



Volume 5 / Issue 2 / September 2025

Review Article

Nanotechnology in Oral And Maxillofacial Surgery

Elif Ceyda Kayasöken¹, Selime Ecem Sinanoğlu¹, Mehdi Babaei¹, Mesture Ayfer Kaynar^{1*}

¹Istanbul Yeni Yuzyıl University, Faculty of Dentistry, Oral and Maxillofacial Surgery, Istanbul, Turkey

*Corresponding author: ayferkaynar@gmail.com

Kayasöken, Elif Ceyda., Sinanoğlu, Selime Ecem., Babaei, Mehdi., Kaynar, Mesture Ayfer. "Nanotechnology in Oral And Maxillofacial Surgery". *Acta Stomatologica Cappadocia*. 5;2 (September 2025): 57-85.

DOI: <https://doi.org/10.54995/ASC.5.2.5>

Received: 10.03.2025; Accepted: 10.09.2025

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



Nanotechnology in Oral And Maxillofacial Surgery

Elif Ceyda Kayasöken, Selime Ecem Sinanoğlu, Mehdi Babaei,

Mesture Ayfer Kaynar

Abstract

Nanotechnology has rapidly advanced in the fields of science and medicine over the past few decades. Thanks to developments in medicine, it has gained increasing popularity in oral, dental, and maxillofacial surgery. This review article discusses recent advancements in nanotechnology, particularly in bone regeneration, diagnosis and treatment of oral cancer, drug delivery systems, and dental implants.

Keywords: Dental implant, drug delivery system, nanoskeleton, nanoparticle, nanotechnology, oral cancer, oral surgery.

Özet

Nanoteknoloji geçtiğimiz birkaç on senede bilim ve tıp alanında hızlı bir gelişim göstermektedir. Özellikle tıp alanındaki gelişmeler sayesinde ağız, diş ve çene cerrahisinde de popülerliğini artırmıştır. Bu derleme makalesinde, nanoteknolojinin özellikle kemik rejenerasyonu, oral kanser tanı ve tedavisinde, ilaç taşıma sisteminde ve dental implantlarda yapılan son gelişmeler konu alınmıştır.

Anahtar kelimeler: Ağız kanseri, ağız cerrahisi, diş implantı, ilaç verme sistemi, nanoiskelet, nanopartikül, nanoteknoloji.

Introduction

The word "nano" originates from the Greek word meaning "dwarf." The concept of nanotechnology was first introduced in detail by Nobel laureate physicist Richard Feynman in his 1959 lecture titled "There's Plenty of Room at the Bottom." At the end of his lecture, he concluded the topic by stating, "This is a development that I think is inevitable." (1,2)

The accepted definition of nanotechnology is the research and development of technology at the atomic, molecular, or macromolecular level; at a scale of approximately 1 to 100 nanometers, to understand the phenomena and materials in nanostructures at a fundamental level and to create and use structures, devices, and systems with new properties and functions due to their small and/or intermediate sizes (3,4).

Nanotechnology has emerged as a research field emerging with various applications in science and technology (5). Due to its unique properties, such as high surface-to-volume ratios and high compressive and bending strengths, scientists have explored different application methods and industries that could benefit from the use of these materials (6,7).

Today, it is observed that nanotechnology shows dynamic development in all fields of medicine:

- Medical diagnosis
- Cancer treatment
- Gene therapy
- Treatment of infections
- Tissue or organ regeneration
- Medical imaging (6)

Literature Review

1. Types of Nanomaterials

The regeneration of oral tissues is very challenging, and accordingly, nanomaterials have great potential for future applications in craniofacial and oral defect-based tissue engineering and regenerative medicine (TE/RM). Nanomaterials are materials that have components smaller than 100 nm in at least one dimension. These may include atomic clusters, grains, fi-

bers, films, nanopores, and composites made of their combinations. One-dimensional nanomaterials are referred to as "sheets," two-dimensional ones as "nanowires" and "nanotubes," and three-dimensional ones are called "quantum dots" (1,8).

1. Fullerenes are carbon allotropes that can adopt different shapes, one of which is carbon nanotubes. The cylindrical shape is derived from the hexagonal lattice structure of carbon atoms, and this structure can fold into a sheet. This molecular arrangement provides significant hardness and tensile strength (50 times that of steel). When an antithrombotic surface is added, carbon nanotubes become suitable for vascular microcatheters, stents, and implants (3,9).

2. Nanoparticles, such as quantum dots (QD), can serve as drug carriers or labels for tracking cells. QDs are particularly suitable for imaging because they emit fluorescence at different wavelengths depending on the particle size (3,9).

3. Nanocomposites are multiphase solid materials in which one of the phases has dimensions smaller than 100 nanometers. In tissue engineering, scaffolds are enhanced with nanoparticle fillers. These fillers are either placed between layers or evenly distributed to increase the surface area (3,9).

The most commonly studied nanomaterials for oral tissues include nanofibers, nanoparticles, nanosheets, nanotubes, and nanospheres. These nanomaterials can be composed of inorganic and organic materials (Figure 1) (10).

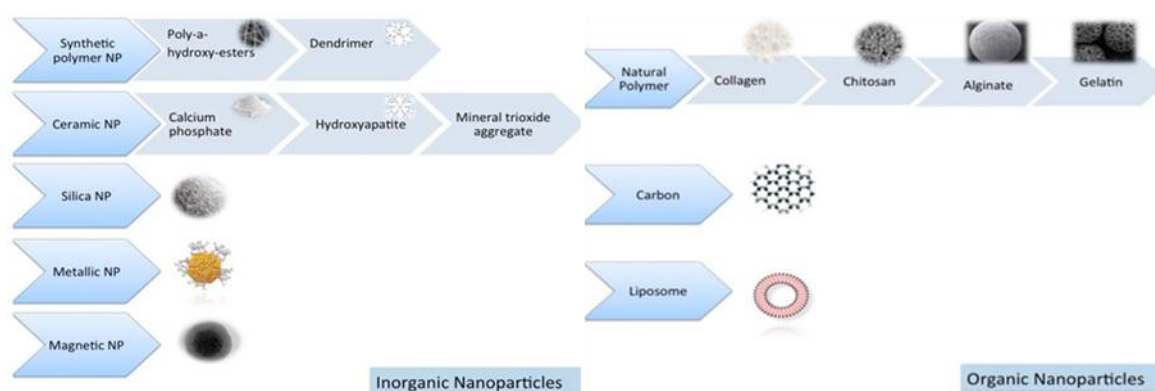


Figure 1: Inorganic and organic nanoparticles (10)

Generally, nanomaterials have excellent physicochemical properties and biomimetic characteristics to enhance cell growth and tissue regeneration. Due to their similarity to extracellular matrices and high porosity, nanomaterials create an ideal environment for cell migration. Additionally, nanotubes and nanoparticles can enhance the chemical and mechanical properties of the scaffold, increase cell migration and proliferation, and promote tissue regeneration. Nano-scaffolds stabilize bioactive agents through encapsulation or surface attachment, encourage molecular internalization, target their distribution within cells, and allow control of biological factor release at the intended site. They can also be used to label cells for continuous tracking and monitoring. Furthermore, nanoparticles can provide improved osseointegration, osteoconduction, and osteoinduction (10).

In oral and maxillofacial surgical applications, nanotechnology has enabled the development of tissue engineering, imaging, drug delivery systems, and contributed to the improvement of implants (Figure 2) (3). These innovations have allowed for better outcomes in surgical treatments and significant progress in the use of biomaterials.

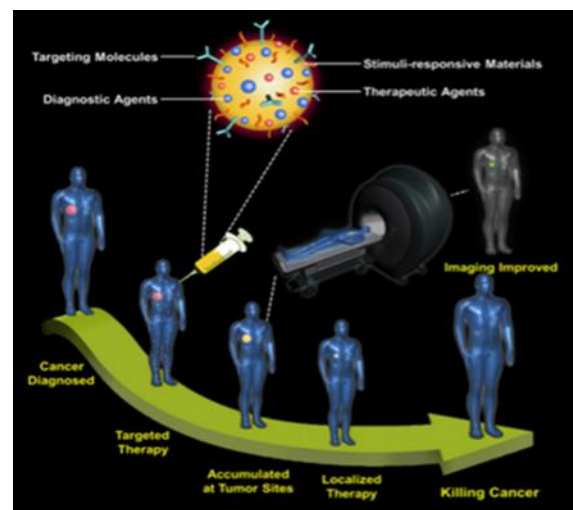


Figure 2: Contribution of Nanotechnology in Summary (3).

2. Nano-Scaffolds for Tissue Engineering

Applications of nanotechnology in oral surgery have primarily focused on enhancement procedures for bone tissue regeneration and improving the osseointegration of oral implants. Nanomaterials aim to overcome the fundamental issues encountered with current scaffolds used for bone regeneration, such as insufficient mechanical strength, instability of released growth factors, and impaired cellular differentiation (10).

