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Applicability of Homologous Fibrin Sealant in Bone Repair: An integrative Review

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Abstract *— The repairing of bone defects is still a challenge for researchers and clinicians. No netheless there are many procedures that use different biomaterials such as scaffolds for bone regeneration however the results are often still unsatisfactory. As a result, the fibrin sealant derived from the interaction between proteins participating in the final blood coagulation cascade, is one of the most promising biopolymers in the tissue engineering field due to its unique characteristics. The present study aimed to perform a systematic review on homologous fibrin sealants highlighting its applicability as a three-dimensional framework in the process of bone regeneration. The database used for search strategy was the PubMed (Medline) and followed the guidelines provided in the PRISMA statement. From an initial 313 articles, only 12 articles between 2009 to 2019 were selected for this review after checking all inclusion and exclusion criterias. Due to this background, it is notable that fibrin sealant is one of the promising biopolymers used for tissue engineering and bone regeneration applications.*

Keywords *— **Fibrin Sealant, Bone Repair, Tissue engineering, Biopolymer, Scaffold.***

I. INTRODUCTION

Bone is a highly dynamic tissue that undergoes a continuous renovation process to maintain its architectural bone structure, mechanical properties and metabolic capacities and when injured is able to reestablish the lost tissue morphofunctional characteristics without compromising the function (SEAL; OTERO; PANITCH, 2001; LOI et al., 2017).

However, this mechanism may or may not occur in large defects, such as tumor resections, unconsolidated fractures, congenital malformations, and the loss or surgical removal of bone fragments (HONMA et al., 2008; SPICER et al., 2012; HETTIARATCHI et al., 2017), in addition, it may require reconstructive operative procedures whose bone grafting is the main treatment technique (POUNTOS; GIANNOUDIS, 2016; BAI et al., 2018).

Among the available bone grafts, the autogen is still considered the gold standard in the bone regeneration techniques because it has osteogenic, osteoinductive and osteoconductive properties combined. Although its use is associated with limited supply, possible complications in the donor site and the unpredictability of bone resorption, which may negatively influence postoperative outcomes (POLLOCK et al., 2008; PILIPCHUK et al., 2015).

Because of these limitations, research is being conducted in order to a new treatment approach for bone regeneration, aiming at the development of biologically active natural materials (GHIASI et al., 2017).

As a result, the fibrin sealant derived from the interaction between proteins participating in the final blood coagulation cascade, is one of the most promising biopolymers in the tissue engineering field due to its unique characteristics (NOORI et al., 2017).

For instance, its excellent biocompatibility, controllable biodegradability, and multi-functional three-dimensional structure that provides support, cell proliferation and differentiation, anchoring surrounded molecules and growth factors and therapeutic agents transport, makes fibrin sealants have remarkable advantages over other biomaterials, besides a candidate

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with potential to assist in engineering of bone tissue (SHIU et al., 2014; SPOTNITZ, 2014; BORIE et al., 2015).

Although, all fibrin sealants contain fibrinogen and thrombin, qualitatively and quantitatively the exact composition varies, such as the velocity of rate of hemostasis, clot biochemistry, viscosity, adhesive strength, durability, fibrin polymerization rate and the three-dimensional structure of the clot, and can directly influence its use (WOZNIAK, 2003; DIETRICH et al., 2013; CUNHA et al., 2015). For this purpose, the present study aimed to perform a systematic review on homologous fibrin sealants highlighting its applicability as a three-dimensional framework in the bone regeneration process.

II. MATERIALS AND METHODS

This review followed the guidelines provided in the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Medical subject heading (MeSH) terms were used in this study. The database used for search strategy was the PubMed (Medline). The search string used was following these terms "**fibrin sealant AND bone repair**".

It has been included all articles in English at periods between 2009 and 2019, with access to the full text, either openly or by signatures available at the University of São Paulo (Brazil).

