Review Article

Unbounding the Future: Nanobiotechnology in Detection and Treatment of Oral Cancer

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Abstract:
Nanotechnology is defined as the design and fabrication of materials, devices and systems with control at nanometer dimensions. Nano devices can detect cancer cells, identify cancer signatures and provide targeted delivery of anti cancer therapeutics to tumour cells. This novel imaging tool can lead to significant improvements in cancer therapy due to earlier detection, accurate staging, and microtumor identification. This paper provides an early glimpse of nanobiotechnology and its application in dentistry with regard to advanced cancer diagnostics, targeted drug delivery and biosensors. The potential application of nanorobotics in early detection of cancer cell is highlighted in the article.
Key Words: Nanotechnology, Nanometer, cancer, microtumour, biosensors, Nanorobotics

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Introduction

The science is good, the engineering is feasible, the paths of approach are many, the consequences are revolutionary and the schedule is- in our lifetimes.[1] Nanotechnology (NT) has emerged as cutting edge advancement combining biomedical science and technology. “NT allows us to make materials that are thousands of times smaller than the smallest cell in the body ‘’said James R Baker Jr, MD, Professor of biologic NT at University of Michigan in Ann Arbor. Because these materials are so small, they can easily get inside cells and change how they work.[2]

The Emergence of Nanotechnology

The term Nanotechnology was first introduced in 1964 by Norio Taniguchi (University of Tokyo) to refer to the ability of engineer materials precisely at the scale of nanometers.[3] However Dr Robert A and Fretias Jr are the pioneer scientists who wrote about nanomedicine, Nanodentistry and its future changes. Nanobiotechnology and bionanotechnology are essential the same synonyms refer to materials and processes at nanometer scale that are based on biological, biomimetic or biologically inspired molecules and nanotechnological devices used to monitor or control biological processes. An example of former is optical switch incorporating biomolecule bacterio-rhodopsin and the example of the latter is the biochip- an array of known DNA fragments used to capture unknown DNA from the sample.[3]

What are Nanoparticles?

A nanometer is a billionth of a meter, or to put it comparatively, about 1/80000 of the diameter of a human hair. Nanoparticles are typically smaller than several hundred nanometers in size, comparable to large biological molecules such as enzymes, receptors and antibodies. With the size of about one hundred to ten thousand times smaller than human cells, these nanoparticles can offer unprecedented interactions with biomolecules both on the surface of and inside the cells which may revolutionize cancer diagnosis and treatment.[4] Nanoparticles offer great promise to improve therapeutic effectiveness and safety profile in cancer treatment through site specificity, their ability to limit multi-drug resistance and efficient delivery of anticancer agents. A wide variety of nanoparticle-based systems those are available for cancer detection, diagnosis and treatment include liposomes, polymeric micelles, nanosystems, nanoshells, fullerene-based derivatives, carbon nanotubes, dendrimers, nanopores, quantum dots, gold nanoparticles, solid lipid nanoparticles, nanowires, paramagnetic nanoparticles etc.[4] The ability of nanoparticles in cancer treatment has dual significance. Firstly, nanoparticles play role as drug carriers. Secondly, they can absorb different wavelengths of light, and when exposed to appropriate wavelengths, nanoparticles heat up without heating the body. Thus, nanoparticles selectively kill cancerous cells.[5] Nanoparticles can enter into smallest capillary vessels due to their ultra-tiny volume size and avoid rapid clearance by phagocytes, so that their duration in the blood stream is greatly prolonged. They can penetrate cell and tissue gaps to arrive at the target organs. They are able to show controlled release properties due to their biodegradability, pH, ion and temperature sensibility of materials. Presently, nanoparticles have been widely used to deliver antibiotics, anticancer agents, radiological agents, vaccines, proteins, polypeptides, antibodies, genes, and so on. Over the years, nanoparticle-based drug delivery and imaging systems have shown huge potential in biological, medical, pathological, and pharmaceutical applications.[5] Multifunctional nanomaterials has been the area of research for scientists and using these, researchers now claim that they have developed process to identify and isolate cancer cells. Researchers have combined magnetic nanoparticles with fluorescent quantum dots and form a single nanosphere that can be used in various applications in the area of biomedicine.[6]

