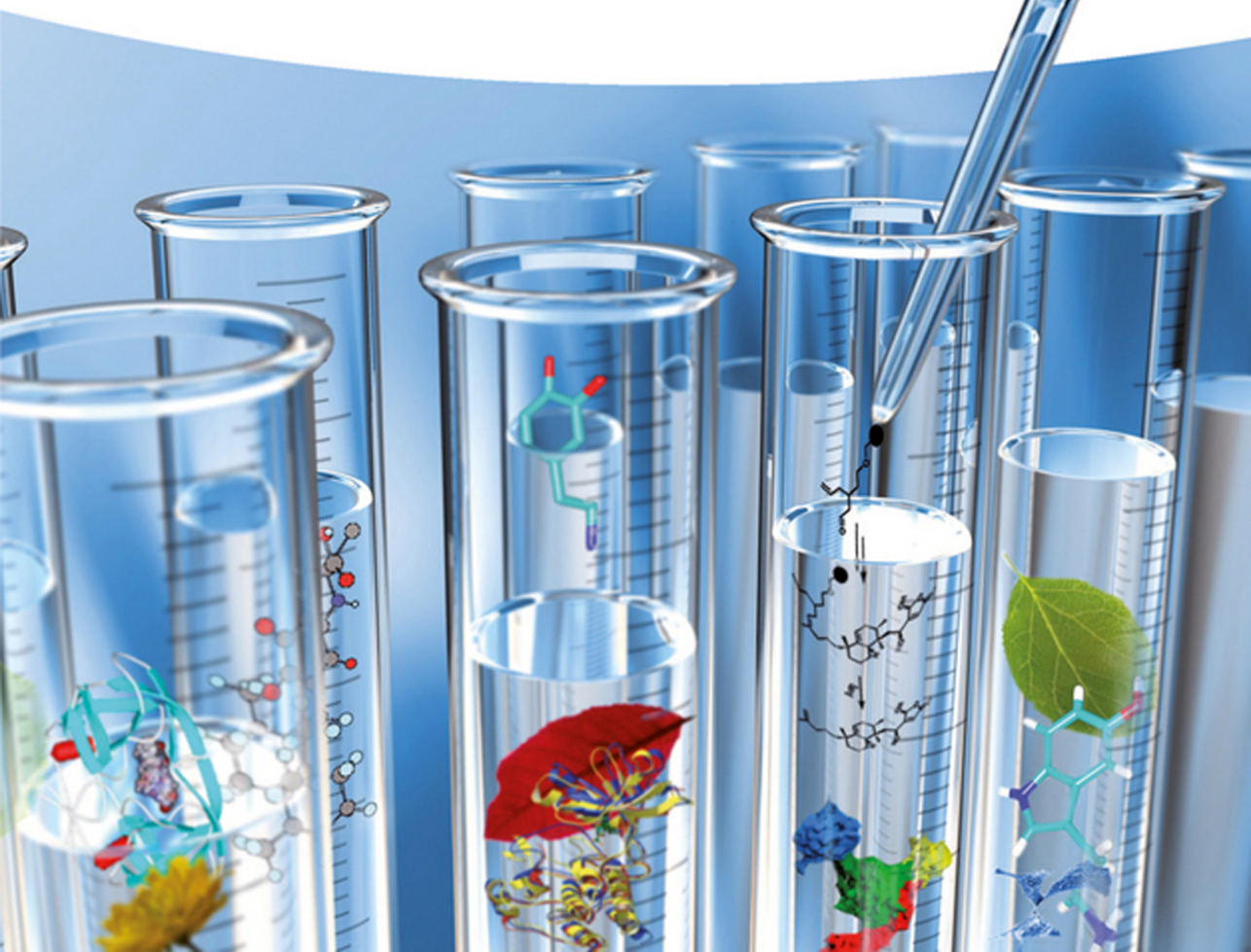


Edited by
Herbert Waldmann and Petra Janning

Concepts and Case Studies in Chemical Biology



Edited by
Herbert Waldmann and
Petra Janning

**Concepts and Case Studies in Chemical
Biology**

Related Titles

Trabocchi, A. (ed.)

Diversity-Oriented Synthesis **Basics and Applications in Organic** **Synthesis, Drug Discovery, and Chemical** **Biology**

2013

Print ISBN: 978-1-118-14565-4, also available
in digital formats

Sierra, M.A., de la Torre, M.C., Cossio, F.P.

More Dead Ends and Detours **En Route to Successful Total Synthesis**

2013

Print ISBN: 978-3-527-32976-2

Christmann, M., Bräse, S. (eds.)

Asymmetric Synthesis II **More Methods and Applications**

2012

Print ISBN: 978-3-527-32900-7, also available
in digital formats

Civjan, N. (ed.)

Chemical Biology **Approaches to Drug Discovery and** **Development to Targeting Disease**

2012

Print ISBN: 978-1-118-10118-6, also available
in digital formats

Luisi, P.P. (ed.)

Chemical Synthetic Biology

2011

Print ISBN: 978-0-470-71397-6, also available
in digital formats

Waldmann, H., Janning, P. (eds.)

Chemical Biology **Learning through Case Studies**

2009

Print ISBN: 978-3-527-32330-2

Edited by Herbert Waldmann and Petra Janning

Concepts and Case Studies in Chemical Biology

WILEY-VCH
Verlag GmbH & Co. KGaA

The Editors

Prof. Dr. Herbert Waldmann
MPI of Molecular Physiology
Otto-Hahn-Str. 11
44227 Dortmund
Germany

Dr. Petra Janning
MPI of Molecular Physiology
Otto-Hahn-Str. 11
44227 Dortmund
Germany

Cover

fotolia.com © Paolo Toscani

We thank Claudia Pieczka, MPI of Molecular Physiology, Dortmund, Germany for preparing the cover illustration.