The titles and abstracts of the articles were evaluated and those that did not meet each inclusion criteria were removed from the review. After second analysis, only articles that used fibrin sealant as a three-dimensional scaffold for the lodging of biologically active cells and molecules in the bone regeneration process were selected for detailed review.

Inclusion Criteria:

- Periods between 2009 – 2019;
- Articles types: full articles available;
- English language;
- In vivo research model;
- Fibrin sealant used as a scaffold for tissue engineering applications.

Exclusion Criteria:

- Any article that did not meet the inclusion criteria listed earlier.

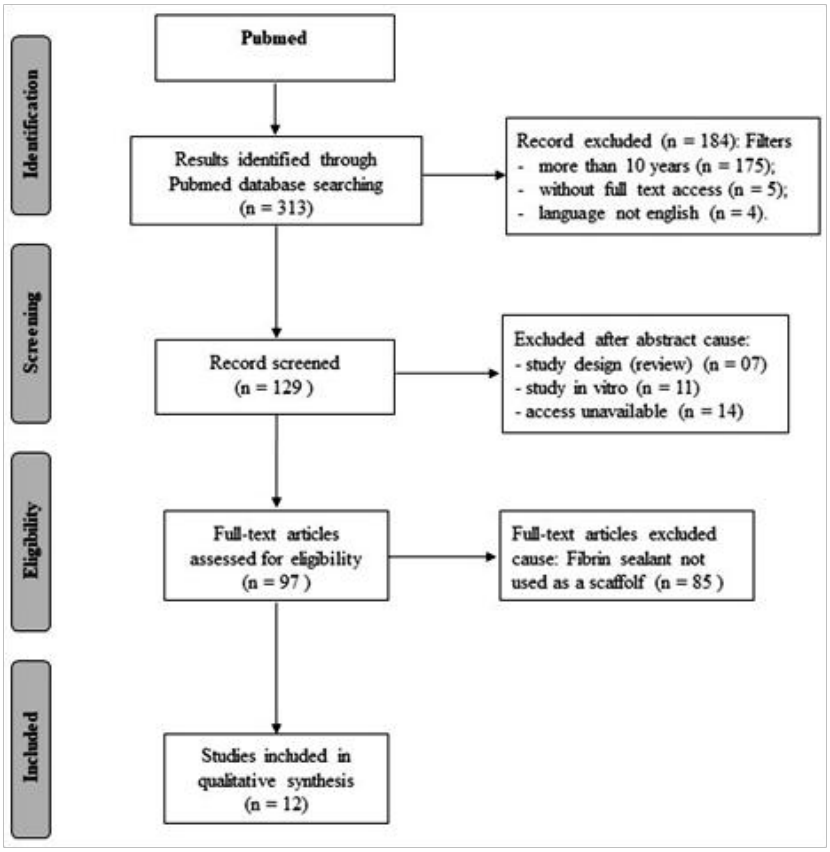

Fig.1: PubMed (Medline) Keywords combination

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III. RESULTS

In total, from an initial 313 articles, only 12 articles were selected for this review (see Table 1) after checking all criterias listed earlier such as periods between 2009 to 2019, full articles available, English language, fibrin sealant used as a scaffold for tissue engineering and in vivo research model. For full search process see Fig. 1.

Table 1 Summarizes of the selected articles about tissue engineering applications of fibrin scaffolds.

