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MEETING REPORT

Principles of engineering tissue regeneration (Sun Valley 2012)

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Meeting Report from the 42nd International Sun Valley Workshop: Musculoskeletal Biology, Sun Valley, ID, USA, 5–8 August 2012

Tissue engineering and regenerative medicine is a maturing interdisciplinary field that integrates bioengineering principles, fundamental biological discoveries and translational medicine to produce new clinical therapies for restoring damaged or diseased tissue function. This workshop session discussed the general principles of engineering tissue regeneration with focus on musculoskeletal tissues. Bone, cartilage, muscle, and other connective tissues are prime targets for regenerative engineering strategies given that musculoskeletal tissue damage associated with acute injury or chronic degeneration represents the most common cause of pain and functional disability worldwide. Clinical efforts to restore structural integrity and function to musculoskeletal tissues are often complicated by the local biomechanical environment, advanced age, adjacent tissue trauma, infection, ischemia conditions, or systemic diseases, which conspire to overwhelm endogenous repair mechanisms. Recent biological discoveries have introduced candidate growth factors, small molecules, and stem cells that may be exploited to promote endogenous repair mechanisms for modulating inflammation, vascularization, cellular function, and extracellular matrix synthesis. However, successful delivery of regenerative biological cues requires careful consideration of bioengineering factors related to biomaterial scaffold design, mass transport, and biomechanical environment.

Dr Guldberg led off the session with an overview and historical context of the field. The first meeting on 'Tissue Engineering' was a workshop organized by the National Science Foundation in 1988 in Lake Tahoe, California. From the beginning, it was recognized that tissue engineering needed to be multidisciplinary with participation from multiple federal agencies, industry and investigators in various areas such as cell biology, medicine and bioengineering. A report from this workshop provided the following definition: 'Tissue engineering is the application of principles and methods of engineering and life sciences toward fundamental understanding of structure–function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve tissue functions.' Although the field of tissue engineering and regenerative medicine has evolved and expanded, this early definition of the field is still highly relevant. A critical step in the maturation of the field occurred in 2005 when the Tissue Engineering and Regenerative Medicine International Society (TERMIS) was formed by consolidating several related organizations. TERMIS now consists of three chapters (for the Americas, Europe and Asia-Pacific) and has over 3700 members worldwide. More importantly, while the gauntlet of commercialization and regulatory barriers remains a significant challenge, clinical therapies that incorporate regenerative technologies are gaining traction.

Dr Guldberg concluded with a general paradigm for engineering tissue regeneration that involves: (i) understanding the impediments that limit the ability of each individual tissue to repair/regenerate, (ii) identifying key inductive signals and common regenerative cues, (iii) developing 'deployment' technologies such as fibers, gels and micro/nanoparticles that provide the spatial and temporal presentation of differentiation cues to augment endogenous repair mechanisms, and (iv) quantitative testing in critical defect- or disease-compromised preclinical models. Dr Guldberg then presented data demonstrating that a new hybrid biomaterials delivery system developed in his laboratory involving an injectable hydrogel loaded with bone morphogenetic protein and contained within a perforated nanofiber mesh outperformed the current clinical standard and completely restored the biomechanical function of large femoral bone defects 12 weeks post treatment.[1–3] He then discussed the role of the *in vivo* biomechanical environment in tissue revascularization and repair. Using a custom-designed internal fixation device and 3D vascular imaging, he showed that early loading inhibits the ingrowth of nascent blood vessels, disrupts the biomaterial–tissue interface and prevents initiation of bone regeneration. However, delaying mechanical loading by just 4 weeks did not disrupt vascular ingrowth or

tissue integration and in fact stimulated an increase in blood vessel thickness and subsequent bone formation.[4]

Dr Hani Awad next addressed a major challenge in cartilage tissue engineering—regeneration of the anisotropic extracellular matrix structure of native articular cartilage. The oriented structure and directional dependent properties of cartilage have important mechanical and biological consequences that may influence integrative repair strategies. He reported that hydrodynamic conditions that mimic the synovial flow fields at the articular surfaces within articular joints induce a boundary region with enhanced interstitial flow[5] that leads to the formation of a superficial layer in tissue-engineered cartilage hydrogels.[6] The biomimetic flow conditions also enhanced the production of cartilage matrix proteoglycan, type II collagen and the surface zone protein Proteoglycan 4 (that is, lubricin). Detailed analysis of collagen in this superficial layer showed a highly aligned fibrillar matrix that resembled the alignment pattern in the surface zone of articular cartilage.[6] These results are consistent with previous findings[7,8] and suggest that stimulating engineered cartilage with synovial fluid flow conditions in hydrodynamic bioreactors may promote the formation of anisotropic superficial zone features similar to those of native articular cartilage.

Dr Gordana Vunjak-Novakovic then described their efforts to create patient-specific, functional human bone for clinical use.[9] The approach involves directing stem cells to assemble functional tissue structures by seeding them into anatomically shaped biomaterial scaffolds, which serve as a template for tissue formation, and culturing the cell-seeded scaffolds in bioreactors designed to enhance mass transport and provide biophysical and biochemical signals.[10,11] She noted that human engineered tissues of high biological fidelity could also be used for studies of disease, drug development and 'human in a dish' screening platforms.[12] For all of these applications, biomaterials, bioreactors and imaging modalities must be integrated. Dr Vunjak-Novakovic next described the ability to tissue engineer living anatomically shaped, clinically sized human bone grafts for craniofacial reconstruction. The complex 3D shape of the bones required a new generation of a perfused 'anatomical' bioreactor integrated with on-line imaging. Dr Vunjak-Novakovic concluded by discussing the evolution of the biomimetic approach to engineering functional human bone/cartilage composites, and some of the current challenges: vascularization, functional integration, remodeling and the establishment of interfaces with adjacent soft tissues.

Dr Hank Donahue's talk addressed the regulation of osteoblastic differentiation by biophysical stimuli, which has the potential to enhance bone formation and healing for musculoskeletal tissue regeneration. He introduced two potent mechanisms by which biophysical signals enhance bone cell differentiation. First, Dr Donahue showed that surface features including hydroxyapatite (HAP) nanotopography strongly affect cell adhesion, osteoblastic differentiation and matrix mineralization. Although the mechanisms are not fully understood, surface topography enhances cytoskeletal organization and focal adhesion kinase (FAK) signaling.[13] Dr Donahue next showed how specific HAP nanotopographies increase osteoblastic differentiation *in vitro* and new bone formation following graft surgery. He also showed that osteogenesis can be regulated by mechanical signals, and provided evidence that nanotopographies can further sensitize cells to the effects of fluid flow, suggesting a potential synergy between fluid flow and nanotopography.[14] He summarized his talk by suggesting that biophysical stimuli including fluid flow and nanotopography, alone or in combinations, represent a promising approach to enhance osteogenesis and improve the healing of musculoskeletal tissues.[15]

Dr Anusuya Das, an ASBMR Harold M. Frost Award Winner, concluded the session with a talk demonstrating that local biomaterials-mediated delivery of a novel S1P sphingolipid receptor-specific drug can accelerate bone regeneration by promoting neovascularization and osteogenesis. This final young investigator talk was a perfect example of the convergence of principles of life sciences, physical sciences and engineering to address unmet clinical needs for restoring function to damaged or degenerated musculoskeletal tissues.

Note: Abstracts from the 42nd International Sun Valley Workshop: Musculoskeletal Biology can be accessed at: http://www.ibmsonline.org/p/cm/ld/fid=156

Conflict of Interest

The authors declare no conflict of interest.

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