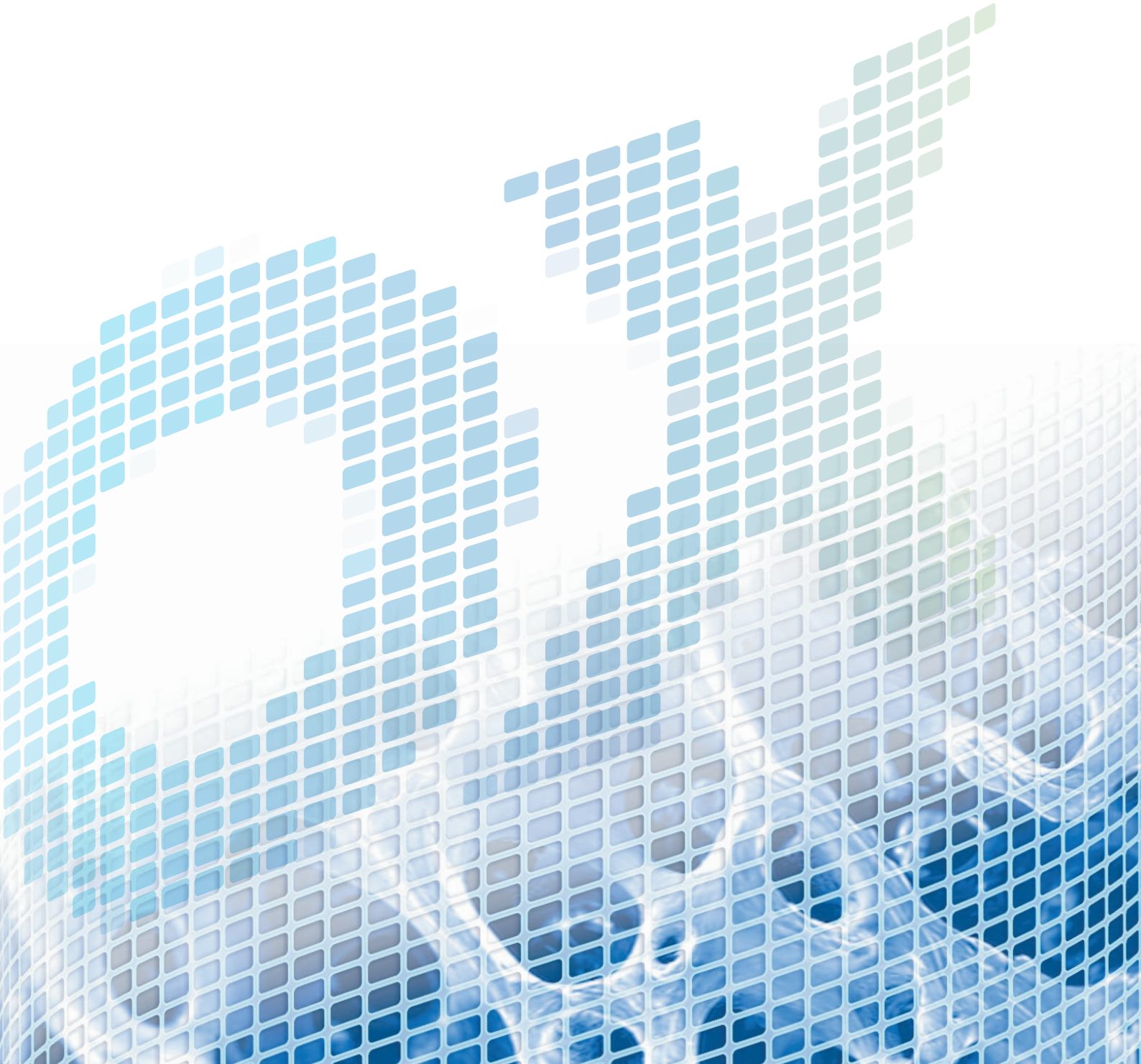
OSTEOXENON® by BIOACTIVA®

*Remodeling the Future*

# The new GBR standard



# Ethics. Safety. Osteoconductivity.

A 15 years experience for the benefit of the Oral Surgeon

## *What is it?*

**OSTEOXENON®** is an advanced line of bone substitutes for regenerating bone in dental surgeries.
**OSTEOXENON®** comes from a 15 years experience in Orthopedics, where this same material is grafted for huge bone reconstructions. This same biotechnological know-how and the same manufacturing process are now being applied to create bone substitutes for Oral and Maxillo-facial Surgery.
**OSTEOXENON®** is conceived and manufactured totally in Italy.

## *Why Equine?*

**OSTEOXENON®** is an heterologous material. Its origin is equine.
This choice is not a chance.

## *Ethics*

**OSTEOXENON® is accepted by the patient:** In a multi-ethnical population comprising people belonging to different religions, patients would not accept other bone grafts (porcine or bovine).

