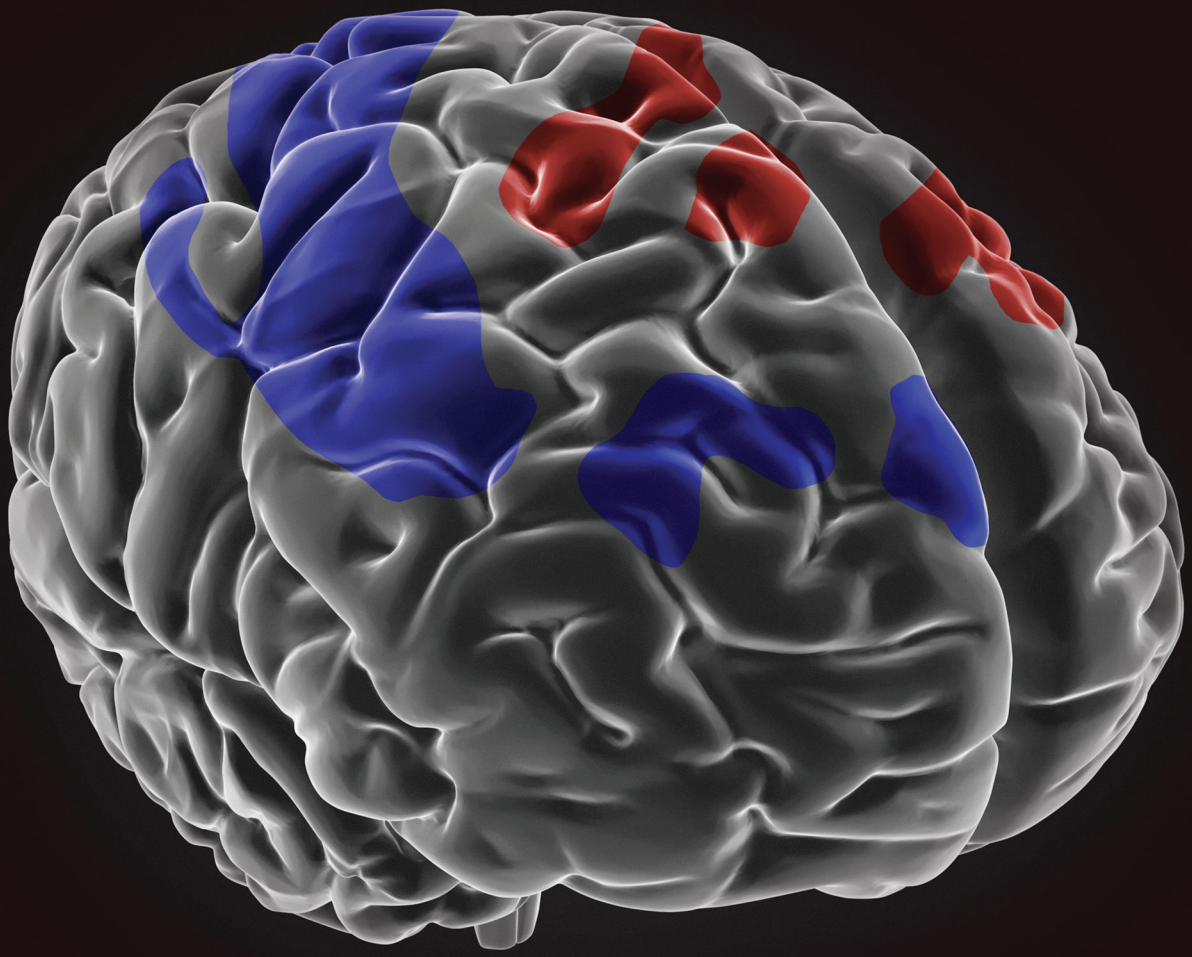

PARKINSON'S DISEASE 2014

ADVANCING RESEARCH, IMPROVING LIVES

PROGRAM MATERIALS

Sponsored by:

NIH National Institute of Neurological Disorders and Stroke

January 6 – 7, 2014
Natcher Conference Center
National Institutes of Health
Bethesda, MD

About our cover:

The program cover image is a stylized version of the Parkinson's Disease Motor-Related Pattern (PDRP), an abnormal pattern of regional brain function observed in MRI studies which shows increased metabolism indicated by red in some brain regions (pallidothalamic, pontine, and motor cortical areas), and decreased metabolism indicated by blue in others (associated lateral premotor and posterior parietal areas).

Original image used with permission of David Eidelberg, M.D.

For further information see: Hirano et al., Journal of Neuroscience 28 (16): 4201-4209.

Welcome Message from Dr. Story C. Landis

Welcome to the National Institute of Neurological Disorders and Stroke (NINDS) conference, "Parkinson's Disease 2014: Advancing Research, Improving Lives."

Remarkable new discoveries and technological advances are rapidly changing the way we study the biological mechanisms of Parkinson's disease, identify paths to improved treatments, and design effective clinical trials. Elucidating mechanisms and developing and testing effective interventions require a diverse set of approaches and perspectives. The NINDS has organized this conference with the primary goal of seeking consensus on, and prioritizing, research recommendations spanning clinical, translational, and basic Parkinson's disease research that we support.

We have assembled a stellar and dedicated group of session chairs and panelists who have worked collaboratively to identify emerging research opportunities in Parkinson's research. While we have divided our working groups into three main research areas, we expect each will inform the others over the course of the next two days, and we look forward to both complementary and unique perspectives.

On behalf of the NINDS, I would like to thank the many people who helped to make this conference possible, especially conference Chair Thomas Montine, Session Co-Chairs Randall Bateman, John Dunlop, Steven Finkbeiner, Virginia Lee, Harry Orr, and Andrew Siderowf, and all the panel members who generously dedicated many hours of their time to this effort and graciously navigated an extraordinarily condensed planning timeline due to the 2013 shutdown of the federal government. I also want to thank the representatives from academia, industry, government, and non-profit and advocacy organizations who are joining us to share their perspectives and to reflect upon how the recommendations during the next two days might be impacted by and have impact on their research programs.

It is our hope that this meeting will foster continued conversation with our partner organizations and facilitate achievement of our common goal to find the causes, improved treatments, and one day a cure, for Parkinson's disease. Our expectation is that the dynamic recommendations that result from this conference will catalyze advances in Parkinson's research here at the NIH and beyond. Thank you for your active participation.

Agenda

January 6, 2014 (Day 1)

8:00 a.m. **Welcome and Introduction**

Story C. Landis, PhD
Director, NINDS

8:15 a.m. **Meeting Goals**

Thomas J. Montine, MD, PhD
Alvord Professor and Chair
Department of Pathology, University of Washington

8:30 a.m. **Bringing Emerging Science to People with Parkinson's Disease through Clinical Research**

Session Chairs: Randall Bateman, MD, and Andrew Siderowf, MD
NINDS Liaisons: Wendy Galpern, MD, PhD, and Walter Koroshetz, MD

Introduction

Randall Bateman, MD
Knight Distinguished Professor of Neurology
Washington University School of Medicine

Andrew Siderowf, MD
Medical Director
Avid Radiopharmaceuticals

8:40 a.m. **Opportunities to Advance Symptomatic Treatment of Motor and Non-motor Features**

Presenter: Werner Poewe, MD
Director, Department of Neurology
Innsbruck Medical University

8:55 a.m. Panel Discussion of Recommendations

Moderator: Andrew Siderowf, MD
Panelists: Karen Marder, MD, MPH; Werner Poewe, MD; Bernard Ravina, MD; Lisa Shulman, MD; Philip Starr, MD, PhD*; and Matthew Stern, MD*

9:15 a.m. **Opportunities for Innovation in Trial Design**

Presenter: Christopher Coffey, PhD
Professor, Department of Biostatistics
University of Iowa

9:30 a.m. Panel Discussion of Recommendations

Moderator: Randall Bateman, MD
Panelists: Christopher Coffey, PhD; Jordan Elm, PhD; Nicholas Kozauer, MD*; Bernard Ravina, MD; Ira Shoulson, MD*; and Philip Starr, MD, PhD*

9:50 a.m. Break

10:20 a.m. **Opportunities to Improve Outcome Measures in PD Research**

Presenter: Lisa M. Shulman, MD
Professor of Neurology
University of Maryland School of Medicine

10:35 a.m. Panel Discussion of Recommendations

Moderator: Andrew Siderowf, MD
Panelists: Jordan Elm, PhD; Nicholas Kozauer, MD*; Lisa Shulman, MD; and Caroline Tanner, MD, PhD

10:55 a.m. **Opportunities for Understanding and Addressing Disease Progression**

Presenter: Caroline Tanner, MD, PhD
Director, Clinical Research
The Parkinson's Institute

11:10 a.m. Panel Discussion of Recommendations

Moderator: Randall Bateman, MD
Panelists: Christopher Coffey, PhD; Karen Marder, MD, MPH; Werner Poewe, MD; Ira Shoulson, MD*; Matthew Stern, MD*; and Caroline Tanner, MD, PhD

11:30 a.m. **Panel Discussion: Priority Ranking of Clinical Research Recommendations**

Moderators: Randall Bateman, MD, and Andrew Siderowf, MD
Panelists: Christopher Coffey, PhD; Jordan Elm, PhD; Karen Marder, MD, MPH; Werner Poewe, MD; Bernard Ravina, MD; Lisa Shulman, MD; and Caroline Tanner, MD, PhD

12:00 p.m. Lunch

1:00 p.m. **Building a Translational Pipeline for Parkinson's Disease Therapeutics**

Session Chairs: John Dunlop, PhD, and Steven Finkbeiner, MD, PhD
NINDS Liaisons: Margaret Sutherland, PhD, and Hao Wang, PhD

Introduction

John Dunlop, PhD
Vice President, Neuroscience
AstraZeneca

Steven Finkbeiner, MD, PhD
Associate Director & Senior Investigator
Gladstone Institute of Neurological Disease
University of California, San Francisco

1:10 p.m. **Patient/Disease Stratification**

Presenter: John Dunlop, PhD
Vice President, Neuroscience
AstraZeneca

1:25 p.m. Panel Discussion of Recommendations

Moderator: John Dunlop, PhD
Panelists: Rudi Balling, PhD; Steven Finkbeiner, MD, PhD; John Hardy, PhD; and Dean Jones, PhD

1:45 p.m. **Target Engagement and Efficacy**

Presenter: Dimitri Krainc, MD, PhD
Professor and Chairman, Department of Neurology
Northwestern University

2:00 p.m. Panel Discussion of Recommendations

Moderator: Steven Finkbeiner, MD, PhD
Panelists: John Dunlop, PhD; John Hardy, PhD; Hartmuth Kolb, PhD*; Dimitri Krainc, MD, PhD; Kalpana Merchant, PhD*; and Richard Youle, PhD

2:20 p.m. **Modeling Parkinson's Disease Pathways: Forward and Reverse Translation**

2:20 p.m. *Presenter:* Michael Lee, PhD
Professor, Department of Neuroscience
University of Minnesota

2:30 p.m. *Presenter:* Clive Svendsen, PhD
Director, Regenerative Medicine Institute
Cedars-Sinai Health System, Los Angeles

2:40 p.m. Panel Discussion of Recommendations

Moderator: Steven Finkbeiner, MD, PhD
Panelists: Wade Harper, PhD; Michael Lee, PhD; Clive Svendsen, PhD; and Richard Youle, PhD

3:00 p.m. Break

3:20 p.m. **Target Identification and Validation: Criteria for Advancement**

Presenter: Richard Youle, PhD
Senior Investigator and Chair, Biochemistry Branch
NINDS, NIH

3:30 p.m. *Presenter:* Wade Harper, PhD
Professor of Cell Biology
Harvard Medical School

3:40 p.m. Panel Discussion of Recommendations

Moderator: Wade Harper, PhD
Panelists: Rudi Balling, PhD; John Hardy, PhD; Dean Jones, PhD; and Dimitri Krainc, MD, PhD

4:00 p.m. **Panel Discussion: Priority Ranking of Translational Research Recommendations**

Moderator: John Dunlop, PhD
Panelists: Rudi Balling, PhD; Steven Finkbeiner, MD, PhD; John Hardy, PhD; Wade Harper, PhD; Dean Jones, PhD; Dimitri Krainc, MD, PhD; Michael Lee, PhD; Clive Svendsen, PhD; and Richard Youle, PhD

4:30 p.m. **Parkinson's Disease Research Evaluation: A Multi-Stakeholder Perspective**

Session Chair: Amy Comstock Rick, JD
NINDS Liaison: Beth-Anne Sieber, PhD

Introduction

Amy Comstock Rick, JD
Chief Executive Officer, Parkinson's Action Network

4:35 p.m. **Research Evaluation: An AAMC Initiative**

Ann C. Bonham, PhD
Chief Scientific Officer, Association of American Medical Colleges

4:45 p.m. **Panel Discussion**

Moderator: Amy Comstock Rick, JD
Panelists: Ann C. Bonham, PhD; Story C. Landis, PhD; Bernard Ravina, MD; Todd Sherer, PhD; and David Sulzer, PhD

January 7, 2014 (Day 2)

9:00 a.m. **Parkinson's Disease Biology: Moving Toward Innovative Treatments**

Session Chairs: Virginia M-Y Lee, PhD, and Harry T. Orr, PhD
NINDS Liaisons: Katrina Gwinn, MD, and Kip Ludwig, PhD

Introduction

Virginia M-Y Lee, PhD
Director, Center for Neurodegenerative Disease Research
University of Pennsylvania Perelman School of Medicine

Harry T. Orr, PhD
Professor of Pathology
University of Minnesota

9:10 a.m. **Pathways and Signaling**

Presenter: Harry T. Orr, PhD
Professor of Pathology
University of Minnesota

9:25 a.m. Panel Discussion of Recommendations

Moderator: Mel Feany, MD, PhD
Panelists: Ted M. Dawson, MD, PhD; Harry T. Orr, PhD; and Andrew Singleton, PhD

9:55 a.m. Break

10:25 a.m. **Protein Processing, Aggregation, and Spread**

Presenter: Virginia M-Y Lee, PhD
Director, Center for Neurodegenerative Disease Research
University of Pennsylvania Perelman School of Medicine

10:40 a.m. Panel Discussion of Recommendations

Moderator: Robert Edwards, MD
Panelists: Hilal Lashuel, PhD; Virginia M-Y Lee, PhD; and J. Paul Taylor, MD, PhD

11:10 a.m. **Circuit Modification**

Presenter: Warren M. Grill, PhD
Professor of Biomedical Engineering
Duke University

11:25 a.m. Panel Discussion of Recommendations

Moderator: Kendall Lee, MD, PhD
Panelists: Ann Graybiel, PhD; Warren M. Grill, PhD; and Mark Schnitzer, PhD*

11:55 a.m. **Panel Discussion: Priority Ranking of Basic Research Recommendations**

Moderators: Virginia M-Y Lee, PhD, and Harry T. Orr, PhD
Panelists: Ted Dawson, MD, PhD; Robert Edwards, MD; Mel Feany, MD, PhD; Ann Graybiel, PhD; Warren M. Grill, PhD; Hilal Lashuel, PhD; Kendall Lee, MD, PhD; Andrew Singleton, PhD; and J. Paul Taylor, MD, PhD

12:30 p.m. Lunch

1:30 p.m. **Public Comment**

Moderators: Thomas J. Montine, MD, PhD, and Beth-Anne Sieber, PhD

2:30 p.m. **Defining Priorities for Parkinson's Disease Research**

Moderator: Thomas J. Montine, MD, PhD
Panelists: Randall Bateman, MD; John Dunlop, PhD; Steven Finkbeiner, MD, PhD; Virginia M-Y Lee, PhD; Harry T. Orr, PhD; and Andrew Siderowf, MD

4:00 p.m. **Closing Comments**

Story C. Landis, PhD
Director, NINDS

4:30 p.m. Adjourn

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*Panel members who participated in research recommendation development, but are unable to attend this conference.

