Abstract
Tissue engineering has become a promising strategy for repairing damaged organs and tissues. Favorable government regulatory framework, continuous technology advancements and increasing research funding drive the market for alternative regenerative medicine therapies. Current mini-review covers key components needed for tissue engineering – cells, scaffold and growth factors as well as method for tissue engineering graft manufacturing. Selected applications – for bone, skin and peripheral nerve regeneration are highlight in the paper.

Introduction
Regenerative medicine, and tissue engineering now expands to practically all areas of healthcare including cardiac, corneal, nerve vascular and liver tissue engineering and regeneration [1]. Favorable government regulatory framework, continuous technology advancements and increasing research funding drive the market for alternative regenerative medicine therapies. Global tissue engineering market is expected to reach USD 11.53 billion by 2022, according to a new report by Grand View Research, Inc (2016).

Tissue engineering combines cells, biomaterials and growth factors to support and regenerate biological tissues. The key objective of tissue engineering is to improve quality of life in a secure way by avoiding various adverse effects of several standard medical therapies [2] and replace or repair damaged tissues by creating new healthy niches enabling cells to grow, proliferate and differentiate [3]. There are also multiple attempts to generate new tissues and even entire organs in vitro, ready to be implanted into the diseased and mechanically damaged sites. This involves e.g. the simulation or mimicry of the extracellular matrix (ECM) [4]. Thus, patient-derived cells can be expanded in culture and prompted to differentiate into a specific tissue or organ, followed by transplantation in a patient with no need of another patient-matching cell/tissue/organ donor.

The earliest clinical applications of human cells include the attempts to regenerate skin tissue using fibroblasts, keratinocytes, or a scaffold (template) in 1980[5]. Soon after, periodontal and alveolar bone tissues were tested for regeneration potential with use of membranes preventing undesirable fibroblasts from invasion there (guided tissue regeneration and guided bone regeneration) [5]. FDA approved marketing authorization for Maci® autologous cultured chondrocytes on porcine collagen membrane for the repair of cartilage defects of the knee in adult patients.

Components for Tissue Engineering
Three key components are needed for tissue engineering – cells, scaffold and growth factors. Whereas cells produce new tissue matrix, scaffold provides the appropriate environment for cells to be able to effectively accomplish their missions. The function of growth factors is to facilitate and promote cells to regenerate new tissue [6].

Although numerous investigations have been undertaken to regenerate various tissues, there are still many critical factors to solve in regenerative medicine [7] including cell source, scaffold construction, cell seeding, culture environment, matrix production quality, mechanical properties of cell-scaffold construct and suitable animal models.

The cell source has an enormous influence on the success of tissue engineering. Cells applicable to tissue engineering may be classified into autologous (patient’s own), allogenic (human other than patient) and xenogenic (animal origin) [8]. Autologous cells are the most appropriate for tissue engineering, whereas allogenic and xenogenic cells are immunogenic and will need an immunosuppressive therapy when a new tissue is engineered. A certain limitation associated with autologous cells is harvesting a sufficient amount of healthy cells with high regenerative potential, especially when a patient is aged or diseased [9]. However, the progress in regenerative medicine area now allows for fast and efficient expansion of several different progenitor cells that are then used for the preparation or tissue engineered pro-medical constructs [10].

