Alzheimer's
Drug Discovery
Foundation

17TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DRUG DISCOVERY

Jersey City, NJ ● *September 12-13, 2016*

PROGRAM and ABSTRACTS

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@TheADDF and #AlzDrugConf

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WELCOME!

On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to our 17th International Conference on Alzheimer's Drug Discovery.

For almost two decades now, our annual meeting has brought together scientists focused on accelerating the development of treatments for Alzheimer's disease and related dementias, while creating opportunities for networking between academia, government, biotechnology, and pharmaceutical companies. Each year brings us one step closer to accomplishing our mission and maintaining our singular focus on the science that is needed to conquer Alzheimer's disease.

We are deeply grateful to our generous sponsors whose support makes this meeting possible: Eli Lilly & Co, Merck Research Laboratories, Roche, Harrington Discovery Institute, Accelerate Cure/Treatments for Alzheimer's Disease, and Rodin Therapeutics. We would also like to thank our exhibitors: Bachem Americas, Inc., Brains On-Line, Envigo, InterVivo Solutions, PsychoGenics, Science Exchange, Inc., and Sylics—be sure to visit their booths throughout the conference. Our sincere appreciation also extends to all of our speakers and chairs for the hard work they do to accelerate drug discovery for Alzheimer's disease and related dementias.

Engaging the next generation of research scientists in this field is more important than ever. We are pleased to announce our 2016 Young Investigator Scholarship winners: Julia Gamache, PhD (cand.), Karolina Janczura, PhD (cand.), Zahra Khazaeipool, MD, MS, Hema Krishnan, PhD, JiaBei Lin, PhD, Korrie Mack, PhD (cand.), Ludovica Monti, PhD (cand.), Daniel Oseid, PhD (cand.), Khaing Win, PhD (cand.), and Helen Wong, PhD. We encourage you to visit their poster presentations which will be displayed throughout the meetings.

To help us plan an even better conference in 2017, please complete the survey to provide us with feedback and suggestions. And save the date for next year's conference, which will take place at the Hyatt Regency, Jersey City on September 11-12, 2017.

Welcome, once again, to the 17th International Conference on Alzheimer's Drug Discovery!

Best Regards,

Howard

Howard Fillit, MD
Founding Executive Director and Chief Science Officer
Alzheimer's Drug Discovery Foundation

ABOUT THE
ALZHEIMER'S DRUG DISCOVERY FOUNDATION

Alzheimer's
Drug Discovery
Foundation

CONQUERING ALZHEIMER'S THROUGH DRUG DISCOVERY

Our mission: To accelerate the discovery of drugs to prevent, treat and cure Alzheimer's disease, related dementias and cognitive aging.

Founded in 1998 by Co-Chairmen Leonard and Ronald Lauder, the ADDF awards grants to leading scientists conducting breakthrough drug discovery and early clinical research.

The ultimate goal of our unique organization is to support the science that will drive the development of drug therapies for Alzheimer's disease.

WHAT WE'VE ACCOMPLISHED

- The ADDF has granted more than **$90 million to fund 500 Alzheimer's drug discovery programs and clinical trials** in academic centers and biotechnology companies in **18 countries**.
- As a measure of success, programs funded by the ADDF have gone on to receive commitments of more than **$2 billion** in follow-on commitments from the government, pharmaceutical companies and venture capital firms.
- In 2015, the ADDF raised **$22.3 million** to support preclinical drug discovery and clinical development programs. 100% of funds raised goes directly to drug research and related scientific programs, thanks to the generosity of a private Lauder Family Foundation that covered all administrative and operational expenses.

OUR CONFERENCES

The Alzheimer's Drug Discovery Foundation organizes two annual scientific conferences as part of our ongoing efforts to increase researchers' knowledge about Alzheimer's disease and the drug discovery process. The conferences promote networking to catalyze the exchange of ideas and foster alliances that accelerate the development of new treatments for AD.

Our annual *International Conference for Alzheimer's Drug Discovery*, to be held next year on September 11-12, 2017, focuses on the discovery and development of drugs targeting Alzheimer's disease and related dementias. The *Drug Discovery for Neurodegeneration* conference, to be held next year on February 12-14, 2017 in San Diego, CA, is designed to educate scientists on the process of translating basic neuroscience research into innovative therapies.

The Alzheimer's Drug Discovery Foundation also plans smaller "catalyst conferences" that center on a relevant topic in the field of neurodegeneration.

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JAD
Journal of Alzheimer's Disease

2016 ADDF YOUNG INVESTIGATOR SCHOLARSHIPS

Congratulations to the recipients of the **ADDF Young Investigator Scholarships!** These scholarships recognize the early achievements of talented young investigators by offering them the opportunity to attend this conference and present posters of their work.

Please visit their poster presentations during the breaks, lunch and networking reception.

The 2016 Young Investigator Scholars are:

Julia Gamache, PhD (cand.), *University of Minnesota*
Karolina Janczura, PhD (cand.), *University of Miami Miller School of Medicine*
Zahra Khazaeipool, MD, *Western University*
Hema Krishnan, PhD, *Harvard Medical School and Massachusetts General Hospital*
JiaBei Lin, PhD, *University of Alabama at Birmingham*
Korrie Mack, PhD (cand.), *University of Pennsylvania, Perelman School of Medicine*
Ludovica Monti, PhD (cand.), *University of Pennsylvania*
Daniel Oseid, PhD (cand.), *Tulane University*
Khaing Win, PhD (cand.), *University of Pennsylvania*
Helen Wong, PhD, *University of Colorado Boulder*

PROGRAM

MONDAY, SEPTEMBER 12	
8:00–5:20pm	Registration
8:00–8:30am	Continental Breakfast
8:30–8:50	**Welcome & Opening Presentation: Setting the Stage for New Alzheimer's Therapeutics** Howard Fillit, MD—*Alzheimer's Drug Discovery Foundation*
8:50–9:30	**Keynote: Novel Approaches to Dealing with Small Sample Sizes** Michael Gold, MD—*PPD*
	Session I: Targeting Neuroinflammation Chair: Diana Shineman, PhD, *Alzheimer's Drug Discovery Foundation*
9:30–9:35	**Session Overview:** Diana Shineman, PhD—*Alzheimer's Drug Discovery Foundation*
9:35–9:55	**Slowing Arginine Utilization by Inhibiting Arginase and Ornithine Decarboxylase with DFMO** Carol Colton, PhD—*Duke University Medical Center (2015 ADDF/Harrington Scholar)*
9:55–10:05	*Q&A*
10:05–10:25	**The Endocannabinoid System as a Therapeutic Target for Alzheimer's Disease** Alexandros Makriyannis, PhD—*Northeastern University*
10:25–10:35	*Q&A*
10:35–11:00	**EXHIBITOR SESSION BREAK**
11:00–11:20	**Inhibiting Neutrophil Extracellular Trap (NET) Formation as a Novel Therapeutic Approach to AD** Paul Thompson, PhD—*University of Massachusetts School of Medicine*
11:20–11:30	*Q&A*
11:30–11:50	**Development of Novel NLRP3 Inflammasome Inhibitors Towards Alzheimer's Disease** Shijun Zhang, PhD—*Virginia Commonwealth University*
11:50–12:00	*Q&A*
12:00–12:20	**Humanization of a First-in-Class Anti-Inflammatory for Alzheimer's Disease Therapy** Danna Zimmer, PhD—*University of Maryland School of Medicine*
12:20–12:30	*Q&A*
12:30–1:35	**LUNCH, POSTER & EXHIBITOR SESSION** ***(All poster presenters should stand by their poster from 12:55-1:35PM)***
	Session II: Novel Strategies for Neuroprotection Chair: Lauren Friedman, PhD, *Alzheimer's Drug Discovery Foundation*
1:35–1:40	**Session Overview:** Lauren Friedman, PhD—*Alzheimer's Drug Discovery Foundation*
1:40–2:00	**NeuroRestore—Development of Positive Allosteric Modulators of TrkA and TrkB** Pontus Forsell, PhD—*AlzeCure Foundation*
2:00–2:10	*Q&A*
2:10–2:30	**Targeting Tau: YTX-1357, a Novel, Oral BBB-Penetrant Small-Molecule in Development for AD and Other Tauopathies** Yukari Perrella, MBA—*Yuma Therapeutics Corp.*
2:30–2:40	*Q&A*
2:40–3:00	**Identification of Small Molecules that Modulate Microglia/Macrophage Uptake in Primary Human Cells** Elizabeth Bradshaw, PhD—*Brigham and Women's Hospital*
3:00–3:10	*Q&A*
3:10–3:40	**EXHIBITOR SESSION BREAK**
3:40–4:00	**Selective HDAC2 Inhibitors for the Treatment of Cognitive Deficits in Alzheimer's Disease** Berkley Lynch, PhD—*Rodin Therapeutics Inc.*
4:00–4:10	*Q&A*
4:10–4:30	**Drug Development and Optimization of Compounds Stabilizing Ryanodine Calcium Channels** Grace Stutzmann, PhD—*Rosalind Franklin University, The Chicago Medical School*
4:30–4:40	*Q&A*
4:40–5:00	**VGF Peptide Delivery for Neuroprotection and the Suppression of Memory Impairment** Stephen Salton, MD, PhD—*Icahn School of Medicine at Mount Sinai*
5:00–5:10	*Q&A*
5:10–5:20	**Closing Remarks and Announcement of Young Investigator Scholarships** Andrew Koemeter-Cox, PhD—*Alzheimer's Drug Discovery Foundation*
5:20–7:00	**NETWORKING RECEPTION WITH POSTER AND EXHIBITOR SESSION**

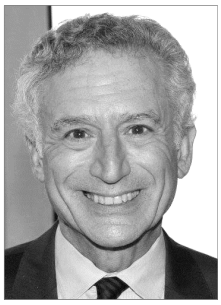
PROGRAM (cont.)

