

# Metallic biomaterials—A review

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## 4.1 Introduction

The aging population has grown exponentially of recent, particularly in developed countries. This has led to drastic increases in the usage of implants, to meet the needs and desires of the aging population to maintain life quality and related activities. Further, there have been urgent requirements to meet the challenges associated with vascular therapy, trauma, cardiology, dental, orthopedics, wound care, etc. To address the different associated challenges, one of the major focal points of the medical community has been on high-performance implantable biomaterials. The market for biomaterials has grown from \$95 billion in 2011 to \$135 billion in the year 2017 (<http://www.marketsandmarkets.com/PressReleases/bio-implants.asp>). A rapid surge in the diversified and improved functionalities of biomaterials has taken place with the advancements in natural, synthetic, and hybrid materials. Together with the growth in the different types of biomaterials, there have been rapid advances in processing techniques of biomaterials, making them suitable to be used as implantable devices [1–4]. The presence of diversified biomaterials has allowed for selection of suitable materials that meet particular objectives, as for instance using metals as electrodes for artificial organs with high electroconductivity, materials for permanent replacement having the characteristics of being chemically inert, or materials with biodegradability properties for the cases in which regenerating of lost tissues or restoration of function is possible [5, 6].

In recent years there has been an intense focus on choosing biomaterials with multifunctionality. For instance, a temporary material for a scaffold may not only lend itself to providing physical support to promote tissue regeneration, but may also provide for other critical biological factors such as fibroblast, morphogenetic protein-2, the growth factors for endothelial growth, etc. One example exhibiting such multifunctionality is the magnesium implant [7–10], which has the required tensile strength, fracture resistance, etc. The kinetics of biodegradation can be controlled by the alloying metals as well as through coatings and emerging mechanical processing for the materials. For instance, surface modifications such as coatings with polymer thin films and with bioactive ceramics can provide multifunctionality to the bioinert metals such as Co and Ti based alloys. Such bioinert materials that are based on Co or Ti are mainly used for load-bearing applications where properties such as corrosion resistance can provide enhanced mechanical stability and reliability and minimized local toxicity to the host, both at the local and systemic levels [11, 12]. The Co and Ti based bioinert materials

possess excellent tensile strength, fatigue stress, and fracture toughness [13, 14]. The multifunctionality bioinert materials have found applications in orthopedics as plates, screws, and artificial joints, as braces and dental implants for orthodontics, as components for neurosurgical devices such as staples, artificial hearts, wires, and stents. In comparison to Co-Cr alloys, the Ti based bioinert materials are the most preferred alternatives because of favorable combinations of corrosion resistance, biocompatibility, elastic modulus, strength, and relatively low weight and density [15].

However, a number of challenges are associated with the applications of diversified implantable materials. One of the challenges is that of controlling the kinetics of biodegradation for some metals, such as Mg or Fe, whereby an early degradation can have an adverse effect on the restoration of the tissue due to loss in mechanical strength. A risk of developing systemic hypersensitivity reactions due to the long-term presence of Co-Cr or Ti alloys in the body may also exist. Osteopenia may result due to stress shielding resulting from modulus differences between these metals and the natural bone tissue [11]. One of the major risks associated with these implants is that of inflammation and infection [16–18]. Such associated risks may undermine the efficiency of the implants and also can lead to loss of tissue in and around the implant [19]. The septic or aseptic loosening in the case of load-bearing implants may lead to incorrect transfer of force, such as that of biting force to the dental implants. The incorrect transfer of load to the implant may lead to its failure once the load goes beyond its fatigue strength [20]. In 20% of the cases of patients with 7–10 years of implant placement, complications such as periimplantitis have been reported [21]. The aforementioned complications associated with the implants can lead to significant health issues in the patients and require additional costs to minimize the complications [22, 23].

A considerable effort has been made to do away with these shortfalls, such as the development of different surface and bulk modification strategies such as acid and plasma etching, laser ablation, ion implantation, etc. The methods for modifying the implants are being researched heavily by the scientific community [24]. The development of 3D printing technology has led to fabrication of biomaterials that have complex geometries and are customized according to the customer requirements [25, 26]. The 3D printing technology can also lead to replication of nano- and microscale features within the material. However, the main challenge of 3D printing technology is to enable the usage of nanoparticles and their melting, which are crucial for the complete assembly. Further, it is difficult to assess the impact of post- and preprocessing done on the implants using 3D printing technology.

The present work explores metallic biomaterials and the key strategies that have been adopted for surface and bulk modifications.

## 4.2 Permanent metallic bioimplants

The commonly used bioinert metals for angioplasty, fracture fixation, and remodeling of bone are Co-Cr alloys, Ti alloys, and surgical stainless steel [14]. These materials have numerous advantages such as excellent mechanical properties and therefore long-term stability in the highly reactive environment. However, the highly reactive

environment in which they function may lead to their degradation, which may in turn result in the release of undesired metallic ions. The released metallic ions cause inflammatory reactions such as osteolysis and may even lead to metal hypersensitivity [27]. The osteolysis undermines the fixation and interferes with the load transfer, resulting in failure of the implant and complications related to surgeries.

#### **4.2.1 *Stainless steel-based bioimplants***

Pure metals were considered as suitable material candidates for the fabrication of implants before the introduction of surgical stainless steel. The pure metals had lower mechanical strength as well as low corrosion resistance [28]. The limitations associated with the pure metals were overcome by the introduction of 18/8 stainless steel [29] which had relatively better corrosion resistance resulting in fewer complications after the surgery. The high percentage of chromium content, i.e., 12%, is the main reason behind the higher corrosion resistance of stainless steel. Together with the chromium content, stainless steel also possesses molybdenum and nickel. The formation of carbides of chromium takes place during high temperature treatment, which is taken care of by the limited carbon percentage ([http://www.worldstainless.org/Files/ISSF/Education/Module\\_03\\_Corrosion\\_Resistance\\_of\\_Stainless\\_Steels.pdf](http://www.worldstainless.org/Files/ISSF/Education/Module_03_Corrosion_Resistance_of_Stainless_Steels.pdf)).

Surgical stainless steel can be classified into Ni-free stainless steel or conventional stainless steel. Although the presence of nickel increases corrosion resistance, it also reduces the biocompatibility [30]. Therefore, to restrict the percentage of nickel, stainless steel is alloyed with nitrogen. The conventional stainless steel is used for load-bearing applications as well as for stents; however, the Ni-free stainless steels are used only for stents. The conventional stainless steel is less biocompatible and corrosion resistant than the titanium-based biomaterials, but the cost of titanium-based biomaterials is relatively higher than that of the stainless steel biomaterials. Also, stents function in a unique oxygen-rich environment where the risk of corrosion is minimized, and therefore the stents from stainless steel are more affordable and appropriate [31]. The carbon content in surgical stainless steel is <0.03%, which is about one-fifth of that present in other metallic biomaterials [32]. The better mechanical properties and ductility of stainless steel allow its usage for bone fracture treatments, where it is used in the form of nails, screws, etc. Fracture plates made from stainless steel provide for temporary support for tissue regeneration.

