

REVIEW

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## Biological Responses to New Advanced Surface Modifications of Endosseous Medical Implants

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**Abstract:** Implantable medical devices are increasingly important in the practice of modern medicine. However, patients with severely poor bone quality and quantity require highest implant osseointegration for the long-term success. A number of newly-developed advanced surface modifications of medical implants have recently been introduced to the medical implant system. Understanding the mechanisms by which osteogenic cells respond to such materials is therefore of major importance in developing the most effective materials to promote functional osseointegration. Diverse studies using materials with a wide range of new surface modification techniques have demonstrated the pivotal role of surface treatments in cell adhesion, proliferation and lineage specific differentiation. These events underlie the tissue responses required for bone healing following implant placement, with the interaction between adsorbed proteins on the implant surface and surrounding cells eliciting body responses to the treated implant surface. This review illustrates tissue responses to the implant material following implant placement and highlights cellular responses to new advanced implant surface modifications. Such information is of utmost importance to further develop several new advanced surface modifications to be used in the new era medical implantable devices.

**Keywords:** biological response, endosseous implant, osseointegration, surface modification

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## Introduction

A number of pathological osseous conditions require fixative and replacement therapies involving the use of medical implant appliances,<sup>1,2</sup> and during the past several years, a number of materials, such as titanium and its alloys, have been used for the fabrication of these medical devices. Criteria such as an acceptable mechanical behaviour and biocompatible chemical composition to avoid adverse tissue reactions have been used to define an ideal implant material for orthopaedic surgery, but the overriding clinical requirement for these materials is to facilitate osteogenesis at the bone-implant interface, i.e. enhance osteoblast differentiation and function.<sup>3</sup> While the shape, length and diameter of a medical implant have been proposed to enhance clinical performances, the type of material and implant surface treatment and coating markedly influence its osteogenic properties.<sup>4</sup> Although many implant materials appear to be capable of enabling bone cell attachment, migration and growth (osteoconduction), their ability to stimulate the proliferation and differentiation of pluripotent mesenchymal cells into bone forming osteoblasts (osteinduction)<sup>5</sup> is nevertheless still unclear. While titanium and a multitude of titanium alloys have been widely used and are generally regarded as the materials of choice due to their high biocompatibility and osteoconductivity,<sup>6,7</sup> other promising implant coating materials, such as hydroxyapatite, bioactive glasses and biologically active agents, have also been used as coating materials in order to enhance bone-to-titanium (alloys) anchorage by facilitating their osteoinductivity.<sup>8-11</sup> Understanding the mechanisms by which osteogenic cells respond to such materials is therefore of major importance in developing the most effective materials to promote functional osseointegration, which is required for the long-term success of implant surgery.<sup>5</sup>

A number of commercially available implant surfaces have proven clinical efficacy (approximately 95% over 5 years).<sup>12</sup> Several attempts have been made to develop new implant surfaces and to study their *in vitro* and *in vivo* properties with respect to osteogenic enhancement in order to obtain a long term success of medical implants in some certain problematic conditions, such as immediate loading medical implants and difficult clinical situations with poor bone quality and quantity. Although the

osteogenic role of these conventional surfaces has been extensively reviewed,<sup>6,13-18</sup> the role of new advanced surface modifications in enhancing implant osseointegration has not yet well documented. This review therefore highlights the biological responses to newly-developed surface modifications of the implant material.

## Tissue Responses to the Implant Material Following Implant Placement

Within a few nanoseconds following implantation, the tissue responds to the implant material surface by allowing water molecules to make contact with the implant surface, thus forming a water layer surrounding the implant.<sup>19</sup> Surface properties of the implanted material have a major influence on the extent and specific interaction pattern of the material surface with this hydration layer, which in turn facilitates proteins and other molecules in the biological micro-environment to adsorb to the material surface.<sup>19,20</sup> In the second stage, from seconds to hours after implantation, the material is subsequently covered by a thin layer of the extracellular matrix proteins; its conformation, orientation and composition are also likely to be affected by the implant material surface.<sup>21-23</sup> The third stage involves the interaction of cells with the 'surface' of the implant via the adsorbed protein layer. The cell-protein bound surface interface, occurring from as short as minutes after and up to days following implant placement, initiates cellular adhesion, migration and differentiation, which occurs from a few hours to several days after implantation.<sup>21</sup> This stage is tightly regulated by numerous biological factors, including extracellular matrix proteins, cell surface-bound and cytoskeletal proteins, by chemical characteristics and topographies at the implant surface and by the released ions/products from the material.<sup>24</sup> The final stage of the body responses to the implant, which can last up to several decades, is the continuing development of the earlier stages, eventually resulting in the formation of functionally active mineralized bone tissue surrounding the implant. However, adverse responses, such as pathological inflammation, fibrous capsule formation and implant failure, can also occur during this stage.<sup>25-27</sup> The future development of modern implant biomaterials is therefore aimed to minimize such effects as well as to promote rapid



wound healing and implant-to-bone integration for the long-term success of an implanted device in the body, which is significantly dependent on the tissue biocompatibility at the site of implantation as well as the physicochemical properties of the material.

