

Preface

ATTEMPTING TO ORGANIZE AND REVIEW THE EXTENSIVE BODY of scientific literature on the biological basis of Alzheimer disease (AD) would seem to be a daunting task. The idea of preparing a book that does so comprehensively emerged from many discussions over the last decade about how this field of inquiry was progressing and how one might integrate the diversity of approaches and findings that it has generated. The editors of this volume took on the responsibility of identifying and sequencing the major topics to be covered and assembling a group of expert authors. As such, we are well aware that there are various ways such a huge body of research could be covered and that some topics will perforce receive more or less attention than others. The editors chose highly knowledgeable and scientifically active investigators in Alzheimer biology to contribute chapters on topics in which they have deep expertise. We are most grateful that virtually everyone invited to write for the book quickly agreed to participate, despite having very busy schedules. The diverse scientific viewpoints and collective wisdom of this talented group will, we hope, enable the volume to provide value to the broad biomedical community as it strives to achieve the intellectually fascinating and medically critical goal of solving AD.

The editors apologize in advance to those readers who may find missing elements or points of disagreement or overlap among the array of scientific findings reviewed here, and we recognize that no one volume can do full justice to this intense and rapidly advancing field. However, we would point out that, depending on its reception, this first comprehensive book reviewing the biological underpinnings of AD will be revised, updated, and thus improved within a few years. In this sense, we hope to have the opportunity to respond to issues we overlooked or covered insufficiently, given the space and time available to complete a project of this magnitude. It is likely that revised editions of this book—if they come to pass—will be even more detailed and compelling than this first effort. Nevertheless, we are hopeful that the multifaceted subjects covered here in considerable depth by distinguished authorities will prove useful to a broad audience of undergraduate, graduate, and medical students, postdoctoral fellows, junior and senior investigators, and, importantly, scientists and clinicians working outside the field of AD research.

Readers familiar with the Alzheimer field may notice that some chapters are coauthored by investigators who have had differing views of the topic under review or have sometimes been competitors. The editors purposely chose this path to encourage the synthesis of diverse perspectives and attempt to achieve clarity and common ground on unsettled issues. We are grateful to all of our chapter authors but particularly to those who at first pass found themselves facing the challenging task of melding disparate ideas and data.

We encourage readers not only to peruse chapters on topics that particularly intrigue—or confuse—they but also to read the first and last chapters of the book. Here, the editors have tried to step back from the wealth of details and convey a sense of what has motivated the global quest to understand the biology of AD, how sometimes competing concepts and lines of inquiry have proceeded, and, most importantly, where we believe this scientifically rich and therapeutically promising field is headed.

The editors thank Barbara Acosta, Richard Sever, and their colleagues at Cold Spring Harbor Laboratory Press for their excellent editorial and compositional efforts in putting this book together and their patience with the inevitable delays and minor crises that arise during such an ambitious undertaking. Each of the editors owes a very special thanks to past and current members of his

Preface

respective laboratory and other local colleagues for innumerable discussions about the science of AD and how to think about its many unresolved questions. We also thank our gifted and dedicated administrative assistants who helped us in this work, especially Ms. Nicole Boucher (at BWH/HMS). One of us (D.J.S.) had the benefit of the careful bibliographical research, data analysis, and sage editorial advice of Marcia Podlisny, Ph.D., who had helped organize information relevant to this volume during an earlier effort some years ago. Finally, we are indebted to our families for their support and forbearance as we added the creation of this book to our already numerous responsibilities. We hope that the outcome will justify the collective efforts of the authors and editors and help illuminate the path toward scientifically well-grounded therapeutics that could ultimately prevent this common and devastating disorder.