Nanostructures for tissue engineering (nano-scaffolds) are biocompatible nanomaterials that mimic the architecture of natural bone. These structures resemble the bone composition made up of collagen fibrils, hydroxyapatite, and proteoglycans, and they promote tissue regeneration by supporting cell adhesion, proliferation, and differentiation. Polylactic acid

(PLA) from polydihydroxy acid derivatives, poly-L-lactic acid (PLLA), polyglycolide (PGA), polycaprolactone (PCL), and nanophase hydroxyapatite (HA) have been widely studied (3,11).

PLLA has been approved by the FDA for use in bone reconstruction surgery. To improve its biological properties, PLLA nanofibers are often combined with hydroxyapatite, activated with arginylglycylaspartic acid (RGD) peptide, or supported with proteins such as bone morphogenetic protein 2 (BMP-2). Studies have shown that PLLA nanofibers facilitate colonization in bone defects and increase bone formation when used with BMP-2.3,12,13 Additionally, it has been shown that the osteointegrative properties of nanophase hydroxyapatite (HA) are enhanced. When bone marrow is added to three-dimensional porous nano-HA scaffolds, their adhesion, proliferation, and differentiation abilities have been observed. Nano-HA, which more closely mimics the nanostructure of natural bones, can be used to produce better implants. These features promise better osseointegration, more natural mechanical properties, reduced immune responses, and better control of cellular responses (3,14).

It has been demonstrated that nanotube structures have great potential for bone regeneration. Rosette nanotubes (RNT) are biomimetic and self-assembling new nanomaterials. Materials coated with RNTs have significantly increased cell regeneration because these structures create a suitable environment for cells (3,15). Carbon nanotubes (CNT) are other suitable scaffold materials that support the proliferation of osteoblasts. CNTs have excellent mechanical properties, which allow them to be used as reinforcement materials when combined with other biomaterials, supporting bone growth (3,16).

3. Effects of Nanotechnology on Imaging

Quantum dots (QD) are nanomaterials with narrow and size-tunable emission spectra that extend from ultraviolet to near-infrared light. They have long-lasting photostability, good photoluminescence, and a high signal-to-noise ratio. Due to these properties, they are particularly suitable for labelling and tracking specific cells and tissues, especially in non-invasive imaging, and can

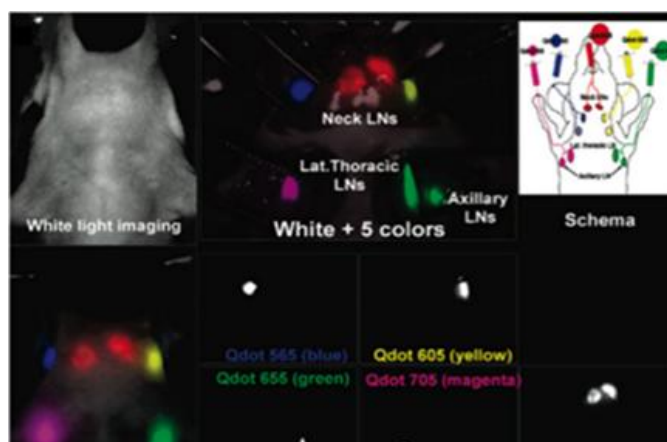


Figure 3: Quantum dots can be used as new imaging agents for lymph node imaging in head and neck cancer (3).

be used for the in vivo diagnosis of diseases and long-term monitoring (Figure 3)³. They provide better contrast and sensitivity in imaging. Quantum dots, when combined with paramagnetic ions, can enhance the quality of MRI images. This combination offers high sensitivity and high resolution, helping to identify tumor cells (3,17).

4. Oral Cancer Treatment and Nanotechnology in Drug Delivery Systems

Due to the very small size of nanoparticles, they are capable of overcoming certain barriers that larger microparticles normally cannot pass, thus reducing systemic toxicity (3,18). Among nanostructured drug delivery systems, liposomes and drug-conjugated nanoparticles (figure 4) (3) are of particular interest, especially in cancer therapy.

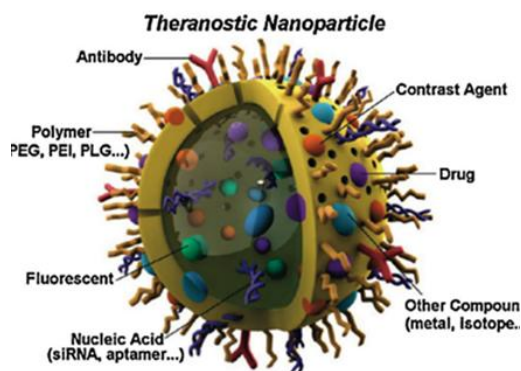


Figure 4: Therapeutic nanoparticle example (3)

4.1. Oral Cancer Diagnosis and Treatment

Oral cancer (oral cavity and oropharynx) is a common and aggressive form of cancer that can invade local tissues, metastasize, and has a high mortality rate. The 5-year mortality rate for oral cancer worldwide is approximately 50% (19,20). This indicates a poor prognosis, particularly for developing countries (21). Recurrence rates for Oral Squamous Cell Carcinoma (OSCC), which constitutes the majority of oral cancers, range from 18% to 76% in patients undergoing standard treatment. The primary factor limiting significant survival improvements is the delay in initiating treatment (22). To confirm the diagnosis of oral cancers, biopsy and histopathological examination are essential before treatment, and if possible, prior cytological findings can also be used as supporting evidence. These lengthy and costly diagnostic tests only delay the initiation of treatment. Delays in the diagnosis of oral cancer lead to extended treatment initiation times and, consequently, a decrease in patient survival rates (21,23,24,25). Although traditional treatment methods, such as surgery and chemoradiotherapy, have advanced in recent decades, they have not yet reached the ideal level. Cancer research, particularly in oral cavity and oropharyngeal cancers, is currently focused on improving diagnostic and therapeutic methods. Nanotechnology plays a crucial role in overcoming all these limitations. It involves the design, production, characterization, and application of nanoscale drug

delivery systems, playing an important role in this field (26). Nanotechnology-based drug delivery systems, including polymeric nanoparticles (PNPs), solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), gold nanoparticles, hydrogels, cyclodextrin complexes, and liquid crystals (LCs), are emerging as promising options to enhance oral cancer treatment and minimize therapy side effects.

4.2. Nanotechnology-Based Drug Delivery Systems

Nanoparticles can be defined as ultra-dispersed solid supermolecular structures with submicrometer sizes ranging from 10 to 1,000 μm . Drugs can be solubilized, entrapped, encapsulated, or bound to the nanoparticulate matrix, which serves as a critical reservoir in drug delivery systems, especially in oncology (27-30).

Nanomaterials used in drug delivery systems can be classified based on their geometry, morphology, chemical composition, uniformity, and aggregation properties: (31)

A) According to geometric classification, nanomaterials are categorized into four groups: zero-dimensional, one-dimensional, two-dimensional, and three-dimensional (Figure 5) (31).

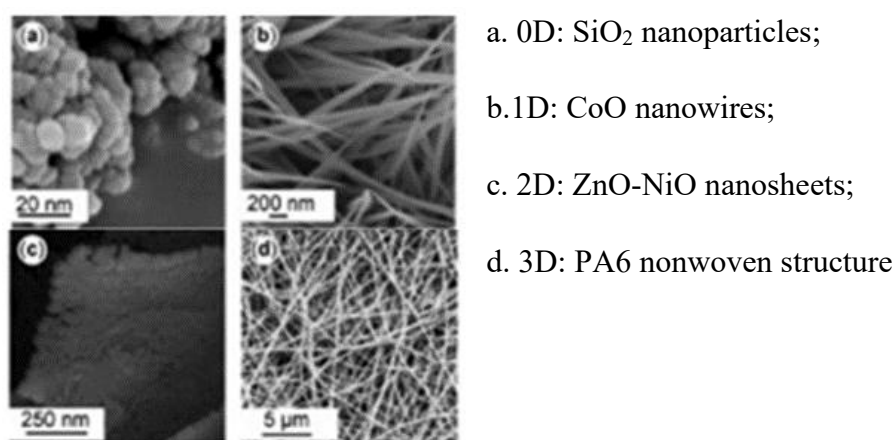


Figure 5: Examples of nanomaterials types (31)

B) Nanomaterials classified according to chemical composition: (31)

1. Metal-Based Nanomaterials. Examples include: Silver nanoparticles, copper nanoparticles, gold nanoparticles.

2. Metal Oxide Nanomaterials. These materials are composed of a combination of oxygen and metal atoms. Examples include: Silica, titanium dioxide (titania).

