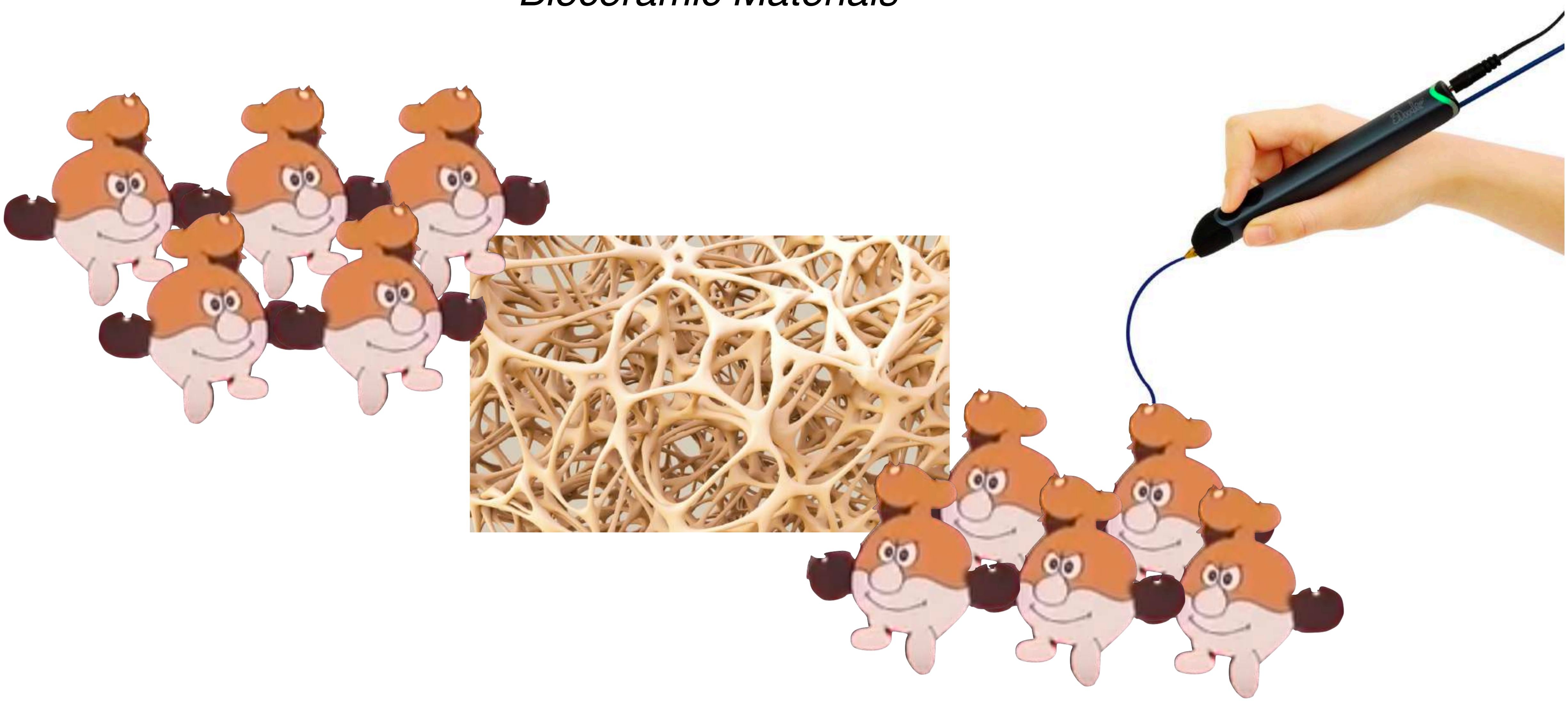
Bioceramic Materials



María González Esguevillas
MacMillan Group Meeting
April 18, 2019

Introduction to Bioceramics

Bioceramic:

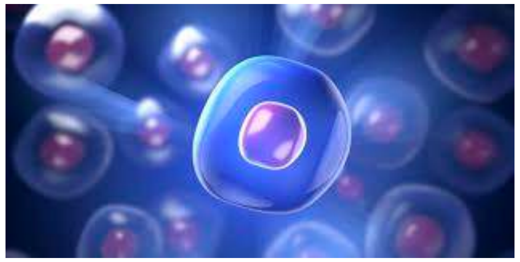
Any ceramic, glass, or glass-ceramic used as a biomaterial, which is a material intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ, or function of the body.

bio-

-ceramic

greek [*bios*]
— life —

greek [*keramikos*]
— relating to products made from clay, pottery and brick —



Baino, F. et al *Frontiers in Bioeng. and Biotech.* ***2015****,* 3, 202

Yeoh, F-Y. et al *J. Biomaterials App.* **2011***, 27,* 345.

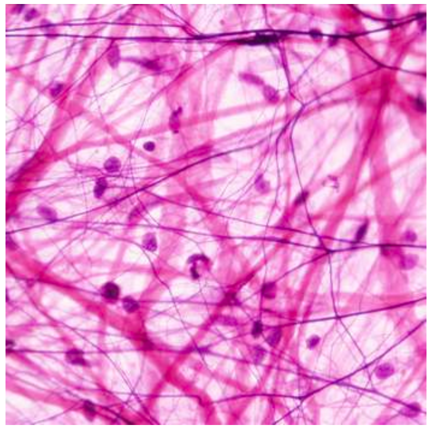
Introduction to Bioceramics

Bioceramic:

A large class of specially designed ceramics for the repair and reconstruction of diseased or damaged parts of the body

BONES

TISSUES



Why are important?

What is the difference between these treatments and others?

Baino, F. et al *Frontiers in Bioeng. and Biotech.* ***2015***, 3, 202

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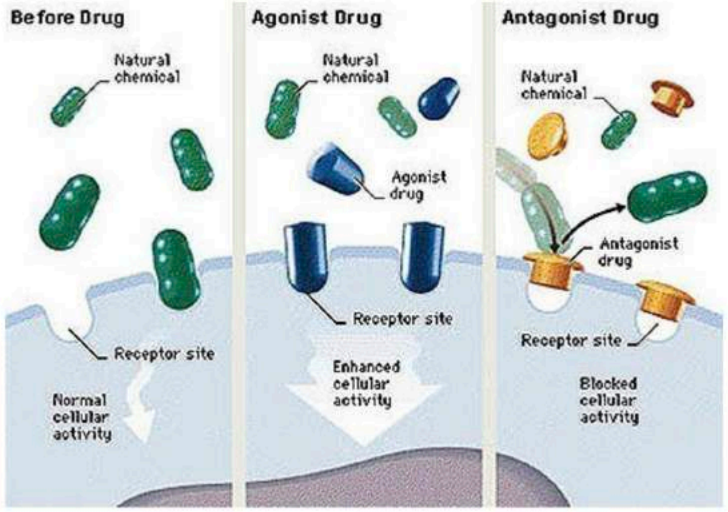
Introduction to Bioceramics

Why are important?

BONES *TISSUES*

What is the difference between these treatments and others?

DISEASE TREATMENTS



- *Causes: virus, bacteria, autoimmune, cancer, genetic diseases*
- *Target identification*
- *Treatment*

Introduction to Bioceramics

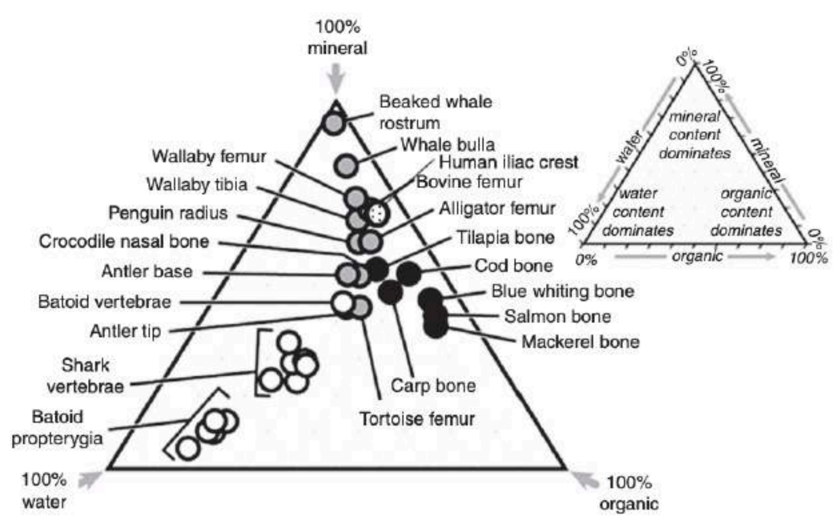
Why are important?

BONES

TISSUES

What is the difference between these treatments and others?

Composition



capable to regenerate tissues

Diseases

- *Fractures*
- *Osteoporosis*
- *Osteomyelitis*
- *Osteosarcoma (cancer)*
- *Hyp dysplasia*

What was the solution for these diseases?

Time or amputation

Introduction to Bioceramics

Why are important?

BONES *TISSUES*

What is the difference between these treatments and others?

Composition

- *25 % water*
- *30 % Organic mineral:*
  cells** (osteoblast, osteoclast, osteocytes, connective tissue) and **collagen
- *45 % Inorganic mineral*
  calcium phosphates** (HA) and **carbonates

capable to regenerate tissues

Diseases

- *Fractures*
- *Osteoporosis*
- *Osteomyelitis*
- *Osteosarcoma (cancer)*
- *Hyp dysplasia*

What was the solution for these diseases?

Time or amputation

Introduction to Bioceramics

History and Evolution of Bioceramics

Neolithic period
7200 BC

pottery

lime plaster

- BC

statues

lime plaster over armatures of reeds

Ancient Romans
1st Century
975 AD

CaO, $CaSO_4$

plaster of Paris

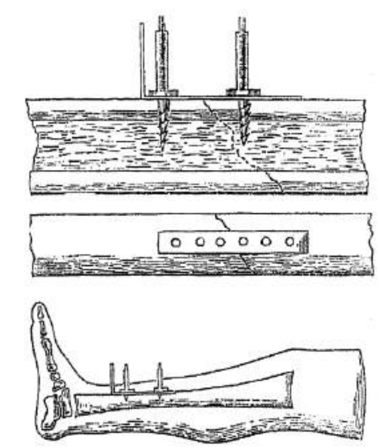
dental use, broken bones, oil painting

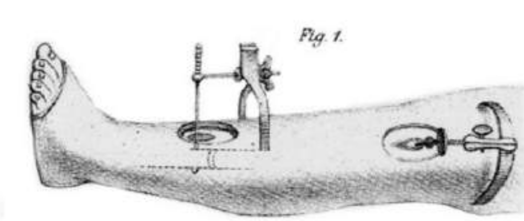
metal or wood prothesis

18th-19th century

Fe, Au, Ag, Pt

metal devices to fix bone fracture





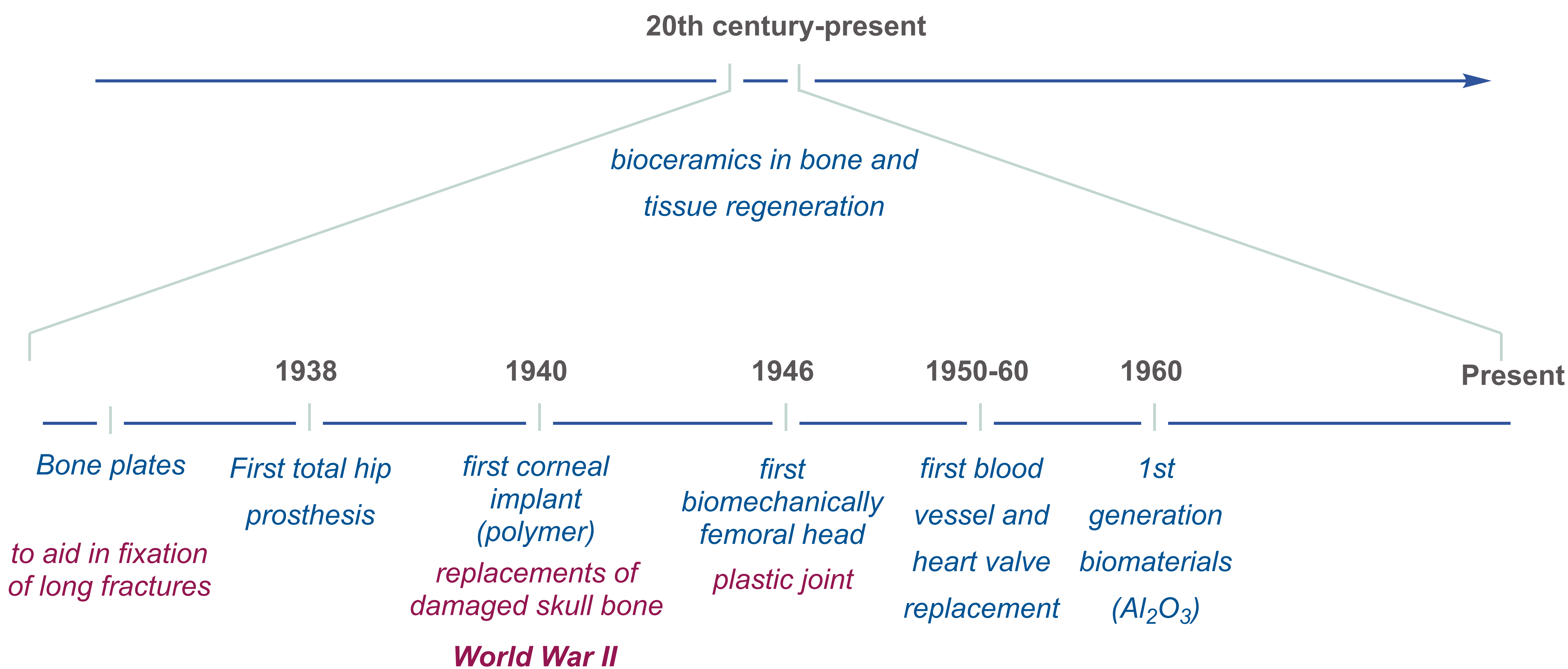
Capel, F. et al *Bol. Soc. Esp. Ceram. Vidr.* ***1987***, 26, 13

Chang, J. et al *Materials Today* ***2019***, 24, 41

Dorozhkin, S. V. et al *Materials Sci. Eng.* **2013**, *33,* 3085.