## *Safety*

**OSTEOXENON® is safe:** the European Directive 2003/32/CE[1] defines equine-derived materials as safer, since no diseases, transmittable from horses to men, are currently known.

## *Osteoconductivity*

**OSTEOXENON® is osteoconductive:** Mammals share a very similar trabecular structure. Equine bones can be cut in order to achieve sections showing the same trabecular structure of human bone.

*Human Bone*

The two bone sections are identical.
*(Source: Bioteck Research Lab)*

*OSTEOXENON®*

# Enzymatic deantigenation: Biotechnology serving the Oral Surgeon

To deantigenate means eliminating all those elements that the immune system will recognize as antigens, inducing an unwanted reaction.

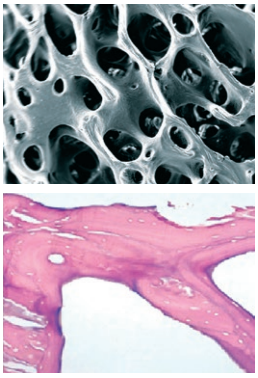
## *Manufacturing process*

**OSTEOXENON®** is achieved through an enzymatic deantigenation process, devised by Bioteck – a leader Company in the field of Bone Substitutes manufacturing.

The **enzymatic process** is an extremely advanced method. It is based on the application of last-generation biotechnological processes. Mixtures of lytic enzymes clean up animal bone from any antigenic component, making it totally biocompatible.

*Scanning Electron Microscopy*

*Hematoxylin-eosin staining*



**OSTEOXENON®**
The enzymatic process eliminates all cells.
*(SEM Service, Biology Dept, Padova University, Italy and Prof. N. Pennelli Histological Lab, Padova, Italy)*

The enzymatic process has two main features: the temperature applied is 37°C and the process is selective. These features give **OSTEOXENON®** **unique-in-the-world-properties, as far as both biological response and clinical outcome are concerned.**

| | *Total remodeling* | *Collagen effects* |
|---|---|---|
| *Enzymatic deantigenation* | Enzymes work in a water solution at 37°C (physiologic conditions). | By adapting the composition of the enzymatic mixture, the process can be made **selective** (some molecular families can be preserved). |
| *OSTEOXENON®* | The mineral component undergoes no modification, either chemical or physical. | The collagen component (Type I Bone Collagen) is totally preserved. |
| *Biological benefit* | The material is not only biocompatible. The mineral component is recognized by osteoclasts as endogenous. After 6-12 months **all the grafted material is remodeled and replaced by the bone of the patient.** | Type I bone collagen **stimulates** a great number of cellular and sub-cellular processes which are at the basis of bone regeneration. |
| *Clinical benefit* | A **real bone regeneration** is achieved. Not only grafting a scaffold, but a true **restitutio ad integrum** of the lost tissue. If osseointegrated implants are going to be placed, they will be inserted into the patient's bone, without the presence of any exogenous material. | The probability of **success** of regenerative surgery will be greater, since the biological conditions are optimal. |

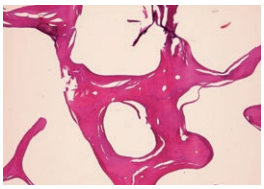
# 37°C: is it really important?

Nature says it is…

## *Preserving bone structure*

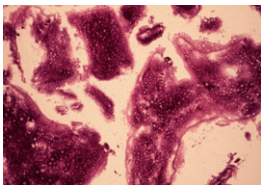
Some manufacturers apply a **thermal deantigenation process,** heating the material at a very high temperature (greater than 600°C!). The organic component sublimates, and can be easily withdrawn. Unfortunately such method causes some chemical and physical modifications to the mineral bone component, altering both its morphology and mechanical properties. Biological properties are compromised: thermal processed bone biomaterials are not only **fragile**, but also **very slowly resorbable**[3], not permitting to achieve a real bone regeneration.

*OSTEOXENON®*



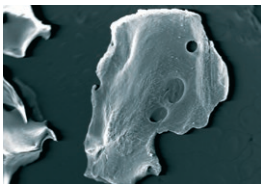
The material is identical to human bone (all cells are eliminated by the enzymatic deantigenation).
*Hematoxylin-eosin staining (20x). Dr. Tshering Dorji, Milano, Italy.*

*Thermally deproteinized bovine bone*



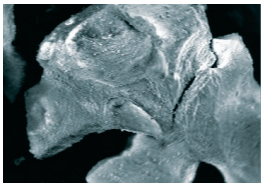
The surface of granules is deeply altered. Their appearance is totally unnatural.
*Hematoxylin-eosin staining (20x).Dr. Tshering Dorji, Milano, Italy.*

*OSTEOXENON®*



The surface of granules is homogeneous, showing no fracture lines.
*SEM Service , Biology Dept, Padova University, Italy .*

*Thermally deproteinized bovine bone*



The surface appears somewhat "dusty". The granule is clearly fragile.
*SEM Service , Biology Dept, Padova University, Italy.*

# Type I bone collagen. Which effects?

**OSTEOXENON®** contains, inside its structure, type I bone collagen unaltered

## *The importance of collagen*

Grafting bone collagen into the defect creates a precise biological condition: osteoblasts themselves, in fact, produce a collagen fiber which is then mineralized by Calcium salts[5].