3. Carbon-Based Nanomaterials. Examples include: Carbon nanotubes, fullerenes.
4. Dendrimers are highly branched, tree-like macromolecules.
5. Nanocomposites.

C) Another Category are Dendrimers: These are highly branched, monodisperse macromolecules composed of three distinct regions: the central core, branching units, and a densely packed surface. The branched structures located on the dendrimer's surface are referred to as dendrons. Dendrons can be chemically modified by attaching or substituting functional groups. These modifications alter the chemical and physical properties of the entire dendrimer.³² Dendrimers are formed through the iterative addition of polymeric layers around a central core. Drug molecules can be transported via covalent bonds or electrostatic interactions with the dendrimer surface, or by encapsulation within the dendrimer's core region (32).

D) Quantum Dots are of significant importance in the medical field and are particularly utilized in cancer imaging and cellular tracking applications. These are semiconductor nanocrystals exhibiting autofluorescent properties. Examples include binary metal complexes such as CdSe, CdS, and CdZn (32-33).

In addition to those mentioned, lipid-based nanomaterials, including solid-lipid nanoparticles, liposomes, and micelles, also hold significant relevance in medicine. Solid-lipid nanoparticles are submicron-sized lipid emulsions in which liquid lipids are replaced by solid lipids. Liposomes, typically 50–200 nm in size, are biocompatible structures that are used as novel drug carriers, particularly for the delivery of biological molecules like genes, peptides, and proteins. Liposomes also provide high drug encapsulation efficiency. Liposomes and bilayer structures are amphiphilic materials with both hydrophilic and hydrophobic properties. These properties coexist within the same structure. Liposomes can encapsulate hydrophilic drugs and maintain an aqueous core, making them capable of binding to cell membranes during endocytosis and continuously releasing drugs. Research has shown that liposomal formulations improve the pharmacokinetics and pharmacodynamics of related products (34-35).

Similarly, micelles are nanomaterials exhibiting amphiphilic properties; in aqueous environments, the hydrophilic parts of the molecules are located on the outer surface, while the hydrophobic components reside in the inner core. These structures can encapsulate hydrophobic drugs within their inner core and protect them from the external environment, while simultaneously being able to absorb polar drugs with their outer surface (Figure 6) (32).

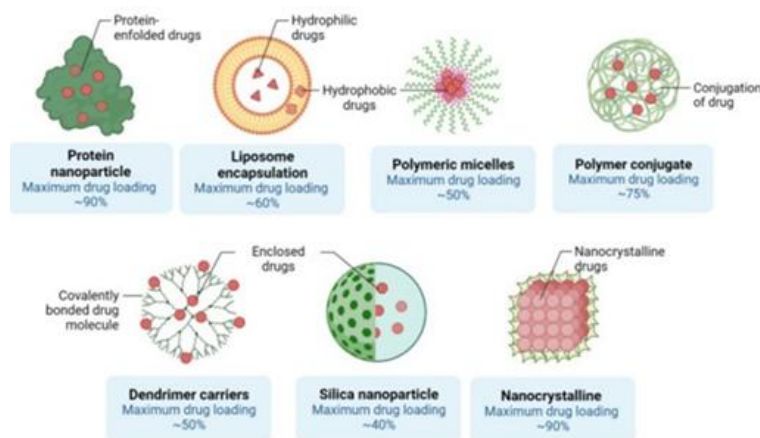


Figure 6: Types of Nanomaterials Used in Drug Delivery Systems (35)

4.3. Durability of Nanomaterials in the Body

The durability of the nanomaterial-drug complex is influenced by renal clearance or the activity level of the reticuloendothelial system (RES), which affects blood circulation through the kidneys. Relatively small nanomaterials are easily cleared by the kidneys, whereas larger nanostructures are removed by the RES. The capture of nanomaterials by RES cells reduces their systemic bioavailability. However, surface functionalization of nanomaterials with water-soluble polyethylene glycol (PEG) chains imparts "stealth-like" properties to these nanostructures, thereby reducing immune responses against them. This modification prevents their detection and phagocytosis by the mononuclear phagocytic system, allowing them to persist in the bloodstream (36-37). Additionally, PEGylation makes the nanomaterials appear as "empty" entities, enabling them to adsorb proteins, which prevents accumulation in biological systems. This property helps to avoid nanoparticle aggregation in solution and the formation of clusters as they enter the vascular system (38-39).

PEGylation, which extends the half-life of nanoparticles, is schematically illustrated in Figure 7.

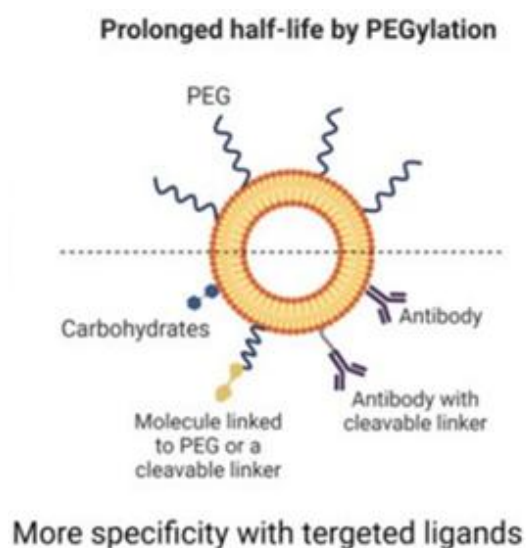


Figure 7: Illustration of nanoparticles with half-life extended through PEGylation (35)

4.4. Advantages and Disadvantages of Nanotechnology in Cancer Diagnosis and Treatment

Advantages:

The unique characteristics of nanoparticles, such as their diminutive size, large surface area-to-mass ratio, and functionalized structures, confer several significant advantages, which include:

- Prolonged circulation time
- Targeted drug delivery to the site of interest
- Enhanced bioavailability
- Reduced systemic toxicity

While advancements in drug delivery using nanotechnological devices have been remarkable, there remain several unresolved challenges that need to be addressed.

Disadvantages:

1. A more comprehensive understanding of the intracellular uptake mechanisms and the biodistribution and clearance of nanodevices in biological tissues is essential.
2. The potential for adverse or off-target effects resulting from the interactions between nanodevices and biological systems, such as free radical generation and damage to adjacent tissues.
3. Scaling up from preclinical trials to large-scale production, the cost of raw materials, and ensuring rigorous quality control for nanodevice fabrication.
4. Difficulties in securing financial support for startup companies that aim to commercialize nanopharmaceuticals.

The challenges faced by targeted drug delivery systems utilizing nanoparticles can be mitigated through an in-depth investigation of the limitations of nanoparticle-based strategies, as well as optimizing the current potential of nanoparticle formulations and devices (40).

4.5. New Approaches

The ultimate goal of cancer therapy is to eradicate as many cancer cells as possible without damaging healthy cells. However, the ability of a drug to target specific regions within the body to achieve desired therapeutic effects remains an area requiring further development.

In this context, nanotechnology-based drug delivery systems are emerging as a potential alternative to overcome some of the barriers previously encountered. These systems exhibit promising features, including superior anti-tumor effects against oral cancers, which conventional chemotherapy cannot achieve. As a result, the U.S. Food and Drug Administration (FDA) recently approved a clinical trial for a nanoparticle-based system for the treatment of solid tumors in humans (26).

Additionally, the submucosal injection of Cuburbitacin BE poly-lactic acid nanoparticles (CuBE-PLA-NPs) for the targeted delivery to cervical lymph nodes and the evaluation of clinical therapeutic efficacy has been assessed. The results showed significantly higher drug concentrations in the cervical lymph nodes following CuBE-PLA-NP injection compared to the control group. Moreover, the drug concentrations in the bloodstream of the CuBE-PLA-NP group were found to be significantly lower than those in the control group (41-42).

Thus, in the near future, oncologists and patients will be able to benefit from suitable nanotechnology-based drug delivery systems, improving therapeutic outcomes while reducing costs. Although clinical studies on oral cancer using nanotechnology are limited, nanotechnology is expected to transform healthcare in dentistry, redefine cancer with novel methodologies, and personalize patient treatment profiles (43). However, further research is needed to translate the concepts of nanotechnology into practical applications and to achieve the correct drug doses and ideal release profiles from these systems. Moreover, studies should continue to better understand the efficacy of these systems for various cancers treated by different molecular and cellular mechanisms (26).

5. Nanotechnology in Implantology

Implants are widely used in dentistry. In fact, titanium is the clinically most suitable material in dentistry. Titanium implants have many advantages, including good biocompatibility, mechanical properties, and generally adequate corrosion resistance. Additionally, titanium is a material with a very low likelihood of causing immunological reactions (6,44).