Introduction to Bioceramics

History and Evolution of Bioceramics



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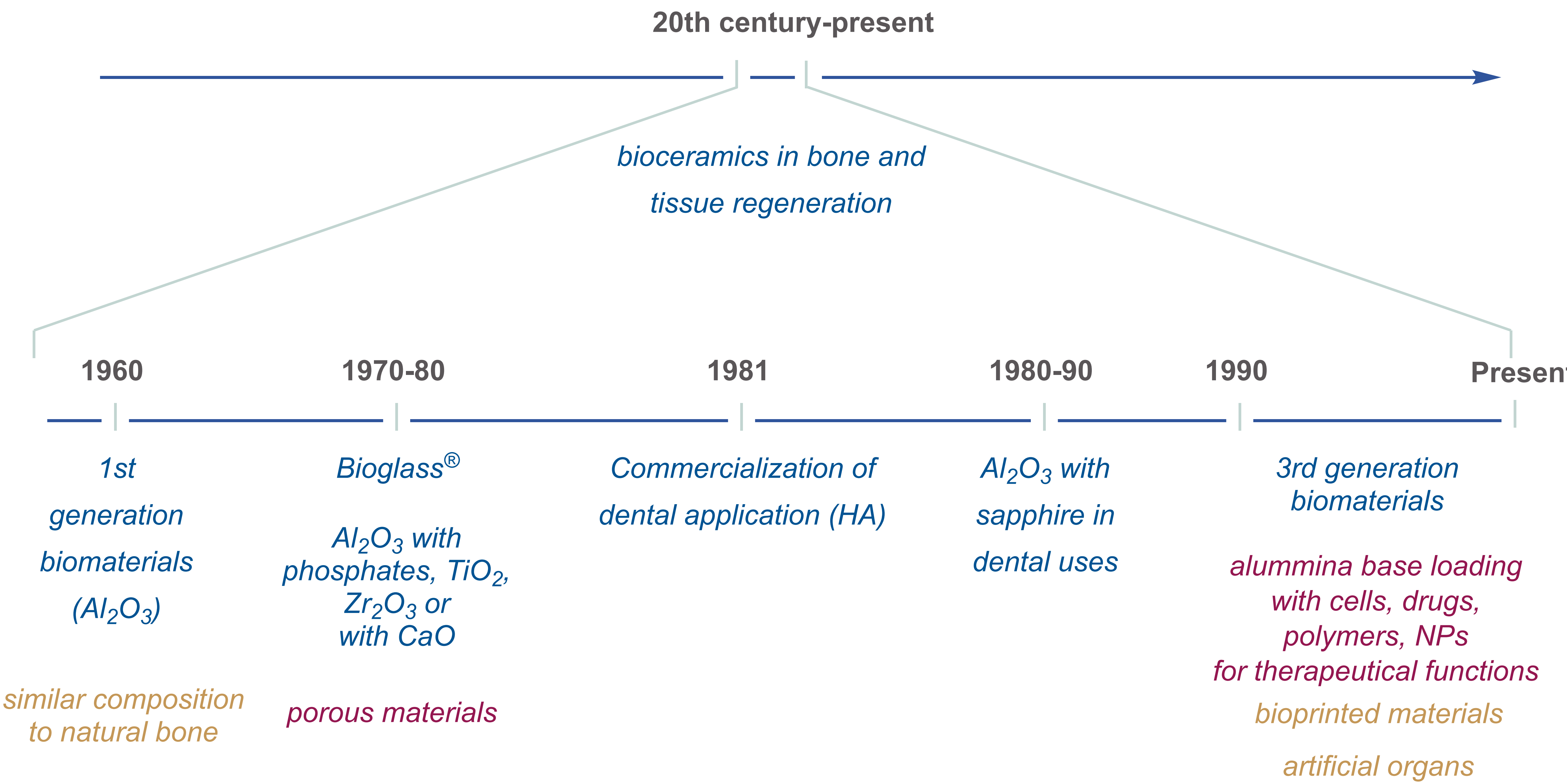

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Bioceramic materials

Requirements and critical issues

Including foreign material into the body, we need to consider different parameters.
Different according with the time

- ***Geometry.***
  — *Must fill the defects and guide during the regeneration process* —
- ***Bioactivity.***
  — *Rapid tissue attachment and stable long-term bonding* —
- ***Biocompatibility.***
  — *Ability to support normal cellular activity* —
- ***Chemical & biological stability/ Biodegradability.***
  — *for indefinitely high stability, temporal devices must degrade gradually and be replace by natural issue*—
- ***Porous structure.***
  — *interconnected porous structure to allow cell penetration, tissue in-growth*—
- ***Biological properties.***
  — *angiogenesis, antibacterial effect,etc by release of appropriate ions*—
- ***Mechanical competence/compliance.***
  — *adequate elastic compliance* —
- ***Fabrication & Commercialization potential.***

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Bioceramic materials

Classification

1st generation

- **Al_2O_3** *or* **ZrO_2**
- ***Synthetic HA*** **$(Ca_{10})PO_4)_6(OH)_2)$**

as cement, granules or in the form of coatings on metallic joint prostheses

- *Cristalline ceramics, similar structure, composition to bone*
- *inert, osteoconductivity: biocompatible, bonds with the host without scar tissue*

- *low mechanical properties*
- *slow resorption rate*

Substitution

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Bioceramic materials

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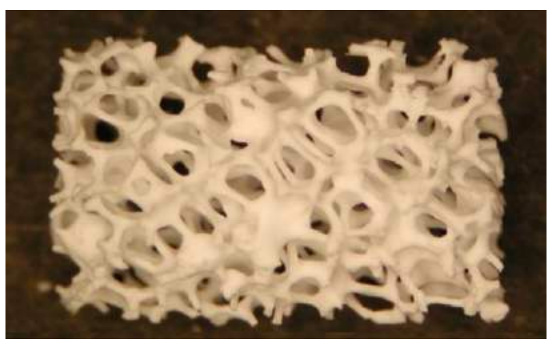
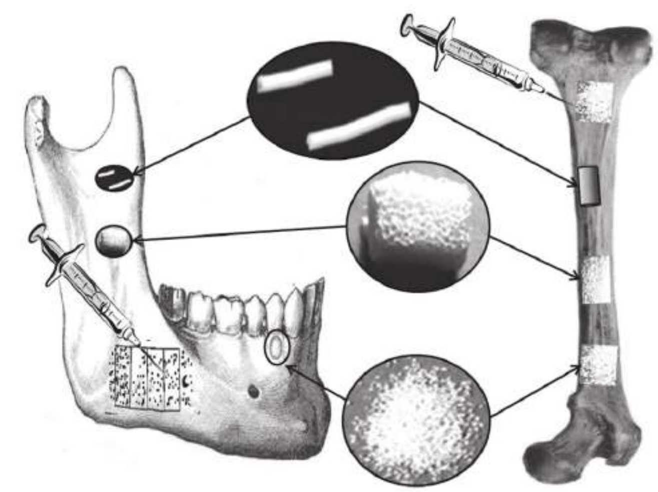


2nd generation

- ***Synthetic HA, calcium phosphate and silica-based BG.***
- ***Bioglass (bioactive glasess)***

porous scaffolds, glass fibers

- *bond with the host, stimulate the cells to produce new tissue*
- *osteoconductivity: biocompatible, bioactive*
- *partially crystalline materials*
- *better mechanical properties: higher elasticity, hardness, wear resistance*



Repair

Capel, F. et al *Bol. Soc. Esp. Ceram. Vidr.* ***1987***, 26, 13

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Bioceramic materials

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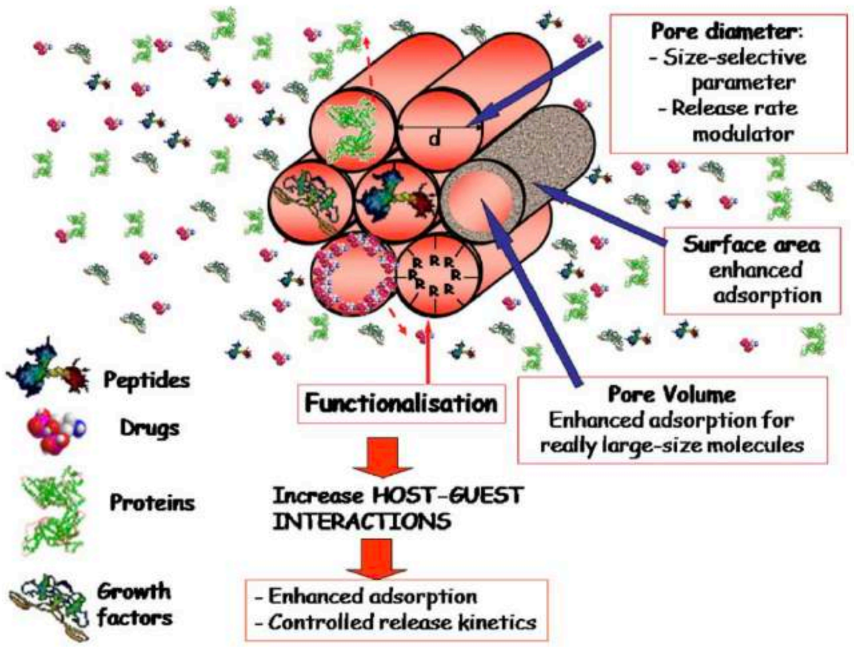
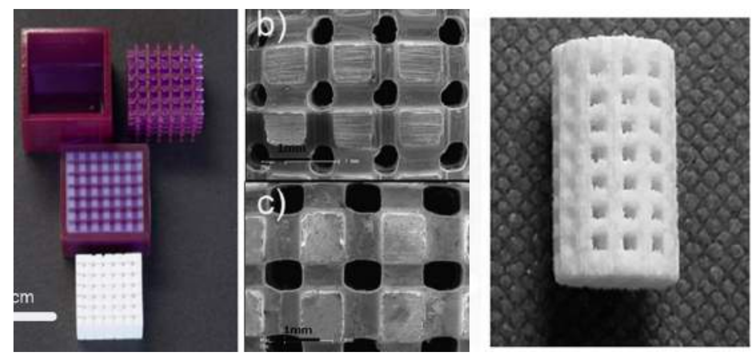
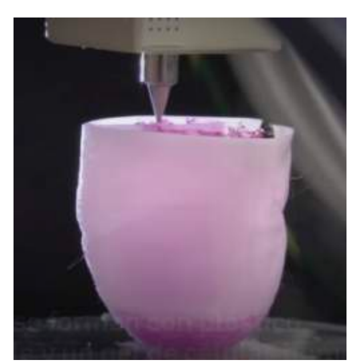






3rd, (4th) generation

- ***Synthetic HA, Bioglass-derived***
- ***Composites, porous foams***

mesoporous glass particles, scaffolds with polymers, proteins, metal, NPs, drugs, stem cells

- *capable to functionalize surface, activate genes for regeneration*
- *bond with proteins, release cells, drugs*
- *degradation rates match with generation of new tissue*
- *high fatigue resistance*

Regeneration

Capel, F. et al *Bol. Soc. Esp. Ceram. Vidr.* ***1987***, 26, 13

Baino, F. et al *Frontiers in Bioeng. and Biotech.* ***2015***, 3, 202

Bioceramic materials

Classification: Body Human Repair

Substitution	Repair	Regeneration
1^{st} generation	**2^{nd} generation**	**3^{rd}, (4^{th}) generation**
■ ***Al_2O_3*** *or* ***ZrO_2*** ■ ***Synthetic HA $(Ca_{10})PO_4)_6(OH)_2)$*** *as cement, granules or in the form of coatings on metallic joint prostheses*	■ ***Synthetic HA, calcium phosphate and silica-based BG.*** ■ ***Bioglass (bioactive glasess)*** *porous scaffolds, glass fibers*	■ ***Synthetic HA, Bioglass-derived*** ■ ***Composites, porous foams*** *mesoporous glass particles, scaffolds with polymers, proteins, metal, NPs, drugs, stem cells*

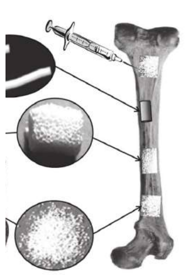
fabrication of prosthesis and implants

Bionic Approach

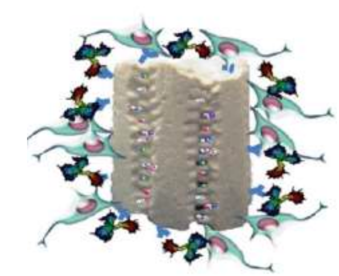
tissue engineering

cell therapy

Regeneration Medical Approach



The human body repair



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Bioceramic materials

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Similar material with different properties. How can we synthesize them?

Capel, F. et al *Bol. Soc. Esp. Ceram. Vidr.* ***1987***, 26, 13

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Bioceramic materials

Fabrication Technologies of bioceramic scaffolds

- **Solid-state reaction.** *Repeated cycles of milling and calcination of the powders*

1st generation   high crystallinity   non-porous material

- **Wet-state reaction.**

Foaming Methods

General method

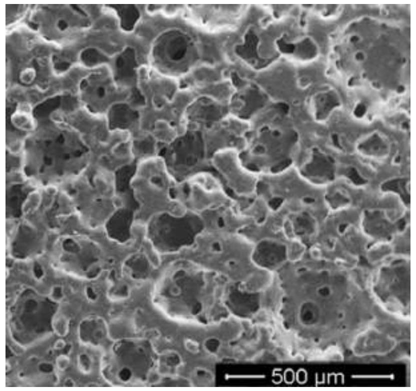
dispersion of gas into a ceramic suspension/colloidal sols. Follow by solidification

⇨

porous from 20um to 2 mm

poor interconnectivity

non-porous external surface



— *bioactive glasses, Ca scaffolds. porosity can be modulated* —

H_2O_2 foaming

mixing ceramic powder with aqueous sol. of H_2O_2.
It´s moulded and stored at 60 ^oC

gel-cast foaming (polymerization)

an organic monomer with an initiator and a catalyst, then add the surfactant

sol-gel foaming

sol-gel technology and mechanical frothing

⇩

hierachical structure with interconnected macropores (promotes cell adhesion)

