Revision 1

Calcium (Ti, Zr) hexaorthophosphate bioceramics for electrically stimulated biomedical implant devices. A position paper.

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Abstract

Osseointegration of biomedical implants as well as healing of broken bones are supported by novel bioceramic materials that, owing to their engineered ionic conductivity, in the presence of an electric field provide accumulation of negative electrical charges close to the interface between an implant and living bone tissue, thus stimulating the rate of bone growth. In this position paper, the structure as well as the chemical, electrical, and biomedical properties of Ca (Ti,Zr) hexaorthophosphates are reviewed. In addition, based on evaluation of the material's properties, a conceptual configuration of a capacity-coupled bone growth stimulator will be presented. The advantage of the proposed novel device over already existing bone-growth stimulators is its provision of the intimate contact of a capacity-coupled electric field with the growing bone tissue as opposed to an externally applied inductively-coupled electromagnetic field, which suffers substantial attenuation when transmitted through soft tissue covering the locus of bone growth. To achieve higher ionic conductivity in Ca (Ti,Zr) hexaorthophosphates, aliovalent doping with highly mobile Na or Li ions intercalated into the only partially occupied M1 sites appears to be a suitable route.

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Introduction

Worldwide, there is an increasing demand for load-bearing hip, knee, and dental endoprosthetic implants, for bone replacement parts in cranial, maxillar-mandibular, and spinal areas, for the ossicular chain of the inner ear, for periodontal pocket obliteration, percutaneous access devices, alveolar ridge and iliac crest augmentation, and osteosynthetic devices for bone healing (Heimann and Lehmann 2015). In 2011, in the United States, 204 total hip arthroplasties were performed per 100,000 population (Dotinga 2015). With 284 cases per 100,000 population, Germany's figure was even higher (Wengler et al. 2014). In Australia, 83 hip arthroplasties per 100,000 population were performed in 2004, increasing to 104 per 100,000 population in 2014 (Bourlioufas 2016). This high and growing demand is the result of the wear and tear the joints providing the ambulatory kinematics suffer during a human lifetime but is also caused by degenerative diseases such as osteoarthritis, rheumatoid arthritis, and osteoporosis, and damage caused by physical harm from external sources.

Arguably, total hip replacement (THR) is one of the most successful and safe surgical procedures today. It combines a sophisticated surgical technique and reliable pain reduction with few limitation during daily activities, in addition to acceptable longevity of the implant and a high success rate should a revision operation be required. State-of-the-art technology features implants with Ti6Al4V alloy shafts, plasma spray-coated with hydroxylapatite (Heimann 2006b) and equipped with an alumina femoral ball articulating against an acetabular cup solidly anchored in the hipbone. The acetabular cup consists of a cp (commercially pure)-titanium shell, lined with cross-linked (XLPE) or ultrahigh-density polyethylene (UHDPE) to assure a low coefficient of friction. Since the synovial fluid acting

in healthy joints as a lubricant is absent in artificial joints, it is vital to select synthetic materials that can achieve the required low friction coefficient. Hence, acetabular cups with alumina inserts are increasingly used to articulate against an alumina ball. This tribological pair exhibits a particularly low coefficient of friction, resulting in linear wear rates of < 5 µm/year (Heimann and Willmann 1998). Recently, femoral balls of alumina-zirconia composite ceramics reinforced with chromium oxide particles (Biolox delta™, Kuntz 2014) are employed and demonstrate linear wear rates < 1 µm/year.

Currently, coating the metal stem of hip endoprosthetic implants by atmospheric plasma spraying (APS) of hydroxylapatite powder with particle diameters of tens to hundreds of micrometers is the most popular, and the only Food and Drug Administration (FDA)-approved, method to coat implant surfaces for clinical use (Heimann 2016). Unfortunately, thermal decomposition of incongruently melting hydroxylapatite in the extremely hot plasma jet, formation of amorphous calcium phosphate (ACP) deposits by quenching of superheated molten particles, enhanced dissolution of the coating in contact with biofluid *in vivo*, and adhesion failure at the coating-metal substrate interface are notorious limitations to this approach. To mitigate these problems, calcium (titanium, zirconium) orthophosphates may be good candidates, providing dense, well-adhering coatings with excellent biocompatibility and osseoconductivity (ability to promote *de novo* formation of bone) as well as comparatively high thermal stability and low solubility *in vivo*. As an added bonus, such compounds will attain substantial ionic conductivity when doped with highly mobile ions such as sodium or lithium that are able to move in response to an electric field within the cavities of the crystalline structure.

Present and future economic advantages of research into such improved implant systems (for example, Eliaz and Metoki 2017) are to be seen in the context of a strongly accelerating

worldwide sales trend of endoprosthetic implants, i.e. artificial devices placed inside the body and used to replace a diseased or missing body part. Today, the worldwide sales of hip and knee orthopaedic surgical joint replacement products are US$ 16.7 billion, anticipated to double by 2022 to reach US$ 33 billion (Winter Green Research 2016). It is evident that such strong health demands should stimulate mineralogists/materials scientists to re-look at the structures and properties of known minerals with a view towards "tweaking" them for renewed or novel service to society.

