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Review Article

Bone Tissue Engineering Application in the Maxillofacial Region

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Abstract

The reconstruction of bone defects in the maxillofacial region represents a serious issue for dental surgeons, especially when facing extensive bone loss as the result of trauma, inflammation, and surgical treatment of tumors. Different reconstruction modalities include bone graft transplants either autologous or heterologous, implants of different biomaterials, etc. but none of these approaches has proven to be fully satisfactory. The use of engineered bone tissue can provide numerous benefits for the patient. First of all, it eliminates donor site morbidity encountered in the case of autogenous bone grafting techniques, and the absence of immune rejection which can occur when using allografts. Bone tissue engineering implies the use of adequate, biodegradable scaffolds for cell seeding, suitable cells with osteogenic potential and finally osteogenesis-inducing factors. A vast variety of biomaterials have been used as matrix for bone tissue engineering applications, among others collagen, chitosan, polylactic and polyglycolic acid, fibrin, hydroxiapatite etc. Porosity, topography, three-dimensional architecture, immunogenicity and mechanical parameters represent scaffold properties with significant influence on bone formation. Most recently, various dental niches are emerging as interesting sources of stem cells for potential application in bone defects reconstruction: dental pulp stem cells, stem cells from human exfoliated deciduous teeth, stem cells from apical papilla, periodontal ligament stem cells and others. These cells are used along with bone morphogenetic proteins (BMPs) which belong to the TGF-β family and represent potent osteoinductive factors. BMP-2, BMP-4 and BMP-7 are the most frequently applied in maxillofacial reconstruction. Finally, in order to achieve the optimal results in tissue engineering, from simple static tissue cultures, tissue production has been moved to bioreactors, devices that try to respond to the challenges of achieving adequate, three-dimensional proliferation of mesenchymal stem cells on biodegradable substrates followed by osteogenic induction of these MSCs and matrix synthesis.

Keywords: Stem Cells; Scaffolds; Osteoinductive Factors; Biomaterials; Tissue Engineering

Introduction

The reconstruction of maxillofacial defects represents a huge clinical problem and challenge for dental surgeons, especially when facing extensive bone loss due to pathological events such as trauma, inflammation, and surgical treatment of tumors. In these cases different approaches for reconstruction include bone graft transplants either autologous, homologous or heterologous grafts, implants of different biomaterials, etc. but none of these modalities has proven to be fully satisfactory [1].

In principle, bone grafts should contain all the key elements required for bone repair: (i) an osteoconductive scaffold, (ii) cells with osteogenic potential, and (iii) growth factors for enhancing osteoinduction and vascularization within the new bone/implant [1]. Each kind of bone graft has its specific advantages as well as some drawbacks. The clinical use of autologous bone graft is limited by a considerable donor site morbidity that increases with the amount of harvested bone. The principal disadvantage of allografts is their relatively poor capacity for osteoconduction and their lack of osteoinductive properties compared with autologous bone [2].

The reconstructive procedure using microvascular free flaps is considered to be the gold standard as it provides, in most cases, a functional reconstruction. However, even microvascular techniques have some disadvantages: they are very demanding for the patient (long intraoperative time and a double surgical field), and

the harvesting of tissue from a donor site produces comorbidity and results in a permanent deficit when a muscle or a bone is included in the flap [3]. For those reasons introducing novel therapeutic modalities has become an imperative.

Bone tissue engineering

Tissue engineering is a rapidly developing field, which combines the disciplines of materials science and biotechnology aiming to develop tissue constructs that can be implanted into the human body [Balasundaram., *et al*.]. It was defined two decades ago as "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function" [4].

The use of engineered bone tissue can provide numerous benefits for the patient. First of all, it eliminates donor site morbidity encountered in the case of autogenous bone grafting techniques, and the absence of immune rejection which can occur when using allografts [Balasundaram., *et al*.].

Three crucial components required for engineering a bone are: (1) scaffolds, (2) cells and (3) cell signaling molecules. More precisely, in order to grow a bone an adequate starting number of cells with osteogenic capacity is needed, as well as an appropriate scaffold to seed the cells onto, factors stimulating osteogenesis, and finally a satisfactory blood supply.

