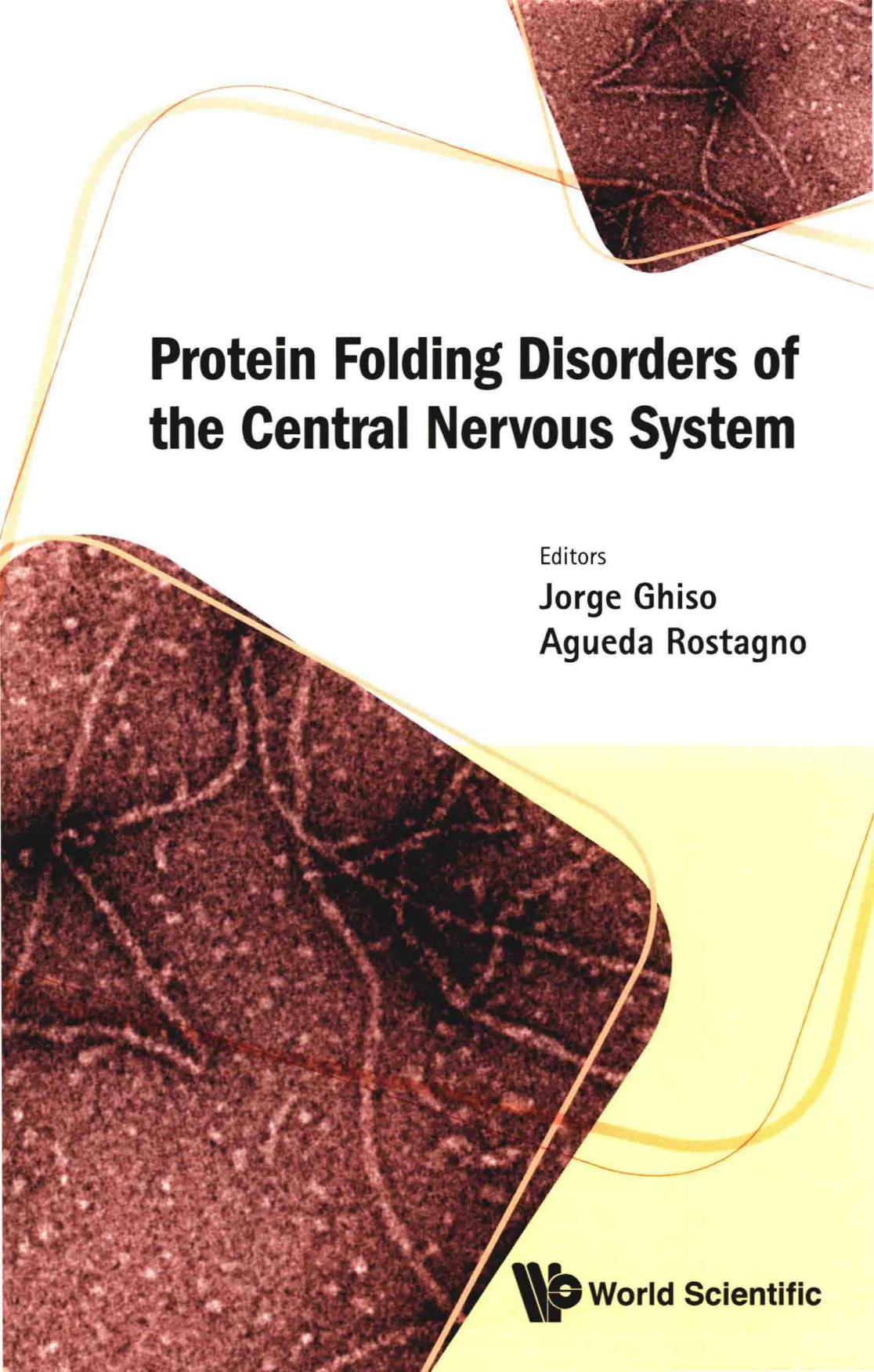

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Editors
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Agueda Rostagno

