



# BIO-CREA

b o n e   &   m e m b r a n e

**Biomaterials for Guided Bone Regeneration**

## TISS'YOU *Regenerative Company*

*Tiss'You is a company founded in 2017 and located in Domagnano (RSM), which develops and produces biomaterials and medical devices for Regenerative Medicine applications, mainly in Orthopedics and Traumatology, Spinal Surgery, Oro-maxillofacial and Dentistry.*

*Despite being a very young company, its founders have been working in the field of biomaterials and tissue regeneration for over 25 years.*



# PATENTS & PRODUCTS

*In 2020 it obtained the EstRem patent and the CE mark for three product families:*

BIO-CREA  
membrane

*Line of fleeces and membranes based on type I equine atelocollagen*

BIO-CREA  
bone

*Line of bone substitutes based on nano-HA*

artHrys  
regenerative peptides

*Solution for injection based on low molecular weight peptides from CH, vitamin C and Mg ions*

**EstRem**  
Esterification Cell Removal Technology

*Deantigenation process for biological tissues*

# COMING SOON

*Another CE mark and another patent release are expected in 2021:*

*Superficial hybridization process of natural bone matrix and titanium implants*

## CHIMERA

*Line of equine bone grafts processed with the EstRem technology*

 **xenys**  
The graft revolution



# BONE REGENERATION

Some tissues encounter more difficulties in triggering their own repair mechanisms, hampered by conditions such as: the absence of oxygen and nutrients, a chronic inflammatory state, a particularly complex tissue matrix to remodel.

In the case of bone tissue, however, regeneration occurs with an excellent chance of success thanks to the good vascularization of the tissue.

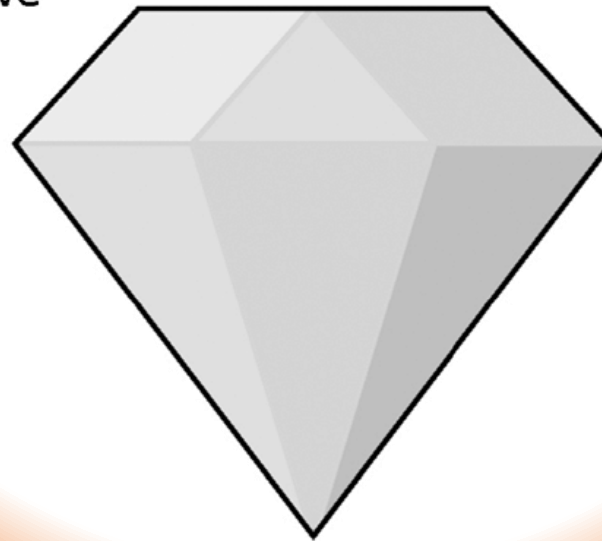


# THE DIAMOND CONCEPT

Although the bone has this propensity for self-healing, bone regeneration is only successful if all the elements of the so-called "Diamond Concept" are present

osteoconductive  
scaffolds

mechanical  
environment



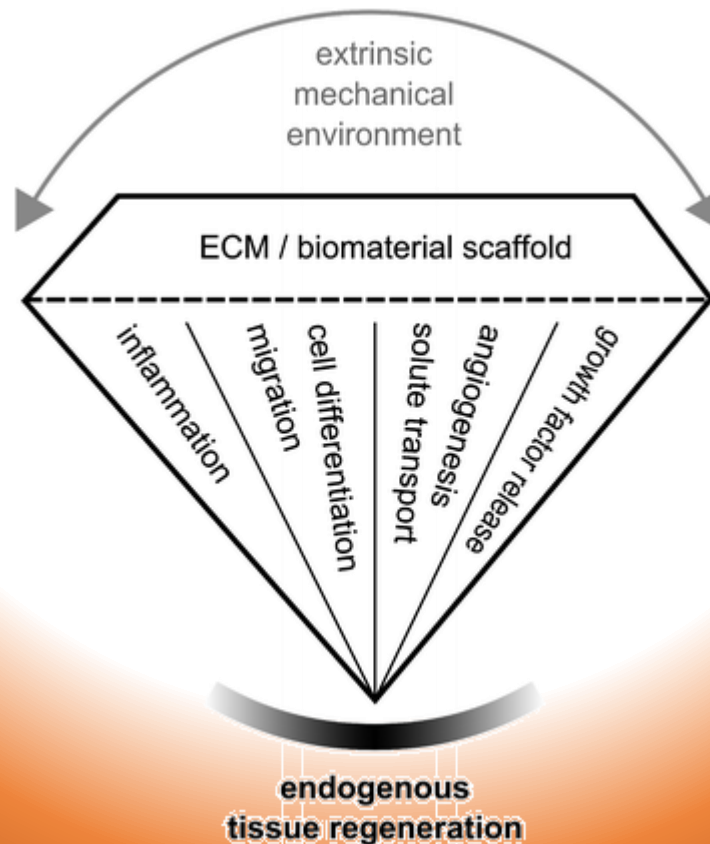
osteogenic  
cells

growth  
factors

vascularity

# THE DIAMOND CONCEPT

Although the bone has this propensity for self-healing, bone regeneration is only successful if all the elements of the so-called "Diamond Concept" are present



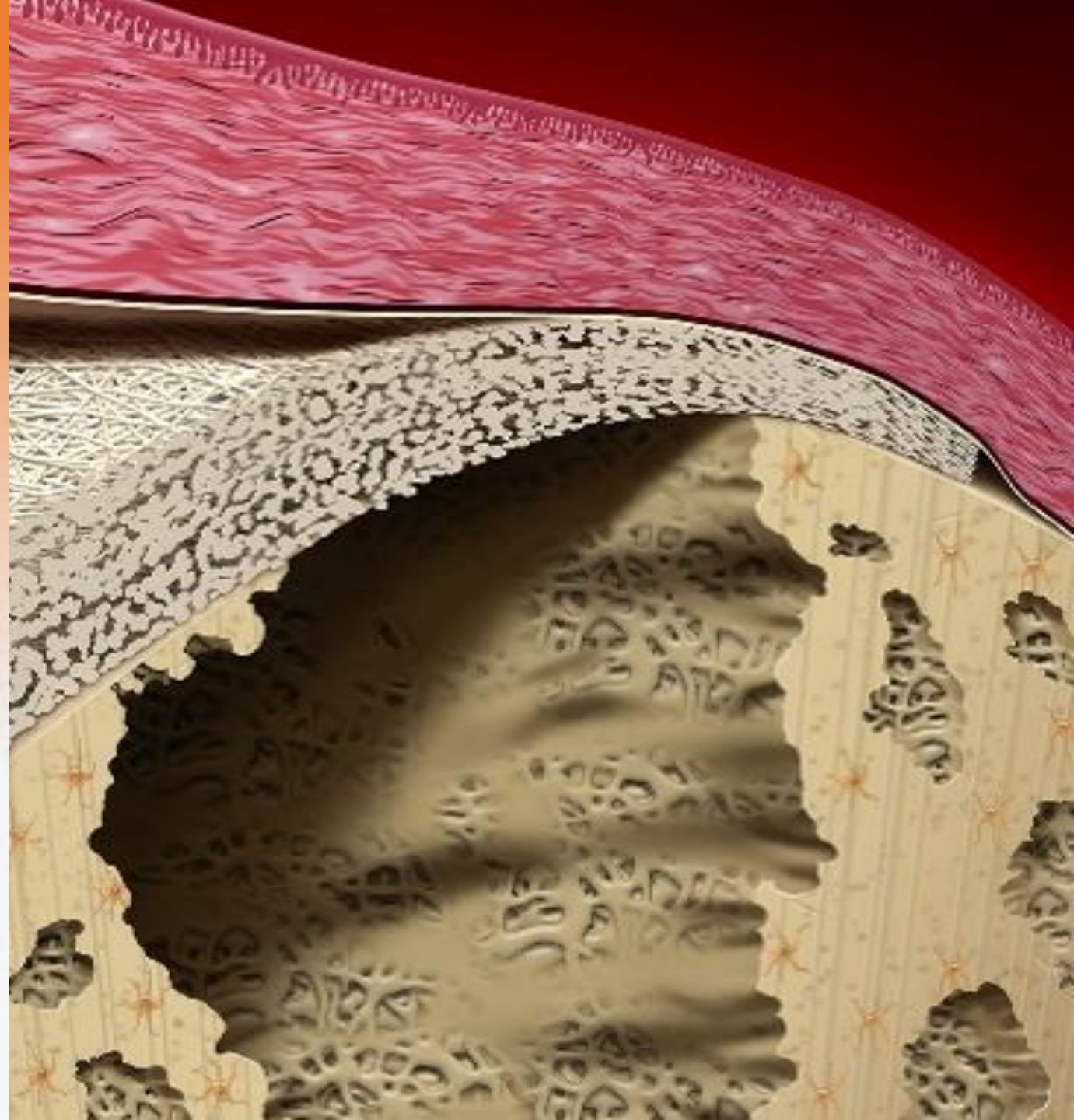
# GUIDED TISSUE REGENERATION

In oral surgery, the contiguity with the mucosa is a further problem for bone regeneration: the infiltration of soft tissue in situ, whose formation takes much shorter times.

