



On the Future Design of Bio-Inspired Polyetheretherketone Dental Implants

Jennifer Knaus, Dietmar Schaffarczyk*, and Helmut Cölfen*

Polyetheretherketone (PEEK) is a promising implant material because of its excellent mechanical characteristics. Although this polymer is a standard material in spinal applications, PEEK is not in use in the manufacturing of dental implants, where titanium is still the most-used material. This may be caused by its relative bio-inertness. By the use of various surface modification techniques, efforts have been made to enhance its osseointegrative characteristics to enable the polymer to be used in dentistry. In this feature paper, the state-of-the-art for dental implants is given and different surface modification techniques of PEEK are discussed. The focus will lie on a covalently attached surface layer mimicking natural bone. The usage of such covalently anchored biomimetic composite materials combines many advantageous properties: A biocompatible organic matrix and a mineral component provide the cells with a surrounding close to natural bone. Bone-related cells may not recognize the implant as a foreign body and therefore, may heal and integrate faster and more firmly. Because neither metal-based nor ceramics are ideal material candidates for a dental implant, the combination of PEEK and a covalently anchored mineralized biopolymer layer may be the start of the desired evolution in dental surgery.

1. Introduction

Dental implants are designed and manufactured to act as artificial replacements of natural dental roots. They are intended to provide a stable anchorage for fixed or removable dental prostheses,^[1–7] and as such they enhance the quality of life for humans with dental degenerations or for partly or fully edentulous patients.^[8–10] Most dental implant systems are divided into

two parts: The implant itself, displaying in most cases a screw design, which is integrated into the jaw of the patient. This is combined with an abutment that guarantees the proper placement of a dental prosthesis, commonly a dental crown.^[11] In literature, over 1300 types of commercial dental implants have been reported, in varying form, material, interface properties, and geometries.^[12] Since more than 60 years, the use of titanium or titanium alloys is state-of-the-art and still the golden standard in dental applications worldwide.^[13–15] Introduced in the early 50s, this metal-based implant material is used in the majority of dental implant surgeries, using a dental implant, which is characterized by the above-mentioned screw design. Because of the screw-design geometry, placing the implant in the patient's jaw guarantees primary mechanical stability, enabling the wound to heal and allowing bone-cells to form new bone.^[16,17]

In the healing phase, the periimplant bone of the jaw gets into direct contact with the oxide layer of the titanium implant surface (bone-implant contact [BIC]), which is always spontaneously formed through contact with air.^[18] Nowadays, the optimization of the implant surfaces is still an essential object of scientific investigations.^[19–26] Within these investigations, specific factors, such as a certain roughness of the implant surface, have been shown to influence the osseointegration of an implant positively.^[27–30]

1.1. Disadvantages of Titanium as Implant Material in Dental Applications

Conventional dental implants are commonly made of titanium or titanium alloys due to their known osseointegrative characteristics. However, problems are being discussed in literature, which may be associated with their material characteristics within the patient's body, such as hypersensitivity, or peri-implant bone overload.^[31] Titanium has an elastic modulus (E-modulus) of 110 GPa.^[32] For cortical bone, an elastic modulus of 13.8 GPa and for spongy bone, an E-modulus of 1.38 GPa^[33] are reported in the literature. This difference of the elastic moduli is discussed as a risk of potential mechanical overloading of the bone, leading to damage of the surrounding parent bone and bone resorption (so-called “stress-shielding”).^[34–37] Nevertheless, this

Dr. J. Knaus, Prof. H. Cölfen
Department of Chemistry, Physical Chemistry
University of Konstanz
Universitätsstraße 10, 78457 Konstanz, Germany
E-mail: helmut.coelfen@uni-konstanz.de

Dr. J. Knaus, Dr. D. Schaffarczyk
stimOS GmbH
Byk-Gulden-Straße 2, 78467 Konstanz, Germany
E-mail: zyk@stimOS.net

 The ORCID identification number(s) for the author(s) of this article can be found under <https://doi.org/10.1002/mabi.201900239>.

© 2019 The Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1002/mabi.201900239

theory is argumentatively incomplete,^[38] as the overloading phenomenon described above may only appear in combination with the presence of bacterial plaque,^[39] but in this context, it must be stated that titanium has a high affinity for plaque deposition, which is an additional possible risk for inflammatory reactions, resulting in peri-implantitis.^[40] Corrosion is also another problem generally related to titanium and titanium alloy implants, as no metal or alloy is entirely inert to corrosion.^[41] For instance, the biocompatibility of Ti-6Al-4V has since been called into question due to reports of the gradual release of aluminum and vanadium ions, from the surface, which can cause local adverse tissue reactions and immunological responses.^[42,43] Thus, researchers continue to search for titanium alloys with improved strength, yet lacking any toxic elements, for medical applications. An alloy containing zirconium has been demonstrated to possess the required mechanical strength and a good resistance to corrosion in biological fluids^[44,45]; however, the elastic modulus of this alloy still remains within the range of values of a conventional titanium alloy.^[46] In dental applications, released metal ions can cause an inflammatory reaction against the implant resulting in implant loss or peri-implantitis. Patients suffering from titanium intolerance are well documented in the literature.^[47–50] Furthermore, from an aesthetical point of view, a metallic implant can be disadvantageous for many patients because the gray color of the implant often is visible through the patient's mucosa.^[51]

1.2. The Use of Zirconium Dioxide in Dental Applications

15 years ago, zirconium dioxide, more commonly known as “zirconia”, an implantable ceramic material, was introduced as an alternative material for titanium.^[52,53] Compared to titanium implants, ceramic implants have comparable osseointegrative characteristics,^[54–56] but zirconium dioxide shows a lower affinity to plaque than titanium.^[56–58] Nowadays, about 5% of dental implants worldwide are made from ceramics.

The E-modulus of 210 GPa can be seen as a disadvantage of zirconium dioxide.^[59] Nevertheless, mechanical testing using a finite element analysis demonstrated a better transfer of the simulated load through the implant to the patient's bone as compared to titanium.^[60,61] Besides these positive material characteristics, unsolved problems with these implants are aging, implant-degradation, and its brittleness. Low temperatures in aqueous surroundings affect the mechanical quality of the material.^[56] In addition, there are currently no long-term clinical studies available, which can provide enough evidence to prove long-term safety and performance of zirconium dioxide implants as a real alternative to titanium implants.^[56,62] In literature, chipping of the veneering porcelain has been reported as one of the main clinical setbacks during application.^[63] This is due to the fact that ceramics are not able to withstand a deformation strain of more than 0.1–0.3% without fracturing and are susceptible to fatigue fracture.^[63]



Jennifer Knaus is laboratory head of stimOS GmbH in Konstanz. Knaus has her Ph.D. in chemistry from the University of Konstanz, working in the group of Prof. Helmut Cölfen and Dr. Elena Sturm. Her research interests include the understanding of basic structure–composition–mechanical properties relationships of natural hard tissues and the development of bioinspired materials for clinical applications, especially focusing on hard tissue substitution materials.



Dietmar Schaffarczyk is managing partner of stimOS GmbH. The company develops innovative technologies and procedures to refine, functionalize, and activate implant materials. stimOS develops implants for spinal fusion and dental surgery. In addition, he is lecturer at the University of Tübingen and an external auditor, Medtech (diploma SAQ), certified quality auditor (European Organization for Quality/EOQ), and lead auditor, medical devices (QS International Ltd.)



Helmut Cölfen is full professor for physical chemistry at the University of Konstanz. His research interests are in the area of nucleation, classical and nonclassical crystallization, biomineralization, synthesis of functional polymers, directed self-assembly of nanoparticles, and fractionating methods of polymer and nanoparticle analysis. His group has made contributions in high-resolution particle size analysis with Angström resolution in solution, mesocrystals, nonclassical nucleation and crystallization, CaCO₃ crystallization, bio-inspired mineralization, synthesis of double hydrophilic block copolymers, and additive-controlled crystallization.

1.3. Polyetheretherketone as a Possible Alternative Material in Dental Applications

Because both titanium and zirconium dioxide have drawbacks, efforts have been made to introduce polyetheretherketone (PEEK) as an alternative implant material for dental applications and to enhance the osseointegrative characteristics of the polymer by various coating materials and coating techniques.^[64,65] Doing this, a stable anchorage of the medical device may be guaranteed, which results not only from the implant design and its geometry but also by inherently achieving a high percentage of BIC.

Over the past few years, PEEK and its composites have attracted a great deal of interest from material scientists and orthopedists. It is a semi-crystalline, high-molecular-weight thermoplastic polymer of the polyaryletherketone polymer family and is described as a high-performance polymer with excellent mechanical and chemical properties. Already in the 1990s, PEEK was certified by the U.S. Food and Drug Administration as an implantable-grade material. It is especially important in orthopedic and traumatic applications and is commonly used in vertebral surgery as a material of interbody fusion cages. PEEK is also used in the reconstruction of defects in the skull.^[66–68] Nowadays, polymers are known in dental applications but strongly limited to the use in healing abutments made of PEEK or in the manufacturing of prosthetic dental medical devices.

Pure PEEK has an E-modulus of 3–4 GPa,^[69] close to that of the natural bone and in between that of cortical and spongy bone. This describes an essential advantage compared with conventional titanium-based implants. A further advantage of PEEK is its readiness to be combined with other materials, which will be addressed further in this article.^[70] This allows for an easy adjustment of the mechanical properties of PEEK even closer to the natural bone. This material property may prevent the undesirable “stress shielding” phenomenon.^[71] Furthermore, PEEK has good resistance to wear and fatigue, resulting in a low coefficient of friction (0.10–0.17) for a large range of sliding conditions, especially when reinforced by carbon fibers.^[72,73] This is even lower than has been determined for titanium alloys (0.36) under tribocorrosion conditions against Al₂O₃ (0.07).^[74,75]

Another positive material characteristic of PEEK or PEEK composites is their radiolucency: PEEK-based implants do not cause any artifacts in computer tomography and magnetic resonance tomography and allow for better observation of the healing phase post-op.^[76–79]

PEEK exhibits good biocompatibility *in vitro* and *in vivo*, causing neither toxic or mutagenic effects nor clinically significant inflammation. However, PEEK is considered biologically inert, which has limited its potential applications. Therefore, improving the bioactivity of PEEK is a considerable challenge that is addressed in numerous strategies.

