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Editorial

Synthetic Extracellular Matrices for Tissue Engineering

Tissue engineering is a multidisciplinary field that aims to regulate tissue structure and function in vivo, and provide more physiologically relevant model systems for *in vitro* studies. Three common strategies for tissue engineering include (1) the delivery of isolated cells or cell substitutes to replace damaged or missing cells, (2) the administration of cell-inducing substances (e.g., morphogens, cytokines), and (3) the growth of cells within three-dimensional matrices or scaffolds, either *ex vivo* or *in situ*. These approaches are rarely exclusive, with most strategies utilizing two or more of these techniques. One important aspect of tissue engineering includes the design and development of materials to serve as a temporary extracellular matrix that can provide sufficient mechanical reinforcement, and offer a platform for delivering bioactive components. Furthermore, successful engineering of tissues will likely be achieved using different techniques, as each tissue has unique metabolic and mechanical properties. Consequently, the discovery of the appropriate combination of cell-inducing strategies and the importance of targeted delivery of bioactive components has necessitated the generation of advanced synthetic extracellular matrices.

The design of synthetic extracellular matrices for tissue engineering applications provides a powerful opportunity to control tissue formation and function. The lack of response often noted in clinical trials following the systemic delivery or bolus injection of various cellular populations or soluble bioactive agents is likely due to the inefficient targeting of these factors, premature degradation as a result of short half lives, or the rapid diffusion of these components away from the target site. Biomaterials derived from both natural (collagen, fibrin, alginate) and synthetic (polyesters and polyurethanes) constituents have been widely used to provide localized delivery of various bioactive factors for a sustained time while also providing sites for cellular colonization and proliferation. The mechanical properties of these materials can be tailored to match those of the regenerating tissue. Lastly, the degradation characteristics of these matrices enable an additional level of control, with tissue invasion ideally correlating with biomaterial degradation, while also offering a means to control the release rate of bioactive molecules.

This theme issue presents three articles focused on the critical issue of creating vascular structures. Large conducting vessels and networks of small distributing vessels are both likely to be of significant direct therapeutic utility in the treatment of cardiovascular disease. Further, the engineering or regeneration of any tissue of significant thickness will require the formation of an appropriate vascular system, and the technologies presented in these articles will likely be of core importance in those efforts. In particular, these articles relate to the development of synthetic extracellular matrices for vascular tissue engineering, using a variety of different materials. Collagen sponges have been widely used as biomaterials to fill bone defects and deliver osteoconductive proteins (e.g. BMP-2 and BMP-7), and Leu *et al.* describe the proangiogenic potential of a bioactive glass/collagen substrate that has the potential to serve as a temporary extracellular matrix. Their data support the hypothesis that biomaterials are more than inert substrates which allow cellular colonization and proliferation, and localized delivery of small amounts of a bioceramic can play an active role in cellular behavior. Yao *et al.* explored the potential of a natural biomaterial, fibrin, to reinforce the mechanical properties of tissue engineered conducting blood vessels derived from smooth muscle cell-seeded fibrin constructs. The addition of a cell-free layer of fibrin surrounding a cell-containing fibrin layer yielded a tissue engineered blood vessel with markedly enhanced mechanical properties which retained its contractility and vascular reactivity. Fibrin is a component of the body's native wound healing response, contains a cocktail of endogenous growth factors, and provides an effective platform for loading and sustained delivery of pharmacological moieties that can direct cellular behavior.

The studies mentioned above were performed *in vitro* using cultured cells, although each is associated with previous studies carried out *in vivo*. Examining the role of biomaterials in tissue engineering within the *in vitro* environment is a critical first step for developing new technologies, as the environment associated with tissue defects targeted for regeneration is commonly less than optimal and may even be hostile. However, *in vitro* data must eventually be validated in living systems. As an example of bridging *in vitro* data with *in vivo* studies, Kong *et al.* investigated the potential of localized plasmid DNA from alginate hydrogels with carefully engineered degradation profiles. Gene therapy is a promising alternative to protein delivery, yet numerous complications related to toxicity and insufficient transgene expression following gene delivery has dampened enthusiasm. In this article, the authors demonstrated that a gene encoding for a potent angiogenic factor (vascular endothelial growth factor) could be delivered over 2 weeks, and the release kinetics were directly related to the degradation of the matrix. The sustained delivery of this genetic material in a murine hindlimb ischemia model yielded enhanced blood perfusion and vascular density, and did not result in pronounced inflammation.

