

The nano era in dentistry

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Abstract

Nanotechnology is a new transnational and transcultural development that is growing rapidly and pervasively. The potential impact of novel Nanodentistry Applications in disease diagnosis, therapy and prevention is foreseen to change oral health care in a fundamental way. This review presents a general overview of the novel nanomaterial and relevant advances of nanotechnology, focusing on promising dental applications. In particular, relevant applications are reported in Restorative dentistry, minimally invasive dental procedures, cancer diagnosis and treatment, molecular imaging and implant dentistry. Many applications are still in their infancy. An increasing number of products are currently under clinical investigation while some are commercially available.

Key words: Implants, minimally invasive, nanodentistry, nanomaterial, nanotechnology

INTRODUCTION

Nanotechnology, the science of the “small” is revolutionizing diverse areas of research product, development, manufacturing and commerce. At the nanoscale size, materials exhibit very different properties from materials of the same composition at a larger scale. Strength, conductivity, color and toxicity all change at the nanoscale and properties can change within the nanoscale as well.

There are two methods by which nanotechnology creates structures: Top down, or bottom up. ‘Top down’ involves reducing the size of an existing structure down to a nanoscale level. ‘Bottom up’ involves manipulating individual atoms and molecules into nanostructures more like traditional biology and chemistry.^[1] Every disease starts at the molecular level. Steps to prevent treat or reverse disease processes on injuries must begin at the same level. Working at nature's scale the nanoscale, researchers are

making exciting advances in applying nanotechnology to meet challenges in medicine and dentistry.

Nanodentistry is defined as the science and technology of diagnosing, treating and preventing oral and dental diseases, relieving pain, preserving and improving dental health using nanostructured material. There are varieties of new dental products available, ranging from implants to oral hygiene products that rely on nanoscale properties. The application of Atomic Force Microscopy (AFM) and Optical interferometry to a range of dentistry issues, including characterization of dental enamel, oral bacteria, biofilms and the role of surface proteins in biomechanical and nanomechanical of bacterial adhesions, is being reviewed. Nanodentistry developments such as saliva exosomes based diagnostics, designing biocompatible, antimicrobial dental implants are revolutionizing the field.^[2]

Although the field of Nanodentistry is still developing and many issues are still to be resolved, the new era of nanotechnology in dentistry could change a common man's view of dentist. It encourages the concept of minimally invasive dentistry, creating a more dentist friendly atmosphere. However, patient awareness and education is important to make them understand the developments in the field and the options available in the treatment.

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BACKGROUND

Richard Feynman proposed the direct manipulation of individual atoms as a more powerful form of synthetic chemistry.^[3]

In 1974, the term nanotechnology was defined by *Norio Taniguchi* as consisting of the processing, separation, consolidation and formation of material by one atom or one molecule.^[4]

The field started to develop in 1980s with the birth of cluster science and the development of Scanning Tunneling Microscope. *Eric Drexler* popularized nanotechnology in 1986 in his book “Engines of Creation: The coming era of Nanotechnology.” Nanotubes, Nanowires and Nanoparticles have been developed and are under investigation for possible uses in everyday areas, including medicine.^[5]

Potential applications in dentistry

Studying dental structures and surfaces from a nanoscale, perspective may lead to better understanding about the structure, function – physiological relationship of dental surface. Using nanocharacterization tools, a variety of oral diseases can be understood at the molecular and cellular level prevented in that way. Nano enabled technologies, thus provided an alternative and superior approach to assess the onset or progression of diseases, to identify targets for treatment intervention, as well as the ability to design more biocompatible microbe resistant dental materials and implants.^[2] Advanced nanocharacterization technology relevant for the elucidation of underlying physio-chemical mechanism favoring biocompatibility and osseointegration of dental implants.

Novel nanomaterials

Nanomaterials include nanoparticles, nanoclusters, nano-crystals, nanotubes, nanofibres, nanowires, nanorods, nanofilms etc., To date numerous nanofabrication technologies such as electro spinning, phase separation, self-assembly processes, thin film deposition, chemical vapor deposition, chemical etching, nano-imprinting photolithographic, are available to synthesize nano materials with ordered or random nanotopographies.^[6]

State-of-art restorative dentistry

The ever-shrinking size of the Nanoparticles in Resin-based composite (RBC) ceramic restorative systems might be envisioned as ‘mimicking’ actual structure.^[7] Nano composite system (1 nm-100 nm) in size has the potential to enhance the adhesion, and provide a stable and natural interface between the mineralized hard tissues of the tooth and these advanced restorative materials.^[8]

Focus is being applied to reformulation of interfacial silanes, which are used to coat and bond inorganic fillers into RBC matrices in dental restoratives.^[7] Nanohybrid resins, nanofillers and nanoadhesives with improved mechanical, physical and chemical property are currently the ubiquitous examples of such technology.