Mesenchimal Stem Cells (MSCs) have been isolated from a range of tissues, including bone marrow, adipose tissue, foetal tissue, placenta, umbilical cord and etc. Despite the remarkably high percentage of MSCs, BM and adipose tissue harvesting process is invasive, traumatic, and the amount of material extracted is limited and requires anaesthesia [11]. Foetal tissues, placenta and umbilical cord are potentially attractive sources of MSCs, since they contain abundant MSCs and can be collected without the requirement for invasive methods, but are not always available when needed [12]. Therefore, exploring new sources and isolation techniques for obtaining such cells is of great interest. Due to the fact that bone marrow derived stem cells circulate in peripheral blood at a very low level under steady-state conditions, it is necessary to mobilize hematopoietic stem/progenitor cells from bone marrow to peripheral blood.
Neovascularization is important in providing nutrients to the regenerating wound bed and removing waste products. MSCs have been shown to secrete and release many factors, such as epidermal growth factor, bFGF, platelet-derived growth factor, TGF-b, VEGF, hepatocyte growth factor, and insulin like growth factor-1, as well as enzymes, such as tissue-type plasminogen activator, uPA, and MMPs, that contribute to angiogenesis [13]. Human MSCs express VEGF as well as nitric oxide, which promote endothelial cell proliferation and vascular permeability [14]. Despite similar multipotency and phenotypes, MSCs from different tissue promote angiogenesis through distinct mechanisms. ASCs mediate vessel morphogenesis through the plasmin system and minimally with MMPs, whereas BMSC stimulate capillary formation solely using membrane-type MMPs [15]. Incorporating cells that secrete angiocrine factors within the scaffold, such as endothelial cells cocultured with mural cell precursors or fibroblasts, can induce de novo blood vessel development to create capillary networks and generate a prevascularized construct [16].

The major function of scaffold is to mimic the natural extracellular matrix (ECM). The scaffold should support proliferation, differentiation, and normal cell function. In addition, a scaffold placed at the regeneration site should prevent disturbing cells from external factors [17]. To fulfill the functions of a scaffold in tissue engineering, the scaffold should meet a number of requirements – it should be biocompatible, should have appropriate porosity and porous microstructure and proper surface chemistry to allow cell attachment, proliferation and differentiation. Scaffolds should possess adequate mechanical properties and controlled biodegradability [18]. The most common reasons for using absorbable polymer scaffolds are to accomplish time-varying mechanical properties and ensure complete dissolution of the implant, eliminating long-term biocompatibility concerns or avoiding secondary surgical operations.

Polymeric scaffolds for tissue engineering can be prepared with a multitude of different techniques, such as freeze drying or emulsion freezing, solvent casting or particulate leaching, phase separation, gas foaming or high pressure processing, melt moulding, 3D-printing, electrospinning, rapid prototyping of solid free-form technologies and combination of these techniques [19]. However, it is difficult to control the internal pore structure, porosity, and pore connectivity of the scaffolds in these processes, making it challenging to form scaffolds with the desired parameters to simulate suitable micro environment for cells. Scaffold manufacturing should focus on both adequate biological properties and cost effective scaffold production for fast implementation in clinical application. Furthermore, the scaffolds often contain residual organic solvent, which can damage cells [20].

Some researchers try to combine different method to prepare ideal 3D scaffold for tissue engineering. Chen H et al. [20] combine the biological 3-D printing, electrospinning, and vacuum freeze drying techniques to fabricate a hierarchical 3-D scaffold. The microporous structure of multi-scale scaffold is beneficial to the infiltration of the nutrient solution, which helps the migration of the cells into the scaffolds. It is confirmed from the HE and MT tests that there are a large number of cells inside the scaffolds, and new blood vessels and collagen fibers grows out.

Kim M et al. [21] used various processing conditions (such as applied electric field, flow rate, nozzle size, and weight fraction of the bioceramic) to obtained (α-TCP)-based scaffold using an electrohydrodynamic printing (EHDP) process. Cellular activities using preosteoblasts (MC3T3-E1) helped confirm that the newly designed bioceramic scaffold demonstrated significantly high metabolic activity and mineralization compare the traditional 3D printed material. Other researchers propose a new strategy to fabricate an alpha-tricalcium-phosphate (α-TCP)/collagen cell-laden scaffold, using preosteoblasts (MC3T3-E1), in which the volume fraction of the ceramic exceeded 70% and was fabricated using a two-step printing process. To fabricate a multi-layered cell-laden scaffold, we manipulated processing parameters, such as the diameter of the printing nozzle, pneumatic pressure, and volume fraction of α-TCP to attain a stable processing region. A cell-laden pure collagen scaffold and an α-TCP/collagen scaffold loaded with cells via a simple dipping method were used as controls. Their pore geometry was similar to that of the experimental scaffold. Physical properties and bioactivities showed that the designed scaffold demonstrated significantly higher cellular activities, including metabolic activity and mineralization, compared with those of the controls [22]. Novel cryogenic 3D printing technique was investigated and developed by Wang C et al. [23] and all. for producing hierarchical porous and recombinant human bone morphogenetic protein-2 (rhBMP-2)-loaded calcium phosphate (Ca-P) nanoparticle/poly(L-lactic acid) nanocomposite scaffolds, in which the Ca-P nanoparticle-incorporated scaffold layer and rhBMP-2-en capsulated scaffold layer were deposited alternatingly using different types of emulsions as printing inks. The mechanical properties of the as-printed scaffolds were comparable to those of human cancellous bone. Sustained releases of Ca2+ ions and rhBMP-2 were achieved and the biological activity of rhBMP-2 was well-preserved. Scaffolds with a desirable hierarchical porous structure and dual delivery of Ca2+ ions and rhBMP-2 exhibited superior performance in directing the behaviors of human bone marrow-derived mesenchymal stem cells and caused improved cell viability, attachment, proliferation, and osteogenic differentiation, which has suggested their great potential for bone tissue engineering.

