nanotechnology in Fabrics page.

Surgery

Nanotechnology has played a major role in all surgical specialties with fabrication of surgical implants and tissue engineering products. They have improved imaging technology, drug delivery systems and scaffolds fabrication with improved material-cell interaction that are useful in surgical practice of wound healing. Surgical tools: Surgical blades made with diamond nano layers has major advantages of • As diamond has a low friction coefficient, it decreases the penetration force in tissues. • It has chemical and biological inertness. It has the property of little physical adhesion to materials or tissues. • Plasma-polished blade available as Diamaze PSD-Plasma Sharpened Diamond. It has a decreased coating thickness from 5-25 ìm to 0.5 ìm with reduced surface roughness to 20-40 nm. They are ideal for precise surgery in the fields of Plastic, ophthalmic and neuro-surgery

1.17 Nanotechnology to fight and cure cancer

Cancer is one of the leading causes of death in the world and remains a difficult disease to treat. Current problems associated with conventional cancer chemotherapies include insolubility of drugs in aqueous medium; delivery of sub-therapeutic doses to target cells; lack of bioavailability; and most importantly, non-specific toxicity to normal tissues. Recent contributions of nanotechnology research address possible solutions to these conundrums. Nevertheless, challenges remain with respect to delivery to specific sites, real time tracking of the delivery system, and control over the release system after the drug has been transported to the target site.

Nanotechnology applications to diagnose and treat cancers are already a reality providing a wide range of new tools and possibilities, from earlier diagnostics and improved imaging to better, more efficient, and more targeted therapies.

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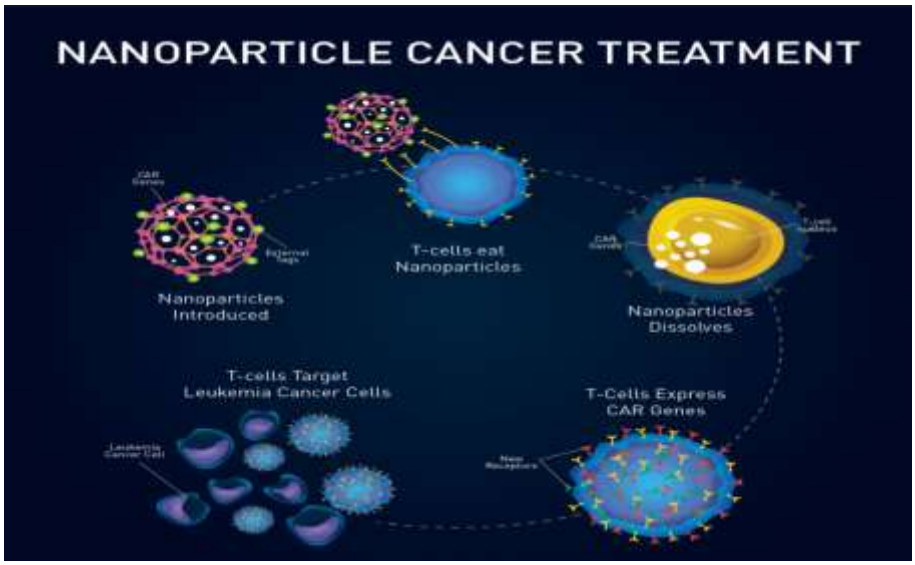

Fig no: 4 Nanoparticle in cancer treatment

1.18 Benefits of Nanotechnology for Cancer

Nanoscale devices are one hundred to ten thousand times smaller than human cells. They are similar in size to large biological molecules ("biomolecules") such as enzymes and receptors. As an example, hemoglobin, the molecule that carries oxygen in red blood cells, is approximately 5 nanometers in diameter.

Nanoscale devices smaller than 50 nanometers can easily enter most cells, while those smaller than 20 nanometers can move out of blood vessels as they circulate through the body. Because of their small size, nanoscale devices can readily interact with biomolecules on both the surface and inside cells. By gaining access to so many areas of the body, they have the potential to detect disease and deliver treatment in ways unimagined before now.

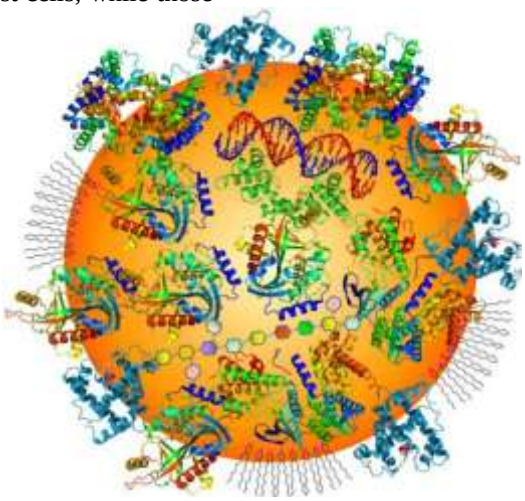

Fig no: 5 Illustration of a protein corona formed on a gold nanoparticle (AuNP) surface upon adsorption of blood serum proteins and other biomolecules

1.19 Passive Tumor Accumulation

An effective cancer drug delivery should achieve high accumulation in tumor and spare the surrounding healthy tissues. The passive localization of many drugs and drug carriers due to their extravasation through leaky vasculature (named the Enhanced Permeability and Retention [EPR] effect) works very well for tumors.As tumor mass grows rapidly, a network of blood vessels needs to expand quickly to accommodate tumor

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cells' need for oxygen and nutrient. This abnormal and poorly regulated vessel generation (i.e. angiogenesis) results in vessel walls with large pores (40 nm to 1 um); these leaky vessels allow relatively large nanoparticles to extravasate into tumor masses. As fast growing tumor mass lacks a functioning lymphatic system, clearance of these nanoparticles is limited and further enhances the accumulation. Through the EPR effect, nanoparticles larger than 8 nm (between 8-100 nm) can passively target tumors by freely pass through large pores and achieve higher intratumoral accumulation. The majority of current nanomedicines for solid tumor treatment rely on EPR effect to ensure high drug accumulation thereby improve treatment efficacy. Without targeting cell types expressing targeting ligand of interest, this drug delivery system is called passive targeting.

Before reaching to the proximity of tumor site for EPR effect to take place, passive targeting requires drug delivery system to be long-circulating to allow sufficient level of drug to the target area. To design nano-drugs that can stay in blood longer, one can "mask" these nano-drugs by modifying the surface with water-soluble polymers such as polyethylene glycol (PEG); PEG is often used to make water-insoluble nanoparticles to be water-soluble in many pre-clinical research laboratories. PEG-coated liposomal doxorubicin (Doxil) is used clinically for breast cancer leveraging passive tumor accumulation. As in vivo surveillance system for macromolecules (i.e., scavenger receptors of the reticuloendothelial system, RES) reportedly showed faster uptake of negatively charged nanoparticles, nano-drugs with a neutral or positive charge are expected to have a longer plasma half-life.

Utilizing EPR effect for passive tumor targeting drug delivery is not without problems. Although EPR effect is a unique phenomenon in solid tumors, the central region of metastatic or larger tumor mass does not exhibit EPR effect, a result of an extreme hypoxic condition. For this reason, there are methods used in the clinics to artificially enhance EPR effect: slow infusion of angiotensin II to increase systolic blood pressure, topical application of NO-releasing agents to expand blood and photodynamic therapy or hyperthermia-mediated vascular permeabilization in solid tumors.

Passive accumulation through EPR effect is the most acceptable drug delivery system for solid tumor treatment. However, size or molecular weight of the nanoparticles is not the sole determinant of the EPR effect, other factors such as surface charge, biocompatibility and in vivo surveillance system for macromolecules should not be ignored in designing the nanomedicine for efficient passive tumor accumulation.

1.20 Active Tumor Targeting

EPR effect, which serves as nanoparticle 'passive tumor targeting' scheme is responsible for accumulation of particles in the tumor region. However, EPR does not promote uptake of nanoparticles into cells; yet nanoparticle/drug cell internalization is required for some of the treatment modalities relying on drug activation within the cell nucleus or cytosol (1). Similarly, delivery of nucleic acids (DNA, siRNA, miRNA) in genetic therapies requires escape of these molecules from endosome so they can reach desired subcellular compartments. In addition, EPR is heterogenous and its strength vary among different tumors and/or patients. For these reasons, active targeting is considered an essential feature for next generation nanoparticle therapeutics. It will enable certain modalities of therapies not achievable with EPR and improve effectiveness of treatments which can be accomplished using EPR, but with less than satisfactory effect. Active targeting of nanoparticles to tumor cells, microenvironment or vasculature, as well as directed delivery to intracellular compartments, can be attained through nanoparticle surface modification with small molecules, antibodies, affibodies, peptides or aptamers.

