Dental Implant Nano-Engineering

Subjects: Biochemical Research Methods
Contributor: Yan Liu

Titanium (Ti) and its alloys offer favorable biocompatibility, mechanical properties and corrosion resistance, which makes them an ideal material choice for dental implants. However, the long-term success of Ti-based dental implants may be challenged due to implant-related infections and inadequate osseointegration. With the development of nanotechnology, nanoscale modifications and the application of nanomaterials have become key areas of focus for research on dental implants. Surface modifications and the use of various coatings, as well as the development of the controlled release of antibiotics or proteins, have improved the osseointegration and soft-tissue integration of dental implants, as well as their antibacterial and immunomodulatory functions.

Keywords: dental implants ; Nano-Engineering ; osseointegration ; TiO2 nanotubes ; surface modification ; nanoparticles ; antibacterial

1. Dental Implants: History, Survival Rates and Related Complications

In the 1960s, the first preclinical and clinical studies revealed that implants made of commercially pure titanium (Ti) could achieve anchorage in bone, which shifted the paradigm in implant dentistry [1]. Direct bone-to-implant contact, known as osseointegration, formed the foundation of oral implantology [2]. In the next two decades, other materials and different shapes of implants were clinically tested, such as ceramic implants made of aluminum oxide [3], non-threaded implants with a Ti plasma-sprayed surface [4], and Ti-aluminum-vanadium implants [5]. By the end of the 1980s, commercially pure Ti became the preferred material choice of implants [6]. In the 1990s, research findings reported that significantly stronger bone response and higher bone-to-implant contact were achieved in moderately rough or microrough implant surfaces [7]. Next, sandblasted and acid-etched surfaces, as well as microporous surfaces produced by anodic oxidation, were marketed [8][9]. In the past 10 years, zirconium dioxide implants showed comparable preclinical and clinical outcomes as those of moderately rough Ti implants [10]. Currently, microrough implant surfaces are the '*gold standard*' in implant dentistry.

Dental implant treatment is highly predictable, with a survival rate of around 95% according to 10-year clinical observations [11][12][13]. Despite the favorable clinical results, there are still implant-related mechanical, biological and functional complications [14][15]. One major complication is peri-implantitis, which can cause bone loss around the implant, eventually leading to implant failure. According to several reviews, more than 20% of patients and 10% of implants will be affected by peri-implantitis 5–10 years after implantation [16][17].

2. Nanoscale Dental Implant Modifications

2.1. Titania Nanotubes

2.1.1. Fabrication Optimization

Titania (TiO_2) nanotubes (TNTs) can be fabricated on Ti or its alloys via electrochemical anodization (EA) [18]. Briefly, EA involves the immersion of a Ti implant as an anode and a bare Ti/Pt electrode (cathode) inside an electrolyte (containing fluoride and water), with the supply of adequate current/voltage [19]. Under controlled and optimized conditions and the attainment of an equilibrium (characterized by metal oxide formation and dissolution), the self-ordering of TiO_2 nanotubes (like test-tubes, open at the top and closed at the bottom) or nanopores (nanotubes fused together, with no distance between them) on the entire surface of the implant occurs [20]. It is noteworthy that EA represents a cost-effective and scalable Ti implant surface modification strategy. Recent attempts to optimize EA to enable clinical translation include fabrication of controlled nanostructures on clinical dental implants [20], superior mechanical stability (nanopores > nanotubes) [21], and fabrication of dual micro-nano structures [22] by preserving the underlying 'gold standard' micro-roughness of dental implants [23]. It is worth noting that EA is a versatile technique that can be used to nano-engineer controlled topographies on various biomedical implants, spanning various metals and alloys, including Ti [24], Ti alloys [25],

Zr [26] and Al [27]. A schematic representation of TNTs and their various characteristics and research challenges is shown in **Figure 1**.

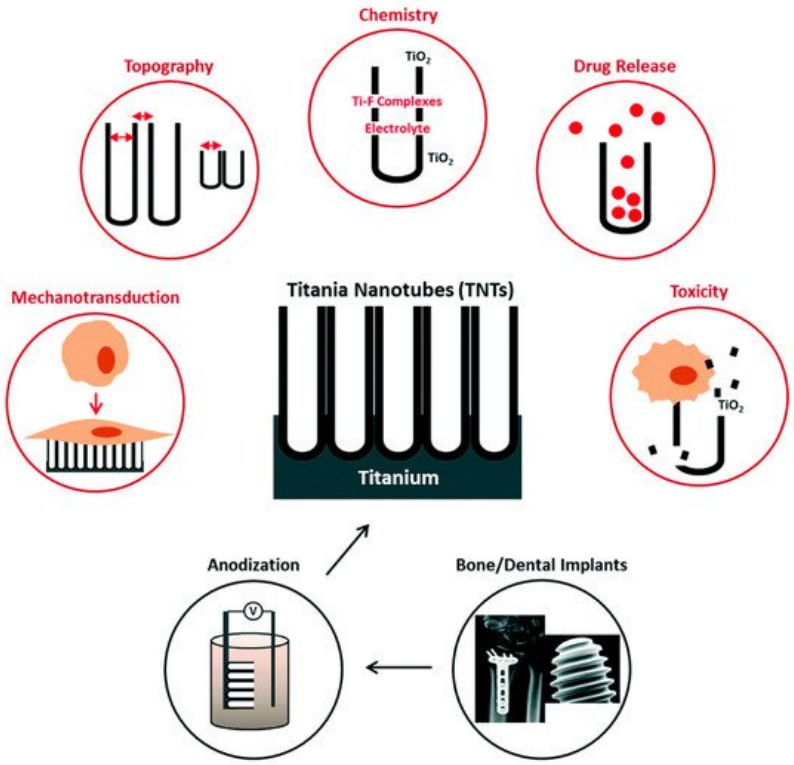

Figure 1. Electrochemically anodized dental implants with titania nanotubes (TNTs) for the purpose of enhanced bioactivity and local therapy. Adapted with permission from [28].

2.1.2. Osseointegration

Attributed to improved bioactivity and the ability to load and release proteins/growth factors, TNTs are a promising surface modification strategy for orchestrating osteogenesis, as established by various in vivo investigations [29][30]. The incorporation of fluoride ions into TNTs during anodization and the mechanical stimulation of osteoblasts also contribute towards the enhancement of osseointegration [31]. Further, to ensure the successful establishment and maintenance of osseointegration, TNTs on Ti implants have loaded with various orthobiologics, including bone morphogenetic protein-2 (BMP-2) [32], platelet-derived growth factor-BB [33], alendronate [34], ibandronate [35], N-acetyl cysteine (NAC) [36], and parathyroid hormone (PTH) [37]. Lee et al. loaded TNT-modified dental mini-screws with N-acetyl cysteine [NAC, a reactive oxygen species (ROS) scavenger with anti-inflammatory and osteogenic properties], implanted them in rat mandibles in vivo and, at 4 weeks, observed significantly enhanced osteointegration at the NAC–TNT sites [36]. In another study, machined dental implant screws were modified with HF etching and EA to fabricate dual micro- and nanotubular structures, which, upon implantation in ovariectomized sheep in vivo for 12 weeks, showed significantly increased pull-out force and bone-implant contact [38]. Further, various nanoparticles, ions or coatings of Sr [39], Ta [40], La [41], and Zn [42] onto/inside TNTs have also shown upregulated osteogenic outcomes.

It is worth noting that various ions or NPs have exhibited favorable osseointegration through their use in in vitro and in vivo investigations; however, these may illicit immunotoxic reactions in a dose-dependent manner and remain the subject of active research. Further, with respect to bone-forming proteins, future investigations into the estimation of the local need for bioactive agents and the evaluation of their release inside the bone micro-environment are needed.

