Preface

Molecular motor complexes 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, the manner in which 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 cargoes 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. In this book, I have assembled a series of chapters written by some of the best-known dynein researchers who examine a broad array of topics ranging from the structural biology of dynein components and the details of the motor mechanism itself to how dyneins power ciliary motility and intracellular transport, the hijacking of dynein motors during viral pathogenesis, and the devastating consequences of dynein dysfunction for human disease.

This book is divided into five broad segments, which of necessity somewhat overlap. It begins with a section on **History and Evolution** that includes a fascinating article from Ian Gibbons (University of California, Berkeley), who first isolated axonemal dyneins from cilia of the alveolate *Tetrahymena pyriformis* in the early 1960s. Gibbons outlines the history of dynein research, incorporating his personal views of the field, and details some of the key insights that drove how our understanding of this complex motor progressed from the early days to the present. This is followed by a chapter from Wickstead (University of Nottingham) and Gull (University of Oxford), who consider the ancient evolutionary origins of dynein components and discuss how they might have arisen prior to the last common eukaryotic ancestor.

Section II focuses on the **Structure and Mechanics of Dynein Motors** and looks at the detailed structure of dynein components. Dyneins are members of the AAA^+ family of ATPases, and, although we have yet to obtain a high-resolution structure of the dynein heavy chain itself, multiple structures of other AAA^+ proteins have been solved. Tucker (EMBL Hamburg Outstation) describes how

this information can be used to inform our understanding of dynein heavy chain structure and this is followed by a chapter by Koonce and Tikhonenko (Wadsworth Center), who detail the current model of the general motor mechanism. Subsequently, Williams et al. (Beckman Research Institute at the City of Hope) describe the high-resolution crystallographic and NMR-based structural work on the intermediate and light chains associated with both cytoplasmic and some axonemal dyneins. The last chapter in this section, by Xu and Gross (University of California, Irvine), examines the biophysics of dynein action with an emphasis on *in vivo* measurements.

We then consider the role of **Dyneins in Ciliary Biology**, where multiple dyneins form the inner and outer arms associated with the axonemal doublet microtubules, which generate the force to power these motile organelles. In addition, a specific dynein isoform closely related to cytoplasmic dynein 1 is involved in assembly of the organelle at its distal tip. This section begins with a chapter by King (University of Connecticut Health Center) describing the basic composition and assembly of these complex axonemal motors. Ishikawa (Paul Scherrer Institute) then describes the latest information derived from cryo-electron microscopic tomography on the organization of these motors *in situ*. We then proceed to a detailed description of axonemal dynein genetics by Yagi and Kamiya (University of Tokyo) and to chapters by Wakabayashi (University of Tokyo) and Alford et al. (Emory University School of Medicine) that focus on the mechanisms by which outer- and inner-arm dyneins respond to a variety of regulatory cues. Subsequently, Porter (University of Minnesota) describes the dynein regulatory complex/nexin link that is a key component required for axonemal motility, and Shingyoji (University of Tokyo) provides a systems-level analysis of regulatory activity within the axoneme. In the final chapter in this section, Witman (University of Massachusetts Medical School) presents a detailed view of the dynein that powers retrograde intraflagellar transport and that is thus required for the assembly of both motile and sensory cilia.

The fourth section, **Cytoplasmic Dynein Biology**, focuses on dyneins that function within the cytoplasm. It begins with a description by Pfister (University of Virginia School of Medicine) and Lo (University of Connecticut Health Center) of the components present in these complexes and details the large isoform variation that can potentially occur and how this correlates with discrete cellular functions. Ori-McKenney et al. (Columbia University) then explain the current model for how force production by cytoplasmic dynein motor units is controlled through interaction with the Lis1 and NudE/NudEL regulatory proteins. This is followed by chapters from Xiang (Uniformed Services University of the Health Sciences) and Kuta et al. (Institute of Neurology, University College London, University of Sussex and Cancer Research UK) that discuss the insights into cytoplasmic dynein function that have been obtained from genetic studies in fungi and mammals. Schroer and Cheong (Johns Hopkins University) then provide an analysis of the dynactin complex, which associates with cytoplasmic

dynein to enhance processivity and is indispensible for many of its intracellular functions, and Vaughan (University of Notre Dame) discusses the specific roles played by dynein during mitosis.

The final section of this book, **Dynein Dysfunction and Disease**, examines what happens when dyneins fail to act appropriately. Pilder (Temple University School of Medicine) examines whether dynein dysfunction might be involved in the fascinating phenomenon of non-Mendelian chromosome segregation in mice. This is followed by a chapter from Mouland and Milev (McGill University), who discuss the role of dynein in viral pathogenesis and how a variety of viruses co-opts dynein motors to move the infectious particle along microtubules from the cell periphery to the nucleus. Moughamian and Holzbaur (University of Pennsylvania School of Medicine) then describe how disruption of cytoplasmic dynein activity is involved in a range of devastating neurodegenerative diseases (including amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease). The final chapter, by Becker-Heck et al. (Universitätsklinik Münster), discusses the complex defects associated with primary ciliary dyskinesia and other ciliopathies (such as infertility, *situs inversus*, and other developmental problems) that occur in humans when axonemal dynein-powered ciliary motility is disrupted.

I would like to extend my thanks to all the authors, who put in so much effort to prepare the chapters for this volume, and also to the staff at Elsevier for their assistance in making this book a reality.

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