Passive targeting (EPR effect) is the process of nanoparticles extravasation from the circulation through the leaky vasculature to the tumor region. The drug molecules carried by nanoparticle are released in the extracellular matrix and diffuse throughout the tumor tissue. The particles carry surface ligands to facilitate active targeting of particles to receptors present on target cell or tissue. Active targeting is expected to enhance nanoparticle/drug accumulation in tumor and also promote their prospective cell uptake through receptor mediated endocytosis. The particles, which are engineered for vascular targeting, incorporate ligands that bind to endothelial cell-surface receptors. The vascular targeting is expected to provide synergistic strategy utilizing both targeting of vascular tissue and cells within the diseased tissue.

Most of the nanotechnology-based strategies which are approved for clinical use or are in advanced clinical trials rely on EPR effect. It is

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expected that next generation nanotherapies will use targeting to enable and enhance intracellular uptake, intracellular trafficking, and penetration of physiological barriers which block drug access to some tumors.

1.21 Approaches for drug vehicles, targeting, and release

It is well-known that the activity of the anticancer drugs is greatly attenuated by the time drug reaches the target, which can render the treatment to be ineffective and increase off-target effects. The effectiveness of anticancer drug treatment can be achieved only when the administered drug is of proper dosage and display maximal activity in the cancer cells. Thus, the nanomaterials used for targeting tumor cells should have the capability of increasing local concentration of the drugs in and around tumor cells, thereby reducing the potential toxicity toward healthy cells. The efficient delivery of nanomaterials to the target tissues can be classified as passive and active targeting, as discussed below

Passive targeting

The most common route of administration of nanomaterial-based anticancer drugs is intravenous injection. This approach bypasses the absorption step across the intestinal epithelium required after oral administration. At tumor sites, the vascular barrier is disrupted, and this enables nanocarriers to accumulate in the tumor tissue as depicted in Fig. 2 . The gaps between the endothelial cells in the tumor vasculature can range from 200 to 2000 nm depending on the tumor type, localization, and environment. Moreover, due to the poor lymphatic function, the nanoparticles are not rapidly cleared and accumulate in the tumor interstitium. This is known as enhanced permeability and retention (EPR) effect, which is the basis of passive targeting. This accumulation of the drug at the tumor sites is a passive process, and it requires prolonged circulation of the drug for appropriate drug delivery. The accumulation of the nanocarriers is essentially depends on physicochemical properties such as size, shape (morphology), surface charge and surface chemistry. The extent and kinetics of nanomaterial accumulation at the tumor site are influenced by their size. The nanocarriers need to be smaller than the cut-off of the proportions in the neovasculature, with the extravasation to the tumor acutely affected by the size of the vehicle. Further, the bio distribution of the nanomaterial–drug formulation is influenced by blood perfusion, passive interactions with biomolecules along the route, and immunological clearance processes such as phagocytosis or renal clearance.

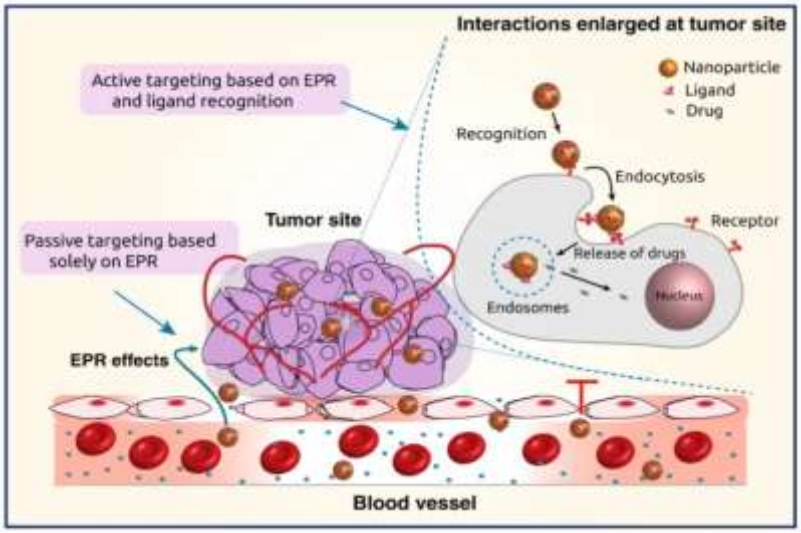

Fig no: 6 Graphical illustration of passive and active drug targeting strategies.

1.22 Targeting Agents

Nanocarriers are used as targeting agents for cancer therapy comprising anticancer drugs, targeting moieties, and polymers. There are a variety of nanocarriers such as liposomes, dendrimers, micelles, carbon nanotubes, nanocapsules, nanospheres, and so forth. Therapeutic agents can be entrapped, covalently bound, encapsulated, or adsorbed to the nanoparticles. Liposomes are composed of lipid bilayers where the core can be either hydrophilic or hydrophobic depending on the number of lipid

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bilayers. Liposomes having a single lipid bilayer contain an aqueous core for encapsulating water soluble drugs, whereas other liposomes having more than a single bilayer entrap lipid soluble drugs. They are readily cleared by the macrophages and are therefore coated with inert polymers for stabilization in the physiological conditions. Liposomes are commonly coated with polyethylene glycol (PEG). In vivo study shows that liposomes coated with hyaluronan (HA) improves circulation time and enhances targeting to HA receptor-expressing tumors. Both active and passive targeting can be achieved with liposomal drug delivery.

Liposomal nanoparticles can conjugate with either antibodies or ligands for selective drug delivery. They possess some advantages that they are biodegradation, nonantigenic and have a high transport rate. They can also be designed for pH sensitive drug delivery or thermotherapy. Dendrimers are branched three dimensional tree-like structures with a multifunctional core. They are synthesized from either synthetic or natural elements such as amino acids, sugars, and nucleotides. Dendrimers can be prepared by controlled polymerization of the monomers maintaining desired shape and size. Multiple entities including both hydrophobic and hydrophilic molecules can be conjugated to dendrimers due to their exclusive branching point. They can also be loaded with drugs using the cavities in their cores through hydrophobic interactions, hydrogen bonds, or chemical linkages. Dendrimers are capable of delivering genes, drugs, anticancer agents, and so forth. Micelles are spherical structures where molecules with a hydrophobic end aggregate to form the central core and the hydrophilic ends of other molecules are in contact with the liquid environment surrounding the core. Micelles are effective carrier for the delivery of water insoluble drugs carried in the hydrophobic core.

1.23 Transport across Tissue Barriers

Nanoparticle or nano-drug delivery is hampered by tissue barriers before the drug can reach the tumor site. Tissue barriers for efficient transporting of nano-drugs to tumor sites include tumor stroma (e.g. biological barriers) and tumor endothelium barriers (e.g. functional barriers). Biological barriers are physical constructs or cell formation that restrict the movement of nanoparticles. Functional barriers can affect the transport of intact nanoparticles or nanomedicine into the tumor mass: elevated interstitial fluid pressure and acidic environment for examples. It is important to design nanoparticles and strategies to overcome these barriers to improve cancer treatment efficacy.

1.24 Tumor microenvironment (TME) is a dynamic system composed of abnormal vasculature, fibroblasts and immune cells, all embedded in an extracellular matrix (ECM). TME poses both biological and functional barriers to nano-drug delivery in cancer treatment. Increase cell density and abnormal vasculature elevate the interstitial fluid pressure within a tumor mass. Such pressure gradient is unfavorable for free diffusion of the nanoparticles and is often a limiting factor for the enhanced permeability and retention (EPR) effect. When tumor mass reaches 106 cells in number, metabolic strains ensue. Often, cells in the core of this proliferating cluster are distanced by 100-200 um from the source of nutrient: 200um is a limiting distance for oxygen diffusion. As a result, cancer cells in the core live at pO2 levels below 2.5-10mmHg and become hypoxic; anoxic metabolic pathway can kick in and generate lactic acid. Nanoparticles become unstable in an acidic environment and delivery of the drugs to target tumor cells will be unpredictable. ECM of the tumor provides nutrient for cancer cells and stromal cell. It is a collection of fibrous proteins and polysaccharides and expands rapidly in aggressive cancer as the result of stromal cell proliferation. The most notorious biological barrier to cancer treatment is pancreatic stroma in pancreatic ductal adenocarcinoma (PADC). Pancreatic cancer stroma has the characteristics of an abnormal and poorly functioning vasculature, altered extracellular matrix, infiltrating macrophages and proliferation of fibroblasts. Not only tumor-stroma interactions have been shown to promote pancreatic cancer cell invasion and metastasis, but TME and tumor stroma also create an unfavorable environment for drug delivery and other forms of cancer treatments.

Because EPR effect is a clinically relevant phenomenon for nano-carriers' tumor penetration, strategies have been developed to address the tumor endothelium barrier. Strategies to reduce interstitial fluid pressure to improve tumor penetration include ECM-targeting pharmacological interventions to normalize vasculature within TME; hypertonic solutions to shrink ECM cells; hyperthermia, radiofrequency (RF) or high-intensity focused ultrasound (HIFU) to enhance nano-drug transport and accumulation.

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These strategies can also alleviate hypoxic conditions in larger tumor mass. Although TME and tumor mass pose a harsh and acidic environment for nano-carrier stability, pH-responsive nano-carrier designs leveraging this unique feature are gaining interest in recent years. Many of the strategies described above are used to address tumor stroma barrier.

