Novel Ceramic Composites for Personalized 3D Structures

M. Ahlhelm[*], E. Schwarzer, U. Scheithauer, T. Moritz, A. Michaelis

Fraunhofer Institut für Keramische Technologien und Systeme (IKTS),
Winterbergstraße 28, D-01277 Dresden, Germany

Abstract

The objective of the presented work is to further introduce a new hybrid shaping technique and develop novel porous, near-net shaped composite structures e.g. for personalized bone replacement materials.

The suspension-based additive manufacturing technique lithography-based ceramic manufacturing enables high structural resolution and the manufacturing of dense (> 99 %) ceramic components with high performance compared to other available AM techniques. On the other hand, freeze foaming offers the possibility to achieve mainly open porous and interconnected sponge-like structures that provably allow the ingrowth and differentiation of human mesenchymal stem cells (hMSCs). The near-net shaping feasibility of this foaming technique was used to foam the inner contours of complex LCM-manufactured ceramic shell structures in the shape of a femoral bone model. After a co-sintering step, they combine to structural composites with dense and porous features in one single 3D structure. This contribution therefore provides insides into a new line of technology comprising a new degree of freedom in personalization and application such as bone replacement materials.

Keywords: Bioceramics, bone replacement materials, freeze foaming, LCM, hybrid shaping

I. Introduction

Against the background of demographic change, considerable research is being conducted to obtain biocompatible materials and implants allowing tissue material ingrowth, osseoconduction and/or resorption of the artificial material. As of today, natural bone is the second most common transplanted tissue after human blood, creating a $ 2.5 billion market for bone graft substitutes (BGS) which is anticipated to continue growing. The expansion of the BGS market is driven by multiple factors, like the aging population and the expanding pool of younger patients as a result of minimally invasive procedures. Bone defects can be caused by various reasons including trauma, teeth loss, arthrosis, implant revision, infectious disease, cancer, and other metabolic conditions. Human bone still offers the best choice for bone replacement. However, complications and risks associated with its use (e.g. donor site morbidity and chronic pain at the site of extraction of autografts; reduced biocompatibility and chance of the transfer of infections with allografts) exceed the complication rate of the grafting itself. Therefore, there is a tremendous need for refining technological steps to manufacture novel components such as synthetic bone graft substitutes that have the ability to replace human bone. Up to now, no holistic approach on the path to BGS exists. Single steps are taken but there is no coherent way to exploit the resources of different branches, technologies and approaches. A line of technology in the form of a modular system/process is needed.

(1) State of the art and recent research

About geometrical and structural complexity, for example, a real bone consists of a denser outer layer (cortical bone) and a porous inside (cancellous/trabecular bone). These different density and porosity sections are relatively easy to achieve as single sections; but research has only recently begun on obtaining just one structure incorporating the two very different sections. In fact, only Additive Manufacturing (AM) enables the required structural complexity for complex-shaped parts e.g. femoral bones. Lithography-based Ceramic Manufacturing (LCM) so far has the highest resolution of all common ceramic additive manufacturing processes (high-performance and nearly dense ceramics with resolution up to 635 dpi [1]) and ensures nearly unlimited freedom in design. Microporous scaffold structures are easy to achieve. However, there are two huge drawbacks: the higher and complex the resolution respectively the structure (e.g. related to the surface area of a layer), the longer the LCM process takes. In addition, the manufactured single layers and walls are dense. Filigree single struts are limited to a diameter of roughly only about 100 μm.

One promising way to fulfill such a demand and combine different structural, even material properties in one component is provided by a co-manufacturing approach of AM technology with conventional and innovative shaping methods. In recent works, the porous filling of a complex LCM-based shell structure was provided by the freeze foaming technique [2,3] to next-generation bone-mimicking composite structures [4]. This technique allows the foaming of almost any desired material to highly porous scaffolds within seconds. Macro- and micro-

* Corresponding author: matthias.ahlhelm@ikts.fraunhofer.de

sized pores are connected by filled and simultaneously microporous struts with diameters ranging from five to several micrometers. Based on the ambient pressure reduction on a suspension of optionally selectable materials (ceramics, metals, etc.) this foaming technique can produce e.g. highly porous foams/scaffolds, which provably enable cell in-growth and differentiation thereof [5]. By linking the combination of techniques with a further combination of materials, even more innovation and novel applications result. Thus, different material properties, e.g. electrical conductivity and insulation, ductility and stiffness or porous and dense features can be combined in one component. The chosen material for the first experiments to manufacture bone-mimicking, dense-porous composite studies was pure zirconia [4]. New research and part of this contribution resulted in successfully combined bioactive hydroxyapatite (HAp) composite structures. In addition, also partially degradable mixtures of ZrO_2 and HAp were achieved [6]. Alternatives for achieving different structural combinations also trying to overcome multiple drawbacks like the ones mentioned above are found e.g. in papers by Roy [7,8] and later follow-up research. He initially explored a hydrothermal method directly forming hydroxyapatite out of corals. Researchers progressed towards composition and microstructural features that are very close to natural bone by testing this method also on other natural sources like e.g. cuttlebone, sea urchin spine, nacre, seashells [9–19]. Ruffini *et al.* further explored hydrothermal transformation using wood- or plant-based parts (Calamus Manna or rattan) to achieve 3D hierarchically organized hydroxyapatite structures. "The resulting scaffold preserved the initial structure of rattan, featuring ideal pore size and interconnectivity for a spongy bone substitute." [20] These approaches are used to obtain structural features that mimic bone in particular in its inner structure. The matter of a complex outer shape remains unresolved.

II. Materials and Methods

The basic principle of the newly introduced hybrid shaping process is to produce an outer shell in this case by means of LCM at first, then fill it with a suspension and conduct the freeze foaming *in-situ*. The last step is a co-debinding/-sintering step to achieve a firm material and form fit, a structural composite. At the beginning of each shaping method is the ceramic suspension. Although there a few commercially available materials for LCM technology (Al_2O_3, ZrO_2, tricalcium phosphate) it is imperative to design and adapt new materials such as this paper's focus: hydroxyapatite and a 50:50 mixture of ZrO_2/HAp in the following named as Z50H50-L (L for LCM). The idea behind the material mix is derived from one of the main issues concerning biomaterials like hydroxyapatite: they are usually too brittle to be used as load-bearing components later. In previous works related to the manufacturing of Freeze Foams, a zirconia/hydroxyapatite material combination was developed (various amounts of vol% ZrO_2 in HAp, in the following named ZxHx), which combines the biocompatibility of said HAp and at the same time the high toughness of zirconia [24]. Such porous structures provably allow osteogenic differentiation whilst exhibiting enhanced compressive strength [21–24]. The same

approach was now also adapted to this paper's suspensions related to freeze foaming.

