2024 Parkinson's Disease Therapeutics Conference

October 17, 2024

New York City

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

Table of Contents

Welcome

Welcome to the 16th 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 $2 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 at **michaeljfox.org** or on **LinkedIn**.

---

michaeljfox.org

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

The Michael J. Fox Foundation for Parkinson's Research
2024 Parkinson's Disease Therapeutics Conference
October 17, 2024
New York, NY

Conference Program

All presentations are followed by Q&A.

7:45 – 8:30 a.m.	**Arrivals and Breakfast**
8:30 – 8:45	**Welcome Remarks** **SOHINI CHOWDHURY**, The Michael J. Fox Foundation
8:45 – 10:30	**Session 1: Progress in the Therapeutics Pipeline**
8:45 – 9:00	**Session Introduction by Session Chair** **BRUCE MORIMOTO, PhD**, Alto Neuroscience
9:00 – 9:20	**Evaluating the Pre-clinical Efficacy of a mGluR5 Silent Allosteric Modulator, ALX-001 (BMS-984923) in Parkinson's Disease Models and Initiation of a First-in-patient Phase 1b Study** **TIMOTHY R. SIEGERT, PhD**, Allyx Therapeutics
9:20 – 9:40	**Discovery of ARV-102 Oral PROTAC® LRRK2 Degrader as a Potential Treatment for Neurodegenerative Disorders** **ANGELA CACACE, PhD**, Arvinas
9:40 – 10:00	**Brain-penetrant Small Molecule GT-02287 is Well-tolerated in Healthy Volunteers, Shows GCase Target Engagement, and Achieves Therapeutic Exposures Shown to Modulate PD Pathobiology in Pre-clinical Models** **JONAS HANNESTAD, MD, PhD**, Gain Therapeutics
10:00 – 10:20	**Small Molecule Activation of TRPML1 to Enhance Lysosome Function and Protein Clearance for the Therapeutic Treatment of Parkinson's Disease** **MARTIN GILL, PhD**, Libra Therapeutics

10:20 – 10:30	**Closing Remarks by Session Chair** **BRUCE MORIMOTO, PhD**, Alto Neuroscience

10:30 – 11:00 Networking Break / Poster Viewing

11:10 a.m. – 2:25 p.m. Session 2: Emerging Tools Enabling Clinical Development

11:00 – 11:10	**Session Introduction by Session Chair** **MARK FRASIER, PhD**, Chief Scientist, The Michael J. Fox Foundation
11:10 – 11:30	**Substantia Nigra Neuromelanin-sensitive MRI and Iron-sensitive MRI Measures: Progress Toward Monitoring and Enrichment Applications in Parkinson's Disease Trials** **DANIEL HUDDLESTON, MD**, Emory School of Medicine
11:30 – 11:50	**Investigation of Pathological α-Synuclein in the Skin as a Biomarker for Parkinson's Disease** **ROLAND HEYM, PhD**, AbbVie
11:50 – 12:05 PM	**Challenges and Opportunities in Clinical Trial Endpoints** **PETER CHIN, MD, MSHS**, Denali Therapeutics
12:05 – 12:35	**PANEL: Progress on Clinical Trial Endpoints** *Moderator:* **CATHERINE KOPIL, PhD**, The Michael J. Fox Foundation *Panelists:* **PETER CHIN, MD, MSHS**, Denali Therapeutics **JOHAN HELLSTEN, PhD**, Lundbeck **TIAGO MESTRE, MD, PhD**, University of Ottawa **THOMAS MOREL, MD, PhD**, UCB

12:35 – 1:40 Lunch / Networking Break / Poster Viewing

1:45 – 2:15	**PANEL: Returning Personal Research Information: A Right and a Need** *Moderator:* **MAGGIE KUHL**, The Michael J. Fox Foundation *Panelists:* **ANGELA BRADBURY, MD**, University of Pennsylvania **KEVIN KWOK, PharmD**, MJFF Patient Advisor **DAVID LEVENTHAL, MBA**, Pfizer **THOMAS TROPEA, DO**, University of Pennsylvania
2:15 – 2:25	**Closing Remarks by Session Chair** **MARK FRASIER, PhD**, Chief Scientist, The Michael J. Fox Foundation

2:25 – 2:45 — **Networking Break / Poster Viewing**

2:50 – 4:45 — **Session 3: A New Framework for Conceptualizing Neurodegenerative Disease**

2:50 – 3:10 — **Session Introduction by Session Chair**
TANYA SIMUNI, MD, Northwestern University

3:10 – 3:30 — **CSF aSyn-SAA and AD Biomarkers in Dementia with Lewy Bodies: Presentation and Progression**
DAVID COUGHLIN, MD, MTR, University of California San Diego

3:30 – 3:50 — **Clinical and Biological Characteristics of Negative CSF α-syn SAA PPMI Participants with a Diagnosis of Sporadic PD at Baseline**
KATHLEEN POSTON, MD, MS, Stanford University

3:50 – 4:10 — **α-Synuclein in the Context of Co-pathology and Dementia**
DUYGU TOSUN-TURGUT, PhD, University of California San Francisco

4:10 – 4:40 — **PANEL: How NSD-ISS, ATN and Biomarker Tools Will Transform Therapeutic Development for Neurodegenerative Diseases**

Moderator: **DIANE STEPHENSON, PhD**, Critical Path Institute

Panelists:
BILLY DUNN, MD, Senior Advisor to MJFF
MARK FRASIER, PhD, The Michael J. Fox Foundation
BRUCE MORIMOTO, PhD, Alto Neuroscience
TANYA SIMUNI, MD, Northwestern University

4:30 – 4:40 — **Closing Remarks**

SOHINI CHOWDHURY, The Michael J. Fox Foundation

4:45 — **Networking Break / Poster Viewing / Cocktail Reception**

Poster Session

Understanding Diversity in a Global Parkinson's Disease Cohort

Maggie Kuhl, The Michael J. Fox Foundation

The Aligning Science Across Parkinson's Initiative: Changing the Way Science is Done to Accelerate Discoveries in Parkinson's Disease Research

Sonya Dumanis, PhD, Aligning Science Across Parkinson's

Ekemini Riley, PhD, Aligning Science Across Parkinson's

Neuron-derived Extracellular Vesicles from Human Blood for Alpha-synuclein Assessment in Diverse Synucleinopathies

Erez Eitan, PhD, Neurodex

Optimization of MDS-UPDRS for Use in Early-stage Parkinson's Disease Clinical Trials

Thomas Morel, MD, PhD, UCB

Diane Stephenson, PhD, Critical Path Institute

Advanced Quantification and Standardisation of Dopaminergic Imaging Markers with the Centamine Scale

Roger Gunn, PhD, XingImaging

Integrated, Collaborative, Multimodal Data Approach in Parkinson's Disease

John Seaman, PhD, Novartis

Targets to Therapies: A New Target De-Risking Initiative at MJFF

Steven Braithwaite, PhD, Bayshore Global

Virginie Buggia Prevot, PhD, Valo Health

Darryle Schoepp, PhD, Independent Pharmaceutical Consultant

Thank You to Our 2024 Sponsors

Gold Sponsors

Mitsubishi Tanabe Pharma America

NeuroDerm™ A Mitsubishi Tanabe Pharma Group Company

UCB Inspired by patients. Driven by science.

NOVARTIS

Silver Sponsors

ALAMAR BIOSCIENCES

AskBio A Bayer Cell & Gene Therapy Platform Company

GE HealthCare

koneksa

MEIRAGTx

MERCK

Sage Therapeutics®

Supporting Sponsors

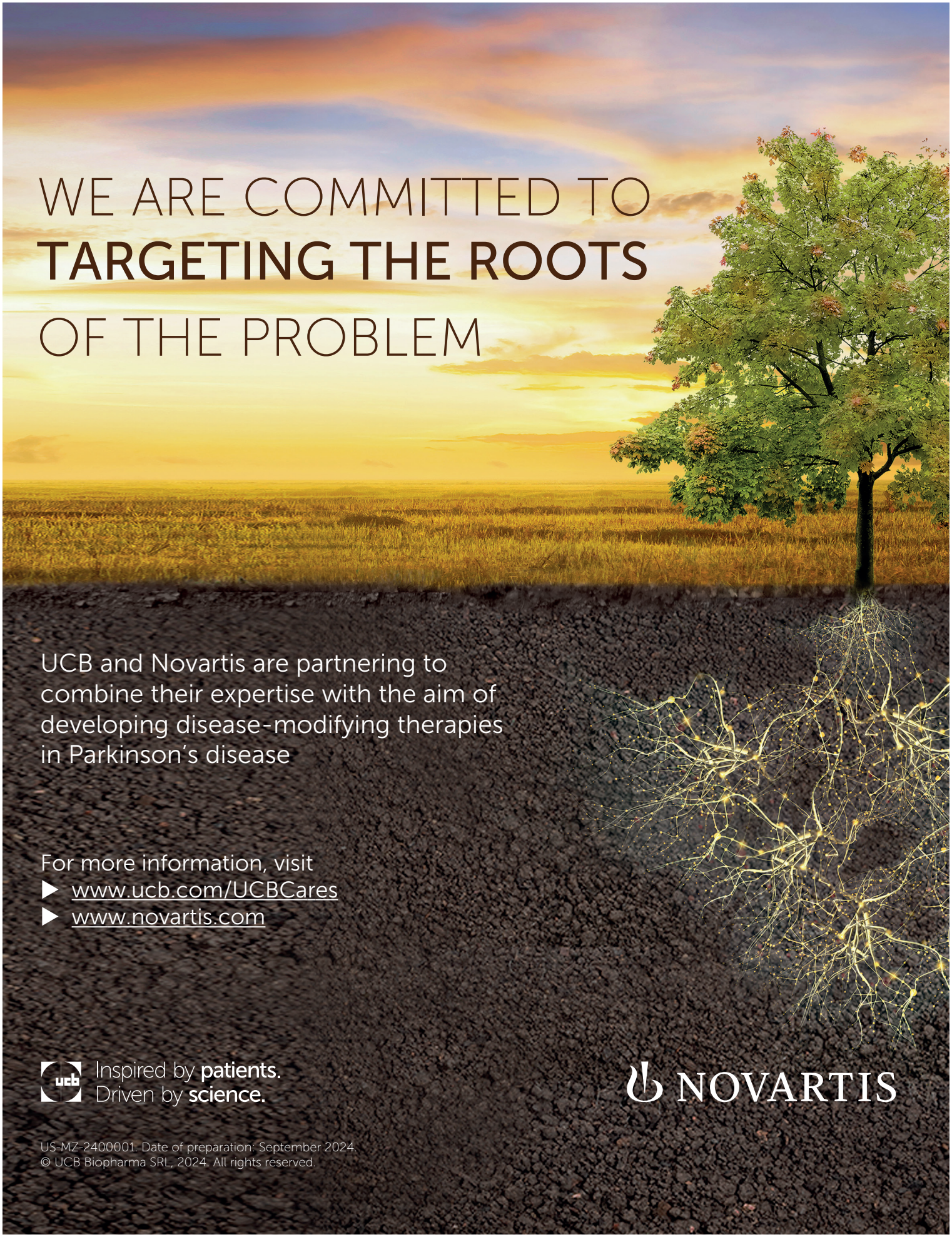
kenai therapeutics

SiteRx

TopGeneBio

If you are interested in sponsoring next year's PD Therapeutics Conference, contact us at researchpartnerships@michaeljfox.org.


