

Preface

REGENERATION IS THE RENEWAL OF CELLS, tissues, or body parts to accommodate day-to-day replacement or as an emergency response to unexpected trauma. We humans can be very good at it—our livers, blood, skeletal muscle, and even the tips of our digits respond to damage or loss with regeneration. We can also struggle at it, for instance after a heart attack, spinal cord injury, limb amputation, or stroke. Many feel that boosting regeneration in key organ systems through science-inspired regenerative therapies will be remembered among the greatest biomedical achievements of the 21st century. We are one-fifth of the way into this century, but the challenges are great and we may be years to decades from realizing this goal.

Regenerative therapies can be guided by understanding what enables, and what prevents, tissue regeneration that occurs naturally in animal species. Laboratory model systems, with their own spectrum of regenerative capabilities, allow scientists to probe examples of regeneration for key concepts and mechanisms. Which species, tissues, and injury contexts should be studied intensively to best inform instructions for human regeneration? The answer is—and has to be—as many as can be studied.

Regeneration is an ancient field of biology, recognized conceptually by ancient Greek, Egyptian, and Hebrew societies. It has continued to capture the attention of both the scientist and layperson. Luminaries have graced the field, including Trembley, Spallanzani, Morgan, and others, establishing critical questions and the foundations for mechanistic studies to come centuries or decades later. The critical context as one reads these chapters is that regeneration has historically been a tough nut to crack. Homeostatic regeneration can be very slow, even unnoticeable, in its gradual replacement of red blood cells or lung epithelium, making it difficult to predict and pinpoint key events; injury-induced regeneration is generally faster. Some of the best regenerators—salamanders, fish, and planarians—have not allowed the conveniences in terms of short generation times and genetic tools available to researchers working with systems like fruit flies and mice. Further, as regeneration is classically an adult event, the genetic manipulations of experimentalists must be sophisticated, conditional approaches that first allow normal development.

In this volume, we strive to provide a holistic view of current knowledge and progress on regeneration, or at least what can be represented across 22 chapters. The chapters in this volume describe regeneration in an array of creatures including flatworms, polyps, insects, salamanders, fish, frogs, birds, and mammals. Regeneration, within any given plant or animal, is achieved through different cellular and molecular mechanisms, and thus we present a cross section of what is known of regeneration in organ systems diving inward from skin to heart. These chapters also cover integrating themes of significant relevance in the field, including how regenerative capacity relates to aging and how the technology of cell reprogramming impacts ideas about regeneration.

As it happens, this volume is timely. Several authors describe incorporation of new single-cell RNA-sequencing technologies to reveal the cellular heterogeneity of regenerating tissues at high resolution, and to describe regenerating cells in more molecular detail. Authors also highlight the introduction of evolved genetic approaches to an increasing number of model systems, including gene-editing techniques that are agnostic to species. These chapters focus attention on how these advances have recently made more accessible many key questions of regeneration biologists from centuries ago. We remind the readers to be aware that regeneration is a mysterious process. We do not have conclusive answers to most of our questions. Moreover, we do not know what all of the questions

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are. These questions can only be derived from further exploration and discovery, guided by comparative biology.

The editors are grateful to all the authors of chapters included here. We are particularly happy that many student and postdoctoral laboratory members were involved in the production of these review pieces, in addition to the accomplished regeneration biologists to whom we extended the initial invitations. We apologize to authors if space precluded attention to their species or tissue of interest. We thank Barbara Acosta, Richard Sever, and colleagues at Cold Spring Harbor Laboratory Press for the opportunity to cover the topic of regeneration and for their dedication and methods that helped this work reach the finish line. We thank Amy Jackson at the Duke Regeneration Center for helping us keep organized, track progress, and meet our timelines. Finally, we would like to take the opportunity to express how fortunate we feel to be performing discovery science in the broad topic of regeneration. This research field is a feast for the curious mind, and we experience constant reminders of this through regular interactions with our dedicated, friendly, and collaborative community of colleagues around the world.

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