



NANOTECHNOLOGY FOR CANCER THERAPY: RECENT DEVELOPMENTS

Roshan Telrandhe*

Kamla Nehru College of Pharmacy, Butibori, Nagpur-441108, Maharashtra, India.

***Corresponding Author: Roshan Telrandhe**

Kamla Nehru College of Pharmacy, Butibori, Nagpur-441108, Maharashtra, India.

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ABSTRACT

This paper is an overview of advances and prospects in applications of nanotechnology for cancer treatment. Nanotechnology is an use for prevention, diagnosis, and treatment .nanotechnology offer a promise for the targeted delivery of drugs, genes and protein to tumor tissue and therefore alleviating the toxicity of anticancer agent in healthy tissues. Cancer is one of the leading causes of death worldwide. Deaths from cancer are continuously rising worldwide with a projection of about 12 million deaths from cancer in 2030. . Nanotechnology is one of the most rapidly growing fields in the 21st century. Many different types of nanosystems have been utilized in diagnostics and therapeutics of various diseases. To subside the disadvantages of conventional cancer therapeutics, nanotechnology has been given considerable attention. In this paper, the current nanotechnologies that can be utilized in oncological interventions will be discussed. These mainly include arrays of nanocantilevers, nanotubes and nanowires for multiplexing detection, multifunctional injectable nanovectors for therapeutics and diagnostics. It is demonstrated how nanotechnology can help solve one of the most challenging and longstanding problems in medicine, which is how to eliminate cancer without harming normal body tissue. This article review current nanotechnology platforms for anticancer drug delivery, including polymeric nanoparticles, liposomes, dendrimers, nanoshells, carbon nanotubes, superparamagnetic nanoparticles and nuclear acid base nanoparticle [DNA, RNA interference (RNAi), and antisense oligonucleotide (ASO)] as well as nanotechnologies for combination therapeutics strategies, for example, nanotechnologies combined with multidrug-resistance modulator, ultrasound, hyperthermia, or photodynamic therapy. The review increases awarnes of advantages in cancer therapy.

KEYWORDS: Nanotechnology; Cancer, Nanoparticles, Nanoectors, Liposomes, Nanobiosensors, Dendrimers, nanoshell, quantum dot, diamondoid, nanocantilevers, Nanowires ,Fullerenes ,Nanotubes and Superparamagnetic nanoparticles.

1. INTRODUCTION

Cancer is leading causes of death worldwide especially in those countries having low and middle financial condition. According to the US National Cancer Institute (OTIR, 2006) "Nanotechnology will change the very foundations of cancer diagnosis, treatment, and prevention". There is uncontrolled division of cells which enter into normal adjacent tissues and destroy them. Often the abnormal cells also spread into other parts of the body via lymph or blood, popularly the situation known as metastasis. According to WHO (World Health Organization), cancer accounted for 7.4 million deaths in 2004 which extended to 7.6 million which was about 13% of all human cell deaths in 2007. In recent years, significant efforts have been devoted to develop nanotechnology to enhance the delivery of anticancer drug to tumor tissue while minimizing its distribution and toxicity in healthy tissue. Many developed innovative nanotechnology platforms, such as polymeric nanoparticles, liposomes, dendrimers, nanoshells, carbon nanotubes, superparamagnetic

nanoparticles, and nucleic acid-based nanoparticles [DNA, RNA interference (RNAi), and antisense oligonucleotide (ASO)], have been applied to the delivery of specific anticancer drugs, including small molecular weight drugs and macromolecules (proteins, peptides or genes). Nanotechnology has at last provided a way for us to rearrange and restructure matter on an atomic scale, allowing us to reach down to the very roots of any problem. Provided that we can thoroughly understand the problem on an atomic scale and develop the know-how to turn our innovative ideas for the perfect solution into reality, we now have all the tools that we need (Mansoori, 2005; Ferrari, 2005; Mansoori and Soelaiman, 2005).

The question is what this powerful new interdisciplinary collection of technology and ideas can do to help us find cures for the worst of our diseases? The answer is with nanotechnology.

Nanotechnology may be defined as the creation of materials, drugs and devices that are used to manipulate matter that are of size in the range of 1100nm³. It has found applications in various fields including electronics, energy production, medicine, pharmaceutical industries to name a few. A nanometer is 1/50,000 times of the width of an average human hair. Moreover, the dimensions of a DNA strand are also in the range of nanometer. the nanotechnology platforms could serve as customizable, targeted drug delivery vehicles capable of carrying large dose of therapeutic agents into malignant cells while avoiding healthy cells.