Mitsubishi Tanabe Pharma America
Tackling the Toughest Challenges
Driving scientific discovery and innovation is at the center of everything we do, and it's more than just a passion – it's a commitment. We work diligently in the pursuit of achieving the impossible every day with one purpose in mind: helping those who are living with serious and debilitating diseases.
To learn more about MTPA, scan the QR code or visit
MT-Pharma-America.com
© 2024 Mitsubishi Tanabe Pharma America, Inc. All rights reserved.
Actor Portrayal. CNP-MTPA-US-0421 06/24


WE ARE COMMITTED TO
TARGETING THE ROOTS
OF THE PROBLEM
UCB and Novartis are partnering to combine their expertise with the aim of developing disease-modifying therapies in Parkinson's disease
For more information, visit
www.ucb.com/UCBCares
www.novartis.com
Inspired by patients.
Driven by science.
NOVARTIS
US-MZ-2400001. Date of preparation: September 2024.
© UCB Biopharma SRL, 2024. All rights reserved.

GE HealthCare

2 million+

Ioflupane I 123 doses supplied
in the last 20 years*

Enabling the human side of healthcare

GE HealthCare Pharma Services' mission is to accelerate diagnostic and therapeutic research, improving patient lives by providing precise, personalized care via innovative neurology and oncology imaging agents and digital solutions.

Our Service

- Enabling Accurate Patient Selection and Monitoring
- Confidence in Patient Scheduling
- Consistent Results when Scaling
- Simplified Study Management Powered by Collaboration

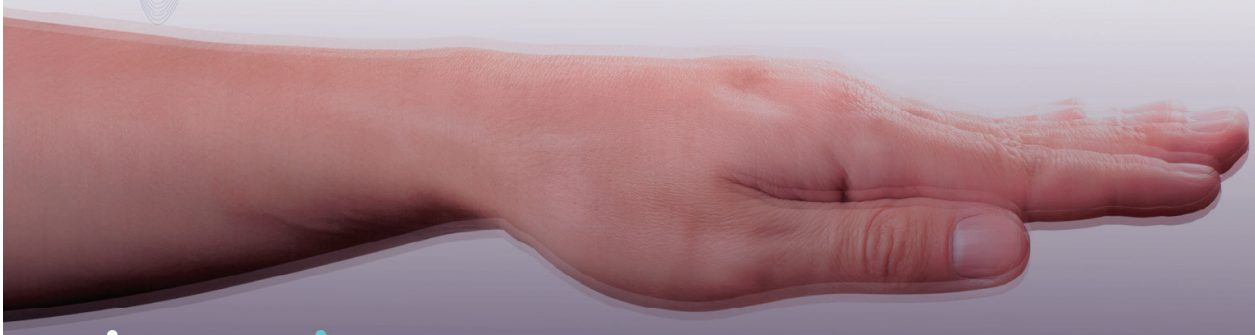
Our Imaging Agents

- Confidence inside the vial and far beyond
- Diagnosis with purpose

*Data on File - GE HealthCare Pharmaceutical Diagnostics Patient Impact letters entitled: Dec 2023

CAN YOUR TREMOR ASSESSMENT QUANTIFY AMPLITUDE IN MILLIMETERS?

HARNESS THE PRECISION OF DIGITAL SENSORS



koneksa

neuroscience@koneksahealth.com

Abstracts

Session 1

Progress in the Therapeutics Pipeline

SESSION CHAIR

Bruce H. Morimoto, PhD
Vice President
Alto Neuroscience, Inc.

Bruce Morimoto, PhD, has spent his career leading project teams in developing innovative medicines for neurodegenerative diseases like PD, AD, ALS and FTD. His responsibilities have encompassed a broad range of drug development activities including manufacturing, nonclinical safety testing, regulatory affairs and translational clinical research. Morimoto held leadership roles at Allon Therapeutics, Celerion, Alkahest and Cerecin. He is on the advisor boards of several biotech companies helping to develop and deploy scientific, regulatory and medical strategy. Morimoto started his career as faculty in the Chemistry Department at Purdue University. He earned his doctorate in biochemistry from the University of California, Los Angeles (UCLA), under the mentorship of Daniel E. Atkinson, and completed postdoctoral training at University of California, Berkeley, with Daniel Koshland Jr.

Timothy R. Siegert, PhD
Co-Founder, President & Chief Operating Officer
Allyx Therapeutics

A scientist and entrepreneur, Timothy R. Siegert, PhD, co-founded Allyx Therapeutics and serves as its Chief Operating Officer. Siegert has led efforts across both business development and research development, securing multiple grants and serving as the principal investigator of ongoing clinical research. Previous to his role at Allyx, Siegert completed the Yale Blavatnik Fellowship for Entrepreneurship. While an inaugural Blavatnik Fellow at Yale, he worked within Yale's Office of Cooperative Research (now Yale Ventures) to build and launch new biotech ventures from the Yale technology portfolio. Siegert is a chemical biologist by training and prior to Yale held a scientist role at Ra Pharmaceuticals in Cambridge, Massachusetts. Siegert holds a BS from Boston College and received his PhD in chemistry from Tufts University.

Abstract

Evaluating the Pre-clinical Efficacy of a mGluR5 Silent Allosteric Modulator, ALX-001 (BMS-984923) in Parkinson's Disease Models and Initiation of a First-in-patient Phase 1b Study

Study Rationale: Parkinson's disease is one of many neurodegenerative diseases that are characterized by misfolded and toxic protein oligomers that build up in the brain over time. Pre-clinical data suggests that cellular prion protein (PrPC) and metabotropic glutamate receptor 5 (mGluR5), receptors present on the synapse of neurons, are responsible for inducing the damaging effect of multiple toxins. This pathway has been thoroughly validated in numerous animal models of Alzheimer's disease with promising preliminary evidence in Parkinson's disease models. A unique mGluR5 silent allosteric modulator was shown to reverse behavioral and pathological defects in numerous AD models by blocking amyloid-beta oligomer toxicity through this pathway. This compound is currently in clinical trials for the treatment of AD.

Hypothesis: We believe this same mGluR5 silent allosteric modulator can also block the toxic effects of alpha-synuclein oligomers in Parkinson's disease and lead to a promising treatment.

Study Design: We evaluated the efficacy of our mGluR5 silent allosteric modulator, ALX-001 (BMS-984923), in a Preformed Fibril (PFF) model of Parkinson's disease to evaluate the ability of the drug to preserve synapses from toxic α-synuclein aggregates.

Impact on Diagnosis/Treatment of Parkinson's disease: ALX-001 (BMS-984923) holds potential as a novel disease modifying oral therapy for Parkinson's disease patients capable of preserving synapses from the toxic effects of α-synuclein independent of direct synuclein engagement.

Next Steps for Development: An 18 subject, placebo-controlled, double-blind and randomized Phase 1b 28-Day repeat dose study of ALX-001 (BMS-984923), NCT06309147, is ongoing in patients with Parkinson's disease to evaluate safety and pharmacokinetics. Next steps include running a Phase 2 proof-of-concept study to evaluate effects of ALX-001 on biomarkers and clinical endpoints in PD patients over longer durations of dosing.

Session 1

Progress in the Therapeutics Pipeline

Angela Cacace, PhD
Chief Scientific Officer
Arvinas

Angela Cacace, PhD, is the Chief Scientific Officer at Arvinas. Cacace has three decades of biopharmaceutical research experience, contributing to four marketed drugs and over 20 development candidates. At Arvinas, she leads research efforts driving innovation and expansion of the targeted degrader small molecule platform, building and advancing a robust pipeline with therapeutic potential to treat cancer and challenging neurologic disorders. Before joining Arvinas, Cacace led the biology team at Fulcrum Therapeutics, delivering two clinical assets for treating Facioscapulohumeral muscular dystrophy and Sickle cell disease. She spent 20 years at Bristol-Myers Squibb in roles of increasing research responsibility in neuroscience, genomics, screening, small molecule lead optimization and alternative therapeutic modalities, including advancing novel antisense oligonucleotides. At Pfizer, she was responsible for discovering an anti-angiogenic antibody development candidate. Cacace received her PhD in pharmacology from Columbia University, completed postdoctoral research at Bristol-Myers Squibb and the National Cancer Institute and received her BS from Fairfield University.