Research Recommendations

Bringing Emerging Science to People with Parkinson's Disease through Clinical Research

January 6, 2014, 8:30 a.m. – 12:00 p.m.

Recommendation 1: Conduct proof-of-concept prevention trials, initially targeting high risk and/or prodromal populations, including biomarker assessment. Observations will be available as a data and tissue resource for future clinical and laboratory investigations.

Recommendation 2: Conduct studies to define the natural history of prodromal Parkinson's Disease (clinical, imaging, biomarkers, pathology including post-mortem), to characterize progression and phenoconversion, to identify the determinants of clinical subtypes, to establish a data and tissue resource for future clinical and laboratory investigation, and develop cost-effective methods for health screening to identify persons with prodromal Parkinson's Disease (PD).

Recommendation 3: Devise and implement longitudinal observational studies, biomarker investigations, randomized clinical trials, and data and bio-specimen sharing resources aimed at characterizing the progressive course of clinically manifest illness, establishing markers of disease, and identifying safe and effective treatments that postpone or ameliorate the intractable disabilities of PD.

Recommendation 4: Initiate prospective studies to define the evolution of non-motor symptoms (NMS, e.g., dementia, psychosis, dysautonomia) and define patient subgroups based on clinical NMS profiles with the goal of developing strategies for treatment and prevention of NMS.

Recommendation 5: Develop biomarkers of target engagement and proximal pharmacodynamic effects for use in early-stage clinical trials.

Recommendation 6: Identify mechanisms responsible for the development of levodopa-resistant motor symptoms (gait and balance problems including gait freezing) and develop novel therapeutic approaches to these problems.

Recommendation 7: Develop improved methods to assess long-term efficacy and potential for disease modification in clinical trials, including: 1) more efficient (better & faster) strategies for screening potential agents; and 2) trial design simulations to assess the performance of trial designs for predicting long-term benefits.

Recommendation 8: Determine factors that could facilitate public health interventions, including risk factor reduction and health services interventions (population-wide and/or individual).

Recommendation 9: Investigate the use of innovative outcome measures to evaluate motor and non-motor features, including patient- and clinician-reported outcomes that leverage emerging IT opportunities, enhance sensitivity and specificity of measurement, and facilitate long-term follow-up of well-characterized cohorts.

Recommendation 10: Develop improved informatics capability that could include: 1) exploration of ways in which "big data" may contribute to learning in the PD space; 2) further develop and promote access to a central data repository for PD trial data; 3) a resource for trial design simulations to inform decisions about efficient trial design for a given intervention.

Recommendation 11: Develop strategies to increase minority participation in research. These initiatives should include mechanisms to assess the effectiveness of these programs and could lead to the establishment of shared resources to facilitate minority recruitment in PD clinical trials.

Recommendation 12: Identify risk factors and pathogenic mechanisms of motor fluctuations and dyskinesias to identify novel targets for prevention and symptomatic therapy for these problems.

<u>Recommendation 1:</u> Conduct proof-of-concept prevention trials, initially targeting high risk and/or prodromal populations, including biomarker assessment. Observations will be available as a data and tissue resource for future clinical and laboratory investigations.

Need: Progressive neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) manifest symptoms only after a substantial amount of neuronal dysfunction and neuron loss have occurred in key areas of the central nervous system. As a result, targeting disease mechanisms in earlier stages (prior to overt neurologic manifestations) is likely to be more successful at preserving function compared to treating at later stages of the disease when neuropathology may be relatively advanced. Therefore, proof-of-concept prevention trials that utilize biomarkers of the PD process in high risk populations provide an opportunity to test and gain information about the potential for PD modification at an early stage of the disease process.

Approaches:

- Identification of high risk populations before significant neurodegeneration has occurred with quantifiable risk of future development of symptoms (e.g., inherited PD due to mutation carriers, alpha-synuclein [α-syn] duplications, prodromal symptoms such as REM-sleep behavior disorder, hyposmia with positive neuroimaging or other high risk markers of phenoconversion).
- Identification of proposed PD modifying agents that could prevent future neurodegeneration and slow the development of symptoms (e.g., immunotherapies, α-syn targets, others).
- Integrate informative biomarkers to generate robust measures of the PD process and inform about target engagement and downstream biological effects (e.g., cerebrospinal fluid [CSF], magnetic resonance imaging [MRI], positron emission tomography [PET]).
- Enable the start of secondary or tertiary prevention trials to generate a database of publicly available results and tissue repositories to accelerate therapeutic development and understanding of the PD process. (e.g., Parkinson's Progression Markers Initiative [PPMI], Dominantly Inherited Alzheimer Network [DIAN], AD Neuroimaging Initiative [ADNI]).

<u>Recommendation 2:</u> Conduct studies to define the natural history of prodromal Parkinson's Disease (clinical, imaging, biomarkers, pathology including post-mortem), to characterize progression and phenoconversion, to identify the determinants of clinical subtypes, to establish a data and tissue resource for future clinical and laboratory investigation, and develop cost-effective methods for health screening to identify persons with prodromal PD.

Need: PD has a prodromal phase and, by the time neurologic symptoms emerge, pathologic changes in the brain are widespread. Earlier detection and intervention are needed in order to optimally intervene in the PD process. The nature and duration of prodromal PD is largely unknown but its characterization is critical to understanding the natural history of PD and its variable clinical phenotypes. Further, understanding the phase of PD before neurologic symptoms emerge will provide the foundation for PD modifying and prevention clinical trials. Identifying at-risk cohorts to serve as a repository of biological and clinical data will be essential to establishing appropriate screening paradigms and early treatment strategies.

Approaches:

- Identify at-risk populations to study the natural history of prodromal PD.
- Correlation studies to determine the relative risk of prodromal markers including hyposmia, REM-sleep behavior disorder, dopamine transporter (DaT) and other imaging on phenoconversion and clinical PD subtype.
- Biomarker studies including genetics, CSF, proteomics and metabolomics to correlate with PD risk and subtype (postural instability-gait disorder, tremor dominant, cognitive impairment).
- Utilize post-mortem studies to better define PD subtypes and their relationship to prodromal markers.
- Assess cost-effective screening paradigms for prodromal PD.

<u>Recommendation 3:</u> Devise and implement longitudinal observational studies, biomarker investigations, randomized clinical trials, and data and bio-specimen sharing resources aimed at characterizing the progressive course of clinically manifest illness, establishing markers of disease, and identifying safe and effective treatments that postpone or ameliorate the intractable disabilities of PD.

Need: Despite the clinically meaningful benefits of dopaminergic therapies, improvement of signs and symptoms is temporary in the setting of progressive illness and disabilities in the form of cognitive impairment and decline, postural instability and falls, confusion and hallucinations, and failing speech and swallowing.

Approaches:

- Characterizing the natural history of best-diagnosed and best-treated PD, including a full array of clinical features and associated biological/genetic markers of progressive disability, would provide a powerful clinical trials platform to gauge the impact and durability of experimental treatments.
- The extent that experimental treatments are effective in postponing or ameliorating such refractory clinical features and disabilities represents a clinically meaningful, measurable, and high standard for determining the value of therapeutic intervention.
- The discovery of biological markers (imaging, tissue, circulating) and genetic types that parallel or predict clinical progression and disability will refine the utility and efficiency of clinical trials.
- Providing an accessible resource that enables sharing of de-identified clinical data, biomarkers and genotypes, will amplify the informativeness and utility of the knowledge that emerges from these long-term studies.
- The longitudinal observational studies, biomarker investigations, randomized clinical trials, and data and bio-specimen sharing resources collectively require long-term longitudinal research be carried out over a horizon of 5-10 years.

<u>Recommendation 4:</u> Initiate prospective studies to define the evolution of non-motor symptoms (NMS, e.g., dementia, psychosis, dysautonomia) and define patient subgroups based on clinical NMS profiles with the goal of developing strategies for treatment and prevention of NMS.

Need: Non-motor symptoms (NMS) are the new "cardinal features" of PD for several reasons: 1) NMS are associated with significant morbidity and mortality, particularly in advanced PD; 2) NMS contribute to the heterogeneity of PD and may be associated with distinct pathologic mechanisms; 3) NMS may represent broad neurodegenerative vulnerability and may be markers of risk for disease progression; and 4) NMS may occur decades before the diagnosis of PD and thus may be used as risk factors for PD onset. In spite of their importance, substantial knowledge gaps remain related to NMS. For example, there is currently no consensus on the range of NMS that should be systematically documented and the instruments that should be used, and there have been very few clinical trials directed specifically at non-motor symptoms. Identification of subgroups of individuals at risk for specific NMS and interventions designed to prevent or treat them would result in improved quality of life for individuals with PD.

Approaches:

- Create longitudinal clinical, biological, and imaging resources from the earliest stages to autopsy studies to improve the accuracy of detection and diagnosis of NMS, with the goal of identifying PD patients with a high risk of specific NMS and if there are subgroups with different clinical trajectories.
- Use patient and caregiver derived information to prioritize investigation of NMS and systematically use validated instruments to determine which are most sensitive and specific for each NMS.
- Determine the relationship between measures of NMS and biological and imaging measures to make clinical trials more efficient.
- Initiate clinical trials for NMS using existing and newly developed symptomatic therapies that address key symptoms such as dementia and psychosis that impact patient function and the burden put on caregivers.

<u>Recommendation 5:</u> Develop biomarkers of target engagement and proximal pharmacodynamic effects for use in early- stage clinical trials.

Need: In addition to safety and pharmacokinetics, early stage trials seek to determine if the experimental agent has engaged the intended biological target and had the appropriate pharmacological effect. Some of these markers may also be useful to enrich the study cohort to ensure that those subjects express the biological target at sufficient levels (e.g., amyloid imaging). Such information is critical for determining dose and regimen and supporting longer term studies to test clinical efficacy. In the absence of these markers, it is not possible to know if the biological hypothesis was tested. Examples of targets in PD in brain tissue, other tissue, or fluids include but are not limited to α-syn, glucocerebrosidase (GBA), leucine-rich repeat kinase 2 (LRRK2), and parkin. Targets such as amyloid-beta (Aβ) and tau may overlap with other neurodegenerative diseases.

Approaches:

- Focused efforts to develop imaging (e.g., α-syn imaging agent) or other assays for a limited set of genetically defined targets that are likely to be key targets for disease modification. These are different from progression markers and need not have longitudinal follow up.
- A variety of different *in vitro* and *in vivo* approaches may be used.
- Focused efforts to study evolving biomarkers from Alzheimer's disease and related neurodegenerative disorders (such as Aβ and tau imaging ligands) to determine their association with features of PD such as cognitive impairment.

<u>Recommendation 6:</u> Identify mechanisms responsible for the development of levodopa-resistant motor symptoms (gait and balance problems including gait freezing) and develop novel therapeutic approaches to these problems.

Need: While levodopa and other dopaminergic therapies generally provide substantial improvement of all cardinal motor features of PD, medical therapies often fail to control gait and balance problems in advanced disease. These levodopa-resistent motor symptoms include postural instability as well as freezing of gait and are a major cause of falls and disability. It is generally assumed that their pathophysiology is driven by non-dopaminergic mechanisms but their exact pathophysiological events by which such symptoms develop in the course of PD are poorly understood. Recent research has hypothesised that dysfunctional cholinergic neurons in the pedunculopontine nucleus may play a role, but attempts to modulate their activity through targeted deep brain stimulation (DBS) or drug therapies have been disappointing. There is an urgent need to better understand the underlying mechanisms and clinicopathological correlations for these symptoms and their risk factors and to develop novel therapies.

Approaches:

- Define dysfunctional motor patterns in patients with gait and balance problems using bodyfixed sensors and other novel computational technology.
- Identify biomakers for the development of postural instability and freezing of gait with advancing PD.
- Identify novel targets for DBS and pharmacological therapies.
- Study the role of non-pharmacological, non-surgical therapies.

<u>Recommendation 7:</u> Develop improved methods to assess long-term efficacy and potential for disease modification in clinical trials, including: 1) more efficient (better & faster) strategies for screening potential agents; and 2) trial design simulations to assess the performance of trial designs for predicting long-term benefits.

Need: Since confirmatory trials of disease modification require long-term follow-up, efficient designs to screen potential agents are needed for PD. In particular, methods and approaches that allow assessing more than one treatment or multiple dosages of the same treatment at the same time would be very attractive. Currently, when a treatment fails to show efficacy in a clinical trial, it is often not clear whether the failure was solely due to the treatment itself or also to some failure or weakness in the trial design or measurement of the disease implemented in the study. Obviously, one cannot blame the design for failure if a treatment does not work. However, at the same time, without knowing if the design works (based on simulations taking into account the disease modeling process over time, as well as an assumed treatment effect expected for an effective intervention) one cannot rule out issues with the design. As novel methods and approaches are developed, it will be important to examine the performance of the designs in situations where the "truth" is known – i.e., an intervention is truly effective or not. Accomplishing this will require groups of clinicians and statisticians working collaboratively to develop and assess potential design strategies, independent of the implementation of any specific trial. In the past, these collaborations have not generally existed.

Approaches:

- Although there is nearly universal agreement that the development of more efficient study designs are needed for PD studies, a current rate-limiting step is that there are few mechanisms available to support the time and effort needed to develop and validate these studies. It is not efficient to do this during the implementation of an actual trial, since that would involve needlessly delaying the recruitment of subjects into the trial.
- The development of improved designs for detecting interventions with disease modifying effects could be accomplished by devoting resources to groups of individuals with the appropriate expertise in this area.
- The assessment of novel designs could be accomplished through simulation studies by the same groups of individuals as above. However, this would also require input from clinical experts to determine potential scenarios that an "effective" treatment might be shown to work (since there are several different options). The inclusion of both groups of individuals would allow the assessment of design properties as a function of real-world expectations, rather than theoretical assumptions.