2. General Strategies to Improve the Bioactivity of PEEK

Generally, many features and properties of the materials determine cellular interaction with surfaces. Additionally, the initial

contact with water and proteins has to be considered, as blood is the first component a bone implant comes in contact with upon implantation. A favorable surface allows for sufficient protein adsorption, in the optimal case with a good protein orientation and receptor–ligand accessibility.^[80,81] The general surface wettability might also play a further role in this, as protein adsorption onto a surface is controlled by hydrophobicity, charge, and chemical properties. These features, in return, also have an influence on cellular behavior on the surface.^[82]

Not only the physico-chemical composition of a biomaterial but also the surface topography of a solid substrate regulates cellular adhesion, migration, proliferation, and differentiation.^[83–85] Many of these factors influence each other upon modification. Currently, two general strategies are being explored to enhance the general osseointegration of PEEK in cementless applications, comprising bioactive composite preparations (**Figure 1(1)**) and surface modifications (**Figure 1(2)**). Among these, the strategies utilizing surface modifications demonstrate the largest and most versatile group due to its numerous options to combine single synthesis routes.

2.1. Composite Preparation

Polymer (nano-)composites have attracted considerable attention and interest worldwide during the last decades. In an attempt to combine the favorable mechanical properties of PEEK with advantageous properties of several bioactive compounds or to enhance the physicochemical and mechanical properties, many combinations of compounds with PEEK have been investigated. One prominent group comprises the carbon fiber reinforced PEEK (CFR PEEK) composites, which are already known for a long time due to their versatility, compatibility with modern imaging technologies, adjustable mechanical properties, and biocompatibility.^[86,87] Other potential composites with PEEK include carbon nanotubes (CNTs);^[87] TiO₂;^[88] ZrO₂;^[89] Al₂O₃;^[90–92] Si₃N₄;^[93–95] ZnO;^[96] SiO₂;^[97] SiC;^[98] calcium silicate^[68,99] nanoparticles; bioglass; combinations of soft-hard nanoparticles, such as Bi₂O₃-SiO₂, CuO-SiO₂, or WS₂-SiC;^[100] polymer blends; or mixtures of the aforementioned.^[101–103] These composite materials did not only demonstrate significantly improved mechanical properties but also a better *in vitro* biocompatibility when compared to pure PEEK. However, for dental applications, the color of the composite materials is of importance because an implant with a color other than white can cause a dark shimmer of the peri-implant soft tissue in cases of thin biotype mucosa and/or mucosa recession around the implant.^[104–107] This is also a yet unsolved problem, for example, for CFR PEEK as well as CNT-filled PEEK, which are black and therefore visible.

Considering that natural bone consists of about 70 wt% of carbonated hydroxyapatite (HA), several methods have been developed to blend different calcium phosphate particles with the polymer to produce bioactive PEEK composites. Such PEEK-HA composites with different volume fractions of HA up to 40 vol% were evaluated *in vitro* and *in vivo*. These studies showed that the composites demonstrated an increased presence of fibroblast cells at the implant surface, which stimulates vascularization.^[108] Other potential calcium phosphate

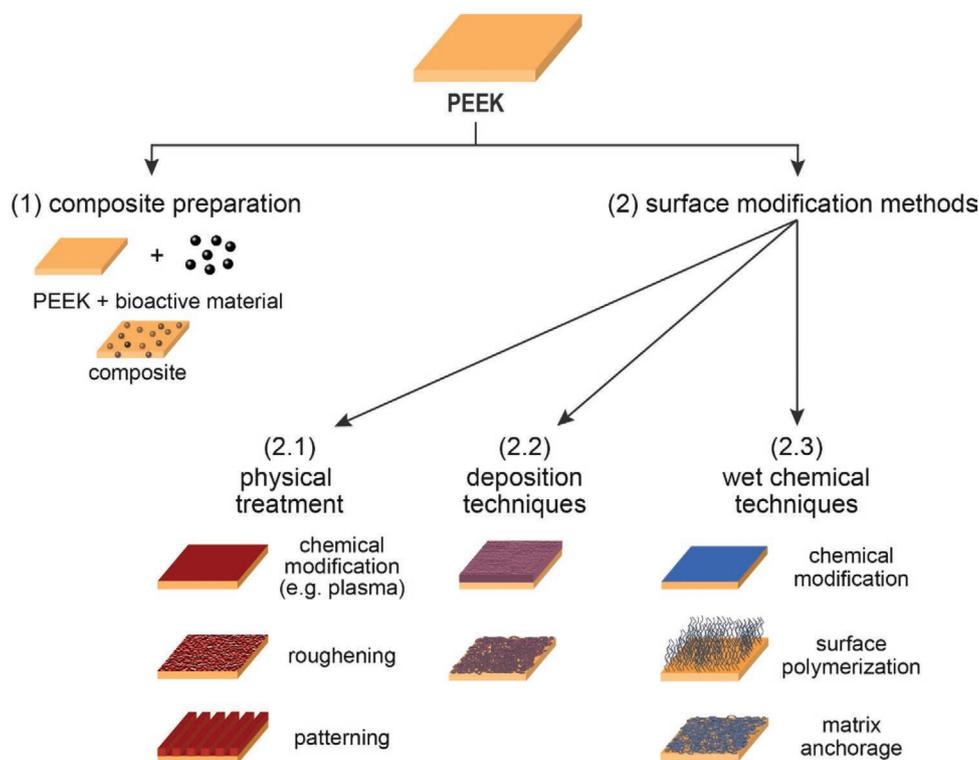


Figure 1. General strategies to improve the biocompatibility of PEEK.

phases, with compositions close to HA, which are β -tricalcium phosphate^[109] or ionically substituted calcium phosphates, such as Sr-substituted HA,^[110] partially fluoride substituted HA,^[111] as well as mixtures of the above mentioned, can be prepared and incorporated as well. Although *in vitro* and *in vivo* studies have provided encouraging results regarding the bioactivity of such PEEK-HA composites, the reports from mechanical characterization are diverse, addressing different disadvantages with respect to clinical applications. On the one hand, loading PEEK with HA particles gives rise to the possibility to adjust the elastic modulus close to that of human cortical bone, an increase of the HA content also resulted in an increase of the tensile modulus and microhardness, and a decrease of the tensile strength and strain to fracture.^[108,112] However, in contrast to carbon and glass fiber additives, HA, in particular, does not show a robust physical/chemical affinity to the PEEK matrix itself, due to the high chemical contrast between the two materials resulting in only a weak binding of the HA particles to PEEK (Figure 2).^[112] Thus, such PEEK-HA composites show great promise as bioactive implants but may involve a trade-off in the load-carrying capacity relative to other PEEK composites.

2.2. Surface Modification Methods

As discussed above, the bone–implant interface plays a crucial role in determining the cellular behavior and in the end, the general performance of an implant. Immediate and fast fixation of the implant in the surrounding bone not only ensures

mechanical stability but also increases the success rate and longevity of the implant. Controlling and engineering the surface composition, its texture, and properties can provide a powerful tool to help assure a fast bone-implant fixation. The modification of the implant surface provides a pivotal opportunity to change the interaction properties of the surface and the surrounding tissue while still retaining advantageous bulk mechanical properties. Furthermore, combinations of the different modification methods are readily available. Within the category



Figure 2. Scanning electron microscopy (SEM) micrograph of a PEEK-HA composite fracture area, demonstrating a debonding of the HA particles from the PEEK matrix. Reproduced with permission.^[112] Copyright 2004, Elsevier. Scale bar: 50 μ m.

of surface modifications intended to improve general features, such as biocompatibility, osseointegration, or antifouling, three general strategies can be differentiated. The group of physical treatment (Section 2.2.1) comprises all methods intended to directly change surface chemistry or topography through physical means. These include the physical modifications to create specific functional groups, increase the surface roughness, or to create regular surface patterns. The group of deposition techniques (Section 2.2.2) summarizes all methods intended to deposit materials, such as a mineral, peptides, or proteins, on the surface. The resulting coatings are usually characterized by a non-covalent interaction to the surface. The last group of wet chemical methods (Section 2.2.3) comprises all methods used to chemically change the surface by immersing the surface in a liquid utilizing wet chemical reactions.

2.2.1. Physical Treatment

Physical treatment allows for a fast change of the surface properties, and these methods can often be readily combined with subsequent reaction steps to further broaden the applications. However, an inherent disadvantage is that these methods can only be applied to areas that are in the direct line-of-sight, and are therefore difficult to apply to implants with complex shapes. A further disadvantage is a need for expensive equipment to apply the intended modification. Nonetheless, a lot of effort and research has been put into the development and implementation of such techniques to improve the performance of PEEK implants.

Chemical Modification: Next to other methods, such as laser treatments,^[113–115] the most prominent modification technique within this group is the plasma treatment, which can be generally used for cleaning, etching, cross-linking, or surface activation. Many different plasma atmospheres have been suggested to precisely alter surface chemistry and wettability. They comprise oxygen (O₂) plasma,^[116–119] H₂O plasma,^[111] nitrogen and oxygen (N₂/O₂) plasma,^[120] ammonia (NH₃) plasma,^[121] oxygen and argon (O₂/Ar) plasma,^[121] ammonia/argon (NH₃/Ar) plasma,^[122] and hydrogen/argon (H₂/Ar) plasma.^[122] Often, an increase in the surface roughness has been reported as a possible concomitant effect, thus further increasing adhesive properties of the surface. Using the so-called plasma immersion ion implantation and deposition technique with a mixture of CH₄/O₂ gases during the plasma treatment, it is possible to deposit oxygen-rich nanofilms on PEEK with high surface energy, which also resulted in improved cell performance.^[123,124]

Roughening: In addition to surface chemistry, surface topography also has an essential influence on the behavior of cells on surfaces.^[83–85,125–127] Macro-scale surface roughness can improve bone–implant fixation through mechanical interlocking. Surface roughness at micro-scale, however, can also profoundly affect the behavior of cells as surface roughness influences hydrophilicity. Cells commonly show different shapes when cultured on substrates with different roughness, and there is abundant evidence that the cell shapes are linked to their behavior, like growth and protein secretion.^[84,85,125] Such topographies can be fabricated by sandblasting, grit blasting,

micromachining, etching, and their combinations.^[128–132] In vitro cultured osteoblasts showed increased adhesion, differentiation, matrix production, and calcification on rough over smooth surfaces, whereas the formation and activity of osteoclasts were reduced, all favoring bone regeneration.^[132,133]

Patterning: A controlled surface texture, including porosity, is a desirable, yet often a more expensive attribute to help improve the interaction between the bone implant and the surrounding tissue. Advancements in micro- and nanofabrication techniques enabled these tailored modifications of substrates. Several methods have been introduced to create regular or irregular patterns on surfaces, comprising, for example, photolithography,^[134] ion or neutral atom beam lithography,^[135] laser interference lithography,^[136] or micro-contact printing.^[137] The general cell response to 2D synthetic topographic substrates depends on a wide array of properties and factors, including cell type, feature size and geometry, and the physical properties of the bulk substrate material, including substrate stiffness.