Both *in vivo* studies and controllable *in vitro* experiments mimicking *in vivo* situation have been important tools to study the effect of biomaterials on living tissues and their interactions with cell functions. This includes biocompatibility test, which is thereby assessed *in vitro* by the observation of viability and bio-functionality of cells on a material surface. Osteoconduction experiments are also carried out *in vitro* by determining the ability of a material soaked in simulated body fluid to facilitate cell attachment, spreading and proliferation.<sup>28–30</sup> This allows the rapid initial screening of materials for further development and optimization for their clinical use. Finally, bioactivity or “osteoiduction” experiments are generally performed *in vitro* by determining the mineralized crystal forming ability of a material, which will subsequently be further established in a well-accepted *in vivo* animal model. It has recently been suggested that conventional histological- and histomorphometrical analysis and micro-computed tomography should be considered as complementary methods for the assessment of peri-implant osteogenesis following implant placement.<sup>31,32</sup> The information derived from the basic understanding regarding the responses of cells to materials may provide important insight into the development of a number of promising surface modifications to be used in endosseous medical implantology in the new era.

## Cellular Responses to Modern Implant Surface Modifications

It is generally accepted that commercially pure titanium and its alloys are gold standard materials for medical implants, and their osteogenic properties can be enhanced by various modifications of the material surface in order to obtain osteogenic-inducing surface chemistry. A number of approaches have been considered in an attempt to achieve rapid and long term success of implant osseointegration. These modern trends include surface roughening at the nanoscale level, the use of biomimetic calcium phosphate coatings and the incorporation of biologically active

agents into medical implants. A summary of the current advanced surface modifications of implants is shown in Table 1.

## Nanoscale surface roughening of medical titanium implants

It is well established that the roughness of implant surfaces plays a crucial role in the biological events following implant placement. It is possible that implant materials with a rough surface topography induce a three-dimensional growth of cells, supporting osteoblast adhesion and differentiation and promoting mesenchymal cells to differentiate along the osteoblast lineage by activation of several osteogenic-associated genes, e.g. core-binding factor 1 (Cbfa1), collagen, alkaline phosphatase, osteonectin, osteopontin and bone sialoprotein.<sup>33–38</sup> It is thus believed that surface topography has a significant influence on the proliferation and differentiation of osteoprogenitor cells. Although presently available data are not consistent, the most commonly observed trends are that as surface roughness increases, the differentiation of osteogenic cells and their synthesis of extracellular matrix increase together

**Table 1.** A summary of the current advanced surface modifications of implants.

1. Nanoscale surface roughening
  - 1.1. Physical compaction
  - 1.2. Molecular self-assembly method
  - 1.3. Chemical modification: acid/alkaline treatment, peroxidation
  - 1.4. Nanoparticle deposition: sol-gel method, crystalline deposition
2. Biomimetic calcium phosphate coatings
  - 2.1. Electrochemical method
  - 2.2. Immersion method
3. Incorporation of biologically active agents
  - 3.1. Osteogenesis-inducing agents: BMPs, TGFs, VEGFs, PDGFs, IGFs
  - 3.2. Bone remodeling-associated agents: bisphosphonates
  - 3.3. Synthetic RGD peptides
  - 3.4. Antibiotics

**Abbreviations:** BMPs: bone morphogenetic proteins; TGF- $\beta$ 1: transforming growth factor  $\beta$ 1; VEGFs: vascular endothelial growth factors; PDGFs: platelet-derived growth factors; IGFs: insulin-like growth factors.



with a concordant decrease in their proliferation. While micron-scale topographic modification of the commercially pure titanium surface has been accepted in the endosseous implant market due to its ability to facilitate osteogenesis at the bone-implant interface,<sup>39,40</sup> increasing evidence has suggested that surface nanotechnology applications to the titanium implant may provide a promising approach to manufacture endosseous implant surface with a greater specific control of osteoblast differentiation and surrounding tissue fate, thus positively regulating implant osseointegration.

