Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Archives of Applied Science Research, 2010, 2 (1) 37-51
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-508X
CODEN (USA) AASRC9

The Role of Nanodrugs for Targeted Drug Delivery in Cancer Treatment

Sweta Gupta[1], Brijesh Singh Yadav[1], Rajesh Kesharwani[1], K. P. Mishra[1], N. K. Singh[2]

[1]*United Research Centre, UIT Campus, Allahabad, India*
[2]*Department of Applied Mechanics (Biotechnology) MNNIT, Allahabad, India*

Abstract

Nanotechnology has achieved the status as one of the critical research endeavors of the early 21st century. Nanoscale devices and components are smaller than human cells (10,000 – 20,000 nm in diameter) & organelles and similar in size to large biological macromolecules such as enzyme & receptors – Hb for e.g., is approx 5 nm in diameter. While the lipid bilayer surrounding the cells are on the order of 6 nm thick. Nanoscale devices are smaller than 50 nm can easily enter most cells, while those smaller than 20 nm can transit out of blood vessels. Therefore, the size of the Nanoscale devices allows them to interact readily with biomolecules on the cell surface and within the cell, often in ways that do not alter the behavior and biochemical properties of those molecules. Such ready access to the interior of a living cell affords the opportunity for unprecedented gains on the clinical and basic frontiers. Nanotechnology research is generating a variety of constructs giving cancer researchers great flexibility in their efforts to change the paradigm of cancer diagnosis, treatment, and prevention. In this study we focused how Cancer Nanotechnology is to develop safer and more effective diagnostic and therapeutic modalities for Cancer therapy.

Keywords: Nanotechnology, Nanoscale devices, Lipid bilayer, Cancer therapy

---

Introduction

A nanometer is billionth of a meter, which is about 1/80,000 of the diameter of a human hair, or ten times the diameter of a hydrogen atom. It manipulates the chemical and physical properties of a substance on molecular level. Nanotechnology alters the way we think, it blurs the boundaries between physics, chemistry and biology, the elimination of these boundaries will pose many challenges and new directions for the organization of education and research.

We define nanoscience as the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger

scale; and nanotechnologies as the design, characterization, production and application of structures, devices and systems by controlling shape and size at the nanometer scale. These technologies have been applied to improve drug delivery and to overcome some of the problems of drug delivery for cancer treatment.

The bulk properties of materials often change dramatically with Nano ingredients. Composites made from particles of Nano-size ceramics or metals smaller than 100 nanometers can suddenly become much stronger than predicted by existing materials-science models. For example, metals with a so-called grain size of around 10 nanometers are as much as seven times harder and tougher than their ordinary counterparts with grain sizes in the hundreds of nanometers. The causes of these drastic changes stem from the weird world of quantum physics. The bulk properties of any material are merely the average of all the quantum forces affecting all the atoms. As you make things smaller and smaller, you eventually reach a point where the averaging no longer works.

The properties of materials can be different at the Nanoscale for two main reasons
First, nanomaterials have a relatively larger surface area when compared to the same mass of material produced in a larger form. This can make materials more chemically reactive (in some cases materials that are inert in their larger form are reactive when produced in their Nanoscale form), and affect their strength or electrical properties.

Second, quantum effects can begin to dominate the behavior of matter at the Nanoscale - particularly at the lower end - affecting the optical, electrical and magnetic behavior of materials. Materials can be produced that are Nanoscale in one dimension (for example, very thin surface coatings), in two dimensions (for example, nanowires and Nanotubes) or in all three dimensions (for example, Nanoparticles).

Cancer

Cancer rapidly overtakes heart diseases as number one killer in America. In 2005, there were 559,312 cancer deaths in US. In 2006, over 500,000 Americans died due to cancer, and in 2007 alone, Cancer killed 8,000,000 people in the world. Cancer is currently the cause of 13% of all deaths. This figure is 30% in U.K, and 25% in US. Cancer has become the leading cause of death. The risk of developing Cancer is 1-in-2 for men and 1- in-3 for women.

Cancer is a highly complex disease that causes cells to divide too rapidly, destroy surrounding tissues and even spread to other parts of the body. Cancer is usually caused by a mutation in DNA, caused by mutagens, e.g. X-rays and gamma- rays. Carcinogens in cigarettes e.g. tar and benzene is another cause. These changes activate Oncogenes in cancer cells, which cause excessive growth of the cells. Also tumor suppressant genes in cancer cells are deactivated, causing the cells to loose control over their usual cell cycle. This also stops the cancer cells from interacting with these cells of the Immune system. When a cell is beyond repair, they are killed by apoptosis, but cancer cells are able to avoid this process due to the tumor suppressant genes being deactivated.

