# BIOREGENERATIVE ENGINEERING

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# BIOREGENERATIVE ENGINEERING: PRINCIPLES AND APPLICATIONS

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# CHAPTER SUMMARIES

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# PREFACE

Nature has created numerous elegant living systems, including the human, based on the hierarchical functional units—molecule, cell, tissue, and organ. A living system develops through a long evolutionary process, during which the system undergoes genotypic and phenotypic changes in response to environmental simuli. Whereas the environmental and genetic factors play critical roles in evolutionary development, they may induce disorders and injuries of the cell, tissue, or organ, resulting in impairment or destruction of the functional units and preventing the living system from functioning and survival. Since these disorders and injuries are inevitable events during the evolutionary process, Nature has designed various mechanisms for the repair or replacement of injured and disordered cells, tissues, or organs, leading to partial or complete restoration of the structure and function of the living system. Among these mechanisms is cell, tissue, and organ regeneration.

*Regeneration* is a natural process by which a mature living system repairs or replaces its lost cells, tissues, and organs by activating specific renewal mechanisms, resulting in the restoration of the structure and function of the system. The application of regeneration principles to the treatment of human disease is known as *regenerative medicine*. During the past decade (since the mid-1990s), extensive investigations have been conducted to elucidate the mechanisms of regeneration, leading to the development of regenerative technologies such as stem cell identification, expansion, and transplantation. It is hoped that the transplanted stem cells can engraft to target tissues or organs, differentiate to specified cell types, replace malfunctioned or lost cells, and thus restore the natural structure and function of involved tissues and organs. Preliminary investigations have demonstrated the potential of stem cell transplantation for the treatment of degenerative disorders and cell injury in experimental tests and clinical trials. However, a simple transplantation of stem cells may not solve all the problems in regenerative medicine, since the selected stem cells may not be designed for the therapy of a specified target tissue or may not be able to differentiate into the desired cell types in an environment that is not established for the stem cells. Thus, fundamental issues in regenerative medicine are how to induce stem cells to differentiate into specified functional cell types under given environmental conditions and how to integrate the stem cell-derived cells into the natural system.

Nature has established numerous barriers that prevent the transformation of stem and progenitor cells to specified cell types in developed adult systems, especially in the vital organs such as the brain, heart, and kidney, and thus hinder the regeneration of disordered or lost cells. To resolve such a problem, it is necessary to establish engineering strategies and technologies that alter the expression of specified genes and modulate the phenotypes of target cells, including stem and progenitor cells, and thus to break Nature's barriers and induce appropriate regeneration of disordered or lost cells. Bioregenerative engineering is a discipline established for addressing these issues.

In definition, *bioregenerative engineering* is to induce, modulate, enhance, and/or control regenerative processes by using engineering approaches and thus to improve the restoration of the structure and function of disordered or lost cells, tissues, and organs. Although the term *bioregenerative engineering* has seldom been used, the concept of bioregenerative engineering has long been applied to regenerative medicine. Typical examples include the enhancement of stem cell proliferation and differentiation by transfecting cells with selected mitogenic genes, the elimination of an undesired function by knocking down or knocking out a selected gene, and the improvement of stem cell engraftment, migration, and differentiation by modulating the content, distribution, and pattern of extracellular matrix in a tissue or organ substitute. Given the nature of the discipline, bioregenerative engineering can be considered the engineering aspect of regenerative medicine.

For the past decade, extensive studies have been conducted and a large amount of information has been accumulated in the area of bioregenerative engineering. A reference that systematically summarizes the bioregenerative engineering literature may assist the readers to understand the principles of and design therapeutic strategies in bioregenerative engineering. It was the hope of the author that this book would serve as such a reference.

The author would like to dedicate this book to his mother Jing-zhen Li, father Ding-an Liu, in-laws Tong Wu and Pei-lan Hou, wife Yu-hua Wu, daughter Diana Liu, and son Charley Liu for their sincere support for the work.

S. Q. Liu

*March 9, 2006*
*Evanston, Illinois*

# INTRODUCTION TO BIOREGENERATIVE ENGINEERING

Bioregenerative engineering is to induce, modulate, and/or control regenerative processes by using molecular, cellular, and tissue engineering approaches and thus improving the restoration of the structure and function of disordered or lost cells, tissues, and/or organs. Bioregenerative engineering is an emerging discipline established by integrating engineering principles and technologies into regenerative medicine. Although the term *bioregenerative engineering* is rarely used, bioregenerative engineering research has been conducted extensively for the past several decades. As we will see throughout the book, this research has elicited significant impacts in essentially all biomedical fields.