Tissues scaffolds

Scaffolds are mechanical constructs that act as supports and carriers for cells and growth factors [5]. The scaffolds should be biodegradable, which implies that they should slowly disappear during the process of tissue regeneration and should be replaced with fully functional host tissue.

A vast variety of biomaterials have been used as matrix for bone tissue engineering applications, among others collagen and chitosan. New polymers such as polylactic acid and polyglycolic acid have also been developed (Table 1). Gel-like matrices such as fibrin have been used for cell immobilization in combination with other scaffolds as well. Porosity, surface chemistry, topography, three-dimensional architecture, immunogenicity and mechanic parameters represent matrix properties which significantly influence bone formation within bioartificial bone substitutes.

Synthetic Polymers	Ref.	Natural Polymers	Ref.	Ceramics	Ref.	Metals	Ref.
Polylactic acid (PLA)	[8]	Gelatin/chitooligosaccharide	[18]	TiO_2	[24]	NiTi	[27]
Poly glycolic acid (PGA)	[9]	Collagen	[19]	HAp	[25]	Titanium alloy	[28]
Poly (lactic-co-glicolic acid) (PLGA)	[10]	Chitosan	[20]	β-TCP	[25]	Magnesium alloy	[29]
Poly ε-caprolactone (PCL)	[11]	Chitosan/collagen/beta-glycerophosphate (β-GP)	[21]	Bioglass	[26]	Porous tantalum	[30]
Polyethylene glycol (PEG)	[12]	Alginate	[22]				
Polybutylene terephthalate (PBT)	[13]	Chitin	[23]				
Polyethylene terephthalate (PET)	[13]						
Polyvinyl alcohol (PVA)	[14]						
Poly propylene fumarate (PPF)	[15]						
Poly aldehyde guluronate (PAG)	[16]						
Polyacrylic acid (PAA)	[17]						

Table 1: Types of materials used in scaffold construction.

One of the most widely used material for scaffold construction, combined with various natural or synthetic polymers, is hydroxyapatite, chemically similar to the inorganic minerals of the bone. For instance, a very good example of innovative product is ALBOOS, a composite scaffold based on calcium hydroxyapatite and poly lactic-co-glycolic acid. It shows a very high porosity and nanotopology suitable for cell adhesion and proliferation; namely, specific composite scaffold construction with ceramic parts, mimics the structural hierarchy of bone, while a thin polymer layer improves mechanical properties and cell attachment and proliferation [5-7].

Osteogenic cells

Today it is still unknown which type of osteogenic cells will be the most suitable for engineering of bone tissue. Isolation and ex-

pansion efficiency, stability of osteoblastic phenotype, *in vivo* bone formation capacity, and long-term safety are essential requirements that have to be met by any type of osteogenic cell for successful clinical application.

The most obvious choice of osteogenic cells would be the differentiated cell type appropriate to the tissues being replicated by the construct. These autogenous primary cells can be harvested by biopsy and expanded *In vitro* using standard cell culture techniques [31] before being seeded onto the scaffold. Osteoblasts possess strong osteogenic potential, and can be used as seed cells for bone regeneration [21]. As bone-forming cells, osteoblasts are able to synthesize and secrete bone matrix, thereby promoting mineralization and bone formation. However, the main disadvantages of osteoblasts application include less availability of donor tissue, lower proliferative capacity *in vitro.*

Another potential cell source that has elicited great interest are stem cells. Stem cells are defined as clonogenic cells capable of both self-renewal and multilineage differentiation. Stem cells are classified as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells according to their source, which also often correlates with their plasticity, i.e. their differentiation potential.

Recently, considerable attempts have been made towards directing ESC differentiation into osteogenic lineage and its use for bone regeneration [32]. It has already been established that ESCs can be differentiated into osteogenic cells and consequently used as a potential cell source for bone tissue engineering [5]. However, there are a lot of obstacles in their use in clinical practice, both ethical and legal, regarding their harvesting, expanding, and potential tumorigenicity [5].

