Review of titanium surface modification techniques and coatings for antibacterial applications

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Abstract:

Implanted biomaterials play a key role in the current success of orthopedic and dental procedures. Pure titanium and its alloys are the most commonly used materials for permanent implants in contact with bone. However, implant-related infections remain among the leading reasons for failure. The most critical pathogenic event in the development of infection on biomaterials is biofilm formation, which starts immediately after bacterial adhesion. In the last decade, numerous studies reported the ability of titanium surface modifications and coatings to minimize bacterial adhesion, inhibit biofilm formation and provide effective bacterial killing to protect implanted biomaterials. In the present review, the different strategies to prevent infection onto titanium surfaces are reported: surface modification and coatings by antibiotics, antimicrobial peptides, inorganic antibacterial metal elements and antibacterial polymers.

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I. Introduction

Titanium (Ti) was discovered in 1790 and was first used as paint additive to obtain white color. Following the second half of the twentieth century, titanium and its alloys started to be widely used in the industry as well as in the biomedical field, particularly in bone fusion, bone fixation and joint replacement surgery (arthroplasty). Due to their excellent mechanical and chemical properties, their good corrosion resistance and biocompatibility, these materials have been, for decades, successfully employed as artificial implants in dental and orthopaedic surgery.[1–3]

Various etiologies of instrumentation failure related to the use of titanium are reported, all of which represent a heavy burden on patient health and healthcare costs nationwide.[4–6] Microbial infection is one of the main causes of implant failure.[4,5] Despite tremendous advances in the quality of healthcare, the probability of infection during a surgical procedure is still high. Currently, the global infection risk is 2-5% in orthopedic surgery. [7] Orthopaedic biomaterials are diverse and used in high volumes, which made hospital-acquired infections (H.A.I or nosocomial infections) a public health priority in developed countries. During the course of surgery, implants are susceptible to bacterial contamination from both skin and mucous membranes [6]. These device-associated infections can rapidly progress as planktonic bacteria first adhere to an implant interface and ultimately evolve into biofilms [8]. Bacteria cause various forms of nosocomial infections. *Staphylococcus aureus* (*S. aureus*) is responsible for H.A.I of surgical wounds and, together with *Staphylococcus epidermidis (S. epi.*), causes infections associated with indwelling medical devices.[9,10] Biofilm-associated infections represent a medical and surgical challenge by the destruction of the adjacent tissue leading to poor vascularization, implant loosening, detachment or even dislocations.[11] Difficulties raised by the diagnosis of implant-related bone infections account for the systematic need to rule it out preoperatively and perioperatively, especially in the setting of any aggressive treatment addressing implant failure.

Bacterial adhesion is generally described by two stages resulting in mature biofilm formation, as illustrated in **Figure 1**. Stage I is the initial interaction which is rapid and reversible between bacterial cell surfaces and material surfaces, while stage II involves specific and nonspecific interactions between proteins on the bacterial surface structures (fimbriae or pili) and binding molecules on the material surface. Stage II is slowly reversible and often termed as irreversible. Thus, it is critical to suppress and eventually eradicate implant-related infections. However, once a mature biofilm has developed on any implant surface, bacterial eradication becomes highly challenging despite the use of antibiotic therapy and repeated surgical irrigation and debridement. Poor penetration of antibiotics due to the biofilm exopolysaccharidic matrix, scarce vascularization, high implant surface, small colony variants or persister cells through mutations of metabolic genes account for the necessity to perform hardware removal whenever simple irrigation and debridement procedures fail to cure infections related to implanted devices. The emergence of resistant strains potentially represents an additional issue whenever antibiotics are administered. To date, no treatment can guarantee rapid and complete biofilm destruction or prevent infection recurrence. Therefore, long-term clinical success depends upon the antimicrobial properties of the implanted materials. Currently, implanted medical devices are still unable to actively resist bacterial adhesion, colonization, and biofilm formation.

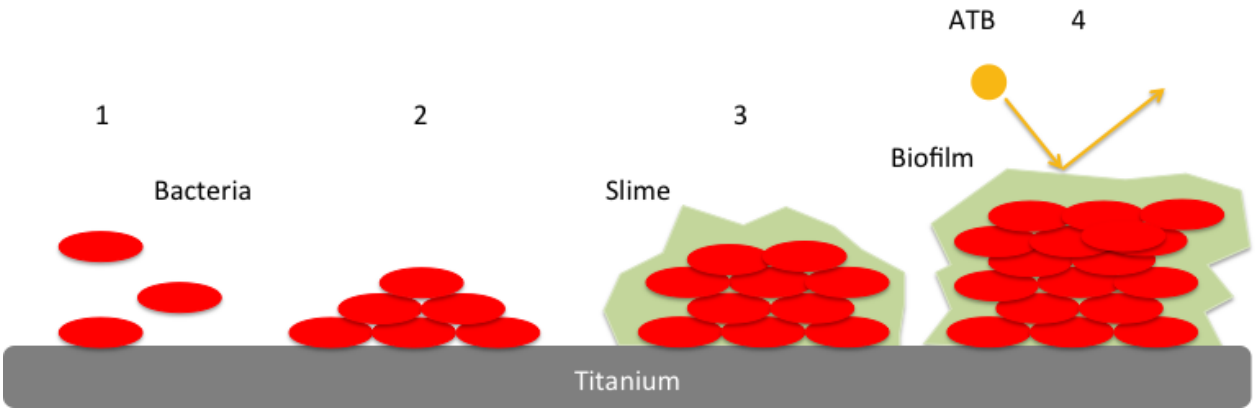


Figure 1: Illustration of the process of titanium surface colonization starting from individual bacterial adhesion across micro-colonies towards formation (1 + 2) and maturation of biofilm (3). Bacteria cannot activate the biofilm-related phenotype before they firmly attach to the titanium surface. After attachment and phenotype change, they are able to produce an exopolysaccharidic matrix that protects them against host immune response and antibiotics.

The prevention of biofilm formation by antimicrobial surfaces is the best way to avoid both the spread of pathogens and material deterioration. To this end, materials must prevent primary adhesion of living planktonic microbial cells from their environment. In general, this can be achieved by either repelling or killing approaching bacteria (**Figure 2**). Surface modification of implanted devices is an effective way to reduce the occurrence of implant-associated infections. It is a relatively straightforward method to modify interfacial properties of medical devices without disrupting bulk properties of materials. Conceptually, it is worth dividing surface treatments into two main categories: surface modification (physical, chemical or combined) and coatings (physical, chemical or combined). Indeed, surface modification implies that the very structure of titanium is modified. This can be performed at the atomic, molecular or textural scales.[12] Coatings imply an apposition or spreading of a substance onto a substrate, hence forming an additional layer on the surface. This can be achieved by various techniques which again may be physical, chemical or a combination of both. Only treatments pertaining to antibacterial activity will be discussed.

Numerous antibacterial macromolecules [13–20], antimicrobial peptides [21–28], inorganic antibacterial metal elements (silver, copper, zinc, …) [29–95] and antibiotics [7,29,96–103] were used to immobilize antimicrobial molecules onto implant interfaces. Furthermore, various strategies, such as physical adsorption for coatings and chemical covalent conjugation (“grafting to” and “grafting from” approaches) for surface modifications were applied to immobilize antimicrobials elements onto titanium surfaces. [104–125]

The aim of this review is to collect and compare studies reporting titanium surface treatments in order to confer antibacterial properties to implants by the introduction of inorganic antibacterial agents or grafting bioactive molecules.

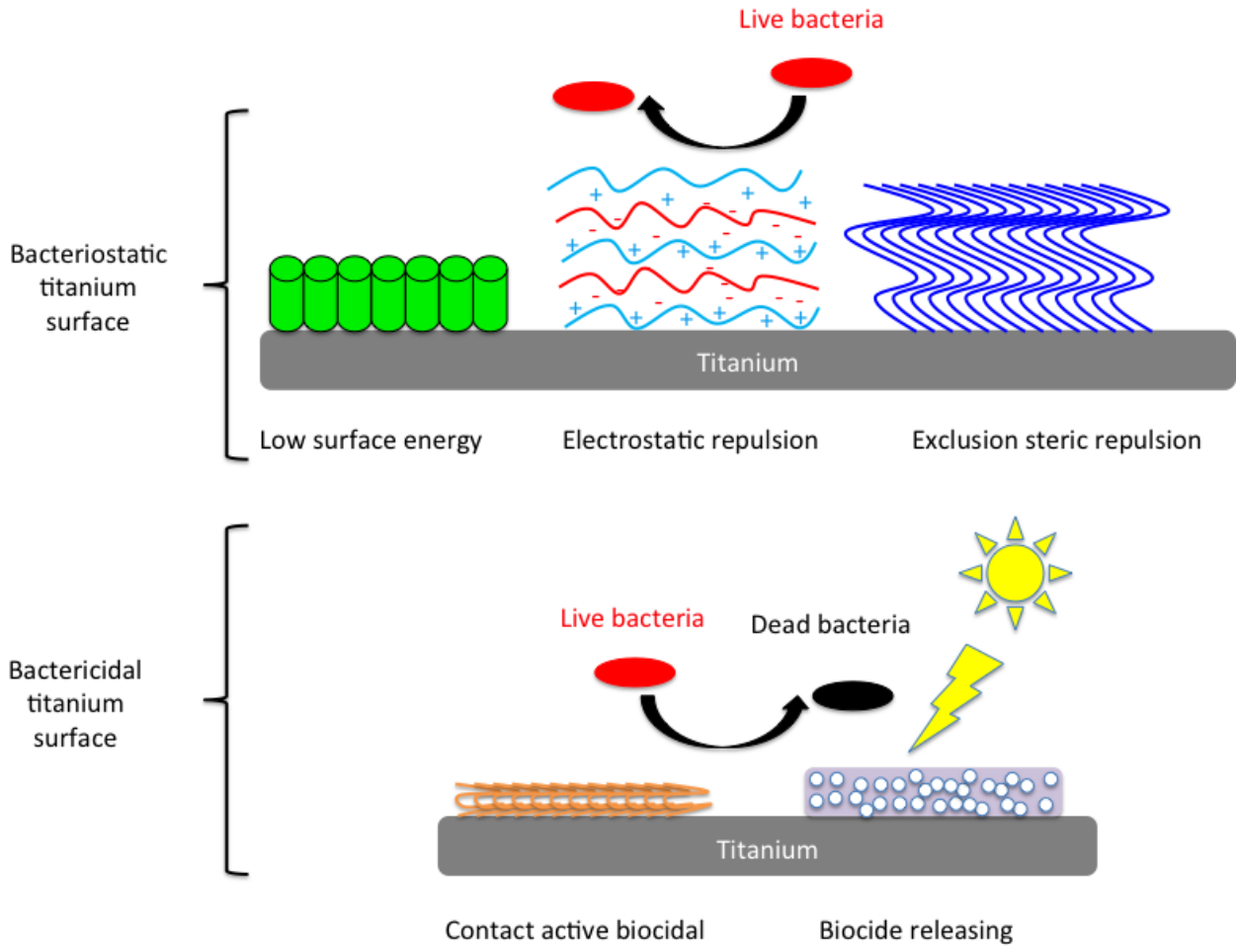


Figure 2: Various examples of antimicrobial surfaces according to mechanism of action: bacteriostatic or bactericidal surfaces.