If the recovery time after a THR operation can be reduced by even a small margin due to accelerated healing of the operational trauma site as well as faster bone in-growth, the overall positive effect on the well-being of the patient, as well as the economy, would be substantial. Speeding up the healing process might be achieved by using an electric field to accelerate bone growth. Such technology could also be applied to construct novel osteosynthetic devices, i.e., surgical fixtures that stabilize and join the ends of fractured bones such as metal plates, pins, or screws. They are designed to increase the healing rate of fresh fractures and osteotomies, i.e., surgical procedures of cutting a bone to either lengthen, shorten, or straighten it, spinal fusions (Gan and Glazer 2006), and delayed or nonunion (pseudoarthrosis) fractures (Griffin et al. 2011) that presently account for up to 10% of all clinically treated bone fractures.

In this position paper, ways will be discussed to construct such devices to accelerate bone healing. Materials need to be developed that combine high biocompatibility, strong osseoconductivity, and low to moderate solubility in the aggressive body environment together with sufficient adhesion to the metallic implant surface, a thermal expansion compatible with that of Ti alloy, and sustainable ionic conductivity. Many of these required properties can be found in transition metal-substituted calcium hexaorthophosphates. Hence,

for some time research has been underway to adapt these structures to design novel improved bioceramics (for example Lugscheider et al. 1995).

Structure of calcium (Ti,Zr) hexaorthophosphates

Calcium titanium hexaorthophosphate, $CaTi_4(PO_4)_6$ and calcium zirconium hexaorthophosphate, $CaZr_4(PO_4)_6$ are members of the NASICON (Na superionic conductor) family, the prototype of which is $NaZr_2(PO_4)_3$ (NZP) (Alamo 1993). The rare natural mineral kosnarite, $KZr_2(PO_4)_3$ (Šljukić et al. 1969; Brownfield et al. 1993), found as a late-stage hydrothermal mineral in some pegmatites, also belongs to this structural group. Related naturally occurring alkali zirconium beryllium phosphates (crystal class 4/mmm, space group $I4_1/amd$) include the rare minerals gainesite, $Na_2Zr_2Be^{[4]}[PO_4]_4 \cdot 1.5H_2O$ (Moore et al. 1983), selwynite, $NaKZr_2Be^{[4]}[PO_4]_4 \cdot 2H_2O$ (Birch et al. 1995) and its Cs analogue, mccrillisite, $NaCsZr_2Be^{[4]}[PO_4]_4 \cdot 1-2H_2O$ (Foord et al. 1994).

The NASICON structure exhibits the highly desirable properties of a low coefficient of linear thermal expansion (Agrawal and Stubican 1985), high thermal shock resistance, low solubility (Scheetz et al. 1994), high radiation and temperature stability, as well as substantial ionic conductivity (Roy et al. 1984; Anantharamulu et al. 2011). The structural formula is $[M1][M2][A^{VI}_2][B^{IV}_3]O_{12}$, whereby M1 and M2 are interstitial vacancy sites, either partially or fully occupied by cations. Small highly charged ions such as Zr or Ti occupy the octahedral A-sites, and Si or P fill the tetrahedral B-sites. Many members of the NASICON group crystallize in the rhombohedral space group $R\bar{3}c$ (space group 167; Hagman and Kierkegaard 1968). The structure consists of vertex-linked $[TiO_6]$ and/or $[ZrO_6]$ octahedra that form chains parallel to the c axis (Fig. 1). These chains are linked by $[PO_4]$ tetrahedra perpendicular to the c axis, resulting in a three-dimensional network. This configuration allows for two kinds of

cavities, M1 and M2; mobile Na cations occupy the M1 cavities, which also align along the *c* axis.

When the monovalent Na or K cations are substituted by a divalent cation such as Ca, the symmetry is lowered to $R\bar{3}$ (space group 148). This happens by ordering of cations and vacancies in the M2 cavities (Woodcock et al. 1999), a configuration that leads to the loss of the *c* glide plane owing to the fact that half the M1 sites are vacant (Alamo 1993). The smaller M2 cavities located between the chains are normally empty and only filled if additional ion contributions are required for charge compensation. The M1 site can be either completely empty as in the case of $\square Nb^{4+}Nb^{5+}(PO_4)_3$ (Leclaire et al. 1989) or partially filled as in $\square_{0.5}Ca^{2+}_{0.5}Ti_2(PO_4)_3$ and $\square_{0.66}La^{3+}_{0.33}Ti_2(PO_4)_3$ (Senbhagaraman et al. 1993).

Properties of calcium (Ti,Zr) hexaorthophosphates

Chemical variability

A characteristic feature of NaSiCON structures is their high chemical flexibility. They can incorporate an unusually large array of cations with oxidation states varying from +1 to +5, a broad Shannon ionic radii range (Shannon 1976) from 0.53 to 1.65 Å, and Pauling electronegativity from 0.9 to 1.7 (Orlova 2002; Vance and Gregg 2012). Vacancy sites account for the structural and chemical variability of the NaSiCON family as well as their remarkable ionic conductivity. Consequently, these materials are considered near universal hosts for radioactive waste immobilization with the potential to accommodate within their crystal structure not only the common nuclear fission products Cs and Sr but also actinides such as Pu, Am, and Cm (Scheetz et al. 1994; Vance and Gregg 2012).