Adult stem cells represent one of the main objects of investigations in bone regeneration research and show great promise for use in the oral and maxillofacial region [14]. The potential bone-generating adult stem cells include bone marrow mesenchymal stem cells (BMSCs), adipose derived stem cells (ASCs). BMSCs were firstly isolated by Friedenstein., et al. in the 1960s and named at the time bone marrow stromal cells. It was demonstrated that, when transplanted, these cells had the ability to form bone, cartilage, adipose cells, and fibrous connective tissue [33]. BMSCs are the most studied cells for the purpose of use in regeneration of orofacial bone defects. BMSCs seeded on poly-dL-lactic–coglycolic acid scaffolds were shown to be effective in the reconstruction of bony defects in pig mandibles. Radiographic analyses showed that tissue-engineered constructs were uniformly radiodense with bone distributed throughout, while the interface between native bone and constructs was indistinct [34]. Most importantly, optimal outcome has been achieved by using autologous BMSCs to repair human bone defects, in particular mandible defects [35]. Compared with BMSCs, ASCs are easier to obtain, carry relatively low donor site morbidity, and are available in large number [36]. The osteogenic capacity of ASCs has received considerable attention with respect to bone regeneration. Various studies have reported that successful repair of bone defects can be achieved by transplanting autologous ASCs into the bone defect sites [37]. Most recently, various dental niches are emerging as interesting sources of stem cells: dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), stem cells from apical papilla (SCAP) [38], periodontal ligament stem cells (PDLSCs), etc [39]. DPSCs, a population of postnatal stem cells residing in the dental pulp are capable of differentiation towards osteoblasts and formation of bone *In vivo* [14]. As such, they represent an interesting cell source for bone regeneration in oral and maxillofacial region. Similarly, MSCs derived from apical papilla are becoming an increasingly attractive stem cell source because they belong to a developing, easily accessible tissue, with cells possessing high-proliferation rate, plasticity and differentiation capacity [38].

Osteoinductive factors

Bone morphogenetic proteins (BMPs) are among the most potent osteoinductive factors. BMPs belong to the TGF-β family and bind to extracellular matrix components such as heparan sulfate and type IV collagen [40]. BMPs [mainly BMP-2 [Dunn., *et al.*], BMP-4 [Stadlinger., *et al.*] and BMP-7 [Giannobile., *et al.*]] have been the more frequently applied in maxillofacial reconstruction. Major bone defects have been engineered by a combination of BMSCs and BMP-7 [35], or by exclusive reliance on the growth factor [35]. In addition, growth factors such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and platelet derived growth factor (PDGF) have also been used successfully in bone regeneration [41].

Bioreactors

Traditional efforts to grow bone *In vitro* relied mainly on culturing cells on scaffolds, with the addition of osteogenic factors, under static conditions, but these conditions would not allow the growth of larger bone grafts for clinical application [42]. A consid-

erable improvement in the field was achieved with the introduction of bioreactors, devices designed to attain optimal conditions to grow cells *In vitro* to be utilized in tissue engineering. The design of a bioreactor primarily depend on the type of tissue that is being constructed. Its function is to provide a suitable, reproducible and easily controlled cell culture environment, in terms of temperature, pH, oxygen and carbon dioxide concentrations, speed of culture medium flow, etc. Bioreactors should also have a simple design in order to reduce the risk of contamination and allow an easy and quick access to the cells/tissue if any technical problem occurs during the culturing process (flow obstruction or culture medium leakage, for instance) [42].