II. Surface modification

Biochemical methods of surface modification are promising approaches to modify and induce an antibacterial effect onto titanium surfaces. Difficulties, however, regarding the stability of the immobilized biomolecules. Besides, physical adsorption of the molecules may not be successful for long-term implantation due to possible desorption. On the other hand, covalent binding may require the use of different chemical reactions, which can be aggressive towards the molecules thereby reducing their bioactive potential.[104]

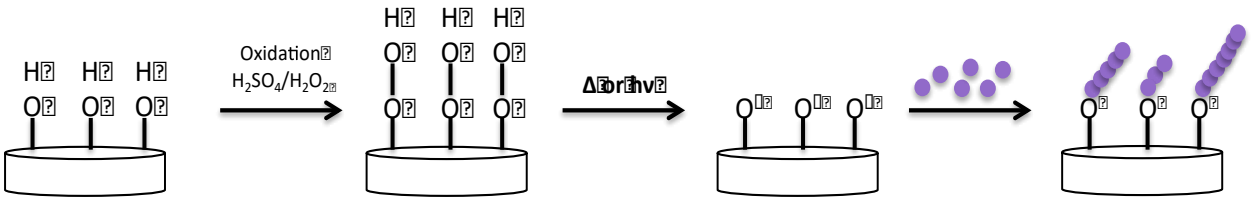
Covalent grafting is one type of surface modification that offers the strongest link between the biomaterial and its coating, producing a more durable interface.[105] Several techniques for covalently grafting of biomolecules and/or bioactive molecules onto titanium surfaces were developed, including

covalent attachment of end-functionalized polymers incorporating an appropriate anchor ("grafting to") or *in-situ* polymerization initiated from the surface ("grafting from").

Nanostructures and surface structuring will be detailed in a third part of surface modifications.

1. Grafting from

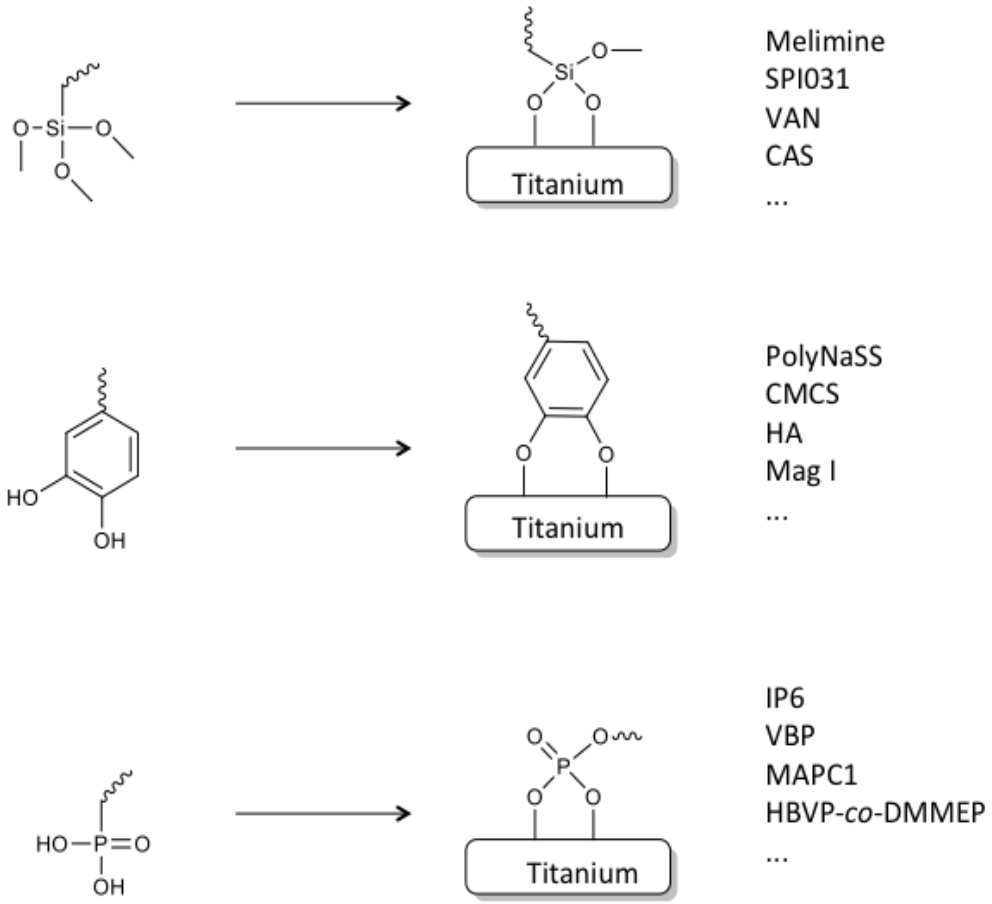
The "grafting from" approach (**Scheme 1**) has attracted considerable attention in recent years for the preparation of tethered polymers onto a solid substrate surface [106]. The direct grafting of an ionic polymer model such as poly(sodium styrene sulfonate (polyNaSS) (**Scheme 1**) in a two-step reaction procedure onto titanium and alloy titanium surfaces was reported [106–113]. Treatment of the titanium surface by a mixture of sulfuric acid and hydrogen peroxide generates titanium hydroxide and titanium peroxide. In the second reaction step, heating or UV irradiation of surfaces, if the substrate is placed in a concentrated solution of sodium styrene sulfonate monomer (NaSS) monomer, induces the decomposition of titanium peroxides with the formation of radicals capable of initiating the polymerization of NaSS.[107–113] A great advantage of polyNaSS grafting relies on its bioactivity, which could partly be explained by its moderate hydrophilic character. A bacterial adhesion study showed that titanium and titanium alloy graft surfaces exhibited high inhibition of *S. aureus* adhesion at levels greater than 70% when compared to non-grafted titanium and titanium alloy surfaces.[107,109,110]



Scheme 1: "Grafting from" technique on titanium surfaces.

2. Grafting to

The "grafting to" strategy permits an indirect grafting thanks to anchor molecules (silane [114–117], catechol [118–121], phosphate [122–125]). It enables titanium functionalization with various molecules in order to confer customized properties (**Scheme 2**).



Scheme 2: A selection of anchors on titanium surfaces with different functionalizations to achieve an antimicrobial surface.

2.1. Silane anchor

Silanization has been successfully used to functionalize metallic biomaterials with bioactive molecules. This method of surface modification allows the covalent attachment of various molecules such as peptides, proteins and polymers through the use of organofunctional alkoxysilane molecules that react with hydroxyl groups present at the surface of the material. The binding of these biomolecules onto aminosilanized samples often requires a reaction with crosslinking agents (*i.e*. glutaraldehyde, maleimide-based molecules) to ensure appropriate chemical reactivity.

Chen et *al.* [114] used a silane anchor to graft Melimine, a synthetic antimicrobial peptide onto titanium surfaces.[115] Melimine has broad spectrum activity against bacteria, fungi and protozoa and has been considered a promising candidate for further development as an antimicrobial coating for biomedical devices and implants. In this study, the *in vitro* and *in vivo* antimicrobial activity of melimine-coated titanium was tested. Titanium surfaces were amine-functionalized with 3-aminopropyltriethoxysilane (APTES) followed by reaction with a bifunctional linker 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylic

3-sulfo-n-hydroxysuccinimide ester (Sulfo-SMCC) to yield a maleimide functionalized surface. Melimine was then tethered to the surface via a thioether linkage through a Michael addition reaction of the cysteine at its *N*-terminus with the maleimide moiety. Melimine coating significantly reduced *in vitro* adhesion and biofilm formation of *P. aeruginosa* (up to 62%) and *S. aureus* (up to 84%) on titanium substrates compared to blank surfaces. The coating was also challenged in both mouse and rat subcutaneous infection models and was able to reduce bacterial load by up to 2 $\log_{10}$ compared to uncoated surfaces. Melimine coatings therefore presented several characteristics that make it a promising candidate for development as a surface antimicrobial agent that can withstand industrial sterilization while ensuring good biocompatibility. Clinical results have not been reported to this date.

Gerits et *al.* [116] developed titanium substrates on which the recently discovered antibacterial agent SPI031, an *N*-alkylated 3, 6-dihalogenocarbazol 1-(sec-butylamino)-3-(3,6-dichloro-9H-carbazol-9-yl)propan-2-ol, was covalently linked (SPI031-Ti) via a silane anchor (3-aminopropyl-triethoxy silane). They found that SPI031-Ti substrates prevent biofilm formation of *S. aureus* and *P. aeruginosainvitro*. In order to test the effectiveness of SPI031-Ti substrates *in vivo*, they used an adapted *in vivo* biomaterial-associated infection model in mice in which SPI031-Ti substrates were implanted subcutaneously and subsequently inoculated with *S. aureus*. A significant reduction in biofilm formation was observed (up to 98%) on SPI031-Ti substrates compared to control substrates. In a different study [117], the same team grafted vancomycin (VAN) and caspofungin (CAS) onto Ti substrates using a silane anchor too. Resistance of the VAN-coated Ti (VAN-Ti) and CAS-coated Ti (CAS-Ti) substrates was tested *in vitro* against *S. aureus* and *C. albicans* biofilms. The efficacy of coated Ti substrates was also tested *in vivo* using an adapted biomaterial-associated murine infection model in which control-Ti, VAN-Ti or CAS-Ti substrates were implanted subcutaneously and subsequently challenged with the respective pathogens. *In vitro* biofilm formation of *S. aureus* and *C. albicans* on VAN-Ti and CAS-Ti substrates, respectively, was significantly reduced compared with biofilm formation on control-Ti. VAN-Ti substrates and CAS-Ti substrates showed a 99.9% biofilm reduction against respectively *S. aureus* and *C. albicans* compared with control titanium.

