PREFACE

Ion channels are integrated membrane proteins forming pores through which ions can pass and travel between cells and extracellular space. The transport through ion channels is passive which means that it does not require participation of metabolic energy and occurs down their electrochemical gradient only. Most channels are selective for ne ion type only. Typically, the pore is so small that ions pass through in a single-file order. Although the human genome sequencing identified more than 400 putative ion channels, only a very small number of these hypothetically identified channels have been cloned and functionally characterized. The widespread tissue distribution of ion channels, along with the multiple physiological consequences of their opening and closing, makes targeting of ion channels very promising targets for development of therapeutics. The validation of ion channels as drug targets provides an enormous market opportunity for their reemergence as key targets in drug discovery. However, in spite of some important drugs, currently in clinical use, which target ion channels, this call of proteins remain significantly underexploited in drug discovery. Furthermore, many existing drugs are poorly selective with significant toxicities or suboptimal efficacy.

This is second of the two parts of thematic volumes of the *Advances in Protein Chemistry and Structural Biology* focusing on recent developments in ion channels studies and their potential as promising therapeutic targets. While the first part of these thematic volumes (Volume 103) focuses more specifically on ion channels as promising treatment targets in neurological and psychiatric disorders, the second part is dedicated on particular ion channel types (eg, connexin hemichannels, P2X7, TRPV1, TRPM8, virus channels) and their role as therapeutic targets in inflammation, pancreatic cancer, eye disorders, and cardiovascular and gastrointestinal diseases. The contribution of automated technologies to ion channel drug discovery is also discussed in detail in this second part of the two volumes.

The first article in this volume considers the central nervous immune system from the perspective that modulating connexin hemichannel opening can prevent tissue damage arising from excessive and uncontrolled inflammation. Authors discuss connexin channel roles in microglia, astrocytes, and endothelial cells in both acute and chronic inflammatory conditions, and in particular describe the role of connexin hemichannels in the inflammasome

pathway where they contribute to both its activation and its spread to neighboring cells. The second chapter describes structural features of P2X7 receptor, chemical properties of its agonist, antagonist, and allosteric modulators, and summarizes recent advances on P2X7 as therapeutic target in infectious, inflammatory, autoimmune, neurological, musculoskeletal, and cancer disorders. The use of P2X7 single nucleotide polymorphisms as diagnostic biomarkers for the development of tailored therapies is also discussed in this second article. The third chapter in this volume is dedicated to the transient receptor potential vanilloid 1 (TRPV1) ion channel. Here authors give an in-depth mechanistic outlook on the TRPV1 channel, and more specifically, they explore the TRPV1 structure, activation, modulation, ligands, and its therapeutic targeting. Another major objective of this third review is to highlight the fact that TRPV1 channel can be treated as an effective therapeutic target for treating several pain- and nonpain-related physiological and pathological states. The fourth article in this volume provides an extensive review and discussion of the transient receptor potential melastatin-subfamily member 8 (TRPM8) ion channel as a potential biomarker and target in cancer.

The next group of articles are focused on the role of different ion channel types in disorders. In the fifth article, authors review the roles of different ion channels expressed in ocular tissues that are involved in ocular disease pathophysiologies and those whose deletion or pharmacological modulation leads to a specific diseases of the eye. These include pathologies such as retinitis pigmentosa, macular degeneration, achromatopsia, glaucoma, cataracts, dry eye, or keratoconjunctivitis among others. Several of disease-associated ion channels are discussed as potential targets for pharmacological intervention or other therapeutic approaches, thus highlighting the importance of these channels in ocular physiology and pathophysiology. The sixth chapter summarizes the physiological and pathological roles of the three types of Ca^{2+}-activated K^+ channels (KCa) in cardiovascular system and put forward the possibility of KCa channels as potential therapeutic target for cardiovascular diseases. The next seventh article discusses extensively the modulation of potassium channels in the smooth muscles as a therapeutic strategy for disorders of the gastrointestinal tract. The eighth chapter in the volume is centered on virus channels and their role as therapeutic targets. Since the discovery that certain small viral membrane proteins, collectively termed as viroporins, can permeabilize host cellular membranes and also behave as ion channels, attempts have been made to link this feature to specific biological roles. Most viroporins identified so far are virulence

factors, and interest has focused toward the discovery of channel inhibitors that would have a therapeutic effect, or be used as research tools to understand the biological roles of viroporin ion channel activity.

The final ninth article explores the use of automated instrumentation for the study of ion channel functionality (and dysfunctionality), particularly in the search for novel pharmacological agents with therapeutic purposes. Their application has now reached out beyond the industrial setting, its original natural enclave, and is making its way into a growing number of academic labs and core facilities. This review presents and discusses the increasing contributions accomplished by a variety of different key automated technologies which have revolutionized the strategies to approach the discovery and development of new drugs targeting ion channels.

Considering the very high number of genetically predicted ion channels, this big group of proteins remain relatively underexploited in terms of their functions, involvement in disorders, and possibilities for therapeutic interventions. Taking into account the recent advances in biomedical knowledge and automated technologies available for searching novel pharmacological agents with therapeutic effects, the aim of this second volume dedicated to ion channels as therapeutic targets is to promote further research in the structure, function, and regulation of different families of ion channels which would result in designing new efficient targeted drugs with significantly fewer adverse effects.

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