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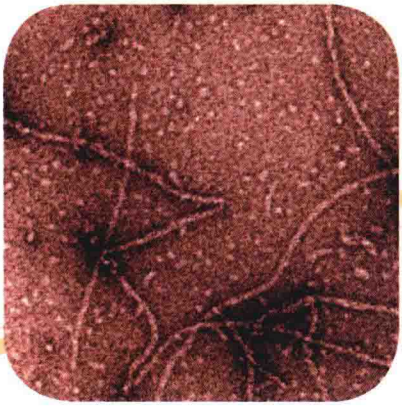

Protein Folding Disorders of the Central Nervous System

This exciting new book explores the dark side of the molecular protein assembly bringing an updated view of how failures in the homeostatic mechanisms that efficiently regulate protein folding leads to the accumulation of structurally abnormal pathogenic assemblies, encompassing an emerging group of diseases collectively known as "Protein Folding Disorders." This complex and diverse group of chronic and progressive entities are bridged together by their relationship to structural transitions in the native state of specific proteinaceous components, which for reasons poorly understood, convert into polymeric aggregates that generate poorly soluble tissue deposits and which are considered today the culprit of the disease pathogenesis in their respective diseases. Despite the diversity in the amino acid sequence of the different proteins involved in these heterogeneous disorders, all the pathologic conformers can trigger cascades of events ultimately resulting in cell dysfunction and death with devastating clinical consequences in many of the most precious aspects of human existence including personality, cognition, memory, and skilled movements.

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Preface

The proteins of a living organism, after synthesis at the ribosome, must properly fold into specific conformational states to successfully perform their biological function. To this aim, all cells possess complex mechanisms to efficiently regulate protein assembly into functionally active and optimally balanced states. In spite of these homeostatic mechanisms set in place, under some conditions, proteins fail to fold correctly, or to remain correctly folded in living systems, a failure that eventually leads to the accumulation of structurally abnormal pathogenic assemblies. The term "protein misfolding disorders" refers to an emerging complex group of chronic and progressive entities in which the pathogenesis of the respective diseases is driven by structural transitions in the native state of specific proteinaceous components into polymeric aggregates which generate poorly soluble tissue deposits.

Here, we took the challenge to organize a book focusing on diseases associated with protein misfolding in the central nervous system (CNS), which we felt needed to be addressed given the growing number of reports linking abnormal protein folding/aggregation to human disease, in general, and neurodegeneration, in particular. Although distinguished by disease-specific pathology and clinical presentations, these disorders share conspicuous similarities. They are mostly of sporadic origin and, since they are largely age-related, their relevance continues to rise as the number of individuals affected by these conformational disorders is expected to

increase as the world population ages. Current therapeutic strategies are only aimed at alleviating symptoms, and in most cases the normal physiological function of the proteins that aggregate in the respective diseases remain unknown. These proteins are, however, all intimately associated with the specific disorders, as mutations in the gene encoding the disease-linked protein, or its precursor, cause early-onset familial disease.

The book is divided into 14 chapters that provide a comprehensive, state-of-the-art perspective of the topic under discussion, bringing insights into the biological/biophysical mechanisms of protein folding and their relationship to CNS diseases linked to aberrant protein conformations. Individual chapters are dedicated to the most common neurodegenerative diseases associated with protein aggregation/fibrillization, focusing on the nature of the pathogenic species and the pathways involved in Alzheimer's, Parkinson's, and Huntington diseases as well as in amyotrophic lateral sclerosis, and prion diseases. A group of contributions is focused on the intracellular pathways and organelles affected by the different disease conditions and the transmissibility of protein misfolding, whereas another set of chapters is dedicated to novel strategies to therapy for these devastating diseases.

The combination of contributions compiled in this volume is expected to be of interest to the large audience of protein chemists, biochemists, and biophysicists from postgraduate level onward, as well as to clinicians, and all scientists with broad interests in aspects relating to structural biology, protein folding, and disease, as well as in the molecular and cellular aspects of disease pathogenesis in the CNS. We hope that this overview on this key biological problem will make this volume a resourceful source of information that bridges together different aspects of these complex problem.