It is not required to effect the hybrid process with completely the same (mixtures of) materials. However, it is certainly helpful since there is one factor less to take care of in the already complex line of interactions (e.g. required similar shrinkage, warpage vs. effects of porosity and microstructure, also in dependence of the particle size and distribution). The shown FESEM images are the result of a NVISION 40, Co. Carl Zeiss SMT AG. The FESEM images of shown Freeze Foams are not from the exact LCM/ Freeze Foam composites in this papers but from single Freeze Foams from prior research [24]. The shown CT images are the result of a CT-Compact, Co. Procon X-Ray (voltage 150 kV max).

(1) Development of suspensions for LCM and processing of test samples

As the first commercially available LCM printer, the CeraFab7500[1] (Lithoz GmbH) was used for manufacturing the LCM shell structures. It allows a resolution of 40 μm in x, y-direction and 25 to 100 μm in z-direction.

The presented materials result in components, which, depending on the material, are either partially or fully bioactive. The future aim, though, is to achieve completely resorbable composite structures, ideally with enhanced mechanical properties. The chosen materials for this paper are: ZrO_2 (TZ-3YS-E; Co. TOSOH) with a $d_{50} = 0.7$ μm and a HAp (Co. Sigma-Aldrich) with a $d_{50} = 2.6$ μm, calcined at 900 °C for 2 h. The pure materials (content: 40 vol%) were each dispersed in a solvent (alcohol) with dispersing agent (BYK-Chemie), a binder (mixture of acrylic resins) and photoinitiator (combination of a camphor derivate and an amine). For the preparation of the suspensions, a planetary centrifugal vacuum mixer (Thinky ARV310) was used (mixing time: 5 min at 2000 rpm). For the HAp/ZrO_2 composite suspensions, 20 vol% ZrO_2 and HAp (together 40 vol%, Z50H50-L) each were dispersed by using the same additives and same preparation methods as before. At first, simple LCM specimens were manufactured based on the CAD data of cubes, tubes, and half-shells. After manufacturing, those specimens were filled with a Freeze Foam. In addition, a complex demonstrator in shape of a femoral bone model was manufactured by means of LCM and filled with a Freeze Foam.

(2) The freeze foaming process

Freeze foaming is used for achieving the desired porous ceramic structures discussed in this paper. The pure HAp and ZrO_2 as well as various ZrO_2/HAp compositions were developed similar to LCM processing. Thereby, the amount of ZrO_2 within the HAp as powder mixture was varied from 20 up to 80 vol% (in the following described as: Z20H80 i.e. 20 vol% ZrO_2 + 80 vol% HAp, furthermore: Z40H60, Z50H50, Z60H40, Z80H20). That step was taken in order to find the right composition for a successful material and form fit to the later outer Z50H50-L shell structure. The two powders were mixed together in a tumble mixer for one hour. Then, each material was dispersed in water with a dispersant (Dolapix CE 64, Co. Zschimmer & Schwarz), a polyvinyl binder and a thicken-

er based on polyurethane. For the preparation and deagglomeration of the suspensions, the centrifugal vacuum mixer (Thinky ARV310) was used (mixing time: 2 x 1 min at 2000 rpm).
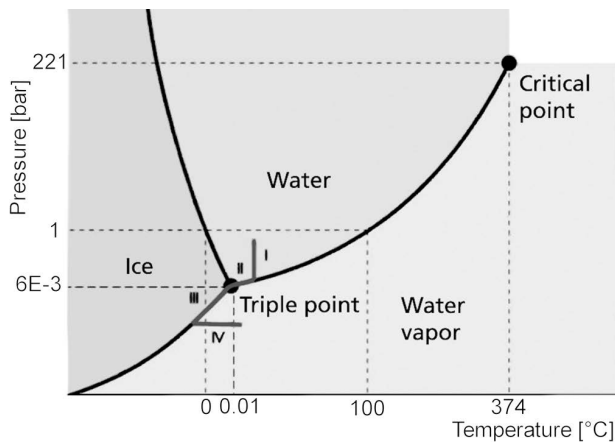

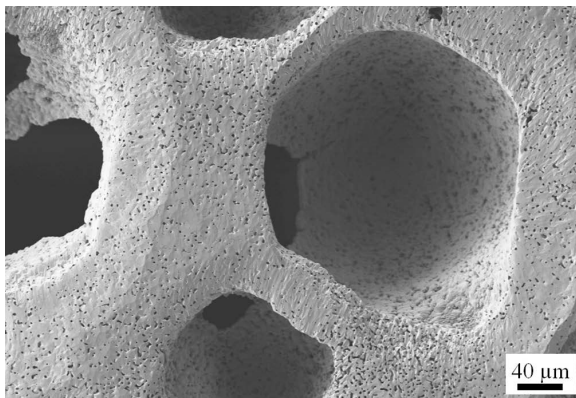**Fig. 1:** Freeze foaming process in p,T-phase diagram of water.

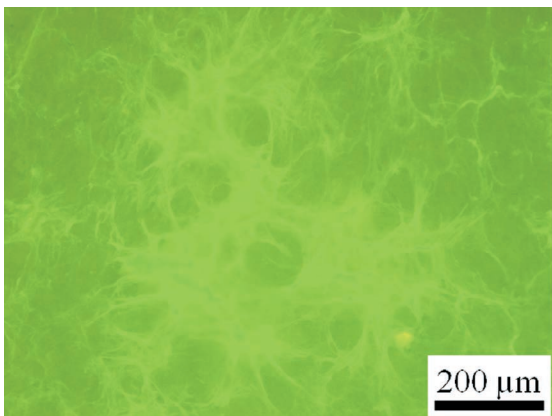**Fig. 2:** FESEM image of a sintered HAp Freeze Foam.

Fig. 3: Collagen-1 proof on HAp Freeze Foam.

