

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Nanobiomaterials in periodontal tissue engineering

Mehdi Razavi^{1,2,3,4}, Erfan Salahinejad⁵, Mina Fahmy⁶, Aatif Nowman⁷, Hossein Jazayeri⁷,
Pinkesh Shah⁶, Daryoosh Vashae⁸, Pouya Tayebi⁹, Lobat Tayebi^{10,11}

¹ *Helmerich Advanced Technology Research Center, School of Material Science and Engineering, Oklahoma State University, Tulsa, OK, USA*

² *Dental Materials Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*

³ *BCAST, Institute of Materials and Manufacturing, Brunel University London, Uxbridge, London, UK*

⁴ *Brunel Institute for Bioengineering, Brunel University London, Uxbridge, London, UK*

⁵ *Faculty of Materials Science and Engineering, K.N. Toosi University of Technology, Tehran, Iran*

⁶ *Marquette University School of Dentistry, Milwaukee, WI, USA*

⁷ *Biomedical Sciences, Marquette University, Milwaukee, WI, USA*

⁸ *School of Electrical and Computer Engineering, North Carolina State University, Raleigh, NC, USA*

⁹ *Department of Surgery, Babol University of Medical Sciences, Babol, Mazandaran, Iran*

¹⁰ *Department of Developmental Sciences, Marquette University School of Dentistry, Milwaukee, WI, USA*

¹¹ *Department of Engineering Science, University of Oxford, Oxford, UK*

1. INTRODUCTION

Periodontitis is an illness highlighted by damage to periodontal tissues, including the periodontal ligament (PDL) and cementum, gingiva, and alveolar bone, and can be accompanied by aesthetic problems, tooth loss, and phonetic issues (Savage et al., 2009). About 48% of US adults suffer from chronic periodontitis, and comparable results have been stated in other countries (Albandar, 2005). Scaling and root planing (SRP) and open flap

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

debridement (OFD) are the usual techniques to heal periodontitis (Shue et al., 2012). Moreover, periodontal treatment processes in recent years have included tissue replacement grafts (soft/hard), guided tissue regeneration (GTR), guided bone regeneration (GBR), root biomodifications, and the delivery of growth factors or gene therapies (Ramseier et al., 2012). Different types of graft materials used in the tissue regeneration need to be biocompatible, non-allergenic, and have no risk of disease transmission. Their mechanical integrity and biodegradation rate should also be appropriate (Darby, 2011). Auto-, allo-, xeno-, and synthetic grafts or alloplasts are the most important grafts used for clinical applications. Autografts have been known as the gold standard in graft materials, achieved from the same individual with the ideal properties required. However, the amount of required bone may be restricted and resorption may be unpredictable (Johansson et al., 2001). In addition, microorganisms in the oral cavity may contaminate the autogenous bone (Young et al., 2001). Allografts and xenografts are graft materials derived from the same and other species, respectively, and are widely used in the clinical setting (Reddi et al., 1987). Alloplastic ceramics and polymer materials with natural and synthetic shapes are biocompatible bone graft substitutes with no risk of disease transmission and no need for a donor site. Applying particular biomedical materials is more effectual compared to OFD in enhancing the treatment levels in periodontal diseases, since the conventional treatments are usually unable to support the regeneration of damaged periodontal tissues (Trombelli et al., 2002; Shirakata et al., 2010).

Several investigations have been conducted on the use of tissue engineering to facilitate periodontal regeneration. Tissue engineering is an interdisciplinary field among material science, cell biology, chemistry, medicine, and engineering, which aims to generate 3D

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

tissues by employing a porous material (scaffold), cells and bioactive molecules (Griffith and Swartz, 2006; Mozafari et al., 2012, 2013; Yazdimamaghani et al., 2014a, 2014d; Tahmasbi Rad et al., 2014; Razavi et al., 2014i; Shahini et al., 2014). The main aim of tissue engineering is the preparation of biomaterials that maintain, improve, or restore tissue function (Lanza et al., 2011; Salahinejad et al., 2013b, 2013d; Yazdanpanah et al., 2012; Yazdimamaghani et al., 2014b, 2014c; Shabafrooz et al., 2014a). Tissue engineering can avoid dilemmas related to tissue damage occurring in other treatments including transplants, via mechanical or surgical devices, which needs to address more state-of-the-art solutions to repair tissue in clinics (Castells-Sala et al., 2013; Yazdimamaghani et al., 2015a; Razavi et al., 2014f). The achievement of both the tissue-engineered construct and permanent implants greatly depends on the selected biomaterial. Advancements in nanobiomaterials are revolutionizing our potential to recognize biological complexities and find solutions for biological problems by growing biomimetic and engineering techniques such as surface modification (Yazdimamaghani et al., 2015b; Salahinejad et al., 2012b, 2013a, 2013c; Razavi et al., 2014b; Ghafari-Nazari et al., 2012; Razavi et al., 2014c; Mozafari et al., 2014). Nanocomposites and nanostructured materials are thought to have a key function in hard tissue research, since natural bone tissue is a distinctive model of a nanocomposite (Razavi et al., 2013, 2014e; Rouhani et al., 2013; Shabafrooz et al., 2014b; Salahinejad et al., 2012a; Yazdimamaghani et al., 2013). The molecular structures of living systems, such as proteins, carbohydrates, nucleic acids, and lipids are examples that have exceptional behaviors determined by their size and patterns at the nanoscale. The shift to nanoscience enabled methods has considerably increased our capability to plan and develop superior tissue substitutes (Razavi et al., 2014a). There are research evidences suggesting that a biomaterial

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

composed of nanostructured constituents is biologically preferred (Webster et al., 2000; Li et al., 2006; Razavi et al., 2014d, 2014g). Thus, nanometer structural components are deemed as promising biomaterials. Recent researches are amending accessible usual biomaterials to hold nanoscale characteristics and to enhance new bone creation stimulating prospects in bone tissue engineering (Razavi et al., 2014h, 2015; Heidari et al., 2015). Moreover, in order to improve osteoconductivity and biological fixation, nanophase materials can be employed to increase the mechanical properties of the porous scaffolds and match them to those of the native tissue (Christenson et al., 2007).

Periodontal tissue engineering using nanobiomaterials is still in its infancy but great strides are being made to advance and enhance protocols for clinical applications. In this chapter, we aim to introduce various nanobiomaterials produced by different techniques for periodontal tissue engineering and to focus on their biological characteristics.

2. POLYMER-BASED NANOBIMATERIALS IN PERIODONTAL TISSUE ENGINEERING

2.1. ALGNINATE

In dentistry, preservation has always been a goal of utmost importance. The ability to preserve an individual's natural dentition for the entire lifespan is continuously being improved and researched upon. Tooth loss not only significantly affects the function of mastication, but can also hinder a person's lifestyle. One of the main causes of tooth loss is periodontal disease (Ali et al., 2011). Periodontal disease is characterized as an inflammatory process condition that deteriorates periodontal tissue, alveolar bone, and connective tissue

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

attachment (Loe, 1993). According to a study conducted by the United States Centers for Disease Control and Prevention, nearly 50% of adults aged over 30% and 70% of adults over 65 suffer from periodontal disease (Thornton-Evans et al., 2013). Thus, it is highly important that we consider various possibilities for the treatment of periodontal disease.

In previous years, treatment options for periodontal disease merely used to range from regular cleaning, scaling, and root planing to various forms of surgery, such as bone grafts and flap surgery. In more recent years, however, the concept of tissue regeneration has come into light. This is a process of recreating the tissue and underlying the structure to repair and restore its form and function. Since the periodontium of adults has lost much of its regenerative capabilities, the challenge lies in finding novel ways to incorporate various biomaterials to replace the lost tissue. Materials such as synthetic and biologic polymers, growth factors, and collagen are already being utilized; nonetheless, alginate is another substance that may provide an alternative method of treatment.

Alginate is a polysaccharide which is either derived from brown algae or biosynthesized from bacteria, where the latter provides a greater degree of modification to regulate the production of alginate with favorable characteristics. It is an anionic substance consisting of β -1,4-linked mannuronic acid and α -L-guluronic acid residues linked in a linear, unbranched fashion. Its excellent biocompatibility and biodegradability, coupled with the relative ease in processing and fairly inexpensive cost provide it with many applications (Chemical Society (Great Britain) and Royal Society of Chemistry (Great Britain)). One derivative of alginate that has been widely used is amphiphilic alginate. The hydrophilic structure of alginates reacts with hydrophobic molecules to create particles and gels in aqueous media, commonly used for drug delivery (Lee and Mooney, 2012). Another derivative is cell-interactive alginate. The

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

alginate molecule in this form is coupled with peptide side chains that aid in cellular interactions, 2D and 2D culturing, and scaffolds in tissue engineering (Lee and Mooney, 2012).

For the purpose of tissue engineering, alginate has been widely used in the form of hydrogels. The composition of hydrogels is fairly simple: hydrophilic polymers and water. However, they are appealing due to their biocompatibility and similarity to the extracellular matrices (ECM), as well as the minimally invasive manner in which they can be administered (Drury and Mooney, 2003). There are several methods to gel alginate, including ionic crosslinking, covalent crosslinking, thermal gelation, and cell crosslinking. In ionic crosslinking, one of the most common methods, alginate is crosslinked to a soluble compound with divalent cations. With this approach, the uniformity and strength of the gel are both maintained using the gelation rate and temperature—the slower the gelation rate and decreased temperature, the better (Kuo and Ma, 2001; Augst et al., 2006). Another method of gelling is covalent crosslinking. This method yields a product that may be toxic and leads to elastic deformation (Lee and Mooney, 2012). Finally, the last method that we will discuss is thermal gelation. With the products of this type of gelation, they can be manipulated to possess different characteristics with varying temperature. This in turn leads to a more catered approach.

For periodontal regeneration, it has been shown that alginate scaffolds can indeed serve as an effective bioactive matrix (Srinivasan et al., 2012). Its hydrophilic nature provides it with the ability to have cells easily seeded onto the scaffolds, while crosslinking makes it an insoluble characteristic capable of becoming a scaffold (Srinivasan et al., 2012). In creating an alginate scaffold with bioglass nanoparticle fillers, the addition of nanobioactive glasses will decrease pore size and increase roughness, in addition to decreasing the rate of decomposition, leading

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

to more biocompatibility and capability to regenerate periodontal tissues. In addition, alginate scaffolds seeded with chitosan (CHT), a cationic polymer, are also shown to be effective in helping regenerate lost bone through osteoblast proliferation, better retaining the shape, and promoting vascularization, as compared to a pure CHT scaffold (Li et al., 2005). Given the data, the use of alginate as a biomaterial has definitely come a long way due to its unique and novel properties.

2.2. CHITOSAN

Inflammatory processes related to healing detrimentally affect the regeneration of periodontium. This in turn results in substandard clinical results, using existing therapies (Mota et al., 2012). Epithelial cells are the first cells to migrate to the site of the injury and act to prevent the bone formation. In this regard, GTR is a method which utilizes a membrane to act as a barrier, which prevents epithelial cells from reaching the area where the tissue is injured (Buser et al., 1990). This method provides the necessary period for osteoblast proliferation as well as bone redevelopment (Kay et al., 1997). Specific requirements need to be met when selecting an appropriate GTR membrane.

