

Nanotechnology: A boon in oral cancer diagnosis and therapeutics

Abhijeet Alok, Sunil Panat, Ashish Aggarwal, Nitin Upadhyay, Nupur Agarwal, Mallika Kishore

Department of Oral Medicine and Radiology, Institute of Dental Sciences, Bareilly, Uttar Pradesh, India

ABSTRACT

Nanotechnology is rapidly developing subdivision of technology that effects on many fields. Medicine is also influenced by nanotechnology. Nanotechnology modified methods can be used in cancer treatment. Nanotechnology can assist to have better diagnosis with less harmful substance. The use of optical nanoparticles provides efficient drug delivery to tumor cells with liposomes and functionalized micelles. Nanotechnology can be also used in molecular imaging with tomography and photoacoustic imaging of tumors and therapy of cancer as photothermal and radiotherapy. Nanotechnology a next generation techniques have many advantages to treat cancer patients from diagnosis to treatment.

Key words: Nanoparticles, nanotechnology, oral cancer

INTRODUCTION

Cancer remains one of the most complex diseases affecting humans with more than 10 million new cases every year and despite the impressive advances that have been made in molecular and cell biology, how cancer cells progress through carcinogenesis and acquire their metastatic ability is still widely debated.^[1] Oral cancer is the third leading cause of death (after heart disease and stroke) in developed countries and the second leading cause of death (after heart disease) in the United States. Oral cancer incidence has been estimated to be 10/100,000 among males in India and it is steadily increasing in North India.^[2] Studies have shown that there were 10 million new cases, 6 million deaths and 22 million people living with cancer world-wide in the year

2000.^[3] It is projected that the number of new cases of all cancers world-wide will be 12.3 and 15.4 million in the year 2010 and 2020, respectively.^[2] In 2008, a total of 1,437,180 new cancer cases and 565,650 cancer deaths were estimated to occur in the United States alone.^[4-6]

Cancer is a highly complex disease to understand,^[7] the most common oral cancer treatments are limited to chemotherapy, radiation and surgery. Limitations in oral cancer treatment are a result of current challenges seen in cancer therapies today, including lack of early disease detection, non-specific systemic distribution, inadequate drug concentrations reaching the tumor and inability to monitor therapeutic responses. Poor drug delivery and residence at the target site leads to significant complications, like multi-drug resistance.^[8] Current clinical diagnostic techniques typically involves invasive biopsy. Further histopathological diagnosis is based on morphological and structural changes at cellular or tissue level, which may not be obvious for early stage tumors.^[9-11]

Nanotechnology has the potential to offer solutions to these current obstacles in cancer therapies, due to its unique size (1-100 nm) and large surface volume ratios.^[12] Nanotechnologies may have properties of self-assembly, stability, specificity, drug encapsulation and biocompatibility as a result of their material composition.^[13] The use of nanometer size molecules, which range from 100 nm or even smaller attain their unique properties. Thus, nanotechnology

Address for correspondence:

Dr. Abhijeet Alok,
Department of Oral Medicine and Radiology,
Institute of Dental Sciences, Pilibhit Bypass Road,
Bareilly - 243 006, Uttar Pradesh, India.
E-mail: drabhijeet786@gmail.com

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can help in early detection of tumors and oral cancer therapeutics. The most well-studied nanoparticles include quantum dots (QDs),^[14,15] carbon nanotubes,^[16] paramagnetic nanoparticles,^[17] liposomes,^[18] gold nanoparticles^[19] and many others.^[13,20] Use of nanoparticles can be from drug screening to drug delivery to diagnosis/monitoring.

PHYSIOLOGY OF NANOPARTICLES

As nanoparticle exists in the same size as proteins or cells, it is suitable for biotagging or labeling which function efficiently in a living organism whose cells are generally 10 µm across. However, the cell parts are much smaller and are in the sub-micron size domain. Even smaller are the proteins with a typical size of just 5 nm, which is comparable with the dimensions of smallest manmade nanoparticles. This simple size comparison gives an idea of using nanoparticles as very small probes that would allow us to spy at the cellular machinery without introducing too much of the interference.^[21] A tight control of the average particle size and a narrow distribution of sizes allow creating very efficient fluorescent probes that emit narrow light in a very wide range of wavelengths. This helps in creating biomarkers with many and well-distinguished colors.^[22]

Nanotechnology has the potential to offer solutions to current obstacles in cancer therapies, due to its unique size (1-100 nm) and large surface-to-volume ratios.^[12] Nanoparticles with the size in the range of 200 nm are known to accumulate at the solid tumor site by the enhanced permeation and retention effect.

