REGENERATIVE PHARMACOLOGY

Regenerative medicine is broadly defined as the repair or replacement of damaged cells, tissues, and organs. It is a multidisciplinary effort in which technologies derive from the fields of cell, developmental, and molecular biology; chemical and material sciences (i.e., nanotechnology); engineering; surgery; transplantation; immunology; molecular genetics; physiology; and pharmacology. As regenerative medicine technologies continue to evolve and expand across the boundaries of numerous scientific disciplines, they remain at the forefront of the translational research frontier with the potential to radically alter the treatment of a wide variety of disease and dysfunction. The goal of this book is to draw attention to the critical role that the pharmacological sciences will undeniably play in the advancement of these treatments. This book is invaluable for advanced students, postdoctoral Fellows, researchers new to the field of regenerative medicine and its companion field, tissue engineering, as well as experienced investigators looking for new research avenues. This is the first state-of-the-art book in this rapidly evolving field of research.

GEORGE J. CHRIST is Professor of Regenerative Medicine and Translational Science and head of the Program in Cell, Tissue and Organ Physiology at the Wake Forest Institute for Regenerative Medicine. He is an affiliate faculty in the Molecular Medicine and Molecular Genetics Programs, as well as the Virginia Tech–Wake Forest University School for Biomedical Engineering and Sciences. He also holds appointments in the Departments of Urology and Physiology and Pharmacology and the Sticht Center for Aging. He is the former director and founder of the Institute for Smooth Muscle Biology at the Albert Einstein College of Medicine. Dr. Christ is an internationally recognized expert in muscle physiology. He is the past chairman of the Division of Systems and Integrative Pharmacology of the American Society of Pharmacology and Experimental Therapeutics (ASPET) and past president of the North Carolina Tissue Engineering and Regenerative Medicine Society. He currently serves on the Executive Committee of the Division for Integrative Systems, Translational and Clinical Pharmacology of ASPET. He is on the editorial board of five journals and has authored more than 200 scientific publications. Dr. Christ has served on both national and international committees related to his expertise and has also served on NIH study sections in the NIDDK, NICHD, NCRR, and NHLBI. He has chaired working groups for both the NIH and the World Health Organization. Dr. Christ is a co-inventor on more than 24 patents (national and international), which are either issued or pending, related to gene therapy for the treatment of human smooth muscle disorders and tissue engineering technologies. He is a co-founder and directing member of Ion Channel Innovations, LLC, a development-stage biotechnology company pioneering the use of gene therapy for the treatment of human smooth muscle disorders. In addition, he is a co-founder and board member of Creative Bioreactor Design, Inc., another early-stage biotechnology company in the expanding field of regenerative medicine and tissue engineering.

KARL-ERIK ANDERSSON, MD, PhD, is Professor of Regenerative Medicine and Urology at Wake Forest Institute for Regenerative Medicine. He also holds appointments in the Departments of Physiology and Pharmacology and Molecular Medicine at Wake Forest University School of Medicine. He has Swedish Specialist Degrees in internal medicine and clinical pharmacology and a PhD in pharmacology from the University of Lund, Sweden. From 1978 to 2006, he was Professor and Chairman of the Department of Experimental and Clinical Pharmacology, University of Lund, and from 1993 to 2000, he was Vice Dean of the Medical Faculty at the University of Lund. Dr. Andersson has received several awards, including a Lifetime Achievement Award from the Society for Urodynamics and Female Urology. Dr. Andersson is a member of many international societies, including the American Urological Association, the European Association of Urology, and the International Society for Sexual Medicine. He has served on both national and international committees related to his expertise in basic and clinical physiology and pharmacology and has also served on NIH study sections in the NIDDK. He has chaired working groups for the International Consultation of Urogenital Diseases, supported by the World Health Organization. He also serves on the editorial boards of several journals, including the *Journal of Urology* (section editor), *Neurourology and Urodynamics* (associate editor), *and European Urology*, and is editor-in-chief of the *Urotoday International Journal*. Dr. Andersson has authored more than 800 articles in peer-reviewed international journals. His current research interests include clinical and basic physiology and pharmacology of the urogenital tract and regenerative medicine.

REGENERATIVE PHARMACOLOGY

Edited by

GEORGE J. CHRIST
Wake Forest Institute for Regenerative Medicine

KARL-ERIK ANDERSSON
Wake Forest Institute for Regenerative Medicine

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This book is dedicated to our parents, families, mentors, students, and colleagues.