Author (Date)	Objective	Component origin and/or Trade name	Implantation Site	Mixture with biomaterials or cells	Conclusion
McDuffee et al. (2012)	To compare the efficacy of osteoprogenitors in fibrin glue to fibrin glue alone in bone healing of surgically induced ostectomies of the fourth metacarpal bones in an equine model.	Homologous (non-commercial)	Metacarpal bone in horses	Osteoprogenitor cells or fibrin sealant alone	Injection of periosteal-derived osteoprogenitors in a fibrin glue carrier into surgically created ostectomies of MC4 does not accelerate bone healing.
Reppenhagen et al. (2012)	To assess the safety and efficiency of a bone substitute as an alternative for autologous bone in the treatment of benign bone tumours and tumour-like lesions.	Homologous Tissucol™ Duo S	Distal tíbia; calcaneal; glenoid in human	Biphasic calcium phosphate granules	The biomaterial represents an easy-to-handle alternative to autologous cancellous bone grafts for the treatment of benign bone tumours and tumour-like lesions.
Zhang et al. (2012)	To clarify whether it could be efficient to reconstruct the alveolar bone by the combination of bone marrow stem cells (BMSCs) without pre-osteoinduction in vitro with fibrin glue (FG).	Homologous (non-commercial)	Rat alveolar bone	Bone marrow stem cells	The results suggest that the strategy of combing BMSCs with FG is effective in the repair of alveolar bone defects. Its clinical application is promising.
Streckbein et al. (2013)	To evaluate the efficacy of bioactive implants (ADSC in fibrin glue) for repair of critical-size mandibular defects in athymic rats.	Homologous Beriplast™ P	Mandibular defects in rats	Adipose-derived stem cells	Fibrin sealant is a suitable biological scaffold for cell transplantation.
Xuan et al. (2014)	To compare the potentials of PRF-mixed Bio-Oss® and Tisseel®-mixed Bio-Oss® to enhance bone regeneration in	Tisseel™	Canine sinus model.	Demineralized bovine bone	The findings from this study suggest that when platelet-rich fibrin is used as an adjunct to Bio-Oss® particles for bone augmentation

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Author (Date)	Objective	Component origin and/or Trade name	Implantation Site	Mixture with biomaterials or cells	Conclusion
	a canine sinus model.				in the maxillary sinus, bone formation in the graft sites is significantly greater than when Tisseel® is used.
Lappalainen et al. (2015)	To evaluate ossification of cranial bone defects comparing the healing of a single piece of autogenous calvarialbone representing a bone flap as in cranioplasty compared to particulated bone slurry with and without fibrin glue to represent bone collected during cranioplasty.	Tisseel™	Rabbit calvarial	Autologous particulate bone	Autogenous bone grafts in various forms such as solid bone flaps or particulated bone treated with fibrin glue were associated with bone healing which was superior to the empty control defects.
Santos et al. (2015)	To compare the potential of bone repair of collagen sponge with fibrin glue in a rat calvarial defect model.	Tissucol™	Rat calvaria	Fibrin sealant alone	Results have shown the benefits of using collagen sponge and fibrin glue to promote new bone formation in rat calvarial bone defects, the latter being discreetly more advantageous.
Zazgyva et al. (2015)	To establish an experimental model and assesses the effect of glass granules fixed with fibrin compared to fibrin alone as fillers of the osteochondral defects created in the weight-bearing and partial weight-bearing regions of the distal femur in six adult rabbits.	Tisseel™ Lyo	Rabbit distal femur	Bioactive glasses	A commercially available fibrin sealant can be successfully used to retain bioactive glass granules in the defects, offering a fast intra-operative and a subsequently stable fixation.
Hao et al. (2016)	To evaluate the efficacy of local injection of bone mesenchymal stem cells (BMSCs) and fibrin glue in the	Homologous (non-commercial)	Rat distal femur	Allogeneic bone mesenchymal stem cells	The analyzes demonstrated that local injection of BMSCs-seeded fibrin glue promoted

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Author (Date)	Objective	Component origin and/or Trade name	Implantation Site	Mixture with biomaterials or cells	Conclusion
	treatment of atrophic nonunion in an animal model.				atrophic nonunion repair.
Mehrabani et al. (2018)	To investigate the healing and regenerative effects of fibrin glue associated with adipose-derived stem cells (ADSCs) and fibrin glue scaffold alone with autologous bone grafts in experimental mandibular defects of the rabbit.	Autologous	Rabbit mandible	Adipose-derived stem cells	The healing process had a significant increase in the thickness of new cortical bone when fibrin glue scaffold associated with Adipose-derived stem cells was used.
Pomini et al. (2019)	To evaluate the support system formed by a xenograft fibrin sealant associated with photobiomodulation therapy of critical defects in rat calvaria.	Tisseel™ Lyo	Rat calvaria	Demineralized bovine bone	The support system formed by the xenograft fibrin sealant associated with the photobiomodulation therapy protocol had a positive effect on the bone repair process.
Rezaei et al. (2019)	To evaluate the effects of PRP and canine BM-MSCs (marrow-derived mesenchymal stem cells - cBM-MSCs) in combination with a suitable carrier (fibrin glue) on periodontal regeneration.	Autologous	Dog class II furcation defects	PRP, cBM-MSCs and alone	More studies should be done in order to recommend an effective therapeutic approach that induces endogenous regenerative processes, such as cell homing.