DENNIS J. SELKOE
ECKHARD MANDELKOW
DAVID M. HOLTZMAN

Index

A

- ABCA1*, knockout mouse, 284
ABCA7, late-onset Alzheimer disease role, 254
ACC-001, amyloid- β immunotherapy, 445
ACE. *See* Angiotensin-converting enzyme
Acetylcholine receptor
 amyloid- β interactions, 195, 320
 muscarinic agonist therapy, 485
 nicotinic agonist therapy, 485
Acetylcholinesterase, inhibitor therapy,
 476–480, 489
Acylpeptide hydrolase (APH), amyloid- β degradation,
 396
AD8, Alzheimer disease screening, 13–14
ADAMs
 ADAM10 and late-onset Alzheimer disease role,
 255–256
 amyloid precursor protein processing, 210–211
Aging
 Alzheimer disease risks, 15
 Alzheimer neuropathology in normal aging, 55–56
 healthy cognitive aging, 10–11
Agitation Inventory, 14
 α -Secretase. *See also* ADAMs
 amyloid precursor protein processing, 210–211
 subcellular sites of processing, 216
AlzGene, late-onset Alzheimer disease variants, 253
AMPA receptor, therapeutic targeting, 486
Amyloid- β
 aggregation
 biophysics, 434–435
 inhibitors
 animal studies, 436–437
 clinical studies, 437–438
 in vitro studies, 435–436
 prospects for study, 438
 amyloid hypothesis of Alzheimer disease, 405–407
 apolipoprotein E
 interactions, 282–284
 receptors
 metabolism regulation, 290–291
 synaptic suppression antagonism, 287–288
 balance between production and clearance, 389–391
 BAPTists versus TAUists, 5–6
 biochemistry in deposits and plaques, 182–185
 cerebrospinal fluid biomarker studies
 isoforms, 92–95, 97, 100
 oligomers, 97
 soluble protein, 97
 cognitive function disruption, 325, 327–328
 diffusible oligomers
 molecular dynamics, 188
 natural oligomers, 188–190
 overview, 186–187
 recombinant oligomers, 188
 synthetic $A\beta$ as substrate for oligomer formation,
 187–188
 fibril structure and properties, 185–186
 forms in neuronal impairment, 318–319
 history of study, 181–182
 immunization therapy
 active immunization
 ACC-001, 445
 AN1792 clinical trial, 441–443
 CAD-106, 445
 mechanism of action, 439–441, 464
 overview, 438
 preclinical observations, 439
 passive immunization, 443–445
 membrane interactions
 electrostatic/charge effects, 194
 hydrophobic interactions, 194
 lipoprotein interactions, 194–195
 phase/interface effects, 193–194
 receptor interactions, 195
 metal ion interactions, 191–193
 plasma biomarkers, 102
 positron emission tomography imaging
 applications, 78–80
 limitations, 80
 principles, 77–78
 production, 212
 proteolytic degradation
 environmental insults, 392
 inhibitors, 398–399
 irreversibility, 392
 protease defining of amyloid- β pools,
 391–392
 protease types
 acylpeptide hydrolase, 396
 angiotensin-converting enzyme, 395
 BACE1, 397
 BACE2, 397–398
 catalytic antibodies, 398

Index

- Amyloid- β (*Continued*)
 cathepsin B, 397
 cathepsin D, 397
 endothelin-converting enzymes, 394
 insulin-degrading enzyme, 395–396
 matrix metalloproteinases, 395
 myelin basic protein, 396
 nepriylsin, 393–394
 nepriylsin-like peptidases, 394
 overview, 392–393
 plasmin, 396
 proteasome, 398
 regulation of amyloid- β levels, 388–389
 sites, 392
 therapeutic targeting, 399
 synaptic function
 early perturbations, 319
 extracellular versus intraneuronal amyloid- β
 effects, 324–325
 oligomer receptors in perturbation, 322
 synaptic depression enhancement, 321–322
 synaptic transmission modulation, 319–321
 therapeutic implications, 328–330
 transgenic mouse models, 304
Amyloid plaque
 clinicopathological correlations, 51
 composition, 48
 definition, 44
 morphology, 49
 topographical distribution, 49–50
Amyloid precursor-like proteins (APLPs), γ -secretase
 processing, 264
Amyloid precursor protein (APP)
 amyloid- β production, 212
 apolipoprotein E receptor regulation of trafficking
 and processing, 289–290
 apoptosis studies, 236
 axonal transport, 233–234
 cell and synaptic adhesion studies, 234
 gene duplication, 373
 gene family, 232
 intracellular signaling, 236
 isoforms
 axon pruning and degeneration, 235
 knockout studies, 239
 loss of function studies
 Caenorhabditis elegans, 236–237
 Drosophila, 236–237
 knockout mice
 combined knockouts, 238
 conditional knockouts, 239–240
 single knockout, 237–238
 proteases
 BACE1, 207–208
 α -secretase, 210–211
 γ -secretase and presenelins, 208–210
 proteolytic processing
 activity-dependent processing, 219–222
 degradation, 219
 overview, 205–206, 232
 subcellular sites of processing, 216, 218
 structure, 232–233
 subcellular localization, 233
 tissue distribution, 233
 trafficking
 endocytic sorting, 211–212
 neurons, 215–217
 polarized trafficking
 secretase sorting, 213, 215
 sorting mechanisms, 212–214
 trophic function, 234–235
 variants in Alzheimer disease
 early-onset familial Alzheimer disease, 251
 overview, 123, 207
AN1792, clinical trial, 441–443
Angiotensin-converting enzyme (ACE), amyloid- β
 degradation, 395
Animal models, Alzheimer disease
 clinical translation concerns, 309–312
 knockout mice, 307–309
 transgenic mice, 303–307
APH. *See* Acylpeptide hydrolase
APLPs. *See* Amyloid precursor-like proteins
APOE ϵ 4
 Alzheimer disease risks, 15, 124, 281
 positron emission tomography brain metabolism
 findings in Alzheimer disease, 76
Apolipoprotein E
 amyloid- β interactions, 194–195, 282–284
 late-onset Alzheimer disease variants, 252–253,
 281–282
 neurobiology, 281
 receptors. *See also specific receptors*
 amyloid- β -induced synaptic suppression
 antagonism, 287–288
 amyloid- β metabolism regulation, 290–291
 amyloid precursor protein trafficking and
 processing regulation, 289–290
 LDLR1 functional overview, 291–293
 LRP1 functional overview, 291–293
 neuroprotection studies, 288–289
 signaling, 285–286
 synaptic plasticity studies, 284–287
 Tau phosphorylation regulation, 286
 types, 280–281
Apoptosis, amyloid precursor protein studies, 236
APP. *See* Amyloid precursor protein
Arachidonic acid, inflammation mediations, 345
Astrocyte
 Alzheimer disease effects, 52
 inflammation mediation, 339–340
Attention, Alzheimer disease deficits, 28

