Bioactive Biomaterials: Potential for Application in Bone Regenerative Medicine

Jelena Najdanović, Jelena Rajković and Stevo Najman

Abstract Critical-sized bone defects can be repaired by using bone tissue engineering (BTE) procedures which rely on the combined use of cells, scaffolds and biologically active molecules. Based on their bioreactivity, biomaterials can be bioinert or bioactive. Bioinert biomaterials cause fibrous capsule formation upon implantation which favors the appearance of micromovements in the implant-tissue interface so the prosthesis fails. Bioactive biomaterials elicit a specific biological response thus avoiding fibrous layer formation and are able to interact with the biological environment. Bioactive biomaterials can be natural (bovine bone mineral matrix, hyaluronic acid, collagen, gelatin, fibrin, agarose, alginate, chitosan, silk) or synthetic (ceramics, metals, polymers, hydrogels and composites). Ceramics (bioactive glasses, glass–ceramics, calcium phosphates ceramics and cements) are most frequently used among these biomaterials due to similarity with the bone mineral phase. Another advantage from the use of ceramics is the presence of biologically active hydroxycarbonate apatite layer formed on the surface of these biomaterials, which represents the bonding interface with the tissues. Bioactive biomaterials have wide application as medical devices and in drug delivery systems. Since cells cannot survive without an adequate blood supply, future directions in bioactive biomaterials applications lies in the construction of bioactive and biodegradable 3D scaffolds that have osteogenic and angiogenic features. A possible alternative to improve osteogenic and angiogenic potential of the applied biomaterials is to incorporate bioactive biomolecules (e.g. growth factors) into the scaffold. One of the future perspectives in this area is the construction of smart biomaterials that respond to their environment in predetermined way regarding the protein release, thus allowing release initiated by microenvironmental conditions.

J. Najdanović · S. Najman (✉)
Department for Cell and Tissue Engineering and Institute
of Biology and Human Genetics, Faculty of Medicine, University of Niš,
Bul. Zorana Đinđića 81, 18000 Niš, Serbia
e-mail: stevo.najman@gmail.com

J. Rajković
Department of Biology and Ecology, Faculty of Sciences and Mathematics,
University of Niš, Višegradska 33, 18000 Niš, Serbia

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1 Introduction to Bioactive Biomaterials in Medicine

Bone remodeling process occurs through whole life. A bone, highly vascularized and dynamic tissue, has high regenerative capacity which means that majority of the fractures can be healed spontaneously. Nevertheless, when critical-sized defects or nonunions occur, surgical interventions are inevitable (Stevens 2008). Critical-sized defects are wounds within a bone that are of such size that cannot heal spontaneously, or in which pathologic process detain regeneration (Allo et al. 2012).

Large bone defects can be reconstructed by using a gold standard in bone regenerative medicine—autografts (Schroeder and Mosheiff 2011). Autografts are osteoinductive and osteoconductive and have numerous osteogenic cells and adequate blood supply that altogether support graft viability (Schroeder and Mosheiff 2011). To avoid autologous bone harvest procedure, which represents health risks for the patient, alternative is the use of allografts (Bishop and Pelzer 2007). However, allografts lack vascular network (Griffith et al. 2005), osteoinductive growth factors as well as osteogenic cells (Cornejo et al. 2012). The other possibility for regeneration of large bone defects are bone tissue engineering (BTE) procedures which rely on the combined use of cells, scaffolds and biologically active molecules (Healy and Guldberd 2007; O'Keefe and Mao 2011; Najdanović et al. 2016). During bone tissue regeneration, the host cells respond to an osteogenic signal, while three-dimensional (3D) scaffold supports the growth of responsive host cells and allow the formation of extracellular matrix (ECM) and a vascularized host bed (Burg et al. 2000).

Biomaterials for BTE must be able to promote differentiation of progenitor cells into osteoblasts (osteoinductive), support bone growth encourage the ingrowth of the surrounding bone (osteoconductive), and to integrate into existing bone (osseointegration) (Stevens 2008). Any biomaterial applied in BTE must be bioresorbable and replaced with newly regenerated biological tissue in the body (Langer and Vacanti 1993).

The term "osseointegration" was first mentioned in 1965 by Brånemark in order to describe the successful fixation of implant into bone tissue (Brånemark et al. 2001). During osseointegration, osteoblast precursors accumulate, bone matrix forms and biomineral formation can eventually occur. The response of bone to an osseointegrated implant is similar to the response that occurs during bone fracture healing and includes the formation of blood clot upon implantation (Davies 2003). A blood clot is a peculiar scaffold for blood cells and, at the same time, a source of biological signals and differentiation factors inductive for the osteogenic process

(Puleo and Nanci 1999). Osteogenic transcription factors regulate osteogenic differentiation of mesenchymal stem cells (MSCs) and regulate expression of the following genes: osteocalcin, osteopontin, bone sialoprotein, alkaline phosphatase and collagen type-I (ALP) (Long 2011). Several days after the implantation, osteoblasts secrete a bone matrix directly onto the implant surface that subsequently develops into immature (woven) bone (Davies 2003). At the end, immature bone is being replaced with the mature bone at the implant site, thus providing biological (mechanical) stability of the implant.

1.1 Implant-Tissue Interactions

Interactions between the implant and tissue can be extracellular and intracellular. Extracellular interaction is dependent on biomaterial's surface features. Adsorption of non-collagenous proteins and collagen at biomaterials' surface are influenced by surface nanometer scale porosity, biomaterial surface topographic configurations and negatively charged signals. Protein adsorption depends on various features. Interactions between osteoblast receptors and the corresponding protein ligands on the surface contribute to the cellular adhesion. Also, the adsorbed proteins on the implant surface, e.g. bone growth factors and activated enzymes, have a direct influence on the cell differentiation and proliferation. For example, osteoblast proliferation is favored over fibroblast proliferation on the surface of bioactive ceramics (Seitz et al. 1982).

Intracellular interaction is caused by the release of soluble agents from the biomaterial surface. Keeting and his team reported that soluble silicon released from the glass surface was a potent mitogen for human osteoblast-like cells, and that it also increased DNA synthesis and enhanced alkaline phosphatase activity and osteocalcin release (Keeting et al. 1992). It has been shown that osteoblasts' proliferation is more rapid on bioactive glass substrates compared to synthetic HA (Vrouwenvelder et al. 1993).

2 Classification of Biomaterials in Medicine

Reactivity of the biomaterial with the native tissues is of key importance for the construction of the implants (Vallet-Regi and Ruiz-Hernandez 2011). In the past, biomaterials for BTE were constructed to be "bioinert", while biomaterials today are mostly designed to be "bioactive" which refers to ability to interact with the cells and biological molecules and regenerate bone tissue (Langer and Vacanti 1993; Hench and Polak 2002).