In the 1990s, the Guided Tissue Regeneration (GTR) technique was introduced. Through the use of a "barrier" membrane, often in association with grafts, the regeneration of the defect is guided towards the formation of new bone tissue

*Dahlin, C; Linde, A; Gottlow, J; Nyman, S (May 1988)  
"Healing of bone defects by guided tissue regeneration".  
Plastic and Reconstructive Surgery. 81 (5): 672–676.*

*Buser, D.; Brägger, U.; Lang, N. P.; Nyman, S. (1990).  
"Regeneration and enlargement of jaw bone using guided tissue regeneration".  
Clinical Oral Implants Research. 1 (1): 22–32.*



# GUIDED BONE REGENERATION

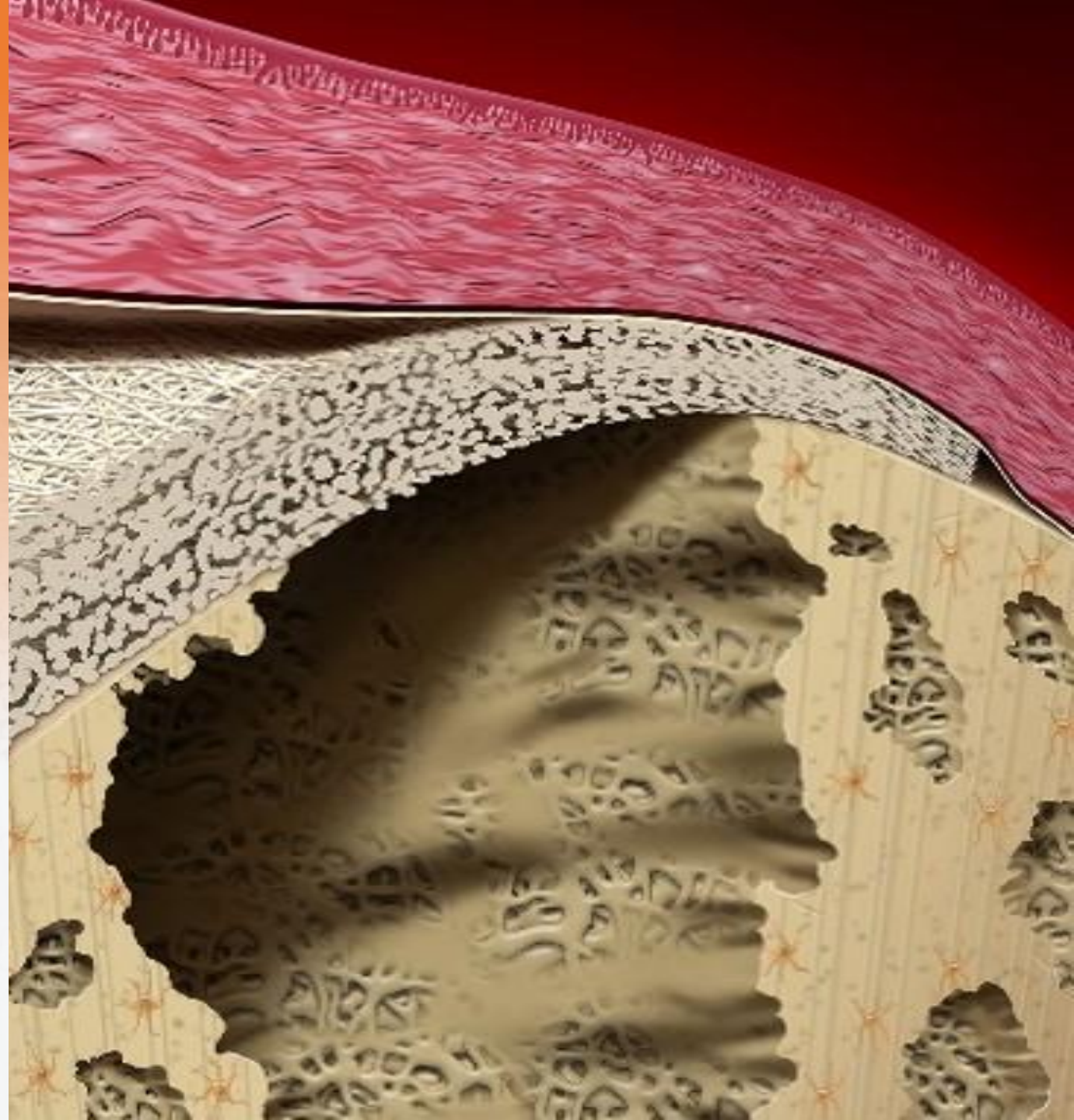
Guided Bone Regeneration is achieved when the osteoprogenitor cells are exclusively allowed to repopulate the bone defect site by preventing the entry of non-osteogenic tissues <sup>1, 2</sup>.

1 - Retzepi M, Donos N.

*Guided Bone Regeneration: biological principle and therapeutic applications.*  
*Clin Oral Implants Res* 2010; 21: 567–576.

2 - Dimitriou R, Mataliotakis GI, Calori GM, Giannoudis PV.

*The role of barrier membranes for guided bone regeneration and restoration of large bone defects: current experimental and clinical evidence.*  
*BMC Med* 2012;.



# GUIDED BONE REGENERATION

It is estimated that up to 40% of osseointegrated implants require GBR for their placement <sup>1</sup>.