Unlike foam-resulting techniques that are often based on the burnout of environmentally harmful organic volatile pore formers and even whole polymer scaffolds, freeze foaming is the direct foaming of almost any desired material (diverse ceramics, metals, etc.) dispersed as aqueous suspension. In contrast to other direct-foaming techniques (e.g. based on environmentally harmful foaming agents, *in-situ* bubble formation through chemical reactions or deliberately injected gas in a suspension), the freeze foaming process is the result of an ambient pressure reduction

on an aqueous suspension in a freeze dryer (in this case: Lyo Alpha 2 – 4, LSCplus, Co. Martin Christ GmbH). The applied vacuum causes an inflation of the suspension medium (transformation of liquid water to water vapor) and additionally, an inflation of residual processing air. Continuing pressure reduction drives the system along the vapor-liquid equilibrium line towards the so-called triple point (see p,T-diagram of water, Fig. 1, II). When passing that point, the now generated proto-foam suddenly freezes and subsequently dries via sublimation (Fig. 1, III-IV). In this respect, the occurring pore formers of resulting Freeze Foams are mostly rising water vapor, air and the sublimation of frozen water. After debinding and sintering ceramic material, the freeze-foamed structures typically exhibit filled struts *ergo*, higher mechanical strength *per se* and a high proportion of open porosity, microporosity and interconnectivity (Fig. 2). These are properties that demonstrably predestine such cellular-structured Freeze Foams for possible use as biocompatible products (see Fig. 3, which displays the proof of osteogenic differentiation on the staining of collagen-1 on a HAp Freeze Foam; source Fraunhofer IBMT) when made of HAp or ZrO_2; even as composite mixture [21–24]. Since freeze foaming offers near-net shaping capabilities, it was also applied to develop porous refractory bricks made of mullite [25, 26]. In this research, however, freeze foaming's manifold possibilities were used to fill geometries of a particular shape from the inside. Equally, a porous matrix structure around any given part could be realized. "Parts that are to be combined with a Freeze Foam can be manufactured either by conventional or by additive manufacturing processes, and thus, offer a wide range of application potential for personalized and surface customizable implant structures to be applied in the field of biomedical technology and engineering." [6]

III. Results and Discussion

The very first hybrid process experiments resulted in bioinert ZrO_2 composite test structures and a ZrO_2 demonstrator of a femoral bone model. Computer tomographic analyses proved a mainly partial form and material fit between dense and porous features [4, 27] (Fig. 4). However, bioinert zirconia structures would remain in the body and not be degraded. That is why the author's aim is to progress towards bioactive and biodegradable bone replacement material with sufficient strength to be used as a possible long-term implant.

(1)   *Manufacturing LCM components*

Thus, the successful approach of strength-enhanced ZrO_2/HAp-composite structures of the Freeze Foams [21–24] was used once more and now also adapted to composite LCM suspensions. Simple test cubes, tubes and half-shells were printed consisting of Z50H50-L composite but also the pure materials ZrO_2 and HAp (selection of specimen Fig. 5). The solid content of the pure and the mixed powders in the corresponding photosensitive suspension was adjusted to 37 vol% in each case. FESEM images of the sintered ZrO_2, HAp and ZrO_2/HAp composite LCM cubes give an impression of the ceramic microstructure.
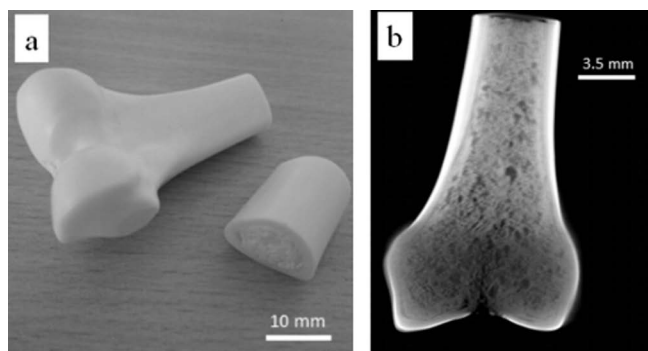
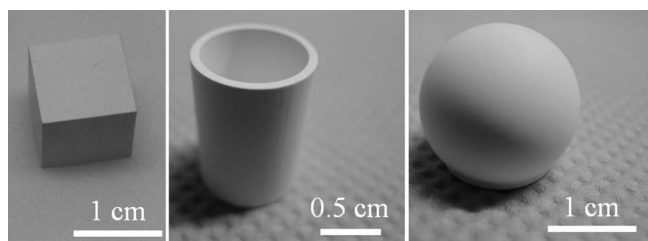**Fig. 4:** Hybrid shaping, a) femoral bone model of ZrO$_2$, b) CT image of the bone model.

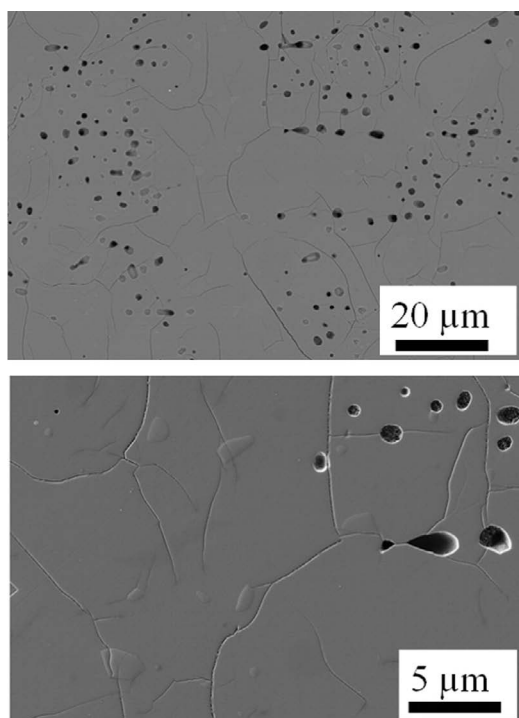**Fig. 5:** LCM-manufactured cubes, tubes, half-shells.

Fig. 7: FESEM image of sintered LCM ZrO$_2$ microstructure.

Fig. 6: FESEM image of sintered LCM HAp microstructure.

Fig. 8: FESEM image of sintered Freeze Foams, a) HAp, b) ZrO$_2$.

(2) Microstructure of LCM shells and Freeze Foams

Hydroxyapatite: Except for some parts, the layerwise manufacturing process of the HAp LCM part is clearly marked by the horizontal pores. In addition, despite some cracks, a smooth HAp microstructure without grain boundaries is observed (Fig. 6).