TUESDAY, SEPTEMBER 13	
8:00–8:30	Continental Breakfast
8:30–8:40	**Day 2 Opening Remarks** Howard Fillit, MD—*Alzheimer's Drug Discovery Foundation*
8:40–9:20	**Keynote: New Advances in Drug Discovery for Alzheimer's Disease** Mansuo Hayashi, PhD—*Eli Lilly and Company*
Session III: Advancing Therapies into Clinical Trials Chair: Penny Dacks, PhD, *Alzheimer's Drug Discovery Foundation*	
9:20–9:25	**Session Overview:** Penny Dacks, PhD—*Alzheimer's Drug Discovery Foundation*
9:25–9:45	**Advancing Development of Novel MI PAMs Toward Clinical Testing** Jerri Rook, PhD—*Vanderbilt University* *(2015 ADDF/Harrington Scholar)*
9:45–9:55	*Q&A*
9:55–10:15	**Effect of Candesartan on Prodromal Alzheimer's Disease and Its Related Biomarkers** Ihab Hajjar, MD—*Emory University School of Medicine*
10:15–10:25	*Q&A*
10:25–10:45	**Therapeutic Effects of Nilotinib in Neurodegenerative Disease** Raymond Scott Turner, MD, PhD—*Georgetown University*
10:45–10:55	*Q&A*
10:55–11:25	**EXHIBITOR SESSION BREAK**
11:25–11:45	**Nabilone in Agitated Patients with Alzheimer's Disease: A Pilot Study of Safety and Efficacy** Krista Lanctôt, PhD— *Sunnybrook Research Institute, University of Toronto*
11:45–11:55	*Q&A*
11:55am–12:15pm	**Accelerating a Phase III MCI Clinical Trial with Phase I Evaluation of a Novel Extended-Release Levetiracetam Formulation** Sharon Rosenzweig-Lipson, PhD—*AgeneBio Inc./IVS Pharma Consulting LLC*
12:15–12:25	*Q&A*
12:25–1:25	**LUNCH, POSTER & EXHIBITOR SESSION** ***(All poster presenters should stand by their poster from 12:50-1:25PM)***
Session IV: Strategies to Accelerate Clinical Development for AD & Related Dementias Chair: Nick McKeehan, *Alzheimer's Drug Discovery Foundation*	
1:25–1:30	**Session Overview:** Nick McKeehan—*Alzheimer's Drug Discovery Foundation*
1:30–1:50	**Development of the O-GlcNAcase Inhibitor ASN-561 for the Treatment of Tauopathies** Dirk Beher, PhD—*Asceneuron SA*
1:50–2:00	*Q&A*
2:00–2:20	**The Evolving Analytical Landscape in Laboratory Medicine: Applications to the Design of TDP-43 Biofluid Diagnostics for FTD** Mari DeMarco, PhD—*University of British Columbia* *(Funded through the ADDF/Association for Frontotemporal Degeneration Partnership Program)*
2:20–2:30	*Q&A*
2:30–2:50	**Combined CSF Biomarkers and GBA Genotype for Diagnosis of LBD** Lawrence Honig, MD, PhD—*Columbia University*
2:50–3:00	*Q&A*
3:00–3:30	**EXHIBITOR SESSION BREAK**
3:30–3:50	**Low-dose Lithium for the Treatment of Behavioral Symptoms in FTD** Edward Huey, MD—*Columbia University* *(Funded through the ADDF/Association for Frontotemporal Degeneration Partnership Program)*
3:50–4:00	*Q&A*
4:00–4:20	**Repurposing the PDE5 Inhibitor Tadalafil for Vascular Cognitive Impairment: A Test of Concept in Older People** Atticus Hainsworth, PhD—*St George's University of London* *(Funded through ADDF's Partnership with the Alzheimer's Society, UK)*
4:20–4:30	*Q&A*
4:30–4:40	**Closing Remarks**—Howard Fillit, MD, *Alzheimer's Drug Discovery Foundation*

BIOS AND ABSTRACTS

CONFERENCE CHAIR

Howard Fillit, MD, Alzheimer's Drug Discovery Foundation



Howard Fillit, MD, a geriatrician, neuroscientist and a leading expert in Alzheimer's disease, is the founding Executive Director of the Alzheimer's Drug Discovery Foundation (ADDF). The ADDF's mission is to accelerate the discovery and development of drugs to prevent, treat and cure Alzheimer's disease, related dementias and cognitive aging. Dr. Fillit has had a distinguished academic medicine career at The Rockefeller University and The Mount Sinai School of Medicine where he is a clinical professor of geriatrics and medicine and professor of neurobiology. He is a co-author of more than 300 scientific and clinical publications, and is the senior editor of the leading international Textbook of Geriatric Medicine and Gerontology.

Previously, Dr. Fillit was the Corporate Medical Director for Medicare at New York Life, responsible for over 125,000 Medicare managed care members in five regional markets. Dr. Fillit has received several awards and honors including the *Rita Hayworth Award for Lifetime Achievement*. He also serves as a consultant to pharmaceutical and biotechnology companies, health care organizations and philanthropies. Throughout his career, he has maintained a limited private practice in consultative geriatric medicine with a focus on Alzheimer's disease and related dementias.

KEYNOTE SPEAKER
Michael Gold, MD, PPD

Michael Gold, MD, graduated from the University of Miami School of Medicine, completed his neurology residency at the Albert Einstein College of Medicine in New York City and his fellowship at the University of Florida College of Medicine. He then practiced neurology with a focus on neurodegenerative disorders at the University of South Florida College of Medicine, where he served as the medical director of the Memory Disorders Clinic and began his participation in clinical trials. He spent several years at large pharmaceutical companies (BMS, J&J and GSK), a biotechnology company (Allon Therapeutics) and specialty companies (UCB) working on neuroscience compounds at all stages of development from first-in-man studies through post-approval studies. He has worked on or lead project teams in PSP, AD, Parkinson's disease (PD), restless leg syndrome (RLS), epilepsy, multiple sclerosis (MS), migraine, neuropathic pain, frontotemporal dementia (FTD), vascular dementia (VaD), Lewy Body Dementia (LBD) and stroke, and he has had the privilege to see several of the compounds he worked on become approved.

Novel Approaches to Dealing with Small Sample Sizes

Michael Gold

PPD, Morrisville, NC, USA

Pilot studies represent a critical aspect of the drug development enterprise. No compound is born with compelling evidence of its efficacy even if it were designed to have very specific effects. Pilot studies are necessary in order to explore aspects of any novel intervention including dose selection, dosing route and frequency, efficacy, safety, feasibility and reproducibility. These pilot studies are often conducted under extreme pressure in terms of resources (people, time and money) leading sponsors to cut corners and thereby jeopardize the integrity and value of these studies. Alternative study designs and analytical approaches represent a viable solution to this dynamic tension between the need to conduct such studies and the constraints imposed on them. Examples of two novel approaches will be presented and discussed with a specific emphasis on CNS indications that suffer from high placebo responses.

I. Targeting Neuroinflammation

Chair: Diana Shineman, PhD—Alzheimer's Drug Discovery Foundation

Slowing Arginine Utilization by Inhibiting Arginase and Ornithine Decarboxylase with DFMO
Carol Colton, PhD—Duke University Medical Center
(2015 ADDF/Harrington Scholar)

The Endocannabinoid System as a Therapeutic Target for Alzheimer Disease
Alexandros Makriyannis, PhD—Northeastern University

Inhibiting Neutrophil Extracellular Trap (NET) Formation as a Novel Therapeutic Approach to AD
Paul Thompson, PhD—University of Massachusetts Medical School

Development of Novel NLRP3 Inflammasome Inhibitors towards AD
Shijun Zhang, PhD—Virginia Commonwealth University

Humanization of a First-in-Class Anti-Inflammatory for AD Therapy
Danna Zimmer, PhD—University of Maryland School of Medicine

SESSION CHAIR
Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation

Diana Shineman, PhD, is the Senior Director for Scientific Affairs at the Alzheimer's Drug Discovery Foundation, where she develops and manages the Foundation's drug discovery and development grant programs and strategic initiatives. Combining scientific and business expertise, the ADDF manages its research funding portfolio to balance risk, stage of development and drug target mechanism of action, ensuring that grants meet key milestones before securing follow-on funding. As a measure of success, projects funded by the ADDF have gone on to garner nearly $2 billion in follow-on funding. The ADDF also works strategically with foundations, government and industry partners to tackle unmet needs in the field. As an example of such an initiative, Dr. Shineman led an interdisciplinary effort to standardize animal model study design to improve research efficiency and translatability.

Dr. Shineman joined the ADDF in 2008. She earned a PhD in Cell and Molecular Biology from the University of Pennsylvania working in the Center for Neurodegenerative Disease Research led by Drs. Virginia Lee and John Trojanowski. She also worked as an Editorial Intern for the Journal of Clinical Investigation and was an active member of the Penn Biotechnology Group. Dr. Shineman received a BA in Biology with a Nutrition concentration from Cornell University, where she was named a Howard Hughes Undergraduate Research Scholar.

In addition to maintaining various professional memberships, Dr. Shineman has also authored numerous articles and peer-reviewed publications.

Carol Colton, PhD, Duke University Medical Center*

Carol Colton, PhD, is a Professor in the Department of Neurology at Duke University Medical Center and an ADDF-Harrington Scholar for 2016. Dr. Colton has focused her career on examining pathophysiological processes in the brain that are associated with neurodegeneration and inflammation.

"When I began my study of brain immunology, the concept of a CNS resident immune cell was heresy. It was clear to me that the logic behind the original immune privilege status of the brain was flawed – species survival dictates that all disease processes initiate an immune response in every tissue throughout the body, including the brain. Thus looking for the brain's primary macrophage, the microglia was an obvious thing to do. I was among the first to study this cell type in the early 1990s'. Importantly, it doesn't matter whether the disease is acute (encephalitis) or chronic (Alzheimer's), immune cells play a role. However, the early idea that all immune responses to disease in the brain were essentially the same (the *neuroinferno* concept) was equally illogical. Our data clearly show a complex immune response that focuses on enhanced protection initially and changes over the time course of the disease and with age. This basic phenomenon is observed in many tissues not just the brain and, again, is an adaptation for survival and extending life in the face of challenges. This type of understanding has opened new avenues to think about AD which hopefully will lead to earlier and more effective treatment."

Recently, Dr. Colton has begun to apply this knowledge to the search for effective therapeutics to treat humans with AD. The success of the ADDF-funded mouse study using pharmacological agents to disrupt immunosuppressive pathways has now led to the development of a clinical trial in humans.