■ All books published by **Wiley-VCH** are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

© 2014 Wiley-VCH Verlag & Co. KGaA,
Boschstr. 12, 69469 Weinheim, Germany

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Print ISBN: 978-3-527-33611-1
ePDF ISBN: 978-3-527-67598-2
ePub ISBN: 978-3-527-67600-2
Mobi ISBN: 978-3-527-67599-9

Cover-Design Adam Design Weinheim, Germany

Typesetting Laserwords Private Limited, Chennai, India

Printing and Binding Markono Print Media Pte Ltd, Singapore

Printed on acid-free paper

Contents

List of Contributors XVII

Introduction and Preface XXV

Abbreviations XXIX

1	Real-Time and Continuous Sensors of Protein Kinase Activity Utilizing Chelation-Enhanced Fluorescence	1
	<i>Laura B. Peterson and Barbara Imperiali</i>	
1.1	Introduction	1
1.2	The Biological Problem	1
1.3	The Chemical Approach	3
1.3.1	Chelation-Enhanced Fluorescence	3
1.3.2	β -Turn-Focused Kinase Activity Sensors	7
1.3.3	Recognition-Domain-Focused Kinase Activity Sensors	7
1.3.4	Chimeric Kinase Activity Sensors	10
1.4	Chemical Biological Research/Evaluation	12
1.4.1	Kinetic Parameters	12
1.4.2	Assessing Kinase Selectivity	12
1.4.3	Kinase Profiling in Cell Lysates and Tissue Homogenates	14
1.5	Conclusions	14
	References	15
 2	 FLiK and FLiP: Direct Binding Assays for the Identification of Stabilizers of Inactive Kinase and Phosphatase Conformations	 17
	<i>Daniel Rauh and Jeffrey R. Simard</i>	
2.1	Introduction – The Biological Problem	17
2.1.1	Kinase Inhibitors – Stabilizing Inactive Enzyme Conformations	17
2.1.2	Monitoring Conformational Changes upon Ligand Binding	19
2.2	The Chemical Approach	20
2.3	Chemical Biological Research/Evaluation	23
2.3.1	Finding the Unexpected	25
2.3.2	Targeting Protein Interfaces – iFLiK	26
2.3.3	Screening Akt	27

2.3.4	Targeting Phosphatases – FLiP	29
2.3.5	Lessons Learned from High-Throughput Screens	31
2.4	Conclusions	34
	References	35
3	Strategies for Designing Specific Protein Tyrosine Phosphatase Inhibitors and Their Intracellular Activation	37
	<i>Birgit Hoeger and Maja Köhn</i>	
3.1	Introduction – The Biological Problem	37
3.1.1	Chemical Inhibition of Protein Tyrosine Phosphatase Activity	37
3.1.2	PTP1B as Inhibitor Target	40
3.2	The Chemical Approach	41
3.2.1	The Concept of Bivalent Ligands – Development of a Specific PTP1B Inhibitor	41
3.2.2	Cell Permeability and Intracellular Activation of a Self-Silenced Inhibitor	43
3.2.3	A Prodrug Strategy to Gain Cell Permeability	44
3.3	Chemical Biological Research/Evaluation	45
3.3.1	An Affinity-Based ELISA Assay to Identify Potent Binders	45
3.3.2	Evaluation of Cell Permeability and Cellular Activity by Monitoring Insulin Receptor Signaling	47
3.4	Conclusions	47
	References	48
4	Design and Application of Chemical Probes for Protein Serine/Threonine Phosphatase Activation	51
	<i>Yansong Wang and Maja Köhn</i>	
4.1	Introduction	51
4.2	The Biological Problem	52
4.3	The Chemical Approach	54
4.4	Chemical Biological Research/Evaluation	57
4.4.1	Selectivity of PDPs toward PP1 over PP2A and PP2B	57
4.4.2	Studying the Functions of PP1 in Mitosis with PDPs	58
4.4.3	Studying the Functions of PP1 in Ca ²⁺ Signaling with PDPs	59
4.5	Conclusion	60
	References	60
5	Autophagy: Assays and Small-Molecule Modulators	63
	<i>Gemma Triola</i>	
5.1	Introduction	63
5.2	The Biological Problem	65
5.2.1	Assays	66
5.2.2	Small-Molecule Modulators of Autophagy	67
5.3	The Chemical Approach	68
5.3.1	Assays	68

5.4	Chemical Biological Evaluation	71
5.5	Conclusion	80
	References	80
6	Elucidation of Protein Function by Chemical Modification	83
	<i>Yaowen Wu and Lei Zhao</i>	
6.1	Introduction	83
6.2	The Biological Problem	84
6.2.1	Small GTPases	84
6.2.2	Autophagy	85
6.3	The Chemical Approach	88
6.3.1	Expressed Protein Ligation and Click Ligation	88
6.3.2	Site-Specific Modification of Proteins	90
6.3.3	Semisynthesis of Lipidated LC3 Protein	94
6.4	Biological Research/Evaluation	97
6.4.1	Thermodynamic Basis of Rab Membrane Targeting	97
6.4.2	Monitoring Protein Unfolding and Refolding Using a Dual-Labeled Protein	99
6.4.3	Semisynthetic Lipidated LC3 Protein Mediates Membrane Fusion	101
6.5	Conclusion	103
	References	103
7	Inhibition of Oncogenic K-Ras Signaling by Targeting K-Ras–PDEδ Interaction	105
	<i>Gemma Triola</i>	
7.1	Introduction	105
7.2	The Biological Problem	105
7.3	The Chemical Approach	108
7.3.1	Chemical Synthesis of Proteins	108
7.3.2	Synthesis of Lipidated Ras Peptides	109
7.3.3	Synthesis of K-Ras4B Protein	110
7.4	Chemical Biological Evaluation	113
7.5	Conclusions	120
	References	121
8	Development of Acyl Protein Thioesterase 1 (APT1) Inhibitor Palmostatin B That Revert Unregulated H/N-Ras Signaling	123
	<i>Frank J. Dekker, Nachiket Vartak, and Christian Hedberg</i>	
8.1	Introduction	123
8.2	The Biological Problem – The Role of APT1 in Ras Signaling	123
8.3	The Chemical Approach	125
8.3.1	The Challenge to Make Small-Molecule Modulators of Protein Function	125
8.3.2	Bioinformatics – Target Clustering	126

