Functional Tissue Engineering

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With 133 Figures

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Preface

Tissue engineering is an exciting new field at the interface of engineering and biology that uses implanted cells, scaffolds, DNA, proteins, protein fragments, and inductive molecules to repair or replace injured or diseased tissues and organs. Tremendous progress in biological and biomaterial aspects of this field have been accomplished to date, and several engineered tissues are now being used clinically. However, tissue engineers face major challenges in repairing or replacing tissues that serve a predominantly biomechanical function.

To meet this challenge, the United States National Committee on Biomechanics in 1998 adopted a new paradigm termed *functional tissue engineering* (FTE) to emphasize the importance of biomechanical considerations in the design and development of cell and matrix-based implants for soft and hard tissue repair. Functional tissue engineering represents a relevant and exciting new discipline in the field of tissue engineering. Since many tissues, such as those of the musculoskeletal, cardiovascular, and dental systems, are accustomed to being mechanically challenged, tissue-engineered constructs used to replace these tissues after injury or disease must certainly do the same. Of course, tissue engineers must also attempt to return normal biological activity in order for the construct to truly integrate with the surrounding tissues. Thus, the term *functional* can have many meanings, such as restoration of metabolic function. The primary focus of this text is on the role of biomechanical function in tissue engineering.

To more clearly delineate the important aspects of functional tissue engineering, the editors and a steering committee (Van C. Mow, Columbia University; Robert M. Nerem, Georgia Institute of Technology; Robert L. Spilker, Rensselaer Polytechnic Institute; Michael V. Sefton, University of Toronto; Savio L.Y. Woo, University of Pittsburgh) organized a Functional Tissue Engineering Workshop in September 2000 that serves as the basis for this text. The FTE conference was fortunate to attract a select group of biomedical engineers, biologists, and clinicians who contributed the chapters appearing in the book. From its inception, the organizers had four primary objectives in running the conference. These objectives were: (1) to increase awareness among tissue engineers about the importance of restoring function when engineering constructs; (2) to identify the critical structural and mechanical requirements needed for each con-

struct; (3) to provide a catalyst for the development of functional criteria in the design, manufacture, and optimization of tissue engineered constructs; and (4) to develop a teaching and reference text for students and investigators in the field of tissue engineering.

Stemming from these objectives were more specific goals of the conference. These goals are briefly described below and are the basis for the structure of the remainder of the book.

Primary Goals of Functional Tissue Engineering

In Vivo and *In Vitro* Responses of Native Tissue

1. **Establish *in vivo* load and deformation histories for native tissues under a wide range of activities of daily living.** These histories provide benchmarks against which tissue-engineered repairs can be compared.
2. **Establish safety factors and relevant biomechanical properties for native tissues under a wide range of activities of daily living.** For example, safety factors or ratios of failure force (determined from *in vitro* failure tests) to peak *in vivo* force need to be established in the normal operating ranges of a native tissue for different activities of daily living. Identify and prioritize structural and material properties determined within these *in vivo* ranges so as to provide useful design parameters for tissue-engineered repairs and replacements. These safety factors and biomechanical properties are likely to change with activity level and tissue location.
3. **Understand the biomechanical properties and structure-function relationships for native tissues.** Develop correlates among the biomechanical properties, tissue structure, and biochemistry of normal tissues.
4. **Determine the regulatory processes (including humoral and neurogenic factors) that cells experience *in vivo* as they interact with the extracellular matrix.** Understanding the critical interplay between biological signaling and mechanical forces *in vivo* is important to designing effective tissue engineered implants.

Functional Requirements and Design Parameters

5. **Identify a minimum set of qualification tests for each tissue type.** Select only those tests that are necessary and sufficient for a successful repair.
6. **Develop accurate computational models and corresponding computer simulation tools.** These models and tools should incorporate the functional demands of a native tissue/organ (mechanical properties and anatomies) to determine baselines so as to compare conditions in repair/regenerated tissue/organ in situ. The data should be subject specific data to characterize the local functional environment (mechanical, electrical, chemical) of tissues at scales ranging from systems, tissues, cells, and molecules. These data sets will provide validated predictions of clinically relevant, functional parameters.
7. **Optimize stress, strain, and strain rate characteristics of engineered constructs in culture and their biological, chemical, and morphological properties.** Design, fabricate, and test cell-matrix constructs in culture that can

tolerate expected *in vivo* loads and deformations (Goal 1) and that possess desirable biomechanical properties (Goal 2). If necessary, develop means to protect the constructs and to prepare the surfaces to improve integration into surrounding tissue (which itself may not be normal). Understand structure-function relationships for these constructs by also characterizing relationships between their biological, chemical, and morphologic properties.