Abstract

Discovery of ARV-102 Oral PROTAC® LRRK2 Degrader as a Potential Treatment for Neurodegenerative Disorders

AUTHORS
Angela M. Cacace, Kaela Kelly, Adam Hendricson, Valerie Guss, Lida Kimmel, Sierra Soletsky, Michele Matchet, Craig Polson, James Herrington, Stefanie Keenan, Greg Cadelina, Jennifer Pizzano, Rashaun Wilson, John Corradi, Leofal Soto, Dustin Revell, Nicholas Adams, Bryan Jackson, Juan Chavez

Study Rationale: Leucine-rich Repeat Kinase 2 (LRRK2) is a large protein involved in many important functions within a cell, including disposing of waste and managing inflammation. When LRRK2 doesn't function properly due to changes in DNA known as mutations, it can lead to disorders that affect the brain and nervous system. These disorders include Parkinson's disease and progressive supranuclear palsy (PSP), conditions that affect many aspects of neurological function. Research suggests that lowering the amount of LRRK2 in cells, which would decrease its activity, could help protect the brain from these diseases.

Hypothesis: PROTAC (PROteolysis Targeting Chimera) protein degraders are designed to attach to specific disease-causing proteins in cells, which results in these proteins being marked for elimination by a natural protein disposal system in the body. We propose that PROTAC technology can be used to remove LRRK2 from cells.

Study Design: We created PROTAC LRRK2 degraders that can be taken by mouth and designed them to get into the brain where they can distribute to the areas of the brain most affected by Parkinson's disease and PSP. We conducted non-human studies to see if these PROTAC LRRK2 degraders could lower the amount of LRRK2 and block its activity.

Impact on Diagnosis/Treatment of Parkinson's disease: In these non-human studies, the PROTAC LRRK2 degraders were effective at lowering levels of LRRK2 as well as tau protein, which has also been linked to brain diseases, including Parkinson's disease. PROTAC LRRK2 degraders caused less damage to lung cells of mice than inhibitors that instead block the activity of LRRK2. Together these results indicated that LRRK2 degradation should be furthered explored as a potential new therapeutic approach.

Next Steps for Development: Our non-human findings support future evaluation of PROTAC LRRK2 degraders in patients with Parkinson's disease or PSP. Our investigational PROTAC LRRK2 degrader, ARV-102, is currently being tested for safety and effects on LRRK2 levels and activity in healthy volunteers.

Session 1

Progress in the Therapeutics Pipeline

Jonas Hannestad, MD, PhD
Chief Medical Officer
Gain Therapeutics

Jonas Hannestad, MD, PhD, has 25 years of experience in the field of neuroscience at both academic and biopharmaceutical organizations with a special emphasis on translational medicine and early clinical development in neurodegeneration. Hannestad is currently Chief Medical Officer at Gain Therapeutics, and previously held clinical development positions at Tranquis Therapeutics, Capacity Bio, Alkahest, Denali Therapeutics, UCB and BMS. He has worked on multiple Parkinson's programs, including GBA, LRRK2, adenosine 2A and alpha-synuclein. He received his MD from the University of Oviedo and a PhD from the University of Messina and completed residency training in internal medicine and psychiatry at Duke University and Yale University.

Abstract

Brain-penetrant Small Molecule GT-02287 is Well-tolerated in Healthy Volunteers, Shows GCase Target Engagement, and Achieves Therapeutic Exposures Shown to Modulate PD Pathobiology in Preclinical Models

AUTHORS

Raffaella Pozzi[1], Michele De Sciscio[2], Manuela Bosetti[1], Sara Cano[1], Agnieszka Marcinowicz[3], Agnieszka Starosciak-Rozwadowska[4], Andreas Schreiner[5], Joanne Taylor[1], Terenzio Ignoni[1], Jonas Hannestad[1]

Study Rationale: The objective of this study was to evaluate the safety and tolerability of GT-02287 in humans for the first time. Mutations in the GBA1 gene, which encodes for the enzyme GCase, increase the risk of developing Parkinson's disease and are associated with faster motor and cognitive decline. GBA1 mutations impact various cellular processes, including GCase activity, lysosomal function, and alpha-synuclein aggregation. GT-02287 binds to GCase, preventing misfolding, facilitating intracellular transport, and increasing enzymatic activity.

[1] Gain Therapeutics Inc, Bethesda, Maryland, USA; 2 CMAX Clinical Research, Adelaide, Australia; 3 Premier Consulting, Morrisville, North Carolina, USA; 4 Premier Research Poland, 5 Premier Research Germany Ltd., Darmstadt, Germany

Hypothesis: When given orally, GT-02287 will be safe and well tolerated, produce plasma levels in the therapeutic range and increase GCase activity in blood.

Study Design: Healthy men (n=40) and women (n=33) were enrolled in this Phase 1 first-in-human study and randomized in a 3:1 ratio to receive active GT-02287 or placebo. Single doses of 2.4, 4.8, 7.7, 10, and 15 mg/kg and multiple doses of 4.8, 7.7, 10, and 13.5 mg/kg (once a day for 14 days) were tested. Clinical laboratory tests, vital signs, ECG recordings, and adverse events (AEs) were monitored to evaluate safety and tolerability. Plasma pharmacokinetics was characterized, and GCase activity in blood was measured.

Results: All single and multiple dose levels tested were generally well tolerated. Over 90% of AEs were mild and limited in duration. The most common AEs were nausea and headache. No serious adverse events occurred. One subject had a transient, mild increase in liver enzymes. The PK profile of GT-02287 was linear across the dose range, and plasma exposures were within the projected therapeutic range. GCase activity in blood increased in subjects who received GT-02287.

Impact on Diagnosis/Treatment of Parkinson's disease: GT-02287 was well tolerated, produced plasma exposures in the projected therapeutic range, and increased GCase activity. GT-02287 has the potential to slow disease progression in people with PD.

Next Steps for Development: A Phase 1b study in individuals with PD with and without GBA1 mutations will be conducted to evaluate the safety and tolerability of GT-02287 over a 3-month dosing period. The study will also characterize the PK and determine whether GT-02287 can increase GCase activity and modulate other relevant biology in people with Parkinson's disease.

Session 1

Progress in the Therapeutics Pipeline

Martin Gill, PhD
Senior Vice President & Head of Research
Libra Therapeutics

Marty Gill, PhD, serves as Senior Vice President and Head of Research for Libra Therapeutics, where he leverages external CROs to advance portfolio programs from high throughput screening into clinical development, as well as, to identify/validate new targets for integration into a portfolio focused on delivering disease-modifying therapies for central nervous system (CNS) indications with high unmet medical need. Prior to joining Libra Therapeutics, Gill served as Head of In-vitro Discovery at Neuropore Therapies, which focused on identifying and advancing small molecule-targeted mechanisms that reduce CNS inflammation and/or reduce protein pathology associated with Parkinson's disease and amyotrophic lateral sclerosis (ALS). In addition, Gill worked at Bristol Myers Squibb, where he served as project lead for traditional small molecule portfolio programs, as well as novel therapeutic portfolio programs, targeting pathogenic mechanisms associated with neurodegeneration and genetically defined disease. Marty received his BA from the University of Missouri-Columbia, his PhD from the University of Texas Medical Branch and held post-doctoral fellowships at Northwestern University, Feinberg School of Medicine and Eli Lilly and Company.

Abstract

Biomarker Development and IND-Enabling Toxicology Support for Novel, Small Molecule TRPML1 Agonists for the Treatment of Parkinson's Disease

Study Rationale: Parkinson's disease patients exhibit decreased ability to remove cellular trash from the brain, resulting from a reduction in trash delivery (macroautophagy) and a reduction in the number and effectiveness of trash cans (lysosomes). Therapeutics, which can improve these two mechanisms, could be beneficial for Parkinson's disease patients both in terms of alleviating symptoms and disease progression.

Hypothesis: TRPML1 is a channel that resides on the lysosome, and activation of TRPML1 has been shown to increase macroautophagy and to increase lysosome function and number in cells. Developing small compounds, which can activate TRPML1, should also enhance macroautophagy and increase lysosome number and function in animals and in humans.

Study Design: In this grant, we seek to identify additional, non-stressful ways to confirm that our therapeutic advancing towards the clinic is working in the brains of those treated with the therapeutic. In addition, we will be conducting animal safety studies, which, if they do not show major adverse findings at levels predicted to achieve activity with giving the therapeutic in the clinic, will enable us to submit to the appropriate government agency our application for approval to conduct clinical trials in humans.

Impact on Diagnosis/Treatment of Parkinson's disease: Success in developing accessible markers for brain activity of a therapeutic in accessible, patient-friendly ways, and confirmation that therapeutic can be given safely at doses predicted to be active in patients in the clinic would provide a strong body of evidence that supports the development of small compounds, which activate TRPML1, for the treatment of Parkinson's disease.

Next Steps for Development: Success in this grant would provide strong support for the continued advancement of Libra's small compound TRPML1 agonists into safety and clinical proof-of-concept studies in the clinic.

Session 2

Emerging Tools Enabling Clinical Development

SESSION CHAIR

Mark Frasier, PhD
Chief Scientist
The Michael J. Fox Foundation for Parkinson's Research

Mark Frasier, PhD, joined the Foundation in 2006. As Chief Scientist, Frasier works with a team of research professionals who stay closely linked to the Parkinson's research community to develop an aggressive and innovative agenda for accelerating research and drug development for Parkinson's disease. This ensures that MJFF research priorities reflect and best serve the ultimate needs of patients. Frasier regularly meets with academic and industry researchers around the world to identify promising proposals to support, providing troubleshooting and ongoing management of projects as they go forward. He also supports the Foundation's priority interest in developing biomarkers for Parkinson's disease that will accelerate clinical trials of new drugs.

Frasier earned an undergraduate degree in Biochemistry from the University of Dayton and a PhD in Pharmacology from Loyola University Chicago. He completed his postdoctoral work in the Neuroscience Discovery Research Group at Eli Lilly, Inc., in Indianapolis, Indiana, where he worked on drug-discovery research in Parkinson's and Alzheimer's disease.