This article deals with the recent development and innovative solution that made possible by advent of nanotechnology and to offer some suggestions for further venues of research and also potential application in cancer therapeutics. The nanotechnologies is also for combination therapeutic strategies

2. Nanotechnology preventive approach

In general, the best way to eliminate a problem is to eliminate the cause. In cancer, the problem can be perceived differently at various stages of the disease. Most apparently, if genetic mutations are the underlying cause, then we must counteract the causes of the mutations. Unfortunately, genetic mutations are caused by artificial or natural carcinogens only some of the time. At other times, they may occur spontaneously during DNA replication and cell division. With present science and technology there is very little we can do to prevent this from happening. However, in all other cases, eliminating the carcinogens is indeed a highly effective way of cancer prevention. But most patients do not recognise the problem until it has actually occurred, which makes preventive medicine a rarely utilised, although a highly effective form of cancer prevention. Even so, is there a way to eliminate cancer through nanotechnology before it starts? Although there is little current research on preventive treatments using nanotechnology, they are indeed possible. After a careful review of the most advanced disease-time nanoscale treatment methods, one can easily see why the proposed nanotechnology alternatives to current preventive treatments have so strongly attracted the attention of the scientific and medical communities in recent years. In fact, nanotechnology-based treatments are no more challenging to devise than the currently used disease-time treatment methods. Nonetheless, it requires time and monetary investments to develop such treatment methods in short time. To demonstrate the viability of the nanotechnology-based treatments, let us consider melanoma for example. Melanoma, a form of skin cancer, is caused primarily by ultraviolet radiation from the Sun. The current method of preventive treatment against bombardment with this kind of harmful radiation involves suspending a substance that either absorbs or scatters ultraviolet radiation in a thick emulsion. We use this emulsion, called sunscreen, to coat our skin prior to prolonged exposure to sunlight. Some of the problems

with this method are that this emulsion can be easily rubbed off and can lose its effectiveness over time, thus needing to be reapplied periodically.

An even bigger problem is that we leave openings in the sunscreen coating during sunscreen application due to macro-scale and micro-scale imperfections in our skin. This allows the Ultra Violet (UV) radiation to permeate through the dead layer of skin, spreading out to a wider area due to slit diffraction and causing more widespread damage. All of these problems take away from the overall effectiveness of this preventive method.

UV radiation is one of the most prominent causes of DNA damage. Since UV radiation is high frequency and thus high energy, it can easily damage the delicate DNA double helix. Individual nucleotide bases readily absorb UV radiation and can become excited after even short-term exposure. This can cause hydrogen bonds between the two complementary chains, and sometimes even the covalent bonds between the phosphate backbone and the ribose to break, causing genetic mutations. The result a mutated genetic sequence and the production of defective proteins.

Some very recent works have shown that it is possible to tag specific types of cells with nanoparticles by conjugating them to targeting agents designed to recognise cell-specific surface proteins (Greider and Blackburn, 1996). Nanoparticles attached to desired drugs or substances can be conjugated to short peptide chains, proteins or artificial nanobodies. If we manufacture nanoparticles attached to UV scattering substances like zinc oxide (ZnO) and titanium oxide (TiO₂), or UV absorbing substances like octyl methoxycinnamate and oxybenzone, and specifically target these nanoparticles to skin cell surface proteins, we can effectively coat these cells with sunscreen on the nanoscale. With this nanotechnology-based preventive treatment method, we would effectively eliminate most of the problems mentioned above. If the cells can be coated directly, the problem of diffraction in case where an area is sparsely coated will be eliminated. The most important issue to consider in this form of treatment is, of course, the toxicity of the substance that is used. The biochemical effects of a substance on the patient's health must be thoroughly evaluated by standard laboratory testing procedures as well as clinical trials before this treatment can be safely implemented. Of course, this is a purely theoretical suggestion, which is based on works that are unrelated to skin cells. It is proposed simply as an example of the potential application of nanotechnology. However, if this method can indeed be turned into reality, the obvious result will be a large reduction in the incident of melanoma due to the sun's radiation.

We now have the ability to quickly and easily map large proteins and model them in three-dimensional space (Gupta et al., 2005), as well as extensive knowledge of

atomic and molecular interactions (Rafii-Tabar and Mansoori, 2004), electronic cloud distributions (Aquilanti et al., 1989). We also have the ability to sequence and manufacture nucleic acid and peptide chains quite easily (Lebl and Hachmann, 2001). Taken together, these techniques give us all that we need in order to specifically target any type of animal cell, provided that it can be distinguished from other cell types by the presence of at least one cell-specific surface protein. Thus, the method discussed above is but one example of many possible applications of the fascinating new nanotechnology known as nanobiotechnology.

3. Nanotechnology approaches for cancerous cell destruction

Preventive treatments are not much good to those who have already developed the disease. And since these are the people who require the most immediate medical help, it is no wonder that a majority of innovative treatments are focused here. Again, there are several ways to view the problem. The traditional approach is to simply eliminate the causing agents, or the cells that make up the tumour and end their paracrine signalling effect. This method actually dates back to the mid-17th century, when John Hunter, a Scottish surgeon first suggested the surgical removal of the tumour (Denmeade and Isaacs, 2002). Of course, we have made great progress in the last 350 years, but the idea remains the same. If we see the cancerous cells of the tumour as the causing agents of the disease, then the obvious strategy is to remove or to destroy them. The most significant recent breakthroughs have been made in this area. A relatively long-standing strategy dating back to the 1950s is to flood the body with substances that are especially toxic to tumour cells. Unfortunately, tumour cells are not dissimilar enough from healthy cells to distinguish one from the other using such large-scale techniques. A drug that is especially toxic to tumour cells is usually also toxic to healthy cells, and simply flooding the entire body with it causes system-wide damage and serious side effects. Almost everyone has heard of or seen chemotherapy patients who have lost their hair, lost significant weight, or developed other serious disorders. It is a common problem and in fact, we have also taken similar approaches to treating other seemingly incurable diseases such as AIDS and Hepatitis C, with similar results. A currently popular treatment for AIDS is a drug cocktail, or a combination of several different drugs, each somewhat effective against the disease. Administered together, these drugs can be effective, but taken constantly in large doses they can also be very damaging to the overall health of the patient. The most commonly used Hepatitis C treatment is as severe.