Agueda Rostagno
Jorge A. Ghiso

List of Contributors

Alejandra D. Alonso ♦ *Department of Biology, Center for Developmental Neuroscience, College of Staten Island, Graduate Center, The City University of New York, New York, NY, USA*

Jorge Busciglio ♦ *Department of Neurobiology and Behavior, Center for the Neurobiology of Learning and Memory, Institute for Memory Impairments and Neurological Disorders, University of California-Irvine, Irvine, CA, USA*

Christina-Maria Cheimonidi ♦ *Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Athens, Greece*

Leah S. Cohen ♦ *Department of Biology, Center for Developmental Neuroscience, College of Staten Island, Graduate Center, The City University of New York, New York, NY, USA*

Nathalie Daude ♦ *Centre for Prions and Protein Folding Diseases, University of Alberta, Edmonton, Alta., Canada*

Zoi Evangelakou ♦ *Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Athens, Greece*

Jeremiah Faith ♦ *Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA*

Paul E. Fraser ♦ *Department of Medical Biophysics, Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ont., Canada*

Jorge A. Ghiso ♦ *Departments of Pathology and Psychiatry, New York University School of Medicine, New York, NY, USA*

Despoina Gianniou ♦ *Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Athens, Greece*

Sentiljana Gumeni ♦ *Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Athens, Greece*

Lap Ho ♦ *Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA*

Hibiki Kawamata ♦ *Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, USA*

Hanna Księżak-Reding ♦ *Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, and Geriatric Research, Education, and Clinical Center — GRECC, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA*

Matthew Mahavongtrakul ♦ *Department of Neurobiology and Behavior, Center for the Neurobiology of Learning and Memory, Institute for Memory Impairments and Neurological Disorders, University of California-Irvine, Irvine, CA, USA*

Giovanni Manfredi ♦ *Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, USA*

Eliezer Masliah ♦ *Departments of Neuroscience and Pathology, University of California-San Diego, La Jolla, CA, USA*

Robert C. C. Mercer ♦ *Department of Medicine, University of Alberta and Centre for Prions and Protein Folding Diseases, University of Alberta, Edmonton, Alta., Canada*

Viktoriya Morozova ♦ *Department of Biology, Center for Developmental Neuroscience, College of Staten Island, Graduate Center, The City University of New York, NY, USA*

Kenjiro Ono ♦ *Department of Neurology, Showa University School of Medicine, Shinagawa-ku, Tokyo, Japan*

Eleni-Dimitra Papanagnou ♦ *Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Athens, Greece*

Giulio M. Pasinetti ♦ *Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, and Geriatric Research, Education, and Clinical Center — GRECC, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA*

Agueda Rostagno ♦ *Department of Pathology, New York University School of Medicine, New York, NY, USA*

Hyung Don Ryoo ♦ *Department of Cell Biology, New York University School of Medicine, New York, NY, USA*

Ali Sharma ♦ *Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA*

Einar M. Sigurdsson ♦ *Departments of Neuroscience and Physiology, and Psychiatry, New York University School of Medicine, New York, NY, USA*

Aimilia D. Sklirou ♦ *Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Athens, Greece*

Brian Spencer ♦ *Department of Pathology, University of California-San Diego, La Jolla, CA, USA*

Kostantinos Tallas ♦ *Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Athens, Greece*

Anurag Tandon ♦ *Department of Medicine, Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ont., Canada*

Naoko Tanese ♦ *Department of Microbiology, New York University School of Medicine, New York, NY, USA*

Ioannis P. Trougakos ♦ *Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Athens, Greece*

Eleni N. Tsakiri ♦ *Department of Cell Biology and Biophysics, Faculty of Biology, University of Athens, Athens, Greece*

Breanna Valcarcel ♦ *Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA*

Emily Vogler ♦ *Department of Neurobiology and Behavior, Center for the Neurobiology of Learning and Memory, Institute for Memory Impairments and Neurological Disorders, University of California-Irvine, Irvine, CA, USA*

Lary C. Walker ♦ *Department of Neurology, Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA*

Jun Wang ♦ *Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, and Geriatric Research, Education, and Clinical Center — GRECC, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA*

Joel C. Watts ♦ *Department of Biochemistry, Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ont., Canada*

David Westaway ♦ *Departments of Medicine and Biochemistry, University of Alberta, Centre for Prions and Protein Folding Diseases, and Centre for Neuroscience, University of Alberta, Edmonton, Alta., Canada*

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