The Krembil Knowledge Gaps in Parkinson's Disease Symposium

Linking Pathogenesis with Disease Modification

Revision vs Reconstruction

April 24-26, 2019 | Marriott Downtown at Toronto Eaton Centre

Time	Session Information – Wednesday, April 24, 2019
12:00 – 13:00	**Registration and Lunch**
THE CONCEPTUAL CHALLENGES	
13:00 – 13:20	**The Challenge of PD as many Diseases – Clinical, Genetic, Pathologic, Environmental Variability** Anthony E Lang, MD *Professor, Department of Medicine, Division of Neurology, University of Toronto* This presentation will provide an overview of the marked heterogeneity and variability of Parkinson's disease. This justifies the concept of "Parkinson's diseases" rather than considering PD as a single disorder with uniform pathogenic mechanisms. This represents a critical challenge to future attempts to establish effective disease modifying therapy.
13:20 – 13:40	**Challenges to Study Disease Modification in Non-Manifesting at Risk Subjects (monogenetic gene carriers, "prodromal PD" using new MDS-Criteria)** Ron Postuma, MD, MSc *Professor, Department of Neurology, McGill University* This presentation will provide an overview of the potential of prodromal PD to ameliorate the disability associated with prodromal PD. We will focus on the most important ways to identify prodromal PD, the challenges of using prodromal PD patients in trials, and potential for trial design.
13:40 – 14:00	**Challenges in Neuropathology: Do "opathologies" represent modifiers of PD (Revision) or an invitation to reconsider PD nosology (Reconstruction)?** John Q. Trojanowski, M.D., Ph.D., (Pathology) *William Maul Measey-Truman G. Schnabel, Jr., M.D.* *Professor of Geriatric Medicine and Gerontology* *Director, Institute on Aging* *Director, NIA Alzheimer's Disease Core Center* *Co-director, Center for Neurodegenerative Disease Research and* *Marian S. Ware Alzheimer Drug Discovery Program* *Professor, Department of Pathology and Laboratory Medicine* *Perelman School of Medicine at the University of Pennsylvania*

14:00 – 14:20	**The Challenge of Revision vs Reconstruction** Alberto J. Espay, MD, MSc, FAAN *Professor of Neurology* *Director and Endowed Chair* *James J. and Joan A. Gardner Center for Parkinson's Disease and Movement Disorders* *University of Cincinnati* This presentation will provide an overview of the disease modeling for PD based on a clinical construct converging on alpha-synuclein aggregation at autopsy. We will challenge the revision efforts related to the underlying assumption that a molecular-biological disorder, targetable for disease modification as a whole, underlies the clinico-pathologic, convergent model of PD. We will highlight the merits of reconstructing the research landscape into a systems biology, divergent model for biomarker discovery and clinical trials testing putative disease modifying interventions.
14:20 – 14:50	**Discussion** José Obeso, Madrid A. Jon Stoessl, CM, MD, FRCPC, FCAHS *Professor & Head, Neurology* *Co-Director, Djavad Mowafaghian Centre for Brain Health* *Canada Research Chair in Parkinson's* *Pacific Parkinson's Research Centre & Parkinson's Foundation Centre of Excellence* *University of British Columbia*
14:50 – 15:15	**Refreshment Break**
EXPERIENCES IN OTHER DISEASES IN NEUROLOGY AND MEDICINE	
15:15 – 15:35	**Alzheimer's Disease – problems of retaining old constructs; examples of reasons for and successes in revising concepts of disease subtyping** George Perry, PhD *Professor of Biology and Chemistry* *Chief Scientist, Brain Health Consortium* *Semmes Foundation Distinguished University Chair in Neurobiology* *The University of Texas at San Antonio*
15:35 – 15:55	**Impact of Breast Cancer Molecular Subtypes on Clinical Decision-Making** Philippe Bedard, MD FRCPC *Associate Professor, Department of Medicine, University of Toronto* *Staff Medical Oncologist, Princess Margaret Cancer Centre – University Health Network*