Two of the major drugs used to treat these diseases are Interleukin-2 and Interferon, and some but not all of the side effects include a weakened immune system, loss of appetite, severe aches, pains, and flu-like symptoms, headaches, heart problems, stomach and digestive tract problems, eye problems, and hair loss, to list just a few

(Gougerot-Pocidallo et al., 1994; Pyrhönen et al., 1999). These alone have some experts frowning their eyebrows, but in addition, many of these treatments have varying levels of psychological effects. While some patients are highly resistant and are lucky enough to get through the treatment with mild to moderate depression, others are plagued with severe depression, irritability, paranoia, insomnia, and even suicidal and homicidal tendencies. A select few are actually driven to suicide or homicide during or immediately after treatment. Yet the biggest setback is that these treatments are effective only some of the time, with the highest success rates ranging only from 25% to 75%. With such poor results, there is a pressing need for newer and more effective forms of treatment. While the subsequent discussion addresses research of treatments specific to cancer, nanotechnology does have the capability to deal with, both, AIDS and Hepatitis C as well as many other problematic conditions that currently have the medical community perplexed and frustrated (Gougerot-Pocidallo et al., 1994; Pyrhönen et al., 1999). Some recent works have explored cancer treatments from nanotechnology perspectives. We shall discuss three of them here:• The first method involves nanoparticles loaded with Paclitaxel, a common agent used to treat prostate cancer (Sahoo et al., 2004). This research compared the efficacy of Paclitaxel-loaded nanoparticles to Cremophore EL, a currently used colloidal suspension of the drug. The research was conducted on living mice, and is therefore relevant to consider research for actual in vivo treatment of prostate cancer in human patients. Paclitaxel was originally used by simply flooding the system via the bloodstream. This method was found to be somewhat ineffective, as sufficient concentrations of the drug in and around the tumour were difficult to achieve without raising the toxicity to an intolerable level, due to the drug's low water solubility. A solution to this problem was later developed in the form of Cremophore EL, which was a suspension of the drug in a thick gel designed to be injected directly into the tumour. This method gave results that were only slightly better because the gel, although concentrating the drug in the desired area, was too thick to allow easy diffusion of the drug, thus not allowing the bulk to come into direct contact with the tumour cells and produce the desired effect. The frequent dosing that was required to maintain sufficient concentration again caused nonspecific toxicity, now in the vicinity of the tumour. The nanoparticle method is simply the next step in the process of finding an effective way of administering Paclitaxel, which aside from these problems has a wide range of effective anti-cancer activity. In their work researchers (Sahoo et al., 2004) took a similar approach to administering the drug preparation, in that they also injected the nanoparticle preparation into the tumour. This was done partly to minimise the uptake of the spheres by macrophages and partly to improve the comparison of the effectiveness of this new treatment with Cremophor EL. The results indicated the survival rates of the mice treated with the Cremophor EL suspension were much lower than those

treated with conjugated nanoparticles, although about the same as those treated with unconjugated nanoparticles. This shows that even unconjugated nanoparticles are as effective as Crempophor EL, while those that are also conjugated for targeting produce much better success rates. Furthermore, tumour growth, which was also monitored, was actually reversed with the use of conjugated nanoparticles at 24 mg/kg for the period of observation (Sahoo et al., 2004). One of the main conclusions to be drawn from these results is that conjugation of nanospheres (spherical nanoparticles) with targeting moieties greatly increases the effectiveness of a treatment. Any further research should be directed primarily in this area. Experience has shown that as we become progressively more skilled at identifying and modelling proteins, we also become better able to create artificial recognition molecules to effectively target these proteins, as mentioned in the preventive treatment section. Thus, further research will likely yield tumour-specific recognition ligands, which will allow us to tailor treatments to specific kinds of cancer. Perhaps in the not so distant future, we may be able to draw some blood from the patient, determine patient-specific/tumour-specific proteins, and send the data away to a lab. A few days later, a drug will be prepared that is highly effective against that specific type of cancer, embedded in nanoparticles, which are conjugated to artificial ligands ready to target the exact proteins that are specific to that patient. • A second potential treatment involves absorption of light by gold nanoparticles (Pitsillides et al., 2003). The method involves gold-coated nanoparticles conjugated to recognition ligands. Gold nanoparticles are frequently used in electron microscopy due to their high electron density. They also have distinct absorption peaks in between ~500–600 nm wavelength electromagnetic radiation (Link and El-Sayed, 1999) for different nanoparticle sizes as shown in Figure 8. The underlying principle is that these particles readily absorb laser radiation and convert it to heat. To achieve the desired results, one may use commercially available gold nanoparticles and conjugate them to certain recognition molecules engineered to target CD8+ lymphocyte cells. CD8, a cell surface protein, was used to distinguish cells among the general population of lymphocytes under study (Pitsillides et al., 2003). Iron-oxide doped latex microspheres were also used in a concurrent study. To distinguish between CD8+ and regular lymphocytes under a fluorescence microscope, a fluorescent dye (R-phycoerythrin) conjugated to anti-CD8 IgG antibodies was used. Each type of sphere was conjugated to recognise the CD8+ protein imbedded within the cell membranes. The cells under study were first labelled with a general fluorescent dye that was non-cell-specific. This fluorescent dye was allowed to penetrate into the cytoplasm. The cells were then conjugated to both kinds of particles and the population labelled with latex microspheres was analysed by a fluorescence microscope. The effectiveness of the gold nanosphere method was gauged by analysing uptake of propidium

