Comparative Study of Nanotechnology based Cancer Treatment: A Systematic Approach

Girish Patil, Shashikant S. Patil, Sachin Sonawane, Amar Khalore, Pushpanjali M. Chouragade

Abstract— Cancer is caused by damage of genes which control the growth and division of cells. Diagnosis is possible by confirming the growth of the cells and treated by rectifying the damaging mechanism of the genes or by stopping the blood supply to the affected cells or by destroying it. Conventional diagnosis methods of the cancer are based on observation of the physical changes in the organ by X-rays and/or CT Scans and are confirmed by biopsy through cell culture. However, the inadequacy of such methods is that these are less sensitivity and the detection is possible only after considerable growth of the cancerous cells. The traditional treatment schemes of cancer are surgery, chemo therapy and radiation therapy having their own limitations. The Nanotechnology based methods emerging as an alternative for cancer diagnosis as well as treatment. Nano Particles (NP) being of a few of nano meters size and the cells being of the size of few microns, NP can penetrate the cells and can interact with the DNA molecules and resulting in improved probability of diagnosis of cancerous cell before its substantial growth. In the nanotechnology based treatment methods, certain NP can be engineered to absorb preferentially certain wave length of radiation and they are controlled to enter in the cancerous cells and burn them under the ambience of radiation. Nanotechnology can be used to create therapeutic agents that target specific cells and deliver toxin to kill them. The NP can easily circulate through the body, detect molecular changes caused by cancer, assist the imaging techniques, release a therapeutic agent and then monitor the effectiveness of the intervention. In this paper, such probabilistic methodologies for diagnosis and treatments based on nanotechnology are discussed. In addition the present status, application and toxic effects of NP and their regulatory aspects are also presented.

Index Terms— Cancer, Nano Material, Molecular Imaging, Nanotechnology,in vitro, in vivo, drug targetting

1 Introduction

Nanotechnology is a fascinating science for many scientists as it offers them many challenges. It can be defined as the science and engineering involved in the design, analysis, characterization, synthesis and use of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale (one-billionth of a meter). Nano science and nanotechnologies have a huge potential to bring benefits in the diverse areas, hence it is seen as the boon for the human health care, especially in the diagnosis and treatment of cancer [1] [3]. Recent developments in nanotechnology have provided researchers with new tools for cancer imaging and treatment. This technology facilitates the advancement of Nano scale devices that can be conjugated with several functional molecules simultaneously. Since these Nano devices are up to 1000 fold smaller than cancer cells, hence they can be relocated through leaky blood vessels and interact with targeted tumor-specific proteins both on the surface of and inside cancer cells [11] [14].

These technologies have been applied to improve drug delivery and to overcome some of the problems of drug delivery for cancer treatment. Several Nano-biotechnologies mostly based on Nanoparticles, are able to play most significant role of drug delivery in cancer. Nanoparticles have given the hope for the recovery from this disease. Although, practicing better drug delivery paths into the body is continued by scientists and ultimately seeking more accurate protocols to eradicate cancer from the society [9].

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Causes of Cancer

Cancer occurs when cells begin to multiply more rapidly than usual and tumors or malignant growths of tissue are formed. Cancer is caused by damage of genes which control the growth and division of cells. Genes carry the instructions for basic functions of cells. Cancerous cell need blood supply for growth. A molecule causes neighboring blood vessel to grow towards the cell to supply the oxygen and valuable nutrients. Cancer is curable by the rectification of the damaging mechanism of the genes or by stopping the blood supply to the cells. Diagnose is possible by confirming the growth of the cells [2].