316L stainless steel is used for fabrication of low-cost copies of actual implants, which are used by surgeons for determination of the actual size of the implant during joint replacement surgery. The traditional approach entailed the use of actual implants, which required repeated cycles of decontamination and sterilization. The mechanical strength of the implant would be undermined because of the fatigue and corrosion induced due to the sterilization and decontamination process [33]. Frame proposed a different approach using laser sintering in fabrication of disposable low-cost copies of implants with 316L stainless steel.

SLS/SLM has been used in fabrication of dental implants with stainless steel. Liquid phase sintering is employed to melt the binding polymer with the aid of a laser beam, which is then used to bind the metal particles. The residual polymer is then

removed by heating the scaffold [34]. The implant of required density is then produced by further infiltration and sintering of bronze.

#### **4.2.2 Titanium and titanium alloy-based bioimplants**

Medical-grade titanium is a much better alternative for high loading rate applications because of its higher strength-to-weight ratio than stainless steel. One of the critical factors for the degree of distress to which the adjacent bones will be subjected is the weight of the alloy [35]. The strength of Ti alloys may be further enhanced with thermal aging, quenching, and annealing [36].

Alloying of Ti is another technique to enhance the mechanical strength of Ti material. For instance, alloying with 5.5–6.5 wt% aluminum and 3.5–4.5 wt% vanadium results in Ti-6Al-4V, which produces a Ti material that has better strength properties than the unalloyed Ti metal [37]. The hardness of Ti increases by 32% with the addition of Al, the other properties remaining intact (<http://www.totalmateria.com/article126.htm>). The strength as well as corrosion resistance of Ti increases with the addition of niobium [38, 39]. However, in cases where bending is of utmost importance for the implant function, the reduced ductility of Ti arising due to alloying leads to its unsuitability for such applications.

Ti lends itself for restoration of anatomically complex areas and its suitability for such applications is further enhanced with the involvement of 3D printing technology. The repair of bifrontal skull defects [40] and reconstruction of the orbital and maxillary floor [41] have been made possible with the 3D-printed titanium implants. The 3D-printed implants offer low operation time, superior aesthetics, long-term stability, and elimination of facial dysfunction in patients in comparison to the conventional system of screws and plates [42]. However, the 3D-printed titanium implants also show susceptibility to infection, as revealed in reconstruction of zygomatico-orbital defects [43].

A customized 3D-printed titanium prosthesis has also been produced for limb salvage surgery. The titanium prosthesis was used to replace the bones lost to scapular Ewing's sarcoma [44]. The implants from Ti-6Al-4V powder were fabricated using an electron beam system. The usage of an electron beam melting system overcomes the challenges arising because of the liquid Ti showing chemical affinity to atmospheric gases and also because of the low ductility of the Ti metal [45]. In order to bring the excessively high moduli closer to that of cortical bone, porosity was introduced into the structure. This was done to minimize stress shielding rather than promoting vascularization or tissue regeneration.

Titanium-based implants have also been produced using direct metal laser sintering (DMLS). The implants produced using DMLS have been used to support bar-retained maxillary overdentures, the survival rates being 97% and the biological complications at 7% [46]. The survival rates for unsplinted DMLS-produced Ti implants supporting ball attachment for mandibular overdentures were also reported to be similar [46, 47].

The integration of the gradients for porosity and Young's modulus for 3D Ti-6Al-4V dental implants is one of the main advantages of the selective laser sintering technique [48]. Sacrificial wax templates can be used for fabrication of Ti scaffolds

with improved anisotropic properties, such as compressive strength and porosity [49]. The durability of the scaffolds is affected significantly by the potentiality to reduce the discrepancies in architecture of the scaffolds [50].

The fatigue resistance of the fabricated dental implants is comparatively more than that of the highly porous titanium implants, which have been obtained using the traditional coating and spraying techniques. The fatigue resistance is 30% lower for the implants produced using traditional methods than those fabricated using the 3D printing technologies. The 3D printing techniques such as SLS also render simultaneous control over the micro- and nanostructures within the geometry as a whole. The other techniques such as solid-state foaming by expansion of the pores filled with argon, sintering of Ti fibers, etc., don't offer simultaneous control [51]. Implants with osseointegrative properties as well as biocompatibility characteristics are produced using the 3D printing techniques [52]. Improved bioresponse and osseointegrativity were shown by beagles implanted with Ti-6Al-4V implants as compared to acid-etched or alumina-blasted implants [53].

### **4.2.3 Cobalt-based bioimplants**

The resistance of Co-based implants is higher in comparison to the Ti alloy-based implants. The enhanced resistance has allowed the Co-based implants to be employed for artificial hip joints wherein wear due to direct contact between the bone plate and the femoral head may result. The combination of high strength and durability is one of the major advantages for the Co-Cr-Mo implants and therefore they are used widely [54]. The elastic modulus of Co-Cr alloy based implants is also relatively higher than the pure Ti or Ti alloys [55, 56].

The Co-Cr alloy-based implants have higher density and elastic modulus in comparison to bone [57]. These characteristics allow for greater stress shielding than that of Ti and Ti alloy-based implants [58]. However, the Co-Cr alloy-based implants have lower biocompatibility and osseointegration capacity than the Ti-based implants. Therefore, Ti-based implants are mainly used for the elements that make direct contact with the bone, whereas the elements such as the rods in spinal fixation that do not interfere with the bone directly are made using Co-Cr-based alloys. It has been, however, revealed that metal corrosion and shredding may result at the site making contact with the Ti or Co implants, due to increasing frictional load. The tissues near the metallic implants experience metallosis, as in the case of total hip arthroplasty, spinal fixation, and knee implants.

The excessive stiffness of the structure in the case of Co-Cr alloy-based implants for the 3D technique to be implemented can be overcome by the incorporation of nano- and microstructures within the bulk geometry. The incorporation and simultaneous control over the nano- and microstructures can result in implants with reduced elastic modulus. Further, the discrepancy of stiffness between the alloyed implants and the bone can also be eliminated using bulk modifications. Co-Cr-based implants with the desired pore architecture and macrogeometry can be produced using the electron beam machining (EBM) technique [59]. The implants showed around 28% contact with the bone when implanted into adult sheep femora for around 26 weeks. Although

this contact percentage was lower than that observed for Ti-6Al-4V implants, the apatite-collagen ratio, densification, and phosphate-carbonate ratio was similar for the Ti and Co-Cr alloy-based implants. Co-Cr porous structures also showed higher osteocyte density at their periphery [59].

