BONEFOAM NETWORK AND INNOVATIVE SHAPING APPROACH TO NEXT-GENERATION BIO SCAFFOLDS

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Fraunhofer
IKTS

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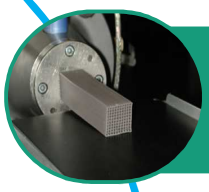
Who we are & what we do

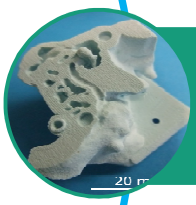
Fraunhofer Institute for Ceramic Technologies and Systems (IKTS)

Work group Shaping (Dr. Tassilo Moritz)



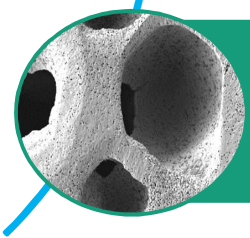
(Thermo)plastic shaping

- Powder Injection Molding (µ-CIM, two-component, in-mold labeling)
- Extrusion etc.



Additive Manufacturing

- Selective Laser Sintering (SLS)
- 3D-Printing and Thermoplastic 3D-Printing (T3DP)
- **Lithography-based Ceramic Manufacturing (LCM)**



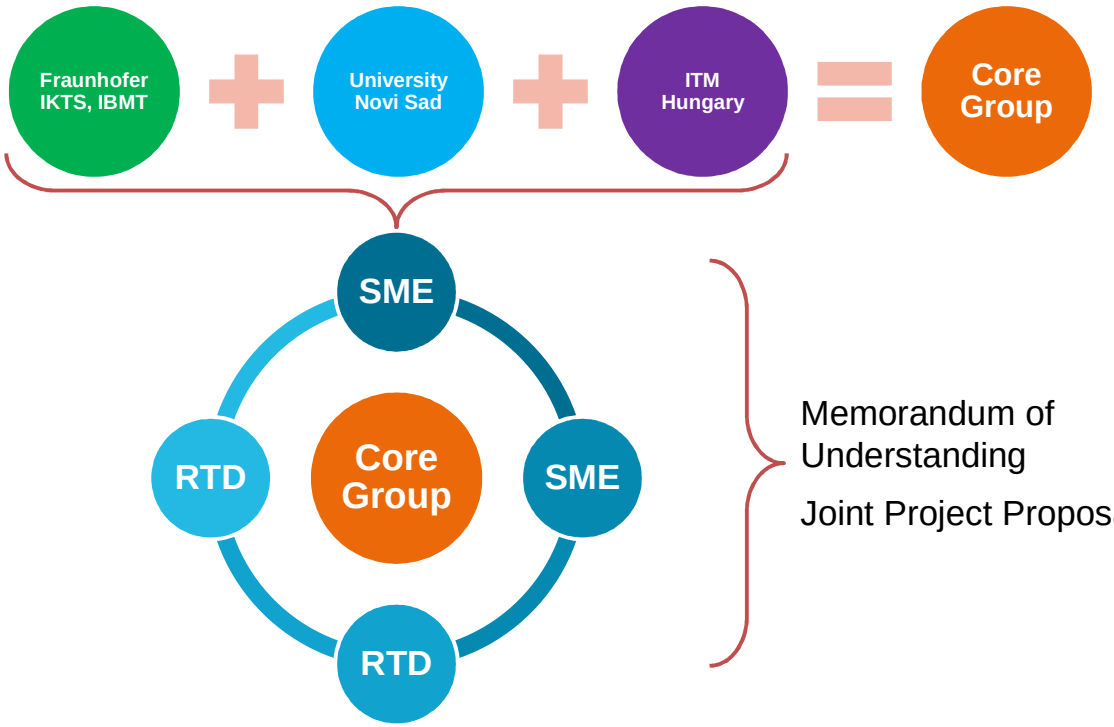
Wet shaping technologies

- Tape casting
- Slip casting
- Freeze shaping technologies

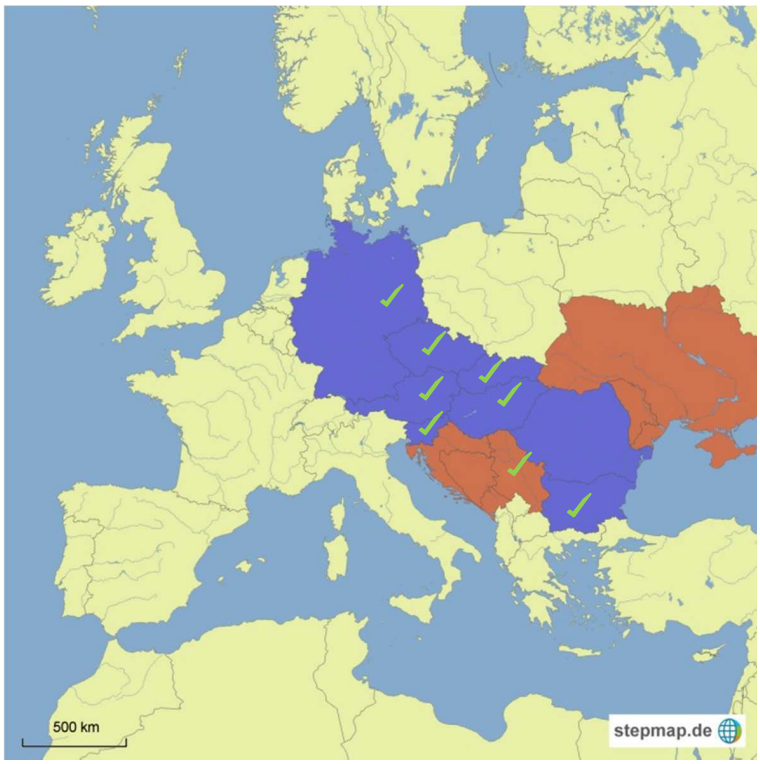
→ **Freeze Foaming**

1. The Project BONEFOAM

Project funded by German Federal Ministry of Education and Research: Development of all-ceramic, bioresorbable bone replacement structures with enhanced mechanical properties via the Direct *Freeze-Foaming* method



Goals



1. To find partners from the Danube states (*primary requirement*) and establish a new network with possible partners for network formation:

Germany, Austria, Czech Republic, Slovakia, Slovenia, Hungary, Romania, Bulgaria (EC-members)

Serbia,

Croatia, Bosnia and Herzegovina, Montenegro, Ukraine, Moldavia

Goals

- 2. To create a **scientific network** with partners in **the field of bio-/medical technology**
  - to develop:
    1. **bone replacement materials**
       1. load bearing: all-ceramic, biocompatible materials with enhanced mechanical properties via the so-called Freeze-Foaming method
       2. non load bearing: via freeze foaming of e.g. polymeric materials
       3. combination of porous and dense part-producing methods
    2. **Surface Modification/Biocidic Surfaces**
    3. **Drug Delivery Systems**
    4. **Bio sensors, etc.**
  - to apply novel techniques (like freeze foaming) for attaining personalized bone replacement structures
  - Tests, Characterization and Evaluation of developed components
  - to get materials and technologies market-ready

A major point of collaboration in the network shall be the application for funding on European level.