Daniel Huddleston, MD
Principal Investigator
Emory School of Medicine

As a physician-scientist, Daniel Huddleston, MD, sees patients with Parkinson's disease and related disorders. He conducts translational MRI research as Principal Investigator of the Parkinsonism Neuroimaging Laboratory at Emory University. His work focuses on MRI approaches to quantify neuromelanin, iron and molecular tissue characteristics relevant to neurodegenerative disease biology in vivo. He received his medical degree from Columbia University, College of Physicians and Surgeons, in 2006. He then completed his neurology residency training at Columbia's Neurological Institute of New York, followed by a fellowship at the Emory Movement Disorders Clinic.

Abstract

Substantia Nigra Neuromelanin-sensitive MRI and Iron-sensitive MRI Measures: Progress toward Monitoring and Enrichment Applications in Parkinson's Disease Trials

Neuroimaging biomarkers for Parkinson's disease (PD) are urgently needed to accelerate the development of novel therapeutics. MRI can be obtained at less cost, more quickly and without confounding medication effects as compared to radionuclide imaging. Neuromelanin-sensitive MRI (NM-MRI) and iron-sensitive MRI methods, including R2* relaxometry and quantitative susceptibility mapping (QSM), can quantify tissue characteristics in substantia nigra (SN) relevant to PD pathophysiology. Numerous studies indicate that these methods can also detect disease effects robustly. However, despite a rapidly growing literature in this area, neuroimaging biomarkers with clear contexts of use for clinical trials have not been established with these modalities. Major limiting factors have included a lack of tools to ensure accurate, disease-relevant feature extraction with high reproducibility and scalability, as well as a need for studies that better establish the longitudinal trajectories of candidate nigral MRI biomarkers. Here we present new results indicating a role for nigral NM-MRI measures adjusted for individual anatomic variability in longitudinal disease monitoring and outcome measurement in PD clinical trials. We also report new findings that R2* measurement within a disease-impacted subregion of SN detects strong PD effects and may be useful in a cohort-enrichment strategy for clinical trials. These measures are extracted using an automated, scalable pipeline, and we are currently pursuing FDA 510K clearance for this technology to make it available for clinical use.

Session 2

Emerging Tools Enabling Clinical Development

Roland Heym, Dr. RER Nat [PhD]
Principal Research Scientist
AbbVie Deutschland

As Principal Research Scientist at AbbVie, Roland Heym, Dr. RER Nat, is dedicated to discovering and developing biomarkers for Alzheimer's and Parkinson's disease projects ranging from pre-clinical to clinical phases. His contributions include the development of seed amplification assays for alpha-synuclein and tau, the discovery of protein biomarkers in extracellular vesicles and the investigation of DDC as a fluidic biomarker for dopaminergic deficit. He collaborates with academic and industry partners in the neurodegeneration field and serves as a scientific advisor to The Michael J. Fox Foundation. Heym studied Molecular Biotechnology at the University of Heidelberg, McGill University in Montreal and LMU in Munich. He obtained his doctoral degree from LMU in 2012 for his biochemical studies of active mRNA transport. Since 2012, he has been working on drug and biomarker discovery for neurodegenerative diseases at AbbVie in Germany.

Abstract

Investigation of Pathological Alpha-synuclein in the Skin as a Biomarker for Parkinson's Disease

Study Rationale: Pathological forms of the protein alpha-synuclein (aSyn) can be detected in the cerebrospinal fluid (CSF) of Parkinson's disease (PD) patients. However, there is a strong need for methods to measure pathological aSyn in biological samples that can be collected less invasively. The skin of many PD patients contains pathological aSyn and thus emerges as an attractive alternative sample to CSF.

Hypothesis: In this study, we investigated the diagnostic accuracy of pathological aSyn in skin as a biomarker for prodromal and clinical stages of PD and compared it to measurements of pathological aSyn in the CSF and the brain.

Study Design: We analyzed postmortem skin samples from 66 PD and control cases with associated data on the distribution and density of pathological aSyn (Lewy bodies) in the brain. Our results suggest that pathological aSyn in the skin is associated with Lewy body pathology in the brainstem and correlated with the density of Lewy bodies in the brain. Then we analyzed 120 antemortem skin biopsies from the Parkinson Progression Marker Initiative cohort. We observed high sensitivity of pathological aSyn in skin for prodromal cases with rapid eye movement sleep behavior disorder (RBD) and advanced PD cases, but surprisingly not for PD cases at the time of clinical diagnosis. Further analysis showed that pathological

αSyn in skin was most strongly associated with sleep abnormalities also in prodromal patients with hyposmia but without RBD.

Impact on Diagnosis/Treatment of Parkinson's disease: Our results support the implementation of skin biopsies for diagnosis of neuronal synuclein disease in the prodromal phase.

Next Steps for Development: Towards clinical application, it will be important to align our protocol for processing and analysis of skin with other stakeholders and confirm our results in large cohorts ideally including longitudinal skin samples and clinical data.

Disclosure: Roland Heym is an employee of AbbVie. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

Session 2

Emerging Tools Enabling Clinical Development

Peter Chin, MD, MSHS
Senior Vice President
Denali Therapeutics

Peter Chin, MD, MSHS, is Senior Vice President of Late Clinical Development at Denali Therapeutics, where he is responsible for late-stage clinical development, clinical outcomes, and drug safety. He completed his B.A. in molecular and cell biology at the U.C. Berkeley, medical degree at Dartmouth, neurology residency at the University of Washington, and Robert Wood Johnson Clinical Scholars fellowship at UCLA, where he also obtained an M.S. in health services research from the School of Public Health. Prior to joining Denali, Chin held roles in Health Economics and Outcomes Research, Clinical Development, and Medical Affairs at Genentech, Novartis, and Roche, contributing to the development and launch of therapies for multiple sclerosis and related conditions. Chin is focused on driving innovative treatments for adult and pediatric neurodegenerative diseases to improve patient outcomes and quality of life.

Session 2

Emerging Tools Enabling Clinical Development

Panel

Progress on Clinical Trial Endpoints

MODERATOR

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

Catherine (Katie) Kopil, PhD, is the Senior Vice President and Head of Clinical Research at The Michael J. Fox Foundation 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. She 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, Katie 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. Katie 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.

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

PANELISTS

Peter Chin, MD, MSHS
Senior Vice President
Denali Therapeutics

Peter Chin, MD, MSHS, is Senior Vice President of Late Clinical Development at Denali Therapeutics, where he is responsible for late-stage clinical development, clinical outcomes, and drug safety. He completed his BA in molecular and cell biology at the U.C. Berkeley, medical degree at Dartmouth, neurology residency at the University of Washington, and Robert Wood Johnson Clinical Scholars fellowship at UCLA, where he

also obtained an MS in health services research from the School of Public Health. Prior to joining Denali, Chin held roles in Health Economics and Outcomes Research, Clinical Development, and Medical Affairs at Genentech, Novartis, and Roche, contributing to the development and launch of therapies for multiple sclerosis and related conditions. Chin is focused on driving innovative treatments for adult and pediatric neurodegenerative diseases to improve patient outcomes and quality of life.

Johan Hellsten, PhD

Senior Specialist, Patient Insights

Lundbeck

Johan Hellsten, PhD, is a Senior Specialist in the Patient Insights team at Lundbeck, whose mission is to leverage Patient-focused Drug Development in all Lundbeck R&D activities.

Johan has been with Lundbeck in various roles in the R&D organization since 2009. After being diagnosed with early onset Parkinson's disease in 2016, Johan increasingly engaged himself in making the voice of the patient heard and eventually joined the then newly established Patient Insights team in 2020.

Johan is a patient advisor to the Critical Path for Parkinson's (CPP) Digital Drug Development Tools (3DT) consortium and coauthor on two publications on the qualitative sub-study from the WATCH-PD trial. He was a member of the 3DT Patient Engagement Task Force that in 2021-2022 produced guidelines, recommendations, and considerations for the integration of Digital Health Technologies (DHTs) in PD clinical trials with the goal of improving patients' experiences completing DHT-based assessments.

Prior to joining Lundbeck, Johan completed doctoral and postdoctoral training in Molecular Psychiatry at Lund University, Sweden. His research focused on neuroplasticity and disease mechanisms related to conditions like chronic stress and depression.

Tiago Mestre, MD, PhD

Associate Professor

University of Ottawa

Tiago Mestre, MD, PhD, is an Associate Professor at the University of Ottawa and a Scientist at the Ottawa Hospital Research Institute, Canada. He holds a Clinical Research Chair in Parkinson disease focused on therapeutic development for unmet care needs, and clinical trial methodology, namely with the development of novel clinical outcome measures. He is developing a patient-reported outcome for early clinical PD: the EARLY-PD PRO. He is the director of the MDS-COA program, and the president of the Canadian Movement Disorders Society.

Session 2

Emerging Tools Enabling Clinical Development

Panel

Progress on Clinical Trial Endpoints

PANELISTS

Thomas Morel, MD, PhD

Global Patient Centred Outcomes Research Lead

UCB

Thomas Morel, MD, PhD, is Global Patient-Centred Outcomes Research Lead at UCB. In this role, Morel ensures that health outcomes most meaningful to patients are at the center of clinical development programs through the design and implementation of patient-centric outcome measurement strategies. Since 2018, Morel has been the principal investigator of the joint UCB/Parkinson's UK/Parkinson's Foundation research project to co-create novel Patient Reported Outcome (PRO) instruments to accurately reflect the experience of people living with early-stage Parkinson's. Since November 2023, Morel is Industry Chair of Critical Path Parkinson's (CPP) pre-competitive working group on patient-centric endpoints for Parkinson's, whose ambition is to address outcomes measurement gaps in Parkinson's drug development. Morel co-leads the CPP Taskforce to optimize MDS-UPDRS for use as primary clinical trial endpoint in early-stage Parkinson's. Rare diseases are another area where Morel has extensive expertise. He is a Therapies Scientific Committee member of the International Rare Diseases Research Consortium (IRDiRC).

Session 2

Emerging Tools Enabling Clinical Development

Panel

Returning Personal Research Information: A Right and a Need

MODERATOR

Maggie Kuhl

Vice President, Head of Patient Engagement

The Michael J. Fox Foundation

As Vice President of Patient Engagement at The Michael J. Fox Foundation, Maggie Kuhl leads a team engaging community partners and gathering patient experience data toward patient-focused drug development, as well as practicing and piloting recruitment and retention methods to enable faster trials. Kuhl directs recruitment strategy for the Foundation's Parkinson's Progression Markers Initiative, a longitudinal observational study with remote screening and enrollment at 50 international sites for thousands of participants. Prior to joining the Foundation in 2013, Kuhl worked in communications at the National Institutes of Health.