Meshed and solid implants can be printed using EBM in addition to foam monoliths. Architecture of  $\text{Cr}_{23}\text{C}_6$  precipitates in the columnar directional form with spacing of around  $2\ \mu\text{m}$  has been observed for the foam ligaments and mesh struts from Co-29Cr-6Mo alloys. The microstructures reveal the directional solidification of the solid cylindrical components in the assembly process [60].

Fine cellular microstructures in CoCrMo implants have been observed when employing selective laser melting (SLM) for the fabrication of Co-based implants. The fine cellular microstructure was a result of subsequent rapid cooling and strong temperature gradients maintained during the melting of the alloy. The grain boundaries were observed to be depleted in Co and enriched in Mo. Such processing steps result in reduced formation of a martensitic  $\epsilon$  phase and minimize the precipitation of carbides at the surface. Further, a highly corrosion-resistant 3D printed implant results from using the SLM fabrication technique [61].

#### 4.2.4 Tantalum-based bioimplants

Tantalum has been investigated for many biomaterial applications owing to its excellent biocompatibility characteristics. The biocompatibility property has aimed tantalum-based bioimplants for environments where biocompatibility and corrosion resistance are the major requirements [62]. A  $\text{Ta}_2\text{O}_5$  protective film on the implant surface provides anticorrosion characteristics to tantalum-based bioimplants [63, 64]. Tantalum is one of the attractive materials for artificial joints because of its excellent bone-bonding characteristics. These can either be used for bulk materials or as a coating on titanium and stainless steel bioimplants, lending them better osseointegration and corrosion resistance [65–68].

The higher elastic modulus as well as the difficulty in fabrication with higher precision are the major limitations to the wider use of tantalum. The elastic modulus of tantalum is above 186 GPa and the density is around  $16.6\ \text{g}/\text{cm}^3$ . The elastic modulus is very high in comparison to cancellous bone (0.1–0.45 GPa) and cortical (10–16 GPa) and, therefore, because of this huge mismatch, the tantalum metal is detrimental [69, 70]. Further, a high melting temperature of around  $3020^\circ\text{C}$  is a major challenge for the bulk production of bioimplants based on tantalum. Patients have been observed to suffer from headaches because of the high conductivity of tantalum when used for cranioplasty [71].

Implants have been manufactured with 50 wt% of Ta and Ti using the SLM manufacturing technique. The Ta nanoparticles were randomly dispersed in the Ti-Ta matrix. Equiaxed grains of  $\beta$  phase Ti and Ta composed the matrix with a random orientation. This results in a  $\beta$  stabilizing effect and rapid solidification [72]. The fabricated Ti-Ta was revealed to possess a higher strength-to-modulus ratio than pure Ti and Ti-6Al-4V alloys.

## 4.3 Biodegradable metals

Biodegradable metals are one of the attractive alternatives to implants made from permanent metals for fracture fixations in cases where complete tissue regeneration is desired. Zinc (Zn), iron (Fe) and magnesium (Mg) are some of the best-explored biodegradable metals, used extensively for cardiovascular and orthopedic applications [73]. These biodegradable metals offer excellent in vivo biocompatibility, have the required mechanical strength to provide support to bone undergoing a regeneration process, and have a controlled degradation profile. The mechanical behavior of bioresorbable metals has been found to be far superior to the bioresorbable polymers [74]. The products of biodegradation of the biodegradable biometals are metabolized by the host cells, unlike the by-products of polymeric products, which result in necrosis and inflammatory issues [75].

### 4.3.1 Magnesium-based biodegradable implants

Magnesium possesses high specific strength among the other candidate biodegradable materials [76] and also has relatively lower density and elastic modulus. The elastic modulus is around 41 GPa and the density is  $1.75 \text{ g/cm}^3$ . These properties are very close to those of bone and therefore aid in minimization of risk pertaining to stress shielding [77]. The Mg-based implants such as rods, plates, and screws provide for the required mechanical strength and degrade gradually, thereby providing space for the regeneration of the bone tissue (<https://www.accessscience.com:443/content/biodegradable-metal-implants/BR0601151>). The gradual degradation leads to positive contribution to the strength and density of the bone, as there is a gradual increase in the force from the implant onto the bone. The biodegradable implant eventually will be fully degraded and thereby minimizes the metal-related sensitivity issues that occur with Co- or Ti-based implants.

The Mg-based biodegradable implants, however, have a rapid rate of corrosion, especially in environments full of biological fluids [78]. The rapid corrosion rate results in release of large  $\text{Mg}^{2+}$  ions, leading to untimely loss in the mechanical strength of the implants [79–81]. The release of hydrogen gas is also very rapid along with the corrosion rate, which may lead to formation of gas pockets around the implant [82]. Thus an extremely higher corrosion rate may hinder the regeneration of the bone. The degradation kinetics of Mg can be controlled via alloying.

The solid free-form (SFF) fabrication technique has been used in preparation of Mg scaffolds with ordered pore macrostructures. The use of SFF has resulted in higher resolution in terms of volume fraction, stiffness, and porosity [83]. Pore dimensions of 6% and 9% and surface roughness of around  $11 \mu\text{m}$  have been achieved with the SFF technology [83, 84]. The surface area achieved was high enough for efficient interactions between cells and surface.

### 4.3.2 Zinc-based biodegradable implants

Zinc is one of the important elements that play a crucial role in the functioning of proteins as well as the related structures. It is an essential element for the proper catalytic

functioning of more than 400 enzymes, including stabilization and folding of protein subdomains. Examples include proteins engaged in replication of nucleic acid, RNA polymerases, and DNA-binding of the factors related to eukaryotic transcription [85]. Since the environment of stent operation is such that most tissues in proximity have good tolerances to Zn ions, Zn is being explored for applications pertaining to bioresorbable metallic stents. The main processes responsible for the corrosion of zinc are the cathodic reduction of the oxygen dissolved and the anodic dissolution [75]. The corrosion rate is also affected with the pH level of the surrounding environment. The corrosion rate of Zn is comparatively lower than that of pure Mg.

Zn-based biodegradable stents do not lead to any inflammatory responses, which was evident when Zn stents were used for rat arteries. Zn and its alloys have also been explored for fixation of fractures, besides their applications for stents. Enhanced corrosion resistance as well as improved mechanical properties are obtained by combining Zn with Mg [73].

### **4.3.3 Iron-based biodegradable implants**

Fe also undergoes local corrosion in the presence of dissolved oxygen. The tendency of iron to dissolve is the lowest in comparison to the other biodegradable metals. The formation of a protective oxide layer over the surface is one of the major reasons for lower corrosion rates. The oxide layer on the surface of Fe acts as a barrier to the rapid degradation phenomenon. The investigations into usage of Fe-based stents have shown no inflammatory responses or thrombosis or excessive toxicity. High radial strength is one of the characteristic properties of Fe stents, which aids in fabrication of extremely thin stents. The ductility of the Fe stents is also higher and hence deployment into the arteries is much easier [75].