Ormocer (an acronym for organically modified ceramics), represent a new technology based on Sol gel synthesis using particles comprising silicones organic polymers and ceramic glasses that are applicable to dental composites.^[9] Ormocer® (VOCO GmbH, Germany) composite technology is used in conjunction with nanoparticle fillers such as ZnO₂ that are widely used in nanocomposite restorative systems.

Silver nanoparticles are being used as an alternative to dental filling agents. The unique advantages of these nanoparticles are the anti wear; antibacterial and antifungal properties enable their use in restorative dentistry.^[10]

Nanorods, used in restorative dentistry have a structure similar to enamel rods. Enamel prism like hydroxyapatite (HA) nano rods have been created that show self-assembly properties, contributing to a practical artificial approximation of a naturally occurring structure.^[11]

Nanorobots—promoting minimally Invasive dental procedures

Inducing local anesthesia through nanodentistry will be possible in the coming years. A colloidal suspension containing millions of active analgesic’s dental nanorobot particles could be installed on the patient’s gingivae. These nanorobots after contacting the surface of the crown or mucosa reach the dentin by migrating into the gingival sulcus and pass painlessly to the target site. On reaching the dentin, the nanorobots enter the dentinal tubule that are 1 to 4 um in diameter and proceeds towards the pulp, guided by a combination of chemical gradient’s temperature differentials and positional navigation, all under the control of the onboard nanocomputer as directed by the dentist.^[12]

Orthodontic nanorobots could directly manipulate the periodontal tissues allowing rapid and painless tooth straightening, rotating and vertical repositioning within minutes to hours.

Dentine hypersensitivity is an acute pain condition that typically occurs when the surface of the root becomes exposed. Among the many approaches^[13] to treating dentine hypersensitivity, one primary approach is occluding dentine tubules, open tubules are sealed and isolated from external stimuli, preventing fluid movement from triggering a pain response.^[14]

Nanorobots can be used extensively in dentistry for procedures such as root canal fillings. They could be equipped with a miniature camera, which will enable to see the root curvature as well as the apical end of the root. They could also be used to clear out infection quickly and effectively. Carriers such as buckyballs could contain antibiotics to combat infection in the targeted area. The carriers could also carry stem cells into the empty root canal space to encourage the growth of new dental pulp and nerve cells; this would recreate the tooth to its natural form, fully functioning and vital as before.^[15]

Nanodentistry could play a vital role in natural tooth maintenance. The appearance and durability of teeth may be improved by replacing upper enamel layers with covalently bonded artificial materials such as sapphire or diamond,^[16] which has 20 to 100 times the hardness and strength of natural enamel, which have embedded carbon nanotubes.

A subocclusal dwelling nanorobotic dentifrice (Dentifrobots) delivered by mouth wash or tooth paste could patrol all supragingival and sub-gingival surfaces at least once a day, metabolizing trapped organic matter into harmless and odorless vapors and performing continuous calculus debridement.^[17]

The driving force nowadays is to make surgery progressively less invasive. The benefits of minimally invasive surgery are decreased injury to tissues and so less scarring, fewer complications, less post-operative pain and faster rehabilitation.^[18] The new set of tools of the nanoscale such as diamond scalpels with a cutting edge of only a few atoms (approx $\times 3$ nm) makes the operative procedure minimally traumatic. Use of titanium alloyed with nanocomposite of aluminium or vanadium surgical instruments, which are corrosive resistant, prevent contamination and spread of infection. A surgical nanorobot, programmed or guided by a human surgeon, could act as a semi-autonomous onsite surgeon inside the human body, when introduced into the body through vascular system or cavities.^[19] Femtosecond lasers used in the surgeries, act like a pair of nanoscissors by vaporizing tissue locally while leaving the adjacent tissues unharmed.^[20]

Enhancing new possibilities in diagnosis and treatment of cancer

Patients with head and neck cancer require staging assessments, invasive treatments and post-treatment monitoring with physical examination, and routine imaging. Nanotechnology appears balanced to provide devices, capable of sensitive and specific anatomic, molecular and biologic imaging; selective therapy of tumors; and low

toxicity, resulting in a significant improvement over the current standard of care.^[21]