In the past, collagen has been readily used to produce GTR membranes. However, due to the fact that collagen is derived from animal materials, there are some associated risks of disease transfer, as well as cultural and ethical concerns. Furthermore, the rapid biodegradation and fast resorption rate result in a limited ability to resist membrane collapse, which may allow undesirable cell types from entering the area where the wound resides (Mota et al., 2012; Bunyaratavej and Wang, 2001). Due to the many limitations of using collagen, CHT, as well

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

as other materials, were investigated. CHT presents several useful properties, including flexibility, biocompatibility, immunogenicity, and antibacterial activity, while it also aids with wound healing (Mota et al., 2012). Furthermore, it was found that CHT may act as a template in the restoration of bone defects, due to its ability to support viable osteoblasts (Lahiji et al., 2000).

2.2.1. Chitosan/bioactive glass

Many inorganic materials have been added to CHT to improve its compatibility and bioactivity (Peter et al., 2010b). Zhang and Zhang (2001) found that there was no apatite formed on the surface of CHT scaffolds alone; thus, it was concluded that to improve the bioactivity of the scaffold it must be combined with other bioactive materials, highlighting the importance of composite scaffolds (Kong et al., 2006a). Bioactive glasses (BGs) display superior bioactivity and biocompatibility and can form a direct chemical bond to the surrounding tissues when placed at the site of osseous defects. The addition of BG to CHT membranes should promote GBR and give a twofold purpose, forming a GTR/GBR membrane (Mota et al., 2012).

Since enhanced cell material interactions have been reported on nanophase ceramics in comparison to microphase ceramics (Webster et al., 2000), biomaterials and particles are being engineered in nanoscale sizes. Bioactive glass nanoparticles (BG-NPS) can be synthesized using the sol gel method (Xia and Chang, 2007). In a study by Mota et al. (2012), it was found that in simulated body fluids (SBF), composite membranes containing CHT/BG-NPS, but not pure CHT membranes, were able to promote the deposition of an apatite layer,

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

which is evidence of the osteoconductive potential. Moreover, when Talebian et al. (2014) prepared a nanofibrous scaffold with CHT-containing polyethylene oxide (PEO) and BG using the electrospinning technique, they found that BG containing the nanofibers could in fact induce the formation of hydroxycarbonate apatite on the surface of the composite after 14 days of immersion in SBF. It was concluded from this study that a CHT/PEO/BG composite may be a potential candidate for use in tissue engineering.

2.2.2. Chitosan/nanohydroxyapatite

One of the main components of human hard tissue, including bones and teeth, is hydroxyapatite (HA) (Kong et al., 2005; Zhang et al., 2007). Hydroxyapatite has been regarded for bone tissue engineering due to its good biocompatibility as well as its osteoconductive, non-inflammatory, non-toxic, and non-immunogenic properties (Jarcho, 1981; Zhang and Ma, 1999). Owing to these favorable characteristics and those previously mentioned for CHT, composites of HA and CHT present good osteoconductivity and biodegradability (Zhang et al., 2007). Kong et al. (2005) developed homogeneous nano-HA/chitosan composite scaffolds through in situ synthesis of nano-HA using the wet chemical method. These scaffolds had a porous structure in order to allow cells to be loaded. The porous structure was prepared by using a lyophilization method. It was found that these spongy scaffolds presented good porosity, allowing some cells the space to grow in the 3D scaffold. This composite scaffold was found to show a better biocompatibility than a pure CHT scaffold in addition to allowing a higher proliferation of cells. They also noted that the

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

porous structure of the scaffolds, along with good biocompatibility, may form a hybrid system in vitro for tissue engineering.

In a study conducted by Zhang et al. (2007), HA/chitosan composite scaffolds were obtained by the freeze-drying method. It was shown that compared to the pure CHT scaffold, the 1% HA/chitosan scaffold had better cytocompatibility. In addition, the human periodontal ligament cells (HPLCs) were able to grow favorably on the 1% HA/chitosan scaffold. Moreover, after implanting the HA/chitosan composite combined with HPLCs into athymic mice, it was found that this scaffold was non-toxic and degradable in vivo, concluding that HA/chitosan scaffolds can have a potential purpose in periodontal tissue engineering.

2.2.3. Chitosan gelatin/nanoBG

Bioactive glass ceramics (BGC), developed by Hench in 1991 (Hench, 1991), are osteoconductive silicate-based materials used for repairing bone. Wheeler and colleagues (2001) noted that BCG coatings are in fact superior to HA in their ability for osteointegration. In addition to their ability to affect osteoblast and bone marrow stromal cell proliferation and differentiation (Bosetti and Cannas, 2005), BCGs can also bond to both soft and hard tissues (Verrier et al., 2004). The sol gel method has been used to produce nanobioactive glass ceramics (nBGC) (Xia and Chang, 2007). A chitosan/nBGC composite scaffold was developed and showed adequate swelling and degradation capability in addition to its ability to become bioactive. In this regard, MTT assay, a direct contact test, and cell attachment studies were completed. Results showed no signs of toxicity in the scaffold (Peter et al., 2010a, 2010b).

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

In another study, Peter et al. (2010a) prepared a composite scaffold by merging chitosan gelatin (CG) with nBGC. They found that porous and biodegradable CG/nBGC scaffolds with adequate microporosity for cell infiltration can be acquired via freezing and lyophilization techniques. Their results showed that swelling, as well as the degradation rate of the composite scaffolds, decreased when nBGC was added, while protein adsorption increased. These composite scaffolds showed good bioactivity and the cell attachment was better in comparison to pure CG scaffolds. It was concluded that CG/nBGC scaffolds are promising nanocomposite materials for alveolar bone tissue engineering.

2.2.4. Chitosan/collagen and transforming factor- β 1 DNA

Some recent studies have focused on the use of scaffolds, stem cells, and growth factors for periodontal tissue engineering (Kao et al., 2005). Because protein delivery does not produce adequate improvements in wound healing due in part to ineffective delivery and poor retention in the wound, gene transfer strategies may be used to overcome these limitations (Chandler et al., 2000; Karthikeyan and Pradeep, 2006). Gene-activated matrix (GAM) technology is a platform for gene delivery. Transforming growth factor- β (TGF- β) has been found to have both chemotactic and mitogenic activities towards PDL cells as well as gingival cells (Nishimura and Terranova, 1996). In addition, Matsuda et al. (1992) found that TGF- β 1 upregulates the production of ECM components, including fibronectin, collagen, proteoglycans, and tenascin. A limitation of TGF- β 1 is localizing the delivery of this short-half-life transforming factor to target cells. To tackle this issue and attain a continuous localized delivery of cytokines over a period of time into target cells, the use of gene therapy

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

techniques is under consideration (Wang et al., 2000; Rex et al., 2004). Incorporation of DNA into GAMs and its subsequent prolonged release may provide an ideal method of tissue engineering (Zhang et al., 2006). In the study conducted by Zhang et al. (2006) CHT/collagen composites in combination with plasmid and virus encoding TGF- β 1 were prepared by using the freeze-drying method and assessed for cytocompatibility through seeding HPLCs into scaffold in vitro. Furthermore, HPLCs combined with the scaffold were implanted into athymic mice in order to evaluate biocompatibility in vivo. The results specified that the gene-activated scaffold showed improved cytocompatibility compared to the pure chitosan/collagen one. The scaffold containing TGF- β 1 exhibited the highest proliferation rate, and the expression of type I and type III collagen was upregulated in the TGF- β 1 scaffold used. These results demonstrated that CHT/collagen scaffolds combined with TGF- β 1 are a good substrate candidate for periodontal tissue engineering.

2.3. POLYLACTIDE

Periodontal bone defects can lead to the loss of teeth, which detrimentally affects not only oral cavity function but also one's appearance. To reconstruct these defects, current treatments rely on autologous or allogeneic tissue grafts; however, there are some limitations, like insufficient biocompatibility, residual pain, desorption of bone, limited graft quantity, and donor site morbidity (August et al., 2000; Hartman et al., 2002; Ahlmann et al., 2002; Boone, 2003; Velchuru et al., 2005; Zijderfeld et al., 2004; Holzle et al., 2007). Some recent studies have focused on evaluating the capacity of a tissue-engineered bone complex with osteoconductive scaffolds in alveolar bone defects. In this regard, nanohydroxyapatite

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

collagen poly (L-lactide), nHAC/PLA, is one of the nanobiomaterials which can be used to reconstruct alveolar bone defects. It is as attractive as a bone substitute because the novel biomimetic strategy used in its generation provides properties similar to natural bones. It has been reported that nanohydroxyapatite and collagens are assembled into mineralized fibril bundles, and then these bundles are uniformly distributed in the PLA matrix to form a porous scaffold (Liao et al., 2004). Cell culture and animal model tests show that composite materials are highly osteoconductive, biocompatible, and bioresorbable; however, the possibility of using nHAC/PLA composites for periodontal regeneration still needs further investigation (Liao et al., 2003, 2004, 2005; He et al., 2011).

2.4. POLY(LACTIC-CO-GLYCOLIC ACID)

As a biodegradable polymer, poly(lactic-co-glycolic acid) (PLGA) has been extensively applied for different biomedical uses for a couple of decades due to its good biocompatibility (Wise, 1995). By altering the ratio of LA to GA in PLGA, the molecular weight, crystallinity, and biodegradability of PLGA can be adjusted (Wise, 1995). Moreover, the degradation products of PLGA have not revealed any cytotoxicity. Crystalline PLGA with high molecular weight can be utilized for surgical sutures, bone screws, and nails with suitable mechanical strength, while amorphous PLGA with a low molecular weight can be applied to drug delivery systems (Pulapura and Kohn, 1992).

Park et al. (2009) manufactured hyaluronic acid (HA) PLGA to be used in periodontal barrier membranes. As a natural linear polysaccharide, hyaluronic acid (HA) has also been utilized for diverse medical applications such as drug delivery and tissue engineering (Ohri et al.,

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaee, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

2004), due to its decent biodegradability, biocompatibility, and osteoconductivity. It can also promote angiogenesis and moderate immune responses (Kuo, 2005). HA is typically modified with adipic acid dihydrazide (ADH) in the solvent of water/ethanol. According to SEM images, HA PLGA nanoparticles were produced in a spherical shape with a particle size of around 150 nm (Figure 1). Bilayer-structured HA PLGA/PLGA blended film, with a thickness of about 33 μm at a weight ratio of 1:2, was also developed by a solvent casting method (Figure 1).

A novel amphiphilic biphasic layer was hypothesized to be employed as a periodontal barrier membrane. Hydrophobic PLGA-rich layers prevent the penetration of soft tissue cells into the film-protected space (Nishiyama et al., 2003; Gao et al., 2004), whereas the hydrophilic HA-rich layer stabilizes clots and enamel bone cells to be joined together into the barrier membrane (Sculean et al., 2003; Zitzmann et al., 2003).

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>



Figure 1. SEM micrographs of (a) HA PLGA nanoparticles and (b) HA PLGA/PLGA blended film with a PLGA top layer and an HA-rich bottom layer (Park et al., 2009).