Zirconia: Small pores are apparent throughout the complete structure of ZrO$_2$, (see Fig. 7). However, there are no visible processing-derived interconnections between the different layers in the component.
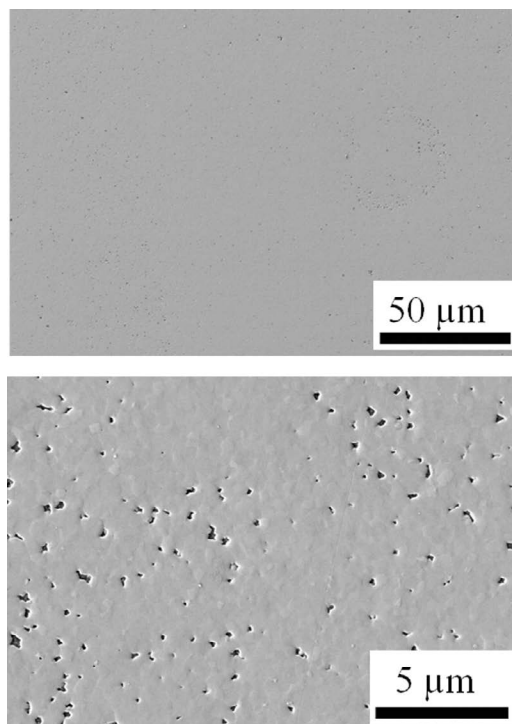
When compared to corresponding typical HAp and ZrO$_2$ Freeze Foams, the microstructure looks similar with the exception of displaying obvious porosity (Fig. 8).

Z50H50-L composite: The LCM microstructure shows a remarkable similarity compared to the filigree ZrO$_2$ scaffolds enclosing entire clusters of HAp in the porous Freeze Foam (Fig. 9 [24]). The prominent distinguishing feature, though, is the obvious display of the single-cured layers within the LCM part. Zirconia (light-gray colored) is the material that predominantly defines the border between

each new printed layer (Fig. 10). In both cases a filigree network of ZrO_2 (light gray) encloses bigger clusters of HAp (dark gray). The effect of the inhomogeneous material distribution in the Z50H50-L material in terms of mechanical and biological effects has not been evaluated yet and provides reasons for further research.
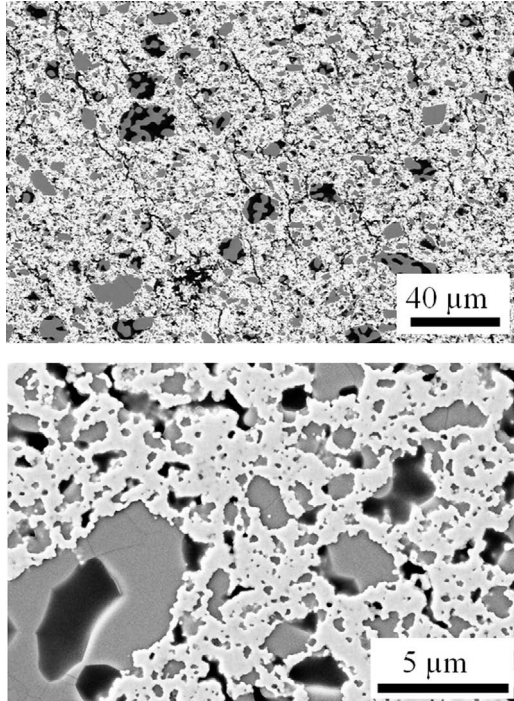

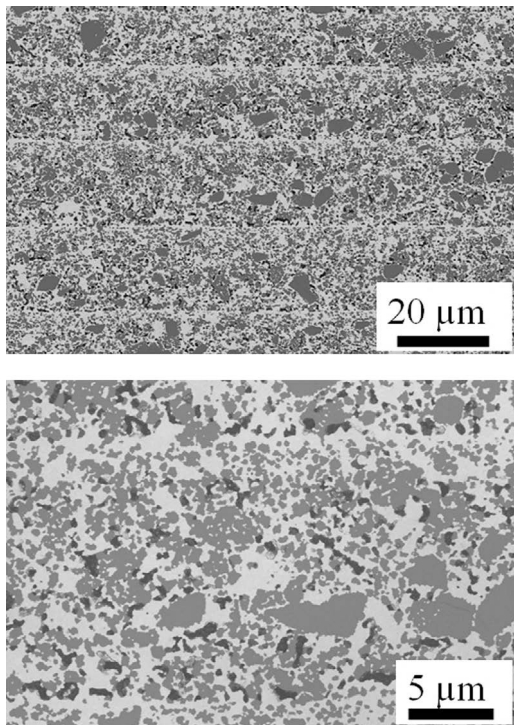**Fig. 9:** FESEM image of sintered ZxHx Freeze Foam.

Fig. 10: FESEM image of sintered Z50H50-L microstructure.

(3) Manufacturing Z50H50-L – Z50H50 Freeze Foam composites

To be filled and foamed by a Freeze Foam, the LCM-shaped components need at least one opening in the outer shell. The exact location and size is adjustable and a matter of application-relevant construction. After pre-sintering of the LCM-manufactured specimen at 900 °C (to prevent crack formation upon Freeze Foam combination because of different shrinkage during the debinding process), the test specimens were filled with a Z50H50 suspension suitable for freeze foaming, made according to Section II(2). The solid content amounts to 38 vol%. After co-debinding/-sintering, intact tests parts were achieved (Fig. 11 a). However, a CT analysis showed that there is no connection between the LCM and the Freeze Foam section (Fig. 11 b). More research and experiments are needed to understand exactly why the foam and LCM structure delaminated. So far, the main reason is seen in the different shrinkage of the porous and dense parts.
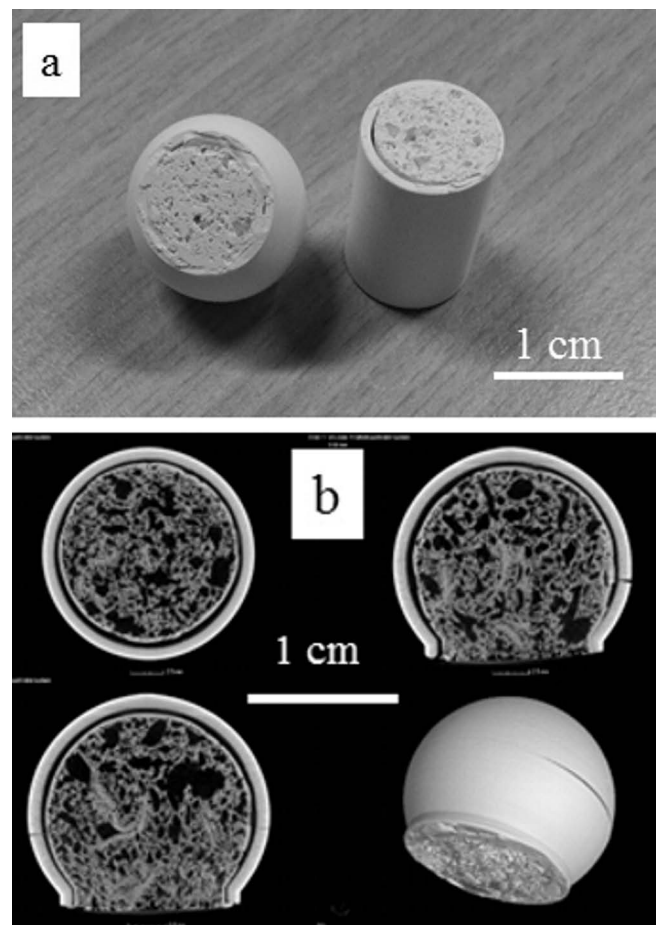

Fig. 11: a) Sintered Z50H50-L-Z50H50 Freeze Foam composite, b) CT image of Z50H50-L-Z50H50 Freeze Foam composite.