2.1.3. Soft-Tissue Integration (STI)

Studies relating to the use of TNTs for enhancing STI for dental implants are very limited, as reviewed elsewhere [43]. Recently, Gulati et al. reported the enhanced proliferation and adhesion of human gingival fibroblasts (HGFs) on dual-micro-nano anisotropic TiO_2 nanopores [22]. Further, beginning at 1 day of culture, the HGFs started to align parallel to the nanopores; and the gene expression analysis (type I collagen, type III collagen and integrin β1) indicated a wound-healing profile that promoted substrate–cell and cell–cell interactions [44]. Further, anodization combined with heat treatment has also been used to upregulate fibroblast activity. Briefly, the proliferation and adhesion of gingival epithelial cells were enhanced on heat-treated anodized Ti surfaces, which was attributed to hydrothermal treatment precipitation of hydroxyapatite crystals [45]. Alternatively, hydrothermally treated TNTs have been reported to upregulate the integrin α5

and β4 expressions of gingival epithelial cells [46], the adhesion of murine fibroblast-like NIH/3T3 cells and the expression of adhesion kinase [47], as compared to unmodified TNTs.

The biofunctionalization of TNTs has also been explored in order to enhance the functions of fibroblasts and epithelial cells towards augmenting STI. For instance, Xu et al. reported that the inhibition of human gingival epithelial cells on TNTs was reversed when the electrochemical deposition of CaP was performed on TNTs, which was attributed to the local elution of Ca and P ions [48]. Next, Liu et al. investigated the influence of bovine serum albumin (BSA) loading inside TNTs on HGF functions [49]. Unmodified TNTs promoted early HGF adhesion and COL-1 secretion; however, BSA-TNTs enhanced early HGF adhesion, while suppressing late proliferation and COL-1 secretion. It is interesting that contradictory behaviors among bioactive coatings on TNTs have been reported and further in-depth investigation into the influence of these modifications on the STI performance is needed. Furthermore, the local elution of fibroblast growth factor-2 (FGF-2, immobilized on Ag nanoparticles) from TNTs effectively enhanced the proliferation, adhesion and extra-cellular matrix formation in the cultured HGFs [50]. Augmented proliferation, adhesion, and expression of VEGF and LAMA1 genes in vitro was observed, which were pronounced after the loading of 500 ng/mL of FGF-2.

2.1.4. Antibacterial Functions

The local release of therapeutics from TNTs has been widely explored towards optimizing the loading and local elution of potent antibacterial agents [51]. It is noteworthy that within minutes of implantation, saliva proteins adhere to the dental implant, forming a pellicle, and early colonizers such as *Streptococci* adhere to these pellicles within 48h [52]. This can be followed by secondary colonizers, including *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* [53]. These bacteria can further lead to peri-implantitis [54]. Once a biofilm is established, the routine administration of antibiotics is insufficient and, hence, local therapy using dental implants has been proposed. Further, TNTs can enhance bacterial adhesion due to their nano-scale roughness, increased number of dead bacteria and amorphous nature. Hence, the synergistic antibacterial functions of TNT-modified dental implants are needed to prevent bacterial colonization and implant failure. Further, the size and crystal structure of TNTs influences bacterial adhesion properties. Ercan et al. investigated the influence of the size and the heat treatment of TNTs on their antibacterial effect and reported that heat-treated and 80 nm diameter TNTs exhibit strong antibacterial effects [55]. Similarly, when comparing 15, 50 and 100 nm diameter TNTs, the lowest number of adherent bacteria were reported on the smallest-diameter TNTs [56]. Further, annealed TNTs show the best bactericidal response, as reported by Mazare et al. [57] and Podporska-Carroll et al. [58].

Various commonly prescribed antibiotics including Gentamicin [59], Vancomycin [60], Minocycline, Amoxicillin, Cephalothin [61], Cefuroxime [62] and Cecropin B [63] have been incorporated inside TNT-modified Ti implants to enable local antibacterial functions. Further, to target methicillin-resistant *Staphylococcus aureus* (MRSA), antimicrobial peptides (AMPs) such as HHC-36 have been loaded inside TNTs to achieve a bactericidal effect of almost 99.9% against MRSA [64]. Biopolymer coatings have also been applied to antibiotic-loaded TNTs to: (a) control drug release, (b) promote bioactivity, and (c) harness the inherent antibacterial property of biopolymers in order to provide long-term antibacterial functions. As a result, bare/drug-loaded TNTs have been modified with chitosan [65], polydopamine [66], silk fibroin [67] and PLGA (poly(lactic-co-glycolic acid)), which exhibited synergistic bioactivity and antibacterial enhancements. In addition, various antibacterial ions and nanoparticles (NPs), such as Ag [68], Au [69], Cu [70][71], B, P, Ca [72], Ga [73], Mg [74], ZnO [75], etc., have also been immobilized on or incorporated inside TNTs, with or without the use of hydroxyapatite or biopolymers, using techniques such as micro-arc oxidation, chemical reduction, photo-irradiation, spin-coating, and sputtering.

Multiple synergistic therapies, including osseointegration, immunomodulation, soft-tissue integration and antibacterial functions can also be enabled using nano-engineered Ti with TNTs. For instance, TNTs modified by Ag via plasma immersion ion implantation (PIII) showed excellent antibacterial effects against *P. gingivalis* and *A. actinomycetemcomitans*, while enhancing the bioactivity of epithelial cells and fibroblasts in vitro and reducing inflammatory responses in vivo [76]. Similarly, hydrothermally doped Mg-TNTs exhibited upregulated osteoprogenitor cell adhesion and proliferation (without cytotoxicity) and suppressed osteoclastogenesis, while showing long-lasting antimicrobial effects against methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA) and *E. coli* [74].

2.1.5. Immuno-Modulation

The modulation of the host immuno-inflammatory response is crucial to the timely establishment of osseointegration. Hence, attempts have been made to obtain immunomodulatory functions from modified TNTs [28]. These include the influence of physical/chemical characteristics and the local elution of anti-inflammatory drugs from TNTs. The influence of Ti nanotopography on immune cells, including macrophages, monocytes and neutrophils, has supported the attenuation

of inflammation [77][78]. Clearly, the presence of nano-scale cues controls macrophage adhesion and inflammatory cytokine production. Similarly, in vitro cultures of such cells on TNTs have also established the influence TNTs nanotopography on immuno-inflammatory responses [22].

Smith et al. reported reduced functions (viability, adhesion, proliferation and spreading) of immune cells on TNTs, as compared with bare Ti [79]. Alternatively, other studies have shown enhanced nitric oxide and the absence of foreign-body giant cells on TNTs [79][80]. With respect to the nanotube diameters, inconsistent results have been obtained, with some studies indicating 60–70 nm diameters as the most immuno-compatible [79][81]. Further, Ma et al. compared the functions of monocytes/macrophages on nanotubes and polished Ti, and reported post-attachment stretching inhibition (repulsed adhesion), enhanced M2 phenotype (wound healing) and suppressed M1 phenotype (pro-inflammatory) polarization for TNTs anodized at 5V [82]. Furthermore, to understand the mechanism behind selective immunomodulation due to TNTs, Neacsu et al. reported that this effect is attributed to the suppression of the phosphorylation of MAPK (mitogen-activated protein kinase) signaling molecules (p38, ERK1/2, and JNK) on TNTs [83]. More recently, using 50 and 70 nm diameter anodized anisotropic TiO_2 nanopores, we showed that macrophage proliferation was significantly reduced on the 70 nm nanopores [22]. Further, the spread of macrophage on nanopores indicated an oval morphology, which was suggestive of an inactivated state.

The local elution of potent drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), bypasses the limitations associated with systemic administration (delayed bone healing and toxicity). These drugs have been loaded inside TNTs for the purpose of local release. Briefly, Ibuprofen [84], Indomethacin [85], Dexamethasone [86], Aspirin [87], Sodium naproxen [88], Quercetin [89], Enrofloxacin [90], Propolis [91] and immunomodulatory cytokines [92] have been successfully loaded and locally eluted from TNTs in vitro. Further, to achieve substantial loading and the delayed/controlled release of anti-inflammatory drugs, approaches including biopolymer coating on drug-loaded TNTs [93][94], polymeric micelle encapsulation of drugs prior to loading [95], the periodic tailoring of TNTs [96], the chemical intercalation of drugs inside TNTs [97] and trigger-based release [98][99] have been reported for TNT-based Ti implants. Additionally, metal ions and nanoparticles (NPs), including Au [69], Ag [100] and Zn [101] have also been incorporated on/inside TNTs to impart synergistic immunomodulatory functions with antibacterial or osteogenic activity. More recently, super-hydrophilic TNTs were fabricated via anodization and hydrogenation, and significantly reduced macrophage proliferation; upregulated M2 and downregulated M1 surface markers were exhibited on the modified TNTs, translating into effective immunomodulation and wound healing functionality [102]. It is also noteworthy that various in vivo tests of TNT modifications intended for use in various therapies, including antibacterial [51], osteogenic [29] or anti-cancer [103] applications, have established the immuno-compatibility of TNTs.