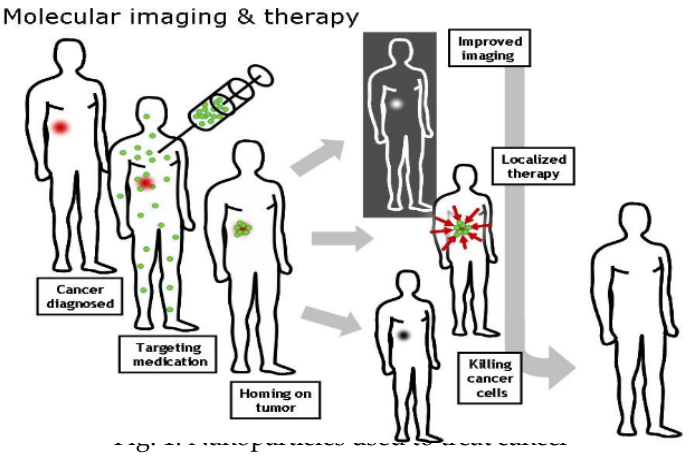
Treatment of Cancer

One of the treatment options is surgery. That is, remove the cancerous part. However, the limitation is that one loses the organ and the cancer may appear again. Further, the surgery is not possible for all types of cases of the cancer. Second option is radiation therapy. In this the cancerous cells are burnt by radiation of specific frequency band and the intensity. The limitation of this method is that even the healthy cells get burnt, cancerous cells burning are not uniform and the burnt part may become dead and nonfunctional. A next option can be chemotherapy; Cancerous cells are killed by drugs toxic to cells or by stopping cells from taking nutrients needed to di-

vide the cells or stop the mechanism responsible for division of the cell. If the cancer is in advanced stage, these are not very sensitive and the detection is possible only after substantial growth of the cancerous cells [2].

Nanotechnology in Cancer Treatment

Nano Particles (NP) can pass through the cells and reach to the DNA molecules/Genes and this may cause the propagation of major damage in genes of future generation**.** Certain NP can be designed to absorb specific wavelength of radiation and they can be passed through cancerous cells in order to burn them. Nanotechnology can be used to create therapeutic agents that target specific cells and deliver toxin to burn them. The NP can detect cancer associated atomic variation and assist with imaging, discharge a healing agent and then monitor the effectiveness of the intervention [3].



Source: Journal of Applied Pharmaceutical Science 01 (03); 2011: 25-29

2 History of Nanotechnology

The prefix "Nano" derives from the Greek word for "dwarf." One nanometer (nm) is equal to 10 water molecules. A human hair is typically 80,000 nm wide, and a red blood cell has the width typically 7000 nm. An Atoms size is generally smaller than 1 nm. The conceptual underpinnings of nanotechnologies were first laid out in 1959 by the physicist Richard Feynman; he explored the possibility of manipulating material at the scale of individual atoms/ molecules. The term "nanotechnology" was used first in 1974, when a researcher 'Norio Taniguchi', University of Tokyo mentioned it to refer the ability of physical materials precisely at the nanometer scale. The primary driving force for miniaturization at that time came from the electronics manufacturing [1].

Nanotechnology in general is the study of creating machines under the size of 100 nanometers. In more recent times, many impressive new advances are being made in nanotechnology in the medical field that enables doctors to diagnose cancer earlier and more effectively. With these advances being made, the research is headed in the direction to find complete cure for cancer. For years now, oncologists have only been able to view cancerous cells or sites using fairly conventional methods, which are very effective in the cancer detection. It is known that the ability to detect cancerous cells or cells in the precancerous stage relies on the ability to monitor slight changes in molecular composition of the damaged cells. Some Nano devices are being developed that could detect alterations of a cell's DNA that is a precursor to the development of cancer tumors. Other Nano devices are being developed that would have the capability to bind to cancer cells and not normal cells, thus making detection easier. Still other Nano devices could detect cancer "biomarkers" in a sample of human blood far earlier than current tests allow. The advantages of these methods are that they can detect cancer early, without exploratory surgery, and without physically altering the cells being examined. Nanotechnology doesn't just stop at detection but is being developed to assist in the treatment of cancer as well [2] [6].

Nanotechnology devices can be put into the body loaded with targeting information and powerful cancer treating drugs [7].