Solubility

In protein-free simulated body fluid (TRIS (tris[hydroxymethyl]aminomethan)-HCl buffer; Kokubo et al. 1990), calcium (Ti, Zr) hexaorthophosphate ceramics show solubility at least one order of magnitude lower than that of hydroxylapatite and, in particular, tricalcium phosphate (Schneider 2002). Figure 2 shows the solubility of several proposed bioceramic materials in protein-free simulated body fluid (pf-SBF). Since the $CaTiZr_3(PO_4)_6$ composition exhibited the lowest solubility (position F in Fig. 2), this composition has been considered a potential bioceramic material with high biostability *in vitro* (Szmukler-Moncler et al. 1992; Schneider et al. 1998; Schneider 2002). Hence, in subsequent experiments this composition was selected. The composition $CaTi_4(PO_4)_6$ (position C in Fig. 2) has been suggested as a long-term stable carrier for immobilization of enzymes (Suzuki et al. 1991).

Powder synthesis and coating deposition

Plasma-sprayed hydroxylapatite is still considered the 'gold standard' of osseoconductive biomedical coatings (Campbell 2003; Demnati et al. 2014; Heimann 2016), but preliminary experiments have been performed to test calcium hexaorthophosphate compounds containing transition metals such as titanium and zirconium (Lugscheider et al. 1995; Reisel 1996; Schneider et al. 1998, 2001; Heimann 2006a).

Ceramic powder with the target composition $CaTiZr_3(PO_4)_6$ was synthesized by solid state reaction of mixed oxides, using stoichiometric amounts of $CaCO_3$ (Merck; 99% purity), TiO_2 (Riedel-deHaen; 99.5% purity) and ZrO_2 (ChemPur; 99.9% purity), mixed with H_3PO_4 (Merck; 85% purity). The mixture was homogenized, dried between 150 and 170°C for 27

hours, milled and isostatically pressed at 40 MPa into tablets. The tablets were heat-treated according to a sequence of heating steps at $400^{\circ}C$ (1 h), $800^{\circ}C$ (1 h), $1000^{\circ}C$ (2 h), $1300^{\circ}C$ (72 h), and $1425^{\circ}C$ (1 h). After sintering, the tablets were crushed and comminuted, and classified by wet sieving. It should be emphasized that maintaining a heating rate of $10^{\circ}C/min$ during sintering, adhering to the indicated temperature regimes, as well as the type of phosphorus carriers are critical factors for successful synthesis. For example, employing $(NH_4)_2HPO_4$ results in enhanced formation of undesired reaction products such as rutile, baddeleyite, and zirconium diphosphate. Since ZrO_2 reacts only sluggishly, $ZrOCl_2$ has been utilized to speed up the reaction rate, However, in this case besides stoichiometric $CaTiZr_3(PO_4)_6$, a Ti-depleted $CaTi_{0.5}\square_{0.5}Zr_3(PO_4)_6$ phase formed, whereby the missing TiO_2 precipitated as the polymorph rutile at grain boundaries of the polycrystalline product.

Using $CaTiZr_3(PO_4)_6$ powder as feedstock material for plasma-sprayed coatings on Ti6Al4V substrates, parametric studies were carried out by Heimann (2006a, 2010) to evaluate the influence on six dependent coating properties of seven intrinsic and extrinsic plasma spray parameters varied at two levels using statistical design of experiments (SDE) methodology. The coating thickness was found to increase with increasing plasma power and powder feed rate but with decreasing argon gas flow rate and powder grain size. The average porosity of the plasma-sprayed coatings was 17.0 ± 4.4 vol% (N = 12). Maximum porosity was found to be 24 vol%. For thin coatings (60 μm), the pore size distribution was unimodal with preferential mean pore diameter of 10.8 μm, but multimodal in thicker coatings (180 μm) with frequency maxima at pore diameters of 12, 24, and 36 μm (Heimann 2006a, 2010). Such pore size ranges would support in-growth of osteoblasts. The tensile adhesion strength of coatings to a Ti6Al4V substrate increased strongly with increasing powder grain size and moderately with increasing powder gas feed rate but decreasing plasma power, reaching a

maximum value of 18 MPa. Thinner coatings show higher adhesion strength, in line with expectation.

Problems still exist, however, regarding the compromised thermal stability of the materials when subjected to a hot plasma jet in excess of 15,000 K. In addition to thermal decomposition phases such as zirconium pyrophosphate (ZrP_2O_7), rutile (TiO_2), and baddeleyite (m-ZrO_2), amorphous and quenched phases of variable composition are formed during plasma spraying. This may be related either to incongruent melting of the precursor material associated with massive loss of phosphorus or to an inherent structural instability caused by the high lattice vacancy concentration of the NASICON structure (Reisel 1996; Heimann 2006a; Heimann 2010). Figure 3A is a cross-section of a porous plasma-sprayed coating that shows a dark grey target $CaTiZr_3(PO_4)_6$ phase (point 1) embedded in two P-depleted phases with the nominal compositions $Ca(Ti,Zr)_{4.5}O_{4.6}(PO_4)_{3.6}$ (medium grey, point 2) and $Ca(Ti,Zr)_{4.2}O_{6.85}(PO_4)_{1.7}$ (light grey streaks at splat boundaries, point 3). In addition, exsolved m-ZrO_2 is present as tiny spherical precipitates (bright, point 4). Phases 2 and 3 consist of submicroscopic crystallites of $CaTiO_3$, $CaZrO_3$, $Zr_2P_2O_7$, and various Ca phosphates together with an amorphous phase that accounts for the elevated background between 10 and 15° 2Θ in the XRD pattern shown in Fig. 3B,c. Clearly, avoidance of the pronounced chemical and structural inhomogeneity of the plasma-sprayed coatings requires much more research. To limit thermal decomposition and thus to prevent coating inhomogeneity, non-thermal deposition techniques may be adapted such as sol-gel, electrochemical (ECD) or electrophoretic (EPD) deposition, or plasma electrolytic oxidation (PEO) (Heimann and Lehmann 2015).

