Review Article

Nanomaterials in Periodontal Tissue Engineering

Smriti Balaji*, Dr. Priyalochana Gajendran
Saveetha Dental College and Hospital, 162-Masilamani Nagar, Velappanchavadi-77, Chennai, India.
***Corresponding author's E-mail:** smritibalaji@gmail.com

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ABSTRACT

The aim is to understand different nanomaterials used in periodontal tissue engineering. The application of dentistry of Nanomaterials and tissue engineering have revolutionised perspectives. Tissue engineering is based on stem cell, signalling molecule and scaffold trial. Periodontal regeneration remains ideal goal for clinicians in the treatment of various periodontal tissue engineering. Various regenerative treatment modalities used so far have shown limited success. The advancement in nanotechnology has the potential to become important in achieving predictable periodontal regeneration .

Keywords: Nanomaterials, engineering, scaffolds, periodontal, advancements.

INTRODUCTION

Recently, much attention has been paid to the use of nanomaterials in periodontal tissue engineering. Scientists in the field of regenerative engineering are looking for new ways to apply the principles of material science, bioengineering to construct substitutes for biological tissues that will restore and maintain normal function of diseased or injured tissues[1]. A nanomaterial in tissue engineering has revolutionized perspectives and complements traditional restorative/surgery techniques and benefits from recent advances in stem cell biology, genomics and proteomics. Applications of such developed technology in dental science, and periodontics in particular, are no exception as periodontal destruction can be found to increase with older age.

Nanomaterials were used for the first time in dentistry in 2002 with the inclusion of nano fillers in composite resins for dental reconstruction. Nanomaterials have evolved in recent years with significant progress in the development of various metallic and polymeric materials structured in nano scales, and development of various biomaterials that form ideal interfaces with tissues. Using natural processes as a guide, substantial advances have been made at the interface of nanomaterials and biology, including the fabrication of nanofiber materials for three-dimensional cell culture and tissue engineering[1]. Nano particles have been used in therapeutic application are the fact that nano particles exist in the same size domain as proteins.

Nanomaterials

Nanomaterials are materials with components less than 100 nm in atleast one dimension, grains less than 100 nm in size, fibers that are less than 100 nm in diameter, films that are less than 100 nm in thickness in the form of nanopowders, nanoscaffolds, nanogels or nanomembranes. Nanomaterials are being developed for a number of biomedical and biotechnological applications such as drug delivery, enzyme immobilization and DNA transfection. Major nanoparticles are being explored widely for various applications of which the management of periodontal diseases could be a prime target. Major nanomaterials include- nanotubes, nanoplatelets, nanorods, nanofibrils and quantum wires, all of which are less than 100 nm in diameter. Advantages of nanostructures include high colloidal stability, improves dispersibility, capacity to be developed into nanodomains or nanophases leading to unique nanobuilding blocks with inbuilt nanocontrol and nanodelivery systems. Nanomaterials can be organic (eg: chitosan, silk fibroin) or synthetic (eg: PGLA nanoparticles, dendrimers).

Structure and Diseases of Periodontal Tissues

The periodontium is defined as the supporting structures that comprises of root cementum, periodontal ligament, alveolar bone (bone lining the tooth socket) and the part of gingiva facing the tooth i.e dentogingival junction[5].

Cementum is a hard avascular connective tissue that covers the tooth root. Its primary function is to invest and attach the principle periodontal ligament fibers periodontal ligament is a soft specialized connective tissue situated between the cementum and the bone forming the socket wall. It plays a major role in a) supporting the tooth in their sockets b) permitting them to withstand varied forces of mastication and c) acts as a cell reservoir for tissue homeostasis and repair / regeneration.

Alveolar process is the thickened ridge of the bone containing the tooth socket. It consists of outer cortical plates (buccal, lingual, and palatal) of compact bone, a central spongiosa, and bone lining the alveolus (alveolar bone). The alveolar bone plays an important action of support and it is continually renewed in response to functional forces.