Quite common for biomaterials are three basic geometries, which include nanopit arrays, nanopost arrays, and nanogratings.^[85,125,138] Using laser interference lithography it is possible to create nanogratings, featuring equidistant lamellae ranging from several nanometers to even micrometer interlamellar distance (**Figure 3a**). Since changes in nontopographic features and their sizes are often coupled with changes in the physicochemical properties of the surface, it is difficult to identify the contributing effect to the cell–surface interaction. Nevertheless, some general trends may be extracted from the growing body of literature on various biomaterials studying the influence of topographic features on cellular morphology, attachment-, adhesion-, migration-, proliferation-, and differentiation behavior.^[84,85] Exemplarily, it has been demonstrated that the direction of cellular growth is influenced by the topography of the surface of materials they grow on, and studies accordingly suggest to create surfaces with structures of appropriate dimensions to control the attachment and growth. Furthermore, it is possible to control the orientation of the cells in the desired growth direction, as is demonstrated in **Figure 3b**, where fibroblast cells align along the lamellae, which were created by laser interference lithography.

2.2.2. Deposition Techniques

Another strategy to change the surface properties of materials involves the deposition of organic or inorganic substances on the surface. To produce such bioactive coatings, a large number of methods have been deployed, such as cold spray technique,^[139] spin coating techniques,^[140] aerosol deposition,^[141] ionic plasma deposition, plasma immersion ion implantation and deposition,^[124] electron beam deposition,^[142] vacuum plasma spraying,^[143] physical vapor deposition,^[144] microwave-assisted coating processes,^[2] or by wet chemical precipitation.^[120] Using these techniques, it is possible to coat many different bioactive materials, such as TiO₂,^[145–147] Mg,^[144] magnesium phosphates,^[2] or various calcium phosphate phases onto the surface of PEEK. Within this group of bioactive materials, a layer of HA often remains the material of choice and

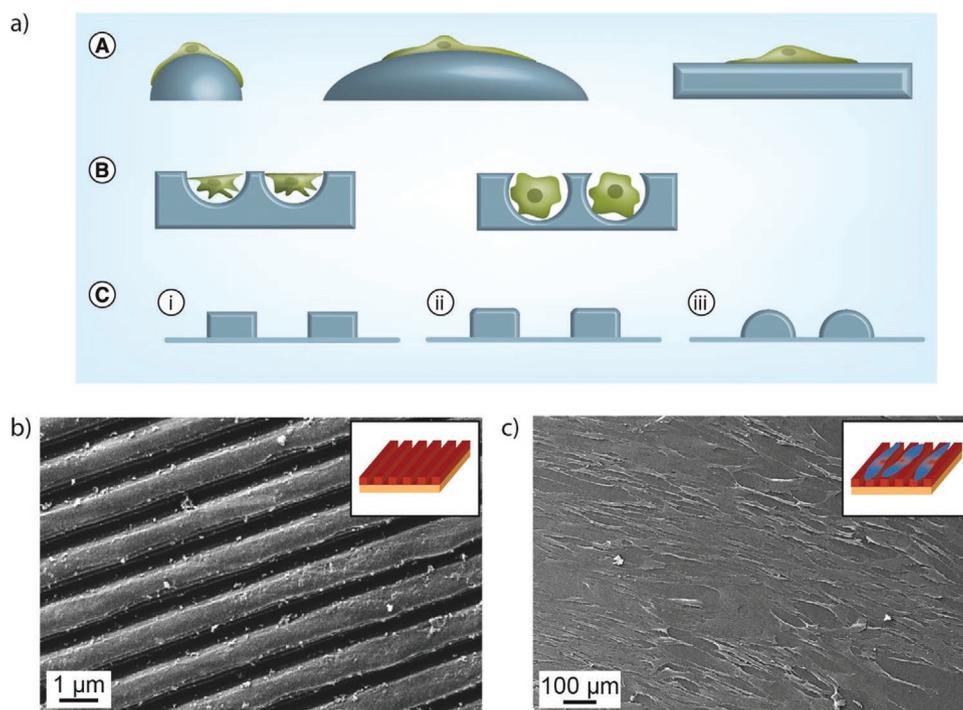


Figure 3. The behavior of cells can be influenced by the surface topography using regular patterns. a) Scheme illustrating the influence of surface patterns on cells upon contact with curvature (A), pits (B), or pillars (C) with differently sharp edges (i–iii). Reproduced with permission.^[84] Copyright 2013, Taylor and Francis. b) SEM image of a regularly spaced topographic pattern on PEEK with ridges and grooves, created by laser interference lithography (own unpublished data). c) SEM images of critical-point dried NIH3T3 fibroblasts plated on these ridge arrays. Schematics not drawn to scale (own unpublished data).

is now extensively produced in industry. The rationale is that because of the chemical similarity of HA to the natural bone counterpart, the bone-related cells may not recognize the HA-coated implant as a foreign body, and therefore may heal and integrate faster and more firmly. Indeed, in vitro studies and in vivo studies in rabbits demonstrated that HA-coated PEEK surfaces showed better osseointegrative properties than uncoated implants.^[139,140]

Other calcium phosphate phases (e.g., tricalcium phosphates) or ionically substituted calcium phosphates (e.g., silicate-substituted strontium apatite^[148]) can also be co-sprayed with HA to modulate the coating properties, for example, reactivity and resorption rate. However, within the methodology of several of these techniques, it is possible that the HA can decompose into other phases or typical ionic substitution groups within the crystal lattice, such as carbonate, and can be removed from the mineral due to the heat during the deposition, for example, due to the plasma flame temperature. Thus, the obtained coatings can deviate from the calcium phosphate powder input. A further disadvantage of such deposition-based coatings is the usually very weak adhesion strength of the coating to the substrate due to the large chemical contrast between the dissimilar surfaces. Therefore, it is inherently at risk of delamination due to its non-covalent character during load application in clinical use.^[112,149] Additional to delamination, individual particles may detach from the surface upon mechanical load and cause inflammation. Similar to the methods that rely on physical treatment, a lack of direct line-of-sight might cause an inhomogeneous coating on the surface of the material.

2.2.3. Wet Chemical Methods

PEEK as a member of the polyaryletherketone family has an aromatic molecular backbone, with combinations of ketone and ether functional groups between the aryl rings. This particular chemical structure makes PEEK chemically and physically inert but also provides opportunities for chemical modification. Because all wet chemical methods work by immersion of the PEEK-material into a reaction solution, the methods within this group overcome the general disadvantage of an incomplete coating of the implant surface due to lack of the direct line-of-site of the physical deposition methods.

Chemical Modification: Due to the stability of PEEK, chemical surface modification is quite challenging. By the treatment of PEEK with sulfuric acid or methane sulfonic acid, the aromatic backbone can be sulfonated.^[150] The resulting in vitro cellular behavior, in vivo osseointegration, and apatite-forming ability of the surface-sulfonated PEEK were investigated.^[151] The results showed that in systems with carefully removed residual sulfuric acid, the resulting material demonstrated enhanced biocompatibility and osseointegration compared with pure PEEK. The sulfonation process is often accompanied by a change in the mechanical properties. It was found that the crystallinity of PEEK can be reduced and the solubility of PEEK in different solvents changes quite drastically during sulfonation, even becoming water soluble with a very high sulfonation degree.^[150,152] Using this approach can be feasible for surface structuring or further surface modifications by attachment of further bioactive molecules.^[153] For example, applying a low

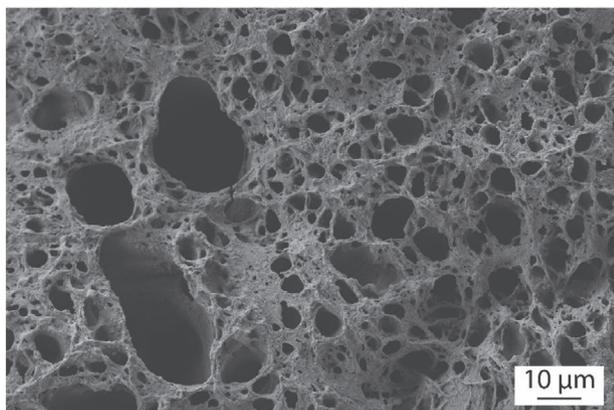


Figure 4. 3D porous network on a PEEK surface after sulfonation and subsequent water immersion.

degree of sulfonation and subsequent water immersion, a 3D porous network can be produced on PEEK (**Figure 4**) resembling spongy bone and therefore, a promising environment for cells.