8.3.3	Compound Collection Synthesis	126
8.3.4	<i>In vitro</i> Enzyme Inhibition Studies	129
8.3.5	Mechanistic Investigation on APT1 Inhibition	129
8.4	Chemical Biological Research/Evaluation	130
8.4.1	<i>In vivo</i> Enzyme Inhibition Studies	130
8.4.2	Palmitoestrogens Inhibit Depalmitoylation of Ras GTPases	132
8.4.3	Palmitoestrogens Disturb the Localization of Ras GTPases	134
8.4.4	Palmitoestrogens Inhibit Downstream Signaling of Ras GTPases	135
8.5	Conclusions	136
	References	138
9	Functional Analysis of Host–Pathogen Posttranslational Modification Crosstalk of Rab Proteins	141
	<i>Christian Hedberg, Roger S. Goody, and Aymelt Itzen</i>	
9.1	Introduction	141
9.2	The Biological Problem	141
9.2.1	Posttranslational Modifications	141
9.2.2	Adenylation of Small GTPases	142
9.3	The Chemical Approach	143
9.3.1	Preparative Adenylation of Rab1	144
9.3.2	Identification of the Site of Adenylation	145
9.3.3	Synthesis of Site-Specifically Adenylated Peptides	146
9.3.4	Generation and Application of α -AMP-Tyr/Ser/Thr-Antibodies	146
9.3.5	Detection of Adenylation by MS Techniques	150
9.4	Chemical Biological Research/Evaluation	150
9.4.1	Functional Consequences of Adenylation	151
9.4.2	Detection of Adenylated Proteins in Mammalian Cell Lysates	152
9.5	Conclusions	152
	References	153
10	Chemical Biology Approach to Suppression of Statin-Induced Muscle Toxicity	155
	<i>Bridget K. Wagner</i>	
10.1	Introduction	155
10.2	The Biological Problem	155
10.3	The Chemical Approach	157
10.3.1	Generation of a Compendium of Mitochondrial Activity	157
10.4	Chemical Biology Research/Evaluation	158
10.4.1	Chemical Epistasis Analysis	158
10.4.2	High-Throughput Screening	160
10.5	Conclusion	161
	References	162

11	A Target Identification System Based on MorphoBase, ChemProteoBase, and Photo-Cross-Linking Beads 163
	<i>Hiroyuki Osada, Makoto Muroi, Yasumitsu Kondoh, and Yushi Futamura</i>
11.1	Introduction 163
11.2	The Biological Problem 163
11.3	Chemical Approaches 165
11.3.1	MorphoBase 165
11.3.2	ChemProteoBase 166
11.3.3	Photo-Cross-Linking Beads 169
11.4	Chemical Biological Research/Evaluation 171
11.4.1	NPD6689/NPD8617/NPD8969 171
11.4.2	BNS-22 172
11.4.3	Methyl-Gerferin 173
11.4.4	Xanthohumol 173
11.5	Conclusion 174
	References 174
12	Activity-Based Proteasome Profiling in Medicinal Chemistry and Chemical Biology 177
	<i>Gerjan de Bruin, Nan Li, Guillem Paniagua, Lianne Willems, Bo-Tao Xin, Martijn Verdoes, Paul Geurink, Wouter van der Linden, Mario van der Stelt, Gijs van der Marel, Herman Overkleeft, and Bogdan Florea</i>
12.1	Introduction 177
12.2	The Biological Problem 177
12.3	The Chemical Approach 179
12.3.1	Comparative and Competitive Activity-Based Proteasome Profiling 181
12.3.2	Two-Step Activity-Based Proteasome Profiling 183
12.4	Biological Research/Evaluation 186
12.4.1	Identification of Proteasome Active Sites 187
12.5	Conclusions 188
	References 189
13	Rational Design of Activity-Based Retaining β-Exoglucosidase Probes 191
	<i>Kah-Yee Li, Wouter Kallemeyn, Jianbing Jiang, Marthe Walvoort, Lianne Willems, Thomas Beenakker, Hans van den Elst, Gijs van der Marel, Jeroen Codée, Hans Aerts, Bogdan Florea, Rolf Boot, Martin Witte, and Herman Overkleeft</i>
13.1	Introduction 191
13.2	The Biological Problem 191
13.3	The Chemical Approach 192
13.3.1	Development of a Human Acid Glucosylceramidase Activity-Based Probe 195

