Alzheimer’s disease research has undergone a major revolution over the last 10 years, and a combination of molecular genetics and biochemical pathology has identified key proteins involved in the pathological sequence of events that cause the disease. These proteins are: the amyloid precursor protein (APP) and its proteolytic fragments, particularly the β-amyloid peptide; the microtubular-associated protein tau; the presenilin proteins; and apolipoprotein E (ApoE). We are now at an exciting point, at which we are close to defining and integrating the neuronal signal-transduction events that impinge on, or emanate from, these proteins to cause the brain degeneration in Alzheimer’s disease. Progress in this area has identified, and will hopefully continue to identify, specific therapeutic targets for treatment of Alzheimer’s disease, while also providing a model for elucidating other neurodegenerative disorders. In September 1999 the Biochemical Society devoted its Annual Symposium at University College Cork, Ireland, to the topic of Neuronal Signal Transduction and Alzheimer’s Disease. The Symposium, sponsored by Elan Corporation, Novartis and Pfizer, was attended by many of the key researchers in this area. This book aims to present and integrate the latest research on this topic from some of the major researchers in this field.

Genetic studies have been invaluable in uncovering the fundamental molecular defects that can cause Alzheimer’s disease. Chapter 5 discusses the role of genetics in deciphering the molecular causes of Alzheimer’s disease and other primary neurodegenerative disorders. Chapter 6 looks at how knowledge of tau gene mutations enables us to understand the signals that lead to brain degeneration and dementia. Chapters 18 and 19 examine the application of molecular genetics to the creation of transgenic mouse models of Alzheimer’s disease.

Specific chapters consider various aspects of APP, tau, presenilin and ApoE signal-transduction biology.

Understanding the mechanisms controlling APP proteolysis and function is a crucial area of Alzheimer’s disease research, as the excessive production and deposition of β-amyloid in neuritic plaques is considered by many to be the central driving force for the disease. Chapter 1 discusses progress towards identification of inhibitors of β-amyloid production and fibrillization. Chapters 2 and 4 examine the signalling role of β-amyloid and the C-100 terminus of APP, respectively. Chapter 14 explores the role of β-amyloid-induced oxidative and inflammatory pathways in Alzheimer’s disease, while Chapters 18 and 19 look at the potential of overexpressing mutant APP to create transgenic animal models of Alzheimer’s disease. Chapter 3 considers the importance of post-
translational modifications in APP processing and function, and Chapters 15–17 discuss the role of endoplasmic reticular function, receptor–G-protein signalling and intracellular calcium homeostasis in APP processing, and β-amyloid deposition in the Alzheimer’s disease brain.

The microtubular-associated protein tau is the main component of the neurofibrillary tangle lesions that are a defining neuropathological characteristic of Alzheimer’s disease. The recent discovery that mutations in the \( \tau \) gene can cause fronto-temporal dementia with Parkinsonism (FTDP-17) has drawn even more attention to identifying the cellular mechanisms by which this protein contributes to brain degeneration in Alzheimer’s disease and other dementia disorders. Chapter 7 reviews the role of \( \tau \) gene mutations in neurodegeneration and Alzheimer’s disease. Chapters 8 and 9 discuss the latest research on the signalling mechanisms underlying tau phosphorylation and the role this may play in tau function and neurodegeneration. Chapter 11 considers evidence for interactions between ApoE and the neuronal cytoskeleton, with particular reference to tau. Chapters 16 and 17 discuss data suggesting that dysfunctional receptor–G-protein function and altered intracellular calcium homeostasis are related to tau hyperphosphorylation and neurofibrillary tangle formation in the Alzheimer’s disease brain. Chapter 19 reflects on work attempting to make transgenic models that recapitulate Alzheimer’s disease pathology by overexpressing tau.

Mis-sense mutations in presenilin genes are the most common cause of early onset, familial Alzheimer’s disease. The presenilin proteins have been discovered to impact on a number of diverse signal-transduction pathways involved in development, apoptosis and calcium ion homoeostasis. The discovery that presenilin mutations cause an overproduction of β-amyloid-42, is of central importance when considering the role of these proteins in the pathogenesis of Alzheimer’s disease. Chapter 9 reviews the signal-transduction function of presenilin proteins and their involvement in the development of Alzheimer’s disease. Chapters 18 and 19 contemplate the transgenic Alzheimer’s disease mouse models which overexpress mutant presenilin.