Further modification strategies target the keto-group as the anchor point toward a functionalized surface. Wet chemical methods open the way to the whole set of possible subsequent surface chemistry and immobilization strategies of a wide variety of molecules, which will be addressed further below. For most synthesis routes, the reduction of the keto-group to the hydroxylated polymer (PEEK-OH) poses the first step as a versatile intermediate for following covalent anchorage of molecules on the way to create functional group displaying surfaces. Like this, a carboxylated polymer (PEEK-COOH^[154]) was prepared by coupling a succinic anhydride to PEEK-OH (**Figure 5a**), aminated molecules, or amino carboxylated molecules^[155] or even phosphorylated surfaces (PEEK-PO₄H₂) can be prepared using a phosphorous oxychloride and 2,4,6-collidine-mediated synthesis.^[154] However, in vitro evaluations of these modified materials remained rare so far. An investigation of Noiset et al. however demonstrated a higher wettability and increased biocompatibility on the modified materials compared to the unmodified PEEK using Caco2 human colon cells.^[156,157] Further chemical functionalization possibilities lie in the direct amidation of the PEEK surface by the reaction with diamine

molecules (e.g., ethylenediamine) through the creation of imine-moieties (Schiff base) (**Figure 5b**).^[158]

Many other further possibilities exist to equip the surface with functional groups or combine several coupling techniques, rendering this synthesis route as a promising way to interactively adjust and optimize subsequent reactions.

Surface Polymerization: In general, graft polymerization is performed most frequently using a surface-initiated graft polymerization (“grafting from”) method. With this method, the monomers are directly polymerized from the surface using suitable initiators or comonomers. The other technique comprises the “grafting to” methods, in which the polymer adsorbs or chemically binds to the substrate; for example, the reaction of the end groups of a polymer with the functional groups of the substrate. The “grafting from” method has the advantage over the “grafting to” method to form a high-density polymer interface. Using photo-initiators, it was possible to graft a biocompatible 2-methacryloyloxyethyl phosphorylcholine (MPC) onto a PEEK surface, creating a hydrophilic, nanometer-scale modified PEEK surface.^[159] Another example demonstrates the synthesis of a layer of acrylic acid polymer brushes^[160] or the polymerization of vinyl phosphonic acid on the surface.^[142] The authors could show that the resulting materials possess greatly improved biocompatibility and demonstrated improved osseointegrative behavior in vitro and in vivo.

UV-assisted surface photograft polymerization is a further example for a surface functionalization method that provides a short reaction time and is effective for a variety of monomers. Due to the inherent benzophenone structure in PEEK, it is possible to generate free radicals on exposure to UV radiation.^[161] This can be used for a lot of further synthesis reactions, such as the grafting of different polymer chains on the surface of PEEK (**Figure 6**). Using this method, it was possible to functionalize the PEEK surface with polystyrene (PS), vinyl phosphonic acid (VPA), butyl acrylate (BA), acrylic acid (AA), polyacrylic acid (PAA), and monomethoxy-terminated oligo (ethylene glycol) methacrylate (MeOEGMA).^[162]

Matrix Anchorage: In vivo, the natural surroundings of the cells within the bone is comprised of a hydroxyapatite–collagen composite material with a highly sophisticated structure. Next to the majority component HA, the other parts of natural bone and teeth include proteins and other large biomolecules, such as glycosaminoglycans. Furthermore, most cells adhere to and

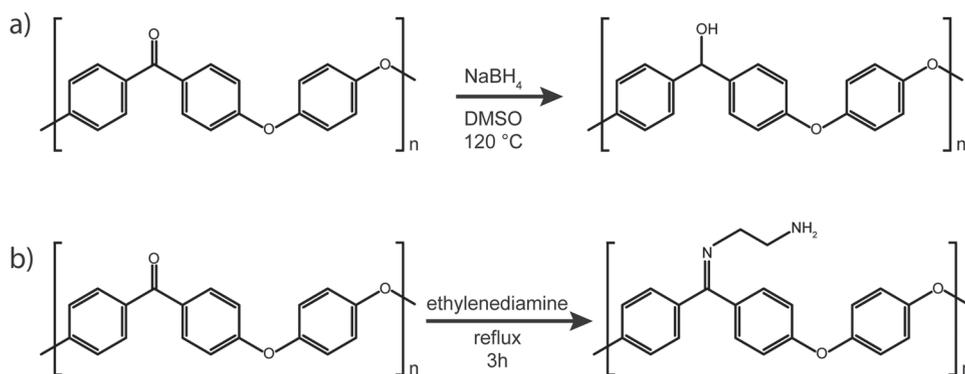


Figure 5. Exemplary reaction mechanism of PEEK reduction to PEEK-OH (a) and surface amidation by the reaction with ethylene diamine, creating a Schiff base (b).

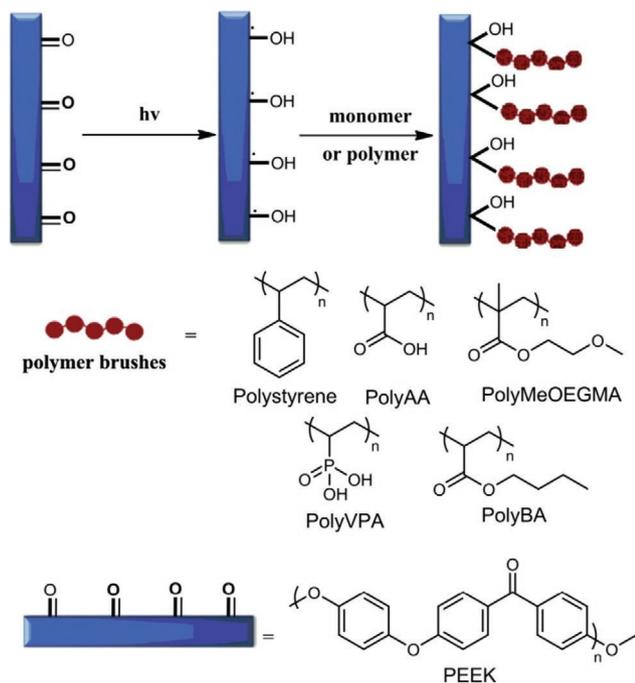


Figure 6. Schematic demonstration of the generation of free radicals and subsequent polymerization of monomers on the PEEK surface. Reproduced with permission.^[162] Copyright 2014, Elsevier.

spread on a biological matrix called the extracellular matrix (ECM). The ECM functions as a scaffold facilitating the transfer of signals to adhering cells via specific proteins (such as collagen or fibronectin), which are recognized by cellular receptors. Thus, the logical thought arises to equip the bioinert surface of PEEK with selected peptides or proteins, which are part of the natural surroundings of cells to improve the cellular response to the bone implant material. Utilizing the described surface-activating chemical techniques as a first step and combining them with established peptide-coupling chemistry, it is possible to covalently bind a whole set of biocompatible molecules onto the surface of PEEK, overcoming the general risk of delamination of coatings.^[163] Using this approach, it is also possible to covalently attach a matrix of gelatin, which is a denatured form of collagen, on the surface of PEEK and to mineralize it with calcium phosphate to produce a bone-mimetic surface layer.^[155,164]

As it is the essential sequence mediating cell adhesion in many ECM proteins, the immobilization of Arg-Gly-Asp (RGD)-containing peptides has received significant interest.^[165,166] Consequently, RGD-containing peptides or proteins of different sequences and conformations have been immobilized onto biomaterials by many researchers.^[165,167–169] The performance of these coatings was evaluated by *in vitro* cell cultures to test their effectiveness for cellular adhesion and cellular behavior, demonstrating their applicability in medical use. Improved cell adhesion and proliferation were reported. However, variables like surface peptide density or sequence design (e.g., flanking amino acids according to the natural sequence) appeared to have significant effects on the cellular response as well.^[165]

3. The Future of Dental Implant Coatings—Bio-Inspired Solutions

To reach a long-term success of an implant, several factors are prosthetic biomechanical factors and patient hygiene crucial after the initial stages of osseointegration. However, to reach a good osseointegration and implant performance, a dental implant material must fulfill several, partly seemingly contradictory demands, as was discussed above.

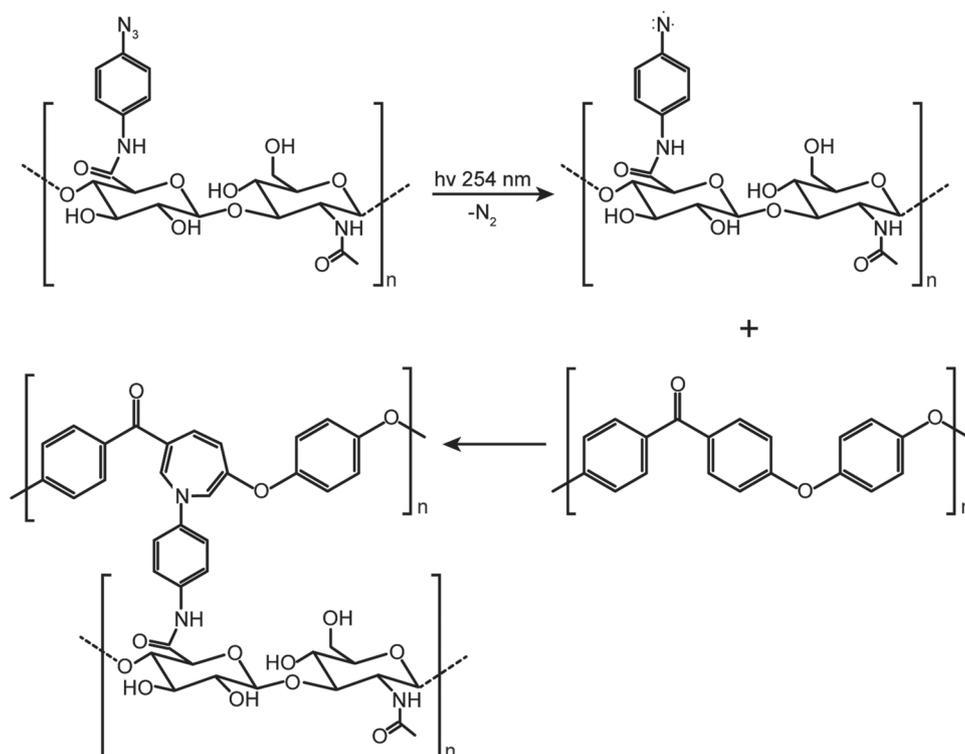
These are

- Translucency to X-rays or common tomography methods in order to allow for monitoring of the healing process
- Mechanical properties between cortical and trabecular (spongy) bone
- Possibility of chemical or physical surface modification both in topology and chemistry
- Primary stability
- Fast osseointegration for fast healing and connection to the existing bone tissue and the parental bone
- No detrimental delamination or particle loosening from the implant surface
- Easy and low-cost production from commonly available chemicals and syntheses strategies
- All these demands for itself and in combination with each other must fulfill regulatory requirements, allowing the newly developed dental implant to enter the market

Unfortunately, a commercially available implant fulfilling all of the above-mentioned necessary requirements for a successful implant does not yet exist. Therefore, there is obviously plenty of room for improvement of dental implants. What also becomes clear from the above discussion is that bioinspired approaches in combination with rethought implant geometries have a high potential to lead to a finally successful dental implant with vast implications on new designs of bone implants due to the similarity of the biomineral.