13.3.2	Cyclophellitol Aziridine Is a Broad-Spectrum Activity-Based Retaining β -Exoglucosidase Probe 198
13.4	Biological Research/Evaluation 201
13.4.1	<i>In situ</i> Monitoring of Active-Site-Directed GBA Chemical/Pharmacological Chaperones 201
13.4.2	Mapping of Human Retaining β -Glucosidase Active Site Residues 203
13.5	Conclusions 203
	References 205
14	Modulation of ClpP Protease Activity: from Antibiotics to Antivirulence 207
	<i>Malte Gersch and Stephan A. Sieber</i>
14.1	Introduction 207
14.2	The Biological Problem 207
14.3	The Chemical Approach 209
14.4	The Discovery of a Novel Antibiotic Mechanism 210
14.4.1	Target Identification 210
14.4.2	Target Validation 214
14.4.3	Mechanism of Action 214
14.5	The Antivirulence Approach 215
14.6	Conclusions 219
	References 219
15	Affinity-Based Isolation of Molecular Targets of Clinically Used Drugs 221
	<i>Shin-ichi Sato and Motonari Uesugi</i>
15.1	Introduction – The Biological/Medicinal Problem 221
15.2	The Chemical Approach 221
15.3	Chemical Biological Research 225
15.3.1	Lessons from Isolation of FK506-Binding Protein (FKBP) Using FK506 225
15.3.2	Lessons from Isolation of Cereblon (CRBN) Using Thalidomide 226
15.3.3	Lessons from Isolation of Glyoxalase 1 (GLO1) Using Indomethacin 227
15.4	Conclusion 228
	References 228
16	Identification of the Targets of Natural-Product-Inspired Mitotic Inhibitors 231
	<i>Kamal Kumar and Slava Ziegler</i>
16.1	Introduction 231
16.2	The Biological Problem 231
16.2.1	Mitosis and Modulation of Mitosis by Small Molecules 231
16.2.2	Phenotypic Screening 234

16.2.3	Target Identification and Confirmation	236
16.3	The Chemical Approach	236
16.3.1	Design and Synthesis of Natural-Product-Inspired Compound Collections	236
16.4	Chemical Biological Evaluation	239
16.4.1	Phenotypic Screen for Mitotic Inhibitors	239
16.4.2	Identification of the Target Protein(s) of Centrocountin 1	241
16.4.3	Confirmation of the Target Candidates	243
16.5	Conclusion	246
	References	247
17	Finding a Needle in a Haystack. Identification of Tankyrase, a Novel Therapeutic Target of the Wnt Pathway Using Chemical Genetics	249
	<i>Atwood K. Cheung and Feng Cong</i>	
17.1	Introduction	249
17.2	The Biological Problem	250
17.2.1	Modulating the Wnt Signaling Pathway for Cancer Therapeutics	250
17.3	The Chemical Approach	251
17.3.1	Screening Approach	251
17.3.2	Chemical Proteomics Target Identification	251
17.3.3	Target Validation	254
17.4	Chemical Biological Research/Evaluation	254
17.4.1	Identification of XAV939 as a Wnt Pathway Inhibitor	254
17.4.2	XAV939 Regulates Axin Protein Levels by Inhibiting Tankyrases	256
17.4.3	Validation of Tankyrase as the Target for XAV939	257
17.4.4	XAV939 Inhibits TNKS-Mediated Ubiquitination and PARsylation of Axin	258
17.4.5	TNKS Inhibitor Blocks the Growth of Colon Cancer Cells	258
17.4.6	Crystal Structure of XAV939 and TNKS1	259
17.5	Conclusion	260
	References	261
18	The Identification of the Molecular Receptor of the Plant Hormone Absciscic Acid	265
	<i>Julian Oeljeklaus and Markus Kaiser</i>	
18.1	Introduction	265
18.2	The Biological Problem	267
18.3	The Chemical Genetics Approach	268
18.3.1	Identification of a Synthetic ABA-Agonist Using a Chemical Genetics Screen	268
18.3.2	Target Gene Identification of Pyrabactin	270
18.4	The Chemical Biology Approach	273

18.4.1	Elucidation of the Functional ABA-Receptor Complex	273
18.4.2	Validation and Further Structural Studies on the ABA–Receptor Mechanism	279
18.5	Conclusion	282
	References	283
19	Chemical Biology in Plants: Finding New Connections between Pathways Using the Small Molecule Sortin1	285
	<i>Chunhua Zhang, Glenn R. Hicks, and Natasha V. Raikhel</i>	
19.1	Introduction	285
19.2	The Biological Problem	285
19.3	The Chemical Approach	286
19.3.1	Chemical Library Screening	286
19.3.2	Identification of Pathway(s) that are Targeted by Sortin1	287
19.3.3	Sortin1-Hypersensitive Mutants Link Vacuolar Trafficking to Flavonoids Metabolism	289
19.3.4	Sortin1 Resembles the Effects of Buthionine Sulfoximine (BSO)	290
19.3.5	Substructures Required for Sortin1 Bioactivity	290
19.4	Biological Research/Evaluation	292
19.4.1	Chemicals That Disrupt Yeast Vacuolar Trafficking also Target Plant Vacuolar Trafficking Pathway	292
19.4.2	Sortin1 Disrupts Vacuolar Trafficking of both Proteins and Flavonoids	292
19.4.3	Mechanism of Sortin1 Action	293
19.5	Conclusion	293
	Acknowledgment	293
	References	294
20	Selective Targeting of Protein Interactions Mediated by BET Bromodomains	295
	<i>Susanne Müller, Hannah Lingard, and Stefan Knapp</i>	
20.1	Introduction	295
20.2	The Biological Problem	295
20.2.1	Druggability of the BET Acetyl-Lysine-Binding Pocket	297
20.3	The Chemical Approach	298
20.3.1	Development of High-Throughput Assays	298
20.3.2	Secondary Screening Assays	300
20.3.3	Cellular Testing	300
20.3.4	Discovery of Acetyl-Lysine Competitive Inhibitors	300
20.3.4.1	Acetyl-Lysine Mimetic Fragments Crystallized with Bromodomains	300
20.3.4.2	Discovery of Benzo- and Thienodiazepines	302
20.3.4.3	Other BET Inhibitors	302
20.4	Chemical/Biological Investigations	305