However, with the advantages are associated certain limitations that result in undesirable consequences. For instance, incomplete corrosion has been revealed for Fe stents. To avoid this, alloying has been suggested as an alternative, to increase the rate of degradation. However, control of the formation of by-products of iron oxide degradation as well as the influx of metallic ions into the surrounding tissues is required. The increased quantity of Fe in the system can lead to inflammation, damage to lipid membranes, an increment in free radicals, and damage to DNA and proteins [1].

Further, Fe-based bioimplants may interfere with magnetic resonance imaging (MRI) because of the magnetic nature of iron. A strong magnetic field may cause tremendous heating of the stents, resulting in change in shape as well as position of the stents. However, such effects have positive impacts that if harnessed could enhance the therapeutic outcome of any treatment. For instance, osseous tissue generation can be stimulated by employing porous scaffolds with iron nanoparticles. The intracellular pathways associated with bone formation are activated as a result of application of an external magnetic field [86]. Triggering of drug release can also be accomplished using external magnetic fields. The heat generated locally can be used for thermal therapy of cancer and also could treat any implant-associated infections.

## 4.4 Limitations of biomaterials

Metallic biomaterials are being used widely for the fabrication of different prosthetic parts. Thus it is essential to have knowledge of the limitations associated with these biomaterials. Also it is essential to understand the different strategies that could be adopted to overcome or minimize these limitations. The present section illuminates some of the limitations and the different strategies for overcoming such limitations.

### 4.4.1 *Biocompatibility*

Both permanent and biodegradable metal-based implants are biocompatible; the biocompatibility is negatively affected by untimely degradation and excessive wear. This may lead to hindrances in healing and hence to long-term damage [87]. The biocompatibility may also be reduced as a result of techniques used for enhancing the mechanical properties as well as the corrosion resistance of the material. For instance, inflammation in the tissues surrounding the implant increases with the addition of Ni or Ti [88]. Such issues can, however, be minimized to some extent by avoiding direct contact between the implants and the cells surrounding the implants. For instance, Co-Cr based rods can be affixed to the bone using biocompatible Ti screws [89]. Interactions between the host cells and the surface are also affected when employing strategies for preventing bacterial contamination. Using such strategies can also hinder osseointegration [90, 91].

The process of osseointegration as well as that of cell attachment is stimulated by additional surface roughness and porosity. The strategies for achieving such modifications range from sandblasting to laser ablation. For example, the required surface roughness over the implants can be produced by sandblasting Ti with large grit acid. This provides a suitable environment for growth and attachment of cells [92]. The surface modification strategies can directly affect the manner in which the surfaces and pathogenic microorganisms interact with each other [93, 94].

Biocompatibility can also be increased by bulk modifications such as those of alloying elements that stimulate for cell attachment and proliferation, introduction of porosity in a controlled manner, or changing the structure of the grains. Complex modifications such as providing complex interconnected architectures and channels have been made possible with the promising and emerging technology of 3D printing [95, 96]. The degradation profile of the material can be altered by increasing the surface area in contact with the corrosive implant surroundings. However, this may lead to development of sarcoma as result of substantial release of ions from the implants [97]. This can be minimized by using a thin film of polymer or ceramic as a coating on the surface of the 3D scaffolds.

A suitable modification technique must be selected that doesn't compromise the required dimensions and at the same time ensures connectivity of internal channels and pores. For metal scaffolds, techniques such as solvent casting or spray-, dip-, or spin-coatings can be used. These techniques produce a thin layer of a film that may suffer from nonuniformity of surface roughness, chemical functionalities, etc. [98]. The fine internal structures of the implants can be affected negatively with a nonuniform film thickness.

### 4.4.2 Surface colonization and formation of biofilm

The implants that promote host cell-surface modifications and simultaneously prevent the formation of biofilm are highly desired. The attachment of protein takes place on introducing an implant into the body of a patient, along with the colonization of the surface by the host and pathogenic cells [99]. In certain instances in which this colonization doesn't occur, long-term antimicrobial strategies are followed to prevent the formation of a biofilm [100, 101]. One of the strategies for the antibacterial coating includes the use of silver nanoparticles for Ti-based bioimplants.

One of the emerging and promising technological fields is plasma-based biomedical technologies, which have been used widely for decontamination at low temperatures in the food industry and for tissue regeneration [102–106]. Cellular activities are significantly altered when the cells are treated with plasma. This results in controlling the processes responsible for the formation of biofilm, carcinogenesis, and tissue regeneration [102, 103]. Plasma-enabled biomedical technologies are also used for carrying out long-lasting controlled surface modifications [93, 94]. This also includes chemical functionalization and deposition of films with antibacterial properties [107–109]. Plasma has also been used for the deposition of surface nanostructures of highly complex nature from a wide range of materials [17, 18, 110] that can aid in a wider control over the attachment behavior of microorganisms and cells.

Chemical gradients have been successfully obtained in 3D porous scaffolds using the technique of plasma deposition, resulting in enhanced cell viability in comparison to untreated materials [111–113]. It is also possible to add the different N- or O-functional groups and their combinations and to deposit nano- and microscale features throughout the porous structure [114].

## 4.5 Conclusions

The present work reviews the currently used biomaterials with their limitations and the strategies that have been adopted for their modifications. However, the need for new or modified materials can only address the challenges that are associated with the current implants. The biomaterials should not only minimize the medical complications but also should be aesthetically comfortable for the patients. Significant values can be associated with future biomaterials using the current material engineering techniques. The next-generation implants are to be manufactured using nanomaterials that can serve multiple purposes.

## References

- [1] D. Hong, D.T. Chou, O.I. Velikokhatnyi, A. Roy, B. Lee, I. Swink, P.N. Kumta, Binder-jetting 3D printing and alloy development of new biodegradable Fe-Mn-Ca/Mg alloys, *Acta Biomater.* 45 (2016) 375–386.
- [2] O.O. Ige, L.E. Umoru, S. Aribi, Natural products: a minefield of biomaterials, *ISRN Mater. Sci.* 2012 (2012).

