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Kinase Screening and Profiling

Methods and Protocols

Edited by

Hicham Zegzouti and Said A. Goueli

Promega Corporation, Madison, Wisconsin, USA

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Editors
Hicham Zegzouti
Promega Corporation
Madison, WI, USA

Said A. Goueli
Promega Corporation
Madison, WI, USA

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Preface

Protein kinases play a central role in cellular physiology and diverse biological processes and thus alterations in their expression or activity have considerable consequences. Based on the critical role they play in regulation of normal and abnormal cellular growth and differentiation, these enzymes prove to be very valuable therapeutic targets. It has been estimated that over 60% of current discovery programs in pharmaceutical companies are focused on protein kinase inhibitors. As of 2015 there are 30 small molecule kinase inhibitors approved for human oncology and for autoimmune diseases and over 150 are currently in clinical trials. These drugs have grossed over $30 billion and projected to reach over $40 billion in 2 years. It is worth noting that the majority of these clinical trials target only 42 protein kinases and about 50% of these inhibitors target kinases which already have approved drugs. Furthermore, over 100 kinases have unknown function and 50% of all kinases are largely uncharacterized. Thus there is significant hope for breakthrough therapies directed towards previously untargeted kinases.

Although so much success has been achieved with developing novel therapeutics for protein kinases in multiple disorders, many hurdles and obstacles had to be overcome at the early stages of considering protein kinases as validated drug target. These include the high concentration of cellular ATP for developing ATP competitive inhibitors, structural similarities for developing selective inhibitors against specific kinase, cellular permeability of the drugs, and above all cellular toxicities as kinases are involved in multiple functions and play intricate role in several signaling pathways. Incorrect or incomplete assessment of cellular selectivity substantially increases the risk of unexpected toxicities at later stages of drug development.

In addressing these issues and with the expectations of expanding the therapeutic potential of targeting as many kinases as possible, we believe a volume devoted to the screening and profiling of protein kinase inhibitors or activators will be timely. The volume will cover current technologies that are in practice at various academic and industrial research laboratories. It covers several facets of the drug discovery processes starting with target identification, assay development, and screening chemical libraries for hit identification and lead optimization. The screening strategies have been mainly done through biochemical assays with emerging trend for cellular kinase screening. The profiling part of the volume discusses several strategies and techniques that are required to minimize off-target hits and minimize cellular toxicities that are caused by liability kinases. We have been fortunate to have a diverse list of experienced authors whose main focus is on the kinases as drug target with different strategies in reaching that goal. We hope this volume will benefit scientists and researchers who are interested in this field of drug discovery.

Madison, WI, USA

Hicham Zegzouti
Said A. Goueli

Contents

Contributors

Hee-Chul Ahn • *Department of Pharmacy, Dongguk University-Seoul, Goyang, Gyeonggi, Republic of Korea*

Christophe Antczak • *HTS Core Facility, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Center for Proteomic Chemistry, Novartis Institutes for Biomedical Research, Cambridge, MA, USA*

Douglas S. Auld • *Center for Proteomic Chemistry, Novartis Institutes for Biomedical Research, Cambridge, MA, USA*

Silke M. Bauer • *Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tuebingen, Tuebingen, Germany*

Eun Jeong Cho • *Texas Screening Alliance for Cancer Therapeutics, and College of Pharmacy, The University of Texas at Austin, Austin, TX, USA*

Kevin N. Dalby • *Division of Medicinal Chemistry and Texas Screening Alliance for Cancer Therapeutics, The University of Texas at Austin, Austin, TX, USA*

Mindy I. Davis • *Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, MD, USA*

Channing J. Der • *Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Ashwini K. Devkota • *Texas Screening Alliance for Cancer Therapeutics, The University of Texas at Austin, Austin, TX, USA*

Hakim Djaballah • *HTS Core Facility, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Institut Pasteur Korea, Seongnam-si, Gyeonggi-do, South Korea*

Krisna C. Duong-ly • *Cancer Biology Program, Fox Chase Cancer Center, Philadelphia, PA, USA*

Leanna R. Gentry • *Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Said A. Goueli • *Promega Corporation, Research and Development, Madison, WI, USA; University of Wisconsin School of Medicine and Public Health, Madison, WI, USA*

Klaus M. Hahn • *Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Byeonggu Han • *Department of Pharmacy, Dongguk University-Seoul, Goyang, Gyeonggi, Republic of Korea*

Jacquelyn Hennek • *Promega Corporation, Research and Development Department, Madison, WI, USA*

James Inglese • *Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, MD, USA*

Yong Jia • *Genomics Institute of the Novartis Research Foundation, San Diego, CA, USA*

Jose Juarez • *Genomics Institute of Novartis Research Foundation, San Diego, CA, USA*

Andrei V. Karginov • *Department of Pharmacology, University of Illinois at Chicago, Chicago, IL, USA*

Jakub M. Kubiak • *Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tuebingen, Tuebingen, Germany*
Shenshen Lai • *Kinexus Bioinformatics Corporation, Vancouver, BC, Canada*
Stefan Laufer • *Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tuebingen, Tuebingen, Germany*
Mari Manuia • *Genomics Institute of the Novartis Research Foundation, San Diego, CA, USA*
Chad J. Miller • *Department of Pharmacology, Yale University School of Medicine, New Haven, CT, USA*
Dehua Pei • *Department of Chemistry and Biochemistry, The Ohio State University, Columbus, OH, USA*
Steven Pelech • *Kinexus Bioinformatics Corporation, Vancouver, BC, Canada; Department of Medicine, University of British Columbia, Vancouver, BC, Canada*
Jeffrey R. Peterson • *Cancer Biology Program, Fox Chase Cancer Center, Philadelphia, PA, USA*
Ulrich Rothbauer • *Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tuebingen, Tuebingen, Germany*
Moritoshi Sato • *Graduate School of Arts and Sciences, The University of Tokyo, Tokyo, Japan*
Xiaoqing Shi • *Kinexus Bioinformatics Corporation, Vancouver, BC, Canada*
Andrew W. Tao • *University of Michigan, Ann Arbor, MI, USA*
Clint D.J. Tavares • *Division of Medicinal Chemistry, The University of Texas at Austin, Austin, TX, USA*
Thi B. Trinh • *Department of Chemistry and Biochemistry, The Ohio State University, Columbus, OH, USA*
Benjamin E. Turk • *Department of Pharmacology, Yale University School of Medicine, New Haven, CT, USA*
Yoshio Umezawa • *Department of Chemistry, School of Science, The University of Tokyo, Tokyo, Japan*
Jolanta Vidugiriene • *Research and Development Department, Promega Corporation, Madison, WI, USA*
Dirk F.H. Winkler • *Kinexus Bioinformatics Corporation, Vancouver, BC, Canada*
Hicham Zegzouti • *Promega Corporation, Research and Development Department, Madison, WI, USA*
Hong Zhang • *Kinexus Bioinformatics Corporation, Vancouver, BC, Canada*