Figure 2 indicates the histological image of bone defect regions recovered after the bone regeneration of control, OSSIX™ membrane, PLGA, and HA PLGA/PLGA films as periodontal barrier membranes for 8 weeks. PLGA and HA PLGA/PLGA films were degraded, and the amount of bone generation for both is comparable to that by the OSSIX™ membrane. The amount of bone regeneration for the HA PLGA/PLGA film was around 63.1% after 3 months, and PLGA film did not show significant bone regeneration, compared to the HA PLGA/PLGA film (Park et al., 2009).

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

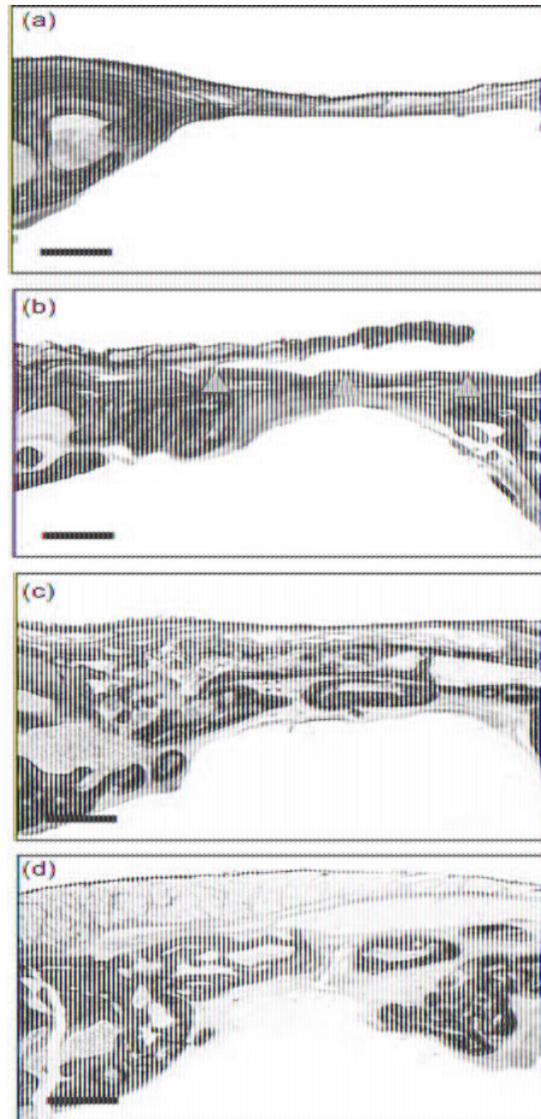


Figure 2. Histological images of calvarial bone defect regions of rats after bone regeneration of (a) control, (b) OSSIX™ membrane, (c) PLGA, and (d) HA PLGA/PLGA for 8 weeks

(scale bar: 1 mm) (Park et al., 2009).

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

2.5. POLYCAPROLACTONE

The theory of GTR is commonly used in the regeneration of periodontal defects by a membrane in order to avoid faster-growing connective tissues and to provide time for the reconstruction of PDL, cementum, and bone (Karring et al., 1993). Moreover, the idea of GBR is engaged in dental implants wherein a material is applied to boost bone ingrowth while preventing fibrous tissue ingrowth into the grafted site (Llambe's et al., 2007; Park and Wang, 2007). As a barrier, membranes can be applied to make space for the gradual regeneration of periodontal and bone tissues and to avoid soft tissue ingrowth. Normally, commercial GTR/GBR materials are made of polymers, including non-degradable and biodegradable ones of polytetrafluoroethylene (PTFE), TefGen, polylactide (PLA), polyglycolide (PGA), polycarbonate, and collagen. The key challenges for these polymers in clinical applications are weak mechanical properties and slow bone production. The most favorable biodegradable material for GTR/GBR needs to be strong, and have the ability to enhance bone formation, and support cell proliferation and differentiation. Bone-like ceramics such as hydroxyapatite, calcium phosphate, and calcium carbonate are added to polymeric membranes to overcome the aforementioned problems (Schwarz et al., 2007; Liao et al., 2005; Fujihara et al., 2005). Compared to micron-sized components, nanosized particles are able to enhance cell adhesion and protein absorption (Webster et al., 2001; Balasundaram et al., 2006).

Polycaprolactone (PCL) is one of the biomaterials known to be a soft and hard tissue biocompatible material, which is being utilized in degradable sutures, implants, drug delivery systems, and bone grafts (Kweon et al., 2003). Yang et al. (2009) developed a GTR/GBR

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

biodegradable membrane system composed of biodegradable poly(ϵ caprolactone) (PCL) and nano-apatite (nAp) using an electrospinning technique. They produced three different compositions, including n0 (nAp:PCL50:100), n25 (nAp:PCL 525:100), and n50 (nAp:PCL 550:100) with fiber diameters from 320 to 430 nm. SEM micrographs of the produced membrane are presented in Figure 3, showing the morphology of the fibers and the distribution of nAp particles through the material (Yang et al., 2009).

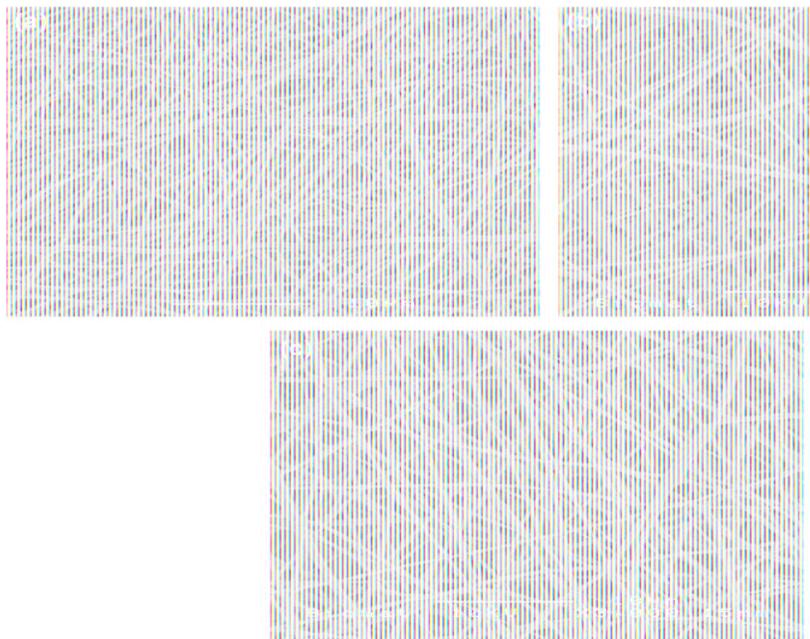


Figure 3. SEM photomicrographs of the three electrospun fibrous membranes: (a) n0; (b) n25; and (c) n50 (Yang et al., 2009).

The addition of nAp improved mechanical properties, including tensile modulus, failure strain, and energy per volume of the membranes, whereas the n25 membrane indicated the highest value among the others (Yang et al., 2009). The uniform distribution of nanoceramic particles may also be the reason for the higher mechanical strength, compared to pure PCL

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

(Kim, 2007). In regard to the bone-forming ability of PCL nAp composites, all fibers were entirely covered by nanotextured cauliflower-like calcium phosphate coatings after 1 month. The partial dissolution of nAp and releasing calcium ions provided the nucleation sites required for the deposition of bioactive minerals (Kokubo, 1998).

As can be observed in Figure 4, cells have been well adhered and spread on the surfaces of all the membranes after 4 days and indicated apparent proliferation towards day 16 (Yang et al., 2009). Different studies have also confirmed that hydroxyapatite provides an appropriate environment for the differentiation of osteoblast-like cells (Ozawa and Kasugai, 1996; Yuasa et al., 2004).

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaee, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

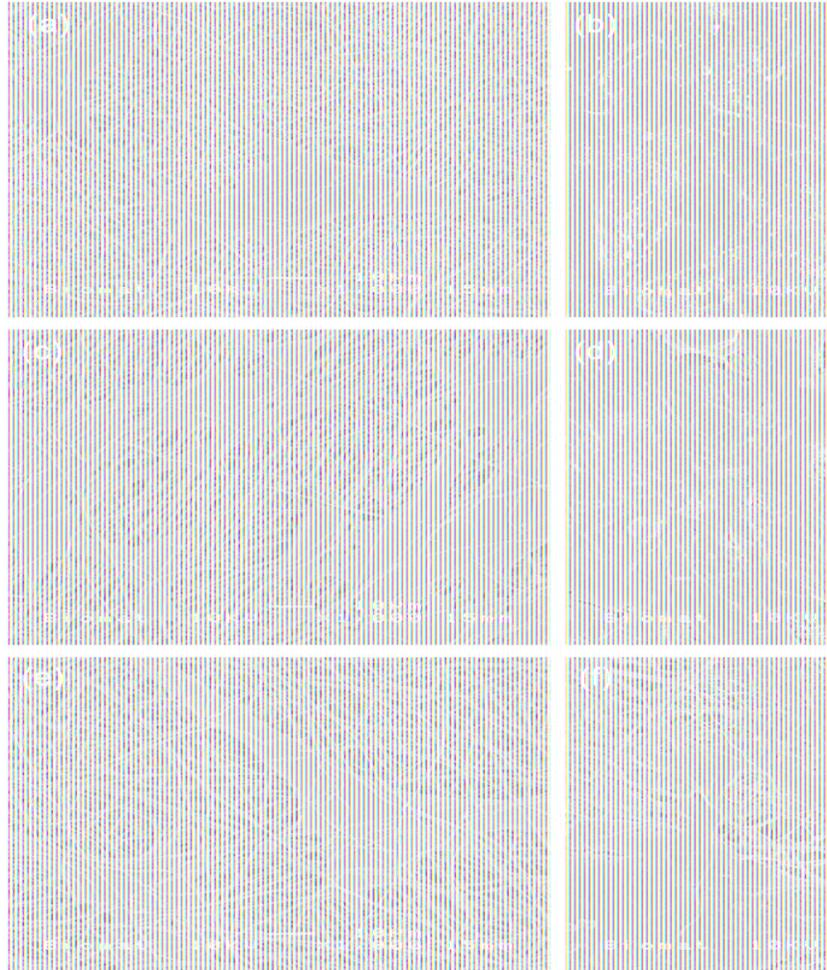


Figure 4. SEM micrographs of rat bone marrow cells cultured on: (a) n0, (c) n25, and (e) n50 for day 4; (b) n0, (d) n25, and (f) n50 for day 16 (Yang et al., 2009).

2.6. POLY(DL-LACTIDE-CO- ϵ -CAPROLACTONE)

The use of poly(DL-lactide-co- ϵ -caprolactone) in periodontal tissue engineering has become instrumental in advancing scaffold successes. Its advantages over traditional homogeneous polymers, such as PLA and PCL, allow for versatility to accommodate patient needs. It also

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

provides a solid foundational material upon functionally graded membranes (FGMs), whose purpose is to consolidate the benefits of various biomaterials, while minimizing ultimate risks and problems each material may pose individually. In each application, PLCL gives the best opportunity for engineers to tailor the polymer in every facet, allowing variations in every aspect of the scaffold, from mechanical strength to biocompatibility. This increases the probability of recreating an environment that is similar to the native ECM.