2.1 Bioinert Biomaterials

Bioinert biomaterials are used in order to reduce the immune reaction and the reaction to foreign body as much as possible (Hench 1980). After implantation of a bioinert biomaterial, fibrous capsule surrounds the material as an answer to the foreign body (Castner and Ratner 2002). Subsequently, a formed capsule favors the appearance of micromovements in the implant-tissue interface. As a consequence, the prosthesis fails and it must be replaced (Salinas et al. 2013).

To overcome such problems, two approaches have been developed: biological fixation and bioactive fixation (Cao and Hench 1996). Biological fixation represents the construction of materials with rough surfaces and pores larger than 100 μm which allow tissue ingrowth and angiogenesis. During bioactive fixation, intimate biomaterial-bone apposition is established which has a mechanically strong bond as a consequence (Salinas et al. 2013).

In earlier experimental and clinical applications, bioinert biomaterials were thought to be superior over bioactive ones because these biomaterials generate a minimal tissue response. Nevertheless, survivability of bioinert implants decrease in long-term periods (>10 years) so the development of bioactive biomaterials became more attractive in tissue engineering (Hench 1998a).

2.2 Bioactive Biomaterials

The term “bioactivity” relates to all interactions and effects that materials exert on cells thus activating responses or leading to specific cell behaviors (Navarro et al. 2008). Bioactive biomaterials are created in such way that elicit a specific biological response and avoid fibrous layer formation. These biomaterials have interaction with the biological environment thus enhancing the biological response as well as the tissue/surface bonding (Navarro et al. 2008). Bioactive biomaterials provide an environment that is consistent with bone growth. This enables development of mineralizing interface which is a natural bond junction between living and non-living biomaterials (Cao end Hench 1996).

Mineralization and binding between the bone tissue and the implant are one of the most important approaches for increasing bioactivity during the repair (Navarro et al. 2008). Also, mechanical properties of the bioactive biomaterial are important. The structure of bone determines its mechanical properties while mechanical load determines bone structure during repair. Therefore, the perfect bioactive biomaterial should enhance newly formed bone formation which has mechanical properties similar to the normal host bone site (Hench 1998b).

Amongst the crucial factors in the design of bioactive biomaterials are the pore size and interconnection of pores (Davis et al. 2005). Large interconnected pores promote colonization of biomaterials (Karande et al. 2004), but if the pores are extremely large, the consequence is impaired vascularization because endothelial

cells cannot bridge the pores larger than a cell diameter (Salem et al. 2002). Integrity of the material is also affected by the size of pores so the cellular effects should be in balance with the mechanical properties of applied biomaterial (Karande et al. 2004). When the pores are smaller than 100 nm, diffusion of nutrients and factors are affected, which lead to the failure of implanted grafts and poor survival of implanted cells (Zimmermann et al. 2004). Pore length and numbers has an influence on the diffusion of nutrients and factors in the polymers (Botchwey et al. 2003). Very small pores in hydrogels constructed from self-assembling peptides support adhesion of endothelial cells and formation of capillary network as well as rapid cell migration (Narmoneva et al. 2005).

Bioactive materials are osteoconductive since they provide the surfaces adequate to support the adhesion and proliferation of osteoblasts (Hench and West 1996). Among them, there are also osteoinductive materials which, besides facilitating bone growth, have a role in conducting bone formation (Hench and West 1996). While osteoconduction is an extracellular response, osteoinduction is an intracellular response induced by the release of large amounts of Si (IV) and Ca^{2+} ions which stimulate the genes response in order to produce the bone formation (Salinas et al. 2013).

Based on the type of effect exerted on bone tissue, bioactive biomaterials divide into two classes—Class A and Class B. The bioactive glasses that enhance bone proliferation and differentiation of progenitors (osteoproduction) due to reactivity at a cellular level in the body has a Class A bioactivity. In contrast to that, Class B bioactive biomaterials, such as synthetic HA, lead only to bone growth along the implant surface—osteoconduction (Hench and West 1996). It has been shown that bone proliferation in vivo is enhanced in the presence of bioactive glasses with the same or even greater growth rate compared to an autogeneous bone applied for same defect (Hench and West 1996). As a consequence of the enhanced osteogenic behavior, production of biological growth factors is also enhanced and therefore, cell proliferation and the formation of newly organized tissues are stimulated (Hench 1998a).

Class A bioactive materials are able to form a biologically active hydroxycarbonate apatite (HCA) layer on their surfaces in vivo within a few minutes to a few hours (Cao and Hench 1996; Hench and West 1996), while well-crystallized HCA layer onto Class B bioactive materials need more than one week to be formed (Hench and West 1996). Sol–gel chemistry can be used to synthesize HCA coatings on various types of substrates which are formed probably by the mechanism of heterogeneous nucleation of HCA crystals within the nanometer-sized pores that create supersaturated Ca–P solutions (Pereira and Hench 1996).

It is thought that the biomaterials which will enhance tissue regeneration should have higher molecular control of interfacial reactions than the one in Class A bioactive biomaterials. The molecular control comprises the release control of the elements and chemical compounds which activate the genes important for mitosis and cell differentiation. Resorption of bioactive materials is also important and it is

controlled at molecular level by the metabolic processes of the tissue which is being replaced. The genetic activation of the enzymes and growth factors synthesis and the ability to adsorb and desorb biologically active molecules without losing the conformation and biological function are also important. Sol–gel processing provides the chemical control of a biomaterial's dissolution rate and surface chemical binding sites (Hench 1998a).

Class A bioactive biomaterials can form a biologically active, hydrated silica-gel layer on their surfaces a few minutes after exposure to the body fluids either in vivo or in vitro. This hydrated silica-gel layer is highly porous three-dimensional network which is totally interpenetrated with pore liquid (Hench 1998a). Pore-liquid networks can be enriched by incorporation of various organic and biological molecules (Avnir et al. 1997). A spectrum of differing volume fraction and size distributions of porosities can be accomplished in films (Brinker et al. 1995) and porous matrices (Hench and Orefice 1997) by changing the production conditions.

3 Bioactive Biomaterials in Bone Regenerative Medicine

The clinical survivability of the biomaterials such as bioactive glasses, ceramics, glass-ceramics, and composites is higher than in the case of bioinert biomaterials (Cao and Hench 1996; Hench and West 1996). Among the successful clinical applications of bioactive biomaterials are bioactive synthetic hydroxyapatite coatings and filling of bone defects (Ratner et al. 2004), bioactive glass middle-ear prostheses, endosseous alveolar ridge maintenance implants (Cao and Hench 1996) and bioactive A/W glass-ceramic in iliac crest donor site repair and replacement of vertebrae (Cao and Hench 1996).