Another formidable tissue barrier for drugs and nanoparticle delivery is the blood-brain barrier (BBB). BBB is a physical barrier in the central nervous system to prevent harmful substances from entering the brain. It consists of endothelial cells which are sealed in continuous tight junction around the capillaries. Outside the layer of epithelial cell is covered by astrocytes that further contribute to the selectivity of substance passage. As BBB keeps harmful substances from the brain, it also restricts the delivery of therapeutics for brain diseases, such as brain tumors and other neurological diseases. There have been tremendous efforts in overcoming the BBB for drug delivery in general. The multi-valent feature of nanoparticles makes nano-carriers appealing in designing BBB-crossing delivering strategies. One promising nanoparticle design has transferrin receptor-targeting moiety to facilitate transportation of these nanoparticles across the BBB.

In the fight against cancer, half of the battle is won based on its early detection. Nanotechnology provides new molecular contrast agents and materials to enable earlier and more accurate initial diagnosis as well as in continual monitoring of cancer patient treatment.Although not yet deployed clinically for cancer detection or diagnosis, nanoparticles are already on the market in numerous medical screens and tests, with the most widespread use that of gold nanoparticles in home pregnancy tests. Nanoparticles are also at the heart of the Verigene® system from Nanosphere and the T2MR system from T2 Biosystems, currently used in hospitals for a variety of indications.

For cancer, nanodevices are being investigated for the capture of blood borne biomarkers, including cancer-associated proteins circulating tumor cells, circulating tumor DNA, and tumor-shed exosomes. Nano-enabled sensors are capable of high sensitivity, specificity and multiplexed measurements. Next generation devices couple capture with genetic analysis to further elucidate a patient's cancer and potential treatments and disease course.Already clinically established as contrast agents for anatomical structure, nanoparticles are being developed to act as molecular imaging agents, reporting on the presence of cancer-relevant genetic mutations or the functional characteristics of tumor cells. This information can be used to choose a treatment course or alter a therapeutic plan. Bioactivatable nanoparticles that change properties in response to factors or processes within the body act as dynamic reporters of in vivo states and can provide both spatial and temporal information on disease progression and therapeutic response.

1.25 Types of nanoparticles used as drug delivery systems

Nanoparticles useful as drug delivery systems these are submicron sized particles (3–200 nm), devices or systems that can be made by using a variety of materials including lipids (liposomes), polymers (polymeric nanoparticles, micelles or dendrimers), viruses (viral nanoparticles) and even organometallic compound.

Polymer-based drug carriers Depending on the method of preparation of polymeric-based drug carriers, the drug is either covalently bound to or physically entrapped in polymer matrix [40]. The resulting compounds may have the structure of capsules (polymeric nanoparticles or polymer–drug conjugates), amphiphilic core/ shell (polymeric micelles), or may be hyper branched macromolecules. Polymers used as drug conjugates can be divided into two groups one is natural polymers and other is synthetic polymers.

Polymeric nanoparticles (polymer–drug conjugates) Albumin, chitosan and heparin are naturally occurring polymers and have been used as a material of choice for the delivery of DNA, oligonucleotides and protein, as well as drugs. Recently, serum albumin is included as a carrier for the formulation of paclitaxel nanoparticle [nanometer-sized albumin-bound paclitaxel (Abraxane); Figure 3(A)], has been used in the clinic for the treatment of metastatic breast cancer . Besides metastatic breast cancer, Abraxane has also been evaluated in clinical trials for many other cancers including non-small-cell lung cancer (phase II trial) and advanced non-haematologic malignancies (phase I and pharmacokinetics trials; .PGA was the first biodegradable polymer to be used for conjugate synthesis among other synthetic polymers such as N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), polystyrene-maleic anhydride copolymer, polyethylene glycol

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(PEG) and poly-L-glutamic acid (PGA). Several representative chemotherapeutics that are used widely in the clinic have been tested as conjugates with PGA in vitro and in vivo and showed encouraging abilities to circumvent the shortcomings of their free drug counterparts. Among them, Xyotax (PGA paclitaxel; [30]) and CT-2106 (PGA-camptothecin ;) are now in clinical trials. HPMA and PEG are the most widely used non-biodegradable synthetic polymers. PK1, which is a conjugate of HPMA with doxorubicin, was the synthetic polymer-drug conjugate to be evaluated in clinical trials as an anticancer agent. A phase I clinical trial has been completed in patients with a variety of tumours that were refractory or resistant to prior therapy such as chemotherapy and/or radiation. PK1 should be further evaluated in the next level of clinical trials.

Lipid-based drug carriers

Liposomes first described in 1965, liposomes are one of the first nanoparticle platforms to be applied in medicine. Today, there are more than 11 formulations which are approved for clinical use, with many more in clinical and preclinical development. Liposomes are self-assembling closed colloidal structures composed of lipid bilayers having a spherical shape in which an outer lipid bilayer surrounds a central aqueous space (Figure 3(D)). Their biocompatible and biodegradable compositions, as well as their unique ability to encapsulate hydrophilic agents in their aqueous core and hydrophobic agents within their lamellae, make liposomes excellent therapeutic carriers. To improve their stability and circulation halflife, liposomes can also be coated with polymers such as polyethylene glycol (PEG). Liposomal drug formulations typically improve the pharmacokinetics and bio distribution of a drug. For example, PEGylated liposomal doxorubicin reduces the volume of distribution of doxorubicin from 1000 l/m2 in the free drug form to 2.8 l/m2 by restricting the distribution within the plasma. Furthermore, it can achieve higher drug concentrations within tumour while reducing drug concentration in normal tissues, such as heart . Currently, several kinds of cancer drugs have been applied to this lipid-based system using a variety of preparation methods. Among them, liposomal formulations of the anthracyclines doxorubicin (Doxil, Myocet) and daunorubicin (DaunoXome) are approved for the treatment of metastatic breast cancer and AIDS-related Kaposi's sarcoma . Besides these approved agents, many liposomal chemotherapeutics are currently being evaluated in clinical trials. The next generation of liposomal drugs may be immunoliposomes, which selectively deliver the drug to the desired sites of action.

Thermoresponsive systems

Thermoresponsive drug delivery is among the most explored stimuli-responsive strategies and has been widely explored in oncology. Thermoresponsiveness is usually governed by a nonlinear sharp change with temperature in the properties of at least one component of the nanocarrier material. Such a sharp response triggers the release of the drug following a variation in the surrounding temperature. Ideally, thermosensitive nanocarriers should retain their load at body temperature (37° C), and rapidly deliver the drug within a locally heated tumour (40–42° C) Nano chemotherapeutics counteract rapid blood-passage time and washout from the tumor.

Nanoshells

Owing to their non-invasiveness and the possibility of remote spatial and temporal control, in the past few years a large variety of photo responsive systems has been engineered to achieve on-demand drug release in response to illumination of a specific wavelength (in the ultraviolet, visible or near infrared (NIR) regions) . The different strategies available rely on either repeatable on–off drug-release or one-time event triggered by photo sensitiveness-induced structural modifications of the nanocarriers. For instance, doxorubicin-loaded hollow gold nanospheres showed accelerated drug release when irradiated at 808 nm, allowing enhanced anticancer activity and reduced systemic toxicity compared with the free-drug treatment

Nanotechnology based imaging contrast agents being developed and translated today, offer the ability to specifically target and greatly enhance detection of tumor in vivo by way of conventional scanning devices, such as magnetic resonance imaging (MRI), (PET), and computed tomography (CT). Moreover, current nanoscale imaging platforms are enabling novel imaging modalities not traditional utilized for clinical cancer treatment and diagnosis, for example photoacoustic tomography (PAT), Raman spectroscopic imaging and multimodal imaging (i.e., contrast agents specific to several imaging modalities simultaneously). Nanotechnology enables all of these platforms by way of its ability to carry multiple components simultaneously (e.g., cancer

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cell-specific targeting agents or traditional imaging contrast agents) and nanoscale materials that are themselves the contrast agents of which enable greatly enhanced signal.