2.2. Nanoparticles

NPs can enable multiple therapies at the surface of dental implants, including antibiofouling, osseo- and soft-tissue integration and immunomodulation [104][105]. While NPs have been utilized towards controlled therapies for periodontal, orthodontic, endodontic and restorative treatments, this section will primarily focus on the uses of NP-modified Ti dental implants in implant-based local therapy [106]. As reported in the previous section, NP-doped TNTs have also been widely explored in the context of the controlled release of NPs, which aims to strike a balance between therapy and toxicity.

2.2.1. Silver

Ag NPs are one of the most widely used dentistry restoration and dental implant doping choices due to their outstanding antimicrobial properties [107]. Ag adheres to the bacterial cell wall and the cytoplasmic membrane electrostatically, which causes structural disruption [106]. This results in extensive damage to bacterial DNA, proteins and lipids, resulting in the inhibition of bacterial growth/viability and effective bactericidal action. Besides, Ag NPs can also stimulate osteogenesis and soft-tissue integration, making them an ideal choice for dental implant surface modification [108]. For instance, dental abutments modified with Ag NP suspension prevented *C. albicans* contamination, in comparison with the controls of unmodified abutments [109]. Further, citrate-capped Ag NPs offered bactericidal effects against *S. aureus* and *P. aeruginosa* [110]. Ti implants deposited with Ag NPs using anodic spark deposition have also been co-doped with Si, Ca, P and Na ions, to offer synergistic antibacterial (*S. epidermidis*, *S. mutans* and *E. coli*) and osteogenic (human osteoblast-like cells, SAOS-2) functions [111]. Similarly, to confirm that the used dosage of Ag NPs is safe, a culture of HGFs on Ag NPs/Ti was performed in vitro and the results confirmed no adverse effects [112]. Further, Ag NPs have also been immobilized on Ti implants pre-modified with hydroxyapatite [113], hydrogen titanate [114], chitosan/hyaluronic acid multilayer [115], nanoporous silica coatings [116], Pt and Au [117], and sandblasting and acid-etching [118] in order to achieve superior antibacterial and bioactivity effects. However, while Ag NPs offer effective antimicrobial action, they may cause cytotoxicity via the release of free Ag+ ions, ROS production, transport across blood-brain-barrier, and inflammation [106].

In a manner that is also applicable to other NPs discussed below, the toxicity of NPs depends on their chemical composition, surface charge, size and shape [119]

2.2.2. Zinc

Like Ag NPs, Zn/ZnO NPs are not only antimicrobial but also osteogenic, hence their use in the modification of dental implants [104]. Zn is an essential element in all biological tissues and offers antibacterial effects against a wide range of microbes; however, its aggregation can cause cytotoxicity in mammalian cells [120]. To demonstrate its effectiveness against oral biofilms, Kulshrestha et al. reported that graphene/zinc oxide nanocomposite showed a significant reduction in biofilm formation [121]. Further, Hu et al. incorporated Zn into TiO_2 coatings on Ti implants through plasma electrolytic oxidation and observed superior bactericidal and bone-forming effects [122]. In 2017, Li et al. synthesized N-halamine labeled Silica/ZnO hybrid nanoparticles to functionalize Ti implants to enable antibacterial functions [123]. The hybrid NP-modified Ti exhibited excellent antibacterial activity against *P. aeruginosa*, *E. coli* and *S. aureus*, without any cytotoxicity against MC3T3-E1 preosteoblast in vitro. Recently, selective laser-melted porous Ti was biofunctionalized using Ag and Zn NPs via plasma electrolytic oxidation and tested against methicillin-resistant *Staphylococcus aureus* (MRSA) [124]. The results confirmed that 75% Ag and 25% Zn fully eradicated both adherent and planktonic bacteria in vitro and ex vivo. Further, Zn-modified Ti (0% Ag) enhanced the metabolic activity of preosteoblasts, indicating its suitability for dual osteogenic and antibacterial implant modification. Further, it is worth noting that ZnO NPs may cause cell apoptosis or necrosis and DNA damage [125]

2.2.3. Copper

CuO NPs offer advantages over Ag NPs, including cost-effectiveness, chemical stability and ease of combining with polymers, which makes them an attractive choice for biomaterial applications [126]. Further, Cu NPs have antibacterial, osteogenic and angiogenic properties [127], and have been applied towards the enhancement of both the bioactivity and the antimicrobial properties of Ti dental implants [128]. More recently, van Hengel et al. incorporated varying amounts of Ag and Cu NPs into TiO_2 coating on additively manufactured Ti–6Al–4V porous implants via plasma electrolytic oxidation [129]. Further, 75% Ag and 25% Cu caused the eradication of all bacteria in a murine femora model ex vivo, while only Cu NP-modified implants (0% Ag) augmented the metabolic activity of pre-osteoblastic MC3T3-E1 cells in vitro. Alternatively, Ti-6Al-7Nb alloy dental implants were coated with Cu NPs and cultured with *P. gingivalis* in vitro, and the findings suggested that Cu NPs can aid in local infection control around implants [130]. In 2020, Xia et al. reported the use of plasma immersion ion implantation and deposition (PIIID) technology to modify Ti implants with C/Cu NPs co-implantation [131]. The modified implants displayed superior mechanical and corrosion resistance properties and enhanced the antibacterial performance of Ti implants (against *S. aureus* and *E. coli*) without causing cytotoxicity (to mouse osteoblast cells) in vitro. In a more dental implant setting, Cu-deposited (micro-/nanoparticles) commercially pure (cp) grade 4 Ti discs (via spark-assisted anodization) were shown to exhibit dose-dependent antibacterial effects against peri-implantitis-associated strain *P. gingivalis* [132]. Similarly, micro-arc oxidation Cu NP-doped TiO_2 coatings showed excellent antibacterial activity, while augmenting the proliferation and adhesion of osteoblast and endothelial cells in vitro [71]. The interaction of Cu NPs with microbes and the bioactivity and toxicity evaluations of Cu NPs can be found elsewhere [133].

2.2.4. Zirconia

Zirconium (Zr) and zirconia (ZrO_2) are rising as dental implant material choices due to their biocompatibility, corrosion resistance and superior mechanical properties [26]. It is established that Zr^{4+} ions can interact with negatively charged bacterial membranes and cause cell damage and death [134]. Furthermore, Zr-based implants have been electrochemically anodized in order to fabricate controlled ZrO_2 nanostructures, including nanotubes and nanopores, which can augment implant bioactivity due to their nanoscale roughness [26][135][136]. For instance, anodized Zr cylinders were placed in rat femur osteotomy models in vivo, and accelerated bone formation was obtained, in comparison with the controls of unmodified Zr [137]. Further, Indira et al. reported the dip coating of Zr ions into anodized TNTs to form $ZrTiO_4$ over the nanotubes, which exhibited enhanced bioactivity (HAp formation in Hank's solution in vitro) and corrosion resistance [138]. Similarly, the application of a Zr film on a TiNi alloy via plasma immersion ion implantation and deposition (PIIID) augmented its corrosion resistance [139]. Nanotube formation has also been extended to TiZr alloys. For instance, Grigorescu et al. used two-step EA to fabricate nanotubes of varied diameters and observed an increase in hydrophilicity with reduction in diameter [140]. Further, the smallest nanotube diameters exhibited the highest antibacterial effects against *E. coli*. While ZrO_2/Zr is extensively used as a dental implant material, the leaching of Zr NPs may initiate cytotoxicity. For instance, the application of both Zr and TiO_2 NPs in a dose-dependent fashion could lead to osteoblast morphology changes and apoptosis, affecting both osteoblast differentiation and osteogenesis at high dosages [141].

