Drug Discovery Approaches for the Treatment of Neurodegenerative Disorders

Alzheimer's Disease

Edited by
Adeboye Adejare

DRUG DISCOVERY APPROACHES FOR THE TREATMENT OF NEURODEGENERATIVE DISORDERS

ALZHEIMER'S DISEASE

Edited by

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Dedication

I would like to dedicate this book to my teachers and students. I am extremely fortunate to have had a great set of mentors in research from undergraduate (Dr. Harold M. Goff, The University of Iowa) to MS (Dr. David F. Weimer, The University of Iowa) to Ph.D. (Dr. Duane D. Miller, The Ohio State University) and finally postdoctoral studies (Dr. Kenneth L. Kirk, National Institutes of Health). I have also been blessed by a great set of students and postdoctoral associates. Many of them are authors of several of the chapters in the book.

Finally, I would like to dedicate the book to my greatest teacher, I. Abiola Adejare, none other than my father. Though you have moved on to "ibi agba re" (where elders go), the seeds that you sowed continue to bear great fruits.

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Foreword

Despite vastly increased understanding of the pathogenic cascades that underlie numerous neurodegenerative disorders, the last two decades have seen few inroads in terms of development of successful therapies. For the most, those therapies that have been approved are symptomatic in nature and do not significantly alter disease course. It is important that we learn from both our failures and our successes so that we may more efficiently develop therapies that meet our medical needs. Indeed, given the economic, societal, and personal toll of common and less common neurodegenerative diseases, we cannot collectively afford to fail. This book provides an overview, using Alzheimer's disease for illustration and a review of successes and failures to date, to help point out the paradigms necessary for successful therapeutic discovery and their translation into therapies that benefit patients. Diagnostic paradigms, epidemiology studies, current therapeutics targets (eg, amyloid, tau, APOE, energy metabolism, various receptors, cholesterol, and fat metabolism), and strategies for drug discovery are described. The value and also limits of preclinical models are also elaborated. The book also provides insights into the physicochemical properties that are necessary for such drugs, the role of in vivo models in evaluating potential efficacy, and a compendium of current agents in clinical trials. In addition, nonpharmacological treatment approaches and the national plan and resources available for anyone embarking on research in this area are discussed.

The editor, Adeboye Adejare, is an outstanding medicinal chemist and a professor at the Philadelphia College of Pharmacy, University of the Sciences, in Philadelphia. He has over 40 publications and four issued patents. He has served on many grant review committees that focus on CNS drug discovery including the National Institutes of Health, National Science Foundation, and Alzheimer's Association panels. He has also served as a consultant to the Food and Drug Administration, the Educational Testing Service (College Board, Princeton, New Jersey), as well as to many companies. He is editor of the Pharmaceutical Chemistry section of the 22nd edition of *Remington: The Science and Practice of Pharmacy*. The authors are experts in their various areas and several have industrial and/or clinical experiences.

The book is designed for college graduates involved in the drug discovery process, whether in academia, research institutes, or the pharmaceutical industry, and for chemists who are involved in drug design and those involved in clinical trials. Also laboratories and start-up companies that do not have access to extensive resources may find the book useful.

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Preface

The incidence of neurodegenerative disorders (NDs) keeps increasing. This increase is in part due to the fact that we are living longer, thanks to advances in the treatments of microbial infections, cardiovascular disorders, cancer, and other diseases. A good illustration of the dilemma presented by NDs is with Alzheimer's disease (AD). Prevalence has a high correlation with age. The Alzheimer Association estimates that there are about 5.4 million people living with AD and that given the current trajectory in longevity, as many as 13.8 million people may be battling the disease by 2050 (www.alz.org). The last US Food and Drug Administration-approved new chemical entity for AD was in 2003. So, while the need is increasing, treatment options have been very limited and stagnant for over a decade. Many clinical trials have failed to yield promising results. The costs to society using social or financial measures are staggering and increasing. A similar scenario holds for other NDs such as Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease though the numbers of people affected and therefore societal burden are lower. This situation calls for a fresh look at drug discovery for NDs, hence this book.

From reading literature and serving on many NDs drug discovery grant review panels, it became clear to me that while many of those efforts may be good science and certainly worthwhile, they may not necessarily lead to the main goals of the investigators, which in many instances are drugs for AD. This observation is further supported by the many clinical trials that failed to reach desired end points. A goal of this book is to provide a comprehensive look at drug discovery in this space. The approach to drug discovery for NDs is necessarily very different from those for microbial infections, cardiovascular disorders, cancer, and others. We have to deal with blood–brain barrier permeability issues in addition to complexity of the neuron and the chronic nature of the disease. The book provides information that investigators may find very useful, from where to go for research funding to which drugs are in clinical trials, what are their mechanisms of action, and by which company.

