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# Nano technology in oral medicine

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## Abstract

Nanotechnology, or nano science, refers to the research and development of an applied science at the atomic, molecular, or macromolecular levels (i.e., molecular engineering, manufacturing).

The prefix ‘‘nano’’ is defined as a unit of measurement in which the characteristic dimension is one billionth of a unit. Although the nano scale is small in size, its potential is vast.

As nanotechnology expands in other fields, clinicians, scientists, and manufacturers are working to discover the uses and advances in biomedical sciences. Applications of nanotechnology in medical and dental fields have only approached the horizon with opportunities and possibilities for the future that can only be limited by our imagination.

Here, we present a dynamic view of dental tissues, an adoption of which may lead to finer, more effective and minimally invasive reparation approaches. By doing so, we aim at providing insights into some of the breakthroughs relevant to understanding the genesis of dental tissues at the nano structural level or generating dental materials with nanoscale critical boundaries.

This paper provides an early glimpse of nanotechnology applications in oral medicine and dentistry to illustrate their potentially far-reaching impacts on clinical practice. It also narrates the safety issues concerning nanotechnology applications

**Keywords**: Dentistry; Nanomaterials; Nanoscience; Nanotechnology

## Introduction

The word “nano,” is derived from the Greek word (nanos) meaning “dwarf,” which literally refers to 1 billionth of a physical size.1One nanometer (nm) is a unit of length that equals billionth of a meter. The size of atoms is approximately 0.1 nm. The size of a usable nanostructure is 1 to 100 nm. It means the area of nanotechnology works at the level of atoms and molecules.[1]

The material properties have significantly altered following the micro-to-nano shift in the scale. Hence a new field was born to explain these rather strange phenomena, named nano science and the application of its discoveries termed nanotechnology[2]

Disease diagnosis, treatment, and prevention. These technological innovations, referred to as nano medicines by the National Institutes of Health (Bethesda, MD, USA), have the potential to turn molecular discoveries arising from genomics and proteomics into widespread benefit for patients.

Nano medicine is a large subject area and includes nano particles that act as biological mimetics (e.g., functionalized carbon nanotubes), “nano machines” (e.g., those made from interchangeable DNA parts and DNA scaffolds such as octahedron and stick cube), nano fibers and polymeric nano constructs as biomaterials (e.g., molecular self-assembly and nano fibers of peptides and peptide-amphiphiles for tissue engineering, shape-memory polymers as molecular switches, nano porous membranes), and nano scale micro fabrication-based devices (e.g., silicon microchips for drug release and micro machined hollow needles and two-dimensional needle arrays from single crystal silicon), sensors and laboratory diagnostics.

New potential treatment opportunities in dentistry include, local anesthesia, dentition renaturalization, permanent hypersensitivity cure, complete orthodontic realignments during a single office visit, covalently bonded diamondized enamel, and continuous oral health maintenance using mechanical dentifrobots.[3]

**Physiology of nanoparticles**

As nano particle exists in the same size as proteins or cells, it is suitable for bio tagging or labelling 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 nano particles.

This simple size comparison gives an idea of using nano particles as very small probes that would allow us to spy at the cellular machinery without introducing too much of the interference.[4]

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.[5]

**History of nanotechnology**

Nano particles were used by artisans as far back as the 9th century in Mesopotamia for generating a glittering effect on the surface of pots.[3] Pottery from the Middle Ages and Renaissance often retain a distinct gold or copper colored metallic luster.[6]

The luster originated within the film itself, which contained silver and copper nanoparticles dispersed homogeneously in the glassy matrix of the ceramic glaze.[7] The concepts that seeded nanotechnology were first discussed in 1959 by renowned physicist Richard Feynman in his talk “There's Plenty of Room at the Bottom” in which he described the possibility of synthesis via direct manipulation of atoms.

The term "nano-technology" was first used by Norio Taniguchi in 1974, though it was not widely known.[2,3] In the 1980s, two inventions which enabled the imaging of individual atoms or molecules as well as their manipulation led to significant progress in the field of nanotechnology. Gerd Binnig invented scanning tunnelling microscopy (STM) while Henrich Rohrer invented atomic force microscopy.

