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Perspective

NanoBioTechnology-guided 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 Odontología, 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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In parallel to the tremendous leap achieved by Growth Factor-assisted Distraction Osteogenesis and Histiogenesis,[1] recent developments in the application of nanotechnology seem to widely-open the doors for further advances in the fields of biomaterials, drug delivery, tissue engineering and regenerative medicine. In deed, *nanotechnology*, first introduced over half a century ago, helps, at a fundamental level, to manipulate distinct atoms and molecules to design and produce novel structures and materials (size scale ranging 1-1000nm) with unique, improved or desirable physico-chemical, biological and mechanical characteristics and properties. Hence, such an emerging field is rendered diverse, multi- and inter-disciplinary, where it involves the need for a decent understanding of biology, chemistry, physics, and mathematics, at the least. On the other hand, nanobiotechnology (or bio-nano-technology), refers to scientific and technological advances in the intersecting fields of health care and biology, with an emphasis on their interface with nano-scale sciences.

In dentistry, *nanotechnology* and *nano*biotechnology have recently drawn the attention of scientists and clinicians to potentially-significant advances in the detection, prediction, diagnosis, treatment and prevention of oral and maxillofacial diseases; deemed an un-avoidable development (and need) for the progress of our art-based-on-science field. Indeed, *nano*Dentistry[2] is defined today as the science and technology of maintaining *near-perfect oral health* using *nanomaterials*, *nanodiagnostics* and *nanorobotics*, alongside the application of principles of pharmaceutics, tissue engineering and regenerative medicine. For instance, *nano*materials are studied to overcome the physical, chemical and mechanical characteristics of conventional dental materials.

It is projected that *nano*Dentistry possesses a significant potential to emerge and yield (soon) a new generation of technologically-advanced clinical tools and devices for dento-oral and maxilla-facial healthcare, including: *nano*robotic localized analgesics (for greater control, patient safety and comfort); *nano*robotic dentifrice (for superior and halitosis-free oral health care); orthodontic *nano*robots (for rapid and painless tooth movement without need for braces); bio-nano-enamel (*nano*rod -like calcium hydroxyapatite crystals arranged in parallel); *nano*-electro-mechanical systems (for oral cancer detection and diagnosis); *nano*vectors and dendrimer nanoparticles (for gene and drug delivery in the treatment of oral cancer) and much more "smart" *nano*biomaterials under development for cartilage endodontic pulp repair, periodontal ligament regeneration, extraction socket preservation and restoration, salivary gland radioprotection, implant osseointegration, cartilage regeneration of the temporomandibular joint and the treatment of oro-facial fractures, to list a few. So, bone augmentation and osteodistraction cannot be excluded applications.[1]

Explicitly, nano-sized particles made from synthetic polymers and natural polymers are dosage forms that have consummated much attention for the localized and release-controlled delivery of growth factors due to their attractive tendency to amass in sites of inflammation.[3,4] Compared to microparticles, nanoparticle and

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nanofiber delivery systems have demonstrated superiority in terms of longer residencies in general circulation, consequently extending the bioactivity of the entrapped molecule.[3,4] In a good example of a combined localized and release-controlled delivery system, PLGA nanospheres (NS) immobilized onto prefabricated nanofibrous PLLA scaffolds were used to load and deliver *rh*BMP-7.[3]

OP-1 delivered from NS-scaffolds induced significant ectopic bone formation while passive adsorption of the protein into the scaffold resulted in failure of bone induction either due to the loss of protein bioactivity or its rapid release from the scaffolds upon implantation *in vivo*. Our core-shell nanoparticulate delivery system formulated via the layer-by-layer (L-b-L) electrostatic-based self-assembly of a shell of alternating layers of anionic. The bioactivity of released (linear and multi-step over an extended period of 45 days) *rh*BMP-7, controlled through the L-b-L design, was maintained via enhancing pre-osteoblast differentiation. Further, the increase in shell thickness slowed the rate of protein diffusion compared to faster burst release from uncoated liposomal cores.[5]

In our rabbit model of tibial distraction osteogenesis, accelerated osteogenesis was evident following a single injection of the nanoparticles loaded with a dose of no more than 1µg *rh*BMP-7 in comparison to earlier results from a single injection of *rh*BMP-7 (75µg in saline), accentuating the role of the injectable localized and release-controlled nanoparticles.[6] Other groups have been increasingly investigating injectable scaffolds for drug delivery; *in situ*. A fine example is the work of Hasirci and co-workers where they developed over the years several 3-D scaffolds for the *sequential* delivery of BMPs.[7]

One system consisted of microspheres of polyelectrolyte complexes of poly(4-vinyl pyridine) and alginate loaded with both proteins and incorporated in PLGA scaffolds. While neither cytokine delivery had any direct effect on cellular proliferation; their co-administration enhanced osteogenic differentiation to a higher degree than single administration. This was suggested to be due to the physical properties (pore size and distribution) of the foams.