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Contributors

Karl-Erik Andersson, MD, PhD
Professor
Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine
Winston-Salem, NC

Anthony Atala, MD
Chair, Department of Urology
Director, Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine
Winston-Salem, NC

Atta Behfar, MD, PhD
Assistant Professor
Marriott Heart Disease Research Program
Division of Cardiovascular Diseases
Mayo Clinic
Rochester, MN

Timothy A. Bertram, DVM, PhD
President, Research & Development
Chief Science Officer
Tengion, Inc.
Winston-Salem, NC

Stefanie Biechler, PhD
Biomedical Engineering Program
University of South Carolina School of Medicine
Columbia, SC

Peter R. Brink, PhD
Professor and Chair, Department of Physiology and Biophysics
Institute for Molecular Cardiology
Stony Brook University
Stony Brook, NY

David Burmeister, PhD
Postdoctoral Fellow
Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine
Winston-Salem, NC

Martin K. Childers, DO, PhD
Professor
Department of Rehabilitation Medicine
Institute for Stem Cell and Regenerative Medicine
University of Washington
Seattle, WA

George J. Christ, PhD
Professor
Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine
Winston-Salem, NC

Ira S. Cohen, MD, PhD
Professor, Department of Physiology and Biophysics
Director, Institute for Molecular Cardiology
Stony Brook University
Stony Brook, NY

Stephen A. Fann, MD
Associate Professor
Department of Surgery
Medical University of South Carolina
Charleston, SC

Harold I. Friedman, MD
Professor and Chief
Department of Surgery, Division of Plastic Surgery
University of South Carolina School of Medicine
Columbia, SC

Mark E. Furth, PhD
Chief Technology Officer
Comprehensive Cancer Center
Wake Forest School of Medicine
Winston-Salem, NC

Peter A. Galie
Graduate Research Assistant
Department of Biomedical Engineering
University of Michigan
Ann Arbor, MI

Gautam S. Ghatnekar, DVM, PhD
CEO and President
FirstString Research Inc.
Charleston, SC

Richard L. Goodwin, PhD
Associate Professor
Department of Cell Biology and Anatomy
University of South Carolina School of Medicine
Columbia, SC

Robert G. Gourdie, PhD, FAHA
Professor and Center Director
Virginia Tech Carilion Research Institute and
Virginia Tech–Wake Forest University School of Biomedical Engineering and Sciences
Roanoke, VA

Roche de Guzman, PhD
Postdoctoral Fellow
Virginia Tech–Wake Forest University School of Biomedical Engineering and Sciences
Virginia Polytechnic Institute and State University
Blacksburg, VA

Benjamin S. Harrison, PhD
Associate Professor
Wake Forest Institute for Regenerative Medicine
Wake Forest University Health Sciences
Winston-Salem, NC

Johnny Huard, PhD
Stem Cell Research Center
Department of Orthopedic Surgery
Department of Bioengineering
McGowan Institute of Regenerative Medicine
University of Pittsburgh
Pittsburgh, PA

Emily Ongstad, MS
Graduate Student
Clemson University–Medical University of South Carolina
Bioengineering Program
Virginia Tech Carilion Research Institute
Charleston, SC

Jay D. Potts, PhD
Associate Professor
Department of Cell Biology and Anatomy
University of South Carolina School of Medicine
Columbia, SC

Lola M. Reid, PhD
Professor
Department of Cell and Molecular Physiology
and Program in Molecular Biology and Biotechnology
University of North Carolina at Chapel Hill
Chapel Hill, NC

Justin M. Saul, PhD
Associate Professor
Department of Chemical and Paper Engineering
School of Applied Engineering and Science
Miami University
Oxford, OH

G. Sitta Sittampalam, PhD
National Center for Advancing Translational Sciences
National Institutes of Health
Therapeutics for Rare and Neglected Diseases
Rockville, MD

Bert Spilker, PhD, MD
Pharmaceutical Consultant
Bethesda, MD

Jan P. Stegemann, PhD
Associate Professor
Department of Biomedical Engineering
University of Michigan
Ann Arbor, MI

Andre Terzic, MD, PhD
Professor
Marriott Heart Disease Research Program
Division of Cardiovascular Diseases
Mayo Clinic
Rochester, MN