- ATXN1*, late-onset Alzheimer disease role, 253–254
Autophagic vacuole (AV), accumulation in neurons, 373
AV. *See* Autophagic vacuole
Axona (Ketasyn), Alzheimer disease treatment studies, 484–485, 488
- B**
- BACE1
amyloid- β degradation, 397
amyloid precursor protein processing, 207–208, 423–426
cerebrospinal fluid biomarker studies, 97
inhibitors, 431–433
knockout mouse, 308
polarized sorting, 213, 215
structure, 426, 432
subcellular sites of processing, 216, 218
- BACE2
amyloid- β degradation, 397–398
inhibitors, 431–433
- BBB. *See* Blood–brain barrier
Begacestat, presenelin inhibition, 270–271
Behavioral variant frontotemporal dementia. *See* Frontotemporal lobar degeneration
 β -Secretase. *See* BACE1
BIN1. *See* Bridging integrator 1
Biomarkers. *See* Cerebrospinal fluid; Plasma biomarkers
Blood–brain barrier (BBB), dysfunction in Alzheimer disease
GLUT1, 409
LRP, 410–413
overview, 409
RAGE, 410
vascular-specific gene expression, 413–414
BMS-708163, presenelin inhibition, 270–271, 430–431
Body weight, Alzheimer disease risk factor, 119
Bridging integrator 1 (BIN1), variants in Alzheimer disease, 123
- C**
- C9ORF72*, frontotemporal lobar degeneration mutations, 169–170
CAA. *See* Cerebral amyloid angiopathy
CAD-106, amyloid- β immunotherapy, 445
Cambridge Mental Disorders of the Elderly Examination, 14
Carbamazepine, agitation management in Alzheimer disease, 481
Cathepsin B, amyloid- β degradation, 397
Cathepsin D, amyloid- β degradation, 397
CBF. *See* Cerebral blood flow
CBS. *See* Corticobasal syndrome
CD2AP, late-onset Alzheimer disease role, 254
CD33, late-onset Alzheimer disease role, 253–254
CDK5, inhibitor therapy, 461
CDR. *See* Clinical Dementia Rating
CERAD Behavior Rating Scale for Dementia, 14
Cerebral amyloid angiopathy (CAA)
apolipoprotein E knockout mice, 283
clinicopathological correlations, 51–52
composition, 51
definition, 44
microvascular degeneration, 409
morphology, 51
topographical distribution, 51
Cerebral blood flow (CBF), Alzheimer disease findings, 408–409
Cerebrolysin, Alzheimer disease treatment studies, 483, 487
Cerebrospinal fluid (CSF), biomarkers for Alzheimer disease
amyloid- β
isoforms, 92–95, 97, 100
oligomers, 97
soluble protein, 97
BACE1, 97
clinical trial application
diagnosis/enrichment of Alzheimer disease cases, 103
drug response monitoring, 105–106
safety monitoring, 104–105
stratification of Alzheimer disease cases, 103–104
combination studies, 94, 106–107
diagnostic performance
Alzheimer disease with dementia, 94–95
autopsy-verified Alzheimer disease, 95
preclinical Alzheimer disease, 95–96
prodromal Alzheimer disease, 95
endophenotypes in genetic studies, 106
GAP-43, 100
inflammation and oxidative stress markers, 100–101
neurofilament proteins, 100
overview, 92–93, 98–99
prospects, 106–107
Stable Isotope Labeling Kinetics, 101–102
Tau
phosphorylation, 93–94
total protein, 92–93
visinin-like protein-1, 100
CHMP2B, frontotemporal lobar degeneration mutations, 171
Clinical Dementia Rating (CDR), 14
Clock Drawing test, 14
Clusterin
late-onset Alzheimer disease role, 254
variants in Alzheimer disease, 123
Cognitive enhancement, Alzheimer disease protection, 122–123

