Alzheimer's
Drug Discovery
Foundation

15TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DRUG DISCOVERY

Jersey City ● *September 8-9, 2014*

PROGRAM and ABSTRACTS

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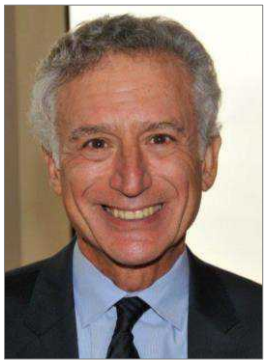
WELCOME!



On behalf of the Alzheimer's Drug Discovery Foundation (ADDF), I am pleased to welcome you to our *15th International Conference on Alzheimer's Drug Discovery.*

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

We are deeply grateful to our generous sponsors whose support makes this meeting possible: Eli Lilly & Company, Merck Research Laboratories, Pfizer Inc., Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Oryzon, and PsychoGenics. We would also like to thank our exhibitors: Able Cerebral, Amylgen, Biosensis, Brains On-Line, International Discovery Services & Consulting (IDSC), InterVivo Solutions, QPS, ReproCELL, Ricerca, Sanguine, Taconic, 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.

Engaging the next generation of research scientists in this field is more important than ever. We are pleased to announce our 2014 Young Investigator Scholarship winners. We encourage you to visit their poster presentations which will be displayed throughout the meetings.

To help us plan an even better conference in 2015, please complete the survey to provide us with feedback and suggestions.

Welcome, once again, to the *15th International Conference on Alzheimer's Drug Discovery*!

Best Regards,

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 **$66 million to fund 448 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 2013, 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 international scientific conferences as part of our ongoing efforts to increase researchers' knowledge about Alzheimer's disease and the drug discovery process. The conferences promote networking to catalyze the exchange of ideas and foster alliances that accelerate the development of new treatments for AD.

Our annual *International Conference for Alzheimer's Drug Discovery*, held in the fall, focuses on the discovery and development of drugs targeting Alzheimer's disease and related dementias. The *Drug Discovery for Neurodegeneration* conference, held in the spring, is designed to educate scientists on the process of translating basic neuroscience research into innovative therapies.

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

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2014 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 the poster presentations during the breaks, lunch and networking reception.

The 2014 Young Investigator Scholars are:

Narjes Baazaoui, PhD (cand.), *The New York Institute for Basic Research*
Jasmeer Chhatwal, MD, PhD, *Massachusetts General Hospital*
Dhwanil Dalwadi, PhD (cand.), *University of North Texas Health Science Center*
Julia Gerson, BS, *University of Texas Medical Branch*
Laura Haas, MS, PhD (cand.), *Yale University*
Holly Hunsberger, MS, *West Virginia University*
Jane Kovalevich, PhD, *University of Pennsylvania*
Li Liu, PhD, *University of Pennsylvania*
Diego Mastroeni, PhD, *Banner Sun Health Research Institute*
Malathi Narayan, PhD, *Byrd Alzheimer's Institute-University of South Florida*
John Steele, PhD, *University of California, San Diego*
Nickeisha Stephenson, PhD, *Massachusetts General Hospital & Harvard Medical School*
Jennifer Tuscher, BS, *University of Wisconsin-Milwaukee*
Alissa Tuttle, BS, *University of North Texas Health Science Center*
Heather Wilkins, PhD, *University of Kansas Medical Center*

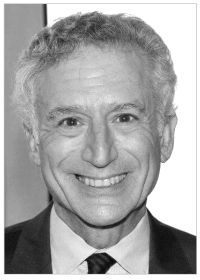
PROGRAM

Monday, September 8	
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: Epigenetic Protection of the Aging Brain** Li-Huei Tsai, PhD, Massachusetts Institute of Technology
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 Antagonists for the Suppression of Inflammation and Neuropathology** Thota Ganesh, PhD, Emory University
9:55 – 10:05	*Q&A*
10:05 – 10:25	**Modulation of Human ApoE Isoform Levels as a Therapeutic Target** Mary Jo LaDu, PhD, University of Illinois at Chicago
10:25 – 10:35	*Q&A*
10:35 – 11:00	**POSTER AND EXHIBITOR SESSION BREAK**
11:00 – 11:20	**Modulation of Peripheral Inflammation and Immune Cell Traffic in AD by XPro1595** Malú Tansey, PhD, Emory University School of Medicine
11:20 – 11:30	*Q&A*
11:30 – 11:50	**Targeting ApoE and ApoE Receptor Pathways for Alzheimer's Disease Therapy** Guojun Bu, PhD, Mayo Clinic
11:50 – 12:00	*Q&A*
12:00 – 12:20	**ApoJ/Clusterin Peptide as a Novel Therapeutic Agent for Alzheimer's Disease** Ling Li, PhD, University of Minnesota
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: Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation**	
1:35 – 1:40	**Session Overview** Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation
1:40 – 2:00	**p75 Small Molecule Ligands – In Silico Screening to Clinical Development** Frank Longo, MD, PhD, Stanford University and PharmatrophiX
2:00 – 2:10	*Q&A*
2:10 – 2:30	**In Vivo Characterization of Novel mGlu5 PAMs in Aged Rats** Jerri Rook, PhD, Vanderbilt Center of Neuroscience Drug Discovery
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	**POSTER AND EXHIBITOR SESSION BREAK**
3:40 – 4:00	**Stabilizing Ryanodine Calcium Channels as a Novel Drug Development Strategy** Grace Stutzmann, PhD, Rosalind Franklin University of Medicine and Sciences
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
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** Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation
5:20 – 7:00	**NETWORKING RECEPTION / POSTER AND EXHIBITOR SESSION**

Tuesday, September 9	
8:00 – 8:30	**Continental Breakfast**
8:30 – 9:10	**Plenary: Tau Therapeutics in Development** Michael Gold, MS, MD, UCB Biosciences, 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	**Novel White Matter Tract Integrity Metrics Sensitive to Alzheimer's Disease Progression** Els Fieremans, PhD, New York University School of Medicine
9:35 – 9:45	*Q&A*
9:45 – 10:05	**Cannabinoid CB2 Radioligands for PET Imaging of Neuroinflammation in Alzheimer's Disease** Andrew Horti, PhD, Johns Hopkins University School of Medicine
10:05 – 10:15	*Q&A*
10:15 – 10:35	**CSF proNGF: A Putative Biomarker for Alzheimer's Disease** Elliott Mufson, PhD, Barrow Neurological Institute
10:35 – 10:45	*Q&A*
10:45 – 11:05	**POSTER AND EXHIBITOR SESSION BREAK**
11:05 – 11:25	**Radiopharmaceutical Development for Imaging Metabotropic Glutamate Subtype 5 Receptors (mGluR5) in Alzheimer's Disease Patients with PET** Neil Vasdev, PhD, Massachusetts General Hospital
11:25 – 11:35	*Q&A*
11:35 – 11:55	**Safety/Tolerability and Effects on Cognitive Impairment, Impaired Cerebral Cortical Metabolism and Oxidative Stress of R(+)Pramipexole Administered to Subjects with Early Alzheimer's Disease** James Bennett, MD, PhD, Virginia Commonwealth University
11:55 – 12:05	*Q&A*
12:05 – 12:25	**Circulating Aβ Complexes: A Window on Aβ Clearance and a Screening Tool for Alzheimer's Disease** **Funded through the ADDF-New York Academy of Sciences (NYAS) Challenge Grant* Blaine Roberts, PhD, Florey Institute of Neuroscience and Mental Health
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	**The Effect of Novel Heat Shock Protein 90 (Hsp90) Inhibitors on Tau Pathology** Yukari Perrella, MBA, Yuma Therapeutics Corporation
1:50 – 2:00	*Q&A*
2:00 – 2:20	**Brain Slice Screen for Anti-microRNA Drug Lead Candidates for Tau-associated FTD** Donald Lo, PhD, Duke Center for Drug Discovery
2:20 – 2:30	*Q&A*
2:30 – 2:50	**Testing of GLX1112 in an Alzheimer's Mouse Model** Thadd Reeder, PhD, Glialogix, Inc.
2:50 – 3:00	*Q&A*
3:00 – 3:20	**POSTER AND EXHIBITOR SESSION BREAK**
3:20 – 3:40	**Development of an Antisense Therapy and Pharmacodynamic Marker(s) to Treat C9ORF72 ALS/FTD RNA Toxicity** **Funded through the ADDF-Association for Frontotemporal Degeneration (AFTD) Partnership Program* Chris Donnelly, PhD, Johns Hopkins University School of Medicine
3:40 – 3:50	*Q&A*
3:50 – 4:10	**Development of Epigenetic Modulator, ORY-2001, for Neurodegenerative Disease** Carlos Buesa, PhD, Oryzon Genomics, SA
4:10 – 4:20	*Q&A*
4:20 – 4:30	**Closing Remarks** Howard Fillit, MD, Alzheimer's Drug Discovery Foundation

BIOS AND ABSTRACTS

CONFERENCE CHAIR
Howard Fillit, MD, Alzheimer's Drug Discovery Foundation



Howard Fillit, MD, a geriatrician, neuroscientist and a leading expert in Alzheimer's disease, is the founding Executive Director of the Institute for the Study of Aging (ISOA), an Estée Lauder family foundation founded in 1998, and the Alzheimer's Drug Discovery Foundation (ADDF), an affiliated public charity founded in 2004. ISOA and ADDF share a common mission of accelerating drug discovery for Alzheimer's disease through venture philanthropy.

Dr. Fillit has had a distinguished academic medical 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 was previously the Corporate Medical Director for Medicare at New York Life, responsible for over 125,000 Medicare managed care members in five regional markets. He is the author or co-author of more than 250 scientific and clinical publications, and is the senior editor of the leading international Textbook of Geriatric Medicine and Gerontology.

Dr. Fillit has received several awards and honors including the *Rita Hayworth Award for Lifetime Achievement* from the Alzheimer's Association. He also serves as a consultant to pharmaceutical and biotechnology companies, health care organizations and philanthropies.