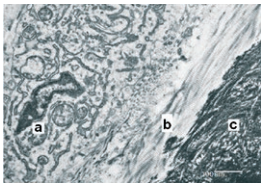
The same tridimensional structure of the collagen fiber allows the crystal formation through a physical process called **epitaxy**[5].

Beyond this physical effect, collagen exerts also many important biological actions[6-15]: type I bone collagen, in fact:

## *The benefits of collagen*

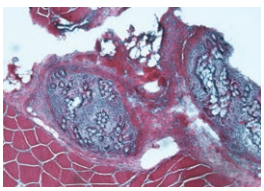
- interacts with the beta 1 subunit of the integrins of the cellular surface of the osteoblasts to foster adhesion of the cells to the grafted material
- acts as a coactivator necessary for the action of the morphogenetic proteins (BMPs) to foster the stimulating action of the endogenous growth factors
- binds the soluble growth factors, turning them into insoluble factors: it thus protects them from proteolysis and increases their half-life, lengthening the duration of regenerative stimulation
- controls access of the extracellular factors to the bone crystal being formed, physiologically modulating bone mineralization
- modulates transduction of the proliferation and differentiation signal in the osteoblastic cells, controlling the remodeling process
- interacts with the mesenchymal cells coming from the bone marrow, inducing their adhesion, proliferation and differentiation in osteoblasts
- promotes bone regeneration when grafted in bone defects, wielding a direct pro-regenerative action
- it can even stimulate the expression of the coding genes for receptor II of the BMPs, making the cells more sensitive to the regenerating signals

## *Osteoblasts*



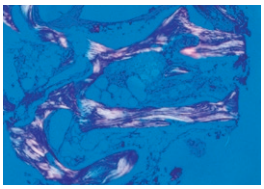

Osteoblasts produce a great amount of collagen matrix that becomes a **substrate** for the deposition of Calcium salts.
A. osteoblast portion
B. collagen fibers (still not mineralized)
C. mineralized collagen fibers

## *OX® grafts*



**Epitaxy of the OX® series.**
When grafted in rat's muscles **OX®** bone substitutes induce the formation of Calcium salts crystals. Probably this is catalyzed by the same presence of native collagen in the grafts.
*Dept. of Biomedical Experimental Sciences, Padova University, Italy.*

## *Bone collagen*



Bone collagen presence in the **OX®** bone grafts **can be shown** also through polarized light: collagen fibers, having a regular structure, show a typical refringence that makes them appear brighter.
*Prof. N. Pennelli Histological Lab, Padova, Italy.*

# From biological benefits to clinical success

## OSTEOXENON® gives clinical success a biological rationale

**OSTEOXENON®** bone grafts provide the oral surgeon with the real answers a bone substitute should give:

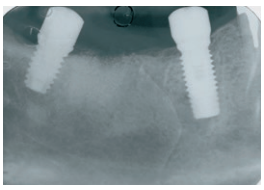
> total replacement with the own patient's bone (total remodeling)
> total volume preservation
> regenerative stimulation

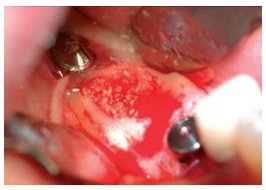
### *Total replacement*

**OSTEOXENON®** is remodeled and resorbed through the action of osteoclasts.

This occurs following a totally physiologic kinetic: as the patient's bone remodels in 6-12 months, the same happens to **OSTEOXENON®**: after this period of time it is totally replaced by the bone of the patient.

This is possible since **OX®**, unlike other materials, is recognized as an optimal substrate by osteoclasts, which remodel it in a physiological way[16]. Only in this case, in fact, the process can end with the complete substitution of the graft.





Adjacent post-extractive sockets. **OX®** (position 46) and deproteinized bovine bone (position 47). X-rays and 6-months second surgery. Bovine bone did not undergo remodeling, and discrete granules can be still observed. **OX®** instead underwent total remodeling, being replaced by the bone of the patient. *(Dr. M. Ludovichetti, Padova, Italy)*

### *Volume preservation*

If the material remodels physiologically, no volume loss can be observed. If resorption is too fast (for example, as it happens with Calcium Sulphate), or too slow (like it happens with hydroxyapatite), the endogenous bone volume is never equal to the volume grafted.
**OSTEOXENON®**, instead, undergoing osteoclastic remodeling, allows to preserve the volume being grafted[17].

