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# Micro- and Nanoengineering of Biomaterials for Healthcare Applications

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Many advances in healthcare industry have been enabled by innovations in materials science and engineering. Materials science has revolutionized medicine in a range of applications from the implantable stents for treating occluded blood vessels to degradable polymers for cancer drug delivery (Langer et al). While much attention has been given to the chemistry and the physical properties of these materials, it is now clear that the architecture of these materials is also important for directing their biological performance (Khademhosseini et al). Thus, appreciating the intricacies of materials architecture as well as combining these advantages with advances in materials chemistry may ignite future advances in biomedical industry. This issue of *Advanced Healthcare Materials* was especially commissioned and prepared to highlight the latest advances in the application of micro- and nanoscale engineering of materials for various biological and biomedical applications. This issue comprises a number of original research articles and state-of-the-art reviews on the development and applications of micro- and nanoscale technologies for biomedicine.

With advances in cell biology it is becoming increasingly clear that cells can respond to their surrounding microenvironment and particularly to the micro- and nanoscale cues in an efficient and controlled manner. For example, it is known that much of the extracellular matrix (ECM) fibers in the body, such as collagen fibrils, are in the orders of a few tens of nanometers in diameter. Cells can sense and respond to these spatially oriented cues by reorganizing their cytoskeleton as well as activating specific signal transduction pathways. Furthermore, the intricate organization of cells and their spatial organization relative to each other and the surrounding ECM is important in regulating their cell fate decisions.

One area that has been broadly utilized micro- and nanoscale techniques to control the behavior of cells is through surface patterning. In a paper in this issue of the journal Jiang and colleagues discuss the various approaches to pattern surfaces (Zheng et al). In particular, they demonstrate that the combination of surface chemistry and microengineering can be used to regulate the cellular adhesion and morphology. In addition to surface chemistry, surface topology can also be used for influencing the surrounding biology for medical applications. Two papers in this issue highlight specific aspects of the engineering of surface topography for regulating biological systems. Guvendiren and Burdick demonstrate the use of a microengineered surface topography that is dynamically regulated for controlling stem cell behavior (Guvendiren et al). They show that strain responsive dynamically actuated buckling patterns could be used to gain novel insights into mesenchymal stem cell (MSC) alignment and differentiation. Such work could be of great interest in designing the next generation of scaffolds for bone and cartilage tissue engineering applications. Fratzel and colleagues describe engineering of geometry as a guiding principle for regulating stem cell behavior (Fratzel et al). Their work demonstrates that the shape of engineered pores in scaffolds can change the dynamics of matrix disposition by osteoblasts and that pore shape is of great importance in the resulting tissue formation. In addition, Xia and colleagues discuss the development of size-controlled inverse opal-like geometries, which was used to create controlled porosity within polymeric scaffolds (Choi et al). It was demonstrated that smaller pores formed small blood vessels with poor penetration

depth whereas larger pores formed larger vessels at lower densities with higher penetration depths. Thus by regulating the pore microarchitecture the resulting blood vessels were controlled.

Engineered surface topography can also be used for biomedical applications. One such area that has recently emerged is the use of micro- and nanoscale topography as adhesive materials. Some biological organisms, such as geckos, use hierarchical hairs on their toe pads as adhesive surfaces to climb walls and trees. By using a bioinspired approach, Suh and colleagues have developed a micropillar based adhesive patch (Bae et al). They used replica molding and selective inking to generate composite elastomeric micropillars that were adhesive and mechanically robust. Such surface features can be incorporated on various medical devices as adhesives in applications beyond the skin patch and open new opportunities in utilizing nanoscale topography for medical application.

Nanoparticles have also been broadly used for various biomedical applications. Due to their small size, nanoparticles can penetrate tissues and be uptaken by cells, thus they provide immense opportunity in drug delivery, imaging and biosensing. In this issue a number of papers highlight the latest advances in the application of nanoparticles for various therapeutic applications. One area that has drawn a great deal of attention is the application of nanoparticles for cancer therapeutics. Couvreur and colleagues describe the development of cancer therapies for tumor treatment (Couvreur et al). Given the small size of these particles and their tendency to accumulate in the tumors, this area has great potential in delivering therapies directly to tumors while minimizing side effects associated with toxic chemotherapies. Another area that has attracted significant interest is to use nano- and microparticles for immune therapeutics. The goal of this area of research is to sensitize the immune system by delivering antigens to generate a vaccine. Roy and colleagues discuss the latest advances in this area and provide an overview of the use of polymeric nano- and microparticles in developing effective vaccines by understanding and modulating the B and T cell responses (Roy et al).

In addition to drugs and antigens, other types of therapeutics can also be delivered using nanoparticles. Recently, siRNA delivery has become a highly active area of research due to the advances in understanding and utilizing siRNA for various therapies. In this issue, Leroux and colleagues describe the development of novel calcium phosphate-based nanoparticles for the delivery of siRNA molecules (Giger et al). Nanoparticles can also be loaded with other types of cargo. For example, Webster and colleagues demonstrate the utility of superparamagnetic iron oxide nanoparticles (SPIONs) for the delivery of anti-bacterial materials by conjugating these particles with silver and delivering the resulting particles to biofilms (Durmus et al). By targeted delivery of silver-SPION conjugates, these particles could potentially be used in place of antibiotics for which some bacteria have developed resistance.

Engineering the physical and biochemical properties of biomaterial is of great interest for fabricating scaffolds for tissue engineering. Engineered materials can be fabricated

with micro- and nanoscale to control cell-material interactions to address major problems in tissue engineering such as vascularization, and biomimetic tissue function (Peppas et al, Bae 2 (Sci. Trans. Med)). Two review articles in this issue present the latest advances in the engineering of approaches to induce tissue regeneration (Hubbell et al, Thibault et al). Hubbell and colleagues describe the latest advances in engineering biomaterials that can induce healing and regeneration (Hubbell et al). Furthermore, Thibault et al discuss the application of such advances for the engineering of bone replacements (Thibault et al).

In addition to integrating biomimetic features in materials, other types of modifications can be used to enhance tissue formation. For example, Ambrosio, Guarino and colleagues describe the formation of conductive materials that can be fabricated in the shape of porous scaffolds to enhance the regeneration of neural tissues (Ambrosio et al). Such conductive materials can induce the coupling of electrical signals in the forming tissue and have been shown to also enhance the regeneration of other electrically active tissues, such as the myocardium. Taken together these approaches provide significant promise for enhancing tissue regeneration in vivo.

Microfabricated structures can also be used to control tissue culture conditions to regulate the differentiation of stem cells. Previously it has been demonstrated that microfabricated wells can be used to control the formation of stem cell aggregates with controlled sizes and shapes. In this issue, Lee and colleagues demonstrate an advance in this area by generating an array of concave microwells that can be seeded with stem cells (Lee et al). In another related paper, Schukur et al demonstrate that size-controlled stem cell aggregates that were generated using microfabricated wells could be seeded inside engineered hydrogels that could be used to direct the differentiation of the cells to endothelial or cardiac fates based on chemical modifications to the hydrogel adhesiveness (Schukur et al).

Biochemical and biomechanical microenvironment has also been shown to be of great importance in directing the differentiation of adult stem cells. In a paper published by Papoutsakis and colleagues (Jiang et al) a comparative analysis of chemical and nanomechanical materials properties of the stem cell microenvironment is performed to analyze its effect on the expansion and differentiation of adult MSCs and hematopoietic stem cells (HSCs). Their results demonstrate that although MSCs and HSCs have distinct adhesive properties, both of these cell types can sense the properties of the surrounding biomaterials including surface chemistry, topography and matrix elasticity. This understanding may be of great value in engineering the next generation of bioreactors that aim to induce the expansion and differentiation of such cell types for regenerative medicine applications.

Another area that has seen major advances in the past few years is the development of bioinspired materials that utilize the principles of biology for advancing human healthcare. One such material that has gained great attention is silk. Given its biocompatibility and mechanical properties, silk has proven to be a mechanically robust and biocompatible material. A paper in this issue by Kaplan and colleagues discusses

the development of silk-based protein biomaterials for wound healing applications (Gil et al). Silk-based dressings were used in combination with soluble growth factors and drugs to aid in the healing of cutaneous injury in a murine model. Such scaffolds were systematically analyzed based on their processing conditions (as silk films, porous films or electrospun nanofibers) and the mode of growth factor delivery (drug coatings or loading into the material) to optimize the resulting wound healing response. Such a systematic approach demonstrates a powerful approach for developing novel wound healing treatments.

In addition to silk, other types of bioinspired materials have been engineered to induce desired biological responses. In one example, Heilshorn and colleagues (Benitez et al) developed peptide-based materials that were inspired by elastin sequences. They demonstrated that the materials could generate electrospun nanofibers with biological and mechanical properties that mimicked native elastin molecules. Similarly, nanoengineered peptide-based materials have been developed for a range of other applications. In another example of this strategy, Stupp and colleagues (Zha et al) describe the use of peptide amphiphiles (PAs) for cancer therapy. PAs are made from peptides conjugated to hydrophobic tail groups that can self-assemble into nanofibers or membranes. By manipulating the sequences of the PAs, membranes with nanoscale porosity were engineered and used for sustained release of cytotoxic compounds for anti-cancer therapeutics. These results demonstrate the emerging use of nanoscale materials from peptide-based biomaterials for biomedical applications.

Biosensing is another area where micro- and nanoscale materials may result in significant advances. In many medical diagnostic or therapeutic applications, sensing is of great importance. One of the most important sensing applications is in sensing blood glucose concentrations for diabetes. Takeuchi and colleagues discuss the development of implantable biosensors for continuous glucose monitoring for diabetes applications (Morimoto et al). Although currently there are sensors available for many analytes, such as glucose, the development of miniaturized sensors that can be implanted may one day dramatically improve patient compliance and quality of life.

As the papers in this special issue illustrate, significant progress has been made in developing advanced micro- and nanoengineered biomaterials for a variety of healthcare applications. Given the significant advances that have been made in the past few years and the pace of current advancements, this field of research is highly promising for addressing major biomedical challenges and improving human health.

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