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NANOTECHNOLOGY IN CANCER THERAPY

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ABSTRACT

Nanotechnology is the study and use of structures between 1 nanometer and 100 nanometers in size. Nanotechnology is definitely a medical boon for diagnosis, treatment and prevention of cancer diseases. Nanoparticulate technology is of particular use in developing a new generation of more effective cancer therapies capable of overcoming many biological, biophysical and biomedical barriers that the body stages against a standard intervention. Nanoparticles that deliver chemotherapy drugs directly to cancer cells are under development. Nanomedicine application areas include drugdelivery, therapy, diagonistic, imaging and antimicrobial techniques. The formed nano particles can be used in wide range of therapeutic treatment of cancer. To overcome problems of systemic toxicity associated with chemotherapy and enhance treatment resolution of cancer therapies, nanotechnology is increasingly providing many novel approaches, especially to energy-based cancer therapies. Nonmaterial and biomarkers of cancer, general principle of drug targeting to cancer, intracellular mechanisms, and nanoparticles based formulation in market, several recent applications in medicine as diagnostic and therapeutic are discussed. This article aim to overview on all the parts of nanotechnology in cancer therapy.

Keywords: Nanotechnology, Nanomedicine, Nanomedicine, Drug delivery, Chemotherapy, Biomarker.

1. INTRODUCTION

The word "Nano" is derived from the greek word νᾶνος (nanos) for dwarf. A nanometer is a billionth *of a meter*, that is, about 1/80,000 of the diameter of a human hair, or 10 times the diameter of a hydrogen atom. When the physicist and Nobel laureate Richard Feynman challenged the science community to think small in his 1959 lecture 'There's Plenty of Room at the Bottom', he planted the seeds of a new era in science and technology that is today's Nanotechnology [1]. There are more than 300 claimed nanotechnology products already on the market [2].

2. CANCER DISEASE

Cancer is a leading cause of death worldwide. From a total of 58 million deaths worldwide in 2005,Cancer accounts for 7.6 million (or 13%) of all deaths. More than 70% of all cancer deaths in 2005,Occurred in low and middle-income countries. Deaths from cancer in the world are projected to continue rising, with an estimated 9 million people dying from cancer in 2015 and 11.4 million dyingin 2030. The most frequent cancer types worldwide are:

(a) Among men: lung, stomach, liver, colorectal, oesophagus and prostate; and
(b) Among women: breast, lung stomach, colorectal and cervical (Pan American Health Organization, WHO 2006).

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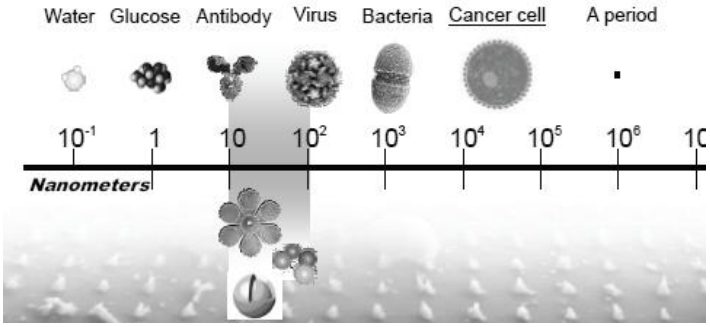

Fig 1: Different size range of materials on nanoscale

Biomarkers Of Cancer

Biomarkers include altered or mutant genes, RNAs, proteins, carbohydrates, lipids, and small metabolite molecules, and their altered expressions that are correlated with a biological behavior or a clinical outcome. Most cancer biomarkers are discovered by molecular profiling studies based on an association or correlation between a molecular signature and cancer behavior. In the cases of both breast and prostate cancer, a deadly step is the appearance of so-called lethal phenotypes, such as bone-metastatic, hormone-independent, and radiation and chemotherapy-resistant phenotypes. It has been hypothesized that each of these aggressive behaviors or phenotypes could be understood and predicted by a defining set of biomarkers.