The editor is extremely grateful to the outstanding scientists who opted to write chapters in their various areas of expertise despite their very busy schedules. Broadly, the book can be divided into five parts. Part I has four chapters and deals with an introduction to NDs, AD diagnosis, national plan and resources to address AD, and current medications. Chapter 3 on national plan and resources to address AD is fairly unique to this book. Part II consists of Chapter 5, which deals with physicochemical properties desired for an AD medication especially if it is to be administered orally, which is the preferred route in most cases. These guidelines are for potential small molecule therapies, regardless of mechanisms of action. Part III deals with drug targets, from various pharmacological receptors to the amyloid hypothesis, tau proteins, cholesterol and fat metabolism as well as energy metabolism. These were covered in Chapters 6 to 10. Part IV deals with in vivo models that can be utilized in drug discovery, from simple ones such as *Caenorhabditis elegans* (Chapter 11) to rodents (Chapter 12), as well as advantages and limitations presented by each model. The last part

deals with relevant topics that are not necessarily covered in many drug discovery books but which are very relevant in these efforts. Chapter 13 deals with drugs at different phases of clinical trials including mechanisms of action and sponsoring companies. The final chapter deals with nonpharmacological treatment approaches, which range from cognitive training to diet and environmental modification. These approaches can attenuate AD and therefore be part of a comprehensive plan where they exert synergistic effects with drugs.

The book is designed for scientists involved in drug discovery, from chemists to pharmacologists and clinicians; be they in academia, research institutes, or the pharmaceutical industry. Others such as physicians, patients, and their families may find it useful, for example, in deciding in which clinical trials to participate. The book has been written in such a manner that anyone with a college education especially in the sciences can read and understand the many topics. It can also be used as a textbook for upper-level undergraduate and graduate courses on drug discovery in the area of neuroscience addressed.

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Acknowledgments

The good news is that we are living longer! This development is in part because of progress in addressing several health care challenges such as microbial infections, cardiovascular disorders, and even cancer. The not-so-good news is that diseases associated with aging such as neurodegenerative disorders are increasing. Examples of these neurodegenerative disorders are Alzheimer's and Parkinson's diseases. Given the limited availability of medications, the unmet needs, and the very high failure rate in clinical trials, it appeared to me that a comprehensive look at addressing drug discovery for neurodegenerative disorders in the form of a book was clearly needed. The paradigm for drug discovery for neurodegeneration is certainly very different from those for antiinfectives, cancer, and many other diseases. Around 2012, I began discussions with Elsevier, Inc. about such a book. In the meantime, I was fortunate to be able to attend two relevant National Institutes of Health meetings, namely, Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention (May 14–15, 2012) and Alzheimer's Disease-Related Dementias: Research Challenges and Opportunities (ADRD) (May 1–2, 2013). This period was when the idea of this book began to take hold. I then set out to teach a graduate-level special topics course on "Drug Discovery for Neurodegenerative Disorders" in 2013. By the end of the course, the outline for the book began to emerge.

I would like to thank all authors in the book. I set out to identify the broad areas for drug discovery for neurodegenerative disorders using Alzheimer's disease as an illustration since it is the most prevalent and has major increasing need. I contacted several experts in the various areas and in different countries since the matter is global in nature. I am thankful and grateful that they responded in a positive manner, resulting in an outstanding piece of work.

I am also thankful to the reviewers for providing excellent feedback to the authors. The reviewers include Laura Finn, Michael Dybek, Mohammed Alamri, Drs. Adegoke Adeniji, Hadiyah-Nicole Green, Joy L. Britten-Webb, Jason Wallach, and Zeynep Ates-Alagoz. The gentle persistence of Kristine Jones, Senior Acquisitions Manager, and help of Molly McLaughlin, Editorial Project Manager, both of Elsevier, Inc., are also gratefully acknowledged. I am also grateful to Dr. Todd E. Golde for the Foreword.

I would also like to acknowledge the support for my career in academia and for this book granted by my family, starting from my lovely wife Adekemi to our children Adeboye Jr. (AJ), Adekunle, Aderonke, and Adeola. I would also like to thank many people who have been helpful in one way or another, with special thanks going to my mother, Ayoola Adejare.

Contents

CHAPTER

1

Neurodegenerative Disorders: Why Do We Need New Therapies?

T.A. Yacoubian

OUTLINE

INTRODUCTION

Neurodegeneration covers a wide spectrum of neurological disorders. These disorders can manifest with many different symptoms, including cognitive impairment, speech difficulties, and motor dysfunction. The underlying pathological hallmark shared by neurodegenerative disorders is the loss of neuronal populations in the brain and/or spinal cord. The particular areas of the brain and spinal cord in which neuronal loss occurs dictate the clinical features of a given neurodegenerative disorder. Neurodegenerative disorders include common and uncommon diseases including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal

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degeneration (CBD), frontotemporal dementia (FTD), spinocerebellar ataxia (SCA) disorders, and spinal muscular atrophy, among others. This chapter is not meant to be an all-inclusive review of this large and diverse group of disorders but to serve as an introduction to neurodegeneration in general. In this chapter, we will focus on AD, along with PD, HD, and ALS, as examples of the more common neurodegenerative disorders to discuss some of the similarities and differences among this broad class of neurological disorders.