Bioregenerative engineering stems from several scientific disciplines, including molecular engineering, cellular engineering, and tissue engineering and may be considered the engineering aspect of regenerative medicine. *Regenerative medicine* is an emerging discipline that addresses restoration of the structure and function of disordered or lost cells, tissues, and organs on the basis of stem cell biology. Strategies for regenerative medicine are to identify and prepare stem and/or progenitor cells and transplant and/or stimulate the identified cells to or in a target tissue, where the stem and/or progenitor cells can differentiate into specified cell types in an appropriate regional environment and thus restore the structure and function of the injured or lost cells. Compared to regenerative medicine, bioregenerative engineering emphasizes the engineering modulation of the regenerative processes at the molecular, cellular, and tissue levels (Fig. I.1).

Regenerative engineering at the molecular level, which may be referred to as *molecular regenerative engineering*, addresses the promotion and control of molecular and cellular activities (e.g., cell signaling, gene expression, cell division, differentiation, migration, adhesion, secretion, and contraction/relaxation); the activation and control of residential stem and progenitor cells; the mobilization and recruitment of remote stem and progenitor cells; and the formation of functional structures by controlled administration of proteins, genes, antisense oligonucleotides, siRNA, and pharmacological substances. Examples of molecular regenerative engineering include the control of a target signaling pathway, the regulation of specific gene expression, and the enhancement or reduction in the proliferation and differentiation of a specified cell type by transfecting target cells with growth regulator genes.

Regenerative engineering at the cellular level, which may be referred to as *cellular regenerative engineering*, addresses the preparation, modulation, and transplantation of autogenous and/or allogenic stem/progenitor cells in a controlled manner, resulting in enhanced regeneration of functional cells and structures. Examples of cellular regenerative engineering include the transplantation of hematopoietic stem and progenitor cells to repopulate impaired leukocytes due to leukemia, the transplantation of embryonic and bone marrow-derived stem cells to the heart to differentiate into cardiomyocytes in cardiac infarction, and the transplantation of neuronal stem cells to the brain to alleviate the symptoms of Alzheimer's and Parkinson's diseases.

Regenerative engineering at the tissue level, which may be referred to as *tissue regenerative engineering*, addresses the construction of tissue-mimicking scaffolds integrated with mature, stem, or progenitor cells, and the implantation of the tissue scaffolds into target organs, thus inducing, enhancing, and/or controlling the regeneration of functional cells and tissues. An artificial scaffold may either function as a tissue substitute or serve as a framework for the regeneration of lost tissues. Examples of tissue regenerative engineering include the construction and implantation of artificial tissues and organs, such as joints, heart valves, and blood vessels. Other approaches, such as reduction of stretch-induced vascular bypass graft injury by structural reinforcement and stimulation of intestinal expansion by mechanical stretching, can also be used to engineer the regeneration at the tissue level. The overall goal of the three regenerative engineering approaches is to improve the therapeutic effects of regenerative medicine (Fig. I.1).

An important basis for bioregenerative engineering is that the cell is capable of conducting natural regenerative processes in response to cell injury and death. Examples of cell regeneration include the renewal of blood cells, epithelial cells in the gastrointestinal system and the skin, endothelial and smooth muscle cells in the vascular system, and hepatocytes. While certain cell types, such as the blood cell and epithelial cell, conduct rapid and intensive regeneration even under physiological conditions, other cell types, such as the neuron and cardiomyocyte, experience very limited regeneration even in response to cell injury and death. These cell-specific characteristics are evolved based on the intrinsic regenerative mechanisms unique to distinct cell types. The clarification of the control mechanisms of cell regeneration is an important task for regenerative engineering research.

The human body is an integrated system composed of a hierarchy of structures, including molecules, cells, tissues, and organs. Although Nature has designed and created these structures with nearly perfect functionality and protective mechanisms, unnecessary or even harmful alterations do occur as a result of gene mutation and environmental stimulation by chemical, biological, and physical pathogens, resulting in pathogenic disorders that may harm or destroy the physiological systems. In response to these changes, the molecules, cells, tissues, and organs are capable of detecting and repairing pathogenic disorders to a certain extent. However, the repairing capability is limited and dependent on a number of factors, including the state of the human protective systems, the nature of gene mutation, and the type and strength of environmental pathogens. In the case of defect or impairment of the protective mechanisms and/or exposure to an unusual pathogen, the human systems may not be able to conduct self-repair or regeneration processes. In severe cases, death is the ultimate consequence. Bioregenerative engineering is established to enhance and improve the repair and regeneration processes and thus to help the human systems recover from pathological disorders.