To realize the above properties, a bioinspired/biomimetic covalently bound coating to the implant surface, ideally only a few nanometers thick to ensure that each polymer chain is surface connected, would be the ideal situation. If this thin surface layer ideally composed of collagen or gelatin is mineralized by calcium phosphate, the ideal modification of a bone implant—regardless if it is PEEK, titanium, or zirconium dioxide—would be reached. However, in reality, the layers can be thicker up to a few hundred nanometers. This is potentially weakening the adherence of the biomimetic collagen/gelatin layer to the implant surface, but on the other hand, the implementation of the calcium-phosphate mineral generates physical cross-links so that, in fact, even a few hundred nanometer thick layers do not easily delaminate. Therefore, if the covalently linked polymer surface layers exceed the contour length of the primarily bound polymer molecules, this does not mean that a thicker layer gets delaminated due to the implemented mineral acting as a further physical cross-linker. In fact, this situation corresponds to that in bulk bone. Therefore, a tunable variety of the surface layer thickness potentially exists by subsequent deposition cycles.

The coupling chemistry for PEEK was already described in chapter 2.2.3. The linkers for covalent surface modification



Scheme 1. Reaction scheme of the UV-light-assisted coupling of azidoaniline modified hyaluronic acid according to ref. [158].

of titanium or zirconium dioxide can be based on silanes/siloxanes as an example and were already literature reported.^[170] However, as was introduced in chapter 1, the elastic modulus of titanium and zirconium dioxide is by far higher than that of natural bone with all the discussed disadvantages, leading researchers to still search for better options or modifications of these material types for serious consideration for future dental or bone implants.

Due to its very good mechanical properties, PEEK itself would be a promising polymeric candidate, but its chemical and biological inertness poses a major problem for its use as an implant material. Therefore, it is meaningful to use the already available coupling chemistry to this polymer, to covalently couple bio-inspired nanometer-thick coatings for improved osseointegration.

Below, we show the results of our coupling of alginic acid to PEEK with subsequent mineralization. Polysaccharides, such as alginic acid, chitosan, or hyaluronic acid, are an attractive alternative to proteins, as many of them are known as biocompatible materials for a long time. In contrast to protein-based biomaterials or coatings, these materials do not suffer from the downsides of animal-derived proteins like collagen or gelatin, which have an inherent danger of prion contamination (Creutzfeldt-Jakob disease). In addition, a refusal of collagen/gelatin-based material may occur by patients simply because of religious (e.g., pig-derived sources) or ethical reasons. This is the basis for our first preliminary experiments toward a covalently anchored alginate-calcium phosphate composite to a PEEK surface.

Generally, it is possible to couple alginic acid onto PEEK using a wet chemical route or a UV-light-assisted coupling

route. The wet chemical synthesis route can start with a surface amidation (see Figure 5b), followed by the coupling of alginic acid via amide bonds using established carbodiimide chemistry. The UV-light-assisted synthesis route is demonstrated in the following. Within this route, the PEEK is immersed in a solution of a modified alginic acid. This modification comprises the coupling of a photoactive azidoaniline linker onto the -COOH side-chains of the alginic acid with the help of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) coupling chemistry. Similar to the demonstrated example of hyaluronic acid,^[158,171] azidoaniline modified alginic acid could react in a reaction pathway according to **Scheme 1**.^[172,173] After irradiation with 254 nm UV-light, the azide can decompose and a very reactive intermediate nitrene compound is formed.^[174] This nitrene can partake in many chemical reactions, such as C-H insertion reactions or cycloadditions, in this case covalently binding the alginic acid onto the PEEK surface.^[175-177]

In order to create a surface closer to that of the natural bone, this matrix was subsequently mineralized with calcium phosphate in a closely controlled mineralization process. After photo-coupling of the alginate, the surface shows the appearance of a spongy, homogeneous layer on the surface, partly covered by larger fibers (see **Figure 7a**). The water contact angle also decreased from previously 90° of pure PEEK to 57.42° ± 5.04° showing a much higher wettability. After mineralization, very small crystallites appeared on the surface, which can be recognized due to their higher electron contrast in the image, and which consist of Ca and P (see **Figure 7b**). Furthermore, the water contact angle increased slightly to 73.52° ± 0.96°.

On the basis of the known literature as well as our recent experiments, we see the future of dental implants in the

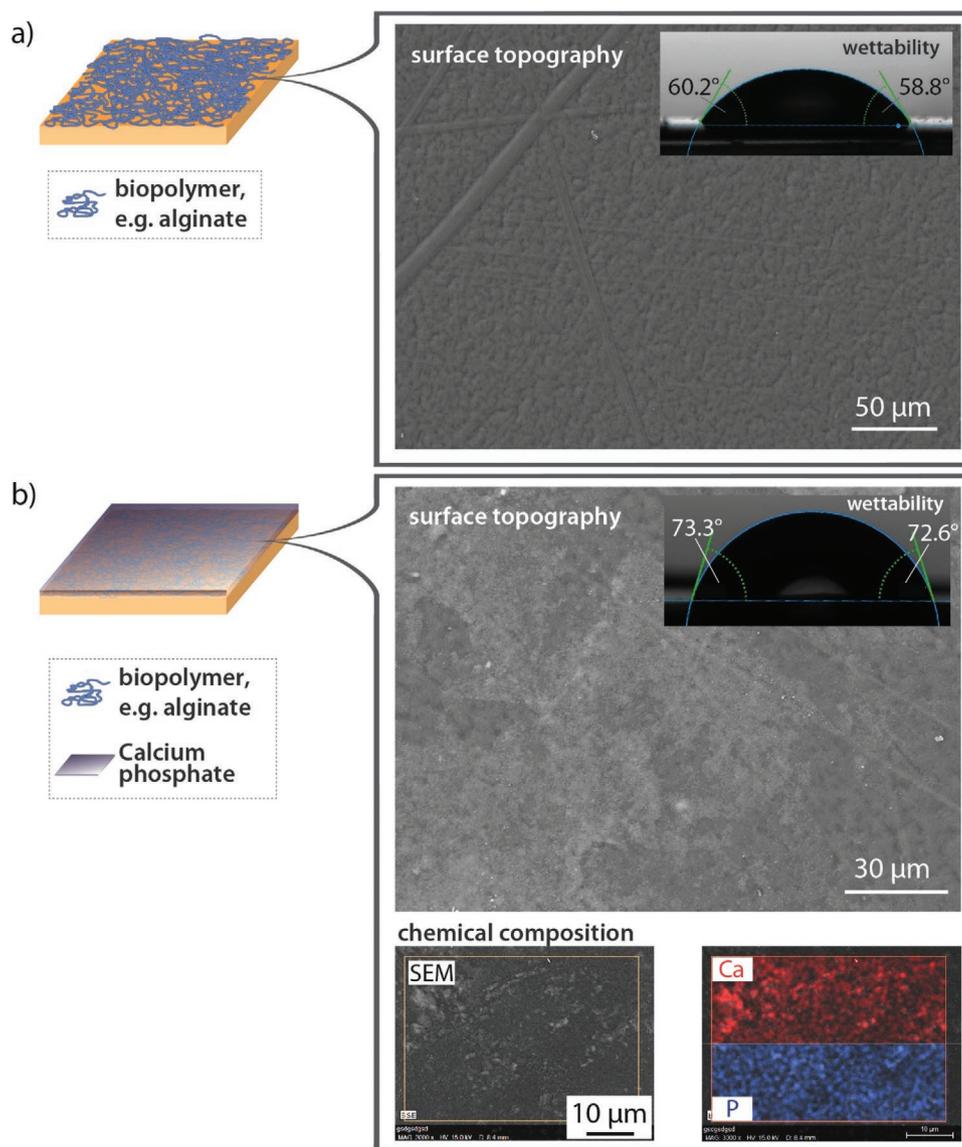


Figure 7. First results of the chemically anchored alginate–calcium phosphate composite coating on PEEK. a) SEM micrograph of the surface topography and water contact angle (inset) after photocoupling of alginate. b) SEM micrograph of the surface topography and water contact angle (inset) after mineralization with calcium phosphate. Lower panel: SEM image (left) with corresponding mapping (right) of the surface after subsequent mineralization of the alginate matrix with calcium phosphate.

design and development of PEEK-based bioinspired and biomimetic surfaces that promote the desired fast and lasting ingrowth into the surrounding bone. The use of covalently anchored biomimetic composite materials combines many advantageous properties. Covalent linkage and a thin layer prevent easy delamination. An established biocompatible organic matrix and a mineral component provide the cells an environment similar in chemistry and structure to natural bone, rendering the direct PEEK surface invisible to the human body. Bone-related cells may not recognize the implant as a foreign body, and therefore may heal and integrate faster and more firmly.

We expect that future research will further demonstrate such new bio-inspired surface designs, introducing a set of biocompatible, covalently anchored composite coatings. This will

allow selecting the features required for specific implants to investigate the required tissue response and adjust them to the patient's needs and wishes.

4. Conclusions

Because neither metal-based (e.g., titanium) nor ceramics (e.g., zirconium dioxide) are ideal material candidates for an optimal dental implant, and each of those materials shows inherent disadvantageous properties, it is justified to further expand and examine modified PEEK-materials as a promising alternative for dental implant applications. The different described surface-refining technologies already show noteworthy results in vitro and in vivo.

Consequently, the determining success lies in the combination of different technologies, based on chemical (covalently bound biomimetic surface layer) as well as physical surface modifications (topology) and new implant designs. This combination of osseointegrative surface modification technologies and a clearly defined topography and implant geometry (design) could give PEEK-dental implants the primary stability, which is necessary to guarantee an optimal implant healing process. Further research work will be necessary to reveal this ideal combination for future dental implants.