<u>Recommendation 8:</u> Determine factors that could facilitate public health interventions, including risk factor reduction and health services interventions (population-wide and/or individual).

Need: The number of PD cases in the United States will continue to increase with the population aging, causing a huge social and economic burden; preventing PD is critical. PD is a complex disorder, with genetic and environmental determinants, providing an opportunity for identification of at-risk persons and population-wide risk reduction. PD has a long prodromal phase, providing a window of opportunity for disease modifying interventions. Knowledge gaps that must be addressed to achieve these goals include understanding risk and preventative factors, characteristics of prodromal state(s) and determinants of disease progression. This knowledge is needed to develop interventions to prevent PD onset or slow progression.

Approaches:

- Investigate PD, "at risk" and control populations to identify risk and preventative factors (genetic, environmental, epigenetic).
- Characterize prodromal PD features (clinical, biomarkers) and the natural history of prodromal disease progression.
- Determine an efficient population screening method to identify persons for preventive interventions.
- Develop methods for implementing preventive interventions and assessing their efficacy.
- Achieving these goals will require the combined efforts of basic scientists, epidemiologists and clinicians to identify preventive measures and persons at risk for PD.

<u>Recommendation 9:</u> Investigate the use of innovative outcome measures to evaluate motor and non-motor features, including patient- and clinician-reported outcomes that leverage emerging IT opportunities, enhance sensitivity and specificity of measurement, and facilitate long-term follow-up of well-characterized cohorts.

Need: Outcomes measurement is a cornerstone of clinical research. Limitations in outcomes measurement serve as a "common denominator" resulting in limitations across the breadth of clinical research. Our understanding of PD has expanded to include more diverse manifestations (motor and non-motor) with greater insight into disability associated with individual symptoms (falls, fatigue, freezing, cognitive impairment). However, high quality tools for assessment of these diverse symptoms have not been adequately investigated. Modern measurement principles provide new opportunities to improve the quality of applied outcome measures including improved sensitivity, specificity, and practicality with the use of emerging technologies.

Approaches:

- Perform comparative studies of the sensitivity and specificity of available instruments including NIH NeuroQoL, PROMIS, Toolbox, and Common Data Elements, with a focus on the optimum application of patient- and clinician-reported outcomes and physical/cognitive performance measures.
- Investigate the magnitude of clinically important differences on a range of patient- and clinician-reported outcomes and physical/cognitive performance measures.
- Investigate the comparative feasibility and validity of diverse methods of data collection including computerized tablet, smartphone, remote monitoring and computerized adaptive testing.
- Investigate the potential to use electronic medical records or remote assessment approaches (telemedicine) to capture long-term outcomes in clinical research cohorts.

<u>Recommendation 10:</u> Develop improved informatics capability that could include: 1) exploration of ways in which "big data" may contribute to learning in the PD space; 2) further develop and promote access to a central data repository for PD trial data; and 3) a resource for trial design simulations to inform decisions about efficient trial design for a given intervention.

Need: A more detailed understanding of the natural history of PD, both before and after diagnosis, and the characterization of PD subtypes would accelerate developments of effective treatments. Making use of existing datasets is the most efficient way to address these questions. Moreover, the design of clinical trials needs access to existing longitudinal data to appropriately model and simulate design operating characteristics. Although there are recommended common data elements and requirements for sharing data publically, the technical aspects of combining or pooling datasets across multiple sources requires a considerable investment of time and expertise. PD trials and well-designed cohort studies provide the highest quality data and are a resource that needs to be preserved. Administrative data sources, such as electronic medical records, are a growing resource but require planning to utilize.

Approaches:

- To maximize the usefulness of existing datasets, a central repository to standardize and uniformly archive existing and future trial data is a needed resource.
- A central body to manage the standardization of datasets and provide a user-friendly end product would ensure that existing trial data are used appropriately to answer questions beyond the original intent for which they were collected. This central body would likely involve an ongoing team of data managers, programmers, and statisticians with the appropriate expertise in this area.
- Support the development of informatics to archive administrative data sources and explore ways to overcome barriers to use such as: access, ethical challenges, de-identification of data, and common data items.

<u>Recommendation 11:</u> Develop strategies to increase minority participation in research. These initiatives should include mechanisms to assess the effectiveness of these programs and could lead to the establishment of shared resources to facilitate minority recruitment in PD clinical trials.

Need: Members of ethnic and racial minorities have historically been underrepresented in PD research, and participation is substantially lower for PD than for other neurological disorders such as Alzheimer's disease and stroke. To date, the specific barriers to minority research participation have not been successfully addressed. Greater minority participation would provide a basis to understand possible biological differences in the expression of PD in minority groups and give confidence in the generalizability of research results to these populations.

Approaches:

- Undertake studies to address biological and clinical differences in the expression of PD in minority populations.
- Identify specific barriers to greater minority participation in PD research studies (e.g., stigma, cognitive/psychiatric impairment, use of proxies, access to clinical research sites) and develop actionable and measurable policy guidelines and recommendations for recruitment, enrollment and retention of minorities in PD research.
- Undertake demonstration programs to test strategies that facilitate minority participation in PD research. These programs should include clearly defined plans to assess their effectiveness.
- Develop a best practices toolkit and other shared resources targeted toward community members, researchers, and government. These resources could include:
    - Rosters of local and regional research champions in minority populations
    - Training program for researchers on effective strategies to recruit, enroll, and retain minority participants
    - Access to infrastructure belonging to NINDS research programs that have successfully included minority populations
    - Initiatives to defray costs related to minority recruitment and retention

<u>Recommendation 12:</u> Identify risk factors and pathogenic mechanisms of motor fluctuations and dyskinesias to identify novel targets for prevention and symptomatic therapy for these problems.

Need: After chronic levodopa therapy in PD, patients develop a stereotyped pattern of motor dysfunction in which they cycle between an effectively medicated "on" state with good mobility, and an unmedicated, immobile state, in spite of frequent medication dosing and the use of levodopa extenders such as COMT inhibitors and slow release formulations. The "on" state is often accompanied by excess involuntary movements (dyskinesias). Currently there are several symptomatic treatments for fluctuations and dyskinesias, including deep brain stimulation and, potentially, continuous intestinal infusion of duodopa. The knowledge gaps in this area include the neural basis for fluctuations/dyskinesias, the neural basis for the efficacy of surgical therapy (e.g., DBS) and the risk factors for development. A better understanding of these mechanisms will improve current symptomatic therapies and perhaps slow onset of fluctuations/dyskinesias in individuals identified as having highest risk.

Approaches:

- Develop novel neurophysiological and imaging tools to understand neural networks responsible for the development of motor fluctuations and dyskinesias.
- Identify genetic and other biomarkers for motor complication risk.
- Define novel targets for symptomatic therapies of motor complications.

Building a Translational Pipeline for Parkinson's Disease Therapeutics

January 6, 2014, 1:00 p.m. – 4:30 p.m.

Recommendation 1: Develop patient stratification strategies and support technologies that define disease signatures that represent more homogeneous cohorts for translational research. To stratify PD patients objectively, disease signatures should define slow- and fast-progressing PD, prodromal PD, and non-motor symptoms of disease.

Recommendation 2: Develop novel and specific alpha-synuclein (α-syn) PET imaging agents and assays to measure α-syn burden, validated in both animal models and human tissue.

Recommendation 3: Support the development of translational resources with greater power to predict efficacy and biomarker outcomes in clinical trials. These resources would include well-characterized replication sets of non-integrating induced pluripotent stem cell (iPSC) lines from sporadic cases and from patients with each major PD-causing gene mutation.

Recommendation 4: Support the development of an integrated PD database that includes data from genetic, biomarker, clinical research, and clinical trials with informatics support for integration of existing databases in PD and other chronic neurodegenerative diseases.

Recommendation 5: For preclinical studies targeting α-syn metabolism, α-syn pathology and/or neurodegeneration caused by α-syn, procedures and models used should be standardized, with consensus guidelines developed for appropriate use of existing models, replication of results across labs, and recommendations for future model development.

Recommendation 6: Develop and apply intermediate markers of drug efficacy in early PD translational studies to support more cost-effective and smaller proof-of-concept studies.

Recommendation 7: Define the required attributes of targets emerging from basic science efforts that would justify their advancement into translational studies in PD.

Recommendation 8: Develop a thorough understanding of targets and pathways associated with pathogenesis and pathophysiology of PD with emphasis on those that are validated via human genetics and biology.

Recommendation 9: Investigate the relationship between α-syn misfolding and mitochondrial function to further understand pathways that intersect in PD.

Recommendation 10: Develop tools and technologies for measuring pathway architecture and flux in PD and integrate findings from these approaches across 'omics' platforms into a systems level understanding of pathogenesis and a blueprint for effective therapeutic intervention.

<u>Recommendation 1:</u> Develop patient stratification strategies and support technologies that define disease signatures that represent more homogeneous cohorts for translational research. To stratify PD patients objectively, disease signatures should define slow and fast progressing PD, prodromal PD, and non-motor symptoms of disease.

Need: PD is a clinical diagnosis/classification with clinical endpoints and there is a need to supplement this in order to improve sensitivity and specificity. This is further confounded, as most patients don't have an identifiable cause that can be attributed to their diagnosis. If PD indeed has different causes, then therapeutic strategies are needed that enable the selection of patients who are most likely to benefit from the intended therapeutic. Current clinical trials are powered to detect effects assuming the majority of enrolled patients are responsive, so if only a subset would potentially benefit from the test agent, the clinical trial will fail even if the agent is effective.

Approaches:

- Identify the most promising biomarkers for patient stratification.
- Develop sensitive imaging and biofluid assays for α-syn to assess Lewy body (LB) pathology and soluble species of α-syn, respectively.
- Develop novel genetic and genomic markers, markers of neuronal health and synaptic proteins
- Develop an understanding of the factors contributing to heterogeneity in the rate of progression of PD.
- Use currently available high-resolution metabolomics tools to analyze blood, urine, and CSF samples from extensively phenotyped PD patients categorized according to slow and rapid progression to determine metabolic sub-classifications.
- Genome-wide association study (GWAS) data have provided useful characterization of genetic risk factors for PD; studies evaluating metabolic interactions with risk alleles are likely to provide new insight into disease mechanisms and potential for new therapeutic targets, especially for prevention or disease delay.

<u>Recommendation 2:</u> Develop novel and specific alpha-synuclein (α-syn) PET imaging agents and assays to measure α-syn burden, validated in both animal models and human tissue.

Need: Definitive non-invasive confirmation of α-syn pathology is critical to support the accuracy of clinical diagnosis and can be used in combination with CSF measures of α-syn, to track the temporal profile of disease progression and to monitor the effect of directly targeted α-syn therapeutics. Improvements or changes in α-syn levels may result not only from therapies targeted directly at α-syn but also from other successful therapies. Measurement of multiple α-syn species can be used as a pharmacodynamic marker.

Approaches:

- Selective and potent α-syn tracers can be discovered in analogy to amyloid-beta (Aβ) and paired helical filament (PHF)-tau. Selectivity for α-syn over other amyloid proteins can be attained by following structure-activity trends, maximizing α-syn selectivity and minimizing binding to other amyloid proteins. α-syn, being a pathological hallmark of PD, much like Aβ and tau are pathological hallmarks of AD, may serve as a diagnostic target for PD diagnosis and for monitoring disease progression.
- PET imaging is well suited for detecting α-syn in the living brain using a suitable PET ligand.
- Validated and standardized assay methodologies are needed to measure soluble, oligomeric and post-translational modified forms of α-syn in plasma and CSF.

<u>Recommendation 3:</u> Support the development of translational resources with greater power to predict efficacy and biomarker outcomes in clinical trials. These resources would include well-characterized replication sets of non-integrating induced pluripotent stem cell (iPSC) lines from sporadic cases and from patients with each major PD-causing gene mutation.

Need: To move the PD field forward we need a better understanding of the underlying basic mechanisms of disease, translation of these mechanisms into potential therapies and cutting edge clinical trials. Because of the poor track record of translating results from preclinical rodent toxin models to results in humans, the relevance of mechanisms discovered with these models to PD has been questioned, and the investment by industry in developing therapies for PD is less than it might be. Thus, an important goal will be to create tools and models that can be used to study PD biology in a human context and in turn yield results that provide greater guidance for PD therapeutic development.

Approaches:

- iPSC technology is now readily available and should be integrated into all translational efforts for PD. There should be well-characterized sets of non-integrating lines available from 10 sporadic cases and 10 cases from patients with each major PD-causing gene mutation. Each mutant line should have a matching isogenic control corrected using gene targeting. iPSC line development should involve those patients with extensive clinical characterization and whose contributed biosamples have been used in 'omic' studies. These lines should be available as frozen suspensions of neural progenitors specified to either a forebrain or hindbrain fate that can simply be thawed and plated by the PD researcher for use in their studies.
- Efforts should support predictive and interactive studies that inform on relevant clinical PD phenotypes such as dopamine biology, pesticide sensitivity, etc. and which can provide readouts that can in turn be provided to clinical studies to help establish a relationship between cellular readouts and patient phenotypes.
- Research should support innovation that drives maturation and enhanced complexity of cell based assay systems (e.g. 3-D systems, nigral/striatal co-cultures, transplantation of cells into immune deficient mice).
- Specific efforts should be made to validate the utility of iPSC models for providing information that predicts clinical findings. One approach would be to use systems biological and computational approaches to determine which iPSC phenotypes, if any, correlate to clinical features of the patient from whom the cells came. If some set of iPSC phenotypes proved to predict clinical progression, for example, this type of analysis could be used in the future to stratify patients for a clinical trial. Similarly, efforts could be made in industry to retain tissue samples from patients enrolled in a clinical trial that could be used to make iPSCs selectively from responders and non-responders to determine whether the results for specific patients in the clinical trial could be predicted from the responses of their iPSCs.
- The likelihood of new mechanistic insights from toxin models of PD seems low, given the extent to which they have already been characterized and the limited power

these models have had for predicting clinical trial results. Thus, the development of new animal models of PD should emphasize genetic causes or transmissibility mechanisms where the likelihood of novel mechanistic insights is higher.

<u>Recommendation 4:</u> Support the development of an integrated PD database that includes data from genetic, biomarker, clinical research, and clinical trials with informatics support for integration of existing databases in PD and other chronic neurodegenerative diseases.