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IV. DISCUSSION

The aim of the present study was to perform a systematic review of the homologous fibrin sealants unique properties as a support material for cell adhesion, migration, proliferation and differentiation, and to enhance the physical and biological osteoconductive biomaterials properties.

The advances achieved in reconstructive surgical techniques combined with the development and natural biopolymers improvement by tissue engineering have attracted the attention of several research groups because it is a promising alternative to existing treatments (CHEN; LIU, 2016).

Among the available sealants, fibrin sealants are the most promising in this field due to the combination of excellent biocompatibility, biodegradability and intrinsic bioactivity. Additionally, over the last few decades emphasis has been placed on the importance of fibrin sealant properties in the repair of bone defects in different anatomical regions (NOORI et al., 2017).

As a consequence, it has been searched for alternative methods to obtain blood components, for this reason, a group of researchers from Center for the Study of Venoms and Venomous Animals (CEVAP-Unesp-Botucatu-SP-Brazil) has developed a fibrin adhesive derived from the snake *Crotalus durissus terrificus* venom and the buffalo blood. In its composition, the cryoprecipitate containing fibrinogen and coagulation factors are derived from the buffalo blood (*Bubalus bubalis*), and the functional thrombin by gyroxin, a thrombin-like protein derived from the snake (FERREIRA, 2014; BISCOLA et al., 2017; FERREIRA et al., 2017; MOZAFARI et al., 2018).

Likewise, fibrin biopolymer is a clinically useful tool due to flexibility and applications diversity such as nerve injury repair, chronic ulcer treatment, and bone repair (BUCHAIM et al., 2015, 2016, 2017; DE OLIVEIRA GONÇALVES et al., 2016; ROSSO et al., 2017).

Hence several studies have been reported the use of fibrin sealants as a support for mesenchymal stromal cells (MSCs) and stem cells derived from adipose tissue to facilitate cell attachment, growth and differentiation, allowing enhancement of expansion and survival in the area implanted (RYU et al., 2005; KALBERMATTEN et al., 2008; VADALÀ et al., 2008).

In the same time, the insertion of these cells into the three-dimensional fibrin network has presented promising results in the process of bone repair in several models (ZHANG et al., 2012; STRECKBEIN et al., 2013; HAO et al., 2016; MEHRABANI et al., 2018; REZAEI et al., 2019). In addition, these researchers suggested that fibrin sealant is able to lead a stem cells microenvironment, without deforming its structure, increasing cell survival time and therefore being effective in repairing bone defects.

However, previous results from McDuffee et al. (2012) contradict the previously mentioned results, since they affirm that osteoprogenitor cells inserted in the three-dimensional network formed by fibrin sealant is not able to accelerate the process of bone consolidation.

Despite, the fibrin sealants have beneficial characteristics in the bone regeneration, it is still not possible to have precise control over the microarchitecture of these materials and good tensile strength (GUÉHENNEC; LAYROLLE; DACULSI, 2004). Consequently, is necessary to associate with materials that have great scaffolding potential in many tissue engineering applications in order to minimize or eliminate these limitations. In this way, it allows the manufacture of multifunctional scaffolds with greater resistance mechanics, the graft greater stability in the surgical site, and longer time of cellular support throughout the process of bone repair (AHMED; DARE; HINCKE, 2008).

