Available on line www.jocpr.com

Journal of Chemical and Pharmaceutical Research

ISSN No: 0975-7384
CODEN(USA): JCPRC5

J. Chem. Pharm. Res., 2010, 2(5): 161-168

Nanotechnology in Cancer Therapy: A Review

Navedul haque[1*], Rafallah R. Khalel[2], N. Parvez [3], S. Yadav[4], N. Hwisa[3]
M. S. Al-Sharif[3], B. Z. Awen[3] and K. Molvi[3]

[1]University Department of Chemistry, B.R.A. Bihar University, Muzaffarpur, Bihar, India
[2]Department of Laboratory Medicine, Faculty of Medical Technology, Derna, Libya
[3]College of Pharmacy, University of Al Jabal Al Garbhi, Al-Zawia, Libya
[4]Department of Chemistry, Swami Shraddhanand College, University of Delhi, Alipur, India.

ABSTRACT

Nanotechnology is the study and use of structures between 1 nanometer and 100 nanometers in size. Cancer is the leading cause of death among people younger than 85 years. . Nanoparticles that deliver chemotherapy drugs directly to cancer cells are under development. Nanomedicine application areas includes drug delivery,therapy,diagonistic,imaging and antimicrobial techniques. Fears over the possible dangers of some nanotechnologies has started growing. This article aims at giving an overview of the present status of nanotechnology in cancer therapy.

Keywords: Nanotechnology, Nanomedicine, Application of nanomedicine, Nanomedicine for cancer, Risks of nanotechnology

INTRODUCTION

Nanotechnology

The word "Nano" is derived from the greek word ν□νος (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] 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 [2]

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,anti-bacterial 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 [3] 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 [4]

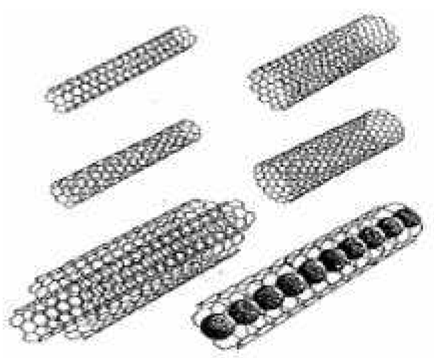

Figure 1: Schematic representation of monolayer or multiplayer carbon nanotube

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 [5] 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 [6]

Characterization of Nanoparticles

Table 1: Different parameters & characterization methods for nanoparticles

Parameters	Characterization methods
Particle size & size distribution	Photon correlation spectroscopy, Scanning electron microscopy (SEM), Transmission electron microscopy (TEM), Atomic force microscopy (AFM), Mercury porositometry, Laser defractrometry [7,8]
Charge determination	Laser droplet anemometry, Zeta potentiometer [9]
Surface hydrophobicity	Water contact angle measurements, rose bangle (dye) binding, hydrophobic interaction chromatography, X-ray photoelectron spectroscopy [10,11]
Chemical analysis of surface	Static secondary ion mass spectrometry, sorptometer [12]
Carrier drug interaction	Differential scanning calorimetry [13]
Nanoparticle dispersion stability	Critical flocculation temperature(CFT) [14]
Release profile	In-vitro release characteristic under physiologic & sink condition [15-17]
Drug stability	Bioassay of drug extracted from nanoparticle, chemical analysis of drug [18]

NANOTECHNOLOGY IN MEDICINE - 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 currently under development, other researchers reserve the term nanomedicine to refer to longer range research that involves the use of manufactured nano-robots to make repairs at the cellular level. While nanomedicine potentially offers promising new value propositions and revenue streams, it also could completely displace certain classes of drugs. For example, currently-employed chemotherapeutic agents are being substituted with novel nanoparticle reformulations. Today, commercial nanomedicine is at a nascent stage of development and it's full potential years or decades away. Currently, the most advanced area of nanomedicine is the development and use of nanoparticles for drug delivery.

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.

Cancer Therapy Advances Using Nanotechnology

Cancer is leading cause of death in the United State among people younger than 85 years. Statistics have revealed that the number of cancer related death has remained about the same. It is universally accepted that early detection of cancer is essential even before anatomic anomalies are visible. A major challenge in cancer diagnostic in the 21st century is to able to determine the exact relationship between cancer biomarkers and the clinical pathology, as well as to be able to non-invasively detect tumour at an early stage for maximum therapeutic benefit.

In cancer therapy, targeting and localized delivery are the key challenges. To wage an effective war against cancer, we have the ability to selectively attack the cancer cells, while saving the normal tissue from excessive burdens of drug toxicity. There is the need for a new generation of new therapies for cancer.