Multi-functionality is the key advantage of Nanoparticles over traditional approaches. Targeting ligands, imaging labels, therapeutic drugs, and many other functional modalities can be integrated into the Nanoparticles to allow for targeted molecular imaging and molecular therapy of cancer.^[22] The nanomaterials have the inherent advantage of possessing unique functional properties for cancer detection and treatment. Nanomaterial is classified in the size domain of proteins and cells. Hence, they have been used as biological tags by interfacing the Nanoparticles with biocompatible molecules (biological, small organic molecules or bioinorganic interface).^[23] Different kinds of Nanoparticles suitable for drug and gene delivery probing DNA structures, etc., exist. They include liposomes, polymeric Nanoparticles (Nanospheres and nanocapsules, solid lipid particles, nanocrystals, polymer therapeutics such as dendrimers, fullerenes and inorganic Nanoparticles, e.g., gold and magnetic Nanoparticles).

Dendritic polymeric nano devices can detect cancer cells, identify cancer signature, and provide targeted delivery of anti-cancer therapeutics.^[24] Carbon nanotubes scan down DNA, and look for single nucleotide polymorphism.

Nanowires having the unique properties of selectivity and specificity, can be designed to sense molecular markers of malignant cells. Nanoparticles contrast agents are being developed for tumor detection purposes such as nuclear magnetic resonance imaging.^[24]

Whereas several Nanoparticles have been developed, plasmonic gold Nanoparticles appear interesting because of their facile surface chemistry, relatively limited toxicity, and novel optimal properties useful for concurrent imaging and therapy. Gold nanotechnology brings forth ultra sensitive optical imaging and multiple therapeutic options that may be used in unison. Gold Nanoparticles can be applied therapeutically for photo-thermal therapy,^[25] intra-vascular drug/gene delivery^[26] and ionizing radiation enhancement.^[27]

Nanotech based cancer therapeutics and diagnosis, over the past decade, has evolved from nano-sized drug particle to functional nanomaterial that are capable of delivering heat, ionizing radiation and chemotherapeutic agents. By incorporating multidisciplinary engineering innovation in nanotechnology, an avenue for development of enhanced, miniaturized and low cost diagnostic/imaging instruments and treatment machines are opened.^[28] The future possibility of tackling “pain the bitter side of cancer

therapy,” through nanotechnology would be considered one of the biggest break through achievement.^[29]

Biomimetic tools for tissue engineering

Tissue engineering consists of three components: Cells, growth factors and Scaffolds. Cells re-populate the damage/missing tissue or organ. Growth factors, which are natural, physiological molecules that interact with cells and direct them to express specific proteins and acquire particular functions. Scaffold which acts as a support for the growth of cells and ensures that the correct form of replaced tissues is achieved.

Since natural tissues or organs are nanometer in dimension, and cells directly interact with (and create) nanostructured extra cellular matrices; the biomimetic features and excellent physio-chemical properties of non-material play a key role in stimulating cell growth as well as guided tissue regeneration. Currently, numerous researchers are trying to fabricate cyto-compatible biomimetic nanomaterial scaffolds, encapsulating cells (such as stem cells, chondrocytes and osteoblast, etc) for tissue engineering application.^[30]

Advances in implant dentistry

Dental implant therapy has been one of the most significant advances in dentistry in the past three decades. Osseointegration is widely accepted in clinical dentistry as the basis for dental implant success. Failure to achieve osseointegration can be attributed to one or more implant, local anatomic, local biologic, systemic or functional factors.^[31,32]

A dental implant system is a typical and excellent example of integrated product using multiple disciplines, including surface modification and surface physics and chemistry. The success and longevity of dental implants are strongly governed by surface characteristics.^[33] Three factors have become key areas for the development of improved implant device topography. Nanoscale surface structuring, which would optimize cell colonization; surface chemistry, which attempts to control and optimize the chemical surface properties of an implant material; and wettability, due to the observation that cell adhesion and subsequent activity are generally better on hydrophilic surfaces. Structuring and chemistry modification would require nanoscale processes while engineered nanomaterial would play a role in increasing wettability.^[34]

Nanostructured biocompatible coatings

Nanostructured hydroxyapatite coatings for implant have attracted attention during the last decade. Hydroxyapatite promotes bone formation around implant, increases osteo-blasts function such as adhesion proliferation and mineralization. However, it is unlikely that bulk synthetic

hydroxyapatite will be used as load bearing implants, since fracture toughness ($\sim 1.0 \text{ m Pa} * \text{m}^{1/2}$) and flexural strengths ($<140 \text{ m Pa}$) are low (Ogiso *et al.* 1996). Currently, In-framat, Inc (Farmington, Connecticut, USA) is developing next generation nanostructured hydroxyapatite coating using a room temperature electrophoretic deposition technique. New families of “smart” nanophase (i.e. grain size less than 100 nm in at least one direction) coatings that will enhance bone integration and promote better device fixation are being developed by Spire Biomedical Inc. (Bedford Massachusetts, USA). These nanophase coatings are modified to selectively encourage hard tissue growth on implant while discouraging the format of soft-tissue growth that can result in implant failure.

