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## Preface

Aimed at studying human diseases, animal models emerged in the 1800s and underwent a real boom during the last decades. The discovery of new therapies for neurological disorders is especially predicated on the use of animal models both to identify new therapeutic targets and to carry out preclinical drug trials. Of primary concern to a neuroscience researcher is the selection of the most relevant animal model to achieve his or her research goals. Researchers are challenged to develop models that recapitulate the disorder in question, which is often not as straightforward as it may seem. Quite often they are confronted with the choice between models that reproduce cardinal pathological features of the disorders caused by mechanisms that may not necessarily occur in the patients versus models that are based on known etiological mechanisms that may not reproduce all clinical features. This is also the case in many neurological conditions that may be accompanied by dementia, as will be evidenced in this volume.

Dementia is defined as the loss of mental processing ability, including communication, abstract thinking, judgment, and ultimately physical abilities. Dementia typically also results in behavioral and personality changes, depending on the area(s) of the brain affected. Irrespective of etiology, dementia symptomatology significantly interferes with social and occupational functioning.

By definition, dementia refers to a syndrome consisting of a range of symptoms commonly found in people with brain diseases characterized by damage to and consequent loss of brain cells. Losing brain cells is a natural process linked to aging, but with illnesses that may lead to dementia, this loss occurs at a much faster rate resulting in abnormal brain function.

Currently, Alzheimer's disease is the most common neurological disease of adulthood, almost twice as common as stroke or epilepsy and as common as congestive heart disease. Since the elderly are the fastest growing segment of the population, the dementia epidemic poses major consequences for the health and aged care systems. It is forecasted that the worldwide number of elderly people suffering from dementia will rise to 63 million in 2030 and to 114 million by 2050. The concurrent direct (related to medical care) and indirect (reduced productivity due to illness) costs have attracted the attention of health care policy makers and motivated intensification of dementia-related research.

Preclinical research based on animal models is pivotal to our knowledge of underlying molecular mechanisms and the drug discovery pipeline for dementia aiming at the development of therapeutic strategies alleviating or preventing this devastating disorder. Part I of this volume deals with more general aspects of animal modeling as well as the related ethical issues and focuses on the dementia drug discovery pipeline. In Part II, essential methodological considerations when starting animal model research are dealt with, ranging from the choice of a certain species or strain to patenting issues. The quality and utility of any animal model should be assessed through rigorous validation; a valid model resembles the human condition in etiology, pathophysiology, symptomatology, and response to established therapeutics. Part III of this book, therefore, compiles various levels of validation including pathological, behavioral, neurochemical, pharmacological, and imaging aspects.

Neurodegeneration is the most common biological cause of dementia, with Alzheimer's disease accounting for more than 50% of the dementing subjects making it the fourth leading cause of death in Western society. Consequently, a large part of this volume (Part IV) deals with animal models of Alzheimer's disease, ranging from nonmammalian models such as fruit flies and zebra fish, over lesion and infusion-based models to the large number of available transgenic models. Given the boost transgenesis and gene targeting techniques have given to the development of valid phenocopies of the human condition, the included models are not exhaustive but give rather a representative sample of the available models. For an updated overview of available genetically modified models, we refer the readers to specialized websites, as e.g. <http://www.alzforum.org>. The subsequent chapters of Part V deal with other neurodegenerative conditions attended with dementia: Parkinson's disease, metachromatic leukodystrophy and adrenoleukodystrophy, amyotrophic lateral sclerosis, and frontotemporal dementia.

Dementia is not just limited to the degenerative types of dementia. Dementia after all refers to a syndrome which does not always follow the same course of development. In some cases, the person's condition may improve or remain stable over time. Types of vascular dementia, the second most common cause of dementia, are discussed in Part VI. The subsequent chapters touch upon (partially) reversible dementia types. Since various diseases or injuries may lie at the basis of these types of dementia, ranging amongst others from infections to trauma, metabolic, hormonal and toxic disorders, and tumors, only a limited selection of these types of dementia appears in this volume. Parts VII through IX reflect on animal models of, respectively, normal pressure hydrocephalus, trauma- and toxic-induced dementia.

New therapeutic avenues are opened up based on recent insights in pathophysiological mechanisms underlying dementia. This book stresses the importance of extensively validated animal models in drug discovery and development to predict clinical activity. Clinical research focuses on the diagnosis of Alzheimer's disease and related conditions in an early stage based on specific biomarkers. When conversion of mild cognitive impairment to dementia can be predicted, disease modifying treatment strategies become indispensable. Moreover, more attention is being paid to Behavioral and Psychological Signs and Symptoms of Dementia (BPSD). Animal models, therefore, should also aim at mimicking BPSD-related behaviors that will allow the evaluation of new psychopharmacological strategies.

This book will appeal to a broad readership as dementia represents an increasing socio-economical burden in our graying population. With contributions from prominent investigators in the broad field of dementia, this book brings together a wide spectrum of expertise, from neuropathologists, pharmacists, biochemists, and biologists to clinical neurologists. As a *Neuromethods* title, this book provides a detailed, yet accessible, overview of currently available animal models in the field of dementia research, and touches, as well, upon more general areas linked to the development and use of animal models. The book will appeal to both experienced animal researchers as well as investigators on the verge of starting animal model-based dementia research.

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