PLENARY SPEAKER

Li-Huei Tsai, PhD, Massachusetts Institute of Technology

Li-Huei Tsai, PhD, began her doctorate degree at the University of Texas Southwestern and completed her postdoctoral fellowship at Cold Spring Harbor Laboratory and Massachusetts General Hospital. She was appointed Assistant Professor of Pathology at Harvard Medical School in 1994, and promoted to Professor of Pathology in 2002. In 2006, she relocated her lab to MIT and became the Picower Professor of Neuroscience and was named Director of the Picower Institute for Learning & Memory in 2009.

Dr. Tsai was elected Fellow of the American Association for the Advancement of Science in 2008 and Member of the Institute of Medicine in 2011. Her research focuses on the elucidation of the cellular, molecular and circuit mechanisms contributing to the development and manifestation of the pathology and symptoms of Alzheimer's disease.

Epigenetic Protection of the Aging Brain

Li-Huei Tsai

Massachusetts Institute of Technology, Cambridge, MA, USA

Epigenetic mechanisms mediate environmental stimuli-induced changes in gene expression. In the nervous system, neurons respond rapidly to neuronal activity, alter gene expression, and express synaptic plasticity. We have previously shown that HDAC2 associates with, and negatively influences, learning and memory genes. The expression and activity of HDAC2 is increased in cellular and animal models of Alzheimer's disease (AD), as well as in the brains of AD patients, and this increased HDAC2 leads directly to the silencing of genes important for learning and memory. Inhibition of the activity of HDAC2 restores learning abilities in mouse models of AD even after severe neuronal loss has occurred. In stark contrast, the activity of HDAC1 is neuroprotective in the brain. In mouse models of AD, the activity of HDAC1 is crucial for neuronal DNA damage response and repair, and its reduced activity is correlated with neurodegeneration. Furthermore, HDAC1 may also impact the levels of β-amyloid peptides. Small molecule activators of HDAC1 hold promise for the amelioration of AD-like pathology, such as DNA damage, neuronal death and amyloid pathology. In this presentation, I will introduce you to the roles of these enigmatic epigenetic factors and discuss how we are attempting to alter their function to promote neuroprotection and ameliorate AD phenotypes both in mouse models and in human neural cells.

I. Apolipoproteins and Neuroinflammation

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

EP2 Antagonists for the Suppression of Inflammation and Neuropathology
Thota Ganesh, PhD, Emory University

Modulation of Human ApoE Isoform Levels as a Therapeutic Target
Mary Jo LaDu, PhD, University of Illinois at Chicago

Modulation of Peripheral Inflammation and Immune Cell Traffic in AD by XPro1595
Malú Tansey, PhD, Emory University School of Medicine

Targeting ApoE and ApoE Receptor Pathways for Alzheimer's Disease Therapy
Guojun Bu, PhD, Mayo Clinic

ApoJ/Clusterin Peptide as a Novel Therapeutic Agent for Alzheimer's Disease
Ling Li, PhD, University of Minnesota

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 $3 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 PhD in Cell and Molecular Biology from the University of Pennsylvania working in the Center for Neurodegenerative Disease Research led by Drs. Virginia Lee and John Trojanowski. She also worked as an Editorial Intern for the Journal of Clinical Investigation and was an active member of the Penn Biotechnology Group. 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

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.

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. His past research includes: synthesis of bioactive molecules (e.g. Taxol and epothilones) and investigation of the biochemical mechanisms, development of small molecule inhibitors for heat shock protein 90 (Hsp90), histonemethyltransferase and NADPH oxidase enzymes.

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 Antagonists for Suppression of Inflammation and Neuropathology

Thota Ganesh

Emory University, Atlanta, GA, USA

Alzheimer's disease (AD) is a leading cause of dementia in the elderly. Currently about 5.4 million Americans (1 in 8 persons 65 or older) are living with AD, and the number is expected to triple by the year 2050, yet there is no therapy available to block the inevitable cognitive decline from the disease. The small molecule drugs that have been developed based on amyloid cascade hypothesis did not show a clear clinical benefit so far. Thus, it would be very important to study novel drug targets and small molecules that work through novel mode of biological action for future AD therapy.

Prostanoid EP2 receptor is emerging as a novel biological target promoting inflammation and subsequent neuropathology in a variety of neurodegenerative disease models including AD. In vitro and in vivo studies from EP2 knockout models show that chronic activation of EP2 in the brain exacerbates AD pathology. However, no tests have been done 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. We also demonstrated that a lead EP2 antagonist suppresses the inflammation, and neurodegeneration in a model of epilepsy. We now poised to demonstrate whether EP2 antagonism will blunt the neuropathology in a 5XFAD mouse model of AD. We will also optimize the drug-like properties of these EP2 antagonists to use in slowly evolving animal models of AD and eventually in humans.

Mary Jo LaDu, PhD, University of Illinois at Chicago

Mary Jo LaDu, PhD, received a BA from Grinnell College in Art History, and went on to earn her PhD in Physiology and Biophysics from the University of Illinois at Chicago. Her post-doc at the University of Chicago focused on the role of apolipoprotein E (apoE) in cardiovascular disease. As a faculty member at Northwestern University, the direction of her research changed to Alzheimer's disease (AD), specifically the role of *APOE4*, the greatest genetic risk factor for AD.

Her work focuses on the structural and functional properties of, and interactions between, apoE and amyloid-β peptide (Aβ), particularly oligomeric Aβ (oAβ), which is likely the proximal neurotoxin in the disease. Dr. LaDu's lab uses an integrated approach to address the complexity of apoE/Aβ interactions, including biochemical, cell biology, and neuroscience methods with *in vitro*, *ex vivo*, and *in vivo* models. Her work has played an important role in the field, including the development of novel detection methods for oAβ and apoE/Aβ complexes, likely mechanistic biomarkers, as well as a tractable AD mouse model for the study of apoE and Aβ interactions *in vivo*.

Dr. LaDu is a Professor in the Department of Anatomy and Cell Biology at the University of Illinois at Chicago in the College of Medicine. She serves on the Executive Committees of the College of Medicine and the Faculty Senate, and was selected Faculty of the year in 2013. She has been NIH-funded since 1995 and is currently the Program Director of a multi-site Program Project Grant on the role of apoE and apoE receptors in neurodegeneration.

Modulation of Human ApoE Isoform Levels as a Therapeutic Target

Mary Jo LaDu

University of Illinois at Chicago, Chicago, IL, USA

In Alzheimer's disease (AD)-transgenic (Tg) mice, recent data suggests Bexarotene (Bex), a retinoid X receptor (RXR) agonist, reduces levels of soluble Aβ and plaques, either by increasing levels of mouse apolipoprotein E (apoE), or increasing expression of ABCA1/ABCG1 and lipid transport to apoE-containing lipoproteins. However, concern persists about the use of Bex with human *APOE4*, the greatest risk factor for AD. If *APOE4* imparts a toxic-gain of function, then Bex-induced increases in apoE4 expression will likely increase Aβ levels, while a loss of function would suggest that apoE4 is less lipidated, and thus Bex may be beneficial. Thus, novel EFAD-Tg mice (overexpressing human Aβ42 with human *APOE3 or APOE4*) were treated with Bex (100mg/kg/day), LG268, a more selective RXR agonist (104.3mg/kg/day equimolar to Bex), or vehicle control in 3 treatment paradigms: T1) 7-day oral gavage (5.75-6M); T2) 7-day hydrogel to mimic sustained drug release (5.75-6M); and, T3) 30-day hydrogel (5-6M). Hippocampus (HP) and cortex (CX) brain regions were analyzed. In the vehicle control groups, soluble levels of Aβ and oAβ are: E4FAD-HP > E3FAD-HP > E4FAD-CX $\geq$ E3FAD-CX, while apoE lipidation exhibits the reverse pattern. In the E4FAD-HP, short-term Bex and LG treatment support the hypothesis:

RXR agonists→↑ABCA1→↑apoE4 lipidation→↑apoE4/Aβ complex→↓ soluble Aβ→↑synaptic viability.

However, in the 30-day prevention treatment, no beneficial effects were observed in the E4FAD-HP (5-6 months), likely the effect of sustained systemic hepatomegaly-inducing stress effects on the CNS. Further, in E3FAD-CX and E4FAD-CX, brain regions with the lowest Aβ levels at the time of treatment, RXR agonists actually increased soluble Aβ levels, effects likely independent of changes in ABCA1/apoE lipidation in the CNS, but the result of systemic hepatomegaly. Together, these data suggest that Bex/LG268 can address a loss of function associated with reduced lipidation of apoE4 in the presence of increased levels of soluble Aβ. However, prior to significant accumulation of Aβ, RXR agonist treatment actually increased soluble Aβ levels in E3FAD mice and in brain regions with less Aβ pathology. Further studies are vital to determine if RXR agonists are an *APOE4*-specific AD therapeutic, and for addressing systemic side effects that may limit their translational application for AD-prevention.

Malú Tansey, PhD, Emory University School of Medicine

Malú Gámez Tansey, PhD, graduated from Stanford University in Palo Alto, California with a BS/MS in Biological Sciences and received a PhD in Physiology from The University of Texas Southwestern Graduate School of Biomedical Sciences in Dallas, Texas. During her postdoctoral training at Washington University Medical School in the laboratory of Eugene M. Johnson Jr. she and her colleagues identified and characterized new members of the GDNF family of ligands (GFLs: Neurturin, Persephin, and Artemin) known for their potent neuroprotective actions.

As group leader of Chemical Genetics at Xencor Inc., she and her colleagues developed a new class of anti-inflammatory compounds (TNF inhibitors) using a proprietary protein engineering platform. In 2002, she set up her own research program at UT Southwestern to investigate mechanisms of neuroinflammation that impact neuron function and survival with the long-term goal of developing new anti-inflammatory therapies for age-related neurodegenerative diseases like Parkinson's and Alzheimer's. In 2009, she moved to Atlanta and she is now a tenured associate professor of Physiology and member of the Center for Neurodegenerative Diseases at Emory University School of Medicine in Atlanta, GA.

The basic and translational research in her lab is aimed at understanding mechanisms underlying brain- immune system interactions in health and disease and leveraging this information to identify individuals at risk for age-related neurodegeneration and develop biomarker-directed interventional neuroprotective trials.