Biomarkers have tremendous therapeutic impact in clinical oncology, especially if the biomarker is detected before clinical symptoms or enable real-time monitoring of drug response. Protein signatures in cancer provide valuable information that may be an aid to more effective diagnosis, prognosis, and response to therapy. The recent progress of proteomics has opened new avenues for cancer-related biomarker discovery. Advances in proteomics are contributing to the understanding of patho-physiology of neoplasia, cancer diagnosis, and anticancer drug discovery. Continued refinement of techniques and methods to determine the abundance and status of proteins holds great promise for the future study of cancer and the development of cancer therapies.

Early diagnosis of cancer is difficult because of the lack of specific symptoms in early disease and the limited understanding of etiology and on cogenesis. For example, blood tumor markers for breast cancer such as cancer antigen (CA) 15-3 are useless for early detection because of low Sensitivity. More than 98% of cervical cancer is related to human papilloma virus (HPV) infection. The identification and functional verification of host proteins associated with HPV E6 and E7 oncoproteins may provide useful information for the understanding of cervical Carcinogenesis and the development of cervical cancer-specific markers. There is a critical need for expedited development of biomarkers and their use to improve diagnosis and treatment for cancer.

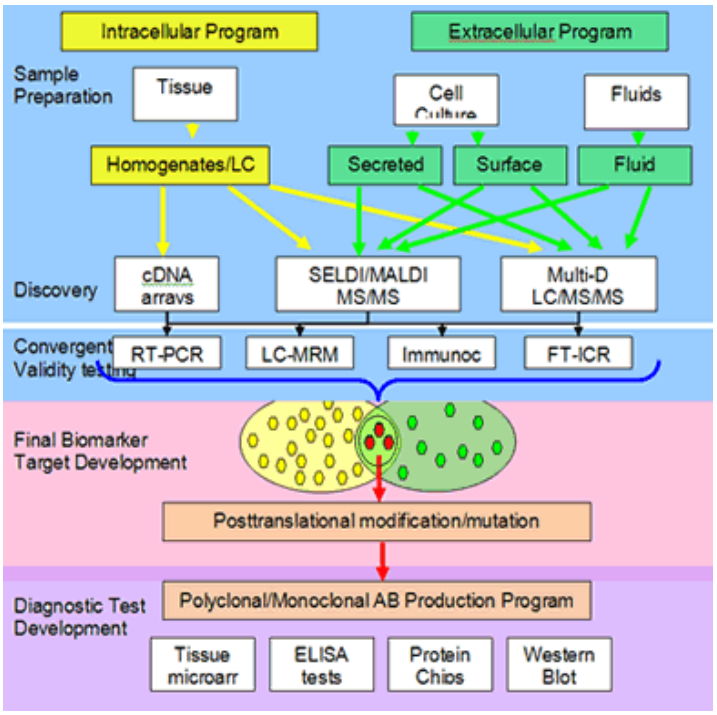

Fig.2: Biomarkers of cancer

3. NANOTECHNOLOGY

Nanotechnology is defined as the study and use of structures between 1 nanometer and 100 nanometers in size. Nanotechnology is the synergy of mechanical, electrical, chemical engineering, material sciences, microelectronics, and biological screening. Nanotechnologies are the design, production, characterization, and application of structures, devices and systems by controlling shape and size at nanometer scale. There are more than 300 claimed nanotechnology products already on the market [3].

Nanotechnology in Energy Based Therapies

Some promising focus areas in energy-based therapy research are photodynamic, alternating magnetic field, microwave, radio frequency (RF), high intensity focused ultrasound (HIFU), and cryoablation therapies, each with their own advantages and disadvantages An advantage of these methods over systemic treatments or surgical resection is a more localized destruction of diseased tissue while minimizing possible side effects such as systemic toxicity or infection. Also, these methods are considered minimally invasive and are primarily investigated as outpatient procedures. Energy-based therapies destroy tumor cells by causing a local temperature excursion within the designated treatment area.

