Current applications of nanotechnology in dentistry: a review

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With the increasing demand for advances in diagnosis and treatment modalities, nanotechnology is being considered as a groundbreaking and viable research subject. This technology, which deals with matter in nanodimensions, has widened our views of poorly understood health issues and provided novel means of diagnosis and treatment. Researchers in the field of dentistry have explored the potential of nanoparticles in existing therapeutic modalities with moderate success. The key implementations in the field of dentistry include local drug delivery agents, restorative materials, bone graft materials, and implant surface modifications. This review provides detailed insights about current developments in the field of dentistry, and discusses potential future uses of nanotechnology.

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The term *nanotechnology* is derived from the Greek word *nanos*, meaning dwarf. The Nobel Prize winning physicist, Richard P. Feynman, during his 1959 *Plenty of Room at the Bottom* speech to the American Physical Society, had first projected this dimension of discoveries at a billionth meter scale.[1] The term nanotechnology was introduced by Norio Taniguchi in 1974, when he referred to a "production technique to get extra high accuracy and ultra-fine dimensions."[2] Later in 1986, K. Eric Drexler contributed to its development by introducing the concept of molecular nanotechnology in his 1986 publication, *Engines of creation: the coming era of nanotechnology.*[3] Applications in the field started in the 1980s with the invention of the scanning tunneling microscopes and the discovery of carbon nanotubes and fullerenes.[4-6] However, major initiatives began at the beginning of this century, thus ushering in the era of nanotechnology.

According to the *National Nanotechnology Initiative*, a United States government research and development program, nanotechnology involves the

> *…research and technological development at atomic, molecular, or macromolecular levels, in the length scale of approximately 1-100 nanometer (nm) range, with creation and use of structures, devices, and systems that have novel properties and functions as a result of their small and/or intermediate size; and ability to control or manipulate matter on the atomic scale.*[7]

Nanotechnology involves the development of materials, devices, and systems exhibiting properties that are different from those found on a larger scale. In the nanodimension range of 1-100 nm, the lower limit is marked by the size of a hydrogen atom (0.25 nm) and the upper limit commences from a size where phenomena different from larger structures start appearing. In layman's terms, if a child's marble is compared to a nanometer, a meter would appear as the earth's diameter.

This novel scale of technology has appealed to researchers of various fields including medicine and dentistry. An overview of the general applications of nanotechnology will provide a better understanding of the concept. However, this review will focus on the current applications of nanotechnology in dentistry, and the novel materials and techniques that have been developed using its principles for disease diagnosis, prevention, rehabilitation, and pulp/periodontal regeneration.

A brief insight into general developments

Current nanotechnological research falls under 2 approaches. The bottoms-up approach deals with the creation and development of new 'intelligent' materials or devices, wherein various processes are utilized to induce nanostructures to self-assemble at a desired scale and then organize into higher macroscale structures.[8,9] Various particles formulated at the nanoscale include nanorods, nanotubes, quantum dots, fullerenes, liposomes, and nanocapsules. The top-down approach deals with the enhancement of existing materials, where the existing structures are contracted and miniaturized into the nanorange with their molecules consecutively rearranged to achieve the desired properties.[8,9] Research in the medical sector is directed toward the development and application of nanodevices in the sphere of diagnostics, drug delivery, and therapeutics.

The diagnostic discipline emphasizes the manufacture of new sensing devices, and the *nanotization* of existing devices, to make them more compact and less invasive. This includes the development of collection and analyzing platforms for mass identification of diseases and their associated markers. Various in vivo nanomeric diagnostic devices, which can be easily introduced into the human body, have been developed either *de novo* or as design alterations of existing devices. Once inside the vascular system, subsequent directions can be provided to the devices via specific surface targeting molecules that can identify the required tissue receptors. These proposed novelties are being researched and tested for any secondary fallouts or disadvantages. A list of diagnostic devices in Table 1 provides a brief introduction to their functioning and application.[10-13]

The in vitro systems act when a sample tissue or fluid has been harvested from the human system. The conventional in vitro diagnostic aids, such as mass

Table 1. A brief description of nanotechnological in vivo diagnostic devices.[10-13]

Nanodevices	Functioning mechanism and applications
Special sensor nanobots	These are nanorobots, which can be inserted through the skin into the blood vessels, where they check blood contents and warn of an abnormal variation, such as hyperglycemia.[10]
Quantum dots	These are nanometer-sized semiconductor crystals that glow when illuminated by ultraviolet light. Their linkage to antibodies against specific cancer proteins enables sensitive detection of cancer cells.[11]
Superparamagnetic iron oxide nanoparticles (SPIONs)	These are multilayered polymeric shells with an iron oxide core. These shells can carry contrast agents with different aqueous solubilities. Specific surface anti-nucleosome antibodies help identify targeted tumor sites, where the compromised clearance mechanisms of the tissues help in their retention and improved MRI imaging.[12]
Nanopunch	This is a paramagnetic biopsy tool consisting of layered copper, nickel, silicon, and chromium, in the shape of a claw. With temperature change, the differing coefficients of expansion cause the claw to open and close to collect the specimen. Once tissue is harvested from the site, the punch could be collected from the urine sample by a magnetic trap.[13]