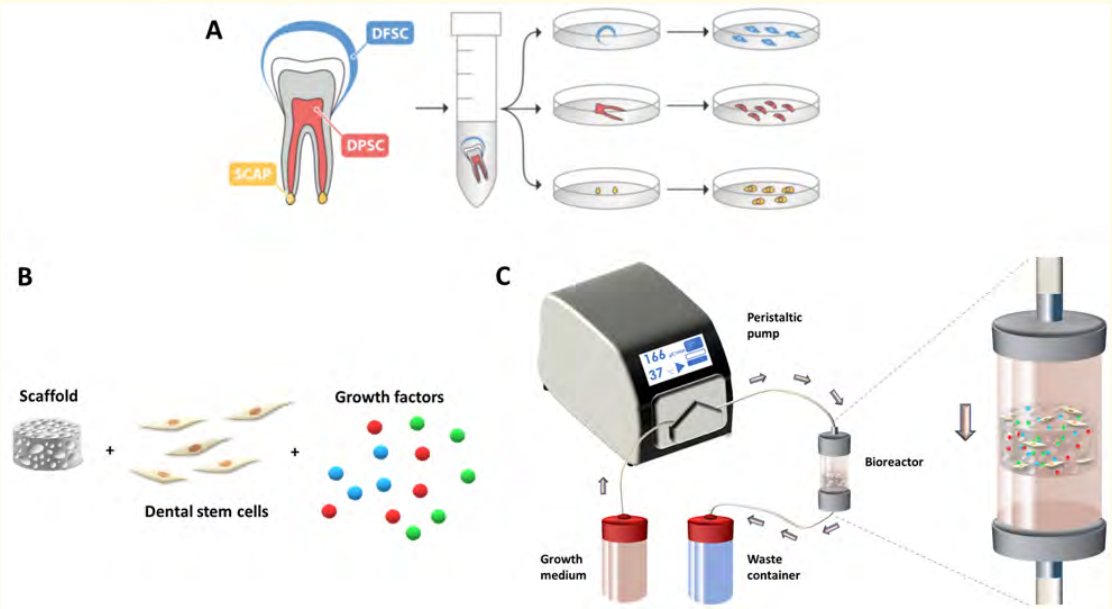

Figure 1: A-different sources of dental stem cells; B-main components used in tissue engineering; C-basic elements of a bioreactor system.

In a typical "bone bioreactor" dynamic settings mimicking physiological conditions are a requisite. It must be emphasized that mechanical (biophysical) stimuli are crucial for successful bone remodelling and regeneration. The bioreactor tries to respond to all the challenges: achieving adequate, uniform three-dimensional proliferation of mesenchymal stem cells on a biodegradable substrate followed by the osteogenic commitment of these MSCs and matrix synthesis. Bioreactors for bone engineering applications are generally classified into rotating wall vessels, spinner flasks, perfusion (direct and indirect) bioreactors, Compression Bioreactors and Combined Systems [42-50].

Conclusion

It can be concluded that a large body of promising data have accumulated, obtained both on *In vitro* experimental models and *In vivo* experiments performed on small and large animals. However, translation to clinical use is much slower. Although cell based therapies and tissue engineering are in the focus of research, there is still a lot of debate related to the most suitable types of scaffolds, types and number of cells and osteogenesis-stimulating factors to be utilized in bone regeneration in general, and more specifically in maxillofacial reconstructive therapy.

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Conflict of Interest

All the authors declare no financial interest or any conflict of interest.

Bibliography

1. Cancedda Ranieri., *et al*. "A Tissue Engineering Approach to Bone Repair in Large Animal Models and in Clinical Practice". *Biomaterials* (2007).

2. Heise U., *et al*. "Hydroxyapatite Ceramic as a Bone Substitute". *International Orthopaedics* (1990).

3. Brown James Stephen. "Deep Circumflex Iliac Artery Free Flap with Internal Oblique Muscle as a New Method of Immediate Reconstruction of Maxillectomy Defect". *Head and Neck* (1996).

4. Langer Robert and Joseph P Vacanti. "Tissue Engineering". *Science* (1993).

5. Petrovic Milan., *et al*. "Self-assembly of biomimetic hydroxyapatite on the surface of different polymer thin films". *Journal of Ceramic Processing Research* 13 (2012): 398-404.

6. Jokanović Vukoman, *et al*. "In Vivo Investigation of ALBO-OS Scaffold Based on Hydroxyapatite and PLGA". *Journal of Nanomaterials* (2016).

7. Markovic Dejan., *et al*. "Biološki Aspekti Primene Nanomaterijala u Tkivnom Inženjerstvu". *Chemical Industry and Chemical Engineering Quarterly* (2016).

8. Koob Sebastian., *et al*. "Bone Formation and Neovascularization Mediated by Mesenchymal Stem Cells and Endothelial Cells in Critical-Sized Calvarial Defects". *Tissue Engineering Part A* 17 (2011): 311-321.

9. Rodríguez-Fuentes Nayeli., *et al*. "Isolation of Human Mesenchymal Stem Cells and Their Cultivation on the Porous Bone Matrix". *Journal of Visualized Experiments* (2015): e51999.

10. Makadia Hiren kumar K and Steven J Siegel. "Poly Lactic-Co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier". *Polymers* 3 (2011): 1377-1397.

