Preface

Molecular motors are required for a vast array of cellular functions and consequently have attracted the attention of many biologists and clinicians. Over the last several decades, much has been learned about the mechanisms of action of molecular motors and the consequences of their dysfunction; for example, how members of the myosin and kinesin superfamilies convert ATP hydrolysis to mechanical work is now understood in exquisite detail. However, one class of motor—the dyneins—which translocate along microtubules has stood out in terms of their complexity and the difficulties encountered in trying to understand their structural and functional attributes. Not only are the motor units themselves enormous (over 500 kDa each), which in and of itself imparts a whole host of technical challenges, but these motor subunits are associated with a complicated array of additional components that play key roles in stable formation of the holoenzymes, binding appropriate cargos and regulating motor function in response to a wide variety of ever-changing regulatory inputs. Likewise, the array of activities that dyneins participate in and the consequences of their malfunction are myriad and complex.

The first edition of *Dyneins: Structure, Biology and Disease* was published in 2012 as a single volume containing 24 chapters. Since then, enormous progress has been made in many areas of dynein biology including, for example, understanding the structural basis of dynein motor function, the mechanisms of cytoplasmic preassembly of axonemal dyneins, and the consequences of dynein dysfunction for human disease. In this second edition, the scope has been greatly expanded, necessitating two volumes with a total of 40 chapters, to try and capture the major advances that have recently been made. Only two chapters (on the initial discovery of dynein and on the role of dynein in non-Mendelian transmission of mouse *t* haplotypes) are reprinted directly from the first edition with only minor alterations; all the others are either completely new or highly updated and modified from the originals. In addition, a website (http://booksite.elsevier.com/9780128094716) accompanies these volumes and includes videos of dynein-based motility and other materials that complement specific chapters. Each chapter is written by true experts in their respective fields, and it is my hope that this compendium will prove useful both to seasoned dynein researchers and to those thinking about entering the field for the first time and studying this fascinating and enormously complex family of molecular motors.

This two-volume work is divided into five broad segments. The first volume is devoted to the *Biology of Dynein Motors* and starts with a section concerning the history of dynein research and the evolutionary biology of dyneins. The initial discovery of dynein in cilia is described by Gibbons, and the subsequent

identification of cytoplasmic dynein is detailed by Vallee. This is followed by a chapter from Wickstead who describes dynein phylogenetic bioinformatics and plots the evolutionary biology of these motors, including discussion of how these unusual AAA+ motors might have arisen prior to the last eukaryotic common ancestor. The second section examines dyneins in the context of ciliary biology. Desai et al. detail the current understanding of the complex mechanisms by which these massive multicomponent axonemal motors are initially assembled in cytoplasm, and King covers their detailed biochemical composition. The arrangement of dyneins within the axonemal superstructure is described by Ishikawa, and Yagi and Kamiya discuss the genetics of axonemal dyneins and how studies in a broad array of model systems have resulted in major conceptual advances. The multiple mechanisms of outer- and inner-arm axonemal dynein regulation are detailed in chapters by King and Hwang et al., and the role of the dynein regulatory complex is described by Porter. Shingyoji analyzes dynein-driven ciliary/flagellar motility from a more physiological perspective, while Ueki and Wakabayashi discuss dynein-mediated photoresponses, including waveform conversion and redox-based control of dynein function in response to altered light conditions. The final chapter in this section by Witman and Hou describes our current understanding of the specialized dynein that powers retrograde intraflagellar transport and which is required for assembly of both motile and nonmotile (primary) cilia. The final section in Volume 1 covers the biology of cytoplasmic dynein. The subunit composition of this complex motor is described by Pfister, while McKenney details the regulatory mechanisms controlling motor activity. Insights into dynein function derived from fungal genetics are reviewed by Xiang, and details of how dynactin modifies dynein function are described by Ketcham and Schroer. The last four chapters in this section examine dyneins role in mitotic checkpoint silencing (Lewis and Chan), its functions at the nuclear envelope, cortex, and kinetochore during mitosis (Hinchcliffe and Vaughan), the mechanisms of microtubule plus end tracking (Jha and Surrey), and how dynein impacts gametogenesis, embryogenesis, and neuronal function in *Drosophila* (Neisch et al.).

The second volume subtitled *Dynein Structure, Mechanics, and Disease* is built around two sections. The first is focused on dynein structure and mechanics—an area that has seen massive strides in the last few years. Oiwa and colleagues describe the analysis of dynein structure and mechanism as determined from electron microscopic studies. This is followed by Schmidt and Carter who describe the dynein heavy chain structure and power stroke mechanism based on crystallographic and cryo electron microscopy studies. This is followed by a chapter by Williams et al. detailing our current understanding of the high-resolution structure of the intermediate and light chains that are needed for assembly of the dynein particle. Biochemical methods to purify native and recombinant dyneins are described by Inaba. The next three chapters cover motor mechanics: Yildiz details single molecule mechanics in vitro, Shubeita

et al. consider dynein biophysics in vivo, and Hancock describes the mechanics of bidirectional transport. Steinman and Kapoor detail dynein inhibitors ranging from the phosphate analogue vanadate, originally identified as a dynein inhibitory factor in commercial preparations of ATP, to the more recently identified ciliobrevins. The final chapter in this section by Geyer et al. provides a practical guide to computational modeling of dynein activity and how this generates flagellar waveforms; a Matlab code enabling the reader to perform their own analyses can be downloaded from the website (http://booksite.elsevier.com/9780128094716) that accompanies these volumes. The last section describes the consequences of dynein dysfunction and how in many situations it leads to human disease. Milev et al. describe how viruses manipulate host dynein motors. Terenzio et al. discuss the use of mouse genetics to probe the consequences of cytoplasmic dynein dysfunction, and Doobin and Vallee detail how the regulation of this motor impacts brain development. This is followed by chapters examining the role of dyneins as causative factors in primary ciliary dyskinesia and other ciliopathies (Loges and Omran), and how disrupting dynein-mediated retrograde intraflagellar transport leads to severe skeletal abnormalities (Schmidts and Mitchison). Price et al. then describe the effects of chronic alcohol exposure on dynein function, while Imhof and Hill discuss dynein-based motility of parasitic protozoa, and Vincent details an intriguing connection between a dynein light chain and congenital mirror movement disorder. The final chapter by Pilder examines the potential role of dyneins in non-Mendelian chromosomal inheritance in mice.

Finally, I would like to extend my thanks to all the authors, who spent so much time and effort in preparing chapters for these volumes, and to the staff at Elsevier for all their assistance in making this second edition a reality.

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