Discussion

In the last decade, progress in developing nano sized hybrid therapeutics and drug delivery systems has been remarkable. Nanomedicine seeks to deliver a valuable set of research tools and clinically useful devices in the near future. A good flow of related technologies is also in development. But are these ‘nanomedicines’ really new? The educated answer is ‘not really’. The concepts of antibody-conjugates, liposomes and polymer-conjugates stem from the 1970s. Of late they are seen as competing technologies that would emerge as a ‘magic bullet’ for all drug targeting applications.[4] One of the most important factors in effective cancer treatment is the detection of cancerous tumor cells in an early and perhaps curable stage. Thus, the detection time frame has an enormous effect on a patient's prognosis. Nanotechnology brings new hope to the field of cancer detection research, owing to nanoparticles unique physical and chemical properties, giving them the potential to be used as a synthetic scaffold for imaging probes in the detection and monitoring of cancer. Figure 1 and 2 highlights comparison between age old cancer treatment and the recent nanotechnology treatment.

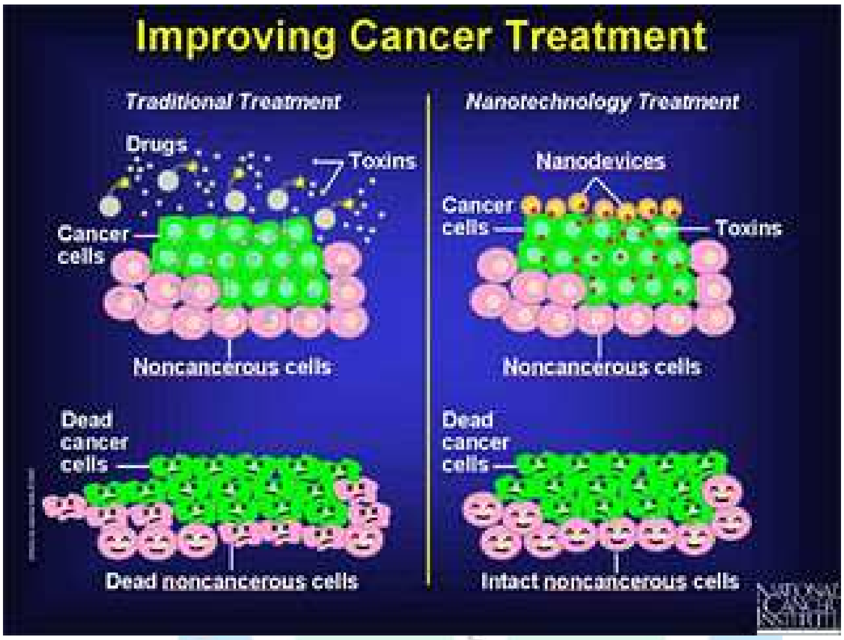

Figure 1: Comparison between age old cancer treatment and new Nanotechnology treatment