### *Regenerative stimulation*

**OSTEOXENON®**, since it contains native type I bone collagen, creates the best condition for bone regeneration to occur.

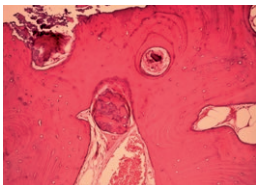
But it provides also the oral surgeon with the possibility of stimulating the regenerative process with osteopromoting DBMs (Demineralized Bone Matrixes) that prompt the osteogenic process.

In vitro studies showed, in fact, that their action is based on the **stimulation** of blood vessels endothelial cells to migrate into the graft, and of bone marrow cells to express pro-regenerative growth factors.

There is a first **evidence** of their capability of accelerating bone regeneration[18].

Surely this allows to increase the probability of success of bone regeneration surgeries.

### *Results*



Bone regeneration, osteopromoting DBMs added. Results after 6 months. The quality of the regenerated tissue is easily appreciable from the hematoxylin-eosin staining.
*(Prof. Danilo Alessio Di Stefano, Milan, Italy)*

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# The products

Once grafted, **OX®** bone substitutes behave according to the physiologic kinetic of patient's bone remodeling, and are completely replaced by newly-formed bone in a natural time.

## OX® Granules


**> OX37** Cancellous granules
**1 bottle - 0.25 g ≈ 0.5 cc**
granules 0.5/1 mm

**> OX30** Cancellous granules
**1 bottle - 0.5 g ≈ 1 cc**
granules 0.5/1 mm

**> OX33** Cancellous granules
**1 bottle - 1 g ≈ 2 cc**
granules 2/3 mm

**> OX34** Cancellous granules
**1 bottle - 1 g ≈ 2 cc**
granules 2/4 mm

**> OX38** Cancellous granules
**1 bottle - 2 g ≈ 4 cc**
granules 0.5/1 mm

**> OX39** Cancellous granules
**1 bottle - 2 g ≈ 4 cc**
granules 2/3 mm

**> OX40** Cortical granules
**1 bottle - 0.5 g ≈ 1 cc**
granules 0.5/1 mm

**> OX35** Cortical-cancellous Mix
**1 bottle - 0.25 g ≈ 0.5 cc**
granules 0.5/1 mm

**> OX31** Cortical-cancellous Mix
**1 bottle - 0.5 g ≈ 1 cc**
granules 0.5/1 mm

**> OX32** Cortical-cancellous Mix
**1 bottle - 1 g ≈ 2 cc**
granules 0.5/1 mm

**> OX41** Cortical-cancellous Mix
**1 bottle - 2 g ≈ 4 cc**
granules 0.5/1 mm

**> OMC-030** Calcitos
**6 bottles - 0.5 g ~ 1 cc**
granules 0.5/1 mm

## OX® Flex

**> OX01** Cancellous
**1 pc 25 x 25 x 3 mm**

**> OX02** Cortical
**1 pc 25 x 25 x 2-2.5 mm**

## OX® Mix gel

**> OX21**
**2 syringes, 0.25 ml each**

**> OX22**
**2 syringes, 0.50 ml each**

## OX® Collagen Gel

**> OX06**
**2 syringes, 0.25 ml each**

**> OX07**
**2 syringes, 0.50 ml each**

## OX® Cancellous Blocks

**> OX51**
**1 pc 10 x 10 x 10 mm**

**> OX52**
**1 pc 10 x 10 x 20 mm**

**> OX54**
**2 pcs 10 x 20 x 3 mm**

**> OX55**
**2 pcs 10 x 20 x 5 mm**

**> OX55R**
**1 pc 15 x 30 x 5 mm**

## OX® Membrane

**> BCG-XC30** Collagen
**1 membrane 30 x 25 x 0.2 mm**

**> HRT-001** Pericardium
**1 membrane 30 x 25 x 0.2 mm**

**> HRT-002** Pericardium
**1 membrane 50 x 30 x 0.2 mm**

**> HRT-003** Pericardium
**2 membranes 15 x 20 x 0.2 mm**

**> OX03** Cortical
**1 membrane 25 x 25 x 0.2 mm**

**> OX04** Cortical
**1 membrane 50 x 25 x 0.2 mm**

## OX® Angiostad DBM

**> OX11**
Osteopromoting gel
**2 syringes, 0.50 ml each**

## OX® Activagen DBM

**> OX14**
Osteopromoting granules
**1 bottle, 0.5 cc**

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