Calcium Phosphate Ceramics

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SUMMER SCHOOL
CERAMIC & GLASS SCIENCE & TECHNOLOGY, APPLICATION TO BIOCERAMICS & BIOGLASSES

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Outline

1 Synthetic bone grafts: concept and applications

2 Why Calcium phosphates?

3 Calcium phosphate sources: natural vs synthetic

4 High-T vs low-T calcium phosphates

5 Porosity in Calcium Phosphates

6 Biological performance of Calcium Phosphates: resorption, bioactivity and osteoinduction

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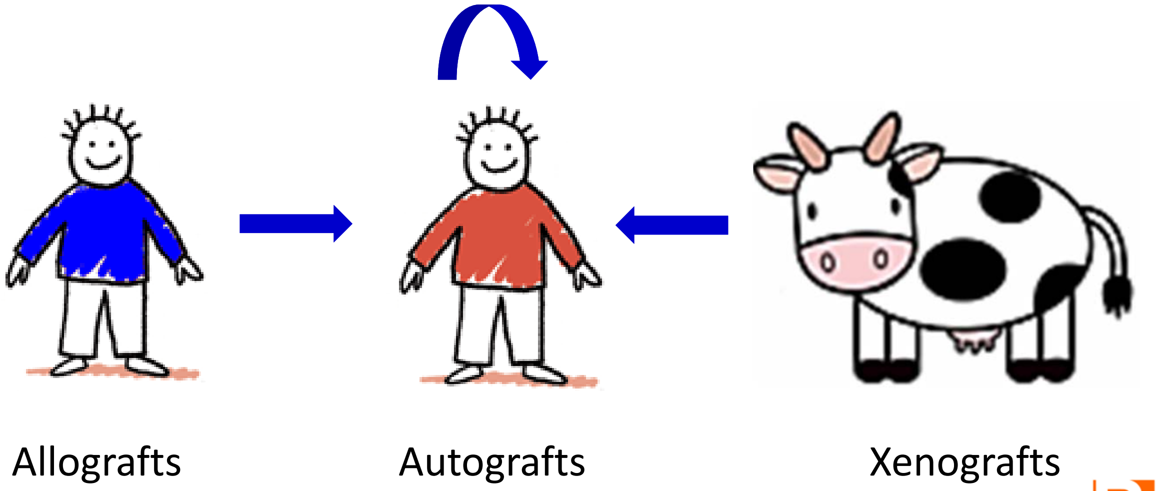
Bone Grafting procedures

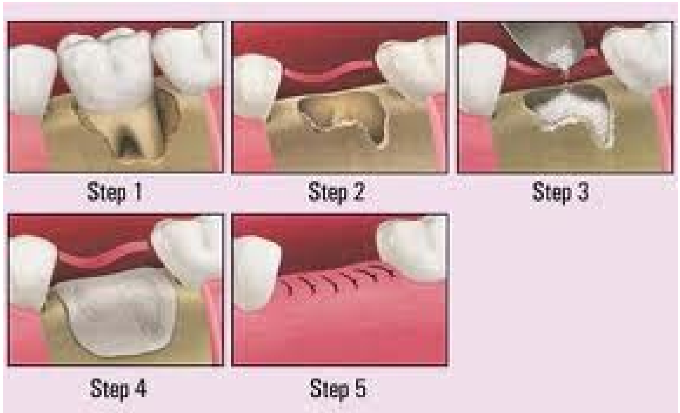
2 million bone grafting procedures worldwide every year

≈ 1 million in Europe

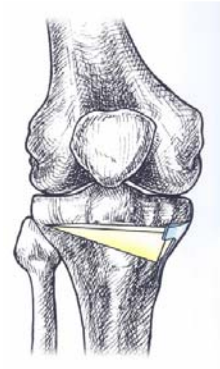
Greenwald AS et al. J Bone Joint Surg Am. 2001;83-A, suppl 2, part 2:98-103.

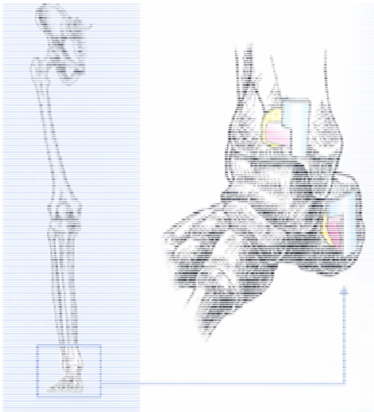


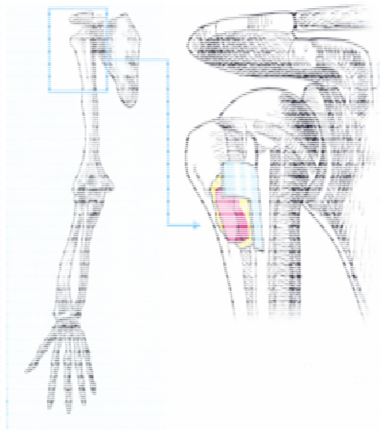
Applications of synthetic bone grafts



Applications of synthetic bone grafts







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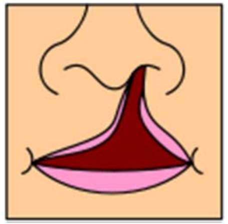
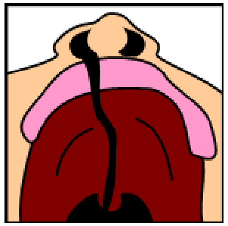
Applications of synthetic bone grafts

Treatment of bone tumors is one of the clinical fields were bone grafts are required





Maxillofacial reconstruction
(cleft lip and palate)