References

1. Branemark, P.I.; Adell, R.; Breine, U.; Hansson, B.O.; Lindstrom, J.; Ohlsson, A. Intra-osseous anchorage of dental pro stheses: I. Experimental studies. Scand. J. Plast. Reconstr. Surg. 1969, 3, 81–100.
2. Branemark, P.I.; Hansson, B.O.; Adell, R.; Breine, U.; Lindstrom, J.; Hallen, O.; Ohman, A. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. Scand. J. Plast. Reconstr. Surg. Suppl. 1977, 1 6, 1–132.
3. Schulte, W.; Kleineikenscheidt, H.; Lindner, K.; Schareyka, R. The Tubingen immediate implant in clinical studies. Dtsc h. Zahnarztl. Z. 1978, 33, 348–359.
4. Kirsch, A.; Ackermann, K.L. The IMZ osteointegrated implant system. Dent. Clin. N. Am. 1989, 33, 733–791.
5. Niznick, G.A. The Core-Vent implant system. Oral Health 1983, 73, 13–17.
6. Buser, D.; Sennerby, L.; De Bruyn, H. Modern implant dentistry based on osseointegration: 50 years of progress, curre nt trends and open questions. Periodontology 2000 2017, 73, 7–21.
7. Buser, D.; Schenk, R.K.; Steinemann, S.; Fiorellini, J.P.; Fox, C.H.; Stich, H. Influence of surface characteristics on bon e integration of titanium implants. A histomorphometric study in miniature pigs. J. Biomed. Mater. Res. 1991, 25, 889–9 02.
8. Buser, D.; Nydegger, T.; Hirt, H.P.; Cochran, D.L.; Nolte, L.P. Removal torque values of titanium implants in the maxilla of miniature pigs. Int. J. Oral Maxillofac. Implant. 1998, 13, 611–619.
9. Buser, D.; Nydegger, T.; Oxland, T.; Cochran, D.L.; Schenk, R.K.; Hirt, H.P.; Snetivy, D.; Nolte, L.P. Interface shear stre ngth of titanium implants with a sandblasted and acid-etched surface: A biomechanical study in the maxilla of miniature pigs. J. Biomed. Mater. Res. 1999, 45, 75–83.
10. Cionca, N.; Hashim, D.; Mombelli, A. Zirconia dental implants: Where are we now, and where are we heading? Periodo ntology 2000 2017, 73, 241–258.
11. Buser, D.; Janner, S.F.; Wittneben, J.G.; Bragger, U.; Ramseier, C.A.; Salvi, G.E. 10-year survival and success rates of 511 titanium implants with a sandblasted and acid-etched surface: A retrospective study in 303 partially edentulous pati ents. Clin. Implant. Dent. Relat. Res. 2012, 14, 839–851.
12. Degidi, M.; Nardi, D.; Piattelli, A. 10-year follow-up of immediately loaded implants with TiUnite porous anodized surfac e. Clin. Implant. Dent. Relat. Res. 2012, 14, 828–838.
13. Fischer, K.; Stenberg, T. Prospective 10-year cohort study based on a randomized controlled trial (RCT) on implant-sup ported full-arch maxillary prostheses. Part 1: Sandblasted and acid-etched implants and mucosal tissue. Clin. Implant. Dent. Relat. Res. 2012, 14, 808–815.
14. Wennerberg, A.; Albrektsson, T.; Chrcanovic, B. Long-term clinical outcome of implants with different surface modificati ons. Eur. J. Oral Implantol. 2018, 11 (Suppl. S1), S123–S136.
15. Albrektsson, T.; Canullo, L.; Cochran, D.; De Bruyn, H. "Peri-Implantitis": A Complication of a Foreign Body or a Man-M ade "Disease". Facts and Fiction. Clin. Implant. Dent. Relat. Res. 2016, 18, 840–849.
16. Fu, J.H.; Wang, H.L. Breaking the wave of peri-implantitis. Periodontology 2000 2020, 84, 145–160.
17. Berglundh, T.; Armitage, G.; Araujo, M.G.; Avila-Ortiz, G.; Blanco, J.; Camargo, P.M.; Chen, S.; Cochran, D.; Derks, J.; Figuero, E.; et al. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J. Periodontol. 2018, 89 (Suppl. S1), S3 13–S318.
18. Gulati, K.; Kogawa, M.; Maher, S.; Atkins, G.; Findlay, D.; Losic, D. Titania nanotubes for local drug delivery from impla nt surfaces. In Electrochemically Engineered Nanoporous Materials; Springer International Publishing AG: Berlin, Germ any, 2015; pp. 307–355.
19. Gulati, K.; Santos, A.; Findlay, D.; Losic, D. Optimizing Anodization Conditions for the Growth of Titania Nanotubes on Curved Surfaces. J. Phys. Chem. C 2015, 119, 16033–16045.
20. Li, T.; Gulati, K.; Wang, N.; Zhang, Z.; Ivanovski, S. Bridging the gap: Optimized fabrication of robust titania nanostructu res on complex implant geometries towards clinical translation. J. Colloid Interface Sci. 2018, 529, 452–463.
21. Li, T.; Gulati, K.; Wang, N.; Zhang, Z.; Ivanovski, S. Understanding and augmenting the stability of therapeutic nanotub es on anodized titanium implants. Mater. Sci. Eng. C 2018, 88, 182–195.
22. Gulati, K.; Moon, H.-J.; Li, T.; Sudheesh Kumar, P.T.; Ivanovski, S. Titania nanopores with dual micro-/nano-topography for selective cellular bioactivity. Mater. Sci. Eng. C 2018, 91, 624–630.

23. Gulati, K.; Li, T.; Ivanovski, S. Consume or Conserve: Microroughness of Titanium Implants toward Fabrication of Dual Micro–Nanotopography. ACS Biomater. Sci. Eng. 2018, 4, 3125–3131.

24. Guo, T.; Oztug, N.A.K.; Han, P.; Ivanovski, S.; Gulati, K. Old is Gold: Electrolyte Aging Influences the Topography, Chemistry, and Bioactivity of Anodized TiO2 Nanopores. Acs Appl. Mater. Inter. 2021, 13, 7897–7912.

25. Gulati, K.; Prideaux, M.; Kogawa, M.; Lima-Marques, L.; Atkins, G.J.; Findlay, D.M.; Losic, D. Anodized 3D–printed titanium implants with dual micro- and nano-scale topography promote interaction with human osteoblasts and osteocyte-like cells. J. Tissue Eng. Regen. Med. 2017, 11, 3313–3325.

26. Chopra, D.; Gulati, K.; Ivanovski, S. Towards Clinical Translation: Optimized Fabrication of Controlled Nanostructures on Implant-Relevant Curved Zirconium Surfaces. Nanomaterials 2021, 11, 868.

27. Saji, V.S.; Kumeria, T.; Gulati, K.; Prideaux, M.; Rahman, S.; Alsawat, M.; Santos, A.; Atkins, G.J.; Losic, D. Localized drug delivery of selenium (Se) using nanoporous anodic aluminium oxide for bone implants. J. Mater. Chem. B 2015, 3, 7090–7098.

28. Gulati, K.; Hamlet, S.M.; Ivanovski, S. Tailoring the immuno-responsiveness of anodized nano-engineered titanium implants. J. Mater. Chem. B 2018, 6, 2677–2689.

29. Gulati, K.; Maher, S.; Findlay, D.M.; Losic, D. Titania nanotubes for orchestrating osteogenesis at the bone–implant interface. Nanomedicine 2016, 11, 1847–1864.

30. Gulati, K.; Ivanovski, S. Dental implants modified with drug releasing titania nanotubes: Therapeutic potential and developmental challenges. Expert Opin. Drug Deliv. 2017, 14, 1009–1024.

31. Zhang, H.; Yang, S.; Masako, N.; Lee, D.J.; Cooper, L.F.; Ko, C.-C. Proliferation of preosteoblasts on TiO 2 nanotubes is FAK/RhoA related. RSC Adv. 2015, 5, 38117–38124.

