MBCP™ Technology: Smart Alloplastic Grafts For Bone Tissue Regeneration

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Abstract: Bioceramic bone substitutes made of calcium phosphate are numerous, but their chemical composition alone do not ensure that they will behave as a ''smart scaffold''. This article describes the proprietary MBCP™ technology developed by Biomatlante S.A., building on the expertise of R. Legeros (University of New York, USA) and G. Daculsi (University of Nantes, France), the inventors of Biphasic Calcium Phosphate (BCP) in the 80's. At the core of Biomatlante expertise lays a holistic approach of engineering biomaterials with biomimetic properties. This paper reports correlations between the physicochemical properties of BCP scaffolds and the induced biological responses as well as raising the crucial importance of controlling all critical aspects behind the conception of a biomaterial, namely materials science, biology and medicine.

Keywords: Bioceramics; Biomimetism; Bioactivity; Osteoconduction; Osteoinduction

INTRODUCTION

Biphasic Calcium Phosphate (BCP) consists of a bioactive mixture of highly crystalline HA (Hydroxyapatite) and β-TCP (Tri Calcium Phosphate). The concept resides in an optimum balance of the more stable phase of HA and the more soluble β-TCP. The biomaterial is soluble and gradually dissolves in the body, inducing bone regeneration at the expense of the BCP.

Just as the last decade focused on synthetic bone substitute fillers, evolution of the biomaterials and developments in surgical techniques in association with osteosynthesis; the next decade will focus on the association of these advanced synthetic BCP scaffold with cells, active principle ingredients (such as BMPs) and biological derivatives (such as concentrated autologous bone marrow). Developing targeted delivery systems used in combination with minimally invasive surgical techniques is the subject of intense focus. Maximizing the regenerative potential of the biological host using the best suited treatment option is clearly the new challenge in Ortho-Biology. Success in this rests on four distinct yet complementary elements:

- Advanced Scaffolds: fully synthetic and resorbable, well characterized and optimized for Tissue Engineering, Cell Therapy, Drug and Gene Delivery
- Cells: How do we identify, harvest, and stimulate Cell precursors?
- Signal: the orthopaedic genome, pharmacogenomics and targeted therapies
- Surgical technologies: how to combine matrices, cells and signals

WHAT ARE THE MOST RELEVANT PROPERTIES FOR SCAFFOLDS DEDICATED TO BONE REGENERATION?

Biomimicry towards bone chemistry

Apatite crystallographic phase

Native bone is constituted of a mineral phase known as a carbonated apatite, very similar to hydroxyapatite (HA) phase, and collagen biopolymer fibres. Alloplastic bioceramics containing apatitic crystals such as HA or β-TCP feature similar mechanical properties as native bone[1]. Moreover, only apatitic scaffolds may be directly involved in the bone remodeling cycle, as they are resorbed by osteoclasts which leads to an inversion of the osteoclast-osteoblast step and related apposition of new bone at its surface[2].

The apatite crystal size is also an important parameter as it influences two significant factors:

- The specific surface area, thus the release of proteins
- The kinetics of dissolution (the smaller the crystals are, the quicker they dissolve)

The specific manufacturing process used by Biomatlante ensure that MBCP™ crystals are only a few hundred nanometers.

Calcium, phosphate ions release

The ionic environment is a seminal factor promoting osteogenic cells line activity and bone metabolism. Calcium and phosphate play a significant role in the chemical precipitation phenomenon leading to the formation of

biological apatite crystals and the mineralization of the extracellular matrix[3].
Bearing the above in mind, the most biomimetic biomaterials are clearly bioceramics made of calcium (Ca) and phosphate (P). Within the realm of bioceramics, stoichiometric hydroxyapatite (HA) and beta-tricalcium phosphate (β-TCP) are well-known to be the reference in terms of biomimicry towards bone properties[4]. No other class of biomaterial, whether metallic or polymeric, can provide apatitic crystallography and calcium-phosphate ions release enhancing bone metabolism (Table 1).

Table 1 Biomimicry towards bone chemistry of the 3 main classes of Biomaterials

	Bioceramics such a MBCP™	Metals such as TA6V or 316L	Polymers such as polycaprolactone (PCL) or polylactic acid (PLA)
Apatitic lattice?	YES	NO	NO
Ca, P ions release?	YES	NO	NO
=> Biomimicry towards bone chemistry?	YES	NO	NO

BIOMIMICRY TOWARDS BONE MICROSTRUCTURE

Macropores: Osteoconductive and cell-protective niches

Spongious bone is highly porous with trabecular architecture enabling cellular and vascular invasion. This macroporosity is one of the mandatory characteristic for any bone substitute if it is to be effective in terms of cellular adhesion and proliferation into concavities acting as protective niches for osteogenic cells[5].