	This presentation will provide an overview of how breast cancer treatment has been advanced by an improved understanding of the molecular classification of disease. Identification of estrogen-receptor and HER2-receptor positive subtypes have led to the development targeted therapies that improved long-term survival. The challenges of advancing novel targeted therapies for rare subtypes defined by genomic driver alterations will be discussed.
15:55 – 16:15	**The Transformation of Cystic Fibrosis: Molecular therapies for a diverse range of genetic causes** Steven M. Rowe, MD, MSPH *Professor, Department of Medicine, Pediatrics, and Cell Developmental & Integrative Biology* *Director, Gregory Fleming James Cystic Fibrosis Research Center* *Nancy R. and Eugene C. Gwaltney Family Endowed Chair for Medical Research* *University of Alabama at Birmingham* This presentation will discuss how the field determined the underlying genetic basis of cystic fibrosis by sub-phenotyping the disorder into molecular causes. Using that information, new treatments that address the basic defect have rapidly evolved and promise to complete transform the disease landscape.
16:15 – 16:45	**Discussion** Alberto J. Espay, MD, MSc, FAAN *Professor of Neurology* *Director and Endowed Chair* *James J. and Joan A. Gardner Center for Parkinson's Disease and Movement Disorders* *University of Cincinnati* Francesca Morgante, MD, PhD *Reader in Neurology, St. George's University of London, London, UK*

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Time	Session Information – Thursday April 25, 2019
7:00 – 8:00	**Registration and Continental Breakfast**
DISEASE MECHANISMS	
8:00 – 8:30	**Transmission of Misfolded Proteins in Neurodegenerative Disorders: A Common Mechanism of Disease Progression** Virginia M.-Y. Lee, Ph.D. (Neuroscience) *Professor, Department of Pathology and Laboratory Medicine* *Perelman School of Medicine at the University of Pennsylvania* *The John H. Ware 3rd Professor in Alzheimer's Research* *Director, Center for Neurodegenerative Disease Research and* *Marian S. Ware Alzheimer Program* This presentation will discuss cell-to-cell transmission of misfolded proteins through templated recruitment as a common mechanism for the onset and progression of various neurodegenerative disorders. Furthermore, the presence of conformationally diverse "strains" for synucleinopathies will be discussed.
8:30 – 8:50	**Mechanistic Insights into GBA1-Associated Parkinson's Disease and Development of Targeted Therapies** Dimitri Krainc, MD, PhD *Aaron Montgomery Ward Professor* *Chairman, Davee Department of Neurology* *Director, Center for Neurogenetics* *Northwestern University Feinberg School of Medicine* The convergence of mitochondrial and lysosomal dysfunction in midbrain neurons from PD patients and development of targeted therapies for GBA1-linked Parkinson's disease will be discussed in this presentation.
8:50 – 9:10	**A Genetic Basis for Synaptic-Endosomal Dysfunction in Parkinson's Disease** Matt Farrer PhD (Neurogenetics) *Professor, Department of Medical Genetics, University of British Columba* Major components of the molecular 'engine' that underlies Parkinson's disease have been identified. Those discoveries point to convergent pathways and processes awry in the disease. My talk will centre on vesicular trafficking and synaptic-endosomal dysfunction, contributed by mutations in SNCA, LRRK2, VPS35 and DNAJC proteins, and the amazing therapeutic opportunities they herald.

9:10 – 9:40	**Discussion** Adriano Aguzzi MD, PhD, DVM hc FRCPath *Professor, Director of the Institute of Neuropathology, University Hospital Zurich, Switzerland* Ronan Fleming, PhD (Systems biology) *Assistant Professor, Faculty of Science, Leiden University*
9:40 – 10:10	**Refreshment Break**
10:10 – 10:30	**LRRK2 as a Therapeutic Target for Parkinson's Disease – Revise or Reconstruct** Lorraine Kalia, MD, PhD, FRCPC *Assistant Professor, Division of Neurology, Department of Medicine, University of Toronto* *Scientist, Krembil Research Institute & Tanz Centre for Research in Neurodegenerative Diseases* *Staff Neurologist, Edmond J. Safra Program in Parkinson's Disease & Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital* This presentation will review whether LRRK2 dysfunction is a common contributor to Parkinson's disease and discuss the potential impact on disease modification trials.
10:30 – 10:50	**Bioenergetic Determinants of Neuronal Vulnerability in Parkinson's Disease** D. James Surmeier, Ph.D. *Nathan Smith Davis Professor and Chair* *Department of Physiology* *Northwestern University* Mitochondrial dysfunction has long been implicated in PD pathogenesis. What has been missing is an explanation of why mitochondrial dysfunction should occur in the small collection of neurons lost in PD. The presentation will attempt to fill that gap.
10:50 – 11:10	**Neuroinflammation and Role of the Microbiome in Parkinson Disease** David G. Standaert, MD, PhD *John N. Whitaker Professor and Chair, Department of Neurology, University of Alabama at Birmingham* This presentation will provide an overview of the role of neuroinflammation in Parkinson disease, and review the role of both innate brain immune mechanisms and