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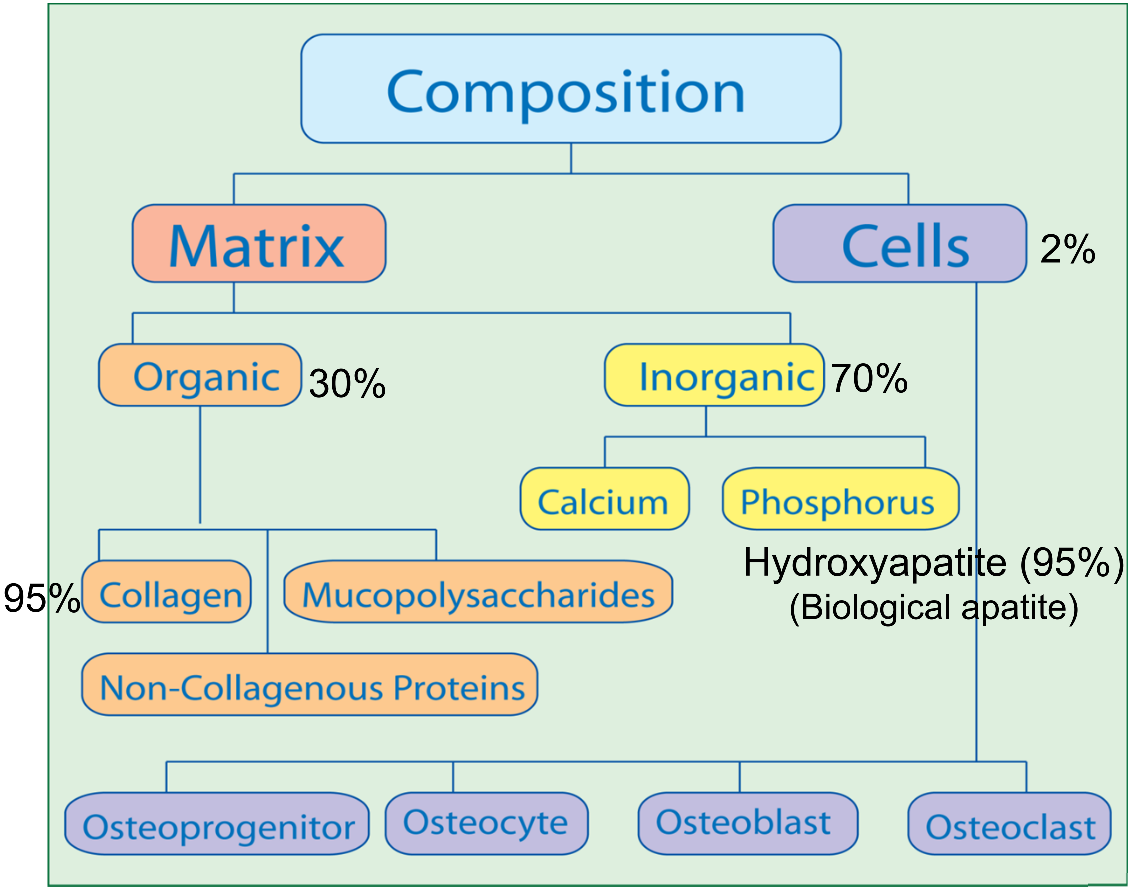
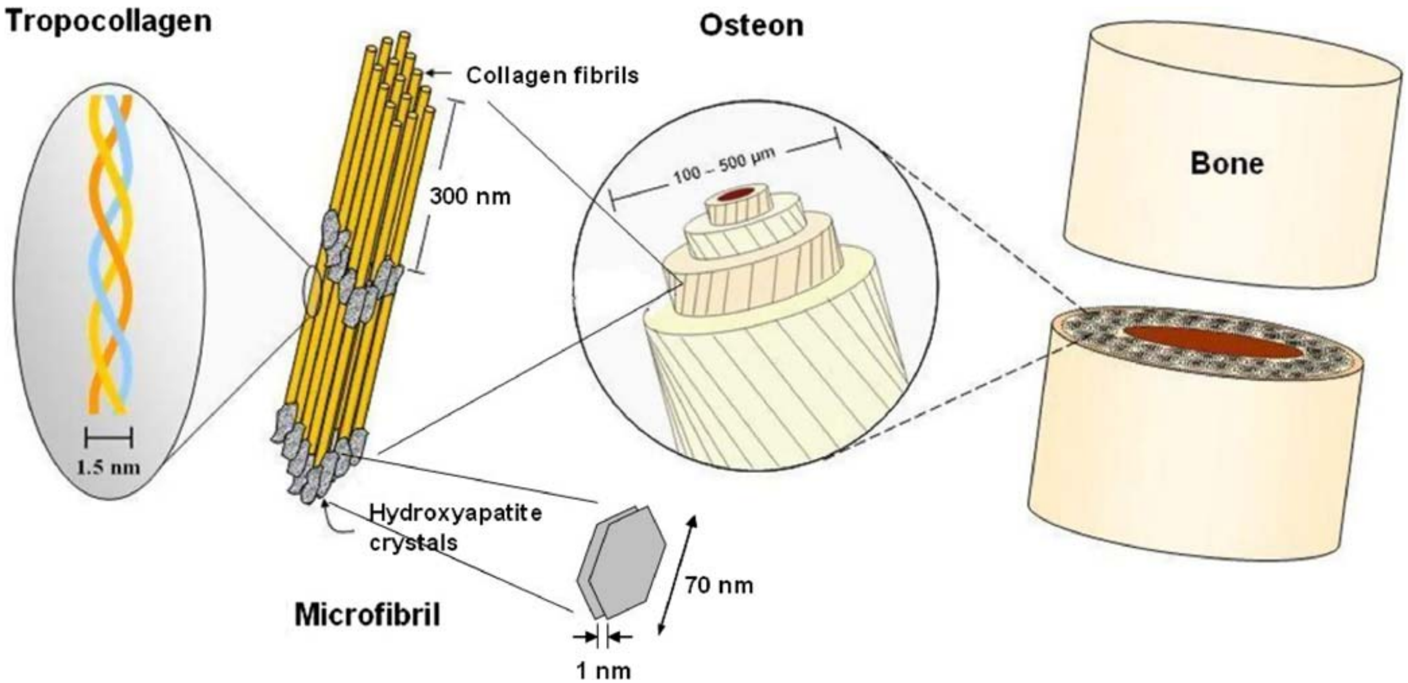
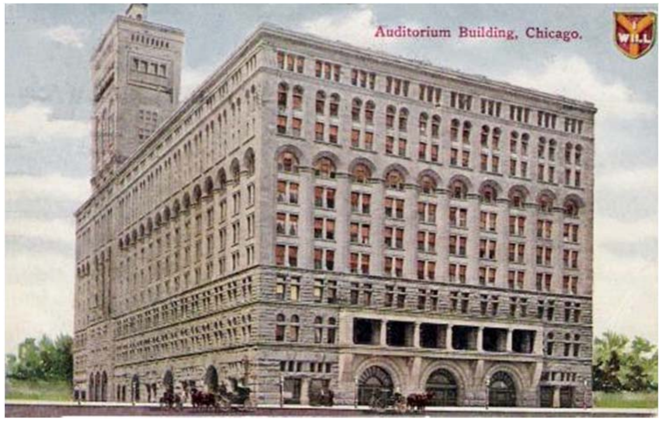
Why Calcium Phosphates?



Why Calcium Phosphates?





"Form follows function" Louis Sullivan (1896)

Hard tissue functions

Bone

- ✓ Mechanical: support and protection – strength and toughness
- ✓ Metabolic: Ion reservoir / Protein and growth factor regulation
- ✓ Autorepair

Dental Enamel

- ✓ Mechanical: to tear and chew food - hardness, resistance to abrasion
- ✓ Resistance to acidic dissolution
- ✓ Partial re-mineralization

Conventional Calcium Phosphates

Calcium Phosphates:

Hydroxyapatite
β-Tricalcium Phosphate
Biphasic Calcium Phosphates (HA/β-TCP)

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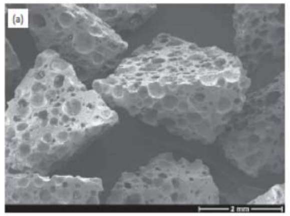
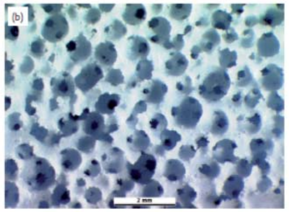
Shapes and Forms

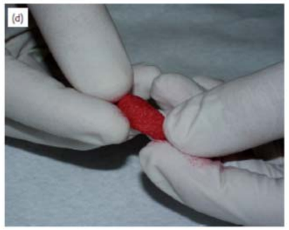
Granules
(0.1-5 mm)