32. Balasundaram, G.; Yao, C.; Webster, T.J. TiO2 nanotubes functionalized with regions of bone morphogenetic protein-2 increases osteoblast adhesion. J. Biomed. Mater. Res. Part A 2008, 84, 447–453.

33. Zhang, W.; Jin, Y.; Qian, S.; Li, J.; Chang, Q.; Ye, D.; Pan, H.; Zhang, M.; Cao, H.; Liu, X. Vacuum extraction enhances rhPDGF-BB immobilization on nanotubes to improve implant osseointegration in ovariectomized rats. Nanomed. Nanotechnol. Biol. Med. 2014, 10, 1809–1818.

34. Shen, X.; Ma, P.; Hu, Y.; Xu, G.; Xu, K.; Chen, W.; Ran, Q.; Dai, L.; Yu, Y.; Mu, C. Alendronate-loaded hydroxyapatite-TiO2 nanotubes for improved bone formation in osteoporotic rabbits. J. Mater. Chem. B 2016, 4, 1423–1436.

35. Lee, S.J.; Oh, T.J.; Bae, T.S.; Lee, M.H.; Soh, Y.; Kim, B.I.; Kim, H.S. Effect of bisphosphonates on anodized and heat-treated titanium surfaces: An animal experimental study. J. Periodontol. 2011, 82, 1035–1042.

36. Lee, Y.-H.; Bhattarai, G.; Park, I.-S.; Kim, G.-R.; Kim, G.-E.; Lee, M.-H.; Yi, H.-K. Bone regeneration around N-acetyl cysteine-loaded nanotube titanium dental implant in rat mandible. Biomaterials 2013, 34, 10199–10208.

37. Gulati, K.; Kogawa, M.; Prideaux, M.; Findlay, D.M.; Atkins, G.J.; Losic, D. 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.

38. Xiao, J.; Zhou, H.; Zhao, L.; Sun, Y.; Guan, S.; Liu, B.; Kong, L. The effect of hierarchical micro/nanosurface titanium implant on osseointegration in ovariectomized sheep. Osteoporos. Int. 2011, 22, 1907–1913.

39. Zhao, L.; Wang, H.; Huo, K.; Zhang, X.; Wang, W.; Zhang, Y.; Wu, Z.; Chu, P.K. The osteogenic activity of strontium loaded titania nanotube arrays on titanium substrates. Biomaterials 2013, 34, 19–29.

40. Frandsen, C.J.; Brammer, K.S.; Noh, K.; Johnston, G.; Jin, S. Tantalum coating on TiO2 nanotubes induces superior rate of matrix mineralization and osteofunctionality in human osteoblasts. Mater. Sci. Eng. C 2014, 37, 332–341.

41. Zhang, X.; Zhang, X.; Wang, B.; Lan, J.; Yang, H.; Wang, Z.; Chang, X.; Wang, S.; Ma, X.; Qiao, H.; et al. Synergistic effects of lanthanum and strontium to enhance the osteogenic activity of TiO2 nanotube biological interface. Ceram. Int. 2020, 46, 13969–13979.

42. Huo, K.; Zhang, X.; Wang, H.; Zhao, L.; Liu, X.; Chu, P.K. Osteogenic activity and antibacterial effects on titanium surfaces modified with Zn-incorporated nanotube arrays. Biomaterials 2013, 34, 3467–3478.

43. Guo, T.Q.; Gulati, K.; Arora, H.; Han, P.P.; Fournier, B.; Ivanovski, S. Orchestrating soft tissue integration at the transmucosal region of titanium implants. Acta Biomater. 2021, 124, 33–49.

44. Gulati, K.; Moon, H.J.; Kumar, P.T.S.; Han, P.P.; Ivanovski, S. Anodized anisotropic titanium surfaces for enhanced guidance of gingival fibroblasts. Mat. Sci. Eng. C-Mater. 2020, 112, 110860.

45. Takebe, J.; Miyata, K.; Miura, S.; Ito, S. Effects of the nanotopographic surface structure of commercially pure titanium following anodization–hydrothermal treatment on gene expression and adhesion in gingival epithelial cells. Mater. Sci. Eng. C 2014, 42, 273–279.

46. Miyata, K.; Takebe, J. Anodized-hydrothermally treated titanium with a nanotopographic surface structure regulates integrin-α6β4 and laminin-5 gene expression in adherent murine gingival epithelial cells. J. Prosthodont. Res. 2013, 57, 99–108.

47. Miura, S.; Takebe, J. Biological behavior of fibroblast-like cells cultured on anodized-hydrothermally treated titanium with a nanotopographic surface structure. J. Prosthodont. Res. 2012, 56, 178–186.

48. Xu, R.; Hu, X.; Yu, X.; Wan, S.; Wu, F.; Ouyang, J.; Deng, F. Micro-/nano-topography of selective laser melting titanium enhances adhesion and proliferation and regulates adhesion-related gene expressions of human gingival fibroblasts and human gingival epithelial cells. Int. J. Nanomed. 2018, 13, 5045–5057.

49. Liu, X.; Zhou, X.; Li, S.; Lai, R.; Zhou, Z.; Zhang, Y.; Zhou, L. Effects of titania nanotubes with or without bovine serum albumin loaded on human gingival fibroblasts. Int. J. Nanomed. 2014, 9, 1185–1198.

50. Ma, Q.; Mei, S.; Ji, K.; Zhang, Y.; Chu, P.K. Immobilization of Ag nanoparticles/FGF-2 on a modified titanium implant surface and improved human gingival fibroblasts behavior. J. Biomed. Mater. Res. Part. A 2011, 98A, 274–286.

51. Chopra, D.; Gulati, K.; Ivanovski, S. Understanding and optimizing the antibacterial functions of anodized nano-engineered titanium implants. Acta Biomater. 2021, 127, 80–101.

52. Guo, T.; Gulati, K.; Arora, H.; Han, P.; Fournier, B.; Ivanovski, S. Race to invade: Understanding soft tissue integration at the transmucosal region of titanium dental implants. Dent. Mater. 2021, 37, 816–831.

53. Hao, Y.; Huang, X.; Zhou, X.; Li, M.; Ren, B.; Peng, X.; Cheng, L. Influence of Dental Prosthesis and Restorative Materials Interface on Oral Biofilms. Int. J. Mol. Sci. 2018, 19, 3157.

54. Shibli, J.A.; Melo, L.; Ferrari, D.S.; Figueiredo, L.C.; Faveri, M.; Feres, M. Composition of supra- and subgingival biofilm of subjects with healthy and diseased implants. Clin. Oral Implant. Res. 2008, 19, 975–982.

55. Ercan, B.; Taylor, E.; Alpaslan, E.; Webster, T.J. Diameter of titanium nanotubes influences anti-bacterial efficacy. Nanotechnology 2011, 22, 295102.

56. Narendrakumar, K.; Kulkarni, M.; Addison, O.; Mazare, A.; Junkar, I.; Schmuki, P.; Sammons, R.; Iglič, A. Adherence of oral streptococci to nanostructured titanium surfaces. Dent. Mater. 2015, 31, 1460–1468.

57. Mazare, A.; Totea, G.; Burnei, C.; Schmuki, P.; Demetrescu, I.; Ionita, D. Corrosion, antibacterial activity and haemocompatibility of TiO2 nanotubes as a function of their annealing temperature. Corros. Sci. 2016, 103, 215–222.

58. Podporska-Carroll, J.; Panaitescu, E.; Quilty, B.; Wang, L.; Menon, L.; Pillai, S.C. Antimicrobial properties of highly efficient photocatalytic TiO2 nanotubes. Appl. Catal. B Environ. 2015, 176–177, 70–75.

59. Pawlik, A.; Jarosz, M.; Syrek, K.; Sulka, G.D. Co-delivery of ibuprofen and gentamicin from nanoporous anodic titanium dioxide layers. Colloids Surf. B Biointerfaces 2017, 152, 95–102.

60. Ionita, D.; Bajenaru-Georgescu, D.; Totea, G.; Mazare, A.; Schmuki, P.; Demetrescu, I. Activity of vancomycin release from bioinspired coatings of hydroxyapatite or TiO2 nanotubes. Int. J. Pharm. 2017, 517, 296–302.