11. Kokubo Tadashi., *et al*. "Novel Bioactive Materials with Different Mechanical Properties". *Biomaterials* (2003).

12. Kang Hye Won., *et al*. "Fabrication of Porous Gelatin Scaffolds for Tissue Engineering". *Biomaterials* 20 (1999): 1339-1344.

13. Woo Byung H., *et al*. "Preparation, Characterization and in Vivo Evaluation of 120-Day Poly(D,L-Lactide) Leuprolide Microspheres". *Journal of Controlled Release* (2001).

14. Zhang Zhiyuan. "Bone Regeneration by Stem Cell and Tissue Engineering in Oral and Maxillofacial Region". *Frontiers of Medicine in China* 5 (2011): 401-413.

15. Farack J., *et al*. "The Effect of Perfusion Culture on Proliferation and Differentiation of Human Mesenchymal Stem Cells on Biocorrodible Bone Replacement Material". *Materials Science and Engineering B: Solid-State Materials for Advanced Technology* 20 (2011): 1767-1772.

16. Yusop AH., *et al*. "Porous Biodegradable Metals for Hard Tissue Scaffolds: A Review". *International Journal of Biomaterials* (2012).

17. Bobyn JD., *et al*. "Characteristics of Bone Ingrowth and Interface Mechanics of a New Porous Tantalum Biomaterial". *The Journal of Bone and Joint Surgery* 81.5 (1999): 907-914.

18. Ratanavaraporn J., *et al*. "Comparison of Gelatin and Collagen Scaffolds for Fibroblast Cell Culture". *Journal of Metals, Materials and Minerals* (2006).

19. Niu Li Na., *et al*. "Collagen Intrafibrillar Mineralization as a Result of the Balance between Osmotic Equilibrium and Electroneutrality". *Nature Materials* (2017).

20. Nandi Samit K., *et al*. "Protein Growth Factors Loaded Highly Porous Chitosan Scaffold: A Comparison of Bone Healing Properties". *Materials Science and Engineering C* (2013).

21. Wang Shaoyi., *et al*. "Systematic Evaluation of a Tissue-Engineered Bone for Maxillary Sinus Augmentation in Large Animal Canine Model". *Bone* (2010).

22. Suarez-Gonzalez Darilis., *et al*. "Controlled Nucleation of Hydroxyapatite on Alginate Scaffolds for Stem Cell-Based Bone Tissue Engineering". *Journal of Biomedical Materials Research - Part A* 95 (2010): 222-234.

23. Yan Jun., *et al*. "Cross-Linking Characteristics and Mechanical Properties of an Injectable Biomaterial Composed of Polypropylene Fumarate and Polycaprolactone Co-Polymer". *Journal of Biomaterials Science, Polymer Edition* (2011).

24. Tiainen Hanna., *et al*. "Ultra-Porous Titanium Oxide Scaffold with High Compressive Strength". *Journal of Materials Science: Materials in Medicine* 21 (2010): 2783-2792.

25. Seitz Hermann., *et al*. "Three-Dimensional Printing of Porous Ceramic Scaffolds for Bone Tissue Engineering". *Journal of Biomedical Materials Research - Part B Applied Biomaterials* 74 (2005): 782-788.

26. Bose Susmita and Solaiman Tarafder. "Calcium Phosphate Ceramic Systems in Growth Factor and Drug Delivery for Bone Tissue Engineering: A Review". *Acta Biomaterialia* 8.4 (2012): 1401-1421.

27. Tamaddon Maryam., *et al*. "Intrinsic Osteoinductivity of Porous Titanium Scaffold for Bone Tissue Engineering". *International Journal of Biomaterials* (2017).

28. Dabrowski Bogdan., *et al*. "Highly Porous Titanium Scaffolds for Orthopaedic Applications". *Journal of Biomedical Materials Research - Part B Applied Biomaterials* 95 (2010): 53-61.

29. Witte F., *et al*. "Biodegradable Magnesium Scaffolds: Part II: Peri-Implant Bone Remodeling". *Journal of Biomedical Materials Research - Part A* (2007).

30. Balla Vamsi Krishna., *et al*. "Porous Tantalum Structures for Bone Implants: Fabrication, Mechanical and in Vitro Biological Properties". *Acta Biomaterialia* (2010).

