Orientations for clinical use of BMP

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What is the origin of BMPs and how extensive is the synonymy employed to identify them?

The morphogenetic proteins of the bone are responsible for signaling to induce bone formation. BMPs (bone morphogenetic proteins) represent a family with more than 20 reported proteins, which are part of the transforming growth ß factor family (TGF-ß), activating and inhibiting the differentiation and growth factors (GDF). They are involved in embryonic development and in the formation of the skeleton. Since the work of Urist[3] in 1965, demonstrating that the demineralized bone matrix could induce the formation of cartilage and bone in ectopic sites, many researchers have endeavored to clarify the activity of matrix components.

Minimal amounts of these proteins are present in the mature skeleton, participating in their maintenance and repair of bone fractures. Urist[3] demonstrated that, by placing portions of demineralized and lyophilized allogeneic bone matrix in the muscle of mice, there was bone formation, i.e., bone matrix had agents capable of inducing osteoblasts formation (Fig 1).

Urist and Strates,[5] in 1971, through extensive laboratory research observed and identified these agents, naming BMPs. Although the exact function and interrelation of each BMP are not yet completely understood, evidences indicate its role as part of a complex number of factors regulating cell differentiation, increasing the expression of chondroblasts and osteoblasts in injured bone sites. The possible evolutionary conservation of structural and functional BMPs genes suggests critical regulatory roles in the process of differentiation during development (Tab 1).

What does "recombinant BMP" mean from the point of view of nomenclature, origin, advantages and disadvantages?

As a result of a long process of purification of the bones, insignificant amounts of BMP were obtained. Later, the rhBMP-2 molecule (recombinant human bone morphogenetic protein) was sequenced and cloned by Wozney,[2] in 1988, and this technology now allows its production on a large scale to be used clinically and in the laboratory.

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Figure 1 - Allogenic demineralized and lyophilized bone matrix that has been isolated by Urist. The photograph is courtesy of Dr. Neil Blumenthal, who had the opportunity to work with Dr. Urist in the Department of Orthopaedics at the University of California (UCLA), Los Angeles. This was one of the matrices used in the article of Urist.[3]

Table 1 - Function and synonymy of BMP types.

BMP Types	Functions
BMP-2	Osteoinductive, apoptosis, differentiation of osteoblasts
BMP-3	Inhibits osteogenesis (Osteogenin)
BMP-4	Osteoinductive, lung development and ocular system
BMP-5	Chondrogenesis
BMP-6	Chondrogenesis, differentiation of osteoblasts
BMP-7	(OP-1) Osteoinductive, liver development
BMP-8	(OP-2) Osteoinductive
BMP-9	Hepatogenesis, neural system development
BMP-10	Heart development
BMP-11	Morphogenesis of neural system and mesodermal origin organs
BMP-12	Development of tendons and iliac bones
BMP-13	Development of tendons and ligaments
BMP-14	Chondrogenesis
BMP-15	Modifies the activity of FSH

When placed in a proper medium, rhBMP-2 induces bone formation. The start of the process does not necessarily proceed by introduction of bone forming cells. Rather, rhBMP-2 acts locally to concentrate in the site mesenchymal host cells and influence their differentiation into bone forming cells. It has mitogenic activity, but selectively. In order to have an effect which can be observed clinically, "super-physiological" doses are required, around 200,000 times the estimated physiological concentration of BMP-2 naturally found in bone. A variety of complications associated with surgery or the use of rhBMP-2 may occur alone or in combination. Some of them can be serious and affect its outcome. Additional surgery may also be needed to correct these complications.

Some possible complications include:

- Allergic reaction.
- Death.
- Development of respiratory problems.
- The formation of exuberant and / or ectopic bone.
- Edema.
- Erythematosus tissue.
- Fetal development complications.
- Hematoma.
- Incisional complications.
- Infection.
- Inflammation.
- Pain.
- Formation of scars.
- Damage to tissues or nerves.

The recombinant human BMP-2, through a carrier, has demonstrated clinical relevance in the induction of bone formation for some maxillofacial / oral indications. However, the carrier, or vehicle, is the "Achilles heel" of rhBMP-2.

The development of research focused on the formulation of carrier systems for BMPs is proven to be necessary, in a therapeutic perspective. The use of collagen

and carrier systems associated with collagen, although widespread, is related to some disadvantages. Among these disadvantages are included the poor mechanical stability, the immune response and the potential for transmission of viral antigens.

The ideal carrier substrate would fulfill the following requirements: Relative insolubility in physiological conditions, being biodegradable, protect against proteolytic activities, act as a substrate for cell adhesion and proliferation, immunologically inert, maintain the BMP bioavailable through controlled biological degradation and having mechanical stability to promote the union of bone defects.