Index

- Cognitive reserve, Alzheimer disease protection, 120–121
- Complement, inflammation mediation, 341–343
- Complement receptor 1 (CR1), variants in Alzheimer disease, 123, 254
- Copper, amyloid- β interactions, 192–193
- Corticobasal syndrome (CBS)
clinical presentation, 162
histopathology, 163, 165
- COX. *See* Cyclooxygenase
- CR1. *See* Complement receptor 1
- CSE. *See* Cerebrospinal fluid
- Curcumin, Alzheimer disease treatment studies, 490
- CX-1837, Alzheimer disease treatment studies, 486
- Cyclooxygenase (COX)
inflammation mediation, 345
therapeutic targeting in Alzheimer disease, 347–348, 428, 487, 490
- D**
- Definite Alzheimer disease, diagnostic criteria, 11–12, 54
- Dementia
definition, 11
detection, 11, 13–14
- Dementia with Lewy bodies (DLB)
Alzheimer disease differential diagnosis, 18, 30–31
Lewy body ubiquitination, 363–364
overlap with Alzheimer disease, 56–57
- Dense-core plaque, definition, 44
- Depression
Alzheimer disease differential diagnosis, 19
antidepressants in Alzheimer disease, 481
- Diabetes type II, Alzheimer disease risk factor, 119
- Diffuse plaque, definition, 44
- Dimebon (Latrepidine), Alzheimer disease treatment studies, 487, 489
- DLB. *See* Dementia with Lewy bodies
- Docosahexaenoic acid (DHA), Alzheimer disease treatment studies, 483, 487
- Donepezil, acetylcholinesterase inhibition, 476, 478–479
- Down syndrome, 327
- E**
- E2012, presenelin inhibition, 430
- Early-onset familial Alzheimer disease (EO-FAD), genetics, 249–252, 497
- ECes. *See* Endothelin-converting enzymes
- Economic impact, Alzheimer disease, 9
- EHT0202. *See* Etazolate
- ELND006, presenelin inhibition, 431
- Endothelin-converting enzymes (ECes), amyloid- β degradation, 394
- EO-FAD. *See* Early-onset familial Alzheimer disease
- EPHA1, late-onset Alzheimer disease role, 254
- Epidemiology, Alzheimer disease
definitions and criteria, 115–116
genetic epidemiology
common variants, 124
late-onset Alzheimer disease, 124
rare variants, 123–124
incidence, 9, 116–117
inflammation, 346–347t
prevalence, 9, 116–117
protective factors
cognitive enhancement, 122–123
cognitive reserve, 120–121
diet, 121–122
exercise, 122
risk factors
body weight, 119
cerebrovascular disease, 118
diabetes type II, 119
hypertension, 118–119
smoking, 119–120
traumatic brain injury, 120
risk stratification and treatment, 500
- Episodic memory, Alzheimer disease deficits, 26–27
- Epothilone D, microtubule stabilization in Alzheimer disease, 460
- ERT. *See* Estrogen replacement therapy
- Estrogen replacement therapy (ERT), Alzheimer disease treatment studies, 487, 490
- Etazolate (EHT0202), Alzheimer disease treatment studies, 486
- Executive function, Alzheimer disease deficits, 28–29
- Exercise, Alzheimer disease protection, 122
- F**
- Fluorodeoxyglucose. *See* Positron emission tomography
- Flurbiprofen, presenelin inhibition, 428–429
- fMRI. *See* Functional magnetic resonance imaging
- Folic acid, Alzheimer disease treatment studies, 484
- Frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17)
clinical presentation, 163
histopathology, 166
Tau mutations, 457
- Frontotemporal lobar degeneration (FTLD)
Alzheimer disease
differential diagnosis, 18–19, 31–32
overlap, 171–173
behavioral variant and Alzheimer disease differential diagnosis, 32–33, 35
clinical presentation
behavioral variant, 161
corticobasal syndrome, 162
logopenic progressive aphasia, 162

