

Alzheimer's Drug Discovery Foundation

I 9TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DRUG DISCOVERY

Jersey City, NJ • September 17-18, 2018

PROGRAM and ABSTRACTS

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WELCOME!



On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to our 19th 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: Merck Research Laboratories, Pfizer CTI, Taub Institute for Research on Alzheimer's Disease and the Aging Brain. We would also like to thank our exhibitors: Affirmativ Group, Canopy Biosciences, Charles River, Collaborative Drug Discovery, Forschungszentrum Jülich GmbH, InterVivo Solutions, NanoString Technologies, and Science Exchange. Our sincere appreciation also extends to all our speakers 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 2018 Young Investigator Scholarship winners: Alexander Conley, PhD, Vanderbilt University Medical Center, Kevin Clayton, PhD (cand.), Boston University School of Medicine, Pierre-Francois Meyer, PhD (cand.), McGill University, Farhan Ali, PhD, Yale School of Medicine, Michael Dybek, PhD (cand.), University of the Sciences, Joshua Foster, PhD (cand.), The Ohio State University, Jaclyn Iannucci, BS, University of Rhode Island, Cutler Lewandowski, PhD (cand.), University of Illinois at Chicago, Priya Prakash, PhD (cand.), Purdue University, Myuri Ruthirakuhan, PhD (cand.), Sunnybrook Health Sciences Centre, Nathaniel Safren, PhD, University of Michigan, Paul Seidler, PhD, UCLA, and Tamar Ziehm, PhD, Research Center Jülich. We encourage you to visit their poster presentations which will be displayed throughout the meeting.

To help us plan an even better conference in 2019, please complete the survey to provide us with feedback and suggestions.

Welcome, once again, to the 19th International Conference on Alzheimer's Drug Discovery!

Best Regards,

oward

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.

WHAT WE'VE ACCOMPLISHED

- The ADDF has granted more than \$115 million to fund more than 585 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 2017, the ADDF raised **\$14 million** to support preclinical drug discovery and clinical development programs. 100% of funds raised went 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, held in the fall, focuses on the discovery and development of drugs targeting Alzheimer's disease and related dementias. The Drug Discovery for Neurodegeneration conference, held in the spring, 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.

SUPPORTERS/EXHIBITORS

Conference Presented by:



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2018 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 2018 Young Investigator Scholars are:

Farhan Ali, PhD, Yale School of Medicine, New Haven, CT, United States
Michael Dybek, PhD (cand.), University of the Sciences, Philadelphia, PA, United States
Joshua Foster, PhD (cand.), The Ohio State University, Columbus, OH, United States
Jaclyn Iannucci, BS, University of Rhode Island, Kingston, RI, United States
Cutler Lewandowski, PhD (cand.), University of Illinois at Chicago, Chicago, IL, United States
Priya Prakash, PhD (cand.), Purdue University, West Lafayette, IN, United States
Myuri Ruthirakuhan, PhD (cand.), Sunnybrook Health Sciences Centre, Toronto, ON, Canada
Nathaniel Safren, PhD, University of Michigan, Ann Arbor, MI, United States
Paul Seidler, PhD, UCLA, Los Angeles, CA, United States
Tamar Ziehm, PhD, Research Center Jülich, Germany

Three Young Investigator Scholars have been selected to present their work in a 10-minute oral presentation on Tuesday, September 18, at 11:50 am. The recipients of this opportunity are:

Alexander Conley, PhD, Vanderbilt University Medical Center, Nashville, TN, United States Kevin Clayton, PhD (cand.), Boston University School of Medicine, Boston, MA, United States Pierre-Francois Meyer, PhD (cand.), McGill University, Montreal, QC, Canada

PROGRAM

Monday, September 17

8:00am–5:30pm	Registration	
8:00–8:30am	Continental Breakfast	
8:30–8:50	Welcome & Opening Presentation: Setting the Stage for New Alzheimer's Disease Therapeutics Howard Fillit, MD—Alzheimer's Drug Discovery Foundation	
8:50–9:20	KEYNOTE: Challenges in CNS Clinical Trials Michael Gold, MD, MS—AbbVie	
9:20-9:30	Discussion and Q&A	
Session I: GENE THERAPY AND ALTERNATIVE MODALITIES FOR NEURODEGENERATIVE DISEASES Chair: Lauren Friedman, PhD—Alzheimer's Drug Discovery Foundation		
9:30–9:35	Session Overview: Lauren Friedman, PhD—Alzheimer's Drug Discovery Foundation	
9:35–9:55	RNAi-based Modulation of Gene Expression in CNS: Implications for Alzheimer's Disease Anastasia Khvorova, PhD—RNA Therapeutics Institute, University of Massachusetts Medical School	
9:55–10:05	Q&A	
10:05-10:25	Translation to the Clinic of AAVrh.10-mediated Delivery to the CNS of the Apolipoprotein E2 Gene for Treatment of Alzheimer's Disease Ronald Crystal, MD—Weill Cornell Medical College	
10:25-10:35	Q&A	
10:35-11:00	EXHIBITOR SESSION BREAK	
11:00-11:20	WVE-3972-01, an Investigational Stereopure Antisense Oligonucleotide, Preferentially Knocks Down G4C2 Repeat- Containing C9ORF72 Transcripts Yuanjing Liu, PhD—WAVE Life Science	
11:20-11:30	Q&A	
11:30–11:50	Safety and Efficacy of Longeveron Mesenchymal Stem Cells (LMSCs) to Treat Patients with Mild Alzheimer's Anthony Oliva, PhD—Longeveron LLC	
I I:50am— I 2:00pm	Q&A	
12:00-12:30	POSTER SESSION	
12:30-1:35	LUNCH	
Session II: NOVEL SMALL MOLECULE APPROACHES TO DEMENTIA Chair: Yuko Hara, PhD—Alzheimer's Drug Discovery Foundation		
1:35–1:40	Session Overview: Yuko Hara, PhD—Alzheimer's Drug Discovery Foundation	
1:40–2:00	Development of Small Molecule Activators of Glutamate Transporter EAAT2 Translation for Alzheimer's Disease Chien-Iiang Glenn Lin, PhD—Ohio State University ADDF/Harrington Scholar	
2:00-2:10	Q&A	
2:10–2:30	Targeting Inflammatory Resolution as Preventative and Therapeutic Strategies for Alzheimer's Disease Masashi Kitazawa, PhD—University of California, Irvine	
2:30–2:40	Q&A	
2:40–3:00	Development of Small Molecule Mitochondria-targeted Therapeutic for Alzheimer's Disease Eugenia Trushina, PhD—Mayo Clinic	
3:00-3:10	Q&A	
3:10-3:40	EXHIBITOR SESSION BREAK	
3:40-4:00	Targeting Mitochondrial TDP-43 To Treat Alzheimer's Disease Xinglong Wang, PhD—Case Western Reserve University ADDF/Association for Frontotemporal Degeneration Partnership Program	
4:00-4:10	Q&A	
4:10-4:30	mGlu5 PAMs for the Treatment of Alzheimer's Disease Jerri Rook, PhD—Vanderbilt Center of Neuroscience Drug Discovery	
4:30-4:40	Q&A	
4:40–5:00	Exploratory Optimization of New CX3CRI Modulators for the Treatment of Alzheimer's Disease Mary Hamby, PhD—The Neurodegeneration Consortium, MD Anderson Cancer Center	
5:00-5:10	Q&A	
5:10-5:20	Closing Remarks and Announcement of Young Investigator Scholarships Nicole Bjorklund, PhD—Alzheimer's Drug Discovery Foundation	

Tuesday, September 18	
8:00-8:30am	Continental Breakfast
8:30-8:35	Day 2 Opening Remarks Howard Fillit, MD—Alzheimer's Drug Discovery Foundation
8:35–9:05	KEYNOTE: FNIH Biomarker Initiatives in Neuroscience—Consortium Efforts in the Development of Biomarkers for Drug Development Rosa Canet-Avilés, PhD—Foundation for the National Institutes of Health (FNIH)
9:05-9:15	Discussion and Q&A
Session III: BI Chair: Meriel C	OMARKERS Dwen, PhD—Alzheimer's Drug Discovery Foundation
9:15-9:20	Session Overview: Meriel Owen, PhD—Alzheimer's Drug Discovery Foundation
9:20–9:40	Epigenetic Mechanisms in Human Memory: Quantification by Non-invasive PET Imaging in the Aged Brain Jacob Hooker, PhD—Massachusetts General Hospital
9:40–9:50	Q&A
9:50-10:10	Abeta Complexes and Other Proteins Targets from Blood as Early Indicators of Amyloid Accumulation in the Brain Blaine Roberts, MD—Florey Institute of Neuroscience and Mental Health
10:10-10:20	Q&A
10:20-10:50	EXHIBITOR SESSION BREAK
10:50–11:10	Quantitative Assessment by Mass Spectrometry of Amyloid beta 42 and 40 in Plasma as a Peripheral Indicator of Brain Amyloidosis Tim West, PhD—C2N Diagnostics ADDF/Association for Frontotemporal Degeneration Partnership Program
11:10-11:20	Q&A
11:20-11:40	Isolation of Neurally-derived Exosomes from Blood for the Diagnosis and Staging of Sporadic Alzheimer's Disease Diana Cha, PhD—Brigham & Women's Hospital
11:40-11:50	Q&A
11:50am- 12:35pm 12:35-1:35	EMERGING CONCEPTS: DATA BLITZ Chair: Meriel Owen, PhD—Alzheimer's Drug Discovery Foundation Young Investigator #1: Pierre-François Meyer, PhD (c)—McGill University Young Investigator #2: Kevin Clayton, PhD (c)—Boston University School of Medicine Young Investigator #3: Alexander Conley, PhD—Vanderbilt University Medical Center LUNCH AND POSTER SESSION
12.00 1.00	All poster presenters should stand by their poster from 1:05-1:35PM
Session IV: CLINICAL TRIALS Chair: Nicholas McKeehan—Alzheimer's Drug Discovery Foundation	
1:35-1:40	Session Overview: Nicholas McKeehan—Alzheimer's Drug Discovery Foundation
1:40 –2:00	A Proof-of-Concept Clinical Research Study of Efavirenz in patients with Alzheimer's Disease Irina Pikuleva, PhD—Case Western Reserve University
2:00-2:10	Q&A
2:10–2:30	Safety and Efficacy of Nabilone in Patients with Moderate to Severe Alzheimer's Disease: A Pilot Study Krista Lanctôt, PhD—Sunnybrook Research Institute, University of Toronto
2:30–2:40	Q&A
2:40–3:00	Dopaminergic Therapy for Alzheimer's Disease Patients Giacomo Koch, MD, PhD—Santa Lucia Foundation
3:00-3:10	Q&A
3:10-3:30	Phase I Study of the Putative Cognitive Enhancer VU319, a Muscarinic MIPositive Allosteric Modulator for Alzheimer's Disease Paul Newhouse, MD—Vanderbilt University Medical Center
3:30-3:40	Q&A
3:40-4:00	Evaluating the Effects of the Novel GLP-I Analogue, Liraglutide, in Patients with Alzheimer's Disease (ELAD Study) Paul Edison, MD, MRCP, PhD, FRCPI—Imperial College London
4:00-4:10	Q&A
4:10-4:20pm	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—AbbVie