Electrical conductivity

Quantitative data on the electrical conductivity of calcium orthophosphates with various Ca/P ratios (Nagai et al. 1991), hydroxylapatite (Nagai and Nishino 1988; Gittings et al. 2009), and Ca (Ti,Zr) hexaorthophosphates are few and far between in literature sources. Moreover, the data appear to differ considerably depending on the chemical composition and preparation conditions. The dielectric permittivity of Ca(Ti,Zr) hexaorthophosphates was reported to be 15.4, somewhat lower than that of dense hydroxylapatite, which shows room temperature values around 20 (Gittings et al. 2009), and was also found to be porosity dependent (Hoepfner and Case 2002). Silva et al. (2006) measured as around $4.0 \cdot 10^{-12}$ S·m^{-1} the DC conductivity of mechanochemically (Bayer and Clausen-Schaumann 2005; James et al. 2012) produced $CaTi_4(PO_4)_6$, using high-energy, dry, ball milling of a mixture of $Ca(H_2PO_4)_2$ and TiO_2 for 15 hours. Mechanochemistry deals with chemical transformations initiated or sustained by mechanical force such as ball milling, thus coupling of mechanical and chemical phenomena on a molecular scale. The field has been advancing particularly rapidly, from a laboratory curiosity to a widely applicable technique that not only enables a cleaner route to chemical transformations but offers completely new opportunities in making and screening for molecules and materials (Do and Friščić 2017).

However, in the work of Silva et al. (2006), the reaction product obtained by milling still contained large amounts of the starting materials, attesting to an incomplete reaction. Hence, the reported conductivity value was presumably compromised by the presence of unreacted precursor compounds.

In contrast to this, the orders of magnitude higher ionic conductivity of Na- or Li-based NaSiCON structures in the range of 10^{-2} S·m^{-1} (Xie et al. 2011) can be associated with the high concentration of the charge-carrying alkali ions. The higher charge mobility of alkali ions results from their hopping among interstitial sites, compared to the less mobile calcium ions. Hence, to achieve higher ionic conductivity of Ca (Ti,Zr) hexaorthophosphates,

aliovalent doping with highly mobile Na or Li ions intercalated into the only partially occupied M1 sites appears to be a suitable route

Osseoconductivity

Calcium hexaorthophosphate ceramics have shown positive interaction with living tissue by providing osseoconductive function. Osseoconductivity is the ability of a material to foster the in-growth of bone cells, blood capillaries, and perivascular tissue into the gap between implant and existing bone, with strong chemical bonding along the interface triggered by the adsorption of bone-growth-mediating proteins at the synthetic biomaterial surface.

Cell tests *in vitro*

To confirm biocompatibility, osteoconductive potential and, in particular, absence of cytotoxicity, plasma-sprayed coatings of $CaTiZr_3(PO_4)_6$ composition were tested to determine their cell proliferation and cell vitality capabilities. *In vitro* biocompatibility tests with primary rat bone marrow cells showed substantial cell proliferation in the presence of fetal bovine serum (Heimann 2006a, 2012).

Knabe et al. (2004) grew human bone-derived cells on sintered calcium (Ti,Zr) hexaorthophosphate samples, and tested for expression of various biochemical indicators for cell proliferation and cell vitality, such as levels of osteocalcin, osteonectin, osteopontin, alkaline phosphatase, and bone sialoprotein. Compositions conforming specifically to $CaTiZr_3(PO_4)_6$ displayed maximum osteoblastic differentiation including sufficient expression of an array of osteogenic markers thus suggesting a high degree of osseoconductive potential. Similar results were reported for the growth of bone marrow stromal cells cultured on calcium

titanium phosphate microspheres to be used as potential scaffolds for bone reconstruction (Barrias et al. 2005).

Animal tests *in vivo*

Earlier *in vivo* tests with $CaZr_4(PO_4)_6$ disks implanted into the distal epiphyseal parts (lower end parts) of femura and tibiae of dogs showed that a direct and stable contact between implant and bone was established. After 9 months, extensive remodelling of osteons had occurred in direct contact with the biomaterial without noticeable resorption of the latter (Szmukler-Moncler et al. 1992). This work was indeed a key experiment that established the *in vivo* osseoconductive capacity and stability of this novel class of bioceramic materials sufficiently well.

Later, survey animal experiments were conducted by Heimann (2006a) to estimate the biological performance of atmospheric plasma-sprayed $CaTiZr_3(PO_4)_6$ coatings (Heimann 2006b; Heimann 2008). Biomedical Ti6Al4V rods (130 mm length, 12 mm diameter) covered by an approximately 150 μm-thick plasma-sprayed coating were inserted into the femoral medulla of sheep. All animals were able to fully bear their weight until the end of the observation period of 6 months. The selected model of a cylindrical rod, positioned in the central cavity of the long bone shaft (medulla), closely resembles the geometrical situation of a typical human endoprosthetic stem replacement operation (Heimann et al. 2004). The simulated cylindrical prosthesis stems were positioned in the medulla at a rather large distance from the cortical bone wall. Since the establishment of a solid bony bridge between corticalis (hard, outer shell of bone) and implant requires some time, a thin coating with limited resorption resistance would not have been sufficient to guarantee complete bony integration. Hence, the rather high coating thickness of about 150 μm was selected. Large-scale bony

integration was confirmed, expressed by dense bridging connections between the implant and the surrounding cortical bone (Fig. 4A). However, since the part of the implant oriented towards the marrow-filled medulla did not reveal continuous bone deposition but only spotty lamellar bony in-growth structures (Fig. 4B), suitable ways must be found to accelerate bone in-growth. Such ways may include application of an electric field either by a direct electric current or by capacitive coupling via a 'biocapacitor' device that has been conceptually described below. An encouraging observation was that the animal tests proved that 150 μm thick coatings based on $CaTiZr_3(PO_4)_6$ applied to Ti6Al4V rods implanted in the femura of sheep led to strong neoformation of dense bone at a stable interface between the implant and its bioceramic coating without the delamination frequently observed with hydroxylapatite coatings (Müller 2001).