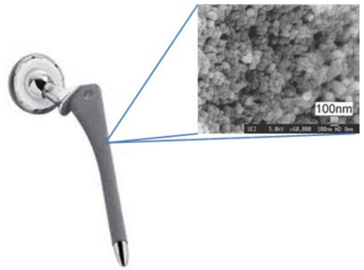


Block

Cement



Putty



Coating

M. Bohner, Materials today (2010) 13:24-30

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Origin of commercial CaP

Natural

- Bovine bone
- Coral

Synthetic

- High temperature
- Low temperature

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CaP of natural origin

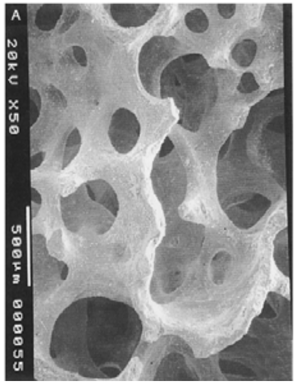
Coralline Hydroxyapatite

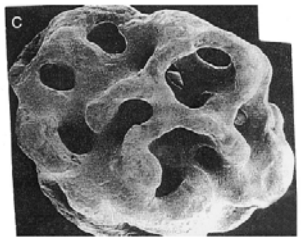
- Hydrothermal conversion (260 ºC, 15,000 psi) of coral (mostly $CaCO_3$, calcite form) in the presence of ammonium phosphate to hydroxyapatite *(Interpore™ and Pro-Osteon™ manufactured by Interpore International, Inc, Irvine, CA)*

$4CaCO_3 + 6(NH_4)2HPO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + H_2O + CO_2$

- F, Sr, and CO_3 present in the coral become incorporated in the resulting hydroxyapatite. Other ions (Mg) become incorporated in the minor β-TCP component that forms after hydrothermal conversion.

Trabecular bovine bone-derived hydroxyapatite (Endobon™),





Coralline hydroxyapatite (Interpore ™).

R.Z. LeGeros, Clin. Orthop. Rel. Res. 395 (2002): 81–98

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CaP of natural origin

Bovine-bone Derived Apatites

2 types, depending on the method of preparation:

(1) unsintered *(Bio-Oss™, by Geistlich Biomaterials, Geistlich, Switzerland)*

(3) sintered *(Osteograf-N™ by CeraMed Co Denver, CO and Endobon™ by Merck Co, Darmstadt, Germany).*

- The unsintered bone mineral consists of small crystals of bone apatite (carbonatehydroxyapatite) and other trace elements originally present in bone, whereas the sintered bone mineral consists of much larger apatite crystals without CO_3 when sintered above 1000 ºC.
- Safety concerns after mad cow disease (Creutzfeldt–Jakob disease): bovine-derived graft biomaterials may carry a risk of prion transmission to patients.

Wenz B, Oesch B, Horst M. Biomaterials. 22 (2001):1599-606.

Kim Y, Nowzari H, Rich SK.Clin Implant Dent Relat Res. 15 (2013):645-53.

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Synthetic CaP

High Temperature

- Sintered ceramics
- Coatings (plasma spray)

Low Temperature: Biomimetic CaPs

- Calcium phosphate cements
- Biomimetic coatings
- CaP Nanoparticles

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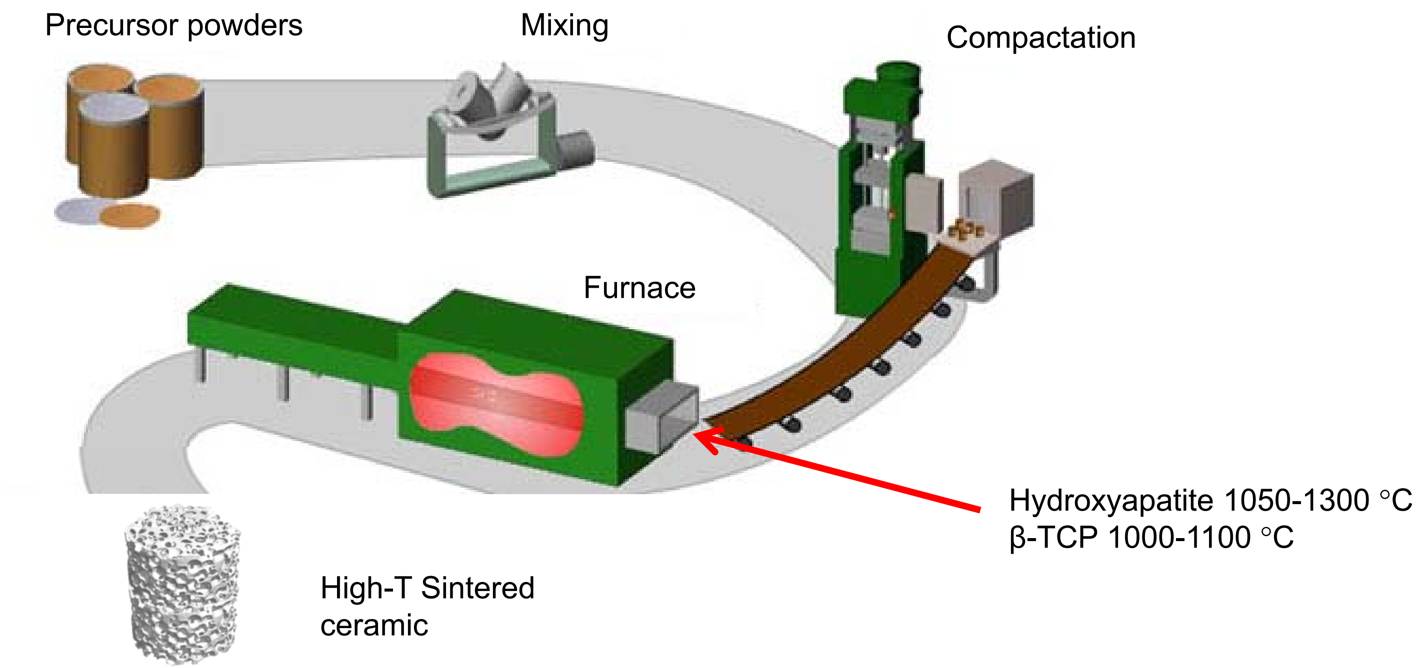
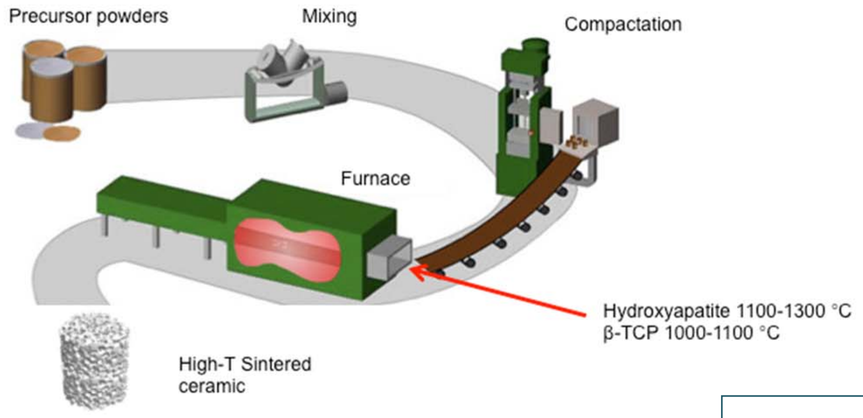
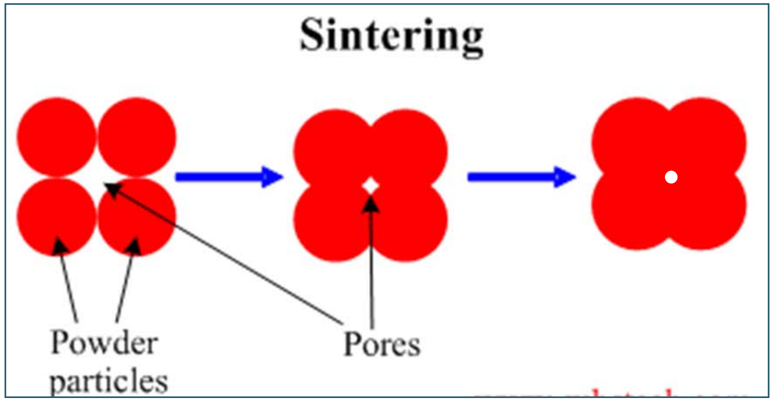
High Temperature CaPs: Sintered ceramics