Panagiotis A. Tsonis, PhD
Professor, Department of Biology
Director, Center for Tissue Regeneration and Engineering at Dayton
University of Dayton
Dayton, OH

Virginijus Valiunas, PhD
Research Associate Professor
Department of Physiology and Biophysics
Institute for Molecular Cardiology
Stony Brook University
Stony Brook, NY

Mark Van Dyke, PhD
Associate Professor
Virginia Tech–Wake Forest University School of Biomedical Engineering and Sciences
Virginia Polytechnic Institute and State University
Blacksburg, VA

J. B. Vella, MD, PhD
Stem Cell Research Center
Department of Orthopedic Surgery
Department of Bioengineering
University of Pittsburgh
Pittsburgh, PA

M. Natalia Vergara, PhD
Postdoctoral Fellow
Wilmer Eye Institute
Department of Ophthalmology
Johns Hopkins University, School of Medicine
Baltimore, MD

Belinda J. Wagner, PhD
President
Biographic Design Consulting
Winston-Salem, NC

J. Koudy Williams, DVM
Professor
Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine
Winston-Salem, NC

James Yoo, MD, PhD
Professor and Chief Scientific Officer
Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine
Winston-Salem, NC

Michael J. Yost, PhD
Associate Professor
Department of Surgery
Medical University of South Carolina
Charleston, SC

Foreword

Regenerative pharmacology is poised to revolutionize human treatment options in medicine and define a new medical frontier. Prepared minds have recognized the convergence of discoveries in pharmacology, molecular biology, and genetics with those of nanotechnology, advanced analytical techniques, and biomaterials resulting in the ability to initiate differentiation and regeneration of cells, tissues, and organs.

Dating back thousands of years, ancient civilizations documented how they imagined being able to regenerate limbs lost in battle or trauma. For centuries, the regenerative characteristics of salamanders, chicks, and other animals were known but it was only within the past four decades that scientists began to mobilize the integrative thinkers, resources, and enabling technologies to identify and address the reality of cellular differentiation. Understanding of hematopoietic stem cell differentiation led to the first life-saving regenerative intervention for bone-marrow transplantation in the mid 1970s and, over the next 15 years, scientists refined genetic engineering to succeed at more complicated hematopoietic cell interventions resulting in FDA-approved recombinant therapies to enhance regeneration of red blood cells and granulocytes. Yet, to take regenerative therapies to the next level, where pluripotent cells could be differentiated, de-differentiated, and reprogrammed, it meant that the nature of the regenerative biomedical research community itself needed to be remodeled.

Centers of Excellence in stem-cell and regenerative research were established and now serve as welcoming institutions where creative "new alloy" scientists, who possess a wide range of interdisciplinary expertise and skills in enabling technologies, can work toward a similar goal. These multidisciplinary scientists are funded to focus on teamwork and characterizing regenerative interventions that unite specific biology, physics, genetics, chemistry, and enabling technologies in a way that was only imagined in the past. Following his discoveries of alpha and beta adrenergic receptors in 1948, and therapeutic use of beta-blockers for the treatment of blood pressure and heart disease, Dr. Raymond P. Ahlquist remarked "... at this time

being a pharmacologist is akin to being a physiologist with a screwdriver." Today, a regenerative pharmacologist must surely be equipped with a hardware store of tools.

The impending impact of regenerative therapeutic intervention cannot be overstated in considering improvements to quality of life and reductions in healthcare costs. In the near term, the pharmaceutical industry will seek the talent and technology to develop research and interventions requiring partnerships with the NIH and with the FDA for approvals. The negative long-term physical, emotional and financial impact of birth deformities, traumatic injury, and dismemberment will be mitigated with future regenerative therapies and definitive treatments for life-long illnesses like diabetes and cardiovascular disease will be part of our history. With the complexity of the human organism itself, interdisciplinary teams of biomedical scientists are now identifying and replicating the sequence and symphony of essential factors that initiate, modulate, differentiate, de-differentiate, and remodel cells and tissues for organ regeneration. Today, scientists are pharmacologically able to guide pluripotent cells to differentiate along predictable paths of development, producing various heart cells and valves, cardiac tissues, urinary bladders, and other tissues with histologically appropriate layers, differentiation, innervations, and functionally appropriate contractions.