Cells adhering on scaffolds are exposed to tribological frictions occurring either with instruments during surgery, between scaffolds (granules), or with surrounding tissues inside the defect after mechanical solicitations. The macropores of scaffolds with a concave surface provide natural niches to cells, thus minimizing these unavoidable and deleterious effects. On the other hand, scaffolds that have a predominantly convex surface, such as rounded or tubular, do not provide bone cells with a favourable environment. The optimal macroporosity for cell colonization has been determined between 100 and 500 micrometers[6], mimicking the structure of natural bone.

Micropores: Enhancing Bioactivity

The second level of porosity is defined as microporosity (below 10 micrometers)[6], which is also crucial for enhancing the bioactivity of scaffolds by allowing for the penetration of biological fluids. The higher the microporosity, the higher the specific surface area (SSA) which enhances protein adsorptions with osteoinductive trophic factors such as Bone Morphogenic Proteins (BMPs). A higher SSA from a higher microporosity also increases the dissolution rate of Ca-P resorbable scaffolds. Typical SSA of non-microporous scaffolds is below 1m²/g, while MBCP™ technology provide at least 2-3 m²/g.

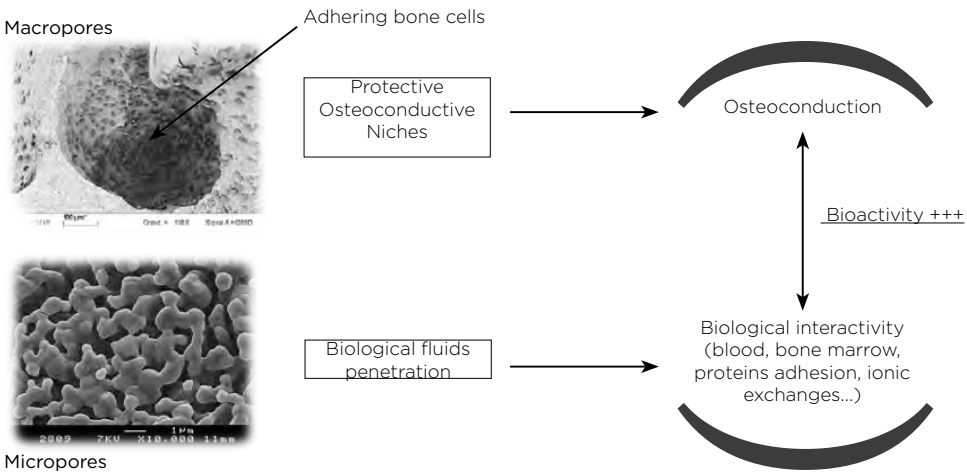


Figure 1 Biological response to double macro-micro porosity of MBCP™ technology

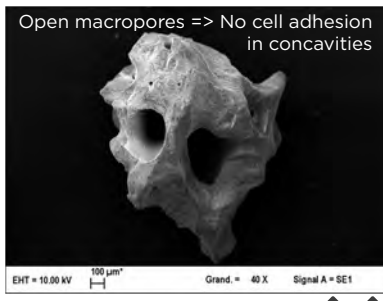
ARE ALL CaP BIOCERAMICS BORN EQUAL IN TERMS OF CRYSTALLOGRAPHY, AND POROSITY?

Many alloplastic grafts made of calcium phosphate (CaP) are available on the market, all intended for bone regeneration. However, a comparative study of their crystallography and microstructure demonstrates a range of properties significantly different once implanted in vivo, as alluded previously. Physico-chemical characterizations with scanning electron microscopy (SEM), mercury

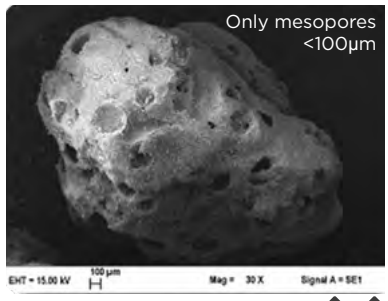
porosimetry, pycnometry and specific surface area (SSA) measurements demonstrates that MBCP™ technology is arguably the most relevant scaffold available (Table 2 and 3) thanks to its unique macro-microporosity stemming from the proprietary manufacturing process unique to Biomatlante. Other scaffolds (BioOss™, CalciResorb35™, Granulado™, Actifuse™ and Ceraform™ to name but a few) do not meet all above described quality criteria required in a "smart scaffold" design.