Commonly, this procedure is applied through a minimally invasive probe insertion technique or the focusing of external high energy sources. Although the individual implementation of these thermal ablation methodologies are different depending on the energy source, the fundamental therapeutic mechanisms for these therapies can be divided into two categories, damage from heating to hyperthermic temperatures (usually > 43°C) or damage\ from cooling or freezing to cryothermic temperatures (usually < -20°C). The therapeutic benefit from both of these types of treatment are strongly temperature and time dependent with differing degrees of damage existing throughout a given treatment gradient, in the complete kill zone, hyperthermic damage has been characterized by protein denaturation, cellular membrane damage, and vascular injury Alternatively, cryothermic damage has been characterized by mechanical damage from ice formation, cellular dehydration, ischemia from vascular damage, and post treatment immunological response. Of the energy sources mentioned, all induce hyperthermic damage with the exception of cryoablation, which induces cryothermic damage. Although these methodologies have promising potential applications, they have problems that cannot be overlooked.

Thermal ablation treatments are susceptible to uneven distribution of temperature profiles, and in the case of hyperthermic treatments, the treated area is not readily visible during the procedure and must be estimated from models or experimentation. Furthermore, the methods of implementation for the delivery of the thermal energy required for these treatments cause unintended damage to surrounding healthy tissue.

In contrast, the iceball formed during cryothermic ablation treatment is visible through ultrasound or CT and easily tracked, but the determination of effectively treated area with temperature < -20 □C within the iceball is uncertain and must either be directly measured or estimated through models and experimentation. The fluctuation in temperature gradient and uncertainty in treated area causes ablation treatments to be less specific than intended and in some cases possibly incomplete as shown in figure 4.

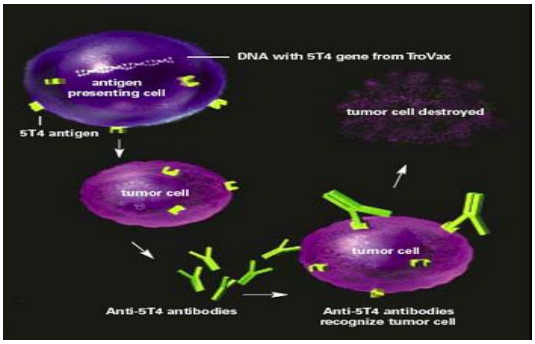

Fig. 3 Nanotechnology of cancer

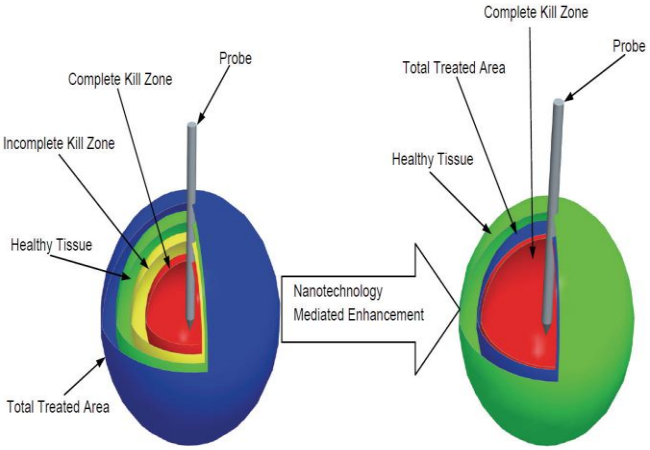

Fig 4. Illustration of nanotechnology mediated enhancements that can improve energy-based cancer therapies. Classical energy-based treatments have limitations in treatment area visualization causing the total treated area to overlap with healthy tissue. Also, unquantified thermal distribution causes an uncertainty in the complete kill zone (left). By using nanotechnology mediated combined modality treatments, the total treatment area can be visualized to minimize healthy tissue overlap, and the complete kill zone can be expanded to the treated area edge.

4. NANOPARTICLES

Nanoparticles can be defined as particles less than 100nm in diameter that exhibit new or enhanced size-dependent properties compared with larger particles of the same material. Nanoparticles exist widely in the natural world. For example; the products of photochemical and volcanic activity. Nanoparticles have also been created for thousands of years as products of combustion and food cooking, and more recently from vehicle exhausts.

Scientists have been studying and working with nanoparticles for centuries, but the effectiveness of their work has been hampered by their inability to see the structure of nanoparticles. In recent decades the development of microscopes capable of displaying particles as small as atoms has allowed scientists to see what they are working with. In fact, nanoparticles embrace a wide spectrum of applications sparking another industrial revolution.