The most common Cancer treatments are limited to chemotherapy, radiation treatment, and surgery. Limitations in Cancer treatment are a result of challenges seen in cancer therapies today, including lack of early disease detection, non-specific systemic distribution, inadequate drug concentration reaching the tumor, and inability to monitor therapeutic responses. Poor drug delivery and residence at the target site leads to significant complications, such as Multiple Drug Resistance. Chemotherapy can cause a variety of ailments, including hair loss, digestive problems, nausea, and lack of energy and mouth ulcers. Chemotherapy fails to cure cancer because some tumor cells develop resistance to multiple anticancer drugs. Resistance develops when cancer cells begin expressing a protein p-glycoprotein, which pumps anticancer drugs out of the cell as quickly as they cross through the cell's outer membrane.

Why Nanotechnology in Cancer

Nanoscale devices are somewhere from 100-1000 times smaller than human cells. They are similar in size to large biological molecules such as enzymes and receptors. As an e.g. Hemoglobin, the molecule that carries oxygen in RBC is approximately 5nm in diameter. Nanoscale devices smaller than 50nm can easily enter most cells, while those smaller than 20nm can move out of blood vessels as they circulate through the body.

Because of their small size, Nanoscale devices can readily interact with the biomolecules on the surface of cells and inside of cells, without changing the behavior and biological properties of these molecules [1]. 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. And since biological processes including events that lead to cancer, occur at the Nanoscale at and inside cells, Nanotechnology offers a wealth of tools that provide cancer researchers, a new and innovative ways to diagnose and treat cancer. Nanoparticles also carry the potential for targeted and time-release drugs. A potent dose of drugs could be delivered to a specific area but engineered to release over a planned period to ensure maximum effectiveness and the patient's safety.

Because of their small size, Nanoparticles can accommodate tens of thousands of atoms or small molecules, such as Magnetic Resonance Imaging contrast agent gadolinium[2] , creating the opportunities for improved detection sensitivity of diseases such as Cancer at its earliest stage.

One more benefit of use of Nanoparticles in cancer is due to their surface chemistry. Modification of Nanoparticles outer layer allows a large variety of chemical, molecular, and biological entities to be covalently or otherwise bound to it. Manipulation of this corona confers advantageous properties to the particles, such as increased solubility and biocompatibility. Attaching hydrophobic polymers to the surface, such as Polyethylene glycol, greatly increases the hydration (i.e. solubility) of the Nanoparticles and can protect attached proteins from enzymatic degradation when used for in vivo application [3]. The surface addition of PEG ("pegylation") and other hydrophilic polymers also increases the in vivo compatibility of nanoparticles. When injected intravascularly, uncoated Nanoparticles are cleared rapidly injected intravascularly, uncoated nanoparticles are cleared rapidly from the blood stream by the Reticulo Endothelial System [4]. Nanoparticles coated with hydrophilic polymers have prolonged half-lives, believed to result from decreased opsonization and subsequent clearance by macrophages [5].

Nanodevices are capable of detecting cancer at its earliest stage, pinpointing its location within the body, delivering anticancer drugs specifically to malignant cells, and determining if these drugs are killing malignant cells. Nanotechnology will serve as multifunctional tools that will not only be used with any number of diagnostic and therapeutic agents but will change the very foundation of cancer diagnosis, treatment and prevention.

One strategy to concentrate cancer drugs only in their target tissue is through a mechanism known as enhanced permeability and retention effect (EPR) which happens in solid tumors. In fact, the network of blood vessels in many solid tumors has been shown to differ considerably from normal vasculature and to contain gaps in which tumor cells lack close contact with perfusing vessels, which ultimately leads to increased permeability. In this situation, drug delivery systems which are usually excluded from entering into tissues can extravasate into tumors and increase drug concentration 10-fold or more than administration of the same dose of free drug.

Nanoparticles for Drug Delivery

Nanoparticles used as drug delivery vehicles are generally less than 100 nm in at least one dimension, and consist of different biodegradable materials such as natural or synthetic polymers, lipids or metals. Nanoparticles are taken up by cells more efficiently than larger micro molecules and therefore, could be used as effective transport and delivery system. For therapeutic applications, drugs can either be integrated in the matrix of the particle or attached to the particle surface. A drug targeting system should be able to control the fate of a drug entering the biological environment. Nanosystems with different compositions and biological properties have been extensively investigated for drug and gene delivery application.

Controlled release polymer systems deliver drugs in the optimum dosage for long periods, thus increasing the efficacy of the drug, maximizing patient compliance and enhancing the ability to use highly toxic, poorly soluble or relatively unstable drugs. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting. An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumours as a result of the enhanced vascular permeability of tumour tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.