2.2. Catechol anchor

A different strategy is to graft polymers with a catechol group onto titanium surfaces, catechol acting as the anchor for chemical linkage. A distinction is commonly made between three different approaches. The first one is the direct polymerization from the substrate surface by using an initiator bringing a catechol group. Another approach is to functionalize a polymer with a molecule loading a catechol group and subsequently anchor the polymer onto the desired surface as used by Chouirfa et *al.* [118] In a third type of approach, catechol is first anchored to the surface of TiO_2, then, by click-reaction with a functionalized polymer, the latter is grafted onto the titanium surface [118]. Recently, Chouirfa [119] grafted polyNaSS (polyanion) onto titanium surfaces *via* a dopamine anchor and showed a positive response against *S. aureus.* Various molecular weights of polyNaSS were studied and it was shown that the bulkier polyNaSS was, the higher the bacteriostatic effect was: 36, 58 and 65% of *S. aureus* growth inhibition for respectively 5, 10 and 35 kDa polyNaSS. The authors showed a significant effect of molecular weight, indeed, the bigger the polymer was, the more significant its anti-bacterial effect was.

In one *in vitro* study [120], Ti substrates were functionalized by first covalently grafting either dopamine followed by carboxymethyl chitosan (CMCS) or hyaluronic acid-catechol (HAC). Antibacterial assays with *S. aureus* showed that the polysaccharide-modified substrates significantly decreased bacterial adhesion. CMCS-functionalized Ti demonstrated better antibacterial property than HAC-functionalized Ti since CMCS is bactericidal while HA only inhibits the adhesion of bacteria without killing them. The number of viable S. *aureus* cells on Ti-CMCS and Ti-HAC decreased to 16% and 54% compared with control titanium, respectively.

An antimicrobial peptide, Magainin I (Mag), was grafted to a titanium oxide surface, via 3 steps: i) the binding of the catechol group (Cat), ii) coupling with PEG and iii) functionalization with Magainin I peptide [121]. In this strategy, PEG is both antiadhesive and enables covalent peptide immobilization. The antiadhesive properties of PEG, and antibacterial activity of the anchored Magainin I, were individually tested against Gram-positive bacteria, *Listeria ivanovii*. The results revealed that bacterial adhesion was considerably reduced, accompanied by a growth inhibition of the remaining adherent bacteria, 70% on Ti-Cat-PEG and 90% on Ti-Cat-PEG-Mag. CFU count, after adhesion onto clean Ti, was higher than on any of the modified surfaces. A slight decrease was observed on Ti-Cat whereas, on Ti-Cat-PEG, the number of live bacterial cells was divided by two. The most drastic reduction was observed on Ti-Cat-PEG-Mag compared with control Ti.

2.3. Phosphor-based anchor

Phosphates and phosphonates can covalently link to metal oxide surfaces such as TiO_2 and are commonly used as crosslinker agents to functionalize surfaces with other molecules eventually tuning surface properties to those of interest. Phosphonate linkers present the advantage of being more stable than other commonly used coupling agents like silanes, which suffer from hydrolytic instability in aqueous environments at physiological pHs. The use of robust and stable coatings under physiological conditions in biomedical applications is of high interest, and phosphates or phosphonates bound to metal oxides are stable in these conditions.

Córdoba et *al*. [122] presented a method to directly functionalize Ti surfaces covalently with Myo-inositol hexaphosphate (IP6), without using a crosslinker molecule, through the reaction of the phosphate groups of IP6 with the TiO_2 layer of Ti substrates. The effect of the grafted surfaces on the adhesion and biofilm viability of oral microorganism *S. sanguinis* was studied. It appeared that Ti-IP6 surfaces decreased the adhesion of *Strep. sanguinis.* These results indicated that the functionalization of titanium surfaces with IP6 protected the material against bacterial adhesion. Besides, some bactericidal effect of IP6 could be expected, as found by Moon et *al*. [123] on *P. gingivalis.*

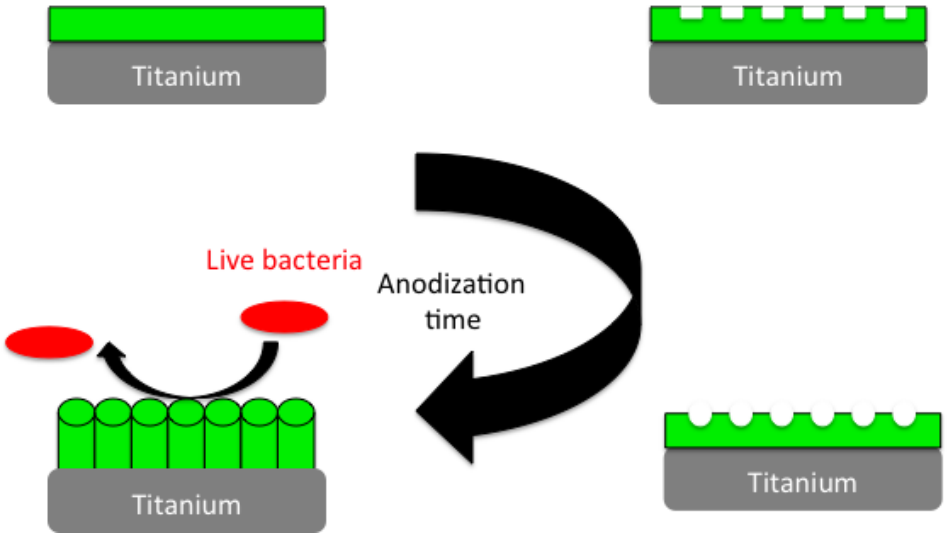
Other examples of the use of phosphonate, such as 4-vinylpyridine with vinylbenzylphosphonate or dimethyl(2-methacryloyloxy-ethyl) phosphonate are found in the literature with a preparation by free radical polymerization. Calliess et al. showed a reduction of adherent bacteria up to 95% compared with blank titanium controls [124]. In their study, they demonstrated *in vitro* that polymer surface coatings can be antimicrobial against *S. epidermidis* and *S. aureus.* Similarly with phosphonate, Pfaffenroth et *al.* [125] synthetized copolymers of 4-vinyl-N-hexylpyridinium bromide (HBVP) and dimethyl(2-methacryloyloxyethyl) (DMMEP) phosphonate self-assembled to form ultrathin layers on titanium surfaces that showed antimicrobial activity and good biocompatibility. Antibacterial activity was assessed by investigating *Strep. Mutans* adherence. The antimicrobial effect of the surface was enhanced by an increase in the content of DMMEP within the copolymer. The introduction of hydrophilic monomers improved the antibacterial effect of the copolymers compared to poly(HBVP) homopolymer and in particular compositions with low amounts of HBVP showed strong effects.

3. Nano-structures and surface structuring

Nanostructured surfaces are currently of great interest.[15–19] Consequently, nanoscale surface patterning methods have been applied to fabricate different nanopatterns (e.g., ordered stripes, pits, pillars or squares). Recently Narendrakumar et *al.* [15] reported TiO_2 nanotubes coating onto titanium surfaces, and such anodized nanostructures have demonstrated a certain degree of antibacterial properties associated with their diameter and contact angle. In addition, for a given diameter, nanopores might have less bacterial adhesion than nanotubes. In this study, the authors used two *Streptoccocus (Strep.)* strains*: Strep. mutans* and *Strep. sanguinis.* The same conclusions were observed by Ercan et *al.* [16] and showed that surface nanomodification of Ti significantly changed bacterial response. According to the authors [16], several parameters are implied such as: surface chemistry, Ti crystallinity and nanotube size. Heat treatment significantly decreased the number of dead *S. aureus* and *S. epi.* bacteria adhering to Ti surfaces, while larger Ti nanotubes (60 and 80 nm diameters) consistently decreased the number of live bacteria when each was compared to conventional Ti. Combining these two treatments (heat treatment and controlled Ti nanotube formation through anodization) decreased adhesion of both live and dead bacteria for both *S. aureus* and *S. epi.*[16] These results indicated that controlled anodized Ti nanotube formation and heat treatment are strong candidates for the design of future implantable materials with improved tissue growth properties and antimicrobial behavior.

Barbour et *al.* [17] studied the effect of titanium crystal structures on the capacity of *Strep. gordonii* to adhere onto surfaces. Bacterial coverage was reduced more significantly on anatase surfaces than rutile surfaces.

Overall, nanostructuring and surface structuring has been demonstrated to be effective against the following bacteria: *Strep. Mutans* [15,18], *Strep. Salivarius* [18], *Strep. Sanguinis* [15,18], *Strep. Gordonii* [17], *S. aureus* [16], *S. epidermidis* [16], *P.* aeruginosa.[19]



Scheme 3: Formation process of nanotubes on titanium surfaces. Before anodization, a nanoscale TiO_2 passivation layer is present on Ti surfaces and whenever a constant voltage is applied, pits are formed on the TiO_2 layer. As anodization time increases, pits grow longer and larger resulting in nanopore formation. After a specific anodization time, nanotubes are formed on the Ti surface.

Scheme 3 presents the different possible architectures of TiO_2 layers according to the anodization time.

III. COATINGS

1. Physical modification

Coatings achieved by mainly physical modifications will be discussed below and divided between bacteriostatic and bactericidal coatings. Obviously, it is impossible to strictly demarcate physical from chemical coatings as some techniques may appeal to multiple physical and chemical processes. However, we relied mostly on the main idea behind each process.

1.1 Bacteriostatic materials

A change in the surface chemistry and/or structure of the bulk implant can be achieved either by chemically or physically altering the TiO_2 surface layer (e.g., oxidation or mechanical modifications such as roughening/polishing/texturing). Consequently, various molecules described below can be grafted in

order to repel bacteria electrostatically without killing them. Bacteriostatic titanium surfaces can be designed by hydrogel coatings mostly based on PEG (polyethylene glycol) or similar hydrogel forming polymers, by highly negatively charged polymers or ultra hydrophobic modifications.

1.1.1 Polycations and polysaccharide coatings

Several authors [13,126,127] associated the RGD peptide with a macromolecule such as a polycation (poly(L-lysine) PLL), a polysaccharide (chitosan), a polymer (poly(ethylene glycol) PEG). Harris et al. [13] designed an innovative macromolecule PLL-*g*-PEG-RGD which was coated on the titanium surface. The amount of reduction for both *S. aureus* and *S. epidermidis* was 98%, 93-95% for *S. mutans*, and 88% for *P. aeruginosa* [126]. Yet, this was essentially the result of the PLL-*g*-PEG and not the RGD peptide. Indeed, longer polymer chains reduced Lifshitz-Van der Waals forces and permitted bacterial adhesion decrease (*S. aureus*). This observation was also found by Chua et *al.* [127] following the coating of titanium surfaces with several layers of two polysaccharides (hyaluronic acid (HA) and chitosan (CH)). Their strategy was to incorporate RGD peptides into the layers. The antibacterial effect resulted from the combined effect of the two polysaccharides and averaged an adhesion reduction of 80% on *S. aureus*.

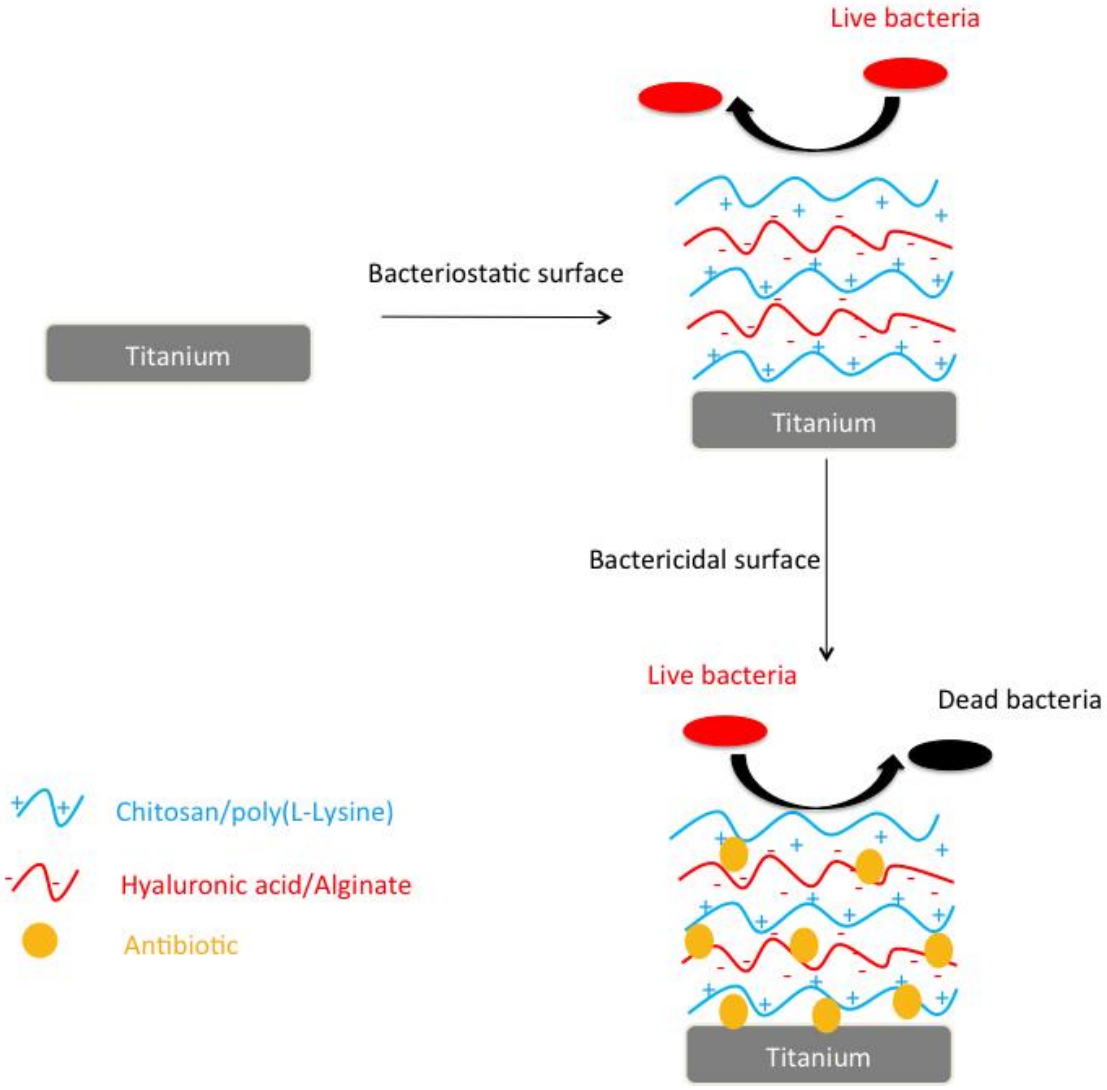
Chua et *al.* [128] showed an adherence decrease of *E. coli* (*Escherichia coli)* and *S. aureus* using different layers of chitosan (CH) and hyaluronic acid (HA). Both of these polymers have an anti-bacteria effect: CH is a polycationic polymers which has a bactericidal action whereas HA, a polyanionic polymer, shows a bacterial inhibitory effect. Bacterial adhesion is increased on hydrophobic materials. The rationale was that coating with hydrophilic polymers as HA and CH rendered treated surfaces more hydrophilic (water contact angle ≈33-44°). Thus, the inhibitory effects of HA/CH layers against bacterial adhesion may be attributed to the increased surface hydrophilicity.

Yazici et *al.* [129] designed bifunctional peptides with a high-affinity Ti-binding property on the one end and an antimicrobial peptide (AMP) motif on the other end (LKLLKKLLKLLKKL). This AMP is composed of several Arg and Lys units which are well-known for cationic properties. Surfaces modified with both chimeric peptides were found to significantly reduce bacterial adhesion against *S. mutans*, *S. epi.*, and *E. coli* compared to pure titanium.[129]

Polysaccharides such as chitosan and hyaluronic acid could inhibit the adhesion of bacteria to titanium [130,131] since they were claimed to interfere with surface linkage between titanium and biofilm. In fact, in one study, antibacterial multilayer coatings loaded with minocycline, which is a broad-spectrum tetracycline antibiotic, on Ti surface substrates using chitosan and alginate were made based upon a layer-by-layer (LbL) self-assembly technique.[132] Regarding chitosan and alginate coatings, they are thought to have a surface charge and hydrophilicity that could be biostatic, hence maintaining the

antibacterial ability after the complete release of minocycline. This also resulted in an improved sustainability of minocycline release. Thus, the antibacterial activity was improved. This type of strategies could inhibit the immediate colonization of bacteria onto implant surfaces in the course of dental implant surgery, and thereby prevent and reduce the occurrence of peri-implantitis.[132] Such coatings, similar to numerous polymeric coatings, have unknown effects under mechanical constraints. Thus, if such coatings are applied on implants, a careful insertion without screwing is recommended to preserve the coating. Nevertheless, this is deemed to be impractical for implant application.

Scheme 4 represents the concept of the LbL with bacteriostatic or bactericidal purposes just by introducing an antibiotic. By layering different appropriate polymers, titanium surfaces are functionalized accordingly and display new features.

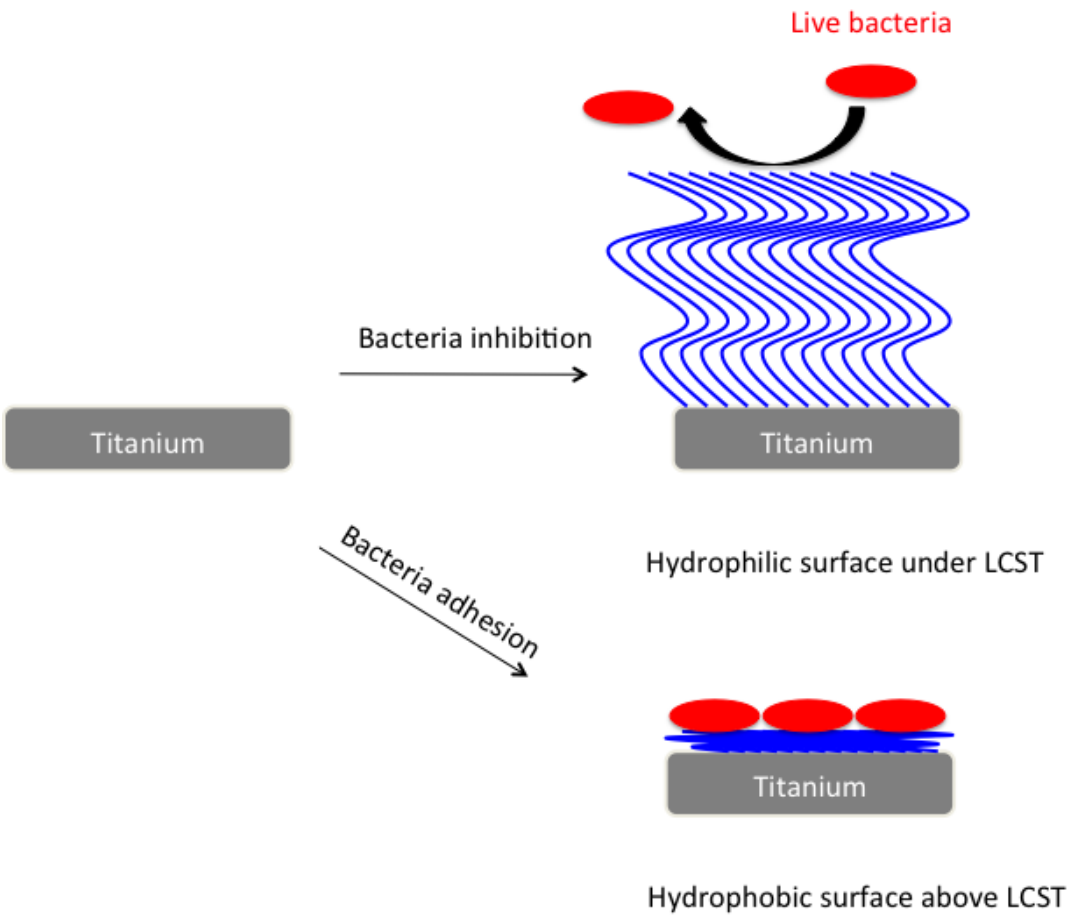


Scheme 4: Layer by layer coating of polycationic and polyanionic polymers to make bacteriostatic surfaces. Then, thanks to the introduction of an antibiotic, titanium surfaces become both bacteriostatic and bactericidal.

1.1.2 « Smart » polymers

Poly(*N*-isopropylacrylamide) (polyNIPAM) is one of the most studied and widely-used environmentally sensitive (smart) polymers for controlling wettability of surfaces. PolyNIPAM is a thermoresponsive polymer that exhibits a lower critical solubility temperature (LCST) in water at 32°C. At temperatures below LCST, polyNIPAM is soluble in water and is hydrophilic with an extended coil conformation. On the other hand, at temperatures above LCST, polyNIPAM undergoes a phase transition to water-insoluble and displays a collapsed hydrophobic structure. In the initial reports on the use of polyNIPAM as a biofouling-release agent, Ista et *al.* [133] exploited the stimuli-responsive wettability of polyNIPAM for the preparation of fouling-release surfaces.

Lee et *al.* [14] coated titanium surfaces with a thermo-responsive polymer (polyNIPAM) which can change polymer length and properties according to temperature variations. PolyNIPAM is a means of controlling bacterial attachment prevention (*P. gingivalis* and *S. aureus*). Indeed, Ti surfaces coated with polyNIPAM can detach bacteria when the temperature decreases. **Scheme 5** represents the role of polyNIPAM variable properties according to temperature. Thus, polyNIPAM-coated titanium surfaces prevent bacterial adhesion below LCST.



Scheme 5: PolyNIPAM below LCST swells and hinders bacterial adhesion, at the contrary above its LCST polyNIPAM shrinks and the bacteria adhesion is permitted.

1.2 Bactericidal materials

Bactericidal elements permit to kill bacteria by numerous ways such as perturbing bacterial membrane (either destruction or synthesis inhibition), blocking ATP synthase, preventing cell respiration, blocking DNA replication, interrupting protein synthesis, thanks to an important variety of molecules since the discovery of penicillin by Fleming in 1928.[134] Antibiotics are the most known though they are not the only strategy.

1.2.1 Polymer coating

Microbial cells generally carry a negative net charge at their surface due to their membrane proteins, teichoic acids of Gram-positive bacteria, and negatively charged phospholipids at the outer membrane of Gram-negative bacteria. This way, polycations are attracted and if they have a proportionate

amphiphilic character, they are able to disrupt the outer as well as the cytoplasmic membrane and enable lysis of the cell resulting in cell death. Schaer et *al.* [20] studied the effect of a hydrophobic polycation *N,N*-dodecyl,methyl-PEI (PEI: polyethylenimine) on *S. aureus*. The presence of the polymer coating on titanium surfaces was effective by preventing biofilm formation.

1.2.2 Antimicrobial peptides

Kazemzadeh-Narbat et *al.* [21] used a cationic peptide called Tet213 (KRWWKWWRRC) on both *S. aureus* and *P. aeruginosa*. In this case, the antimicrobial peptide (AMP) was loaded inside calcium phosphate (CaP-AMP), which was coated on titanium surfaces. According to the authors, CaP-AMP kills both *S. aureus* and *P. aeruginosa* bacteria within 30 min *in vitro*.

Another AMP called GL13K, derived from parotid secretory protein (PSP), has been shown to be both bactericidal and bacteriostatic.[22,131] *In vitro* antimicrobial studies have found that a GL13K peptide coating is bactericidal and inhibits biofilm growth for pathogens related to peri-implantitis, such as *P. gingivalis*, *Strep. gordonii* and *P. aeruginosa* under static growth conditions.[23,24] Furthermore, AMP surfaces displayed antimicrobial activity under dynamic growth conditions against *Strep. Gordonii* [25] and under static growth conditions against *S. epidermidis* and *E. coli.*[26] This passive antimicrobial coating resisted hydrolytic and mechanical challenges and exhibited no significant release of peptides from the modified titanium surface. A multifunctional streptococcal collagen-mimetic protein coating reduced the bacterial adherence *of S. aureus* and *S. epidermidis*.[27] Consequently, a costly design of synthetic peptides becomes a necessary step in order to fabricate bioactive coatings immobilized with active AMPs.[28]

Titanium substrates can be functionalized with the hLf1-11 peptide as a potent AMP by physical adsorption. An outstanding reduction in bacterial adhesion and biofilm formation of *Strep. sanguinis* and *Lactobacillus salivarius* was observed on the biofunctionalized surfaces compared to the control group.[135]

1.2.3 Ion-implanted surfaces

Elements such as fluorine (F), zinc (Zn) calcium (Ca), chlorine (Cl), iodine (I), copper (Cu), cerium (Ce) or selenium (Se) may be incorporated into titanium or hydroxyapatite coatings by anodic oxidation of the corresponding ions. The bactericidal activity of these ions seems to depend on their gradual release from specimens into surrounding tissues. One mechanism of bacteriostasis is hydroxylation into highly reactive components, such as HCl, HOCl, TiOH, hydrogen peroxide (H_2O_2) or superoxide (O^{2-}), as these cause oxidation of bacterial cell membranes, resulting in increased cell permeability and ultimately in cell death. Additionally, ion-implanted surfaces may act bactericidally, as the ions may inhibit bacterial

metabolism.[52,53,55–63,136] To this date, a single ion candidate has been extensively tested in clinical trials with good clinical outcome despite gradual leaching over time: iodine-supported titanium implants as described initially by Shirai et *al.*[60]

Chemical modification of anodically oxidized titanium by incorporation of ions reduces growth of biofilm in one, two and three species models of *E. coli* [137], *P. gingivalis* [65], *Strep. mutans* [66], *S. aureus* [67] and *A. acti nomycetemcomitans.*[45,46,68] Bacterial counts on ion-implanted surfaces were reduced by 55-80% compared to pure titanium.[53] However, it is unclear how anodic oxidation without ion-implantation influences bacterial adhesion to titanium [68–70]. Titanium samples treated with cold atmospheric plasma display strong antimicrobial activity against *E. coli.*[71]

1.2.4 Photoactivatable bioactive titanium

Titanium oxide (titania, TiO_2) is a typical non-toxic photo-chemically active semiconductor with high photoactivity, which use is being explored to produce biomaterial surfaces with self-disinfecting properties.[138] TiO_2 surfaces undergo photo-activation when, under aerobic conditions, they are irradiated with appropriate photon energies. The principles and mechanisms of TiO_2 photo-catalysis have been reviewed in detail by Hashimoto et *al*.[139]

Ultraviolet A (UVA) light is an electromagnetic radiation with a wavelength between 315 and 380 nm that causes chemical reactions and biological effects by interacting with organic molecules. UV light-induced photo-functionalization of titanium dioxide (TiO_2) removes hydrocarbon contamination and results in a super-hydrophilic surface, which decomposes adsorbed organic impurities by oxidation. Secondary oxidation initiated by reactive oxygen species (ROS) seems to be the necessary step to achieve antimicrobial activity **(Scheme 6).**[59] ROS are chemically reactive molecules containing oxygen, such as superoxide or hydrogen peroxide. The bactericidal action of irradiated titania surfaces is due to reactions of photo oxidation that involve O_2 and H_2O with the formation of hydroxyl radicals ($HO^{\bullet}$) and the direct and indirect oxidation of organic substances. Other reactive oxygen species, such as H_2O_2 and O_2 produced by photo oxidation, have also been implicated in bacterial inactivation, with H_2O_2 acting at a greater distance from the photoactive surface than hydroxyl radicals. It has been confirmed that these active oxygen species can destroy the outer membrane of bacterial cells.[140,141]

After 120 min of UVA illumination, the survival rate of *A. actinomycetemcomitans* and *F. nucleatum* on a photocatalytic TiO_2 surface was reduced to less than 1% compared to a commercially pure titanium control surface.[142] Visai et *al.* [138] found a transitory increase in hydrophilicity and significantly increased Zn binding capacity, which in turn led to a significant reduction in three oral streptococcal strains on TiO_2 surfaces illuminated with UV light. In an *in vitro* study under static and dynamic conditions, UVA illumination prior to bacterial colonization induced a reduction in adhesion rates and a significant decrease in the adhesion strength of *S. epidermidis* and *S. aureus*, without altering biocompatibility.[143] In a multispecies study authors found a positive effect on the attachment and biofilm formation of complex oral microbial communities to UV treated titanium.[144]

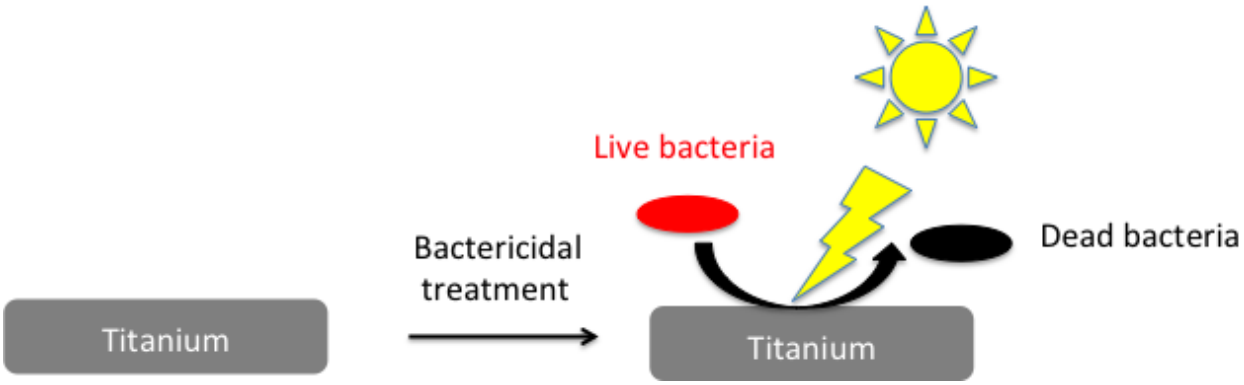
Discharging the surface of a titanium implant in sodium chloride solution anodizes the titanium surface by forming a superficial layer of $TiCl_3$. Subsequently, the modified surface is gradually hydrolyzed, which leads to the formation of Ti-OH and the bactericidal hypochlorous acid:

$$TiCl_3 + H_2O \rightarrow Ti–OH + HClO + HCl$$

Associated with the hydrolysis, the hydrophilicity of the titanium implant is increased by the formation of Ti-OH on the surface. The slow-released hypochlorous acid induces antibacterial properties to the modified titanium surface, while the remaining Ti-OH increases the hydrophilicity.[145]

Table 1: Examples of photoactivatable bioactive biomaterials.[31]

Photoactivatable material	*In vitro* tested efficacy
TiO_2	Very broad spectrum
TiO_2 nanoparticles	*E. Coli, Pseudomonas, Bacteroides fragilis, S. aureus, Enterococcus hirae*
Sulfur-doped nanocrystalline titania	*Micrococcus lylae*
Nitrogen-doped TiO_2	*Shigella flexneri, Vibrio parahaemolyticus, A. actinomycetemcomitans*



Scheme 6: Bactericidal treatment by UV light.

