New Drugs and Targets for Asthma and COPD
New Drugs and Targets for Asthma and COPD

Volume Editors

Trevor T. Hansel  London  
Peter J. Barnes  London

80 figures, 67 in color, 46 tables, 2010
Contents

Corresponding authors ........................................................................................................ IX
Foreword .................................................................................................................... XIII
Preface ......................................................................................................................... XIV

Introduction

New drugs and targets for asthma and COPD ................................................................. 3
Trevor T. Hansel and Peter J. Barnes

Bronchodilators

Indacaterol: A new once-daily long-acting β₂-adrenoceptor agonist (LABA) ............... 27
Jutta Beier, Alexandre Trifilieff and Mark Higgins

Aclidinium bromide, a novel long-acting muscarinic antagonist (LAMA) .................. 33
Amadeu Gavaldà and Esther Garcia-Gil

Dual-pharmacology bronchodilators for the treatment of COPD ............................... 39
John R. Jacobsen, Jayashree Aiyar, Sharath Hegde, Adam Hughes and Mathai Mammen

IgE- and epithelial-directed approaches

IgE-directed approaches: A general strategy for the treatment of atopic diseases .... 49
Franz Kricek

Therapy directed against thymic stromal lymphopoietin (TSLP) ............................... 55
Matthew J. Edwards

T-cell co-stimulator blockade

ICOS and B7RP-1: Novel targets for monoclonal antibodies .................................... 63
Gianluca Carlesso, Anthony J. Coyle and Ronald Herbst
Pattern recognition receptors

**Toll-like receptor 2 as a therapeutic target in lung disease** .......................... 69
Jane A. Mitchell, Rosalinda Sorrentino, Neil Cartwright and Mark Paul-Clark

**Toll-like receptor 3** ........................................ 73
Michael Carty and Andrew Bowie

**Toll-like receptor 4** ........................................ 81
Ian Sabroe

**Toll-like receptor 7 and 8 agonists** ........................................ 87
Hanna Harant

**Toll-like receptor 9 activation with CpG oligodeoxynucleotides for asthma therapy** ........ 95
Joel N. Kline and Arthur M. Krieg

Cytokines

**IL-5-directed approaches in the treatment of eosinophil-driven disease** ................ 103
Richard Marshall and Isidore Faiferman

**Monoclonal antibody therapy directed against interleukin-5 receptor α: MEDI-563** ........ 109
Roland Kolbeck, Masamichi Koike, Kazuhiro Kawasaki, Katsumasa Iwashita, George L. Spitalny, Nobuo Hanai, Peter A. Kiener, David Gossage, Nestor A. Molfin and Anthony J. Coyle

**IL-4- and IL-13-directed approaches** ........................................ 115
Larry Borish, John W. Steinke, Marion Kasaian and Samuel J. Goldman

**Aerovant (recombinant human interleukin-4 variant)** ........................................ 123
Malinda V. Longphre and Rick W. Fuller

**An anti-interleukin-13 receptor α1 antibody for the treatment of asthma** .............. 127
Maria Elena Fuentes and Karim Dabbagh

**Interleukin-7-directed approaches** ........................................ 131
Zaiba Shamim, Klaus Müller and Lars P. Ryder

**Monoclonal antibody therapy directed against interleukin-9: MEDI-528** .............. 137
Alison A. Humbles, Jennifer L. Reed, Joseph Parker, Peter A. Kiener, Nestor A. Molfin, Roland Kolbeck and Anthony J. Coyle

**Targeting interleukin-17 in the lungs** ........................................ 141
Stefan Ivanov and Anders Lindén

Chemokines

**Chemokine CCR3 antagonists** ........................................ 153
Ash Bahl, Brian Springthorpe and Rob Riley

**Therapeutic potential of CCR4 antagonists** ........................................ 161
David Hall, Alison Ford and Simon Hodgson
### Adhesion molecules

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very late activation antigen-4 (VLA-4) antagonists</strong></td>
<td>169</td>
</tr>
<tr>
<td>Peter Vanderslice and Darren G. Woodside</td>
<td></td>
</tr>
<tr>
<td><strong>Selectin antagonists and their potential impact for the treatment of inflammatory lung diseases</strong></td>
<td>175</td>
</tr>
<tr>
<td>Ewald M. Aydt, Daniel Bock and Gerhard Wolff</td>
<td></td>
</tr>
</tbody>
</table>

