



Alzheimer's
Drug Discovery
Foundation

18th INTERNATIONAL CONFERENCE ON **ALZHEIMER'S** DRUG DISCOVERY

Jersey City, NJ ◆ September 11-12, 2017

PROGRAM and ABSTRACTS

www.alzdiscovery.org

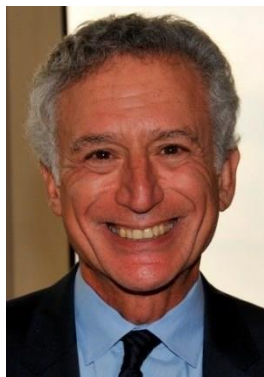


@TheADDF and #AlzDrugConf

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WELCOME!



On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to our *18th 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 & Company, Merck Research Laboratories, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Accelerate Cures/Treatments for Alzheimer's Disease, Charles River, and Harrington Discovery Institute. We would also like to thank our exhibitors; Brains On-Line, ChemBridge Corporation, Collaborative Drug Discovery, InterVivo Solutions, PsychoGenics, Renovo Neural, Inc, and Science Exchange and our media partners for their contribution. 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 2017 Young Investigator Scholarship winners: Hazem Abdelkarim, PhD, Mohammad Parvez Alam, PhD, Ramon Velazquez, PhD, Samuel Belfer, PhD (cand.), Kenneth Dahl, PhD, Eloise Ferreira, PhD, Holly Hunsberger, PhD, Yujin Kim, PhD (cand.), Zhibin Liang, PhD (cand.), Georgina Perez-Garcia, PhD, Andreia Silva da Rocha, BS, Levi Smith, PharmD, PhD (cand.), and Yiwei Wang, PhD (cand.). We encourage you attend the Data Blitz session and to visit their poster presentations which will be displayed throughout the meetings.

To help us plan an even better conference in 2018, please complete the survey to provide us with feedback and suggestions.

Welcome, once again, to the *18th International Conference on Alzheimer's Drug Discovery*!

Best Regards,

A handwritten signature in black ink that reads "Howard". The script is fluid and cursive, with a large 'H' and a long, sweeping tail on the 'd'.

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 **\$100 million to fund 550 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 2016, the ADDF raised **\$23 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*, 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.

Conference Presented by:



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2017 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 2017 Young Investigator Scholars are:

- **Samuel Belfer, PhD (cand.),** *University of Pennsylvania, Philadelphia, PA, USA*
- **Kenneth Dahl, PhD,** *Harvard Medical School and Massachusetts General Hospital, Boston, MA, USA*
- **Eloise Ferreira, PhD,** *University of the Witwatersrand, Johannesburg, South Africa*
- **Holly Hunsberger, PhD,** *Columbia University Medical Center, New York, NY, USA*
- **Yujin Kim, PhD (cand.),** *Mayo Clinic, Jacksonville, FL, USA*
- **Zhibin Liang, PhD (cand.),** *University of Hawaii at Manoa, Honolulu, HI, USA*
- **Georgina Perez-Garcia, PhD,** *Icahn School of Medicine at Mount Sinai, New York, NY, USA*
- **Andreia Silva da Rocha, BS,** *Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil*
- **Levi Smith, PharmD, PhD (cand.),** *Yale University, New Haven, CT, USA*
- **Yiwei Wang, PhD (cand.),** *University of Southern California, Los Angeles, CA, USA*

NEW THIS YEAR! 3 Young Investigator Scholars were selected to present their work in a 10-minute oral presentation. The recipients of this opportunity are:

- **Hazem Abdelkarim, PhD,** *University of Illinois at Chicago, IL, USA*
- **Mohammad Parvez Alam, PhD,** *University of California, Los Angeles, CA, USA*
- **Ramon Velazquez, PhD,** *Arizona State University, Tempe, AZ, USA*

PROGRAM

MONDAY, SEPTEMBER 11

8:00–5:30pm	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— <i>Alzheimer's Drug Discovery Foundation</i>
8:50–9:20	Keynote: Challenges in Developing Microglia--Targeted Therapeutics Stefan Lohmer, PhD— <i>Axxam SpA</i>
9:20–9:30	Q&A
Session I: Neuroinflammation	
Chair: Nick McKeehan, <i>Alzheimer's Drug Discovery Foundation</i>	
9:30–9:35	Session Overview: Nick McKeehan— <i>Alzheimer's Drug Discovery Foundation</i>
9:35–9:55	Lead Optimization of CRAC Channel Inhibitors for the Treatment of Alzheimer's Disease Milton Greenberg, PhD— <i>Vivreon Biosciences, LLC</i>
9:55–10:05	Q&A
10:05–10:25	Fingolimod Therapy in Models of Alzheimer's Disease Alpaslan Dedeoglu, MD, PhD— <i>Boston VA Medical Center and Boston University</i>
10:25–10:35	Q&A
10:35–11:00	EXHIBITOR SESSION BREAK
11:00–11:20	A Platform for Novel CNS Protein Kinase Inhibitor Discovery: IND-enabling Studies of an Isoform Selective Stress Kinase Inhibitor Candidate D. Martin Watterson, PhD— <i>Northwestern University</i>
11:20–11:30	Q&A
11:30–11:50	Nilvad Add-on Study: The Effects of Nilvadipine on Blood Pressure, Cerebral Autoregulation, -Blood Flow and -Damage in Alzheimer's Disease Jurgen Claassen, MD, PhD— <i>Radboud University Medical Center</i>
11:50–12:00	Q&A
12:00–12:20	Phase I Clinical Trial Results to Evaluate Safety and Anti-Inflammatory Actions of GC021109 in Patients with Alzheimer's Disease Philip Haydon, PhD— <i>GliaCure, Inc.</i>
12:20–12:30	Q&A
12:30–1:35	LUNCH and POSTER SESSION (All poster presenters should stand by their poster from 1:00–1:35PM)
Session II: Neuroprotection and Neural Regeneration	
Chair: Lauren Friedman, PhD, <i>Alzheimer's Drug Discovery Foundation</i>	
1:35–1:40	Session Overview: Lauren Friedman, PhD— <i>Alzheimer's Drug Discovery Foundation</i>
1:40–2:00	Testing of Selective DYRK1A Inhibitors as a Novel Treatment for Alzheimer's Disease Travis Duncley, PhD— <i>Arizona State University (ADDF/Harrington Scholar)</i>
2:00–2:10	Q&A
2:10–2:30	Fragment-Based Inhibitor Design of Human SCPs for Neuron Regeneration Yan Jessie Zhang, PhD— <i>University of Texas, Austin</i>
2:30–2:40	Q&A
2:40–3:00	Selective Cyclophilin Inhibitors for Neurodegeneration Michael Peel, PhD— <i>Cypralis Ltd.</i>
3:00–3:10	Q&A
3:10–3:40	EXHIBITOR SESSION BREAK
3:40–4:00	Therapeutic Potential of Dual Leucine Zipper Kinase Inhibitors in Alzheimer's Disease William Ray, PhD— <i>MD Anderson Cancer Center</i>
4:00–4:10	Q&A
4:10–4:30	Novel Regenerative Disease-Modifying Therapies for Alzheimer's Disease Leen Kawas, PhD— <i>M3 Biotechnology, Inc.</i>
4:30–4:40	Q&A
4:40–5:00	Results from a Pilot Clinical Trial of Allopregnanolone: A Regenerative Therapy for Alzheimer's Disease Roberta Diaz Brinton, PhD— <i>University of Arizona Health Sciences</i>
5:00–5:10	Q&A
5:10–5:20	Closing Remarks and Announcement of Young Investigator Scholarships Andrew Koemeter-Cox, PhD— <i>Alzheimer's Drug Discovery Foundation</i>
5:20–7:00	NETWORKING RECEPTION

PROGRAM (cont.)

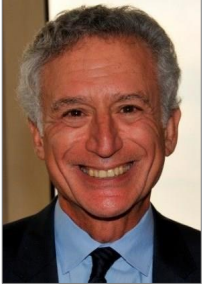
TUESDAY, SEPTEMBER 12

8:00–8:30	Continental Breakfast
8:30–8:35	Day 2 Opening Remarks Howard Fillit, MD—Alzheimer's Drug Discovery Foundation
8:35–9:05	KEYNOTE: Applying Radiochemical Approaches to Investigating Novel Targets for Neurodegenerative Disease Neil Vasdev, PhD—Massachusetts General Hospital and Harvard Medical School
9:05–9:15	Discussion and Q&A
Session III: Epigenetics and Cognitive Enhancing Chair: Yuko Hara, PhD, Alzheimer's Drug Discovery Foundation	
9:15–9:20	Session Overview: Yuko Hara, PhD—Alzheimer's Drug Discovery Foundation
9:20–9:40	Measuring Synaptic Vesicle Glycoprotein 2A (SV2A) Levels as a Translatable Marker of Pro-Synaptic Effects of HDAC Class I Selective Inhibitors Maria Quinton, PhD—Rodin Therapeutics
9:40–9:50	Q&A
9:50–10:10	Anti-Hypertension Drug Class: Which is the 'Best' at Reducing the Risk for AD? Lenore Launer, PhD—National Institutes of Health, National Institute on Aging
10:10–10:20	Q&A
10:20–10:50	EXHIBITOR SESSION BREAK
10:50–11:10	Glutamatergic Dysfunction in Cognitive Aging: Repurposing Riluzole for Mild Alzheimer's Disease Ana Pereira, MD—Icahn School of Medicine at Mount Sinai and The Rockefeller University
11:10–11:20	Q&A
11:20–11:40	Clinical Development of a Dual LSD1/MAO-B Inhibitor ORY-2001 Tamara Maes, PhD—Oryzon Genomics S.A.
11:40–11:50	Q&A
11:50am–12:10pm	A Phase IIa, Double-blind, Placebo-controlled, Biomarker Study of Atomoxetine in Subjects with Mild Cognitive Impairment Allan Levey, MD, PhD—Emory University
12:10–12:20	Q&A
12:20–12:50	EMERGING CONCEPTS: DATA BLITZ Young Investigator #1: Mohammad Parvez Alam, PhD—University of California Los Angeles Young Investigator #2: Hazem Abdelkarim, PhD—University of Illinois at Chicago Young Investigator #3: Ramon Velazquez, PhD—Arizona State University
12:50–1:45	LUNCH and POSTER SESSION <i>(All poster presenters should stand by their poster from 1:10-1:45PM)</i>
Session IV: Misfolded Proteins and Proteostasis Chair: Andrew Koemeter-Cox, PhD, Alzheimer's Drug Discovery Foundation	
1:45–1:50	Session Overview: Andrew Koemeter-Cox—Alzheimer's Drug Discovery Foundation
1:50–2:10	Small Molecule PDI Modulators Suppress Neurodegeneration Brent Stockwell, PhD—Columbia University
2:10–2:20	Q&A
2:20–2:40	Potent Small Molecule Inducers of Autophagy as Potential Agents to Lower Tau Levels and to Treat AD Steven Finkbeiner, MD, PhD—Gladstone Institutes and University of California, San Francisco
2:40–2:50	Q&A
2:50–3:10	Mitochondrial TDP-43 as a Novel Therapeutic Target for FTD Xinglong Wang, PhD—Case Western Reserve University School of Medicine <i>(Funded through the ADDF/Association for Frontotemporal Degeneration Partnership Program)</i>
3:10–3:20	Q&A
3:20–3:40	Tau Inside Neurally-Derived Extracellular Vesicles Dominic Walsh, PhD—Brigham & Women's Hospital and Harvard Medical School
3:40–3:50	Q&A
3:50–4:00	Closing Remarks: Howard Fillit, MD—Alzheimer's Drug Discovery Foundation