- motor neuron disease, 163
 - progressive nonfluent aphasia, 161–162
 - progressive supranuclear palsy, 162–163
 - semantic dementia, 161
 - gene mutations
 - C9ORF72*, 169–170
 - CHMP2B*, 171
 - FUS*, 170
 - MAPT*, 164, 169
 - TARDBP*, 170
 - VCP*, 170–171
 - histopathology
 - FTLD-FUS, 168
 - FTLD-Tau, 163–167
 - FTLD-TDP, 167–168
 - FTLD-UPS, 168
 - history of study, 159–161
 - FTDP-17. *See* Frontotemporal dementia and Parkinsonism linked to chromosome 17
 - FTLD. *See* Frontotemporal lobar degeneration
 - Functional magnetic resonance imaging (fMRI)
 - Alzheimer disease studies, 72–74
 - principles, 72
 - FUS*
 - frontotemporal lobar degeneration mutations, 170
 - FTLD-FUS, 168
 - Fyn, Tau interactions, 148
- G**
- Galantamine, acetylcholinesterase inhibition, 479
 - γ -Secretase. *See also* Nicastrin; *PEN2*; Presenelins
 - amyloid precursor protein processing, 208–210, 423–426
 - inhibitors, 269–271, 426–431
 - membrane topology, 262
 - Notch signaling, 269
 - stoichiometry of complex, 262
 - structure, 425
 - structure-function relationships, 265–266
 - subcellular sites of processing, 218–219
 - Gantenerumab, clinical trials, 445
 - GAP-43, cerebrospinal fluid biomarker studies, 100
 - GDS. *See* Geriatric Depression Scale; Global Deterioration Scale
 - General Practitioner Assessment of Cognition (GPCOG), 14
 - Geriatric Depression Scale (GDS), 14
 - Ginkgo biloba*, Alzheimer disease treatment studies, 482, 488
 - Global Deterioration Scale (GDS), 14
 - GLUT1, blood–brain barrier dysfunction in Alzheimer disease, 409
 - Glycogen synthase kinase 3 β (GSK3 β)
 - apolipoprotein E receptor signaling, 285
 - inhibitor therapy, 461
 - GPCOG. *See* General Practitioner Assessment of Cognition
 - Granovacuolar degeneration (GVD), 52
 - Growth hormone, Alzheimer disease treatment studies, 487
 - GSK3 β . *See* Glycogen synthase kinase 3 β
 - GSK933776A, clinical trials, 445
 - GVD. *See* Granovacuolar degeneration
- H**
- Heat shock protein-70 (HSP70), Tau binding
 - with CHIP, 463
 - Heat shock protein-90 (HSP90), therapeutic targeting, 463
 - Hippocampus, amyloid- β effects, 327, 329
 - Hirano bodies, 52
 - Histamine receptor, H3 antagonist therapy, 486
 - Homocysteine, levels in Alzheimer disease, 483–484
 - Homotaurine, Alzheimer disease treatment studies, 484
 - HSP70. *See* Heat shock protein-70
 - HSP90. *See* Heat shock protein-90
 - Huperzine A, Alzheimer disease treatment studies, 483
 - Hypertension, Alzheimer disease risk factor, 118–119
- I**
- IDE. *See* Insulin-degrading enzyme
 - Idebenone, Alzheimer disease treatment studies, 488
 - Incidence. *See* Epidemiology, Alzheimer disease
 - Inflammation
 - Alzheimer disease studies
 - epidemiology, 346–347
 - gene polymorphisms in inflammation pathways, 345–346
 - prevention trials, 348
 - prospects for study, 348–349, 499
 - treatment trials, 347–348
 - arachidonic acid, 345
 - cellular mediators
 - astrocyte, 339–340
 - microglia, 336–339
 - neuron, 340–341
 - oligodendrocyte, 340
 - cerebrospinal fluid biomarkers for Alzheimer disease, 100–101
 - complement system, 341–343
 - cyclooxygenase, 345
 - cytokines and chemokines, 343–344
 - Toll-like receptors, 344–345
 - Insulin, Alzheimer disease treatment studies, 486–487

Index

Insulin-degrading enzyme (IDE), amyloid- β
degradation, 395–396
Iron, amyloid- β interactions, 193