The electrospinning method is the most common due to its capability to produce fibrous materials with their structure and fiber diameters similar to those of natural extracellular matrix (ECM). Some advantages of electrospun scaffolds include the presence of high surface area for cell attachment and high porosity to facilitate nutrient and waste exchange [24]. Solution electrospinning is also a simple and inexpensive scaffold fabrication technique, and a wide range of polymeric solutions can be used to fabricate the scaffolds. However, the main disadvantage of electrospinning is the involvement of toxic organic solvents during fabrication, which can be harmful to cells [25]. However some methods as melt electrospinning, which does not involve the use of organic solvents and NanoMatrix3D-
electrospinning (NM3D) are now promising alternatives to solution electrospinning [26]. On the other hand side, fibers obtained from melt electrospinning process are thicker than those fabricated from solution electrospinning. NM3D has some advantage over conventional electrospinning as it uses optimized and steriley produced products. NM3D provides cells with greater space for proliferation, and cells cultivated in NM3D are immersed in the cultivation medium bottom. NM3D products are primarily used for research of cell adhesion, expansion and differentiation in vitro.

Synthetic polymers (macromolecules) are the primary materials for scaffolds in various tissue engineering applications [14]. They are classified as absorbable and non absorbable polymers. The resorbable polyesters are predominant among synthetic polymers. They include polyactic acid (PLA), polyglycolic acid (PGA), polyactic-polyglycolic acid (PLGA), polyethylene glycol (PEG), PEG with PLGA (PEG-PLGA), and polycaprolactone (PCL) [27]. PLA and PGA are synthetic polymers with excellent biomaterial characteristics that are dependent on the ability to control their synthesis, which influences the final surface characteristics, they are degraded in the body by chemicals and not cell-mediated processes [28]. Their rapid degradation and low mechanical strength, difficulties associated with their production, and their uncertain interaction with cells are disadvantages as it could cause early failure of the graft. PLGA is a copolymer obtained by the union of lactic and glycolic acid through ester bonds. The different relationships between the two monomers and the different sequences that can be obtained greatly increase the variability of the final scaffold used in clinical practice, with several different formulations and resorption times [29]. PEG is a polymer with a high molecular weight and is very resistant to resorption and it has been used in combination with MSCs and peptides with good results [29]. PCL has good mechanical characteristics and very long resorption times (of up to three years) and degrades via hydrolysis of the ester bonds [30]. It has been combined with HA and chitosan to form hybrid scaffolds with better mechanical resistance and has also been used in association with MSCs and growth factors [31].

More attractive but less controlled base for scaffolds are natural polymers such as collagen, cellulose, gelatin, silk, hyaluronic acid, chitin and chitosan. Numerous research in copolymers of PLA-collagen, PCL-chitosan etc. have shown better cell response and increasing mechanical properties as well as better bio-resorption comparing isolated polymers [32].

