

Handbook of Therapeutic Antibodies

Volume 1: Defining the Right Antibody Composition
Second Edition

Edited by Stefan Dübel and Janice M. Reichert

WILEY Blackwell

WILEY Blackwell

WILEY Blackwell

WILEY Blackwell

of
es

odies
ition
thert

of
es

odies
ition
thert

of
es

odies
ostics
ition
thert

Edited by
Stefan Dübel and
Janice M. Reichert

Handbook of Therapeutic Antibodies

Related Titles

Chamow, S.M., Ryll, T., Lowman, H.B.,
Farson, D. (eds.)

Therapeutic Fc-Fusion Proteins

2014
Print ISBN: 978-3-527-33317-2, also available in
digital formats

Knäblein, J. (ed.)

Modern Biopharmaceuticals

Recent Success Stories

2013
Print ISBN: 978-3-527-32283-1, also available in
digital formats

Pathak, Y., Benita, S. (eds.)

Antibody-Mediated Drug Delivery Systems

Concepts, Technology, and Applications

2012
Print ISBN: 978-0-470-61281-1, also available in
digital formats

Kratz, F., Senter, P., Steinhagen, H. (eds.)

Drug Delivery in Oncology

From Basic Research to Cancer Therapy

2011
Print ISBN: 978-3-527-32823-9, also available in
digital formats

Tovey, M.G. (ed.)

Detection and Quantification of Antibodies to Biopharmaceuticals

Practical and Applied Considerations

2011
Print ISBN: 978-0-470-56666-4, also available in
digital formats

Edited by Stefan Dübel and Janice M. Reichert

Handbook of Therapeutic Antibodies

Volume I: Defining the Right Antibody Composition

Second Edition

WILEY Blackwell

Edited by Stefan Dübel and Janice M. Reichert

Handbook of Therapeutic Antibodies

Volume II: Clinical Development of Antibodies

Second Edition

WILEY Blackwell

Edited by Stefan Dübel and Janice M. Reichert

Handbook of Therapeutic Antibodies

Volume III: Approved Therapeutic Antibodies

Second Edition

WILEY Blackwell

Edited by Stefan Dübel and Janice M. Reichert

Handbook of Therapeutic Antibodies

Volume IV: Approved Therapeutic Antibodies and in vivo
Diagnostics

Second Edition

WILEY Blackwell

Editors

Prof. Dr. Stefan Dübel

Technische Universität Braunschweig
Institute of Biochemistry
Biotechnology and Bioinformatics
Spielmannstr. 7
38106 Braunschweig
Germany

Dr. Janice M. Reichert

Reichert Biotechnology Consulting LLC
Prospect Street 247
Framingham, MA
USA

Cover

Antibodies have become standard therapy in many therapeutic areas including cancer, inflammation, osteoporosis, autoimmune, cardiovascular, ophthalmic and infectious diseases. Early successes in the treatment of leukemia and lymphoma by rituximab and alemtuzumab spawned the development of ofatumumab and obinutuzumab, antibodies that kill tumor cells more potently via diverse mechanisms. The cover is an artist's impression of lymphocytic leukemia cells under therapeutic antibody attack. The image was developed by Joost M. Bakker, www.scicomvisuals.com.

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 can 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 authors shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

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>](http://dnb.d-nb.de).

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

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical, and Medical business with Blackwell Publishing.

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: 978-3-527-32937-3

ePDF ISBN: 978-3-527-68245-4

ePub ISBN: 978-3-527-68244-7

Mobi ISBN: 978-3-527-68243-0

oBook ISBN: 978-3-527-68242-3

Cover Design Formgeber, Mannheim, Germany

Typesetting Laserwords Private Limited, Chennai, India

Printing and Binding Markono Print Media, Pte Ltd., Singapore

Printed on acid-free paper

Contents

Volume I: Defining the Right Antibody Composition

Quick Reference List of Antibodies by International Nonproprietary Name *XXIII*

Quick Reference List of Antibodies by Brand Name *XXV*

A Greeting by the Editors *XXVII*

Foreword to the First Edition *XXIX*

Foreword to the Second Edition *XXXI*

List of Contributors *XXXIII*

Abbreviations *LI*

Appendix: Marketed Monoclonal Antibodies Compendium *LXXXIII*

1 Therapeutic Antibodies – from Past to Future 1

Stefan Dübel and Janice M. Reichert

1.1 An Exciting Start – and a Long Trek 1

1.2 The Gold Rush 6

1.3 Success and Setbacks 7

1.4 The Gleaming Horizon 10

References 12

Further Reading 12

Part I: Selecting and Shaping the Antibody Molecule 15

2 Selection Strategies for Monoclonal Antibodies 17

Gerhard Moldenhauer

2.1 Introduction 17

2.2 Historical Remarks 18

2.3 Antibody Structure and Function 19

2.3.1 Membrane-Bound and Secreted Forms of Antibodies 19

2.3.2 Monoclonal Antibodies 21

2.4 Production of Monoclonal Antibodies 21

2.4.1 Immunization 21

2.4.2	Myeloma Cell Lines	22
2.4.3	Cell Fusion	23
2.4.4	Drug Selection of Hybridomas	25
2.4.5	Screening Hybridoma Cultures for Specific Antibody	26
2.4.5.1	Enzyme-Linked Immunosorbent Assay (ELISA)	27
2.4.5.2	Flow Cytometry	27
2.4.5.3	Immunohistology and Immunocytology	28
2.4.5.4	Cytotoxicity Assays	29
2.4.5.5	Screening for Function	30
2.4.6	Cloning	30
2.4.7	Expansion and Freezing of Hybridoma Clones	30
2.5	Purification and Modification of Monoclonal Antibodies	31
2.5.1	Mass Culture and Purification of Monoclonal Antibody	31
2.5.2	Fragmentation of Monoclonal IgG Antibodies	32
2.5.3	Labeling of Monoclonal Antibodies	32
2.6	Monoclonal Antibodies for Tumor Therapy	33
2.6.1	Leukocyte Differentiation Antigens	33
2.6.2	Epithelial Differentiation Antigens	33
2.6.3	Mechanisms of Action of Monoclonal Antibodies	34
2.6.4	Human Monoclonal Antibodies	35
2.7	Outlook	36
	References	37
3	Antibody Phage Display	43
	<i>Michael Hust, André Frenzel, Florian Tomszak, Jonas Kügler, and Stefan Dübel</i>	
3.1	Introduction	43
3.2	Phage Display	45
3.3	Selection and Screening	46
3.4	Phage Display Vectors	48
3.5	Phage Display Libraries	57
3.6	Construction of Phage Display Libraries	58
	Acknowledgments	65
	References	65
4	Transgenic Animals Derived by DNA Microinjection	77
	<i>Marianne Brüggemann, Michael J. Osborn, Biao Ma, Suzanne Avis, Ignacio Anegón, and Roland Buelow</i>	
4.1	Introduction	77
4.2	Construction of Human Ig Transloci	78
4.2.1	IgH	78
4.2.2	Igκ	80
4.2.3	Igλ	80
4.3	BAC Integration	81

4.4	Designer Zinc Finger Endonucleases to Silence Endogenous Ig Loci	82
4.5	Expression Comparison of Fully Human and Chimeric IgH Loci	83
4.6	Outlook	85
	References	85
5	Humanization Strategies	89
	<i>José W. Saldanha</i>	
5.1	Introduction	89
5.2	History of Humanization	89
5.3	CDR-Grafting	90
5.4	The Design Cycle	92
5.4.1	Analysis of the Source (Donor) Sequence	92
5.4.1.1	Complementarity-Determining Regions (CDRs)	92
5.4.1.2	Canonical Residues	93
5.4.1.3	Interface Packing Residues	93
5.4.1.4	Rare Framework Residues	94
5.4.1.5	N- or O-Glycosylation Sites	95
5.4.2	Three-Dimensional Computer Modeling of the Antibody Structure	95
5.4.3	Choice of Human Framework Sequences	97
5.4.3.1	Fixed Frameworks or Best-Fit?	100
5.4.3.2	VL/VH Frameworks from the Same or Different Clone?	100
5.4.3.3	Human Subgroup Consensus or Expressed Framework?	101
5.4.3.4	Germline Frameworks	101
5.4.3.5	Database Search	101
5.4.4	Identifying Putative Backmutations	102
5.4.5	Stability	104
5.5	Other Approaches to Antibody Humanization	104
5.5.1	Resurfacing/Veneering	104
5.5.2	SDR-Transfer	105
5.5.3	Removal of T- and B-Cell Epitopes	106
5.5.4	Phage Libraries	106
	References	107
6	Antibody Affinity	115
	<i>André Frenzel, Lorin Roskos, Scott Klakamp, Meina Liang, Rosalin Arends, and Larry Green</i>	
6.1	Introduction	115
6.2	Affinity Maturation	115
6.2.1	Affinity Maturation <i>In Vivo</i>	115
6.2.2	Affinity Maturation <i>In Vitro</i>	117
6.3	Antibody Affinity: Antigen Binding and Potency	120
6.4	Binding and Potency <i>In Vitro</i>	121
6.5	Binding and Potency <i>In Vivo</i>	123

- 6.6 Selection of High-Affinity Antibodies from Hybridoma Cell Lines 126
- 6.7 Generation of Antibodies against Soluble Antigens 126
- 6.8 Generation of Antibodies against Cell Surface Antigens 127
- 6.9 Determination of Antibody Affinity 128
- 6.10 Surface Plasmon Resonance 128
- 6.11 Other Methods for Determining Antibody Affinity 131
- 6.12 Conclusion 134
References 134

- 7 Fc Engineering 141**
Mathias Peipp, Stefanie Derer, Stefan Lohse, Christian Kellner, and Thomas Valerius
- 7.1 Mechanisms of Action of Monoclonal Antibodies 141
 - 7.1.1 Introduction 141
 - 7.1.2 Preclinical Evidence 142
 - 7.1.3 Clinical Evidence 144
- 7.2 Modifying Effector Functions 145
 - 7.2.1 Antibody Isotype 145
 - 7.2.1.1 IgG Antibodies 145
 - 7.2.1.2 IgA Antibodies 149
 - 7.2.2 Altered Fc Receptor Binding 151
 - 7.2.2.1 Introduction 151
 - 7.2.2.2 Protein-Engineered Antibodies 151
 - 7.2.3 Altered Complement Activation 157
- 7.3 Modifying Antibodies' Pharmacokinetics 158
 - 7.3.1 Introduction 158
 - 7.3.2 Modifying Binding to FcRn 159
- 7.4 Summary and Conclusions 160
References 160

- 8 Glycosylation of Antibody Molecules 171**
Roy Jefferis
- 8.1 Introduction 171
- 8.2 Overview of the IgG Molecule 172
- 8.3 Quaternary Structure of IgG-Fc: The Protein Moiety 174
- 8.4 The IgG-Fc Oligosaccharide Moiety 176
- 8.5 IgG-Fc Protein/Oligosaccharide Interactions 177
- 8.6 Protective Mechanisms Activated by Immune Complexes 180
- 8.7 Role of IgG Glycoforms in Recognition by Cellular FcγRs 180
- 8.8 The Influence of Fucose and Bisecting *N*-Acetylglucosamine on IgG-Fc Activities 180
- 8.9 The Influence of Galactosylation on IgG-Fc Activities 182
- 8.10 Sialylation of IgG-Fc Oligosaccharides 184
- 8.11 Chemo-Enzymatic Synthesis of Novel IgG-Fc Glycans 185

- 8.12 Restoration of Functionality to Aglycosylated IgG-Fc 186
- 8.13 IgG-Fab Glycosylation 187
- 8.14 Conclusion 189
- References 189

9 Bioinformatics Tools for Analysis of Antibodies 201

Andrew C.R. Martin and James Allen

- 9.1 Introduction 201
- 9.1.1 Brief Review of Antibody Structure 201
- 9.1.2 Conventions Used in this Chapter 202
- 9.2 Numbering Schemes for Antibodies 202
- 9.2.1 The Kabat Numbering Scheme 203
- 9.2.1.1 The Chothia Numbering Scheme 204
- 9.2.2 The IMGT Numbering Scheme 206
- 9.2.3 Honegger and Plückthun (Aho) Numbering Scheme 206
- 9.2.4 Enhanced Chothia (Martin) Numbering Scheme 206
- 9.2.5 Numbering Scheme Summary 206
- 9.3 Definition of the CDRs and Related Regions 208
- 9.4 Antibody Sequence Data 209
- 9.4.1 Antibody Sequence Databanks 210
- 9.4.2 Germline Sequence Databases 211
- 9.4.3 Web Resources for Analyzing Antibody Sequence Data 211
- 9.4.3.1 Kabat Data 211
- 9.4.3.2 IMGT Data 212
- 9.5 Antibody Structure Data 213
- 9.6 Screening New Antibody Sequences 213
- 9.6.1 Tools for Assigning Subgroups 213
- 9.6.2 Identifying Germline Components 214
- 9.6.3 Identifying Unusual Features 214
- 9.6.4 Assessing “Humanness” of Sequences 214
- 9.7 abYsis – An Integrated Antibody Sequence and Structure Resource 215
- 9.8 Antibody Structure Prediction 216
- 9.8.1 Build the Framework 216
- 9.8.2 Build the CDRs 216
- 9.8.3 Automated Modeling Tools 217
- 9.9 Sequence Families 218
- 9.9.1 Families and Subgroups 218
- 9.9.2 Human Family Chronology 219
- 9.9.2.1 Human Heavy Chain Variable Genes (V_H) 219
- 9.9.2.2 Human Light Chain Variable Genes (V_L and V_K) 219
- 9.9.3 Mouse Family Chronology 220
- 9.9.3.1 Mouse Heavy Chain Variable Genes (V_H) 220
- 9.9.3.2 Mouse Light Chain Variable Genes (V_K and V_L) 220
- 9.9.4 Correspondence between Human and Mouse Families 221

9.9.4.1	Heavy Chain Variable Genes (V_H)	221
9.9.4.2	Light Chain Variable Genes (V_K and V_L)	221
9.10	Summary	222
	References	223
	Websites	226
10	How to Use IMGT[®] for Therapeutic Antibody Engineering	229
	<i>Marie-Paule Lefranc</i>	
10.1	Introduction	229
10.2	Fundamental Information from IMGT-ONTOLOGY Concepts	232
10.2.1	IDENTIFICATION: IMGT [®] Standardized Keywords	232
10.2.2	DESCRIPTION: IMGT [®] Standardized Labels	233
10.2.3	CLASSIFICATION: IMGT [®] Standardized Genes and Alleles	233
10.2.4	NUMEROTATION: IMGT Unique Numbering and IMGT Colliers de Perles	236
10.2.4.1	IMGT Unique Numbering for V and C Domains	236
10.2.4.2	IMGT Collier de Perles	237
10.3	IMGT [®] Tools and Databases	241
10.3.1	IMGT/Collier-de-Perles Tool	241
10.3.2	IMGT/3Dstructure-DB	241
10.3.3	IMGT/2Dstructure-DB	244
10.3.4	IMGT/DomainGapAlign	244
10.3.5	IMGT/V-QUEST	245
10.3.6	IMGT/HighV-QUEST	246
10.4	Examples of IMGT [®] Web Resources for Antibody Engineering and Humanization	246
10.4.1	Antibody V Domain Humanization	246
10.4.1.1	CDR-IMGT Grafting	246
10.4.1.2	Amino Acid Interactions between FR-IMGT and CDR-IMGT	247
10.4.2	Only-Heavy-Chain Antibodies	247
10.4.2.1	Dromedary IgG2 and IgG3	247
10.4.2.2	Human Heavy Chain Diseases (HCD)	248
10.4.2.3	Nurse Shark IgN	248
10.4.3	IGHG CH Amino Acid Positions	249
10.4.3.1	N-Linked Glycosylation Site CH2 N84.4	249
10.4.3.2	Knobs-into-Holes CH3 T22 and Y86	249
10.4.3.3	Interface Ball-and-Socket-Like Joints	251
10.4.3.4	IGHG1 Alleles and G1m Allotypes	251
10.5	Conclusions	253
	Acknowledgments	255
	Abbreviations	257
	References	257
	Website	263