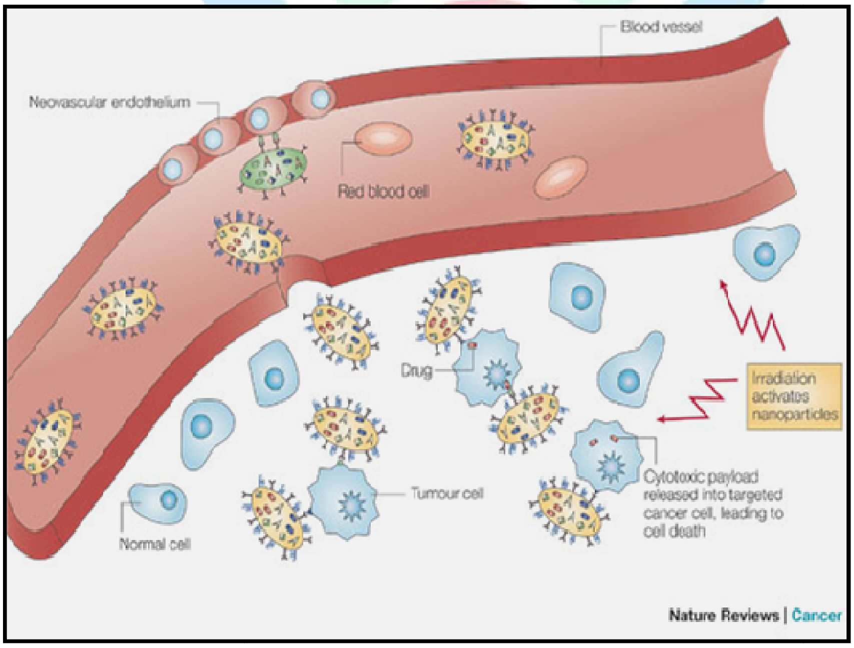

Figure 2: Treatment of cancer by Nanoparticles

Nanoparticles surface properties are tunable, meaning their injectable solutions can be made without using toxic organic solvents to attach water-insoluble anticancer agents. This, along with nanoparticles ability to perform passive or active tumor targeting, makes them an excellent platform for diagnostic imaging and treatment. Thus, nanotechnology-based imaging modalities have made a significant entry into cancer research with their highly sensitive probes for cancer detection.[7] Various nanoparticles and their potential application in tumour diagnosis and treatment include:

Liposomes: Liposomes are small artificial spherical vesicles composed of non-toxic phospholipids and cholesterol, which self associate into bilayers to encapsulate drugs, genes and other biomolecules on aqueous interior [5]. Liposomes are within the size-range of 25 nm to 10 µm, depending on their preparation method. Various therapeutic agent loaded liposomes are being extensively tested as targeted delivery for fighting against cancer[8] as clearly demonstrated in Figure 3. Liposomes of certain sizes, typically less than 400 nm, can rapidly penetrate tumor sites from the blood, but are kept in the blood stream by the endothelial wall in healthy tissue vasculature.[5]

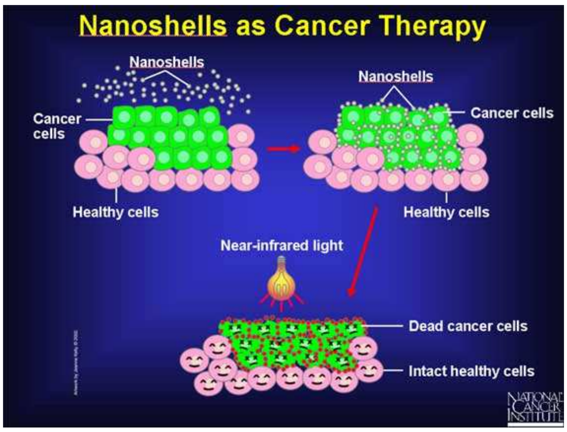

Figure 4: Nanoshells in Cancer Therapy

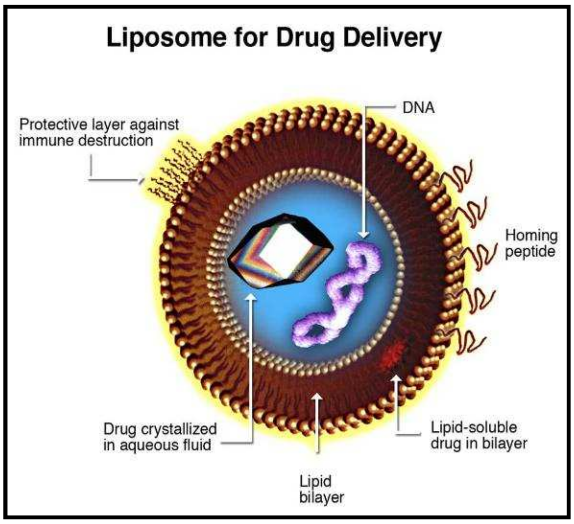

Figure 3: Liposome for drug delivery

Nanoshells: Nanoshells are another attractive platform for cancer diagnosis and cancer therapy. They are mainly metal based nanoparticles. Nanoshells have a core of silica with a top layer of gold.[5] By changing the thickness of the gold layer, the alteration in optical absorption properties of these nanoshells is possible when radiated with near-IR laser. The near–IR laser illuminates the tissue and the light will be absorbed by nanoshells to generate intense heat. Thus, nanoshells get active to destroy only the cancerous cells thermally without damaging the surrounding healthy cells.[9] Because of their size, nanoshells will prefere ntially concentrate in cancer lesion sites. Thi s physical selectivity occurs through a pheno menon called Enhanced permeation retentio n (EPR). Antibodies and/or therapeutic anticancer agents can be attached to their surfaces, enabling those nanoshells to target cancerous cells or tumors.[5] The therapeutic application of Nanoshells in treatment of cancer is demonstrated in Figure 4.