Achievements

BONEFOAM

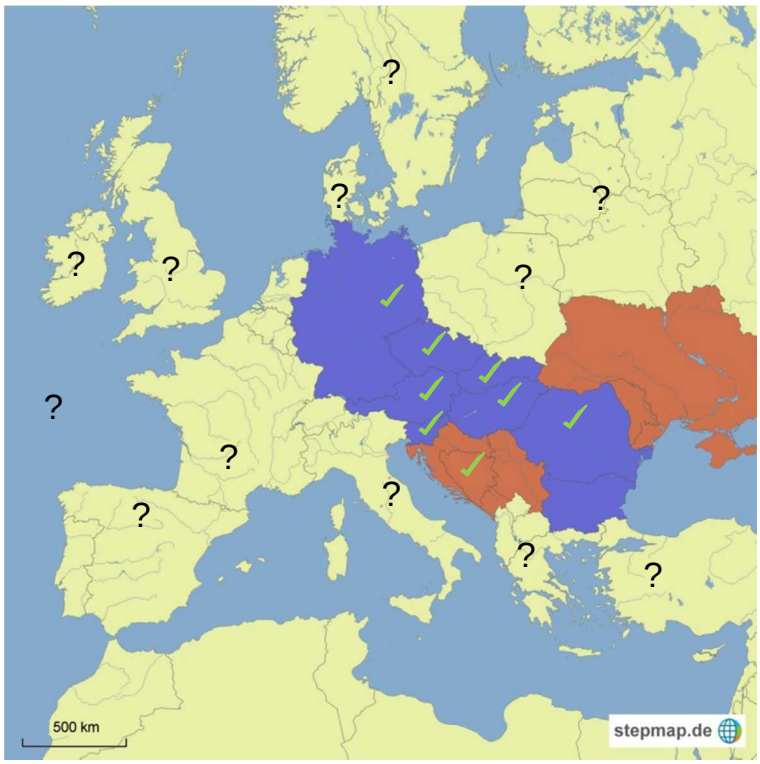
- Phase 1 (October 2013 – September 2014):
  - Market survey
  - Two Workshops (Dresden, Germany, May 2014 and Szeged, Hungary, July 2014)
  - a total of 32 participants, 8 partnering countries
  - 7 SME[1]
  - 8 Research and Development Institutes/Universities[2]
  - 2 two-stage proposals PHC 14 and PHC 16 (Rare diseases and Tools and technologies for advanced therapies)
- Phase 2 (May 2015 – April 2016)
  - Workshop in Dresden June 1st – 2nd
  - 2 joint proposals for H2020 FETOpen call

[1] Lithoz, ITM/NanoTi, Nanocolltech, CROmed Research and Service Center, Lacerta Ltd., OFI Technology & Innovation GmbH, UVR-FIA

[2] Fraunhofer IBMT & IKTS, University of Szeged, University of Novi Sad, Slovak Academy of Sciences, Brno University of Technology, Jožef Stefan Institute, Bulgarian Academy of Sciences

Further Goals

BONEFOAM



1. To find **new** partners from **all over the EU and beyond** (End consumer, Clinics, SME, R&D)

2. To **strengthen the network** for

3. sustainable and **joint reasearch activities** in the field of **biomedical technologies**

Challenges approached

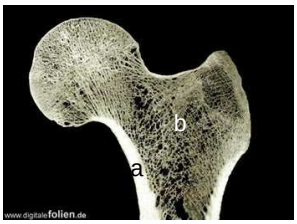
- Increase in life expactency
- Need for bone replacement materials also due to:
  - Bone destructing diseases
  - Defects from accidents
- Solutions to date:
  - Endogenous (natural) bone graft substitutes
  - Synthetic bone graft substitutes (BGS)
    - dense and porous
      - Metal (Ti, Ti-alloys)
      - Polymers (PEEK, PA)
      - Ceramics (ZrO_2, Al_2O_3, Hydroxyapatite (HAp) or TCP)
- demand of an ideal BGS: biocompatible, bioresorbable, osteoconductive, osteoinductive, **structurally similar to bone**

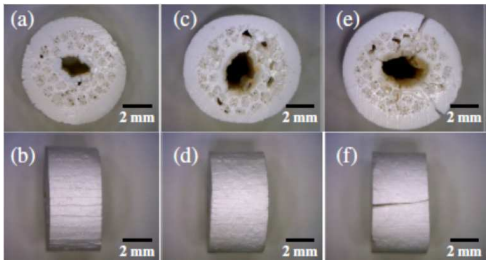
State of the Art ⇔ Innovation

- Ceramic bone graft substitutes:
  - Various geometries (bricks, prisms, granules, balls)
  - Complex shapes in terms of dense shell (*cortical bone*, a) and porous filling (*cancellous bone*, b), like a real bone?
  - First approaches:
    - ZrO_2 shell/porous HAp filling
    - Use: for small bone defects (segments of finger bones)
    - **Unresolved:**
      - Complex outer shape
      - Larger specimen