NANOTECHNOLOGY IN ORAL CANCER DIAGNOSIS

QDs are utilized for conduction of cell motility assay and to study cell-signaling events involved in migration and differentiate between invasive and noninvasive cancer cell lines.^[23]

An innovative approach based on biobarcode amplification for both protein and nucleic acid detection is used. This approach uses both colloidal gold nanoparticles and magnetic microbeads, gold nanoparticles modified with both target capture strands and bar code strands that are subsequently hybridized to bar code deoxyribonucleic acid (DNA) and magnetic microparticles modified with target capture strands. In the presence of target DNA, the gold nanoparticles and the magnetic microbeads form sandwich structures that are magnetically separated from the solution and are further washed to remove the unhybridized barcode DNA. The barcodes (100-1000/target) are detected by using a colorimetric method.^[24]

The optical detection technique (Fluorescence and ultraviolet vis. absorption methods) is the most commonly used technique to detect the presence of cancer and

image cancer tissues with the assistance of biomarker or functionalized nanomaterials; where nanoparticles either fluoresce or change their optical properties, when they bind to cancer-affected tissues.^[25]

Various functions can be carried out by devices based on micro/submicron technologies using silicon or engineered polymers. The existence of advanced and low cost semiconductor and microchip manufacturing technologies has provided scientists and researchers to develop micron-sized sensors systems known as micro/nano electro-mechanical systems (MEMS).^[25]

Bio-MEMS have been used as a diagnostic tool in cancer therapy, by incorporation of novel-functional or novel-shaped nanomaterials and biomolecular markers. This makes it possible to study the fundamental biological mechanisms that dictate health and disease. Based on the cell-molecular machinery and signal transduction mechanisms, nanomedicines can be synthesized which can act as artificial cells and help in targeted molecular drug delivery combined with therapeutic imaging.^[25]

Cell-based biosensors work on the principle that multiple biochemical pathways are followed to translate the molecular code on the oncogenes into a malignant tissue. A living cell can be integrated in a microsystem as the primary transduction mechanism. The cells would detect the key bio-chemical factories/labs laboratories and can amplify a chemical signal. This can be detected by either monitoring physical parameters (such as electrical activity, structural changes) or chemical parameters (production of “messenger” molecules).

Bioconjugated particles and devices are also under development for early cancer detection in body fluids such as blood and serum. These nanoscale devices operate on the principles of selectively capturing cancer cells or target proteins. The sensors are often coated with a cancer-specific antibody or other biorecognition ligands so that the capture of a cancer cell or target protein yields an electrical, mechanical, or optical signal for detection. Another promising area of research is the use of nanoparticles for detection and analysis of circulating tumor cells and biomarkers in blood/serum samples. Through the combinatorial use of magnetic nanoparticles and semiconductor QDs, it is possible to increase the ability to capture and evaluate these rare circulating cancer cells.

NANOTECHNOLOGY IN ORAL CANCER TREATMENT

Bio-products, tools, devices, materials are influenced from consequences of research and developments on nanotechnology. With nanotechnology, more useful devices and better drugs for diseases will be developed. The number

of research in cancer treatment with nanotechnologically modified drugs is increasing day-to-day and has had some good results on this issue. Nanotechnological improvements can be used for cancer patients; because nanotechnology can be used for better cancer diagnosis, more efficient drug delivery to tumor cells and molecular targeted cancer therapy.^[26]

GOLD NANOPARTICLES

Nanotechnology, an interdisciplinary research field involving chemistry, engineering, biology and medicine, has great potential for early detection, accurate diagnosis and personalized treatment of cancer.^[27] There are many subtypes of gold nanoparticles such as gold nanosphere, gold nanocages, gold nanosphere, gold nanorods, surface enhanced raman spectroscopy (SERS) nanoparticles.