Several experimental and clinical trials have demonstrated the synergistic characteristics of fibrin sealant associated with materials that have great scaffolding potential led to satisfactory results (REPPENHAGEN et al., 2012; XUAN et al., 2014; LAPPALAINEN et al., 2015; ZAZGYVA et al., 2015; POMINI et al., 2019).

V. CONCLUSION

Due to this background, it is notable that fibrin sealant is one of the promising biopolymers used for tissue engineering and bone regeneration applications. Indeed, the combination with different types of bone grafts, biomolecules and stem cells make this scaffold unique and attractive feature for futures studies.

Nevertheless, there is a necessity for additional studies, for evaluation the concentrations of the components, as a fibrinogen and thrombin, which directly interfere in the density of the network, allowing or not the cellular migration and consequently the bone consolidation.

REFERENCES

[1] AHMED, T. A. E.; DARE, E. V.; HINCKE, M. Fibrin: A Versatile Scaffold for Tissue Engineering Applications. **Tissue Eng Part B Rev.**, v. 14, n. 2, p. 110306231744007, 2008.

[2] BAI, X. et al. Bioactive hydrogels for bone regeneration. **Bioact Mater.**, v. 3, n. 4, p. 401–417, 2018. Disponível em: <https://doi.org/10.1016/j.bioactmat.2018.05.006>.

[3] BISCOLA, N. P. et al. Multiple uses of fibrin sealant for nervous system treatment following injury and disease. **J Venom Anim Toxins Incl Trop Dis.**, v. 23, n. 1, p. 1–11, 2017.

[4] BORIE, E. et al. Platelet-rich fibrin application in dentistry: a literature review. **Int J Clin Exp Med.**, v. 8, n. 5, p. 7922–9, 2015. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/26221349%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4509294>.

[5] BUCHAIM, D. et al. The new heterologous fibrin sealant in combination with low-level laser therapy (LLLT) in the repair of the buccal branch of the facial nerve. **Lasers Med Sci.**, v. 31, n. 5, p. 965–972, 2016. Disponível em: <http://dx.doi.org/10.1007/s10103-016-1939-2>.

[6] BUCHAIM, D. V. et al. Efficacy of Laser Photobiomodulation on Morphological and Functional Repair of the Facial Nerve. **Photomed Laser Surg.**, v. 35, n. 8, p. 442–449, 2017.

[7] BUCHAIM, R. L. et al. Effect of low-level laser therapy (LLLT) on peripheral nerve regeneration using fibrin glue derived from snake venom. **Injury**, v. 46, n. 4, p. 655–660, 2015. Disponível em: <http://dx.doi.org/10.1016/j.injury.2015.01.031>.

[8] CHEN, F. M.; LIU, X. Advancing biomaterials of human origin for tissue engineering. **Prog Polym Sci.**, v. 53, p. 86–168, 2016. Disponível em: <http://dx.doi.org/10.1016/j.progpolymsci.2015.02.004>.

[9] CUNHA, M. R. da et al. Hydroxyapatite and a New Fibrin Sealant Derived from Snake Venom as Scaffold to Treatment of Cranial Defects in Rats. **Materials Research**, v. 18, n. 1, p. 196–203, 2015.

[10] DE OLIVEIRA GONÇALVES, J. et al. Effects of low-level laser therapy on autogenous bone graft stabilized with a new heterologous fibrin sealant. **J Photochem Photobiol B.**, v. 162, p. 663–668, 2016. Disponível em: <http://dx.doi.org/10.1016/j.jphotobiol.2016.07.023>.

[11] DIETRICH, M. et al. Fibrin-based tissue engineering: comparison of different methods of autologous fibrinogen isolation. **Tissue Eng Part C Methods.**, v. 19, n. 3, p. 216–26, 2013. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/22889109>.

[12] FERREIRA, R. S. Autologous or heterologous fibrin sealant scaffold: Which is the better choice? **J Venom Anim Toxins Incl Trop Dis.**, v. 20, n. 1, p. 1–2, 2014.