Controlled drug release and subsequent biodegradation are important for developing successful formulations. Potential release mechanisms involve: (i) desorption of surface-bound /adsorbed

drugs; (ii) diffusion through the carrier matrix; (iii) diffusion (in the case of Nanocapsules) through the carrier wall; (iv) carrier matrix erosion; and (v) a combined erosion /diffusion process. The mode of delivery can be the difference between a drug's success and failure, as the choice of a drug is often influenced by the way the medicine is administered. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature).

Nanoscale materials can be used as drug delivery vehicles to develop highly selective and effective therapeutic and diagnostic modalities. [6, 7, 8]

Advantages with Nanoparticles in comparison to micro particles:
1.Nanoscale particles can travel through the blood stream without sedimentation of the Microvasculature.
2.Small Nanoparticles can circulate in the body and penetrate tissues such as tumors.
3.Nanoparticles can be taken up by the cells through natural means such as endocytosis.
4.Nanoparticles have large surface area to volume ratio, that helps in diffusion also leading to special properties such as increased heat and chemical resistance. [9]

In general, targeted nanoparticles comprise the drug, the encapsulating material and the surface coating. The encapsulating material could be made from biodegradable polymers, dendrimer (treelike macromolecules with branching tendrils that reach out from a central core) or liposomes (spherical lipid bilayer). Controlled release of drugs (such as small molecules, DNA, RNA or proteins) from the encapsulating material is achieved by the release of encapsulated drugs through surface or bulk erosion, diffusion, or triggered by the external environment, such as changes in pH, light, temperature or by the presence of analyses such as glucose[10]. Controlled-release biodegradable nanoparticles can be made from a wide variety of polymers including poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly (lactic co-glycolic acid) (PLGA) and polyanhydride. PGA, PLA and their co-polymer PLGA are common biocompatible polymers that are used for making nanoparticles.

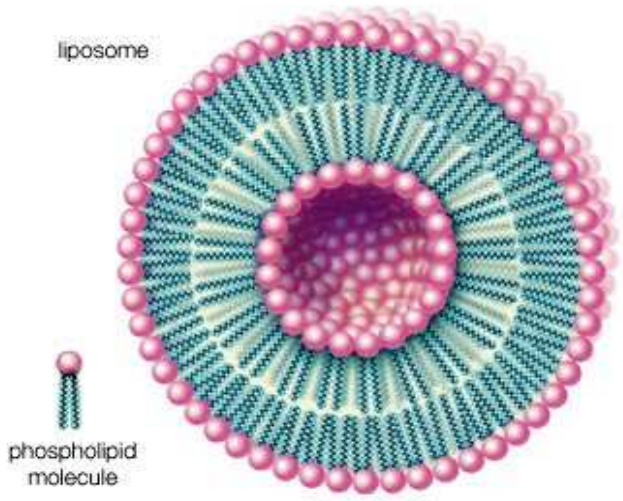
In order to control the targeted drug delivery of intravenously delivered nanoparticles, nanoparticles interactions with other cells, such as macrophages must be controlled. Various approaches have been developed to control these interactions, ranging from changing the size of the particle to changing nanoparticles surface properties. To remove nonspecific protein adhesion and decrease uptake by macrophages, nanoparticles can be functionalized using protein replant materials, such as poly (ethylene glycol) (PEG) [11] and polysaccharides [12, 13]. Nonadhesive surface coatings increase the circulation time of the nanoparticles [12] and reduce toxic effects associated with non-targeted delivery [14, 15].

Also, noncovalent approaches have been used to surface modify nanoparticles. For example, the layer-by-layer deposition of ionic polymers has been used to change surface properties of nanoparticles, such as quantum dots [16]. Layer-by-layer methods alter the surface charge of nanoparticles, which has been shown to regulate nanoparticles biodistribution. For example,

increasing the charge of cationic pegylated liposomes decreases their accumulation in the spleen and blood, while increasing their uptake by the liver and tumor vessels [17].

To target Nanoparticles to the desired tissues, a number of methods have been developed. These include physical means such as controlling the size, charge and hydrophobicity of the particles. In addition, targeting molecules, such as antibodies and peptides, that recognize specific cell surface proteins and receptors, can be conjugated to the nanoparticles surface to specifically target specific cell types. Antibodies and peptides have been successfully used to target nanoparticles to a number of desired cell types and provide powerful means of directing controlled-release Nanoparticles to specific sites in the body. Potential disadvantages of antibody- and' peptide-based targeting include their batch-to-batch variation and their potential immunogenecity. Aptamers, a class of DNA- or RNA-based ligands, may overcome some of the limitations associated with antibody- and peptide-based drug delivery. Aptamers have been conjugated to Nanoparticles to generate nanoparticles that can target prostate cancer cells [18, 19].

Liposomes



Liposomes are the "first generation" Nanoscale Drug Delivery Devices. They are small artificial vesicles of spherical shape that can be produced from natural nontoxic phospholipids and cholesterol. Because of their size, hydrophobic and hydrophilic character and biocompatibility, liposomes are promising systems for drug delivery. Liposomes properties vary substantially with lipid composition, size, surface charge and the method of preparation. Liposomes are able to pass along the smallest arteriole and endothelial fenestrations without causing clotting.

Three classes based on their size and numbers of bilayer are

- Small unilamellar vesicle
- Large unilamellar vesicle
- Multi lamellar vesicle

The choice of bilayer components determines the 'rigidity' or 'fluidity' and the charge of the bilayer. The introduction of positively or negatively charged lipids provides the liposomes a

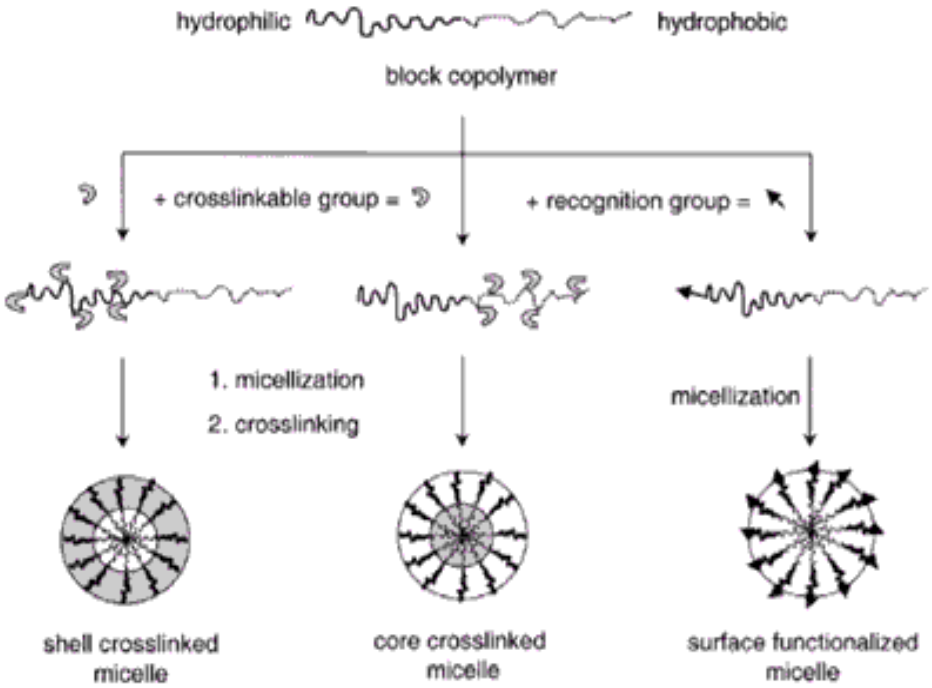
surface charge. Drugs associated with the liposomes are effective in reducing systemic toxicity and preventing early degradation of the encapsulated drug after introduction into the target organ. Liposomes surfaces can be readily modified by attaching units to bilayer (Shealth liposomes) to enhance their circulation time in the bloodstream. Liposomes can be conjugated to antibody or ligands to enhance target specific drug therapy. Liposomes are composed of double lipid bilayer, which encloses an aqueous phase that can be employed to transport anticancer drugs. Some factors must be taken intro account when preparing liposomal formulation including size, surface charge, and membrane fluidity. All these formulations issues have implications on the pharmacokinetics, biodistribution and bioavailability of the entrapped therapeutic product. Channel proteins can be incorporated without loss of their activity within the hydrophobic domain of vesicle membranes, acting as a size-selective filter, only allowing passive diffusion of small solutes such as ions, nutrients and antibiotics. Thus, drugs that are encapsulated in a nanocage-functionalised with channel proteins are effectively protected from premature degradation by proteolytic enzymes. The drug molecule, however, is able to diffuse through the channel, driven by the concentration difference between the interior and the exterior of the nanocage.

Recent applications

- Radiation guided drug delivery of liposomal cisplatin to tumor blood vessels results in Improved tumor growth delay.
- Vincristine – liposome showed efficacy against the transformed or aggressive non-Hodgkin's Lymphomas and presented less neurotoxicity than the free drug.
- Liposomes containing daunorubicin is currently being evaluated with some effectiveness for the treatment of Central Nervous System tumors
- Doxorubicin liposomes have shown significant activity against AIDS related Kaposi's Sarcoma, breast and Ovarian cancers in different clinical trials

Micelles

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water- solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micelles core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition, the corona may prevent recognition by the reticuloendothelial system and therefore preliminary elimination of the micelles from the bloodstream. A final feature that makes amphiphilic block copolymers attractive for drug delivery applications is the fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles. Functionalization of block copolymers with cross linkable groups can increase the stability of the corresponding micelles and improve their temporal control. Substitution of block copolymer micelles with specific ligands is a very promising strategy to a broader range of sites of activity with a much higher selectivity.



Block copolymer micelles

Dendrimmrs

Dendrimers are discovered in the early 1980s. They are manmade molecules, about the size of an average protein, highly branched and monodisperse macromolecules with symmetrical architecture [Tomalia, Naylor et al. 1990]. Branching shape increases the surface area to which therapeutic agents or other biologically active molecules can be attached. They consist of a central core, branching units and terminal functional groups. The core together with the internal units, determine the environment of the Nanocavities and consequently their solubilizing properties, whereas the external groups the solubility and chemical behaviour of these polymers. Targeting effectiveness is affected by attaching targeting ligands at the external surface of dendrimers, while their stability and protection from the Mononuclear Phagocyte System (MPS) is being achieved by functionalization of the dendrimers with polyethylene glycol chains (PEG).Particles displaying amine group (cationic) on the outer surface of dendrimer were significantly more cytotoxic than carboxylic (anionic) terminated dendrimer.

They are attractive systems for drug delivery because of their nanometer size range, ease of preparation and functionalization, and their ability to display multiple copies of surface groups for biological reorganization processes [20, 21]. Interaction of dendrimer macromolecules with the molecular environment is predominantly controlled by their terminal group. By modifying their termini, the interior of a dendrimer may be made hydrophilic while its exterior surface is hydrophobic or vice versa. A single dendrimer can carry a molecule that recognizes cancer cells, a therapeutic agent to kill those cells and a molecule that recognizes the signals of cell death. It is hoped that dendrimers can be manipulated to release their content only in the presence of certain trigger molecules associated with cancer. After drug releases, the dendrimers may also report back whether they are successfully killing their targets.

Recent applications

• 5 Flurouracil is known to have remarkable antitumor activity, but it has high toxic side effects. PAMAM dendrimers after acetylation can form dendrimer - 5 Fluorouracil conjugates which upon hydrolysis releases free 5 Flurouracil, thus minimizing toxicity.

• In one experiment, Folic acids were attached to the terminal branches of Dendrimer, which targets high affinity folate receptor found on the malignant cells, the indicator fluorescin, and either of the anticancer drug methotrexate or paclitaxel to a single dendrimer. Cancer cells recognize Folic acids as vitamins and endocytose the whole Dendrimer, across the membrane and into the cell including the toxic drug, which then kills the cancerous cell. This mechanism of killing cancer cell is known as Trojan horse trickery. It improved the cytotoxic response of cells to methotrexate 100 folds over free drug [Quintana, 2002]. Both invitro and in vivo experiments showed that these Nanodevices delivered its therapeutic payload specifically to folate receptor positive cells while simultaneously labeling these cells for fluorescent detection. Fluorescent indicator of cell death was linked to the dendrimer, which provided evidence that the therapeutic compound was not only delivered to its target cells but also produced the desired effect.

Nanoclinics

These are multifunctional Nanodevices, which may also enable new types of therapeutic approaches or broader application of existing approaching to killing malignant cells.

For e.g. silica coated lipid micelles containing LH-RH as a targeting agent have been used to deliver iron oxide particles to LH-RH receptor positive cancer cells. Once these Nanoclinics have been taken up by the target cell, they cannot only be imagined using MRI, but can also be turned into molecular scale scalpels applying a rapidly oscillating magnetic field causes the entrapped Fe_2O_3 molecules to become hot enough to kill the cell. The critical factor operating here is that Nanoparticles can entrap 10,000 or more Fe_2O_3 molecules, providing both enhanced sensitivity for detection and enough thermal mass to destroy the cell.

Nanoshell

They are miniscule beads having core of silica and a metallic outer layer (usually gold). By manipulating the thickness of the layers making up the Nanoshells, the beads can be designed that absorb specific wavelength of light. The most useful Nanoshells are those that absorb near infrared region light that can easily penetrate several centimeters in human tissues. Absorption of light by Nanoshell creates an intense heat that is lethal to cells. Because of their size Nanoshells will preferentially concentrate in cancer lesion sites. This physical selectivity occurs through a phenomenon called EPR.