Part II: Modified Antibodies 265**11 Bispecific Antibodies 267***Dafne Müller and Roland E. Kontermann*

- 11.1 Introduction 267
- 11.2 The Generation of Bispecific Antibodies 268
 - 11.2.1 Somatic Hybridization 268
 - 11.2.2 Chemical Conjugation 269
 - 11.2.3 Recombinant Bispecific Antibody Molecules 271
 - 11.2.3.1 Small Recombinant Bispecific Antibody Formats Derived from the Variable Domain 272
 - 11.2.3.2 Recombinant Bispecific Antibody Formats Generated by Fusing an Antigen-Binding Site to an IgG 275
 - 11.2.3.3 Recombinant Bispecific Antibody Formats Containing Asymmetric Heterodimerization Domains 276
- 11.3 Bispecific Antibodies and Retargeting of Effector Cells 278
 - 11.3.1 Retargeting of Cytotoxic T Lymphocytes 279
 - 11.3.2 Retargeting of Fc Receptor Bearing Effector Cells 283
- 11.4 Bispecific Antibodies and Retargeting of Effector Molecules 285
 - 11.4.1 Bispecific Antibodies and Radioimmunotherapy 286
 - 11.4.2 Bispecific Antibodies and Targeting of Toxins and Drugs 288
- 11.5 Dual Targeting Strategies with Bispecific Antibodies 289
- 11.6 Bispecific Antibodies and Somatic Gene Therapy 291
- 11.7 Outlook Update 293
 - References 293

12 Single-Domain Antibodies: An Overview 311*Carrie Enever, Edward Coulstock, Malgorzata Pupecka-Swider, and Bruce Hamilton*

- 12.1 Introduction 311
- 12.2 Historical Perspective 312
 - 12.2.1 Overview 312
 - 12.2.2 Companies 312
 - 12.2.3 Assets in the Clinic 314
- 12.3 How are sdAbs Isolated? 314
 - 12.3.1 Introduction 314
 - 12.3.2 Single-Domain Antibody Library Generation 317
 - 12.3.2.1 Immune Library Generation 317
 - 12.3.2.2 Naïve Library Generation 317
 - 12.3.2.3 Synthetic Library Generation 317
 - 12.3.2.4 Transgenic Animals 318
 - 12.3.3 Selection Technologies 319
 - 12.3.3.1 Phage Display 319
 - 12.3.3.2 Yeast and Bacterial Display 319
 - 12.3.3.3 Alternative Display Methods 320

12.3.4	Affinity Maturation	321
12.4	Target Space	321
12.4.1	Structural Differences	322
12.4.2	Cryptic and Conformational Epitopes	323
12.4.3	Routes of Administration	324
12.4.4	Modularity	324
12.4.5	Tissue Penetration	325
12.4.6	Diagnostic Application	325
12.5	Bi-specifics and Targeted Payloads	326
12.6	Pharmacokinetics/Biodistribution and Half-Life Extension Technologies	328
12.6.1	PEGylation	328
12.6.2	Fc-Fusion	329
12.6.3	Albumin Binding	330
12.7	Imaging	332
12.8	Outlook	334
	Acknowledgments	334
	References	334
13	Antibody–Drug Conjugates: New Frontier in Cancer Therapeutics	341
	<i>Rajeeva Singh, John M. Lambert, and Ravi V. J. Chari</i>	
13.1	Introduction	341
13.2	Currently Approved ADCs for Cancer Treatment	344
13.3	Cytotoxic Compounds in ADCs	346
13.3.1	Microtubule-Targeted Cytotoxic Agents	346
13.3.2	DNA- or DNA-Topoisomerase-Targeted Cytotoxic Agents	352
13.4	Linkers in ADCs	353
13.4.1	Noncleavable Thioether Linkers	354
13.4.2	Disulfide Linkers	355
13.4.3	Peptide Linkers	356
13.4.4	Hydrazone Linkage	356
13.4.5	Carbonate Linkage	356
13.4.6	Site of Linkage	357
13.5	Antibody in ADCs	358
13.6	Conclusions	358
	References	359
14	Antibody-Targeted Drugs: From Chemical Immunoconjugates to Recombinant Fusion Proteins	363
	<i>Athanasios Mavratzas, Michaela A.E. Arndt, Stefan Kiesgen, and Jürgen Krauss</i>	
14.1	Introduction	363
14.2	Lessons Learned from Chemical Immunoconjugates	363
14.2.1	Evolution	363
14.2.2	Linker Stability	364

- 14.2.3 Cross-Linkage Heterogeneity 369
- 14.2.4 Characteristics of Target Antigens 370
- 14.2.5 Characteristics of Effector Moities 372
- 14.3 Recombinant Cytotoxic Fusion Proteins 374
- References 378

Part III: Emerging Technologies 391

15 Emerging Technologies for Antibody Selection 393

Mingyue He and Michael J. Taussig

- 15.1 Introduction 393
- 15.2 Display Technologies 394
- 15.3 Antibody Libraries 395
- 15.4 Antibody Selection and Maturation *In vitro* 397
- 15.5 Linking Antibodies to mRNA: Ribosome and mRNA Display 398
- 15.6 Advantages of Ribosome Display 399
- 15.7 Ribosome Display Systems 399
 - 15.7.1 Prokaryotic: *E. coli* S30 399
 - 15.7.2 Eukaryotic: Rabbit Reticulocyte 400
 - 15.7.3 Ribosome Display Constructs 400
 - 15.7.4 Monosome versus Polysome Display 401
- 15.8 Antibody Generation by Ribosome Display 402
- 15.9 Summary 402
- References 402

16 Anti-Idiotypic Antibodies 407

Alejandro López-Requena, Oscar R. Burrone, and Rolando Pérez

- 16.1 Introduction 407
- 16.2 Basic Concepts 408
- 16.3 Physiological Role of Anti-idiotypic Antibodies 412
 - 16.3.1 Self/Non-self Discrimination 412
 - 16.3.2 Therapeutic Effect of the Pool of Intravenous Immunoglobulins (IVIg) on Autoimmune Diseases 413
- 16.4 Anti-Idiotypic Antibody Responses 414
- 16.5 Anti-Idiotypic Antibodies in Cancer 415
- 16.6 Anti-idiotypic Antibodies in Other Diseases 417
- 16.7 Concluding Remarks 418
- References 419

17 Non-Antibody Scaffolds as Alternative Therapeutic Agents 435

Markus Fiedler and Arne Skerra

- 17.1 Introduction 435
- 17.2 Motivation for Therapeutic Use of Alternative Binding Proteins 437
- 17.3 Single Domain Immunoglobulins 448

17.4	Scaffold Proteins Presenting a Contiguous Hypervariable Loop Region	450
17.5	Scaffold Proteins for Display of Individual Extended Loops	454
17.6	Scaffold Proteins Providing a Rigid Secondary Structure Interface	457
17.7	Non-Antibody Scaffolds Stepping into the Clinic	461
17.8	Conclusions and Outlook: Therapeutic Potential and Ongoing Developments	463
	References	464
18	Antibody-Directed Enzyme Prodrug Therapy (ADEPT)	475
	<i>Surinder K. Sharma, Kerry A. Chester and Kenneth D. Bagshawe</i>	
18.1	Introduction and Basic Principles of ADEPT	475
18.2	Pre-clinical Studies	477
18.2.1	CPG2 and Benzoic Mustard Prodrugs	477
18.2.2	Other Enzyme/Prodrug Systems	478
18.2.3	Catalytic Antibodies	478
18.3	Clinical Studies	479
18.3.1	F(ab) 2 Fragments Conjugated to CPG2	479
18.3.2	Recombinant scFv-CPG2 Fusion Protein	479
18.4	Immunogenicity	480
18.5	Important Considerations/Outlook	481
	Acknowledgments	482
	Abbreviations	482
	References	482
19	Engineered Antibody Domains as Candidate Therapeutics	487
	<i>Weizao Chen, Ponraj Prabakaran, and Dimiter S. Dimitrov</i>	
19.1	Introduction	487
19.2	eAd Structure and Function	489
19.2.1	V _H H	492
19.2.2	VNAR	492
19.2.3	VH and VL	494
19.2.4	CH2	495
19.3	eAd Libraries	495
19.3.1	Generation of eAd Libraries from Naturally Occurring HCABs	495
19.3.2	Generation of Semi-Synthetic and Synthetic eAd Libraries	496
19.3.3	Generation of eAd Libraries with Grafted <i>In Vivo</i> Formed CDRs	497
19.4	eAds against HIV-1	498
19.4.1	eAds to the CoRbs of HIV-1 gp120	499
19.4.2	eAds to the CD4bs of HIV-1 gp120	500
19.4.3	eAds to the MPER of HIV-1 gp41	500
19.4.4	eAds to HIV-1 Coreceptors	501
19.4.5	Implications for HIV-1 Vaccine Immunogen Design	501
19.5	eAds Targeting Cancer	502

- 19.5.1 eAds for Cancer Imaging 502
- 19.5.2 eAds for Cancer Therapy 503
- 19.5.2.1 eAds Blocking Cancer Cell Signaling 503
- 19.5.2.2 eAds for Cancer Drug Targeting 503
- 19.5.2.3 eAds Targeting Cancer-Related Soluble Ligands for Their Irreversible Removal 504
- 19.6 eAds against Inflammation 505
- 19.6.1 eAds against Rheumatoid Arthritis (RA) 505
- 19.6.2 eAds against Inflammatory Bowel Disease (IBD) 507
- 19.7 eAds against Hematological Disorders 507
- 19.8 Conclusions 508
- Acknowledgments 508
- References 508

- 20 Chimeric Antigen Receptors –“CARs” 519**
Ulf Petrausch and Thomas Schirrmann
- 20.1 Introduction 519
- 20.2 Chimeric Antigen Receptors –“CARs” 521
- 20.2.1 Antigen Recognition of Antibodies and T Cell Receptors 521
- 20.2.2 General Design of Chimeric Immunoglobulin T Cell Receptors 522
- 20.2.3 Double Chain CARs 523
- 20.2.4 Single-Chain CARs 524
- 20.2.5 The First Signal of the CAR 525
- 20.2.6 Signal Domains Employing Downstream Signal Molecules 526
- 20.2.7 The Transmembrane Domain – More Than Only a Membrane Anchor? 528
- 20.2.8 Extracellular Spacer Domains Promote CAR Expression and Function 528
- 20.2.9 The Second and Third Signals of the CAR 529
- 20.3 Preclinical Studies 530
- 20.3.1 Retroviral Gene Transfer into T Lymphocytes 530
- 20.3.2 “Naked” Gene Delivery Systems 532
- 20.3.3 Enrichment of CAR Transfected Effector Cells 532
- 20.3.4 Effector Functions of CAR Gene-Modified Effector Lymphocytes 533
- 20.3.5 Memory Function of Redirected T Cells 533
- 20.3.6 Animal Models 537
- 20.4 Therapeutic Considerations 538
- 20.4.1 Adoptive Cellular Immunotherapy 538
- 20.4.2 Clinical Studies with CAR-Modified T Lymphocytes 540
- 20.5 Perspectives 545
- 20.5.1 Tumor Taxis and Application of the CAR⁺ Effector Cells 545
- 20.5.2 Neovascularization of Solid Tumors – Barrier or Target? 546
- 20.5.3 Rejection of Receptor Gene-Modified Effector Lymphocytes 546
- 20.6 Conclusions 547
- References 547

21	Emerging Alternative Production Systems	561
	<i>Benjamin Sommer, Holger Laux, Andre Frenzel, and Thomas Jostock</i>	
21.1	Introduction	561
21.2	Production Systems	562
21.2.1	Prokaryotic Expression Systems	562
21.2.1.1	<i>Escherichia coli</i>	562
21.2.1.2	<i>Pseudomonas fluorescens</i>	564
21.2.1.3	<i>Bacillus</i> Species	564
21.2.2	Eukaryotic Expression Systems	565
21.2.2.1	Yeast	565
21.2.2.2	Filamentous Fungi	569
21.2.2.3	Insect Cells	570
21.2.2.4	Mammalian Cells	571
21.2.2.5	Plants	579
21.2.2.6	Transgenic Animals	580
21.3	Outlook	581
	Abbreviations	583
	References	583

Volume II: Clinical Development of Antibodies

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

Part IV: The Way into the Clinic 601

22	Process Development and Manufacturing of Therapeutic Antibodies	603
	<i>Alexander Jacobi, Barbara Enenkel, Patrick Garidel, Christian Eckermann, Mathias Knappenberger, Ingo Presser, and Hitto Kaufmann</i>	
23	The Immunogenicity of Therapeutic Antibodies	665
	<i>Melody Sauerborn</i>	
24	Biosimilar Monoclonal Antibodies	681
	<i>Susanne D. Pippig, Carsten Brockmeyer, and Robert E. Zoubek</i>	
25	Patent Issues Relating to Therapeutic Antibodies	705
	<i>Barbara Rigby, Michael Braunagel, and Deborah Owen</i>	

Part V: Therapeutic Antibody Pipeline 735

- 26 Monoclonal Antibody Cancer Treatments in Phase III Clinical Trials 737**
Ulf Petrausch and Peter Markus Deckert
- 27 Antibodies in Cancer Treatment: Early Clinical Development 787**
Matthew Zibelman, Hossein Borghaei, and Anthony J. Olszanski
- 28 Targeting Angiogenesis by Therapeutic Antibodies 823**
Onat Kadioglu, Ean Jeong Seo, and Thomas Efferth
- 29 Antibodies in Phase III Studies for Immunological Disorders 851**
Penelope Ward and Mark Bodmer
- 30 Monoclonal Antibodies in Phase 1 and 2 Studies for Immunological Disorders 927**
Frank R. Brennan
- 31 MAbs Targeting Soluble Mediators in Phase 1 and 2 Clinical Studies Immunological Disorders 969**
Frank R. Brennan
- 32 T Cell Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1079**
Frank R. Brennan
- 33 B-Cell Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1115**
Frank R. Brennan
- 34 Inhibitors of Leukocyte Adhesion and Migration in Phase 1 and 2 Clinical Studies for Immunological Disorders 1127**
Frank R. Brennan
- 35 Toll-Like Receptor Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1145**
Frank R. Brennan
- 36 IgE Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1159**
Frank R. Brennan
- 37 Complement Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1165**
Frank R. Brennan

38 **mAbs Targeting Apoptosis, Angiogenesis Inhibitors, and Other mAbs in Phase 1 and 2 Clinical Studies for Immunological Disorders** 1175
Frank R. Brennan

39 ***In vitro* Studies and Clinical Trials about Monoclonal Antibodies Used in Infectiology** 1195
Guillaume Desoubeaux

40 **Immunotherapeutics for Neurological Disorders** 1215
Anne Messer, Kevin Manley, and Cynthia A. Lemere

Part VI: Gaining Marketing Approval 1231

41 **Regulatory Considerations in the Development of Monoclonal Antibodies for Diagnosis and Therapy** 1233
Marjorie A. Shapiro, Patrick G. Swann, and M. Stacey Ricci

42 **Regulatory Review: Clinical to Market Transition** 1263
Gabriele Dallmann

43 **Monoclonal Antibody Nomenclature for Clinical Studies (USA)** 1283
Stephanie C. Shubat

Volume III: Approved Therapeutic Antibodies

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

Part VII: Approved Therapeutic Antibodies 1289

44 **Oligoclonal and Polyclonal Antibody Preparations** 1291
Rishab K. Gupta and Mark C. Glassy

45 **Adalimumab (Humira®)** 1309
Janice M. Reichert

46 **Alemtuzumab (Lemtrada, MabCampath)** 1323
Thomas Elter, Michael Hallek, and Janice M. Reichert