3 Tools of Nanotechnology

Some of the tools of nanotechnology having applications in cancer detection and treatment are the following [1]-[4]-[5]:

3.1 Nanopores

Another interesting Nano device is the Nano pore. Improved methods of reading the genetic code will help researchers detect errors in genes that may contribute to cancer. Scientists believe Nano pores, tiny holes that allow DNA to pass through one strand makes DNA sequencing more efficient. As DNA passes through a Nano pore, scientists can monitor the shape and electrical properties of each entity. Because these properties are unique for each of the four bases that make up the genes, scientists can focus and treat the passage of DNA through a Nano pore to decipher the encoded signal [1].

3.2 Nano Tubes (<100 nm)

Nanotubes are smaller than Nano pores. Nanotubes & carbon rods, about half the diameter of a molecule of DNA, can be secondhand to identify DNA changes associated with cancer. It helps to exactly pin point location of the mutation, such regions associated with cancer are first tagged with molecules.

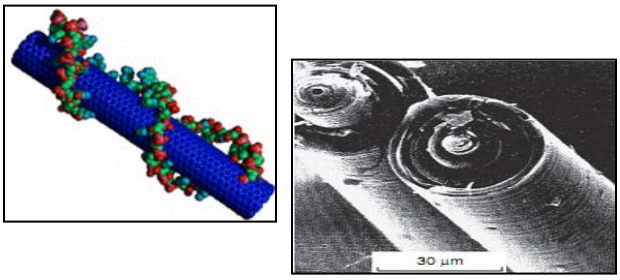


Fig. 2. Schematics of a functionalised single-walled carbon nanotube with Cyanine Dye #3 Labelled DNA (Cy3-DNA) Courtesy: Kam et al. (2001)

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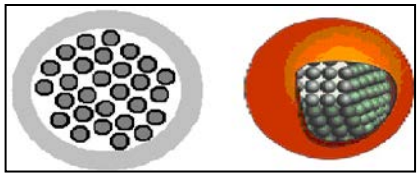
3.3 Quantum Dots (2-10 nm)

These are tiny crystals that glow when these are stimulated by UV light. The fluid beads filled with such crystals when stimulated by UV light, the colors they emit light up the interested sequence. The combination of quantum dotes of various sizes in a solo bead probes can be built, which releases a distinct spectrum of several colors and intensities of light.

(a)



(b)

Fig. 3. (a) Changing color of quantum dots according to size of dots.
(b)Semiconductor Nano size crystalline quantum dots (Courtesy: Ocean NanoTech).

3.4 Nano shells (10–300 nm)

NS being the tiny gold plated beads are one of the recent inventions in Nano technology. NS are made up by controlling the thickness of the layers, these beads can absorb definite wavelength of light. As we know, the infrared light can straightforwardly penetrate more than a few centimeters in human muscles and tissues, the Nano shells that absorb infrared are found more useful. Light absorption by NS creates an intense heat that is lethal to cells. Nano shells can be linked to antibodies that recognize affected cells. The heat generated by the light-absorbing Nano shells has successfully killed tumor cells while leaving neighboring cells intact.

3.5 Dendrimer (<15 nm)

A number of nanoparticles that will facilitate drug delivery are available now days. One molecule is capable to link treatment with detection and diagnostic is known as dendrimer. Their branching shape facilitates vast amounts of surface area to which therapeutic agents or other biologically active molecules can be attached. A dendrimer has potential to carry a molecule that recognizes affected cells, a therapeutic agent and a molecule that recognizes the signals of killed cell. Dendrimers can be manipulated to release their contents only in the presence of certain trigger molecules of cancer. Below mentioned drug releases, the dendrimers may also report back whether they are successfully killing their targets.