Nanotechnology involves materials that have a nanoscale topography or comprise nano-sized materials, which generally have a size range between 1 and 100 nm. Several methods have been proposed to create nanofeatures on titanium implant surfaces, for example, physical approach by compaction of nanoparticles (such as titanium dioxide (TiO<sub>2</sub>)), molecular self-assembly method, chemical modification by acid/alkaline treatment or peroxidation, nanoparticle deposition (such as sol-gel and discrete crystalline deposition).<sup>41</sup> While a number of methods have already been utilized to treat titanium orthopedic implants available commercially, most of nanotechnology-based surface modifications are currently undergoing the research and development process. A number of *in vitro* experiments have shown that nanoscale structures, but not smooth surfaces, markedly increase osteoconductivity of materials by facilitating the attachment and proliferation of mesenchymal stem cells and osteogenic cells.<sup>41-47</sup> It has been reported that metallic implant materials, such as titanium and its alloys, and some traditional polymeric materials treated with either nanoparticulate alumina or titanium using ionic plasma deposition and nitrogen ion immersion plasma deposition techniques show greater nanoscale roughness with increased osteoblast adhesion compared with the control untreated surfaces.<sup>48</sup>

It is not yet clear how nanoscale roughened topography influences its target cells. It is possible that nano-roughness topology regulates the interfacial forces that direct re-organization of cytoskeletal and cell surface receptor proteins. Moreover, nanoscale roughness could also modify the protein adsorption and conformation of integrin-binding adhesion

molecules and thus modulating intracellular integrin pathway. This eventually results in controlling transcriptional events in the nucleus that guide target cells to undergo osteoblast differentiation, hence promoting implant osseointegration.

Although mechanisms by which nano-roughness enhances cell adhesion are not yet well understood, it has been suggested that initial attachment of cells to implant surfaces occurs through well-developed filopodia, directly exploring surface irregularities of the implant.<sup>44</sup> This is found to be primary adhesion structures in cell-to-extracellular matrix interaction. The roughness at nanometer thus provides positive guidance for osteogenic cells to attach, leading to enhanced cellular attachment via the selective attachment of osteoblasts to the implant surface.<sup>44</sup> This selective attachment process might result in the improvement of initial healing around medical implants with nanoscale roughened surfaces. On the other hand, cells attach to a smooth surface by focal adhesions around their surface membrane as primary attachment structures because repulsive signals from the environment lead to the retraction of filopodia back to the cell bodies.<sup>44</sup> This results in flattened cells with reduced cellular attachment to their surrounding substrates. Intriguingly, Prince and colleagues<sup>49</sup> reported that nanometer dimension fibers selectively enhanced osteoblast adhesion, whereas they decreased adhesion of smooth muscle cells, fibroblasts and chondrocytes. Such selective cell adhesion property therefore offers an advantage of a nano-roughened surface over its counterpart surface with respect to its potential to induce true direct bone contact but not unfavourable integration such as fibro-osseous integration.

In addition to the positive effect of nanostructured surfaces on osteoconductivity, it has also been shown to facilitate the implant material osteoinductive property by enhancing osteoblast differentiation of stem/progenitor cells. Recent studies have shown strong cell responses of mesenchymal populations and osteoprogenitors to nanofeatures with increased levels of two important bone matrix proteins, osteocalcin and osteopontin.<sup>50,51</sup> It is also suggested that progenitor cells are, in fact, more responsive to topography than more mature cell types and that they are actively seeking cues from their micro-environment.<sup>52</sup> Moreover, Oh and colleagues<sup>53</sup>





have recently shown that the optimal dimension (approximately 70–100 nm diameter) of nanotube titanium oxide surface structures markedly drove differentiation of human mesenchymal stem cells into osteoblasts without the use of supplemented osteogenic-inducing factors *in vitro*, whereas increased stem cell adhesion without osteoblast differentiation of the stem cells was found in nanotubes with approximately 30 nm diameter. The reason for this is not yet well established, but it is possible that such optimal pore size may allow functionally-relevant stem cell elongation that in turn influences cytoskeletal stress, thus promoting stem cell differentiation into osteoblastic cells.