Hydroxyapatite, in bulk and granular forms, was used as bone spacers and fillers (Shores and Holmes 1993). Glass-ceramic A–W, due to its high mechanical strength and good bone-bonding ability, has been used as artificial vertebrae, intervertebral discs, and iliac crests in dense bulk form (Yamamuro 1993).

The success was made in the application of BG particulate in the 6-mm defect in a rabbit femur by Oonishi et al. (1997). New trabecular bone was formed within one week, while after three weeks regenerated trabecular bone formed around the bioactive glass particles throughout the defect and bonded the particles together. Synthetic HA particulate did not succeed to fill the same defect even after twelve weeks of the surgical procedure. In this later case, the bridges between bone ends did not grow in thickness and only a small amount of bone were found between HA particles (Oonishi et al. 1997).

Wheeler et al. demonstrated that the accelerated bone formation was accompanied by resorption of the gel glass particles in 3 months. Active mineralization occurred throughout the grafted bone defects, with osteoblasts lining the new bone, formed around the gel-glass particulates. All grafted defects had significantly more bone within the area than the unfilled controls (Wheeler and Stokes 1997).

Wheeler and his associates (Wheeler et al. 1998) examined bone regeneration in cancellous skeletal defects of rabbits distal femur augmented with USB (90–710-μm particle size) or OV (300–355-μm particle size) bioactive glass particles and compared it with normal cancellous bone. Statistically higher bone quantity was found in the defect filled with USB and NORM than in the defect with OV ($p < 0.05$) at both observation points (4 and 12 weeks). This can be explained by the larger mean particle size of the OV than the USB particles combined with more numerous particles within the USB-grafted defects. Greater particles number in combination with the smaller particle size caused greater surface area of bioactive glass in the USB-filled defects, which further provided more sites for osteoblast adhesion and osseous formation than in the defects filled with OV.

Bioactive calcium phosphates and silica-based glasses are suitable for small bone defects filling (Yuan et al. 2010) where the bone regeneration kinetics is preferable over mechanical properties (Salinas and Vallet-Regı 2013). Due to their fragility and low resistance to fatigue, these types of bioactive biomaterials are inappropriate choice for large bone defects repair.

Bioactive biomaterials that have application in bone regenerative medicine could be classified as natural and synthetic bone substitutes (Fig. 1). Nanomaterials belong to a special class of bioactive biomaterials that comprises both natural and synthetic biomaterials (Fig. 1).

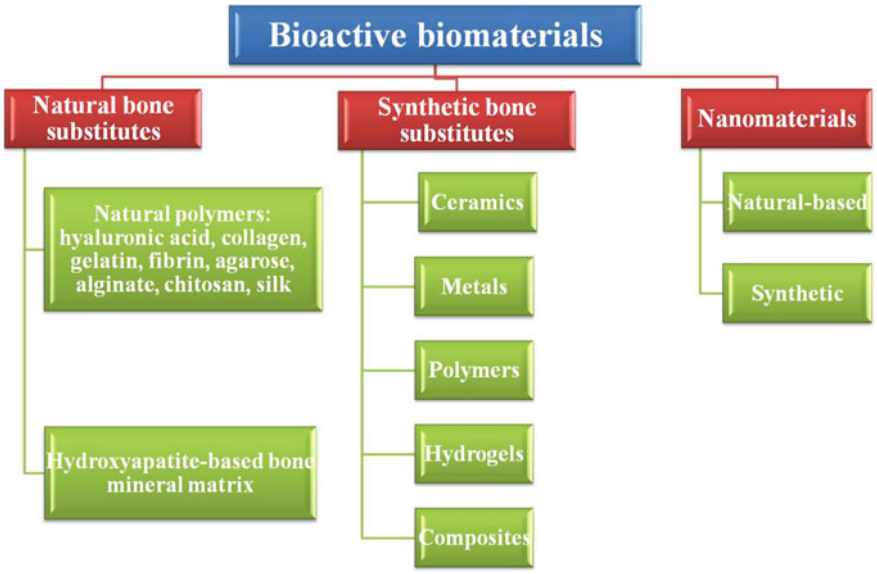

Fig. 1 Types of bioactive biomaterials that have application in bone regenerative medicine

3.1 *Natural Bone Substitutes*

In our laboratory, we are dealing with bone biology and bone regeneration in animal models. For this purpose, various biomaterials as bone substitutes and scaffolds for cells, growth factors and drugs are exploited. Commercial, hydroxyapatite-based bone mineral matrix (BMM) Bio-Oss® (Geistlich-Pharma, Wolhusen, Switzerland) combined with platelet-rich plasma (PRP) as a source of growth factors and adipose-derived stem cells (ADSCs) in vitro induced towards endothelial cells (ECs) were used to provide "biological triad" principle in subcutaneous implants (Fig. 2). Such combination caused increased vascularization in bioengineered implants and more pronounced osteogenic process (Najdanović et al. 2015). Also, in vitro osteoinduced ADSCs delivered with PRP on BMM as a carrier (Fig. 2) induced formation of osteocalcin-positive callus-like tissue in ectopic implants and intensive resorption of BMM granules (Cvetković et al. 2015).

In a simulated intraoperative procedure, we have shown that subcutaneous implants composed of BMM as a carrier, PRP and freshly isolated adipose derived stromal vascular fraction cells, rapidly triggered osteogenic process and had excellent osteogenic capacity (Najman et al. 2016). The same BMM combined with blood diluted with inflammatory macrophages has shown a favorable effect on the process of angiogenesis and synthesis of an organic fraction of bone matrix

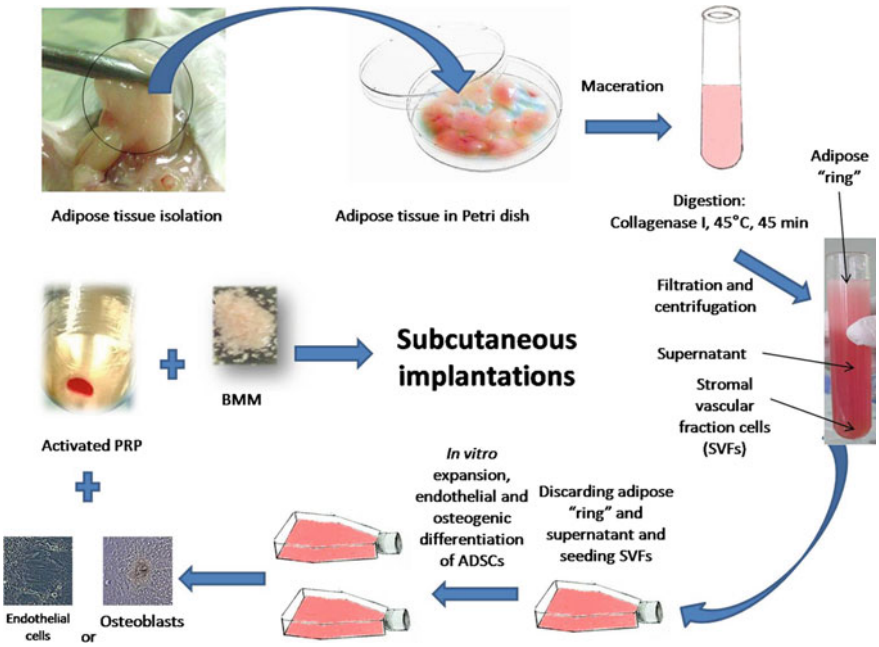

Fig. 2 Preparation of subcutaneous bioengineered implants according to the triad model with cells, scaffold and regulatory signals