BGS HAp/TCP by Ceramisys

Orbital implants by Ceramisys

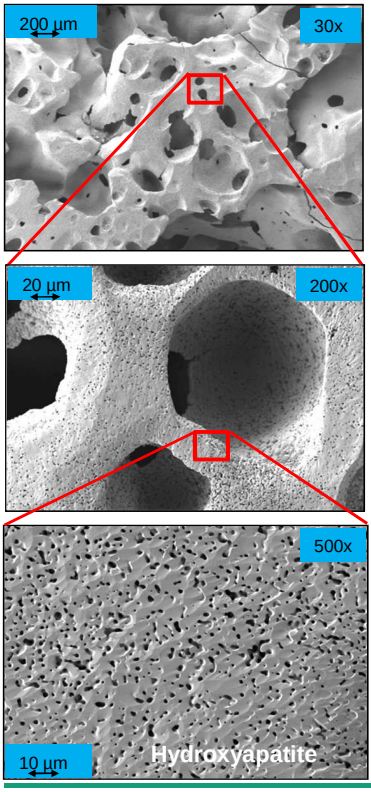


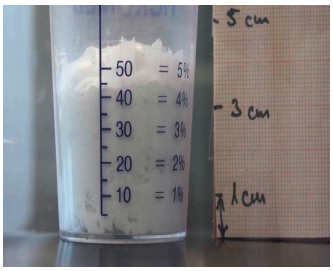


Dong-Woo Jang et al.: Microwave sintering and in vitro study of defect-free stable porous multilayered HAp–ZrO2 artificial bone scaffold; Sci. Technol. Adv. Mater. 13 (2012) 035009 (9pp)

1. Freeze Foams as porous structures

Advantages (structural)





- Foam with high amount of open porosity (- 95%)
- Meso- to macropores
- Interconnectivity and microporosity
- Technique: **Freeze Foaming**
  - Based on pressure reduction in a freeze dryer
  - Pores through rising water vapour & sublimation
  - Patent: DE 10 2008 000 100
- Near-net shaping possibility → personalization

Freeze Foaming

Advantages (biological)

- Cytotoxicity tests (L929, mouse fibroblasts, fluorescein diactetate and propidium iodide):
  - All *foam structures are biocompatible*:
    - Biocompatibility validated in hydroxyapatite, zirconia and combinations of thereof to strength enhancement up 60 MPa → „Novel synthetic bone replacement material“
      Patents: DE 10 2012 211 390, EP 2682137
- Differentiation approaches: hMSCs, alkaline phosphatase (ALP) and collagene I
  - *Prove of osteogenic differentiation* on the detection of ALP (as early marker) and collagene I
  - *Proliferation could be maintained* with a simultaneous increase in the compressive strength of up to 60 MPa
- **Freeze foaming allows individual near-net shaping to synthetic biocompatible potential bone structures**

Why not combine with Additive Manufacturing?

2. Additive Manufacturing (AM) to complex 3D structures

LCM – Lithography based Ceramic Manufacturing

[2] CeraFab 7500, Lithoz GmbH

Cooperation with IKTS

AM (LCM)

we offer:

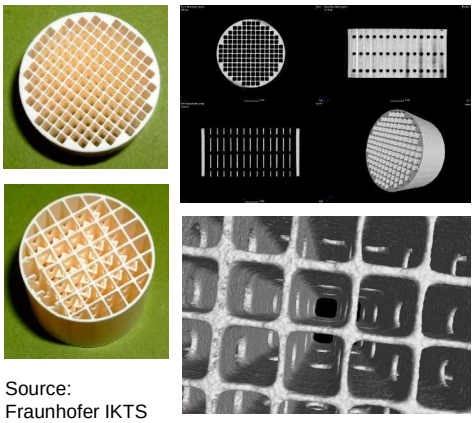
1. Material & paste development
2. Design and functional simulation
3. Part building