Baino, F. et al *Frontiers in Bioeng. and Biotech.* ***2015****,* 3, 202

Bioceramic materials

Fabrication Technologies of bioceramic scaffolds

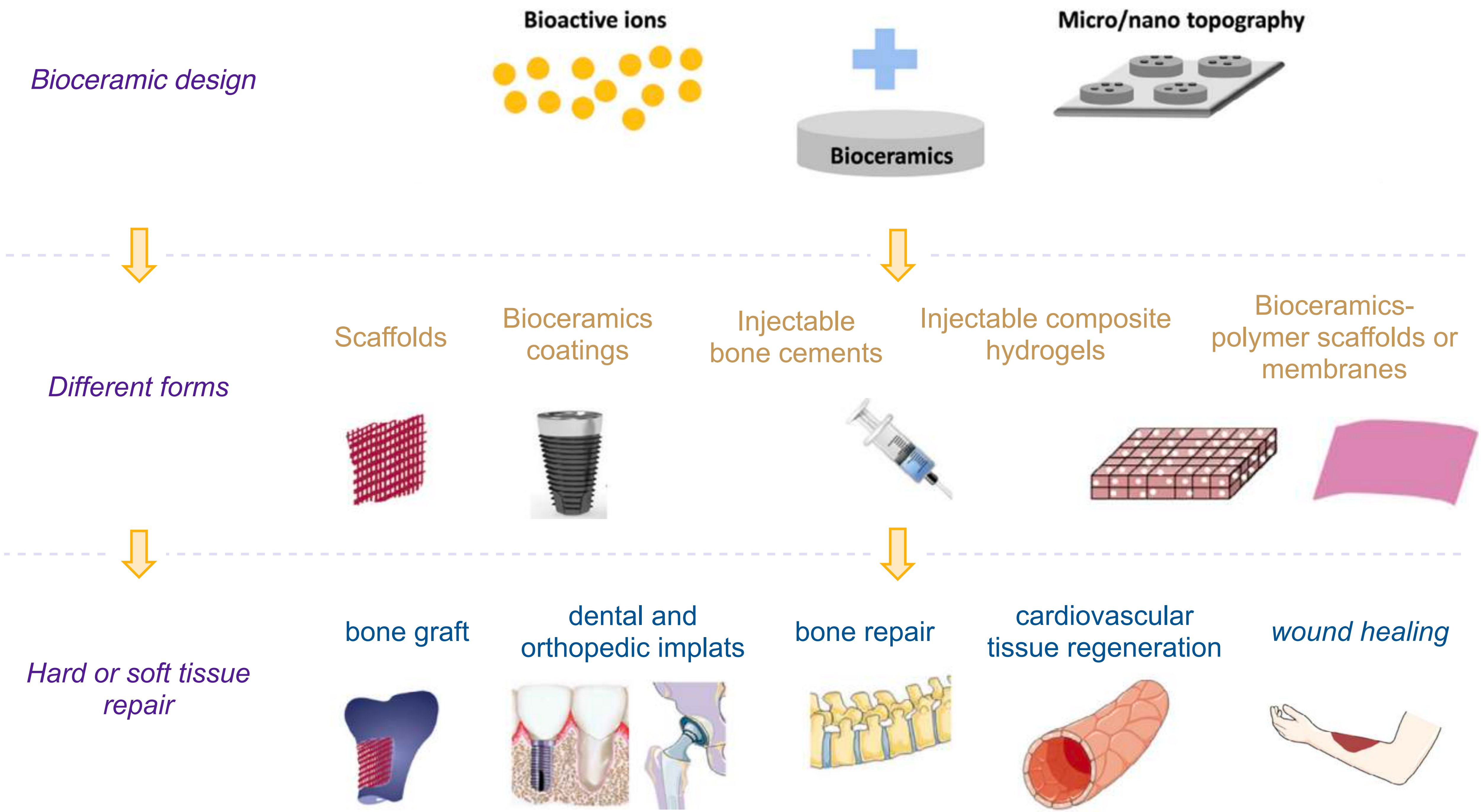
- Wet-state reaction.

Starch consolidation	*corn-, rice-, or potato granules as pore former mix with ceramic powder in water*	*low-cost, environment-friendly* *poorly interconnected pores*
Organic Phase Burning-out	*ceramic powder with a solid polymeric phase (natural or synthetic)*	*high-mechanical strength* *non homogeneous distribution*
Sponge Replica Method	*foam-like ceramic scaffolds for tissue engineering* *ceramic impregnation with cells (any binding agent)*	*simple, personalized scaffolds* *poor mechanical properties*
Solid freeform Fabrication (SFF)	*SLA: ceramic powder and photocurable monomer (laser beam)* *SLS: nano-HA, TCP, composites (CO_2 laser beam)* *3D-printing: any ceramic material*	*highly reproducible, compositional variation* *high compression and flexure* *trapped powder issue*

Baino, F. et al *Frontiers in Bioeng. and Biotech.* **2015**, *3*, 202

Bioceramic materials

From the scaffold design to the application



CChang, J. et al *Materials Today* ***2019**,* 24, 41

Bioceramic materials

Application in tissue engineering

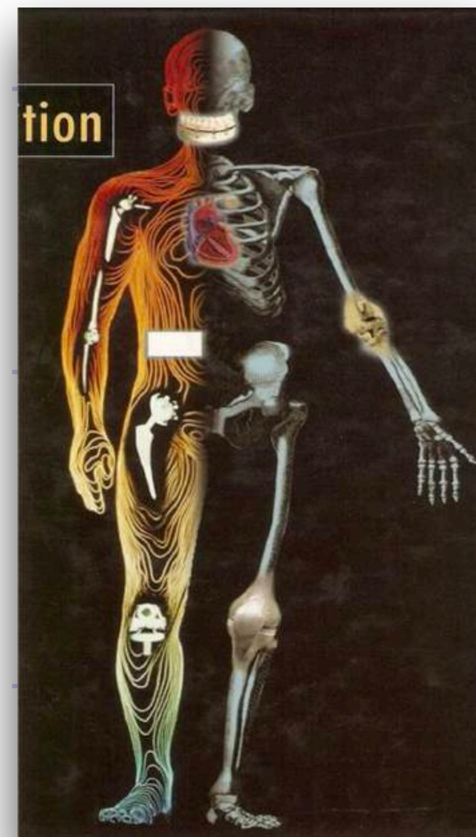
HA, calcium phospahtes, Bioglass

Bone defect repair

Joint prosthesis

Orbital implant

Wound healing



Bioactive glass (polymers, phosphates) or MBG (mesoporous bioactive glass)

Skin tissue engineering

Lung tissue engineering

Muscle tissue engineering

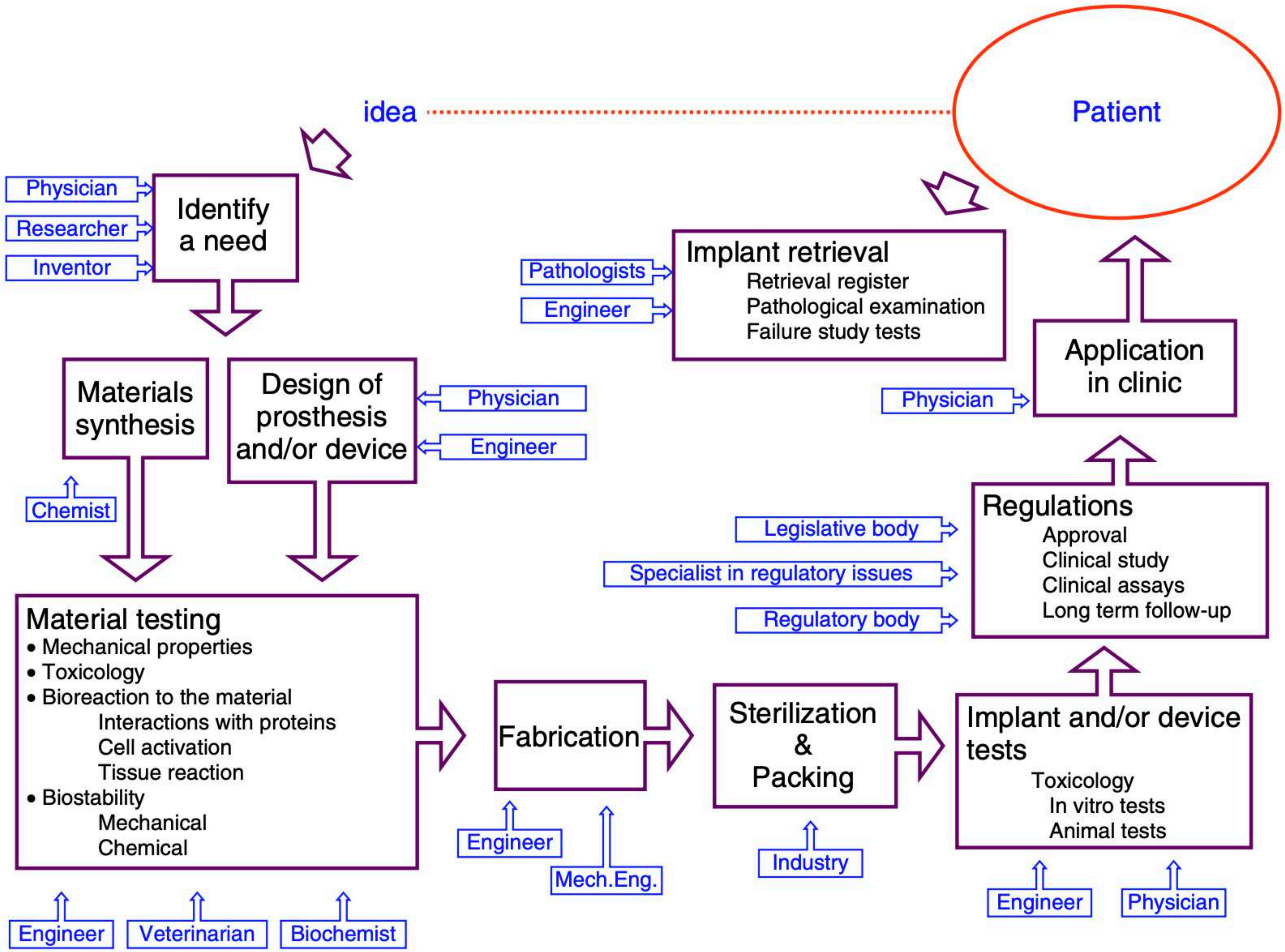
Peripheral nerve repair

non-osseous applications: *gastric ulcers, injectable radioactive glasses for killing cancer cell in liver tumor, cardiac tissue engineering, nerve regeneration*

Baino, F. et al *Frontiers in Bioeng. and Biotech.* ***2015***, 3, 202

Bioceramic materials

Workflow



Vallet-Regí, M. *Bioceramics. Bio-Ceramics with Clinical Application.* 2**014**, 1-16

Bone regeneration with micro/nano hybrid-structured BCP bioceramics

Segmental bone defect and induced immunoregulation of MSCs

■ Synthesis of bioceramics.

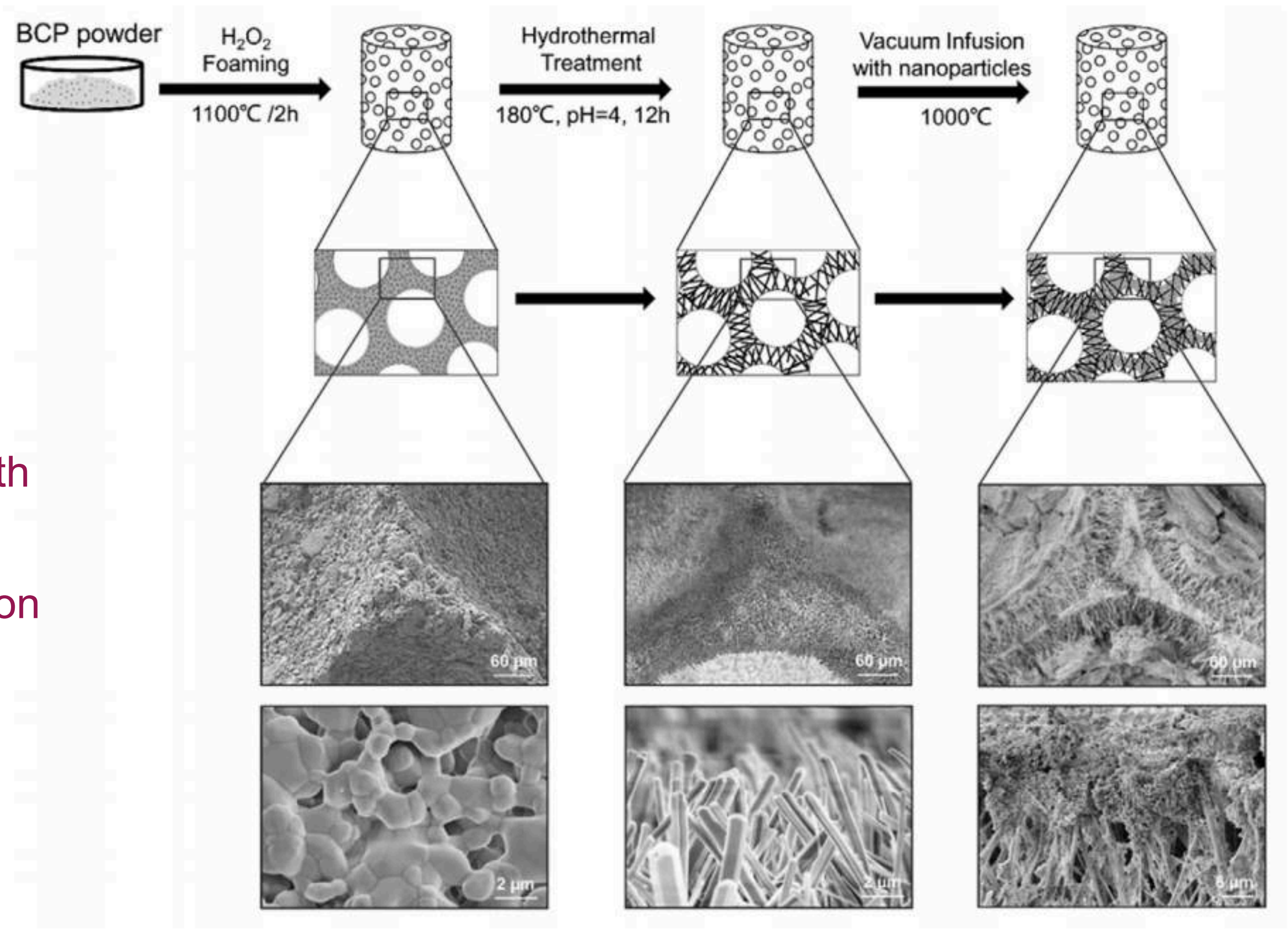
HA: hydroxyapatite

β-TCP: tricalcium phosphate

BCP: biphasic calcium phosphate (combination of HA, TCP)

hBCP: micro-whisker scaffold BCP and nanoparticles

1. Chemical precipitation
2. Porous BCP by H_2O_2 foaming
3. Hydrothermal treatment to growth of micro-whiskers
4. BCP-Nanoparticle slurry adsortion