### Mediator receptor antagonists

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histamine H₄ receptor antagonists</strong></td>
<td>187</td>
</tr>
<tr>
<td>Paul J. Dunford and Robin L. Thurmond</td>
<td></td>
</tr>
<tr>
<td><strong>Antagonists of the prostaglandin D₂ receptor CRTH2</strong></td>
<td>193</td>
</tr>
<tr>
<td>Roy Pettipher and Trevor T. Hansel</td>
<td></td>
</tr>
</tbody>
</table>

### Enzyme inhibitors

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-Lipoxygenase inhibition</strong></td>
<td>201</td>
</tr>
<tr>
<td>Jaime L. Masferrer, Craig Wegner and Matt Graneto</td>
<td></td>
</tr>
<tr>
<td><strong>Utility of cytosolic phospholipase A₂α (cPLA₂α) inhibitors in the treatment of asthma</strong></td>
<td>207</td>
</tr>
<tr>
<td>James D. Clark and Cara M.M. Williams</td>
<td></td>
</tr>
</tbody>
</table>

### Antioxidants

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antioxidant therapeutic strategies</strong></td>
<td>215</td>
</tr>
<tr>
<td>Paul Kirkham and Irfan Rahman</td>
<td></td>
</tr>
</tbody>
</table>

### Protease inhibitors

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small-molecule neutrophil elastase inhibitors as therapies for respiratory disease</strong></td>
<td>225</td>
</tr>
<tr>
<td>Mary F. Fitzgerald</td>
<td></td>
</tr>
<tr>
<td><strong>The role of MMP-9 and MMP-12 inhibitors in inflammation</strong></td>
<td>231</td>
</tr>
<tr>
<td>S. Wong, M.A. Birrell, M.G. Belvisi, K. Stenvall and C.P. Bertrand</td>
<td></td>
</tr>
<tr>
<td><strong>α₁-Antitrypsin therapy</strong></td>
<td>237</td>
</tr>
<tr>
<td>Philip J. Barr and Philip A. Pemberton</td>
<td></td>
</tr>
</tbody>
</table>

### Inhibitors of fibrosis and vessels

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proteinase-activated receptor-1 inhibitors</strong></td>
<td>245</td>
</tr>
<tr>
<td>Rachel C. Chambers</td>
<td></td>
</tr>
<tr>
<td><strong>Integrin-mediated transforming growth factor-β activation</strong></td>
<td>251</td>
</tr>
<tr>
<td>Gisli Jenkins and Dean Sheppard</td>
<td></td>
</tr>
<tr>
<td><strong>Small-molecule inhibitors of transforming growth factor-β type I receptor kinase (ALK5)</strong></td>
<td>255</td>
</tr>
<tr>
<td>Darren H. Wong and Linda S. Higginns</td>
<td></td>
</tr>
<tr>
<td><strong>Serum amyloid P: A novel antifibrotic agent with therapeutic potential</strong></td>
<td>261</td>
</tr>
<tr>
<td>Mark L. Lupher, Jr. and W. Scott Willett</td>
<td></td>
</tr>
</tbody>
</table>
Inhibitors of cell signaling and transcription

Phosphodiesterase type 4 (PDE4) inhibition: The search for effective therapy with minimal side effects .......................... 269
Mike Yeadon, Nick Clarke and Jon Ward

Therapy directed against c-kit (CD117) and PDGF transmembrane receptor tyrosine kinases .......................... 279
Christoph Walker, David Rodman and Trevor T. Hansel

Syk kinase inhibitors ............................................. 283
Jane Denyer and Vipul Patel

Targeting protein kinase C-θ for asthma .................................. 289
Divya Chaudhary, Diane H. Boschelli and Marion T. Kasaian

Nucleic acid therapy

A multitargeted antisense therapy directed at CCR3 and the common β-chain of IL-3/IL-5/GM-CSF .......................... 297
Luc Paquet, Paolo Renzi, Nicolay Ferrari and Mark Parry-Billings

Author Index .......................................................... 303

Subject Index .......................................................... 304
Corresponding authors