Dr. George J. Christ and Dr. Karl-Erik Andersson are congratulated for an outstanding book, *Regenerative Pharmacology*, which should be required reading for all biomedical scientists, medical students, integrative pharmacologists/physiologists, and indeed contemporary healthcare practitioners, regardless of specialty. *Regenerative Pharmacology* is a premier foundational treatise that introduces the topic and complexities of regenerative medicine and specifically describes new major developments in regenerative therapies. The book captures the evolution of many proposed regenerative interventions and, in an unassuming manner, the authors communicate in conversational style, to deliver details of their work in extensively referenced chapters.

Regenerative Pharmacology is a milestone publication and a definitive reference work for truly state-of-the-art discussions on stem and progenitor cells, bioreactor technology, and wound healing. This reference provides for in-depth understandings of regeneration of cardiac, kidney, bladder, and muscle cells and tissues, as well as micro/nano technology for delivery of therapeutic agents, active factors embedded in biomaterials, enabling technologies, implanted materials, and tissue-engineered constructs.

Congratulations to the editors for compiling this work. Congratulations to the editors and chapter authors for sharing their world-level expertise and for the manner in which the fundamentals of their work are introduced in understandable terms and then built upon to state-of-the-art discussions and future directions. The authors are among the top experts in this new frontier of biomedical research and truly represent

the "new alloy" scientists and pioneers who will shape our lives with their regenerative research and therapies of the future.

Dennis C. Marshall, RN, MS, PhD
Immediate Past Chairperson, Executive Member,
Division for Integrative System, Translational and
Clinical Pharmacology, American Society
for Pharmacology and Experimental Therapeutics and
Subcommittee for Clinical and Translational Research,
Federation of American Societies for
Experimental Biology and
Executive Director,
Medical Affairs Ferring Pharmaceuticals Inc.

Preface

The concept for this book, although based on years of prior research and learning, was definitively established several years ago when we coined the phrase "regenerative pharmacology," and moreover, wrote our first article introducing the topic and the potential implications for pharmacologists (Andersson & Christ, Mol. Int., 2007). Since that time, the field has truly exploded, although the underlying purpose for this first edited volume on the subject remains the same: namely, to get pharmacologists more involved in this field of research by exposing them to the tools, opportunities, challenges, and expertise that will be required to ensure awareness and galvanize involvement. In addition, we hope that the excellent material provided by the diversity of experts in this volume will spark new multidisciplinary conversations among all of the stakeholders. In our opinion, the field of regenerative medicine and its companion field, tissue engineering, would benefit significantly from the more rigorous application of pharmacological sciences. Specifically, despite enormous progress and promise, regenerative medicine and tissue engineering would still profit from a greater focus on the evaluation of functional outcomes and endpoints. In particular, a more extensive characterization of basic pharmacodynamics (excitation-contraction coupling mechanisms, rigorous analysis of concentration-response curve (CRC) data using standard pharmacological analyses/methods, estimation of receptor affinity, receptor subtypes, intrinsic activity, efficacy, potency, etc.) is required. In addition, we posit that greater emphasis on the pharmacology and physiology of various regenerative medicine and tissue engineering approaches is critical to increase understanding of tissue/organ regeneration and repair processes, as well as to enhance the rate of technology development and eventual clinical translation. In this volume we have brought together diverse fields of research, ranging from materials chemistry and functionalized biomaterials to stem cells, high-throughput drug screening and bioreactors for in vitro tissue engineering, as well as in vivo studies of wound healing and tissue and organ regeneration and repair. Again, we hope that the outcome will be recognition by all parties of the importance of the cross-fertilization of ideas and

tighter integration of the pharmacological sciences into the regenerative medicine and tissue engineering translational research enterprise. In fact, the image on the cover of this book, a 3D torus, is a simile for the ultimate complexity (and beauty) of tissue and organ regeneration and repair, as well as their eventual manipulation by pharmacology. That is, once we understand the properties of the knot, we can use pharmacology to drive regenerative medicine and tissue engineering technologies toward the creation of very precisely regulated tissue and organ structures with the requisite functional characteristics. We envision this book as the first volume of a series that will grow in parallel with this exciting field of research, and moreover, describe the journey at various points along the path. We look forward to the enormous possibilities for improved human health that can result from further development of regenerative pharmacology, and remind the reader that this is only the beginning of a long voyage.

George J. Christ, PhD
Karl-Erik Andersson, MD, PhD
Winston-Salem, NC, USA

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