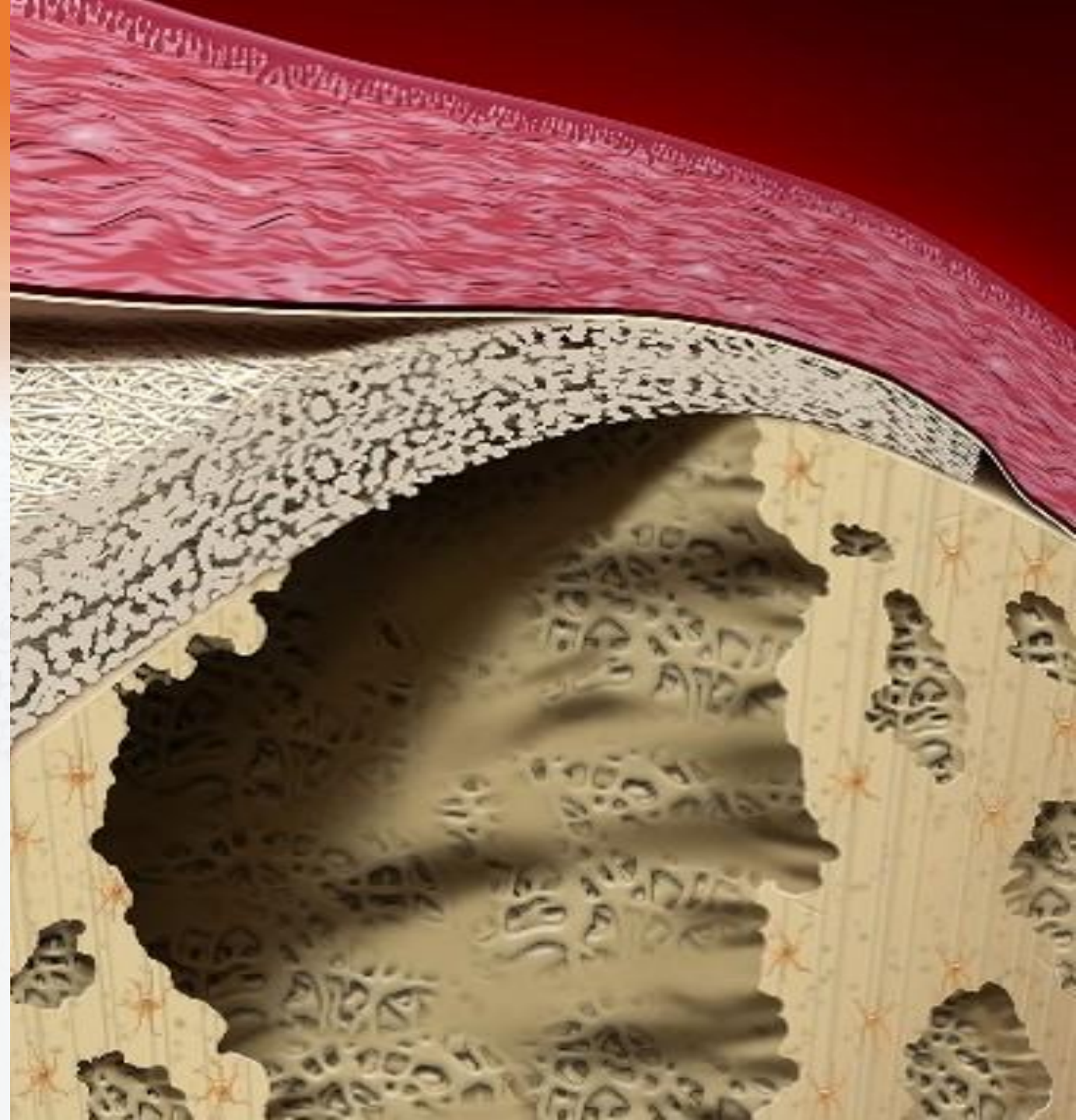
Several reports have indicated that the survival rates of implants placed in sites increased by GBR are similar to those reported for implants placed in uncontaminated sites <sup>2,3,4</sup>.

1 - Bornstein MM, Halbritter S, Harnisch H, Weber HP, Buser D.  
*A retrospective analysis of patients referred for implant placement to a specialty clinic: indications, surgical procedures, and early failures.*  
*Int J Oral Maxillofac Implants* 2008; 23: 1109–1116.

2 - Donos N, Mardas N, Chadha V.  
*Clinical outcomes of implants following lateral bone augmentation: systematic assessment of available options (barrier membranes, bone grafts, split osteotomy).*  
*J Clin Periodontol* 2008; 35: 173–202.

3 - Clementini M, Morlupi A, Canullo L, Agrestini C, Barlattani A.  
*Success rate of dental implants inserted in horizontal and vertical guided bone regenerated areas: a systematic review.*  
*Int J Oral Maxillofac Surg* 2012; 41: 847–852.

4 - Jensen SS, Terheyden H.  
*Bone augmentation procedures in localized defects in the alveolar ridge: clinical results with different bone grafts and bone-substitute materials.*  
*Int J Oral Maxillofac Implants* 2009; 24(Suppl): 218–236.



# THE BIOMATERIALS FOR GBR BY TISS'YOU



BIO-CREA  
bone

Complete line of  
***synthetic bone substitutes***  
&  
***collagen membranes.***



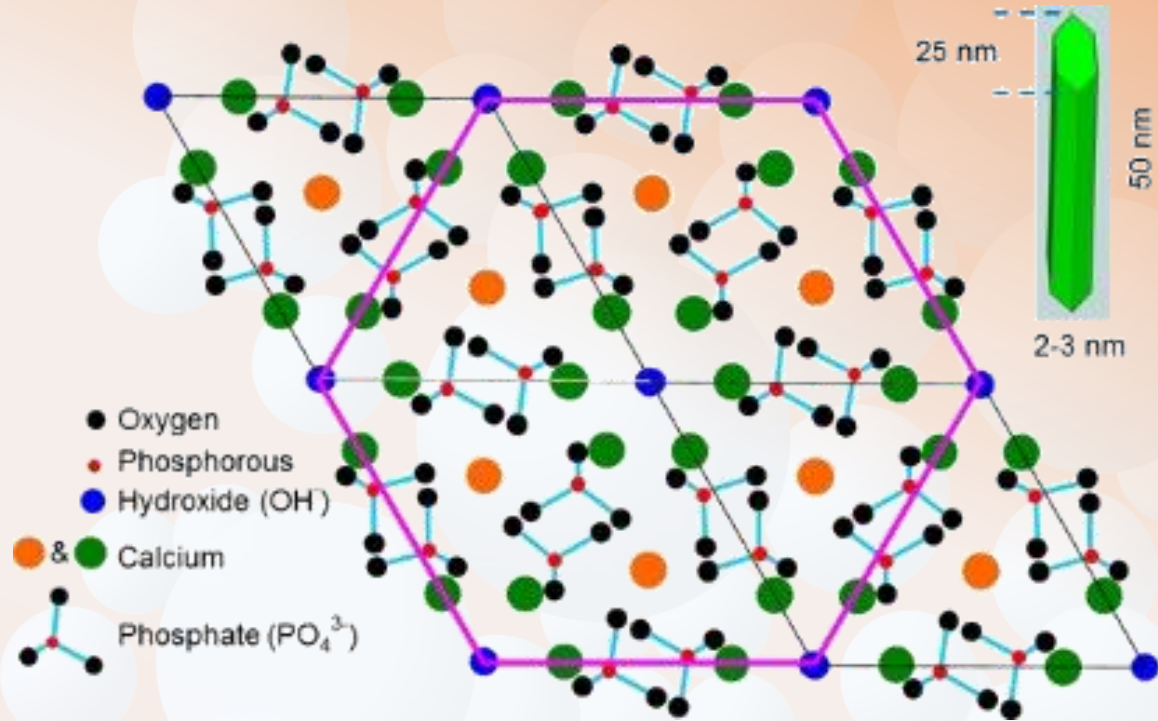
BIO-CREA  
membrane





BIO-CREA  
bone

Nano-structured bio-mimetic hydroxyapatite

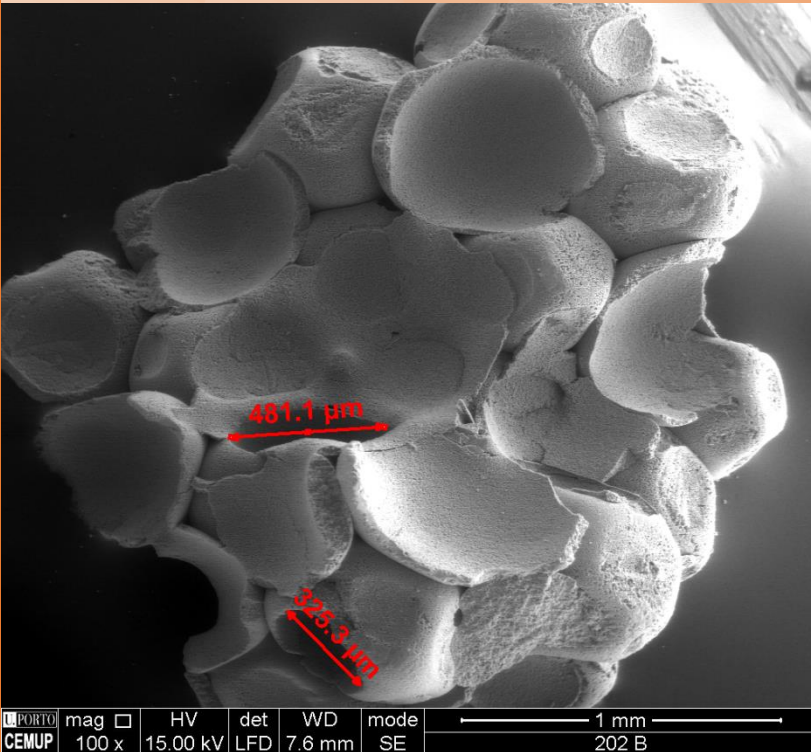


The mineralized component, which in adults makes up 60-70% of the entire bone, is mainly composed of calcium phosphate (86%) in the form of hydroxyapatite (HA) crystals.

