2023 Parkinson's Disease Therapeutics Conference

October 19, 2023
New York City

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

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Welcome

Welcome to the 15th Annual Parkinson's Disease Therapeutics Conference. The Michael J. Fox Foundation (MJFF) appreciates the value of collaboration and bringing the Parkinson's research and clinician communities together to share ideas and present new findings.

Recent discoveries in the Parkinson's research community only prove that we are on the right track. Our access to robust data continues to expand by leaps and bounds, fueled by the ever-growing Parkinson's Progression Markers Initiative data set. This information helps us learn more about the genetic and cellular process driving Parkinson's as well as patients' clinical experience of the disease. We expect the field to grow even more rapidly as new funders create more opportunities to pursue Parkinson's research breakthroughs.

Today, many of our colleagues will share their progress and give us a window into the successes we will be talking about next year and in the years to come.

MJFF is committed to your research and to providing the resources you need to pursue it. We encourage you to talk to us and the other attendees in the hope you leave this meeting with new ideas and contacts to advance your research.

Sincerely,

Sohini Chowdhury
Chief Program Officer

About The Michael J. Fox Foundation for Parkinson's Research

As the world's largest nonprofit funder of Parkinson's research, The Michael J. Fox Foundation is dedicated to accelerating a cure for Parkinson's disease and improved therapies for those living with the condition today. The Foundation pursues its goals through an aggressively funded, highly targeted research program coupled with active global engagement of scientists, Parkinson's patients, business leaders, clinical trial participants, donors, and volunteers. In addition to funding $1.75 billion in research to date, the Foundation has fundamentally altered the trajectory of progress toward a cure.

Operating at the hub of worldwide Parkinson's research, the Foundation forges groundbreaking collaborations with industry leaders, academic scientists and government research funders; creates a robust open-access data set and biosample library to speed scientific breakthroughs and treatment with its landmark clinical study, PPMI; increases the flow of participants into Parkinson's disease clinical trials with its online tool, Fox Trial Finder; promotes Parkinson's awareness through high-profile advocacy, events, and outreach; and coordinates the grassroots involvement of thousands of Team Fox members around the world. For more information, visit us on **michaeljfox.org**, Facebook, Twitter, LinkedIn.

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The Michael J. Fox Foundation for Parkinson's Research
2023 Parkinson's Disease Therapeutics Conference
October 19, 2023
New York, NY

Conference Program

All presentations are followed by Q&A.

7:45 – 8:30 AM	**Breakfast**

8:30 – 8:45	**Welcome Remarks**
	SOHINI CHOWDHURY, The Michael J. Fox Foundation

8:45 – 11:10 **SESSION 1: Advances in Emerging Targets and Therapeutic Development**

8:45 – 8:55	**Introductory Remarks from Session Chair**
	KAROLY NIKOLICH, PhD, Bayshore Global Management, Stanford University
8:55 – 9:15	**GP2—Globalizing Parkinson's Disease Genetics**
	ANDREW SINGLETON, PhD, National Institutes of Health
9:15 – 9:35	**Examination of Total Cell-Free RNA in Matched CSF and Plasma Samples from BioFIND**
	KENDALL VAN KEUREN-JENSEN, PhD, Translational Genomics Research Institute
9:35 – 9:55	**Identification of TMEM175 Activators as Candidate Disease-Modification Therapeutics for Parkinson Disease**
	DAVID STONE, PhD, Cerevel Therapeutics
9:55 – 10:15	**Development of USP30 Inhibitors for Parkinson's Disease**
	PAUL THOMPSON, PhD, Mission Therapeutics
10:15 – 10:35	**Kv1.3 Blockade to Resolve Neuroinflammation in Parkinson's Disease**
	NIELS PLATH, PhD, Muna Therapeutics
10:35 – 10:40	**Closing Remarks from Session Chair**

10:40 – 11:10   **Networking Break / Poster Viewing**

11:10 AM – 3:00 PM   **SESSION 2: Advances in the Classification and Measurement of Parkinson's**

11:10 – 11:20   **Introductory Remarks from Session Chair**
KATHLEEN POSTON, MD, MS, Stanford University

11:20 – 11:40   **Neuropathology of Lewy Body Diseases**
THOMAS MONTINE, MD, PhD, Stanford University

11:40 – 12:00   **Biological Definition and Integrated Staging System for Neuronal Synuclein Disease: Accelerating Therapeutics for Synucleinopathy**
KENNETH MAREK, MD, Institute for Neurodegenerative Disorders

12:00 – 12:20   **Alpha-Synuclein Seed Amplification Assays: Current Utility and Future Prospects to Aid Therapeutic Development**
KALPANA MERCHANT, PhD, Northwestern University, TransThera Consulting Co.

12:20 – 1:25   **Networking Break / Poster Viewing / Lunch**

1:25 – 1:40   **Overview of Pre-Competitive Molecular Imaging Consortium**
JAMIE EBERLING, PhD, The Michael J. Fox Foundation

1:40 – 2:00   **Digital Measures in Parkinson's Disease: WATCH-PD Study**
JAMIE ADAMS, MD, University of Rochester

2:00 – 2:20   **De-Risking Therapeutic Development: The Power of Mitophagy Biomarkers in PD**
WILLIAM SHRADER, PhD, AcureX

2:20 – 2:25   **Closing Remarks from Session Chair**

2:30 – 3:00   **Networking Break / Poster Viewing**

3:00 – 4:30   **SESSION 3: A Look Ahead: Stakeholder Perspectives on the Future of Parkinson's Research**

3:00 – 3:40   **Applying the Neuronal Synuclein Disease Integrated Staging System to Clinical Trials**
Moderator: **KARL KIEBURTZ, MD, MPH**, University of Rochester

GENNARO PAGANO, MD, MSC, PHD, EMBA, FEAN, Roche

TIEN DAM, MD, Neumora Therapeutics

TANYA FISCHER, MD, PhD, Biohaven

3:45 – 4:25	**Advancing the Use of Patient Voice to Drive Successful R&D**
	Moderator: **CATHERINE KOPIL, PhD**, The Michael J. Fox Foundation
	VICTORIA DIBIASO, MPH, BSCN, Sanofi
	ALISON HANDLER, PharmD, RPh, Novartis
	GARY RAFALOFF, MS, MJFF Patient Council Member
	SOANIA MATHUR, MD, MJFF Patient Council Member

4:30 – 4:40	**Closing Remarks**
	SOHINI CHOWDHURY, The Michael J. Fox Foundation

4:40 – 6:00	**Cocktail Reception / Poster Viewing**

Poster Session

Jeff Hausdorff, PhD

Tel Aviv Medical Center

A Machine Learning Contest to Automatically Detect Freezing of Gait: Results and Insights

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Alastair Noyce, MD, PhD

Queen Mary University of London

The London-Dhaka Project — the Prevalence and Assessment of Cognitive Impairment in Parkinson's Disease

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Nicole Polinski, PhD

The Michael J. Fox Foundation

Research Resources Available Through the Michael J. Fox Foundation for Parkinson's Research

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Tanya Simuni, MD, FAAN

Northwestern University

Path to Prevention (P2P) Trial: Study Design and Status Update

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Diane Stephenson, PhD

Critical Path Institute

Aligning with Regulators to Advance Patient-Reported Outcome Assessments that are Fit-for-Purpose in Early-Stage Parkinson's Disease Clinical Trials

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John Streiff, PhD

AeroNeph Therapeutics

Hit-to-Lead STING Inhibitor Small Molecule Development for Parkinson's Disease

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Peter Vangheluwe, PhD

KU Leuven

The Lysosomal Polyamine Transporter ATP13A2, an Emerging Drug Target for Parkinson's Disease

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Dustin Watson

The Michael J. Fox Foundation

Advocate for Parkinson's Policy

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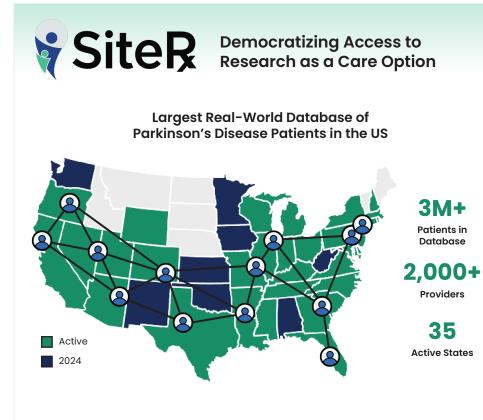
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Genetic Variants: LRRK2, GBA, and more. Genetic testing workflows available.

Parkinson's Symptoms: Dyskinesia, bradykinesia, cognitive impairment (PDD), psychosis, tremor & rigidity.

Treatment History: Carbidopa/levadopa, treatment naïve, etc.

Related Disorders: Dementia with lewy bodies, essential tremor, etc.

Abstracts

Session 1

Advances in Emerging Targets and Therapeutic Development

Karoly Nikolich
Advisor, Bayshore Global Management; Adjunct Professor,
Stanford University Medical School

Karoly Nikolich, PhD, is an advisor to Catalyst4, part of Bayshore Global Management. He also serves as advisor to Pivotal Bioventures and the plasma company, Grifols. During the 1980s, he led Genentech's entry into neuroscience and participated in the development of numerous protein therapeutics for stroke and neurodegenerative diseases. Nikolich was Vice President of Research at Lynx Therapeutics, co-founder of AGY Therapeutics, Amnestix, Neurofluidics, Chase Pharmaceuticals, Circuit Therapeutics and Alkahest. He has been on boards and scientific advisory boards of a number of neurotherapeutics and biotech companies. He has been Adjunct Professor in the Department of Psychiatry at Stanford University Medical School. Nikolich is a graduate of Eotvos University in Budapest and worked as a postdoctoral fellow at Tulane University and UCSF before joining Genentech.

Session 1

Advances in Emerging Targets and Therapeutic Development

Andrew Singleton, PhD

NIH Distinguished Investigator, Director of the Center for
Alzheimer's and Related Dementias, National Institutes of Health

Andrew Singleton, PhD, received his BSc from the University of Sunderland, and his PhD from the University of Newcastle upon Tyne, UK. His postdoctoral studies were spent at the Mayo Clinic in Florida. Singleton moved to the National Institute on Aging at NIH in 2001. He is an NIH Distinguished Investigator and Director of the Center for Alzheimer's and Related Dementias at NIH. Singleton has published more than 700 articles on a wide variety of topics. His group works on the genetic basis of neurodegenerative disorders. The goal of this research is to identify genetic variability that causes or contributes to disease and to use this knowledge to understand the molecular processes underlying disease.

Abstract

The Global Parkinson's Genetics Program (GP2) is a resource program of the Aligning Science Across Parkinson's (ASAP) initiative supported in collaboration with The Michael J. Fox Foundation for Parkinson's Disease Research (MJFF). GP2 is focused on improving our understanding of the genetic architecture of Parkinson's disease (PD) and making this knowledge globally relevant. GP2 is made up of member organizations around the world that are coming together to create a global research community dedicated to rapidly addressing emerging research needs in PD. The work of GP2 is aimed at using genetics knowledge to accelerate the path to the development and deployment of therapeutic strategies for PD.

The work of GP2 spans both simple monogenic and complex forms of PD. As a part of GP2 comprehensive genetic data will be generated on more than 200,000 individuals from around the world. Currently, GP2 has partnerships with more than 200 cohorts from more than 60 different countries, with more than 170,000 samples in the analytical pipeline.

Although still in its early stages, GP2 has begun to make foundational discoveries in the genetics space. Using multi ancestry genetic meta analysis to identify new risk loci for PD, and to fine map existing loci, in addition to identifying a new and remarkably common genetic risk factor in individual of Western African ancestry. This work marks the beginning of GP2's efforts to expand our understanding of the basis of PD, to create worldwide expertise in genetics, and to make these results and this work, globally relevant.

Session 1

Advances in Emerging Targets and Therapeutic Development

Kendall Van Keuren-Jensen, PhD

Professor, Translational Genomics Research Institute

Kendall Van Keuren-Jensen, PhD, has been in the Neurogenomics Division at TGen for the last 16 years where she is currently a Professor and a Deputy Director for the institute. She is also the Director of the TGen Center for Noninvasive Diagnostics with an active research program in assessing ways to capture extracellular vesicles from accessible biofluids and investigate their cargo. Keuren-Jensen's focus has been on isolating subpopulations of extracellular vesicles in accessible biofluids and examining, primarily, their RNA contents. Kendall received her BA from Boston University, double majoring in Biology and Anthropology; she received an MS in Pharmacology and Toxicology from the University of Kansas. Her PhD work was in Neurobiology and Behavior from Stonybrook University at Cold Spring Harbor Laboratory in New York.

Abstract

Advances in Emerging Targets and Therapeutic Development

Kendall Van Keuren-Jensen, PhD

Study Rationale: RNA metabolism is tightly regulated in cells. Disruptions in any part of the process, splicing, transport, or turnover, can be translated to a measurable readout of cellular dysfunction. Disease-related perturbations in RNA metabolism and RNA expression levels are detectable in Parkinson's disease (PD) brain and can make their way out into peripheral circulation. We investigated the extracellular RNA profile in two biofluids, plasma and CSF, collected at the same time from participants with Parkinson's disease and age-similar controls. We examined the utility of each biofluid for instructing us on various symptoms of disease.

Hypothesis: Directly comparing total extracellular RNA collected from two biofluids provides a dataset that can be mined and leveraged to inform biofluid choices in future experiments.

Next Steps for Development: The continuation of projects that examine extracellular RNAs — and target the vehicles they travel in (extracellular vesicles, EVs) – has implications for monitoring disease, even the potential for understanding the roles of different cell types in disease progression. Extracellular RNA readouts could be made more impactful by using cell type-enriched membrane proteins that are carried on the surface of EVs. These EVs can be captured and mined for data that come from the cell-of-origin. Comparisons of these captured EVs, with what we know from total cell free RNA changes in different biofluids, will continue to improve the diagnostic potential of EVs for Parkinson's disease.

Session 1

Advances in Emerging Targets and Therapeutic Development

David Stone, PhD
Vice President, Genetics and Target Identification, Cerevel Therapeutics

Dave Stone, PhD, has studied neurodegenerative disease for almost 30 years. He held a faculty position at Harvard Medical School until 2000, when he joined the pharmaceutical industry to work on drug development. Since then, Stone has applied genetics and genomics across pipeline stages (including target identification, safety and clinical trials) to enable the development of novel therapeutics. While at Merck he led the team which ran one of the first-ever genome-wide siRNA screens (amyloid processing) and was a co-discoverer of the KIF5A association with ALS. Stone led the team which uncovered the functional link between TMEM175 and Parkinson's disease. For the past 10 years he has worked on the cellular phenotypes driven by genetic risk factors for Parkinson's such as TMEM175 and their connection to disease. In 2019 he joined Cerevel Therapeutics as the Head of Genetics, where he oversees target identification, validation and program entry into Cerevel's pipeline.

Abstract

Identification of TMEM175 Activators as Candidate Disease-Modification Therapeutics for Parkinson's Disease

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David Stone, PhD

Study Rationale: In order to design therapeutics for the greatest number of Parkinson's disease (PD) patients, we are targeting genes showing common genetic variation that affect disease risk. TMEM175 is a lysosomal ion channel with some of the strongest genetic linkage evidence to the common/sporadic form of Parkinson's disease. Genetic variants that reduce channel function increase disease risk, while those that increase function decrease disease risk. We are developing TMEM175 channel openers that can be safely given to patients in the hope that these will slow or stop the progression of Parkinson's disease.

Hypothesis: Our aim is to develop small molecule TMEM175 channel openers and determine if they can positively affect lysosomal function and can be tested as candidate therapeutics for the treatment of Parkinson's disease.

Study Design: We have screened roughly 1 million compounds and found several chemical classes that can open the TMEM175 channel. For some classes we have determined how they bind to the channel when opening it. We have tested these in various cellular models and examined how they

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regulate lysosome function. We are now working to make these compounds more drug-like to ensure that they can get into the brain and that they are safe for patients. Those that safely open the channel will later be tested in people with Parkinson's disease to see if they slow disease progression.

Impact on Diagnosis/Treatment of Parkinson's disease: Today there are drugs that can treat the symptoms of Parkinson's disease, but no therapies that can stop or slow its progression. Our compounds are being designed with an aim to slow the progression of Parkinson's disease.

Next Steps for Development: After finding the molecule and biomarkers for a candidate therapeutic, tests on safety and efficacy will be performed to ensure that the molecule can be given to patients without causing adverse events. Then we will move into clinical trials to determine if our compounds do in fact slow the progression of Parkinson's disease.

Session 1

Advances in Emerging Targets and Therapeutic Development

Paul Thompson, PhD
Chief Scientific Officer, Mission Therapeutics

Paul has worked in industry for over 20 years, leading projects at target identification through to POC in many therapeutic areas, focusing on neurological disorders. During his time at Mission Therapeutics, Paul has served as Vice President of Clinical Development before moving to the Chief Scientific Officer role in 2020. He has been responsible for identification, development and transition to clinic of USP30 inhibitors, one of which, MTX652, has completed phase I studies this year. He currently leads the CNS USP30 program as this transitions to clinic in Q4 2023. Prior to Mission Therapeutics, Paul held positions as Clinical Science Director at Ono Pharma and Director of Discovery Medicine Neurology at GSK.

Abstract

Development of USP30 Inhibitors for Parkinson's Disease

Paul Thompson, PhD

A major unmet need for Parkinson's disease (PD) patients is a treatment that slows or prevents the progression of disease. Mitochondrial dysfunction is considered a key pathophysiological driver of Parkinson's disease and several disease-associated gene mutations affect proteins involved in a dysfunctional mitochondria ubiquitin-dependent clearance mechanism known as mitophagy, including PINK1 and the ubiquitin E3 ligase, Parkin. USP30 is a deubiquitylating enzyme uniquely localized to the mitochondria that removes ubiquitin groups and is a negative regulator of the PINK1/Parkin pathway and mitophagy. Inhibiting USP30 has therefore been proposed as a therapeutic mechanism for protecting vulnerable dopamine producing neurons in PD.

Mission Therapeutics has developed a potent, selective and orally bioavailable, CNS penetrant USP30 inhibitor called MTX325, which is about to enter clinical development, starting an FIH trial in Dec 2023. MTX325 demonstrates expected pharmacological and mechanistic activity in vitro, enhancing mitochondrial quality control processes in cell lines and IPSC-derived DA neurons. CNS penetration has been demonstrated in both small models and non-small models, with a clear PK/PD relationship to support dose setting for efficacy studies. An MJFF grant award in 2021 supported investigation of MTX325 in an exploratory model of familial PD, the Parkin KO model, which

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provided some positive signals for MTX325 on reducing systemic inflammation. However, the study did not provide evidence for dopaminergic loss in the Parkin KO models, thus MTX325 was not able to show any benefit on this readout. However, in parallel to these studies, Mission collaborated with Harvard Medical School and Universities of Cambridge and Dundee, demonstrating efficacy of MTX325 in an alpha-synuclein driven in vivo model of chronic dopaminergic loss, reproducing data observed with genetic removal of USP30. Characterization of MTX325 and the synuclein in vivo model collaborative data will be the focus of this short presentation.

Overall, these data support progression of MTX325 into clinical development for disease modification in PD.

Session 1

Advances in Emerging Targets and Therapeutic Development

Niels Plath, PhD

Chief Scientific Officer, Muna Therapeutics

Niels Plath, PhD, is the Chief Scientific Officer of Muna Therapeutics, a biotech company focused on disease modifying therapies for neurodegenerative disorders. He serves as an advisor for the FWO Belgium, the Innovation Foundation Denmark, the University of Copenhagen and several biotech companies and academic institutions in Europe and the US.

Prior to joining Muna, Plath was the acting Global Head of Research and Vice President, Neuroscience at Lundbeck. He led multi-disciplinary teams based in Denmark and the US working on discovery and early development stage projects for patients across neurological and psychiatric disorders.

Before joining the pharmaceutical industry, Plath pursued an academic career at the Free University Berlin, Germany where he completed postdoctoral studies on the molecular mechanisms of neuronal plasticity and learning and memory. He has authored more than 40 scientific papers, given numerous talks at international conferences and served as a reviewer for grant agencies and leading journals.

Abstract

Kv1.3 Blockade to Resolve Neuroinflammation in Parkinson's Disease

Niels Plath, PhD, Rita Balice-Gordon, PhD, Ivana Geric, PhD

Study Rationale: Inflammation of the brain is increasingly recognized as a key component in the pathology of Parkinson's disease (PD). Microglia cells are drivers of brain inflammation, becoming activated when brain cells are damaged or stressed. While microglial activation initially protects the brain, it can become excessive and lead to chronic, damaging inflammation. In PD, chronic neuroinflammation contributes to neuron damage and loss, worsening symptoms. An ion channel called Kv1.3 is expressed by and is required for microglial activation. Several lines of evidence have suggested that blockade of Kv1.3 reduces microglia activation, abrogates neuroinflammation, protects neurons and alleviates symptoms in small models of PD.

Hypothesis: We are testing the hypothesis that small molecules that can selectively block Kv1.3 will reduce human microglial activation and neuroinflammation, supporting development of Kv1.3 blockers for the treatment of PD.

Study Design: We identified small molecule, selective and brain exposed Kv1.3 blockers. We have profiled these molecules on the isolated Kv1.3 channel protein in structural biology and biophysical assays, in electrophysiological assessments in cells expressing human Kv1.3, and on human-derived microglia cells expressing Kv1.3. We have also assessed Kv1.3 blockers in human microglia xenografted into the brain of small models with inflammation or disease-causing stimuli.

Impact on Diagnosis/Treatment of Parkinson's disease: To date, no treatments that slow or stop the progression of PD are available for patients. We are developing Kv1.3 selective blockers as novel drug candidates, to establish clinical safety and efficacy in PD patients, with the aim of stopping disease progression, enhancing neuronal survival and slowing or stopping PD progression and improving symptoms that limit quality of life.

Next Steps for Development: We are working to identify candidate molecules suitable for testing in clinical studies within the next 3-6 months. Clinical candidates will then be assessed for safety in models following the regulatory guidelines, before entering clinical studies in volunteers without PD as well as individuals with PD.

Session 2

Advances in the Classification and Measurement of Parkinson's

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Kathleen Poston, MD, MS
Edward F. and Irene Thiele Pimley Professor in Neurology and Neurological Sciences and (by courtesy) Neurosurgery, Stanford University

Kathleen Poston, PhD, is the Edward F. and Irene Thiele Pimley Professor in Neurology and Neurological Sciences and (by courtesy) Neurosurgery at Stanford University. She received her bachelor's of Science in Bioengineering at the University of Pennsylvania, her master's degree in biomedical engineering and her medical degree at Vanderbilt University. Poston completed her Neurology residency training at UCSF, completed a fellowship in clinical Movement Disorders at Columbia University and post-doctoral research training in Functional Neuroimaging at the Feinstein Institute. Poston's research and clinical emphasis focus on the non-motor impairments, such as dementia, that develop in patients with synucleinopathies. Poston is Chief of the Movement Disorders division and holds an appointment in the Memory Disorders division. She is a founding member of the Stanford Alzheimer's Disease Research Center, co-Director for the Stanford Lewy Body Dementia Association Research Center of Excellence and Director of the Stanford Parkinson's Foundation Center of Excellence.

Thomas J. Montine, MD, PhD
Endowed Professor in Pathology Chair, Stanford University

Thomas Montine, MD, PhD, was the Alvord Endowed Professor and Chair of the Department of Pathology at the University of Washington, where he also was Director Alzheimer's Disease Research Center and Pacific Udall Center. In 2016, Montine was appointed Chair of the Department of Pathology at Stanford University and the Stanford Medicine Endowed Professor. He was the 2015 President of the American Association of Neuropathologists and led or co-led NIH initiatives to revise diagnostic guidelines for Alzheimer's disease, developed research priorities for the National Alzheimer's Plan and developed national research priorities for Parkinson's disease. Montine currently chairs the FDA Advisory Committee on Peripheral and Central Nervous System Drugs. The focus of the Montine Laboratory is on the molecular and biochemical bases of cognitive impairment in aging and neurodegenerative diseases. The Montine Laboratory addresses this prevalent, unmet medical need through a combination of neuropathology, genomics, biomarker development, medicinal chemistry and experimental studies that test hypotheses about mechanisms of neuron injury and action of novel neuroprotectants.

Session 2

Advances in Emerging Targets and Therapeutic Development

Jamie Eberling, PhD

Senior Vice President, Research Resources, The Michael J. Fox Foundation

Jamie Eberling, PhD, is the Senior Vice President of Research Resources at The Michael J. Fox Foundation (MJFF) and oversees the Foundation's imaging portfolio with a particular emphasis on PET tracer development. She is responsible for building and advancing the alpha-synuclein tracer development program, one of the highest research priorities for MJFF.

Prior to joining MJFF, Jamie was a research scientist at the Lawrence Berkeley National Laboratory where she used PET imaging to evaluate the efficacy of gene therapy approaches for Parkinson's disease.

Jamie received her BS and PhD in Biological Psychology from the University of California, Berkeley.

Session 2

Advances in Emerging Targets and Therapeutic Development

Kenneth Marek, MD

President, Institute for Neurodegenerative Disorders

Kenneth Marek, MD, is a Distinguished Scientist at the Institute for Neurodegenerative Disorders. Marek's major research interests include identification of biomarkers for early detection, assessment of disease progression and development of new treatments for Parkinson's disease, Alzheimer disease and related neurodegenerative disorders. He has authored numerous neurology and neuroscience publications on these topics. Marek is the principal investigator of several ongoing multi-center international studies including the Parkinson Progression Marker Initiative (PPMI) and the Parkinson Associated Risk Syndrome (PARS) study. Marek serves as a special scientific advisor to The Michael J. Fox Foundation. He also was a co-founder of Molecular NeuroImaging and XingImaging, companies providing discovery and clinical neuroimaging research services.

Abstract

Biological Definition and Integrated Staging System for Neuronal Synuclein Disease: Accelerating Therapeutics for Synucleinopathy

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Kenneth Marek, MD

Neuronal aggregates of misfolded, pathological species of alpha-synuclein (asyn) are the pathological hallmark of Parkinson's disease (PD), Dementia with Lewy Bodies (DLB) and related conditions. Currently, these alpha-synucleinopathies are diagnosed based on traditional clinical criteria, but these criteria are flawed because they are unable to identify disease during early stages of neurodegeneration. In addition, current clinical criteria often result in a study cohort that is heterogenous with regard to baseline characteristic and disease progression. A biologic definition for alpha-synucleinopathies would inform our understanding of early disease, reduce disease heterogeneity and provide a framework to track disease progression that would accelerate therapeutic development.

Neuronal Synuclein Disease (NSD), defined by in vivo detection of n-asyn (S) allows us to combine PD and DLB under a unifying biologic definition. Recent data demonstrating that neuronal alpha-synuclein (n-asyn), previously only measured post-mortem, can be reliably detected in life using the asyn seed amplication assay (SAA), enables this paradigm shift. Further, individuals with n-asyn are at high risk for developing dopaminergic neuronal dysfunction (D), a second key biologic anchor for NSD.

While we recognize it is a radical deviation from the traditional clinical definition of neurodegenerative syndromes, proposing NSD defined by its biology is crucial to further understanding of disease pathophysiology, enabling therapeutic intervention prior to symptom onset, and detecting biologically defined NSD subsets to ensure therapeutics are targeted to specific biology.

The biological definition allows us to propose the NSD Integrated Biologic and Clinical Staging System (NSD-ISS). The early stages (Stages 1-2) are defined entirely by the presence of biomarkers and do not require clinical symptoms while later stages (Stages 3-6) require both biologic anchors (S and D) and functional impairment caused by clinical signs/symptoms. The NSD definition and NSD-ISS research framework are essential to advancing biologically targeted therapeutics and enabling interventional trials at early disease stages even prior to onset of symptoms. This strategy, rooted in biology, will both enable and accelerate therapeutic development for synucleinopathies.

Session 2

Advances in Emerging Targets and Therapeutic Development

Kalpana Merchant, PhD
Adjunct Professor of Neurology, Northwestern University; TransThera Consulting Co.

Kalpana Merchant, PhD, is a neurobiologist and translational neuroscientist who has led and contributed to the discovery and development of drugs for neurological and psychiatric disorders for over 30 years. She retired from Eli Lilly where she was the Chief Scientific Officer for Tailored Therapeutics-Neuroscience, a team accountable for personalized therapies and associated biomarkers for the neuroscience portfolio. Kalpana had joined Eli Lilly after 10 years of neuroscience drug discovery research at Pharmacia Corp. She has held Chief Executive/Scientific Officer roles at start-up biopharmaceutical companies, serves on several Boards as well as Scientific Advisory Boards. She is an Adjunct Professor of Neurology at Northwestern University, a senior advisor to The Michael J. Fox Foundation, appointed to the Oregon Innovation Council and has served on advisory boards at the National Institutes of Health. Kalpana received her PhD in neuropharmacology from the University of Utah. Following a postdoctoral fellowship at the University of Washington, she remained at the institute as Assistant Professor of Psychiatry, later transitioning to the pharmaceutical industry.

Abstract

Alpha-Synuclein Seed Amplification Assays: Current Utility and Future Prospects to Aid Therapeutic Development

Kalpana Merchant, PhD

Alpha-synuclein (aSyn) Seed Amplification Assays (aSyn-SAA) performed on antemortem cerebrospinal fluid (CSF) have high sensitivity and specificity to diagnose Parkinson's disease. Importantly, it has enabled the first biological definition of Neuronal aSyn Disease (NSD) and appears to detect individuals prior to clinical diagnosis of PD. In aggregate, these results indicate that CSF aSyn-SAA would aid therapeutic development by enabling patient enrichment as well as assessment of a pharmacodynamic response.

However, there are a few limitations of the current aSyn-SAA that need to be addressed to strengthen its utility for therapeutic development. One, further investigation of CSF aSyn-SAA in cohorts that resemble the general PD population is lacking currently. Second, as configured today, the assays provide a binary result indicating either positivity or negativity on the readouts. Third, for its broader applicability, it would be beneficial to have an assay that can detect aSyn aggregates in

less invasively obtained peripheral biomatrices as well as one that is scalable and available outside of the current qualified laboratories. To this end, progress is being made by a number of groups, some funded by the MJFF.

This talk will highlight initiatives and emerging promising results that address the limitations of the current aSyn-SAAs stated above. Specifically, there are encouraging results on the diagnostic utility of aSyn-SAA on skin biopsies, nasal swabs, submandibular glands, and blood indicating that one or more of these peripheral tissues. Whether these assays may supplement or supplant the CSF aSyn-SAA remains to be seen. Towards a quantitative assay, several scalable and orthogonal technology platforms are under investigation and show promising results. Thus, it seems plausible that soon, a scalable test that can quantitatively assess aSyn aggregates may become available to identify individuals with aSyn pathology prior to clinical diagnosis and monitor the progression of pathology, ideally on blood or other less invasive biomatrices.

Session 2

Advances in Emerging Targets and Therapeutic Development

William D. Shrader, PhD
CEO, CSO, AcureX

Prior to Acurex Biosciences, Wlliam B. Shrader, PhD, ran research and development at Edison Pharmaceuticals, where he and his team advanced three drugs into the clinic for ALS, Parkinson's disease and orphan neurodegenerative diseases. EPI-589 is partnered with Sunovion/Sumitomo and is in phase 2b clinical trials for ALS and Parkinson's disease. PTC Therapeutics acquired Vatiquinone™ and is in pivotal approval trials for pediatric seizure. Earlier at Celera Genomics, Shrader invented, advanced and partnered with AbbVie, the tissue factor/factor VIIa inhibitor (PCI-27483) for pancreatic cancer. Shrader holds a PhD in organic chemistry from the University of California, Berkeley and was on the California Institute of Technology faculty as an NIH postdoctoral fellow. Shrader has authored 30 peer-reviewed scientific publications and is an inventor on 21 issued US patents.

Abstract

De-Risking Therapeutic Development: The Power of Mitophagy Biomarkers in PD

William D. Shrader, PhD

Recent studies indicate that the mitochondrial protein Miro1 may serve as a biological definition of both genetic and sporadic forms of Parkinson's disease (PD). In PD patient cells with old or damaged mitochondria, Miro1 exhibits impaired detachment from the mitochondria, consequently delaying the initiation of mitophagy. Conversely, in individuals without PD, Miro1 disengages from the mitochondria efficiently, allowing for normal mitophagy. This defect in Miro1-mediated mitophagy is observable in multiple cell types from PD subjects, including postmortem central nervous system tissue, fibroblasts, PBMCs, and iPSC-derived dopaminergic neurons. Acurex is leveraging this Miro1 dysfunction, particularly as measured in PD patient PBMCs, as a peripheral biomarker for PD pathology and therapeutic response in forthcoming clinical trials.

Session 3

A Look Ahead: Stakeholder Perspectives on the Future of Parkinson's Research

Karl Kieburtz, MD, MPH

Professor of Neurology, University of Rochester

Karl Kieburtz, MD, MPH, is a neurologist and clinical researcher. After an undergraduate degree in Neuroscience at Amherst College, he completed his MD and MPH degrees and neurology residency, at the University of Rochester. He was the initial Robert J Joynt Professor in the Department of Neurology, and is currently Professor of Neurology, at the University of Rochester. He was the founding Director of the Center of Health & Technology (CHET) and served as the Director of the Clinical and Translational Science Institute and Senior Associate Dean for Clinical Research at the University of Rochester. Kieburtz was the past Chair of the Parkinson Study Group Executive Committee and has been global Principal Investigator for more than 50 multi-center and multi-national clinical trials, including the large NIH-sponsored multi- center NET-PD study. He was elected as a Fellow in the American Association for the Advancement of Sciences in 2014. He cofounded Clintrex Research Corporation in 2008, providing scientific and regulatory advisory services to companies developing CNS therapies.

Gennaro Pagano, MD, MSc, PhD, eMBA, FEAN

Group Leader & Expert Medical Director in Neuroscience and Rare Disease, Roche

Gennaro Pagano, MD, MSc, PhD, eMBA, FEAN, is a physician-neuroscientist and pharma medical director with over 15 years of translational research in academia and early clinical development. He is leading the early clinical development of Prasinezumab for Parkinson's disease at Roche Pharma Research & Early Development (pRED). He served as PSAB Chair of the PPMI (2020-2021) and is currently serving as the Industry co-director of Critical Path for Parkinson's disease, and Honorary Clinical Associate Professor at University of Exeter Medical School, London.

He obtained a Doctor of Medicine (MD) at University of Naples Federico II, Master in Epidemiology (MSc) at University of Milan, Doctor of Philosophy (PhD) in Clinical Neuroscience at King's College London, and postdoctoral training in PET imaging with focus on genetics, preclinical and prodromal Parkinson's disease at Imperial College London. He also completed fellowships in movement disorders/neuroimaging at Mount Sinai Medical Center in New York and Cedars Sinai Medical Center in Los Angeles.

Tanya Fischer, MD, PhD
Chief Development Officer and Head of Translational Medicine, Biohaven

Tanya Fischer, MD, PhD, currently is the Chief Development Officer and Head of Translational Medicine at Biohaven. Prior to joining Biohaven in 2022, she served as the Vice President of CNS Development at Alnylam Pharmaceuticals and was a Global Project Head at Sanofi in the Multiple Sclerosis, Neurology and Gene Therapy Therapeutic Area. While at Alnylam, she was responsible for expanding the CNS pipeline, initiating a Phase 1 trial. At Sanofi, she was responsible for leading the flagship global project teams in clinical development (Phase 1 through Phase 3) for a rare genetic form of Parkinson's disease and related rare neurodegenerative diseases (such as Gaucher disease (type 3) and GM2 gangliosidosis, as well as genetic forms of ophthalmology.

Fischer is a neurologist, with clinical subspecialties in demyelinating diseases and chronic neuropathic pain. Fischer did her Neurology residency at Yale New Haven Hospital. As an Associate Professor at Yale University in Neurology, her research focused on genetic and acquired forms of pain (ion channels (especially in Nav 1.7) and diabetic neuropathy) with a variety of peer-reviewed paper. She was awarded the prestigious Presidential Early Career Award for Scientists and Engineers (PECASE) Award in 2011. The PECASE Awards are intended to recognize some of the finest scientists and engineers who, while early in their research careers, show exceptional potential for leadership at the frontiers of scientific knowledge during the twenty-first century.

Tien Dam, MD
Vice President, Clinical Development, Neumora Therapeutics

Tien Dam, MD, has served as Vice President, Clinical Development at Neumora Therapeutics since July 2023. From September 2017 to July 2023, Dam worked at Biogen and held increasing leadership roles, including serving as the Head of Movement Disorders, where she was responsible for programs in Parkinson's disease, atypical Parkinsonism and ataxia. Prior to that, Dam worked at Merck for Alzheimer's disease. Prior to joining the pharmaceutical industry, Dam was in academia with research, teaching and clinical responsibilities during her tenure in the Departments of Medicine at Columbia University and UCSD.

Dam holds a BS in Biomedical Sciences from UCR and an MD from UCLA. She completed an Internal Medicine residency and Geriatrics fellowship at UCSD.

Catherine Kopil, PhD
Senior Vice President, Clinical Research, The Michael J. Fox Foundation

Catherine (Katie) Kopil, PhD, is the Senior Vice President of Clinical Research at The Michael J. Fox Foundation (MJFF) where she focuses on building the Foundation's capacity as an unprecedented stakeholder in Parkinson's drug development — a nimble, patient-focused problem-solver whose efforts are demonstrably accelerating progress toward treatment breakthroughs. Kopil leads a team investing in solutions to de-risk clinical development for Parkinson's and related disorders. Katie and her team support field-enabling efforts including seminal natural history studies like the Parkinson's Progression Markers Initiative, alignment on regulatory acceptable endpoints for clinical trials, and integrating patient perspectives throughout R&D.

Prior to joining the Foundation, Kopil completed doctoral and postdoctoral training in Neuroscience and Bioengineering respectively at the University of Pennsylvania. Her research focused on brain injury that occurs during acute trauma such as cardiac arrest and concussion. Kopil also helped speed clinical research as a clinical trial coordinator at Memorial Sloan-Kettering Cancer Center in NYC, which is where her dual passions for science and serving patients first intersected.

Kopil graduated from Princeton University with a BA in Psychology and holds a PhD in Neuroscience from the University of Pennsylvania.

Victoria DiBiaso, MPH, BScN
Global Head, Patient Informed Development & Health Value Translation, Sanofi

Victoria DiBiaso, MPH, BScN, has over 25 years of clinical research experience. She holds a Master of Public Health, is a nurse by training and wife of a person with Parkinson's disease. She has been recognized as one of the Top 20 Industry Innovators through integrating patient communities into R&D decision making. She was one of the first industry leaders to establish a series of trial sites & patient networks to provide advisory expertise to development staged clinical programs. These upfront partnerships have helped transform R&D models whereby therapies are developed WITH patients and their stakeholders to reflect their priorities. DiBiaso recently established, and Chairs, the US based PALADIN Consortium bringing together advocacy and industry leaders to optimize collaborations that hold the potential to transform the pace of medicines development. DiBiaso is also an advocate for Parkinson's disease. She has supported clinical research education efforts, ran 4 marathons and climbed Mount Kilimanjaro on behalf of the MJFF community.

Alison Handler, PharmD, RPh
Director, US Patient Engagement, Neuroscience, Novartis

Alison Handler, PharmD, RPh, is an accomplished, highly driven and patient-focused transformational industry leader with experience serving medically underserved patient populations to ensure equitable access to healthcare services and treatments across the patient journey. She received a BS in Pharmacy from Rutgers University College of Pharmacy, a Doctorate in Pharmacy from Nova Southeastern University College of Pharmacy and completed a Managed Care Residency at Horizon BCBSNJ. With over 22 years in pharma across Pfizer, NovoNordisk, Celgene, BMS and Novartis, her expertise includes Market Access, Patient Advocacy/Engagement and strong clinical knowledge across Neuroscience, Hematology, Oncology, Cardiovascular and Immunology. As a pharmacist and advocate for her father and four family members with Parkinson's disease, she is thrilled to bring her personal and professional passions together to drive advances in treatment. Handler is a proud wife, mother of 2 teenage boys, yoga enthusiast and enjoys giving back to her community in non-profit board member and volunteer roles.

Gary Rafaloff, MS
Patient Research Advocate, MJFF Patient Council

Gary Rafaloff, MS, is an accomplished businessperson and entrepreneur with over 47 years of professional experience in finance, management, organizational consulting and business development. He spent 25 years as a senior executive on Wall Street, was President of a regional Securities Broker/Dealer for 11 years, founded numerous private companies and Private Equity partnerships and has lectured at local universities. Rafaloff was diagnosed with Parkinson's disease in 2012 and now devote much of his time as a consultant, advocate and ambassador in the Parkinson's community. His interest is focused on current clinical drug research for new interventional treatments. Gary works with prominent Foundations, clinicians, research and fund-raising organizations and biotech pharmaceutical companies. He has co-authored numerous articles and abstracts on Parkinson's research which have appeared in well-known journals, publications and conferences. Rafaloff is a co-author of the annual review "Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline," published in the Journal of Parkinson's Disease.

Soania Mathur, MD
Co-Founder, PD Avengers, MJFF Patient Council Member

Soania Mathur, MD, is a family physician living outside of Toronto, Ontario, Canada who resigned her clinical practice twelve years following her diagnosis of Young Onset Parkinson's Disease at age 28. Now she is a dedicated speaker, writer, educator and Parkinson's advocate. Her platform, **UnshakeableMD** serves as a resource for patient education as well as an outlet for her personal experiences with this disease.

Mathur is an active speaker in Canada and internationally, serves on committees and boards for several organizations, including the MJFF Patient Council and has authored several published papers and online pieces that focus on patient education, empowerment and the vital importance of involving patients in all areas of clinical research.

Recently she co-founded **PD Avengers**, a self-funded, global alliance of Parkinson's advocates dedicated to unifying the global PD community to add urgency to the areas of wellness, research and advocacy, to end Parkinson's.

Poster Session

Jeffrey Hausdorff, PhD

Professor, Faculty of Medicine and School of Neuroscience, Tel Aviv University
Director, Center for the Study of Movement Cognition, and Mobility, Tel Aviv
Sourasky Medical Center Tel Aviv Medical Center

Jeffrey Hausdorff, PhD, and the research team that he leads aim to better understand, evaluate, and treat alterations in gait and balance that are associated with aging and disease. Hausdorff studies gait, balance, motor control and brain function, with a special focus on gait variability, wearable devices, freezing of gait, falls and Parkinson's disease. His cutting-edge research in this area has been funded by the National Institutes of Health and by private agencies and has been widely recognized. In 2013, he received the Gerontology Society of America's Excellence in Rehabilitation of Aging Persons Award, and in 2023, he was awarded the Aufzien Foundation Prize for established researcher in Parkinson's disease. His publications have been cited more than 83,000 times, placing him among the more influential scientists.

Abstract

A Machine Learning Contest to Automatically Detect Freezing of Gait: Results and Insights

Jeffrey M. Hausdorff, PhD

Study Rationale: Freezing of gait (FOG) is a poorly understood problem that markedly impairs the walking abilities and independence of about 60-80% of people who have Parkinson's disease (PD). The absence of a low-cost, objective way to accurately detect and quantify the occurrence of FOG curtails research and treatment of FOG. Pilot studies suggest that wearable devices (e.g., accelerometers) combined with machine learning algorithms have the potential to address this gap.

Hypothesis: We speculated that a machine learning contest, based on a relatively large, publicly accessible database of FOG events combined with accelerometer signals and accurate labels of the start and end of each FOG event, would empower AI experts from across the globe to develop new and better algorithms to automatically detect the occurrence of FOG from an accelerometer worn on the lower back of people who have PD and FOG.

Study Design: A 3-month machine learning contest was held on the Kaggle web-based platform. The competition ended with 10,133 registrations and 1,361 teams from 83 countries; 24,862 different solutions were submitted. The first-place solution detected FOG events accurately and precisely,

with few false positives and false negatives. Correlations between the gold standard reference and the first-place model predictions were high.

Impact on Diagnosis/Treatment of Parkinson's disease: This positive experience demonstrates that machine learning contests can be used to introduce experts from AI to PD challenges and to harness their expertise in a relatively short period of time. Moreover, the results suggest that this approach can be used as a low-cost, objective way of detecting and quantifying FOG.

Next Steps for Development: When applied to acceleration signals collected in subjects who wore an accelerometer on their lower back continuously for 1 week, the new algorithm identified, for the first time, specific hours during the day when FOG peaked. Although follow-up confirmation studies are needed, these results appear to offer a means of quantifying FOG in "supervised", clinical settings as well as in "unsupervised", daily living settings and set the stage for the development and assessment of targeted interventions that could be applied to treat FOG and reduce its negative impact on health-related quality of life.

Poster Session

Alastair Noyce, MSc, MRCP, PhD, FHEA

Professor of Neurology and Neuroepidemiology, Center for Preventive Neurology,
Wolfson Institute of Population Health, Queen Mary University of London,
Consultant Neurology, Barts Health NHS Trust

Alastair Noyce, MSc, MRCP, PhD, FHEA, is a Professor in Neurology and Neuroepidemiology at the Centre for Preventive Neurology, Wolfson Institute of Population Health, Queen Mary University of London, and a Consultant Neurologist at Barts Health NHS Trust.

His research group at the CPN focuses on Parkinson's disease and other neurodegenerative disorders, particularly early identification and epidemiology, which includes environmental, clinical and genetic determinants. His group receives funding from Parkinson's UK, Cure Parkinson's, Barts Charity, The Michael J. Fox Foundation, Aligning Science Across Parkinson's and Innovate UK.

He leads the PREDICT-PD study and he is the Principal Investigator on the East London Parkinson's disease project. He is a steering committee member of the Global Parkinson's Genetics Program and leads a focus on the genetics of prodromal PD and the Training and Networking group. He is Chair of the International Parkinson and Movement Disorder Society Epidemiology Study Group, a member of the MDS prodromal sub-committee and the Early Onset PD Task Force, a member of the International RBD Study Group, and faculty for the MDS LEAP leadership program. He is Associate Editor of the Journal of Parkinson's Disease.

Abstract

The London-Dhaka Project — the Prevalence and Assessment of Cognitive Impairment in Parkinson's Disease

Alastair Noyce, MSc, MRCP, PhD, FHEA; Prof Ahsan Habib; T. Zannat, KC. Dey, A. Zirra, ABSMS. Haque, E. Camboe, T. Haque, S. Waters, D. Mair, C. Marshall, AJ. Noyce

Study Rationale: Cognitive impairment and dementia are feared complications of Parkinson's disease. Approximately half of patients have been diagnosed with dementia at 10 years from diagnosis with Parkinson's disease, but most studies predominantly include patients who are White and well-educated. Some studies suggest that cognitive impairment may be higher in certain ethnic groups.

The aim of this study is to investigate the prevalence of cognitive impairment in a diverse group of patients with Parkinson's disease from East London (UK) and in Dhaka (Bangladesh). The study will compare standard instruments for assessing cognition with alternatives that might perform better in diverse patient groups or in patients who are not fluent in English.

Hypothesis: We aim to explore whether the prevalence of cognitive impairment in South Asian patients is higher than in White patients with PD, but that this difference is smaller than suggested by widely used cognitive tests such as the Montreal Cognitive Assessment.

Study Design: The London-Dhaka Parkinson's Cognition Study (LDPCS) is a cross-sectional, case-control study. Patients with a diagnosis of Parkinson's disease are recruited from movement disorder clinics at Barts Health NHS Trust (UK) and Bangabandhu Sheikh Mujib Medical University (Bangladesh), along with healthy individuals. The UK cohort represents a sub-group of the East London Parkinson Disease (ELPD) project.

At each site, we aim to recruit at least 200 new patients and 100 healthy controls over 2 years. Data collection includes clinical and demographic information, questionnaires, cognitive assessment tools (established and novel), neuropsychiatric assessment tools, and collection of samples for biomarkers.

Impact on Diagnosis/Treatment of Parkinson's disease: Studying cognitive impairment in diverse groups with Parkinson's disease will contribute to our overall understanding of Parkinson's dementia and how common it is. We believe that current assessment tools are not 'culturally fair' and over-estimate the prevalence of dementia in certain groups. Better tools for screening for cognitive impairment are needed and will inform clinical trial design.

Next Steps for Development: Over the next 15 months we will complete recruitment and analyze the results. We will report on the prevalence of dementia and make recommendations about the best tools to assess cognition. This will enhance clinical care and help design better clinical trials that enroll a diverse range of patients.

Poster Session

Nicole Polinski, PhD

Director, Preclinical Tools and Model Program, The Michael J. Fox Foundation

Nicole Polinski, PhD, received her PhD in Neuroscience from Michigan State University investigating the impact of age on viral vector-mediated gene therapy for neurodegenerative diseases. Polinski serves as Director of the Preclinical Tools and Models Program at MJFF. Her current role includes managing the team at MJFF responsible for generating and distributing preclinical tools and models to the research community. This includes working with Parkinson's disease experts to identify gaps in the research tool space and designing tools to fill those gaps, managing 30+ business relationships, negotiating contracts and agreements, coordinating dozens of collaborations for tool generation/characterization, and leading the MJFF Industry Tools Consortium. In addition, Polinski assists with the Access Data and Biospecimens program serving as scientific support for the team. Within all of these roles, Polinski works to embody the MJFF principles of urgency, adaptability, collaboration and resourcefulness.