[13] FERREIRA, R. S. et al. Heterologous fibrin sealant derived from snake venom: From bench to bedside - an overview. **J Venom Anim Toxins Incl Trop Dis.**, v. 23, n. 1, p. 1–12, 2017.

[14] GHIASI, M. S. et al. Bone fracture healing in mechanobiological modeling: A review of principles and methods. **Bone Rep.**, v. 6, p. 87–100, 2017.

[15] GUÉHENNEC, L. Le; LAYROLLE, P.; DACULSI, G. A review of bioceramics and fibrin sealant. **Eur Cell Mater.**, 2004.

[16] HAO, C. et al. Local Injection of Bone Mesenchymal Stem Cells and Fibrin Glue Promotes the Repair of Bone Atrophic Nonunion In Vivo. **Adv Ther.**, v. 33, n. 5, p. 824–833, 2016.

[17] HETTIARATCHI, M. H. et al. Enhanced in vivo retention of low dose BMP-2 via heparin microparticle delivery does not accelerate bone healing in a critically sized femoral defect. **Acta Biomater.**, v. 59, n. May, p. 21–32, 2017. Disponível em: <http://dx.doi.org/10.1016/j.actbio.2017.06.028>.

[18] HONMA, T. et al. Bone formation in rat calvaria ceases within a limited period regardless of completion of defect repair. **Oral Dis.**, v. 14, n. 5, p. 457–464, 2008.

[19] KALBERMATTEN, D. F. et al. Fibrin matrix for suspension of regenerative cells in an artificial nerve conduit. **J Plast Reconstr Aesthet Surg.**, v. 61, n. 6, p. 669–675, 2008.

[20] LAPPALAINEN, O. et al. Healing of rabbit calvarial critical-sized defects using autogenous bone grafts and fibrin glue. **Childs Nerv Syst.**, v. 31, n. 4, p. 581–587, 2015.

[21] LOI, F. et al. Inflammation, Fracture and Bone Repair Florence. **Bone**, v. 2, n. 2, p. 119–130, 2017.

[22] MEHRABANI, D. et al. Comparison of the regenerative effect of adipose-derived stem cells, fibrin glue scaffold, and autologous bone graft in experimental mandibular defect in rabbit. **Dent Traumatol.**, v. 34, n. 6, p. 413–420, 2018.

[23] MOZAFARI, R. et al. Combination of heterologous fibrin sealant and bioengineered human embryonic stem cells to improve regeneration following autogenous sciatic nerve grafting repair. **J Venom Anim Toxins Incl Trop Dis.**, v. 24, n. 1, p. 1–16, 2018.

[24] NOORI, A. et al. A review of fibrin and fibrin composites for bone tissue engineering. **Int J Nanomedicine.**, v. 12, p. 4937–4961, 2017.

[25] PILIPCHUK, S. P. et al. Tissue Engineering for Bone Regeneration and Osseointegration in the Oral Cavity. **Dent Mater**, v. 31, n. 4, p. 317–338, 2015.

[26] POLLOCK, R. et al. Donor site morbidity following iliac crest bone harvesting for cervical fusion: A comparison between minimally invasive and open techniques. **Eur Spine J.**, v. 17, n. 6, p. 845–852, 2008.

[27] POMINI, K. T. et al. Fibrin Sealant Derived from Human Plasma as a Scaffold for Bone Grafts Associated with Photobiomodulation Therapy. **Int J Mol Sci.**, v. 20, n. 7, p. 1761, 2019. Disponível em: <https://www.mdpi.com/1422-0067/20/7/1761>.

[28] POUNTOS, I.; GIANNOUDIS, P. Is there a role of coral bone substitutes in bone repair? **Injury**, v. 47, n. 12, p. 2606–2613, 2016. Disponível em: <http://dx.doi.org/10.1016/j.injury.2016.10.025>.

[29] REPPENHAGEN, S. et al. Biphasic bone substitute and fibrin sealant for treatment of benign bone tumours and tumour-like lesions. **Int Orthop.**, v. 36, n. 1, p. 139–148, 2012.