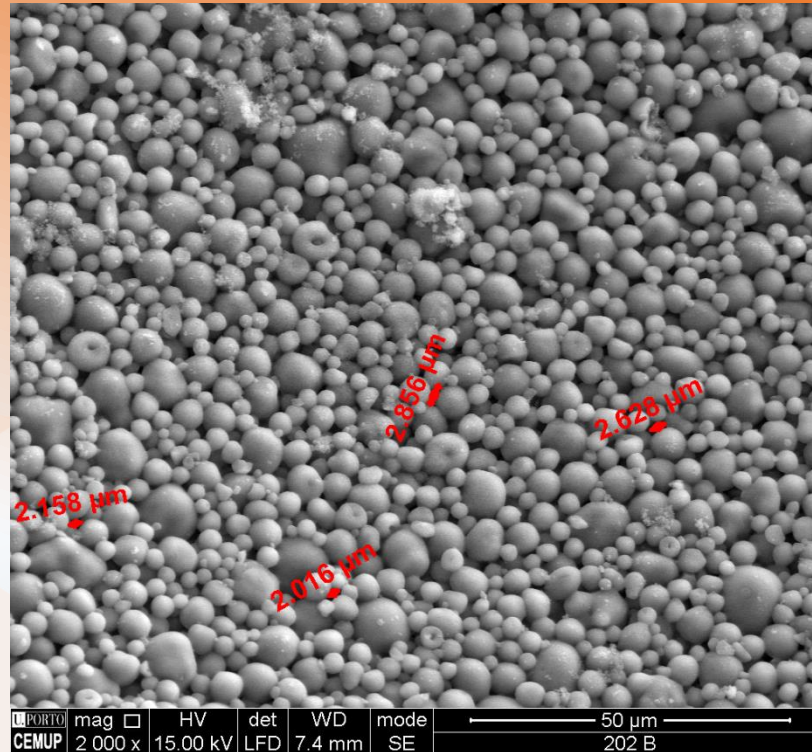
The apatite crystals are all extremely small in size and can therefore be considered nano-structured materials.

*BIO-CREA is the new line of synthetic bone substitutes based on highly pure nano-structured and bio-mimetic HA.*

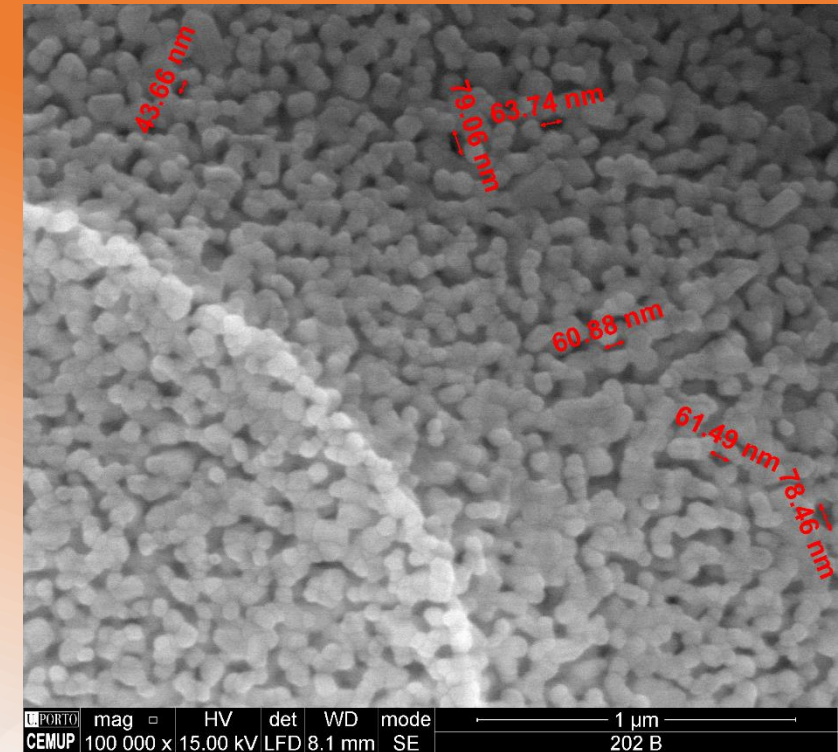
*bio-mimetic HA: similarity in size, crystal structure and chemical composition*



Macro-porosity 200-500  $\mu\text{m}$

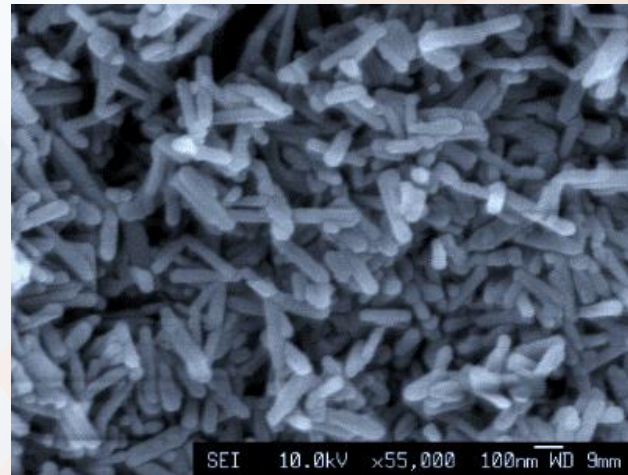
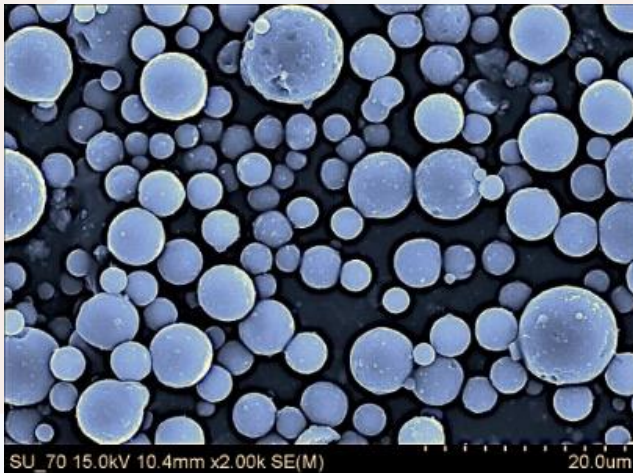