1.2.5 Nanomaterials

Nanoparticles (NP) are defined as clusters of atoms of size ranging from 1-100 nm, with a very large surface area to volume ratio. Copper, zinc, magnesium and especially silver and gold NPs display

antimicrobial activity [72] and are therefore possible candidate molecules for antimicrobial implant surface modifications. Nanomaterials are used to create unique surfaces with altered physical and chemical characteristics.

Because ion release is the main action of metallic silver, silver NPs are used to enlarge the available silver specific surface. Hence, using silver NPs amplifies silver ion release and consequently the antimicrobial effect of a surface. The overall antimicrobial efficiency of nanomaterials is however controversial. Some authors did not find a convincing decrease or even an increase in bacterial colonization on nanomaterials in comparison to untreated titanium.[73–75,146] Others found reductions in bacterial counts *in vitro* up to 90% compared to commercially pure titanium on nano-Ti surfaces and up to 100% for nano-AgHA when tested against *E. coli*, *S. epidermidis* and *S. aureus*.[76–82] It has recently been shown that a titanium nanotube surface exhibited antimicrobial properties and down-regulated the glycosyltransferase genes of *Strep. Mutans* [83]. All studies that tested surfaces with a combination of nanostructures and organic or inorganic antimicrobial chemical compounds on the nano-level found reduced bacterial adhesion and viability.[103,73,74,81,84–88] Surfaces containing Ag NPs particularly show excellent biocidal activity towards *S. aureus* [89,90], and *E. coli.*[29,53,73,85–88,145]

Zhao et *al.* [91] demonstrated that nAg could act longer on bacteria than most antibiotics, possibly due to the release of nAg from the coating. A study has described a method to modify Ti/TiO_2 surfaces with citrate-capped nAg. These nanoparticles spontaneously adsorb on Ti/TiO_2, forming nanometer sized aggregates consisting of individual nAg that homogeneously cover the surface. The modified nAg–Ti/TiO_2 surface exhibits a good resistance to colonization by *P. aeruginosa*.[92] Though silver is able to kill bacteria and has no cytotoxic effect on osteoblasts and epithelial cells [93] at low doses, this could not be guaranteed at high doses.[94] Therefore, a suitable coating is necessary to load and release silver.

The antimicrobial properties of a nanocomposite coating formed by polysaccharide 1-deoxylactit-1-yl chitosan (Chitlac) and silver nanoparticles (nAg) on methacrylate thermosets were analyzed. Methacrylate thermoset is a kind of biomaterials which is commonly employed for orthopedic and dental applications. The Chitlac-nAg system showed satisfying anti-bacterial and anti-biofilm activity. *In vitro* observation, a steady silver release accompanied by anti-microbial ability lose was detected in physiological conditions as time went on. However, there was still effective protection against bacterial colonization after 3 weeks which could be explained by the residual silver. The sufficiently high level of silver content released at the beginning can kill the bacteria rapidly to prevent the development of resistant pathogens.[95] Although the silver concentration decreased after several weeks, the bactericidal effect was still effective is this system.

1.2.6 Citric acid

To assess the effectiveness of different chemotherapeutic agents on biofilm contaminated titanium surfaces, *Strep. mutans* biofilms and polymicrobial biofilms were grown on titanium discs and treated by various chemical agents. A study has found H_2O_2, Ardox-X (atopical teeth whitening gel) and citric acid (CA) killed significantly more *Strep. mutans* compared with the other treatments.[147] H_2O_2 and CA removed significantly more protein than water, whilst CA and the combination treatments of Ardox-X followed by CA, H_2O_2 followed by CA were significantly more effective against the polymicrobial biofilms than chlorhexidine, H_2O_2 and Ardox-X. Among the chemicals tested, CA demonstrated the greatest decontamination capacity with respect to both the killing and the removal of biofilm cells. Moreover, the combination of effects is clinically desirable because it promotes biocompatibility and healing around a previously contaminated implant surface.[148] Although the mechanism of biofilm removal is unknown, it could be due to the adsorption of CA on the titanium surface under certain pH forming "acid clusters" (*i.e.* aggregation of molecules) [149]. This causes the disruption of calcium-ion bridges which represents the chemical binding sites within the biofilm connecting the EPS polymeric chains.[150]

1.2.7 Antibiotic and antiseptic coatings

One of the approaches to avoid bacterial infection on implants, and hence prevent biofouling, is to cover them with the coatings that can release antibiotics or antiseptics in the local niche. Such coatings can be prepared either by soaking the carrier material in a solution containing antibiotics/antiseptics or by directly impregnating antibiotics/antiseptics onto the coating material.

1.2.7.1 Antibiotics

Local delivery of antibiotics at the implant site might be an efficient strategy against biofilms which can display several advantages. Firstly, in case high local doses do not cause any systemic toxicity, high efficacy can be achieved at the specific local site. Additionally, local delivery of antibiotics allows targeting specific peri-implantitis pathogens, preventing potential antibiotic resistance. Various surface coatings have been developed to achieve the effect of controlled release of antibiotics *in vitro*. Some requirements concern both antibiotics and coating materials. In regard to antibiotics, a broad antibacterial spectrum and thermostable properties represent the most critical requirements, since coating procedures are usually conducted at high temperatures. Gentamicin is a commonly used antibiotic in such applications partly due to its relatively broad antibacterial spectrum. Furthermore, it is one of the rare kinds of thermostable antibiotics and is one of the most widely used antibiotics for titanium coating. Besides, cephalothin, carbenicillin, amoxicillin, cefamandol, tobramycin, and vancomycin have also been used in coatings on bone implants.[7] On the other hand, the drug incorporation strategy into coatings as well as drug release rates from coatings are two important aspects, for they can highly influence the effectiveness of antibiotics. Materials such as polyurethane, biodegradable polymers and calcium phosphates (including carbonated hydroxyapatite and porous hydroxyapatite) are presented as representative examples of coatings which can meet these requirements.[96] A major drawback of this approach is that every drug delivery method has intrinsic

limitations. The positive effect will disappear since drug elution is finite. Moreover, the local toxicity on surrounding tissues needs to be fully investigated.

Systemic antibiotics are administered as adjuncts to mechanical irrigation and debridement and/or additional surgical procedures on affected dental implants heavily colonized by putative bacterial pathogens. As a result, systemic antibiotic therapy is often advised as a part of peri-implantitis treatment protocols, similar to the use of systemic antibiotics in periodontitis treatment, despite an absence to date of strong supporting scientific data.[97]

The drugs investigated included conventional antibiotics such as amoxicillin, vancomycin, gentamicin, tetracycline, minocycline or cephalotin, which were incorporated in controlled release devices. Antibiotics were capable of reducing bacterial colonization with *Strep. mutans* [98,99], *S. epi.* [132], *S. aureus* [100], *P. aeruginosa* [101] and *E. coli* [29,102,103] on titanium surfaces.

1.2.7.2 Silver

Silver is an inorganic antimicrobial agent which has long been known for its antiseptic effects, although the use of silver decreased with the dissemination of antibiotics. The urgent need for effective strategies to fight the growing number of multi-resistant bacteria has recently revived interest in silver and numerous studies have reported the use of silver-coated materials to reduce bacterial infections associated with orthopedic and dental implants. Inorganic antibiotic materials have several advantages compared to traditional organic agents; these include chemical stability, thermal resistance and protracted action [29]. In addition, silver has a wide spectrum of antibacterial susceptibility, a low propensity for bacterial resistance, and the ability to inhibit polymicrobial colonization.[30]

The main antibacterial effect of silver is mediated by the release of biocidal Ag^+ ions, which interact with the bacterial cell wall and disturb its permeability, inactivate essential proteins and cause DNA condensation.[31] Silver exhibits a rather broad spectrum of antimicrobial activity and has not yet increased the risk of bacterial resistance. Pathogens found at infected oral implant sites, including *Strep. mutans* [32], *S. aureus* [33,34], *Strep. oralis* [31] and *A. actinomycetemcomitans* [36] were killed or significantly reduced upon contact with silver-implanted surfaces. All tested silver surfaces, such as hydroxyapatite (HA)-silver-surfaces [30,36–43] or plasma sprayed silver-implanted HA shared good antimicrobial activity.

Li et *al.* [45] elaborated silver loaded gelatin microspheres and incorporated them into porous titanium to produce antibacterial implants. The silver loaded samples were able to inhibit bacterial growth (*S. aureus* and *E. coli*). Gelatin microsphere vectors can control the silver release rate to reach high antibacterial efficacy.

Silver is certainly the most commonly used metal to confer anti-infective properties to biomedical devices for its oligodynamic antibacterial activity, *i.e.* exhibiting bactericidal/bacteriostatic activity at very low concentrations. However, since its early identification as a convenient anti-infective

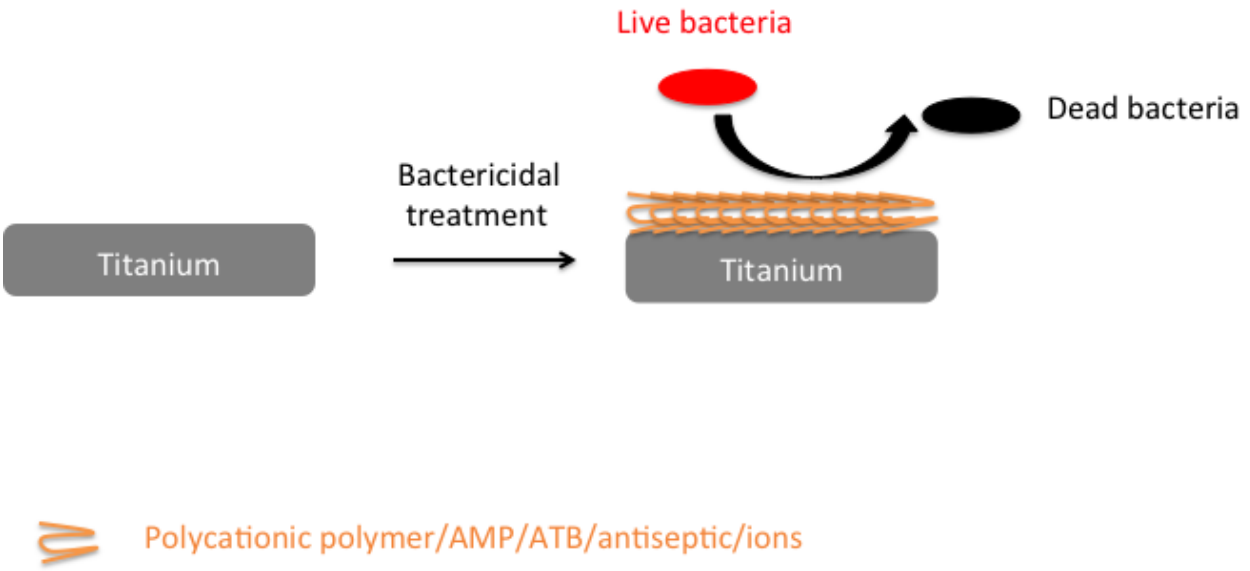
biomaterial, the use of silver as bulk material in medical devices has progressively been ceasing over time. Following an opposite trend, the utilization of this element in thin nanocoatings, in doped solid or hydrogel materials, in the formulation of bioactive alloys and glasses, and in form of micro- and nanoparticles has progressively been flourishing. At present silver has become one of the most widely used anti-infective substances, especially utilized in impregnated catheters, skin dressings and revision implants for oncologic orthopedic reconstructive surgery. Controversially, a debate still persists over the possible inactivation of silver mediated antibacterial activity in physiological fluids and over the low biocompatibility index of silver determined by the low threshold concentration for cytotoxic effects, especially when in the form of nanoparticles.[31,46]