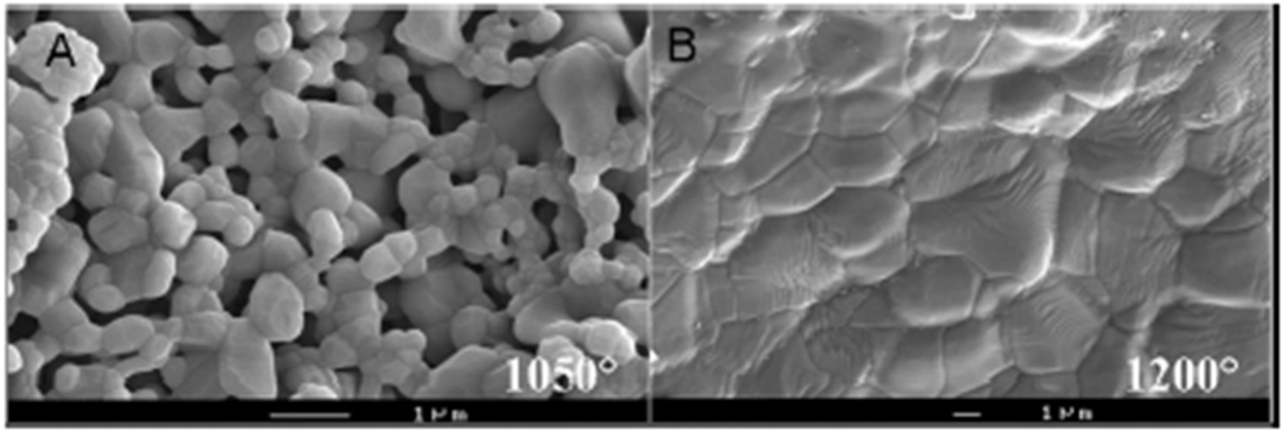


High Temperature CaPs: Sintered ceramics





High Temperature CaPs: Sintered ceramics



LeGeros, R.Z. Chem. Rev. 2008, 108, 4742–4753

High T CaP ceramics vs low T biomimetic CaP

High Temperature

- Sintered ceramics
- Coatings (plasma spray)

Low Temperature: Biomimetic CaPs

- Calcium phosphate cements
- Biomimetic coatings
- CaP Nanoparticles

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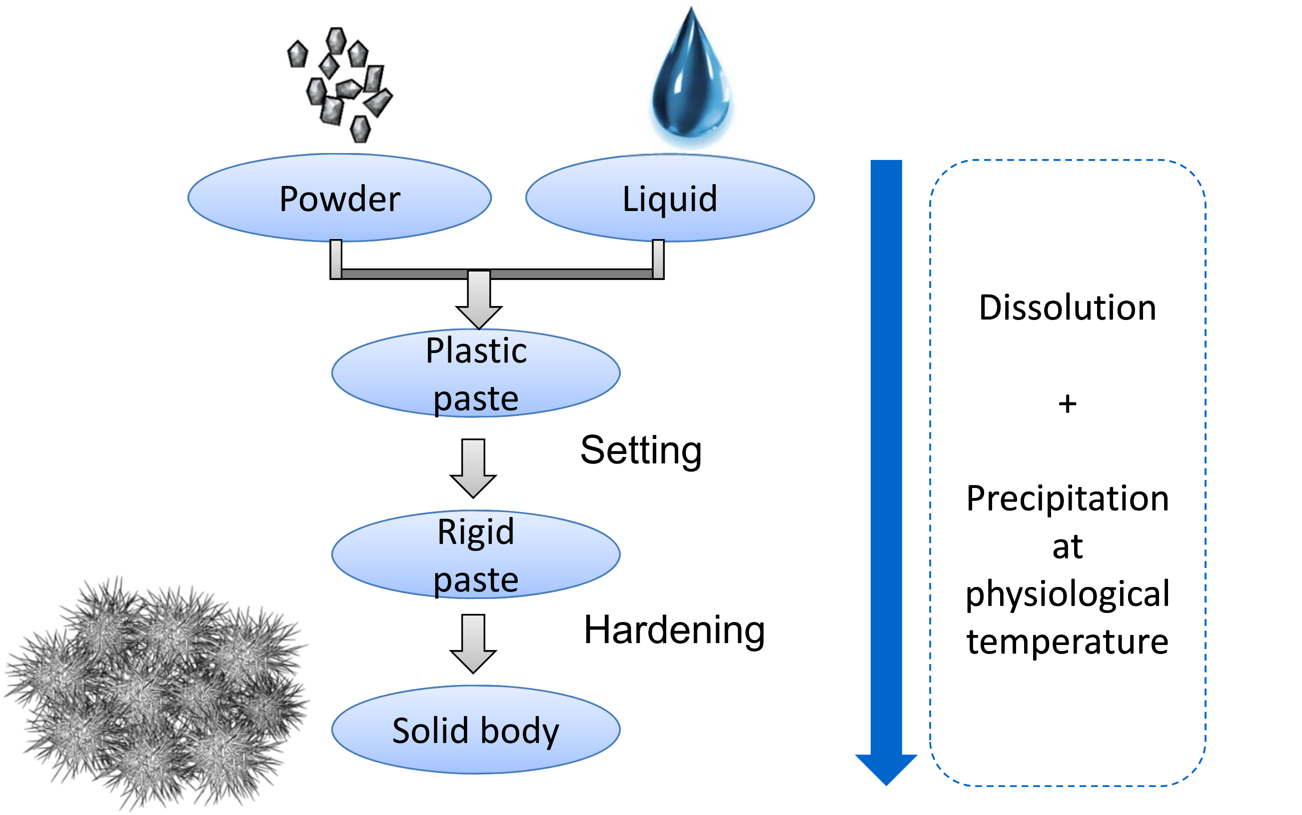
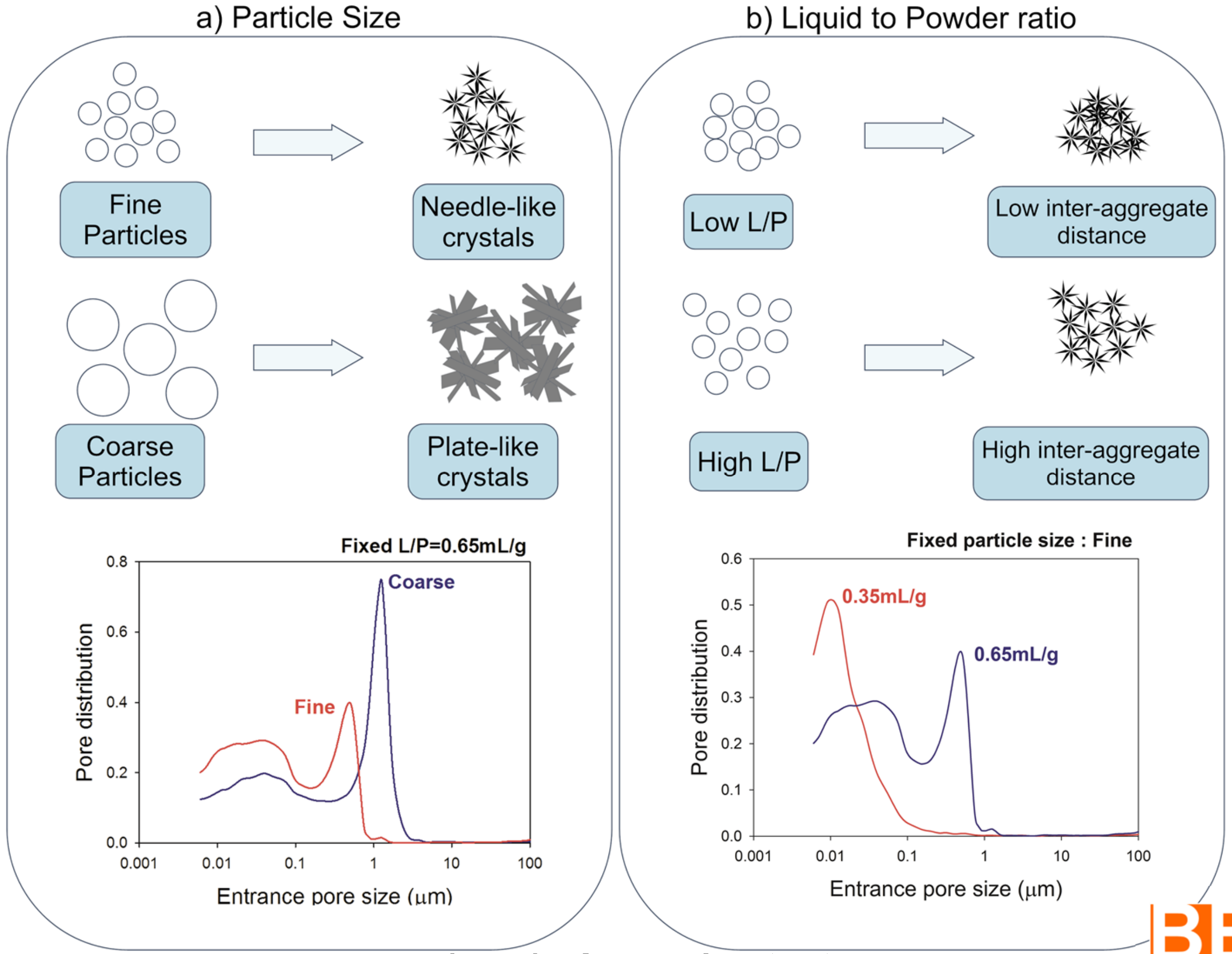
Low T setting reaction