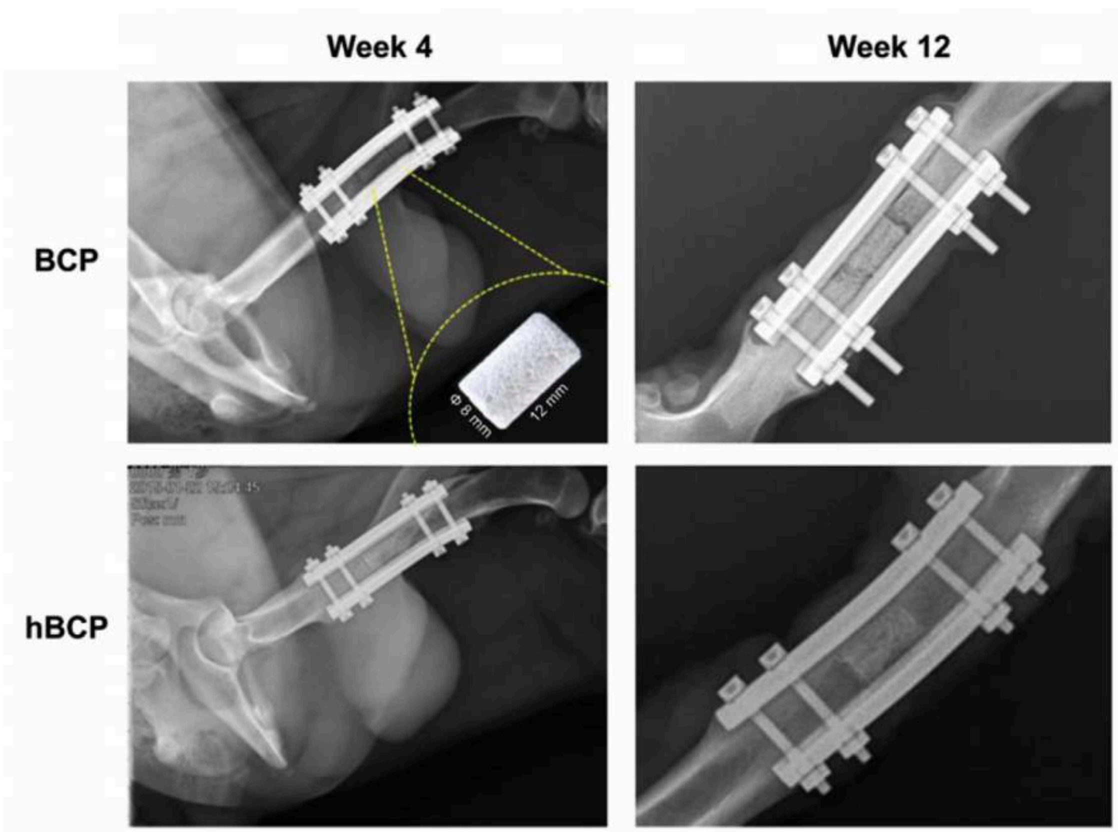


Yang, X. et al. *Biomaterials* **2017**, *147*, 133-144

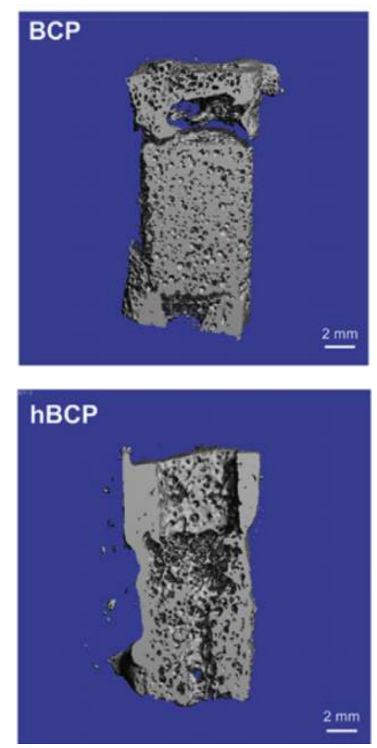
Bone regeneration with micro/nano hybrid-structured BCP bioceramics

Segmental bone defect and induced immunoregulation of MSCs

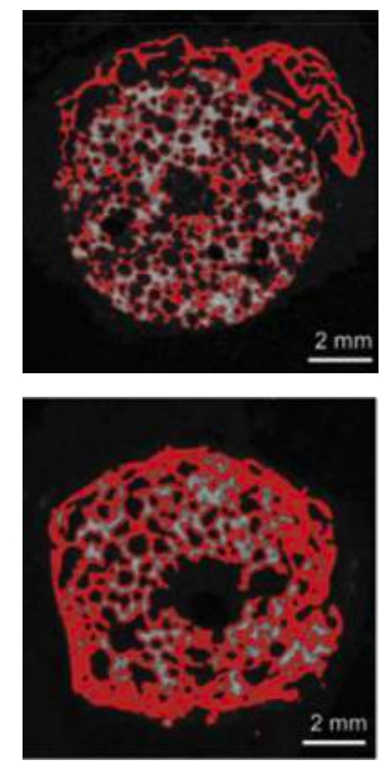
- Result for bone regeneration.



the contour of the ends were no longer ditinguishable from the host bone for hBCP



better integration with host bone tisse



control group: uneven amount of bone material at periphery (callus formation)

hBCP group: tissue tightly enfolded

bone substitution in both groups due to the interconnected porous structure.

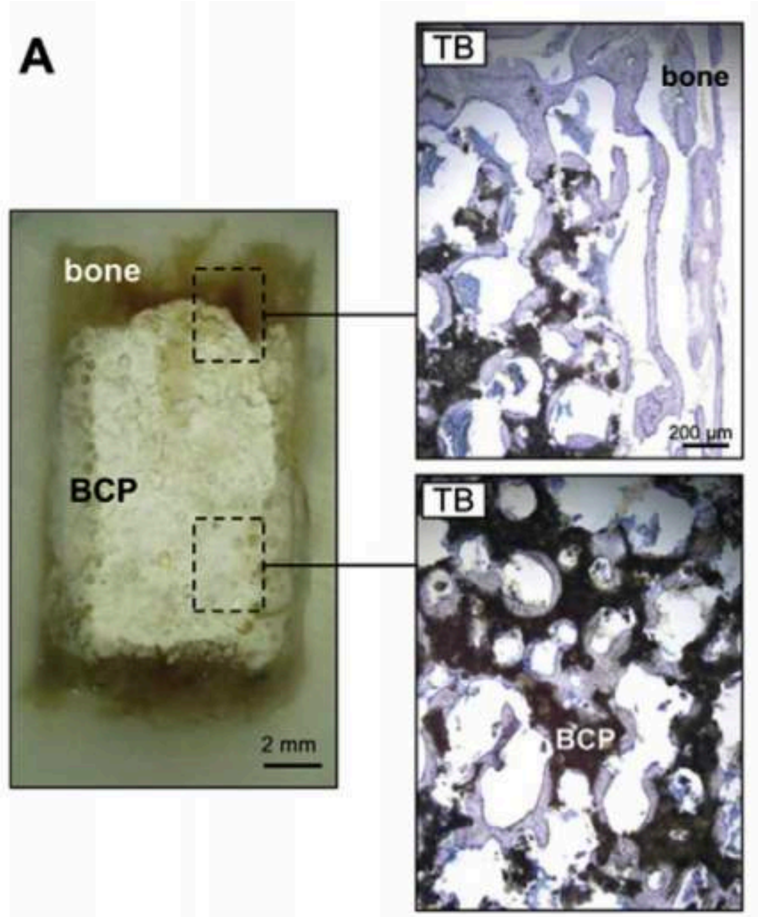
Yang, X. et al. *Biomaterials* **2017**, *147*, 133-144

Bone regeneration with micro/nano hybrid-structured BCP bioceramics

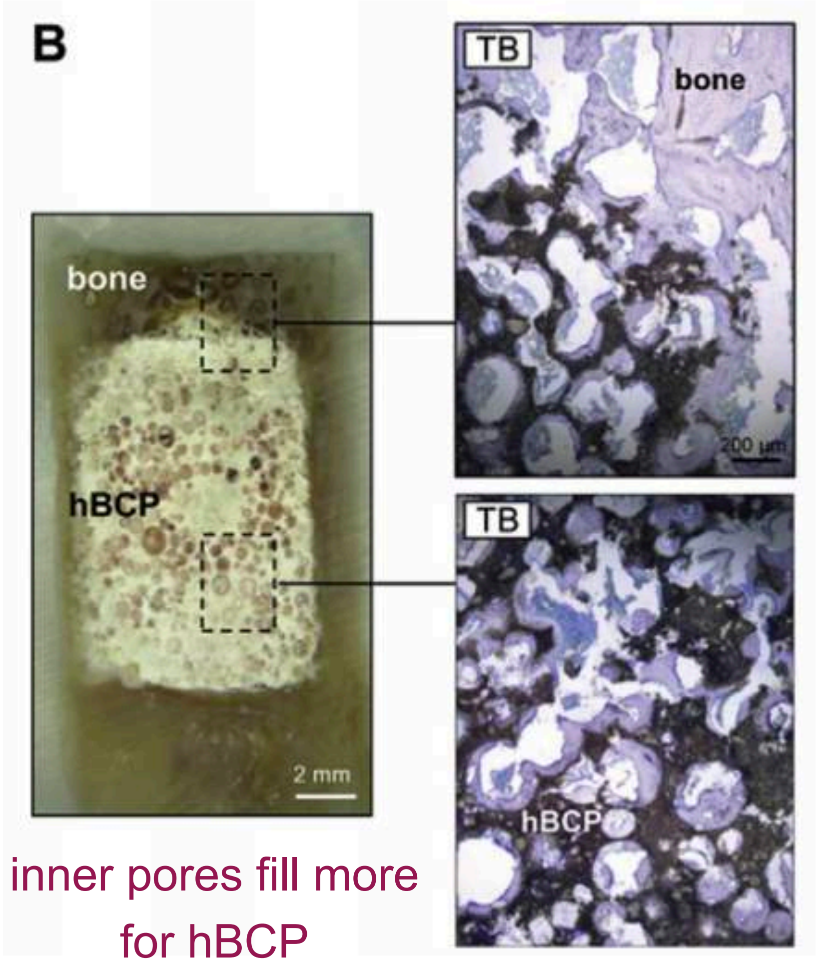
Segmental bone defect and induced immunoregulation of MSCs

■ Result for bone regeneration.

good host bone integration and osteoconductive ability



in blue:
newly formed bone



inner pores fill more for hBCP

closely attached to the wall of inner pores of the bioceramics

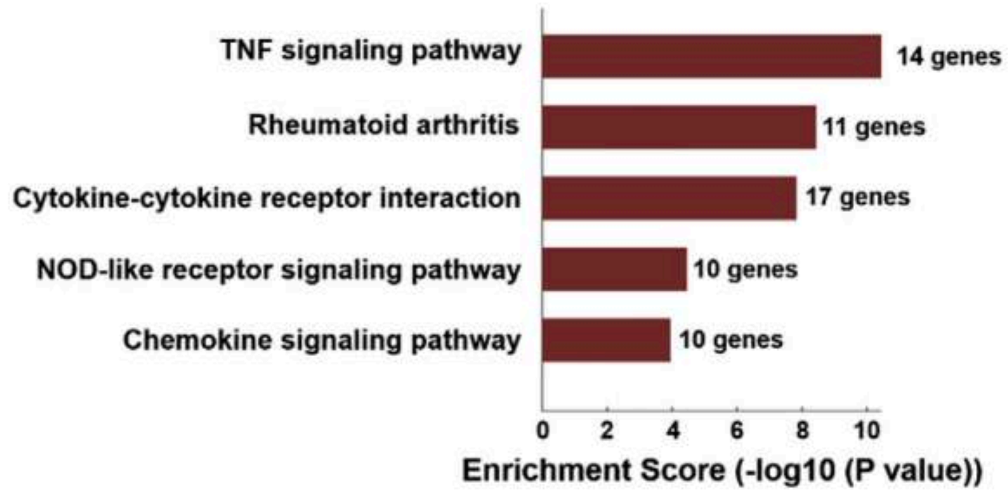
lower elasticity for newly formed bone

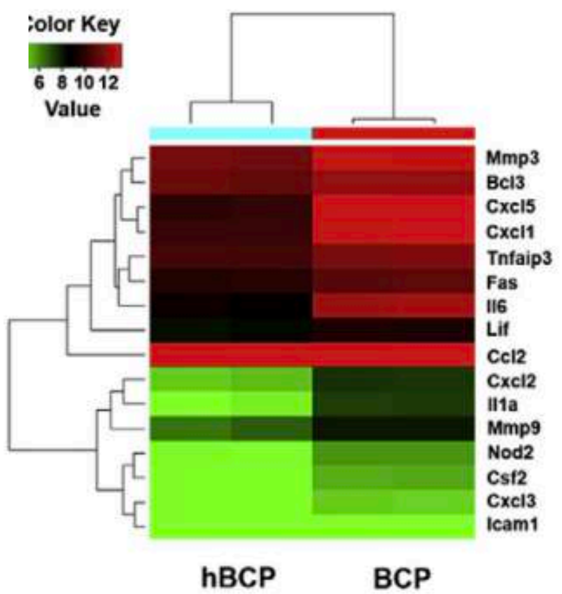
Yang, X. et al. *Biomaterials* **2017**, *147*, 133-144

Bone regeneration with micro/nano hybrid-structured BCP bioceramics

Segmental bone defect and induced immunoregulation of MSCs

■ Result for gene expression.





27,255 genes were evaluated

(594 genes upregulated and 287 downregulated).

Genes associated with inflammatory response. TNF (tumor necrosis factor) was the most involved

micro/nano hBCP could be a potential alternative for regeneration of bone at early stage of implantation and for the treatment of massive bone defects

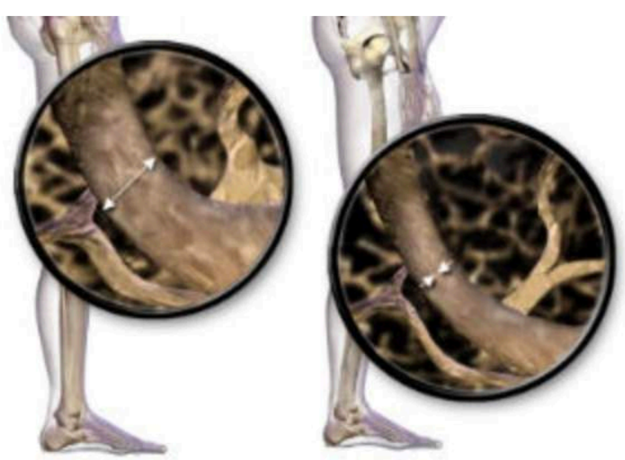
Yang, X. et al. *Biomaterials* **2017**, *147*, 133-144

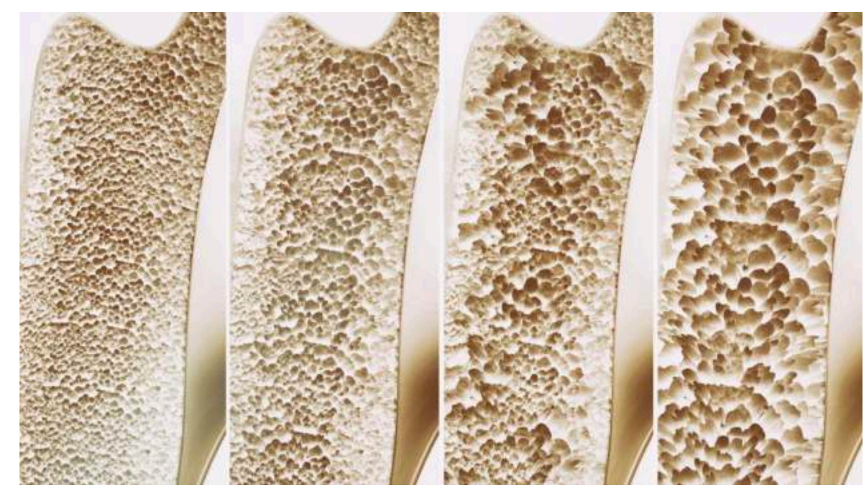
Akermanite bioceramics

Osteogenesis, angiogenesis for osteoporotic bone regeneration

- Osteoporosis.