Although the acidic and saline conditions in the oral cavity can lead to electrochemical reactions between the implant and tissues, the corrosion resistance of titanium implants is not absolute. Under such conditions, implants are still prone to releasing wear particles and ions, which can lead to local immune responses, material degradation, and ultimately implant failure. Another factor influencing corrosion is the effect of microorganisms. The impact of their

enzyme-dependent activities can cause the loss of the surface passivation, thereby increasing the rate of corrosion (6,45).

Implants designed with the addition of nanoarchitecture aim to be resistant to infection, reduce the body's immune response, have higher integration, and release degradable drugs over time.⁴⁶

Surface properties of nanocomposite implants can be modified to alter the immune response developed against the implant or the ability of bacteria to colonize it; there is a theory that the reduction in immune response is more dependent on the surface properties rather than the chemistry of the nanometric materials (3,47).

Uncoated implants generally exhibit lower osseointegration, which leads to impaired long-term healing. The surface roughness increases protein and tissue adsorption and proliferation on the implant. One of the advantages of coating implants is the increase in stress transfer; a thicker coating can provide better stress reduction, and the nanoporous structure can lead to a more homogeneous stress distribution (6).

Among the surface treatments of clinically used implants are mechanical processing, sandblasting, acid etching, sandblasting and acid etching, anodization, and plasma treatment (46,48).

Mechanical processing is considered a pioneering modification strategy applied to dental implants, supported by the significant work of P.I. Brånemark and his group (46,49). This process involves shaping the base material using harder metals at high rotational speeds, and this process reveals properties ranging from macro to micro scale; these properties have evolved from manual processing to digitally controlled processing methods.⁴⁶

The combination of sandblasting and acid etching (SLA or sandblasted large-grit acid-etched) is a popular option in clinical practice. Studies have reported that accelerated osseointegration occurs within 1-2 months on micro/nano SLA implant surfaces. This bidirectional physical and chemical process is considered the most effective dental implant surface modification strategy, showing long-term success in pre-clinical and clinical research (46,50,51).

Controlled titanium (TiO₂) nanostructures, such as nanotubes and nanopores, can be produced on titanium-based implants using electrochemical anodization (EA). This process allows the formation of regular nanotube and nanopore structures on Ti implants. This process results in titanium oxidation (TiO₂) driven by the electric field, and fluoride-induced TiO₂

dissolution in a fluoride-containing organic electrolyte, leading to the self-organization of titanium nanotubes/nanopores upon reaching electrochemical equilibrium. By adjusting EA parameters like electrolyte composition (water/fluoride content), voltage, current, and duration, various nanostructures, including nanotubes, nanopores, nanograss, and nanotemplates, can be produced. Optimum EA ensures controlled nanostructures are produced on these surfaces (Figure 8) (46). Anodization parameters, electrolyte age, composition (water/fluoride content), anodization voltage, current, or duration can be adjusted to produce complex nanostructures on the implant surfaces. Titanium nanotubes (TNTs) are hollow, test tube-like structures with open tops and closed bottoms, and their modification has been widely researched to enhance cell biological activity. Most of the research suggests that TNTs are recommended as an implant modification to enhance osseointegration (bone integration) (46,52).

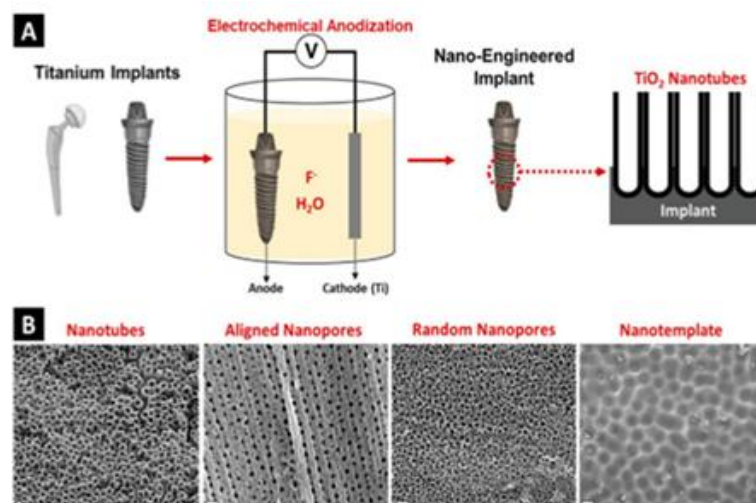


Figure 8: Various titanium nanotubes obtained as a result of electrochemical anodization⁴⁶

Plasma treatment, on the other hand, involves coating the implant with the desired material through melting and sintering in a vacuum or low-pressure environment. As a result, the implant surface is coated with micro/nano-scale layers; however, these adhesive layers may peel off or separate; therefore, careful surgical handling may be required during implant placement (46).

The anodization and production of titanium nanotubes (TNT) on Ti implants is considered an ideal nano-engineering strategy based on key reasons such as easy and cost-effective

production, anodizing complex shapes and geometries, ease of arranging nanostructures, enhanced biological activity, preservation of micro-roughness, and broad in vitro and in vivo support.

Nanomaterials are typically used as surface coatings, playing a special role by allowing changes in topology (increased surface area of the coating with bone) and biological activity (enhancement of healing and cell adhesion). The use of nanomaterials offers the possibility of optimizing the topography of the implanted region by adding hierarchical micro/nanostructures to the surface; this not only significantly increases the surface area but also strengthens osseointegration (3).

For example, a commonly used implant alloy, Ti-6Al-4V, has been coated with hierarchical topography by plasma spraying HT or Sr-HT micron-sized powders onto commercially available Ti alloy plates. As a result of this process, a micron-rough ceramic was coated with surface nanoparticles of strontium-substituted hardystonite (Sr-HT). Another implant was coated with classical hydroxyapatite (HAp), while the Sr-HT-coated implant showed improved cell adhesion, remineralization, and new bone tissue formation, with a synergistic effect between the hierarchical topography and dissolution products (6,53).

Calcium silicate (CS)-based nanocoatings are also used to enhance osseointegration. The combination of atmospheric plasma spraying (APS) and hydrothermal technology (HT) imparts desirable characteristics, including high crystallinity to the coating, and enhances its degradation rate, crucial for the storage and transport of potential implants (6,54).

Compared to traditional CS coatings, nanostructured CS coatings offer improved hydroxyapatite mineralization, enhanced cell adhesion, increased cell proliferation, better osteogenic differentiation, and higher angiogenic factor levels (6,54).

The advantages brought by these titanium nanotubes created on the implant surface are summarized in figure 9.

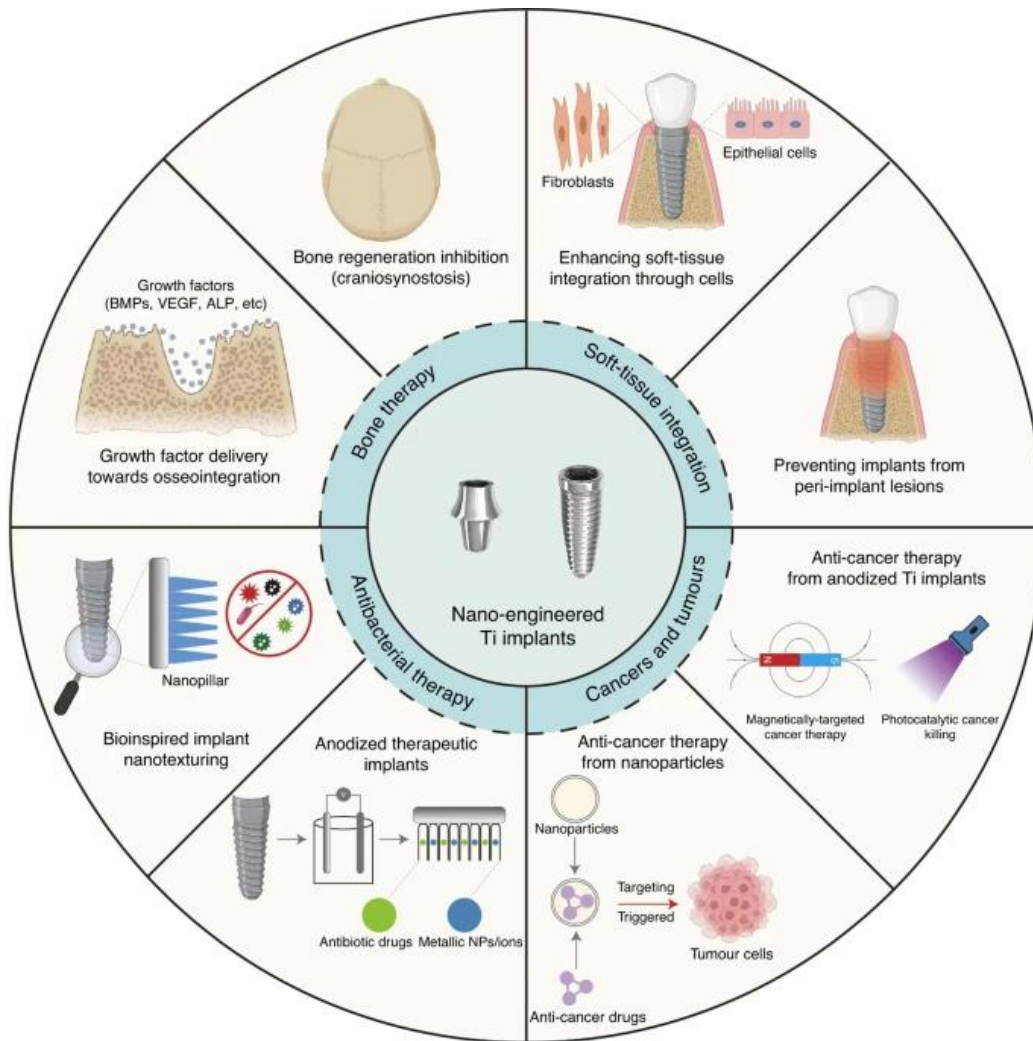


Figure 9: The advantages brought by these titanium nanotubes created on the implant surface³