- 47 **Basiliximab (Simulect®) and Daclizumab (Zenapax®)** 1375
Nadim Mahmud, Burcin Taner, and Nasimul Ahsan
- 48 **Belimumab (Benlysta®)** 1405
Pamela M. K Lutalo, Natasha Jordan, Thi-Sau Migone, and David P. D’Cruz
- 49 **Brentuximab Vedotin (Adcetris®) for the Treatment of CD30-Positive Hematologic Malignancies** 1417
Niels W.C.J. van de Donk and Eugen Dhimolea
- 50 **Canakinumab (ILARIS®)** 1445
Hermann Gram
- 51 **Catumaxomab (Removab) – Trifunctional Antibodies: Combining Direct Tumor Cell Killing with Therapeutic Vaccination** 1463
Horst Lindhofer, Michael Stanglmaier, Raymund Buhmann, Michael Jäger, Daniel Klunker, Peter Ruf, and Juergen Hess
- 52 **Cetuximab (Erbix) 1501**
Sonja Wilke and Michael Hust
- 53 **Denosumab (Prolia®)** 1521
Torsten Meyer
- 54 **Efalizumab (Raptiva)** 1531
Karlheinz Schmitt-Rau
- 55 **Calicheamicin Conjugates: Gemtuzumab Ozogamicin (Mylotarg), Inotuzumab Ozogamicin** 1545
Matthias Peipp and Martin Gramatzki
- 56 **Golimumab (Simponi®)** 1565
Sohini Mazumdar and Janice M. Reichert
- 57 **Yttrium-90 Ibritumomab Tiuxetan (Zevalin®)** 1579
Karin Hohloch, Björn Chapuy, and Lorenz Trümper
- 58 **Infliximab (Remicade®)** 1599
Christian Antoni and Maria Wiekowski
- 59 **Ipilimumab (Yervoy®)** 1619
Teresa Alonso Gordo, Javier Puente Vázquez, and Eduardo Díaz-Rubio

- 60** **Muromonab-CD3 (Orthoclone OKT®3)** 1645
Harald Becker and Janice M. Reichert
- 61** **Nimotuzumab: A Humanized Anti-EGFR Antibody** 1679
Tania Crombet Ramos
- 62** **Obinutuzumab (Gazyva®), a Novel Glycoengineered Type II CD20 Antibody for the Treatment of Chronic Lymphocytic Leukemia and Non-Hodgkin's Lymphoma** 1695
Christian Klein, Marina Bacac, Pablo Umaña, and Michael Wenger
- Volume IV: Approved Therapeutic Antibodies and in vivo Diagnostics**
- Quick Reference List of Antibodies by International Nonproprietary Name** XXIII
- Quick Reference List of Antibodies by Brand Name** XXV
- A Greeting by the Editors** XXVII
- Foreword to the First Edition** XXIX
- Foreword to the Second Edition** XXXI
- List of Contributors** XXXIII
- Abbreviations** LI
- Appendix: Marketed Monoclonal Antibodies Compendium** LXXXIII
- 63** **Ofatumumab (Arzerra®): a Next-Generation Human Therapeutic CD20 Antibody with Potent Complement-Dependent Cytotoxicity** 1733
Margaret A. Lindorfer, Joost M. Bakker, Paul W.H.I. Parren, and Ronald P. Taylor
- 64** **Omalizumab (Xolair) – Anti-Immunoglobulin E Treatment in Allergic Diseases** 1775
Claus Kroegel and Martin Foerster
- 65** **Palivizumab (Synagis®)** 1825
Louis Bont
- 66** **Panitumumab (Vectibix®): A Treatment for Metastatic Colorectal Cancer** 1855
Jonas Kügler
- 67** **Pertuzumab (Perjeta®)** 1871
Jose Angel García-Saénz, Fernando Moreno Anton, and Coralía Bueno Muiño

- 68 **Ranibizumab (Lucentis): a New Anti-Angiogenic Treatment in Ophthalmology** 1883
Nicolas Leveziel, Marc Ohresser, and Gilles Paintaud
- 69 **Raxibacumab, Human Monoclonal Antibody against Anthrax Toxin** 1899
Sally D. Bolmer and Thi-Sau Migone
- 70 **Rituximab (Rituxan®)** 1909
Axel Böhnke and Michael Wenger
- 71 **Tocilizumab (Actemra®)** 2023
Graeme Jones and Changhai Ding
- 72 **Trastuzumab (Herceptin®) and Ado-Trastuzumab Emtrastine (Kadcyla®): Treatments for HER2-Positive Breast Cancer** 2041
Ruhe Chowdhury and Paul Ellis
- 73 **Ustekinumab (Stelara®)** 2069
Oya Cingoz, Stefan Dübel, and Janice M. Reichert
- 74 **Abciximab (Reopro®), Bevacizumab (Avastin®), Certolizumab Pegol (Cimzia®), Eculizumab (Soliris®), Natalizumab (Tysabri®)** 2087
Janice M. Reichert
- 75 **Itolizumab (Alzumab®), Mogamulizumab (Poteligeo®), and Tositumomab (Bexxar®)** 2113
Stefan Dübel
- Part VIII: In vivo Diagnostics** 2121
- 76 **Radiolabeled Antibodies for Diagnostic Imaging** 2123
Christopher J. Palestro
- Index** 2143

Contents

Volume I: Defining the Right Antibody Composition

Quick Reference List of Antibodies by International Nonproprietary Name *XXIII*

Quick Reference List of Antibodies by Brand Name *XXV*

A Greeting by the Editors *XXVII*

Foreword to the First Edition *XXIX*

Foreword to the Second Edition *XXXI*

List of Contributors *XXXIII*

Abbreviations *LI*

Appendix: Marketed Monoclonal Antibodies Compendium *LXXXIII*

- 1 **Therapeutic Antibodies – from Past to Future** 1
Stefan Dübel and Janice M. Reichert

- Part I: Selecting and Shaping the Antibody Molecule** 15

- 2 **Selection Strategies for Monoclonal Antibodies** 17
Gerhard Moldenhauer

- 3 **Antibody Phage Display** 43
Michael Hust, André Frenzel, Florian Tomszak, Jonas Kügler, and Stefan Dübel

- 4 **Transgenic Animals Derived by DNA Microinjection** 77
Marianne Brüggemann, Michael J. Osborn, Biao Ma, Suzanne Avis, Ignacio Anegón, and Roland Buelow

- 5 **Humanization Strategies** 89
José W. Saldanha

- 6 **Antibody Affinity** 115
André Frenzel, Lorin Roskos, Scott Klakamp, Meina Liang, Rosalin Arends, and Larry Green

- 7 Fc Engineering 141**
Matthias Peipp, Stefanie Derer, Stefan Lohse, Christian Kellner, and Thomas Valerius
- 8 Glycosylation of Antibody Molecules 171**
Roy Jefferis
- 9 Bioinformatics Tools for Analysis of Antibodies 201**
Andrew C.R. Martin and James Allen
- 10 How to Use IMGT® for Therapeutic Antibody Engineering 229**
Marie-Paule Lefranc
- Part II: Modified Antibodies 265**
- 11 Bispecific Antibodies 267**
Dafne Müller and Roland E. Kontermann
- 12 Single-Domain Antibodies: An Overview 311**
Carrie Enever, Edward Coulstock, Malgorzata Pupecka-Swider, and Bruce Hamilton
- 13 Antibody–Drug Conjugates: New Frontier in Cancer Therapeutics 341**
Rajeeva Singh, John M. Lambert, and Ravi V. J. Chari
- 14 Antibody-Targeted Drugs: From Chemical Immunoconjugates to Recombinant Fusion Proteins 363**
Athanasios Mavratzas, Michaela A.E. Arndt, Stefan Kiesgen, and Jürgen Krauss
- Part III: Emerging Technologies 391**
- 15 Emerging Technologies for Antibody Selection 393**
Mingyue He and Michael J. Taussig
- 16 Anti-Idiotypic Antibodies 407**
Alejandro López-Requena, Oscar R. Burrone, and Rolando Pérez
- 17 Non-Antibody Scaffolds as Alternative Therapeutic Agents 435**
Markus Fiedler and Arne Skerra
- 18 Antibody-Directed Enzyme Prodrug Therapy (ADEPT) 475**
Surinder K. Sharma, Kerry A. Chester and Kenneth D. Bagshawe

- 19 Engineered Antibody Domains as Candidate Therapeutics 487**
Weizao Chen, Ponraj Prabakaran, and Dimiter S. Dimitrov
- 20 Chimeric Antigen Receptors –“CARs” 519**
Ulf Petrausch and Thomas Schirrmann
- 21 Emerging Alternative Production Systems 561**
Benjamin Sommer, Holger Laux, Andre Frenzel, and Thomas Jostock

Volume II: Clinical Development of Antibodies

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

Part IV: The Way into the Clinic 601

- 22 Process Development and Manufacturing of Therapeutic Antibodies 603**
Alexander Jacobi, Barbara Enenkel, Patrick Garidel, Christian Eckermann, Mathias Knappenberger, Ingo Presser, and Hitto Kaufmann
- 22.1 Introduction 603
- 22.2 Upstream Processing 604
- 22.2.1 Expression Systems 605
- 22.2.2 Cell Culture Media 614
- 22.2.3 Cell Culture Process Design 614
- 22.2.4 Cell Culture Process Optimization 617
- 22.3 Downstream Processing 618
- 22.3.1 Platform Technologies for Downstream Processing of Monoclonal Antibodies 620
- 22.3.2 Primary Recovery 622
- 22.3.2.1 Ultra/Diafiltration (UF/DF) 622
- 22.3.2.2 Affinity Chromatography 622
- 22.3.3 Purification and Polishing 623
- 22.3.3.1 Hydrophobic Interaction Chromatography 623
- 22.3.3.2 Ion-Exchange Chromatography 623
- 22.3.3.3 Cation-Exchange Chromatography 624
- 22.3.3.4 Anion-Exchange Chromatography 624
- 22.3.4 Validation of DNA Removal and Virus Clearance 624

22.3.4.1	Validation of DNA Removal	624
22.3.4.2	Virus Clearance	625
22.3.5	Final UF/DF for Drug Substance Manufacturing	625
22.3.6	New Trends in Downstream Processing	626
22.3.6.1	Resins and Ligands	626
22.3.6.2	Separation Technologies	626
22.3.7	Downstream Processing Concepts	627
22.3.7.1	Automation/Miniaturization	627
22.3.7.2	Disposable and Single-Use Concepts	627
22.3.7.3	Development Concepts	628
22.4	Formulation Development	628
22.4.1	Challenges during Early Drug Product Development Phase of Biopharmaceuticals: Liquid Formulation and Freeze-Dried Formulations	629
22.4.2	Strategies and Analytical Tools for Drug Product Development	631
22.4.3	Automation Strategies for Rapid Formulation Development	635
22.4.4	Stabilization of Liquid Protein Formulations by Excipients	635
22.4.5	Stabilization of Freeze-Dried Protein Formulations by Excipients	638
22.4.6	From Low-Concentrated Liquid Formulations (LCLF) to High-Concentrated Liquid Formulations (HCLF)	638
22.5	Commercial Manufacturing Processes	639
22.5.1	Introduction	639
22.5.2	Upstream Manufacturing	640
22.5.3	Harvest	642
22.5.4	Downstream Manufacturing	643
22.5.5	Economy of Scale	645
22.5.6	Process Characterization and Validation	646
22.6	Analytics	647
22.6.1	Protein Characterization and Quality Control Testing	647
22.6.1.1	Characterization and Physicochemical Properties	647
22.6.2	Purity, Heterogeneity, Integrity, Impurities, Contaminants, and Potency	647
22.6.2.1	Purity	647
22.6.2.2	Carbohydrate Heterogeneity	648
22.6.2.3	Overall Structural Confirmation	648
22.6.2.4	Impurities	648
22.6.2.5	Contaminants	650
22.6.2.6	Potency	650
22.6.3	Quality Control Testing	651
22.6.4	Stability Testing	651
22.6.5	Comparability and Risk Assessment	653
22.7	Overall Process Development Strategies and Outlook	654
	Acknowledgments	655
	References	655

23	The Immunogenicity of Therapeutic Antibodies	665
	<i>Melody Sauerborn</i>	
23.1	Introduction	665
23.2	Immunogenicity and the Immune System	667
23.3	Factors Influencing Immunogenicity	668
23.4	Clinical Consequences of Immunogenicity of Abs	671
23.5	Bioanalytical Assessment of ADAs against Therapeutic Antibodies	671
23.6	Immunogenicity Prediction Tools	673
23.7	Reduction of Immunogenicity of Abs	674
23.8	A Look into the Future –The Rise of Antibody-Based Drugs	675
23.9	Conclusions	678
	References	678
24	Biosimilar Monoclonal Antibodies	681
	<i>Susanne D. Pippig, Carsten Brockmeyer, and Robert E. Zoubek</i>	
24.1	Introduction	681
24.2	EU Approach to Biosimilars	682
24.3	US Biosimilars	684
24.4	Follow-On Monoclonal Antibodies in Emerging Markets	684
24.5	Technical Development and Analytical Characterization of Biosimilar Monoclonal Antibodies	685
24.5.1	Excerpt of Frequently Observed Modifications	687
24.5.2	Manufacturing Process Development	691
24.6	Non-Clinical and Clinical Development of Biosimilar Monoclonal Antibodies/Pharmacovigilance and Risk Management	693
24.6.1	Preclinical Development	694
24.6.2	Clinical Development	697
24.6.2.1	Pharmacokinetics and Pharmacodynamics	697
24.6.2.2	Clinical Efficacy and Safety	699
24.6.2.3	Pharmacovigilance and Risk Management	701
	Acknowledgments	701
	Abbreviations	701
	References	702
25	Patent Issues Relating to Therapeutic Antibodies	705
	<i>Barbara Rigby, Michael Braunagel, and Deborah Owen</i>	
25.1	Why Patents Matter	705
25.2	Types of Patent Protection in the Field of Therapeutic Antibodies	706
25.2.1	Novel Antibodies	707
25.2.2	Therapeutic Applications of Antibodies	708
25.2.3	Antibody Modifications	709
25.2.4	Methodology Patents	710
25.2.5	Overlapping Portfolios	710
25.3	Freedom to Operate	711

25.3.1	Introduction	711
25.3.2	Exemptions from Infringement	712
25.3.3	Freedom-to-Operate Search	713
25.3.4	Freedom-to-Operate Analysis	714
25.3.5	Strategic Considerations	714
25.3.6	Antibody Patent Landscape	715
25.3.6.1	Antigen	717
25.3.6.2	Antibody Format	717
25.3.6.3	Functional Enhancements	718
25.3.6.4	Production Systems	718
25.4	Protecting New Developments	718
25.4.1	Patentability	718
25.4.2	Timelines for a Patent Application and Costs	719
25.4.3	Filing Strategies	722
25.5	Management of Own and Third-Party Patents	723
25.5.1	Patent Ownership	723
25.5.2	Patent Term	723
25.5.3	Patent Term Extensions	724
25.5.4	Other Forms of Exclusivity	724
25.5.5	Monitoring Patents	725
25.5.6	Influencing Patent Examination (Third-Party Observations)	725
25.5.7	Attacking Patents	726
25.6	Patent Exploitation Options and Business Models	726
25.6.1	Transactions in Patents	726
25.6.1.1	Licensing	727
25.6.1.2	Sale	728
25.6.2	Business Strategies and Patent Exploitation	729
25.6.2.1	Fee for Service, Contract Research Organisation (CRO)	729
25.6.2.2	Partnered Discovery	730
25.6.2.3	Innovative Companies	730
25.6.2.4	Generic and Biosimilar Producers	731
25.6.2.5	Out-Licensing	731
25.6.3	Funding	731
25.6.4	Due Diligence	732
25.7	Outlook	733
25.8	Reference Materials and Further Reading	734

Part V: Therapeutic Antibody Pipeline 735

26 Monoclonal Antibody Cancer Treatments in Phase III Clinical Trials 737

Ulf Petrausch and Peter Markus Deckert

26.1	Introduction	737
26.2	Antibodies for Use in Lymphoma and Related Diseases	753
26.2.1	B-Cellular Non-Hodgkin's Lymphoma	753

