Neurodegeneration: Opportunities for Collaboration Across Disease-Specific Research and Development Communities - *A Workshop*

April 30 – May 1, 2012

Pew DC Conference Center
901 E Street, NW, Washington, DC

Background: Neurodegenerative diseases are becoming increasingly more prevalent in the United States due to the aging population. Implications of these diseases are grave, both for individual and family quality of life and for healthcare costs. Recent findings have revealed potential commonalities and parallelisms in genetic and cellular mechanisms across neurodegenerative diseases. Enhanced sharing of research findings and collaboration across research communities could potentially help advance basic scientific knowledge about each disease and about neurodegeneration and neurodegenerative diseases in general. Furthermore, enhanced basic scientific understanding could facilitate therapeutics development for neurodegenerative disorders, including therapeutics that may address more than one neurodegenerative disease. This workshop will explore commonalities across neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and frontotemporal dementia, and identify potential opportunities for collaboration across the respective research and development communities. Speakers and participants will be invited from academia; pharmaceutical and biotechnology industries; government agencies such as NIH, NSF, and VA; and disease advocacy groups.

Meeting Objectives: The objectives of this workshop are to look across the neurodegenerative diseases—including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and frontotemporal dementia—and:

- Identify and discuss commonalities related to genetic and cellular mechanisms.
- Identify areas of fundamental science needed to facilitate therapeutics development.
- Explore areas of potential collaboration among the respective research communities and sponsors.

DAY ONE: April 30, 2012

Note: Breakfast will be available from 7:30 a.m.

8:00 a.m. **Welcome and Opening Remarks**

STORY LANDIS, *Workshop Co-Chair*
Director
National Institute of Neurological Disorders and Stroke

JOHN TROJANOWSKI, *Workshop Co-Chair*
Co-Director, Center for Neurodegenerative Disease Research
University of Pennsylvania

8:10 a.m. **U.S. Department of Veterans Affairs and Neurodegeneration Research: Current Efforts and Future Goals**

JOEL KUPERSMITH
Chief Research and Development Officer
U.S. Department of Veterans Affairs

SESSION I: OVERVIEW OF COMMON FEATURES ACROSS NEURODEGENERATIVE DISEASES

Session Objectives: The objectives of this session are to provide a genetic, clinical and pathological framework to the notion that commonalities exist across neurodegenerative diseases. While this meeting focuses on discreet diagnostic entities, it is likely that this section may use examples from entitites that cross these boundaries. Specifically this session will:

- Provide an overview of the genetic complexity of different neurodegenerative diseases.
- Discuss common and distinguishing features of the genetics of different neurodegenerative diseases.
- Discuss the clinical heterogeneity of monogenic disorders.
- Describe and discuss how pathology is likely to inform us about etiologic overlap between entities and provide illustrative examples of this overlap.
- Discuss the rationale for looking across neurodegenerative diseases to advance scientific understanding and explore innovative approaches to therapeutics development.

8:20 a.m. **Genetic Overlap and Complexity of Phenotypical Expression**

ANDREW SINGLETON, *Session Chair*
Senior Investigator, Laboratory of Neurogenetics
National Institute on Aging

8:30 a.m. **Pathological Overlap**

DENNIS W. DICKSON
Professor of Laboratory Medicine and Pathology
Mayo Clinic

8:40 a.m. **Translational Route Challenges: Is Combining Diseases Informative or a Distraction?**

ADRIAN J. IVINSON
Director, Harvard NeuroDiscovery Center
Harvard Medical School

8:50 a.m. Discussion Among Speakers and Attendees

SESSION 2: PROTEIN AGGREGATION IN NEURODEGENERATIVE DISEASES

Session Objectives: The objectives of this session are to look at protein aggregation across the neurodegenerative diseases—including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and frontotemporal dementia—and:

- Highlight commonalities related to protein aggregation across these diseases, e.g., autophagy.
- Discuss promising opportunities for collaboration among the respective research communities.
- Identify areas of fundamental research about protein aggregation that would facilitate biomarker and therapeutics development.
- Identify the next steps that research sponsors, investigators, and others should take to facilitate collaborative research and drug development in this area, including frameworks for partnerships and collaboration.

9:10 a.m. **Overview of Status of the Field and Session Objectives**

JOHN DUNLOP, *Session Co-Chair*
Vice President, Discovery
Neuroscience Innovative Medicine Unit
AstraZeneca

LUCIE BRUIJN, *Session Co-Chair*
Chief Scientist
Amyotrophic Lateral Sclerosis Association

9:20 a.m. **Proteostasis Challenges in Neurodegenerative Diseases**

RICK MORIMOTO
Professor of Molecular Biosciences
Northwestern University

9:30 a.m. Discussion Among Speakers and Attendees

9:45 a.m. **The Selective Degradation of Misfolded Proteins and Protection against Neurodegenerative Diseases**