K

Ketasyn. *See* Axona

L

Language, Alzheimer disease deficits, 27
Late-onset Alzheimer disease (LOAD), genetics
AlzGene, 253
APOE, 252–253
genome-wide association studies, 253–255
overview, 124
Latrepidine. *See* Dimebon
LDLR1
amyloid- β metabolism regulation, 290–291
amyloid precursor protein trafficking and processing
regulation, 289–290
functional overview, 291–293
Leuprolide, Alzheimer disease treatment studies, 488
Lewy body. *See* Dementia with Lewy bodies
Lithium chloride, Tau phosphorylation inhibition
therapy, 461, 464, 487
LOAD. *See* Late-onset Alzheimer disease
Logopenic progressive aphasia (LPA)
clinical presentation, 162
histopathology, 163
Long-term depression (LTD)
amyloid- β oligomer enhancement, 322–324
lysosomal network defects in induction, 376
LPA. *See* Logopenic progressive aphasia
LRP1
amyloid- β metabolism regulation, 290–291
amyloid precursor protein trafficking and processing
regulation, 289–290
blood–brain barrier dysfunction in Alzheimer
disease, 410–413
functional overview, 291–293
knockout mouse, 286
LTD. *See* Long-term depression
LY450139. *See* Semagacestat
LY451395, Alzheimer disease treatment
studies, 486
LY2062430, clinical trials, 444–445
LY2811376, BACE inhibition, 432–434
Lysosomal network
Alzheimer disease role
genetic findings, 373–375
molecular pathology, 371–373
neuritic dystrophy, 375
neurodegeneration, 377
protein clearance failure and amyloidogenesis,
375–376

synaptic dysfunction, 376–377
tauopathy, 376
overview, 359–361, 369–371
therapeutic targeting, 377–378

M

Magnetic resonance imaging (MRI). *See also* Functional
magnetic resonance imaging
diffusion tensor imaging, 80
initial assessment of dementia, 15
principles, 68–69
structural imaging in Alzheimer disease
advantages, 21
atrophy, 69–70
gross features, 45
limitations, 21
progression studies, 70–71
MAPT
early-onset familial Alzheimer disease
mutations, 251
frontotemporal lobar degeneration mutations,
164, 169
Matrix metalloproteinases (MMPs), amyloid- β
degradation, 395
MBP. *See* Myelin basic protein
MCI. *See* Mild cognitive impairment
Memantine, NMDA receptor antagonism and therapy,
480–481
MEOX2, expression in Alzheimer disease, 413–414
Methylene blue, Tau fibrillization inhibition,
466–467
Microglia, inflammation mediation, 336–339
Microglia, Alzheimer disease effects, 52
Mild Alzheimer disease
clinical presentation, 16
neuropathology, 54–55
Mild cognitive impairment (MCI)
diagnostic criteria, 19–20
neuropathology, 54–55
nonsteroidal anti-inflammatory drug prevention
trials, 348
Mini-Mental Status Examination (MMSE), 14, 100,
429, 475
MK-0752, presenelin inhibition, 428
MMPs. *See* Matrix metalloproteinases
MMSE. *See* Mini-Mental Status Examination
MND. *See* Motor neuron disease
Moderate Alzheimer disease, clinical presentation,
16–17
Mortality, Alzheimer disease, 10, 16
Motor neuron disease (MND), frontotemporal
dementia, 163, 170
MRI. *See* Magnetic resonance imaging
MSA6A/MSA4E, late-onset Alzheimer
disease role, 254

