
Development of Therapeutic Agents Handbook

Edited by
Shayne Cox Gad



DEVELOPMENT OF THERAPEUTIC AGENTS HANDBOOK

SHAYNE COX GAD, PH.D., D.A.B.T.

Gad Consulting Services

Cary, North Carolina

 **WILEY**

A JOHN WILEY & SONS, INC., PUBLICATION

Copyright © 2012 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permissions>.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Development of therapeutic agents handbook / [edited by] Shayne Cox Gad.
p. cm.

ISBN 978-0-471-21385-7 (cloth)

1. Drugs--Research--Handbooks, manuals, etc. 2. Drugs--Design--Handbooks, manuals, etc. 3. Pharmaceutical chemistry--Handbooks, manuals, etc. 4. Drug development--Handbooks, manuals, etc. I. Gad, Shayne C., 1948-

RM301.25.D47 2011

615'.19--dc22

2011007552

Printed in the United States of America

ePDF ISBN: 978-1-118-07710-8

ePub ISBN: 978-1-118-07711-5

10 9 8 7 6 5 4 3 2 1

CONTENTS

PREFACE	ix
CONTRIBUTORS	xi
PART I FUNDAMENTALS AND CONCEPTS	1
1. Current Needs for New Therapeutic Agents and Discovery Strategies—A Systems Pharmacology Approach	3
<i>Sophie C. Desbiens and David H. Farb</i>	
2. Target Selection in Drug Discovery	25
<i>Charles F. Albright</i>	
3. New Drug Applications	35
<i>John S. McInnes</i>	
4. From Concept to the Clinics: Development of Cancer Therapeutics	47
<i>Balveen Kaur, Gregory B. Lesinski, and Abhik Ray Chaudhary</i>	
5. Development of Countermeasures for Bioterrorism in the United States	73
<i>Gregory H. Levine and Jeffrey L. Handwerker</i>	
6. Development and Application of Conformation-Selective Integrin Antibodies	91
<i>Nathan S. Astrof, Dan Peer, and Motomu Shimaoka</i>	
7. Pain Management Market Overview	113
<i>Anita Holdcroft</i>	
8. Antiviral Market Overview	127
<i>Anita Arora, Natalia Mendoza, and Stephen K. Tyring</i>	
PART II METHODS AND TECHNIQUES IN DRUG DISCOVERY AND DEVELOPMENT	145
9. High-Throughput Screening for Small-Molecule Drug Discovery	147
<i>C. Parker and J.-H. Zhang</i>	

10. Mass Spectrometry	181
<i>Robert D. English and Anthony M. Haag</i>	
11. Molecular Screening for Therapeutic Agents	207
<i>R. Damoiseaux</i>	
12. Accelerator Mass Spectrometry and Positron Emission Tomography in Human Microdosing	241
<i>Zhengdong Cheng</i>	
13. Development of Antimicrobial Peptides as Therapeutic Agents	285
<i>Robert S. Hodges, Ziqing Jiang, James Whitehurst, and Colin T. Mant</i>	
14. Antibodies for Human Diseases	359
<i>Guo-Liang Yu and Jian Ni</i>	
15. Combinatorial Compounds and Drug Discovery	399
<i>James C. Bigelow</i>	
16. Locoregional Chemoradiotherapy of Cancer Using Hydrogel	413
<i>David J. Yang, Ali Azhdarinia, Hiroaki Kurihara, Jerry Bryant, and E. Edmund Kim</i>	
17. RNAi-Mediated Therapeutics	425
<i>Núria Morral and Scott R. Witting</i>	
18. Crystallography	445
<i>Carl H. Schwalbe</i>	
19. PEGylation	463
<i>Sanju Dhawan, Deepak N. Kapoor, Rishi Kapil, Manoj Kumar, and Ankur Bansal</i>	
20. Gold Standard Animal Models	517
<i>Carol Castaneda and Michael S. LaPointe</i>	
21. Discovery of Vaccine Adjuvants	533
<i>Fiona A. Sharp and Ed C. Lavelle</i>	
22. Oral Delivery of Macromolecules for the Development of Therapeutic Agents	547
<i>Hye J. Lee and Chanmi Choi</i>	
23. Aerosol Drug Delivery to the Lungs	565
<i>Andrew R. Martin and Warren H. Finlay</i>	
24. Resistance to Antiplatelet Therapy	589
<i>Paul A. Gurbel and Udaya S. Tantry</i>	
25. Antibiotic Development	611
<i>Robert L. Bettiker and Jason C. Gallagher</i>	
PART III THERAPEUTICS TOPICS	629
26. Antimicrobial Resistance in Biofilms: A Sticky Situation	631
<i>Shu Yeong Queck and Michael Otto</i>	
27. Drotrecogin Alfa Activated (Recombinant Human Activated Protein C, Xigris)	645
<i>Byungse Suh and Rafik Samuel</i>	