Slowing Arginine Utilization by Inhibiting Arginase and Ornithine Decarboxylase with DFMO

Carol Colton

Duke University Medical Center, Durham, NC, USA

As recognized by ADDF, the search for AD therapeutics is best served by widening our search for potential mechanisms involved in the neurodegenerative process. Recently the brain's immune response has emerged as a critical therapeutic direction. Although immune changes in AD have been known for many years, the importance and mechanisms of an immune response in the disease process has been elusive. The production of pro-inflammatory mediators as seen in an acute immune response is the most familiar mechanism for immune mediated cell death and by-stander injury in the brain. Treatment with non-steroidal anti-inflammatory agents (NSAIDS) to block this immune action, however, has shown varied promise with multiple trial failures and more recently, complex outcomes. What has been largely overlooked is that immune cells also kill pathogens (and other cells) by regulation of amino acid metabolism. The most common mechanism of immune mediated nutrient deprivation involves an active reduction of environmental arginine levels, a semi-essential amino acid that is used in numerous biochemical pathways. My lab has explored how immune changes may result in neuronal death and associated AD-like pathology in a mouse model of AD. Our study of CVN-AD mice show that abnormal arginine utilization by microglia, the brains primary immune cell, is a result of pathological immunosuppressive mechanisms that begin with induction of increased arginase activity. This immune activity, in turn, facilitates polyamine production via the activation of ornithine decarboxylase (ODC). To restore the brain amino acid balance, we have interrupted the dysregulated immune-driven metabolic system at 2 points; that is, by treating CVN-AD mice with agents that reduce the activity of arginase or reduce ODC activity. The most beneficial response was found using difluromethylornithine (DFMO- an ODC inhibitor) to treat CVN-AD mice as a preventative before significant pathology is observed. Our studies indicate that early treatment with DFMO can reduce amyloid production, block learning and memory loss and prevent immune changes typically found in CVN-AD mice brain. Treatment at more advanced AD-like pathologies is less effective at the doses tested. Because DFMO has been widely considered as a treatment of cancer in the human population, can cross the blood brain barrier and has a reasonable safety toxicity profile, we are currently in the process of preparing an investigator initiated exploratory clinical trial to study early AD progression in a human population. We anticipate a 3- site trial may be possible in 2017.

**2015 ADDF/Harrington Scholar*

Alexandros Makriyannis, PhD, Northeastern University

Alexandros Makriyannis, PhD, is the George Behrakis Chair of Pharmaceutical Biotechnology at Northeastern University, Boston, MA, and is the Founder and Director of the Center for Drug Discovery. He is a highly successful medicinal chemist and is well recognized nationally and internationally for his important contributions in endocannabinoid research. Inventor of over 50 issued U.S. patents, Makriyannis played an important role in the discovery of this relatively newly characterized biochemical system that regulates many physiological functions including pain, neuroprotection, addiction, immunomodulation and cognition.

Over the past four decades, his laboratory has designed and synthesized some of the key pharmacological endocannabinoid probes that are widely used and serve as leads for the development of new medications. He has also made important contributions aimed at understanding the molecular basis of cannabinoid activity.

He has been a creative pioneer in the field of chemical biology where he combined the use of medicinal chemistry, biochemistry, molecular biology and biophysics. His work is recognized for its high level of originality. Some of his compounds are in advanced preclinical trials for the treatment of metabolic disorders and liver function, neuropathic pain, addiction and neurodegenerative diseases.

The Endocannabinoid System as a Therapeutic Target for Alzheimer Disease

Alexandros Makriyannis

Northeastern University, Boston, MA, USA

Fatty acid amide hydrolase (FAAH) inhibitors represent an innovative approach for the treatment of Alzheimer's disease (AD). In earlier work, we have shown that FAAH inhibitors provided neuroprotection in mice when challenged with the chemical kainic acid, and also have significantly decreased seizures using a brain rat model. Furthermore, preliminary data studying the role of FAAH inhibitors in animal models of AD have suggested that FAAH inhibition offers therapeutic potential to treat AD deficits, such as learning and memory. Thus, FAAH inhibition offers the opportunity of an entirely new target for disease-modification in AD. We have studied FAAH inhibitors in a neuroprotection model, where animals were treated with kainic acid to induce seizures. FAAH inhibitors significantly reduced seizure severity compared to animals that only received vehicle after the kainic acid treatment. We are currently pursuing studies to evaluate the most successful compounds in an AD model related to learning and memory. Soluble Aβ oligomers have been shown to potently block hippocampal long-term potentiation (LTP), an electrophysiological correlate of learning and memory. Currently, hippocampal slices are treated with FAAH inhibitors plus soluble oligo Aβ (oAβ) to study the neuropharmacological mechanisms of the inhibitors protection against oAβ toxicity.

Paul Thompson, PhD, University of Massachusetts Medical School

Paul Thompson, PhD, is a Professor and the Director of Chemical Biology in the Department of Biochemistry and Molecular Pharmacology at University of Massachusetts Medical School in Worcester, MA, where his research focuses on the development of novel therapeutics for a range of diseases including cancer, rheumatoid arthritis, inflammatory bowel disease, and lupus. In particular, he is a world leader in the biology and biochemistry of the Protein Arginine Deiminases.

Dr. Thompson received his BSc and PhD degrees from McMaster University in Canada before moving to the US to take a postdoctoral position with Philip Cole at the Johns Hopkins School of Medicine. He then moved to the University of South Carolina to begin his independent career before moving to the Department of Chemistry at The Scripps Research Institute, Scripps Florida, in May 2010. Dr. Thompson subsequently moved to UMASS Medical School in Aug 2014.

He has published more than 95 articles in major scientific journals including Nature, Cell, Nature Structural and Molecular Biology, and the Journal of the American Chemical Society. Dr. Thompson has also won a number of awards including a Canadian Institutes of Health Research Postdoctoral Fellowship and a Camille Dreyfus Teacher-Scholar Award.

Inhibiting Neutrophil Extracellular Trap (NET) Formation as a Novel Therapeutic Approach to Alzheimer's Disease

Paul Thompson

UMASS Medical School in Worcester, MA

Alzheimer's disease (AD) is characterized by a progressive deterioration of cognitive function, however, current therapeutic approaches have shown limited clinical utility. Inflammation is also pathological hallmark of AD and understanding the underlying mechanisms may facilitate the development of new treatments. Recent data show that neutrophils adhere in brain vessels and migrate inside the parenchyma where they release Neutrophil Extracellular Traps (NETs) in animal models of AD. Humans with AD also show evidence of neutrophils adhering and spreading inside brain venules as well as the parenchyma, where they produce NETs, suggesting that blocking NET formation may have therapeutic potential in AD.

Aberrant NET formation is a hallmark of other chronic systemic inflammatory diseases including rheumatoid arthritis (RA), lupus, ulcerative colitis, and atherosclerosis. NET formation is a pro-inflammatory form of cell death that results in the extrusion of chromatin to form a web-like structure that can either capture pathogens, promote blood clotting, or more generally promote inflammation. Notably, this process causes collateral tissue damage in chronic inflammatory diseases by releasing redox generating enzymes (i.e., MPO), active proteases (e.g., neutrophil elastase), and cytokines.

NET formation requires histone citrullination to facilitate the unraveling and extrusion of chromatin fibers. This post-translational modification of arginine to form citrulline is catalyzed by the Protein Arginine Deiminases (PADs). Notably, PAD inhibitors demonstrate remarkable efficacy in a range of NET driven diseases including RA, lupus, ulcerative colitis, and atherosclerosis. PAD inhibitors also show efficacy in other diseases, including multiple sclerosis, hypoxic ischemia, and spinal cord injury whose etiology may also involve aberrant NET formation.

Given the evidence supporting a role for neutrophils and NET formation in the etiology of AD, the PIs seek to test the hypothesis that aberrantly upregulated NET formation contributes to the pathology of AD and that PADs inhibitors represent a novel therapeutic strategy for AD.

Shijun Zhang, PhD, Virginia Commonwealth University

Shijun Zhang, PhD, is currently an associate professor of medicinal chemistry at the School of Pharmacy, Virginia Commonwealth University (VCU).

Dr. Zhang received his PhD with a focus on medicinal chemistry from Wayne State University in 2014, and then moved to University of Minnesota to finish his postdoctoral training. He joined the School of Pharmacy, VCU in 2017 as a faculty member.

The enduring research theme in Dr. Zhang's laboratory has been an interest in development of small molecule compounds as chemical tools and potential therapeutic agents for CNS and inflammatory disorders. Specific therapeutic areas that Zhang's laboratory has been working on include Alzheimer's disease, multiple sclerosis, traumatic brain injury, and acute myocardial infarction.

Development of Novel NLRP3 Inflammasome Inhibitors towards Alzheimer's Disease

Shijun Zhang

Virginia Commonwealth University, Richmond, VA, USA

Neuroinflammation and the NLRP3 inflammasome, the regulator of the maturation and production of IL-1ß, have been indicated a critical role in the pathogenesis of Alzheimer's disease (AD). Therefore, it would be of significant importance to develop novel NLRP3 inflammasome inhibitors with well-defined mode of action (MOA), which will complement ongoing molecular and genetic studies, help further unravel the roles of NLRP3 inflammasome in the pathogenesis of AD, and ultimately facilitate the development of novel NLRP3 inflammasome inhibitors as effective AD treatments. Recently, we have developed a small molecule and selective NLRP3 inflammasome inhibitor that shows both in vitro and in vivo activities by blocking the formation of the NLRP3 inflammasome complex. In this presentation, data from mechanistic studies and transgenic mouse AD model will be provided to reveal the mode of action and the effects on AD pathologies and cognitive functions of this small molecule inhibitor. Structure-activity relationship studies will also be discussed to provide guidance for further structural optimization of this chemical scaffold.

Danna Zimmer, PhD, University of Maryland School of Medicine

Danna Zimmer, PhD, is an Associate Professor in the Department of Biochemistry & Molecular Biology and member of the Marlene and Stewart Greenebaum Cancer Center at the University of Maryland School of Medicine in Baltimore, MD. She also serves as Section Leader for the In Vivo Biology & Drug Testing (IVBDT) group within the Center for Biomolecular Therapeutics (CBT), a system-wide academic drug discovery center.

As leader of the IVBDT group, Dr. Zimmer assists scientists in academia and industry with in vivo target validation, pharmacokinetic, pharmacodynamic and efficacy studies for lead therapeutics and diagnostics for oncology, infectious diseases, neurological disorders and metabolic diseases. Projects include small molecules as well as complex biologics, and represent the entire spectrum of the drug discovery pipeline from target identification to pre-clinical candidates.
Her own research program focuses on the development of pharmacological strategies for normalizing aberrant calcium signaling and inflammation in neurological disorders.

Humanization of a First-in-Class Anti-Inflammatory for Alzheimer's Disease Therapy

Danna Zimmer

University of Maryland School of Medicine, Baltimore, MD, USA

There is an urgent need to identify first-in-class agents for the treatment of Alzheimer's disease (AD) that have a high probability of clinical success. We are developing an innovative technology that uses passive immunotherapy with an antibody directed against a novel proinflammatory ligand, S100B, to block a detrimental "cytokine cycle" that drives AD. Studies from our group and others in a variety of pre-clinical models consistently demonstrate that S100B activation exacerbates and genetic ablation mitigates neuroinflammation and cognitive dysfunction. In proof-of-concept studies, our technology was as effective as genetic ablation in mitigating neuroinflammation, synaptic loss, AD pathology and cognitive dysfunction. Current studies focus on the identification of a humanized candidate that is suitable for clinical development and ultimately clinical trials in AD patients. Unlike other anti-inflammatory agents that have failed in clinical trials due to increased vascular risk, chronic inhibition of this target is not toxic nor does it cause immune suppression. In humans, genetic polymorphisms in the S100B gene are associated with increased risk of AD/dementia. In addition, S100B levels are elevated in familial and sporadic AD and directly correlate with cognitive dysfunction in some populations. Furthermore, the human and mouse S100B proteins differ by only a single amino acid, and modulate the same receptors in pre-clinical models and human AD specimens. The available clinical data, validated mechanisms of action in preclinical as well as clinical specimens, and absence of dose-limiting toxicities are strong indicators that this technology will ultimately benefit AD patients.

II. Novel Strategies for Neuroprotection

Chair: Lauren Friedman, PhD—Alzheimer's Drug Discovery Foundation

NeuroRestore—Development of Positive Allosteric Modulators of TrkA and TrkB
Pontus Forsell, PhD—AlzeCure Foundation

Targeting Tau: YTX-1357, a Novel, Oral BBB-Penetrant Small-Molecule in Development for AD and Other Tauopathies
Yukari Perrella, MBA—Yuma Therapeutics Corp.

Identification of Small Molecules That Modulate Microglia/Macrophage Uptake in Primary Human Cells
Elizabeth Bradshaw, PhD—Brigham and Women's Hospital

Selective HDAC2 Inhibitors for the Treatment of Cognitive Deficits in Alzheimer's Disease
Berkley Lynch, PhD—Rodin Therapeutics Inc.

Drug Development and Optimization of Compounds Stabilizing Ryanodine Calcium Channels
Grace Stutzmann, PhD—Rosalind Franklin University, The Chicago Medical School

VGF Peptide Delivery for Neuroprotection and the Suppression of Memory Impairment
Stephen Salton, MD, PhD—Icahn School of Medicine at Mount Sinai

SESSION CHAIR
Lauren Friedman, PhD, Alzheimer's Drug Discovery Foundation

Lauren Friedman, PhD, is the Associate Director of Scientific Programs at the Alzheimer's Drug Discovery Foundation (ADDF) where she supports the management of the ADDF's drug discovery portfolio by providing scientific and strategic review of preclinical drug discovery proposals and tracking program progress.

Additionally, she manages the ADDF ACCESS program, which provides a virtual network of contract research organizations (CRO) and consultants, and offers educational resources on drug discovery and CRO selection and management. Dr. Friedman completed her postdoctoral training at Columbia University where she studied modulators of autophagy in Alzheimer's disease. She earned a PhD in Neuroscience at the Icahn School of Medicine at Mount Sinai where she studied molecular mechanisms underlying the development and degeneration of brain circuits involved in autism and Parkinson's disease.

Dr. Friedman received a BS in Biopsychology from Tufts University. She has authored numerous peer-reviewed publications and is a member of the Society for Neuroscience, New York Academy of Sciences and the Association for Women in Science.

Pontus Forsell, PhD, AlzeCure Foundation

Pontus Forsell, PhD, is Project Leader at AlzeCure, responsibile for driving the in vitro pharmacology related questions and related studies.

Dr. Forsell is an in vitro pharmacologist by training with a special interest in neurodegeneration and inflammation. This was further strengthened by his postdoctoral studies at Merck (Montreal, Canada). In addition to this, Dr. Forsell also has more than 17 years of experience in drug discovery research within both, small biotech and large pharmaceutical companies (Merck and AstraZeneca).

Dr. Forsell has worked with external partners as well as with internal drug discovery projects. He has an extensive experience in management and laboratory work. He believes that the daily work in the laboratory is of high importance to all researchers and thus remains a principal scientist active in the lab.

The current project builds logically on his prior work on NGF/TrkA and BDNF/TrkB performed at AstraZeneca. He had worked for 3 years on drug discovery research focusing on ways to intervene with or enhance neurotrophin signaling. In parallel with that, he was responsible for assay development within Neuroscience at AstraZeneca as well as the part of the project generation team.

NeuroRestore—Development of Positive Allosteric Modulators of TrkA and TrkB

Pontus Forsell, PhD

AlzeCure Foundation, Huddinge, Sweden

Studies of the physiology and pathophysiology of NGF and BDNF have clearly demonstrated involvement of these two neurotrophins in neuronal and synaptic function and survival, supporting the hypothesis that a compound that potentiates these signaling pathways could be an effective treatment for several neurodegenerative disorders. Clinical trial with administration of NGF supports its role in Alzheimer's disease. Based on this growing body of evidence, the NeuroRestore project aims to develop a positive allosteric modulator (PAM) capable of enhancing the effects of BDNF/TrkB- and NGF/TrkA-signaling, for the treatment of Alzheimer's disease.

Specifically, we have screened approximately 30,000 structurally diverse compounds from several different compound libraries. Active compounds were re-tested at different concentrations and EC-curves were generated for approximately 35 compounds. We investigated six different chemical series more closely by near neighbor expansion. We have now limited our lead optimization effort to three series, which we currently are exploring, with medicinal chemistry efforts. We have improved potency approximately 100-fold for one of the series and we are continuing to improve potency, but also parameters such as solubility and pharmacokinetic properties. We are studying pharmacokinetic properties and BBB-crossover in mice. Recent data demonstrate that one of our series can attenuate scopolamine-induced memory impairment in mice.

We will present our screening cascade and results from the ongoing lead optimization.

Yukari Perrella, MBA, Yuma Therapeutics Corp.

Yukari Perrella is President and founder of Yuma Therapeutics.

Ms. Perrella has more than 25 years of experience in the healthcare field, including operations, business development, finance and research. Previously, she was vice president at Alseres Pharmaceuticals, a public neuroscience company.

Ms. Perrella held positions of increasing responsibilities at several privately owned and publicly traded biotechnology companies. She worked in research at Massachusetts General Hospital, Boston Children's Hospital and Harvard School of Public Health.

Targeting Tau: YTX-1357, a Novel, Oral BBB-Penetrant Small-Molecule in Development for AD and Other Tauopathies

Yukari Perrella

Yuma Therapeutics Corp., Brookline, MA, USA

Yuma Therapeutics Corporation has generated a novel, proprietary Hsp90 inhibitor, YTX-1357, as a clinical development candidate for the treatment of Alzheimer's disease (AD) and other tauopathies. Neurofibrillary tangles composed of the protein, Tau, are a hallmark of AD believed to be responsible for dementia; hyperphosphorylated Tau becomes insoluble and aggregates inside neurons. Hsp90 inhibition a) reduces Tau phosphorylation by inhibiting certain kinases and b) increases Tau clearance by enhancing solubility and proteasomal degradation via Hsp70 induction. YTX-1357 has excellent physicochemical characteristics, is orally bioavailable and penetrates the brain. In two transgenic mouse model studies of human tauopathy, mice treated daily for 28- and 84-days with YTX-1357 showed significant decreases in total Tau and phosphorylated Tau protein levels in the brain. Hsp90 target engagement by YTX-1357 was demonstrated by the significant increase of Hsp70 level in plasma. In the 84-day study, YTX-1357 demonstrated dose-dependent improvement in spatial learning and memory in behavioral tests, ameliorated brain atrophy and reduced NFT load. No weight change or adverse effects were observed during these studies. In vitro ADMET shows no hERG liability and no effects on the most clinically-relevant CYP450 isoforms. Yuma intends to conduct IND-enabling studies, file an IND and conduct a first-in-man clinical trial supported by novel biomarker strategies.

Elizabeth Bradshaw, PhD, Brigham and Women's Hospital

Elizabeth Bradshaw, PhD, obtained her doctorate from Tufts University, Department of Biochemistry. She then joined the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital and Harvard Medical School as a Research Fellow. In 2014, she was promoted to the rank of Assistant Professor.

A main focus of Dr. Bradshaw's work has been understanding the role of the innate immune system in complex diseases. Interestingly, the genome-wide association studies for Alzheimer's disease implicated the involvement of the innate immune system in this disease. Currently, one of Dr. Bradshaw's major research interests is the translation of findings from genome-wide association studies in neurodegenerative diseases, such as Alzheimer's disease, to molecular outcomes and potentially therapeutically targetable molecules.

Identification of Small Molecules That Modulate Microglia/Macrophage Uptake in Primary Human Cells

Elizabeth Bradshaw

Brigham and Women's Hospital, Boston, MA, USA

Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized by progressive cognitive decline and dementia. Genome-wide association studies (GWAS) have identified several genes that are not only associated with AD susceptibility, but are also key molecules for innate immune cells such as microglia and macrophages. We and others found that the innate immune locus, CD33, not only modified CD33 protein expression, but also uptake ability of the cells. This effect on the state of activation of the cells is present both in younger and older subjects, suggesting that the functional consequences of the CD33 locus may be exerted from the earliest stages of AD pathophysiology, which probably occurs in middle age. We hypothesized that altered myeloid function driven by high CD33 protein expression contributes to the onset of AD, and therefore pursued identification of chemical agents, using high throughput screening, that reduce CD33 surface concentration on monocytes of subjects with the risk allele to the levels seen on monocytes from subjects of the protective allele. Beyond the association of CD33, TREM2, a molecule important for phagocytosis in myeloid cells, has also been implicated in susceptibility to AD. While these innate immune cells are now at the forefront of identifying new therapeutic routes for AD, the question of whether to activate or suppress these cells maybe an oversimplification. We hypothesis that increasing phagocytic capacity of these cells to clear amyloid and cellular debris could be beneficial, but it should be done in a way that limits a pro-inflammatory cytokine response that could be detrimental and diminish the gains made by increasing phagocytic ability. We are now attempting to identify small molecules from libraries of biologically active compounds, which modulate uptake ability in primary human monocytes polarized with a CNS cytokine milieu. Small molecule hits will then be evaluated for production of a panel of cytokines. We hope that this study will provide an avenue for therapeutic advancement in AD by identifying drugs that could be repurposed for AD.

