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Perspective

Growth Factor-assisted Distraction Osteogenesis and Histiogenesis.

Sergio M. Olate[1,2] & Ziyad S. Haidar.[3,4]

Affiliations: [1]Facultad de Odontología, Universidad de La Frontera. Temuco, Chile. [2]Centro de Excelencia en estudios Morfológicos y Quirúrgicos (CEMyQ), Universidad de La Frontera, Temuco, Chile. [3]BioMAT'X, Facultad de Odontología, Universidad de Los Andes. Santiago, Chile.[4]Facultad de Medicina, Universidad de los Andes. Santiago, Chile.

Corresponding author: Ziyad S. Haidar. Facultad de Odontología, Universidad de los Andes, Mons. Álvaro del Portillo 12.455. Las Condes, Santiago, Chile. Phone: (56-2) 26181372. Ext. (56-2) 22149468. E-mail: zhaidar@uandes.cl

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Bone is one of the "organs" with the most *spontaneous* regenerative capabilities in the human body. Principally, a dynamic connective tissue formed as a direct result of the self assembly and mineralization of the extracellular matrix produced primarily by bone-forming cells or osteoblasts, in a remarkable orchestra-like interaction with two other cell types *(at least to-date)*; osteocytes and osteoclasts maintaining and resorbing bone, respectively.

Yet, it continues to be the second most transplanted tissue after blood with *millions* of bone grafts performed annually. Indeed, an osseous defect can cause serious functional abnormalities and aesthetic deformities - thereby impacting overall quality of life. Such defects may result from congenital abnormalities, ablative surgery or traumatic avulsion, to name a few (Figure 1A). Luckily, small bone defects tend to heal efficiently via the afore-mentioned physiological regenerative processes. On the other hand, healing of bone fractures and reconstruction of critical-sized bone defects continue to present a significant challenge for orthopedists, traumatologists and maxillofacial surgeons, alike, as well as their patients and care-givers. Indeed, for osteoregeneration to yield proper *-fracture-* healing, mechanical stability in the defect site, osteogenic cells, and osteoinductive growth factors in combination with a suitable carrier or delivery system, conceptualized a decade ago (in 2007) as the *"Diamond Concept"* are necessary (Figure 1B).[1]

Yet, the long-standing autologous bone grafts continue to be routinely employed despite the well-documented deficiencies such as limited graft accessibility, donor site morbidity and increased costs. As a fine alternative, distraction osteogenesis; a prevailing surgical technique widely used for bone lengthening, is becoming increasingly popular in clinical craniofacial orthopedics and oro-maxillofacial (and mid-face) orthognathics since the documentation of the first clinical mandibular distraction osteogenesis back in the 1990s.[2]

Briefly, distraction osteogenesis biologically resembles fracture healing and includes performing an osteotomy followed by gradually distracting (pulling away) the two bone segments resulting in mechanically-induced endogenous tissue engineering and *de novo* bone formation within the distracted gap. While graft-free, a main limitation of the procedure remains the lengthy period of time required for the newly formed bone to consolidate entailing prolonged external fixation (thereby diminishing the high concentration of anabolic growth factors in the regenerate due to cortical and cancellous bone remodelling and maturation) with considerable morbidity.[3,4]

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Treatment outcomes and quantity:quality of regenerate from osteodistraction (and histiogenesis: specialized soft tissue growth) can also be affected by the presence of systemic disease and use of medications. Hence, the drive for developing novel bone tissue engineering methods continues, with 3 main strategies undergoing vigorous investigation: the transduction of genes encoding cytokines with osteogenic capacity into cells at repair sites *(gene therapy)*; the transplantation of cultured osteogenic cells derived from host bone marrow *(cell therapy)* and the application of osteoinductive growth factors *(protein therapy)*.

Gene- and stem cell-based therapy will probably represent the next major advance however presently are still in their infancy regarding safety and efficacy. Protein therapy, on the other hand, has demonstrated considerable practical promise, mainly via incorporating osteogenic morphogens such as bone morphogenetic proteins (BMPs) even so with *some* limitations and shortcomings.