A wide range of exogenous growth factors are currently being used in bone tissue engineering: transforming growth factor beta (TGF-b1), fibroblast growth factor (FGF), insulin growth factor (IGF), vascular endothelial growth factor (VEGF), PDGF, and bone morphogenic proteins (BMPs) etc. [33,34]. Wen B et al. [35] have shown that application of BMP-2 (50 μg) to Straumann Bone Ceramic leads to significant mineralisation and new bone formation compared the non-loaded scaffolds. As shown by Chang HC et al. [36] BMP-loaded PLGA microspheres effectively promoted osteogenic potential of the gelatin/HA/β-TCP composite and facilitated supra-alveolar ridge augmentation in vivo. Enhancement in osteogenic differentiation and osteoinductivity of bioactive glass have also been achieved by incorporation of BMP-2 [37]. It is still not clear the safety of BMP clinical application due to possible risk of cancer induce that reported by Poynton & Lane [38]. Some researchers suggest dose depends of BMP to cancer risk [39] but optimal amount of this protein is not clear. Dynamic mechanical loading is other strong anabolic signal in the skeleton, increasing osteogenic differentiation of bone mesenchymal stem cells and increasing the bone-forming activity of osteoblasts [40]. Despite these numerous findings, the ideal stimuli for bone tissue regeneration has not been yet established.

### Tissue Engineering Selected Application

Treatment of skeletal defects has remained a challenging part of many reconstructive surgeries. Currently, autologous bone is assumed to be the gold standard for bone grafting [41]. Bone substitute materials are recommended when the quantity of autogenous bone needed is greater than available amounts of autogenous bone [42] and when there is a risk of morbidity at the donor site [43]. Bone tissue engineering is emerging as a possible solution for regeneration of bone in a number of applications. For effective utilization, scaffolds still need modifications to impart biological cues that drive diverse cellular functions such as adhesion, migration, survival, proliferation, differentiation, and biomineralization [34]. A top-down approach for building bioactive and cell instructive biomaterial scaffolds is to create scaffold-ECM hybrid constructs by depositing extracellular matrix secreted by tissue-specific/stem cells on bare biomaterial scaffolds. Different synthetic materials have been used for scaffold construction. Because synthetics are chemically created, and are part of a controlled manufacturing process, their physical properties (i.e., composition, morphology, and resorbability) are exceptionally reproducible. Combination of natural and synthetic polymers shows some advantages in bone tissue engineering. Some studies indicate positive effect of PCL/chitosan [44], PCL/collagen [45]. PLA/hydroxyapatite [46], TEA/BOC-treated chitosan [47] for bone regeneration. Natural and synthetic polymers has been used to improve some existing solution for bone engineering e.g. bioactive glass scaffolds, that have weak mechanical properties. Wei Xiao et al. [48] and coauthors suggest to use of adherent polymer layer to the external surface of strong porous bioactive glass. These bioactive glass-PLA composites, combining bioactivity, high strength, high work of fracture and an internal architecture shown to be conducive to bone infiltration, could provide optimal implants for healing structural bone defects. But the ideal combination of scaffold/cell type and growth factors for tissue engineering constructions is not yet defined.

Chronic wounds affect over 4 million individuals and pose a significant burden to the US healthcare system [49]. Advances in tissue engineering have allowed for the development of cell-based wound dressings that promote wound healing by improving cell migration and differentiation. Most cell-based dressings utilize a scaffold upon which cells are seeded. Scaffolds are designed to easily integrate with host tissue and provide an optimal environment for cell growth and differentiation. The
cells themselves further encourage the progression of tissue formation [50]. Skin transplantation cannot be performed in large skin defects because of low diffusion and limited interaction with the host environment for nutrients, gas exchange, and removing the waste products. Collagen, chitosan, hyaluronic acid, fibrin, and gelatin are all natural materials used to produce biomimetic scaffolds, which have been applied for the repair and reconstruction of various tissues [51]. Synthetic polymers have some advantages compared with natural polymers. They are strong and have controllable degradation rates, are less expensive, having more reliable sources of raw material and can provide a wide range of physical properties using various fabrication techniques [52]. Despite acceptable results in epithelialization of keratinocytes with synthetic polymers, no successful epidermal graft has been achieved, due to their limited cellular recognition and tissue compatibility. Synthetic polymers in combination with natural polymers can be used for temporary dressing, epidermal/dermal cell carriers, or full-thickness skin equivalent [53]. PLGA/collagen [54], PLA/chitosan [55], PCL/chitosan [56], PCL/collagen [57] currently used for skin graft development.