Michael Gold, MD, currently serves as Vice-president for CNS Development at AbbVie. Prior to joining AbbVie, Dr. Gold spent several years in large pharmaceutical companies (BMS, J&J and GSK) in roles of increasing responsibility as well as in senior leadership roles in several biotech companies (CMO of Allon Therapeutics and Accera Inc.), in a specialty pharmaceutical company (UCB) and a short stint in a CRO (PPD). Dr. Gold has worked across all stages of CNS drug development, on small molecules, biologicals, drug-device combinations and diagnostics.

Dr. Gold and his teams have worked on compounds for AD, PD, Stroke, RLS, migraine, epilepsy, MS, chronic somatic and neuropathic pain resulting in a number of successful approvals in the US, EU and Japan. Dr. Gold earned his BS (Chemistry, cum laude), MS (Mathematics and Computer Science) and MD degrees at the University of Miami, completed his Neurology training at the Albert Einstein College of Medicine in New York and then completed a fellowship in Behavioral Neurology at the University of Florida College of Medicine. After completing his training, Dr. Gold was appointed as an Assistant Professor in the Department of Neurology at the University of South Florida (Tampa) where he provided care for patients, trained medical students, residents and fellows. During his tenure at USF, Dr. Gold was appointed as the Medical Director for USF's Memory Disorder Clinic, where patients from a large catchment area with a broad range of cognitive impairments were evaluated, treated and offered participation in clinical trials.

Over the last 20 years, Dr. Gold has been involved in a large number of clinical trials for neurodegenerative disorders from the investigator, sponsor and CRO perspectives and has continuously pushed for the adoption of innovative designs in clinical trials. Dr. Gold has served on a number of Scientific Advisory Boards for biotech companies, serves as a grant reviewer for several philanthropic organizations and serves as an editor and reviewer for several peer-reviewed medical journals and has been invited to present at several international scientific conferences. Dr. Gold is an author of approximately 50 peer-reviewed publications.

Challenges in CNS Clinical Trials

Michael Gold

AbbVie, Cambridge, MA, United States

Clinical trials for CNS indications are notorious for being complicated, expensive, hard to recruit for and most of all, for their very low success rates. Given all these problems, one can reasonably ask whether clinical research for disorders affecting the CNS is a futile enterprise. At the same time, one cannot ignore the immense unmet medical need due to neurological and particularly neurodegenerative disorders and the resulting moral imperative to solve the clinical trial problems. Substantial progress has been made with regards to many of the problems facing the clinical research enterprise and that progress seems to be both accelerating and expanding. Novel technologies and methodologies are finding their way into the clinical trial ecology that may allow much more efficient and effective trials to be conducted. It is also important to recognize that some of the reasons for the high failure rate of CNS trials (particularly in AD), are now being discussed and debated more openly and that as result of this re-evaluation, novel therapeutic approaches are finally seeing the light of day.

I. GENE THERAPY AND ALTERNATIVE MODALITIES FOR NEURODEGENERATIVE DISEASES

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



Lauren Friedman, PhD, directs the Scientific Affairs team and manages ADDF's scientific portfolio of academic and biotech investments. She proactively sources and evaluates programs developing therapeutics and biomarkers for Alzheimer's disease and related dementias. She works closely with investigators to design development plans and monitor program progress. She also manages ADDF's partnerships with industry and other non-profit organizations to leverage additional funding and resources for portfolio programs.

Dr. Friedman completed her postdoctoral training at Columbia University, where she studied modulators of autophagy in Alzheimer's disease. She earned a doctorate in neuroscience at the Icahn School of Medicine at Mount Sinai, where she focused on molecular mechanisms underlying the development and degeneration of brain circuits involved in autism and Parkinson's disease. While at Mount Sinai, Dr. Friedman founded MiNDS, a neuroscience outreach program that strives to make neuroscience education more engaging and accessible. She received a bachelor's degree in biopsychology from Tufts University.

RNAi-based Modulation of Gene Expression in CNS: Implications for Alzheimer's Disease Anastasia Khvorova, PhD—RNA Therapeutics Institute, University of Massachusetts Medical School

Translation to the Clinic of AAVrh.10-mediated Delivery to the CNS of the Apolipoprotein E2 Gene for Treatment of Alzheimer's Disease Ronald Crystal, MD—Weill Cornell Medical College

WVE-3972-01, an Investigational Stereopure Antisense Oligonucleotide, Preferentially Knocks Down G4C2 Repeat-Containing C9ORF72 Transcripts Yuanjing Liu, PhD—Wave Life Science

Safety and Efficacy of Longeveron Mesenchymal Stem Cells (LMSCs) to Treat Patients with Mild Alzheimer's Disease Anthony Oliva, PhD—Longeveron LLC

Anastasia Khvorova, PhD—RNA Therapeutics Institute, University of Massachusetts Medical School



Anastasia Khvorova, PhD, has more than twenty years of experience developing oligonucleotide technology and therapeutics. She is a professor in the RNA Therapeutics Institute and Program in Molecular Medicine at the University of Massachusetts Medical School (UMMS). Her lab brings together hardcore organic and oligonucleotide chemists, RNA biologists, and pharmacologists to develop novel approaches and solutions to understanding natural and therapeutic RNA trafficking and delivery. She established the RTI's Nucleic Acid Chemistry Center, which provides expertise inRNA chemistry to labs within and outside UMMS, andis the only non-profit center in North America capable of synthesizing complex RNAs at scales necessary to support both in vitro and in vivo

studies.

Dr. Khvorova joined UMMS after several years in industry, during which she served as Chief Scientific Officer at lead biotech companies (Dharmacon, ThermoFisher; RXi Pharmaceuticals) and co-founded several startups. She serves as director of the Oligonucleotide Therapeutics Society. Dr. Khvorova is named as inventor on more than 150 patents and 200 patent applications, and she has authored more than 50 peer-reviewed publications, including seminal articles inCell, Nature, and Nature Biotechnology (citation index exceeding 2000 per article) defining the field ofRNAi drug design and development. Dr. Khvorova is principal investigator on four major National Institutes of Health grants.

RNAi-based Modulation of Gene Expression in CNS: Implications for Alzheimer's Disease

Chantal Ferguson¹, Anastasia Grigorenko², Evgeny Rogaev² and Anastasia Khvorova¹

¹RNA Therapeutics Institute, University of Massachusetts Medical School, Worcester, MA, United States ²Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, United States

RNA interference (RNAi) enables simple and specific modulation of gene expression as long as the chemical architecture supporting efficient in vivo delivery is defined. We recently have developed a novel central nervous system (CNS)-active RNAi scaffold that supports sustained modulation of gene expression in hippocampus and cortex, key regions of the brain involved in the progression of Alzheimer's Disease (AD). Compounds using this scaffold demonstrate a duration of effect in rodents exceeding six months following a single administration, and wide distribution and efficacy in cynomolgus monkey.

AD is a complex disease, with recent data implicating multiple pathways in disease development and progression. CNS-RNAi enables combinatorial regulation of gene expression in CNS, a path toward development of disease-modifying treatments in AD. Pilot data on the development of ApoE-targeting, CNS-active RNAi will be presented.

Ronald Crystal, MD—Weill Cornell Medical College



Ronald Crystal, MD, is Professor and Chairman of the Department of Genetic Medicine at the Weill Medical College of Cornell University, where he is also the Bruce Webster Professor of Internal Medicine, Director of the Belfer Gene Therapy Core Facility and Attending Physician at the NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

Over the past 25 years, his laboratory has focused on developing gene therapy strategies to treat currently untreatable chronic disorders.