iodide (C₂₇H₃₄N₄I₂, CAS: 25535-16-4) and subsequently measuring FITC fluorescence. The experiment consisted of two stages. During the first stage, the cells were briefly irradiated with a 532 nm or 565 nm laser. The duration of the pulses for the nanoparticle run was kept under 10 ns. For the microparticle run, the duration was kept under 1 μs. A microsphere run was carried out in order to allow observation under a light microscope as well as to compare its effectiveness to the nanosphere run. During the microscale experiment, the frame-grabber was used to record an image of the field approximately 100 ns after irradiation. The observations showed an interesting phenomenon known as cavitation due to phase transition. Cavitation is caused by the rapid temperature increase, which causes the water in the immediate vicinity of the particle to vapourise and to form a bubble as the vapour pressure overcomes the surface tension of the liquid. As the bubble grows in volume, it cannot sustain itself and collapses inward. The impact can be so violent that for smaller particles, it can cause fragmentation. Particle fragments have been observed which support this phenomena (Pitsillides et al., 2003). This phenomena is believed to be the mechanism of cell destruction and responsible for the subsequently observed cell death. Cell death was confirmed by the leaking out of the fluorescent dye due to lacerated cell membranes. Theoretical calculations of the temperature distribution in and around the spheres were carried out using the Goldenberg and Tranter heat transfer model (Goldenberg and Tranter, 1952) assuming uniformly heated homogeneous spheres embedded in an infinite homogeneous medium. When appropriate numerical values for radiation rate, radius and conductivities are inserted in the model the researchers found that irradiation of the spheres caused a rapid increase in temperature of the order of thousands of degrees Kelvin which is the reason for sudden formation of bubble and its rapid growth. The conclusions to be drawn from this study are that light-responsive nanoparticles are potent tools for nanosurgery and cancer treatment. They are highly effective cell-destruction agents that can be targeted quite effectively at specific cell types by the use of the appropriate recognition molecules. As one of the leading applications of nanoparticles, this technique deserved extra attention from prospective researchers. In fact, some current investigations (Loo et al., 2001; Hirsch et al., 2003) have successfully applied this technology to biological systems in vivo. A study done on mice has recently shown to be just as effective in leading to complete remission and elimination of malignant tumours, and is scheduled to enter clinical trials in humans in the near future (Farokhzad et al., 2001). • Finally, the third nanoparticle method for direct cell destruction to be discussed is the magnetic nanoparticle hyperthermia method (Jordan et al., 1999). It is hypothesised that the relatively old concept of hyperthermia can be combined with methods in nanotechnology to achieve previously unequalled positive results. Hyperthermia is a biological term used

to describe the phenomenon that occurs when living cells or tissues are heated to temperatures slightly above the highest that can occur naturally. In humans, the hyperthermic temperature range falls between 41°C and 46°C. When human cells are briefly brought into this temperature range, almost irreversible cell damage can result. An added effect of these changes is the lowered resistance of cells to radiation damage. Magnetic fluid hyperthermia is a method for cancer treatment that has been around for nearly 50 years. It involves using small magnetic particles that respond to an externally applied magnetic field by heating up. This study was done in vivo with murine mammary carcinoma cells transplanted in the hind leg of mice. The mice were treated for 30 minutes at a steady intratumoural temperature of 47°C. The study was the first to use nanosized particles to achieve hyperthermic conditions and has managed to prove the method to be quite effective. In the study, nanoparticles were used to coat the tumour cells, which were then subjected to magnetic fields from 50 kHz to 100 kHz using a prototype AC magnetic field applicator. One benefit of using this method is that it can be applied internally, thus opening up the prospect of treating types of cancer that involve deep-seated tissues and organs. An added benefit is that cells that have picked up some of the particles cannot get rid of them, and thus, every daughter cell will have one half of the amount of particles present on the mother cell. If the initial concentration of the particles is sufficiently high, there is a possibility of re-treatments. The particles, which consist of aminosilan shell magnetite with a core diameter of about 10 nm, are strongly adhesive to human colon adenocarcinoma cells. However, this effect is either far decreased or not observed at all with other kinds of cells, making prospective conjugation to recognition ligands a necessity. When this study was done, conjugation nanotechnology (Santra and Tan, 2001) was not yet readily available. However, with all of the recent advances in the production of artificial antibodies and other recognition ligands, this method could be greatly improved by targeting the particles to specific types of cells (Johannsen et al., 2001).