As a whole, neurodegenerative disorders are common. AD is the most common neurodegenerative disorder. AD is the sixth-leading cause of death in the United States (Murphy et al., 2013). Approximately 5 million Americans over the age of 65 had AD in 2010, which translates to about 11% of Americans over age 65 as having AD (Alzheimer's Association, 2014; Hebert et al., 2013). With the expected aging of the US population, it is estimated that 13.8 million older Americans will have AD in 2050 (Hebert et al., 2013). The second most common neurodegenerative disorder is PD, with an estimated prevalence of PD in the United States of about 630,000 cases in 2010 (Kowal et al., 2013). As with AD, the prevalence of PD is age related, with a dramatic increase in prevalence after age 65. While the prevalence is estimated at 0.3% in the general US population, the prevalence rate is 1–2% over age 65 and 4–5% over age 85 (Dorsey et al., 2007; Hirtz et al., 2007; Kowal et al., 2013; Noyes et al., 2006; Weintraub et al., 2008). As with AD, the prevalence of PD is dramatically increasing, with an expected doubling of PD prevalence by the year 2040 (Dorsey et al., 2007; Kowal et al., 2013).

With the anticipated rise in AD and PD cases in the next several decades, the expected societal burden and financial costs of these two disorders are sky-rocketing. In the case of AD and related dementias, the estimated total health care costs were $214 billion in 2014, with about 70% paid by Medicare and Medicaid (Alzheimer's Association, 2014). Additionally, it is estimated that 17.7 billion hours of unpaid care was provided by caregivers for patients with AD and other dementias in 2013, valued at about $220.2 billion (Alzheimer's Association, 2014). Given the expected increase in AD prevalence, the predicted health care costs for AD will reach $1.2 trillion in 2050 (Alzheimer's Association, 2014). The anticipated costs for PD are less, because of the lower prevalence, but are still considerable. Estimated medical costs secondary to PD were about $8 billion in the United States in 2010, and costs caused by reduced employment and other indirect costs were estimated at $6.3 billion in 2010 (Kowal et al., 2013). By 2050, the projected medical costs secondary to PD will reach $18.5 billion (Kowal et al., 2013). While other neurodegenerative disorders are less common, they still cause considerable disability and loss of life.

CLINICAL FEATURES OF COMMON NEURODEGENERATIVE DISORDERS

While all neurodegenerative diseases are marked by neuronal loss and atrophy, these disorders vary greatly in the clinical manifestations of the disorder. Some disorders, such as AD or FTD, are marked by significant cognitive decline, while other disorders, such as PD and ALS, are initially marked by motor impairment. Some disorders, such as HD, can have motor, psychiatric, and cognitive impairment as predominant features early on. The common neurodegenerative disorders can usually be distinguished by a thorough neurological evaluation, yet the rarer disorders, such as PSP and MSA, can often be difficult to distinguish from their

more common relatives early on in the disease course. While each neurodegenerative disorder has its distinguishing features, these diseases can look somewhat similar at the end stage with patients becoming bed bound, mute, incontinent, and unable to care for self.

Alzheimer's disease, the most common neurodegenerative disorder, is marked by memory impairment. Patients initially present with memory dysfunction. Episodic memory is typically affected, with more recent events being more difficult to remember and a tendency of more distant memories preserved initially. Patients also have early impairment in semantic memory, memory involving knowledge of facts about the world, but procedural memory is not affected. Other cognitive dimensions involved in AD include language, visuospatial function, praxis, and executive function. AD patients have language difficulties that manifest early in the disease as reduced verbal fluency and naming. Anosognosia, or lack of awareness of cognitive decline, is common in AD. Patients often have neuropsychiatric disturbances, including depression, delusions, hallucinations, behavioral disturbances such as agitation, and personality changes. However, these features can be seen in other neurodegenerative dementias, such as FTD and DLB, and the constellation of other neurological features is used for distinguishing these disorders.

PD has been classically defined as a motor disorder. The cardinal motor features of PD include resting tremor, bradykinesia, rigidity, and gait imbalance. However, the nonmotor features of PD have been increasingly recognized in the last decade. Nonmotor features of PD include cognitive impairment, psychiatric symptoms, autonomic dysfunction, and sleep disturbances. Autonomic dysfunction includes constipation, gastrointestinal motility issues, urinary symptoms, orthostatic hypotension, and sexual dysfunction. Common psychiatric features include depression and anxiety. In later stages of PD, patients develop cognitive decline and potentially full-blown dementia. In contrast to AD, memory impairment is not typically seen in PD, but cognitive impairment in PD is marked by deficits in attention and executive function, hallucinations, and psychosis. Sleep disturbances include sleep apnea, daytime sleepiness, and rapid eye movement sleep behavior disorder (RBD). Certain nonmotor features, such as RBD, loss of sense of smell, and constipation, are likely the initial features of PD that may predate the motor features by 10 or more years.