61. Park, S.W.; Lee, D.; Choi, Y.S.; Jeon, H.B.; Lee, C.-H.; Moon, J.-H.; Kwon, I.K. Mesoporous TiO2 implants for loading high dosage of antibacterial agent. Appl. Surf. Sci. 2014, 303, 140–146.

62. Chennell, P.; Feschet-Chassot, E.; Devers, T.; Awitor, K.; Descamps, S.; Sautou, V. In vitro evaluation of TiO2 nanotubes as cefuroxime carriers on orthopaedic implants for the prevention of periprosthetic joint infections. Int. J. Pharm. 2013, 455, 298–305.

63. Shen, X.; Zhang, F.; Li, K.; Qin, C.; Ma, P.; Dai, L.; Cai, K. Cecropin B loaded TiO2 nanotubes coated with hyaluronidase sensitive multilayers for reducing bacterial adhesion. Mater. Des. 2016, 92, 1007–1017.

64. Ma, M.; Kazemzadeh-Narbat, M.; Hui, Y.; Lu, S.; Ding, C.; Chen, D.D.; Hancock, R.E.; Wang, R. Local delivery of antimicrobial peptides using self-organized TiO2 nanotube arrays for peri-implant infections. J. Biomed. Mater. Res. Part A 2012, 100, 278–285.

65. Kumeria, T.; Mon, H.; Aw, M.S.; Gulati, K.; Santos, A.; Griesser, H.J.; Losic, D. Advanced biopolymer-coated drug-releasing titania nanotubes (TNTs) implants with simultaneously enhanced osteoblast adhesion and antibacterial properties. Colloids Surf. B Biointerfaces 2015, 130, 255–263.

66. Ding, X.; Zhang, Y.; Ling, J.; Lin, C. Rapid mussel-inspired synthesis of PDA-Zn-Ag nanofilms on TiO2 nanotubes for optimizing the antibacterial activity and biocompatibility by doping polydopamine with zinc at a higher temperature. Colloids Surf. B Biointerfaces 2018, 171, 101–109.

67. Fathi, M.; Akbari, B.; Taheriazam, A. Antibiotics drug release controlling and osteoblast adhesion from titania nanotubes arrays using silk fibroin coating. Mater. Sci. Eng. C 2019, 103, 109743.

68. Gao, A.; Hang, R.; Huang, X.; Zhao, L.; Zhang, X.; Wang, L.; Tang, B.; Ma, S.; Chu, P.K. The effects of titania nanotubes with embedded silver oxide nanoparticles on bacteria and osteoblasts. Biomaterials 2014, 35, 4223–4235.

69. Xu, W.; Qi, M.; Li, X.; Liu, X.; Wang, L.; Yu, W.; Liu, M.; Lan, A.; Zhou, Y.; Song, Y. TiO2 nanotubes modified with Au na noparticles for visible-light enhanced antibacterial and anti-inflammatory capabilities. J. Electroanal. Chem. 2019, 842, 66–73.

70. Zong, M.; Bai, L.; Liu, Y.; Wang, X.; Zhang, X.; Huang, X.; Hang, R.; Tang, B. Antibacterial ability and angiogenic activit y of Cu-Ti-O nanotube arrays. Mater. Sci. Eng. C 2017, 71, 93–99.

71. Zhang, X.; Li, J.; Wang, X.; Wang, Y.; Hang, R.; Huang, X.; Tang, B.; Chu, P.K. Effects of copper nanoparticles in porou s TiO2 coatings on bacterial resistance and cytocompatibility of osteoblasts and endothelial cells. Mater. Sci. Eng. C 20 18, 82, 110–120.

72. Sopchenski, L.; Cogo, S.; Dias-Ntipanyj, M.; Elifio-Espósito, S.; Popat, K.; Soares, P. Bioactive and antibacterial boron doped TiO2 coating obtained by PEO. Appl. Surf. Sci. 2018, 458, 49–58.

73. Dong, J.; Fang, D.; Zhang, L.; Shan, Q.; Huang, Y. Gallium-doped titania nanotubes elicit anti-bacterial efficacy in vivo against Escherichia coli and Staphylococcus aureus biofilm. Materialia 2019, 5, 100209.

74. Yang, Y.; Liu, L.; Luo, H.; Zhang, D.; Lei, S.; Zhou, K. Dual-purpose magnesium-incorporated titanium nanotubes for co mbating bacterial infection and ameliorating osteolysis to realize better osseointegration. ACS Biomater. Sci. Eng. 201 9, 5, 5368–5383.

75. Xiang, Y.; Liu, X.; Mao, C.; Liu, X.; Cui, Z.; Yang, X.; Yeung, K.W.; Zheng, Y.; Wu, S. Infection-prevention on Ti implants by controlled drug release from folic acid/ZnO quantum dots sealed titania nanotubes. Mater. Sci. Eng. C 2018, 85, 214 –224.

76. Mei, S.; Wang, H.; Wang, W.; Tong, L.; Pan, H.; Ruan, C.; Ma, Q.; Liu, M.; Yang, H.; Zhang, L. Antibacterial effects and biocompatibility of titanium surfaces with graded silver incorporation in titania nanotubes. Biomaterials 2014, 35, 4255– 4265.

77. Alfarsi, M.A.; Hamlet, S.M.; Ivanovski, S. Titanium surface hydrophilicity modulates the human macrophage inflammato ry cytokine response. J. Biomed. Mater. Res. Part A 2014, 102, 60–67.

78. Hamlet, S.; Ivanovski, S. Inflammatory cytokine response to titanium chemical composition and nanoscale calcium pho sphate surface modification. Acta Biomater. 2011, 7, 2345–2353.

79. Neacsu, P.; Mazare, A.; Cimpean, A.; Park, J.; Costache, M.; Schmuki, P.; Demetrescu, I. Reduced inflammatory activit y of RAW 264.7 macrophages on titania nanotube modified Ti surface. Int. J. Biochem. Cell Biol. 2014, 55, 187–195.

80. Smith, B.S.; Capellato, P.; Kelley, S.; Gonzalez-Juarrero, M.; Popat, K.C. Reduced in vitro immune response on titania nanotube arrays compared to titanium surface. Biomater. Sci. 2013, 1, 322–332.

81. Rajyalakshmi, A.; Ercan, B.; Balasubramanian, K.; Webster, T.J. Reduced adhesion of macrophages on anodized titani um with select nanotube surface features. Int. J. Nanomed. 2011, 6, 1765–1771.

82. Ma, Q.-L.; Zhao, L.-Z.; Liu, R.-R.; Jin, B.-Q.; Song, W.; Wang, Y.; Zhang, Y.-S.; Chen, L.-H.; Zhang, Y.-M. Improved impl ant osseointegration of a nanostructured titanium surface via mediation of macrophage polarization. Biomaterials 2014, 35, 9853–9867.

83. Neacsu, P.; Mazare, A.; Schmuki, P.; Cimpean, A. Attenuation of the macrophage inflammatory activity by TiO2; nanotu bes via inhibition of MAPK and NF-κB pathways. Int. J. Nanomed. 2015, 10, 6455–6467.

84. Doadrio, A.L.; Conde, A.; Arenas, M.A.; Hernández-López, J.M.; de Damborenea, J.J.; Pérez-Jorge, C.; Esteban, J.; Va llet-Regí, M. Use of anodized titanium alloy as drug carrier: Ibuprofen as model of drug releasing. Int. J. Pharm. 2015, 4 92, 207–212.

85. Karan, G.; Gerald, J.A.; David, M.F.; Dusan, L. Nano-engineered titanium for enhanced bone therapy. In Proceedings o f the SPIE, San Diego, CA, USA, 11 September 2013.

86. Shen, K.; Tang, Q.; Fang, X.; Zhang, C.; Zhu, Z.; Hou, Y.; Lai, M. The sustained release of dexamethasone from TiO2 n anotubes reinforced by chitosan to enhance osteoblast function and anti-inflammation activity. Mater. Sci. Eng. C 2020, 116, 111241.