The finding that polymorphic variation in APOE (the gene encoding ApoE) was associated with an altered risk of developing Alzheimer’s disease was a significant advance in Alzheimer’s disease research. This immediately prompted a search for the mechanisms by which different APOE alleles can cause an increased propensity to develop Alzheimer’s disease. The complex signal-transduction mechanisms by which ApoE functions are described in Chapter 10. Chapter 11 reviews evidence for and against the interaction of ApoE with the cytoskeleton, with particular focus on the tau protein. Chapter 12 considers the mechanisms by which ApoE might influence neuronal and glial signalling, as well as the possible interaction of ApoE with β-amyloid. Chapter 19 describes phenotypic effects of ApoE4 overexpression in transgenic mice.

Other chapters in the book discuss central signal-transduction events which are aberrant in the Alzheimer’s disease post-mortem brain, and which may underly both plaque and tau pathology, and the progressive neurodegeneration associated with the disease. These events are receptor–G-protein function
(Chapter 16) and intracellular calcium homeostasis (Chapter 17). The role of calcium in Alzheimer’s disease is also reviewed in Chapter 15, which presents data suggesting that the endoplasmic reticulum may be a focal point for the neurodegenerative cascade that is Alzheimer’s disease.

Therapies that ameliorate the pathogenesis of Alzheimer’s disease are a primary goal of research into the sequence of molecular events that cause the disease. Many chapters discuss possible treatment strategies emanating from research findings. Current therapies attempt to upregulate acetylcholine cholinergic signal transduction using cholinomimetic drugs. Chapter 13 presents data exploring the key genes that are regulated by activation of muscarinic acetylcholine receptors, pointing to possible novel therapeutic targets. Chapter 14 describes the key role of oxidative stress and inflammatory pathways in Alzheimer’s disease, and provides some ideas about possible therapeutic targets. In an invited lecture, Professor I. Lieberburg (Elan Corporation) presented exciting findings which suggest that administering β-amyloid may block the excessive build-up of β-amyloid in Alzheimer’s disease.

Unravelling and identifying the primary and central signal transduction events that lead to Alzheimer’s disease provides many future challenges for scientific research. This book aims to summarize the current status of research in this area and will hopefully stimulate further investigation in this vital research field.

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Abbreviations

ABAD  β-amyloid peptide binding alcohol dehydrogenase
AC    adenylate cyclase
ACh   acetylcholine
AChe  acetylcholinesterase
AD    Alzheimer’s disease
AGE   advanced glycation endproducts
ApoE  apolipoprotein E
APP   β-amyloid precursor protein
Aβ    β-amyloid
Aβ40  40-amino-acid form of β-amyloid
[Ca²⁺]i intracellular calcium
CaMKII calcium/calmodulin-dependent kinase II
CBD   corticobasal degeneration
CDK   cyclin-dependent kinase
CLIP  chymotrypsin-like activity of the proteasome
CNS   central nervous system
COX   cyclo-oxygenase
CSF   cerebrospinal fluid
DLB   dementia with Lewy bodies
EGF   epidermal growth factor
ER    endoplasmic reticulum
ERK   extracellular signal-related kinase
FAD   familial Alzheimer’s disease
FTDP-17 frontotemporal dementia with Parkinsonism linked to chromosome 17
GFP   green fluorescent protein
GSK-3 glycogen synthase kinase-3
HDL   high-density lipoprotein
IL-1  interleukin-1
iNOS  inducible nitric oxide synthase
JNK   c-Jun N-terminal kinase
KPI   Kunitz protease inhibitor
LDL   low-density lipoprotein
LPS   lipopolysaccharide
LRP   low-density lipoprotein receptor-related protein
LTP   long-term potentiation
mACHR muscarinic acetylcholine receptor
MAP   mitogen-activated protein
xii  Abbreviations

M-CSF  macrophage-colony stimulating factor
NCAM  neural cell adhesion molecule
NFT  neurofibrillary tangle
NF-κB  nuclear factor κB
NGF  nerve growth factor
NMDA  N-methyl-D-aspartate
NO  nitric oxide
NPRAP  neuron-specific plakophilin-related armadillo protein
NSAID  non-steroidal anti-inflammatory drug
Par-4  prostate apoptosis response-4
PHF  paired helical filament
PI-3K  phosphoinositide 3-kinase
PKA  cAMP-dependent protein kinase
PKC  protein kinase C
PLA₂  phospholipase A₂
PS  presenilin
PSA  polysialic acid
PSP  progressive supranuclear palsy
RAGE  receptor for advanced glycation endproducts
RAP  receptor-associated protein
RyR  ryanodine receptor
sAPPα  secreted form of β-amyloid precursor protein
SERCA  sarcoplasmic/endoplasmic reticulum Ca²⁺-ATPase
SOD  superoxide dismutase
TM  transmembrane
TNF-α  tumour necrosis factor-α
VLDL  very-low-density lipoprotein