(4) Manufacturing HAp LCM-ZxHx Freeze Foams

Therefore, in the next series of experiments the author used HAp-only LCM parts and combined them with ZxHx composite Freeze Foam. The background is the idea that a denser HAp shell made by means of LCM should be more stable than a porous HAp structure; the whole LCM-Freeze Foam composite with a compressive-strength-enhanced ZxHx inner Freeze Foam even more so. The solid content of the Freeze Foam composite suspensions varied between 35 and 43 vol%. A series of experiments showed that all green-in-green processed and later

co-debinded/-sintered parts broke apart. Therefore, prior to being filled with a Freeze Foam, the LCM HAp shells were heated up to 900 °C as described in Section III(3). After debinding and co-sintering, the hybrid shaping resulted in ceramic composite structures with a distinctive HAp outer shape made by LCM and a porous ZxHx filling. Only Z20H80, Z40H60 (Fig. 12 a, b) and Z50H50 stayed intact though. Supposedly, because of different shrinkage behavior, the remaining specimens broke apart. The LCM shell seems to have shrunken onto the foam, resulting in excessive crack formation. However, CT-analysis show that only Z20H80 and Z40H60 composites are mainly fully connected to the HAp shell (Fig. 12 a, b). The CT reconstructions also show inhomogeneous shrinkage of the HAp LCM part. Further experiments have to be conducted in order to optimize the shrinkage and make it more homogeneous, else crack formation and part failure will be the result. The ZxHx composites that broke apart did so most likely because the coefficient of thermal expansion of the composite foam and the HAp shell differed too widely. Changing the solid content of said foams might lead to success.

Alternatively, the HAp amount of the LCM shell structures can be altered. The Freeze Foams so far were chosen, however, because of earlier research expertise.

(5) Manufacturing HAp-only LCM-Freeze Foam composites

With the use of only hydroxyapatite, the composites in principle are finally becoming fully bioactive and degradable. LCM-manufactured HAp parts were filled with a HAp suspension (41 vol% solid content) processed according to SectionII(2) and freeze-foamed *in-situ*. Experiments showed that the pure ZrO_2 or ZxHx composites were impossible to manufacture as intact scaffolds without pre-sintering first. However, the first try on HAp-only structures to process them not pre-sintered-to green but instead green-in-green was successful. No prior pre-sintering of the LCM part at 900 °C was needed. Co-debinding/-sintering resulted in sintered HAp-only structures that showed no visible gap/delamination between the denser LCM section and the porous Freeze Foam section (Fig. 13a). CT analysis confirmed the visual impression: LCM and Freeze Foam sections are fully connected via complete material and form fit (Fig. 13 b). However, since the CT images might not have the proper resolution to truly resolve small cracks or delamination at the interface, further composites need to be analyzed e.g. with FESEM, to get a closer look at the interface connection.
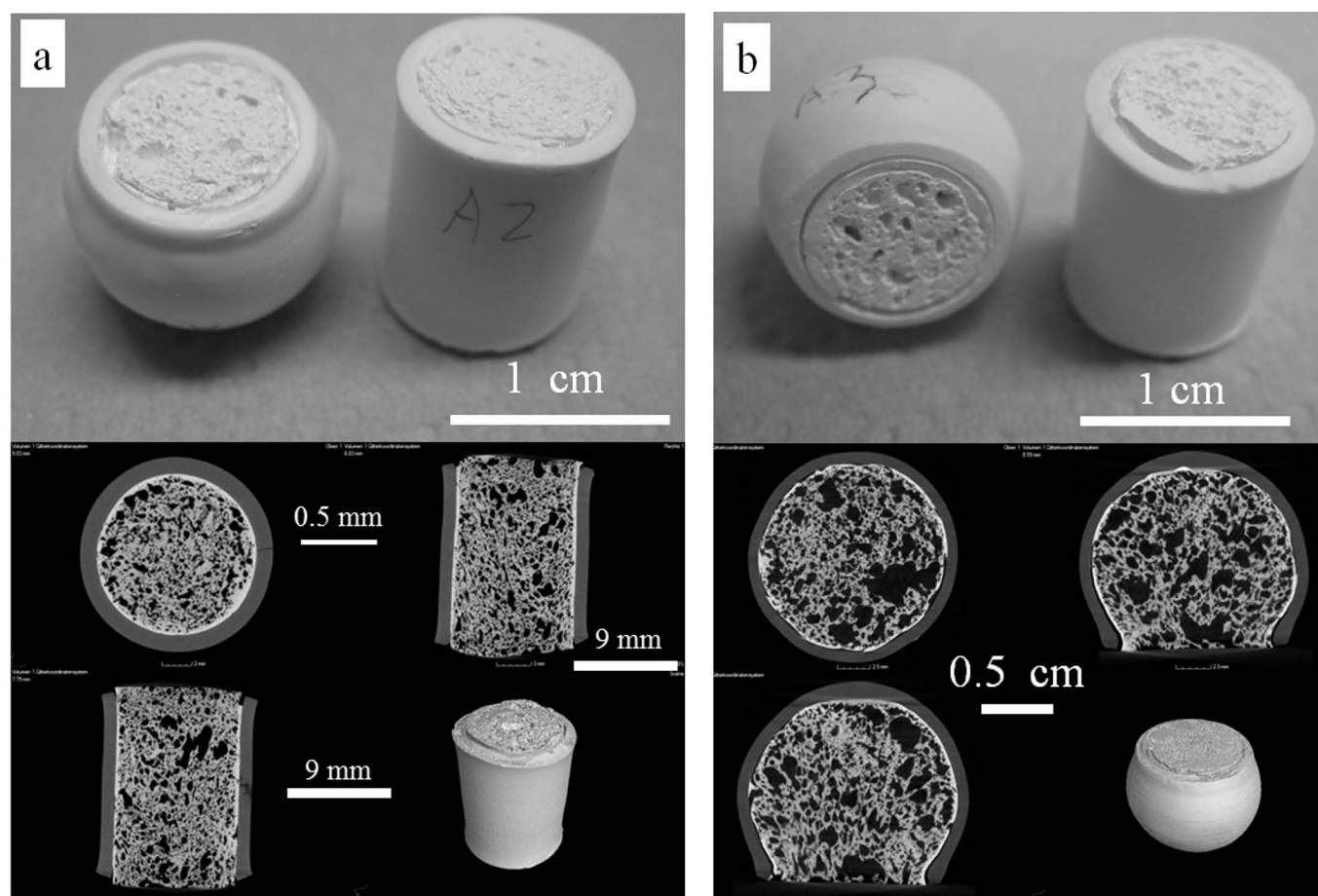