Quantum Dots (QD):

QDs usually consist of an inorganic transition metal core/shell system. (Figure 5) These inorganic-organic composite nanoparticles are extremely efficient agents for cancer detection in vivo owing to their small size, which offers them unhindered access to the systemic circulation, and at the same time their ability to conjugate targeting molecules that direct specific accumulation in neoplastic sites. Additionally, QDs have sufficient surface area to attach therapeutic agents and tumor-specific moieties for simultaneous drug delivery as well as in vivo imaging and tissue engineering. Depending on size and the core/shell system, QDs have the ability to emit light across the visible and infrared wavelength spectrum. Thus one can choose a suitable color of light emission. The main advantage of the QDs is that with a single light source, the variously-sized QDs can be excited while preserving the narrow emission of each individual particle/wavelength. Moreover, QDs have the ability to incorporate different markers simultaneously (multiplexing), enabling numerous targets to be imaged in a single experiment.[7]

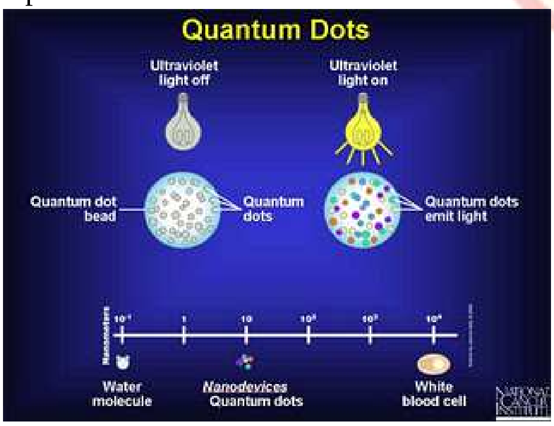

Figure 5: Quantum Dots

Dendrimers:

They are perfect monodisperse macromolecules with regular and highly branched 3-D architecture. The emerging role of dendrimers for anticancer therapies and diagnostic imaging has highlighted the advantages of these well-defined materials as the newest class of macromolecular nanoscale delivery devices.[5] Figure 6 highlights the potential use of dendrimers in detection and treatment of cancer. Dendrimers used in drug delivery and imaging are usually 10 to 100 nm in diameter with multiple functional groups on their surfaces rendering them an ideal carrier systems for targeted drug delivery. Scientists and researchers have fashioned dendrimers into an effective and sophisticated anticancer therapy machines carrying 5 important chemical tools:

- A molecule designed to bind cancerous cells and tumors
- Fluorescence upon locating genetic mutations
- To assist in imaging tumor shape using X rays
- Carrying therapeutic agents released on demand and
- Signaling when cancerous cells are finally dead.[10]

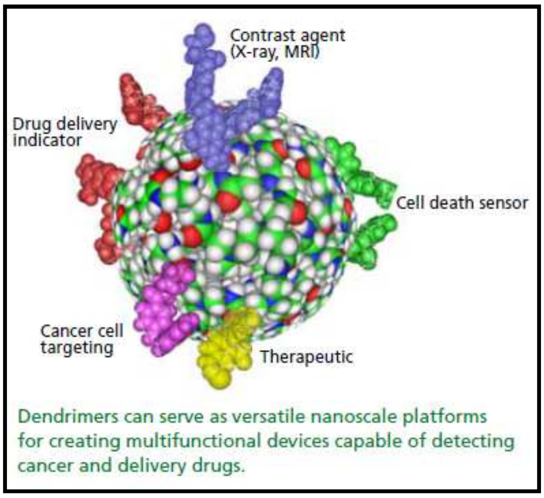

Figure 6: Dendrimers

Carbon Nanotubes:

Carbon nanotubes consist of carbon atoms exclusively arranged in a series of condensed benzene rings rolled-up into tubular architecture. Tumor targeting carbon nanotubes have been synthesized covalently attaching multiple copies of tumor specific monoclonal antibodies, radiation ion chelates and various fluorescent probes.[5] The surface of carbon nanotubes can be modified with proteins for cellular uptake. Then they are heated up upon absorbing near-IR light wave. When exposed to near-IR light, carbon nanotubes quickly release excess energy as heat (~70ºC) which can kill cancerous cells.[11] Another advantage of carbon tube is that they help in detection of altered gene coding as shown in Figure 7.