Mechanisms of acceleration of bone growth by an electric field

Physicians have used electrical currents to heal bone fractures since the mid-19th century (Hannouche et al. 2001). Since then, the effect of electrical stimulation on bone growth has been studied and well documented (for example Bassett 1965, 1971; Kuzyk and Schemitsch 2009; Mobini et al. 2017). Along the way, the growth of bone was found to be affected by the presence of materials with different dielectric behavior, as suggested by the discovery of the so-called 'bioelectric phenomenon' in bone (Fukada and Yasuda 1957; Shamos at al. 1963; Bassett 1968). Mechanically triggered electrical charge separation acts as the prime mechanism during remodelling of a broken bone whereby the structure and function of growing bone cells and extracellular structures are being influenced by piezoelectric and streaming potentials in the range of several tens of millivolts (Bassett 1971). Electrical and electromagnetic fields are thought to play a role in bone healing through the same principles as in mechanical stress applications. Mechanical load applied to bone develops a strain

gradient that drives interstitial fluid through the canaliculi from regions of high to low pressure and exposes osteocyte membranes to flow-related shear stress, as well as to electrical potentials subsequent to the streaming process (Hannouche et al. 2001). Hence, application of electric fields to the fracture site mimics the effect of mechanical stress on bone.

Many clinical studies have shown that electrical stimulation of bone growth via fields aligned parallel to the axis of a long bone reduces the time required for endosteal callus remodelling and, hence, speeds up the healing process (for example Weigert 1973; Weinstein 1976; Colella et al. 1981; Berry et al. 1986; Wang et al. 2009; Nakamura et al. 2014). It was further observed that a pulsed, transverse electric field tends to accelerate the growth of bone more effectively than a static, non-varying field does (Watson et al. 1975).

The effects of direct electrical current as well as capacitive and inductive coupling have all been investigated as promising techniques to enhance fracture healing through proliferation and differentiation of osteogenic cells. Such studies have shown that electrical stimulation leads to intracellular processes by which bone cell proliferation may occur (Kuzyk and Schemitsch 2009; Hiemer et al. 2016). However, the origin and function of bioelectric potentials are not known with certainty yet (Galkowski et al. 2009) and, hence, have been subject to intense, and often controversial, discussion. Bioelectric potentials presumably establish diffusion gradients of ionic currents that are able to concentrate polarizable molecules, collagenous proteins, non-collagenous polyanionic proteins (NCPs) and electrolytes at the wound site. For example, there is evidence that the concentration of Ca^{2+} ions at the negative electrode is higher than that in an unstimulated fracture. Calcium ions formed by depolymerisation of mucopolysaccharides are initially stored in mitochondria and released by a change of the potential of the mitochondrial membrane via the cytoplasm and the cell membrane into the extracellular matrix (ECM; Rubin and Saffir 1970). Then at the

wound site, nucleation of calcium phosphate occurs and produces crystallization centers of apatite microcrystals. This suggests that an external electric field will influence the process of releasing Ca (and P) ions by intensifying the important role that membrane potentials play in the process of wound healing.

In conclusion, there is indication that bone growth rates can be accelerated in the presence of an electric field. For example, the Biomet® SpinalPak® Non-invasive Spine Fusion Stimulator System (Biomet 2009) is a non-invasive bone growth stimulator indicated as an adjunct electrical treatment to primary lumbar spinal fusion surgery. The ASNIS-IIIs Screw System marketed by Stryker GmbH (Duisburg, Germany), based on the bipolar induction screw system (BISS) by Mittelmeier et al. (2004), provides a maximum electrical current of 700 mV and is already being applied in clinical practice for the treatment of avascular necrosis (cellular death of bone tissue) of the femoral head, fracture of the femoral neck, and subtalar arthrodesis (surgical stiffening of the joint beneath the ankle bone) (Hiemer et al. 2016).

Research suggests that such electrical stimulation produce lower complication rates compared to other invasive methods, because implantable forms of DC stimulators provide constant stimulation of bone directly at the fracture site as well as increased patient compliance. Nevertheless, there is a great need for thorough explorations of success rates and cost-effectiveness of electrical stimulation methods in general (Ciombor and Aaron 2005; Galkowski et al. 2009).

Considering the non-invasive electrical stimulation route, upregulation of various bone morphogenetic growth factors have been observed in various pre-clinical *in vitro* cellular and *in vivo* animal studies (for example Brighton et al. 2001; Wang et al. 2006). In addition, some

studies have revealed that improved bone in-growth and bone cell activity occurred in polarized hydroxylapatite implants inserted into the femoral condyle of rabbits with complete bone mineralization as early as 3 weeks after surgery (for example Itoh et al. 2006).