Fig. 12: a) HAp LCM-Z20H80 Freeze Foam composite and CT, b) HAp LCM-Z40H60 Freeze Foam composite and CT.
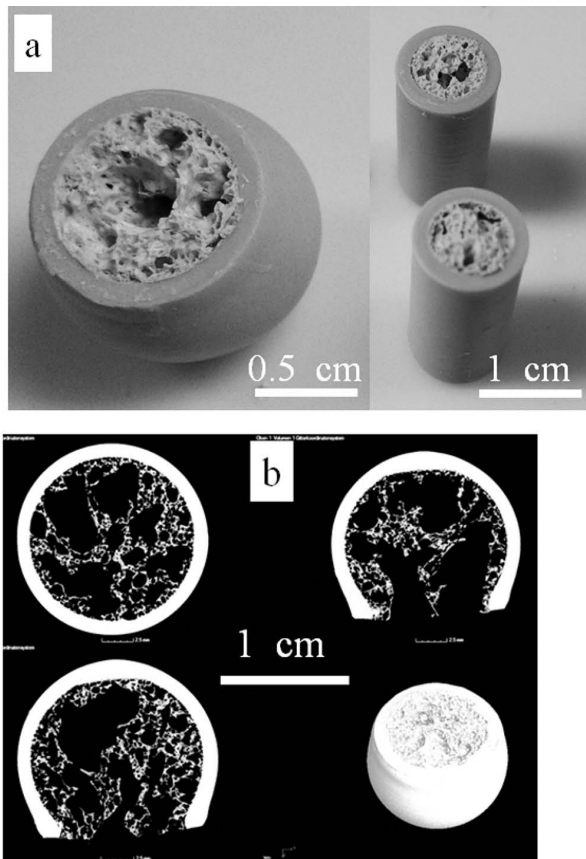
Fig. 13: a) HAp-only LCM-Freeze Foam composite, b) CT image of the HAp-only LCM-Freeze Foam composite.

(6) Femoral bone model as complex HAp-only Freeze Foam-LCM composite

In a similar way as the ZrO_2-only approach of a femoral bone model (see Fig. 4), a HAp-only femoral bone model was manufactured by means of LCM (Fig. 14) and later filled with a Freeze Foam. So far, experiments have shown that such complex geometries have their very own effect on the shrinkage behavior. Like with the pure ZrO_2 and mentioned ZxHx composite structures (III(3)/III(4)) one of the HAp-only LCM bone shells was pre-sintered at 900 °C prior to the Freeze Foam filling and later debinding/sintering. The second LCM shell stayed in the green-state and underwent green-to-green *in-situ* freeze foaming prior to its later co-debinding/-sintering. A first look after debinding the pre-sintered freeze-foam-filled bone mod-

el shows a rather good result. LCM shell and porous filling are intact (Fig. 15). Most of all, the CT analysis shows mainly a proper interface connection of the two sections dense and porous (Fig. 16). However, the foaming itself was not optimal since bigger voids are visible mainly in the head of the femoral bone. Here, the filling of the LCM shell with Freeze Foam suspension needs to be optimized. The porous-looking layer on the surface of the femoral head in Fig. 16, furthest right, is a remainder of the Freeze Foam right after foaming. The foam happened to leak out of the bone model's shaft and became fixed to the lower LCM part's surface.
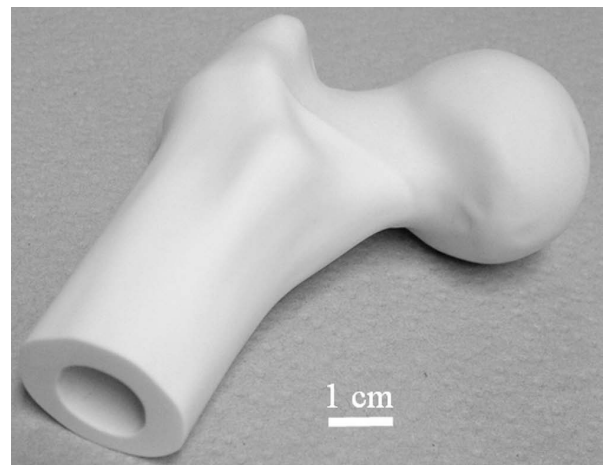

Fig. 14: LCM femoral bone model made of HAp (green-state).

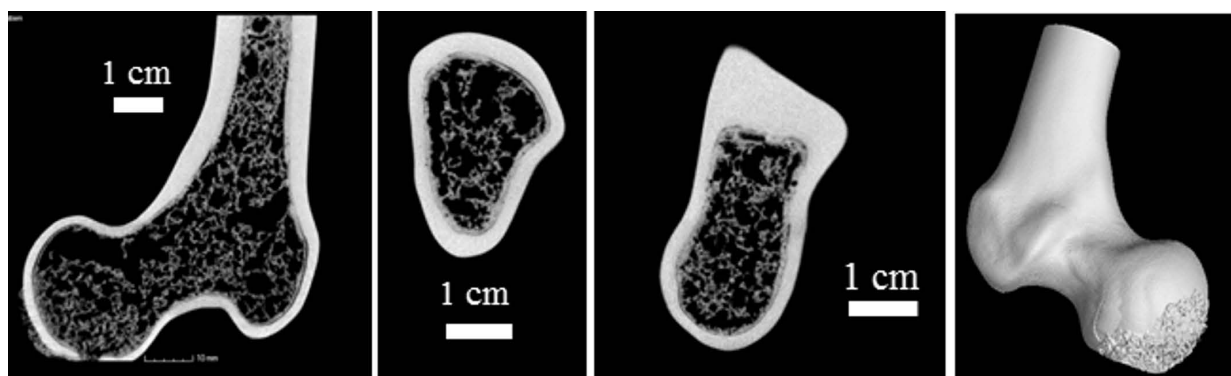**Fig. 15:** HAp LCM- Freeze Foam bone model (debinded state).

