PREFACE

Since the composition and structure of DNA was first revealed more than half a century ago, advances in genetics have been nothing short of remarkable. Fifty years later, we have seen an exponential increase in the amount of research generated in genetics at all levels of analysis, including the discovery of genes that produce a broad range of diseases and disorders, as well as the completion of the human genome project. In addition, the genomes of a number of model organisms, including both mouse and rat, have been deciphered. Consequently, development of research in the neurosciences at the behavioral, biological, and physiological levels has accelerated in the last 20 years. Not only are we now in a position to develop meaningful genotype–phenotype relationships for complex neurobehavioral and neuropsychiatric disorders, we may also be at a point where we can create animal models of human psychiatric illness, determine the pathophysiology of these disorders, and perhaps advance genetic and other forms of molecular therapy.

The creation of transgenic and knockout mice and, in the last decade, the development of transgenic and knockout mouse models of genetic disorders associated with neurobehavioral and neuropsychiatric dysfunction, has been extraordinary. In recent years, mouse models have been created for cognitive and learning impairment (e.g., fragile X syndrome and nonsyndromal X-linked mental retardation), for pervasive developmental disorders (Rett syndrome), for psychosis and schizophrenia (del22q11), and for anxiety and depression.

Considering that the use of infrahuman animals in experiments to study the principles of behavior and rules of neuroscience is a relatively recent phenomenon, it is important to determine whether, or to what extent, infrahuman animals model human disabilities. This is particularly the case for researchers who study complex neurobehavioral and neuropsychiatric disorders such as schizophrenia, depression, mental retardation, and autism.

What, then, are the necessary and sufficient criteria to demonstrate that a given infrahuman organism is a proper model for neuropsychiatric dysfunction? Given the current state of transgenic and knockout technology, neuroscience, and means by which to evaluate animal behavior, we are now in a position to examine transgenic and knock-

out mouse models and the extent to which they mimic human illness. The goal of *Transgenic and Knockout Models of Neuropsychiatric Disorders* is to provide the reader with a clear and comprehensive assessment of how and whether genetic abnormalities produced in transgenic and knockout mouse models manifest neuropsychiatric disorders.

To accomplish this, we have divided the text into three main sections. In Part I, Chapter 1, we introduce and provide an overview of the history and assessment of neuropsychiatric disorders, and the controversial notion of continuity of species of human and infrahuman behavior articulated in Darwin's theory of evolution. In Chapter 2, we examine attempts to utilize infrahuman animals in experiments designed to improve our understanding of human behavior and psychiatric disease. Chapter 3 presents an epistemological argument concerning the problem of language in transgenic and knockout animal models, and whether nonhuman models of complex neuropsychiatric dysfunctions involving language are feasible. Chapter 4 presents the counterargument, noting how operant conditioning procedures can be used with infrahuman animals and transgenic and knockout mice in particular to study complex behavioral disorders.

In Part II, we present current research on transgenic and knockout models leading to the analysis of neurocognitive dysfunction—neurobiological disorders producing learning disabilities and mental retardation. Chapter 5 shows how mouse models can be used to examine the pathogenesis of human neurological diseases, particularly polyglutamate disorders. Chapter 6 provides a comprehensive review of several transgenic and knockout mouse models of mental retardation, noting the similarities and differences of neurocognitive development and function in humans compared to their mouse counterparts. Chapter 7 examines speech and language function, and how one gene associated with speech and language impairment and conserved evolutionarily in infrahuman organisms may be useful in examining human speech disorders using mouse models. Chapter 8 examines mouse models of genetic disorders associated with a high risk of developing autism, and the difficulties of developing mouse analogs of human disorders that involve cognitive, social, and speech and language dysfunction.

Part III focuses on neuropsychiatric dysfunctions: psychosis and schizophrenia, and the mood disorders: anxiety, depression, and

bipolar disorder. Chapter 9 discusses the difficulties in developing a mouse model for schizophrenia imposed by the constraints involving diagnosis, brain development, and the polygenic etiology of the disorder. Chapter 10 investigates the use of infrahuman animals to examine the cognitive and negative affect features of psychosis, and how NR1-deficient mice can be used as a model. Chapter 11 reviews anxiety and fear in mutant mice in an ethological setting, and the effects of drugs in modifying their behavior. Chapter 12 examines a variety of mutant mouse models in several animal experimental paradigms to assess anxiety and depression, as well as the effect of strain differences on behavior. Chapter 13 presents an overview of neurochemical, neuroendocrine, and behavioral changes in bipolar disorder, and the available mutant mouse models in which some aspects of the disorder are emulated.

We hope our readers find this comprehensive overview of animal models of neuropsychiatric disorders to be a useful tool in their research and classrooms.

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http://www.springer.com/978-1-58829-507-1

Transgenic and Knockout Models of Neuropsychiatric Disorders

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2006, XII, 296 p. 20 illus., Hardcover
ISBN: 978-1-58829-507-1
A product of Humana Press