Patients who have injuries or traumas in the nervous system often suffer from the loss of sensory or motor function, and neuropathic pains because nerves have a very limited capacity to regenerate [58]. In the peripheral nervous system, direct end-to-end surgical reconnection is a common method of treatment for nerve transaction injuries when the injury gap is small. The use of autograft, allograft or xenograft has many limitations, including donor scarcity, multiple surgeries, donor site morbidity, scarring, and the need for an allograft patient to take immunosuppressants indefinitely after surgery to avoid rejection [59]. The application of cell-based nerve regeneration therapies has been considered as a promising strategy for the treatment of large peripheral nerve injuries. Some 3D grafts for nerve conduits were developed and successfully tested both in vitro and in vivo. Gelatin-based nanoporous [60], silk fibroin/silk sericin [61], water-based biodegradable polyurethane, PLGA, PLA/collagen, PCL [62] with Mesenchimal Stem Cells (MSCs), neural stem/progenitor cells (KT98/FI B-GP) and Schwann cell have shown promising results during long term in-vivo studies.

Conclusion

Tissue engineering is expanded to all the areas of reconstructive surgery but still has some limitation for wide clinical application due to gaps between experimental research and clinical practice. Polymers and Biomolecules, such as collagen and chitosan are agents of choice for scaffold development but it is desirable to improve their mechanical properties and custom manufacturing. Growth factors and drug-delivery concept in tissue engineered materials can manage tissue development, decrease bacterial inflammation and enhance tissue regeneration. Combination of different methods for scaffold development (electrospinning, 3D printing, sol-gel) allow to create custom scaffolds for tissue replacement.

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Conflict of Interest

None.

References

1. Bracaglia LG, Smith BT, Watson E, Arumugasamy N, Mikos AG, et al. (2017) 3D Printing for the design and fabrication of polymer-based gradient scaffolds. Acta Biomater 56: 3-13.
2. Bedian L, Rodriguez AM, Varghese GH, Parra Saldivar R, Iqbal HM (2017) Bio-based materials with novel characteristics for tissue engineering applications-A review. Int J Biol Macromol 98: 837-846.
3. Jagur Grodzinski J (2006) Polymers for tissue engineering, medical devices, and regenerative medicine. Concise general review of recent studies. Polym Adv Technol 17(6): 395-418.
4. Ozdil D, Aydin H (2014) Polymers for medical and tissue engineering applications. J Chem Technol Biotechnol 189(12): 1793-1810.
5. Gruber R, Stadlinger B, Terheyden H (2016) Cell-to-cell communication in guided bone regeneration: molecular and cellular mechanisms. Clin Oral Implants Res 28(9): 1139-1146.
6. Spurin JW 3rd, Nelson CM (2017) Building branched tissue structures: from single cell guidance to coordinated construction. Philos Trans R Soc Lond B Biol Sci 372(1720).
7. Ngadiman NH, Noordin MY, Idris A, Kurniawan D (2017) A review of evolution of electrospun tissue engineering scaffold: From two dimensions to three dimensions. Proc Inst Mech Eng H 231(7): 597-616.
8. Yam GH, Williams GP, Setiawan M, Yusoff NZ, Lee XW, et al. (2017) Nerve regeneration by human corneal stromal keratocytes and stromal fibroblasts. Sci Rep 7: 45396.
9. Zhang JX, Guo WM, Li P, Liu SY, et al. (2017) Adipose tissue-derived periocytes for cartilage tissue engineering. Curr Stem Cell Res Ther 12(6): 513-521.
10. Klar AS, Zimoch J, Biedermann T (2017) Skin tissue engineering: application of adipose-derived stem cells. Biomed Res Int 2017: 9747010.
11. Kassis I, Zangi L, Rivkin R, Levdansky L, Samuel S, et al. (2006) Isolation of mesenchymal stem cells from G-CSF-mobilized human peripheral blood using fibrin microbeads. Bone Marrow Transplant 37(10): 967-976.
12. Sato K, Yamawaki Ogata A, Kanemoto I, Usui A, Narita Y (2016) Isolation and characterisation of peripheral blood-derived feline mesenchymal stem cells. Vet J 216: 183-188.
13. Strong AL, Neumeister MW, Levi B (2017) Stem cells and tissue engineering: regeneration of the skin and its contents. ClinPlast Surg 44(3): 635-650.
14. Coluzza F, Atrash J, Saratchandra P, Carabelli I, Chester AH, et al. (2014) Shear stress and VEGF enhance endothelial differentiation of human adipose-derived stem cells. Growth Factors 32(5): 139-149.
15. Kachgal S, Putnam AJ (2011) Mesenchymal stem cells from adipose and bone marrow promote angiogenesis via distinct cytokine and protease expression mechanisms. Angiogenesis 14(1): 47-59.
16. Levenberg S, Rouwkema J, Macdonald M, Garfein ES, Kohane DS, et al. (2005) Engineering vascularized skeletal muscle tissue. Nat Biotechnol 23(7): 879-884.
17. Geccarelli G, Presta R, Benedetti L, Gusella De Angelis MG, Lupi SM, et al. (2017) Emerging perspectives in scaffold for tissue engineering in oral surgery. Stem Cells Int 2017: 4585401.