Osteoporosis (porous bones) is a condition that affects the bones,
*causing them to **become weak and more likely to fracture**.*
It is characterized by low bone mass, poor bone strength and microarchitectural deterioration of bone.
Osteoporosis occurs when the creation of new bone doesn´t keep with the removal of old bone (osteoclast and osteoblast function) and there is loss of calcium ions.





- invisible disease
- depends on the sex, age, raze, country
- estrogen deficiency

treatments for fractures and pains, not to regenerate the bones

— Osteogenesis and angiogenesis are the formation of new bones and blood vessels —

Yin, Z. et al. *Sci. Rep.* **2016**, *6*, 22005

Akermanite bioceramics

Osteogenesis, angiogenesis for osteoporotic bone regeneration

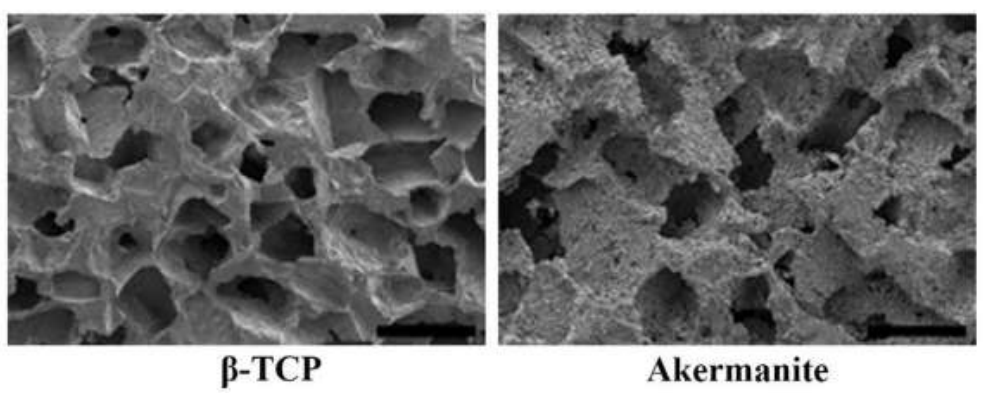
■ Akermanite bioceramics ($Ca_2MgSi_2O_7$).

— synthesis by sol-gel process — *β-TCP* *or* *akermanite scaffolds (using PEG as porogens)*

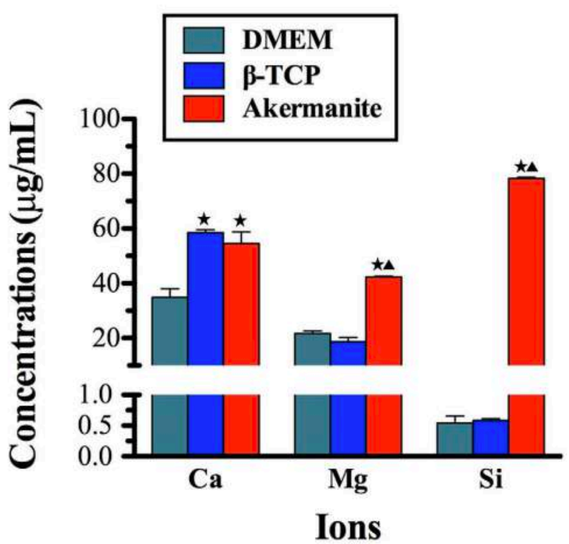
⇩

culture cell in akermanite or *β-TCP* extract (BMSCs-OVX) or in vivo experiments (fill the defect with the bioceramics)

- synthesis-



porous material



composition

BMSCs-OVX = bone marrow stromal cells derivered from ovariectomized rats

Yin, Z. et al. *Sci. Rep.* **2016**, *6*, 22005

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Osteogenesis, angiogenesis for osteoporotic bone regeneration

- Akermanite bioceramics ($Ca_2MgSi_2O_7$).

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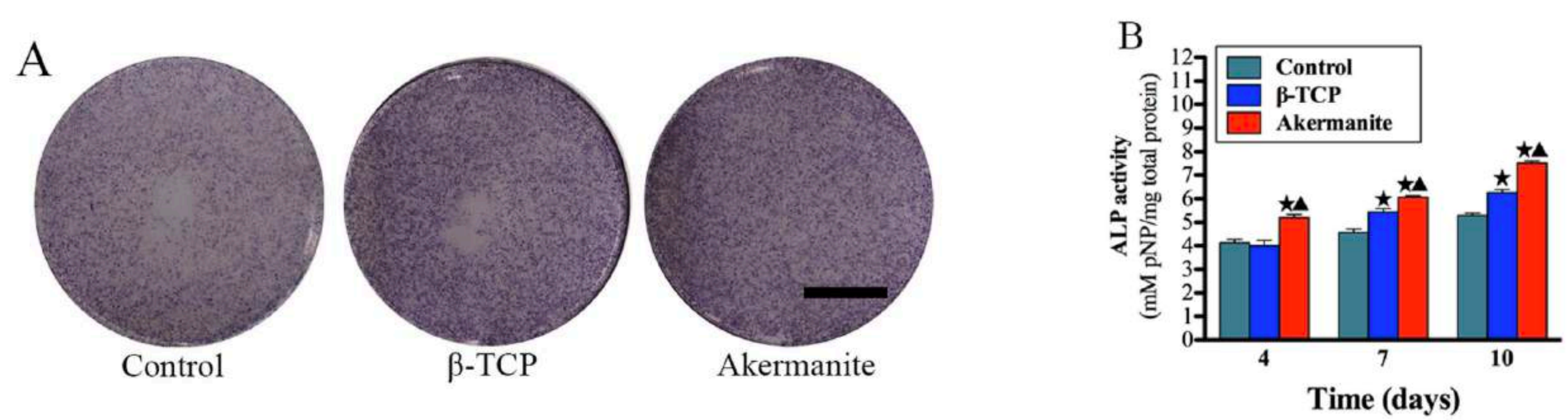
⇩

culture cell in akermanite or *β-TCP* extract (BMSCs-OVX) or in vivo experiments (fill the defect with the bioceramics)

- in vitro assay-

Effect of akermanite extract on the expression of osteogenic, angiogenic and osteoclastogenic genes

good response for osteogenesis and angiogenesis



Increase the osteoblast formation with the culture cell time

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Yin, Z. et al. *Sci. Rep.* **2016**, *6*, 22005

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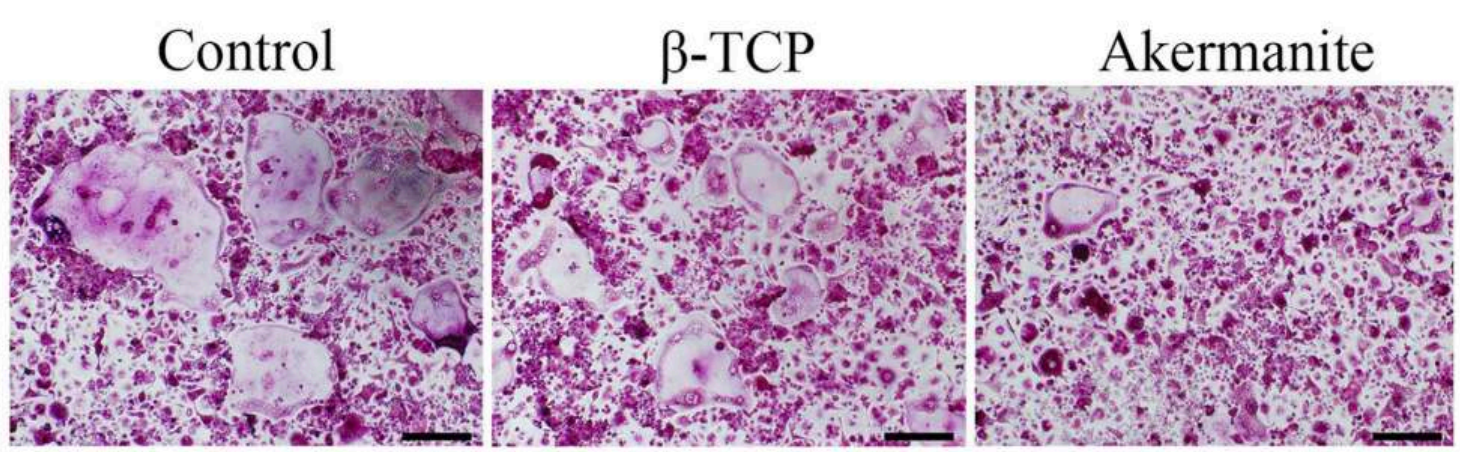
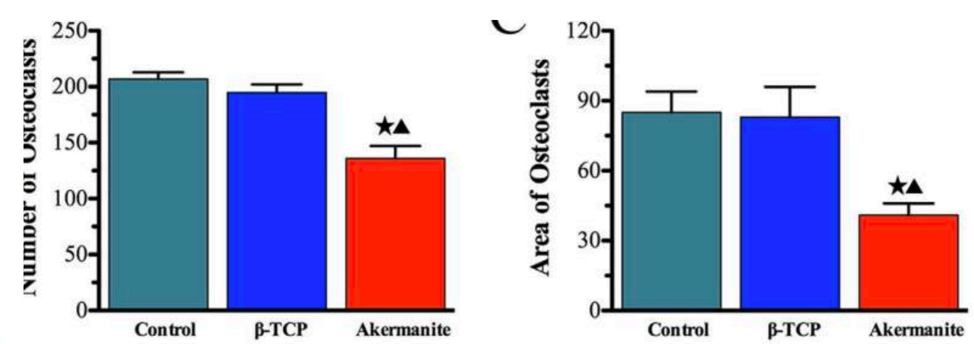




great response for suppression of osteoclastogenesis

Decrease the osteoclast formation with the culture cell time
Inhibist bone degradation

BMSCs-OVX = bone marrow stromal cells derivered from ovariectomized rats

Yin, Z. et al. *Sci. Rep.* **2016**, *6*, 22005

Akermanite bioceramics

Osteogenesis, angiogenesis for osteoporotic bone regeneration

- Akermanite bioceramics ($Ca_2MgSi_2O_7$).

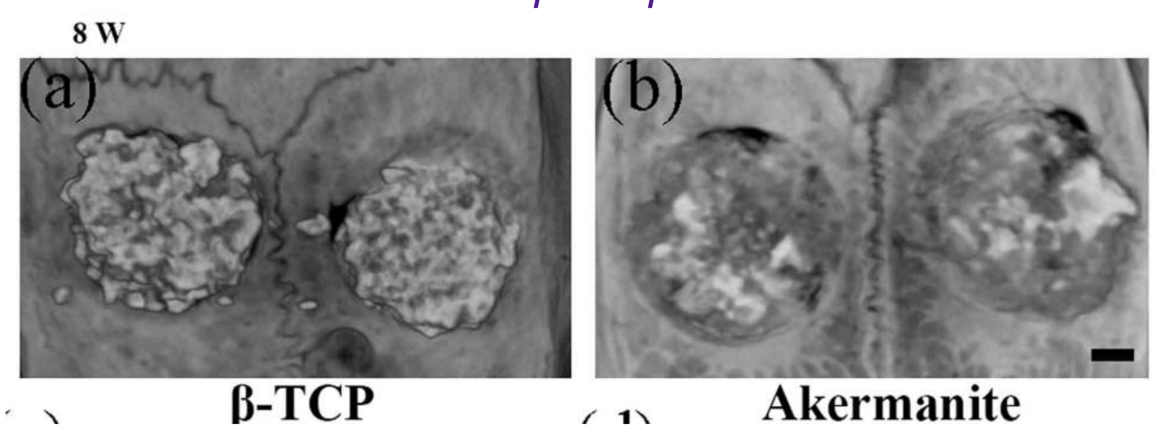
— synthesis by sol-gel process — *β-TCP* *or* *akermanite scaffolds (using PEG as porogens)*

⇩

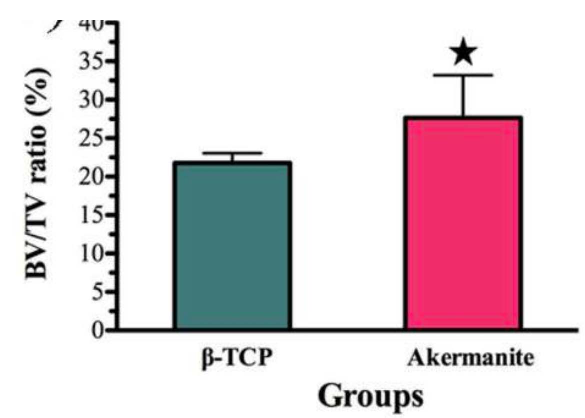
culture cell in akermanite or *β-TCP* extract (BMSCs-OVX) or in vivo experiments (fill the defect with the bioceramics)

- in vivo assay-

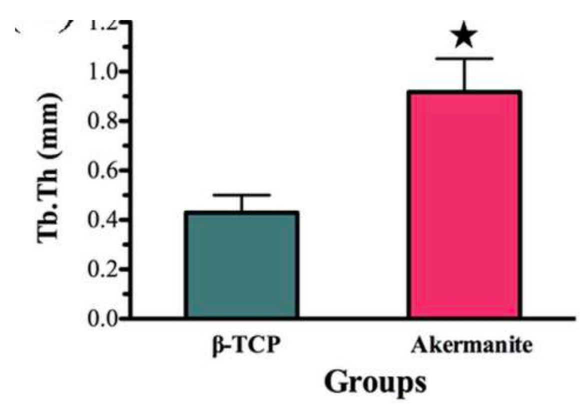
8 weeks postoperation



bone reconstruction more effective for akermanite scaffold



bone volume/tissue volume



3-D measure of trabecular thickness

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Yin, Z. et al. *Sci. Rep.* **2016**, *6*, 22005

