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Abstract Nanodentistry is an emerging field with significant potential to yield new generation of technologically advanced clinical tools and devices for oral healthcare. Nanoscale topology and quantitative biomechanical or biophysical analysis of dental surfaces are of significant interest. In particular, using Atomic force microscopy techniques—diseases such as dental caries, tooth hypersensitivity, and oral cancer can be quantified based on morphological, biophysical and biochemical nanoscale properties of tooth surface itself and dental materials or oral fluids such as saliva. An outlook on future "nanodentistry" developments such as saliva exosomes based diagnostics, designing biocompatible, antimicrobial dental implants and personalized dental healthcare is presented. This article examines current applications of nanotechnology alongside proposed applications in the future and aims to demonstrate that, as well as a good deal of science fiction, there is some tangible science fact emerging from this novel multidisciplinary science.

Keywords Nano-characterization · Nanodentistry · Biofilms · Implants · Atomic force microscopy · Nanodentistry "top-down" and "bottom-up" · Nanorobots

Introduction

Emerging technologies and new nanoscale information have the potential to transform dental practice by advancing all aspects of dental diagnostics, therapeutics and cosmetic dentistry into a new paradigm of state-of-the-art patient care beyond traditional oral care methods and procedures. One of the key changes is the application of new research tools that have changed the size-scale of dental research. Studying dental structures and surfaces from a nanoscale perspective leads to better understanding of the structure function-physiological relationship of dental surfaces. Using nanocharacterization tools, a variety of oral diseases can be understood at the molecular and cellular levels and thereby prevented. Nano-enabled technologies thus provides an alternative and superior approach to assess the onset or progression of diseases, to identify targets for treatment interventions as well as the ability to design more biocompatible, microbe resistant dental materials and implants. This article aims to provide an early glimpse of nanodental applications alongside proposed applications in the future.

Historical Background

The history of nanotechnology is dotted with a certain amount of skepticism. Some people hold firmly that this is a brand new form of scientific evolution that did not develop until the late 1980s or early 1990s. Others have found evidence that the history of nanotechnology can be traced back to the year 1959. Still other scientists hold the belief that humans have unwittingly employed practical nanotechnological methods for thousands of years, perhaps even longer, for example in making steel, paintings and in vulcanizing rubber. Each of these processes rely on the properties of stochastically-formed atomic ensembles mere nanometers in size, and are distinguished from chemistry in that they don't rely on the properties of individual molecules [1]. Either way, as scientific development goes, nanotechnology is still a relatively fresh and new arena of scientific research.

The first mention of some of the distinguishing concepts in nanotechnology (but predating use of that name) was in 1867 by James Clerk Maxwell when he proposed as a thought experiment a tiny entity known as Maxwell's Demon able to handle individual molecules. The first observations and size measurements of nano-particles was made during the first decade of the 20th century. They are mostly associated with Richard Adolf Zsigmondy who made a detailed study of gold sols and other nanomaterials with sizes down to 10 nm and less. He published a book in 1914 [2]. He used ultramicroscope that employs the dark field method for seeing particles with sizes much less than light wavelength. Zsigmondy was also the first who used nanometer explicitly for characterizing particle size. He determined it as 1/1,000,000 of millimeter. He developed the first system classification based on particle size in the nanometer range [1, 2].

Conceptual Origins

The topic of nanotechnology was again touched upon by "There's Plenty of Room at the Bottom," a talk given by physicist Richard Feynman at an American Physical Society meeting at Caltech on December 29, 1959 [3]. Feynman described a process by which the ability to manipulate individual atoms and molecules might be developed, using one set of precise tools to build and operate another proportionally smaller set, so on down to the needed scale. It was not possible for us to manipulate single atoms or molecules because they were far too small for our tools. Thus, his speech was completely theoretical and seemingly fantastic. He described how the laws of physics do not limit our ability to manipulate single atoms and molecules. Instead, it was our lack of the appropriate methods for doing so. However, he correctly predicted that the time would come in which atomically precise manipulation of matter would inevitably arrive [3].