Session 2

Emerging Tools Enabling Clinical Development

Panel

Returning Personal Research Information: A Right and a Need

PANELISTS

Angela Bradbury, MD

Associate Professor, Division of Hematology-Oncology
University of Pennsylvania

Angela Bradbury, MD, completed her residency in internal medicine and fellowships in hematology/oncology and clinical medical ethics at the University of Chicago. She is an Associate Professor in the Department of Medicine, Division of Hematology-Oncology, at the University of Pennsylvania and has a secondary appointment in the Department of Medical Ethics and Health Policy. She is also the founder and Executive Director of the Penn Telegenetics Program, a national program offering remote genetic services to improve access to genetic medicine. Bradbury is a physician scientist known for research defining clinical standards for genetic services. This includes establishing remote telehealth services as evidence-based delivery alternatives with increased impact during the COVID pandemic. Her research methods have extended beyond cancer, demonstrating impact across genetic medicine. Bradbury has also been a leader in ELSI research providing empiric data on the risks and benefits of returning genetic research results and genetic testing of youth.

Kevin Kwok, PharmD

MJFF Patient Advisor

Kevin Kwok, PharmD, was diagnosed with Young Onset Parkinson's Disease in 2009 at age 48. He is a retired biopharma executive and led operational and advisory roles in both Pharma and research stage biotech companies. After diagnosis, Kwok pivoted his career to focus on patient engagement and patient focused drug development (PFDD). Today he is a patient advisor to The Michael J. Fox Foundation for Parkinson's Research, the Parkinson's Foundation, Critical Path, the National Academy of Science, Medicine & Technology and serves on the board of the Davis Phinney Foundation. Kwok earned his Doctor of Pharmacy degree at the University of Michigan. He is a frequent speaker and author on Parkinson's advocacy topics and recently published the paper "Parkinson's Disease: Still Waiting for a Cure" in Clinical and Translational Sciences.

PANELISTS

David P. Leventhal, MBA

Senior Director, Data Sharing & Disclosure Lead
Pfizer, Inc.

David Leventhal, MBA, is the Data Sharing & Disclosure Lead at Pfizer. He oversees the implementation of Pfizer's Clinical Trial Data Sharing and Disclosure Polices and serves as a single point of leadership for enterprise-wide sharing of sponsored clinical trial data. Additionally, he and his team are responsible for fulfilling Pfizer's commitment to transparency by publicly disclosing accurate and timely study information and results, thereby providing access to information for patients, healthcare providers, and the scientific community. Leventhal has been with Pfizer for 28 years, and in that time has served in a variety of R&D and innovation functions including program management, business portfolio management, and Clinical Trial Operations. He holds a Board of Director's seat at Healthix, a not-for-profit health information exchange regulated and funded by the New York State Department of Health. Healthix is the largest public health information exchange (HIE) in the United States, stewarding the data of over 20 million individuals. Leventhal received his bachelor's degree from Hofstra University and his master's degree in business administration from Rensselaer Polytechnic Institute.

Thomas Tropea, DO

Assistant Professor of Neurology
University of Pennsylvania

Session 3

A New Framework for Conceptualizing Neurodegenerative Disease

SESSION CHAIR

Tanya Simuni, MD

Arthur C. Nielsen Jr. Professor of Neurology
Director, Parkinson's Disease and Movement Disorders Center
Northwestern Feinberg School of Medicine

Tanya Simuni, MD, 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 PD. Simuni serves on several Steering Committees for the PD national clinical trials, several committees for PSG and the PF. She is the Site PI and Steering Committee member for the largest PD biomarker 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.

David Coughlin, MD, MTR

Assistant Professor
University of California San Diego

David Coughlin, MD, MTR, is an assistant professor and movement disorders neurologist at the University of California San Diego department of Neurosciences, where his clinical practice is focused on the diagnosis and management of neurodegenerative diseases like Parkinson's disease, dementia with Lewy bodies and other conditions. He leads a translational neuropathology laboratory in support of in vivo biomarker development by conducting studies to understand how emerging biomarkers relate to neuropathology in neurodegenerative disease and clinical outcomes. Coughlin additionally serves as the co-director of the UCSD Shiley Marcos Alzheimer's disease research center's Neuropathology Core and the UCSD Movement disorders fellowship co-director.

Abstract

CSF αSyn-SAA and Alzheimer's Disease Profiles in Presentation and Cognitive Progression in Dementia with Lewy Bodies

Study Rationale: Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementing illness. Pathologically, DLB is marked by the accumulation of alpha-synuclein deposits throughout the brain. The presence of alpha-synuclein pathology was formerly only detectable at autopsy but recently alpha-synuclein seed amplification assays can detect pathogenic alpha-synuclein seeds in cerebrospinal fluid, a major advance for the field. Furthermore, in DLB, Alzheimer's disease pathology co-occurs in approximately 70% of cases. Understanding which patients who have been clinically diagnosed with DLB in fact harbor alpha-synuclein pathology and Alzheimer's disease co-pathology is essential to understanding biologically based disease progression in this condition.

Hypothesis: Here we sought to establish biomarker profiles of alpha-synuclein and Alzheimer's disease biomarkers in clinically diagnosed DLB cases to examine their clinical differences and cognitive trajectories.

Study Design: Cerebrospinal fluid (CSF) samples obtained within 1 year of baseline assessments from participants of the DLB consortium study were analyzed for alpha synuclein seed amplification via the Amprion SynTap assay. CSF Aβ42/40, ptau-181, and total-tau were analyzed, and cut-points defined as per Jain et al. Alzheimers Dement. 2024. Cross-sectional comparisons of demographics, core DLB features, cognitive impairment and objective smell testing (<15th %ile of age/sex predictive performance defining hyposmia) in participants with different CSF profiles was performed. Rates of cognitive decline in participants with different CSF profiles were also assessed.

Impact on Diagnosis/Treatment of Parkinson's disease: Recently, the Neuronal Synuclein Disease Integrated Staging System (NSD-ISS) has proposed to treat Parkinson's disease and DLB together as they have similar biomarker profiles and similar Lewy body pathology at autopsy. In both conditions, AD co-pathology is common, and the influences clinical progression may justify stratification within clinical trials or combination therapies based on these multiple pathologies.

Next Steps for Development: We will continue to examine trajectories of detailed cognitive progression in these cases as well as the presence and evaluation of certain imaging biomarkers i.e. DAT and MRI measures.

Session 3

A New Framework for Conceptualizing Neurodegenerative Disease

Kathleen L. Poston, MD, MS
Edward F. and Irene Thiele Pimley Professor in Neurology and Neurological Sciences
Stanford University

Kathleen Poston, MD, MS, 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 MD at Vanderbilt University. She 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.

Abstract

Clinical and Biological Characteristics of Negative CSF α-Syn SAA PPMI Participants with Diagnosis of Sporadic PD at Baseline

Study Rationale: Recent studies have shown 5-10% of people thought to have sporadic (non-genetic) Parkinson's disease (PD) at time of diagnosis do not show evidence of a synucleinopathy on biomarker testing with the CSF Seed Amplification Assay (negative CSF α-syn SAA). Given the interest of synuclein testing for clinical trial enrollment it is critical to understand the clinical and biological characteristics, and ultimately accurate pathological diagnosis, of these negative SAA patients.

Hypothesis: PPMI participants enrolled with a diagnosis of PD, who have a negative CSF α-syn SAA at baseline will have unique characteristics compared to those with synuclein detected (positive CSF α-syn SAA).

Study Design: We analyzed data from the PPMI sporadic PD cohort (i.e. no identifiable LRRK2 or GBA mutations), identifying participants who had a negative CSF α-syn SAA (n = 78) or positive CSF α-syn SAA (n = 838) result during their baseline assessment. A comprehensive array of baseline clinical and biological characteristics was assessed including motor and non-motor disease scales as well as fluid biomarkers and dopamine transporter imaging.

Impact on Diagnosis/Treatment of Parkinson's disease: Sporadic PD participants in the PPMI cohort with negative CSF α-syn SAA at their baseline evaluation have similar baseline clinical characteristics as those with positive CSF α-syn SAA, except for substantially lower rate of hyposmia amongst the negative SAA PD participants. Without CSF SAA data these two groups were not otherwise clinically or biologically distinguishable at baseline. However, there were differences in longitudinal change over time with the negative CSF α-syn SAA individuals developing more severe symptoms; one negative CSF α-syn SAA individual was confirmed to be MSA at autopsy.

Next Steps for Development: We will determine the longitudinal changes in biological and imaging data in the negative CSF α-syn SAA compared to the positive CSF α-syn SAA over the first 2-3 years of the study.

Session 3

A New Framework for Conceptualizing Neurodegenerative Disease

Duygu Tosun-Turgut, PhD
Professor of Radiology and Biomedical Imaging
University of California San Francisco

Duygu Tosun-Turgut, PhD, is a Professor in the Department of Radiology and Biomedical Imaging at the University of California, San Francisco and Founding Director of the Medical Imaging Informatics and Artificial Intelligence at the San Francisco Veterans Affairs Medical Center. The goal of Tosun's research program is to apply advanced imaging technology to identify multi-disciplinary and multi-modality biomarkers to detect the pathophysiological progression of neuropathologies before they cause irreversible damage to the brain. She aims to develop validated imaging markers, potentially providing a means of monitoring the efficacy and regional specificity of drug therapy for neurodegenerative diseases. This will have a broad use in early diagnosis, facilitating initiation of prevention strategies in those at risk, and boost the power of drug therapy trials by selecting those at greatest risk of neurodegenerative diseases. Tosun's research program has been funded by the National Institutes of Health, California Department of Public Health, Alzheimer's Association and The Michael J. Fox Foundation.