The success of the implant is largely dependent on the quality of surface modifications, which are related to osteointegration, immune system response, and infection control. The ideal scenario is to maximize the therapeutic release and safely direct it to the implant's micro-environment, especially to the trauma site. These therapeutic agents can be bound to the surface of titanium (Ti) implants by modifying them with polymers, hydrogels, or nanoparticles. This way, the healing process can be accelerated, biocompatibility improved, and the long-term success of the implant can be ensured (46,55,56,57).

Some compounds added to TNTs to enhance osteointegration are as follows:

- **Bone Morphogenetic Protein-2 (BMP-2):** This is the most commonly used orthopedic biological substance for modifying titanium (Ti) implants with TNTs to enhance implant osteogenesis (46).

• **Strontium ranelate:** This anti-osteoporotic drug is used to guide research on the integration of strontium (Sr) into titanium (Ti) implants (46,58).

• **Pamidronic acid (PDA):** It enhances osseointegration and reduces bone resorption. It also demonstrates biocompatibility with osteoblasts and hematopoietic stem cells, while inducing apoptosis in osteoclasts derived from hematopoietic stem cells (46,59).

• Studies conducted with **parathyroid hormone (PTH)** and **fetal bovine serum (FBS)** have also shown an increase in osteogenic activity (46,60,61).

Ideal titanium nanostructures with antibacterial modifications should prevent adhesion, inhibit colonization, prevent biofilm formation, and stop proliferation. In the past decade, research for the design of next-generation bacteriostatic and bactericidal implants has focused on micro and nanoscale topographic modifications to prevent biofilm formation (46,62). With the rise of implant-associated infections, research has shifted toward providing local treatment through implant coatings and the loading and release of potent antibiotic agents (63,64). The high surface area of nanotopography and reduced shear forces enhance the adhesion of bacteria and osteoblasts. Ti implants anodized with TNTs have been found to have great potential for providing controlled local therapy to combat infections (46,53).

Biomimetic nanotexturing applied to implant surfaces (such as the creation of nanopillars, nanodroplets, or nanohairs, which mimic dragonfly wings or lizard skin) has exhibited antibacterial activity through a 'spiked bed' mechanism. Although static nanoscale implant topography can initially prevent adhesion, it may also protect attached and dead bacteria, as well as other microbes, from the underlying surface. Therefore, the development of 'dynamic' modifications, which trigger bactericidal activity in response to electrical or magnetic fields, has become increasingly important (63,64).

The goal is to address the drawbacks of systemic treatments by enhancing surface conditions, enabling local drug release, maximizing therapeutic efficacy, and ensuring safe delivery to the trauma site within the implant's microenvironment. These therapeutic substances can be attached to the surface of titanium (Ti) implants through modification with polymers, hydrogels, or nanoparticles (55,56,57).

Studies have shown positive developments in infection control through the loading of gentamicin and vancomycin onto nanotubes that release antibiotics (46,65-67). These loadings are possible due to the coating of the implant surface with biopolymers.

The placement of drug-releasing implants can result in high drug concentrations that may cause local cytotoxicity and potentially trigger bacterial adhesion again. Therapeutic release can be controlled by adjusting TNT size or coating drug-loaded TNTs with degradable biopolymers like polydopamine (PDA), PLGA [poly(lactic-co-glycolic acid)], and chitosan to achieve sustained long-term release (46,68).

Another method involves integrating strong metallic/semimetallic ions or nanoparticles onto or into TNT-based titanium (Ti) implants to provide potent bactericidal functions. Examples of added ions and nanoparticles include silver (Ag), gold (Au), copper (Cu), boron (B), phosphorus (P), calcium (Ca), gallium (Ga), selenium (Se), magnesium (Mg), fluorine (F), and zinc (Zn) (46).

Additionally, studies have been conducted with ibuprofen to reduce the anti-inflammatory response.⁶ Modification of titanium nanotubes illustrated in figure 10 (46), advantages and disadvantages of modifications added to TNTs illustrated in figure 11 (69,70).

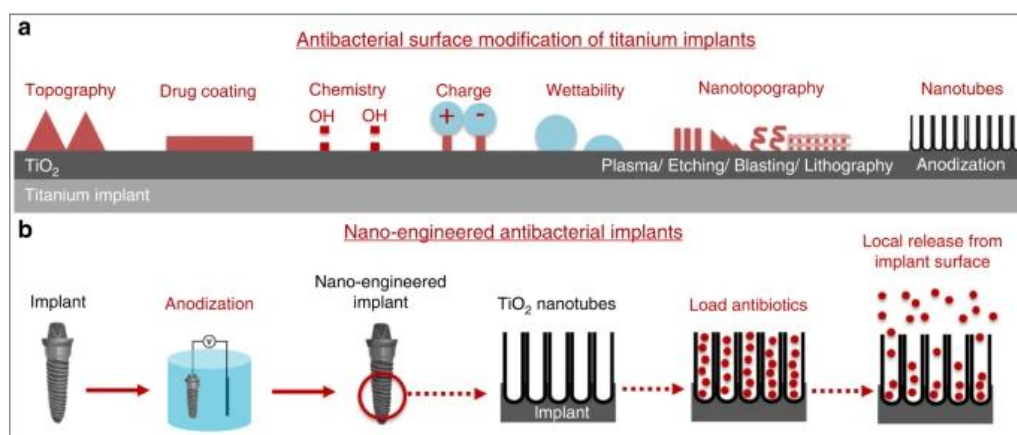


Figure 10: Antibacterial modification of Ti implant surfaces: a. different physical and chemical surface modification techniques; and b. electrochemically anodized Ti implants featuring TiO₂ nanotubes for localized antibiotic release (46).