4. Nanoparticles

From the natural or synthesized polymers the polymeric nanoparticles are prepared. As compared to large sized particles, nanoparticles exhibit new or enhanced size dependant properties. Clearly, the most current disease-time nanotechnology-based treatment methods involve the use of some type of nanoparticle. Therefore, a brief description of bio-medical nanoparticles is in order. A general nanoparticle consists of a core that can have a constitution ranging from very simple to highly complex, depending on the intended application. The core can contain one or several payload drugs, as well as permeation and visibility enhancers. The surface may be bare or conjugated to targeting ligands, like antibody (Singer, 1959) or polyethylene glycol ligands (Tabata et al., 1997; Mehvar, 2000) to prevent macrophage uptake of the nanoparticle. In addition to nanoparticles made of

gold, iron oxide, titanium oxide, and zinc oxide other nanostructures. Several types of nanoparticles have been developed and utilized in MRI (Magnetic Resonance Imaging) contrast. These include iron oxide based nanoparticles^[11], gadolinium based nanoparticles^[12] to name a few. Local biology and pathology condition information can be obtained with the help of MRI. These are based on the nuclear magnetic resonance signals which are based on the hydrogen nuclei present in different pathological conditions in an organism.^[13] In addition to these, antibody conjugated gold nanoparticles have also been utilized for cancer diagnostics.

Polymeric nanoparticles can deliver not only small molecular weight drugs but also macromolecules such as genes and proteins. A system made up of poly (D, L-lactide-co-glycolide) nanoparticles, a potent protease inhibitor (cystatin) and cytokeratin-specific monoclonal antibody, has been reported. It can neutralize the activity of excessive proteolysis in order to prevent the metastatic and invasive potential of breast tumor cells. To stabilize the surface of nanoparticle or achieve active targeting, conjugating, grafting and adsorbing hydrophilic polymers, such as polyethylene glycol (PEG), are usually used. Copolymer pegylation and folate conjugation can improve the stability of self-assemblies in aqueous medium and the tumor site selectivity in vivo of ring-opening metathesis polymerization-based copolymers. By covalent coupling of humanized monoclonal antibodies (anti-HER2) to paclitaxel-loaded poly (D, L-lactic acid) nanoparticles, immunonanoparticles were prepared to actively target tumor cells which overexpress HER2 receptors. Recently, Patil produced PLA-PEG-ligand conjugate nanoparticles by a single-step surface functionalizing technique, and found that simultaneous functionalization with biotin and folic acid induced great efficacy of paclitaxel-loaded nanoparticles in a MCF-7 tumor xenograft model by enhancing drug accumulation in tumors. Mitoxantrone-loaded polybutylcyanoacrylate nanoparticles (DHAD-PBCA-NPs) have presented a good effect on orthotopically transplanted hepatocellular carcinoma (HCC) in nude mice. Therefore, the activity and toxicity of DHAD-PBCA-NPs in individuals with unresected HCC were evaluated in a phase II clinical trial. The median survival was much longer in the DHAD-PBCA-NPs group than in the DHAD injection group (5.46 months vs. 3.23 months).

Multimode imaging contrast nanoagents have also been developed combining biological targeting and magnetic resonance. Polymeric nanoparticles are currently the most widely investigated nanotechnology platform for cancer therapy, despite many challenging defects or drawbacks need to be resolved before clinical application. It is also considered as the most promising vehicle for site-targeting anti-cancer drug delivery and disease diagnosis because of its good variability of chemical structures through chemical modification and the resulting flexibility of physicochemical

characteristics enabling its diverse drug delivery applications.

5. Nanovectors

Nanovectors are nanoparticle of hollow or solid structure and it can be used as various anticancer drugs, targeting moieties and detection agents. The presence of targeting moieties attributes to their specificity; thereby reduction in toxic effects may be seen. These have been of interest of use as nanotechnological devices in cancer. They are intravascular injectables considered for drug delivery and imaging in cancer. Nanovectors may be classified into different generation nanovectors—namely, first generation, second generation and third generation nanovectors.^[15] The first generation nanovectors are not targeted specifically against any biological molecule on the tumor cells.^[16] An example of this would be albumin bound Paclitaxel. It has found its application in breast cancer chemotherapy. This chemotherapy enabled to overcome solubility problems related to Paclitaxel and improve the toxicity profile of conventional Paclitaxel therapy which was formulated with chemophor.^[17] The second generation of nanovectors was evolved for specific targeting. These nanovectors were developed to recognize and target specific biological molecules on the cancer cells (active targeting). Active targeting is one in which the therapeutic moiety or the drug is able to recognize and target specific moieties to the desired target on its own. This reduces the toxicity and would also improve therapeutic index. Coupling of high affinity ligands and specific antigens on the surfaces of nanoparticles^[18] is an example of this generation of nanovectors. As compared to the first generation, they have improved biodistribution and reduced toxicity profile. The antigens on the cancer cells allow efficient uptake of targeted drugs through endocytosis (receptor mediated). The active drug delivery consists of several components like drug conjugated polymer and ligands/antibodies which are specific and bind to the specific tumor antigens/receptors. An example of this generation of nanovectors is liposome entrapped drugs with phospholipid-anchored folic acid-PEG conjugates put forth by Gabizon et al.^[19] However, further studies need to be carried out for its effective application in cancer therapeutics. The third generation of nanovectors is currently under development which is multi stage strategy based²⁰. The first stage particle can be biodegradable silicon microparticles which are having pores within them. They are designed to pass through the circulatory system and recognize the disease specific endothelium. The second stage particles are multitypes of nanoparticle which are loaded within the first stage particles. They are within the pores of the first stage particles and are set free towards the tumor mass. They are small enough (less than 20nm) to easily cross the interendothelial junctions. They contain different payloads for therapy and imaging. They can effectively be utilized for cancer in future. Certain anticancer nanovectors have been developed which are targeted to tumors with the help of external magnetic field. Laurance

et al have demonstrated their work on anticancer nanovectors based on superparamagnetic iron oxide nanoparticles.^[21] Nanovectors were designed with iron oxide nanoparticles constituting the core. Coating of the nanoparticles was carried out by incorporation of the nanoparticles in the polymer matrix or their surface was functionalized with polymers. They concluded that such nanovectors can be applied in cases when the solid tumor is close to the body surface. In addition, highly flexible nanovectors have also been developed with the aid of adhesion controlling and improving drug targeting and drug delivery.