Complex 3D structures

Miniaturization

Mixer and reactors

- Alumina (high purity): density 99,4 % and higher
- Zirconia (3mol.-% stabilized): density 99,1 % and higher



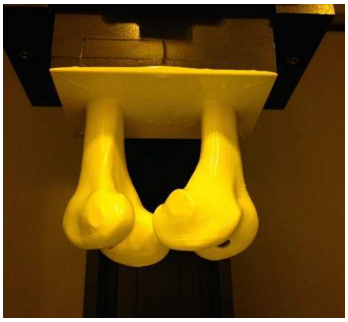
Source:
Fraunhofer IKTS

3. Next-generation Bio Scaffolds

LCM + Freeze Foaming

- Demonstrator
  - LCM-manufactured femural bone model (shell)
  - filled with a Freeze Foam

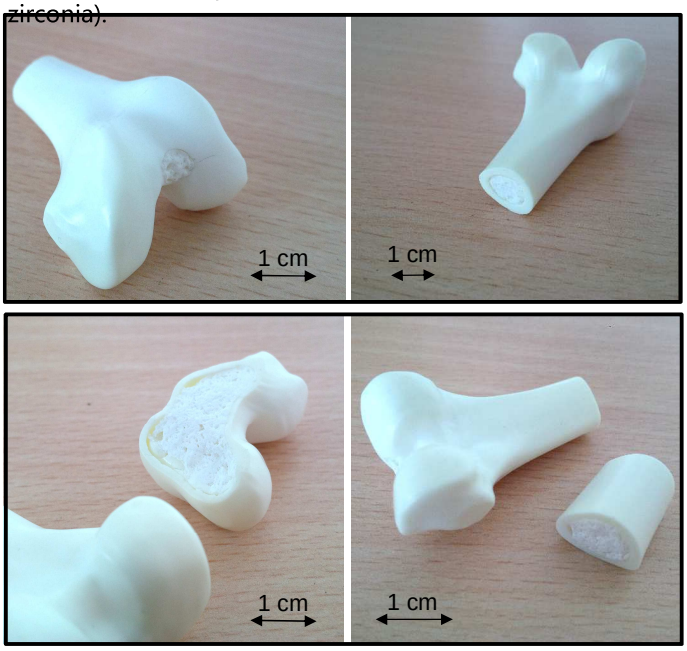
LCM



Günther, P.; Master's Thesis, 2015

1. Partial sintering (LCM Part)
2. in-situ Freeze Foaming
3. Co-Sintering

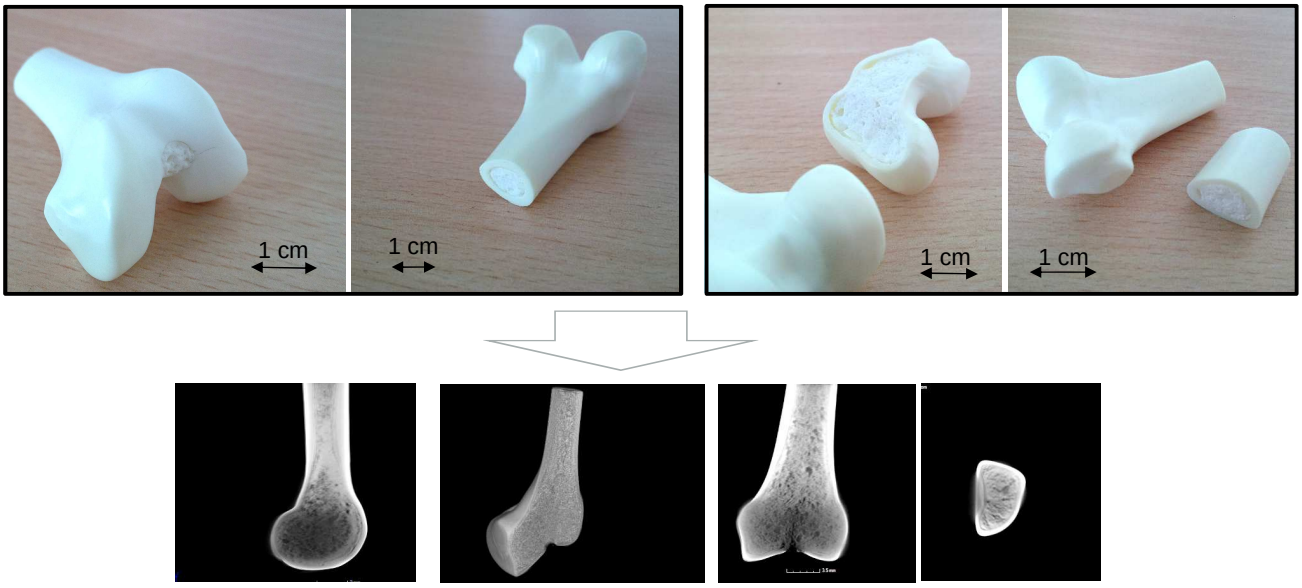
Femural head composite structure (sintered zirconia).