Need: An enabling approach would be to develop PD signatures by collecting high resolution molecular data (e.g., whole genome sequencing, transcriptomics, epigenomics, metabolomics, proteomics, iPSC phenotypic data, etc.) and apply systems approaches to determine whether signatures of PD emerge that have important predictive value for clinical features, such as onset, progression, symptom profile and/or to identify new pathways and targets implicated in the pathophysiology of the disease. It is anticipated that disease signatures developed at different times would reveal whether the abnormalities found in patients cluster into a single group or multiple groups. Samples from clinical trials in PD should also be mined using the approaches described above to determine the extent to which responses among different PD patients are homogeneous or heterogeneous.

Approaches:

- Deploy systems approaches ("omics") on their own and in combination, especially using human information to develop an understanding of disease and effects of perturbations.
- Develop computational tools integration such as machine learning and other approaches to integrate disparate types of data into a global expression of disease signatures and to investigate the prognostic value of multidimensional data sets for disease progression (now) and response to therapy (longer term).
- Deploy funds in support of open access databases and shared resources

<u>Recommendation 5</u>: For preclinical studies targeting α-syn metabolism, α-syn pathology, and/or neurodegeneration caused by α-syn, procedures and models used should be standardized, with consensus guidelines developed for appropriate use of existing models, replication of results across labs, and recommendations for future model development.

Need: Using a standard set of models and procedures will facilitate direct comparison of various preclinical studies within labs and across different labs and treatment options. Even for the α-syn based models, there is a confusing array of possible models with very different outcome measures.

Approaches:

- Identify a few models that might be "predictive" for clinical trials and appropriate outcome measures that should be used.
- If non-standard models are used, define appropriate outcome measures for targeting α-syn.
- Determine if α-syn causes common abnormalities in different models (transgenic, inoculation-spreading, virus-induced, and cell based).
- Provide standardized collection of pathological tissues from animal models and human cases for unbiased pathway/omics analysis.
- Organize NINDS sponsored workshop/panel to develop consensus guidelines for preclinical use of animal models for the assessment of *in vivo* assays. These guidelines should be reviewed regularly and modified.

<u>Recommendation 6:</u> Develop and apply intermediate markers of drug efficacy in early PD translational studies to support more cost-effective and smaller proof-of-concept studies.

Need: Current clinical trials for disease modification in PD are expensive and require long periods of study and large numbers of patients. Future investment in such trials and indeed in PD therapeutic development is jeopardized due to the lack of previous success, and the finite resources within the overall funding system. Intermediate markers of drug efficacy could support shorter and more cost effective proof-of-concept studies and ensure a continued investment in therapeutic development in PD.

Approaches:

- Neurophysiology markers such as beta oscillations assessed by EEG/MEG need to be validated and studied in longitudinal trials to qualify their use in early trials.
- Neuroimaging biomarkers such as diffusion tensor imaging or connectivity maps generated using MRI or blood oxygen level-dependent (BOLD)-MRI need to be investigated further to assess their utility in shorter-term (e.g., 6 months) trials.
- Studies conducted by KineMed indicate deficits in vesicular transport in Parkinson's disease using CSF proteomics approaches in conjunction with labeling of the proteins via deuterated water ingestion. This functional end point could potentially provide a measure of efficacy at a shorter time point for therapies targeting α-syn.
- It is critical to understand the turnover rate of α-syn at different stages of PD. Leucine labeling studies, such as the ones conducted by Bateman et al., for Aβ, may provide a method to assess α-syn dynamics.

<u>Recommendation 7:</u> Define the required attributes of targets emerging from basic science efforts that would justify their advancement into translational studies in Parkinson's disease.

Need: There are examples of failed high profile clinical studies of compounds in PD that have not been firmly grounded in a solid understanding of the mechanism of action of the compound tested as the intended therapeutic, or in some cases its molecular mode of action, and such compounds have advanced to full blown clinical studies without any attempts at early translational studies such as target engagement or pharmacodynamics markers of drug action. There is a need to stop investment in such compounds in favor of those targets and compounds that are amenable to more rigorous translation approaches.

Approaches:

- Focus on targets that are firmly grounded in mechanistic studies and provide reproducible readouts in cell based systems (e.g., iPSC-derived neurons, etc.).
- Prioritize targets that can be detected and modulated *in vivo* with therapeutic approaches (e.g., enzyme activity in accessible peripheral compartments or central nervous system).
- Consider targets that are already "validated" in patients via genetic linkages between carriers of recessive genes and risk for common pathologies (e.g., GBA1 and PD).
- Insist on the development of target engagement biomarkers/companion diagnostics before a clinical trial is initiated to ensure that the results regarding the validity of the target are conclusive, whether they are positive or negative.

<u>Recommendation 8:</u> Develop a thorough understanding of targets and pathways associated with pathogenesis and pathophysiology of PD with emphasis on those that are validated via human genetics and biology.

Need: There is a need to agree on the most compelling and key pathways that are emerging in Parkinson's disease and that have a strong foundation in human genetics or human biology, and to focus rigorous efforts to determine the most promising of these for future therapeutic development. At the same time there is a need to identify promising targets that have not yet been identified.

Approaches:

- Confirm the validity of targets and pathways using human derived information such as genetics, tissue and fluid omics approaches.
- Develop a well curated biobank including brain tissue, CSF, blood, plasma, DNA, skin etc.
- Determine whether there are convergent pathway(s) between dominant and recessive Parkinson's disease and whether this is contributing to sporadic PD.
- Deploy genetic screens in *C. elegans* or Drosophila for enhancers and suppressors of genes already linked to PD to reveal new genetic steps in the known PD pathways and identify new drug targets.
- Deploy complementary small interfering RNA (siRNA) screens for genes in mammalian cells in defined PD pathways. Cell-based RNA interference (RNAi) screens assessing wild type or mutant α-syn expression, aggregation or autophagic engulfment might also be explored. Chemical genomic strategies stemming from cell based phenotypic drug screens could yield new drug targets following identification of the chemical targets.
- Investigate the role of organelle trafficking deficits in PD pathogenesis.

<u>Recommendation 9:</u> Investigate the relationship between α-syn misfolding and mitochondrial function to further understand pathways that intersect in Parkinson's disease.

Need: There is strong evidence for both α-syn misfolding and mitochondrial dysfunction in PD. One key question for translational drug development is whether these are unrelated causes of PD or if these two processes intersect to cause neuron death. If the two pathways intersect, which is upstream? In other words, might α-syn misfolding impair mitochondria or might mitochondrial dysfunction augment α-syn aggregation. Autosomal recessive Parkinson's Disease (ARPD), such as that caused by parkin mutations, are associated with selective loss of dopamine neurons, lack of non-motor deficits, lack of α-syn pathology, and slow progression (some lasting several decades). These clinical features are very different from idiopathic PD. Given the neurodegeneration in ARPD and demonstrated loss of function of a single gene product, there is a possibility to approach autosomal recessive PD like enzyme deficiency disorders.

Approaches:

- Determine what is needed for disease modifying therapy for ARPD patients.
- Determine the best predictive models for preclinical evaluation.
- Explore phenotypically relevant mouse models of α-syn mutation crossed into parkin -/-, PINK1-/-, or mitochondrial POLG mutant (Mutator) backgrounds or other mitochondrial stressed mice to determine if there is synergy between α-syn aggregation and mitochondrial stress in causing dopaminergic neuron loss. One could also consider iPSC models from patients to assess crossover between the two pathways *in vitro*.

<u>Recommendation 10:</u> Develop tools and technologies for measuring pathway architecture and flux in PD and integrate findings from these approaches across 'omics' platforms into a systems level understanding of pathogenesis and a blueprint for effective therapeutic intervention.

Need: Many of the systems affected in PD and related diseases are dynamic, and involve protein and organelle trafficking. In contrast, the majority of studies do not examine the flux of molecules through these dynamic systems. Likewise, defects in, for example, mitochondrial homeostasis can also affect metabolism in different ways but how and where bottlenecks form in synthetic networks is largely unknown. One can think of PD mutations as promoting a change in state (or perhaps an ensemble of states) of protein and metabolome networks. Moreover, protein modification states within crucial networks may also undergo a change in state. This involves both discovery-based quantification of networks and modifications in different cell states as well as targeted analysis of particular selected proteins and modifications.

Approaches:

- Determine what networks need to be interrogated (i.e., what networks are most closely related to events that lead to disease), and what technologies are best suited for elucidating changes in state and flux.
- Deploy established and emerging proteomic technologies including AQUA (Absolute Quantification), Tandem Mass Tagging (TMT), and Multiple Reaction Monitoring (MRM) that can allow the dynamics of protein networks to be interrogated on a scale that was not possible even several years ago.
- Develop experimental cell systems, possibly including iPSCs that properly query/model specific genetic defects linked with PD.
- Quantify protein modifications such as phosphorylation, ubiquitylation, and acetylation in both networks as well as at the global level.

Parkinson's Disease Biology: Moving Toward Innovative Treatments

January 7, 2014, 9:00 a.m. - 12:30 p.m.

Recommendation 1: Develop transmission models of alpha-synuclein (α-syn) and tau pathology, and determine the mechanisms of propagation, release, and uptake of these misfolded proteins, including the role of strains.

Recommendation 2: Elucidate the normal and abnormal function of α-syn and its relationship to other PD genes (e.g., glucocerebrosidase [GBA], LRRK2, ATP13A2, PINK1, and parkin).

Recommendation 3: Understand how different cell populations change in their coding properties, firing patterns, and neural circuit dynamics over time, how these changes relate to behavior and motor control, and how therapeutic interventions may affect such changes.

Recommendation 4: Generate and characterize a panel of PD-specific induced pluripotent stem cells (sporadic and genetic, including isogenic lines) for 'omic' (RNA sequencing, proteomics, methylation, etc.) pathway analysis and other approaches.

Recommendation 5: Integrate comprehensive datasets. Perform functional and genetic analyses across large data sets.

Recommendation 6: Develop approaches to exploit direct access to the human brain in persons with PD during neurosurgical procedures such as deep brain stimulation (DBS) and using non-invasive imaging technologies such as 7T MRI and high resolution research tomograph positron emission tomography (HRRT PET).

Recommendation 7: Develop a more detailed understanding of the genetic basis of PD.

Recommendation 8: Develop a more detailed understanding of the molecular determinants and mechanisms of α-syn and tau aggregation (oligomer and fibril formation), disaggregation, and clearance.

Recommendation 9: Use a combination of sensor technologies and imaging to develop a more precise understanding of the neural circuit dynamics in PD that enable the development of next-generation therapeutic devices.

Recommendation 10: Develop more comprehensive understanding of the role of catabolic pathways in PD, including assessment of both the ubiquitin-proteasome and the autophagy-lysosomal systems.

Recommendation 11: Advance our understanding of neural circuits, circuit analysis techniques, PD animal models, and optogenetic and related imaging technologies to improve existing therapies and generate next-generation therapies for PD.

<u>Recommendation 1:</u> Develop transmission models of α-syn and tau pathology, and determine the mechanisms of propagation, release and uptake of these misfolded proteins, including the role of strains.

Need: Emerging evidence strongly implicates cell-to-cell transmission of misfolded proteins through templated recruitment as a common mechanism for the onset and progression of many neurodegenerative disorders including α-syn and tau in PD, PD with dementia (PDD) and Dementia with Lewy bodies (DLB) as well as amyloid-beta (Aβ) and tau in Alzheimer's disease (AD). The newly evolved "transmission hypothesis" for non-prion neurodegenerative diseases provides a highly plausible and compelling explanation for the stereotypical spread of pathological aggregates in PD/PDD, DLB, AD, and other neurodegenerative diseases. This hypothesis also offers a fresh perspective on processes underlying the onset and progression of these CNS disorders. Specifically, for α-syn and tau, aggregate-containing lysates and/or synthetic fibrils assembled from recombinant proteins template or seed their soluble counterparts to fibrillize in cultured cells and/or living animals, even without overexpression of the disease protein in PD models. Other evidence implicates distinct conformers or "strains" of misfolded α-syn and tau as the molecular basis for remarkable disease heterogeneity and co-morbidities. For example, one α-syn strain preferentially recruited monomeric tau to seed formation of neurofibrillary tangles (NFTs), the signature lesions of AD, but NFTs also are common in PDD since a third of patients with PDD show concomitant AD pathology in addition to abundant cortical Lewy bodies (LBs) while brain lysates of different tauopathies to seed tau pathology characteristic of the different tauopathies. However, our knowledge related to the concepts of transmission and strains are rudimentary. Hence, there is an urgent need to develop an in depth understanding of these processes as well as to elucidate the mechanism(s) of disease protein spread in order to identify novel targets for PD therapies.

Approaches: A multiple disciplinary approach including biochemistry, biophysics, molecular biology, cell biology, neuropathology, behavioral tests, and neuroimaging and circuit analyses will be used to:

- Establish and characterize transmission models of α-syn and tau pathology in non-transgenic mice, rats and non-human primates to more authentically model PD, PDD, DLB, and other synucleinopathies.
- Determine the sequence and structural determinants of α-syn and tau that are essential for cell-to-cell transmission and spreading of α-syn and tau pathology, the potential role of distinct α-syn and tau strains to cross seed each other as well as transmit different forms of PD, DLB, and PDD.
- Identify mechanisms for release of α-syn and tau pathological conformers that transmit disease, the uptake of these pathological conformers by other normal neurons and glial cells *in vitro* and *in vivo*.
- Elucidate mechanisms underlying the recruitment and corruption of endogenous normal α-syn and tau proteins to fibrillize as well as the normal cellular processes (e.g., proteastasis) that fail to block seeded propagation and accumulation of these pathologies in cell and animal models in PD and other synucleinopathies.

- Understand how heritable genetic factors (e.g., mutations and polymorphisms in the genes encoding α-syn, tau, GBA, LRRK2, parkin, and PINK1) modulate transmission of α-syn and tau pathologies in genetically engineered mice.

<u>Recommendation 2:</u> Elucidate the normal and abnormal function of α-syn and its relationship to other PD genes (e.g., GBA, LRRK2, ATP13A2, PINK1, and parkin).

Need: The amount of wild type α-syn expressed appears to be a strong predictor of risk for PD, in both familial and sporadic forms of the disease. Although it is generally considered that the amount of protein expressed influences the risk of misfolding and the acquisition of abnormal, pathologic function, we do not know whether an increase in the normal function of α-syn also contributes to degeneration. Aggregation may in fact lower the amount of soluble α-syn, reducing its function with pathologic consequences. It will also be important to understand the effects of reducing α-syn since many current therapeutic approaches target the protein. In addition, changes in conformation associated with the normal function of α-syn may predispose to misfolding or contribute directly to pathologic effects when misdirected to organelles with which α-syn does not normally associate, such as mitochondria and lysosomes. Neural activity may influence the behavior of α-syn, and conversely, α-syn may influence basal ganglia circuits. The apparent requirement for α-syn in MPTP toxicity further implicates the normal function of the protein in degeneration. For all these reasons, it is essential to elucidate the normal function of this protein, which will be important even if many current theories about pathogenesis are either not correct or not relevant. It will be particularly important to elucidate the relationship of α-syn to other PD genes since many of these (e.g., GBA and LRRK2) cause a synucleinopathy.

Approaches:

- Use α-syn knockout mice to elucidate the normal function of the protein. Better cell-based assays will become important to distinguish the direct effects of α-syn from indirect effects due to changes in membrane lipid composition, for example, and to reassess the effect of PD-associated mutations. It will also be important to understand how the family of synuclein proteins including beta (β-) and gamma (γ)- as well as α-syn influence transmitter metabolism and sensitivity to exogenous toxins.
- Determine how the loss of α-syn function influences the behavior of basal ganglia circuits. α-Syn may have physiological effects that are not cell autonomous and underlie its role in degeneration.
- Identify the physiological mechanisms that regulate α-syn expression *in vivo*. Considerable attention has been paid to clearance of the protein, but α-syn was independently identified on multiple occasions as a gene induced by a range of stimuli from growth factors to toxins.
- Use the information about normal function of α-syn to guide the analysis of knockout mice lacking GBA, LRRK2, and other PD genes and determine their epistatic relationship.
- Elucidate the relationship between α-syn and organelles implicated in PD, in particular mitochondria and lysosomes.
- Determine whether dysfunction precedes or follows protein aggregation in patients with PD. In addition to post mortem analysis, this will require early identification of patients at risk by non-motor symptoms, genetics or imaging (which will in turn

depend on a better understanding of the relationship between aggregation of recombinant synuclein *in vitro* and Lewy pathology).

<u>Recommendation 3:</u> Understand how different cell populations change in their coding properties, firing patterns, and neural circuit dynamics over time, how these changes relate to behavior and motor control, and how therapeutic interventions may affect such changes.

Need: Despite decades of study, the dopamine system is not fully understood. However, neuroscience is uncovering evidence for large-scale network activity dynamics and neuroplasticity in brain circuits, including those thought to be core circuits disabled in PD. There is an opportunity with new methods coming into neuroscience to help fill the gaps in our knowledge of Parkinson's related circuits. In particular, we need information regarding the specific cell types and molecules involved in these pathways. Capitalizing on new methods we can determine with precision how PD related circuits encode information, and how these circuits are altered over time due to the genetic, neurochemical, and bioelectrical changes associated with PD.

Approaches:

- Circuit mapping with state-of-the-art electrophysiological and anatomical methods to develop circuit plan including connectivity, activity dynamics and micro-circuit interactions.
- Circuit manipulations applied at key mapped nodes by advanced optogenetic and related (e.g. DREADD) manipulations and microfluidic methods as well as improved models of DBS.
- Application of chronic, not only acute, monitoring techniques of electrical activity in Parkinson's circuits combined with neurochemical activity monitoring (e.g. Fast-scan voltammetry and calcium ($Ca2^{+}$) imaging and two-photon imaging.
- Development of next-generation neurofeedback techniques for therapeutic use to reconfigure vulnerable circuits.

<u>Recommendation 4:</u> Generate and characterize a panel of PD-specific induced pluripotent stem cells (sporadic and genetic, including isogenic lines) for 'omic' (RNA sequencing, proteomics, methylation, etc.) pathway analysis and other approaches.

Need: Recent developments in the reprogramming of human somatic cells to pluripotency with defined factors have the potential to revolutionize the study of the underlying pathogenesis of a variety of human disorders. PD is the most common movement disorder that is due, in part, to the preferential loss of dopamine (DA) neurons. The relative selective degeneration of DA neurons makes PD a particularly attractive human neurodegenerative disease to establish patient specific cells in culture. Successful implementation has the potential to transform the study and treatment of PD by providing new molecular insights into the pathogenesis of PD. Moreover, the potential discovery of biochemical and/or molecular markers could be ultimately used as biomarkers to monitor the progression of PD.

Approaches:

- To phenotypically characterize genetic and sporadic PD specific induced pluripotent stem cell (iPSC)-derived neurons and glia at the cellular, physiologic, molecular, genomic, and proteomic level.
- To develop facile and rapid methods for differentiating pluripotent stem cells into mature DA neurons and apply rigorous tools to interrogate differentiated human DA neurons including cell-sorting markers.
- To develop and refine methods for studying the molecular and physiologic properties of transplanted human DA neurons in rodent and non-human primate models
- To use PD specific iPSC-derived neurons and glia to elucidate mechanisms of neurodegeneration that is relevant PD and related disorders.

<u>Recommendation 5:</u> Integrate comprehensive datasets. Perform functional and genetic analyses across large data sets.

Need: There has recently been an explosion of information derived from large-scale experimental approaches in PD-focused research. These comprehensive analyses include, but are not limited to, genetic screens in model organisms, expression and epigenomic analyses in patient tissue and appropriate models (iPSC, mouse and other mammalian models), genome-wide association studies (GWAS) and large scale drug screens. While all these approaches are important individually, there now exists a critical unmet need to integrate comprehensive data sets to most effectively identify pathways and mechanisms that impact key disease phenotypes and pinpoint the most promising therapeutic targets.

Approaches:

- Gather and integrate data from multiple comprehensive data sets, including model organism and human genetic studies, expression, and epigenomic analyses in a variety of relevant model systems, and comprehensive drug screens. Create a system to promote rapid and open data dissemination from all large scale screens.
- Development and implementation of novel and effective tools of analysis and integration of large data sets will be key to the success of these efforts. This would likely include a "genome browser" style interface, and creation of a PD specific pathway/network that can be browsed and augmented.
- Given the increased recognition of the importance of non-motor symptoms in PD, ensure that data sets derive from patient populations, cell types and models that can address pathways involved in both motor symptoms, and key non-motor manifestations of PD.
- It is expected that in many of these efforts a more system wide approach to understand the interplay of chronological age, the genome, the epigenome, gene expression and splicing, and protein modification in the context of a cell system or vulnerable tissue will be needed to provide key mechanistic insights.
- Pathways and proteins identified through large-scale data set integration and system wide data analysis approaches must then be validated mechanistically in the appropriate experimental models.

<u>Recommendation 6:</u> Develop approaches to exploit direct access to the human brain in persons with PD during neurosurgical procedures such as deep brain stimulation (DBS) and using non-invasive imaging technologies such as 7T MRI and high resolution research tomograph positron emission tomography (HRRT PET).

Need: Although a number of animal models of PD have been developed and new models continue to advance, no model is yet able to recapitulate the spectrum of features, either symptoms or neuropathology, or the time course of disease progression in humans with PD. Thus, it is critical to advance studies in human subjects, and several recent advances have made this possible. First, the rapid growth of functional neurosurgical procedures, especially deep brain stimulation, provides unprecedented direct intraoperative access to the human brain. In parallel, continued development of non-invasive imaging modalities, including high resolution MRI and PET, provide approaches to quantify the structural and biochemical changes that occur during the onset and progression of PD. These reverse translation activities are essential parallel adjuncts to studies in animal models to understand, validate, and improve the relevance of these animal models for both basic science PD research and translational efforts.

Approaches:

- Develop and validate hardware and software tools that enable intraoperative perturbation and recording of relevant variables (electrical, neurochemical) in the human brain, including regulatory strategies to enable application and dissemination of these tools.
- Establish quantitative relationships between patterns of neural activity, including electrical, chemical, and metabolic, and symptoms to track disease progression and establish relevant biomarkers.
- Develop contrast agents/ligands to enable quantitative imaging of structure and biochemistry in the parkinsonian brain.
- Conduct parallel studies in humans and animals to understand better the limitations of current animal models to provide therapeutic leads.

<u>Recommendation 7:</u> Develop a more detailed understanding of the genetic basis of PD.

Need: Genetic work in PD continues at a fast pace. This effort has expanded from its initial success in monogenic forms of the disease, to include understanding of the genetic architecture of apparently idiopathic PD. The field has now put forth a major collaborative effort in genetics, resulting in the identification of 28 independent loci for disease risk. While this progress is beginning to shed insight into the fundamental etiologic processes (e.g., Rab-7L1 and LRRK2), more needs to be done. The immediate needs are threefold. First, moving from our understanding that a locus is associated with disease, to proving which transcript is the biological effector of this association. Second, expanding our genetic dissection of risk; third, to expand the genetic efforts beyond simple risk, to include disease related traits such as age at onset, progression, presentation of motor and non-motor features, and response to treatment. While each of these promises to shed light into our understanding of the basis of disease, and in turn a path toward etiologic based therapy, the latter point is essential to understand the heterogeneity of disease, an understanding that is required for the prediction of progression (critical for clinical trials) and for the application of personalized therapeutics.

Approaches*:* The majority of these projects require large collaborative efforts, and in some cases a medium- to long-term investment in patient ascertainment and longitudinal assessment.

- Detailed efforts to understand the role of genetic risk variability on gene expression (including splicing) and protein expression (including isoforms and modifications) in relevant tissue. Plausibly brain and iPSC-derived neurons, iPSC-derived glia. This would require a major effort assessing hundreds of candidates in large numbers of samples.
- Resequencing of known PD loci in thousands of samples to identify common variant risk alleles, and rare disease linked variants.
- Exome/genome sequencing in tens of thousands of samples. This will take the form of pooling extant data and investment in new sequencing.
- Deeper genotype/phenotype assessment. Comprehensive genetic analysis in cohorts with existing longitudinal data. Investment in new cohorts for longitudinal assessment. In the first instance genetic approaches are likely to be limited to evidence based candidate assessment, but can be expanded to genome wide discovery with sufficient numbers.

<u>Recommendation 8:</u> Develop a more detailed understanding of the molecular determinants and mechanisms of α-syn and tau aggregation (oligomer and fibril formation), disaggregation, and clearance.

Need: Several lines of evidence demonstrate that α-syn aggregation plays a central role in the etiology of PD (both familial and sporadic forms) and that tau aggregation contributes to other neurodegenerative disorders characterized by parkinsonism. However, very little is known about the structure and dynamic properties of different α-syn and tau aggregates such as oligomers, fibrils and Lewy Bodies (LBs) and neurofibrillary tangles (NFTs), and the molecular determinants, cellular mechanisms and pathways that regulate their formation, clearance and toxicity. In addition, it remains to be determined what role sequence variants and post-translational modifications play in modulating these processes. Several factors contribute to this knowledge gap, including 1) the lack of model systems (cellular and higher organisms) that accurately recapitulate α-syn and tau aggregation and the formation/accumulation of LBs/NFTs in the brains of patients with parkinsonism; 2) the lack of experimental tools/approaches to directly observe these processes; and 3) difficulties in isolating intact α-syn in LBs and tau in NFTs from human brains. Filling this knowledge gap by delineating α-syn and tau aggregation, clearance and functional pathways will facilitate development of novel therapies for neurodegenerative disorders characterized by parkinsonism.

Approaches:

- Develop and apply state of the art biophysical and super-resolution imaging techniques including single molecule microscopy to achieve both qualitative and quantitative characterization as well as real time monitoring of structural properties to study the dynamics of α-syn and tau oligomerization, fibril formation, dissociation and clearance *in vitro,* in cells, in animal models and in human biological samples.
- Determine the role of post-translational modifications in regulating α-syn and tau aggregation, disaggregation and clearance *in vitro* as well as in cellular and *in vivo* models of neurodegenerative parkinsonian synucleinopathies and tauopathies.
- Develop and validate cellular, organotypic slice culture, and animal models that recapitulate more faithfully α-syn and tau pathology and/or toxicity in the human brain. Emphasis should be on creating models that accurately recapitulate the physiological location and expression levels of α-syn and tau to avoid potential artifacts associated with non-physiological contexts and protein expression levels.
- Determine the role of the cellular environment (e.g., presence of dopamine and membrane interactions) in the oligomerization and fibrillization of α-syn and tau.
- Determine the mechanisms by which tau and tau aggregation influence the aggregation and toxicity of α-syn and vice versa.

<u>Recommendation 9:</u> Use a combination of sensor technologies and imaging to develop a more precise understanding of the neural circuit dynamics in PD that enable the development of next-generation therapeutic devices.

Need: Despite the established clinical efficacy, the mechanism of deep brain stimulation (DBS) in PD is incompletely understood. Because ablative neurosurgery for PD is similarly effective for treating PD, the stimulation-evoked silencing of pathologically hyperactive neurons was initially postulated as the primary mechanism. However, more recent studies have reported activation of output nuclei from DBS target structures such as subthalamic nuclei (STN) and globus pallidus interna (GPi). The neural network activation hypothesis has enormous implications for DBS mechanism of action. Indeed, DBS should evoke target-specific changes in neural activity in interconnected structures within the basal ganglia complex that ultimately underlie clinical benefit. Nevertheless, our understanding of these distal effects of DBS remains far from complete, in large part because of the technical difficulties in using imaging and sensor technologies for global assessment of neural activity in animal models and in human patients with an implanted device. Further refinement of our understanding of the mechanism of DBS is critical to enable the optimization of DBS for patients with PD.

Approaches:

- Using state of art imaging technologies (such as functional MRI[fMRI] or high resolution research tomograph [HRRT] PET), identify target-specific changes in neural activity in interconnected structures within the basal ganglia complex that ultimately underlie clinical benefit during DBS.
- Using state of art sensor technologies (such as fast scan cyclic voltammetry or amperometry), interrogate the dynamic neurotransmitter and related molecule changes that occur within the DBS target structure as well as their functionally interconnected basal ganglia complex and correlate with clinical outcome measures.
- Develop combination imaging and sensor technologies that can be deployed in human patients and animal models to allow for global network assessment during DBS.
- Develop predictive mechanistic models of neural circuit dynamic changes during DBS using precise target specific activation patterns on imaging and neurotransmitter dynamic changes.
- Using understanding of mechanism of action of DBS, develop next generation of therapeutic devices that utilize closed loop architecture.

<u>Recommendation 10</u>: ***Develop more comprehensive understanding of the role of catabolic pathways in PD, including assessment of both the ubiquitin-proteasome and the autophagy-lysosomal systems.***

Need: Over the last decade, substantial evidence has accrued suggesting that disturbances in cellular catabolic pathways are central to the pathogenesis of PD. Human genetic studies, cell biology approaches and animal studies have implicated disturbances in either or both of the two major intracellular catabolic pathways: the ubiquitin-proteasome system and the autophagy-lysosomal system. In some cases (e.g., GBA or ATP13A2) a global cellular disturbance in the catabolism of macromolecules is implicated. In other cases (e.g., PINK1 or parkin) more discrete catabolic defects may be at work. Yet despite compelling evidence implicating catabolic defects in PD, substantial gaps in knowledge remain. Our knowledge of the normal role of PD-related genes in the functioning of catabolic pathways and how this functioning is impacted by disease variants is incomplete. The downstream consequences of catabolic pathway defects on cellular physiology relevant to PD remain to be fully elucidated. Finally, the pervasiveness of these putative defects in catabolic pathways amongst different subgroups of PD patients is unclear.

Approaches: Interdisciplinary approaches that integrate human genetic studies with genetically tractable models, mammalian models, and emerging human stem cell-derived models to address the following needs:

- To understand the normal role(s) of PD-associated genes in the functioning of the ubiquitin-proteasome system, the autophagy-lysosomal system, or cross talk between these systems, and how disease-associated variants alter these activities.
- To understand the downstream consequences of PD-related catabolic pathway defects on cellular physiology (e.g., synaptic function, mitochondrial function).
- To assess the contribution of catabolic pathway defects to promoting or limiting other pathogenic mechanisms implicated in PD (e.g., cell-to-cell spread of α-syn and/or tau).
- To elucidate the pervasiveness and severity of catabolic pathway defects in familial and sporadic populations of PD patients (e.g., early onset vs. late onset, sporadic vs. familial, association with specific genetic variants).

<u>Recommendation 11:</u> Advance our understanding of neural circuits, circuit analysis techniques, PD animal models, and optogenetic and related imaging technologies to improve existing therapies and generate next-generation therapies for PD.

Need: Treatments that ameliorate symptoms of PD modify the dynamics of large-scale neural circuits. Yet, due to the complexity of the neural circuits that go awry in PD, and our still limited understanding of their normal and pathophysiological states, more effective treatments would undoubtedly result from a clearer understanding of the circuitry and its dynamics. Recently, a new generation of technologies has emerged that collectively hold the potential to answer many of the outstanding questions about the neural circuits involved in PD. These exciting technologies include optogenetic means for activating and inhibiting specific cell types using light, imaging techniques for visualizing the dynamics of genetically defined cell types during animal behavior, computational methods for analysis of large-scale imaging data, methods of high-resolution circuit reconstruction, and genetically encoded fluorescent sensors that report neural Ca^{2+} excitation, voltage depolarization, or release of neurotransmitter or neuromodulator. Application of these approaches in animal models of PD will likely yield substantial insights into circuit structure and dynamics, as well as improved therapies based directly on these insights.

Approaches:

- By using imaging techniques that reveal the dynamics of genetically identified cell types in freely behaving animal models, identify normal patterns of neural circuit activity, how these patterns relate to mammalian behavior, and how these patterns and behavior go awry in PD.
- Create high-resolution maps of how PD alters both long-range and local neuronal microcircuitry, and relate these anatomical and cytoarchitectural changes to the alterations in circuit dynamics and mammalian behavior. Ideally, these maps should be based on the same individual animals studied while alive in large-scale studies of neural dynamics and behavior, to facilitate detailed conceptual links between the various data sets.
- Develop suitable computational methods that can characterize and classify large-scale imaging data sets, in such a manner that these computational methods could facilitate next-generation, large-scale screens for new pharmacologic or DBS treatments using large colonies of animals and automated computational assessment of treatment efficacy.
- Use imaging techniques in freely behaving animals, in conjunction with fluorescent sensors of calcium, voltage, and transmitter/modulator release dynamics, to evaluate in identified cell types the acute and long-term effects (e.g., circuit plasticity) of existing treatments, either pharmacological or DBS, and to assay new therapies.
- Extend existing optogenetic and imaging techniques that are chiefly used today in rodent models of PD so that these technologies can be readily used in primate models of the disease.

- To identify novel disease biomarkers, develop tandem methodologies in PD animal models, combining measurements that can be performed in human subjects with optogenetic and imaging methods that are normally restricted to animals. Successful outcomes will involve measurements that can be performed clinically as well as an understanding of what the novel biomarkers reflect at the microscopic or circuit-level scales.

Abbreviations

α-syn	alpha-synuclein
Aβ	amyloid-beta
AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ALS	amyotrophic lateral sclerosis
AQUA	Absolute Quantification
ARPD	autosomal recessive Parkinson's Disease
BOLD	blood oxygen level-dependent
Ca^{2+}	calcium
COMT	catechol-O-methyltransferase
CSF	cerebrospinal fluid
DA	dopamine
DaT	dopamine transporter
DBS	deep brain stimulation
DIAN	Dominantly Inherited Alzheimer Network
DLB	Dementia with Lewy bodies
DREADD	Designer Receptors Exclusively Activated by Designer Drugs
EEG	electroencephalograthy
fMRI	functional magnetic resonance imaging
GBA	glucocerebrosidase
GPi	globus pallidus interna
GWAS	genome-wide association study
HRRT PET	high resolution research tomograph positron emission tomography
iPSC	induced pluripotent stem cell
LB	Lewy body
LRRK2	leucine-rich repeat kinase 2
MEG	magnetoencephalography
MPTP	1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
MRM	Multiple Reaction Monitoring
NFT	neurofibrillary tangle
NMS	non-motor symptoms
PD	Parkinson's Disease
PDD	Parkinson's Disease with dementia
PET	positron emission tomography
PHF	paired helical filament
PINK1	PTEN-induced putative kinase 1
PPMI	Parkinson's Progression Markers Initiative

REM	rapid eye movement
RNAi	RNA interference
siRNA	small interfering RNA
STN	subthalamic nuclei
TMT	Tandem Mass Tagging

Biographies

Rudi Balling, PhD, is a developmental biologist and geneticist. He studied human and animal nutrition at the University of Bonn and Washington State University, and received his doctorate in human nutrition from the University of Aachen, Germany. In 1993, he became director of the Institute of Mammalian Genetics at the GSF National Research Center for Environment and Health in Munich, after completing research posts at Mount Sinai Research Hospital in Toronto, Canada, and the Max Planck Institutes of Biophysical Chemistry in Göttingen and Immunobiology in Freiburg, Germany. In 2001, he took over the position as scientific director of the Helmholtz Centre for Infection Research in Braunschweig. In 2009, Professor Balling was a guest professor at the Broad Institute of Massachusetts Institute of Technology/Harvard University prior to his appointment that year as founding director of the Luxembourg Centre for Systems Biomedicine. Professor Balling was coordinator of the German Human Genome Project (1996–2000), the European ESFRI-project EATRIS (European Advanced Translational Medicine Research Infrastructure) (2008–2010), and the Bill and Melinda Gates Grand Challenges Consortium on the Development of Vaccine Animal Models (2005–2009).

Randall J. Bateman, MD, received his medical degree, with special emphasis on the neurosciences, from Case Western Reserve University School of Medicine in Cleveland, Ohio. He completed a medical internship at Barnes-Jewish Hospital, St. Louis, Missouri, followed by a neurology residency at Washington University in St. Louis (WUSTL). He then completed postdoctoral research training under David M. Holtzman, MD , and a clinical research fellowship at the Washington University Alzheimer's Disease Research Center under John Morris, MD. Dr. Bateman is currently the Charles F. and Joanne Knight Distinguished Professor of Neurology at WUSTL. His research focuses on improved understanding of the biological basis of Alzheimer's disease (AD), especially autosomal dominant AD, and the development of better biomarkers and treatments for improved clinical management. In addition, he is the Director of the Trials Unit (TU), Associate Director, and Clinical Core Leader for the Dominantly Inherited Alzheimer Network (DIAN). He is the recipient of multiple grants and awards from the NIH, foundations and the pharmaceutical industry. Recent honors include: the 2011 Alzheimer's Association Zenith Fellows Award, the 2011 Glenn Award for Research in Biological Mechanisms of Aging and the 2012 MetLife Promising Investigator Award.

Ann C. Bonham, PhD, directs the Association of American Medical College's (AAMC) programs that support all aspects of research and training. As the primary AAMC contact for external research organizations, Dr. Bonham addresses policy issues affecting research through engagement with key officials in the public and private sectors. Dr. Bonham also works closely with AAMC constituents to address their research needs, and represents the association on the national stage in forums dealing with research policy and administration. Prior to joining the association, Dr. Bonham served as executive associate dean for academic affairs and professor of pharmacology and internal medicine at the University of California, Davis, School of Medicine, where she oversaw the school's research, undergraduate medical education, and faculty academic programs. Dr. Bonham received

her doctoral degree in pharmacology from the University of Iowa College of Medicine and completed a postdoctoral fellowship at Northwestern University School of Medicine.

Christopher S. Coffey, PhD, is Professor at the University of Iowa and the director of its Clinical Trials Statistical and Data management Center. Dr. Coffey received his doctorate in biostatistics from the University of North Carolina at Chapel Hill. He has served as the primary statistician for clinical trials in stroke, obesity, traumatic brain injury, headache, and hypertension. He also currently serves as the principal investigator of the Data Coordinating Center for the NINDS-funded Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) and the Statistics Core for the Michael J. Fox Foundation's Parkinson's Progression Markers Initiative (PPMI). He has served on the NINDS clinical trials study section, currently serves as a member of several of data and safety monitoring boards, is a statistical editor for *Stroke*, and chairs the Program Committee of the Society for Clinical Trials.

Ted M. Dawson, MD, PhD, received an MD and PhD in pharmacology from the University of Utah in Salt Lake City, where he also completed an internship in internal medicine. He is the Leonard and Madlyn Abramson Professor in Neurodegenerative Diseases and Director of the Institute for Cell Engineering at the Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Dawson's honors include the Derek Denny-Brown Young Neurological Scholar Award, the Paul Beeson Physician Faculty Scholar Award, and the Santiago Grisolia Medal. He was elected to the Association of American Physicians and he is a fellow of the American Association for the Advancement of Science. Dr. Dawson has been at the forefront of research into the biology and pathobiology of mutant proteins linked to familial Parkinson's disease (PD). These studies are providing novel opportunities for therapies aimed at preventing the degenerative process of PD and other neurodegenerative disorders.

John Dunlop, PhD, joined AstraZeneca to lead preclinical discovery efforts. Formerly, Dr. Dunlop was the Chief Operating Officer in the Neuroscience Research Unit at Pfizer with responsibility for the preclinical portfolios in neurology and psychiatry. Dr. Dunlop joined Pfizer as part of the Wyeth integration and previously held roles as head of psychiatry and acting head of neuroscience at Wyeth. Trained as a neuropharmacologist, Dr. Dunlop's research interests include the role of proteostatic mechanisms and mitochondrial dysfunction in neurodegenerative diseases and on the emerging genetics of psychiatric disorders. He co-directs the recently established AstraZeneca Tufts laboratory for basic and translation research, and leads the AstraZeneca collaboration with the Vanderbilt Center for Neuroscience Drug Discovery to discover novel positive allosteric modulators of the muscarinic M4 receptor subtype. Dr. Dunlop is a member of the scientific advisory board for the Taube-Koret Center for Neurodegenerative Disease Research at the Gladstone Institute in San Francisco, California, has recently served in scientific advisory roles to the Michael J. Fox Foundation and ALS Association, and is a member of an NINDS study section that reviews translational grant applications in neurological disorders.

Robert Edwards, MD, graduated from Johns Hopkins University School of Medicine, Baltimore, Maryland, and trained in clinical neurology at the University of California, San Francisco (UCSF) and in molecular neuroscience with William Rutter, PhD. Currently a professor of neurology and physiology at UCSF, where he also sees patients with Parkinson's disease (PD), Dr. Edwards has studied the molecular mechanisms involved in neurotransmitter release and their role in neuropsychiatric disease. His lab identified three distinct families of proteins that transport neurotransmitters into synaptic vesicles. He has a long-standing interest in PD, and now focuses on

the presynaptic protein alpha (α)-synuclein. He is a member of the Institute of Medicine and has received a number of awards, including two Established Investigator Awards from the National Alliance for Research on Schizophrenia and Depression. He also serves on the scientific advisory board of the National Parkinson Foundation.

Jordan J. Elm, PhD, is an Assistant Professor of Biostatistics in the Department of Public Health Sciences at the Medical University of South Carolina (MUSC) in Charleston and is a biostatistician for the Data Coordination Unit at MUSC. She has been involved in the design, conduct, and analysis of multicenter, randomized Phase II and III clinical trials in the areas of Parkinson's disease, stroke, and emergency medicine and has provided statistical support for the NINDS Exploratory Trials in PD (NET-PD) and the Neurological Emergencies Treatment Trials (NETT) Network. Dr. Elm's research is focused on adaptive trial designs, futility designs, measurement validation, and approaches to measuring neuroprotection in neurology.

Mel Feany, MD, PhD, received her doctorate degrees from Harvard University. She is a Professor of Pathology at Harvard Medical School and Brigham and Women's Hospital in Boston, Massachusetts. Dr. Feany's laboratory models human neurodegenerative diseases in Drosophila. Her laboratory has described some of the first fly models of common human neurodegenerative diseases, including Parkinson's disease (PD) and Alzheimer's disease. The Feany laboratory has subsequently used Drosophila genetics followed by analysis of vertebrate models and human tissue to identify and validate cellular and molecular pathways mediating neuronal death in PD and related neurodegenerative disorders.

Steven Finkbeiner, MD, PhD, earned his medical and neuroscience doctoral degrees from Yale University. Dr. Finkbeiner is the Associate Director and Senior Investigator at the Gladstone Institute of Neurological Disease (GIND), and the Director of the Taube-Koret Center for Neurodegenerative Disease Research and the Hellman Family Foundation Alzheimer's Disease Research Program in San Francisco, California. He is also a Professor of Neurology and Physiology at the University of California, San Francisco (UCSF). He completed an internship in internal medicine and chief residency in neurology at UCSF, followed by a research fellowship at Harvard Medical School, and was one of the first investigators at GIND. Dr. Finkbeiner is a fellow of the American Neurological Association and is a member of many scientific and professional societies. He is active in graduate training and is a member of the Neuroscience, Biomedical Sciences and Medical Scientist Training Programs at UCSF. Dr. Finkbeiner studies the molecular mechanisms that are responsible for learning, memory, and neurodegeneration. A major focus of his work in neurodegenerative disease has been the role of protein dyshomeostasis in Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and frontotemporal dementia.

Ann Graybiel, PhD, received her doctorate from the Massachusetts Institute of Technology in Cambridge. In 2008, she was named Institute Professor, the highest academic award at MIT, and in 2012 she shared the Kavli Prize in neuroscience. Her research has focused on how the regions of the forebrain that influence movement, mood, and motivation — the basal ganglia and neural pathways interconnecting the basal ganglia with the cerebral cortex — operate in normal and abnormal conditions. Central to many of these studies is work on brain mechanisms underlying learning and how motivation and emotion are linked to the development of action plans, habits, and repetitive behaviors. Her laboratory has a special focus on understanding how such mechanisms can become dysfunctional in neurologic disorders such as Parkinson's disease and Huntington's

disease, and in neuropsychiatric disorders, including obsessive-compulsive disorder and autism. Dr. Graybiel and her group use methods ranging from multi-electrode recordings from neurons in the brain to genetic engineering to approach these issues. Dr. Graybiel is a member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences.

