



Heart Development and Regeneration

Volume 2

Edited by
Nadia Rosenthal and
Richard P. Harvey



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Heart Development and Regeneration

Volume II



Heart Plate 2 was inspired by the artistry of Franco Mari, a living master of Majolica ceramic decoration working from Deruta, Italy. Each design band represents a theme in the volume. Motifs from center outward: circuit, discovery, access, dynamic, progenitor, renewal. *Artwork by Nadia Rosenthal.*

*“Come potreste descrivere a parole questo cuore,
senza riempire un libro intero?”*

*(How could you describe this heart in words,
without filling a whole book?)*

*Note written by Leonardo da Vinci beside an anatomical
drawing of the heart, 1513.*

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Developmental biology is slowly but surely moving to center stage in cardiovascular science and practice as a result of the increasing realization of its potential for understanding the basic mechanisms of a wide variety of congenital and acquired heart diseases. This stems from the fact that many of the factors which are operational during morphogenesis of the heart during fetal life continue to influence growth and adaptation during postnatal life. In addition, the developmental origins and lineages of different cells influence their behavior in adult life. Defining these factors offers exciting possibilities for developing novel therapies.

The recent sustained progress in the field has been driven by a handful of enthusiastic individuals around the world who have had the foresight to see the potential of the subspecialty, coupled with the availability of sophisticated experimental approaches involving genetic, molecular, imaging and engineering tools, which are being used alone or in combination.

Heart Development and Regeneration represents a unique achievement in bringing together leaders in the field presenting current knowledge in a lucid form, making it accessible to a wide range of readers. The inclusion of several chapters on regenerative therapy, arguably the hottest topic in medicine today, represents a natural extension to the topics of developmental biology.

Surgery is often likened to plumbing. There is no self-respecting plumber who would tackle a complex plumbing system in a building without demanding to see the blueprint of how this was put together in the first place!

I am confident that this book will be of great value and offer unique opportunities to both clinicians and researchers in almost every realm of cardiovascular science, medicine and surgery.

*Professor Sir Magdi Yacoub FRS
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It has now been a decade since our book *Heart Development* was published, and the field has again exploded. A more integrated picture of development, physiology and disease is emerging from our deeper investigations of the genes, proteins and cells, and the functional interactions between them, which build the cardiovascular system. This picture has been immeasurably enhanced by our explorations across the evolutionary landscape. Ten years ago, only a handful of cardiovascular malformations, the most common type of birth defect, could be associated with causative factors, but recent studies have uncovered the genetic basis of many more, and with the advent of forward mutagenic screens in fish and mice, genome-wide association studies in humans, and next generation sequencing, these investigations are now set on an entirely new course, with implications for genetic testing, counseling, long-term patient follow up and choice of intervention.

Much of the progress has been technical: advances in genomics, proteomics, transgenesis and imaging have supplied more exacting tools to dissect and manipulate the embryo and the adult. Furthermore, the amount of biological data generated over the past decade has overwhelmed our ability to understand it without powerful computational approaches. It is logical, then, that these approaches have made it possible to explore cardiac functionality with quantitative models of cells, tissues and organs. By far the most important development over the last decade has been in stem cell biology, yielding access to early processes in the embryo determining cell lineage, as mimicked in the differentiation of embryonic stem cells into cardiomyocytes, as well as providing a new understanding of adult lineages heretofore unimagined, ushering in exciting prospects for their use in regenerative medicine.

Additional important advances have been more conceptual, reflecting the shifting emphasis of the field towards integrative systems biology and the important role that noncoding RNAs and epigenetics play in the cardiac gene regulatory network and cardiovascular disease. Ten years ago, issues of lineage potency, stemness, robustness and meta-stable chromatin states were the purview of a small group of purists. Now they are fast becoming our bread and butter. In the world of systems biology, individual regulatory genes are seen as part of an information

machine encoded in the genome, rather than individual enzymes working in an isolated pathway. The search for logic in regulatory circuitry is now well and truly focused at this level. The dominance of genetic determination and reductionism has given way to an appreciation of whole cell integration of activity, informing our approach to the study of cardiac growth and morphogenesis, and causality in disease. Epigenetic regulatory mechanisms assume a more prominent position in our models and the relationship between genome and phenotype grows more intimate. In the developing heart, as in other biological systems, it is becoming increasingly difficult to separate genetic instructions from the process of carrying them out, to distinguish plan from execution.

Heart Development and Regeneration, published in two volumes, attempts to capture a collective snapshot of this fast moving field. Volume I covers the early stages of cardiovascular determination, growth and morphogenesis across the phylogenetic tree, whereas Volume II reviews recent advances in transcriptional and post-transcriptional regulation, epigenetic circuits, systems analysis, the theory and evolution of stem cells, and the molecular and cellular basis of cardiac repair. The chapters are written by the world's experts and provide up-to-date reports from their laboratories, while treating the newcomer to a rich grounding in classical developmental biology of the cardiovascular system.

These books together represent a comprehensive catalog of the individual parts of the whole as we currently know them. They relay current progress on compiling the instructions for putting the parts together in the context of how form and function are generated in the cardiovascular system to sustain life, and how these processes go awry in disease. The stories told in these chapters are full of models; how we study the biology of the developing and regenerating heart is model-dependent, and therefore our models must remain flexible and responsive to the influx of new data. Integrative models are nowhere more relevant than in the cardiovascular system, where function substantially instructs form. Among all the complex organs, the developing heart is exceptionally susceptible to malformation; human congenital heart defects affect an astonishing 0.7% of live births. Although many defects have genetic underpinnings, very few are attributable to a single gene

or protein malfunction. Their origins will in many cases be subtle, context-dependent and grounded in the architecture of the regulatory network, with the environment playing a major role. The results from modeling the feedback loops between physiological function and gene expression may in the beginning seem counterintuitive, yet as we understand these at a systems level, we will gain vital clues to the development of preventative therapeutic approaches or clinical interventions.

As researchers and editors, we have prepared these volumes as a celebration of the beauty and complexity of heart development, its evolution and recapitulation in the context of regeneration. Working closely with our colleagues has been a rewarding experience and we thank them all for their generous donations of time and expertise, for the care and pride in their work, and for their patience in helping us keep these books current through several updates and refinements over the past two years. We thank

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*Nadia Rosenthal
Richard Harvey
Sydney, August 2009*

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Part 1 Heart Evolution

1.1. Evolutionary Origins of Hearts

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