Translation to the Clinic of AAVrh.10-mediated Delivery to the CNS of the Apolipoprotein E2 Gene for Treatment of Alzheimer's Disease

Ronald Crystal

Weill Cornell Medical College, New York, NY, United States

The APOE gene is a common risk factor for Alzheimer's disease, with APOE4 homozygotes at 15-fold increased risk and the APOE2 gene decreasing risk. Preclinical studies with Alzheimer's mouse models have demonstrated that adenoassociated virus AAVrh.10-mediated gene transfer of the APOE2 gene markedly decreases the amount of CNS amyloid-beta peptide accumulation in APOE4-expressing mice. Studies in non-human primates have shown that AAVrh.10-mediated intra-cisternal delivery of the human APOE2 coding sequence safely and effectively distributes APOE2 throughout the brain. Based on these studies, with the support of the Alzheimer's Drug Discovery Foundation, we are moving forward with a clinical trial of AAVrh.10hAPOE2 CNS therapy in APOE4 homozygotes with early onset Alzheimer's disease.

Yuanjing Liu, PhD—WAVE Life Science



Yuanjing Liu, PhD, is a scientist at WAVE Life Sciences in Cambridge, MA. She had received her PhD in 2015 from the University of Florida and has 11 years of experience in molecular biology and biomedicine labs.

Dr. Liu is a project leader who had supported the development of essential tools to benefit ALS research including mouse models and antibodies.

WVE-3972-01, an Investigational Stereopure Antisense Oligonucleotide, Preferentially Knocks Down G4C2 Repeat-Containing C9ORF72 Transcripts

Yuanjing Liu

WAVE Life Science, Cambridge, MA, United States

Anthony Oliva, PhD—Longeveron LLC



Anthony Oliva, PhD, earned his undergraduate degree in Biological Sciences from the University of Chicago, and his PhD in Neuroscience from Baylor College of Medicine where he developed autofluorescent-protein animal models for studying interneuron function and injury in the brain. Dr. Oliva continued his research as a post-doctoral fellow at the Oregon Health and Science University, and then became an assistant scientist with The Miami Project to Cure Paralysis, and director of the Viral Vector Core Facility at the University of Miami Miller School of Medicine. He then joined the Herbert Wertheim College of Medicine at Florida International University as an assistant professor.

In 2015, Dr. Oliva joined Longeveron as the newly-formed company's senior scientist, leading its clinical programs for using stem cell therapy to treat Alzheimer's disease and other indications. He is the principal investigator on a number of company-awarded grants, including grants from the Alzheimer's Association, Maryland Stem Cell Research Fund TECDO, and the National Institutes of Health.

Safety and Efficacy of Longeveron Mesenchymal Stem Cells (LMSCs) to Treat Patients with Mild Alzheimer's Disease

Anthony Oliva

Longeveron LLC

The pathological features of Alzheimer's disease (AD) are complex and include not only the hallmarks of beta-amyloid deposits and neurofibrillary tangles, but also neurovascular disruption and a pro-inflammatory state, among other features. Mesenchymal stem cells (MSCs) are strong therapeutic candidates for AD via the potential to treat multiple pathophysiological features of the disease. MSCs are multipotent cells that are immunoprivileged, and therefore can be used as allogeneic product. MSCs also have a well-documented high safety profile, making them attractive for human therapeutic use. In AD animal model studies, treatment with allogeneic MSCs led to beta-amyloid clearance, promoted neurogenesis and neuronal differentiation, and resulted in significant functional performance improvements. AD and related dementias are also associated with a number of risk factor, including aging-related physical frailty (aging frailty). We recently completed a Phase I/II clinical study to examine the safety and efficacy of allogeneic MSCs for treating aging frailty. This treatment was found to be safe and led to significant improvements in multiple measures of aging frailty and sustained reduction in pro-inflammatory biomarkers. Performance on the mini-mental state examination (MMSE) also improved, suggesting the potential of allogeneic MSCs for improving cognitive status. Combined, the preclinical and clinical evidence suggests that allogeneic MSCs can be of potential therapeutic value to AD sufferers. We are conducting a randomized, double-blinded, placebo-controlled Phase I/II clinical trial to examine a proprietary formulation of MSCs, called Longeveron MSCs (LMSCs), for potential therapeutic value to those with clinically-diagnosed mild AD (ClinicalTrials.gov Identifier: NCT02600130). The primary endpoint of this first-in-human study is subject safety. Provisional efficacy is also being examined via functional performance measures, patient and caregiver reported outcomes, and biomarker assays. Given the demonstrated high-safety profile and mechanisms of action of allogeneic MSCs, this type of cellular therapy offers exciting potential as an effective and affordable "off-theshelf" product for treating AD.

We thank the Alzheimer's Association for its generous support of this project via a Part the Cloud grant (award number PTC C-16-422443).

II. NOVEL SMALL MOLECULE APPROACHES TO DEMENTIA

Chair: Yuko Hara, PhD—Alzheimer's Drug Discovery Foundation



Yuko Hara, PhD, is Director of the ADDF's Aging and Alzheimer's Prevention team. In this capacity, she critically evaluates the scientific evidence behind therapies to promote brain health and/or prevent Alzheimer's disease. She also investigates potential risk factors as well as research proposals on prevention therapies.

Dr. Hara was previously an Assistant Professor in Neuroscience at the Icahn School of Medicine at Mount Sinai, where she remains an adjunct faculty member. Her research focused on brain aging, specifically how estrogens and reproductive aging influence the aging brain's synapses and

mitochondria. She earned a doctorate in neurology and neuroscience at Weill Graduate School of Medical Sciences of Cornell University and a bachelor's degree in biology from Cornell University, with additional study at Keio University in Japan.

Dr. Hara has authored numerous peer-reviewed publications, including articles in PNAS and Journal of Neuroscience.

Development of Small Molecule Activators of Glutamate Transporter EAAT2 Translation for Alzheimer's Disease

Chien-liang Glenn Lin, PhD—Ohio State University

Targeting Inflammatory Resolution as Preventative and Therapeutic Strategies for Alzheimer's Disease Masashi Kitazawa, PhD—University of California, Irvine

Development of Small Molecule Mitochondria-targeted Therapeutic for Alzheimer's Disease Eugenia Trushina, PhD—Mayo Clinic

Targeting Mitochondrial TDP-43 To Treat Alzheimer's Disease

Xinglong Wang, PhD—Case Western Reserve University

mGlu5 PAMs for the Treatment of Alzheimer's Disease

Jerri Rook, PhD—Vanderbilt Center of Neuroscience Drug Discovery

Exploratory Optimization of New CX3CR1 Modulators for the Treatment of Alzheimer's Disease

Mary Hamby, PhD—The Neurodegeneration Consortium, MD Anderson Cancer Center

Chien-liang Glenn Lin, PhD—Ohio State University



Chien-liang Glenn Lin, PhD, completed his doctorate in Molecular Biology and Biochemistry at the Johns Hopkins University in 1995. He completed his postdoctoral research in the Department of Neurology at Johns Hopkins University.

Dr. Lin joined the Department of Neuroscience at The Ohio State University (OSU) in 1999, where he focused his research on molecular mechanisms underlying neurodegenerative diseases including Alzheimer's disease. His recent research focuses specifically on the role of glutamate transporter EAAT2 in the regulation of synaptic plasticity and function and in the pathogenesis of Alzheimer's disease.

Currently, Dr. Lin is a full professor at OSU. He has published numerous papers in major journals and holds four patents.

Development of Small Molecule Activators of Glutamate Transporter EAAT2 Translation for Alzheimer's Disease

Chien-liang Glenn Lin^{1*}, Kevin Hodgetts²

¹Ohio State University, Columbus, OH, United States ²Brigham and Women's Hospital and Harvard Medical School, Laboratory for Drug Discovery in Neurodegeneration, Cambridge, Massachusetts, United States

Glutamate transporter EAAT2 is localized primarily in the peri-synaptic processes of astrocytes closely associated with excitatory synaptic contacts. EAAT2 plays a critical role in the maintenance of glutamate homeostasis in the brain. EAAT2 also plays an essential role in cognitive memory functions. However, loss of EAAT2 protein and function is commonly found in Alzheimer's disease (AD) patients, and it is an early event in disease pathology. We have discovered a novel series of small molecules that can increase EAAT2 expression via a novel translational activation mechanism. We have proven that these molecules are capable of restoring EAAT2 protein to normal levels, improving cognitive functions, restoring synaptic integrity, and reducing amyloid deposition in APPSw, Ind. mice. In addition, we have recently found that these molecules are also capable of preventing neurodegeneration and reducing tau phosphorylation and neurofibrillary tangle in rTg(tauP301L)4510 mice. Studies on the mechanism of compound action reveal that the compound binds to the target protein and triggers pathways that result in the local up-regulation of proteins involved in different functions in astrocytic processes. This leads to strengthening of the structural and functional properties of astrocytic processes. One effect is the immediate up-regulation of proteins involved in EAAT2 glutamate uptake. Importantly, enhanced plasticity of the astrocytic processes by the compound consequently strengthens synaptic plasticity. This project is currently at the clinical candidate selection phase. We have generated and evaluated >350 analogs of the initial lead compound. From these analogs, we have selected the best three orally active compounds as potential clinical candidates. After extensive investigation of these compounds, we have selected a molecule that meets all in vitro/in vivo DMPK, safety, selectivity and efficacy criteria as the clinical candidate. We will move this candidate forward to IND enabling studies.

*ADDF/Harrington Scholar

Masashi Kitazawa, PhD—University of California, Irvine



Masashi Kitazawa, PhD, is Associate Professor in the Department of Medicine and the Center for Occupational and Environmental Health at the University of California, Irvine. He received his PhD in Toxicology in 2003 from Iowa State University, with a research emphasis on environmental toxicants in neurodegenerative diseases under the mentorship of Dr. Anumantha Kanthasamy. He then worked as a post-doctoral fellow with Dr. Frank LaFerla at the University of California, Irvine, studying on the role of inflammation in Alzheimer's disease (AD) and inclusion body myositis.