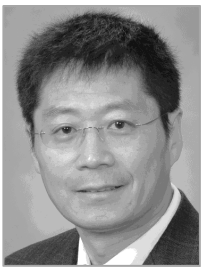
Modulation of Peripheral Inflammation and Immune Cell Traffic in AD by XPro1595

Malú Tansey

Emory University School of Medicine, Atlanta, GA, USA

Blood brain barrier (BBB) permeability can be increased by chronic inflammatory conditions in the periphery and in particular, elevated levels of the pro-inflammatory cytokine soluble Tumor Necrosis Factor (solTNF) and evidence of increased BBB permeability is present in brains of AD patients. Clinically, conditions associated with systemic inflammation, such as diabetes and obesity have recently been associated with the development of dementia. The chronic inflammation associated with these conditions can be modeled in rodents via chronic intraperitoneal administration of low-dose lipopolysaccharide (LPS), a dosing paradigm that induces systemic inflammation and triggers neuroinflammation. Using the fast-progressing 5xFAD transgenic mouse model of AD, we are testing the hypothesis that solTNF signaling peripherally and centrally accelerate AD-like pathology through mechanisms that involve increased BBB permeability, altered regulation of peripheral immune cell traffic to the CNS, and chronic neuroinflammation. To augment the translational relevance of our studies, our objective is to achieve targeted neutralization of solTNF with the novel and brain-permeable anti-solTNF biologic XPro1595. We expect peripheral administration of XPro1595 to restore BBB permeability, to ameliorate age-dependent progression of brain inflammation, and to block or delay the typical course of AD-like pathology in these mice as well as the accelerating effects of chronic systemic inflammation.

Guojun Bu, PhD, Mayo Clinic



Guojun Bu, PhD, is a Professor of Neuroscience at the Mayo Clinic, Jacksonville. His primary research interest is to understand why APOE4 is a strong risk factor for Alzheimer's disease and how this pathway can be targeted for therapy. He is a leader in the field of research related to the biology and pathobiology of apoE and its receptors that belong to the low-density lipoprotein receptor (LDLR) family. His scientific contributions have garnered numerous awards, including the Zenith Fellows Award from the Alzheimer's Association and the Established Investigator Award from the American Heart Association. Dr. Bu also serves as Co-Editor-in-Chief of Molecular Neuro-degeneration.

Dr. Bu received his undergraduate degree in biology from Beijing Normal University, China. He received the PhD degree in biochemistry and molecular biology from Virginia Tech and completed his postdoctoral training in cell biology at Washington University School of Medicine in St. Louis. He then served as a Professor of Cell Biology and Neuroscience at Washington University School of Medicine until 2010 when he moved his research laboratory to Mayo Clinic.

Targeting ApoE and ApoE Receptor Pathways for Alzheimer's Disease Therapy

Guojun Bu

Mayo Clinic, Jacksonville, Florida, USA

Apolipoprotein E (apoE) is a major cholesterol carrier in the brain. Among the three human APOE gene alleles (APOE2, APOE3, and APOE4), APOE4 is the strongest genetic risk factor for late-onset Alzheimer's disease (AD). The accumulation of amyloid-β (Aβ) is a central event in AD pathogenesis. Increasing evidence demonstrates that apoE isoforms differentially regulate AD-related pathways through both Aβ-dependent and Aβ-independent mechanisms; therefore, modulating apoE secretion, lipidation, and function might be an attractive approach for AD therapy. We performed several drug screens for compounds that modulate apoE production and/or lipidation using immortalized astrocytes derived from human apoE-targeted replacement mice. We identified two classes of apoE modulators. The first class of compounds are retinoic acid (RA) isomers, including all-trans-RA, 9-cis-RA, and 13-cis-RA. These compounds increase apoE secretion and lipidation by modulating the expression of the cholesterol transporter ABCA1 and ABCG1 through retinoid X receptor (RXR) and/or RA receptor. Notably, effects of these compounds are similar to that reported for RXR agonist bexarotene; however, at least one of these compound 9-cis-RA exhibits less cytotoxicity. We also demonstrated that oral administration of bexarotene or 9-cis-RA significantly increases the levels of apoE, ABCA1, and ABCG1 in mouse brains. The second class of compounds uniquely stabilizes apoE following its secretion without changing its expression. We are currently studying the underlying mechanisms of these compounds and addressing their in vivo effects. Finally, to examine potential beneficial or harmful effects of modulating apoE isoforms, we have generated cell-type specific and inducible mouse models overexpressing apoE3 or apoE4. Preliminary results from these mice will be presented and discussed. Together, our results demonstrate that increasing apoE production or lipidation can be beneficial in an isoform-dependent manner and that apoE modulators can be explored as potential drugs for AD therapy.

Ling Li, PhD, University of Minnesota

Ling Li, PhD, is a Professor and the VFW Endowed Chair of Pharmacotherapy for the Elderly in the Department of Experimental and Clinical Pharmacology at the University of Minnesota.

She obtained her Bachelor's and Master's degrees in Veterinary Medicine and Experimental Pathology from Yangzhou University, China, and her PhD degree in Molecular, Cellular, and Developmental Biology from Iowa State University. She received her postdoctoral research training on lipoprotein metabolism/atherosclerosis at the Rockefeller University in New York and on Neurobiology of Alzheimer's disease at the University of Alabama at Birmingham (UAB). She was an Assistant Professor and then an Associate Professor in the Department of Medicine at UAB until 2010 when she relocated to the University of Minnesota.

Dr. Li's research interests focus on the connections between cardiovascular disease, diabetes, and Alzheimer's disease in their pathogenic mechanisms and therapeutic strategies, using a combination of behavioral, electrophysiological, and biochemical approaches in transgenic and knockout mouse models.

Her research has been supported by grants from the National Institutes of Health (NIH), the Alzheimer's Association, the American Federation for Aging Research, the American Heart Association, the American Health Assistance Foundation (the BrightFocus Foundation), the Lowder Foundation, and the University of Minnesota Academic Health Center. One of the ongoing research projects investigates the therapeutic potential of apolipoprotein/HDL mimetic peptides for Alzheimer's and related disorders, supported partly by the Alzheimer's Drug Discovery Foundation.

ApoJ/Clusterin Peptide as a Novel Therapeutic Agent for Alzheimer's Disease

Ling Li

University of Minnesota, Minneapolis, MN, USA

Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which there are no effective therapies. Compelling evidence indicates that AD and cardiovascular disease share common risk factors and pathogenic mechanisms. Apolipoproteins are essential structural components of lipoproteins and mediate a variety of biological functions that play important roles in the development of cardiovascular disease and AD. Apolipoprotein J (apoJ), also known as clusterin, is an apolipoprotein associated with high density lipoproteins (HDL) in the plasma and in the brain. Recent genetic studies have identified the gene of apoJ (*CLU*) as one of the top-ranking loci associated with late-onset AD after apoE4, a primary genetic risk factor for AD. ApoJ is a multifunctional protein; it binds amyloid-β protein (Aβ), inhibits Aβ aggregation, promotes Aβ clearance across the blood-brain barrier (BBB), and modulates inflammatory and immune functions in the brain. A 10-amino acid peptide derived from an integral sequence of apoJ, apoJ[113-122], has been shown to mimic the properties of apoJ. It reduces atherosclerosis in apoE-null mice and improves anti-inflammatory properties of plasma HDL in monkeys. The present study was designed to investigate the therapeutic potential of apoJ[113-122] for AD. Our results show that apoJ[113-122] inhibits the aggregation of Aβ *in vitro* in a dose-dependent manner, protects neuronal cells from Aβ-induced toxicity, and reverses Aβ-induced disruption of microtubule dynamics in neuronal cells. In addition, apoJ[113-122] treatment enhances synaptic plasticity in hippocampal slices from wild-type mice and promotes anti-inflammatory activity of HDL in the plasma of APP/PS1 mice, a model of AD. Moreover, apoJ[113-122] effectively crosses the human cerebral microvascular endothelial cell (hCMEC/D3) monolayer, an *in vitro* model of human BBB, rendering it a promising therapeutic agent for AD. Animal experiments are underway to test the efficacy of apoJ[113-122] treatment to mitigate Aβ deposition, synaptic dysfunction, and cognitive impairment in the APP/PS1 mouse model of AD.

II. Neuroprotection, Mitochondrial Function and Synaptic Plasticity

Chair: Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation

p75 Small Molecule Ligands – In Silico Screening to Clinical Development
Frank Longo, MD, PhD, Stanford University and PharmatrophiX

In Vivo Characterization of Novel mGlu5 PAMs in Aged Rats
Jerri Rook, PhD, Vanderbilt Center of Neuroscience Drug Discovery

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

Stabilizing Ryanodine Calcium Channels as a Novel Drug Development Strategy
Grace Stutzmann, PhD, Rosalind Franklin University of Medicine and Sciences

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

Rachel Lane, PhD, Alzheimer's Drug Discovery Foundation

Rachel Lane, PhD, is the Associate Director of Scientific Affairs at the Alzheimer's Drug Discovery Foundation. Dr. Lane's responsibilities include development and management of all aspects of the Foundation's drug discovery programs in addition to the development of resources to address critical unmet needs in the field.

Dr. Lane earned her PhD in Molecular Biology and Biotechnology from the University of Sheffield, United Kingdom before completing three years of postdoctoral training at the Mount Sinai School of Medicine in New York. Dr. Lane's postdoctoral research, in a team led by Dr. Sam Gandy, uncovered common mechanistic links between Alzheimer's disease and type 2 diabetes mellitus. In addition to her experience in basic research, Dr. Lane gained experience in drug development through her position as an Analyst Intern at a New York based Venture Capital firm and the Fundamentals of the Bioscience Industry Program at New York's Stony Brook University, for which she received a Directors Scholarship. She is a member of the Society for Neuroscience and the New York Academy of Sciences and has published numerous first authored research publications and reviews in peer reviewed journals.

Frank Longo, MD, PhD, Stanford University and PharmatrophiX

Frank Longo, MD, PhD, is Professor and Chairman of the Department of Neurology and Neurological Sciences at Stanford University.

He received his MD in 1981 and PhD in Neurosciences in 1983 from UC San Diego. He completed his neurology and fellowship training in the Department of Neurology at UC San Francisco where he was then recruited as an assistant professor and promoted to professor and vice chair. From 2001 to 2005 he was chair of the Department of Neurology at the University of North Carolina-Chapel Hill and since 2006 has served as chair of the Department of Neurology and Neurological Sciences at Stanford.