Fig. 16: CT of HAp LCM-Freeze Foam bone model (debinded state).

After sintering, however, the green-in-green processed LCM-Freeze Foam composite shows a crack along the whole part. However, the porous section seems to be fully connected to the denser LCM section (Fig. 17).
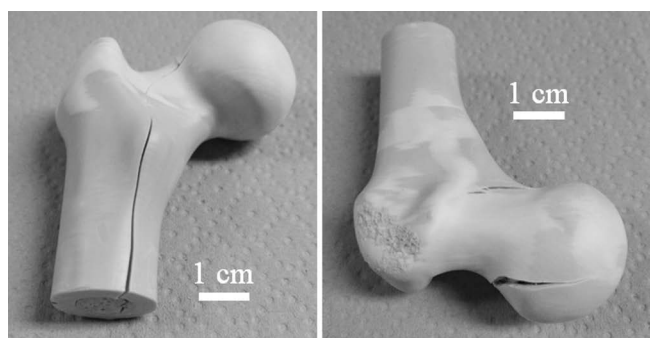

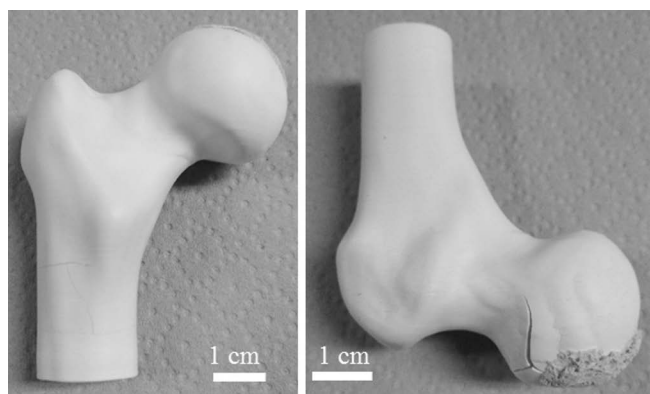**Fig. 17:** Sintered HAp LCM- Freeze Foam model (green-in-green).

Fig. 18: Sintered HAp LCM- Freeze Foam model (p.sintered-green).

The pre-sintered-to-green processed bone model looks much better, albeit with some small cracks (Fig. 18). However, CT reconstruction shows a complete detachment of the porous Freeze Foam section from the denser LCM shell (Fig. 19). Additionally, the outer part of the porous section comprises a visibly denser layer, which is most likely due to the compression of the foam against the inner wall of the LCM part. The same composite in debinded state (Fig. 16) showed no imperative sign of detachment despite the already denser outer layer of the foam. Since such a thing is not obvious with the green-in-green

processed composite, the author suggests the wetting behavior between the pre-sintered LCM shell and the green Freeze Foam as the cause.

Regarding the aimed-at connection of porous and dense parts made by the two shown different technologies, the way to success might be green-in-green processing as the specimen already proved (see Section III(5)). For these complex structures though, the solution might lie in optimizing the solid contents of LCM and Freeze Foam components and therefore porosities and shrinkage. Alternatively, the pre-sintered LCM shell could be treated with an additive that influences the wetting angle in order to provide a later successful connection to the porous part.

Regarding the partly foamed porous surface of the femoral head, it stayed stable after debinding and sintering and therefore could be used in the future as deliberate surface modification of various components.

IV. Conclusions and Outlook

This paper introduces the new hybrid shaping technique as a further developed combination of additive manufacturing and freeze foaming. This co-manufacturing approach allows the manufacturing of composite structures comprising an outer denser and optionally complex 3D geometry and an inner porous filling. Previous publications showed the manufacturing of a bioinert zirconia femoral bone model. This paper shows the successful adaption to now material-dependent bioactive/degradable and even partially bioactive/degradable composite structures. A possible use as personalized and customer-adapted bone replacement material for artificial segments for larger bone defects is provided. However, more research is needed (e.g. dilatometry of the different materials and structural features) in order to successfully manufacture complex structures like the completely bioactive femoral head bone model without any failures. In that way, personalized structures are feasible which have the potential to become the next generation of biocomposites combining dense and porous structures in one single part, just like a real bone does. Besides optimizing the suspension filling or the solid content as well as the amount of ZrO_2 in the composite, the next steps have to focus on the mechanical characterization and stability of the dense-porous connection and most of all, on biocompatibility tests.
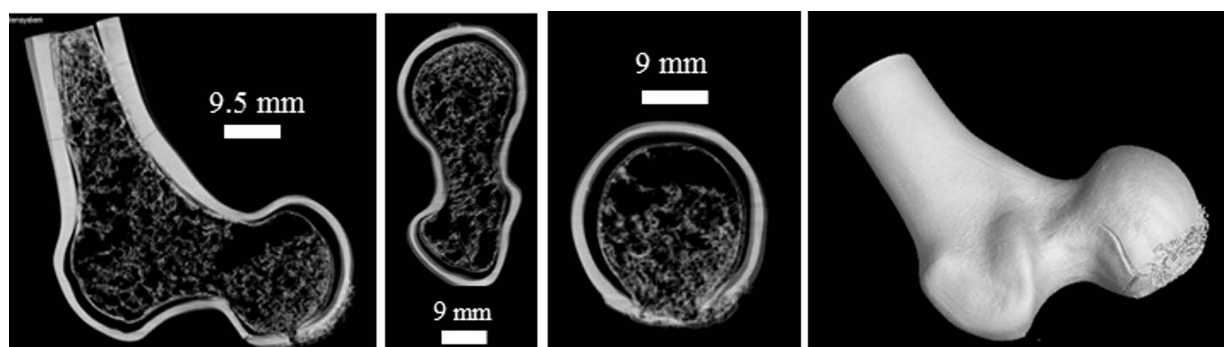

Fig. 19: CT of sintered HAp LCM-Freeze Foam (p.sintered-green).

The authors hope that the advantages of combining AM with other techniques in order to limit the particular drawbacks and profit from new possibilities in structures and approaches have been shown, not just in biomedical technology as shown here but also e.g. in lightweight and other advanced applications.

Acknowledgement

References

1   Homa, J.: Rapid prototyping of high performance ceramics opens new opportunities for the CIM industry, *Powder Inject. Molding Int.*, **6**, [3], 65 – 68, (2012).

2   Moritz, T.: Light-weight green compact and molded article made of a ceramic and/or powder-metallurgical material, and the method for the production of thereof. German Patent DE102008000100, (2008).

3   Ahlhelm, M., Moritz, T.: Freeze Foaming: A promising approach for synthesizing cellular ceramic materials. In: Proceedings of the International Conference on Cellular Materials Cellmat, Dresden, 2010.