Abstract

a-Synuclein in the Context of Co-pathology and Dementia

Study Rationale: Alzheimer's disease (AD) and Lewy body disease (LBD), characterized by the pathological deposition of amyloid-beta (Aβ) and alpha-synuclein (α-syn), respectively, are commonly identified at autopsy. Up to half (25-50%) of autopsy cases exhibit Lewy body (LB) co-pathology in sporadic early- and late-onset AD, familial/inherited AD, and Down's Syndrome AD cases. Pathological coexistence implies a potential interplay between Aβ and α-syn in the human brain. Despite the unique stereotypical progression of each pathology, evidence suggests that these pathways potentially may overlap at later disease stages, implicating a synergistic process known as 'crosstalk'.

Hypothesis: We hypothesize that SAA-positivity would correspond to greater rates of cognitive decline and earlier onset of cognitive impairment. Further, we postulate that the emergence of α-syn pathology is dependent on pre-existing AD Aβ pathology, and the apolipoprotein E (APOE) ε4 allele exerts a significant influence over this interplay, since ε4 has been increasingly recognized as a common genetic risk factor for both AD and LBD.

Study Design: 1637 cross-sectional and 407 longitudinal CSF samples from ADNI are tested with SAA. We examine longitudinal dynamics of Aβ, α-synuclein seeds, and p-tau181, along with global and domain-specific cognition in stable SAA+, stable SAA–, and those who converted to SAA+ from SAA–.

Impact on Diagnosis/Treatment of Parkinson's disease: Our results highlight the potential for interplay between Aβ and α-syn and their impact on disease progression, emphasizing the importance of further investigation into their underlying mechanisms in the context of co-pathologies.

Next Steps for Development: The longitudinal tracking of SAA+ alongside other biomarkers prompt consideration of differential diagnosis between AD and other neurodegenerative conditions, especially DLB. Moving forward, it is imperative to broaden the detection of LB-pathology in diverse cohorts to enhance our understanding of the causes and triggers of co-pathologies.

Session 3

A New Framework for Conceptualizing Neurodegenerative Disease

Panel

How NSD-ISS, ATN and Biomarker Tools will Transform Therapeutic Development for Neurodegenerative Disorders

MODERATOR

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.

Session 3

A New Framework for Conceptualizing Neurodegenerative Disease

Panel

How NSD-ISS, ATN and Biomarker Tools will Transform Therapeutic Development for Neurodegenerative Disorders

PANELISTS

Mark Frasier, PhD
Chief Scientist
The Michael J. Fox Foundation for Parkinson's Research

Mark Frasier, PhD, joined the Foundation in 2006. As Chief Scientist, Frasier works with a team of research professionals who stay closely linked to the Parkinson's research community to develop an aggressive and innovative agenda for accelerating research and drug development for Parkinson's disease. This ensures that MJFF research priorities reflect and best serve the ultimate needs of patients. Frasier regularly meets with academic and industry researchers around the world to identify promising proposals to support, providing troubleshooting and ongoing management of projects as they go forward. He also supports the Foundation's priority interest in developing biomarkers for Parkinson's disease that will accelerate clinical trials of new drugs.

Frasier earned an undergraduate degree in Biochemistry from the University of Dayton and a PhD in Pharmacology from Loyola University Chicago. He completed his postdoctoral work in the Neuroscience Discovery Research Group at Eli Lilly, Inc., in Indianapolis, Indiana, where he worked on drug-discovery research in Parkinson's and Alzheimer's disease.

Session 3

A New Framework for Conceptualizing Neurodegenerative Disease

Panel

How NSD-ISS, ATN and Biomarker Tools will Transform Therapeutic Development for Neurodegenerative Disorders

PANELISTS

Bruce H. Morimoto, PhD

Vice President, Drug Development
Alto Neuroscience

Bruce Morimoto, PhD, has spent his career leading project teams in developing innovative medicines for neurodegenerative diseases like PD, AD, ALS and FTD. His responsibilities have encompassed a broad range of drug development activities including manufacturing, nonclinical safety testing, regulatory affairs and translational clinical research. Morimoto held leadership roles at Allon Therapeutics, Celerion, Alkahest and Cerecin. He is on the advisor boards of several biotech companies helping to develop and deploy scientific, regulatory and medical strategy. Morimoto started his career in the faculty in the Chemistry Department at Purdue University. He earned his doctorate in biochemistry from the University of California, Los Angeles (UCLA) under the mentorship of Daniel E. Atkinson, and completed postdoctoral training at University of California, Berkeley with Daniel Koshland Jr.

Tanya Simuni, MD

Arthur C. Nielsen Jr. Professor of Neurology
Director, Parkinson's Disease and Movement Disorders Center
Northwestern Feinberg School of Medicine

Tanya Simuni, MD, 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 PD. Simuni serves on several Steering Committees for the PD national clinical trials, several committees for PSG and the PF. She is the Site PI and Steering Committee member for the largest PD biomarker 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.

Billy Dunn, MD

Senior Advisor

The Michael J. Fox Foundation

Billy Dunn, MD, was the founding director of the Office of Neuroscience, Center for Drug Evaluation and Research, at the U.S. Food and Drug Administration, a position he held since the founding of the office in 2019 through February 2023. He was responsible for the regulatory oversight of all research conducted to support neuroscience drug development, including the regulation and review of investigational new drug applications and marketing applications for drug and biologic products. From 2005 to 2019, he held positions of increasing seniority in the Division of Neurology Products, Center for Drug Evaluation and Research, including his role as director of that division. Dunn is a trained neurologist and vascular neurologist with experience in basic research, clinical research, and clinical care. He earned his BA from the University of Virginia and his MD from the F. Edward Hébert School of Medicine in Bethesda, Maryland.

Poster Session

Understanding Diversity in a Global Parkinson's Disease Cohort

Maggie Kuhl
Vice President, Head of Patient Engagement
The Michael J. Fox Foundation

As Vice President of Patient Engagement at The Michael J. Fox Foundation, Maggie leads a team engaging community partners and gathering patient experience data toward patient-focused drug development, as well as practicing and piloting recruitment and retention methods to enable faster trials. Kuhl directs recruitment strategy for the Foundation's Parkinson's Progression Markers Initiative, a longitudinal observational study with remote screening and enrollment at 50 international sites for thousands of participants. Prior to joining the Foundation in 2013, she worked in communications at the National Institutes of Health.

Abstract

Like most observational studies of people with Parkinson's disease (PD), the Parkinson's Progression Markers Initiative (PPMI) has historically under-enrolled participants from marginalized backgrounds. In 2020, the PPMI Steering Committee approved the formation of a dedicated taskforce for diversity, equity, and inclusion (DEI) initiatives in PPMI. The taskforce is composed of a movement disorders neurologist, a clinical psychologist who also serves as the recruitment/retention lead for PPMI, a genetic counselor, and representatives from the MJFF Patient Engagement Team, including the VP of DEI Strategy and Insights. Taskforce activities in the first four years have focused on three major areas: (1) study-wide initiatives such as coordinator training, reformulation of the race/ethnicity questions to better reflect participant understanding of ancestral origins, and a new question on sexual orientation and gender identity; (2) site-specific initiatives like DEI pilot grants, site-level translation efforts; and (3) alignment with other MJFF-funded studies such as BLAAC-PD and GP2 through cross-marketing efforts. From 2020 to 2024, these efforts resulted in a 12x increase in the number of Black/African-American participants, a 5x increase in the number of Asian participants, and a 3x increase in the number of Hispanic/Latino participants. Planned activities for 2025 and beyond include the rollout of updated race/ethnicity questions through the online myPPMI portal and return of results to all participants as a way to increase trust and retention in the study as a whole. Sustained and innovative integration of DEI activities into all aspects of clinical studies yields a more diverse cohort, better reflective of the global population of people with PD.

Poster Session

The Aligning Science Across Parkinson's Initiative: Changing the Way Science is Done to Accelerate Discoveries in Parkinson's Disease Research

Sonya Dumanis, PhD
Deputy Director
Aligning Science Across Parkinson's

Sonya Dumanis, PhD, is the Deputy Director of Aligning Science Across Parkinson's.

Previously, Dumanis was the Vice President of Research and Innovation at the Epilepsy Foundation. While there, she oversaw the growth of the Epilepsy Therapy Project, an entrepreneurship incubator providing seed funding and mentorship to epilepsy startups, launched the Epilepsy Innovation Institute, an innovation incubator tackling high risk projects in the epilepsy space, and supported early career research development through the Next Generation Programs. Dumanis has been with the Epilepsy Foundation since 2016. Prior to joining the Epilepsy Foundation, she worked at the Milken Institute Center for Strategic Philanthropy, tasked with identifying key philanthropic opportunities poised to have a transformative impact on the state of research and developing research programs.

Dumanis completed her postdoctoral training at both the Johns Hopkins University and the Max-Delbrück Center in Berlin, Germany. She earned her PhD in neuroscience from Georgetown University. She has authored numerous scientific articles and received several honors, including an Alexander von Humboldt Postdoctoral Research Fellowship, a National Science Foundation fellowship, a national research service award from the National Institutes of Health, the Harold N Glassman Award for best science dissertation at Georgetown University, and the Mark A. Smith prize from the Journal of Neurochemistry. Dumanis has demonstrated a strong commitment to science outreach, developing several educational initiatives such as the Georgetown Medical Center Graduate Student Research Grants program and the Epilepsy Foundation / Danny Did startup accelerator course.

Ekemini A. U. Riley, PhD
Managing Director
Aligning Science Across Parkinson's

Ekemini A. U. Riley, PhD, is the Managing Director of Aligning Science Across Parkinson's (ASAP), a research funding initiative that coordinates targeted basic research and resources to uncover the roots of Parkinson's disease. Prior to ASAP, Riley was a director at the Milken Institute Center for Strategic Philanthropy where she helped to shape and co-direct the center's medical research practice. She designed and facilitated several multi-sectors think tank sessions to inform the strategic deployment of philanthropic capital, crafted research programs and seeded multi-funder collaboration. She led the development and launch of ASAP as

well as the Gilbert Family Foundation's Gene Therapy and Vision Restoration Initiatives. Her work also laid the foundation for Play It Forward Pittsburgh, an organ donation awareness campaign in Pittsburgh. Riley completed her BA in Natural Sciences from Johns Hopkins University and PhD in Molecular Medicine from the University of Maryland School of Medicine. Her doctoral research focused on gene regulation of internal blood clotting and tumor suppressor protein.

