Cumhuriyet Dental Journal: 2021; 24(4)
e-ISSN 2146-2852
Doi:10.7126/cumudj.974945

Review

AN EXPLORATORY REVIEW OF CURRENT TRENDS IN NANODENTISTRY

ABSTRACT

Nanotechnology is a cutting-edge concept that is evolving manifolds in various fields of science and medicine and is by no means exceptional to dentistry. Nanotechnology is popularly known as the 'science of the small' that deals with particles of size 1-10nm. Methods like top-down or bottom-up approaches are used in manufacturing nanoparticles and nanorobots, catering to the needs of medical diagnostics and therapeutics. Nanorobotics advances medicine through miniaturization from microelectronics to nanoelectronics. Nanotechnology can be applied to all fields of dentistry such as to create nano implants, nano-drug delivery systems, nanocomposites and nano impression materials. Additionally, it helps in orthodontic tooth movement, alleviating hypersensitivity, and effective anesthesia. This paper highlights the various applications of nanotechnology in dentistry and also mentions the clinical trials performed to have a more focused approach to practicing nanodentistry. Apart from this the paper briefly explains the benefits of integrating artificial intelligence and nanotechnology for creating more personalized treatment options and also its role in Covid 19 vaccines.

Key words: Nanotechnology, artificial intelligence, nanoparticles, nanocomposite.

*Hima Bindu Reddy[1]
Jasmine Crena[1]
PSG Prakash[1]
Sangeetha Subramanian[1]
Devapriya Appukuttan[1]

ORCID IDs of the authors:
H.B.R.
J.C. 0000-0001-9788-3898
PSG.P. 0000-0003-4243-5865
S.S. 0000-0002- 9352-6081
D.A. 0000-0003-2109-1135

[1] Department of Periodontics, SRM dental college and Hospital, Ramapuram, Chennai, India.

Received : 05.08.2021
Accepted : 17.11.2021

How to Cite Reddy HB, Crena J, Prakash PSG, Subramanian S, Appukuttan D. An Exploratory Review of Current Trends in Nanodentistry. Cumhuriyet Dent J 2021;24:4:448-461.

***Corresponding Author:**
Department of Periodontics, SRM dental college and Hospital, Ramapuram, Chennai, India.
Phone: + 91 9940140992 **E-mail:** himabindu573@gmail.com

INTRODUCTION

Nanotechnology is popularly known as the 'science of the small' that deals with particles of size 1-10nm.[1] Richard Feynman introduced nanotechnology in the year 1959 and is considered the father of nanotechnology.[2] Nanomedicine is a field that is transforming the approach in diagnosis, treatment, prevention of diseases, alleviating pain, improving human health by using the molecular tools and molecular knowledge of the human body.

Nanoparticles in medicine can enter living cells effortlessly as they are much smaller than those used in chemical and industrial applications. There are two approaches to fabricate nanomaterials. The bottom-up approach creates nanoparticles from molecular components that self-assemble via molecular recognition, and the top-down approach builds nano-objects from larger entities.[3] Table 1 gives examples of nanomaterials fabricated through the two approaches.

Table 1. Nanomaterials fabricated through top-down and bottom-up approach.

Top-down approach	Bottom-up approach
Nanocomposites	Dentinal hypersensitivity
Nanosolutions	Nanodentifrices
Nanocapsulation	Local anesthesia
Bone replacements	Tooth repair
Impression materials	Tooth positioning
	Oral cancer diagnosis

Nanotechnology and dentistry

Similar to nanomedicine, nanodentistry has evolved multi-folds and has diverse applications in all fields of dentistry. It holds a good promise of providing personalized treatment options with improved efficacy and reduced side effects. In the past few years, numerous reviews have been done in the literature on nanodentistry. However, clinical trials focusing on the practice of nanodentistry are limited due to factors like cost, technique sensitivity, and obtaining similar results to other contemporary materials. Thus, we look forward to highlighting the clinical trials undertaken recently in the different fields of Dentistry in this exploratory review to have a more focused approach to practicing Nanodentistry rather than seeing it as a future perspective. Thus, Nanodentistry is not the future but is happening now, and let's look forward to becoming nanodentists.

Nanoparticles

Nanoparticles include particulate substances, which have a size of 100nm at least in one dimension. Nanoparticles are composed of three layers; the surface layer, shell, and core layer.[4] A variety of small molecules, metal ions, surfactants, and polymers make up the surface layer. The shell layer is a chemically different material from the core in all aspects, and the core is the central portion of the nanoparticle.[5] Based on the chemical and physical properties they can be classified as carbon-based nanoparticles, metal-based nanoparticles, ceramic-based nanoparticles, polymeric-based nanoparticles, lipid-based nanoparticles, semiconductor-based nanoparticles.[6] (Figure 1)

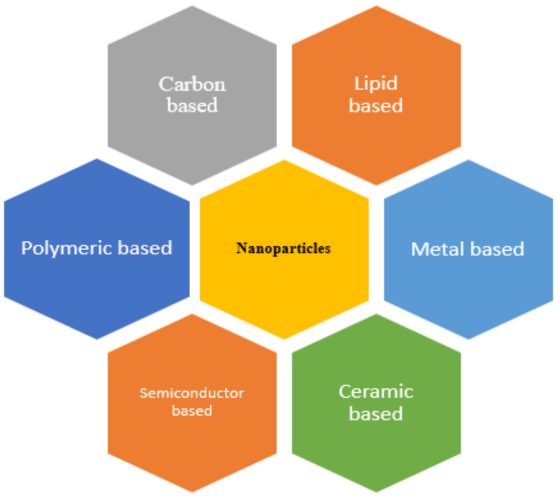

Figure 1. Classification of nanoparticles based on physical and chemical properties.