Nanoshells can be decorated to carry molecular conjugates to the antigens that are expressed on the cancer cells themselves or in the tumor microenvironment. This second degree of specificity preferentially links the Nanoshell to the tumor and not to neighboring healthy cells. Then energy can be supplied externally to these cells. The specific property associated with Nanoshells allows for the absorption of this directed energy, creating an intense heat that selectively kills the tumor cells. The external energy can be mechanical, radio frequency; optical - therapeutic action is the same. Result is greater efficacy of therapeutic treatment and a significantly reduced set of side effects. In vitro the non-targeted Nanoshells did not show cytotoxicity for the tumor cells,

whereas after binding to the tumor cells cell death could be obtained after laser activation (Lowery et al 2006; Bernardi et al 2007; Stern et al 2007). Also in vivo positive results were obtained with photo thermal ablation therapy in a mouse model for colon carcinoma after intravenous administration of PEG coated gold Nanoshells of approximately 130 nm (O'Neal et al 2004).

Cantilevers

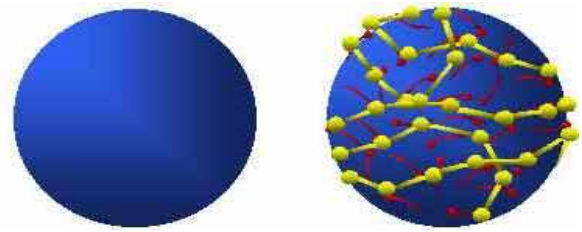
They are tiny bars built using semiconductor lithographic techniques. These can be coated with molecules capable of binding specific substrates- DNA complementary to a specific gene sequence, for e.g. such micron sized devices, comprising many nanometer sized Cantilevers; can detect single molecules of DNA or Protein. As cancer cells secrete its molecular products, the antibodies coated on the Cantilever fingers selectively binds to these secreted proteins. These antibodies have been designed to pick up one or more different, specific molecular expression from a cancer cell. The properties of cantilevers change as a result of the binding of the event. Researchers can read this change in real time and provide not only information about the presence and absence but also concentration of different molecular expression. Nanoscale cantilever can provide rapid and sensitive detection of cancer related molecules.

Nanoscale devices have the potential to radically change cancer therapy for the better and to dramatically increase the number of highly effective therapeutic agents. Nanoscale constructs can serve as customizable, targeted drug delivery vehicles capable of ferrying large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells, greatly reducing or eliminating the often unpalatable side effects that accompany many current cancer therapies.

Polymeric Nanoparticles

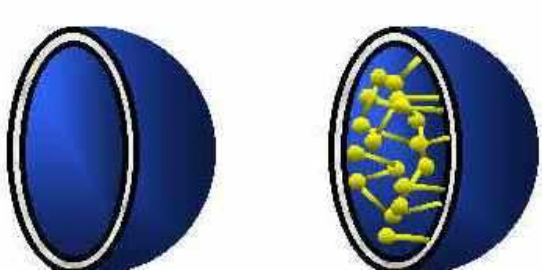
Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 10 nm to 1000 nm [22]. The drug of interest is dissolved, entrapped, adsorbed, attached or encapsulated into the Nanoparticles matrix, thus protecting it against chemical and enzymatic degradation. Depending on the method of preparation, Nanoparticles, Nanospheres or Nanocapsules can be obtained with different properties and release characteristics for the encapsulated therapeutic agents.

Nanospheres



Nanospheres are matrix systems in which the drug is physically and uniformly dispersed.

Nanocapsule



Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane

Nanoparticles as drug carriers can be formed from both biodegradable polymers and non-biodegradable polymers. In recent years, biodegradable polymeric Nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organs / tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through the peroral route.

Nanocrystals

Nanocrystals [also called Quantum dots or nanodots] are crystalline clumps of a few hundred atoms, coated with an insulating outer shell of a different material [23]. Qdots are generally composed of atoms from group II - VI or III – V of the periodic table and are defined as particles with physical dimensions smaller than the excitation Bohr radius [24]. When a photon of visible light hits such a minute particle, a quantum – physics reflect confines all the photon's energy to the crystal core before being emitted as extraordinary bright fluorescence.

The QDots absorb light at a wide range of wavelengths, but emit almost monochromatic light of a wavelength that depends on the size of the crystals [25]

Qdots can be attached to biological materials, such as cells, proteins and nucleic acids. Qdots can be designed to emit light at any wavelength from the infrared to ultraviolet. Larger Qdots emit red light, whereas smaller crystals emit light at the blue end of the spectrum. Qdots' fluorescence is so bright that it is possible to detect a cell carrying a single crystal [26]. Qdots are inorganic and so they are very stable, and their inert surface coating makes them less toxic than organic dyes.

Advantage of Nanotechnology

Nanotechnology will allow making high-quality products at a very low cost, and also allow making new nanofactories at the same low cost and at a very rapid speed. Nanotechnology offers not just better products, but a vastly improved means of production for e.g. as many copies of data files as we want can be taken out from your computer at a very or no cost. With time, manufacture of products will become as cheap as the copying of files. So this is what nanotechnology is, and so it is often seen as the next industrial revolution. Nanoscale materials are used in electronic, magnetic and optoelectronic, biomedical, pharmaceutical, cosmetic, energy, catalytic and materials applications [27].

