Alzheimer's
Drug Discovery
Foundation

16TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DRUG DISCOVERY

Jersey City, NJ ● *October 5-6, 2015*

PROGRAM and ABSTRACTS

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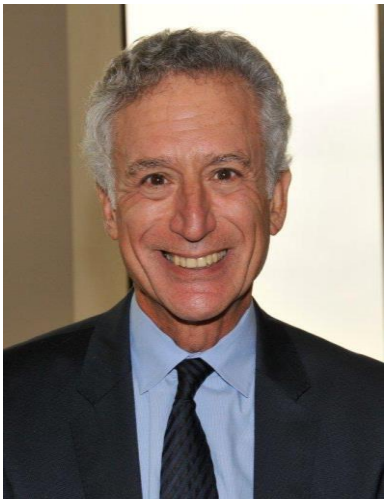
WELCOME!



On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to our *16th International Conference on Alzheimer's Drug Discovery.*

For almost two decades, 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.

Engaging the next generation of research scientists in this field is more important than ever. We are pleased to announce our 2015 Young Investigator Scholarship winners. We encourage you to visit their poster presentations which will be displayed throughout the meetings.

We are deeply grateful to our generous sponsors whose support makes this meeting possible: Eli Lilly, Pfizer Inc., Genentech, and Taub Institute for Research on Alzheimer's Disease and the Aging Brain. We would also like to thank our exhibitors: Brains On-Line, Envigo, GeneTools LLC, InterVivo Solutions, InviCRO/MedChem Imaging, OnDeckBiotech, Piramal Discovery Solutions, PyschoGenics, QPS, Singulex Inc., Solvias Inc., and Valley Biosystems and our media partners for their contribution. Our sincere appreciation also extends to all of our speakers and chairs for the hard work they do to accelerate drug discovery for Alzheimer's disease and related dementias.

To help us plan an even better conference in 2016, please complete the survey to provide us with feedback and suggestions.

Welcome, once again, to the *16th International Conference on Alzheimer's Drug Discovery*!

Best Regards,

Howard

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

ABOUT THE ALZHEIMER'S DRUG DISCOVERY FOUNDATION

Alzheimer's
Drug Discovery
Foundation

CONQUERING ALZHEIMER'S THROUGH DRUG DISCOVERY

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

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

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

WHAT WE'VE ACCOMPLISHED

- The ADDF has granted more than **$79 million to fund 498 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 nearly **$2 billion** in follow-on commitments from the government, pharmaceutical companies and venture capital firms.
- In 2014, the ADDF raised **~$10million** to support preclinical drug discovery and clinical development programs. 100% of funds raised went directly to drug research and related scientific programs, thanks to the generosity of a private Lauder Family Foundation that covered all administrative and operational expenses.

OUR CONFERENCES

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

Our annual *International Conference for Alzheimer's Drug Discovery*, held next year, on September 12-13, 2016, focuses on the discovery and development of drugs targeting Alzheimer's disease and related dementias. The *Drug Discovery for Neurodegeneration* conference, held next year, on March 6-8, 2016, is designed to educate scientists on the process of translating basic neuroscience research into innovative therapies.

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

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JAD Journal of Alzheimer's Disease

alzheimer's research&therapy

2015 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 2015 Young Investigator Scholars are:

Manel Ben Aissa, PhD, *University of Illinois at Chicago*
Termpanit Chalermpalanupap, PhD (cand.), *Emory University*
Ajay Chandgude, PhD (cand.), *University of Groningen*
Joshua Jackson MS, PhD (cand.) *University of Manchester*
Syed Faraz Kazim, MD, PhD (cand.), *SUNY Downstate Medical Center/NYSIBR*
Sue Lee, *University of Illinois at Chicago*
Emily Mason, *Vanderbilt University*
Ashley Nilson, *University of Texas Medical Branch*
Dov Shamir, PhD (cand.), *NYU School of Medicine*
Tara Weitz, PhD, *University of Southern California*
Jiang Wu, MD, *The Cleveland Clinic*

PROGRAM

Monday, October 5	
8:00 – 8:30	**Registration & Continental Breakfast**
8:30 – 8:50	**Welcome & Opening Remarks** Howard Fillit, MD, Alzheimer's Drug Discovery Foundation
8:50 – 9:30	**Plenary: Neuroinflammation: Mechanisms and Targets** Richard Ransohoff, MD, PhD, Biogen
SESSION I. Apolipoproteins and Neuroinflammation **Chair: Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation**	
9:30 – 9:35	**Session Overview** Diana Shineman, PhD, Alzheimer's Drug Discovery Foundation
9:35 – 9:55	**EP2 Inhibitors for Alzheimer's Disease** Thota Ganesh, PhD, Emory University **A 2014 ADDF/Harrington Scholar*
9:55 – 10:05	*Q&A*
10:05 – 10:25	**Prevention of Glial Neuroinflammation in Alzheimer's Disease – Targeting a Novel Receptor to Preserve Neurocognitive Function** Mohamed Naguib, MD, Cleveland Clinic Foundation
10:25 – 10:35	*Q&A*
10:35 – 11:00	**EXHIBITOR SESSION BREAK**
11:00 – 11:20	**Small Molecule P2X7 Antagonist for Alzheimer's Disease Treatment** Paolo Pevarello, PhD, Axxam SpA
11:20 – 11:30	*Q&A*
11:30 – 11:50	**APOE2 – Based Gene Therapy Approaches to Alleviate Alzheimer's Disease Neuropathological Hallmarks** Eloise Hudry, PhD, Massachusetts General Hopsital/Harvard Medical School
11:50 – 12:00	*Q&A*
12:00 – 12:20	**Slowing Arginine Utilization by Inhibiting Arginase and Ornithine Decarboxlyase with DFMO** Carol Colton, PhD, Duke University Medical Center **A 2015 ADDF/Harrington Scholar*
12:20 – 12:30	*Q&A*
12:30 – 1:35	**LUNCH / POSTER AND EXHIBITOR SESSION** **All poster presenters should stand by their posters from 12:50 to 1:35 pm*
SESSION II. Neuroprotection, Mitochondrial Function and Synaptic Plasticity **Chair: Lauren Friedman, PhD, Alzheimer's Drug Discovery Foundation**	
1:35 – 1:40	**Session Overview** Lauren Friedman, PhD, Alzheimer's Drug Discovery Foundation
1:40 – 2:00	**Novel GLP-1 and GIP Dual Receptor Agonist Peptides Show Neuroprotective Effects** Christian Holscher, PhD, Lancaster University **Funded through the ADDF/Alzheimer's Society UK Partnership Program*
2:00 – 2:10	*Q&A*
2:10 – 2:30	**Fingolimod Therapy in Models of Alzheimer's Disease** Alpaslan Dedeoglu, MD, PhD, Boston University School of Medicine
2:30 – 2:40	*Q&A*
2:40 – 3:00	**Development of Klotho Enhancers as Novel Therapeutics for Alzheimer's Disease** Carmela Abraham, PhD, Boston University School of Medicine
3:00 – 3:10	*Q&A*
3:10 – 3:40	**EXHIBITOR SESSION BREAK**
3:40 – 4:00	**Selective HDAC2 Inhibitors for the Treatment of Cognitive Deficits in Alzheimer's Disease** Martin Jefson, PhD, Rodin Therapeutics
4:00 – 4:10	*Q&A*
4:10 – 4:30	**Development of Small Molecule Activators of Glutamate Transporter EAAT2 Translation for Alzheimer's Disease** Chien-Liang Glenn Lin, PhD, Ohio State University **A 2014 ADDF/Harrington Scholar*
4:30 – 4:40	*Q&A*

4:40 – 5:00	**Lead Discovery of Novel Small Molecule Compounds Effective in Modulation of Cellular Energetics** Eugenia Trushina, PhD, Mayo Clinic
5:00 – 5:10	*Q&A*
5:10 – 5:20	**Closing Remarks and Announcement of Young Investigator Awards** Aaron Carman, PhD, Alzheimer's Drug Discovery Foundation
5:20 – 7:00	**NETWORKING RECEPTION / POSTER AND EXHIBITOR SESSION**

Tuesday, October 6	
8:00 – 8:30	**Continental Breakfast**
8:30 – 9:10	**Plenary: Progress and Future Directions in Tau Imaging** Eric Hostetler, PhD, Merck & Co., Inc.
SESSION III. Translatable Biomarkers to Accelerate Clinical Development **Chair: Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation**	
9:10 – 9:15	**Session Overview** Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation
9:15 – 9:35	**A Novel fMRI Biomarker of Asymptomatic Alzheimer's Disease** Xiong Jiang, PhD, Georgetown University
9:35 – 9:45	*Q&A*
9:45 – 10:05	**Integrative Genomic Approach to Prioritize Targets for Drug Discovery and Development in Alzheimer's Disease and Aging-Related Cognitive Decline** Nathalie Pochet, PhD, Brigham & Women's Hospital
10:05 – 10:15	*Q&A*
10:15 – 10:35	**The P2Y6 Receptor as a Therapeutic Target for Alzheimer's Disease** Philip Haydon, PhD, GliaCure, Inc.
10:35 – 10:45	*Q&A*
10:45 – 11:05	**EXHIBITOR SESSION BREAK**
11:05 – 11:25	**Benfotiamine in Alzheimer's Disease: A Pilot Study** Gary Gibson, PhD, Weill Cornell Medical College
11:25 – 11:35	*Q&A*
11:35 – 11:55	**Cortical Gray-White Matter Junction Pattern of Retention of the Tauopathy Ligand 18F-T807 (Avid-1451) in Clinically Probable CTE** Samuel Gandy, MD, PhD, Icahn School of Medicine at Mount Sinai
11:55 – 12:05	*Q&A*
12:05 – 12:25	**LLCBrainWire: Predictive Imaging-based Biomarker Technology for Alzheimer's Disease** Ashish Raj, PhD, BrainWire
12:25 – 12:35	*Q&A*
12:35 – 1:25	**LUNCH / POSTER AND EXHIBITOR SESSION** **All poster presenters should stand by their posters from 12:55 to 1:25 pm*
SESSION IV. Tau, TDP-43, Progranulin and Protein Clearance **Chair: Aaron Carman, PhD, Alzheimer's Drug Discovery Foundation**	
1:25 – 1:30	**Session Overview** Aaron Carman, PhD, Alzheimer's Drug Discovery Foundation
1:30 – 1:50	**Pim 1 Inhibition as New Therapeutic Target for Alzheimer's Disease** Salvatore Oddo, PhD, Banner Sun Health Research Institute
1:50 – 2:00	*Q&A*
2:00 – 2:20	**Rational Desgin of Small Molecules Targeting RNA Repeat Expansions** Matthew Disney, PhD, The Scripps Research Institute **Funded through the ADDF/Association of Frontotemporal Degeneration Partnership Program*
2:20 – 2:30	*Q&A*
2:30 – 2:50	**Novel Diagnostic CSF Biomarkers for Pathological Subtypes of FTD** Marta Del Campo Milan, PhD, VU University Medical Center **Funded through the ADDF/Association of Frontotemporal Degeneration Partnership Program*
2:50 – 3:00	*Q&A*
3:00 – 3:20	**EXHIBITOR SESSION BREAK**
3:20 – 3:40	**Adeno-Associated Virus Gene Therapy of Progranulin-Related Frontotemporal Dementia** Larry Altstiel, MD, PhD, Provectra Therapeutics, Inc.

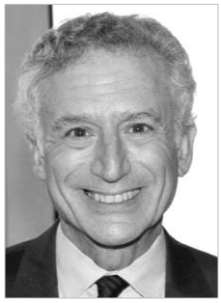
3:40 – 3:50	*Q&A*
3:50 – 4:10	**FTD Trafficking Assays and Compound Screening: Inhibiting Sortilin-dependent Progranulin Endocytosis** Scott Sneddon, PhD, Sharp Edge Labs, Inc.
4:10 – 4:20	*Q&A*
4:20 – 4:30	**Closing Remarks** Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

BIOS AND ABSTRACTS

Review conference program, speaker bios and abstracts along with postercasts at our mobile app accessible through the QR code below or by visiting http://my.yapp.us/ADDFADD

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.

PLENARY SPEAKER
Richard Ransohoff, MD, PhD, Biogen

Richard Ransohoff, MD, is Senior Research Fellow and VP, Neuroimmunology at Biogen and Adjunct Professor of Molecular Medicine, Cleveland Clinic Lerner College of Medicine. He completed residencies in Internal Medicine at Mt. Sinai Medical Center (Cleveland) and Neurology (Cleveland Clinic). He performed post-doctoral research work in the Department of Molecular Biology and Microbiology with Timothy W. Nilsen. From 1984 – 2014 he was a Staff Member at the Cleveland Clinic.

Dr. Ransohoff has research experience in neuroscience, neuroimmunology and neuro-inflammation. He lists more than 380 scientific articles and reviews in PubMed, and edited four books. He has trained over 70 students and post-doctoral fellows who now hold positions in both academics and industry. He has served as regular member of NIH Study Sections (1995-2000; 2010-2016), and as the Chair of Scientific Review Panel B, National Multiple Sclerosis Society (2003-08); External Advisor, Program Project on Alexander's Disease (2001-present); External Advisor, MS Lesion Project (National MS Society) (2003-2011); Steering Committee, NIH Therapeutics Development Program for Spinal Muscular Atrophy (2003-2012); External Advisor, European Union Project on "Mechanisms of Brain Inflammation" (2004-2006); Editorial Board, *Journal of Neuroimmunology* (1998-present); Section Editor, *Journal of Immunology* (2002-2006); Advisory Editorial Board, *Trends in Immunology* (2003-present); Highlights Advisory Board, *Nature Reviews Immunology* (2005-2012), Associate Editor of Neurology® (2006-2014) and founding Editor of *N2: Neurology®: Neuroimmunology and Neuroinflammation.*

Dr. Ransohoff received the John J. Dystel Award for MS Research from the National MS Society and American Academy of Neurology (2012) and was named in the "Best Doctors" compendium from 1996-2014 for his expertise in patient care of individuals with MS. Among other awards, he is a Fellow of the AAAS, a member of the Association of American Physicians, a Fellow of the American Neurological Association for which he delivered the F.E. Bennett Memorial Lectureship (2009).

Neuroinflammation: Mechanisms and Targets

Richard Ransohoff

Biogen, Cambridge, MA, USA

Broadly speaking, central nervous system (CNS) neuroinflammation involves two things:

- The response of reactive CNS elements such as microglia to altered homeostasis
- Impingement of systemic inflammatory events on the CNS.

In practice, much of neuroinflammation centers on microglia, which are CNS cells with profound capacity to exert injury or contribute to repair, by virtue of their myeloid provenance. This presentation will briefly review concepts of CNS immune privilege and surveillance before focusing on microglia.

Microglia arise during primitive hematopoiesis and initially enter the developing murine brain around E10.5, before other glia and prior to neuronal differentiation. During development, microglia interact extensively with neurons, helping to establish neuronal populations through influences on survival, apoptosis and corpse-clearance. As neuron-to-neuron contacts are forming during early postnatal life, microglia refine neuronal networks by synaptic pruning.

Microglia are unique among tissue macrophages because they are entirely self-renewing from local sources throughout life and in view of their sequestration away from plasma constituents by the blood brain barrier. In adult life microglia perform crucial functions which are required for motor learning and maintenance of adult neurogenesis, among many others. For this reason, loss of physiological function during the microglial reaction to injury is equally if not more pathogenically significant than gain of (mostly speculative) toxic properties.

I. Apolipoproteins and Neuroinflammation

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

EP2 Inhibitors for Alzheimer's Disease
Thota Ganesh, PhD, Emory University School of Medicine

Prevention of Glial Neuroinflammation in Alzheimer's Disease – Targeting a Novel Receptor to Preserve Neurocognitive Function
Mohamed Naguib, MD, Cleveland Clinic

Small Molecule P2X7 Antagonists for Alzheimer's Disease Treatment
Paolo Pevarello, PhD, Axxam SpA

APOE2 – Based Gene Therapy Approaches to Alleviate Alzheimer's Disease Neuropathological Hallmarks
Eloise Hudry, PhD, Massachusetts General Hospital/Harvard Medical School

Slowing Arginine Utilization by Inhibiting Arginase and Ornithine Decarboxylase with DFMO
Carol Colton, PhD, Duke University Medical Center

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

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

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

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

Thota Ganesh, PhD, Emory University School of Medicine

Thota Ganesh, PhD, obtained his MSc and PhD degrees from Osmania University, Hyderabad, India. After his postdoctoral studies at IIT-Bombay (India), University of Durham (UK) and Virginia Tech (USA), he began working as an Assistant Professor at Department of Pharmacology, Emory University School of Medicine.

Dr. Ganesh's current research focuses on developing small molecule agents to mitigate the inflammatory pathologies in neurodegenerative diseases, including epilepsy and Alzheimer's disease.

Dr. Ganesh is an author or co-author of more than 50 publications in peer-reviewed journals in the areas of medicinal chemistry, biochemistry and pharmacology.

EP2 Inhibitors for Alzheimer's Disease

Thota Ganesh *(2014 ADDF/Harrington Scholar)*

Emory University School of Medicine, Atlanta, GA, USA

PGE_2 receptor EP2 plays an exacerbating role in the development of Alzheimer's disease (AD). It has been demonstrated that EP2 deletion in transgenic model of AD is beneficial in suppression of AD pathology and behavioral deficits. However, no tests have been conducted by pharmacological inhibition of this receptor in vivo to advance EP2 receptor as a druggable target, due to lack of available EP2 antagonists until recently. We recently created a class of highly potent, selective antagonists for EP2, and demonstrated that this lead EP2 antagonist suppresses the inflammation and neurodegeneration in a model of status epilepticus. In ADDF grant period, we developed a formulation, dosing method, examined in vivo toxicity of the current the lead EP2 antagonist, and, currently conducting experiments to demonstrate whether EP2 antagonism will blunt the neuropathology in a 5xFAD mouse model of AD.

Mohamed Naguib, MD, Cleveland Clinic

Mohamed Naguib, MD, is currently a professor of Anesthesiology at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio and a staff anesthesiologist, Department of General Anesthesiology, Cleveland Clinic, Cleveland, Ohio. Dr. Naguib is certified from both the American Board of Anesthesiology and the College of Anaesthetists of Ireland. Dr. Naguib held several positions as a tenured professor at both the University of Iowa and University of Texas MD Anderson Cancer Center. He has served on several Editorial boards and is currently an Associate Editor at *Anesthesia & Analgesia*. He has also served on the Board of Directors of the International Society of Anaesthetic Pharmacology (ISAP) and he is also currently the Vice President.

Dr. Naguib's major research focus has centered on cannabinoid receptor modulators and drug development. His research on epigenetic regulation of genes involved in cognition, and his recent data (including findings recently published in *Nature Neuroscience*), have contributed to an understanding of epigenetic and molecular mechanisms involved in the modulation of learning and memory process in Alzheimer's disease. Dr. Naguib is currently involved with a development program for MDA7, a small novel neuroprotective molecule which acts on the cannabinoid type 2 receptors on microglia in the CNS. MDA7 decreases neuroinflammation and subsequent neuronal injury in a variety of animal models of different conditions including Alzheimer's disease and neuropathic pain. The Alzheimer's Drug Discovery Foundation is currently funding Dr. Naguib's drug development program.

Prevention of Glial Neuroinflammation in Alzheimer's Disease – Targeting a Novel Receptor to Preserve Neurocognitive Function

Mohamed Naguib

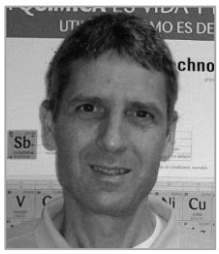
Cleveland Clinic, Cleveland, OH, USA

The abnormal accumulation of amyloid-beta (Aβ) peptides and tau in the brains of patients with Alzheimer's disease (AD) induces extensive neuroinflammation characterized by the production of the proinflammatory chemoki nes, cytokines, and neurotoxins by the activated microglia, resulting in the progressive loss of central neuronal circuits, synaptic plasticity, and, eventually, memory deficiency. Activated microglia are linked to both the initiation and maintenance of this neuroinflammatory process in AD. This neuroinflammatory process appears to contribute to and/or reflect neuronal dysfunction in the brain and is found to be inversely correlated with the cognitive function in AD.

The cannabinoid receptor (CB) family currently includes two cloned metabotropic receptors: CB1 (found predominantly in the brain) and CB2 (found primarily in the peripheral immune system and to a lesser degree in the central nervous system and microglia). Healthy brain tissue does not express CB2 receptors. Rather, CB2 receptors are upregulated in reactive microglial cells in AD and other neuroinflammatory disorders. This finding suggests that the upregulation of CB2 receptors tends to attenuate the activation of early pro-inflammatory microglial signaling pathways associated with AD.

We have shown that inhibition of glial activation with CB2 receptor agonists preserves synaptic plasticity and cognitive capacities. Our work established MDA7, 1-((3-benzyl-3-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl) piperidine as a novel, blood brain barrier-permeable, and highly selective CB2 agonist. The neuroprotective effect of MDA7 is mediated through the prevention of glial activation in vivo and in in vitro models. MDA7 treatment (i) ameliorated the expression of CD11b (microglia marker) and glial fibrillary acidic protein (astrocyte marker), (ii) decreased the secretion of interleukin-1, (iii) promoted Aβ clearance, and (iv) restored synaptic plasticity, cognition, and memory.

Paolo Pevarello, PhD, Axxam SpA



Paolo Pevarello, PhD, is a medicinal chemist with more than 30 years of experience in the pharmaceutical industry and in public research. He has worked in many different roles with large and small pharmaceutical companies.

Dr. Pevarello and his teams have been instrumental in the discovery of several clinical-stage compounds in the CNS and Oncology therapeutic areas.

Dr. Pevarello is the author of over 100 peer-reviewed publications and patents.

Small Molecule P2X7 Antagonists for Alzheimer's Disease Treatment

Paolo Pevarello

Axxam SpA, Milan, Italy

The chronic neuroinflammatory process triggered by reactive microglia has emerged recently as an important factor in Alzheimer's Disease (AD). Several lines of evidence point towards the purinergic P2X7 ion channel as a central mediator of neuroinflammation. Therefore, P2X7 antagonists with good CNS penetration may prove to be additional weapons for the treatment of neurodegenerative conditions. Although some P2X7 antagonists have been recently disclosed with good CNS penetration, there is still a need for a compound to be validated as a suitable, efficacious agent in AD preclinical models. We started a project aimed at finding P2X7 antagonists with good brain penetration to be validated in preclinical models of AD.

In a previous phase of the project we developed a novel chemotype for P2X7 antagonists with a good potential for development in a CNS setting. In a hit-to-lead effort we have identified several compounds with an in vivo PK profile suitable for further progression into pharmacological studies. The progress of a lead compounds towards validation of this approach will be highlighted as well as the status reached by our most advanced compounds.

Eloise Hudry, PhD, Massachusetts General Hospital/Harvard Medical School

Eloise Hudry, PhD, is an Instructor in Neurology at the Harvard Medical School in the MassGeneral Institute for Neurodegenerative Disease. She focuses her research on newly developed viral vectors to unravel the pathological processes in play in Alzheimer's disease (AD). She is particularly interested in understanding how the various isoforms of Apolipoprotein E impact the disease, with a specific focus on evaluating the feasibility and benefit associated with APOE2-based gene therapy strategies.

Dr. Hudry completed her doctorate degree in France in the lab of Professor Aubourg (Rene Descartes University, Paris 5), an expert of gene therapy approaches to treat genetic neurodegenerative disorders. Following this, Dr. Hudry joined the lab of Professor Hyman at Harvard Medical School in the MassGeneral Institute for Neurodegenerative Disease (MIND).

During her post-doctoral training from 2009 to 2013, she combined advanced microscopy techniques (multiphoton imaging, array tomography, in vivo microdialysis) with adeno-associated vector (AAV) gene transfer strategies to investigate the molecular mechanisms underlying amyloid pathology and neuronal function changes associated with AD in the brain of transgenic mouse models. She now leads a small APOE group within the Alzheimer's Research Unit at HMS/MIND.

APOE2 – Based Gene Therapy Approaches to Alleviate Alzheimer's Disease Neuropathological Hallmarks

Eloise Hudry

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

The genetic association between the apolipoprotein E alleles and the sporadic form of Alzheimer's disease (AD) was established more than two decades ago; the presence of *APOE4* dramatically increases the prevalence of the disease whereas *APOE2* has an opposite impact. To some extent, APOE2 may be considered as a natural "clinical agent" effective at diminishing the risk to develop the disease by 50% and at delaying the onset of AD by more than two decades compared with APOE4/4 carriers, a protective effect still unprecedented among other therapeutic strategies. However, because of the rarity of this allele in the human population, the mechanisms of action of APOE2 largely remain unknown and the relevance and/or feasibility of specific APOE2-based therapeutic approaches still need to be investigated.

Developing new therapies for neurodegenerative diseases remains particularly challenging due to the presence of the blood brain barrier (BBB) that isolates the central nervous system (CNS) from the rest of the organism. As a consequence, liposomal formulas, nanoparticles and viral vectors have aroused a great interest to improve gene delivery to the brain. Among them, adeno-associated vectors (AAV) offer the advantage of being safe, mildly immunogenic and highly efficient at sustainably transducing different neural cell types. In addition, the concomitant identification of new serotypes that can cross the BBB and of restricted promoters now offer the unique opportunity to target a specific cell type after peripheral administration. This is of particular interest in the case of APOE2-based gene therapy for AD, as *APOE,* is mainly expressed by astrocytes and AD neuropathological lesions are widespread in the CNS. Novel gene transfer approaches will help us understand and evaluate the therapeutic impact of APOE2 in the context of AD.

In the present study, we have demonstrated that a single intravenous injection of ev-AAV, a novel vector tool corresponding to microvesicles-associated AAV, achieves effective and non-toxic gene delivery in the brain. Ev-AAV generally outperforms conventional AAV and leads to the widespread expression of a reporter gene within the intact tissue, reaching on average 13.44±0.8% of astrocytes throughout the CNS. In addition, the use of a GFA promoter specifically restricts the expression within this cell type, with no measureable off-target expression in neurons. Based on these encouraging results and our knowledge that a small added amount of APOE2 could favorably interfere with the course of AD (Hudry E et al. *Sci Trans Med.* 2013), we are now taking advantage of this new gene transfer approach to evaluate the therapeutic benefit of APOE2 overexpression on the progression of amyloidosis and Aβ neurotoxicity in vivo, after amyloid deposition has started.

Carol Colton, PhD, Duke University Medical Center

Carol A. Colton, PhD, is a Research Professor in the Division of Neurology, Department of Medicine at Duke University Medical Center. The Colton Lab has been actively involved in studying the brain's immune response in the initiation and progression of brain disease. In particular, they have contributed and continue to contribute important data and concepts to the field by exploring the varied roles of microglia in neuroinflammation. Dr. Colton and her team were among the first to show that microglia are part of the brain's immune system. The group's studies helped to define the secretory and functional profile of microglia and demonstrated the importance of microglia to the local redox regulation of the brain environment. Importantly, Dr. Colton's early studies using human microglia provided evidence for their similarity and for their differences to rodent microglia, leading to a better appreciation of immune differences when modeling human disease. The Colton lab's more recent work has focused on understanding immune changes and their impact during chronic inflammatory diseases in the brain such as in Alzheimer's disease. This direction for their work stresses 2 basic principles; 1) the critical requirement for considering the temporal changes in inflammation that occur in chronic disease and 2) that immunosuppression is a major factor in the disease process. Using the dual concepts of immunosuppression and the inherent differences between human and rodent redox immune responses, they have developed a novel and important mouse model of AD that, for the first time, shows complete AD-like disease progression in mice. To date this mouse has yielded valuable and novel insights into the neurodegenerative disease process that leads to AD. Most importantly, the Colton Lab has now shown that key amino acid metabolic pathways in the brain are immune regulated in our mouse model of AD, and when activated during disease, lead to amino acid deprivation and subsequent cell death in neurons. The group's newest studies explore the mechanisms of onset of these immune changes that lead to brain deterioration.

Slowing Arginine Utilization by Inhibiting Arginase and Ornithine Decarboxylase with DFMO

Carol Colton *(2015 ADDF/Harrington Scholar)*

Duke University Medical Center, Durham, NC, USA

The pathogenesis of Alzheimer's disease (AD) is a critical unsolved question; and although recent studies have demonstrated a strong association between altered brain immune responses and disease progression, the mechanistic cause of neuronal dysfunction and death is unknown. We have previously described the unique CVN-AD mouse model of AD, in which immune-mediated nitric oxide is lowered to mimic human levels, resulting in a mouse model that demonstrates the cardinal features of AD, including amyloid deposition, hyperphosphorylated and aggregated tau, behavioral changes, and age-dependent hippocampal neuronal loss. Using this mouse model, we studied longitudinal changes in brain immunity in relation to neuronal loss and, contrary to the predominant view that AD pathology is driven by an initial pro-inflammatory response, we find that the pathology in CVN-AD mice is driven by local immune suppression. Areas of hippocampal neuronal death in CVN-AD mice are associated with the presence of immunosuppressive $CD11c^{+}$ microglia and extracellular arginase, resulting in arginine catabolism and reduced levels of total brain arginine. Using flow cytometry we have isolated CD11c+ microglia from brains of our mouse model and compared these to non CD11c+ microglia in CVN-AD mice and to microglia in control mice. We have used an unbiased Affimetrix gene screen to identify genes expressed by this cell type and these data clearly indicate an overall immunosuppressive characteristic. The close regional association of these CD11c+ immunosuppressive microglia and AD pathology in our model suggest a causative role for immunosuppression in AD. One primary mechanism for bystander tissue damage under these conditions is nutrient deprivation of the surrounding cells caused by increased consumption of nutrients including essential amino acids initiated during immunosuppression. The brain is particularly sensitive to amino acid deprivation because the blood brain barrier restricts entry of arginine and other amino acids from the plasma. Consequently, the brain levels of critical amino acids such as arginine are significantly lower than plasma under normal conditions and worsen with disease.

Our data and data from recent publications on humans with AD support the above mechanism. Further evidence that this disease mechanism participates in the pathological damage in CVN-AD mice was found by treating CVN-AD mice with an agent that reverses the increased arginine utilization. Di fluoro methyl ornithine (DFMO), an inhibitor of arginase and ornithine decarboxylase, protected the mice from AD-like pathology and significantly decreased CD11c and other indices of abnormal immune gene expression. Importantly, studies at two different ages at start of treatment show improved memory and learning in treated mice. Our findings strongly implicate local immune-mediated amino acid catabolism as a novel and potentially critical mechanism mediating the age-dependent and regional loss of neurons in humans with AD. This study also provides the potential for new therapeutic approaches to AD.

II. Neuroprotection, Mitochondrial Function and Synaptic Plasticity

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

Novel GLP-1 and GIP Dual Receptor Agonist Peptides Show Neuroprotective Effects
Christian Holscher, PhD, Lancaster University

Fingolimod Therapy in Models of Alzheimer's Disease
Alpaslan Dedeoglu, MD, PhD, Boston University School of Medicine

Development of Klotho Enhancers as Novel Therapeutics for Alzheimer's Disease
Carmela Abraham, PhD, Boston University School of Medicine

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

Development of Small Molecule Activators of Glutamate Transporter EAAT2 Translation for Alzheimer's Disease
Chien-Liang Glenn Lin, PhD, Ohio State University

Lead Discovery of Novel Small Molecule Compounds Effective in Modulation of Cellular Energetics
Eugenia Trushina, PhD, Mayo Clinic

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

Lauren Friedman, PhD, is the Assistant 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.

Christian Holscher, PhD, Lancaster University

Christian Holscher, PhD, is Professor of Neuroscience in the department of Biomedical Sciences and Life Sciences at Lancaster University, England. He completed his first degree in Physiology at the University of Tübingen in Germany and continued his career in England, working at several universities such as Oxford University and the Open University. His research is focused on the development of novel drug treatments for Alzheimer's and Parkinson's disease.

Dr. Holscher investigates the interaction between diabetes and neurodegeneration, which led him to discover the neuroprotective properties of incretin analogues, which are currently on the market to treat type 2 diabetes. His research techniques include transgenic animal models of Alzheimer's and Parkinson's disease to profile new drug candidates in preclinical studies. One of the drugs profiled by him is now in clinical trials in patients with Alzheimer's disease (collaboration with Imperial College at the Hammersmith Hospital, London). Further trials in patients with Parkinson's disease are starting (Cedar-Sinai Hospital in L.A., USA).

Dr. Holscher has published 120 scientific papers and has authored two books. His research has been funded by the Alzheimer's Society, the Alzheimer Research UK, the Cure Parkinson's Trust UK, the Alzheimer Drug Discovery Foundation, Research Council grants and The Wellcome Trust.

Novel GLP-1 and GIP Dual Receptor Agonist Peptides Show Neuroprotective Effects*

Christian Holscher

Lancaster University, Lancaster, UK

The incretin hormones Glucagon-like Polypeptide (GIP) and Glucagon-like peptide 1 (GLP-1) are growth factors. GLP-1 mimetics are on the market as treatments for type 2 diabetes and are well tolerated. We have shown previously that these drugs as well as GIP analogues have neuroprotective properties in animal models of Alzheimer's disease. A clinical trial testing the GLP-1 analogue liraglutide is currently ongoing, funded in part by the ADDF. Newer peptides have been developed that activate both GLP-1 and GIP receptors. In first clinical trials in patients with diabetes, these dual agonists have shown superior effects compared to liraglutide. Here we demonstrate the neuroprotective effects in the APP/PS1 mouse model of AD and in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's Disease. MPTP was injected once-daily (20mg/kg i.p.) for 7 days, and drugs were injected once-daily for 14 days i.p.. When comparing liraglutide (25nmol/kg) and Dual Agonist (10nmol/kg), it was found that the dual agonist was superior in preventing the MPTP- induced motor impairment (Rotarod, open field locomotion, catalepsy test), reduction in Tyrosine Hydroxylase (TH) levels (dopamine synthesis) in the substantia nigra and basal ganglia, a reduction of the pro-apoptotic signaling molecule BAX and an increase in the anti-apoptotic signaling molecule Bcl-2. 7 month old APP/PS1 mice were treated once-daily with GLP-1 and GIP analogues for 8 weeks. Memory loss, amyloid plaque load, soluble oligomers and inflammation in the brain (IBA-1 levels) were much reduced by the drug. Synapse loss was prevented, and BDNF levels in the brain were increased by drug treatment. Experiments with a novel dual GLP-1/GIP agonist peptide are currently ongoing. The results demonstrate that the novel dual agonist shows promise as a potent drug treatment for AD and PD.

**Funded through the ADDF/Alzheimer's Society UK Partnership Program*

Alpaslan Dedeoglu, MD, PhD, Boston University School of Medicine

Alpaslan Dedeoglu, MD, PhD, is Research Health Scientist and Director of Translational Neuro-therapeutics Laboratory at VA Boston Healthcare System and Associate Professor of Neurology at Boston University Medical School.

Dr. Dedeoglu obtained his medical degree from the Istanbul University in 1986. He then moved to Tucson for postgraduate training in Neuropharmacology at the University of Arizona Health Sciences Center and received his PhD in Neuropharmacology from Marmara University in 1992. After completing a post-doctoral fellowship at Massachusetts General Hospital, he moved to the VA and Boston University in 2000.

His major research interest is 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 University School of Medicine, Boston, MA, USA

Alzheimer's disease (AD) is characterized neuropathologically by extracellular senile plaques composed of aggregated amyloid ßpeptide (Aß) and intracellular neurofibrillary tangles (NFT) composed of abnormally hyper-phosphorylated tau protein (p-tau). Neuroinflammation is a prominent feature of AD brain with widespread activation of microglia and astrocytes that correlates with the extent of brain atrophy and cognitive decline. Disease-modifying treatments for AD focused on eliminating Aß and tau aggregates have not proven to be clinically effective. Brain derived neurotrophic factor (BDNF) signaling, which is critical for hippocampal and cortical neuronal viability and synaptic plasticity, is abnormal in AD and may contribute to neurodegeneration in AD. Sphingosine 1-phosphate (S1P) receptors, expressed on a wide range of cells, are a novel attractive target for the modulation of inflammatory processes in neurodegenerative diseases. Fingolimod (FTY720), an analogue of sphingosine and a SP1 agonist, was recently approved as the first oral disease-modifying therapy for multiple sclerosis. In MS Fingolimod-phosphate via high-affinity receptor binding to lymphocyte S1P1 induces S1P1 down-regulation that prevents lymphocyte egress from lymphoid tissues, thereby reducing autoaggressive lymphocyte infiltration into the central nervous system (CNS). Fingolimod easily crosses the brain blood barrier (BBB) and directly inhibits production of pro-inflammatory cytokines from astrocytes and microglia, enhances synaptic strength, and increases neurotrophic factor expression in microglia and neurons. The neuroprotective effects of Fingolimod have been reported in models of epilepsy, spinal cord injury, cerebral ischemia, and Rett syndrome**.** Fingolimod was shown to reduce amyloid-beta production in neuronal cultures and to attenuate beta-amyloid peptide 42 (Aß42)-induced impairment of spatial learning and memory in rats. Our studies in transgenic 5xFAD mice show that oral Fingolimod treatment reduces Aß concentration and plaque formation, decreases activation of microglia and astrocytes and increases the number of doublecortin (DCX)-stained cells in the DG. Changes in the neurochemical profile of the hippocampus analyzed by magnetic resonance spectroscopy supports the neuroprotective effects of fingolimod in 5xFAD mice.

Carmela Abraham, PhD, Boston University School of Medicine

Carmela Abraham, PhD, obtained her PhD in Neuroscience at Harvard University. She then moved to Boston University School of Medicine where she is Professor of Biochemistry and Pharmacology & Experimental Therapeutics.

Her laboratory studies the molecular mechanisms leading to normal brain aging and the pathological processes that culminate in Alzheimer's disease (AD). By utilizing the rhesus monkey as a model for understanding changes that occur during non-pathological aging her group discovered that the anti-aging protein Klotho is down regulated with age. Klotho is also significantly reduced in the AD brain but its function in brain was unknown. Dr. Abraham and her colleagues embarked on elucidating Klotho's role in the CNS. The group discovered that Klotho protects neurons against various insults, including the neurotoxic amyloid beta peptide, and induces the maturation of oligodendrocyte progenitor cells into mature, myelinating cells. This is particular important in multiple sclerosis (MS) where oligodendrocyte progenitor cells fail to mature and produce myelin to repair demyelinated axons. As part of her translational research, Dr. Abraham identified small molecule compounds that enhance Klotho expression and plans to test them in mouse models of AD and MS.

Dr. Abraham is the recipient of the Zenith and Temple awards from the Alzheimer's Association and the Massachusetts Neuroscience Consortium Award.

Development of Klotho Enhancers as Novel Therapeutics for Alzheimer's Disease

Carmela R. Abraham[1], Ci-Di Chen[1], Kevin Hodgetts[2], Ella Zeldich[1]

[1]*Boston University School of Medicine, Boston, MA, USA*
[2]*Laboratory for Drug Discovery in Neurodegeneration, Brigham and Women's Hospital, Boston, MA, USA*

In Alzheimer's disease (AD), amyloid beta peptides (Aβ) accumulate in the brain and are toxic to neurons and synapses. Strategies either to interfere with Aβ formation or enhance its clearance have not succeeded in slowing the progression of the disease. We propose a novel approach intended to protect neurons from the toxicity of Aβ and other age-related insults. Studying the anti-aging protein Klotho, our group has made five important discoveries that have profound relevance to AD and, likely, other neurodegenerative disorders.

We found that:
1) the levels of Klotho, which protects mice and humans from aging and disease, are much lower in the aged healthy brain and in animal models of AD,
2) Klotho is able to rescue hippocampal neurons from Aβ and from oxidative stress and death induced by glutamate,
3) a potentially novel molecular mechanism is responsible for the Klotho-induced neuroprotection,
4) increasing Klotho expression in an AD mouse model rescues the behavioral and LTP abnormalities in these mice, and
5) small molecule compounds that were developed from a high throughput screen to enhance Klotho expression, can mimic Klotho's neuroprotective functions and rescue neurons from death. One such compound increases Klotho RNA and protein expression in the mouse brain. Furthermore, humans who are heterozygous for a Klotho polymorphism called KL-VS have more circulating Klotho and better cognition.

In summary, Klotho exhibits neuroprotective properties and, therefore, Klotho enhancing small molecule compounds that cross the blood-brain barrier could become novel therapeutics for AD and other neurodegenerative diseases.

Martin Jefson, PhD, Rodin Therapeutics Inc.

Martin Jefson, PhD, is a consultant to Atlas Venture and serves as Chief Scientific Officer of two discovery-stage Atlas portfolio companies, Rodin Therapeutics Inc., focused in the area of behavioral epigenetics, and Ataxion, which is pursuing novel small-molecule ion channel modulators to treat rare, debilitating, and underserved neurologic diseases.

Trained as an organic chemist, Dr. Jefson did his thesis work with Professor Jerrold Meinwald at Cornell University and received his PhD in 1982. Immediately afterwards, he joined Pfizer Central Research in Groton CT where he spent the next 27 years. Early in that tenure, Dr. Jefson worked in the Veterinary Medicine Discovery Chemistry group, collaborating to co-invent the fluoroquinolone antibacterial danofloxacin mesylate (Advocin), which is approved for use worldwide for the treatment of respiratory disease in cattle and poultry. In 1994, he moved to the CNS Discovery Research group as a Manager of Medicinal Chemistry, and held numerous positions of increasing responsibility over the next 15 years. In 2001, Dr. Jefson was named the head of CNS Discovery Research for Groton, and in 2007 he was appointed the head of CNS Research for Pfizer. Between 1994 and 2009, more than 40 development candidates were discovered by teams that he lead or managed, including many prototype molecules with novel mechanisms of action. Some of these compounds are still active in development, and one of them, the nicotinic receptor partial agonist varenicline (Chantix) is approved worldwide as an aid to smoking cessation.

Since leaving Pfizer in 2009, Dr. Jefson has worked as a pharmaceutical research consultant, supporting the efforts of several venture capital partnerships and more than 20 biotechnology and pharmaceutical companies.

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

Martin Jefson

Rodin Therapeutics Inc., Cambridge, MA, USA

Epigenetic factors have been shown to play an important role in cognition. In particular, histone acetylation appears to play a role in regulation of genes important to synaptic function, learning and memory. In human Alzheimer disease (AD) brains, as well as in animal models of neurodegeneration, up-regulation of the histone deacetylase 2 (HDAC2) appears to impose an epigenetic blockade on neuronal plasticity genes. Non-selective HDAC inhibitors were found to enhance associative and spatial learning in wild-type mice, as well as to increase the expression of synaptic and dendritic proteins in the hippocampus. Genetic manipulations as well as pharmacological inhibition of HDAC2 using non-selective HDAC inhibitors have been shown to reverse decreased synaptic gene expression and improve cognitive function in animal models of neurodegenerative diseases. However, existing HDAC inhibitors, primarily optimized for use in oncology, inhibit either all Class I HDACs or are pan-HDAC inhibitors – none are HDAC2 selective. Chronic therapeutic utilization of these non-selective HDAC inhibitors has been hindered by severe safety limitations, most notably thrombocytopenia. These effects may be related to the simultaneous inhibition of both HDAC1 and HDAC2. If one of these two HDACs is inhibited, compensatory up-regulation of the other appears to be sufficient for normal hematopoiesis. Thus, an inhibitor that selectively reduces HDAC2 function, and spares HDAC1 function, is proposed to be useful for treating cognitive deficits in AD and free of the clinical side effects seen with non-specific HDAC inhibitors. Rodin Therapeutics is pursuing selective HDAC2 inhibitors through a structure-based optimization of kinetically selective isoenzyme inhibitors. Our most advanced compounds have shown enhancement of synaptic gene expression in rat primary neurons, enhancement of LTP in rat hippocampal slices and positive effects in acute behavioral assay in young, wild type mice. Additionally, these compounds have shown reduced effects on genes involved in hematopoiesis as well as reduced hematological toxicity. The progress and future direction of this work will be described.

Chien-Liang Glenn Lin, PhD, Ohio State University

Chien-Liang Glenn Lin, PhD, is Professor of Neuroscience at Ohio State University College of Medicine.

Dr. Lin completed his doctorate in Molecular Biology and Biochemistry at the Johns Hopkins University in 1995. He completed his postdoctoral research in the Department of Neurology at the Johns Hopkins University.

Dr. Lin joined the Department of Neuroscience at the Ohio State University in 1999, where he directed his research to molecular mechanisms underlying neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis (ALS) and epilepsy.

His recent research focuses on the role of glutamate transporter EAAT2 in the regulation of synaptic plasticity and function and in the pathogenesis of neurodegenerative diseases. He has published numerous papers in major journals and holds four patents.

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

Chien-Liang Glenn Lin *(2014 ADDF/Harrington Scholar)*

Ohio State University, Columbus, OH, USA

The glutamate transporter EAAT2 is localized primarily on the peri-synaptic processes of astrocytes closely associated with excitatory synaptic contacts and is responsible for 80-90% of all glutamate transport in the central nervous system. EAAT2 plays a critical role in the homeostatic regulation of extracellular glutamate levels and in preventing glutamate-mediated excitotoxicity. Several lines of evidence indicate that EAAT2 plays an essential role in cognitive functions. Dysfunction of EAAT2 expression results in cognitive impairment. Loss of EAAT2 protein is a common phenomenon observed in Alzheimer's disease (AD) patients and animal models. We previously investigated whether restored EAAT2 protein and function could benefit cognitive functions and pathology in $APP_{Sw,Ind}$ mice, an animal model of AD. A transgenic mouse approach via crossing EAAT2 transgenic mice with $APP_{Sw,Ind.}$ mice, and a pharmacological approach using a novel EAAT2 translational activator, LDN/OSU-0212320, were conducted. Findings from both approaches demonstrated that restored EAAT2 protein function significantly improved cognitive functions, restored synaptic integrity, and reduced amyloid plaques. Importantly, the observed benefits were sustained one month following compound treatment cessation, suggesting that EAAT2 is a potential disease modifier with therapeutic potential for AD. LDN/OSU-0212320 belongs to a pyridazine-based lead series, which we previously identified via a high-throughput screen. We are currently working on the optimization of this lead series and have identified several compounds with excellent potency and good oral bioavailability. In addition, we investigate the underlying mechanisms by which increased EAAT2 reverses Alzheimer phenotypes and the underlying mechanisms of compound action. The results will be presented at the conference. This project is a collaboration with Laboratory for Drug Discovery for Neurodegeneration, Brigham & Women's Hospital, Harvard Medical School.

Eugenia Trushina, PhD, Mayo Clinic

Eugenia Trushina, PhD, is an Associate Professor in the Department of Neurology and Department of Molecular Pharmacology and Experimental Therapeutics at the Mayo Clinic, Rochester. She received her doctoral degree in organic chemistry from Saratov State University in Russia. Dr. Trushina completed her postdoctoral training at the Mayo Clinic, Rochester where she worked with Drs. C. McMurray, R. Pagano and M. McNiven studying mechanisms of multiple neurodegenerative diseases including Huntington's (HD) and Alzheimer's Diseases (AD).

Dr. Trushina's research program is focused on the revealing early molecular mechanisms of neurodegeneration the role of mitochondria in particular. Her current research projects involve the development of new mitochondria-targeted therapeutic approaches and metabolomic-based biomarkers for early disease diagnosis.

Dr. Trushina is a recipient of the NIH, BrightFocus, GHR, ADDF and Mayo Clinic Research Awards.

Lead Discovery of Novel Small Molecule Compounds Effective in Modulation of Cellular Energetics

Eugenia Trushina

Mayo Clinic, Rochester, MN, USA

Alzheimer's Disease (AD) presently affects more than 5 million Americans with numbers expected to grow. This is a terrible epidemic with no effective treatment and with multiple failed clinical trials focused on prevention of amyloid beta (Aβ) production. Alternative approaches are urgently needed. We have found that modulation of mitochondrial energetics with mild inhibition of Complex I activity with small molecule tricyclic pyrone compound prevents the development of AD in three transgenic animal models of familial AD (FAD). In vivo treatment reversed memory deficits in APP, PS1 and APP/PS1mice prior to and following the appearance of AD pathology. Investigation of the molecular mechanism revealed that lead compound competes with the FMN for binding to the redox center of Complex I mildly inhibiting its activity without inducing reactive oxygen radical production or inflammation in vivo. Metabolic adaptation results in the activation of AMP-activated protein kinase (AMPK) signaling leading to a reduction of glycogen synthase kinase 3b (GSK3b) activity, levels of Ab and pTau, restoration of axonal trafficking and increased levels of brain-derived neurotrophic factor (BDNF) and synaptic proteins in vivo. Based on these findings, we developed novel compounds with properties superior to the lead. I will discuss current state of the project development.

PLENARY SPEAKER
Eric Hostetler, PhD, Merck

Eric Hostetler, PhD, is the head of the Translational Imaging Biomarker organization at Merck, which utilizes a broad range of imaging modalities to discover, qualify, and employ imaging biomarkers to aid drug discovery and development.

Dr. Hostetler received his PhD in Organic Chemistry with Dr. John Katz's group at the University of Illinois Urbana-Champaign in 1998, where his dissertation focused on novel chemistry methods for incorporation of PET radioisotopes. He continued in the field of nuclear imaging with a postdoctoral appointment at the Washington University St. Louis School of Medicine in the Mallinckrodt Institute of Radiology.

Dr. Hostetler subsequently joined Merck's Imaging Department in 2000. Since then he has had various roles at Merck, including director of the PET tracer group, where he contributed to the discovery of novel PET tracers for 12 different targets, primarily for the purpose of guiding neuroscience drug development.

Progress and Future Directions in Tau Imaging

Eric Hostetler

Merck, Kenilworth, NJ, US

To enable the clinical development of disease-modifying therapies for Alzheimer's Disease (AD), there is a clear need for a biomarker which correlates strongly with disease progression. One biomarker approach of high interest is to quantify the progression of neurofibrillary tangles, also referred to as tau pathology. The density and spread of tau pathology has been shown to correlate well with disease progression in the analysis of post-mortem AD brains. Positron Emission Tomography (PET) is a non-invasive imaging technology which could enable longitudinal quantification of tau pathology in vivo given a small molecule with the appropriate tau binding characteristics which can also be radiolabeled with a short-lived positron-emitting isotope. To this end, several tau PET tracers have been evaluated in both healthy and AD patients. The results communicated from these initial studies have provided promise for the use of tau PET tracers to quantify changes in tau pathology. This presentation will focus on the challenges which remain in discovering an ideal tau PET tracer, the advantages a second generation tau PET tracer could bring, and how tau PET can enhance our understanding and ultimately enable discovery of disease-modifying drugs for AD and other tau-driven neurodegenerative diseases.

III. Translatable Biomarkers to Accelerate Clinical Development

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

A Novel fMRI Biomarker of Asymptomatic Alzheimer's Disease
Xiong Jiang, PhD, Georgetown University Medical Center

Integrative Genomic Approach to Prioritize Targets for Drug Discovery and Development in Alzheimer's Disease and Aging-Related Cognitive Decline
Nathalie Pochet, PhD, Brigham & Women's Hospital

The P2Y6 Receptor as a Therapeutic Target for Alzheimer's Disease
Philip Haydon, PhD, GliaCure, Inc.

Benfotiamine in Alzheimer's Disease: A Pilot Study
Gary Gibson, PhD, Weill Cornell Medical College

Cortical Gray Matter-White Junction Pattern of Retention of the Tauopathy Ligand 18F-T807 (Avid-1451) in Clinically Probable CTE
Samuel Gandy, MD, PhD, Icahn School of Medicine at Mount Sinai

LLCBrainWire: Predictive Imaging-based Biomarker Technology for Alzheimer's Disease
Ashish Raj, PhD, BrainWire

SESSION CHAIR

Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation

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

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

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

Xiong Jiang, PhD, Georgetown University Medical Center

Xiong Jiang, PhD, is an Assistant Professor of Neuroscience at Georgetown University Medical Center.

Dr. Jiang received his Bachelor of Science in Computer Science, Master of Science in Biophysics, PhD in Experimental Psychology (Cognitive Neuroscience), and postdoctoral training in Computational Neuroscience and Neuroimaging.

His research interests are to use neuroimaging techniques like functional magnetic resonance imaging (fMRI) to study brain function and dysfunction. During recent years, his research has been focusing on developing novel fMRI techniques that can detect and assess neuronal dysfunction in individuals with neurodegenerative diseases, such as Alzheimer's disease.

A Novel fMRI Biomarker of Asymptomatic Alzheimer's Disease

Xiong Jiang

Georgetown University Medical Center, Washington D.C., USA

Alzheimer's disease (AD) is a neurodegenerative disease and the most common cause of dementia. With no known cures or disease-modifying therapies, there is a pressing need to find biomarkers that can accurately assess disease status, predict future disease progression, and evaluate the effects of disease-modifying agents in asymptomatic patients.

However, despite recent efforts and significant progress in research, the reliable detection of pre-symptomatic and prodromal AD and evaluation of drug treatment remains a major challenge. Given that AD is hypothesized to lead to changes in neuronal function long before detectable behavioral symptoms and/or anatomical changes, functional magnetic resonance imaging (fMRI), with its ability to image brain function, has the potential to be a critical tool in the early detection of AD and the evaluation of treatments as a non-invasive technique.

Here we aimed to verify and validate a novel fMRI technique in assessing AD progression. Preliminary results suggest this novel technique may have the potential to reveal early neuropathological changes at a rather early stage of AD. We are working to validate and advance this technique with a large sample size.

Nathalie Pochet, PhD, Brigham & Women's Hospital

Nathalie Pochet, PhD, is an independent investigator in the Program for Translational Neuropsychiatric Genomics within the Department of Neurology at Brigham and Women's Hospital and Harvard Medical School.

She has trained in the fields of engineering in computer science, bioinformatics, and artificial intelligence, and is an expert in genome and transcriptome analysis. As a postdoctoral fellow at the FAS Center for Systems Biology at Harvard and at the Broad Institute of MIT and Harvard, she made groundbreaking discoveries in fundamentals of evolution, in the rare Mendelian kidney disease MCKD1, and in the human malaria parasite Plasmodium falciparum.

Integrative Genomic Approach to Prioritize Targets for Drug Discovery and Development in Alzheimer's Disease and Aging-Related Cognitive Decline

Nathalie Pochet

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

Complex diseases such as Alzheimer's disease (AD) and aging-related cognitive decline (CD) are caused by a combination of genetic, environmental, and lifestyle factors. Molecular pathways that are associated with both genetic and environmental contributions have been identified. However, causal mechanisms have eluded numerous attempts at fine mapping despite intensive research. Unraveling regulatory mechanisms involving the genetic and epigenetic disruptions driving these molecular pathways will uncover novel drug targets for AD and CD.

We sequenced RNA from the dorsolateral prefrontal cortex of 550 individuals from two prospective cohort studies on aging: the Religious Order Study and the Memory and Aging Project. The subjects were all non-demented at the start of the study and had differing extents of aging-related cognitive decline at death, ranging from cognitively non-impaired individuals to individuals clinically diagnosed with AD. We have additional genome-wide genotype, miRNA, DNA methylation, and histone modification (H3K9Ac) data from the same brain region, further informing our RNA analyses.

Here we developed a systematic method to discover disease mechanisms and therapeutic targets in AD and CD. We leveraged and enhanced computational strategies to integrate the multiple levels of genomic data we have. First, we identified the underlying regulatory mechanisms to better understand the molecular and mechanistic basis of AD and CD. Second, we prioritized targets for drug discovery and development while simultaneously understanding the impact of perturbing these targets in AD and CD. Our approach facilitates the design of increasingly specific strategies for better diagnosis and therapy of AD and CD.

Philip Haydon, PhD, GliaCure, Inc.

Philip Haydon, PhD, is President of GliaCure and the Annetta and Gustav Grisard Professor and Chair in the Department of Neuroscience at Tufts. In 1994, Dr. Haydon's laboratory discovered that astrocytes can release the chemical transmitter glutamate in response to receptor-induced Ca2+ elevations and that this glial-mediated signal can activate neighboring neurons.

In 1999 he coined the expression "the tripartite synapse" to recognize the important role that astrocytes play in tuning and modulating synaptic transmission. More recently, Dr. Haydon has begun studies on microglia and has emphasized identification of the mechanisms regulating phagocytosis by this subtype of glial cell. He has discovered the importance of reactivation of the microglial phagocytotic pathway that normally declines in Alzheimer's disease.

In addition to his academic background Dr. Haydon has significant experience in commercial enterprises. He was a founding partner in three small businesses, including Prairie Technologies, Inc.

The P2Y6 receptor as a Therapeutic Target for Alzheimer's Disease

Philip Haydon

GliaCure Inc., Boston, MA, USA

The purinergic P2Y6 receptor is preferentially expressed by microglia in the CNS, where it is known to stimulate phagocytosis, and by T cells systemically, where it exerts anti-inflammatory roles. The levels of uridine, the precursor of UDP, the endogenous ligand for the P2Y6 receptor, are decreased in the CSF of patients with Alzheimer's disease, raising the potential that enhancing the levels of agonists for these receptors would be beneficial in the disorder. To test this possibility, we injected UDP i.c.v. in PSAPP mice and demonstrated that it rapidly reduced amyloid deposition using longitudinal two photon microscopy (i.e., in three days), increased amyloid uptake into microglia, reversed deficits in synaptic plasticity and restored contextual fear conditioning.

Using P2Y6 receptor-expressing cells we tested rationally designed novel chemical entities for their ability to mobilize intracellular Ca2+ and identified compounds with selectivity for P2Y6 over P2Y2 and P2Y4 receptors. With these compounds we performed phenotypic screening and identified GC021109 as a candidate for progression. GC021109, delivered i.p. once daily for seven days, reduced amyloid deposition in 6-month-old mice and, when delivered daily from 3 months to 6 months of age, reduced the accumulation of amyloid, prevented deficits in contextual fear conditioning and reduced the accumulation of cytokines IL-12(p70), IL-10, and IL-4, all of which have been implicated in Alzheimer's disease.

IND-enabling toxicology studies together with studies in healthy volunteers demonstrated that GC021109 is safe and well tolerated and exhibits excellent pharmacokinetic parameters. GC021109 is currently being studied in a Phase 1b multiple ascending dose study in patients with mild to moderate Alzheimer's disease. Together these studies demonstrate that modulation of P2Y6 receptors, acting through parallel anti-inflammatory and phagocytic mechanisms of action, has the potential to treat Alzheimer's disease.

Supported by funds from the Alzheimer's Drug Discovery Foundation and GliaCure, Inc.

Gary Gibson, PhD, Weill Cornell Medical College

Gary Gibson, PhD, is Professor of Neuroscience, Weill Cornell Medical College, the Brain and Mind Research Institute, Burke Medical Research Institute. His peer-reviewed publications include 166 research papers; 78 chapters and as edited a book based on a NY Academy of Sciences meeting on mitochondria.

His research has explored the role of mitochondria, metabolism and calcium in brain function and dysfunction. His studies have been directed toward better understanding of Alzheimer's disease (AD) in order to develop new therapies. His research strategy is to use autopsy brains and living cells from patients with AD to identify novel, clinically relevant abnormalities [e.g., abnormalities calcium, thiamine (vitamin B1) dependent enzymes and mitochondrial enzymes] that will provide a foundation to understand the mechanism of changes in neurons. He then models the abnormalities with proteins, cells and animals to understand the underlying mechanisms and to develop new therapeutic approaches. Thiamine dependent enzymes are diminished in tissues from AD patients, and interfering with thiamine dependent enzymes can exacerbate plaque formation, phosphorylation of tau and the calcium changes that occur in cells from AD patients or animal models of AD. Thus, reversing these changes is an attractive therapeutic target. The goal of our research is to understand what causes these changes, their implications for brain disease and to develop strategies to reverse them.

Benfotiamine in Alzheimer's Disease: A Pilot Study

Gary Gibson

Weill Cornell Medical College, New York, NY, USA

Despite major advances in early diagnosis, neuroimaging, and biomarker research, no disease-modifying therapies are available for Alzheimer's Disease (AD). Reduced brain glucose metabolism always accompanies AD and is an outstanding biomarker of disease progression. Reduced glucose metabolism can lead to diminished synaptic function, reduced brain function and the development of AD like pathology including plaques and tangles. Thus, increasing brain glucose utilization is an attractive therapeutic target.

Plausible mechanisms link the reduction in glucose metabolism to a decline in thiamine (vitamin B1) dependent processes in the brain. Thiamine dependent enzymes are critical to normal brain glucose utilization, and all are diminished in AD in parallel with a decline in clinical dementia rating scores. In humans and/or animals, thiamine deficiency diminishes brain metabolism and cognition, while promoting AD like pathology including plaques and tangles.

On the other hand, elevating brain thiamine increases brain metabolism and cognition in humans and animals. In animal models of AD, elevated thiamine diminishes AD-like pathology. These findings suggest that increasing brain thiamine should be beneficial in AD. Diabetics are also thiamine deficient. The thiamine analogue benfotiamine has proven to be an effective and safe way to increase thiamine 5-10 times more than thiamine and keep it high for hours. Thus, treating AD patients with benfotiamine may be a safe way to delay the reduction in brain glucose utilization and slow further decline in cognition in AD patients.

Samuel Gandy, MD, PhD, Icahn School of Medicine at Mount Sinai

Samuel Gandy, MD, PhD, is Mount Sinai Professor of Alzheimer's Disease Research, Professor of Neurology and Psychiatry, Associate Director of the Mount Sinai Alzheimer's Disease Research Center in New York City, and Chairman Emeritus of the National Medical and Scientific Advisory Council of the Alzheimer's Association.

Dr. Gandy is an international expert in the metabolism of the sticky substance called amyloid that clogs the brain in patients with Alzheimer's disease. In 1989, Gandy and his team discovered the first drugs that could lower formation of amyloid.

Dr. Gandy has written more than 150 original papers, chapters and reviews on this topic. Dr. Gandy has received continuous NIH funding for his research on amyloid metabolism since 1986. Dr. Gandy is a member of the Faculty of 1000 Biology and serves as a Consulting Editor for The Journal of Clinical Investigation. He also serves on the Editorial Advisory Boards for the journals Public Library of Science-Medicine (PLoSM), Neurodegenerative Diseases, and Current Alzheimer Research. He is Associate Editor of the journals Molecular Neurodegeneration and Alzheimer Disease and Associated Disorders.

Cortical Gray Matter-White Junction Pattern of Retention of the Tauopathy Ligand 18F-T807 (Avid-1451) in Clinically Probable CTE

Samuel Gandy[1], Dara L. Dickstein[1], Karin Knesaurek[1], Jennifer Short[1], Mariel Pullman[1], Mary Sano[1], Ash Rafique[1], Barry Jordan[2], Heidi Bender[1], Martin Goldstein[1], Wayne Gordon[1], Kristen Dams-O'Connor[1], James Stone[4], Steven T DeKosky[3], Patrick Hof[1], Lale Kostakoglu[1]

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Molecular neuroimaging has enabled the study of cerebral proteopathy in the setting of Alzheimer's disease (AD) and frontotemporal dementia (FTD). With regard to traumatic brain injury (TBI), two potential uses can be envisioned: (1) Amyloid imaging in the acute or chronic phase in order to assess the possibility of either post-traumatic AD and/or chronic traumatic encephalopathy. (While CTE is primarily a tauopathy, about 50 percent of CTE cases have cerebral amyloidosis, often in association with the APOE4 allele; Menon and colleagues have detected post-traumatic cerebral amyloidosis from 2 wk to 1 yr post TBI). (2) Tauopathy imaging in the chronic phase seeking to detect the signature lesions of CTE. We have embarked upon studies relevant to each of the two scenarios described above. For our investigation of acute post-traumatic cerebral amyloidosis, we have studied 6 high risk boxers from ages 29-42 using amyloid imaging with either [18F]florbetapir or [18F]florbetaben. The high risk boxer designation is assigned because of numbers of knockouts and/or duration of loss of consciousness. None of these boxers showed any immediately recognizable ligand retention. Further quantitative analysis is underway. For our investigation of tauopathy, we have studied six subjects with histories of either single severe or mild repetitive TBI. The two subjects with the greatest clinical psychological and/or cognitive impairment showed substantial retention of [18F]T807 (Avid-1451). In one subject, the pattern of ligand retention bore a striking resemblance to the distribution of CTE tauopathy; i.e., most intense at the gray matter-white matter junctions. These data support the possibility that [18F]T807 (Avid-1451) imaging may, in some cases, be useful in identifying the tauopathy of CTE during life. Further clinico-pathological correlation will be required before the pathological underpinning of this ligand retention pattern can be established.

Supported by ADDF & US Department of Veterans Affairs

IV. Tau, TDP-43, Progranulin and Protein Clearance

Chair: Aaron Carman, PhD, Alzheimer's Drug Discovery Foundation

Pim I Inhibition as a New Therapeutic Target for Alzheimer's Disease
Salvatore Oddo, PhD, Banner Sun Health Research Institute

Rational Design of Small Molecules Targeting RNA Repeat Expansions
Matthew Disney, PhD, The Scripps Research Institute

Novel Diagnostic CSF Biomarkers for Pathological Subtypes of FTD
Marta Del Campo Milan, PhD, VU University Medical Center

Adeno-Associated Virus Gene Therapy of Progranulin-Related Frontotemporal Dementia
Larry Altstiel, MD, PhD, Provectra Therapeutics, Inc.

FTD Trafficking Assays and Compound Screening: Inhibiting Sortilin-dependent Progranulin Endocytosis
Scott Sneddon, PhD, JD, Sharp Edge Labs

SESSION CHAIR

Aaron Carman, PhD, Alzheimer's Drug Discovery Foundation

Aaron Carman, PhD, is the Assistant Director for Aging and Alzheimer's Prevention at the Alzheimer's Drug Discovery Foundation. The mission of this program, started in March of 2012, is to provide a credible scientific voice to the general public, medical, and scientific communities in the evaluation and assessment of potential therapies to prevent and delay cognitive aging, Alzheimer's disease and related dementias.

Dr. Carman trained as a postdoctoral fellow at Memorial Sloan-Kettering Cancer Center where he studied novel small-molecule therapeutics for tau-based neurodegeneration. His earlier postdoctoral training at Cornell University with Margaret Bynoe focused on manipulating blood-brain barrier permeability through adenosine receptor signaling as a novel CNS drug-delivery system. Dr. Carman earned his doctorate in Microbiology and Molecular Genetics with Michael Lorenz at University of Texas Health Science Center in Houston where he studied alternate carbon metabolism in the human fungal pathogen *Candida albicans*. He earned his BS in Microbiology from Kansas State University.

Dr. Carman has authored numerous peer-reviewed publications and is a member of the New York Academy of Sciences, Society for Neuroscience and the Gerontological Society of America.

Salvatore Oddo, PhD, Banner Sun Health Research Institute

Salvatore Oddo, PhD, is the Principal Investigator of a grant from the National Institute of Health, which is focused on elucidating the role of the mammalian target of rapamycin on the pathogenesis of Alzheimer's disease. He received his undergraduate degree in Molecular Biology from the University of Catania, Italy, and his graduate degree in Neurobiology of Learning and Memory from the University of California, Irvine.

Dr. Oddo's research focuses on understanding the molecular mechanisms underlying memory deficits in Alzheimer's disease. Using animal models, he showed that dysfunction signaling transduction pathways that are critical for learning and memory play a pivotal role in the cognitive decline associated with Alzheimer's disease. Dr. Oddo has published more than 70 research articles in international peer-reviewed journals. In recognition of his contribution to the aging and Alzheimer's disease fields, he has been the recipient of several national and international awards.

Pim 1 Inhibition as a New Therapeutic Target for Alzheimer's Disease

Salvatore Oddo

Banner Sun Health Research Institute, Phoenix, AZ, USA

The Alzheimer disease (AD) brain is characterized by two types of protein aggregates, neurofibrillary tangles (NFTs), comprised of hyperphosphorylated tau, and amyloid plaques, comprised of amyloid-β (Aβ). We have identified the mammalian target of rapamycin (mTOR) as a potential molecular link between Aβ, tau and cognitive decline. Pim1, is a protein kinase that that regulates mTOR signaling by phosphorylating PRAS40, a component of the mTORC1 that physically binds to mTOR to inhibit its signaling. Phosphorylated PRAS40 releases from mTOR and allows mTOR signaling. In this work, we tested the hypothesis that Pim1- mediated mTOR hyperactivity contributes to cognitive dysfunction associated with AD. We will show that treatment with a small molecule inhibitor of Pim1 ameliorate learning deficits in 3xTg-AD mice, a widely used animal model of AD. The cognitive improvement was associated with a decrease in Aβ and tau pathology. Overall, our data highlight a novel approach to reducing AD-like pathology in mice.

Matthew Disney, PhD, The Scripps Research Institute

Matthew Disney, PhD, began his independent career in 2005 and moved to the Department of Chemistry at The Scripps Research Institute in 2010, where he is currently Professor. He received his BS from the University of Maryland, College Park, and his PhD at the University of Rochester and completed postdoctoral training at the Massachusetts Institute of Technology and the Swiss Federal Institute of Technology (ETH, Zürich, Switzerland).

His laboratory is focused on understanding RNA-ligand interactions, and using this information to rationally design small molecules that modulate RNA function or toxicity from only sequence. His laboratory has recently reported success targeting RNA repeat expansions that cause incurable genetic disorders, including myotonic muscular dystrophy type 1, Huntington's disease, and amyotrophic lateral sclerosis, in cellular and animal models of disease as well as various RNAs involved in cancer.

Matt has received various awards including the Camille & Henry Dreyfus New Faculty Award, The Camille & Henry Dreyfus Teacher-Scholar Award, the Research Corporation Cottrell Scholar Award, the Eli Lily Award in Biological Chemistry, the David W. Robertson Award for Excellence in Medicinal Chemistry, and the David Y. Gin New Investigator Award from the American Chemical Society.

Rational Design of Small Molecules Targeting RNA Repeat Expansions*

Matthew Disney

The Scripps Research Institute, Jupiter, FL, USA

RNA repeats expansions have been shown to cause a variety of diseases via many mechanisms. Thus, the development of compounds that target these RNAs and modulate disease-associated pathways could provide a route to therapeutic development. Herein, we describe various methods that have been developed and implemented to target disease-associated RNA repeat expansions by using small molecules. The approaches described include traditional small molecules, covalent small molecules, and compounds that are synthesized on-site. In this latter approach a click chemistry approach was developed in which cell-permeable, low molecules weight drug precursors enter disease affected cells and when they bind to their target, the compounds are transformed into potent modulators of disease function by using a disease affected cell as a round bottomed flask and a disease-causing biomolecule as a drug synthesis catalyst. Our goal is to develop these approaches into pre-clinical lead candidates.

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

Marta Del Campo Milan, PhD, VU University Medical Center

Marta Del Campo, PhD, is currently working as a post-doctoral researcher with Dr. Charlotte Teunissen at the Neurochemistry laboratory of the Clinical Chemistry Department at the VUMC. She received her BS in Biology and MS in Biotechnology from the Universidad Autonoma de Madrid (Spain).

She completed her PhD under the European Neuroscience Campus Network and the Erasmus Mundus Joint Doctorate program within the Clinical Chemistry Department and Alzheimer's Center at the VU Medical Center in Amsterdam.

Dr. Del Campo's research is focused on identifying novel potential protein biomarkers for the differential and early diagnosis of different neurodegenerative disorders such as Alzheimer's disease and frontotemporal dementia. In addition, she is interested on understanding whether the novel biomarkers identified indicate abnormalities in specific molecular mechanisms and its role in the development of the different dementias.

Novel Diagnostic CSF Biomarkers for Pathological Subtypes of FTD*

Marta Del Campo, Marleen Koel-Simmelink, Naura Elias, Yolande Pijnenburg, Charlotte Teunissen

VU University Medical Center, Amsterdam, Netherlands

Frontotemporal dementia (FTD) is the second most prevalent dementia in patients below the age of 65 and the third most common dementia in all age groups. FTD is clinically classified in different subtypes based on the patients' phenotype (i.e. behavior and personality changes, language disturbances) but it is often misdiagnosed as another type of dementia such as Alzheimer's disease (AD) or as a psychiatric disorder. Importantly, the underlying neuro-pathological changes in the different FTD subtypes are highly heterogeneous. Thus, while FTD is used to describe the clinical syndrome, frontotemporal lobar degeneration (FTLD) is used for pathological diagnosis. FTLD is classified in different subtypes based on the main misfolded protein aggregates found within the brain such as tau (FTLD-tau) or the trans-activator regulatory DNA binding protein 43 (TDP43, FTLD-TDP), which likely require distinct pharmacological therapy.

Unfortunately, to date there are still no effective biomarkers able to discriminate FTLD from other dementias nor the different FTLD subtypes, which halts the selection of appropriate patients for drugs trials aimed at specific pathophysiological targets. In order to unravel novel discriminatory biomarkers, we have mapped changes in the proteome of ante-mortem cerebrospinal fluid (CSF) of well-characterized FTD patients with confirmed tau or TDP-43 pathology and controls using a hypothesis-free proteomics approach. A validation analysis using specific ELISAs has been performed for several identified biomarker candidates, in which we included a larger cohort of patients with different FTLD subtypes as well as other dementias (i.e. AD, Vascular dementia and Dementia with Lewy Bodies). This study reveals not only novel CSF biomarker candidates able to discriminate the different FTLD-subtypes, but it also pinpoints to potential molecular mechanisms involved in the development of FTLD.

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

Scott Sneddon, PhD, JD, Sharp Edge Labs

Scott Sneddon, PhD, JD, is President and CEO at Sharp Edge Labs, a preclinical drug development company. Dr. Sneddon received his undergraduate BPhil. degree at the Pennsylvania State University in Molecular Biophysics, his PhD from Carnegie Mellon University in Chemistry & Biophysics and his JD degree from the School of Law at Columbia University.

Following his graduate work, Dr. Sneddon joined the New Leads Drug Discovery group at Pfizer Central Research where he helped build the structure-based design and structural chemistry groups. At Pfizer, Dr. Sneddon was part of the group that developed Lipinski's "Rules of Five", was an early pioneer in high throughput screening, early-ADME/PK, combinatorial chemistry and combinatorial library generation and molecule diversity assessment. He was engaged in all phases of drug discovery and preclinical development across Pfizer's therapeutics areas.

Dr. Sneddon left Pfizer to co-found the Drug Discovery Program at Genzyme in Cambridge Massachusetts where he oversaw medicinal chemistry and in-vitro biology (including assay development and high throughput screening). During his 10 years with the Drug Discovery Group his group implemented several dozen cellular high throughput screens, identified leads, and progress compounds into the clinic in areas including Multiple Sclerosis, Transplant Rejection, Cystic Fibrosis, Infectious Disease and Cancer.

Following Law School, Dr. Sneddon practiced law at a large downtown Boston Law Firm, specializing in Technology Companies and Venture Capital Financing. He later developed an Intellectual Property Practice and is a licensed patent attorney. Dr. Sneddon joined Sharp Edge Labs in 2011 as its CEO, and has been building the company to become a leader in the area of protein trafficking, and especially the development of trafficking assays for drug discovery. Sharp Edge Labs has discovery programs in Parkinson's disease, Frontotemporal Dementia/Alzheimer's and Cystic Fibrosis.

FTD Trafficking Assays and Compound Screening: Inhibiting Sortilin-dependent Progranulin Endocytosis

Scott Sneddon

Sharp Edge Labs, Pittsburgh, PA, USA

The role of progranulin as a neuroprotective factor is well established. Familial FTD is associated with Progranulin haploinsufficiency, that is, loss of one copy of the GRN gene, resulting in a decreased level of free Progranulin (PGN). Furthermore, depressed Progranulin levels are a key prognostic indicator of FTD in sporadic disease (and Alzheimer's). It has been known for some time that Sortilin is a natural cell-surface scavenger for PGN, and that binding of PGN to Sortilin leads to its endocytosis and degradation, resulting in lower progranulin, and, in theory, less progranulin neuroprotection. The hypothesis has been advanced that if the Sortilin-dependent endocytosis of PGN can be inhibited, that circulating PGN levels would increase, and that would be neuroprotective in FTD, and in other neurodegenerative diseases including Alzheimer's and ALS. In this work we have developed a high throughput library screening assay to test that hypothesis. The technology underlying that screen, the assay data quality, and initial library screening results will be discussed during the presentation.

NOTES