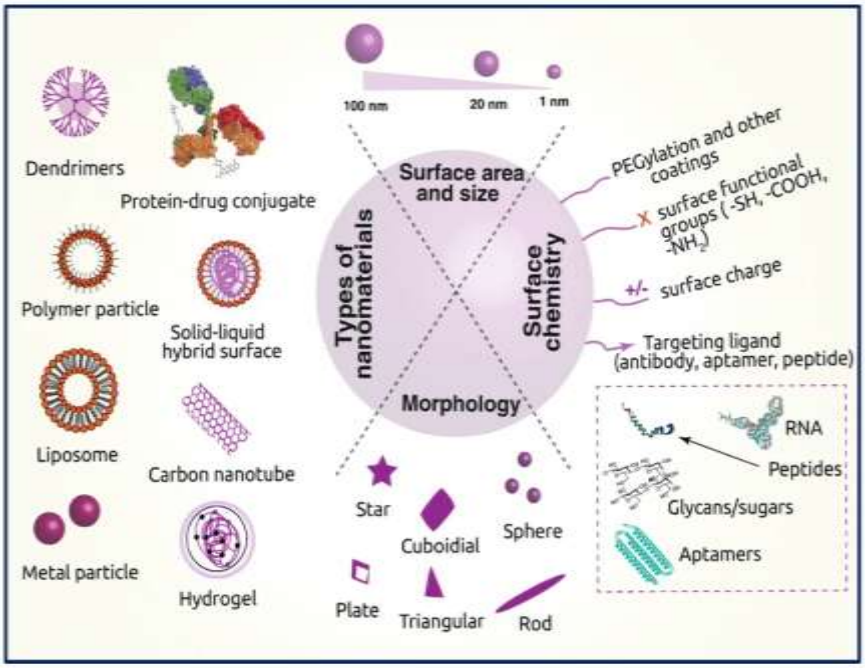

Fig no : 7 Schematic representation of different types of nanomaterials employed in cancer therapy, their important physical properties and surface chemistry required to carry drugs

1.26 Nanomaterial as drug delivery agents

A wide range of nanotherapeutics, composed of organic and inorganic nanomaterials have been developed with multiple types of drugs or molecules for cancer imaging, detection and treatment. In this section, multiple nanocarriers have been discussed including liposomes, dendrimers, polymeric nanoparticles, and metal nanoparticles.

Inorganic nanoparticles

This category of nanomaterials forms a significant fraction of current drug delivery systems due to their precise control of size and shape, tunable physicochemical properties, controlled surface chemistry and diverse multifunctionality. A range of inorganic nanomaterials have been developed in recent past with meticulous properties and employed in biomedical applications especially in cancer treatment and management. Among the inorganic nanomaterials, metal nanoparticles and metal oxides have gained noteworthy consideration due to their exceptional properties and recent progress in the fundamental understanding through the development of innovative techniques. Other major nanomaterials that have noticeable contribution in drug delivery are carbon-based nanostructures and mesoporous silica nanoparticles.

NCI-funded research has produced many notable examples over the last several years. For example, researchers at Stanford University and Memorial Sloan Kettering Cancer Center developed multimodal nanoparticles capable of delineating the margins of brain tumors both preoperatively and intraoperatively. These MRI-PAT-Raman nanoparticles are able to be used both to track tumor growth and surgical staging, by way of MRI, but also in the same particle be used during surgical resection of brain tumor to give the surgeon ‘eyes’ down to the single cancer cell level, increasing the potential tumor specific tissue removal.

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Table no: 1 various nanoparticle based delivery systems with their therapeutic and diagnostic uses in cancer therapy.

Nanoparticle based delivery systems	Therapeutic and diagnostic use
Liposomes	Controlled and targeted drug delivery; Targeted gene delivery.
Nanoshells	Tumor targeting
Fullerene based derivatives	As targeting and imaging agent
Carbon nanotube	Drug gene and DNA delivery; Tumor targeting
Dendrimers	Targeted drug delivery
Quantum dots	As targeting and imaging agent
Gold nanoparticles	Targeted delivery and imaging agent
Solid lipid nanoparticle (SLN)	Controlled and targeted drug delivery
Nonowires	As targeting and imaging agent
Paramagnetic nanoparticles	As targeting and imaging agent

For metastatic melanoma, researchers at MSKCC and Cornell University have developed silica-hybrid nanoparticles ('C-dots') that deliver both PET and optical imaging contrast in the same platform. These nanoparticles are actively targeted to the cancer with cRGDY peptides that target this specific tumor type and have already made it successfully through initial clinical trials.

Another clinical cancer imaging problem being addressed by nanoscale solutions is prostate cancer. Researchers at Stanford University recently have been developing nanotechnologies that give both anatomical size and location of prostate cancer cells (Nano bubbles for ultrasound imaging) and functional information to avoid over diagnosis/treatment as well as to monitor progression (self-assembling nanoparticles for photoacoustic imaging). The Nano platforms developed by this group are coupled directly to their recently approved handheld transrectal ultrasound and photoacoustic (TRUSPA) device. Ultimately offering a more effective, integrated and less invasive technique to image and biopsy prostate cancers for diagnosis and prognostication prior to performing common interventions (surgical resection, radiotherapy, etc.).

Similarly, gold nanoparticles are being used to enhance light scattering for endoscopic techniques that can be used during colonoscopies. One really powerful potential that has always been envisioned for nanotechnology in cancer has been the potential to simultaneously image and deliver therapy in vivo and several groups have been pushing forward these 'theranostic' nanoscale platforms. One group at Emory University has been developing one of these for ovarian and pancreatic cancers, which are traditionally harder to deliver therapeutics to. Their platform for pancreatic cancer can break through the fibrotic stromal tissue of which these tumors are protected by in the pancreas. After traversing through this barrier, they are composed of magnetic iron cores which allow MRI contrast for diagnosis and deliver small-molecule drugs directly to cancer cells to treat.

Finally, nanotechnology is enabling the visualization of molecular markers that identify specific stages and cancer cell death induced by therapy, allowing doctors to see cells and

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molecules undetectable through conventional imaging. A group at Stanford has developed the Target-Enabled in Situ Ligand Assembly (TESLA) nanoparticle system. This is based off nanoparticles which form directly in the body after IV-injection of molecular precursors. The precursors contain specific sequences of atoms which can only form larger nanoparticles after being cleaved by enzymes produced by cancer cells during apoptosis (i.e., cell death) and carry various image contrast agents to monitor (PET, MRI, etc.) local tumor response to therapies. Being able to track cancer cell death in vivo and at the molecular level is extremely important for delivering effective dosing regimens and/or precisely administering novel therapies or combinations.

1.27 Drug release strategy

Payload delivery capacity depends on how effectively drugs have been packaged, and how drug release mechanisms are programmed into the nanosystems. Drug 'packaging' efficacy depends on encapsulation or drug conjugation efficiency. Different nanoparticles provide different means of entrapping drug molecules, as described later in the section. Modulating rate of drug release in response to an activation signal constitutes an essential strategy to achieve controlled release purposes as well as maintaining effective therapeutic dosage over a stretch of time. Tere are two categories of nanosystems, open-loop control systems and closed-loop control systems, grouped according to what activation factors stimulate drug release as schematically shown in Fig 8. In open-loop control systems, external factors such as magnetic pulses, thermal, acoustic pulses or electric fields control drug release. In contrast, in closed-loop systems the drug release rate is controlled by the presence and intensity of internal stimuli in the vicinity of the target sites . A few current strategies are based on the 'chemistry' programmed into the nanosystems that are responsive towards pH or temperature, erosion due to the local chemical environment, redox reaction-based release, and enzyme-mediated release as discussed below

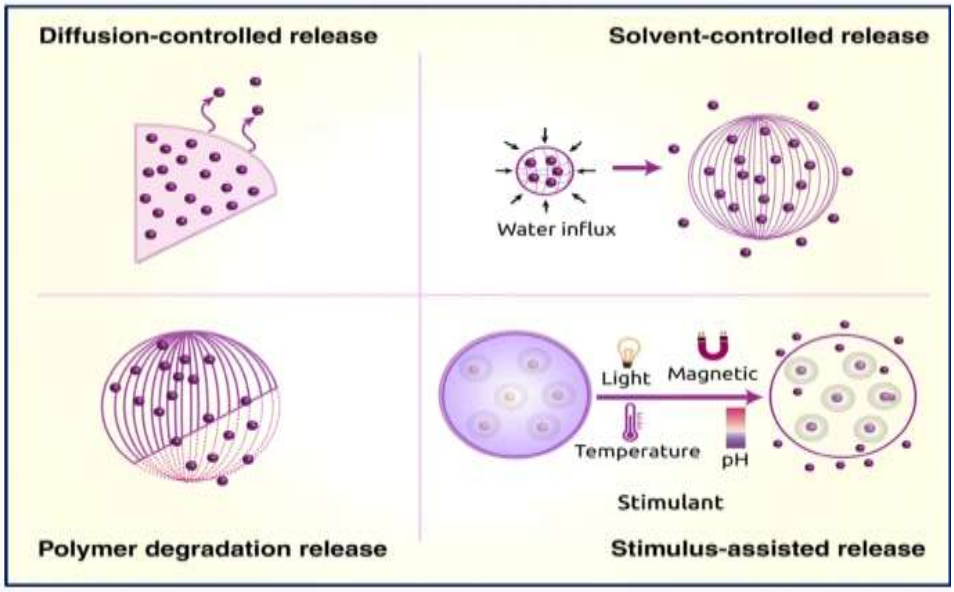

Fig no: 8 Schematic depiction of diffusion-, solvent-controlled, polymer degradation, and other stimuli reliant drug release

1.28 Redox-activated drug release

In redox-activated drug release mechanism, a redox responsive nanocarrier containing functional groups that reacts upon contact with oxidizing and/or reducing environment in and around cancer cells (peroxides, GSH, and free radicals), undergoing to chemical bond cleavage [63]. The chemical changes can also introduce changes in the hydrophobicity of the polymer, changing the integrity of nanoparticles and thereby leading to release of drug cargo. For example, in poly (propylene sulfde) polymer nanoparticles, disulfide bonds act as a redox-responsive motif, and upon reacting with H2O2 leads to a change of hydrophobicity of the polymers causing a collapse of nanoparticles and thus drug release. Redox-response moieties can also respond to the stimuli in a non-linear fashion.