Inspired by Feynman's concepts, K. Eric Drexler independently used the term "nanotechnology" in his 1986 book Engines of Creation:

The Coming Era of Nanotechnology. In 1991, Saumio Iijima discovered carbon nanotubes and by 2000, the United States government launched the National Nanotechnology Initiative (NNI – a federal visionary research and development programme for nanotechnology-based investments through the coordination of 16 various US departments and independent agencies) and these paved way for the progress in research and development in the field of nanotechnology.[7]

**Nanotechnology in oral medicine and radiology**

**Nano diagnostics**

Nano diagnostics is the use of nano devices for the early disease identification. In in-vitro diagnostics, nano medicine could increase the efficiency and reliability of the diagnostics using human fluids saliva or tissues samples by using selective nano devices, to make multiple analyses at sub cellular scale. In in- vivo diagnostics, nano medicine could develop devices able to work inside the human body in order to identify the early presence of a disease, to identify and quantify toxic molecules, tumor cells.[8]

**Nanorobots**

Nanorobots may release inhibitors, antagonists or down regulators for the pyrogenic pathway in a targeted fashion to selectively absorb the endogenous pyrogens, chemically modify them, and then release them back into the body in a harmless inactivated form. The non-pyrogenic nanorobots used in vivo are bulk teflon, carbon powder and monocrystal sapphire. Pyrogenic nanorobots are alumina, silica and trace elements like copper and zinc[8].

**Diagnosis and imaging**

Scientists have successfully produced microchips that are coated with human molecules. The chip is designed to emit an electrical impulse signal when the molecules detect signs of a disease.

Special sensor nanobots can be inserted into the blood under the skin where they check blood contents and warn of any possible diseases. They can also be used to monitor the sugar level in the blood. Advantages of using such nanobots are that they are very cheap to produce and easily portable.[8]

**Diagnosis and management of oral cancer**

**Nanoscale cantilevers**

These are flexible beams resembling a row of diving boards that can be engineered to bind to molecules associated with cancer. Nanopores these are tiny holes that allow DNA to pass through one strand at a time. They will make DNA sequencing more efficient[10]

**Nanotubes**

These are carbon rods about half the diameter of a molecule of DNA that not only can detect the presence of altered genes but also may help researchers pinpoint the exact location of those changes.[10]

**Dendrimers**

These are highly branched macromolecules with a controlled three-dimensional architecture. The branched structure makes it possible to attach other molecules like drugs and contrast agents to the cancer cell surface.[10]

**Nano shells**

These are miniscule beads coated with gold. By manipulating the thickness of the layers making up the Nano shells, scientists can design these beads to absorb near-infrared light, creating an intense heat that is lethal to cancer cells.[10]

nano shells have a core of silica and a metallic outer layer. Nanotechnology in cancer pain: Nanotechnology has exhibited a remarkable progress over the past 20 years in the management of pain in cancer patients.[10]

Recent applications at the nanoscale level include novel drug-delivery systems, such implantable drug delivery devices, transdermal or transmucosal patches, and micro-needles. Oral transmucosal fentanyl citrate (OTFC; Actiq®, Cephalon, UK) is the first medication developed specifically for the treatment of breakthrough pain and provides its active ingredient, fentanyl, in a unique oral transmucosal delivery system, utilizing micro fabrication technology, offering personal pain control for cancer patients.[10]

**Digital Dental Imaging**

In digital radiographies obtained by nanophosphor scintillators, the radiation dose is diminished and high-quality images are obtained.[10]

**Recent advances**

**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.[11]

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.[12]

The epidermal growth factor receptor is a cell surface receptor biomarker that is over expressed in epithelial cancer but not in normal cell. The ant epidermal 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.[13]

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.

Gold nanoparticles have been investigated in diverse areas such as in vitro assays, in vitro and in vivo imaging, cancer therapy and drug delivery.[14]

**Quantam Dots**

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.[15]

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).

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.[16,17]

**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 nano particles or nano capsules 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 nano assemblers, should be controlled by computer to perform specialized jobs. The nano assemblers 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.