Nanotechnology has the potential to have a revolutionary impact on cancer diagnosis and therapy. The use of nanotechnology in cancer treatment offers the possibility of destroying cancer tumours with minimal damage to healthy tissue and organs. Most efforts to improve cancer treatment through nanotechnology is at the research or development, stage; a few methods, however, have reached the pre-clinical or clinical trial stage.One treatment involves targeted chemotherapy that delivers a tumor-killing agent called tumour necrosis factor alpha (TNF) to cancer tumors. TNF is attached to a gold nanoparticle along with Thiol-derivatized polyethylene glycol (PEG-THIOL), which hides the TNF bearing nanoparticle from the immune system. This allows the nanoparticle to flow through the blood stream without being attacked. This targeted chemotherapy method to deliver TNF and other chemotherapy drugs to cancer tumours is developed by CytImmune company [19]

One heat therapy to destroy cancer tumors using nanoparticles is called AuroShell™. It was developed by Drs. Naomi Halas and Jennifer West of Rice University in the 1990s.The AuroShell™ nanoparticles circulate through a patients bloodstream, exiting where the blood vessels are leaking at the site of cancer tumors. Once the nanoparticles accumulate at the tumour the AuroShell™ nanoparticles are 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 AuroShell™ that has been approved for a pilot trial with human patients.Targeted heat therapy is being developed to destroy breast cancer tumours also. In this method antibodies that are strongly attracted to proteins produced in one type of breast cancer cell are attached to nanotubes, causing the nanotubes to accumulate at the tumour. Infrared light from a laser is absorbed by the nanotubes and produces heat that incinerates the tumour [20]

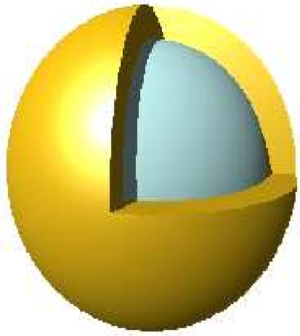

Figure 2: IV Bag of AuroShells® **Individual AuroShell® Particle**

X-ray therapy may be able to destroy cancer tumours using a nanoparticle called NBTXR3. The NBTXR3 nanoparticles, when activated by x-rays, generate electrons that cause the destruction of cancer tumors to which they have attached themselves. This is intended to be used in place of radiation therapy with much less damage to healthy tissue. Nanobiotix has released preclinical results for this technique [21]

There are efforts underway to develop oral administration of several different drugs using a variety of nanoparticles.The drug is encapsulated in a nanoparticle which helps it pass through the stomach to deliver the drug into the bloodstream. BioDelivery Sciences company has progressed to the clinical testing stage with a drug for treating systemic fungal diseases using a nanoparticle called a cochleate.

An intriguing targeted chemotherapy method uses one nanoparticle to deliver the chemotherapy drug and a separate nanoparticle to guide the drug carrier to the tumor. Another method that targets individual cancer cells inserts gold nanoparticles into the cells, then shines a laser on the nanoparticles. The heat explodes the cancer cells. Using gold nanoparticles to deliver platinum to cancer tumors may reduce the side effects of platinum cancer therapy. The toxicity level of platinum depends upon the molecule it is bonded to (the oxidation state of the platinum). So the researchers chose a platinum containing molecule that has low toxicity to attach to the gold nanoparticles. When the platinum bearing nanoparticle reaches a cancer tumor it encounters an acidic solution which changes the platinum to it's toxic state, in which it can kill cancer cells.

Iron (III) oxide nanoparticles can be used to improve MRI images of cancer tumors. The nanoparticle is coated with a peptide that binds to a cancer tumor. Once the nanoparticles are attached to the tumor, the magnetic property of the iron oxide enhances the images from the Magnetic Resonance Imagining scan. Magnetic nanoparticles that attach to cancer cells in the blood stream may allow the cancer cells to be removed before they establish new tumors [22]

In another technique, the drug carrying nanoparticle (a liposome) is attached to amino acids that bind to this protein, so the increased level of protein at the tumor speeds up the accumulation of the chemotherapy drug carrying liposome at the tumor. Sensors based upon nanoparticles or nanowires can detect proteins related to specific types of cancer cells in blood samples. This could allow early detection of cancer. T2 Biosystems uses superparamagnetic nanoparticles that bind to the cancer indicating protein and cluster together. These clusters provide a magnetic resonance signal indicating the presence of the cancer related protein. Abraxis BioScience, Incorporation *Abraxane* is an albumin-bound nanoparticle formulation of the widely used anticancer drug, Paclitaxel (Taxol). It is the only albumin-bound solvent-free taxane nanoparticulate formulation (~130 nm) that takes advantage of albumin to transport Paclitaxel into tumor cells. It was approved by the FDA in 2005 for use in patients with metastatic breast cancer who have failed combination therapy [23]

Also delivery of short interfering RNAs (siRNA) is interesting because siRNA simply stops the cancer tumor from growing and there is the potential to tailor synthetic siRNA to the version of cancer in an individual patient. Calando Pharmaceuticals, Inc. is a privately held biopharmaceutical company funded by Arrowhead Research Corporation. The company has developed proprietary therapeutic cyclodextrin-containing polymer RNA interference (RNAi) delivery technology and demonstrated the first clear in vivo sequence-specific gene inhibition in tumors. Calando's technology for RNAi is called RONDEL. Specifically, it employs small interfering RNA (siRNA) as the therapeutic RNA. Calando's nanoparticle delivery system is designed for IV injection. According to the company, upon delivery of the RNA-containing nanoparticles, the targeting ligand binds to membrane receptors on the targeted cell surface enabling the nanoparticles to be taken up into the cell via endocytosis [24a]