26.2.1.1	Ofatumumab	753
26.2.1.2	Obinutuzumab	754
26.2.1.3	Epratuzumab (Anti-CD22)	755
26.2.1.4	Inotuzumab Ozogamicin (Anti-CD22)	756
26.2.1.5	Galiximab (Anti-CD80)	757
26.2.1.6	Elotuzumab (Anti-CS1)	757
26.2.2	T-Cellular Non-Hodgkin's Lymphoma	758
26.2.2.1	Zanolimumab (Anti-CD4)	758
26.2.3	Hodgkin's Lymphoma	759
26.2.3.1	Brentuximab Vedotin (Anti-CD30–Monomethyl Auristatin E)	759
26.3	Anti-EpCAM Antibodies: A Lesson in History and What Remains	760
26.4	Antibodies Against Epithelial Growth Factor Targets	761
26.4.1	Antibodies against EGFR	761
26.4.2	Trastuzumab Emtansine (Her2/Neu)	763
26.4.3	Ramucirumab (VEGF-R)	764
26.5	Insulin-Like Growth Factor Type I Receptor Antibodies	765
26.5.1	Ganitumab	765
26.5.2	Dalotuzumab	766
26.5.3	Cixutumumab	766
26.5.4	Figitumumab	767
26.6	Antibodies for Use in Renal Cell Carcinoma	767
26.6.1	Girentuximab (Carbonic Anhydrase IX)	767
26.6.2	Naptumomab Estafenatox (5T4)	768
26.7	Antibodies for Use in Ovarian Cancer	769
26.7.1	Farletuzumab	769
26.7.2	Oregovomab	769
26.8	Blockage of Immunological Checkpoints	770
26.8.1	Ipilimumab (Anti-CTLA4)	771
26.8.2	Nivolumab (Anti-PD1)	772
26.9	Miscellaneous Diseases and Targets	773
26.9.1	Rilotumumab	773
26.9.2	Onartuzumab	773
26.9.3	Racotumomab	774
26.9.4	Pentumomab	775
26.9.5	Denosumab	775
26.10	Summary	776
	References	777
27	Antibodies in Cancer Treatment: Early Clinical Development	787
	<i>Matthew Zibelman, Hossein Borghaei, and Anthony J. Olszanski</i>	
27.1	Introduction	787
27.2	Harnessing Innate Immunity	788
27.2.1	Antibody-Dependent Cytotoxicity	789
27.2.2	Complement-Dependent Cytotoxicity	791

27.2.3	Immunomodulating Antibodies	792
27.3	Alteration of Intracellular Signaling	795
27.3.1	Ligand Inhibition	796
27.3.2	Ligand-Dependent Cell Receptor Inhibition	798
27.3.3	Ligand-Independent Alteration of Signal Transduction	800
27.4	Immunoconjugates	802
27.4.1	Antibody-Drug Conjugates	804
27.4.2	Radioimmunoconjugates	806
27.4.3	Bispecific Antibodies and Bispecific T-Cell Engagers (BiTEs)	807
27.5	The Three U's: Mechanisms of Unique, Unclear, or Unknown Function	809
27.5.1	Unclear or Unknown Mechanisms	809
27.5.2	Unique Mechanisms	811
27.6	Summary	812
	References	813
28	Targeting Angiogenesis by Therapeutic Antibodies	823
	<i>Onat Kadioglu, Ean Jeong Seo, and Thomas Efferth</i>	
28.1	Introduction	823
28.1.1	Angiogenesis in Cancer Development	823
28.1.2	Angiogenic Switch	824
28.1.3	Role of Macrophages for Angiogenesis	825
28.1.4	Molecular Regulators of Angiogenesis	825
28.1.4.1	Vascular Endothelial Growth Factor (VEGF)	825
28.1.4.2	Basic Fibroblast Growth Factor (bFGF)	827
28.1.4.3	Other Angiogenic Stimulators	827
28.1.4.4	Angiogenesis Inhibitors	828
28.1.5	Damaged Vessels Favor Angiogenesis	830
28.2	Therapeutic Antibodies	830
28.2.1	Targeting the EGF and VEGF Pathways	831
28.2.2	Targeting VEGF Ligand	833
28.2.3	Multiple Signaling Routes of VEGF	835
28.2.3.1	Antibodies	835
28.2.3.2	Fusion Constructs	835
28.2.3.3	Resistance Mechanisms	836
28.2.4	Targeting Other Angiogenesis Components	836
28.2.4.1	Angiopoietin Type 2	836
28.2.4.2	Angiotensin-2 Receptor	837
28.2.4.3	Integrins	837
28.2.4.4	Cadherins	838
28.2.4.5	Targeting MET Tyrosine Kinase	838
28.2.4.6	Extracellular Matrix	839
28.3	Conclusion	841
	Abbreviations	841
	References	843

29 Antibodies in Phase III Studies for Immunological Disorders 851*Penelope Ward and Mark Bodmer*

- 29.1 Introduction 851
- 29.2 Antibody Targets in Phase III Trials 852
 - 29.2.1 Catalytic Protease Targets 852
 - 29.2.1.1 Pro-protein Convertase Subtilisin Kexin (PCSK)-9 852
 - 29.2.2 Bone Metabolism Target 859
 - 29.2.2.1 Sclerostin 859
 - 29.2.3 Cytokine/Chemokine Targets 866
 - 29.2.3.1 Interleukin 6 and Interleukin-6 Receptor 866
 - 29.2.3.2 Interleukin-1 β 873
 - 29.2.3.3 Interleukin-5 876
 - 29.2.3.4 Interleukin-13 883
 - 29.2.3.5 Interleukin-17A and Interleukin-17A Receptor 885
 - 29.2.3.6 Interleukin-23 897
 - 29.2.4 Adhesion Molecule Targets 899
 - 29.2.4.1 α 4 β 7 Integrin 899
 - 29.2.5 Cell-Surface Receptor Targets 901
 - 29.2.5.1 CD6 901
 - 29.2.5.2 CD20 902
 - 29.2.5.3 CD22 904
 - 29.2.6 Amyloid Protein Targets 905
 - 29.2.6.1 Amyloid β Protein 905
- 29.3 Summary 909
- References 910

30 Monoclonal Antibodies in Phase 1 and 2 Studies for Immunological Disorders 927*Frank R. Brennan*

- 30.1 Introduction 927
- 30.2 General Overview of the Immune System and Key Pathways Driving Inflammatory Diseases 934
- 30.3 Review of the Major Inflammatory Diseases Targeted by mAbs, Goals of Current Therapies and How These Might Be Met by Existing and Emerging Biologics 936
 - 30.3.1 Rheumatoid Arthritis 936
 - 30.3.2 Psoriasis and Psoriatic Arthritis 937
 - 30.3.3 Inflammatory Bowel Disease 938
 - 30.3.4 Multiple Sclerosis 939
 - 30.3.5 Systemic Lupus Erythematosus 941
 - 30.3.6 Ocular Diseases (Uveitis and Age-Related Macular Degeneration (AMD)) 943
 - 30.3.6.1 Uveitis 943
 - 30.3.6.2 Age-Related Macular Degeneration (AMD) 944
 - 30.3.7 Allergic Diseases: Asthma and Atopic Dermatitis 945

30.3.7.1	Asthma	945
30.3.7.2	Atopic Dermatitis	948
30.3.8	Diabetes	949
30.3.8.1	Type 1 Diabetes	949
30.3.8.2	Type II Diabetes	950
30.3.9	Organ Transplantation – Graft Rejection	951
30.3.10	Other Immunological Diseases	953
30.4	Mechanisms of Target Modulation Utilized by Monoclonal Antibodies	954
30.5	Optimizing mAbs for Efficacy and Safety	954
30.6	Summary	956
	References	957
31	MABs Targeting Soluble Mediators in Phase 1 and 2 Clinical Studies Immunological Disorders	969
	<i>Frank R. Brennan</i>	
31.1	Introduction	969
31.1.1	MABs Targeting Soluble Mediators	970
31.1.1.1	Cytokine Inhibitors	970
31.1.1.2	Chemokine Inhibitors	1015
31.1.1.3	Growth Factor Inhibitors	1023
	References	1028
32	T Cell Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders	1079
	<i>Frank R. Brennan</i>	
32.1	Introduction	1079
32.2	T-Cell Inhibitors	1079
32.2.1	Anti-T Cell $\alpha\beta$	1079
32.2.2	Anti-CD3	1081
32.2.3	Anti-CD4	1083
32.2.4	Anti-CD100 (Semaphorin 4D)	1085
32.3	Anti-T-Cell Costimulators	1086
32.3.1	Anti-CD28	1087
32.3.2	Anti-ICOSL (B7RP-1)	1088
32.3.3	Anti-OX40/OX40L	1091
32.3.4	Anti-HVEM/LIGHT	1093
32.3.5	Anti-CD26 (DPPIV)	1095
32.3.6	Anti-NKG2A	1097
	References	1098
33	B-Cell Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders	1115
	<i>Frank R. Brennan</i>	
33.1	Introduction	1115

- 33.2 Anti-CD19 1115
- 33.3 Anti-BAFF (Blys) 1117
- 33.4 Anti-CD20 1119
- References 1121

- 34 Inhibitors of Leukocyte Adhesion and Migration in Phase 1 and 2 Clinical Studies for Immunological Disorders 1127**
Frank R. Brennan
- 34.1 Introduction 1127
- 34.2 Inhibitors of Leukocyte Adhesion and Migration 1128
 - 34.2.1 Anti- α 4 β 7/MAdCAM-1 1128
 - 34.2.2 Anti- α 1 β 1 Integrin (VLA-1) 1131
 - 34.2.3 Anti- α 2 β 1 Integrin (VLA-2) 1133
 - 34.2.4 Anti-VAP-1 1134
 - 34.2.5 Anti-CD162 (P-Selectin Glycoprotein Ligand; PSGL-1) 1136
 - References 1138

- 35 Toll-Like Receptor Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1145**
Frank R. Brennan
- 35.1 Introduction 1145
- 35.2 Toll-Like Receptor Inhibitors 1146
 - 35.2.1 Anti-TLR2 1146
 - 35.2.2 Anti-TLR3 1147
 - 35.2.3 Anti-TLR4 1149
 - References 1151

- 36 IgE Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1159**
Frank R. Brennan
- 36.1 Introduction 1159
- 36.2 IgE Inhibitors 1161
 - 36.2.1 Anti-IgE 1161
 - 36.2.2 Anti-IgE M1' 1162
 - References 1163

- 37 Complement Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1165**
Frank R. Brennan
- 37.1 Introduction 1165
- 37.2 Complement Inhibitors 1166
 - 37.2.1 Anti-C5/C5a/C5aR 1166
 - 37.2.2 Anti-Factor D 1169
 - References 1171

38	mAbs Targeting Apoptosis, Angiogenesis Inhibitors, and Other mAbs in Phase 1 and 2 Clinical Studies for Immunological Disorders 1175
	<i>Frank R. Brennan</i>
38.1	mAbs Targeting Apoptosis 1175
38.1.1	Anti-Fas (CD95) 1175
38.2	Angiogenesis Inhibitors 1177
38.2.1	Anti-VEGF 1177
38.2.2	Anti-S1P 1178
38.3	Other mAbs 1181
38.3.1	Anti-MMP-9 1181
38.3.2	Anti-LINGO-1 1182
38.3.3	Anti-MRSV env 1183
38.3.4	Anti-fibronectin-IL-10 Fusion Protein 1185
	References 1185
39	<i>In vitro</i> Studies and Clinical Trials about Monoclonal Antibodies Used in Infectiology 1195
	<i>Guillaume Desoubeaux</i>
39.1	Introduction and Infectious Context 1195
39.2	Historical of Antibodies Used in Infectiology and Previous Clinical Trials 1196
39.3	General Mechanisms of Action 1196
39.4	Mode of Production of Anti-Infectious Antibodies 1197
39.5	Anti-Infectious Monoclonal Antibodies Against Bacteria and Associated Toxins 1197
39.6	Viral Diseases and Anti-Infectious Monoclonal Antibodies 1201
39.7	Perspectives and Future Development of Antimycotic Monoclonal Antibodies 1207
39.8	Conclusion 1207
	Acknowledgments 1207
	Author Contributions 1208
	Funding 1208
	Transparency Declarations Sections and Conflicts of Interest 1208
	References 1208
40	Immunotherapeutics for Neurological Disorders 1215
	<i>Anne Messer, Kevin Manley, and Cynthia A. Lemere</i>
40.1	Introduction 1215
40.1.1	Overview of Advantages and Challenges of Immunotherapy for Neurological Diseases 1215
40.1.2	Neurological Disease Targets 1216
40.1.3	Active Versus Passive Immunotherapy 1216
40.2	Alzheimer's Disease 1217
40.2.1	Disease and Target 1217
40.2.2	Active Immunotherapy for A β 1218

40.2.3	Passive Immunotherapy for A β	1218
40.2.4	Immunotherapy Directed at A β -Related Targets	1220
40.2.5	Immunotherapy Directed at Tau	1220
40.3	Parkinson's Disease and Dementia with Lewy Bodies	1220
40.3.1	Disease and Targets	1220
40.3.1.1	Active Immunotherapy – Preclinical	1221
40.3.1.2	Active Immunotherapy – Clinical	1221
40.3.2	Passive Immunotherapy	1221
40.3.2.1	Passive Immunotherapy with Full-Length Antibody	1221
40.3.2.2	Passive Immunotherapy with Intrabodies	1221
40.4	Huntington's Disease	1222
40.4.1	Disease and Target	1222
40.4.2	Passive Immunotherapy with Intrabodies	1222
40.4.3	Active Immunotherapy with DNA Vaccines	1223
40.5	Amyotrophic Lateral Sclerosis	1223
40.5.1	Disease and Target	1223
40.5.2	Active Immunotherapy	1224
40.5.3	Passive Immunotherapy	1224
40.6	Transmissible Spongiform Encephalopathies	1224
40.6.1	Disease and Target	1224
40.6.2	Active Immunotherapy	1225
40.6.3	Passive Immunotherapy	1225
40.7	Conclusion	1225
	Acknowledgments	1226
	References	1226

Part VI: Gaining Marketing Approval 1231

41	Regulatory Considerations in the Development of Monoclonal Antibodies for Diagnosis and Therapy	1233
	<i>Marjorie A. Shapiro, Patrick G. Swann, and M. Stacey Ricci</i>	
41.1	Introduction	1233
41.2	Regulatory Authority	1237
41.3	Chemistry, Manufacturing, and Controls Considerations	1240
41.3.1	Cell Line Qualification	1240
41.3.2	Quality Control Testing	1242
41.3.3	Transmissible Spongiform Encephalopathy (TSE)	1244
41.3.4	Product Stability	1245
41.3.5	Reference Standard	1245
41.3.6	Viral Clearance and Inactivation Studies	1246
41.3.7	Abbreviated Product Safety Testing for Feasibility Trials in Serious or Immediately Life-Threatening Conditions	1246
41.3.8	Comparability	1247
41.3.9	Quality by Design	1248
41.4	Considerations for Nonclinical Testing	1249

41.4.1	Components of a Nonclinical Safety Testing Program	1250
41.4.2	Relevant Species	1251
41.4.3	Pharmacology and Pharmacokinetic Studies	1252
41.4.4	Toxicology	1254
41.5	Immunogenicity	1255
41.5.1	Nonclinical	1255
41.5.2	Clinical	1256
41.6	Conclusions	1257
	Acknowledgments	1258
	References	1258
42	Regulatory Review: Clinical to Market Transition	1263
	<i>Gabriele Dallmann</i>	
42.1	Introduction	1263
42.2	General Considerations for the Clinical Development of mAbs	1264
42.3	The Need for Regulatory Validation of the Development Program	1266
42.4	The Approach of Agencies for Clinical Review of mAb	1266
42.4.1	Clinical Review Approach	1266
42.4.2	Approval Timelines	1267
42.4.3	Fast Approval – When the Data Are Compelling	1268
42.5	Strategic Regulatory Options for Rapid Market Access	1270
42.6	Pivotal Clinical Trials for mAb	1271
42.7	Specific Considerations for Early Development Clinic Studies of mAb	1272
42.7.1	Scope of Comparability Investigations During Clinical Development and the Life Cycle of mAbs	1275
42.7.2	Pre-authorization Interactions with Agencies – The Scientific Advice Procedure	1276
42.7.3	Clinical Trial Authorization of mAb	1277
42.7.4	Risk Management Plan	1278
42.7.5	mAb Typical Post-marketing Activities	1279
	References	1280
43	Monoclonal Antibody Nomenclature for Clinical Studies (USA)	1283
	<i>Stephanie C. Shubat</i>	
43.1	Elements of a Name	1283
43.2	Sequence of Stems and Infixes	1284
43.2.1	Prefix	1284
43.3	Target/Disease Class Infix	1284
43.3.1	Source Infix	1285
43.4	USAN Modified Designations for Monoclonal Antibodies	1286
43.5	Required Application Information	1287