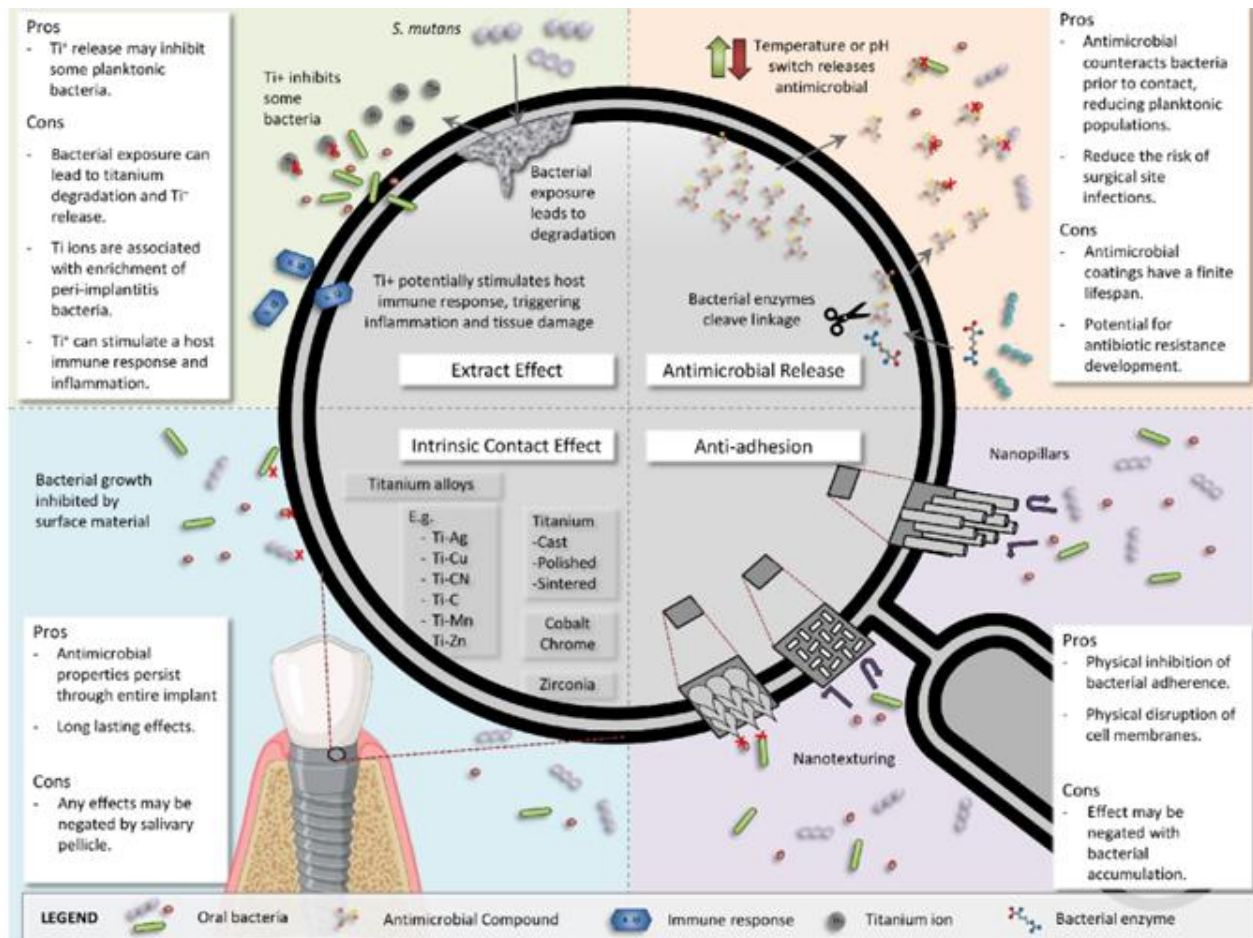


Figure 11: Illustration of the advantages and disadvantages of modifications added to TNTs (69,70)

6. Nanoanesthesia

Anesthetic nanorobots are still at the conceptual level. This idea involves the use of a suspension containing nanobots that can reach the dentin and move toward the dental pulp. The navigation factor could be, for example, a temperature gradient, chemical agents, or a computer used externally by the dentist. Once reaching the site of action, the nanobots would alter neurotransmission and maintain this state until the medical procedure is completed. Despite the growing opportunities for developing such technological structures since the discovery of scanning tunneling microscopy and atomic force microscopy, there has been no significant further development (1,6).

7. Potential Side Effects and Limitations

In order to fully utilize nanotechnology and minimize potential toxic effects, the long-term health impacts of nanoparticles must be thoroughly researched. The reduced size of nanomaterials can cause some potential issues. As they move through the body, nanoparticles may accumulate in target organs (liver, lungs, kidneys, heart, and spleen), penetrate cell membranes and mitochondria, and trigger a series of negative events. For example, manganese oxide, titanium dioxide, aluminum oxide, zinc oxide, and silver can accumulate and cause harmful reactions, or a nanoparticle may be small enough to cross the blood-brain barrier (3,71). High surface area ratios make nanoparticles biologically active, which can lead to outcomes such as infection and oxidative stress. For successful tissue engineering, scaffolds must be developed in a way that provides necessary oxygen and nutrients to dense cellular clusters in all organs (10,46,72).

The release of Ti particles and ions (including nanoparticles) results from (tribo-)corrosion. The presence of unintended or released nanoparticles (NPs) due to surface corrosion of the implant can also lead to specific toxicity. NPs loaded onto the implant surface (e.g., metals and drugs) can be unexpectedly released. These released NPs may interact chemically or physically with biological fluids, regardless of their composition.

Uncontrolled and high drug/protein concentrations, along with the contact between Ti (particles or ions) and tissues at the implant site, can lead to toxic effects on the surrounding tissues or newly regenerating bone. Ti particles cause an increase in osteoclast differentiation and resorption activity, continuously triggering the release of RANK-L and pro-inflammatory cytokines (such as IL-1 and TNF- β) (46,73). This can create a vicious cycle that enhances osteoclastogenesis, contributing to the corrosion of Ti dental implants and causing the accumulation of metal ions/particles in the cytoplasm of precursor cells. All of these events trigger a pro-inflammatory response from immune cells, negatively impacting tissue integration and wound healing (46).

Due to their small size, metal types (NPs or ions) and ROS can diffuse through nuclear pores and enter the nucleus. AgNPs, Au, and metal oxides such as TiO₂ or ZnO can act as DNA intercalators, causing severe oxidative DNA damage (46,74).

As previously mentioned, Ti implants designed with nano-engineering have extraordinary potential in terms of biological activity and therapeutic applications. However, important questions arise regarding the transition from the laboratory to clinical applications. The clinical translation of nano-engineered Ti dental implants faces the following challenges (Figure 12): (23)

- Optimization of production
- Achieving local sustained drug release
- Enhancement of biological activity
- Adaptation of in vivo models
- Achieving corrosion resistance and electrochemical stability
- Selection of sterilization process (23)

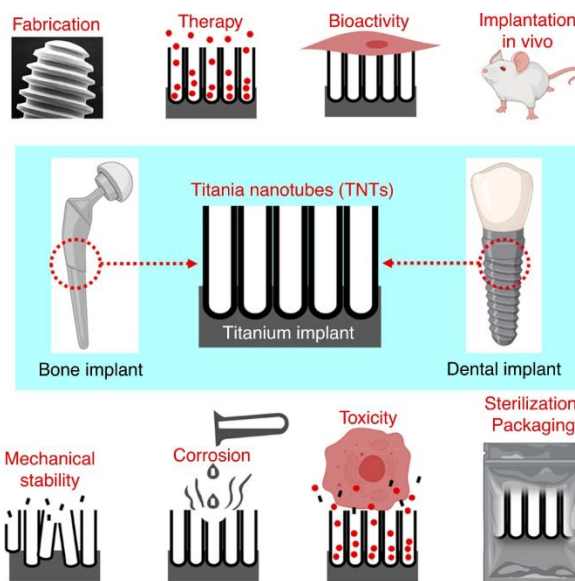


Figure 12: Clinical transition challenges (46)

It is anticipated that advanced engineering and design approaches will increase the effectiveness and safety of these implants, thereby expanding their applications in the field of dentistry (46).

Conclusion

The integration of regenerative nanotechnology into oral and maxillofacial surgery is advancing at an accelerated pace, with recent breakthroughs highlighting its transformative potential. Nanomaterials exhibit exceptional physical, chemical, and biomimetic properties that facilitate cellular proliferation and tissue regeneration, positioning them as promising candidates for future therapeutic interventions. Although the use of biomaterials for bone regeneration is well-established, the application of nanoscience and nanotechnology in oral and maxillofacial surgery remains an emerging and rapidly evolving field, offering novel avenues for clinical advancement.

Although some nanostructures have not yet proven effective for clinical use, certain innovative nanostructures offer promising new therapeutic benefits for cancer treatment in the near future. Both in cultured cells and in vivo experimental animals, long-term and short-

term toxicity evaluations must be conducted for these nanomaterials until they receive FDA approval for clinical application. However, nanotechnology has successfully developed innovative methods for cancer diagnosis, management, and monitoring throughout the 21st century, and continues to support our commitment to early intervention by identifying the molecular pathways of cancer.

The integration of nanotechnology into the development of titanium dental implants presents both exciting opportunities and significant challenges. While the potential of nano-engineered implants for improving biological activity, therapeutic outcomes, and long-term stability is evident, several obstacles remain in terms of production optimization, achieving sustained drug release, enhancing biological interactions, and ensuring corrosion resistance. Additionally, the safe clinical application of these implants requires careful consideration of potential toxicity, as nanoparticle accumulation in vital organs, the release of metal ions, and oxidative stress could lead to adverse effects. The clinical translation of nano-engineered titanium dental implants requires further research, especially in optimizing the balance between efficacy and safety. Addressing these challenges through advanced engineering methods and in vivo model adaptation is crucial for enhancing implant performance and expanding their application in the field of dentistry. The "set and forget" concept-based implants are expected to be the future of dental applications, ensuring early stability and long-term success. This will minimize the need for treatment or corrections, reducing clinical visits and patient complaints. It will make it possible to achieve a high success rate in both healthy and at-risk patient conditions. Achieving this will pave the way for a broader implant market, including orthopedic implants, joint replacements, and craniofacial implants.

Regenerative nanotechnology in oral and maxillofacial surgery offers significant potential for improving tissue regeneration and therapeutic outcomes, particularly in dental implants and cancer treatments. However, challenges remain in optimizing production, achieving sustained drug release, ensuring corrosion resistance, and assessing the potential toxicity of nanoparticles, necessitating further research for safe clinical application.