Micro-porosity 2-3  $\mu\text{m}$



Nano-porosity 40-80 nm

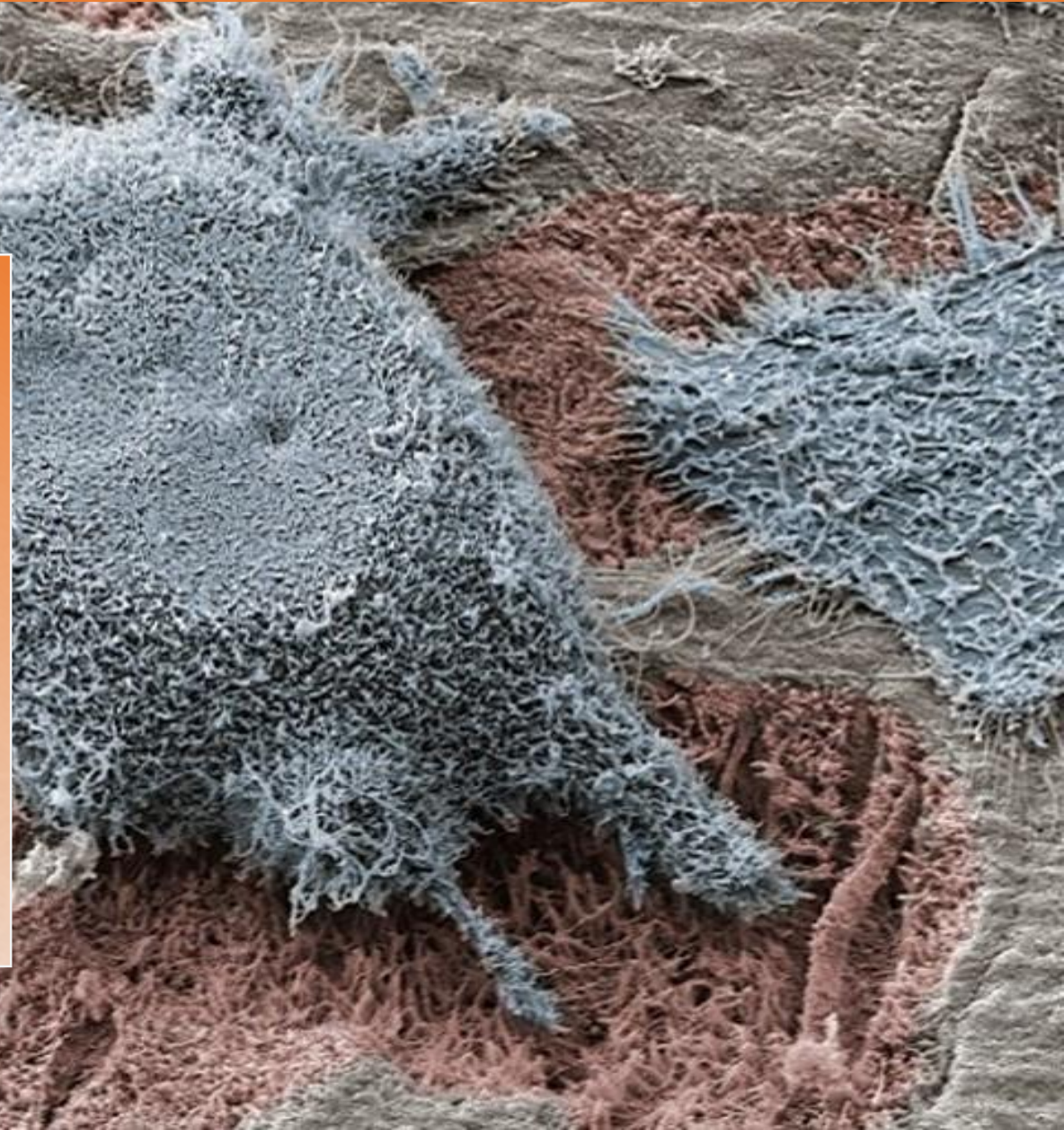
Chemical formula:  $\text{Ca}_{10}(\text{PO}_4)_6 (\text{OH})_2$



- *Total biocompatibility;*
- *no toxicity or inflammation;*
- *nano-crystals of HA <50 nm*
- *high surface / volume ratio;*
- *high surface activity;*
- *it chemically binds to the bone and stimulates its growth through a direct action on osteoblasts.*

Ca / P ratio of 1.67 identical to natural HA

- Promotes rapid bone regeneration and early vascularization thanks to its **osteoconductive** and **osteostimulating** properties;
- encourages protein adsorption and osteoblast adhesion;
- improves the functions of osteoblasts;
- completely degradable by osteoclasts action;
- replaced by newly formed bone during the healing process.





*Implantation in a rabbit tibial bone defect at 12 weeks*

*Marked bone regeneration with overgrowth into the subcutis, with very small multifocal lacunae (arrowheads).*

No residue of the grafted material due to the complete remodeling by osteoclastic activity.



*Negative control* -Same animal as above; the other tibial defect was covered by narrow bands of new bone separated by large lacunae (arrowheads).

Subchronic toxicity and intraosseous implant of Tiss'yous HA Injectable Paste in rabbit.  
Biochem Study code G-8 - Final report

DENSE GRANULES

POROUS CHIPS

INJECTABLE PASTE

MOLDABLE CRUNCH

Regular spherical granules consisting of micrometric aggregates of HA nano-particles.  
Their high density makes them degradable in longer times than porous chips (cortical bone).  
The regular shape allows the formation of homogeneous inter-granular pores.



500-1000  $\mu\text{m}$ , from 0,5 to 4 cc in single or multiple packaging of 6 vials:

BCB-D0501	BIO-CREA dense granules (0,5-1 mm) 0,5 cc - 1 pc
BCB-D0506	BIO-CREA dense granules (0,5-1 mm) 0,5 cc - 6 pcs
BCB-D1001	BIO-CREA dense granules (0,5-1 mm) 1 cc - 1 pc
BCB-D1006	BIO-CREA dense granules (0,5-1 mm) 1 cc - 6 pcs
BCB-D2001	BIO-CREA dense granules (0,5-1 mm) 2 cc - 1 pc
BCB-D2006	BIO-CREA dense granules (0,5-1 mm) 2 cc - 6 pcs
BCB-D4001	BIO-CREA dense granules (0,5-1 mm) 4 cc - 1 pc
BCB-D4006	BIO-CREA dense granules (0,5-1 mm) 4cc - 6 pcs

Regular spherical granules consisting of micrometric aggregates of HA nano-particles. Their high density makes them degradable in longer times than porous chips (cortical bone). The regular shape allows the formation of homogeneous inter-granular pores.



1-2 mm 2cc in single packaging:

BCB-D20201 BIO-CREA dense granules (1 -2 mm) 2 cc - 1 pc

Porous chips of irregular shape consisting of micrometric aggregates of nano-HA particles. Similar to cancellous bone chips, they can be easily mixed with biological fluids or autologous grafts.



500-1000  $\mu\text{m}$ , from 0,5 to 1 cc in single or multiple packaging of 6 vials:

BCB-P0501	BIO-CRE porous chips (0,5-1 mm) 0,5cc - 1 pc
BCB-P0506	BIO-CREA porous chips (0,5-1 mm) 0,5cc - 6 pcs
BCB-P1001	BIO-CREA porous chips (0,5-1 mm) 1cc - 1 pc
BCB-P1006	BIO-CREA porous chips (0,5-1 mm) 1cc - 6 pcs

Porous chips of irregular shape consisting of micrometric aggregates of nano-HA particles. Similar to cancellous bone chips, they can be easily mixed with biological fluids or autologous grafts.



1-2 mm size, available in 1 and 2 cc in single or multiple packaging of 6 vials:

BCB-P20101	BIO-CREA porous chips (1-2 mm) 1cc - 1 pc
BCB-P20106	BIO-CREA porous chips (1-2 mm) 1cc - 6 pcs
BCB-P20201	BIO-CREA porous chips (1-2 mm) 2cc - 1 pc
BCB-P20206	BIO-CREA porous chips (1-2 mm) 2cc - 6 pcs

The porous chips (500-1000  $\mu\text{m}$ ) are also available in special curved syringes with a filter on the head that allows them to be rehydrated or mixed with autologous biological fluids, directly inside the syringe.