Nanorobots

Nanorobotics pioneered by Adriano Cavalcani is a technology which converts nanoparticles into miniature nanorobots.[7] These Nanorobots consist of carbon atoms in a diamondoid structure which include parts like Manipulator's gripper, Telescopic macromanipulator, Biomolecular Sensor, Acoustic Sensor, Antenna, Connector, and others as portrayed in figure 2 Nanorobots have inert properties, which evades the reaction of the immune system, thereby allowing them to have an unimpeded function.[1]

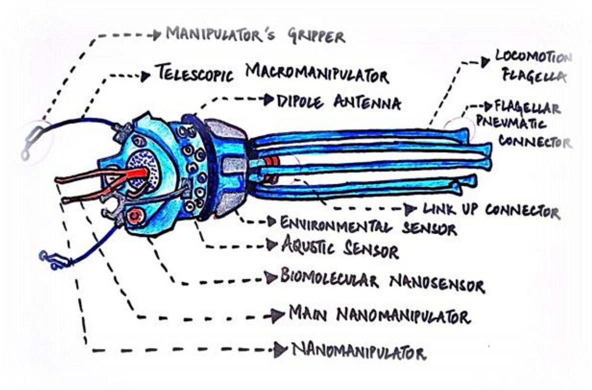

Figure 2. schematic diagram of a Nanorobot

They use glucose or natural body sugars and oxygen as a source for propulsion.[8] Each nanorobot could be modified with specific functions depending on the biochemical stimulus provided.[1] Nanorobots are expected to provide advances in medicine through miniaturization from microelectronics to nanoelectronics.[9] The application of nanotechnology in the field of Artificial intelligence is the future of science and this combined technology when integrated in the field of medicine would cater to improvise various setbacks in the diagnosis and the therapeutic aspects of medicine as well as in dentistry which has also been briefly explained in this article.

Recent Advances in Nanodentistry

Broadly materials used in medicine have been classified into 3 main avenues - diagnostics, drug delivery and bone grafts and implants.[10]

Nanodiagnostics

Oral fluid nanosensor test (OFNASET): has been recently introduced in the market to detect cancers through salivary biomarkers. OFNASET uses bionanotechnology, cyclic enzymatic amplification, and microfluidics self-assembled monolayers (SAM) which gives accurate results.[11]

Nanoscale cantilever: Another nanodiagnostic device that helps in the rapid detection of cancer-related molecules that are flexible in build and resemble rows of divided boards. The cancer-related molecules bind to the sensors in the device and cause conformational changes in shape.[12]

Nanopores and nanotubes: Nanopores help in efficient DNA sequencing by acting as a filter for DNA strands. Nanotubes are made of carbon that helps in detecting altered genes.[12]

Quantum dots (QD): They are nanocrystals that fluoresce when illuminated by ultraviolet light, made of semiconductor materials. They bind to proteins associated with cancer cells and therefore help with the detection of cancer. These fluorophores have unique photophysical properties that also overcome the limitations of using conventional dyes. They are also known to detect metastasis of cancer.[13]

Optical Nanobiosensor: It is a fiber-optic-based, compact analytical system that detects substances by producing a signal that is proportionate to the concentration of the measured substance. They contain a biological element such as an enzyme, protein, nucleic acid, or a receptor that recognizes the substance and passes it to the inbuilt optical transducer which in turn produces a signal. They are highly sensitive and specific devices and are cost-effective.[14]

Lab-on-a-chip methods: These are silicon chips with chemically activated beads embedded in them. They help in analysing and diagnosing various diseases by detecting biomarkers. They are cost-effective and require a small sample size.[15]

Nano CT: Nano CT one of the Diagnostic methods like micro CT have been used in dental applications like evaluation of various materials like composite using resolution of around 450 nm compared to micro CT evaluation which has a resolution of 2 µm. This clearly shows us that greater details of the ultrastructural properties could be evaluated. Thus nano diagnostics could be useful in effective and critical evaluation of biomaterials as well as their action in the respective sites could be studied in detail. In soft tissue evaluation contrast -enhanced nano CT reveals soft tissues like the ones stained with

Haemotaoxylin and Eosin stain of odontoblasts. The nano contrast CT involves the use of a specific contrast dye which depends on the tissue type and volume. One of the most important applications of nano CT is the 3D visualization of the dental tissues and subsequent spatial analyses, both descriptive and quantitative.[16]

Nano Drug Delivery systems

Oral infections are very complex diseases, thus requiring antimicrobial nano drug delivery systems to combat the same which aid in site-specific wound healing.

Nanoelectromechanical systems (NEMS) are devices integrating electrical and mechanical functionality on the nanoscale level.[17] They make use of motors, pumps or mechanical actuators to form a functional, biological and chemical nano systems. Bio-nanoelectromechanical systems (BioNEMS) are bio-hybrid systems that combine biological and structural elements on a nanoscale level. They include DNA or proteins combined with mechanical nanostructures. It can develop low-cost, biocompatible, and controlled drug delivery devices. It is available in both sustained and pulsatile delivery of the drug. It works as multiple reservoir-based devices, simultaneously delivering multiple drugs.[18] Figures 3 and 4 show drug delivery devices that work on an osmotic pump and spring-powered pump.

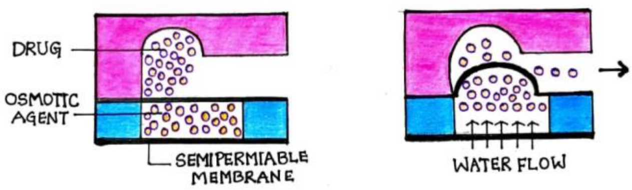

Figure 3. Osmotic pump

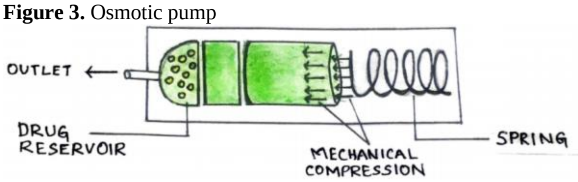

Figure 4. Spring powered pump

Nanoneedles and nanotweezers

Nano needles made of silicon are now being developed to aid in effective and sustained drug delivery. They are fabricated using various procedures such as Vapour– liquid–solid (VLS) growth of nanoneedles, Metal- assisted chemical etch of nanoneedles and Focused ion beam etch of nanoneedles. There are many types of nano needles such as solid, porous and hollow nano needles based on the loading and release characteristics of the needle.[19] Nowadays needles with nanosized stainless steel crystals incorporated into them are available commercially (Sandvik Bioline 1RK91™, Sandvik, smt.sandvik.com).[12]

Nanotweezers are nano devices which help in the construction of the human cell. Recent studies reported in literature shows that nanotweezers could be used to manipulate single organelles by trapping and extracting them from various parts of the body. These tweezers effectively interact with single cells thus helping us to understand their signaling pathways of interaction during an external stimuli.[20]

Nano coated Dental Implants

Dental implants have undergone various advances, however, share few drawbacks too. A major disadvantage for titanium alloy as oral implant material is relatively poor wear resistance. To overcome this drawback, nanostructured ceramic coatings such as TiN (titanium nitride) (Is this a ceramic material?), ZrO2/Al2O3, Si3N4/ TiO2, and ZrO2/SiO2 are used.[21]

Many studies have demonstrated increased function of osteoblasts on nanoparticles compared to conventional materials (Figure 5).