These metallic gold nanoparticles exhibit a unique optical response to resonantly scatter light when excited at their surface plasmon resonance frequency.^[28] The epidermal growth factor receptor is a cell surface receptor biomarker that is over expressed in epithelial cancer but not in normal cell. The antiepidermal growth factor receptor antibody conjugated nanoparticles specifically and homogeneously bind to the surface of cancer type cells with 600% greater affinity than to non-cancerous cell.^[29] The successful conjugation of antibodies on gold nanoparticles can be ascertained by the addition of 10% common salt which also leads to aggregation of gold nanoparticles and result in visible color change from red to purple or gray.^[30] Gold nanoparticles have been investigated in diverse areas such as *in vitro* assays, *in vitro* and *in vivo* imaging, cancer therapy and drug delivery.

Gold nanoshells are capable of enhancing the contrast of blood vessels *in vivo* suggested their potential use in magnetic resonance (MR) angiography as blood pool agents.

SERS is an optical technique that offers many advantages over traditional technologies, such as fluorescence and chemiluminescence, including better sensitivity, high levels of multiplexing, robustness and superior performance in blood and other biological matrices.^[31]

QDS

One of the promising diagnostic tools for cancer diagnosis is fluorescent nanoparticle such as organic dye doped nanoparticles, QDs that enable highly sensitive optical imaging of cancer at cellular and animal level.

Medical physicists at the University of Virginia have created a novel way to kill tumor cells using nanoparticles and light. The technique, devised by Wensha Yang, an instructor in radiation oncology employs QDs. QDs are semiconductor nanostructures, 25 billionths of a meter in diameter,

which can confine electrons in three dimensions and emit light when exposed to ultraviolet radiation.^[32] QDs are fluorescent nanoparticles with sizes of 2-10 nm that contain a core of 100s-1000s of atoms of group II and VI elements (e.g., cadmium, technetium, zinc and selenide) or group III (e.g., tantalum) and V elements (e.g., indium).^[33,34] These can be used as photosensitizers and carriers. They can give rise to reactive oxygen species and thus will be lethal to the target cells.

QDs contain a core of cadmium selenide and a zinc sulfide shell, surrounded by coordinating ligand and an amphiphilic polymer coating. They are most commonly used for biological application.^[34,35] This structure enables QDs to emit powerful fluorescence that differs in nature from organic dyes. QDs can be tuned to emit at between 450 nm and 850 nm (i.e., from ultraviolet to near infrared) by changing the size or chemical composition of the nanoparticle. This produces many QDs colors, which can be visualized simultaneously with one light source. QDs emit narrow symmetrical emission peaks with minimum overlap between spectra, allowing unique resolution of their spectra and measurement of fluorescent intensity from several multicolor fluorophores by real-time quantitative spectroscopy. QDs also have a greater surface area and more functionalities that can be used for linking to multiple diagnostic (e.g. radioisotopic or magnetic) and therapeutic (e.g. anticancer) agents. Disadvantages include toxic effect of metal core.^[36-39]

NANOCAPSULE

It is now possible to engineer tiny containers the size of a virus to deliver drugs and other materials with almost 100% efficiency to targeted cells in the bloodstream. According to a new Cornell study, the technique could 1 day be used to deliver vaccines, drugs or genetic material to treat cancer and blood and immunological disorders. Drug targeting by nanoparticles or nanocapsules offers the following enormous advantages as examples: Reduces dosage, ensures the pharmaceutical effects and minimizes side-effects; protects drugs against degradation and enhances drug stability. Tiny machines, known as nanoassemblers, should be controlled by computer to perform specialized jobs. The nanoassemblers could be smaller than a cell nucleus so that they could fit into places that are hard to reach by hand or with other technology.^[40]

Nanoparticles can penetrate through small capillaries, which allow efficient drug accumulation at target sites. A sustained and controlled release of drugs at target sites over a period of days or even weeks is possible.

CARBON NANOTUBES

Single walled carbon nanotubes (SWNTs) are a recent and innovative technological advancement in the world