Table 2. Drug delivery devices.[4,6]

Nanotubes	• First described by Iijima in 1991[6] • Sheets of graphene that can be rolled into hollow cylinders
Carbon fullerenes	• First described by Kroto et al in 1985[4] • Insoluble hollow spheres of carbon, also known as *buckyballs*
Magnetic nanoparticles	• Dual core particles acting via thermal exchange coupling • Can be coated with drug particles in a lipid layer
Lipid nanoparticles	• Biodegradable drug-filled lipid particles without an outer coating • Can penetrate stratum corneum

spectrometry (MS), have been modified with the addition of nanomeric particles on MS planar surfaces (nanotexturing).[14] Relatively newer systems include nanoparticle bar codes and nanomechanical cantilevers that employ the application of magnetic field and optical beam deflection, respectively, in order to interpret biomolecular interactions.[15]

Currently, various nanoparticles suitable for drug and gene delivery are being designed and tested for safety, control, and appropriate use. Drug delivery systems are therapeutic arrangements that can control the release of drugs and deliver the medications optimally (Table 2). One such agent, nanotubes, are open-ended barrels that can carry minute quantities of drugs within their 50-100 nm wide drug cell. The open ends of these tubes are covered with pH or thermosensitive caps, which break down upon reaching inflamed sites.

Similarly, carbon fullerenes and polymeric nanoparticles can also be formulated as drug delivery vehicles.[16,17] These carriers possess antibody-modified surfaces, which enable drug delivery to specific target sites that are inaccessible to carrier-free drugs.[17] Recently, 2-layered iron oxide magnetic nanoparticles were used in an animal study for cancer tissue destruction.[18] After these nanoparticles are injected into tumors, and a magnetic field is applied, exchange coupling takes place between the 2 layers, resulting in locally increased temperature which can potentially destroy the cancer tissue.

Apart from these particles, an innovation in existing transdermal drug delivery systems is being developed in the form of nanostructured lipid carriers. These physiological lipid nanospheres are biodegradable, and exhibit both reduced toxicity and increased penetrability. They improve the shelf life of photosensitive compounds by enhancing their chemical stability.[19,20] The inclusion of nanospheres encapsulating local anesthetic agents within carrier vehicles could help direct the drug to the desired delivery site and prolong its effect, thereby reducing its toxicity.[21,22] The aforementioned systems are only a few of the many currently being researched.

The field of dentistry is receiving unprecedented support from the biotechnological sector, in the form of novel innovations that include improvised diagnostic aids and treatment devices. Current dental research involves progressive ingress into the preventive, diagnostic, reconstructive, regenerative, restorative, and rehabilitative domains (Chart).

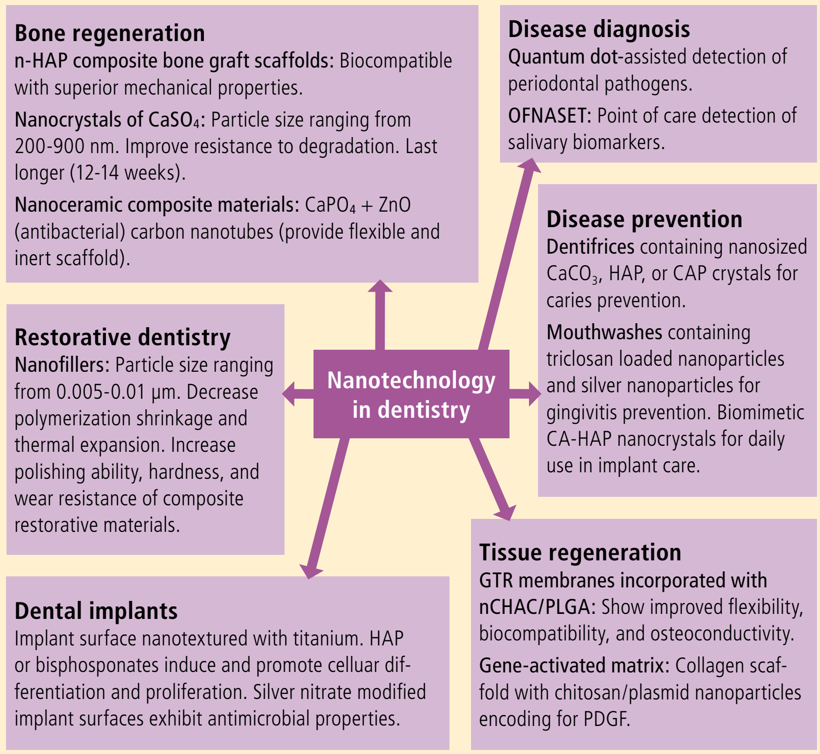
Diagnostic dentistry

Dental caries and periodontal disease are the most common maladies affecting the human race. Methods to prevent and combat them have been devised, discussed, and implemented since ancient times. However, there is a constant need for improved tools and techniques. Nanotechnology, with its ever-increasing scope, provides dental research new opporunities for progress.

Biofilms are considered the root cause of most dental and periodontal diseases. Specific pathogenic microorganisms have been associated with the development of dental caries and plaque-induced periodontal infections. Technology employing nanosized quantum dots based on immunofluorescence enables the labelling of specific bacteria, which eases their identification and removal. This technique provides excellent single cell resolution for both in vivo and in vitro labeling of periodontal pathogens.[23]

Apart from dental caries and plaque-induced periodontal disorders, the oral cavity is often afflicted by autoimmune disorders and carcinomatous changes. Highly sensitive diagnostic techniques involving better revelations of autoantibodies, dysplastic cells, and salivary biomarkers are required for apt diagnosis and early treatment. Cost-effective technological advancements on this front will help promote a widespread implementation of salivary diagnostics. The Oral Fluid Nano Sensor Test (OFNASET, The Wong Lab, University of California, Los Angeles) is a highly sensitive, specific, portable, and automated nanoelectromechanical system, which enables point-of-care detection of salivary proteomic biomarkers and nucleic acids specific for oral cancer, including 4 mRNA biomarkers (SAT, ODZ, IL-8, and IL-1β) and 2 proteomic biomarkers (thioredoxin and IL-8).[24]

Chart. Current applications of nanotechnology in dentistry.



Abbreviations: CaCO3, calcium carbonate; CA-HAP, calcium hydroxyapatite; CAP, carbonate apatite; CaSO4, calcium sulphate; GTR, guided tissue regeneration; HAP, hydroxyapatite; nCHAC/PLGA, nanocarbonated hydroxyapatite/collagen/polylactic-co-glycolic acid; NHAP, nanocrystalline hydroxyapatite; OFNASET, Oral Fluid Nano Sensor Test; PDGF, platelet-derived growth factor; ZnO, zinc oxide.

Preventive dentistry

In the sphere of preventive plaque control measures, dentifrices and mouthwashes form the most widely used products. Dentifrices can be incorporated with specific agents that help prevent dental caries, remineralize early carious lesions, and aid in desensitization of abraded teeth. The process of enamel remineralization is governed by the local concentration of apatite minerals. Nanosized calcium carbonate particles or hydroxyapatite crystals are similar to the morphology and crystal structure of enamel.[25] In a study of a test dentifrice containing nanosized calcium carbonate particles, Nakashima et al found 48.8% improvement on the remineralization of artifically produced subsurface enamel lesions.[26] Dentifrices for dental hypersensitivity that incorporate nanohydroxyapatite (n-HAP) or nanocarbonate apatite (n-CAP) particles are currently being tested. n-CAP is similar to the inorganic component of teeth and is known to have a high solubility and a more neutral pH. When compared to conventional agents, n-CAP has proven to be an efficacious short-term desensitizing dentifrice.[27]

Mouthwashes containing nanoparticles loaded with triclosan and silver nanoparticles have demonstrated plaque control potential. The colloidal suspensions of triclosan nanoparticles have shown high substantitvity due to the use of bioadhesive polymers in the system.[28] This technology is based on a polyanhydride bioadhesive nanoparticulate platform, which ensures high mucoadhesive capacity for 8 hours, increased encapsulation capacity, a more homogenous particle size (250 nm), and longer shelf life (2 years).[29] This creates a controlled-release system with bioadhesive properties due to the presence of a positively charged surfactant on the microparticle surface. This system can be incorporated into gels, toothpastes, and mouthwashes for the treatment and prevention of periodontal diseases.[30]

Apart from regular dental care, there has been nanotechnology research into implant care and the prevention of peri-implant diseases. Mouthwashes containing biomimetic carbonate-hydroxyapatite nanocrystals have been shown to preserve the implant titanium oxide layer by protecting it against surface oxidative processes. These nanocrystals also reduce implant surface roughness by depositing hydroxyapatite into the streaks present on the titanium surface. This decrease in surface roughness provides better prevention against plaque accumulation and peri-implant pathologies.[31]

Restorative dentistry

The incorporation of nanofiller particles in composite resins has given rise to a new class of materials with improved properties over micro- and macrofilled composites. Nanofillers reduce the polymerization shrinkage and thermal expansion, and enhance the polishing ability, hardness, and wear resistance of composites.[32,33] The size of these particles range from 0.005-0.01 µm. At this size, the optical properties of the resin and the filler particles become a fraction of the wavelength of light. Consequently, these particles cease to reflect back light, resulting in a more physiologic color expression by the material. The bottoms-up approach is required for the production of nanofiller particles. Two different types of nanofillers, nanomers (5-75 nm) and nanoclusters (2-20 nm) have been synthesized. Their incorporation into an existing resin matrix system has been shown to improve the optical and polishing properties of microfill composites and the strength of hybrid composites.[32]

An improvement has also been made to resin-modified glass ionomer cement (RMGIC) with the addition of nanosized fillers. This has been reported to improve the polishability and esthetic properties of the RMGIC.[34] The inclusion of nanofilled resins in posterior restorative GIC self-adhesive coatings has also demonstrated high hydrophilicity and protection against abrasive wear.[35] The low viscosity of the coating provides an optimal seal and glaze to the GIC surface, which gives time for the restoration to mature and increases its esthetic properties.[35] Thus, it could be stated that these improvements in filler technology can be used to develop new resin-based dental restoratives with enhanced mechanical properties.[36,37]

Regenerative dentistry

Bone grafting

Bone grafting has been the primary component of periodontal regenerative dentistry since 1923, when Hegedus successfully attempted the use of extraoral autogenous bone in the oral cavity to treat advanced pyorrhea.[38] Artificial bone substitutes were concomittantly developed in order to avoid the drawbacks of second site surgery and inconsistent graft quantity. Different alloplastic bone grafts are being developed with nanoscale particles. The most popular ones to date are nanoHAP (n-HAP) bone grafts, which are available in crystalline, chitosan-associated and titanium-reinforced forms.[39-41] These n-HAP composite bone graft scaffolds are highly biocompatible, have superior mechanical properties, and induce better cellular responses compared to 'plain' chitosan scaffolds.[42,43] A clinical study comparing the use of nanocrystalline HAP (NHAP) paste vs open flap debridement (control) in intrabony defects demonstrated clinically significant outcomes in the NHAP group, with a clinical attachment level gain of 3.6 ± 1.6 mm vs the control group's gain of 1.8 ± 1.2 mm.[44] This indicated that the use of an NHAP paste significantly improved the clinical outcome when compared to open flap debridement.

Apart from HAP, the use of calcium sulphate ($CaSO_4$) as a biodegradable and osteoconductive bone substitute has been utilized since 1892.[45,46] As $CaSO_4$ degrades, calcium phosphate forms, which helps in the attachment of osteoblasts and new bone deposition. Nanosized crystals of conventional $CaSO_4$ bone grafts have now developed, with particulate sizes ranging from 200-900 nm, while the conventional $CaSO_4$ bone graft particle size ranges from 30-40 µm. These nanoparticles are further condensed into pellets of 425-1000 µm. This nanotization of particles results in a graft material which is more resistant to degradation and lasts longer (12-14 weeks) than conventional $CaSO_4$ (4-6 weeks). This rate of degradation matches the rate of bone growth in the intrabony defects, resulting in better treatment outcomes.[47]

An antibacterial nanoceramic composite material has recently been developed by impregnating nanocalcium phosphate, walled carbon nanotubes, and zinc oxide (ZnO) nanoparticles into an alginate polymer matrix.[48] Carbon nanotubes provide a strong, flexible, and inert scaffold on which cells could proliferate and deposit new bone, while the ZnO nanoparticles provide the antibacterial properties. This material enhances HAP formation in bone defects.[48] The use of nanoparticulate bone grafts show promise in postextraction ridge preservation, intrabony defects regeneration, root perforations, sinus-lift procedures, implant dehiscence, and fenestration corrections.

Nanoparticles can also be designed—using ultrasonic assessment of the bone quality and structure—to simulate bone.[49] Current research is focused on generating nanoparticle composite and nanofiber scaffolds to increase mechanical strength and support cell growth and differentiation in required osseous architectures. Genetic material delivery systems that will encode for osteogenic growth factors are also being developed.[50]

Guided tissue regeneration

The concept of guided tissue regeneration (GTR) is being researched to replace earlier functional graded membranes with novel 3-layered membranes.[51] The former system included bilayered GTR membranes with a porous surface on one side (for cellular ingrowth), and a smooth surface on the opposite side (for cellular occlusion). A novel system has come up with a 3-layered GTR membrane composed of an innermost layer made of 8% nanocarbonated hydroxyapatite/collagen/polylactic-co-glycolic acid (nCHAC/PLGA) porous membrane, a middle layer of 4% nCHAC/PLGA, and an outer layer of PLGA nonporous membrane. These 3 layers combine to form a highly flexible, biocompatible, osteoconductive, and biodegradable composite membrane. When osteoblastic cells were cultured on this membrane, they showed a more positive response compared to a pure PLGA membrane.[51]

Tissue engineering

Recent events have generated research on new approaches to tissue engineering and local gene delivery systems in periodontal tissue regeneration. A gene-activated matrix (GAM) provides a platform to combine these 2 techniques. GAM provides a structural template for therapeutic gene expression and fills the defects for cell adhesion and proliferation, as well as the synthesis of extracellular matrix. A recent development in this aspect is a GAM composed of chitosan/collagen scaffold acting as a 3-dimensional carrier, incorporated with chitosan/plasmid nanoparticles that encode platelet-derived growth factor. This matrix demonstrated a sustained and steady release of condensed plasmid DNA over 6 weeks, which resulted in a high in vitro proliferation of cultured periodontal ligament fibroblasts, thus demonstrating potential for periodontal tissue engineering.[52]

Nerve regeneration

Nanoparticles can also be applied to reconstruct damaged nerves, with self-aggregating rod-like nanofibers called *amphiphiles*. Aggregated amphiphiles may reach up to several micrometers in length and can be utilized in vivo to bridge tissue defects in the spinal cord.[53] This application holds huge potential in the oral surgical arena, such as the possible reconstruction of a damaged inferior alveolar nerve after extensive oral surgical procedures.

Pulp regeneration

Nanotechnology has potential in the region of dental pulp regeneration. The development of tissues to replace diseased or damaged dental pulp can provide a revolutionary alternative to pulp removal. The α-melanocyte-stimulating hormone (α-MSH) is known to possess anti-inflammatory properties. Recently, it has been suggested that nanofilms containing α-MSH could help revitalize damaged teeth.[54] Further research is needed to evaluate these proposed therapeutic and regenerative approaches.

Rehabilitative dentistry

The introduction of dental implants has revolutionized the rehabilitative dental procedures. Various implant surface modifications are now being tested to improve the bone-to-implant contact ratio, mimic the cellular environment, and favor the process of osseointegration.[55] Surface characteristics determine the biocompatibility and biointegration of implants by regulating their surface energy, composition, roughness, and topography.[56] A nanostructured surface possesses a large fraction of defects, such as grain boundaries and dislocations, with a resultant texture that strongly influences the surface's chemical and physical properties.[56] Implants coated with nanotextured titanium, hydroxyapatite, or pharmacological agents such as bisphosponates may induce and promote cellular differentiation and proliferation. In a proposed topological modification for implants involving nanodot structures, Pan et al found that 50 nm-sized nanodots enhanced osteoblast cell population by 44%, minimized apoptotic-like cell death, and enhanced focal cell adhesion by 73%.[57]

Recently, trials have also been conducted to introduce antimicrobial bioactive implant surfaces. Nanostructured crystalline titanium dioxide coatings deposited by cathodic arc have exhibited ultraviolet (UV)-induced bactericidal effects against *Staphylococcus epidermidis,* with a 90% reduction of viable bacteria within 2 minutes of the UV dose.[58] Comparable antimicrobial results were also demonstrated by silver nitrate-loaded nanotitania surfaces and silver nanoparticle-modified titanium (Ti-nAg) surfaces.[59-61] Silver nanoparticles possess a broad-spectrum of antibacterial activity and a lower propensity to induce microbial resistance. Therefore these compounds can be used as effective growth inhibitors against various microorganisms.[30] Although the antibacterial mechanism of silver nitrate nanoparticles is yet to be clearly deciphered, their clinical usage might decrease the incidence of postsurgical peri-implant infections and potentiate therapeutic measures.[62]

Miniaturization: the downside of nanotechnology

The human race has always strived toward newer, more progressive technologies. Each new technology brings forth its share of specific advantages and disadvantages. Although nanotechnology is more than a decade old, no ecologic or toxic effects were reported before 2005.[63,64] Nanotoxicology is defined as a science that deals with the adverse effects of engineered nanodevices and nanostructures in living organisms.[65]

Techniques promising major breakthroughs in medical and dental sectors might also have a downside, and hence, must undergo stringent testing before human application. Some areas of concern include the unplanned entry of nanoparticles through the skin (via hair follicles), or through the respiratory tract, with the potential to penetrate vital organs.[66-68] Safety protocols should be formulated and practiced during the early innovative stages of engineered nanomaterials to proactively curtail the development of counterproductive devices.[69] Before commencing large-scale production of nanodevices, potential environmental hazards created due to waste generation should be considered. Further research is required to determine the mobility, reactivity, ecotoxicity, and persistence of nanoparticles in the environment.[70]

Conclusion

Nanotechnology is a relatively novel field, which involves manipulation of matter at the molecular level, including individual molecules and the interactions among them. It focuses on achieving positional control with a high degree of specificity, thereby achieving the desired physical and chemical properties. There has been an upsurge in interest in deciphering the property of matter at this dimension, thus making nanotechnology one of the most promising and influential areas of scientific research. The current applications of nanotechnology in various fields of dentistry have been reviewed in this article. These applications will pave the way for further research opportunities in device and drug development, thus commencing an era of unprecedented advances in dental diagnostics and therapeutics.

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Disclaimer

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References

1. Feynman RP. There's plenty of room at the bottom. *Eng Sci.* 1960;23:22-36.
2. Taniguchi N. *Proceedings of the International Conference on Precision Engineering (ICPE).* Tokyo, Japan. 1974:18-23.
3. Drexler KE. *Engines Of Creation: The Coming Era Of Nanotechnology.* New York: Anchor Press; 1986:99-129.
4. Kroto HW, Heath JR, O'Brien SC, Smalley RE. C60: buckminsterfullerene. *Nature.* 1985;318:162-163.
5. Kraetschmer W, Lamb LD, Fostiropoulos K, Huffman DR. Solid C60: a new form of carbon. *Nature.* 1990; 347:354-358.
6. Iijima S. Helical microtubules of graphite carbon. *Nature.* 1991;354:56-58.
7. United States National Nanotechnology Initiative. *National Nanotechnology Initiative.* Available at: http://www.nano.gov/. Accessed March 26, 2014.
8. Cyril NG, Lung K. *Where Will Nanotechnology Take us in the 21st Century?* Available at: http://www.ysjournal.com/temp/YoungScientissJ1634-3214608_085546.pdf. Accessed March 26, 2014.
9. Silva GA. Introduction to nanotechnology and its applications to medicine. *Surg Neurol.* 2004;61(3):216-220.
10. Yu B, Long N, Moussy Y, Moussy F. A long-term flexible minimally-invasive implantable glucose biosensor based on an epoxy-enhanced polyurethane membrane. *Biosens Bioelectron.* 2006;21(12):2275-2282.
11. Bhowmik D, Chiranjib, Chandira MR, Jayakar B. Role of nanotechnology in novel drug delivery system. *J Pharma Sci Tech.* 2009;1(1):20-35.
12. Mahmoudi M, Sant S, Wang B, Laurent S, Sen T. Superparamagnetic iron oxide nanoparticles (SPIONs): development, surface modification and applications in chemotherapy. *Adv Drug Deliv Rev.* 2011;63(1-2):24-46.
13. Nasir A. *Nanodermatology: A Bright Glimpse Just Beyond the Horizon - Part I.* Available at: http://www.skintherapyletter.com/2010/15.8/1.html. Accessed March 26, 2014.
14. Bakry R, Vallant RM, Najam-ul-Haq M, et al. Medicinal applications of fullerenes. *Int J Nanomedicine.* 2007; 2(4):639-649.
15. Cheng MM, Cuda G, Bunimovich YL, et al. Nanotechnologies for biomolecular detection and medical diagnostics. *Curr Opin Chem Biol.* 2006;10(1):11-19.
16. Yarin AL. Nanofibers, nanofluidics, nanoparticles and nanobots for drug and protein delivery systems. [abstract] Available at: http://www.scipharm.at/download.asp?id=692. Accessed March 26, 2014.
17. van Vlerken LE, Amiji MM. Multi-functional polymeric nanoparticles for tumour-targeted drug delivery. *Expert Opin Drug Deliv.* 2006;3(2):205-216.
18. Lee JH, Jang JT, Choi JS, et al. Exchange-coupled magnetic nanoparticles for efficient heat induction. *Nat Nanotechnol.* 2011;6(7):418-422.

19. Dubey A, Prabhu P, Kamath JV. Nano structured lipid carriers: a novel topical drug delivery system. *Int J Pharm Tech Res.* 2012;4(2):705-714.
20. Muller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv Drug Deliv Rev.* 2002;54(Suppl 1):S131-S155.
21. Tan JP, Tan MB, Tam MK. Application of nanogel systems in the administration of local anesthetics. *Local and Reg Anesth.* 2010;3:93-100.
22. Gorner T, Gref R, Michenot D, Sommer F, Tran MN, Dellacherie E. Lidocaine-loaded biodegradable nanospheres. I. Optimization of the drug incorporation into the polymer matrix. *J Control Release.* 1999;57(3): 259-268.
23. Chalmers NI, Palmer RJ, Thumm LD, Sullivan R, Wenyuan S, Kolenbrander PE. Use of quantum dot luminescent probes to achieve single-cell resolution of human oral bacteria in biofilms. *Applied Env Microbiol.* 2007; 73(2):630-636.
24. Gau V, Wong D. Oral fluid nanosensor test (OFNASET) with advanced electrochemical-based molecular analysis platform. *Ann N Y Acad Sci.* 2007;1098:401-410.
25. Vandiver J, Dean D, Patel N, Bonfield W, Ortiz C. Nanoscale variation in surface charge of synthetic hydroxyapatite detected by chemically and spatially specific high resolution force spectroscopy. *Biomaterials.* 2005;26:271-283.
26. Nakashima S, Yoshie M, Sano H, Bahar A. Effect of a test dentifrice containing nano-sized calcium carbonate on remineralization of enamel lesions in vitro. *J Oral Sci.* 2009;51(1):69-77.
27. Lee SY, Kwon HK, Kim BI. Effect of dentinal tubule occlusion by dentifrice containing nano-carbonate apatite. *J Oral Rehabil.* 2008;35(11):847-853.
28. BioNanoPlus Drug Delivery Technologies. *Antiseptic Mouthwash.* Available at: http://bionanoplus.com/antiseptic-mouth-wash.html. Accessed March 26, 2014.
29. BioNanoPlus Drug Delivery Technologies. *NANO GES.* Available at: http://bionanoplus.com/nano-ges.html. Accessed March 26, 2014.
30. Pragati S, Ashok S, Kuldeep S. Recent advances in periodontal drug delivery systems. *Int J Drug Deliv.* 2009; 1:1-14.
31. Lelli M, Marchisio O, Foltran I, et al. Different corrosive effects on hydroxyapatite nanocrystals and amine fluoride-based mouthwashes on dental titanium brackets: a comparative in vitro study. *Int J Nanomedicine.* 2013;8:307-314.
32. Mitra SB, Wu D, Holmes BN. An application of nanotechnology in advanced dental materials. *J Am Dent Assoc.* 2003;134(10):1382-1390.
33. Dresch W, Volpato S, Gomes JC, Ribeiro NR, Reis A, Loguercio AD. Clinical evaluation of a nanofilled composite in posterior teeth: 12-month results. *Oper Dent.* 2006;31(4):409-417.
34. Vaikuntam J. Resin-modified glass ionomer cements (RM GICs) implications for use in pediatric dentistry. *J Dent Child.* 1997;64(2):131-134.
35. Tanaka K, Kato K, Noguchi T, Nakaseko H, Akahane S. Change in translucency of posterior restorative glass-ionomer cements. [IADR Abstract 2025] Available at: https://iadr.confex.com/iadr/2007orleans/techprogramforcd/A89310.htm. Accessed March 26, 2014.
36. Furmann BR, Nicolella D, Wellinghof ST, et al. A radiopaque zirconia microfiller for translucent composite restoratives. [abstract] *J Dent Res.* 2000;79:246.
37. Youngblood TA, Nicolella DP, Lankford J, et al. Wear and select mechanical properties of a zirconia nanofilled resin composite. *J Dent Res.* 2000;79:365.
38. Hegedus Z. The rebuilding of the alveolar processes by bone transplantation. *Dent Cosmos.* 1923;65:736-742.
39. Singh VP, Nayak DG, Uppoor AS, Shah D. Clinical and radiographic evaluation of nano-crystalline hydroxyapatite bone graft (Sybograf) in combination with bioresorbable collagen membrane (Periocol) in periodontal intrabony defects. *Dent Res J (Isfahan).* 2012;9(1):60-67.
40. Reves BT, Jennings JA, Bumgardner JD, Haggard WO. Preparation and functional assessment of composite chitosan-nano-hydroxyapatite scaffolds for bone regeneration. *J Funct Biomater.* 2012;3:114-130.
41. Kailasanathan C, Selvakumar N, Naidu V. Structure and properties of titania reinforced nano-hydroxyapatite/gelatin bio-composites for bone graft materials. *Ceram Int.* 2012;38(1):571-579.
42. Chesnutt BM, Viano AM, Yuan Y, et al. Design and characterization of a novel chitosan/nanocrystalline calcium phosphate composite scaffold for bone regeneration. *J Biomed Mater Res.* 2009;88(2):491-502.
43. Chesnutt BM, Yuan Y, Buddington K, Haggard WO, Bumgardner JD. Composite chitosan/nano-hydroxyapatite scaffolds induce osteocalcin production by osteoblasts in vitro and support bone formation in vivo. *Tissue Eng Part A.* 2009;15(9):2571-2579.