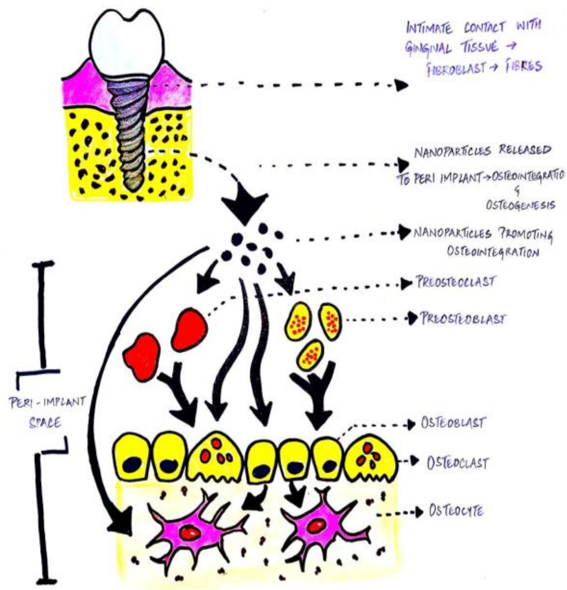

Figure 5. Nanoparticles promoting osseointegration.

Yao *et al.* created nanometer surface features on titanium and Ti6Al4V implants by anodization, a quick and relatively inexpensive electrochemical method. The results showed that the anodized surfaces had higher root-mean-square roughness at nanoscale dimensions than the unanodized Ti-based surfaces.[22] In addition blood clot retention and osseointegration is improved. Anodized Ti6Al4V dental implants show better results when placed in regions with poor bone quality or in cases with immediate loading protocol.[23]

The versatility of nanomaterials may allow the fabrication of implants with various porosities, pore shapes, and mechanical properties that can mimic the complex architecture of bone-specific sites to optimize bone tissue regeneration.[24] Table 2 summarizes the clinical trials done on nano implants.

Table 2. Clinical Trials on Dental Implants

Sl.no	**year**	**Author**	**Nanomaterial used**	**Clinical trial done**
1	2018	Zia Arshad Khan[25]	Nanopore surface implant	**Evaluation of peri-implant tissues around nanopore surface implants with or without platelet-rich fibrin: a clinicoradiographic, randomized clinical study** showed that the mean difference in the probing depth between the two groups was insignificant. Thus, it was concluded that additional graft materials would not be required when using a nanopore surface implant.
2	2010	Luigi Canullo [26]	e-PTFE membrane and nanostructured Mg-HAP	**Early implant loading after vertical ridge augmentation (VRA) using e-PTFE titanium reinforced membrane and nanostructured hydroxyapatite a 2- year prospective study** aimed to evaluate survival of implants, loaded 14 weeks after vertical ridge augmentation (VRA). It was concluded that VRA around rough surface implants using e-PTFE membrane and nanostructured Magnesium-Hydroxyapatite can be successful even in cases with early loading.

Graft materials

Nanotechnology enhances the characteristics of bone grafts by improving the uptake, biocompatibility, proliferation of the tissues, and pore size. An optimal interconnected porous network of micro and nanoscale features allows increased bone formation, cellular migration, proliferation and vascularization.[27]

Bone grafts essentially consist of scaffold, cells and extracellular matrix. Incorporation of carbon nanotubes and nanofibers enables the flexibility and strength, thus providing enhanced mechanical properties. Cellular adhesion through adsorption of proteins like fibronectin causes bone formation. The extracellular matrix thus formed shows increased vascularization, osteoblastic adhesion and also the resultant osseointegration providing a potential bone healing property.

Polyvinyl alcohol shows increased mechanical strength, excellent biocompatibility and less metallic impurities.[28]

Bionanocomposites have found application as scaffold matrix by way of their increased surface area to volume ratio, close contact to surrounding tissues, increased biocompatibility, osteoconductivity, cell adhesion properties, cellular proliferation.

Alginate infused with bioactive glass has been found to have increased biomineralization, protein adsorption properties, cellular adhesion and proliferation of human periodontal ligament fibroblasts.[29]

Other interesting facts were that of increased ALP activity of the human PDL fibroblast cells cultured on the scaffold.

Gelatin has shown to have excellent cell adhesive properties, high biocompatibility, biodegradability, low immunogenicity. In periodontal regeneration, scaffolds incorporated with nanoparticle on gelatin in the concentration of 2.5% gel /2.5% HA and 2.5% gel/ 5% HA have been shown to have properties such as cell attachment, proliferation of PDL fibroblast cells.[30]

Chitosan another nanobiocomposite has shown very minimal foreign body reaction. The positive cell surface charge has enabled cell growth, attachment, and cell differentiation.

A major advantage of chitosan is that when placed in hydrated environments, chitosan turns into a flexible material which is more rigid than materials like PLA, PGA. Studies have shown that use of a combination of chitosan along with bioactive glass nanoparticles have shown improved bioactivity, promoted human PDL cells metabolic activity. This suggests its use as a guided tissue regeneration membrane.[31]

Different surface morphologies are required to enhance the proliferation of osteoblasts and fibroblasts. By maintaining some fundamental constraints regarding pore size and interconnectedness the response of osteogenic cells and their precursors to micro and nanotextured morphologies on planar surfaces can be reproduced on three-dimensional scaffolds.[24]

Documented disadvantages of scaffolds include inflammation, limited cell turnover, and growth factor expression.[14]

Clinical reports, highlight the use of nanofibers that release antimicrobial particles, hence paving the way for use as a scaffold for tissue engineering purposes.[32] The self-assembly property of the nanomaterials at body temperature directs bone growth; combating multifactorial diseases like periodontal disease and Osteomyelitis.[33] Self-assembling peptides like RAD16-I when transplanted, can assist with new callus formation and inhibit demineralization.[34]

Nano Antihypersensitivity Agents

Hypersensitivity has become a common problem encountered in dental setup. In hypersensitive teeth, the dentinal tubules have surface densities eight times more than nonsensitive teeth.[35] Nanotechnology has effectively addressed this problem by creating nanorobots that traverse through the dentinal tubules and occlude them providing relief to the patient.[36] Also, the nanoparticles have remineralizing property which helps in reducing sensitivity.[37] Table 3 shows the clinical trials conducted using nanomaterials for treating dentinal hypersensitivity.

