

## An Overview on Bone Tissue Engineering and Regenerative Medicine: Current Challenges, Future Directions and Strategies

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Rec date: Nov 25, 2014, Acc date: Nov 27, 2014, Pub date: Nov 28, 2014

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### Editorial

Large bone defects in the setting of large tissue loss could occur due to of many reasons such as multiple, gunshot, comminuted, and or other complicated fractures, bone tumors (e.g. osteosarcoma), massive avascular necrosis, severe osteomyelitis, advanced osteoporosis and open fractures [1]. In such cases, a considerable amount of diseased bone that has no vascular supply or cannot be used in bone reconstructive surgery, should be removed from the patient's body and the resulting defect should be stabilized and filled or reconstructed with bone substitutes [1,2]. Unfortunately classic options such as auto- and allografts have significant limitations and thus, alternative strategies should be used to reconstruct such large bone defects [1]. Another goal is to accelerate and enhance the quality of the bone repair in the shortest possible time [1]. In the last decade, tissue engineering and regenerative medicine (TERM) in its new concept by means of combination of tissue scaffolds, healing promotive factors and cells or stem cells have been introduced to orthopedic research and sports medicine [1,2]. Although several TERM based products have been introduced to the market in the recent years, none of them provided an acceptable solution with favorable outcome at long term follow-up [2]. Novel strategies using TERM based products are still under investigation.

For designing a suitable bone substitute TERM based graft, some important characteristics have to be considered including, osteoconduction, osteoinduction, osteoincorporation, osteointegration and osteogenesis [2]. In addition, the graft should have biocompatibility and biodegradability [2]. To date, no TERM based graft having all the above mentioned characteristics has been designed, manufactured and its efficacy on bone healing and regeneration investigated. To design such a desirable graft, two points should be kept in mind including: 1) the composition of the graft should mimic the native healthy bone matrix. 2) the architecture of the graft should mimic the healing environment. To address these issues, the graft should be produced by using natural based polymers such as collagen, elastin, gelatin, hydroxyapatite, chitosan and three- or octa calcium phosphate [2]. These polymers provide optimum grades of biocompatibility and biodegradability. Unfortunately, most of the commercially available grafts are produced from synthetic polymers such as polyglycolic acid, polygalactin 910, and polydioxanone having low biodegradability and prolong the chronic inflammation which is not clinically pleasant [2]. Natural polymers have also an optimum osteoconductivity; the ability of a graft to guide tissue regeneration between bone edges [2]. However the biodegradability of the natural polymers is fast thus the implanted graft may not contributed in all

parts of the healing process therefore, combining natural rapid absorbable (as major part) with synthetic low absorbable (as minor part) polymers, a hybrid scaffold can be produced with controllable absorbability [2,3]. Using natural polymers as major part of a graft also increases the osteoincorporative and osteointegrative properties of a TERM based graft because natural molecules have excellent bioactivity during bone repair [2]. The major challenge is the osteoinductivity of the TERM based grafts. In fact, there are few options for inducing bone mineralization and bone formation so that most of the TERM based grafts can only trigger osteoconduction with low effectiveness on osteoinduction. In such cases, the new tissue fills the defect completely but has inferior mechanical property so that it would not be able to tolerate weight bearing forces due to the lack of mineralization [2,3]. The most investigated osteoinductive agent is a group of bone morphogenetic proteins (BMPs), in which the type II is a popular type [3]. However, the BMPs have significant limitations and their high cost is their most important limitation [3]. Alternative osteoinductive agents are currently under investigation [4-8]. Platelet rich plasma and platelet gel are natural sources of growth factors and could contribute to bone induction however concerns are arising in their real efficacy on the healing process [2,4]. Recent studies have suggested that platelets may have only a modulatory role on inflammation and their growth factors may not be a major contributor during healing [4]. Strontium and bisphosphonates (e.g. alendronate) have been shown to reduce osteoporosis and recent investigations suggest their role on osteoinduction. However, these compounds inhibit osteoclastic reaction which is a part of bone remodeling [5,6]. Another option is nanocrystalline hydroxyapatite (nHA). nHA has been suggested to have osteoinductive property because HA in its nanoform has superior specific surface area than its microstructure form and thus it has a superior biologic activity [7]. Statins such as simvastatin and lovastatin are routinely used for reducing blood cholesterol while recent investigations showed their beneficial roles during bone formation and mineralization [8]. However, to induce bone formation by statins, significantly higher doses than clinical use, should be used which is a great concern in clinical practice [2]. Controlled drug delivery through the TERM based grafts may solve this issue in the future [3]. As the final solution, pre-differentiated osteoblasts or mesenchymal stem cells together with mature osteocytes could be seeded on the TERM based grafts to induce bone formation. All these strategies are new and under investigation [2,3].

Future approaches should focus on newer strategies such as three dimensional printing, scaffold free strategies and controlled drug delivery systems in order to solve these limitations. Unfortunately most of the TERM based investigations are in vitro with low value in

translational medicine. The real efficacy of novel and newer TERM approaches should be tested in clinically relevant animal models with proper methodology and design in order to better clarify the in vivo roles of TERM during bone healing and regeneration. Some concerns such as host-graft interaction, viability of the implanted cells, duration of the post-implanting inflammation and the graft behavior in the host body should carefully be addressed.

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