References

1. Bhardwaj A, Bhardwaj A, Misuriya A, Maroli S, Manjula S, Singh AK. Nanotechnology in dentistry: Present and future. *J Int Oral Health*. 2014 Feb;6(1):121-6. Epub 2014 Feb 26. PMID: 24653616; PMCID: PMC3959150.
2. Freitas RA Jr. Nanodentistry. *J Am Dent Assoc* 2000;131(11):1559-65.
3. Shakib K, et al. Regenerative nanotechnology in oral and maxillofacial surgery. *Br J Oral Maxillofac Surg* (2014), <http://dx.doi.org/10.1016/j.bjoms.2014.08.006>
4. National Science Foundation. Nanotechnology definition (NSET, February 2000). Available from URL: <http://www.nsf.gov/crssprgm/nano/reports/ombnifty50.jsp>
5. Haugen, H.J.; Makhtari, S.; Ahmadi, S.; Hussain, B. The Antibacterial and Cytotoxic Effects of Silver Nanoparticles Coated Titanium Implants: A Narrative Review. *Materials* 2022, 15, 5025. <https://doi.org/10.3390/ma15145025>
6. Glowacka-Sobotta, A.; Ziental, D.; Czarczynska-Goslinska, B.; Michalak, M.; Wysocki, M.; Güzel, E.; Sobotta, L. Nanotechnology for Dentistry: Prospects and Applications. *Nanomaterials* 2023, 13, 2130. <https://doi.org/10.3390/nano13142130>
7. Wu, Q.; Miao, W.; Zhang, Y.; Gao, H.; Hui, D. Mechanical Properties of Nanomaterials: A Review. *Nanotechnol. Rev.* 2020;9,259–273. [CrossRef]
8. Nagpal A, Kaur J, Sharma S, Bansal A, Sachdev P. Nanotechnology-the Era Of Molecular Dentistry. *Indian J Dent Sci* 2011;3: 80-2.
9. Loizidou M, Seifalian AM. Nanotechnology and its applications in surgery. *Br J Surg* 2010;97:463–5.
10. Funda G, Taschieri S, Bruno GA, Grecchi E, Paolo S, Girolamo D, Del Fabbro M. Nanotechnology Scaffolds for Alveolar Bone Regeneration. *Materials (Basel)*. 2020 Jan 3;13(1):201. doi: 10.3390/ma13010201. PMID: 31947750; PMCID: PMC6982209.
11. He L, Liu B, Xipeng G, et al. Microstructure and properties of nanofibrous PCL-b-PLLA scaffolds for cartilage tissue engineering. *Eur Cell Mater* 2009;18:63–74
12. Schofer MD, Roessler PP, Schaefer J, et al. Electrospun PLLA nanofiber scaffolds and their use in combination with BMP-2 for reconstruction of bone defects. *PLoS One* 2011;6:e25462.
13. Schofer MD, Tünnermann L, Kaiser H, et al. Functionalisation of PLLA nanofiber scaffolds using a possible cooperative effect between collagen type I and BMP-2:

- impact on colonization and bone formation in vivo. *J Mater Sci Mater Med* 2012;23:2227–33
14. Adamopoulos O, Papadopoulos T. Nanostructured bioceramics for maxillofacial applications. *J Mater Sci Mater Med* 2007;18:1587–97
 15. Sun L, Zhang L, Hemraz UD, Fenniri H, Webster TJ. Bioactive rosette nanotube-hydroxyapatite nanocomposites improve osteoblast functions. *Tissue Eng Part A* 2012;18:1741–50
 16. Sahithi K, Swetha M, Ramasamy K, Srinivasan N, Selvamurugan N. Polymeric composites containing carbon nanotubes for bone tissue engineering. *Int J Biol Macromol* 2010;46:281–3.
 17. Kobayashi H, Hama Y, Koyama Y, et al. Simultaneous multicolor imaging of five different lymphatic basins using quantum dots. *Nano Lett* 2007;7:1711–6
 18. Huo S, Jin S, Ma X, et al. Ultrasmall gold nanoparticles as carriers for nucleus-based gene therapy due to size-dependent nuclear entry. *ACS Nano* 2014;8:5852–62
 19. Kantola S, Parikka M, Jokinen K, et al. Prognostic factors in tongue cancer – relative importance of demographic, clinical and histopathological factors. *Br J Cancer*. 2000;83(5):614–619.)
 20. Carvalho AL, Magrin J, Kowalski LP. Sites of recurrence in oral and oropharyngeal cancers according to the treatment approach. *Oral Dis*. 2003;9(3):112–118.)
 21. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69–90.)
 22. Shah JP, Lydiatt W. Treatment of cancer of the head and neck. *CA Cancer J Clin*. 1995;45(6):352–368.)
 23. Onofre MA, Sposto MR, Navarro CM, Motta ME, Turatti E, Almeida RT. Potentially malignant epithelial oral lesions: discrepancies between clinical and histological diagnosis. *Oral Dis*. 1997;3(3):148–152.)
 24. Scully C, editor. Cancer. In: *Oral and Maxillofacial Medicine: The Basis of Diagnosis and Treatment*. 3rd ed. New York, NY: Churchill Livingstone Elsevier; 2013:204–217).

25. Csikar J, Aravani A, Godson J, Day M, Wilkinson J. Incidence of oral cancer among South Asians and those of other ethnic groups by sex in West Yorkshire and England, 2001–2006. *Br J Oral Maxillofac Surg*. 2013;51(1):25–29).
26. Calixto G. , Bernegossi J., Fonseca-Santos B., Chorilli M. 2014 Nanotechnology-based drug delivery systems for treatment of oral cancer. *International Journal of Nanomedicine* 2014;9 3719–3735)
27. Kumar GP, Rajeshwarrao P. Nonionic surfactant vesicular systems for effective drug delivery – an overview. *Acta Pharm Sin B*. 2011;1(4): 208–219.
28. Neha B, Ganesh B, Preeti K. Drug delivery to the brain using polymeric nanoparticles: a review. *International Journal of Pharmaceutical and Life Sciences*. 2013;2(3): 107–132.
29. Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. *Clin Cancer Res*. 2008;14(5): 1310–1316.
30. Couvreur P. Nanoparticles in drug delivery: past, present and future. *Adv Drug Deliv Rev*. 2013;65(1):21–23.
31. Saleh TA, Gupta VK. In Saleh TA, Gupta VK, authors. *Nanomaterial and polymer membranes*. Germany: Elsevier, 2016; s. 83-133.
32. Witharana S, Napagoda MT, *Nanotechnology in Modern Medicine* Springer Nature Singapore Pte Ltd, 2023.
33. Zhang H, Yee D, Wang C. Quantum dots for cancer diagnosis and therapy: biological and clinical perspectives. *Nanomedicine* 2008;3(1), 83–91.
34. Lee M-K. Liposomes for enhanced bioavailability of water-insoluble drugs: In Vivo evidence and recent approaches. *Pharmaceutics*. 2020; 12: 264.
35. Mosleh-Shirazi S, Abbasi M, Moaddeli M. R., Vaez A., Shafiee M. , Kasaei S.R., Amani A.M., Hatam S., 2022 *Nanotechnology Advances in the Detection and Treatment of Cancer : An Overview* ; 2022 ; 6(4): 400-423.
36. Yetisgin AA, Cetinel S, Zuvim M, Kosar A, Kutlu O. Therapeutic Nanoparticles and Their Targeted Delivery Applications. *Molecules*. 2020; 25: 2193.
37. Hara E, Makino A, Kurihara K, Yamamoto F, Ozeki E, Kimura S. Pharmacokinetic change of nanoparticulate formulation "Lactosome" on multiple administrations. *International immunopharmacology*. 2012; 14: 261-6

38. Jokerst JV, Lobovkina T, Zare RN, Gambhir SS. Nanoparticle PEGylation for imaging and therapy. *Nanomedicine (Lond)*. 2011; 6: 715-28.
39. Liang W, Dong Y, Shao R, Zhang S, Wu X, Huang X, et al. Application of nanoparticles in drug delivery for the treatment of osteosarcoma: focussing on the liposomes. *Journal of Drug Targeting*. 2022: 1-13.
40. Benjamin N. Ho, Claire M. Pfeffer and Amareshwar T.K. Singh. 2017 , Update on Nanotechnology-based Drug Delivery Systems in Cancer Treatment doi:10.21873/anticancerres.12044)
41. Eifer AC, Thaxton CS. Nanoparticle therapeutics: FDA approval, clinical trials, regulatory pathways, and case study. In: Hurst SJ, editor. *Biomedical Nanotechnology: Methods and Protocols*. New York: Humana Press; 2011:235–338. 204.
42. Yang K, Wen Y, Wang C. [Clinical application of anticancer nanoparticles targeting metastasis foci of cervical lymph nodes in patients with oral carcinoma]. *Hua Xi Kou Qiang Yi Xue Za Zhi*. 2003;21(6): 447–450. Chinese.
43. Hull LC, Farrell D, Grodzinski P. Highlights of recent developments and trends in cancer nanotechnology research-View from NCI Alliance for Nanotechnology in Cancer. *Biotechnol Adv*. Epub 12 August, 2013.
44. Meng, W.; Zhou, Y.; Zhang, Y.; Cai, Q.; Yang, L.; Zhao, J.; Li, C. Osteoblast Behavior on Hierarchical Micro-/Nano-Structured Titanium Surface. *J. Bionic Eng*. 2011, 8, 234–241. [CrossRef]
45. Chaturvedi, T. An Overview of the Corrosion Aspect of Dental Implants (Titanium and Its Alloys). *Indian J. Dent. Res*. 2009, 20, 91–98. [CrossRef]
46. Karan Gulati, Divya Chopra, Necla Asli Kocak-Oztug, Elise Verron. Fit and forget: The future of dental implant therapy via nanotechnology. *Advanced Drug Delivery Reviews* 199 (2023) 114900. <https://doi.org/10.1016/j.addr.2023.114900>
47. Sahithi K, Swetha M, Ramasamy K, Srinivasan N, Selvamurugan N. Polymeric composites containing carbon nanotubes for bone tissue engineering. *Int J Biol Macromol* 2010;46:281–3.
48. M.F. Kunrath, T.C. Muradás, N. Penha, M.M. Campos, Innovative surfaces and alloys for dental implants: What about biointerface-safety concerns?, *Dent. Mater*. 2021; 37(10),1447–1462.

49. R. Adell, U. Lekholm, B. Rockler, P.-I. Brånemark, A 15-year study of osseointegrated implants in the treatment of the edentulous jaw, *Int. J. Oral Surg.* 1981;10(6),387–416.
50. R. Rasouli, A. Barhoum, H. Uludag, A review of nanostructured surfaces and materials for dental implants: surface coating, patterning and functionalization for improved performance, *Biomater. Sci.* 2018;6,(6),1312–1338.
51. D.L. Cochran, D. Buser, C.M. Ten Bruggenkate, D. Weingart, T.M. Taylor, J.P. Bernard, F. Peters, J.P. Simpson, The use of reduced healing times on ITI implants with a sandblasted and acid-etched (SLA) surface: Early results from clinical trials on ITI SLA implants, *Clin. Oral Implants Res.* 2002;13(2),144– 153.
52. D. Chopra, T. Guo, S. Ivanovski, K. Gulati, Single-step nano-engineering of multiple micro-rough metals via anodization, *Nano Res.* 2023;16(1),1320– 1329.
53. Zhang, W.; Wang, G.; Liu, Y.; Zhao, X.; Zou, D.; Zhu, C.; Jin, Y.; Huang, Q.; Sun, J.; Liu, X.; et al. The Synergistic Effect of Hierarchical Micro/Nano-Topography and Bioactive Ions for Enhanced Osseointegration. *Biomaterials* 2013, 34, 3184–3195. [CrossRef] [PubMed]
54. Pye, A.D.; Lockhart, D.E.A.; Dawson, M.P.; Murray, C.A.; Smith, A.J. A Review of Dental Implants and Infection. *J. Hosp. Infect.* 2009, 72, 104–110. [CrossRef] [PubMed]
55. N. Hossain, M.A. Islam, M.A. Chowdhury, A. Alam, Advances of nanoparticles employment in dental implant applications, *Applied Surface Science Advances* 12 (2022).
56. S.E. Alavi, N. Panah, F. Page, M. Gholami, A. Dastfal, L.A. Sharma, H. Ebrahimi Shahmabadi, Hydrogel-based therapeutic coatings for dental implants, *Eur. Polym. J.* 181 (2022).
57. V.S. Saji, Recent Updates on Supramolecular-Based Drug Delivery – Macrocycles and Supramolecular Gels, *Chem. Rec.* 22 (7) (2022) e202200053. [92] L. Trombelli, R. Farina, A. Marzola, L. Bozzi, B. Liljenberg, J. Lindhe, Modeling and remodeling of human extraction sockets, *J. Clin. Periodontol.* 2008;35(7), 630–639.

58. L. Zhao, H. Wang, K. Huo, X. Zhang, W. Wang, Y. Zhang, Z. Wu, P.K. Chu, The osteogenic activity of strontium loaded titania nanotube arrays on titanium substrates, *Biomaterials* 2013;34(1),19–29
59. T.-H. Koo, J.S. Borah, Z.-C. Xing, S.-M. Moon, Y. Jeong, I.-K. Kang, Immobilization of pamidronic acids on the nanotube surface of titanium discs and their interaction with bone cells, *Nanoscale Res. Lett.* 2013;8,1–9
60. K. Gulati, M. Kogawa, M. Prideaux, D.M. Findlay, G.J. Atkins, D. Losic, Drug releasing nano-engineered titanium implants: therapeutic efficacy in 3D cell culture model, controlled release and stability, *Mater. Sci. Eng. C* 2016;69,831–840.
61. J. Peng, X. Zhang, Z. Li, Y. Liu, X. Yang, Titania nanotube delivery fetal bovine serum for enhancing MC3T3-E1 activity and osteogenic gene expression, *Mater. Sci. Eng. C* 2015;56,438–443
62. D. Chopra, K. Gulati, S. Ivanovski, Understanding and optimizing the antibacterial functions of anodized nano-engineered titanium implants, *Acta Biomater.* 2021;127,80–101.
63. A. Tripathy, P. Sen, B. Su, W.H. Briscoe, Natural and bioinspired nanostructured bactericidal surfaces, *Adv. Colloid Interface Sci.* 2017;248,85–104.
64. D. Chopra, K. Gulati, S. Ivanovski, Bed of nails: bioinspired nano-texturing towards antibacterial and bioactivity functions, *Materials Today Advances* 2021;12.
65. K.C. Popat, M. Eltgroth, T.J. LaTempa, C.A. Grimes, T.A. Desai, Decreased Staphylococcus epidermis adhesion and increased osteoblast functionality on antibiotic-loaded titania nanotubes, *Biomaterials* 2007;28(32), 4880–4888.
66. A. Pawlik, M. Jarosz, K. Syrek, G.D. Sulka, Co-delivery of ibuprofen and gentamicin from nanoporous anodic titanium dioxide layers, *Colloids Surf. B Biointerfaces* 2017;152,95–102.
67. D. Ionita, D. Bajenaru-Georgescu, G. Totea, A. Mazare, P. Schmuki, I. Demetrescu, Activity of vancomycin release from bioinspired coatings of hydroxyapatite or TiO₂ nanotubes, *Int. J. Pharm.* 2017;512(1-2),296–302.
68. K. Gulati, S. Ramakrishnan, M.S. Aw, G.J. Atkins, D.M. Findlay, D. Losic, Biocompatible polymer coating of titania nanotube arrays for improved drug elution and osteoblast adhesion, *Acta Biomater.* 2012;8(1),449–456.

69. Gulati, K., Ding, C., Guo, T. et al. Craniofacial therapy: advanced local therapies from nano-engineered titanium implants to treat craniofacial conditions. *Int J Oral Sci* 15, 2023;15(15). <https://doi.org/10.1038/s41368-023-00220-9>
70. J.J. Vernon, E.M. Raïf, J. Aw, E. Attenborough, A. Jha, T. Do, Dental implant surfaces and their interaction with the oral microbiome, *Dentistry Review* 2 2022;4.
71. Karmakar, A.; Zhang, Q.; Zhang, Y. Neurotoxicity of nanoscale materials. *J. Food Drug Anal.* 2014, 22, 147–160. [Google Scholar] [CrossRef] [Green Version]
72. C.H. Yang, Y.T. Wang, W.F. Tsai, C.F. Ai, M.C. Lin, H.H. Huang, Effect of oxygen plasma immersion ion implantation treatment on corrosion resistance and cell adhesion of titanium surface, *Clin. Oral Implants Res.* 2011;22(12), 1426–1432.
73. Y. Li, C. Wong, J. Xiong, P. Hodgson, C. Wen, Cytotoxicity of titanium and titanium alloying elements, *J. Dent. Res.* 2010;89,5,493–497.
74. N. Poier, J. Hochstöger, S. Hackenberg, A. Scherzad, M. Bregenzer, D. Schopper, N. Kleinsasser, Effects of zinc oxide nanoparticles in huvec: Cyto-and genotoxicity and functional impairment after long-term and repetitive exposure in vitro, *Int. J. Nanomedicine* 2020,15, 4441.