Copolymerization of various compounds has become necessary in order to serve rigorous demands necessitated in forming scaffolds for tissue engineering. There should be a balance of various factors that must be achieved in scaffold design to ideally serve its function, and copolymerization helps serve this need. Some of these factors, such as porosity (size, design, and structure of pores within a designed scaffold), biodegradability, and mechanical strength, must be optimized in order to achieve the best possible results. One caveat is that many of these factors have inverse relationships and a change in one characteristic can affect another aspect of a scaffold. For example, porosity is a necessary factor to consider when designing a scaffold, as it determines the level of cellular development in damaged tissues, and can serve as the hub of vascularization and bone growth in tissue regeneration. However, an increase in porosity can lead to compromise of the mechanical strength of a given scaffold (Sudarmadji et al., 2011; Chen et al., 2014). Copolymerizations allow a combination of certain monomers and polymers to take advantage of certain characteristics of each respective biomaterial. This copolymerization creates scaffolds that can be customized to suit specific biomedical needs.

Copolymerizations of two aliphatic biodegradable polyesters, PLA and PCL, have proven to be successful in a variety of tissue regeneration and biomedical processes. Individually, both homopolymers of PLA and PCL, as seen above, present advantages and disadvantages in

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

terms of designing a scaffold. PLA is advantageous because of its ability to degrade relatively quickly into non-toxic biodegradable compounds such as lactic acid (Bottino et al., 2012). This means there is a small effect of degradation on the system, as the byproducts naturally leave the body along with other biological wastes. However, PLA has a problem at times in clinical applications due to its high glass transition temperature (Fernandez et al., 2012), creating a crystalline structure at most normal temperatures in a clinical environment. This leads to a low elongation rate in the process, meaning that the polymer cannot handle pressures and forces associated with its clinical applications. PCL, on the other hand, has a very low glass transition temperature of around 65 °C, proving it to be a very strong and elastic material for clinical applications. In addition, it has been successful in steroid delivery in other biomedical applications, testifying to its ability to be compatible in a biological system. However, the downside of PCL is its long degradation period, upwards of 24 months, which makes it unreliable as a biodegradable scaffold (Yang et al., 2001). Ultimately, both polymers have been proven to have reliable characteristics yet are not without shortcomings that are difficult to overcome in clinical applications. This is where the need for polymerization of these two compounds comes into effect. Copolymerizations of these two polymers began in an attempt to harness the capabilities of these two compounds, the elasticity and strength of PCL and the degradation time and degradation products of PLA. To attain the ideal characteristics of PLA and PCL, copolymerization of the compounds is necessitated. The bonding mechanism of PLA and PCL is a ring opening polymerization of the monomers. The change in structure from ring to a product yields several physical characteristics, manifesting themselves in the end product. The structural integrity, degradation rates, and tensile strengths are altered by a variety of factors, ranging from the

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

temperature at which it is synthesized to the ratio of PLA to PCL. However, due to patient variability on a case by-case basis, the ratio of PLA to PCL will vary.

Even though there is variability in the data, general trends by which PLCL exists relative to its homomeric substituents are clear. PLCL has been shown to have degradation times less than both PLA and PCL. This is seemingly due to the decrease in crystallinity, leading to an increase in water absorption by the structure, which increases hydrolytic cleavage in the chemical structure (Jeong et al., 2004). A periodontal scaffold needs to be mechanically stable for 4-6 weeks, and a variety of tests conducted have shown that this can be achieved with an optimized PLCL molecule (Bottino et al., 2011a). Depending on the shape and structure by which the PLCL scaffold is designed, an in vivo placement can last with functional mechanical strength for 15 weeks (Jeong et al., 2004). Tensile strengths and molecular weight also fall in between the values of PCL and PLA, and these features can be advantageous to control when designing a scaffold for a specific purpose. Another factor that can be altered in this copolymerization is the physical state of PLCL at a given temperature. At room temperature, PLCL, depending on the PLA:PCL ratio, can also vary in its physical state, ranging from a hard and gummy solid to an elastomer (Kwon et al., 2005). In terms of periodontal engineering though, the elasticity of the compound is the most important factor. From this, we can realize the benefits that copolymerizations present for periodontal engineering. By altering the production and ultimately components of PLCL, there can be a variety of distinct scaffolds that can be produced.

In general, synthetic polymers like PLCL and PLA are found to be of great benefit in periodontal therapy because of their biodegradability, enabling one surgical procedure to be done rather than two. However, it has been shown that, in general, cell response to these

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

materials is not favorable. On the cellular level, they are defective and present different porosity, fiber diameters, and general fiber defects, which differentiate it from the native ECM and makes biocompatibility difficult (Bottino et al., 2011a). On the other hand, biopolymers, as seen in the previous sections, are ideal in terms of biocompatibility, but have degradation problems in periodontal engineering; that is, they have various structural and mechanical issues that need to be overcome. Similar to homopolymers like PLA and PCL, which were combined to improve characteristics, synthetic polymers like PLCL can be combined with biopolymers like collagen and gelatin, which has been shown to increase biocompatibility and overall tissue regeneration success (Bottino et al., 2011a).

Figure 5 shows a schematic illustration of a spatially designed and functionally graded periodontal membrane (FGM). The use of FGMs enhances the effectiveness of a scaffold by alleviating the drawbacks of using a synthetic polymer scaffold by combining them with biopolymers. FGM design calls for the presence of a core layer (CL) at its center and surface layers (SL), which interact with the surrounding tissue(s) (Chen and Jin, 2010; Bottino et al., 2011a). The graded structure allows clinicians and tissue engineers to use unique materials at different layers. Specifically, in terms of periodontal scaffolds, a FGM can be created with differing materials used on both SL, one to interact with the bone tissue and the other to interact with the epithelial tissue (Bottino et al., 2011a). Thus, specific materials can interact with specific tissues, creating an ideal environment for regeneration. Each of these layers can also be laced with different nanobiomaterials that will further increase the chance of success. The used materials can be both biopolymers, such as collagen, and synthetic polymers, like PLCL.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

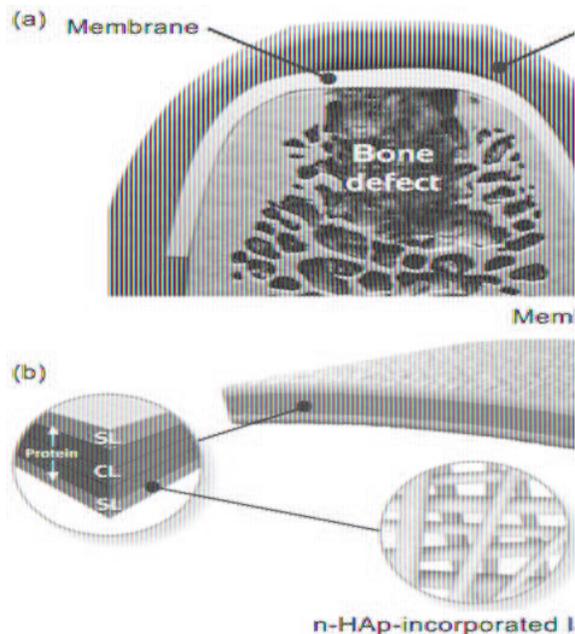


Figure 5. Schematic illustration of a spatially designed and functionally graded periodontal membrane. (a) Membrane placed in a guided bone regeneration scenario and (b) details of the core layer (CL) and the functional surface layers (SL) interfacing bone (nanohydroxyapatite, n-HAp) and epithelial (metronidazole, MET) tissues (Bottino et al., 2011b).

The use of PLCL in FGMs has provided an improvement over its predecessors. The general formulation involves a combination of both polymer and protein, each with varying capacities in their graded structures. One approach that has been proven to be successful in emulating ECM proposes a graded structure, with PLCL at the core and a protein/polymer ternary blend (PLCL:PLA:GEL) as the SL to enhance biocompatibility (Bottino et al., 2011a). The prime benefit of using gelatin, or other natural biopolymers, is its biocompatibility and its ability to increase cell differentiation and adhesion (Lee et al., 2008). The addition of gelatin throughout the graded membrane SL and parts of the CL increases

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

biocompatibility. Gelatin is also added to CL at certain locations because it has been observed that adding biopolymers like gelatin can increase the tensile strength of the compound. The combination of biopolymers and synthetic polymers is optimized to a ratio to best fit the needs of the scaffold, and is then made into a homogeneous mixture via electrospinning.

Other biological materials are added to the SL to enhance the success rate of the scaffold placement. In the case of periodontal scaffolds, the addition of hydroxyapatite nanoparticles (n-HAP), as a core component of bone matter, to the SL in contact with the bone tissue aids the overall biocompatibility (Ferraz et al., 2004). This also allows for greater bone growth in the region, creating an environment that replicates the native ECM. Antibiotics like metronidazole benzoate (MET) can be added to the SL facing the epithelial tissue to prevent infection in the tissue, thereby aiding the overall recovery process (Bottino et al., 2012).

2.7. COLLAGEN

In the recent past, there has been a surge in the application of different materials, including synthetic polymers, biological polymers, and mesenchymal stem cells, for periodontium. In this regard, the integration of collagen, as a structural protein serving as the essential component of connective tissues, into three-dimensional scaffolds which are implanted following periodontal injury, necrosis, or inflammation has attracted wide attention in tissue regeneration. The mimicry of cell and matrix environments surrounding the collagen scaffold is not only indicative of its potent regenerative ability, but also it is necessary for the proper induction of osteoblast differentiation and proliferation, which will result in the repair of

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

bone tissue. The synthesis of matrices surrounding the scaffold is needed to ensure the sustainable integrity of tissues. The goal of this application is to design a replica of the periodontal microenvironment and to preserve the biochemical nature of the periodontium (Ibara et al., 2013). On the other hand, nanoparticle delivery of biological or synthetic agents is extremely effective, due to its histocompatibility and cell attachment capability (Ibara et al., 2013). In addition, three-dimensional scaffolds to be implanted would become very durable and able to withstand compressive forces without breaking if composed of nanoparticles (Ibara et al., 2013). Also, biomineralization and cell adhesion can further be induced, leading to an accelerated healing process (Kong et al., 2006b). Therefore, nanosized particles will aid this process following contact with tissues targeted for reformation. The advent of periodontal tissue engineering with the use of nanomaterials, especially collagen, can significantly facilitate the growth and repair of bone and connective tissues.

Collagen is an advantageous material because it can thicken the periodontium and also attract various fibroblasts that will similarly contribute to tissue regeneration (Bunyaratavej and Wang, 2001). This is widely recognized as an anchor for the structural framework of many tissues in the human body. Collagen is also considered safe for the human body, because it will neither activate an autoimmune response nor produce metabolic byproducts that are toxic, upon biodegradation (Bartold et al., 2006). Over time, the collagen scaffolds stimulate the expression of mRNA for different proteins, most notably bone morphogenic proteins that are responsible for osteogenesis (Xiao et al., 2003). Given these important contributions, collagen can potentially be used in periodontal tissue engineering, but its rate of degradation can be problematic. Surrounding pressures and invasion can contribute to the contraction and

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

degradation of the scaffold, making it difficult to control the optimal repair capability after implantation (Malafaya et al., 2007).