Volume III: Approved Therapeutic Antibodies

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

Part VII: Approved Therapeutic Antibodies 1289

- 44 **Oligoclonal and Polyclonal Antibody Preparations** 1291
Rishab K. Gupta and Mark C. Glassy
- 45 **Adalimumab (Humira®)** 1309
Janice M. Reichert
- 46 **Alemtuzumab (Lemtrada, MabCampath)** 1323
Thomas Elter, Michael Hallek, and Janice M. Reichert
- 47 **Basiliximab (Simulect®) and Daclizumab (Zenapax®)** 1375
Nadim Mahmud, Burcin Taner, and Nasimul Ahsan
- 48 **Belimumab (Benlysta®)** 1405
Pamela M. K Lutalo, Natasha Jordan, Thi-Sau Migone, and David P. D'Cruz
- 49 **Brentuximab Vedotin (Adcetris®) for the Treatment of CD30-Positive Hematologic Malignancies** 1417
Niels W.C.J. van de Donk and Eugen Dhimolea
- 50 **Canakinumab (ILARIS®)** 1445
Hermann Gram
- 51 **Catumaxomab (Removab) – Trifunctional Antibodies: Combining Direct Tumor Cell Killing with Therapeutic Vaccination** 1463
Horst Lindhofer, Michael Stanglmaier, Raymund Buhmann, Michael Jäger, Daniel Klunker, Peter Ruf, and Juergen Hess
- 52 **Cetuximab (Erbixub)** 1501
Sonja Wilke and Michael Hust
- 53 **Denosumab (Prolia®)** 1521
Torsten Meyer

- 54 **Efalizumab (Raptiva)** 1531
Karlheinz Schmitt-Rau
- 55 **Calicheamicin Conjugates: Gemtuzumab Ozogamicin (Mylotarg), Inotuzumab Ozogamicin** 1545
Matthias Peipp and Martin Gramatzki
- 56 **Golimumab (Simponi®)** 1565
Sohini Mazumdar and Janice M. Reichert
- 57 **Yttrium-90 Ibritumomab Tiuxetan (Zevalin®)** 1579
Karin Hohloch, Björn Chapuy, and Lorenz Trümper
- 58 **Infliximab (Remicade®)** 1599
Christian Antoni and Maria Wiekowski
- 59 **Ipilimumab (Yervoy®)** 1619
Teresa Alonso Gordo, Javier Puente Vázquez, and Eduardo Díaz-Rubio
- 60 **Muromonab-CD3 (Orthoclone OKT®3)** 1645
Harald Becker and Janice M. Reichert
- 61 **Nimotuzumab: A Humanized Anti-EGFR Antibody** 1679
Tania Crombet Ramos
- 62 **Obinutuzumab (Gazyva®), a Novel Glycoengineered Type II CD20 Antibody for the Treatment of Chronic Lymphocytic Leukemia and Non-Hodgkin's Lymphoma** 1695
Christian Klein, Marina Bacac, Pablo Umaña, and Michael Wenger

Volume IV: Approved Therapeutic Antibodies and in vivo Diagnostics

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

- 63 **Ofatumumab (Arzerra®): a Next-Generation Human Therapeutic CD20 Antibody with Potent Complement-Dependent Cytotoxicity** 1733
Margaret A. Lindorfer, Joost M. Bakker, Paul W.H.I. Parren, and Ronald P. Taylor

- 64 **Omalizumab (Xolair) – Anti-Immunoglobulin E Treatment in Allergic Diseases** 1775
Claus Kroegel and Martin Foerster
- 65 **Palivizumab (Synagis®)** 1825
Louis Bont
- 66 **Panitumumab (Vectibix®): A Treatment for Metastatic Colorectal Cancer** 1855
Jonas Kügler
- 67 **Pertuzumab (Perjeta®)** 1871
Jose Angel García-Saénz, Fernando Moreno Anton, and Coralía Bueno Muiño
- 68 **Ranibizumab (Lucentis): a New Anti-Angiogenic Treatment in Ophthalmology** 1883
Nicolas Leveziel, Marc Ohresser, and Gilles Paintaud
- 69 **Raxibacumab, Human Monoclonal Antibody against Anthrax Toxin** 1899
Sally D. Bolmer and Thi-Sau Migone
- 70 **Rituximab (Rituxan®)** 1909
Axel Böhnke and Michael Wenger
- 71 **Tocilizumab (Actemra®)** 2023
Graeme Jones and Changhai Ding
- 72 **Trastuzumab (Herceptin®) and Ado-Trastuzumab Emtansine (Kadcyla®): Treatments for HER2-Positive Breast Cancer** 2041
Ruhe Chowdhury and Paul Ellis
- 73 **Ustekinumab (Stelara®)** 2069
Oya Cingoz, Stefan Dübel, and Janice M. Reichert
- 74 **Abciximab (Reopro®), Bevacizumab (Avastin®), Certolizumab Pegol (Cimzia®), Eculizumab (Soliris®), Natalizumab (Tysabri®)** 2087
Janice M. Reichert
- 75 **Itolizumab (Alzumab®), Mogamulizumab (Poteligeo®), and Tositumomab (Bexxar®)** 2113
Stefan Dübel

Part VIII: In vivo Diagnostics 2071

76 Radiolabeled Antibodies for Diagnostic Imaging 2123

Christopher J. Palestro

Index 2143

Contents

Volume I: Defining the Right Antibody Composition

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

- 1 **Therapeutic Antibodies – from Past to Future** 1
Stefan Dübel and Janice M. Reichert
- Part I: Selecting and Shaping the Antibody Molecule** 15
- 2 **Selection Strategies for Monoclonal Antibodies** 17
Gerhard Moldenhauer
- 3 **Antibody Phage Display** 43
Michael Hust, André Frenzel, Florian Tomszak, Jonas Kügler, and Stefan Dübel
- 4 **Transgenic Animals Derived by DNA Microinjection** 77
Marianne Brüggemann, Michael J. Osborn, Biao Ma, Suzanne Avis, Ignacio Anegón, and Roland Buelow
- 5 **Humanization Strategies** 89
José W. Saldanha
- 6 **Antibody Affinity** 115
André Frenzel, Lorin Roskos, Scott Klakamp, Meina Liang, Rosalin Arends, and Larry Green

- 7 Fc Engineering 141**
Matthias Peipp, Stefanie Derer, Stefan Lohse, Christian Kellner, and Thomas Valerius
- 8 Glycosylation of Antibody Molecules 171**
Roy Jefferis
- 9 Bioinformatics Tools for Analysis of Antibodies 201**
Andrew C.R. Martin and James Allen
- Part II: Modified Antibodies 265**
- 11 Bispecific Antibodies 267**
Dafne Müller and Roland E. Kontermann
- 12 Single-Domain Antibodies: An Overview 311**
Carrie Enever, Edward Coulstock, Malgorzata Pupecka-Swider, and Bruce Hamilton
- 13 Antibody–Drug Conjugates: New Frontier in Cancer Therapeutics 341**
Rajeeva Singh, John M. Lambert, and Ravi V. J. Chari
- 14 Antibody-Targeted Drugs: From Chemical Immunoconjugates to Recombinant Fusion Proteins 363**
Athanasios Mavratzas, Michaela A.E. Arndt, Stefan Kiesgen, and Jürgen Krauss
- Part III: Emerging Technologies 391**
- 15 Emerging Technologies for Antibody Selection 393**
Mingyue He and Michael J. Taussig
- 16 Anti-Idiotypic Antibodies 407**
Alejandro López-Requena, Oscar R. Burrone, and Rolando Pérez
- 17 Non-Antibody Scaffolds as Alternative Therapeutic Agents 435**
Markus Fiedler and Arne Skerra
- 18 Antibody-Directed Enzyme Prodrug Therapy (ADEPT) 475**
Surinder K. Sharma, Kerry A. Chester and Kenneth D. Bagshawe
- 19 Engineered Antibody Domains as Candidate Therapeutics 487**
Weizao Chen, Ponraj Prabakaran, and Dimiter S. Dimitrov

- 20 **Chimeric Antigen Receptors –“CARs”** 519
Ulf Petrausch and Thomas Schirrmann
- 21 **Emerging Alternative Production Systems** 561
Benjamin Sommer, Holger Laux, Andre Frenzel, and Thomas Jostock
- Volume II: Clinical Development of Antibodies**
- Quick Reference List of Antibodies by International Nonproprietary Name** XXIII
- Quick Reference List of Antibodies by Brand Name** XXV
- A Greeting by the Editors** XXVII
- Foreword to the First Edition** XXIX
- Foreword to the Second Edition** XXXI
- List of Contributors** XXXIII
- Abbreviations** LI
- Appendix: Marketed Monoclonal Antibodies Compendium** LXXXIII
- Part IV: The Way into the Clinic** 601
- 22 **Process Development and Manufacturing of Therapeutic Antibodies** 603
Alexander Jacobi, Barbara Enenkel, Patrick Garidel, Christian Eckermann, Mathias Knappenberger, Ingo Presser, and Hitto Kaufmann
- 23 **The Immunogenicity of Therapeutic Antibodies** 665
Melody Sauerborn
- 24 **Biosimilar Monoclonal Antibodies** 681
Susanne D. Pippig, Carsten Brockmeyer, and Robert E. Zoubek
- 25 **Patent Issues Relating to Therapeutic Antibodies** 705
Barbara Rigby, Michael Braunagel, and Deborah Owen
- Part V: Therapeutic Antibody Pipeline** 735
- 26 **Monoclonal Antibody Cancer Treatments in Phase III Clinical Trials** 737
Ulf Petrausch and Peter Markus Deckert
- 27 **Antibodies in Cancer Treatment: Early Clinical Development** 787
Matthew Zibelman, Hossein Borghaei, and Anthony J. Olszanski
- 28 **Targeting Angiogenesis by Therapeutic Antibodies** 823
Onat Kadioglu, Ean Jeong Seo, and Thomas Efferth

- 29 **Antibodies in Phase III Studies for Immunological Disorders** 851
Penelope Ward and Mark Bodmer
- 30 **Monoclonal Antibodies in Phase 1 and 2 Studies for Immunological Disorders** 927
Frank R. Brennan
- 31 **MABs Targeting Soluble Mediators in Phase 1 and 2 Clinical Studies Immunological Disorders** 969
Frank R. Brennan
- 32 **T Cell Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders** 1079
Frank R. Brennan
- 33 **B-Cell Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders** 1115
Frank R. Brennan
- 34 **Inhibitors of Leukocyte Adhesion and Migration in Phase 1 and 2 Clinical Studies for Immunological Disorders** 1127
Frank R. Brennan
- 35 **Toll-Like Receptor Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders** 1145
Frank R. Brennan
- 36 **IgE Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders** 1159
Frank R. Brennan
- 37 **Complement Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders** 1165
Frank R. Brennan
- 38 **mAbs Targeting Apoptosis, Angiogenesis Inhibitors, and Other mAbs in Phase 1 and 2 Clinical Studies for Immunological Disorders** 1175
Frank R. Brennan
- 39 ***In vitro* Studies and Clinical Trials about Monoclonal Antibodies Used in Infectiology** 1195
Guillaume Desoubeaux
- 40 **Immunotherapeutics for Neurological Disorders** 1215
Anne Messer, Kevin Manley, and Cynthia A. Lemere

Part VI: Gaining Marketing Approval 1231

- 41 Regulatory Considerations in the Development of Monoclonal Antibodies for Diagnosis and Therapy 1233**
Marjorie A. Shapiro, Patrick G. Swann, and M. Stacey Ricci
- 42 Regulatory Review: Clinical to Market Transition 1263**
Gabriele Dallmann
- 43 Monoclonal Antibody Nomenclature for Clinical Studies (USA) 1283**
Stephanie C. Shubat

Volume III: Approved Therapeutic Antibodies

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

Part VII: Approved Therapeutic Antibodies 1289

- 44 Oligoclonal and Polyclonal Antibody Preparations 1291**
Rishab K. Gupta and Mark C. Glassy
- 44.1 Introduction 1291
- 44.2 Oligoclonal Antibodies 1291
- 44.3 General Questions/Concerns 1293
- 44.4 Uses/Applications of Oligoclonal Antibodies 1293
- 44.5 Infectious Disease 1295
- 44.5.1 Virology 1295
- 44.5.2 Cancer 1295
- 44.6 FDA/Regulatory Considerations 1295
- 44.7 Polyclonal Antibodies 1296
- 44.8 Production of Polyclonal Antibodies 1297
- 44.9 Immunogen Properties and Preparations 1298
- 44.10 Carrier Proteins for Immunogen Preparation 1298
- 44.11 Choice of Animal 1299
- 44.12 Adjuvants 1299
- 44.13 Route of Injection 1300
- 44.14 Collecting and Processing of Blood 1300
- 44.15 Antibody Purification 1300

44.16	Polyclonal Antibody Derives Therapeutics (Clinical Utility)	1301
44.17	Recombinant Polyclonal Antibodies	1302
44.18	Summary	1303
	References	1304
45	Adalimumab (Humira®)	1309
	<i>Janice M. Reichert</i>	
45.1	Overview	1309
45.2	Basic Principles of Clinical Use	1310
45.3	Safety	1310
45.4	Use in Approved Indications	1312
45.5	Clinical Studies in Intestinal Behçet Disease	1313
45.6	Clinical Studies in Uveitis	1314
45.7	Clinical Studies in Hidradenitis Suppurativa	1316
45.8	Early-Stage Clinical Studies in Sarcoidosis	1318
	References	1319
46	Alemtuzumab (Lemtrada, MabCampath)	1323
	<i>Thomas Elter, Michael Hallek, and Janice M. Reichert</i>	
46.1	Overview	1323
46.2	Basic Principles	1324
46.3	Antibody Features and Production	1324
46.4	Molecular Target and Target Expression	1325
46.5	Mechanism of Cell Lysis	1327
46.6	Immunogenicity and Antiglobulin Response	1328
46.7	Pharmacokinetic Studies	1329
46.8	Clinical Studies in Chronic Lymphocytic Leukemia (CLL)	1330
46.8.1	Relapsed/Refractory CLL	1330
46.8.2	Minimal Residual Disease in CLL	1336
46.8.3	Treatment-Naive CLL	1338
46.8.3.1	Chemoimmunotherapy Combinations	1339
46.8.3.2	Immunotherapy Combination	1342
46.8.4	Safety of Alemtuzumab in CLL	1343
46.8.4.1	Infusion-Related Adverse Events	1343
46.8.4.2	Hematologic Toxicities	1344
46.8.4.3	Immunosuppression and Infectious Events	1346
46.9	Clinical Studies in Multiple Sclerosis	1347
46.10	Clinical Studies in Other Indications	1353
46.10.1	T-Cell Lymphomas (Cutaneous/Peripheral T-Cell Lymphoma)	1353
46.10.2	T-Cell Prolymphocytic Leukemia (T-PLL)	1355
46.10.3	Adult T-Cell Leukemia	1356
46.10.4	Non-Hodgkin's Lymphoma (NHL)	1357
46.10.5	Multiple Myeloma and Acute Leukemias	1359
46.10.6	Rheumatoid Arthritis	1359

- 46.10.7 Donor T-Cell Depletion (Prevention of GvHD) and Prevention of Graft Rejection 1360
- 46.10.7.1 Reduced-Intensity/Nonmyeloablative Conditioning 1361
- 46.10.7.2 Safety 1363
- 46.10.7.3 Prevention of GvHD in Solid Organ Transplantation 1363
References 1365
- 47 Basiliximab (Simulect®) and Daclizumab (Zenapax®) 1375**
Nadim Mahmud, Burcin Taner, and Nasimul Ahsan
- 47.1 Background 1375
- 47.1.1 Solid Organ Transplantation and IL-2R-Based Therapy 1377
- 47.2 Clinical Use in Human Organ Transplantation 1378
- 47.2.1 Renal Transplantation 1378
- 47.2.1.1 IL-2R Monoclonal Antibodies versus Placebo 1378
- 47.2.1.2 Basiliximab versus Other Lymphocyte-Depleting Agents 1379
- 47.2.1.3 Modified-Dose Daclizumab Studies 1379
- 47.2.1.4 Steroid-Sparing Protocols 1380
- 47.2.1.5 Calcineurin Inhibitor-Sparing Protocols 1381
- 47.2.1.6 Basiliximab versus Daclizumab 1382
- 47.2.2 Applications in Adult Non-renal Transplantation 1383
- 47.2.2.1 Liver 1383
- 47.2.2.2 Lung 1385
- 47.2.2.3 Heart 1386
- 47.2.2.4 Pancreas 1387
- 47.3 Clinical Use of IL-2R Antibodies in Non-organ Transplant Conditions 1388
- 47.3.1 Multiple Sclerosis 1388
- 47.3.2 Adult T-Cell Leukemia 1392
- 47.3.3 Tropical Spastic Paraparesis and HTLV-Associated Myelopathy 1393
- 47.3.4 Noninfectious Ocular Inflammatory Disease (Uveitis) 1393
- 47.3.5 Age-Related Macular Degeneration 1394
- 47.3.6 Graft Versus Host Disease 1394
- 47.4 Conclusion 1395
References 1396
- 48 Belimumab (Benlysta®) 1405**
Pamela M. K Lutalo, Natasha Jordan, Thi-Sau Migone, and David P. D'Cruz
- 48.1 Introduction 1405
- 48.2 Basic Principles 1405
- 48.3 Clinical Aspects of Belimumab Therapy 1407
- 48.3.1 Belimumab Clinical Trial Data 1407
- 48.3.2 Safety of Belimumab in Clinical Practice 1409
- 48.3.2.1 Common Side Effects 1409
- 48.3.3 Hypersensitivity Adverse Events 1410

48.3.4	Immunosuppression-Related Adverse Events	1410
48.3.5	Malignancy Adverse Events	1410
48.3.6	Reproduction Adverse Events	1411
48.3.7	Psychiatric Adverse Events	1411
48.3.8	Mortality Adverse Events	1411
48.3.9	New Belimumab Clinical Trials	1411
48.4	Summary	1413
	List of abbreviations	1413
	References	1414
49	Brentuximab Vedotin (Adcetris®) for the Treatment of CD30-Positive Hematologic Malignancies	1417
	<i>Niels W.C.J. van de Donk and Eugen Dhimolea</i>	
49.1	Introduction	1417
49.2	CD30	1418
49.3	Preclinical Activity of Brentuximab Vedotin	1419
49.4	Clinical Development of Brentuximab Vedotin	1420
49.4.1	Hodgkin Lymphoma	1420
49.4.1.1	Brentuximab Vedotin in Relapsed/Refractory Hodgkin Lymphoma	1421
49.4.1.2	Brentuximab Vedotin Before or After Auto-SCT	1427
49.4.1.3	Allogeneic Transplant Following Brentuximab Vedotin	1427
49.4.1.4	Brentuximab Vedotin in Newly Diagnosed Hodgkin Lymphoma	1429
49.4.2	Systemic Anaplastic Large Cell Lymphoma	1432
49.4.2.1	Brentuximab Vedotin in Relapsed/Refractory Anaplastic Large Cell Lymphoma	1432
49.4.2.2	Brentuximab Vedotin in Newly Diagnosed Anaplastic Large Cell Lymphoma	1433
49.4.3	Primary Cutaneous CD30-Positive Lymphoproliferative Disorders	1433
49.4.3.1	Brentuximab for the Treatment of Primary Cutaneous CD30-Positive Lymphoproliferative Disorders	1435
49.4.4	Other CD30-Positive Hematologic Malignancies	1435
49.5	Future Perspectives	1435
	Acknowledgments	1437
	References	1437
50	Canakinumab (ILARIS®)	1445
	<i>Hermann Gram</i>	
50.1	Introduction	1445
50.2	Production, Pharmacology, and Pharmacokinetics of Canakinumab	1446
50.2.1	Marketed Drug Product	1446
50.3	Clinical Trials	1447

- 50.3.1 Cryopyrin-Associated Periodic Syndrome (CAPS) 1448
- 50.3.2 Gouty Arthritis 1450
- 50.3.3 Systemic Juvenile Idiopathic Arthritis (sJIA) 1452
- 50.3.4 Rheumatoid Arthritis 1454
- 50.3.5 Type II Diabetes 1456
- 50.3.6 Cardiovascular Risk 1457
- 50.4 Outlook and Summary 1458
- References 1458

- 51 Catumaxomab (Removab) – Trifunctional Antibodies: Combining Direct Tumor Cell Killing with Therapeutic Vaccination 1463**
Horst Lindhofer, Michael Stanglmaier, Raymund Buhmann, Michael Jäger, Daniel Klunker, Peter Ruf, and Juergen Hess
- 51.1 Introduction 1463
- 51.1.1 Bispecific Antibodies Revisited 1464
- 51.1.2 Focus on the trAb Immunogenicity in the World of Human(ized) bsAb Formats 1466
- 51.2 Manufacturing of trAbs 1467
- 51.3 The Mode of Action of trAbs in Tumor Treatment 1468
- 51.3.1 The Role of the Fc Region 1470
- 51.3.2 Vaccination-Like Effects Evoked by trAbs 1470
- 51.3.3 TrAbs Can Be Combined with Chemotherapy and Eliminate Tumor Cells with Low Target Antigen Expression 1473
- 51.4 From Bench to Bedside with the Triomab® trAb Family 1474
- 51.4.1 Anti-EpCAM × Anti-CD3 Catumaxomab for Malignant Ascites Treatment 1474
- 51.4.1.1 Systemic Treatment Outcome of Catumaxomab with Locoregional Administration 1478
- 51.4.1.2 Catumaxomab-Based Treatment Regimes Against Peritoneal Carcinomatosis 1479
- 51.4.1.3 With Catumaxomab toward Gastric Cancer Treatment 1480
- 51.4.1.4 Intra- and Postoperative Application of Catumaxomab in Patients with Ovarian Cancer 1481
- 51.4.2 Anti-HER2/neu × Anti-CD3 Ertumaxomab 1482
- 51.4.3 Anti-CD20 × Anti-CD3 Lymphomun 1484
- 51.4.4 Anti-GD2 × Anti-CD3 Ektomab 1488
- 51.5 Potential Biomarkers Along trAb Treatment Concept 1490
- 51.5.1 First Indicator for the Therapeutic Outcome: Development of Humoral ADA Responses 1490
- 51.5.2 Initial Relative Lymphocyte Count as Pretherapeutic Indicator for Treatment Success 1491
- 51.6 Concluding Remarks 1491
- Acknowledgments 1492
- References 1492

- 52 Cetuximab (Erbix)[®]** 1501
Sonja Wilke and Michael Hust
- 52.1 Nature, Role in Disease, Biology of the Target 1501
 - 52.1.1 Biochemistry and Biology of Epidermal Growth Factor Receptor (EGFR) 1501
 - 52.1.2 Role in Cancer 1502
 - 52.2 Origin and Development of Erbitux 1503
 - 52.2.1 Monoclonal Antibody 225 1503
 - 52.2.2 Chimerization 1503
 - 52.3 Mechanism of Action 1503
 - 52.3.1 Cetuximab Mechanism of Action 1503
 - 52.3.2 KRAS and Cetuximab 1505
 - 52.4 Preclinical and Clinical Results 1506
 - 52.4.1 Preclinical Results 1506
 - 52.4.2 Clinical Results for Colon Cancer 1506
 - 52.4.2.1 Monotherapy 1506
 - 52.4.2.2 Combination Therapy 1507
 - 52.4.3 Clinical Results for SCCHN 1509
 - 52.4.3.1 Monotherapy 1509
 - 52.4.3.2 Combination Therapy 1509
 - 52.4.4 Clinical Results for NSCLC 1510
 - 52.4.4.1 Monotherapy 1510
 - 52.4.4.2 Combination Therapy 1510
 - 52.4.5 Clinical Results of Other Tumors 1511
 - 52.5 Production 1511
 - 52.6 Cetuximab in Clinics 1511
 - 52.7 Outlook 1512
 - References 1512
 - Websites 1520
- 53 Denosumab (Prolia)[®]** 1521
Torsten Meyer
- 53.1 Introduction 1521
 - 53.2 Clinical Studies 1522
 - 53.2.1 Phase 1 Study 1522
 - 53.2.2 Phase 2 Study 1523
 - 53.2.3 Phase 3 Studies 1524
 - 53.2.3.1 Phase 3 Study FREEDOM 1524
 - 53.2.3.2 Phase 3 Study STAND 1525
 - 53.2.3.3 Phase 3 Study HALT 1526
 - 53.3 Guidelines of the FDA (Website of FDA) for Denosumab (Prolia) 1526
 - 53.3.1 Guidelines of the FDA (Website of FDA) for Denosumab (Xgeva) 1527
 - 53.4 Summary and Outlook 1527

References 1527

Websites 1529

54 Efalizumab (Raptiva) 1531*Karlheinz Schmitt-Rau*

54.1 Introduction 1531

54.2 Development and Characterization of the Antibody 1531

54.3 Efalizumab in the Treatment of Psoriasis 1533

54.3.1 Psoriasis: Prevalence, Characteristics, and Therapeutic Options 1533

54.3.2 Pathogenesis of Psoriasis 1533

54.3.2.1 T-Cell Activation 1533

54.3.2.2 T-Cell Migration and Extravasation 1534

54.3.2.3 T-Cell Reactivation 1534

54.3.3 Efalizumab: Mechanism of Action 1535

54.4 Pharmacology and Toxicology of Efalizumab 1535

54.4.1 Preclinical Studies 1535

54.4.2 Pharmacodynamics 1536

54.4.3 Pharmacokinetics 1537

54.5 Clinical Development of Efalizumab 1538

54.5.1 Randomized, Placebo-Controlled, Double-Blind Studies 1538

54.5.2 Long-Term Efficacy 1538

54.6 Health-Related Quality of Life (HRQoL) 1539

54.7 Safety and Tolerability 1539

54.8 Efalizumab: Reassessment of Benefit–Risk Ratio and Suspension of Marketing Authorization 1540

References 1541

55 Calicheamicin Conjugates: Gemtuzumab Ozogamicin (Mylotarg), Inotuzumab Ozogamicin 1545*Matthias Peipp and Martin Gramatzki*

55.1 Introduction 1545

55.2 Target Antigen Selection in Therapy with ADC 1546

55.2.1 CD33 in AML 1546

55.2.2 CD22 Expression in B-Cell Neoplasias 1547

55.3 Conjugate Design/Preclinical Activity 1548

55.3.1 Gemtuzumab Ozogamicin 1548

55.3.2 Inotuzumab Ozogamicin 1549

55.3.3 The IgG4 Moiety 1549

55.3.4 Calicheamicin 1549

55.3.5 Design of Antibody–Calicheamicin Conjugates, Choice of Linker 1550

55.4 Mechanisms of Action 1552

55.5 Potential Mechanisms of Resistance 1552

55.6 Clinical Trials 1553

55.6.1 Gemtuzumab Ozogamicin (GO) 1553

55.6.2	Inotuzumab Ozogamicin	1555
55.7	Summary and Conclusions	1556
	References	1556
56	Golimumab (Simponi®)	1565
	<i>Sohini Mazumdar and Janice M. Reichert</i>	
56.1	Introduction	1565
56.2	Characterization and Preclinical Evaluation	1568
56.3	First-in-Humans Study	1568
56.4	Pivotal Clinical Studies	1569
56.4.1	Rheumatoid Arthritis	1569
56.4.1.1	GO-FORWARD, GO-AFTER, and GO-BEFORE Studies in RA Patients	1570
56.4.2	Psoriatic Arthritis	1571
56.4.3	Ankylosing Spondylitis	1572
56.4.4	Ulcerative Colitis	1573
56.4.5	Ongoing Clinical Study in Juvenile Idiopathic Arthritis	1574
56.5	Market Competitors	1575
	References	1575
57	Yttrium-90 Ibritumomab Tiuxetan (Zevalin®)	1579
	<i>Karin Hohloch, Björn Chapuy, and Lorenz Trümper</i>	
57.1	Introduction	1579
57.1.1	Epidemiology of Non-Hodgkin's Lymphoma	1579
57.1.2	Standard Therapy of NHL	1580
57.1.3	CD20-Targeted Immunotherapy of NHL	1580
57.2	Basic Principles of Radioimmunotherapy	1581
57.3	Development and Advantages of ⁹⁰ Y-Ibritumomab Tiuxetan	1582
57.3.1	Preparation of ⁹⁰ Y-Ibritumomab Tiuxetan	1582
57.3.2	Dosing of ⁹⁰ Y-Ibritumomab Tiuxetan	1584
57.4	Preclinical and Clinical Results	1585
57.4.1	Preclinical Results	1585
57.4.2	Clinical Therapeutic Efficacy	1585
57.4.3	Adverse Events	1586
57.4.4	Considerations for the Use of ⁹⁰ Y-Ibritumomab Tiuxetan	1587
57.5	Outlook	1588
57.5.1	Novel Indications	1588
57.5.1.1	Aggressive (DLBCL) NHL	1588
57.5.1.2	RIT in Mantle Cell Lymphoma	1588
57.5.2	Combination Therapy	1589
57.5.3	⁹⁰ Y-Ibritumomab Tiuxetan Consolidation of Frontline Chemotherapy	1589
57.5.4	⁹⁰ Y-Ibritumomab Tiuxetan as Conditioning Regimen for Stem Cell Transplantation	1590
	References	1592

- 58 *Infliximab (Remicade®)* 1599**
Christian Antoni and Maria Wiekowski
- 58.1 Antibody Characteristics 1599
 - 58.2 Preclinical Characterization 1600
 - 58.3 Pharmacokinetics 1600
 - 58.4 Clinical Response 1601
 - 58.4.1 Therapeutic Indications 1601
 - 58.4.1.1 Crohn's Disease 1602
 - 58.4.1.2 Rheumatoid Arthritis 1603
 - 58.4.1.3 Ankylosing Spondylitis 1605
 - 58.4.1.4 Psoriatic Arthritis 1606
 - 58.4.1.5 Psoriasis 1607
 - 58.4.1.6 Ulcerative Colitis 1608
 - 58.4.1.7 Pediatric Ulcerative Colitis 1609
 - 58.5 Safety 1609
 - 58.5.1 Serious Infections 1609
 - 58.5.2 Antibody Formation against Infliximab 1611
 - 58.5.3 Infusion Reactions/Delayed Hypersensitivity Reactions 1611
 - 58.5.4 Autoantibody Formation 1612
 - 58.5.5 Neurological Disorders/Demyelinating Disease 1612
 - 58.5.6 Malignancies/Lymphoma 1612
 - 58.5.7 Congestive Heart Failure 1613
 - 58.5.8 Other Adverse Events (Hepatic Events and Pregnancy Outcome) 1613
 - 58.6 Summary 1614
 - References 1614
- 59 *Ipilimumab (Yervoy®)* 1619**
Teresa Alonso Gordo, Javier Puente Vázquez, and Eduardo Díaz-Rubio
- 59.1 Introduction 1619
 - 59.2 Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) 1620
 - 59.3 Ipilimumab, Mechanism of Action 1621
 - 59.4 Pharmacokinetics 1622
 - 59.5 Melanoma 1622
 - 59.5.1 Initial Phase II Trials 1623
 - 59.5.2 Phase II Studies 1625
 - 59.5.3 Phase III Trials 1628
 - 59.5.4 Long Responders 1629
 - 59.5.5 Searching for Biomarkers 1630
 - 59.6 Prostate Cancer 1631
 - 59.7 Lung Cancer 1633
 - 59.8 Patterns of Response with Ipilimumab (Immune-Related Response Criteria) 1634
 - 59.9 Adverse Events 1636

- 59.10 Conclusions 1641
- References 1641

- 60 Muromonab-CD3 (Orthoclone OKT®3) 1645**
Harald Becker and Janice M. Reichert
- 60.1 Introduction 1645
- 60.2 Production of mAbs 1646
- 60.3 Pharmacology of Muromonab-CD3 1647
- 60.3.1 Pharmacokinetic Properties of Muromonab-CD3 1648
- 60.3.2 Pharmacodynamics of Muromonab-CD3 1649
- 60.3.3 Activation of Human T Cells 1650
- 60.3.4 Immunogenicity 1650
- 60.3.5 Interactions 1651
- 60.4 Therapeutic Use 1652
- 60.4.1 Renal and or Renal–Pancreas Transplant Recipients 1656
- 60.4.2 Liver Transplant Recipients 1659
- 60.4.3 Cardiac Transplant Recipients 1659
- 60.5 Cytokine Release Syndrome 1659
- 60.5.1 Pathophysiology of Cytokine Release Syndrome 1662
- 60.5.2 Symptoms of Cytokine Release Syndrome 1663
- 60.5.3 Muromonab-CD3 and Cytokine Release Syndrome 1665
- 60.5.4 Management of Cytokine Release Syndrome 1666
- 60.5.4.1 Methylprednisolone 1666
- 60.5.4.2 Pentoxifylline 1668
- 60.5.4.3 Indomethacin 1669
- 60.5.4.4 Recombinant Human Soluble Tumor Necrosis Factor Receptor 1669
- 60.5.4.5 Anti-TNF mAbs 1670
- 60.6 Consequences of Immunosuppression 1670
- 60.6.1 Infections 1670
- 60.6.2 Neoplasia 1671
- 60.7 Withdrawal from the Market 1672
- References 1672

- 61 Nimotuzumab: A Humanized Anti-EGFR Antibody 1679**
Tania Crombet Ramos
- 61.1 Overview 1679
- 61.2 Head and Neck 1679
- 61.3 Glioma 1682
- 61.4 Pediatric Glioma 1684
- 61.5 Esophageal and Gastric Cancer 1684
- 61.6 Pancreatic Cancer 1685
- 61.7 Non-Small Cell Lung Cancer (NSCLC) 1686
- 61.7.1 Patient Selection 1687
- 61.7.2 Optimal Duration of Therapy 1688
- 61.7.3 Pharmacodynamic Evaluation 1689

- 61.7.4 Safety 1690
- 61.8 Concluding Remarks 1690
References 1690
- 62 Obinutuzumab (Gazyva®), a Novel Glycoengineered Type II CD20 Antibody for the Treatment of Chronic Lymphocytic Leukemia and Non-Hodgkin's Lymphoma 1695**
Christian Klein, Marina Bacac, Pablo Umaña, and Michael Wenger
- 62.1 *In vitro* Mechanism of Action of Type I and Type II CD20 Antibodies 1695
- 62.2 Generation of Obinutuzumab 1697
- 62.3 Obinutuzumab is a Classical Type II CD20 Antibody 1698
- 62.4 The Epitope Recognized by Obinutuzumab 1699
- 62.5 CDC Activity of Obinutuzumab 1701
- 62.6 Direct Cell Death Induction by Obinutuzumab 1702
- 62.7 Glycoengineering of Obinutuzumab 1704
- 62.8 *In vitro* NK Cell and Neutrophil ADCC and Macrophage ADCP Activity of Obinutuzumab 1706
- 62.9 *Ex vivo* Whole Blood B-Cell Depletion by Obinutuzumab 1708
- 62.10 *In vivo* Activity of Obinutuzumab in Xenograft Models 1709
- 62.11 *In vivo* Activity of Obinutuzumab in Combination with Chemotherapy, Bcl-2, and MDM2 Inhibitors 1712
- 62.12 B-Cell Depletion by Obinutuzumab in Cynomolgus Monkeys 1713
- 62.13 Conclusion from Nonclinical Pharmacology Studies with Obinutuzumab 1714
- 62.14 Clinical Experiences with Obinutuzumab 1715
- 62.15 Early Clinical Experience with Obinutuzumab in B-Cell Lymphoma 1715
- 62.15.1 BO20999 Phase 1 1715
- 62.15.2 BO21003 Phase I 1715
- 62.15.3 JO21900 1717
- 62.16 Phase Ib and II Experience with Obinutuzumab in B-Cell Lymphoma 1717
- 62.16.1 BO20999 Randomized Phase II in Indolent B-Cell Lymphoma 1717
- 62.16.2 BO21003 Randomized Phase II in Indolent Lymphoma 1718
- 62.16.3 BO20999 Randomized Phase II in Aggressive B-Cell Lymphoma 1719
- 62.16.4 BO21000 Randomized Phase II with Chemotherapy in Relapsed/Refractory Indolent B-Cell Lymphoma 1720
- 62.16.5 BO21000 Randomized Phase II with Chemotherapy in Previously Untreated Indolent B-Cell Lymphoma 1720
- 62.17 Phase III Studies with Obinutuzumab in B-Cell Lymphoma 1721
- 62.18 Obinutuzumab in CLL: Early Experience and Ongoing Phase II Studies 1722

- 62.19 Phase III Experience with Obinutuzumab: The CLL11 Trial 1722
References 1723

Volume IV: Approved Therapeutic Antibodies and in vivo Diagnostics

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

- 63 **Ofatumumab (Arzerra®): a Next-Generation Human Therapeutic CD20 Antibody with Potent Complement-Dependent Cytotoxicity** 1733
Margaret A. Lindorfer, Joost M. Bakker, Paul W.H.I. Parren, and Ronald P. Taylor
- 64 **Omalizumab (Xolair) – Anti-Immunoglobulin E Treatment in Allergic Diseases** 1775
Claus Kroegel and Martin Foerster
- 65 **Palivizumab (Synagis®)** 1825
Louis Bont
- 66 **Panitumumab (Vectibix®): A Treatment for Metastatic Colorectal Cancer** 1855
Jonas Kügler
- 67 **Pertuzumab (Perjeta®)** 1871
Jose Angel García-Saénz, Fernando Moreno Anton, and Coralía Bueno Muiño
- 68 **Ranibizumab (Lucentis): a New Anti-Angiogenic Treatment in Ophthalmology** 1883
Nicolas Leveziel, Marc Ohresser, and Gilles Paintaud
- 69 **Raxibacumab, Human Monoclonal Antibody against Anthrax Toxin** 1899
Sally D. Bolmer and Thi-Sau Migone

- 70 **Rituximab (Rituxan®)** 1909
Axel Böhnke and Michael Wenger
- 71 **Tocilizumab (Actemra®)** 2023
Graeme Jones and Changhai Ding
- 72 **Trastuzumab (Herceptin®) and Ado-Trastuzumab Emtansine (Kadcyla®): Treatments for HER2-Positive Breast Cancer** 2041
Ruhe Chowdhury and Paul Ellis
- 73 **Ustekinumab (Stelara®)** 2069
Oya Cingoz, Stefan Dübel, and Janice M. Reichert
- 74 **Abciximab (Reopro®), Bevacizumab (Avastin®), Certolizumab Pegol (Cimzia®), Eculizumab (Soliris®), Natalizumab (Tysabri®)** 2087
Janice M. Reichert
- 75 **Itolizumab (Alzumab®), Mogamulizumab (Poteligeo®), and Tositumomab (Bexxar®)** 2063
Stefan Dübel
- Part VIII: In vivo Diagnostics** 2121
- 76 **Radiolabeled Antibodies for Diagnostic Imaging** 2123
Christopher J. Palestro
- Index** 2143

Contents

Volume I: Defining the Right Antibody Composition

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

- 1 **Therapeutic Antibodies – from Past to Future** 1
Stefan Dübel and Janice M. Reichert
- Part I: Selecting and Shaping the Antibody Molecule** 15
- 2 **Selection Strategies for Monoclonal Antibodies** 17
Gerhard Moldenhauer
- 3 **Antibody Phage Display** 43
Michael Hust, André Frenzel, Florian Tomszak, Jonas Kügler, and Stefan Dübel
- 4 **Transgenic Animals Derived by DNA Microinjection** 77
Marianne Brüggemann, Michael J. Osborn, Biao Ma, Suzanne Avis, Ignacio Anegón, and Roland Buelow
- 5 **Humanization Strategies** 89
José W. Saldanha
- 6 **Antibody Affinity** 115
André Frenzel, Lorin Roskos, Scott Klakamp, Meina Liang, Rosalin Arends, and Larry Green

- 7 Fc Engineering 141**
Matthias Peipp, Stefanie Derer, Stefan Lohse, Christian Kellner, and Thomas Valerius
- 8 Glycosylation of Antibody Molecules 171**
Roy Jefferis
- 9 Bioinformatics Tools for Analysis of Antibodies 201**
Andrew C.R. Martin and James Allen
- 10 How to Use IMGT[®] for Therapeutic Antibody Engineering 229**
Marie-Paule Lefranc
- Part II: Modified Antibodies 265**
- 11 Bispecific Antibodies 267**
Dafne Müller and Roland E. Kontermann
- 12 Single-Domain Antibodies: An Overview 311**
Carrie Enever, Edward Coulstock, Malgorzata Pupecka-Swider, and Bruce Hamilton
- 13 Antibody–Drug Conjugates: New Frontier in Cancer Therapeutics 341**
Rajeeva Singh, John M. Lambert, and Ravi V. J. Chari
- 14 Antibody-Targeted Drugs: From Chemical Immunoconjugates to Recombinant Fusion Proteins 363**
Athanasios Mavratzas, Michaela A.E. Arndt, Stefan Kiesgen, and Jürgen Krauss
- Part III: Emerging Technologies 391**
- 15 Emerging Technologies for Antibody Selection 393**
Mingyue He and Michael J. Taussig
- 16 Anti-Idiotypic Antibodies 407**
Alejandro López-Requena, Oscar R. Burrone, and Rolando Pérez
- 17 Non-Antibody Scaffolds as Alternative Therapeutic Agents 435**
Markus Fiedler and Arne Skerra
- 18 Antibody-Directed Enzyme Prodrug Therapy (ADEPT) 475**
Surinder K. Sharma, Kerry A. Chester and Kenneth D. Bagshawe

- 19 Engineered Antibody Domains as Candidate Therapeutics 487**
Weizao Chen, Ponraj Prabakaran, and Dimiter S. Dimitrov
- 20 Chimeric Antigen Receptors –“CARs” 519**
Ulf Petrausch and Thomas Schirrmann
- 21 Emerging Alternative Production Systems 561**
Benjamin Sommer, Holger Laux, Andre Frenzel, and Thomas Jostock

Volume II: Clinical Development of Antibodies

Quick Reference List of Antibodies by International Nonproprietary Name XXIII

Quick Reference List of Antibodies by Brand Name XXV

A Greeting by the Editors XXVII

Foreword to the First Edition XXIX

Foreword to the Second Edition XXXI

List of Contributors XXXIII

Abbreviations LI

Appendix: Marketed Monoclonal Antibodies Compendium LXXXIII

Part IV: The Way into the Clinic 601

- 22 Process Development and Manufacturing of Therapeutic Antibodies 603**
Alexander Jacobi, Barbara Enenkel, Patrick Garidel, Christian Eckermann, Mathias Knappenberger, Ingo Presser, and Hitto Kaufmann
- 23 The Immunogenicity of Therapeutic Antibodies 665**
Melody Sauerborn
- 24 Biosimilar Monoclonal Antibodies 681**
Susanne D. Pippig, Carsten Brockmeyer, and Robert E. Zoubek
- 25 Patent Issues Relating to Therapeutic Antibodies 705**
Barbara Rigby, Michael Braunagel, and Deborah Owen

Part V: Therapeutic Antibody Pipeline 735

- 26 Monoclonal Antibody Cancer Treatments in Phase III Clinical Trials 737**
Ulf Petrausch and Peter Markus Deckert
- 27 Antibodies in Cancer Treatment: Early Clinical Development 787**
Matthew Zibelman, Hossein Borghaei, and Anthony J. Olszanski

- 28 Targeting Angiogenesis by Therapeutic Antibodies 823**
Onat Kadioglu, Ean Jeong Seo, and Thomas Efferth
- 29 Antibodies in Phase III Studies for Immunological Disorders 851**
Penelope Ward and Mark Bodmer
- 30 Monoclonal Antibodies in Phase 1 and 2 Studies for Immunological Disorders 927**
Frank R. Brennan
- 31 MAbs Targeting Soluble Mediators in Phase 1 and 2 Clinical Studies Immunological Disorders 969**
Frank R. Brennan
- 32 T Cell Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1079**
Frank R. Brennan
- 33 B-Cell Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1115**
Frank R. Brennan
- 34 Inhibitors of Leukocyte Adhesion and Migration in Phase 1 and 2 Clinical Studies for Immunological Disorders 1127**
Frank R. Brennan
- 35 Toll-Like Receptor Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1145**
Frank R. Brennan
- 36 IgE Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1159**
Frank R. Brennan
- 37 Complement Inhibitors in Phase 1 and 2 Clinical Studies for Immunological Disorders 1165**
Frank R. Brennan
- 38 mAbs Targeting Apoptosis, Angiogenesis Inhibitors, and Other mAbs in Phase 1 and 2 Clinical Studies for Immunological Disorders 1175**
Frank R. Brennan
- 39 *In vitro* Studies and Clinical Trials about Monoclonal Antibodies Used in Infectiology 1195**
Guillaume Desoubeaux

- 40 **Immunotherapeutics for Neurological Disorders** 1215
Anne Messer, Kevin Manley, and Cynthia A. Lemere
- Part VI: Gaining Marketing Approval** 1231
- 41 **Regulatory Considerations in the Development of Monoclonal Antibodies for Diagnosis and Therapy** 1233
Marjorie A. Shapiro, Patrick G. Swann, and M. Stacey Ricci
- 42 **Regulatory Review: Clinical to Market Transition** 1263
Gabriele Dallmann
- 43 **Monoclonal Antibody Nomenclature for Clinical Studies (USA)** 1283
Stephanie C. Shubat
- Volume III: Approved Therapeutic Antibodies**
- Quick Reference List of Antibodies by International Nonproprietary Name** XXIII
- Quick Reference List of Antibodies by Brand Name** XXV
- A Greeting by the Editors** XXVII
- Foreword to the First Edition** XXIX
- Foreword to the Second Edition** XXXI
- List of Contributors** XXXIII
- Abbreviations** LI
- Appendix: Marketed Monoclonal Antibodies Compendium** LXXXIII
- Part VII: Approved Therapeutic Antibodies** 1289
- 44 **Oligoclonal and Polyclonal Antibody Preparations** 1291
Rishab K. Gupta and Mark C. Glassy
- 45 **Adalimumab (Humira®)** 1309
Janice M. Reichert
- 46 **Alemtuzumab (Lemtrada, MabCampath)** 1323
Thomas Elter, Michael Hallek, and Janice M. Reichert
- 47 **Basiliximab (Simulect®) and Daclizumab (Zenapax®)** 1375
Nadim Mahmud, Burcin Taner, and Nasimul Ahsan
- 48 **Belimumab (Benlysta®)** 1405
Pamela M. K Lutalo, Natasha Jordan, Thi-Sau Migone, and David P. D’Cruz