[30] REZAEI, M. et al. Transplantation of Bone Marrow-Derived Mesenchymal Stem Cells, Platelet-Rich Plasma, and Fibrin Glue for Periodontal Regeneration. **Int J Periodontics Restorative Dent.**, v. 39, n. 1, p. e32–e45, 2019. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/30543731>.

[31] ROSSO, M. et al. Journal of Photochemistry & Photobiology , B : Biology Stimulation of morphofunctional repair of the facial nerve with photobiomodulation , using the end-to-side technique or a new heterologous fibrin sealant. **J Photochem Photobiol B.**, v. 175, n. May, p. 20–28, 2017.

[32] RYU, J. H. et al. Implantation of bone marrow mononuclear cells using injectable fibrin matrix enhances neovascularization in infarcted myocardium. **Biomaterials**, v. 26, n. 3, p. 319–326, 2005.

[33] SEAL, B.; OTERO, T.; PANITCH, A. Polymeric biomaterials for tissue and organ regeneration. **Mater Sci Eng R Rep.**, v. 34, n. 4–5, p. 147–230, 2001. Disponível em: <http://www.sciencedirect.com/science/article/pii/S0927796X01000353?via%3Dihub>.

[34] SHIU, H. et al. Formation of Blood Clot on Biomaterial Implants Influences Bone Healing. **Tissue Eng Part B Rev.**, v. 20, n. 6, p. 697–712, 2014.

https://dx.doi.org/10.22161/ijaers.673 *ISSN: 2349-6495(P) | 2456-1908(O)*

[35] SPICER, P. et al. Evaluation of Bone Regeneration Using the Rat Critical Size Calvarial Defect. **Nat Protoc.**, v. 7, n. 10, p. 1918–1929, 2012. Disponível em: <http://www.nature.com/doifinder/10.1038/nprot.2012.113>.

[36] SPOTNITZ, W. Fibrin Sealant : The Only Approved Hemostat , Sealant , and Adhesive — a Laboratory and Clinical Perspective. **ISRN Surg.**, v. 4, 2014.

[37] STRECKBEIN, P. et al. Reconstruction of critical-size mandibular defects in immunoincompetent rats with human adipose-derived stromal cells. **J Craniomaxillofac Surg.**, v. 41, n. 6, p. 496–503, 2013. Disponível em: <http://dx.doi.org/10.1016/j.jcms.2013.04.002>.

[38] VADALÀ, G. et al. Use of autologous bone marrow cells concentrate enriched with platelet-rich fibrin on corticocancellous bone allograft for posterolateral multilevel cervical fusion. **J Tissue Eng Regen Med.**, v. 6, n. October, p. 135–143, 2008.

[39] WOZNIAK, G. Fibrin sealants in supporting surgical techniques: The importance of individual components. **Cardiovasc Surg.**, v. 11, n. SUPPL. 1, p. 17–21, 2003.

[40] XUAN, F. et al. A comparative study of the regenerative effect of sinus bone grafting with platelet-rich fi brin-mixed Bio-Oss Ò and commercial fi brin-mixed Bio-Oss Ò : An experimental study. **J Craniomaxillofac Surg.**, v. 42, n. 4, p. e47–e50, 2014. Disponível em: <http://dx.doi.org/10.1016/j.jcms.2013.05.029>.

[41] ZAZGYVA, A. M. et al. S53P4 bioactive glass and fibrin glue for the treatment of osteochondral lesions of the knee – A preliminary in vivo study in rabbits. **Rom J Morphol Embryol.**, v. 56, n. 3, p. 1085–1090, 2015.

[42] ZHANG, L. et al. In vivo alveolar bone regeneration by bone marrow stem cells/fibrin glue composition. **Arch Oral Biol.**, v. 57, n. 3, p. 238–244, 2012. Disponível em: <http://dx.doi.org/10.1016/j.archoralbio.2011.08.025>.