1.2.7.3 Chlorexidine

Chlorhexidine (CHX) has been believed to be effective in the therapy of mucositis and peri-implantitis [47]. It was found that, with the additional use of 2% CHX, more anaerobic bacteria on the implant surface were killed than using mechanical debridement alone. In fact, 2% c CHX was shown to be the most effective concentration previously, achieving a total viable biofilm reduction ranging from 96.2% to more than 99.99%, depending on the time of exposure and the stage of biofilm development.[48] It was also reported that an oral irrigator combined with 0.2% CHX is effective in reducing biofilms attached to rough titanium surfaces immediately after cleaning [49]. However, there seemed to be no significant difference in bleeding reduction, suppuration, probing pocket depth and radiographic bone loss.[50] It was also reported that CHX can be adsorbed by the titanium surface [51], due to fact that CHX is a positively-charged biguanide compound.

Another study performed by Barbour et *al.* [17] showed the bactericidal effect of the CHX on *Strep. gordonii.* Titanium surfaces (anatase and rutile) were immersed in a solution of CHX (100 mg/L) for 1 min, after which time CHX adsorption is believed to be maximal. Adsorption with CHX resulted in a greater proportional reduction in bacterial coverage (80% for anatase and 40% for rutile).

Scheme 7 summarizes the existing bactericidal coatings with their different substrates such as polycationic polymers, AMP, ATB and antiseptics.



Scheme 7: Bactericidal treament of a titanium surface by polycationic polymers, antimicrobial peptides (AMP), antibiotics (ATB), antiseptics or ions.

1.3 Plasma spray technology

Thermal spraying consists of depositing at high velocity finely divided materials in a molten or semi-molten condition to form a coating. It therefore requires a heat source. Thermal spraying encompasses among others plasma spray. The latter has been extensively used to form titania coatings of excellent mechanical, chemical, and physical properties.

Nanosized titania powders were plasma sprayed onto titanium substrates before grafting an additional layer of gentamycin-loaded collagen I to achieve biocompatible and antibacterial surfaces. However, the described growth inhibition against *S.aureus* persisted no longer than 30 days.[70] Ti foil coatings comprising biofunctionalized silver nanoparticles with varied biomolecule templates showed substantial antibacterial activity in solution against *S.aureus.* Biofunctionalized specimens were also reported to be non-toxic and did not impair osteoblasts growth or adhesion compared to Ti.[151] Cao et *al.* [152] ingenuously demonstrated that larger silver nanoparticles (Ag NPs size 5-25nm), when incorporated by plasma immersion implantation and deposition into titanium oxide coatings previously plasma sprayed on CpTi substrates, had a significantly higher antibacterial activity against *S.aureus* and *E.coli* than smaller silver nanoparticles, while maintaining good cytocompatibility on osteoblasts.

Miola et *al.* [153] applied silver-doped glass-coatings onto orthopaedic titanium alloy substrates via plasma spray and found that the silver enrichment of the surfaces caused a significant bacteriostatic

effect without any consequence on fibroblast cell adhesion and proliferation (up to 24h). Hydroxyapatite (HA) is a widely commercially available coatings for orthopaedic and dental implants. Indeed, it plays a fundamental role in bone mineralization and has been shown to enhance fast osteointegration.[154] Because of its excellent biocompatibility, bioactivity, osteoconductivity and non-toxic properties, HA coatings quickly appeared as an ideal of choice for anti-infectious coating strategies. For this reason, coatings made of HA doped with "antibacterial" ions, such as silver & strontium,[155] silver,[156–158] were developed with success regarding antibacterial activity.

1.4 Plasma immersion ion implantation and deposition (PIII&D)

Described in 1987 by Conrad et *al.* [159], PIII&D has gained significant popularity as an anti-infectious coating technique for titanium surfaces over the past ten years. In this scenario, plasma is produced by an electrical discharge inside a vaccum chamber with a workpiece stage, a plasma source and a high-voltage pulse modulator.[160] The principle is to generate a plasma sheath around substrates of virtually any shapes. This is achieved by exchanging electrons from the substrate with positive plasma ions. Eventually positive ions are accelerated and implanted vertically into the substrate surface. An ion-oxide film with graded changes on the body material surface is then produced. Obvious benefits are an enhanced integration both between the coating and the surface of interest and between tissues and the coating.[161] An early application of PIII&D to confer antibacterial activity to treated titanium surfaces was illustrated by Yoshinari et *al.* [162] in 2001. They reported that F^- ion implantation significantly decreased bacterial growth of both *P. gingivalis* and *A. actinomycetemcomitans* (periodontopathic bacteria). Later in 2010, Xu et *al.* [61] successfully incorporated Zn ions onto titanium surfaces and showed a significant decrease in bacterial counts after a 48h contact compared with controls. PIII&D was also utilized on titanium nanotubes in order to embed Ag^+ at different depths without breaking the nanotubular structure.[163] Coated surfaces displayed a vast majority of dead bacteria after a 24h culture with oral pathogens, both gram positive bacteria (*P. gingivalis*) and gram negative bacteria (*A. actinomycetemcomitans*). The antibacterial effect was persistent even after seven days. Interestingly, nanotubes displayed increased bacterial viability than control polished titanium due to structural differences and excellent hydrophilicity of nanotubes according to the authors. More recently, the incorporation of Mg ions onto titanium surfaces was shown to have a favorable effect on the osteogenicity of the produced biomaterial and its antibacterial activity. The highest obtained antibacterial ratios of treated surfaces against *E. coli* and *P. aeruginosa* compared with control Ti were 20 ± 6% and ∼58 ± 4%, respectively.[164]

1.5 Physical vapor deposition (PVD)

Physical Vapor Deposition (PVD) represents a coating strategy consisting of vaporizing solid metal in a high vacuum environment and depositing it on electrically conductive materials. PVD is a versatile coating method that allows the deposition of all types of inorganic materials and some types of organic materials. It is considered environmentally friendly and is associated with good corrosion resistance. However, coating complex shapes remains an important drawback. Brohede et *al.* [165] used PVD to build an adhesion enhancing gradient layer of titanium oxide at the interface and a bioactive anatase

TiO2 composition at the surface. The bioactive side was used in a second step to graft hydroxyapatite (HA) in order to facilitate both bone in-growth and drug delivery following antibiotic loading. This resulted in the creation of a versatile fast-loading (15 min) with slow antibiotic release coating (24 h). Kang et *al.* [166] used PVD to create an antibacterial TiAgN thin film coated on pure titanium specimens. The antibacterial coating was efficient against *S. mutans* and no cytotoxic effects were not found on human gingival fibroblast (HGF). Ji et *al.* [167] compared the antibacterial activity of different coating modalities for TiN thin films: PVD with direct current (DC) magnetron sputtering to plasma-assisted chemical vapor deposition (PACVD). They found no difference on the adhesion of *S. mutans* to these surfaces.

1.6 Graphene and its derivatives

Graphene is a relatively new player in the field as it was first isolated in 2004 via simple mechanical exfoliation of graphite.[168] Graphene sheets are two-dimensional, one-atom-thick layers of sp2-bonded carbon atoms. They are connected in a hexagonal network. Their excellent electronic, optical and mechanical properties account for the reputation of graphene. Classically produced by CVD, the main issue raised by graphene in coating technologies was its transfer onto substrates. Indeed, the classic wet transfer technique opposed an obstacle that mandated alternative strategies: water was easily trapped between the coating and substrate causing folds and cracks after.[169] Dubey et *al.* [170] adapted a dry transfer technique to titanium surfaces while it had been previously described by Morin et *al.* [171] They also showed that graphene-coated titanium was cytocompatible anddecreased the formation of biofilms from *S. mutans* and *E. faecalis*. Using CVD coupled with a wet technique transfer (using polymethyl methacrylate or PMMA), Gu et al. stabilized the graphene coating with a thermal treatment (described above). Thin films of graphene oxide (GO) combined with Ag nanoparticles were applied onto titanium surfaces via electroplating and UV by Jin et al. with significant adhesion and growth inhibition of *S. mutans* and *P. gingivalis*. Also, cell viability was inversely proportional to the contents of GO and Ag in the coating.[172] GO raised a significant interest in the scientific community thanks to its excellent biocompatibility. Indeed, Jia et al. outlined the importance of structural and lateral size properties of graphene (GO and reduced GO) self-assemblies.[173] The importance of the number of GO layers was shown by Qiu et *al*.[174] In fact, increasing the layer number of GO resulted in enhanced antibacterial and osteogenic effects compared to pure titanium controls. Qian et *al.* [175] studied minocycline-loaded GO and successfully established a combination of direct contact killing by GO and delayed release-killing by minocycline hydrochloride on *S. aureus*, *S. mutans* and *E. coli* with no detrimental effect on cytocompatibility (human gingival fibroblasts).