Berkley Lynch, PhD, Rodin Therapeutics Inc.

Berkley Lynch, PhD, has worked in neuroscience drug discovery for over fifteen years, focusing most recently on diseases of neurodegeneration. He holds a PhD in biochemistry from The Rockefeller University in NYC.

Dr. Lynch has expertise in a range of preclinical drug development activities, including biochemistry, cell and molecular biology, and in vitro and in vivo pharmacology. In his career, he has worked at ARIAD Pharmaceuticals, UCB, Link Medicine, and Dotmatics Inc. Dr. Lynch has lead research identifying targets, developing assays, and testing compounds using in vitro and in vivo models of neurological disorders ranging from epilepsy, to Alzheimer's and other neurodegenerative diseases.

He now serves as Senior Director of CNS Research at Rodin Therapeutics, focused on the development of HDAC inhibitors for treating neurodegenerative diseases.

Selective HDAC2 Inhibitors for the Treatment of Cognitive Deficits in Alzheimer's Disease

Berkley Lynch

Rodin Therapeutics Inc., Cambridge, MA, USA

Cognitive decline is a major symptom of Alzheimer's disease and other neurodegenerative pathologies. Effective therapeutics have been a challenge to develop, and new targets and approaches are needed. Rodin Therapeutics is developing small molecule inhibitors of histone deacetylases (HDACs); an enzyme family regulating gene expression, whose isoforms can exist in various multiprotein complexes. HDAC enzymes, and especially the isoform HDAC2 and protein complexes to which it belongs, have been strongly linked to synaptic plasticity, learning, and memory, and are promising therapeutic targets for Alzheimer's disease. The Rodin approach is to focus on achieving selective inhibition, using a combination of strategies. Progress in developing a platform of evidence supporting the development of Rodin compounds will be reviewed.

Grace Stutzmann, PhD, Rosalind Franklin University, The Chicago Medical School

Grace Stutzmann, PhD, is an Associate Professor in the Department of Neuroscience at The Chicago Medical School/Rosalind Franklin University of Medicine and Science, where she studies early cellular mechanisms of Alzheimer's disease and is developing novel therapeutic approaches to treat neurodegenerative disorders.

She received her PhD in Neuroscience from New York University/The Center for Neural Science in 1999. She then trained as a postdoctoral fellow in the Departments of Pharmacology and Psychiatry at Yale School of Medicine under George Aghajanian, MD, and then at UC Irvine in the Department of Neurobiology & Behavior, and The Institute for Brain Aging and Dementia with Frank LaFerla, PhD and Ian Parker, PhD, FRS.

In 2005, she moved to the Chicago Medical School as an Assistant Professor in the Department of Neuroscience, where she is currently. Dr. Stutzmann's research is and has been supported by the NIH, Alzheimer's Drug Discovery Foundation, the Alzheimer's Association, the American Federation for Aging Research, The Schweppe Foundation, and the VA.

Dr. Stutzmann has served on numerous NIH, foundation, and international review committees, as well as scientific advisory boards. She has presented over 60 lectures at international symposia and universities since 2006. Honors include fellowships from NIH, the Young Investigator Award from The Institute for Brain Aging and Dementia, The NeuroImaging Award from AFAR, and The Board of Trustees Award from RFUMS/CMS.

Drug Development and Optimization of Compounds Stabilizing Ryanodine Calcium Channels

Grace Stutzmann

Rosalind Franklin University, The Chicago Medical School, North Chicago, IL, USA

Alzheimer's Disease (AD) is a progressive neurodegenerative disease driven by multivariate mechanisms. Of particular interest is an early upregulation of the ER-localized ryanodine receptor (RyR2) in brains of MCI and AD patients, and in mouse models of AD. The increase in RyR-evoked Ca2+ release accelerates many AD features, including the synaptic deficits associated with memory impairment. Previous studies have used dantrolene, an RyR negative allosteric modulator, to demonstrated that RyR stabilization restores Ca2+ homeostasis, reduces amyloid and tau pathology, and preserves synaptic integrity in AD mice. In order to address the off-target effects and poor solubility of dantrolene, we have synthesized and screened a number of dantrolene analogs for their ability to normalize intracellular Ca2+ signaling in neurons from AD mice and model cells. Many of our novel compounds demonstrate RyR-regulating activity similar or superior to dantrolene but with improved medicinal chemistry properties. In addition, we have generated novel structural cores, distinct from dantrolene, that show RyR-modifying properties in cellular models of AD. Here we show therapeutic effects from a series of our novel compounds using real-time Ca2+ imaging, biochemical, neurophysiological and synaptic plasticity approaches. tested in animal and cell models We found that targeting the RyR2 restores normal intracellular Ca2+ signaling, preserves synaptic plasticity, and reduces histopathology in AD models. In conjunction with these studies, we are also optimizing new screening tool methods using human induced neurons (iN) derived from patient iPSC. Using whole cell patch clamp recordings and 2-photon calcium imaging from iN from AD and control patients, we detail defects in calcium dynamics and neuronal signaling in neurons derived from human AD patients and describe effects of our novel RyR-targeted compounds in these clinically-relevant neuronal models.

Stephen Salton, MD, PhD, Icahn School of Medicine at Mount Sinai

Stephen Salton, MD, PhD, attended the University of Pennsylvania, graduating with magna cum laude honors in Biochemistry. He completed the MD/PhD program at New York University School of Medicine, and following an internship and residency in internal medicine at Bellevue Hospital in New York, conducted postdoctoral research in molecular neuroendocrinology at Columbia University College of Physicians and Surgeons and Mount Sinai School of Medicine.

Dr. Salton has received a number of academic/scientific honors including a Medical Scientist Training Program Award, Pfizer Post-Doctoral and Scholar Awards, Pew Scholars Award in the Biomedical Sciences, Irma T. Hirschl-Monique Weill-Caulier Career Scientist Award, and NARSAD van Ameringen Investigator Award. He has held faculty positions at the Icahn School of Medicine at Mount Sinai since 1989 and is currently a tenured Professor in the Departments of Neuroscience and Geriatrics.

Dr. Salton's molecular neurobiology lab investigates the mechanisms and gene products that mediate neurotrophic growth factor regulation of neural development and nervous system function, impacting the understanding of depression, memory, body weight control, neuropathic pain, and neurodegeneration. He additionally plays an active role in the broader educational mission of the institution, and contributes to a number of committees at Mount Sinai that oversee its academic and teaching missions. Dr. Salton has been Co-Director responsible for overseeing the administration and operation of the Neuroscience Graduate Training Area since 2000, authoring the application securing Mount Sinai's Neuroscience PhD granting program that was approved in 2007 by NYU and the NY State Education Dept, and is currently a PI of two NIH-supported T32 training programs.

VGF Peptide Delivery for Neuroprotection and the Suppression of Memory Impairment

Stephen Salton

Icahn School of Medicine at Mount Sinai, New York, NY, USA

Cognitive decline in Alzheimer's disease (AD) features decreased synaptic plasticity, lowered brain activity, and accelerated neuronal loss during the pathological progression of the disease. A major research goal has therefore been to identify therapeutic avenues that modify disease progression, and neurotrophins have historically been of particular interest in age- and disease-related cognitive dysfunction. VGF (non-acronymic) is a secreted neuronal and endocrine protein, expression of which is induced by neurotrophic growth factors, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). VGF and its C-terminal peptide, TLQP-21 (VGF peptides are named by their four N-terminal amino acids and length), protect cells from ER-stress and neuroexcitotoxicity-induced cell death, while treatment with the VGF C-terminal peptide TLQP-62 increases hippocampal neurogenesis, modulates synaptic plasticity, and improves contextual fear memory. Previous work from our lab and others has demonstrated a significant decline in VGF expression in the brains of patients with neurodegenerative disease, including AD and amyotrophic lateral sclerosis (ALS). Moreover, in a recent longitudinal study utilizing high-resolution proteomics analysis, VGF was reported as a strong candidate biomarker of AD progression, with an estimated 10% decrease in CSF levels of VGF per year in diseased patients but not in age-matched controls. These data indicate that decreased VGF expression in brain and CSF is associated with neurodegenerative disease. Could VGF be mechanistically involved in disease pathogenesis and/or progression? We hypothesize that in AD patients, the decline in brain VGF levels could, under the destructive effects of toxic Abeta42 and phospho-Tau accumulation, further impair synaptic integrity and accelerate neuronal cell death. We propose to investigate whether chronic icv delivery of specific VGF-derived peptides, including TLQP-62 and TLQP-21, reverses and/or delays onset of memory deficits and progressive neurodegeneration in the Alzheimer's disease mouse model, 5xFAD, which develops both pathological amyloid deposits and hippocampal-based memory dysfunction at 4-6 months of age. By completing the proposed experiments, we will establish whether delivery of VGF peptides or small molecule analogs could represent alternative treatment modalities for AD patients.

Andrew Koemeter-Cox, PhD, Alzheimer's Drug Discovery Foundation

Andrew Koemeter-Cox, PhD, works on the ADDF's scientific initiatives, including the ACCESS program. In this capacity, he assists with reviews of funding proposals and manages the ACCESS website, which connects researchers with CROs and other drug discovery expertise.

Dr. Koemeter-Cox was most recently a postdoctoral fellow at the Icahn School of Medicine at Mount Sinai, where he studied the epigenetics of axon regeneration in the context of spinal cord injury. From 2007 until 2009, he was a research technician with the United States Army Medical Research Institute of Chemical Defense (USAMRICD), assisting with studies on neuroprotection strategies. Dr. Koemeter-Cox earned a doctorate in biomedical science from The Ohio State University College of Medicine and a bachelor's degree in biochemistry from the University of Delaware. He is a member of the New York Academy of Sciences, where he serves as a mentor for several programs.

KEYNOTE SPEAKER
Mansuo Hayashi, PhD, Eli Lilly & Co., Inc.

Mansuo Hayashi, PhD, focuses on discovering novel therapies for neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease.

During a decade of industrial experience at Merck Research Laboratories, Chugai/Roche Pharmaceuticals and Eli Lilly, she has led several disease-modifying (tau) and symptomatic discovery programs through stages from target validation to preclinical candidate selection, and established extensive expertise in managing both small and large molecule discovery programs.