(Živković et al. 2015). Bio-Oss granules supplemented with PRP have also served as carriers for different forms of vitamin D which is utilized in the regeneration of osteoporotic bone (Fig. 3). Cholecalciferol and alfacalcidol, locally applied with this bioactive carrier/scaffold in the area of femoral defect, decrease the resorption of Bio-Oss particles, delay early bone regeneration and induce the formation of new healthy bone tissue in the case of alfacalcidol or high amount of the well mineralized bone tissue in the case of cholecalciferol (Rajković et al. 2015).

An important bioactive effect in various tissues, including bone and cartilage, has been shown by using some natural polymers: hyaluronic acid, collagen, gelatin, fibrin, agarose, alginate, chitosan, silk.

Hyaluronic acid has been applied for surgical adhesions, knee pain (Furth et al. 2007), cartilage regeneration (Jazayeri et al. 2017).

Although collagen is mostly used in soft tissue regeneration (Furth et al. 2007), it has been found that collagen-based osteochondral grafts have consistently integrated layer structure and good porosity as well as mechanical properties (Levingstone et al. 2014).

Main use of gelatin is cartilage tissue regeneration, while fibrin is a potential scaffold for stem cell cultures which could be further used in bone and cartilage tissue engineering (Jazayeri et al. 2017).

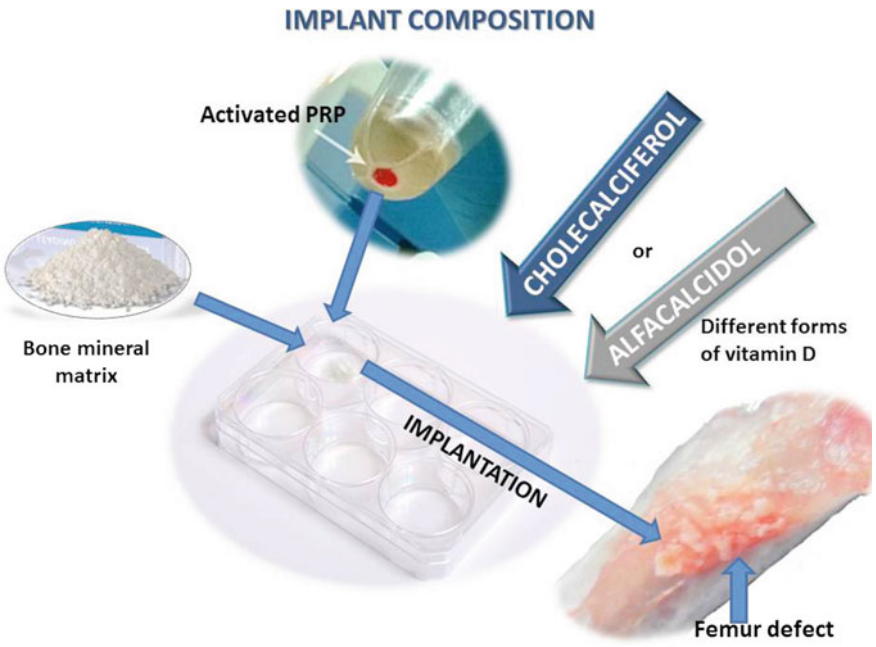

Fig. 3 Preparing of orthotopic implants of BMM granules supplemented with PRP as carriers for different forms of vitamin D in the regeneration of osteoporotic bone

It has been shown that agarose scaffolds increase stem cells' differentiation into chondocytes (Awad et al. 2004). These scaffolds are the versatile ones for the application in bone tissue engineering (Jazayeri et al. 2017).

Alginate can be used in the form of hydrogels that bears cell-adhesion ligands (Langer and Tirrell 2004). These biomaterials have been applied as scaffolds for cell encapsulation and transplantation, which brought good results regarding engineering such bone tissue that can grow out of modest numbers of implanted cells (Alsberg et al. 2002) and in drug delivery (Tonnesen and Karlsen 2002).

Chitosan-based injectable materials and its derivatives could be applied as osteogenic bone substitutes (Shi et al. 2006). Ge and his associates found that combinations of chemically modificated hyaluronic acid and also chitin-chitosan-HA biomaterial promoted neovascularization, had osteoinductive effects and rapidly degraded in vivo (Ge et al. 2004). The other advantage of chitosan application in bone regenerative medicine is the ability to induce recruitment and attachment of osteogenic cells (Kim et al. 2002). It was also found that scaffolds composed of chitosan/alginate/hydroxyapatite, which was the carrier for recombinant BMP-2 and mesenchymal stem cells, had excellent effect on formation of new bone that resulted in almost completed repair of critical sized bone defects in rats 12 weeks after implantations (He et al. 2014).

Due to its biocompatibility and slow degradation rate (Hege and Schiller 2015), silk is good candidate for application in bone regenerative medicine. In spite of that, silk lacks osteoinductivity, so the addition of osteoinductive factors to silk is necessary (Huang et al. 2014). Huang and associates examined the effect of osteoinductive-nanoscaled silk/HA composite scaffolds and found that the addition of hydroxyapatite to silk enhanced biocompatibility and mechanical strength of the scaffolds (Huang et al. 2014).

One of the most attractive directions in bone regenerative medicine is the use of bioinspired biomaterials. Construction of such biomaterials is based on mimicking natural biological design in order to construct synthetic biomaterials (Green et al. 2016). For example, this mechanism has been applied for the construction of boundary between bone replacements and natural bone in a rat calvarial defect. The boundary was made out of glue substrate that was secreted by *Phragmatopoma californica*, a sandcastle worm (Winslow et al. 2010). The glue was moderately resorbed and replaced by new lamellar bone.

3.2 Synthetic Bone Substitutes

3.2.1 Ceramics

Ceramic materials, which include bioactive glasses (BGs), glass–ceramics, calcium phosphates ceramics (CaPs) and cements (Navarro et al. 2008), are mostly used as bone defect fillers (Vogel et al. 2001). These biomaterials are similar to the bone mineral phase and have structural and surface features which enable binding to the

bone without forming an interface that consists of fibrous connective tissue (Schepers et al. 1991).