	the involvement of blood leukocytes. The role of the microbiome as a potential modulator of these responses will be discussed. Emerging evidence suggests that neuroinflammation is a critical driver of progression in Parkinson disease.
11:10 – 12:10	**Discussion** Patrik Brundin, MD, PhD *Associate Research Director, Center for Neurodegenerative Science Van Andel Research Institute* Andrew Singleton PhD *Distinguished Investigator,* *Chief, Laboratory of Neurogenetics,* *National Institute on Aging,* *National Institutes of Health, Bethesda*
12:10 – 13:10	**Lunch**
TRANSPLANTATION & OTHER STRATEGIES directed primarily at augmenting dopamine function (Neurorescue/Neurorestoration-based treatments)	
13:10 – 13:30	**YES - Nigrostriatal dopamine will remain a primary target and reinnervation should be pursued** Roger A Barker BA, MBBS, MRCP, PhD, FMedSci *Professor, Clinical Neuroscience, Department of Clinical Neuroscience, University of Cambridge*
13:30 – 13:50	**NO – Nigrostriatal dopamine will not remain a primary target and reinnervation should not be pursued** Jeffrey H. Kordower, PhD *The Alla V. and Solomon Jesmer Professor of Neurological Sciences, Rush University Medical Center, Chicago*
13:50 – 14:30	**Rebuttal and Discussion** Andres Lozano, OC, MD, PhD, FRCSC, FRSC *University Professor and Dan Family Chairman of Neurosurgery, University of Toronto* Alfonso Fasano, MD, PhD *Professor of Neurology – University of Toronto* *Clinician Investigator – Krembil Research Institute* *Movement Disorders Centre - Toronto Western Hospital*

14:30 – 15:00	**Break**
BIG DATA, MACHINE LEARNING, NEW TECHNIQUES, VIRTUAL COHORTS	
	Revision: Aggregation from existing clinically-defined cohorts: Pros and Cons Caroline Williams-Gray BMBCh, MRCP, PhD *Clinical Senior Research Associate and Honorary Consultant Neurologist, Department of Clinical Neurosciences, University of Cambridge/Cambridge University Hospitals NHS Trust, UK*
15:00 – 15:30	This presentation will discuss longitudinal cohort studies in Parkinson's disease and consider what they have taught us about the natural history and heterogeneity of this condition. Key findings from individual cohort studies will be presented, as well as examples of successful integration of multi-cohort data leading to the development of predictive models of disease outcome. The benefits and challenges of combining datasets to facilitate better disease modelling and stratification tools will be considered.
	Thermodynamically Inspired Biomarkers – Transferring Concepts from Physics and Ecology to Medicine Rudi Balling, PhD *Director, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg*
15:30 – 16:00	Chronic diseases can be looked at as perturbations of complex adaptive systems and are often characterized by critical transitions or catastrophic shifts. They have been studied intensively in theoretical and applied physics, ecology and economics. Critical transitions also occur in the course of chronic diseases. If we could understand the underlying mechanisms and the dynamics of critical transitions involved in the development of diseases, we would be better equipped to predict and eventual prevent them from arising.
	Discussion Todd Sherer, PhD (Neuroscience) *CEO, The Michael J. Fox Foundation for Parkinsons Research*
16:00 – 16:40	Antonio Strafella MD, PhD, FRCPC *Canada Research Chair in Movement Disorders & Neuroimaging* *Professor, Department of Medicine/Neurology, TWH-UHN* *Senior Scientist, Krembil Research Institute, UHN,* *Senior Scientist, Research Imaging Centre, CAMH* *University of Toronto*