Abstract

Aligning Science Across Parkinson's (ASAP) is a coordinated research initiative designed to accelerate discoveries for Parkinson's disease (PD) by promoting collaboration, generating scientific resources, and sharing data. ASAP, which is managed by the Coalition for Aligning Science and implemented by The Michael J. Fox Foundation for Parkinson's Research, supports programs that work to address resource needs and knowledge gaps in the PD field.

The ASAP Collaborative Research Network (CRN) is an international, multidisciplinary, and multi-institutional network of 35 teams working together through team-based approaches to address high-priority research questions that can enhance understanding of PD. The first of its kind, the CRN is changing the way that science is done by fostering an environment that supports productive collaboration, encourages diverse perspectives, and embraces the value of openness and transparency to accelerate outcomes and the impact of findings. Since its inception, the CRN has generated nearly 2000 research outputs and nearly 400 articles with findings that span multiple disciplines, ranging from insights into endolysosomal and mitochondrial pathways to understanding synuclein biology to circuitry physiology.

Currently, CRN projects are focused on three key scientific themes: PD functional genomics, neuro-immune interactions, and circuitry and brain-body interactions. In 2025, ASAP will be hosting two new open competitive funding opportunities to spur additional discovery in Parkinson's disease. The CRN 2025 funding opportunities will focus on two new themes related to dissecting mechanisms that contribute to PD heterogeneity and the development of novel tools to study emerging targets, with the goal of funneling new ideas into the research and development pipeline. Interested in learning more? Visit parkinsonsroadmap.org!

Poster Session

Neuron-derived Extracellular Vesicles from Human Blood for Alpha-synuclein Assessment in Diverse Synucleinopathies

Erez Eitan, PhD
Chief Scientific Officer
NeuroDex Inc.

Erez Eitan, PhD, is the Chief Scientific Officer and founding scientist of NeuroDex, a startup biotechnology company committed to developing diagnostic tests for diverse neurological conditions. Eitan is a neuroscientist studying neuron-derived extracellular vesicle utilization as a biomarker discovery. He did his postdoctoral research at the National Institute on Aging (NIA), where he was among the first to study extracellular vesicles. Eitan published over 30 papers in peer-reviewed journals covering multiple topics, including the role of extracellular vesicles in the prion-like propagation of amyloid beta and Alpha-synuclein. Development and utilization of immunoaffinity isolation of extracellular vesicles from the blood as a biomarker platform for neurodegenerative diseases. Currently, as chief scientific officer at NeuroDex, Eitan is working on validating extracellular vesicle-based blood tests for neurodegenerative diseases, making them ready for clinical use.

Abstract

Study Rationale: Parkinson's disease, Lewy body dementia, and multiple system atrophy are predominant synucleinopathies, with an estimated 2.5 million cases in the USA. Recently, synuclein seeding assay (SAA) using cerebrospinal fluid (CSF) became the first liquid biomarker for synucleinopathies. However, the need for reliable blood biomarkers remains urgent since, unlike CSF, blood biomarkers could facilitate regular monitoring and screening. Brain neurons release small extracellular vesicles into plasma and contain representative proteins and RNA. We developed a technology for specific capture of neuron-derived extracellular vesicles (NDE) from blood plasma as a biomarker platform for diverse synucleinopathies.

Hypothesis: NDE enrichment from blood plasma using a novel technology, ExoSORT, enables consistent detection of the elevated alpha-synuclein (aSyn) levels in patients with synucleinopathy compared to healthy control donors. This finding suggests that NDEs could serve as a reliable biomarker for synucleinopathies.

Study Design: α-Synuclein (aSyn) was measured in plasma NDEs isolated using ExoSORT. Clinical proof of concept was conducted across four cohorts: Cohort I included 77 healthy controls, 113 patients diagnosed with synucleinopathy and 37 with Alzheimer's Disease (AD); Cohort II included 9 controls and 37 patients with Lewy Body Dementia (LBD, 13 with GBA mutations); Cohort III included 15 controls and 30 dementia patients, 15 with and 15 without tauopathy; Cohort IV comprised 15 healthy controls, 15 LBD, and 15 AD

patients, with all diagnoses confirmed by postmortem pathology. In all cohorts, patients with synucleinopathy and dementia exhibited significant differences from healthy controls, independent of GBA mutations or tau biomarkers. Notably, in Cohort IV, significant differences existed between patients with and without postmortem-confirmed Lewy bodies.

Impact on Diagnosis/Treatment of Parkinson's disease: These findings indicate that NDE aSyn is significantly elevated in synucleinopathy and identify blood NDEs as a promising biomarker platform for early diagnosis of synucleinopathies, differentiating them from other dementia types, monitoring disease progression, and treating response. This advancement could greatly enhance decision-making and personalized treatment in clinical settings.

Next Steps for Development: Further validation of our results requires a large, well-curated cohort, such as PPMI. Such a study would also allow for comparing the biomarker performance of blood NDEs with that of CSF SAA. Complete analytical validation and scale-up of the current protocol are currently underway.

Poster Session

Optimization of MDS-UPDRS for Use in Early-stage Parkinson's Disease Clinical Trials

Thomas Morel, PhD
Global Patient-Centred Outcomes Research Lead
UCB

Thomas Morel, PhD, is Global Patient-Centred Outcomes Research Lead at UCB. In this role, Morel ensures that health outcomes most meaningful to patients are at the center of clinical development programs through the design and implementation of patient-centric outcome measurement strategies. Since 2018, Morel has been the principal investigator of the joint UCB/Parkinson's UK/Parkinson's Foundation research project to co-create novel Patient Reported Outcome (PRO) instruments to accurately reflect the experience of people living with early-stage Parkinson's. Since November 2023, Morel is Industry Chair of Critical Path Parkinson's (CPP) pre-competitive working group on patient-centric endpoints for Parkinson's, whose ambition is to address outcomes measurement gaps in Parkinson's drug development. Morel co-leads the CPP Taskforce to optimize MDS-UPDRS for use as primary clinical trial endpoint in early-stage Parkinson's. Rare diseases are another area where Thomas has extensive expertise. He is a Therapies Scientific Committee member of the International Rare Diseases Research Consortium (IRDiRC).

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

Authors: Thomas Morel, PhD; Catherine Kopil,PhD; Nicolai Ayasse, PhD; Diane Stephenson, PhD; Tiago Mestre, MD; Tanya Simuni, MD; Cheryl Coon, PhD

A multistakeholder pre-competitive collaboration has been established under the umbrella of Critical Path Institute's Critical Path for Parkinson's (CPP) to provide a neutral forum to align with regulatory agencies on possible primary efficacy endpoints based on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Such endpoints are needed by sponsors navigating the novel landscape of disease-modifying treatments in early Parkinson's disease (PD; Hoehn & Yahr ≤ 2). Goals include the identification of a subset of items from the MDS-UPDRS that are targeted to early PD, responsive to change, and clinically meaningful and to align on ways to combine the items into interpretable scores and viable endpoints. Qualitative and quantitative evidence sources were identified through CPP member contributions and published literature representing a range of study designs, research questions, populations, and methodology. Evidence has been compiled and analyzed to support regulatory discussions on item subsets. The collaboration is now pursuing the generation of supportive evidence to confirm item subsets, scoring, and endpoint construction. This initiative demonstrates a successful collaborative model for generating a swift solution to an urgent drug development need by assembling a representative group of stakeholder perspectives along with generous sharing of consolidated item-level evidence.

Poster Session

Integrated, Collaborative, Multimodal Data Approach in Parkinson's Disease

John Seaman, PhD
Director of Biostatistics
Novartis Pharmaceuticals Corporation

John Seaman, PhD, is director of biostatistics for Novartis Pharmaceuticals Corporation with over 14 years of experience across multiple therapeutic areas and development phases. His work spans the development of clinical trials and programs, exploration of digital endpoints and tests, and is now the analytics team lead for the collaboration between MJFF and Novartis to improve disease understanding, define progression, disease staging and identify more sensitive endpoints and biomarkers to enable and accelerate the development of disease modifying therapies.

Abstract

Authors: Amit Khanna, Piet Aarden, John Seaman, Mari Niemi (NVS), Ken Marek, Ethan Brown, Craig Stanley, Mark Fraser (MJFF, PPMI)

Study Rationale: Parkinson's Disease (PD) is complex with heterogeneous symptoms and progression. While established clinical endpoints exist, they are not sensitive in early stages of PD and are often confounded by the use of symptomatic treatment. These challenges pose a significant hurdle for drug development in PD.

Novartis and The Michael J. Fox Foundation for Parkinson's Research (MJFF), including study leadership from the Parkinson's Progression Markers Initiative (PPMI), have established a data collaboration focused on multi-modal data to improve disease understanding, define progression, disease staging and identify more sensitive endpoints and biomarkers with the aim to enable and accelerate the development of disease modifying therapies.

Hypothesis: The joint team will explore measures of disease progression and enhancement opportunities of the Neuronal Synuclein Disease Integrated Staging System (NSD-ISS) using multi-modal data approaches.

Study Design: To better understand disease progression, the team will identify outcome measures that change over time and how the measures, individually or in combination, optimally represent disease progression. Additionally, the team aims to examine patient subgroups and identify distinct patterns of progression within them. The team will examine the characteristics of the NSD-ISS staging system and explore the possibility of incorporating multi-modal outcomes to enhance and refine the staging system. Patterns in changing stages, model-based assessments of measured outcomes, and exploration of

longitudinal characteristics will be explored to enhance the staging system and understand its usefulness in drug development.