What are the commercial products available in the national and global market containing BMP alone or combined with other substances?

All biomaterials which may have bone origin contain BMP. However, the industry does not usually quantify in the packings. The regulator agency American Food and Drugs Administration (FDA) has approved first, in 2002, the use of the product Infuse® Bone Graft for spine orthopedic surgery (lumbar spinal fusion) and in 2004, as a bone graft to reduce long bone fractures with loss of substance. Only in March of 2007 was authorized its use in surgery of maxillary sinus lifting and alveolar defects correction. In 2008, this procedure was released in Brazil by the National Sanitary Surveillance Agency, Anvisa. The BMP-7 t(OP-1®; Stryker) is only sold in the USA.

What are the indications and contraindications of these products?

Patients with bone loss in the upper and lower arches can use rhBMP-2 to repair it. It is a procedure that generates less trauma and provides better chances to success, when compared to other regenerative therapies, including those that use the patient's own bone (autogenous bone). Any patient in need of increased bone structure can use rhBMP-2. However, there is contraindication for pregnant women. Additionally, it is recommended that women who received this therapy do not become pregnant within a year after treatment. The use of rhBMP-2 is also not suitable for lactating women, to patients with infection near the incision area and people who are under radiation therapy, chemotherapy, and steroids therapy.

Adverse effects can be observed for cases where the patient has hypersensitivity to rhBMP-2 or bovine collagen type 1, which is the sponge where is carried the protein.

What are the biological effects of BMP as a mediator in the repair process?

When an adequate concentration of rhBMP-2 is placed on an absorbable collagen sponge (ACS) and implanted in the body it is induced new bone tissue at the implantation site.

The mesenchymal stem cells, around the tissues of the implanted area, come into contact first with the rhBMP-2/ACS. The collagen sponge degrades or dissolves, and these stem cells begin to differentiate into osteoblastic cells, initiating the formation of trabecular bone or cartilage. The blood vessel formation (angiogenesis) is also observed at the same time.

The first step in the process of bone formation induced by rhBMP-2/ACS is the migration of bone forming cells to the area. Chemotaxis involves stimulation of cell migration in response to a chemical signal. Mesenchymal stem cells and osteoblasts from bleeding bone, muscle, and the periosteum infiltrate the rhBMP-2/ACS implant. In-vitro studies have shown that rhBMP-2 can stimulate the specific chemotactic migration of bone-forming cells, promoting in its surrounding the

proliferation of several multi-potent cell lines, which are capable of differentiating into osteoblasts. This differentiation of mesenchymal stem cells into bone-forming osteoblasts plays an essential role in the induction of new bone, which was also demonstrated in preclinical studies. The rhBMP-2 binds to specific receptors on the surface of the MSC and causes them to differentiate into bone-forming cells.

Pre-clinical studies have supported that the bone formation initiated by rhBMP-2/ACS is a self-limiting process, forming a predictable volume of bone. The bone formation process develops from the outside of the rhBMP-2/ACS implant towards the center until the entire implant is replaced by trabecular bone. The ability of rhBMP-2 to induce new bone formation is dependent upon its concentration. The rate of bone formation, the amount of bone formed, and the density of the resulting bone are positively correlated with both the concentration of rhBMP-2 and the length of time that rhBMP-2 is present at the implant site.

Remodeling of the trabecular bone induced by rhBMP-2/ACS occurs in a manner that is consistent with the biomechanical forces placed on it. Radiographic, biomechanical, and histologic evaluation of the induced bone indicates that it functions biologically and biomechanically as native bone. Furthermore, pre-clinical studies have indicated that the bone induced by rhBMP-2/ACS can repair itself, if fractured, in a manner indistinguishable from native bone healing (Fig. 2, Table 2).

Besides its role in the processes of repair of bone tissue, the strongest evidences for the involvement of BMPs in embryogenesis derive from isolating mRNAs for BMPs in several tissues, suggesting multiple functions in both morphogenesis and in formation pattern outside the skeleton. In situ hybridization showed that the mRNA of BMP-2 is expressed during development of members, heart, teeth, eyes and craniofacial mesenchyme.

In the commercial form of presentation, the product retains these properties and characteristics?

In the United States are offered six types (sizes) of different kits, in Brazil only three. The kit should be single use and their biodegradation takes about two hours. It is expected that the Infuse Bone Graft® maintains the properties and features promised by the industry and recommended by the manufacturer, provided that it is accurately targeted and used for the proposed purpose.