With support from the Alzheimer's Drug Discovery Foundation, Alzheimer's Association, and the NIH, he and his team have elucidated novel mechanisms and executed translational work pioneering small molecule treatment strategies for Alzheimer's and other neurodegenerative diseases. In 2005, while at UNC, he founded PharmatrophiX, a company focused on the commercial development of these therapies. A lead candidate compound for Alzheimer's disease has successfully completed phase I human trials.

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p75 Small Molecule Ligands – In Silico Screening to Clinical Development

Frank Longo

Stanford University, Stanford, CA, USA

The p75 neurotrophin receptor regulates multiple signaling networks and nodes that are likely fundamentally involved in loss of synaptic function as well as degeneration of spines, synapses and neurons in Alzheimer's disease (AD). Using in silico screening of small molecule libraries, along with subsequent small molecule modification, we identified a number of small molecule ligands that modulate p75 to inhibit degenerative patterns of intracellular signaling. Effects include: inhibition of amyloid-beta (Aβ)-induced tau phosphorylation, misfolding and mislocalization; inhibition/reversal of spine/neurite loss in late-stage AD mice; prevention of Aβ-induced loss of LTP in two slice models and prevention of behavior deficits in multiple AD mouse models. A lead compound has successfully completed phase 1 safety and pharmacokinetic studies in young and elderly normal subjects and work leading to a phase 2a trial is underway.

Jerri Rook, PhD, Vanderbilt Center of Neuroscience Drug Discovery

Jerri Rook, PhD, is an Assistant Professor of Pharmacology at Vanderbilt University in the Vanderbilt Center for Neuroscience Drug Discovery. Dr. Rook received her PhD degree in Pharmacology from the University of Kansas Medical Center in 2008 where she was supported by the KUMC Biomedical Research Training Program Award. She then pursued her postdoctoral studies in the laboratory of P. Jeffrey Conn, PhD, at Vanderbilt University before accepting a faculty position in 2012.

Dr. Rook has served as an author on several primary research articles in peer-reviewed scientific journals and frequently presents her work at both national and international meetings. She is currently the member of the American Society for Pharmacology and Experimental Therapeutics and Society for Neuroscience.

In Vivo Characterization of Novel mGlu5 PAMs in Aged Rats

Jerri Rook

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

Alzheimer's disease (AD) is the most common form of dementia and is characterized by the progressive decline in cognitive function, with the primary deficits being hippocampal-mediated learning and memory loss. Recent studies suggest the involvement of glutamate in the pathology of the disease, as levels are decreased in the hippocampus of patients with AD. Glutamate modulates excitatory postsynaptic currents via metabotropic glutamate receptor. Metabotropic glutamate receptor subtype 5 (mGlu5) is the most highly expressed mGlu in the hippocampus and is a close signaling partner of the N-methyl-D-aspartate receptor (NMDAR). NMDAR is critical in regulating hippocampal synaptic plasticity and essential for hippocampal-dependent cognitive function. Therefore, increased activation of mGlu5 offers an exciting new therapeutic strategy to enhance cognitive function in patients suffering from AD. Recently, our group has developed a series of highly potent, selective mGlu5 positive allosteric modulators (PAMs) with enhanced physiochemical and pharmacokinetic properties for in vivo studies, providing an unprecedented opportunity to evaluate the potential of selective potentiation of mGlu5 as a novel target for the treatment of symptoms associated with AD. As opposed to direct activation of mGlu5, PAMs dramatically potentiate the response of the receptor to its endogenous ligand glutamate and offer high selectivity while avoiding unwanted side-effects seen with direct activation. Similar to AD patients, aged rats have a loss of hippocampal synaptic function, brain hypometabolism, as well as impaired cognitive function and provide a preclinical animal model that accurately emulates the human disease state. These studies utilize the aged rat model to characterize the ability of our novel mGlu5 PAMs to restore the deficits associated with altered neuronal activity and impaired cognitive function observed in AD.

Carmela Abraham, PhD, Boston University School of Medicine

Carmela R. Abraham, PhD, obtained her doctorate degree 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 downregulated 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 oligodendrocytes, where Klotho induces their differentiation into 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.

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

Carmela R. Abraham, PhD[1], Ci-Di Chen, PhD[1], Marcie A. Glicksman, PhD[2], Kevin Hodgetts, PhD[2] and Ella Zeldich, PhD[1]

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

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 four 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, in brains of AD patients and animal models of AD, 2) Klotho is able to rescue hippocampal neurons from Aβ and from oxidative stress and death induced by the excitotoxic amino acid glutamate, 3) a potentially novel molecular mechanism is responsible for the Klotho-induced neuroprotection, and 4) small molecule compounds that were developed from hits from a high throughput screen to enhance Klotho expression, can mimic Klotho's neuroprotective functions and rescue neurons from death. 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 to neurons and, therefore, Klotho enhancing small molecule compounds that cross the blood-brain barrier could become novel therapeutics for AD and other neurodegenerative diseases.

Grace Stutzmann, PhD, Rosalind Franklin University of Medicine and Sciences

Grace Stutzmann, PhD, is an Associate Professor in the Department of Neuroscience at The Chicago Medical School/Rosalind Franklin University of Medicine and Science, where she studies early cellular mechanisms of Alzheimer's disease and novel therapeutic approaches to neurodegenerative disorders. She received her PhD in Neuroscience from New York University/The Center for Neural Science in 1999, working in the laboratory of Joseph LeDoux, PhD. She then trained as a postdoctoral fellow in the Departments of Pharmacology and Psychiatry at Yale School of Medicine under George Aghajanian, MD Subsequently, she completed a second postdoctoral fellowship at UC Irvine in the Department of Neurobiology, and The Institute for Brain Aging and Dementia with Frank LaFerla, PhD and Ian Parker, PhD.

In 2005, she moved to the Chicago Medical School/RFUMS as an Assistant Professor in the Department of Neuroscience, where she is currently. Dr. Stutzmann's research is and has been supported by the NIH and foundations, including NIH RO1 and R21 awards, the Alzheimer's Association, the Alzheimer's Drug Discovery Foundation, the American Federation for Aging Research, The Schweppe Foundation, and the VA. Dr. Stutzmann has served on several ad hoc grant review committees, including five NIH study sections. She has presented over 40 lectures at international symposia and universities since 2006.

Honors include postdoctoral fellowships from NIH (NIMH and NIA), the Young Investigator Award from The Institute for Brain Aging and Dementia, The NeuroImaging Award from AFAR, and The Board of Trustees Award from RFU/CMS. She is a member of the Editorial Board of Frontiers in Pharmacology of Ion Channel and Channelopathies, and PlosOne.

Stabilizing Ryanodine Calcium Channels as a Novel Drug Development Strategy

Grace Stutzmann, Clark Briggs, Shreaya Chakroborty, Corinne Schneider, Nicolas Kapecki, Rosalind Helfrich

Rosalind Franklin University of Medicine and Sciences, North Chicago, IL, USA

Abnormalities in ER calcium channels have been widely demonstrated in human AD patients and in animal and cellular models of AD. In particular, the large conductance RyR calcium channel has been implicated, with specific increases in RyR2 expression at early or preclinical disease stages. Increased RyR-evoked calcium release is linked with synaptic structure and plasticity deficits, increased amyloid and tau pathology, memory impairments, and activation of oxidative stress – all of which are central to AD characterization. Stabilizing the RyR with the pan-RyR allosteric modulator, dantrolene, has proven highly effective at preventing a wide range of AD features in model systems. Yet, this compound is not ideal for CNS targets. A more strategic therapeutic approach is to target the RyR2 with a similar allosteric modulator as a means to normalize calcium signaling and prevent the progression of a multitude of AD pathological features.

To this end, we have developed and tested a series of small molecules targeting the RyR2 with good safety and CNS bioavailability. We then assayed these compounds using calcium imaging approaches, biochemical assays, neurophysiological and synaptic transmission studies, and anatomical approaches in N2A cells, acute hippocampal slice preparations, and chronically-treated 3xTg-AD mice to test the validity of the RyR2 target and establish efficacy in preventing AD pathology in these systems.

In summary, we have found that normalizing RyR function, and the RyR2 in particular, is highly effective in restoring normal calcium signaling in neurons from AD mouse models, and subsequently, preserves synaptic structure and plasticity, and reduces histopathology and oxidative stress. As synaptic loss is the most likely cause of memory loss in AD, targeting the RyR2 calcium channel may be a highly effective and novel therapeutic strategy for preventing cognitive deficits in AD.

Chien-Liang Glenn Lin, PhD, Ohio State University

Chien-Liang Glenn Lin, PhD, completed his doctorate in Molecular Biology and Biochemistry at the Johns Hopkins University in 1995. He performed 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

Ohio State University, Columbus, Ohio, 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 CNS. EAAT2 plays a critical role in the homeostatic regulation of extracellular glutamate levels and in preventing glutamate-mediated neurotoxicity. EAAT2 also plays an essential role in cognitive functions. In a mouse model of AD, AβPPswe /PS1ΔE9 mice lacking one allele for EAAT2 exhibit accelerated cognitive deficits. Pharmacologically blocking EAAT2 function results in impaired spatial memory in rats. Loss of EAAT2 protein is a common phenomenon observed in Alzheimer's disease (AD) patients and animal models. To investigate whether restored EAAT2 protein and function could provide any beneficial effects, we crossed EAAT2 transgenic mice, which have a 1.5-2 fold increase in EAAT2 protein levels, with APPSw,Ind mice, an animal model of AD. We found that crossed mice exhibited restored EAAT2 protein levels and function and, most importantly, significantly improved cognitive functions, restored synaptic integrity, and reduced amyloid plaques. These results suggest that activation of EAAT2 expression is a potential therapeutic approach. EAAT2 can be up-regulated by transcriptional or translational activation. We previously executed high-throughput screening to search for compounds that increase EAAT2 translation. We took the translational activation approach because loss of EAAT2 protein in AD patients is probably due to disturbances at the post-transcriptional level, as EAAT2 mRNA is not decreased. Through this screen and subsequent studies, three lead compound series were identified. We have focused our attention on a pyridazine-based lead series. A compound, LDN/OSU-0212320, from this series was tested in APPSw,Ind mice. The results showed that LDN/OSU-0212320 was capable of restoring EAAT2 protein levels and function and significantly improved cognitive functions and reduced pathology in APPSw,Ind mice. 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. We are currently focused on the development of this compound series for human use, the underlying mechanisms by which increased EAAT2 reverses Alzheimer phenotypes, and the underlying mechanisms of compound action.

