Tissue Engineering

The Science of Tissue Engineering

The new field of tissue engineering has the objective of producing substitutes for a variety of human tissues and organs in need of repair or restoration. A widely accepted definition of tissue engineering is the application of the principles and methods of engineering and life sciences toward the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve functions.

The medical need for tissue and organ substitutes is enormous, in part because of the scarcity of organs for transplantation and in part because of the difficulties in overcoming immune responses to transplants. For example, more than 300,000 people with liver failure are admitted to U.S. hospitals each year, at a cost to society in medical expenses and lost wages of approximately $11 billion. Although several groups are working to develop a bioartificial liver, none has yet succeeded, and 30,000 people a year die from this disease. Important gains could be realized even if such a device were functional for only two weeks and could act as a temporary bridge to transplantation.

Research in tissue engineering is resoundingly multidisciplinary. Unlike the revolution in recombinant DNA technology and the production of therapeutic proteins, which was fueled predominantly by molecular biologists, the field of tissue engineering is a loose confederation of chemical engineers, physicians and surgeons, mechanical engineers, cell and molecular biologists, electrical engineers, immunologists, biochemists, and materials scientists.

Such a collection of varied disciplines is required for two reasons. First, tissue engineered products, present and future, are relatively complex, and their manufacture is complicated. Although many hurdles had to be overcome before recombinant DNA technology could be used for the manufacture of therapeutic proteins, the central paradigm was the production of a pharmaceutical. The issues confronted were fundamentally similar to those presented by the production of conventional pharmaceuticals, namely scale-up, purity, stability, and storage, even though the recombinant proteins are more complex.

Moreover, gene splicing technology is similar regardless of the gene being spliced, so that production of one recombinant protein is more or less like production of the next. This is not true for tissue engineered products, which are as varied in form and function as the tissues and organs of the body.

Again taking the liver as an example, most efforts to develop a bioartificial liver are focused on building an ex vivo device that would house functional hepatocytes. Production of such a cell-device hybrid requires not only methods for the isolation and purification of large numbers of viable hepatocytes, but also a device that provides an optimal environment for hepatocyte function and an optimal interface with the patient.

Second, the required operating conditions and specifications of tissue engineered products are diverse and multifactorial. All pharmaceuticals have essentially the same generic set of standards governing their formulation and use. Tissue engineered products must meet some of the same standards, such as toxicity, but there are additional parameters such as biomechanical forces and biocompatibility that affect their performance. Thus, tissue engineered products, which mimic multiple cell and tissue functions, must satisfy multiple design criteria and have correspondingly complex validation procedures.

By way of example, the artificial dermis currently available is a collagen-glycosaminoglycan cross-linked sponge with a top layer of silicone that acts as an epidermal barrier. Many interactive parameters were optimized in the design, including concentrations of collagen and glycosaminoglycans, porosity, mechanical strength, and cross-linking of the sponge as it relates to the biodegradation rate.

Medical needs for tissue and organ substitutes arise from congenital defects, trauma, infectious diseases, inherited diseases, environmental and age-related diseases, end-stage organ failure, and tumor resection. Thus, tissue engineered products can potentially influence the practice of medicine in many areas.

In trauma and plastic surgery, artificial skins are currently available for the treatment of burns and other defects of the skin. In endocrinology, encapsulated pancreatic islets are being tested for the treatment of diabetes. In orthopedics, new materials are being tested for artificial bone and bone repair. In rheumatology, cultured chondrocytes are currently available for restoring cartilage function. In neurosurgery, bioactive conduits to

See "The Artificial Liver" by Norman L. Sussman and James H. Kelly (May/June 1995), "Encapsulated Cell Therapy" by Robert P. Lanza and William L. Chick (July/August 1995) and "Bioengineered Skin Substitutes" by Jeffrey R. Morgan and Martin L. Yarmush (July/August 1997).

promote nerve regeneration are undergoing tests in animals. And in cardiology, tissue engineered heart valve leaflets are being tested in animal studies.

These examples demonstrate that the science of tissue engineering uses a wide range of technologies and is pursuing multiple research thrusts. Cells are central to many approaches, so a significant focus of the field is on methods for the ex vivo culture and manipulation of specific cell types. Efforts are being made to improve the proliferation of cells as well as to understand an ideal milieu for maximal function. Also important are efforts to identify and propagate stem cells, which are less differentiated cells of great growth potential that can be induced to differentiate along multiple pathways into the functional cells of specific organs.

Tissues and organs are three-dimensional structures with a highly ordered and functional extracellular matrix that, at a minimum, organizes cells and holds them together. The tissue engineering equivalent of the extracellular matrix is called a scaffold and may consist of natural or synthetic polymers, or both. Such extracellular matrix analogs are used alone or in combination with cells or bioactive molecules such as growth factor proteins to promote tissue repair or induce tissue formation.

The science of tissue engineering is relatively young. As with any new field struggling to gain legitimacy, the mix of promises and potential often exceeds current capabilities. Much excitement is generated by the rush to test the latest tissue engineered prototypes, but although these tests are at times informative and often successful, a basic science of tissue engineering must emerge to assure longevity for the field.

Basic science must tackle some difficult fundamental problems that are obstacles to the efforts of the entire tissue engineering field. Such problems as immune recognition of cells, the cascade of wound healing events, and the cellular and molecular basis of the foreign body reaction to implants are important areas of overlap with tissue engineering.

Other fundamental principles directly revelant to the goals of tissue engineering are improved understanding of the mass transport of substances within tissues and the importance of topology and three-dimensional structure to tissue function. Valuable lessons can also be learned from such seemingly distant fields as developmental biology, which seeks to determine the principles governing the formation of organs during embryonic development.

In forthcoming issues of **SCIENCE & MEDICINE**, this new department will describe research advances in tissue engineering. From time to time, articles will examine efforts to engineer specific tissues or organs as well as clinical trials of new tissue and organ substitutes. However, the goal of the majority of these articles will be to highlight fundamental scientific and engineering principles relevant to the goals of tissue engineering and clinical medicine. Our hope is to familiarize readers with present and future medical products of tissue engineering and, most importantly, the science and research that gave rise to these products.

JEFFREY R. MORGAN
MARTIN L. YARMUSH

Shriners Burns Research Center
Massachusetts General Hospital

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