The Biology of Heart Disease

A subject collection from *Cold Spring Harbor Perspectives in Medicine*

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COLD SPRING HARBOR LABORATORY PRESS
Cold Spring Harbor, New York • www.cshlpress.org

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Articles online at www.perspectivesinmedicine.org

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Front cover artwork: Leonardo da Vinci's last and greatest anatomical campaign was an investigation of the heart. (A bovine heart was used for most of his dissections.) Shown are two views of an ox's heart, displaying the aortic valve and coronary arteries. da Vinci regarded the three-cusped valves of the heart as a perfect example of mathematical necessity in the workings of nature. Despite his understanding of the valves, he never grasped the idea of circulation, instead adhering to the ancient theory of the flux and reflux of the blood between the two ventricles. (Image printed with permission from Royal Collection Trust/© Her Majesty Queen Elizabeth II 2014.)

Library of Congress Cataloging-in-Publication Data

The biology of heart disease/edited by Margaret Buckingham, Christine L. Mummery, and Kenneth R. Chien.
p. ; cm.
"A subject collection from Cold Spring Harbor perspectives in medicine".
Includes bibliographical references and index.
ISBN 978-1-936113-86-6 (hardcover : alk. paper)
I. Buckingham, Margaret E., editor. II. Mummery, C. L. (Christine L.), 1953- editor. III. Chien, Kenneth R., editor. IV. Cold Spring Harbor perspectives in medicine.
[DNLM: 1. Heart Defects, Congenital--embryology. 2. Heart Defects, Congenital--genetics. 3. Genetic Predisposition to Disease. 4. Regenerative Medicine--methods. WG 220]

RC687
616.1'2043--dc23

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This book is dedicated to our mentors
and the members of our respective laboratories.

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Preface

Biomedical innovation often occurs at the interface between fields of scientific research and new technologies. Recent major leaps in cardiovascular biology and medicine clearly support this view, and *The Biology of Heart Disease* has been designed to capture the exciting impact of new technology in the arenas of developmental and stem cell biology, regenerative medicine, and genetics.

In developmental biology, a map for cardiovascular lineages has been developed via a variety of lineage-tracing techniques, leading to a deeper understanding of the origins of the heart during the earliest stages of embryonic development. The identification of distinct heart progenitor families and the signals that drive their cell fate decisions are leading to new insights into congenital heart disease, which remains the major malformation in children, affecting more than one in 50 live births. Cross-fertilization of insights from hematopoiesis, skeletal muscle myogenesis, and neurogenesis in multiple model systems, ranging from zebrafish to mouse, has uncovered conserved signaling pathways and regulatory principles that are changing the way we view heart development.

In the field of stem cell biology, the advent of induced pluripotent stem (iPS) cell and embryonic stem (ES) cell model systems has led to the development of entirely human-based in vitro models of human disease in which the direct comparison of genetically matched (isogenic) disease and healthy pairs is facilitating new insight into underlying disease mechanisms. These in vitro cell systems, which provide human models of cardiogenesis, present new opportunities to evaluate pathways uncovered in murine systems, using advanced tools to quickly and specifically knock out and knock in genes of interest via new genome-editing tools with RNA-guided endonuclease technology. The ability to directly convert cardiac fibroblasts to a cardiomyocyte-like state with transcription factors and microRNAs has led to the design of new strategies for regenerative cardiology. In addition, new chemically modified mRNA technology to directly express any protein at will in the intact heart in vivo and to drive heart progenitor cell fate toward therapeutic end points represents a new approach to controlling the genetic program in the setting of cardiac disease without traditional gene therapy vectors. The identification of new paracrine factors that have been implicated in heart repair is leading to clinically tractable approaches for specific forms of cardiac disease. Finally, the ability to generate billions of human cardiac muscle cells from pluripotent stem cell models is offering new hope for the generation of heart parts and/or alternative tissue engineering strategies for regenerative cardiology.

The development of next-generation DNA sequencing is revolutionizing human cardiovascular genetics. With relatively shallow pedigrees, autosomal recessive genotypes can now be easily and quickly uncovered, as has been witnessed for a number of new genes responsible for familial dyslipidemias. The low cost and efficiency of high-throughput DNA sequencing, even for extremely large coding regions, has led to the identification of mutations in titin responsible for a large subset of idiopathic dilated cardiomyopathies. Whole-genome sequencing is leading to the identification of new targets for cardiovascular drug discovery, as well as to new approaches to understanding the genetics of cardiovascular drug side effects. Genome-wide screens in human pluripotent stem cell models via advances in CRISPR (clustered regularly interspaced short palindromic repeat) technologies, coupled with these sequencing advances, hold great promise for further functional annotation of novel genes for important cardiovascular phenotypes.

As many of these recent advances have been made within academia itself, it is not surprising that large pharmaceutical companies and biotechnology have moved closer to biomedical research

institutions, both physically and intellectually. New paradigms for academic–private sector collaboration are actively being established on a global level (i.e., United States, Europe, China, etc.); this book includes two discussions of these new developments from differing perspectives.

A book of this scope would not be possible without the help of many colleagues, both in academia and in the publishing world. We particularly would like to thank Richard Sever for the invitation to have *The Biology of Heart Disease* join the other prestigious titles within the *Perspectives* series for CSHL Press and Barbara Acosta for her steadfast help throughout the entire publication process. Our Associate Editors, Ralph Knöll and Karl-Ludwig Laugwitz, have been key in overseeing the review of individual chapters and in making suggestions for others. On behalf of our entire team, we sincerely hope you enjoy reading about these exciting new developments in the biology of heart disease.

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