Warren M. Grill, PhD, received a doctorate in biomedical engineering from Case Western Reserve University, Cleveland, Ohio. Dr. Grill is the Addy Distinguished Professor of Biomedical Engineering at Duke University in Research Triangle, North Carolina, with secondary appointments in electrical and computer engineering, neurobiology, and surgery. Dr. Grill teaches courses on circuits and instrumentation, bioelectricity, and on the fundamentals and applications of electrical stimulation. At Duke, he received the Capers & Marion McDonald Award for Excellence in Teaching and Research, was inducted into the Bass Society of Fellows, and was awarded Outstanding Postdoctoral Mentor. He is co-founder, director, and chief scientific officer of NDI Medical, which focuses on innovative neurodevice technology; director and chief scientific advisor at SPR Therapeutics, which has developed a novel therapy for treating pain; and co-founder, director, and chief scientific officer of Deep Brain Innovations, which has developed a novel approach to brain stimulation for neurological disorders. Dr. Grill serves on many boards and committees and was elected as a fellow of the American Institute of Medical and Biological Engineering in 2007 and as a fellow of the Biomedical Engineering Society in 2011.

John Hardy, PhD, received his doctorate in Neuropharmacology from Imperial College in London, United Kingdom. In 1991, he led the group that found the first mutation in the amyloid gene that caused Alzheimer's disease (AD), which led him and others to formulate the amyloid hypothesis for the disease. He later became the Chair of the Department of Neuroscience at the Mayo Clinic in Jacksonville, Florida. He was also part of the consortium that identified mutations in the tau gene in Pick's disease. Professor Hardy transferred to the NIH as the Chief of the Laboratory of Neurogenetics, where he was part of the group that found triplications in the synuclein gene that causes Parkinson's disease (PD). He returned to the department of molecular neuroscience at the Institute of Neurology in London in 2007. He has won the Allied Signal, Potamkin, MetLife, and Kaul Prizes for his work on AD, and the Anna Marie Opprecht Prize for his work on PD. He was awarded the 2011 Khalid Iqbal Lifetime Achievement Award in Alzheimer's Disease Research and the IFRAD 2011 European Grand Prize for Alzheimer's Research. He was elected a member of the Academy of Medical Sciences and was awarded an honorary doctor of medicine degree by the University of Umeå, Sweden. He was elected a Fellow of the Royal Society in 2009 and in 2010 was awarded an honorary doctor of science degree by the University of Newcastle, UK.

Wade Harper, PhD, is the Bert and Natalie Vallee Professor of Molecular Pathology in the Department of Cell Biology at Harvard Medical School. He received his doctorate in chemistry from the Georgia Institute of Technology in Atlanta prior to completing postdoctoral studies in biological chemistry at Harvard Medical School. In 1988, he joined the faculty in the department of biochemistry at Baylor College of Medicine in Houston, Texas, before moving to Harvard Medical School in 2003. His awards include the American Cancer Society Junior Faculty Award, the Michael Debakey Award for Excellence in Research in 1994 and in 2000 for the discovery of cyclin-dependent kinase inhibitors and the SCF ubiquitin ligase, the Vallee Visiting Professorship, and the Pioneer Award from the International Forum on Proteomics. Dr. Harper's work focuses on the analysis of ubiquitin-driven signaling systems and his research on the cell cycle led to the co-discovery of the Cullin-RING finger based ubiquitin ligase (CRL) system — a major class of enzymes

that control the stability of hundreds of cellular proteins, some of which are involved in cell cycle control, transcription, innate immunity, and the DNA damage response.

Dean P. Jones, PhD, received his doctorate in biochemistry from Oregon Health Sciences University, Portland. Dr. Jones is a Professor in the Department of Medicine (Pulmonary Division) at Emory University, Atlanta, Georgia. As a postdoctoral fellow, he studied nutritional biochemistry at Cornell University in Ithaca, New York, and molecular toxicology at the Karolinska Institute in Stockholm, Sweden. He joined Emory University as an assistant professor of biochemistry in 1979 and was subsequently promoted to associate professor in 1985 and professor of biochemistry in 1990. He became professor of medicine in 2003. His central research focus is on redox mechanisms of oxidative stress. Dr. Jones currently directs the Emory Clinical Biomarkers Laboratory, which focuses on oxidative stress biomarkers and applications of 1H-NMR spectroscopy and Fourier-transform mass spectrometry for high-throughput clinical metabolomic analyses of nutritional and environmental factors in human health and disease.

Hartmuth Kolb, PhD, recently joined Johnson & Johnson as Director of the Neuroscience Biomarkers Division. He received his PhD in organic chemistry from the Imperial College of Science, Technology and Medicine in London, United Kingdom, and completed his postdoctoral work at the Scripps Research Institute under the supervision of Professor Barry Sharpless. While working with Dr. Sharpless, Dr. Kolb co-authored the first publication on the development of a set of powerful, highly reliable, and selective reactions for the rapid synthesis of compounds and combinatorial libraries through heteroatom links (C-X-C), an approach called "click chemistry". While Vice President of Molecular Imaging Biomarker Research (MIBR) at Siemens Healthcare, Dr. Kolb leveraged click chemistry to develop a portfolio of investigational radiopharmaceuticals for [^{18}F]-positron emission tomography (PET) imaging. Through this approach, the Siemens Healthcare molecular imaging team identified [^{18}F]-PET tracers that possess strong binding affinity and selectivity toward tau protein aggregates. Dr. Kolb's research interests include natural product and carbohydrate synthesis, investigation of reaction mechanisms, molecular modeling, medicinal chemistry, process chemistry, and combinatorial chemistry.

Nicholas A. Kozauer, MD, earned his medical doctorate from the Rutgers New Jersey Medical School in Newark. He completed his Adult Psychiatry residency at Georgetown University Hospital in Washington, DC where he served as Chief Resident. He then completed a research and clinical fellowship in Neuropsychiatry and Geriatric Psychiatry at the Johns Hopkins University Medical Center, Baltimore, Maryland. Dr. Kozauer served on the faculty of the Johns Hopkins Department of Psychiatry as an Assistant Professor in the Division of Geriatric Psychiatry and Neuropsychiatry. In addition, he previously served as the Director of Neuropsychiatry at the Copper Ridge Institute in Sykesville, Maryland, where he remains involved in teaching and training. Dr. Kozauer is the Clinical Team Leader in the U.S. Food and Drug Administration's Division of Neurology Products, Center for Drug Evaluation and Research, where he covers several indications including Alzheimer's disease.

Dimitri Krainc, MD, PhD, is the Aaron Montgomery Ward Professor and Chairman, Department of Neurology, Northwestern University, Feinberg School of Medicine in Chicago, Illinois. The overarching goal of Dr. Krainc's laboratory is to study rare diseases as a window to understanding neurodegeneration across the lifespan. His laboratory focuses on rare lysosomal diseases such as Gaucher's disease to identify specific targets and mechanisms that contribute to neurodegeneration in Parkinson's disease and related synucleinopathies. It is expected that such defined targets will facilitate mechanism-based development of targeted therapies for neurodegenerative disorders. To

validate and study these targets and pathways in human neurons, they have used induced pluripotent stem cells (iPSCs) generated by reprogramming of patient-specific skin fibroblasts. These iPSCs are differentiated into specific neuronal subtypes in order to study converging pathways of mitochondrial and lysosomal dysfunction. In collaboration with the NINDS iPSC Consortium, novel technologies have been developed to further characterize the contribution of genetic, epigenetic, and environmental factors to distinct neuronal phenotypes in iPSC neurons and their relevance for therapeutic development in neurodegenerative disorders.

Story C. Landis, PhD, has been Director of the NINDS since 2003. A native of New England, Dr. Landis received her PhD from Harvard University. After postdoctoral work at Harvard University, she served on the faculty of the Department of Neurobiology. In 1985, she joined the faculty of Case Western Reserve University School of Medicine in Cleveland, Ohio, where she created the Department of Neurosciences which, under her leadership, achieved an international reputation for excellence. Throughout her research career, Dr. Landis has made fundamental contributions to the understanding of nervous system development. She has garnered many honors, is an elected fellow of the Institute of Medicine, the American Academy of Arts and Sciences, and the American Association for the Advancement of Science, and in 2002 was elected President of the Society for Neuroscience. In 2011, Dr. Landis was the recipient of the Morris K. Udall Award for Public Service in recognition of her commitment to Parkinson's disease research. Dr. Landis joined the NINDS in 1995 as Scientific Director and worked to re-engineer the Institute's intramural research programs and to bring a sense of unity and common purpose to 200 neuroscience laboratories from 11 NIH Institutes. As NINDS Director, Dr. Landis oversees an annual budget of $1.5 billion that supports research by investigators in public and private institutions across the country, as well as by scientists working in its intramural program. Together with the directors of NIH's National Institute of Mental Health (NIMH) and National Institute on Aging (NIA), she co-chairs the NIH Blueprint for Neuroscience Research, an effort to support trans-NIH activities in the brain sciences, which is directing the implementation of the NIH BRAIN Initiative.

Hilal A. Lashuel, PhD, received his doctoral degree from Texas A&M University and the Scripps Research Institute. After obtaining his doctoral degree, he became a research fellow at the Picower Institute for Medical Research in Long Island, New York. In 2001, he moved to Harvard Medical School and the Brigham and Women's Hospital as a research fellow in the Center for Neurologic Diseases and was later promoted to an instructor in neurology at Harvard Medical School. During his tenure at Harvard University, his work focused on understanding the mechanisms of protein misfolding and fibrillogenesis and the role of these processes in the pathogenesis of Parkinson's disease and Alzheimer's disease. In 2005, Dr. Lashuel moved to Switzerland to join the Brain Mind Institute at the Swiss Federal Institute of Technology in Lausanne as assistant professor in neurosciences. Currently, Dr. Lashuel is an associate professor of life sciences and the director of the laboratory of molecular and chemical biology of neurodegeneration. Current research efforts in the Lashuel laboratory focus on understanding the molecular mechanisms of neurodegeneration and developing novel strategies to diagnose and treat neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

Kendall H. Lee, MD, PhD, received his medical and doctorate degrees from Yale University. Dr. Lee is a consultant in the department of neurosurgery, associate professor of physiology and biomedical engineering at the Mayo Clinic (Rochester, Minnesota), and a Commander in the U.S. Navy Reserve. He completed a residency in neurosurgery at Dartmouth-Hitchcock Medical Center, with an

emphasis on deep brain stimulation surgery and stereotactic and functional neurosurgery, and a postdoctoral research fellowship in electrochemistry. In 2006, Dr. Lee joined the Mayo Clinic as a stereotactic and functional neurosurgeon with clinical emphasis on deep brain stimulation, and serves as Director of Mayo Neural Engineering Laboratories.

Michael Lee, PhD, is a Professor of Neuroscience and Co-Director of Center for Neurodegenerative Disease-Institute for Translational Neuroscience at the University of Minnesota in Minneapolis. Previously, Dr. Lee was an associate professor of neuropathology and Morris K. Udall Parkinson's Disease Center project leader at Johns Hopkins University, Baltimore, Maryland. After a long tenure as faculty at Johns Hopkins University, Dr. Lee joined the University of Minnesota. Dr. Lee is internationally recognized for his work on transgenic mouse models of neurodegenerative disease, including motor neuron disease, Alzheimer's disease (AD), and Parkinson's disease (PD). His current work focuses on defining in vivo pathogenic and neurodegenerative mechanisms that are relevant to PD via the studies of alpha (α)-synuclein and LRRK2 transgenic mouse models.

Virginia M-Y Lee, PhD, MBA, received a doctoral degree in biochemistry from the University of California, San Francisco. Dr. Lee is the John H. Ware Third Professor in Alzheimer's Research in the Department of Pathology and Laboratory Medicine at Perelman School of Medicine, University of Pennsylvania in Philadelphia. She pursued postdoctoral studies in pharmacology at the Rudolf Magnus Institute at the University of Utrecht in the Netherlands and in experimental neuropathology at Children's Hospital Medical Center and Harvard Medical School in Boston, after which she assumed the position of associate senior research investigator at Smith Kline & French, Inc., in Philadelphia. Dr. Lee joined the faculty of the department of pathology and laboratory medicine at the University of Pennsylvania School of Medicine, where she rose to the rank of professor. While a Penn faculty member, Dr. Lee obtained an Executive MBA from the Wharton School of the University of Pennsylvania in Philadelphia.

Karen Marder, MD, MPH, received her medical degree at Cornell University Medical College in New York and her MPH in epidemiology from Columbia University School of Public Health. She is the Sally Kerlin Professor of Neurology at the Columbia University Medical Center. She has served as the Chief of the Division of Aging and Dementia since 1991 and has directed the United Council for Neurologic Subspecialities Fellowship in Behavioral Neurology and Neuropsychiatry since its inception in 2003. Her research and clinical care have focused on the epidemiology and treatment of cognitive, behavioral, and motor impairments in a range of neurodegenerative diseases, including Parkinson's disease (PD), Huntington's disease, HIV dementia, and Alzheimer's disease. Since 1998, she has focused on characterizing the earliest motor and non-motor signs associated with genetic forms of PD. She has served as both co-chair and chair of the executive committee of the Parkinson Study Group. She serves as Associate Director of the Irving Institute for Clinical and Translational Research and is co-principal investigator of the Columbia-Weil Cornell NeuroNEXT site.

Kalpana Merchant, PhD, is the Chief Scientific Officer for Translational Science at Eli Lilly. She received her doctorate in neuropharmacology from the University of Utah. Following a postdoctoral research fellowship at University of Washington, she was appointed as an Assistant Professor of Psychiatry at the University of Washington. She was recruited to Lilly in 2003 from a position of Senior Research Advisor and Fellow at Pharmacia, where she had contributed to neuroscience drug discovery research for 10 years. Dr. Merchant's research focuses on elucidating disease mechanisms associated with Parkinson's disease, Alzheimer's disease, and neuropsychiatric

disorders, and connecting the biology of drug targets to disease biology. She is engaged in the wider scientific community via her service on NIH study sections, workshops and advisory panels, and the scientific advisory board for the Michael J. Fox Foundation for Parkinson's Research, as well as membership in several national and international professional societies.

Thomas J. Montine, MD, PhD, received his PhD in pharmacology from the University of Rochester (New York), and his MD from McGill University in Montreal, Canada. His work focuses on the structural and molecular bases of cognitive impairment that occurs with advancing age, and how these processes merge with Alzheimer's disease and Parkinson's disease. The goal is to define key pathogenic steps through fundamental and clinical research, and thereby identify new potential therapeutic targets to protect cognitive function. Dr. Montine's laboratory addresses these prevalent medical problems through a combination of epidemiology-neuropathology, genomics-neuropathology, biomarkers for clinical investigation and clinical trials, and experimental studies that test hypotheses concerning neuroprotection from free radical injury and innate immune activation in specific regions of the brain.