20.5	Conclusion	305
	References	306
21	The Impact of Distant Polypharmacology in the Chemical Biology of PARPs	309
	<i>Albert A. Antolín and Jordi Mestres</i>	
21.1	Introduction	309
21.2	The Biological Problem	309
21.2.1	Studying the Function of Proteins Using Chemical Probes with Unknown Polypharmacology	309
21.2.2	Development of Poly(ADP-Ribose)Polymerase-1 (PARP-1) Chemical Probes and Follow-on Drugs	311
21.2.3	Unexpected Differential Effects between PARP Inhibitors	312
21.3	The Chemical Approach	312
21.3.1	Molecular Informatics	312
21.3.2	<i>In silico</i> Target Profiling	313
21.4	Chemical Biological Research/Evaluation	315
21.4.1	<i>In silico</i> Identification and <i>In Vitro</i> Confirmation of Novel Targets for PJ34	315
21.4.2	Implications for the Use of PJ34 and Follow-on Drugs	316
21.5	Conclusions	319
	References	320
22	Splicing Inhibitors: From Small Molecule to RNA Metabolism	323
	<i>Tilman Schneider-Poetsch and Minoru Yoshida</i>	
22.1	Introduction	323
22.2	The Biological Problem	323
22.2.1	Splicing	323
22.2.2	Alternative Splicing	325
22.2.3	mRNA Processing	326
22.3	The Chemical Approach	326
22.3.1	The First Splicing Inhibitors	326
22.3.2	Inhibition	328
22.4	Chemical Biological Research/Evaluation	331
22.4.1	Cellular Effect	331
22.4.2	Clinical Utility	331
22.5	Conclusion	333
	References	333
23	Photochemical Control of Gene Function in Zebrafish Embryos with Light-Activated Morpholinos	337
	<i>Qingyang Liu and Alexander Deiters</i>	
23.1	Introduction	337
23.2	The Biological Problem	337
23.3	The Chemical Approach	340

23.3.1	Hairpin-Caged MO	340
23.3.2	Sense-Caged MO	342
23.3.3	Nucleobase-Caged MO	344
23.3.4	Cyclic-Caged MO	345
23.4	Chemical Biological Research/Evaluation	347
23.5	Conclusion	349
	Acknowledgment	349
	References	349
24	Life Cell Imaging of mRNA Using PNA FIT Probes	351
	<i>Andrea Knoll, Susann Kummer, Felix Hövelmann, Andreas Herrmann, and Oliver Seitz</i>	
24.1	Introduction	351
24.2	The Biological Problem	351
24.2.1	Selection of Biological Targets	352
24.3	The Chemical Approach	352
24.3.1	Design and Synthesis of PNA FIT Probes	352
24.4	Chemical Biological Research/Validation	355
24.4.1	Probe Validation by Fluorescence Measurement	355
24.4.2	Quantitation of Viral mRNA by qPCR	356
24.4.3	Imaging of Viral mRNA in Living Cells	358
24.5	Conclusion	361
	References	362
25	Targeting the Transcriptional Hub β-Catenin Using Stapled Peptides	365
	<i>Tom N. Grossmann and Gregory L. Verdine</i>	
25.1	Introduction	365
25.2	The Biological Problem	365
25.2.1	Canonical Wnt Signaling	366
25.2.2	Oncogenic Activation of Wnt Signaling	366
25.3	The Chemical Approach: Hydrocarbon Peptide Stapling	368
25.4	The Biological Approach: Phage-Display-Based Optimization	371
25.5	Biochemical and Biological Evaluation	375
25.6	Conclusions	376
	References	377
26	Diversity-Oriented Synthesis: Developing New Chemical Tools to Probe and Modulate Biological Systems	379
	<i>Warren R. J. D. Galloway, David Wilcke, Feilin Nie, Kathy Hadje-Georgiou, Luca Laraia, and David R. Spring</i>	
26.1	Introduction	379
26.2	The Biological Problem	379
26.2.1	How to Discover New Chemical Modulators of Biological Function?	379

26.2.2	Sources of Small Molecules for Screening	380
26.2.2.1	Natural Products	380
26.2.2.2	Chemical Synthesis and the Need for Structural Diversity	380
26.3	The Chemical Approach	382
26.3.1	Diversity-Oriented Synthesis	382
26.3.1.1	DOS and Scaffold Diversity	382
26.4	Chemical Biology Research	384
26.4.1	DOS as a Tool for Identifying New Modulators of Mitosis	384
26.4.1.1	DOS Library Synthesis	384
26.4.1.2	Biological Studies: Phenotypic Screening for Antimitotic Effects	384
26.4.1.3	Biological Studies: Target Identification	385
26.5	Conclusion	388
	References	388
27	Scaffold Diversity Synthesis with Branching Cascades Strategy	391
	<i>Kamal Kumar</i>	
27.1	Introduction	391
27.2	The Biological/Pharmacological Problem: Discovering Small Bioactive Molecules	391
27.3	The Chemical Approach: Scaffold Diversity	395
27.3.1	Beyond the Biased Exploration of Chemical Space	395
27.3.2	Scaffold Diversity Synthesis	397
27.4	Chemical/Biological Evaluation – Branching Cascades Strategy in Scaffold Diversity Synthesis	399
27.5	Conclusions	409
	References	410
	Index	415

List of Contributors

Hans Aerts

University of Amsterdam
Department of Medical
Biochemistry
Academic Medical Centre
Amsterdam
The Netherlands

Albert A. Antolín

Universitat Pompeu Fabra
Systems Pharmacology
Research Program on Biomedical
Informatics
IMIM Hospital del Mar Medical
Research Institute
Doctor Aiguader 88
08003 Barcelona
Spain