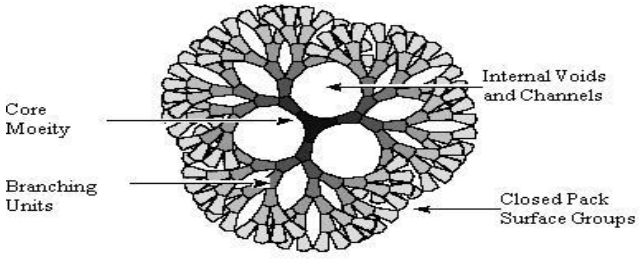


Fig. 4. The Dendritic Structure

TABLE 1
SUMMARY OF CURRENT NANOPARTICLES

Name	*Size*	*Composition Details*
Quantum Dots	2-10 nm	Colloidal fluorescent semiconductor Nano crystals. Central core consists of elements from groups II - VI of the periodic table.
Dendrimer	<15 nm	Highly branched synthetic polymers with a layered architecture - consisting of a central core, an internal region, and several terminal groups
Carbon Nanotubes (CNT)	<100 nm	Coaxial graphite sheets
Liposomes	50-100 nm	Phospholipid vesicles. Classified by size and the number of layers - multi-, oligo-, or unilamellar.

4 Detection and Diagnosis through Nanotechnology

Cancer diagnosis through nanotechnology is another significant matter of concern which is to be addressed. Early detection of the disease is of vital importance, in order to provide early and therefore more effective cancer treatment. Two approaches to cancer detection may be envisioned and they include

- in vitro (laboratory-based) diagnostics
- in vivo diagnostics.

4.1 In vitro (laboratory-based) diagnostics

In vitro (laboratory-based) nanotechnology based diagnostics methods are inspired from the concept of computer chips. With the use of some recent research work in Nano arrays, multiple bimolecular markers can be detected at very low concentrations in several biological fluids.
Currently two equally effective Nano array methods are available.

- In first method, a high-sensitivity electronic ammeter is used to which nanowires are connected. Each nanowire is designed to be a good binding site for a specific biomolecule. The bio fluid under study is passed through a channel where it is allowed to come into direct contact with

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wire. The change in molecular binds is responsible for variation in conductance of the wires and this property is useful in detection.

In second method, a Nano array of Atomic Force Microscope (AFM) cantilevers which are equipped with antibodies specific to selected molecules. The array is submerged in a bio fluid where the molecules that are present are allowed to bind to the antibodies. As they bind, they cause the levers to deflect, and the deflection is measured by a combination of a highly focused laser beam and sensitive photo detectors, with a technique similar to that used in Atomic Force Microscope. The data yield by all these methods is highly accurate, up to the concentrations in the range of PPM [3] [5] [8].

4.1 In vivo diagnostics

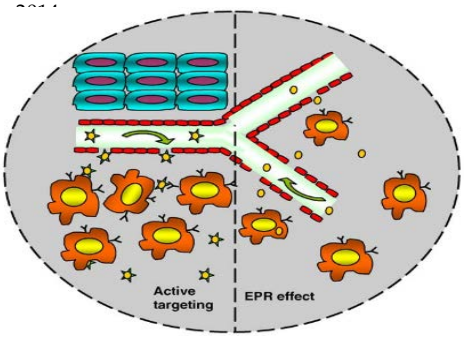
In vivo technique is currently under development. One of the methods utilizes Nano arrays similar to that in vitro technique. However, due to conditions that are much more adverse in a subject, upper concentrations of the desired molecules are necessary for accurate and precise detection. Implanting biosensors directly into the patient and to have them relay gathered information to an external data collector is another possible method. The major issue that still remains unresolved is bio fouling, or the nonspecific adoption of serum proteins to the sensors. Since serum proteins are present in healthy as well as malignant environments [5] [6] [7].

5 Aspects of Targeted Cancer Therapy

Ideally, for anticancer drugs to be effective in cancer treatment, they should first be able to reach the desired tumor tissues through the penetration of barriers in the body with minimal loss of volume or activity in the blood circulation. Next, after reaching the tumor cells, drugs shall be efficient to selectively kill tumor cells without affecting normal cells with a controlled release mechanism of the active form. These strategies are connected with improvements in patient survival, by raising the cellular concentration of drugs and reducing dose-limiting toxicities. In principle, nanoparticle delivery of anticancer drugs to tumor tissue can be achieved by either passive or active targeting. The right-hand part of the figure 7 depicts the increased accumulation of nanoparticles in tumor owing to leaky tumor vasculature, leading to the enhanced permeability and retention effect. The left-hand part of the figure shows active targeting mediated by targeted nanoparticles.