Table 2 Macrostructure of 6 different bioceramics scaffolds at the same magnification

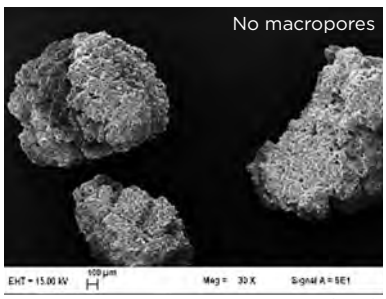
MBCP™



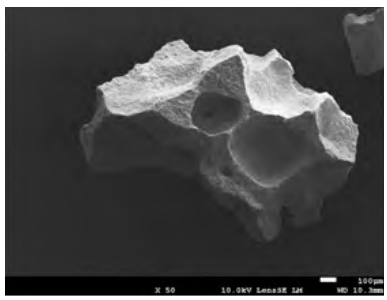
BioOss™



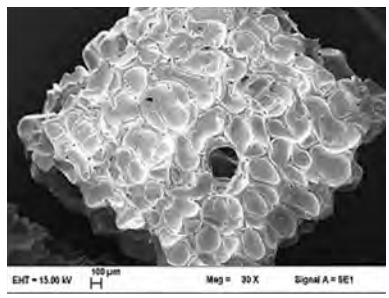
CalciResorb 35™



Granulado™

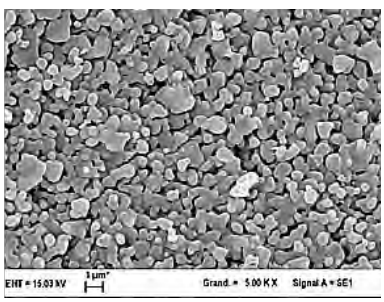


Actifuse™

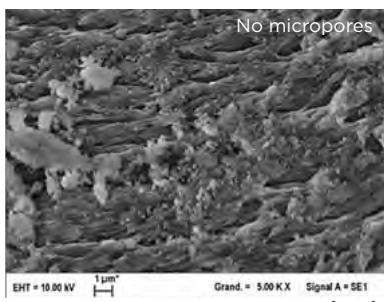


Ceraform™

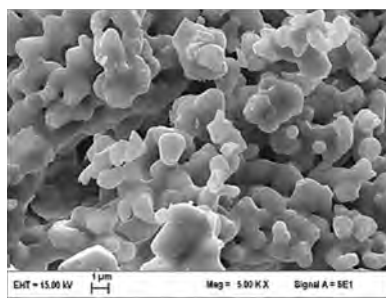
Table 3 Microstructure of 6 different bioceramics scaffolds at the same magnification



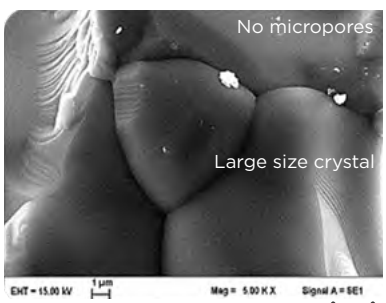
MBCP™



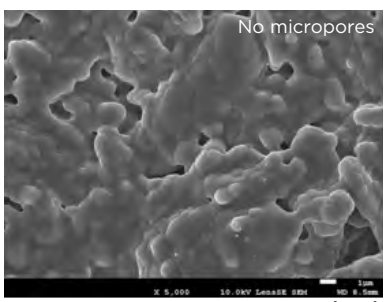
BioOss™



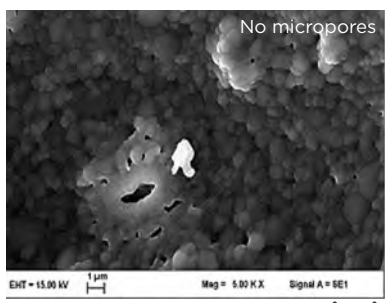
CalciResorb 35™



Granulado™



Actifuse™



Ceraform™

The table below details all characteristics of these 6 scaffolds made of calcium phosphate with the correlation between their physicochemical properties and biological relevance. Only MBCP™ technology provides both microporosity and macroporosity combined with biomimetic crystallographic phases HA/β-TCP. Only the association of these 3 essential characteristics combine to create a "smart scaffold" necessary for optimal bone regeneration (Table 4).

Table 4 Correlation between physicochemical properties and biological relevance

Properties/Scaffolds	**MBCP™ Technology**	**BioOss™**	**Calci-Resorb35™**	**Granulado™ Keramedic**	**Actifuse™**	**Ceraform™**
Biomimetic: Apatitic CaP	YES	YES	YES	YES	YES	YES
Bioactive: Microporosity	YES	NO	YES	NO	NO	NO
Osteoconductive: Macroporosity	YES	YES	NO	NO	YES	YES
=> **Smart Scaffolds?**	YES	NO	NO	NO	NO	NO
=> **Osteoinductive/ Osteopromotive?**	YES[7]	?	?	?	?	?

CONCLUSION

Despite the growing availability of synthetic bone substitutes, the presence of calcium (Ca) and phosphate (P) is the only commonality between the different scaffolds available. Surgeons should be fully aware of the seminal differences in physicochemical properties between these biomaterials as they consequently induce very different biological responses. The presence of both microporosity for body fluids invasion, macroporosity with concavities acting as osteoconductive niches and small apatite crystals for faster dissolution are the main quality criteria required to act as a "smart scaffold" whose MBCP™ technology is the reference.

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