The functional purpose of collagen scaffolds is enhanced by using a variety of nanoparticles, such as fibroblast growth factor 2 (FGF2) and β -tricalcium phosphate (β -TCP). FGF2 and β -TCP strengthen cytocompatibility between the scaffold and surrounding cells to hasten remodeling of the tissue (Ibara et al., 2013). Compared to an implant containing collagen as the sole biological component, one that is composed of collagen in addition to FGF2 and β -TCP greatly exhibits a higher measure of compressive strength and induction of osteoblast differentiation and activity. FGF2 is responsible for revascularization and endothelial cell proliferation. Moreover, it has the ability to transform mesenchymal stem cells into cells with osteogenic capacity, thereby inducing bone reformation. FGF2 is extremely potent and influences a diverse array of tissue components. The proliferation of gingival cells along with the attachment and dispersal of those of the ligament define the growth factor's regenerative role. However, it has a negative feedback on collagen to ensure that it does not harden the periodontium. Clinical trials have been performed to test the efficacy of scaffolds containing the combination of biomolecules, β -TCP and FGF2, which work in cohort to reconstruct the periodontal tissue in mild tissue injury and severe injury alike. The consolidation of these nanoparticles in the collagen scaffolds will also be succeeded by bone augmentation (Murakami, 2011).

Lesions affecting bone on the upper and lower jaws are treated with calcium-based materials in order to produce an osteoinductive effect. To do so, β -TCP is used to coat the scaffold along with collagen and FGF2, as previously mentioned, to propagate an exhaustive regeneration process that will include the affected bone. Despite the fact that β -TCP is

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

relatively novel in application; its biodegradability and favorable clinical outcome make it an essential component of scaffold delivery (Shue et al., 2012). The collagen scaffolds coated with β -TCP and FGF2 act as a hybrid with a complete framework for regenerative capacity. Furthermore, they synthesize ECM and provide a microenvironment for cells to migrate and adhere in the proper orientation for repairing the tissue. The expression of mRNA coding morphogenic proteins and the osteoconductivity induced by this complex are advantageous as a treatment option. FGF2 can restore the blood supply in the periodontium and increase oxygen and nutrient delivery, so that necrosis can be avoided. The potency of collagen as a structural protein throughout the human body gives it a tremendous potential for clinical applications in the future. Conclusively, it is noted that the collagen's effects on tissue healing and cell activity are positively reinforced by the addition of β -TCP and FGF2, producing a mechanically strong, durable complex that is biodegradable and facilitates the periodontal reconstruction mechanism (Ibara et al., 2013).

3. CERAMIC-BASED SCAFFOLDS IN PERIODONTAL TISSUE ENGINEERING

3.1. NANOHYDROXYAPATITE

One of the most widely used biomedical materials in clinical applications for repairing hard tissues is hydroxyapatite (HA) (Benlidayi et al., 2008; Santis et al., 2011; Jensen et al., 2012). HA is able to directly bond to the host hard tissue due to its similarity with the chemical composition and structure of the natural bone (Wang et al., 2007; De Bruijn et al., 1995). However, its inconsistent cell reactions, as a result of its surface properties, have restricted its applications in the regeneration of different locations of bone defects (Wang et al., 2007;

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Deligianni et al., 2000). To solve this problem, HA has been synthesized in nanoparticle configurations to show increased protein adsorption capacity (Wei and Ma, 2004). Furthermore, a newly developed nanocrystalline hydroxyapatite has been introduced for regeneration procedures in bone defects (Gerber et al., 2001). The development of such a nanomaterial, compared to micromaterials, leads to an excellent bonding with surrounding tissues, quick biodegradation characteristics, and absorption of a high number of biomolecules on the surface. High healing rates of osseous defects after employing nano-HA have been reported during in vivo examinations (Henkel et al., 2005). Moreover, the biological integration and complete degradation of the material, because of the existence of osteoclastic cells during the remodeling process, can be obtained (Henkel et al., 2005). Previous research has found more periodontal regeneration within the gap protected by a barrier membrane, compared to the defects with no membrane, regardless of the bone graft materials (Cortellini and Tonetti, 2005).

Lee et al. (2012) generated one-wall periodontal defects in dogs and evaluated tissue responses to the use of a block bone graft consisting of nano-HA. The nano-HA scaffolds were fabricated using HA nanoparticles and a polymeric sponge. All defects were gradually healed with minimal signs of bone inflammation. Radiographic images confirmed the creation of more radiopaque mineralized tissues in defect sites treated with the nano-HA scaffold, compared to the sham surgery control. The feature of the mineralized tissue at the defect sites was different from that of the natural bone tissue; with agglomerated fine particles in close contact with the bone, a denuded root surface, and also a small number of particles monitored outside the graft area. Also, a connective tissue, which contains collagen fibers and fibroblasts filling gaps within the n-HA scaffold grafts, and new vessels were seen

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

around the particles. The amounts of 0.8560.67 and 2.2760.38 mm were reported for bone regeneration of the control and experimental groups, respectively, according to the μ CT analysis (Lee et al., 2012).

The interaction between biomaterials and PDL cells is an important factor for periodontal wound regeneration. For this reason, Kasaj et al. (2008) investigated the interactions of the nano-HA bone graft with the human PDL fibroblasts. The nano-HA had more of an effect on the cell proliferation compared to the ECM proteins fibronectin and type I collagen (Figure 6) (Kasaj et al., 2008).

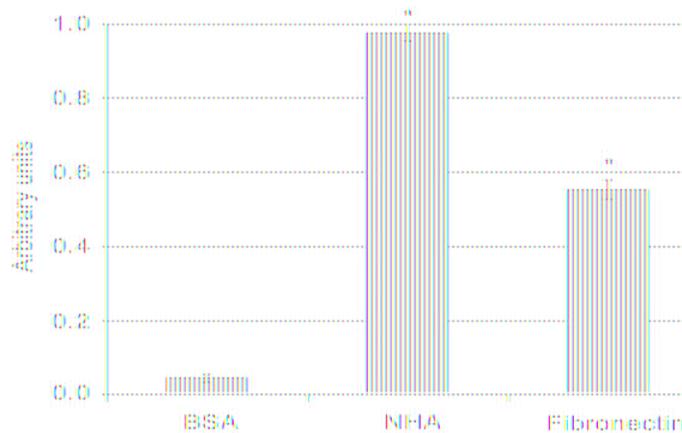


Figure 6. Effect of nano-HA, fibronectin, and collagen on PDL cell proliferation (Kasaj et al., 2008).

Nano-HA is a strong stimulator for PDL cell attachment and proliferation, which may be due to the activation of epidermal growth factor receptor. Moreover, due to the existence of porosity inside the nano-HA bone graft, the autologous proteins and blood plasma may easily be infiltrated through the open pore structure (Gerber et al., 2006). In this regard, Sun et al. (2007) indicated that nanophase HA can encourage PDL fibroblast proliferation and

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

osteogenic differentiation, and has better compatibility and dissolvability in comparison to the dense HA. Differences in the structural, physicochemical and bioactive properties of the nano- and micron-sized HA could be the main reason for the better regenerative and osteoproduative properties.

4. CONCLUSIONS

The most common reason for damage in tooth attachment and loss in adults is periodontitis. Tissue engineering using biodegradable porous materials can be an approach to facilitate the formation of periodontal tissues. Several investigations have been conducted on the use of tissue engineering for periodontal regeneration. In this chapter, we introduced different potential nano-scaled biomaterials, including polymer- and ceramic-based scaffolds, employed in periodontal tissue engineering for an effective regeneration of lost tissues, albeit by focusing on their biological characteristics. In this regard, we considered alginate, CHT, polylactide, poly(lactic-co-glycolic acid), polycaprolactone, poly(DL-lactide-co- ϵ -caprolactone), and collagen as polymer-based nanobiomaterials in periodontal tissue engineering. Nanohydroxyapatite was also discussed as a ceramic-based nanobiomaterial used in the area.

REFERENCES

Ahlmann, E., Patzakis, M., Roidis, N., Shepherd, L., Holtom, P., 2002. Comparison of anterior and posterior iliac crest bone grafts in terms of harvest-site morbidity and functional outcomes. *J. Bone Jt. Surg.* 84, 716-720.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Albandar, J.M., 2005. Epidemiology and risk factors of periodontal diseases. *Dent. Clin. North. Am.* 49, 517-532.

Ali, J., Pramod, K., Tahir, M.A., Ansari, S.H., 2011. Autoimmune responses in periodontal diseases. *Autoimmun. Rev.* 10, 426-431.

Augst, A.D., Kong, H.J., Mooney, D.J., 2006. Alginate hydrogels as biomaterials. *Macromol. Biosci.* 6, 623-633.

August, M., Tompach, P., Chang, Y., Kaban, L., 2000. Factors influencing the long-term outcome of mandibular reconstruction. *J. Oral Maxillofac. Surg.* 58, 731-737.

Balasundaram, G., Sato, M., Webster, T.J., 2006. Using hydroxyapatite nanoparticles and decreased crystallinity to promote osteoblast adhesion similar to functionalizing with RGD. *Biomaterials* 27, 2798-2805.

Bartold, P.M., Xiao, Y., Lyngstaadas, S.P., Paine, M.L., Snead, M.L., 2006. Principles and applications of cell delivery systems for periodontal regeneration. *Periodontol.* 2000, 41, 123-135.

Benlidayi, M.E., Ku"rkcu", M., Oz, I.A., Sertdemir, Y., 2008. Comparison of two different forms of bovine-derived hydroxyapatite in sinus augmentation and simultaneous implant placement: an experimental study. *Int. J. Oral Maxillofac. Implants* 24, 704-711.

Boone, D.W., 2003. Complications of iliac crest graft and bone grafting alternatives in foot and ankle surgery. *Foot Ankle Clin.* 8, 1-14.

Bosetti, M., Cannas, M., 2005. The effect of bioactive glasses on bone marrow stromal cells differentiation. *Biomaterials* 26, 3873-3879.

Bottino, M.C., Thomas, V., Janowski, G.M., 2011a. A novel spatially designed and functionally graded electrospun membrane for periodontal regeneration. *Acta Biomater.* 7, 216-224.

Bottino, M.C., Thomas, V., Schmidt, G., Vohra, Y.K., Chu, T.M., Kowolik, M.J., et al., 2012. Recent advances in the development of GTR/GBR membranes for periodontal regeneration—a materials perspective. *Dent. Mater.* 28, 703-721.

Bunyaratavej, P., Wang, H.-L., 2001. Collagen membranes: a review. *J. Periodontol.* 72, 215-229.

Buser, D., Bra"gger, U., Lang, N., Nyman, S., 1990. Regeneration and enlargement of jaw bone using guided tissue regeneration. *Clin. Oral Implants Res.* 1, 22-32.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Castells-Sala, C., Alemany-Ribes, M., Fernandez-Munos, T., Recha-Sancho, L., LopezChicon, P., Aloy-Reverte, C., et al., 2013. Current applications of tissue engineering in biomedicine. *J. Biochip Tissue Chip S2*: 004.

Chandler, L.A., Ma, C., Gonzalez, A.M., Doukas, J., Nguyen, T., Pierce, G.F., et al., 2000. Matrix-enabled gene transfer for cutaneous wound repair. *Wound Repair Regen.* 8, 473-479.

Chemical Society (Great Britain) & Royal Society of Chemistry (Great Britain), *Carbohydrate chemistry. A specialist periodical report*. London: Royal Society of Chemistry.

Chen, F.M., Jin, Y., 2010. Periodontal tissue engineering and regeneration: current approaches and expanding opportunities. *Tissue Eng. B. Rev.* 16, 219-255.

Chen, Q., Bairo, F., Spriano, S., Pugno, N.M., Vitale-Brovarone, C., 2014. Modelling of the strength porosity relationship in glass-ceramic foam scaffolds for bone repair. *J. Eur. Ceram. Soc.* 34, 2663-2673.

Christenson, E.M., Anseth, K.S., Van Den Beucken, J.J., Chan, C.K., Ercan, B., Jansen, J.A., et al., 2007. Nanobiomaterial applications in orthopedics. *J. Orthop. Res.* 25, 11-22.

Cortellini, P., Tonetti, M.S., 2005. Clinical performance of a regenerative strategy for intrabony defects: scientific evidence and clinical experience. *J. Periodontol.* 76, 341-350.

Darby, I., 2011. Periodontal materials. *Aust. Dent. J.* 56, 107-118.

De Bruijn, J., Van Blitterswijk, C., Davies, J., 1995. Initial bone matrix formation at the hydroxyapatite interface in vivo. *J. Biomed. Mater. Res.* 29, 89-99.

Deligianni, D.D., Katsala, N.D., Koutsoukos, P.G., Missirlis, Y.F., 2000. Effect of surface roughness of hydroxyapatite on human bone marrow cell adhesion, proliferation, differentiation and detachment strength. *Biomaterials* 22, 87-96.

Drury, J.L., Mooney, D.J., 2003. Hydrogels for tissue engineering: scaffold design variables and applications. *Biomaterials* 24, 4337-4351.

Fernandez, J., Etxeberria, A., Sarasua, J.R., 2012. Synthesis, structure and properties of poly(L-lactide-co-epsilon-caprolactone) statistical copolymers. *J. Mech. Behav. Biomed. Mater.* 9, 100-112.

Ferraz, M.P., Monteiro, F.J., Manuel, C.M., 2004. Hydroxyapatite nanoparticles: a review of preparation methodologies. *J Appl. Biomater. Biomech.* 2, 74-80.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

- Fujihara, K., Kotaki, M., Ramakrishna, S., 2005. Guided bone regeneration membrane made of polycaprolactone/calcium carbonate composite nano-fibers. *Biomaterials* 26, 4139-4147.
- Gao, X., Cui, Y., Levenson, R.M., Chung, L.W., Nie, S., 2004. In vivo cancer targeting and imaging with semiconductor quantum dots. *Nat. Biotechnol.* 22, 969-976.
- Gerber, T., Traykova, T., Henkel, K.-O., Bienengra"ber, V., 2001. A new sol gel derived bone grafting material. *Key Eng. Mater.* 218, 399-404.
- Gerber, T., Holzhu"ter, G., Go"tz, W., Bienengra"ber, V., Henkel, K.-O., Rumpel, E., 2006. Nanostructuring of biomaterials—a pathway to bone grafting substitute. *Eur. J. Trauma* 32, 132-140.
- Ghafari-Nazari, A., Moztarzadeh, F., Rabiee, S.M., Rajabloo, T., Mozafari, M., Tayebi, L., 2012. Antibacterial activity of silver photodeposited nepheline thin film coatings. *Ceram. Int.* 38, 5445-5451.
- Griffith, L.G., Swartz, M.A., 2006. Capturing complex 3D tissue physiology in vitro. *Nat. Rev. Mol. Cell. Biol.* 7, 211-224.
- Hartman, E.H., Spauwen, P.H., Jansen, J.A., 2002. Donor-site complications in vascularized bone flap surgery. *Invest. Surg.* 15, 185-197.
- He, H., Yu, J., Cao, J., Wang, D., Zhang, H., Liu, H., 2011. Biocompatibility and osteogenic capacity of periodontal ligament stem cells on nHAC/PLA and HA/TCP scaffolds. *J. Biomater. Sci. Polym. Ed.* 22, 179-194.
- Heidari, F., Bahrololoom, M.E., Vashae, D., Tayebi, L., 2015. In situ preparation of iron oxide nanoparticles in natural hydroxyapatite/chitosan matrix for bone tissue engineering application. *Ceram. Int.* 41, 3094-3100.
- Hench, L.L., 1991. Bioceramics: from concept to clinic. *J. Am. Ceram. Soc.* 74, 1487-1510.
- Henkel, K.-O., Bienengra"ber, V., Lenz, S., Gerber, T., 2005. Comparison of a new kind of calcium phosphate formula versus conventional calcium phosphate matrices in treating bone defects—a long-term investigation in pigs. *Key Eng. Mater.* 284, 885-888.
- Ho"lzle, F., Kesting, M., Ho"lzle, G., Watola, A., Loeffelbein, D., Ervens, J., et al., 2007. Clinical outcome and patient satisfaction after mandibular reconstruction with free fibula flaps. *Int. J. Oral Maxillofac. Surg.* 36, 802-806.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaee, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Ibara, A., Miyaji, H., Fugetsu, B., Nishida, E., Takita, H., Tanaka, S., et al., 2013. Osteoconductivity and biodegradability of collagen scaffold coated with nano- β -TCP and fibroblast growth factor 2. *J. Nanomater.* 2013, 46.

Jarcho, M., 1981. Calcium-phosphate ceramics as hard tissue prosthetics. *Clin. Orthop. Relat. Res.*, 259-278.

Jensen, T., Schou, S., Stavropoulos, A., Terheyden, H., Holmstrup, P., 2012. Maxillary sinus floor augmentation with Bio-Oss or Bio-Oss mixed with autogenous bone as graft: a systematic review. *Clin. Oral Implants Res.* 23, 263-273.

Jeong, S.I., Kim, B.S., Kang, S.W., Kwon, J.H., Lee, Y.M., Kim, S.H., et al., 2004. In vivo biocompatibility and degradation behavior of elastic poly(L-lactide-co-epsilon-caprolactone) scaffolds. *Biomaterials* 25, 5939-5946.

Johansson, B., Grepe, A., Wannfors, K., Hirsch, J., 2001. A clinical study of changes in the volume of bone grafts in the atrophic maxilla. *Dento. Maxillofac. Radiol.* 30, 157-161.

Kao, R.T., Conte, G., Nishimine, D., Dault, S., 2005. Tissue engineering for periodontal regeneration. *J. Calif. Dent. Assoc.* 33, 205-215.

Karring, T., Nyman, S., Gottlow, J., Laurell, L., 1993. Development of the biological concept of guided tissue regeneration—animal and human studies. *Periodontol.* 2000 1, 26-35.

Karthikeyan, B., Pradeep, A., 2006. Gene therapy in periodontics: a review and future implications. *J. Contemp. Dent. Pract.* 7, 83-91.

Kasaj, A., Willershausen, B., Reichert, C., Gortan-Kasaj, A., Zafiroopoulos, G.-G., Schmidt, M., 2008. Human periodontal fibroblast response to a nanostructured hydroxyapatite bone replacement graft in vitro. *Arch. Oral Biol.* 53, 683-689.

Kay, S., Wisner-Lynch, L., Marxer, M., Lynch, S., 1997. Guided bone regeneration: integration of a resorbable membrane and a bone graft material. *Prac. Periodontics Aesthet. Dent.* 9, 185-194.

Kim, H.W., 2007. Biomedical nanocomposites of hydroxyapatite/polycaprolactone obtained by surfactant mediation. *J. Biomed. Mater. Res. A* 83, 169-177.

Kokubo, T., 1998. Apatite formation on surfaces of ceramics, metals and polymers in body environment. *Acta Mater.* 46, 2519-2527.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashaei, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Kong, L., Gao, Y., Cao, W., Gong, Y., Zhao, N., Zhang, X., 2005. Preparation and characterization of nano-hydroxyapatite/chitosan composite scaffolds. *J. Biomed. Mater. Res. A* 75, 275-282.

Kong, L., Gao, Y., Lu, G., Gong, Y., Zhao, N., Zhang, X., 2006a. A study on the bioactivity of chitosan/nano-hydroxyapatite composite scaffolds for bone tissue engineering. *Eur. Polym. J.* 42, 3171-3179.

Kong, L.X., Peng, Z., Li, S.D., Bartold, P.M., 2006b. Nanotechnology and its role in the management of periodontal diseases. *Periodontol.* 2000 40, 184-196.

Kuo, J., 2005. *Practical Aspects of Hyaluronan Based Medical Products*. CRC Press, Taylor & Francis Group, US.

Kuo, C.K., Ma, P.X., 2001. Ionically crosslinked alginate hydrogels as scaffolds for tissue engineering: part 1. Structure, gelation rate and mechanical properties. *Biomaterials* 22, 511-521.

Kweon, H., Yoo, M.K., Park, I.K., Kim, T.H., Lee, H.C., Lee, H.-S., et al., 2003. A novel degradable polycaprolactone networks for tissue engineering. *Biomaterials* 24, 801-808.

Kwon, I.K., Kidoaki, S., Matsuda, T., 2005. Electrospun nano- to microfiber fabrics made of biodegradable copolyesters: structural characteristics, mechanical properties and cell adhesion potential. *Biomaterials* 26, 3929-3939.

Lahiji, A., Sohrabi, A., Hungerford, D.S., Frondoza, C.G., 2000. Chitosan supports the expression of extracellular matrix proteins in human osteoblasts and chondrocytes. *J. Biomed. Mater. Res.* 51, 586-595.

Lanza, R., Langer, R., Vacanti, J.P., 2011. *Principles of Tissue Engineering*. Academic Press.

Lee, K.Y., Mooney, D.J., 2012. Alginate: properties and biomedical applications. *Prog. Polym. Sci.* 37, 106-126.

Lee, J., Tae, G., Kim, Y.H., Park, I.S., Kim, S.H., Kim, S.H., 2008. The effect of gelatin incorporation into electrospun poly(L-lactide-co-epsilon-caprolactone) fibers on mechanical properties and cytocompatibility. *Biomaterials* 29, 1872-1879.

