CONTENTS

PREFACE xi

ACKNOWLEDGMENTS xiii

CONTRIBUTORS xv

CHAPTER 1 BACE, APP PROCESSING, AND SIGNAL TRANSDUCTION IN ALZHEIMER’S DISEASE 1

Dale E. Bredesen and Edward H. Koo

1.1 Introduction 1
1.2 BACE Cleavage of APP as a Molecular Switching Mechanism 2
1.3 AD: An Imbalance in Cellular Dependence? 3
1.4 BACE Cleavage, Caspase Cleavage, and Neuronal Trophic Dependence 4
1.5 BACE Cleavage of APP, Dependence Receptors, and Alzheimer Pathology 5
1.6 Key Mutations Proximal of APP Processing to Aβ 9
1.7 Final Remarks 10

CHAPTER 2 IDENTIFICATION OF BACE AS A TARGET IN ALZHEIMER’S DISEASE 15

Robert L. Heinrikson and Sukanto Sinha

2.1 Introduction 15
2.2 The Search for β-Secretase 17
2.3 Validation of the BACE Target 27
2.4 Final Remarks 28

CHAPTER 3 BACE BIOLOGICAL ASSAYS 35

Alfredo G. Tomasselli and Michael J. Bienkowski

3.1 Introduction 35
3.2 Clinical and Physiological Hallmarks of Alzheimer’s Disease (AD) 36
3.3 APP Processing 36
3.4 Aspartyl Protease Classification 37
3.5 BACE Structure 38
3.6 Mechanism, Kinetics, Inhibition, and Specificity 39
3.7 Assay Strategies for Inhibitor Finding and Development 45
3.8 Common Assays Used to Identify and Study Inhibitors 48
3.9 BACE Assays 50
3.10 Final Remarks 54
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Authors</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Peptidic, Peptidomimetic, and HTS-Derived BACE Inhibitors</td>
<td>James P. Beck and Dustin J. Mergott</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>Fragment-Based Approaches for Identification of BACE Inhibitors</td>
<td>Andreas Kuglstatter and Michael Hennig</td>
<td>107</td>
</tr>
<tr>
<td>6</td>
<td>Structure-Based Design of BACE Inhibitors: Technical and Practical Aspects of Preparation, 3-Dimensional Structure, and Computational Analysis</td>
<td>Felix F. Vajdos, Veerabahu Shanmugasundaram, and Alfredo G. Tomasselli</td>
<td>123</td>
</tr>
<tr>
<td>7</td>
<td>Pharmacological Models for Preclinical Testing: From Mouse to Dog to Nonhuman Primates</td>
<td>Jason L. Eriksen, Michael Paul Murphy, and Elizabeth Head</td>
<td>159</td>
</tr>
</tbody>
</table>
CHAPTER 8  ADSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME), EFFICACY, AND TOXICOLOGY FOR BACE INHIBITORS 177

Ishrut Hussain and Emmanuel Demont

8.1 Introduction 177
8.2 Development of BACE Inhibitors with Optimized ADME Properties 180
8.3 In Vivo Efficacy of BACE Inhibitors 188
8.4 Toxicology of BACE Inhibitors 192
8.5 Final Remarks 193

CHAPTER 9  CLINICAL TRIALS FOR DISEASE-MODIFYING DRUGS SUCH AS BACE INHIBITORS 197

Henry H. Hsu

9.1 Introduction 197
9.2 Update on Beta-Amyloid Therapies in Clinical Development 198
9.3 Clinical Development of BACE Inhibitors and Other Disease-Modifying Drugs 203
9.4 Final Remarks 212

CHAPTER 10  FUTURE STRATEGIES FOR DEVELOPMENT OF NOVEL BACE INHIBITORS: ANTI-APP β-SITE ANTIBODY AND APP BINDING SMALL MOLECULE APPROACHES FOR ALZHEIMER’S DISEASE 217

Beka Solomon, Michal Arbel-Ornath, Clare Peters-Libeu, and Varghese John

10.1 Introduction 217
10.2 β-Secretase: Discovery, Function, and Inhibitors 218
10.3 Generation of Aβ Peptides via the Endocytic Pathway 220
10.4 Generation of Anti-APP β-Site Antibodies 221
10.5 Antibody Interference with Aβ Production in Cellular Model 223
10.6 Antibody Interference with Aβ Production in Animal Models 226
10.7 Identification of APP Binding Small Molecules that Block β-Site Cleavage of APP 228
10.8 Final Remarks 230

AFTERWORD 235

Ruth Abraham

Introduction 235
Artwork as a Measure of the Progression of AD 236

INDEX 243