5.1 Active targeting

Localized diseases such as cancer or inflammation not only have leaky epitopes or receptors that can be used as targets. Therefore, Nano medicines can also be actively targeted to these sites. Ligands that specifically bind to surface epitopes or receptors, preferentially over expressed at affected areas are coupled to the surface having long circulating Nano carriers. Ligand-mediated active binding to sites and cellular uptake are particularly valuable to therapeutics that are not taken up easily by cells and require fusion or other processes to access



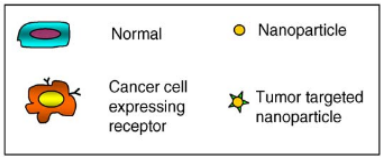


Fig. 4. Tumor targeting
Source: Drug Discovery Today Vol.15, No. 19/20 Oct. 2010

their cellular areas. Targeting enhances the circulation of Nano medicine within the tumor interstitial. More recently, active targeting has been explored to deliver drugs into resistant affected cells [7] [12].

5.1 Passive targeting

Passive targeting occurs due to extravasations of the nanoparticles at the diseased site where the microvasculature is permeable. Examples are tumor and inflamed tissues. Tumor vascular leakiness is the result of increased angiogenesis and the presence of cytokines and other vasoactive factors that enhance permeability. The majority of solid tumors exhibit a vascular pore cutoff size between 380 and 780 nm, although tumor vasculature organization may differ depending on the tumor type, its growth rate and microenvironment. This Nano size window offers the opportunity to increase drug accumulation and local concentration in target sites such as tumor or inflamed sites by extravasations, and considerably to reduce drug circulation and toxicity to normal tissues. Recently, researchers have also developed other approaches to increase local micro vascular permeability and further enhance delivery to solid tumors and other targeted cells [6] [10].

6 Current Progress in Cancer Nanotechnology

Today, clinical, cancer-related nanotechnology research is proceeding on two main fronts: laboratory-based diagnostics and in vivo diagnostics imaging and therapeutics. Here are just a few of the illustrative highlights of progress in these areas, as well as with the use of nanotechnology to extend our understanding of cancer cellular and molecular biology.

6.1 Nanotechnology and Molecular Imaging

1-2 nanometer-wide wires built on a micron-scale silicon grid can be coated with monoclonal antibodies directed against various tumor markers, leading to a hundredfold increase in sensitivity over current diagnostic techniques with minimal sample preparation. Nano scale "lab-on-a-chip" applications are now capable of conducting real-time analysis of single biochemical markers. Quantum dots have been used to tag and follow multiple individual molecules within cells, providing an opportunity to study the biochemical and genetic systems that go awry in cancer. Nano scale "harvesting" devices have collected proteins capable of distinguishing cancerous tissue from normal tissue.

6.2 Nanotechnology and In Vivo Imaging

Nano scale MRI contrast agents, containing paramagnetic iron nanoparticles, dramatically improve the ability to detect metastatic lesions in lymph nodes associated with breast and prostate cancer. Gold nanoparticles demonstrate usefulness contrast agents for in vivo endoscopic optical imaging of specific molecular cancer markers. Gas-filled lipid nanoparticles have shown promise for use as acoustically activated imaging agents, and perhaps targeted drug delivery systems, for tumors with a spatial resolution of 0.5 to 1.0 millimeters and a temporal timeframe of several images per second. Her-2 conjugated, gold-coated nanoparticles with a dielectric silicon core can identify breast carcinoma cells in vivo. Once bound to their target cells, these nanoparticles were subjected to increased optical power, turning them into Nano scale thermal scalpels that attain cell-killing temperatures.