3. Next-generation Bio Scaffolds

LCM + Freeze Foaming

- Computer tomographic reconstruction of the demonstrator bone model



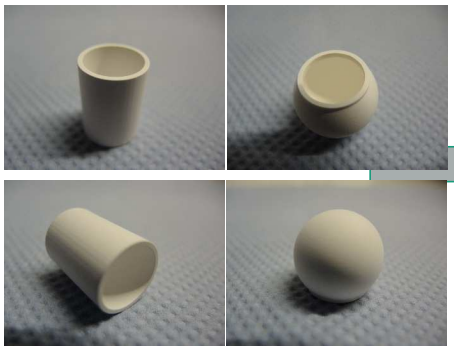
- Mainly partial or complete form and material fit between Freeze Foam and dense LCM shell → connected cortical and cancellous features

3. Next-generation Bio Scaffolds

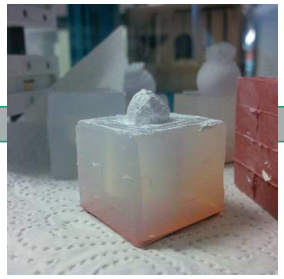
LCM + Freeze Foaming

- **towards biodegradable** material
  - ZrO_2/Hydroxyapatite (50:50 Vol.-%) composite by LCM and Freeze Foaming

1. LCM parts



2. In-situ Freeze Foaming

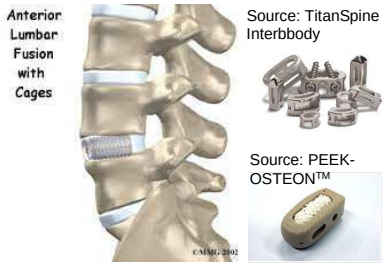


3. Co-manufacturing to LCM/Freeze Foam composites

  - Green state → sintering and interface characterization
  - Aim: enhanced compressive strength (due to zirconia) whilst retained bioactivity (due to hydroxyapatite) → long term implant
  - Next: fully resorbable complex structures

Status, Prospects & new Partners

- *Phase of development*:
  - Proof-of-concept (biocompatibility & osteogenic activity, in-vitro + co-manufacturing)
  - Recently adressing issues for better reproducibility and in-depth understanding of the process
- *Prospects*:
  - Bone replacement materials: biocompatible, bioresorbable, osteoconductive, osteoinductive, **structurally similar to bone** → demand
  - Interbody fusion cages etc. and combine different materials and geometries
- *New projects, R&D and partners*:
  - Biomedical and pharmaceutical expertise for product specification and surface treatment
  - End-user for clinical and mechanical testing (especially in-vivo testings)
    - Surgeons, Orthopaedics, Physicians
  - **Partners for common projects in the field of novel porous structures**



Source: TitanSpine Interbbody

Source: PEEK-OSTEON™

Thank you very much!

Joining the network, generating new ideas and executing new bilateral and EU-projects is very much appreciated.

Many thanks to BMBF (project BONEFOAM 01DS13010/01DS15004), Fraunhofer and COST NEWGEN