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 and associated biomarkers using multiple cellular and animal models. She was among the first to demonstrate the role mitochondrial dynamics and function play in disease progression in multiple animal models of HD and AD. Recently, Dr. Trushina applied metabolomics profiling to the brain tissue, CSF and plasma from animal models of AD and patients with different disease severity. The results of these studies suggest that metabolic profiling in blood recapitulates changes in CSF supporting high probability of identifying blood-based biomarkers for early AD diagnosis. Her current research projects involve the development of new mitochondria-targeted therapeutic approaches.

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

Modulation of mitochondrial function is beneficial in various diseases. Here we demonstrate that treatment with novel metabolic modulator tricyclic pyrone compound CP2 prevents the development of Alzheimer's disease (AD) in three transgenic animal models. CP2 averts cognitive and behavior phenotype in animals 14 months of age treated *in utero*, and in animals treated at pre-symptomatic stage. We found that CP2 penetrates the blood brain barrier, accumulates in mitochondria and specifically binds to the flavin mononucleotide redox center of respiratory complex I. Such modulation of mitochondrial respiration in primary neurons and in brain tissue of CP2-treated AD animals results in an increase in AMP/ATP ratio, activation of AMPK, inhibition of GSK3β, reduction of tau, restoration of axonal trafficking and increased synaptic activity. The therapeutic efficacy of CP2 was accompanied with partial reduction of brain amyloid. Our results strongly suggest that targeting mitochondrial function represents novel therapeutic strategy for AD. I will discuss our current progress toward the development of novel patentable molecules with CP2-like properties.

PLENARY SPEAKER
Michael Gold, MS, MD, UCB Biosciences, Inc.

Michael Gold, MS, MD, has spent the last 15 years in the pharmaceutical industry and most recently (January 2013) joined UCB BioSciences as the Vice President/Head of the CNS Clinical Practice. In this role, Michael is accountable for providing expertise in neurology and CNS-related drug development to a variety of stake-holders within the company.

Prior to joining UCB Michael worked with Bristol-Myers Squibb, GSK and Allon Therapeutics.

Michael was awarded a BS degree in Chemistry, an MS degree in Mathematics/Computer Science and an MD degree from the University of Miami.

Tau Therapeutics in Development

Michael Gold

UCB Biosciences, Inc., Raleigh, NC, US

A variety of tau-directed therapies for the treatment of AD and other tauopathies have emerged over the last couple of years. These new approaches have re-invigorated a sector of the pharmaceutical industry and a clinical research community that has suffered from untenable failure rates. Emerging data on the pathological role of tau and its prion-like properties suggests that it represents the proximate cause of neuronal dysfunction and death and therefore potentially effective at clinical stages of disease. The desire to validate these approaches in patients with a known tauopathy has resulted in a resurgent interest in rarer tauopathies such as PSP and CBD as "proof-of-concept" patient populations. Tau-directed therapies are emerging as viable and tractable disease-modifying approaches that have the potential to address the massive and growing unmet medical need in patients with tauopathies.

III. Translatable Biomarkers to Accelerate Clinical Development

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

Novel White Matter Tract Integrity Metrics Sensitive to Alzheimer's Disease Progression
Els Fieremans, PhD, New York University School of Medicine

Cannabinoid CB2 Radioligands for PET Imaging of Neuroinflammation in Alzheimer's Disease
Andrew Horti, PhD, Johns Hopkins University School of Medicine

CSF proNGF: A Putative Biomarker for Alzheimer's Disease
Elliott Mufson, PhD, Barrow Neurological Institute

Radiopharmaceutical Development for Imaging Metabotropic Glutamate Subtype 5 Receptors (mGluR5) in AD patients with PET
Neil Vasdev, PhD, Massachusetts General Hospital

Safety/Tolerability and Effects on Cognitive Impairment, Impaired Cerebral Cortical Metabolism and Oxidative Stress of R(+)Pramipexole Administered to Subjects with Early Alzheimer's Disease
James Bennett, MD, PhD, Virginia Commonwealth University

Circulating Aβ Complexes: A Window on Aβ Clearance and a Screening Tool for Alzheimer's Disease
Blaine Roberts, PhD, Florey Institute of Neuroscience and Mental Health

SESSION CHAIR

Penny Dacks, PhD, Alzheimer's Drug Discovery Foundation

Penny Dacks, PhD, is the Assistant Director, Aging and Alzheimer's Disease Prevention at the Alzheimer's Drug Discovery Foundation. The goal of this program is to accelerate the development and validation of compounds to slow brain aging and prevent age-related neurodegenerative diseases.

Dr. Dacks earned her PhD in Neuroscience with Naomi Rance at the University of Arizona and worked as a postdoctoral fellow with Charles Mobbs at the Mount Sinai School of Medicine. She trained at the Molecular Biology of Aging course at the Woods Hole Marine Biological Laboratory. Her research examined how the hypothalamus regulates energy balance in response to signals from the blood including estrogens, sugars, and fatty acids. This work led to numerous peer-reviewed publications and was funded by fellowships from the National Institute of Aging and several non-profit foundations.

Dr. Dacks is a Science Writing Associate at the New York Academy of Sciences. She is an active member of the Society for Neuroscience and has contributed to their professional development programs. At the University of Arizona she represented the Neuroscience student body on numerous administrative committees. She is a member of the Association for Women in Science and the Endocrine Society. She earned her BSc Honors degree in Life Sciences from Queen's University in Ontario, Canada.

Els Fieremans, PhD, New York University School of Medicine

Els Fieremans, PhD, is an Assistant Professor in the Department of Radiology at New York University School of Medicine. She obtained a MSc. Degree in physics in 2003 and doctoral degree in biomedical engineering in 2008 at Ghent University in Belgium. Dr. Fieremans then received her postdoctoral training at New York University, New York, where she joined the faculty in 2010.

Her research interests involve the development and validation of new neuroimaging biomarkers and their translation into clinical applications using advanced biophysical modeling. In particular, she developed MRI biomarkers for white matter tract integrity obtained with clinically usable imaging protocols, that may serve as candidates for early biomarkers and surrogate markers of neurodegenerative disorders. She has applied these imaging markers to investigate changes in white matter integrity in subjects with mild cognitive impairment and Alzheimer's disease.

Her work is funded by the NIH and private foundations including ADDF.

Novel White Matter Tract Integrity Metrics Sensitive to Alzheimer's Disease Progression

Els Fieremans

New York University School of Medicine, New York, NY, USA

Although Alzheimer disease (AD) is typically considered a gray matter disease, postmortem studies have provided evidence of pathological changes in white matter occurring early in the course of AD, while in vivo MRI studies report correlations between white matter damage and disease severity.

In this study, we compare the white matter integrity in subjects with mild cognitive impairment (MCI) and AD with age-matched healthy controls, using diffusion MRI, a powerful method that is sensitive to microstructural loss preceding atrophy. White matter integrity is assessed using diffusional kurtosis imaging (DKI), a clinically feasible diffusion method. We recently provided a biophysical interpretation of the DKI signal in terms of specific white matter tract integrity metrics, including the axonal water fraction, a marker for axonal loss; and the radial and axial extra-axonal diffusivities, markers for demyelination and other extra-axonal changes, including inflammation.

When investigating these white matter tract integrity metrics in a cross-sectional study that simulates the course of AD, we found that these novel markers were able to both detect and differentiate specific tissue changes in MCI and AD. Interestingly, our findings suggest that widespread breakdown in myelin integrity occurs first in the transition from normal aging to the amnestic mild cognitive impairment (aMCI) stage (AUC=0.95, P<.001), whereas a loss in axonal density occurs later in the disease from aMCI to AD (AUC=0.84, P=.01). Regional analyses of these metrics reveal their marked functional relevance to cognitive processing speed ($r = |0.80\text{-}0.82|$, P<.001). Furthermore, we applied the same white matter tract integrity metrics and found that loss of axonal density and myelin breakdown were particularly observed in late-myelinating tracts through the course of the disease.

Andrew Horti, PhD, Johns Hopkins University School of Medicine

Andrew Horti, PhD, obtained his dotorate degree in organic synthesis and physical chemistry at the Leningrad Institute of Technology. Subsequently he worked as a research scientist on the Anti-Cancer Drug program for the same university. In 1992, after the collapse of USSR, Andrew moved to USA where he resided in Baltimore, Maryland and New Haven, Connecticut doing research in PET radiochemistry that was supported by the Johns Hopkins and Yale Universities and NIDA/NIH.

Currently, he is an Associate Professor in the Division of Nuclear Medicine at the Johns Hopkins Medicine. Dr. Horti's main scientific interest is design and development of PET radiotracers for CNS. His group has pioneered the development of PET radioligands for nicotinic and cannabinoid receptors that are now used worldwide in human subjects and animals.

He is author or co-author of over 150 scientific publications. He is an Editorial Board Member of Nuclear Medicine & Biology and other international journals. Andrew's research is supported by the NIH and private foundation grants and he was awarded the NIDA Director's Award.