Periodontal diseases include gingivitis and periodontitis. Gingivitis is the mildest form of periodontal disease characterized by redness, swelling and bleeding. Gingivitis often leads to periodontitis resulting in destruction of the supporting apparatus of the teeth. There are several direct and indirect mechanisms involved in the initial changes in the superficial tissues and progressive destruction of connective tissue and bone. Direct mechanisms include enzymes released by the plaque bacteria eg: hyaluronidase, collagenase etc. Finally agents produced by the plaque organisms indirectly stimulate the host-mediated responses that lead to tissue destruction. In order to retrieve the damaged tissues, regeneration of these tissues is necessary, which is done using various techniques such as flap surgery, bone grafts and GTR (guided tissue regeneration). However the major drawback of the above techniques is the formation of long junctional epithelium rather than true regeneration. Hence the choice of ideal regenerative technique still remains a debate which leads to the need for tissue engineering which involves scaffolds, signaling molecules and stem cells[39].

Nanomaterials for Periodontal Tissue Engineering

Among the dental and medical field, periodontics was among the first to regenerate the structure and functions of damaged tissues through the use of barriers which were able to replicate the exact regeneration of hard and soft tissues in the periodontal apparatus. Introduction of the use of nanomaterials has led to further advances for example nanopowders and the periodontal membranes required in techniques like GTR and GBR (guided bone regeneration) were obtained from nanotechnological methods such as film casting and electrospinning[4]

The advancement of nanotechnology then allowed to structure membranes with different layers which consisted of core layer and two functional surfaces in contact with the bone (nanoHA) and the epithelium (metronidazole) and the core layer obtained by a central portion of PLCL (polyactidecaprolactone) and by the two layers of PLC/PLA hydrogels. Very interesting are the degree of precision involved in biphasic scaffolds made of FDM (Fusion Deposition modeling) for bone and alectrospun micro fibrous membrane for periodontal ligament deliberating simultaneous regeneration of alveolar bone and periodontal ligament complex.[4]

Types of Nanomaterials

Organic nanomaterials

1) **Chitosan Nanoparticles (CNPs)**
For the past few years, there has been increasing interest in the use of chitosan and chitin for various applications in dental science. Chitosan is obtained from partial deacetylation from chitin which is a positively charged polysaccharide found in crustaceans[7]. Advantages include: biocompatibility, mucus adhesion, low cost, no cytotoxicity[8-13]. Researchers have reinforced bioactive scaffolds containing CNPs incorporated with protein growth factors for bone tissue regeneration[13,14] with promising *in vivo* results. Titanium implants laminated with CNPs loaded with biologically active bone morphogenetic protein-2 (BMP-2) managed to instigate ectopic bone growth on mice[14].CNPs displayed antibacterial properties solely because of their polycationic charge, with higher reactivity in nanoform than in bulk[15,16]. CNPs could be integrated into toothpastes or even used in dental prophylactic therapies aimed at minimizing the bacterial biofilms present in the oral cavity.

2) **Composite chitosan nanoparticles**

Researchers have attempted to combine chitosan particles with different polymeric or inorganic or organic substances due to its disadvantages such as poor mechanical and processing properties or insolubility in common organic solvents.

a) Composite materials have prudent characteristics in biomedical applications because it has the ability to blend the advantages of chitosan with the added substance. Composite CNPs have also been developed for bone tissue engineering. Recent studies have exhibited that bone regeneration could be assisted by PCL(poly-caprolactone) nanofibers scaffolds containing CNPs i) Advantage of chitosan-PCL copolymer is i) its biocompatibility with bone cells[35], ii) nanofiber matrices of PCL-chitosan functionalized with collagen I led to higher alkaline phosphatase (ALP) activity and mineralization of rat bone marrow-derived stromal cells[36].

b) Chitosan-gold nanoparticles have managed to augment osseointegration of dental implants [37] incorporated with anti-inflammatory molecule PPAR (peroxisome proliferator activated receptor gamma) or with the transcription factor c-myb. Chitosan-gold nanoparticles with PPAR were used to modify dental implants in vitro, but also in vivo with rat mandible. These modified implants led to the formation of new bone with high mineral density and reduced inflammation. Since the anti-inflammatory effect of PPAR has been demonstrated in periodontitis[38], chitosan gold nanoparticles can be combined with PPAR for future use in periodontal regeneration.

c) An important bioactive molecule – hydroxyapatite plays a major role in guided bone regeneration. Hence several composite hydroxyapatite-containing nanomaterials have been developed. For example, biocompatible coatings of cellulose acetate nanofibers and composites of hydroxyapatite nanoparticles and chitosan brought about the formation of bone like apatite layer on implants.

