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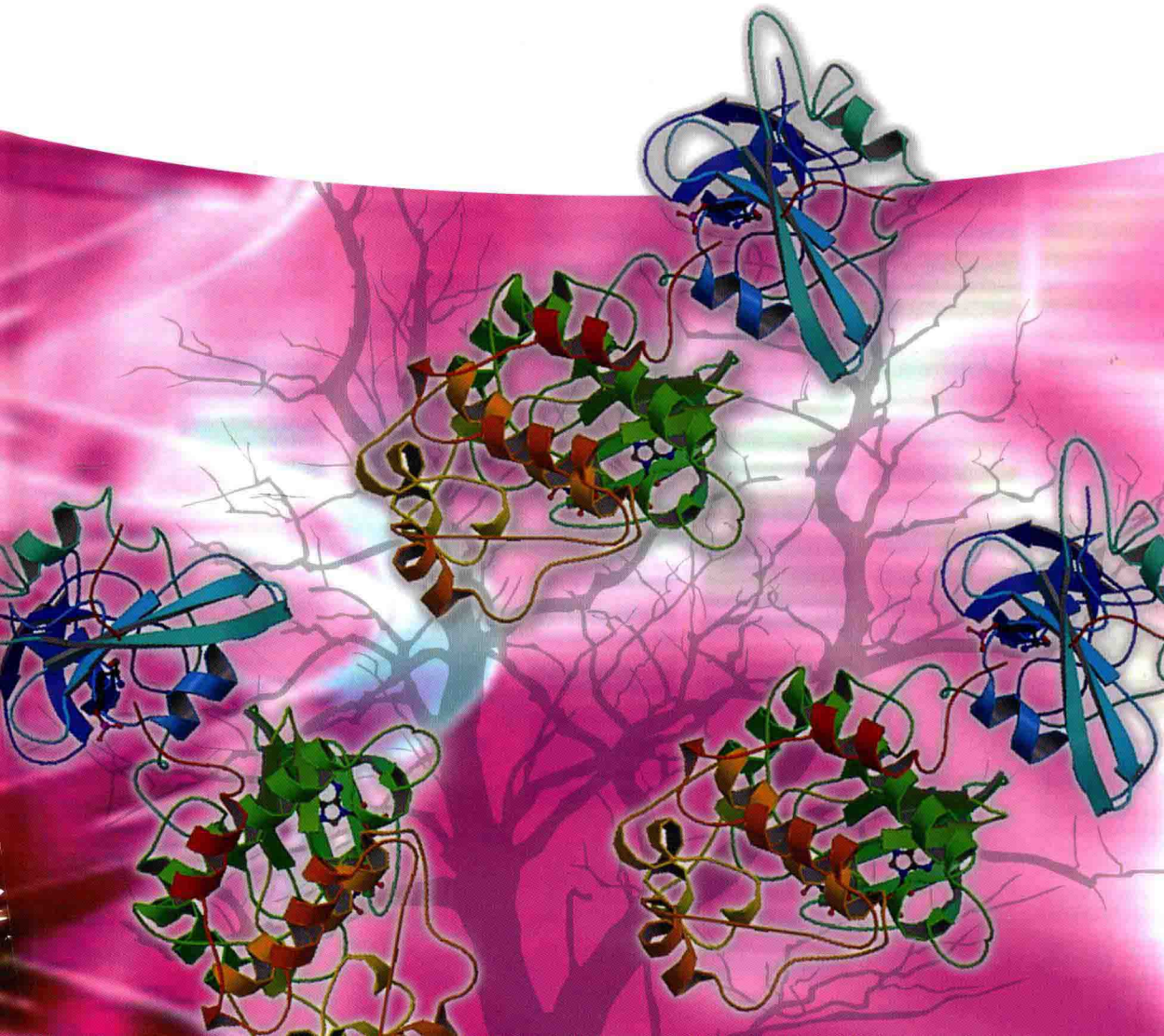
kinomics

Approaches and Applications



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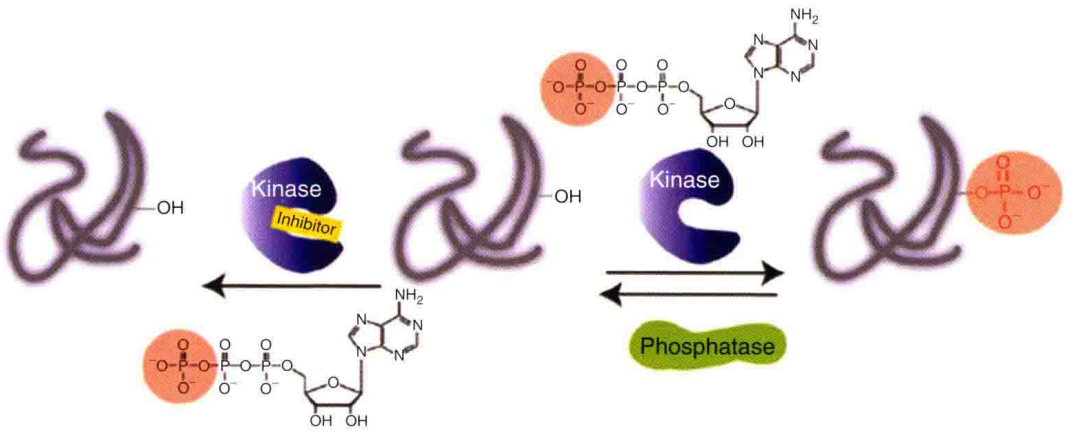
Preface

This book is the result of a friendship and an idea. When we worked together on protein phosphorylations, we were looking for a compendium that deals with the various aspects of phosphorylation chemistry, and biology and were frustrated by a lack of such books. This frustration was shared by other scientists, including students who wished to learn more about this exiting and complex topic at the interface of biomedicine, pharmacy, biochemistry, biology, and chemistry. When the idea was hatched, we struggled with the concept of an edited book versus a single author book. But given the interdisciplinarity of this theme, we felt that it is best to let those who are specialists in the field speak to the matter.

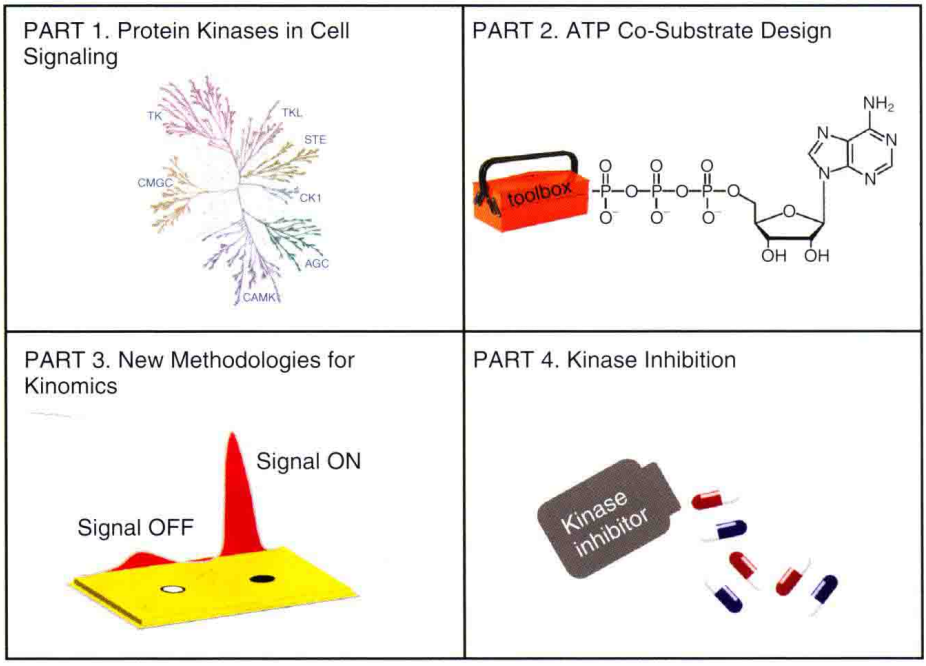
And here were are … we decided to go on this adventure and bring together a group of experts who have one thing in common – their interest in phosphorylations and how this fundamental process impacts our daily lives – from diseases to honey bees and from cell death to drug discovery. We are all impacted by this perceptively simple reaction that is common to life on this planet – and who knows, maybe beyond.