28.	Anti-Inflammatory Therapeutics	655
	<i>Marion M. Chan and Dunne Fong</i>	
29.	Anti-Inflammatory/Analgesics: An In-depth Look at p38 MAP Kinases	673
	<i>Kelly L. Brown</i>	
30.	Cardiovascular Disease: In-Depth Look	707
	<i>Nicholas B. Norgard and Mazen S. Abu-Fadel</i>	
31.	Ezetimibe and Cholesterol Absorption	723
	<i>Stefan Oswald and Werner Siegmund</i>	
32.	Cardiology—In-Depth Look: Kinases as Therapeutic Targets in the Heart	743
	<i>Karin Mauer and J. Emilio Exaire</i>	
33.	Statins in the Reduction of Cardiovascular Events	773
	<i>Rajesh Sachdeva, Bradley Hughes, and Jawahar L. Mehta</i>	
34.	Cardiology—In-Depth Look: Advances in Antiplatelet Therapy	785
	<i>Karin Mauer and Jorge F. Saucedo</i>	
35.	Gastrointestinal Disorders: A Focus on Acid-Suppressive Agents	813
	<i>Brian Hemstreet</i>	
36.	Pharmacology of Vasopressin and the Renin–Angiotensin–Aldosterone System	825
	<i>Elizabeth J. Brant, Albert Q. Lam, and Julian L. Seifter</i>	
37.	New Drugs and Nutraceuticals in the Treatment of Osteoarthritis	847
	<i>Y. Henrotin and J.-Y. Reginster</i>	
38.	Development of Anticytokine Agents for Rheumatoid Arthritis	881
	<i>Jonathan Sherlock, Christopher D. Buckley, and Karim Raza</i>	
39.	Overview of CNS Neuropharmaceuticals	897
	<i>Tauser Roxana-Georgiana and Antohe Dan-Stefan</i>	
40.	Thinking Outside the Box in Alzheimer Disease Treatment	929
	<i>Rudy J. Castellani, Michael W. Marlatt, Akihiko Nunomura, Paula I. Moreira, Hyoung-Gon Lee, Gemma Casadesus, Xiongwei Zhu, George Perry, and Mark A. Smith</i>	
41.	Neurotrophic Factors as Novel Therapeutic Targets	943
	<i>Stephen D. Skaper</i>	
42.	Oncology	963
	<i>Arkadiusz Z. Dudek and Steven F. Powell</i>	
43.	Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia	999
	<i>Muhammad Mansoor Alam and Moshe Talpaz</i>	
44.	Aromatase Inhibitors for Breast Cancer	1011
	<i>Akm Hossain and Jame Abraham</i>	
45.	Evolution of Selective Estrogen and Androgen Receptor Modulators: Status of Current Therapy and New Drug Development	1019
	<i>Gregory T. Wurz and Michael W. DeGregorio</i>	

46.	In-Depth Look: Anti-TNF-α Therapies	1045
	<i>Satadal Chatterjee and Shobhan Gaddameedhi</i>	
47.	Development of Therapeutic Agents: The Maternal—Fetal Perspective	1093
	<i>C. Gedeon, F. Garcia Bournissen, and G. Koren</i>	
48.	History of Antipsychotic Drug Development	1111
	<i>Shankar S. Gollapudi and Rajan Radhakrishnan</i>	
49.	Radiopharmaceuticals and Medical Imaging: Development of Radioimmunoconjugates for Radioimmunoimaging and Radioimmunotherapy of Malignant Diseases	1137
	<i>Gang Niu and Xiaoyuan Chen</i>	
50.	Therapeutic Drug Development for Kidney Diseases	1159
	<i>Mitchell H. Rosner, Joshua King, and Peter Monteleone</i>	
51.	Targeting Chemokines and Angiogenesis in Rheumatoid Arthritis	1185
	<i>Zoltán Szekanecz and Alisa E. Koch</i>	
52.	Development of Therapeutic Agents: Methods and Approaches in the Development of Vaccines against Protozoan Parasites	1207
	<i>Catherine Ivory and Kris Chadee</i>	
53.	Toxicology	1221
	<i>John H. Duffus</i>	
54.	Development of Phosphodiesterase 4 Inhibitors for Allergic and Nonallergic Inflammatory Diseases of the Airways	1233
	<i>Mark A. Giembycz</i>	
	INDEX	1251