Prof. Feynman described such atomic scale fabrication as a bottom-up approach, as opposed to the top-down approach that we are accustomed to. The current top-down method for manufacturing involves the construction of parts through methods such as cutting, carving and molding. Using these methods, we have been able to fabricate a remarkable variety of machinery and electronics devices. However, the sizes at which we can make these devices is severely limited by our ability to cut, carve and mould. Bottom-up manufacturing, on the other hand, would provide components made of single molecules, which are held together by covalent forces that are far stronger than the forces that hold together macro-scale components. Furthermore, the amount of information that could be stored in devices build from the bottom-up would be enormous [3, 4].

The word assigned to this type of scientific advancement is known to have come from a article that was released in 1974 written from the Tokyo Science University. There, a student, Norio Taniguchi, coined the term "nanotechnology" in his article and the name stuck firmly from then on [5]. 'Nano-technology' mainly consists of the processing, separation, consolidation, and deformation of materials by one atom or one molecule. Since that time the definition of nanotechnology has generally been extended to include features as large as 100 nm. Nano derived from a Greek word for the Dwarf, is combined with a noun to form words such as nanometer, nanotechnology, or nanorobot. A nanometer is one billionth of a meter. Since it is not easy to visualise the scale of a nanometer, a comparison with objects of appreciable dimensions is helpful. If the height of an average human being were scaled from the stretch from the earth to the moon, then each person's atom would be about the size of the baseball (approx. 10 cms in diameter). A nanometer would then be about five baseballs in a row [6].

In nanotechnology, researchers look for ways to use microscopic devices entities to perform tasks that are being done by hand or with equipment. Tiny machines, known as nanoassemblers, could be controlled by computer to perform specialized jobs. The nanoassemblers could be smaller than a cell nucleus so that they could fit into places that are hard to reach by hand or with other technology [7].

Nanodentistry

Healthcare along with society on the whole, is facing a major revolution in the wake of ongoing technological developments in the field of nanotechnology. Nanodentistry will make possible the maintenance of near perfect oral health by employing nanomaterials, including tissue engineering, and ultimately, dental nanorobots [7, 8]. New potential treatment opportunities in dentistry may include: local anaesthesia, dentition renaturalization, and permanent hypersensitivity cure, complete orthodontic realignments during a single office visit, covalently bonded diamondised enamel, and continuous oral health maintenance using mechanical dentifrobots, to destroy bacteria in the mouth that cause dental caries or even repair spots on the teeth where decay has set in, by use of computer to direct these tiny workers in their tasks [7]. When the first micro-size dental nanorobots are constructed, dental nanorobots might use specific motility mechanisms to crawl or swim through human tissue with navigational precision, acquire energy, sense, and manipulate their surroundings, achieve safe cytopenetration and use any of the multitude techniques to monitor, interrupt, or alter nerve impulse traffic in individual nerve cells in real time. These nanorobot functions may be controlled by an onboard nanocomputer that executes preprogrammed instructions in response to local sensor stimuli. Alternatively, the dentist may issue strategic instructions by transmitting orders directly to in vivo nanorobots via acoustic signals or other means [6, 7].

Nanodentistry as Bottom-up Approach [8]

Inducing Local Anaesthesia In the era of nanodentistry a colloidal suspension containing millions of active analgesic micron-size dental robots will be instilled on the patient's gingiva. After contacting the surface of crown or mucosa, the ambulating nanorobots reach the pulp via the gingival sulcus, lamina propria and dentinal tubules. Once installed in the pulp, the analgesic dental robots may be commanded by the dentist to shut down all sensitivity in any particular tooth that requires treatment. After oral procedures are completed, the dentist orders the nanorobots to restore all sensation, to relinquish control of nerve traffic and to egress from the tooth by similar pathways used for ingress [6, 8].

Major Tooth Repair Nanodental techniques may evolve through several stages of tissue engineering procedures, tissue regeneration, and later involving the growth of whole new teeth in vitro. Mainly nanorobotics manufacture and installation of a biologically autologous whole tooth replacement that includes both mineral and cellular components will lead to complete dentition replacement therapy [9].