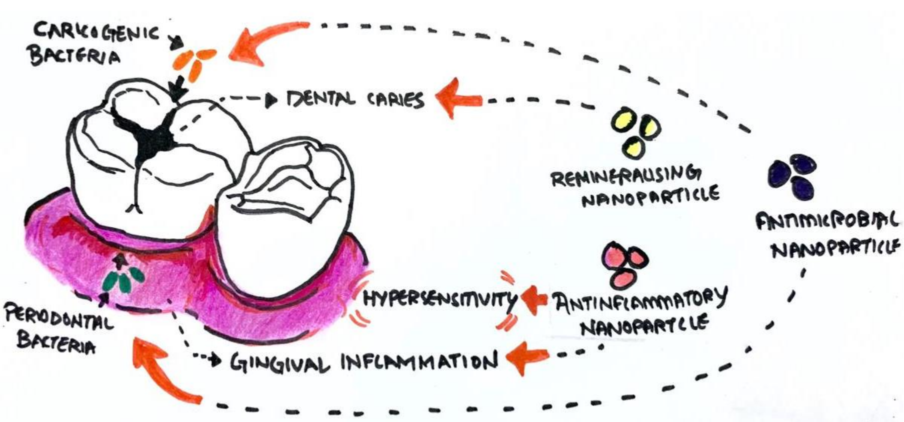

Figure 6. Remineralization, antimicrobial and anti-inflammatory properties of nanoparticles.

Table 3. Clinical Trials conducted using nanomaterials for treating dentinal hypersensitivity.

Sl.no	Year	Author	Nanomaterial	Clinical trial outcome
1	2019	James R Fernando[38]	SnF_2 and CPP-ACP nanocomplexes	**Self-assembly of dental surface nanofilaments and remineralization by SnF 2 and CPP-ACP nanocomplexes.** This uses in vitro studies and a double-blind, randomized controlled, cross-over design in situ clinical trial and shows that SnF2 and CPP-ACP interact to form a nanofilament coating on the tooth surface and that together they are superior in their ability to promote dental remineralization and reduce hypersensitivity.
2	2014	Michele Vano[39]	Nanohydroxyapatite	**Effectiveness of nano-hydroxyapatite toothpaste in reducing dentin hypersensitivity: a double-blind randomized controlled trial.** The findings of the study encourage the application of nano-hydroxyapatite in fluoride-free toothpaste as an effective desensitizing agent providing quick relief from symptoms after 2 and 4 weeks.

Nano aided Anesthesia

Navigation technology in the form of nanorobots also termed as nanobots induces oral analgesia. When these nanorobots reach the pulp, it results in reversible and temporary loss of pain and sensitivity in the tooth or area of interest. They can be computer-controlled by the dentist, and this property helps to reverse or restore the anesthetic activity.[40]

Nanotechnology-modified liposomal nanoformulations are small nanovesicles encased in a phospholipid bilayer.[26] Which has effective pain control and aiding quick recovery.[41,42] They also reduce the side effects of the anesthetic; for example, liposomal bupivacaine maintains a minimum concentration needed to deliver the therapeutic effect for 3 days without increasing the concentration of the active constituent in the body. In conclusion, liposomal bupivacaine has reduced cardiac toxic effects.[43]

Nano aided Orthodontics

Nanoelectromechanical systems (NEMS) have their broader application in orthodontics recently. Electrical energy generates mechanical forces which enhance tooth movement as shown in animal studies.[44] These animal studies reveal that electric stimulation using low amperes enzymatic micro battery (15-20 microamps) enhances cellular enzymatic phosphorylation activities, which lead to accelerated bone remodeling. This device uses glucose as the fuel for the micro battery and is placed on the gingiva near the alveolar bone to facilitate orthodontic tooth movement. (Figure 7) But several issues have to be considered, such as the effect of food, pH, and biocompatibility.[44]

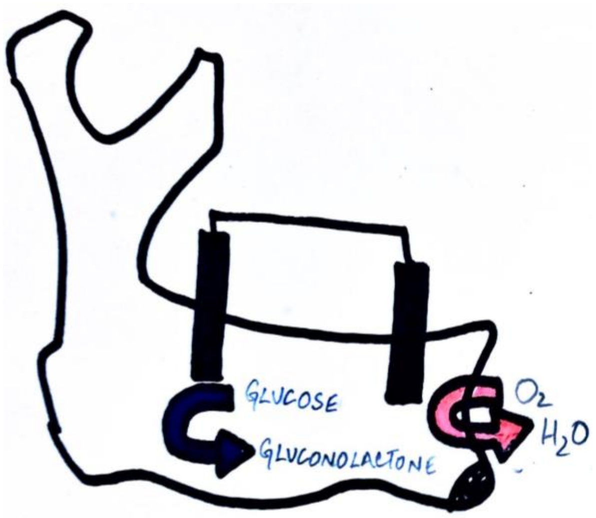

Figure 7. Oral biocatalytic fuel cell. The following reaction generating electricity for enhancing orthodontic tooth movement occurs: Glucose+O2→gluconolactone+H2O/H2O2

Temporary anchorage devices manufactured with smooth titanium surfaces when aided with titanium nanotubes enhance initial osseointegration and serve as an interfacial layer between the newly formed bone and the temporary anchorage devices during orthodontic tooth movement.[45]

Nanotechnology in the field of restorative dentistry and endodontics has seen major research in 4 main types of material- composites, GIC, adhesives and endodontic materials.