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This complexity allows a prompt reaction to the high concentration of stimuli, but not to low concentrations, achieving controlled specificity.

1.29 Imaging In Vivo

Current imaging methods can only detect cancers once they have made a visible change to a tissue, by which time, thousands of cells will have proliferated and perhaps metastasized. And even when visible, the nature of the tumor—malignant or benign—and the characteristics that might make it responsive to a particular treatment must be assessed through tissue biopsies. Furthermore, while some primary malignancies can be determined to be metastatic, tumor pre-seeding of metastatic sites and micro-metastases are extremely difficult to detect with modern imaging modalities, even if the tissue in which they commonly occur are known, a priori. Finally, surgical resection of tumor tissue remains the standard of care for many tumor types and surgeons must weigh the consequences of removing often vital healthy tissue versus the cancerous mass which has grown non-uniformly within. Ultimately, removal of cancer cells at the single cell level is not possible with current surgical techniques.

1.30 Sensing In Vitro

Nanotechnology-enabled in vitro diagnostic devices offer high sensitivity and selectivity, and capability to perform simultaneous measurements of multiple targets. Well-established fabrication techniques (e.g., lithography) can be used to manufacture integrated, portable devices or point-of-care systems. A diagnostic device or biosensor contains a biological recognition element, which through biochemical reaction can detect the presence, activity or concentration of a specific biological molecule in the solution. This reaction could be associated, for example with: binding of antigen and antibody, hybridization of two single stranded DNA fragments, or binding of capture ligand to the cell surface epitope. A transducer part of the detection device is used to convert the biochemical event into a quantifiable signal which can be measured. The transduction mechanisms can rely on light, magnetic, or electronic effects.

Several devices have been designed for detection of various biological signatures from serum or tissue. Few examples of diagnostic devices relying on nanotechnology or nanoparticles are given .The bio-barcode assay was designed as a sandwich immunoassay in the laboratory of Chad Mirkin at Northwestern University. It utilizes magnetic nanoparticles (MMPs) which are functionalized with monoclonal antibodies specific to the target protein of interest and then mixed with the sample to promote capture of target proteins. The MMP-protein hybrid structures are then combined with gold nanoparticle (Au-NP) probes which carry DNA-barcodes. Target protein-specific DNA barcodes are released into solution and detected using the scanometric assay with sensitivities in femto-picomolar range.

James Heath's laboratory at Caltech designed sandwich immunoassay devices which rely on DNA-encoded antibody libraries (DEAL). DEAL technique uses DNA-directed immobilization of antibodies in microfluidic channels allowing to convert a pre-patterned single stranded (ss) DNA barcode microarray into an antibody microarray. DNA oligomers attached onto the sensor surface are robust and can withstand elevated temperatures of channel fabrication. Subsequent flow-through of the DNA-antibody conjugates in channels transforms the DNA microarray into an antibody microarray and allow to perform multiplex surface-bound sandwich immunoassays. These devices allow for on-chip blood separation and measurement of large protein panels directly from blood.

Diagnostic Magnetic Resonance (DMR) sensor platform was designed in the laboratory of Ralph Weissleder at Massachusetts General Hospital. The DMR mechanism exploits changes in the transverse relaxation signal of water molecules in a magnetic field as a sensing mechanism for magnetic nanoparticle labeledanalytes. Highly integrated systems including microfluidic processing circuits and nuclear magnetic resonance (NMR) detection head with high signal to noise ratio were built and are capable of to detect presence of cells, vesicles, and proteins in clinical samples.

The devices described above are capable of analyzing large panels of biological signatures at the same time providing for high level of multiplexing. The data analysis can establish correlations among different biomarker levels and map correlations of network signaling and thus provide tools for patient stratification based on their response to different treatments and ultimately improve therapeutic efficacy of the one selected. New advancements in microfluidic technologies opened opportunities to integrate sample preparation and sample processing with biosensors and to realize fully integrated devices that directly

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deliver full data for a medical diagnosis from a single sample.

1.31 Measuring Response to Therapy and the Liquid Biopsy

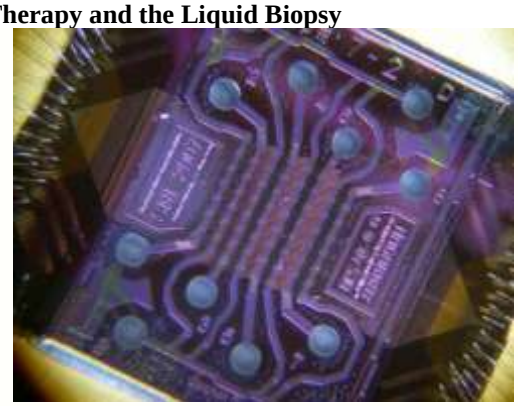

Fig no: 9 Imaged here is a microfluidic magneto-nano chip with 8 by 8 sensors arrays and 8 microfluidic channels. These chips are being developed to monitor protein profiles in blood samples from cancer patients to improve therapeutic effectiveness.

Measurement of an individual patient's response to therapeutics during the course of their disease is the basis for precise and prognostic medical care. Accurate and disease relevant monitoring can allow for optimized treatment regimens (e.g., therapeutic course correction, drug combinations, and dose attenuation), preemptive clinical decision making (e.g., therapeutic responders vs. non-responders, and more), and patient stratification for clinical trials. Beyond the more traditional gold standards of in vivo imaging, tissue biopsy and in vitro diagnostics available for this purpose, the "liquid biopsy" offers the ability to measure response to therapy by way of simple and serial blood draws. Traditional biopsies involve resection of small volumes of the tumor tissue directly, and thus, remain invasive procedures that cannot offer the sampling necessitated to track disease progression relative to the course of therapy or the dynamics of its evolving biology. Liquid biopsies rely on the fact that tumors shed material (e.g., cells, DNA, other cancer-specific biomolecules) into circulation, over time and in response to therapy. Although, the amount of materials shed by any given tumor and / or stage is typically at incredibly low concentrations relative to the rest of the blood's constituents (e.g., erythrocytes, leukocytes, thrombocytes, plasma, etc.). This requires specific and sensitive tools to detect, capture, and purify the circulating tumor material relative to the rest. Nanotechnology is enabling these tools to become reality.

Treatment and Therapy

Cancer therapies are currently limited to surgery, radiation, and chemotherapy. All three methods risk damage to normal tissues or incomplete eradication of the cancer. Nanotechnology offers the means to target chemotherapies directly and selectively to cancerous cells and neoplasms, guide in surgical resection of tumors, and enhance the therapeutic efficacy of radiation-based and other currenttreatmentmodalities.All of this can add up to a decreased risk to the patient and an increased probability of survival.

Research on nanotechnology cancer therapy extends beyond drug delivery into the creation of new therapeutics available only through use of nanomaterial properties. Although small compared to cells, nanoparticles are large enough to encapsulate many small molecule compounds, which can be of multiple types. At the same time, the relatively large surface area of nanoparticle can be functionalized with ligands, including small molecules, DNA or RNA strands, peptides, aptamers or antibodies. These ligands can be used for therapeutic effect or to direct nanoparticle fate in vivo. These properties enable combination drug delivery, multi-modality treatment and combined therapeutic and diagnostic, known as "theranostic," action. The physical properties of nanoparticles, such as energy absorption and re-radiation, can also be used to disrupt diseased tissue, as in laser ablation and hyperthermia applications.

Integrated development of innovative nanoparticle packages and active pharmaceutical ingredients will also enable exploration of a wider

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repertoire of active ingredients, no longer confined to those with acceptable pharmokinetic or biocompatibility behavior. In addition, immunogenic cargo and surface coatings are being investigated as both adjuvants to nanoparticle-mediated and traditional radio- and chemotherapy as well as stand-alone therapies. Innovative strategies include the design of nanoparticles as artificial antigen presenting cells and in vivo depots of immunostimulatory factors that exploit nanostructured architecture for sustained anti-tumor activity.

Table no:2 Some nanoparticles used for medical applications.