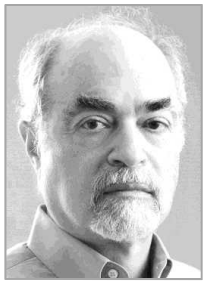
Cannabinoid CB2 Radioligands for PET Imaging of Neuroinflammation in Alzheimer's Disease

Alena Savonenko, Tatiana Melnikova, Yuchuan Wang, Hayden Ravert, Yongjun Gao, Deidre Lee, Eugenia Cho, Nuzhat Sayyida, Andrew Hiatt, Juan Troncoso, Robert F. Dannals, Martin Pomper, Andrew G. Horti

Johns Hopkins University School of Medicine, Baltimore, MD, USA

Currently, there is an urgent need for identification and development of biomarkers useful for early diagnosis and therapeutic monitoring of Alzheimer's disease (AD). Here, we used a model of early AD (APPswe/PS1ΔE9 mice) to investigate the cellular distribution of cannabinoid 2 (CB2) receptors in the brains of amyloid-bearing mice and suitability of this target as an imaging biomarker of neuroinflammation. In PET studies a CB2-selective radioligand [^{11}C]A836339 demonstrated significant increase of cerebral uptake in the amyloid-bearing mice versus nontransgenic controls (Horti's lab). The specificity of the [^{11}C]A836339 binding in the transgenic mouse brain was demonstrated in the blockade study with CB2-selective ligand AM630. Immunofluorescence studies of CB2 expression in this mouse model revealed increased densities of CB2 receptors associated with glial and particularly microglial markers (CD68) (Savonenko's lab). In contrast to glial cells, contribution of neuron (NeuN marker)-derived CB2 signal was equal between amyloid-bearing and control mice. These data indicate that at stages of amyloidosis without significant neuronal loss the main source of enhanced CB2 PET signals in amyloid-bearing mice is likely an increase in CB2 densities associated with activated microglia. These data also imply that significant loss of neurons as seen at later stages of AD might decrease CB2 PET signal due to loss of neuronally-derived CB2 R and blur the difference between controls and AD subjects. This preclinical study indicates that a CB2 tracer can be used as an imaging biomarker of neuroinflammation in early stages AD when no significant neuronal loss had yet been developed.

Elliott Mufson, PhD, Barrow Neurological Institute



Elliott Mufson, PhD, received his doctorate degree from the State University of New York in Biological Psychology followed by a postdoctoral fellowship in aging in the laboratory of Dr. Donald Stein at Clark University. He then joined the Department of Neurology at the Harvard Medical School, Beth Israel Hospital where he was trained in primate neuroanatomy and the pathobiology of human neurological disease. During this period he produced a series of papers defining the extent and organization of the cholinergic basal forebrain system in the primate brain a major target for most of the currently available drugs for Alzheimer's disease. During his tenure in Boston, he rose to the rank of Assistant Professor in the Department of Neurology and Associate Director of the Derek Denny Brown Laboratory at the Beth Israel Hospital of the Harvard Medical School.

Dr. Mufson was recruited to establish the Sun Health Research Institute in Sun City Arizona, as its Associate Director. In 1991, he moved to the Department of Neurological Sciences at Rush University Medical Center in Chicago, to develop a research program in the neurobiology of early onset Alzheimer's disease.

Currently, he is a Professor of Neurological Sciences and the Alla and Jesmer Chair in Aging at Rush. His research in the area of the cellular and molecular pathobiology of dementia using human autopsy tissue and transgenic models of AD has had a major impact on the field. While at Rush he was instrumental in the development of the human tissue research knows as the Religious Orders Study. Dr. Mufson was recognized as one of the 100 most referenced researchers in neuroscience by the ISH. Currently, he lists 256 peer-reviewed articles, numerous book chapters and reviews as well as grants from the NIH and an award from the Department of Defense.

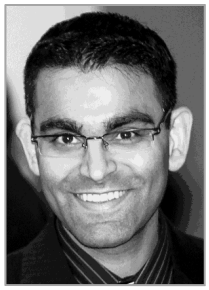
CSF proNGF: A Putative Biomarker for Alzheimer's Disease

Elliott Mufson

Barrow Neurological Institute, Phoenix, AZ, USA

The development of biomarkers for the identification of individuals in the preclinical stages of Alzheimer's disease (AD) is essential for the timely administration of disease modifying therapies. Current efforts have focused on detecting biomarkers associated with changes in amyloid-β (Aβ) peptide and tau protein levels in the cerebral spinal fluid (CSF) of people at varying stages of AD. However, the inherent variability and overlap of AD neuropathology in aged unimpaired control, mild cognitive impairment (MCI) and diseased brain is also reflected by variation of these markers. Therefore, there is a need to augment existing CSF biomarker panels with novel pathological proteins to improve diagnostic accuracy in longitudinal studies. We previously demonstrated an up-regulation of the pro-apoptotic NGF precursor, proNGF, protein in postmortem hippocampus and neocortex of MCI and AD compared to NCI subjects leading to the hypothesize that increased levels of proNGF represent a pathophysiological shift from NGF-mediated cell survival to proNGF-mediated neurodegeneration during AD progression. With this hypothesis in mind, we tested whether CSF proNGF levels could be used as a biomarker for underlying preclinical disease and the onset of cognitive impairment. Immunoblotting studies using postmortem ventricular CSF harvested from participants with a premortem clinical diagnosis of NCI, amnestic MCI (aMCI), or mild/moderate AD revealed a significant 55-70% increase in proNGF levels in CSF samples obtained from aMCI and AD compared to NCI subjects. Furthermore, increased proNGF levels were strongly associated with poorer cognitive performance as measured by MMSE score and a global cognitive z score. We then tested whether increased proNGF also reflects the clinical progression of AD using CSF from living subjects. Lumbar CSF samples revealed a significant increase in proNGF levels in MCI and AD compared to NCI subjects. Taken together, these findings indicate that increased CSF proNGF may be a novel preclinical AD biomarker.

Neil Vasdev, PhD, Massachusetts General Hospital



Neil Vasdev, PhD, is the Director of Radiochemistry at Massachusetts General Hospital and is an Associate Professor in the Department of Radiology at Harvard Medical School. He concurrently graduated (summa cum laude) with a Bachelor of Science in Chemistry and Bachelor of Arts in Psychology from McMaster University.

Prior to starting graduate school he gained experience working in industry as a chemist at Astra Pharma and Glaxo Wellcome. He completed his PhD dissertation in Chemistry at McMaster University while a national scholarship (NSERC), followed by an NSERC postdoctoral fellowship at the E.O. Lawrence Berkeley National Laboratory. In 2004, he joined the University of Toronto's Department of Psychiatry the Centre for Addiction and Mental Health.

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

Radiopharmaceutical Development for Imaging Metabotropic Glutamate Subtype 5 Receptors (mGluR5) in AD patients with PET

Neil Vasdev

Massachusetts General Hospital, Boston, MA, USA

Fluorine-18 labeled FPEB is a metabotropic glutamate receptor subtype 5 (mGluR5) antagonist with high potency, selectivity and brain penetration in rodents, nonhuman primates and human subjects. Our preliminary PET imaging studies with this radiopharmaceutical, as prepared using a commercial automated radiosynthesis unit, have focused on well characterized patients suffering from Alzheimer's disease (AD), who were concurrently imaged with [18F]FDG and [11C]PiB and fMRI. Several lines of evidence point to a critical role for mGluR5 in the pathologic process of AD. Oligomeric Aβ reliably induces abnormal accumulation and over-stabilization of mGluR5 receptors, which is up-regulated in AD, and co-localizes with Aβ. We observed [18F]FPEB binding observed in default network cortices and in medial temporal cortex and hippocampus, in a subject with early mild cognitive impairment. Radiochemical yields for this reaction are low (1–5% uncorrected, relative to starting 18F-fluoride) as this nucleophilic substitution reaction at the meta-position occurs on a non-activated aromatic ring. Furthermore, we optimized the radiosynthesis by using a new radiochemistry method that takes advantage of hypervalent iodine (III) ylide precursors (Nature Communications, 2014, in press). Herein, we also synthesized [18F]FPEB suitable for clinical studies by the most commonly used microfluidic flow platform in radiochemistry (NanoTek®; Advion, Inc.) (Medicinal Chemistry Communications, 2014). This proof of concept work demonstrates that microfluidics flow chemistry systems are capable of synthesizing PET radiopharmaceuticals that are suitable for human use.

James Bennett, MD, PhD, Virginia Commonwealth University

James Bennett, MD, PhD, is a native of St. Petersburg, FL and received his BS in Chemistry with Honors from the University of Florida in 1970. He then attended Johns Hopkins University School of Medicine and received his MD in 1974 and his PhD in Pharmacology in 1977. While a graduate student he worked under Dr. Solomon Snyder and remained in Dr. Snyder's laboratory for a research fellowship from 1976-78. He then completed two years of Internal Medicine residency and came to the University of Virginia in 1980 for his Neurology residency that he finished in 1983. From 1982-83 he was Chief Resident in Neurology. In 1983 he joined the faculty in the Neurology Department as Assistant Professor. In 1990 he was promoted to Associate Professor and he received tenure in 1992. In 1997 he was promoted to Professor of Neurology and Psychiatric Research. In 2004 he was awarded the Arthur and Margaret Ebbert Chair in Medical Science. In 2009 he moved to Virginia Commonwealth University and became Bemiss Professor, Chair of Neurology, and founding Director of the VCU Parkinson's Disease Research and Treatment Center. In 2013 he stepped down from being Chair of Neurology and continued as Director of the Parkinson's Center. He holds joint appointments in the Departments of Psychiatry and Physiology and Biophysics. Dr. Bennett has held numerous research grants from the NIH and private foundations. He was Director of the NIH P50 Udall Parkinson's Disease Research Center at University of Virginia that was funded for 10 years. He has authored 144 peer-reviewed scientific papers and several book chapters. His clinical specialty is movement disorders, particularly Parkinson's disease. His research interest is in the area of the molecular biology of neurodegenerative brain diseases (NBD), the involvement of mitochondria and mitochondrial biogenesis in NBD and development of experimental therapeutics for NBD.