Laboratory evidence has strongly supported the notion of acceleration of bone healing by an applied poled electric field, showing that the growth of hydroxylapatite crystals from simulated body fluid (SBF) is dramatically quickened on negatively polarized dielectric and ferroelectric substrates such as calcium and barium titanates (Yamashita et al. 1996; Baxter et al. 2010). These experiments suggest that a uniform electric field rather than localized charges is the stimulating factor for bone remodelling during the healing process (Calvert and Mann 1997). There is further evidence that biomimetic growth of bone-like hydroxylapatite in an electric field is accelerated by reorientation of the dipole moments between O^{2-} and H^{+} of lattice OH^{-} ions in response to the electric polarization conditions (Fig. 5). In this way, an ordered alignment of OH^{-} columns as present in monoclinic hydroxylapatite (space group $P2_1/b$; Elliott et al. 1973) is attained (Heimann 2007). Positively charged Ca^{2+} ions will be preferentially adsorbed on the negatively charged surface of hydroxylapatite crystallites. There they will attract a cloud of HPO_4^{2-} and HCO_3^{-} ions, causing strong nucleation and eventually precipitation of a thick layer of bone-like apatite. Whereas the polarized state will cause an alignment of the OH^{-} groups in the hydroxylapatite structure, the depolarized state shows randomly oriented OH^{-} groups. This behavior has important implications: although non-periodic fields as encountered by Yamashita et al. (1996) are weak compared to electrostatic fields, even small changes of the local interfacial energy could be sufficient to influence markedly the mechanism of transformation of incipient nuclei into macroscopic mineralized phases (Calvert and Mann 1997).

While polarization orientation of the OH⁻ groups of hydroxylapatite require the presence of an electric field, ferroelectric ceramics with a spontaneous dipole moment do not. However, ferroelectric ceramics such as PZT (lead zirconate titanate, $Pb(Zr,Ti)O_3$) implanted in the shaft of the lower leg bone of roosters in either polarized or depolarized states were found to have a negligible effect on rate and quality of bone formation (Park et al. 1981; Schumacher et al. 1982). Although this poor performance has been related to the combined effects of insufficient load pressure that produced low signal strength, high internal resistance, and incompatible elastic moduli between the chosen ceramics and bone, it does not invalidate the notion of electrical stimulation. Indeed, in other experiments, calcium titanate ($CaTiO_3$) has been implicated in enhanced bone cell deposition *in vitro* on hydroxylapatite surfaces. This example shows that bioactive coatings involving $CaTiO_3$ (CT; space group Pbnm) could increase the osseointegration with juxtaposed bone that is needed for increased implant efficacy (Webster et al. 2003). It is appealing to speculate that the ferroelectric nature of distorted calcium titanate may be a reason for its osseoconductive behavior. If this is the case, the notion that a titanium oxide surface is an important prerequisite of osseoconductivity must be revisited. NASICONs such as sodium zirconium orthophosphate (NZP; space group $R\bar{3}m$) and calcium titanium phosphate (CTP; space group $R\bar{3}$) possess in their crystal structures a symmetry center and thus, are not able to develop a spontaneous ferroelectric moment. However, there exists the still unexplored possibility of an antiferroelectric phase transition from a paraelectric ditrigonal-scalenohedral $\bar{3}m$ symmetry to the lower trigonal-rhombohedral $\bar{3}$ symmetry. Antiferroelectrics are characterized by an interpenetration of sublattices of antiparallel ordered arrays of electric dipoles. Since the adjacent dipole moments cancel each other out, the macroscopic spontaneous polarization is zero, but dielectric anomalies exist (Dalal and Bussmann-Holder 2010) that may be relevant for distribution and propagation of electric charges in calcium titanium phosphate.

Here more work is required to relate the structure to the biological response of the materials. Indeed, the complex interplay of electrical activity of polarized surfaces of synthetic biomaterials such as Ca(Ti,Zr) hexaorthophosphates and their biological responses, likely resulting from preferential adsorption of proteins and ions (Baxter et al. 2010), needs further elucidation.

Qu et al. (2006) have proposed a hypothetical regulation mechanism for bone remodelling under the influence of an electromagnetic field. Damage induced in cortical bone by load changes during daily activities generates microcracks that will be removed by osteoclasts. In turn, several protein-based growth factors present in latent forms in osteocytes are being activated and released into the extracellular matrix (ECM) where they stimulate osteoblasts to refill the cavities produced during osteolysis. An electric field is presumably able to stimulate the multiplication of these growth factors and hence, to accelerate the bone remodelling process.

Very recently, the idea of fourth-generation biomaterials was suggested (Ning et al. 2016), based on integrating electronic systems with the human body to provide powerful diagnostic as well as therapeutic tools for basic research and clinical use. The functionalities of such biomaterial systems include manipulating cellular bioelectric responses for tissue regeneration as well as monitoring cellular responses with the aim to communicate with host tissues via bioelectric signals. There is anticipation that calcium (Ti,Zr) hexaorthophosphates will play a commanding role in the development and clinical testing of such novel fourth-generation bioceramics based on their elevated solid-state ionic conductivity, which may allow them to transmit signals adapted to this task. Consequently, future research should focus on development of a composite coating system for implants with the equivalent circuit of a

capacitor, which by appropriate poling, could store negative electrical charges close to the interface with the growing bone, thus enhancing bone apposition rate as well as bone density.