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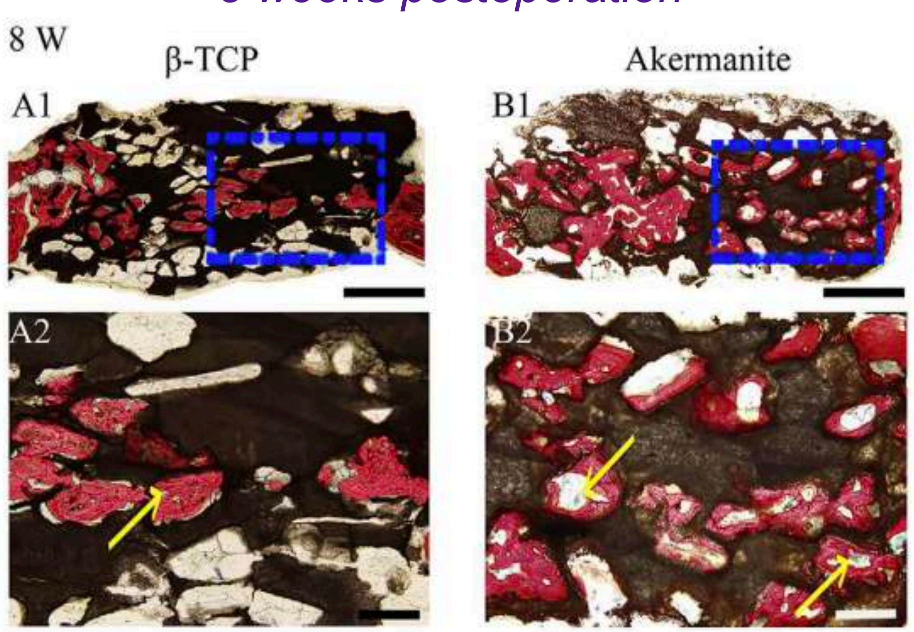
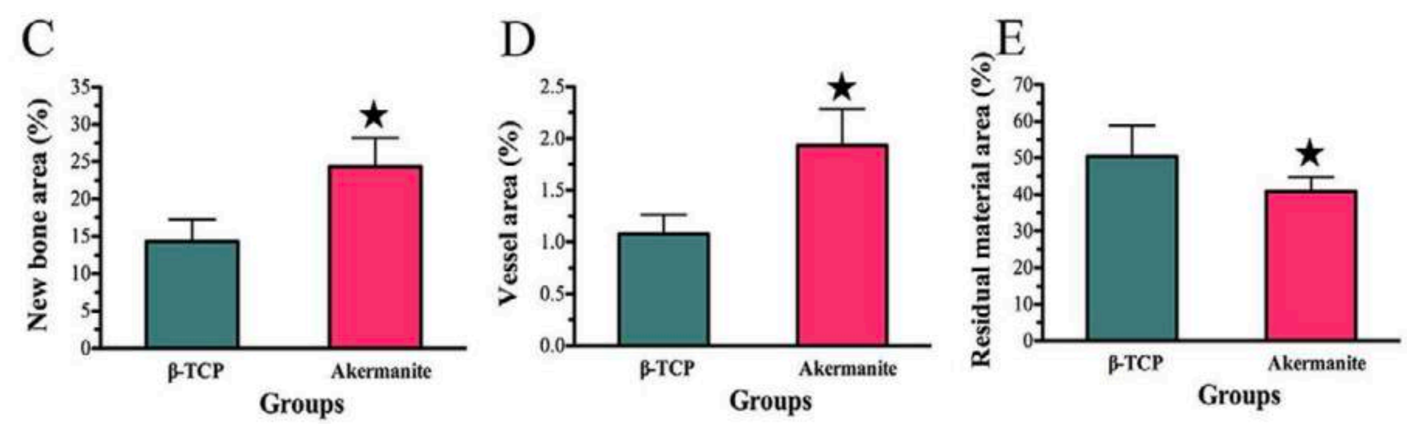


new blood vessel formation



new bone area *new vessel area* *residual material*

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Yin, Z. et al. *Sci. Rep.* **2016**, *6*, 22005

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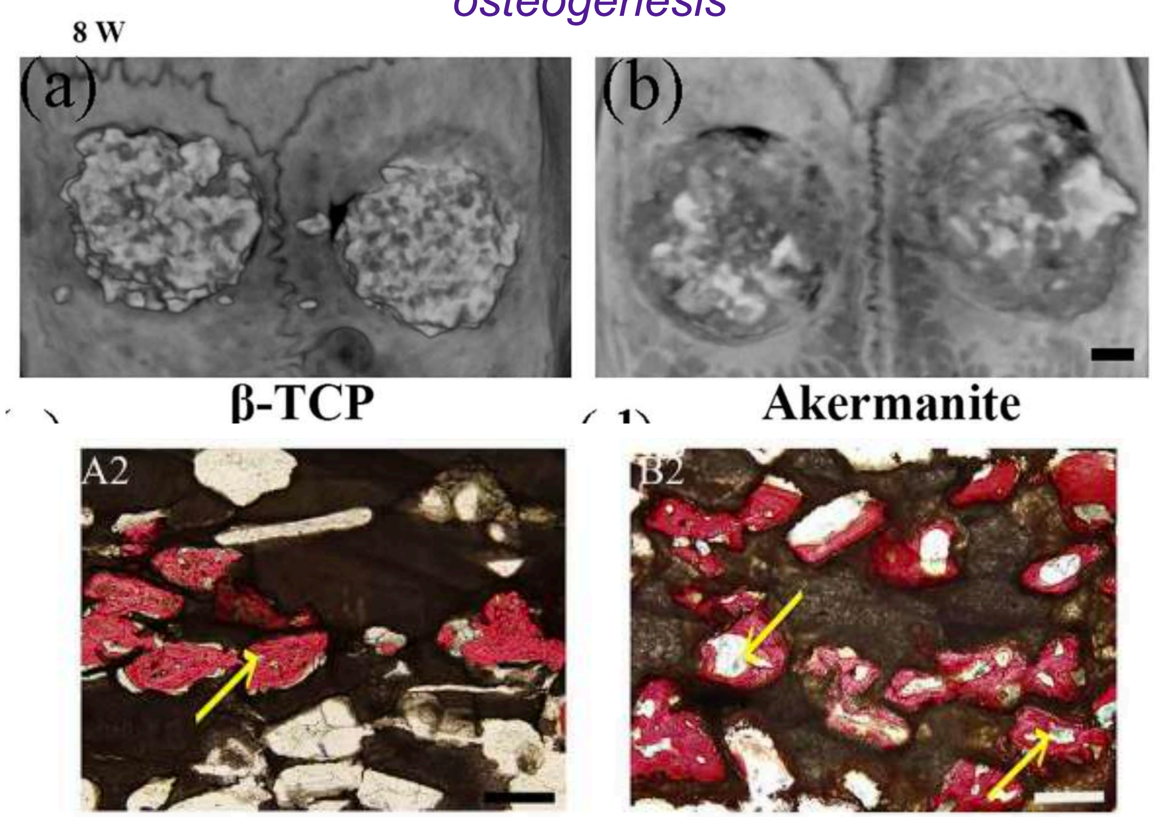
- conclusion-

osteogenesis



angiogenesis

- *Akermanite bioceramics improve cell proliferation, osteogenic differention of OVX-BMSCs and expression of angiogenic factors.*

⇩

High osteoinductive activity, stimulated angiogenesis and inhibited osteoclastogenesis

⇩

The effect of Mg and Si ions on osteogenesis, angiogenesis and osteoclastogenesis

⇩

promising for osteoporotic bone regeneration

Yin, Z. et al. *Sci. Rep.* **2016**, *6*, 22005

Messenchymal stem cells on porous β-TCP ceramic scaffolds

Bone regeneration and angiogenesis by gene transfer

- Gene transfer technology.

Gene therapy can be defined as the deliberate transfer of DNA for therapeutic purposes.
The transplantation of normal genes into cells in place of missing or defective ones in order to correct genetic disorders

- Messenchymal stem cells (MSCs).

primitive cells that can be differentiated into bone-forming cells, adipocytes, hemocytoblast, mastocytes or fibroblast.

- Basic fibroblast growth factor (bFGF).

Accelerate bone healing (osteogenesis and angiogenesis) by promoting the proliferation and differentiation of mesenchymal stem cells (MSCs) and the regeneration of capillary vasculature.

⇩

Gene-based delivery systems

⇩

bFGF-modified gene transfected MSCs seeded on biodegradable porous *β*-tricalcum phosphate ceramics

⇩

for Bone regeneration and Angiogenesis

Tang, S. et al. *Biomed. Mater.* **2006**, *1*, 93

Messenchymal stem cells on porous β-TCP ceramic scaffolds

Bone regeneration and angiogenesis by gene transfer

- β-TCP as ceramic scaffolds (CaO(49%)·P_2O_5(48.8%)· Na_2O (1.3%)· MgO(0.4%).

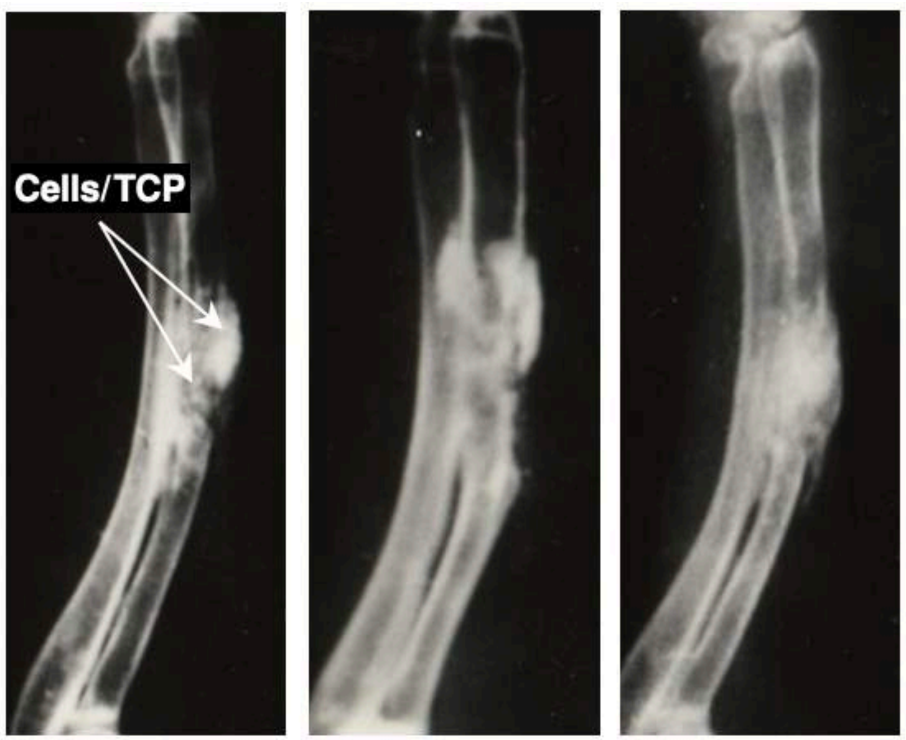
⇩

each β-TCP was seeded with gene-transfected cells

control group:
DNA transfected MSCs/TCP

experimental group:
DNA-bFGF-transfected MSCs/TCP

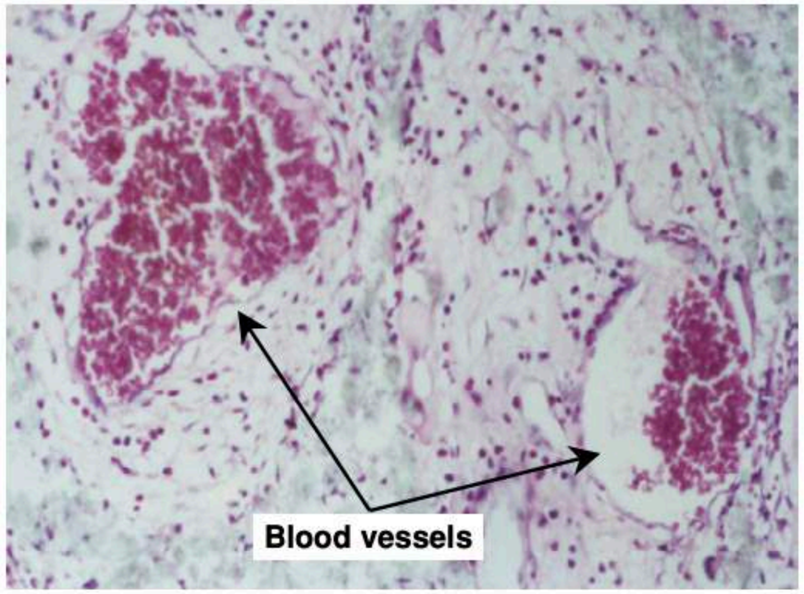
- in vivo-



2 weeks — *callous around defects*

8 weeks — *fixation was united*

12 weeks — *bony union. no deffects*



2 weeks post-operation.
Capillary vasculature in the porous

Tang, S. et al. *Biomed. Mater.* **2006**, *1*, 93

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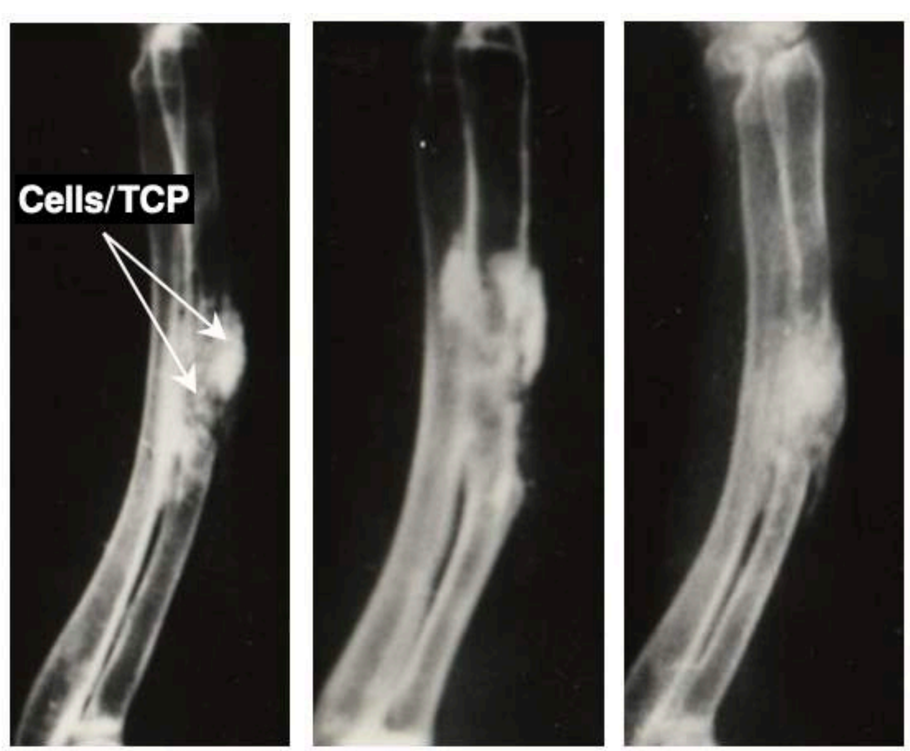