Study phase	Product	Description	Use	Manufacturer
Preclinical	MRX 952	Nanoparticle preparation – to encapsulate camptothecin analogues	Tumors	IMA Rx Therapeutics
Preclinical	Targeted Nano Therapeutics (TNT)™ system	TNT with polymer coated iron oxide magnetic particle	Solid tumors	Triton Biosystems
Preclinical	AuroLase™	Gold nanoshell	Head and neck cancer	Nanospectra Biosciences Inc
Preclinical	Dendrimer-Magnevist#	PAMAM dendrimer	MRI imaging agent	Dendritic Nanotechnologies Inc
Phase 1	VivaGel®	Dendrimer based microbicide gel	HIV prevention	Starpharma Pty Ltd
Phase 1	INGN 401	Nanoparticle formulation of tumour suppression gene FUS1	Lung cancer	Introgen Therapeutics Inc
Phase 1&2	Cyclosert-Camptothecin–IT 101	β-Cylcodextrin polymer drug delivery system	Solid tumours	Calando Pharmaceuticals
Phase 2	VivaGel®	Dendrimer based microbicide gel	HSV prevention	Starpharma Pty Ltd
Phase 2	MRX 815	Nanobubble technology	Treatment of intravascular clot	IMA Rx Therapeutics

1.32 Delivering Chemotherapy

The traditional use of nanotechnology in cancer therapeutics has been to improve the pharmacokinetics and reduce the systemic toxicities of chemotherapies through the selective targeting and delivery of these anticancer drugs to tumor tissues. The advantage of nanosized carriers is that they can increase the delivered drug's overall therapeutic index through nanoformulations in with chemotherapeutics are either encapsulated or conjugated to the surfaces of nanoparticles. This capability is largely due to their tunable size and surface properties. Size is a major factor in the delivery of nanotechnology-based therapeutics to tumor tissues. Selective delivery of nanotherapeutic platforms depends primarily on the passive targeting of tumors through the enhanced permeability and retention (EPR) effect. This phenomenon relies on defects specific to tumor microenvironment such as defects in lymphatic drainage, along with increased tumor vasculature permeability, to allow nanoparticles (<200 nm) to accumulate in the tumor microenvironment. Furthermore, the timing or site of drug release can be controlled by triggered events, such as ultrasound, pH, heat, or by material composition.

Several members of the Alliance are working towards developing nanomaterial-based delivery platforms that will reduce the toxicity of chemotherapeutics and increase their overall

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effectiveness. In the Centers for Cancer Nanotechnology Excellence, the Center for Multiple Myeloma Nanotherapy at Washington University is developing a strategy for photodynamic therapy, which would bypass the toxicity that currently limits the effectiveness of chemotherapy for multiple myeloma patients. This strategy is designed for use in bone marrow, which is normally inaccessible to external radiation sources.

The Innovative Research in Cancer Nanotechnology awardees are focused on understanding the fundamental aspects of nanomaterial interactions with the biological system to improve on the development of cancer therapeutics and diagnostics. Several of these awardees are studying nanoparticle-based delivery and have proposed nanosystems that deliver chemotherapeutics by penetrating through physiological barriers for access to more restricted tumors via targeting and/or mechanical deformation of particles (Yang, Karathanasis, Kabanov). One of them is dedicated to using a synergistic approach for the delivery of paclitaxel and gemcitabine chemotherapeutics in mesoporous silica nanoconstructs (Nel).

1.33 Nano-enabled Immunotherapy

Immunotherapy is a promising new front in cancer treatment encompassing a number of approaches, including checkpoint inhibition and cellular therapies. Although results for some patients have been spectacular, only a minority of patients being treated for just a subset of cancers experience durable responses to these therapies. Expanding the benefits of immunotherapy requires a greater understanding of tumor-host immune system interactions.

New technologies for molecular and functional analysis of single cells are being used to interrogate tumor and immune cells and elucidate molecular indicators and functional immune responses to therapy. To this end, nano-enabled devices and materials are being leveraged to sort, image, and characterize T cells in the Alliance's NanoSystems Biology Cancer Center.

Nanotechnologies are also being investigated to deliver immunotherapy. This includes use of nanoparticles for delivery of immunostimulatory or immunomodulatory molecules in combination with chemo- or radiotherapy or as adjuvants to other immunotherapies. Standalone nanoparticle vaccines are also being designed to raise sufficient T cell response to eradicate 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, an approach being pursued in the Nano Approaches to Modulate Host Cell Response for Cancer Therapy Center at UNC. Researchers in this Center are also investigating the use of nanoparticles to capture antigens from tumors following radiotherapy to create patient specific treatments, similar in principle to a "dendritic cell activating scaffold" currently in a Phase I clinical trial.

Additional uses of nanotechnology for immunotherapy include 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.

1.34 Delivering or Augmenting Radiotherapy

Roughly half of all cancer patients receive some form of radiation therapy over the course of their treatment. Radiation therapy uses high-energy radiation to shrink tumors and kill cancer cells. Radiation therapy kills cancer cells by damaging their DNA inducing cellular apoptosis. Radiation therapy can either damage DNA directly or create charged particles (atoms with an odd or unpaired number of electrons) within the cells that can in turn damage the DNA. Most types of radiation used for cancer treatment utilize X-rays, gamma rays, and charged particles. As such, they are inherently toxic to all cells, not just cancer cells, and are given in doses that are as efficacious as possible while not being too harmful to the body or fatal. Because of this tradeoff between efficacy and safety relative to tumor type, location, and stage, often the efficacy of treatment must remain at reduced levels in order to not be overtly toxic to surrounding tissue or organs near the tumor mass.

Nanotechnology-specific research has been focusing on radiotherapy as a treatment modality that could greatly benefit from nanoscale materials' properties and increased tumor accumulation. The primary mechanisms by which these nanoscale platforms rely are either enhancement of the effect of the radiotherapy, augmentation of the therapy, and/or novel externally applied electromagnetic radiation

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modalities. More specifically, most of these nanotechnology platforms rely on the interaction between X-rays and nanoparticles due to inherent atomic level properties of the materials used. These include high-Z atomic number nanoparticles that enhance the Compton and photoelectric effects of conventional radiation therapy. In essence, increasing efficacy while maintaining the current radiotherapy dosage and its subsequent toxicity to the surrounding tissue. Other platforms utilize X-ray triggered drug-releasing nanoparticles that deliver drug locally at tumor site or to sensitize the cancer cells to radiotherapy in combination with the drug.

Another type of therapy that relies upon external electromagnetic radiation is photodynamic therapy (PDT). It is an effective anticancer procedure for superficial tumor that relies on tumor localization of a photosensitizer followed by light activation to generate cytotoxic reactive oxygen species (ROS). Several nanomaterials platforms are being researched to this end. Often made of a lanthanide- or hafnium-doped high-Z core, once injected these can be externally irradiated by X-rays allowing the nanoparticle core to emit the visible light photons locally at the tumor site. Emission of photons from the particles subsequently activate a nanoparticle-bound or local photosensitizer to generate singlet oxygen (1O2) ROS for tumor destruction.

Furthermore, these nanoparticles can be used as both PDT that generates ROS and for enhanced radiation therapy via the high-Z core. Although many of these platforms are initially being studied in vivo by intratumoral injection for superficial tumor sites, some are being tested for delivery via systemic injection to deep tissue tumors. The primary benefits to the patient would be local delivery of PDT to deep tissue tumor targets, an alternative therapy for cancer cells that have become radiotherapy resistant, and reduction in toxicity (e.g., light sensitivity) common to traditional PDT. Finally, other platforms utilize a form Cherenkov radiation to a similar end, of local photon emission to utilize as a trigger for local PDT. These can be utilized for deep-tissue targets as well.

1.35 Delivering Gene Therapy

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 genetic therapeutics such as small interfering RNAs (siRNAs), and microRNAs (miRNAs). Gene silencing therapeutics, siRNAs, have been reported to have significantly extended half-lives when delivered either encapsulated or conjugated to the surface of nanoparticles. These therapeutics are used in many cases to target 'undruggable' cancer proteins. Additionally, the increased stability of genetic therapies delivered by nanocarriers, and often combined with controlled release, has been shown to prolong their effects.

Members of the Alliance are exploring nanotechnology-based delivery of nucleic acids as effective treatment strategies for a variety of cancers. In particular, the Nucleic Acid-Based Nanoconstructs for the Treatment of Cancer Center at Northwestern University is focused on the design and characterization of spherical nucleic acids for the delivery of RNA therapeutics to treat brain and prostate cancers. Project 1 of the Nano Approaches to Modulate Host Cell Response for Cancer Therapy Center at UNC-Chapel Hill targets vemurafenib resistant melanoma for direct suppression of drug resistance through delivery of siRNA using their polymetformin nanoparticles. Among the Innovative Research in Cancer Nanotechnology awardees, the Ohio State project (Guo), is focused on systematic characterization of in vitro and in vivo RNA nanoparticle behavior for optimized delivery of siRNA to tumor cells, as well as cancer immunotherapeutic.

1.36 Current antibodies used in cancer therapy

Since 1988, 228 mAbs have entered clinical studies for various diseases, with 56% of those currently in clinical development. The first mAb approved for cancer therapy was rituximab (Rituxan™), a chimeric antibody directed against CD20, for non-Hodgkin's lymphomas. Since then, many others have reached the market, including those for the treatment of breast cancer (trastuzumab, Herceptin®), acute myeloid leukemia (gemtuzumabOzogamicin, Mylotarg™), chronic lymphocytic leukemia (alemtuzumab, Campath-1H®), colorectal tumor (cetuximab, Erbitux™) and several types of cancer (bevacizumab, Avastin™). Companies such as Genentech Inc., Amgen, Bristol-Myers-Squibb, Imclone Systems and Trion Pharma represent only a portion of the pharmaceutical companies involved in the antibody market related to cancer therapy.