6. Liposomes

Liposomes are made up of lipids enclosing water core and it is simplest form of nanovectors. It is closed spherical vesicle and it consists of a lipid bilayer which encapsulates an aqueous phase to store drugs. With the size (90-150 nm) which is slightly bigger than the conventional definition (100 nm), liposomes do not constitute novel nanotechnology, but a large portion of them are associated with nanotechnology research. consist of synthetic microscopic fat globules of lipids, which are incredibly biodegradable. They are manufactured to enclose medications for drug delivery like chemotherapy (Basu and Basu, 2002). The fatty layer on liposome confines and protects the enclosed drug until the liposome is delivered and adheres to the outer membrane of target cancer cells. By this process drug toxicity to healthy cells is decreased and its efficacy may be increased. Liposome therapy is a well-developed technology for delivery of chemotherapy drugs (Silva et al., 2001; Torchilin and Weissig, 2003; Duncan et al., 2005).

They have found applications in various cancer indications²³. With the aid of over expression of fenestrations in cancer neovasculature, they increase the drug concentration at the tumor sites (passive targeting). In passive targeting, the drug is targeted to the target site passively owing to the physiological conditions of the body. Various Doxorubin encapsulated liposomal formulations have been clinically utilized for the treatment of Kaposi's sarcoma, breast cancer and refractory ovarian cancer⁹. They were developed to improve therapeutic index of the conventional Doxorubin chemotherapy while maintaining its antitumor activity. Similarly, S. Kommareddy et al have shown effective utilization of gelatin based nanovectors in tumors. Here, PEG modified gelatin based nanovectors were used as safe and effective vehicle for the delivery of systemically administered genes for tumors. Ruthenium and complexes of several other heavy metals have shown potential applications in cancer therapeutics. Lipid based nanovectors containing such complexes have also been put forth as a potential route in cancer.

Forming lipid bilayers through hydrophobic interaction, liposomes are considered as excellent platforms for the

delivery of hydrophobic and hydrophilic drugs. In particular, liposomes present considerable persistence in the blood. It facilitates efficient drug delivery to target tissues. Different lipids have different fatty acid chain lengths, different head groups, and different melting temperatures. Consequently, temperature^[12] or pH-sensitive^[13-15] liposomes can be constructed by manipulating the formulation. The effectiveness of 1-methylxanthine (1-MTX) as a radiosensitizer and the in vivo efficacy of the temperature-sensitive liposomal 1-methylxanthine (tsl-MTX) which combined with regional hyperthermia and ionizing radiation were evaluated.^[12] Intraperitoneal injection of the tsl-MTX inhibited tumor growth in the mouse xenograft tumor model; moreover, the combination of tsl-MTX with regional hyperthermia and ionizing radiation obviously inhibited tumor growth.^[12] Most recently, to target leukemic cells, pH-sensitive immunoliposomes (ILs) including a terminally alkylated N-isopropylacrylamide (NIPAM) in the bilayer were coupled with the anti-CD33 monoclonal antibody.^[15] The pH-sensitive ILs-CD33 immunoliposomes exhibited high cytotoxicity against HL60 cells, suggesting that the pH-sensitive immunoliposomes could be profitable in acute myeloid leukemia therapy. Commercial liposomes have already gained approval from US Food and Drug Administration (FDA). The typical example is doxorubicin-encapsulated liposomes (Doxil), which has strong antitumor activity against a wide range of cancers. It is useful for various purposes.

7. Nanobiosensors

Nanobiosensors are varied types of novel devices emerging with potential applications in cancer. Nanobiosensors have been developed for cancer diagnostics. Nanobiosensors are useful for early diagnosis of cancer. They can also effectively be utilized for the detection of cancer agents such as environmental pollutants, pathogens and carcinogenic gases. A device used for detection of an analyte through combination of a sensitive biological component, transducer along with a detector component is termed as a biosensor. These nanoscale sensors comprise of cancer specific antibody or ligands so that they can selectively capture cancer cells or target proteins. This yields mechanical, optical or electrical signals which can be detected by the detector. The use of nanobiosensors in cancer clinical testing have been increased due to high speed and reduced cost for diagnosis, automation and multi target analysis^[29,30]. For detection of DNA, Quantum dots based sensor has also been developed.