ALS presents with weakness and atrophy in a focal group of muscles and then spreads to contiguous muscles before spreading to other parts of the body. Typically, the weakness first develops in one limb, although in some patients the weakness can begin in bulbar muscles, affecting speech and swallowing. Patients also note fasciculations or muscle twitches. Traditionally, cognitive and behavioral impairments have not been viewed as a feature of ALS, yet patients can have deficits in executive function, anomia, impaired verbal fluency, apathy, and personality changes (Phukan et al., 2007; Ringholz et al., 2005; Witgert et al., 2010). If not the presenting feature of their disease, patients eventually develop severe dysarthria and dysphagia, which impedes their caloric intake and thus worsens their weakness. Patients with ALS decline relatively rapidly and eventually develop respiratory failure.

HD presents clinically with a triad of psychiatric illness, cognitive impairment, and motor dysfunction. When HD manifests during adulthood, patients can present with either motor symptoms or behavioral symptoms initially. Psychiatric symptoms include depression, anxiety, and less likely mania and psychosis. Rates of suicide are very high in patients with HD. Behavioral disturbances are common. HD patients may have aggressive behaviors toward others. Patients also develop cognitive impairment, with decline in attention, motivation,

insight, problem solving, and executive function. They often lack insight into their own illness. The motor dysfunction is typically marked by choreiform movements, which are excessive, involuntary movements involving the limbs, face, tongue, and trunk. Patients develop incoordination, bradykinesia, impaired eye movements, dysarthria, dysphagia, and gait difficulty. The clinical presentation in childhood is quite different. Juvenile HD is marked by akinesia and rigidity along with cerebellar ataxia and seizures. Diagnosis of the disorder is made by genetic testing for the CAG repeat expansion in the *huntingtin* (*htt*) gene.

For many of these disorders, including AD, PD, and ALS, the diagnosis is made based on clinical criteria. There is no specific imaging or laboratory test that can confirm the diagnosis, leading to some diagnostic uncertainty for some patients with evidence of neurodegeneration. This lack of diagnostic uncertainty not only affects individual patients with questions regarding treatment options and prognosis, but affects the field of neurodegeneration as a whole, particularly in the development of new therapies. The lack of clear biomarkers for many of these disorders complicates the design and interpretation of clinical trials. For example, the lack of a therapeutic effect of a new drug in a clinical trial could be affected if a fair number of patients are misdiagnosed and included in the trial. It is also difficult to measure disease progression objectively without distinct biomarkers. For certain disorders, the diagnosis can be confirmed irrefutably. This is true of those diseases caused by genetic mutations, such as HD and SCAs. However, the current cost of genetic testing can be a significant barrier for diagnosis for many patients, as many insurance policies will not cover genetic testing.

PATHOLOGICAL FEATURES OF COMMON NEURODEGENERATIVE DISORDERS

Common pathological features shared among the neurodegenerative disorders are neuronal cell loss, gliosis, atrophy, and pathological protein inclusions. These disorders differ in the details of the neuropathology—which neuronal populations are lost, what proteins are found in inclusions, and the subcellular localization of these inclusions.

In AD, the key pathological features include neuron loss, amyloid plaques, and neurofibrillary tangles. Atrophy is predominant in temporal and parietal cortex because of neuronal loss. Neuron loss is predominant in layers 3 and 5 of the neocortex, CA1 region of the hippocampus, and layers 2 and 5 in the entorhinal cortex. Plaques are composed of abnormal neurites and glial processes surrounding a central core composed of β-amyloid. β-Amyloid can also be found in the cerebral blood vessels. Plaques are mostly found in cerebral cortex and hippocampus. Neurofibrillary tangles are composed of excessively phosphorylated tau protein that form paired helical filaments that are deposited in soma and processes of neurons. In the earliest stages, neurofibrillary tangles develop in the transentorhinal cortex and then spread to the entorhinal cortex and hippocampus prior to neocortical regions (Braak and Braak, 1991, 1995). These tangles are not specific to AD, but are found in other neurodegenerative disorders, including PSP and dementia pugilistica.

PD was classically described as caused by loss of dopaminergic neurons within the substantia nigra with associated Lewy bodies, cytoplasmic aggregates made up predominantly of alpha-synuclein (Spillantini et al., 1997). The motor features of this disorder are caused by the loss of these nigral neurons, but many other brain areas are also involved in PD. Braak