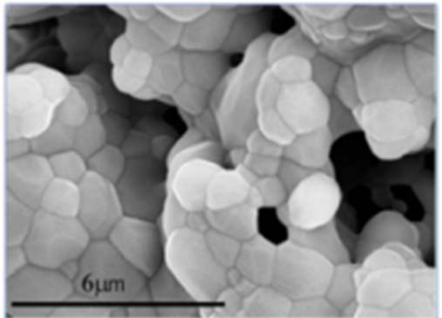


Micro & nanoporosity

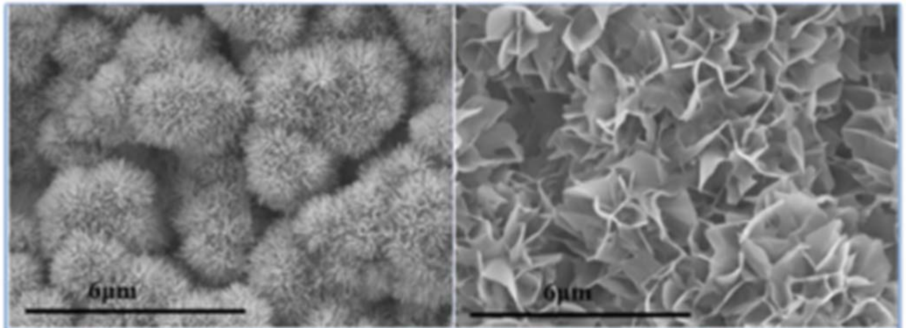


M.P. Ginebra et al., ***Adv Drug Del Rev*** (2012)

High T CaP ceramics vs low T biomimetic CaP



Sintered CaP ceramic



CaPs obtained by a low-temperature self-setting reaction

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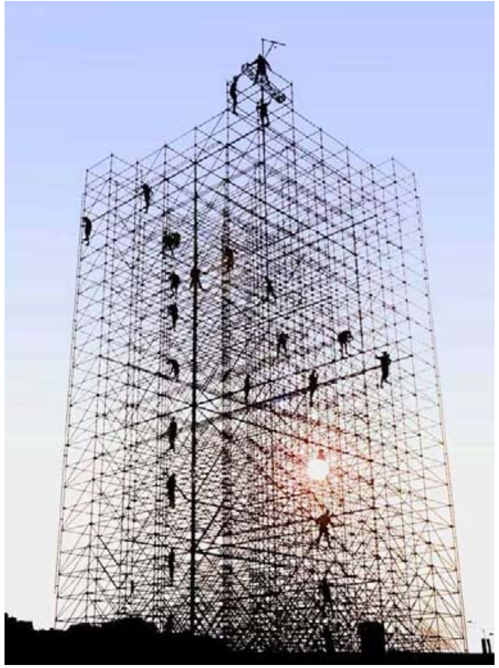
The role of porosity

Micro/nanoporosity:

- Increased bioactivity
- Effect on protein adsorption, and cell adhesion/proliferation
- Permeability: nutrient and cell metabolic waste substances diffusion.



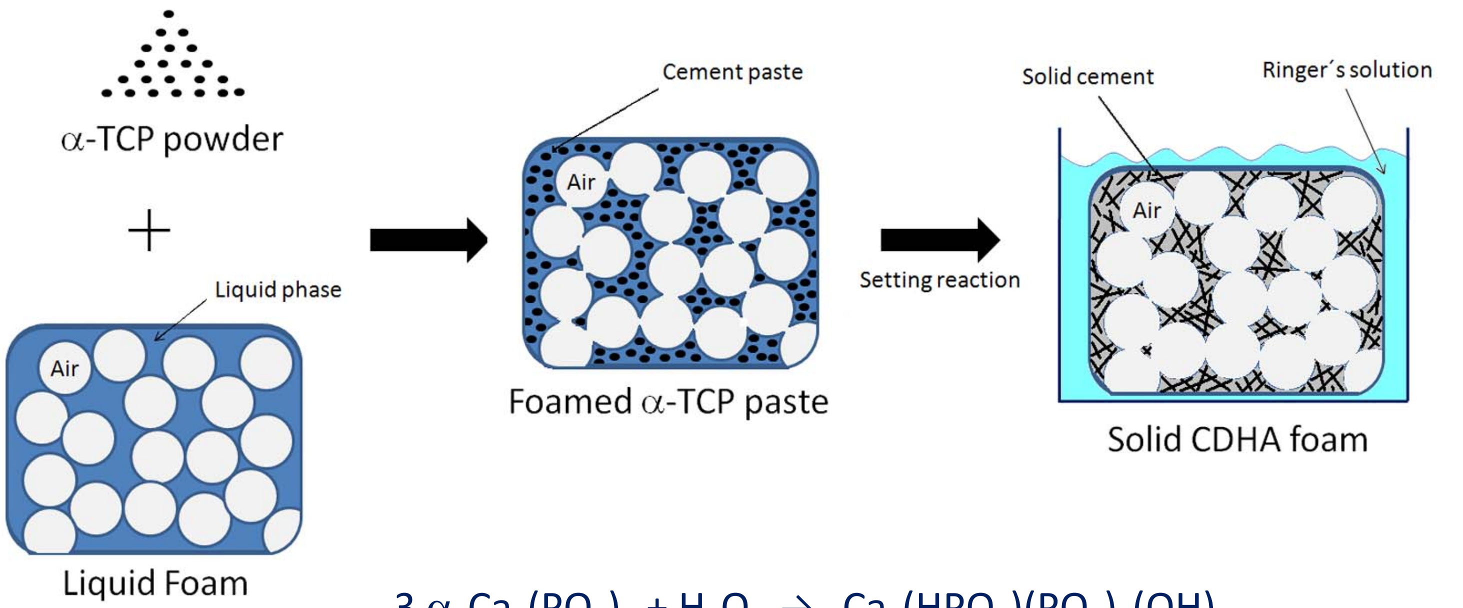
Macroporosity: cell/tissue colonisation.