8. Dendrimers

Dendrimers are the type of nanoparticle and it can be used in cancer. They are unique macromolecules that have applications in developing strategies for nano-scale globular shapes with small cores. Dendrimers, generally possess multiple branches which can be used to carry a variety of agents fulfilling various functions at once. Dendronised polymers are cylindrical macromolecules

that are composed of a linear polymeric backbone and dendritic side chains. The thickness of the polymers is in the range of several nanometers. These nano objects have gained interest because of their cylindrical structure, which provides new unique properties that could be applied within the emerging field of nanotechnology (Zhang et al., 2003). For example, DNA/PAMAM (Polyamidoamine) dendrimer complex is used for DNA delivery to cell nucleus due to its high transfection efficiency and very low toxicity. As highly branched artificial macromolecules with tree-like structures, dendrimers are monodisperse, three-dimensional molecules which have defined molecular weights and host-guest entrapment property. With the size ranging from 1 to 10 nm, dendrimers with different chemical structures and functional groups can be synthesized. Through a series of repeating chemical synthesis on the core, the size and shape of dendrimers are determined by the generation. The key useful character of dendrimers is the branches which can provide vast amounts of surface area for drugs and targeting molecules. Meanwhile, the surface functionalities, interior branching, and chemical composition of the core play a significant role in reactivating the macromolecule. Dendrimer is one of the most elegant nanotechnology platforms for targeted drug delivery. Conjugated with biotin as the targeting moiety, the in vitro targeting ability of partially acetylated generation 5 polyamidoamine (PAMAM) dendrimer (Ac-G5) in HeLa cells was assessed. The multi-functional conjugate Ac-G5-biotin-FITC (fluorescein isothiocyanate) showed much higher cellular uptake than the conjugate without biotin. The energy-dependent uptake process can be blocked effectively by biotin-polymer conjugates, exhibiting an expected dose-response curve.

Poly-amidoamine (PAMAM) dendrimers are favourite candidates for use as the backbone of multitasking therapeutics because of their well-defined surface functionality, good water solubility, low polydispersity and their lack of immunogenicity (Choi et al., 2001). For example, the controlled surface modification followed by conjugation of folate and fluorescein moieties on the surface of a dendrimer is shown to yield molecules capable of targeting to tumour cells through folate receptors (Quintana et al., 2001). There are many ongoing research activities (Fréchet and Tomalia, 2002) in the design of new dendrimers with preferred molecular functionalities.

They are self-assembling synthetic polymers which were used in the MRI of lymphatic drainage in mouse model of breast cancer. Majoros et al have shown the synthesis, characterization and functionality of Poly (Amidoamine) (PAMAM) dendrimer based anticancer therapeutics. Such dendrimer based anticancer systems have found applications for targeted delivery in cancer. In addition to this, AK Patri et al have shown the synthesis and application of an antibody-dendrimer based conjugate system. Such systems have found applications in targeted

delivery in prostate cancer therapeutics²⁶. Xiangyang et al have demonstrated that dendrimer-entrapped gold nanoparticles can be effectively utilized for cancer cell targeting and imaging purposes

9. Nanoshells

Nanoshells are type of other nanoparticles which are being lined up in cancer therapeutics and diagnostics. They are composed of a gold shell surrounding a semiconductor. When they reach the cancer cells, they can be irradiated. These irradiations make them hot which ultimately kill the cancer cells. This technique has been successfully utilized in veneral tumours in mice.

As the layer-by-layer assembly of nanoparticles, polymeric nanoshells (20-60 nm) of diblock copolymers can be made by self-assembly of oppositely charged polymers forming a core/shell structure.^[19] With a biodegradable polymer core and mixed lipid monolayer shell, a system of folic acid-conjugated nanoparticles was developed for targeted delivery of docetaxel.^[20] Gold nanoshells (10 to 300 nm) are optically tunable nanoparticles comprising a dielectric core with a thin gold shell surrounded.^[21] In order to achieving maximal penetration of light through tissue over the near-infrared, gold nanoshells can be designed by adjusting the core radius and the shell thickness.^[21] Laser-activated gold nanoshells thermal ablation is a selective and effective technique for the ablation of prostate cancer in an ectopic tumor model.

10. Quantum dots

A quantum dot is a semiconductor nanocrystal with a diameter of a few nanometers. Because of its small size it behaves like a potential well that confines electrons in three dimensions to a region on the order of the electrons' de Broglie wavelength in size.

Semiconductor nanosize crystalline quantum dots possess quantised energy levels with unique optical and electronic properties. They confine electrons in three dimensions to a region, on the order of the electrons' de Broglie wavelength with varied sizes and shapes, which can be precisely controlled, containing anything from a single electron to a set of hundreds or even thousands of electrons. Modification in their size and structure exhibit many colours in the entire ultraviolet-visible spectrum.

Quantum dots are photoluminescent with a wide absorption spectrum and a narrow emission peak. Quantum dots photoluminescence is used in bio-imaging, biological labelling and diagnostics (Murray et al., 1993; Gao et al., 2001, 2004). Their immense photo-stability aids in the ability to track cell processes for extended periods of time and to give more insight on intermolecular relationships. Size-tunable light emission, improved signal brightness, resistance against photobleaching and simultaneous excitation of multiple fluorescence colours are some of the unique optical and electronic properties of quantum dots. Bioconjugated

quantum dots have produced new possibilities for multiplexed and ultrasensitive imaging of biomolecular targets in animal cells.

11. Diamondoids

Diamondoids are cage hydrocarbons with little adverse health risks, good therapeutic effects and many useful derivatives (Mansoori, 2005; Ramezani and Mansoori, 2006). Extensive amount of investigations have been performed related to synthesis of new diamondoid derivatives with better therapeutic actions and less adverse effects.