2. Chemical modification

2.1. Chemical vapor deposition (CVD)

Chemical Vapor Deposition (CVD) implies a chemical reaction with gaseous reactants in contact with a heated surface. The end-product is a finely controlled coating, both quantitatively (high purity with fine control of chemical product deposition) and qualitatively (surface topography, number of layers). This popular technique proved to be extremely successful in industrial applications (electronics, optics, fiber coatings). However, its use on titanium surfaces for antibacterial coatings has been quite limited to this date. Xu et *al.* [176] described a one-step CVD approach to deposit a small amount of graphitic C_3N_4 on aligned TiO_2 nanotube layers. They successfully demonstrated that this coating had strong photocatalytic antibacterial properties against *E. coli under* visible light (30% survival rate after 3 h). The main limitation of previous similar attempts with TiO_2 nanotubes was that they required UV light for activation.

CVD was also used to produce single-layer graphene sheets (described below) as coatings onto titanium discs.[177] The authors ingeniously showed that a thermal treatment (2h at 160°C) enhanced the adhesion strength of graphene on Ti with no detrimental effect to antibacterial activity. Graphene-coated surfaces decreased the number of *S. aureus* colonies by 40% and *E. coli* colonies by 60%.

2.2. Sol-gel

A sol-gel synthesis aims at forming mineral phases obtained from the polymerization of small molecular precursors. This usually results in a colloidal solution (sol) that may represent an inorganic host for the implementation of guest compounds: organic molecules such as polymers or small particles (nanomaterials).[178] The end-product is a gel that provides an interesting architectural scaffold for trapped “guest” molecules, which is a valuable feature in coating technologies. Moreover, the synthesis process is relatively convenient and allows an excellent control of the coating composition. The resulting gelatinous texture also allows the creation of thin films to be studied independently or coatings apposed on titanium surfaces of virtually any shape for example.

Another advantage of the use of sol-gels as coatings is the possibility to integrate a wide variety of compounds destined to be locally delivered at a controlled rate, such as antibiotics. Radin and Ducheyne [179] used silica sol-gels to create coatings on titanium plates for local vancomycin delivery.

Sol-Gel Derived antibacterial Ag-containing ZnO films were deposited on biomedical titanium and characterized by Fu et *al*. [180] However, the films displayed weak compatibility with L929 cells (murine fibroblasts), antibacterial activity against *E. coli* increased with the silver content of the films.

Gollwitzer et *al.* [181] used a sol-gel copper (II) acetate monohydrate precursor and successfully integrated copper into the final TiO_2-coating hence significantly reducing adhesion of viable bacteria (*S. aureus*) with a favorable biocompatibility-antibacterial activity compromise. Similar results had been found with MRSA by Haenle et *al.* [182] using a similar technique. Previously, Heidenau et *al.* [183] had shown that copper ions displayed the best biocompatibility profile than Ag^+ and Hg^{2+} in the same sol-gel.

Silica-based composite titanium coatings containing AgNPs (AgNP/NSC) were also made by sol-gel technology by Massa et *al*. [184] Significant antibacterial and antibiofilm effects on titanium surfaces were demonstrated against A. actinomycetemcomitans, which could be of use in dental applications.

A uniform Ag/HA composite coating on porous Ti was also formed by sol-gel technology. [185] The authors showed a high antibacterial ratio (>95%), against *E. coli* and *S. albus* displayed by the silver-containing coatings compared with pure HA coatings. In their study, Ag/HA 0.8 surfaces (0.8 wt %Ag) had the best balance between biocompatibility and antibacterial properties.

Horkavcová et *al.* [186] tested titania sol-gels containing silver on TiSi alloy substrates. The coatings demonstrated very good antibacterial effects against both *E. coli* and *S. epidermidis* after 24h of interaction with no evidence of toxicity (L929 and U-2 OS cell lines).

2.3. Nitride coatings

Titanium nitride (TiN) is a material used to improve the surface properties and esthetics of metal tools. It has been documented that TiN has excellent chemical stability and is resistant to high temperatures and to corrosion. Moreover, its biocompatibility has been confirmed. Thanks to its characteristic golden color, it may help to camouflage the implant in areas with thin gingival tissues better than what can be achieved with common titanium surfaces, which are grey.[94]

TiN is characterized as a surface with a very high chemical inertness, hardness, low friction coefficient and corrosion resistance. These reduced surface interaction characteristics may be one reason for the antimicrobial effect of TiN, thus the overall antibacterial effect of nitride surfaces is a matter of discussion. Studies on nitride surfaces are sparse and the results are controversial. Some authors found unaltered or increased bacterial adhesion on nitride titanium surfaces, but others found reduced biofilm formation.[167,187–192] Ji et *al.* [167] found TiN to show antimicrobial effects against *Strep. mutans* but not against *P. gingivalis*.

IV. Discussions

The quest for active surfaces

The tremendous varieties strategies aiming at functionalizing titanium surfaces *in vitro* and in few *in vivo* models clearly show no standard has established a wide consensus in the scientific and medical community. Depending on the desired effect, it is now certain that specific functionalized surfaces will be achieved on medical implants. However, at this point, it is seems illusory to believe that a cheap and scalable engineered implantable surface can promote cell adhesion, guarantee biocompatibility and ensure over a 99.9% non-selective biocidal effect. Multiple barriers are yet to overcome. First, obviously most studies report strictly *in vitro* results. Secondly, *in vivo* studies using relevant animal models that

correspond to the actual application of studied biomaterials are scarce. Thirdly, no study has to this date assessed the interaction with animal or human immune cells.[193]

Device-associated infection complexity

In fact, one should not believe that even if this Graal biomaterial was ever built, it would necessarily automatically solve the problem of implantable device-associated infections. Indeed, the pathogenesis of these infections remains highly complex and misunderstood. Every biofilm is different and the pathogenesis varies depending on the affected tissue in which the device was implanted. Biofilms on orthopedic and dental implants are reputably harder to eradicate due to the poor environing vascular supply and bulkiness of the devices. Indeed, such surfaces are extremely high and remain unexposed to blood supply hence the difficulty of the immune system to combat these infections. Catheter-related biofilms develop in nutrient-rich environments and classically raise fewer clinical issues. Indeed, antibiotics have a choice access to catheters and catheter removal presents little morbidity. Contaminated implants do not always lead to infections and it is safe to believe that auto-sterile implants will not eradicate nosocomial infections in the surgical setting. Conceptually, the goal of an auto-sterile implant would be to display a non-selective effect on pathogens (bacteria, fungi, viruses) to prevent antibiotic resistance, prevent mature biofilm formation on implants in the mid- or long-term follow-up, facilitate the efficacy of a classic combined therapy of antibiotic use, surgical irrigation and debridement and eventually render hardware removals unnecessary.

Most advanced candidates to this date in orthopaedic surgery

In the orthopedics field, silver has been used for more than a decade with toxicity issues that restricted its use in patients with a very high-anticipated postoperative infectious risk. Interestingly, low-amount silver coatings such as Agluna [194] formed by titanium anodization followed by an ion-exchange reaction displayed a lower profile-risk than high-amount silver coatings such as MUTARS® formed by galvanic deposition of elementary silver on a titanium-vanadium implant and followed by an additional layer of gold layer of gold for sustained release of silver ions.[195] Iodine coatings gained significant interest in Japan due to their innocuity and successful initial clinical trials during the past five years.[63,196] In the field of orthopedic coatings, there is to this date only a single Level 2 randomized-controlled study. The authors conducted a large scale European multi-center study comparing the results of antibiotic-coated hydrogels (reconstituted and sprayed intraoperatively with various antibiotics, gentamicin, vancomycin, daptomycin, meropenem, rifampicin, and ciprofloxacin) in the context of traumatology against control implants (various types of implants). There was a significant reduction of infections in the group benefiting from coated implants (Six surgical site infections (4.6%) observed in the control group compared to none in the treated group).[197]

We now more than ever need more clinical evidence in the field of coatings for surgical implants. Before the publication of the previously described trial, Volker Alt reported only 9 published studies with 435 patients: seven case series (level IV evidence) two case series (level III). This is obviously insufficient compared with the magnitude of the effort made by the scientific community to find new molecules.

Gold, palladium and other nanoparticles are used in complex coatings that will be available to surgeons in the mid-long term.

Costs and scientific dispersion represent barriers to scalability of active surfaces

This remains a central topic for industrialized societies with ever-increasing healthcare-related budgets: will the surface treatment be cost-effective? Indeed, most of the molecules described in this review are hardly scalable and could significantly raise the price of implants with little or no clinical benefit. Actually, one may regret that a great deal of research is spent on antibacterial coatings that can never be translated *in vivo.* To address this issue, Cloutier et *al.*[193] highlighted the need for standardized and widely accepted validation methodologies for antibacterial coatings in the setting of specifically structured research that is consistent with its intended clinical application. Moreover, interactions between active surfaces and abrasion in clinical practice are yet to be investigated for most candidates. There is also scarce data on the residual amount of most coatings or active surfaces long after implantation. In theory a permanently treated implant would prevent further bacterial or fungal graft originating from hematogenous dissemination. With dozens of different surface treatments available to render titanium antibacterial, we deemed it necessary to clarify and classify their various syntheses, mechanism of action and pathogenic targets. Given the complex challenges raised by the translation of such research to clinical practice, we believe that the dispersion of scientific efforts directed towards the discovery of new molecules may blind us from further animal and clinical developments of existing solutions that would radically change the shape of healthcare and nosocomial infections.

Other areas of research on antibacterial surfaces

Rather than coating, multiple other approaches were proposed. Among them, the most popular nowadays is nanosurface modeling on bulk materials (drug-free strategies). Indeed, engineering uncoated surfaces which physical surface characteristics would both promote cell adhesion hence facilitating biocompatibility or tissue integration and repel bacteria has been extensively described and is now a mature technology that is currently available to clinicians. A seducing idea would be to combine these nanostructures with increase surface contact and active coatings or grafted molecules.

V. Conclusion

Numerous solutions exist to render titanium surfaces antibacterial. Their different mechanisms and targets were listed in the present study for further clarification of an ever-increasing science that will change the shape of health-care associated infections. Each solution is dependent of different parameters such as the kind of the bacteria, the studied illness, the desired effect (short, medium or long term. In this review, we identified the used solutions to decrease bacterial infections on the titanium surface according two main parts: surface modification and coatings (chemical or physical). Physical modification is cheaper than chemical modification but the modification is often performed in a

short time. However, chemical modification is more expensive and often involves several steps. The increasingly popular research topic of active surfaces has permitted the flourishing development of new molecules that have not yet reached maturity. Improvements in scalability, animal and clinical testing are to be expected in the coming years before any standard arises.

VI. References

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