Nanoscale Observation of Dentine Surfaces and Collagen Network [10] Dental pain such as toothache is a commonly experienced problem and a major reason why patients visit the dentist, thus making the study of tooth enamel, dentine, and its collagen network a necessary endeavour. Microscopic tubes, called dentine tubules, run through dentine, from the pulp beneath, to the junction with the enamel above, down to the nerves. A major component of the organic material in dentine and bone is collagen. Observing the dentine surface structure and collagen networks at the nanoscope scale can help improve restorative and regenerative dentistry, collagen based materials in tissue engineering, and our understanding of disease processes related to bone weakness, such as osteoporosis. Atomic force microscopy is useful in studies of the collagen network and dentine surface changes caused by different chemical agents. The major advantages of AFM includes its ability to "zoom" in and out over the magnification range of both optical and electron microscopies, but under natural imaging conditions in liquid with minimal to no sample preparation, and can produce real-space quantifiable three dimensional images of the surfaces. Thus AFM based structural analysis of dentine and of its collagen components may be critical in understanding the structure of native, fully mineralized, skeletal substrates. This allows us to investigate the material and morphological properties of dental and other connective tissues such as bone in situ and enable early discrimination of various patho-physiological states and disease progression such as osteoporosis where skeletal tissue is mechanically weakened [10].

Dentine Tubules Blocking: To Alleviate Hypersensitivity [10] Dentine hypersensitivity is an acute pain condition that typically occurs when the surface of the root becomes exposed. When the gingiva has receded and cementum removed, the dentine tubules become exposed and opened and then fluid flow along these open tubules caused by mechanical, chemical or thermal stimuli can result in an uncomfortable pain response in the nerve fibers. Natural hypersensitive teeth have eight times higher surface density of dentinal tubules and diameter with twice as large than nonsensitive teeth. Among the many approaches of 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 [11]. AFM has recently been used to observe the effective occlusion of dentine tubules with a new Arginine–Calcium carbonate technology developed for treating sensitive teeth [10, 12]. A desensitizing prophylaxis paste (marketed in the United States as Colgate Sensitive Pro-Relief Desensitizing Paste, Colgate Palmolive, USA) with 8% arginine, calcium carbonate, and prophylaxis-grade silica, has been clinically proven to effectively plug and seal dentine tubules [12, 13]. AFM has shown to be a useful tool for the study of dentine surfaces and collagenous tissues that indicates its potential in understanding oral disease processes. Alternate modes of AFM also prove to be useful in studying dental surfaces, such as piezoresponse force microscopy (PFM) to differentiate between organic and mineral components on dental tissues with nanoscale resolution. Further research utilizing AFM's ability to simultaneously collect qualitative and quantitative analysis of dentine and collagen at the nanoscale should therefore prove essential in providing important insights on the effectiveness of oral treatments for periodontal disease prevention, disease progression, and development in collagen dependant materials such as bone, cartilage, tendons, skin, collagen-based materials in tissue engineering and biomedical device coating [10].

Dental Plaque-antimicrobial Agents for Prevention of Bacterial Biofilms Bacteria are the primary etiologic agents in periodontal disease. It is now well recognized that dental plaque is predominantly a complex bacterial biofilm. These diverse bacterial species have evolved to inhabit the environment of the tooth surface, gingival epithelium, and oral cavity since birth. Amongst these, *Streptococcus mutans* is widely considered to be the principal pathogen responsible for dental caries, one of the most prevalent infectious diseases afflicting humans. They form a well-organized community of bacteria that adheres strongly to dental surfaces and are embedded within an extracellular polysaccharide containing slime layer. *S. mutans* biofilms are usually more resistant to antimicrobial agents than other organisms, as they are encased in the extracellular matrix thereby impeding access of the agent to the bacteria and because the phenotypic changes themselves may render the bacteria more resistant.

However, much of the dental disease conditions, including dental caries, can be prevented by a simple yet effective measure of thorough daily control of dental plaque [14].A wide range of clinical studies has been presented over the years to develop effective strategies to prevent and control periodontitis, such as the effectiveness of therapeutic antimicrobial mouth rinses [15]. Studying bacterial biofilms is relevant to antimicrobial mouth rinse studies, as it enables critical assessments of its effect against the plaque biofilm under actual-use conditions rather than on less resistant organisms that may not be indicative of the mouth rinses effectiveness [14]. Visualization of bacterial cell surface architecture at nanoscale resolution and quantitative studies on biochemical and adhesion properties of bacterial biofilms using AFM provide unique data not measurable by standard optical microscopy [10]. AFM has been successfully applied to investigate nanometer-scale topographical changes resulting from the treatment of *S. mutans* biofilms to various mouth rinse treatments. So far, AFM is the major nanotechnology technique in use for analyses of cells and biofilm surfaces and can provide exquisite topographic imaging, coupled with detailed microphysical and nanophysical probing and characterization of biofilm surfaces [10].