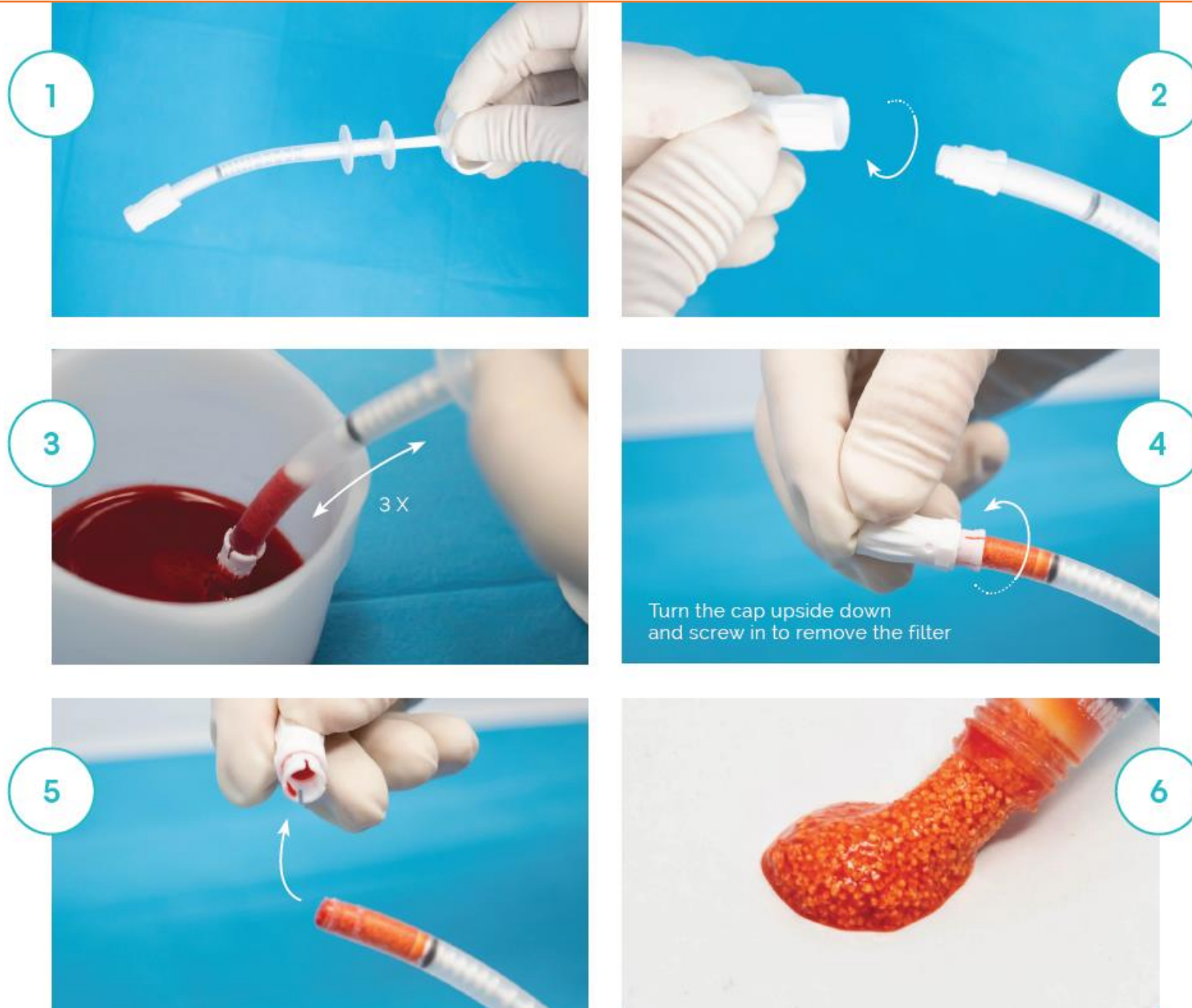


They represent a truly unique solution, which makes mixing the granules and their subsequent grafting extremely manageable.

Available in packs of 1 or 3 syringes in 0.5 cc:

- |            |  |
|------------|--|
| BCB-P050S1 | BIO-CREA porous chips (0,5-1 mm) 0,5cc in filter-cap syringe - 1 syr.  |
| BCB-P050S3 | BIO-CREA porous chips (0,5-1 mm) 0,5cc in filter-cap syringe - 3 syrs. |

# FILTER CAP - INSTRUCTIONS



Injectable paste composed of a high density mixture of nano-crystals and micro-powder of nano-structured HA, in a buffered aqueous solution at physiological pH; available in a wide range of formats (from 0.25 cc to 1 cc). To facilitate in situ application, a thin tip is available inside the package.



Good consistency and adhesiveness. Very high cohesion strength between nano-crystals and powder, with good resistance to washout. Due to the high similarity between nano-HA and the bone mineral component, SpherHA Paste chemically binds to the host tissue.

<b>BCB-PA0251</b>	BIO-CREA injectable paste 0,25 cc - 1 syr.
<b>BCB-PA0253</b>	BIO-CREA injectable paste 0,25 cc - 3 syrs.
<b>BCB-PA0501</b>	BIO-CREA injectable paste 0,5cc - 1 syr. (with tip)
<b>BCB-PA0503</b>	BIO-CREA injectable paste 0,5cc - 3 syrs. (with tip)
<b>BCB-PA1001</b>	BIO-CREA injectable paste 1cc - 1 syr. (with tip)
<b>BCB-PA1003</b>	BIO-CREA injectable paste 1cc - 3 syrs. (with tip)

The Crunch format, thanks to the addition of micro-granules with specific granulometry, has a higher concentration of nano-structured HA than the injectable paste, making it extremely malleable. The "open-mouth" syringes allow the extrusion of the product in the form of a conformable plastic cylinder.



The most concentrated HA formulation. The cohesive strength is lower than the paste and therefore it is recommended to dry the implantation site with gauze before its placement.

BCB-CR0501	BIO-CREA moldable crunch 0,5cc - 1 syr.
BCB-CR0503	BIO-CREA moldable crunch 0,5cc - 3 syrs.
BCB-CR1001	BIO-CREA moldable crunch 1cc - 1 syr.
BCB-CR1003	BIO-CREA moldable crunch 1cc - 3 syrs.

## GRANULES AND CHIPS

Filling of small and medium bone defects, peri-implant and post-extractive defects, small and large maxillary sinus lifts.

Porous chips in filter cap syringe, Can be useful in case of mixing with autologous biological fluids and in sinus lift with vestibular access.

## INJECTABLE PASTE

Filling of periodontal and peri-implant defects, trans-crestal sinus lift.

## MOLDABLE CRUNCH

Filling of periodontal, peri-implant and post-extractive bone defects. It is also indicated for sinus lift with vestibular access.



BIO-CREA  
membrane

Collagen Active Protection



# THE ROLE OF MEMBRANE IN GTR: FROM BARRIER TO BIACTIVE COMPARTMENT

The use of a membrane to avoid interference of non-osteogenic tissues with bone regeneration is a key principle of the GTR .

Novel experimental findings also suggest an active role of the membrane compartment per se in promoting the regenerative processes in the underlying defect during GBR, instead of being purely a passive barrier.<sup>1-2</sup>.

**Collagen membranes stimulate bone formation at the graft site<sup>3</sup>.**

1 - Turri A, Elgali I, Vazirisani F, Johansson A, Emanuelsson L, Dahlin C, Thomsen P, Omar O.  
*GBR is promoted by the molecular events in the membrane compartment.*  
*Biomaterials* 2016; 84: 167–183.

2 - Ibrahim Elgali, Omar Omar, Christer Dahlin, Peter Thomsen.  
*Guided bone regeneration: materials and biological mechanisms revisited*  
*Eos* 2017; <https://doi.org/10.1111/eos.12364>.