Safety/Tolerability and Effects on Cognitive Impairment, Impaired Cerebral Cortical Metabolism and Oxidative Stress of R(+)Pramipexole Administered to Subjects with Early Alzheimer's Disease

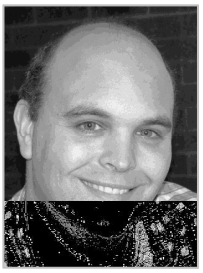
Jeffrey Burns[1], Rebecca Bothwell[1], Paul Welch[1], Eric Vidoni[1], James P. Bennett, Jr.[2]

[1]Alzheimer's Disease Research Center, Kansas University School of Medicine, Kansas City, KS; [2]Parkinson's Disease Research Center, Virginia Commonwealth University, Richmond, VA

Virginia Commonwealth University, Richmond, VA, USA

The molecular abnormalities that lead to the clinical syndromes of mild cognitive impairment (MCI) and progression into Alzheimer's dementia (AD) remain controversial, are likely multifactorial and could vary across individuals. Deficiencies in mitochondrial bioenergetics and increased oxidative stress damage have been found in postmortem MCI and AD brain tissues. R(+)pramipexole (PPX) is an antioxidant benzothiazole that concentrates 6 to 7-fold from plasma into brain and 7 to 10-fold into polarized mitochondria. R(+)PPX has weak affinity for brain D2 dopamine receptors compared its S(-) enantiomer (Mirapex®) and has been safely administered orally to adults with ALS at doses up to 450 mg/day. In the current study, 20 subjects with early AD were recruited to take R(+)PPX at ascending doses to a target dose of 300 mg/day. 18F-FDG-PET brain scans, sera, lumbar CSF and cognitive assessments were obtained at baseline and after maximum R(+)PPX dosing. Safety labs were assayed q2-3 months, and the safety data were independently assessed by an external DSMB. The primary goal of the study was to determine safety and tolerability of R(+)PPX in this population. Secondary goals were to search for biomarkers of R(+)PPX effects. Twenty-two patients were screened; 20 met study criteria and were enrolled. Fifteen subjects completed all study visits. Five withdrew from the study before completing all visits; 4 due to Adverse Events (AEs) and 1 due to travel and testing burden. There were 56 total AEs, 26 of which were considered related to study drug although the lack of a placebo group limits our ability to fully attribute these AEs to R(+)-PPX. None were serious or severe. The most common AEs were sleep-disruption (n=8), irritability/agitation (n=3), increased confusion (n=3), increased libido (n=3), and nausea (n=3). Irritability/agitation, sleep disruption and increased confusion tended to co-occur (n=3 participants reported each of these). 14/15 participants reached 300 mg/day R(+)PPX; 1 reached 200 mg/day R(+)PPX. Overall compliance was 93%. Mean time at final R(+)PPX dose was 95 days (range 33-117). Mean weight change over 6 months was -0.7 kg (range -8.0 to +3.7). Analysis of trough PPX levels in serum and CSF samples showed an unexpectedly wide variation from 13-1380 ng/ml and 23-1390 ng/ml, respectively, and serum and CSF [PPX] were linearly related (r2=0.95) with slope 95% confidence intervals of 0.83-1.1. Pre- and post-intervention cognitive and FDG PET data were collected although there were no clear drug-related effects observed in the overall population. Exploratory analyses of serum and CSF levels of various biomarkers demonstrated some trends that may be attributable to study drug. The small sample size (n=15), lack of placebo group, and short-duration (6 months) of the study limit the ability to assess drug-effects in these outcomes. R(+)PPX in a short duration, open-label study was well tolerated in this small population of early AD subjects. Analysis is ongoing to determine if there are any relationships among serum/CSF [PPX] and outcome measures. Any future studies of R(+)PPX in a similar population will likely require dosage adjustments to reach a minimal target trough serum [PPX].

Blaine Roberts, PhD, Florey Institute of Neuroscience and Mental Health



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

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

Circulating Aβ Complexes: A Window on Aβ Clearance and a Screening Tool for Alzheimer's Disease

Blaine Roberts

Florey Institute of Neuroscience and Mental Health, Victoria, Australia

Despite the prevalence of Alzheimer's disease, the lack of an early and accurate diagnostic test remains a significant hindrance to the field. Accumulation of amyloid in the brain is the major pathological hallmark of Alzheimer's disease. Current positron emission tomography (PET) techniques can detect the presence of amyloid in the brain and it is known that the accumulation of Aβ begins 10-20 years before clinical symptoms occur. Although PET is a powerful technique for the early detection of brain amyloid, there are practical limitations to its wide spread clinical use. Thus, there is a need to develop a blood-based screen that can be implemented in general practice and determine who should be refereed for further testing. We have utilized samples from the Australian Imaging and Biomarker Lifestyle study of ageing (AIBL) to search for blood based protein markers that reflect amyloid in the brain. We have discovered three proteins in the plasma that correlate with the level of brain amyloid. Interestingly, two of these biomarkers were found in complex with Aβ. Measurement of these three proteins results in greater than 85% sensitivity and specificity for detection of brain amyloid. Further, we have shown that these biomarkers are specific for Alzheimer's disease when compared to Parkinson's disease. Overall our results have implications for the mechanisms of Aβ clearance and the development of a blood–based screening tool. Continued validation of these biomarkers will provide vital data about the utility of these markers to screen for brain amyloid and their potential to monitor therapeutic efficacy.

Funded through the ADDF-New York Academy of Sciences (NYAS) Challenge Grant

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

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

The Effect of Novel Heat Shock Protein 90 (Hsp90) Inhibitors on Tau Pathology
Yukari Perrella, MBA, Yuma Therapeutics Corporation

Brain Slice Screen for Anti-microRNA Drug Lead Candidates for Tau-associated FTD
Donald Lo, PhD, Duke Center for Drug Discovery

Testing of GLX1112 in an Alzheimer's Mouse Model
Thadd Reeder, PhD, Glialogix, Inc.

Development of an Antisense Therapy and Pharmacodynamic Marker(s) to treat C9ORF72 ALS/FTD RNA toxicity
Chris Donnelly, PhD, Johns Hopkins University School of Medicine

Development of Epigenetic Modulator, ORY-2001, for Neurodegenerative Disease
Carlos Buesa, PhD, Oryzon Genomics, SA

SESSION CHAIR

Aaron Carman, PhD, Alzheimer's Drug Discovery Foundation

Aaron Carman, PhD, is the Senior Program Manager 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.

Yukari Perrella, MBA, Yuma Therapeutics Corporation

Yukari Perrella, MBA, is a founder of Yuma Therapeutics. Yukari has more than 20 years of experience in the healthcare field, including operations, business development, finance and research. Previously, Yukari was vice president of business development of Alseres Pharmaceuticals, a public neuroscience biotech company where she was responsible for the business development activities of the company.

Prior to Alseres, Yukari was executive director of business development for CombinatoRx. Prior to CombinatoRx, Yukari was head of U.S. operations at Xerion Pharmaceuticals where she ran North American operations and business development for a European biopharmaceutical company. Yukari also held positions of increasing responsibilities at Hybridon, V.I. Technologies, and Imperial Bank.

Yukari worked in research laboratories at Harvard School of Public Health, Children's Hospital, and Massachusetts General Hospital.

The Effect of Novel Heat Shock Protein 90 (Hsp90) Inhibitors on Tau Pathology

Yukari Perrella

Yuma Therapeutics Corporation, Brookline, MA, USA

Heat shock protein 90 (Hsp90) is a chaperone protein that assists other proteins to fold properly, stabilizes proteins against heat stress, and aids in protein degradation. Available data demonstrates that inhibition of Hsp90 decreases aberrant tau phosphorylation through (i) activation of Hsp70, which enhances tau solubility; and (ii) reduction in cyclin dependent kinase (cdk5) and p35 (the neuron-specific regulatory subunit of cdk5) activity. Yuma Therapeutics, together with Laboratory for Drug Discovery in Neurodegeneration (LDDN) at the Brigham and Women's Hospital (BWH), designed and synthesized proprietary heat shock protein 90 (Hsp90) inhibitors with physiochemical properties that are acceptable as an approach to modulate phosphorylated tau.

Donald Lo, PhD, Duke Center for Drug Discovery

Donald Lo, PhD, is Director of the Center for Drug Discovery and Associate Professor in the Department of Neurobiology at Duke University Medical Center, and has been engaged in drug discovery and development for neurodegenerative disorders and stroke for over 15 years.

In 1997, he co-founded and was Chief Scientific Officer of the biotechnology company Cogent Neuroscience, which developed and implemented brain tissue based-assays for stroke, Huntington's disease, and Alzheimer's disease.

The Duke CDD currently pursues multiple neurological drug discovery and development programs in collaboration with numerous academic labs, pharmaceutical firms, biotech companies, and non-profit disease research foundations.

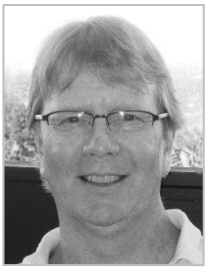
Brain Slice Screen for Anti-microRNA Drug Lead Candidates for Tau-associated FTD

Donald Lo

Duke Center for Drug Discovery, Durham, NC, USA

MicroRNAs (miRs) are short, non-coding RNAs that mediate transcriptional repression of multiple mRNAs containing complementary target sequences, and have emerged as an exciting new class of drug targets for a range of human diseases including CNS neurodegenerative diseases such as FTD. In collaboration with Regulus Therapeutics, a biotechnology company focused on the development of miR-based drugs, we are developing a novel brain slice-based assay to identify potential miR targets whose functional modulation may ameliorate tau-associated neurodegeneration. In addition, we will seek to provide initial proof-of-concept of the druggability of such potential miR targets using Regulus anti-miR technology. The overall goal of the study will be to generate anti-miR lead candidates for further translational studies in preclinical animal models for FTD and other tau-associated neurodegenerative disorders.

Thadd Reeder, PhD, Glialogix, Inc.



Thadd Reeder, PhD, has 15 years of experience in the biotechnology field, with a focus on target identification and validation, preclinical drug development and technology innovation. Following his post-doctoral Damon Runyon Cancer Research fellowship, he was one of the founding scientists of Deltagen, a company focused on functional genomics using large scale mouse knockout technology.

At Deltagen, he developed high throughput genetic engineering technology and directed the company's target identification efforts for multiple disease areas. Following Deltagen, he co-founded Toccata Therapeutics, the first company to develop rapid in vivo drug screening technologies for protein therapeutics. At Toccata, Dr. Reeder directed a large scale in vivo screening program to identify secreted proteins and soluble receptors that could lower A-beta levels in AD mice. More recently, he worked at FivePrime Therapeutics, where he co-directed a large scale collaboration with Pfizer focused on oncology and diabetes and served as project manager for multiple preclinical development programs.

Dr. Reeder co-founded Glialogix and is the Chief Scientific Officer. Dr. Reeder received his PhD in molecular biology from Brandeis University and his BS in biochemistry and biophysics from Oregon State University.