BIOS AND ABSTRACTS

CONFERENCE CHAIR

Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

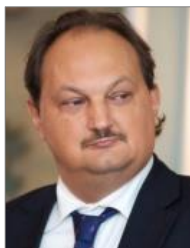


Howard Fillit, MD, a geriatrician, neuroscientist and a leading expert in Alzheimer's disease, is the founding Executive Director of the Alzheimer's Drug Discovery Foundation (ADDF). The ADDF's mission is to accelerate the discovery and development of drugs to prevent, treat and cure Alzheimer's disease, 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

Stefan Lohmer, PhD, Axxam SpA



Stefan Lohmer, PhD, is the President, Chief Executive Officer and Founder of Axxam. Since its inception in 2001, he has positioned Axxam as an innovator for the identification of bioactive small molecules applying high throughput screening for membrane proteins like GPCRs, Transporters and Ion Channels. Nearly all of the company's discovery projects are focused on neuroinflammation and neurodegeneration.

Dr. Lohmer brings more than 25 years of experience in the field of small molecule drug discovery. Prior to founding Axxam, he held various positions with increasing seniority at Bayer Pharmaceuticals, culminating in the World Wide Head of Genomics.

Dr. Lohmer holds a PhD in Molecular Biology and Genetics from the Albertus Magnus University Koeln, Germany. He is an inventor on several patents and has authored 20 peer-reviewed publications. Dr. Lohmer is also a member of the Board in Acousia, a company dedicated for generating treatment opportunities in Hearing Loss.

Challenges in Developing Microglia-targeted Therapeutics

Stefan Lohmer

Axxam SpA, Milan, Italy

Despite microglia being identified 100 years ago, Pio Del Rio-Hortega (1919), our knowledge about microglial ontogeny and functions have only considerably advanced recently.

Microglia are an unusual subpopulation of cells among the mononuclear phagocytes representing approximately 10% of the total cells within the adult central nervous system. Microglia are not derived from bone marrow monocytes, but originate from erythromyeloid progenitors in the yolk sac. Once within the CNS, microglia find a highly specialized environment characterized by the presence of developing neurons and radial glia, but devoid of other glial cells.

Unlike any other tissue-resident macrophage, microglia are separated from the circulatory compartment by the blood brain barrier, and as such develop and survive for their entire lifespan without coming into contact with blood, unless there is a traumatic event.

Recent work has demonstrated, very elegantly, that the classical definition of microglia as “resting”, used to describe physiological conditions, doesn't fit with the current understanding. Even in healthy conditions, microglia never “sleep” but continuously monitor the surrounding environment.

Furthermore, microglia are selectively adapted to serve critical functions of the CNS by instructing programmed cell death and the removal of new neurons, or by pruning, elimination, and maturation of synapses.

The extreme flexibility and sensitivity of microglia, necessary to properly execute their job, are some of the reasons why drug discovery efforts are extremely challenging for these unique immune cells. The emerging “new biology” around microglia will help pave the way for new therapeutic routes.

I. Neuroinflammation

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.

SESSION OVERVIEW

Neuroinflammation has long been recognized as a factor in Alzheimer's patient brains.

Historically, inflammation was thought to be a consequence of the disease process, but new research findings identifying inflammation related genes that increase one's risk of developing Alzheimer's disease have indicated inflammation as a fundamental trigger of disease progression and as a promising therapeutic strategy.

The talks in this session will highlight unique neuroinflammation targets and repurposing opportunities relevant to inflammation.

Lead Optimization of CRAC Channel Inhibitors for the Treatment of Alzheimer's Disease

Milton Greenberg, PhD—Vivreon Biosciences, LLC

Fingolimod Therapy in Models of Alzheimer's Disease

Alpaslan Dedeoglu, MD, PhD— Boston VA Medical Center and Boston University

A Platform for Novel CNS Protein Kinase Inhibitor Discovery: IND-enabling Studies of an Isoform Selective Stress Kinase Inhibitor Candidate

D. Martin Watterson, PhD—Northwestern University

Nilvad Add-on Study: The Effects of Nilvadipine on Blood Pressure, Cerebral Autoregulation, -Blood Flow and -Damage in Alzheimer's Disease

Jurgen Claassen, MD, PhD—Radboud University Medical Center

Phase I Clinical Trial Results to Evaluate Safety and Anti-Inflammatory Actions of GC021109 in Patients with Alzheimer's Disease

Philip Haydon, PhD—GliaCure, Inc.

Milton Greenberg, PhD, Vivreon Biosciences, LLC



Milton Greenberg, PhD, is a co-founder and the President of Vivreon Biosciences, LLC, where his passion is to solve unmet needs in chronic diseases. Dr. Greenberg's research interest is lead optimization and preclinical development of small molecule inhibitors of the Ca^{2+} release-activated Ca^{2+} (CRAC) channel. The CRAC channel is a molecular target required for chronic microgliosis, and Vivreon Biosciences is the first company to pursue the CRAC channel for the treatment of Alzheimer's disease. He led the Vivreon team in assay development, identification of a series of compounds that block CRAC channel function with nanomolar potency, and patent submission.

Dr. Greenberg is also an Assistant Adjunct Professor at the University of California, Irvine. He holds a PhD in Biomedical Sciences from the University of California, Irvine.

Lead Optimization of CRAC Channel Inhibitors for the Treatment of Alzheimer's Disease

Milton Greenberg

Vivreon Biosciences, LLC, San Diego, CA, USA

Vivreon Biosciences is an innovative life sciences company that is developing a series of novel small molecule, Ca^{2+} channel inhibitors for the treatment of Alzheimer's disease (AD). Our lead compound series achieves neuroprotection by an entirely new mechanism – inhibition of Ca^{2+} release-activated Ca^{2+} (CRAC) channels to block microgliosis. Microglial-associated genes are risk factors for AD, and chronic microgliosis contributes to progressive neurodegeneration in AD. The CRAC channel is an exciting new pharmacological target for microgliosis associated with AD, because it is upstream in the inflammatory cascade and necessary for neuroinflammatory responses. To target this pathway for the treatment of AD, Vivreon has discovered a lead compound series with oral bioavailability that penetrates into the central nervous system (CNS) very efficiently, shows no neurotoxicity in the Irwin test of CNS integrity, and demonstrates neuroprotection in a mouse model of microgliosis. The lead series inhibits microgliosis by suppressing M1-like NF- κ B activity, while preserving M2-like phagocytosis. With support from the Alzheimer's Drug Discovery Foundation, we have successfully improved upon these favorable properties through medicinal chemistry lead optimization followed by biological screening. Vivreon's preclinical goal is to develop a clinical candidate molecule, derived from the lead, which is ready for entry into full IND-enabling studies. Upon successful completion of the program, our clinical candidate will be the first to specifically target the CRAC pathway for neuroprotection in AD, thus comprising an entirely new tool in the battle against AD.

Alpaslan Dedeoglu, MD, PhD, Boston VA Medical Center and Boston University



Dr. Alpaslan Dedeoglu graduated with his MD from the Istanbul University and received his PhD in Neuropharmacology from Marmara University. He completed post-doctoral fellowships in Neuropharmacology at the University of Arizona Health Sciences Center and at Massachusetts General Hospital, and is currently a Research Health Scientist and the Director of the Translational Neurotherapeutics Laboratory at VA Boston Healthcare System and an Associate Professor of Neurology at Boston University Medical School. His major research interest focuses in the use of animal models to test novel therapies for neurodegenerative diseases including Alzheimer's disease and Amyotrophic lateral sclerosis. He uses an ample approach to assess the therapeutic effects on multiple outcome measures – behavior, immunohistochemistry, biochemical and neurochemical analyses. His preclinical trials also include magnetic resonance spectroscopy to determine the neurochemical profile of brain tissue increasing the translational value of the studies.

Fingolimod Therapy in Models of Alzheimer's Disease

Alpaslan Dedeoglu

Boston VA Medical Center and Boston University, Boston, MA, USA

There is evidence that lipid metabolism is abnormal in Alzheimer's disease (AD) brain. The abnormal sphingolipid metabolism in AD brains leads to the accumulation of pro-apoptotic and pro-inflammatory ceramides and sphingosine while levels of sphingosine 1-phosphate (SIP) that enhances cell proliferation and antagonizes apoptosis decrease. In AD, SIP levels decline in a region-specific manner during the course of the disease and its levels correlate well with the development of neurofibrillary tangles (NFT) and amyloid β (A β) pathology. Changes in SIP signaling may be central to the inflammatory and immune aspect of AD pathogenesis and the action of specific modulators of the SIP signaling system may improve AD-related pathology and behavior. One such modulator is Fingolimod, a structural analog of sphingosine that like sphingosine gets phosphorylated and activated in vivo. Fingolimod has been approved by the FDA for the treatment of relapsing remitting multiple sclerosis (RRMS). In RRMS Fingolimod prevents the infiltration of lymphocytes into the CNS and, after crossing the blood-brain-barrier, directly promotes remyelination and exerts neuroprotective effects on astrocytes. We have recently reported that Fingolimod, orally given to 5xFAD mice from 1-3 months of age, decreases the activation of microglia and reactive astrocytes, decreases A β levels, and increases neurogenesis. We expanded our original report with a dose response study of Fingolimod (0.03, 0.1, 0.3 and 1 mg/kg/day) in 5xFAD mice treated from 1-8 months of age. As controls, untreated 5xFAD and non-transgenic littermates were included (n=10). At 8 months of age, the learning and memory were analyzed in the water maze test. After that, mice were euthanized and blood and brains were saved for the analysis of complete blood count and for the analysis of AD related pathology, by ELISA, immunohistochemistry and magnetic resonance spectroscopy. Our results showed that at 1mg/kg/day Fingolimod decreased the lymphocyte counts and the A β levels and that lower doses of Fingolimod decreased the activation of microglia and reactive astrocytes, increased neurogenesis, restored the hippocampal levels of GABA and glycerophosphocholine, and improved memory. These results demonstrate that Fingolimod treatment affects a number of different markers of AD pathology and behavior with the lowest dose used, 0.03 mg/kg/day, providing protection for the largest number of variables tested.

D. Martin Watterson, PhD, Northwestern University



Daniel Martin Watterson, PhD, is the John G. Searle Professor at Northwestern University and is Professor of Pharmacology in the Feinberg School of Medicine.