NanoComposites

Incorporating nanofillers in composites improved material characteristics like the smoothness of surfaces resulting in better aesthetics. The remanent minute irregularities formed during finishing and polishing are way smaller than the wavelength of visible light (0.4-0.8 micrometers) thereby minimizing the reflection of light thus warranting good optic properties. They also improve the strength of the composite and reduce polymerization shrinkage.[46]

A rechargeable nano-amorphous calcium phosphate (nACP) filled composite resin (smart material) helps neutralize the acids produced by the bacteria preventing secondary caries. Additionally, the levels of calcium and phosphorus are also maintained.[47] (Figure 8)

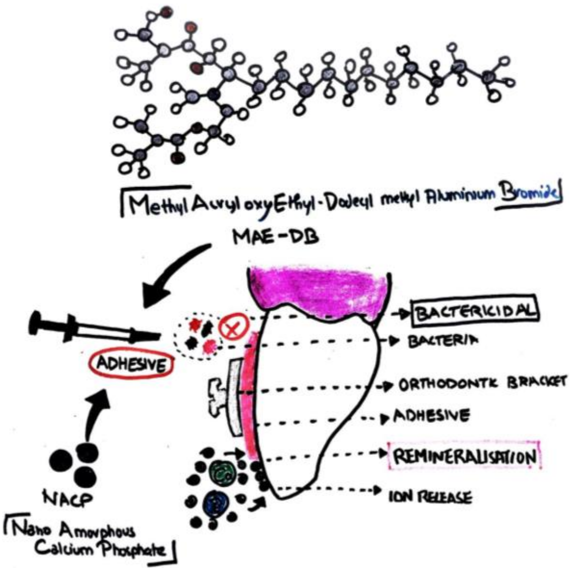

Figure 8. Remineralization and bactericidal effects of nACP.

Dental nanocomposites (bionanocomposites) contain nanofillers and nanofibers with a photopolymerizable resin matrix. The distribution of nanofillers is such that there is increased filler load which in turn increases the viscosity leading to better mechanical properties and reduced polymerization shrinkage. Due to reduced particle size, load-bearing stress is reduced, which results in inhibition of crack propagation.

Nanoparticles of dicalcium phosphate anhydrous- (DCPA-) whiskers, tetracalcium phosphate- (TTCP: $Ca_4(PO_4)_2O$-) whiskers, kaolinite ($Al_2Si_2O_5(OH)_4$), and calcium fluoride are incorporated, which resulted in the highest release of calcium, phosphorous and fluoride owing to their reduced particle size. In addition, calcium and phosphorus release was increased six times in acidic conditions. Due to the unique structure of kaolinite (large surface area), the adsorption of fluoride is higher and therefore can also provide sustained release of fluoride.[48] Table 4 represents the clinical trials done on nanocomposite.

Table 4. Clinical trials on nanocomposites

Sl. no	year	Author	Nanomaterial	Clinical trial
1	2014	Mary A S Melo[49]	Nanostructured Hybrid Fluoridated Restorative Composites.	In Situ Response of Nanostructured Hybrid Fluoridated Restorative Composites on Enamel Demineralization, Surface Roughness, and Ion Release.
2	2014	Jan W V van Dijken[50]	Nanohybrid composite	A randomized 10-year prospective follow-up of Class II nanohybrid and conventional hybrid resin composite restorations This 10 year follow-up study showed good clinical effectiveness of nanohybrid composite in extensive class 2 restorations.
3	2013	Wei Qin[51]		Two-year clinical evaluation of composite resins in non-carious cervical lesions Both restorative materials exhibited acceptable clinical performance in class 5 non carious lesions 2 years post restoration.
4	2013	Umit Candan [52]	fiber-reinforced nanofilled resin composite	Clinical performance of fiber-reinforced nanofilled resin composite in extensively carious posterior teeth of children: 30-month evaluation 13 month evaluation of nanofilled resin composite applied with or without glass-fiber layering showed similar and good results in large cavities of posterior permanent teeth in children.
5	2012	Lei Cheng.[53]	amorphous calcium phosphate and silver nanocomposites	Effect of amorphous calcium phosphate and silver nanocomposites on dental plaque microcosm biofilms Novel amorphous calcium phosphate(NACP) and silver nanoparticles (NAg) nanocomposites possess good mechanical and antibacterial composites reducing biofilm viability and lactic acid production. Thus promising for good dental restorations with remineralizing and antibacterial capabilities.
6	2011	Dina Gamal Taha[54]	Ormocer, Nanofilled, and Nanoceramic composite	Fracture resistance of maxillary premolars with class II MOD cavities restored with Ormocer, Nanofilled, and Nanoceramic composite restorative systems Teeth with microhybrid, ormocer, and nanofilled composite restorations had lower cuspal fracture resistance than those with nanoceramic composite restorations.

Nano- GIC (Nanoionomers)

Glass ionomer cement (GIC) is one of the most versatile materials used in dentistry that has undergone various modifications. Nanotechnology has played a major role in modifying GIC, improving its mechanical properties and the esthetics offered. The first nano-GIC was developed for Ketac™ Nano (3M ESPE, 3mespe.com) with fluor aluminum-silicate technology.[55]

In a study conducted by Alatawi RA et.al in 2019, they produced GIC mixed with hydroxyapatite nanoparticles, this mixture resulted in increased fluoride release and enhanced mechanical properties. In addition, they studied the antibacterial effect of 8% HA wt% against S.mutans, which resulted in a bacterial inhibition zone of about 8.6 mm.[56]

Nano adhesives

These are bonding agents, when incorporated with nanoparticles-show better bond strength, marginal seal, fluoride release, stress absorption, and long shelf-life due to the well-homogenized consistency of the adhesive.[12]

Nano aided Endodontics

Nanoparticles play a major role in material aspects of the endodontic sealers and obturation materials. It improves the handling and physical properties. Additionally, it has antimicrobial properties due to increased pH and improved sealing ability.

Bioceramic-based sealer EndoSequence BC Sealer™ and Silicon-based sealer containing gutta-percha powder and silver nanoparticles (GuttaFlow® 2, Coltene Whaledent) have been introduced. Recently antibacterial quaternary ammonium polyethyleneimine (QPEI) nanoparticles have also been incorporated into other sealers.[57,58]

Recently diamond nanoparticles were incorporated into gutta-percha, and the obturation viewed under digital radiography and micro-computed tomography revealed better adaptation to canal walls and less void formation.[59]

Nano Impression materials

Research in prosthetic impression materials based on nanotechnology is basically of two types: one is to create new inorganic nanomaterials and the other is to improve the surface characteristics of the existing materials by incorporating nanoparticles on the surface helping us to overcome the disadvantage of traditional impression materials which are known to be brittle and low ductility. Thus, incorporation of nanoparticles into ceramic, resin and metals paves the way to attaining better mechanical and structural properties of impression materials.