Classification of Nanoparticles

Nanoparticles are classified based on their dimensions.

i) In one dimension: One-dimensional systems, such as thin films or manufactured surfaces or coatings are one dimensional nanomaterials.. Their applications include corrosion resistant ,wearand scratch resistant ,hydrophobic and self cleaning ,dirt repellent,antibacterial and anti-microbial,catalytically active and chemically functionlaized and tranperacy modulated surfaces.

ii) In two dimension: Nanotubes, nanowires, nanofibers and nanopolymers are two dimensional nanoparticles.

a) Carbon Nanotubes

Carbon nanotubes are a new form of carbon molecule. Wound in a hexagonal network of carbon atoms, these hollow cylinders can

have diameters as small as 0.7 nm and reach several millimeters in length [4]. Each end can be opened or closed by a fullerene half-molecule. These nanotubes can have a single layer (like a straw) or several layers (like a poster rolled in a tube) of coaxial cylinders of increasing diameters in a common axis [5].

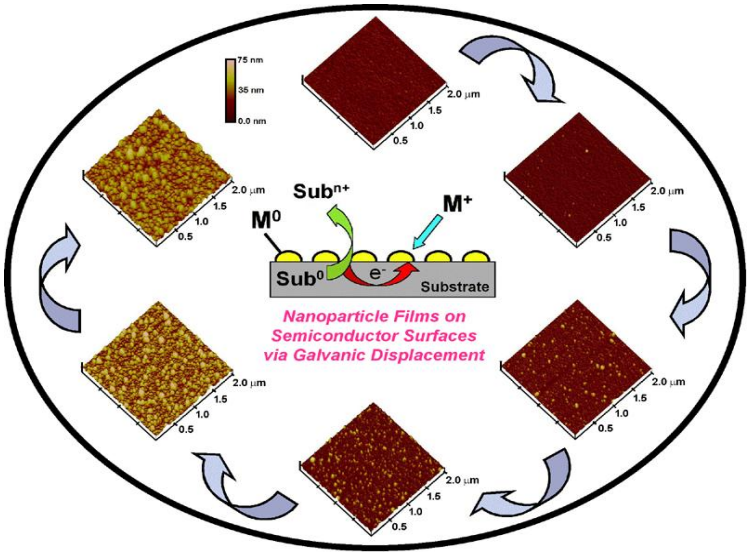

Fig. 5 Nanoparticle Films on Semiconductor Surfaces

iii) In three Dimension: Fullerenes,dendimers and quantum dots are three dimensional nanoparticles.

a) Fullerenes

Fullerenes are spherical cages containing from 28 to more than 100 carbon atoms . Fullerenes are a class of materials displaying unique physical properties. They can be subjected to extreme pressures and regain their original shape when the pressure is released. These molecules do not combine with each other, thus giving them major potential for application as lubricants. Fulllerenes products include drug delivering vehicle and electronic circuit.

b) Dendrimers

Dendrimers represent a new class of controlled-structure polymers with nanometric dimensions. They are considered to be basic elements for large-scale synthesis of organic and inorganic nanostructures with dimensions of 1 to 100 nm, displaying unique properties. Having compatible with organic structures such as DNA, they can also be fabricated to interact with metallic nanocrystals and nanotubes or to possess an encapsulation capacity [6]. Starpharma's lead nanopharmaceutical development product is VivaGel (SPL7013 Gel), a dendrimer-based gel is currently in phase 2 trials. These are used in conventional application, drug delivery, enviormental and water cleaning.

c) Quantum Dots

It represents a special form of spherical nanocrystals from 1 to 10 nm in diameter. They have been developed in the form of semiconductors, insulators, metals, magnetic materials or metallic oxides. Quantum dots are used to track DNA molecules in cells, efficient alternatives to conventional lighting sources, biosensors

used to detect agents of bioligcal warfare.

Advantages of Nanoparticles

- Increased bioavailability
- Dose proportionality
- Decreased toxicity
- Smaller dosage form (i.e., smaller tablet)
- Stable dosage forms of drugs which are either unstable or have unacceptably low bioavailability in non-nanoparticulate dosage forms.
- Increased active agent surface area results in a faster dissolution of the active agent in an aqueous environment, such as the human body. Faster dissolution generally equates with greater bioavailability, smaller drug doses, less toxicity.
- Reduction in fed/fasted variability [7].