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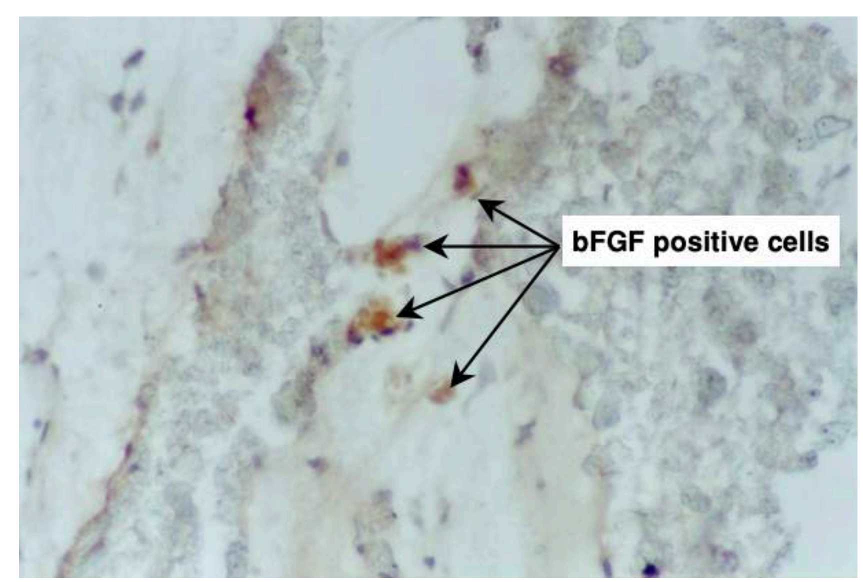
4 weeks



staining cells can be seen in the newly formed bone tissues

Tang, S. et al. *Biomed. Mater.* **2006**, *1*, 93

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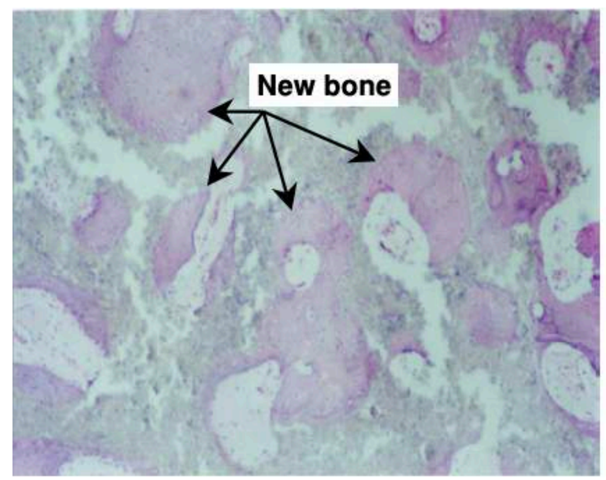

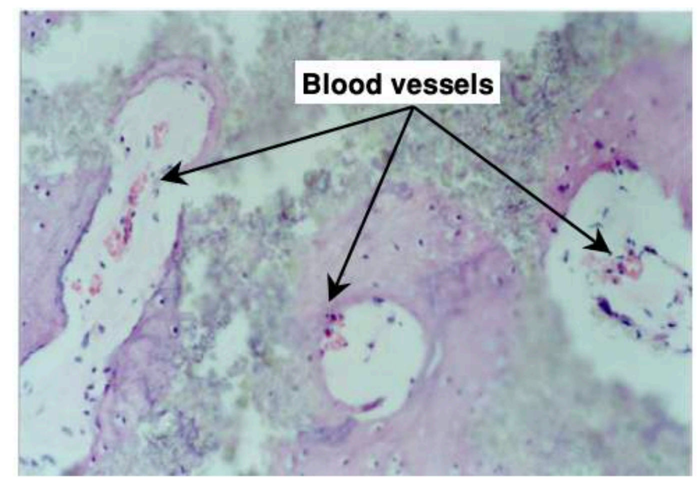

12 weeks post-operation

new bone generated in the entire pore

capillary vasculature formation in the central region area of new bone

Tang, S. et al. *Biomed. Mater.* **2006**, *1*, 93

Messenchymal stem cells on porous β-TCP ceramic scaffolds

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each β-TCP was seeded with gene-transfected cells

control group:
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2 weeks *8 weeks* *12 weeks*

- *angiogenic capacity of bFGF*
- blood supply for the life of seeded cells
- great for bone regeneration

⇨ large bone defect therapies

transfer of bFGF encoding gene into MSCs increases the osteogenic and angiogenic properties

⇩

*Benefit to **accelerate bone healing**, especially caused atrophic nonunion and avascular necrosis of the femoral head*

Tang, S. et al. *Biomed. Mater.* **2006**, *1*, 93

Injectable calcium phosphates and Bioglasses

Different scaffolds in bone regeneration

■ CPC (calcium phosphate cement).

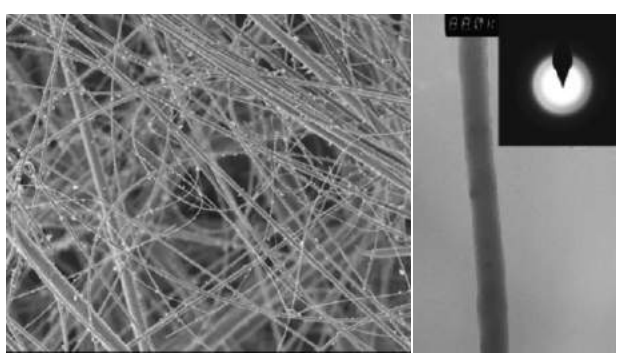
Mixture of β-TCP, $CaHPO_4H_2O$, $CaCO_3$, HA and nano-structures in buffer solution

w or w/o autologous iliac crest bone (ACB)

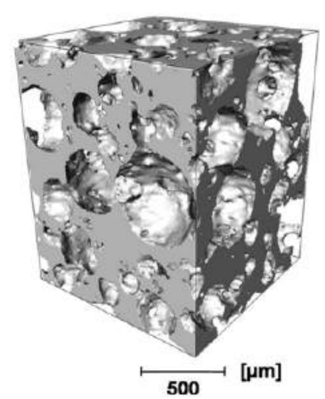
→ *cement for injection* →

bone regeneration after 12 weeks

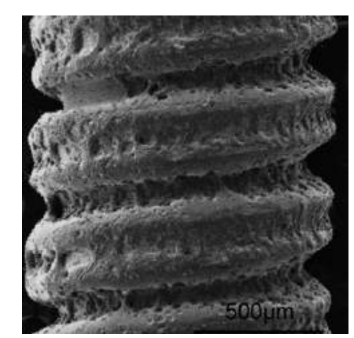
■ Bioglass.



bioactive glass nanofibers



X-ray. BG by gel cast foaming



Ti_6Al_4V dental implant with bioglass coating

Lindfors, N. C. *J. Biomed. Mater. Res. B* **2010**, *94B*, 157
Brauer, D. S. *Angew. Chem. Int. Ed.* **2015**, *54*, 4160
Xinjia, W. et al. *J. Mater. Sci: Mater Med.* **2008**, *19*, 2485

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w or w/o autologous iliac crest bone (ACB)

→ *cement for injection* →

bone regeneration after 12 weeks

■ Bioglass.

BonAlive S53P4

→

commercial available for BonAlive

bone regeneration	*benign bone tumor surgery*
trauma, spine surgery	*inhibiting bacterial growth*
mastoid surgery	*bone infection surgery*

Lindfors, N. C. *J. Biomed. Mater. Res. B* **2010**, *94B*, 157
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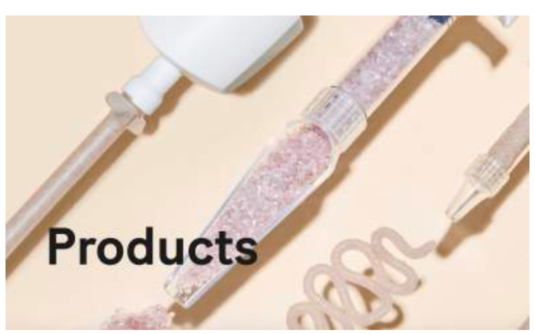
w or w/o autologous iliac crest bone (ACB)

→ *cement for injection* →

bone regeneration after 12 weeks

■ Bioglass.

Aneurysmal bone cyst



BonAlive®

→

pre-operative

post-operative

cavity filled with BG

long-term follow up

dense appearance

long-term follow up

remants of glass granules in the bone

Lindfors, N. C. *J. Biomed. Mater. Res. B* **2010**, *94B*, 157

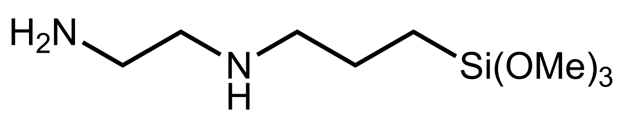
Brauer, D. S. *Angew. Chem. Int. Ed.* **2015**, *54*, 4160

Xinjia, W. et al. *J. Mater. Sci: Mater Med.* **2008**, *19*, 2485

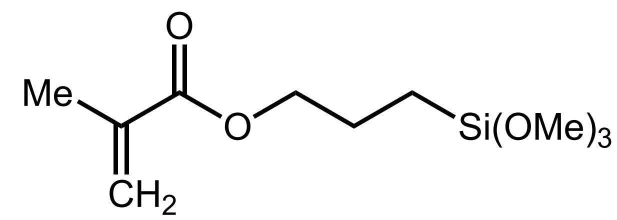
Other biomaterials

Drug delivery, 3-D printing

- Drug encapsulated in hybrid bioceramics.

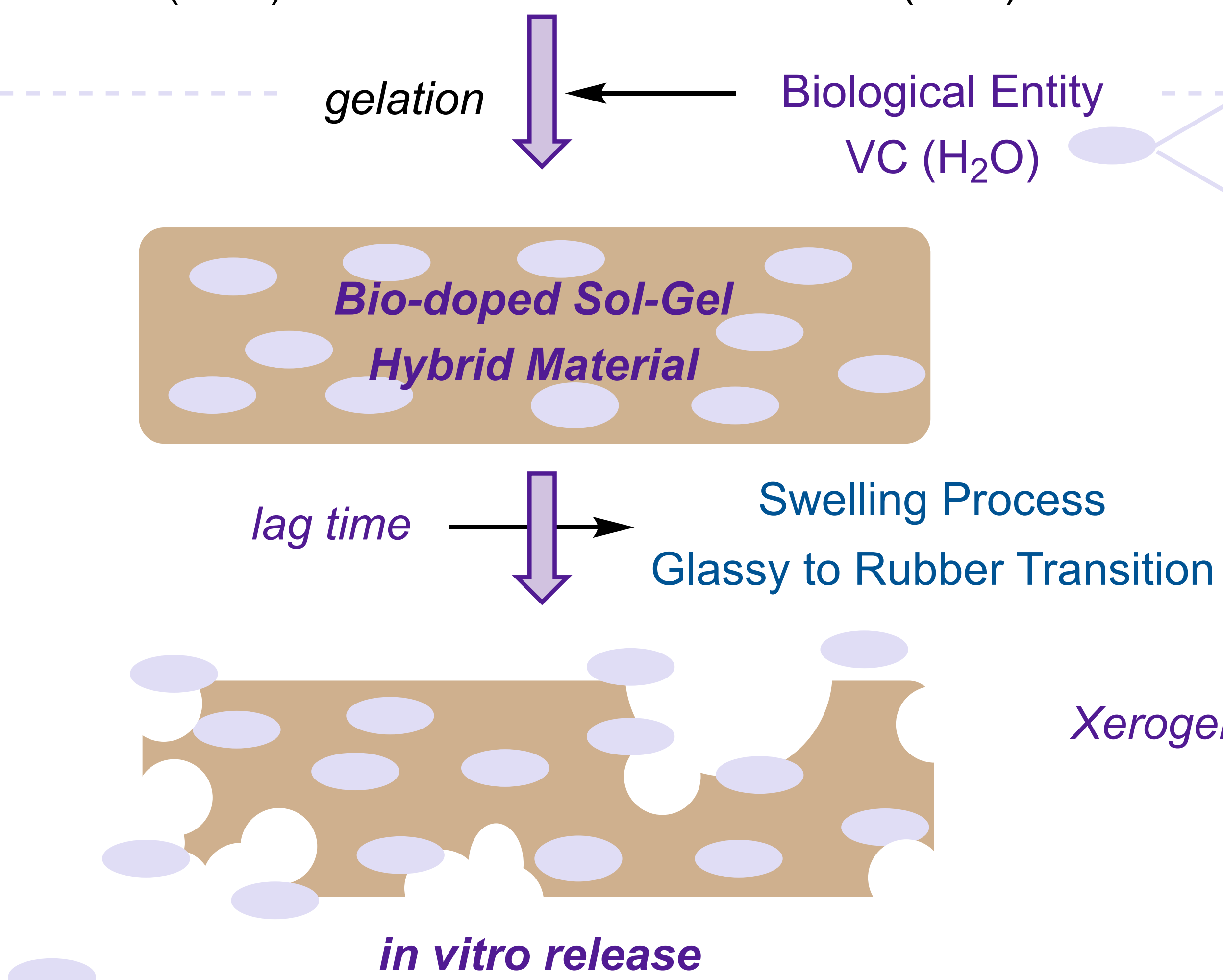


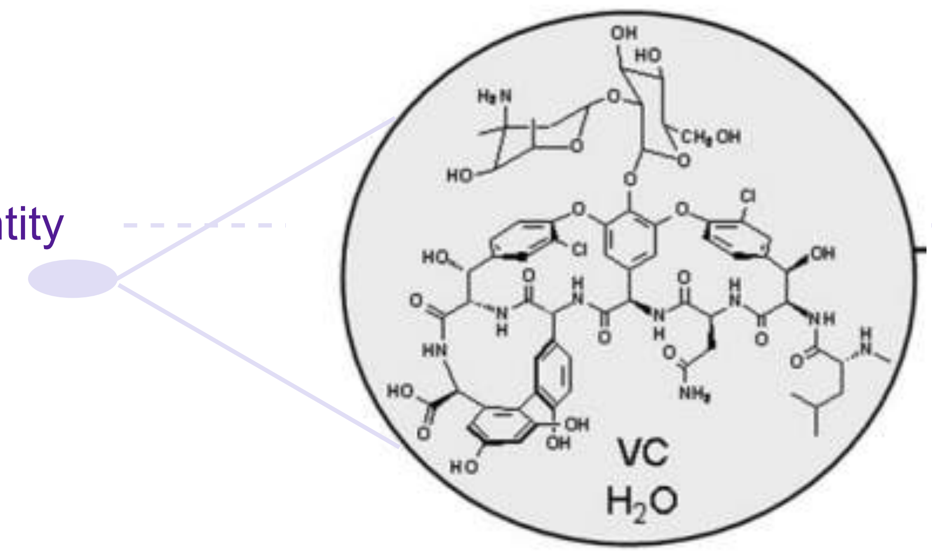
DAMO (0.40)