Nanostructure metaloceramic coatings are in the early stage of development. A nanocrystalline multi-layer (Cr/CrTi/CrTiN) coating was deposited on Co-

Cr-Mo substrate.^[35] The Cr/CrTi metallic layer at the interface increases the adhesion to the Co-Cr substrate whereas CrTiN surface layer is covalent in nature, and enhances scratch resistance and wear of the coating. Nanoporous ceramic implant coatings use a different approach to improve implant properties, i.e. anodisation of aluminum. This technique was used to create a nanoporous aluminum layer on top of titanium alloy implants.^[36] Nanoporous alumina has the potential of being rendered by loading the porous structure with appropriate bioactive agents improving cell response and facilitate osseoinductive activity.^[37]

Titanium and Titanium alloys are novels which have been successfully used as dental implants because these materials have good integration with adjacent bone surface without forming a fibrous tissue interface. For the optimization of bone growth, surface treatment has been applied such as surface roughening by sand blasting, hydroxyapatite coating;^[38] formation of titanium dioxide or titania^[39] etc.

Growth factors and biomolecules can also be immobilized onto implants to enhance growth and integration. TiO₂ nanotubes produced by anodisation have been proposed as drug eluting coatings for implantable devices.^[40] The surface of the tubes can be functionalized to attach biomolecules, such as bovine serum albumin. Bone Morphogenic Protein (BMP) has been immobilized on the surface of Ti based implant to enhance bioactivity and bone formation.^[41] The advantage of immobilizing BMP is that it allows controlled administration and avoids the problems associated with overdosing. Implants have been coated with nanocrystalline diamonds to increase the surface area and facilitate immobilization of BMP.^[42] The differentiation and proliferation of cells without changing the overall texture of the specimen can be achieved using these diamonds.^[43]

Implant surface modifications

Several studies have suggested that materials with nanopatterned surface produce from various chemistries, such as metal polymers, composites and ceramics, exhibit better osseointegration when compared to conventional materials.^[44-46]

Nano-patterned surface provided a higher effective surface area and nanocavities when compared to the conventional micro-rough surfaces. These properties are crucial for the initial protein adsorption that is very important in regulating the cellular interactions on the implant surface.

Among all engineering based implant surface modifications the CaP, coating has received significant attention.^[47] This material has chemical similarity to the natural bone. Biomimetic CaP coatings improve the osseointegration of implants and show promising slow delivery systems for growth factors and other bioactive molecules.^[48]

The goal of nanotechnology is to build active and intelligent implants and structures that will interact with their surroundings, respond to environmental changes, deliver appropriate molecules or drugs and actively direct cellular events.^[49] However, the extrapolation of the techniques used for the fabrication of dental implants, to ensure that these features are robust enough to survive implantation, the reliability of test performed in vivo effect of nanoscale manipulation are still open technological challenges.

Safety issues

Although benefits of nanotechnology are widely publicized, and their widespread use is just beginning, concerns are being raised relating to the safety of non-material in a variety of products. Nano particles have a large surface area volume ratio. The greater the specific surface area, the more chance it could lead to increased rate of absorption through the skin, lungs or digestive tract. This could cause un-wanted effects in the lungs and other organs throughout the body, as non-degradable Nanoparticles could accumulate.^[15]

Most nanosized spherical solid materials will easily enter the lungs and reach the alveoli.^[50] This primary toxic effect is to induce inflammation in the respiratory tract, causing tissue damage and subsequent systemic effects.^[51] Transport to the blood stream to other vital organs or tissues throughout the body may result into cardiovascular and other extra pulmonary effect.^[52] Penetration via skin might facilitate the production of reactive molecules that could lead to cell damage.

In view of the fact that many non-material, new or miniaturized bulk particles are ready to enter the market,

it is probably wise that authorities and legislators support fundamental research to construct a scientifically valid, low-cost, fast-throughput toxicity test battery to screen non-material for toxicity and bio persistence.

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