The roughness of the material also plays a significant role in the bacterial attachment process, presumably when the surface irregularities are comparable to the bacterial size and can protect them from unfavourable environment. In general, most commonly found bacteria range between 0.5 and 5  $\mu\text{m}$ . Thus, it is possible that surface roughness on a scale much smaller than the bacteria would not be expected to influence the initial attachment. It is noteworthy that while osteoblastic cells are selectively adhered onto nanoscale surface, bacterial adhesion and growth on such surface is reduced.<sup>54</sup> Moreover, Mitik-Dineva and colleagues<sup>55</sup> reported that surface modification by etching, which resulted in a 70% reduction in the nanoscale roughness of the glass surface, significantly increase the number of bacteria adhering to the surface, suggesting that bacteria are sensitive to nanoscale surface roughness. Since the adhesion of bacteria to implant surfaces is also a key factor for the failure of implant osseointegration, this initial report suggests that such nanometer-roughness may provide favourable condition for successful osseointegration by preventing post-operative bacterial infection. Future comprehensive studies on the role of the nanotopography in bacteria are undoubtedly required to develop a clinically-successful medical implant system.

While a number of novel nanophase materials may be a promising alternative implant material, potential pitfalls or undesirable side effects associated with the use of nanomaterials in medical applications are also of important concern.<sup>56</sup> Nanostructured implants by physical compaction of

nanoparticles could possibly be problematic due to loosening particles, resulting in an accumulation of nano-sized wear debris. Although the role of micron-sized wear particles in long term post-operative surgery is well-known, the effect of nano-sized debris generation in bone micro-environment is still poorly investigated. Thus, more detailed *in vivo* experiments in this context are required before the full benefits of nanotechnology in implant surgery can be widely recognized.

### Biomimetic calcium phosphate coatings on medical titanium implants

Delamination of calcium phosphate coating from the titanium implant surface causes a long term failure of osseointegration of the conventional plasma-sprayed hydroxyapatite-coated titanium implant. A new coating method, mimicking the natural process of bone mineralization, has been recently developed in order to avoid the drawbacks of such coatings. In this biomimetic approach, precipitation of calcium phosphate apatite crystals from simulated body fluids forms a coating on the titanium surface at room temperature.<sup>57,58</sup> In order to enhance the deposition of coatings from aqueous solutions, a number of methods have been used. The electrochemical method involves the deposition of calcium phosphate by using a titanium cathode and a platinum anode to generate a current.<sup>59,60</sup> This method is generally performed in acidic calcium phosphate solutions and gives rise to brushite coating formation which is subsequently converted into apatite by hydrothermal processing. Moreover, the electrochemical deposition conducted in simulated body fluid buffered at neutral pH can also produce a carbonated apatite coating directly on the titanium surfaces.<sup>61</sup> This method gives possible impeccable control of the calcium phosphate thickness on all types of complicated surfaces with a short coating time and high reproducibility and efficacy.<sup>62</sup> The second method involves immersion in simulated body fluid which allows calcium phosphate to precipitate onto titanium surfaces.<sup>57,58</sup> This method involves the heterogeneous nucleation and growth of bone-like crystals on the surface of the implant. An implant is first treated with an alkaline in order to form titanium hydroxyl groups on the titanium surface, serving as nucleating points, followed by



the crystal growth of the coating. In general, these subsequent events help promote the heterogeneous nucleation of the calcium phosphate.

Bone cell responses to biomimetically produced calcium phosphate materials have previously been shown. For example, these materials promote surface adhesion and proliferation of both osteoblastic and osteoclastic cells *in vitro*.<sup>63,64</sup> It has also been reported that biomimetic calcium phosphate coatings are more soluble in physiological fluids and more resorbable by osteoclasts than high temperature plasma-sprayed hydroxyapatite coatings.<sup>65,66</sup> Thus, these materials might be useful to enhance favorable bone remodeling, an important process in bone healing involving osteoclastic resorption and subsequent bone formation by osteoblasts. Although the osseointegration of titanium implants coated biomimetically has not yet been compared with other surface treatments in pre-clinical models, biomimetic coatings have been shown to provide a greater bone-implant contact compared with their counterpart uncoated surfaces.<sup>67,68</sup>

The osteogenic effect of biomimetic calcium phosphate-coated implants has been assumed to be comparable to the conventional calcium phosphate coatings. Previous *in vivo* studies have shown that hydroxyapatite coatings stimulate bone growth compared with uncoated titanium alloys.<sup>69,70</sup> Although enhanced bone integration is also observed when hydroxyapatite-coated and uncoated implants are both implanted into the same animal,<sup>71,72</sup> trials with human patients have shown the advantages of hydroxyapatite-coated devices compared with their non-coated counterparts, such as increased implant survival, radiographic stability, lack of pain, and inhibition of implant movement.<sup>73,74</sup> It has also been shown that hydroxyapatite facilitates osteoblast differentiation of cultured marrow stromal, pre-osteoblastic and bone-derived cells.<sup>75-77</sup> However, to increase the relatively poor mechanical properties of hydroxyapatite, various modifications have recently been introduced to the hydroxyapatite system, for example, glass-reinforced hydroxyapatite composite materials, which were further found to enhance the expression of bone sialoprotein and osteonectin by osteoblastic cells compared with cells cultured on pure hydroxyapatite alone.<sup>78</sup>