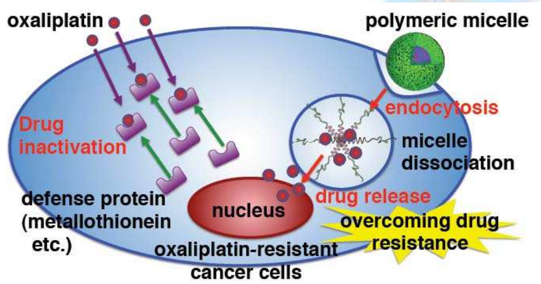

Fig 8: Polymeric Micelles in Cancer treatment

Nanowires:

Nanowires are glowing silica wires in nanoscale. They are about five times smaller than virus and several times stronger than spider silk.[5] Nanowire based arrays have significant impact for early diagnosis of cancer, and cancer treatment. The nanowire-based delivery enables simultaneous detection of multiple analytes such as cancer biomarkers in a single chip, as well as fundamental kinetic studies for biomolecular reactions.[14]

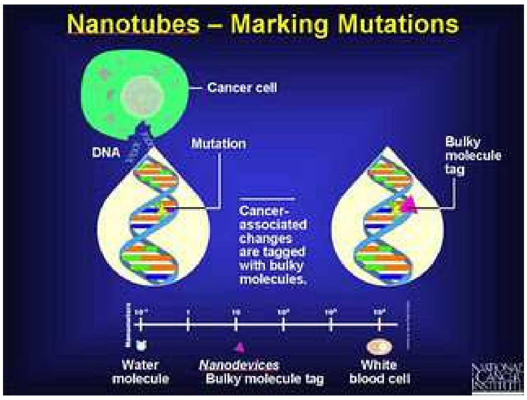

Figure 7: Carbon Nanotubes in detecting genetic mutation

Polymeric Micelles:

Polymeric micelles are supramolecular self assemblies of block copolymers. They represent spherical, colloidal nanoscale particles with unique core-shell structure. Polymeric micelles have demonstrated high durability in the blood stream and effective tumor accumulation after their systemic administration.[12] They are currently recognized as one of the most promising nanocarrier system for drug and gene delivery in the treatment of cancers.[5] They demonstrate tumor-infiltrating ability as well as controlled release of drugs, which is most important for the complete eradication of tumor mass, as shown in Figure 8. Multifunctional polymeric micelles may be designed and developed to facilitate simultaneous drug delivery and related imaging in cancer therapeutics.[13]

Fullerene-based Derivatives:

Fullerene-based derivatives are crystalline particles in form of carbon atoms that has huge potential in cancer therapy. The cage structure of fullerene is ideal for attaching anticancer agents or even radiological agents to increase treatment efficacy for diagnosis and eradication of cancerous cells. Their good stability makes them unique candidates for safely delivering highly toxic substances to tumors.[15]

Micro and Nano-scale cantilever arrays:
They are developed for an ultra sensitive bio-assay. This bio sensor array has the potential to offer high-throughput detection of proteins, DNA, RNA and peptides (Figure 9). These cantilevers can bond specific reagents to detect and measure the presence of particular antigens and/or complementary DNA sequence at much earlier stages of disease compared to current medical diagnostic technologies.[16] The physical properties of cantilever change in real time and provide information about the presence and concentration of different molecular expression.[17]