Dr. Hayashi obtained her PhD in Molecular Biology at Princeton University, and conducted postdoctoral research at the MIT laboratory of Dr. Susumu Tonegawa (1987 Nobel Laureate).

New Advances in Drug Discovery for Alzheimer's Disease

Mansuo Hayashi

Eli Lilly & Co., Inc., Indianapolis, IN, USA

Drug discovery for Alzheimer's Disease (AD) has primarily focused on targeting the amyloid plaques and neurofibrillary tangles, two pathological hallmarks of AD, and aimed to prevent the formation and/or promote the clearance of Abeta or tau protein aggregates. Many of these new therapeutic approaches have emerged as we gain novel mechanistic insights of these processes, and notably, develop experimental tools and assays to interrogate these mechanisms. One such example is the hypothesis of prion-like spread of tau, which originated from anatomical findings from postmortem AD brains (Braak staging) and has been strongly supported by recent in vitro and in vivo experimental data demonstrating the trans-cellular spread of tau pathology. Targeting the extracellular spreading tau, academic and industry teams have leveraged the scientific insights and assays to execute tau immunotherapy programs, advancing several vaccines and antibodies into the clinic. With new AD genes identified via modern genetic tools like GWAS (genome wide association study), we envision the synergy between academia and industry will not only reveal key insights of these genes/pathways in AD pathogenesis, but also yield viable drug targets.

III. Advancing Therapies into Clinical Trials

Chair: Penny Dacks, PhD—Alzheimer's Drug Discovery Foundation

Advancing Development of Novel MI PAMs Toward Clinical Testing
Jerri Rook, PhD—Vanderbilt University
(2015 ADDF/Harrington Scholar)

Effect of Candesartan on Prodromal Alzheimer's Disease and Its Related Biomarkers
Ihab Hajjar, MD—Emory University School of Medicine

Therapeutic Effects of Nilotinib in Neurodegenerative Disease
Raymond Scott Turner, MD, PhD—Georgetown University

Nabilone in Agitated Patients with Alzheimer's Disease: A Pilot Study of Safety and Efficacy
Krista Lanctôt, PhD—Sunnybrook Research Institute, University of Toronto

Accelerating a Phase III MCI Clinical Trial with Phase I Evaluation of a Novel Extended-Release Levetiracetam Formulation
Sharon Rosenzweig-Lipson, PhD—AgeneBio Inc/IVS Pharma Consulting

SESSION CHAIR

Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation

Penny Dacks, PhD, is the Director for Aging and Alzheimer's Prevention at the ADDF. Dr. Dacks is responsible for all aspects of this program, started in 2012 with the mission to evaluate, communicate and accelerate the development of scientific evidence for proposed strategies to promote health aging and prevent Alzheimer's disease, related dementias and cognitive aging.

As part of this mission, Cognitive Vitality (www.CognitiveVitality.org) was launched in early 2014 to provide an open resource to the public on the state-of-the-science behind any and all suggested preventative therapies. The program has internal evaluations on more than 120 potential preventative therapies and works to accelerate the development of prevention therapies with strategic grant funding, conferences, advisory panels and peer-reviewed scientific papers. Active areas of interest include epidemiological evidence on potential preventative treatments, validation of preventative treatments with short-term biomarker-based randomized trials, computational modeling and big-data approaches to predict therapeutic efficacy, crowd-sourcing of data and data analytics and the application of aging biology to therapeutic development.

Dr. Dacks trained in neuroscience at the Mount Sinai School of Medicine, the University of Arizona, and Queen's University (Canada) with individual fellowships from the National Institute of Health, the Evelyn F. McKnight Brain Research Foundation, the ARCS Foundation and the Hilda and Preston Davis Foundation. She has authored over 18 peer-reviewed scientific articles and is a member of the Society for Neuroscience, the Gerontological Society of America, the Endocrine Society and the Association for Women in Science.

Jerri Rook, PhD, Vanderbilt University*

Jerri Rook, PhD, received her PhD degree in Pharmacology from the University of Kansas Medical Center. She then pursued her postdoctoral studies in the laboratory of P. Jeffrey Conn, Ph.D. at Vanderbilt University before being appointed Assistant Professor of Pharmacology and the Vanderbilt Center for Neuroscience Drug Discovery.

Dr. Rook has received multiple awards for her scientific contributions including the Butler-Williams Scholars Award from the National Institute on Aging, the Alzheimer's Drug Discovery Foundation and Harrington Discovery Institute Scholar Award, and the Vanderbilt Faculty Research Scholar Award. Her research focuses on the mechanisms underlying the progression of neurodegeneration and the discovery of novel therapeutic strategies for Alzheimer's disease.

Advancing Development of Novel M1 PAMs Toward Clinical Testing

Jerry Rook

Vanderbilt Center of Neuroscience Drug Discovery, Nashville, TN, USA

A significant number of preclinical behavioral and human clinical studies provide strong evidence that enhanced cholinergic transmission or activation of muscarinic acetylcholine receptors (mAChRs), notably the M1 subtype, have exciting therapeutic potential for the treatment of cognitive impairments of Alzheimer's disease (AD). However, previous M1 activators have failed in clinical development due to a lack of true specificity for M1 and adverse effects associated with activation of other mAChR subtypes (M2-M5). Recently, our group has developed a highly potent, selective series of M1 positive allosteric modulators (PAMs) with enhanced physiochemical and pharmacokinetic properties for in vivo studies, providing an unprecedented opportunity to evaluate the potential of selective potentiation of M1 as a novel target for the treatment of symptoms associated with AD. As opposed to direct activation of M1, PAMs dramatically potentiate the response of the receptor to its endogenous ligand acetylcholine and offer high selectivity while avoiding unwanted side-effects seen with direct activation. Optimized M1 PAMs have been rigorously characterized to establish their potency and efficacy at M1 and excellent selectivity versus other mAChR subtypes. In addition, ancillary pharmacology depicts a clean profile at other clinically relevant receptors. Pharmacokinetic (PK) studies in rats and nonhuman primates demonstrate ideal oral bioavailability and CNS exposure. Moreover, behavioral studies confirm robust efficacy in multiple preclinical rodent models of improved cognitive performance. Finally, no adverse effects were observed in either rodents or NHPs.

**2015 ADDF/Harrington Scholar*

Ihab Hajjar, MD, Emory University School of Medicine

Ihab Hajjar, MD, is a geriatrician and clinical investigator with a focus on the link between hypertension and vascular disease with Alzheimer's disease. He is studying the effects of antihypertensive medications that modulate the renin angiotensin system on both prevention of cognitive decline and as potential therapeutic modalities for early dementia. Dr. Hajjar has published more than 50 scientific articles and book chapters and has been funded by grants from National Institute of Health and other governmental and private organizations since 2001. Dr. Hajjar sees patients with cognitive disorders and/or vascular risk factors at the Memory Disorder Clinic at Emory University.

Effect of Candesartan on Prodromal Alzheimer's Disease and Its Related Biomarkers

Ihab Hajjar

Emory University School of Medicine, Atlanta, GA, USA

Accumulating evidence suggests that the brain renin angiotensin system is involved in the amyloid hypothesis (Ab cascades) and vascular mechanisms of Alzheimer's disease. Studies in animal models suggest that ARBs have cognitive protective effects that are related to their ability to 1) decrease production and oligomerization and 2) increase degradation of Ab and their vascular effects (improve blood–brain barrier, restore endothelial function, decrease inflammation, and increase cerebral blood flow). Human observational studies have further suggested that ARB use is associated with decreased risk of Alzheimer's disease and protection against future cognitive decline. Our work has suggested that ARB use is associated with decreased amyloid deposition in the brain in Alzheimer's disease and can provide cognitive protection in those with mild cognitive impairment, a prodromal state for Alzheimer's disease, and dementia. Our two ongoing studies testing the use of ARBs in hypertension with MCI and in prodromal AD without hypertension will answer the question of whether ARBs should be considered for treatment for AD.

Raymond Scott Turner, MD, PhD, Georgetown University

Scott Turner, MD, PhD, is Professor of Neurology and Director of the Memory Disorders Program at Georgetown University Medical Center, Washington, DC. Previously, he was Chief of the Neurology Service at the VA Ann Arbor Healthcare System and Associate Professor and Associate Chair in the Department of Neurology, University of Michigan. He was awarded MD and PhD degrees from Emory University, Atlanta, and completed his internship, residency, and fellowship at the University of Pennsylvania, Philadelphia. He was recruited to Georgetown in 2008.

Dr. Turner has received numerous prestigious awards, including a fellowship from the Howard Hughes Medical Institute and a Paul Beeson Scholarship. He lectures widely, serves as a reviewer for granting agencies and biomedical journals, and has published more than seventy peer-reviewed papers, editorials, and book chapters. He is board-certified in Psychiatry and Neurology.

The Memory Disorders Program at Georgetown University provides clinical care to individuals with memory disorders and seeks individuals with mild cognitive impairment or mild dementia due to Alzheimer's disease, and their study partners, to join us in research. The goals are to discover and validate new biomarkers in addition to discovering more effective strategies to prevent and treat individuals with dementia due to Alzheimer's disease.

Therapeutic Effects of Nilotinib in Neurodegenerative Disease

R. Scott Turner, MD, PhD[1], Fernando Pagan, MD[2], and Charbel Moussa, MD, PhD[1]

[1]Department of Neurology, Georgetown University, and [2]MedStar Georgetown University Hospital, Washington, DC, USA

The two defining neuropathologies of Alzheimer's disease (AD) are neurofibrillary tangles (NFTs) comprised primarily of phosphorylated Tau (pTau) and Aβ/amyloid plaques. Aβ/amyloid and pTau/NFT accumulation with aging may be due in part to impaired autophagic clearance resulting in proteostasis, protein aggregates, and neurotoxicity. Thus, promotion of autophagy may degrade Aβ and pTau to prevent or slow progressive cognitive decline. Activation of the tyrosine kinase *Abl* is associated with increased pTau in animal models of AD and in human AD brain. The *Bcr-Abl* inhibitor nilotinib (Tasigna) is an FDA-approved tyrosine kinase inhibitor (TKI) for the treatment for chronic myeloid leukemia. Our pre-clinical data with animal models of neurodegeneration demonstrate that nilotinib penetrates the blood-brain barrier, promotes autophagic degradation of Aβ/amyloid and pTau/NFTs, attenuates neuroinflammation, and improves cognition. A pilot study of low-dose nilotinib treatment in individuals with Parkinson's disease or Lewy body dementia demonstrated its safety and tolerability, as well as indications of clinical efficacy (Pagan et al., J. of Parkinson's disease, 2016, in press). We hypothesize that Nilotinib will alter CSF Aβ and pTau levels, modulate blood and CSF immune markers, and improve cognitive function in subjects with mild to moderate AD. Specifically, we propose a randomized, double-blind, Phase 2 study to repurpose nilotinib and determine its safety and tolerability in 42 subjects with mild-moderate dementia and a biomarker-supported diagnosis of AD. We will determine the effects of nilotinib treatment on CSF Aβ40, Aβ42, total Tau, and pTau, inflammatory markers in CSF, serum, and plasma, and cognitive function. With proven safety and tolerability, and suggestions of efficacy, results from this study may support a larger randomized, double-blind, placebo-controlled, multi-center Phase 3 trial of nilotinib for AD. TKI-mediated promotion of autophagy may be a novel treatment strategy for individuals with neurodegenerative disorders of aging characterized by proteostasis.