- [3] J.Z. Lu, L.J. Wu, G.F. Sun, K.Y. Luo, Y.K. Zhang, J. Cai...X.M. Luo, Microstructural response and grain refinement mechanism of commercially pure titanium subjected to multiple laser shock peening impacts, *Acta Mater.* 127 (2017) 252–266.
- [4] P. Trivedi, K.C. Nune, R.D.K. Misra, S. Goel, R. Jayganthan, A. Srinivasan, Grain refinement to submicron regime in multiaxial forged Mg-2Zn-2Gd alloy and relationship to mechanical properties, *Mater. Sci. Eng. A* 668 (2016) 59–65.
- [5] S. Bhat, A. Kumar, Biomaterials and bioengineering tomorrow's healthcare, *Biomater* 3 (3) (2013) e24717.
- [6] J. Henkel, M.A. Woodruff, D.R. Epari, R. Steck, V. Glatt, I.C. Dickinson... D.W. Huttmacher, Bone regeneration based on tissue engineering conceptions—a 21st century perspective, *Bone Res.* 1 (2013) 216–248.
- [7] N. Hort, Y. Huang, D. Fechner, M. Störmer, C. Blawert, F. Witte...F. Feyerabend, Magnesium alloys as implant materials—principles of property design for Mg–RE alloys, *Acta Biomater.* 6 (5) (2010) 1714–1725.
- [8] M.P. Staiger, A.M. Pietak, J. Huadmai, G. Dias, Magnesium and its alloys as orthopedic biomaterials: a review, *Biomaterials* 27 (9) (2006) 1728–1734.
- [9] H. Wang, Y. Estrin, H. Fu, G. Song, Z. Zúberová, The effect of pre-processing and grain structure on the bio-corrosion and fatigue resistance of magnesium alloy AZ31, *Adv. Eng. Mater.* 9 (11) (2007) 967–972.
- [10] J. Zhang, C. Xu, Y. Jing, S. Lv, S. Liu, D. Fang...R. Wu, New horizon for high performance Mg-based biomaterial with uniform degradation behavior: formation of stacking faults, *Sci. Rep.* 5 (2015) 13933.
- [11] E.P. Ivanova, K. Bazaka, R.J. Crawford, *New Functional Biomaterials for Medicine and Healthcare*, Woodhead Publishing, Cambridge, UK, 2014.
- [12] A. Srivastav, An overview of metallic biomaterials for bone support and replacement, in: *Bioomedical Engineering*, Trends in Materials Science, InTech, 2011.
- [13] L. Pacifici, F. De Angelis, A. Orefici, A. Cielo, Metals used in maxillofacial surgery, *ORAL Implantol.* 9 (Suppl. 1/2016 to N 4/2016) (2016) 107.
- [14] M. Saini, Y. Singh, P. Arora, V. Arora, K. Jain, Implant biomaterials: a comprehensive review, *World J. Clin. Cases* 3 (1) (2015) 52.
- [15] M. Niinomi, M. Nakai, Titanium-based biomaterials for preventing stress shielding between implant devices and bone, *Int. J. Biomater.* 2011 (2011).
- [16] K. Bazaka, M.V. Jacob, Implantable devices: issues and challenges, *Electronics* 2 (1) (2012) 1–34.
- [17] K. Bazaka, M.V. Jacob, K. Ostrikov, Sustainable life cycles of natural-precursor-derived nanocarbons, *Chem. Rev.* 116 (1) (2015) 163–214.
- [18] K. Bazaka, M.V. Jacob, W. Chrzanowski, K. Ostrikov, Anti-bacterial surfaces: natural agents, mechanisms of action, and plasma surface modification, *RSC Adv.* 5 (60) (2015) 48739–48759.
- [19] M. Cappiello, R. Luongo, D. Di Iorio, C. Bugea, R. Cocchetto, R. Celletti, Evaluation of peri-implant bone loss around platform-switched implants, *Int. J. Periodontics Restorative Dent.* 28 (4) (2008) 347–355.
- [20] K. Prasad, O. Bazaka, M. Chua, M. Rochford, L. Fedrick, J. Spoor...D. Markwell, Metallic biomaterials: current challenges and opportunities, *Materials* 10 (8) (2017) 884.
- [21] L.D. Campelo, J.R.D. Camara, Flapless implant surgery: a 10-year clinical retrospective analysis, *Int. J. Oral Maxillofac. Implants* 17 (2) (2002).
- [22] K. Bazaka, M.V. Jacob, R.J. Crawford, E.P. Ivanova, Efficient surface modification of biomaterial to prevent biofilm formation and the attachment of microorganisms, *Appl. Microbiol. Biotechnol.* 95 (2) (2012) 299–311.

- [23] G.A. Van der Weijden, K.M. Van Bommel, S. Renvert, Implant therapy in partially edentulous, periodontally compromised patients: a review, *J. Clin. Periodontol.* 32 (5) (2005) 506–511.
- [24] S.V. Murphy, A. Atala, 3D bioprinting of tissues and organs, *Nat. Biotechnol.* 32 (8) (2014) 773.
- [25] K. Jakab, C. Norotte, F. Marga, K. Murphy, G. Vunjak-Novakovic, G. Forgacs, Tissue engineering by self-assembly and bio-printing of living cells, *Biofabrication* 2 (2) (2010) 022001.
- [26] V. Mironov, N. Reis, B. Derby, Bioprinting: a beginning, *Tissue Eng.* 12 (4) (2006) 631–634.
- [27] S.C. Mears, S.L. Kates, A guide to improving the care of patients with fragility fractures, edition 2, *Geriatr. Orthop. Surg. Rehabil.* 6 (2) (2015) 58–120.
- [28] H.K. Uthoff, P. Poitras, D.S. Backman, Internal plate fixation of fractures: short history and recent developments, *J. Orthop. Sci.* 11 (2) (2006) 118–126.
- [29] W.H. Hatfield, Rustless steels as applied to automobiles and aircraft, *Proc. Inst. Automobile Eng.* 25 (2) (1931) 285–304.
- [30] P. Ducheyne, D.H. Kohn, *Materials Science and Technology—A Comprehensive Treatment, Medical and Dental Materials*, Weinheim Vol. 14, 1998, pp. 39–41.
- [31] P. Driscoll, *Materials Used in Stent Construction*, Biddeford, ME, MedMarket Diligence, LLC, 2009.
- [32] M. Sumita, Present status and future trend of metallic materials used in orthopedics, *Orthop. Surg.* 48 (1997) 927–934.
- [33] M. Frame, Low cost orthopaedic implant trials created using 3D printing technology, *Bone Joint J.* 98 (Supp. 1) (2016) 134.
- [34] J.P. Kruth, B. Vandenbroucke, J. Van Vaerenbergh, I. Naert, in: *Rapid manufacturing of dental prostheses by means of selective laser sintering/melting*, Proceedings of the AFPR S, 4, 2005, pp. 176–186.
- [35] D.C. Hansen, Metal corrosion in the human body: the ultimate bio-corrosion scenario, *Electrochem. Soc. Interface* 17 (2) (2008) 31.
- [36] O. Mouzin, K. Søballe, J.E. Bechtold, Loading improves anchorage of hydroxyapatite implants more than titanium implants, *J. Biomed. Mater. Res. A* 58 (1) (2001) 61–68.
- [37] X. Zhao, M. Niinomi, M. Nakai, T. Ishimoto, T. Nakano, Development of high Zr-containing Ti-based alloys with low Young's modulus for use in removable implants, *Mater. Sci. Eng. C* 31 (7) (2011) 1436–1444.
- [38] H. Nakada, T. Sakae, Y. Tanimoto, M. Teranishi, T. Kato, T. Watanabe...R.Z. LeGeros, Assessment of the quality of newly formed bone around titanium alloy implants by using X-ray photoelectron spectroscopy, *Int. J. Biomater.* 2012 (2012).
- [39] S.L.M. Ribeiro Filho, C.H. Lauro, A.H.S. Bueno, L.C. Brandão, Effects of the dynamic tapping process on the biocompatibility of Ti-6Al-4V alloy in simulated human body environment, *Arab. J. Sci. Eng.* 41 (11) (2016) 4313–4326.
- [40] I. Levchenko, K.K. Ostrikov, J. Zheng, X. Li, M. Keidar, K.B. Teo, Scalable graphene production: perspectives and challenges of plasma applications, *Nanoscale* 8 (20) (2016) 10511–10527.
- [41] B. Lethaus, P. Kessler, R. Boeckman, L.J. Poort, R. Tolba, Reconstruction of a maxillary defect with a fibula graft and titanium mesh using CAD/CAM techniques, *Head Face Med* 6 (1) (2010) 16.
- [42] K. Malhotra, A. Sharma, G. Giraddi, A.K. Shahi, Versatility of titanium 3D plate in comparison with conventional titanium miniplate fixation for the management of mandibular fracture, *J. Maxillofac. Oral Surg.* 11 (3) (2012) 284–290.