ALFRED GOLDBERG
Professor of Cell Biology
Harvard Medical School

9:55 a.m. Discussion

10:10 a.m. BREAK

10:25 a.m. **Autophagy in Neurodegenerative Disease**

ANA MARIA CUERVO
Professor, Department of Developmental and Molecular Biology
Albert Einstein College of Medicine

10:35 a.m. Discussion

10:50 a.m. **Protein Aggregation in Amyotrophic Lateral Sclerosis and Huntington's Disease**

CLAUDIO HETZ
Professor, University of Chile
Adjunct Professor, Harvard School of Public Health

11:00 a.m. Discussion

11:15 a.m. **Development of Assay Systems in Observing Aggregates and Development of Small Molecules**

STEVEN FINKBEINER
Director, Taube-Koret Center, Gladstone Institute for Neurodegenerative Disease
Professor, University of California San Francisco

11:25 a.m. Discussion

11:40 a.m. **Drug Discovery Efforts**

WARREN HIRST
Associate Research Fellow, Neurodegeneration & Neurologic Diseases
Pfizer

11:50 a.m. Discussion

12:30 p.m. LUNCH

SESSION 3: MITOCHONDRIAL PATHOLOGY AND NEURODEGENERATIVE DISEASE

Session Objectives: The objectives of this session are to look at mitochondrial pathobiology across the neurodegenerative diseases—including Alzheimer's disease and other dementias, Parkinson's disease, and amyotrophic lateral sclerosis—and to:

- Highlight differences and commonalities related to mitochondrial dysfunction and pathology across the diseases.
- Discuss opportunities for the development of mitochondria-related biomarkers and therapeutic interventions.
- Identify next steps that research sponsors, investigators, and others should take to facilitate collaborative research and drug development in this area, including frameworks for partnerships and collaboration.

1:30 p.m. **Overview of Status of the Field and Session Objectives**

LENNART MUCKE, *Session Chair*
Director and Senior Investigator, Gladstone Institute of Neurological Disease
Professor of Neurology and Neuroscience
University of California, San Francisco

1:40 p.m. **Systems Biology and Disease**

VAMSI K. MOOTHA
Professor
Department of Systems Biology, Harvard Medical School
Department of Medicine, Massachusetts General Hospital

1:50 p.m. Discussion Among Speakers and Attendees

2:05 p.m. **Neuronal Cell Death in Human Neurological Disorders and their Animal/Cell Models**

LEE MARTIN
Professor of Pathology, Neuroscience
Johns Hopkins University

2:15 p.m. Discussion

2:30 p.m. **Parkinson's Disease**

RICHARD J. YOULE
Senior Investigator
National Institute of Neurological Disorders and Stroke

2:40 p.m. Discussion

2:55 p.m. BREAK

3:10 p.m. **Amyotrophic Lateral Sclerosis and Huntington's Disease**

NEIL KOWALL
Professor of Neurology and Pathology, Boston University
Chief of Neurology, VA Boston Healthcare System

3:20 p.m. Discussion

3:35 p.m. **Alzheimer's Disease**

DOUGLAS C. WALLACE
Director, Center for Mitochondrial and Epigenomic Medicine
Michael and Charles Barnett Chair of Pediatric Mitochondrial Medicine and Metabolic Disease
The Children's Hospital of Philadelphia

3:45 p.m. Discussion

4:45 p.m. **Wrap-Up: Highlights and Key Themes of Day 1**

STORY LANDIS, *Workshop Co-Chair*
JOHN TROJANOWSKI, *Workshop Co-Chair*

5:00 p.m. ADJOURN DAY 1

DAY 2: May 1, 2012

Note: Breakfast will be available from 7:30 a.m.

8:00 a.m. **Welcome and Objectives of Day 2**

STORY LANDIS, *Workshop Co-Chair*
Director
National Institute of Neurological Disorders and Stroke

JOHN TROJANOWSKI, *Workshop Co-Chair*
Co-Director, Center for Neurodegenerative Disease Research
University of Pennsylvania

SESSION 4: NEURODEGENERATIVE DISEASE TRANSMISSION AND IMMUNE THERAPY

Session Objectives: The objectives of this session are to:

- Provide an overview of the latest concepts on transmission of neurodegenerative diseases, including evidence that suggests that disease progression may occur through the cell-to-cell spread of pathological disease proteins.
- Explore how targeting transmissible species of a-syn as well as tau and Abeta using immune therapy may be used to treat Parkinson's Disease and Alzheimer's Disease, respectively.
- Identify the next steps that research sponsors, investigators, and others should take to facilitate collaborative research and drug development in this area, including frameworks for partnerships and collaboration.