3) Silk Fibroin nanoparticles

Silk fibroin is a natural biomaterial that has been studied as a substrate for tissue engineered cartilage, bone, ligaments, nerves and also for drug delivery applications. Silk fibroin is a structural protein isolated from silk fibers separated from the cocoons of the silkworm Bobymexmori[20, 21]. Silk fibroin nanoparticles could have numerous applications in dentistry, but mainly in bone regeneration procedures, where they have been used in the form of nanospheres, nanofibrous membranes, or nanofibrous scaffolds[22]. Studies found that experimental nanofibrous electrospun silk scaffolds incorporated with bone morphogenetic protein-2 supported human mesenchymal stem cells osteogenic differentiation[23]. Also recently, a thin nanofibrous membrane containing silk fibroin/chitosan/ nanohydroxyapatite/ bone morphogenetic protein-2, subcutaneously implanted together with human mesenchymal stem cells, resulted in ectopic bone formation in vivo[24]. The chitin/silk fibroin blend nanofibrous matrix, containing 75% chitin and 25% SF, has been shown to promote excellent cell attachment and spreading for human keratinocytes and fibroblasts[25].

Synthetic organic Nano-delivery systems

1) PGLA Nanoparticles

Poly (lactic-co-glycolic acid) PLGA, is one of the most opportunely developed biodegradable polymers. PLGA has attracted considerable diligence due to its impressive properties: 1. biodegradability and biocompatibility. 2. method of production adapted to various forms of drugs *e.g.* hydrophilic or hydrophobic small molecules or macromolecules and 3. possibility to target nanoparticles to specific organs or cells[26].

Although PLGA nanofibers are widely used in the manufacture of scaffolds for tissue regeneration and despite their biocompatibility, the clinical applications of pure PLGA for bone regeneration are hindered by its poor osteoconductivity[28, 29].

2) Composite PLGA nanoparticles

Since pure PLGA have a drawback of osteo conductivity in bone regeneration, varieties of composite scaffolds have been developed. Nanosized composite PLGA systems have been desirable in inducing osteogenic differentiation of stem cells for example: PLGA/collagen nanofibers with calcium phosphate, PLGA/ poly (3-hydroxybutyrate-co-3-hydroxyvalerate) nanoparticles etc. Some of the PLGA composite nanosystems such as PLGA/collagen/calcium phosphate nanomembrane were able to support osteogenic differentiation on their own while other nanostructures needed the incorporation of growth factors like (bone morphogenetic protein) BMP-2,BMP-7, insulin like growth factor -1. Interestingly, PLGA nanoparticles have future approaches in chondrogenic, adipogenic or osteogenic new tissue formation[5, 6].

3) Dendrimers

Dendrimers are synthetic, highly branched polymers with micelle like behavior. Reports show that dendrimers may be used as releasing-scaffolds for releasing anti-periodontopathogenic agents[30]; implant surface coating with phosphoserine and polylysine-dendrimers do not improve their osteointegration[31] while other studies report that they can build up osteoblast differentiation[32]; poly-amidoamine-dendrimer molecules have anti-adhesive properties and modulate the oral bacterial response; dentine surface coating with poly-amidoamine-dendrimers can induce hydroxidapatite formation and thus contribute to dentinal tube occlusion[33, 34].

4) Lipid nanoparticles and liposomes

Solid lipid nanoparticles are one of the beneficial drug carrier systems which enacts as a solid substitute to carriers such as micro nanoparticles. These particles have several advantages such as physically stable system, small size (50-100 nm),high drug loading, low toxicity and improved delivery of lipophilic active compounds. Unfortunately, there are very few studies that focus on the interaction between these nanoparticles and the biology of oral cavity.

Liposomes are spherical vesicles with a diameter ranging from 20 nm to several micrometers, which are made up of natural lipids like phospholipids with several attributes like non toxicity, non-immunogenic and biodegradable. They are the most employed nanodevices used to encapsulate antibiotics for treating intracellular infections and therefore could have promising applications in periodontology. Recent studies have framed antibiotic incorporating liposomes for use against various periodontal pathogens including liposomes containing metronidazole against S.mutans, chlorhexidine and triclosan for Streptococcus oralis, triclosan against Streptococcus sanguis. Liposomes incorporating bovine lactoferrin (LbLF) could be used for periodontal prevention in patients undergoing orthodontic treatments[36-38].

CONCLUSION

Although the achievement of the goal of complete regeneration of the periodontal tissues (cementum, periodontal ligament and bone) for periodontal management may not be possible for many years, recent developments in nanomaterials and nanotechnology have provided a promising insight into the commercial applications of nanomaterials in the management of periodontal diseases[1]. Despite the various properties , there are certain limitations which have been studied for example PGLA has poor drug loading coupled with high release burst of the drug, and also PGLA gets degraded by hydrolysis to the two initial acids unlike chitosan and silk fibroin which can alter the pH at the delivery site. Other pitfalls related to organic nanoparticles such as chitosan and silk fibroin are variation in properties b) insufficient data of their impact on oral environment.

The combinatorial use of various stem cells, signaling molecules, and nanostructures (with creation of specific rigid or not rigid scaffolds) has already been obtained, in animals, for the regeneration of damaged dental tissues. However, there are still several problems concerning the safety and standardization of techniques that must be solved in the near future before clinical application in humans.

REFERENCES

1. Nanotechnology and its role in the management of periodontal diseases, LING XU E KONG, ZHENG PENG, SI-DONG LI & P. MARK BARTOLD, Periodontology 2000, Vol. 40, 2006, 184–196.
2. Nanodentistry: Combining Nanostructured Materials and Stem Cells for Dental Tissue Regeneration, Thimios A Mitsiadis; Anna Woloszyk; Lucia Jiménez-Rojo, Nanomedicine. 7(11), 2012, 1743-1753.
3. Organic Nanomaterials and Their Applications in the Treatment of Oral Diseases ,Maria Justina Roxana Virlan , Daniela Miricescu, Radu Radulescu, Cristina M. Sabliov, Alexandra Totan, Bogdan Calenic ,and Maria Greabu, MDPI, Received: 15 December 2015; Accepted: 28 January 2016; Published: 9 February 2016.
4. Biopolymer-Based Nanoparticles for Drug/Gene Delivery and Tissue Engineering, Sachiko Kaihara Nitta and Keiji Numata, Int. J. Mol. Sci. 2013, 14, 1629-1654
5. Structure of periodontal tissues in health and disease, ANTONIO NANCI & DIETER D. BOSSHARDT, Periodontology 2000,Vol.40,2006, 11-28
6. Nanomaterials for Tissue Engineering In Dentistry ,Manila Chieruzzi 1,*, Stefano Pagano 2,*, Silvia Moretti ,Roberto Pinna, Egle Milia, Luigi Torre and Stefano Eramo , MDPI, Received: 30 May 2016; Accepted: 18 July 2016; Published: 21 July 2016
7. Electrospun biomimetics caffold of hydroxyapatite/chitosan supports enhanced osteogenic differentiation of mMSCs. Nanotechnology, 5. Peng, H.; Yin, Z.; Liu, H.; Chen, X.; Feng, B.; Yuan, H.; Su, B.; Ouyang, H.; Zhang, Y. 2012, 23, 485102. [PubMed]
8. Applications of chitosan and chitosan derivatives in drug delivery.Bansal, V.; Sharma, P.K.; Sharma, N.; Pal, O.P.; Malviya, R. Adv. Biol. Res. 2011, 5, 28–37.
9. Bernkop-Schnürch, A.; Dünnhaupt, S. Chitosan-based drug delivery systems. Eur. J. Pharm. Biopharm. 81, 2012, 463–469. [PubMed]
10. Laurencin, C.T.; Ashe, K.M.; Henry, N.; Kan, H.M.; Lo, K.W.-H. Delivery of small molecules for bone regenerative engineering: Preclinical studies and potential clinical applications. Drug Discov. Today 19, 2014, 794–800. [PubMed]
11. Sonia, T.; Sharma, C.P. Chitosan and its derivatives for drug delivery perspective. In Chitosan for Biomaterials I;Springer: Heidelberg, Germany, 2011, pp. 23–53.
12. Chen, J.; Pan, P.; Zhang, Y.; Zhong, S.; Zhang, Q. Preparation of chitosan/nano hydroxyapatiteorganic-inorganic hybrid microspheres for bone repair. Colloids Surf. B Biointerfaces 134, 2015, 401–407. [PubMed]
13. Poth, N.; Seiffart, V.; Gross, G.; Menzel, H.; Dempwolf, W. Biodegradable chitosan nanoparticle coatings ontitanium for the delivery of BMP-2. Biomolecules 5, 2015, 3–19. [PubMed]
14. Eap, S.; Ferrand, A.; Schiavi, J.; Keller, L.; Kokten, T.; Fioretti, F.; Mainard, D.; Ladam, G.; Benkirane-Jessel, N.Collagen implants equipped with “fish scale”-like nanoreservoirs of growth factors for bone regeneration. Nanomedicine 9, 2014, 1253–1261. [PubMed]
15. Shrestha, A.; Zhilong, S.; Gee, N.K.; Kishen, A. Nanoparticulates for antibiofilm treatment and effect of agingon its antibacterial activity. J. Endod. 36, 2010, 1030–1035.[PubMed]
16. Shrestha, A.; Kishen, A. The effect of tissue inhibitors on the antibacterial activity of chitosan nanoparticlesand photodynamic therapy. J. Endod. 38, 2012, 1275–1278. [PubMed]
17. Chronopoulou, L.; Nocca, G.; Castagnola, M.; Paludetti, G.; Ortaggi, G.; Sciubba, F.; Bevilacqua, M.; Lupi, A.; Gambarini, G.; Palocci, C. Chitosan based nanoparticles functionalized with peptidomimetic derivatives for oral drug delivery. New Biotechnol. 33, 2016, 23–31. [PubMed
18. Liu, H.; Chen, B.; Mao, Z.; Gao, C. Chitosan nanoparticles for loading of toothpaste actives and adhesion on tooth analogs. J. Appl. Polym. Sci. 2007, 106, 4248–4256.
19. Meinel, L.; Betz, O.; Fajardo, R.; Hofmann, S.; Nazarian, A.; Cory, E.; Hilbe, M.; McCool, J.; Langer, R.;Vunjak-Novakovic, G. Silk based biomaterials to heal critical sized femur defects. Bone 39, 2006, 922–931.
20. Vepari, C.; Kaplan, D.L. Silk as a biomaterial. Prog. Polym.Sci. 2007, 32, 991–1007. [PubMed]
21. Wang, X.; Wenk, E.; Matsumoto, A.; Meinel, L.; Li, C.; Kaplan, D.L. Silk microspheres for encapsulation and controlled release. J. Control. Release 2007, 117, 360–370. [PubMed]
22. Greabu, M.; Virlan, M.J.R.; Calenic, B.; Zaharia, C. Silk fibroin and potential uses in regenerative dentistry—A systematic review. Stomatol. Educ. J. 1, 2015, 108–115
23. Li, C.; Vepari, C.; Jin, H.-J.; Kim, H.J.; Kaplan, D.L. Electrospun silk-BMP-2 scaffolds for bone tissue engineering. Biomaterials 27, 2006, 3115–3124. [PubMed]
24. Shalumon, K.; Lai, G.-J.; Chen, C.-H.; Chen, J.-P. Modulation of bone-specific tissue regeneration by incorporating bone morphogenetic protein and controlling the shell thickness of silk fibroin/chitosan/nanohydroxyapatite core-shell nanofibrous membranes. ACS Appl. Mater. Interfaces 7, 2015, 21170–21181
25. Park, K.E.; Jung, S.Y.; Lee, S.J.; Min, B.-M.; Park, W.H. Biomimetic nanofibrous scaffolds: Preparation and characterization of chitin/silk fibroin blend nanofibers. Int. J. Biol. Macromol. 38, 2006, 165–173.
26. PLGA-based nanoparticles: An overview of biomedical applications, Fabienne Danhiera, Eduardo Ansorenaa, Joana M. Silvaa, b, Régis Cocoa, Aude Le Bretona, Véronique Préata, a Université Catholique de Louvain, Louvain Drug Research Institute, Pharmaceutics and Drug Delivery, Avenue Mounier, B1 73.12, 1200 Brussels, Belgium, Journal of Controlled Release, Volume 161, Issue 2, 20 July 2012, Pages 505–522
27. Pagonis, T.C.; Chen, J.; Fontana, C.R.; Devalapally, H.; Ruggiero, K.; Song, X.; Foschi, F.; Dunham, J.Skobe, Z.; Yamazaki, H. Nanoparticle-based endodontic antimicrobial photodynamic therapy. J. Endod. 36, 2010, 322–328
28. Gentile, P.; Chiono, V.; Carmagnola, I.; Hatton, P.V. An overview of poly(lactic-co-glycolic) acid (PLGA)-based biomaterials for bone tissue engineering. Int. J. Mol. Sci. 15, 2014, 3640–3659.

29. Mehrasa, M.; Asadollahi, M.A.; Ghaedi, K.; Salehi, H.; Arpanaei, A. Electrospun aligned PLGA and PLGA/gelatin nanofibers embedded with silica nanoparticles for tissue engineering. Int. J. Biol. Macromol. 79, 2015, 687–695.