How can the professional purchase rhBMP and what are the necessary precautions regarding the quality and reliability of the product?

In Brazil, the recombinant human bone protein is commercialized in São Paulo, by an authorized representative. Provided that the biomaterial is bone, it will always have BMP in its composition. However, we do not know the percentage of BMP contained in the product, because the industry omits the information and does not quantify that percentage. Thus, we, surgeons and clinical professionals, most of the time work entirely in the dark, only believing that in the end everything will be all right.

In the beginning of the osseointegration advent, it was of paramount importance to deeply research to the pre-commercialization of any new product. An extraordinary time was consumed before these biomaterials were used. In the contemporary system, economic power and "commercial greed" of industry reversed the whole process to the point where new products are routinely presented to the profession with an inadequate and insufficient investigation. Clinicians are more often exposed to try new devices and report on its

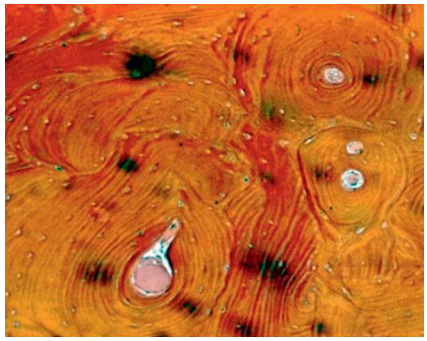

Figure 2 - Photomicrograph of an alveolar defect filled with rhBMP-2/αBSM, showing new lamellar bone formation and Haversian systems (4x)

Table 2 - RhBMP-2 mechanisms of action in absorbable collagen sponge (ACS).

1	Implantation	rhBMP-2/ACS is implanted
2	Chemotaxis	Migration of Mesenchymal Stem Cells and other bone-forming cells to the site of implantation
3	Proliferation	rhBMP-2/ACS provides an environment where stem cells multiply prior to differentiation
4	Differentiation	rhBMP-2 binds to specific receptors on the stem cell surface inducing them to differentiate into osteoblasts
5	Bone formation and Angiogenesis	Osteoblasts respond to local mechanical forces to produce new mineralized tissue within the ACS. New blood vessel formation is observed at the same time
6	Remodeling	Body continues to remodel bone in response to the local environmental and mechanical forces, resulting in normal trabecular bone

performance and success, but without communicating the patient about the empirical "research". It is a very dangerous and not scientifical approach, which does not predict any good for the implantodontists. The off-label use (when the clinician chooses to use the therapy with new products which were insufficiently evaluated or which the "risk-benefit ratio" is uncertain) needs to be reconsidered when the surgeon makes use of these products especially in cases where there is no scientific evidence attesting or certifying their effectiveness, such as in surgery in craniomaxillofacial reconstruction of mandibular defects after mandibular resections, alveolar ridges reconstruction for subsequent prosthetic rehabilitation and reconstruction of alveolar clefts. In studies and multicenter randomized clinical trials level 1 in humans, only the commercially titled product Infuse Bone Graft® has been shown by means of microscopic tissue sections, growth of new bone.

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Dario Augusto Oliveira Miranda is a professor at the Dental Clinic of the State University of Feira de Santana, Bahia, since 1995. MSc in Dentistry in the areas of Periodontics and Implantology by the University of Illinois at Chicago – College of Dentistry, under the guidance of Professor Neil Blumenthal. In 1999, he started researching on growth factor together with Professor Ufl Wikesjö (Atlanta, USA) and John Wozney (Harvard), studying the rhBMP (recombinant human bone morphogenetic protein), which has the property to induce the bone tissue formation in areas of resorption. He has presented preliminary results of this research during the meeting of the American Academy of Periodontology, being selected among the eight best works to represent the latest advances in research in Periodontics, in Orban Competition.

He attended the meeting of the Midwest Society of Periodontology, held in Chicago, Illinois, and obtained the first place certificate.

In the presentation at the Osseointegration Academy of Dallas, Texas, he also got the first place among 60 other studies assessed, of Canadians, Swedes, Japanese, Swiss and American researchers.

Traditional research colleges participated in these competitions, such as Harvard University, University of Boston, University of Michigan, University of Texas, among others.

Professor Dario Miranda is diplomate by the American Academy of Osseointegration.

Balint Orban Memorial Competition, American Academy of Periodontology (AAP) - Pennsylvania.

The Midwest Society of Periodontology - Chicago.

Honour Award to the most successful of the year. Dr. Dayn C. Boitet, president of the AO (Academy of Osseointegration), welcomes Dr. Dario A. Miranda, who won the award for Best Oral Presentation Summary - Dallas.