Abstract

Resources Available Through the Michael J. Fox Foundation for Parkinson's Research

Nicole K. Polinski, Gloria Thakuria, Anna Schwartz, Elisia Clark, Josh Gottesman, Dave Alonso, Yasir Karim, Leslie Kirsch, Jamie Eberling

For the past 23 years, The Michael J. Fox Foundation for Parkinson's Research (MJFF) has supported the Parkinson's disease (PD) research community by funding research in PD biology, biomarkers, and preclinical through clinical therapeutic developments. Over the past 15 years, MJFF has also expanded our role in the PD research space to provide non-financial resources to align the field and speed new discoveries and developments. These resources include (1) biosamples from a number of PD clinical studies, (2) clinical, genetic, biologic, and patient-reported outcome data from PD clinical studies, and (3) preclinical tools such as antibodies, proteins, cell lines, viral vectors, rodent models, etc. Herein we provide an overview of the many resources MJFF makes available to the research community, with details on how to browse and access resources that are currently available. We also highlight upcoming resources that are currently in development to provide insight into what will be available in the future. Finally, we provide information on how to contact MJFF to ask questions about existing resources, provide feedback and suggest additional resources MJFF could consider developing for the research community.

Poster Session

Tanya Simuni, MD, FAAN

Arthur C. Nielsen Jr. Professor of Neurology, Director, Movement Disorders Center, Northwestern University Feinberg School of Medicine

Tanya Simuni, MD, FAAN, joined the faculty of the Northwestern University Feinberg School of Medicine in 2000 to build a multidisciplinary movement disorders center that is recognized by the Parkinson's Foundation, Huntington Disease Society of America and Wilson's Foundation as a Center of Excellence and serves as a training model in the region. She is the lead investigator of several clinical trials on experimental pharmacology, non-motor manifestations and pharmacological management of Parkinson's Disease (PD). She serves on several Steering Committees for the PD national clinical trials, several committees for PSG and the PF. She is the Site principal investigator (PI) and Steering Committee member for the largest PD biomarker initiative, Parkinson's Progression Markers Initiative (PPMI study), and site PI for the Network for Excellence in Neuroscience Clinical Trials (NEXT). Simuni is an active member of the American Academy of Neurology, American Neurological Association, the Movement Disorders Society as well as the Parkinson's Study Group.

Abstract

Path to Prevention (P2P) Trial: Study Design and Status Update

Tanya Simuni, MD Christopher S. Coffey, PhD, Andrew Siderowf, MD, Caroline Tanner, MD, PhD, Sohini Chowdhury, Catherine Kopil, PhD, Todd Sherer, PhD, Michael Brumm, PhD, Karl Kieburtz, MD, Kimberly Fabrizio, Ben Saville, Cora Allen-Savietta, Barbara Wendelberger, Amy Crawford and Ken Marek, MD on behalf of the PPMI Investigators

To describe the study design and proposed timeline of the first interventional study in Neuronal-Synuclein Disease (NSD).

Background: P2P is a platform, Phase 2 randomized double blind multi-center, multi-regimen clinical trial that is planned to evaluate the safety and early efficacy of investigational products for the treatment of biomarker-defined prodromal PD. Since the launch of the initiative, we have defined a new biological term Neuronal -Synuclein Disease (NSD) and plan to transition to the NSD stage–based inclusion criteria.

NSD is defined by presence of alpha-synuclein pathology, ultimately dopamine dysfunction, and stage dependent motor and non-motor clinical manifestations and related functional impairment. These participants were previously clinically defined as Parkinson's disease, Dementia with Lewy Bodies and Prodromal. The study is "nested" within the Parkinson's Progression Marker Initiative (PPMI) and sponsored by the MJFF.

Methods: P2P is a perpetual platform trial with a single Master Protocol dictating the conduct of the trial and regimen specific subprotocols outlining intervention specific aspects for each arm. Qualified participants will be recruited from the PPMI participants, based on NSD Stage 2B criteria defined by the presence of alpha-synuclein neuronal pathology (SAA in spinal fluid), dopaminergic dysfunction (DaTscan imaging) and clinical phenotype defined by presence of any of the following: Clinically detectable nonmotor/ subtle motor abnormalities but no functional impairment (Stage 2B).

The study's Multiple Primary Endpoints include 1) DAT imaging as measured by the rate of progression in the mean striatum Specific Binding Ratio (SBR) and 2) rate of progression in the MDS-UPDRS part III score. Secondary endpoints include safety, tolerability and feasibility. The study will have an array of exploratory clinical (including digital) and biomarker measures. Participants will first be randomized equally among all regimen-specific sub-protocols for which they are eligible. After randomization to a specific subprotocol, participants will be randomized to an active arm or placebo (N=125 per arm) in a K:1 ratio with K denoting the number of active interventions. Intervention duration will be at least 24 months (until the last participant in that regimen completes 24 months). The study is 82% powered to detect a slowing in either primary endpoint for each regimen, assuming a 20% slowing in DAT and a 35% slowing in MDS-UPDRS Part III.

Results: Interventions are being selected by a Therapeutic Evaluation Committee from > 15 industry submitted applications. The study targets to start enrolment in the first 2 regimens in 2025.

Conclusion: We report the design of the first platform interventional study targeting NSD Stage 2B population. Platform design allows efficiency of operational infrastructure, ability to share placebo arm and perpetual testing of the promising interventional candidates.

Poster Session

Diane Stephenson, PhD

Executive Director, Critical Path Institute

Diane Stephenson, PhD, is a neuroscientist by training with 30 years combined experience in academic neuroscience and drug discovery. She is passionate about translational science and has a long-time dedication to the discovery of therapies to treat diseases of the nervous system. Stephenson received her undergraduate degree in Biochemistry at the University of California and her PhD in Medical Neurobiology from Indiana University. She spent most of her career as a translational neuroscientist at the largest pharmaceutical companies focusing on disease areas including Alzheimer's, Parkinson's, Stroke, ALS and Autism Spectrum Disorders. Stephenson joined Critical Path Institute in 2011 and has launched several new programs with a focus on global collaborations to accelerate treatments for brain disorders. She presently leads Critical Path for Parkinson's (CPP), a multinational consortium comprised of academic experts, industry scientists, patient advocacy groups and regulatory experts collectively aimed at accelerating drug development tools for Parkinson's disease.

Abstract

Aligning with Regulators to Advance Patient-Reported Outcome Assessments that are Fit-for-Purpose in Early-Stage Parkinson's Disease Clinical Trials

Sonya Eremenco, Diane Stephenson, PhD

Project Title: Aligning with regulators to advance patient-reported outcome assessments that are fit-for-purpose in early-stage Parkinson's disease clinical trials

Study Rationale: There is a lack of clinical outcome assessments (COAs) consistent with U.S. FDA patient-focused drug development (PFDD) guidance for use as clinical trial endpoint measures in early-stage Parkinson's disease (PD). Aligning with regulatory agencies promises to streamline the path for acceptance of COAs to support endpoints in clinical trials

The Critical Path Institute's Clinical Outcome Assessment Program (COAP) has multiple examples of success in qualifying PRO measures including several in collaboration with academic experts across multiple disease areas.

This project focuses on leveraging existing qualitative data to identify concept(s) of interest for patient-reported outcome (PRO) measure development for early-stage PD.

Hypothesis: Existing HealthMeasures item banks (e.g., PROMIS, Neuro-QoL) contain sufficient content and can be mapped to existing qualitative data to develop fit-for-purpose COAs for use in PD clinical trials.

Study Design: The Critical Path for Parkinson's Digital Drug Development tool team in collaboration with University of Rochester CPP 3DT initiative has leveraged a case study called WATCH-PD aimed to advance the regulatory maturity of digital health technologies for early PD.

Qualitative patient-level interviews were carried out at FDA's recommendation FDA and led to the generation of personal symptom maps that consist of both motor and nonmotor symptom domains bothersome to people with early-stage PD.

The C-Path team in collaboration with Northwestern University will carry out secondary qualitative analysis of WATCH-PD symptom maps (N=40) focusing on obtaining detail and to document and summarize key aspects of the selected concepts of interest (COI(s)) (frequency, intensity, degree of difficulty, etc.),

The above analyses will inform conceptual model development and item selection from HealthMeasures Item Banks.