Testing of GLX1112 in an Alzheimer's Mouse Model

Thadd Reeder

Glialogix, Inc., Greenbrae, CA, USA

Glialogix is developing GLX1112 for treatment of chronic neurodegenerative diseases. GLX1112 is designed to have dual neuroprotective activities: inhibit glutamate excitotoxicity and reduce the levels of activated microglia and astrocytes. GLX1112 is a reformulated version of an FDA-approved drug currently used for non-neurological indications. The reformulation is designed to optimize the PK properties of the Active Pharmaceutical Ingredient (API) and increase the therapeutic index when used for CNS indications. Our lead indication is Progressive Multiple Sclerosis (P-MS). In a prior clinical trial in P-MS, the API in GLX1112 showed strong evidence of clinical efficacy: treated subjects showed a >100% decrease in time-to-progression compared to placebo. The API in GLX1112 has also demonstrated efficacy in preclinical models of ALS and neuropathic pain.

With support from ADDF, the API in GLX1112 was tested in the CVN model (APPSwDI/NOS2-/-) of AD. The CVN model was chosen because it was reported to have high levels of neuroinflammation and significant loss of hippocampal neurons. Dosing of animals began at month 9 and continued for 3 months. Behavior tests were conducted at 9 and 12 months and histology performed at 12 months. Treatment with GLX1112 had no effect on soluble or insoluble levels of A-beta by either ELISA or IHC analysis. Contrary to previous reports, the CVN animals did not show a significant increase in microglial or astrocyte activation by IHC, nor did they show a loss in the numbers of hippocampal neurons. In the open field test, treatment with GLX1112 restored the habituation response in CVN animals to levels seen in the WT mice, suggesting a positive effect on memory. In the Barnes maze, the results were inconsistent, with GLX1112 treatment increasing the number of incorrect nose pokes but also improving the learning index during the testing regimen compared to the vehicle treated CVN mice. The results from these behavioral tests as well as the promising results in other neurodegenerative diseases may warrant further investigation of GLX1112 in Alzheimer's, in particular, testing in additional behavioral and/or electrophysiological models.

Chris Donnelly, PhD, Johns Hopkins University School of Medicine

Christopher Donnelly, PhD, is a senior postdoctoral fellow at Johns Hopkins University in the department of Neurology and the Brain Science Institute. Dr. Donnelly received his doctorate in Molecular Biology and Genetics from the University of Delaware in 2011.

During his graduate training, Dr. Donnelly worked at A.I. DuPont Hospital for Children under Jeffery Twiss, MD, PhD where he studied the role of RNA transport and translation in axon regeneration and neuronal repair. In the summer of 2011, Dr. Donnelly began work at Johns Hopkins training under Jeffrey Rothstein, MD, PhD where he has since investigated the role of RNA toxicity in ALS and FTD.

Dr. Donnelly's research is centered on identifying novel molecular mechanisms of neurodegeneration employing iPS stem cell models with the hope of identifying novel pathways for therapeutic intervention.

Development of an Antisense Therapy and Pharmacodynamic Marker(s) to treat C9ORF72 ALS/FTD RNA toxicity

Chris Donnelly

Johns Hopkins University School of Medicine, Baltimore, MD, USA

A hexanucleotide 'GGGGCC' repeat expansion in the noncoding region of the C9ORF72 gene has recently been identified as the most common known genetic cause of sporadic and familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). While the pathogenic mechanism behind this mutation is unclear, repeat expansion disorders are the known causes of other neurological/neuromuscular disorders, with some due to expansions in non-coding regions including myotonic dystrophy 1 and 2 (DM1, DM2). In non-coding repeat expansion disorders, pathogenesis may be due to the accumulation of expanded repeat-containing RNA that sequester RNA binding proteins (RBPs). Since animal models are still being generated, to elucidate the pathogenic mechanism behind the C9ORF72 mutation, we have generated iPS cells from C9ORF72 ALS patient fibroblasts. Using iPS-differentiated neurons and astrocytes, we have 1) identified intranuclear (GGGGCC)exp RNA foci in vitro similar to those found in vivo, 2) described dysregulated gene expression in C9ORF72 ALS tissue that match iPS cell lines, 3) have identified (GGGGCC)exp RNA binding partners, 4) determined that C9ORF72 iPS neurons are highly susceptible to extracellular stressors and 5) identified nuclear transport deficits which might lead to the cytoplasmic accumulation of nuclear proteins associated with ALS/FTD. Importantly, all of these pathogenic characteristics are mitigated with antisense therapeutics to the C9ORF72 transcript or small molecules that block interaction of the (GGGGCC)exp RNA from interacting with its binding partners. Taken together, these data indicate a toxic RNA gain-of-function mechanism as a cause of C9ORF72 ALS. These studies also provide candidate antisense therapeutics as well and human pharmacodynamic biomarkers for drug actions that are being developed for clinical trials.

Funded through the ADDF-Association for Frontotemporal Degeneration (AFTD) Partnership Program

Carlos Buesa, PhD, Oryzon Genomics, SA

Carlos Buesa, PhD, got his doctorate degree in Biochemistry from the University of Barcelona, Spain in 1993. He has also taken the executive education programme (PADE) at the IESE Business School in Barcelona and several other additional educational programs in finances.

In 2000, he cofounded Oryzon. Since inception he has served as CEO. Under his leadership the company evolved from a genomics company to a clinical stage pharmaceutical company focused on the development of drugs directed against epigenetic targets. Its forerunner program of LSD1 inhibitors for Oncology is in Phase I/IIA and was licensed to Roche in April 2014 in a multimillion USD deal. Next year, Oryzon plans to move a second LSD1 inhibitor for the treatment of Alzheimer's disease into Phase I studies.

Development of Epigenetic Modulator, ORY-2001, for Neurodegenerative Disease

Mascaró-Crusat, C., Estiarte, A., Valls, N., Ortega, A., Griñan-Ferre, C., Pallàs, M., Guibourt, N., Fyfe, M., Maes, T. and Buesa, C.

Oryzon Genomics, SA, Barcelona, Spain

The etiology of idiopathic Alzheimer's disease (AD), as in many neurodegenerative diseases, is unknown. Aggregation of intracellular proteins is a common hallmark, suggesting this could be a primary mechanism. These changes on protein homeostasis may be caused by an impaired ubiquitin-proteasome degradation system (UPS). In a genomic survey carried out by Oryzon on autopsic brains from PD and dementia with Lewy body (DLB) early stage patients, we found that UCHL-1 gene and protein expression levels were downregulated in the affected brain areas. A similar downregulation is observed in AD. REST/NRSF is a transcription factor involved in the control of expression of many genes expressed in neurons, UCHL1 among them. REST binds to the RE1/NRSE elements in the promoter of neuron specific genes and attracts repressive chromatin epigenetic modifying factors including histone deacetylases (HDACs) and demethylases (LSD1) to the DNA. We have developed a strategy to neutralize this complex via inhibition of the activity of one of its components, LSD1/KDM1A, to redress transcriptional changes or imbalances in AD and other neurodegenerative diseases. Oryzon's LSD1 drug discovery program has produced bispecific LSD1-MAOB inhibitors for the treatment of neurodegenerative disorders taking advantage of the structural similarities between LSD1 and MAO proteins. We have successfully designed advanced compounds and selected one, ORY-2001, that complied with the desired pharmacological profile. Functional assays demonstrated that ORY-2001 restores the memory defects in a non-transgenic Alzheimer's mouse model named SAMP8. SAMP8 mice present accelerated aging and many pathogenic alterations that recapitulate the human disease, including cognitive impairment, memory decay, beta-amyloid deposition, increased expression of tau kinases, inflammation and oxidative stress. Long term oral treatment of SAMP8 mice with ORY-2001 completely rescued the memory and learning defects of SAMP8 mice as determined by the performance of treated animals in the Novel Object Recognition Test (NORT), it redressed some of the transcriptional changes observed in SAMP-8 mice versus the reference strain, and it induced the expression of genes beneficial to memory, including REST target genes. These results open the window for a new therapeutic approach and suggest that LSD1 could be a novel target for Alzheimer's disease and ORY-2001 a disease modifier drug. ORY-2001 is currently undergoing preclinical regulatory toxicology studies and is expected to be ready for CTA/IND submission by the end of next year.

NOTES

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We are united and inspired by the hope for better lives. Since our founding by Col. Eli Lilly in 1876, we have been committed to discovering solutions to our world's most pressing health problems. More than a century later, we remain true to our founding family's vision and values – to create high quality medicines with integrity, excellence and respect for people. Across the globe, you will find Lilly employees working tirelessly to bring life-changing medicines to people who need them, offering support to patients and families living with serious illness, and giving back to their communities and the environment through countless acts of service.

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Pfizer

Good health is vital to all of us, and finding sustainable solutions to the most pressing health care challenges of our world cannot wait. That's why we at Pfizer are committed to applying science and our global resources to improve health and well-being at every stage of life. We strive to provide access to safe, effective and affordable medicines and related health care services to the people who need them. We have a leading portfolio of products and medicines that support wellness and prevention, as well as treatment and cures for diseases across a broad range of therapeutic areas; and we have an industry-leading pipeline of promising new products that have the potential to challenge some of the most feared diseases of our time, like Alzheimer's disease and cancer.

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

Oryzon
Oryzon is today a clinical stage biopharmaceutical company and the leader in EPIGENETICS in Europe. Oryzon's mission is to identify and manipulate biomarkers -genes and proteins- allowing the development of new therapeutic tools in the quest to improve human health – covering unmet clinical needs- and in benefits for our shareholders. Oryzon's vision is to become a world leader company in the field of epigenetic medicine and in the development of therapeutic, biological solutions for cancer and neurodegenerative diseases.

PsychoGenics
PsychoGenics is a contract research organization in neurobiology, providing state of the art preclinical services (behavior, electrophysiology, immunohistochemistry, imaging, etc.) and mouse models for most CNS disease areas. Neurodegenerative disorders, are our company's core competence. We offer well validated pharmacologically induced and genetically modified disease models, optimizing predictive value of preclinical drug development programs. Our models have been used by leading pharmaceutical/biotech companies and are well documented in current scientific literature. PsychoGenics' cube technologies combine sensitive computer vision and precise robotics and informatics to provide unbiased, high throughput *in vivo* screening for CNS drug discovery and phenotyping.