Nano particles 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.[18]

**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.[19]

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.[20]

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.[20]

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.[21]

**Liposomes**

Nano carriers 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 nano carriers with the fundamental understanding of tumor biology.

One way to overcome these limitations is to program the nano carriers 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. Liposome molecules are easily diffused into the cells; since their structures and cell membrane structure can interact very well while drug uptake process.[22,23]

**Nanotechnology Latest Oncolytic Agent**

Silver-based drugs have oligodynamic silver ions which enhance its antimicrobial properties. 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, human herpes virus 8, human papillom virus and epstein-barr virus BK and JC polyomaviruses, respiratory syncytial virus, influenza viruses and parainfluenza viruses, fungemia rotavirus, cytomegalovirus 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. 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 isotonicb 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[23-33]

**Cancer Nano Vaccines**

Vaccine as a form of nano vaccine 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 nano vaccines. Cancer nano vaccines could be designed, manufactured and introduced into the human body to improve health, including cellular repairs at the molecular level.

The nano vaccines are so small that it can easily enter the cell; therefore, nano vaccines 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.[32]

**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.[33]

**Orthodontic Nanorobots**

Orthodontic nanorobots can directly manipulate the periodontal tissue, including gingival, periodontal ligament, cemental, and alveolar tissues, allowing rapid and painless tooth straightening, rotating, and vertical repositioning within minutes to hours. This is in contrast to current molar uprighting techniques, which require weeks or months to complete.

**Tooth Durability and Appearance**

In nano dentistry, sapphire, a nanostructured composite material, increases tooth durability and appearance. Upper enamel layers are replaced by coherently bonded artificial materials, such as sapphire. This material has 100–200 times the hardness and failure strength than ceramic. Like enamel, sapphire is somewhat susceptible to acid corrosion. Sapphire has the best-standard whitening sealant and can be used as a cosmetic alternative.

**Dentifrobots**

Properly configured dentifrobots could identify and destroy pathogenic bacteria residing in the plaque and elsewhere, while allowing the 500 or so species of harmless oral microflora to flourish in a healthy ecosystem.

Dentifrobots would also provide a continuous barrier to halitosis, since bacterial putrefaction is the central metabolic process involved in oral malodor.[34]

**Safety issues**

While nanomaterials and nanotechnologies are expected to yield numerous health and health-care advances, such as more targeted methods of delivering drugs, new cancer therapies, and methods of early detection of diseases, they also might have unwanted effects. The increased rate of absorption is the main concern associated with manufactured nanoparticles.

When materials are made into nanoparticles, their surface area:volume ratio increases. The greater specific surface area (surface area/unit weight) might lead to increased rates of absorption through the skin, lungs, or digestive tract, and might cause unwanted effects to the lungs, as well as other organs.

Apart from what occurs if non-degradable or slowly degradable nanoparticles accumulate in organs, another concern is their potential interaction with biological processes inside the body; because of their large surface, nanoparticles, upon exposure to tissue and fluids, will immediately absorb onto their surface some of the macromolecules they encounter.

However, the particles must be absorbed in sufficient quantities in order to pose a health risk. The large number of variables influencing toxicity means that it is difficult to generalize the health risks associated with exposure to nanomaterials; each new nanomaterial must be assessed individually, and all material properties must be taken into account. As the use of nanomaterials increases worldwide, concerns for worker and user safety are mounting.[35]

**Conclusion**

As with all technologies, nanotechnology carries a significant potential for misuse and abuse on a scale and scope never seen before.

Nano devices cannot be seen, yet possess powerful capabilities. They have the potential to bring about significant benefits, such as improved health, better use of natural resources, and reduced environmental pollution.

At present, applied nanotechnology to medicine and dentistry is in its infancy, with most of the research at the basic science level, as the field attempts to organize itself. As such, viable clinical applications are still years away, but despite this the current pace of development is impressive.

Nanotechnology has the potential to provide controlled release devices with autonomous operation guided by need. Applications of nanotechnologies in medicine are especially promising, and such areas as disease diagnosis, drug delivery targeted at specific sites in the body, and molecular imaging are being intensively investigated.

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