In 2012, he joined the University of California, Merced, as a faculty member and established an independent lab focusing on the understanding the mechanisms linking environmental exposure, inflammation, and AD. He then was recruited to the University of California, Irvine in 2016, where his lab continues to work on deciphering the role of inflammation in AD from both therapeutic and environmental risk aspects.

Current research projects include identifying early transcriptomic changes in microglia leading to AD phenotypes following environmental copper exposure, the role of inflammation-induced microRNAs in regulating brain LRPI and plasticity-related proteins, and therapeutic efficacy of a small compound activating the inflammatory resolution pathway in AD mouse model. These projects have been supported by grants and fellowships from the NIH, Alzheimer's Association, and ADDF.

Targeting Inflammatory Resolution as Preventative and Therapeutic Strategies for Alzheimer's Disease

Masashi Kitazawa

University of California, Irvine, CA, United States

Sustained neuroinflammation and the failure to resolve it to tissue homeostasis have been implicated in key pathological features for Alzheimer's disease (AD). In the brain, such conditions may trigger harmful microenvironments for neurons, and inflammation-triggered perturbed microglia activation leads to impairment of efficient containment and clearance of neurotoxic A β species. Thus, successful cessation of aberrant inflammation is essential to restore neuroprotective homeostasis and functional recovery. In earlier work, we have shown a potent neuroprotective and disease-modifying role of the inflammatory resolution driven by lipid-based pro-resolving molecule, 15-epi-lipoxin, in two transgenic mouse models of AD. In an effort of developing small molecules, we have one lead compound mimicking lipoxin activity, and it effectively activated phagocytosis and clearance of A β in vitro. This lipoxin analogue is well-tolerated in rats and mice, with plasma half-life of approximately 17 hrs, which is substantially longer than that in endogenous lipoxin. It also penetrates the blood-brain barrier and reaches the brain. In this presentation, I will present preliminary pharmacokinetics profile, acute toxicity, and tolerance of this compound in mice, which validate its pharmacological potentials, as well as current progress and timeline of preventative and therapeutic preclinical studies of this lead compound in 3xTg-AD mice.

Eugenia Trushina, PhD—Mayo Clinic



Eugenia (Jania) Trushina, PhD, is an Associate Professor in the Department of Neurology and the Department of Molecular Pharmacology and Experimental Therapeutics at the Mayo Clinic Rochester. She received her doctoral degree in organic chemistry from Saratov State University in Russia. Dr. Trushina completed her postdoctoral training at the Mayo Clinic, Rochester studying redox chemistry related to nitric oxide and mechanisms of mitochondrial dynamics in Huntington's Disease.

Dr. Trushina's translational research program is focused on the mechanisms of neurodegenerative diseases, particularly as they intersect with studies on aging and metabolic disorders, and the development of mitochondria-targeted therapeutics. Her group developed novel small molecule mitochondria-targeted therapeutics for Alzheimer's Disease, which is now in the lead optimization and preclinical characterization stage. Dr. Trushina is a recipient of the NIH NINDS, NIA, NIEHS, BrightFocus, GHR, ADDF, and Mayo Clinic Research Awards.

Development of Small Molecule Mitochondria-targeted Therapeutic for Alzheimer's Disease

Eugenia Trushina

Mayo Clinic, Minneapolis, MN, United States

Recent studies demonstrate that genetic or pharmacological induction of mitochondrial stress response results in decreased protein aggregation, restored organismal fitness and healthspan, thereby ultimately delaying the development of age-related conditions including neurodegeneration. Recent work in my laboratory has been focused on the identification of molecular mechanisms involved in neuroprotection triggered by partial mitochondrial complex I inhibitors. In collaboration with multiple CROs and consultants, we have developed a robust drug discovery program with the ultimate goal to produce first-in-class disease-modifying small molecule therapies for AD. I will discuss our approach to medicinal chemistry, PK/PD and safety studies, and translational biomarker development that we are currently undertaking to ensure successful transition of this approach to clinical trials.

Xinglong Wang, PhD—Case Western Reserve University



Xinglong Wang, PhD, is an Associate Professor at the Department of Pathology at the Case Western Reserve University. He studies the mechanism(s) underlying neuronal death in various major neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS).

His recent research activities focus on mitochondrial dysfunction and TDP-43 proteinopathies, two prominent pathological features in these devastating diseases. His lab provided the first evidence of TDP-43 accumulation within mitochondria in neurodegenerative diseases, and

suggested the targeting TDP-43 in mitochondria as a potential novel therapeutic approach for neurodegeneration. The lab is now pursuing the physiological function of TDP-43 in mitochondria and the identification of small molecular inhibitors of TDP-43 in mitochondria.

Dr. Wang has authored or co-authored over 80 papers, many in top tier journals. Dr. Wang has been the recipient of the ISN Young Scientist Lectureship Award and ASIP Experimental Pathologist-in-Graduate Training Award.

Targeting Mitochondrial TDP-43 To Treat Alzheimer's Disease

Xinglong Wang

Case Western Reserve University, Cleveland, OH, United States

Alzheimer's disease (AD) is the leading cause of dementia in the elderly, characterized clinically by progressive decline in cognitive function and neuropathologically by the presence of senile plaques and neuropal loss in the brain. While current drugs for AD are always employed as symptomatic therapies with variable benefits, there is no treatment to delay its progression or halt neurodegeneration. TAR DNA-binding protein 43 (TDP-43) proteinopathy has increasingly been implicated as a prominent histopathological feature crucial for cognitive impairment in AD. We identified mitochondria as critical targets of TDP-43 neurotoxicity. Here, we demonstrate that the suppression of TDP-43 mitochondrial localization protects against neuronal loss and behavioral deficits in widely-used 5XFAD transgenic mice recapitulating AD-related phenotypes. In AD patients and 5XFAD mice, the level of TDP-43 is increased in mitochondria, and TDP-43 highly co-localizes with mitochondria in brain neurons exhibiting TDP-43 proteinopathy. Chronic administration of a TDP-43 mitochondrial localization inhibitory peptide, PMI, greatly alleviates TDP-43 proteinopathy, mitochondrial abnormalities, microgliosis and even neuronal loss without significant effect on amyloid plague load in 12-month-old 5XFAD mice well after the onset of symptoms. Additionally, PMI drastically improves the cognitive and motor function in 12-month-old 5XFAD mice and completely prevents the onset of mild cognitive impairment in 5-month-old 5XFAD mice. These data indicate that TDP-43 in mitochondria is likely involved in AD pathogenesis and that the inhibitor of TDP-43 mitochondrial localization may be a valuable drug to treat underlying AD.

ADDF/Association for Frontotemporal Degeneration Partnership Program

Jerri Rook, PhD—Vanderbilt Center of Neuroscience Drug Discovery



Jerri Rook, PhD, is Assistant Professor of Pharmacology and the Vanderbilt Center for Neuroscience Drug Discovery at Vanderbilt University. Dr. Rook received her PhD in Pharmacology, Toxicology and Therapeutics at the University of Kansas Medical Center. She then pursued her postdoctoral studies at Vanderbilt University in the laboratory of P. Jeffrey Conn, PhD.

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. Dr. Rook also serves on the Scientific Review Board for the Alzheimer's Drug Discovery Foundation.

Dr. Rook's research focuses on the mechanisms underlying the progression of neurodegeneration and the discovery of novel therapeutic strategies for Alzheimer's disease.

mGlu5 PAMs for the Treatment of Alzheimer's Disease

Jerri Rook

Vanderbilt Center of Neuroscience Drug Discovery, Franklin, TN, United States

Alzheimer's disease (AD) is the most frequently observed cause of dementia and age-related cognitive decline. Glutamate is the primary excitatory neurotransmitter of the central nervous system (CNS) and glutamatergic transmission is severely disrupted in AD. In recent years, the metabotropic glutamate receptor subtype 5 (mGlu5) has emerged as an exciting new target for new therapeutic agents that could be used to reduce impaired cognitive function in patients suffering from AD. The mGlu5 receptor is the most highly expressed mGlu receptor subtype in the hippocampus and cortical regions that are known to be impacted in AD patients. Most notably, mGlu5 plays critical roles in multiple forms of synaptic plasticity that are thought to underlie learning and memory and other forms of cognitive function. Interestingly, recent studies suggest that proteins important for mGlu5 function are lost and that mGlu5 signaling is impaired in tissue from AD patients. These studies raise the exciting possibility that highly selective activators of mGlu5 could provide a novel approach to reverse the pathophysiological changes associated with AD. Over the past decade, highly selective positive allosteric modulators (PAMs) of mGlu5 have emerged as a promising new approach for improving cognitive function in schizophrenia and other non-degenerative CNS disorders. As opposed to direct activation of mGlu5, PAMs potentiate the response of the receptor to its endogenous ligand, glutamate, and offer high selectivity while avoiding unwanted side-effects seen with direct activation of the receptor.

We performed a series of studies to test the hypothesis that acute administration of the mGlu5 PAM, VU0092273, will provide efficacy in improving impaired cognitive function and reverse changes in cerebral metabolic activity in the CK-p25 mouse model of AD. Our data demonstrate that mGlu5 PAMs are able to reverse deficits in hippocampal synaptic plasticity, as well as multiple models of cognitive function in this mouse model of neurodegeneration. Additionally, using [18F]FDG PET imaging, we show that selective mGlu5 activation restores normal glucose metabolism in CK-p25 mice. These data provide exciting evidence that mGlu5 PAMs can alleviate the diminished neural and cognitive function in a preclinical model of AD.

Mary Hamby, PhD—The Neurodegeneration Consortium, MD Anderson Cancer Center



Mary Hamby, PhD, joined the Neurodegeneration Consortium at MD Anderson in February 2016, where she leads the neuroinflammation drug discovery efforts towards the goal of discovering novel therapeutics for Alzheimer's disease.

Previously, Dr. Hamby was a neuroinflammation specialist at Lundbeck within the neuroinflammation division focused on targeting microglia for several CNS disorders including Alzheimer's disease. Prior to entering the drug discovery space, Dr. Hamby did a postdoctoral fellowship in glial biology and neuroinflammation at the University of California, Los Angeles.

Dr. Hamby earned her PhD in Biomedical Science at the University of Connecticut, where her research focused on understanding the differential regulation of astrocyte and microglial gene expression by inflammatory mediators.

Exploratory Optimization of New CX3CR1 Modulators for the Treatment of Alzheimer's Disease

Mary Hamby

The Neurodegeneration Consortium, MD Anderson Cancer Center, Houston, TX, United States

Human genetics points to microglia as a key player in Alzheimer's disease (AD), and underscores the targeting of key microglia biologies as a promising therapeutic strategy for AD. The fractalkine receptor, CX3CR1, is a Gi-coupled GPCR which is selectively expressed by microglia and activated by its endogenous ligand fractalkine (CX3CLI), expressed by neurons, either in a membrane-tethered or soluble form. Under normal physiological conditions, CX3CRI activation appears to limit inflammation and promote homeostatic activities such as synaptic maintenance and plasticity, but in AD, CX3CRI is downregulated which corresponds with a phenotypic change of the microglia from a homeostatic to a disease-associated microglia (DAM) pro-inflammatory phenotype. While genetic deletion of CX3CRI in AD models demonstrates a clear role of CX3CRI signaling in AD through altering amyloid beta and tau pathology, brain inflammation, and memory and cognition, there is a lack of in vivo CNS-penetrant tools, both agonists and antagonists, to properly assess the therapeutic benefit of altering CX3CRI signaling in AD models. To address this, we took advantage of a robust screening assay and new 240,000 compound library for high-throughput screening. We identified agonist and antagonist hits that progressed through the screening funnel to successfully confirm potency, selectivity and cross-species activity. Currently, we are focusing our medicinal chemistry efforts on a lead agonist series. We have established a struture-activity relationship with identification of more potent and robust agonists that have good physicochemical properies, and are predicted to be CNS penetrant. Our lead agonist series exhibits activity in several orthogonal assays including a GTP S assay, a heterologous native Gi cell model and, importantly, in a native cell assays using myeloid cells. Our lead series is capable of emulating FKN by triggering CX3CR1-dependent Gi signaling and competing with membrane-tethered FKN in a cell adhesion assay. Acceptable in vitro ADME was found for some of our most potent analogs in our lead series, and in vivo PK is underway to assess whether we now have a tool compound for in vivo PoC studies to assess the role of CX3CR1 in AD and other relevant models.

KEYNOTE SPEAKER Rosa Canet-Avilés, PhD—Foundation for the National Institutes of Health (FNIH)



Rosa Canet-Avilés, PhD, is a Science Program Manager for Neuroscience at the Foundation for the National Institutes of Health (FNIH). In her role she leads a portfolio of multiple multi-year CNS disorders-related initiatives in Alzheimer's Disease, Autism Spectrum Disorders, and Parkinson's Disease totaling \$100M+ under three public-private partnerships. She manages the Biomarkers Consortium Neuroscience Steering Committee, the Accelerating Medicines Partnership (AMP) in Alzheimer's Disease and the AMP in Parkinson's Disease, and the Alzheimer's disease Neuroimaging Initiative. Dr. Rosa Canet-Avilés served previously as a Science Program Officer for Neuroscience at the California Institute for Regenerative Medicine (CIRM). In her role, she planned

and devised translational research programs, policies and procedures to implement and monitor the organization's overall research and development strategy. Prior to that, Dr. Canet-Avilés served as a scientist leading some of the Neurodegeneration programs at Amgen Inc. Dr. Canet-Avilés group was responsible for the discovery and validation of therapeutic targets for Parkinson's and Alzheimer's Diseases.

Dr Canet-Avilés completed post-doctoral programs at the Mayo Medical school in Neuroscience, at the National Institutes on Aging (Laboratory of Neurogenetics) and a final industry post-doctoral position at Elan Inc. Dr. Canet-Avilés earned her PhD degree in Neuroscience from the School of Medicine at Leeds University, UK. She also holds a BS in Organic Chemistry from the Central University of Barcelona and a Masters in Quality Management from the Catalan Institute of Technology, Barcelona, Spain.

FNIH Biomarker Initiatives in Neuroscience – Consortium Efforts in the Development of Biomarkers for Drug Development

Rosa Canet-Avilés

Foundation for the National Institutes of Health (FNIH), North Bethesda, MD, United States

The role of biomarkers has been exponentially increasing in guiding decisions in every phase of drug development, from drug discovery and preclinical evaluations through each phase of clinical trials and into post-marketing studies. Regulatory qualification of biomarkers for a specific use in drug development and regulatory decision making is a complex process involving several steps of evidence generation and analytical and clinical validation. As a result, developing a biomarker with the goal of regulatory qualification for a specific context of use across drug development programs often requires significant resources and expertise. Consortia provide a framework for such collaborations.

Over the past 10 years the Foundation for the NIH (FNIH) Biomarkers Consortium (BC) has launched more than 20 projects in 13 different disease areas. Its work also has been instrumental in testing new models for clinical trials. To date, the work of the BC has supported the advancement of six therapeutics in the drug development process and helped generate four separate FDA Guidance documents. Within Neuroscience, the BC structure has allowed for real time and open discussion of concerns which otherwise would have remained within the walls of each stakeholder for a much longer period. Under the BC umbrella, several neuroscience initiatives have been catalyzed and international partnerships formed that deal with issues of assay harmonization, performance and validation of biomarkers for neurodegenerative and neurodevelopmental disorders. An overview will be provided of the achievements, challenges and lessons learned that have informed the next steps and opportunities moving forward.

III. BIOMARKERS

Chair: Meriel Owen, PhD—Alzheimer's Drug Discovery Foundation



Meriel Owen, PhD, is a member of the ADDF's scientific affairs team. She supports the scientific portfolio through strategic review and program management.

Dr. Owen earned her doctorate in neuroscience from Northwestern University, where she used neuroimaging and robotic techniques to better understand the neural mechanisms underlying motor impairment after stroke. She received a MSc from University College London in clinical neuroscience and a bachelor's degree in cognitive science from the University of California, Berkeley. Dr. Owen is also interested in the intersection between neuroscience and

entrepreneurship.

During her graduate studies, she completed the Kellogg Management Program for scientists and engineers, was selected as a Northwestern Leadership Fellow, and co-founded a startup company that won the Neuro Startup Challenge.

Epigenetic Mechanisms in Human Memory: Quantification by Non-invasive PET Imaging in the Aged Brain

Jacob Hooker, PhD-Massachusetts General Hospital

Abeta Complexes and Other Proteins Targets from Blood as Early Indicators of Amyloid Accumulation in the Brain Blaine Roberts, MD— Florey Institute of Neuroscience and Mental Health

Quantitative Assessment by Mass Spectrometry of Amyloid beta 42 and 40 in Plasma as a Peripheral Indicator of Brain Amyloidosis Tim West PhD - C2N Diagnostics

Tim West, PhD—C2N Diagnostics

Isolation of Neurally-derived Exosomes from Blood for the Diagnosis and Staging of Sporadic Alzheimer's Disease Diana Cha, PhD—Brigham & Women's Hospital

EMERGING CONCEPTS: DATA BLITZ

Young Investigator #1: Pierre-François Meyer, PhD (c)—McGill University Young Investigator #2: Kevin Clayton, PhD (c)—Boston University School of Medicine Young Investigator #3: Alexander Conley, PhD—Vanderbilt University Medical Center

Jacob Hooker, PhD—Massachusetts General Hospital



Jacob Hooker, PhD, has built his career on the concept that measuring neurochemistry in the living human brain can have a profound impact on human health and wellbeing. Through the development of new tools and techniques, Prof. Hooker is advancing our fundamental understanding of diseases and disorders like Alzheimer's and autism.

His work has led to many landmark firsts—first human neuroepigenetic imaging technology, first linkage between glial activation and chronic low back pain, first demonstration of dynamic neurochemical imaging (fPET)—and catalyzes others to achieve advances of their own. He has dramatically expanded the capabilities of PET imaging by pioneering new radiotracer synthesis

methods, radiotracers and concepts. At the Martinos Center for Biomedical Imaging at Massachusetts General Hospital, he founded and directs a first-in-class imaging facility that merges functional MRI and positron emission tomography for neurochemical study.

Dr. Hooker is currently an associate professor of radiology at Harvard Medical School. To learn more about the work coming from his lab and his incredible collaborators, visit: http://hookerlab.martinos.org.

Epigenetic Mechanisms in Human Memory: Quantification by Non-invasive PET Imaging in the Aged Brain

Jacob Hooker

Massachusetts General Hospital, Boston, MA, United States

Dysregulation of histone deacetylases (HDACs), a family of epigenetic enzymes, could tip the balance from healthy to pathological aging. Hypoacetylation of specific histone marks is linked to age-related neurodegenerative diseases, as demonstrated by preclinical and post mortem studies. In rodent models, HDAC expression and enzymatic activity increase with age in the hippocampus, leading to reductions in processes including histone acetylation, transcription of synaptic plasticity genes, and memory formation. The extent to which these observations relate to human neurobiology is unknown and specifically: 1) the location of HDAC changes in the brain over the human lifespan is not known; 2) sex differences in HDAC brain expression have not been measured; 3) changes in HDAC accompanying neurodegeneration, e.g. in Alzheimer's disease, have not been addressed in the living brain. These knowledge gaps are profound and compelled us to develop an imaging agent for class-I HDACs. Using [11C]Martinostat, an HDAC positron emission tomography (PET) radiotracer, we previously mapped HDAC expression in healthy young-adults and have recently extended our work to measure HDAC expression patterns of healthy subjects across the adult lifespan, in both men and women. Further, we have measured pathology-related changes that occur in Alzheimer's disease.

In this presentation, I will show: I) relative HDAC expression increases with age in cerebral white matter and correlates with age-associated disruptions in white matter microstructure; 2) sex-specific in vivo HDAC expression patterns exist in brain regions associated with socio-emotional processes and memory; 3) HDAC is consistently reduced in individuals with AD within the posterior cingulate, precuneus, inferior parietal, lateral temporal, and hippocampal cortices.

Blaine Roberts, MD—Florey Institute of Neuroscience and Mental Health



Blaine Roberts, MD, is an Associate Professor at the Florey Institute of Neuroscience and Mental Health at the University of Melbourne. He obtained his Bachelor of Science in Chemistry at Montana State University and his PhD in Biochemistry and Biophysics from Oregon State University.

His research group focuses on using proteomics to understand Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. He has an interest in understanding the role of metals in biology and has developed new proteomic technologies to measure metalloproteins. Further on, his group is using proteomics to characterize new blood borne biomarkers for Alzheimer's

and Parkinson's disease.

A β Complexes and Other Proteins Targets from Blood as Early Indicators of Amyloid Accumulation in the Brain

Blaine Roberts

Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia

Despite the prevalence of Alzheimer's disease, the lack of an early and accurate diagnostic test remains a significant hindrance to the field. Accumulation of amyloid in the brain is the major pathological hallmark of Alzheimer's disease. Pathological studies and molecular imaging using positron emission tomography (PET) for brain amyloid have demonstrated that accumulation of A β amyloid begins 20 years before clinical symptoms occur. This provides a large preclinical window for the prevention of Alzheimer's disease. However, PET or cerebral spinal fluid (CSF) are not practical for wide spread clinical use without prior symptoms. Thus, there is a need to develop a blood-based screen that can be implemented in general practice and determine who should be refereed for further testing and clinical trials. We have utilized samples from the Australian Imaging and Biomarker Lifestyle study of ageing (AIBL) to search for blood-based protein markers that reflect amyloid in the brain. Further, we have discovered that red blood cells contain proteins that correlate with brain amyloid. We will discuss our efforts to validate and qualify these protein markers for the diagnosis of Alzheimer's disease at the earliest point possible.

Tim West, PhD—C2N Diagnostics



Tim West, PhD, is the vice president of research and development at C2N Diagnostics. Since the company's inception in 2008, he has been overseeing multiple clinical and preclinical studies using the stable isotope labeling kinetics assay for measuring the effects of drugs on amyloid beta metabolism. Dr. West also oversaw development of methods for quantifying amyloid beta and other peptides in biofluids, using highly targeted quantitative mass spectrometry. He is the principal investigator on multiple grants from institutions such as the Alzheimer's Drug Discovery Foundation, Alzheimer's Association, the NIH, and the Michael J Fox Foundation. Dr. West helped oversee the development of the anti-tau antibody C2N-8E12.

Dr. West obtained his PhD in molecular cell biology and neuroscience from Washington University School of Medicine in Saint Louis. Here, Dr. West was also a recipient of a Kauffman Fellowship for Bio-Entrepreneurship. He received his BSc Honors in Molecular Biology at University College London.

Quantitative Assessment by Mass Spectrometry of Amyloid beta 42 and 40 in Plasma as a Peripheral Indicator of Brain Amyloidosis

Tim West

C2N Diagnostics, Saint Louis, MO, United States

Recent work from multiple groups has shown that amyloid beta concentrations in plasma can be used as an indicator of brain amyloidosis. C2N Diagnostics and our collaborators at Washington University have specifically focused on the use of quantitative mass spectrometry for absolute identification and quantification of amyloid beta peptides in human plasma samples. Consistent with findings in CSF and with other groups findings in plasma, we find that the ratio of Aβ42 to Aβ40 in plasma can be used to identify people with and without brain amyloidosis. The availability of a plasma test for pre-screening clinical trial participants has the potential for greatly increasing the speed of enrollment of patients with amyloidosis into clinical trials.

ADDF/Association for Frontotemporal Degeneration Partnership Program

Diana Cha, PhD—Brigham & Women's Hospital



Diana Cha, PhD, is conducting research focusing on how cells communicate with other cells during normal development and how alterations in these pathways contribute to disease. Her PhD was completed at Vanderbilt University under the guidance of Dr. James Patton, where she focused on the use of cell culture models to study the mechanisms and functional roles of extracellular RNAs secreted in tiny vesicles, called exosomes, in colorectal cancer cells. She had found that certain small RNAs, called micro RNAs (miRNAs), were secreted in exosomes exclusively by mutant cancer cells and could be taken up by healthy cells to influence gene expression. The goal was to identify candidate RNA biomarkers to create a non-invasive test for detecting certain types

of colorectal cancer and to guide potential efficacious treatments depending on a patient's tumor mutational status.

This work led to several first and second author publications, the Graduate Research Excellence award in Biological Sciences, the Giesla Mosig travel award to present at the Keystone extracellular vesicle meeting, as well as nomination for the CGS/Proquest distinguished dissertation award. Under the guidance of Dr. Dominic Walsh, an internationally recognized leader in AD research, Dr. Cha is further expanding her research training in exosomes to pursue her interests in the detection and development of biomarkers in Alzheimer's disease, as well as exploring non-cell autonomous mechanisms involved in neuropathologies.

Isolation of Neurally-derived Exosomes from Blood for the Diagnosis and Staging of Sporadic Alzheimer's Disease

Diana Cha

Brigham & Women's Hospital, Boston, MA, United States

The onset of Alzheimer's disease (AD) has a lengthy preclinical period before symptoms appear, making early diagnosis difficult. Furthermore, 20-30% of individuals diagnosed as having AD have other neurological disorders, while some individuals with AD are misdiagnosed. Currently, tests involved in diagnosis rely on measuring levels of two key proteins in AD: amyloid β eta (A β) and tau, but require sophisticated and expensive brain imaging techniques, or invasive sampling of cerebrospinal fluid (CSF). Given that early pathological changes are asymptomatic, there is an urgent need for an inexpensive and non-invasive test, such as blood-based biomarkers, that can be used to aid the diagnosis and prognosis of AD. Recently, it was discovered that brain cells release small extracellular vesicles (EVs) that contain contents reflecting the cell of origin. A subset of these vesicles are referred to as exosomes and can pass from the brain into the blood. Examining brain-derived exosomes in blood provides a non-invasive and cost-effective opportunity to detect changes occurring in the brain. Measuring key analytes, such as tau and A β , in brain exosomes isolated from blood can be used to aid diagnosis of AD. In our recent studies we have used: (1) clinical interviews and measurement of A β and tau in CSF to definitively identify 77 individuals as AD (n=18), mild cognitive impairment (MCI) of the AD type (n=17), and normal cognitively intact (NCI) controls (n=42); (2) we have prepared brain exosomes from the blood of these 77 individuals and completed measurement of tau and phospho- tau (p181). We are currently investigating whether our methods will yield an effective blood test for AD.

EMERGING CONCEPTS: DATA BLITZ

Pierre-Francois Meyer, PhD (cand.)—McGill University



Pierre-Francois Meyer, PhD (cand.), completed an undergraduate degree in Biology at Université Joseph Fourier, France in 2014. During that time he had the incredible opportunity to complete a semester abroad at Boston University where he developed a strong interest in neuroscience in general and neurodegenerative diseases in particular. He then pursued a master's degree at University College London's Institute of Neurology at Queen Square. After his year there, he joined Dr. John Breitner at McGill University's Center for Studies on the Prevention of Alzheimer's disease. He is currently pursuing his PhD studying the possible role of inflammatory mechanisms in AD pathogenesis and symptom expression.

CSF Proteins Indicate Biological Pathways of Symptomatic Resilience to AD Pathology

Kevin Clayton, PhD (cand.)—Boston University School of Medicine



Kevin Clayton, PhD (cand.), attended the Massachusetts Institute of Technology for his undergraduate career, graduating with a Bachelor's of Science in Chemical Engineering and a minor in biology in 2014. While an undergraduate, he worked three years in a material science lab where he tested and helped design microfluidic devices, resulting in his contribution to three publications. Kevin then entered into the medical research field and joined the Biomolecular Pharmacology PhD program at Boston University School of Medicine. He joined the Laboratory of Molecular Neurotherapeutics led by Tsuneya Ikezu of the Pharmacology department. Since then, he has written a review on microglia and proteopathy recently published in Frontiers and contributed to a publication that was accepted to the Journal of

Biological Chemistry on the characterization of a drug screening platform, which is the basis for his talk.

TREM2-TYROBP Coupling Modulation for the Reduction of Alzheimer's-mediated Neuroinflammation

Alexander Conley, PhD—Vanderbilt University Medical Center



Alexander Conley, PhD, is a second-year postdoctoral fellow at the Center for Cognitive Medicine, at Vanderbilt University Medical Center. Dr. Conley received his PhD in Cognitive Neuroscience from the University of Newcastle, Australia.

Dr. Conley works with Paul Newhouse, MD, on testing novel cholinergic compounds for the treatment of Alzheimer's and Mild Cognitive Impairment. His research specifically revolves around utilising cognitive tasks and neuroimaging to identify target engagement of these compounds.

Cognitive and Electrophysiological Markers of Cholinergic Functioning Following Administration of Muscarinic MI PAMs

IV. CLINICAL TRIALS

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.

A Proof-of-Concept Clinical Research Study of Efavirenz in Patients with Alzheimer's Disease Irina Pikuleva, PhD—Case Western Reserve University

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

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

Dopaminergic Therapy for Alzheimer's Disease Patients

Giacomo Koch, MD, PhD—Santa Lucia Foundation

Phase I Study of the Putative Cognitive Enhancer VU319, a Muscarinic MIPositive Allosteric Modulator for Alzheimer's Disease

Paul Newhouse, MD—Vanderbilt University Medical Center

Evaluating the Effects of the Novel GLP-I Analogue, Liraglutide, in Patients with Alzheimer's Disease (ELAD Study)

Paul Edison, MD, MRCP, PhD, FRCPI—Imperial College London

Irina Pikuleva, PhD—Case Western Reserve University



Irina Pikuleva, PhD, is the Carl F. Asseff Professor of Ophthalmology and the Director of the Visual Sciences Research Center at Case Western Reserve University.

Dr. Pikuleva received her PhD degree in Bioorganic Chemistry from the Byelorussian Academy of Sciences followed by postdoctoral training in Biochemistry at Vanderbilt University. In 1999, Dr. Pikuleva became a faculty member in the Department of Pharmacology and Toxicology at the University of Texas Medical Branch and then moved in 2008 to Case Western Reserve University.

The two major areas of research in Dr. Pikuleva's laboratory are studies of cholesterol metabolism in the brain and retina. The ultimate goal of these studies is to identify new therapeutic targets and treatments for diseases of the brain (Alzheimer's disease) and the eye (age-related macular degeneration and diabetic retinopathy).

A Proof-of-Concept Clinical Research Study of Efavirenz in Patients with Alzheimer's Disease

Irina Pikuleva

Case Western Reserve University, Cleveland, OH, United States

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Efavirenz is an FDA-approved anti-retroviral medication typically prescribed at 600 mg per day. CYP46A1 is the CNSspecific enzyme that converts cholesterol to 24-hydroxycholesterol, thereby controlling cholesterol elimination and turnover in the brain. We seek to investigate whether low dose efavirenz (50 mg/day and 200 mg/day) will engage and activate CYP46A1 in Alzheimer's disease (AD) patients. This study is designed as a two-center, randomized, placebocontrolled trial in 36 clinically-stable subjects with mild cognitive impairment/early dementia due to AD. Three groups of 12 participants each will receive either placebo or one of the two low doses of efavirenz (50 mg or 200 mg). Efavirenz or placebo will be given daily for 20 weeks. Four subjects from each of the two efavirenz groups will also participate in a unique Stable Isotope Labeling Kinetics protocol with deuterated water to more precisely measure efavirenz's effects on CNS cholesterol turnover. At various points throughout the study, participants will undergo neurological exams, neuropsychiatric assessments, and have blood, cerebral spinal fluid, and urine analyzed. This clinical study has already received an FDA exemption from the Investigational New Drug regulations and was also approved by the Institutional Review Boards. Patient recruitment should start in August of 2018.This will be the first clinical study to evaluate CYP46A1 and cerebral cholesterol turnover as pharmacologic targets in AD, as well as the anti-HIV drug efavirenz as a potential anti-AD medication.

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



Krista Lanctôt, PhD, has a PhD in Clinical Pharmacology from the University of Toronto, with additional training in pharmacoepidemiology. She is currently a Senior Scientist in Geriatric Psychiatry and in the Hurvitz Brain Sciences Program at Sunnybrook Research Institute, and the Head of Neuropsychopharmacology Research. She is a Full Professor of Psychiatry and Pharmacology/ Toxicology at the University of Toronto, Toronto, Ontario, Canada. Dr. Lanctôt is an active researcher in clinical pharmacology with over 250 publications. Her group's 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 and neuroimaging to further understand these symptoms and target pharmacotherapy.

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

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Background: Agitation is a common and persistent symptom in those with Alzheimer's disease (AD) and current pharmacotherapies have modest efficacy and/or poor safety.

Objective: To investigate the efficacy and safety of the synthetic cannabinoid nabilone for agitation in patients with moderate-to-severe AD.

Methods: This 14-week randomized double-blind cross-over trial compared nabilone (target: 1-2mg) to placebo (6 weeks each) with a 1-week washout between phases. Patients had AD (standardized Mini-Mental State Examination ($sMMSE \leq 24$)) and agitation (Neuropsychiatric Inventory-Nursing Home version (NPI-NH)-agitation/aggression subscore \geq 3). The primary outcome was agitation (Cohen Mansfield Agitation Inventory (CMAI)). Secondary outcomes included overall neuropsychiatric symptoms (NPI-NH), NPI-NH caregiver distress), cognition (sMMSE and Severe Impairment Battery (SIB) or Alzheimer's Disease Assessment Scale of Cognition), global impression (Clinician's Global Impression of Change (CGIC)), and adverse events.

Results: Thirty-nine patients (mean \pm SD age=87 \pm 10, sMMSE=6.5 \pm 6.8, CMAI=67.9 \pm 17.6, NPI-NH total=34.3 \pm 15.8, 77% male) were randomized. There were no cross-over or treatment-order effects. Treatment differences [95% CI] in CMAI (b=-4.0 [-6.5 to -1.5], p=0.003), NPI-NH total (b=-4.6 [-7.5 to -1.6], p=0.004), NPI-NH caregiver distress score (b=-1.7 [-3.4 to -0.07, p=0.041) and sMMSE (b=1.1 [0.1 to 2.0], p=0.026) all favoured nabilone. However, in those who completed the SIB (n=25) treatment differences favoured placebo (b=-4.6 [-7.3 to -1.8], p=0.003). CGIC improvement during nabilone (47%) and placebo (23%) was not significantly different (McNemar's Test, p=0.02), but treatment-limiting sedation was not significantly different (McNemar's Test, p=0.02), but

Conclusions: Nabilone significantly improved agitation in patients with moderate-to-severe AD. However, sedation and cognition should be closely monitored.

Funding: Alzheimer's Drug Discovery Foundation and Alzheimer Society of Canada.

Giacomo Koch, MD, PhD—Santa Lucia Foundation



Giacomo Koch, MD, PhD, is a neurologist and neuroscientist leading the non-invasive brain stimulation lab at Santa Lucia Foundation in Rome.

Dr. Koch has a long-lasting experience in clinical neurophysiology of the motor system and of cognitive functions, with a translational approach for rehabilitation of stroke and neurodegenerative disorders. His main expertise is in the application of non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS),

mainly used in combination with structural and functional magnetic resonance imaging (MRI) and in combination with electroencephalography (EEG). The main goals of his research are to understand the mechanisms underlying cortical plasticity and cortical connectivity in the healthy human brain, in order to develop novel therapeutic approaches for recovery of neurological functions. Prof. Koch is actively investigating the mechanisms of cortical plasticity in patients with Alzheimer's disease.

He was among the firsts to demonstrate the impairment of long term potenatiation (LTP) in this neurological condition and how dopaminergic therapy could potentially restore such abnormalities.

Dr. Koch has published >200 papers in peer reviewed journals (H index: 54).

Dopaminergic Therapy for Alzheimer's Disease Patients

Giacomo Koch

Santa Lucia Foundation, Rome, Italy

I will present our ongoing study funded by the ADDF on the effects of dopaminergic therapy in mild AD patients. This is a phase IIa 24-week, prospective, randomized, double-blind placebo-controlled study. The study is designed to evaluate the efficacy, safety, and tolerability of rotigotine transdermal patch 4 mg/24 hr versus placebo as add-on therapy with AChEI in patients with mild AD (Effects of Dopaminergic Therapy in Patients with Alzheimer's Disease (DOPAD); ClinicalTrials.gov Identifier: NCT03250741). The first aim is to verify the potential clinical impact of dopaminergic agonists on cognitive functions in patients with mild AD. The second aim is to test if rotigotine change brain physiology. We use multimodal neurophysiological tools such as transcranial magnetic stimulation combined with electroencephalography (TMS/EEG) to measure changes in cortical reactivity in the prefrontal cortex. We screened 145 AD patients. 96 AD patients have been found eligible for the purposes of the study and willed to participate. They have been randomly assigned to drug/placebo administration accordingly to the biostatistician model of randomization taking in account APOE genotype. 94 AD patients completed the study and have been evaluated with cognitive/behavioral evaluation after 24 weeks of rotigotine/placebo treatment. Preliminary results will be presented at the conference.

Paul Newhouse, MD—Vanderbilt University Medical Center



Paul Newhouse, MD, holds the Jim Turner Chair in Cognitive Disorders at Vanderbilt University School of Medicine and is Professor of Psychiatry, Pharmacology, and Medicine. He is Director of the Vanderbilt Center for Cognitive Medicine (VCCM) in the Department of Psychiatry and Behavioral Sciences at Vanderbilt University Medical Center. He is also a physician-scientist at the Veterans Affairs Tennessee Valley Health Systems Geriatric Research, Education, and Clinical Center (GRECC).

Dr. Newhouse received his undergraduate education at Kansas State University, attended medical school at Loyola University, Stritch School of Medicine, and completed his residency training in psychiatry at the Walter Reed Army Medical Center followed by a fellowship in Geriatric

Psychopharmacology Research at the National Institute of Mental Health. He is a diplomat of the American Board of Psychiatry and Neurology in both General Psychiatry and Geriatric Psychiatry and was awarded the American Psychiatric Association Profiles in Courage award in 2002 and the Loyola University Alumnus of the Year Award for Research in 2017.

Dr. Newhouse's research has focused on brain cholinergic mechanisms in cognitive aging and the role of nicotinic cholinergic receptor systems in normal and impaired cognitive functioning in humans. His work established the importance of brain nicotinic cholinergic receptor systems in normal cognitive processes and established these receptors as a therapeutic target in Alzheimer's disease and related conditions. He has pioneered the development of human models for new cognitive drug development including early first-in-human studies to the design and implementation of national multicenter trials. He has emphasized the development of novel cholinergic agents for clinical use in cognitive disorders and has established novel brain imaging and biomarker-based measures of brain drug effects through the use of novel pharmacologic-imaging methodologies. His research has been continuously funded by NIH since 1989 and he is funded currently by the National Institute on Aging, the Alzheimer's Association, the Alzheimer's Drug Discovery Foundation, and other private companies and foundations.

Phase I Study of the Putative Cognitive Enhancer VU319, a Muscarinic MIPositive Allosteric Modulator for Alzheimer's Disease

Paul Newhouse

Vanderbilt University Medical Center, Nashville, TN, United States

Loss of cholinergic signaling is principally related to cognitive decline in Alzheimer's Disease (AD) and stimulation of these receptors improves cognitive performance. While acetylcholinesterase inhibitors (AChEI) are modestly helpful in the early stages of AD, neurodegeneration limits their effectiveness, and warrants the development of alternative cholinergic treatments. Treatments that target the MI muscarinic cholinergic receptor may augment the effects and lengthen the effectiveness of AChEI's. Efforts to develop MI-selective agonists all showed cross-reactivity with M2 and M3 receptors and failed due to side effects. We have a mature development program for muscarinic cholinergic MI-positive allosteric modulators (PAM) with a lead compound VU0467319 (VU319), a highly selective MIPAM that has advanced to Phase I.

VU319 potentiates the response of the M1 receptor to acetylcholine, enhancing activity-dependent signaling. VU319 and related compounds show M1-mediated effects on hippocampal synaptic plasticity, excitatory drive to prefrontal cortex, and basal ganglia function and have robust effects on domains of both hippocampal and prefrontal cortical-dependent cognitive function in animal models that reflect cognitive domains impaired in AD. Preclinical PK and TK results show excellent oral bioavailability with the potential for once or twice daily dosing and no typical muscarinic toxicity at plasma levels consistent with CNS activity. These results support the hypothesis that M1-selective PAMs may have efficacy in improving cognitive function in AD.

Phase I studies consist not only of standard measures to establish maximum tolerated doses and safety, combining updated approaches to single and multiple ascending dose studies, but also to establish a functional biomarker of central MI target engagement. We explored whether VU319 treatment may potentiate MI in the CNS in humans by evaluating changes in electroencephalography (EEG) functions (e.g. altered ERPs, QEEG, and sleep EEG) at doses that do not produce typical muscarinic side effects. Oddball and memory ERP tasks are used to evaluate cognitive impact of MIPAM stimulation of Ach receptors. Additionally, we utilized specific cholinergically-responsive attention, psychomotor, and cognitive tasks developed in our laboratory. Together with safety measures, these novel cognitive biomarkers will establish the dose range to be used in future clinical studies utilizing measures that are relevant for improving cognitive function in AD.

Paul Edison, MD, MRCP, PhD, FRCPI—Imperial College London



Paul Edison, MD, MRCP, PhD, FRCPI, is a Clinical Senior Lecturer in the Division of Brain Sciences at Imperial College London and an honorary Professor at Cardiff University, Wales. He is also a Consultant Physician at Hammersmith Hospital, London.

Dr. Edison's research has focused on neuroimaging with novel molecular probes using PET and magnetic resonance techniques for imaging pathophysiological changes associated with Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases. He has extensive experience in PET imaging in different neurodegenerative and neuroinflammatory conditions. Combined with his clinical expertise in different types of degenerative diseases and dementia, he has investigated the relationship between

amyloid deposition, microglial activation, and glucose metabolism in different disorders, along with evaluating different transporters in the brain. His work in assessing microglial activation and amyloid load showed that both of these are increased in Alzheimer's disease, and microglial activation correlates with cognition in late stage of the disease, while amyloid load does not correlate with cognition. He has also demonstrated that there are two peaks of microglial activation in Alzheimer's trajectory. He was an MRC clinical research fellow before he became a HEFCE clinical senior lecturer.

His work now focuses on neuroinflammation, and the interplay between inflammation and immunity in neurodegenerative and neuroinflammatory disease, and relating these with genetic information. He is also evaluating the methods of modulating inflammation and amyloid in Alzheimer's disease, and the influence of cardiometabolic factors on the development of neurodegenerative diseases by means of clinical and pre-clinical studies. He leads the Imperial College Memory Research centre, and is the Chief Investigator of several imaging studies using PET and MRI, and heads multicentre studies evaluating novel treatment of Alzheimer's and other neurodegenerative diseases. He also runs a memory clinic at Imperial College Healthcare NHS Trust.

Evaluating the Effects of the Novel GLP-I Analogue, Liraglutide, in Patients with AD (ELAD Study)

Paul Edison

Imperial College London, London, United Kingdom

Liraglutide is a GLP-I analogue licensed for the treatment of type 2 diabetes mellitus (T2DM), a condition which has been identified as a risk factor for Alzheimer's disease (AD). It has been demonstrated that insulin signaling is desensitized in the brains of AD patients. Liraglutide has shown to have neuroprotective effect by multiple mechanism. Liraglutide does not cause hypoglycaemia in non-diabetic subjects.

The ELAD study is a multicenter, randomized, placebo-controlled, double-blind, Phase IIb trial of liraglutide in 206 patients with mild AD (MMSE \geq 22), conducted in several centers in the UK, and led by Imperial College London. Patients are randomized on a 1:1 ratio to receive liraglutide (1.8 mg daily by subcutaneous injection) or matching placebo.

The primary objective of the study is:

The change in cerebral glucose metabolic rate (rCMRglc) in the cortical regions (hippocampal, medial temporal lobe and posterior cingulate) from baseline to follow up (12 months) in the treatment group compared with the placebo group.

The secondary objectives of the study are:

- 1. The change from baseline to 12 months in z-scores for the ADAS Exec. (ADAS Cog and the Executive domain scores from the Neuropsychological Test Battery), CDR-SoB, and ADCS-ADL in the treatment group compared with the placebo group
- 2. The incidence and severity of treatment emergent adverse events or clinically important changes in safety assessments over 12 months
- 3. The changes in the MRI volume measures (entorhinal cortex and hippocampal volume, and ventricular volume), diffusion tensor imaging (DTI) and MR spectra from baseline to 12 months in the treatment group compared with the placebo group.
- 4. To establish whether there is a reduction in microglial activation in subjects with mild to moderate AD following daily subcutaneous injection of liraglutide for I year using TSPO PET
- 5. The change in the hippocampal, entorhinal and other cortical regional changes in tau deposition in treatment group compared to the placebo group.
- 6. Changes in levels of cortical amyloid load in treatment group compared to the placebo group.

NOTES



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The Centers for Therapeutic Innovation (CTI) is a pioneering research and development network initiated by pharma that uses an open innovation model to bring great ideas to fruition. Part of Pfizer, we are an entrepreneurial group that partners with leading academic medical centers and disease foundations with the aim of translating promising science into clinical candidates.

Our work is based on authentic collaboration, reflected in shared decision making and aligned incentives. We are committed to bringing together cutting-edge academic and industry resources to develop medicines faster and more efficiently. With locations in Massachusetts, New York and California, our facilities are conveniently located on or near academic campuses, allowing our partners to work closely with Pfizer scientists to translate research ideas into clinical applications, with the ultimate goal of moving a therapeutic hypothesis through Proof-of-Mechanism (PoM) in humans. Through CTI, Pfizer is transforming the traditional model of drug discovery. By departing from the historical pharma model of R&D, we are working to solve key challenges—namely the high cost and substantial time investment—of drug discovery. CTI is rewiring the R&D ecosystem to offer new, targeted therapies to patients living with disease.

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The Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University Medical Center and NewYork-Presbyterian Hospital brings together researchers and clinicians across disciplines to uncover the causes of Alzheimer's, Parkinson's, and other age-related brain diseases, and to discover ways to treat, prevent, and ultimately cure these diseases. In collaboration with the Departments of Pathology & Cell Biology and Neurology, research in the Taub Institute integrates genetic analysis, molecular and cellular studies, and clinical investigation to better understand complex neurodegenerative disorders. Funding for the Taub Institute's Alzheimer's Disease Research Center is provided by the NIH National Institute on Aging. In 2016, the Taub Institute was designated as a Center of Excellence for Alzheimer's Disease by the New York State Department of Health. For more information, visit the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at http://www.cumc.columbia.edu/dept/taub/