18. Hosseinpour S, Ghazizadeh Ahsae M, Rezai Rad M, Baghani M, Motamedian SR, et al. (2017) Application of selected scaffolds for bone tissue engineering: a systematic review. Oral Maxillofac Surg 21(2): 109-129.

19. Zema L, Melocchi A, Maroni A, Garzaniga A (2017) 3D printing of medicinal products and the challenge of personalized therapy. J Pharm Sci 106(7): 1697-1705.

20. Chen H, Xie S, Yang Y, Zhang J, Zhang Z (2017) Multiscale regeneration scaffold in vitro and in vivo. J Biomed Mater Res B Appl Biomater.

21. Kim M, Yun HS, Kim GH (2017) Electric-field assisted 3D-fibrous bioceramic-based scaffolds for bone tissue regeneration: Fabrication, characterization, and in vitro cellular activities. Sci Rep 7(1): 3166.

22. Kim WJ, Yun HS, Kim GH (2017) An innovative cell-laden α-TCP/collagen scaffold fabricated using a two-step printing process for potential application in regenerating hard tissues. Sci Rep 7(1): 3181.

23. Wang C, Zhao Q, Wang M (2017) Cryogenic 3D printing for producing hierarchical porous and rhBMP-2-loaded Ca-P/PLLA nanocomposite scaffolds for bone tissue engineering. Biofabrication 9(2): 025031.

24. Zarghami N, Sheerivalkou R, Fattahi A, Mohajeri A, Dadashpour M, et al. (2017) An overview on application of natural substances incorporated with electrospun nanofibrous scaffolds to development of innovative wound dressings. Mini Rev Med Chem.

25. Kitsara M, Agbulut O, Kontziamasis D, Chen Y, Menasché P (2017) Fibers for hearts: A critical review on electrospinning for cardiac tissue engineering. Acta Biomater 48: 20-40.

26. Vyslouzilova L, Berezkivova L, Vodseckalkova K, Vejsadova L (2016) Unique nanofibrous scaffolds for cell culture. International conference Biomimplantologie. Brno 28-29.

27. Pilipchuk SP, Plonka AB, Monje A (2015) Tissue engineering for bone regeneration and osseointegration in the oral cavity. Dent Mater 31(4): 317-338.

28. Tanatweethum N, Liu W, Goebel W, Li D, Chu T (2015) Fabrication of Poly-Hactic acid/dicalcium phosphate dihydrate composite scaffolds with high mechanical strength-implications for bone tissue engineering. J Funct Biomater 6(4): 1036-1053.