Nanoparticle Drugs and its Application

Nanoparticle drugs are designed by encapsulating, covalently attaching or adsorbing therapeutic and diagnostic agents to the nanoparticle. Recently Food and Drug Administration (FDA) approved AbraxaneTM an albumin -paclitaxel (TaxolTM) nanoparticle drug for the breast cancer treatment. Nanoparticle structure was designed by linking hydrophobic cancer drug (Taxol) and tumor-targeting ligand to hydrophilic and biodegradable polymer which delivers 50% higher dose of active agent TaxolTM to the targeted tumor areas. Some nanoparticles used for medical application.

5. NANOMEDICINE

Nanotechnology offers great visions of improved, personalized treatment of disease. The hope is that personalized medicine will make it possible to develop and administer the appropriate drug, at the appropriate dose, at the appropriate time to the appropriate patient. The benefits of this approach are accuracy, efficacy, safety and speed. Some techniques are only imagined, while others are at various stages of testing, or actually being used today. While some researchers use the term nanomedicine to refer to applications of nanoparticles

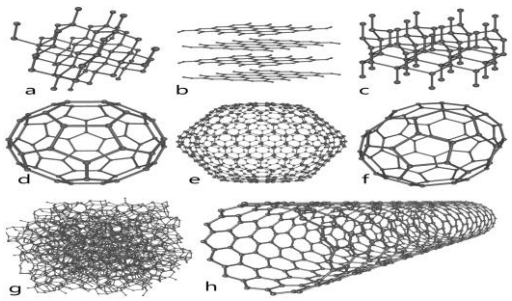

Fig. 6 Carbon Nanotubes and Fullerenes

Nanomedicine Application Area: Drug Delivery

Currently, the most advanced area of nanomedicine is the development and use of nanoparticles for drug delivery.One application of nanotechnology in medicine currently being developed involves employing nanoparticles to deliver drugs, heat, light or other substances to specific types of cells (such as cancer cells). Particles are engineered so that they are attracted to diseased cells, which allows direct treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of disease. For example, nanoparticles that deliver chemotherapy drugs directly to cancer cells are under development.

Nanomedicine Application Area: Therapy Techniques

Buckyballs may be used to trap free radicals generated during an allergic reaction and block the inflammation that results from an allergic reaction. Nanoshells may be used to concentrate the heat from infrared light to destroy cancer cells with minimal damage to surrounding healthy cells. Nanospectra Biosciences has developed such a treatment using nanoshells illuminated by an infrared laser that has been approved for a pilot trial with human patients.

Nanoparticles, when activated by x-rays, generate electrons that cause the destruction of cancer cells to which they have attached themselves. This is intended to be used in place radiation therapy with much less damage to healthy tissue. Nanobiotix has released preclinical results for this technique [8]. Aluminosilicate nanoparticles can more quickly reduce bleeding in trauma patients by absorbing water, causing blood in a wound to clot quickly. Z-Medica is producing a medical gauze that uses aluminosilicate nanoparticles [9]. Nanofibers can stimulate the production of cartilage in damaged joints.

Nanomedicine Application Area: Diagnostic and Imaging Techniques

Quantum Dots (qdots) may be used in the future for locating cancer tumors in patients and in the near future for performing diagnostic tests in samples. Invitrogen's website provides information about qdots that are available for both uses, although at this time the use "in vivo" (in a living creature) is limited to experiments with lab animals. Nanosphere has clinical study results with their Verigene system involving it's ability to detect four different nucleic acids, while another system being developed by T2 Biosystems uses magnetic nanoparticles to identify specimens, including proteins, nucleic acids, and other materials [10,11].

Nanomedicine Application Area: Anti-Microbial Techniques

One of the earliest nanomedicine applications was the use of nanocrystalline silver which is as an antimicrobial agent for the treatment of wounds [12]. A nanoparticle cream has been shown to fight staph infections. The nanoparticles contain nitric oxide gas, which is known to kill bacteria. Studies on mice have shown that using the nanoparticle cream to release nitric oxide gas at the site of staph abscesses significantly reduced the infection [13].