Thomas Beenakker

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Rolf Boot

University of Amsterdam
Department of Medical
Biochemistry
Academic Medical Centre
Amsterdam
The Netherlands

Gerjan de Bruin

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Atwood K. Cheung

Novartis Institutes for
BioMedical Research, Inc.
Global Discovery Chemistry
250 Massachusetts Avenue
Cambridge, MA 02139
USA

Jeroen Codée

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Feng Cong

Novartis Institutes for
BioMedical Research, Inc.
Developmental and Molecular
Pathways
250 Massachusetts Avenue
Cambridge, MA 02139
USA

Alexander Deiters

University of Pittsburgh
Department of Chemistry
Chevron Science Center
219 Parkman Avenue
Pittsburgh, PA 15260
USA

Frank J. Dekker

Groningen University
Department of Pharmaceutical
Gene Modulation
Antonius Deusinglaan 1
9713 av Groningen
Netherlands

Hans van den Elst

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Bogdan Florea

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Yushi Futamura

RIKEN
Antibiotics Laboratory
2-1 Hirosawa
Wako
Saitama 351-0198
Japan

Warren R. J. D. Galloway

University of Cambridge
Department of Chemistry
Lensfield Road
Cambridge CB2 1 EW
UK

Malte Gersch

Technische Universität München
Department of Chemistry
Lichtenbergstraße 4
85748 Garching
Germany

Paul Geurink

The Netherlands Cancer Institute
(NKI)
Division of Cell Biology
Plesmanlaan 121
CX 1066 Amsterdam
The Netherlands

Roger S. Goody

Max Planck Institute of
Molecular Physiology
Department of Physical
Biochemistry
Otto-Hahn-Straße 11
44227 Dortmund
Germany

Tom N. Grossmann

Chemical Genomics Centre of
the Max Planck Society
Otto-Hahn-Straße 15
44227 Dortmund
Germany

Kathy Hadje-Georgiou

University of Cambridge
Department of Chemistry
Lensfield Road
Cambridge CB2 1 EW
UK

Christian Hedberg

Max Planck Institute of
Molecular Physiology
Department of Chemical Biology
Otto-Hahn-Straße 11
44227 Dortmund
Germany

Andreas Herrmann

Humboldt University Berlin
 Department of Biology
 Invalidenstrasse 42
 10115 Berlin
 Germany

Glenn R. Hicks

University of California
 Riverside
 Center for Plant Cell Biology and
 Department of Botany and Plant
 Sciences
 900 University Avenue
 Riverside, CA 92521
 USA

Birgit Hoeger

European Molecular Biology
 Laboratory (EMBL)
 Genome Biology Unit
 Meyerhofstrasse 1
 69117 Heidelberg
 Germany

Felix Hövelmann

Humboldt University Berlin
 Department of Chemistry
 Brook-Taylor-Straße 2
 12489 Berlin
 Germany

Barbara Imperiali

Massachusetts Institute of
 Technology
 Departments of Biology and
 Chemistry
 68-380, 77 Massachusetts
 Avenue
 Cambridge, MA 02139
 USA

Aymelt Itzen

Technische Universität München
 Center of Integrated Protein
 Science Munich
 Department Chemie
 AG Proteinchemie
 Lichtenbergstraße 4
 85748 Garching
 Germany

Jianbing Jiang

Leiden University
 Leiden Institute of Chemistry
 Einsteinweg 55
 CC 2333 Leiden
 The Netherlands

Markus Kaiser

Universität Duisburg-Essen
 Zentrum für Medizinische
 Biotechnologie
 Fakultät für Biologie
 Universitätsstrasse 2
 45117 Essen
 Germany

Wouter Kallemeijn

University of Amsterdam
 Department of Medical
 Biochemistry
 Academic Medical Centre
 Amsterdam
 The Netherlands

Stefan Knapp

University of Oxford
 Nuffield Department of Clinical
 Medicine
 Structural Genomics
 Consortium and Target
 Discovery Institute
 Roosevelt Drive
 Oxford OX3 7FZ
 UK

Andrea Knoll

Humboldt University Berlin
Department of Chemistry
Brook-Taylor-Straße 2
12489 Berlin
Germany

Maja Köhn

European Molecular Biology
Laboratory (EMBL)
Genome Biology Unit
Meyerhofstrasse 1
69117 Heidelberg
Germany

Yasumitsu Kondoh

RIKEN Center for Sustainable
Resource Science (CSRS)
Chemical Biology Research
Group
2-1 Hirosawa
Wako
Saitama 351-0198
Japan

and

RIKEN
Antibiotics Laboratory
2-1 Hirosawa
Wako
Saitama 351-0198
Japan

Kamal Kumar

Max Planck Institute of
Molecular Physiology
Department of Chemical Biology
Otto-Hahn-Straße 11
44227 Dortmund
Germany

Susann Kummer

Universitätsklinikum Heidelberg
Department of Infectiology
Im Neuenheimer Feld 324
69120 Heidelberg
Germany

Luca Laraia

University of Cambridge
Department of Chemistry
Lensfield Road
Cambridge CB2 1 EW
UK

Kah-Yee Li

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Nan Li

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Hannah Lingard

University of Oxford
Nuffield Department of Clinical
Medicine
Structural Genomics
Consortium and Target
Discovery Institute
Roosevelt Drive
Oxford OX3 7FZ
UK

Wouter van der Linden

Stanford University
 Department of Pathology
 School of Medicine
 300 Pasteur Drive
 Stanford, CA 94305-5324
 USA

Qingyang Liu

North Carolina State University
 Department of Chemistry
 2620 Yarbrough Drive
 Raleigh, NC 27695-8204
 USA

Gijs van der Marel

Leiden University
 Leiden Institute of Chemistry
 Einsteinweg 55
 CC 2333 Leiden
 The Netherlands