Krista Lanctôt, PhD, Sunnybrook Research Institute, University of Toronto

Krista L. Lanctôt, PhD, is a clinical pharmacologist, having received her PhD from the Department of Pharmacology, University of Toronto in 1998, with additional training in pharmacoepidemiology. She is currently a Senior Scientist in the Hurvitz Brain Sciences Program at Sunnybrook Research Institute, the Head of Neuropsychopharmacology Research and the Executive Director of the Medical Outcomes and Research in Economics (MORE®) Research Centre, a research group focusing on outcomes research. She is a Full Professor in the Departments of Psychiatry and Pharmacology/Toxicology, University of Toronto, Toronto, Ontario, Canada.

Dr. Lanctôt is an active researcher in clinical pharmacology and has published over 200 manuscripts. Her research has focused on optimizing the pharmacotherapy of cognition and neuropsychiatric symptoms associated with dementia and in predementia states. In addition to running randomized controlled trials, her group uses biomarkers, pharmacologic challenge, neuroimaging and genetics to further understand these symptoms and target pharmacotherapy. She also teaches at undergraduate and graduate levels through her appointment at the University of Toronto.

Nabilone in Agitated Patients with Alzheimer's Disease: A Pilot Study of Safety and Efficacy

Krista Lanctôt

Sunnybrook Research Institute, University of Toronto, Toronto, ON, Canada

Agitation is frequently observed in patients with Alzheimer's disease (AD), particularly in patients at moderate to severe stages. Agitation is associated with increased caregiver burden, decreased quality of life, more rapid disease progression and increased weight loss. While antipsychotics have randomized controlled trials supporting their use for agitation in AD, they have only modest efficacy and serious safety concerns such as increased risk of mortality. As such, identifying potential new therapeutic agents for the treatment of agitation in AD is imperative.

With the development of synthetic Δ9-tetrahydrocannabinol (THC) analogues, the therapeutic potential of cannabinoids can now be evaluated. THC analogues are cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) agonists. As demonstrated in other populations, CB1 agonists induce sedation and analgesia and increase appetite; key problems in those with advanced AD. Further, a recent case series suggested positive effects of the synthetic THC analogue nabilone on agitation in dementia. Importantly, in addition to psychotropic effects, emerging evidence suggests CB2 agonism confers neuroprotective (inhibit Aβ-induced microglial activation and excitotoxicty) and anti-inflammatory abilities, which can decrease oxidative stress, in stark contrast to the negative effects of antipsychotics. As such, this system is of high potential relevance to agitated patients with AD.

This will be a double-blind, cross-over randomized placebo controlled trial (RCT) comparing 6 weeks of nabilone to 6 weeks of placebo, with a 1-week washout preceding each treatment phase. Eligible patients (n=40) with moderate-to-severe AD and clinically significant agitation will be randomized to receive either nabilone (.5 – 2 mg) or placebo (1:1 ratio) for 6 weeks each. The primary outcome will be agitation, as measured by the Cohen-Mansfield Agitation Inventory. The secondary outcomes will include overall behaviour, cognition and global impression. Exploratory outcomes include pain, nutritional status, safety and biomarkers of oxidative/nitrosative stress, inflammation and cholesterol metabolism. Our goal is to determine whether nabilone is a safe and efficacious pharmacological option for managing agitation, with benefits for pain and weight. Positive results would warrant a larger study with potential, practice-changing impact, and as such, would fill a therapeutic gap.

Sharon Rosenzweig-Lipson, PhD, AgeneBio Inc/IVS Pharma Consulting

Sharon Rosenzweig-Lipson, PhD, is AgeneBio's Vice President of Research and Development. In this position, she provides expertise in screening strategies, in vivo models, translation and early clinical development strategy.

Dr. Rosenzweig-Lipson is also the founder of IVS Pharma Consulting. She has more than 20 years of experience developing compounds for psychiatric and neurologic indications in the pharmaceutical industry, including American Cyanamid, American Home Products, Wyeth and Pfizer. Dr. Rosenzweig-Lipson has successfully led teams from the earliest exploratory studies through to Phase II Proof of Concept Trials.

Prior to her current positions, Dr. Rosenzweig-Lipson held the roles of Head of Translational Neuroscience and In Vivo Head of Psychiatry at Wyeth Research.

Dr. Rosenzweig-Lipson received her BA in Biological Basis of Behavior from the University of Pennsylvania and her PhD in Behavioral Neuroscience from Harvard University.

Accelerating a Phase III MCI Clinical Trial with Phase I Evaluation of a Novel Extended-Release Levetiracetam Formulation

Sharon Rosenzweig-Lipson

AgeneBio, Baltimore, MD, USA

AGB101 (220 mg; low dose levetiracetam) is poised to enter Phase III clinical development for the treatment of MCI due to AD (HOPE4MCI) trial. AGB101 is hypothesized to slow progression of MCI due to AD by restoring entorhinal/hippocampal network balance. During this phase of the disease, fMRI studies show hippocampal overactivity and entorhinal cortex under activity. As shown in a Phase II study, AGB101 restores this network balance by attenuating hippocampal overactivity and restoring entorhinal cortex activity. Drug levels in amnestic MCI patients were determined to be 2.9 ± 0.29 μg/mL (mean ± sem) for the 125 mg cohort and 4.4 ± 0.53 ug/mL for the 250 mg cohort. The ineffective dose of 500 mg provided a drug level of 7.91 ± 0.92 ug/mL. These levels of drug exposure are well below typical ranges for efficacy of levetiracetam as an antiepileptic agent, where doses of 1000-3000 mg/day are typical, achieving levels of 10-40 μg/mL. The efficacious exposures observed in amnestic MCI patients were consistent with animal studies in age-impaired rats in which exposures of 1.9 – 3.9 μg/mL were efficacious and an exposure of 7.8 μg/mL was ineffective.

In preparation for the Phase 3 trial, two novel low dose extended release formulations of AGB101 (low dose levetiracetam) were developed to ensure once daily dosing at the efficacious exposures observed in Phase 2. We conducted a crossover food effect study of the novel formulations of AGB101 at doses of 190 and 220 mg. The purposes of the study were to confirm the exposures associated with efficacy in the Phase 2 trial and in age-impaired rats were observed from the novel formulations and were maintained over the course of the daytime hours, to confirm the formulation PK profile was consistent with once daily dosing and to determine if there were any food effects on the PK profile. AGB101 (220 mg) met all preset criteria. Sustained plasma levels of levetiracetam consistent with Phase 2 efficacy were observed over a 14-hour period. The PK profile was consistent with an extended release formulation suitable for once daily dosing. There were no food effects on Cmax or AUC. This dose/formulation is suitable for use in the upcoming Phase 3 program in MCI due to AD.

IV. Strategies to Accelerate Clinical Development for Alzheimer's and Related Dementias

Chair: Nick McKeehan—Alzheimer's Drug Discovery Foundation

Development of the O-GlcNAcase Inhibitor ASN-561 for the Treatment of Tauopathies
Dirk Beher, PhD—Asceneuron SA

The Evolving Analytical Landscape in Laboratory Medicine: Applications to the Design of TDP-43 Biofluid Diagnostics for FTD
Mari DeMarco, PhD—University of British Columbia
Funded through the ADDF/Association for Frontotemporal Degeneration Partnership Program

Combined CSF Biomarkers and GBA Genotype for Diagnosis of LBD
Lawrence Honig, MD, PhD—Columbia University

Low-dose Lithium for the Treatment of Behavioral Symptoms in FTD
Edward Huey, MD—Columbia University
Funded through the ADDF/Association for Frontotemporal Degeneration Partnership Program

Repurposing the PDE5 Inhibitor Tadalafil for Vascular Cognitive Impairment: A Test of Concept in Older People
Atticus Hainsworth, PhD—St George's University of London
Funded through ADDF's Partnership with the Alzheimer's Society, UK

SESSION CHAIR

Nick McKeehan, Alzheimer's Drug Discovery Foundation

Nick McKeehan is a member of the ADDF's Aging and Alzheimer's Prevention program. He evaluates the scientific evidence for and against therapies to promote brain health and/or prevent Alzheimer's disease at our website CognitiveVitality.org and contributes regularly to the site's blog.

Mr. McKeehan previously served as Chief Intern at Mid Atlantic Bio Angels (MABA) and was a research technician at Albert Einstein College of Medicine investigating repair capabilities of the brain. Mr. McKeehan received a bachelor of science degree in biology from Purdue University, where he was awarded a Howard Hughes Scholarship. He also writes about the biotechnology industry for 1st Pitch Life Science.

Dirk Beher, PhD, Asceneuron SA

Dirk Beher, PhD, is the Chief Executive Officer, a Founder and member of the Board of Directors of Asceneuron SA. Under his leadership, Asceneuron has raised CHF 36 million from leading venture capital firms besides from securing alternative funding. Since its inception, he has strategically positioned the company as an emerging leader in the field of orally bioavailable drugs for treating orphan tauopathies and Alzheimer's disease.

Dr. Beher brings more than 24 years of experience in the field of Alzheimer's disease/neurodegeneration and spent over 18 years in drug discovery in pharma and biotech. Prior to Asceneuron, he has held various positions with increasing responsibilities at major pharmaceutical and biopharmaceutical companies such as Merck Sharp & Dohme (Merck & Co.), Amgen and Merck KGaA in locations around the globe.