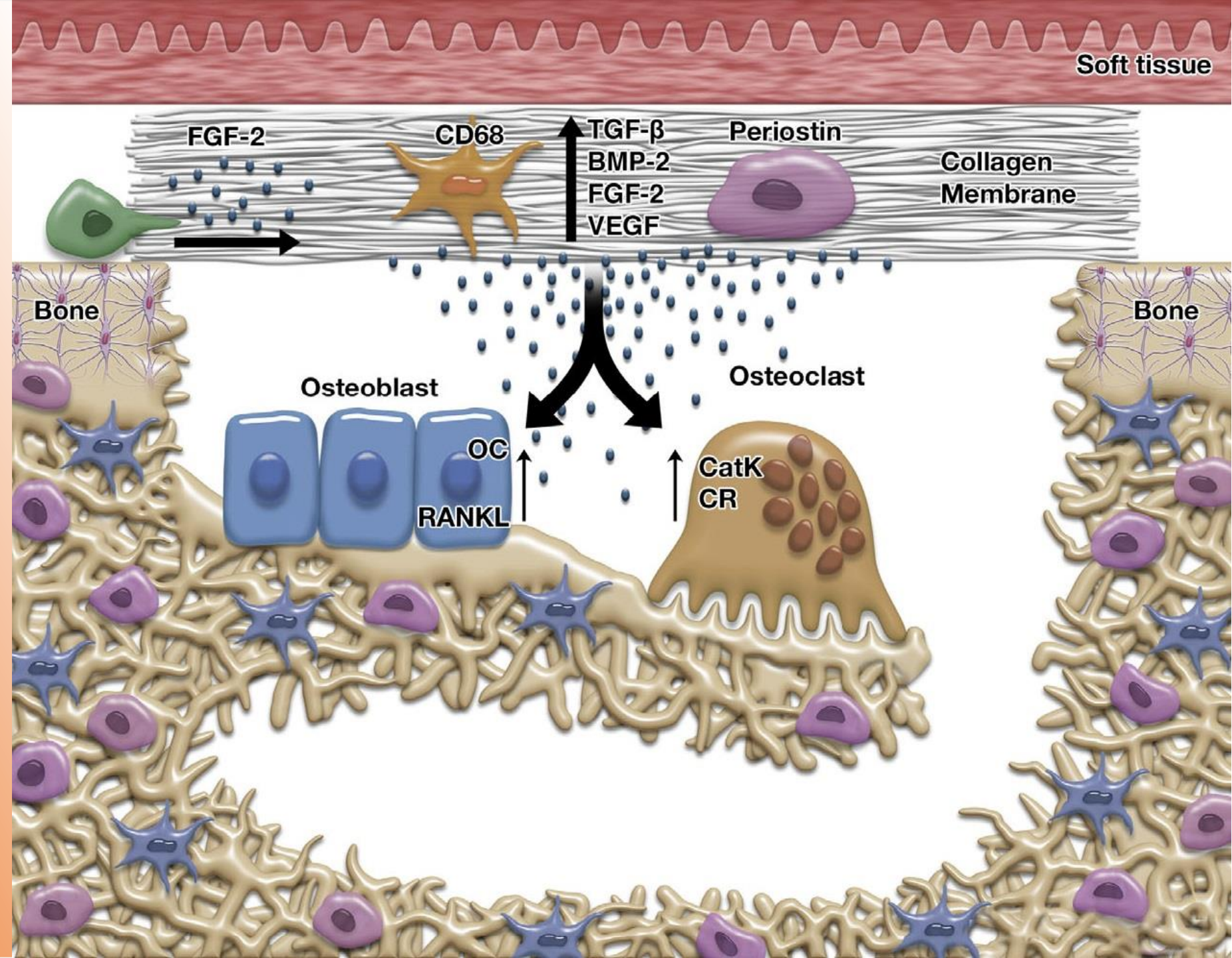
3 - Taguchi Y, Amizuka N, Nakadate M, Ohnishi H, Fujii N, Oda K, Nomura S, Maeda T.  
*A histological evaluation for guided bone regeneration induced by a collagenous membrane.*  
*Biomaterials* 2005; 26:

# ACTIVITY

"...The cellular and molecular cascades include: migration of different cells (e.g. monocytes/macrophages and periostin-positive osteoprogenitors) from the surrounding tissue into the membrane. The cells which have migrated into the membrane express and secrete factors pivotal for bone formation and bone remodeling. This promotes the development of mature remodeled bone in the underlying defect, by stimulating the activity of osteoblasts and osteoclasts,. The presence of the membrane and its bioactive properties promote a higher degree of bone regeneration and restitution of the defect in comparison with the defect without membrane."

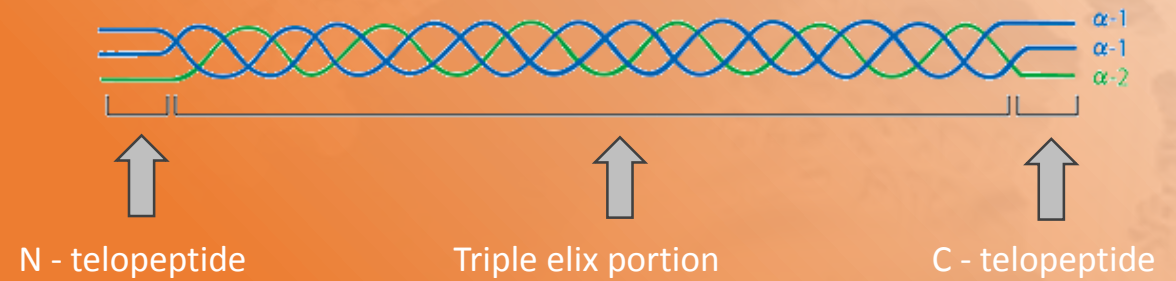
## LEGENDA

BMP-2, bone morphogenetic protein 2;  
CatK, cathepsin K;  
CD68, cluster of differentiation 68;  
CR, calcitonin receptor;  
FGF-2, fibroblast growth factor 2;  
OC, osteocalcin;  
RANKL, receptor activator of nuclear factor kappa-B ligand;  
TGF- $\beta$ , transforming growth factor- $\beta$ ;  
VEGF, vascular endothelial growth factor.




# HIGHLY PURIFIED ATELOCOLLAGEN

*BIO-CREA is the new line of resorbable membranes for the protection of the implantation site from soft tissue, based on highly purified type I atelocollagen of equine origin.*



Atelocollagen

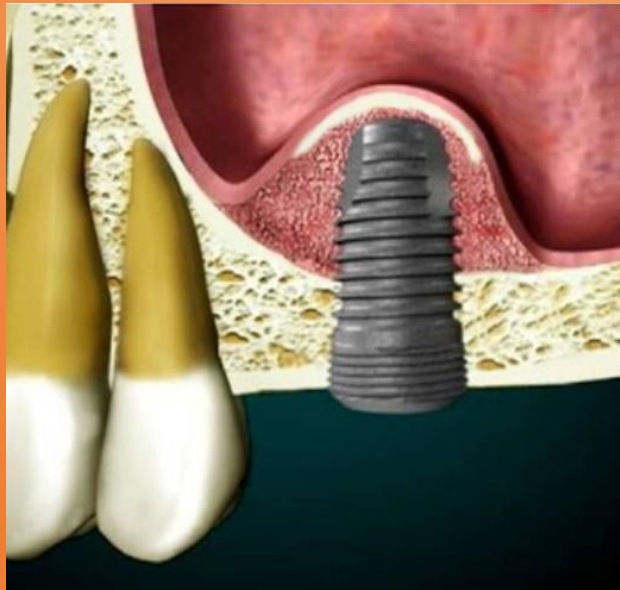
# MAIN FEATURES

- 
- *Equine type I atelocollagen*
  - *Totally safe and biocompatible*
  - *Easy to apply and to adapt to the site*
  - *No need for fixation*
  - *Completely absorbable*
  - *4 to 6 weeks of protection*

# INDICATIONS

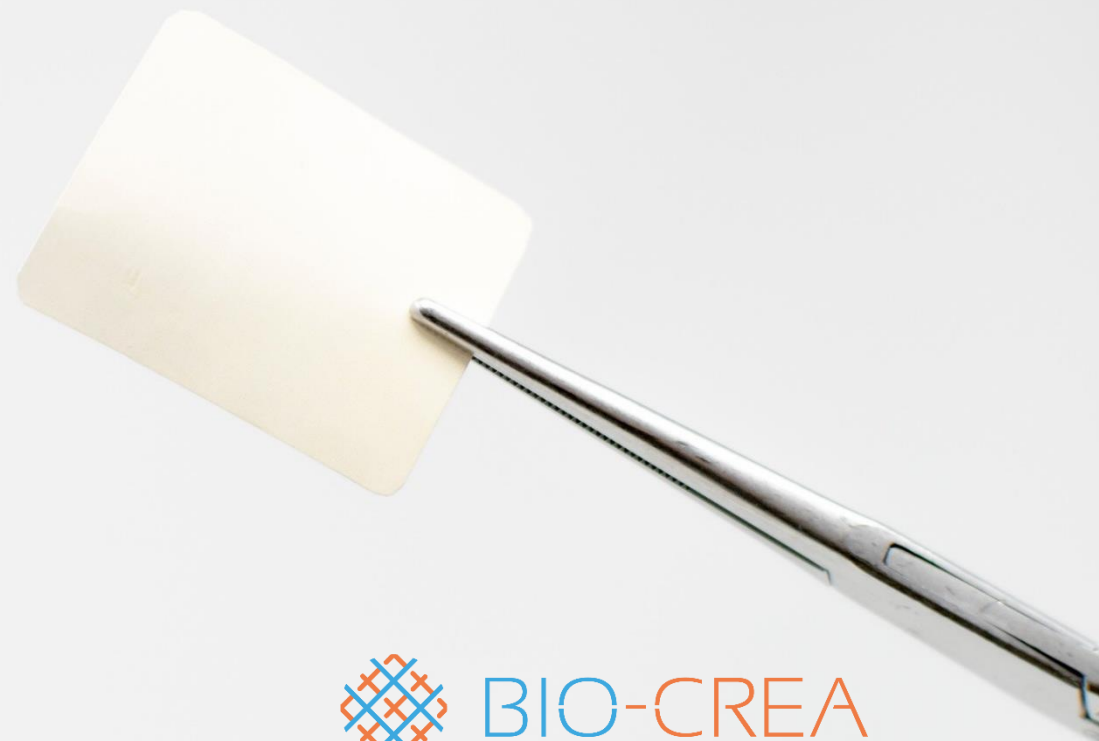


- *Protection of peri-implant bone defects.*
- *Closure of small lacerations of Schneider membrane.*
- *Restoration of small bone dehiscences.*
- *Socket protection.*
- *Coverage of the bone access in sinus lift procedures.*