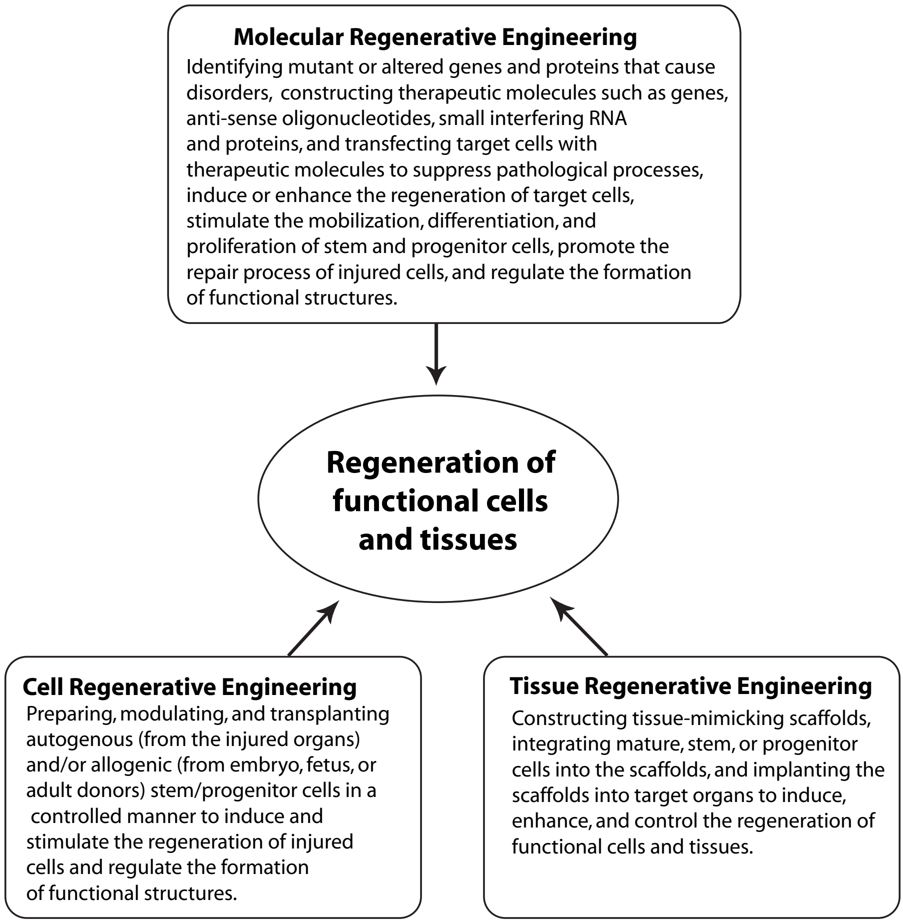


**Figure I.1.** Regenerative engineering at the molecular, cellular, and tissue levels.

During the past decade, regenerative medicine has become a popular research topic. However, current work relies primarily on simple engineering approaches, such as cell collection, expansion, and transplantation. These approaches may not change the fundamental course of natural processes and thus may not be sufficient to achieve optimal therapeutic effects. For certain types of vital organ, such as the brain and heart, Nature does not develop sophisticated regenerative mechanisms, presumably because these organs are well protected from environmental hazards and are not subject to frequent injury. However, injury and disorder do occur in these vital organs, often with deadly consequences. Thus, simple engineering approaches that do not alter the natural process may not be effective in inducing and enhancing the regeneration of these organs. A sophisticated engineering strategy and technology may be necessary to overcome Nature's barriers and to achieve the goal of regenerative therapies for these vital organs. Although it is a challenging task, regenerative therapies can be significantly improved by incorporating engineering principles and technologies into regenerative medicine.

The primary goal of this book is to introduce to the principles and technologies of bioregenerative engineering. Since bioregenerative engineering is built on the basis of various biomedical disciplines, including molecular biology, cell biology, developmental biology, physiology, pathology and bioengineering, the book will also address these fundamental disciplines. The book consists of two parts: the foundations of bioregenerative engineering, and the principles and applications of bioregenerative engineering. The first part covers the molecular, cellular, and developmental foundations of bioregenerative engineering. The second part covers general mechanisms and technologies of bioregenerative engineering, as well as the application of bioregenerative engineering to selected organ systems. For each organ system, the engineering tests and therapies are discussed at the molecular, cellular, and tissue levels, if applicable.

For the past decade, bioregenerative engineering has undergone rapid development, and engineering-based therapeutic approaches have been extensively tested in experimental models and clinical trials. A large amount of information has been accumulated in the literature. Although it is difficult to cover the information in all aspects in a single book, it was the hope of the author that this book would introduce to the readers the fundamental concepts, experimental approaches, and potential applications of bioregenerative engineering.