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BIOMATERIALS INNOVATION

Regenerative Engineering

THIS YEAR MARKS THE 25TH ANNIVERSARY OF THE FIELD OF TISSUE ENGINEERING. The bioengineer Y. C. Fung first proposed the term at a 1987 meeting of the National Science Foundation's Director for Engineering, Bioengineering and Research to Aid the Handicapped Program. Great interest in the field heightened with the paper by Langer and Vacanti in *Science* (*1*), which described it as "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ." Laurencin further defined it as "the application of biological, chemical and engineering principals towards the repair, restoration, or regeneration of living tissue using biomaterials, cells, and factors alone or in combination" (*2*).

Over the past 25 years, advances have been made in biomaterials-based tissue engineering research to repair organ systems. In the past decade, three areas of technology have emerged and have added to the "toolbox" available to biomaterials scientists and engineers, presenting exciting possibilities to moving beyond maintaining or repairing tissue to regenerating them. First, our appreciation of phenomena taking place in the nano-regime gained appreciation in the late 1990s and ushered in nanotechnology as a tool for engineering tissues, and advances in materials science have allowed us to harness those tools. Second, stem cell science has matured to where the use of stem cells is an everyday tool. We now have a deeper understanding of both adult and embryonic stem cells, and have developed and characterized induced pluripotent stem cells. Third, we have gained a more sophisticated understanding of developmental biology mechanisms in the salamander and the newt, and the role of the blastema in regeneration which has furthered our efforts in wound repair and regeneration. Each of these scientific advances has matured to the extent that they are now regarded as tools rather than simply concepts and ideas. It is with this in mind that we believe the future of tissue engineering lies in what can be termed "regenerative engineering."

We define regenerative engineering as the integration of tissue engineering with advanced material science, stem cell science, and areas of developmental biology. Regenerative engineering will harness and expand these newly developed tools toward the regeneration of complex tissues (*3*). Whereas tissue engineering sought to encourage interdisciplinary teams from the fields of engineering, science, and medicine, we see regenerative engineering as an expansion of this approach—a "convergence" (*4*) of tissue engineering with the three distinct fields above, to move beyond interdisciplinary scientific teams with siloed expertise toward an era in which scientists, engineers, physicists, and clinicians will have integrated training that spans these disciplines.

ADVANCED BIOMATERIALS SCIENCE

Tissue engineering has largely focused on the restoration and repair of individual tissues and organs, but over the past 25 years, scientific, engineering, and medical advances have allowed us to start considering the regeneration of complex tissues and biological systems. For instance, the traditional tissue engineering approach has used biomaterials from a limited pool of biodegradable and nondegradable polymers and ceramics to form three-dimensional structures to facilitate repair. The choice of biomaterials, however, has increased over the past 25 years to include polymers that can be designed with a range of mechanical properties, degradation rates, and chemical functionality. The polyphosphazenes are one good example. These and other advanced materials support a greater diversity of applications because their chemical versatility allows the polymer to be designed for a specific tissue or application rather than relying on extant materials repurposed as biomaterials.

Nanoscale control over scaffold architecture has led to a greater understanding of cellular sensitivity to topography. These tools are now being used to selectively control cell behavior—a potentially valuable resource when the inclusion of proteins and growth factors is not clinically possible and a requisite tool to move beyond single-tissue repair to complex multitissue regeneration. Biomaterials-based tissue engineering has also historically included the use and delivery of signaling molecules, such as growth factors, generally

one or two at a time, but advances in materials science have permitted multiplexed delivery with greater quantitative and temporal control over delivery kinetics and more sophisticated biochemical modifications, owing in part to the availability of new polymer subtypes.

Advanced biomaterials will play an important role in translating regenerative engineering to humans. Whereas other technologies aimed at regeneration encounter difficulties in translating functional characteristics from mouse to rabbit to larger animals to humans (effector molecules like BMP-2, for instance, which requires supraphysiological concentrations to obtain a physiological response), biomaterials have been found in many settings to have better functional outcomes in larger versus smaller animals and, in some cases, may have similar inductive capacity to effector molecules, capable of differentiating undifferentiated stem cells toward prescribed lineages.

STEM CELL SCIENCE

Recently, the Society for Biomaterials challenged each of six National Academy members to describe their perceived grand challenge for the field over the next 25 years (*3*). Limb regeneration was put forth by Laurencin to be one of the primary challenges. Although signaling molecules will continue to be an important regenerative engineering tool toward this challenge, cells represent the fundamental building block of new tissues. Recent and continuing advances in stem cell technology will play an essential role moving forward, especially in areas such as whole-limb regeneration. Whereas tissue engineering has largely focused on primary cells isolated from targeted tissues, regenerative engineering has set its sights on stem cell technology. What has become clear over the past decade is that cells alone are not enough—they need scaffolds or materials for physical structure to retain cell populations after implantation, to guide multipotential cells that are recruited or delivered to the repair site, or to provide a template for cells to lay down new extracellular matrices. The capacity for a synthetic substrate to be the driver of these cells toward multiple lineages solely through material-based cues is emerging, with many of these cues at the nanoscale as substrate-surface modifications. These inducible materials are now being designed with specific cell lineages in mind so as to allow distinct tissue types to regenerate next to one another. Micro- and nanoscale fabrication techniques will further this goal.

THE ROLE OF DEVELOPMENTAL BIOLOGY

Challenges associated with attaching macromolecules to scaffolds for subsequent delivery have encouraged small-molecule delivery. Many small molecules have shown great efficacy in promoting tissue regeneration, in some cases recapitulating cues from developmental biology; for example, cyclic adenosine 5′-monophosphate (cAMP), which is found ubiquitously in mammalian cells and acts as a messenger to other molecules to control diverse cellular processes such as differentiation and morphogenesis. Our group has recently demonstrated that a cAMP-dependent protein kinase (PKA)–specific cAMP derivative promotes in vitro osteoblastic differentiation in osteoblast-like cells and mesenchymal stem cells (*5*), suggesting that cAMP/PKA signaling is important for osteogenesis. Beyond bone, dibutyryl cAMP enhances cartilage differentiation in the limb-bud mesoderm both in cell cultures and in organ cultures (*6*), suggesting that there is a role for this small molecule in complex tissue regeneration. The goal moving forward is to identify similar molecules from developmental biology that, alone or in concert with others, effect complex tissue regeneration. Such combinations could even be controlled in time so that varying morphogen or small-molecule concentrations can work synergistically to guide tissue development or regeneration. Advanced biomaterials can be designed to impart spatiotemporal control over molecule release kinetics or to prevent effector molecule release and adhere them to the material, depending on the needs of the tissue being regenerated.

THE NEXT 25 YEARS

We wish to mention some important caveats. First, regenerative engineering will not be a panacea. Novel treatments and cures will not come easily and quickly, but they will come. The toolbox that we have discussed will undergo enlargement over the next 25 years to include new strategies, perhaps mergers with seemingly disparate technologies, such as biophysics, smart bionics, and the healing power of the mind. As surgeons, we have always admired the ability of the body to self-heal. Finding ways to control and augment these self-healing mechanisms will be an important goal in regenerative engineering.

As we look forward to the next 25 years, we feel that moving beyond individual tissue repair to complex tissues (*3*) and biological systems is necessary. This concerted regenerative engineering effort capitalizes on the concept of convergence (*4*) by incorporating advanced materials science, stem cell science, and developmental biology. With the regenerative toolbox described above, we feel that regenerative engineering will allow for exciting and dynamic choices for tackling important clinical challenges.

– Cato T. Laurencin and Yusuf Khan

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