Dr. Beher holds a PhD and an MS in Biology from the Ruprecht-Karls University Heidelberg, Germany. He holds seven patents and currently authors 49 peer-reviewed publications and reviews.

Development of the O-GlcNAcase Inhibitor ASN-561 for the Treatment of Tauopathies

Dirk Beher

Asceneuron SA, Lausanne, Switzerland

The formation of intraneuronal neurofibrillary tangles (NFTs) consisting of abnormally hyperphosphorylated tau protein is a key contributor to the neurodegeneration in Alzheimer's disease and other tauopathies. In preclinical models, this pathological process can be pharmacologically modulated with specific inhibitors of the glycoside hydrolase O-GlcNAcase. Mechanistically, O-GlcNAcase inhibition blocks the removal of O-linked N-acetylglucosamine (O-GlcNAc) moieties from serine and threonine residues in the tau protein. This leads to an accumulation of O-GlcNAcylated tau that appears to be less prone to aggregation into toxic oligomers and NFTs. We describe the development of the clinical candidate O-GlcNAcase inhibitor ASN-561 starting from a lead optimization campaign. ASN-561 is a highly brain penetrant molecule which in a preclinical proof of concept study reduced tau pathology in P301S tau transgenic mice. Given its drug-like properties, the further development of this molecule is warranted to ultimately enable human clinical studies in patients suffering from tauopathies.

Mari DeMarco, PhD, University of British Columbia

Mari DeMarco, PhD, DAABCC, FACB, is a clinical assistant professor of Pathology and Laboratory Medicine at the University of British Columbia, a clinical chemist at St Paul's Hospital, and an investigator with the Centre for Heart Lung Innovation, in Vancouver, Canada. She received her PhD from the University of Washington, and completed her clinical chemistry fellowship at Washington University School of Medicine.

She is the recipient of the American Association for Clinical Chemistry award for Outstanding Scientific Achievement by a Young Investigator and has been named as a Michael Smith Foundation for Health Research Scholar. With a strong interest in bridging biomedical science, analytical chemistry and laboratory medicine, her research group specializes in new methodological approaches for quantitation protein biomarkers with an emphasis on advancing clinical diagnostics for neurodegenerative disorders.

The Evolving Analytical Landscape in Laboratory Medicine: Applications to the Design of TDP-43 Biofluid Diagnostics for FTD*

Mari DeMarco

University of British Columbia, Vancouver, BC, Canada

For FTD and related neurodegenerative disorders, biofluid diagnostics are in need for patient care (prognosis and diagnosis) and to assist in the quest for disease-modifying therapeutics (e.g. clinical trial enrolment). Publications and funding for biomarker discovery efforts have experienced exponential growth over the past 15 years; however, translation of these research findings into practical clinical tests has not followed a similar trajectory. In this session we will take stock of the current biomarker climate and translation pipeline. We will also explore the shifting analytical landscape in laboratory medicine, where immunoassays have for decades been the mainstay for protein biomarker identification and quantitation. Mass spectrometry, initially implemented in clinical laboratories due to its superior selectivity for small molecule analysis, is now spreading its influence into the protein sphere. Using real-world examples from our biomarker translation efforts, we will explore advantages and disadvantages of the evolving analytical landscape, and how we are leveraging this knowledge to accelerate clinical test development and implementation for neurodegenerative disorders.

**Funded through the ADDF/Association for Frontotemporal Degeneration Partnership Program*

Lawrence Honig, MD, PhD, Columbia University

Lawrence Honig, MD, PhD, is a Professor of Neurology at Columbia University Medical Center. He is a clinical neurologist and a neuroscientist, with particular specialization with respect to degenerative conditions affecting the brain, including Alzheimer's disease. He holds appointments in the Neurology Department, the Gertrude H. Sergievsky Center, and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain. He received his undergraduate A.B. degree from Cornell University College of Arts and Sciences, his PhD doctoral degree in Molecular Biology at the University of California at Berkeley, and his MD medical doctoral degree at the University of Miami (Florida). He subsequently trained in Internal Medicine and Neurology at Stanford University Medical Center (California). He held faculty appointments at Stanford University School of Medicine, and then at the University of Texas Southwestern Medical Center at Dallas, prior to his move to Columbia University in New York City in the year 2000.

Dr. Honig's interests are focused on aging and neurodegenerative disorders including Alzheimer disease, Lewy Body Dementia, Frontotemporal dementia, and Creutzfeldt-Jakob disease syndrome, immune-mediated encephalitides. His activities include clinical care, drug study and observational clinical research, and translational investigations on molecular biomarkers of aging and dementia.

Combined CSF Biomarkers and GBA Genotype for Diagnosis of LBD

Lawrence Honig

Taub Institute for Research on Alzheimer's Disease, Columbia University, New York, NY, USA

Edward Huey, MD, Columbia University

Edward (Ted) Huey, MD, is an Assistant Professor of Psychiatry and Neurology at Columbia University College of Physicians and Surgeons (New York, NY), in the Departments of Psychiatry (Division of Geriatric Psychiatry) and Neurology (Division of Aging and Dementia), the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, and the Gertrude H. Sergievsky Center.

Dr. Huey obtained his BA in psychology from Yale University. He received his medical degree from the Stanford University School of Medicine in 1999. He completed an internship and a residency in Adult Psychiatry at the Stanford University Medical Center in Stanford, California. He was elected to be the chief resident for the program in his final year of residency. He then completed a clinical research fellowship and was an Assistant Clinical Investigator in the Cognitive Neuroscience Section of the National Institute of Neurological Disorders and Stroke in the National Institutes of Health in Bethesda, MD. He was then the Director of Clinical Science of the Litwin-Zucker Research Center for the Study of Alzheimer's Disease and Memory Disorders of the Feinstein Institute, North-Shore / Long Island Jewish Medical Center. He joined the Columbia University faculty in 2010.

Dr. Huey's research has focused on patients with frontotemporal lobar degeneration (FTLD) and related disorders. He studies the genetics of FTLD and is interested in the range of phenotypes associated with mutations that can cause FTLD. He also uses imaging in patients with FTLD and brain injury to explore the neuroanatomy of complex behavior, neuropsychiatric symptoms, and emotion in patients with brain dysfunction. A third interest is in the role of the dopamine system in the pathogenesis and treatment of the symptoms of FTLD. He is the recipient of a NIH / NINDS Pathway to Independence Award to research novel medication treatments and imaging biomarkers for FTLD. He sees patients in the Lucy G. Moses Center for Memory and Behavioral Disorders of the Neurological Institute and in the Memory Disorders Center of the New York State Psychiatric Institute.

Low-dose Lithium for the Treatment of Behavioral Symptoms in FTD*

Edward Huey

Columbia University, New York, NY, USA

Frontotemporal dementia (FTD) is a progressive neurodegenerative illness that affects the frontal and anterior temporal lobes of the brain. Changes in behavior, including agitation, aggression, and repetitive behaviors, are common symptoms in FTD. We currently do not have good treatments for these symptoms in FTD. We will discuss the opportunities and challenges in the development of treatments for the symptoms of FTD and other non-Alzheimer's dementias, and how these treatments can inform and be informed by the research on treatments for the symptoms of Alzheimer's disease, including a discussion of the first simultaneous trials of a treatment, low dose lithium, in patients with FTD and Alzheimer's disease.

**Funded through the ADDF/Association for Frontotemporal Degeneration Partnership Program*

Atticus Hainsworth, PhD, St George's University of London

Atticus Hainsworth, PhD, is a Senior Lecturer in Cerebrovascular Disease at St George's University of London, UK.

Dr. Hainsworth is an expert in the pathology of cerebral small vessel disease, the primary cause of vascular cognitive impairment. His interests are in the pathological processes that underlie small vessel disease and associated white matter lesions. He has explored pathogenic mechanisms of small vessel disease in human brain tissue derived from large cohorts (primarily the OPTIMA and MRC-CFAS cohorts). He has also provided systematic reviews of animal models relevant to VCID (most recently for Stroke, Madigan et al. 2016).

Dr. Hainsworth received his undergraduate training in Natural Sciences from Cambridge University and his PhD in Physiology & Biophysics from Rush Medical Center, Chicago. He is Chief Investigator on the PASTIS trial, jointly-funded by ADDF and the UK Alzheimers Society, testing tadalafil for repurposing in vascular cognitive impairment.

Repurposing the PDE5 Inhibitor Tadalafil for Vascular Cognitive Impairment: A Test of Concept in Older People*

Atticus Hainsworth

St George's University of London, London, United Kingdom

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The main cause of vascular cognitive impairment (VCI) is cerebral small vessel disease. There are no licensed medications for small vessel disease or for VCI. Tadalafil (MW 389) is a potent phosphodiesterase-5 inhibitor, widely-used worldwide for erectile dysfunction. The mechanism is prolongation of the vasodilatory action of NO-induced cGMP in arteriolar myocytes. Tadalafil has a plasma half-life of 17 h in healthy young adults, and well-documented brain penetration (brain:plasma ratio 1:10). By contrast, sildenafil has a shorter plasma half-life (4 h) without evidenced brain penetration. We hypothesized that tadalafil will increase regional cerebral blood flow (CBF) in deep brain areas that are affected by small vessel disease.

Participants receive a single dose of tadalafil (20 mg) or placebo orally, at least 7 days apart, in a fully blinded, randomized cross-over design. We aim to recruit 54 participants, aged 50 or more, with radiological and clinical evidence of small vessel disease. The primary outcome is change in CBF in deep white matter and deep grey matter nuclei. CBF is measured before, and 3-5 h after dosing, by arterial spin labelling MRI, which requires no radioactive tracers or Gd-based contrast agent. Secondary outcomes are changes in CBF in cortical grey matter and changes in neuropsychological parameters, including attention and cognitive speed (Reaction Time, Speed of Information Processing, Digit Span and Semantic Fluency).

Trail Name: Perfusion by Arterial Spin labelling following single dose Tadalafil in Small vessel disease (PASTIS). https://clinicaltrials.gov/ct2/show/NCT02450253

**Funded through ADDF's Partnership with the Alzheimer's Society, UK*

NOTES

Alzheimer's **Drug Discovery** Foundation

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Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD)

Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) is a coalition of more than 50 national nonprofit organizations working with regulators, researchers. and industry to speed up the development of more effective treatments and potential cures for AD. ACT-AD is committed to bringing these transformational therapies to patients, providers, and families in the next decade by making the approval of improved symptomatic treatments and disease-modifying therapies for Alzheimer's disease a top national priority.

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