The research articles featured in this theme issue are examples of the focused efforts to utilize biomaterials as a tool to engineer vascular tissues specifically, but the material systems and concepts are widely applicable in the field. In addition to their potential clinical utility, these systems may also serve as valuable tools to improve our understanding of the biology related to certain physiological and pathological conditions. Further advances in tissue engineering will likely be achievable through the development of biomaterials that mimic to an even greater extent the multifunctionality of the extracellular matrix.

David Mooney is the Gordon McKay Professor of Bioengineering in the Harvard School of Engineering and Applied Sciences at Harvard University. His laboratory is focused on the design and synthesis of materials that define microenvironments, or niches, that regulate the fate of either transplanted cell populations or cells already resident in tissues. These polymeric systems mimic the native extracellular matrix in their spatiotemporal control of information presentation to cells, and may find special utility in controlling stem cell populations. The applications of these systems include the regeneration of damaged or diseased tissues (tissue engineering), or the targeted destruction of undesirable tissue masses in the body. Dr. Mooney was previously a faculty member at the University of Michigan, and his education and training is from the University of Wisconsin, Massachusetts Institute of Technology, and Harvard Medical School. He is a Fellow of the American Institute of the Medical and Biological Engineering, a NIH MERIT awardee, the recipient of the Clemson Award from the Society for Biomaterials, and has received the NSF CAREER award. His inventions have been licensed by eight companies for development and he is active on industrial scientific advisory boards.

J. Kent Leach is Assistant Professor in the Department of Biomedical Engineering, University of California, Davis, CA, USA. His laboratory aims to engineer functional replacement and temporary bridge tissues while also developing model systems to study physiological and pathophysiological tissue formation. Two primary areas on interest include the development of novel biomaterials and the sustained delivery of macromolecules from various biomaterials to promote tissue regeneration. His education is from the University of Arkansas and University of Oklahoma, while he received postdoctoral training at the University of Michigan and Harvard University.

INTERVIEW QUESTIONS FOR DR. KENT LEACH AND DAVID MOONEY

1. What do you think holds the key to your success as researchers?

A driving curiosity about how things work, a desire to solve problems, and a short memory of criticism have been quite helpful. The scientific process of investigation and communication of findings is based on criticism and is often quite negative to new ideas, so obtaining real joy from your ideas and findings is crucial to forge onward over time.

2. What do you consider to be your key research accomplishments?

Two accomplishments to date that I consider to be quite important is our development of (1) technologies that enable blood vessel formation and function to be engineered via localized and sustained delivery of morphogens and cells (angiogenesis on demand), and (2) materials that regulate, via well defined molecular pathways, the fate of transplanted cells and greatly enhance their ability to form new tissues or regenerate existing, damaged tissues.

3. What was the turning point in your career?

(Mooney) I had the opportunity to work on the scale-up process for a small molecule drug while working at Dow Chemical. The idea that I could utilize my engineering abilities and training to help people and solve medical problems led me to graduate school and a career in the biomedical arena.

(Leach) While in graduate school, my advisor provided to me the chance to shift gears on my project and personalize it, perhaps to a greater degree than many of my peers. The exciting events which unfolded as a result of this opportunity fanned my research curiosity and eventually led me to an academic career in the biomedical and drug delivery area.