Cost benefits

- Enhanced drug delivery leads to superior performance characteristics of the product.
- Lifespan of the blockbuster drugs can be resurrected by reformulating the drug through Novel drug delivery system.
- The effective patent protection can be enhanced.
- Drug delivery formulation involves low-cost research compared to that for the discovery of a new molecule.
- Minimizing use of expensive drugs would reduce the cost of the product.

Future Opportunities and Challenges

Today, much of the science on the Nanoscale is basic research, designed to reach a better understanding of how matter behaves on this small scale. The surface area of Nanomaterials being large, the phenomena like friction and sticking are more important than they are in large systems. These factors will affect the use of Nanomaterials both inside and outside the body. Nanostructures being so small; the body may clear them too rapidly to be effective in detection or imaging. Larger Nanoparticles may accumulate in vital organs, creating a toxicity problem.
Nanoparticles and Nanoformulations have already been applied as drug delivery systems with great success; and Nanoparticulate drug delivery systems have still greater potential for many applications, including anti-tumour therapy, gene therapy, AIDS therapy and radiotherapy, in the delivery of proteins, antibiotics, virostatics, and vaccines and as vesicles to pass the blood-brain barrier.

Nanoparticles provide massive advantages regarding drug targeting, delivery and release and, with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in Nanomedicine. The main goals are to improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers. The cytotoxicity of Nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research.

There are many technological challenges to be met, in developing the following techniques:

- Nano-drug delivery systems that deliver large but highly localized quantities of drugs to specific areas to be released in controlled ways
- Controllable release profiles, especially for sensitive drugs
- Materials for Nanoparticles that are biocompatible and biodegradable
- Architectures / structures, such as biomimetic polymers, Nanotubes
- Virus-like systems for intracellular delivery
- Nanoparticles to improve devices such as implantable devices/Nanochips for Nanoparticles release, or multi reservoir drug delivery-chips
- Nanoparticles for tissue engineering; e.g. for the delivery of cytokines to control cellular growth and differentiation, and stimulate regeneration; or for coating implants with Nanoparticles in biodegradable polymer layers for sustained release
- Advanced polymeric carriers for the delivery of therapeutic peptide/proteins (biopharmaceutics)

- Combined therapy and medical imaging, for example, Nanoparticles for diagnosis and manipulation during surgery (e.g. thermotherapy with magnetic particles)
- Universal formulation schemes that can be used as intravenous, intramuscular or peroral drugs
- Cell and gene targeting systems
- User-friendly lab-on-a-chip devices for point-of-care and disease prevention and control at home
- Devices for detecting changes in magnetic or physical properties after specific binding of ligands on paramagnetic Nanoparticles that can correlate with the amount of ligand
- Better disease markers in terms of sensitivity and specificity

Recent Nano Advancement

Combining Two Drugs in One Nanoparticles Overcomes Multidrug Resistance

Cancer cells, like bacteria, can develop resistance to drug therapy. In fact, research suggests strongly that multidrug-resistant cancer cells that remain alive after chemotherapy are responsible for the reappearance of tumors and the poor prognosis for patients whose cancer recurs. One new approach that shows promise in overcoming such multidrug resistance is to combine two different anticancer agents in one Nanoscale construct, providing a one-two punch that can prove lethal to such resistant cells.

Mansoor Amiji, Ph.D., principal investigator of the National Cancer Institute-funded Nanotherapeutic Strategy for Multidrug Resistant Tumors Platform Partnership at Northeastern University, and postdoctoral fellow Srinivas Ganta, Ph.D., created a nanoemulsion entrapping both paclitaxel and curcumin. The former compound is a widely used anticancer agent, whereas the latter comes from the spice turmeric and has been shown to inhibit several cancer-related processes.

The investigators prepared their Nanoformulations by mixing the two drugs with flaxseed oil, the emulsifier lecithin from egg yolks, and the biocompatible polymer polyethylene glycol. To help track these Nanoformulations, the investigators also added a fluorescent dye to the mixture. Ultrasonification for 10 minutes produced stable, nanosize droplets that were readily taken up by tumor cells grown in culture. In addition, the Nanoformulations had significant anticancer activity that surpassed that of either of the two drugs administered together or separately, particularly in multidrug-resistant cells. Biochemical assays showed that the curcumin component inhibited P-glycoprotein, which tumor cells use to excrete anticancer agents and protect themselves from the effects of those agents. Both drugs also had the effect of triggering apoptosis in the treated cells.