Nanoceramics have superplasticity and show good toughness, ductility, hardness, and strength which is four to five times higher than those of the traditional materials. For example, at 100°C the microhardness of nano-TiO_2 ceramics is 13,000 kN/mm2, while that of ordinary TiO_2 ceramics is lower than 2,000 kN/mm2.[60]

Poly methyl methacrylate (PMMA) is one of the dental materials that is indispensable and the incorporation of nanotechnology has improved its characteristics multifold. Carbon Nanotubes (CNT) and carbon nanofibrils have been used as additives in impression materials to improve the properties of PMMA. Studies show better impact strength of PMMA matrix, when prepared using with even smaller amounts of single-wall nanotubes as additives using a dry powder mixing method.[61]

Recent applications in other fields of medicine

We would also like to highlight the recent applications of nanotechnology in other fields of medicine like artificial intelligence, cancer detection and covid 19 vaccines. Though these topics are not within the scope of the article, yet we would like to bring to the readers the diverse applications which could be further explored.

Artificial intelligence and nanomedicine

Artificial intelligence (AI) is one of the newfangled technologies being researched extensively in the field of medicine.

Integrating artificial intelligence and nanotechnology is instrumental in the field of nanomedicine and dentistry. It helps in enhancing patient data acquisition and improves the design of nanomaterials and diagnostic and therapeutic efficacy. AI bridges the gap of heterogeneous patient treatment modalities by providing custom-made treatment options by analyzing the patient requirements.[62] It aids in making appropriate combinations of drugs and the nanomaterial to be used for carrying the drug by using pattern analysis and classification algorithms.

Cancer detection through Integration of Artificial Intelligence and Nanotechnology

Artificial intelligence has improved cancer detection and treatment in many ways. IBM Watson for use in oncology helps in providing a more personalized therapy to cancer patients. It collects information from medical journals, textbooks, clinical data and analyses patient medical records, along with the oncologist’s expertise, which could render the best treatment to the patient. Microsoft’s Hanover project and

Google's DeepMind are other platforms working on AI in medicine.[63]

In a recent study, Wang *et al.* developed feedback system control, a widely used platform for unmodified and nanotechnology-modified therapeutic optimizations. The authors used AI to standardize drug dose combinations that would produce maximum cytotoxicity. They studied nanodiamond-doxorubicin, nanodiamond-mitoxantrone, nanodiamond-bleomycin, and unmodified paclitaxel combinations on many breast cancer cell lines. The results showed that when compared to randomly selected nanomedicine combinations, AI-optimized nanomedicine drug combinations gave a better performance.[64]

Application of nanotechnology for covid-19 vaccines

Covid - 19 vaccines have become the need of the hour, and nanotechnology can invariably play a role in vaccine development. Research in a Nano ImmunoEngineering, University of California, Faculty proposed the idea of a plant virus using a peptide-based approach, which could be fabricated as COVID-19 Nano-vaccine patch and microneedle that could be painlessly self-administered by patients. It can efficiently deliver antigens, serve as adjuvant platforms and mimic viral structures.[65]

WHO in January 2021 considered BNT162b2 as an emergency vaccine which is a lipid nanoparticle-formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein.[66]

Safety issues:

The extensive use of nanomaterials in medical applications has raised concerns about the safety and toxicity levels. This is because of the associated rate of increased absorption into the cells of the skin, Lung mucosa, digestive tract cells, and other parts of the body. Toxic effects include DNA damage which when evaluated in a study, showed that copper oxide and titanium dioxide nanoparticles were highly toxic compared to iron oxide, zinc oxide, carbon nanotubes.[12]

CONCLUSIONS

Nanotechnology will soon become the key aspect of the development of any diagnostic aid or treatment option and is inevitably the most emerging interdisciplinary field in medicine and dentistry. It has brought the treatment approach to the level of the size of the cells of the body and can as well render treatment that is more specific and personalized to the patient. It can be integrated with other disciplines of science and technology such as artificial intelligence and improve the efficiency of diagnosis and treatment multifold. Clinical trials in the field of Nanodentistry have been evolving at a very slow pace, in this review, we presented some of the recent developments in terms of clinical trials and incorporate high quality restorative and disease prevention strategies. Further, we like to conclude by Nanodentistry is definitely a promising field and when incorporated into our day-to-day practice could enhance the quality of interdisciplinary treatment modalities. Thus, let's march towards a change and aim for precision-based Dentistry which could be positively obtained using the perfect material of choice “the Nanos” in all the dental fraternity branches.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENT

We thank Sagnic Tarat, undergraduate student at SRM Dental College, Ramapuram for using his artistic skills to provide us diagrammatic illustrations.

REFERENCES

1. Saxena S, Pramod BJ, Dayananda BC, Nagaraju K. Design, architecture and application of nanorobotics in oncology. Indian J Cancer. 2015;52:236-241.

2. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The History of Nanoscience and Nanotechnology: From Chemical-Physical Applications to Nanomedicine. Molecules. 2019;25:112.

3. Iqbal P, Preece JA, Mendes PM. Nanotechnology: The “Top-Down” and “Bottom-Up” Approaches. Supramolecular chemistry: from molecules to nanomaterials. 2012 Mar 15.

4. Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L, Muller RN. Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. Chemical reviews. 2008;108:2064-2110.

5. Shin WK, Cho J, Kannan AG, Lee YS, Kim DW. Cross-linked Composite Gel Polymer Electrolyte using Mesoporous Methacrylate-Functionalized SiO2 Nanoparticles for Lithium-Ion Polymer Batteries. Sci Rep. 2016; 6:26332.

6. Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. Arab. J. Chem. 2019;12:908-31.

7. Cavalcanti A, Shirinzadeh B, Zhang M, Kretly LC. Nanorobot Hardware Architecture for Medical Defense. Sensors (Basel). 2008;8:2932-2958.

8. Dolev S, Narayanan RP, Rosenblit M. Design of nanorobots for exposing cancer cells. Nanotechnology. 2019;30:315501.

9. Cavalcanti A, Shirinzadeh B, Freitas RA Jr, Kretly LC. Medical nanorobot architecture based on nanobioelectronics. Recent Pat Nanotechnol. 2007;1:1-10.