Conceptual design of a 'bio'capacitor

In the proposed 'bio'capacitor device, a Na-doped $CaTiZr_3(PO_4)_6$ (Na:CTZ$_3$P$_3$) coating will act as functional part of a bone-growth stimulator intended to accelerate bone in-growth in contact with biomedical implants such as hip endoprostheses and osteosynthetic bone healing devices. Other uses may include its application as a driver for iontophoretic transdermal drug delivery (Rawat et al. 2008; Ogata et al. 2012). Electrically conducting biocompatible ceramics may also be used in microfluidic biosensors to provide powerful tools for biological analyses, clinical diagnostics, toxicity monitoring, as well as DNA, cellular, and protein analyses (Luo and Eitel 2017).

The enhanced electric conductivity of this coating material will allow coupling (Goodwin et al. 1999) of a weak electric field capacitively into the implant by storing negative charges in the immediate vicinity of the growing bone tissue. Through an engineered layered coating system, consisting of a succession of a bioinert conductive Ti6Al4V alloy substrate//bioinert dielectric titania bond coat//electrically conducting bioactive $Na:CaTiZr_3(PO_4)_6$ coating, a device with the equivalent circuit of a capacitor will be formed (Fig. 6A).

Thin PTFE-coated Pt-Ir lead wires (0.5-0.7 mm diameter) attached to the bare titanium alloy and embedded in the conductive coating layer will be connected to a DC power source (Ni-Cd battery, Mallory cell, or other voltage sources) carried outside the body or concealed subcutaneously. The power source provides a weak electric field that by proper poling will store negative charges close to the growing bone. It is further advised to deposit a

hydroxylapatite layer with interconnected porosity (Wang et al. 2009) on top of the Na:CaTiZr$_3$(PO$_4$)$_6$ layer (Fig. 6B). The physiological biofluid enclosed by the pores will be electrically charged, and a streaming potential driven by electrokinetic force will be established (Chang and Yeo 2009). As suggested by Wang et al. (2009), bone in-growth into a hydroxylapatite matrix with high interpore connectivity would be supported by electrical polarization, and controlled by cooperative interaction between osseoconductivity of hydroxylapatite and enhanced osteogenic cell activity induced by electric charges stored at the pore surfaces. Such three-layer arrangements could further improve the performance of the device by exploiting the highly osseoconductive nature of hydroxylapatite. Atmospheric (powder) plasma spraying (APS) or suspension plasma spraying (SPS) may be deposition techniques of choice. However, other non-thermal solution-based techniques may well be adopted, such as biomimetic, sol-gel, electrochemical (ECD) or electrophoretic (EPD) deposition, or plasma electrolytic oxidation (PEO) (Campbell 2003; Heimann and Lehmann 2015).

Implications

Calcium (Ti,Zr) hexaorthophosphates constitute a novel class of bioceramic materials that, based on their favorable chemical, electrical, and biomedical properties, promise successful application to accelerate bony integration of endoprosthetic implant devices and to speed up healing of broken bones. A novel device has been proposed for this purpose the advantage of which, over already existing bone-growth stimulators, is its ability to provide the intimate contact of a capacitively-coupled electric field with the growing bone tissue as opposed to an externally applied inductively-coupled electromagnetic field, which suffers substantial attenuation when transmitted through soft tissue covering the locus of bone growth. Consequently, a much better performance of the electric power source can be expected due to a comparatively high capacity immediately adjacent to the bone. The electric field strength can be optimized by simultaneously increasing the surface area of the conductors (Schmitt et

al. 1997) and decreasing their separation distance, i.e. decreasing the thickness of the dielectric titania layer. The surface area of the Ti6Al4V implant can be increased by appropriate grit blasting, whereas an increase of the $CaTiZr_3(PO_4)_6$ surface area can be obtained through engineering its porosity, for example by applying suspension (Gross and Saber-Samandari 2009) or solution precursor plasma spraying techniques (Candidato et al. 2017). Variation in porosity of the dielectric titanium oxide layer will affect the dielectric permittivity, which can be tuned to the demand.

To achieve higher ionic conductivity of Ca (Ti,Zr) hexaorthophosphates, aliovalent doping with highly mobile Na or Li ions intercalated into the only partially occupied M1 sites appears to be a suitable route. Indeed, such doped compounds have been suggested as solid-state electrode materials for oxide-based fuel cells (for example Delmas et al. 1988; Ortiz et al. 2014; Jolley et al. 2015; Wachsman and Jolley 2016; Jian et al. 2017). In addition, it should be emphasized that an electrically conducting Na-intercalated bioceramic $Na:CaTiZr_3(PO_4)_6$ layer is not biologically passive but rather provides an osseoconductive function that entices osteoblasts to grow into the porous layer and thus anchor the implant solidly to the bone.

The favorable properties of NASICON-structured materials make them adaptable to many technological needs, which include, besides their potential use as next-generation bioceramics, sequestration matrices for radioactive nuclear waste, solid-state electrolytes, electrodes for molten sodium-ion batteries, gas sensors, and other future applications. In addition, research into application of NASICON materials with increased ionic conductivity illustrates one of the ways in which the specialized needs of biomaterials have spurred innovation in the use of natural mineral structures. This could inspire mineralogists to take a stronger interest not only in biomaterials *per se*, but also in exploring innovative ways to apply minerals and/or their structures to current and future technological challenges.