87. Ma, A.; You, Y.; Chen, B.; Wang, W.; Liu, J.; Qi, H.; Liang, Y.; Li, Y.; Li, C. Icariin/Aspirin Composite Coating on TiO2 Na notubes Surface Induce Immunomodulatory Effect of Macrophage and Improve Osteoblast Activity. Coatings 2020, 10, 427.

88. Shokuhfar, T.; Sinha-Ray, S.; Sukotjo, C.; Yarin, A.L. Intercalation of anti-inflammatory drug molecules within TiO2 nano tubes. RSC Adv. 2013, 3, 17380–17386.

89. Mohan, L.; Anandan, C.; Rajendran, N. Drug release characteristics of quercetin-loaded TiO2 nanotubes coated with c hitosan. Int. J. Biol. Macromol. 2016, 93, 1633–1638.

90. Lai, S.; Zhang, W.; Liu, F.; Wu, C.; Zeng, D.; Sun, Y.; Xu, Y.; Fang, Y.; Zhou, W. TiO2 Nanotubes as Animal Drug Deliver y System and In vitro Controlled Release. J. Nanosci. Nanotechnol. 2013, 13, 91–97.
91. Somsanith, N.; Kim, Y.-K.; Jang, Y.-S.; Lee, Y.-H.; Yi, H.-K.; Jang, J.-H.; Kim, K.-A.; Bae, T.-S.; Lee, M.-H. Enhancing of Osseointegration with Propolis-Loaded TiO2 Nanotubes in Rat Mandible for Dental Implants. Materials 2018, 11, 61.
92. Gao, L.; Li, M.; Yin, L.; Zhao, C.; Chen, J.; Zhou, J.; Duan, K.; Feng, B. Dual-inflammatory cytokines on TiO2 nanotube-coated surfaces used for regulating macrophage polarization in bone implants. J. Biomed. Mater. Res. Part A 2018, 10 6, 1878–1886.
93. Yin, X.; Li, Y.; Yang, C.; Weng, J.; Wang, J.; Zhou, J.; Feng, B. Alginate/chitosan multilayer films coated on IL-4-loaded TiO2 nanotubes for modulation of macrophage phenotype. Int. J. Biol. Macromol. 2019, 133, 503–513.
94. Gulati, K.; Ramakrishnan, S.; Aw, M.S.; Atkins, G.J.; Findlay, D.M.; Losic, D. Biocompatible polymer coating of titania n anotube arrays for improved drug elution and osteoblast adhesion. Acta Biomater. 2012, 8, 449–456.
95. Aw, M.S.; Gulati, K.; Losic, D. Controlling Drug Release from Titania Nanotube Arrays Using Polymer Nanocarriers and Biopolymer Coating. J. Biomater. Nanobiotechnology 2011, 2, 8.
96. Gulati, K.; Kant, K.; Findlay, D.; Losic, D. Periodically tailored titania nanotubes for enhanced drug loading and releasin g performances. J. Mater. Chem. B 2015, 3, 2553–2559.
97. Mandal, S.S.; Jose, D.; Bhattacharyya, A.J. Role of surface chemistry in modulating drug release kinetics in titania nan otubes. Mater. Chem. Phys. 2014, 147, 247–253.
98. Gulati, K.; Maher, S.; Chandrasekaran, S.; Findlay, D.M.; Losic, D. Conversion of titania (TiO2) into conductive titanium (Ti) nanotube arrays for combined drug-delivery and electrical stimulation therapy. J. Mater. Chem. B 2016, 4, 371–375.
99. Jayasree, A.; Ivanovski, S.; Gulati, K. ON or OFF: Triggered therapies from anodized nano-engineered titanium implant s. J. Control. Release 2021, 333, 521–535.
100. Chen, J.; Dai, S.; Liu, L.; Maitz, M.F.; Liao, Y.; Cui, J.; Zhao, A.; Yang, P.; Huang, N.; Wang, Y. Photo-functionalized TiO 2 nanotubes decorated with multifunctional Ag nanoparticles for enhanced vascular biocompatibility. Bioact. Mater. 202 1, 6, 45–54.
101. Yao, S.; Feng, X.; Lu, J.; Zheng, Y.; Wang, X.; Volinsky, A.A.; Wang, L.-N. Antibacterial activity and inflammation inhibiti on of ZnO nanoparticles embedded TiO2 nanotubes. Nanotechnology 2018, 29, 244003.
102. Gao, S.; Lu, R.; Wang, X.; Chou, J.; Wang, N.; Huai, X.; Wang, C.; Zhao, Y.; Chen, S. Immune response of macrophag es on super-hydrophilic TiO2 nanotube arrays. J. Biomater. Appl. 2020, 34, 1239–1253.
103. Kaur, G.; Willsmore, T.; Gulati, K.; Zinonos, I.; Wang, Y.; Kurian, M.; Hay, S.; Losic, D.; Evdokiou, A. Titanium wire impla nts with nanotube arrays: A study model for localized cancer treatment. Biomaterials 2016, 101, 176–188.
104. Priyadarsini, S.; Mukherjee, S.; Mishra, M. Nanoparticles used in dentistry: A review. J. Oral Biol. Craniofacial Res. 201 8, 8, 58–67.
105. Jandt, K.D.; Watts, D.C. Nanotechnology in dentistry: Present and future perspectives on dental nanomaterials. Dent. Mater. 2020, 36, 1365–1378.
106. Noronha, V.T.; Paula, A.J.; Durán, G.; Galembeck, A.; Cogo-Müller, K.; Franz-Montan, M.; Durán, N. Silver nanoparticle s in dentistry. Dent. Mater. 2017, 33, 1110–1126.
107. Bapat, R.A.; Chaubal, T.V.; Joshi, C.P.; Bapat, P.R.; Choudhury, H.; Pandey, M.; Gorain, B.; Kesharwani, P. An overview of application of silver nanoparticles for biomaterials in dentistry. Mater. Sci. Eng. C 2018, 91, 881–898.
108. Cao, H.; Liu, X.; Meng, F.; Chu, P.K. Biological actions of silver nanoparticles embedded in titanium controlled by micro-galvanic effects. Biomaterials 2011, 32, 693–705.
109. Matsubara, V.H.; Igai, F.; Tamaki, R.; Tortamano Neto, P.; Nakamae, A.E.M.; Mori, M. Use of silver nanoparticles reduc es internal contamination of external hexagon implants by Candida albicans. Braz. Dent. J. 2015, 26, 458–462.
110. Flores, C.Y.; Miñán, A.G.; Grillo, C.A.; Salvarezza, R.C.; Vericat, C.; Schilardi, P.L. Citrate-capped silver nanoparticles s howing good bactericidal effect against both planktonic and sessile bacteria and a low cytotoxicity to osteoblastic cells. ACS Appl. Mater. Interfaces 2013, 5, 3149–3159.
111. Della Valle, C.; Visai, L.; Santin, M.; Cigada, A.; Candiani, G.; Pezzoli, D.; Arciola, C.R.; Imbriani, M.; Chiesa, R. A novel antibacterial modification treatment of titanium capable to improve osseointegration. Int. J. Artif. Organs 2012, 35, 864–875.
112. Cochis, A.; Azzimonti, B.; Della Valle, C.; Chiesa, R.; Arciola, C.R.; Rimondini, L. Biofilm formation on titanium implants counteracted by grafting gallium and silver ions. J. Biomed. Mater. Res. Part A 2015, 103, 1176–1187.

113. Fu, C.; Zhang, X.; Savino, K.; Gabrys, P.; Gao, Y.; Chaimayo, W.; Miller, B.L.; Yates, M.Z. Antimicrobial silver-hydroxya patite composite coatings through two-stage electrochemical synthesis. Surf. Coat. Technol. 2016, 301, 13–19.

114. Wang, Z.; Sun, Y.; Wang, D.; Liu, H.; Boughton, R.I. In situ fabrication of silver nanoparticle-filled hydrogen titanate nan otube layer on metallic titanium surface for bacteriostatic and biocompatible implantation. Int. J. Nanomed. 2013, 8, 29 03.