The smallest diamondoid molecule is named adamantane. Adamantane derivatives are readily synthesised (Orzeszko et al., 2000) and have found many medicinal applications including for cancer treatment. For example, it has been proven that adamantylamino-pyrimidines and -pyridines are strong stimulants of tumour necrosis factor- α (TNF- α) (Kazimierzczuk et al., 2001). TNF is referred to a substance that can improve the body's natural response to cancer by killing the cancer cells. Another example is 1, 6 -diaminodiamantane (Malik et al., 1991) which possesses an antitumour and antibacterial activity. Attaching some short peptidic sequences to adamantane makes it possible to design novel antagonists. The bradykinin antagonist, which is used as an anti-cancer agent, is an example (Reissmann et al., 2000).

Also dimethyladamantylmaleimide has been effective for growth inhibition of human colon cancer (Wang et al., 2001). A wise course of action would be to direct our collective research and development efforts into improving and expanding nanoparticle science. Nanoparticles already have a multitude of applications and will likely have many more in the near future. Any discoveries that are made in this area will surely benefit fields other than medicine and cancer research, and should therefore be designated as an interdisciplinary goal.

12. Nanocantilevers

Multimolecular mechanical sensing devices like nanocantilevers have also been emerged as one of the promising approaches. Nanocantilevers comprise of large number of beams. When specific biomolecules bind, deflection of beam takes place which is observed by laser light or other methods. The flexible beams are coated with molecules capable of binding to cancer biomarkers.

13. Nanowires, Fullerenes and Nanotubes

Nanowires, fullerenes and nanotubes are amongst others which are considered for cancer therapeutics and diagnostics. Fullerenes are nanostructured arrangement of carbon atoms in specific soccer like architecture. They may also form nanotubes which are cylindrical carbon atom assemblies. Nanotubes and fullerenes have found several specific sensing applications. For instance,

Nanotubes have been developed as high specificity sensors of antibody signatures of autoimmune disease and SNPs (single nucleotide polymorphism). Nanowires are other class of nanotechnology that has been developed. They are sensing wires coated with antibodies like molecules to bind to proteins of interest. Silicon nanowires are one such real time detectors for simultaneous molecular binding effects.

14. Superparamagnetic nanoparticles

Superparamagnetic nanoparticles, iron oxide magnetic nanoparticles with particle sizes of about 20 nm, are composed of Fe_2O_3 or Fe_3O_4 and do not keep any magnetism after removal of the magnetic field, hence, may be used in vivo. Superparamagnetic nanoparticles can be used as contrast agents for magnetic resonance imaging (MRI), can be used for cancer thermal therapy, and can concentrate in target sites through an external magnetic field. Functionalized with recombinant single chain Fv antibody fragments (scFv), superparamagnetic iron oxide nanoparticles (SPIONs) could be used to target and image cancer cells. Conjugated to luteinizing hormone releasing hormone (LHRH), SPIONs not only achieve breast cancer cell targeting but also play the role as contrast agents in the MRI of breast cancer xenografts. The post-mortem neuropathologic studies of glioblastoma multiforme (GBM) patients treated with thermotherapy using magnetic nanoparticles were reported. Magnetic nanoparticles were injected into the tumor and then heated in an alternating magnetic field. The instillation of magnetic nanoparticles in GBM patients induced the uptake of nanoparticles in macrophages to a major extent, and the uptake was further promoted by magnetic fluid hyperthermia (MFH) therapy.

15. Advantage, challenge and future prospect of nanotechnology for cancer therapy

Nanotechnology has many advantages in cancer therapy. With small size, nanotechnology platforms can enter tumor vasculature via EPR. Besides, functionalization with hydrophilic polymer/oligomer can offer a long circulation half-life and prolong the exposure time of tumor tissue to anticancer agents; whereas inclusion of tissue-recognition residues, such as antibodies, lectins and ligands which are specific for cancer cells, can help nanotechnology platforms achieve tumor cell targeting. For overcoming MDR of cancer cells, a major challenge in effective cancer therapy, combinations of multi-functional nanotechnology platforms and other therapies have been developed and achieved significant successes. However, there are still challenges to the development and application of nanotechnology platforms in cancer therapy, such as limited knowledge of the cancer cell physiology, small variety and poor functionalization of medical nanomaterials, and deficiency of clinical evaluation criteria. Nonetheless, with further advances in functionalization base on thorough understanding of the physiological features of cancer cells, nanotechnology

platforms hold the promise of essentially changing the practice of oncology, allowing easy and effective targeted therapies.

The application of nanotechnology in clinical use in cancer has found several drawbacks and challenges. Endothelial cell barriers on vessels, cellular uptake of therapeutic agent, clearance of drugs from circulation, heterogeneity among tumors are the present challenges. To conclude, the present cancer therapy needs advancement. However, cancer nanotechnology definitely can provide a breakthrough to eradicate cancer related death. Varied types of nanodevices have been developed which can effectively be applied in cancer therapeutics and diagnostics. Still extensive research needs to be carried out for effective utilization of cancer nanotechnology in clinic. There is need to identify favorable physiochemical properties and favorable nanodevices that will help to overcome multiple barriers

16. REFERENCES

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