- [43] J. Li, P. Li, H. Lu, L. Shen, W. Tian, J. Long, W. Tang, Digital design and individually fabricated titanium implants for the reconstruction of traumatic zygomatico-orbital defects, *J. Craniofac. Surg.* 24 (2) (2013) 363–368.
- [44] H. Fan, J. Fu, X. Li, Y. Pei, X. Li, G. Pei, Z. Guo, Implantation of customized 3-D printed titanium prosthesis in limb salvage surgery: a case series and review of the literature, *World J. Surg. Oncol.* 13 (1) (2015) 308.
- [45] S. Ponader, C. Von Wilmsowsky, M. Widenmayer, R. Lutz, P. Heintl, C. Körner... K.A. Schlegel, In vivo performance of selective electron beam-melted Ti-6Al-4V structures, *J. Biomed. Mater. Res. A* 92 (1) (2010) 56–62.
- [46] F. Mangano, F. Luongo, J.A. Shibli, S. Anil, C. Mangano, Maxillary overdentures supported by four splinted direct metal laser sintering implants: a 3-year prospective clinical study, *Int. J. Dent.* 2014 (2014).
- [47] F. Mangano, S. Pozzi-Taubert, P.A. Zecca, G. Luongo, R.L. Sammons, C. Mangano, Immediate restoration of fixed partial prostheses supported by one-piece narrow-diameter selective laser sintering implants: a 2-year prospective study in the posterior jaws of 16 patients, *Implant. Dent.* 22 (4) (2013) 388–393.
- [48] T. Traini, C. Mangano, R.L. Sammons, F. Mangano, A. Macchi, A. Piattelli, Direct laser metal sintering as a new approach to fabrication of an isoelastic functionally graded material for manufacture of porous titanium dental implants, *Dent. Mater.* 24 (11) (2008) 1525–1533.
- [49] G.E. Ryan, A.S. Pandit, D.P. Apatsidis, Porous titanium scaffolds fabricated using a rapid prototyping and powder metallurgy technique, *Biomaterials* 29 (27) (2008) 3625–3635.
- [50] C. Mangano, M. Raspanti, T. Traini, A. Piattelli, R. Sammons, Stereo imaging and cytocompatibility of a model dental implant surface formed by direct laser fabrication, *J. Biomed. Mater. Res. A* 88 (3) (2009) 823–831.
- [51] S. Tunchel, A. Blay, R. Kolerman, E. Mijiritsky, J.A. Shibli, 3D printing/additive manufacturing single titanium dental implants: a prospective multicenter study with 3 years of follow-up, *Int. J. Dent.* 2016 (2016).
- [52] C. Mangano, A. De Rosa, V. Desiderio, R. d'Aquino, A. Piattelli, F. De Francesco... G. Papaccio, The osteoblastic differentiation of dental pulp stem cells and bone formation on different titanium surface textures, *Biomaterials* 31 (13) (2010) 3543–3551.
- [53] L. Witek, C. Marin, R. Granato, E.A. Bonfante, F. Campos, J. Bisinotto...P.G. Coelho, Characterization and in vivo evaluation of laser sintered dental endosseous implants in dogs, *J. Biomed. Mater. Res. B Appl. Biomater.* 100 (6) (2012) 1566–1573.
- [54] M. Niinomi, Recent metallic materials for biomedical applications, *Metall. Mater. Trans. A* 33 (3) (2002) 477.
- [55] A. Aherwar, A.K. Singh, A. Patnaik, Cobalt based alloy: a better choice biomaterial for hip implants, *Trends Biomater. Artif. Organs* 30 (1) (2016) 50–55.
- [56] S.J. Li, R. Yang, S. Li, Y.L. Hao, Y.Y. Cui, M. Niinomi, Z.X. Guo, Wear characteristics of Ti-Nb-Ta-Zr and Ti-6Al-4V alloys for biomedical applications, *Wear* 257 (9–10) (2004) 869–876.
- [57] Y. Li, C. Yang, H. Zhao, S. Qu, X. Li, Y. Li, New developments of Ti-based alloys for biomedical applications, *Materials* 7 (3) (2014) 1709–1800.
- [58] S. Nayak, B. Bhushan, R. Jayaganthan, P. Gopinath, R.D. Agarwal, D. Lahiri, Strengthening of Mg based alloy through grain refinement for orthopaedic application, *J. Mech. Behav. Biomed. Mater.* 59 (2016) 57–70.
- [59] F.A. Shah, O. Omar, F. Suska, A. Snis, A. Matic, L. Emanuelsson...A. Palmquist, Long-term osseointegration of 3D printed CoCr constructs with an interconnected open-pore architecture prepared by electron beam melting, *Acta Biomater.* 36 (2016) 296–309.