Harry T. Orr, PhD, received his doctoral degree in neuroscience from Washington University in St. Louis, Missouri. Dr. Orr is the Tulloch Professor of Genetics and Director of the Institute for Translational Neuroscience at the University of Minnesota School of Medicine, Minneapolis. He has a long-standing and highly productive NINDS-supported research program on the use of genetics, biochemical, and behavioral approaches in the study of the human polyglutamine neurodegenerative disease spinocerebellar ataxia type 1 (SCA1). His group, in collaboration with Dr. Huda Zoghbi at Baylor University, cloned the SCA1 gene. They went on to establish the first transgenic mouse model of a polyglutamine disease. This model is the center of continued studies on the normal function of the SCA1 gene product ataxin-1, as well as the SCA1 pathogenic process.

Werner Poewe, MD, is Professor of Neurology and Director of the Department of Neurology at Innsbruck Medical University, Austria. Professor Poewe's research interests include the clinical pharmacology of Parkinson's disease and dystonia. He has served as President of the International Movement Disorder Society, Chair of the MDS European Section, President of the Austrian Society of Neurology, as well as president of the Austrian Parkinson's Disease Society. Professor Poewe is a corresponding member of the American Neurological Association and the French Neurological Society, and an honorary member of the German Neurological Society. In 1995, he received the Walther-Birkmayer-Prize of the Austrian PD Society, and in 2006, he received the Dingebauer Prize of the German Neurological Society.

Bernard Ravina, MD, MS, received his medical degree from Johns Hopkins University in Baltimore, Maryland, and completed residency training in neurology and a fellowship in Parkinson's disease and movement disorders at the University of Pennsylvania. He received his master of science degree in clinical epidemiology and biostatistics from the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics. Dr. Ravina was also a medical officer at the NINDS, where he developed a program of Phase II clinical trials in Parkinson's disease, and had oversight of clinical trials in stroke and amyotrophic lateral sclerosis. Dr. Ravina currently is a Medical Director of Translational Neurology at Biogen Idec in Cambridge, Massachusetts. His research focuses on the development of biomarkers and therapeutics for neurodegenerative disorders. Prior to joining Biogen Idec, Dr. Ravina was Associate Professor of neurology, Director of the Movement and Inherited Neurological Disorders Unit, and Associate Chair of Neurology for Clinical Research at the University of Rochester School of Medicine and Dentistry.

Amy Comstock Rick, JD, received her juris doctor degree from the University of Michigan in Ann Arbor. Ms. Rick is the Chief Executive Officer of Parkinson's Action Network (PAN). PAN's national advocacy network educates the public and lawmakers about the effects of PD and the need for federal research funding and policy support. Ms. Rick also serves as an officer or board member with several national coalitions and councils. Ms. Rick has testified before several congressional committees and subcommittees and was honored as an innovator by the Genetic Alliance for her work on federal embryonic stem cell research policy. Prior to joining PAN, Ms. Rick was the U.S. Senate-confirmed Director of the U.S. Office of Government Ethics, and associate counsel to the President in the White House Counsel's Office. She began her federal service in 1988 as an attorney at the U.S. Department of Education, and left in 1998 as assistant general counsel for ethics.

Mark Schnitzer, PhD, is an Associate Professor with a joint appointment in the Departments of Biological Sciences and of Applied Physics at Stanford University School of Medicine. He is a faculty member of the Neuroscience, Biophysics, and Molecular Imaging Programs, as well as of the Stanford Neuroscience Institute. Dr. Schnitzer has received several awards, including the NIH Director's Pioneer Award and the Michael & Kate Bárány Young Investigator Award, Biophysical Society. In 2008, he was named an Investigator of the Howard Hughes Medical Institute. Dr. Schnitzer has long-standing interests in neural circuit dynamics and optical imaging.

Todd Sherer, PhD, received his doctoral degree in neuroscience from the University of Virginia School of Medicine in Charlottesville. Dr. Sherer is the Chief Executive Officer of the Michael J. Fox Foundation for Parkinson's Research (MJFF). He directs the organization's research strategy and is responsible for the organization's overall scientific and fundraising direction to speed treatment breakthroughs and a cure for Parkinson's disease (PD). Today he is one of the world's foremost experts on the science and business of Parkinson's drug development. Dr. Sherer is a member of the board of directors of the Parkinson's Action Network and participates in the Institute of Medicine of the National Academies Forum on Neuroscience and Nervous System Disorders. He is a collaborating scientist for the Coalition Against Major Diseases and a member of the CINAPS Advisory Committee at the NINDS. Dr. Sherer also serves on the National Center for Advancing Translational Sciences Council and the Cures Acceleration Network Review Board at the NIH. Additionally, Dr. Sherer was selected to serve as a council member on Faster Cures' The Research Acceleration and Innovation Network (TRAIN) program.

Ira Shoulson, MD, received his medical degree from the University of Rochester and completed his postdoctoral training in medicine, neurology, and experimental therapeutics at the University of Rochester and at the NIH. Dr. Shoulson is Professor of Neurology, Pharmacology, and Human Science and Director of the Program for Regulatory Science and Medicine at Georgetown University, Washington, DC. Dr. Shoulson founded the Parkinson Study Group and the Huntington Study Group. He was formerly a health policy fellow in the U.S. Senate, a member of the NINDS Advisory Council, and president of the American Society for Experimental NeuroTherapeutics. He is currently principal investigator of the U.S. Food and Drug Administration-Georgetown University Collaborating Center of Excellence in Regulatory Science and Innovation, associate editor of *JAMA Neurology*, and an elected member of the Institute of Medicine of the National Academy of Sciences.

Lisa M. Shulman, MD, is a neurologist specializing in Parkinson's disease and other movement disorders. In addition to neurology, her background includes training in nursing, education, and health policy. She is currently Professor of Neurology and co-Director of the Maryland Parkinson's Disease and Movement Disorders Center at the University of Maryland School of Medicine in

Baltimore. Dr. Shulman is the endowed Eugenia Brin Professor of Parkinson's Disease and Movement Disorders and the Rosalyn Newman Distinguished Scholar in Parkinson's Disease. She was elected to serve on the board of directors and is currently the secretary of the American Academy of Neurology.

Andrew Siderowf, MD, received his medical degree from Duke University and a master of science degree in clinical epidemiology from the University of Pennsylvania. Dr. Siderowf currently is the Medical Director at Avid Radiopharmaceuticals. Following a residency in neurology at the University of Pennsylvania, Dr. Siderowf completed an NIH-funded fellowship at the University of Rochester in movement disorders and experimental therapeutics, and he was then on the faculty at the University of Pennsylvania. He has received research funding from the NINDS, the Michael J. Fox Foundation, and the National Parkinson Foundation. His research interests include clinical evaluation of biomarkers and assessment of patient-oriented outcome measures for clinical trials in Parkinson's disease and Alzheimer's disease.

Andrew Singleton, PhD, received his doctorate from the University of Newcastle upon Tyne, where he studied genetic causes and contributors to dementia. Dr. Singleton did postdoctoral training at the Mayo Clinic in Jacksonville, Florida, studying the genetic basis of neurological diseases such as dystonia, ataxia, essential tremor, and Parkinson's disease. In 2001 he joined the National Institute on Aging (NIA) as an Investigator within the newly created Laboratory of Neurogenetics. In 2007 Dr. Singleton became a Senior Investigator within NIA. Dr. Singleton was selected for the NIH Director's award in 2008. Dr. Singleton serves on the editorial board of Annals of Neurology, Neurogenetics and Neurodegenerative Diseases, and is a member of the Scientific Advisory board for the Michael J. Fox Foundation for Parkinson's Research, the Dystonia Medical Research Foundation and the Lewy Body Dementia Association. Dr. Singleton's group investigates the genetic and cellular mechanisms underlying simple-Mendelian and complex neurological diseases.

Philip A. Starr, MD, PhD, is the Dolores Cakebread Endowed Chair of Neurological Surgery and the Co-Director of the Functional Neurosurgery Program at the University of California, San Francisco. He is also Surgical Director for the Parkinson's Disease Research, Education, and Clinical Center (PADRECC) at the San Francisco Veteran's Affairs Medical Center. Dr. Starr's research interests include physiology of the basal ganglia, clinical trials of novel surgical therapeutics in movement disorders, and the use of interventional magnetic resonance imaging (iMRI) for functional neurosurgery.and was an investigator for the Department of Veterans Affairs/NIH trial of deep brain stimulation (DBS) for Parkinson's disease (PD). Dr. Starr is also surgical investigator on several clinical trials of gene transfer approaches for the treatment of PD. He earned a medical degree at the Harvard Medical School and completed a residency at Brigham and Women's Hospital in neurosurgery. He completed a fellowship at Emory University Hospital in surgery for movement disorders.

Matthew B. Stern, MD, received his medical degree from Duke University. Dr. Stern is the Parker Family Professor of Neurology and the Director of the Parkinson's Disease and Movement Disorders Center at the University of Pennsylvania. He completed his training in neurology at the University of Pennsylvania. Dr. Stern has served on the executive committee of the American Academy of Neurology's Movement Disorders Section and is a fellow of the American Neurological Association. Dr. Stern has been principal investigator or co-principal investigator of many studies related to Parkinson's disease (PD) and movement disorders. He was also co-chair of the Veterans

Affairs Cooperative Study investigating deep brain stimulation in PD, and founding director of the Philadelphia Veterans Affairs Parkinson's Disease Research, Education, and Clinical Center (PADRECC). He is the President of the International Parkinson's Disease and Movement Disorder Society.

David Sulzer, PhD, received his doctorate from Columbia University in New York. He investigates the function and alteration of synapses at the cortex and basal ganglia, including the dopamine system in normal behaviors such as habit formation and action selection, and in diseases of the dopamine system. His laboratory's work has made fundamental contributions to understanding the roles of these synapses in Parkinson's disease, Huntington's disease, schizophrenia, autism, and drug addiction. Dr. Sulzer's lab developed new optical, electrophysiological, and electrochemical methods, including the first direct recordings of quantal neurotransmitter release from synapses, the fundamental unit of neurotransmission, and the first optical methods to observe neurotransmitter release and reuptake. His work increased the understanding of the life cycle of synaptic vesicles, cellular structures that package neurotransmitter release. The Sulzer lab has published more than 140 papers on this research and has received awards from the McKnight, Helmsely, Picower, Michael J. Fox, Simons, and Huntington's Disease Society of America Foundations, as well as NIH and National Alliance for Research on Schizophrenia and Depression.

Clive Svendsen, PhD, received his doctoral degree from the University of Cambridge in England, where he established a stem cell research group. At the University of Wisconsin in Madison, he was the professor of neurology and anatomy, director of an NIH-funded stem cell training program, and co-director of the Stem Cell and Regenerative Medicine Center. Dr. Svendsen established and presently directs the Cedars-Sinai Regenerative Medicine Institute in Los Angeles, California. One focus of his research is to derive cells from patients with specific disorders, which can then be "reprogrammed" to a primitive state and used as powerful models of human disease. Dr. Svendsen led the first groups to successfully model both spinal muscular atrophy and, more recently, Huntington's disease. The other side of his research involves cutting-edge clinical trials. He was involved with one of the first growth factor treatments for Parkinson's disease (PD) and is currently working closely with neurosurgeons, neurologists, and other scientists to develop novel ways of using stem cells modified to release powerful growth factors to treat patients with neurological diseases such as amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease, and PD.

Caroline M. Tanner, MD, PhD, received her medical degree at Loyola University and her doctorate in environmental health sciences at the University of California, Berkeley. She completed a residency in neurology and fellowship in clinical neuropharmacology and movement disorders at Rush University in Chicago. Dr. Tanner is currently the Director of Clinical Research at the Parkinson's Institute, Sunnyvale, CA. Her clinical practice specializes in movement disorders, including Parkinson's disease (PD), atypical parkinsonism, and dystonia. Her research interests include epidemiology, environmental and genetic determinants, biomarkers, early detection, non-motor disease features, and interventions for the secondary prevention, disease modification, and symptomatic treatment of movement disorders. Dr. Tanner is past co-chair of the Parkinson Study Group (PSG), and has conducted numerous clinical trials with the PSG, NINDS Exploratory Trials in Parkinson's Disease (NET-PD), and the Chinese Parkinson Study Group in China. Dr. Tanner chairs the Epidemiology Task Force of the International Parkinson and Movement Disorders Society, serves on the Executive Steering Committee of the NINDS PD Common Data Elements Project, the

Executive Council on the Sections and Subspecialties of the American Academy of Neurology, and chairs several clinical trial data monitoring committees.

J. Paul Taylor, MD, PhD, received his medical and doctoral degrees summa cum laude from Jefferson Medical College, Philadelphia, Pennsylvania. His residency in neurology was at the University of Pennsylvania and his fellowship was in the neurogenetics branch of NINDS where he trained with Kurt Fischbeck, MD. Dr. Taylor joined the neurology faculty at the University of Pennsylvania and established a research program studying the molecular genetics of neurological diseases. Dr. Taylor later moved his research program to St. Jude Children's Research Hospital, Memphis, Tennessee. Dr. Taylor's work has been featured in *Nature*, *Science*, *Cell*, and *Neuron*. He is also the founding organizer of the biennial RNA Metabolism in Neurological Disease Meeting, which is held as a satellite meeting of the Society for Neuroscience's annual meeting. Dr. Taylor was honored by election as fellow of the American Society for Clinical Investigation in 2010 and fellow of the American Neurological Association in 2013.

Richard J. Youle, PhD, is Chief of the Biochemistry Section, NINDS Division of Intramural Research. He received his doctorate degree from the University of South Carolina where he worked on the protein toxin ricin. He joined the lab of David Neville, MD, at the NIH's National Institute of Mental Health (NIMH) for postdoctoral work on the engineering of new cell-type-specific protein toxins. He joined the Surgical Neurology Branch of NINDS in 1985 as a principal investigator, where he has developed new treatment strategies for brain tumors. His lab is now exploring the molecular mechanisms of programmed cell death and engineering therapeutic proteins to regulate cell survival.

NIH Campus Map and Dining Options

The Natcher Conference Center has a cafeteria that is located on the main level and open from 6:30 a.m. to 2:30 p.m.; there are also a convenience store and a vending machine on the main level. An alternate full-service cafeteria is located in nearby Lister Hill Center (building 38A), and there is a large food court in the NIH Clinical Center (Building 10), which is a 5- to 10-minute walk from Natcher.