Title: eBone System: Systems Biology Approach for Bone Regeneration

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Engineering vascularized bone tissue for scaffolding and repairing remains a significant clinical problem. One major challenge is to develop systematic models based on coordinated experiments. Bone regeneration via tissue engineering efforts involves a series of dynamic events that involves the scaffolds, signaling cues, vascularization, as well as the interactions between them. Given many in-vitro and in-vivo experimental efforts to promote osteogenesis and angiogenesis, such coordinated processes during bone regeneration have often only been examined from individual aspects, and thus a predictive and translational model is yet missing. Another challenge is to understand the underlying mechanisms of the synergistic effects from temporal combinations of growth factor cues. It has long been known that bone development or post-trauma wound repairing involves a series of growth factors expressed in-situ in well-controlled temporal sequences. Such temporal combinations of growth factor cues play crucial roles in osteogenic differentiation of Mesenchymal Stem Cells (MSCs) and successful bone formation and functions, but the underlying mechanisms yet remain mysterious, which significantly limit the prediction of effective growth factor delivery and the design of growth factor release scaffolds. The third challenge in bone tissue engineering is the establishment of a well functional vascular network. The utmost goal of this project is to address these challenges by integrating biological experiments, material engineering, and multi-scale modeling to systematically optimize the bone regeneration. The system is called sBone system. Our studies cast new lights on addressing these challenges. 1) Using the classical BMP2/IGF1 dual-growth-factor temporal combination system as the biological model, our systems biology research, especially the functional module based signaling pathway inference using sequential Monte Carlo approaches (mSMC) and the multi-time-scale model, supported by coordinated experiments and multi-scale bio-assay and high-throughput screening, demonstrated the induction of Smad1/2 signaling pathways of MSCs by BMP2, which gradually remodels the expression pattern of Runx2 and Osx pathways, and thus sensitizes MSCs to the late IGF1 cue. Meanwhile we also showed the capabilities of accurately and independently controlling release rates of individual growth factors by integrating the slow-release chitosan hydrogels and delayed release gelatin micro-beads embedded in artificial bone scaffolds. We engineered the BMP2/IGF1 dual controlled release bone scaffolds and proved the hypothesis remains valid for the bone regeneration in three-dimensional (3D) macro-porous β-calcium phosphate (TCP) scaffolds. 2) We developed novel 3D multi-scale system models to study the effects of temporal combination of growth factors controlled by the gelatin micro-beads releasing system and the vascularization events from the pre-embedded human umbilical vein endothelial cell (HUVEC) central channels of macro-porous TCP scaffolds and the effects on bone regeneration. Our preliminary studies indicate that the 3D multi-scale models can be potentially applied to predicting vascularized bone regeneration with specific growth factor combinations and scaffold designs.