29. Willerth S, Sakiyama Elbert S (2008) Combining stem cells and biomaterial scaffolds for constructing tissues and cell delivery. In: Willerth S & Sakiyama Elbert S (Eds.), Stem Book, Harvard Stem Cell Institute, Cambridge, UK.

30. Rezwan K, Chen QZ, Blaker JJ, Boccaccini AR (2006) Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering. Biomaterials 27(18): 3413-3431.

31. D’Anto V, Raucci MG, Guirro V, Martina S, Valletta R, et al. (2016) Behaviour of human mesenchymal stem cells on chemically synthesized HA-PCL scaffolds for hard tissue regeneration. J Tissue Eng Regen Med 10(2): E147-E154.

32. Wang X, Wu X, Xing H, Zhang G, Shi Q, et al. (2017) Porous nanohydroxyapatite/collagen scaffolds loading insulin PLGA particles for restoration of critical size bone defect. ACS Appl Mater Interfaces 9(13): 11380-11391.

33. Shayesteh YS, Khajesteh A, Soleimani M, Alkhasi M, Khoshabahan A, et al. (2008) Sinus augmentation using human mesenchymal stem cells loaded into a β-tricalcium phosphate/hydroxyapatite scaffold. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 106(2): 203-209.

34. Knesedy V, Kasper FK (2016) Approaches for building bioactive elements into synthetic scaffolds for bone tissue engineering. J Mater Chem B Mater Biol Med 4(42): 6773-6786.

35. Wen B, Shafer D, Schleier P, Pendrys D, Kuhn L, et al. (2017) Implant-guided supracrestal alveolar bone growth using scaffolds, BMP-2, and novel scaffold-retaining device. Clin Oral Implants Res 28(11): 1411-1420.

36. Chang HC, Yang C, Feng F, Lin FH, Wang CH, et al. (2017) Bone morphogenetic protein-2 loaded poly (DL-lactide-glycolide) microspheres enhance osteogenic potential of gelatin/hydroxyapatite/β-tricalcium phosphate cocrystal composite for alveolar ridge augmentation. J Formos Med Assoc.

37. Keothongkham K, Charoenphandhu N, Thongbunchoo J, Sunthornsararat P, Krishnamra N, et al. (2017) Evaluation of bioactive glass incorporated poly(caprolactone)-poly(vinyl alcohol) matrix and the effect of BMP-2 modification. Mater Sci Eng C Mater Biol Appl 74: 47-54.

38. Peyton AR, Lane JM (2002) Safety profile for the clinical use of bone morphogenetic proteins in the spine. Spine (Phila Pa 1976) 27(16 Suppl 1): 540-548.

39. Devine JG, Dettori JR, France JC, Brodt E, McGuire RA (2012) The use of rhBMP in spine surgery: is there a cancer risk? Evid Based Spine Care J 3(2): 35-41.

40. Lynch MR, Chou AE, Lee MJ, Marcott SC, Polam nju PV, et al. (2016) Three-dimensional mechanical loading modulates the osteogenic response of mesenchymal stem cells to tumor-derived soluble signals. Tissue Eng Part A 22(15-16): 1006-1015.

41. Behnia H, Khajesteh A, Esmaeelinejad M, Naghdli N (2012) Growth factor carriers in bone formation: a systematic review. Journal of Islamic Dental Association of Iran 24: 150-167.

42. Hasani A, Khajesteh A, Alkhasi M, Vaziri H (2009) Measurement of volume changes of sinus floor augmentation covered with buccal fat pad: a case series study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 107(3): 369-374.

43. Khajesteh A, Behnia H, Dachtli SC, Stevens M (2012) Current trends in mesenchymal stem cell application in bone augmentation: a review of the literature. J Oral Maxillofac Surg 70(4): 972-982.

44. Shalumon KT, Sowmya S, Sathish D, Chennazhi KP, Nair SV, et al. (2013) Effect of incorporation of nanoscale bioactive glass and hydroxyapatite in PCL/chitosan nanofibers for bone and periodontal tissue engineering. J Biomed Nanotechnol 9(3): 430-440.