Ash Bahl ..........................  p. 153
Discovery Director New Opportunities
AstraZeneca R&D Charnwood
Bakewell Road
Loughborough, Leics LE11 5RH (UK)
Tel. +44 1509 644600
Fax +44 1509 645527
E-Mail ash.bahl@astrazeneca.com

Philip J. Barr ......................  p. 237
Arriva Pharmaceuticals
1010 Atlantic Avenue
Alameda, CA 94501 (USA)
E-Mail philipjbarr@aol.com

Maria G. Belvisi ...................  p. 231
Head, Respiratory Pharmacology Group
Airway Disease Section
National Heart & Lung Institute
Faculty of Medicine
1st Floor, Room 109
Sir Alexander Fleming Building (SAF)
South Kensington Campus
Exhibition Road
Imperial College London
London SW7 2AZ (UK)
Tel. +44 207 594 7828
Fax +44 207 594 3100
E-Mail m.belvisi@imperial.ac.uk

Daniel Bock .......................  p. 175
Director Preclinical R&D
Acting Director Clinical Development
Revotar Biopharmaceuticals AG
Neuendorfstrasse 24a
DE–16761 Hennigsdorf (Germany)
Tel. +49 3302 202 5082
Fax +49 3302 202 5011
E-Mail d.bock@revotar-ag.de

Larry Borish ......................  p. 115
Professor of Medicine
Asthma and Allergic Disease Center
University of Virginia
Charlottesville, VA 22908 (USA)
Tel. +1 434 243 6570
E-Mail lb4m@virginia.edu

Andrew Bowie .....................  p. 73
School of Biochemistry and Immunology
Trinity College
Dublin 2 (Ireland)
Tel. +353 1 896 2435
Fax +353 1 677 2400
E-Mail agbowie@tcd.ie

Gianluca Carlesso ..................  p. 63
MedImmune
One MedImmune Way
Gaithersburg, MD 20878 (USA)
E-Mail CarlessoG@MedImmune.com
Rachel C. Chambers  p. 245
Reader in Respiratory Cell & Molecular Biology
Division of Medicine Postgraduate Tutor
Centre for Respiratory Research
Division of Medicine
University College London
Rayne Building
5 University Street
London WC1E 6JJ (UK)
Tel. +44 207 679 6978
Fax +44 207 679 6973
E-Mail r.chambers@ucl.ac.uk

Divya Chaudhary  p. 289
Principal Research Scientist II
Inflammation
Wyeth Research
200 Cambridge Park Drive
Cambridge, MA 02140 (USA)
Tel. +1 617 665 5428
Fax +1 617 665 5584
E-Mail Divya.Chaudhary@pfizer.com

James D. Clark  p. 207
Senior Director
Inflammation Signaling, Inflammation
and Immunology
Pfizer Research
200 Cambridge Park Drive
Cambridge, MA 02140 (USA)
Tel. +1 617 665 5475
Fax +1 617 665 5499
E-Mail james.d.clark@pfizer.com

Jane Denyer  p. 283
Respiratory CEDD
GlaxoSmithKline Medicines Research Centre
Gunnels Wood Road
Stevenage, Herts SG1 2NY (UK)
Tel. +44 1438 763810
E-Mail jane.c.denyer@gsk.com

Paul J. Dunford  p. 187
Johnson & Johnson Pharmaceutical Res. & Dev.
3210 Merryfield Row
San Diego, CA 92121 (USA)
E-Mail PDunford@PRDUS.JNJ.COM

Matthew J. Edwards  p. 55
Novartis Horsham Research Centre
Wimblehurst Road
Horsham, West Sussex RH12 5AB (UK)
E-Mail matt.edwards@novartis.com

Nicolay Ferrari  p. 297
Director, Pharmacology
Topigen Pharmaceuticals Inc.
2901 Rachel, Suite 13
Montréal, Québec H1W 4A4 (Canada)
Tel. +1 514 868 0077
Fax +1 514 868 0011
E-Mail nicolay.ferrari@topigen.com

Mary F. Fitzgerald  p. 225
Argenta Discovery Ltd.
8-9 Spire Green Centre
Harlow, Essex CM19 5TR (UK)
E-Mail Mary.Fitzgerald@argenta-discovery.com

Maria Elena Fuentes  p. 127
Roche Palo Alto LLC
3431 Hillview Ave.
Palo Alto, CA 94304 (USA)
Tel. +1 650 354 2350
E-Mail maria.fuentes@roche.com