Simultaneously with the implantation procedure, time-dependent kinetic modification of the ceramics surface begins. Hydroxycarbonate apatite (HCA) layer developed at the biomaterial surface is bioactive and represents the bonding interface with tissues due to its similarity with the mineral bone phase (Hench 1998b). Bioactive glasses applied in BTE are able to induce bone tissue growth processes—enzyme activity (Aksay and Weiner 1998), revascularization (Keshaw et al. 2005) as well as osteoblast differentiation from mesenchymal stem cells and osteoblast adhesion (Lu et al. 2005; Schepers et al. 1991).

During the early implantation period, apatite layer formation on the ceramic surface precede bone matrix integration into apatite (Kokubo 1990). This apatite layer contains nano-crystals of carbonate-ion-containing apatite with structure and crystallinity similar to the one in bone mineral phase (Kokubo 1990). Osteoblasts that proliferate on the apatite form a biological apatite/collagen extracellular matrix (Loty et al. 2000), thus enabling direct contact between surface of the apatite layer and surrounding bone (Kokubo et al. 2003).

Immersion of bioactive biomaterials into a simulated body fluid (SBF), an aqueous solution with mostly the same ingredients as human extracellular fluid, is another approach applied to achieve a bone-like apatite layer formation. SBF is cell-free and protein-free, so the apatite layer is formed due to the chemical reaction between bioactive ceramics and the surrounding fluid. Thanks to such features of SBF, new types of biomaterials that are bioactive have been designed—glass-ceramics, organic–inorganic hybrids, coatings as well as bioresorbable ceramics (Ohtsuki et al. 2009).

Some of the most frequently used ceramics in medicine are: Bioglasss in the Na_2O–CaO–SiO_2–P_2O_5 system (Hench et al. 1971), hydroxyapatite (HA) ($Ca_{10}(PO_4)_6(OH)_2$ (Jarcho et al. 1977), β-tricalcium phosphate (TCP) ($Ca_3(PO_4)_2$ (Rejda et al. 1977), HA/TCP bi-phase ceramic (Daculsi et al. 1990), glass ceramic A–W containing crystalline oxyfluoroapatite ($Ca_{10}(PO_4)_6$(O, F2)) and β-wollastonite (CaO × SiO_2) in an MgO–CaO–SiO_2 glassy matrix (Kokubo et al. 1982).

In 1971, Hench and associates made the first bioactive glass Bioglass® by the conventional melt-derived process (Hench et al. 1971). Nowadays, it exists in the particulate form of following commercial products: Perioglas® (periodontal bone filler), Novabone® (orthopedic bone filler), Novamin (additive for toothpaste), but its disadvantage is that it cannot be made into a scaffold because it crystallizes on sintering and forms a glass-ceramic. A Sol–gel derived glass is a procedure for production of scaffolds from bioactive glasses. It is developed as an alternative to the traditional melt processing in order to ensure an interconnected nanoporous structure through the whole glass (Jones 2009). Nanoporosity influence cell response, especially osteoblast response (Biggs et al. 2007). Nevertheless, the greatest advantage of bioglass prepared by sol–gel method is the introduced foaming step that creates porous scaffolds with interconnected macropore networks.

45S5 Bioglasst (USB) is an effective graft material for the use in oral and maxillofacial bone surgery (Oguntebi et al. 1993), mostly because of its bioactivity based on the following composition −45% SiO_2, 24.5% CaO, 24.5% Na_2O, and 6% P_2O_5. Such composition of USB stimulates apatite gel layer formation on the surface of the particles, which attracts osteoprogenitor cells and osteoblasts, thus stimulating formation of bone (Hench et al. 1991). USB has a wide range of particle size (from 90 to 710 mm) which was shown as an optimal feature for bone tissue regeneration of critical-sized calvaria defects (Bergman and Litkowski 1995). Numerous studies have proved the potential of 45S5 bioactive glass for skeletal applications (Piotrowski et al. 1975).

Bioactive gel-glasses are advantageous over bioactive glasses, such as 45S5 Bioglasst (BG), for several reasons. Among these reasons is the absence of Na_2O in the Bioactive gel-glasses structure, which ensures that there is no rapid increase in interfacial pH following the surface reactions. Also, a large surface silanols-rich area can be obtained in situ in the gel-glasses by controlling the ultrastructure processing, aging, and stabilization treatments. Therefore, bioactive gel-glasses can nucleate a biologically active HCA layer within minutes more rapidly than bioactive melt glasses with much lower contents of silica. Thanks to sol–gel processing, bioactive compositions can obtain wide range of silica content and variable levels of CaO and P_2O_5 (Pereira et al. 1994).

Bioactive glasses can also be designed to deliver ions which activate complex gene transduction pathways and thus enhance cell differentiation and osteogenesis (Hench and Polak 2002; Tsigkou et al. 2007). Crystalline HA can be used for the adjustment of resorption rate of bioactive glasses and bioceramics. Other calcium phosphates possess a greater capacity to be resorbed but their strength for sustaining load is lower (Oonishi et al. 1995).

Biologically relevant levels of soluble ions of Si, Ca, P, and Na can be released by bioactive glass surfaces. These ions further promote intra- and extra-cellular responses (Xynos et al. 2001). Bioactive glasses based on borate support cell proliferation and differentiation in vitro (Fu et al. 2010a; Marion et al. 2005) as well as the tissue infiltration in vivo (Fu et al. 2010b), while bioactive glasses which have Cu, Zn or S as components favors bone growth (Fu et al. 2010a; Wang et al. 2011; Zheng et al. 2012).

3.2.2 Metals

Since none of the orthopedic metallic biomaterials is bioactive by itself, there are two methods to make them bioactive: coating implants' surface with a bioactive ceramic and chemical modification of the biomaterials' surface. The second procedure is used in order to accomplish deposition of a bioactive ceramic in vivo or to promote adhesion of cells and proteins and other interactions between tissue and biomaterial (Navarro et al. 2008).

Some metals may become bioactive due to ceramic component formed on their surfaces by chemical etching process. For example, as a result of the chemical

reaction of TiO_2 with NaOH, a sodium hydrogen titanate gel layer is formed. Subsequently, the thermal treatment produces amorphous sodium titanate which displays a bioactive response (Salinas and Vallet-Regı 2013).