30. Backlund, C.; Sergesketter, A.; Offenbacher, S.; Schoenfisch, M. Antibacterial efficacy of exogenous nitric oxide on periodontal pathogens. J. Dent. Res. 93, 2014, 1089–1094. [PubMed].

31. 31. 4. Bengazi, F.; Lang, N.P.; Canciani, E.; Viganò, P.; Velez, J.U.; Botticelli, D. Osseointegration of implants with dendrimers surface characteristics installed conventionally or with piezosurgery®. A comparative study in the dog.Clin.Oral Implant. Res. 25, 2014, 10–15. [PubMed].

32. Galli, C.; Piemontese, M.; Meikle, S.T.; Santin, M.; Macaluso, G.M.; Passeri, G. Biomimetic coating with phosphoserine-tethered poly(epsilon-lysine) dendrons on titanium surfaces enhances wnt and osteoblastic differentiation. Clin.Oral Implant.Res. 25, 2014, e133–e139.

33. Wang, T.; Yang, S.; Wang, L.; Feng, H. Use of poly (amidoamine) dendrimer for dentinal tubule occlusion: A preliminary study. PLoS ONE 2015, 10, e0124735. [PubMed].

34. Zhang, H.; Yang, J.; Liang, K.; Li, J.; He, L.; Yang, X.; Peng, S.; Chen, X.; Ding, C.; Li, J. Effective dentin restorative material based on phosphate-terminated dendrimer as artificial protein. Colloids Surf. B Biointerfaces 128, 2015, 304–314. [PubMed].

35. Jing, X.; Mi, H.-Y.; Peng, J.; Peng, X.-F.; Turng, L.-S. Electrospun aligned poly (propylene carbonate) microfibers with chitosan nanofibers as tissue engineering scaffolds. Carbohydr.Polym. 117, 2015, 941–949. [CrossRef] [PubMed].

36. Cheng, Y.; Ramos, D.; Lee, P.; Liang, D.; Yu, X.; Kumbar, S.G. Collagen functionalized bioactive nanofiber matrices for osteogenic differentiation of mesenchymal stem cells: Bone tissue engineering. J. Biomed. Nanotechnol. 10, 2014, 287–298. [CrossRef] [PubMed.

37. Bhattarai, G.; Lee, Y.; Lee, M.; Yi, H. Gene delivery of c-myb increases bone formation surrounding oral implants. J. Dent. Res. 92, 2013, 840–845. [CrossRef] [PubMed].

38. Hassumi, M.Y.; Silva-Filho, V.J.; Campos-Júnior, J.C.; Vieira, S.M.; Cunha, F.Q.; Alves, P.M.; Alves, J.B.; Kawai, T.; Gonçalves, R.B.; Napimoga, M.H. Ppar-γ agonist rosiglitazone prevents inflammatory periodontal bone loss by inhibiting osteoclastogenesis. Int. Immunopharmacol. 9, 2009, 1150–1158. [CrossRef] [PubMed].

39. The role of bacteria in periodontal diseases,HARALD LOE',Bulletin of the World Health Organization, 59 (6), 1981, 821-825.

40. Kawazoe, A.; Inubushi, T.; Miyauchi, M.; Ishikado, A.; Tanaka, E.; Tanne, K.; Takata, T. Orally administered liposomal lactoferrin inhibits inflammation-related bone breakdown without interrupting orthodontic tooth movement. J. Periodontol. 84, 2013, 1454–1462

41. Applications of chitosan and chitosan derivatives in drug delivery.Bansal, V.; Sharma, P.K.; Sharma, N.; Pal, O.P.; Malviya, R. Adv. Biol. Res. 5, 2011, 28–37.

42. Bernkop-Schnürch, A.; Dünnhaupt, S. Chitosan-based drug delivery systems. Eur. J. Pharm. Biopharm. 2012,81, 463–469. [PubMed]

43. Laurencin, C.T.; Ashe, K.M.; Henry, N.; Kan, H.M.; Lo, K.W.-H. Delivery of small molecules for boneregenerative engineering: Preclinical studies and potential clinical applications. Drug Discov. Today 19, 2014, 794–800. [PubMed].

44. Sonia, T.; Sharma, C.P. Chitosan and its derivatives for drug delivery perspective. In Chitosan for Biomaterials I;Springer: Heidelberg, Germany, 2011, pp. 23–53.

45. Chen, J.; Pan, P.; Zhang, Y.; Zhong, S.; Zhang, Q. Preparation of chitosan/nano hydroxyapatiteorganic-inorganic hybrid microspheres for bone repair. Colloids Surf. B Biointerfaces 134, 2015, 401–407. [PubMed]

46. Poth, N.; Seiffart, V.; Gross, G.; Menzel, H.; Dempwolf, W. Biodegradable chitosan nanoparticle coatings ontitanium for the delivery of BMP-2. Biomolecules 5, 2015, 3–19. [PubMed].

47. Eap, S.; Ferrand, A.; Schiavi, J.; Keller, L.; Kokten, T.; Fioretti, F.; Mainard, D.; Ladam, G.; Benkirane-Jessel, N.Collagen implants equipped with "fish scale"-like nanoreservoirs of growth factors for bone regeneration.Nanomedicine 9, 2014, 1253–1261. [PubMed].

48. Shrestha, A.; Zhilong, S.; Gee, N.K.; Kishen, A. Nanoparticulates for antibiofilm treatment and effect of agingon its antibacterial activity. J. Endod. 36, 2010, 1030–1035. [PubMed]

49. Shrestha, A.; Kishen, A. The effect of tissue inhibitors on the antibacterial activity of chitosan nanoparticlesand photodynamic therapy. J. Endod. 38, 2012, 1275–1278. [PubMed].

50. Chronopoulou, L.; Nocca, G.; Castagnola, M.; Paludetti, G.; Ortaggi, G.; Sciubba, F.; Bevilacqua, M.; Lupi, A.;Gambarini, G.; Palocci, C. Chitosan based nanoparticles functionalized with peptidomimetic derivatives for oral drug delivery. New Biotechnol. 33, 2016, 23–31. [PubMed.

51. Liu, H.; Chen, B.; Mao, Z.; Gao, C. Chitosan nanoparticles for loading of toothpaste actives and adhesion on tooth analogs. J. Appl. Polym. Sci. 106, 2007, 4248–4256.

52. Meinel, L.; Betz, O.; Fajardo, R.; Hofmann, S.; Nazarian, A.; Cory, E.; Hilbe, M.; McCool, J.; Langer, R.;Vunjak-Novakovic, G. Silk based biomaterials to heal critical sized femur defects. Bone 39, 2006, 922–931.

53. Vepari, C.; Kaplan, D.L. Silk as a biomaterial. Prog.Polym.Sci. 32, 2007, 991–1007. [PubMed]

54. Wang, X.; Wenk, E.; Matsumoto, A.; Meinel, L.; Li, C.; Kaplan, D.L. Silk microspheres for encapsulation and controlled release. J. Control. Release 117, 2007, 360–370. [PubMed]

55. Greabu, M.; Virlan, M.J.R.; Calenic, B.; Zaharia, C. Silk fibroin and potential uses in regenerative dentistry—A systematic review. Stomatol. Educ. J. 2015, 1, 108–115

56. Li, C.; Vepari, C.; Jin, H.-J.; Kim, H.J.; Kaplan, D.L. Electrospun silk-BMP-2 scaffolds for bone tissue engineering. Biomaterials 2006, 27, 3115–3124. [PubMed]

57. Shalumon, K.; Lai, G.-J.; Chen, C.-H.; Chen, J.-P.Modulation of bone-specific tissue regeneration by incorporating bone morphogenetic protein and controlling the shell thickness of silk fibroin/chitosan/nanohydroxyapatite core-shell nanofibrous membranes. ACS Appl. Mater. Interfaces 7, 2015, 21170–21181.

58. Park, K.E.; Jung, S.Y.; Lee, S.J.; Min, B.-M.; Park, W.H. Biomimetic nanofibrous scaffolds: Preparation and characterization of chitin/silk fibroin blend nanofibers. Int. J. Biol. Macromol. 38, 2006, 165–173.

59. PLGA-based nanoparticles: An overview of biomedical applications, Fabienne Danhiera, Eduardo Ansorenaa, Joana M. Silvaa, b, Régis Cocoa, Aude Le Bretona, Véronique Préata, a Université Catholique de Louvain, Louvain Drug Research Institute, Pharmaceutics and Drug Delivery, Avenue Mounier, B1 73.12, 1200 Brussels, Belgium, Journal of Controlled Release,Volume 161, Issue 2, 20 July 2012, Pages 505–522.