- Myelin basic protein (MBP), amyloid- β degradation, 396
- Myocardin, expression in Alzheimer disease, 413–414
- N**
- NAP, microtubule stabilization in Alzheimer disease, 460
- Neprilysin, 393–394
- Nerve growth factor (NGF), gene therapy, 488, 490–491
- Neurofibrillary tangles (NFTs)
- animal models, 305–306
 - clinicopathological correlations, 47–48
 - composition, 46
 - definition, 44
 - lysosomal network defects in tauopathy, 376
 - morphology, 46–47
 - topographical distribution, 47
 - ubiquitination, 365–366
- Neurofilament proteins, cerebrospinal fluid biomarker studies, 100
- Neuron, loss in Alzheimer disease, 52–53
- Neuropil thread, definition, 44
- Neuropsychiatric Inventory (NPI), 14, 477
- Neurovascular unit (NVU), components and dysfunction in Alzheimer disease, 407–408
- NFTs. *See* Neurofibrillary tangles
- NGF. *See* Nerve growth factor
- Nicastrin, 261
- NMDA receptor. *See* *N*-Methyl-D-aspartate receptor
- N*-Methyl-D-aspartate (NMDA) receptor
- amyloid- β interactions, 195
 - amyloid precursor protein level effects, 220
 - dimebon antagonism, 489
 - memantine antagonism and therapy, 480–481
 - reelin effects, 287
- Notch, γ -secretase
- signaling, 269
 - sparing inhibitors, 270–271, 430
- NPI. *See* Neuropsychiatric Inventory
- NVU. *See* Neurovascular unit
- O**
- Oligodendrocyte, inflammation mediation, 340
- Omega-3 fatty acids, Alzheimer disease protection, 121
- P**
- Paired helical filament (PHF)
- Tau structure, 138–140
 - ubiquitin discovery, 361–363
- Parkinson's disease (PD), dementia overlap with Alzheimer disease, 56
- Pathological criteria, Alzheimer disease diagnosis, 53–54
- PAXIP1*, early-onset familial Alzheimer disease mutations, 251
- PCA. *See* Posterior cortical atrophy
- PD. *See* Parkinson's disease
- PDE. *See* Phosphodiesterase
- PEN2*, early-onset familial Alzheimer disease mutations, 251
- Peroxisome proliferator-activated receptor- γ (PPAR- γ), agonist therapy, 486–487, 489
- PET. *See* Positron emission tomography
- PF-03084014, presenelin inhibition, 428
- PHF. *See* Paired helical filament
- Phosphatidylinositol-binding clathrin assembly protein (PICALM), variants in Alzheimer disease, 123, 254
- Phosphodiesterase (PDE), inhibitor therapy, 486
- PiB. *See* Pittsburgh Compound-B
- PICALM. *See* Phosphatidylinositol-binding clathrin assembly protein
- Pin1, Tau interactions, 148
- Pioglitazone, Alzheimer disease treatment studies, 486
- Pittsburgh Compound-B (PiB), 76, 92, 444
- Plasma biomarkers, Alzheimer disease, 102–103
- Plasmin, amyloid- β degradation, 396
- PNFA. *See* Progressive nonfluent aphasia
- Positron emission tomography (PET)
- amyloid studies
 - applications, 78–80
 - limitations, 80
 - principles, 77–78 - fluorodeoxyglucose studies of Alzheimer disease
 - biomarker utility, 76–77
 - hypometabolism pattern, 75–76
 - limitations, 77
 - overview, 15
 - principles, 74–75
- Possible Alzheimer disease, diagnostic criteria, 11–13, 54
- Posterior cortical atrophy (PCA), Alzheimer disease pathology, 29–30
- PPA. *See* Primary progressive aphasia
- PP2A. *See* Protein phosphatase 2A
- PPAR- γ . *See* Peroxisome proliferator-activated receptor- γ
- Pravastatin, Alzheimer disease treatment studies, 489
- Prednisone, Alzheimer disease trials, 348
- Presenelins
- amyloid precursor protein processing, 208–210
 - early-onset familial Alzheimer disease
 - PSEN1* mutations, 250–251
 - PSEN2* mutations, 251 - functional overview, 262–265
 - genes, 260
 - inhibitors, 269–271, 307, 269–271, 426–431