of chemistry that could be one of the best ways to fight cancer. SWNTs have been shown to shuttle various cargoes across the cellular membrane without cytotoxicity. SWNTs functionalized for biological systems have an interesting relationship with cells. Somatic cells naturally internalize these specialized carbon nanotubes (at 12-15%) through combining carbon nanotubes-cell interactions. They move into cells through the process of endocytosis. They are then able to enter the cytoplasm and nucleus. Although this is a useful ability, in order to fight cancer functionalized SWNTs must be targeted specifically to the malignant tumor cells, ensuring that healthy cells are not adversely affected by the treatment. The cancer cells can therefore be distinguished from healthy cells by locating alterations on them that are not on healthy cells. Coating functionalized SWNTs with peptides and other cell-binding ligands such as monoclonal antibodies allows them to target specific cancerous cells.^[41] Treatment using functionalized SWNTs can begin after they make their way inside the tumor. No effects will be seen until the patient is placed inside a radiofrequency or near infrared region (NIR) field. These two types of radiation were chosen for their ability to pass through the body without damaging body tissue.^[42] Radiofrequency waves have the tendency to penetrate further into the body. Once inside the field SWNTs can effectively convert radiofrequency energy or NIR into heat. They absorb the arriving waves of radiation, giving them energy and in turn causing them to vibrate.^[42] The vibrational movement causes heat to be produced and thermal properties to activate. Vibration of the lattice structure releases phonons, which transfer the heat energy throughout the length of the nanotube. Heat is then dispersed inside the tumor from the entire surface area of the SWNTs causing overheating, protein denaturation and eventually malignant cell death.^[43]

LIPOSOMES

Nanocarriers encounter numerous barriers en route to their target, such as mucosal barriers and non-specific uptake. To address the challenges of targeting tumors with nanotechnology, it is necessary to combine the rational design of nanocarriers with the fundamental understanding of tumor biology. One way to overcome these limitations is to program the nanocarriers so they actively bind to specific cells after extravasation. This binding may be achieved by attaching targeting agents such as ligands molecules that bind to specific receptors on the cell surface to the surface of the nanocarrier by a variety of conjugation chemistries. Although passive targeting approaches form the basis of clinical therapy, they suffer from several limitations. Ubiquitously targeting cells within a tumor is not always feasible because some drugs cannot diffuse efficiently and the random nature of the approach makes it difficult to control the process. This lack of control may induce multiple drug resistance, a situation where chemotherapy treatments fail patients owing to resistance of cancer cells towards one or more drugs.^[20,44,45]

Liposome molecules are easily diffused into the cells; since their structures and cell membrane structure can interact very well while drug uptake process.

NANOTECHNOLOGY LATEST ONCOLYTIC AGENT

Silver-based drugs have oligodynamic silver ions which enhance its antimicrobial properties.^[46] In 2003, Reitz did a retrospective review on the universal antimicrobial effects of oligodynamic Ag^{+2} . Reitz documented that many cancer associated infections such as human immunodeficiency virus^[47,48] human herpesvirus 8,^[49] human papillomavirus^[50] and Epstein-Barr virus 18,^[51] BK and JC polyomaviruses, respiratory syncytial virus, influenza viruses and parainfluenza viruses, fungemia^[52,53] rotavirus^[54,57] cytomegalovirus^[55] and *Streptococcus pneumoniae* are susceptible to oligodynamic Ag^{+2} . Advantage of silver particles is their ability to absorb, interact with and destroy bacteria affecting abnormal human tissue *in situ* or favorably upregulate immune tissues and healing mechanisms.

Marino *et al.*^[56] and Berger *et al.* (1976) confirmed that the effective dosage level of pure oligodynamic Ag^{+} is safe for mammalian tissues. Therefore, based on the studies and from a purely mathematical perspective, 100 cc isotonic Ag^{+} hydrosol with a 25 ppm concentration or less, could be administered as an intravenous drip every day for a year without risking the development of argyria. Likewise, a dose of 500 cc (isotonic) of oligodynamic Ag^{+} administered daily for up to 79 consecutive days or 1000 cc (isotonic) of oligodynamic Ag^{+} administered daily for up to 39 consecutive days still falls short of the risk threshold for developing argyria.

ADVANTAGES OF NANOPARTICLES

The use of nanoparticles has not only revolutionized the field of medicine but has helped in accurate, precise treatment of diseases, drug delivery. Various other uses of nanoparticles in various fields of medicine and cancer are fluorescent biological labels,^[57] drug and gene delivery,^[58] bio detection of pathogens,^[59] detection of proteins,^[60] probing of DNA structure,^[61] tissue engineering,^[62] tumor destruction through heating (hyperthermia),^[63] separation and purification of biological molecules and cells,^[64] MR imaging contrast enhancement^[65] and phagokinetic studies^[66] [Table 1].

LIMITATIONS OF NANOPARTICLES

Cancer targeting is highly dependent on surface chemistry. Biocompatibility is a major issue in use of nanoparticles. Ease of availability all over the world at basic levels (primary health care, government hospitals etc.,) and cost of nanotreatment are the main disadvantages of nanoparticles.