- migration, proliferation and differentiation of osteoblast progenitor cells.
- angiogenesis.

Size > **decens/hundreds μm**

Need of interconnected porosity

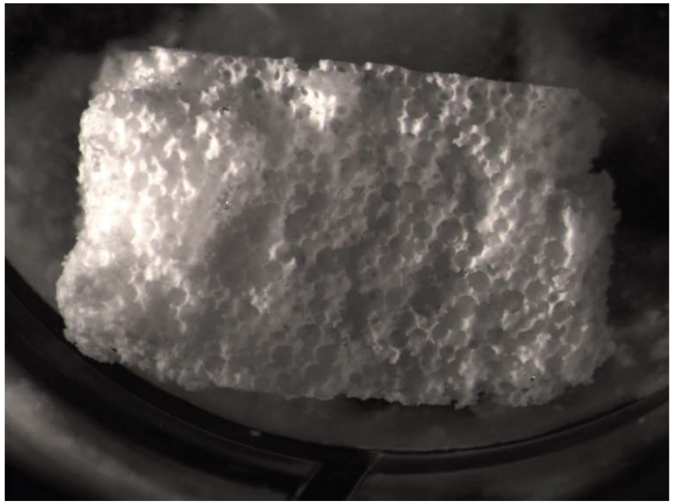
Macroporous CaPs: Injectable Calcium phosphate foams

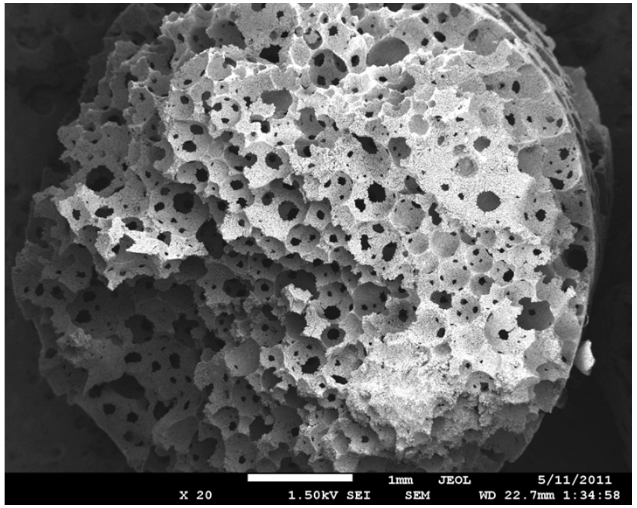


$$3\ \alpha\text{-}Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5(OH)$$

Montufar et el. ***Acta Biomater*** *6 (2010) 876–885*

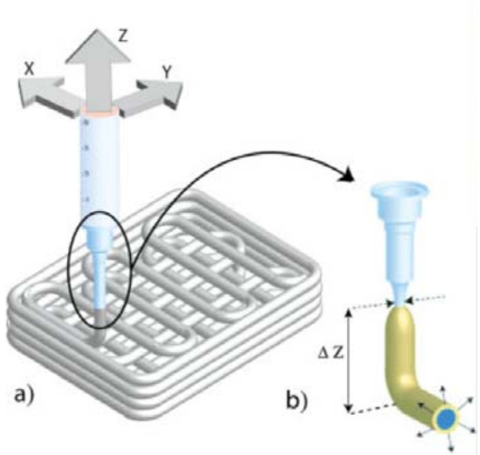
Macroporous CaPs: Injectable Calcium phosphate foams



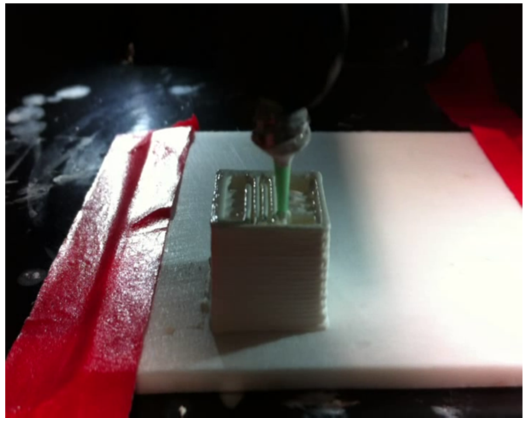


Montufar et el. ***Acta Biomater*** *6 (2010) 876–885*

Macroporous CaPs: 3D printing strategies



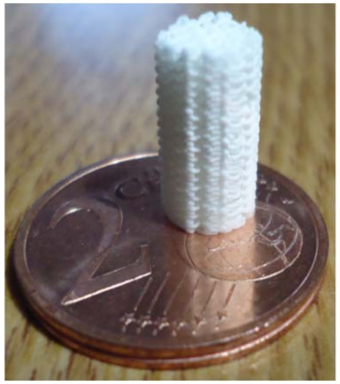
Tomsia et al (2007)



Ceramic ink

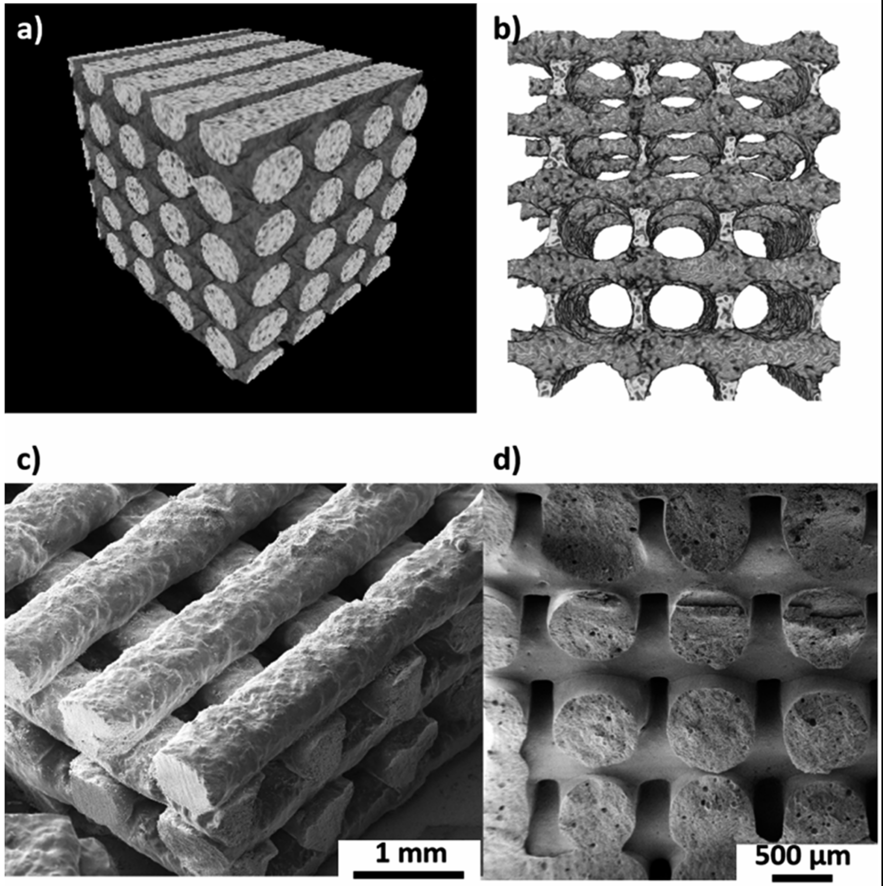
- Non-reactive suspension: Printing + Sintering
- Suspension of reactive ceramic particles → Self-setting scaffolds