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6.3 Nanotechnology and Cancer Therapy

Wide varieties of synthetic Nano scale particles are shown to target tumor cells, enter cancer cells, and release therapeutic agents. Engineered virus particles can serve as multifunctional, targeted non-immunogenic Nano scale devices with potential for a broad range of in vivo uses. Photosensitizers are used in a therapy, where light generates reactive oxygen locally within tumors, have also been entrapped in targeted Nano scale devices. The next step in this work is to also entrap a light-generating system, such as the Lucifer in-luciferase pair, in such a way as to trigger light production only after the nanoparticles have been taken up by a targeted cell. If successful, such an approach would greatly extend the usefulness of photodynamic therapy to include treatment of tumors deep within the body.

6.4 Nanotechnology as a Research Enabler

Construction and testing of Nano platforms can consolidate cell biology lab tests on a chip. These Nano platforms can be constructed to accurately mimic the microenvironment in which a particular cell normally grows, producing a system capable of both perturbing cells and recording their responses in a manner more representatives of how those cells would behave in the body than is observed in cells grown in standard tissue culture systems. A Nano scale device analyzes genome complexity and shows that early-stage tumors expressing similar phenotypes can be distinguished on the basis of how each tumor selects a slightly different approach to derange its genome [13] [14].

7 Applications

Following are some the present applications of nanotechnology based product alongwith their specific uses

TABLE 2
SOME NANOPARTICLES USED FOR MEDICAL APPLICATIONS*

Study phase	Product (Manufacturer)	Description	Use
Preclinical	MRX 952 (IMARx Therapeutics)	Nanoparticle preparation–toencapsulate camptothecin analogues	**Tumours**
Preclinical	Targeted Nano Therapeutics System (Triton Biosystems)	TNT with polymer coated Iron oxide magnetic particle	**Solid Tumours**
Preclinical	AuroLase (Nanospectra Biosciences Inc.)	Gold Nano shell	**Head and neck cancer**
Preclinical	Dendrimer-Magnevist # (Dendritic Nanotechnologies Inc.)	PAMAM dendrimer	**MRI imaging agent**
Phase 1	VivaGel (Starpharma Pty Ltd.)	Dendrimer based microbicide gel	**HIV prevention**
Phase 1	INGN 401 (Introgen Therapeutics Inc.)	Nanoparticle formulation of tumour suppression gene FUS1	**Lung cancer**
Phase 1 & 2	Cyclosert-Camptothecin –IT 101 (Calando Pharmaceuticals)	ß-Cylcodextrin polymer drug delivery system	**Solid Tumours**
Phase 2	VivaGel (Starpharma Pty Ltd.)	Dendrimer based microbicide gel	**HSV prevention**
Phase 2	MRX 815 (IMA Rx Therapeutics)	Nano bubble technology	**Treatment of intravascular clot**
Phase 3	Combidex/Ferumoxtran 10 (AMAG Pharmaceuticals)	Iron oxide nanoparticle	**MRI contrast agent**
Marketed	Abraxane (Abraxis Oncology)	Albumin bound taxane particles	**Non-small cell lung cancer**
Marketed	AmBisome (Astellas Pharma US)	Liposomal preparation of amphotericin B	**Fungal infection**
Marketed	Doxil (Ortho Biotech)	Liposomal doxorubic in	**Ovarian tumour**

* Information obtained from respective company webpage on internet
# Available at Nanotechnology Characterization Laboratory Webpage at http://ncl.cancer.gov/

8 COMPARISON WITH SIMILAR SYSTEMS

Surgery, chemotherapy, radiation therapy, photodynamic therapy, hormonal treatment and Biologic therapy are the main tools of conventional cancer treatment.

