Calcium Signaling: From Physiology to Diseases

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Foreword by Sabu Thomas

It is a distinct honor to have been invited by my colleagues in the calcium channel regulation arena to write the foreword to this very articulate and scientifically state-of-the-art book entitled *Calcium Signaling: From Physiology to Diseases*. The book covers all the areas required to create a robust category and perform a read-across. I am certain that the readers including faculties, researchers, and students will find this book extremely informative, interesting, and inspiring. Hence, I hope that you will find this book as possessing sufficient disclosure and adequate utility. This book aims to simplify the revolution and to fortify the researcher with the information needed to use calcium channel antagonists with complete confidence and the best compound that can be applied for therapy of the individual. The book explores in many ways and makes good sense of the further investigation of channelopathies, and this valuable text opens the doors for the progression that occurs when one discovers a fact, becomes interested, and then begins investigation and discovery of the natural process.

I have 30 years of experience in polymer science and technology, and I contributed greatly to the research and development of nanoscience and nanotechnology. I have received my PhD from IIT–Kharagpur, and then joined as a senior visiting researcher in Katholieke Universiteit, Leuven, Belgium, and Laval University, Quebec, Canada. Subsequently, I served as associate professor and professor at Mahatma Gandhi University, Kottayam, Kerala, India. I am one of the pioneers of the field of polymer science and technology and have published over 750 peer-reviewed research papers, reviews, and book chapters. I have co-edited nearly 60 books, and I am the inventor of 5 patents. I have supervised 79 PhD students, and my h-index is 78 with nearly 28,675 citations. I have delivered over 300 plenary/inaugural and invited lectures in national/international meetings in over 30 countries. I am presently the Director of the International and Inter University Centre for Nanoscience and Nanotechnology and a full professor of polymer science and engineering at the School of Chemical Sciences of Mahatma Gandhi University, Kottayam, Kerala, India. I am an outstanding leader with sustained international acclaims for my work in polymer science and engineering, polymer nanocomposites, elastomers, polymer blends, interpenetrating polymer networks, polymer membranes, green composites and nanocomposites, nanomedicine, and green nanotechnology. My groundbreaking inventions in polymer nanocomposites, polymer

blends, and green nanotechnological and nano-biomedical sciences have made transformative differences in the development of new materials for automotive, space, housing, and biomedical fields.

As a consequence, a large number of books, thick and thin, have been and will continue to be published on various aspects of dysregulation of calcium channels. This monograph is intended to give an overview about the current knowledge of Ca^{2+} signaling in essential physiological processes and aspects of pharmacological targeting of Ca^{2+} channels and other Ca^{2+} handling machineries to attenuate or prevent the progression of certain common disorders associated with Ca^{2+} dysregulation, based on the impressive growth of knowledge in all aspects (cellular, organic, hormonal, structural) of calcium channel proteins that interfere with the physiology of the calcium ion. The introductory chapter describes the influence of Ca^{2+} level and its associated signaling pathways on developmental process and physiological functions. This chapter also gives an overview about the Ca^{2+} homeostasis mechanism and impact of abnormal Ca^{2+} level.

The book analyzes trends in the processing of natural products by using nanotechnology and their implications in calcium-related disorders. It covers some of the most interesting aspects of research in calcium signaling disorders and provides a trustworthy source of current information in this area of research. The elaborated description in chapters will enhance the understanding of calcium ion deficiencies, which will help the readers to gain an in-depth and latest development in the field of nanotechnology in channelopathies. The fifth chapter presents the various calcium channelopathies identified to date and discusses the current knowledge of calcium-regulating diseases. The sixth chapter has discussed the nanotechnology strategies that could help to overcome challenges in treating channelopathies and ease the translation of natural products from bench to clinical application. The better understanding of regulation of oxidative stress can be utilized for devising strategies for the development of novel therapeutic preparations for clinical interventions in oxidative stress and pathogenesis-induced calcium deficiency disorders.