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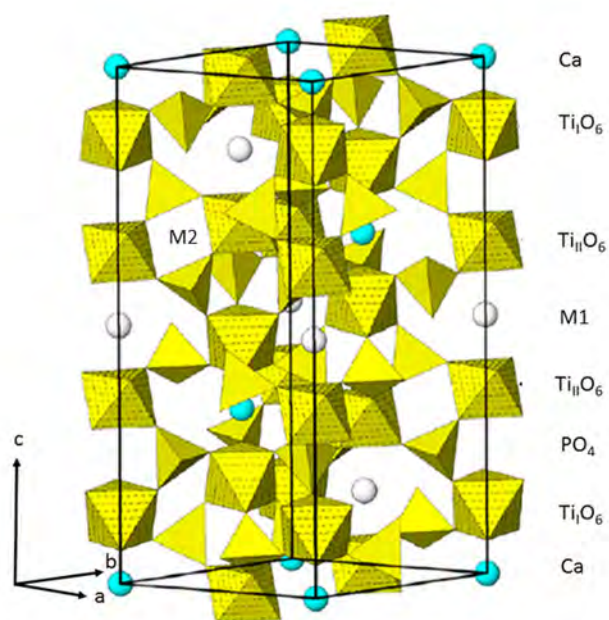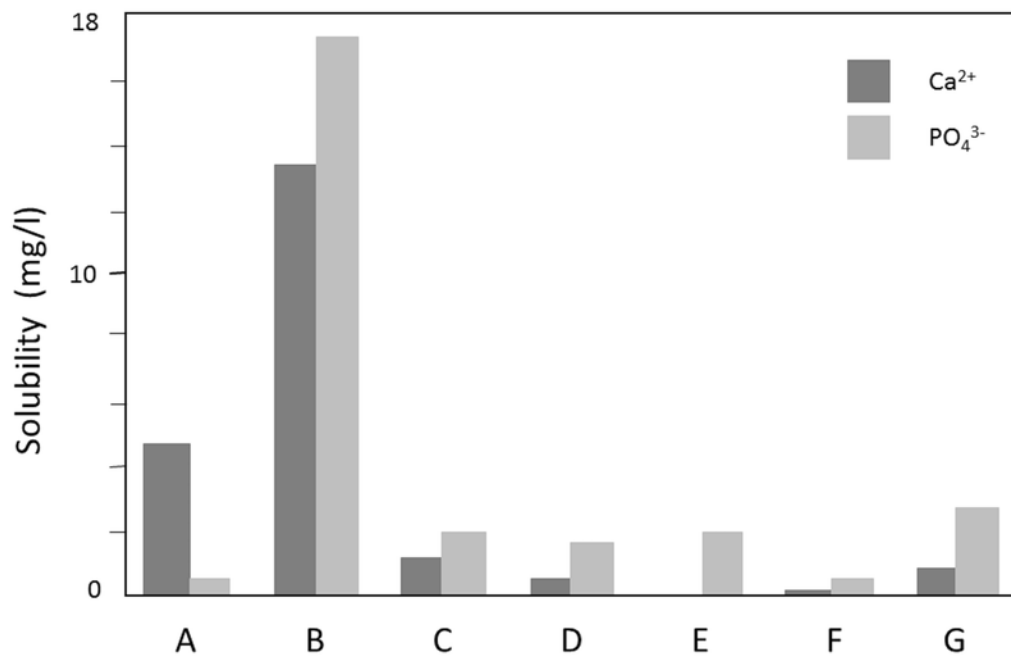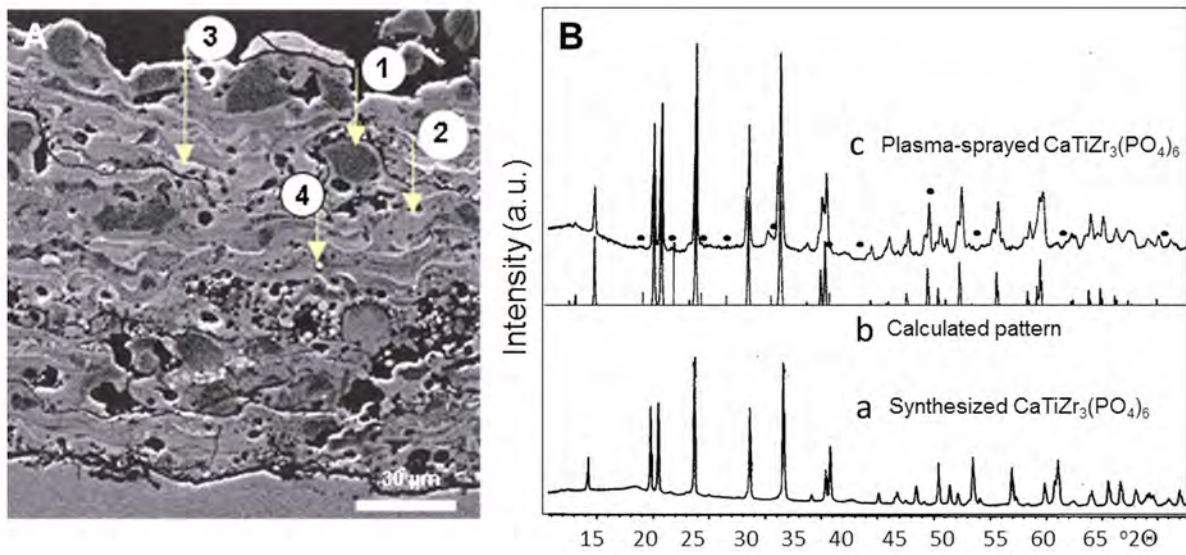
Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6