- [60] L.E. Murr, K.N. Amato, S.J. Li, Y.X. Tian, X.Y. Cheng, S.M. Gaytan...R.B. Wicker, Microstructure and mechanical properties of open-cellular biomaterials prototypes for total knee replacement implants fabricated by electron beam melting, *J. Mech. Behav. Biomed. Mater.* 4 (7) (2011) 1396–1411.
- [61] Y.S. Hedberg, B. Qian, Z. Shen, S. Virtanen, I.O. Wallinder, In vitro biocompatibility of CoCrMo dental alloys fabricated by selective laser melting, *Dent. Mater.* 30 (5) (2014) 525–534.
- [62] R.S. Namur, K.M. Reyes, C.E.B. Marino, Growth and electrochemical stability of compact tantalum oxides obtained in different electrolytes for biomedical applications, *Mater. Res.* 18 (2015) 91–97.
- [63] D. Cristea, I. Ghiuta, D. Munteanu, Tantalum based materials for implants and prostheses applications, *Bull. Transilvania Univ. Brasov Ser. I Eng. Sci.* 8 (2) (2015) 151.
- [64] N. Wang, H. Li, J. Wang, S. Chen, Y. Ma, Z. Zhang, Study on the anticorrosion, biocompatibility, and osteoinductivity of tantalum decorated with tantalum oxide nanotube array films, *ACS Appl. Mater. Interfaces* 4 (9) (2012) 4516–4523.
- [65] V.K. Balla, S. Banerjee, S. Bose, A. Bandyopadhyay, Direct laser processing of a tantalum coating on titanium for bone replacement structures, *Acta Biomater.* 6 (6) (2010) 2329–2334.
- [66] M. Roy, V.K. Balla, A. Bandyopadhyay, S. Bose, MgO-doped tantalum coating on Ti: microstructural study and biocompatibility evaluation, *ACS Appl. Mater. Interfaces* 4 (2) (2012) 577–580.
- [67] P. Sevilla, C. Aparicio, J.A. Planell, F.J. Gil, Comparison of the mechanical properties between tantalum and nickel–titanium foams implant materials for bone ingrowth applications, *J. Alloys Compd.* 439 (1–2) (2007) 67–73.
- [68] M. Stiehler, M. Lind, T. Mygind, A. Baatrup, A. Dolatshahi-Pirouz, H. Li...C. Bünger, Morphology, proliferation, and osteogenic differentiation of mesenchymal stem cells cultured on titanium, tantalum, and chromium surfaces, *J. Biomed. Mater. Res. A* 86 (2) (2008) 448–458.
- [69] Y. Liu, C. Bao, D. Wismeijer, G. Wu, The physicochemical/biological properties of porous tantalum and the potential surface modification techniques to improve its clinical application in dental implantology, *Mater. Sci. Eng. C* 49 (2015) 323–329.
- [70] T. Lu, J. Wen, S. Qian, H. Cao, C. Ning, X. Pan...P.K. Chu, Enhanced osteointegration on tantalum-implanted polyetheretherketone surface with bone-like elastic modulus, *Biomaterials* 51 (2015) 173–183.
- [71] A.M. Shah, H. Jung, S. Skirboll, Materials used in cranioplasty: a history and analysis, *Neurosurg. Focus.* 36 (4) (2014) E19.
- [72] S.L. Sing, W.Y. Yeong, F.E. Wiria, Selective laser melting of titanium alloy with 50 wt% tantalum: microstructure and mechanical properties, *J. Alloys Compd.* 660 (2016) 461–470.
- [73] M. Heiden, E. Walker, L. Stanciu, Magnesium, iron and zinc alloys, the trifecta of bioresorbable orthopaedic and vascular implantation—a review, *J. Biotechnol. Biomater.* 5 (2) (2015) 1.
- [74] D. Zhao, F. Witte, F. Lu, J. Wang, J. Li, L. Qin, Current status on clinical applications of magnesium-based orthopaedic implants: a review from clinical translational perspective, *Biomaterials* 112 (2017) 287–302.
- [75] P.K. Bowen, E.R. Shearier, S. Zhao, R.J. Guillory, F. Zhao, J. Goldman, J.W. Drelich, Biodegradable metals for cardiovascular stents: from clinical concerns to recent Zn alloys, *Adv. Healthc. Mater.* 5 (10) (2016) 1121–1140.

- [76] D. Persaud-Sharma, A. McGoron, Biodegradable magnesium alloys: a review of material development and applications, *J. Biomim. Biomater. Tissue Eng.* 12 (2011) 25–39. Trans Tech Publications.
- [77] T.S. Shih, W.S. Liu, Y.J. Chen, Fatigue of as-extruded AZ61A magnesium alloy, *Mater. Sci. Eng. A* 325 (1–2) (2002) 152–162.
- [78] H.S. Brar, M.O. Platt, M. Sarntinoranont, P.I. Martin, M.V. Manuel, Magnesium as a biodegradable and bioabsorbable material for medical implants, *JOM* 61 (9) (2009) 31–34.
- [79] A. Atrens, M. Liu, N.I.Z. Abidin, Corrosion mechanism applicable to biodegradable magnesium implants, *Mater. Sci. Eng. B* 176 (20) (2011) 1609–1636.
- [80] K. Bazaka, N. Ketheesan, M.V. Jacob, Polymer encapsulation of magnesium to control biodegradability and biocompatibility, *J. Nanosci. Nanotechnol.* 14 (10) (2014) 8087–8093.
- [81] N.T. Kirkland, N. Birbilis, M.P. Staiger, Assessing the corrosion of biodegradable magnesium implants: a critical review of current methodologies and their limitations, *Acta Biomater.* 8 (3) (2012) 925–936.
- [82] G. Song, S. Song, A possible biodegradable magnesium implant material, *Adv. Eng. Mater.* 9 (4) (2007) 298–302.
- [83] T.L. Nguyen, M.P. Staiger, G.J. Dias, T.B. Woodfield, A novel manufacturing route for fabrication of topologically-ordered porous magnesium scaffolds, *Adv. Eng. Mater.* 13 (9) (2011) 872–881.
- [84] M.P. Staiger, I. Kolbeinsson, N.T. Kirkland, T. Nguyen, G. Dias, T.B. Woodfield, Synthesis of topologically-ordered open-cell porous magnesium, *Mater. Lett.* 64 (23) (2010) 2572–2574.
- [85] J.E. Coleman, Zinc proteins: enzymes, storage proteins, transcription factors, and replication proteins, *Annu. Rev. Biochem.* 61 (1) (1992) 897–946.
- [86] A. Ortolani, M. Bianchi, M. Mosca, S. Caravelli, M. Fuiano, M. Marcacci, A. Russo, The prospective opportunities offered by magnetic scaffolds for bone tissue engineering: a review, *Joints* 4 (4) (2016) 228.
- [87] J. Autian, Biological model systems for the testing of the toxicity of biomaterials, in: *Polymers in Medicine and Surgery*, Springer, Boston, MA, 1975, pp. 181–203.
- [88] T.P. Chaturvedi, Corrosive behaviour of implant biomaterials in oral environment, *Mater. Technol.* 31 (12) (2016) 689–695.
- [89] J.J. Jacobs, A.K. Skipor, P.F. Doorn, P. Campbell, T.P. Schmalzried, J. Black, H.C. Amstutz, Cobalt and chromium concentrations in patients with metal on metal total hip replacements, *Clin. Orthop. Relat. Res.* 329 (1996) S256–S263.
- [90] D. Campoccia, L. Montanaro, C.R. Arciola, The significance of infection related to orthopedic devices and issues of antibiotic resistance, *Biomaterials* 27 (11) (2006) 2331–2339.
- [91] R.O. Darouiche, Treatment of infections associated with surgical implants, *N. Engl. J. Med.* 350 (14) (2004) 1422–1429.
- [92] R.Z. Valiev, I.P. Semenova, V.V. Latysh, H. Rack, T.C. Lowe, J. Petruzelka...J. Sochová, Nanostructured titanium for biomedical applications, *Adv. Eng. Mater.* 10 (8) (2008).
- [93] K. Bazaka, R.J. Crawford, E.P. Ivanova, Do bacteria differentiate between degrees of nanoscale surface roughness? *Biotechnol. J.* 6 (9) (2011) 1103–1114.
- [94] K. Bazaka, M.V. Jacob, R.J. Crawford, E.P. Ivanova, Plasma-assisted surface modification of organic biopolymers to prevent bacterial attachment, *Acta Biomater.* 7 (5) (2011) 2015–2028.