45. Tan RP, Lee BS, Chan AH, Yuen SC, Hung J, et al. (2017) Non-invasive tracking of injected bone marrow mononuclear cells to injury and implanted biomaterials. Acta Biomater 53: 379-388.

46. Zhang H, Mao X, Du Z, Jiang W, Han X, et al. (2016) Three dimensional printed macroporous poly(lactic acid)/hydroxyapatite composite scaffolds for promoting bone formation in a critical size rat calvarial defect model. Sci Technol Adv Mater 17(1): 136-148.
47. Su H, Liu KY, Karydis A, Abebe DG, Wu C, et al. (2016) In vitro and in vivo evaluations of a novel post-electrospinning treatment to improve the fibrous structure of chitosan membranes for guided bone regeneration. Biomed Mater 12(1): 015003.

48. Xiao W, Zaeem MA, Li G, Bal BS, Rahaman MN (2017) Tough and strong porous bioactive glass-PLA composites for structural bone repair. J Mater Sci 52(15): 9039-9054.

49. Pourmousa A, Gardner DJ, Johnson MB, Wong AK (2016) An update and review of cell-based wound dressings and their integration into clinical practice. Ann Transl Med 4(23): 457.

50. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, et al. (2009) Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen 17(6): 763-771.

51. Metcalfe AD, Ferguson MWJ (2007) Tissue engineering of replacement skin: the crossroads of biomaterials, wound healing, embryonic development, stem cells and regeneration. JR Soc Interface 4(14): 413-437.

52. Oryan A, Alemzadeh E, Moshiri A (2017) Burn wound healing: present concepts, treatment strategies and future directions. J Wound Care 26(1): 5-19.

53. Patel M, Fisher JP (2008) Biomaterial scaffolds in pediatric tissue engineering Pediatr Res 63(5): 497-501.

54. Sadeghi Avalshahr AR, Khorsand Ghayeni M, Nokhasteh S, Molavi AM, Naderi Meshkin H (2017) Synthesis and characterization of PLGA/collagen composite scaffolds as skin substitute produced by electrospinning through two different approaches. J Mater Sci Mater Med 28(1): 14.

55. Peschel G, Dahse HM, Konrad A, Wieland GD, Mueller PJ, et al. (2008) Growth of keratinocytes on porous films of poly(3-hydroxybutyrate) and poly(4-hydroxybutyrate) blended with hyaluronic acid and chitosan. J Biomed Mater Res A 85(4): 1072-1081.

56. Oh GW, Ko SC, Je JY, Kim YM, Oh J, et al. (2016) Fabrication, characterization and determination of biological activities of poly(ε-caprolactone)/chitosan-caffeic acid composite fibrous mat for wound dressing application. Int J Biol Macromol 93(pt B): 1549-1558.

57. Jin G, Li J, Li K (2017) Photosensitive semiconducting polymer-incorporated nanofibers for promoting the regeneration of skin wound. Mater Sci Eng C Mater Biol Appl 70(pt 2): 1176-1181.

58. Chang WC, Klot M, Sretavan DW (2008) Microtechnology and nanotechnology in nerve repair. Neur ol 30(10): 1053-1062.

59. Cao H, Liu T, Chew SY (2009) The application of nanofibrous scaffolds in neural tissue engineering. Adv Drug Deliv Rev 61(12): 1055-1064.

60. Uz M, Büyükoz M, Sharma AD, Sakaguchi DS, Altinkaya SA, et al. (2017) Gelatin-based 3D conduits for transdifferentiation of mesenchymal stem cells into Schwann cell-like phenotypes. Acta Biomater 53: 293-306.

61. Rao J, Cheng Y, Liu Y, Ye Z, Zhan B, et al. (2017) A multi-walled silk fibroin/silk sericin nerve conduit coated with polylacto-co-glycolic acid sheath for peripheral nerve regeneration. Mater Sci Eng C Mater Biol Appl 73: 319-332.

62. Peng SW, Li CW, Chiu IM, Wang GJ (2017) Nerve guidance conduit with a hybrid structure of a PLGA microfibrous bundle wrapped in a micro/nanostructured membrane. Int J Nanomedicine 12: 421-432.