60. Pagonis, T.C.; Chen, J.; Fontana, C.R.; Devalapally, H.; Ruggiero, K.; Song, X.; Foschi, F.; Dunham, J.Skobe, Z.; Yamazaki, H. Nanoparticle-based endodontic antimicrobial photodynamic therapy. J. Endod. 2010,36, 322–328

61. Gentile, P.; Chiono, V.; Carmagnola, I.; Hatton, P.V. An overview of poly(lactic-co-glycolic) acid (PLGA)-based biomaterials for bone tissue engineering. Int. J. Mol. Sci. 15, 2014, 3640–3659.

62. Mehrasa, M.; Asadollahi, M.A.; Ghaedi, K.; Salehi, H.; Arpanaei, A. Electrospun aligned PLGA and PLGA/gelatin nanofibers embedded with silica nanoparticles for tissue engineering. Int. J. Biol. Macromol. 79, 2015, 687–695.

63. Backlund, C.; Sergesketter, A.; Offenbacher, S.; Schoenfisch, M. Antibacterial efficacy of exogenous nitric oxide on periodontal pathogens. J. Dent. Res. 93, 2014, 1089–1094. [PubMed].

64. Bengazi, F.; Lang, N.P.; Canciani, E.; Viganò, P.; Velez, J.U.; Botticelli, D. Osseointegration of implants with dendrimers surface characteristics installed conventionally or with piezosurgery®. A comparative study in the dog.Clin.Oral Implant. Res. 25, 2014, 10–15. [PubMed]

65. Galli, C.; Piemontese, M.; Meikle, S.T.; Santin, M.; Macaluso, G.M.; Passeri, G. Biomimetic coating with phosphoserine-tethered poly(epsilon-lysine) dendrons on titanium surfaces enhances wnt and osteoblastic differentiation. Clin.Oral Implant. Res. 25, 2014, e133–e139.

66. Wang, T.; Yang, S.; Wang, L.; Feng, H. Use of poly (amidoamine) dendrimer for dentinal tubule occlusion: A preliminary study. PLoS ONE 10, 2015, e0124735. [PubMed]

67. Zhang, H.; Yang, J.; Liang, K.; Li, J.; He, L.; Yang, X.; Peng, S.; Chen, X.; Ding, C.; Li, J. Effective dentin restorative material based on phosphate-terminated dendrimer as artificial protein. Colloids Surf. B Biointerfaces 128, 2015, 304–314. [PubMed]

68. Jing, X.; Mi, H.-Y.; Peng, J.; Peng, X.-F.; Turng, L.-S. Electrospun aligned poly (propylene carbonate) microfibers with chitosan nanofibers as tissue engineering scaffolds. Carbohydr.Polym. 117, 2015, 941–949. [CrossRef] [PubMed]

69. Cheng, Y.; Ramos, D.; Lee, P.; Liang, D.; Yu, X.; Kumbar, S.G. Collagen functionalized bioactive nanofiber matrices for osteogenic differentiation of mesenchymal stem cells: Bone tissue engineering. J. Biomed. Nanotechnol. 10, 2014, 287–298. [CrossRef] [PubMed.

70. Bhattarai, G.; Lee, Y.; Lee, M.; Yi, H. Gene delivery of c-myb increases bone formation surrounding oral implants. J. Dent. Res. 92, 2013, 840–845. [CrossRef] [PubMed]

71. Hassumi, M.Y.; Silva-Filho, V.J.; Campos-Júnior, J.C.; Vieira, S.M.; Cunha, F.Q.; Alves, P.M.; Alves, J.B.; Kawai, T.; Gonçalves, R.B.; Napimoga, M.H. Ppar-γ agonist rosiglitazone prevents inflammatory periodontal bone loss by inhibiting osteoclastogenesis. Int. Immunopharmacol. 9, 2009, 1150–1158. [CrossRef] [PubMed]

72. The role of bacteria in periodontal diseases, HARALD LOE', Bulletin of the World Health Organization, 59 (6), 1981, 821-825.

73. Kawazoe, A.; Inubushi, T.; Miyauchi, M.; Ishikado, A.; Tanaka, E.; Tanne, K.; Takata, T. Orally administered liposomal lactoferrin inhibits inflammation-related bone breakdown without interrupting orthodontic tooth movement. J. Periodontol. 84, 2013, 1454–1462.

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