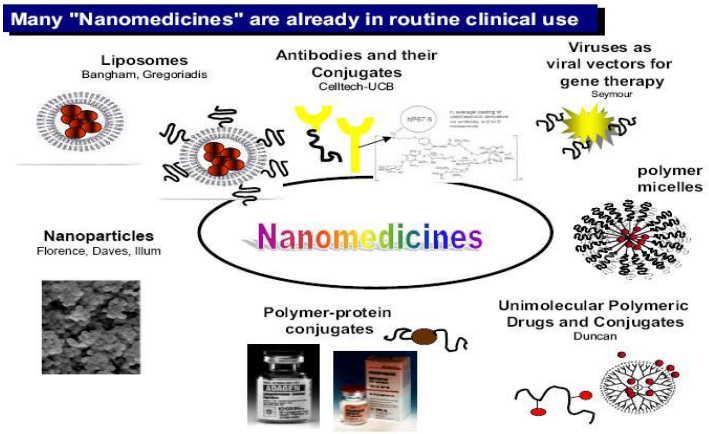

Fig. 7 Nanomedicine used in routine

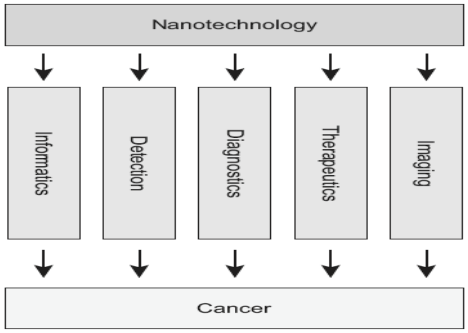

Fig. 8 Schematic diagram showing nanotechnology applications in cancer.

Nanomedicine: Nanorobots and Medicine

Future developments in nanomedicine will be based on the ability to build nanorobots Nanorobots could actually be programmed to repair specific diseased cells, functioning in a similar way to antibodies in our natural healing processes[14] .Molecular manufacturing, also called molecular nanotechnology will provide the ability to build the nanorobots needed for future applications of nanomedicine [15].

Nanomedicine: Future Applications

Future application of nanomedicine may involve the elimination of bacterial infections in a patient within minutes, instead of using treatment with antibiotics over a period of weeks. In future,by the application of nanomedicine ,we may have the ability to perform surgery at the cellular level, removing individual diseased cells and even repairing defective portions of individual cells.It may contribute significantly for lengthening of the human lifespan by repairing cellular level conditions that cause the body to age.

Nanotechnology: The Risks

Fears over the possible dangers of some nanotechnologies may be exaggerated, but they are not necessarily unfounded. Recent studies examining the toxicity of engineered nanomaterials in cell cultures and animals have shown that size, surface area, surface chemistry, solubility and possibly shape all play a role in determining the potential for engineered nanomaterials to cause harm [16]. Three issues stand out as fertile ground for innovative research: monitors for airborne exposure, detectors for waterborne nanomaterials, and smart sensors that can measure both exposure and potential hazards. A global understanding of nanotechnology-specific risks is essential if large and small industries are to operate on a level playing field, and developing economies are not to be denied essential information on designing safe nanotechnologies.

6. DRUG DELIVERY STRATEGIES USED TO FIGHT CANCERS

There are a variety of different delivery strategies [17] that are either currently being used or are in the testing stage to treat human cancers.

Various methods for cancer treatment:

Direct Introduction of anticancer drugs into tumour
• Injection Directly into the tumour • Tumour necrosis therapy • Injection into the arterial blood supply of cancer • Local injection into the tumour for radiopotentiation • Localized delivery of anticancer drugs by electroporation (Electrochemotherapy) • Local delivery by anticancer drugs implants
Routes of Drug delivery
• Intraperitoneal • Intrathecal • Nasal • Oral • Pulmonary inhalation • Subcutaneous injection or implant • Transdermal drug delivery • Vascular route: intravenous, intra-arterial
Systematic delivery targeted to tumour
• Heat-activated targeted drug delivery • Tissue-selective drug delivery for cancer using carrier-mediated transport systems • Tumour-activated prodrug therapy for targeted delivery of chemotherapy • Pressure-induced filtration of drug across vessels to tumour • Promoting selective permeation of the anticancer agent into the tumour • Two-step targeting using bispecific antibody • Site-specific delivery and light-activation of anticancer proteins
Drug delivery targeted to blood vessels of tumour
• Antiangiogenesis therapy • Angiolytic therapy • Drugs to induce clotting in blood vessels of tumour • Vascular targeting agents
Special formulations and carriers of anticancer drugs
• Albumin based drug carriers • Carbohydrate-enhanced chemotherapy • Delivery of proteins and peptides for cancer therapy • Fatty acids as targeting vectors linked to active drugs • Microspheres • Monoclonal antibodies • Nanoparticles • Pegylated liposome's (enclosed in a polyethylene glycol bilayer) • Polyethylene glycol (PEG) technology • Single-chain antigen-binding technology
Transmembrane drug delivery to intracellular targets
• Cytoporter • Receptor-mediated endocytosis • Transduction of proteins and Peptides • Vitamins as carriers for anticancer agents
Biological Therapies
• Antisense therapy • Cell therapy • Gene therapy

- Genetically modified bacteria
- Oncolytic viruses
- RNA interference

Companies involved with the commercialization of nanomaterials for bio - and medical applications:

Sr. No.	Company	Major area of activity	Technology
1.	Advectus Life Science Inc.	Drug delivery	Polymeric nanoparticles engineered to carry anti-tumor drug across the blood-brain barrier
2.	Alnis Biosciences, Inc.	Bio-pharmaceutical	Biodegradable polymeric nanoparticles for drug delivery
3.	Argonide	Membrane filtration	Nanoporous ceramic materials for endotoxin
4.	Biophan Technologies, Inc.	MRI shielding	Nanomagnetic /carbon composite materials to shield medical devices from RF fields
5.	Capsulation Nanoscience AG	Pharmaceutical coating to improve solubility of drugs	Layer-by-layer poly-electrolyte coating, 8-50 nm
6.	Eiffel Technologies	Drug delivery	Reducing size of the drug particles to 50-100 nm
7.	Evident Technologies	Luminescent biomarkers	Semiconductor quantum dots with amine or carboxyl groups on the surface, emission from 350-2500 nm
8.	Immunicon	Tracking and separation of different cell type	Magnetic core surrounded by a polymeric layer coated with antibodies for capturing cell
9.	NanoBio Cortporation	Pharmaceutical	Antimicrobial nano emulsions
10.	NanoCarrier Co., Ltd	Drug delivery	Micellar nanoparticles for encapsulation of drugs, proteins, DNA
11.	NanoPharm AG	Drug delivery	Polybutyilcyanocrylate nanoparticles are coated with drug and then with surfactant can go across the blood brain barrier
12.	Nanoprobes, Inc.	Gold nanoparticles for biological markers	Gold nanoparticles bio-conjugates for TEM and/or fluorescent microscopy
13.	Nanoshpere, Inc.	Gold biomarkers	DNA barcode attached to each nanoprobes for identification purposes, PCR used to amplify the signals, also catalytic silver deposition to amplify the signal using surface plasmon resonance
14.	NanoMed Pharmaceutical, Inc.	Drug delivery	Nanoparticles for drug delivery

7. CONCLUSION

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 biosensing. The development of various nanomaterials and nanotechnology has enabled detection of cancer biomarkers with great precision and sensitivity that could not be achieved before.

Many studies are being conducted on developing sensing mechanisms that will push down the detection limit as far down as possible. As well, various new biomarkers can be discovered and verified with such sensitive tools. It is therefore highly anticipated that in the near future, nanotechnology shall help to detect cancer at an early stage and monitor the disease with much greater precision.

It must be however noted that these new technologies must be validated critically before applying them for clinical diagnosis. Ultimately, if the nanotechnology researchers can establish methods to detect tumors at a very early stage, that is, before tumors begin to vascularize and metastasize, cancer will become a disease that will become amenable to complete cure via surgical resection.

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