Impact on Diagnosis/Treatment of Parkinson's disease: This project aims to streamline the path to regulatory endorsement of COAs that align with FDA's PFDD strategies. By collaborating with multidisciplinary stakeholders that include academic experts, clinicians, psychometricians, regulators and people with lived experience of PD, we will more efficiently develop COAs for use in PD clinical trials to evaluate clinical benefit of new treatments for early-stage PD.

Next Steps for Development: The present focus of the team is to review existing literature and the WATCH-PD personal symptom maps to identify concepts of interest that align with the HealthMeasures item bank.

Poster Session

John Streiff, PhD
AeroNeph Therapeutics

Abstract

Hit-to-Lead STING Inhibitor Small Molecule Development for Parkinson's Disease

Erik Schwiebert, PhD, John Streiff, PhD

Study Rationale: Stimulator of Interferon Genes (STING) is a compelling drug target for all forms of autoimmune disease and autoinflammation. Gain of function mutations in STING or other key proteins in this innate immunity signaling pathway cause rare or niche autoimmune syndromes. Armed with 6 different hit-to-lead chemical classes of STING inhibitors from a human cell-based high-throughput screening campaign on the 3 most common STING isoforms, we wished to determine if their biological and chemical profiles were amenable for development in Parkinson's disease (PD) 82.

Hypothesis: We hypothesized that one or more of our hit-to-lead STING inhibitor small molecules may have eventual therapeutic impact in PD by attenuating the chronic autoinflammation or neuroinflammation component of PD.

Study Design: We have profiled in multiple in vitro assays and panels 5 hit-to-lead STING inhibitor compound classes. One has progressed into a lead class category with the best permeability profile across human cell barrier, the best efficacy/potency in in vitro anti-inflammatory assays measuring type 1 interferons as biomarkers, and in other assays. More recently, in the Eurofins BioMAP systems biology platform, the 'best in class' compound for STING Inhibitor Class H showed robust anti-inflammatory and immune-modulatory profiles and its profile aligned closely with an autoimmune disease drug that is also used to suppress transplanted organ rejection.

Impact on Diagnosis/Treatment of Parkinson's disease: As mentioned in the Hypothesis statement, we predict that the optimal STING inhibitor identified out of our program will quell the chronic neuroinflammatory components of PD.

Next Steps for Development: In the final steps of our MJFF funded project, we are examining the pharmacokinetics of ANT H in escalating doses in mice to determine the dose that drives appearance of the drug in the cerebrospinal fluid and in brain tissue. If successful in terms of blood-brain barrier permeability, a PD mouse model study is planned and will be run on mice over-expressing mutant alpha-synuclein in the substantia nigra, with a full endpoint analysis including behavioral metrics.

Poster Session

Peter Vangheluwe, PhD
KU Leuven

Peter Vangheluwe, PhD, obtained his Master's degrees in bioscience engineering and cellular biotechnology at KU Leuven, Belgium, in 2000. He completed his PhD in Medical Sciences and performed his postdoctoral studies investigating ion transporters in various diseases. He received part of his training at the Membrane Protein Research Group, University of Alberta, Canada and in the P-type ATPase Centre of Excellence at University of Copenhagen, Denmark. He was appointed as assistant professor at KU Leuven in 2011, associate professor in 2016 and professor in 2020. Since 2012, he is head of the Laboratory of Cellular Transport Systems at KU Leuven and his lab has established ATP13A2 as a lysosomal polyamine transporter implicated in Parkinson's disease (PD). He currently investigates how a disturbed polyamine homeostasis contributes to PD and explores therapeutic strategies to correct polyamine imbalances. He's the lead investigator of the ASAP consortium IMPACT-PD studying the implications of disturbed polyamine and glucosylceramide transport in PD. He also actively engages in drug screening and development programs for modulators of polyamine and glucosylceramide transport for PD therapy.

Abstract

The Lysosomal Polyamine Transporter ATP13A2, an Emerging Drug Target for Parkinson's Disease

Peter Vangheluwe, PhD

Study Rationale: Polyamines are neuroprotective agents, and ATP13A2, one of the causative Parkinson's disease genes encodes for a lysosomal polyamine exporter. As such, ATP13A2 regulates cellular polyamine content and polyamine distribution between lysosomes and mitochondria. Conversely, ATP13A2 dysfunction leads to a reduced cellular polyamine content, accumulation of polyamines in lysosomes and shortage of polyamines in mitochondria, which contribute to lysosomal toxicity and mitochondrial oxidative stress.

Hypothesis: We hypothesize that altered plasma and brain polyamine levels may underline the early onset neuroinflammation symptoms in Atp13a2 KO mice. In addition, we hypothesize that ATP13A2 agonists may have therapeutic potential for PD.

Study Design: Brain and plasma polyamine levels in Atp13a2 KO mice are reduced prior to the onset of symptoms. In addition, supplementation of polyamines rescues disease phenotypes, whereas polyamine

deprivation exacerbates symptoms, showing that lower polyamine levels contribute to the manifestation of disease phenotypes. Furthermore, we have purified ATP13A2 and optimized a primary assay to screen for ATP13A2 agonists. We have performed the first high throughput screening on ATP13A2 providing proof of concept that ATP13A2 agonists can be identified for further clinical development.

Impact on Diagnosis/Treatment of Parkinson's disease: We will translate our findings obtained in Atp13a2 KO mice to patients and will determine whether plasma polyamine levels are reduced in patients with sporadic PD or in ATP13A2 carriers with neurodegeneration. In addition, ATP13A2 agonists may have therapeutic value for PD.

Next Steps for Development: A cohort of ATP13A2 carriers will be assembled for a clinical examination and collection of bio-samples for polyamine analysis in preparation of polyamine supplementation trials. Additional screening will take place to identify additional hit matter, which will enter a hit-to-lead cascade for the development of potent ATP13A2 agonists.

Poster Session

Dustin Watson

Director, Government Relations, The Michael J. Fox Foundation

Dustin Watson is Director of Government Relations at The Michael J. Fox Foundation for Parkinson's Research. He is a registered lobbyist based in Washington, DC with thirty years of professional experience developing and managing legislative strategies on behalf of corporations, trade associations, foundations and nonprofit organizations at the local, state, national and international levels. Throughout his career, Watson has advocated for numerous public-interest causes and directed several grassroots campaigns in multiple states, while recruiting, training, and managing advocacy teams of government affairs and public policy staff, consultants and volunteers. He also supported the creation, launch and development of the Center for Business and Public Policy at Georgetown University's McDonough School of Business, secured millions of dollars in federal grants for nonprofit organizations, consulted on six congressional and state-based electoral campaigns, led business operations and federal lobbying services for a political consulting firm and directed government relations and public affairs for three trade associations.

Abstract

The National Plan to End Parkinson's Act (H.R.2365/S.1064)

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On Wednesday, March 29, 2023, the U.S. House of Representatives and U.S. Senate reintroduced the first-ever legislation solely devoted to ending Parkinson's disease. The bill was first introduced last Congress but did not come up for a vote by the time Congress adjourned at the end of its session in December 2022. With bipartisan support and nearly 150 total cosponsors in Congress, the National Plan to End Parkinson's Act (H.R.2365/S.1064) is no-cost legislation that will create an advisory council comprising members of federal agencies, people living with Parkinson's, care partners, researchers, clinicians and other non-federal experts. It also will alleviate financial and health burdens on American families and ensure those living with the disease have access to the care they need.

This bipartisan legislation is led by Senators Shelley Moore Capito (R-WV) and Chris Murphy (D-CT) and Representatives Gus Bilirakis (R-FL) and Paul Tonko (D-NY). The bill was introduced with the support of six additional senators and 12 additional representatives who signed on as cosponsors. A National Plan to End Parkinson's has the potential to dramatically increase federal research funding; develop more effective pathways for treatments and cures; improve early diagnosis; spark new and

improved models for patient care; create standards and measures to prevent Parkinson's disease; address health disparities in diagnosis, treatment and clinical trial participation; and enhance public awareness of the disease.

The public-private advisory council created as part of this legislation will report to Congress on their progress and impact in ending Parkinson's. With the validation of a Parkinson's biomarker earlier this year, there is no better time for the federal government to get involved in supporting research to help find a cure.