His research is focused on elucidation and molecular characterization of signal transduction pathways, the study of their role in pathophysiology, and the development of novel molecular probes to attenuate pathophysiology progression.

Previous academic positions included Professor of Pharmacology and HHMI Investigator at Vanderbilt University School of Medicine, and Associate Professor and Mellon Fellow at The Rockefeller University.

A Platform for Novel CNS Protein Kinase Inhibitor Discovery: IND-enabling Studies of an Isoform Selective Stress Kinase Inhibitor Candidate

D.M. Watterson¹, S.M. Roy¹, J. Pelletier¹, L.J. Van Eldik², M. Windisch³, O. Arancio⁴

¹Northwestern University, Chicago, IL, USA; ²University of Kentucky, Lexington, KY, USA; ³Neuroscios, St. Radegund/Graz, Austria; ⁴Columbia University, New York, NY, USA

Diverse CNS disorders display common pathophysiology progression themes. The innate immunity and synaptic dysfunction theme was examined for intervention potential using in vivo probes delivered from a platform that develops blood-brain barrier penetrant novel small molecules de-risked for major ADMET liabilities. Both single molecular target and phenotypic approaches are used to explore the innate immunity and synaptic dysfunction theme. The molecular target first identified as a regulator of stressor-induced increases of inflammatory cytokines associated with tissue injury is p38MAPK. Brain p38 α MAPK is a S/T protein kinase found in both neurons and glia and activated in Alzheimer's disease (AD) brain. Therefore, development of an isoform selective p38 α MAPKI drug candidate might provide a single target drug with pleiotropic pharmacological effects due to p38 α MAPK up-regulation in both cell types with their distinct pathophysiology. MW01-18-150SRM (= MW150) is a unique, isoform selective, p38 α MAPK inhibitor recently taken through investigational new drug (IND)-enabling safety pharmacology and toxicology testing with promising outcomes.

MW150 was developed through the integrated use of molecular fragment expansion driven by structural genomics and pharmacoinformatics. Structures with detailed information are available to the public through the Protein Database (PDB IDs: 4ZTH, 4EWQ, 4F9W, 4F9Y and 4R3C; control structure 4FA2). The med chem optimization was driven by recursive pharmacological and activity screens to develop novel candidates. Kinome-wide screens were used to monitor isoform selectivity during optimization, yielding p38 α MAPK as the only target with IC₅₀ < 1 μ M. Large-scale functional screens of GPCR agonist and antagonist activity and Panlab panel screens documented lack of crossover to other CNS drug target classes or known adverse event associated targets. Efficacy was demonstrated in two independent AD mouse models based on APP and in the rTg4510 mouse model that expresses the human P301L tau mutation linked with familial frontotemporal dementia.

Concentration dependent inhibition by MW150 of endogenous p38 α MAPK in activated glia was correlated with concentration dependent attenuation of inflammatory cytokine overproduction, indicative of a link between target engagement and a potential pharmacodynamic end point. Dose range finding with toxicokinetics identified NOAELs and the absence of liver injury, a safety issue in previous mixed kinase p38 α MAPKI candidates. Overall, the IND-enabling studies provide significant risk reduction for planned first-in-human investigations. GMP clinical drug substance was released this winter, providing the foundation for immediate start of phase I studies.

The potential impact of future MW150 clinical studies are significant from the perspective of AD, tauopathies and related dementias as it represents an alternative disease modifying intervention that is complementary to extant approaches. Clinical success of MW150 would also impact the prevailing landscape of protein kinase inhibitor drugs as it might help fill the gap in approved CNS kinase inhibitor drugs as well as expand and diversify the S/T protein kinase approved drug armamentarium. Supported by NIH awards R01 R01AG31311 and U01AG043415 and funding from ADDF.

Jurgen Claassen, MD, PhD, Radboud University Medical Center



Jurgen Claassen MD, PhD, works as a geriatrician and clinical scientist at Radboud University Medical Center (Nijmegen, The Netherlands).

He obtained his PhD in cerebral hemodynamic regulation in aging and Alzheimer's disease in a research collaboration with UT Southwestern Medical Center (Dallas, TX).

Dr. Claassen's research focuses on disorders of blood pressure and cerebral blood flow in aging and Alzheimer's disease, and combines circulatory physiology with neuroscience.

Nilvad Add-on Study: The Effects of Nilvadipine on Blood Pressure, Cerebral Autoregulation, -Blood Flow and -Damage in Alzheimer's Disease

Jurgen Claassen

Radboud University Medical Center, Nijmegen, Netherlands

As a substudy to the NILVAD trial, which investigated the effects of nilvadipine (calcium-channel blocker) on cognitive decline in 500 mild to moderate AD patients over 18 months, we investigated, in 51 AD patients, the effects of nilvadipine on blood pressure and cerebral blood flow. Previous studies suggest early cerebrovascular dysfunction in AD linked to vascular effects of amyloid-beta, including reductions in cerebral blood flow and impairment in cerebral autoregulation. In addition, impaired blood pressure control due to baroreflex impairment leading to orthostatic hypotension has been suggested; combined, these factors would predispose to cerebral hypoperfusion. Pilot studies in AD indicated that nilvadipine lowers blood pressure without increased risk of orthostatic hypotension, and without lowering cerebral blood flow—in contrast, increased flow was reported.

We have performed continuous measurements of blood pressure (Finapres) and cerebral blood flow (ultrasound: transcranial Doppler), and structural and perfusion (arterial spin labeling) MRI at baseline and at 6 and 18 months follow-up.

I will discuss recruitment and retainment strategies, and present preliminary results.

Philip Haydon, PhD, GliaCure, Inc.



Philip Haydon, PhD, is considered a pioneer and leader in the field of glia research. In 1999 his group published a seminal work in *Trends in Neuroscience* in which it coined the phrase “the tripartite synapse”. This paper showed that signaling in the brain is an intricate interplay among neurons, glia and neurotransmitters. Dr. Haydon has gone on to create a significant reputation for his research into the role of glia in a range of neurological and neuropsychiatric disorders and the potential for focusing on these cells as therapeutic targets. Based on his research in 2011 he formed the drug discovery company GliaCure, which has gone on to successfully complete a Phase Ib clinical trial in patients with mild and moderate Alzheimer’s disease.

Dr. Haydon’s initial academic appointment was at Iowa State University. During his tenure there he served as Program Director of the Signal Transduction Training Group, Director of the Laboratory of Cell Signaling and Associate Director of the Microanalytical Instrumentation Center. In 2001 he joined the Department of Neuroscience at the University of Pennsylvania as a Full Professor, going on to become the Director of the Center for Dynamic Imaging of Nervous System Function, Director of the Silvio O. Conte Center for Studies of the Tripartite Synapse, and Vice Chair of the Department. He was recruited in 2008 to become the Annetta and Gustav Grisard Professor and Chair of the Department of Neuroscience at Tufts University and, in 2011, was appointed Director of the newly-formed Tufts University Neuroscience Institute.

Dr. Haydon is widely sought after as a speaker on glial research both in the USA and internationally. He has presented over 246 invited lectures, has authored more than 140 peer-reviewed publications, and has served in various capacities on NIH grant review panels.

Phase I Clinical Trial Results to Evaluate Safety and Anti-Inflammatory Actions of GC021109 in Patients with Alzheimer's Disease

Philip Haydon

GliaCure, Inc., Boston, MA, USA

In our studies, we have been investigating both the ability of the P2Y6 receptor to modulate CSF levels of amyloid and the clearance of amyloid from the CNS to the CSF. Treatment of a mouse model of AD with a prodrug of an agonist for the P2Y6 receptor leads to a reduction in CNS amyloid and an elevation of the level of CSF amyloid.

Our observations in this mouse model have been validated by the results of a clinical trial in which we determined that the prodrug, GC021109, leads to elevated CSF amyloid in patients with mild AD. Of great interest, patients carrying the APOE4 allele had a significantly attenuated response to GC021109. These results have led us to postulate that the P2Y6 receptor stimulates a clearance pathway, potentially involving the recently described glymphatic system, which causes the efflux of misfolded proteins, including amyloid, from the interstitial fluid to the CSF. In support of this notion, treatment of mice with GC021109 followed by microinjection of amyloid into their brains leads to increased accumulation of amyloid in the CSF.

II. Neuroprotection and Neural Regeneration

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



Lauren Friedman, PhD, is the Acting 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.

SESSION OVERVIEW

Alzheimer's disease and related dementias are characterized by early loss of synapses and subsequent neurodegeneration.

As such, a growing number of programs are developing drugs to enhance neuronal survival and regeneration and inhibit neuronal cell death mechanisms that are activated by injury or stress.

This session will feature therapeutic approaches that target neurotrophic factors or hormones that promote neuronal survival, strategies to convert neural stem cells into mature neurons, and approaches to prevent neuronal death.

Testing of Selective DYRK1A Inhibitors as a Novel Treatment for Alzheimer's Disease

Travis Dunckley, PhD—Arizona State University

ADDF/Harrington Scholar

Fragment-Based Inhibitor Design of Human SCPs for Neuron Regeneration

Yan Jessie Zhang, PhD—University of Texas, Austin

Selective Cyclophilin D Inhibitors for Neurodegeneration

Michael Peel, PhD—Cypralis Ltd.

Therapeutic Potential of Dual Leucine Zipper Kinase Inhibitors in Alzheimer's Disease

William Ray, PhD—MD Anderson Cancer Center

Novel Regenerative Disease-Modifying Therapies for Alzheimer's Disease

Leen Kawas, PhD—M3 Biotechnology, Inc.

Results from a Pilot Clinical Trial of Allopregnanolone: A Regenerative Therapy for Alzheimer's Disease

Roberta Diaz Brinton, PhD—University of Arizona Health Sciences

Travis Dunkley, PhD, Arizona State University



Travis Dunkley, PhD, is a trained molecular and cellular biologist. He has been studying neurodegenerative diseases for 15 years, with an emphasis on Alzheimer's and Parkinson's diseases. Expertise includes genomic approaches to studying complex human disease and development of cellular assays to measure surrogate phenotypes relevant to neurodegeneration.

He has published numerous papers in these areas. His group was one of the first to identify DYRK1A as an important tau-phosphorylating kinase and developed new assays to screen novel inhibitors for activity.

Dr. Dunkley is currently at the ASU BioDesign Institute, member of the Arizona Alzheimer's consortium, and is the co-Founder of Illuminos Therapeutics.

Testing of Selective DYRK1A Inhibitors as a Novel Treatment for Alzheimer's Disease

Travis Dunkley*

Arizona State University, Tempe, AZ, USA

The hyperphosphorylation of the microtubule-stabilizing protein tau at key epitopes contributes to tau dysfunction and aggregation into neurofibrillary tangles (NFTs), a hallmark pathological finding of Alzheimer's disease (AD) that is highly correlated with dementia severity. Compounds that inhibit the phosphorylation of tau may provide a significant therapeutic option to modify the course of tau dysfunction and cognitive deficits in AD. Similarly, compounds that modulate phosphorylation of amyloid precursor protein (APP) and reduce elevated production of neurotoxic β -amyloid peptides may induce beneficial effects in amyloid plaque reduction with concomitant improvements in cognitive deficits. We earlier reported that dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) directly phosphorylates tau protein and that reduced expression of DYRK1A protein through siRNA-mediated gene silencing caused significant reductions to phosphorylated tau. Utilizing a de novo design approach based on 3 small molecule x-ray structures available in 2012, a sizeable synthetic effort (> 300 small molecule targets prepared) combined with triaging via a thorough tiered screening paradigm has delivered two highly selective, brain penetrant molecules. Dosing in the 3x-TgAD model of AD revealed a well-tolerated small molecule, which simultaneously inhibits phosphorylation of tau and APP, translating into significant reductions of both insoluble phosphorylated tau and amyloid plaques, whilst also alleviating cognitive deficits in these animals. These results suggest that efficient and specific inhibition of DYRK1A activity may provide a viable therapeutic approach for AD through novel dual modulation of both tau and APP pathways.

**ADDF/Harrington Scholar*

Yan Jessie Zhang, PhD, University of Texas, Austin



Yan Jessie Zhang, PhD, is currently an associate professor in the Department of Molecular Biosciences in University of Texas, Austin. Dr. Zhang obtained her PhD from The Scripps Research Institute in 2014 (mentor: Dr. Ian A. Wilson), focusing on the structure-based drug design. Trained by the top crystallographers (Drs. Brian Matthews, Ian Wilson and Joseph Noel), Dr. Zhang specializes in the design of small molecules or the engineering of bio-molecules guided by protein structural information. The fruits of such design are reported in high impact journals such as Nature, Nature Medicine, Nature Immunology and Molecular Cell.

Dr. Zhang received awards recognizing her achievement in research such as Margaret C. Etter Early Career Award in American Crystallographic Association in 2015. She was also voted as Professor of the Year in University of Texas at Austin by student body.

Fragment-Based Inhibitor Design of Human Scps for Neuron Regeneration

Yan Jessie Zhang

University of Texas, Austin, TX, USA

Progression from the pluripotent stem cell to a neural lineage follows a pattern of distinct gene expression. A master silencing complex, REST complex, controls ~10% of neuronal gene expression and functions as a hub to coordinate neural gene expression during differentiation. REST prevents the expression of neuronal gene in stem cells and non-neuronal cells. Inhibiting REST alone is sufficient to lead to neuron differentiation but as a multi-protein complex, REST complex is difficult to target with chemical compounds. A recent discovery showed that a regulatory protein, Scps, can modulate the function of REST. Therefore, we searched for chemical compounds selective to Scps to control the function of REST and promote neuron regeneration.

During our preliminary screening, we were able to identify a compound that selectively inhibits Scps with moderate potency. In order to optimize the efficacy and pharmacological properties, the structure activity relationship was investigated and high-resolution structures were determined. Intriguingly, a unique cation-pi interaction seems to be crucial for the selective inactivation of this human phosphatase. The core for selective inhibition has been identified and compounds were designed with the central scaffold.

Michael Peel, PhD, Cypralis Ltd.



Michael Peel, PhD, has over 25 years' experience in the pharmaceutical industry and joined Cypralis from Scynexis Inc, where he was Executive Director of Discovery. Whilst at Scynexis he was responsible for building the chemistry services group and directing DMPK and biology for in-house research. Dr. Peel also led the in-house cyclophilin inhibitor programs, opening several avenues into new biology and new potential applications for cyclophilin inhibition in virology, ophthalmology and immunology.

Prior to Scynexis, Dr. Peel worked for GlaxoSmithKline., based in Research Triangle Park, North Carolina where he led several research projects in inflammation, cancer and virology, and played a key role in GSK's kinase research effort throughout.

He holds a PhD in chemistry from Sheffield University and undertook his post-doctoral studies at Wayne State University.

Selective Cyclophilin D Inhibitors for Neurodegeneration

Michael Peel

Cypralis Ltd., Cambridge, United Kingdom

The role of mitochondria in determining the fate of cells undergoing programmed cell death has been firmly established over the last decade with activation of the Mitochondrial Permeability Transition Pore (MPTP) emerging as a critical trigger for apoptotic and necrotic processes. Cyclophilin D (Cyp D) is localized to the mitochondria, is a modulator of the MPTP and is regarded by many to be the most practical pharmaceutical target in the mitochondrial transition pore. CypD ablation delays disease onset and extends lifespan in mutant α -synuclein models of Parkinson's disease, while intracerebral delivery of CsA, increased lifespan in a transgenic (SOD1-G93A) model of ALS. Notably, A β mediated mitochondrial, neuronal and synaptic dysfunction can be blocked by the elimination of CypD. The two principal areas that need to be addressed toward demonstration of the effects of cyclophilin D inhibition in neurodegeneration are achieving selective cyclophilin D inhibition activity, and demonstrating brain penetration for the inhibitors.

Cypralis has used x-ray crystal structure data of its lead series bound to CypD to design new compounds that show selectivity toward CypD and demonstrate neuronal cell protection by delayed MPTP opening. Further, the identification of a compound with significant brain exposure following sub-cutaneous dosing will allow, for the first time, evaluation of CypD inhibition in several models of neurodegeneration. The presentation will describe the most recent advances made toward the design and evaluation of advanced compounds from the Cypralis neurodegeneration program.

William Ray, PhD, MD Anderson Cancer Center



William Ray, PhD, is the Director of The Neurodegeneration Consortium (NDC), a multi-institutional collaboration whose mission is to slow, stop, or reverse AD and related neurodegenerative diseases. The NDC is a collaboration between investigators at Baylor College of Medicine, the Massachusetts Institute of Technology, and the drug discovery center based at MD Anderson Cancer Center in Houston, TX.

Prior to joining the NDC in April 2015, Dr. Ray was Director, CNS Research at Takeda Pharmaceuticals, and led several drug discovery projects from basic research into clinical development for schizophrenia, Parkinson's disease, autism, and other CNS disorders. He joined Takeda in 2013 as part of their acquisition of the biotech start-up Envoy Therapeutics, where he was Senior Director and responsible for developing both a pipeline of CNS therapeutics as well as a platform technology. Prior to Envoy Therapeutics, Dr. Ray spent 11 years at Merck, where he led multiple research projects in Alzheimer's disease, including MK-7622, Merck's investigational M1 muscarinic receptor potentiator.

Dr. Ray earned his PhD from Washington University Medical School in Neuroscience.

Therapeutic Potential of Dual Leucine Zipper Kinase Inhibitors in Alzheimer's Disease

William Ray

The Neurodegeneration Consortium, MD Anderson Cancer Center, Houston, TX, USA

Axonal injury triggers an evolutionarily conserved process by which the axon is retracted and, if the injury is severe, the neuron is eliminated. The pathway regulating this response to injury is governed by Dual Leucine Zipper Kinase (DLK), a neuronal serine/threonine MAP kinase that activates the well-studied phospho-Jun N-terminal Kinase (pJNK)/phospho-c-Jun (p-c-Jun) neurodegeneration pathway. Neurons from mice lacking DLK are resistant to a range of acute neuronal insults, and JNK and c-jun phosphorylation in response to axonal damage is nearly completely absent, indicating that DLK is the primary regulator of this key cell death pathway in injured neurons.

While there has been great progress understanding programmed neuronal death during development and resulting from trauma, the mechanisms by which neurons degenerate in slowly progressing conditions such as AD are less clear. Human post-mortem and animal model data have implicated the pJNK/p-c-Jun pathway in AD and other neurodegenerative conditions. However, the role of DLK, if any, has not been addressed.

Here we demonstrate that in AD mouse models, DLK protein accumulates at initial sites of axonal damage in the dystrophic neurites near amyloid plaques (5xFAD mice) and in swollen axons (rTg4510 and p25/CDK5). DLK localization to these structures is also evident in human AD brain specimens. To understand the functional consequences of DLK accumulation, we tested a set of DLK inhibitors and found that they protect mouse dorsal root ganglion neurons from NGF deprivation. Next, we used a selective DLK inhibitor with good brain penetration and a long mouse half-life to determine if DLK is in fact driving the pJNK/p-c-Jun pathway in these animal models. After treatment for 5 days the elevated p-c-Jun in rTg4510 mice was completely normalized, and likewise, sub-chronic DLK inhibition blocked pathway activation in 5xFAD and in p25/CDK5 mice. Based on these data we developed small molecule inhibitors of DLK suitable for pharmacological validation. Our lead molecule is potent against DLK (12 nM IC₅₀), and is highly selective in vitro as determined by kinase panel binding assays, in vivo as determined by kinome-wide receptor occupancy in brain homogenates, and has no significant activity in a broad pharmacology panel. It is orally available with 1:1 free brain/plasma ratio and low clearance across species with a predicted human half-life of 12 hours. This compound has the biophysical, safety, and ADME properties of a preclinical candidate and thus could be suitable to determine if DLK is in fact governing the pJNK/p-c-Jun pathway in human AD patients.

Leen Kawas, PhD, M3 Biotechnology, Inc.



Leen Kawas, PhD, is the CEO at M3 Biotechnology, and has lead the business and financial growth of M3 from early proof-of-concept stage towards human testing planned for this year.

Dr. Kawas won Entrepreneur of the Year award from the Association of Washington Business (December 2016), was selected as one of EY's Winning Women Entrepreneur (November 2016), won the 40 under 40 award from the Puget Sound Business Journal (July 2016), was an Entrepreneur of the Year Finalist for EY (June 2016) and a Young Entrepreneur of the Year Finalist for GeekWire (June 2016). She was named one of Seattle's Most Influential People by Seattle Magazine (November 2015) and one of the Women to Watch in Life Sciences by the Washington Biotechnology and Biomedical Association (July 2015).

She also serves on multiple boards, including the Washington Governor's Life Science Advisory Board, the Scientific Review Board for the Alzheimer's Drug Discovery Foundation and the Alzheimer's Association-Washington local Chapter Board.

Dr. Kawas earned a doctorate in molecular pharmacology from Washington State University, and received the Harriett B. Rigas and Karen DePauw awards for academic achievement and leadership skills. She holds a Doctor of Pharmacy (PharmD) from the University of Jordan. Dr. Kawas also completed the Executive Business Training Program at the Foster School of Business, University of Washington.

Novel Regenerative Disease-Modifying Therapies for Alzheimer's Disease

Leen Kawas

M3 Biotechnology, Inc., Seattle, WA, USA

Alzheimer's disease (AD) is the greatest medicine challenge of the 21st century. Current treatment options remain palliative and do not treat the underlying cause of neurodegeneration in AD. There is no disease-modifying treatment available today capable of altering the course of cognitive decline or restoring lost connections between neurons. Without an effective treatment, the current AD and dementia population is projected to reach 16 million in the US alone by year 2050, posing an urgent public health challenge today. A novel method to restore the lost cognitive function is to activate neurotrophic growth factors. Hepatocyte growth factor (HGF) is a multipotent growth factor for a variety of neurons and glia cells. HGF exhibits great neuroprotective, neurorestorative, and synaptogenic potential, which could prove efficacious against neurodegeneration, an underlying pathology leading to cognitive decline in AD. Activation of HGF and its cognate receptor MET has been shown to slow disease progression and restore function in numerous animal models of neurodegenerative disorders, including AD, Parkinson's disease, and amyotrophic lateral sclerosis. To leverage the neuroprotective capacity of HGF, M3 Biotechnology, Inc. (M3) is developing small molecule therapeutics capable of activating HGF. In nonclinical studies, pro-cognitive effects and neuroprotective properties in the central nervous system (CNS) have been demonstrated. Activation of HGF/Met with the lead molecule therapeutic induced synaptogenesis and synaptogenesis at the cellular level and improved cognitive function and spatial learning and memory in aged, cognitively compromised animal models. In addition, the lead compound induced EEG changes in wild-type and APP/PS1 transgenic mouse model of AD. Much drug development efforts to-date has positioned this small molecule therapeutic to enter first-in-human clinical trials. M3 is initiating a Phase I clinical study where EEG as a translatable biomarker to evaluate CNS safety and measure pharmacodynamic responses will be explored.

Roberta Diaz Brinton, PhD, University of Arizona Health Sciences



Roberta Diaz Brinton, PhD, is the Director of the Center for Innovation in Brain Science at the University of Arizona where she is Professor of Pharmacology and Neurology in the College of Medicine.

Research in the Brinton laboratory focuses on discovery of mechanisms underlying development of Alzheimer's in the aging brain and on translating those discoveries into therapeutics to prevent, delay and treat the disease. Of particular focus is the aging female brain and elucidating mechanisms that underlie the two-fold greater lifetime risk of Alzheimer's disease in women. Brinton has developed therapeutics that restores energy production and neural stem cell regeneration in the brain to prevent and treat Alzheimer's.

Outcomes of her discovery and translational research have led to two NIH funded clinical trials PhytoSERMs for memory complaints in women and Allopregnanolone as regenerative therapeutic for Alzheimer's. Dr. Brinton's research has been continuously funded by NIH from her pre-doctoral years to the present. Current funders of her research include the Alzheimer's Drug Discovery Foundation, National Institute on Aging and the Alzheimer's Association. ADDF funding led to development of the first regenerative neural stem therapy for Alzheimer's disease currently in an NIA funded clinical trial.

Dr. Brinton has 200 publications and holds multiple patents targeting Alzheimer's disease, age-associated neurodegenerative diseases and sustaining neurological health during aging. Her research has appeared in over 100 global media outlets including the New York Times, ABC, CBS and Science Friday. Dr. Brinton was awarded the Alzheimer's Drug Discovery Foundation Scientist of the Year, The Alzheimer's Drug Discovery Foundation Goodes Prize, Woman of the Year by the California State Senate, Science Educator of the Year by the Society for Neuroscience and Los Angeles Magazine Woman of the Year. She was also recognized as one of the Ten Best Minds by US News and World Report. For her decades of commitment to science education for inner city youth of Los Angeles, Dr. Brinton received the Presidential Citizens Medal in 2010 from President Obama.

Results from a Pilot Clinical Trial of Allopregnanolone: A Regenerative Therapy for AD

Roberta Diaz Brinton

University of Arizona Health Sciences, Tucson, AZ, USA

Currently, we are conducting a double-blind placebo controlled Phase 1b/2a clinical trial of the neurosteroid, allopregnanolone (Allo) as the first regenerative therapeutic targeting endogenous neural stems cells in persons with MCI due to Alzheimer's disease (AD) or early AD clinicaltrials.gov/show/NCT02221622. Trial participants include equal numbers of postmenopausal women and men, 55 or older, with a MMSE >20 as per ADNI criteria, who retain capacity to provide informed consent. Primary outcomes include 1) safety measures based on standard clinical laboratory measures and MRI-based amyloid imaging abnormalities (ARIA-H and ARIA-E) and 2) maximally tolerated dose (MAD) established by dose that induces sedation. Secondary outcomes include measures of cognition based on a panel of well-validated cognitive tests and MRI to assess exploratory biomarkers (structural hippocampal and brain volumes, DTI, fMRI). Allo is administered IV at three doses (2, 4 and 6 mg i.v.) once per week over 12 weeks. Each dose-cohort consists of 8 participants randomized to drug or placebo in a 6:2 allocation ratio. Analyses of safety and adverse events were evaluated in 8/8 Cohort 1 participants and 8/8 Cohort 2 participants. Cohort 3 is in progress. No instances of treatment emergent ARIA-H or ARIA-E were observed (none is expected considering the actions of Allo). No laboratory results were above critical values and there were no instances of suicidal ideation. Further, no treatment emergent adverse events or serious adverse events (SAE, defined by 21 CFR 312.32) were attributed to Allo. On the indicator of sedation, all participants in the 2 mg cohort remained 'functioning at high levels' or 'wide awake with maximum scores of 1 or 2, two participants in the 4 mg cohort reported feeling 'not fully alert' with maximum scores of 3 and 4. Initial analyses of cognition using the MOCA, ADAScog-14, and scales on the Cogstate brief battery indicated directional changes favoring Allo compared to placebo. On Quality of Life measures, study participants receiving placebo declined over the course of the 12 weeks whereas participants receiving Allo maintained their baseline capacity suggestive of maintenance of their quality of life over the study period. Pharmacokinetic analyses. PK outcomes from cohort 1 indicate a Cmax ranging from 18 to 73 nM at 30 minutes, and AUC from 3.2 to 15.6 hr*ng/ml, and correlated inversely with body weight. To date, 24 of 24 participants have been enrolled with 20 completing treatment with no safety issues. Preliminary analyses of primary outcomes indicate that Allo given IV once per week is well tolerated with no central or peripheral adverse events. Analyses of secondary outcomes based on cognitive, MRI and quality of life measures are ongoing.

Research supported by the National Institutes on Aging (NIA UFI AG046148) and the Alzheimer's Drug Discovery Foundation to RDB.

KEYNOTE SPEAKER

Neil Vasdev, PhD, Massachusetts General Hospital and Harvard Medical School



Neil Vasdev, PhD, is the Director of Radiochemistry at Massachusetts General Hospital, Associate Director of the Gordon Center for Medical Imaging, and is an Associate Professor in the Department of Radiology at Harvard Medical School. He is also a Co-founder and Managing Director of MedChem Imaging, LLC.

Dr. Vasdev concurrently graduated (summa cum laude) with a Bachelor of Science in Chemistry and Bachelor of Arts in Psychology from McMaster University in 1998. Prior to starting graduate school he gained experience working in industry as a chemist at Astra Pharma and Glaxo Wellcome. He completed his PhD dissertation in Chemistry at McMaster University while a national scholarship (NSERC), followed by an NSERC postdoctoral fellowship at the E.O. Lawrence Berkeley National Laboratory. From 2004-2011 he was on faculty as an Associate Professor at the University of Toronto's Department of Psychiatry and the Centre for Addiction and Mental Health and was recruited to Boston to lead the radiochemistry program at MGH in 2011.

Dr. Vasdev has focused his independent radiopharmaceutical chemistry research on developing radiolabelled imaging agents, often by multi-step radiochemistry reactions, for investigating disorders of the human brain. Several of the radiotracers developed by his laboratory are in preclinical use worldwide and many of these compounds have been used for first in PET human neuroimaging studies. He has received many academic, teaching and presentation awards for his research from organizations including the Society of Nuclear Medicine and the American Chemical Society.

He has published over 100 scientific articles and reviews, and has delivered over 100 national and international presentations on neurological therapeutic and diagnostic discovery.

Applying Radiochemical Approaches to Investigating Novel Targets for Neurodegenerative Disease

Neil Vasdev

Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

This presentation will focus on some non-traditional approaches to prepare PET radiopharmaceuticals for new targets to image the human brain, and aims to show the intricacies of developing PET radiopharmaceuticals from "bench to bedside". Specifically, cutting-edge approaches and technologies for imaging receptors and signal transduction pathways with PET, as well as our recent work to expand beyond the "amyloid cascade hypothesis" of Alzheimer's disease, including tauopathies, will be presented. Several of the neuroimaging agents developed through our academic-pharma partnerships will also be highlighted. The intricacies of transitioning labeled compounds to PET radiopharmaceuticals and our aspiration to work towards the ultimate, albeit impossible, goal in the field: to radiolabel virtually any compound for PET will be raised as points for discussion.

III. Epigenetics and Cognitive Enhancing

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



Yuko Hara, PhD, is a member 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.

SESSION OVERVIEW

Epigenetic mechanisms may play a role in the onset and progression of Alzheimer's disease and represent an emerging area for drug development. Currently available FDA-approved drugs for Alzheimer's disease target the acetylcholinesterase or the NMDA receptor to improve cognitive function. However, many other cognitive-enhancing strategies are under investigation, including those that are approved for other indications.

The talks in this session will highlight advances in epigenetic therapeutics, comparative effectiveness research, and drug repurposing in treating or preventing cognitive symptoms associated with Alzheimer's disease, mild cognitive impairment, and aging.

Measuring Synaptic Vesicle Glycoprotein 2A (SV2A) Levels as a Translatable Marker of Pro-Synaptic Effects of HDAC Class I Selective Inhibitors

Maria Quinton, PhD—Rodin Therapeutics

Anti-Hypertension Drug Class: Which is the 'Best' at Reducing the Risk for Alzheimer's Disease?

Lenore Launer, PhD—National Institutes of Health, National Institute on Aging

Glutamatergic Dysfunction in Cognitive Aging: Repurposing Riluzole for Mild Alzheimer's Disease

Ana Pereira, MD—Icahn School of Medicine at Mount Sinai and The Rockefeller University

Clinical Development of a Dual LSD1/MAO-B Inhibitor ORY-2001

Tamara Maes, PhD—Oryzon Genomics S.A.

A Phase IIa, Double-blind, Placebo-controlled, Biomarker Study of Atomoxetine in Subjects with Mild Cognitive Impairment

Allan Levey, MD, PhD—Emory University

Maria Quinton, PhD, Rodin Therapeutics



Maria Quinton, PhD, has been the Director in Translational Science at Rodin since July 2016. Dr. Quinton is a neuropharmacologist and translational scientist with expertise in multiple disciplines ranging from in vivo behavioral and neurochemistry assays to translational medicine and preclinical pharmacology.

Prior to Rodin, she was a Director in Translational Science at AstraZeneca Neuroscience iMed, where she worked in a virtual environment to develop and implement translational plans for the neuroscience portfolio projects in psychiatric, neurodevelopmental and neurodegenerative disorders. Previously, Dr. Quinton was an Associate Director of NonClinical Pharmacology at Retrophin, where she led the efficacy and preclinical IND enabling studies for RE-024, resulting in a successful IND in April 2015. RE-024 is still advancing as a therapy targeting the underlying cause of pantothenate kinase-associated neurodegeneration (PKAN), a life-threatening neurological disorder.

Between 2007 and 2014, Dr. Quinton worked in Neuropharmacology at Sunovion pharmaceuticals, previously known as Sepracor, where she led several discovery projects and supported all CNS projects with neurochemistry, neuropharmacology and translational studies, either through CROs or internal capabilities.

Throughout her career in drug development, Dr. Quinton has constructed research and development plans for virtual company operation with associated resource requirements, budgets and timelines.

Measuring Synaptic Vesicle Glycoprotein 2A (SV2A) Levels as a Translatable Marker of Pro-Synaptic Effects of HDAC Class I Selective Inhibitors

Maria Quinton

Rodin Therapeutics, Cambridge, MA, USA

Cognitive decline is a major symptom of Alzheimer's disease (AD) and other neurodegenerative pathologies. Decreases in synapses and dendritic spines in the hippocampus are correlated with cognitive deficits in AD patients. Effective therapeutics to treat this cognitive decline have been a challenge to develop, and new targets and approaches are needed.

Histone deacetylases (HDACs) are enzymes that remove acetyl groups on histones, thereby regulating gene expression, including the expression of neuronal proteins critically needed for synaptic plasticity. Rodin Therapeutics is developing small molecule inhibitors of class I HDAC complexes to restore synaptic function. A significant challenge in understanding the role of improving synaptic density in neurological disorders has been the lack of tools to quantify changes in synaptic density in a clinical setting. Synaptic Vesicle protein 2A (SV2A) is a membrane protein found in presynaptic terminals which is essential for synaptic function. Recently, Finnema and colleagues (2016) demonstrated that PET imaging of SV2A using [¹¹C]UCB-J provides a way to image synaptic density in human patients, making this protein of great interest for translational studies.

We show in proof of principle studies that 14 days of daily administration of CI-994, the prototypic Class I selective HDAC inhibitor, significantly increased dendritic spine numbers and synaptic SV2A levels in the hippocampus of wild type mice. We also show that chronic CI-994 administration improves LTP-deficits in the 5xFAD mouse model of AD. Together these findings strongly support that SV2A measurements can be a viable translational approach to study the pro-synaptic effects of HDAC inhibitors in a clinical setting.

Lenore Launer, PhD, National Institutes of Health, National Institute on Aging



Lenore J Launer, PhD, is a Senior Investigator and Chief of the Neuroepidemiology Section in the Intramural Research Program, Institute on Aging, at NIH. Studies in the Neuroepidemiology Section focus on understanding the life course contributions of genetic, inflammatory, metabolic, vascular, and hormonal factors to well characterized continuously and discretely measured sub-clinical and clinical phenotypes of brain disease, and investigating the links between brain disease and other common diseases of old age. To meet these aims, Dr. Launer has served as PI or Co-PI on several large epidemiologic studies, including the HAAS, AGES-Reykjavik Study, and CARDIA, which allow testing in the general population, hypotheses on risk/protective factors, and mechanisms related to brain aging and dementia. Dr. Launer has also led or participated in several international collaborations on the epidemiology and genetics of cognitive, imaging and clinical dementia outcomes, and has served on the Executive Committees for the brain outcomes ascertained in two major NHLBI treatment strategy clinical trials intervening on diabetes and blood pressure.

Anti-Hypertension Drug Class: Which is the ‘Best’ at Reducing the Risk for AD?

Lenore Launer

Intramural Research Program, National Institute on Aging, Baltimore, MD, USA

Basing drug target identification on observational epidemiologic cohort studies has many unique advantages that compliment other strategies for drug discovery; however, there are also limitations to this strategy. The case of hypertension as a risk factor for AD provides an excellent example of how observational epidemiologic data can be used to compliment other research strategies to identify drugs to reduce the risk for AD: There are several observational studies of the association between anti-hypertensive drug class (AHDC) and AD risk, with conflicting results on which drug is the most strongly associated with better cognitive outcomes. In a recent meta-analysis of several studies there was a suggestion that the calcium channel blocker class of anti-hypertensive medications may slightly reduce the incidence of dementia, however, the authors note the benefit of a specific drug class could be mostly due to the amount of blood pressure lowering achieved with the medication. This core dilemma to identifying possible drug targets, was examined in a multi-center study, supported by ADDF, of 6 population-based follow-up studies with a large sample, and a wide population range in blood pressure levels, dementia, cognition and MRI based brain measures. The study design and preliminary results will be presented for the primary analysis on the relationship of AHDC to incident dementia.

Ana Pereira, MD, Icahn School of Medicine at Mount Sinai and The Rockefeller University



Ana Pereira, MD, graduated in Medicine at Universidade Federal de Sao Paulo, Brazil in the top 1% of the class. She was a Post-Doctoral Research Scientist at Columbia University at the Taub Institute for Alzheimer's disease investigating adult neurogenesis with brain imaging techniques in animals and humans. She completed Residency in Neurology at Harvard University and received subspecialty training in Cognitive Neurology at Columbia University. She was an Assistant Professor of Clinical Investigation at the Rockefeller University and she is currently an Assistant Professor of Neurology at Mount Sinai School of Medicine.

She has been studying the susceptibility of glutamatergic neural circuits to age-related cognitive decline and Alzheimer's disease along with potential therapeutic interventions. Her studies have used animal models, structural analysis with confocal and electron microscopy, behavioral assays and RNA sequencing along with parallel translational and clinical studies in patients with Alzheimer's disease and sleep-disordered breathing with use of state-of-the art neuroimaging techniques and neuropsychological measures.

Dr. Pereira is the recipient of the NIH Paul Beeson Emerging Leaders Career Development Award in Aging, the Alzheimer's Drug Discovery Foundation grant, a Dana Foundation award, the BrightFocus Alzheimer's disease Award, the Bernard Schwartz Award for Physician Scientists and others.

Glutamatergic Dysfunction in Cognitive Aging: Repurposing Riluzole for Mild Alzheimer's Disease

Ana Pereira

Icahn School of Medicine at Mount Sinai and The Rockefeller University, New York, NY, USA

My research focuses on furthering our knowledge of the neurobiology of aging and Alzheimer's disease taking into account the selective vulnerability of glutamatergic neural circuits to synaptic changes in aging and neuronal loss in Alzheimer's disease, and seeks to explore mechanisms underlying these susceptibilities along with effective interventions. I have studied glutamatergic neuronal susceptibility with modern quantitative cell biology methods (at the synaptic and spine resolution with electron and confocal microscopy) in conjunction with novel molecular tools (next generation RNA sequencing and open arrays) and functional assays.

Importantly, glutamatergic dysregulation is also intimately related to the release and toxicities of amyloid-beta and phosphorylated tau, the hallmarks of the neuropathology of Alzheimer's disease. I have been studying the pathophysiological mechanisms of cognitive decline in the setting of glutamatergic dysfunction, and in particular with downregulation of the dominant glutamate transporter in the brain, EAAT2, which plays the key role of regulating synaptic transmission, and thereby learning and memory and of preventing glutamate spillover to the extrasynaptic space that make neurons exquisitely sensitive to excitotoxicity. I have utilized transgenic animal models, including a novel conditional EAAT2 knock-out mouse with differential astrocytic and neuronal lines and a diversity of methodological approaches to relate anatomical and molecular findings to functional changes. I have also been conducting translational and clinical studies using neuroimaging as a critical tool, including 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and in vivo proton magnetic resonance spectroscopy (1H MRS). With these technologies, I have been testing the effect of glutamate modulators of mechanistic therapeutic relevance, in particular riluzole, on the cerebral metabolism and cognition of patients with mild Alzheimer's disease.

Tamara Maes, PhD, Oryzon Genomics S.A.



Tamara Maes, PhD, graduated in Chemistry (1992) and has a PhD in Biotechnology (1997) from the University of Ghent, Belgium. She worked as a post-doctoral researcher in the CSIC. In 2000, she co-founded Oryzon Genomics S.A. together with Dr. Carlos Buesa, and has been Chief Scientific Officer since the company's inception.

In 2008, the company launches its first proprietary drug discovery program directed against LSDI. By 2012, Oryzon has developed a global leadership position in the development of LSDI inhibitors with potential uses in oncology and neurodegenerative disease. Oryzon was the first company to complete the pre-clinical to clinical transition with a specific LSDI inhibitor, has three compounds in development for treatment of oncological and neurodegenerative diseases, and will again be the first to evaluate the therapeutic potential of LSDI inhibitors in Phase II trials in Alzheimer's disease and multiple sclerosis. Oryzon is publically traded on the Madrid Stock Exchange (Ticker: ORY) since December 2015.

Clinical Development of a Dual LSDI/MAO-B Inhibitor ORY-2001

Tamara Maes

Oryzon Genomics S.A., Cambridge, MA, USA

Post-translational modifications of histones are closely associated with changes in gene transcription. Histone lysine methyl marks changes are highly relevant and mediated by histone methyltransferases and demethylases. Many diseases are accompanied by transcriptional imbalances and we have developed strategies that aim to modulate these aberrant profiles. Lysine demethylase 1 (LSD1) and the histone deacetylases HDAC1 and 2 are recruited by Zn finger transcription factors to regulate gene expression. LSD1 is expressed in the brain and has a dual role in neuronal stem cell proliferation and neuronal differentiation / neurite extension. Treatment with the brain penetrant LSDI/MAOB inhibitor ORY-2001 rescues memory as assessed by NORT in SAMP-8 mice, a model for accelerated aging and Alzheimer's Disease (AD), and in the R6/1 model for Huntington's Disease (HD). ORY-2001 stimulates the expression of genes involved in cognition and memory and down-regulates an inflammation signature in the hippocampus. The anti-inflammatory effect is further illustrated in a mice experimental autoimmune encephalomyelitis model for multiple sclerosis, where ORY-2001 stops demyelination and immune infiltration. In this talk, we will present the results of the recently finalized Phase I trial with ORY-2001, performed to assess safety, tolerability, pharmacokinetics, pharmacodynamics and brain penetration in healthy young and elderly volunteers and we will present our plans for Phase II trials in patients with AD and multiple sclerosis. This is the first time that the therapeutic effect of the modulation of a histone lysine demethylase will be tested in patients, and is opening the door to an alternative strategy in the treatment of these neurodegenerative diseases.

Allan Levey, MD, PhD, Emory University



Allan Levey, MD, PhD is the Goizueta Foundation Endowed Chair for Alzheimer's Disease Research, and the Betty Gage Holland Professor and Chairman of the Department of Neurology at Emory University. He is also Director of the Emory Alzheimer's Disease Research Center, and the Executive Associate Dean for Research (Interim) in the School of Medicine. Dr. Levey has secondary faculty appointments in the Departments of Pharmacology and Psychiatry and Behavioral Sciences.

A Phase IIa, Double-blind, Placebo-controlled, Biomarker Study of Atomoxetine in Subjects with Mild Cognitive Impairment

Allan Levey, David Weinshenker

Alzheimer's Disease Research Center, Emory University, Atlanta, GA, USA

Several lines of scientific evidence have converged in recent years demonstrating that the locus coeruleus (LC) is the first site of neuropathology in Alzheimer's disease (AD) brain, and that the subsequent loss of norepinephrine (NE) contributes to the clinical and neuropathological features of the disease. Preclinical studies have demonstrated that LC degeneration incites a pro-inflammatory condition that is neurotoxic, reduces A β clearance, and accelerates neuropathology, whereas the rescue of norepinephrine reverses these effects and slows neurodegeneration. Atomoxetine, a selective norepinephrine transport inhibitor, is an ideal drug to translate these findings to humans because it is already FDA-approved and safe in the elderly. Here we present initial findings from a phase II study proof of concept study of atomoxetine in subjects with mild cognitive impairment (MCI) due to AD, with the central hypothesis that atomoxetine will increase central NE levels (i.e., hit the intended target) and reduce CSF pro-inflammatory analytes. The trial was carried out at a single site (Emory University ADRC), with a randomized, placebo-controlled, double-blind, cross-over design, in 39 subjects with MCI due to AD (confirmed by CSF biomarkers). We describe the trial and the variety of safety, cognitive, imaging, and CSF measures that were collected at baseline, 6 months (cross-over), and 12 months.

A Small Molecule Humanin Mimetic As a Candidate for Modulating NMDA-induced Neurotoxicity

Mohammad Parvez Alam¹, Tina Bilousova¹, Patricia Spilman¹, Kanagasabai Vadivel², Dongsheng Bai¹, Denis Evseenko², Varghese John¹

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²*Department of Orthopaedic Surgery, University of Southern California (USC), Los Angeles, CA, USA*

Humanin (HN), a 24-amino acid bioactive peptide, has been shown to increase cell survival of neurons after exposure to A β and NMDA-induced toxicity and thus could be beneficial in the treatment of Alzheimer's disease (AD). The protection by HN is primarily through binding to the gp130 receptor, which is part of a trimeric cell surface complex involving CNTF/WSX1/GPI30. We report here for the first time the elucidation of the binding site of HN to gp130 through modeling, and the identification of a small molecule mimetic that binds at the HN binding site on the receptor. This small molecule mimetic lead candidate, PA2, was identified through screening and exploratory medicinal chemistry using a microfluidic flow chemistry approach to facilitate the syntheses of new analogs of an original 'hit' and SAR optimization. This is a green-chemistry approach for synthesis of bioactive small molecules. The analogs generated have enabled us to gain chemical insights into the SAR of gp130 agonists to protect primary neurons against NMDA-induced excitotoxicity. HN due to its peptidic nature presents challenges in development as a therapeutic for AD. In contrast, the HN mimetic lead candidate PA2 was shown to have good oral brain permeability and is a candidate for further evaluation of the neuroprotection through the gp130 receptor agonism mechanism in NMDA-induced neurotoxicity animal models.

The Development of Novel Peptide Based Therapeutics Against CCR3 Receptor in AD

Hazem Abdelkarim¹, Milica Grozdanovic¹, Ben Hitchinson¹, Kimberly Laffey¹, Nadya Tarasova², Steven Ackerman¹, Vadim Gaponenko¹

¹*University of Illinois at Chicago, Chicago, IL, USA*

²*National Cancer Institute, Bethesda, MD, USA*

Alzheimer's disease (AD), the most common neurodegenerative disorder in the elderly, is characterized by accumulation of protein aggregates of amyloid- β and microtubule associated protein tau. Mechanisms underlying the pathology of AD remain unclear and the development of new therapeutic or prophylactic approaches is needed to treat, prevent, or delay the onset of AD. Neuroinflammation in AD, an important indicator of pathology impacting cognitive function, is mediated by activated astrocytes and microglia that produce pro-inflammatory cytokines, neurotoxins, and chemokines. Chemokines and their receptors are implicated in the pathogenesis of AD. For instance, CXCR2 mediates amyloid- β production and tau pathology. Similarly, an age-related increase in CCR3 and its chemokine CCL11 result in elevated amyloid- β production, tau hyperphosphorylation, and synaptic loss. Few CCR3 inhibitors are currently available. Most of these have poor solubility and target selectivity. Therefore, development of new therapeutic strategies against key chemokine receptors is needed and significant. Here, we describe a novel peptide-based nanoparticle against CCR3 receptor called R321. We used a set of biophysical and biochemical approaches to characterize the inhibitory profile of R321. First, we used dynamic light scattering to show that R321 can self-assemble into water soluble monodisperse structures with a hydrodynamic radius of 7.1 nm. Next, we incorporated the NMR-active ¹³C isotope into the lysine residues and N-termini of proteins using reductive methylation of membranes from rat hematopoietic progenitor Chem-I cells with and without CCR3 overexpression. Our NMR results demonstrate that both R321 and CCL11 bind CCR3 simultaneously. R321 binds the receptor at two independent sites but does not change spectra of CCR3- membranes. The peptide inhibits chemotaxis of CCR3+ cells to CCL11 with an IC₅₀ of 210 nM. In conclusion, R321 is a selective CCR3 inhibitor that forms water soluble nanoparticles in vitro. Collectively, we show that peptide inhibitors of chemokine receptors can be developed. These may eventually become therapeutic or/and prophylactic agents against neuroinflammation in AD.

PimI Inhibition as a Novel Therapeutic Strategy for Alzheimer's Disease

Ramon Velazquez, Darren Shaw, Antonella Caccamo, Salvatore Oddo

Arizona State University, Tempe, AZ, USA

Accumulation of amyloid- β (A β) and neurofibrillary tangles are the prominent neuropathologies in patients with Alzheimer's disease (AD). Strong evidence indicates that an imbalance between production and degradation of key proteins contributes to the pathogenesis of AD. The mammalian target of rapamycin (mTOR) plays a key role in maintaining protein homeostasis as it regulates both protein synthesis and degradation. A key regulator of mTOR activity is the proline-rich AKT substrate 40 kDa (PRAS40), which directly binds to mTOR and reduces its activity. Notably, AD patients have elevated levels of phosphorylated PRAS40 (pPRAS40), which correlate with A β and tau levels as well as cognitive deficits. Physiologically, pPRAS40 is regulated by PimI, a protein kinases of the protooncogene family. We have identified a PimI inhibitor (PimIi) that crosses the blood brain barrier and reduces pPRAS40. Here, we tested the effects of a selective PimIi, on spatial reference and working memory and AD-like pathology in 3xTg-AD mice. PimIi-treated 3xTg-AD mice performed significantly better than their vehicle treated counterparts and as well as non-transgenic mice in a spatial reference memory task after 4 weeks on treatment. Additionally, 3xTg-AD PimIi-treated mice showed a reduction in soluble and insoluble A β 40 and A β 42 levels, as well as a 45.2 % reduction in A β 42 plaques within the hippocampus. Furthermore, phosphorylated tau immunoreactivity was reduced in the hippocampus of PimIi-treated 3xTg-AD mice by 38 %. Mechanistically, these changes were linked to a significant increase in proteasome activity. These data strongly suggest that PimIi might be a valid therapeutic target for AD. Notably, there were peripheral side effects with the PimIi, evident by splenomegaly at autopsy. In light of these side effects, we next proposed a series of experiments in order to reduce peripheral side effects and extend our findings. We are currently developing a strategy to increase the amount of PimIi absorbed by the brain while reducing the concentration in the periphery. Additionally, we plan to examine the PimIi effects on neuronal cell loss in the 5xFAD mouse model of AD. Completion of the proposed work may springboard the use of the PimIi for AD to clinical trials.

IV. Misfolded Proteins and Proteostasis

Chair: 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.

SESSION OVERVIEW

A shared feature of many chronic neurodegenerative diseases is the abnormal accumulation and/or aggregation of misfolded proteins, which often have deleterious neurotoxic and inflammatory consequences.

Due to this common mechanism, many research programs in the neurodegenerative disease space are exploring strategies to ameliorate the effects of toxic protein species.

Talks in this session will cover drug discovery programs pursuing innovative routes towards solving the problem of misfolded proteins and protein accumulation, along with biomarker programs under development.

Small Molecule PDI Modulators Suppress Neurodegeneration

Brent Stockwell, PhD—Columbia University

Potent Small Molecule Inducers of Autophagy as Potential Agents to Lower Tau Levels and to Treat AD

Steven Finkbeiner, MD, PhD—Gladstone Institutes and University of California, San Francisco

Mitochondrial TDP-43 as a Novel Therapeutic Target for FTD

Xinglong Wang, PhD—Case Western Reserve University School of Medicine

Funded through the ADDF/Association for Frontotemporal Degeneration Partnership Program

Tau Inside Neurally-Derived Extracellular Vesicles

Dominic Walsh, PhD—Brigham & Women's Hospital and Harvard Medical School

Brent Stockwell, PhD, Columbia University



Brent R. Stockwell, PhD is a Professor at Columbia University in the Departments of Biological Sciences and Chemistry; he is also Director of the Columbia NYSTEM Chemical Probe Synthesis Facility. His research involves the discovery of precision medicines that can be used to understand and treat cancer and neurodegeneration, with a focus on mechanisms governing cell death. These interdisciplinary investigations have led to new methods of small molecule drug discovery, and the discovery of drug candidates that act through a new form of cell death. Professor Stockwell has received numerous awards, including a Burroughs Wellcome Fund Career Award at the Scientific Interface, a Beckman Young Investigator Award, an HHMI Early Career Scientist Award, the BioAccelerate NYC Prize, the Lenfest Distinguished Columbia Faculty Award and the Great

Teacher of Columbia College Award from the Society of Columbia Graduates. He has trained >100 students, technicians and postdoctoral scientists, published >100 scientific articles, been awarded 14 US patents, and received 42 research grants for >\$30 million. He founded the biotechnology companies CombinatoRx Incorporated, Solaris Therapeutics and Kyras Therapeutics, and is the author of *The Quest for the Cure: The Science and Stories Behind the Next Generation of Medicines*.

Small Molecule PDI Modulators Suppress Neurodegeneration

Brent Stockwell

Columbia University, New York, NY, USA

We discovered that the endoplasmic reticulum (ER) chaperone protein disulfide isomerase (PDI) is a key mediator of oxidative ER stress and apoptotic cell death in response to protein misfolding. This provides a mechanism linking expression of misfolded proteins to cell dysfunction, ER stress, and neurodegeneration, and offers a new therapeutic approach to treating Alzheimer's Disease (AD) and Huntington's Disease. We will describe how PDI mediates oxidative stress and neuronal cell death, and how PDI modulation represents a previously unexplored node for intervening in AD and HD pathogenesis.