Lee, J.-S., Park, W.-Y., Cha, J.-K., Jung, U.-W., Kim, C.-S., Lee, Y.-K., et al., 2012. Periodontal tissue reaction to customized nano-hydroxyapatite block scaffold in onewall intrabony defect: a histologic study in dogs. *J. Periodontal. Implant Sci.* 42, 50-58.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

- Li, W.-J., Jiang, Y.J., Tuan, R.S., 2006. Chondrocyte phenotype in engineered fibrous matrix is regulated by fiber size. *Tissue Eng.* 12, 1775-1785.
- Li, Z., Ramay, H.R., Hauch, K.D., Xiao, D., Zhang, M., 2005. Chitosan alginate hybrid scaffolds for bone tissue engineering. *Biomaterials* 26, 3919-3928.
- Liao, S., Guan, K., Cui, F., Shi, S., Sun, T., 2003. Lumbar spinal fusion with a mineralized collagen matrix and rhBMP-2 in a rabbit model. *Spine* 28, 1954-1960.
- Liao, S., Cu, F., Zhang, W., Feng, Q., 2004. Hierarchically biomimetic bone scaffold materials: nano-HA/collagen/PLA composite. *J. Biomed. Mater. Res. B Appl. Biomater.* 69, 158-165.
- Liao, S., Wang, W., Uo, M., Ohkawa, S., Akasaka, T., Tamura, K., et al., 2005. A threelayered nano-carbonated hydroxyapatite/collagen/PLGA composite membrane for guided tissue regeneration. *Biomaterials* 26, 7564-7571.
- Llambe's, F., Silvestre, F.-J., Caffesse, R., 2007. Vertical guided bone regeneration with bioabsorbable barriers. *J. Periodontol.* 78, 2036-2042.
- Loe, H., 1993. Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* 16, 329-334.
- Malafaya, P.B., Silva, G.A., Reis, R.L., 2007. Natural-origin polymers as carriers and scaffolds for biomolecules and cell delivery in tissue engineering applications. *Adv. Drug Deliv. Rev.* 59, 207-233.
- Matsuda, N., Lin, W.-L., Kumar, N., Cho, M., Genco, R., 1992. Mitogenic, chemotactic, and synthetic responses of rat periodontal ligament fibroblastic cells to polypeptide growth factors in vitro. *J. Periodontol.* 63, 515-525.
- Mota, J., Yu, N., Caridade, S.G., Luz, G.M., Gomes, M.E., Reis, R.L., et al., 2012. Chitosan/bioactive glass nanoparticle composite membranes for periodontal regeneration. *Acta Biomater.* 8, 4173-4180.
- Mozafari, M., Vashae, D., Tayebi, L., Mehraien, M., 2012. *Electroconductive Nanocomposite Scaffolds: A New Strategy into Tissue Engineering and Regenerative Medicine*. INTECH Open Access Publisher.
- Mozafari, M., Salahinejad, E., Shabafrooz, V., Yazdimamaghani, M., Vashae, D., Tayebi, L., 2013. Multilayer bioactive glass/zirconium titanate thin films in bone tissue engineering and regenerative dentistry. *Int. J. Nanomed.* 8, 1665.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, Nanobiomaterials in Hard Tissue Engineering, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Mozafari, M., Salahinejad, E., Sharifi-Asl, S., Macdonald, D., Vashae, D., Tayebi, L., 2014. Innovative surface modification of orthopaedic implants with positive effects on wettability and in vitro anti-corrosion performance. *Surf. Eng.* 30, 688-692.

Murakami, S., 2011. Periodontal tissue regeneration by signaling molecule(s): what role does basic fibroblast growth factor (FGF-2) have in periodontal therapy? *Periodontol.* 2000 56, 188-208.

Nishimura, F., Terranova, V., 1996. Comparative study of the chemotactic responses of periodontal ligament cells and gingival fibroblasts to polypeptide growth factors. *J. Dent. Res.* 75, 986-992.

Nishiyama, N., Okazaki, S., Cabral, H., Miyamoto, M., Kato, Y., Sugiyama, Y., et al., 2003. Novel cisplatin-incorporated polymeric micelles can eradicate solid tumors in mice. *Cancer Res.* 63, 8977-8983.

Ohri, R., Hahn, S.K., Hoffman, A.S., Stayton, P.S., Giachelli, C.M., 2004. Hyaluronic acid grafting mitigates calcification of glutaraldehyde-fixed bovine pericardium. *J. Biomed. Mater. Res. A.* 70, 328-334.

Ozawa, S., Kasugai, S., 1996. Evaluation of implant materials (hydroxyapatite, glassceramics, titanium) in rat bone marrow stromal cell culture. *Biomaterials* 17, 23-29.

Park, S.-H., Wang, H.-L., 2007. Clinical significance of incision location on guided bone regeneration: human study. *J. Periodontol.* 78, 47-51.

Park, J.K., Yeom, J., Oh, E.J., Reddy, M., Kim, J.Y., Cho, D.-W., et al., 2009. Guided bone regeneration by poly (lactic-co-glycolic acid) grafted hyaluronic acid bi-layer films for periodontal barrier applications. *Acta Biomater.* 5, 3394-3403.

Peter, M., Binulal, N., Nair, S., Selvamurugan, N., Tamura, H., Jayakumar, R., 2010a. Novel biodegradable chitosan gelatin/nano-bioactive glass ceramic composite scaffolds for alveolar bone tissue engineering. *Chem. Eng. J.* 158, 353-361.

Peter, M., Binulal, N., Soumya, S., Nair, S., Furuike, T., Tamura, H., et al., 2010b. Nanocomposite scaffolds of bioactive glass ceramic nanoparticles disseminated chitosan matrix for tissue engineering applications. *Carbohydr. Polym.* 79, 284-289.

Pulapura, S., Kohn, J., 1992. Trends in the development of bioresorbable polymers for medical applications. *J. Biomater. Appl.* 6, 216-250.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Ramseier, C.A., Rasperini, G., Batia, S., Giannobile, W.V., 2012. Advanced reconstructive technologies for periodontal tissue repair. *Periodontology* 2000 59, 185-202.

Razavi, M., Fathi, M., Savabi, O., Razavi, S.M., Beni, B.H., Vashae, D., et al., 2013. Surface modification of magnesium alloy implants by nanostructured bredigite coating. *Mater. Lett.* 113, 174-178.

Razavi, M., Fathi, M., Savabi, O., Beni, B.H., Vashae, D., Tayebi, L., 2014a. Nanostructured merwinite bioceramic coating on Mg alloy deposited by electrophoretic deposition. *Ceram. Int.* 40, 9473-9484.

Razavi, M., Fathi, M., Savabi, O., Beni, B.H., Vashae, D., Tayebi, L., 2014b. Surface microstructure and in vitro analysis of nanostructured akermanite ($\text{Ca}_2\text{MgSi}_2\text{O}_7$) Coating on biodegradable magnesium alloy for biomedical applications. *Colloids Surf. B Biointerfaces* 117, 432-440.

Razavi, M., Fathi, M., Savabi, O., Razavi, S.M., Beni, B.H., Vashae, D., et al., 2014c. Controlling the degradation rate of bioactive magnesium implants by electrophoretic deposition of akermanite coating. *Ceram. Int.* 40, 3865-3872.

Razavi, M., Fathi, M., Savabi, O., Razavi, S.M., Heidari, F., Manshaei, M., et al., 2014d. In vivo study of nanostructured diopside ($\text{CaMgSi}_2\text{O}_6$) coating on magnesium alloy as biodegradable orthopedic implants. *Appl. Surf. Sci.* 313, 60-66.

Razavi, M., Fathi, M., Savabi, O., Vashae, D., Tayebi, L., 2014e. Improvement of biodegradability, bioactivity, mechanical integrity and cytocompatibility behavior of biodegradable mg based orthopedic implants using nanostructured bredigite ($\text{Ca}_7\text{MgSi}_4\text{O}_{16}$) bioceramic coated via ASD/EPD technique. *Ann. Biomed. Eng.* 42, 2537-2550.

Razavi, M., Fathi, M., Savabi, O., Vashae, D., Tayebi, L., 2014f. In vitro analysis of electrophoretic deposited fluoridated hydroxyapatite coating on micro-arc oxidized AZ91 magnesium alloy for biomaterials applications. *Metall. Mater. Trans. A*, 1-11.

Razavi, M., Fathi, M., Savabi, O., Vashae, D., Tayebi, L., 2014g. In vitro study of nanostructured diopside coating on Mg alloy orthopedic implants. *Mater. Sci. Eng. C* 41, 168-177.

Razavi, M., Fathi, M., Savabi, O., Vashae, D., Tayebi, L., 2014h. In vivo study of nanostructured akermanite/PEO coating on biodegradable magnesium alloy for biomedical applications. *J. Biomed. Mater. Res. Part A*.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, Nanobiomaterials in Hard Tissue Engineering, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Razavi, M., Fathi, M.H., Savabi, O., Vashae, D., Tayebi, L., 2014i. Biodegradation, bioactivity and in vivo biocompatibility analysis of plasma electrolytic oxidized (PEO) biodegradable Mg implants. *Phys. Sci. Int. J.* 4, 708-722.

Razavi, M., Fathi, M., Savabi, O., Vashae, D., Tayebi, L., 2015. In vivo assessments of bioabsorbable AZ91 magnesium implants coated with nanostructured fluoridated hydroxyapatite by MAO/EPD technique for biomedical applications. *Mater. Sci. Eng. C* 48, 21-27.

Reddi, A., Wientroub, S., Muthukumar, N., 1987. Biologic principles of bone induction. *Orthop. Clin. North Am.* 18, 207-212.

Rex, T., Tsui, I., Hahn, P., Maguire, A., Duan, D., Bennett, J., et al., 2004. Adenovirus-mediated delivery of catalase to retinal pigment epithelial cells protects neighboring photoreceptors from photo-oxidative stress. *Hum. Gene. Ther.* 15, 960-967.

Rouhani, P., Salahinejad, E., Kaul, R., Vashae, D., Tayebi, L., 2013. Nanostructured zirconium titanate fibers prepared by particulate sol gel and cellulose templating techniques. *J. Alloys Comp.* 568, 02-105.

Salahinejad, E., Hadianfard, M., Macdonald, D., Karimi, I., Vashae, D., Tayebi, L., 2012a. Aqueous sol gel synthesis of zirconium titanate ($ZrTiO_4$) nanoparticles using chloride precursors. *Ceram. Int.* 38, 6145-6149.

Salahinejad, E., Hadianfard, M., Macdonald, D., Mozafari, M., Vashae, D., Tayebi, L., 2012b. Zirconium titanate thin film prepared by an aqueous particulate sol gel spin coating process using carboxymethyl cellulose as dispersant. *Mater. Lett.* 88, 5-8.

Salahinejad, E., Hadianfard, M., Macdonald, D., Mozafari, M., Vashae, D., Tayebi, L., 2013a. Multilayer zirconium titanate thin films prepared by a sol gel deposition method. *Ceram. Int.* 39, 1271-1276.

Salahinejad, E., Hadianfard, M., Macdonald, D., Mozafari, M., Vashae, D., Tayebi, L., 2013b. A new double-layer sol gel coating to improve the corrosion resistance of a medical-grade stainless steel in a simulated body fluid. *Mater. Lett.* 97, 162-165.

Salahinejad, E., Hadianfard, M., Macdonald, D., Mozafari, M., Walker, K., Rad, A.T., et al., 2013c. Surface modification of stainless steel orthopedic implants by sol gel $ZrTiO_4$ and $ZrTiO_4$ PMMA coatings. *J. Biomed. Nanotechnol.* 9, 1327-1335.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Salahinejad, E., Hadianfard, M.J., Macdonald, D.D., Sharifi-Asl, S., Mozafari, M., Walker, K.J., et al., 2013d.

In vitro electrochemical corrosion and cell viability studies on nickel-free stainless steel orthopedic implants. *PLoS One* 8, e61633.

Santis, E.D., Botticelli, D., Pantani, F., Pereira, F.P., Beolchini, M., Lang, N.P., 2011. Bone regeneration at

implants placed into extraction sockets of maxillary incisors in dogs. *Clin. Oral Implants. Res.* 22, 430-437.

Savage, A., Eaton, K.A., Moles, D.R., Needleman, I., 2009. A systematic review of definitions of periodontitis

and methods that have been used to identify this disease. *J. Clin. Periodontol.* 36, 458-467.

Schwarz, F., Herten, M., Ferrari, D., Wieland, M., Schmitz, L., Engelhardt, E., et al., 2007. Guided bone

regeneration at dehiscence-type defects using biphasic hydroxyapatite/beta tricalcium phosphate (Bone Ceramic®) or a collagen-coated natural bone mineral (BioOss Collagen®): an immunohistochemical study in dogs. *Int. J. Oral Maxillofac. Surg.* 36, 1198-1206.

Sculean, A., Berakdar, M., Chiantella, G.C., Donos, N., Arweiler, N.B., Brex, M., 2003. Healing of intrabony

defects following treatment with a bovine-derived xenograft and collagen membrane. *J. Clin. Periodontol.* 30, 73-80.

Shabafrooz, V., Mozafari, M., Köhler, G.A., Assefa, S., Vashae, D., Tayebi, L., 2014a. The effect of

hyaluronic acid on biofunctionality of gelatin collagen intestine tissue engineering scaffolds. *J. Biomed. Mater. Res. A.* 102, 3130-3139.

Shabafrooz, V., Mozafari, M., Vashae, D., Tayebi, L., 2014b. Electrospun nanofibers: from filtration

membranes to highly specialized tissue engineering scaffolds. *J. Nanosci. Nanotechnol* 14, 522-534.

Shahini, A., Yazdimamaghani, M., Walker, K.J., Eastman, M.A., Hatami-Marbini, H., Smith, B.J., et al., 2014.

3D conductive nanocomposite scaffold for bone tissue engineering. *Int. J. Nanomed.* 9, 167.

Shirakata, Y., Taniyama, K., Yoshimoto, T., Miyamoto, M., Takeuchi, N., Matsuyama, T., et al., 2010.

Regenerative effect of basic fibroblast growth factor on periodontal healing in two-wall intrabony defects in dogs. *J. Clin. Periodontol.* 37, 374-381.

Shue, L., Yufeng, Z., Mony, U., 2012. Biomaterials for periodontal regeneration: a review of ceramics and

polymers. *Biomater* 2, 271-277.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

- Srinivasan, S., Jayasree, R., Chennazhi, K.P., Nair, S.V., Jayakumar, R., 2012. Biocompatible alginate/nano bioactive glass ceramic composite scaffolds for periodontal tissue regeneration. *Carbohydr. Polym.* 87, 274-283.
- Sudarmadji, N., Tan, J.Y., Leong, K.F., Chua, C.K., Loh, Y.T., 2011. Investigation of the mechanical properties and porosity relationships in selective laser-sintered polyhedral for functionally graded scaffolds. *Acta Biomater.* 7, 530-537.
- Sun, W., Chu, C., Wang, J., Zhao, H., 2007. Comparison of periodontal ligament cells responses to dense and nanophase hydroxyapatite. *J. Mater. Sci. Mater. Med.* 18, 677-683.
- Tahmasbi Rad, A., Ali, N., Kotturi, H.S.R., Yazdimamaghani, M., Smay, J., Vashae, D., et al., 2014. Conducting scaffolds for liver tissue engineering. *J. Biomed. Mater. Res. Part A* 102, 4169-4181.
- Talebian, S., Mehrali, M., Mohan, S., Raghavendran, H.R.B., Mehrali, M., Khanlou, H.M., et al., 2014. Chitosan (PEO)/bioactive glass hybrid nanofibers for bone tissue engineering. *Rsc Adv.* 4, 49144-49152.
- Thornton-Evans, G., Eke, P., Wei, L., Palmer, A., Moeti, R., Hutchins, S., et al., 2013. Periodontitis among adults aged >50 years-United States, 2009-2010. *MMWR Surveill Summ* 62 (3), 129-135.
- Trombelli, L., Heitz, Mayfield, L.J., Needleman, I., Moles, D., Scabbia, A., 2002. A systematic review of graft materials and biological agents for periodontal intraosseous defects. *J. Clin. Periodontol.* 29, 117-135.
- Velchuru, V.R., Satish, S.G., Petri, G.J., Sturzaker, H.G., 2005. Hernia through an iliac crest bone graft site: report of a case and review of the literature. *Bull. Hosp. Jt. Dis. N. Y.* 63, 166.
- Verrier, S., Blaker, J.J., Maquet, V., Hench, L.L., Boccaccini, A.R., 2004. PDLA/ Bioglass (R) composites for soft-tissue and hard-tissue engineering: an in vitro cell biology assessment. *Biomaterials* 25, 3013-3021.
- Wang, H., Li, Y., Zuo, Y., Li, J., Ma, S., Cheng, L., 2007. Biocompatibility and osteogenesis of biomimetic nano-hydroxyapatite/polyamide composite scaffolds for bone tissue engineering. *Biomaterials* 28, 3338-3348.
- Wang, S., Baum, B., Yamano, S., Mankani, M., Sun, D., Jonsson, M., et al., 2000. Adenoviral-mediated gene transfer to mouse salivary glands. *J. Dent. Res.* 79, 701-708.
- Webster, T.J., Ergun, C., Doremus, R.H., Siegel, R.W., Bizios, R., 2000. Enhanced functions of osteoblasts on nanophase ceramics. *Biomaterials* 21, 1803-1810.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Webster, T.J., Ergun, C., Doremus, R.H., Siegel, R.W., Bizios, R., 2001. Enhanced osteoclast-like cell functions on nanophase ceramics. *Biomaterials* 22, 1327-1333.

Wei, G., Ma, P.X., 2004. Structure and properties of nano-hydroxyapatite/polymer composite scaffolds for bone tissue engineering. *Biomaterials* 25, 4749-4757.

Wheeler, D., Montfort, M., Mcloughlin, S., 2001. Differential healing response of bone adjacent to porous implants coated with hydroxyapatite and 45S5 bioactive glass. *J. Biomed. Mater. Res.* 55, 603-612.

Wise, D.L., 1995. *Encyclopedic Handbook of Biomaterials and Bioengineering: v. 1 2. Applications*. CRC Press.

Xia, W., Chang, J., 2007. Preparation and characterization of nano-bioactive-glasses (NBG) by a quick alkali-mediated sol gel method. *Mater. Lett.* 61, 3251-33253.

Xiao, Y., Qian, H., Young, W.G., Bartold, P.M., 2003. Tissue engineering for bone regeneration using differentiated alveolar bone cells in collagen scaffolds. *Tissue Eng.* 9, 1167-1177.

Yang, F., Both, S.K., Yang, X., Walboomers, X.F., Jansen, J.A., 2009. Development of an electrospun nano-apatite/PCL composite membrane for GTR/GBR application. *Acta Biomater.* 5, 3295-3304.

Yang, S., Leong, K.F., Du, Z., Chua, C.K., 2001. The design of scaffolds for use in tissue engineering. Part I. Traditional factors. *Tissue Eng* 7, 679-689.

Yazdanpanah, A., Kamalian, R., Moztafzadeh, F., Mozafari, M., Ravarian, R., Tayebi, L., 2012. Enhancement of fracture toughness in bioactive glass-based nanocomposites with nanocrystalline forsterite as advanced biomaterials for bone tissue engineering applications. *Ceram. Int.* 38, 5007-5014.

Yazdimamaghani, M., Pourvala, T., Motamedi, E., Fathi, B., Vashae, D., Tayebi, L., 2013. Synthesis and characterization of encapsulated nanosilica particles with an acrylic copolymer by in situ emulsion polymerization using thermoresponsive nonionic surfactant. *Materials* 6, 3727-3741.

Yazdimamaghani, M., Razavi, M., Vashae, D., Tayebi, L., 2014a. Development and degradation behavior of magnesium scaffolds coated with polycaprolactone for bone tissue engineering. *Mater. Lett.* 132, 106-110.

Yazdimamaghani, M., Razavi, M., Vashae, D., Tayebi, L., 2014b. Microstructural and mechanical study of PCL coated Mg scaffolds. *Surf. Eng.* 30, 920-926.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Yazdimamaghani, M., Vashae, D., Assefa, S., Shabrangharehdasht, M., Rad, A.T., Eastman, M.A., et al., 2014c. Green synthesis of a new gelatin-based antimicrobial scaffold for tissue engineering. *Mater. Sci. Eng.: C* 39, 235-244.

Yazdimamaghani, M., Vashae, D., Assefa, S., Walker, K., Madihally, S., Kohler, G., et al., 2014d. Hybrid macroporous gelatin/bioactive-glass/nanosilver scaffolds with controlled degradation behavior and antimicrobial activity for bone tissue engineering. *J. Biomed. Nanotechnol.* 10, 911-931.

Yazdimamaghani, M., Razavi, M., Vashae, D., Pothineni, V.R., Rajadas, J., Tayebi, L., 2015a. Significant degradability enhancement in multilayer coating of polycaprolactone-bioactive glass/gelatin-bioactive glass on magnesium scaffold for tissue engineering applications. *Appl. Surf. Sci.*

Yazdimamaghani, M., Razavi, M., Vashae, D., Tayebi, L., 2015b. Surface modification of biodegradable porous Mg bone scaffold using polycaprolactone/bioactive glass composite. *Mater. Sci. Eng: C*.

Young, M.P.J., Carter, D.H., Worthington, H., Korachi, M., Drucker, D.B., 2001. Microbial analysis of bone collected during implant surgery: a clinical and laboratory study. *Clin. Oral Implants Res.* 12, 95-103.

Yuasa, T., Miyamoto, Y., Ishikawa, K., Takechi, M., Momota, Y., Tatehara, S., et al., 2004. Effects of apatite cements on proliferation and differentiation of human osteoblasts in vitro. *Biomaterials* 25, 1159-1166.

Zhang, R.Y., Ma, P.X., 1999. Poly(alpha-hydroxyl acids) hydroxyapatite porous composites for bone-tissue engineering. I. Preparation and morphology. *J. Biomed. Mater. Res.* 44, 446-455.

Zhang, Y., Zhang, M., 2001. Synthesis and characterization of macroporous chitosan/ calcium phosphate composite scaffolds for tissue engineering. *J. Biomed. Mater. Res.* 55, 304-312.

Zhang, Y., Cheng, X., Wang, J., Wang, Y., Shi, B., Huang, C., et al., 2006. Novel chitosan/ collagen scaffold containing transforming growth factor- β 1 DNA for periodontal tissue engineering. *Biochem. Biophys. Res. Commun.* 344, 362-369.

Zhang, Y.-F., Cheng, X.-R., Chen, Y., Shi, B., Chen, X.-H., Xu, D.-X., et al., 2007. Threedimensional nanohydroxyapatite/chitosan scaffolds as potential tissue engineered periodontal tissue. *J. Biomater. Appl.* 21, 333-349.

This is the accepted manuscript (postprint) of the following book chapter:

M. Razavi, E. Salahinejad, M. Fahmy, A. Nowman, H. Jazayeri, P. Shah, D. Vashae, P. Tayebi, L. Tayebi, *Nanobiomaterials in periodontal tissue engineering*, *Nanobiomaterials in Hard Tissue Engineering*, (2016) 323-351.

<https://doi.org/10.1016/B978-0-323-42862-0.00011-0>

Zijderveld, S.A., Ten Bruggenkate, C.M., Van Den Bergh, J.P., Schulten, E.A., 2004. Fractures of the iliac crest after split-thickness bone grafting for preprosthetic surgery: report of 3 cases and review of the literature. *J. Oral Maxillofac. Surg.* 62, 781-786.

Zitzmann, N.U., Rateitschak-Plu"ss, E., Marinello, C.P., 2003. Treatment of angular bone defects with a composite bone grafting material in combination with a collagen membrane. *J. Periodontol.* 74, 687-694.