Macroporous CaPs: 3D printing strategies



Self-setting Ceramic Ink:
Gelatin-αTCP

- Gelatine gellation: initial consolidation of the scaffold
- Subsequently: αTCP hydrolysis to Hydroxyapatite



Y. Maazouz, E. B. Montufar, J. Guillem-Marti, I. Fleps, C. Ohman, C. Persson, M. P. GinebraJ. Mater. Chem. B, 2014, 2, 5378–5386

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Biological performance of CaP

- **Resorption**
- **Bioactivity / Osteoconduction**
- **Osteoinduction**

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Biological performance of CaP: Resorption

Ca/P ionic ratio	Compound	Chemical formula	Solubility at 25 °C, –log(K$_s$)	Solubility at 25 °C, g/L	pH stability range in aqueous solutions at 25°C
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2{\cdot}H_2O$	1.14	~ 18	0.0 – 2.0
0.5	Monocalcium phosphate anhydrous (MCPA)	$Ca(H_2PO_4)_2$	1.14	~ 17	[c]
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$CaHPO_4{\cdot}2H_2O$	6.59	~ 0.088	2.0 – 6.0
1.0	Dicalcium phosphate anhydrous (DCPA), mineral monetite	$CaHPO_4$	6.90	~ 0.048	[c]
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4{\cdot}5H_2O$	96.6	~ 0.0081	5.5 – 7.0
1.5	α-Tricalcium phosphate (α-TCP)	α-$Ca_3(PO_4)_2$	25.5	~ 0.0025	[a]
1.5	β-Tricalcium phosphate (β-TCP)	β-$Ca_3(PO_4)_2$	28.9	~ 0.0005	[a]
1.2 – 2.2	Amorphous calcium phosphate (ACP)	$Ca_xH_y(PO_4)_z{\cdot}nH_2O$, n = 3 – 4.5; 15 – 20% H_2O	[b]	[b]	~ 5 – 12 [d]
1.5 – 1.67	Calcium-deficient hydroxyapatite (CDHA)[e]	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$[f] (0<x<1)	~ 85.1	~ 0.0094	6.5 – 9.5
1.67	Hydroxyapatite (HA)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	~ 0.0003	9.5 – 12
1.67	Fluorapatite (FA)	$Ca_{10}(PO_4)_6F_2$	120.0	~ 0.0002	7 – 12
2.0	Tetracalcium phosphate (TTCP), mineral hilgenstockite	$Ca_4(PO_4)_2O$	38 – 44	~ 0.0007	[a]

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Biological performance of CaP: Resorption

Passive resorption

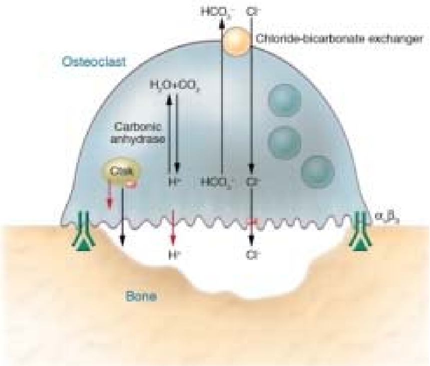
Chemical dissolution

Plaster of Paris (CSH),
Gypsum (CSD),
Dicalcium phosphate dihydrate (DCPD)

Active resorption

Cell-mediated
osteoclasts, macrophages…

Precipitated Hydroxyapatite *
β-Tricalcium phosphate
Biphasic calcium phosphates



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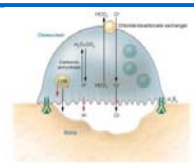

Reactivity:
- ✓ Stoichiometry
- ✓ Cristallinity
- ✓ Specific surface area
- ✓ Porosity

Sintered HA

Non resorbable

HA → Biological HA

Resorbable

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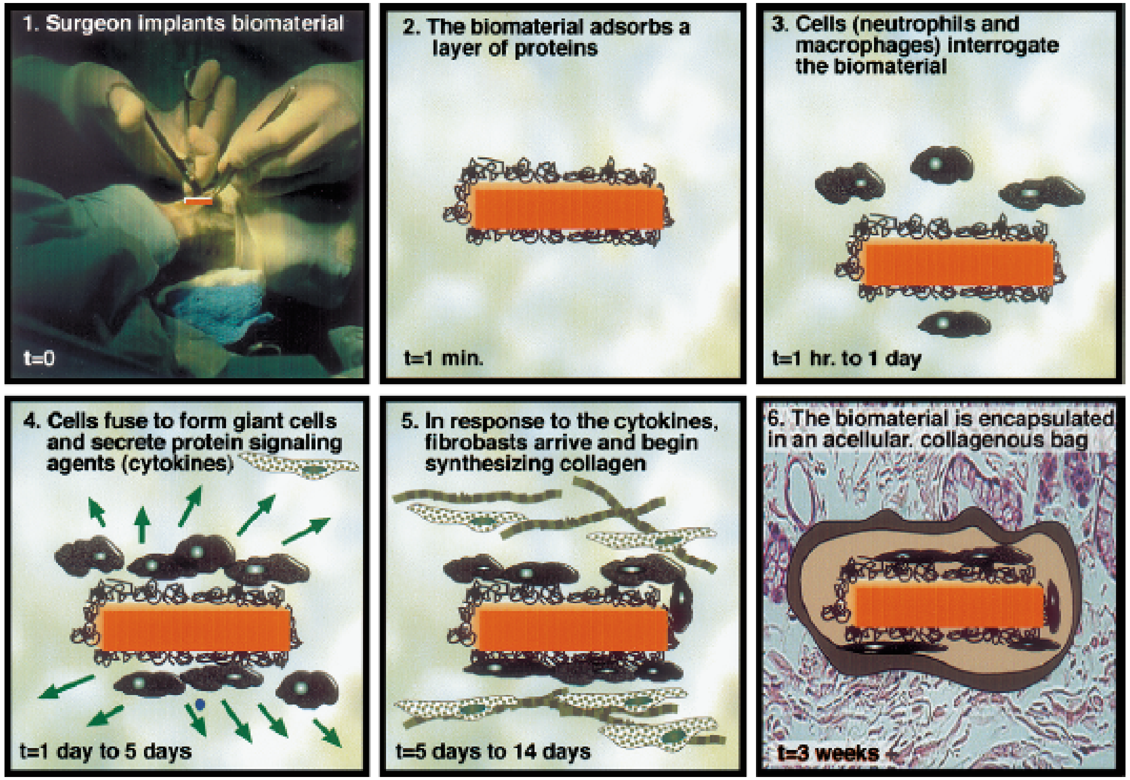
Biological performance of CaP: Bioactivity