However, the cellular effect of such modified hydroxyapatite composites biomimetically coated on core implant materials has not yet been reported. It has also been shown that different types of calcium phosphates coatings demonstrate different cellular responses. For example, a carbonate apatite coating stimulates the proliferation and differentiation of initially developing pre-osteoblasts, whereas in the late stage of their development, an octacalcium phosphate coating significantly enhances osteoblastic proliferation and differentiation compared with the carbonate apatite coating, via the activation of late differentiation marker genes, such as osteocalcin and bone sialoprotein.<sup>79</sup> These data suggest that the osteogenic calcium phosphate-coated implant surfaces processed by this novel biomimetic method not only prevent the delamination of the coated layers from the implant surface, but also stimulate implant osseointegration.

### Incorporation of biologically active agents into medical titanium implants

The surface of implants may be coated with osteogenesis-stimulating agents, such as growth factors, in order to accelerate angiogenesis and bone formation surrounding the endosseous implants. Members of the transforming growth factor  $\beta$  (TGF- $\beta$ ) superfamily (in particular bone morphogenetic proteins (BMPs) and TGF- $\beta$ 1), vascular endothelial growth factors (VEGFs), platelet-derived growth factors (PDGFs) and insulin-like growth factors (IGFs) are some of the most promising candidates for this purpose. For example, incorporation of BMP peptides into medical implants have widely been used to induce and sustain implant osseointegration.<sup>80-83</sup> However, the biologically active product has to be released progressively, and not in a single burst, to the peri-implant micro-environment. Another method to obtain the BMP-incorporated surface is the utilization of a plasmid containing the BMP encoding gene.<sup>84</sup> Although this option may offer a better sustained release profile of the BMP, the outcome could nevertheless be limited due to the poor efficacy of transfecting plasmids into the target cells and the low expression/secretion level of the protein by the transfected target cells. In addition, continuing overexpression of the BMP by plasmid-transfected cells might not be advantageous after the completion of



bone healing following implant placement. In addition to BMPs, much attention has currently been focused on the activation of angiogenesis, a key factor for rapid bone healing, by local and sustained delivery of plasmid DNA encoding for VEGF.<sup>85,86</sup> Incorporation of VEGF gene into the implant surface could thus be a promising modern surface modification in this era medical implantology.

The implant surface could also be loaded with bone remodeling-associated bioactive agents. Incorporation of certain bone antiresorptive drugs, such as bisphosphonates, might be beneficial in clinical application for patients lacking sufficient bone support, e.g. severely resorbed alveolar ridges. It has recently been shown that a chemically-associated bisphosphonate zoledronate onto calcium phosphate compounds inhibits osteoclastic activity and thus reducing bone resorption.<sup>87,88</sup> This might shift the balance of bone remodeling toward the formation of new bone *in vivo*. For example, experimental *in vivo* studies using bisphosphonate-incorporated titanium surfaces demonstrated a significant increase in the amount of supporting bone surrounding the implants.<sup>89–91</sup> However, other experimental studies have demonstrated only a slight increase in implant osseointegration.<sup>92,93</sup> The major concern is the controlled and sustained release of these antiresorptive agents on the titanium implant surface. Due to the great chemical affinity of bisphosphonates for calcium phosphate molecules, incorporation of these agents onto implants could be obtained using the biomimetic coating procedure, previously described. However, the ideal dose of these antiresorptive drugs should be comprehensively determined because an increase in peri-implant bone density has been reported to be bisphosphonate concentration-dependent.<sup>91</sup> Moreover, an unexpected potential adverse effect of these antiresorptive drugs is a possible association with the osteonecrosis of jaw bone.<sup>94–96</sup> The comprehensive studies of such bioactive drugs for endosseous implants must therefore be carefully evaluated pre-clinically before they can be translated into the clinical application.