Dental Implants: Structure, Chemistry and Biocompatibility Dental implantology has a long, well documented history reaching back over thousands of years from ancient times and initial modern reports in the early 19th century to the accidental discovery of osseointegration by Brånemark in 1952. In contrast to a simple mechanical approach where surface contact area and topography are the sole deterministic factors, it is essential to enhance bone bonding and improve stability. Implants using nanaotechnology can effectively expedite bone growth and increase predictability. Bioactive approaches such as osseointegration involve the direct physiochemical bond formation and most commonly involve the use of titanium implants. The addition of nano scale deposits of hydroxyapatite and calcium phosphate creates a more complex implant surface for osteoblast to form [16, 17]. Extensive research on the effects and subsequent optimization of microtopography and surface chemistry has produced ground-breaking strides in materials engineering such as the widely used Osseotite® dental implant (BIOMET 3i, Palm Beach Garden, FL), Straumann with SLActive, Astra Tech with its OsseoSpeed.

Sub-cellular Vesicles as Novel Biomarkers for the Detection of Oral Cancer No other oral diseases are as life threatening as oral and pharyngeal cancer. Worldwide oral cancer is the eleventh most common cancer [18]. Often, oral cancer is preceded by the presence of clinically identifiable premalignant changes. Dental professionals can play a crucial role by identifying these changes during regular once-a-year dental check-up as an effective method for reducing the incidence and mortality of cancer.

Saliva meets the demands for inexpensive, noninvasive and easy-to-use diagnostic medium containing proteomic and genomic markers for molecular disease identification [19]. A specialized class of biomarkers found in human saliva that has gained renewed interest is a unique type of sub-100 nm membrane bound secretory vesicles called “exosomes”. Exosomes are secreted by salivary glands epithelium and released into the salivary fluid via exocytosis. Exosomes possess cell type specific membrane and proteins enclosed in a lipid bilayer. Malignancy and other diseases cause elevated exosome secretion and tumor-antigen enrichment of exosomes associated with cancer cells. Due to their small size, sensitive and quantitative detection tools are needed for detection and characterization of salivary exosomes. Single vesicle structural and surface molecular details on human saliva exosomes considered as potential non-invasive biomarker resource for oral cancer have been studied recently using AFM [10].

Nanocomposites Microfill composites and core materials are manufactured using a “top-down” approach, which means the materials used to make them, such as ceramics, quartz and glasses, start out in bulk form and are pulverized in a grinding mill. However, the milling process cannot reduce the particle size below 100 nm. Conversely, because the particles in nanocomposite materials are so minuscule (1 nm = one billionth of a meter), they have to be synthesized using a “bottom-up” approach that starts at the molecular level; via various chemical processes, the molecules combine to form nanoparticles that are still much smaller than could ever be attained using a top-down manufacturing process.

So why are smaller particles in composite core materials better than larger ones? Because nanoparticles impart several distinct advantages. For example, particles exponentially smaller than the width of a human hair (think one millionth of a millimeter) help improve the material’s compressive strength. Filler particles in the sub-micron size range are also necessary to improve polishability and esthetics like zirconium dioxide [20]. However, strength tests reveal that for a material to possess the strength necessary to withstand fracture under the natural forces of mastication, the particles that make up the material composition must be variable in size. In other words, if all the particles are the same sub-micron size, the material will be brittle and more prone to cracking and fracture once it has cured.

This realization led to the advent of hybrid composites, or composites comprised of a wider distribution of filler particles. This created a better balance of strength and esthetics, but there was still one problem: nanoparticles tend to gravitate toward each other and end up sticking together to form clumps. The scientific term for this unwanted clumping is "agglomeration." The end result is an uneven distribution of particles within the resin matrix, which reduces the material's physical properties and contributes to weak spots. To combat this, the nanotechnology eliminates particle agglomeration by incorporating a proprietary coating process during particle manufacture. This eliminates weak spots for consistent strength throughout the entire "fill" of the core build-up.

Additionally, the even distribution of nanoparticles results in a smoother, creamier consistency and improves the flow characteristics of the material. And, once it is cured to its hardened state, these properties also contribute to the material's dentin-like cuttability and polishability.