Steven Finkbeiner, MD, PhD, Gladstone Institutes and University of California, San Francisco



Steven Finkbeiner, MD, PhD, trained at Yale University, UCSF and Harvard University before joining the faculty at the Gladstone Institutes and UCSF in 1999. Since then, he has been promoted to his current position as a Director at the Gladstone Institutes and a Professor of Neurology and Physiology at UCSF. He also Directs the Taube/Koret Center for Neurodegenerative Disease.

His research has focused on basic science and disease-related questions in neuroscience, particularly fundamental questions related to learning and memory and elucidating mechanisms of neurodegenerative disease and mental illness. In 2009, the Taube/Koret Center was established to find catalyze the development of neurotherapeutics, leveraging discoveries and technology from in the academic laboratory.

Early on, Dr. Finkbeiner developed robotic microscopy, a high throughput longitudinal single cell imaging and analysis approach. It provides a way for scientists to quantify the prognostic value of cellular and molecular changes during a cell's lifetime for some important future event. It helps to overcome limitations in sensitivity and observer bias inherent to conventional approaches based on single snap shots in time, and it has proven to be very valuable for developing a systems understanding of biology and pathobiology, developing disease models particularly based on induced pluripotent stem cells and for finding putative therapeutics. His laboratory has applied the approach in studies of Parkinson's disease, Huntington's disease, ALS, Alzheimer's disease and frontotemporal dementia.

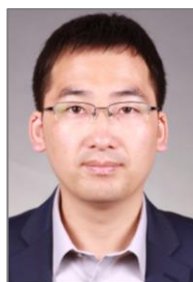
Potent Small Molecule Inducers of Autophagy as Potential Agents to Lower Tau Levels and to Treat Alzheimer's Disease

Steven Finkbeiner

Gladstone Institutes and University of California, San Francisco, CA, USA

The abnormal accumulation of misfolded proteins in the brains of patients who suffer from Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) and Huntington's disease indicates a fundamental mismatch in the production and clearance of misfolded proteins. The observation that mutations in many genes encoding components of the autophagy/lysosome protein clearance pathway give rise to a variety of neurodegenerative diseases further implicates protein dyshomeostasis as an important disease mechanism. Autophagy is one of the two major protein clearance pathways in cells and the only pathway thought to be capable of clearing accumulated toxic misfolded proteins. We hypothesized that stimulating the endogenous autophagy pathway in brain cells could be a therapeutic strategy for treating disorders characterized by protein misfolding and accumulation. We conducted a candidate screen and identified small molecules that induce autophagy in neurons. Using computational chemistry and the initial structure-activity relationships, we developed a pharmacophore and performed in silico screening of a 1M compound library and identified additional small-molecule autophagy inducers that were more potent and had a wider therapeutic window. One of the major challenges of developing autophagy inducers is that many of the conventional assays are slow and insensitive, relying on snap-shot measures of autophagy pathway intermediates to infer flux through the pathway. To overcome this limitation, we developed a new optical pulse-labeling method to directly measure flux through the autophagy pathway, and we adapted it to a high-throughput walkaway robotic microscopy platform. With this platform and medicinal chemistry approaches, we developed potent (nanomolar) compounds with novel chemistry that stimulate autophagy in rodent and human neurons in vitro and in vivo and are protective in rodent and human neuron models of neurodegenerative disorders. The molecules have drug-like properties, are orally bioavailable, have excellent blood-brain barrier penetration, and appear to be safe with chronic dosing. We are continuing to develop these molecules with the goal of choosing a clinical candidate for first-in-human trials.

Xinglong Wang, PhD, Case Western Reserve University School of Medicine



Xinglong Wang, PhD, is an Assistant 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. His 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.

Mitochondrial TDP-43 as a Novel Therapeutic Target for FTD*

Xinglong Wang

Department of Pathology, Case Western Reserve University School of Medicine, Cleveland Ohio, USA

Frontotemporal dementia (FTD) is the second most common form of early-onset dementia caused by neuron loss in the frontal and temporal cortex. The vast majority of FTD cases, referred to as sporadic FTD, are not genetically transmitted and their causes remain unknown. Currently, there is no effective treatment for FTD. Autosomal dominant mutations in TDP-43 are associated with FTD. And, the redistribution of TDP-43 from the nucleus to cytoplasm has been recognized as the pathological hallmark for most frequent subtypes of FTD. Despite an expanding body of evidence suggests the critical role of TDP-43 in FTD, little attempt has been taken to investigate the possibility of targeting TDP-43 for the treatment of FTD. Compared with TDP-43A315T mice or other TDP-43 transgenic mice, hemizygous TDP-43M337V mice demonstrated a low transgene expression and the absence of early lethality and sudden death, which could not only exclude potential side effects caused by transgene overexpression, but also allow the full development of phenotypes after adulthood. In this study, using hemizygous TDP-43M337V mice as an animal model with robust FTD-like cortical neuron degeneration and cognitive deficits, we tested the efficacy of a specific inhibitory peptide of TDP-43 mitochondrial localization, i.e., PMI. We have found that PMI can strikingly reverse mitochondrial, neuronal and behavior impairments in adult heterozygous TDP-43M337V mice even after disease onset. Therefore, our study provides evidence supporting the concept of targeting mitochondrial TDP-43 as a promising novel therapeutic approach for FTD.

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

Dominic Walsh, PhD, Brigham & Women's Hospital and Harvard Medical School



Dominic M. Walsh, PhD, is an Associate Professor at Brigham & Women's Hospital and Harvard Medical School, and Honorary Professor at the Institute of Neurology, University College London. He has authored over 100 peer-reviewed research articles on Alzheimer's disease and more than twenty of his publications have each been cited in excess of 200 times. Dr. Walsh has written a number of widely cited reviews and has given over 100 invited lectures and webinars. He has served as an Editor or Editorial Advisor for several journals and as an ad hoc reviewer for all of the world's leading biomedical journals. His research has been supported by multiple agencies, grants from industry and donations from the general public. In 2014, 2015 and 2016 he was named one of *The World's Most Influential Scientific Minds* by Thomson Reuters and ranked among the top 1% of researchers in the field of Neuroscience and Behavior.

Tau Inside Neurally-Derived Extracellular Vesicles

Dominic Walsh

Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA

Recent Alzheimer's disease (AD) drug trials have highlighted a need for better diagnosis of study participants, and development of biomarkers that can be used to monitor response to therapy. Given the demonstrated utility of quantifying tau and A β in CSF, measurement of these proteins in blood has long been studied, but as yet such analysis has not proved clinically useful. Unlike CSF, the contents of blood are influenced by many organs and therefore changes in blood analytes might not be sensitive to minor changes in brain. On the other hand, measurement of tau and A β in brain-derived blood-borne extracellular vesicles (EVs) should better reflect changes occurring in brain. Progressive cerebral accumulation of tau aggregates (neurofibrillary tangles; NFTs) is a defining feature of AD and an increasingly popular theory which seeks to explain the apparent spread of NFT pathology posits that aggregated tau is passed from neuron to neuron. While it is not clear how a protein such as tau can move from cell to cell, some have suggested that this may involve EVs. Thus, measurement of tau in EVs may both facilitate biomarker development and provide insights on the molecular pathology of AD. We used differential centrifugation to isolate exosomes from human iPSC-derived neurons (iNs) and detected a small amount of mid-region-containing tau (<0.2% of that found free-floating in conditioned media (CM)). However, given that most extracellular tau is not full length, but truncated and that the microtubule binding repeat (MTBR) domains of tau is known to drive aggregation, we also searched for MTBR-containing forms of tau. In neural EVs from 5 different iN lines we detected tau at levels equivalent to ~0.4 to 2.0 pg per ml of CM. To determine if tau was also found in exosomes from human biofluids we isolated exosomes from both CSF and plasma. Since CSF is a relatively simple fluid we again used differential centrifugation to isolate crude EVs. Analysis of CSF exosomes using a mid-region requiring ELISA revealed the presence of low levels of tau, equivalent to ~0.1 pg per ml of CSF. To isolate and analyze neuron-derived exosomes from human plasma we further optimized the method pioneered by the Goetzl and Kapogiannis group. This protocol involves depleting plasma of clotting factors, precipitating exosomes using ExoQuick and isolation of neural exosomes from non-neural exosomes using an anti-L1CAM antibody. Neural exosomes were isolated from the plasma of 40 donors (10 cognitively normal, 10 MCI, and 20 mild AD) and their contents analyzed for 3 distinct forms of tau (mid-region, full length (FL), and p181 tau). The highest amounts of tau were detected using the mid-region assay (608.49 ± 149.23 pg per ml of plasma), whereas the levels of ptau (100.39 ± 14.09 pg per ml of plasma) and FL tau (13.98 ± 2.46 pg per ml of plasma) were considerably lower. There was a tendency for all forms of tau to be higher in exosomes from AD and MCI cases versus exosomes from cognitively normal individuals. The presence of aggregation-competent tau in EVs supports a potential role for EVs in the transfer of tau aggregates from cell to cell. Further studies will be required to examine the potential for tau-containing exosomes to seed aggregation in recipient cells and whether clinically used blood products should be depleted of exosomes, or screened for the presence of exosomes containing aggregation-competent tau.

NOTES



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From developing new therapies that treat and prevent disease to helping people in need, we're committed to improving health and well-being around the world. Our vision is to make a difference in the lives of people globally through our innovative medicines, vaccines, biologic therapies, consumer care and animal health products. We aspire to be the best healthcare company in the world and are dedicated to providing leading innovations and solutions for tomorrow.

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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 AD a top national priority.

Charles River

Charles River applies its deep expertise and extensive capabilities in the field of neuroscience to create innovative, flexible, and efficient solutions to advance neurological drug discovery. Our scientists continue to establish the most relevant *in vitro* and *in vivo* disease models to target the acute and chronic conditions associated with neurodegenerative diseases including Alzheimer's disease, psychiatric disorders, and rare diseases. With access to sophisticated cognitive testing techniques, behavioral and physiological assays, and imaging technologies, our team is uniquely positioned to partner with clients, accelerating drug development from early discovery through the delivery of exciting new therapies for neurological diseases.

Harrington Discovery Institute

The Harrington Discovery Institute at University Hospitals in Cleveland, Ohio – part of The Harrington Project for Discovery & Development – aims to advance medicine and society by enabling our nation's most inventive physician-scientists to turn their discoveries into medicines that improve human health. The institute was created in 2012 with a \$50 million founding gift from the Harrington family and instantiates the commitment they share with University Hospitals to a Vision for a 'Better World'. For more information about The Harrington Project and Harrington Discovery Institute, visit: HarringtonDiscovery.org.

Taub Institute

The Taub Institute for Research on Alzheimer's Disease and the Aging Brain is the nucleus of a dynamic, multidisciplinary endeavor. The Institute brings together Columbia University researchers and clinicians to uncover the causes of Alzheimer's, Parkinson's and other age-related brain diseases and to discover ways to prevent and cure these diseases.

www.alzdiscovery.org