Index

- Presenelins (*Continued*)
knockout mice, 307
Notch signaling, 269
processing, 261
structure, 260
structure-function relationships, 265–267
variants in Alzheimer disease, 123, 266, 268
- Prevalence. *See* Epidemiology, Alzheimer disease
- Primary progressive aphasia (PPA), Alzheimer disease
differential diagnosis, 32–33, 35
- Probable Alzheimer disease, diagnostic criteria,
11–13, 54
- Progressive nonfluent aphasia (PNFA)
clinical presentation, 161–162
histopathology, 163
- Progressive supranuclear palsy (PSP)
clinical presentation, 162–163
histopathology, 163, 165
- Proteasome. *See* Ubiquitin–proteasome system
- Protein phosphatase 2A (PP2A), therapeutic targeting,
462
- PSP. *See* Progressive supranuclear palsy
- R**
- RAGE. *See* Receptor for advanced glycation end products
- Receptor for advanced glycation end products (RAGE)
Alzheimer disease role, 344–345
blood–brain barrier dysfunction in Alzheimer
disease, 410
therapeutic targeting, 490
- Reelin, apolipoprotein E receptor signaling, 285–287
- Research driving forces, Alzheimer disease
competition of ideas and findings, 5–6
personal tragedy, 4
quest for scientific clarity, 3–4
societal crisis, 4–5
- Resveratrol, Alzheimer disease treatment studies, 488,
491
- Risk factors. *See* Epidemiology, Alzheimer disease
- Rivastigmine, acetylcholinesterase inhibition, 476,
478–479
- Rosiglitazone, Alzheimer disease treatment studies,
486–487
- S**
- SBT. *See* Short Blessed Test
- scyllo*-Inositol, amyloid- β aggregation inhibition,
437–438
- SD. *See* Semantic dementia
- Semagacestat (LY450139), presenelin inhibition,
269–270, 427
- Semantic dementia (SD)
clinical presentation, 161
histopathology, 163
- Semantic memory, Alzheimer disease deficits, 27–28
- Serum response factor (SRF), expression in Alzheimer
disease, 413–414
- Seven-Minute Screen, 14
- Severe Alzheimer disease, clinical presentation, 16–17
- Short Blessed Test (SBT), 14
- SILK. *See* Stable Isotope Labeling Kinetics
- Smoking, Alzheimer disease risk factor, 119–120
- SORL1*, variants in Alzheimer disease, 123–124
- SorLA/LR1, amyloid- β production regulation, 212
- Souvenaid, Alzheimer disease treatment studies, 485, 488
- SRE. *See* Serum response factor
- Stable Isotope Labeling Kinetics (SILK), cerebrospinal
fluid biomarker studies, 101–102
- Statins, Alzheimer disease treatment studies, 487, 489
- Stroke, Alzheimer disease risk factor, 118
- Synapse, loss in Alzheimer disease, 53
- T**
- TARDBP*, frontotemporal lobar degeneration
mutations, 170
- Tarenflurbil, presenelin inhibition, 270, 428, 430
- Tau
acetylation, 418, 462
aggregation, 143
Alzheimer disease pathology, 140–143
BAPTists versus TAUists, 5–6
binding partners, 145–149
cerebrospinal fluid biomarker studies
phosphorylation, 93–94
total protein, 92–93
degradation regulation, 369
distribution, 143–145
domains, 134–135
frontotemporal lobar degeneration histopathology,
163–167
FTDP-17 mutations, 457
gene. *See* *MAPT*
glycosylation, 142, 457, 462
history of study, 133–134
immunization therapy, 464–465
isoforms, 135, 456
lysosomal network defects in tauopathy, 376
microtubule binding, 455–456
microtubule interactions, 136–138, 141, 147
paired helical filament structure, 138–140
phosphorylation
inhibitors, 460–463
overview, 141–142
regulation by apolipoprotein E receptor, 286
proteolysis, 142
structure, 135–136
ubiquitination, 363–364
- TDP43
FTLD-TDP, 167–168, 170

- therapeutic targeting
 - challenges, 457–458
 - degradation enhancement, 463–465
 - fibrillization inhibition, 466–467
 - loss-of-function compensation, 459–460
 - phosphorylation inhibitors, 460–463
 - strategies, 458–459
 - Tetrodotoxin (TTX), amyloid precursor protein secretion effects, 220–222
 - Thioflavin T, amyloid- β aggregation studies, 435
 - TLRs. *See* Toll-like receptors
 - Toll-like receptors (TLRs), inflammation mediation, 344–345
 - Tramipolate, amyloid- β aggregation inhibition, 436–437
 - Traumatic brain injury, Alzheimer disease risk factor, 120
 - TTX. *See* Tetrodotoxin
- U**
- Ubiquitin–proteasome system
 - Alzheimer disease role, 367–369
 - amyloid- β degradation, 398
 - FTLD-UPS, 168
 - neurofibrillary tangle ubiquitination, 365–366
 - overview, 359–361
 - paired helical filament ubiquitin, 361–363
 - Tau ubiquitination, 363–364
 - ubiquitination steps, 366
- V**
- VaD. *See* Vascular dementia
 - Valproic acid, Alzheimer disease treatment studies, 487
 - Vascular dementia (VaD), Alzheimer disease differential diagnosis, 17–18, 33–34, 36
 - VCP, frontotemporal lobar degeneration mutations, 170–171
 - Visinin-like protein-1, cerebrospinal fluid biomarker studies, 100
 - Visuospatial ability, Alzheimer disease deficits, 29–30
 - Vitamin B₆, Alzheimer disease treatment studies, 484
 - Vitamin D Alzheimer disease protection, 121
 - Vitamin E, Alzheimer disease treatment studies, 484, 488
- W**
- Working memory, Alzheimer disease deficits, 28
- X**
- Xaliproden, Alzheimer disease treatment studies, 488
- Z**
- Zinc, amyloid- β interactions, 193