8. **Verify *in vivo* load and deformation regimes for engineered tissues.** Determine *in vivo* force and/or deformation histories for already designed tissue engineered repairs for a wide range of activities of daily living. Compare these results with similar histories for native tissues.

Intrinsic Properties of Matrices, Biophysical Factors on Cells and Matrices, and Bioreactors/*In Vitro* Factors

9. **Define carriers to promote functional biological characteristics to enhance tissues and differentiation and incorporation *in vivo.*** Matrices are needed that can withstand the large *in vivo* forces that tissues must often withstand.
10. **Identify bioactive soluble stimulators of tissue regeneration (proteins or their genes)** and study these in the context of appropriate matrices and mechanical environment for each tissue specific application.
11. **Establish how changing mechanical, chemical, and biological regulating factors influence cellular activity in bioreactors and *in vivo* so as to guide tissue repair to be more like normal.** Determine how mechanical stimulation of cell-matrix implants modulates engineered tissue structure and function. Define biological indicators that promote structural enhancement both *ex vivo* and *in vivo.* Characterize bioreactor explant conditions (e.g., stress, strain, pressure, flow velocity, electric potential, and currents) to determine the specificity of mechanical signal transduction mechanism(s), thus enabling the engineering of tissue constructs to be optimized for *in vivo* use.

Assessment of Repair Function

12. **Develop minimally invasive implantation procedures for implants.** Formulate methods and protocols for testing the tissues to be engineered using surrogate markers (biological, imaging, or biomechanical).
13. **Solve implant size issues by exceeding functional limitations of diffusion.** Address problems of vascularization/perfusion.
14. **Explain how host genetic background affects adaptive responses to tissue engineered products, including functional incorporation and remodeling.** Effectively integrate tissue-engineered tissues into adjacent tissues. Correlate the same parameters in a diseased state at the time of reconstruction so as to understand the environment in which the tissue is implanted.

Clinical Evaluation

15. **Set clinical standards to determine whether the repairs and replacements are safe and efficacious after surgery, recognizing the potential impact of patient**

selection on the success of tissue engineering. The clinical tools to evaluate success (clinical, functional, anatomical) must be defined. Develop minimally invasive imaging methods (e.g., PET, FTIR, MRI) to validate biomechanical measurements, to assess remodeling, and to track the fate of implants after surgery. Select quantitative outcome measures to assess product performance in humans. Establish whether the goal of functional tissue engineering is to regenerate normal tissue or simply repair damaged or diseased tissue to meet expected demands.

16. **Establish appropriate (and inappropriate) patient rehabilitation regimes.** Surgical and postsurgical (rehabilitation) principles need to be defined to enhance tissue differentiation, incorporation, and durability.

Obviously, other issues must be considered that are also critical to the success of engineered constructs. These issues include electromechanical coupling (i.e., in muscle and other tissues), vaso-activity, electrical conduction cell-cell communication, cell source, quality control/manufacturing/storage/sterilization (e.g., shelf life, storage, handling procedures must be realistic and feasible). Furthermore, it will be necessary to define the relevance of animal models to the human condition in both health and disease and to correlate these parameters in human tissue to those measured in animal models.

In closing, the conference was truly fortunate to have the financial support of multiple organizations. These organizations included the Whitaker Foundation, the National Science Foundation, Georgia Tech/Emory Center for the Engineering of Living Tissues, and numerous companies including Advanced Tissue Sciences, BioMet, Orthologic, Orquest, Selective Genetics, and Zimmer. The conference was also fortunate to have active participation from representatives of the National Science Foundation (Sohi Rastegar) and the National Institutes of Health, including James Panagis and Harold Slavkin. We hope that this conference and text will set the tone for both research and training in tissue engineering for the next decade and will serve as the paradigm for academic/industrial interactions in this field. The conference is also leading to a synergy between biomaterials, biology, and biomechanics in the next generation of engineered tissue replacements.

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