Amadeu Gavaldà  p. 33
Laboratorios Almirall
R&D Centre
Sant Feliu de Llobregat
Barcelona (Spain)
Tel. +34 932 913 818
Fax +34 932 912 827
E-Mail amadeu.gavalda@almirall.es

David Hall  p. 161
Senior Scientific Investigator
GPCR Lead Optimisation
Respiratory CEDD
GlaxoSmithKline
Gunnels Wood Road
Stevenage, Herts SG1 2NY (UK)
Tel. +44 1438 764022
E-Mail david.a.hall@gsk.com

Trevor T. Hansel  p. 3, 279
Medical Director of iCRU
Honorary Consultant and Reader in
Respiratory Clinical Pharmacology
Imperial Clinical Respiratory Research Unit iCRU
Entrance C, First Floor, Mint Wing
St. Mary’s Hospital
Paddington
London W2 1NY (UK)
Tel. +44 20 3312 5733
E-Mail t.hansel@imperial.ac.uk
Ten years ago I had asked Peter Barnes and Trevor Hansel to do a volume on *New Drugs for Asthma, Allergy and COPD* for the book series *Progress in Respiratory Research*. It turned out a huge success with readers, and we received many requests for an update. We were therefore very pleased when this time round we were contacted by Trevor whether we would be interested in such an update, both he and Peter had been planning for some time. After screening the template of the book, the answer was an enthusiastic yes from my side.

Very similar to the first version, Trevor and Peter succeeded in putting together an attractive mix of chapters written by scientists from the pharmaceutical industry as well as from academia, actually reflecting the real-life scenario in modern drug development. Again, the authors involved in writing the various chapters represent the ‘who’s who’ in the asthma and COPD research field and guarantee scientific excellence. As the reader can see when screening the table of contents, every possible new compound, some of them close to commercialisation, others still at bench level, is discussed. This will make this book of high interest for many years to come.

True to the vision of the *Progress in Respiratory Research* series, we attached great importance to cutting-edge data being presented, which is reflected by the fact that many references include publications of up to 2010. The book is richly illustrated with 80 figures, 67 of which are in colour, and 46 tables. I am convinced that this new volume will again appeal to scientists and clinicians alike and enjoy the success of the first version. My final words are a big thank you to Trevor and Peter for having chosen Karger as their publisher and to all the people at the publisher who have helped me in getting this volume out in record time, well done!

C. T. Bolliger, Cape Town
Ashma and chronic obstructive pulmonary disease (COPD) are amongst the commonest diseases known to man, and it is of enormous concern that both are increasing in incidence. Reassuringly, there have been major advances in asthma management, particularly with the early and more widespread use of inhaled corticosteroids in combination with long-acting β2-agonists. Yet, there remains a pressing need for new and more specific therapies that control asthma or even cure the underlying disease process. Progress in understanding and treating COPD has been much slower, mainly because this disease of older patients has been relatively neglected. None of the treatments available today prevent the relentless progression of COPD and there is an urgent need to develop novel approaches to combat oxidants, inflammation, proteases and fibrosis. Interestingly, insights into processes occurring in rarer lung diseases such as cystic fibrosis and interstitial lung disorders are proving generally applicable in respiratory disease.

The aim of this book is to offer a state-of-the-art description of the exciting progress in research and development that is being made with new therapies for respiratory diseases. We are very aware that many large tomes are readily available that contain review chapters by leading scientific and clinical authorities. On this basis, our intention has been to link the biotechnology and pharmaceutical industry with academic and clinical opinion, as well as the medical needs of patients. In order to develop better therapies, we rely on this partnership, since the modern-day reality is that development of new drugs generally occurs from within the industry.

Following the success of “New Drugs for Asthma, Allergy and COPD” Volume 31 in 'Progress in Respiratory Research’ published by Karger in 2001, it has been a pleasure to prepare this related volume. We are grateful for the assistance of staff at Prous Science (Thomson Reuters) and thank Karger and Chris Bolliger for publishing it in 'Progress in Respiratory Research’.

We hope that the reader will find this book both interesting and helpful, and that this volume will facilitate the provision of better therapy for patients with respiratory diseases.

Trevor T. Hansel and Peter J. Barnes
London, July 2010