- 49 **Brentuximab Vedotin (Adcetris®) for the Treatment of CD30-Positive Hematologic Malignancies** 1417
Niels W.C.J. van de Donk and Eugen Dhimolea
- 50 **Canakinumab (ILARIS®)** 1445
Hermann Gram
- 51 **Catumaxomab (Removab) –Trifunctional Antibodies: Combining Direct Tumor Cell Killing with Therapeutic Vaccination** 1463
Horst Lindhofer, Michael Stanglmaier, Raymund Buhmann, Michael Jäger, Daniel Klunker, Peter Ruf, and Juergen Hess
- 52 **Cetuximab (Erbixub)** 1501
Sonja Wilke and Michael Hust
- 53 **Denosumab (Prolia®)** 1521
Torsten Meyer
- 54 **Efalizumab (Raptiva)** 1531
Karlheinz Schmitt-Rau
- 55 **Calicheamicin Conjugates: Gemtuzumab Ozogamicin (Mylotarg), Inotuzumab Ozogamicin** 1545
Matthias Peipp and Martin Gramatzki
- 56 **Golimumab (Simponi®)** 1565
Sohini Mazumdar and Janice M. Reichert
- 57 **Yttrium-90 Ibritumomab Tiuxetan (Zevalin®)** 1579
Karin Hohloch, Björn Chapuy, and Lorenz Trümper
- 58 **Infliximab (Remicade®)** 1599
Christian Antoni and Maria Wiekowski
- 59 **Ipilimumab (Yervoy®)** 1619
Teresa Alonso Gordo, Javier Puente Vázquez, and Eduardo Díaz-Rubio
- 60 **Muromonab-CD3 (Orthoclone OKT®3)** 1645
Harald Becker and Janice M. Reichert
- 61 **Nimotuzumab: A Humanized Anti-EGFR Antibody** 1679
Tania Crombet Ramos
- 62 **Obinutuzumab (Gazyva®), a Novel Glycoengineered Type II CD20 Antibody for the Treatment of Chronic Lymphocytic Leukemia and Non-Hodgkin's Lymphoma** 1695
Christian Klein, Marina Bacac, Pablo Umaña, and Michael Wenger

Volume IV: Approved Therapeutic Antibodies and in vivo Diagnostics**Quick Reference List of Antibodies by International Nonproprietary Name** XXIII**Quick Reference List of Antibodies by Brand Name** XXV**A Greeting by the Editors** XXVII**Foreword to the First Edition** XXIX**Foreword to the Second Edition** XXXI**List of Contributors** XXXIII**Abbreviations** LI**Appendix: Marketed Monoclonal Antibodies Compendium** LXXXIII

- 63 Ofatumumab (Arzerra®): a Next-Generation Human Therapeutic CD20 Antibody with Potent Complement-Dependent Cytotoxicity** 1733
Margaret A. Lindorfer, Joost M. Bakker, Paul W.H.I. Parren, and Ronald P. Taylor
- 63.1 Introduction and Preliminary Comments 1733
- 63.2 Physical and Immunochemical Characteristics of OFA Compared to RTX 1735
- 63.2.1 Interactions with CD20 1735
- 63.2.2 Development and Characterization of OFA 1737
- 63.2.3 Epitope Characterization 1737
- 63.2.4 *In vitro* Investigations Demonstrate That OFA Is Far More Effective Than RTX in Promoting CDC of Cell Lines and of CLL Cells 1739
- 63.3 Functional Characterizations 1743
- 63.3.1 Dose Requirements for Sustained *In vivo* Activity of OFA in Preclinical Models 1743
- 63.3.2 Clearance from the Circulation via the Mononuclear Phagocytic System (MPS) 1744
- 63.3.3 On the Role of Neutrophils 1745
- 63.3.4 C3b Deposition and Complement Receptors 1745
- 63.3.5 Complement as a Confounding Factor 1745
- 63.3.6 Mouse Models 1746
- 63.3.7 No Apoptosis 1748
- 63.4 CD20: It Is certainly a Good Target, but How Well Characterized Is It? 1748
- 63.4.1 CD20 Is not Shed into the Bloodstream 1748
- 63.4.2 CD20 on B Cells Can Be “Shaved,” Especially When Effector Functions Are Exhausted 1749
- 63.4.3 After OFA or RTX Binding, CD20 Can Indeed Be Internalized, but Slowly 1752
- 63.5 Key Results of Clinical Trials with OFA 1752
- 63.5.1 Introduction 1752
- 63.5.2 OFA Monotherapy for CLL: Phase 1/2 1753
- 63.5.3 OFA Monotherapy for FL: a Dose-Ranging Study 1753

63.5.4	OFA Monotherapy: the Pivotal Trial for CLL	1756
63.5.5	Combination with Chemotherapy: OFA plus FC for CLL	1757
63.5.6	Combination with Chemotherapy: O-CHOP for FL	1758
63.5.7	Combination with Chemotherapy: OFA plus Lenalidomide or Ibrutinib for CLL	1758
63.5.8	OFA Monotherapy: RTX-Refractory FL	1759
63.5.9	Rheumatoid Arthritis	1760
63.6	Summary and Future Directions	1761
	Abbreviations	1762
63.7	Disclosures	1762
	References	1763
64	Omalizumab (Xolair) – Anti-Immunoglobulin E Treatment in Allergic Diseases	1775
	<i>Claus Kroegel and Martin Foerster</i>	
64.1	Introduction	1775
64.2	The Biology of the IgE Molecule	1778
64.2.1	IgE Distribution and Blood Concentration	1779
64.2.2	IgE Synthesis and Regulation	1779
64.3	IgE Receptors	1780
64.3.1	FcεRI (High-Affinity IgE Receptor)	1781
64.3.1.1	FcεRI–IgE Binding	1781
64.3.1.2	FcεRI Activation	1782
64.3.1.3	Regulation of FcεRI Expression	1783
64.3.2	FcεRII (Low-Affinity IgE Receptor, CD23)	1783
64.3.2.1	FcεRII–IgE Binding	1784
64.3.2.2	FcεRII Activation	1784
64.3.2.3	FcεRII/CD23 Functions	1784
64.4	Cell Distribution of IgE	1785
64.4.1	Effector Cell-Associated IgE	1785
64.4.2	Antigen-Presenting Cell-Associated IgE	1786
64.5	Physiologic and Pathophysiologic Significance of IgE	1786
64.6	The Concept of Anti-IgE-Based Treatment	1787
64.7	Construction of the Monoclonal Anti-IgE Molecule	1787
64.7.1	Antibody Generation	1787
64.7.2	Complex Formation and Tissue Distribution	1788
64.7.3	Interactions with IgE	1792
64.8	Efficacy	1792
64.8.1	Preclinical Results	1792
64.8.2	Clinical Studies	1793
64.9	Anti-Inflammatory Effects of Omalizumab	1797
64.9.1	Effects on Serum Free IgE Levels	1797
64.9.2	Effect on Cytokines	1799
64.9.3	Effects on FcεRI Cell Expression	1799
64.9.4	Effect on Dendritic Cell APCs	1800

- 64.9.5 Effect on Eosinophils 1800
- 64.9.6 Effects on B Cells 1801
- 64.10 Pharmacological Properties of Omalizumab 1802
- 64.10.1 Pharmacodynamics 1802
- 64.10.2 Pharmacokinetics 1802
- 64.11 Adverse Effects 1802
- 64.11.1 Systemic Side Effects 1803
- 64.11.2 Local Reactions 1803
- 64.11.3 Serious Adverse Effects 1803
- 64.11.4 Immune Complex Diseases 1804
- 64.11.5 Long-Term Adverse Effects 1804
- 64.12 Indications 1804
- 64.13 Contraindications 1804
- 64.14 Preparation for Use 1805
- 64.15 Administration 1806
- 64.16 Dosing of Omalizumab 1806
- 64.17 Response to Treatment 1808
- 64.17.1 Onset of Action of Anti-Immunoglobulin E Effect 1808
- 64.17.2 Duration of Treatment 1808
- 64.18 Assessment of Therapeutic Response 1809
- 64.19 Monitoring of Therapy 1810
- 64.20 Drug Interactions 1810
- 64.21 Pregnancy and Lactation 1810
- 64.22 Cost 1811
- 64.23 Non-approved Diseases 1811
- 64.23.1 Allergic Rhinitis 1811
- 64.23.2 Urticaria/Angioedema 1812
- 64.23.3 Insect Venom Allergy and Specific Immunotherapy 1813
- 64.23.4 Mast Cell Activation Syndrome (MCAS) 1814
- 64.24 Conclusions 1814
- Acknowledgments 1815
- References 1815
- Websites 1824

- 65 Palivizumab (Synagis®) 1825**
Louis Bont
- 65.1 Nature, Role in Disease, and Biology of the Target 1825
- 65.1.1 Respiratory Syncytial Virus (RSV)-Induced Disease and RSV Epidemiology 1825
- 65.1.2 Target of the Antibody: the RSV Virion 1826
- 65.1.3 Correlates of Protection from Disease 1827
- 65.2 Origin, Engineering, and Humanization of the Antibody 1829
- 65.3 Mechanism of Action and Preclinical Results 1831
- 65.4 Production, Downstream Processing, and Galenics of the Antibody 1833

- 65.5 Summary of Results from Clinical Studies 1835
 - 65.5.1 Phase 3 Trials 1835
 - 65.5.1.1 Palivizumab in Premature Infants 1836
 - 65.5.1.2 Palivizumab in Children with Significant Congenital Heart Disease (CHD) 1838
 - 65.6 Indications and Usage 1839
 - 65.7 Clinical Reports after Approval 1840
 - 65.8 Protective Efficacy as a Function of Palivizumab Serum Concentration? 1842
 - 65.9 Postmarketing Experience with Regard to Adverse Events (AEs) 1843
 - 65.10 Toward Improved Versions of Palivizumab 1845
 - 65.11 Summary 1845
 - Acknowledgments 1846
 - Abbreviations 1846
 - References 1847

- 66 Panitumumab (Vectibix®): A Treatment for Metastatic Colorectal Cancer 1855**
Jonas Kügler
 - 66.1 Introduction 1855
 - 66.1.1 Colorectal Cancer 1855
 - 66.1.2 Epidermal Growth Factor 1855
 - 66.2 Panitumumab (Vectibix) 1856
 - 66.2.1 Panitumumab (Vectibix) Development 1856
 - 66.2.2 Preclinical Results of Panitumumab (Vectibix) 1857
 - 66.2.3 Resistance to Panitumumab (Vectibix) 1857
 - 66.2.4 Approval 1858
 - 66.2.5 Production, Galenics, and Pharmacokinetic Properties of Panitumumab 1858
 - 66.3 Results from Clinical Studies 1859
 - 66.3.1 Phase I Clinical Studies: Safety, Pharmacokinetics, and Activity 1859
 - 66.3.2 Monotherapy of Panitumumab for mCRC 1859
 - 66.3.3 First-Line Combination Therapy of Panitumumab for mCRC 1862
 - 66.3.4 Second-Line Combination Therapy of Panitumumab for mCRC 1862
 - 66.3.5 Antibody Combination Therapy 1863
 - 66.3.6 Panitumumab in Head and Neck Cancer 1864
 - 66.4 Summary and Outlook 1865
 - References 1865

- 67 Pertuzumab (Perjeta®) 1871**
Jose Angel García-Saénz, Fernando Moreno Anton, and Coralía Bueno Muiño
 - 67.1 HER2-Positive Breast Cancer 1871
 - 67.2 Mechanisms of Trastuzumab Resistance 1871
 - 67.2.1 Loss of Trastuzumab Binding 1871

- 67.2.2 Activation of Downstream Signaling Pathways 1872
- 67.2.3 Overexpression of Alternative ErbB Ligands and Dimerization of Receptors 1873
- 67.2.4 Interaction of HER2 with Other Structurally Unrelated Receptors 1873
- 67.3 Preclinical Development 1874
- 67.4 Pertuzumab Clinical Development 1875
- 67.5 Pertuzumab Cardiac Safety Profile 1879
- References 1880

- 68 **Ranibizumab (Lucentis): a New Anti-Angiogenic Treatment in Ophthalmology** 1883**
Nicolas Leveziel, Marc Ohresser, and Gilles Paintaud
- 68.1 Introduction 1883
- 68.1.1 Age-Related Macular Degeneration 1884
- 68.1.2 Diabetic Macular Edema 1886
- 68.1.3 Branch and Central Retinal Vein Occlusion 1886
- 68.1.4 Myopic Choroidal Neovascularization 1886
- 68.2 Ranibizumab: Clinical Studies in Retinal Disorders 1887
- 68.2.1 Exudative AMD 1887
- 68.2.2 Clinical Studies in Diabetic Macular Edema 1889
- 68.2.3 Clinical Studies in Retinal Vein Occlusion 1890
- 68.2.4 Clinical Studies in Myopic Choroidal Neovascularization 1891
- 68.3 Other Molecules with Anti-VEGF Effect of Clinical Use in Retinal Disorders 1891
- 68.3.1 Bevacizumab 1892
- 68.3.2 Afibercept 1893
- References 1894

- 69 **Raxibacumab, Human Monoclonal Antibody against Anthrax Toxin** 1899**
Sally D. Bolmer and Thi-Sau Migone
- 69.1 Introduction 1899
- 69.2 Development of Raxibacumab 1900
- 69.2.1 Anthrax Toxins 1900
- 69.2.2 Molecule Generation and *In vitro* Pharmacology 1901
- 69.2.2.1 Generation of Raxibacumab 1901
- 69.2.2.2 Raxibacumab Mechanism of Action 1901
- 69.3 Demonstration of Effectiveness under the Animal Rule 1901
- 69.3.1 Animal Models 1902
- 69.3.2 Monotherapy Studies 1903
- 69.3.3 Antibiotic Combination Studies 1904
- 69.4 Safety 1905
- 69.4.1 Nonclinical Safety 1905
- 69.4.2 Human Safety 1905

69.5	Dosing	1906
69.6	Indication	1906
69.7	Conclusion	1907
	Abbreviations	1907
	References	1907
70	Rituximab (Rituxan®)	1909
	<i>Axel Böhnke and Michael Wenger</i>	
70.1	Introduction	1909
70.1.1	Production, Design, and Structure of Rituximab	1909
70.1.2	CD20 as a Therapeutic Target	1910
70.1.3	Mode of Action	1911
70.1.4	Preclinical Studies	1913
70.1.5	Pharmacokinetic Studies	1913
70.2	Rituximab Clinical Data in B-Cell Lymphoma	1914
70.2.1	Overview of B-Cell Lymphoma	1914
70.2.1.1	Overview of Indolent and Aggressive B-Cell Lymphoma	1914
70.2.1.2	Overview of CLL	1916
70.2.2	Rituximab plus Chemotherapy Induction Therapy in Indolent B-Cell Lymphoma	1917
70.2.2.1	Rituximab plus Chemotherapy in Previously Untreated Indolent B-Cell Lymphoma	1922
70.2.2.2	Rituximab plus Chemotherapy in Relapsed/Refractory Indolent B-Cell Lymphoma	1927
70.2.2.3	Meta-Analysis of Rituximab and Chemotherapy in Indolent B-Cell Lymphoma	1930
70.2.3	Induction Therapy with Rituximab plus Immune Modulators in Indolent B-Cell Lymphoma	1931
70.2.3.1	Rituximab Plus Immune System Modulators in Previously Untreated Indolent B-Cell Lymphoma	1931
70.2.3.2	Rituximab plus Immune Modulators in Relapsed/Refractory Indolent B-Cell Lymphoma	1932
70.2.4	Induction with Rituximab Monotherapy in Indolent B-Cell Lymphoma	1933
70.2.4.1	Rituximab Monotherapy in Previously Untreated Indolent B-Cell Lymphoma	1933
70.2.4.2	Rituximab Monotherapy in Relapsed Indolent B-Cell Lymphoma	1934
70.2.5	Rituximab in Other Subtypes of Indolent Lymphoma	1935
70.2.5.1	Rituximab in Marginal Zone Lymphoma	1935
70.2.5.2	Rituximab in Small Lymphocytic Lymphoma	1936
70.2.5.3	Rituximab in Waldenström's Macroglobulinemia	1936
70.2.6	Rituximab Maintenance Therapy in Indolent Lymphoma	1937
70.2.6.1	Rituximab Maintenance Therapy Following Monotherapy Induction	1937