8:15 a.m. **Overview of Status of the Field and Session Objectives**

JOHN TROJANOWKSI, *Session Chair*
Co-Director, Center for Neurodegenerative Disease Research
University of Pennsylvania

8:25 a.m. **Transmission of Prions and Alzheimer's Disease Abeta Amyloid**

CLAUDIO SOTO
Professor of Neurology
Director, Center for Alzheimer's Disease and Related Brain Disorders
The University of Texas Medical School at Houston

8:35 a.m. Discussion Among Speakers and Attendees

8:50 a.m. **Transmission of Alzheimer's Disease Abeta Amyloid**

LARY C. WALKER
Research Professor of Neuroscience
Emory University

9:00 a.m. Discussion

9:15 a.m. **Transmission of Alzheimer's Disease Tau Amyloid**

KAREN DUFF
Professor, Department of Pathology
Columbia University

9:25 a.m. Discussion

9:40 a.m. BREAK

10:00 a.m. **Transmission of Parkinson's Disease Alpha-Synuclein Amyloid**

VIRGINIA M.-Y. LEE
The John H. Ware 3rd Professor in Alzheimer's Research
Dept of Pathology and Laboratory Medicine
Director, Center for Neurodegenerative
University of Pennsylvania School of Medicine

10:10 a.m. Discussion

10:25 a.m. **Alpha-Synuclein Immunization for Parkinson's Disease**

DORA GAMES
Head of Pharmacology
Neotope Biosciences

10:35 a.m. Discussion

10:50 a.m. **Tau Immunization for Alzheimer's Disease and Related Tauopathies**

PETER DAVIES
Head
Litwin-Zucker Center for the Study of Alzheimer's Disease and Memory Disorders
The Feinstein Institutei for Medical Research

11:00 a.m. Discussion

11:45 a.m. LUNCH

SESSION 5: ERRORS IN RNA

Session Objectives: The objectives of this session are to:

- Discuss how errors in RNA binding proteins are causes of neurodegenerative diseases, including amyotrophic lateral sclerosis, frontotemporal dementia, and spinal muscular atrophy, as well as triplet nucleotide expansion as a risk factor in disease (e.g., ataxin and ALS).
- Discuss disease mechanisms for diseases with toxic RNAs, including myotonic dystrophy and other triplet nucleotide repeats where there are toxic RNAs or aberrant translation of the expansions.
- Explore potential biomarkers and therapies for RNA binding protein errors in SMA, TDP-43, FUS, and C9ORF72.
- Discuss yeast models to identify therapeutics and the emerging roles of non-coding RNA networks in the pathogenesis of neurodegenerative diseases.
- Identify the next steps that research sponsors, investigators, and others should take to facilitate collaborative research and drug development in this area, including frameworks for partnerships and collaboration.

12:45 p.m. **Overview of Status of the Field and Session Objectives**

DON CLEVELAND, *Session Chair*
Professor and Chair, Department of Cellular andMolecular Medicine
Head, Laboratory for Cell Biology
Ludwig Institute For Cancer Research
University of California, San Diego

12:55 p.m. **Overview of RNA Gain-of-Function Mechanisms in Neurodegenerative Disease**

LAURA RANUM
Professor of Molecular Genetics and Microbiology
University of Florida

1:05 p.m. Discussion

1:20 p.m. **Overview of Therapies for RNA Binding Protein Errors**

FRANK RIGO
Assistant Director, Core Antisense Research
Isis Pharmaceuticals, Inc.

1:30 p.m. Discussion

1:45 p.m. **Yeast Models to Identify Therapeutics**

GREGORY A. PETSKO
Gyula and Katica Tauber Professor of Biochemistry & Chemistry
Brandeis University

1:55 p.m. Discussion

2:10 p.m. **The Emerging Roles of Non-Coding RNA Networks in the Pathogenesis of Neurodegenerative Diseases**

MARK F. MEHLER
Alpern Professor of Neurology, Neuroscience and Psychiatry and Behavioral Sciences
University Chair, The Saul R. Korey Department of Neurology
Albert Einstein College of Medicine

2:20 p.m. Discussion

2:45 p.m. BREAK

SESSION 6: FUTURE DIRECTIONS & NEXT STEPS

Session Objective: A panel will synthesize and discuss key highlights from the workshop presentations and discussions, including:

- Identify key promising areas for future cross-disease research and collaboration.
- Discuss opportunities for partnerships—public/private and across disease-specific communities—to advance neurodegeneration research and therapeutics development.
- Discuss challenges to advancing research and therapeutics development for the neurodegenerative diseases and potential mechanisms to address these challenges.

3:00p.m. Panel Discussion (Session Chairs From Previous Sessions):

STORY LANDIS, *Session Co-Chair*
Director
National Institute of Neurological Disorders and Stroke

JOHN TROJANOWSKI, *Session Co-Chair*
Co-Director, Center for Neurodegenerative Disease Research
University of Pennsylvania

ANDREW SINGLETON
Senior Investigator, Laboratory of Neurogenetics
National Institute on Aging

JOHN DUNLOP
Vice President, Discovery
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DON CLEVELAND
Professor and Chair, Department of Cellular andMolecular Medicine
Head, Laboratory for Cell Biology
Ludwig Institute For Cancer Research
University of California, San Diego

3:30 p.m. Discussion among speakers and attendees

4:30 p.m. ADJOURN