4. Who are the individuals who most influenced your research career?

(Mooney) There have been numerous individuals who had a great influence, but I will mention four in particular here. First, Robert Langer at MIT, from whom I learned to look at the big picture of my research, and to consider the potential of new ideas instead of focusing on criticism. Secondly, Joseph Vacanti of Harvard, who showed me the medical need motivating the field of tissue engineering, and provided a research environment in which I could mature scientifically during graduate school. Third, Donald Ingber, also of Harvard, who taught me most of what I know about the scientific method, and the need to be rigorous in one's research. Finally, Robert Nerem of Georgia Tech, from whom I learned the importance of creating structures in which everyone benefits, and the power of collaborative efforts to accomplish big goals.

(Leach) Two individuals have had a tremendously positive influence on my career. Edgar O'Rear at the University of Oklahoma influenced me by granting space to excel independently while also encouraging me to keep in mind the engineering aspects of research. David Mooney of Harvard provided a research environment with countless opportunities to grow scientifically and professionally.

5. Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does it mean cutting edge science will not likely be featured in the Pharmaceutical Research?

The development of new technologies and ideas for therapies, while often driven by a medical need, frequently also provides new capabilities to address basic questions. Further, the multidisciplinary nature of the tissue engineering field necessitates that there is constant cross-talk between scientists, engineers, and clinicians of varied backgrounds. Pharmaceutical Research provides an extremely valuable vehicle for communication within this diverse audience, and we anticipate that both new technologies, and the fundamental questions that may be addressed with the new capabilities will be published in Pharmaceutical Research.

6. What are the challenges, and where is the field of Synthetic Extracellular Matrices for Tissue Engineering going? How do the articles in the theme section fill the gap?

Future advances in tissue engineering will likely require the development of matrices that can effectively serve a variety of roles, in place of the current generation of materials that more often simply bridge a defect. The rational design of matrices that can enhance tissue formation, whether by improving the mechanical and degradation properties or offering the potential to deliver tissue-inducing substances more effectively, is a critical focus of research. The articles within this theme section demonstrate that the appropriate selection or design of extracellular matrices can have a profoundly positive impact on cell behavior and tissue formation.

One of the major challenges facing this entire field is the development of a new vascular bed to support the metabolic needs of the engineered or regenerating tissues, and all three articles in this theme section address this issue. The development of large, conducting vessels, and networks of small distributing vessels are highlighted in this theme issue, as the ability to create both types of structures is absolutely critical to forming new tissues of any significant volume. In the future, technologies to create both types of vessels must be integrated to create complete vascular networks, and we anticipate this will be a major focus for the next few years.

7. What is the key to developing successful collaborative relationships?

All parties should bring something to the table, whether it is a specialized technique, novel biomaterial or bioactive factor, and both parties must benefit from the interaction. It is best if all parties are fully engaged in the project, and appreciate its various aspects.

8. What is your philosophy of educating graduate students?

We believe that the foremost goal of a Ph.D. education is developing the ability to perform independent research. To accomplish this, students must be given freedom to generate new ideas, and be provided a supportive environment that encourages their creativity and allows them to test their ideas. The advisor should help the student evaluate and develop their ideas (e.g., understand when an idea is ground-breaking *versus* incremental, and the difficulty in pursuing a given idea), and teach them how to effectively communicate their findings to the community.

9. What is the place for collaboration with industry in academia?

The tissue engineering field has historically involved considerable collaboration between industry and academia, and this has often driven progress in the field. Industry often has a better sense of the real problems facing a field, a better ability to translate findings to the clinic, and in certain fields has a better infrastructure to perform measurements than do academic labs. Academic labs will often, though, generate major advances in a field due to their ability to take a more fundamental approach to understanding the problem, and a broader view as to possible solutions. Collaborations between industry and academia can thus result in advances that neither party could make alone, and the fields of pharmaceutical research, biomaterials, and tissue engineering are ideal for these relationships to flourish. However, success depends on partnerships that combine the advantageous features of the two groups (e.g., problem input from industry with creative problem-solving in academics), and not subjugate one to the other (e.g., turning an academic lab into a fee for service enterprise solving minor problems for industry).

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