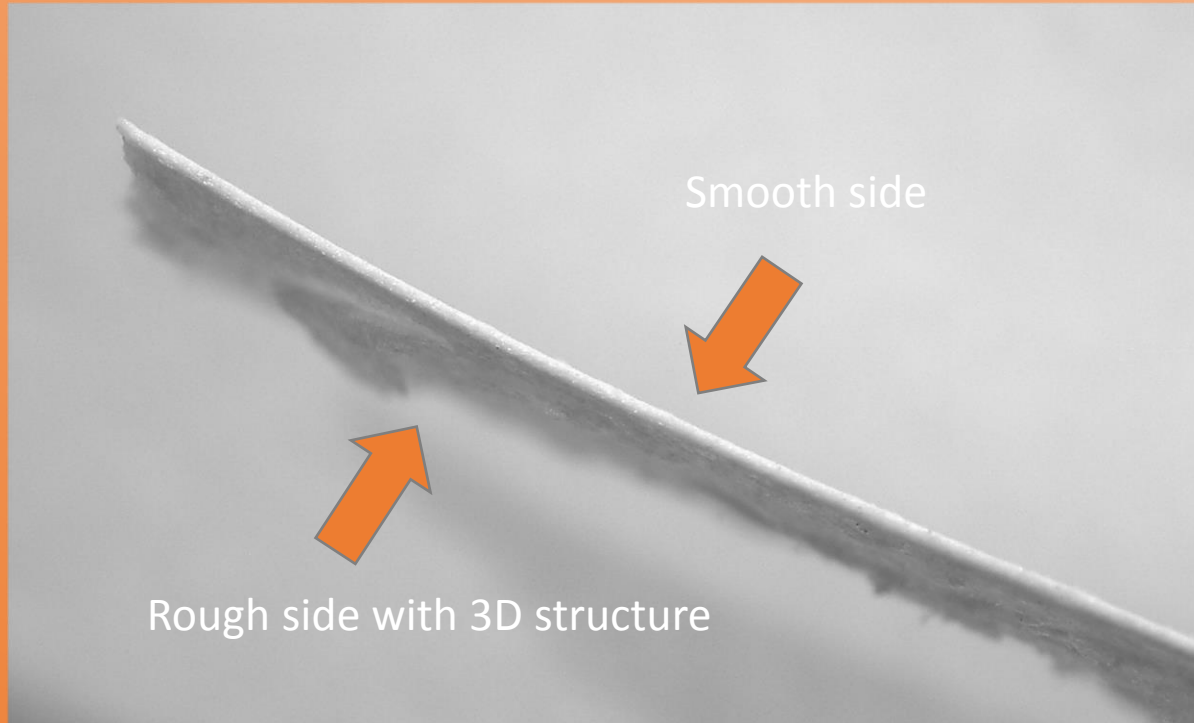


BCM-15201	15 x 20 x 0,2 mm	1 pc
BCM-15206	15 x 20 x 0,2 mm	6 pc
BCM-152010	15 x 20 x 0,2 mm	10 pc
BCM-20201	20 x 20 x 0,2 mm	1 pc
BCM-20206	20 x 20 x 0,2 mm	6 pc
BCM-202010	20 x 20 x 0,2 mm	10 pc
BCM-25251	25 x 25 x 0,2 mm	1 pc
BCM-25256	25 x 25 x 0,2 mm	6 pc
BCM-252510	25 x 25 x 0,2 mm	10 pc
BCM-20301	20 x 30 x 0,2 mm	1 pc
BCM-20306	20 x 30 x 0,2 mm	6 pc
BCM-203010	20 x 30 x 0,2 mm	10 pc
BCM-30401	30 x 40 x 0,2 mm	1 pc

## PRODUCT RANGE



## RS (ROUGH SIDE) MEMBRANE 1/2



Unlike the other membranes of this line, BIO-CREA RS has a rough side characterized by less compact fibers and a larger contact surface available.

Once positioned with the rough side towards the recipient bone and the graft, the membrane guarantees greater stability and an even more favorable environment for cell migration and adhesion.

BCM-2020RS	20 x 20 x 0,2 mm	1 pc
BCM-2525RS	25 x 25 x 0,2 mm	1 pc
BCM-2030RS	20 x 30 x 0,2 mm	1 pc
BCM-3040RS	30 x 40 x 0,2 mm	1 pc



# INSTRUCTIONS FOR USE

*Prepare the implant site by removing any residual fibrous tissue.*

*If necessary, make a few small perforations to encourage bleeding of the recipient bone bed.*

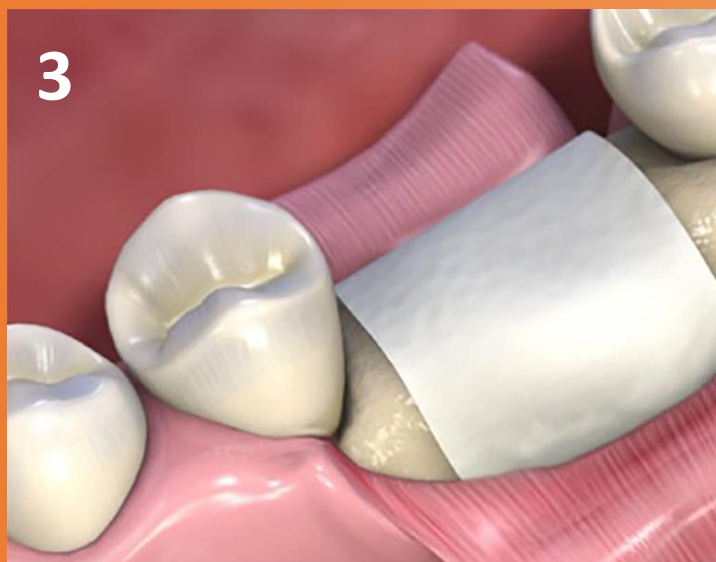
*Fill the defect with granular bone substitutes, taking care to fill the spaces properly avoiding excessive granules compression.*

*BIO-CREA can be cut as needed, before rehydration.*

*Wet it lightly with saline or place it directly without rehydration.*

*The collagen fibers of its structure naturally adhere to the bone surface, ensuring good protection of the implant site.*

*Perform a complete closure of the flaps without creating tension.*



- Nano-structured, bio-mimetic HA
- Total bio-compatibility
- High surface / volume ratio
- Promotes rapid bone regeneration and early vascularization thanks to its **osteoconductive** and **osteostimulating** properties
- Promotes the adsorption of proteins and the adhesion of osteoblasts
- It is completely degraded via osteoclasts and remodeled into patient's own new vital bone
- Available in granules, chips, pasta and crunches to make easier different uses
- Porous chips also available in Filter-Cap syringes
- Convenient multiple pack

- Equine type I highly pure atelocollagen
- Total bio-compatibility and non-reactive
- Protection and **active osteostimulation**
- Easy to apply and to adapt to the site
- Naturally adhesive, it does not require fixation
- Completely absorbable
- 4 to 6 weeks of protection
- RS version for greater stability and better three-dimensional environment for cell adhesion and migration
- Available in many sizes and convenient multiple pack



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