Acknowledgements

D.S. and H.C. contributed equally to this work. The authors acknowledge the Electron Microscopy Center and the Nanostructure Laboratory at the University of Konstanz for analytical support. The authors further thank the laboratory of Prof. Johannes Boneberg for providing the micropatterned PEEK materials and Prof. Christof Hauck for providing the laboratory environment for the in vitro assays.

Conflict of Interest

The authors acknowledge their potential conflict of interest with the contents of this manuscript. stimOS GmbH commercializes part of the presented technology described in this manuscript. Two of the authors are affiliated with this company (J.K. and D.S.) and the third author (H.C.) is co-inventor of a national patent owned by this company on this topic.

Keywords

biomimetic modification, dental implants, osseointegration, polyetheretherketone, titanium

Received: July 7, 2019

Revised: October 10, 2019

Published online: December 4, 2019

- [1] E. Papia, C. Larsson, *Eur. J. Oral Implantol.* **2018**, *11*, S147.
- [2] R. G. Bassetti, M. A. Bassetti, J. Kuttenberger, *Int. J. Prosthodont.* **2018**, *31*, 287.
- [3] F. A. Spitznagel, S. D. Horvath, P. C. Gierthmuehlen, *Eur. J. Oral Implantol.* **2017**, *10*, 89.
- [4] A. Bidra, P. Rungruanganunt, M. Gauthier, *Eur. J. Oral Implantol.* **2017**, *10*, 35.
- [5] C. Goodacre, B. Goodacre, *Eur. J. Oral Implantol.* **2017**, *10*, 13.
- [6] T. R. Walton, D. M. Layton, *Int. J. Oral Max. Impl.* **2017**, *32*, 667.
- [7] C. Guédât, U. Nagy, M. Schimmel, F. Müller, M. Srinivasan, *Clin. Exp. Dental Res.* **2018**, *4*, 132.
- [8] Z. Ali, S. R. Baker, S. Shahrbaaf, N. Martin, M. V. Vettore, *J. Prosthet. Dent.* **2019**, *121*, 59.
- [9] B. K. AlZarea, *J. Clin. Exp. Dent.* **2017**, *9*, e666.
- [10] R. Castillo-Oyagüe, C. Perea, M.-J. Suárez-García, J. Del Río, C. D. Lynch, A. Preciado, *J. Dent.* **2016**, *55*, 82.
- [11] R. Kapoor, K. Singh, S. Kaur, A. Arora, *J. Clin. Diagn. Res.* **2016**, *10*, ZC61.
- [12] R. Junker, A. Dimakis, M. Thoneick, J. A. Jansen, *Clin. Oral. Implants Res.* **2009**, *20*, 185.
- [13] S. Mei, F. Dong, M. S. R. Khan, *J. Oral Maxillofac. Surg.* **2018**, *76*, 2104.e1.
- [14] A. Scarano, E. Crocetta, A. Quaranta, F. Lorusso, *Biomed Res. Int.* **2018**, *2018*, 2349698.
- [15] L. Ottria, D. Lauritano, M. Andreasi Bassi, A. Palmieri, V. Candotto, A. Tagliabue, L. Tettamanti, *J. Biol. Regul. Homeost. Agents* **2018**, *32*, 81.
- [16] D. Heo, Y.-K. Heo, J.-H. Lee, J.-J. Lee, B. Kim, *Implant Dent.* **2017**, *26*, 711.
- [17] P.-I. Branemark, *Scand. J. Plast. Reconstr. Surg. Suppl.* **1977**, *16*, 1.
- [18] S. E. Wheelis, A. G. Montaña-Figueroa, M. Quevedo-Lopez, J. L. Calvo Guirado, *Clin. Implant Dent. Relat. Res.* **2018**, *20*, 838.
- [19] Z. G. Azzawi, T. I. Hamad, S. A. Kadhim, G. A.-H. Naji, *J. Mater. Sci.: Mater. Med.* **2018**, *29*, 96.
- [20] V. Offermanns, O. Z. Andersen, G. Riede, M. Sillassen, C. S. Jeppesen, K. P. Almtoft, H. Talasz, C. Öhman-Mägi, B. Lethaus, R. Tolba, *Acta Biomater.* **2018**, *69*, 385.
- [21] M. Beolchini, N. P. Lang, G. Gómez Moreno, G. Iezzi, D. Botticelli, J. L. Calvo Guirado, *Clin. Oral. Implants Res.* **2016**, *27*, 196.
- [22] J.-W. Koh, Y.-S. Kim, J.-H. Yang, I.-S. Yeo, **2013**.
- [23] U. W. Jung, S. Kim, I. K. Lee, M. S. Kim, J. S. Lee, H. J. Kim, *Clin. Oral. Implants Res.* **2014**, *25*, 1169.
- [24] R. Williamson, J. Disegi, J. Griggs, M. Roach, *J. Mater. Sci.: Mater. Med.* **2013**, *24*, 2327.
- [25] M. B. Guimarães, R. S. Bueno, M. B. G. Blaya, L. M. Hirakata, R. Hübler, *Implant Dent.* **2013**, *22*, 356.
- [26] K. Ito, K. Nanba, T. Nishida, H. Sato, S. Murai, *J. Oral Sci.* **1998**, *40*, 37.
- [27] D. Perrin, S. Szmukler-Moncler, C. Echikou, P. Pointaire, J. P. Bernard, *Clin. Oral. Implants Res.* **2002**, *13*, 465.
- [28] S. A. Gehrke, B. A. Dedavid, J. S. Aramburú, L. Pérez-Díaz, J. L. C. Guirado, P. M. Canales, P. N. De Aza, *Biomed Res. Int.* **2018**, *2018*.
- [29] A. Wennerberg, T. Albrektsson, *Clin. Oral. Implants Res.* **2009**, *20*, 172.
- [30] L. Le Guéhennec, A. Soueidan, P. Layrolle, Y. Amouriq, *Dent. Mater.* **2007**, *23*, 844.
- [31] A. Siddiqi, A. G. T. Payne, R. K. De Silva, W. J. Duncan, *Clin. Oral. Implants Res.* **2011**, *22*, 673.
- [32] R. Skalak, *J. Prosthet. Dent.* **1983**, *49*, 843.
- [33] J. Soumeire, J. Dejou, *J. Oral Rehabil.* **1999**, *26*, 394.
- [34] M. Quirynen, I. Naert, D. Van Steenberghe, *Clin. Oral. Implants Res.* **1992**, *3*, 104.
- [35] F. Isidor, *Clin. Oral. Implants Res.* **1996**, *7*, 143.
- [36] J. B. Brunski, *Adv. Dent. Res.* **1999**, *13*, 99.
- [37] M. Nagasawa, R. Takano, T. Maeda, K. Uoshima, *Int. J. Oral Max. Impl.* **2013**, *28*, 109.
- [38] C. H. Hämmerle, D. Tarnow, *J. Clin. Periodontol.* **2018**, *45*, S267.
- [39] L. Chambrone, L. A. Chambrone, L. A. Lima, *J. Periodontol.* **2010**, *81*, 1367.
- [40] S. Roehling, M. Astasov-Frauenhoffer, I. Hauser-Gerspach, O. Braissant, H. Woelfler, T. Waltimo, H. Kniha, M. Gahlert, *J. Periodontol.* **2017**, *88*, 298.
- [41] P. C. Schallock, T. Menné, J. D. Johansen, J. S. Taylor, H. I. Maibach, C. Lidén, M. Bruze, J. P. Thyssen, *Contact Dermatitis* **2012**, *66*, 4.
- [42] Y. Li, C. Wong, J. Xiong, P. Hodgson, C. Wen, *J. Dent. Res.* **2010**, *89*, 493.
- [43] Y. Okazaki, E. Gotoh, *Biomaterials* **2005**, *26*, 11.
- [44] M. A. Khan, R. L. Williams, D. F. Williams, *Biomaterials* **1999**, *20*, 765.
- [45] Y. M. Zhang, F. Chai, J.-C. Hornez, C. L. Li, Y. M. Zhao, M. Traisnel, H. F. Hildebrand, *Biomed. Mater.* **2009**, *4*, 015004.
- [46] D. R. N. Correa, F. B. Vicente, T. A. G. Donato, V. E. Arana-Chavez, M. A. R. Buzalaf, C. R. Grandini, *Mater. Sci. Eng., C* **2014**, *34*, 354.
- [47] M. Hosoki, K. Nishigawa, Y. Miyamoto, G. Ohe, Y. Matsuka, *J. Prosthodont. Res.* **2016**, *60*, 213.
- [48] Y. Sun, Y. Hu, Q. Yuan, J. Yu, X. Wu, Z. Du, X. Wu, J. Hu, *J. Neurosurg.* **2018**, *131*, 1.