Jordi Mestres

Universitat Pompeu Fabra
 Systems Pharmacology
 Research Program on Biomedical
 Informatics
 IMIM Hospital del Mar Medical
 Research Institute
 Doctor Aiguader 88
 08003 Barcelona
 Spain

Susanne Müller

University of Oxford
 Nuffield Department of Clinical
 Medicine
 Structural Genomics
 Consortium and Target
 Discovery Institute
 Roosevelt Drive
 Oxford OX3 7FZ
 UK

Makoto Muroi

RIKEN Center for Sustainable
 Resource Science (CSRS)
 Chemical Biology Research
 Group
 2-1 Hirosawa
 Wako
 Saitama 351-0198
 Japan

and

RIKEN
 Antibiotics Laboratory
 Hirosawa 2-1
 Wako
 Saitama 351-0198
 Japan

Feilin Nie

University of Cambridge
 Department of Chemistry
 Lensfield Road
 Cambridge CB2 1 EW
 UK

Julian Oeljeklaus

Universität Duisburg-Essen
 Zentrum für Medizinische
 Biotechnologie
 Fakultät für Biologie
 Universitätsstrasse 2
 45117 Essen
 Germany

Hiroyuki Osada

RIKEN Center for Sustainable
Resource Science (CSRS)
Chemical Biology Research
Group
Hirosawa 2-1
Wako
Saitama 351-0198
Japan

and

RIKEN
Antibiotics Laboratory
Hirosawa 2-1
Wako
Saitama 351-0198
Japan

Herman Overkleeft

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Guillem Paniagua

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Laura B. Peterson

Massachusetts Institute of
Technology
Departments of Biology and
Chemistry
68-380, 77 Massachusetts
Avenue
Cambridge, MA 02139
USA

Natasha V. Raikhel

University of California
Riverside
Center for Plant Cell Biology and
Department of Botany and Plant
Sciences
900 University Avenue
Riverside, CA 92521
USA

Daniel Rauh

Technische Universität
Dortmund
Fakultät für Chemie und
Chemische Biologie
Otto-Hahn-Straße 6
44227 Dortmund
Germany

Shin-ichi Sato

Kyoto University
Institute for Integrated
Cell-Material Sciences
(WPI-iCeMS)
Kyoto 611-0011
Japan

Tilmann Schneider-Poetsch

RIKEN
Chemical Genetics Laboratory
Hirosawa 2-1
Wako
Saitama 351-0198
Japan

Oliver Seitz

Humboldt University Berlin
Department of Chemistry
Brook-Taylor-Straße 2
12489 Berlin
Germany

Stephan A. Sieber

Technische Universität München
 Department of Chemistry
 Lichtenbergstraße 4
 85748 Garching
 Germany

Jeffrey R. Simard

Amgen, Inc.
 360 Binney St.
 Cambridge, MA 02142
 USA

David R. Spring

University of Cambridge
 Department of Chemistry
 Lensfield Road
 Cambridge CB2 1 EW
 UK

Mario van der Stelt

Leiden University
 Leiden Institute of Chemistry
 Einsteinweg 55
 CC 2333 Leiden
 The Netherlands

Gemma Triola

Spanish National Research
 Council (CSIC)
 Institute of Advanced Chemistry
 of Catalonia (IQAC)
 Department of Biomedical
 Chemistry
 Jordi Girona 18-26
 08034 Barcelona
 Spain

Nachiket Vartak

Max Planck Institute of
 Molecular Physiology
 Department of Chemical Biology
 Otto-Hahn-Straße 11
 44227 Dortmund
 Germany

Motonari Uesugi

Kyoto University
 Institute for Integrated
 Cell-Material Sciences
 (WPI-iCeMS)
 Kyoto 611-0011
 Japan

and

Kyoto University
 Institute for Chemical Research
 Uji, Kyoto 611-0011
 Japan

Gregory L. Verdone

Harvard University
 Departments of Stem Cell &
 Regenerative Biology
 Chemistry & Chemical Biology,
 and Molecular & Cellular Biology
 Cambridge, MA 02138
 USA

Martijn Verdoes

Radboud University
 Department of Tumor
 Immunology
 Nijmegen Medical Centre
 Geert Grooteplein 26/28
 GA 6525 Nijmegen
 The Netherlands

Bridget K. Wagner

Broad Institute
 Center for the Science of
 Therapeutics
 7 Cambridge Center 3027
 Cambridge, MA 02142
 USA

Marthe Walvoort

Massachusetts Institute of
Technology
Department of Biology
77 Massachusetts Avenue
Cambridge, MA 02139
USA

Yansong Wang

European Molecular Biology
Laboratory (EMBL)
Genome Biology Unit
Meyerhofstrasse 1
69117 Heidelberg
Germany

David Wilcke

University of Cambridge
Department of Chemistry
Lensfield Road
Cambridge CB2 1 EW
UK

Lianne Willems

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Martin Witte

University of Groningen
Stratingh Institute of Chemistry
Bio-Organic Chemistry
Nijenborgh 7
AG 9747 Groningen
The Netherlands

Yaowen Wu

Chemical Genomics Centre of
the Max Planck Society
Otto-Hahn-Straße 15
44227 Dortmund
Germany

Bo-Tao Xin

Leiden University
Leiden Institute of Chemistry
Einsteinweg 55
CC 2333 Leiden
The Netherlands

Minoru Yoshida

RIKEN
Chemical Genetics Laboratory
Hirosawa 2-1
Wako
Saitama 351-0198
Japan

Chunhua Zhang

University of California
Riverside
Center for Plant Cell Biology and
Department of Botany and Plant
Sciences
900 University Avenue
Riverside, CA 92521
USA

Lei Zhao

Chemical Genomics Centre of
the Max Planck Society
Otto-Hahn-Straße 15
44227 Dortmund
Germany

Slava Ziegler

Max Planck Institute of
Molecular Physiology
Department of Chemical Biology
Otto-Hahn-Straße 11
44227 Dortmund
Germany

Introduction and Preface

“Chemical Biology may be defined as the application of chemical methods and techniques to the study of biological phenomena, that is, chemical biology research seeks new insights into biology by means of an approach originating from an enabling chemistry tool box.