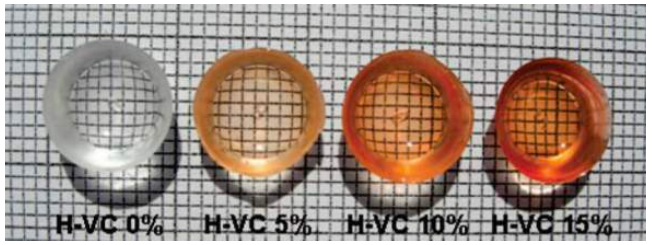


MPS (0.60)

sol-gel precursors







Xerogel with different concentrations of vancomycin

Zero-release period up to 38 h
VC release during 8 days

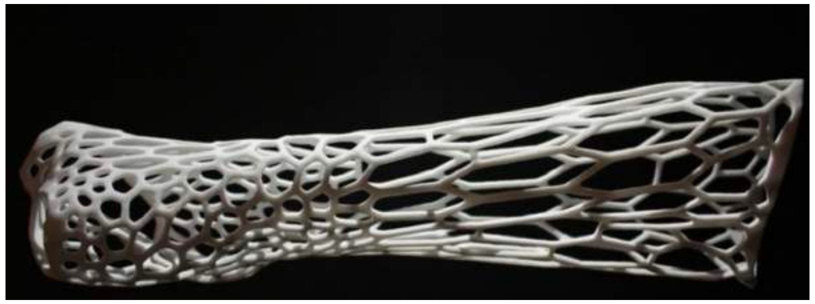
Vallet-Regí, M. et al. *Chem. Mater.* **2008**, *20*, 4826
Vallet-Regí, M. et al. *Adv. Mater.* **2011**, *23*, 5177

Current-future bioceramics

Drug delivery, 3-D printing

■ Bone fixation and organ design.

plaster of Paris

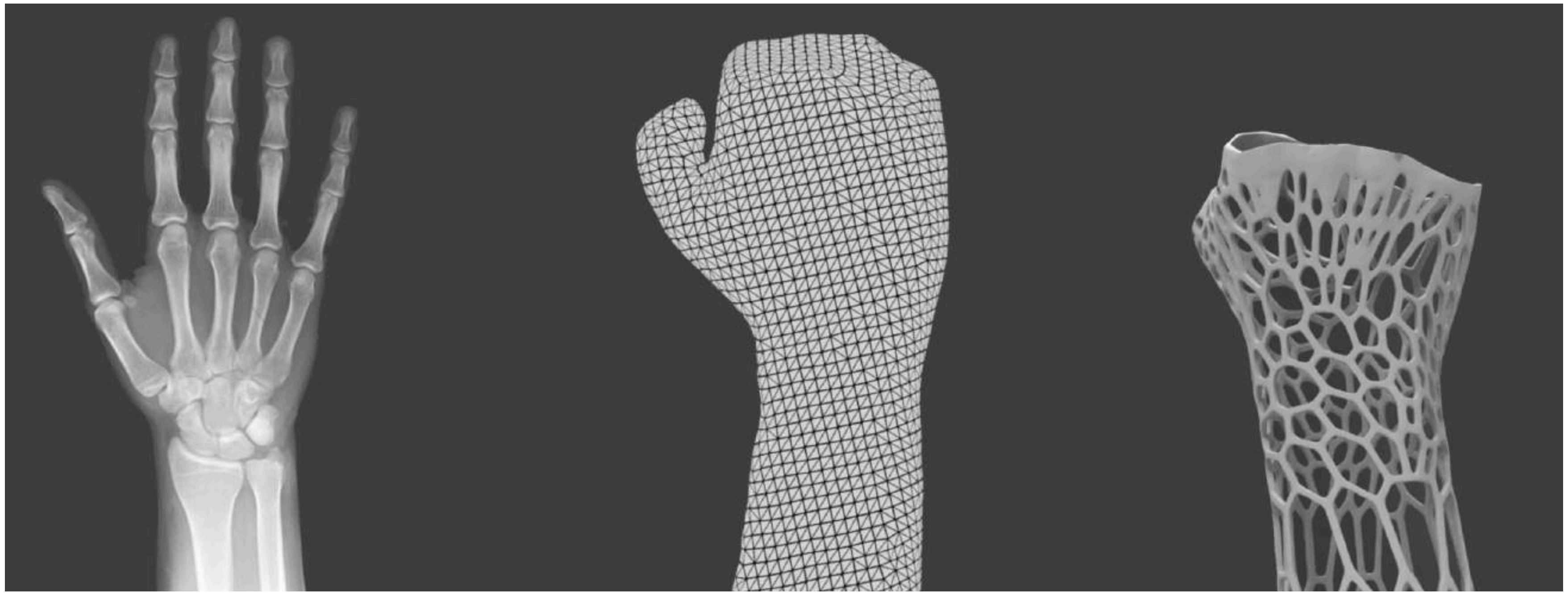


Cortex®

3D impressions

treatment process

X-RAY — 3D-SCAN — 3D-PRINT



Current-future bioceramics

Drug delivery, 3-D printing

- Organ design. 3D-print transplantable.

Issues

- *Not enough transplantable organs*
- *After a transplant, the patient is treated with drugs or immunosuppressants*

⇨

3D-Organ

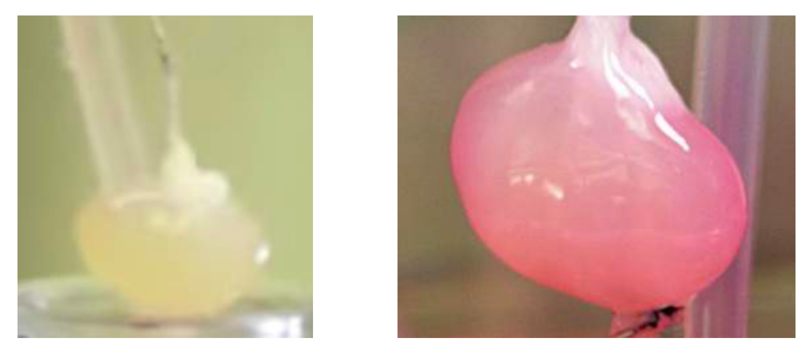
- *Printing cells in a small area we can build a 3D-organ*
- *Need to use the desired cells*
- *Bioinks which provide a porous structure*

- First approach for kidney transplant. Using a donor kidney with patient culture cells.

Clean the healthy kidney removing the donor cells

Collagen preserve the organ structure

cultured patient cells placed on the kidney



rat kidney

Current-future bioceramics

Drug delivery, 3-D printing

- Second approach for organ transplant.

Process 3D-printing

Tissue from patient ⇨ *culture cells* ⇨ *3D structure (printer) using previous cells* ⇨ *transplant* ⇨ *3D-mold disappear and the cells generate new tissue creating the new organ*

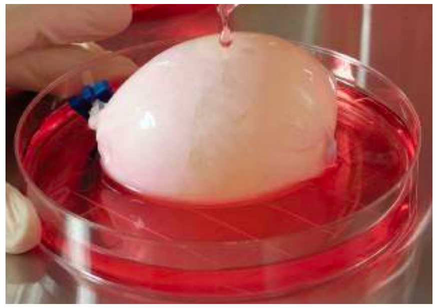
- Classification according to the printing complexity

Flat structures

skin tissues

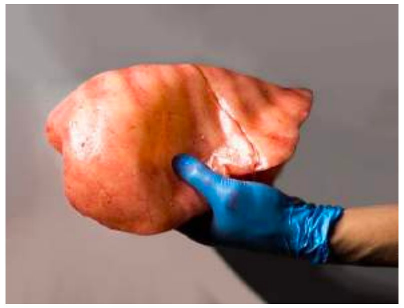
Tubular structures

blood vessels



Hollow non-tubular organs

bladder, stomach



Organs level 4

lung, heart

high complexity

only for study
not transplants

Current-future bioceramics

Drug delivery, 3-D printing

- Second approach for organ transplant.

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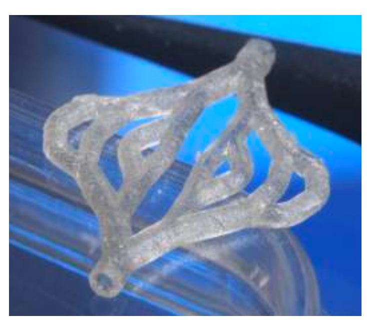

Tubular structures

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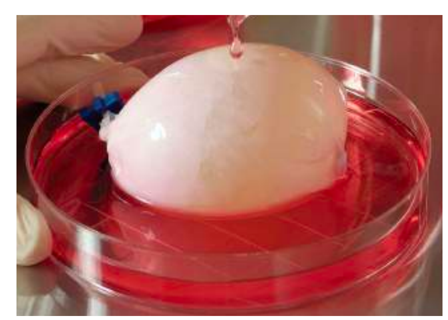

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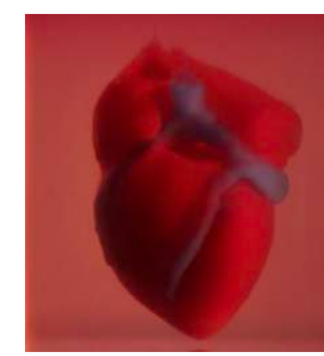


Organs level 4

lung, heart

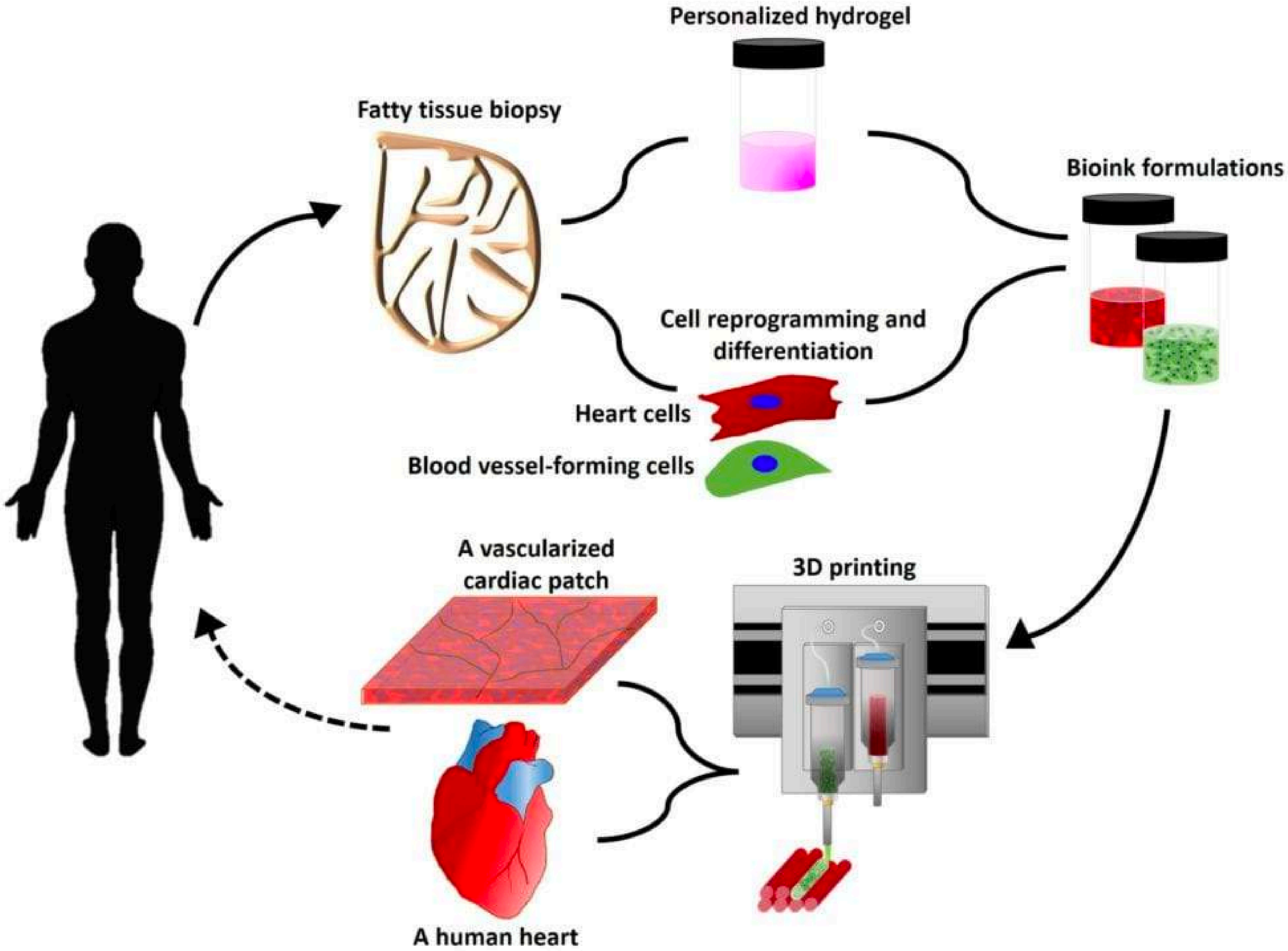
first useful heart for transplant

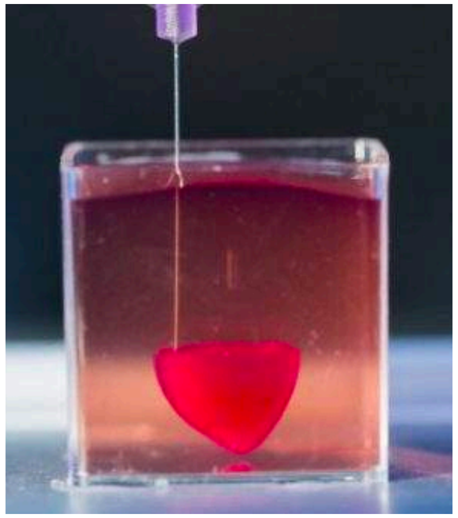
University of Tel Aviv
April 15th 2019

Current-future bioceramics

3D-printed organs

- First 3-D heart.





Dvir, T. et al. *Adv. Sci.* **2019**, 1900344

Bioceramic Materials

María González Esguevillas

MacMillan Group Meeting

April 18, 2019