Impact on Diagnosis/Treatment of Parkinson's disease: Identification of the markers of PD progression and enhancement of the NSD-ISS could lead to improved drug development programs and disease tracking in patients.

Furthering the understanding of the markers of disease progression may open the door to novel endpoints that are more sensitive to changes in PD at various stages to benefit novel therapeutic development.

Next Steps for Development: Data integration, harmonization and connecting data modalities are currently ongoing. The team is developing a work plan based on defined key scientific questions to gain first insights into the various data modalities.

Poster Session

Targets to Therapies: A New Target De-Risking Initiative at MJFF

Steven Braithwaite, PhD
Deputy Chief Scientific Officer
Bayshore Global Management

Steven Braithwaite, PhD, is a passionate scientist and executive focused on impacting patients' lives. His career has been in industry where he can bring this to reality, open-minded to a range of therapeutic areas. Braithwaite has had success in founding his own companies, being instrumental in very early-stage endeavors that have led to major acquisitions and in large Pharma. He most recently was CEO of Alkahest, a Silicon Valley based biotech company that was acquired by Grifols, pushing frontiers in understanding aging, leading to the advancement of multiple therapeutic candidates into the clinic. He also founded MentiNova, a clinical repurposing company, is Adjunct Professor of Neurology at Rutgers University, and has previously led scientific and business efforts at Circuit Therapeutics, Signum Biosciences and Wyeth/Pfizer. He has held a postdoctoral position at Stanford University, gained a PhD from the University of Bristol and an undergraduate degree from the University of Cambridge.

Virginie Buggia Prevot, PhD
Senior Director, Drug Discovery
Valo Health

Virginie Buggia-Prevot, PhD, is a drug discovery scientist with more than 20 years of experience in neurodegenerative diseases. She is the Senior Director of Drug Discovery at Valo Health, a technology company focused on utilizing large scale data and artificial intelligence (AI)-driven computation to discover and develop therapeutics, having joined the company in 2020. In her role she leads Neurology Discovery, developing human-centric computational approaches to discover and validate new targets for neurodegenerative diseases and leads drug discovery programs leveraging Valo's Opal Computational Platform™, including projects within Valo's partnership with Novo Nordisk.

Prior to Valo, Prevot led the novel target discovery and validation group at the Neurodegeneration Consortium embedded in the Therapeutic Division of MD Anderson. The mission of the Neurodegeneration Consortium is to identify targets for neurodegenerative diseases by collaborating with academic leaders of the field and translating the knowledge into therapeutic interventions. Her work on a neuroprotective small molecule program contributed to the launch of Magnolia Neurosciences, a company focused on the development of a new class of neuroprotective medicines and was awarded a grant from MJFF to evaluate its potential in Parkinson's disease. Using data generated by Prevot and her team, a new strategic research agreement was formed with Denali Therapeutics to develop new therapies for Alzheimer's disease. In 2020, Virginie was named as one of Citeline's "In Vivo Rising Leaders" in the list's inaugural year and is now

published annually, recognizing talent across the life sciences industry globally for their leadership in driving unique health care initiatives.

Prevot trained for five years in the lab of Lasker Award recipient, Professor Alim Louis Benabid, who pioneered deep brain stimulation for Parkinson's disease. She then received her PhD in cell and molecular biology from the University of Nice Sophia-Antipolis and completed her post-doctoral training at the Neurobiology Department of the University of Chicago.

Darryle Schoepp, PhD

Independent Pharmaceutical Consultant

Darryle Schoepp, PhD, has over thirty years of experience in the discovery and development of innovative Neuroscience therapeutics that includes 20 years at Eli Lilly as a scientist and leader of the Neuroscience department, and 12 years at Merck as the CNS Therapeutic area leader.

As a scientist he has over 200 publications and is the inventor of 15 US patents. His bench and leadership roles have led to the discovery and development of over 20 novel first in class agents for psychiatric and neurological diseases. These include the first AMPA/kainate and metabotropic receptor negative and positive modulators (e.g. tezampanel, talampanel, LY354740, LY341595, eglumetad and pomoglumetad) investigated for migraine, pain, cognition, Alzheimers and Parkinson's disease, anxiety disorders and schizophrenia. While at Lilly, he was a co-discoverer of the compound LY246736 (alipimovan/Entereg) a first in class peripherally restricted opioid antagonist for post-operative ileus. At Merck his team developed and launched the first in class orexin receptor antagonist Suvorexant (Belsomra) for insomnia and discovered the novel first in class oral CGRP antagonists ubrogepant (Ubrelvy) and atogepant (Qulipta) for migraine treatment and prevention (commercialized by Allergan/Abbvie).

Schoepp received his bachelor's degree in pharmacy from North Dakota State University and his doctoral degree in Pharmacology and Toxicology from West Virginia University. Currently Schoepp is an independent pharmaceutical research and development consultant who serves on advisory boards including Lundbeck (SAB Chair), Lieber Institute, and Pharma Foundation Drug Discovery (advisory committee), and NIH Neurotherapeutics Blueprint (External Oversight Committee).

Poster Session

Advanced Quantification and Standardization of Dopaminergic Imaging Markers with the Centamine Scale

Roger Gunn, PhD
Chief Science Officer
Xing Imaging – A Xing Imaging Company

Roger Gunn, PhD, is an international expert in imaging and drug development. He has discovered, developed and translated imaging techniques to measure biological processes for drug development and they are now central to biomarker strategies of pharmaceutical companies. In his current role as Chief Science Officer at Xing Imaging, he is heading the R&D of new biomarkers & analytics and leading the design, analysis and delivery of clinical imaging trials for pharmaceutical companies. He is also Emeritus Professor of Molecular Neuroimaging at Imperial College and Founder of the analytics software company MIAKAT Ltd. He has published over 200 peer reviewed papers in the field of imaging, neuroscience and drug development with an H-index of 75 and has delivered over 80 invited lectures. His career has involved positions on research councils, consultancy to pharmaceutical companies and the training and mentoring of PhD students and clinical research fellows.

Abstract

Markers of dopaminergic neuronal loss, like [123I]Ioflupane (DAT) SPECT and [18F]AV133 (VMAT2) PET, are central outcome measures in clinical trials of novel PD therapies and are used for subject eligibility and longitudinal assessment of disease modification. The ability to improve image quantification, further enhancing signal-to-noise, and use multiple dopaminergic imaging markers as part of a single clinical trial would significantly expand access to imaging infrastructure, increase the power and speed of clinical trials whilst also simplifying their deployment and execution.

Head-to-head [123I]Ioflupane (DAT) SPECT and [18F]AV133 (VMAT2) PET imaging data in 41 Parkinson's Disease subjects from the Parkinson's Progression Markers Initiative (PPMI) who had a baseline and at least one longitudinal follow up scan were used in this work.

Advanced Image Quantification: The advanced analytical pipeline developed in MIAKATTM included motion correction, frame averaging, spatial normalisation and application of regions of interest in template space. The reference region was chosen to be the cerebral white matter. This enabled calculation of the specific binding ratio (SBR) outcome measure in the putamen. The results were assessed in terms of their longitudinal power and demonstrated improvements for [123I]Ioflupane (DAT) SPECT over previous analyses (signal-to-noise showed an ~50% increase at 12 m and over 100% increase at 24 m) and even greater power for [18F]AV133 (VMAT2) PET.

The Centamine Scale: The Centamine scale is being developed as a harmonized quantification approach for imaging markers of dopaminergic neuronal loss. The approach is analogous to the development of the Centiloid scale for Amyloid imaging markers which has had significant impact on the successful development of disease modifying drugs for Alzheimer's disease. The method derives a linear mapping from head-to-head imaging data obtained from different dopaminergic imaging markers in the same subjects. For [123I]Ioflupane (DAT) SPECT and [18F]AV133 (VMAT2) PET, a strong linear relationship was obtained: for putamen, AV133 SBR = 1.97 DAT SBR (95% CI = 1.88, 2.07). This enabled mapping of all data to a common scale, termed Centamines, using mean healthy control DaT SBR value to anchor the scale at 100% (Figure 1.).

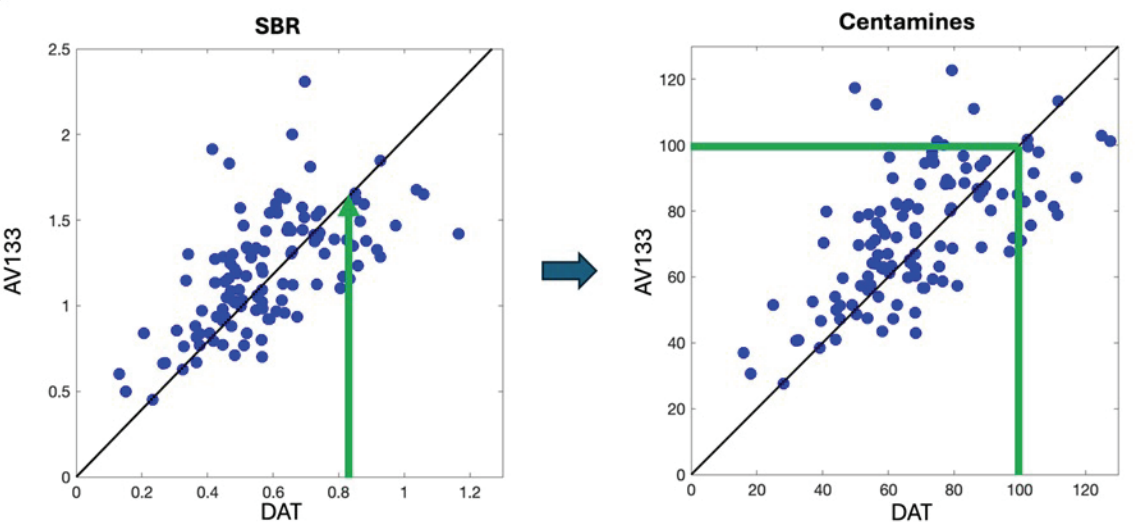


Figure 1:
Relationship between [18F]AV-133 PET and DaT SPECT SBR and conversion to the Centamine scale

michaeljfox.org

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH