

19

Topics in Medicinal Chemistry

Editorial Board:

P.R. Bernstein, Rose Valley, USA

A. Buschauer, Regensburg, Germany

G.I. Georg, Minneapolis, USA

J.A. Lowe, Stonington, USA

N.A. Meanwell, Wallingford, USA

A.K. Saxena, Lucknow, India

U. Stilz, Malov, Denmark

C.T. Supuran, Sesto Fiorentino, Italy

Aims and Scope

Drug research requires interdisciplinary team-work at the interface between chemistry, biology and medicine. Therefore, the new topic-related series Topics in Medicinal Chemistry will cover all relevant aspects of drug research, e.g. pathobiochemistry of diseases, identification and validation of (emerging) drug targets, structural biology, drugability of targets, drug design approaches, chemogenomics, synthetic chemistry including combinatorial methods, bioorganic chemistry, natural compounds, high-throughput screening, pharmacological in vitro and in vivo investigations, drug-receptor interactions on the molecular level, structure-activity relationships, drug absorption, distribution, metabolism, elimination, toxicology and pharmacogenomics.

In general, special volumes are edited by well known guest editors.

In references Topics in Medicinal Chemistry is abbreviated Top Med Chem and is cited as a journal.

More information about this series at <http://www.springer.com/series/7355>

Shelli R. McAlpine • Adrienne Lesley Edkins
Editors

Heat Shock Protein Inhibitors

Success Stories

With contributions by

J.L. Brodsky · G.L. Blatch · L.K. Buckton · A.L. Edkins ·
J.E. Gestwicki · X. Li · A. Manos-Turvey · S. McAlpine ·
S.R. McAlpine · J. McConnell · J.R. McConnell ·
R. Mehmood · E.-R. Pesce · P. Phillips · H. Shao ·
G. Sharbeen · S.R. Srinivasan · Y. Wang · P. Wipf

 Springer

Editors

Shelli R. McAlpine
School of Chemistry
University of New South Wales
Sidney
New South Wales, Australia

Adrienne Lesley Edkins
Biomedical Biotechnology Research Unit
(BioBRU)
Department of Biochemistry and Microbiology
Rhodes University
Grahamstown, South Africa

ISSN 1862-2461

Topics in Medicinal Chemistry

ISBN 978-3-319-32605-4

DOI 10.1007/978-3-319-32607-8

ISSN 1862-247X (electronic)

ISBN 978-3-319-32607-8 (eBook)

Library of Congress Control Number: 2016938782

© Springer International Publishing Switzerland 2016

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made.

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Preface

Protein folding and degradation are key cellular processes that must be carefully regulated in the crowded and compartmentalised cellular environment. The physiological process of proteostasis must also be maintained in times of stress, where an additional burden is placed on cells due to alterations in protein structure and function. The ability of the cell to maintain appropriate protein homeostasis under both physiological conditions and during cellular upheaval is largely dependent on a phenomenon known as the stress response. The stress response is an evolutionarily conserved and often predictable response that results in the upregulation or activation of a cohort of proteins, known collectively as molecular chaperones that serve to ameliorate the consequences of protein misfolding. Selected members of the heat shock proteins (e.g. Hsp90 and Hsp70) represent the largest and best-characterised family of molecular chaperones.

Many heat shock proteins (Hsps) function as molecular chaperones, regulating a range of processes associated with protein homeostasis, including protein folding, aggregation suppression and protein degradation. The activities of these Hsps are finely tuned and usually driven by the formation of complexes with cofactors. Understanding the mechanistic details by which these Hsps function as molecular chaperones has led to their analysis in human diseases. Hsps have been implicated in either the aetiology or prevention of many human diseases, ranging from cancer to Alzheimer's and infectious diseases. Hsps have been identified as putative drug targets for therapeutic intervention. In this book, the authors provide critical insight into the identification and development of inhibitors against selected Hsps as future therapies for human disease.

Specifically, topics include discussions on Hsp90, Hsp70, Hsp47, Hsp40 and Hsp27. Describing inhibitors that modulate Hsp90 or Hsp70 or a combination of these two inhibitors provides an overview of the most recent drugs targeting these Hsps. Finally, these chapters provide insight into potential new routes for modulating these Hsps. However, despite these success stories, there are currently no Hsp inhibitors that have completed clinical trials and are in routine use for treating patients. As discussed within these chapters, there are opportunities to develop new

molecular inhibitors for these therapeutically relevant Hsps. The wide range of Hsps and their functional control of the cell make these chaperones highly relevant to all therapeutic areas.

Sidney, Australia
Grahamstown, South Africa

Shelli R. McAlpine
Adrienne Lesley Edkins

Contents

Targeting the C-Terminus of Hsp90 as a Cancer Therapy	1
Jeanette McConnell, Yao Wang, and Shelli McAlpine	
Hsp90 Co-chaperones as Drug Targets in Cancer: Current Perspectives	21
Adrienne L. Edkins	
Evaluating Dual Hsp90 and Hsp70 Inhibition as a Cancer Therapy	55
Laura K. Buckton, Yao Wang, Jeanette R. McConnell, and Shelli R. McAlpine	
The Effect of Structure and Mechanism of the Hsp70 Chaperone on the Ability to Identify Chemical Modulators and Therapeutics	81
Alexandra Manos-Turvey, Jeffrey L. Brodsky, and Peter Wipf	
Allosteric Inhibitors of Hsp70: Drugging the Second Chaperone of Tumorigenesis	131
Sharan R. Srinivasan, Hao Shao, Xiaokai Li, and Jason E. Gestwicki	
Hsp40 Co-chaperones as Drug Targets: Towards the Development of Specific Inhibitors	163
Eva-Rachele Pesce, Gregory L. Blatch, and Adrienne L. Edkins	
HSP47: The New Heat Shock Protein Therapeutic Target	197
George Sharbeen, Shelli McAlpine, and Phoebe Phillips	
Heat Shock Protein 27: Structure, Function, Cellular Role and Inhibitors	221
Rashid Mehmood and Shelli R. McAlpine	
Index	235