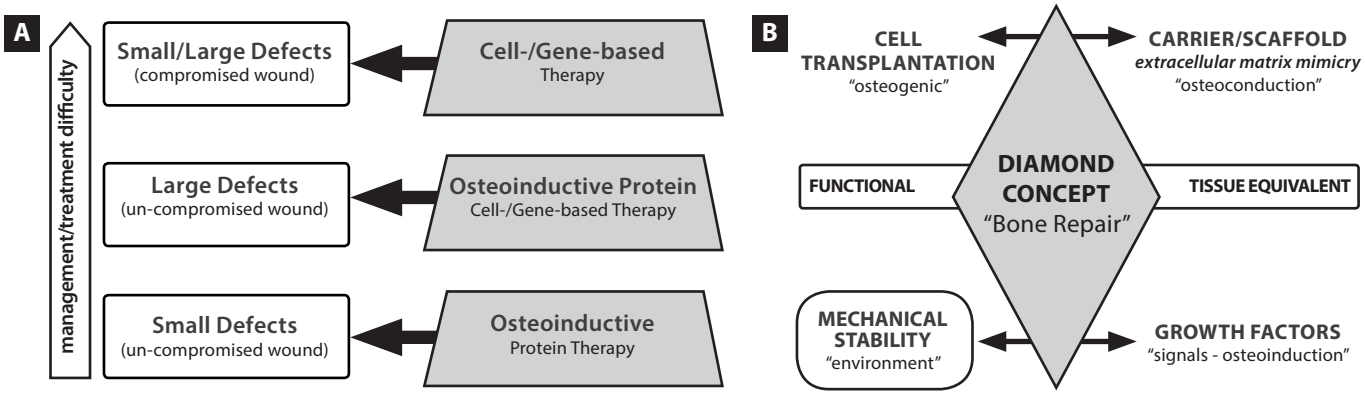
Briefly, BMPs are potent cytokines able to induce new bone formation *in vitro* and *in vivo*; and have been *efficacious* in the reconstruction of long bones, spine, as well as the craniofacial skeleton; pre-clinically and clinically.[4,5] While osteodistraction is not a FDA-authorized indication and/or application, attempts to manipulate regenerate bone using commercially-available BMPs, mainly BMP-2 (InductOs®, Infuse®) and BMP-7/OP-1 (Osigraft®), have been used off-label. The first and foremost caution (yet controversial) is that growth factors may involve a risk of inducing cancer; especially in children, despite conclusions from large cohort studies (use of BMP-2 in lumbar spondyloses in the elderly) not reporting such risk. In Canada, for example, growth factors can be indicated during pediatric osteodistraction to enhance healing and augment the bone grafting procedures in cases of orthopaedic non-union.[4-6]

BMPs act locally; yet, the exact/full cellular and molecular mechanisms are not fully understood. Small amounts induce cellular responses *in vitro*, however, when administered *in vivo*, rapid degradation and consequently insufficient and improper tissue regeneration occurs. Further, we know today that the clinical efficacy of recombinant human (*rh*) forms of BMPs will always depend on the carrier system used to ensure an effective delivery of adequate protein concentrations to the desired site.[4,6] While several materials for *rh*BMPs delivery have been developed, only specific collagen-based formulations for *rh*BMP-2 and *rh*OP-1 (*rh*BMP-7) obtained FDA approval for their *restricted* use in humans; orthopaedic and spinal fusion applications[4-7]

It is also clear that there can be no one single best-fit delivery system for all growth factors, pathologies or indications, especially so in critical-sized defects. Likewise, there is probably not a single desirable pharmacokinetic profile that is predictive of success. Few have investigated the influence of release kinetics on bone regeneration, remodelling and repair. Maintaining a critical threshold concentration of exogenous cytokines at the defect site (or callus in cases of osteodistraction) for the necessary period of time (temporal distribution) is crucial. For example, higher retention times for BMP-2 were more osteoinductive when compared to short-term delivery at the equivalent dosage.[4,8]

It is apparent today that extremes of release (bolus injections or prolonged low level release) and speed (slow *versus* fast) are not necessarily or significantly beneficial to bone induction. Nonetheless, while timing of the protein

Figure 1. A. Bone Tissue Engineering approaches according to complexity/difficulty of osseous defect. **B.** The Diamond ◊Concept (introducing stability to earlier Δ Triad) for osseoregeneration leading to a functional 'engineered' vascularized tissue equivalent.



release is important, the dynamic nature of the healing zone makes it difficult to assess the state of the defect. It is also noteworthy to the interested reader that different animal models; species, ages and sizes, may have varying optimum release profiles. It is important thereby to emphasize again that the enhancement of bone healing by BMPs is predominantly dependant on the parameters of a combined localized and release-controlled carrier/delivery system including the aforementioned: protein release kinetics and retention, BMP dose size/concentration, mechanism of release and nature of the vehicle used in terms of biomaterial(s) and design/geometry.

Collectively, novel controlled-release carriers need to contain the cytokine(s), prevent ectopic/heterotopic bone formation and utilize safe and cost-effective dosages. They should have the ability to provoke optimal localized inflammatory responses, be biocompatible and are often required to be bio-resorbable. Processing conditions need to prevent protein aggregation or denaturation. Also, they have to be easily and cost-effectively manufactured for large-scale production. Appropriate storage, stability, handling and sterilization conditions are favored as well. All such desirable and eagirly-pursued/-awaited progressions need to serve and facilitate the sought-after approval by regulatory agencies; a far from easy, economic or rapid translational process.

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