Nanoproducts Corporation has successfully manufactured nonagglomerated discrete nanoparticles that are homogeneously distributed in resins or coatings to produce nanocomposites. The nanofiller used includes an aluminosilicate powder having a mean particle size of 80 ran and a 1:4 M ratio of alumina to silica and a refractive index of 1.508 [7]. Advantages include superior hardness, superior flexural strength, modulus of elasticity and translucency, 50% reduction in filling shrinkage and Excellent handling properties [7].Trade name: Filtek O Supreme Universal Restorative P Lire Nano O [8].

Nanosolution produce unique and dispersible nanoparticles, which can be used in bonding agents. This ensures homogeneity and ensures that the adhesive is perfectly mixed everytime [7]. The latest generation of bonding agents are self etching, one step materials. The silica nanofiller contributes to higher bond strength performance while providing a stable, dispersed, filled adhesive that prevents particle settling, eliminating the need to be shaken prior to use [7]. Trade name: Adper O Single Bond Plus Adhesive Single Bond [8].

Impression Materials Nanofillers are integrated in vinylpolysiloxanes, producing a unique addition of siloxane impression materials. The material has better flow, improved hydrophilic properties and enhanced detail precision [7]. Trade name: Nanotech Elite H–D [8].

Nanoencapsulation SWRI [South West Research Institute] has developed targeted release systems that encompass nanocapsules including novel vaccines, antibiotics and drug delivery with reduced side effects. At present, targeted delivery of genes and drugs to human liver has been developed by Osaka University in Japan 2003. Engineered Hepatitis B virus envelope L particles were allowed to form hollow nanoparticles displaying a peptide that is indispensable for liver-specific entry by the virus in humans. Future specialized nanoparticles could be engineered to target oral tissues, including cells derived from the periodontium (Yamada et al. 2003) [7, 8].

Other Products Manufactured by SWRI [8]

a. Protective clothing and filtration masks, using anti-pathogenic nanoemulsions and nanoparticles
b. Medical appendages for instantaneous healing
- Biodegradable nanofibres—delivery platform for haemostatic
- Wound dressings with silk nanofibres in development
- Nanocrystalline silver particles with antimicrobial properties on wound dressings [Acticoat™, UK]

c. Bone targeting nanocarriers: Calcium phosphate-based biomaterial has been developed. This bone biomaterial is an easily flowable, moldable paste that conforms to and interdigitates with host bone. It supports growth of cartilage and bone cells.

Bone Replacement Materials will assist in the repair and regenerations of cellular tissue in the bone. Hydroxyapatite nanoparticles [8] used to treat bone defects are

- Ostim® (Osartis GmbH, Germany) HA
- VITOSSO (Orthovita, Inc, USA) HA +TCP
- NanOSS™ (Angstrom Medica, USA) HA

Nanoneedles Suture needles incorporating nano-sized stainless steel crystals have been developed. Trade name: Sandvik Bioline, RK 91™ needles [AB Sandvik, Sweden]. Nanotweezers are also under development which will make cell-surgery possible in the near future [8].

Nanorobotic Dentifrice (dentifrobots) Subocclusal dwelling nanorobotic dentifrice delivered by mouthwash or toothpaste could patrol all supragingival and subgingival surfaces at least once a day, metabolising trapped organic matter into harmless and odorless vapors and performing continuous calculus debridement.

These invisibly small dentifrobots [1–10 μ], crawling at 1–10 μ/sec, would be inexpensive, purely mechanical devices, that would safely deactivate themselves if swallowed and would be programmed with strict occlusal avoidance protocol [8].

How Safe are These Nanorobots?

The nonpyrogenic nanorobots used in vivo are bulk Teflon, carbon powder and monocrystal sapphire. Pyrogenic nanorobots are alumina, silica and trace elements like copper and zinc. If inherent nanodevice surface pyrogenicity cannot be avoided, the pyrogenic pathway is controlled by in vivo medical nanorobots. Nanorobots may release inhibitors, antagonists or downregulators 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 [7, 8, 21].

Conclusion

Nanotechnology will change dentistry, healthcare, and human life more profoundly than many developments of the past. Nanotechnology holds promise for advanced diagnostics, targeted drug delivery, and biosensors making health care more effective and affordable. In the long-term, medical nanorobots will allow instant pathogen diagnosis and extermination, individual cell surgery in vivo, and improvement of natural physiological function. Molecular technology is destined to become the core technology underlying all of 21st century medicine and dentistry.

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