115. Zhong, X.; Song, Y.; Yang, P.; Wang, Y.; Jiang, S.; Zhang, X.; Li, C. Titanium surface priming with phase-transited lysoz yme to establish a silver nanoparticle-loaded chitosan/hyaluronic acid antibacterial multilayer via layer-by-layer self-ass embly. PLoS ONE 2016, 11, e0146957.

116. Massa, M.A.; Covarrubias, C.; Bittner, M.; Fuentevilla, I.A.; Capetillo, P.; Von Marttens, A.; Carvajal, J.C. Synthesis of n ew antibacterial composite coating for titanium based on highly ordered nanoporous silica and silver nanoparticles. Mat er. Sci. Eng. C 2014, 45, 146–153.

117. Svensson, S.; Suska, F.; Emanuelsson, L.; Palmquist, A.; Norlindh, B.; Trobos, M.; Bäckros, H.; Persson, L.; Rydja, G.; Ohrlander, M. Osseointegration of titanium with an antimicrobial nanostructured noble metal coating. Nanomed. Nanote chnol. Biol. Med. 2013, 9, 1048–1056.

118. Qiao, S.; Cao, H.; Zhao, X.; Lo, H.; Zhuang, L.; Gu, Y.; Shi, J.; Liu, X.; Lai, H. Ag-plasma modification enhances bone a pposition around titanium dental implants: An animal study in Labrador dogs. Int. J. Nanomed. 2015, 10, 653.

119. Sukhanova, A.; Bozrova, S.; Sokolov, P.; Berestovoy, M.; Karaulov, A.; Nabiev, I. Dependence of nanoparticle toxicity o n their physical and chemical properties. Nanoscale Res. Lett. 2018, 13, 1–21.

120. Yuan, J.-H.; Chen, Y.; Zha, H.-X.; Song, L.-J.; Li, C.-Y.; Li, J.-Q.; Xia, X.-H. Determination, characterization and cytotoxi city on HELF cells of ZnO nanoparticles. Colloids Surf. B Biointerfaces 2010, 76, 145–150.

121. Kulshrestha, S.; Khan, S.; Meena, R.; Singh, B.R.; Khan, A.U. A graphene/zinc oxide nanocomposite film protects dent al implant surfaces against cariogenic Streptococcus mutans. Biofouling 2014, 30, 1281–1294.

122. Hu, H.; Zhang, W.; Qiao, Y.; Jiang, X.; Liu, X.; Ding, C. Antibacterial activity and increased bone marrow stem cell functi ons of Zn-incorporated TiO2 coatings on titanium. Acta Biomater. 2012, 8, 904–915.

123. Li, Y.; Liu, X.; Tan, L.; Cui, Z.; Yang, X.; Yeung, K.W.K.; Pan, H.; Wu, S. Construction of N-halamine labeled silica/zinc o xide hybrid nanoparticles for enhancing antibacterial ability of Ti implants. Mater. Sci. Eng. C 2017, 76, 50–58.

124. van Hengel, I.A.J.; Putra, N.E.; Tierolf, M.W.A.M.; Minneboo, M.; Fluit, A.C.; Fratila-Apachitei, L.E.; Apachitei, I.; Zadpo or, A.A. Biofunctionalization of selective laser melted porous titanium using silver and zinc nanoparticles to prevent infe ctions by antibiotic-resistant bacteria. Acta Biomater. 2020, 107, 325–337.

125. Kononenko, V.; Repar, N.; Marušič, N.; Drašler, B.; Romih, T.; Hočevar, S.; Drobne, D. Comparative in vitro genotoxicity study of ZnO nanoparticles, ZnO macroparticles and ZnCl2 to MDCK kidney cells: Size matters. Toxicol. Vitr. 2017, 40, 256–263.

126. Ren, G.; Hu, D.; Cheng, E.W.; Vargas-Reus, M.A.; Reip, P.; Allaker, R.P. Characterisation of copper oxide nanoparticles for antimicrobial applications. Int. J. Antimicrob. Agents 2009, 33, 587–590.

127. Burghardt, I.; Lüthen, F.; Prinz, C.; Kreikemeyer, B.; Zietz, C.; Neumann, H.-G.; Rychly, J. A dual function of copper in d esigning regenerative implants. Biomaterials 2015, 44, 36–44.

128. Thukkaram, M.; Vaidulych, M.; Kylián, O.; Rigole, P.; Aliakbarshirazi, S.; Asadian, M.; Nikiforov, A.; Biederman, H.; Coe nye, T.; Du Laing, G.; et al. Biological activity and antimicrobial property of Cu/a-C:H nanocomposites and nanolayered coatings on titanium substrates. Mater. Sci. Eng. C 2021, 119, 111513.

129. van Hengel, I.; Tierolf, M.; Valerio, V.; Minneboo, M.; Fluit, A.; Fratila-Apachitei, L.; Apachitei, I.; Zadpoor, A. Self-defend ing additively manufactured bone implants bearing silver and copper nanoparticles. J. Mater. Chem. B 2020, 8, 1589–1 602.

130. Hameed, H.A.; Ariffin, A.; Luddin, N.; Husein, A. Evaluation of antibacterial properties of copper nanoparticles surface c oating on titanium dental implant. J. Pharm. Sci. Res. 2018, 10, 1157–1160.

131. Xia, C.; Ma, X.; Zhang, X.; Li, K.; Tan, J.; Qiao, Y.; Liu, X. Enhanced physicochemical and biological properties of C/Cu dual ions implanted medical titanium. Bioact. Mater. 2020, 5, 377–386.

132. Astasov-Frauenhoffer, M.; Koegel, S.; Waltimo, T.; Zimmermann, A.; Walker, C.; Hauser-Gerspach, I.; Jung, C. Antimicr obial efficacy of copper-doped titanium surfaces for dental implants. J. Mater. Sci. Mater. Med. 2019, 30, 1–9.

133. Ingle, A.P.; Duran, N.; Rai, M. Bioactivity, mechanism of action, and cytotoxicity of copper-based nanoparticles: A revie w. Appl. Microbiol. Biotechnol. 2014, 98, 1001–1009.

134. Zhao, Y.; Jamesh, M.I.; Li, W.K.; Wu, G.; Wang, C.; Zheng, Y.; Yeung, K.W.; Chu, P.K. Enhanced antimicrobial propertie s, cytocompatibility, and corrosion resistance of plasma-modified biodegradable magnesium alloys. Acta Biomater. 201

4, 10, 544–556.

135. Chopra, D.; Gulati, K.; Ivanovski, S. Micro + Nano: Conserving the Gold Standard Microroughness to Nanoengineer Zirconium Dental Implants. ACS Biomater. Sci. Eng. 2021, 7, 3069–3074.
136. Guo, L.; Zhao, J.; Wang, X.; Xu, R.; Lu, Z.; Li, Y. Bioactivity of zirconia nanotube arrays fabricated by electrochemical anodization. Mater. Sci. Eng. C 2009, 29, 1174–1177.
137. Katunar, M.R.; Sanchez, A.G.; Coquillat, A.S.; Civantos, A.; Campos, E.M.; Ballarre, J.; Vico, T.; Baca, M.; Ramos, V.; Cere, S. In vitro and in vivo characterization of anodised zirconium as a potential material for biomedical applications. Mater. Sci. Eng. C 2017, 75, 957–968.
138. Indira, K.; KamachiMudali, U.; Rajendran, N. In vitro bioactivity and corrosion resistance of Zr incorporated TiO2 nanotube arrays for orthopaedic applications. Appl. Surf. Sci. 2014, 316, 264–275.
139. Zheng, Y.F.; Liu, D.; Liu, X.L.; Li, L. Enhanced corrosion resistance of Zr coating on biomedical TiNi alloy prepared by plasma immersion ion implantation and deposition. Appl. Surf. Sci. 2008, 255, 512–514.
140. Grigorescu, S.; Ungureanu, C.; Kirchgeorg, R.; Schmuki, P.; Demetrescu, I. Various sized nanotubes on TiZr for antibacterial surfaces. Appl. Surf. Sci. 2013, 270, 190–196.
141. Ye, M.; Shi, B. Zirconia nanoparticles-induced toxic effects in osteoblast-like 3T3-E1 cells. Nanoscale Res. Lett. 2018, 13, 1–12.