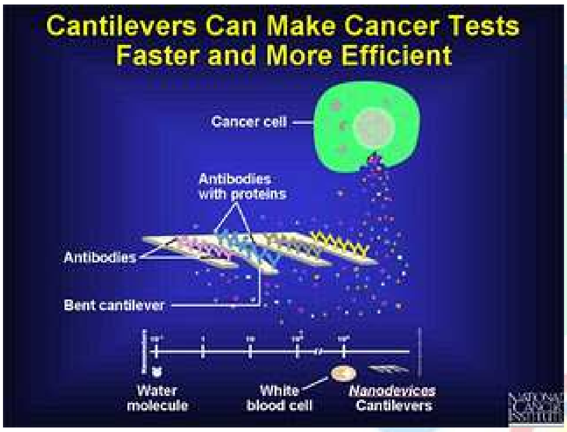

Figure 9: Nanocantilever in detection of Cancer

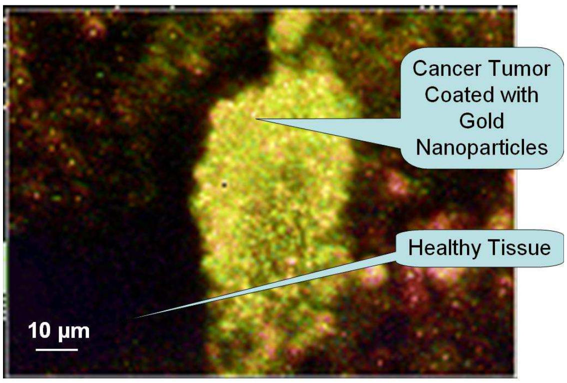

Fig 11: Cancer cells after incubation with Anti EGFR antibody conjugated gold nanoparticles

Nanopore:
These contain tiny hole that allows DNA to pass through one strand at a time making DNA sequencing more efficient as represented in Figure 10. This will help researchers to detect errors in genes that contribute to cancer.[17]

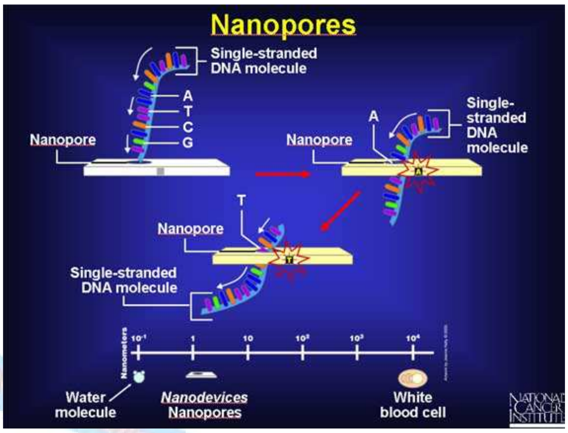

Fig 10: Nanopores in detecting genetic errors

Gold Nanoparticles:
The metallic gold nanoparticles exhibit a unique optical response to resonantly scatter light when excited at their surface Plasmon resonance frequency. The epidermal growth factor receptor (EGFR) is a cell surface receptor biomarker that is overexpressed in epithelial cancer but not in normal cells. The anti EGFR antibody conjugated nanoparticles specifically and homogeneously binds to the surface of the cancer cells with 600% greater affinity than to the noncancerous cells.[18] (Figure 11). This will elicit an optical contrast resulting in a visible color change from red to purple or gray. Raman spectroscopy is the most promising imaging technique for gold nanoparticles based contrast agents. Antibody conjugated gold nanorods were reported to give a Raman spectrum that is greatly enhanced, sharpened, and Polarized.[4] Surface enhanced Raman scattering spectra of saliva from closely packed gold

nanoparticles of normal cells and oral cancer cells were also differentiable. Thus, showed a promising result of using saliva as an assay for early diagnosis of oral cancer.[19] Various killing mechanisms of cancer cells by Gold Nanoparticles have been proposed. The one most commonly discussed, that has become an extensive area of research, is based on the formation of a bubble around the overheated gold nanoparticle in a liquid environment followed by generation of acoustic and shock waves and protein inactivation. In particular, gold nanoclusters attached to a cell membrane can lead to dramatic increase in bubble formation efficiency, resulting in more severe cancer cell damage at a laser strength that is safer for normal tissue. For environments with a lack of sufficient amount of liquid for efficient bubble generation, such as bones or dense solid tumors, other killing mechanisms are being sought. For instance, one is a 'gold atom bullet' that moves from the explosion zone with kinetic energy sufficiently large to mechanically damage the surrounding cellular structure. Another is the melting of cell walls by hot gold nanoparticles and subsequent destruction of the cell by gold nanoclusters.[20]

Magnetic nanoparticles:

Magnetic nanoparticles are able to target cancerous cells and have potential use in cancer therapeutics (Figure 12). The effect of magnetic nanoparticles is due to super paramagnetic iron oxides, typically Fe_2O_3 and Fe_3O_4, which do not retain their magnetic property when removed from the magnetic field[5]. Their paramagnetic characteristics have made them good candidate for the destruction of tumors in vivo through hypothermia.[5]

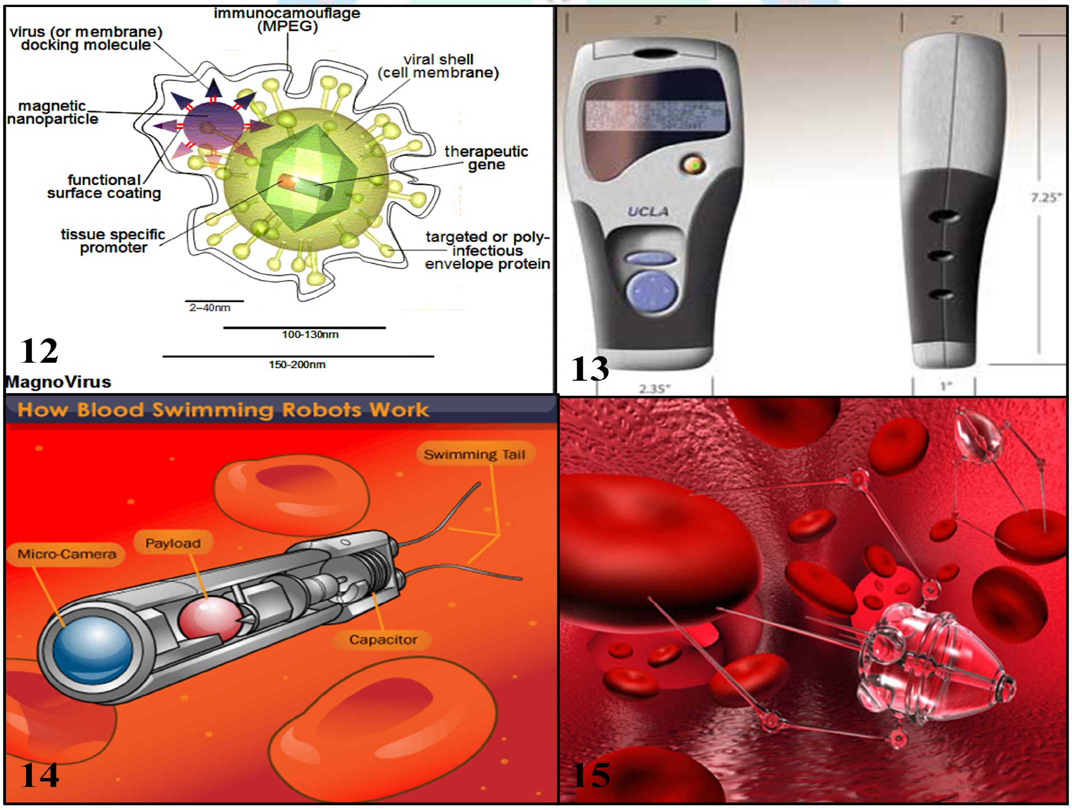

Figure: 12) Magnetic Nanoparticles in Cancer therapautics; 13) Oral Fluid Nanosensor Test Kit; 14) Parts of Nanorobot; 15) Microbivore in Bloodstream

Other applications of nanotechnology in detection of oral cancer[21] are as follows:

Nano Electromechanical Systems (NEMS)
Nanotechnology based NEMS biosensors that exhibit exquisite sensitivity and specificity for analyte Detection, down to single molecule level is being developed. They convert (bio) chemical to electrical signal.[22]

Oral Fluid NanoSensor Test (OFNASET)
The Oral Fluid NanoSensor Test (OFNASET) technology is used for multiplex detection of salivary biomarkers for oral cancer (Figure 13). It has been demonstrated that the combination of two salivary proteomic biomarkers (thioredoxin and IL-8) and four salivary mRNA biomarkers (SAT, ODZ, IL-8, and IL-1b) can detect oral cancer with high specificity and sensitivity.[23]

Optical Nanobiosensor
The nanobiosensor is a unique fiberoptics-based tool which allows the minimally invasive analysis of Intracellular components such as cytochrome c, which is a very important protein to produce cellular energy. It is known to be involved in apoptosis as well.[24]

Treatment of Oral Cancer[25]

- NANOMATERIALS FOR BRACHYTHERAPY
- BrachySil TM (Sivida, Australia) delivers 32P, clinical trial.
- Drug Delivery across the Blood-Brain Barrier/More effective treatment of brain tumors, Alzheimer's, Parkinson's in development
- Nano-vectors for Gene Therapy
- Non-viral gene delivery systems

Application of Nanorobotics In Diagnosis and Treatment of Cancer: Nanorobots
The ultimate tool of Nanomedicine is the Medical Nanorobot – a robot the size of a bacterium, composed of many thousands of molecule-size mechanical parts perhaps resembling macroscale gears, bearings, and ratchets, possibly composed of a strong diamond-like material. A nanorobot that would travel through the bloodstream must be smaller than the red cells in our blood – tiny enough to squeeze through even the narrowest capillaries in the human body (Figure 14) [26] One medical nanorobot called a "microbivore" (Figure 15) could act as an artificial mechanical white cell, seeking out and digesting unwanted pathogens including bacteria, viruses, or fungi in the bloodstream. A patient with a bloodborne infection is injected with a dose of about 100 billion microbivores (about 1 cc). When a targeted bacterium bumps into a microbivore, the microbe sticks to the nanorobot's surface. Telescoping grapples emerge from the microbivore's hull and transport the pathogen toward the front of the device, in bucket-brigade style into the microbivore's "mouth." Once inside, the microbe is minced and digested into amino acids, mononucleotides, simple fatty acids and sugars in just minutes. These basic molecules are then harmlessly discharged back into the bloodstream through an exhaust port at the rear of the device. A complete treatment might take a few hours, far faster than the days or weeks often needed for antibiotics to work, and no microbe can evolve multidrug resistance to these machines as they can to antibiotics. When the nanorobotic treatment is finished, the doctor broadcasts an ultrasound signal and the nanorobots exit the body through the kidneys, to be excreted with the urine in due course.[26]
Related nanorobots could be programmed to quickly recognize and digest even the tiniest

aggregates of early cancer cells. Medical nanorobots could also be used to perform surgery on individual cells. In one proposed procedure, a cell repair nanorobot called a “chromallocyte”, controlled by a physician, would extract all existing chromosomes from a diseased cell and insert fresh new ones in their place. This process is called chromosome replacement therapy. The replacement chromosomes are manufactured outside of the patient’s body using a desktop nanofactory optimized for organic molecules. The patient’s own individual genome serves as the blueprint to fabricate the new genetic material. Each chromallocyte is loaded with a single copy of a digitally corrected chromosome set. After injection, each device travels to its target tissue cell, enters the nucleus, replaces old worn-out genes with new chromosome copies, then exits the cell and is removed from the body. If the patient chooses, inherited defective genes could be replaced with non-defective base-pair sequences, permanently curing any genetic disease and even permitting cancerous cells to be reprogrammed to a healthy state. Perhaps most importantly, chromosome replacement therapy could correct the accumulating genetic damage and mutations that lead to cellular aging.[26]

The potential impact of medical nanorobotics is enormous. Rather than using drugs that act statistically and have unwanted side effects, we can deploy therapeutic nanomachines that act with digital precision, have no side effects, and can report exactly what they did back to the physician. Test results, ranging from simple blood panels to full genomic sequencing, should be available to the doctor within minutes of sample collection from the patient. Continuous medical monitoring by embedded nanorobotic systems, as exemplified by the programmable dermal display, can permit very early disease detection by physicians. Medical nanorobotics holds the greatest promise for curing disease and extending the human health span. With diligent effort, the first fruits of this advanced nanomedicine could begin to appear in clinical treatment sometime during the 2020s.

Conclusion

As Dr H.G.Weels rightly quoted “What on earth would man do with himself if something did not stand his way?” Nanobiotechnology has strong potential to revolutionize dentistry to diagnose and treat deadly disease like oral cancer. Nanomedicine will allow a more personalized treatment for many diseases, exploiting the in-depth understanding of disease on a molecular level. The multimodal nanoparticles have the potential to be used as diagnostic as well as therapeutic agents in oral cancer.

Dr Gregory Fahy described Nanorobots as ‘living organism, naturally existing, and fabulously complex systems of molecular nanotechnology’. Although research into nanorobots is still into preliminary stages, the promise of such technology is endless.

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