The chemical biological approach often starts with the analysis of a biological phenomenon in order to deduce structural information, for instance, about biomacromolecules or small molecules that interact with them. On the basis of this information, unsolved chemical problems are identified and the ability of the synthetic chemist to design and prepare tailor-made reagents and tool compounds, that is, proteins equipped with reporter groups and tags or potent and selective small molecule modulators of protein function, is employed as key enabling technology for subsequent research. Very frequently, the biochemical and biophysical properties of these reagents need to be determined for the proper design and execution of biological experiments, giving new insights into the originally motivating biological phenomenon. The results gleaned thereby may then lead to a better understanding of biology and fuel additional cycles of chemical biology research following the same logic Figure 1 illustrates the cycle of chemical biology research.

By its very nature, chemical biology is multidisciplinary and needs to bridge the approaches and cultures of the neighboring sciences, chemistry, biology, and physics, within a given research group or in collaborations between groups of complementary expertise (as is very frequently the case).

Thus, education in chemical biology requires training in these disciplines on a more or less advanced level. A chemical biology textbook, planned and organized similar to that of established textbooks of the individual disciplines mentioned, would have to face the challenge of not growing too large to be readable but at the same time be sufficiently comprehensive to cover the individual disciplines in the required scientific depth.

An alternative, and probably more efficient and appropriate, approach to chemical biology education may be to resort to the well-established, proven textbooks of chemistry, biology, and physics for in-depth courses and to complement them by lecture series, seminars, and practical courses that demonstrate the combination

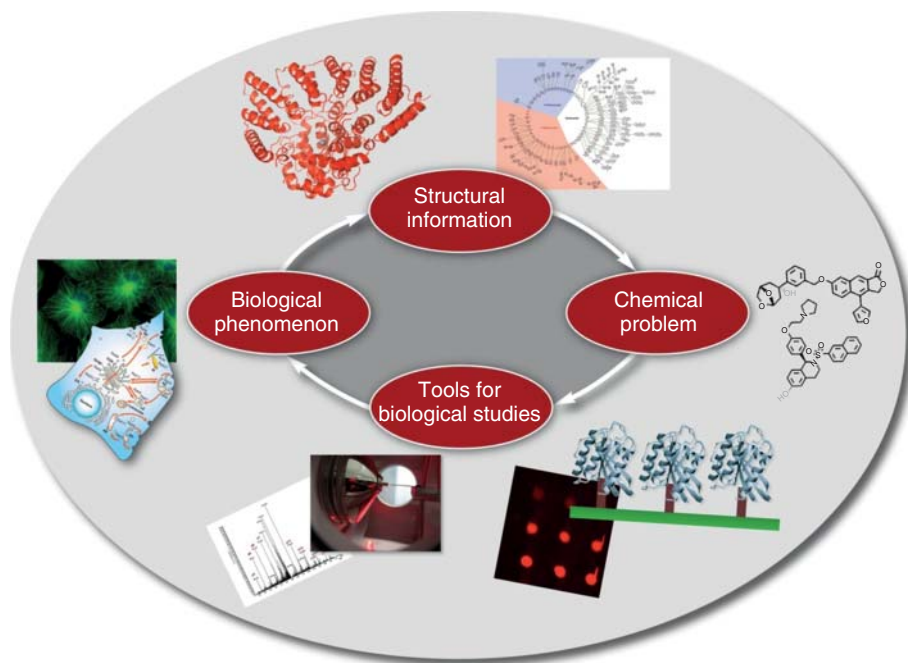


Figure 1 Illustration of the cycle of chemical biology research.

of and the interplay between these sciences and the corresponding experimental techniques in chemical biology.” [1]

With this goal in mind, we planned and prepared our previous book *Chemical Biology: Learning through Case Studies* [1] in 2009. By concentrating on a series of individual successful cases of chemical biology research, it highlighted the combination of the different sciences involved in gaining new insights into biological phenomena with approaches originating from chemistry and integrating biophysics, biochemistry, and other disciplines whenever required.

The same concept has been chosen for this new book, entitled *Concepts and Case Studies in Chemical Biology*. It covers 27 new case studies in Chemical Biology, reflecting the rapid growth in this interdisciplinary topic since 2009.

Again, in each chapter, initially a biological problem is presented. To address this problem, a chemical approach is described and both together lead to chemical biology research. Following this line, for several different examples the reader is introduced into thinking and research in Chemical Biology, arriving at important scientific results and techniques and methods used in this field at the same time.

In contrary to the previous *Learning through Case Studies* book, we asked the researchers themselves to write a case study that has the origin in their own lab, rather than writing the chapters based on literature reports only.

We hope the book will be a valuable source of information for advanced students, postdoctoral researchers, and researchers working on the borderline between chemistry, biology, and biochemistry.

We are grateful to all authors of the individual chapters for their excellent work and trust in the concept. We are also grateful to Bernadette Gmeiner and Dr Anne Brennfürer from Wiley-VCH for their editorial help and encouragement.

Dortmund, February 2014

Petra Janning
Herbert Waldmann

References

1. Waldmann, H. and Janning, P. (eds)
(2009) *Chemical Biology – Learning through Case Studies*, Wiley-VCH Verlag GmbH, Weinheim.