- [49] K. C. Olsen, P. Barnes, K. Morton, P. Norris, *Dermatitis* **2016**, *27*, 229.
- [50] S. Hettige, J. S. Norris, *Acta Neurochir.* **2012**, *154*, 1725.
- [51] K. Ajlouni, W. Elshahawy, R. Ajlouni, A. Sadakah, *J. Prosthet. Dent.* **2018**, *119*, 426.
- [52] T. Minamizato, *J. Prosthet. Dent.* **1990**, *63*, 677.
- [53] A. E. Rodriguez, M. Monzavi, C. L. Yokoyama, H. Nowzari, *J. Esthet. Restor. Dent.* **2018**, *30*, 538.
- [54] J.-H. Dubruielle, E. Viguier, G. Le Naour, M.-T. Dubruielle, M. Auriol, Y. Le Charpentier, *Int. J. Oral Maxillofac. Implants* **1999**, *14*, 271.
- [55] S. Schultze-Mosgau, H. Schliephake, M. Radespiel-Tröger, F. W. Neukam, *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* **2000**, *89*, 91.
- [56] N. Cionca, D. Hashim, A. Mombelli, *Periodontol.* **2000** **2017**, *73*, 241.
- [57] A. Scarano, M. Piattelli, S. Caputi, G. A. Favero, A. Piattelli, *J. Periodontol.* **2004**, *75*, 292.
- [58] L. Rimondini, L. Cerroni, A. Carrassi, P. Torriceni, *Int. J. Oral Maxillofac. Implants* **2002**, *17*, 793.
- [59] J. M. Parmigiani-Izquierdo, M. E. Cabaña-Muñoz, J. J. Merino, A. Sánchez-Pérez, *Int. J. Implant Dent.* **2017**, *3*, 5.
- [60] C. A. V. Lopez, M. A. A. Vasco, E. Ruales, K. A. Bedoya, C. M. Benfatti, O. L. Bezzon, T. M. Deliberador, *J. Oral Implantol.* **2018**, *44*, 409.
- [61] M. G. Bankoğlu, H. Yılmaz, *J. Prosthet. Dent.* **2016**, *116*, 346.
- [62] M. H. Adánez, H. Nishihara, W. Att, *J. Prosthodont. Res.* **2018**, *62*, 397.
- [63] B. Al-Amleh, K. Lyons, M. Swain, *J. Oral Rehabil.* **2010**, *37*, 641.
- [64] S. Mishra, R. Chowdhary, *Clin. Implant Dent. Relat. Res.* **2019**, *21*, 208.
- [65] S. Najeeb, Z. Khurshid, J. P. Matinlinna, F. Siddiqui, M. Z. Nassani, K. Baroudi, *Int. J. Dent.* **2015**, *2015*, 381759.
- [66] K. Mursch, J. Behnke-Mursch, *World Neurosurg.* **2018**, *117*, 142.
- [67] S. E. van de Vijfeijken, T. J. Múnker, R. Spijker, L. H. Karssemakers, W. P. Vandertop, A. G. Becking, D. T. Ubbink, A. Becking, L. Dubois, L. Karssemakers, *World Neurosurg.* **2018**, *117*, 443.e8.
- [68] I. Y. Kim, A. Sugino, K. Kikuta, C. Ohtsuki, S. B. Cho, *J. Biomater. Appl.* **2009**, *24*, 105.
- [69] S. M. Kurtz, *PEEK Biomaterials Handbook*, William Andrew, Norwich, NY **2019**.
- [70] H. B. Skinner, *Clin. Orthop. Relat. Res.* **1988**, *235*, 224.
- [71] C. S. Li, C. Vannabouathong, S. Sprague, M. Bhandari, *Clin. Med. Insights Arthritis Musculoskelet. Disord.* **2015**, *8*, 33.
- [72] P. Werner, V. Altstädt, R. Jaskulka, O. Jacobs, J. K. Sandler, M. S. Shaffer, A. H. Windle, *Wear* **2004**, *257*, 1006.
- [73] K. Friedrich, H. Sue, P. Liu, A. Almajid, *Tribol. Int.* **2011**, *44*, 1032.
- [74] M. Sampaio, M. Buciumeanu, B. Henriques, F. S. Silva, J. C. M. Souza, J. R. Gomes, *J. Mech. Behav. Biomed. Mater.* **2016**, *54*, 123.
- [75] M. Sampaio, M. Buciumeanu, B. Henriques, F. S. Silva, J. C. M. Souza, J. R. Gomes, *J. Mech. Behav. Biomed. Mater.* **2016**, *60*, 212.
- [76] B. Di Maggio, P. Sessa, P. Mantelli, P. Maniscalco, F. Rivera, G. M. Calori, L. Bisogno, G. Scaravilli, M. Caforio, *Injury* **2017**, *48*, S34.
- [77] Y. Zhang, L. Zhang, X. R. Zhu, A. K. Lee, M. Chambers, L. Dong, *Int. J. Radiat. Oncol. Biol. Phys.* **2007**, *67*, 924.
- [78] F. Draenert, E. Copenrath, P. Herzog, S. Müller, U. Mueller-Lisse, *Dentomaxillofac. Radiol.* **2007**, *36*, 198.
- [79] A. Parsa, N. Ibrahim, B. Hassan, K. Syriopoulos, Pvd. Stelt, *Dentomaxillofac. Radiol.* **2014**, *43*, 20140019.
- [80] P. R. Kuzyk, E. H. Schemitsch, *Indian Journal of Orthop.* **2011**, *45*, 108.
- [81] D. A. Puleo, A. Nanci, *Biomaterials* **1999**, *20*, 2311.
- [82] R. A. Gittens, L. Scheideler, F. Rupp, S. L. Hyzy, J. Geis-Gerstorf, Z. Schwartz, B. D. Boyan, *Acta Biomater.* **2014**, *10*, 2907.
- [83] M. M. Stevens, J. H. George, *Science* **2005**, *310*, 1135.
- [84] A. G. Harvey, E. W. Hill, A. Bayat, *Expert Rev. Med. Devices* **2013**, *10*, 257.
- [85] C. J. Bettinger, R. Langer, J. T. Borenstein, *Angew. Chem., Int. Ed.* **2009**, *48*, 5406.
- [86] J. Sandler, P. Werner, M. S. Shaffer, V. Demchuk, V. Altstädt, A. H. Windle, *Composites, Part A* **2002**, *33*, 1033.
- [87] D. S. Bangarusampath, H. Ruckdäschel, V. Altstädt, J. K. W. Sandler, D. Garray, M. S. P. Shaffer, *Polymer* **2009**, *50*, 5803.
- [88] X. Wu, X. Liu, J. Wei, J. Ma, F. Deng, S. Wei, *Int. J. Nanomed.* **2012**, *7*, 1215.
- [89] Q. Wang, Q. Xue, H. Liu, W. Shen, J. Xu, *Wear* **1996**, *198*, 216.
- [90] M. C. Kuo, C. M. Tsai, J. C. Huang, M. Chen, *Mater. Chem. Phys.* **2005**, *90*, 185.
- [91] H.-B. Qiao, Q. Guo, A.-G. Tian, G.-L. Pan, L.-B. Xu, *Tribol. Int.* **2007**, *40*, 105.
- [92] R. Goyal, A. Tiwari, U. Mulik, Y. Negi, *J. Appl. Polym. Sci.* **2008**, *110*, 3379.
- [93] G. Shi, M. Q. Zhang, M. Z. Rong, B. Wetzel, K. Friedrich, *Wear* **2003**, *254*, 784.
- [94] Q. Wang, J. Xu, W. Shen, W. Liu, *Wear* **1996**, *196*, 82.
- [95] V. Balaji, A. Tiwari, R. Goyal, *J. Appl. Polym. Sci.* **2011**, *119*, 311.
- [96] A. M. Díez-Pascual, C. Xu, R. Luque, *J. Mater. Chem. B* **2014**, *2*, 3065.
- [97] Q. Wang, Q. Xue, W. Shen, *Tribol. Int.* **1997**, *30*, 193.
- [98] Q.-J. Xue, Q.-H. Wang, *Wear* **1997**, *213*, 54.
- [99] R. Ma, Z. Yu, S. Tang, Y. Pan, J. Wei, T. Tang, *Int. J. Nanomed.* **2016**, *11*, 6023.
- [100] L. Guo, G. Zhang, D. Wang, F. Zhao, T. Wang, Q. Wang, *Composites, Part A* **2017**, *102*, 400.
- [101] A. M. Díez-Pascual, A. L. Díez-Vicente, *ACS Appl. Mater. Interfaces* **2015**, *7*, 5561.
- [102] N. Knör, A. Gebhard, F. Hauptert, A. Schlarb, *Mech. Compos. Mater.* **2009**, *45*, 199.
- [103] M. Harmand, J. Cougoulic, in *A New Biocompatible Biomaterial: PEEK/β-TCP/TiO2 Composite*, Sydney 9WBC Congress, Sydney **2004**.
- [104] M. Andreiotelli, H. J. Wenz, R. J. Kohal, *Clin. Oral. Implants Res.* **2009**, *20*, 32.
- [105] I. Sailer, A. Zembic, R. E. Jung, C. H. F. Hämmerle, A. Mattioli, *Eur. J. Esthet. Dent.* **2007**, *2*, 296.
- [106] R. Glauser, I. Sailer, A. Wohlwend, S. Studer, M. Schibli, P. Schärer, *Int. J. Prosthodont.* **2004**, *17*, 285.
- [107] E. D. Tetelman, C. A. Babbush, *Implant Dent.* **2008**, *17*, 51.
- [108] M. A. Bakar, M. Cheng, S. Tang, S. Yu, K. Liao, C. Tan, K. Khor, P. Cheang, *Biomaterials* **2003**, *24*, 2245.
- [109] L. Petrovic, D. Pohle, H. Münstedt, T. Rechtenwald, K. Schlegel, S. Rupprecht, *J. Biomed. Sci.* **2006**, *13*, 41.
- [110] K. Wong, C. Wong, W. Liu, H. Pan, M. Fong, W. Lam, W. Cheung, W. Tang, K. Chiu, K. Luk, *Biomaterials* **2009**, *30*, 3810.
- [111] L. Wang, S. He, X. Wu, S. Liang, Z. Mu, J. Wei, F. Deng, Y. Deng, S. Wei, *Biomaterials* **2014**, *35*, 6758.
- [112] S. Tang, P. Cheang, M. AbuBakar, K. Khor, K. Liao, *Int. J. Fatigue* **2004**, *26*, 49.
- [113] C. Akkan, M. Hammadeh, S. Brück, H. Park, M. Veith, H. Abdul-Khaliq, C. Aktas, *Mater. Lett.* **2013**, *109*, 261.
- [114] A. Wilson, I. Jones, F. Salamat-Zadeh, J. F. Watts, *Int. J. Adhes. Adhes.* **2015**, *62*, 69.
- [115] M. Schmidt, D. Pohle, T. Rechtenwald, *CIRP Ann.* **2007**, *56*, 205.
- [116] S.-W. Ha, R. Hauert, K.-H. Ernst, E. Wintermantel, *Surf. Coat. Technol.* **1997**, *96*, 293.
- [117] N. Inagaki, S. Tasaka, T. Horiuchi, R. Suyama, *J. Appl. Polym. Sci.* **1998**, *68*, 271.
- [118] E. T. J. Rochford, A. H. C. Poulsson, J. Salavarieta Varela, P. Lezuo, R. G. Richards, T. F. Moriarty, *Colloids Surf., B* **2014**, *113*, 213.