10. Webster T.J., Ahn E.S. Nanostructured biomaterials for tissue engineering bone. Tissue Engineering II. Springer; 2007; pp. 275–308.

11. 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.

12. Shashirekha G, Jena A, Mohapatra S. Nanotechnology in Dentistry: Clinical Applications, Benefits, and Hazards. Compendium of continuing education in dentistry (Jamesburg, NJ: 1995). 2017;38:e1-4.

13. Peng CW, Li Y. Application of quantum dots-based biotechnology in cancer diagnosis: current status and future perspectives. Journal of Nanomaterials. 2010 Jan 1;2010.

14. Song JM, Kasili PM, Griffin GD, Vo-Dinh T. Detection of cytochrome C in a single cell using an optical nanobiosensor. Anal Chem. 2004;76:2591-2594.

15. Christodoulides N, Floriano PN, Miller CS, et al. Lab-on-a-chip methods for point-of-care measurements of salivary biomarkers of periodontitis. Ann N Y Acad Sci. 2007;1098:411-428.

16. Haugen HJ, Qasim SB, Matinlinna JP, Vallittu P, Nogueira LP. Nano-CT as tool for characterization of dental resin composites. Scientific reports. 2020;10:1-2.

17. Tan, A., R. Jeyaraj, and S. F. De Lacey. "Nanotechnology in neurosurgical oncology." Nanotechnology in Cancer. 2017;139-170.

18. X.J. Li, Yu Zhou. Controlled drug delivery using microfluidic devices, In Woodhead Publishing Series in Biomaterials, ch-Microfluidic Devices for Biomedical Applications, Woodhead Publishing,2013; 167-185e.

19. Chiappini, C., and C. Almeida. "Silicon nanoneedles for drug delivery." Semiconducting Silicon Nanowires for Biomedical Applications. Woodhead Publishing, 2014;144-167.

20. Nadappuram B P, Cadinu P, Barik A, et al. Nanoscale tweezers for single-cell biopsies[J]. Nature nanotechnology, 2019;14: 80-88.

21. Van Bael S, Kerckhofs G, Moesen M, Pyka G, Schrooten J, Kruth JP. Micro-CT-based improvement of geometrical and mechanical controllability of selective laser melted Ti6Al4V porous structures. Mater. Sci. Eng. 2011;528:7423-7431.

22. Yao C, Perla V, McKenzie JL, Slamovich EB, Webster TJ. Anodized Ti and Ti6Al4V possessing nanometer surface features enhances osteoblast adhesion. J. Biomed. Nanotech. 2005;1:68-73.

23. Traini T, Murmura G, Sinjari B, Perfetti G, Scarano A, D'Arcangelo C, Caputi S. The surface anodization of titanium dental implants improves blood clot formation followed by osseointegration. Coatings. 2018;8:252.

24. Harvey EJ, Henderson JE, Vengallatore ST. Nanotechnology and bone healing. J. Orthop. Trauma. 2010;24:S25-30.

25. Khan ZA, Jhingran R, Bains VK, Madan R, Srivastava R, Rizvi I. Evaluation of peri-implant tissues around nanopore surface implants with or without platelet rich fibrin: a clinico-radiographic study. Biomed Mater 2018;13:025002.

26. Canullo L, Sisti A. Early implant loading after vertical ridge augmentation (VRA) using e-PTFE titanium-reinforced membrane and nano-structured hydroxyapatite: 2-year prospective study. Eur J Oral Implantol. 2010;3:59-69.

27. Stylios G, Wan T, Giannoudis P. Present status and future potential of enhancing bone healing using nanotechnology. Injury. 2007;38:S63-74.

28. Vajtai R. Springer Handbook of Nanomaterials. In: Kumar V., Tripathi B., Srivastava A., Saxena P.S., editors. Nanocomposites as Bone Implant Material. Springer; 2013;pp. 941–976.

29. Srinivasan S, Jayasree R, Chennazhi K P, et al. Biocompatible alginate/nano bioactive glass ceramic composite scaffolds for periodontal tissue regeneration[J]. Carbohydrate Polymers, 2012, 87: 274-283.

30. Rungsiyanont S, Dhanesuan N, Swasdison S, et al. Evaluation of biomimetic scaffold of gelatin–hydroxyapatite crosslink as a novel scaffold for tissue engineering: Biocompatibility evaluation with human PDL fibroblasts, human mesenchymal stromal cells, and primary bone cells[J]. Journal of biomaterials applications, 2012, 27: 47-54.

31. Mota J, Yu N, Caridade S G, et al. Chitosan/bioactive glass nanoparticle composite membranes for periodontal regeneration[J]. Acta biomaterialia, 2012, 8: 4173-4180.

32. Funda G, Taschieri S, Bruno GA, Grecchi E, Paolo S, Girolamo D, Del Fabbro M. Nanotechnology scaffolds for alveolar bone regeneration. Materials. 2020;13:201.

33. Chun AL, Moralez JG, Webster TJ, Fenniri H. Helical rosette nanotubes: a biomimetic coating for orthopedics? Biomaterials. 2005;26:7304-7309.

34. Kirkham J., Firth A., Vernals D., Boden N., Robinson C., Shore R.C., Brookes S.J., Aggeli A. Self-assembling peptide scaffolds promote enamel remineralization. J. Dent. Res. 2007;86:426–430.

35. West NX, Lussi A, Seong J, Hellwig E. Dentin hypersensitivity: pain mechanisms and aetiology of exposed cervical dentin. Clin Oral Investig. 2013;17 Suppl 1:S9-19.

36. Sumit M, Gurtu A, Singhal A, Mehrotra A. “Nanotechnology: its implications in conservative dentistry and endodontics. J Dent Sci J DENT SCI. 2013;9-13.

37. Low SB, Allen EP, Kontogiorgos ED. Reduction in dental hypersensitivity with nano-hydroxyapatite, potassium nitrate, sodium monoflurophosphate and antioxidants. Open Dent J. 2015:92.

38. Fernando JR, Shen P, Sim CP, Chen YY, Walker GD, Yuan Y, Reynolds C, Stanton DP, MacRae CM, Reynolds EC. Self-assembly of dental surface nanofilaments and remineralisation by SnF 2 and CPP-ACP nanocomplexes. Sci. Rep. 2019;9:1-0.