New developments have also occurred in the immunoconjugate field and many of them are currently being explored by the pharmaceutical

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industry. Immunoconjugates include antibodies linked to cancer-killing agents such as drugs, cytokines, toxins and radioisotopes. The objective is for the antibody to act as a transporter for the cancer-killing agent, concentrating the agent directly in the cancer cell, with minimal damage to healthy cells. Although conjugated antibodies showed toxicity in the past, more recent approaches under development appear to decrease unwanted side effects. Pharmaceutical companies are developing immunoconjugates independently, forming partnerships with specialized players and even acquiring small biotech companies that are focused on the field of immunoconjugates.

Although the challenge of their potential immunogenicity requires special attention, there are several practical advantages to immunoconjugates over single antibodies. These include lower dosages, which may lead to lower treatment costs and fewer side effects; the reintroduction of antibodies that historically have shown low efficacy in isolation; the possibility of using bacteria or plant cells to produce immunoconjugates rather than using mammalian cell cultures (decreasing costs and complexity) and the large number of potential combinations (antibodies-cancer killing agents) that are possible. The advantages of immunoconjugates over single antibodies make them crucial players in new cancer therapy developments.

1.37 Nanoscale and Nanostructure-Based therapeutics

Chemotherapy, radiation therapy and surgery are the most common types of cancer treatments available today. More recent treatments, which are at various stages of development, include angiogenesis inhibitor therapy, biological therapies (including interferons, interleukins, colony-stimulating factors, monoclonal antibodies, vaccines, gene therapy and nonspecific immunomodulating agents), bone marrow and peripheral blood stem cell transplantation, laser therapy, hyperthermia, photodynamic therapy and targeted cancer therapies. In the last two decades, a large number of nanoscale and nanostructure-based therapeutic and diagnostic agents have been developed, not only for cancer treatment but also for its prevention and diagnosis. Targeted cancer, hyperthermia, photodynamic and gene therapies are just some of the cancer treatments that use engineered nanomaterials. These therapies can be used in isolation or in combination with other cancer treatments, thereby taking advantage of their ability to target tumors (actively or passively), to respond to physical or chemical stimulation (internal or external) and to deliver therapeutic genes to the cell nuclei.

The main objective of nanomaterials in cancer treatment is to deliver a therapeutic moiety to tumor cells in a controlled manner (depending on the required pharmacokinetic) while minimizing side effects and preventing drug resistance. Nanoscale and nanostructured materials may also be used in diagnosis to detect and prevent pathologies as soon as possible, ideally being able to sense cancer cells and associated biomarkers. Compared to conventional therapies, nanoparticles show six clear advantages in cancer treatment and/or diagnosis: (1) they can be synthesized in specific sizes and with surface characteristics to penetrate tumors by taking advantage of the enhanced permeation and retention effect (EPR) (a mechanism known as passive targeting); (2) they can be engineered to target tumor cells by surface functionalization with biomolecules that attach to tumor-specific cell markers (a mechanism known as active targeting); (3) they can be engineered to penetrate cells and physiological barriers (e.g., blood-brain barrier, blood-retinal barrier); (4) they can increase the plasma half-life of carried chemotherapeutic drugs, which are usually highly hydrophobic; (5) they can protect a therapeutic payload from biological degradation; and (6) they can be synthesized as multifunctional platforms for combined imaging and therapeutic applications (theragnostic nanoparticles). Examples of various nanostructured materials with potential applications in oncology.

1.38 In Vitro and In Vivo Models for the Study of Urinary Bladder Cancer

Experimental models are used to better explain tumour behaviour, to evaluate the effect of chemo preventive agents, and to study the efficacy of antineoplastic drugs. Such experimental research can be achieved by means of in vitro and in vivo models.

In vitro models. To date, cultured urinary bladder cells represent the most frequently used in vitro bladder cell model. These models usually consist of isolated urinary bladder cancer cell lines and have been established as a valid in vitro model not only to study the mechanism involved in urinary bladder cancer development but also to evaluate anti-neoplastic drug efficacy. In 1970, Rigby and Franks established the first human urinary bladder cancer cell line, designated as RT4

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Since then, many other human urinary bladder cancer cell lines have been established and characterized according to their origin, grade and stage. A great proportion of these cell lines was established from invasive and metastic tumours, benefiting the investigation of late tumour progression and metastic lesions. On the other hand, few non-muscle-invasive human urinary bladder cancer cell lines are available, which is a disadvantage in the investigation of non-muscle-invasive urinary bladder cancer. Urinary bladder cancer cell lines may also be established from rodents exposed to urothelial chemical carcinogens. In 1971, Toyoshima and collaborators established the Nara urinary bladder cancer II (NBT-II) cell line, a rat cell line obtained from a urinary bladder tumour chemically induced by N-Butyl-N-(-4-hydroxybutyl) nitrosamine (BBN) . In the same year, three more urinary bladder cancer cell lines were established from tumours induced by the combined use of N-2-fluorenylacetamide and cyclophosphamide in Fischer 344 female rats, two of them epithelial (BC_5 and BC_6) and one fibroblastic (BC7). Five years later, two mouse urinary bladder cancer cell lines were established using the carcinogen N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) and, more recently, seven chemically-induced mouse urinary bladder cancer cell lines (BC13, BC29, BC30, BC46, BC57, BC58 and BC59) were established from tumours developed in C57BL/6 mice exposed to BBN .

1.39 Advantages and Disadvantages of In Vitro and In Vivo Models

As yet, there is not an ideal experimental model for urinary bladder cancer study since both in vitro and in vivo models have limitations. However, with the information obtained from both models, a better understanding of urothelial bladder carcinogenesis is possible. In pre-clinical studies, the antitumour efficacy of a new drug is first evaluated in in vitro models and later in animal models. One of the greatest advantages of in vitro models application is that they offer the possibility to maintain cells in completely controlled environmental conditions, allowing the study of specific cellular and molecular pathways in shortened experimental timescales, being less expensive than animal models and less time-consuming. In contrast, the greatest limitation of this model is that cells growing in vitro are not the exact dissociated replicates of their in vivo counterparts. The use of monolayer cell cultures is usually restricted to a single or at most two cell types. Tumours are composed not only of neoplastic cells but also of stroma and inflammatory cells, which gives a tumour a three-dimensional structure, interacting and influencing its growth. The impossibility of tumour angiogenesis and metastasis studies can be considered as limitations of in vitro studies, since these are complex processes with many different mechanisms involved. It is, therefore, clearly difficult to perform in vitro assays which totally simulate these processes and only a combination of methods will be able to provide a clear picture. In vitro studies can also provide important information concerning the parameters of pharmacodynamics. To better-understand pharmacokinetics, it is necessary to use in vivo models, since these models offer the best approach for effectively combining and interpreting the major determinants of drug kinetics across species. Likewise, in vitro studies do not predict the adverse effects of drugs.

For this reason, in vivo models remain important: they preserve the three-dimensional tumour structure with cell-cell interactions and allow for pharmacokinetic and toxicity evaluation of the compounds. Significant limitations of in vivo studies include the necessity for animal facilities, they are also more time consuming, and involve high involved.

1.40 In Vitro Studies to Assess the Efficacy of Antineoplastic and Other Drugs

In the past thirty years, more than 40 studies were conducted in order to evaluate the activity of antineoplastic drugs, making use of several human urinary bladder cancer cell lines, as well as a wide range of methodologies. It is clearly perceptible that out of the 40 different urinary bladder cancer cell lines used, the T24 muscle-invasive cell line is the one most employed, followed by the HT1376, RT112 and RT4 cell lines. Currently, there is a broad range of methodologies available to assess the in vitro efficacy of drugs, but assays such as 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), clonogenic, flow cytometry and western blot are regularly used. In vitro models have already provided the basis for study of the activity of many antineoplastic drugs. However, alkylating drugs, namely cisplatin and MMC, as well as anti-metabolite drugs, such as gemcitabine, are among the ones most investigated, whether in isolation or combination therapy. Other

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antineoplastic drugs with different mechanisms of action have also been analyzed, examples are inhibitors of the mammalian target of rapamycin (mTOR) (rapamycin, everolimus), topoisomerase II (epirubicin, doxorubicin, etoposide) and of mitotic spindle formation (paclitaxel, vincristine, vinorelbine). Many of these drugs already tested in vitro (approximately 26) have progressed to clinical studies of urinary bladder cancer. Nevertheless, none of them demonstrated superior efficacy when compared to the drugs currently used in urinary bladder cancer treatment, which is why none of them have been approved as a new therapy.