The integrins are a superfamily of cell adhesion receptors necessary for cell-to-cell and cell-to-matrix attachments, which play an important role in cell signalling and consequently control

the biological activity of the cells. Therefore, the coating of titanium implant surface that contains binding sites for integrin receptors may potentially enhance peri-implant osteogenesis. Synthetic RGD peptides (Arg-Gly-Asp) coated onto the surface of implant materials increase bone-to-implant contact and newly formed peri-implant bone,<sup>97</sup> presumably by enhancing early cellular attachment to the implant surface. Moreover, the RGD coating has been shown to promote the bone-bonding ability of the coated implants.<sup>98</sup> The osteogenic role of RGD coating has also been demonstrated in *in vivo* implants, which are unavoidably surrounded in part by gaps, to improve mechanical implant fixation with a considerable increase in bone and a marked decrease in fibrous tissue formation.<sup>99</sup> Significantly increased cell spreading, cell proliferation and expression of the osteocalcin gene were observed in primary calvarial osteoblasts grown on the RGD-immobilized surfaces compared with those in the control surfaces, suggesting the enhanced functions of osteoblasts cultured on the RGD-modified surfaces.<sup>100</sup> Moreover, the role of RGD-coated titanium implants in bone formation has also been reported in the rat femur bone. The study showed that 4 weeks postoperatively following implant placement, mechanical pull-out testing revealed that the average interfacial shear strength of peptide modified implants was greater than the control group,<sup>101</sup> further supporting that the RGD peptide coating may promote implant osseointegration. However, long term evaluation of such modification in larger animal models is undoubtedly important to establish its significant role in enhancing *in vivo* implant osseointegration.

Interestingly, it has been demonstrated that coatings of implant surface by a combination of different bioactive molecules synergistically influence osteogenic events. For example, when RGD peptides coupled to a bisphosphonate were chemically adsorbed on titanium discs, adhesion and spreading of osteoblastic cells together with the formation of biomineralization were markedly enhanced.<sup>102</sup> Moreover, nanoscale roughened surfaces with RGD peptide coating provided an optimum surface for cell adhesion, spreading, and cytoskeletal organization, and also enhanced the expression of integrins.<sup>45</sup> However, the effect of combination coatings on new



bone formation at the implant site *in vivo* is thus far lacking.

While several lines of evidence suggest the osteogenic-enhancing role of the RGD coating, a recent study has shown that RGD-coated hydroxyapatite discs significantly inhibited total bone formation as well as the amount of new bone formed at the peri-implant site.<sup>103</sup> It is noteworthy that RGD coatings, which are widely believed to promote cell-biomaterial interactions, could have a negative effect on hydroxyapatite implant performance, suggesting that for biomaterials that are highly interactive with the tissue microenvironment, e.g. hydroxyapatite, the ultimate effects of RGD peptides will depend upon how signaling from these peptides integrates with endogenous processes such as protein adsorption.

Antibiotic incorporation into implant coatings has also recently been introduced. Calcium-based coatings of an implant material can bind to antibiotics, such as cephalothin, carbenicillin, amoxicillin, cefamandol, tobramycin, gentamicin and vancomycin, which are able to release from the coating material. These releasing antibiotics also remain their bacterial inhibition property.<sup>104</sup> For example, tobramycin-supplemented coatings on titanium alloys release functionally active tobramycin that could suppresses growth of *Staphylococcus aureus* bacteria.<sup>105</sup> Moreover, recent reports suggest that antibiotics incorporated in polyester urethane coatings on implants significantly inhibit bacterial colonization and prevent bacterial resistance.<sup>106,107</sup> The data suggest that certain antibiotics could be utilized to prevent post-operative bacterial infection and thus potentially enhancing implant osseointegration following implant placement. Moreover, future studies focusing on the drug release, method of drug incorporation and chemical structures of the antibiotic that facilitate their incorporation capacity, would be of utmost importance to develop a novel antibiotic-incorporated coating material for medical implants.

## Conclusion

Studies of recent advanced surface modifications of implants have provided insight into potential benefits for endosseous implant therapy by positively controlling osteogenic responses of progenitor cells

and thus stimulating both *in vitro* and *in vivo* bone formation. How these modern surface modifications may be used clinically in patients to accelerate implant osseointegration remains largely unexplored. It is noteworthy that the currently available implants differ in their topography and chemistry, in their design and in their bulk material composition. It is therefore difficult to draw specific conclusions from the data available regarding the surface modification alone. However, all previously reported data suggest that these new advanced surface modifications offer promising solutions to clinical problems where rapid and optimal implant osseointegration is critically required.

## Disclosure

The authors report no conflicts of interest.

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