44. Kasaj A, Rohrig B, Zafiropoulos GG, Willershausen B. Clinical evaluation of nanocrystalline hydroxyapatite paste in the treatment of human periodontal bony defects—a randomized controlled clinical trial: 6-month results. *J Periodontol.* 2008;79(3):394-400.
45. Greenwald AS, Boden SD, Goldberg VM, et al. Bone-graft substitutes: facts, fictions, and applications. *J Bone Joint Surg Am.* 2001;83-A(Suppl 2 Pt 2):98-103.
46. Kelly CM, Wilkins RM, Gitelis S, Hartjen C, Watson JT, Kim PT. The use of a surgical grade calcium sulfate as a bone graft substitute: results of a multicenter trial. *Clin Orthop Relat Res.* 2001;382:42-50.
47. Kathuria R, Pandit N, Jain A, Bali D, Gupta S. Comparative evaluation of two forms of calcium sulfate hemihydrate for the treatment of infrabony defects. *Indian J of Dent Sci.* 2012;4(2):30-36.
48. Beherei HH, El-Magharby A, Abdel-Aal MS. Preparation and characterization of novel antibacterial nano-ceramic-composites for bone grafting. *Der Pharma Chemica.* 2011;3(6):10-27.
49. Tautzenberger A, Kovtun A, Ignatius A. Nanoparticles and their potential for application in bone. *Int J Nanomedicine.* 2012;7:4545-4557.
50. Kim K, Fisher JP. Nanoparticle technology in bone tissue engineering. *J Drug Target.* 2007;15(4):241-252.
51. Liao S, Wang W, Uo M, Ohkawa S, Akasaka T, Tamura K, Cui F, Watari F. A three-layered nano-carbonated hydroxyapatite/collagen/PLGA composite membrane for guided tissue regeneration. *Biomaterials.* 2007; 26(36):7564-7571.
52. Peng L, Cheng X, Zhuo R, et al. Novel gene-activated matrix with embedded chitosan/plasmid DNA nanoparticles encoding PDGF for periodontal tissue engineering. *J Biomed Mater Res.* 2009;90(2):564-576.
53. Ellis-Behnke RG, Liang YX, You SW, et al. Nano neuro knitting: peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision. *Proc Natl Acad Sci U S A.* 2006;103(13):5054-5059.
54. Fioretti F, Palomares CM, Helms M, et al. Nanostructured assemblies for dental application. *ACS Nano.* 2010;4(6):3277-3287.
55. Simon Z, Watson PA. Biomimetic dental implants—new ways to enhance osseointegration. *J Can Dent Assoc.* 2002;68(5):286-288.
56. Nayar S, Bhuminathan S, Muthuvignesh J. Upsurge of nanotechnology in dentistry and dental implants. *Indian J Multidiscipl Dent.* 2011;1(5):264-269.
57. Pan HA, Hung YC, Chiou JC, Tai SM, Chen HH, Huang GS. Nanosurface design of dental implants for improved cell growth and function. *Nanotechnology.* 2012;23(33):335703.
58. Lilja M, Forsgren J, Welch K, Astrand M, Engqvist H, Stromme M. Photocatalytic and antimicrobial properties of surgical implant coatings of titanium dioxide deposited though cathodic arc evaporation. *Biotechnol Lett.* 2012;34(12):2299-2305.
59. Cao H, Liu X, Meng F, Chu PK. Biological actions of silver nanoparticles embedded in titanium controlled by micro-galvanic effects. *Biomaterials.* 2011;32(3): 693-705.
60. Feng Y, Cao C, Li BE, Liu XY, Dong YQ. Primary study on the antibacterial property of silver-loaded nanotitania coatings [in Chinese]. *Zhonghua Yi Xue Za Zhi.* 2008;88(29):2077-2080.
61. Juan L, Zhimin Z, Anchun M, Lei L, Jingchao Z. Deposition of silver nanoparticles on titanium surface for antibacterial effect. *Int J Nanomedicine.* 2010;5:261-267.
62. Tolaymat TM, El Badawy AM, Genaidy A, Scheckel KG, Luxton TP, Suidan M. An evidence-based environmental perspective of manufactured silver nanoparticle in syntheses and applications: a systematic review and critical appraisal of peer-reviewed scientific papers. *Sci Total Environ.* 2010;408(5):999-1006.
63. Kahru A, Ivask A. Mapping the dawn of nanoecotoxicological research. *Acc Chem Res.* 2013;46(3):823-833.
64. Biswas P, Wu CY. Nanoparticles and the environment. *J Air Waste Manag Assoc.* 2005;55(6):708-746.
65. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology:an emerging discipline evolving from studies of ultrafine particles. *Env Health Perspect.* 2005;113(7):823-839.
66. Oberdorster G. Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. *J Intern Med.* 2010;267(1):89-105.
67. Kreyling WG, Semmler M, Erbe F, et al. Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. *J Toxicol Environ Health.* 2002;65(20):1513-1530.
68. Muller RH, Keck CM. Drug delivery to the brain—realization by novel drug carriers. *J Nanosci Nanotechnol.* 2004;4:471-483.
69. Som C, Nowack B, Krug HF, Wick P. Toward the development of decision supporting tools that can be used for safe production and use of nanomaterials. *Acc Chem Res.* 2013;46(3):863-872.
70. Simonet BM, Valcarcel M. Monitoring nanoparticles in the environment. *Anal Bioanal Chem.* 2009;393(1): 17-21.

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