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Time	Session Information - Friday April 26, 2019
7:00 – 8:00	**Registration and Continental Breakfast**
TRIALS – BIOMARKERS, TRIAL DESIGNS, CONSORTIUMS, ETC. WHAT CAN BE PURSUED IN THE NEAR FUTURE AND HOW?	
8:00 – 8:30	**Fit-for-Purpose Applicationsn of Biomarkers in PD Drug Development** Jesse M. Cedarbaum, MD *Vice President, Neurology Early Clinical Development, Biogen* A Biomarker is not a Biomarker is not a Biomarker. This presentation will explore the varying applications of biomarkers in the drug development process and explore the need for greater preclinical exploration of biomarker responses prior to inclusion in human clinical trials.
8:30 – 9:00	**Discussion** Kenneth Marek, MD *Distinguished Scientist* *Institute for Neurodegenerative Disorders*
TRIALS – TRIAL DESIGNS INCLUDING LESSONS LEARNED	
9:00 – 9:30	**Novel trial designs of "disease modifying therapy" in oncology (e.g., I-SPY2) and other diseases** Christopher S. Coffey, PhD (Biostatistics) *Professor, Department of Biostatistics, University of Iowa* *Director, Clinical Trials Statistical and Data Management Center* This presentation will provide a general overview of adaptive designs, and their potential utility in PD studies. A particular emphasis will be on the existing use of master protocols in other disease areas, and a discussion of how such an approach might fit within the future PD research space.
9:30 – 10:00	**Time for a New Framework for 'Disease Modifying' Clinical Trials in Parkinson's Disease** Karl Kieburtz MD MPH *Professor of Neurology, University of Rochester* The presentation will review the vocabulary, trial designs and results of prior clinical trials aimed at improving the long term outcome in PD. A new framework for such

	trials, including terminology, outcomes and analyses, will be proposed. This framework may improve the regulatory process for evaluating the results of PD clinical trials.
10:00 – 10:20	**Break**
10:20 – 10:50	**Lessons from Anti-Amyloid-β Immunotherapies in AD** Howard Chertkow, MD, FRCP, FCAHS *Professor of Medicine (Neurology), University of Toronto* *Chair in Cognitive Neurology and Innovation and Senior Scientist, Rotman Research Institute and Baycrest Health Science* More than 80% of research funds spent on Alzheimer Disease in the past 25 years have gone to explore the amyloid hypothesis of AD causation, but no anti-amyloid immunotherapy medications have succeeded or been delivered to the marketplace. While there are multiple explanations for this situation, there are also lessons to be learned regarding drug development and testing in neurodegenerative diseases. We will explore these, look at the reasons for some of the failures, and point towards a better approach for the future.
10:50 – 11:20	**Role of Novel Endpoints and Evaluations of Response** Michael Schwarzschild, MD PhD *Julieanne Dorn Professor of Neurology, Harvard Medical School* *Massachusetts General Hospital, Boston* This presentation will provide an overview of classic, current and potential future endpoints gauging disease modification in phase 2/3 trials in people with Parkinson's disease. Emerging opportunities to measure disease progression in genetically at-risk or prodromal populations will be highlighted.
11:20 – 11:50	**Regulatory Modifications that Could Facilitate Development of a Neuroprotective Therapy for PD** C Warren Olanow MD, FRCPC, FRCP(hon) – (Neurology) *Professor and Chairman Emeritus, Dept of Neurology* *Professor Emeritus, Dept of Neuroscience* *Mount Sinai School of Medicine, New York* *Clintrex, CEO* Research studies have identified multiple novel targets and putative disease modifying agents in PD. However, in order to encourage the billions of dollars in investment necessary for the development of these agents, a regulatory pathway for

	drug approval and labelling have become a priority. This presentation will consider steps the regulatory agencies might take to facilitate the development of a disease modifying agent for PD
11:50 – 12:35	**Discussion** Hubert H. Fernandez, MD *James and Constance Brown Family Endowed Chair in Movement Disorders* *Director, Center for Neurological Restoration Neurological Institute, Cleveland Clinic* *Professor of Medicine (Neurology) Cleveland Clinic Lerner College of Medicine* David G. Standaert, MD, PhD *John N. Whitaker Professor and Chair, Department of Neurology, University of Alabama at Birmingham*
12:35 – 12:50	**Concluding Summary/Remarks** Anthony E Lang, MD *Professor, Department of Medicine, Division of Neurology, University of Toronto*