With best wishes,

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and Technology,
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Foreword by Noah Weisleder

The field of calcium signaling research is vast and evolving rapidly in both basic research and clinical therapeutics. When I was asked to write a foreword for this book, my immediate thought was that there are many monographs and comprehensive textbooks focusing on Ca^{2+} signaling that cover a wide variety of topics at various levels of detail, so why the need for another book in this increasingly crowded field? This book is distinguished from the currently available literature in that it provides a concise summary of the basic mechanisms of cellular Ca^{2+} signaling and how these mechanisms are linked with the emergence of common, devastating pathological disorders. The authors build on current knowledge to detail the link between Ca^{2+} deregulation and the molecular pathology of diseases. They explain these complex concepts with straightforward language that allows greater accessibility to a wide audience. The succinct text will assist the novice in understanding Ca^{2+} signaling research, while the up-to-date information on the current state of Ca^{2+} signaling and pathophysiology will be of interest to experts in the field.

I have been interested in Ca^{2+} signaling research at all stages of my career. I received my BS in biotechnology and molecular biology from Worcester Polytechnic Institute and a PhD in cell biology from Baylor College of Medicine. This led to my postdoctoral studies at Robert Wood Johnson Medical School where I went on to join the faculty as assistant professor in the Department of Physiology and Biophysics. Currently, I am an associate professor and director of graduate studies in the Department of Physiology and Cell Biology at Ohio State University, as well as an investigator in the Davis Heart and Lung Research Institute. I have published numerous peer-reviewed publications or book chapters in the fields of muscle physiology, cardiovascular disease, cytoskeletal dynamics, membrane repair, and cellular Ca^{2+} homeostasis in normal physiology and disease states. I have chaired sessions at national and international meetings on Ca^{2+} signaling and muscle physiology. Additionally, I am an inventor of numerous US and international patents. These inventions became the basis for the formation of TRIM-edicine, a biotechnology company developing protein therapeutic targeting regenerative medicine applications, where I was a founder and served as chief scientific officer. Thanks to these accomplishments, I received a fellowship from the American Heart Association, a Pathway to Independence Award from the National Institutes of Health, and the Kauffman Foundation Outstanding Postdoctoral Entrepreneur Award.

As a researcher and teacher, I particularly appreciate the accessibility and simplicity of the contents of this book which covers many aspects of Ca^{2+} signaling including its role in physiological processes, dysregulation of Ca^{2+} gradients, and Ca^{2+} handling molecule contribution to the pathogenesis of several disorders like neurodegenerative diseases, muscle disorders, and chronic pain. Furthermore, they discuss the promise of targeting Ca^{2+} transporting receptors and select proteins for treating neurological, muscle, and other disorders. Finally, they address the benefits of natural products in treating Ca^{2+} disorders and how nanotechnology can help improve the therapeutic effects of naturally available Ca^{2+} channel modulators. The authors present their multidisciplinary approaches in a single, readily accessible book to provide a reliable reference for students and investigators interested in Ca^{2+} signaling research.

Each chapter of this book contains insight that will be useful to scientists at all levels. The introductory chapter describes the influence of intracellular Ca^{2+} levels and how changes in this critical variable affect signaling pathways that influence developmental processes and physiological functions. This chapter also gives an overview of Ca^{2+} homeostasis regulatory mechanisms and the impact of abnormal Ca^{2+} levels. Chapter 2 focuses on regulation of Ca^{2+} in muscle physiology by summarizing the involvement of Ca^{2+} ion channels in muscle physiology and pathophysiology. The third chapter provides a broad overview of Ca^{2+}-permeable ion channel contributions to nociception pathways. Chapter 4 expands on the role of Ca^{2+} signaling in the nervous system by examining the contribution of altered Ca^{2+} regulation in the progression of neurological disorders. This focus on pathophysiology continues in Chap. 5 to summarize the physiological function of voltage-dependent Ca^{2+} channels and how various channelopathies develop due to changes in Ca^{2+} signaling through these channels. The final chapter expands on the channelopathy theme by detailing nanotechnology strategies that could help to overcome challenges in treating channelopathies and ease the translation of natural products from bench to clinical applications.