This work, which was detailed in the paper “Co administration of paclitaxel and curcumin in nanoemulsion formulations to overcome multidrug resistance in tumor cells,” was supported by the NCI Alliance for Nanotechnology in Cancer, a comprehensive initiative designed to accelerate the application of nanotechnology to the prevention, diagnosis, and treatment of cancer. An abstract is available at the journal’s Web site.

Conclusion

Disease and ill health are caused largely by damage at the molecular and cellular level. Nanotechnology, "the manufacturing technology of the 21st century," should let us economically build a broad range of complex molecular machines (including, not incidentally, molecular computers).

Such tools will let medicine, for the first time; intervene in a sophisticated and controlled way at the cellular and molecular level. They could remove obstructions in the circulatory system, kill cancer cells, or take over the function of sub cellular organelles. Just as today we have the artificial heart, so in the future we could have the artificial mitochondrion

Nanoparticulate technology can prove to be very useful in cancer medical care allowing for effective and targeted drug delivery by overcoming the many biological, biophysical and biomedical impediments that the physical body mounts against a standard intervention such as the administration of medicinal drugs or contrast agents.

To help meet the goal of eliminating death and suffering from cancer by 2015, The National Cancer Institute is engaged in efforts to harness the power of Nanotechnology to radially change the way we diagnose, image and treat cancer.

"Nanotechnology is going to be the shaping of the future in cancer therapy"

Reference

[1] K .Bogumia. Kubik, M. Sugisaka, "Molecular biology to nanotechnology and Nanomedicine Biosystems" 65, 123- 138 (**2002**)
[2] A. M., Morawski, P. M Winter, K. C.Crowder, S. D Caruthers, R. Fuhrhop, W.Scott, J.D.Robertson, D.R.Abendschein, G.M.Lanza, Wickline, *Magn. Reson. Med*. 51, 480-486. S. A. (**2004**)
[3] J. M. Harris, R. B .Chess, *Nat. Rev.Drug Discovery*. 2, 214- 221. (**2003**)
[4] I. Brigger, C Dubernet, P. Couveur, *Adv.Drug Deliv. Rev*. 54, 631-651. (**2002**)
[5] S.M. Moghimi, Sczebeni, *J. Stealth Prog.Lipid Res*.42, 463-478. (**2003**)
[6] J. R.McCarthy, *et al., Nano Lett*, 5 (12), pp. 2552–2556 (**2005**).
[7] X. Gao, *et al., Nat Biotechnol*, 22 (8), pp. 969–976 (**2004**).
[8] R.Langer, and D. A. Tirrell, *Nature*,428 (6982), pp. 487–492 (**2004**).
[9] Priya Pathak and V. K. Katiyar, Multi-Functional Nanoparticles and Their Role in Cancer Drug Delivery – A Review, 3, 1-17, **2007**.
[10] R. Langer, and D. A. Tirrell, *Nature*, 428 (6982), pp. 487–492 (**2004**).
[11] R.Gref, *et al., Science*, 263 (5153), pp. 1600–1603 (**1994**).
[12] C. Lemarchand, *et al., Eur J PharmBiopharm*, 58 (2), pp. 327–341 (**2004**).
[13] C. Lemarchand, *et al, Biomaterials* 27 (1), pp. 108–118 (**2006**).
[14] S.Gibaud, *et al., Eur J Cancer*, 30A (6), pp. 820–826 (**1994**).
[15] M.Demoy, *et al.***,** *Pharm Res*, 14 (4), pp. 463–468 (**1997**).
[16] S.Jaffar, *et al.***,** *Nano Letters***,** 4 (8), pp. 1421–1425 (**2004**).
[17] R. B.Campbell, *et al.***,** *Cancer Res*, 62 (23), pp. 6831–6836 (**2002**).

[18] O. C., Farokhzad, *et al., Cancer Res*, 64 (21), pp. 7668–7672 (**2004**).
[19] O. C Farokhzad, *et al., Anal Chem.*, 77 (17), pp. 5453–5459 (**2005**).
[20] A. Quintana, et al. Pharm. Res. 19. 1310.(**2002**)
[21] O.L.Padilla De Jesus. et al, *Bioconjugate Chem*. 13. 453- 461. (**2002**)
[22] L Brigger, et al. *Adv. Drug Deliv. Rev*. 54, 631-651(**2002**)
[23] D.F. Emerich, et al. *Expert Opin. Biol. Ther*.3,655- 663(**2003**)
[24] M.E. Akerman, et al *Proc. Natl. Acad. Sd*. U.S.A. 99, 12617 – 12621. (**2002**)
[25] W. C. Chan, et al. *Curr. Opin. Biotechnol*. 13, 40 – 46.(**2002**)
[26] M .Han,.etal. *Nat. Biotechnol*. 19, 631-635(**2001**)
[27] P. Mitchell, *Nat Biotechnol*. 19, 1013m – 1017(**2001**)