So, what is this reaction that this book is dealing with? To a chemist, it is the transfer of the γ-phosphate group from adenosine triphosphate (ATP) to a substrate protein catalyzed by protein kinases. To a biochemist, this reaction is one of the key regulatory mechanisms that turn complex cellular functions on and off.



To a biomedical scientist, this reaction is linked to a plethora of diseases. It is a value target for drug discovery. It is a reaction that impacts our lives in more than one way, and to some readers it will be surprising to discover the many implications of this important biological transformation. Protein kinases are the key to this group transfer and the kinomics is their study in a range of contexts that require a multidisciplinary approach and a tool set that draws from various scientific disciplines.

This book is structured into four sections. The first section provides an overview of protein kinases and their functions. Mann gives a structured introduction to this important reaction and provides a chemical biology overview and discusses important aspects including analogue-sensitive kinases. This is followed by three chapters focusing on particular kinases starting with Litchfield's discussion of the interplay between protein kinases and caspases, a class of proteases involved in apoptosis, which require activation by protein-kinases–catalyzed phosphorylation. Pinna discusses the unique kinase Fam20C, which is a genuine casein kinase and phosphorylates this protein under physiological conditions. It phosphorylates the S-x-E/pS motif, and this particular n+2 motif is a critical feature for this particular kinase. While overactivity/overexpression of protein kinases has been linked to various cancers, Doerig provides an angle to the kinomics that is less widely known. His chapter deals with the kinomics of malaria parasites and makes a strong case for malaria-related kinases as drug targets for disease treatment.



The second section of this book deals with the all-important ATP co-substrate, which serves as the phosphate source. Pflum provides a comprehensive overview

of the synthesis of new ATP bioconjugates, which are tools for the study of enzyme kinetics. This is followed by a chapter on the use of electrochemistry to study protein-kinase-catalyzed transformations using a range of redox probes to from nanoparticles to solution probes to metallocene-ATP bioconjugates.

Section three gives an overview over methodologies currently used in the study of the kinome. This section starts with the highly versatile Phos-tag technology, discussed by Kinoshita, in which metal coordination to a phosphate is exploited on surfaces, on beads, and in solution. Napper provides an overview of the use of array technology coupled with publically available bioinformatics packages in infectious diseases with a distinct agricultural angle, which sheds a new light on the impact of this reaction on the economy.

Carlson discusses an interesting group of kinases that phosphorylate histidine residues, an important transformation in bacteria. Again, the specter of a new approach to antibiotics is discussed in which His-kinases may be strategically targeted. Wallace discusses a range of methods used in kinome analysis from peptide arrays for high-throughput screening to the use of mass spectrometry to identify protein kinases substrates.

We have reached the last section of our book, and it deals with the most challenging aspects – interfering with kinomics and the development of drugs that are both specific and selective. Are protein kinases "druggable"? This question requires a modification. Are they selectively "druggable"? Can we inhibit one particular kinase without impacting the function of closely related kinases or pathways? How can we differentiate diseased versus healthy state of an organism in which metabolic pathways are common? The answer is a qualified "maybe." Gunning provides an example of targeting JAK-activated dimerization of STAT3, which is involved in gene transcription. Small molecules can be used to prevent dimerization and are an interesting target for therapy. Hartinger gives an overview of the use of metal-containing drugs and their interaction with protein kinases and phosphatases, responsible for dephosphorylations.

This book is the result of hard work by all scientists who playfully engaged in years of research without losing sight of the relevance of their efforts. This book would not have been possible without a team of co-authors, students, and postdoctoral fellows.

To the Reader.

Please enjoy this book as much as we enjoyed working on it together. We apologize for errors that may have crept in. They are entirely intended.

Live long and phosphorylate!

Rochester, MI, USA,
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April 1, 2015

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