- [119] A. H. Poulsson, D. Eglin, S. Zeiter, K. Camenisch, C. Sprecher, Y. Agarwal, D. Nehrbass, J. Wilson, R. G. Richards, *Biomaterials* **2014**, *35*, 3717.
- [120] S.-W. Ha, M. Kirch, F. Birchler, K.-L. Eckert, J. Mayer, E. Wintermantel, C. Sittig, I. Pfund-Klingenfuss, M. Textor, N. Spencer, *J. Mater. Sci.: Mater. Med.* **1997**, *8*, 683.
- [121] J. Waser-Althaus, A. Salamon, M. Waser, C. Padeste, M. Kreutzer, U. Pieleles, B. Müller, K. Peters, *J. Mater. Sci.: Mater. Med.* **2014**, *25*, 515.
- [122] D. Briem, S. Strametz, K. Schröder, N. Meenen, W. Lehmann, W. Linhart, A. Ohl, J. Rueger, *J. Mater. Sci.: Mater. Med.* **2005**, *16*, 671.
- [123] F. Awaja, S. Zhang, N. James, D. R. McKenzie, *Plasma Processes Polym.* **2010**, *7*, 1010.
- [124] F. Awaja, D. V. Bax, S. Zhang, N. James, D. R. McKenzie, *Plasma Processes Polym.* **2012**, *9*, 355.
- [125] E. K. Yim, S. W. Pang, K. W. Leong, *Exp. Cell Res.* **2007**, *313*, 1820.
- [126] D. D. Deligianni, N. D. Katsala, P. G. Koutsoukos, Y. F. Missirlis, *Biomaterials* **2000**, *22*, 87.
- [127] F. Lüthen, R. Lange, P. Becker, J. Rychly, U. Beck, J. B. Nebe, *Biomaterials* **2005**, *26*, 2423.
- [128] P. R. Schmidlin, B. Stawarczyk, M. Wieland, T. Attin, C. H. Hämmerle, J. Fischer, *Dent. Mater.* **2010**, *26*, 553.
- [129] L. Hallmann, A. Mehl, N. Sereno, C. H. Hämmerle, *Appl. Surf. Sci.* **2012**, *258*, 7213.
- [130] N. T. Evans, F. B. Torstrick, C. S. D. Lee, K. M. Dupont, D. L. Safranski, W. A. Chang, A. E. Macedo, A. S. P. Lin, J. M. Boothby, D. C. Whittingslow, R. A. Carson, R. E. Guldberg, K. Gall, *Acta Biomater.* **2015**, *13*, 159.
- [131] X. Bourges, C. Gobin, *US20100010632A1*, **2010**.
- [132] G. Daculsi, E. Goyenvalle, E. Aguado, in *Improvement of Bone Ingrowth on PEEK Surface Implant*, Key Engineering Materials, Trans Tech Publ, Aedermannsdorf, Switzerland **2012**, pp. 795–799.
- [133] A. Xu, X. Liu, X. Gao, F. Deng, Y. Deng, S. Wei, *Mater. Sci. Eng., C* **2015**, *48*, 592.
- [134] C. Henneuse-Boxus, E. Dulière, J. Marchand-Brynaert, *Eur. Polym. J.* **2001**, *37*, 9.
- [135] J. Khoury, S. R. Kirkpatrick, M. Maxwell, R. E. Cherian, A. Kirkpatrick, R. C. Svruga, *Nucl. Instrum. Methods Phys. Res. Sect. B* **2013**, *307*, 630.
- [136] A. F. Lasagni, D. F. Acevedo, C. A. Barbero, F. Mücklich, *Adv. Eng. Mater.* **2007**, *9*, 99.
- [137] A. M. Kendale, D. L. Trumper, *US7117790*, **2010**.
- [138] A. I. Teixeira, G. A. McKie, J. D. Foley, P. J. Bertics, P. F. Nealey, C. J. Murphy, *Biomaterials* **2006**, *27*, 3945.
- [139] J. H. Lee, H. L. Jang, K. M. Lee, H.-R. Baek, K. Jin, K. S. Hong, J. H. Noh, H.-K. Lee, *Acta Biomater.* **2013**, *9*, 6177.
- [140] S. Barkarmo, A. Wennerberg, M. Hoffman, P. Kjellin, K. Breiding, P. Handa, V. Stenport, *J. Biomed. Mater. Res., Part A* **2013**, *101A*, 465.
- [141] B.-D. Hahn, D.-S. Park, J.-J. Choi, J. Ryu, W.-H. Yoon, J.-H. Choi, J.-W. Kim, C.-W. Ahn, H.-E. Kim, B.-H. Yoon, *Appl. Surf. Sci.* **2013**, *283*, 6.
- [142] Y. Zheng, L. Liu, L. Xiao, Q. Zhang, Y. Liu, *Colloids Surf., B* **2019**, *173*, 591.
- [143] S.-W. Ha, A. Gisepp, J. Mayer, E. Wintermantel, H. Gruner, M. Wieland, *J. Mater. Sci.: Mater. Med.* **1997**, *8*, 891.
- [144] X. Yu, M. Ibrahim, Z. Liu, H. Yang, L. Tan, K. Yang, *Bioactive Materials* **2018**, *3*, 139.
- [145] H.-K. Tsou, P.-Y. Hsieh, C.-J. Chung, C.-H. Tang, T.-W. Shyr, J.-L. He, *Surf. Coat. Technol.* **2009**, *204*, 1121.
- [146] S. Cook, A. Rust-Dawicki, *J. Oral Implantol.* **1995**, *21*, 176.
- [147] C.-M. Han, E.-J. Lee, H.-E. Kim, Y.-H. Koh, K. N. Kim, Y. Ha, S.-U. Kuh, *Biomaterials* **2010**, *31*, 3465.
- [148] A. Furukawa, M. Akahane, Y. Tanaka, in *CO₂ Laser Bonding of Silicate-Substituted Strontium Apatite on PEEK and Osteointegration on its Surface*, Key Engineering Materials, Trans Tech Publ, Aedermannsdorf, Switzerland, **2018**, pp. 145–150.
- [149] D. M. Devine, J. Hahn, R. G. Richards, H. Gruner, R. Wieling, S. G. Pearce, *J. Biomed. Mater. Res., Part B* **2013**, *101B*, 591.
- [150] R. Y. M. Huang, P. Shao, C. M. Burns, X. Feng, *J. Appl. Polym. Sci.* **2001**, *82*, 2651.
- [151] Y. Zhao, H. M. Wong, W. Wang, P. Li, Z. Xu, E. Y. W. Chong, C. H. Yan, K. W. K. Yeung, P. K. Chu, *Biomaterials* **2013**, *34*, 9264.
- [152] H. N. Beck, *J. Appl. Polym. Sci.* **1992**, *45*, 1361.
- [153] C. Wang, S. Wang, Y. Yang, Z. Jiang, Y. Deng, S. Song, W. Yang, Z.-G. Chen, *J. Biomater. Sci., Polym. Ed.* **2018**, *29*, 1595.
- [154] Y. Zheng, C. Xiong, S. Zhang, X. Li, L. Zhang, *Mater. Sci. Eng., C* **2015**, *55*, 512.
- [155] H. Cölfen, L. Tian, J. Knaus, *DE102015002398A1*, **2015**.
- [156] O. Noiset, Y.-J. Schneider, J. Marchand-Brynaert, *J. Biomater. Sci., Polym. Ed.* **2000**, *11*, 767.
- [157] Y. Zheng, C. Xiong, L. Zhang, *Mater. Lett.* **2016**, *164*, 60.
- [158] D. Schaffarczyk, M. Gießl, H. Cölfen, *DE102016122837A1*, **2016**.
- [159] K. Ishihara, M. Kyomoto, *J. Photopolym. Sci. Technol.* **2010**, *23*, 161.
- [160] X. Zhao, D. Xiong, K. Wang, N. Wang, *Mater. Sci. Eng., C* **2017**, *75*, 777.
- [161] J. Deng, L. Wang, L. Liu, W. Yang, *Prog. Polym. Sci.* **2009**, *34*, 156.
- [162] A. Yousaf, A. Farrukh, Z. Oluz, E. Tuncel, H. Duran, S. Y. Doğan, T. Tekinay, H. ur Rehman, B. Yameen, *React. Funct. Polym.* **2014**, *83*, 70.
- [163] O. Noiset, Y.-J. Schneider, J. Marchand-Brynaert, *J. Biomater. Sci., Polym. Ed.* **1999**, *10*, 657.
- [164] H. Cölfen, L. Tian, J. Knaus, *EP3261684A1*, **2019**.
- [165] U. Hersel, C. Dahmen, H. Kessler, *Biomaterials* **2003**, *24*, 4385.
- [166] M. D. Pierschbacher, E. Ruoslahti, *Nature* **1984**, *309*, 30.
- [167] T. J. Dennes, J. Schwartz, *J. Am. Chem. Soc.* **2009**, *131*, 3456.
- [168] M. Becker, S. Lorenz, D. Strand, C.-F. Vahl, M. Gabriel, *Sci. World J.* **2013**, *2013*, 616535.
- [169] Y. Zheng, C. Xiong, X. Li, L. Zhang, *Appl. Surf. Sci.* **2014**, *320*, 93.
- [170] H. Ao, Y. Xie, H. Tan, X. Wu, G. Liu, A. Qin, X. Zheng, T. Tang, *J. Biomed. Mater. Res., Part A* **2014**, *102*, 204.
- [171] T. Sugawara, T. Matsuda, *Macromolecules* **1994**, *27*, 7809.
- [172] G. Chen, Y. Ito, Y. Imanishi, A. Magnani, S. Lamponi, R. Barbucci, *Bioconjugate Chem.* **1997**, *8*, 730.
- [173] T. Sugawara, T. Matsuda, *Langmuir* **1995**, *11*, 2272.
- [174] R. Belloli, *J. Chem. Educ.* **1971**, *48*, 422.
- [175] H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048.
- [176] C. G. Savarin, C. Grisé, J. A. Murry, R. A. Reamer, D. L. Hughes, *Org. Lett.* **2007**, *9*, 981.
- [177] Z. Li, X. Ding, C. He, *J. Org. Chem.* **2006**, *71*, 5876.