Table 1: Advantages and disadvantages of nanoparticles

Types	Advantages	Disadvantages
Gold nanoparticles	Increased contrast	Biocompatibility
	Less invasive	Optical signal not strong
	No photo bleaching	Toxicity
		Tumor targeting efficacy low
Quantum dots	Multiple molecular targets simultaneously	Toxicity effect of metal core
	Fluorescence of high quality and energy	
Nanocapsule	Efficient drug accumulation at site	
	Sustained drug release for weeks	
Carbon nanotubes	Less cytotoxic	
Liposomes	Biocompatibility	
	Biodegradability	
	Isolation of drugs from surrounding environment	
	Ability to entrap both hydrophilic and hydrophobic drugs	

RECENT ADVANCES

At present, the majority of commercial nanoparticle applications in medicine are geared towards drug delivery. In biosciences, nanoparticles are replacing organic dyes in the applications that require high photo-stability as well as high multiplexing capabilities. The major trend in further development of nanomaterials is to make them multifunctional and controllable by external signals or by the local environment thus essentially turning them into nano-devices.^[67]

CANCER NANOVACCINES

Vaccine as a form of nanovaccine in the treatment of cancer is still under development. The first type, prophylactic vaccines, triggers humoral and cellular immunity and is administered into healthy individuals in order to prevent them from getting cancer. The human papilloma virus vaccine is an example of a prophylactic vaccine. For those who already have cancer, there is a second type of vaccine called cancer nanovaccines.

Cancer nanovaccines could be designed, manufactured and introduced into the human body to improve health, including cellular repairs at the molecular level. The nanovaccines are so small that it can easily enter the cell; therefore, nanovaccines can be used *in vivo* or *in vitro* for biological applications. This has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications and drug delivery vehicles. Drug consumption and associated side-effects can be significantly lowered by depositing the active agent at the desired location.

NANOMEDICINE HEAT THERAPY

Just like radiotherapy for cancer, heat therapy uses nanoparticles and hence that treatment is targeted at the

cancer cells. Like radiation therapy, a laser optic probe is used, which basically ensures that the infrared radiation is directed at the tumor and allows the treatment to be through the skin, from outside the body. Therefore, this new heat treatment is very similar to the current method of radiation therapy, but the nanoparticles alter the treatment in that they cause minimal damage to the healthy tissue.

ETHICAL ISSUE

Nanoscience and nanotechnology, like any other knowledge and associated practices that were developed in the past are engaged in a debate about the degree of desirability of this technology from different value-premises and interpretations of the new technoscience. In the Western countries, research on ethical, legal, social and environmental dimensions of nanoscience and nanotechnology has been recognized as a legitimate field of inquiry. The fact that nanomedicine is a new development, with nanotechnology treatments being completely different from other cancer treatments, there could be a lot of confusion and difficulty in regulating nanotechnology treatment and its uses. For these reasons, it could be hard to create rules and risk assessments for nanotechnology, which could therefore allow it to be used unsafely.

CONCLUSION

Despite tremendous advances in cancer therapy, many scientific, technological and clinical challenges remain that will require a highly interdisciplinary and collaborative approach to overcome cancer disease. With advances in cancer biology and explosive development in material science and imaging technology, we have reason to be optimistic that we are at the critical threshold of a major breakthrough in the treatment of cancer. As the capabilities of multifunctional nanoplateforms continue to increase, the integration of cancer biology, diagnostic imaging and materials science in the future will be essential, not just for theranostic medicine, but for cancer therapy overall.

Multifunctionality is the key advantage of nanoparticles over traditional approaches. Targeting ligands, imaging labels, therapeutic drugs and many other functional moieties can all be integrated into the nanoparticle conjugate to allow for targeted molecular imaging and molecular therapy of cancer. Gold nanoparticle is unique in a sense because of its intriguing optical properties which can be exploited for both imaging and therapeutic applications.

Nanoparticles hold new promise as means for earlier detection and better treatment of cancer. Imagine a future where nanoparticles can help detect cancer before it even has a chance to manifest and selectively destroy cancer cells while leaving the normal cells unharmed. Cancer, in such a circumstance, could become a highly manageable condition.

However, despite our current research there is much we still do not understand. Nanoparticles offer a new avenue to tackle these challenges.

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