1.41 Recent technological advances in the coupling of complex microfluidics and nanoscale materials have allowed the high-purity capture and downstream functional characterization of circulating tumor cells (CTCs), cell-free tumor DNA, microemboli, exosomes, proteins, neoantigens, and more. Recent examples include, capture and subsequent release of CTCs within microfluidic systems to maintain viable cells for downstream whole genome sequencing, ex vivo expansion, RNA sequencing, and more. Of these examples, one type of device uses magnetic nanoparticles to enrich whole blood prior to magnetic separation within the microfluidic and the other device uses thermoresponsivenanopolymers that specifically capture CTCs as they flow through the microfluidic then release upon a change in temperature once blood processing is complete. In both cases, the detection sensitivities are very high (e.g., for enumeration >95%) and capture purity is much higher than other non-nanomaterial based devices. Furthermore, the processing times are increasing every year as the technology evolves, currently averaging 10 mL blood per 30 minutes.

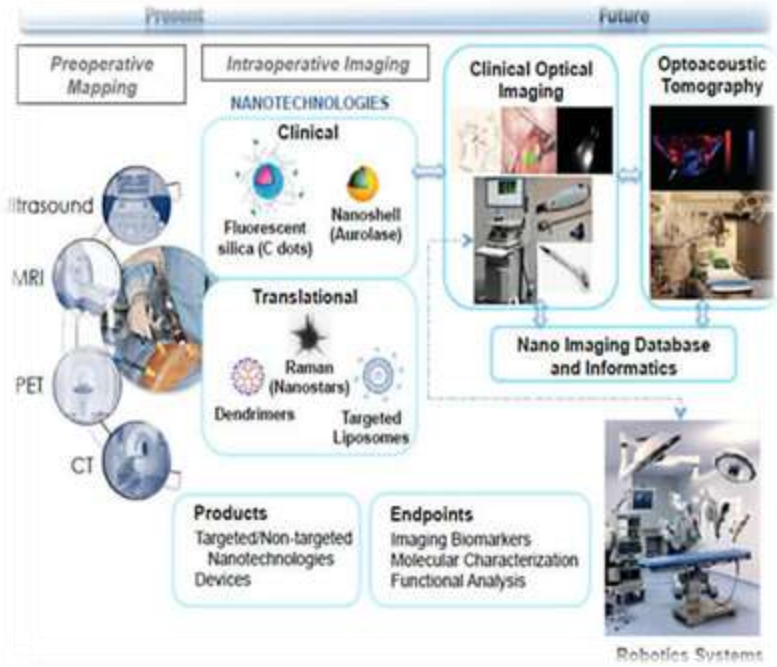

Fig no: 10 Present and future of NanoOncology Image-guided Surgical Suite. Preoperative conventional imaging tools are used to screen for disease and inform optically- driven minimally-invasive and open surgical procedures.

1.42 Challenges in Nano drug delivery

The use of diverse nanomaterials with desired properties and recent progress in the drug delivery arena have revealed outstanding challenges in cancer therapy and management. It is anticipated that the nanomaterials will revolutionize the entire health care system based on the dramatic developments made in drug delivery sector over the past few decades. However, the design of effective cancer nanotherapeutics remains a great challenge, and only a few nanoformulations have entered clinical trials. A schematic representation of the major challenges in the delivery of cancer nanotherapeutics is depicted in Fig. 9. The physicochemical properties of nanomaterials play a significant role in the biocompatibility, and toxicity in the biological systems. Therefore, synthesis and characterization of the nanomaterials for drug delivery need to be carefully performed to avoid the potential

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unwanted toxicity of nanocarriers to healthy cells. Additionally, since these nanocarriers interact with the biomolecules and may tend to aggregate forming a protein corona, disturbing the regular function of nanomedicine formulations and rendering them ineffective in controlling the cancer cell growth. In conjunction to physicochemical properties, the nanomaterial storage and stability may also have an influence on their pharmacological performance.

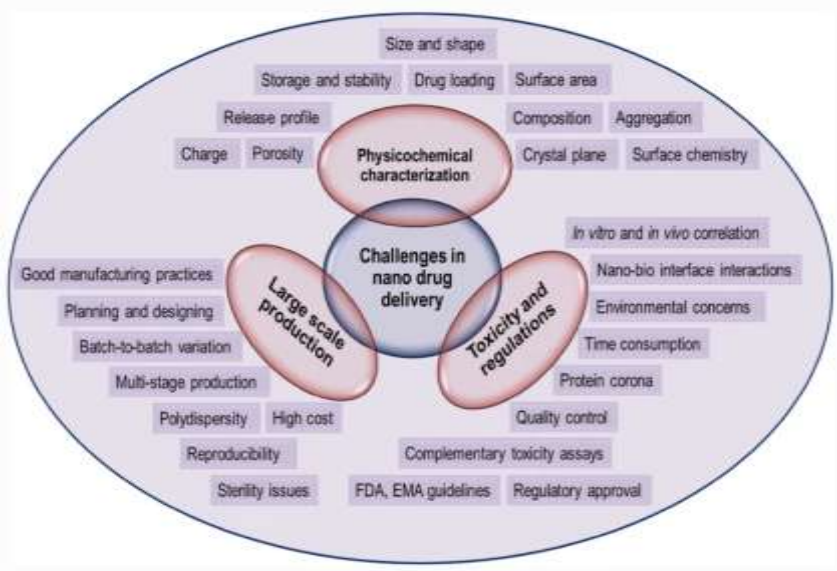

Fig no: 11 Schematic illustration representing various challenges involved in the delivery of cancer nanotherapeutics

Another challenge in drug delivery is the safety for human health, as issues may be associated with nanomaterial, and may not have immediate impact or may not be noticeable quickly. The use of nanocarriers in the treatment of cancer may result in unwanted toxicity through unfavorable interactions with biological entities. Several studies have revealed the detrimental properties of nanocarriers due to their toxicity Therefore, 'Nano toxicology' a branch of nanomedicine has emerged as an essential field of research, paving the way for the assessment of toxicity of nanoparticles. In addition to all the above, a significant setback in nanomedicine commercialization is the clinical translation due to the lack of in-depth understanding of nano-bio interfacial interactions. Specifically, the lack of in vitro/in vivo correlation of drug release profiles is a major lingering issue.

Furthermore, the manufacturing of nanomedicine products for commercialization is a key obstacle, as large scale-production is technically challenging. Generally, only small quantities of nanomedicine are used for pre-clinical and clinical trial studies. The large-scale production of nanoformulations, however, is quite challenging as their physicochemical properties may vary from batch to batch. Moreover, the involvement of complicated multi-stage processes of production of nanotherapeutics and the high cost of raw materials renders thesenanotherapeutics an expensive option. Consequently, the use of well-planned and -designed manufacturing processes are essential, and the clinical benefit must be huge which can justify the manufacturing costs.

1.43 Future directions

Although nanomedicine is a relatively new branch of science, its translation into clinical care has been rapid. Nanoparticle chemotherapeutics are composed to influence the treatment of most cancers. To fully understand the advantages and disadvantages of nanoparticle therapeutics, more clinical data are needed it can also help in identifying the best applications for nanochemotherapeutics. Thus, it is crucial to develop and carry out well-designed clinical trials to further the development of these drugs. Clinical investigators should fully understand the particular nanoparticles they are investigating and design trials that take advantage of nanoparticle properties. More complex targeted systems, which can release nanochemotherapeutics at a target site when exposed to external stimuli such as light and

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temperature, are also under development. Another potential is to develop more nanoparticles capable of delivering combination chemotherapeutics.

II. CONCLUSION

From this literature survey has tried to summarize the history and evolution of the most common types of cancer treatments available today, but also new therapies under study in the last years.Nanotechnology is offering new products, which either used alone, due to their intrinsic properties, or in combination with other biomolecules (anti-tumoral drugs, folic acid, albumin, antibodies, and aptamers) could be used to target cancer cells. However, the history tells us that the fight against cancer is not an easy task.Cancer nanotechnology field has the potential to better monitor therapeutic efficacy, provide novel methods for detecting and profiling early stage cancers, and for enabling surgeons to delineate tumor margins and sentinel lymph nodes.Nanomaterials have unique features that are attractive, and can be applied to bio sensing. The development of various nanomaterials and nanotechnology has enabled detection of cancer biomarkers with great precision and sensitivity that could not be achieved before. Anti-cancer drug delivery specifically to cancer cells remains a major challenge. Due to the lack of drug availability, adverse side effects and drug resistance, the conventional therapy failed to achieve proper treatment of cancer.Nanotechnology has great potential to radically improve current approaches to the diagnosis and treatment of patients with various types of cancer. Nanotechnology has already begun to have a significant impact on the treatment of patients by improving major challenges for the future including optimization of design and engineering of cancer targeted materials.Many types of cancers are able to resist to conventional therapies, and different combinations of drugs and therapies (e.g., surgery together with radiotherapy and chemotherapy) are usually the only way to destroy tumoral cells.The future of nanomedicine will no doubt yield innovative platforms for cancer treatment, and the study presented herein may improve the general consideration of anticancer treatment with nanoparticles.

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