This book will provide a useful reference for those interested in the role of Ca^{2+} signaling in physiology and pathophysiology, as well as for those who are interested in targeting Ca^{2+} signaling as a therapeutic approach for various disease states. I congratulate the authors on producing a straightforward text that can be useful to researchers with different levels of expertise. I hope that this work will help to expand interest in the essential field of Ca^{2+} signaling research.

With best wishes,

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Preface

The evolution process of living organisms offered a well-established communication between millions of cells in higher organisms like humans. Calcium (Ca^{2+}) is one such element involved in the cellular communication system. This versatile bio-element contributes to nearly all the aspects of developmental and physiological processes of all living organisms. In fact, there is no genesis or movement of organisms without Ca^{2+} due to its fundamental role in embryogenesis, skeleton formation, and muscle function. Unlike other ions, Ca^{2+} has the capability to translate the extracellular signal into a different type of response which depends on a very tight spatial and temporal control of intracellular Ca^{2+} level. Thus, Ca^{2+} homeostasis is an integral part of normal physiological functions of any eukaryotic organism including humans. In the last several decades, a dramatic progress has been made to understand the complex process of Ca^{2+} signaling and homeostasis. However, the molecular events that initiate/regulate the Ca^{2+} influx and efflux remain in need of further study for better understanding of the activity of Ca^{2+} in a biological system. This monograph is intended to give an overview about the current knowledge of Ca^{2+} signaling in essential physiological processes and aspects of pharmacological targeting of Ca^{2+} channels and other Ca^{2+} handling machineries to attenuate or prevent the progression of certain common disorders associated with Ca^{2+} dysregulation.

As the Ca^{2+} signaling is a diverse field, it is difficult for us to cover all the areas, and more specifically, we felt difficulties in determining the focus and target readers. We have mainly focused on the functional role of Ca^{2+} in muscle and neural physiology and providing current knowledge on the link between Ca^{2+} dysregulation and the development of pathological conditions in muscle disorders, neurodegenerative diseases, and pain. Although we have not covered all the molecules and signaling pathways involved in the regulation and activation of Ca^{2+} signaling, we have summarized the characteristic features and functions of major molecules and receptors involved in the transport, activation, and regulation of Ca^{2+}. In recent years, the advancement of molecular studies has not only unveiled the structural basis of Ca^{2+} channels but also expanded the list of human diseases associated with defects in Ca^{2+} channels and other Ca^{2+} handling machineries. Taking this into account, we have illustrated in the sixth chapter about the naturally available Ca^{2+} channel activators and inhibitors and their pharmacological benefits in treating various Ca^{2+} dysregulation-associated disorders. The most important part of this monograph covers the advantage of integration of nanotechnology to the preparation of

natural product-based therapeutics. We have provided a crisp up-to-date account on the different methods of nanocarrier preparation. This chapter also describes the efficiency of the nanocarrier delivery system, in the aspect of targeted delivery, improved bioavailability, and therapeutic efficacy, for the administration of phytoactive constituents with Ca^{2+} channel-modulating capability.