A new approach to cancer treatment has been through a combination of radiation and photodynamic therapies.The assumption is that supplementing conventional radiation therapy wit photodynamic therapy (PDT) will enable the the use of lower doses of radiation. Under this concept, scintillating or persistent luminescence nanoparticles with attached photosensitizers such as pyrophyrins are used as as an in vivo agent for photodynamic therapy.The nanoparticle PDT agents are delivered to the treatment site. Upon exposure to ionozing radiation such as X-rays , the naonparticles emit scintillation or persistent luminescence ,which in turn activates the photosensitizers ; as a consequences ,singlet oxygen (O2) is produced. Studies has shown that O2 can be effective in killing of cancer cells. This is the conventional innovation involves the use of in vivo luminescenct nanoparticle so that an external light source is not required to support PDT. Consequently, application of the therapycanbe more localized and the potential of damaged of the healthy cell is reduced. This new modality will provide an efficient low cost approach to PDT while still offering the benefits of augememted radiation therapy at lower doses. [24b]

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 [25]. 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 [26]. 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 [27, 28]

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 [29] 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 [30].

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 [31] Molecular manufacturing, also called molecular nanotechnology will provide the ability to build the nanorobots needed for future applications of nanomedicine [32]

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 [33] 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.

REFERENCES

[1] AD Maynard; RJ Aitken; T Butz; V Colvin; K Donaldson; G. Oberdörster; MA Philbert; J Ryan; A Seaton; V Stone; SS Tinkle; L Tran, NJ Walker; DB Warheit. *Nature*, **2006,** 444, 267-269.
[2] The Nanotechnology Consumer Products Inventory (Woodrow Wilson International Center for Scholars, Washington DC, **2006**). Published online at http://www.nanotechproject.org/consumerproducts
[3] A Hett. Nenotechnology : small matter, many unknowns, 2004, http://www.swissre.com
[4] S Iijima. *Nature*, **1991**, 354, 56-58.
[5] DA Tomalia; *Aldrichimica Acta*., **2004**, 37(2), 39-57.
[6] PT Edward; MS Michele. Application of nanotechnology: A case study in the pharmaceutical area. **2004**. http:// www.foley.com .
[7] SJ Douglas; SS Davis; L Illum. *Ther. Drug Carr. Syst*., **1987**, 3 (3), 233-261.
[8] R. Gref; Y Minamitake; MT Peracchia; V Trubetskoy; VP Torchilin; R Langer. *Science*, **1994**, 263,1600-1603.
[9] C Sestier; MF Da-silva; D Sabolovic; J Roger; JN Pons. *Electrophoresis*, **1998** 19(7), 1220-1226.
[10] H Carstensen; BW Muller; RH Muller. *Int. J Pharm.*, **1991**, 67, 29-37.
[11] PD Scholes; AGA Coombes; L Illum; SS Davis; JF Watts; C Ustariz; M Vert; MC Davies. *J. Controlled Release*, **1999**, 59: 261.
[12] Z Sarbak; A Staczyk; M Kramer-Wachowiak; *Powder Technology*, **2004**, 145(2), 82-87.
[13] B. Sarmento; D Ferreira; F Veiga; A Ribeiro. *Carbohydrate Polymers*, **2006**, 66(1): 1-7.
[14] C Schmidt; R Bodmeier. *J Control Rel*., **1999**, 57(2): 115-125.
[15] J Kreuter. *Int. J. Pharm*. **1983**, 14, 43-58.
[16] J Kreuter. *J Control Rel*., **1991**, 16, 169-176.
[17] B Magenheim; MY Levy; S Benita. *Int J Pharm*., **1993**, 94, 115-123.
[18] MJ Santander-Ortega; AB Jódar-Reyes; N Csaba; D Bastos-González; JL Ortega-Vinuesa. *Journal of Colloid and Interface Science*, **2006**, 302(2): 522-529.
[19] www.cytimmune.com
[20] http://www.nanospectra.com/clinicians/aurolasetherapy.html
[21] http://www.nanotechwire.com/news
[22] http://www.physorg.com/news65705979.html
[23] www.drugs.com/nda/abraxane_040308.html
[24] (a) http://www.calandopharma.com/
(b) P Pandey. Application of nanotechnology in cancer Treatment. UGC seminar on Application Of Nanosciences and Nanotechnology
[25] http://www.nanobiotix.com/
[26] http://www.linkedin.com/companies/z-medica
[27] http://www.nanosphere.us/
[28] http://www.t2biosystems.com/Site/
[29] Kbhol@nucryst.com
[30] www.ncbi.nlm.nih.gov/pubmed/19387479
[31] www.nanorobotdesign.com
[32] www.foresight.org
[33] G Oberdörster; E Oberdörster, J Oberdörster. *Environ. Health Perspect.*, **2005,** 13, 823–840.