39. Vano M, Derchi G, Barone A, Covani U. Effectiveness of nano-hydroxyapatite toothpaste in reducing dentin hypersensitivity: a double-blind randomized controlled trial. Quintessence Int. 2014;45.

40. Verma S, Chevvuri R, Sharma H. Nanotechnology in dentistry: Unleashing the hidden gems. J. Indian Soc. Periodontol. 2018;22:196.

41. Li Y, Zhao H, Duan LR, Li H, Yang Q, Tu HH, Cao W, Wang SW. Preparation, characterization and evaluation of bufalin liposomes coated with citrus pectin. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2014;444:54-62.

42. Moradkhani MR, Karimi A, Negahdari B. Nanotechnology application to local anaesthesia (LA). Artif Cells Nanomed Biotechnol. 2018;46:355-360.

43. Richard BM, Newton P, Ott LR, Haan D, Brubaker AN, Cole PI, Ross PE, Rebelatto MC, Nelson KG. The Safety of EXPAREL ® (Bupivacaine Liposome Injectable Suspension) Administered by Peripheral Nerve Block in Rabbits and Dogs. J Drug Deliv. 2012;2012:962101.

44. Karthikeyan Subramani, Waqar Ahmed, James K Hartsfield Jr. Nanobiomaterials in Clinical Dentistry: 1st Edition (Elsevier, 2012).

45. Miyawaki, S., Koyama, I., Inoue, M., Mishima,K., Sugahara, T., & Takano-Yamamoto, T. Factors associated with the stability of titanium screws placed in the posterior region for orthodontic anchorage. American Journal of Orthodontics and Dentofacial Orthopedics,2003;124:373-378.

46. Türkün Ş, Uzer Çelik E. One-year clinical performance of compomer and nanofill composite restorations applied with an antibacterial adhesive. Acta Odontol. Turc.2007; 1.

47. Xie X, Wang L, Xing D, Arola DD, Weir MD, Bai Y, Xu HH. Protein-repellent and antibacterial functions of a calcium phosphate rechargeable nanocomposite. J Dent. 2016;52:15-22.

48. Lee JH, Kim HW, Seo SJ. Polymer-ceramic bionanocomposites for dental application. Journal of Nanomaterials. 2016;2016.

49. Melo MA, Codes BM, Passos VF, Lima JP, Rodrigues LK. In situ response of nanostructured hybrid fluoridated restorative composites on enamel demineralization, surface roughness and ion release. Eur J Prosthodont Restor Dent. 2014;22:185-190.

50. Van Dijken JW, Pallesen U. A randomized 10-year prospective follow-up of Class II nanohybrid and conventional hybrid resin composite restorations. J Adhes Dent. 2014;16:585-592.

51. Qin W, Song Z, Ye YY, Lin ZM. Two-year clinical evaluation of composite resins in non-carious cervical lesions. Clin Oral Investig. 2013;17:799-804.

52. Candan U, Eronat N, Onçağ O. Clinical performance of fiber-reinforced nanofilled resin composite in extensively carious posterior teeth of children: 30-month evaluation. J Clin Pediatr Dent. 2013;38:1-6.

53. Cheng L, Weir MD, Xu HH, Antonucci JM, Lin NJ, Lin-Gibson S, Xu SM, Zhou X. Effect of amorphous calcium phosphate and silver nanocomposites on dental plaque microcosm biofilms. J Biomed Mater Res B Appl Biomater. 2012;100:1378-1386.

54. Taha DG, Abdel-Samad AA, Mahmoud SH. Fracture resistance of maxillary premolars with Class II MOD cavities restored with ormocer, nanofilled, and nanoceramic composite restorative systems. Quintessence Int. 2011;42(7).

55. Chandki R, Kala M, Kumar KN, et al. Nanodentistry: exploring the beauty of miniature. J Clin Exp Dent. 2012;4:119-124

56. Alatawi RA, Elsayed NH, Mohamed WS. Influence of hydroxyapatite nanoparticles on the properties of glass ionomer cement. Journal of Materials Research and Technology. 2019;8:344-349.

57. Raj V, Mumjitha MS. Formation and surface characterization of nanostructured Al 2 O 3-TiO 2 coatings. Bull. Mater. Sci. 2014;37:1411-1418.

58. Cooper CA, Ravich D, Lips D, Mayer J, Wagner HD. Distribution and alignment of carbon nanotubes and nanofibrils in a polymer matrix. COMPOS SCI TECHNOL. 2002;62:1105-1112.

59. Beyth N, Houri-Haddad Y, Baraness-Hadar L, Yudovin-Farber I, Domb AJ, Weiss EI. Surface antimicrobial activity and biocompatibility of incorporated polyethylenimine nanoparticles. Biomaterials. 2008;29:4157-4163.

60. Zoufan K, Jiang J, Komabayashi T, Wang YH, Safavi KE, Zhu Q. Cytotoxicity evaluation of Gutta Flow and Endo Sequence BC sealers. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112:657-661.

61. Abramovitz I, Beyth N, Weinberg G, Borenstein A, Polak D, Kesler-Shvero D, Houri-Haddad Y. In vitro biocompatibility of endodontic sealers incorporating antibacterial nanoparticles. J. Nanomater. 2012;2012.

62. Ahmed Z, Mohamed K, Zeeshan S, Dong X. Artificial intelligence with multi-functional machine learning platform development for better healthcare and precision medicine. Database (Oxford). 2020;2020:010.

63. IBM Watson for Oncology (2019). www.ibm.com/in-en/marketplace/clinical-decision-support-oncology Google Scholar.

64. Wang H, Lee DK, Chen KY, Chen JY, Zhang K, Silva A, Ho CM, Ho D. Mechanism-independent optimization of combinatorial nanodiamond and unmodified drug delivery using a phenotypically driven platform technology. ACS nano. 2015;9:3332-3344.

65. Shin MD, Shukla S, Chung YH, Beiss V, Chan SK, Ortega-Rivera OA, Wirth DM, Chen A, Sack M, Pokorski JK, Steinmetz NF. COVID-19 vaccine development and a potential nanomaterial path forward. Nat Nanotechnol. 2020;646-655.

66. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383:2603-2615.