Osseointegration of an implant can be improved by coating the implants with inorganic and organic components that are similar to the ones in physiological extracellular bone matrix (ECM) (de Jonge et al. 2005). These depositions of bioactive biomaterials enable direct implant–bone bonding and enhance implant osseointegration due to the accelerated speed and amount of new bone formed at the interface (de Jonge et al. 2005). Described cell-biomaterial interactions are mediated by integrins which also probably cooperate with osteogenic factors that accumulate on the implant surface thus regulating proliferation and differentiation of osteoblasts (Siebers et al. 2005). The coating which had the successful application in BTE are nano-CaP/collagen and CaP/ALP composite coating onto titanium surfaces (de Jonge et al. 2009), growth factors loaded on collagen or CaP-coated implants (Li et al. 2010) and DNA-based coating onto titanium implants using the layer-by-layer (LbL) deposition technique (Schouten et al. 2010).

3.2.3 Polymers

Polymers can be either biological or synthetic. Biological polymers contain inherent biological informations that are necessary for induction of chemotactic responses as well as cell attachment. The alterative for biological polymers are synthetic ones which can be produced into various three-dimensional scaffolds with different porosities and surface characteristics (Stevens 2008).

Biological polymers physodic (P2) and 3-hydroxy physodic acid (P3), that are main compounds of methanol extracts (ME) isolated from the lichen *Hypogymnia physodes*, induced a significant decrease in the HeLa cells viability and proliferation in vitro (Stojanović et al. 2014). Obtained data are interesting for further investigation of biological activity of these biopolymers. It has been shown that lichen derivates have pro-apoptotic effects on tissues around bone implants which might be a mechanism for protection from cancer development in different tissues (Odabasoglu et al. 2012). This could be a possible future direction for examination of physodic (P2), 3-hydroxy physodic acid (P3) and ME of the *H. physodes* as bioactive agents in BTE.

Synthetic hydroxyapatite (sHA, $Ca_{10}(PO_4)_6(OH)_2$) is one of the most applied materials for bone defect reparation due to its similarity to the bone mineral, as well as its bioactivity and osteoconductivity (LeGeros 2002). Various commercial porous forms of sHA are in use (e.g. ApaPore® (Apatech Ltd., Elstree, UK)), but their resorption rate is low so they can be only used for bone augmentation (mechanical support of diseased bone), and not for regeneration. Silicon or carbonate substituted apatites can be used for increasing their resorption rate which is still slow (Jones 2009).

Functional groups and binding sites at the polymers surface influence their bioactivity. In order to achieve bioactivity, polymer surface can be modified usually by physisorption of proteins and peptides on the surface, dipcoating and amino- and carboxyl-directed immobilization of biomolecules (Ma et al. 2002) or biochemically in order to induce mineralization with HA layers (Kato et al. 1996).

3.2.4 Hydrogels

In order to supply three-dimensional cellular microenvironment with high content of water, hydrogels can be obtained by using minimally invasive techniques and gelled in situ by photocrosslinking or ionically (Stevens 2008). Due to viscoelasticity, hydrogels could be applicable in regeneration of cartilage (Stevens et al. 2004) and bone (Lutolf et al. 2003). Our team have shown that although 2-hydroxyethyl methacrylate, poly(alkylene glycol) (meth)acrylates and itaconic acid are able to swell in phosphate buffer, physical integrity and soft and rubbery consistency of these biomaterials are maintained even when swelling experiments were performed for a long time after reaching the equilibrium state (Takić-Miladinov et al. 2016). Also, the tested hydrogels induce genotoxic effects, which intensity depend on chemical composition, extract concentration and degree of crosslinking of these hydrogels.

3.2.5 Composites

Inorganic-organic composites "mimic" the composite nature of the native bone regarding to combined toughness of a polymer phase and compressive strength of an inorganic phase. Nanosized inorganic component are probably more bioactive than the micro-sized components (Stevens 2008). Since cell's transmembrane integrin receptors bind biologically active peptide motifs, e.g. arginine-glycine-aspartic acid (RGD), implementation of such motifs is among most applied methods for enhancing functionality of these biomaterials (Bökel and Brown 2002). Optimization of biodegradability of the applied biomaterial with the one specific for remodeling and regeneration of native bone tissue can be achieved with proteolytically degradable peptide motifs that are recognized by cell-secreted matrix metalloproteases (Lutolf et al. 2003).

Biodegradable polymers can be combined with bioactive inorganic materials in order to construct nanocomposites and organic-inorganic (O/I) hybrids (Allo et al. 2012). Better cell attachment and responses could be achieved by modification of the surface of nanocomposites or O/I hybrids via changing functional groups present at the surface of these biomaterials. As a consequence, vascularization is successful and mineralization occurs in the scaffolds. The limitation of porous 3D nanocomposites and O/I hybrids scaffolds are unknown long-term in vivo behavior regarding angiogenic stimulus, degradation and ion release kinetics (Allo et al. 2012).

3.3 Nanomaterials

Nanomaterials represent a special type of biomaterials that can be found in nature but also can be synthetic (Adlakha-Hutcheon et al. 2009). Nanomaterial-based scaffolds have significant application both in tissue engineering and in drug delivery. Due to biodegradability, these biomaterials support cell growth and infiltration in a manner that natural replacement with new biological tissue occurs, which is of significance in bone regenerative medine (Marchesan and Prato 2013). Since smart nanodevices target site of the certain disease, an external signal induce controlled release of multiple agents, which is powerful mechanism for drug delivery. Graphene-based nanomaterials are applicable in bone tissue engineering (Shin et al. 2016). For example, the beneficial effect of graphene-based biomaterials on enhancement of adherence, proliferation, and differentiation of osteogenic cells was estimated (Shi et al. 2012; Venkatesan et al. 2014). In addition, graphene can be used to replace the effect of BMP-2 as an inductive factor for cell differentiation (Nayak et al. 2011) or in order to boost osteoconductivity via stimulation of osteogenic cells differentiation and biomineralization process (Kim et al. 2011).

4 Bioactive Biomaterials in Dentistry

Bioactive biomaterials play a key role in dentistry where they are used for a dental treatment, in the therapy of the pulp and root canal as well as in dental surgery (Goldberg and Smith 2004; Mauth et al. 2007; Grotra and Subbarao 2012). They are essential in restoring impaired teeth and jaw bone structure. A wide range of biomaterials is used in dentistry including inorganic salt, polymers, ceramics, metals and composites. Bioceramics and bioglasses have a wide spread application in dentistry and medicine because they interact with and induce regeneration of the surrounded tissue which is important for successful regeneration.

Biocompatible white powder, which consists of ceramics particles, can be used in root canal repair due to the ability to stimulate cementogenesis and form a hermetic seal in the root canal (Sharma et al. 2013). Portland cement or Mineral trioxide aggregate (MTA) is a type of the bioactive material, composed of calcium and silicate, which maintains pulp and periodontal tissue vitality (Roberts et al. 2008) and has characteristic of apatite formation.

Calcium phosphates are good choice for both craniofacial and dental applications (Thein-Han et al. 2012). Likewise, hydroxyapatite was applied for the production of HA-based (n-HA/polyamide (PA)) biomaterials by using CAD/CAM technology and implanted into a fracture of mandibular condyle. The results of the treatment showed that patients gained a jaw contour that had proper temporomandibular joint activity (Li et al. 2011).

Bioglass and Bioglass-type glasses particulates were used with success in periodontal bone repair (Wilson et al. 1993). Bioactive glass BaG 45S5 is very

reliable at the sites of tooth extraction for the tooth roots treatment and maintaining a solid ridge for dentures (Jazayeri et al. 2017). Biosilicate is a bioactive glass-ceramic used for open dentinal tubules of a vital tooth. These bioactive glass-ceramic induce HCA (hydroxyl carbonate apatite) deposition in open dentinal tubules thus offering a new opportunity for treating dentine hypersensitivity (Tirapelli et al. 2010).

For maxillofacial and craniofacial surgery, synthetic bone materials and freeze-dried bone are in use, while β-Tricalciumphosphate (β-TCP) and histoacryl are good filling materials for the bone defects treatments (Sharma et al. 2013).

Poly (lactid) acid/hydroxyapatite (PLLA/HA) is a polymer matrix composite material that has been successfully used as anosteochondral construct for mandible bone regeneration (Schek et al. 2005) and Ceramic Matrix Composites are used in order to increase mechanical strength of the construct to resist load-bearing applications, chiefly in the jaw compression (Friedman et al. 1991). For the necessary step in oral and maxillofacial surgery—guided tissue regeneration, polymers including tissue-derived collagen (Karfeld-Sulzer and Weber 2012; Wang and Carroll 2001) and synthetic polyesters (Karfeld-Sulzer and Weber 2012; Gentile et al. 2011) are frequently used.

Dentin extracellular matrix proteins (ECMPs) and Dentonin (peptide) are amongst the most promising biomolecules for application in pulp repair and regeneration (Goldberg et al. 2006). ECMPs can stimulate proliferation and differentiation of dental pulp stem cell and their migration to sites of injury, while Dentonin activates reparative mineralization of the cornal pulp and root canal lumen.

Emdogain, a biomaterial composed of porcine proteins, can be applied in periodontal regeneration after gum disease and injuries.

Among the metals, most frequently used biodegradable metals (BMs) are Mg-based BMs due to efficacy in maxillofacial bone defects treatment (Li et al. 2014).

In the field of prosthetics, due to low cytotoxicity, silicone oral tissue conditioners are suitable for daily dental practice (Krunić et al. 2011).

5 Bioactive Biomaterials in Drug Delivery Systems

The application of biomaterials as carriers for sustained and controlled drug delivery has become a very popular approach in the treatment of different diseases. By using drug delivery systems, target sites in the body can obtain an effective concentration of drug avoiding the side effects of systemic treatment.

In the case of impaired bone regeneration associated with bone metabolic disorders, local delivery of anti-osteoporotic drugs and anabolic agents (e.g. growth factors) using bone substitutes causes more rapid bone “answer” to the treatment and provide a better osseointegration of implants (Kyllönen et al. 2015).

Besides the good choice of anabolic drug, an adequate selection of delivery system is essential. In order to be used as systems for the drug delivery, biomaterial should be synthesized as a biocompatible and should provide long and gradual drug release. Most of the biomaterials used in tissue engineering are biodegradable and this feature is particularly important for local drug releasement.

Different synthetic and natural polymers, bioceramics and biocomposites that are widely used as scaffolds for tissue engineering may serve as carriers for drug delivery. After the incorporation or absorption, obtained bioactive implants release drugs in their surroundings affecting the bone regeneration and osseointegration.

Biomaterials based on calcium and phosphates are often used for bone regeneration as a bone substitutes and, therefore, represent good candidates as bioactive local drug delivery carriers. Because of the similarity with an inorganic bone phase, these biomaterials exhibit osteoconductive properties and may be resorbed by osteoclasts thus enabling sustained drug release (Kyllönen et al. 2015; Verron et al. 2010). CaPs based biomaterials are available in the form of powders, granules, ceramic, cement and coatings.

The potential ways for the local drug delivery in bone disorders involve implants coating, the application of injectable forms of bone cements and gels and, in the cases of large bone defects, application of bioactive scaffolds for tissue regeneration (Kyllönen et al. 2015).

Calcium phosphate cements (CPC) are suitable carriers for the local drug delivery due to their osteoconductivity, good protein absorbability and gradual release of different agents (Guo et al. 2005; van de Watering et al. 2012; Wu et al. 2012; Ginebra et al. 2006). During the system designing, a chosen drug or growth factor may be incorporated into the solid or liquid phase of the cement or first incorporated in the microparticles that can be inserted into the delivery system. Using cements in combination with growth factors showed a favorable impact on bone regeneration, especially in osteoporotic conditions (Blom et al. 2001; van de Watering et al. 2012).

Disadvantage of this system is a need for enough space in the bone fracture area, in order to deliver required amount of the chosen drug (Kyllönen et al. 2015). Also, CPCs are slowly biodegradable in vivo and suffer of the lack of porosity which may be improved with various modifications (Xu et al. 2004).

Utilization of bone cement as a carrier for antimicrobial drugs is particularly recommended against infection associated with implant application (Neut et al. 2005).

Heat produced during the polymerization and postpolymerization treatments in cold-polymerized PMMA (Kostić et al. 2011), a non-biodegradable acrylic cements which is commonly used for implant fixation in orthopedics and dental surgery, restrict the range of drugs to deliver but they found to be very effective in delivering antibiotics (Minelli and Benini 2007).

Implant coatings is strategy of particular importance for metallic inert materials that are often used for hard tissue repair (Goodman et al. 2013). Drug insertion in coatings represents a good strategy in bone fracture healing due to the capability of

the delivered agents to influence on implant osseointegration. Metal implants can be coated with the suitable drug directly, but the better results in the treating of bone fractures can be achieved by absorption or incorporation of the drug onto the CaP materials which can be used as coatings around the implant (Liu et al. 2007). Hydroxyapatite coatings can be the way to deliver growth factors, DNA or various bioactive molecules (Sachse et al. 2005; Yu et al. 2012; Goodman et al. 2013). This approach enabled gradual releasement of the applied drug and enhanced osseointegration of the implant in experimental animals. Using anti-osteoporotic drugs as components of the coatings may improve bone microarchitecture around the titanium implant in osteoporotic rat tibiae (Pyo et al. 2014). The lack of this strategy is the possibility of the drug releasement only in near vicinity of the implant and the general resistance of the coating (Kyllönen et al. 2015).

A wide range of synthetic and natural polymers, ceramics and metals are available in the forms of micro- and nano-particles which represent very important systems for the delivery and sustained release of various agents for the treatment of a broad spectrum of diseases (Chau et al. 2008).

Particulated forms of biomaterials may adsorb or encapsulate drugs and deliver them to the place of releasement. Particles can be used alone, combined within cements, hydrogels and scaffolds or even form a coatings on implants. In any of these cases, the selected drug is being physically or chemically incorporated in/onto the particles and thus protected from degradation until its release begins in the target tissue. Different scaffolds with incorporated drug-loaded particles found to be more effective in enhancing osteogenesis in comparison with the scaffold alone with adsorbed BMP-2 (Wei et al. 2007). Controlled drug releasement depends on particle size, material properties, their degradability and formulation of delivery systems (Kim and Pack 2006). Pharmacokinetics of the applied drug is of a key importance for the selection of suitable system for their delivery.

Biodegradable polymer microparticles are the most common particulated biomaterial that has been used for controlled drug delivery due to biocompatibility and degradation mechanisms (Makadia and Siegel 2011). In bone therapy, PLGA based particles in combination with growth factors showed to stimulate osteogenic cell differentiation (Kirby et al. 2011).

Ca- and P-based particles have advantage over the other materials in bone regeneration, because of the similarity with the inorganic bone composition and high osteoconductivity as well as biocompatibility and bioactivity. Hydroxyapatite particles have a high affinity for proteins and other bioactive molecules and can be used with high efficiency to load and deliver drugs such as bisphosphonates (BP), growth factors etc. which are used in osteoporotic bone therapies (Lee et al. 2011). Combination with bioresorbable polymers such as PLGA, provide better systems for drug delivery because of slow PLGA degradation under physiological conditions. Sustained release of BP from PLGA/hydroxyapatite composite or from hydroxyaptite microsphere, reduces local osteoclastic activities (Boanini et al. 2008; Seshima et al. 2006).

HA/PLGA or HA alone nanoparticles that have been used as bioactive systems for vitamin D delivery have also showed to improve regeneration of osteoporotic bone (Ignjatović et al. 2013)

In addition to bone therapy, nanostructures are attractive biomaterials for other biomedical application because of their small sizes and an ability to deliver drugs inside target cells. They represent an effective approach in tumor therapy due to the possibility of targeting tumor cells, and avoiding side effects of conventional chemotherapy. Cell-specific targeting can be achieved by active mechanism, by applying functionalized NPs, or passive mechanisms, which refers to the effect of enhanced permeability and retention effect (EPR) (Acharya and Sahoo 2011; Steichen et al. 2013). Different nanostructures, such are liposomes, dendrimers, polymers, silicon or carbon materials, magnetic and gold nanoparticles, can serve as carriers for local drug delivery (De Jong and Borm 2008; Wilczewska et al. 2012). PLGA particles are widely in use as drug delivery systems due to low toxicity, biodegradability, biocompatibility and possibility for controlled and constant release of carried agents (Bala et al. 2004; Sadat et al. 2014). So far, they have been used for delivery of anti-cancer therapy, immunomodulatory agents, anti-hypertensive drugs and hormones. Carbon nanomaterials are widely examined as chemotherapy, carriers for genes and proteins, designed for potential applications in the cancer treatment (Liu et al. 2008, 2011). We have demonstrated that carbon nanotubes functionalized with a Toll-like receptor 7 agonist have immunomodulatory effects on human dendritic cells which can be applied in therapies (Čolić et al. 2014).

In cancer diagnostic and therapy, gold nanoparticles (GNPs) are also found as perspective carriers and agents for drug delivery because of their specific physical and chemical properties (Huang et al. 2007). Beside their tunable size and shape which enable controlled plasmon resonance for photo thermal therapeutic treatments by conversion of near-infrared light into thermal energy, they are biocompatible, not toxic and capable for drug delivery due to small dimensions and large surface area for functionalization with drugs, genes and biomolecules (Han et al. 2007). In our study, we investigated the effect of differently sized GNPs on functions of immune, dendritic, cells and found that 10 nm-sized GNPs have more powerful inhibitory effects on antitumor functions as well as maturation of DCs, in comparison with larger 50 nm-sized GNPs (Tomić et al. 2014).

Biomaterials used in medicine as medical devices are associated with risk of microbial infection. Bacteria growth made biofilms on their surfaces that are resistant to antibiotics and host immunity and may cause implant failure.

The approach of biomaterial coating with antimicrobial agents such as antimicrobial polymers, antibiotics, plant extracts etc. was found to be effective in obtaining therapeutically bioactive materials for the infection prevention. Plant extracts have shown great success in combating the various strains of bacteria. *Staphylococcus aureus* is the most frequent causer of biofilm formation on the material surfaces and therefore the coatings which prevent its colonization and

biofilm growth are favorable. In addition to the biomaterials testing, we are dealing with antimicrobial, antioxidant and cytotoxic effects of different plant extracts often used in Ethnomedicine. *Inula helenium* and *Carlinae radix* essential oils showed significant antimicrobial effect against *Staphylococcus aureus* (Stojanović-Radić et al. 2012a, b). The potential use of these plant extracts as coatings on biomaterials, in order to prevent infection, is subjected to our further research.

6 Future Directions and Perspectives

Biomaterials from the so-called "third-generation" were constructed in the way so that, at the molecular level, are able to trigger specific cellular responses (Hench and Polak 2002) and to integrate the biodegradability and bioactivity concepts. Also, these biomaterials must be able to promote specific cellular actions and performances. The bioactivation of the biomaterials' surface induced with biomolecules guide and stimulate cell migration, adhesion, proliferation as well as differentiation towards the certain cell line (Navarro et al. 2008).

Injectable cement composite mixed with living cells was obtained by involving undifferentiated bone marrow stromal cells into a hydrogel containing CaP particles. This kind of biomaterials are well vascularized and integrated into the host tissue upon implantation which has been shown on the mouse model (Trojani et al. 2006).

Development of bioactive and biodegradable 3D scaffolds with osteogenic and angiogenic potential is a major challenge, because cells cannot survive without an adequate blood supply. A possible alternative to improve osteogenic and angiogenic potential of the materials is incorporation of the active biomolecules such as growth factors into the scaffold (Allo et al. 2012).

Since shape, architecture and mechanical support are not enough for providing long-lasting structure for developing scaffold (Furth et al. 2007), designing of the smart biomaterials became one of the most important future directions in construction of bioactive materials (Davis et al. 2005). Smart biomaterials actively participate in functional tissue development (Furth et al. 2007). These biomaterials respond to their environment in previously determined manner which includes protein release. Consequently, delayed release as well as release stimulated by microenvironmental factors is possible (Anderson et al. 2004). Since microenvironmental factors have the influence on progenitor and stem cells differentiation, modification of bioactive injectable materials by using peptide-like nanofibers may be one of the key solutions in future cell therapies (Davis et al. 2005).

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