4   Ahlhelm, M., Günther, P., Scheithauer, U., Schwarzer, E., Günther, A., Slawik, T., Moritz, T., Michaelis, A.: Innovative and novel manufacturing methods of ceramics and metal-ceramic composites for biomedical applications, *J. Eur. Ceram. Soc.*, **36**, [12], 2883 – 2888, (2016).

5   Ahlhelm, M., Zybell, K., Gorjup, E., von Briesen, H., Moritz, T.: Freeze-foaming-a new approach to manufacture ceramic cellular structures allowing the ingrowth and differentiation of mesenchymal stem cells. In: Proceedings of the 13th International Meeting and Seminar on Ceramics, Cells and Tissues 13th CCT, Faenza, Italy, 2011.

6   Schwarzer, E., Ahlhelm, M., Scheithauer, U., Moritz, T., Michaelis, A.: Development of photo-curable ceramic suspensions usable for additive manufacturing combined with Freeze Foaming. In: Proceedings of the 3rd Fraunhofer Direct Digital Manufacturing Conference DDMC2016, Berlin, 2016.

7   Roy, D.M., Eysel, W., Dinger, D.: Hydrothermal synthesis of various carbonate containing calcium hydroxyapatites, *Mater. Res. Bull.*, **9**, 35 – 39, (1974).

8   Roy, D.M., Linnehan, S.K.: Hydroxyapatite formed from coral skeletal carbonate by hydrothermal exchange, *Nature*, **247**, 220 – 222, (1974).

9   Sivakumar, M., Kumar, T.S.S., Shantha, K.L., Rao, K.P.: Development of hydroxyapatite derived from indian coral, *Biomaterials*, **17**, 1709 – 1714, (1996).

10   Xu, Y., Wang, D., Yang, L., Tang, H.: Hydrothermal conversion of coral into hydroxyapatite, *Mater. Charact.*, **47**, 83 – 87, (2001).

11   Dan, N.: Synthesis of hierarchical materials, *Trends Biotechnol.*, **18**, 370 – 374, (2000).

12   Fratzl, P., Weinkamer, R.: Nature's hierarchical materials, *Prog. Mater Sci.*, **52**, 1263 – 1334, (2007).

13   Kusmanto, F., Walker, G., Gan, Q., Walsh, P., Buchanan, F., Dickson, G., McCaigue, M., Maggs, C., Dring, M.: Development of composite tissue scaffolds containing naturally sourced microporous hydroxyapatite, *Chem. Eng. J.*, **139**, 398 – 407, (2008).

14   Rocha, J., Lemos, A., Agathopoulos, S., Kannan, S., Valerio, P., Ferreira, J.: Hydrothermal growth of hydroxyapatite scaffolds from aragonitic cuttlefish bones, *J. Biomed. Mater. Res., Part A*, **77A**, 160 – 168, (2006).

15   Vecchio, K., Zhang, X., Massie, J., Wang, M., Kim, C.: Conversion of bulk seashells to biocompatible hydroxyapatite for bone implants, *Acta Biomater.*, **3**, 910 – 918, (2007).

16   Vecchio, K., Zhang, X., Massie, J., Wang, M., Kim, C.: Conversion of sea urchin spines to Mg-substituted tricalcium phosphate for bone implants, *Acta Biomater.*, **3**, 785 – 793, (2007).

17   Walsh, P., Buchanan, F., Dring, M., Maggs, C., Bell, S., Walker, G.: Low-pressure synthesis and characterisation of hydroxyapatite derived from mineralise red algae, *Chem. Eng. J.*, **137**, 173 – 179, (2008).

18   Wu, S.L., Liu, X.M., Hu, T., Chu, P.K., Ho, J.P.Y., Chan, Y.L., Yeung, K.W.K., Chu, C.L., Hung, T.F., Huo, K.F., Chung, C.Y., Lu, W.W., Cheung, K.M.C., Luk, K.D.K.: A biomimetic hierarchical scaffold: Natural growth of nanotitanates on three-dimensional microporous Ti-based metals, *Nano Lett.*, **8**, 3803 – 3808, (2008).

19   Zhang, X., Vecchio, K.S.: Creation of dense hydroxyapatite (synthetic bone) by hydrothermal conversion of seashells, *Mater. Sci. Eng. C-Biomimetic Supramol. Syst.*, **26**, 1445 – 1450, (2006).

20   Ruffini, A., Sprio, S., Tampieri, A.:Study of the hydrothermal transformation of wood-derived calcium carbonate into 3D hierarchically organized hydroxyapatite, *Chem. Eng. J.*, **217**, 150 – 158 (2013).

21   Ahlhelm, M., Moritz, T.: Synthetic bone substitute material and method for producing the same. European Patent EP2682137A3, (2013).

22   Ahlhelm, M., Moritz, T.: Production of a biocompatible hydroxyapatite-ZrO_2 hybrid form with the method of freeze-foaming, (in German), in Schriftenreihe Werkstoffe und Werkstofftechnische Anwendungen 41, Hrsg., B. Wielage, Chemnitz: Deutsche Gesellschaft für Materialkunde e.V. DGM, 2011.

23   Ahlhelm, M., Gorjup, E., von Briesen, H., Moritz, T., Michaelis, A.: Freeze-foaming – A promising approach to manufacture strength enhanced ceramic cellular structures allowing the ingrowth and differentiation of human mesenchymal stem cells, in: Proceedings of MiMe-Materials in Medicine, International Conference 1st edition MIME, Faenza, Italy, 2013.

24   Ahlhelm, M.: Freeze Foams – Development of cellular structures for various applications, (in German), in Schriftenreihe Kompetenzen in Keramik, Band 32, Hrsg.: Fraunhofer IKTS, Dresden; Alexander Michaelis, Fraunhofer Verlag, ISBN 978 – 3-8396 – 0977 – 4, 2016.

25   Ahlhelm, M., Fruhstorfer, J., Moritz, T., Michaelis, A.: Producing lightweight refractory bricks with the direct freeze foaming method, (in German), *Keramische Zeitschrift*, **6**, [63], 405 – 409, (2011).

26   Ahlhelm, M., Fruhstorfer, J., Moritz, T., Michaelis, A.: The manufacturing of lightweight refractories by direct freeze foaming technique, *Interceram*, **6**, [60], 394 – 399, (2011).

27   Günther, P.: Development of porosity-graded structures on the basis of zirconium dioxide with the combination of additive manufacturing and direct freeze foaming, (in German), Master's Thesis, Hochschule Koblenz/Fraunhofer IKTS Dresden, (2015).