The central theme of this monograph is giving the fundamental mechanisms of Ca^{2+} influx and efflux from cells, the pathological consequences of defect and/or disturbance of Ca^{2+} handling machineries and Ca^{2+}-associated signaling molecules, and the efficacy of nanotechnology system in delivering natural product-based Ca^{2+} channel modulators. We have made an effort to unify all the content of scattered research literature in this area of research and tried to provide in-depth contents about the topics we have chosen. Overall, this monograph is not just a collection of papers, but it is an essence of the diverse Ca^{2+} signaling field and demonstrates that Ca^{2+} channels and other Ca^{2+} homeostatic machineries can be a therapeutic target for multiple disorders. In all chapters, we have provided the basic information relevant to the topics, and at the same time, we have described the perspective knowledge about Ca^{2+} homeostasis. Thus, we believe that this monograph could be an informative resource, in the form of a condensed handbook, for research students as well as advanced researchers. As nanotechnology has broken many barriers in natural product-based medicine to bring them into clinical settings, we believe that the contemporary contents of this monograph may present some useful information and new ideas to all categories of readers, in particular, to beginners. If this is indeed achieved, then our efforts will have succeeded and we would be happy.

Kurnool, India — Senthilkumar Rajagopal
Qingdao, China — Murugavel Ponnusamy

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About the Authors

Senthilkumar Rajagopal is presently a recipient of Ramalingaswami Re-entry Fellowship (Department of Biotechnology, Ministry of Science and Technology, Government of India) and coordinator at the Department of Biochemistry in Rayalaseema University, Kurnool, AP, India. He has handled the project entitled "G-Protein-Coupled Receptor-Mediated Intracellular Mechanisms by Alcohol-Induced Digestive Disorders in the Gastrointestinal Tract" while working as DBT-Ramalingaswami re-entry fellow (Scientist D) from 2013 to 2015 at the Department of Zoology, Nizam College, Osmania University, Hyderabad, India, and later he moved to the Department of Biochemistry, Rayalaseema University, Kurnool, AP, as a Ramalingaswami re-entry fellow. Previously, he had worked as postdoctoral research fellow at the University of Virginia, Dana-Farber Cancer Institute, Harvard University, and Virginia Commonwealth University. His research interests are majorly focused on deciphering the role of various signaling molecules in the patho-physiology of organisms and their clinical implications. His doctorate research involved studying the role of glycine in ethanol-induced hepatotoxicity. This work was carried out at the Department of Biochemistry and Biotechnology, Annamalai University, Tamil Nadu, India. Till now, he had published more than 47 papers in various international peer-reviewed journals. He has been editor of two book series: Digestive Diseases – Research and Clinical Developments and Hepatology Research and Clinical Developments. Furthermore, he has contributed chapters to more than 14 books. He is an active member of various international scientific organizations and societies and serves as an associate editor; a review, technical, and lead guest editor; and an editorial board member on various prestigious international journals. His contribution toward neuroscience field has been applauded in the form of a Gourmand World Cookbook Award which was presented as a special award by the Society of Neuroscience. He is an active life member of various societies including the Indian Society of Cell Biology (ISCB), Society of Biological Chemists (SBC) India, Indian Society for Atherosclerosis Research (ISAR), Indian Science Congress Association (ISCA), Society for Free Radical Research (SFRR) India, Indian Society of Cell Biology (ISCB), Indian Biophysical Society (IBS), and Science Advisory Board of Bioinformatics, LLC (USA), and a member of the Royal Society of Chemistry (RSC), UK.

Murugavel Ponnusamy is working as postdoctoral research associate at the Center for Developmental Cardiology, Institute for Translational Medicine, Qingdao University, China. His research interest includes molecular pharmacology, cellular signaling, tissue repair and regeneration, and experimental therapeutics. Previously, he had worked as postdoctoral fellow at the Division of Renal Diseases, Department of Medicine, Rhode Island Hospital, Brown University-Alpert Medical School, USA, under the supervision of Dr. Shougang Zhuang. His PhD research was focused on elucidating the effect of diallyl tetrasulfide on cadmium-induced toxicity (an in vivo and in vitro study), which was carried at Annamalai University, India. In a short time, he has been able to publish more than 28 papers in various national and international peer-reviewed journals and contributed four chapters to different books. He is an active member of various societies including the Society of Biological Scientists of India (SOBSI), Indian Society of Cell Biology (ISCB), and Society of Biological Chemists (SBC) India.