- [95] H.N. Chia, B.M. Wu, Recent advances in 3D printing of biomaterials, *J. Biol. Eng.* 9 (1) (2015) 4.
- [96] S.J. Hollister, Porous scaffold design for tissue engineering, *Nat. Mater.* 4 (7) (2005) 518.
- [97] S.F.S. Shirazi, S. Gharehkhani, M. Mehrali, H. Yarmand, H.S.C. Metselaar, N.A. Kadri, N.A.A. Osman, A review on powder-based additive manufacturing for tissue engineering: selective laser sintering and inkjet 3D printing, *Sci. Technol. Adv. Mater.* 16 (3) (2015) 033502.
- [98] J. Vaithilingam, S. Kilsby, R.D. Goodridge, S.D. Christie, S. Edmondson, R.J. Hague, Functionalisation of Ti6Al4V components fabricated using selective laser melting with a bioactive compound, *Mater. Sci. Eng. C* 46 (2015) 52–61.
- [99] V.T. Pham, V.K. Truong, A. Orłowska, S. Ghanaati, M. Barbeck, P. Booms... C.J. Kirkpatrick, “Race for the surface”: eukaryotic cells can win, *ACS Appl. Mater. Interfaces* 8 (34) (2016) 22025–22031.
- [100] V. Antoci Jr., C.S. Adams, J. Parvizi, H.M. Davidson, R.J. Composto, T.A. Freeman... N.J. Hickok, The inhibition of *Staphylococcus epidermidis* biofilm formation by vancomycin-modified titanium alloy and implications for the treatment of periprosthetic infection, *Biomaterials* 29 (35) (2008) 4684–4690.
- [101] S. Fujimura, T. Sato, S. Hayakawa, M. Kawamura, E. Furukawa, A. Watanabe, Antimicrobial efficacy of combined clarithromycin plus daptomycin against biofilms-formed methicillin-resistant *Staphylococcus aureus* on titanium medical devices, *J. Infect. Chemother.* 21 (10) (2015) 756–759.
- [102] M. Ishaq, K. Bazaka, K. Ostrikov, Pro-apoptotic NOXA is implicated in atmospheric-pressure plasma-induced melanoma cell death, *J. Phys. D. Appl. Phys.* 48 (46) (2015) 464002.
- [103] M. Ishaq, K. Bazaka, K. Ostrikov, Intracellular effects of atmospheric-pressure plasmas on melanoma cancer cells, *Phys. Plasma.* 22 (12) (2015) 122003.
- [104] M. Ishaq, A. Rowe, K. Bazaka, M. Krockenberger, M.D. Evans, K.K. Ostrikov, Effect of atmospheric-pressure plasmas on drug resistant melanoma: the challenges of translating in vitro outcomes into animal models, *Plasma Med.* 6 (1) (2016) 67–83.
- [105] X.Q. Wang, F.P. Wang, W. Chen, J. Huang, K. Bazaka, K.K. Ostrikov, Non-equilibrium plasma prevention of *Schistosoma japonicum* transmission, *Sci. Rep.* 6 (2016) 35353.
- [106] R. Zhou, R. Zhou, X. Zhang, J. Li, X. Wang, Q. Chen, K.K. Ostrikov, Synergistic effect of atmospheric-pressure plasma and TiO<sub>2</sub> photocatalysis on inactivation of *Escherichia coli* cells in aqueous media, *Sci. Rep.* 6 (2016) 39552.
- [107] J. Ahmad, K. Bazaka, M.V. Jacob, Optical and surface characterization of radio frequency plasma polymerized 1-isopropyl-4-methyl-1, 4-cyclohexadiene thin films, *Electronics* 3 (2) (2014) 266–281.
- [108] M.V. Jacob, K. Bazaka, D. Taguchi, T. Manaka, M. Iwamoto, Electron-blocking hole-transport polyterpenol thin films, *Chem. Phys. Lett.* 528 (2012) 26–28.
- [109] M.V. Jacob, N.S. Olsen, L.J. Anderson, K. Bazaka, R.A. Shanks, Plasma polymerised thin films for flexible electronic applications, *Thin Solid Films* 546 (2013) 167–170.
- [110] M.V. Jacob, R.S. Rawat, B. Ouyang, K. Bazaka, D.S. Kumar, D. Taguchi... O.K. Varghese, Catalyst-free plasma enhanced growth of graphene from sustainable sources, *Nano Lett.* 15 (9) (2015) 5702–5708.
- [111] F. Intranuovo, R. Gristina, F. Brun, S. Mohammadi, G. Ceccone, E. Sardella... P. Favia, Plasma modification of PCL porous scaffolds fabricated by solvent-casting/particulate-leaching for tissue engineering, *Plasma Process. Polym.* 11 (2) (2014) 184–195.

- [112] L. Safinia, N. Datan, M. Höhse, A. Mantalaris, A. Bismarck, Towards a methodology for the effective surface modification of porous polymer scaffolds, *Biomaterials* 26 (36) (2005) 7537–7547.
- [113] Y. Wan, C. Tu, J. Yang, J. Bei, S. Wang, Influences of ammonia plasma treatment on modifying depth and degradation of poly (L-lactide) scaffolds, *Biomaterials* 27 (13) (2006) 2699–2704.
- [114] M. Domingos, F. Intranuovo, A. Gloria, R. Gristina, L. Ambrosio, P.J. Bártolo, P. Favia, Improved osteoblast cell affinity on plasma-modified 3-D extruded PCL scaffolds, *Acta Biomater.* 9 (4) (2013) 5997–6005.

## Further reading

- [115] F.G. Mangano, A. Caprioglio, L. Levrini, D. Farronato, P.A. Zecca, C. Mangano, Immediate loading of mandibular overdentures supported by one-piece, direct metal laser sintering mini-implants: a short-term prospective clinical study, *J. Periodontol.* 86 (2) (2015) 192–200.