D.G. Castner, B.D. Ratner / Surface Science 500 (2002) 28–60

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Biological performance of CaP: Bioactivity

Bioceramics

Bioinert

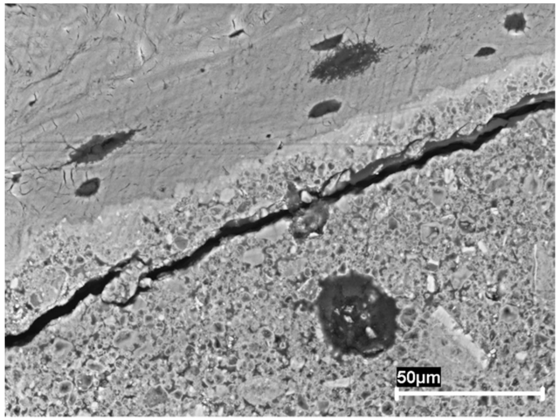
Alumina
Zircona

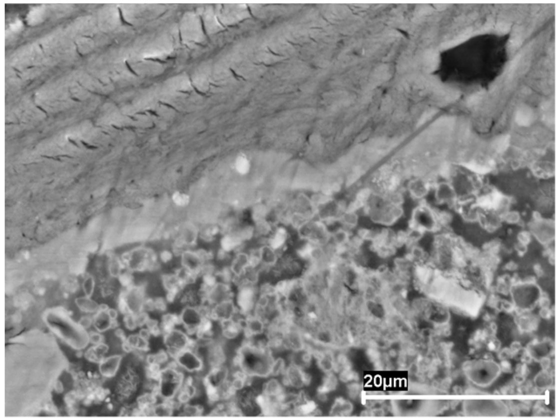
Bioactive

Bioactive glasses and glass ceramics
Calcium phosphates

+/- biodegradable

Biological performance of CaP: Bioactivity





S. del Valle, M.P. Ginebra et al. J Mater Sci: Mater Med (2007) 18:353–361

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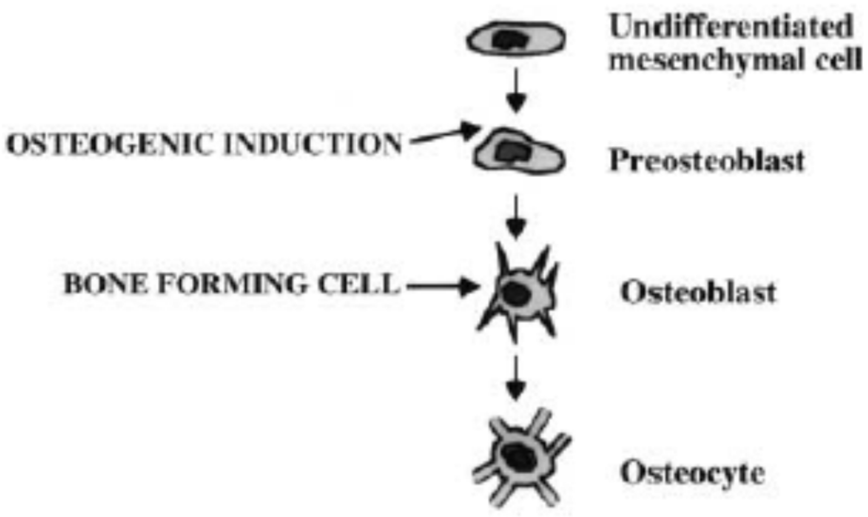
Biological performance of CaP: Osteoinduction

La osteoinduction: differentiation of mesenchymal stem cells (pluripotent) to the osteoblastic phenotype.



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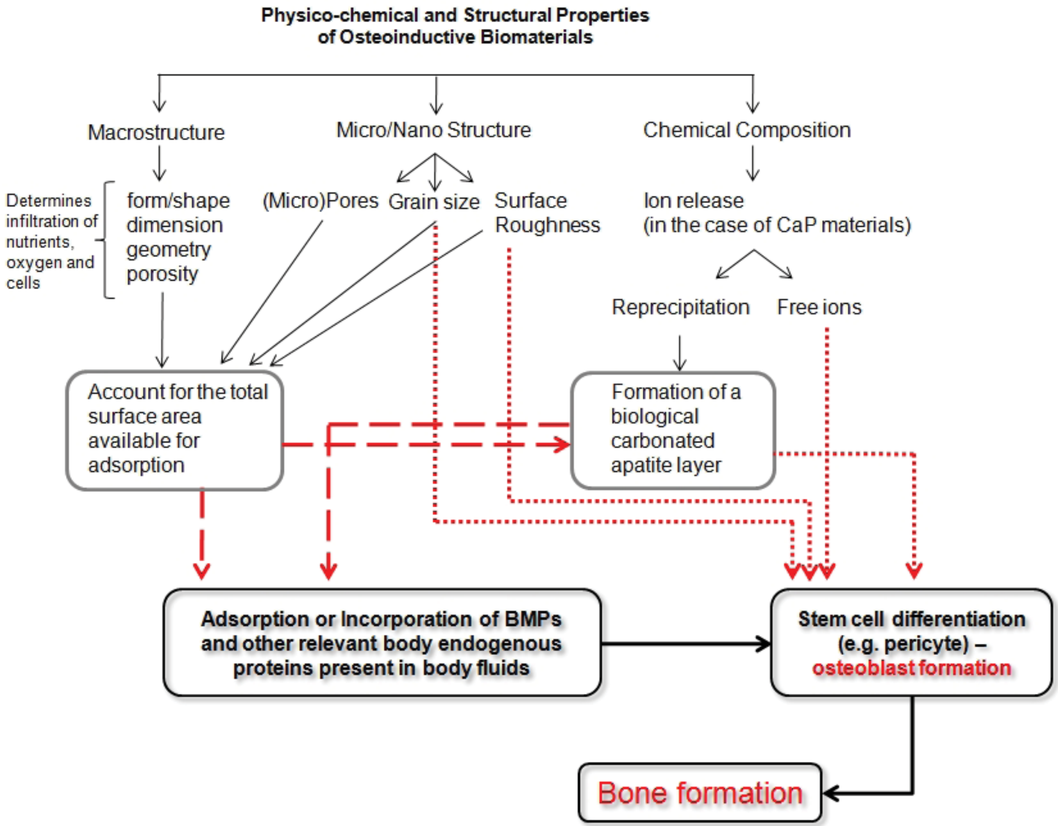
Biological performance of CaP: Osteoinduction

Two strategies to trigger osteoinduction:

1. Incorporation of bone morphogenetic proteins (BMPs) in the biomaterials.
2. Designing intrinsically osteoinductive biomaterials

Biological performance of CaP: Osteoinduction



M. C. Barradas, H. Yuan, C. A. Van Blitterswijk, P. Habibovic, Eur. Cells Mater. 21 (2011), 407–29

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Summary

- CaP have unique properties as synthetic bone grafts
- CaP can be obtained either from natural sources of by synthetic processes either at high-T or low-T
- The biological performance of CaP (resorption, bioactivity and osteoinduction) depends not only on their composition but also on their porosity and textural properties. Their control can allow actively directing the material-cell/tissue interaction.
- CaP processing is compatible with promising strategies for the fabrication of macroporous CaP scaffolds for tissue engineering and bone regeneration.

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SEVENTH FRAMEWORK PROGRAMME

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN

Agència de Gestió d'Ajuts Universitaris i de Recerca

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Thank you!

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