It is safe, today, to point out that injectable and multiple growth factor delivery systems are mounting interest as they could provide a less invasive method for the regeneration and repair of osseous defects with clinical indications including fresh fractures, non-union or delayed union, large bone defects associated with osseous tumor resection as well as the acceleration of periodontal therapy hence avoiding extensive/secondary surgery and in some cases, even shortening the overall treatment period.[3-6,8,9]

Nonetheless, since growth factors act in a coordinated cascade of events to restore bone, delivering multiple combinations of growth factors should be approached with caution regarding the choice of specific morphogens. For example, the sequential release of BMP-2 in combination with IGF-1 has already been explored, yet with commercialization-related difficulties. *rh*BMP-2 and bFGF absorbed to a collagen sponge resulted in decreased bone formation in a rabbit model of tibial fracture.[4]

Today, for orthopaedic and craniofacial reconstruction, the challenge remains to deliver osteoinductive growth factors in ways that would ensure consistent clinical success in humans (function and esthetic). BMP therapy should focus on the development of customizable, localized and release-controlled delivery materials and systems with the surgical practicality (preferably, injectable) and adjustable simultaneous growth factor(s) release profiles, according to defect site, size and vascularity.

Indeed, given the complex nature – and microenvironment – of osseoregeneration, it is possible that multiple growth factor delivery exhibiting both stimulatory and inhibitory responses on bone formation (variable release characteristics in response to physiological requirements) be the best-fit solution clinically, with caution to the choice of combinations.

Reported pre-clinical and clinical bone tissue engineering and regeneration, while satisfactory, can still be controversial. Yet, we can agree that efficacy, time and cost continue as main limitations. This is especially true in the case of distraction osteogenesis. Indeed, the focal question is: *"how to accelerate the osteodistraction procedure, in general, and the consolidation of regenerate bone, in specific, so that the fixator can be removed at an earlier time?"*

Further, "in mandibular osteodistraction, specifically (in comparison to endochondral long bone osteodistraction), what are the underlying governing mechanisms for enhanced *de novo* intramembranous osseoregeneration?" At BioMAT'X-Chile (Available at http://www.uandes.cl/facultad-de-medicina/biomateriales-laboratorio-de-ingenieria-de-tejidos-craneo-maxilo-facial.html), we are focused to pursue and attempt to tackle such questions.

In parallel, innovating the "ideal" osteo-/osseo-regenerative biomaterial, preferably injectable, remains our prime need and challenge. The future of osteo-/osseo-distraction (and skeletal bone-related health, in general) will closely rely on translational *nano*Medicine and *nano*Dentistry with smart and/or intelligent, safe and effective *nano*biomaterials and nano-based systems that combine *customizable* agent loading, encapsulation, active targeting, pre-/post-diagnostic imaging and multi-load release pharmacokinetics: a highly-anticipated and eagerly-awaited paradigm shift in endochondral (indirect) and intramembranous (direct) *de novo* bone tissue ossification, engineering and regeneration. To re-emphasize, today, this calls for a critical understanding of the cellular and molecular fundamental basis governing

the mechanically-induced biological interaction between the cells in play and the nano-systems. In parallel, for a perfectly-coordinated osteogenesis, best-fit animal model(s) are lacking.

Our earlier work also identified DKK-1 (a negative regulator of Wnt signaling) as a target for Wnt/β-catenin signaling pathway modulation. Ongoing research at Bio-MAT'X-Chile, employs a unique, high-value and complex animal model of "mandibular" distraction osteogenesis and histiogenesis to elucidate the underlying cellular and molecular mechanisms of hard and soft tissue regeneration and repair under mechanical stress, following the local and single administration of a release-controlled nano-hydrogel hybrid loaded with modified core-shell nanocapsules into the distracted gap as a "miRNA-mediated DKK-1 gene silencing delivery system" to safely control and locally modulate the Wnt/β-catenin signaling pathway.

We expect this approach would help better understand the underlying bio-mechanisms, reveal and identify clinical targets for use in the design and development of novel, safe and effective therapies, thereby improving current methods and/or introducing alternative clinical strategies, primarily, in terms of quality, quantity and rate, of *de novo* hard and soft tissue healing, in the cranio-oro-maxillo-facial complex, with a multidisciplinary bench-top to bed-side translational vision.

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