- One of the treatment options is surgery. That is, remove the cancerous part. However, the limitation is that one loses the organ and the cancer may appear again. Further, the surgery is not possible for all types of cases of the cancer.
- Second option is radiation therapy. In this the cancerous cells are burnt by radiation of specific frequency band and the intensity. The limitation of this method is that even the healthy cells get damaged, this damage/ burning is not even and the burnt part may become dead and nonfunctional.
- The third option is chemotherapy. That is, cancerous cells are killed by drugs toxic to cells or by stopping cells from taking nutrients needed to divide the cells or stop the mechanism responsible for division of the cell. Normally a combination of drugs is given so that drugs affect all the three aspects of the cancer treatment. The major obstacle is that the treatment may harm to healthy blood cells.
- Photodynamic therapy (PDT) is another approach still under development to provide localized cancer treatment. PDT capitalizes on the attraction of "hematoporphyrin" molecules. Sometime after the sensitizer is administered, tumour area is focused with light of a particular frequency, either exterior or from inserted fiber optics. The chemical reaction is activated by energy from light that further releases oxygen and damages and kills cancer cells physically.
- Hormonal treatment has been successful for types of cancer that are "hormone dependent". The internally generated hormones are controlled by drugs. Drugs bind to receptors on the surface of tumor tissues and do not allow the cell to grow. In general such drugs have to be taken over a long period under the prescription by specialist, following surgery to prevent metastatic disease.
- "Biologic therapy," the most recent approach in conventional cancer treatment, refers to "cancer treatment that produces antitumor effects primarily through the action of natural host defense mechanisms or by the administration of natural mammalian substances'. The Biologic treatments for cancer are new and called as "biotherapy", developed from observations and experimentation in the late 19th century. Biotherapy is based on the principle that tumor cells are immunologically "different" from non – affected cells, and the immune system can be manipulated to destroy cancer cells. But all these methods have several side-effects like: Hair loss, Loss of appetite and nutritional problems, Peripheral neuropathy, Diarrhea, Skin damage [4].
- Nanotechnology has proved to be very effective in treating cancer and is much safer than the usual chemotherapy. There are several reasons that nanotechnology could help transform cancer research and clinical approaches to cancer care:
- Most biological processes, including those processes leading to cancer, occur at the Nano scale. For cancer researchers, the ability of Nano scale devices to easily access the interior of a living cell affords the opportunity for unprecedented gains on both clinical and basic research frontiers.
- The ability to simultaneously interact with proteins and nucleic acids at the molecular level will provide a better understanding of the complex regulatory patterns that govern the behavior of cells in their normal state as well as the transformation into malignant cells [1] [5].

8 DISCUSSION AND FUTURE DIRECTION

Work is currently being done to find ways to safely move these new research tools into medical practice. Nanotechnology is proceeding on two main fronts: laboratory-based diagnostics and in vivo diagnostics and therapeutics. Nano devices can provide rapid and sensitive detection of cancer-related molecules by enabling scientists to detect molecular changes even when they occur only in a small percentage of cells. Nanotechnology is providing a critical bridge between the physical sciences and engineering and modern molecular biology. Researchers are trying to discover the principles of the Nano scale world by studying the behavior of biomolecules and their assemblies. Engineers are building a host of Nano scale tools such as dendrimers, nanotubes, and Nano pores, quantum dots that are required to develop the systems biology models of malignancy needed to better diagnose and treat cancer. Nanotechnology is benefiting from the combined efforts of scientists from a wide range of disciplines, in the Material and biological sciences, which may produce many different types and sizes of Nano scale devices, each with its own useful characteristics.

The field of Nano medicine has a bright future with the emergence of several promising approaches for delivery of therapeutic agents and imaging using the advantages of the Nano scale carriers. Various initiatives from both the federal agencies as well as industry support the continual research into the application of nanotechnology to improve drug delivery and molecular imaging. However, it is also recognized that as research moves toward developing smaller and smaller devices and agents, larger multidisciplinary teams are needed for success. Collaboration also requires greater communication between various disciplines, including medicine, engineering, materials science, information technology, and physics, to expand on existing knowledge. Future studies should also aim to address a number of challenges faced in Nano medicine application. First, additional preclinical and clinical studies in relevant animal models and disease states should be per-

formed to substantiate proof of concept. Second, a number of these

Novel Nano scale systems still lack of secured and correct information. Long-term studies should be carried out beyond "proof-of-concept" studies. Third, issues related to scale-up and manufacturing should be addressed. Finally, the cost of these Nano medicines should be in an acceptable low range to be successful in the clinics.

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