31. Cilent BG., *et al*. "Phenotypic and Cytogenetic Characterization of Human Bladder Urothelia Expanded in Vitro". *Journal of Urology* (1994).

32. Jukes Jojanneke M., *et al*. "Skeletal Tissue Engineering Using Embryonic Stem Cells". *Journal of Tissue Engineering and Regenerative Medicine (*2010).

33. Friedenstein AJ., *et al*. "Heterotopic of Bone Marrow. Analysis of Precursor Cells for Osteogenic and Hematopoietic Tissues". *Transplantation* 6 (1968).

34. Abukawa Haru., *et al*. "Reconstruction of Mandibular Defects with Autologous Tissue-Engineered Bone". *Journal of Oral and Maxillofacial Surgery* (2004).

35. Warnke Ph., *et al*. "Growth and Transplantation of a Custom Vascularised Bone Graft in a Man". *Lancet* 364 *(*2004).

36. Katz Adam J., *et al*. "Cell Surface and Transcriptional Characterization of Human Adipose-Derived Adherent Stromal (HADAS) Cells". *Stem Cells* 23.3 (2005): 412-423.

37. Cowan Catherine M., *et al*. "Adipose-Derived Adult Stromal Cells Heal Critical-Size Mouse Calvarial Defects". *Nature Biotechnology* 22 (2004): 560-567.

38. Simonovic Jelena., *et al*. "Differentiation of stem cells from apical papilla into neural lineage using graphene dispersion and single walled carbon nanotubes". *Journal of Biomedical Materials Research Part A* (2018).

39. Ward B., *et al*. "Bioengineering Strategies for Regeneration of Craniofacial Bone: A Review of Emerging Technologies". *Oral Diseases* (2010).

40. Hari Reddi A. "Role of Morphogenetic Proteins in Skeletal Tissue Engineering and Regeneration". *Nature Biotechnology* (1998).

41. Li Anna., *et al*. "PDGF-AA Promotes Osteogenic Differentiation and Migration of Mesenchymal Stem Cell by down-Regulating PDGFRa and Derepressing BMP-Smad1/5/8 Signaling". *PLoS ONE* (2014).

42. Sladkova Martina and Giuseppe Maria de Peppo. "Bioreactor Systems for Human Bone Tissue Engineering". *Processes* 2 (2014): 494-525.

43. Gröger Andreas., *et al*. "Tissue Engineering of Bone for Mandibular Augmentation in Immunocompetent Minipigs: Preliminary Study". *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery* 37 (2003).

44. Johnson Philip J., *et al*. "Tissue-Engineered Fibrin Scaffolds Containing Neural Progenitors Enhance Functional Recovery in a Subacute Model of SCI". *Soft Matter* 20 (2010).

45. Mankani Mahesh H., *et al*. "In Vivo Bone Formation by Human Bone Marrow Stromal Cells: Effect of Carrier Particle Size and Shape". *Biotechnology and Bioengineering* (2001).

46. Petite H., *et al*. "Tissue-Engineered Bone Regeneration". *Nature Biotechnology* (2000).

47. Schantz Jan-Thorsten., *et al*. "Repair of Calvarial Defects with Customized Tissue-Engineered Bone Grafts I. Evaluation of Osteogenesis in a Three-Dimensional Culture System". *Tissue Engineering* (2003).

48. Shi Xinfeng., *et al*. "In Vitro Cytotoxicity of Single-Walled Carbon Nanotube/Biodegradable Polymer Nanocomposites". *Journal of Biomedical Materials Research - Part A* 86 (2008): 813-823.

49. Sikavitsas Vassilios I., *et al*. "Influence of the in Vitro Culture Period on the in Vivo Performance of Cell/Titanium Bone Tissue-Engineered Constructs Using a Rat Cranial Critical Size Defect Model". *Journal of Biomedical Materials Research - Part A* (2003).

50. Stangenberg Lars., *et al*. "Differentiation of Osteoblasts in Three-Dimensional Culture in Processed Cancellous Bone Matrix: Quantitative Analysis of Gene Expression Based on Real-Time Reverse Transcription- Polymerase Chain Reaction". *Tissue Engineering* (2005).

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